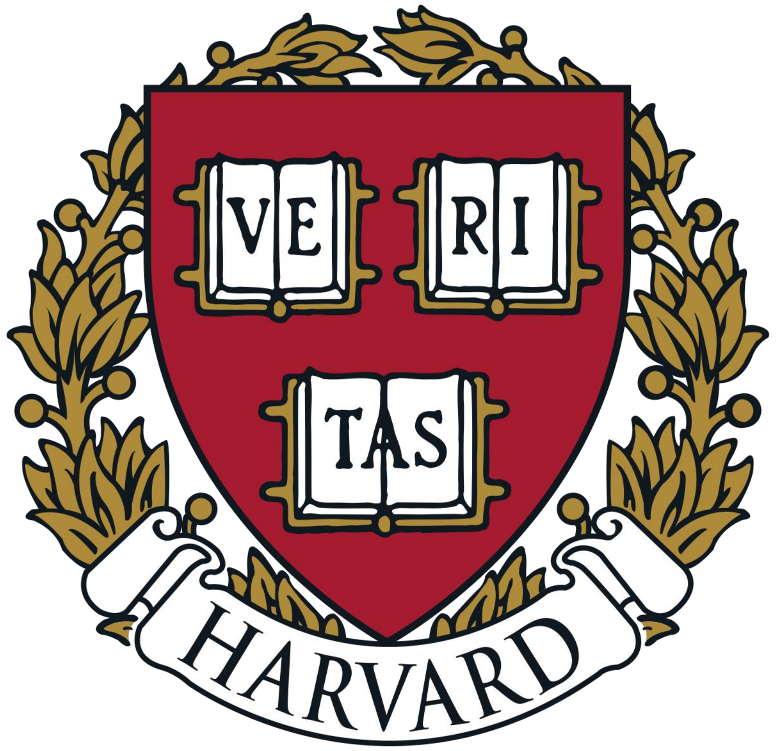
Chemistry 206

Advanced Organic Chemistry

Harvard University

Author: D.A.Evans

Advanced Organic Chemistry



Remember to look up at the stars
And not down at your feet.
Try to make sense of what you see and wonder about what makes the universe exist.
Be curious!

--------------------- *Stephen Hawking*

CONTENTS

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 1

Introduction to FMO Theory

- General Bonding Considerations
- The H_2 Molecule Revisited (Again!)
- Donor & Acceptor Properties of Bonding & Antibonding States
- Hyperconjugation and "Negative" Hyperconjugation
- Anomeric and Related Effects

Reading Assignment for week:

A. Carey & Sundberg: **Part A**; Chapter 1

B. Fleming, Chapter 1 & 2

C. Fukui, *Acc. Chem. Res.* **1971**, *4*, 57.

D. O. J. Curnow, *J. Chem. Ed.* **1998**, *75*, 910.

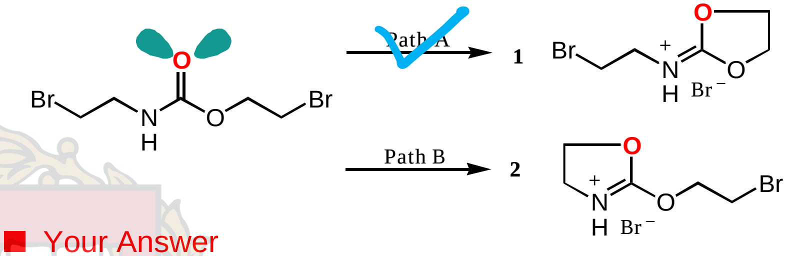
E. J. I. Brauman, *Science*, **2002**, *295*, 2245.

Matthew D. Shair

Wednesday,
September 18, 2002

Problem of the Day

The molecule illustrated below can react through either Path A or Path B to form salt **1** or salt **2**. In both instances the carbonyl oxygen functions as the nucleophile in an intramolecular alkylation. What is the preferred reaction path for the transformation in question?

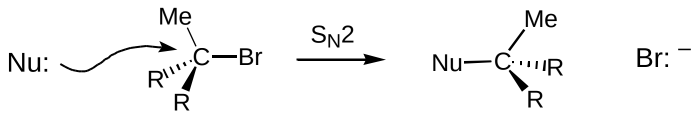


Your Answer

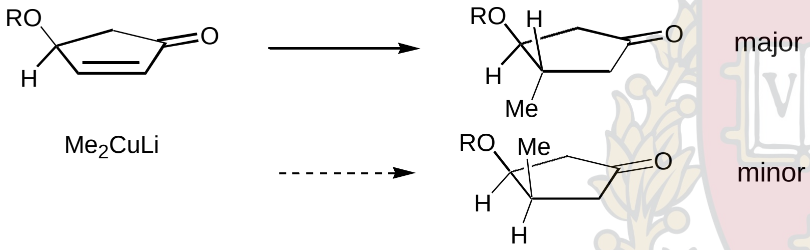
Universal Effects Governing Chemical Reactions
There are three:

Steric Effects

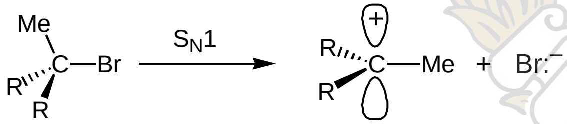
Nonbonding interactions (Van der Waals repulsion) between substituents within a molecule or between reacting molecules



J. I. Brauman, *Science*, **2002**, *295*, 2245.



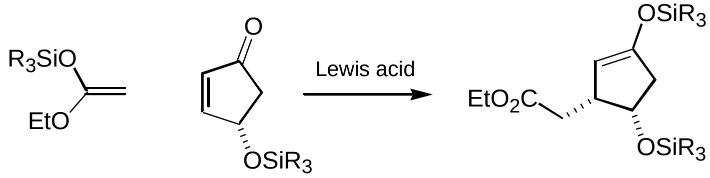
Electronic Effects (Inductive Effects):



rate decreases as R becomes more electronegative

Inductive Effects: Through-bond polarization
Field Effects: Through-space polarization

Your thoughts on this transformation



Danishefsky, *JOC* **1991**, *56*, 387

diastereoselection >94 : 6

Stereoelectronic Effects

Geometrical constraints placed upon ground and transition states by orbital overlap considerations.

Fukui Postulate for reactions:

"During the course of chemical reactions, the interaction of the highest filled (HOMO) and lowest unfilled (antibonding) molecular orbital (LUMO) in reacting species is very important to the stabilization of the transition structure."

General Reaction Types

Radical Reactions (~10%): $A\cdot + B\cdot \longrightarrow A\text{—}B$

Polar Reactions (~90%): $A(:) + B(+) \longrightarrow A\text{—}B$

Lewis Base ↑ Lewis Acid ↑

FMO concepts extend the donor-acceptor paradigm to non-obvious families of reactions

Examples to consider

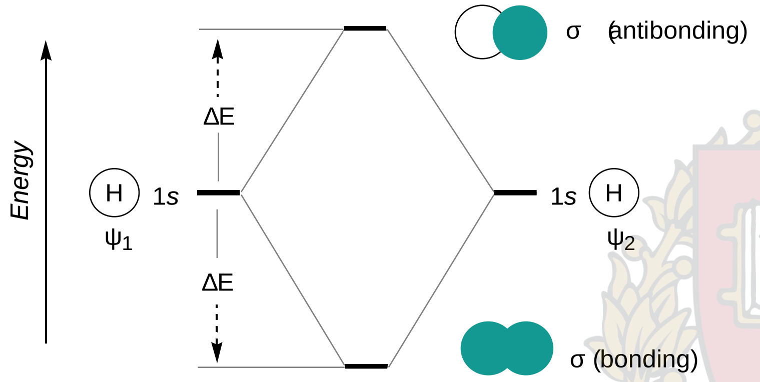
$H_2 + 2\,Li(0) \longrightarrow 2\,LiH$

$CH_3\text{–}I + Mg(0) \longrightarrow CH_3\text{–}MgBr$

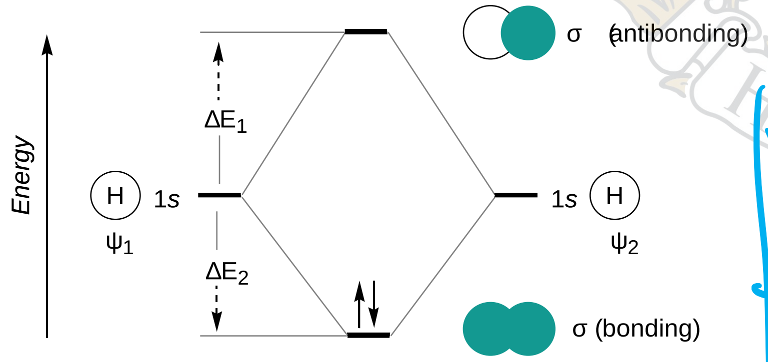
The H_2 Molecule (again!!)

Let's combine two hydrogen atoms to form the hydrogen molecule. Mathematically, linear combinations of the 2 atomic 1s states create two new orbitals, one is bonding, and one antibonding:

■ **Rule one**: A linear combination of n atomic states will create n MOs.



Let's now add the two electrons to the new MO, one from each H atom:



Note that ΔE_1 is greater than ΔE_2. Why?

Linear Combination of Atomic Orbitals (LCAO): Orbital Coefficients

■ **Rule Two**:

Each MO is constructed by taking a linear combination of the individual atomic orbitals (AO):

Bonding MO $\sigma = C_1\psi_1 + C_2\psi_2$

Antibonding MO $\sigma\ = C^*_1\psi_1 - C^*_2\psi_2$

The coefficients, C_1 and C_2, represent the contribution of each AO.

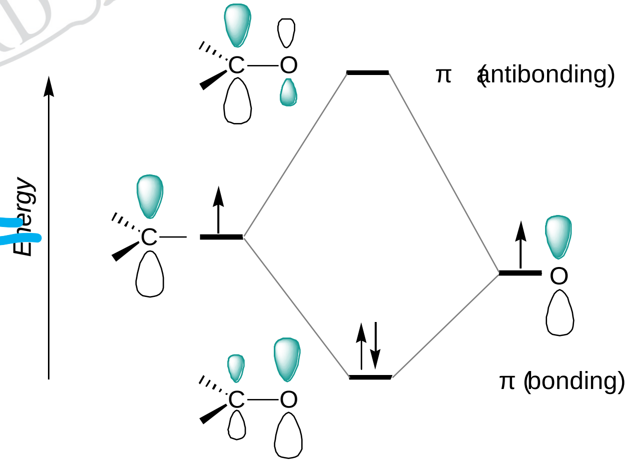
■ **Rule Three**: $(C_1)^2 + (C_2)^2 = 1$

The squares of the C-values are a measure of the electron population in neighborhood of atoms in question

■ **Rule Four**: bonding$(C_1)^2$+ antibonding$(C^*_1)^2$= 1

In LCAO method, both wave functions must each contribute one net orbital

Consider the pi -bond of a C=O function: In the ground state pi-C–O is polarized toward Oxygen. Note (Rule 4) that the antibonding MO is polarized in the opposite direction.



■ *Bond strengths (Bond dissociation energies) are composed of a covalent contribution (δ E_{cov}) and an ionic contribution (δ E_{ionic}).*

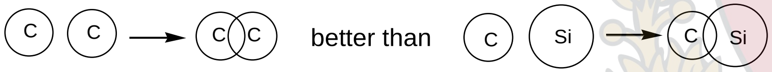
Bond Energy (BDE) = δ $E_{covalent}$ + δ E_{ionic} (Fleming, page 27)

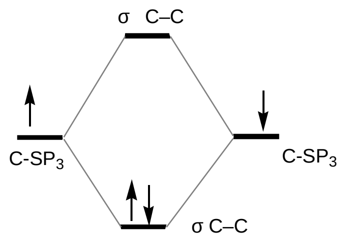
When one compares bond strengths between C–C and C–X, where X is some other element such as O, N, F, Si, or S, keep in mind that covalent and ionic contributions vary independently. Hence, the mapping of trends is not a trivial exercise.

Useful generalizations on covalent bonding

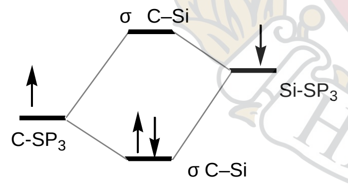
■ *Overlap between orbitals of comparable energy is more effective than overlap between orbitals of differing energy.*

For example, consider elements in Group IV, Carbon and Silicon. We know that C-C bonds are considerably stronger by Ca. 20 kcal mol^{-1} than C-Si bonds.





$H_3C–CH_3$ BDE = 88 kcal/mol
Bond length = 1.534 Å



$H_3C–SiH_3$ BDE ~ 70 kcal/mol
Bond length = 1.87 Å

This trend is even more dramatic with pi-bonds:

π C–C = 65 kcal/mol π C–Si = 36 kcal/mol π Si–Si = 23 kcal/mol

■ *Weak bonds will have corresponding low-lying antibonds.*

Formation of a weak bond will lead to a corresponding low-lying antibonding orbital. Such structures are reactive as both nucleophiles & electrophiles

■ *Orbital orientation strongly affects the strength of the resulting bond.*

For σ Bonds:

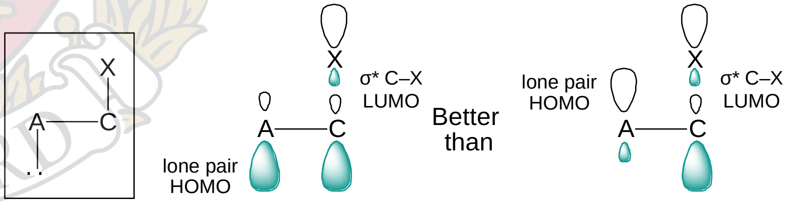
For π Bonds:

This is a simple notion with very important consequences. It surfaces in the delocalized bonding which occurs in the competing anti (favored) syn (disfavored) E2 elimination reactions. Review this situation.

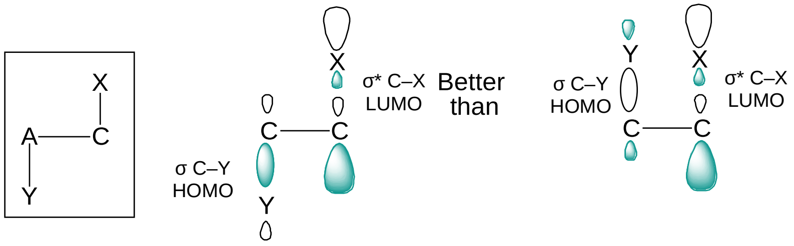
■ *An anti orientation of filled and unfilled orbitals leads to better overlap.*

This is a corrollary to the preceding generalization. There are two common situations.

Case-1: Anti Nonbonding electron pair & C–X bond



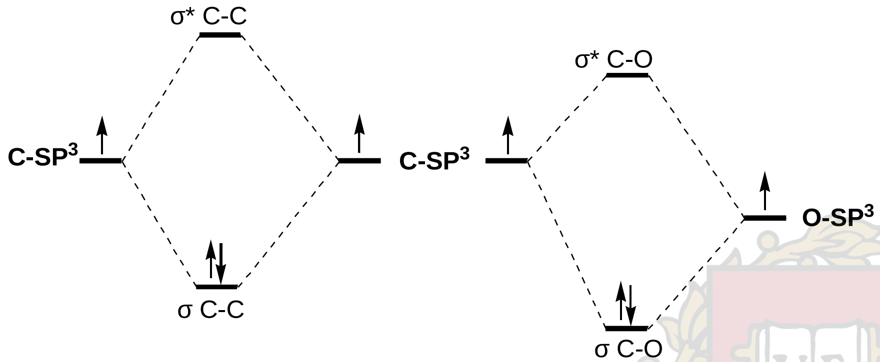
Case-2: Two anti sigma bonds



Donor-Acceptor Properties of Bonding and Antibonding States

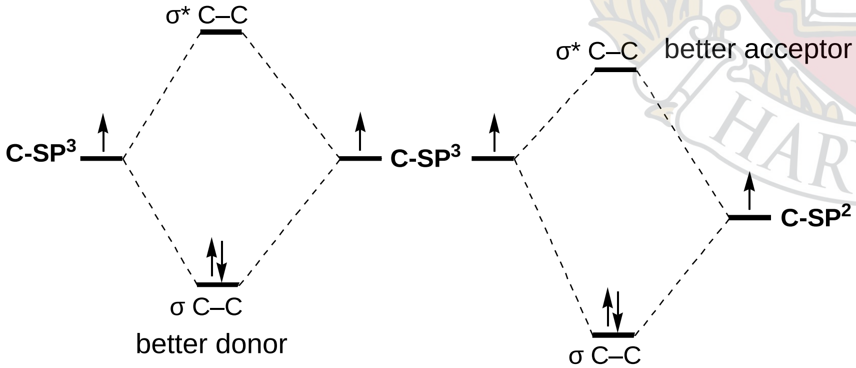
Donor Acceptor Properties of C-C & C-O Bonds

Consider the energy level diagrams for both bonding & antibonding orbitals for C–C and C–O bonds.



- The greater electronegativity of oxygen lowers both the bonding & antibonding C-O states. Hence:
  - σ C–C is a better donor orbital than σ C–O
  - σ C–O is a better acceptor orbital than σ C–C

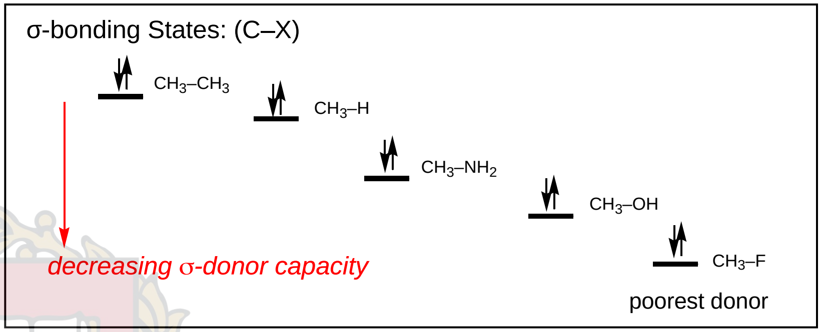
Donor Acceptor Properties of C_{SP3}-C_{SP3} & C_{SP3}-C_{SP2} Bonds

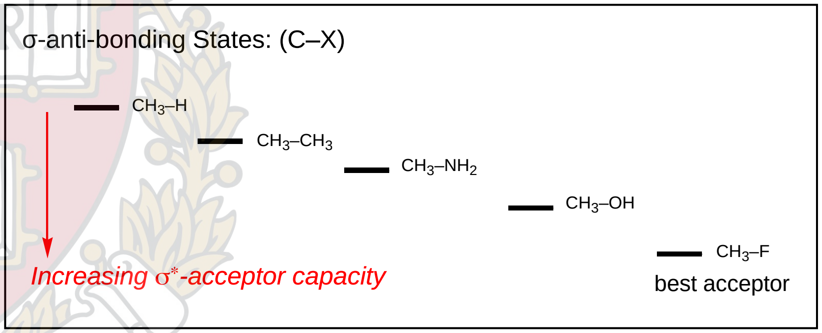


- The greater electronegativity of C_{SP2} lowers both the bonding & antibonding C–C states. Hence:
  - σ C_{SP3}-C_{SP3} is a better donor orbital than σ C_{SP3}-C_{SP2}
  - σ C_{SP3}-C_{SP2} is a better acceptor orbital than σ C_{SP3}-C_{SP3}

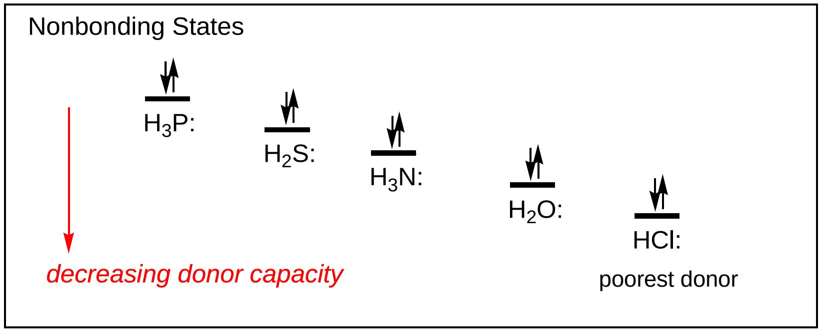
Hierarchy of Donor & Acceptor States

Following trends are made on the basis of comparing the bonding and antibonding states for the molecule CH_3–X where X = C, N, O, F, & H.



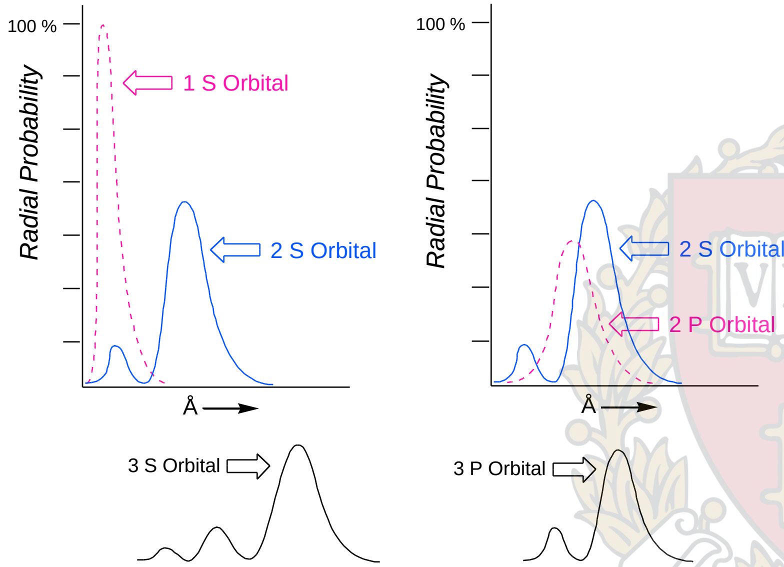


The following are trends for the energy levels of *nonbonding states* of several common molecules. Trend was established by photoelectron spectroscopy.



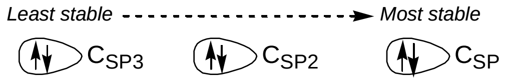
Electrons in 2S states "see" a greater effective nuclear charge than electrons in 2P states.

This becomes apparent when the radial probability functions for S and P-states are examined: The radial probability functions for the hydrogen atom S & P states are shown below.



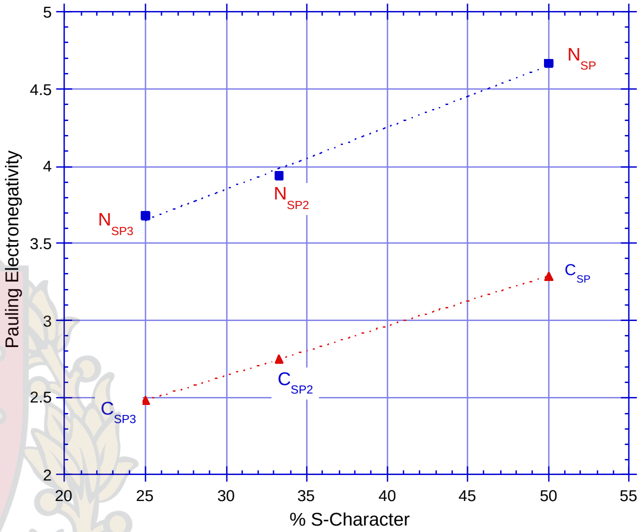
S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in S-states "see" a higher nuclear charge.

Above observation correctly implies that the stability of nonbonding electron pairs is directly proportional to the % of S-character in the doubly occupied orbital

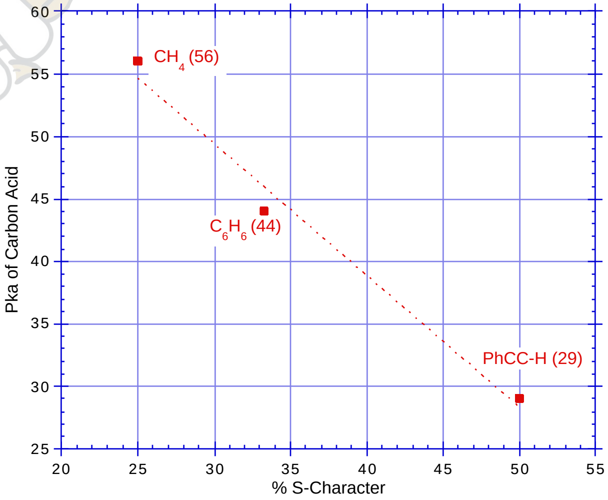


The above trend indicates that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

There is a linear relationship between %S character & Pauling electronegativity



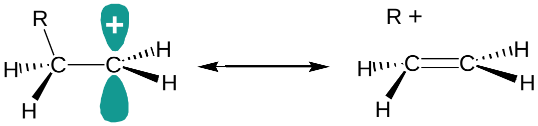
There is a direct relationship between %S character & hydrocarbon acidity



Hyperconjugation: Carbocation Stabilization

■ The interaction of a vicinal bonding orbital with a p-orbital is referred to as hyperconjugation.

This is a traditional vehicle for using valence bond to denote charge delocalization.

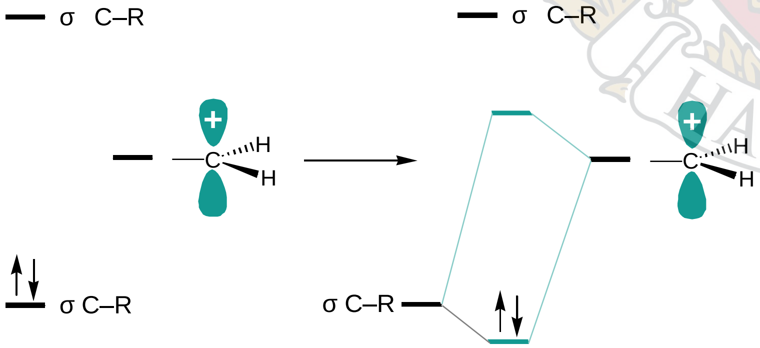


The graphic illustrates the fact that the C-R bonding electrons can "delocalize" to stabilize the electron deficient carbocationic center.

Note that the general rules of drawing resonance structures still hold: the positions of all atoms must not be changed.

Stereoelectronic Requirement for Hyperconjugation:
Syn-planar orientation between interacting orbitals

The Molecular Orbital Description



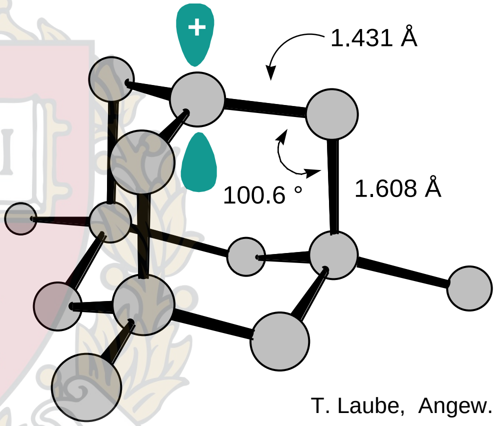
■ Take a linear combination of σ C–R and CSP$_2$ p-orbital:

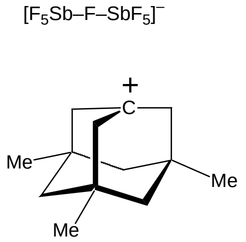
The new occupied bonding orbital is lower in energy. When you stabilize the electrons is a system you stabilize the system itself.

Physical Evidence for Hyperconjugation

■ Bonds participating in the hyperconjugative interaction, e.g. C–R, will be lengthened while the C(+)–C bond will be shortened.

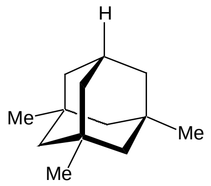
First X-ray Structure of an Aliphatic Carbocation

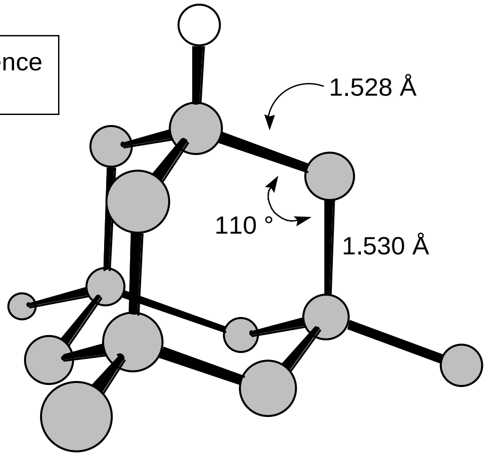




T. Laube, Angew. *Chem. Int. Ed.* **1986**, *25*, 349

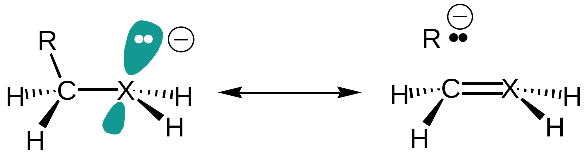
The Adamantane Reference (MM-2)





"Negative" Hyperconjugation

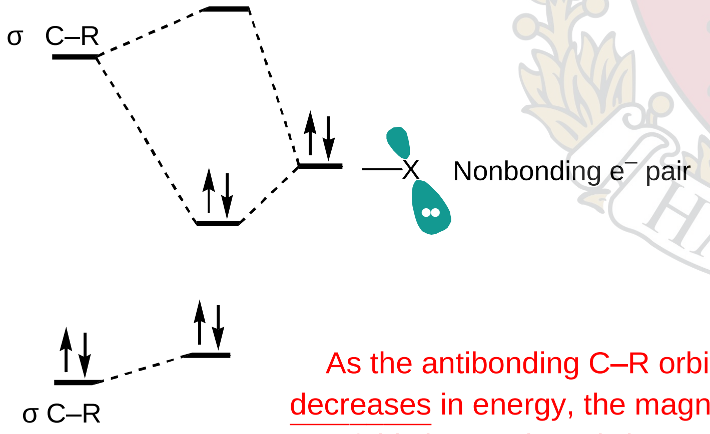
- Delocalization of nonbonding electron pairs into vicinal antibonding orbitals is also possible



This decloalization is referred to as "Negative" hyperconjugation

Since nonbonding electrons prefer hybrid orbitals rather that P orbitals, this orbital can adopt either a syn or anti relationship to the vicinal C–R bond.

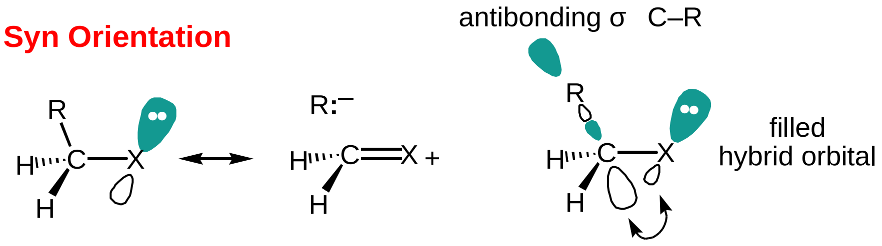
The Molecular Orbital Description



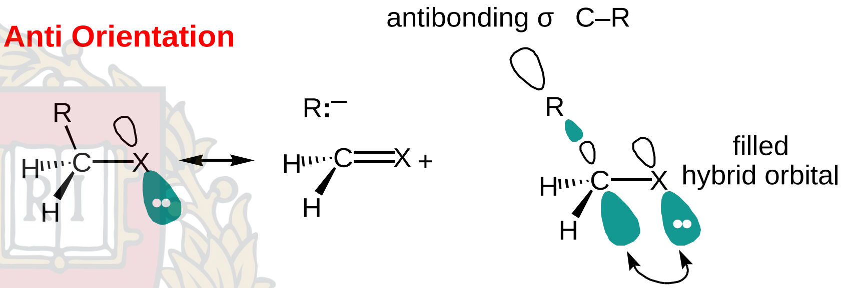
As the antibonding C–R orbital decreases in energy, the magnitude of this interaction will increase

Note that σ C–R is slightly destabilized

Syn Orientation



Anti Orientation



- Overlap between two orbitals is better in the anti orientation as stated in "Bonding Generalizations" handout.

The Expected Structural Perturbations

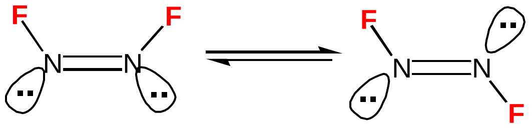
Change in Structure	Spectroscopic Probe
Shorter C–X bond	X-ray crystallography
Longer C–R bond	X-ray crystallography
Stronger C–X bond	Infrared Spectroscopy
Weaker C–R bond	Infrared Spectroscopy
Greater e-density at R	NMR Spectroscopy
Less e-density at X	NMR Spectroscopy

Lone Pair Delocalization: N_2F_2

The interaction of filled orbitals with adjacent antibonding orbitals can have an ordering effect on the structure which will stabilize a particular geometry. Here are several examples:

Case 1: N_2F_2

This molecule can exist as either cis or trans isomers



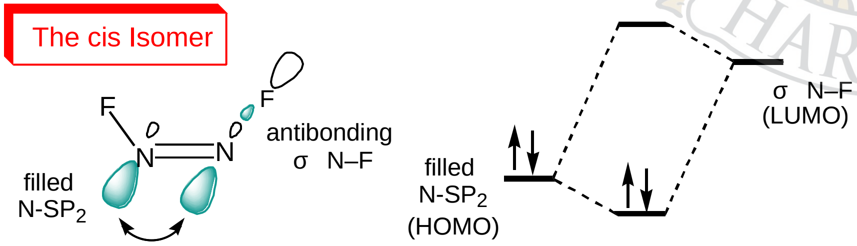
There are two logical reasons why the trans isomer should be more stable than the cis isomer.

- The nonbonding lone pair orbitals in the cis isomer will be destabilizing due to electron-electron repulsion.
- The individual C–F dipoles are mutually repulsive (pointing in same direction) in the cis isomer.

In fact the cis isomer is favored by 3 kcal/ mol at 25 °C.

Let's look at the interaction with the lone pairs with the adjacent C–F antibonding orbitals.

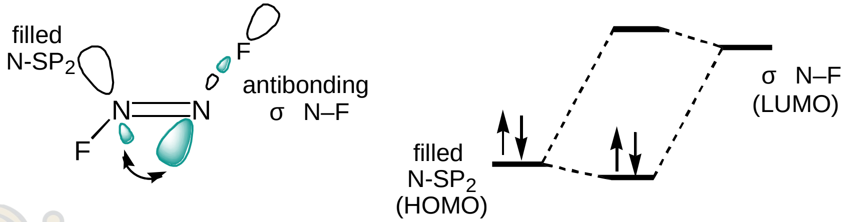
The cis Isomer



- Note that by taking a linear combination of the nonbonding and antibonding orbitals you generate a more stable bonding situation.
- Note that two such interactions occur in the molecule even though only one has been illustrated.

The trans Isomer

Now carry out the same analysis with the same 2 orbitals present in the trans isomer.



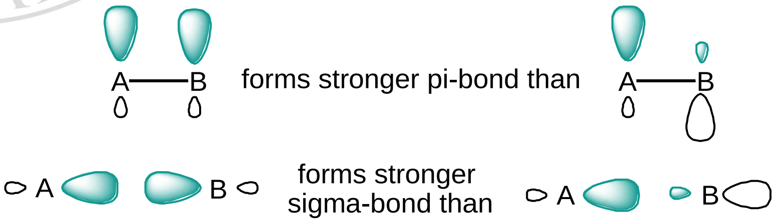
- In this geometry the "small lobe" of the filled $N\text{-}SP_2$ is required to overlap with the large lobe of the antibonding C–F orbital. Hence, when the new MO's are generated the new bonding orbital is not as stabilizing as for the cis isomer.

Conclusions

- Lone pair delocalization appears to override electron-electron and dipole-dipole repulsion in the stabilization of the cis isomer.
- This HOMO-LUMO delocalization is stronger in the cis isomer due to better orbital overlap.

Important Take-home Lesson

Orbital orientation is important for optimal orbital overlap.

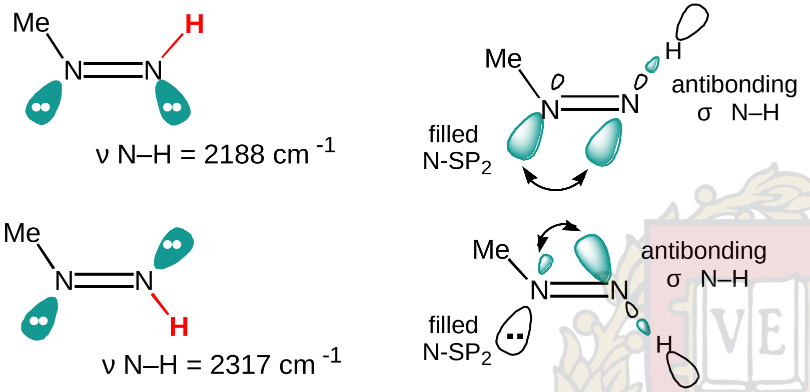


This is a simple notion with very important consequences. It surfaces in the delocalized bonding which occurs in the competing anti (favored) syn (disfavored) E2 elimination reactions. Review this situation.

The Anomeric Effect and Related Issues

Infrared evidence for lone pair delocalization into vicinal antibonding orbitals.

The N–H stretching frequency of cis-methyl diazene is 200 cm-1 lower than the trans isomer.



ν N–H = 2188 cm $^{-1}$

ν N–H = 2317 cm $^{-1}$

- The low-frequency N–H shift in the cis isomer is a result of N–H bond weakening due to presence of the anti lone par on the vicinal nitrogen which is interacting with the N–H antibonding orbital. Note that the orbital overlap is not nearly as good from the trans isomer

N. C. Craig & co-workers *JACS* **1979**, *101*, 2480.

Aldehyde C–H Infrared Stretching Frequencies

The IR C–H stretching frequency for aldehydes is lower than the closely related olefin C–H stretching frequency. For years this observation has gone unexplained.

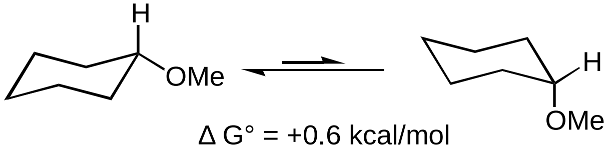
ν C–H = 2730 cm $^{-1}$

ν C–H = 3050 cm $^{-1}$

- We now conclude that this is another example of the vicinal lone pair effect.

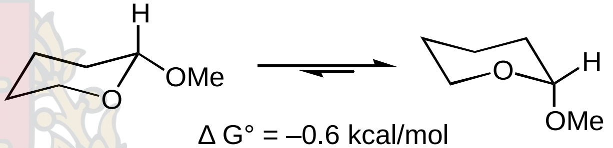
The Anomeric Effect

It is not unexpected that the methoxyl substituent on a cyclohexane ring prefers to adopt the equatorial conformation.



Δ G° = +0.6 kcal/mol

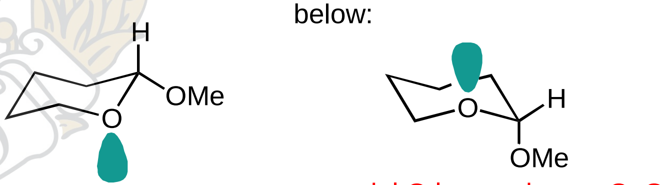
What is unexpected is that the closely related 2-methoxytetrahydropyran prefers the axial conformation:



Δ G° = –0.6 kcal/mol

- That effect which provides the stabilization of the axial OR conformer which overrides the inherent steric bias of the substituent is referred to as the anomeric effect.

Principal HOMO-LUMO interaction from each conformation is illustrated below:

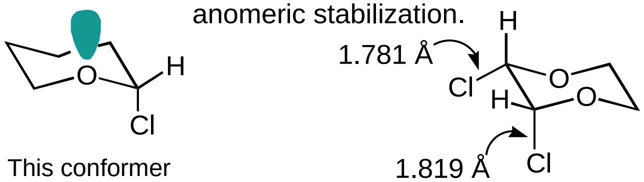


axial O lone pair ↔ σ C–H

axial O lone pair ↔ σ C–O

- Since the antibonding C–O orbital is a better acceptor orbital than the antibonding C–H bond, the axial OMe conformer is better stabilized by this interaction which is worth ca 1.2 kcal/mol.

Other electronegative substituents such as Cl, SR etc. also participate in anomeric stabilization.



1.781 Å

1.819 Å

This conformer preferred by 1.8 kcal/mol

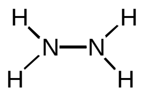
Why is axial C–Cl bond longer ?

Lone Pair Delocalization: The Gauche Effect

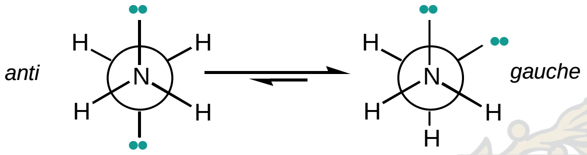
The interaction of filled orbitals with adjacent antibonding orbitals can have an ordering effect on the structure which will stabilize a particular conformation.
Here are several examples of such a phenomon called the gauche effect:

Hydrazine

Hydrazine can exist in either gauche or anti conformations (relative to lone pairs).



observed HNNH
dihedral angle Ca 90°

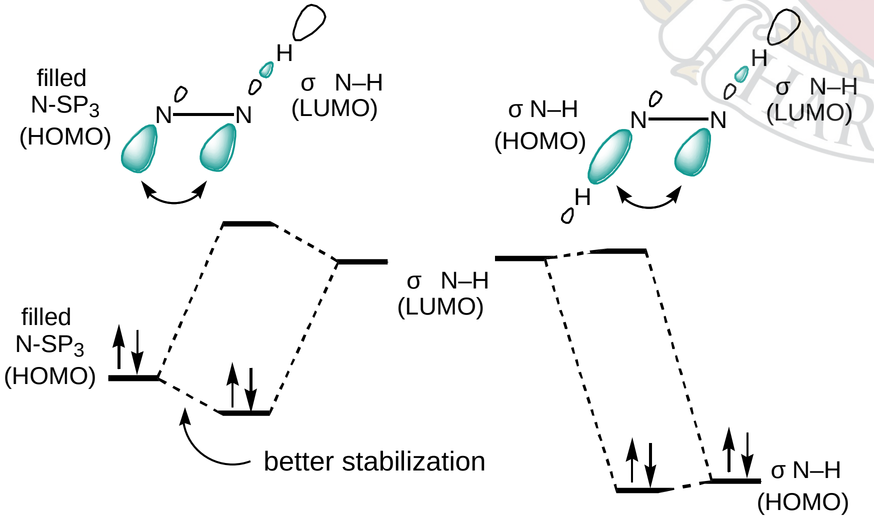


There is a logical reason why the anti isomer should be more stable than the gauche isomer. The nonbonding lone pair orbitals in the gauche isomer should be destabilizing due to electron-electron repulsion.

In fact, the gauche conformation is favored. Hence we have neglected an important stabilization feature in the structure.

HOMO-LUMO Interactions

Orbital overlap between filled (bonding) and antibonding states is best in the anti orientation. HOMO-LUMO delocalization is possible between: (a) N-lone pair ↔ σ N–H; (b) σ N–H ↔ σ N–H



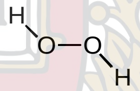
The closer in energy the HOMO and LUMO the better the resulting stabilization through delocalization.

- Hence, N-lone pair ↔ σ N–H delocalization better than σ N–H ↔ σ N–H delocalization.
- Hence, hydrazine will adopt the gauche conformation where both N-lone pairs will be anti to an antibonding acceptor orbital.

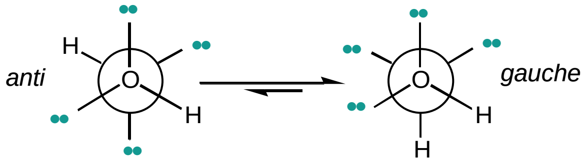
The trend observed for hydrazine holds for oxygen derivatives as well

Hydrogen peroxide

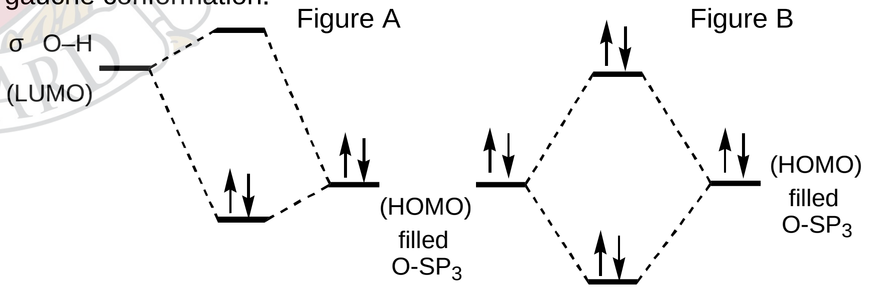
H_2O_2 can exist in either gauche or anti conformations (relative to hydrogens). The gauche conformer is prefered.



observed HOOH
dihedral angle Ca 90°



- Major stabilizing interaction is the delocalization of O-lone pairs into the C–H antibonding orbitals (Figure A). Note that there are no such stabilizing interactions in the anti conformation while there are 2 in the gauche conformation.



- Note that you achieve no net stabilization of the system by generating molecular orbitals from two filled states (Figure B).

Problem: Consider the structures XCH_2–OH where X = OCH_3 and F. What is the most favorable conformation of each molecule? Illustrate the dihedral angle relationship along the C–O bond.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 2

Stereoelectronic Effects-1

- Anomeric and Related Effects
- Electrophilic & Nucleophilic Substitution Reactions
- The S_N2 Reaction: Stereoelectronic Effects
- Olefin Epoxidation: Stereoelectronic Effects
- Baeyer-Villiger Reaction: Stereoelectronic Effects
- Olefin Bromination: Stereoelectronic Effects
- **H**ard & **S**oft **A**cid and **B**ases (Not to be covered in class)
  HSAB Discussion: Fleming Chapter 3

Matthew D. Shair

Friday,
September 20, 2002

Useful LIterature Reviews

Kirby, A. J. (**1982**). The Anomeric Effect and Related Stereoelectronic Effects at Oxygen. New York, Springer Verlag.

Box, V. G. S. (**1990**). “The role of lone pair interactions in the chemistry of the monosaccharides. The anomeric effect.” *Heterocycles* **31**: 1157.

Box, V. G. S. (**1998**). “The anomeric effect of monosaccharides and their derivatives. Insights from the new QVBMM molecular mechanics force field.” *Heterocycles* **48**(11): 2389-2417.

Graczyk, P. P. and M. Mikolajczyk (**1994**). “Anomeric effect: origin and consequences.” *Top. Stereochem*. **21**: 159-349.

Juaristi, E. and G. Cuevas (**1992**). “Recent studies on the anomeric effect.” *Tetrahedron* **48**: 5019.

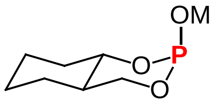
Plavec, J., C. Thibaudeau, et al. (**1996**). “How do the Energetics of the Stereoelectronic Gauche and Anomeric Effects Modulate the Conformation of Nucleos(t)ides?” *Pure Appl. Chem*. **68**: 2137-44.

Thatcher, G. R. J., Ed. (**1993**). The Anomeric Effect and Associated Stereoelectronic Effects. Washington DC, American Chemical Society.

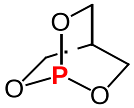
■ Problem of the Day (First hr exam, 1999)

The three phosphites illustrated below exhibit a 750-fold span in reactivity with a test electrophile (eq 1) (Gorenstein, *JACS* **1984**, *106*, 7831).

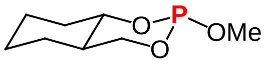
$$(RO)_3P \quad + \quad El(+) \quad \longrightarrow \quad (RO)_3\overset{+}{P}–El \qquad (1)$$



A



B



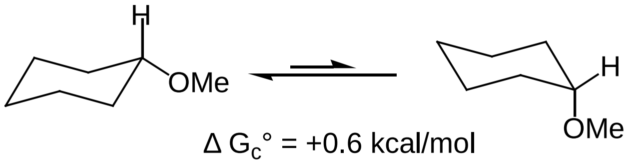
C

Rank the phosphites from the least to the most nucleophilic and provide a concise explanation for your predicted reactivity order.

The Anomeric Effect: Negative Hyperconjugation

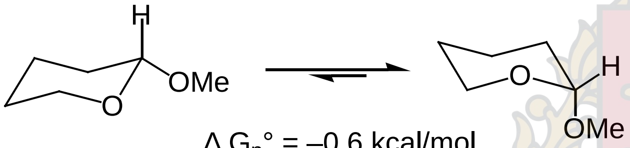
The Anomeric Effect

It is not unexpected that the methoxyl substituent on a cyclohexane ring prefers to adopt the equatorial conformation.



Δ $G_c°$ = +0.6 kcal/mol

What is unexpected is that the closely related 2-methoxytetrahydropyran prefers the axial conformation:



Δ $G_p°$ = –0.6 kcal/mol

That effect which provides the stabilization of the axial OR conformer which overrides the inherent steric bias of the substituent is referred to as the anomeric effect.

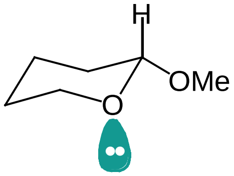
Let anomeric effect = A

$$\Delta G_p° = \Delta G_c° + A$$

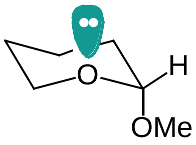
$$A = \Delta G_p° - \Delta G_c°$$

A = –0.6 kcal/mol – 0.6 kcal/mol = –1.2 kcal/mol

Principal HOMO-LUMO interaction from each conformation is illustrated below:



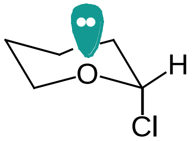
axial O lone pair↔σ* C–H



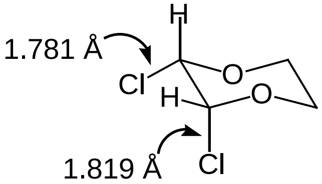
axial O lone pair↔σ* C–O

■ Since the antibonding C–O orbital is a better acceptor orbital than the antibonding C–H bond, the axial OMe conformer is better stabilized by this interaction which is worth ca. 1.2 kcal/mol.

Other electronegative substituents such as Cl, SR etc also participate in anomeric stabilization.

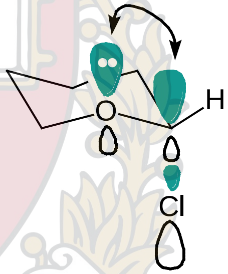


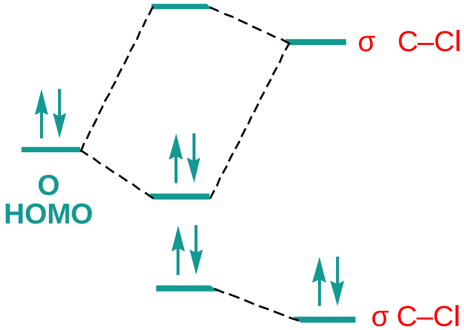
This conformer preferred by 1.8 kcal/mol



Why is axial C–Cl bond longer ?

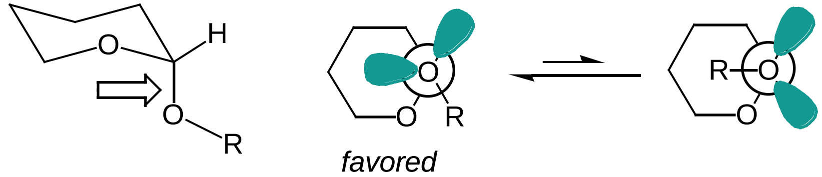
axial O lone pair↔σ C–Cl





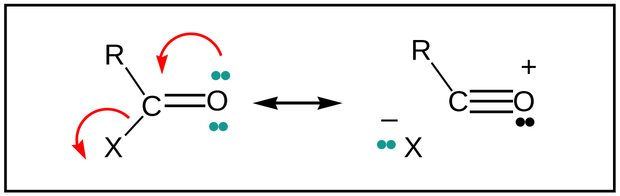
The Exo-Anomeric Effect

■ There is also a rotational bias that is imposed on the exocyclic C–OR bond where one of the oxygen lone pairs prevers to be anti to the ring sigma C–O bond

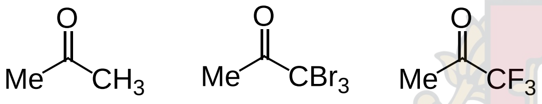


A. J. Kirby, *The Anomeric and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, 1983
E. Jurasti, G. Cuevas, *The Anomeric Effect, CRC Press*, 1995

Do the following valence bond resonance structures have meaning?

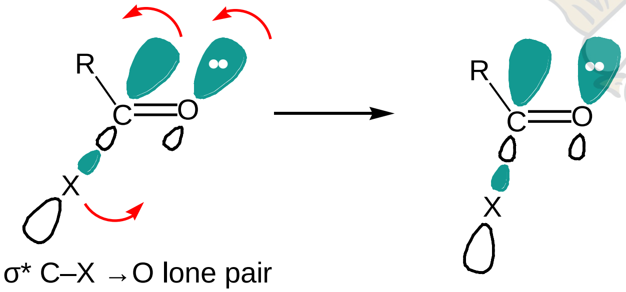


Prediction: As X becomes more electronegative, the IR frequency should increase



$\upsilon_{C=O}$ (cm^{-1})	1720	1750	1780

Prediction: As the indicated pi-bonding increases, the X–C–O bond angle should decrease. This distortion improves overlap.



σ* C–X → O lone pair

Evidence for this distortion has been obtained by X-ray crystallography

Corey, *Tetrahedron Lett*. **1992**, *33*, 7103-7106

Aldehyde C–H Infrared Stretching Frequencies

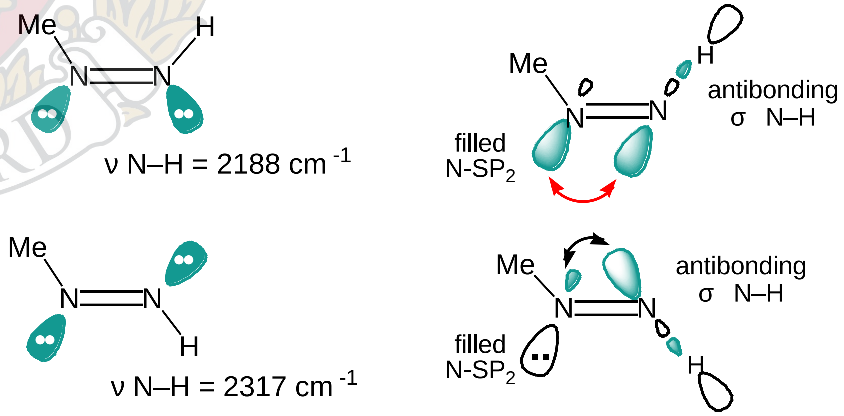
Prediction: The IR C–H stretching frequency for aldehydes is lower than the closely related olefin C–H stretching frequency. For years this observation has gone unexplained.

ν C–H = 2730 cm $^{-1}$ ν C–H = 3050 cm $^{-1}$

Sigma conjugation of the lone pair anti to the H will weaken the bond. This will result in a low frequency shift.

Infrared evidence for lone pair delocalization into vicinal antibonding orbitals.

The N–H stretching frequency of cis-methyl diazene is 200 cm^{-1} lower than the trans isomer.

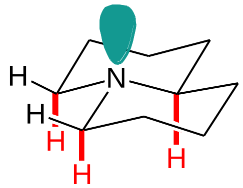


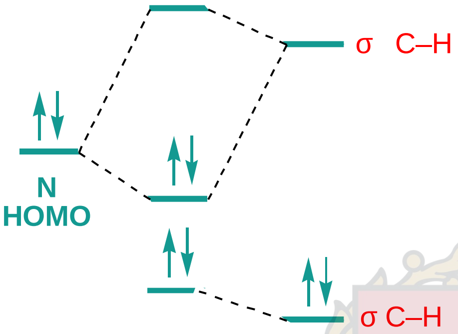
■ The low-frequency shift of the cis isomer is a result of N–H bond weakening due to the anti lone pair on the adjacent (vicinal) nitrogen which is interacting with the N–H antibonding orbital. Note that the orbital overlap is not nearly as good from the trans isomer.

N. C. Craig & co-workers *JACS* **1979**, *101*, 2480.

The Anomeric Effect: Nitrogen-Based Systems

Observation: C–H bonds anti-periplanar to nitrogen lone pairs are spectroscopically distinct from their equatorial C–H bond counterparts





Spectroscopic Evidence for Conjugation

Infrared Bohlmann Bands

Characteristic bands in the IR between 2700 and 2800 cm^{-1} for C-H$_4$, C-H$_6$, & C-H$_{10}$ stretch

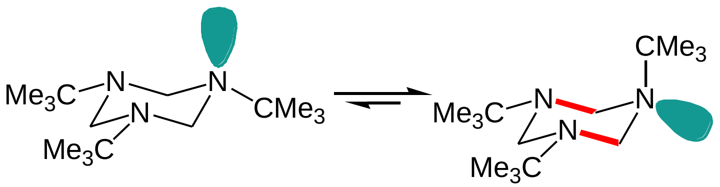
Bohlmann, *Ber.* **1958** *91* 2157

Reviews: McKean, *Chem Soc. Rev.* **1978** *7* 399
L. J. Bellamy, D. W. Mayo, *J. Phys. Chem.* **1976** *80* 1271

NMR : Shielding of H antiperiplanar to N lone pair

H$_{10}$ (axial): shifted furthest upfield
H$_6$, H$_4$: $\Delta\delta = \delta H_{axial} - \delta H_{equatorial} = -0.93$ ppm
Protonation on nitrogen reduces Δδ to -0.5ppm

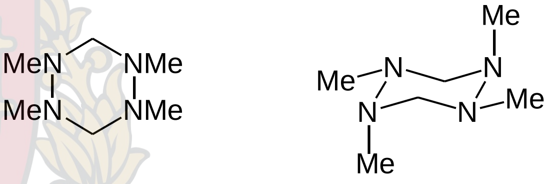
H. P. Hamlow et. al., *Tet. Lett.* **1964** 2553
J. B. Lambert et. al., *JACS* **1967** *89* 3761



ΔG° = – 0.35kcal/mol

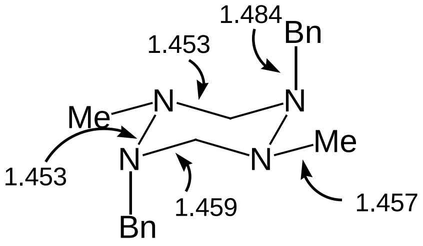
A. R. Katritzky et. al., *J. Chemm. Soc. B* **1970** 135

Favored Solution Structure (NMR)



J. E. Anderson, J. D. Roberts, *JACS* **1967** *96* 4186

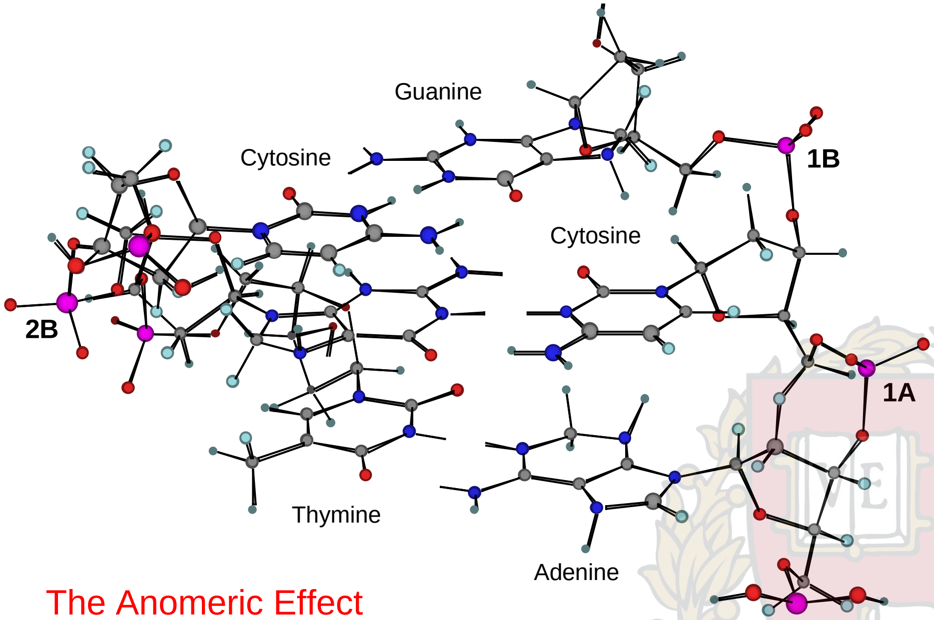
Favored Solid State Structure (X-ray crystallography)



A. R. Katrizky et. al., *J. C. S. Perkin II* **1980** 1733

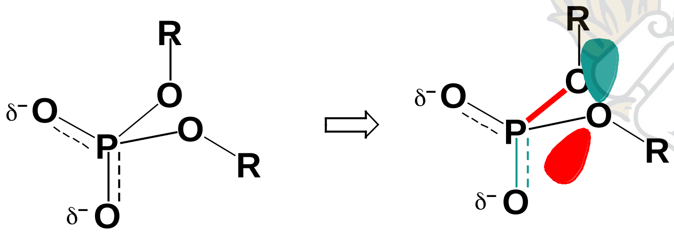
Anomeric Effects in DNA Phosphodiesters

Calculated Structure of ACG–TGC Duplex

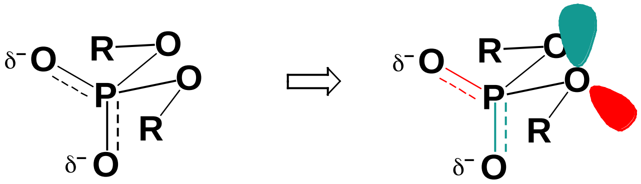


The Anomeric Effect

Acceptor orbital hierarchy: δ^{*} P–OR * > δ^{*} P–O^{-}



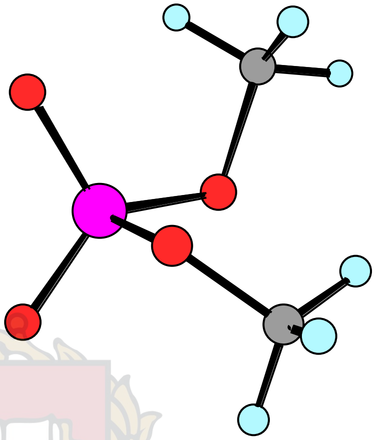
Gauche-Gauche conformation



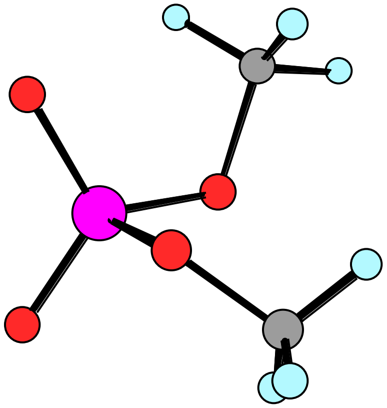
Anti-Anti conformation

Gauche-Gauche conformation affords a better donor-acceptor relationship

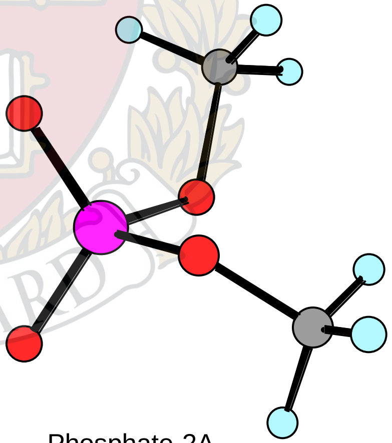
The Phospho-Diesters Excised from Crystal Structure



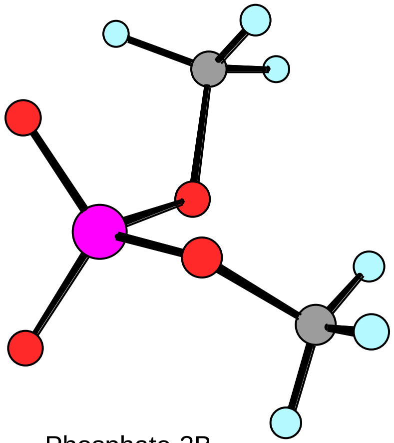
Phosphate-1A



Phosphate-1B



Phosphate-2A



Phosphate-2B

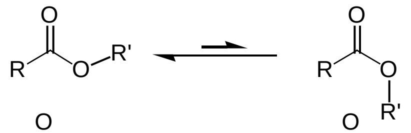
Oxygen lone pairs may establish a simultaneous hyperconjugative relationship with both acceptor orbitals only in the illustrated conformation.

Plavec, et al. (**1996**). “How do the Energetics of the Stereoelectronic Gauche & Anomeric Effects Modulate the Conformation of Nucleos(t)ides? ” Pure Appl. Chem. **68**: 2137-44.

Carboxylic Acids (& Esters): Anomeric Effects Again?

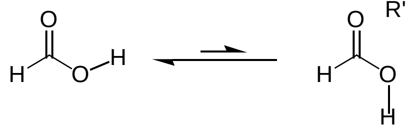
■ **Conformations:** There are 2 planar conformations.

(Z) Conformer



(E) Conformer

Specific Case:
Formic Acid

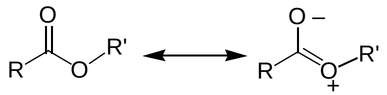


ΔG° = +2 kcal/mol

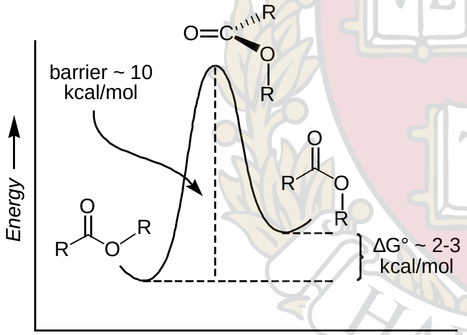
The (E) conformation of both acids and esters is less stable by 2-3 kcal/mol. If this equilibrium were governed only by steric effects one would predict that the (E) conformation of formic acid would be more stable (H smaller than =O). Since this is not the case, there are electronic effects which must also be considered. These effects will be introduced shortly.

■ **Rotational Barriers:** There is hindered rotation about the =C–OR bond.

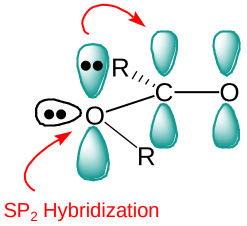
These resonance structures suggest hindered rotation about =C–OR bond. This is indeed observed:



Rotational barriers are ~ 10 kcal/mol
This is a measure of the strength of the pi bond.



■ **Lone Pair Conjugation:** The oxygen lone pairs conjugate with the C=O.

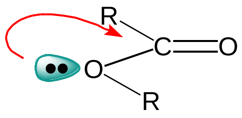


The filled oxygen p-orbital interacts with pi (and pi*) C=O to form a 3-centered 4-electron bonding system.

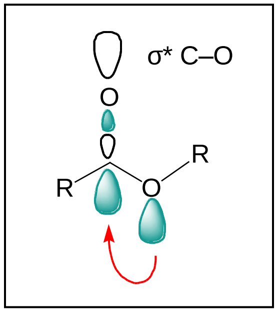
■ **Oxygen Hybridization:** Note that the alkyl oxygen is Sp2. Rehybridization is driven by system to optimize pi-bonding.

■ **Hyperconjugation:** Let us now focus on the oxygen lone pair in the hybrid orbital lying in the sigma framework of the C=O plane.

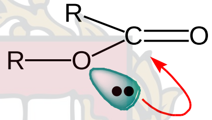
(Z) Conformer



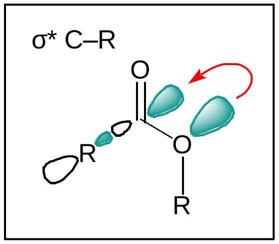
In the (Z) conformation this lone pair is aligned to overlap with σ* C–O.



(E) Conformer



In the (E) conformation this lone pair is aligned to overlap with σ* C–R.

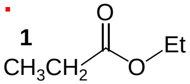


Since σ* C–O is a better acceptor than σ* C–R (where R is a carbon substituent) it follows that the (Z) conformation is stabilized by this interaction.

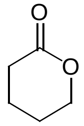
Esters versus Lactones: Questions to Ponder.

Esters strongly prefer to adopt the (Z) conformation while small-ring lactones such as **2** are constrained to exist in the (Z) conformation. From the preceding discussion explain the following:

1



2

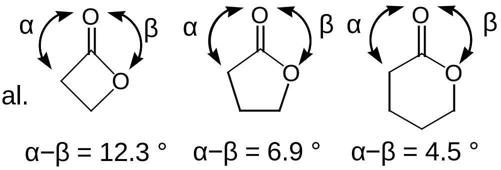


versus

1) Lactone **2** is significantly more susceptible to nucleophilic attack at the carbonyl carbon than **1**? Explain.

2) Lactone **2** is significantly more prone to enolization than **1**? In fact the pKa of **2** is ~25 while ester **1** is ~30 (DMSO). Explain.

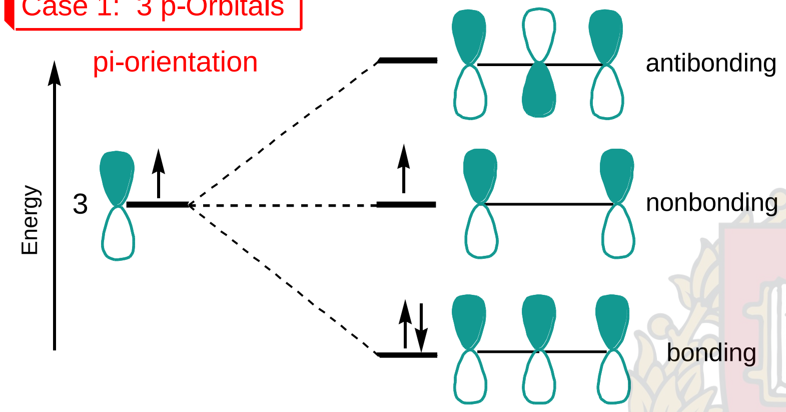
3) In 1985 Burgi, on carefully studying the X-ray structures of a number of lactones, noted that the O-C-C (α) & O-C-O (β) bond angles were not equal. Explain the indicated trend in bond angle changes.



Consider the linear combination of three atomic orbitals. The resulting molecular orbitals (MOs) usually consist of one bonding, one nonbonding and one antibonding MO.

Case 1: 3 p-Orbitals

pi-orientation



Note that the more nodes there are in the wave function, the higher its energy.

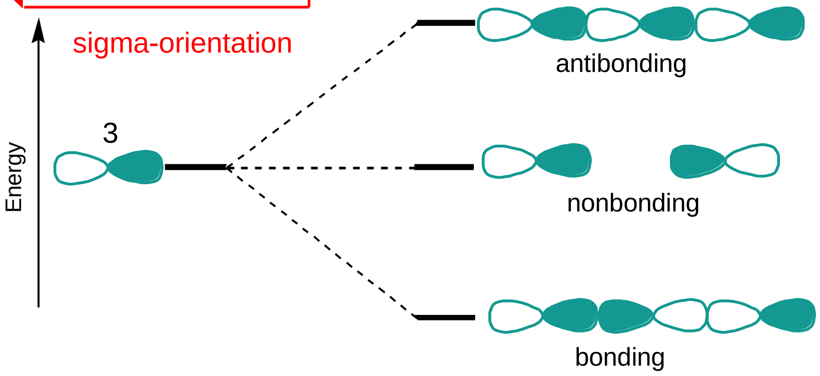
$H_2C{=}CH{-}\overset{+}{C}H_2$ **Allyl carbonium ion:** both pi-electrons in bonding state

$H_2C{=}CH{-}\overset{\bullet}{C}H_2$ **Allyl Radical:** 2 electrons in bonding obital plus one in nonbonding MO.

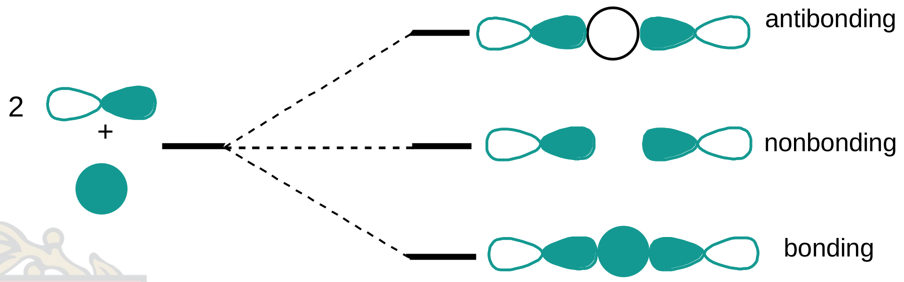
$H_2C{=}CH{-}\overset{-}{C}H_2$ **Allyl Carbanion:** 2 electrons in bonding obital plus 2 in nonbonding MO.

Case 2: 3 p-Orbitals

sigma-orientation



Case 3: 2 p-Orbitals; 1 s-orbital

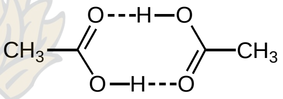


Case 4: 2 s-Orbitals; 1 p-orbital

Do this as an exercise

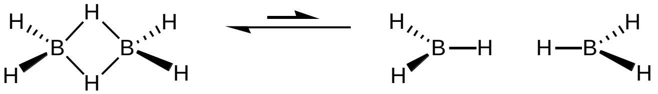
Examples of three-center bonds in organic chemistry

A. H-bonds: (3-center, 4 electron)



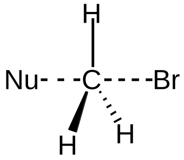
The acetic acid dimer is stabilized by ca 15 kcal/mol

B. H-B-H bonds: (3-center, 2 electron)



diborane stabilized by 35 kcal/mol

C. The S_N2 Transition state: (3-center, 4 electron)

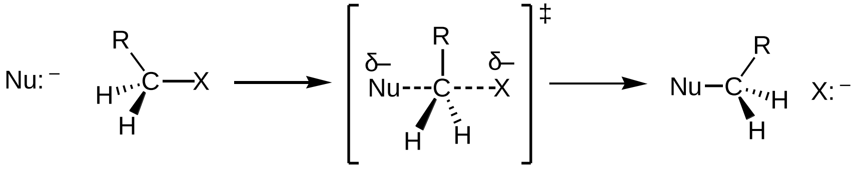


The SN 2 transition state approximates a case 2 situation with a central carbon p-orbital

The three orbitals in reactant molecules used are:
1 nonbonding MO from Nucleophile (2 electrons)
1 bonding MO σ C–Br (2 electrons)
1 antibonding MO σ* C–Br

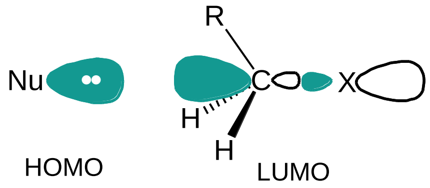
Substitution Reactions: General Considerations

Why do S_N2 Reactions proceed with backside displacement?



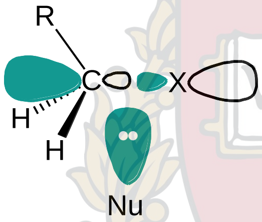
Given the fact that the LUMO on the electrophile is the C–X antibonding orblital, Nucleophilic attack could occur with either inversion or retention.

Inversion



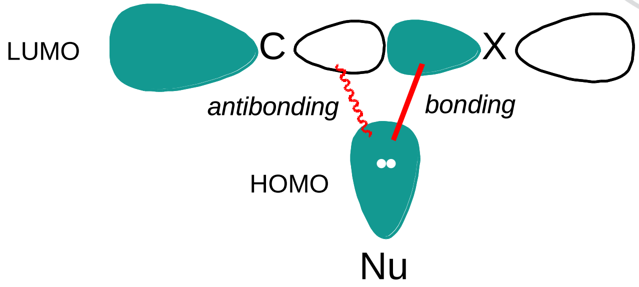
Constructive overlap between Nu & σ*C–X

Retention



Overlap from this geometry results in no net bonding interaction

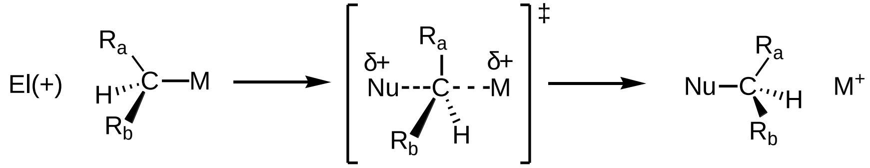
Expanded view of σ*C–X



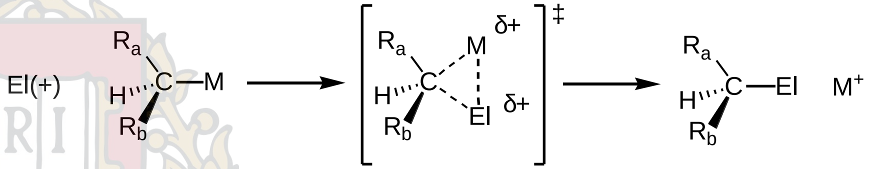
Fleming, page 75-76

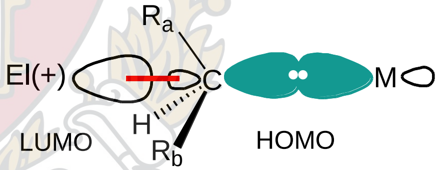
Electrophilic substitution at saturated carbon may occur with either inversion of retention

Inversion

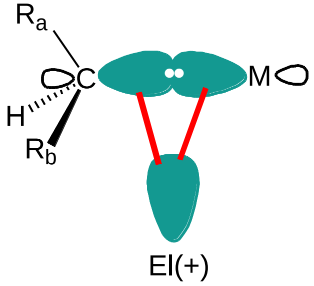


Retention



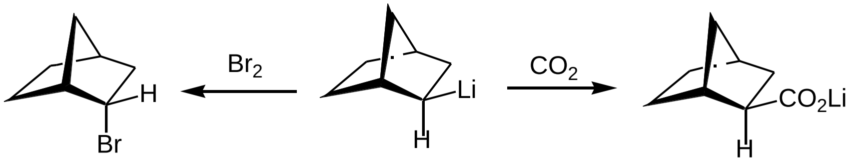


Inversion



Retention

Examples

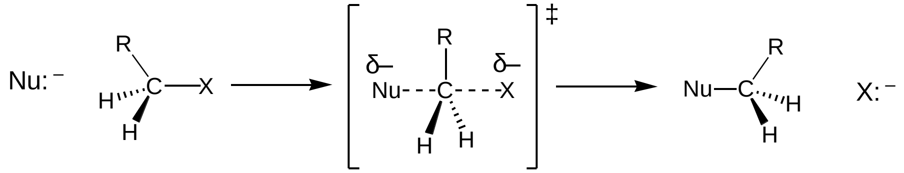


predominant inversion

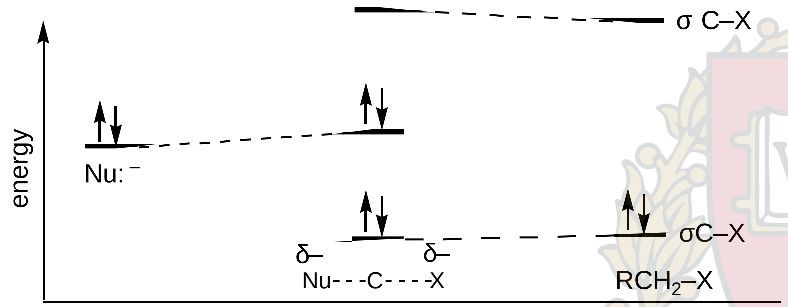
predominant retention

Stereochemistry frequently determined by electrophile structure

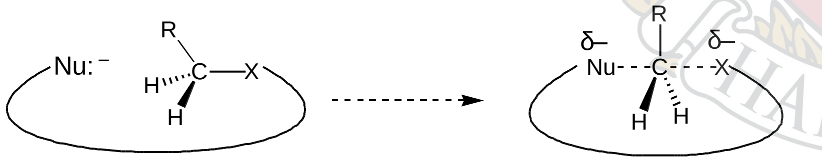
The reaction under discussion:



■ The Nu–C–X bonding interaction is that of a 3-center, 4-electron bond. The frontier orbitals which are involved are the nonbonding orbital from Nu as well as σC–X and σ C–X:



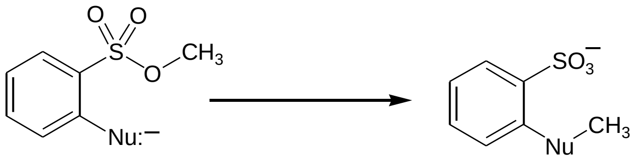
■ Experiments have been designed to probe inherent requirement for achieving a 180 ° Nu–C–X bond angle: Here both Nu and leaving group are constrained to be part of the same ring.



"tethered reactants" "constrained transition state"

The Eschenmoser Experiment (1970): *Helv. Chim Acta* **1970**, *53*, 2059

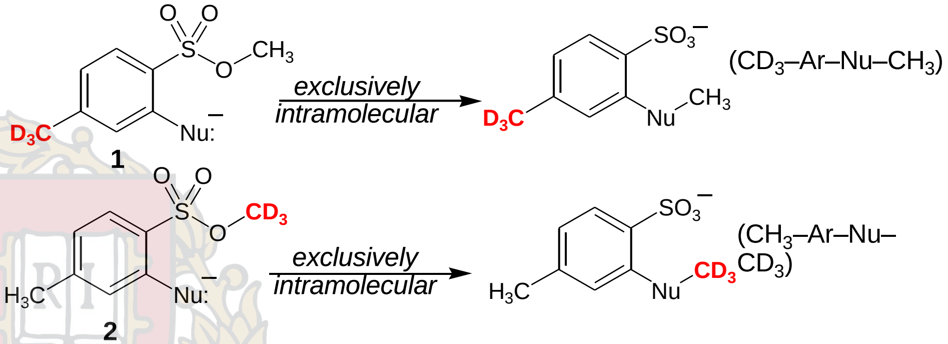
■ The reaction illustrated below proceeds exclusively through bimolecular pathway in contrast to the apparent availability of the intramolecular path.



The use of isotope labels to probe mechanism.

1 and **2** containing deuterium labels either on the aromatic ring or on the methyl group were prepared. A 1:1-mixture of **1** and **2** were allowed to react.

■ If the rxn was **exclusively intramolecular**, the products would only contain only three deuterium atoms:



■ If the reaction was **exclusively intermolecular**, products would only contain differing amounts of D-label depending on which two partners underwent reaction. The deuterium content might be analyzed by mass spectrometry. Here are the possibilities:

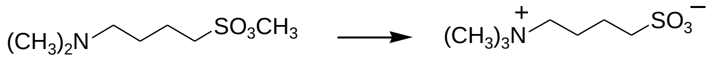
1 + **1** ⟶	D_3-product	2 CD_3–Ar–Nu–CH_3
2 + **2** ⟶	D'_3-product	2 CH_3–Ar–Nu–CD_3
1 + **2** ⟶	D_6-product	1 CD_3–Ar–Nu–CD_3
	D_0-product	1 CH_3–Ar–Nu–CH_3

Hence, for the strictly intermolecular situation one should see the following ratios $D_0 : D_3 : D'_3 : D_6 = 1 : 2 : 2 : 1$.

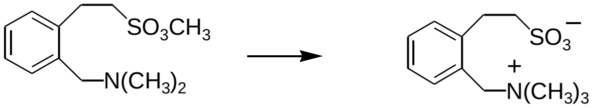
The product isotope distribution in the Eschenmoser expt was found to be exclusively that derived from the intermolecular pathway!

Other Cases:

exclusively intermolecular

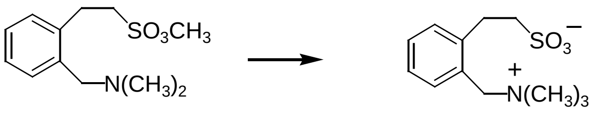


16% intramolecular
84% intermolecular

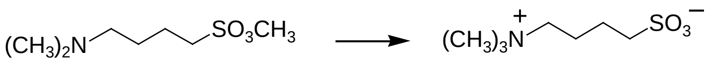


Hence, the Nu–C–X 180 ° transition state bond angle must be rigidly maintained for the reaction to take place.

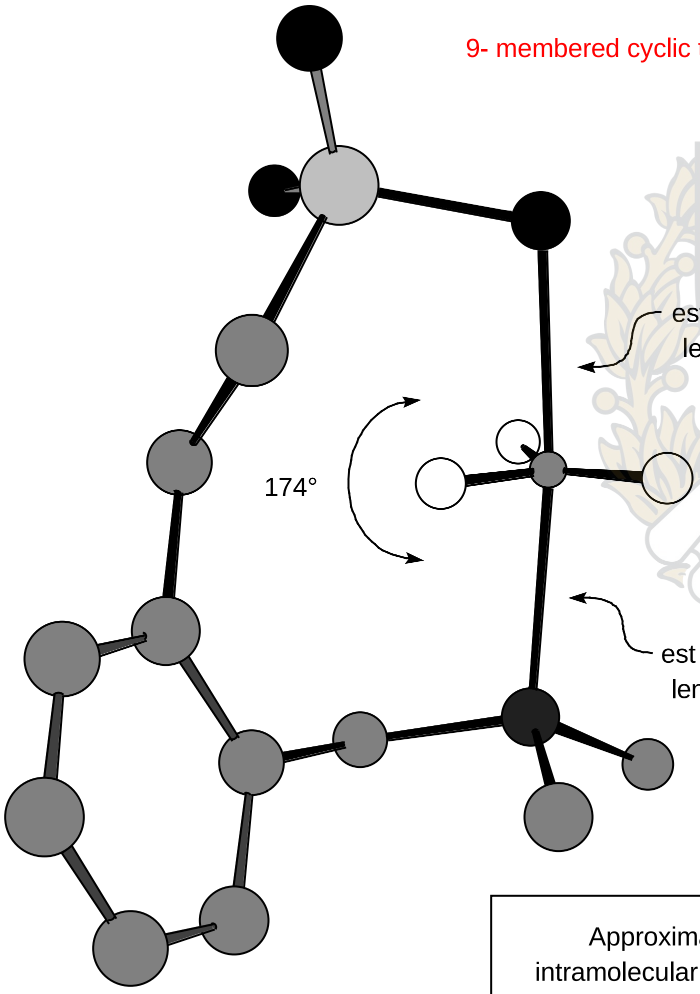
Intramolecular methyl transfer: Speculation on the transition structures



16% intramolecular; 84% intermolecular



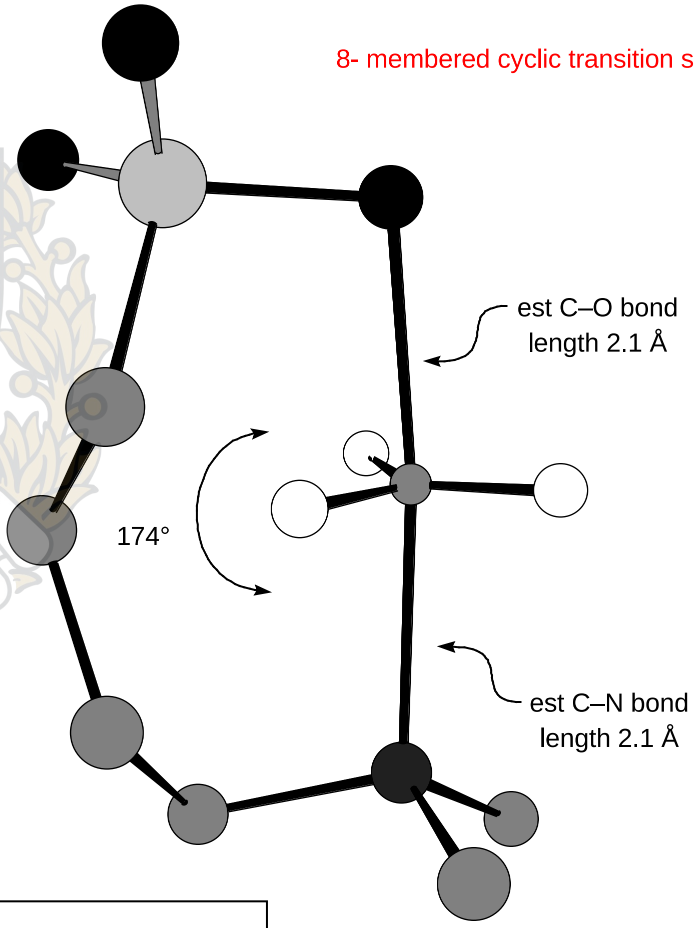
exclusively intermolecular



9- membered cyclic transition state

est C–O bond length 2.1 Å

est C–N bond length 2.1 Å



8- membered cyclic transition state

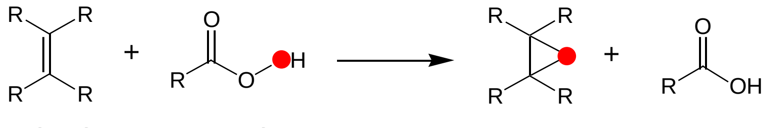
est C–O bond length 2.1 Å

est C–N bond length 2.1 Å

Approximate representation of the transition states of the intramolecular alkylation reactions. Transition state C–O and C–N bond lengths were estimated to be 1.5x(C–X) bond length of 1.4 Å

Olefin Epoxidation via Peracids: An Introduction

The General Reaction:



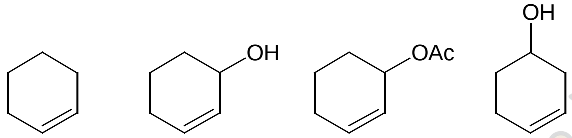
HOMO
πC–C

LUMO
σ*O–O

note labeled oxygen is transferfed

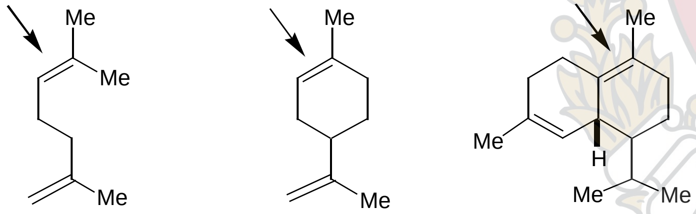
O-O bond energy: ~35 kcal/mol

Reaction rates are governed by olefin nucleophilicity. The rates of epoxidation of the indicated olefin relative to cyclohexene are provided below:

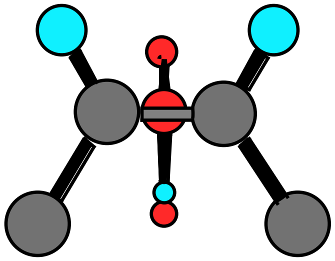


1.0 0.6 0.05 0.4

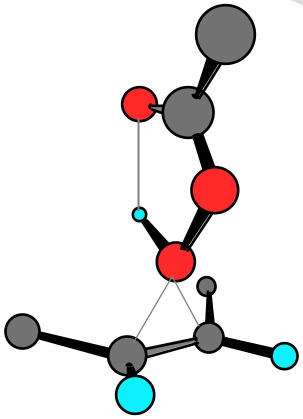
The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



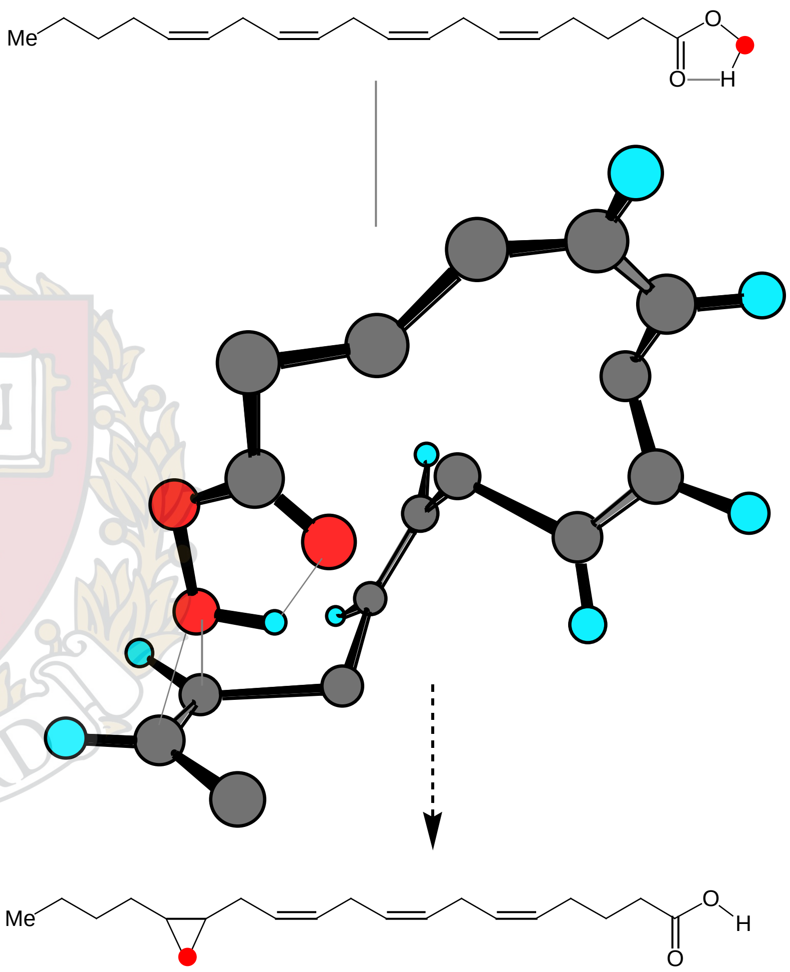
The transition state:



View from below olefin



Per-arachidonic acid Epoxidation



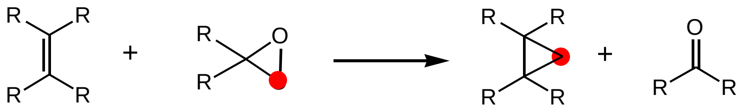
E. J. Corey, *JACS* **101**, 1586 (1979)

For a more detailed study see P. Beak, *JACS* **113**, 6281 (1991)

For theoretical studies of TS see R. D. Bach, *JACS* **1991**, *113*, 2338
R. D. Bach, *J. Org. Chem* **2000**, *65*, 6715

Olefin Epoxidation with Dioxiranes

■ The General Reaction:



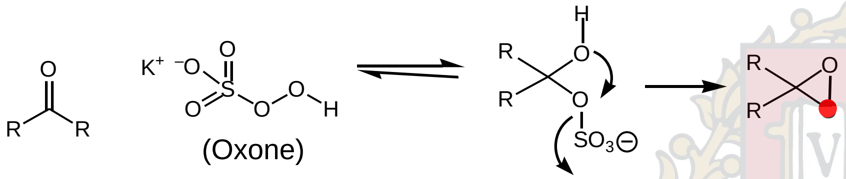
HOMO
πC–C

LUMO
σ*O–O

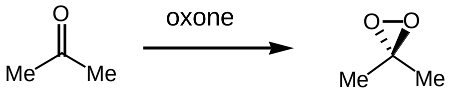
note labeled oxygen is transferfed

O-O bond energy: ~35 kcal/mol

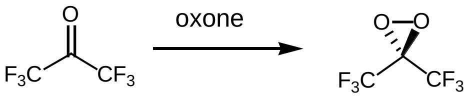
■ Synthesis of the Dioxirane Oxidant



Synthetically Useful Dioxirane Synthesis



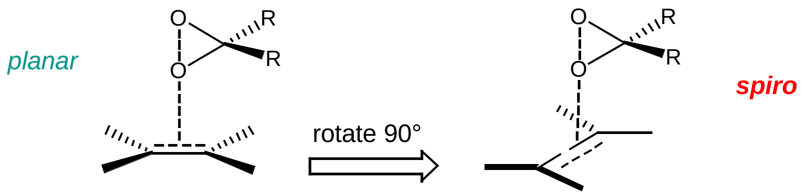
co-distill to give
~0.1 M soln of
dioxirane in acetone



co-distill to give
~0.6 M soln of dioxirane
in hexafluoroacetone

Curci, *JOC*, **1980**, 4758 & **1988**, 3890;
JACS **1991**, 7654.

Transition State for the Dioxirane Mediated Olefin Epoxidation

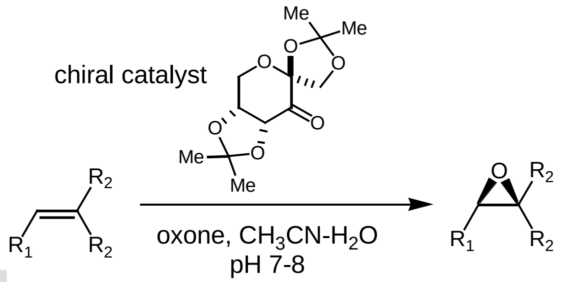


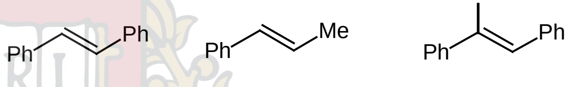
stabilizing $O_{lp} \rightarrow \pi^*$ C=C
cis olefins react ~10 times faster than *trans*

Houk, *JACS*, **1997**, 12982.

Asymmetric Epoxidation with Chiral Ketones

Review: Frohn & Shi, *Syn Lett* **2000**, 1979-2000

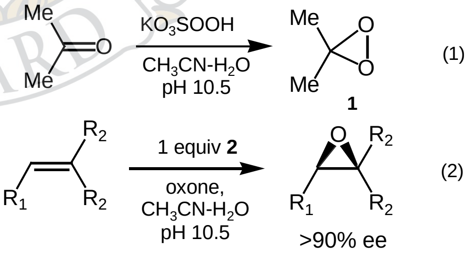




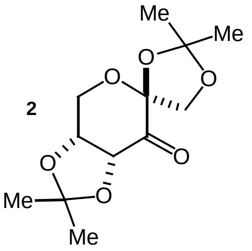
>95% ee | 84% ee | 92% ee

Question: First hour Exam 2000

Question 4. (15 points). The useful epoxidation reagent dimethyldioxirane (**1**) may be prepared from "oxone" (KO_3SOOH) and acetone (eq 1). In an extension of this epoxidation concept, Shi has described a family of chiral fructose-derived ketones such as **2** that, in the presence of "oxone", mediate the asymmetric epoxidation of di- and tri-substituted olefins with excellent enantioselectivities (>90% ee) (*JACS* **1997**, *119*, 11224).



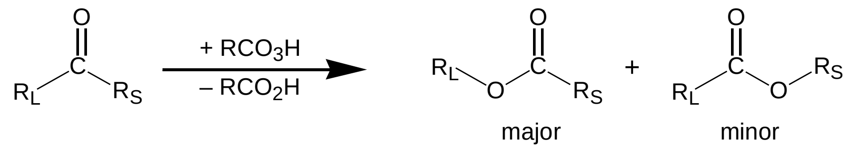
2



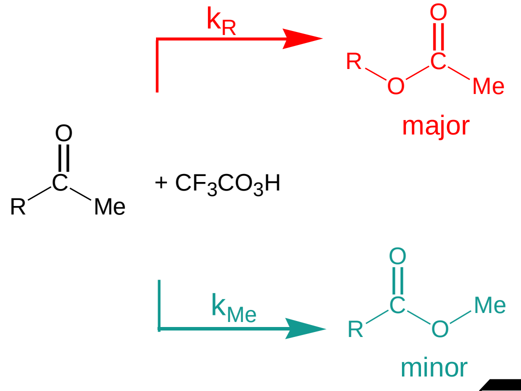
Part A (8 points). Provide a mechanism for the epoxidation of ethylene with dimethyldioxirane (**1**). Use three-dimensional representations, where relevant, to illustrate the ***relative*** stereochemical aspects of the oxygen transfer step. Clearly identify the frontier orbitals involved in the epoxidation.

Part B (7 points). Now superimpose chiral ketone **2** on to your mechanism proposed above and rationalize the sense of asymmetric induction of the epoxidation of trisubstituted olefins (eq 2). Use three-dimensional representations, where relevant, to illustrate the ***absolute*** stereochemical aspects of the oxygen transfer step.

Let R_L and R_S be Sterically large and small substituents.

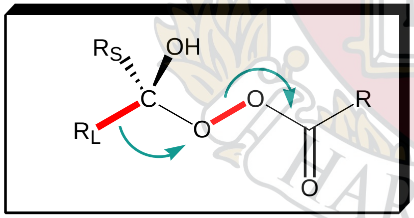


The major product is that wherein oxygen has been inserted into theR_L–Carbonyl bond.



R	k_R / K_{Me}
CH_3CH_2	72
$CH_3(CH_2)_2$	150
$(CH_3)_3C$	830
$PhCH_2$	>2000

The Intermediate

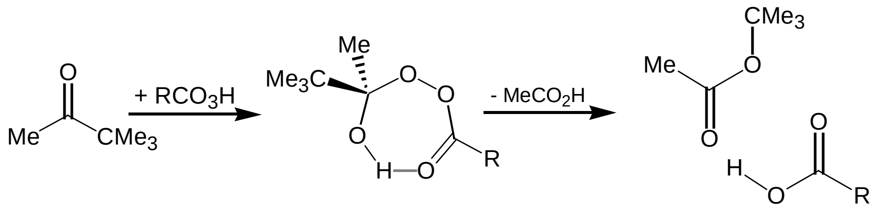


The important stereoelectronic components to this rearrangement:

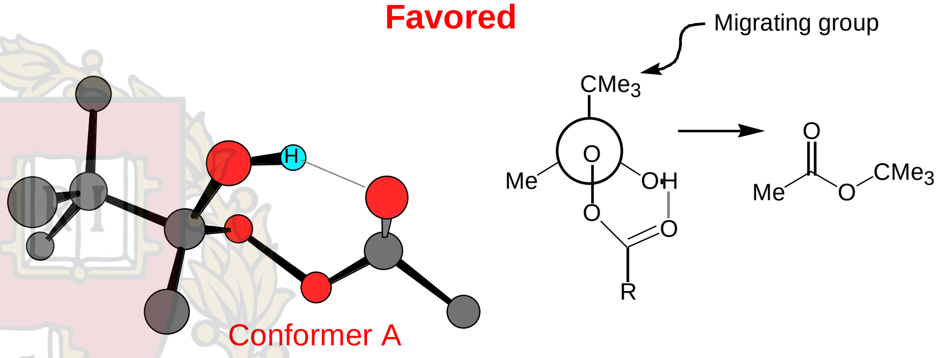
1. The R_L–C–O–O dihedral angle must be180° due to the HOMO LUMO interaction σ-R_L–C ↔ σ -O–O.

2. The C–O–O–C' dihedral angle will be ca. 60° due to the gauche effect (O-lone pairs ↔ σ -C–O).

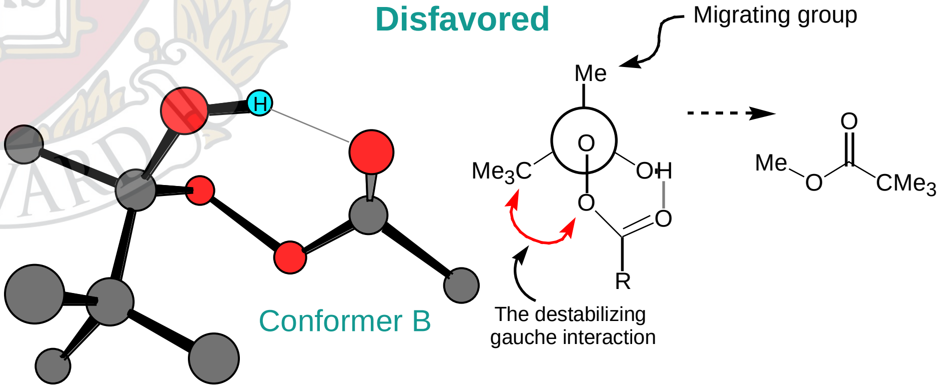
This gauche geometry is probably reinforced by intramolecular hydrogen bonding as illustrated on the opposite page:



Favored



Disfavored



Steric effects destabilize Conformer B relative to Conformer A; hence, the reaction is thought to proceed via a transition state similar to A.

For relevant papers see:
Crudden, *Angew. Chem. Int. Ed* **2000**, *39*, 2852-2855 **(pdf)**
Kishi, *JACS* **1998**, *120*, 9392 **(pdf)**

FMO-Theory/HSAB Principle 1

Hard and Soft Acids and Bases (HSAB-Principle)

Reading Assignment: Fleming, Chapter 3, p33-46

Pearson, *JACS* **1963**, *85*, 3533.

Hard Acids prefer to interact with **hard** bases
Soft acids prefer to interact with **soft** bases.

Softness: Polarizability; soft nucleophiles have electron clouds, which can be polarized (deformed) easily.

Hardness: Charged species with small ion radii, high charge density.

→ Qualitative scaling possible:

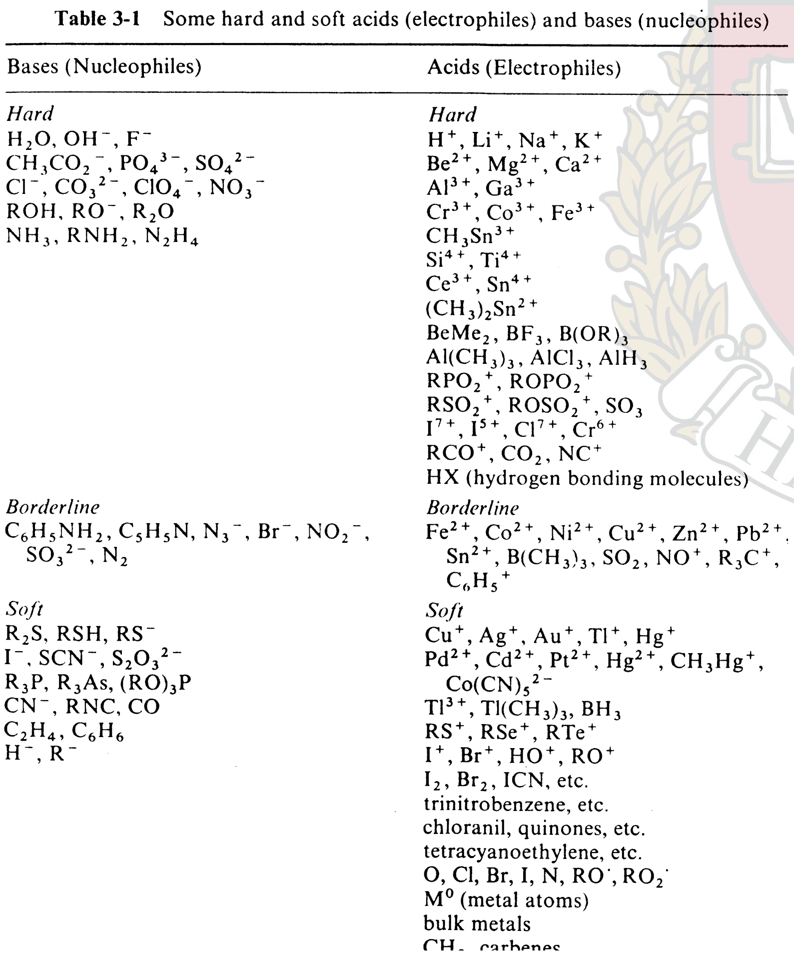


Table 3-1 Some hard and soft acids (electrophiles) and bases (nucleophiles)

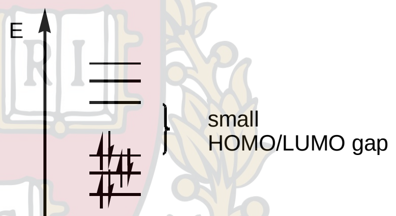
Bases (Nucleophiles)	Acids (Electrophiles)
Hard	*Hard*
H_2O, OH^-, F^- $CH_3CO_2^-$, PO_4^{3-}, SO_4^{2-} Cl^-, CO_3^{2-}, ClO_4^-, NO_3^- ROH, RO^-, R_2O NH_3, RNH_2, N_2H_4	H^+, Li^+, Na^+, K^+ Be^{2+}, Mg^{2+}, Ca^{2+} Al^{3+}, Ga^{3+} Cr^{3+}, Co^{3+}, Fe^{3+} CH_3Sn^{3+} Si^{4+}, Ti^{4+} Ce^{3+}, Sn^{4+} $(CH_3)_2Sn^{2+}$ $BeMe_2$, BF_3, $B(OR)_3$ $Al(CH_3)_3$, $AlCl_3$, AlH_3 RPO_2^+, $ROPO_2^+$ RSO_2^+, $ROSO_2^+$, SO_3 I^{7+}, I^{5+}, Cl^{7+}, Cr^{6+} RCO^+, CO_2, NC^+ HX (hydrogen bonding molecules)
Borderline	*Borderline*
$C_6H_5NH_2$, C_5H_5N, N_3^-, Br^-, NO_2^-, SO_3^{2-}, N_2	Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, Sn^{2+}, $B(CH_3)_3$, SO_2, NO^+, R_3C^+, $C_6H_5^+$
Soft	*Soft*
R_2S, RSH, RS^- I^-, SCN^-, $S_2O_3^{2-}$ R_3P, R_3As, $(RO)_3P$ CN^-, RNC, CO C_2H_4, C_6H_6 H^-, R^-	Cu^+, Ag^+, Au^+, Tl^+, Hg^+ Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, CH_3Hg^+, $Co(CN)_5^{2-}$ Tl^{3+}, $Tl(CH_3)_3$, BH_3 RS^+, RSe^+, RTe^+ I^+, Br^+, HO^+, RO^+ I_2, Br_2, ICN, etc. trinitrobenzene, etc. chloranil, quinones, etc. tetracyanoethylene, etc. O, Cl, Br, I, N, $RO^\cdot$, $RO_2^\cdot$ M^0 (metal atoms) bulk metals CH, carbenes

FMO-Theory and Klopman-Salem equation provide an understanding of this empirical principle:

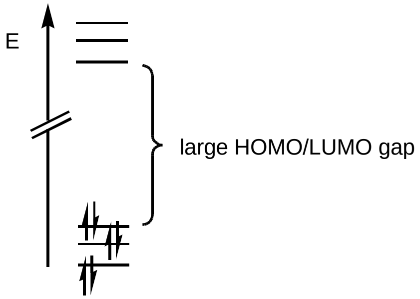
Hard Acids have usually a positive charge, small ion radii (high charge density), energy rich (high lying) LUMO.
Soft Acids are usually uncharged and large (low charge density), they have an energy poor (low lying) LUMO (usually with large MO coefficient).
Hard Bases usually have a negative charge, small ion radii (high charge density), energy poor (low lying) HOMO.
Soft Bases are usually uncharged and large (low charge density), energy rich (high lying) HOMO (usually with large MO coefficient).

Molecular Orbital Energies of an

idealized Soft Species

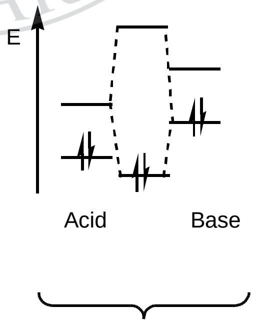


idealized Hard Species



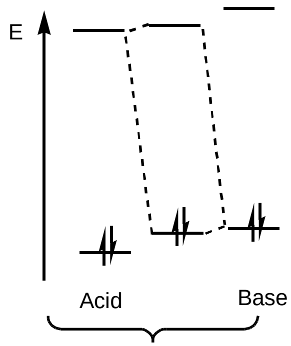
FMO-Theory for interaction:

Soft-Soft



Significant Energy gain through HOMO/LUMO interaction

Hard-Hard



Only neglectable energy gain through orbital interaction.

Klopman-Salem Equation for the interaction of a Nucleophile N (Lewis-Base) and an Electrophile E (Lewis-Acid).

$$\Delta E = -\underbrace{\frac{Q_N Q_E}{\varepsilon R_{NE}}}_{\textbf{Coulomb Term}} + \underbrace{\frac{2(c_N c_E \beta)^2}{E_{HOMO}(N) - E_{LUMO}(E)}}_{\textbf{Frontier Orbital Term}}$$

Q: Charge density
ε: Dielectricity constant
R: distance (N-E)
c: coefficient of MO
β: Resonance Integral
E: Energy of MO

Soft-Soft Interactions: Coulomb term small (low charge density). Dominant interaction is the frontier orbital interaction because of a small $\Delta E(HOMO_N/LUMO_E)$. formation of covalent bonds

Hard-Hard Interactions: Frontier orbital term small because of large $\Delta E(HOMO_N/LUMO_E)$. Dominant interaction is described by the Coulomb term (Q is large for hard species), i.e. electrostatic interaction. formation of ionic bonds

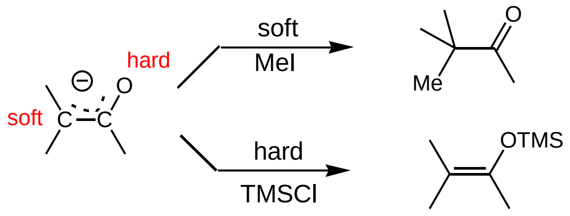
Hard-Soft Interactions: Neither energy term provides significant energy gain through interaction. Hence, Hard-Soft interactions are unfavorable.

Table 3-2 Calculated softness character for inorganic nucleophiles and electrophiles

Nucleophile	HOMO $E^{\neq}$ (eV)		Electrophile	LUMO $E^{\neq}$ (eV)	
H^-	−7·37	↑	Al^{3+}	6·01	↑
I^-	−8·31		La^{3+}	4·51	
HS^-	−8·59	Soft	Ti^{4+}	4·35	Hard
CN^-	−8·78		Be^{2+}	3·75	
Br^-	−9·22		Mg^{2+}	2·42	
Cl^-	−9·94	Hard	Ca^{2+}	2·33	
HO^-	−10·45		Fe^{3+}	2·22	
H_2O	−(10·73)		Sr^{2+}	2·21	
F^-	−12·18	↓	Cr^{3+}	2·06	
			Ba^{2+}	1·89	
			Ga^{3+}	1·45	
			Cr^{2+}	0·91	
			Fe^{2+}	0·69	
			Li^+	0·49	
			H^+	0·42	
			Ni^{2+}	0·29	
			Na^+	0	
			Cu^{2+}	−0·55	
			Tl^+	−1·88	
			Cd^{2+}	−2·04	
			Cu^+	−2·30	
			Ag^+	−2·82	Soft
			Tl^{3+}	−3·37	
			Au^+	−4·35	
			Hg^{2+}	−4·64	↓

HSAB principle - Application to Chemoselectivity Issues

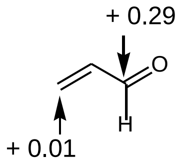
(a) Enolate Alkylation



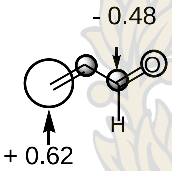
C-Alkylation

O-Alkylation

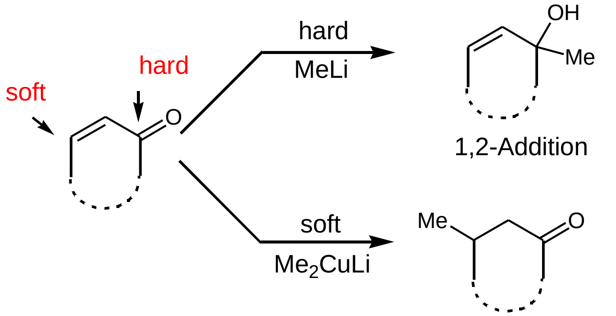
(b) 1,2- vs. 1,4-addition to α,β-unsaturated carbonyl compounds



Charge density



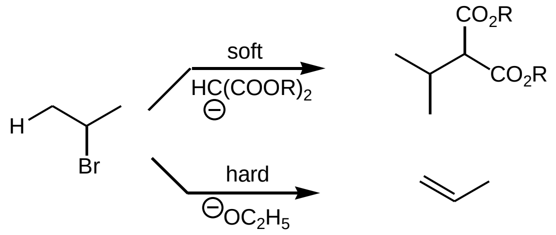
LUMO-coefficients



1,2-Addition

Conjugate Addition

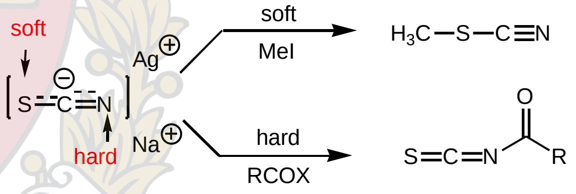
(c) S_N2 vs E2



S_N2

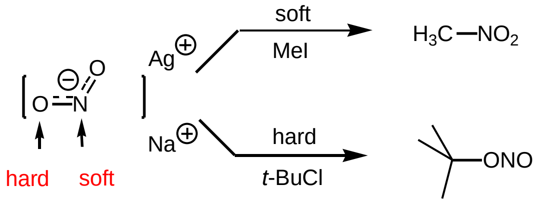
E2

(d) Ambident Nucleophiles



S-Alkylation

N-Acylation



N-Alkylation

O-Alkylation

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 3

Stereoelectronic Effects-3

"Rules for Ring Closure: Baldwin's Rules"

Kirby, "Stereoelectronic Effects" Chapters 4, 5

Useful LIterature Reviews

Johnson, C. D. (**1993**). “Stereoelectronic effects in the formation of 5- and 6-membered rings: the role of Baldwin's rules.” *Acc. Chem. Res.* **26**: 476-82. **(Handout)**

Beak, P. (**1992**). “Determinations of transition-state geometries by the endocyclic restriction test: mechanisms of substitution at nonstereogenic atoms.” *Acc. Chem. Res*. **25**: 215. **(Handout)**

D. A. Evans

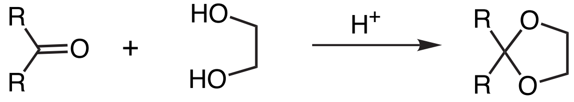
Friday,
September 19, 2003

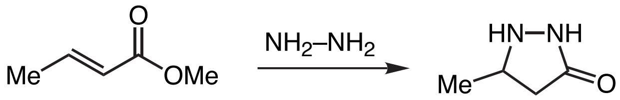
The Primary Literature

Baldwin, *J. Chem. Soc., Chem. Comm.* **1976**, 734, 736.
Baldwin, *J. Chem. Soc., Chem. Comm.* **1977** 233.
Baldwin, J. Org. Chem. **1977**, *42*, 3846.
Baldwin, Tetrahedron **1982**, *38*, 2939.

■ Problems of the Day

Propose mechanisms for the following reactions





Ring Closure and Stereoelectronic Connsiderations An Examination of Baldwin's Rules

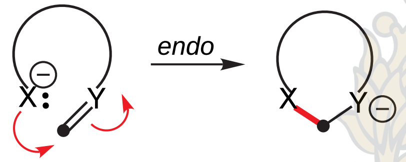
"Baldwin's Rules" provides a qualitative set of generalizations on the probability of a given ring closure.

There are circumstances where the "rules" don't apply.

- They do not apply to non-first-row elements participating in the cyclization event. The longer bond lengths and larger atomic radii of 2nd row elements result in relaxed geometrical constraints.

For example, a change in a heteroatom from O to S could result in relaxation of a given geometric constraint.

X = O vs S

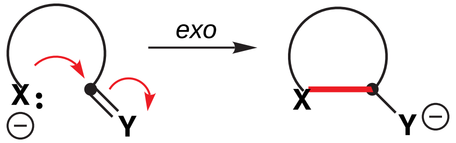


- The "rules" do not apply to electrocyclic processes.

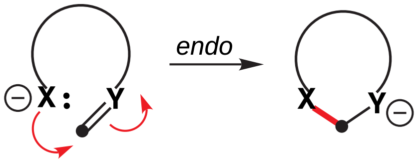
Nomenclature

Classes of Ring Closing Processes

A. Exo-cyclization modes identified by the breaking bond being positioned exocyclic to the forming cycle.



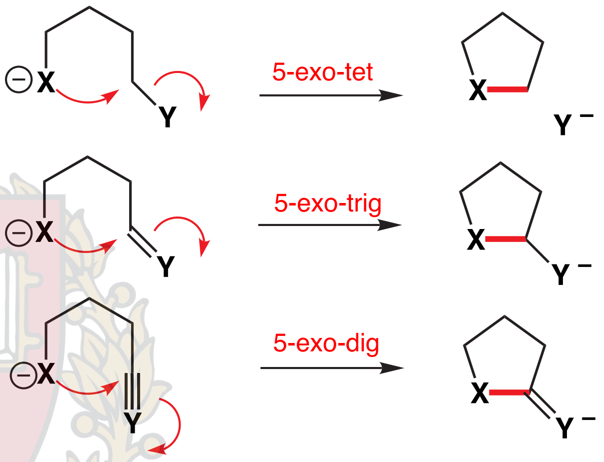
B. Endo-cyclization modes identified by the breaking bond being positioned endocyclic to the forming cycle.



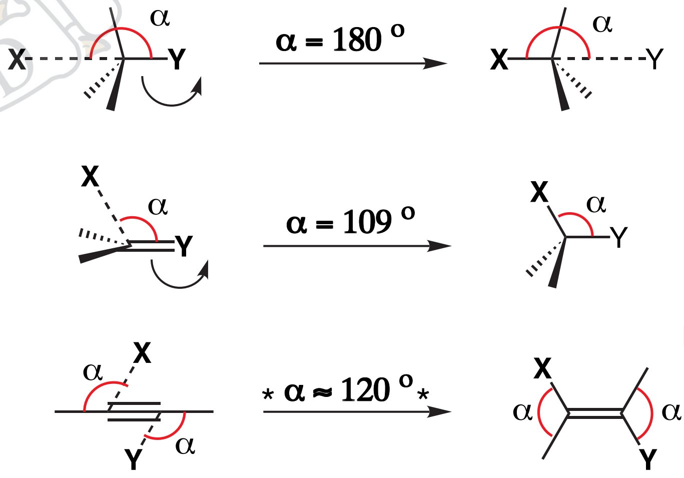
X = first-row element
N, O

C. Nucleophilic ring closures sub-classified according to hybridization state of **electrophilic** component:
(tetrahedral = tet; trigonal = trig; digonal = dig)

D. Nucleophilic ring closures further subclassified according to size of the fomed ring. For example:



Required trajectories (Baldwin):



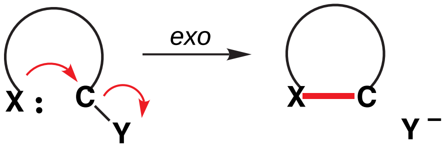
Will come back to this case later

Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

Rules for Ring Closure: SP3 Carbon & Related Systems

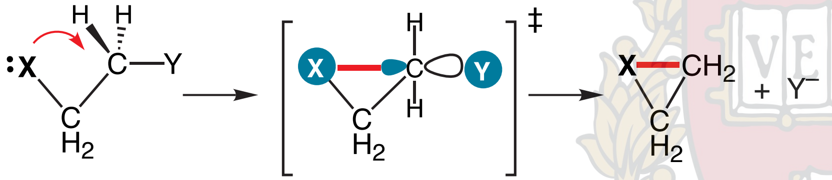
Tetrahedral Carbon

All exo cyclization modes are allowed: (n-exo-tet, n = 3→)



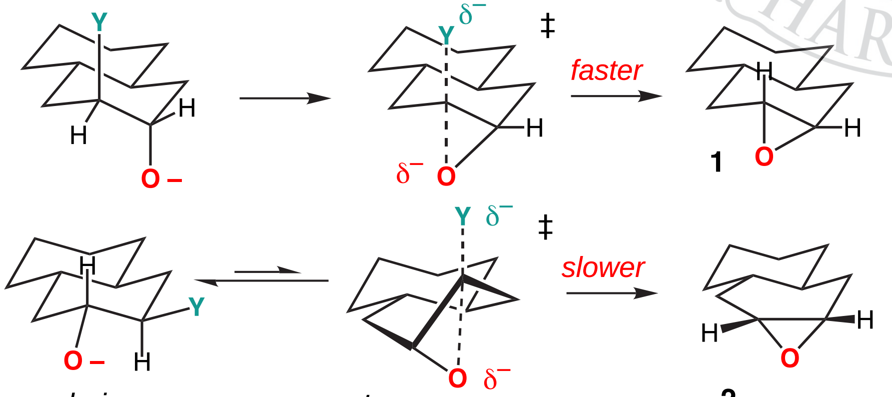
There are stereoelectronic issues to consider for **n-exo-tet** cyclizations

Formation of 3-Membered Rings (3-exo-tet)



Conformational Effects in Epoxide Ring Formation/cleavage

Those stereoelectronic effects that operate in ring cleavage also influence ring formation. Consider a rigid cyclohexene oxide system:



1

2

chair

boat

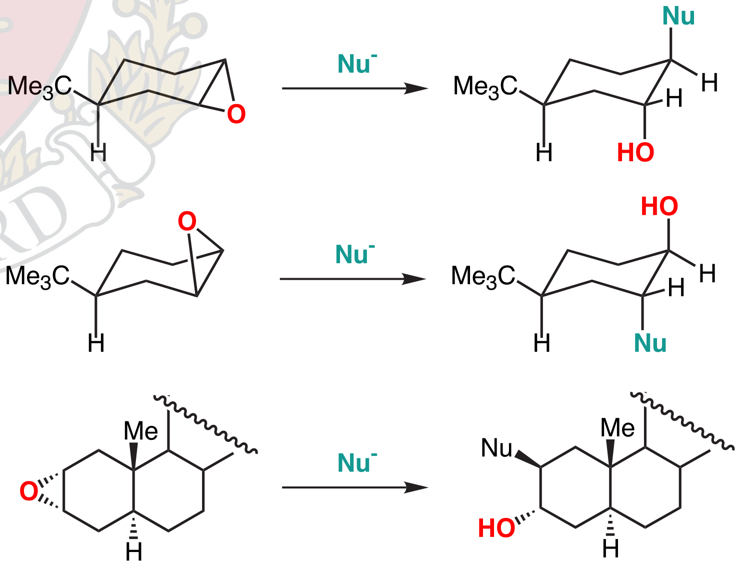
FÜRST-PLATTNER RULE

In this simple model, the transition-state leading to **1** involves the diaxial orientation of nucleophile and leaving group. This orientation affords the best overlap of the anti-bonding C–Y orbital and the nonbonding electron pairs on the nucleophile O⁻.

In the formation of the diastereomeric epoxide **2**, the proper alignment of orbitals may only be achieved by cyclization through the less-favored boat conformer. Accordingly, while both cyclizations are "allowed", there are large rate differences the the rates of ring closure.

While the FÜRST-PLATTNER RULE deals wilth the microscopic reverse, in the opening of epoxides by nucleophiles, the stereoelectronic arguments are the same.

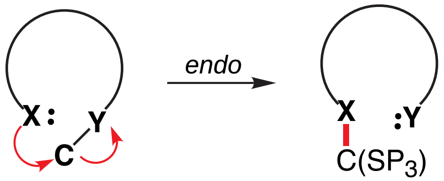
Stereoelectronic Effects in Epoxide Ring Cleavage



"The diaxial nucleophilic ring cleavage of epoxides"
For more information on epoxide cleavage see **Handout 03A.**

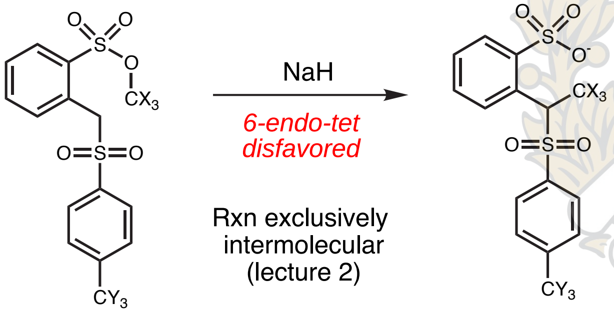
Tetrahedral Carbon

Endo cyclization modes that are disallowed (n-endo-tet, n = 3→~9)



The stereoelectronic requirement for a 180° X–C–Y bond angle is only met when the endo cyclization ring size reaches 9 or 10 members.

Case 1: Eschenmoser, *Helvetica Chim. Acta* **1970**, *53*, 2059.

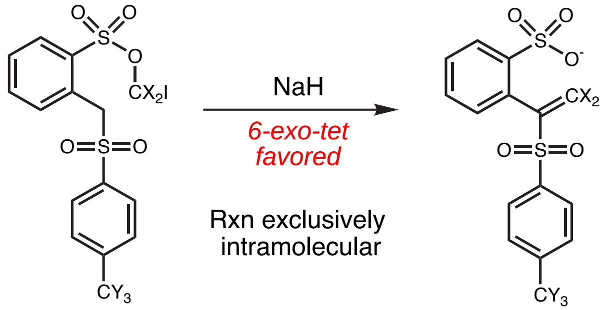


NaH

6-endo-tet disfavored

Rxn exclusively intermolecular (lecture 2)

Cyclization exclusively intermolecular. However the exocyclic analog is exclusively intramolecular

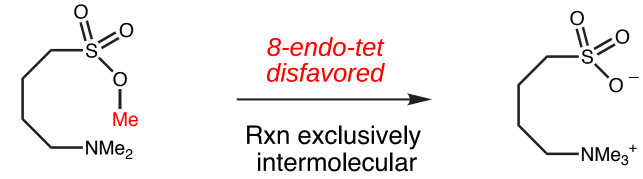


NaH

6-exo-tet favored

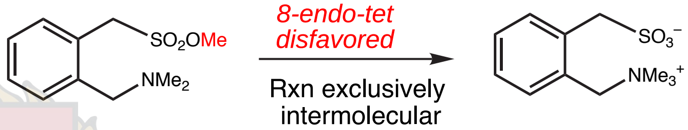
Rxn exclusively intramolecular

Case 2: King, *J.C.S. Chem. Comm.*, **1979**, 1140.



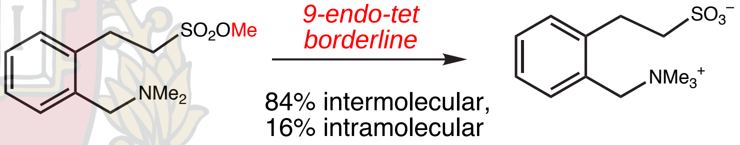
8-endo-tet disfavored

Rxn exclusively intermolecular



8-endo-tet disfavored

Rxn exclusively intermolecular



9-endo-tet borderline

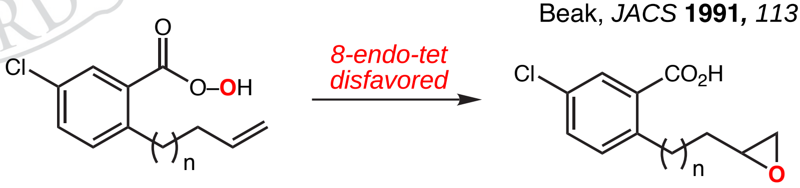
84% intermolecular, 16% intramolecular

Conclusions

Allowed endo cyclization modes will require transition state ring sizes of at least nine members.

Intramolecular epoxidation has also been evaluated

Beak, *JACS* **1991,** *113*, 6281.



8-endo-tet disfavored

n = 1: rxn exclusively intermolecular
n = 9: rxn is intramolecular

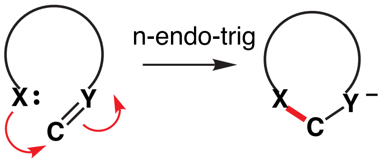
Beak states that the conclusions made with carbon substitution also hold for oxygen atom transfer.

Beak, P. (**1992**). "Determinations of transition-state geometries by the endocyclic restriction test: mechanisms of substitution at nonstereogenic atoms." *Acc. Chem. Res.* **25**: 215.

Rules for Ring Closure: SP2 Carbon & Related Systems

Trigonal Carbon

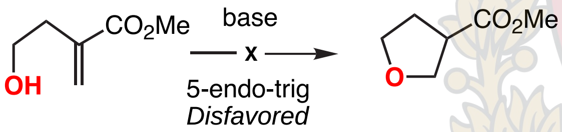
Endo cyclization modes that are disallowed (3 to 5-endo-trig)



X = first-row element

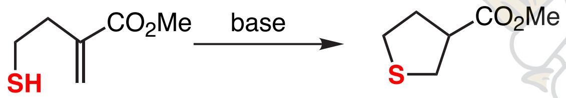
The 5-endo-trig cyclization is a watershed case

Case 1: Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.



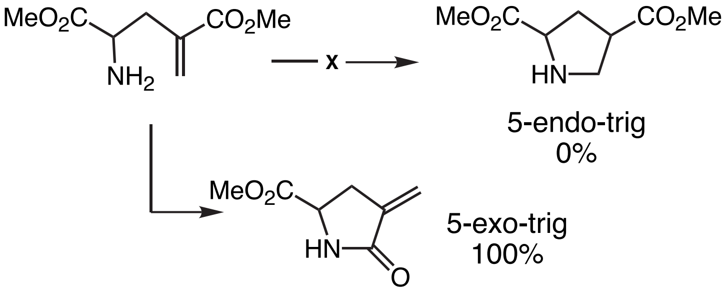
5-endo-trig
Disfavored

however



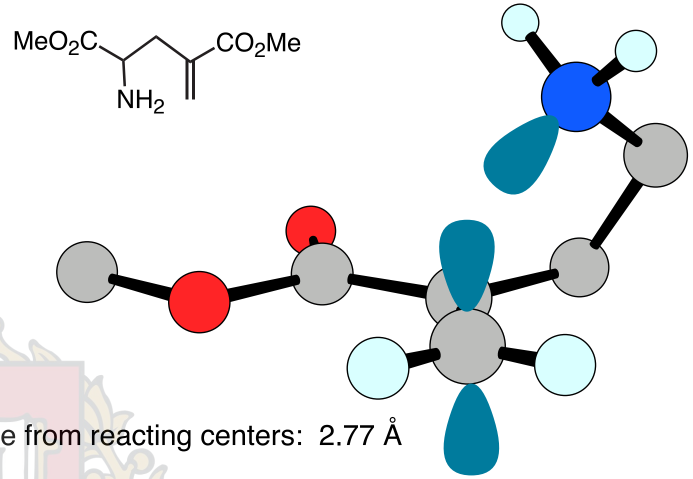
Second row atom relaxes the cyclization geometrical requirement

Case 2: Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 736.



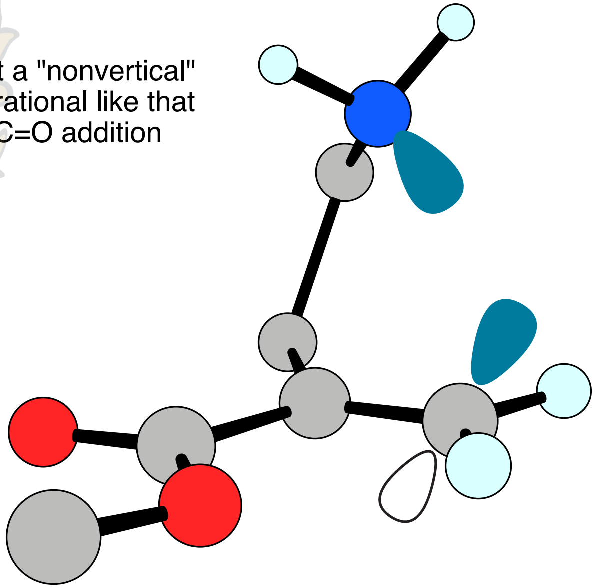
5-endo-trig
0%

5-exo-trig
100%



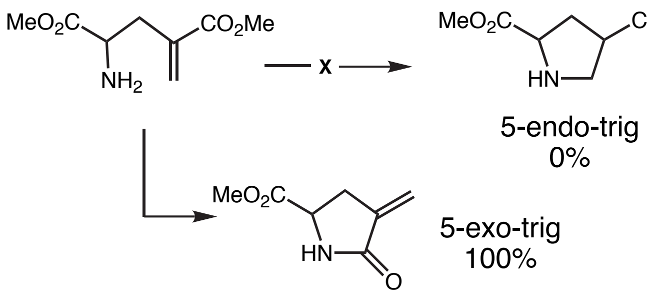
distance from reacting centers: 2.77 Å

It is possible that a "nonvertical" trajectory is operational like that suspected in C=O addition

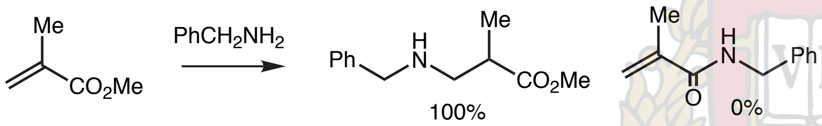


Rules for Ring Closure: SP2 Carbon & Related Systems

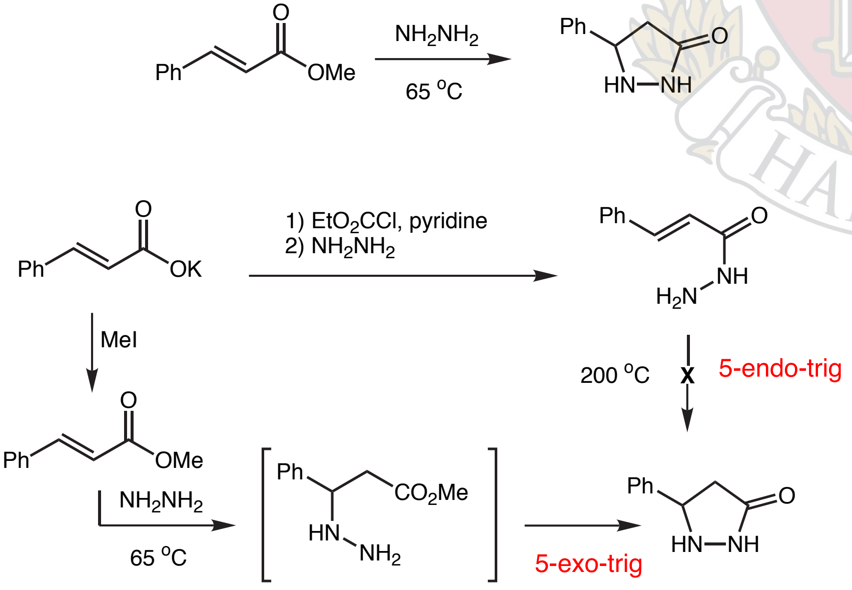
Case 2: continued...



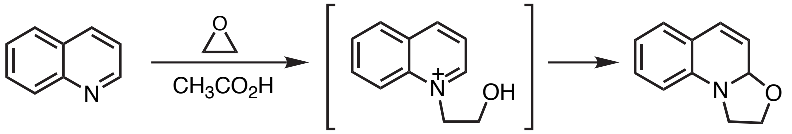
Control experiment: Intermolecular reaction favors conjugate addtion.



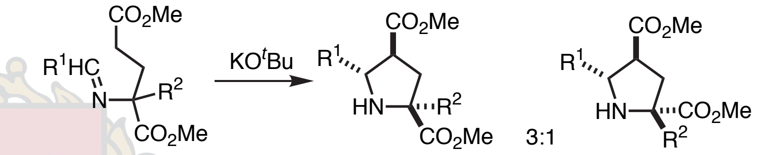
Case 3:



Apparent exceptions to disallowed 5-endo-trig cyclization process



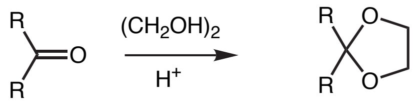
Filer, *J. Am. Chem. Soc.* **1979**, *44*, 285.

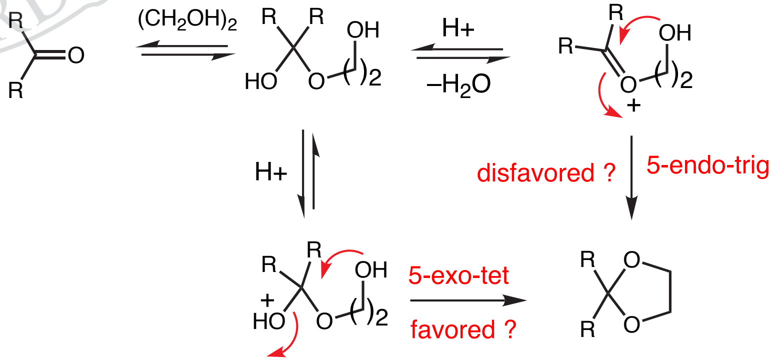


R^1 = aryl, R^2 = aryl, alkyl

Grigg, *J. Chem. Soc., Chem. Commun.* **1980**, 648.

Does the illustrated ketalization process necessarily violate "the rules"?



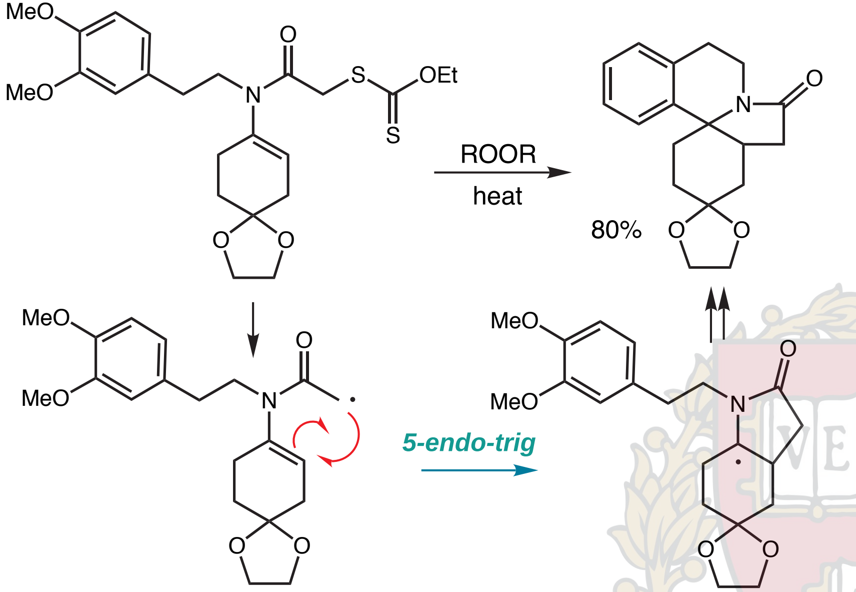


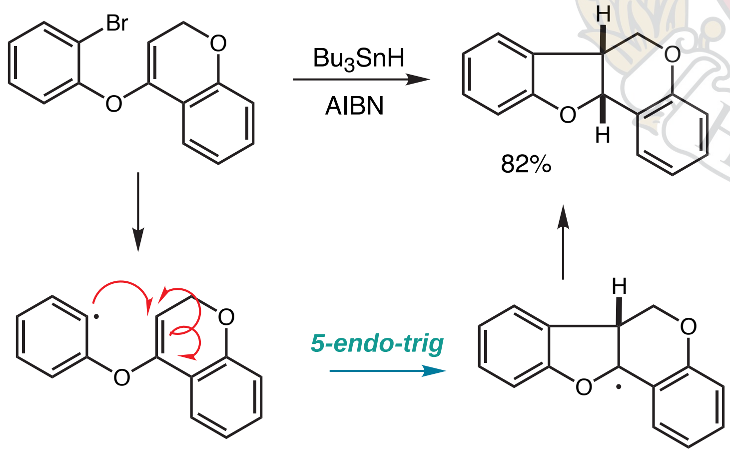
Johnson, C. D. (**1993**). "Stereoelectronic effects in the formation of 5- and 6-membered rings: the role of Baldwin's rules." *Acc. Chem. Res.* **26**: 476-82.

Rules for Ring Closure: SP2 Carbon & Related Systems

More Exceptions

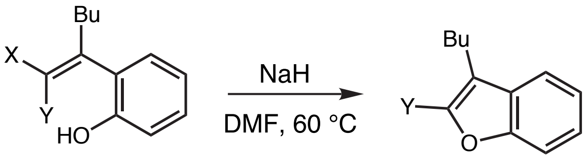
Zard, *Org. Lett.* **2002**, *4*, 1135





Chem. Comm **2088**, 28

Review: "5-Endo-Trig Radical Cyclizatons" Ishibashi, et al *Synthesis* **2002**, 695-713, **PDF on Course Website**

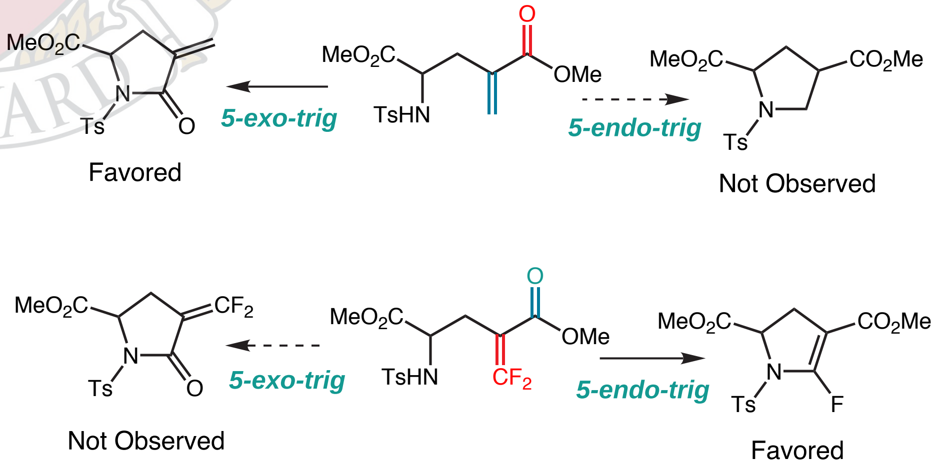


X	Y	Cond	Yield
F	F	DMF, 60 °C, 2 h	80
F	H	DMF, 80 °C, 43 h	17
Cl	Cl	DMF, 60 °C, 8 h	—
Br	Br	DMF, 60 °C, 5 h	15

Ichikawa, et al *Synthesis* **2002**, 1917-1936, **PDF on Course Website**

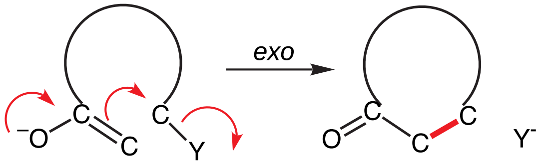
Numerous other cases are provided in this review.

Revisiting Case 2 with Fluorines

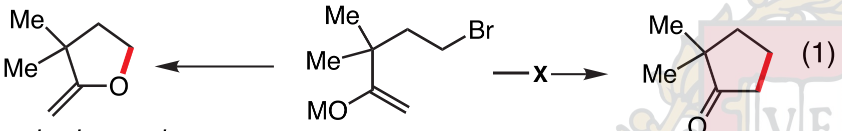


Rules for Ring Closure: SP2 Carbon & Related Systems

Trigonal Carbon: Exocyclic Enolate Alkylation

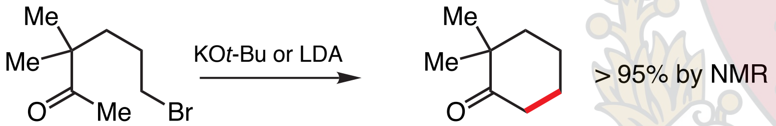


■ By definition, an exo-tet cyclization, but stereoelectronically behaves as an endo trig.



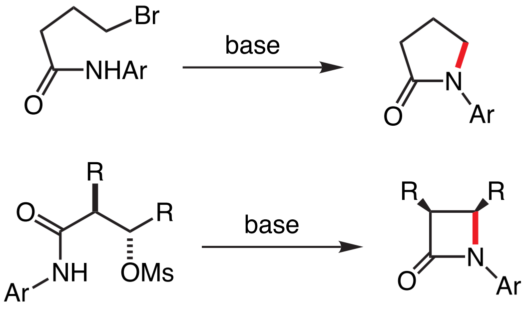
only observed product

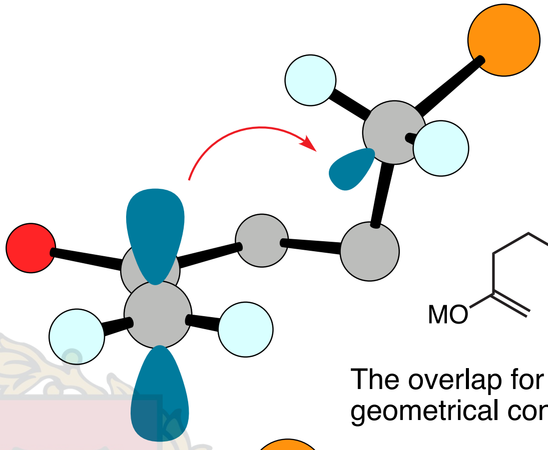
However:



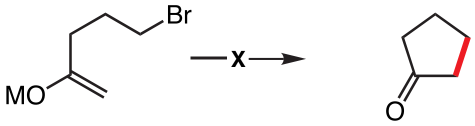
Baldwin, *J. Chem. Soc., Chem. Commun.* **1977**, 233.

■ Given the failure of the enolate alkylation shown above (eq 1), explain why these two cyclizations are successful.

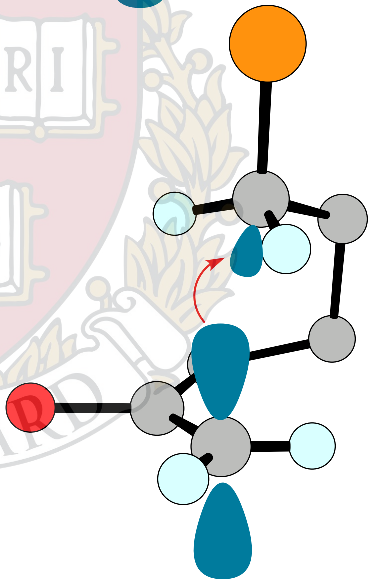




distance between reacting centers: 3.37Å

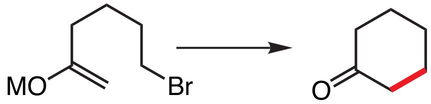


The overlap for C-alkylation is poor due to geometrical constraints of 5-membered ring

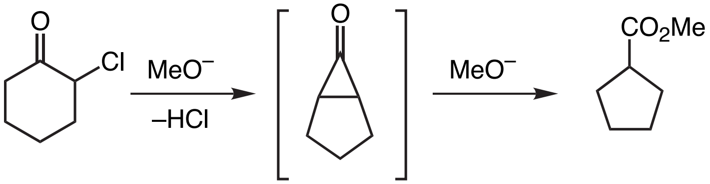


distance between reacting centers: 3.04Å

The relaxed geometrical constraint provided by the added CH_2 group now renders the 6-membered cyclization possible

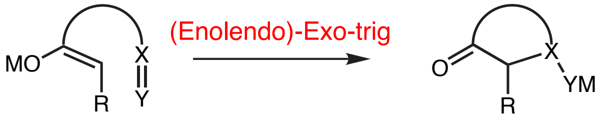


Favorskii Rearrangement (Carey, Pt B, pp 609-610)
Your thoughts on the mechanism

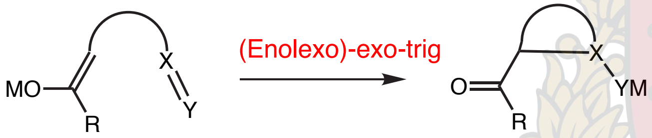


Trigonal Carbon: *Intramolecular Aldol Condensations*

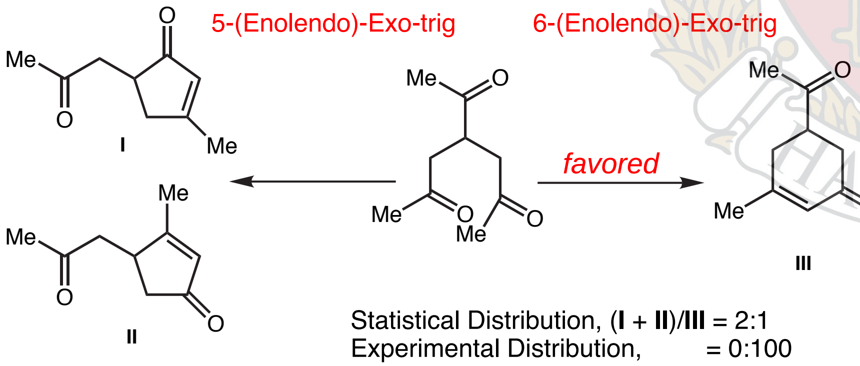
Baldwin, *Tetrahedron* **1982**, *38*, 2939



Favored: 6-7-(enolendo)-exo-trig
Disfavored: 3-5-(enolendo)-exo-trig



Favored: 3-7-(enolexo)-exo-trig



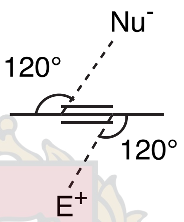
Statistical Distribution, (**I** + **II**)/**III** = 2:1
Experimental Distribution, = 0:100

(KOH, MeOH, r.t., 5 min, 77% y.)

Caution: Baldwin's conclusions assume that the **RDS** is ring closure; however, it is well known (by some!) that the rate determining step is dehydration in a base-catalyzed aldol condensation.

Digonal Carbon: Cyclizations on to Acetylenes

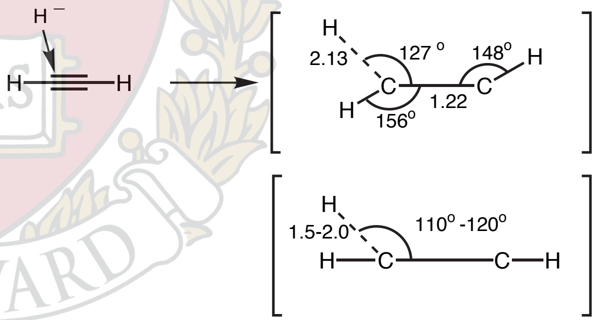
DIGONAL: Angle of approach for attack on triple bonds



Baldwin:

- 3 and 4-Exo-dig are disfavored
- 5 to 7-Exo-dig are favored
- 3 to 7-Endo-dig are favored

Ab initio SCF 4-31G calculations for the interaction of hydride with acetylene:



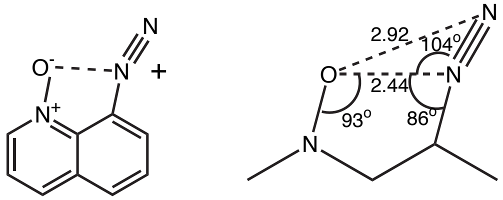
4-31G basis set

Houk, *J.ACS.* **1979**, *101*, 1340.

STO-3G minimal basis set

Dunitz, *Helv Chim. Acta* **1978**, *61*, 2538.

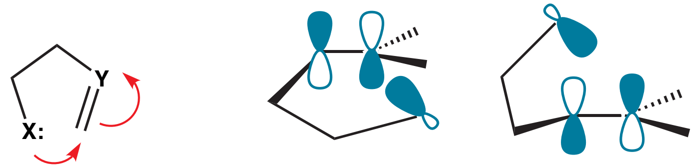
Crystal Structures do not support Baldwin



J. Dunitz and J. Wallis *J. C. S. Chem. Comm.* **1984**, 671.

Endo Digonal versus Endo Trigonal Cyclizations

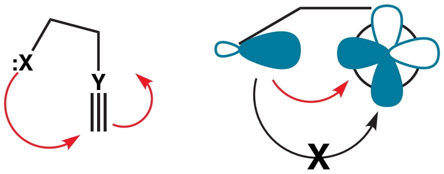
5-endo-trig



In-plane approach; nucleophile lone pair is orthogonal to π*

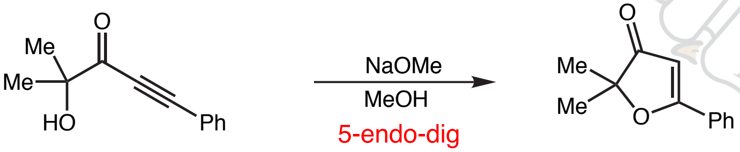
Out-of-plane approach; nucleophile lone pair can't achieve Bürgi-Dunitz angle

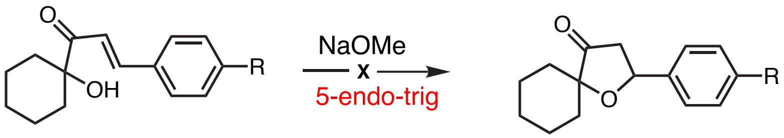
5-endo-dig



Allowed due to in-plane pi orbitals

For an opposing viewpoint to Baldwin's view of nucleophile trajectories, see Menger's article on directionality in solution organic chemistry: *Tetrahedron* **1983**, *39*, 1013.





R = H, OMe

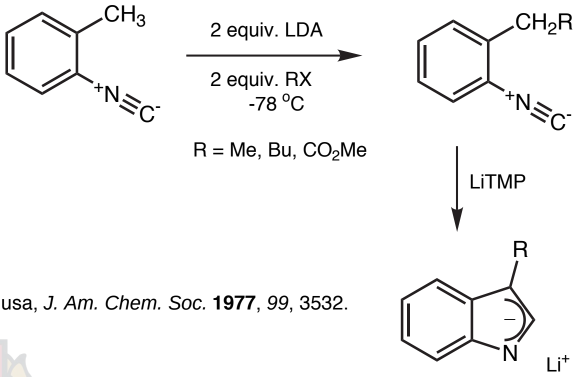
however, the acid catalyzed version does cyclize

Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 736.

Johnson, *Can. J. Chem.* **1990**, *68*, 1780

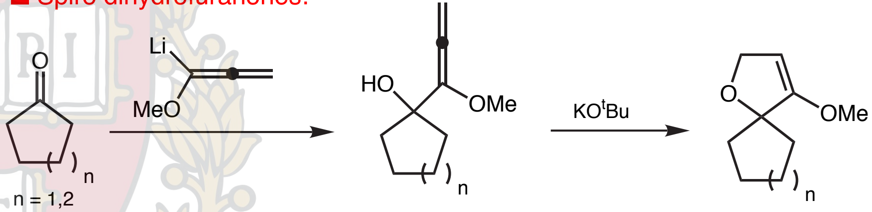
J. Am. Chem. Soc. **1983**, *105*, 5090
J. Chem. Soc., Chem. Commun. **1982**, 36.

■ Indole synthesis:



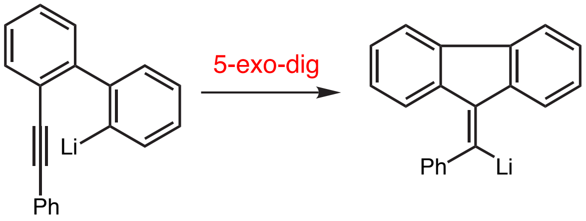
Saegusa, *J. Am. Chem. Soc.* **1977**, *99*, 3532.

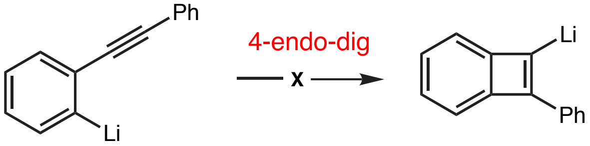
■ Spiro dihydrofuranones:



Developing negative charge on the central allenic carbon is in the same plane as the OMe group

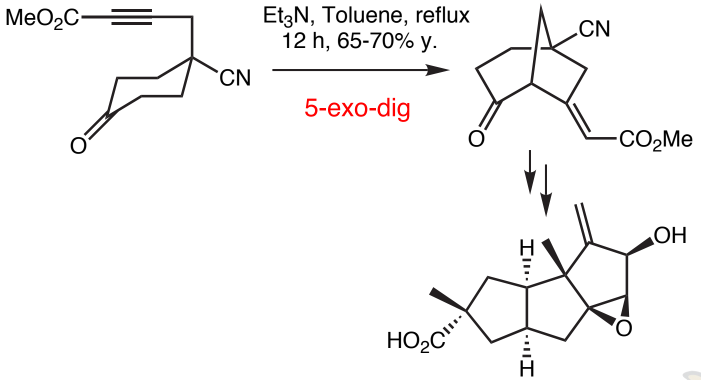
Magnus, *J. Am. Chem. Soc.* **1978**, *100*, 7746.





Rules for Ring Closure: SP Carbon & Related Systems

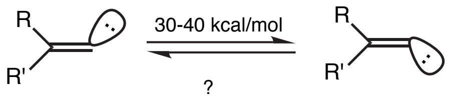
Digonal Cyclizations: Interesting Examples

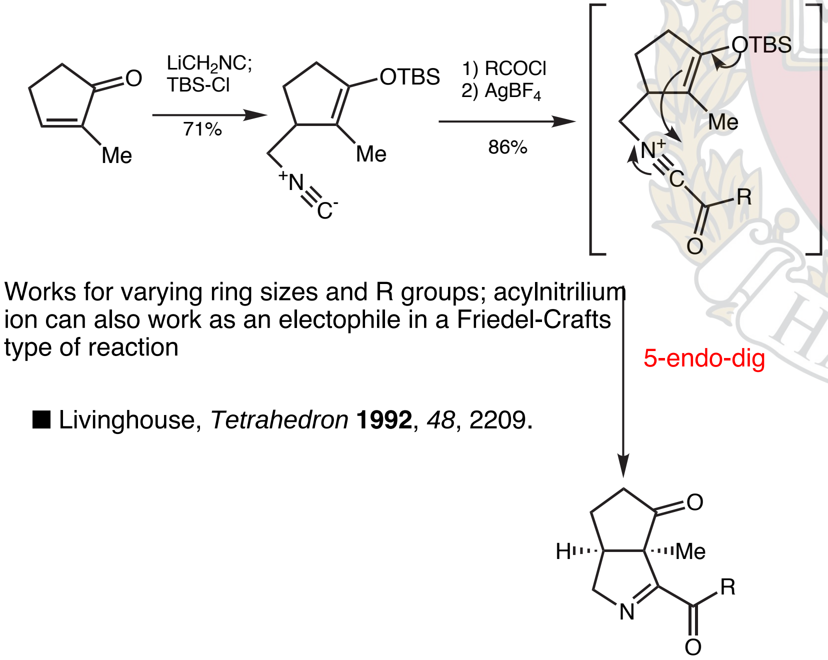


Hirsutic Acid C

- Trost, *J. Am. Chem. Soc.*, **1979**, *101*, 1284.

Proposes E-olefin geometry, E/Z > 95:5





Works for varying ring sizes and R groups; acylnitrilium ion can also work as an electophile in a Friedel-Crafts type of reaction

- Livinghouse, *Tetrahedron* **1992**, *48*, 2209.

Conclusions and Caveats

- Baldwin's Rules are an effective first line of analysis in evaluating the stereoelectronics of a given ring closure
- Baldwin's Rules have provided an important foundation for the study of reaction mechanism
- Competition studies between different modes of cyclization only give information about relative rates, and are not an absolute indicator of whether a process is "favored" or "disfavored"
- Structural modifications can dramatically affect the cyclization mode; beware of imines and epoxides

	EXO			**ENDO**		
	Tet	**Trig**	**Dig**	**Tet**	**Trig**	**Dig**
3	√	√	x		x	√
4	√	√	x		x	√
5	√	√	√	x	x	√
6	√	√	√	x	√	√
7	√	√	√	x	√	√

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 4

Acyclic Conformational Analysis-1

- Ethane, Propane, Butane & Pentane Conformations
- Introduction to Allylic Strain

Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapters 2 & 3

R. W. Hoffmann, *Chem. Rev*. **1989**, *89*, 1841-1860
Allylic 1-3-Strain as a Controlling Element in Stereoselective Transformations

R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl*. ***2000***, *39*, 2054-2070
Conformation Design of Open-Chain Compounds

F. Weinhold, *Angew. Science* ***2001***, *411*, 539-541
"A New Twist on Molecular Shape"

Matthew D. Shair

Wednesday,
September 25, 2002

Useful LIterature Reviews

Eliel, E. L., S. H. Wilen, et al. (1994). Stereochemistry of Organic Compounds. New York, Wiley.

Juaristi, E. (1991). Introduction to Stereochemistry and Conformational Analysis. New York, Wiley.

Juaristi, E., Ed. (1995). Conformational Behavior of Six-Membered Rings: Analysis, Dynamics and Stereochemical Effects. (Series: Methods in Stereochemical Analysis). Weinheim, Germany, VCH.

Schweizer, W. B. (1994). Conformational Analysis. Structure Correlation, Vol 1 and 2. H. B. Burgi and J. D. Dunitz. Weinheim, Germany, V C H Verlagsgesellschaft**:** 369-404.

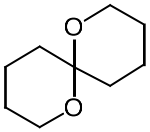
Kleinpeter, E. (1997). "Conformational Analysis of Saturated Six-Membered Oxygen-Containing Heterocyclic Rings." Adv. Heterocycl. Chem. **69**: 217-69.

Glass, R. R., Ed. (1988). Conformational Analysis of Medium-Sized Ring Heterocycles. Weinheim, VCH.

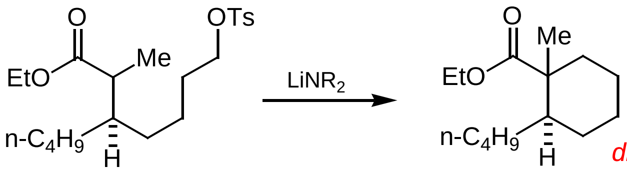
Bucourt, R. (1973). "The Torsion Angle Concept in Conformational Analysis." Top. Stereochem. **8**: 159.

Problems of the Day

Predict the most stable conformation of the indicated dioxospiran?



Can you predict the stereochemical outcome of this reaction?

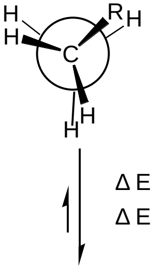


diastereoselection 98:2

The following discussion is intended to provide a general overview of acyclic conformational analysis

Ethane & Propane

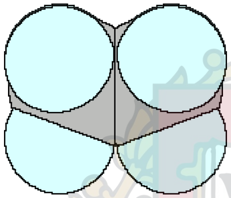
The conformational isomerism in these 2 structures reveals a gratifying level of internal consistency.



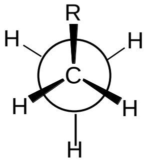
eclipsed conformation

$\Delta E = +3.0$ kcal mol^{-1} (R = H)

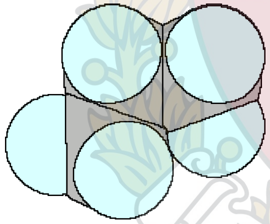
$\Delta E = +3.4$ kcal mol^{-1} (R = Me)



Van derWaals radii of vicinal hydrogens do not overlap in ethane



staggered conformation



In propane there is a discernable interaction

For purposes of analysis, each eclipsed conformer may be broken up into its component destabilizing interactions.

Incremental Contributions to the Barrier.

Structure	Eclipsed atoms	δE (kcal mol $^{-1}$)
ethane	3 (H ↔ H)	+1.0 kcal mol $^{-1}$
propane	2 (H ↔ H) 1 (H ↔ Me)	+1.0 kcal mol $^{-1}$ +1.4 kcal mol $^{-1}$

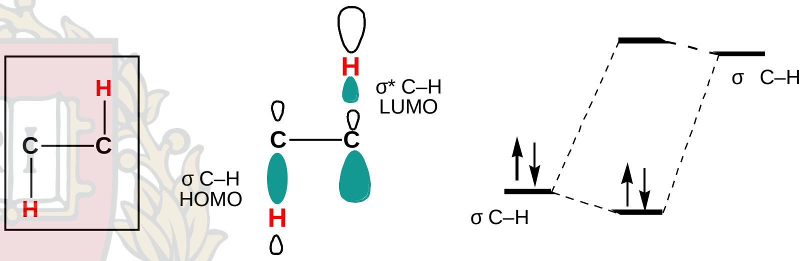
Ethane Rotational Barrier: The FMO View

F. Weinhold, *Angew. Science* **2001**, *411*, 539-541"*A New Twist on Molecular Shape*"

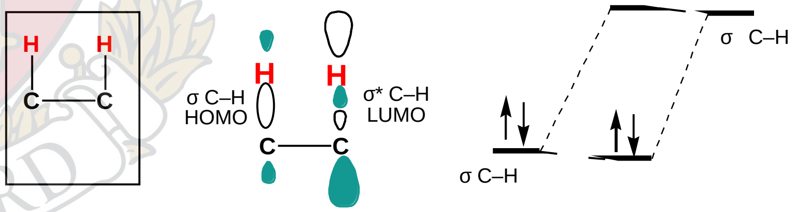
One can see from the space-filling models that the Van der Waals radii of the hydrogens do not overlap in the eclipsed ethane conformation. This makes the steric argument for the barrier untenable.

One explanation for the rotational barrier in ethane is that better overlap is possible in the staggered conformation than in the eclipsed conformation as shown below.

In the staggered conformation there are 3 anti-periplanar C–H Bonds



In the eclipsed conformation there are 3 syn-periplanar C–H Bonds

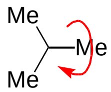


Following this argument one might conclude that:

- The staggered conformer has a better orbital match between bonding and antibonding states.
- The staggered conformer can form more delocalized molecular orbitals.

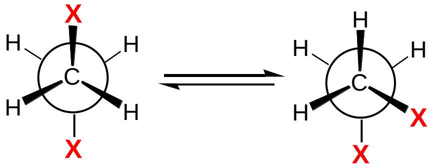
J. P. Lowe was the first to propose this explanation

"A Simple Molecuar Orbital Explanation for the Barrier to Internal Rotation in Ethane and Other Molecules"
J. P. Lowe, *JACS* **1970**, *92*, 3799



Calculate the the rotational barrier about the C1-C2 bond in isobutane

The 1,2-Dihaloethanes



X = Cl; $\Delta H° = +0.9–1.3$ kcal/mol

X = Br; $\Delta H° = +1.4–1.8$ kcal/mol

X = F; $\Delta H° = –0.6-0.9$ kcal/mol

Observation: While the anti conformers are favored for X = Cl, Br, the gauche conformation is prefered for 1,2-difluroethane. Explain.

Discuss with class the origin of the gauche stabiliation of the difluoro anaolg.

Relationship between ΔG and Keq and pKa

Recall that: $\Delta G° = –RT \ Ln \ K$

or

$\Delta G° = –2.3RT \ Log_{10}K$

At 298 K: 2.3RT = 1.4 (ΔG in kcal $Mol^{–1}$)

$$\Delta G°_{298} = –1.4 \ Log_{10}Keq$$

Since $pKeq = – Log_{10}Keq$

$$\boxed{\Delta G°_{298} = 1.4 \ pKeq}$$

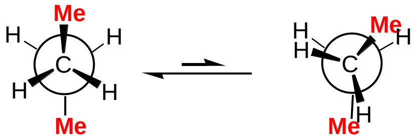
Hence, pK is proportional to the free energy change

Keq	pKeq	ΔG°
1.0	0	0
10	-1	–1.4
100	-2	–2.8 kcal /mol

Butane

Using the eclipsing interactions extracted from propane & ethane we should be able to estimate all but one of the eclipsed butane conformations

staggered conformation



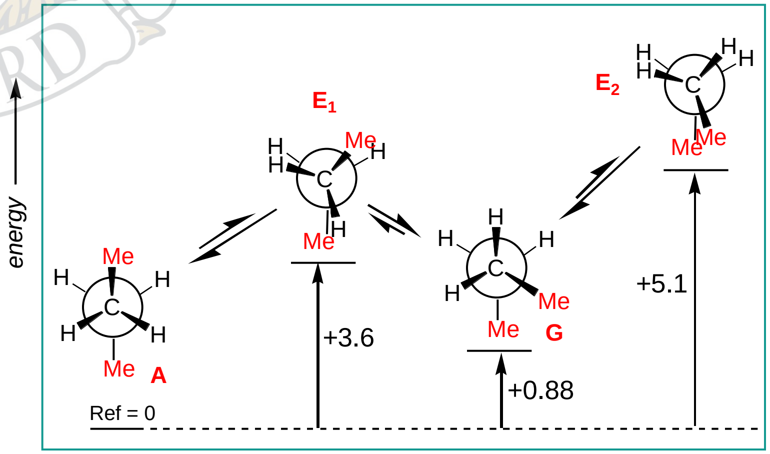
eclipsed conformation

ΔE = ?

Eclipsed atoms	δE (kcal mol^{-1})
1 (H ↔ H)	+1.0 kcal mol^{-1}
2 (H ↔ Me)	+2.8 kcal mol^{-1}
ΔE est =	3.8 kcal mol^{-1}

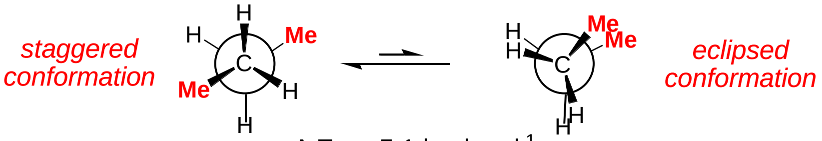
The estimated value of +3.8 agrees quite well with the value of +3.6 reported by Allinger (*J. Comp. Chem.* **1980**, *1*, 181-184)

n-Butane Torsional Energy Profile



Butane continued

From the torsional energy profile established by Allinger, we should be able to extract the contribution of the Me↔Me eclipsing interaction to the barrier:



$\Delta E = +5.1 \text{ kcal mol}^{-1}$

Let's extract out the magnitide of the Me–Me interaction

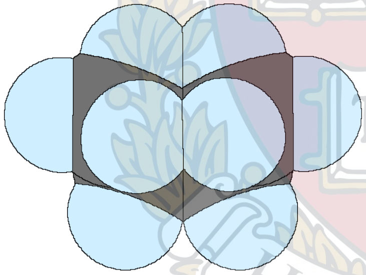
$$2\,(H \leftrightarrow H) \; + \; 1\,(Me \leftrightarrow Me) \; = \; +5.1$$

$$1\,(Me \leftrightarrow Me) \; = \; +5.1 \; - \; 2\,(H \leftrightarrow H)$$

$$\mathbf{1\,(Me \leftrightarrow Me) \; = \; +3.1}$$

Incremental Contributions to the Barrier.

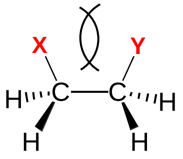
Eclipsed atoms	δ E (kcal mol $^{-1}$)
2 (H↔H)	+2.0
1 (Me↔Me)	+2.2



Eclipsed Butane conformation

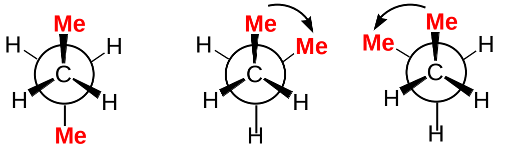
From the energy profiles of ethane, propane, and n-butane, one may extract the useful eclipsing interactions summarized below:

Hierarchy of Eclipsing Interactions



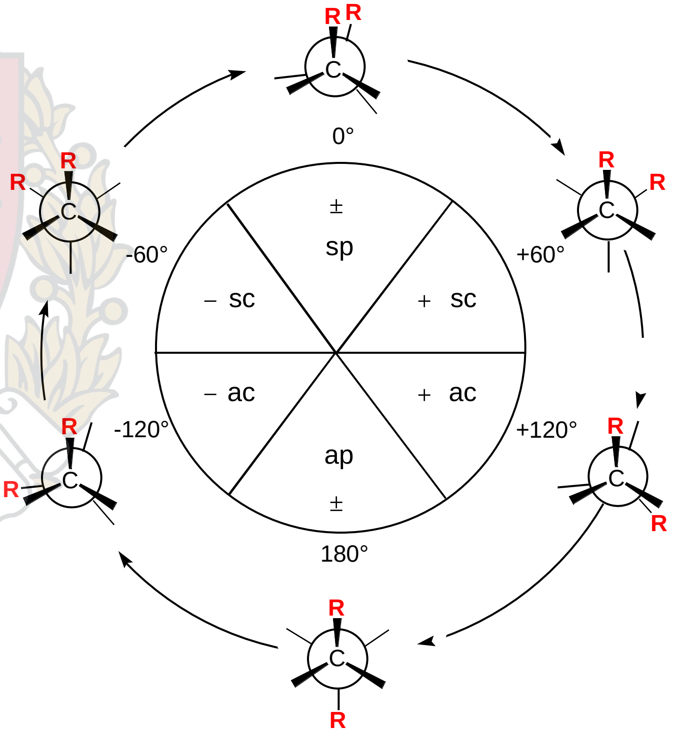
X—Y	δ E kcal mol $^{-1}$
H—H	+1.0
H—Me	+1.4
Me—Me	**+3.1**

Nomenclature for staggered conformers:



	trans or t or (anti)	gauche(+) or g^+	gauche(-) or g^-
Conformer population at 298 K:	70%	15%	15%

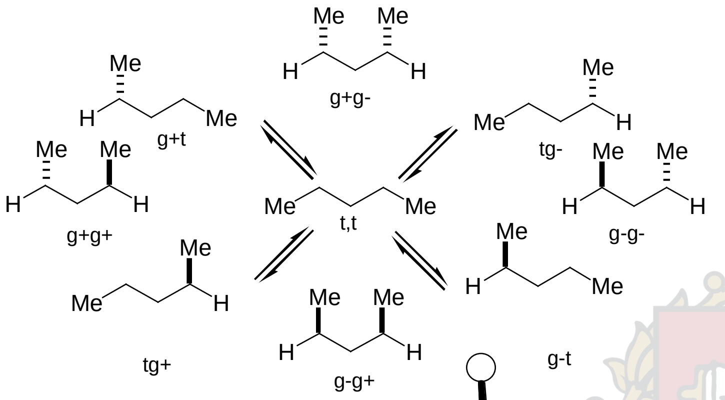
General nomenclature for diastereomers resulting from rotation about a single bond (Klyne, Prelog, *Experientia* **1960**, *16*, 521.)

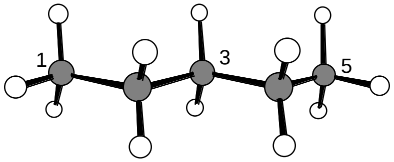


	Torsion angle	Designation	Symbol	*n*-Butane Conformer
Energy Maxima →	0 ± 30°	± syn periplanar	± sp	E_2
Energy Minima - - →	+60 ± 30°	+ syn-clinal	+ sc (g+)	G
→	+120 ± 30°	+ anti-clinal	+ ac	E_1
- - →	180 ± 30°	antiperiplanar	ap (anti or t)	A
→	-120 ± 30°	- anti-clinal	- ac	E_1
- - →	-60 ± 30°	- syn-clinal	- sc (g-)	G

n-Pentane

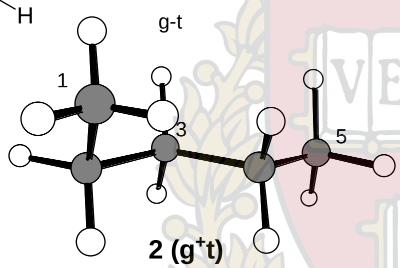
Rotation about both the C_2-C_3 and C_3-C_4 bonds in either direction (+ or -):





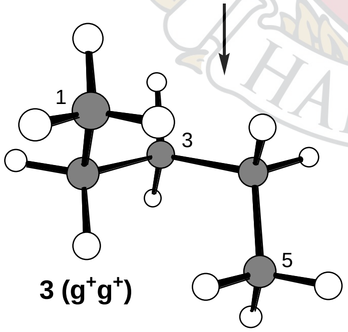
1 (t,t)

Anti(2,3)-Anti(3,4)



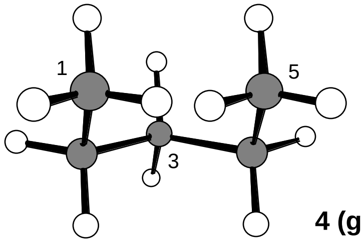
2 (g^+t)

Gauche(2,3)-Anti(3,4)



3 (g^+g^+)

Gauche(2,3)-Gauche(3,4)

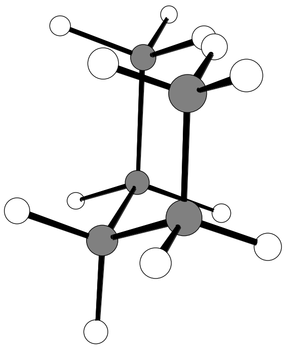


4 (g^+g^-)

Gauche(2,3)-Gauche'(3,4)
double gauche pentane

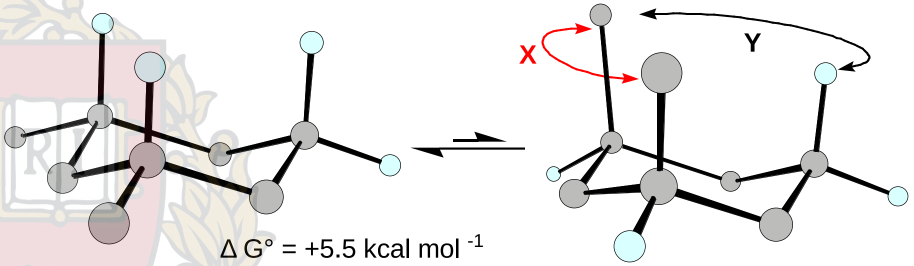
From prior discussion, you should be able to estimate energies of **2** & **3** (relative to **1**). On the other hand, the least stable conformer **4** requires additional data before is relative energy can be evaluated.

The double-gauche pentane conformation



The new high-energy conformation: **(g^+g^-)**

Estimate of 1,3-Dimethyl Eclipsing Interaction

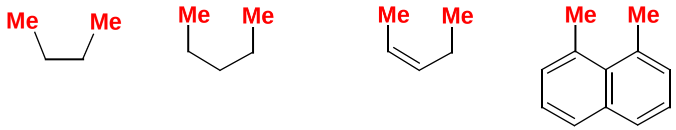


$\Delta G^\circ = +5.5 \text{ kcal mol}^{-1}$
$\Delta G^\circ = X + 2Y$ where:
$X = 1,3(\text{Me} \leftrightarrow \text{Me})$ & $Y = 1,3(\text{Me} \leftrightarrow \text{H})$

$1,3(\text{Me} \leftrightarrow \text{H}) = \text{Skew-butane} = 0.88 \text{ kcal mol}^{-1}$
$1,3(\text{Me} \leftrightarrow \text{Me}) = \Delta G^\circ - 2Y = 5.5 - 1.76 = +3.7 \text{ kcal mol}^{-1}$

$$\boxed{1,3(\text{Me} \leftrightarrow \text{Me}) = +3.7 \text{ kcal mol}^{-1}}$$

Estimates of In-Plane 1,2 &1,3-Dimethyl Eclipsing Interactions

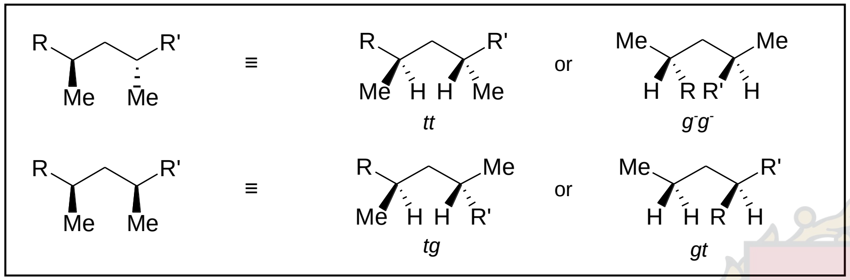


~ 2.2 ~ 3.7 ~3.9 ~ 7.6

It may be concluded that in-plane 1,3(Me ↔ Me) interactions are Ca +4 kcal/mol while 1,2(Me ↔ Me) interactions are destabliizing by Ca 2.2 kcal/mol.

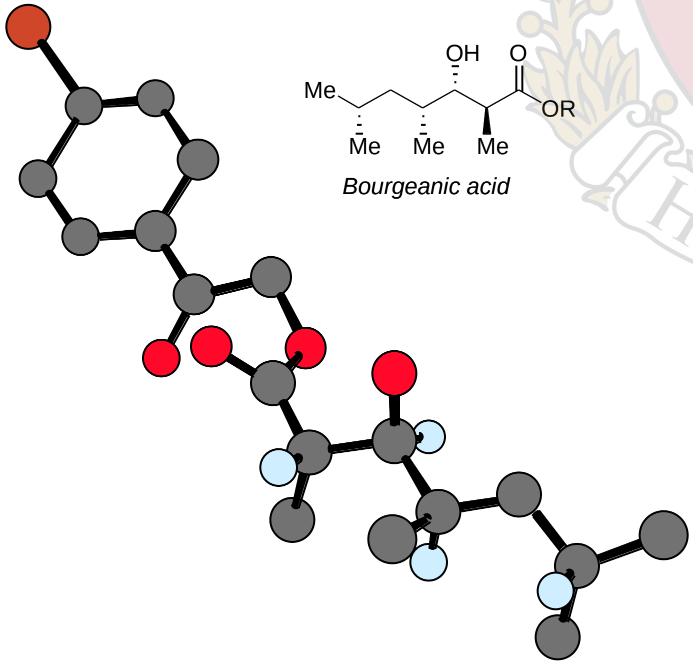
The syn-Pentane Interaction - Consequences

(R. W. Hoffmann, *ACIE* **1992**, *31*, 1124-1134.)



Consequences for the preferred conformation of polyketide natural products

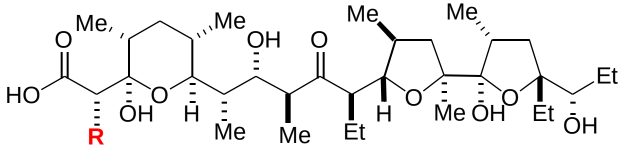
Analyze the conformation found in the crystal state of a bourgeanic acid derivative!



Bourgeanic acid

Lactol & Ketol Polyether Antibioitics

The conformation of these structures are strongly influenced by the acyclic stereocenters

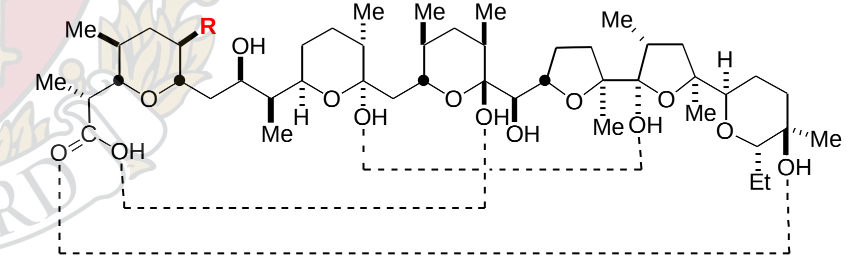


Ferensimycin B, R = Me
Lysocellin, R = H

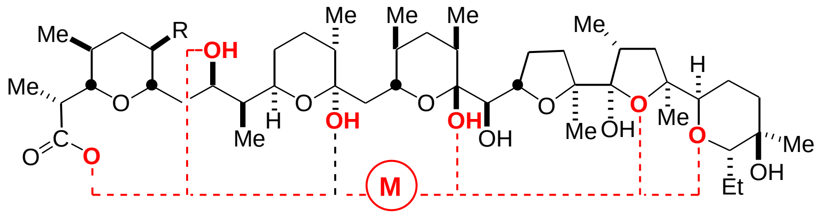
The conformation of these structures are strongly influenced by the acyclic stereocenters and internal H-bonding

Alborixin R = Me; X-206 R = H

Internal H-Bonding



Metal ion ligation sites (M = Ag, K)

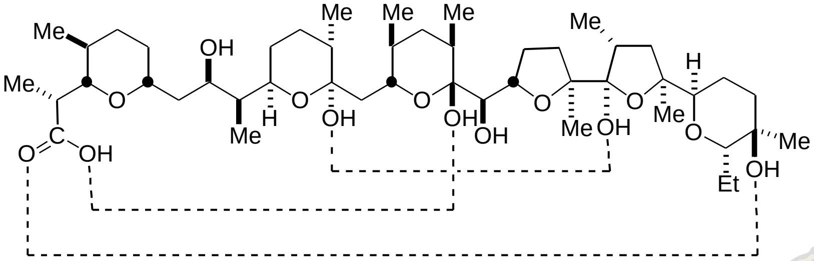


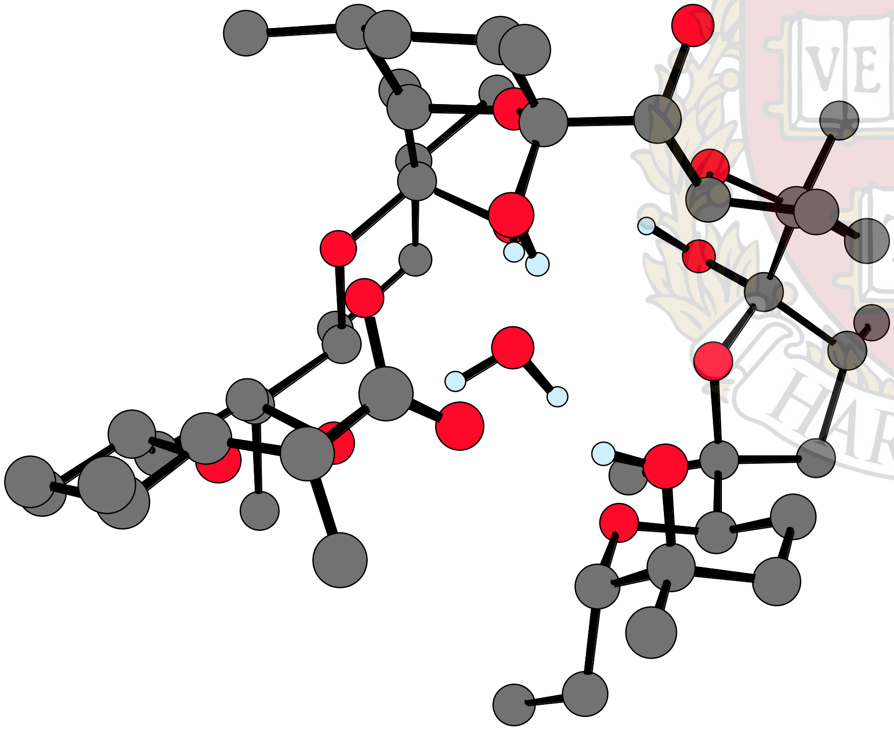
Synthesis: Evans, Bender, Morris, *JACS* **1988**, *110*, 2506

Conformational Analysis: Ionophore X-206/X-rays

X-ray of Ionophore X-206 H_2O

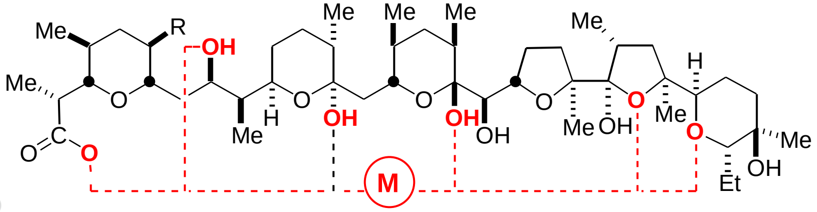
Internal H-Bonding

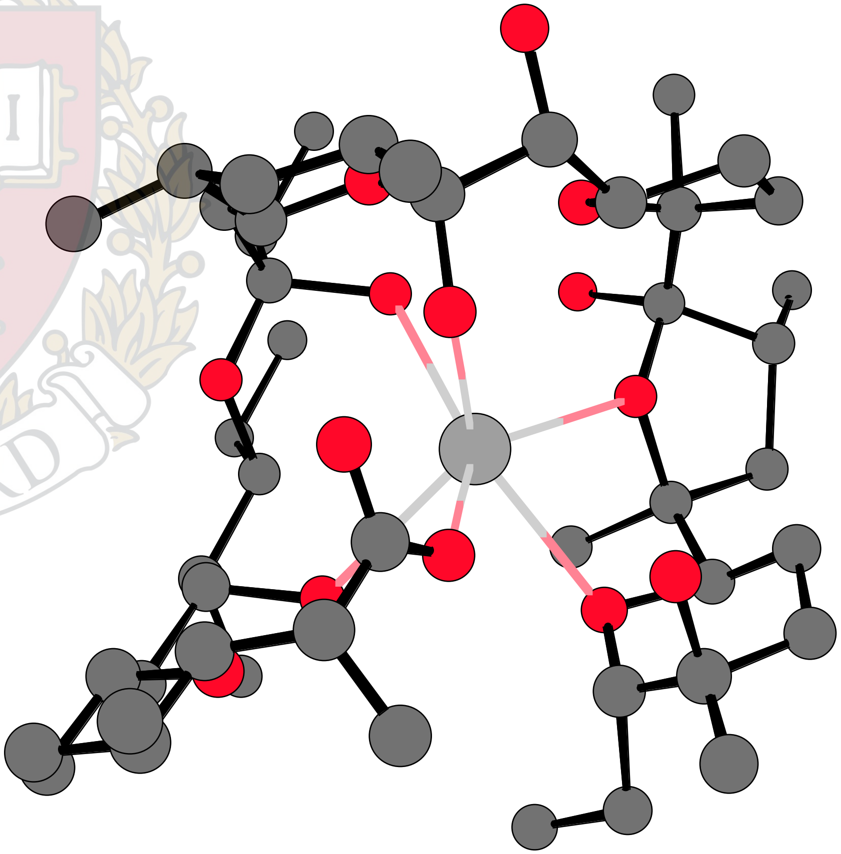




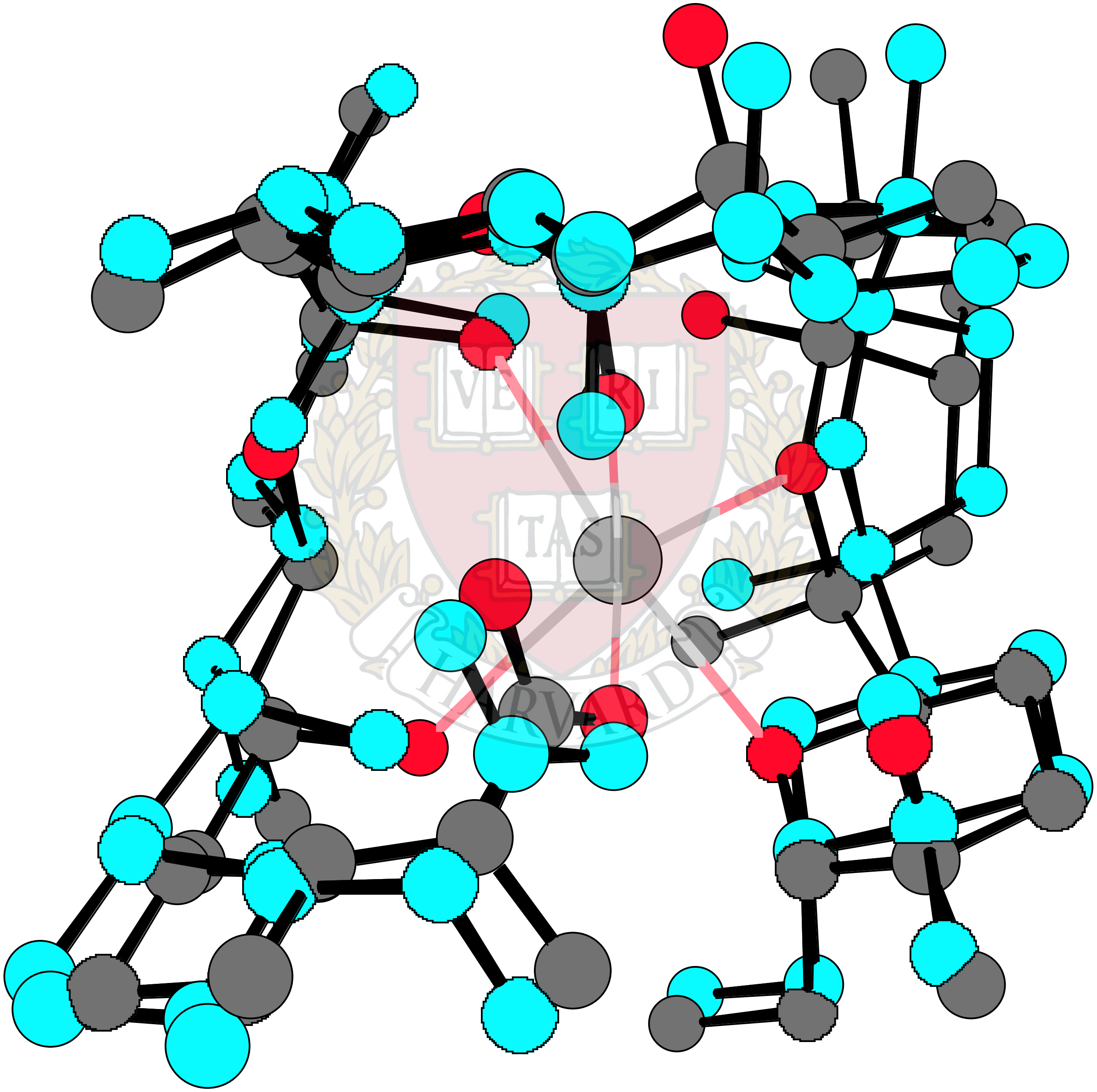
X-ray of Ionophore X-206 - Ag^+ - Complex

Metal ion ligation sites (M = Ag, K)





Conformational Analysis: Ionophore X-206/X-ray overlay



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 5

Acyclic Conformational Analysis-2

- Conformations of Simple Olefinic Substrates
- Introduction to Allylic Strain
- Introduction to Allylic Strain-2: Amides and Enolates

Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapters 2 & 3

R. W. Hoffmann, *Chem. Rev*. **1989**, *89*, 1841-1860
Allylic 1-3-Strain as a Controlling Element in Stereoselective Transformations

R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* ***2000***, *39*, 2054-2070
Conformation Design of Open-Chain Compounds

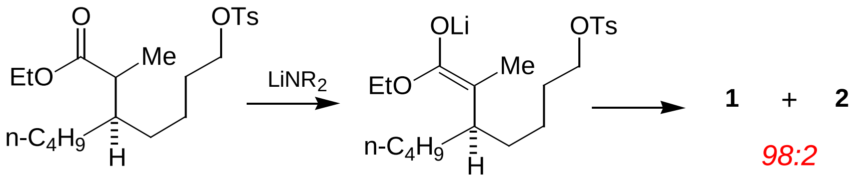
F. Weinhold, *Angew. Science* ***2001***, *411*, 539-541
"A New Twist on Molecular Shape"

Carl A. Morales

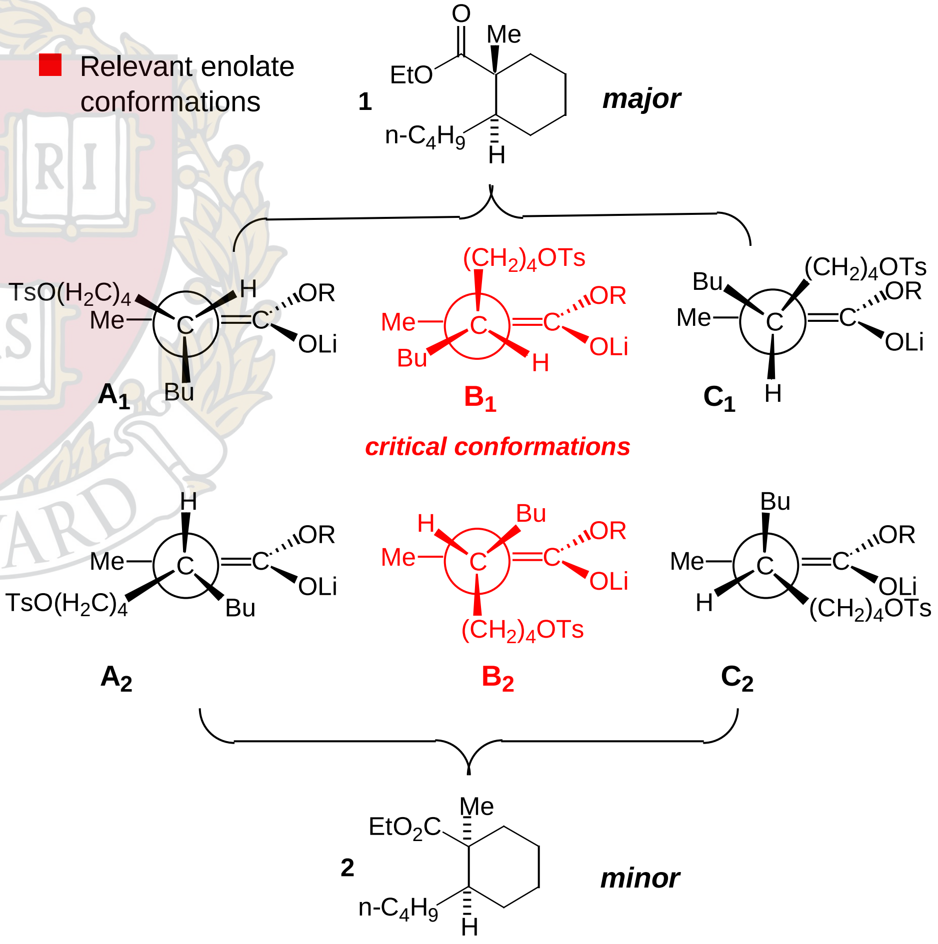
Friday,
September 27, 2002

Problems of the Day: (To be discussed)

Can you predict the stereochemical outcome of this reaction?

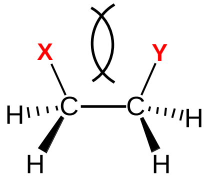


Relevant enolate conformations



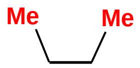
Useful Destabilizing Interactions to Remember

Hierarchy of Vicinal Eclipsing Interactions

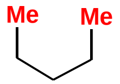


X—Y	δ E kcal mol $^{-1}$
H—H	+1.0
H—Me	+1.4
Me—Me	**+3.1**

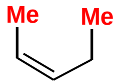
Estimates of In-Plane 1,2 & 1,3-Dimethyl Eclipsing Interactions



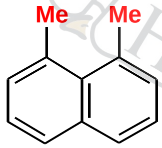
~ 3.1



~ 3.7

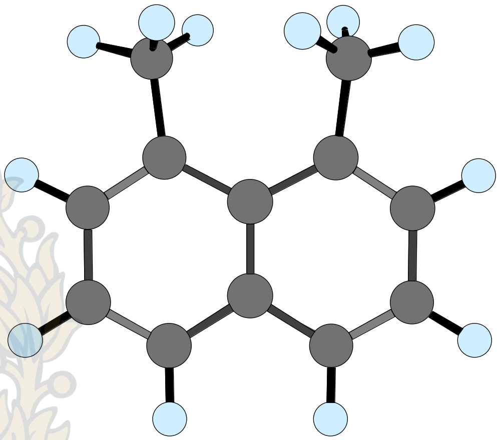


~3.9



~ 7.6

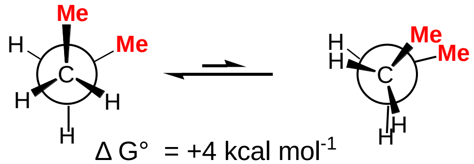
It may be concluded that in-plane 1,3(Me ↔ Me) interactions are Ca +4 kcal/mol while 1,2(Me ↔ Me) interactions are destabliizing by Ca +3 kcal/mol.



minimized structure

Simple olefins exhibit unusal conformational properties relative to their saturated counterparts

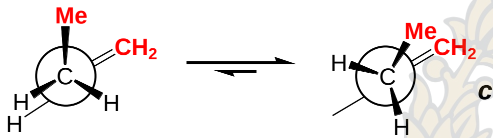
Butane versus 1-Butene



staggered conformation

eclipsed conformation

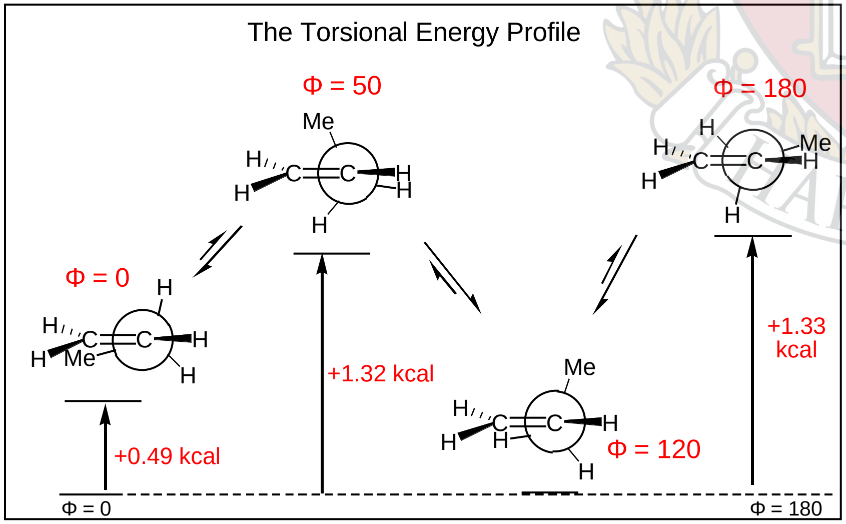
Δ G° = +4 kcal mol^{-1}



staggered conformation

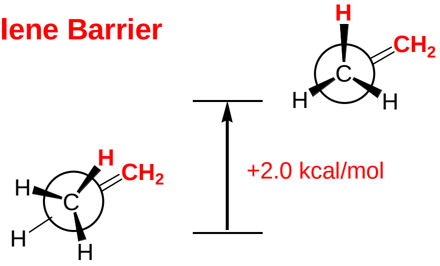
eclipsed conformation

Δ G° = –0.8.3 kcal mol^{-1}


The Torsional Energy Profile

Conforms to *ab initio* (3-21G) values:
Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985,** *107,* 5035.

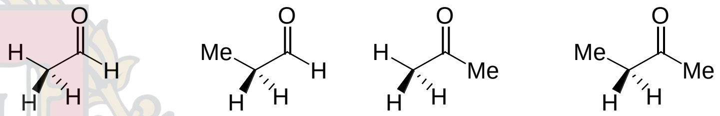
■ The Propylene Barrier



staggered conformation

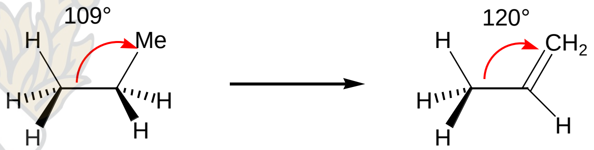
eclipsed conformation

■ Acetaldehyde exhibits a similar conformational bias



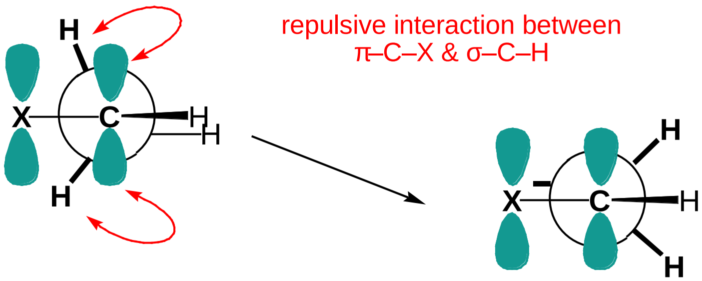
The low-energy conformation in each of above cases is eclisped

Propane versus Propene



Hybridilzation change opens up the C–C–C bond angle

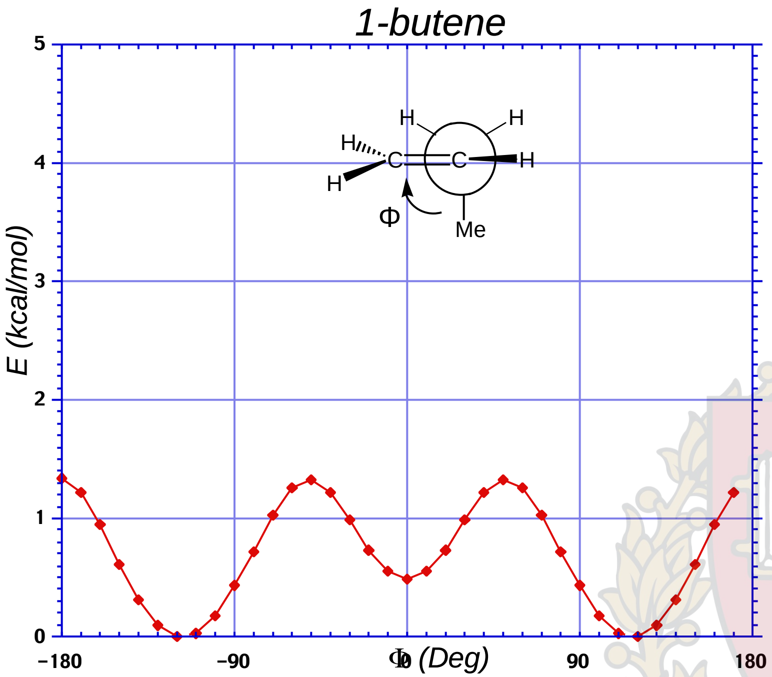
New destabilizing effect

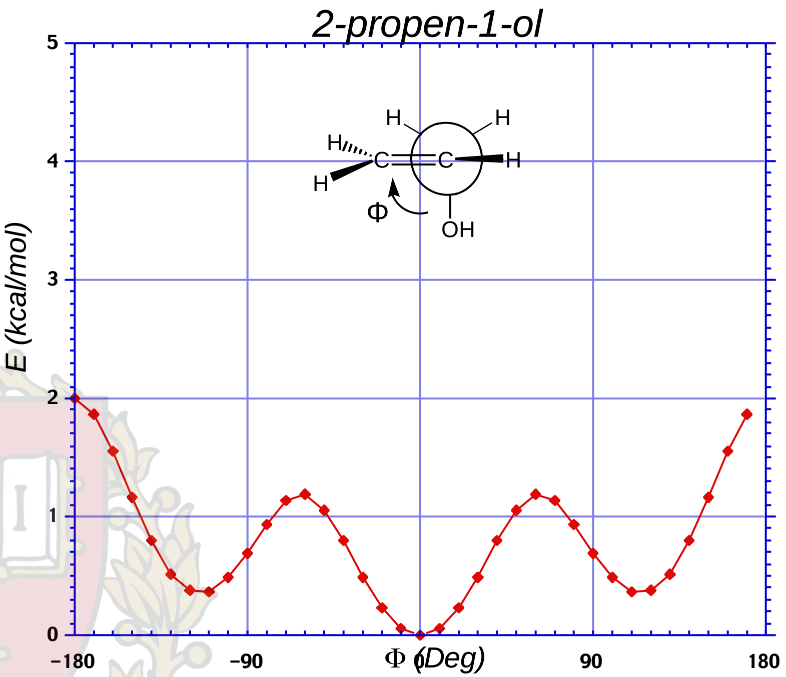


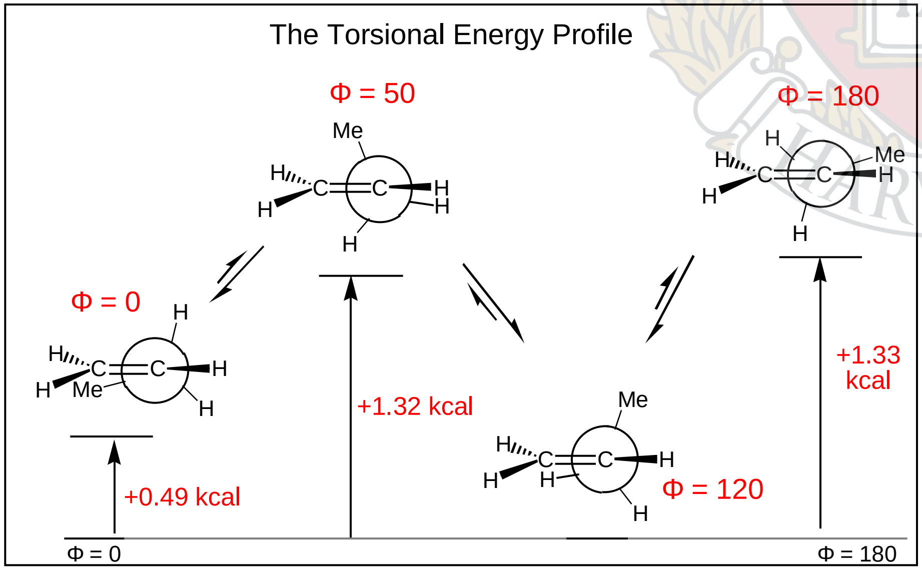
repulsive interaction between
π–C–X & σ–C–H

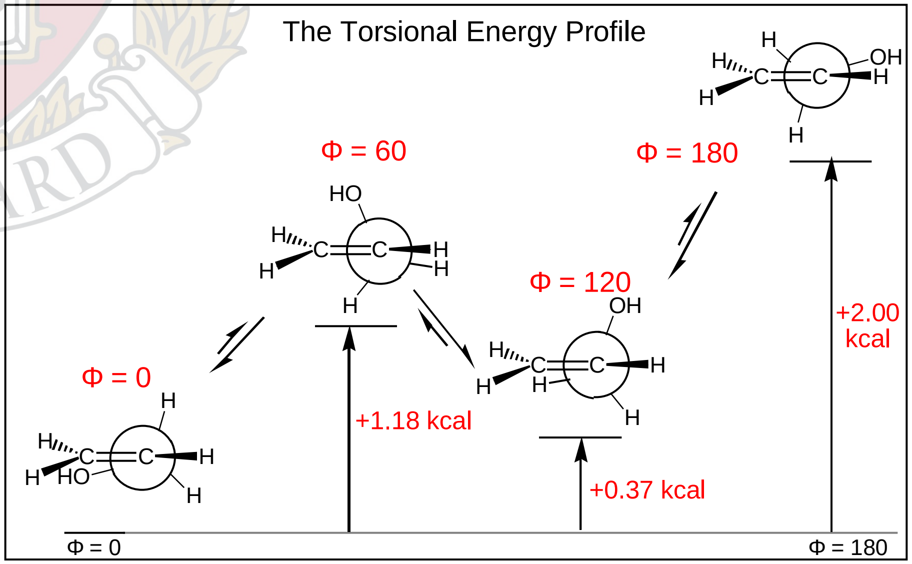
K. Wiberg, *JACS* **1985**, *107*, 5035-5041
K. Houk, *JACS* **1987**, *109*, 6591-6600

Conformational Barriers to Rotation: Olefin A-1,2 Interactions


1-butene

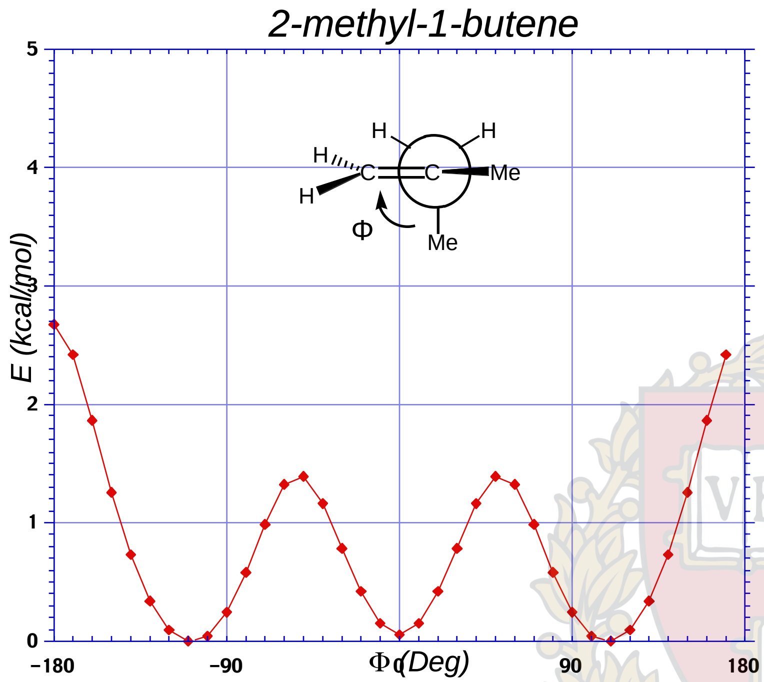

2-propen-1-ol


The Torsional Energy Profile

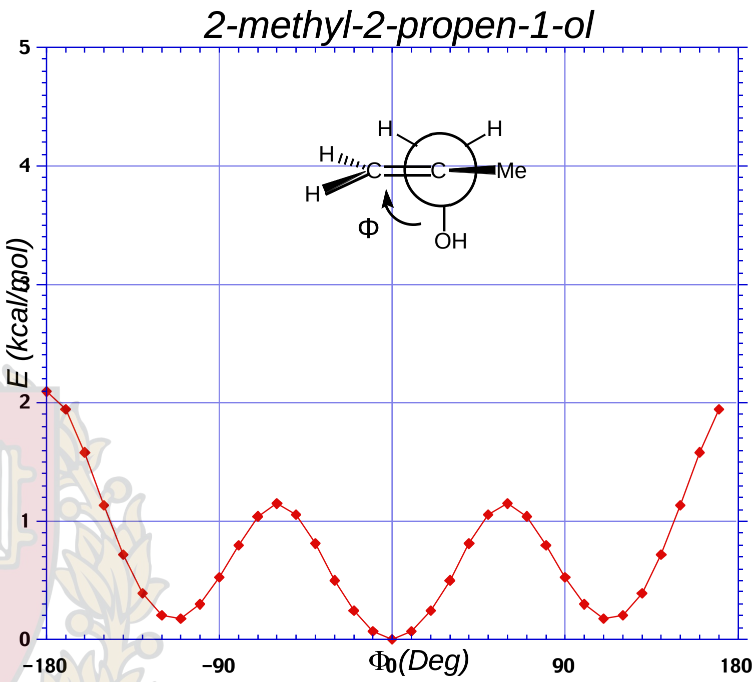

The Torsional Energy Profile

Conforms to *ab initio* (3-21G) values:
Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985,** *107,* 5035.

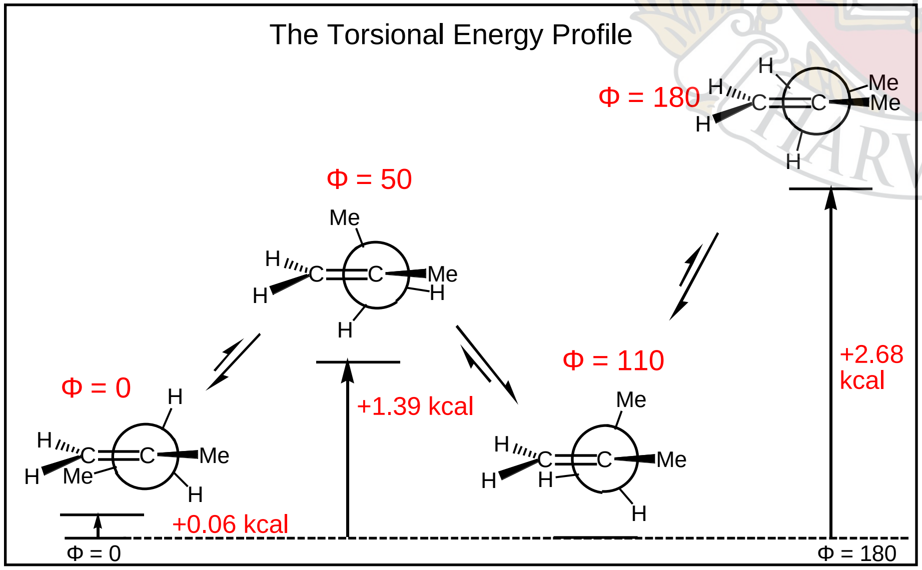
Conformational Barriers to Rotation: Olefin A-1,2 Interactions-2



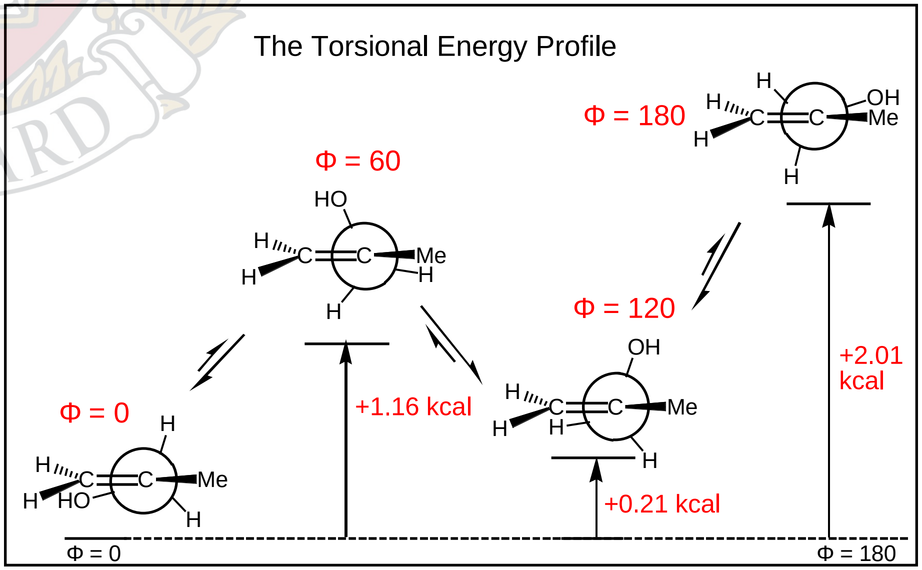
2-methyl-1-butene



2-methyl-2-propen-1-ol

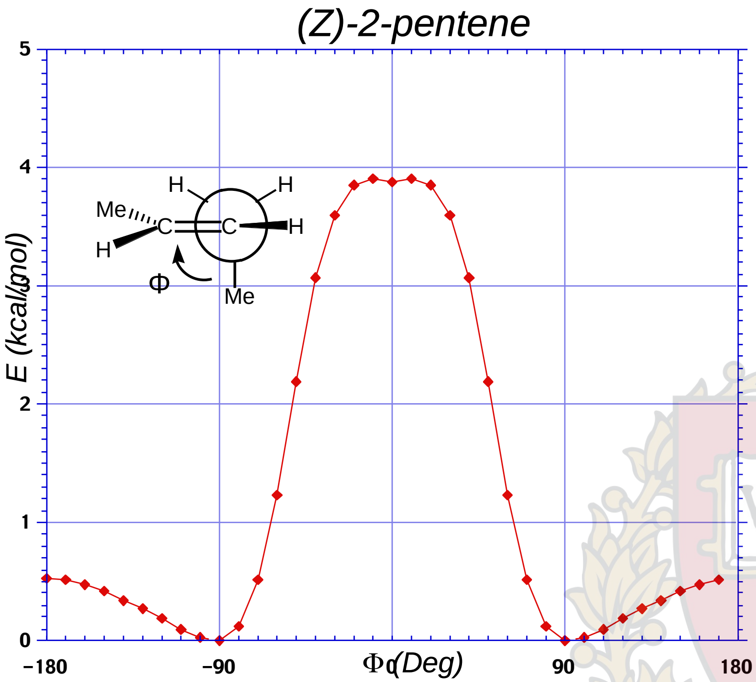


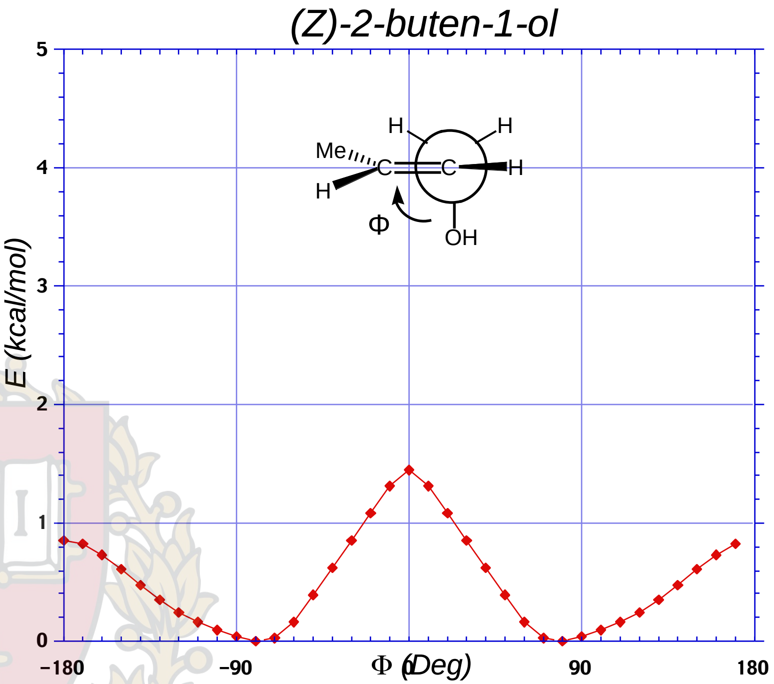
The Torsional Energy Profile

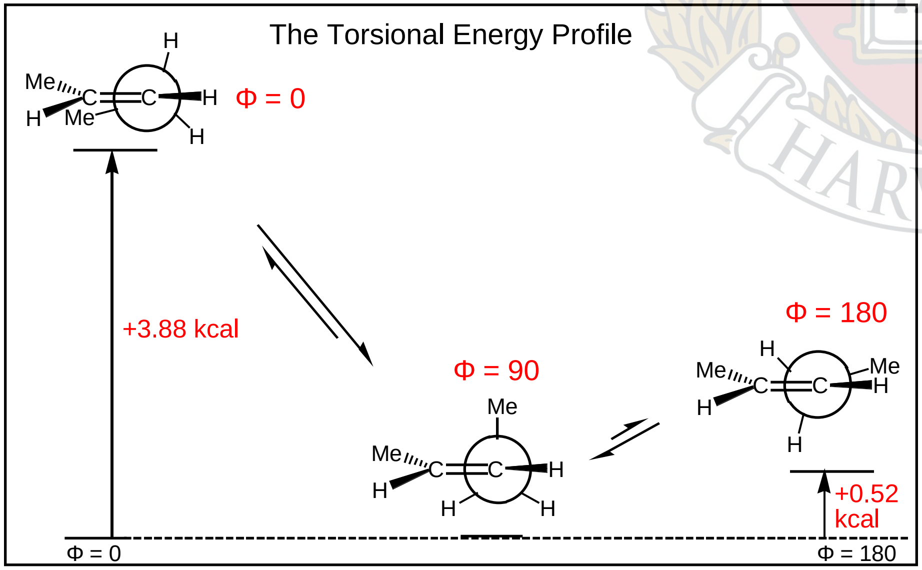


The Torsional Energy Profile

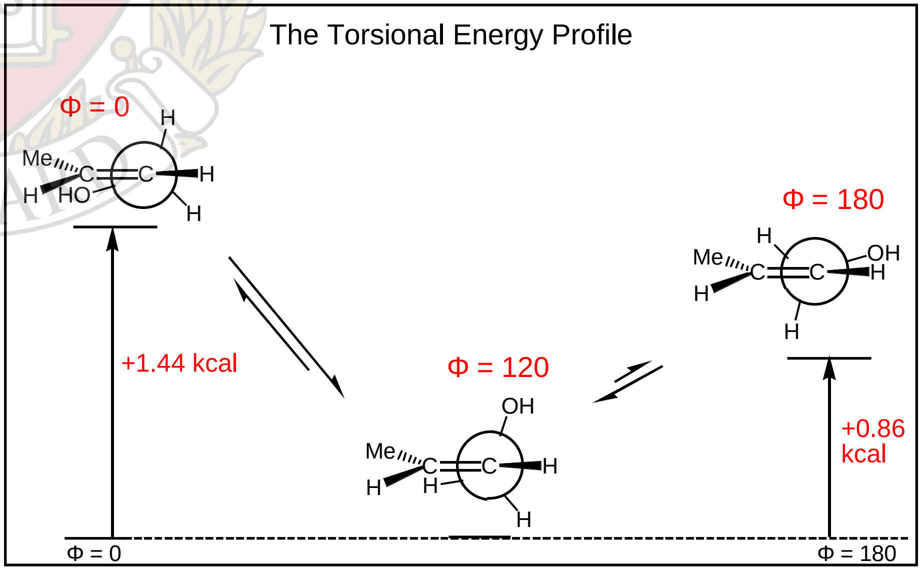
Conformational Barriers to Rotation: Olefin A-1,3 Interactions


(Z)-2-pentene


(Z)-2-buten-1-ol

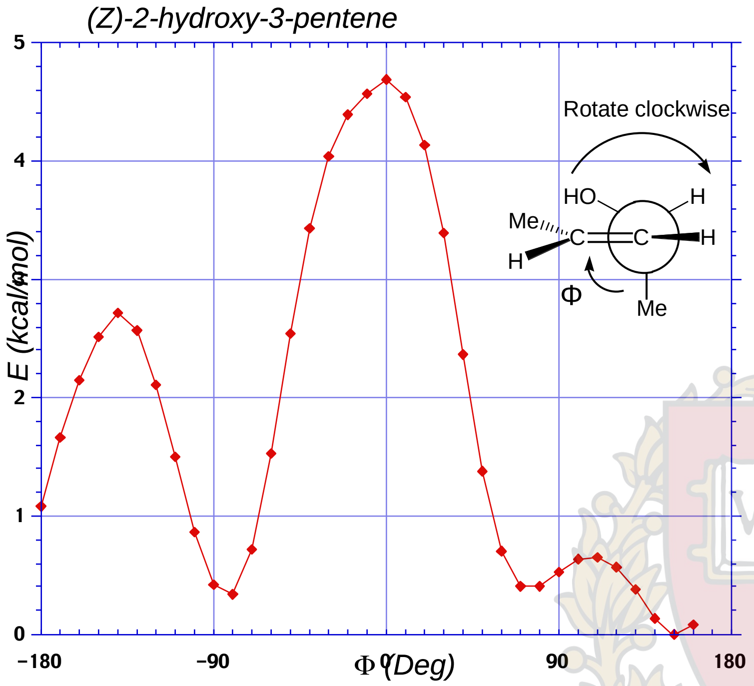

The Torsional Energy Profile

Values calculated using MM2 (molecular mechanics) force fields via the Macromodel multiconformation search.

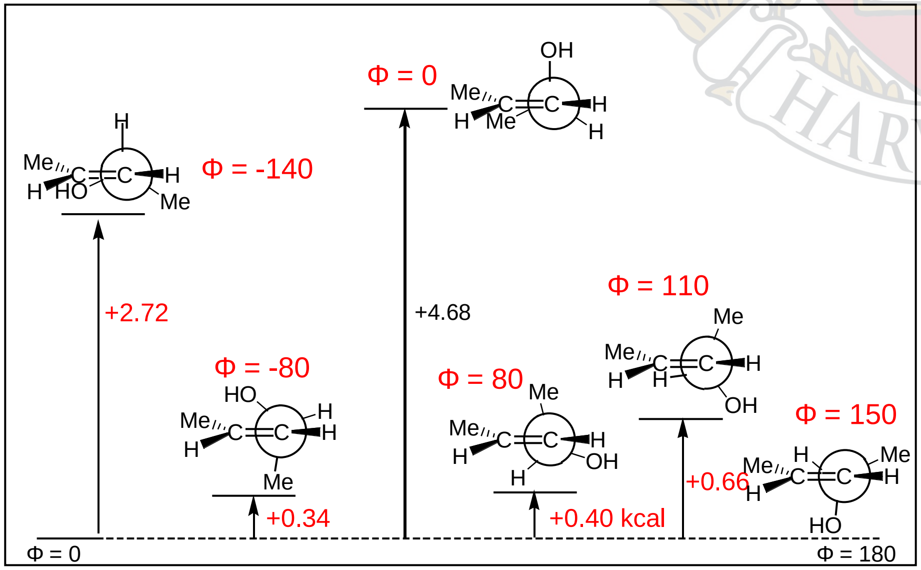

The Torsional Energy Profile

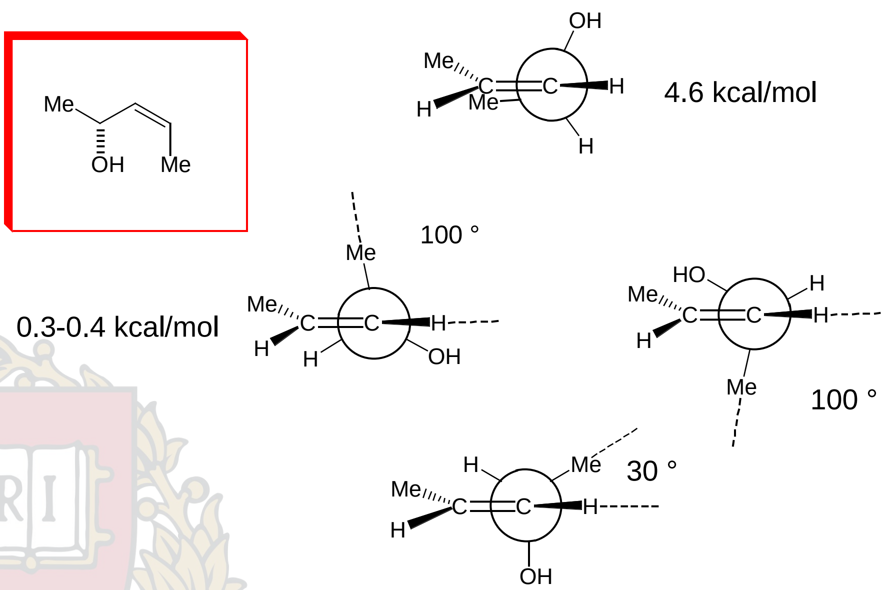
Review: Hoffman, R. W. *Chem. Rev.* **1989,** *89,* 1841.

Conformational Barriers to Rotation: Olefin A-1,3 Interactions-2

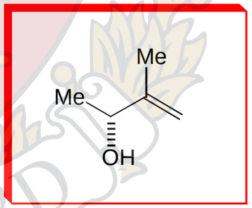


The Torsional Energy Profile

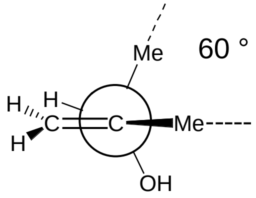




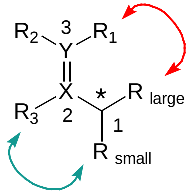
Lowest energy conformer



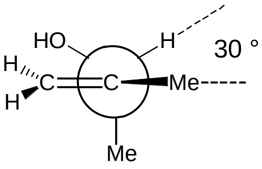
2.7 kcal/mol



A(1,3) interaction 4.0 kcal/mol

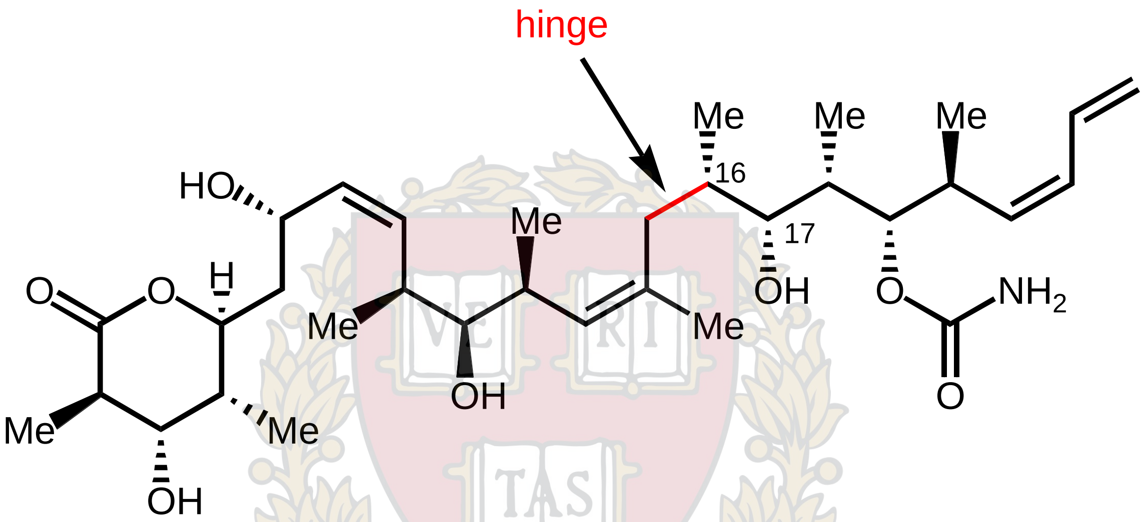


A(1,2) interaction 2.7 kcal/mol (MM2)



Lowest energy conformer

Discodermolide



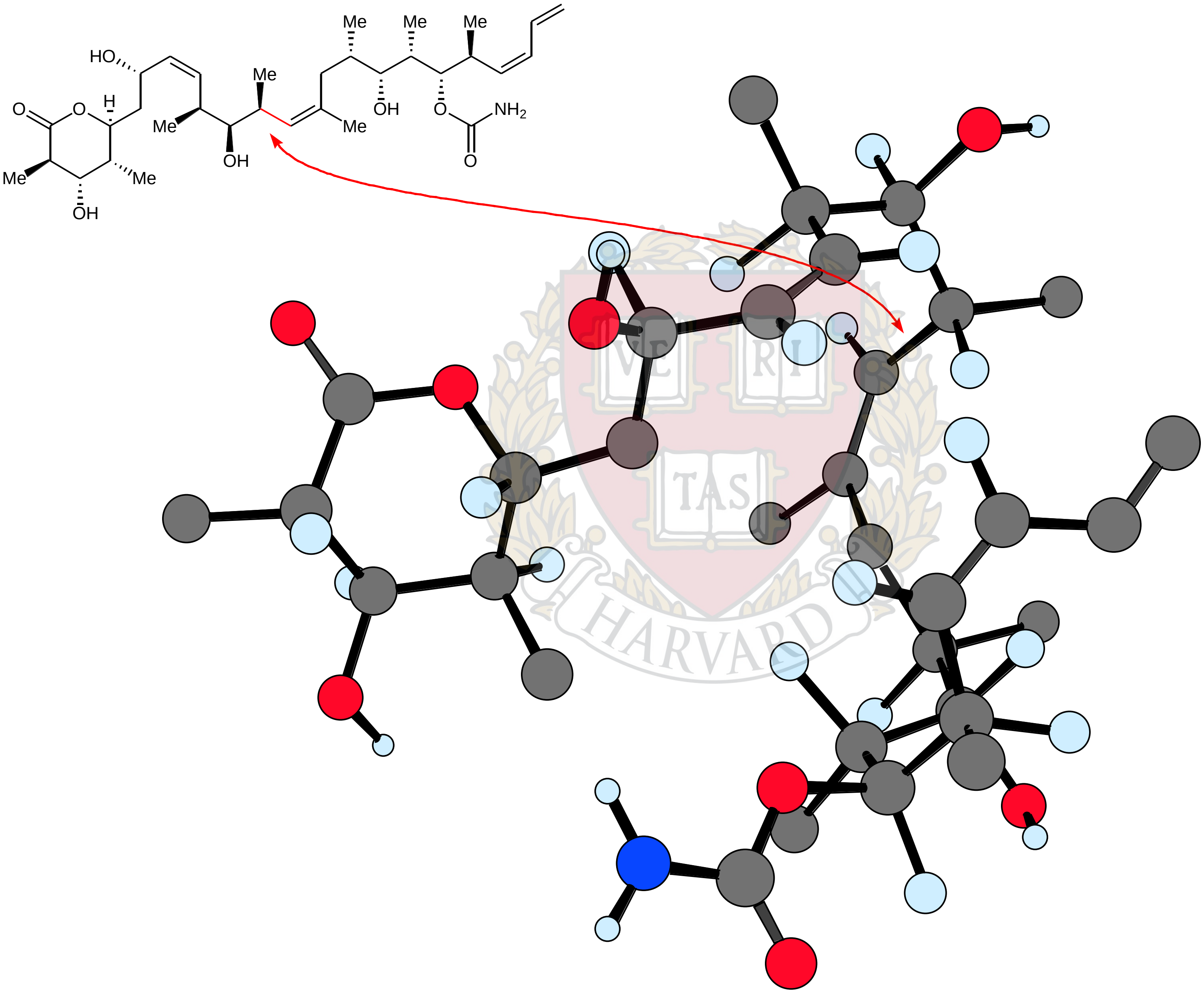
- immunosuppressive activity
- potent microtubule-stabilizing agent
(antitumor activity similar to that of taxol)

The epimers at C16 and C17 have no or almost no biological activity.

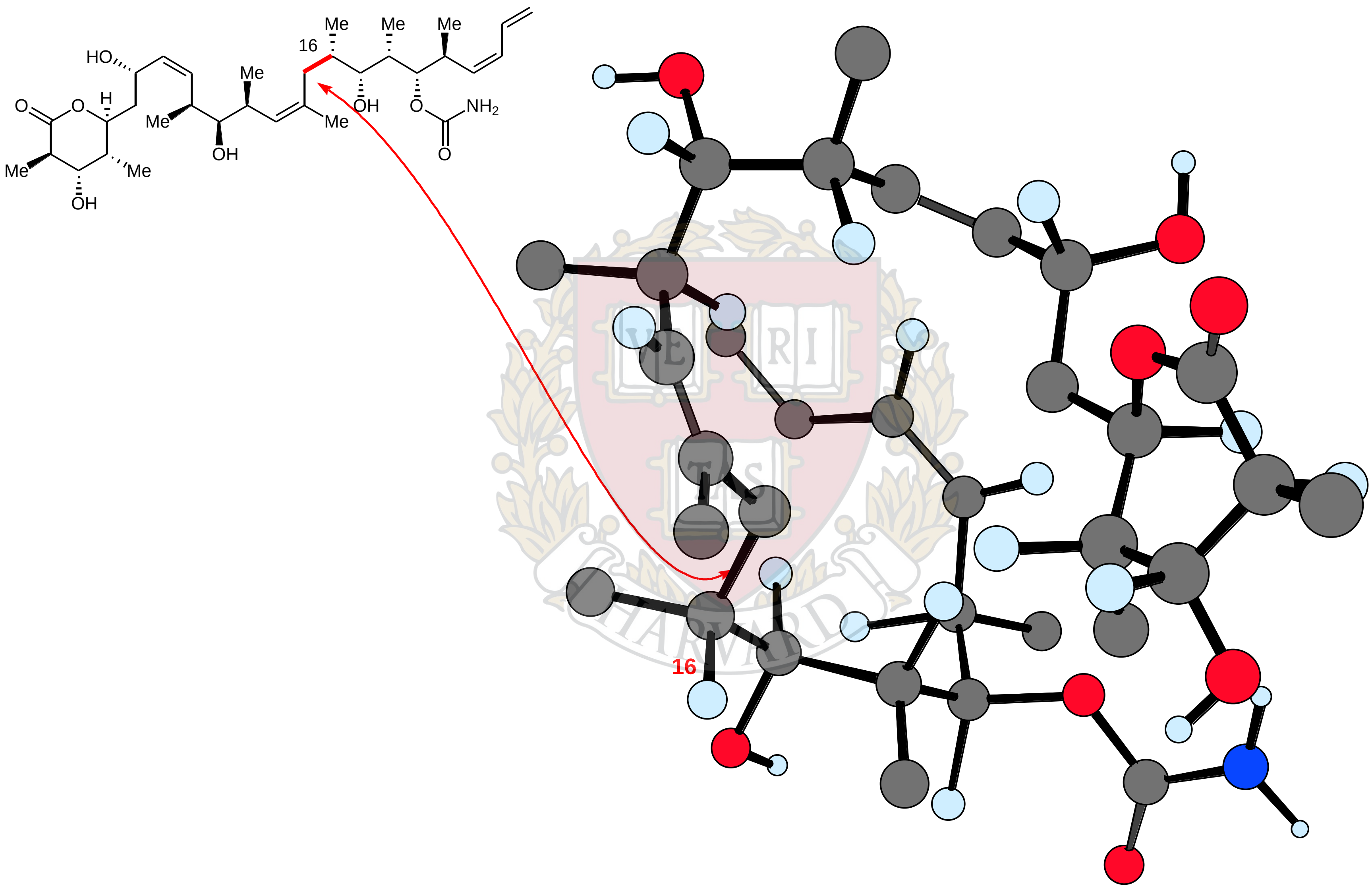
The conformation about C16 and C17 is critical to discodermolide's biological activity.

S. L. Schreiber et al. *JACS* **1996**, *118*, 11061.

Conformational Analysis - Discodermolide X-ray 1

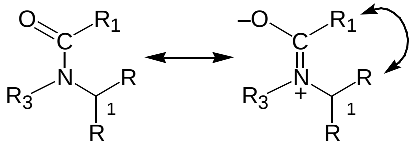


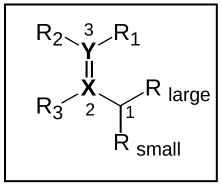
Conformational Analysis - Discodermolide X-ray 2



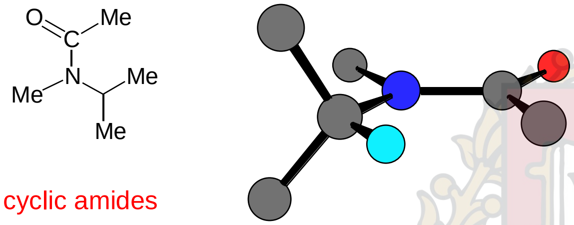
Allylic Strain & Amide Conformation

Consider the resonance structures of an amide:

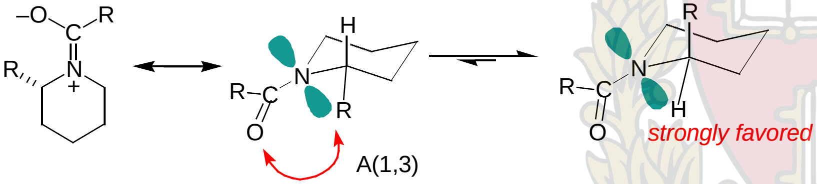




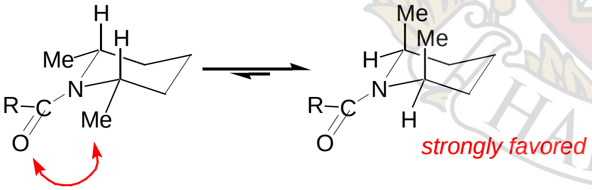
A(1,3) interactions between the "allylic substituent" and the R1 moiety will strongly influence the torsion angle between N & C1.

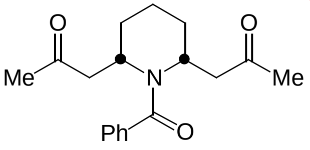


conformations of cyclic amides



Chow
Can. J. Chem. **1968**, *46*, 2821



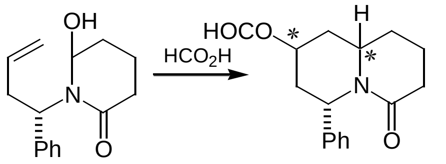


published X-ray structure of this amide shows chair diaxial conformation

Quick, *J. Org. Chem.* **1978**, *43*, 2705

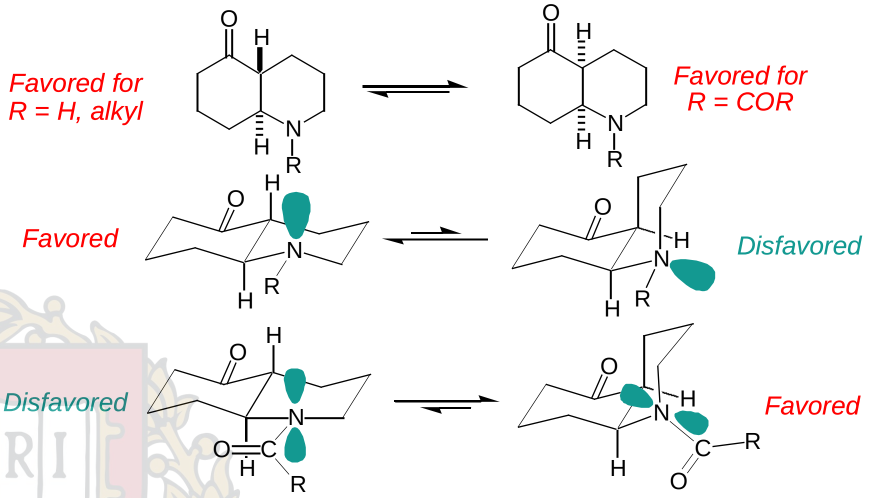
Problem: Predict the stereochemical outcome of this cyclization.

D. Hart, *JACS* **1980**, *102*, 397

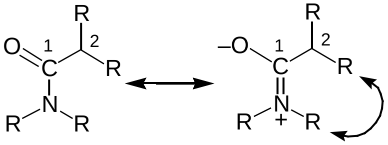


diastereoselection >95%

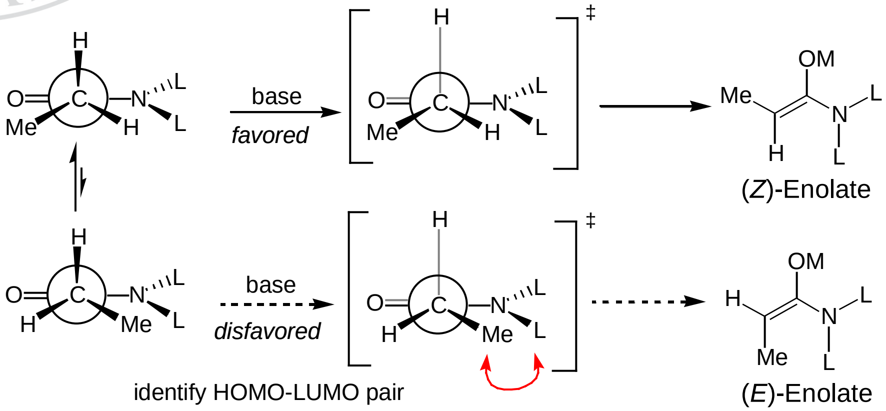
The selection of amide protecting group may be done with the knowledge that altered conformational preferences may result:



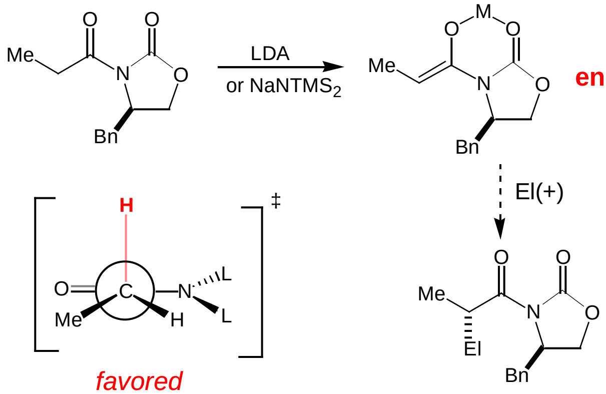
A(1,3) interaction between the C2 & amide substituents will strongly influence the torsion angle between C1 & C2.



As a result, amides afford (Z) enolates under all conditions



A(1,3) Strain and Chiral Enolate Design

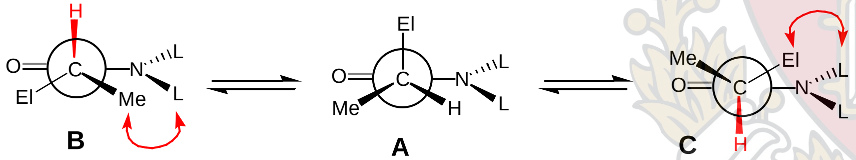


enolization selectivity >100:1

JACS. **1982**,*104*, 1737.

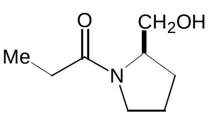
favored enolization geometry

- In the enolate alkylation process product epimerization is a serious problem. Allylic strain suppresses product enolization through the intervention of allylic strain

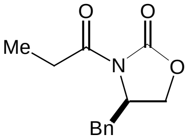


While conformers **B** and **C** meet the stereoelectronic requirement for enolization, they are much higher in energy than conformer **A**. Further, as deprotonation is initiated, A(1,3) destabilization contributes significantly to reducing the kinetic acidity of the system

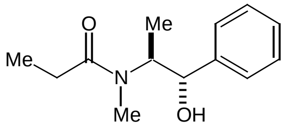
These allylic strain attributes are an integral part of the design criteria of chiral amide and imide-based enolate systems



Evans
Tetr Lett. **1977**, *29*, 2495

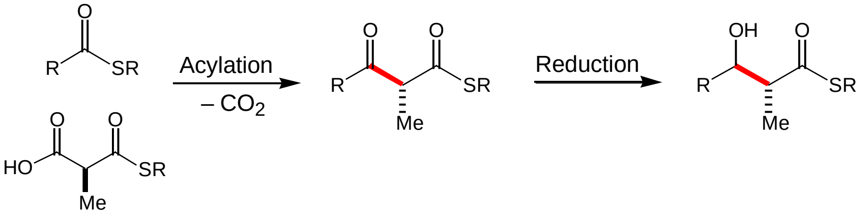


Evans
JACS **1982**,*104*, 1737.

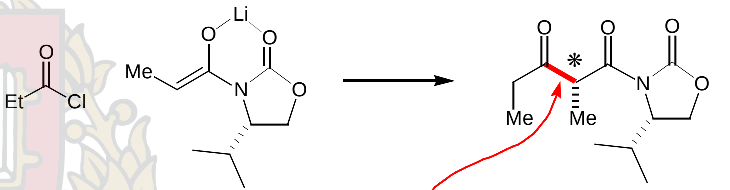


Myers
JACS **1997**, *119*, 6496

Polypropionate Biosynthesis: The Acylation Event



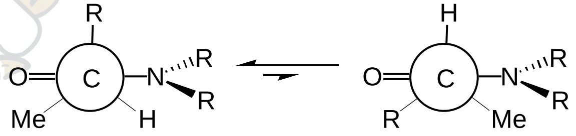
First laboratory analogue of the acylation event



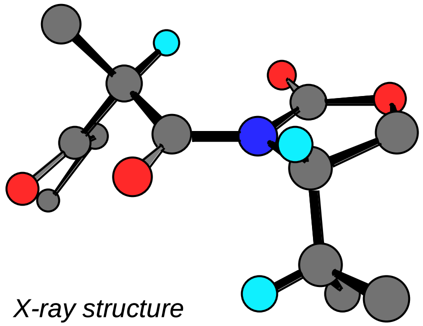
*with M. Ennis JACS **1984**, 106, 1154.*

Diastereoselection ~ 97 : 3

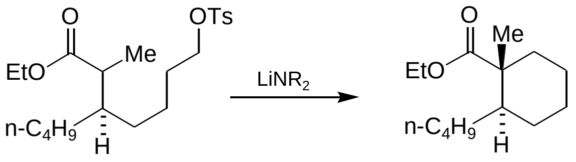
Why does'nt the acylation product rapidy epimerize at the exocyclic stereocenter??



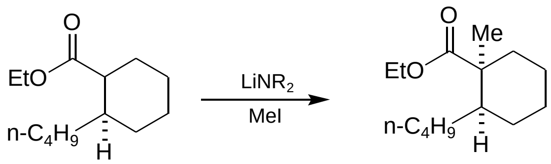
favored



X-ray structure

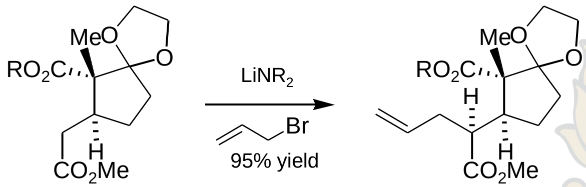


diastereoselection 98:2



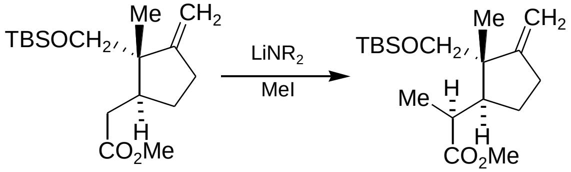
diastereoselection 89:11

D. Kim & Co-workers, *Tetrahedron Lett*. **1986**, *27*, 943.



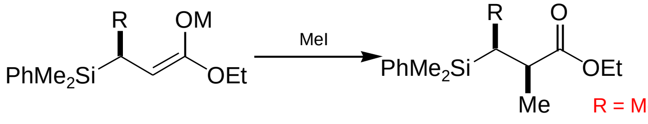
"one isomer"

G. Stork & Co-workers, *Tetrahedron Lett*. **1987**, *28*, 2088.



"one isomer"

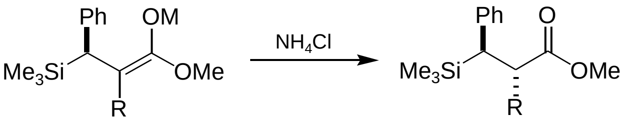
T. Money & Co-workers, *Chem. Commun*. **1986**, 288.



R = Me: *diastereoselection 99:1*

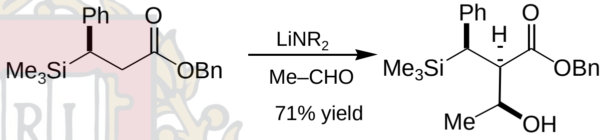
R = Ph: *diastereoselection 97:3*

I. Fleming & Co-workers, *Chem. Commun*. **1984**, 28.



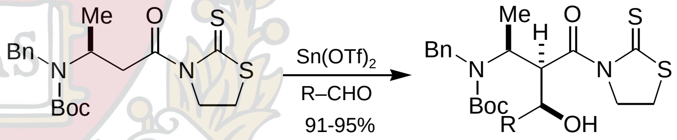
R-substituent	*diastereoselection*
R = Me	87:13
R = Et	80:20
R = $CHMe_2$	40:60　major diastereomer opposite to that shown

I. Fleming & Co-workers, *Chem. Commun*. **1985**, 318.
Y. Yamamoto & Co-workers, *Chem. Commun*. **1984**, 904.



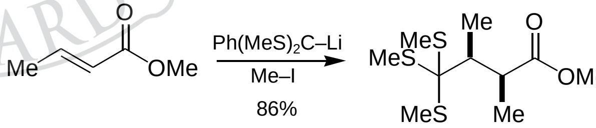
diastereoselection 90:10 at C_3
one isomer at C_2

I. Fleming & Co-workers, *Chem. Commun*. **1986**, 1198.



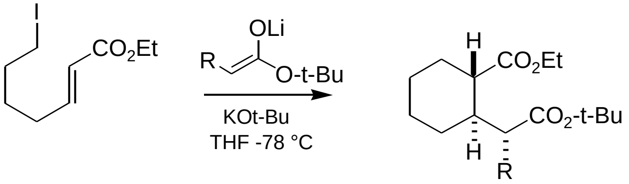
diastereoselection >95%

T. Mukaiyama & Co-workers, *Chem. Letters* **1986**, 637



diastereoselection 99:1

K. Koga & Co-workers, *Tetrahedron Letters* **1985**, *26*, 3031.



R = H: one isomer
R = Me: > 15 :1

Y. Yamaguchi & Co-workers, *Tetrahedron Letters* **1985**, *26*,1723.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 6

Conformational Analysis-3

- Cyclopropane
- Conformational Analysis of $C_4 \rightarrow C_8$ Rings

Reading Assignment for week

A. Carey & Sundberg: **Part A**; Chapter 3

de Meijere, "Bonding Properties of Cyclopropane & their Chemical Characteristics"
Angew Chem. Int. Ed. **1979**, *18*, 809-826 (handout)

Snyder, J. P. *JACS*, **2000**, *122*, 544.

Matthew D. Shair

Monday,
September 30, 2002

Conformational Analysis of Cyclic Systems

Three Types of Strain:

Prelog Strain: van der Waals interactions

Baeyer Strain: bond angle distortion away from the ideal

Pitzer Strain: torsional rotation about a sigma bond

Baeyer Strain for selected ring sizes

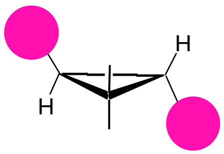
size of ring	Ht of Combustion (kcal/mol)	Total Strain (kcal/mol)	Strain per CH_2 (kcal.mol)	"angle strain" deviation from 109°28'
3	499.8	27.5	9.17	24°44'
4	656.1	26.3	6.58	9°44'
5	793.5	6.2	1.24	0°44'
6	944.8	0.1	0.02	-5°16'
7	1108.3	6.2	0.89	
8	1269.2	9.7	1.21	
9	1429.6	12.6	1.40	
10	1586.8	12.4	1.24	
11	1743.1	11.3	1.02	
12	1893.4	4.1	0.34	
13	2051.9	5.2	0.40	
14	2206.1	1.9	0.14	
15	2363.5	1.9	0.13	

Eliel, E. L., Wilen, S. H. *Stereochemistry of Organic Compounds*
Chapter 11, John Wiley & Sons, 1994.

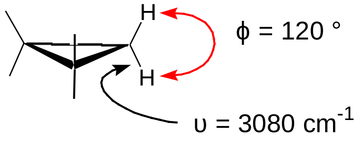
- Baeyer "angle strain" is calculated from the deviation of the *planar* bond angles from the ideal tetrahedral bond angle.
- Discrepancies between calculated strain/CH_2 and the "angle strain" results from puckering to minimize van der Waals or eclipsing torsional strain between vicinal hydrogens.
- Why is there an increase in strain for medium sized rings even though they also can access puckered conformations free of angle strain? The answer is *transannular strain*- van der Waals interactions between hydrogens across the ring.

Cyclopropane: Bonding, Conformation, Carbonium Ion Stabilization

Cyclopropane



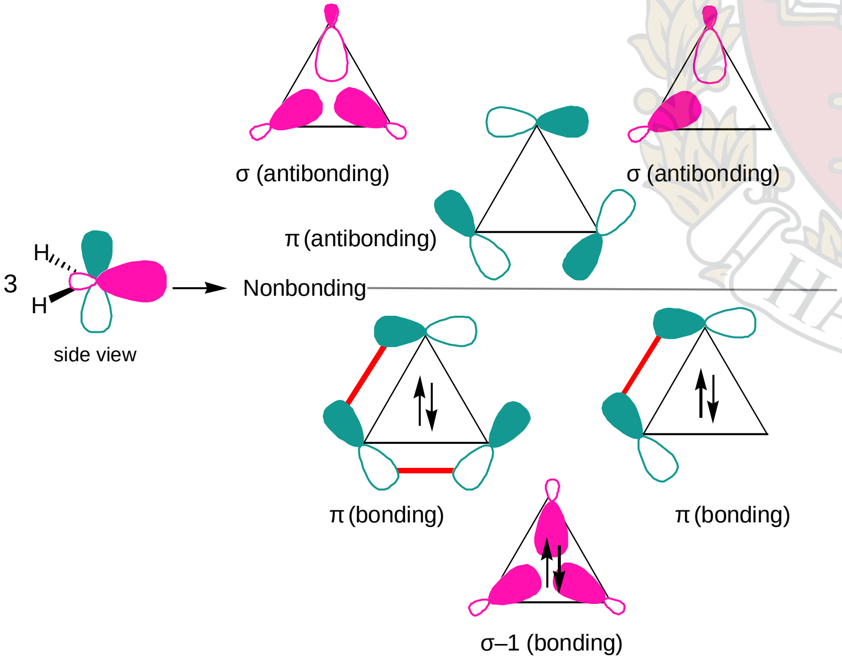
- ■ Necessarily *planar*.
- ■ Subtituents are therefore eclipsed.
- ■ Disubstitution prefers to be *trans.*



- ■ Almost sp^2, not sp^3

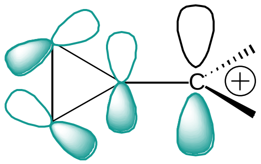
Walsh Model for Strained Rings:

- ■ Rather than σ and σ* c-c bonds, cyclopropane has sp^2 and p-type orbitals instead.

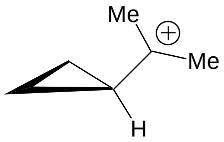


de Meijere, "Bonding Properties of Cyclopropane & their Chemical Characteristics"
Angew Chem. Int. Ed. **1979**, *18*, 809-826 (handout)

Carbocation Stabilization via Cyclopropylgroups

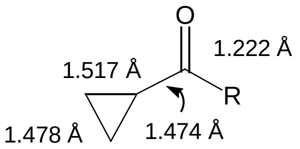


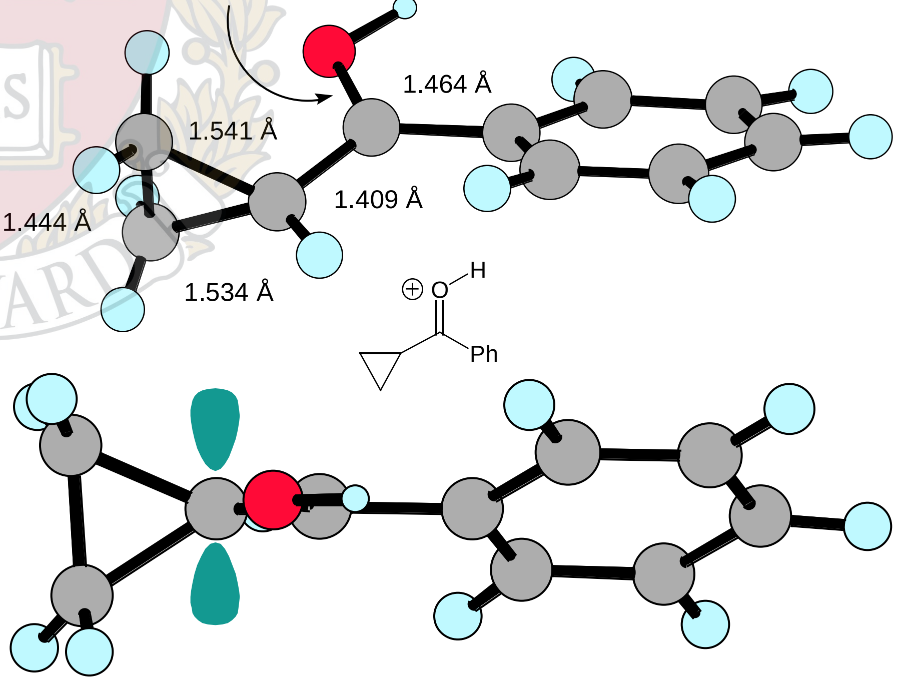
A rotational barrier of about 13.7 kcal/mol is observed in following example:



NMR in super acids
δ(CH_3) = 2.6 and 3.2 ppm

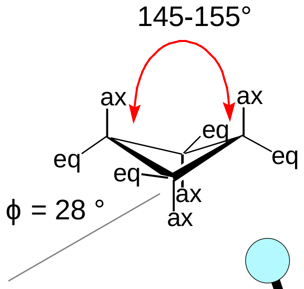
X-ray Structures support this orientation



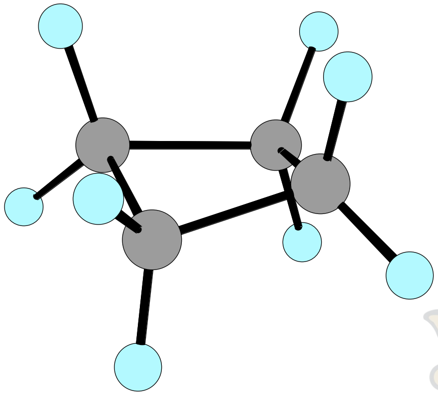


R. F. Childs, *JACS* **1986**, *108*, 1692

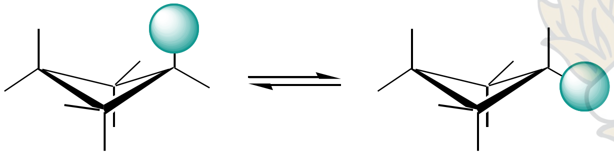
Cyclobutane



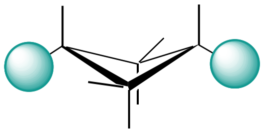
- Eclipsing torsional strain overrides increased bond angle strain by puckering.
- Ring barrier to inversion is 1.45 kcal/mol.



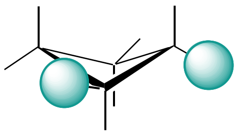
(MM2)



- **ΔG = 1 kcal/mol favoring R = Me equatorial**

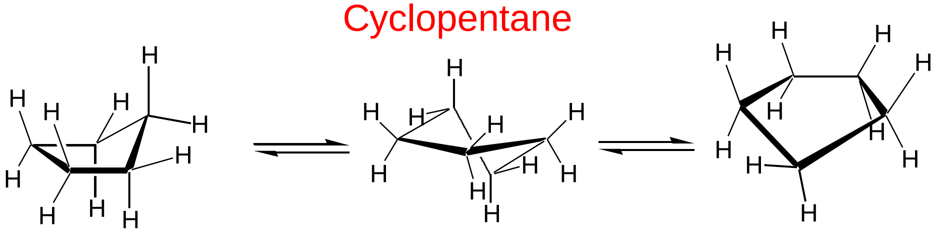


- 1,3 Disubstitution prefers *cis* diequatorial to *trans* by 0.58 kcal/mol for di-bromo cmpd.



- 1,2 Disubstitution prefers *trans* diequatorial to *cis* by 1.3 kcal/mol for diacid (roughly equivalent to the cyclohexyl analogue.)

Cyclopentane

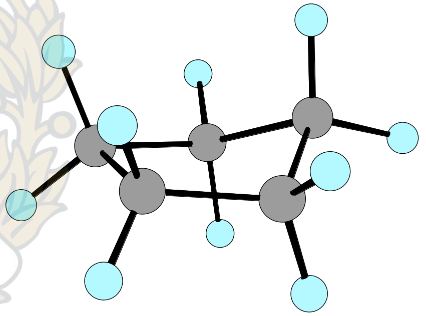


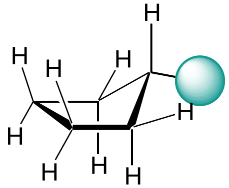
C$_s$ Envelope   C$_2$ Half-Chair   C$_s$ Envelope

- Two lowest energy conformations (10 envelope and 10 half chair conformations C$_s$ favored by only 0.5 kcal/mol) in rapid conformational flux (pseudorotation) which causes the molecule to appear to have a single out-of-plane atom "bulge" which rotates about the ring.
- Since there is no "natural" conformation of cyclopentane, the ring conforms to minimize interactions of any substituents present.

C$_s$ Envelope

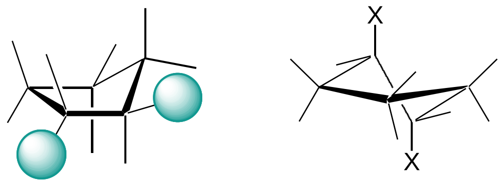
(MM2)

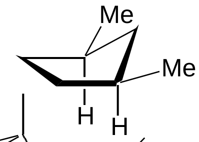




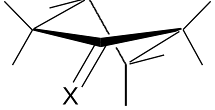
- A single substituent prefers the equatorial position of the flap of the envelope (barrier ca. 3.4 kcal/mol, R = CH$_3$).

- 1,2 Disubstitution prefers *trans* for steric/torsional reasons (alkyl groups) and dipole reasons (polar groups).





- 1,3 Disubstitution: **Cis**-1,3-dimethyl cyclopentane 0.5 kcal/mol **more stable** than trans.

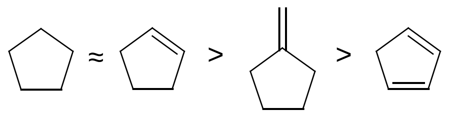


- A carbonyl or methylene prefers the planar position of the half-chair (barrier 1.15 kcal/mol for cyclopentanone).

Conformational Analysis: Cyclic Systems-3

Methylenecyclopentane and Cyclopentene

Strain trends:

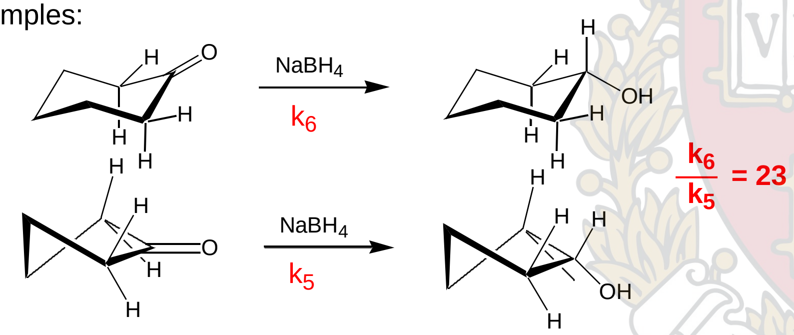


- ■ Decrease in eclipsing strain more than compensates for the increase in angle strain.

Relative to cyclohexane derivatives, those of cyclopentane prefer an sp^2 center in the ring to minimize eclipsing interactions.

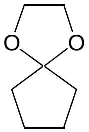
"Reactions will proceed in such a manner as to favor the formation or retention of an exo double bond in the 5-ring and to avoid the formation or retention of the exo double bond in the 6-ring systems." Brown, H. C., Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467.

Examples:

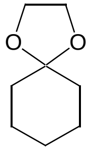


$\frac{k_6}{k_5} = 23$

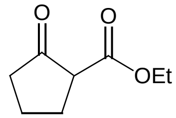
Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221.



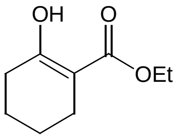
hydrolyzes
13 times faster than



Conan, J-Y.; Natat, A.; Priolet, D. *Bull. Soc. Chim., Fr.* **1976**, 1935.



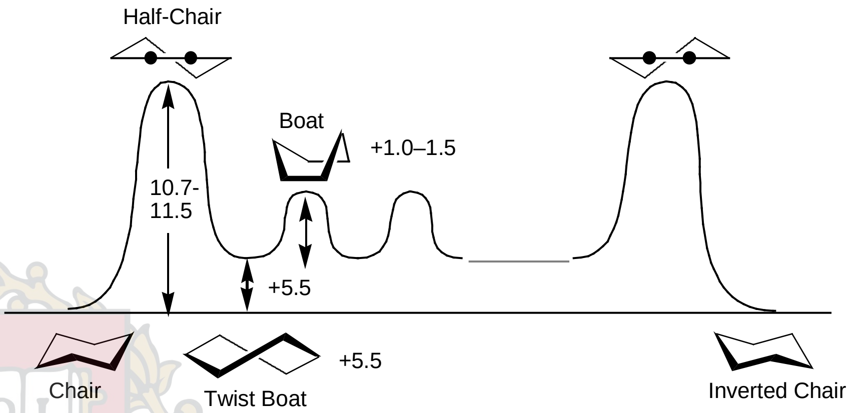
95.5:4.5 keto:enol

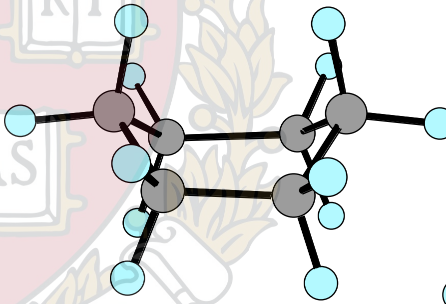


76:24 enol:keto

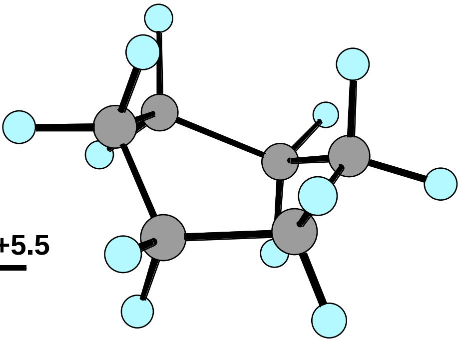
Brown, H. C., Brewster, J. H.; Shechter, H. *JACS* **1954**, *76*, 467.

Cyclohexane Energy Profile (kcal/mol)



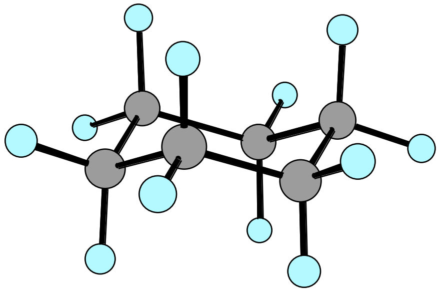


ΔE = +6.5-7.0



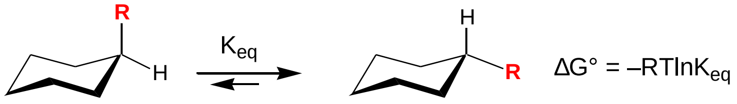
ΔE = +5.5

The barrier: +10.7-11.5

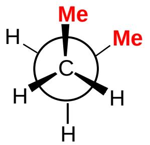


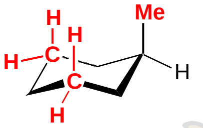
E = 0

Monosubstituted Cyclohexanes: *A* Values



- Me - axial has **2 gauche butane interactions** more than Me-equatorial.
  Expected destabilization: ≈ 2(0.88) kcal/mol = ~1.8 kcal/mol;
  Observed: 1.74 kcal/mol





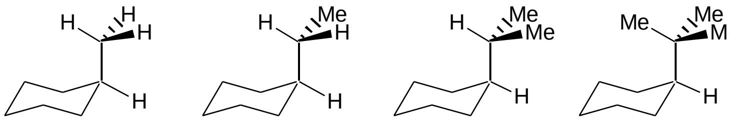
- The *A*– Value, or -ΔG°, is the preference of the substituent for the equatorial position.

Table 3.6. Conformational Free Energies ($-\Delta G^\circ$) for Substituent Groups

Substituent	$-\Delta G^\circ$ (kcal/mol)	Ref.
$-F$	0.24–0.28	a
$-Cl$	0.53	a
$-Br$	0.48	a
$-I$	0.47	a
$-CH_3$	1.8	b
$-CH_2CH_3$	1.8	b
$-CH(CH_3)_2$	2.1	b
$-C(CH_3)_3$	>4.5	c
$-CH{=}CH_2$	1.7	d
$-C{\equiv}CH$	0.5	e
$-C_6H_5$	2.9	d
$-CN$	0.15–0.25	a
$-O_2CCH_3$	0.71	a
$-CO_2H$	1.35	c
$-CO_2C_2H_5$	1.1–1.2	c
$-OH$ (aprotic solvents)	0.52	c
$-OH$ (protic solvents)	0.87	c
$-OCH_3$	0.60	c
$-NO_2$	1.16	a
$-HgBr$	0	a

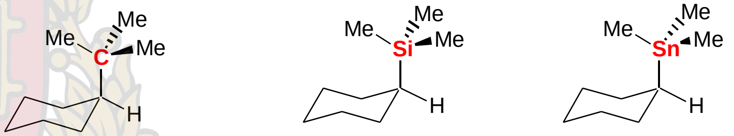
a. F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.* **3**, 140 (1971).
b. N. L. Allinger and L. A. Freiberg, *J. Org. Chem.* **31**, 804 (1966).
c. J. A. Hirsch, *Top Stereochem.* **1**, 199 (1967).
d. E. L. Eliel and M. Manoharan, *J. Org. Chem.* **46**, 1959 (1981).
e. H. J. Schneider and V. Hoppen, *J. Org. Chem.* **43**, 3866 (1978).

A Values depend on the *relative size* of the particular substituent.



A–Value 1.74 1.80 2.15 5.0

The "relative size" of a substituent and the associated A-value may not correlate. For example, consider the –CMe $_3$ and –SiMe $_3$ substituents. While the –SiMe $_3$ substituent has a larger covalent radius, is has a smaller A-value:

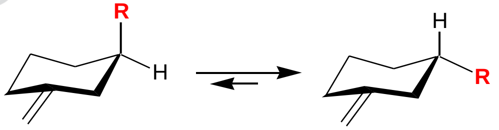


A–Value 4.5-5.0 2.5 1.1

Can you explain these observations?

- The impact of double bonds on A-values:

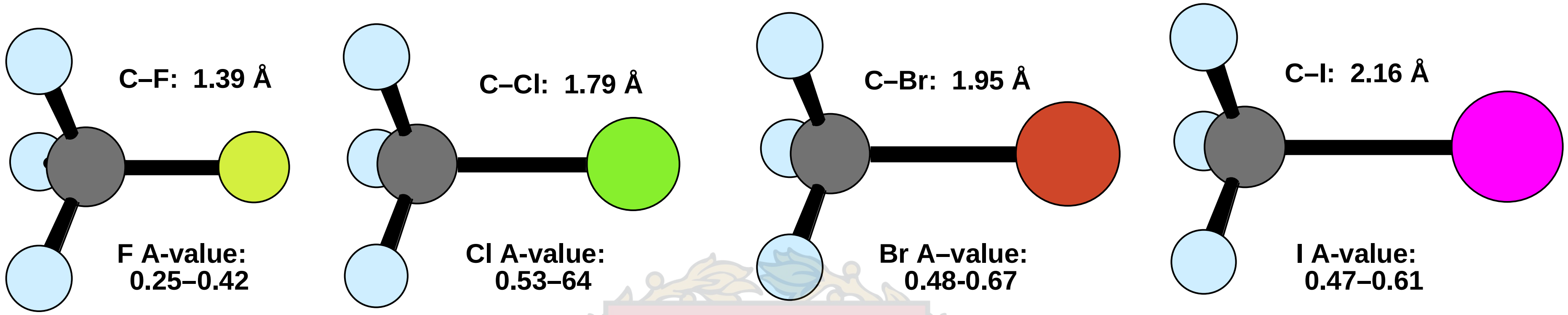
Lambert, *Accts. Chem. Res.* **1987**, *20*, 454



substituent	–ΔG°	A-value (cyclohexane)
R = Me	0.8	1.74
R = OMe	0.8	0.6
R = OAc	0.6	0.71

The Me substituent appears to respond strictly to the decrease in nonbonding interactions in axial conformer. With the more polar substituents, electrostatic effects due to the trigonal ring carbon offset the decreased steric environment.

Bond Lengths and A-Values of Methyl Halides



C–F: 1.39 Å

F A-value: 0.25–0.42

C–Cl: 1.79 Å

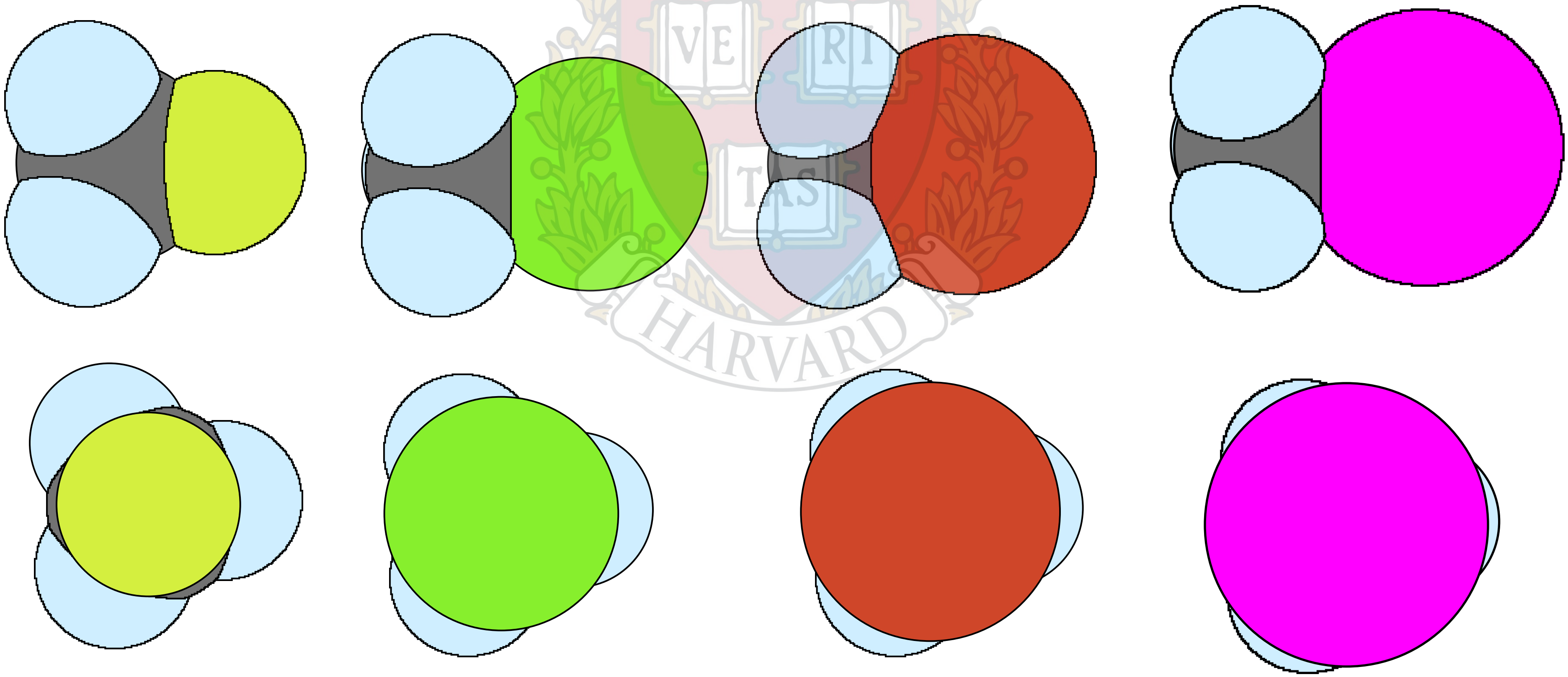
Cl A-value: 0.53–64

C–Br: 1.95 Å

Br A–value: 0.48-0.67

C–I: 2.16 Å

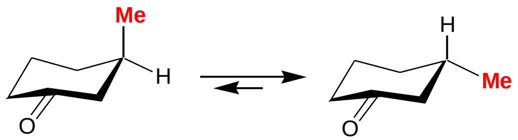
I A-value: 0.47–0.61



Chem 3D Pro (Verson 5.0)

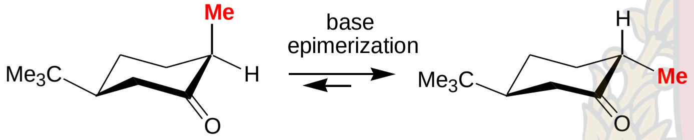
The impact of trigonal Carbon

- Let's now compare look at the carbonyl analog in the 3-position



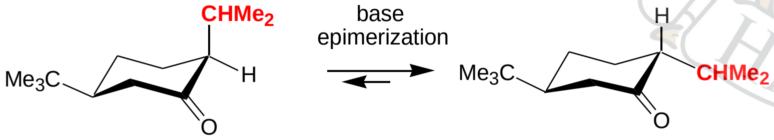
ΔG° = –1.36 kcal/mol
versus –1.74 for cyclohexane

- Let's now compare look at the carbonyl analog in the 2-position

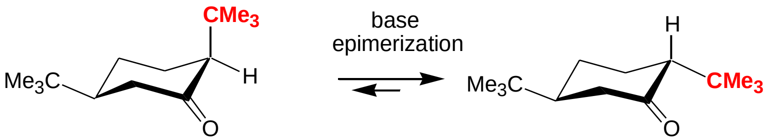


ΔG° = –1.56 kcal/mol
versus –1.74 for cyclohexane

However, the larger alkyl groups do not follow the expected trend.
Can you explain? (see Eliel, page 732)



ΔG° = –0.59 kcal/mol
versus –2.15 for cyclohexane

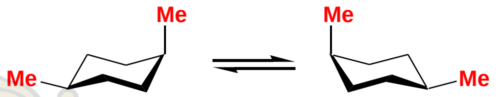


ΔG° = –1.62 kcal/mol
versus –5.0 for cyclohexane

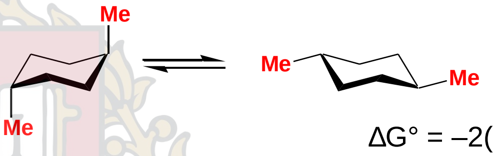
Polysubstituted Cyclohexane *A* Values

- As long as the substituents on the ring do not interact in either conformation, their A-values are roughly additive

1,4 Disubstitution: *A* Values are roughly additive.

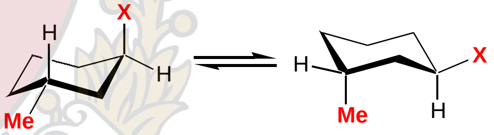


ΔG° = 0 kcal/mol

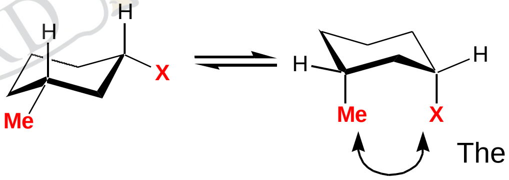


ΔG° = –2(1.74) = –3.48 kcal/mol

1,3 Disubstitution: *A* Values are only additive in the trans diastereomer

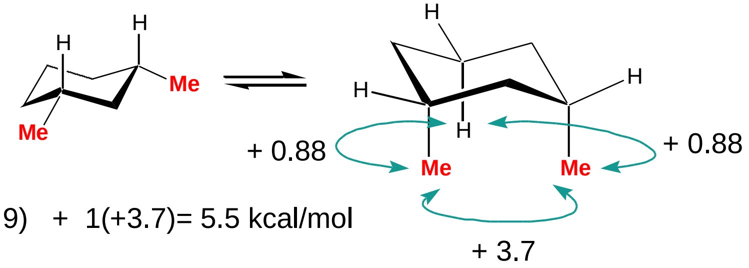


ΔG° = A(Me) – A(X)



The new interaction!

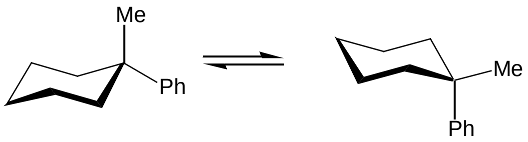
For X = Me



ΔG° = 2(.9) + 1(+3.7)= 5.5 kcal/mol

Conformational Analysis: Cyclic Systems-6

Let's now consider geminal substitution



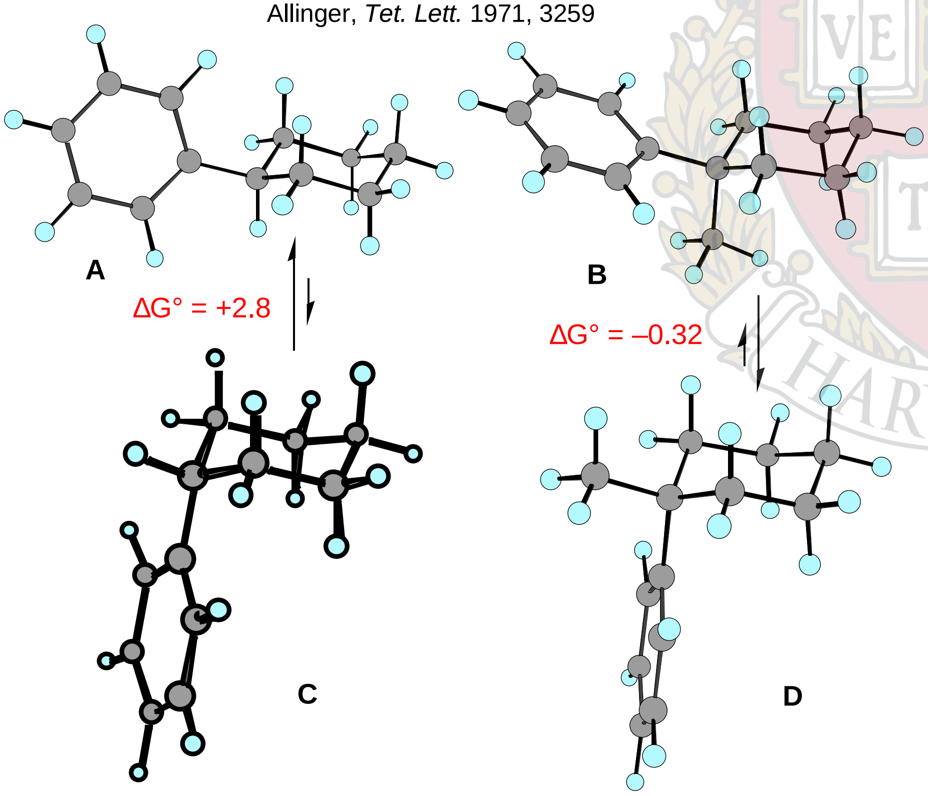
The prediction: ΔG° = A(Ph) – A(Me)

ΔG° = +2.8 – 1.7 = +1.1 kcal/mol

Observed: ΔG° = –0.32 kcal/mol

Hence, when the two substituents are mutually interacting you can predict neither the magnitude or the direction of the equilibrium. Let's analyze this case.

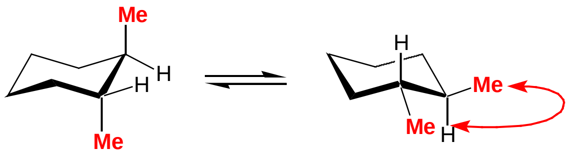
Allinger, *Tet. Lett.* 1971, 3259



Note the difference in the Ph substituent in **A** & **B**.

Let's now consider vicinal substitution

Case 1:



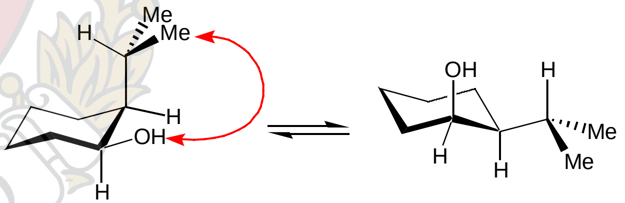
The prediction: ΔG° = 1 gauche butane – 2A(Me)

ΔG° = +0.88 – 2(1.74) = +2.6 kcal/mol

Observed: ΔG° = +2.74 kcal/mol

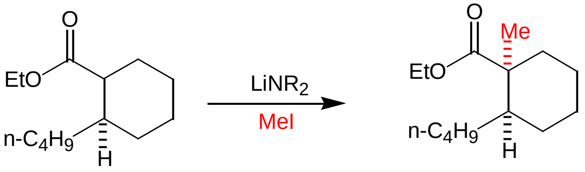
If the added gauche butane destabilization in the di-equatorial conformer had not been added, the estimate would have been off.

Case 2:



The conformer which places the isopropyl group equatorial is much more strongly preferred than would be suggested by *A*- Values. This is due to a syn pentane OH/Me interaction.

Problem:
Can you rationalize the stereochemical outcome of this reaction?



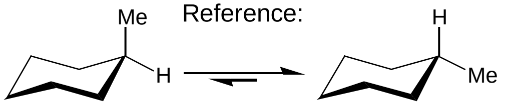
diastereoselection 89:11

D. Kim & Co-workers, *Tetrahedron Lett*. **1986**, *27*, 943.

Heteroatom-Substituted 6-Membered Rings

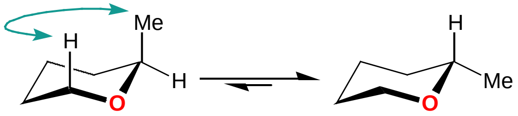
- 🟥 A-values at the 2-position in both the O & N heterocycles are larger than expected. This is due to the shorter C–O (1.43 Å), and C–N (1.47 Å) bond lengths relative to carbon (C–C; 1.53 Å). The combination of bond length and bond angle change increases the indicated 1,3-diaxial interaction (see eq 1, 4).

Reference:



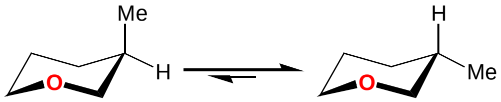
$-\Delta G^\circ = 1.74$ kcal/mol

(1)



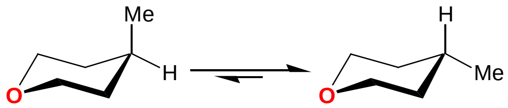
$-\Delta G^\circ = 2.86$ kcal/mol

(2)



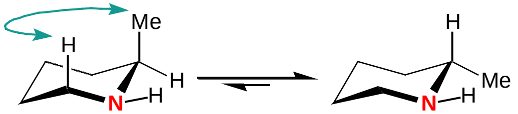
$-\Delta G^\circ = 1.43$ kcal/mol

(3)



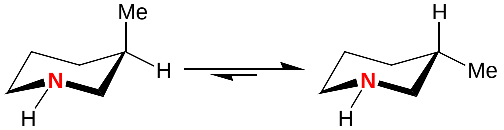
$-\Delta G^\circ = 1.95$ kcal/mol

(4)



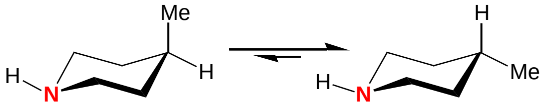
$-\Delta G^\circ = 2.5$ kcal/mol

(5)



$-\Delta G^\circ = 1.6$ kcal/mol

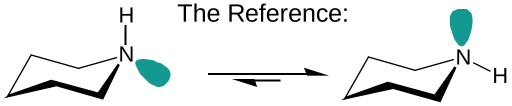
(6)



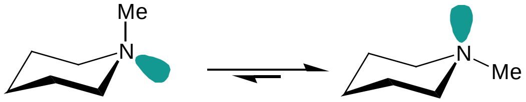
$-\Delta G^\circ = 1.9$ kcal/mol

A-Values for *N*-Substituents in Piperidine

The Reference:

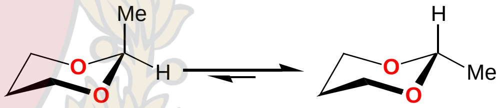


$-\Delta G^\circ = 0.36$ kcal/mol

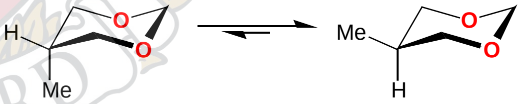


$-\Delta G^\circ = 3.0$ kcal/mol

- 🟥 Hydrogen is "bigger" than the N–lone Pair.
- 🟥 The A-value of N–substituents is slightly larger than the corresponding cyclohexane value. Rationalize

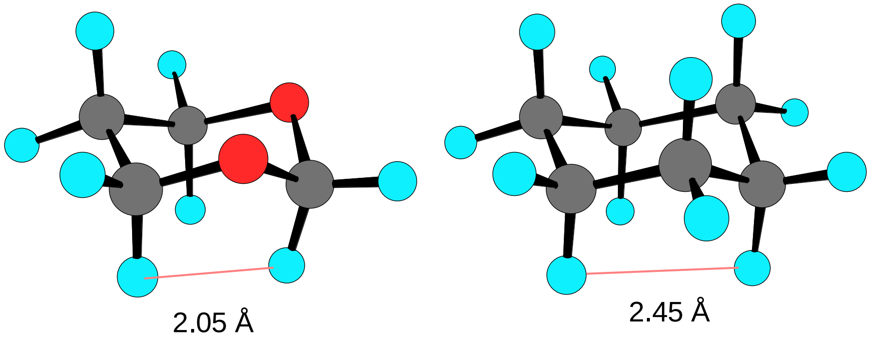


$-\Delta G^\circ = 4.0$ kcal/mol

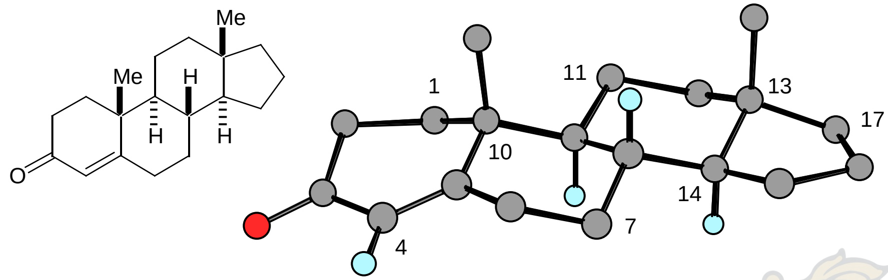


$-\Delta G^\circ = 0.8$ kcal/mol

- 🟥 The indicated distance is 2.05 Å. The analogous H–H distance in Cyclohexane is 2.45 Å

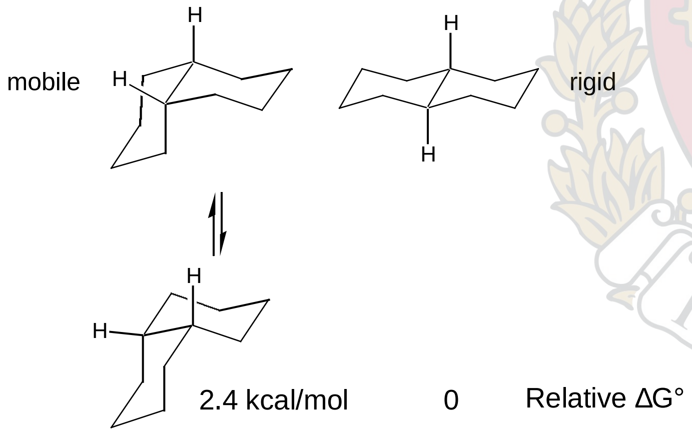


Conformations of Bicyclic Ring Systems

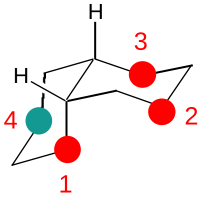


The steroid nucleus provided the stimulation for the development of conformational analysis, particularly of polycyclic ring systems. D. H. R. Barton was awarded a Nobel prize in 1969 for his contributions in this area.

Decalin Ring System (6/6)



Let's identify the destabilizing gauche butane interactions in the cis isomer



Gauche-butane interactions

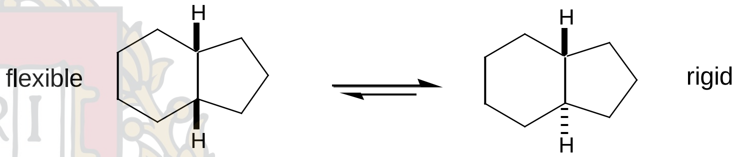
C1 → C2
C1 → C3
C4 → C3

ΔG°(est) = 3(0.88) = 2.64 kcal/mol

Estimate the energy difference between the two methyl-decalins shown below.

see Elier, p 780

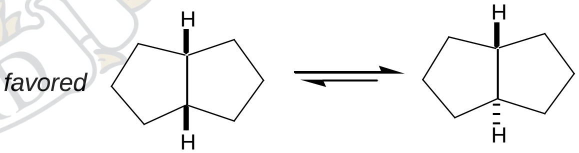
Hydrindane Ring System (6/5)



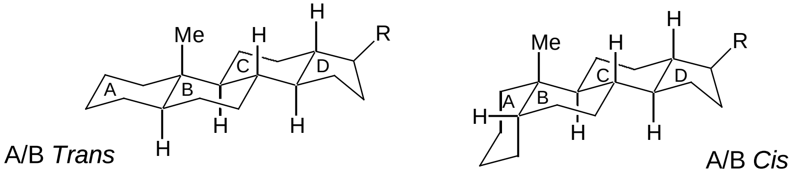
ΔG° = –0.5 kcal/mol

- The turnover to favor the *cis* fusion results from the entropic preference for the less ordered *cis* isomer.

The 5-5 Ring System



ΔG° = +6.4 kcal/mol

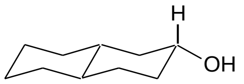


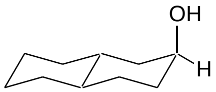
Rationalize the conformational flexibility of a *A/B Trans* vs. *A/B Cis* Steroid!

Different reactivity for axial and equatorial substituents

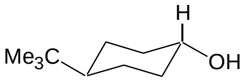
Axial substituents are more hindered, thus less reactive in many transformations

- Acetylation with Ac_2O/Py



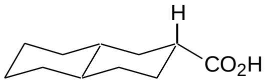


k_{rel} 1 0.13

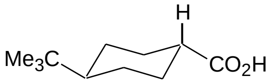


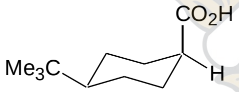
k_{rel} 1 0.27

- Acid-catalyzed esterification



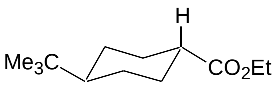
k_{rel} 1 0.04

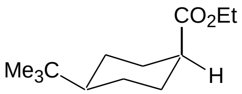




k_{rel} 1 0.05

- Ester Saponification

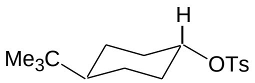


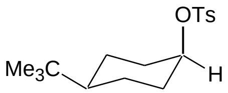


k_{rel} 20 1

For a more detailed discussion of this topic see:
Eliel, E. L., S. H. Wilen, et al. (1994). *Stereochemistry of Organic Compounds pp 720-726*

- S_N2 Reactions (Displacement with Ph–S⁻)

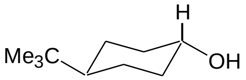


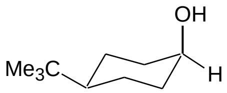


k_{rel} 1 31

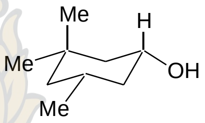
The axial diastereomer is not always slower reacting:

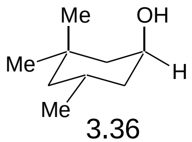
- Alcohol Oxidation with Cr(6+)





k_{rel} 1 3.2

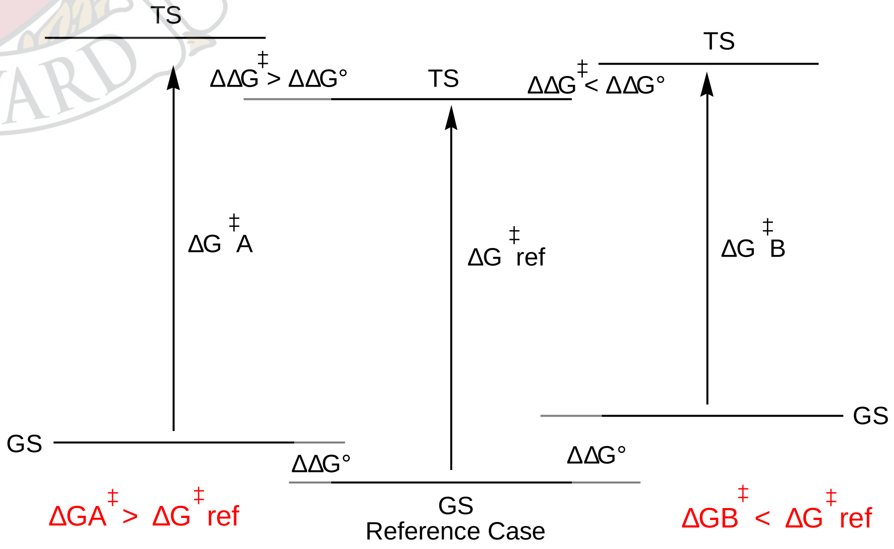




k_{rel} 1 3.36

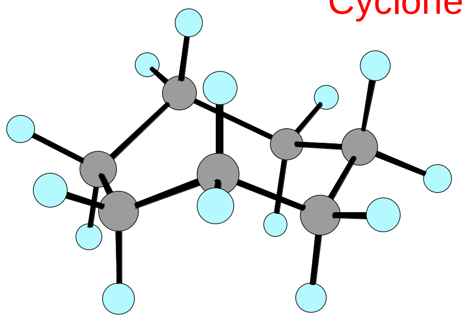
The rate-determining step is breakdown of the chromate ester. This is an apparent case of strain acceleration

Steric Hindrance and Steric Assistance

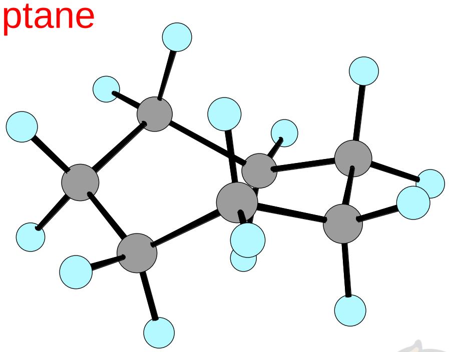


Conformational Analysis: Cylcoheptane

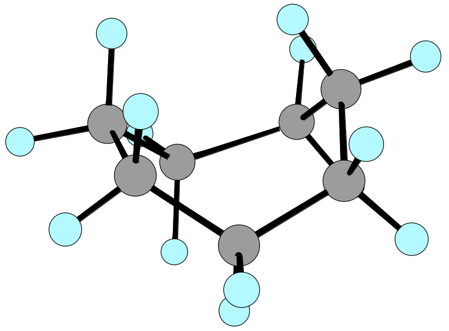
Cycloheptane



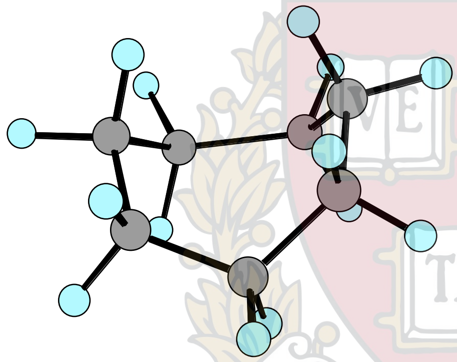
Chair (2.16 kcal/mol)



Twist-Chair (0 kcal/mol)



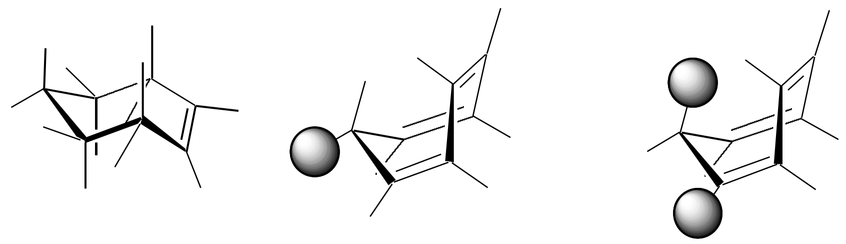
Boat (3.02 kcal/mol)



Twist-Boat (2.49 kcal/mol)

Hendrickson, J. B. *JACS* **1961**, *83*, 4537.
See Eliel, page 762+

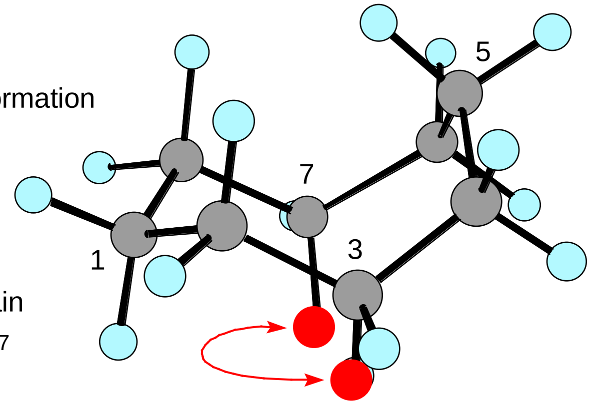
Olefins are preferentially orientated to eliminate eclipsing interactions.



Cyclooctane

Chair-Boat
Lowest-energy conformation

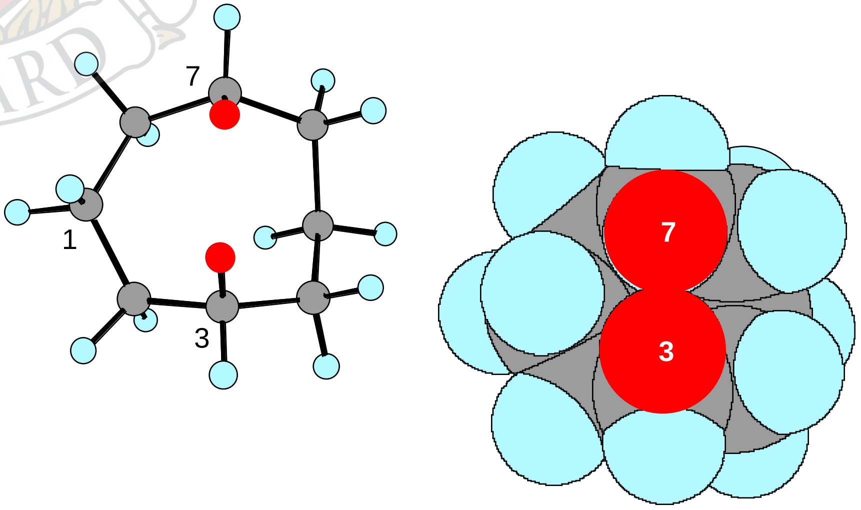
Transannular strain between C_3 & C_7



Ring strain originates in eclipsing interactions and transannular van der Waals interactions

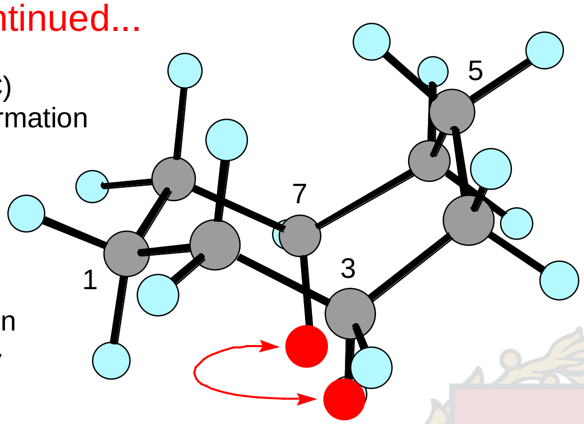
Methyl position	1	2	**3**	4	5
ΔG (pseudoeqatorial) / (pseudoaxial) (kcal/mol)	1.8	2.8	**>4.5**	-0.3	6.1

Underside view of boat-chair C3 & C7 eclipsing interactions



Cyclooctane continued...

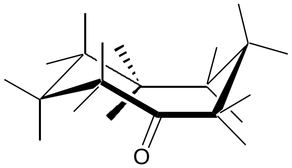
Chair-Boat (**BC**)
Lowest-energy conformation



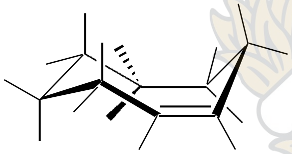
Transannular strain between C_3 & C_7

Methyl position	1	2	3	4	5
ΔG $\frac{\text{(pseudoeqatorial)}}{\text{(pseudoaxial) (kcal/mol)}}$	1.8	2.8	>4.5	-0.3	6.1

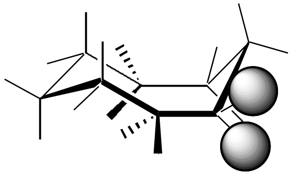
Cyclooctane derivatives



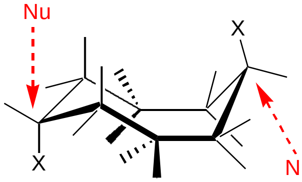
Carbonyl is positioned at C_3 or C_7



Olefin is positioned at C_3-C_4 or C_6-C_7

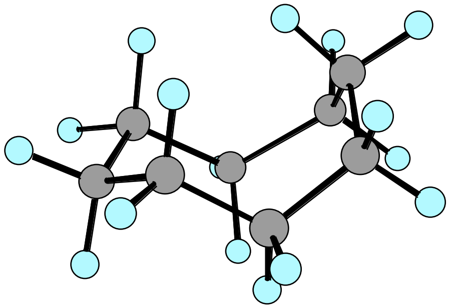


Disubstitution occurs at C_4 or C_6

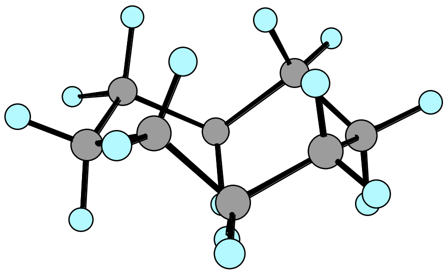


S_N2 occurs at C_1 and C_5

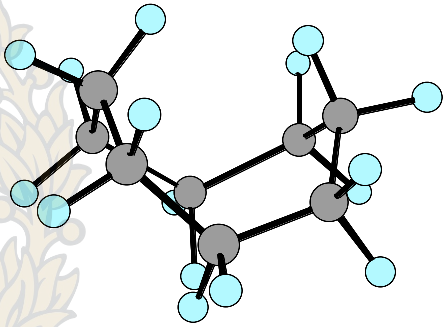
Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 1981.



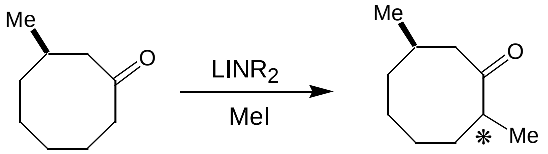
Chair-Boat (**CB**) conformation
reference structure



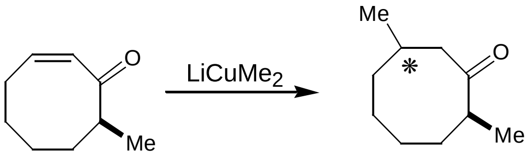
Chair-Chair (**CC**) conformation
(+1-1.6 kcal/mol)



Boat-Boat (**BB**) conformation
(>+ 8 kcal/mol)



Predict
stereochemistry

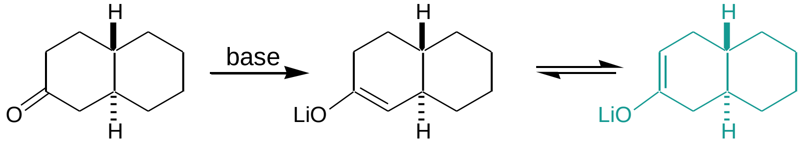


Predict
stereochemistry

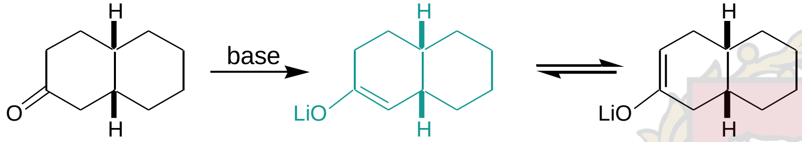
Conformational Transmission

Observation:

Relative enolate stability correlates to ring junction stereochemistry



ratio: 13 : 87

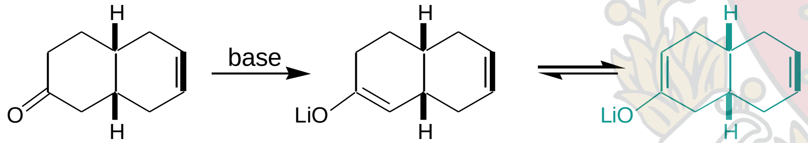


ratio: 70 : 30

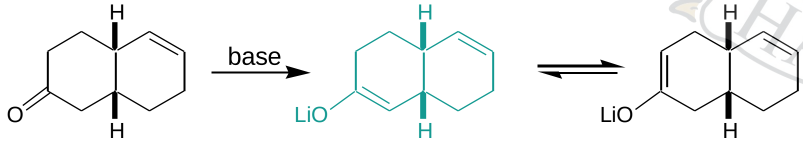
House, *JOC* **1965**, *30*, 1341

Observation:

Relative enolate stability seems to be correlated to position of C=C



ratio: 10 : 90

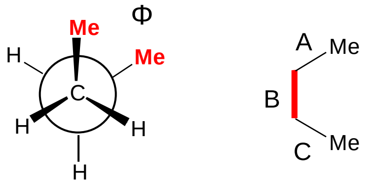


ratio: 92 : 8

How do we explain the experimental observations shown above?

Readings: Velluz etal, *Angew. Chemie, Int Ed*. **1965**, *4*, 181-270

Let Φ be defined as the torsion or dihedral angle for butane

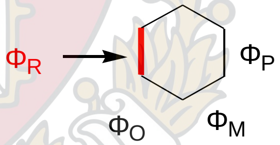


Φ illustrated may be designated as Φ B.

Let's now consider cyclohexane

Perfect chair	real chair
Φ = 60°	Φ = 56°
CCC 109° 28'	CCC 111°

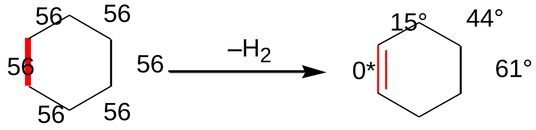
Given cyclohexane with an identified torsion angle ΦR, if ΦR either increases or decreases wht effects in angle change are transmitted to ΦO, ΦM, and ΦP?



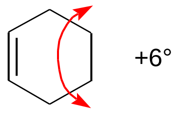
	$\Phi_R = 56°$	$\Phi_R = 0°$	[Δ]
Φ_O	56	15	–41°
Φ_M	56	44	–11°
Φ_P	56	61	+6°

$[\Delta] = \Phi_R(0°) - \Phi_R(56°)$

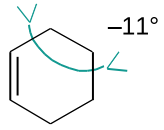
Operation:



Hence, relative to cyclohexane, the following notation for torsion angle change may be denoted:

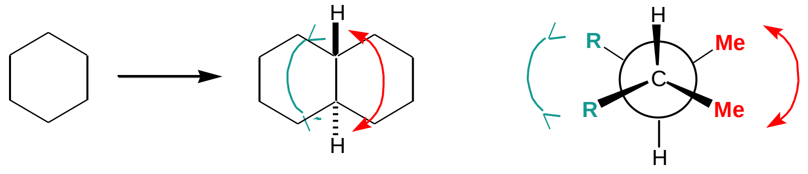


For Φ_P

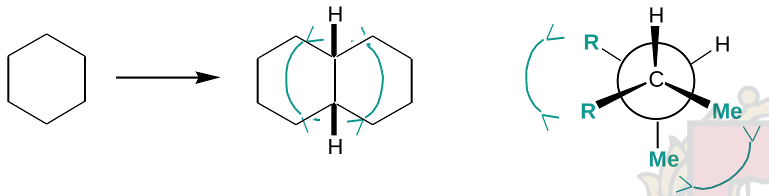


For Φ_M

Operation:

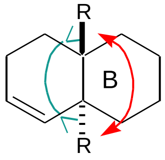


Operation:



Simple Application: Reinforcing Torsional Effects

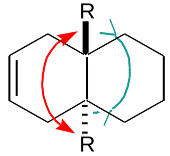
Which C=C bond isomer is more stable?



1) C=C will open up ring=B torsion angle

2) Ring B will resist increase in its ring fusion torsion angle

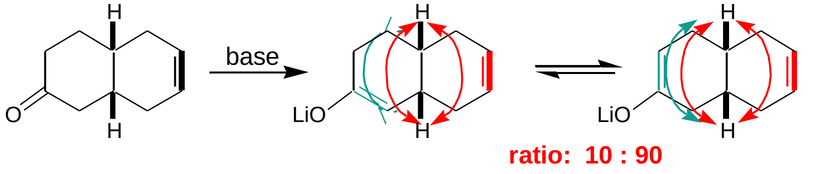
3) Therefore torsion effects are opposed



1) C=C will close down ring=B torsion angle

2) Ring B will accomodate decrease in its ring fusion torsion angle

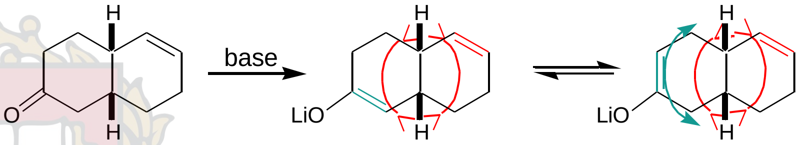
3) Therefore torsion effects are reinforcing



ratio: 10 : 90

effects opposing

effects reinforcing

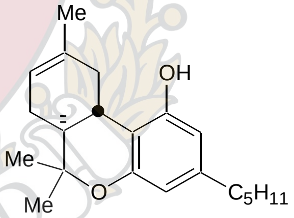


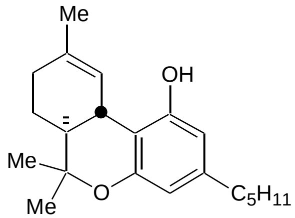
ratio: 92 : 8

effects reinforcing

effects opposing

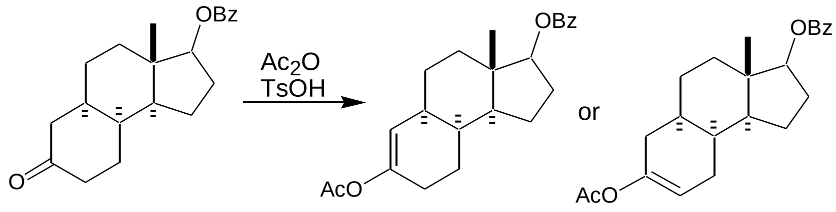
Question: Which is the more stable C=C isomer in the two THC structures?





R. W. Kierstead, *JACS* **1967**, *89*, 5934

Question: Which enol acetate is more stable?



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 7

Conformational Analysis-4

- Conformational Analysis of $C_6 \rightarrow C_8$ Rings continued
- Transition State Torsional Effects
- Curtin–Hammett Principle

Reading Assignment for week

Eliel & Wilen, Stereochemistry of Carbon Compounds"
Chapter 11 ***(on reserve in CCB library)***

A. Carey & Sundberg: **Part A**; Chapter 4
"Study & Descrption of Reaction Mechanisms"

K. Houk, *Science.* **1986**, *231*, 1108-1117
Theory & Modeling of Stereoselective Organic Reactions ***(Handout)***

J. I. Seeman, *J. Chem. Ed*. **1986,** *63,* 42-48
The Curtin-Hammett Principle ***(Handout)***

Matthew D. Shair

Wednesday,
October 2, 2002

Other Reading Material

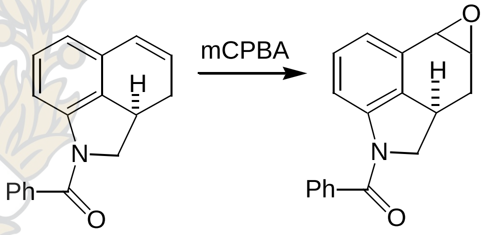
The Curtin-Hammett Principle

Leading References:

- **J. I. Seeman, *J. Chem. Ed*. 1986, *63,* 42-48.**
- J. I. Seeman, *Chem Rev*. **1983,** *83,* 83-134.
- Eliel, pp. 647-655
- Carey & Sundberg,Part A, CH 4, pp 187-250

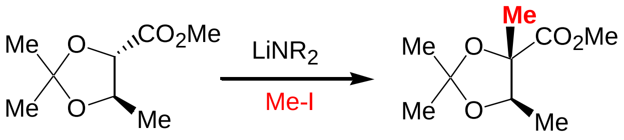
Problems of the Day: (To be discussed)

Predict the stereochemical outcome of this reaction. The diastereoselection is 99:1



Martinelli, et.al. *Tett. Lett.* **1989**, *30*, 3935

Rationalizethe stereochemical outcome of this reaction.



diastereoselection is 8:1.

Ladner, et.al. *Angew. Chemie, Int. Ed* **1982**, *21*, 449-450

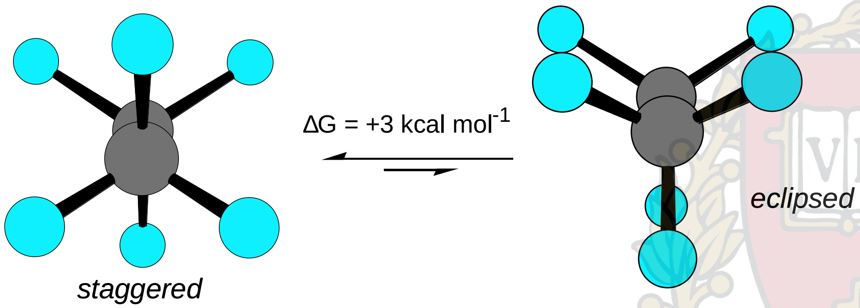
Torsional Effects

Torsional Strain: the resistance to rotation about a bond

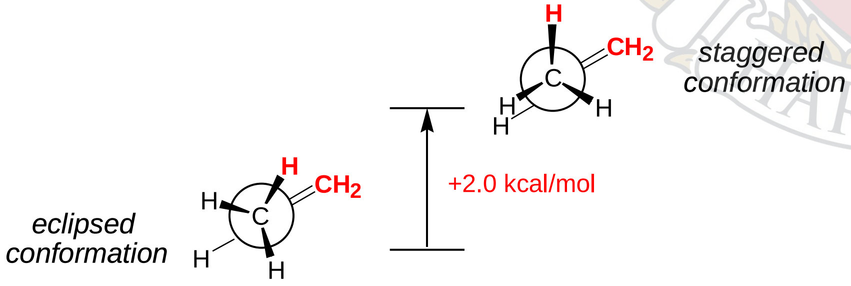
Torsional energy: the energy required to obtain rotation about a bond

Torsional Angle: also known as dihedral angle

Torsional steering: Stereoselectivity originating from transition state torsional energy considerations



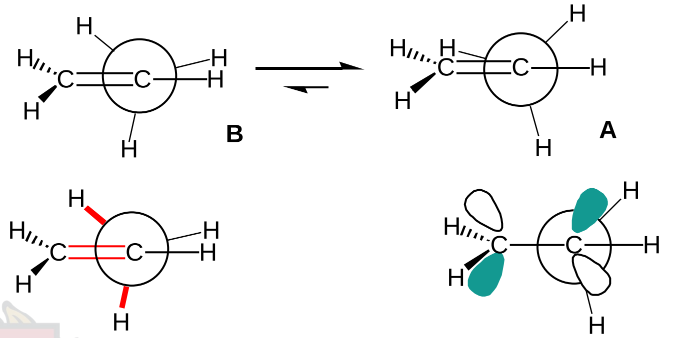
Torsional Strain (Pitzer Strain): Ethane



Wiberg K. B.; Martin, E. *J. Amer. Chem. Soc.* **1985**, *107*, 5035-5041.

See Lecture 5 for previous discussion

Relevant Orbital Interactions:

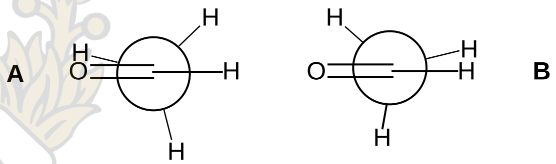


σ C–H & π electrons are destabilizing

σ C–H's properly aligned for π overlap hence better delocalization

Dorigo, A. E.; Pratt, D. W.; Houk, K. N. *JACS* **1987**, *109*, 6591-6600.

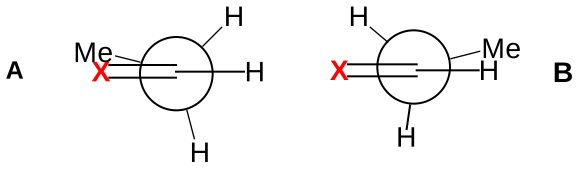
Conformational Preferences: Acetaldehyde



The eclipsed conformation (conformation **A**) is preferred. Polarization of the carbonyl decreases the 4 electron destabilizing Rotational barrier: 1.14 kcal/mol

Houk, *JACS* **1983**, *105*, 5980-5988.

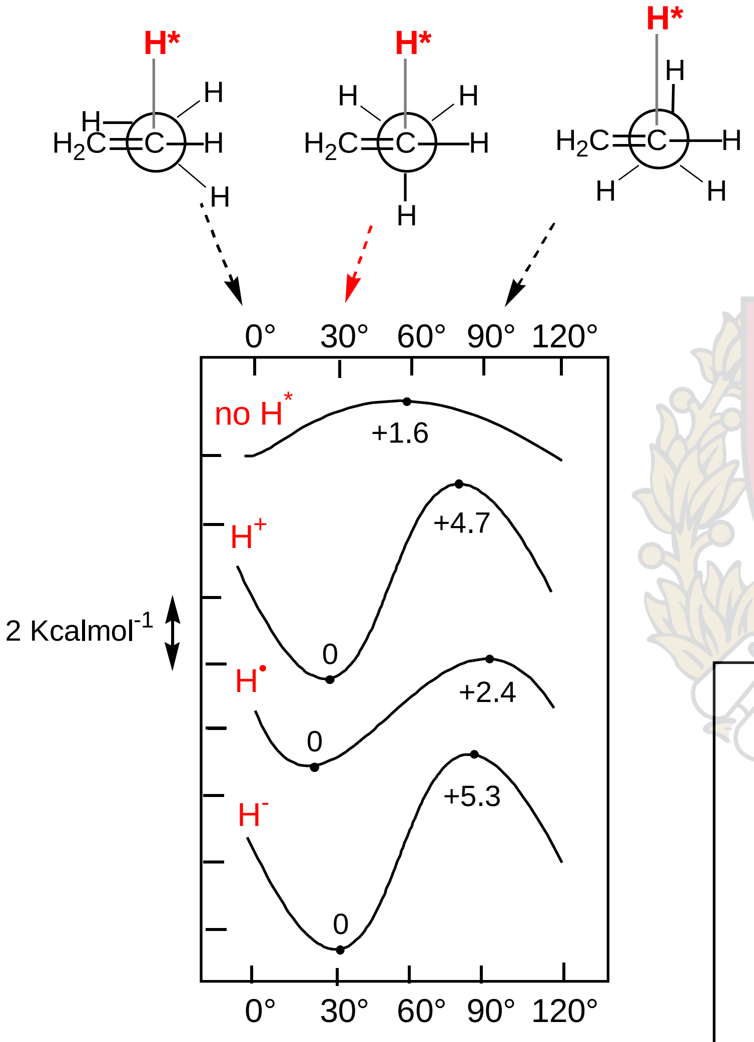
Conformational Preferences 1-Butene ($X = CH_2$); Propanal ($X = O$)



Conformation A is preferred. There is little steric repulsion between the methyl and the X-group in conformation A.

Transition State Torsional Effects According to Houk

Houk: "Torsional effects in transition states are more important than in ground states"

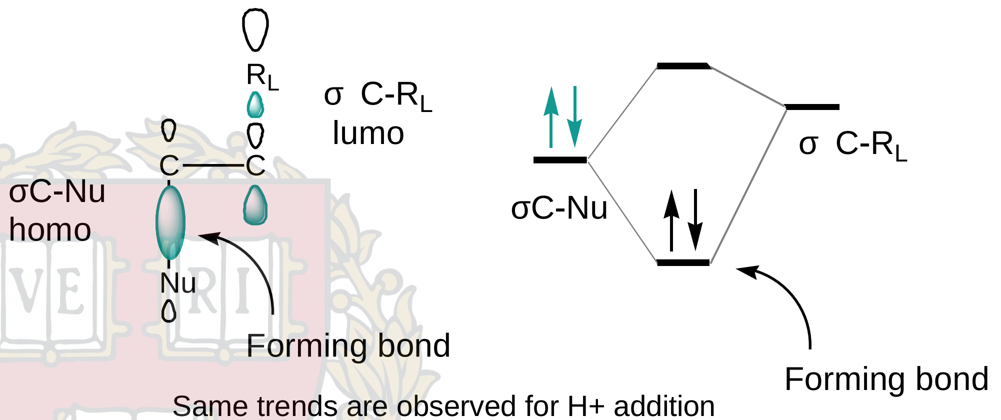


Houk, *JACS* **1981**, *103*, 2438

Houk, *JACS* **1982**, *104*, 7162

Transition states

H-radical and H-anion: antiperiplanar σ C–R orbital stabilized the TS illustrated for Nu addition

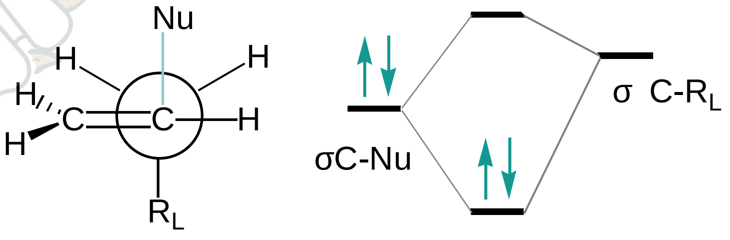


Same trends are observed for H+ addition

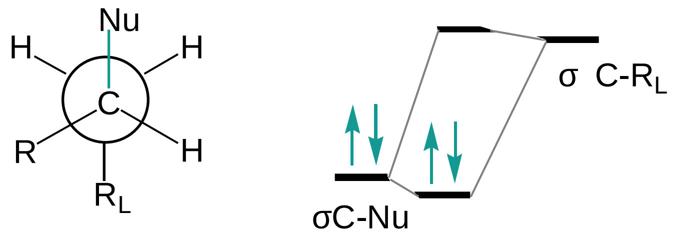
Houk, *Science* **1981**, *231*, 1108-1117

"The Theory and Modeling of Stereoselective Organic Reactions"

Transition state



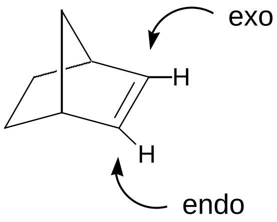
Ground state



Transition State Torsional Effects: Olefin Additions

■ Olefin Addition Reactions: Case one

How do we account for the high exo selectivities in addition reactions to norbornene?



Highly exo selective for electrophilic, nucleophilic and cycloaddition reactions

Rate enhancement due to strain

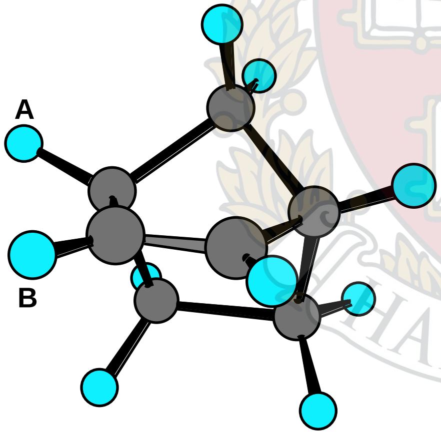
The Controversy over origin of high exoselectivities

Steric effects

Least nuclear motion

Orbital distortion

Schleyer: torsional steering



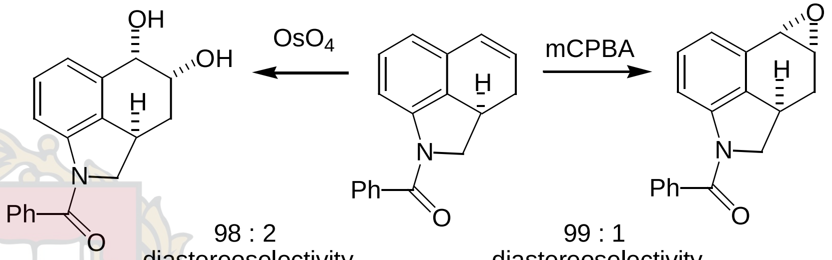
Schleyer, P. R. *J. Amer. Chem. Soc.* **1967**, *89*, 701.

Addition from exo face avoids eclipsing A & B hydrogens

(better hyperconjugative stabilization of transition state)

■ Olefin Addition Reactions: Case two

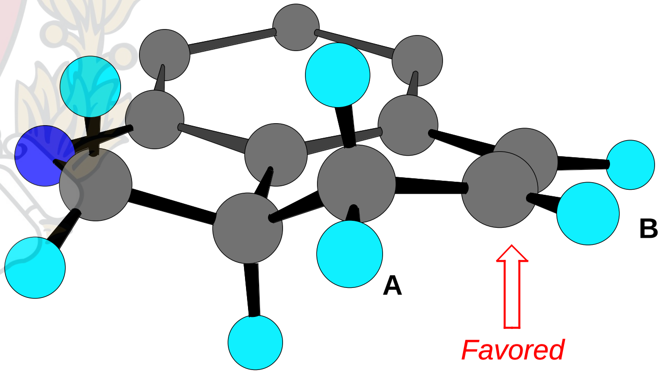
How do we account for the high selectilvities in the oxidation of the indicated olefin?



98 : 2 diastereoselectivity

99 : 1 diastereoselectivity

Nitrogen protecting group does not affect selectivities



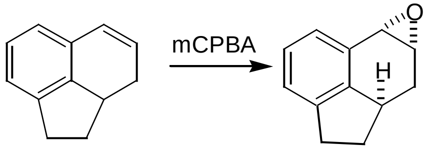
Martinelli, et.al. *Tett. Lett.* **1989**, *30*, 3935

Addition from indicated olefin face avoids eclipsing A & B H's

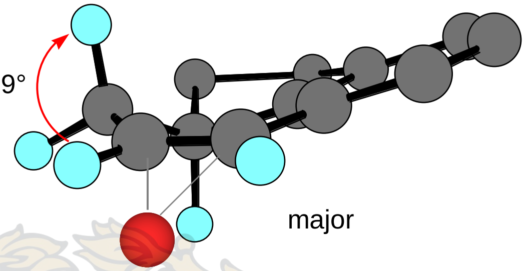
(better hyperconjugative stabilization of transition state)

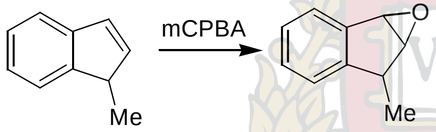
Martinelli has carried out further studies on related structures...........

Martinelli: Torsional steering important in selectivity

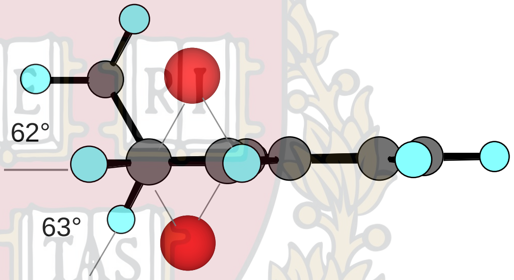


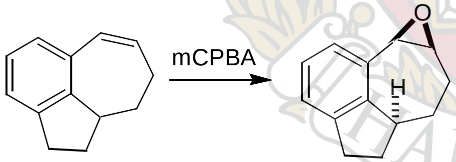
99 : 1 diastereoselectivity



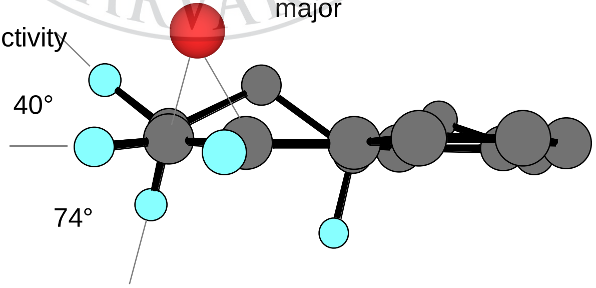


50 : 50 diastereoselectivity





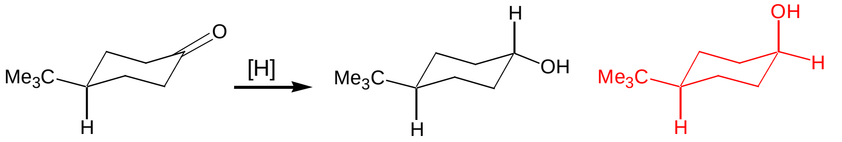
99 : 1 diastereoselectivity



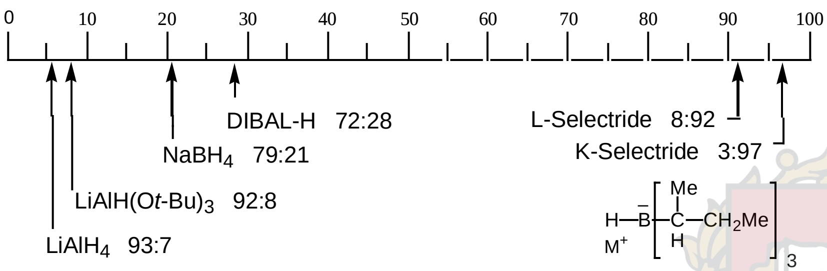
Authors propose that diastereoselection controlled by TS torsional effects

Martinelli & Houk, *J. Org. Chem.* **1994**, *59*, 2204.

Stereoselective Reductions: Cyclic Systems

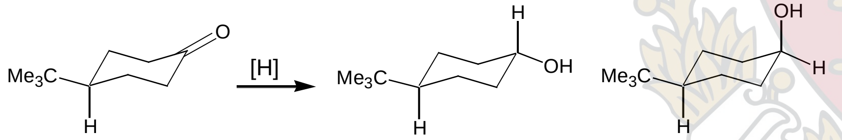


% Axial Diastereomer →

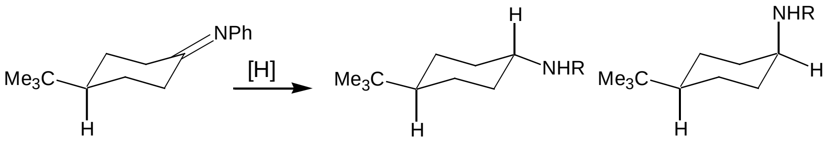


Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

The most stereoselective Reductions



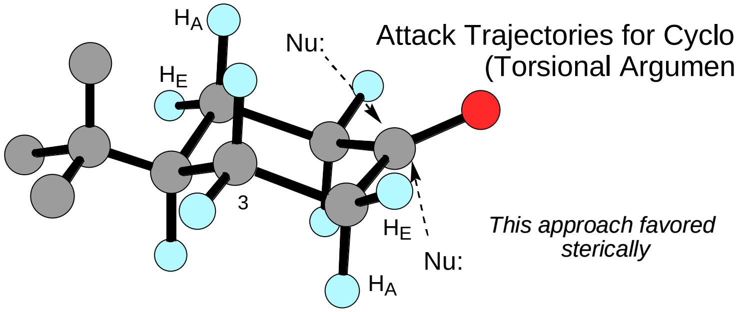
Reagent	Ratio
KBH(s-Bu)$_3$	03 :97
Li in NH$_3$	99 :01



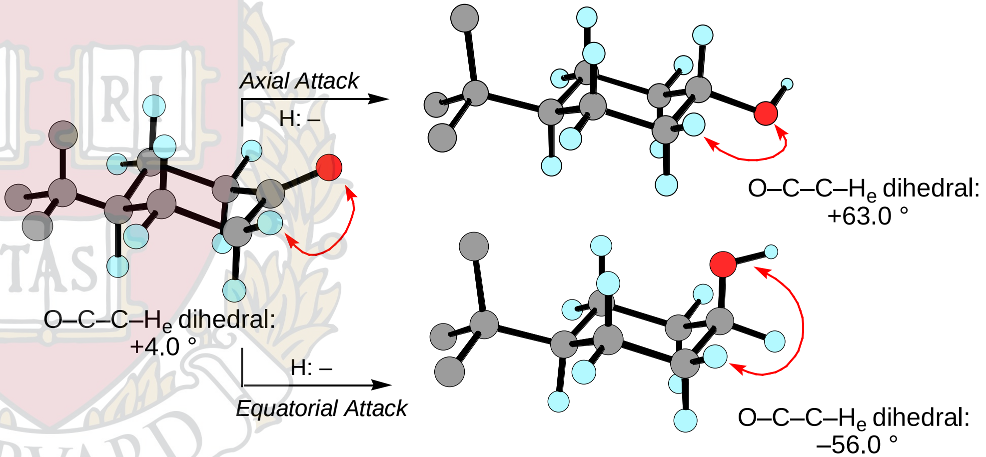
(R)	Reagent	Ratio
R = Bn	LiBH(s-Bu)$_3$	03 :97
R = Ph	LiBH(s-Bu)$_3$	01 :99
	Al/Hg/MeOH	~90 :10

Ganem, *Tet. Let* **1981**, *22*, 3447
Hutchins, *JOC* **1983**, *48*, 3412
private communication

Attack Trajectories for Cyclohexanone (Torsional Argument)



The steric hindrance encountered by Nu-attack from the axial C=O face by the axial ring substituents (hydrogens in this case) at the 3-positions is more severe than the steric hinderance encountered from Nu-attack from the equatorial C=O face.



The Issues Associated with the Reduction Process

Steric Effects:	Attack across equatorial C=O face sterically more favorable.
Torsional Effects:	However, attack across the axial face of the C=O group avoids development of eclipsing interactions in the transition state. (Note the dihedral angle sign changes between reactants & products shown above). These "torsional effects" favor axial attack.

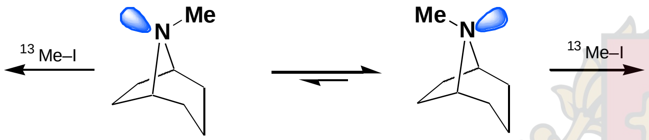
Prediction For "small" hydride reagents such as LiAlH$_4$, torsional effects are felt to be dominant and this explains the predisposition for axial attack.

Prediction For "large" hydride reagents such as H–BR$_4$, steric effects now are dominant and this explains the predisposition for equatorial attack.

Leading References: J. I. Seeman, *J. Chem. Ed*. **1986,** *63,* 42-48.
J. I. Seeman, *Chem Rev*. **1983,** *83,* 83-134.
See also Eliel, pp. 647-655

How does the conformation of a molecule effect its reactivity?

Consider the following example:



Do the two different conformers react at the same rate, or different rates?
What factors determine the product distribution?

The situation:

Consider two interconverting conformers, A and B, each of which can undergo a reaction resulting in two different products, P_A and P_B.

$$\underset{major}{P_A} \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} \underset{minor}{P_B} \qquad (1)$$

We'll consider two limiting cases:

(1) The rate of reaction is *faster* than the rate of conformational interconversion

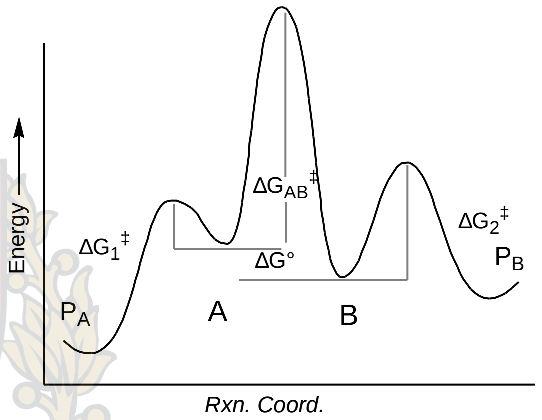
(2) The rate of reaction is *slower* than the rate of conformational interconversion

If the rates of conformationall interconversion and reaction are comparable, the reactants are not in equilibrium during the course of the reaction and complex mathmatical solutions are necessary. See Seeman, *Chem. Rev.* **1983**, 83 - 144 for analytical solutions.

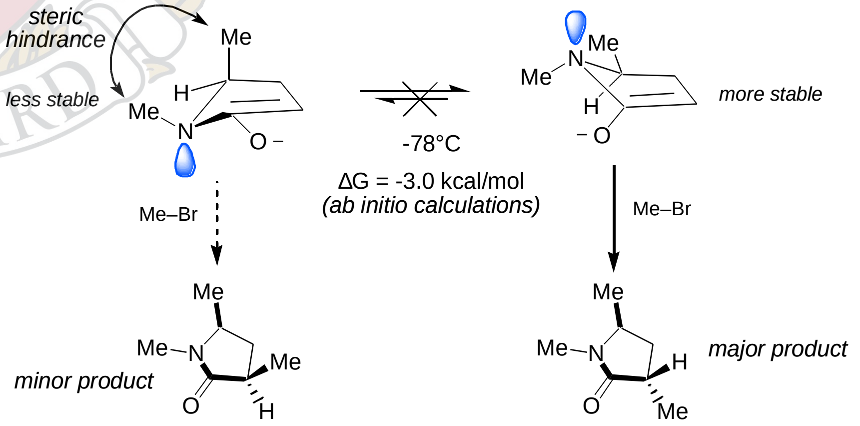
Case 1: "Kinetic Quench"

k_1, k_2 >> k_A, k_B: If the rates of reaction are **faster** than the rate of interconversion, A and B cannot equilibrate during the course of the reaction, and the product distribution (P_B/P_A) will reflect the initial composition.

$$\frac{[P_B]}{[P_A]} = \frac{[B]_o}{[A]_o}$$



In this case, the product distribution depends solely on the initial ratio of the two conformers.



ΔG = -3.0 kcal/mol
(ab initio calculations)

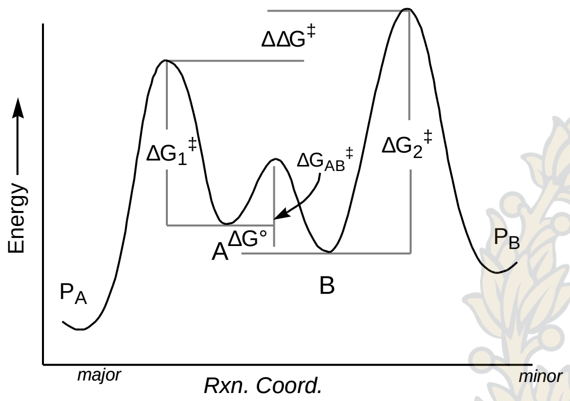
While enolate conformers can be equilibrated at higher temperatures, the products of alkylation at -78° C always reflect the initial ratio of enloate isomers.

Padwa, *JACS* **1997** 4565

Case 2: Curtin-Hammett Conditons

k_1, k_2 << k_A, k_B: If the rates of reaction are much **slower** than the rate of interconversion, ($\Delta G_{AB}^{\ddagger}$ is small relative to $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$), then the ratio of A to B is constant throughout the course of the reaction.

$$P_A \xleftarrow[\text{slow}]{k_1} A \underset{\text{fast}}{\overset{k_A}{\underset{k_B}{\rightleftharpoons}}} B \xrightarrow[\text{slow}]{k_2} P_B \qquad (1)$$



The Derivation:

Using the rate equations $\frac{d[P_A]}{dt} = k_1[A]$ and $\frac{d[P_B]}{dt} = k_2[B]$ we can write:

$$\frac{d[P_B]}{d[P_A]} = \frac{k_2[B]}{k_1[A]} \quad \text{or} \quad d[P_B] = \frac{k_2[B]}{k_1[A]}\, d[P_A] \qquad (2)$$

Since A and B are in equilibrium, we can substitute $K_{eq} = \frac{[B]}{[A]}$

$$\int d[P_B] = \frac{k_2}{k_1} K_{eq} \int d[P_A] \quad \text{Integrating, we get} \quad \frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq} \qquad (3)$$

When A and B are in rapid equilibrium, we must consider the rates of reaction of the conformers as well as the equilibrium constant when analyzing the product ratio.

To relate this quantity to ΔG values, recall that $\Delta G^{o} = -RT \ln K_{eq}$ or $K_{eq} = e^{-\Delta G°/RT}$, $k_1 = e^{-\Delta G_1^{\ddagger}/RT}$, and $k_2 = e^{-\Delta G_2^{\ddagger}/RT}$. Substituting this into the above equation:

$$\frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq} = \frac{e^{-\Delta G_2^{\ddagger}/RT}}{e^{-\Delta G_1^{\ddagger}/RT}} \left(e^{-\Delta G°/RT}\right) = e^{-\Delta G_2^{\ddagger}/RT} e^{-\Delta G°/RT} e^{\Delta G_1^{\ddagger}/RT} \qquad (4)$$

Combining terms:

$$\boxed{\frac{[P_B]}{[P_A]} = e^{-(\Delta G_2^{\ddagger} + \Delta G° - \Delta G_1^{\ddagger})/RT} \quad \text{or} \quad \frac{[P_B]}{[P_A]} = e^{-\Delta\Delta G^{\ddagger}/RT}}$$

Where $\Delta\Delta G^{\ddagger} = \Delta G_2^{\ddagger} + \Delta G° - \Delta G_1^{\ddagger}$

Curtin - Hammett Principle: The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.

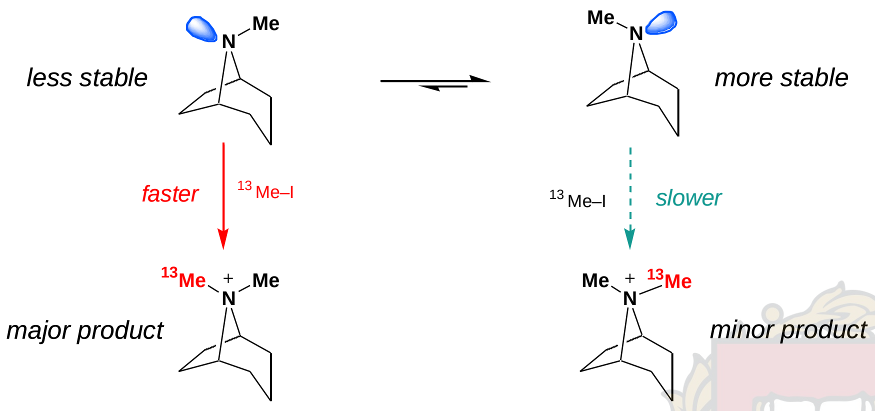
Within these limits, we can envision three scenarios:

- If both conformers react at the **same rate**, the product distribution will be the same as the ratio of conformers at equilibrium.
- If the **major conformer** is also the faster reacting conformer, the product from the major conformer should prevail, and will not reflect the equilibrium distribution.
- If the **minor conformer** is the faster reacting conformer, the product ratio will depend on all three variables in eq (2), and the observed product distribution will not reflect the equilibrium distribution.

This derivation implies that you could potentially isolate a product which is derived from a conformer that you can't even observe in the ground state!

Some Curtin-Hammett Examples

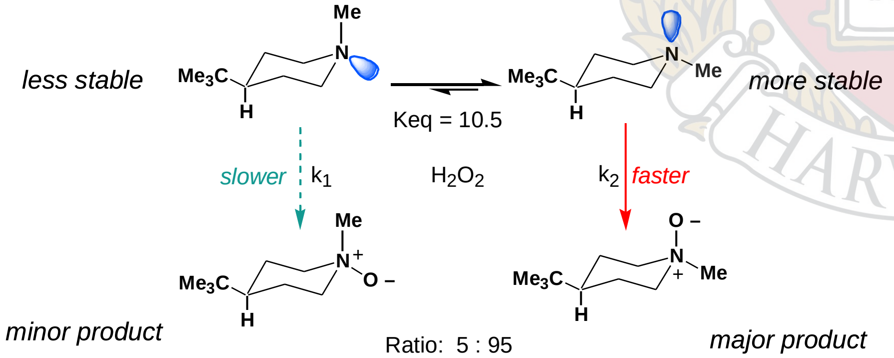
Tropane alkylation is a well-known example.



The less stable conformer reacts much faster than the more stable conformer, resulting in an unexpected major product!

JOC **1974** 319

Oxidation of piperidines:

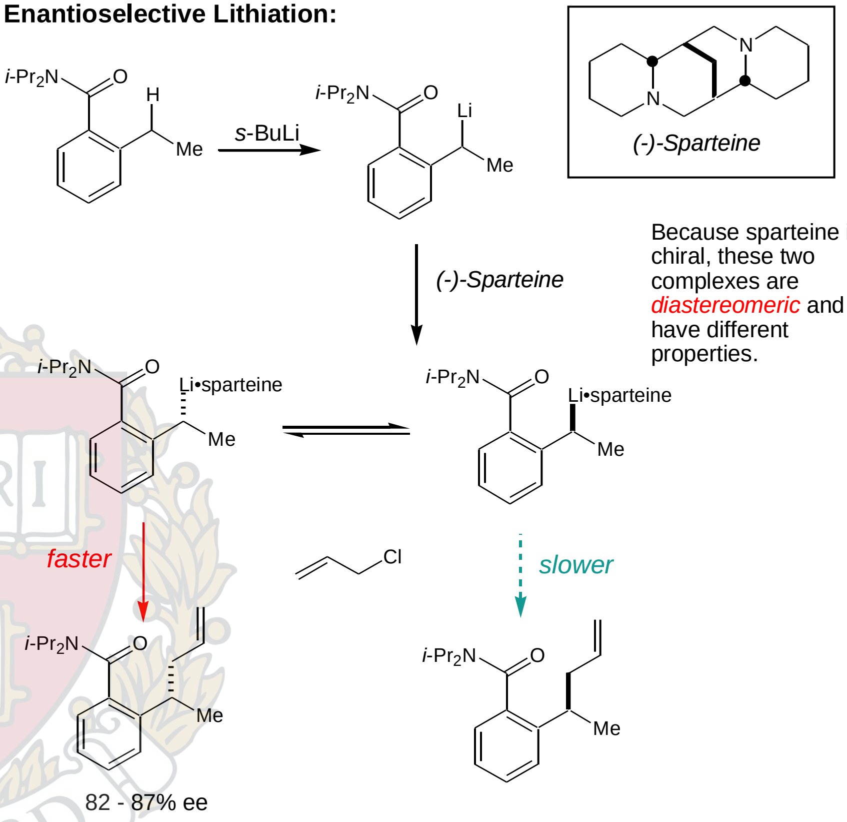


When the equilibrium constant is known, the Curtin-Hammett derivation can be used to calculate the relative rates of reaction of the two conformers. Substituting the above data into $[P_B]/[P_A] = k_2K/k_1$, the ratio $k_2/k_1 \sim 2$.

Note that in this case, the more stable conformer is also the faster reacting conformer!

Tet. **1972** 573
Tet. **1977** 915

Enantioselective Lithiation:



Because sparteine is chiral, these two complexes are *diastereomeric* and have different properties.

Enantioselectivities are the same, regardless of whether or not the starting material is chiral, even at low temperatures. Further, reaction in the absence of (-)-sparteine results in racemic product.

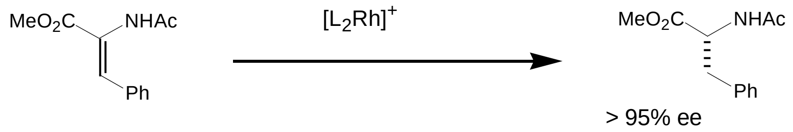
Note that the two alkyllithium complexes MUST be in equilibrium, as the enantioselectivity is the same over the course of the reaction. If they were not equilibrating, the enantioselectivity should be higher at lower conversions.

This is a case of ***Dynamic Kinetic Resolution***: Two enantiomeric alkyl lithium complexes are equilibrating during the course of a reaction with an electrophile.

Beak, *Acc. Chem. Res*, **1996**, 552

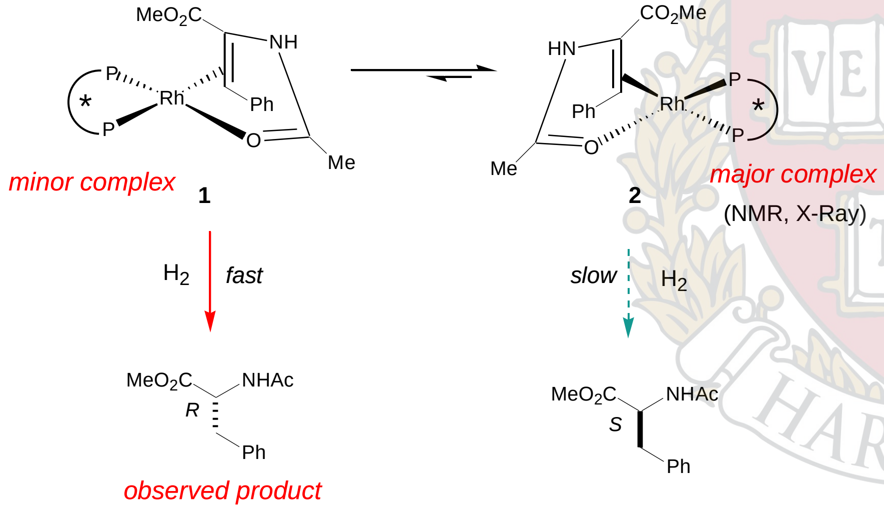
Mechanism of Asymmetric Hydrogenation

The asymmetric hydrogenation of prochiral olefins catalyzed by Rhodium is an important catalytic process.



Enantioselectivities are generally very high when the ligand is a chelating diphosphine. (ee's are given for S,S-CHIRAPHOS)

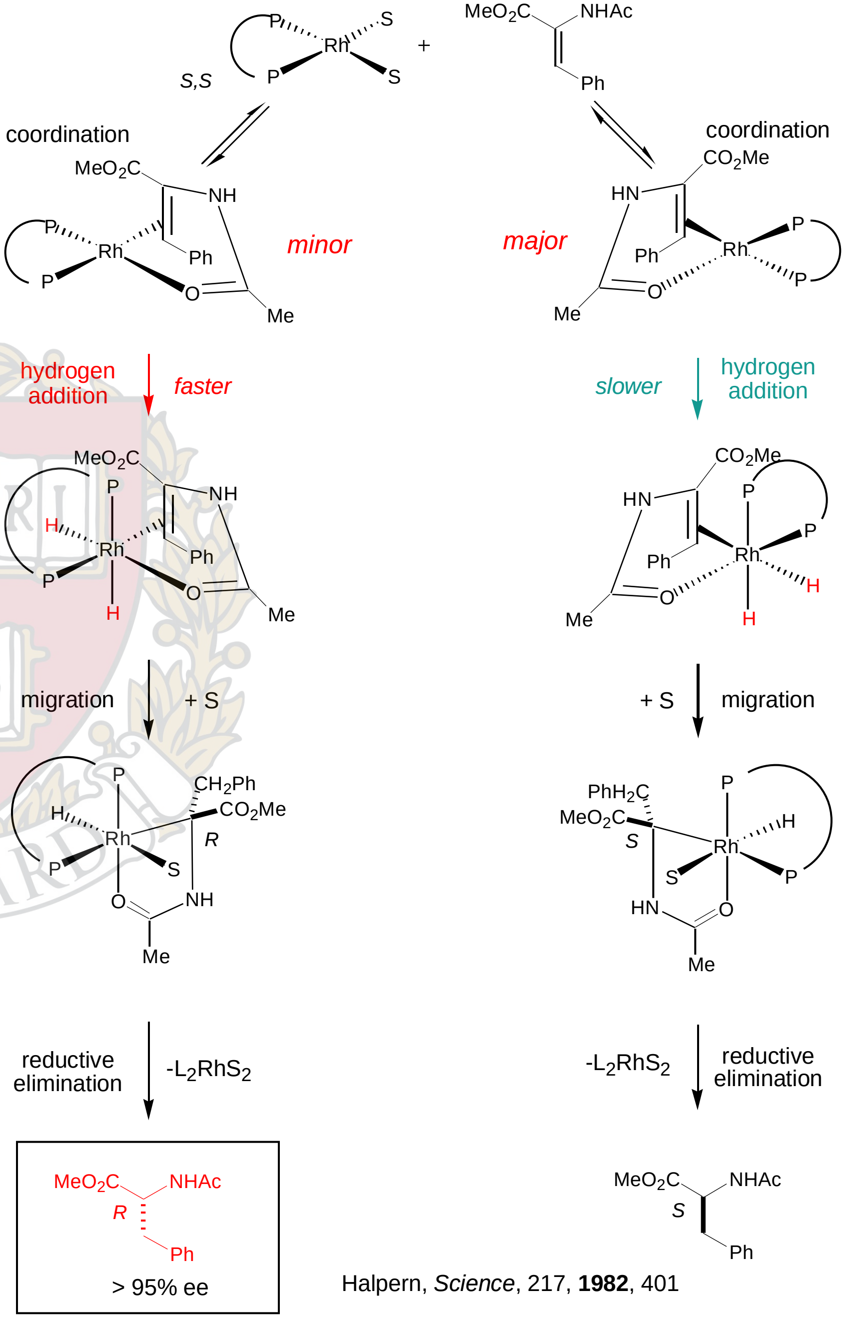
When a chiral ligand is used, there are two diastereomeric complexes which may be formed:



Observations:

- Complex 2 is the only diasteromer observed for the catalyst-substrate complex (1HNMR, X-Ray crystallography) in the absence of hydrogen
- The enantioselectivity is strongly dependant on the pressure of H_2, and degrades rapidly at higher hydrogen pressures
- The observed enantiomer is exclusively derived from the minor complex 2

These observations may be explained using the ***Curtin - Hammett Principle***

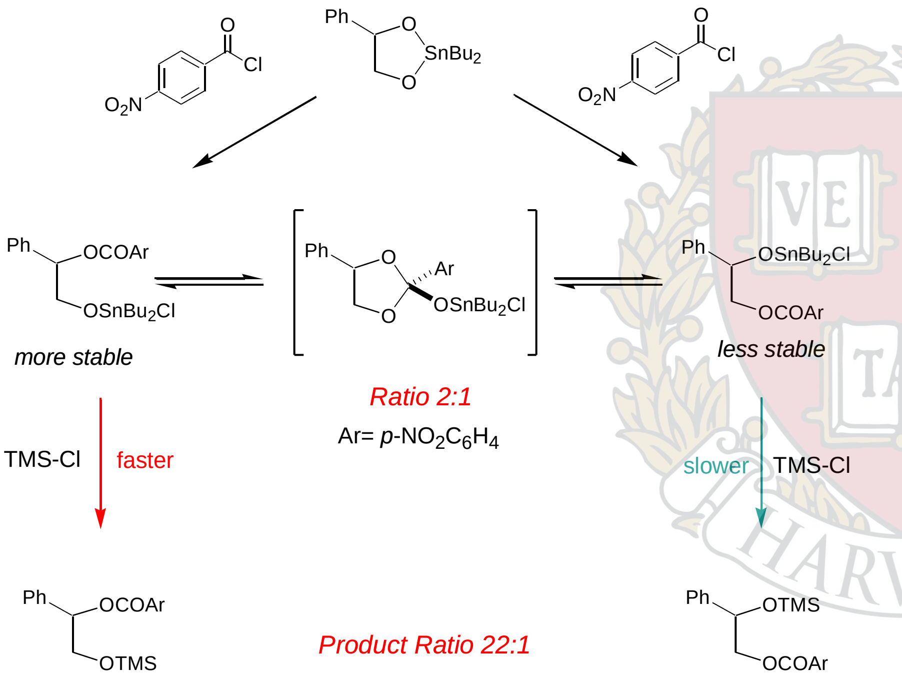


Halpern, *Science*, 217, **1982**, 401

The Curtin-Hammett treatment can be extended to ANY case where different products are formed from two rapidly intereconverting starting materials, whether they are conformers, tautomers or isomers.

$$\underset{\textit{major}}{P_A} \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow{k_2} \underset{\textit{minor}}{P_B}$$

Stannylene ketals provide an efficient way to acylate the more hindered site of 1,2-diols.



The two stannyl esters are in equilibrium at room temperature, and the more stable isomer is initially formed more slowly. The stannyl esters are allowed to equilibrate before quenching with TMS-Cl, which reacts more rapidly with the less hindered primary alkoxystannane.

JOC **1996**, 5257

"It was pointed out by Professor L. P. Hammett in 1950 (private communication) that ..."

David Y. Curtin, 1954

" Because Curtin is very generous in attributing credit, this is sometimes referrred to as the Curtin-Hammett principle rather than the Curtin principle."

Louis Plack Hammett, 1970

Curtin - Hammett Principle: *The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.*

THE TAKE-HOME LESSON:

Never assume that the most stable conformation of a compound is the most reactive. It may be, but then again, it may not.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 8

Olefin Addition Reactions–1

- Hydroboration
- Epoxidation & Directed Epoxidation

Reading Assignment for week

A. Carey & Sundberg: **Part B**; Chapter 4
"Electrophilic Additions to C–C Multilple Bonds"

K. Houk, *Science.* **1986**, *231*, 1108-1117
Theory & Modeling of Stereoselective Organic Reactions ***(Handout)***

K. Houk, *Tetrahedron.* **1984**, *40*, 2257-2274
Theoretical Studies of Stereoselective Hydroboration Reactions ***(Handout)***

D. A. Evans

Friday,
September 28, 2001

Other Reading Material

Smith, K. and A. Pelter (1991). Hydroboration of C=C and Alkynes. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 8: 703.

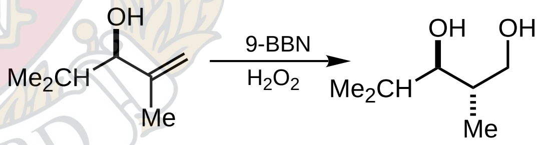
Beletskaya, I. and A. Pelter (1997). “Hydroborations catalysed by transition metal complexes.” Tetrahedron 53(14): 4957-5026.

Brown, H. C. and P. K. Jadhav (1983). Asymmetric Hydroboration. Asymmetric Synthesis. J. D. Morrison. New York, AP. 2: 1.

Hoveyda, A. H., D. A. Evans, et al. (1993). “Substrate-directable chemical reactions.” Chem. Rev. 93: 1307-70.

Problems of the Day: (To be discussed)

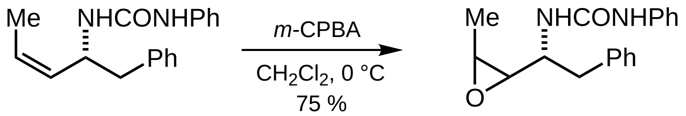
Rationalize the stereochemical outcome of this reaction



diastereoselection 24:1

W. C. Still & J. C. Barrish, *J. Am. Chem. Soc.* **1983**, *105*, 2487.

Predict the stereochemical outcome of this reaction



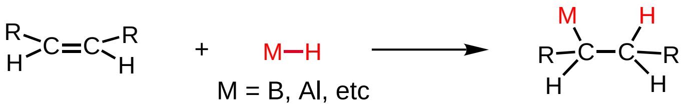
Diastereoselection = 95 : 5

Roush, *J. Org. Chem.* **1987**, *52*, 5127.

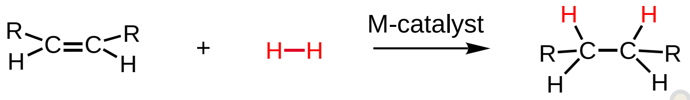
Olefin Addition Reactions: Introduction

Representative Cis-Addition Processes

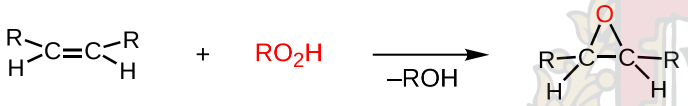
- Hydrometallation



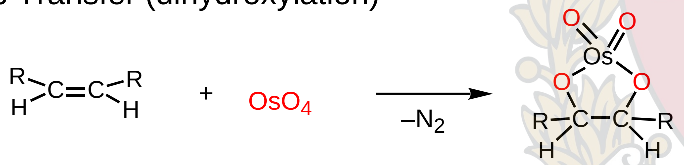
- Hydrogenation



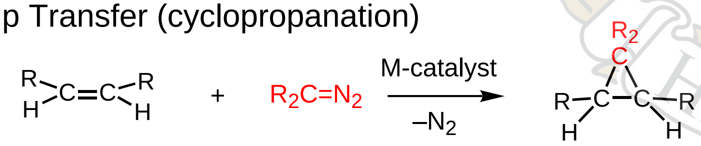
- Group Transfer (epoxidation)



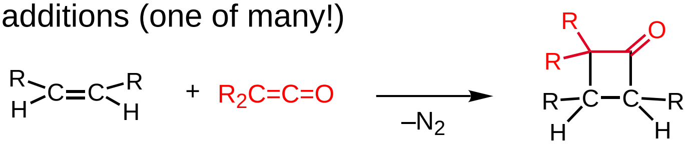
- Group Transfer (dihydroxylation)



- Group Transfer (cyclopropanation)



- Cycloadditions (one of many!)



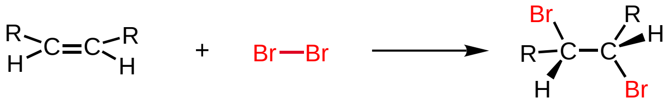
Attributes:

Each process adds to the C=C via a stereospecific process

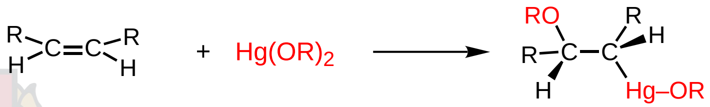
Intermediates *may* be involved in some of the indicated reactions

Representative Trans-Addition Processes

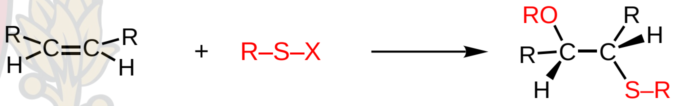
- Halogenation



- Oxy–metallation (M = Hg(II), Tl(III))

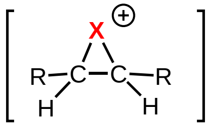


- Oxy–sulfenation (M = S(II), Se(II))



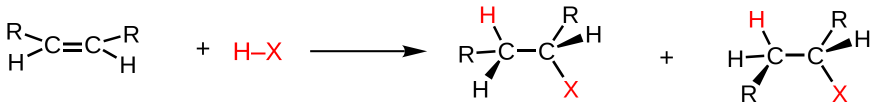
Attributes:

Each process may proceed via an bridged intermediate where X is the initiating electrophile



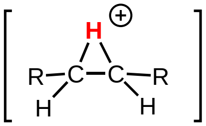
Olefin substitution may disrupt bridging

- Addition of hydrogen halides



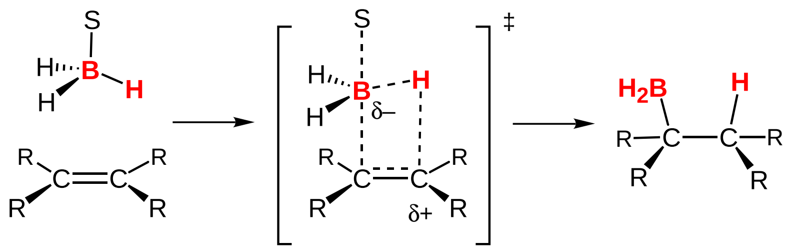
Attributes:

Process may proceed via an bridged intermediate where H+ is the initiating electrophile

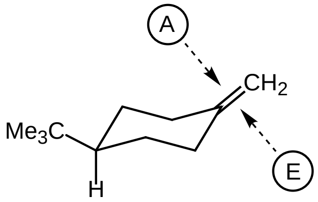


Olefin substitution, reaction conditions as well as halide type may disrupt bridging

- The basic process

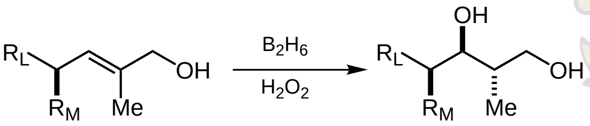


- Response to steric effects: Here is a good calibration system:



Oxidant	Ratio, A:E	Reference
MCPBA	69:31	*JOC*, **1967**, *32*, 1363
BH_3, H_2O_2	34:66	*JOC*, **1970**, *35*, 2654

- Acyclic hydroboration can be controlled by A(1,3) interactions:

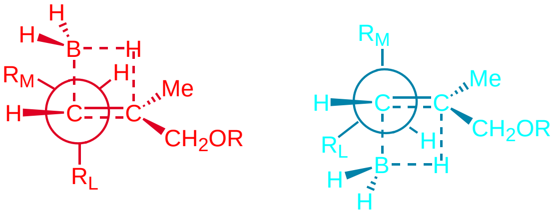


major diastereomer

control elements

A(1,3) allylic strain
Steric effects; R_L vs R_M
Staggered transition states

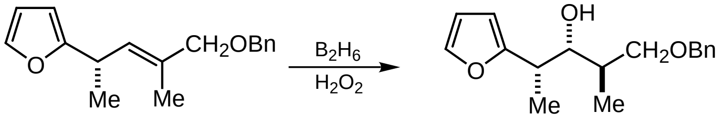
major



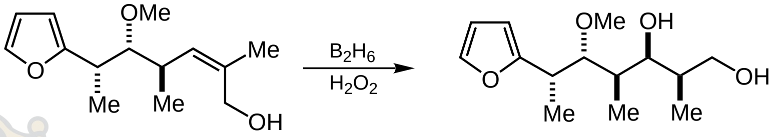
minor

Houk, "*Theoretical Studies of Stereoselective Hydroboration Reactions*"
Tetrahedron **1984**, *40*, 2257 **(Handout)**

Hydroborations dominated by A(1,3) Strain

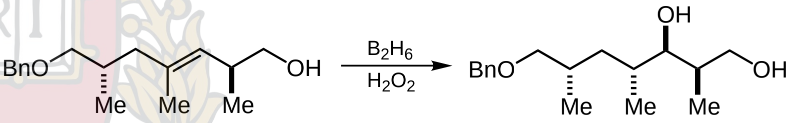


diastereoselection 8:1



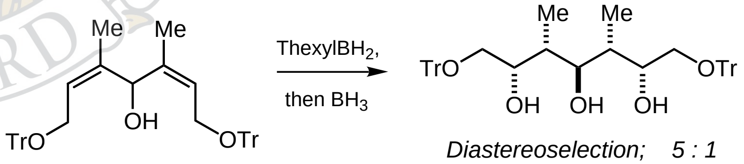
diastereoselection 12:1

Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **1979**, *101*, 259.

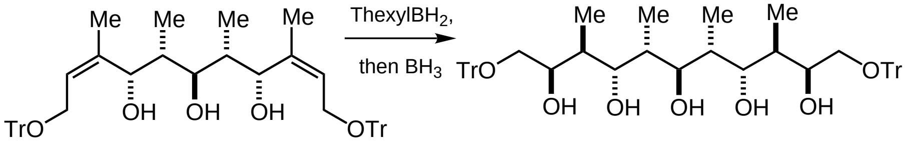


Diastereoselection = 3:1

C. H. Heathcock et. al. *Tetrahedron Lett* **1984** *25* 243.



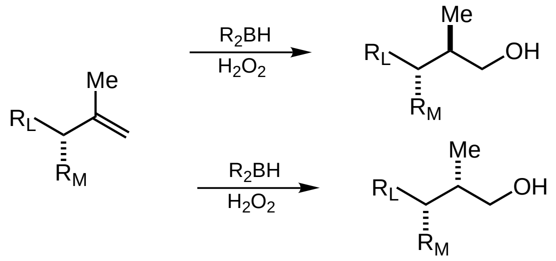
Diastereoselection; 5 : 1



Diastereoselection; 4: 1

Still, W.C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

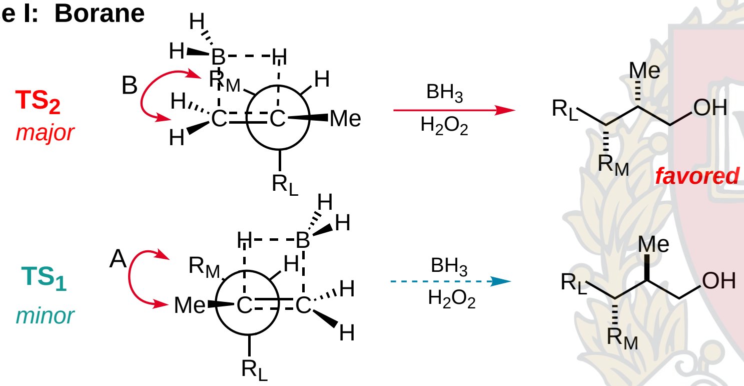
What about the following substitution pattern?



R_2BH structure is a potential variable

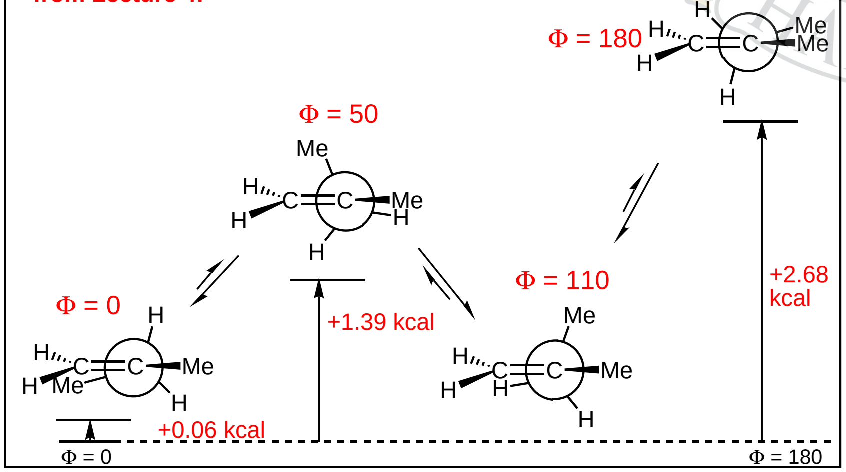
Houk's rules: Orient R_L anti-periplanar to incoming reagents to avoid TS eclipsing:

■ Case I: Borane

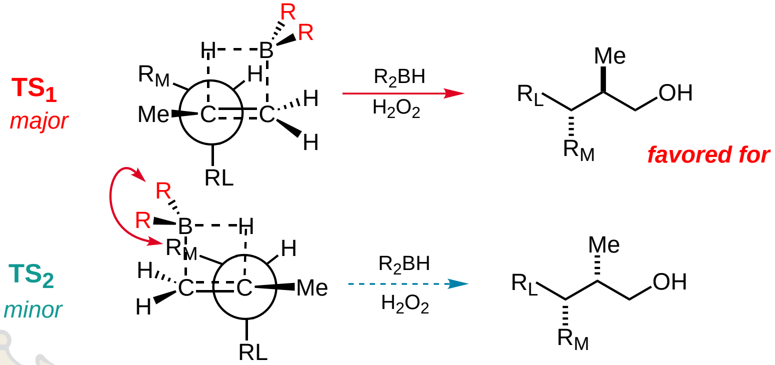


favored for BH_3

from Lecture 4: The Torsional Energy Profile



■ Case II: Dialkylboranes

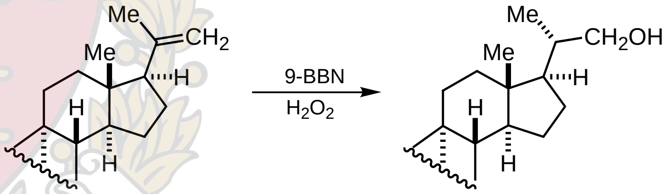


favored for R_2BH

Midland finds that TS_1 favored for R_2BH reagents, but TS_1 ~ TS_2 for BH_3

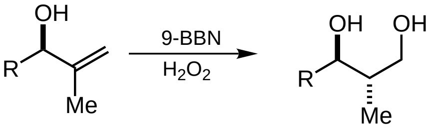
Others have found that TS_1 favored over TS_2 for BH_3

Representative Examples



M. M. Midland & Co-workers, *J. Am. Chem. Soc.* **1983**, *105*, 3725..

R_2BH	*diastereoselection*
borane methylsulfide	1 : 1
thexylborane	4 : 1
9-BBN	14 : 1
dicyclohexylborane	26 : 1

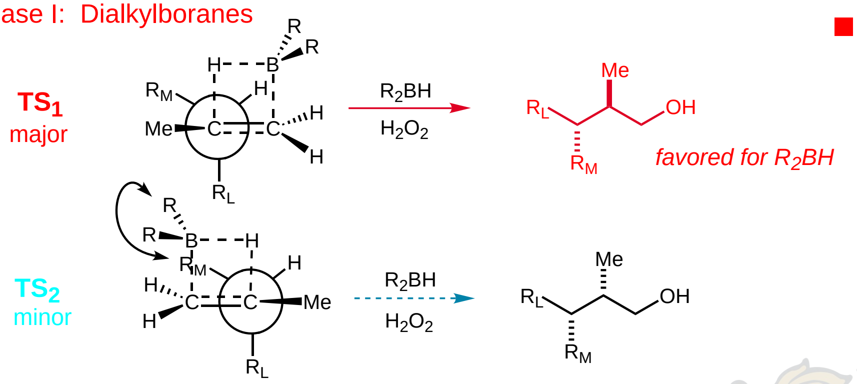


R = n-Bu: *diastereoselection 11:1*
R = $CHMe_2$: *diastereoselection 24:1*

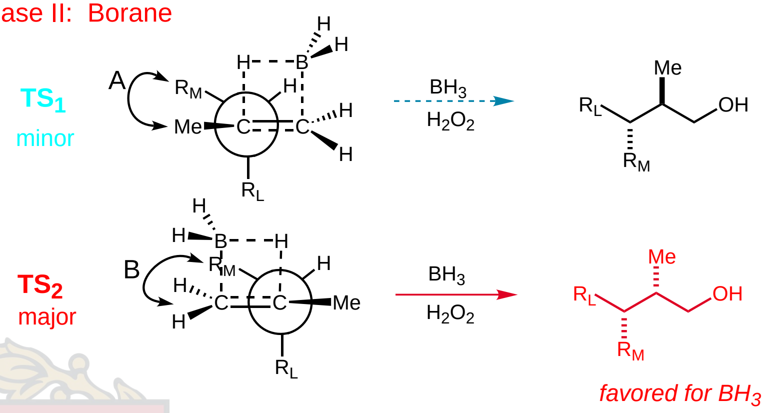
Model is consistent if you presume HO = R_M; R = R_L

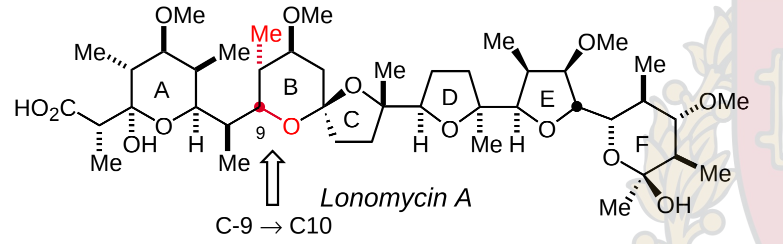
W. C. Still & J. C. Barrish, *J. Am. Chem. Soc.* **1983**, *105*, 2487.

■ Case I: Dialkylboranes

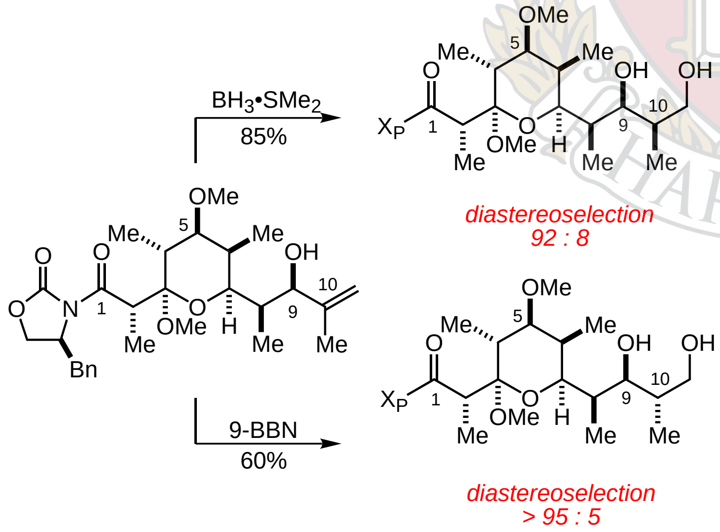


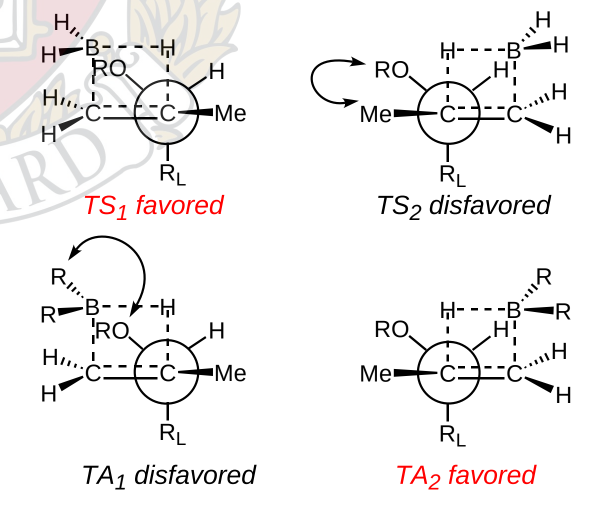
■ Case II: Borane





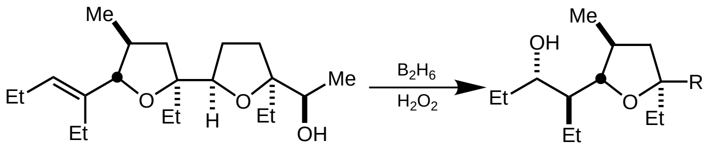
Evans, Ratz, Huff, Sheppard, *JACS* **1995**, *117*, 3448-3467.





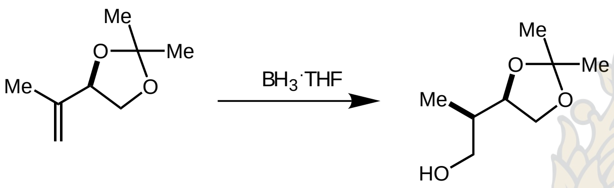
Represetative Hydroboration Examples: Acyclic Control

For each of the examples shown below, attempt to rationalize the stereochemical outcome of the reaction in terms of one of the models presented in the discussion.



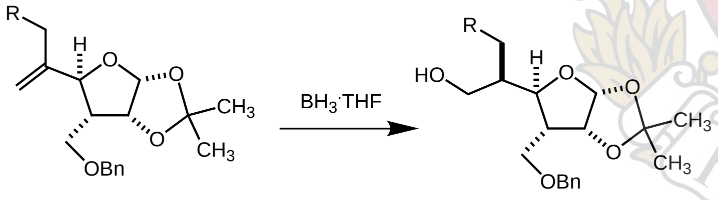
"one isomer"

Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **1978**, *100*, 2933.



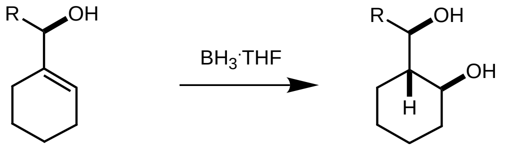
Mori, K.
Tetrahedron **1976**, *32*, 1979

diastereoselection 12:1



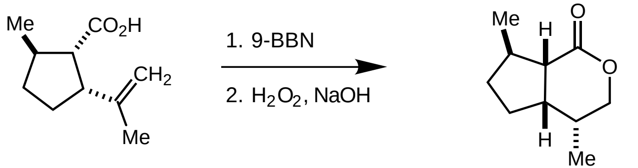
Oikawa et. al.
Tetrahedron Lett. **1983**, *19*, 1987.

R=H; Diastereoselection = 6.8:1
R=OBn Diastereoselection = 6.6:1



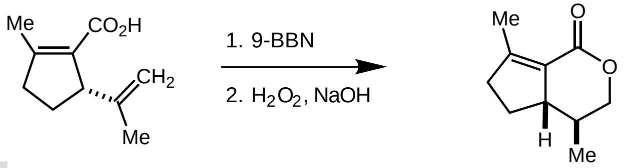
Birtwistle et. al.
Tetrahedron Lett. **1986**, *25*, 243.

R = CH_3; Diastereoselction = 6.7:1
R = isopropyl "One Compound"



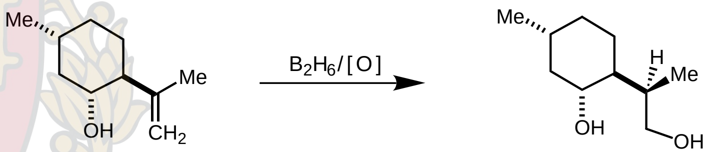
Wolinsky, J.; Eustace, E. J.
J. Org. Chem. **1972**, *37*, 3376.

Diastereoselection = 7:1

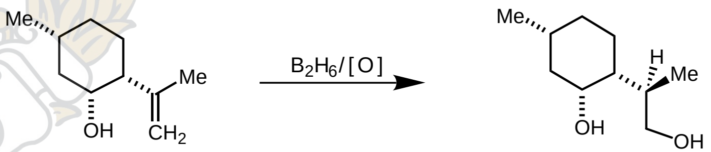


Wolinsky, J.; Nelson, D.
Tetrahedron. **1968**, *25*, 3767.

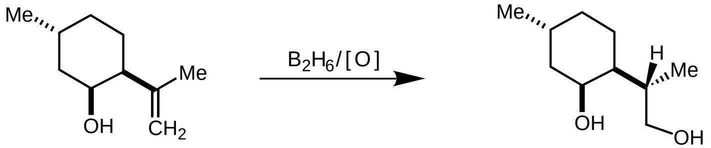
Diastereoselection = 10:1



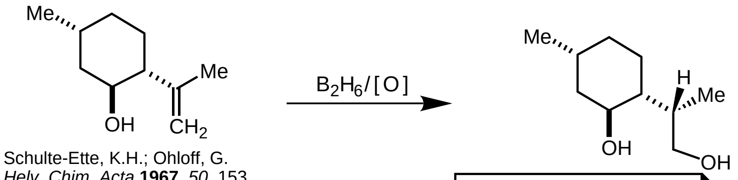
Diastereoselection = 19:1



Diastereoselection = 32:1



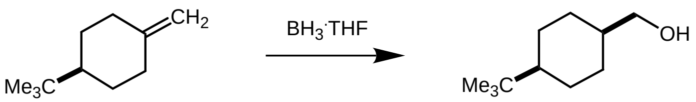
Diastereoselection = 10:1



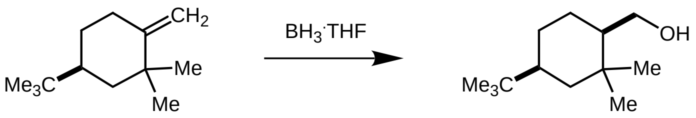
Schulte-Ette, K.H.; Ohloff, G.
Helv. Chim. Acta **1967**, *50*, 153.

Diastereoselection = 4.6:1

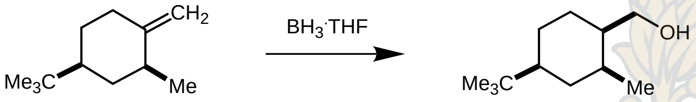
Representative Hydroboration Examples: Cyclic Systems



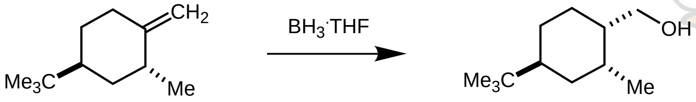
Diastereoselection = 2.1:1



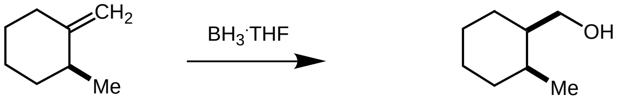
Diastereoselection = 1.2:1



Diastereoselection = 3.3:1

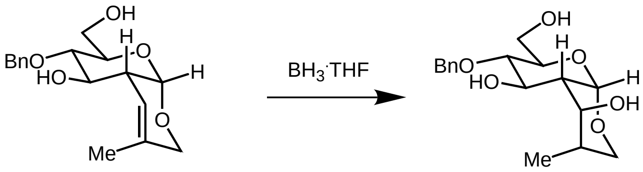


Diastereoselection = 2.4:1



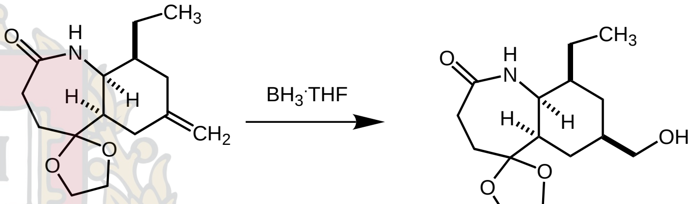
Y. Senda et. al.
Tetrahedron **1977**, *33*, 2933.

Diastereoselection = 4.9:1
(Compare with H.C. Brown's case, with 9-BBN; 1.5:1)



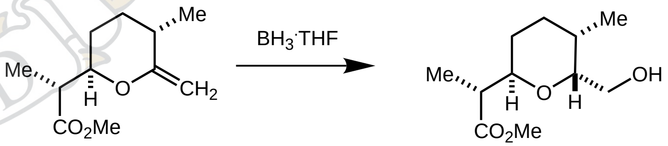
B. Fraser-Reid et. al.
J. Am. Chem. Soc. **1984**, *106*, 731.

Major isomer; no ratio given.



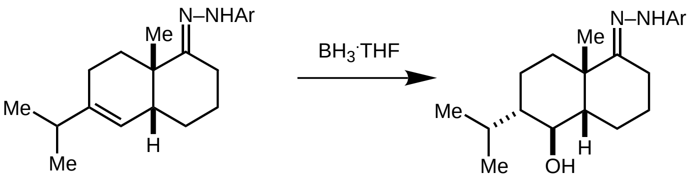
Sallay, S. I.
J. Am. Chem. Soc. **1967**, *89*, 6762.

90% yield, *no diastereoselection given*



Ley, S. et.al.
J. Chem. Soc. Chem. Commun. **1983** 630.

55% yield with the diastereomeric alcohol produced in an unspecified amount. Recycling of the minor isomer further provided 15% of the desired material



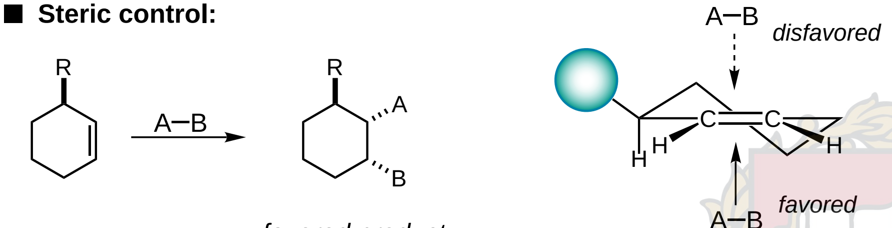
McMurry, J. E.
J. Am. Chem. Soc. **1968**, *90*, 6321.

Minor diastereomer not detected

Stereochemical Control Elements for all reactions

- Steric & Electronic Factors
- Stereoelectronic Considerations
- Associative Substrate-Reagent Interactions

Steric control:

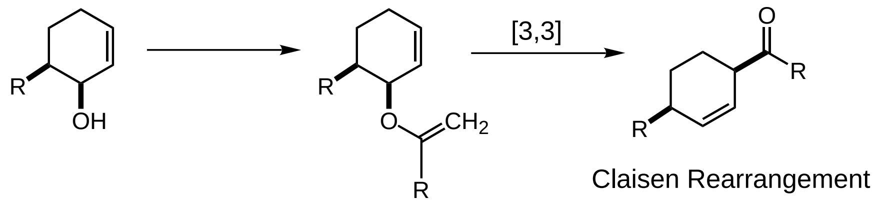


favored product

Nonbonding Interactions disfavor the syn diastereoface

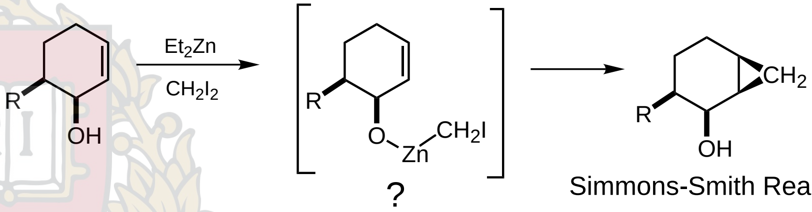
Heteroatom-directed Reactions

Mechanism-based: (HO & C=C must be allylic)



Claisen Rearrangement

via Reagent Ligation

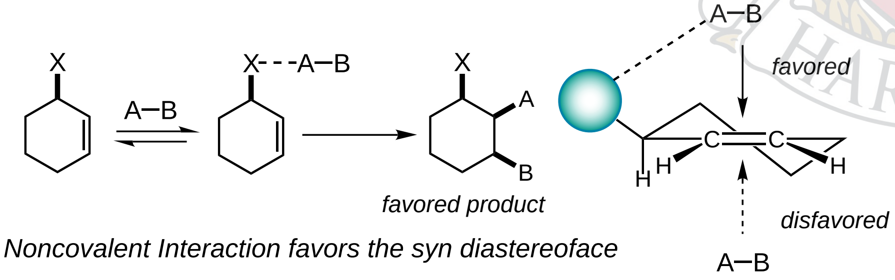


Simmons-Smith Reaction

Directed Reactions

Review: Hoveyda, Evans, Fu *Chem. Reviews* **1993**, *93*, 1307

Associative Substrate-Reagent Interactions



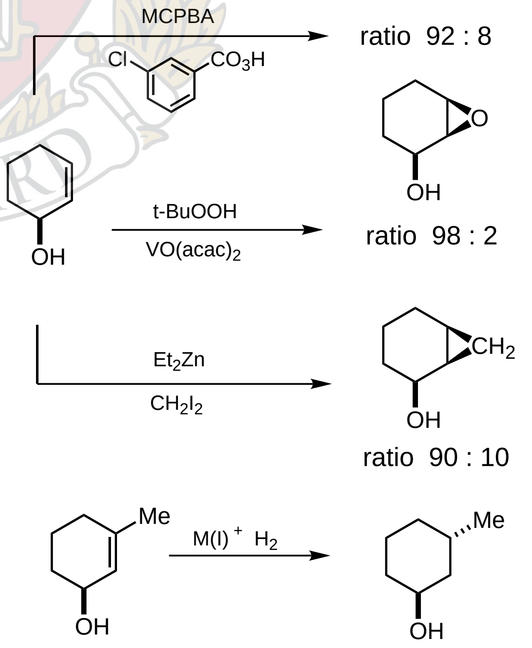
favored product

Noncovalent Interaction favors the syn diastereoface

Agenda

- Directed Oxidations
  - Epoxidation
  - Hydroboration
- Directed Reductions
  - Hydrogenation
  - Hydride reduction
- Directed C–C Bond Constructions

Hydroxyl-directed Reactions



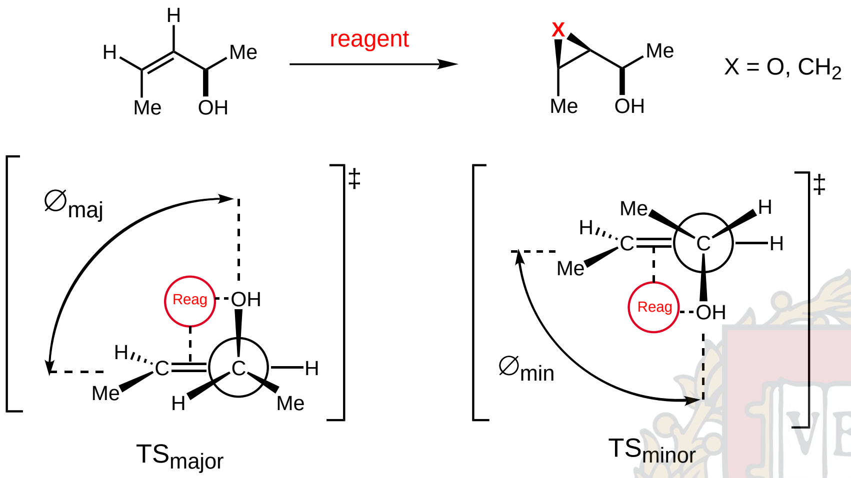
Henbest
J. Chem. Soc. 1958, (1957)

Sharpless
JACS **95**, 6136, (1973)

Winstein
JACS **91**, 6892, (1969)

(Ir^+) Stork
JACS **105**, 1072 (1983)
(Rh^+) Evans
JACS **106**, 3866 (1984)

Orientation of the Directing Group



Orientation of directing group is not the same for all reactons

Reagent	Selectivity	Φ Estimate
t-BuO_2H, V^{+5}	71 : 29	~ 50 °
RCO_3H	95 : 5	~ 120 °
CH_2I_2, Zn–Cu	> 99 : 1	?

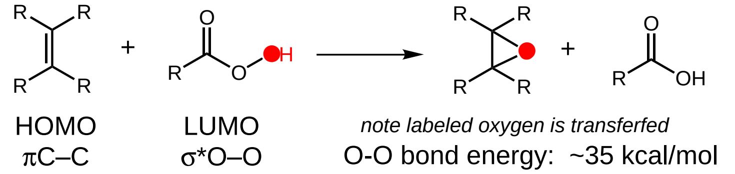
The transition state bite angles for the above reactions are either not known or have been only crudely estimated.

The "best guesses" are provided.

Peracid Epoxidation

A. Rao in *Comprehensive Organic Synthesis,* Trost, Ed., **1992**, Vol 7, Chapter 3.1

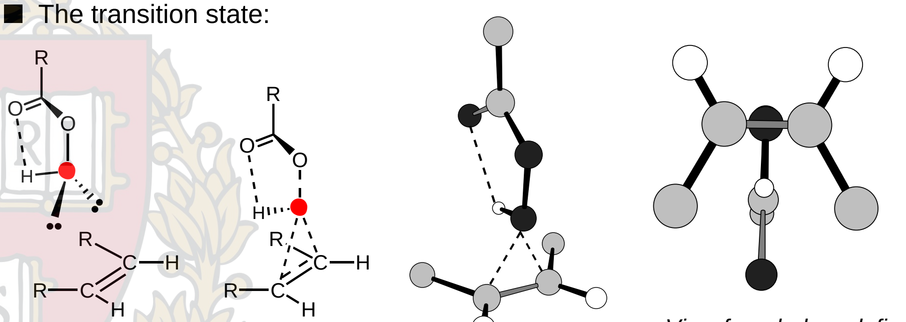
- General Reaction:



note labeled oxygen is transferfed

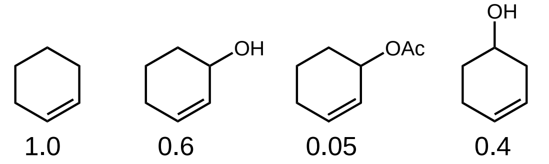
O-O bond energy: ~35 kcal/mol

- The transition state:

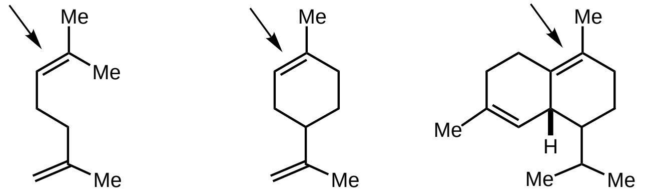


View from below olefin

- Reaction rates are governed by olefin nucleophilicity. The rates of epoxidation of the indicated olefin relative to cyclohexene are provided below:

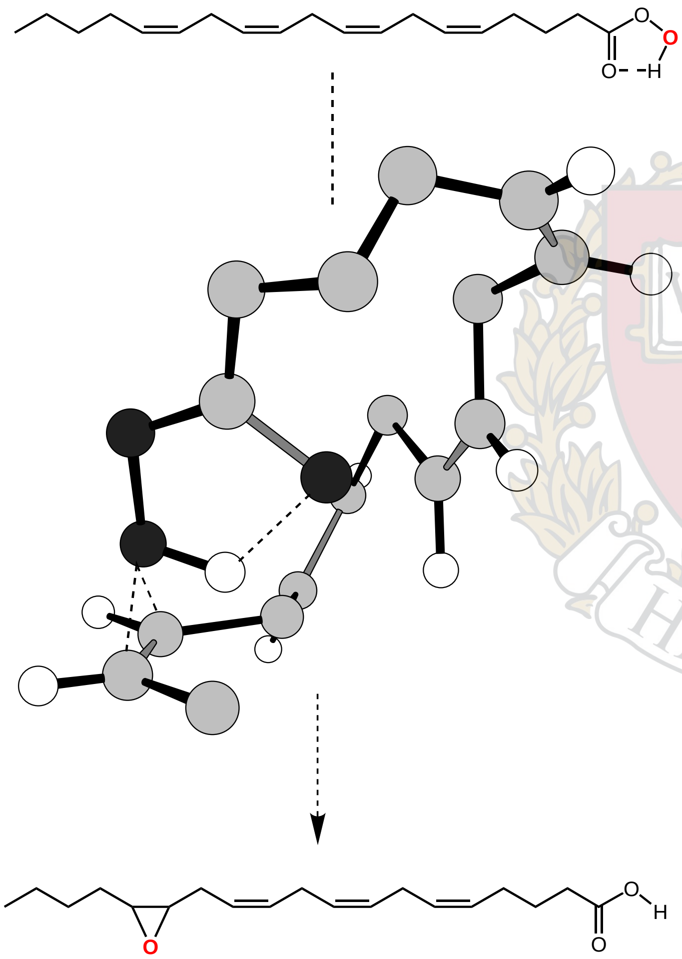


- The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



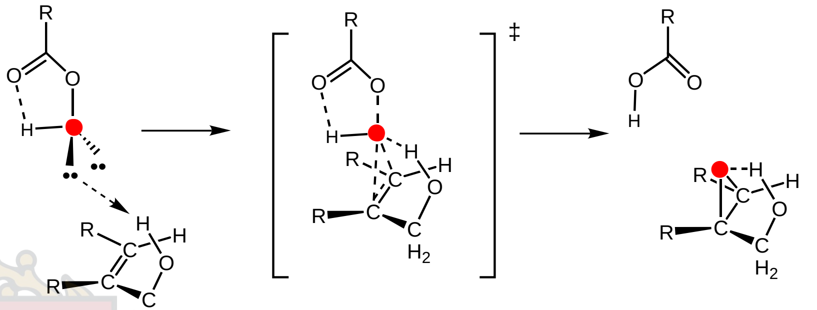
Stereoelectronic Implications of intramolecular Peracid Epoxidation

- Per-arachidonic acid Epoxidation: Corey, *JACS* **101**, 1586 (1979)



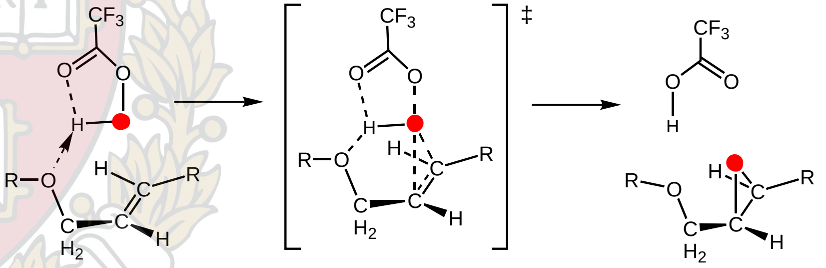
The Directed Peracid Epoxidation

- **Transition State Hydrogen Bonding: Substrate as H-bond donor (Henbest)**

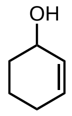
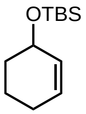
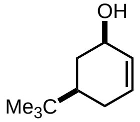
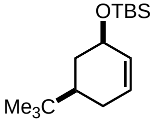
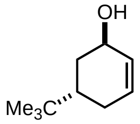
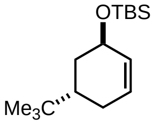


require allylic or homoallylic alcohol

- **Transition State Hydrogen Bonding: Peracid as H-bond donor (Ganem)**



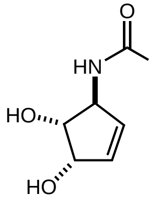
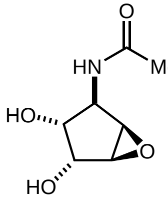
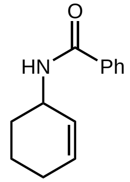
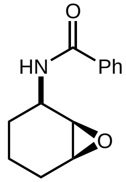
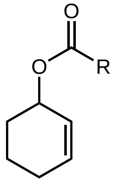
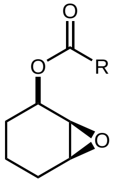
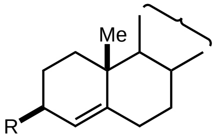
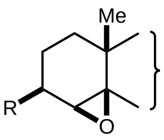
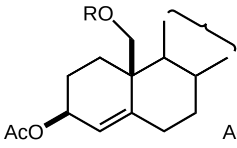
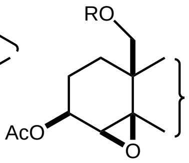
require more acidic peracid both allylic alcohols and ethers OK

	Syn : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)		*Syn* : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)
	24 : 1	50 : 1		1 : 7	5 : 1
	24 : 1	100 : 1		1 : 8	12 : 1
	5 : 1	100 : 1		1 : 4	1 : 6

Ganem *Tet. Let.* **1985**, *26*, 4895

Diastereoselective Peracid Epoxidation

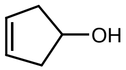
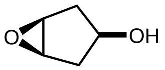
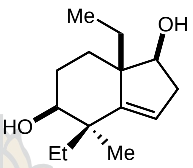
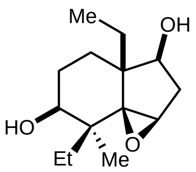
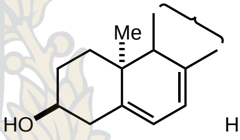
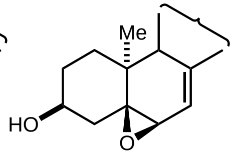
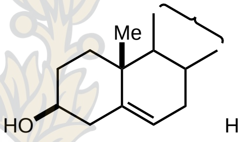
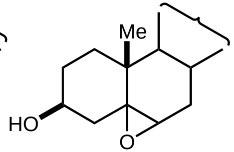
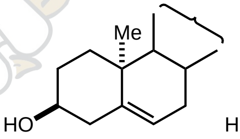
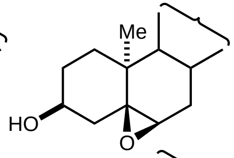
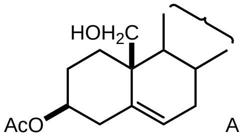
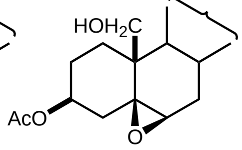
Epoxidation of Cyclic Olefins with Amide &Urethane Directing Groups

Substrate	Major Product	Selectivity
		"highly selective"
		"highly selective"
		a. R = NH_2 3 : 1 b. R = NHBn 5 : 1 c. R = NMe_2 10 : 1
		a. R = OCONHBn >20 : 1 b. R = $OCONMe_2$ >20 : 1
		a. R = $CONH_2$ 6 : 1 b. R = CONHBn >10 : 1 c. R = $CONMe_2$ 2 : 1

Conditions: Perbenzoic acid, or meta-chlorobenzoic acid in benzene.

(Table 11, p1316, from the Evans, Hoveyda, Fu review article)

Epoxidation of Cyclic Homoallylic Alcohols

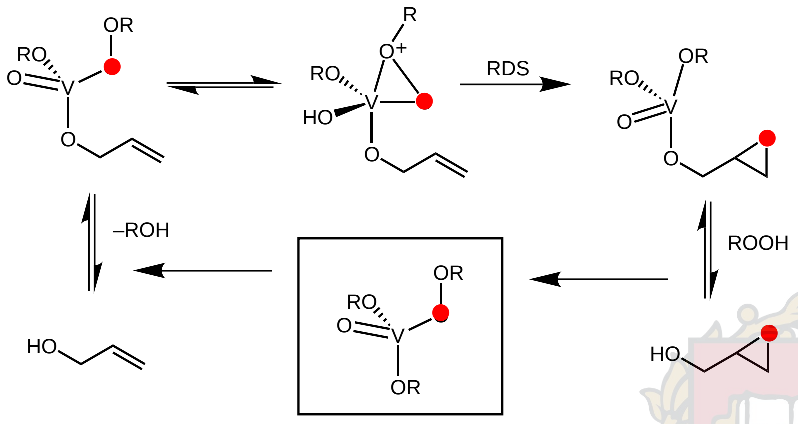
Substrate	Major Product	Selectivity
		9 : 1
		"highly selective"
		16 : 1
		1 : 1
		21 : 1
		5 : 1

Conditions: Perbenzoic acid, or meta-chloroperbenzoic acid in benzene or cyclopentane.

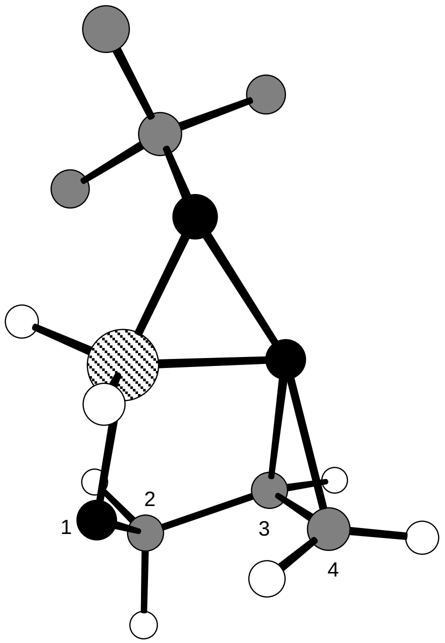
(Table 14, p1318, from the Evans, Hoveyda, Fu review article)

Sharpless Epoxidation (V+5)

The Sharpless Epoxidation

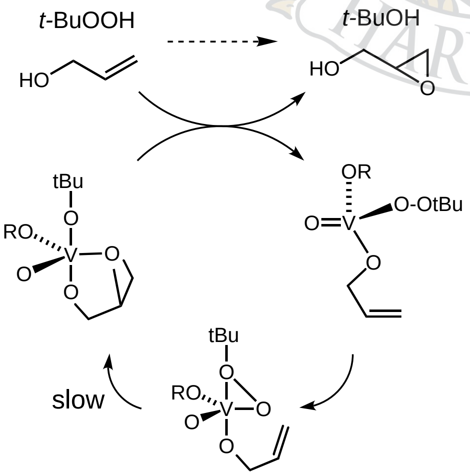


Aldrichimica Acta, **12**, 63 (1979)

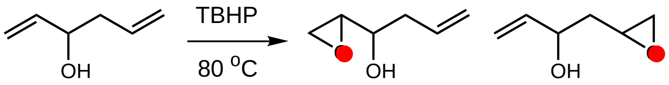


Chem 3D Transition State

$O–C_2–C_3–C_4$ = 41°
The Sharpless estimate: ~50°

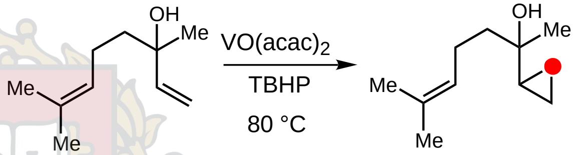


■ The literature precedent: Sheng, Zajecek, *J. Org. Chem.* **1970**, *35*, 1839

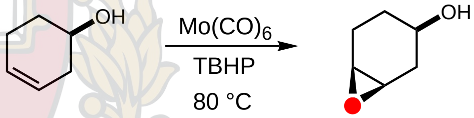


Catalyst		
	$VO(acac)_2$	4 : 1
	$Mo(CO)_6$	1 : 1

■ Next step: Sharpless, Michaelson *JACS* **1973**, *95*, 6136

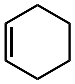
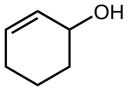
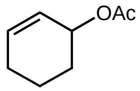
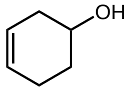


Regioselection 20:1



Stereoselection 98:2
(90 % yield)

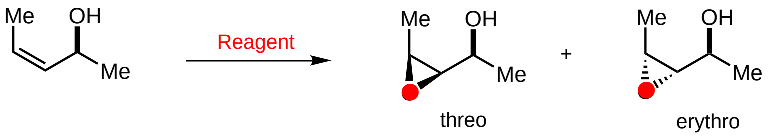
Relative Rates (Diastereoselectivities) for the Epoxidation of Cyclohexene Derivatives *JACS* **1973**, *95*, 6136

Substrate	$k_{rel}^{a,b}$ (diastereoselectivity^{c})		
	peracid	$Mo(CO)_6$	$VO(acac)_2$
	1.00	1.00	1.00
 OH	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)
 OAc	0.046 (37 : 63)	0.07 (40 : 60)	--
 OH	0.42 (60 : 40)	11.0 (98 : 2)	10.0 (98 : 2)

[a,b] The relative rate data apply only to a given column.
Values in parenthesis refer to the ratio of syn:anti epoxide.

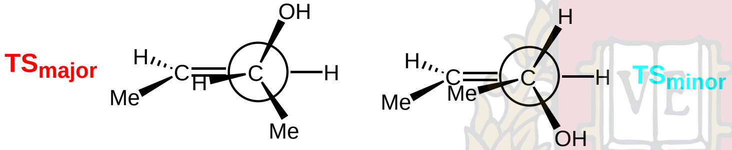
Epoxidation of Acyclic Alcohols

■ Allylic Alcohols:

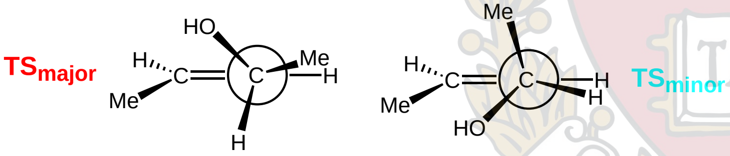


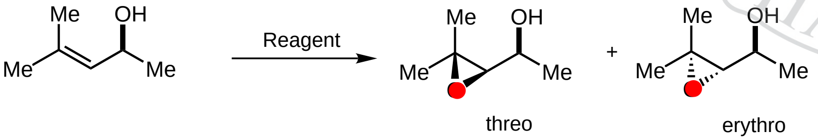
Φ Estimate	Reagent	Ratio
~ 120 °	*m*-CPBA	95 : 5
40-50 °	*t*-BuOOH / VO(acac)$_2$	71 : 29
	t-BuOOH / Mo(CO)$_6$	84 : 16

■ RCO$_3$H Transition States: Φ ~ 120 °



■ V(+) Transition States: Φ ~ 45 °

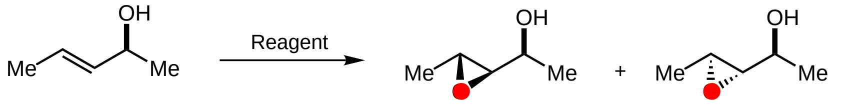




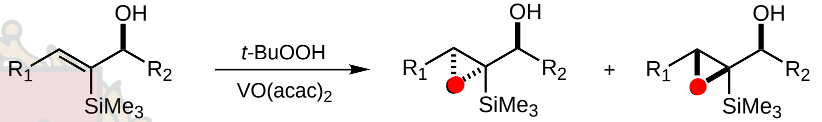
K. Oshima & Coworkers
Tetrahedron Lett. **1980**, *21*, 1657, 4843.

K. B. Sharpless & Coworkers
Tetrahedron Lett. **1979**, *20*, 4733.

Reagent	Ratio
m-CPBA	95 : 5
t-BuOOH / VO(acac)$_2$	86 : 14
t-BuOOH / Mo(CO)$_6$	95 : 5
t-BuOOH / (*t*-BuO)$_3$Al	100 : 0

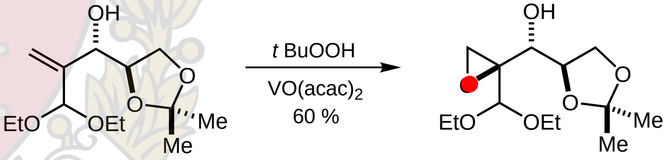


Reagent	Ratio
m-CPBA	64 : 36
t-BuOOH / VO(acac)$_2$	29 : 71
t-BuOOH / Mo(CO)$_6$	62 : 38
t-BuOOH / (*t*-BuO)$_3$Al	64 : 36

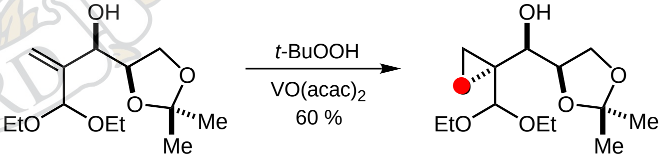


Oshima, *Tetrahedron Lett.* **1982**, *23*, 3387.

R$_1$	R$_2$	Yield	Ratio
H	Bu	84 %	99 : 1
C$_5$H$_{11}$	Me	70 %	99 : 1

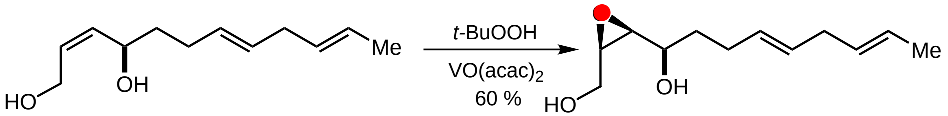


only isomer



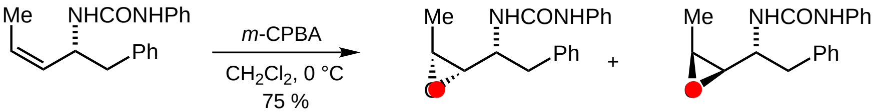
only isomer

Depezay, *Tetrahedron Lett.* **1978**, *19*, 2869.



Boeckman, *JACS* **1977**, *99*, 2805.

Diastereoselection = 7 : 1

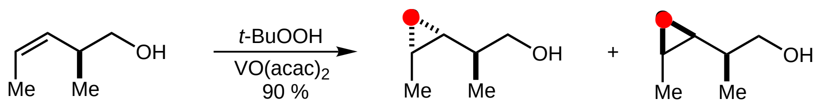


Roush, *J. Org. Chem.* **1987**, *52*, 5127.

Diastereoselection = 95 : 5

Epoxidation of Acyclic Homoallylic Alcohols

Homoallylic Alcohols (Mihelich, *JACS* **1981**, *103*, 7690)

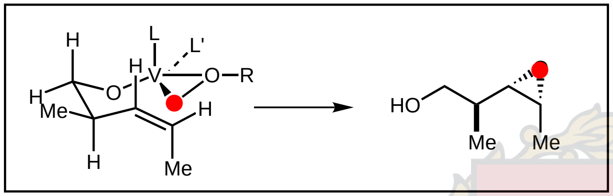


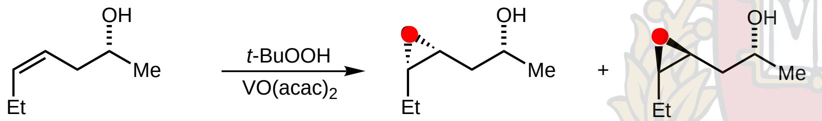
Diastereoselection > 400 : 1

Control Elements

A(1,3) Strain

Directed Rxn

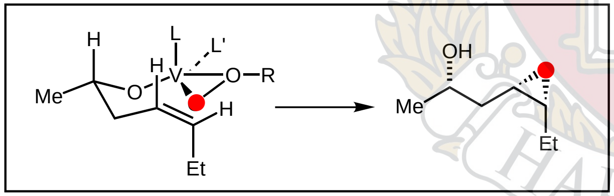




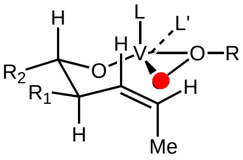
Diastereoselection 12 : 1

Control Elements

Directed Rxn

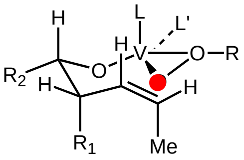


Prediction



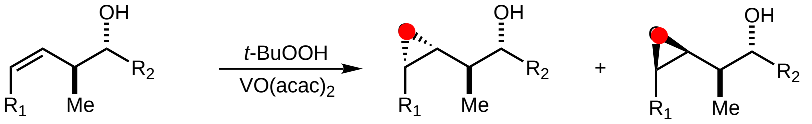
Anti diastereomer

Anti should be more diastereoselective than syn



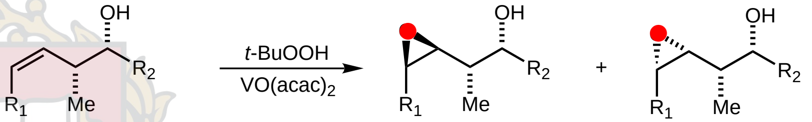
Syn diastereomer

Anti diastereomer

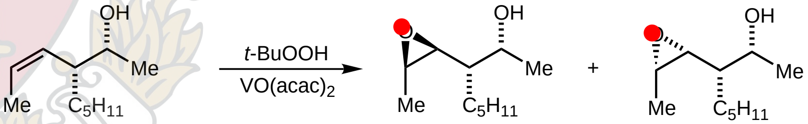


R_1	R_2	Yield	Ratio
C_6H_{13}	Me	92 %	104 : 1
Me	*i*-Pr	97 %	> 400 : 1

Syn diastereomer



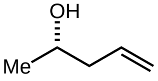
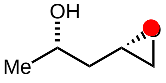
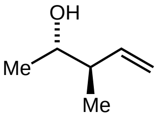
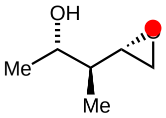
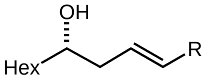
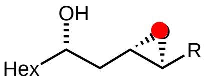
R_1	R_2	Yield	Ratio
C_6H_{13}	Me	73 %	70 : 1
Me	Me	70 %	85 : 1
Me	C_5H_{11}	81 %	16 :1



E. D. Mihelich & Coworkers
J. Am. Chem. Soc. **1981**, *103*, 7690.

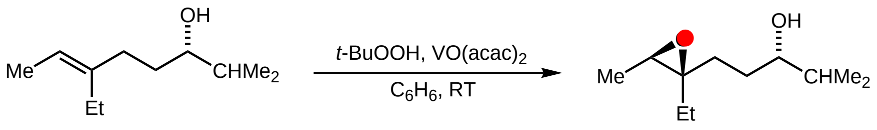
Diastereoselection = 211 : 1

Epoxidation of Homoallylic Alcohols with TBHP, VO(acac)$_2$

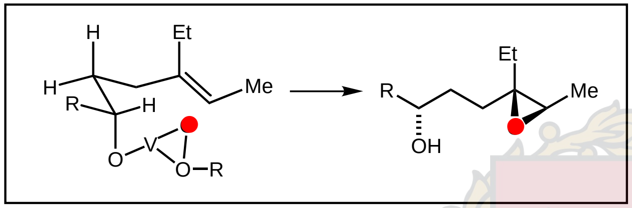
Substrate	Product	Selectivity
		2 : 1
		4.6 : 1
 R = $(CH_2)_7CO_2Me$		1.4 : 1

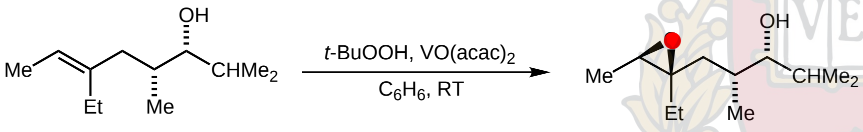
Epoxidation of Acyclic Homoallylic Alcohols

Bishomoallylic Alcohols (Kishi, *Tet. Lett.* **1978**, *19*, 2741)



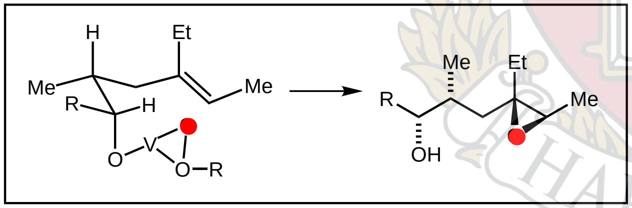
diastereoselection ~ 9 : 1

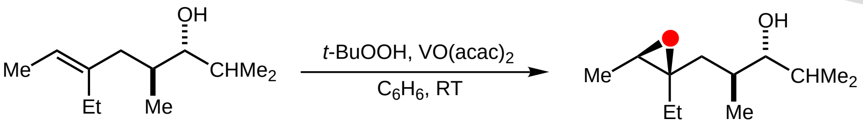




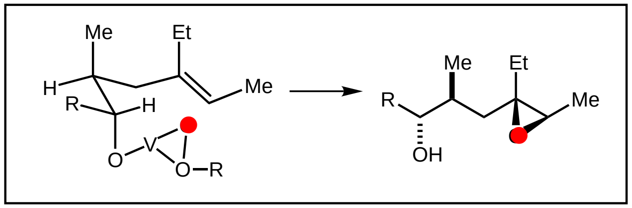
diastereoselection ~ 20 : 1

2nd stereocenter is reinforcing

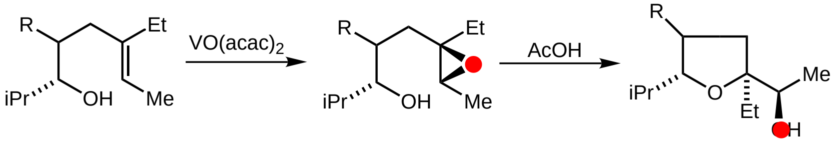




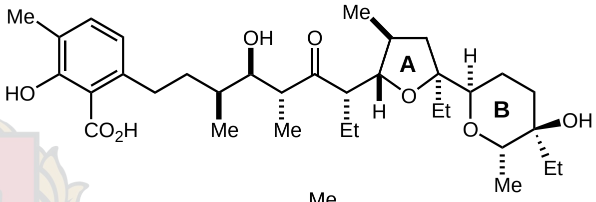
diastereoselection ~ 6 : 1

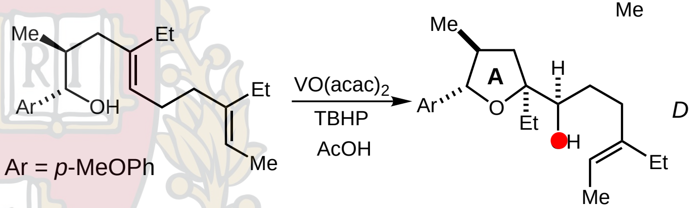


Epoxidation & Cyclization of Bishomoallylic Alcohols



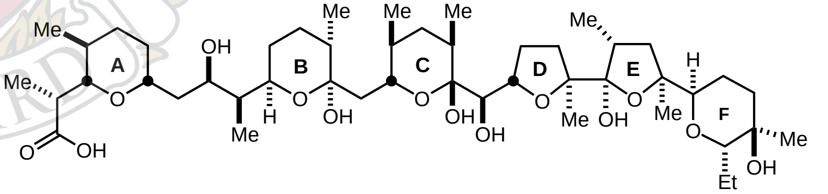
The Kishi Lasalocid Synthesis (*JACS* **1978**, *100*, 2933)

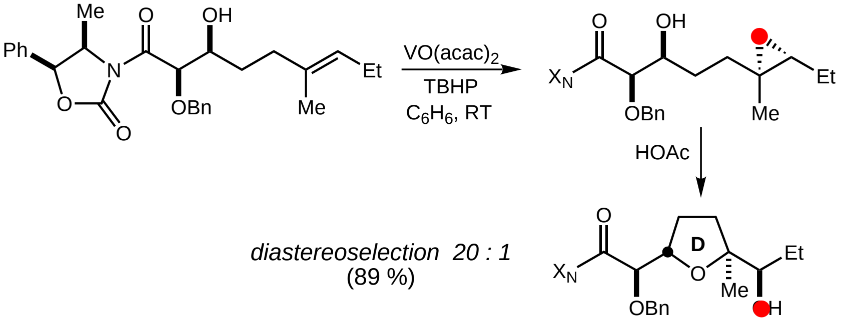




Diastereoselection 8:1

Evans X-206 Synthesis JACS **1988**, *110*, 2506.





diastereoselection 20 : 1
(89 %)

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 9

Olefin Addition Reactions–2

- Epoxidation & Directed Epoxidation
- Hydrogenation
- Hydride Reduction

Reading Assignment for week

A. Carey & Sundberg: **Part B**; Chapter 4
"Electrophilic Additions to C–C Multilple Bonds"

K. Houk, *Science.* **1986**, *231*, 1108-1117
Theory & Modeling of Stereoselective Organic Reactions ***(Handout)***

K. Houk, *Tetrahedron.* **1984**, *40*, 2257-2274
Theoretical Studies of Stereoselective Hydroboration Reactions ***(Handout)***

Hoveyda, Evans, & Fu (**1993**). *Substrate-directable chemical reactions*. Chem. Rev. 93: 1307-70 ***(Handout)***

Matthew D. Shair

Monday,
October 7, 2002

Other Reading Material

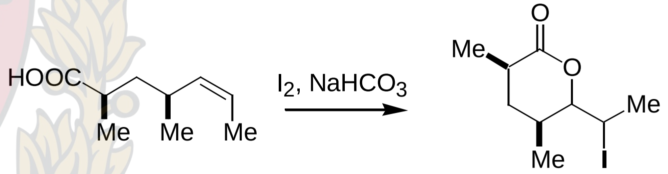
Takaya, H., T. Ohta, et al. (**1993**). Asymmetric Hydrogenation. Catalytic Asymmetric Synthesis. I. Ojima. New York, VCH**:** 1-39.

Bolm, C. (**1993**). "Enantioselective transition metal-catalyzed hydrogenation for the asymmetric synthesis of amines." Angew. Chem., Int. Ed. Engl. **32**: 232.

For a recent general review of the Simmons-Smith reaction see: Charette & Beauchemin, *Organic Reactions*, **58**, 1-415 (2001)

Problems of the Day: (To be discussed)

Predict the stereochemical outcome of the indicated reaction.

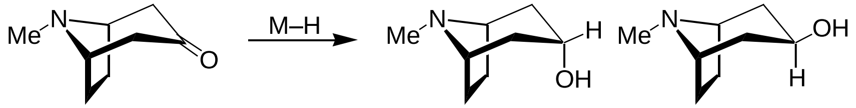


Kinetic Control: 3 eq. I_2, MeCN, $NaHCO_3$, 0°C

diastereoselection: 20:1

Bartlett, P. A.; Richardson, D.; Myerson, J. *Tetrahedron* **1984**, *12*, 2317

Rationalize the stereochemical outcome of the indicated reaction.



R. Noyori
Bull. Chem. Soc. Japan **47**, 2617, (1974)

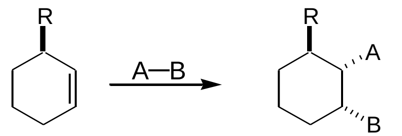
R_2AlH	97 : 3
$LiAlH_4$	28 : 72

Directed Reactions: An Introduction

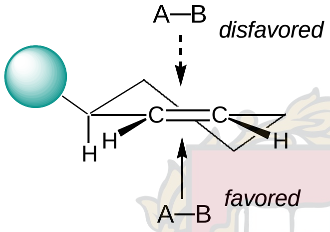
Stereochemical Control Elements for all reactions

- Steric & Electronic Factors
- Stereoelectronic Considerations
- Associative Substrate-Reagent Interactions

- **Steric control:**



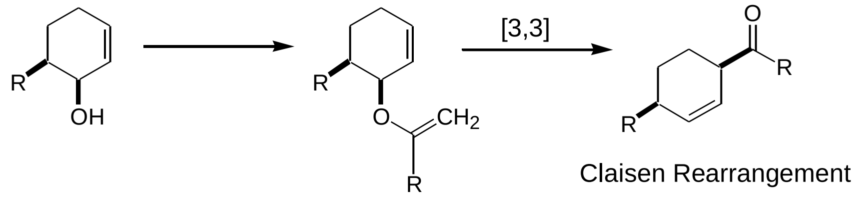
favored product



Nonbonding Interactions disfavor the syn diastereoface

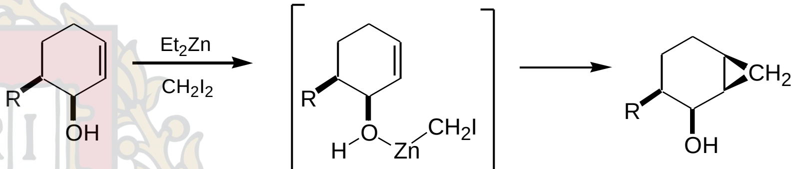
Heteroatom-directed Reactions

Mechanism-based: (HO & C=C must be allylic)



Claisen Rearrangement

via Reagent Ligation

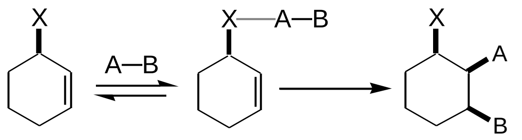


Simmons-Smith Reaction

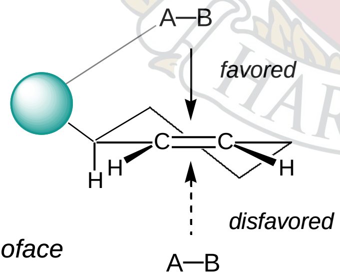
Directed Reactions

Review: Hoveyda, Evans, Fu *Chem. Reviews* **1993**, *93*, 1307

- **Associative Substrate-Reagent Interactions**



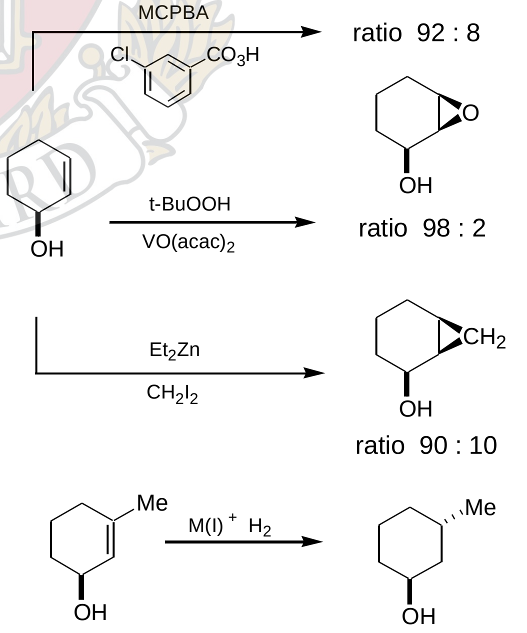
favored product



Noncovalent Interaction favors the syn diastereoface

Agenda
- Directed Oxidations
  - Epoxidation
  - Hydroboration
- Directed Reductions
  - Hydrogenation
  - Hydride reduction
- Directed C–C Bond Constructions

Hydroxyl-directed Reactions



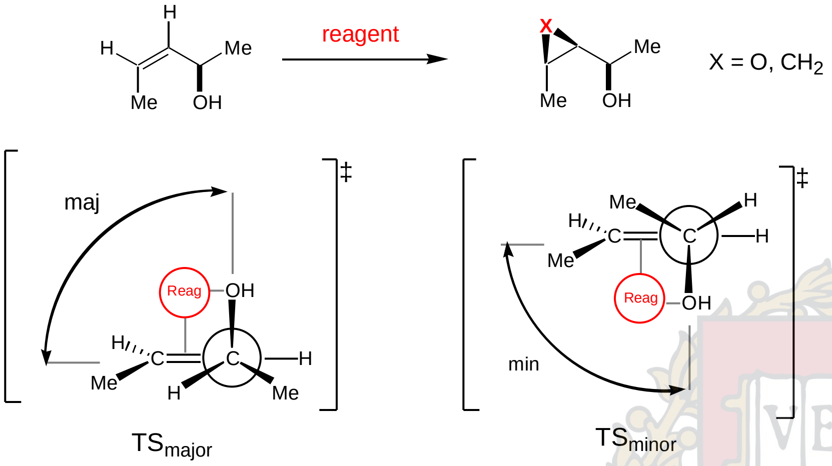
ratio 92 : 8 — Henbest
J. Chem. Soc. 1958, (1957)

ratio 98 : 2 — Sharpless
JACS **95**, 6136, (1973)

ratio 90 : 10 — Winstein
JACS **91**, 6892, (1969)

(Ir^+) Stork
JACS **105**, 1072 (1983)
(Rh^+) Evans
JACS **106**, 3866 (1984)

Orientation of the Directing Group



Orientation of directing group is not the same for all reactons

Reagent	Selectivity	Φ Estimate
t-BuO_2H, V^{+5}	71 : 29	~ 50 °
RCO_3H	95 : 5	~ 120 °
CH_2I_2, Zn–Cu	> 99 : 1	?

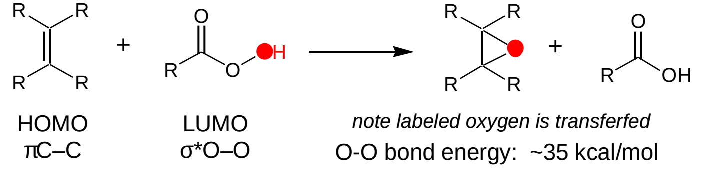
The transition state bite angles for the above reactions are either not known or have been only crudely estimated.

The "best guesses" are provided.

Peracid Epoxidation

A. Rao in *Comprehensive Organic Synthesis,* Trost, Ed., **1992**, Vol 7, Chapter 3.1

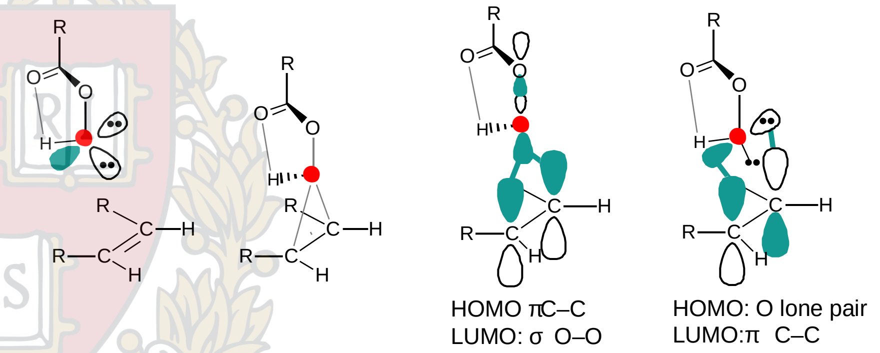
■ General Reaction:



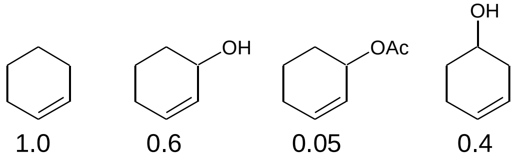
note labeled oxygen is transferfed

O-O bond energy: ~35 kcal/mol

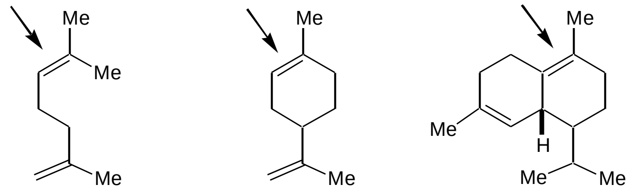
■ Transition state: What about lone pairs. [Consider ● to be Sp^2 hybridized].



■ Reaction rates are governed by olefin nucleophilicity. The rates of epoxidation of the indicated olefin relative to cyclohexene are provided below:



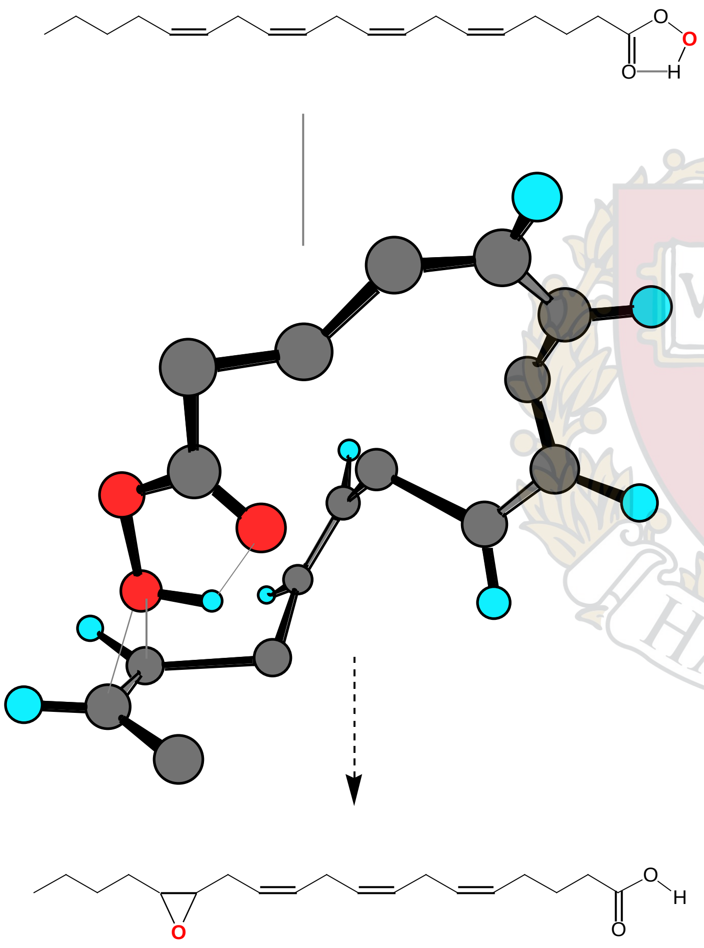
■ The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



Diastereoselective Peracid Epoxidation

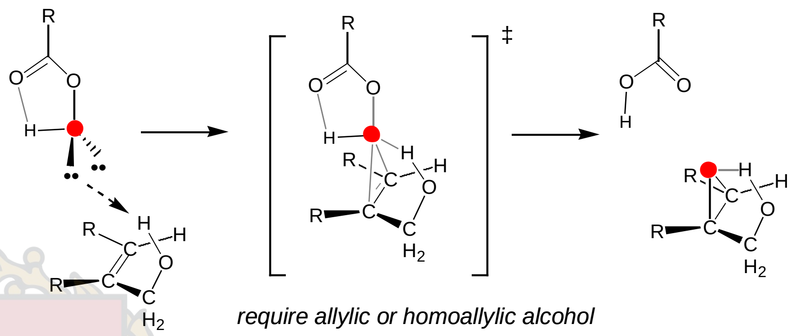
Stereoelectronic Implications of intramolecular Peracid Epoxidation

- **Per-arachidonic acid Epoxidation:** Corey, *JACS* **101**, 1586 (1979)



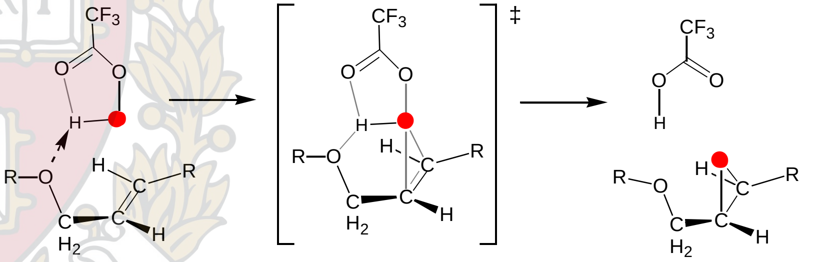
The Directed Peracid Epoxidation

- **Transition State Hydrogen Bonding: Substrate as H-bond donor (Henbest)**

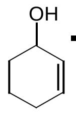
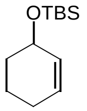
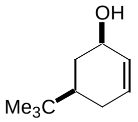
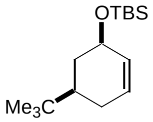
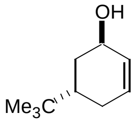
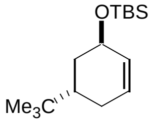


require allylic or homoallylic alcohol

- **Transition State Hydrogen Bonding: Peracid as H-bond donor (Ganem)**

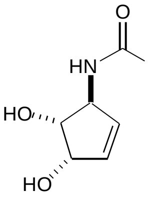
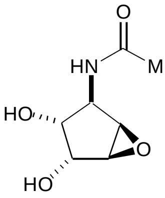
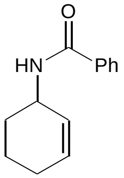
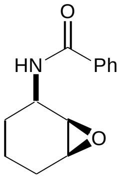
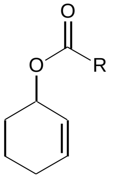
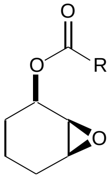
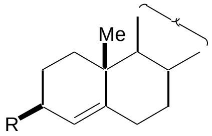
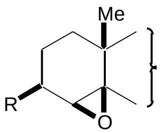
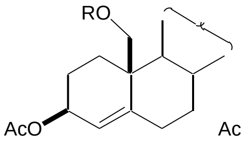
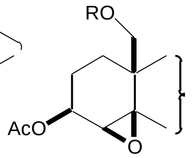


require more acidic peracid both allylic alcohols and ethers OK

	Syn : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)		*Syn* : *Anti* (*m*-CPBA)	*Syn* : *Anti* (CF_3CO_3H)
	24 : 1	50 : 1		1 : 7	5 : 1
	24 : 1	100 : 1		1 : 8	12 : 1
	5 : 1	100 : 1		1 : 4	1 : 6

Ganem *Tet. Lett.* **1985**, *26*, 4895

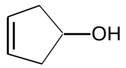
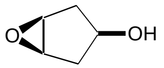
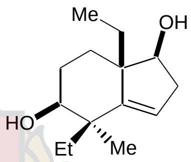
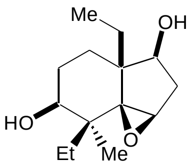
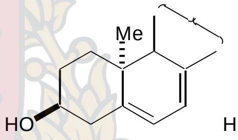
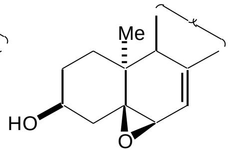
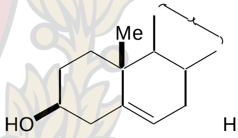
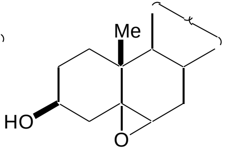
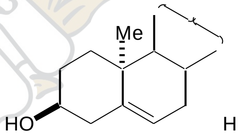
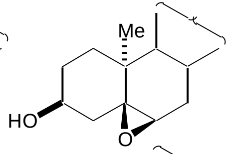
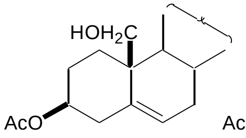
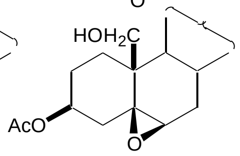
Epoxidation of Cyclic Olefins with Amide &Urethane Directing Groups

Substrate	Major Product		Selectivity
			"highly selective"
			"highly selective"
		a. R = NH_2 b. R = NHBn c. R = NMe_2	3 : 1 5 : 1 10 : 1
		a. R = OCONHBn b. R = $OCONMe_2$	>20 : 1 >20 : 1
		a. R = $CONH_2$ b. R = CONHBn c. R = $CONMe_2$	6 : 1 >10 : 1 2 : 1

Conditions: Perbenzoic acid, or meta-chlorobenzoic acid in benzene.

(Table 11, p1316, from the Evans, Hoveyda, Fu review article)

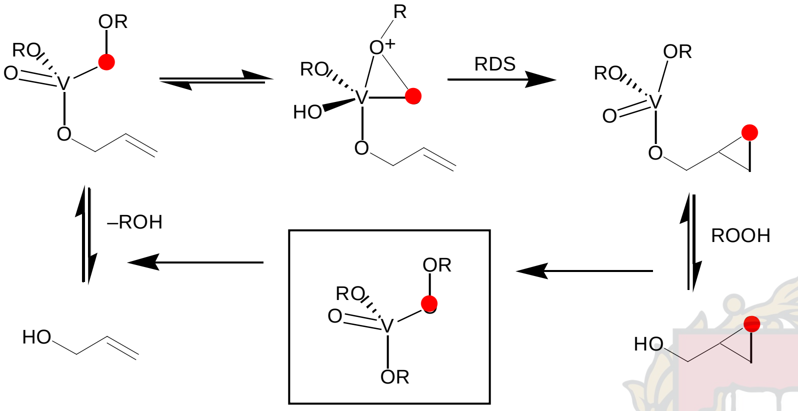
Epoxidation of Cyclic Homoallylic Alcohols

Substrate	Major Product	Selectivity
		9 : 1
		"highly selective"
		16 : 1
		1 : 1
		21 : 1
		5 : 1

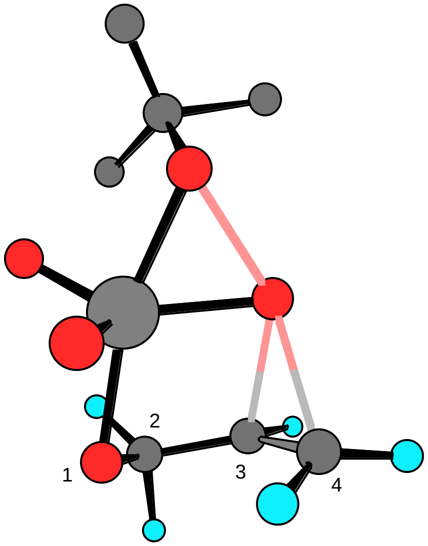
Conditions: Perbenzoic acid, or meta-chloroperbenzoic acid in benzene or cyclopentane.

(Table 14, p1318, from the Evans, Hoveyda, Fu review article)

The Sharpless Epoxidation

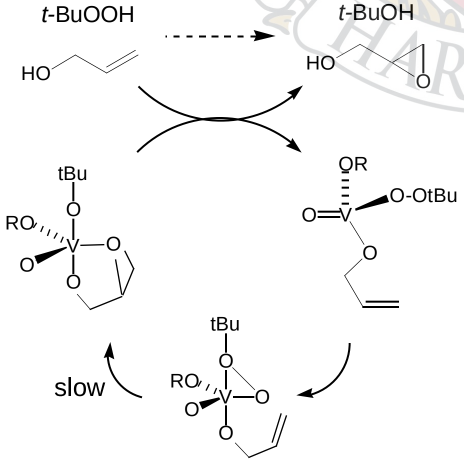


Aldrichimica Acta, **12**, 63 (1979)

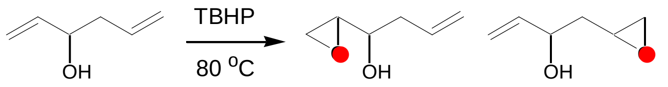


Chem 3D Transition State

O–C_2–C_3–C_4 = 41°
The Sharpless estimate: ~50°

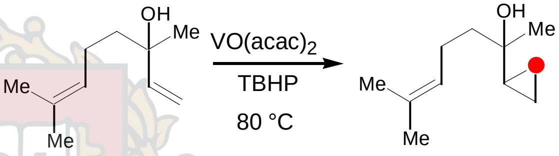


- The literature precedent: Sheng, Zajecek, *J. Org. Chem.* **1970**, *35*, 1839

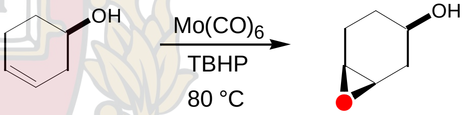


Catalyst		
	$VO(acac)_2$	4 : 1
	$Mo(CO)_6$	1 : 1

- Next step: Sharpless, Michaelson *JACS* **1973**, *95*, 6136

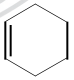
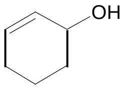
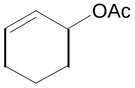
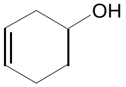


Regioselection 20:1



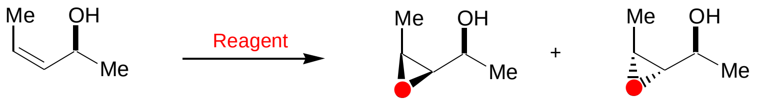
Stereoselection 98:2
(90 % yield)

Relative Rates (Diastereoselectivities) for the Epoxidation of Cyclohexene Derivatives JACS **1973**, *95*, 6136

Substrate	$k_{rel}^{a,b}$ (diastereoselectivity^{c})		
	peracid	$Mo(CO)_6$	$VO(acac)_2$
	1.00	1.00	1.00
 OH	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)
 OAc	0.046 (37 : 63)	0.07 (40 : 60)	--
 OH	0.42 (60 : 40)	11.0 (98 : 2)	10.0 (98 : 2)

[a,b] The relative rate data apply only to a given column. Values in parenthesis refer to the ratio of syn:anti epoxide.

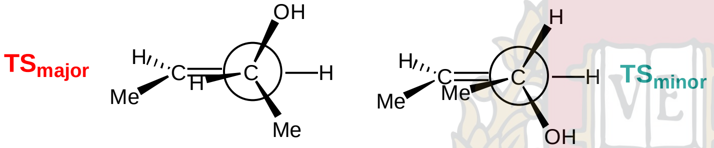
■ Allylic Alcohols:



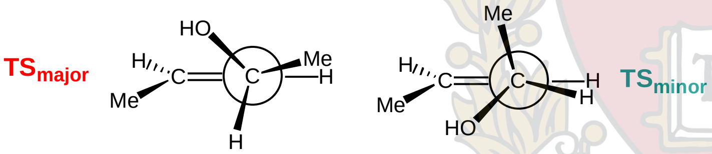
threo erythro

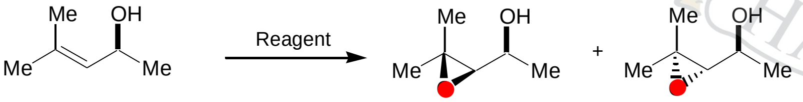
Φ Estimate	Reagent	Ratio
~ 120 °	*m*-CPBA	95 : 5
40-50 °	*t*-BuOOH / VO(acac)$_2$	71 : 29
	t-BuOOH / Mo(CO)$_6$	84 : 16

■ RCO$_3$H Transition States: Φ ~ 120 °



■ V(+) Transition States: Φ ~ 45 °



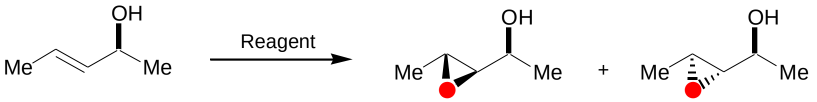


threo erythro

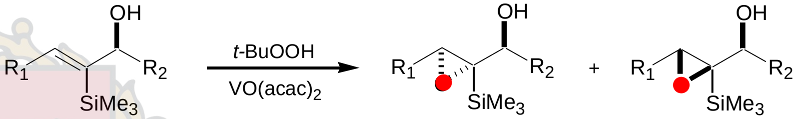
K. Oshima & Coworkers
Tetrahedron Lett. **1980**, *21*, 1657, 4843.

K. B. Sharpless & Coworkers
Tetrahedron Lett. **1979**, *20*, 4733.

Reagent	Ratio
m-CPBA	95 : 5
t-BuOOH / VO(acac)$_2$	86 : 14
t-BuOOH / Mo(CO)$_6$	95 : 5
t-BuOOH / (*t*-BuO)$_3$Al	100 : 0

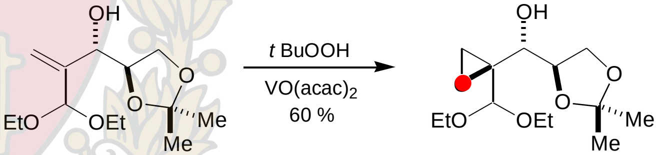


Reagent	Ratio
m-CPBA	64 : 36
t-BuOOH / VO(acac)$_2$	29 : 71
t-BuOOH / Mo(CO)$_6$	62 : 38
t-BuOOH / (*t*-BuO)$_3$Al	64 : 36

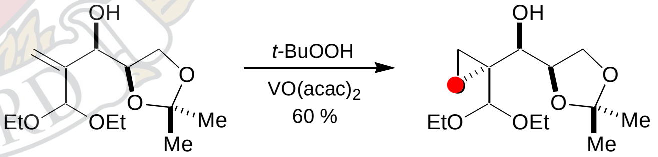


Oshima, *Tetrahedron Lett.* **1982**, *23*, 3387.

R_1	R_2	Yield	Ratio
H	Bu	84 %	99 : 1
C_5H_{11}	Me	70 %	99 : 1

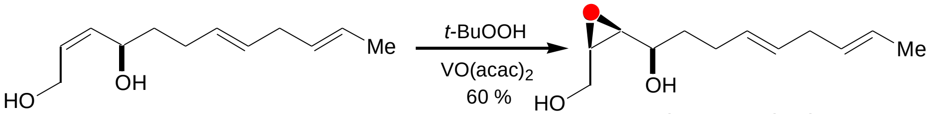


only isomer



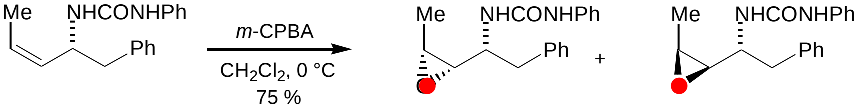
only isomer

Depezay, *Tetrahedron Lett.* **1978**, *19*, 2869.



Boeckman, *JACS* **1977**, *99*, 2805.

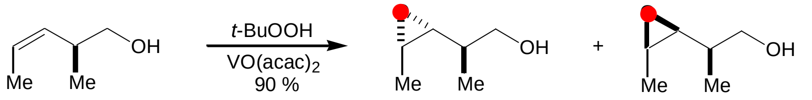
Diastereoselection = 7 : 1



Roush, *J. Org. Chem.* **1987**, *52*, 5127.

Diastereoselection = 95 : 5

Homoallylic Alcohols (Mihelich, *JACS* **1981**, *103*, 7690)

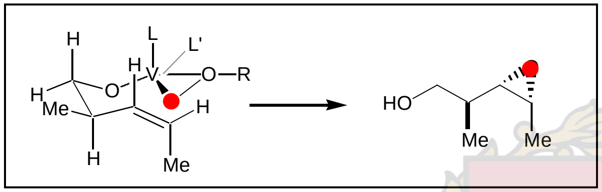


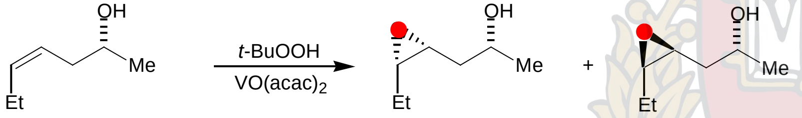
Diastereoselection > 400 : 1

Control Elements

A(1,3) Strain

Directed Rxn

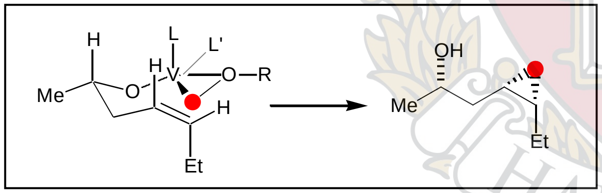




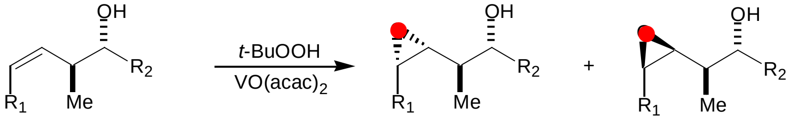
Diastereoselection 12 : 1

Control Elements

Directed Rxn

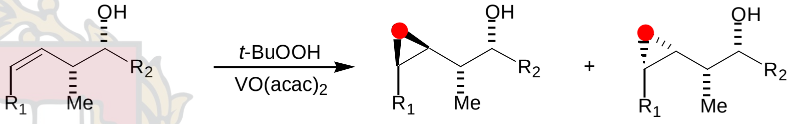


Anti diastereomer

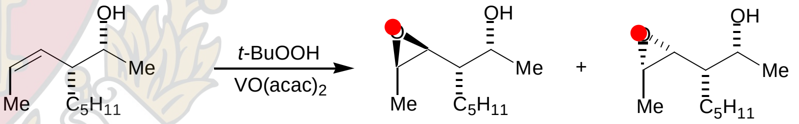


R_1	R_2	Yield	Ratio
C_6H_{13}	Me	92 %	104 : 1
Me	*i*-Pr	97 %	> 400 : 1

Syn diastereomer



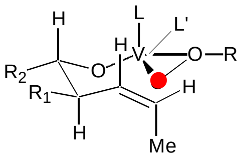
R_1	R_2	Yield	Ratio
C_6H_{13}	Me	73 %	70 : 1
Me	Me	70 %	85 : 1
Me	C_5H_{11}	81 %	16 :1



E. D. Mihelich & Coworkers
J. Am. Chem. Soc. **1981**, *103*, 7690.

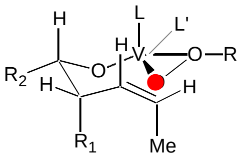
Diastereoselection = 211 : 1

Prediction



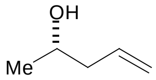
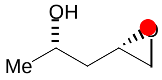
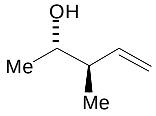
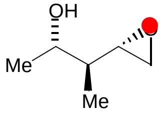
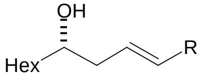
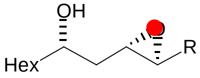
Anti diastereomer

Anti should be more diastereoselective than syn



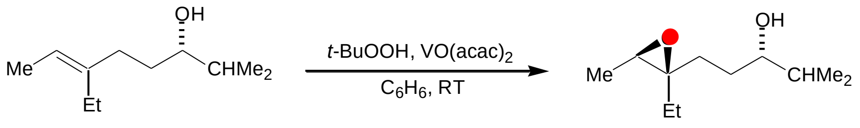
Syn diastereomer

Epoxidation of Homoallylic Alcohols with TBHP, VO(acac)$_2$

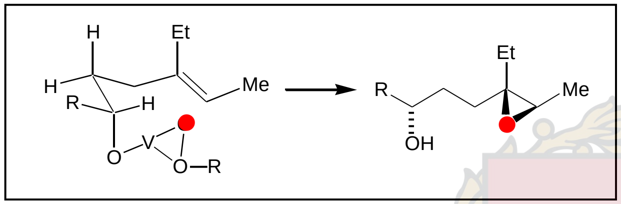
Substrate	Product	Selectivity
		2 : 1
		4.6 : 1
 R = $(CH_2)_7CO_2Me$		1.4 : 1

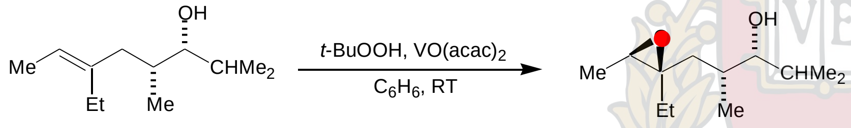
Epoxidation of Acyclic Homoallylic Alcohols

Bishomoallylic Alcohols (Kishi, *Tet. Lett.* **1978**, *19*, 2741)



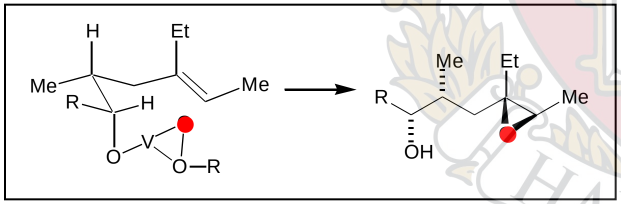
diastereoselection ~ 9 : 1

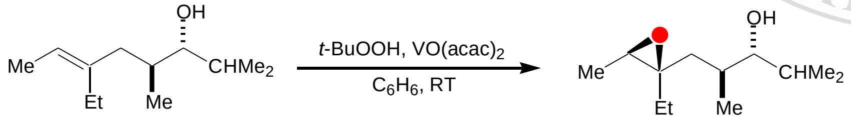




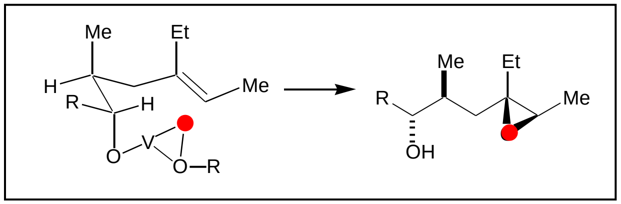
diastereoselection ~ 20 : 1

2nd stereocenter is reinforcing

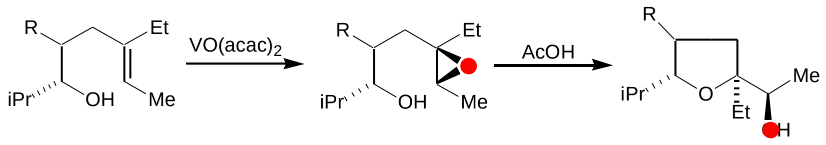




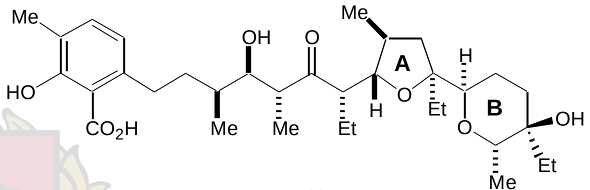
diastereoselection ~ 6 : 1

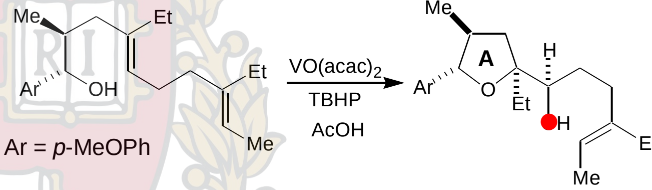


Epoxidation & Cyclization of Bishomoallylic Alcohols



The Kishi Lasalocid Synthesis (*JACS* **1978**, *100*, 2933)

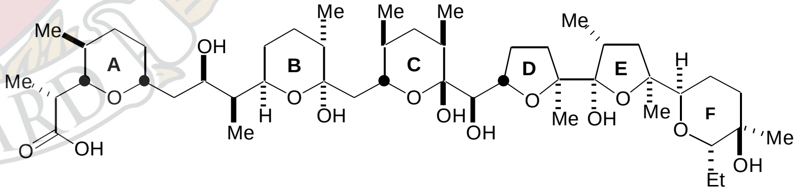


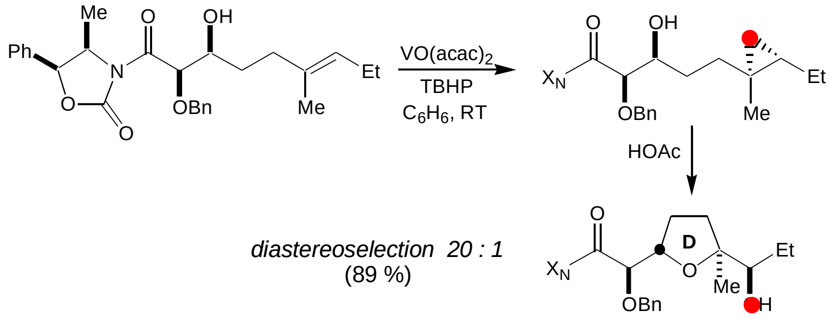


Ar = *p*-MeOPh

Diastereoselection 8:1

Evans X-206 Synthesis JACS **1988**, *110*, 2506.





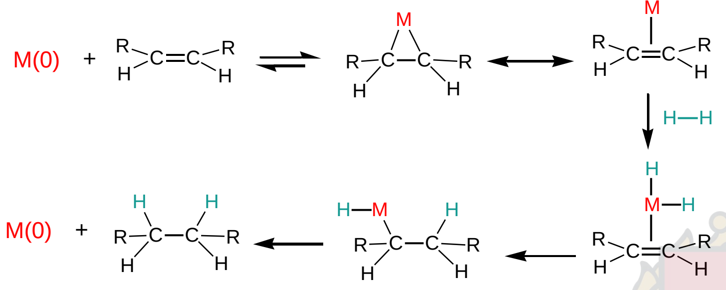
diastereoselection 20 : 1
(89 %)

Diastereoselective Hydrogenation: Introduction

The Hydrogenation Reaction

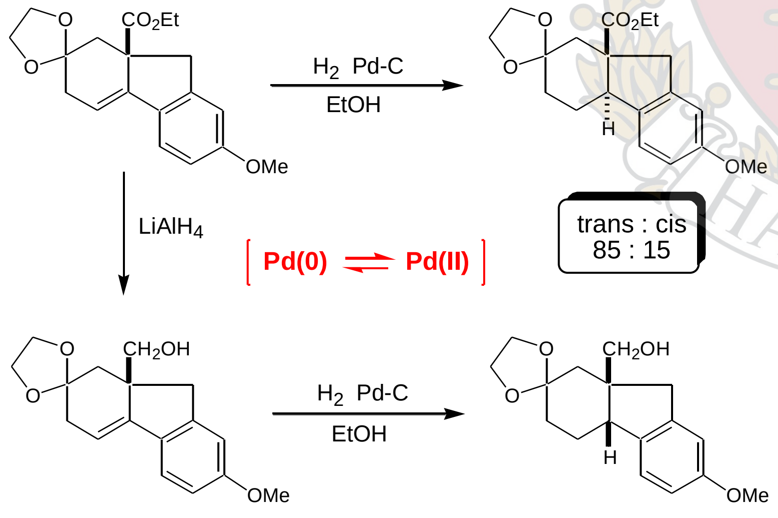
Relevant Review articles: J. M. Brown, *Angew. Chem. Int. Edit.* **26**, 190-203 (1987).

- General Mechanism



Historically, primary stereochemical control designed around analysis of steric environment in vicinity of C=C.

However, the influence of polar effects was documented



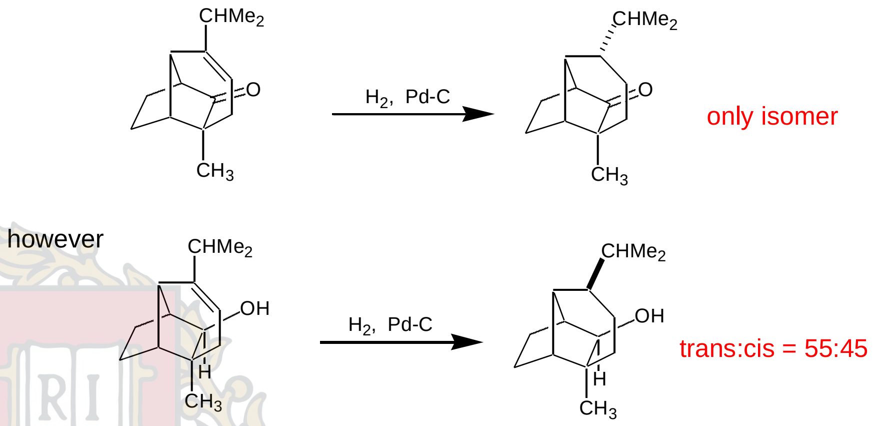
Pd(0) ⇌ **Pd(II)**

trans : cis
85 : 15

trans : cis
5 : 95

Thompson, *J.Org. Chem.* **36**, 2577 (1971)

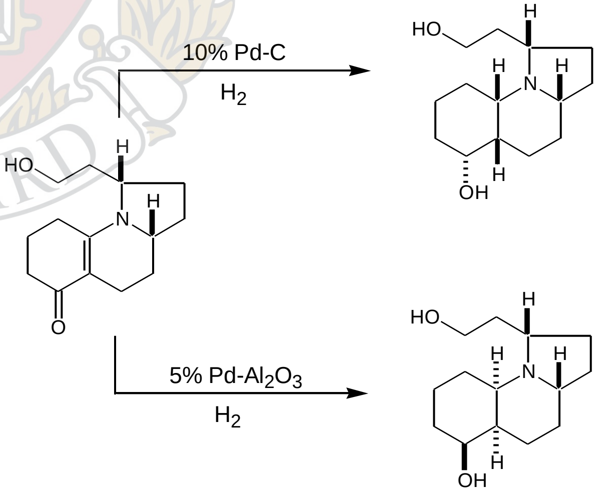
Polar functional groups may play a role in controlling the diastereoselectivity of the hydrogenation process; however, the control elements were not well-defined.



only isomer

trans:cis = 55:45

J. E. McMurry & Co-workers, *Tetrahedron Lett.*. 3731 (1970)



Steric Control

sole product

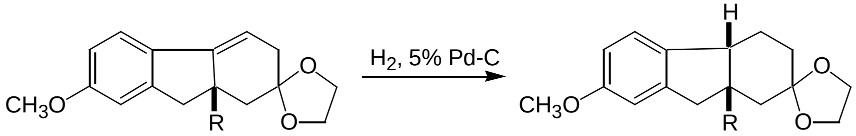
Directed ?

12 : 1

Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **102**, 7156 (1980)

Diastereoselective Hydrogenation: Introduction-2

The first rational attempt to identify those FGs which will direct the reaction

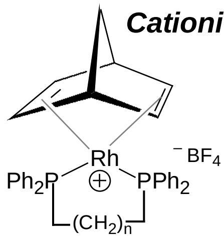


10

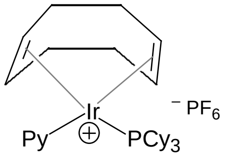
R	cis : trans
CH_2OH	95 : 5
CHO	93 : 7
CN	75 : 25
COONa	55 : 45
COOH	18 : 82
COOMe	15 : 85
COMe	14 : 86
$CONH_2$	10 : 90

H. Thompson & Co-workers, *J. Am. Chem. Soc.* **95**, 838 (1973)

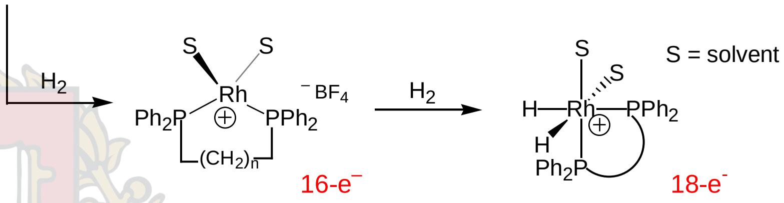
Cationic Hydrogenation Catalysts



Schrock & Osborne,
J. Am. Chem. Soc. **91**, 2816 (1969)

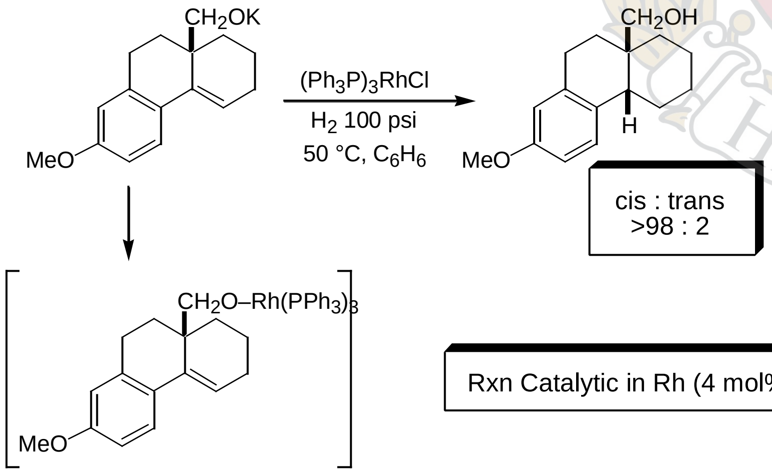


R. Crabtree
J. Organomet. Chem. **168**, 183 (1979)



Rh(+I): d8

The first rational attempt to associate catalyst with substrate:

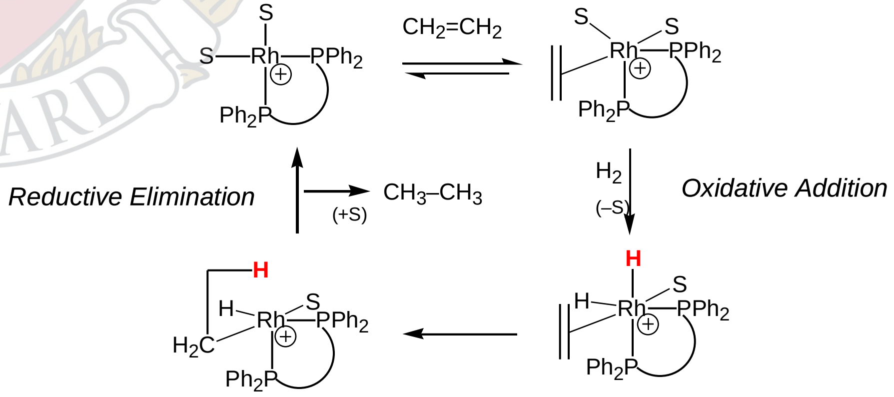


Rxn Catalytic in Rh (4 mol%)

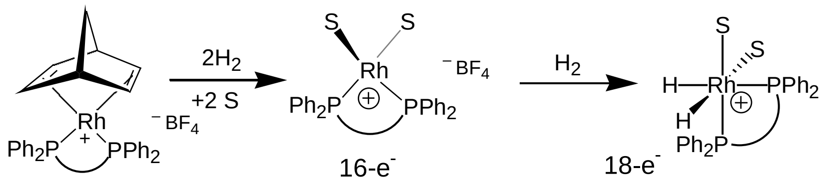
Thompson & Coworkers, *J. Am. Chem. Soc.* **97**, 6232 (1974)

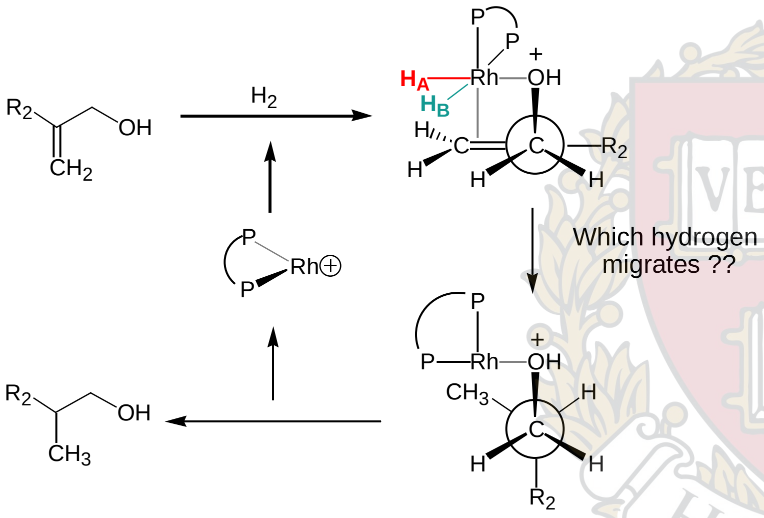
Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.

S = solvent

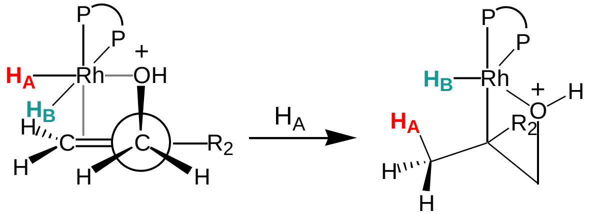


Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.



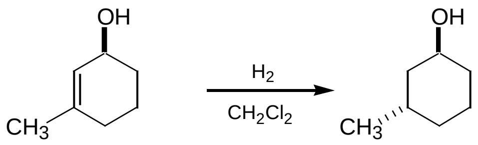


A potential stereoelectronic effect

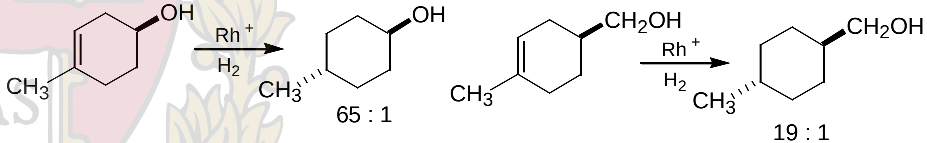


That H atom lying parallel to the pi-system (H_A) should migrate preferentially if the dihydride is an intermediate.

D. A. Evans & M. M. Morrissey *JACS* **106**, 3866 (1984)

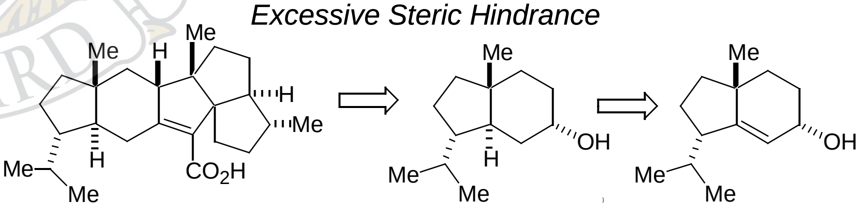


Catalyst	Mol% Catalyst	H_2 Pressure	trans:cis (Yield)
$Rh(DIPHOS\text{-}4)^+$	17.5	15 psi H_2	200 : 1 (89%)
	3.5	375 psi H_2	300 : 1 (95%)
Ir(pyr)PCy_3	20.0	15 psi H_2	50 : 1 (82%)
	2.5	15 psi H_2	150 : 1 (85%)

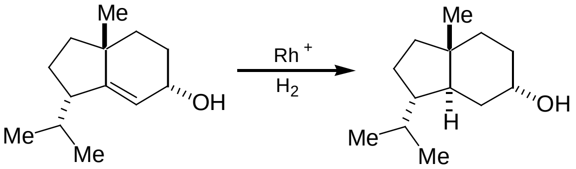


$Rh(DIPHOS\text{-}4)^+$ H_2 1000 psi CH_2Cl_2

Excessive Steric Hindrance



Retigeranic Acid



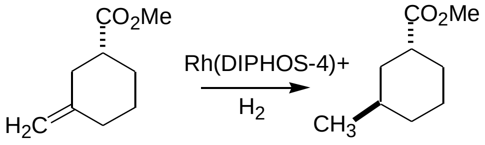
75 : 1 (95%)

$Rh(DIPHOS\text{-}4)^+$ H_2 800 psi THF

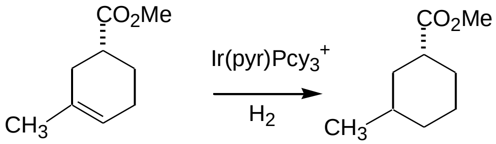
THF is important to success of rxn to buffer the Lewis acidity of the catalyst which causes elimination of ROH under normal conditions

Diastereoaselective Hydrogenation: Cyclic Substrates

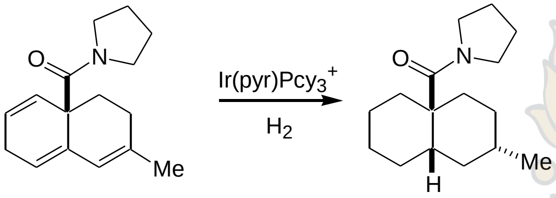
Polar functional groups other than OH may also direct the process



diastereoselection 91 : 9

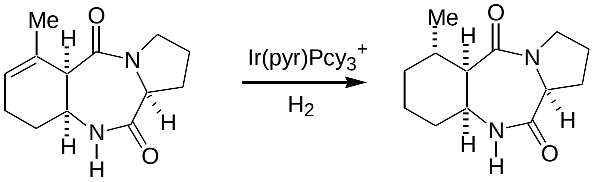


diastereoselection 89:11

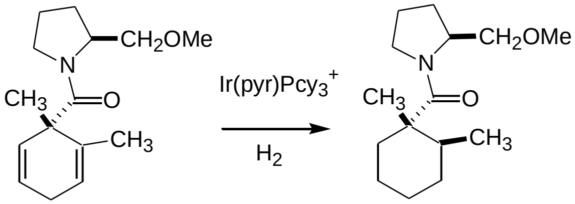


diastereoselection >99:1

J.M. Brown and S.A. Hall, *J. Organomet. Chem.*, **1985**, *285*, 333.

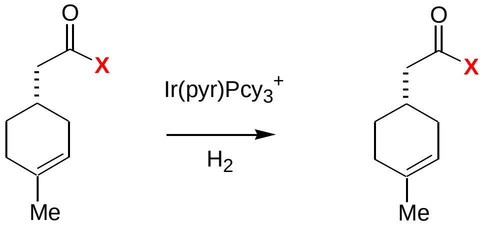


diastereoselection >99:1

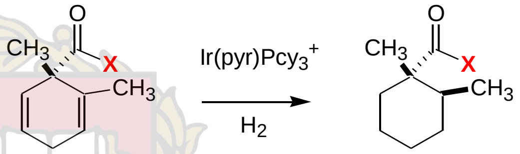


diastereoselection >99:1

A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, *50*, 5907.

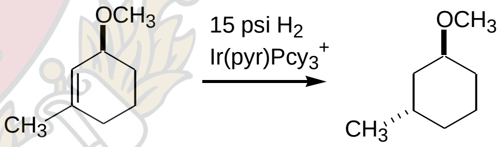


X	Diastereoselection
OMe	55:45
NC_4H_8	99:1



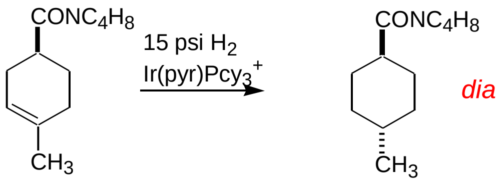
X	Diastereoselection
OMe	99:1
NC_4H_8	>99:1

A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, *50*, 5907.



diastereoselection >99:1

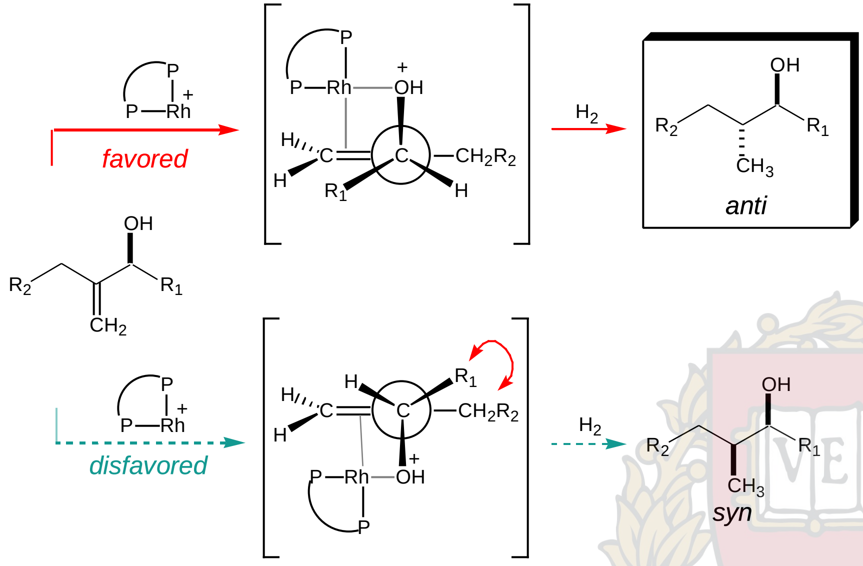
R.H. Crabtree and M.W. Davis, *J. Org. Chem.*, **1986**, *51*, 2655.

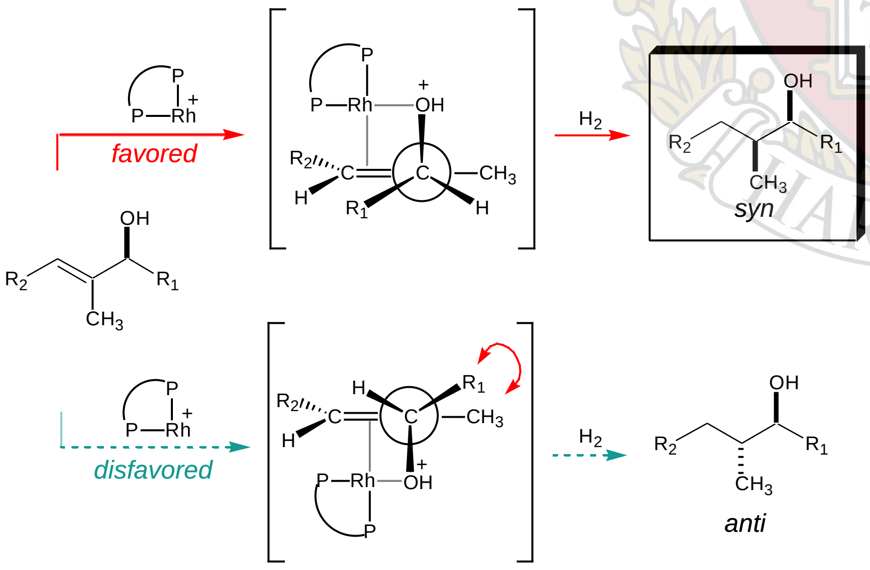


diastereoselection >99:1

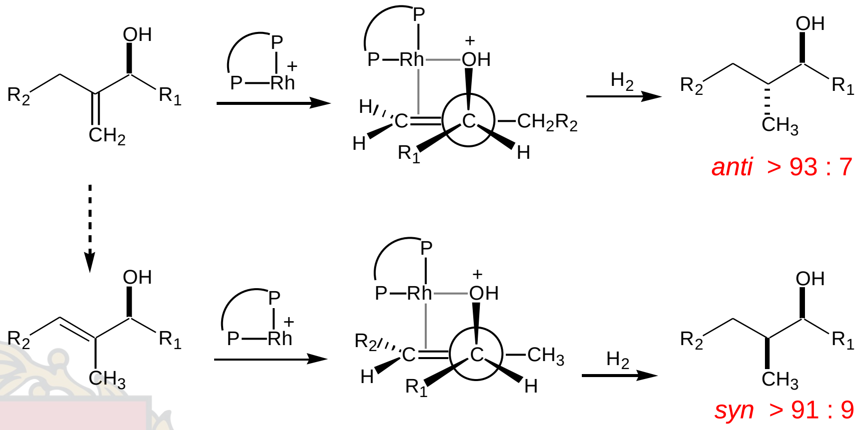
A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, *50*, 5907.

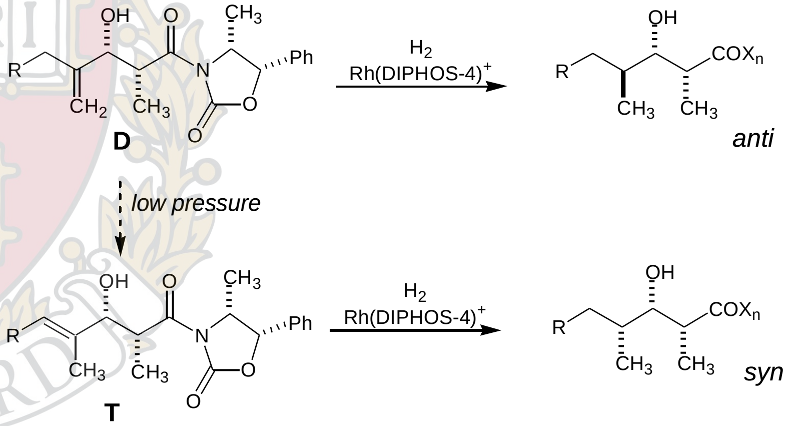
Acyclic Allylic Alcohols





D. A. Evans & M. M. Morrissey *JACS* **106**, 3866 (1984)

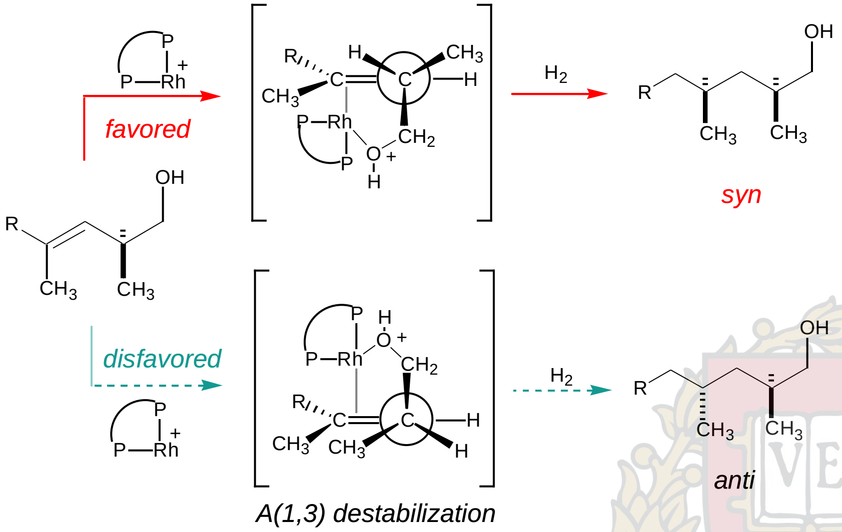


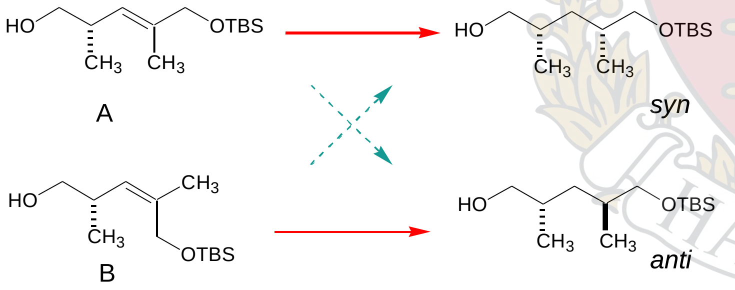


	Hydroxy-Olefin	Anti : Syn Ratio 15 psi H_2	 640 psi H_2
D	R = CH_3	25 : 75 (23%)	93 : 7
	R = $(CH_3)_2CH$	52 : 48 (35%)	94 : 6
	R = Ph	71 : 29 (-)	93 : 7
T	R = CH_3	13 : 87 (6%)	9 : 91
	R = $(CH_3)_2CH$	12 : 88 (8%)	8 : 92
	R = Ph	21 : 79 (-)	6 : 94

Diastereoaselective Hydrogenation: Acyclic Substrates

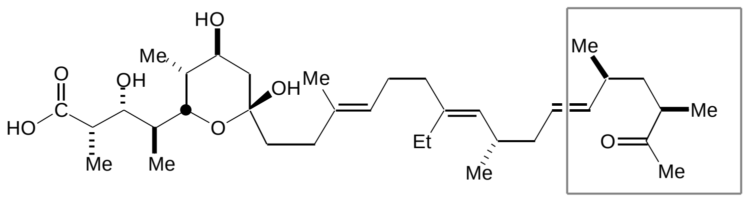
Homoallylic Alcohols Evans, Morrissey *Tetrahedron Lett.* **26** 6005 (1985)

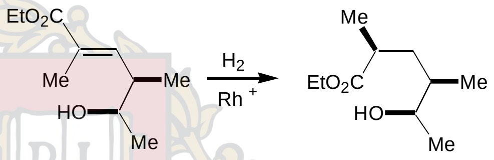




Olefin	Catalyst (H_2 Pressure)	syn : anti
A	Rh(DIPHOS-4)$^+$ (1000 psi)	95 : 5
A	Ir(pyr)PCy$_3^+$ (15 psi, 2.5 mol%)	73 : 27
B	Rh(DIPHOS-4)$^+$ (1000 psi)	9 : 91

The Premonensin Synthesis

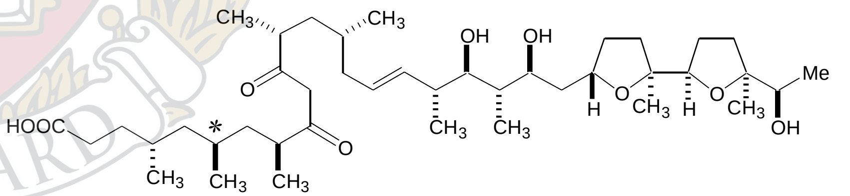


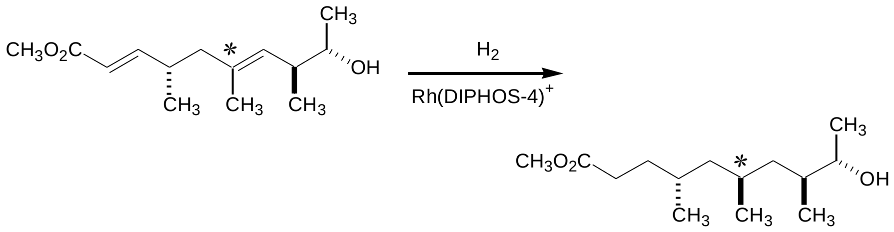


Catalyst	Ratio
Rh(DIPHOS-4)$^+$	85 : 15
Rh(–)(BINAP)$^+$	65 : 35
Rh(+)(BINAP)$^+$	98 : 2 (90%)

Evans, DiMare, *JACS*, **1986**, *108*, 2476)

The Ionomycin Synthesis





Diastereoselection: 94 : 6 (93%)

with Dow, Shih, Zahler, Takacs, *JACS* **1990**, *112*, 5290

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 10

Olefin Addition Reactions–3

- Olefin Bromination
- Olefin Oxymercuration
- Halolactonization
- Simmons-Smith Reaction

■ Reading Assignment for week

A. Carey & Sundberg: **Part B**; Chapter 4
"Electrophilic Additions to C–C Multilple Bonds"

Hoveyda, Evans, & Fu (**1993**). *Substrate-Directable Chemical Reactions*. *Chem. Rev*. **93**: 1307-70 ***(Handout)***

R.S. Brown . Acc. Chem. Res. **1996**. *30*. 131-137.

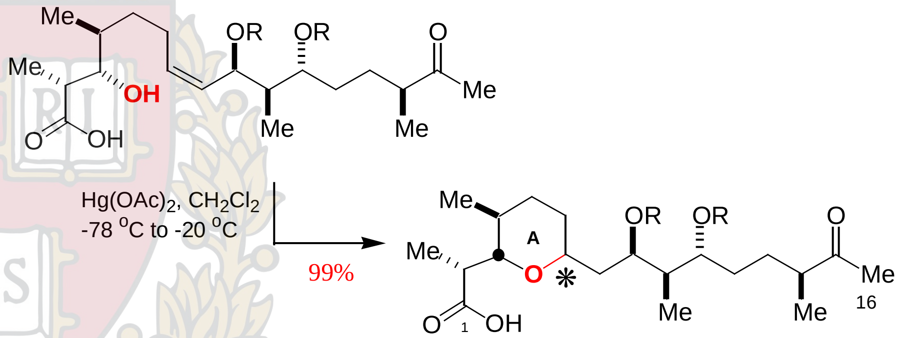
Matthew D. Shair

Wednesday,
October 9, 2002

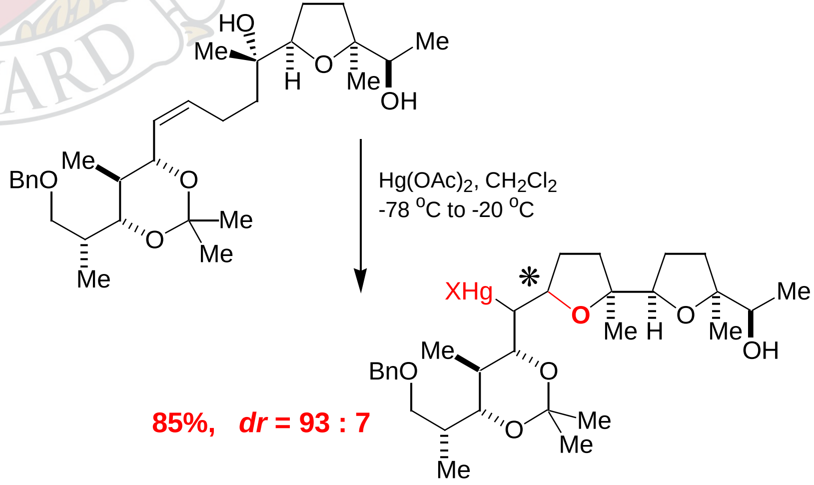
Bromoniun Ions or β-Bromocarbocations in Olefin Bromination. A Kinetic Approach to Product Selectivities
M-F. Ruasse, *Accts. Chem. Res.* **1990**, *23*, 87 **(handout)**

Investigation of the early Steps in Electrophilic Bromination through the Study of the Reaction of Sterically Encumbered Olefins
R. S. Brown, *Accts. Chem. Res.* **1997**, *30*, 131 **(handout)**

■ Predict stereochemical outcome

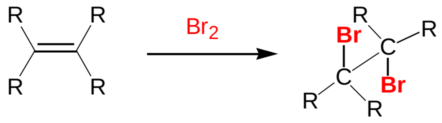


99%, *single diastereomer*



85%, *dr* = 93 : 7

Introduction



- Reaction is first order in alkene

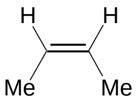
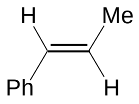
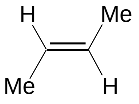
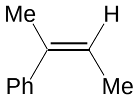
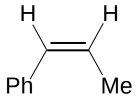
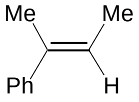
At low concentrations of Br_2, rxn is also **first order in Br_2**

At higher concentrations of Br_2 in nonpolar solvents rxn is **second order in Br_2**.

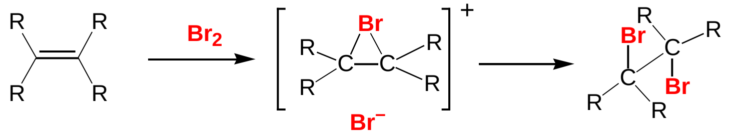
- Substituent Effects on Bromination Rates

Alkene	k_{rel}
$CH_2{=}CH_2$	1
$CH_3CH{=}CH_2$	61
n-$PrCH{=}CH_2$	70
i-$PrCH{=}CH_2$	57
t-$BuCH{=}CH_2$	27
$(CH_3)_2C{=}CH_2$	5470
cis-$CH_3CH{=}CHCH_3$	2620
trans-$CH_3CH{=}CHCH_3$	1700
$(CH_3)_2C{=}CHCH_3$	130,000
$(CH_3)_2C{=}C(CH_3)_2$	1,800,000

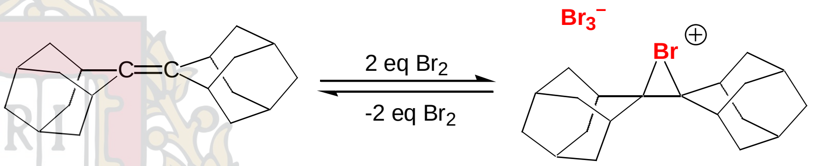
- Stereochemical outcome versus structure (Br_2 in HOAc @ 25°)

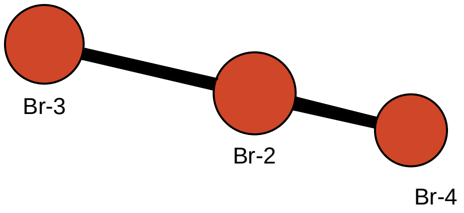
Alkene	% anti addition	Alkene	% anti addition
	100%		83%
	100%		63%
	73%		68%

- Bromonium ion origin of the anti (trans) selectivity first suggested by Roberts, *JACS* **1937**, *59*, 947

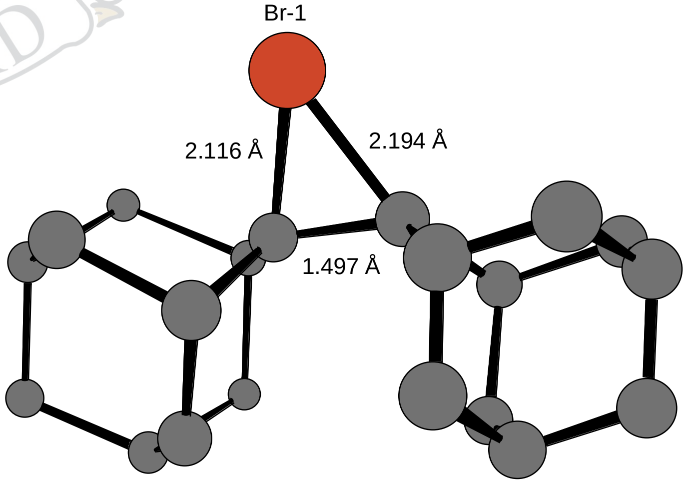


- First X-ray Structure of a bromonuium ion: Brown, *JACS* **1985**, *107*, 4504

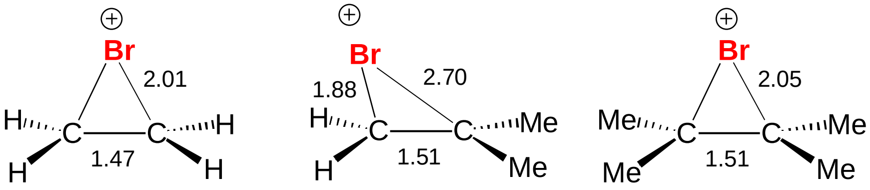




X-ray structure



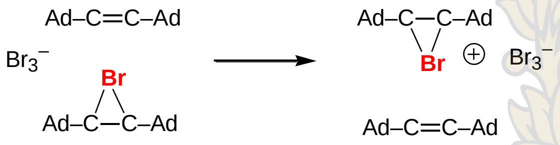
- Calculated Geometries of Substituted Bromonium Ions
  Ruasse, *Chem Commun.* **1990**, 898

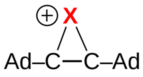


Note; the C–Br bond lengths in previous X-ray structure are 2.116 Å.

- Bromonium Ions undergo fast exchange with olefins
  Brown, *Accts. Chem. Res.* **1997**, *30*, 131

Unprecedented until 1991 (Bennet, JACS **1991**, *113*, 8532)

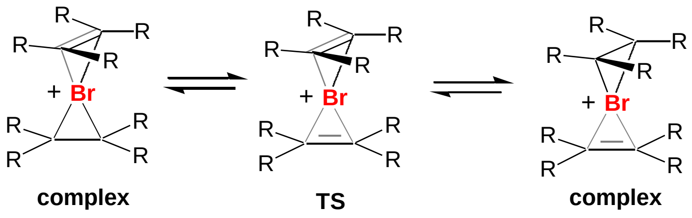




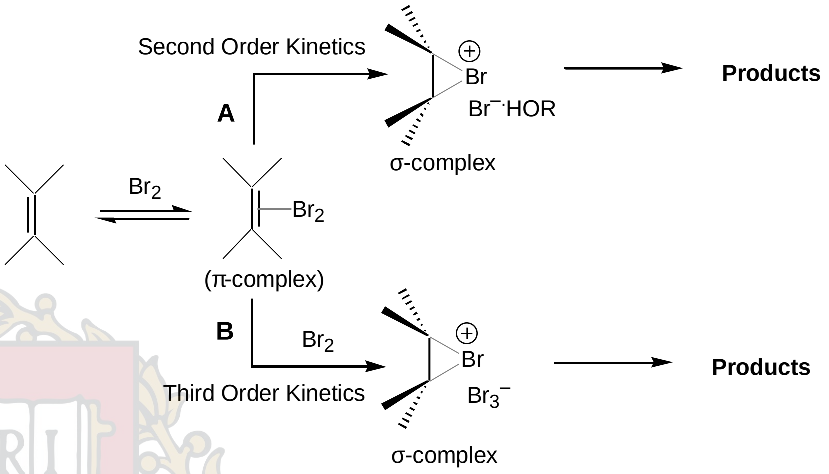
X = Br: exchange rate: $2 \times 10^6\ M^{-1}\ s^{-1}$

X = I : exchange rate: $8 \times 10^6\ M^{-1}\ s^{-1}$

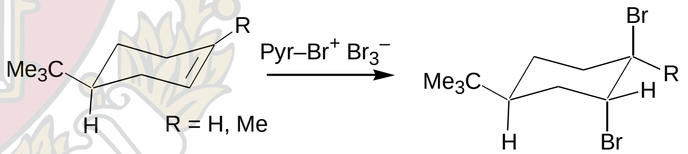
There is an intermediate in the halogen transfer (ab initio calcs):



Overall Reaction Mechanism

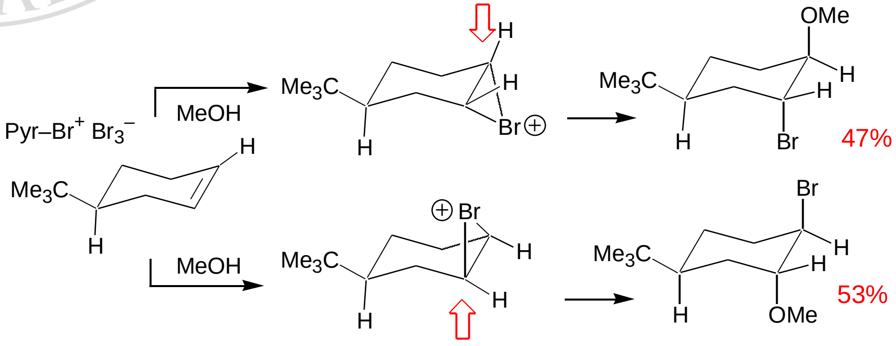


Bromination of Cyclohexene Derivatives **Pasto, *JACS* 1970, *92*, 7480**



exclusive product

Diaxial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening (**Lecture-3**).

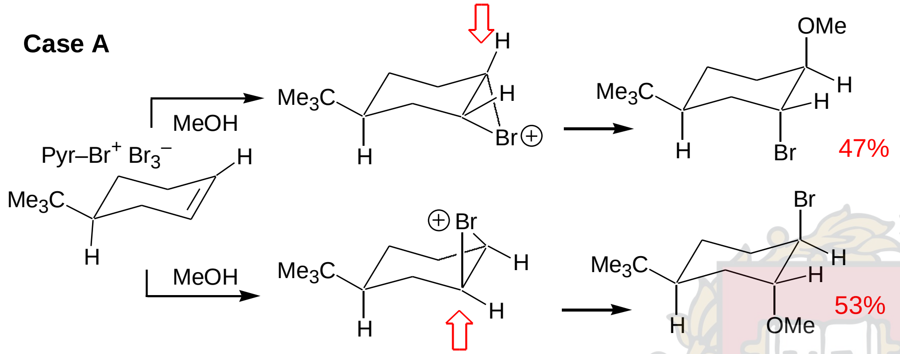


It appears that bromine attack from both olefin faces occurs wilth near equal probability.

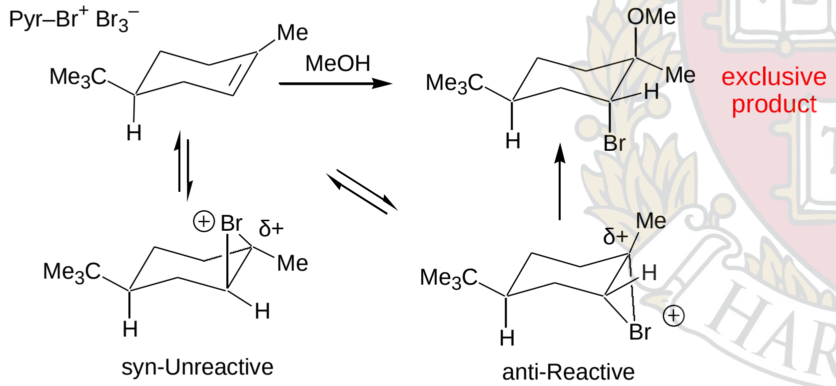
Bromination of Cyclohexene Derivatives **Pasto, *JACS* 1970, *92*, 7480**

Diaxial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening. (Lecture-2)

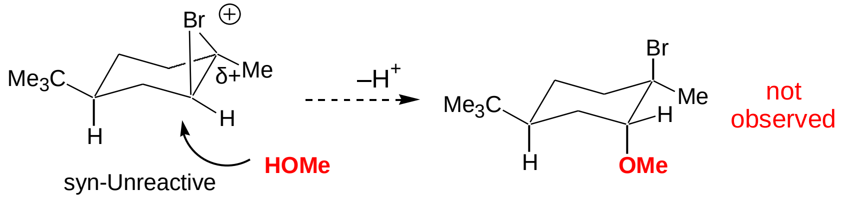
Case A



Case B



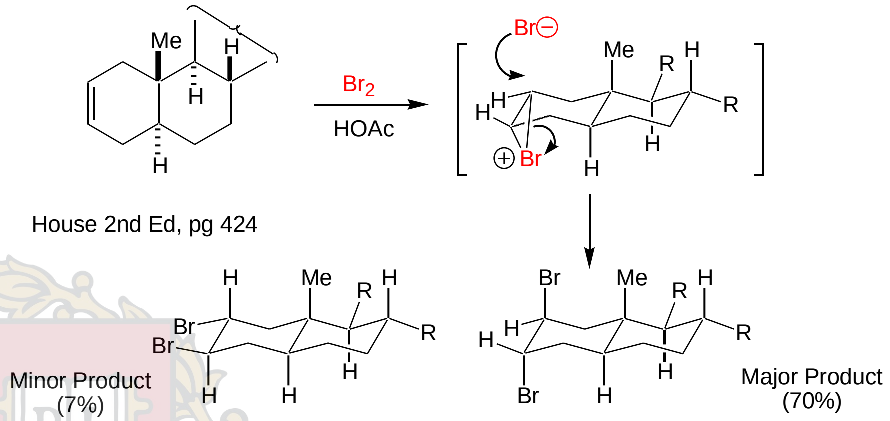
exclusive product



not observed

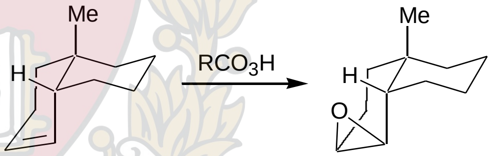
From Case **A**, one assumes that both bromonium ions are formed; however, for the syn isomer to react, ring opeing must proceed against the polarization due to Methyl substituent.

Representative Examples of Diastereoselective Bromination



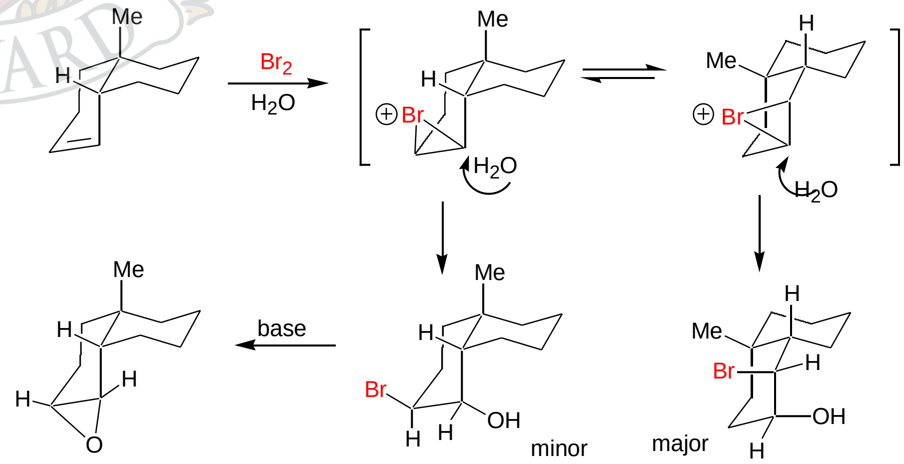
House 2nd Ed, pg 424

How to generate either epoxide from a conformatinaly biased olefin



Epoxidation controlled by steric effects imposed by cis-fused ring

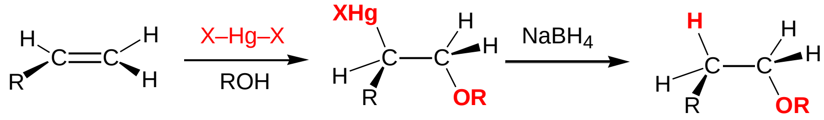
How do we construct the other epoxide diastereomer??



both bromohydrins afford same product

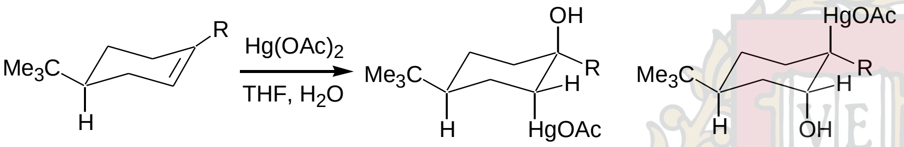
Oxymercuration **Pasto, *JACS* 1970, *92*, 7480**

The basic process:

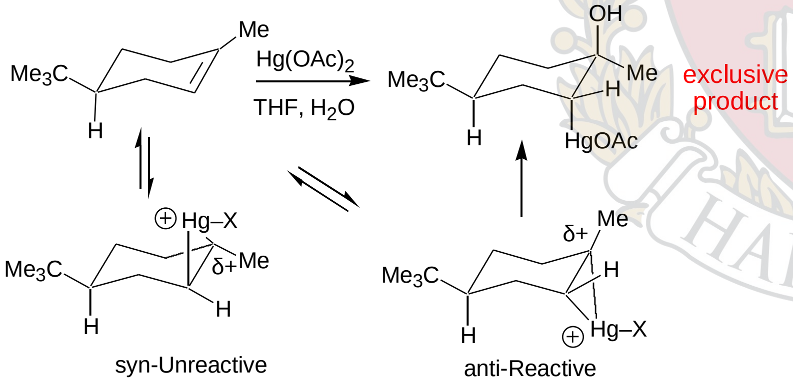


Kinetics: Halpern, *JACS* **1967**, *89*, 6427 Reduction: Pasto, *JACS* **199**, *91*, 719
Overview: B rown, *JOC* **1981**, *46*, 3810.

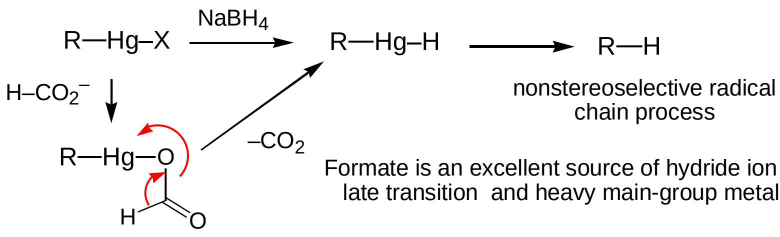
Oxy-Mercuration & bromination follow identical pathways (Pasto)



R = H	41%	48%
R = Me	100%	



Reduction of the Hg–C bond



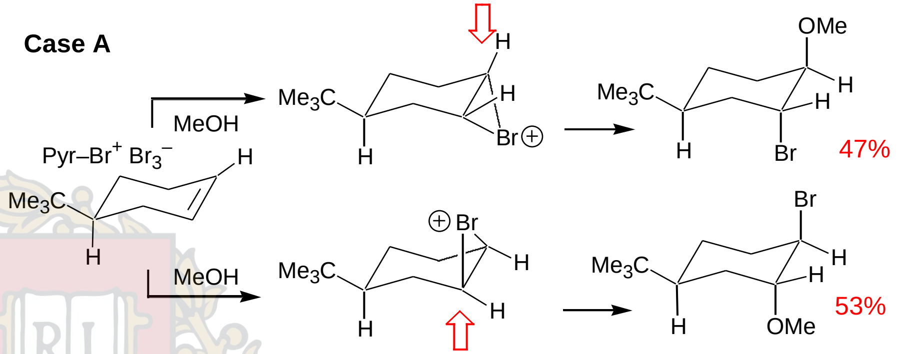
nonstereoselective radical chain process

Formate is an excellent source of hydride ion for late transition and heavy main-group metals

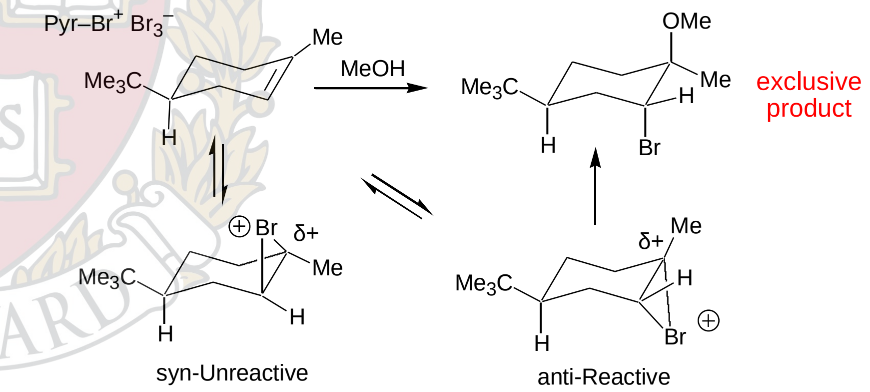
Bromination of Cyclohexene Derivatives **Pasto, *JACS* 1970, *92*, 7480**

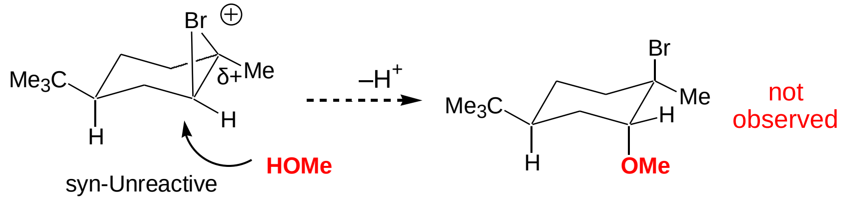
Diaxial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening. (Lecture-2)

Case A



Case B

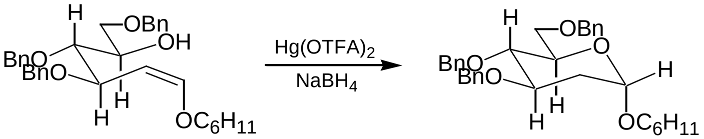




From Case **A**, one assumes that both bromonium ions are formed; however, for the syn isomer to react, ring opeing must proceed against the polarization due to Methyl substituent.

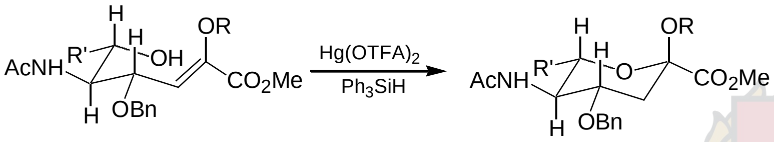
Oxymercuration Examples

Diastereoselective ring closures via oxymercuration



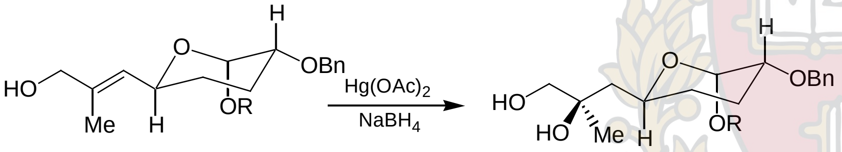
α:β = 96 : 4

Mukaiyama, *Chem. Lett.* **1981**, 683



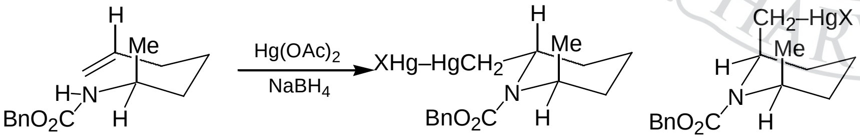
"one isomer"

Sinay, *Tet. Lett.* **1984**, *25*, 3071



Isobe, *Tet. Lett.* **1985**, *26*, 5199

Kinetic vs Thermodynamic control:



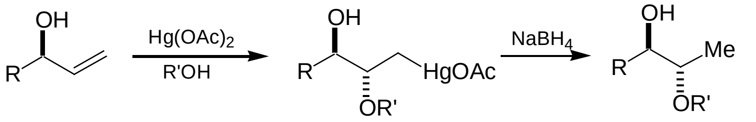
Harding, *JOC* **1984**, 49, 2838

$Hg(OAc)_2$: short rxn times : 40 : 60

$Hg(OTFA)_2$: longer rxn times : 2 : 98

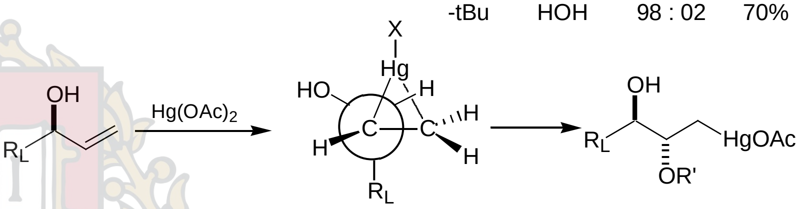
With more electrophilic Hg(II) salt, more polar solvents, and longer rxn times, the rxn may be rendered reversible.

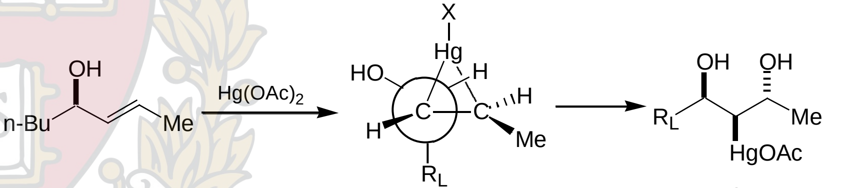
Acyclic allylic alcohols:



Giese, *Tet. Lett.* **1985**, *26*, 1197

R	R'OH	Ratio	yield
-Et	HOH	76 : 24	65%
-Et	MeOH	93 : 07	72%
-Ph	HOH	88 : 12	66%
-tBu	HOH	98 : 02	70%

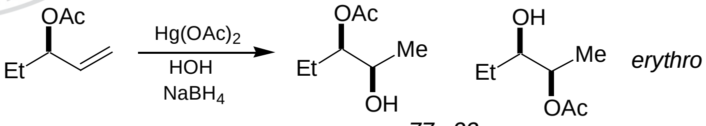




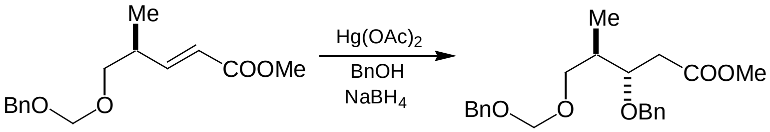
syn:anti = 80 :20

Chamberlin, *Tetrahedron* **1984**, *40*, 2297

O-acetate participation will turn over the stereochemical course of the rxn



77 : 23



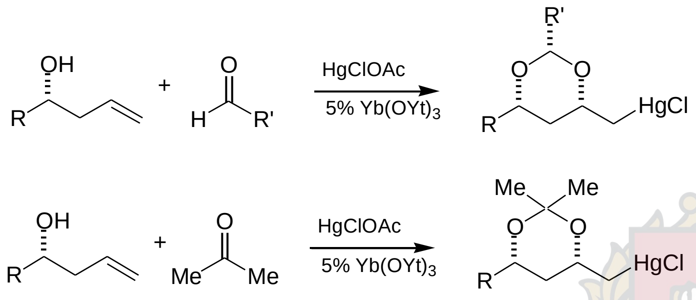
Seebach, *JACS* **1983**, *105*, 7407

diastereoselection = 83 : 17 (79%)

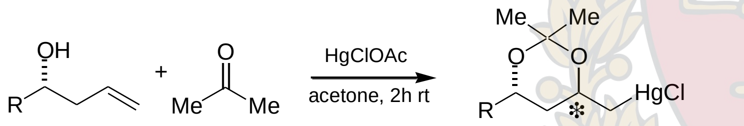
Oxymercuration via Hemiketals & Hemiacetals

J. L. Leighton et. al, *Org. Lett.* **2000**, *2*, 3197-3199

■ General Reaction: diastereoselection >10:1



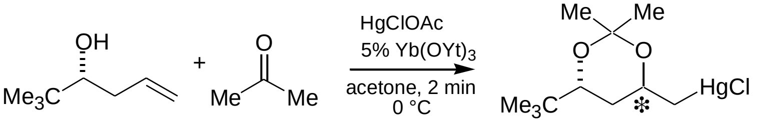
■ Mechanistic Observations:



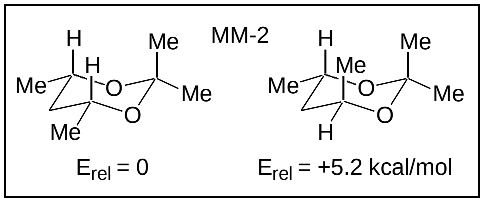
~1:1-mixture of diastereomers
Product formed in low yield.
much recovered starting material

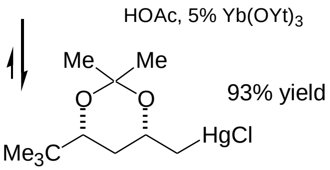
Lewis acid addends were surveyed. the logic for this step was two-fold:

(A) Lewis acid would promote the formation of the putative hemiketal imtermediate.
(B) Lewis acid would promote reversability of the oxymercuration process



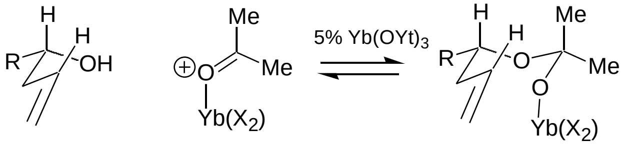
~1:1-mixture of diastereomers



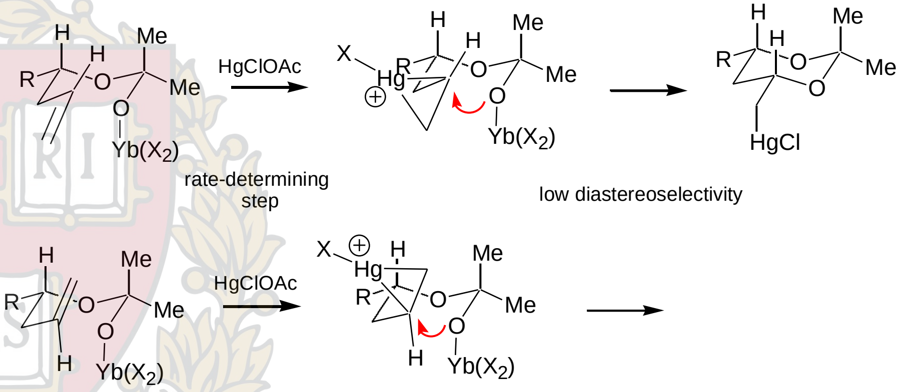


Proposed Mechanism

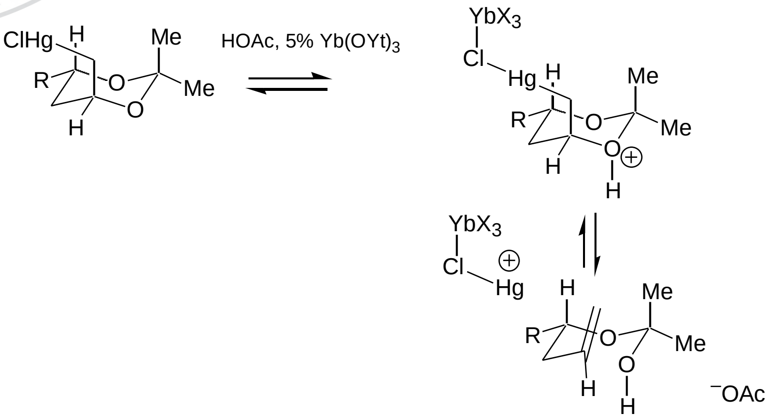
■ Lewis acid catalyzes formation of hemiketal



■ The Oxymercuration Step (Kinetic Phase)

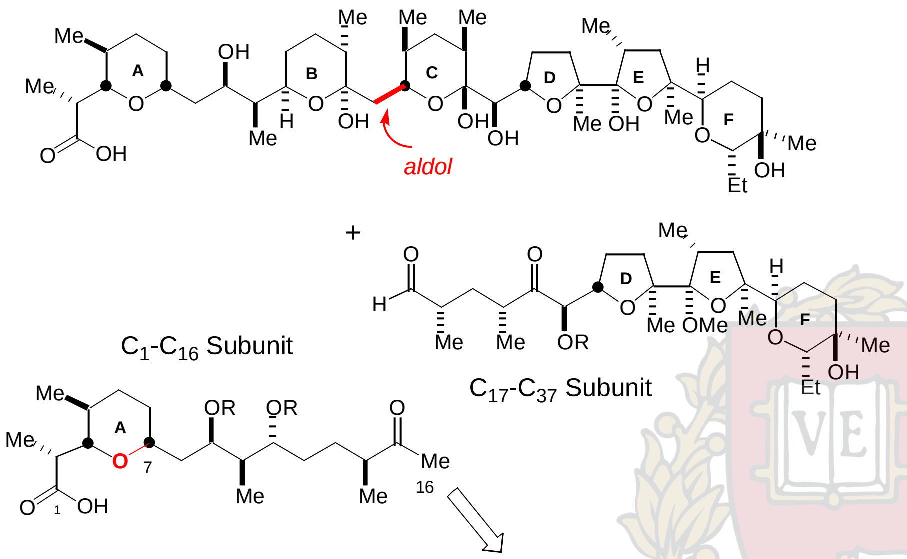


Leighton presumes that mercurium ion formation is rate-determining under kinetic conditions.
At higher temperatures and longer reaction times the products are shown to interconvert.



Oxymercuration Examples: X-206 & Lonomycin Syntheses

X-206 Synthesis (with S. Bender, *JACS* 1988, *110*, 2506)

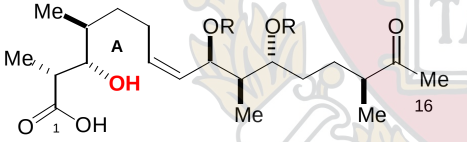


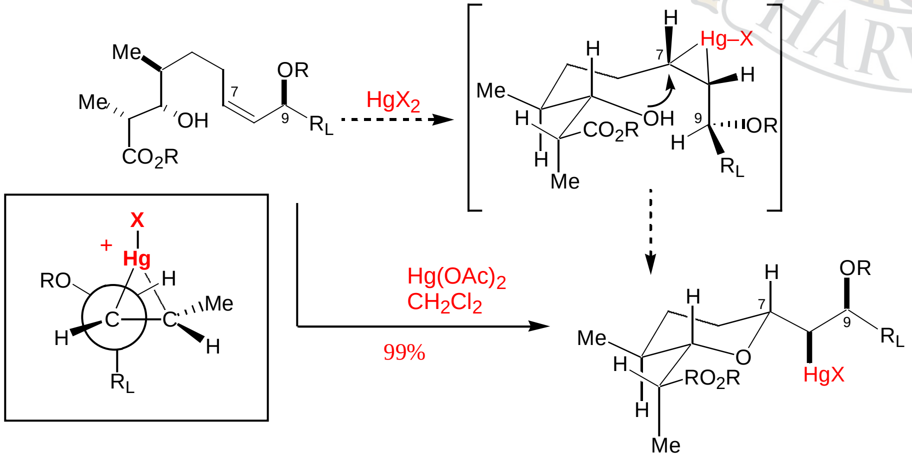
C_1-C_{16} Subunit

C_{17}-C_{37} Subunit

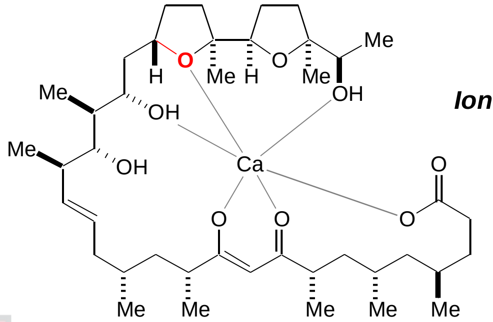
Assemblage strategy for Ring A:

Predicted stereochemical outcome:

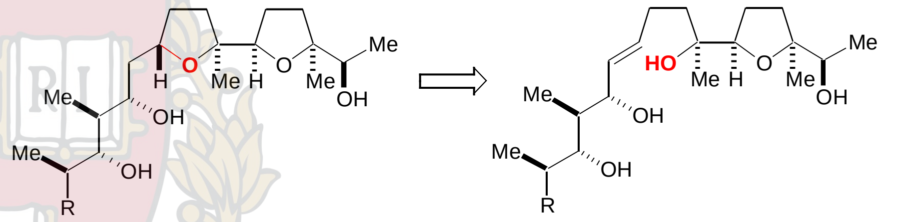


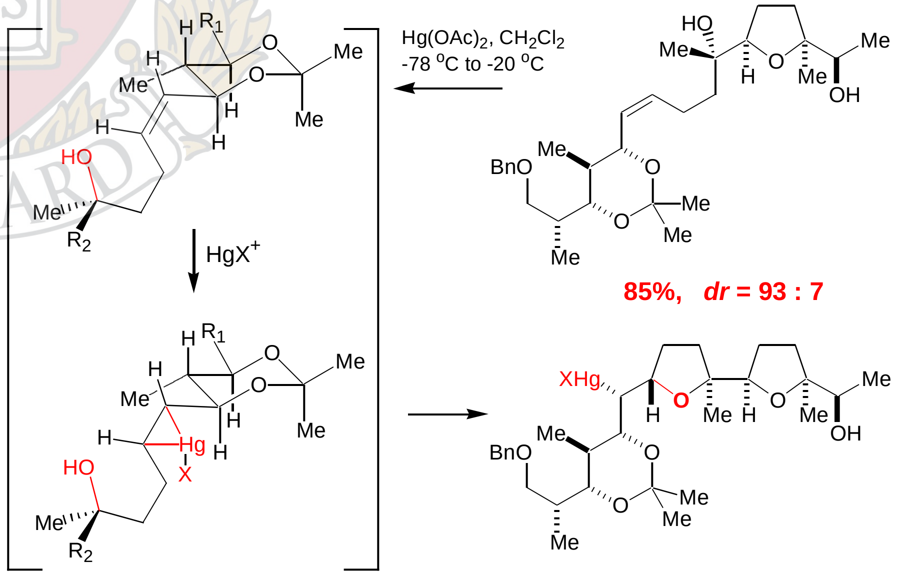


Ionomycin Synthesis (with Dow & Shih, *JACS* 1990, *112*, 5290)



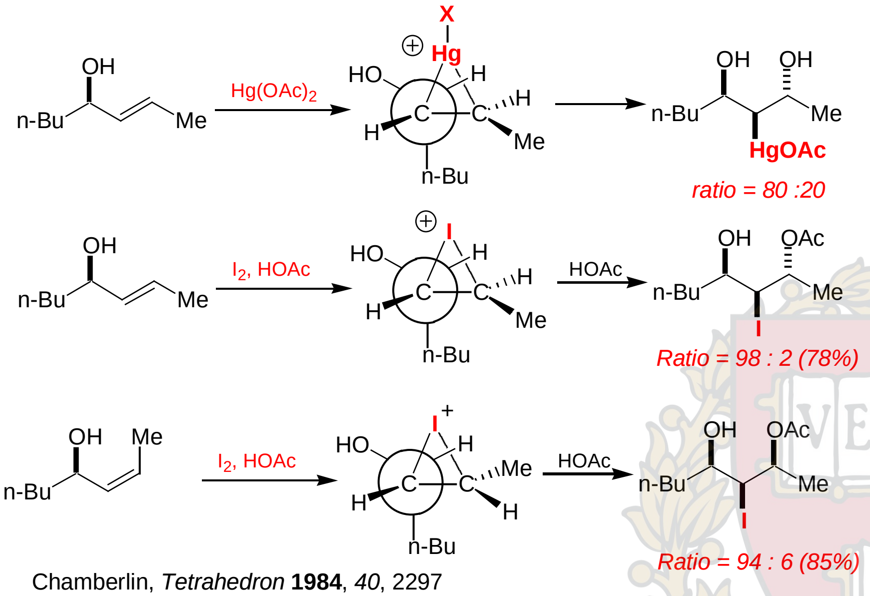
Ionomycin Calcium Complex





85%, *dr* = 93 : 7

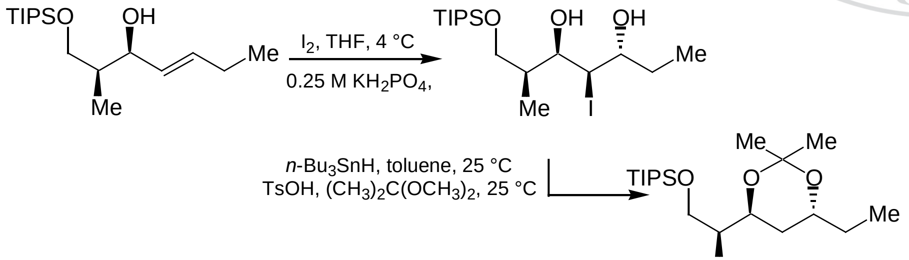
Other electrophilic olefin addition reactions afford the same stereochemical outcome



Chamberlin, *Tetrahedron* **1984**, *40*, 2297

This is an exceptional approach to the creation of either syn or anti 1,3-dioxygen relationships

- Chamberlin methodology employed in cytovaricin synthesis (*JACS* **1990**, *112*, 7001)

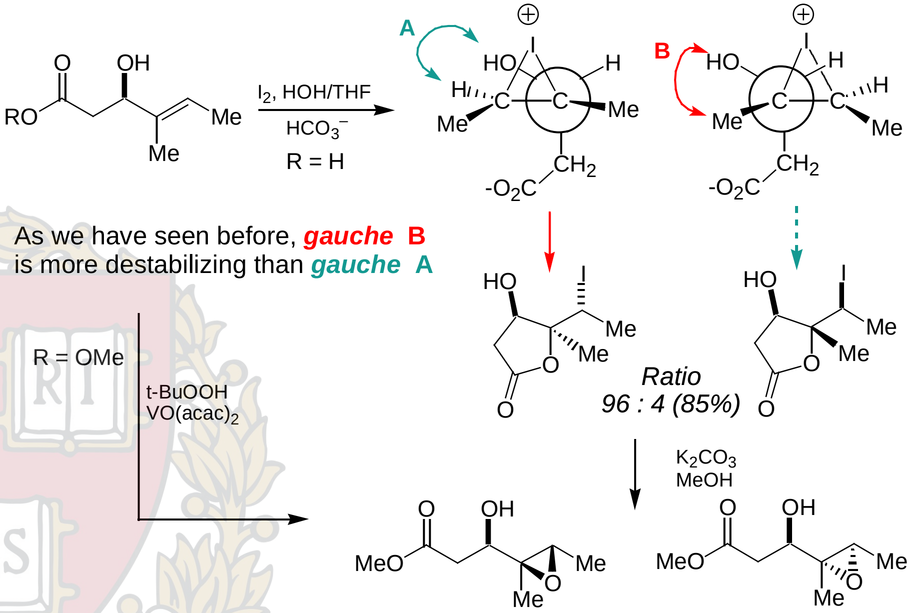


This methodology superior to oxymercuration alternative which was evaluated first

diastereoselection 96 : 4

Iodine-induced lactonization is also highly stereoselective

- Chamberlin (*JACS* **1983**, *105*, 5819)



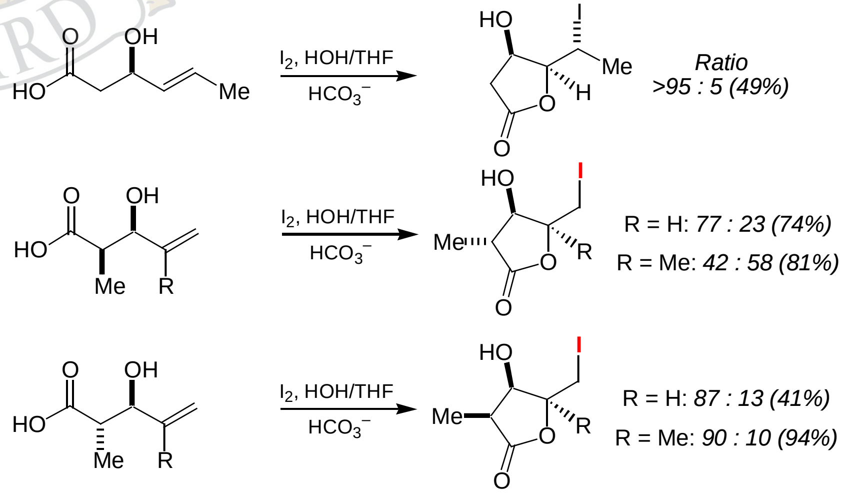
As we have seen before, ***gauche* B** is more destabilizing than ***gauche* A**

Ratio 96 : 4 (85%)

Lactonization Ratio = 96 : 4

Epoxidation Ratio = 3 : 97

- Other cases:

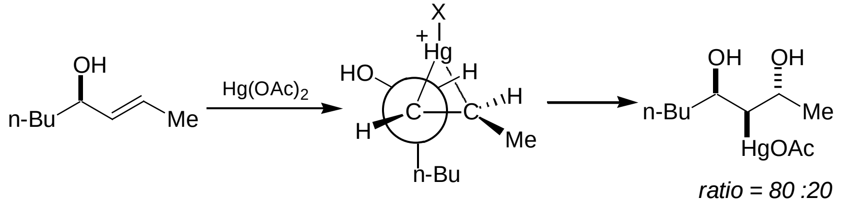


Ratio >95 : 5 (49%)

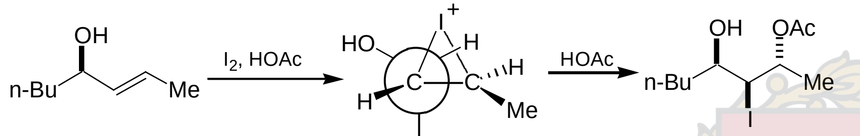
R = H: *77 : 23 (74%)*
R = Me: *42 : 58 (81%)*

R = H: *87 : 13 (41%)*
R = Me: *90 : 10 (94%)*

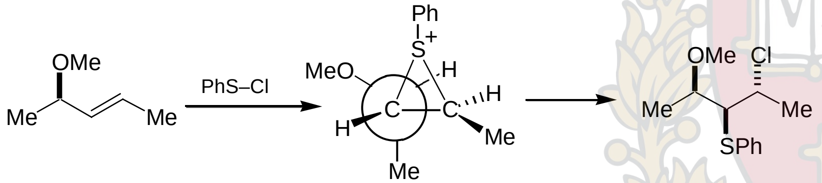
Olefin Sulfenation follows the preceding stereochemical analogies



ratio = 80 :20

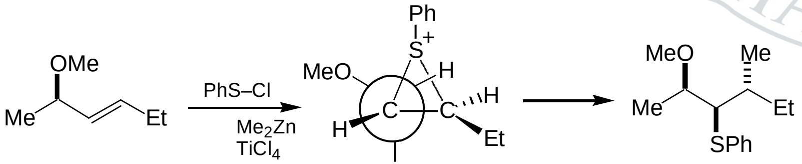


Ratio = 98 : 2 (78%)

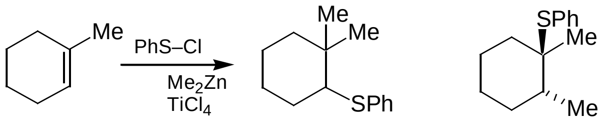


Reetz, *Angew. Chem. Int. Ed.* **1987**, *26*, 1028

The above stereochemistry is inferred from the following reaction:

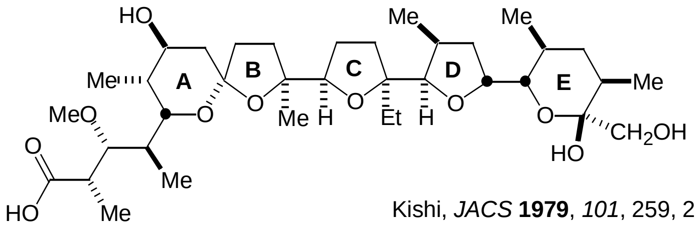


Ratio = 99 : 1 (40%)



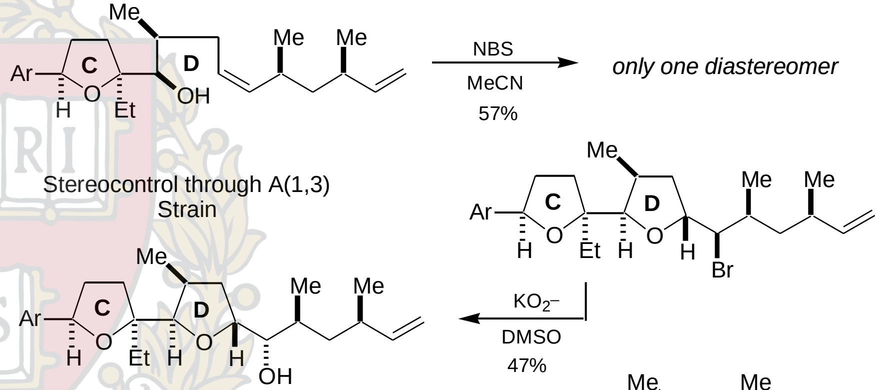
Ratio = 95 : 5 (59%)

Halogen-induced heterocyclization in the synthesis of monensin



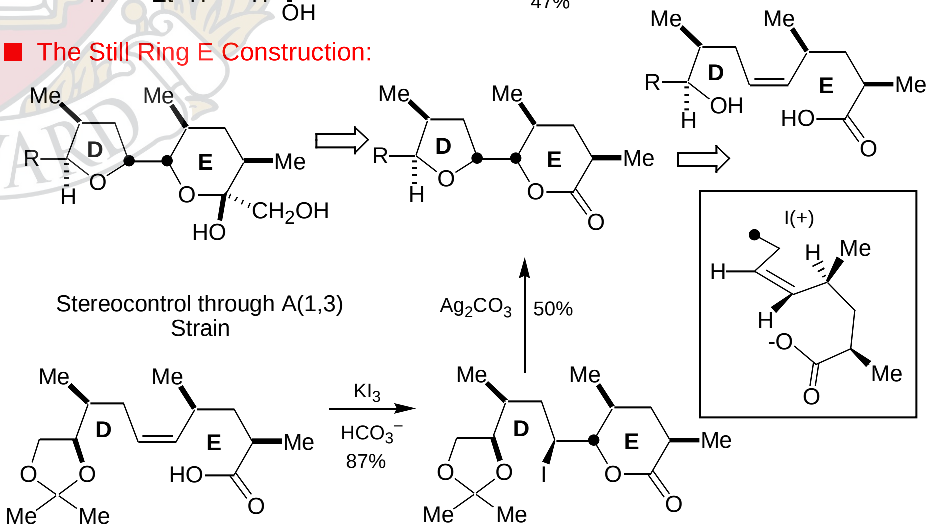
Kishi, *JACS* **1979**, *101*, 259, 260, 262
Still, *JACS* **1980**, *103*, 2117-2121

The Kishi Ring D Construction:



Stereocontrol through A(1,3) Strain

The Still Ring E Construction:

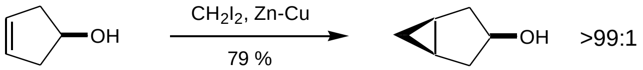


Stereocontrol through A(1,3) Strain

El(+)-induced heterocyclization ⇨ Cardillo, *Tetrahedron* **1990**, *46*, 3321-3408
Bartlett, *Asymmetric Synthesis* **1984**, *3*, Chap 6, 411-454

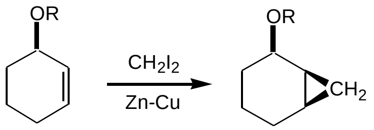
The Simmons-Smith Reaction

For a recent general review of the Simmons-Smith reaction see:
Charette & Beauchemin, *Organic Reactions*, **58**, 1-415 (2001)



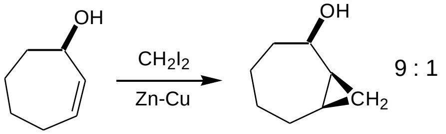
S. Winstein, *JACS* **1959**, *81*, 6523; **1961**, *83*, 3235; **1969**, *91*, 6892

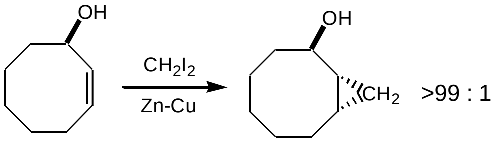
A large rate acceleration relative to simple olefins was observed.



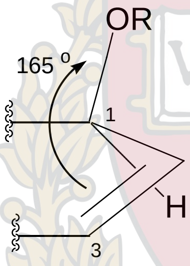
R = OMe: >99:1 Dauben, *JACS* **1963**, *85*, 468

R = OAc: 4:1 Sawada, *JOC* **1968**, *33*, 1767





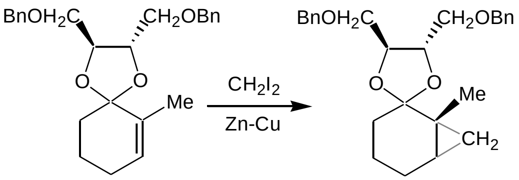
epoxidation also gives anti adduct



O–C_1–C_2–C_3 dihedral = 165 °

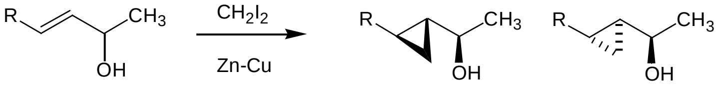
S. Winstein, *JACS*, **1969**, *91*, 6892

Absolute control of stereochemistry is possible through chiral ketal auxiliaries



diastereoselection 20:1

Yamamoto, *JACS*, **1985**, *107*, 8254
Mash, *JACS*, **1985**, *107*, 8256
Yamamoto, *Tetrahedron*, **1986**, *42*, 6458

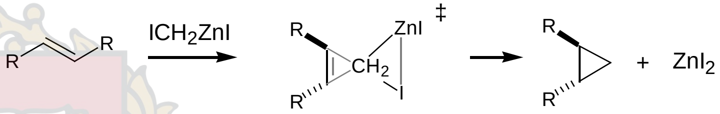


M. Pereyre and Co-workers
J. Chem. Res. (S) **1979**, 179

R	Ratio		
CH_3	57	:	43
Et	64	:	36
tBu	67	:	33

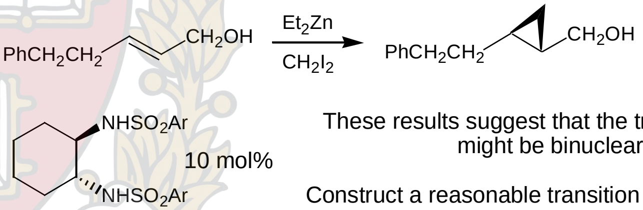
■ The classical mechanism

CH_2I_2 + Zn ⟶ ICH_2ZnI



■ Enantioselective Simmons-Smith Variants:

Kobayashi, *Tet. Let.* **1992**, *33*, 2575



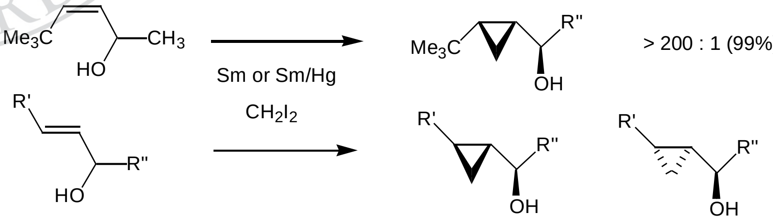
80% ee (82% yield)

These results suggest that the transition state might be binuclear.

Construct a reasonable transition structure which accomdates the data

■ Low-valent Samarium Variants:

Molander,*JOC* **1987**, *52*, 3942



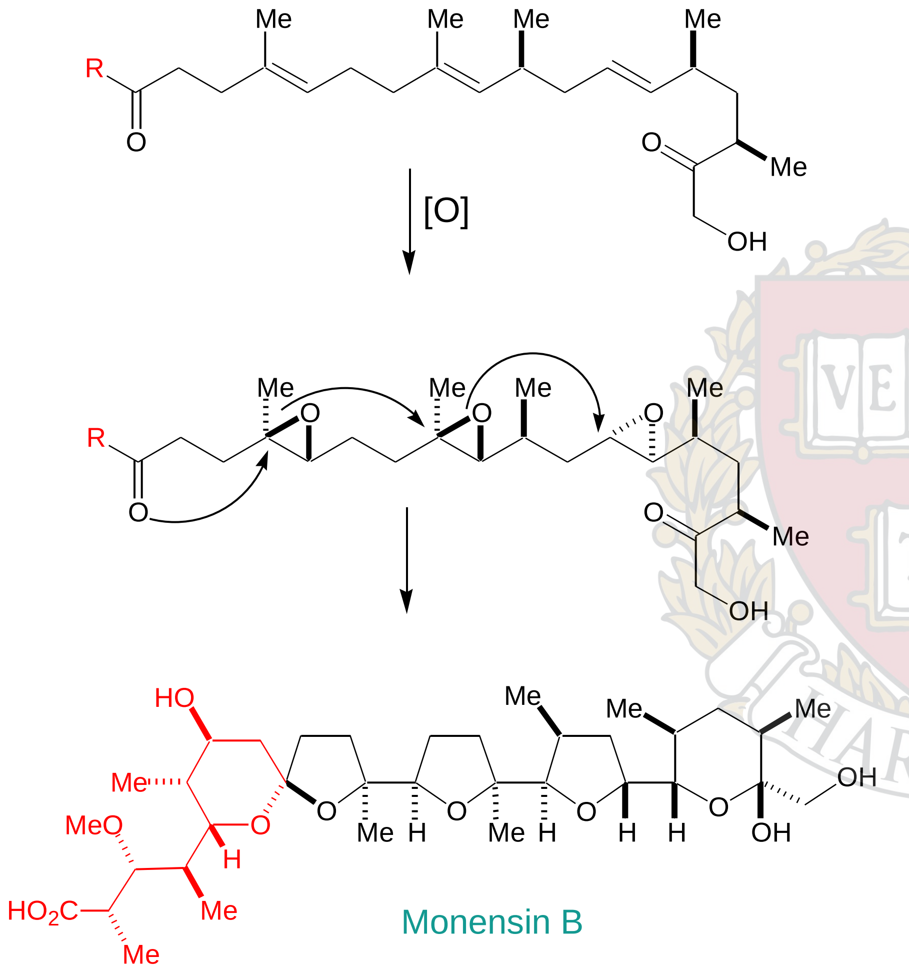
> 200 : 1 (99%)

Isolated alkenes and homoallylic alcohols are inert to these reaction conditions.

G. A. Molander and J. B. Etter
J. Org. Chem. **1987**, *52*, 3942

R'	R"	Ratio		
Ph	nBu	1	:	1.4
Ph	iPr	> 200	:	1
Ph	tBu	> 200	:	1
tBu	CH_3	1	:	5.1
tBu	iPr	> 200	:	1

One plausible biosynthetic proposal for polyether natural products:

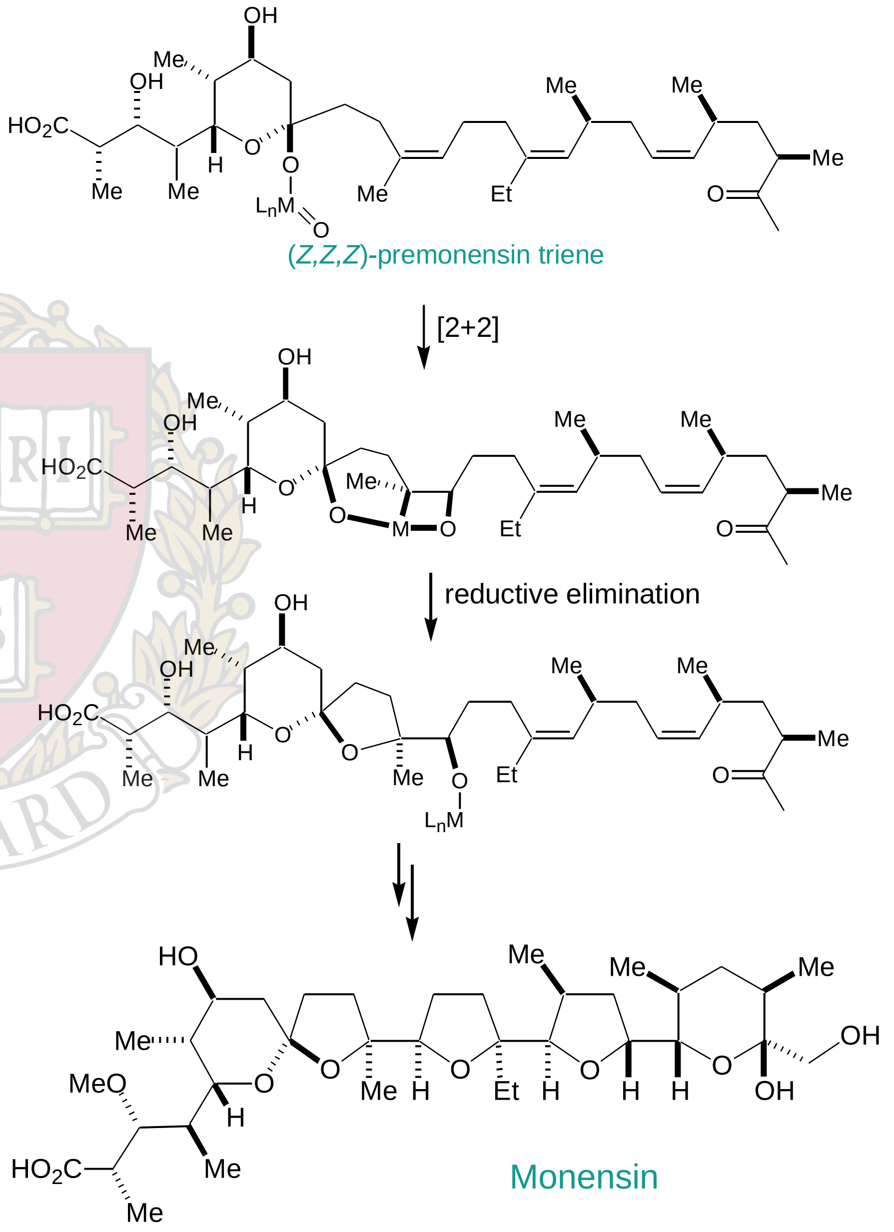


Monensin B

from lecture 7

Cane, D. E. *JACS*, **1983**, *105*, 3394.
Cane, D. E. *JACS*, **1982**, *104*, 7274.

An alternate biosynthetic proposal:

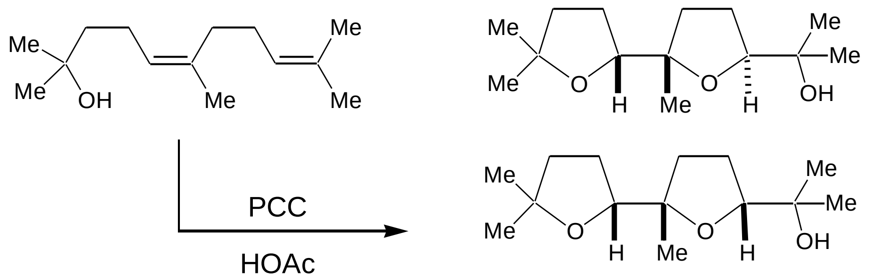


(*Z*,*Z*,*Z*)-premonensin triene

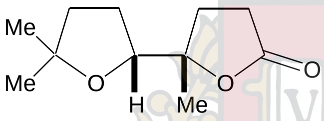
Monensin

Townsend, C. A.; Basak, A. *Tetrahedron*, **1991**, *47*, 2591.

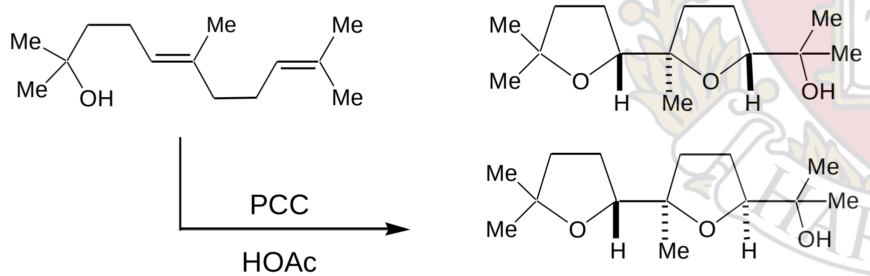
A biomimetic model for *syn*-oxidative polycyclization:



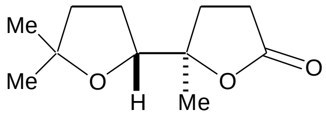
9% combined, 11:1 (*trans*:*cis*)



38%, 9.9:1



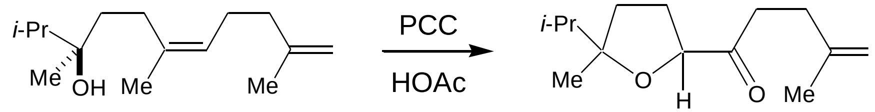
19% combined, 3.7:1 (*trans*:*cis*)



24%, 17:1

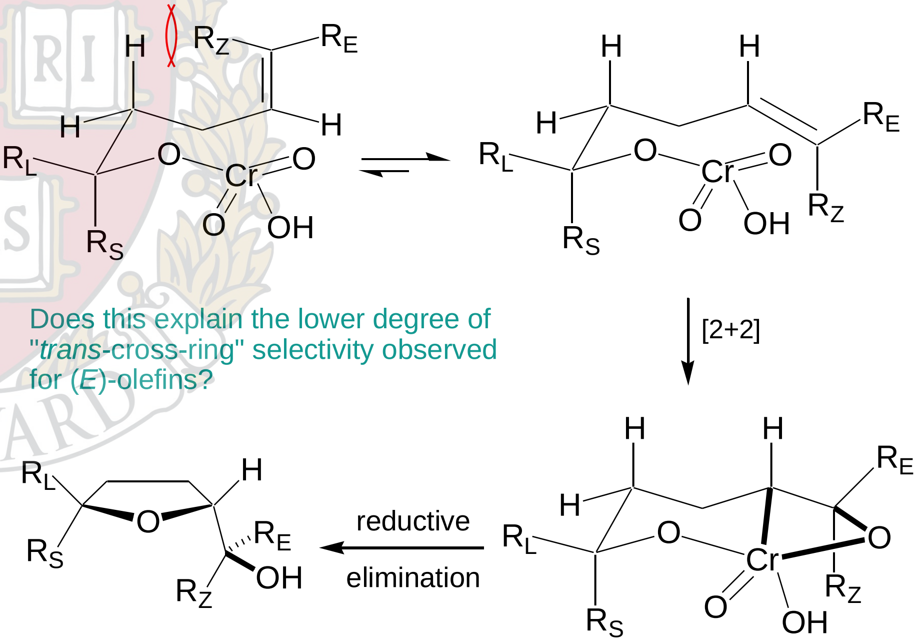
High *syn*-stereospecificity for tertiary alcohols

But for secondary alcohols...



...simple oxidation occurs more rapidly than oxidative cyclization.

Conformational model for *syn*-oxidative cyclization:

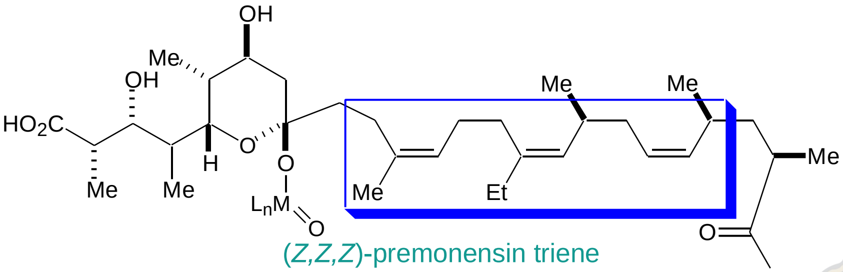


Does this explain the lower degree of "*trans*-cross-ring" selectivity observed for (*E*)-olefins?

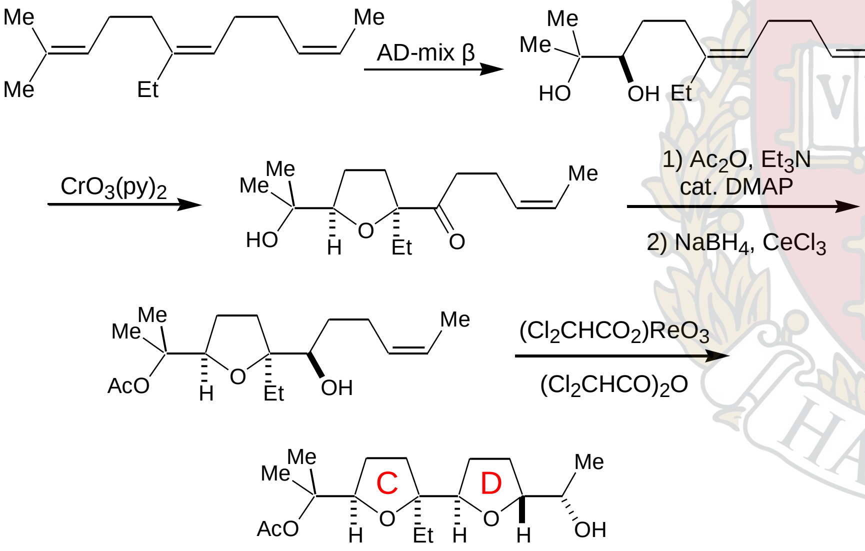
trans-substituted tetrahydrofuran

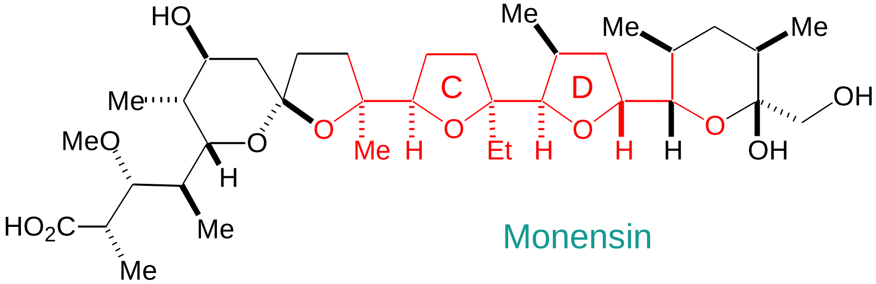
McDonald, F. E. *JACS*, **1994**, *116*, 7921.

Application of the model for *syn*-oxidative polycyclization using an all (*Z*)-polyolefin:



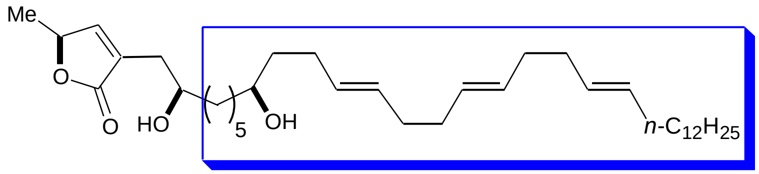
(*Z,Z,Z*)-premonensin triene



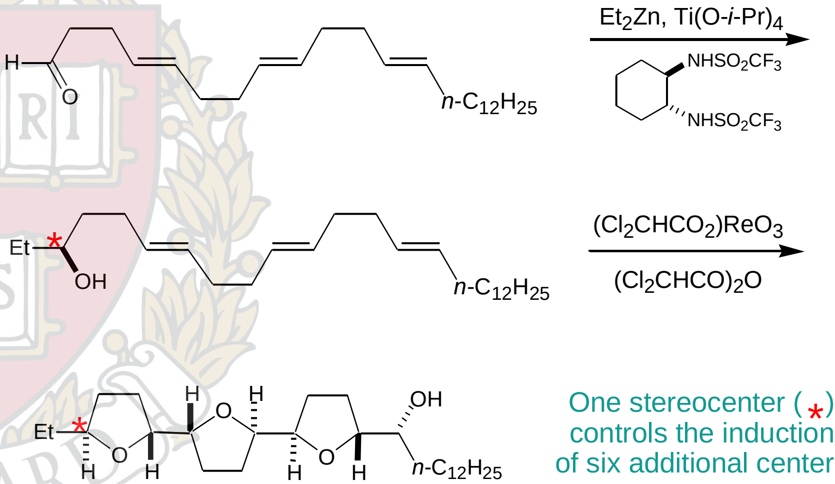


Monensin

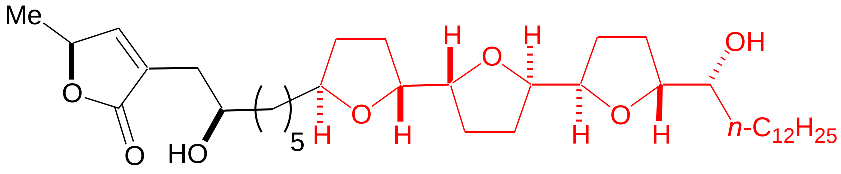
Application of the model for *syn*-oxidative polycyclization on an all (*E*)-polyolefin:



(*E,E,E*)-pregoniocin triene



One stereocenter (*) controls the induction of six additional centers.



Goniocin

McDonald, F. E. *Pure App. Chem.*, **1998**, *70*, 355.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 11

Pericyclic Reactions–1

- Introduction to Pericyclic Reactions
- Electrocyclic Reactions
- Sigmatropic Reactions
- Cycloaddition Reactions

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Fleming: Chapter 4
Thermal Pericyclic Reactions

Matthew D. Shair

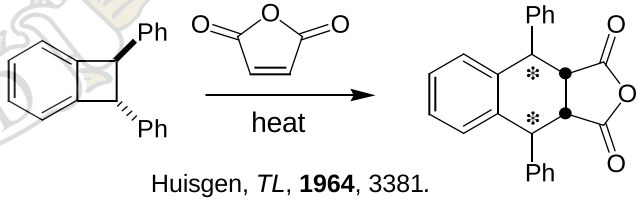
Friday,
October 11, 2002

Other Reading Material:

- Woodward-Hoffmann Theory
  R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970.
- Frontier Molecular Orbital Theory
  I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John-Wiley and Sons, New York, 1976.
- Dewar-Zimmerman Theory
  T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry, 3rd Ed.*, Harper & Row, New York, 1987.
- General Reference
  R. E. Lehr and A. P. Marchand, *Orbital Symmetry: A Problem Solving Approach*, Academic Press, New York, 1972.

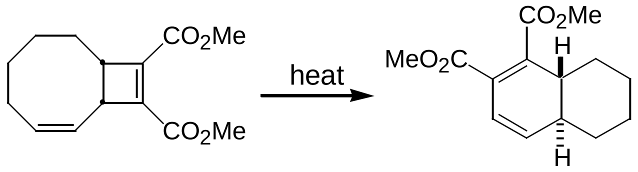
Problems of the Day:

Predict the stereochemical outcome of this reaction.



Huisgen, *TL*, **1964**, 3381.

Suggest a mechanism for the following reaction.



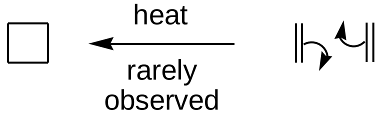
Bloomfield, *TL*, **1969**, 3719.

Pericyclic Reactions - Introduction/Definitions

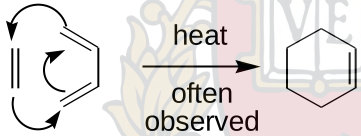
A pericyclic reaction is characterized as a change in bonding relationships that takes place as a ***continuous, concerted reorganization of electrons***. The term "***concerted***" specifies that there is ***one single transition state*** and therefore ***no*** ***intermediates*** are involved in the process. To maintain ***continuous electron flow***, pericyclic reactions occur through ***cyclic transition states***.
More precisely: The cyclic transition state must correspond to an arrangement of the ***participating orbitals*** which has to ***maintain a bonding interaction*** between the reaction components throughout the course of the reaction.

Some factors to consider in our analysis:

The number of electrons involved has a profound influence on reactivity:

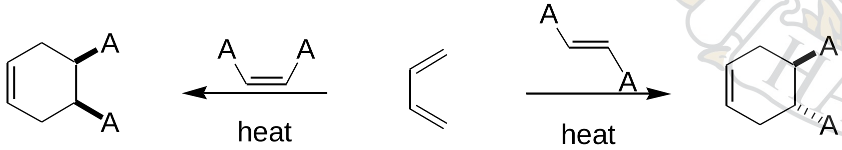


4 electrons

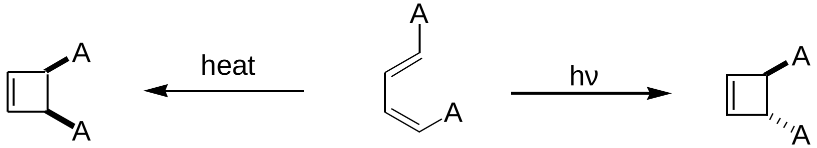


6 electrons

Pericyclic reactions are stereospecific:



Reactions behave differently depending on the conditions used (i.e. thermal versus photochemical conditions):



The Theories:

Three theories are commonly used to explain and predict pericyclic reactions. We will only concern ourselves with two of these theories.

1) Fukui: Frontier Molecular Orbital Interactions

- Much easier to use than the original orbital symmetry arguments
- HOMO/LUMO interactions

2) Dewar-Zimmerman: Aromatic Transition States

- The easiest to apply for all reaction types, but it is not as easy to understand why it it valid
- Aromatic or antiaromatic transition states

3) Woodward-Hoffmann: Conservation of Orbital Symmetry

- First theory to explain and predict the outcome of many reactions
- Correlation diagrams

On the three methods:

"There are several ways of applying the orbital-symmetry principle to cycloaddition reactions, three of which are used more frequently than others. Of these three, we will discuss two: the frontier-orbital method and the Möbius-Hückel method. The third, called the correlation diagram method, is less convenient to apply than the other two."
Jerry March in "Advanced Organic Chemistry"

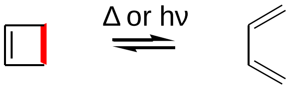
The Five Major Categories of Pericyclic Reactions

(1) ELECTROCYCLIC RING CLOSURE/RING OPENING:

An electrocyclic ring closure is the creation of a new sigma bond at the expense of the terminal p orbitals of a conjugated pi system. There is a corresponding reorganization of the conjugated pi system. We usually classify the reaction according to the number of electrons involved.

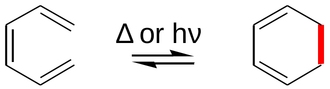
Examples:

A 4 e^- electrocyclic reaction



Cyclobutene Butadiene

A 6 e^- electrocyclic reaction



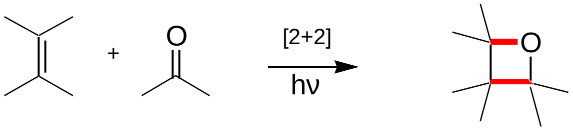
1,3,5-Hexatriene 1,3-Cyclohexadiene

Pericyclic Reactions: Major Classes

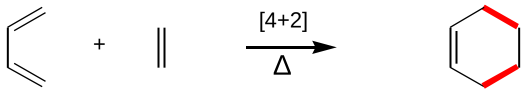
(2) CYCLOADDITION REACTIONS/CYCLOREVERSION REACTIONS:

A cycloaddition reaction is the union of two smaller, independent pi systems. Sigma bonds are created at the expense of pi bonds. A cycloaddition can occur in an intramolecular sense, but it must be between two **independent** pi systems. Cycloaddition reactions are referred to as [**m + n**] additions when a system of **m** conjugated *atoms* combines with a system of **n** conjugated *atoms*. A cycloreversion is simply the reverse of a cycloaddition.

Examples:



A 2+2 cycloaddition. The Paterno-Büchi reaction.

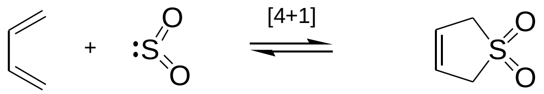


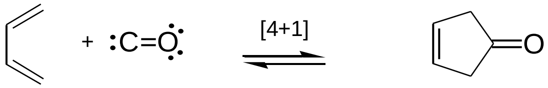
A 4+2 cycloaddition. The Diels-Alder reaction.

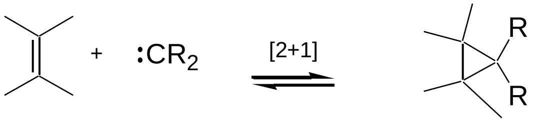
(3) CHELETROPIC REACTIONS:

Cheletropic reactions are a special group of cycloaddition/cycloreversion reactions. Two bonds are formed or broken at a single atom. The nomenclature for cheletropic reactions is the same as for cycloadditions.

Examples:



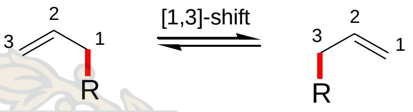


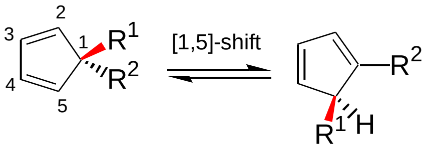


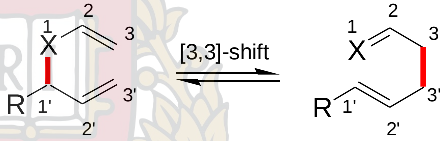
(4) SIGMATROPIC REARRANGEMENTS:

A sigmatropic rearrangement is the migration of a sigma bond from one position in a conjugated system to another position in the system, accompanied by reorganization of the connecting pi bonds. The number of pi and sigma bonds remains constant. The rearrangement is an [**m,n**] shift when the sigma bond migrates across **m** atoms of one system and **n** atoms of the second system.

Examples:







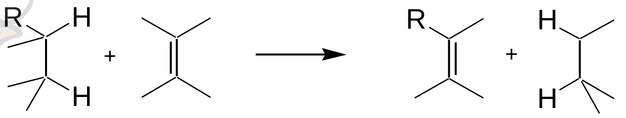
X=CR$_2$, Cope rearrangement
X=O, Claisen rearrangement

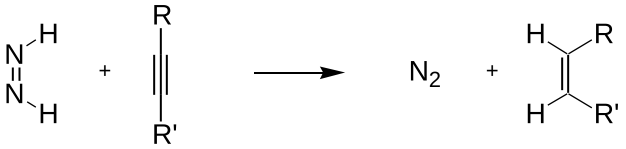
(5) GROUP TRANSFER REACTIONS:

In a group transfer reaction one or more groups get transferred to a second reaction partner.

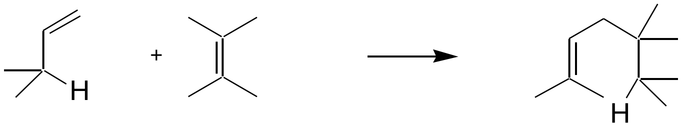
Examples:

Hydrogen Transfer:





Ene Reaction:



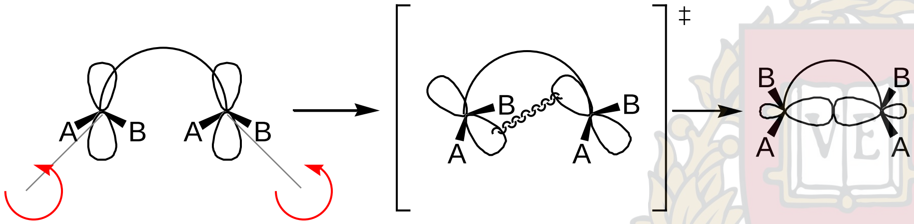
ELECTROCYCLIC RING CLOSURE/RING OPENING:

The Stereochemical issues:

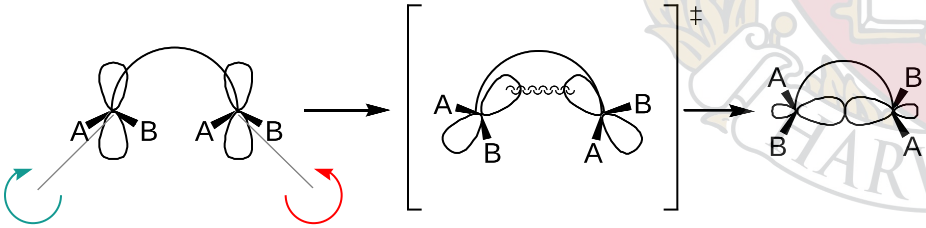
Ring closure can occur in two distinct ways. This has consequences with regard to:

- ■ The orbital lobes that interact
- ■ The disposition of substituents on the termini

Conrotatory Closure: The termini rotate in the **same direction**



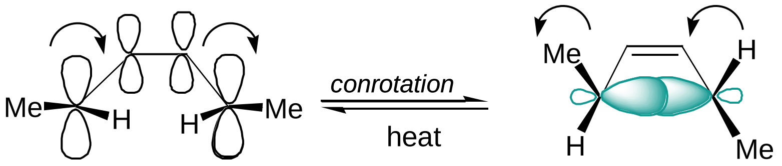
Disrotatory Closure: The termini rotate in **opposite directions**

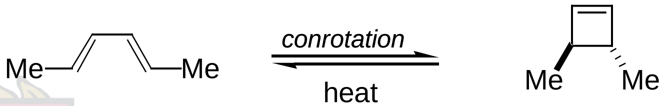


Empirical Observations:

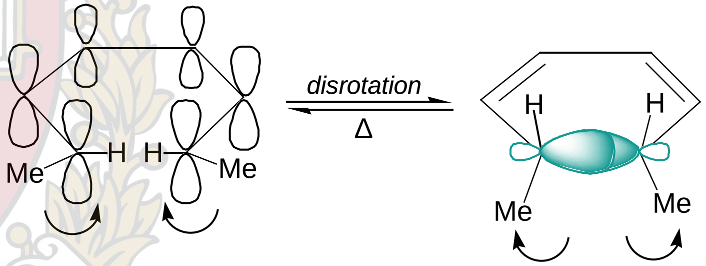
It was noted that butadienes undergo conrotatory closure under thermal conditions, while hexatrienes undergo disrotatory closure under thermal conditions. The microscopic reverse reactions also occur with the same rotational sense (i.e. cyclobutenes open in a conrotatory sense when heated, and cyclohexadienes open in a disrotatory sense when heated.)

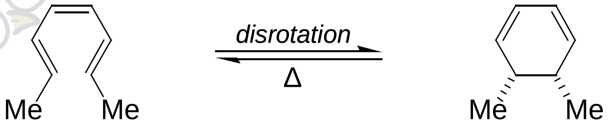
Butadiene to cyclobutene: A 4-electron (4q) system



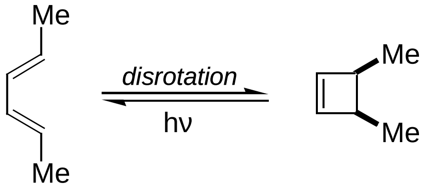


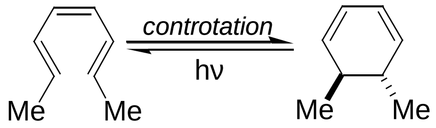
Hextriene to cyclohexadiene: A 6-electron (4q+2) system



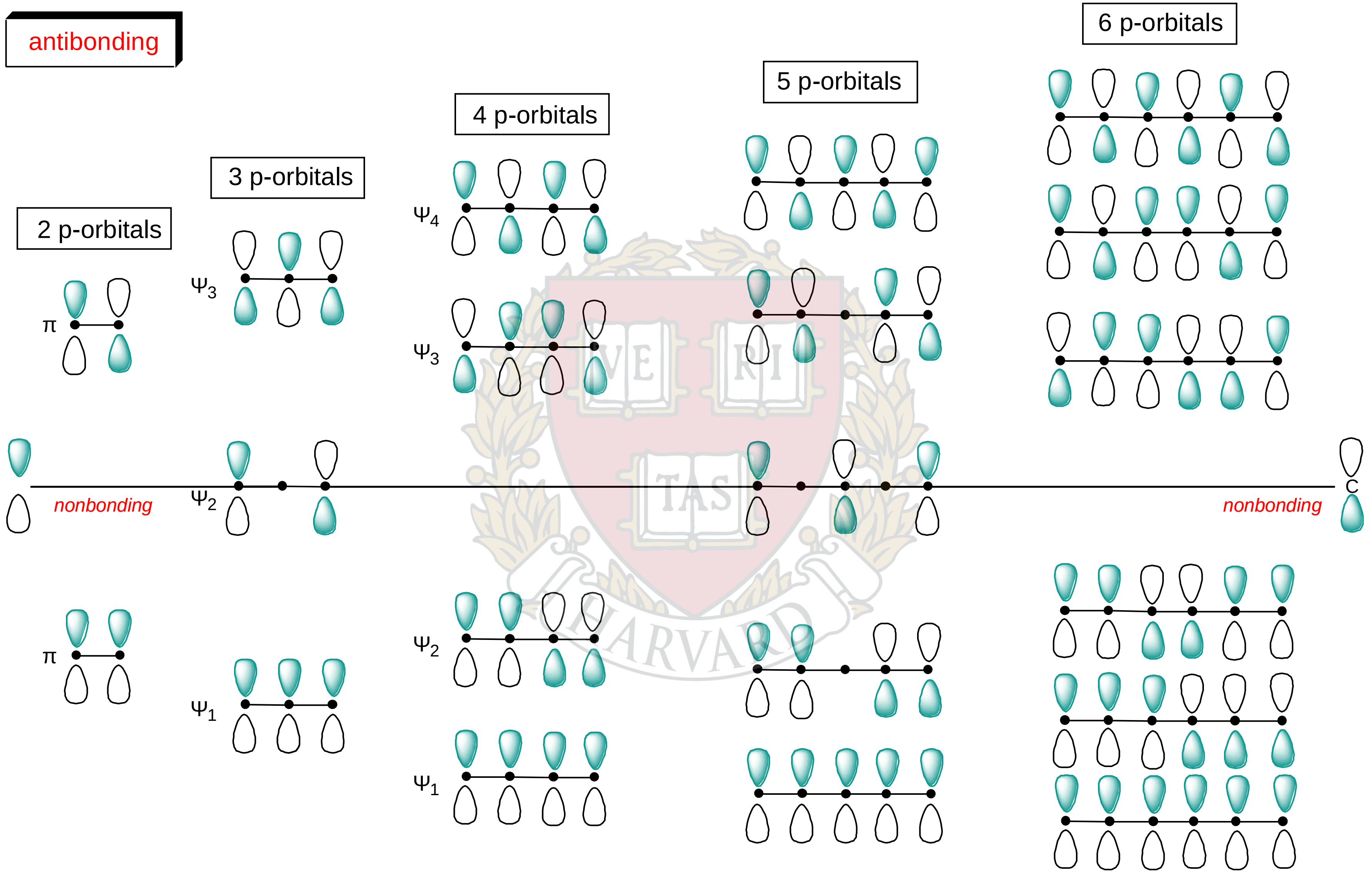


It was also noted that changing the "reagent" from heat to light reversed this reactivity pattern. Under photochemical conditions 4 electron systems undergo disrotatory motion, while 6 electron systems undergo conrotatory motion.





Conjugated pi systems



bonding

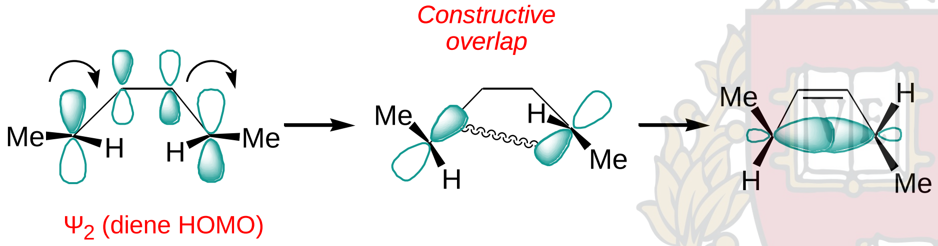
There are no nodal planes in the most stable bonding MO. With each higher MO, one additional nodal plane is added. The more nodes, the higher the orbital energy.

■ FMO Treatment of Electrocyclic reactions.

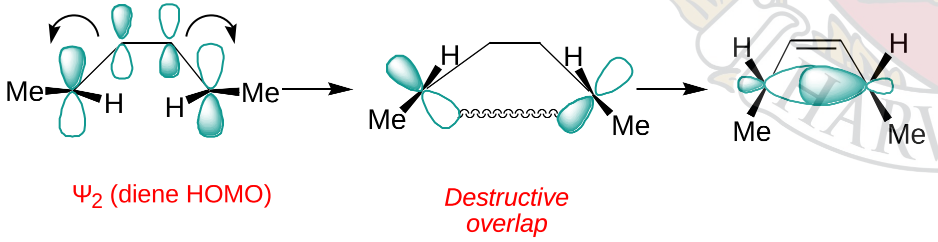
- ■ Examine the interactions that occur in the HOMO as the reaction proceeds.
- ■ If the overlap is constructive (i.e. of the same phase) then the reaction is "allowed."
- ■ If the overlap is destructive (i.e. of different phases) then the reaction is "forbidden."

Thermal Activation:

Conrotatory Closure: (Allowed and observed)



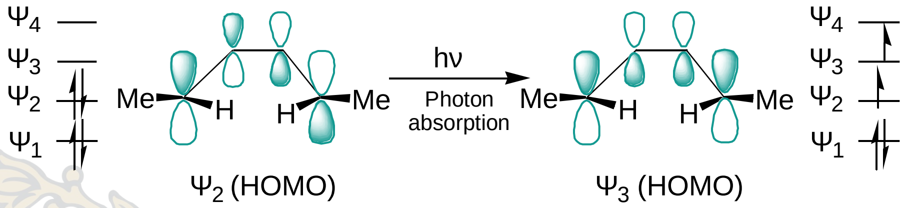
Disrotatory Closure: (Forbidden and not observed)



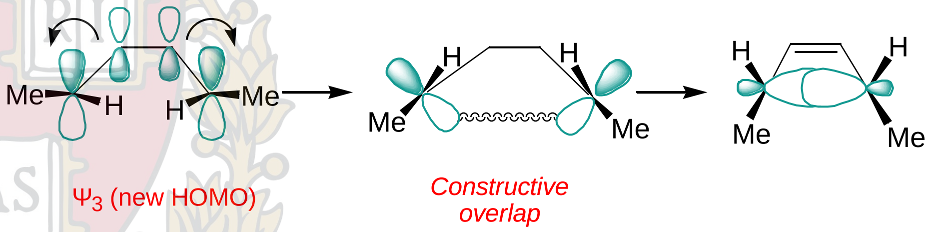
A similar analysis for the hexatriene system proves that under thermal conditions, disrotation is allowed and conrotation is forbidden.

Photochemical Activation:

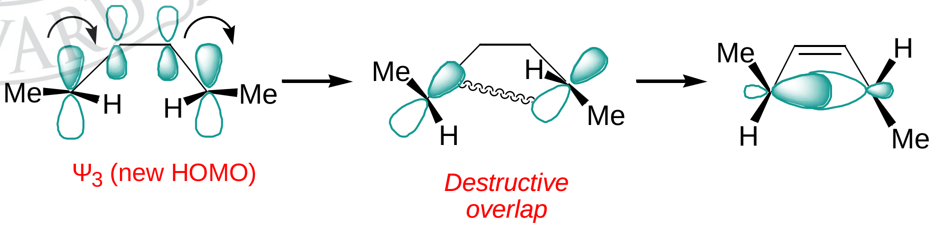
When light is used to initiate an electrocyclic reaction, an electron is excited from Ψ_2 to Ψ_3. Treating Ψ_3 as the HOMO now shows that disrotatory closure is allowed and conrotatory closure is forbidden.



Disrotatory Closure: (Allowed and observed)



Conrotatory Closure: (Forbidden and not observed)



We have so far proven which *ring closures* are allowed and which are forbidden. Do we now have to go back and examine all the *ring openings*?

NO!

The principle of microscopic reversiblity says that if the reaction is allowed in one direction, it must be allowed in the other direction.

Electrocyclic Reactions: Dewar-Zimmerman

The Dewar-Zimmerman analysis is based on identifying transition states as aromatic or antiaromatic. We will not go into the theory behind why this treatment works, but it will give the same predictions as FMO or Orbital Symmetry treatments, and is fundamentally equivalent to them.

Using the Dewar-Zimmerman model:

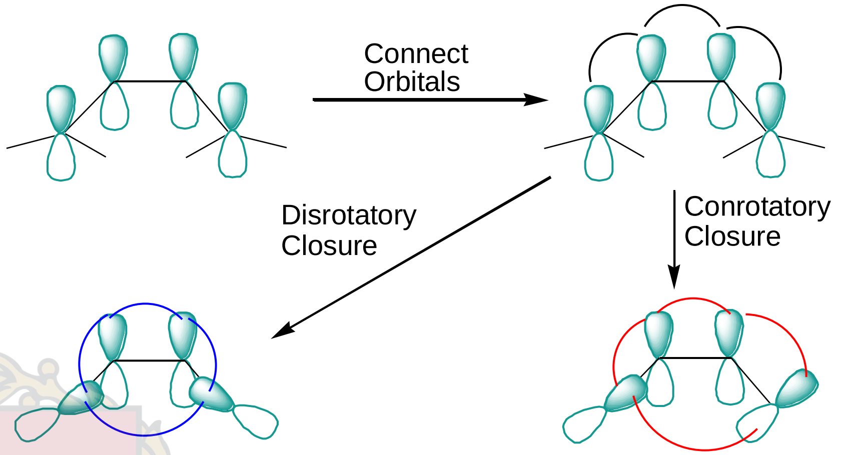
- Choose a basis set of 2p atomic orbitals for all atoms involved (1s for hydrogen atoms).
- Assign phases to the orbitals. Any phases will suffice. It is **not** important to identify this basis set with any molecular orbital.
- Connect the orbitals that interact in the starting material, before the reaction begins.
- Allow the reaction to proceed according to the geometry postulated. Connect those lobes that begin to interact that were not interacting in the starting materials.
- Count the number of phase inversions that occur as the electrons flow around the circuit. Note that a phase inversion **within** an orbital **is not counted**.
- Based on the phase inversions, identify the topology of the system.

Odd number of phase inversions: Möbius topology
Even number of phase inversions: Hückel topology

- Assign the transition state as aromatic or antiaromatic, based on the number of electrons present.

System	Aromatic	Antiaromatic
Hückel	4q + 2	4q
Möbius	4q	4q + 2

- If the transition state is aromatic, then the reaction will be allowed thermally. If the transition state is antiaromatic, then the reaction will be allowed photochemically.


Connect Orbitals

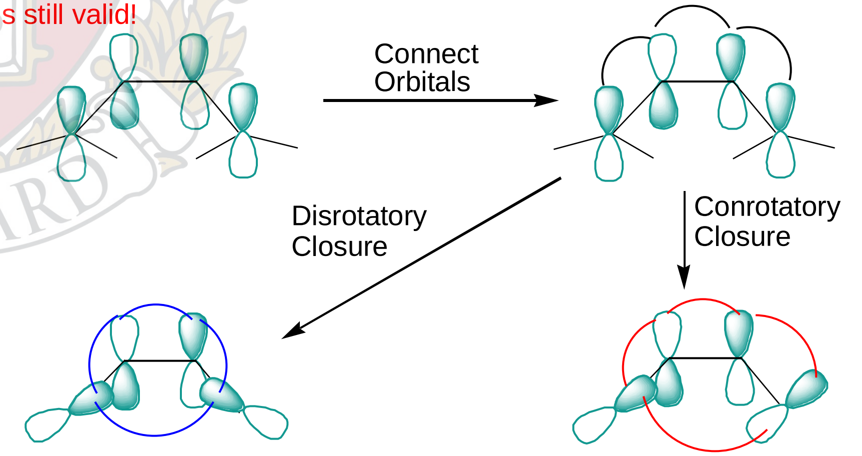
Disrotatory Closure

Conrotatory Closure

Zero Phase Inversions
Hückel Topology
4 electrons in system
Antiaromatic and
Forbidden

One Phase Inversion
Möbius Topology
4 electrons in system
Aromatic and
Allowed

Note that I can change the phase of an abitrary orbital and the analysis is still valid!


Connect Orbitals

Disrotatory Closure

Conrotatory Closure

Two Phase Inversions
Hückel Topology
4 electrons in system
Antiaromatic and
Forbidden

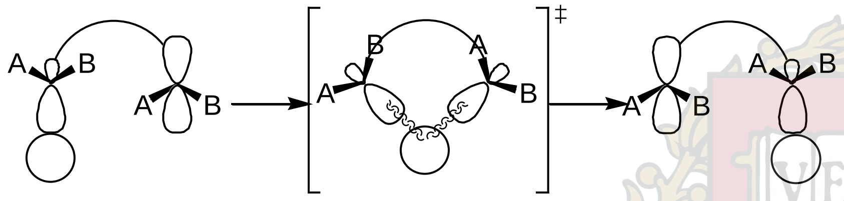
Three Phase Inversions
Möbius Topology
4 electrons in system
Aromatic and
Allowed

[1,3]-Sigmatropic Rearrangements: FMO Analysis

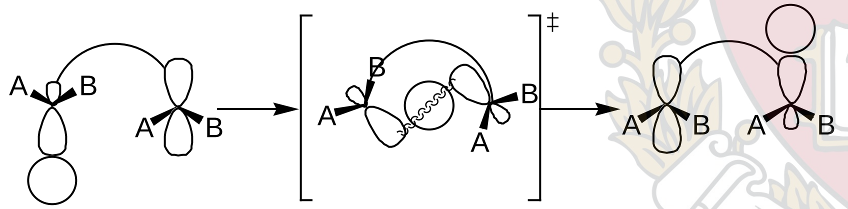
The Stereochemical issues:

The migrating group can migrate across the conjugated pi system in one of two ways. If the group migrates on the same side of the system, it is said to migrate **suprafacially** with respect to that system. If the group migrates from one side of the pi system to the other, it is said to migrate **antarafacially** with respect to that system.

Suprafacial migration: The group moves across the same face.



Antarafacial migration: The group moves from one face to the other.



Sigmatropic Rearrangements: FMO Analysis

- Imagine the two pieces fragmenting into a cation/anion pair, (or a pair of radicals) and examine the HOMO/LUMO interaction.

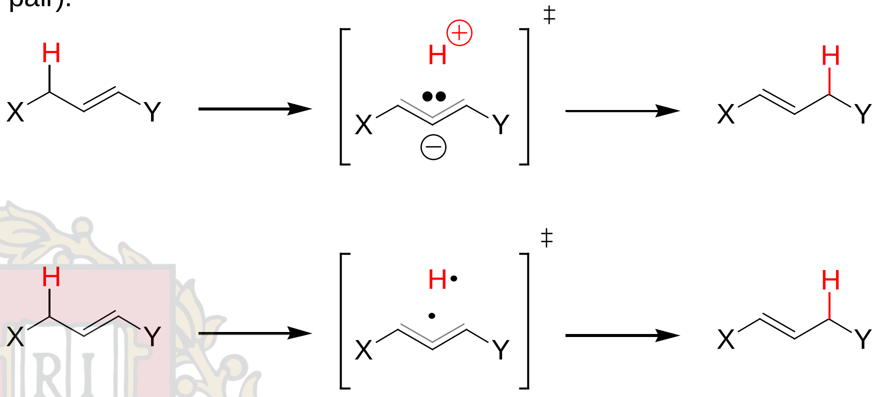
- If the overlap is constructive at both termini then the reaction is allowed. If the overlap is destructive at either terminus then the reaction is forbidden.

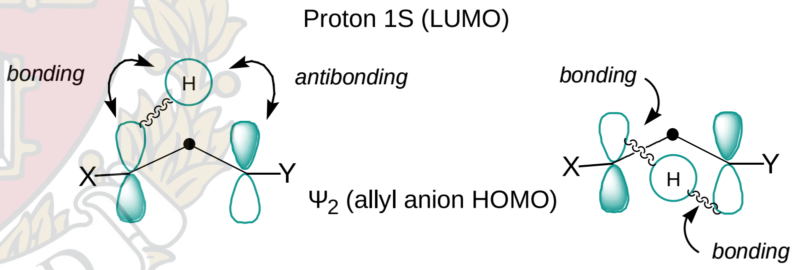
- If the migrating atom is carbon, then we can also entertain the possiblity of the alkyl group migrating with inversion of configuration (antarafacial on the single atom).

- If the migrating atom is hydrogen, then it cannot migrate with inversion.

- [1,3] Sigmatropic Rearrangements (H migration)

- Construct TS by considering an allyl anion and the proton (or radical pair):





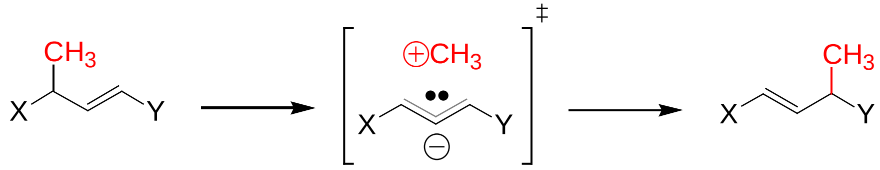
Suprafacial Geometry *Antarafacial Geometry*

- The analysis works if you consider the other ionic reaction, or consider a radical reaction. In each case it is the same pair of orbitals interacting.

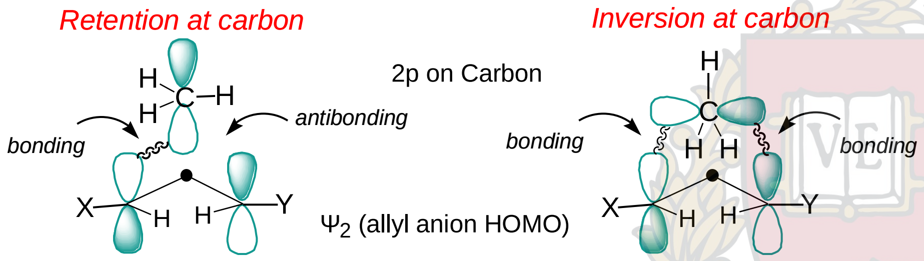
- The suprafacial migration is forbidden and the bridging distance too great for the antarafacial migration. Hence, [1,3] hydrogen migrations are not observed under thermal conditions.

- Under photochemical conditions, the [1,3] rearrangement is allowed suprafacially. How would you predict this using FMO?

- [1,3] Sigmatropic Rearrangements (C migration)



- Construct TS by considering an allyl anion and the methyl cation:



Suprafacial on allyl fragment *Suprafacial on allyl fragment*

- The analysis works if you consider the other ionic reaction, or consider a radical reaction. In each case it is the same pair of orbitals interacting.

- Under photochemical conditions, the [1,3] rearrangement is allowed suprafacially with retention of stereochemistry.

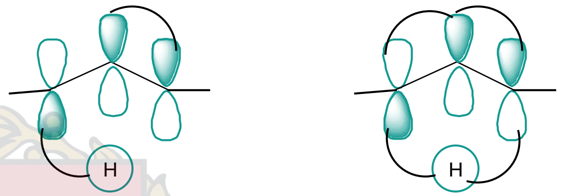
- The stereochemical constraints on the migration of carbon with inversion of configuration is highly disfavored on the basis of strain. Such rearrangements are rare and usually only occur in highly strained systems.

Using a similar analysis, one can prove that [1,5] hydrogen and alkyl shifts should be allowed when suprafacial on the pi component and proceeding with retention. Please refer to Fleming for more applications of FMO theory to [1,n] sigmatropic shifts.

Sigmatropic Rearrangements: Dewar-Zimmerman

Dewar-Zimmerman also predicts the [1,3] suprafacial migration to be forbidden.

The basis set of s and p orbitals with arbitrary phase:

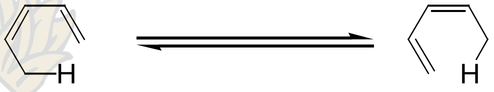


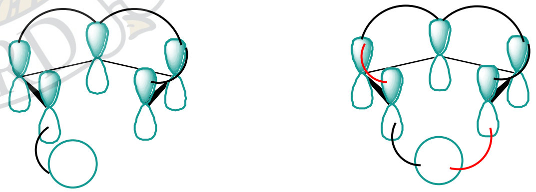
Two Phase Inversions
Hückel Topology
Four Electrons
Forbidden thermally

Orbital interactions in the parent system

Completing the circuit across the bottom face

The [1,5] shift of a hydrogen atom across a diene.





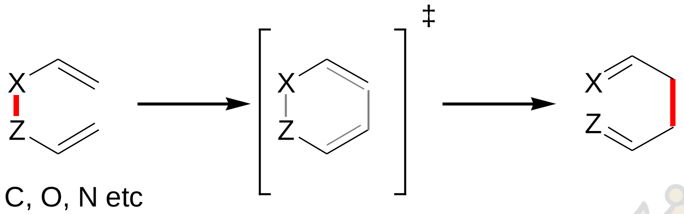
Zero Phase Inversions
Hückel Topology
Six Electrons
Allowed thermally

Orbital interactions in the parent system

Completing the circuit across the bottom face

[3,3] Rearrangements:

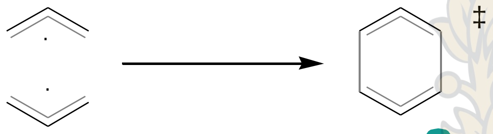
A thermally allowed reaction in either of two geometries, the "chair" or the "boat" geometry. Depicted below is the "chair" geometry. You should be able to work out the details of the "boat" geometry yourself.

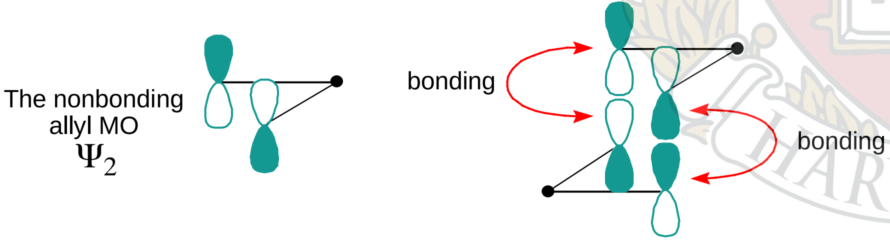


X & Z = C, O, N etc

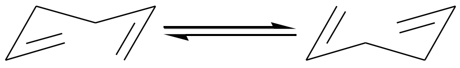
The FMO Analysis:

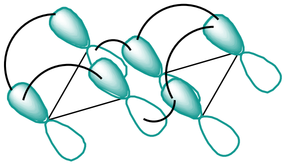
Bring two Allyl radicals together to access for a possible bonding interaction between termini.





The Dewar-Zimmerman Analysis:





Two Phase Inversions
Hückel Topology
Six Electrons
Allowed Thermally

■ The Toggle Algorithm:

The toggle algorithm is a simple way to take one reaction of each class that you remember is allowed (or forbidden) and derive if the reaction is allowed or forbidden under new conditions.

■ How does it work?

All of the various parameters of the pericyclic reaction are the input variables, the "switches."
The output is either "allowed" or "forbidden."
Write out all the relevant parameters of a reaction together with the known result.
Each time you change a parameter by one incremental value ("toggle a switch"), the output will switch.
This is the prediction of the reaction under the new parameters.

■ So it's nothing really new, is it?

No, its just a convenient way to rederive predictions without memorizing a table of selection rules.

An Example:

Take the [1,3] sigmatropic rearrangement of an alkyl group. We know this is forbidden under thermal conditions in a supra-supra manner, and so we make it the first entry in the table.

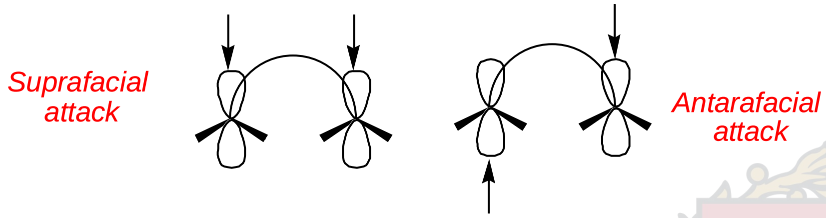
Rearrangement	Conditions	Component 1	Component 2	Output
[1,3]	Heat	Suprafacial	Suprafacial	Forbidden
[1,3]	Heat	Antarafacial	Suprafacial	Allowed
[1,3]	Light	Antarafacial	Suprafacial	Forbidden
[1,5]	Heat	Suprafacial	Suprafacial	?

Each incremental change in the "input" registers changes the "output" register by one. Multiple changes simply toggle the output back and forth. What is the prediction in the last line?

Cycloaddition Reactions

The Stereochemical issues:

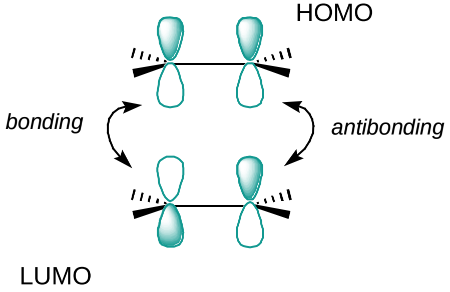
In a cycloaddition, a pi system may be attacked in one of two distinct ways. If the pi system is attacked from the same face, then the reaction is **suprafacial** on that component. If the system is attacked from opposite faces, then the reaction is **antarafacial** on that component.



The [2+2] Cycloaddition: FMO Analysis

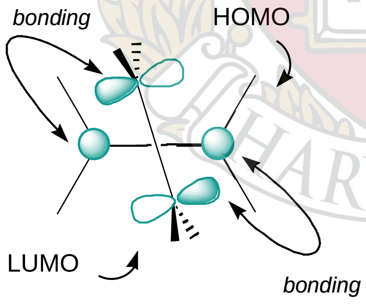
For the [2+2] cycloaddition two different geometries have to be considered.

Suprafacial/Suprafacial



Forbidden

Antarafacial/Suprafacial

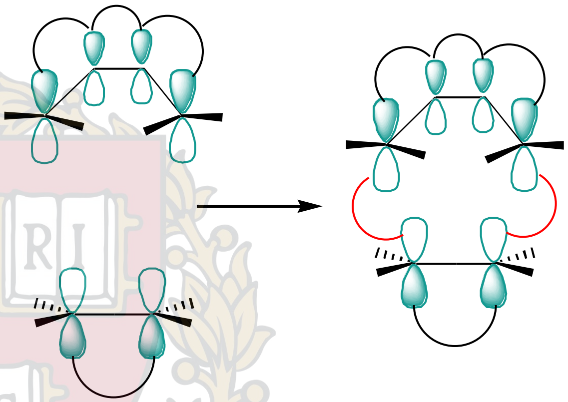


Allowed

The simplest approach (Supra/Supra) is forbidden under thermal activation. The less obvious approach (Antara/Supra) is allowed thermally but geometrically rather congested. It is believed to occur in some very specific cases (e.g. ketenes) where the steric congestion is reduced.

The [4+2] Cycloaddition: Dewar-Zimmerman

The most well known cycloaddition is the Diels-Alder reaction between a four pi component (the diene) and a two pi component (the dienophile). An exhaustive examination of this reaction is forthcoming, so we will limit ourselves to a simple examination.



Zero Phase Inversions
Hückel Topology
Six Electrons
Allowed thermally

Summary:

- There are three fundamentally equivalent methods of analyzing pericyclic reactions: Two are much simpler than the third.
  - Fukui Frontier Molecular Orbital Theory
  - Dewar-Zimmerman Hückel-Möbius Aromatic Transition States
  - Woodward-Hoffmann Correlation Diagrams

- Some methods are easier to use than others, but all are equally correct and no one is superior to another. Conclusions drawn from the correct application of one theory will not be contradicted by another theory.

- The principle of microscopic reversibility allows us to look at a reaction from either the forward direction or the reverse direction.

- There is a general trend that reactions will behave fundamentally different under thermal conditions and photochemical conditions.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 12

Pericyclic Reactions–2

- Electrocyclic Reactions
- Cheletropic Reactions
- Sigmatropic Rearrangements: [1,2], [1,3], [1,5]

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Fleming: Chapter 4
Thermal Pericyclic Reactions

Houk, *et. al. Acc. Chem. Res.* **1996**, *29*, 471-477.

Houk, *et. al. JOC.* **1996**, *61*, 2813-2825.

Matthew D. Shair

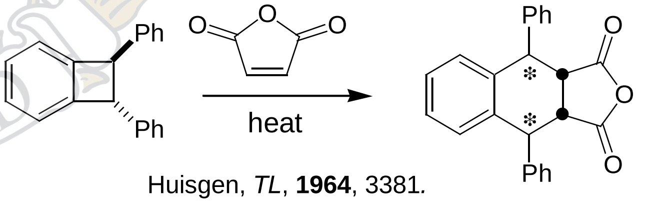
Monday,
Columbus Day,
October 14, 2002

Other Reading Material:

- Woodward-Hoffmann Theory
  R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970.
- Frontier Molecular Orbital Theory
  I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John-Wiley and Sons, New York, 1976.
- Dewar-Zimmerman Theory
  T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry, 3rd Ed.*, Harper & Row, New York, 1987.
- General Reference
  R. E. Lehr and A. P. Marchand, *Orbital Symmetry: A Problem Solving Approach*, Academic Press, New York, 1972.

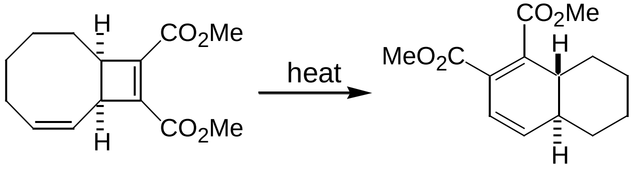
Problems of the Day:

Predict the stereochemical outcome of this reaction.



Huisgen, *TL*, **1964**, 3381.

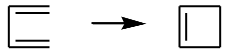
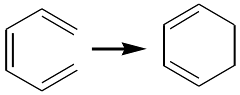
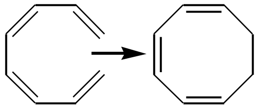
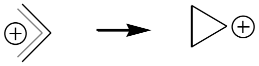
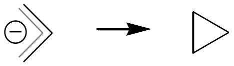
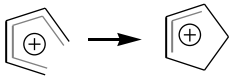
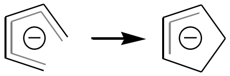
Suggest a mechanism for the following reaction.

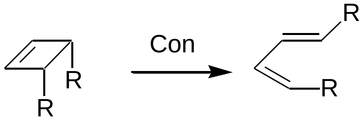


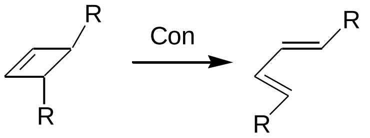
Bloomfield, *TL*, **1969**, 3719.

Electrocyclic Reaction - Selection Rules

	Ground State (Thermal process)	Excited State (Photochemical Process)
4n π e⁻ (n = 1,2...)	conrotatory	disrotatory
4n+2 π e⁻ (n = 0,1,2...)	disrotatory	conrotatory

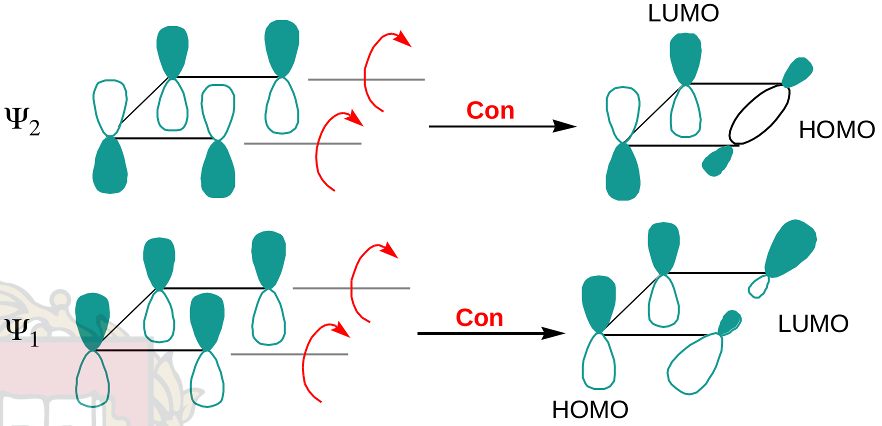
Examples	Ground State	Excited State
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory

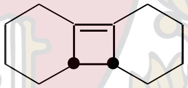
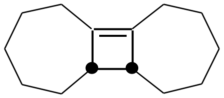
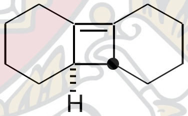
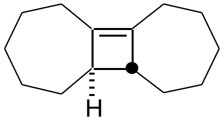




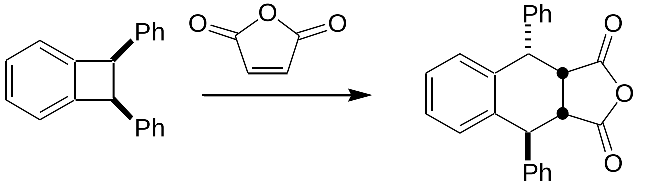
Sterically favored

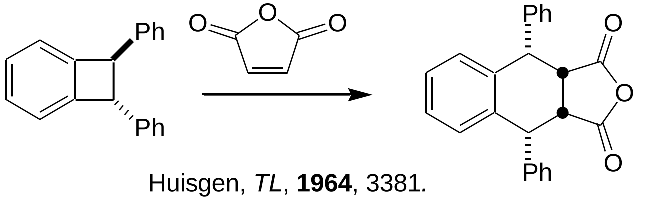
Controtation Ψ_1 and Ψ_2 on to the indicated bonding and anti-bonding orbitals of cyclobutene:



Activation Energy (kcal/mol) for electrocyclic ring opening		Activation Energy (kcal/mol) for electrocyclic ring opening	
	42		45
	29		27

Criegee, *Chem. Ber.* **1968**, *101*, 102.



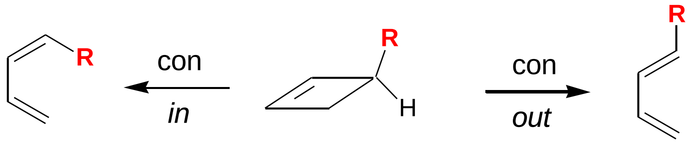


Huisgen, *TL*, **1964**, 3381.

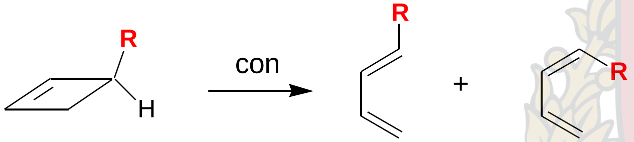
Electrocyclic Processes-2: Torquoselectivity

Torquoselectivilty is defined as the predisposition of a given R substituent for a given conrotatory motion

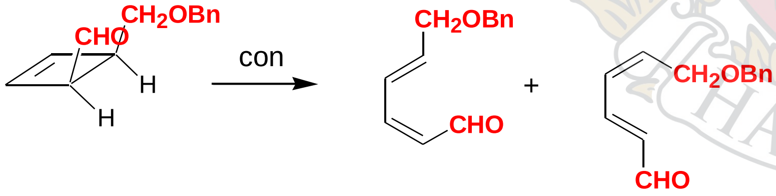
Houk et al. *Acc. Chem. Res* **1996**, 29, 471



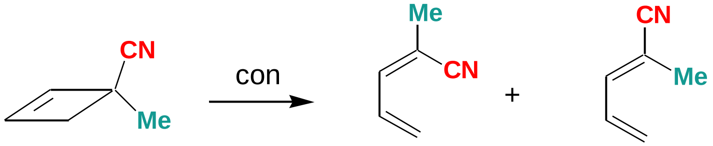
Examples: Donor substituents prefer con–out mode
Pi acceptor substituents prefer con–in mode



R = Me	**only**	none
R = CHO	none	**only**

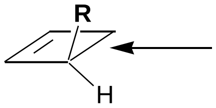


ratio: >20:1

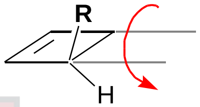


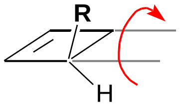
ratio: 4:1

How do we explain? Donor substituents prefer con–out mode
Pi acceptor substituents prefer con–in mode

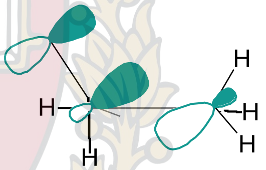


View the 2 conrotatory modes by looking at the breaking sigma bond from this perspective

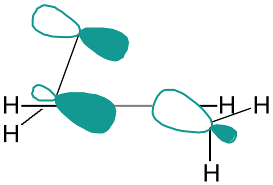




Outward Motion *Inward Motion*

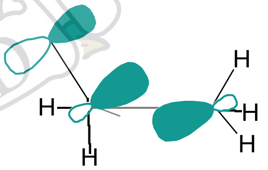


LUMO + p

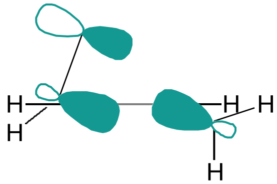


LUMO + p

A



HOMO + p



B

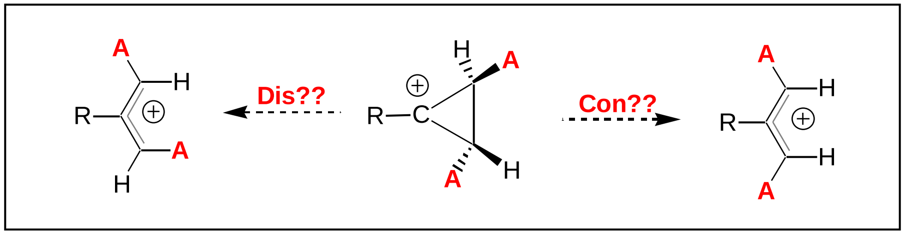
HOMO + p

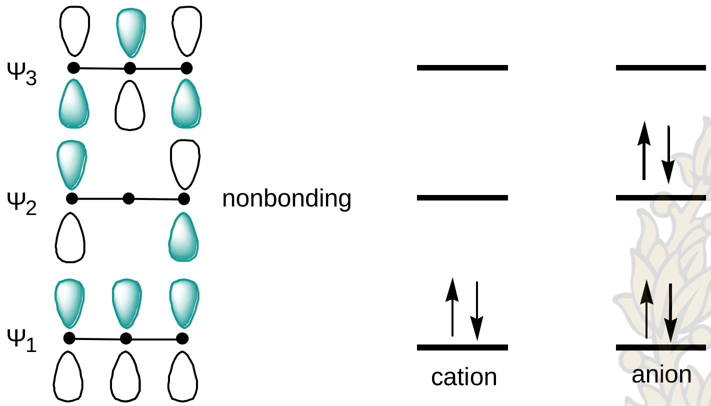
As conrotation begins the energy of the breaking sigma bond rises steeply. Hyperconjugation with a pi* orbital, while possible in both **A** & **B** , is better in **B.** (Houk)

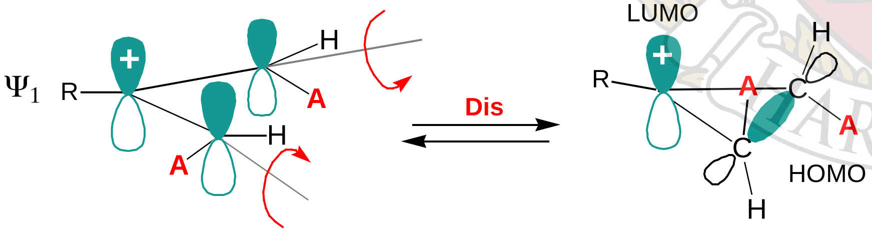
destabilizing 4 electron interation for donor substituents

stabilizing 2 electron interation for acceptor substituents

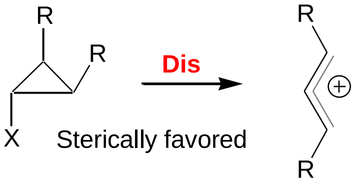
Three-Atom Electrocyclizations (2 electrons)



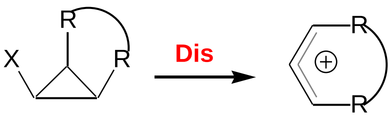




Note that there are two disrotatory modes



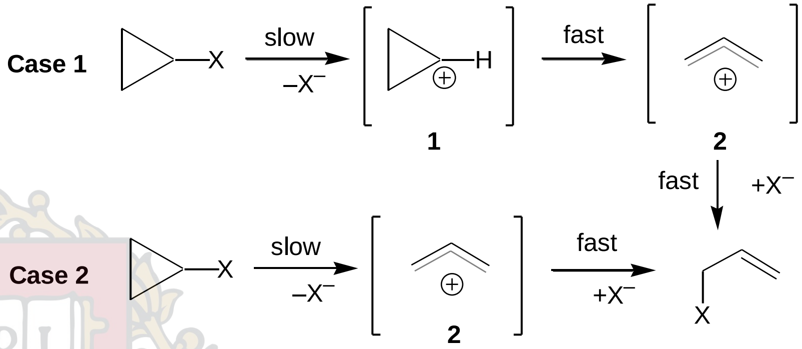
Sterically favored

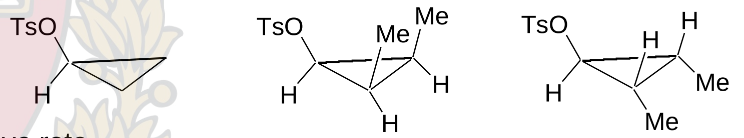


Favored for R = ring

Solvolysis of Cyclopropyl Derivatives

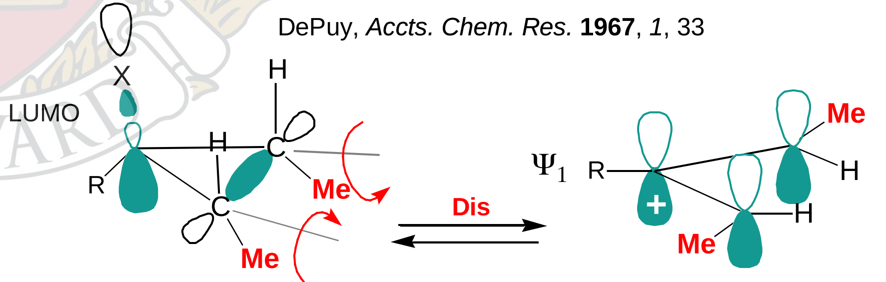
Does solvolysis proceed via cation **1** followed by rearrangement to **2** (Case 1), or does it proceed directly to **2** (Case 2)?



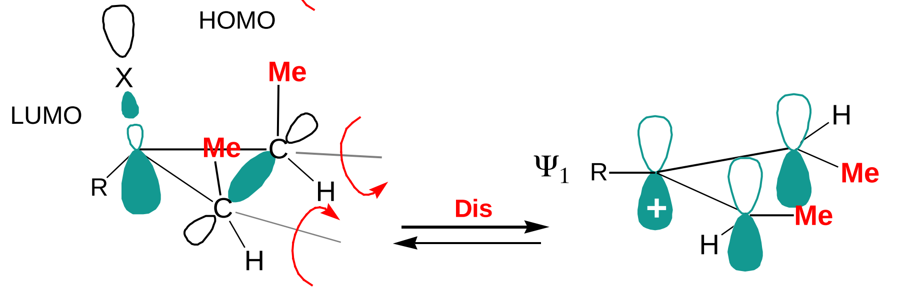


relative rate 1 4 40,000

DePuy, *Accts. Chem. Res.* **1967**, *1*, 33



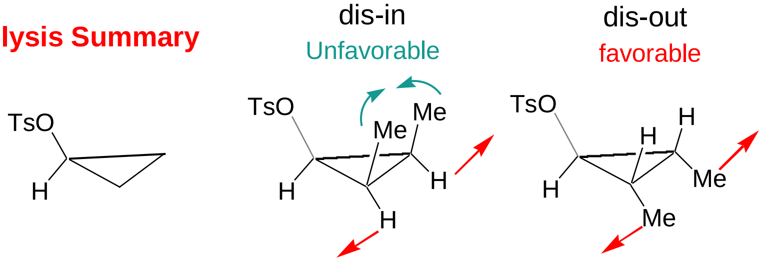
HOMO



HOMO

Electrocyclic Processes-3: 3-Atom Electrocyclizations

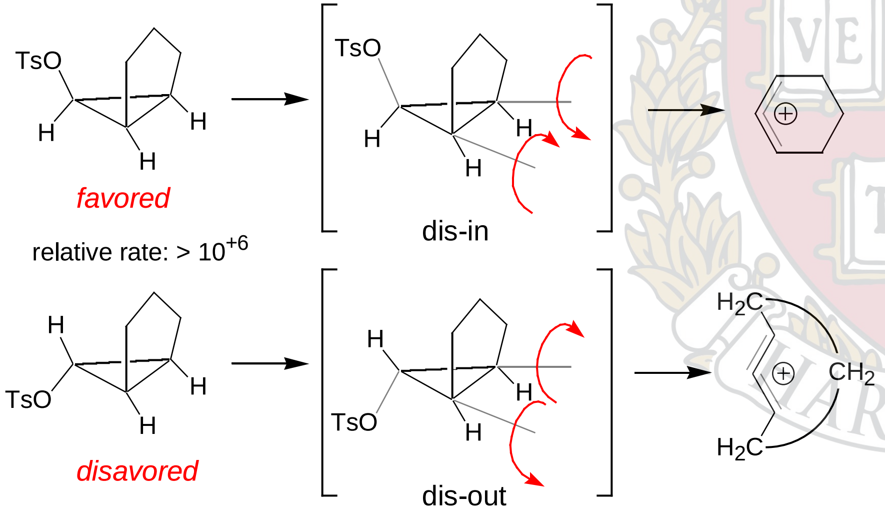
Solvolysis Summary



		dis-in Unfavorable	dis-out favorable
relative rate	1	4	40,000

Ring-fused Cyclopropyl Systems

When the cis substiltutents on the cyclopropyl ring are tied together in a ring the following observsations have been made



favored

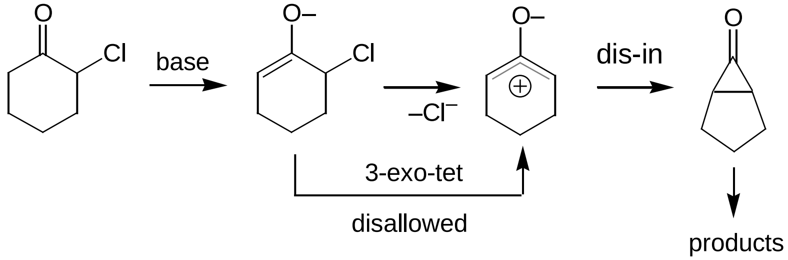
relative rate: > 10^{+6}

dis-in

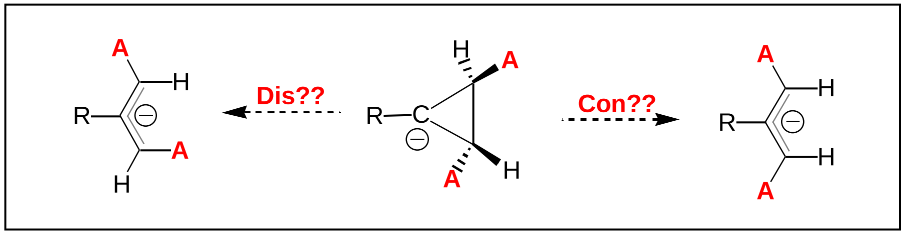
disavored

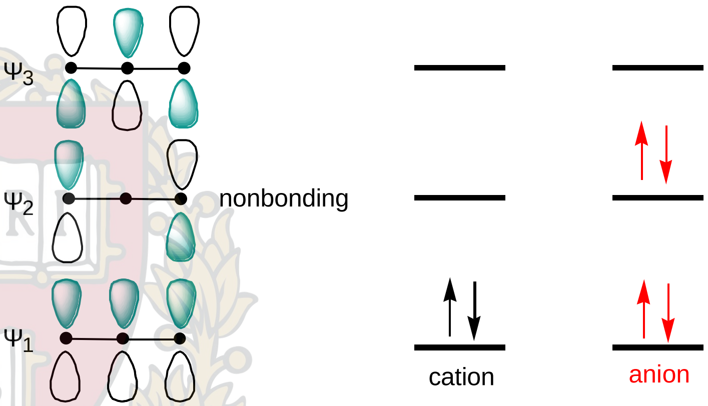
dis-out

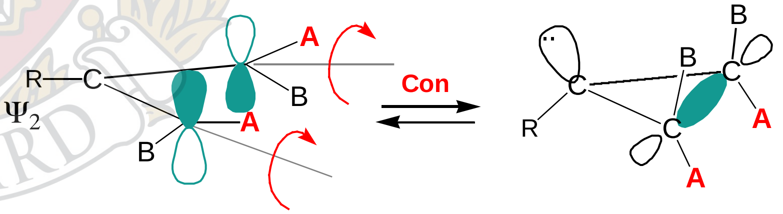
Revisiting the Favorski rearrangement: **(Carey, Part A, pp 506-8)**



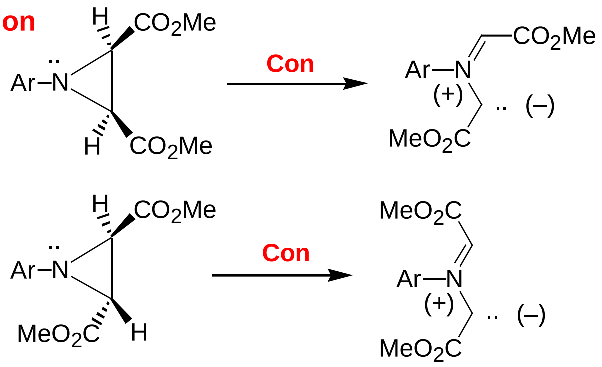
Three-Atom Electrocyclizations (4 electrons)



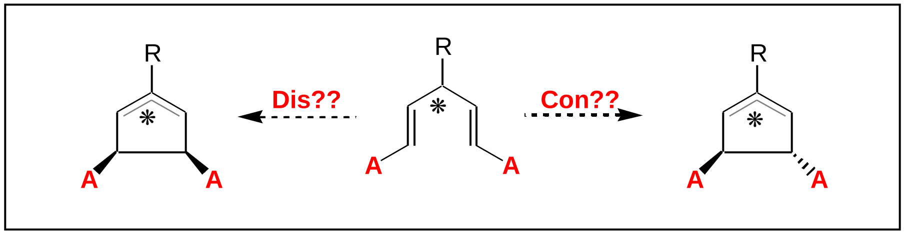


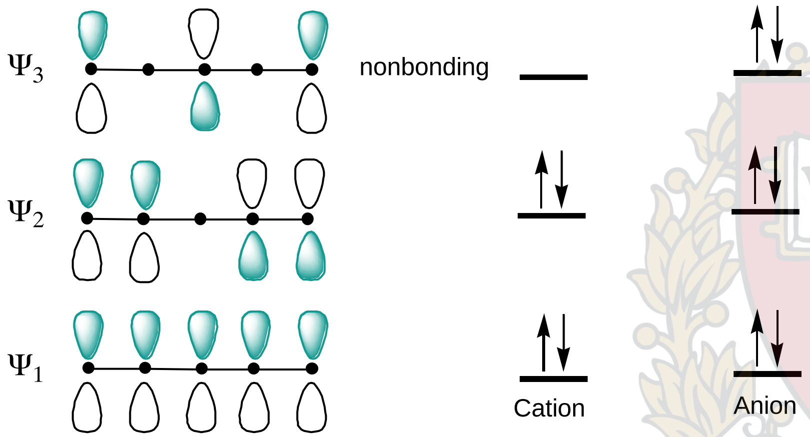


Observation

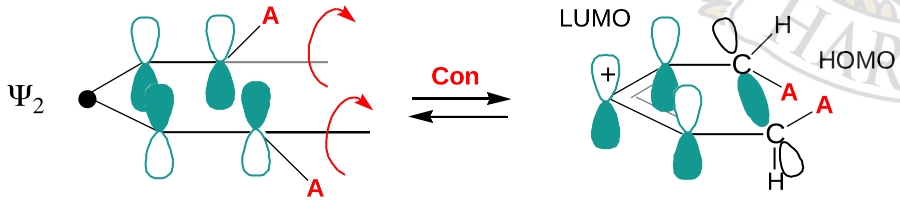


Five-Atom Electrocyclizations (4 electrons)

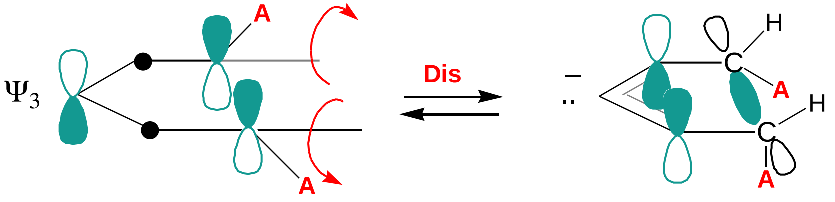




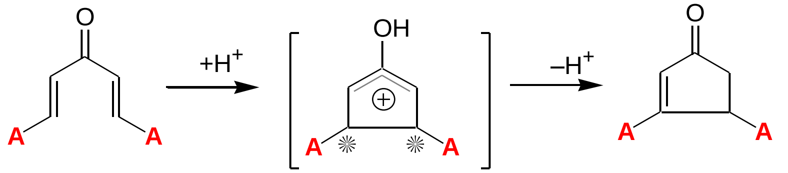
Pentadienyl Cation



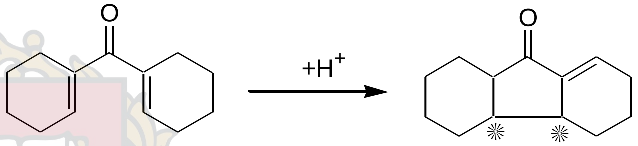
Pentadienyl Anion



The Nazarov Reaction

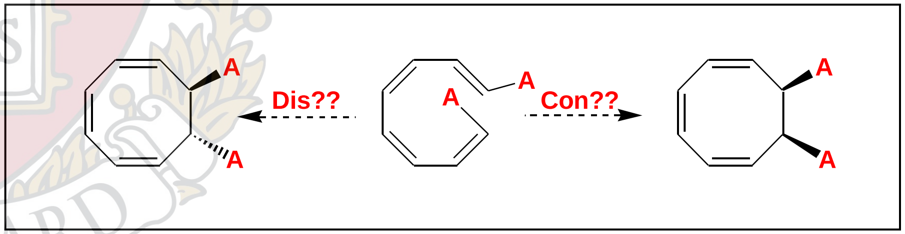


Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5; pp 751.

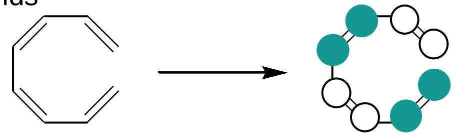


predict stereochemistry

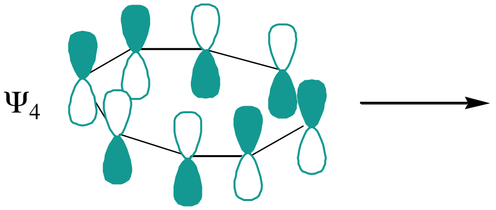
Eight-Atom Electrocyclizations (8 electrons)



Let's use the "Ready" shortcut to find the homo: Nodes will appear at single bonds



symmetry of homo

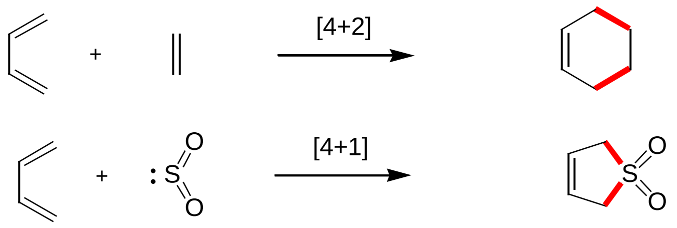


Closure should be conrotatory

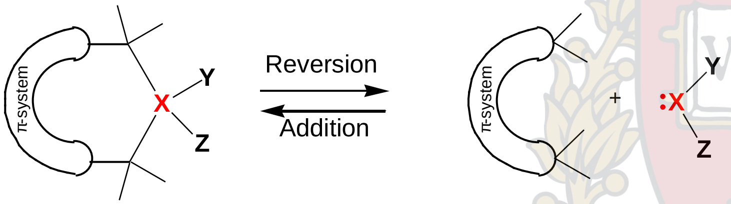
Cheletropic Processes-1

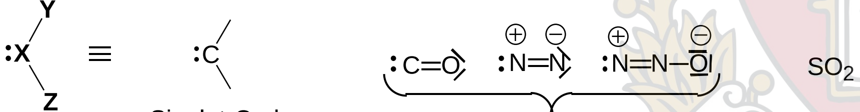
CHELETROPIC REACTIONS: [n+1] Cycloadditions (or Cycloreversions)

Concerted processes in which 2 σ-bonds are made (or broken) which terminate at a single atom.



General



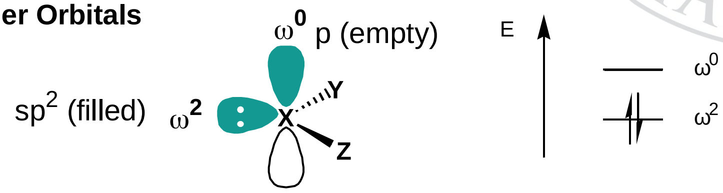


Singlet-Carbene Addition (and Reversion)

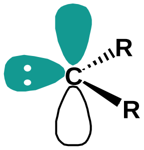
Cycloreversion only

Reversion and Addition

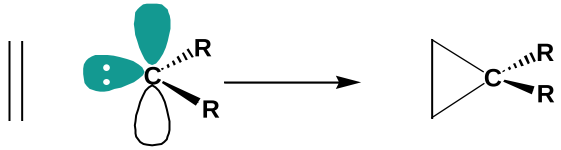
Frontier Orbitals



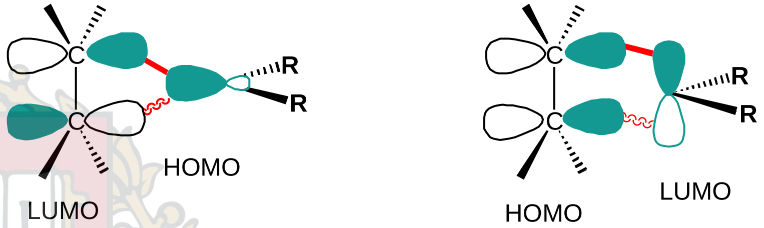
Question: what is orientation of carbene relative to attacking olefin??



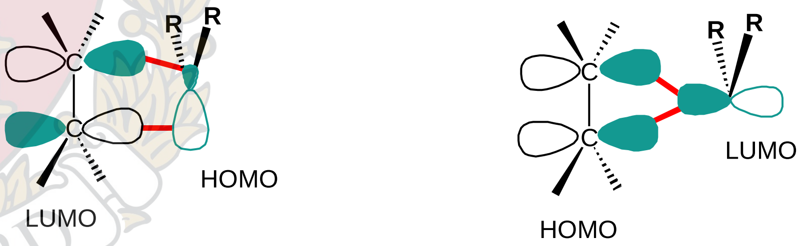
2 + 1 CheletropicReaction: Olefins + Singlet Carbene



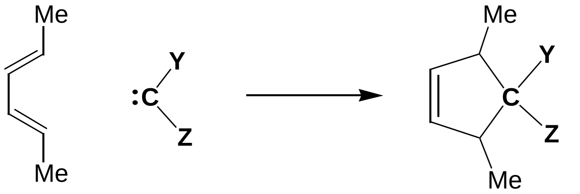
Linear Approach: 2 HOMO-LUMO Interactions



Nonlinear Approach: 2 HOMO-LUMO Interactions



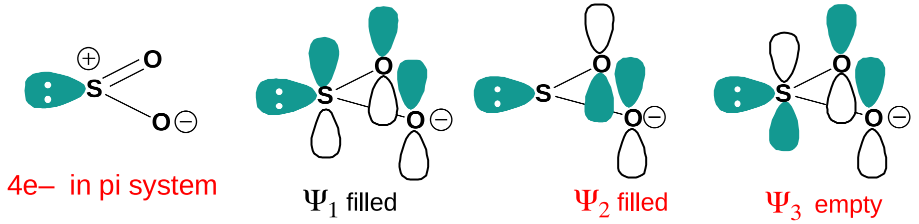
Carry out the analysis of the indicated hypothetical transformation

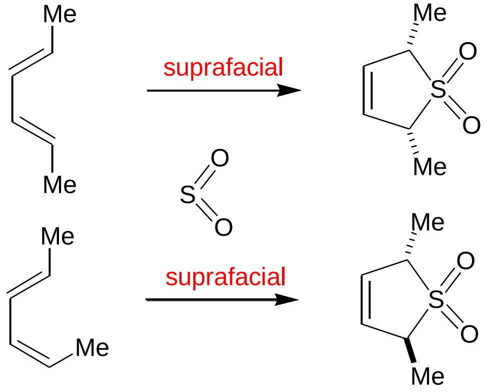


predict approach geometry of carbene

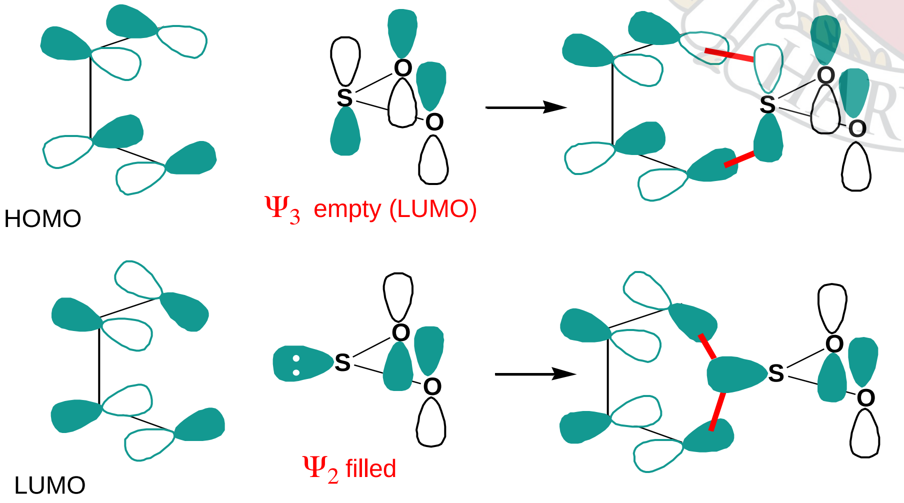
Cheletropic Processes-2

Let's now consider SO_2 as the one-atom component

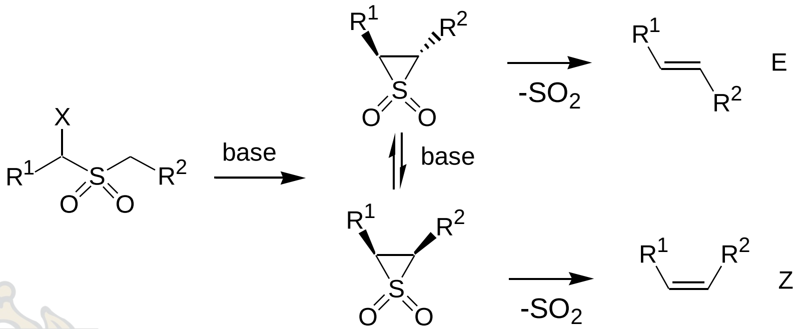




reactions are:
stereospecific & reversible

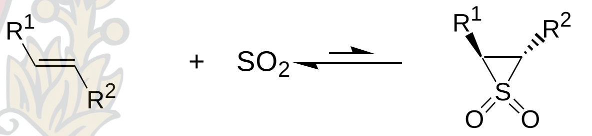


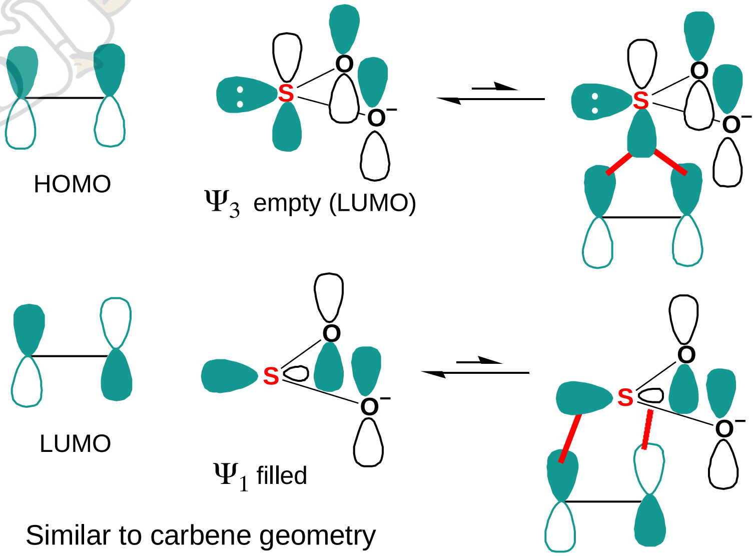
Key step in the *Ramberg Bäcklund* Rearrangement



Clough, J. M. *The Ramberg-Backlund Rearrangement.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 861.
"The Ramberg-Backlund Rearrangement.", Paquette, L. A. *Org. React. (N.Y.)* **1977**, *25*, 1.

Analysis of the Suprafacial SO_2 Extrusion (nonlinear)





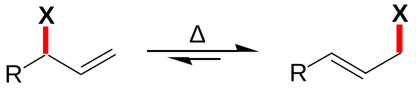
Similar to carbene geometry

Sigmatropic Rearrangements-1

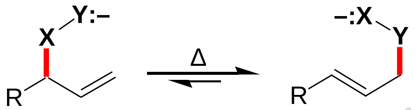
Sigmatropic rearrangements are those reactions in which a sigma bond (& associated substituent) interchanges termini on a conjugated pi system

■ Examples:

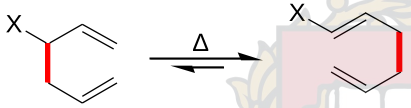
[1,3] Sigmatropic rearrangement



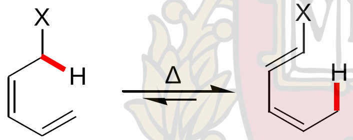
[2,3] Sigmatropic rearrangement



[3,3] Sigmatropic rearrangement

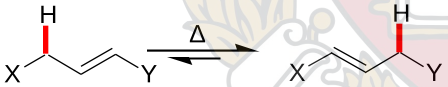


[1,5] Sigmatropic rearrangement

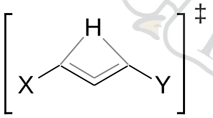


■ [1,3] Sigmatropic Rearrangements (H migration)

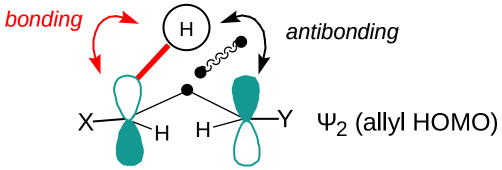
consider the 1,3-migration of H



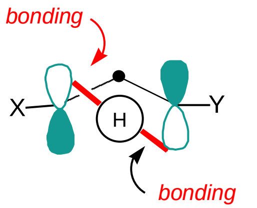
Consider the orbitals needed to contruct the transition state (TS).



■ Construct TS by uniting an allyl and H radical:



Suprafacial Geometry

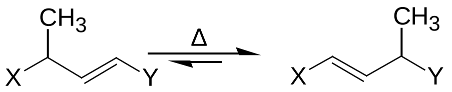


Antarafacial Geometry

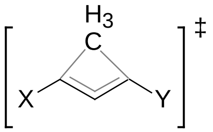
Bridging distance too great for antarafacial migration.

■ [1,3] Sigmatropic Rearrangements (C migration)

consider the 1,3-migration of Carbon

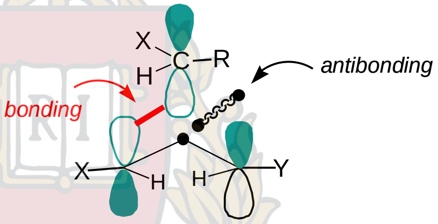


Consider the orbitals needed to contruct the transition state (TS).



❐ Construct TS by uniting an allyl and Me radicals:

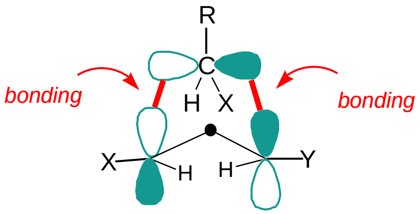
Retention at carbon



Suprafacial on allyl fragment

Sychronous bonding to both termini cannot be achieved from this geometry

Inversion at carbon



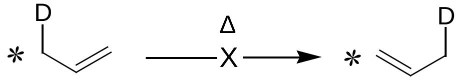
Suprafacial on allyl fragment

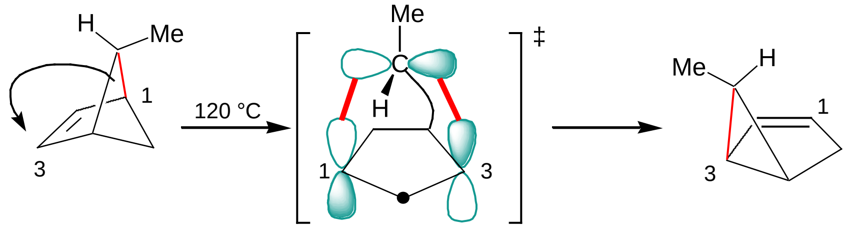
Sychronous bonding to both termini is possible from this geometry

❐ The stereochemical constraints on the suprafacial migration of carbon with inversion of configuration is highly disfavored on the basis of strain.

[1,3]-Sigmatropic rearrangements are not common

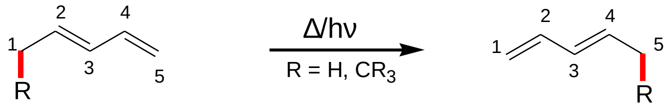
no observed scrambling of labels



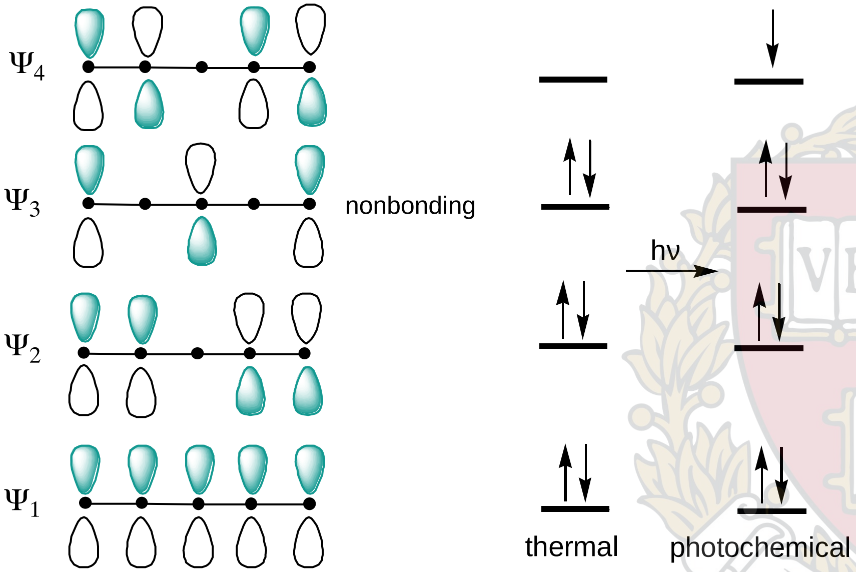


These rearrangements are only seen in systems that are highly strained, an attribute that lowers the activation for rearrangement.

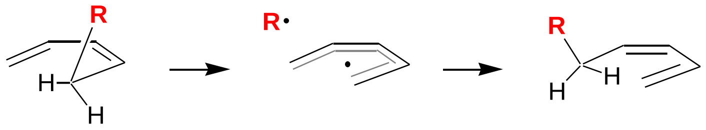
SIGMATROPIC REACTIONS - FMO-Analysis

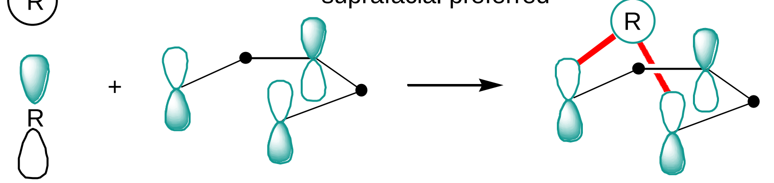


[1,5] Sigmatropic Rearrangements (H migration)



View as cycloadditon between following species:





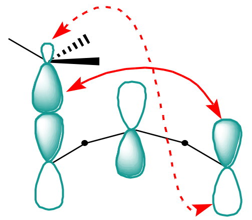
suprafacial preferred

either, or

pentadienyl radical Ψ_3

pentadienyl radical Ψ_3

[1,5] Sigmatropic Rearrangements (C migration)

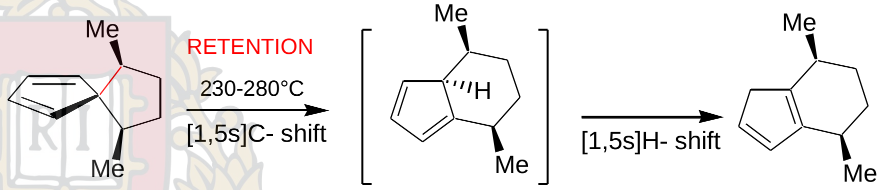


[1s,5s] alkyl shift RETENTION

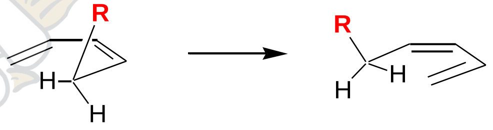
[1a,5a] alkyl shift INVERSION

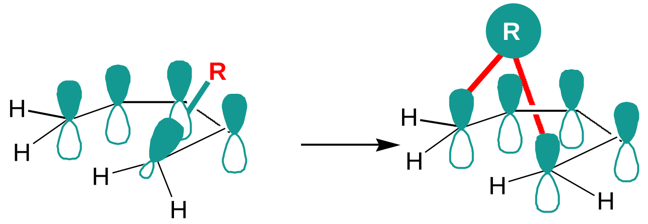
disfavored

[1,5] (C migration): Stereochemical Evaluation



Dewar–Zimmerman Analysis: Retention





0 phase inversions   Huckel toplogy

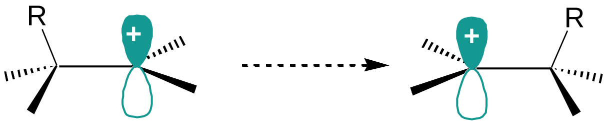
6 electrons

therefore, allowed thermally

Sigmatropic Rearrangements-3

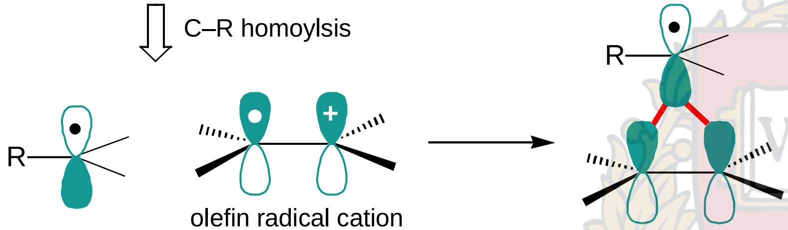
■ [1,2] Sigmatropic Rearrangements: Carbon

[1,2] Concerted sigmatropic rearrangements to cationic centers allowed

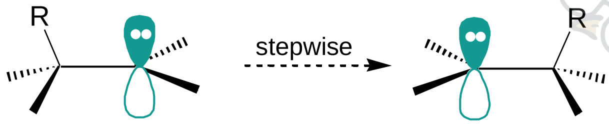


consider as cycloaddition

C–R homoylsis

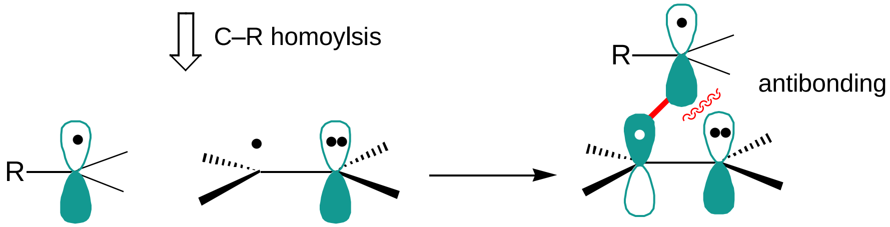


[1,2] Concerted sigmatropic rearrangements to carbanionic centers not observed



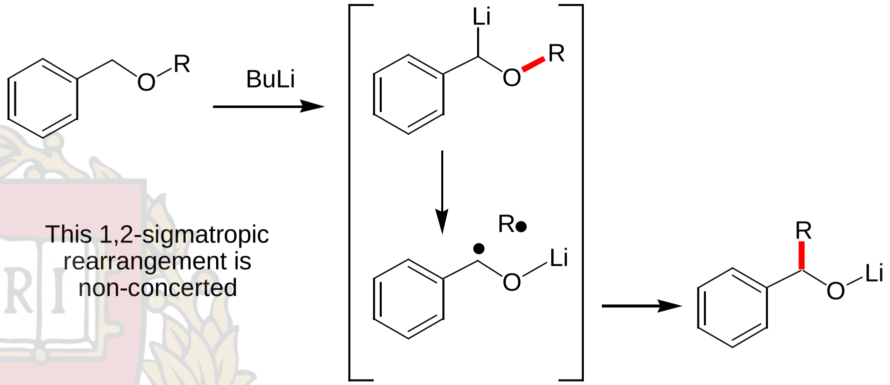
consider as cycloaddition

C–R homoylsis



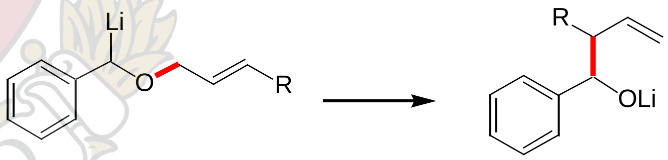
The Wittig Rearrangement [1,2]

"[2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis.", Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.
Marshall, J. A. *The Wittig Rearrangement*.; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 975.

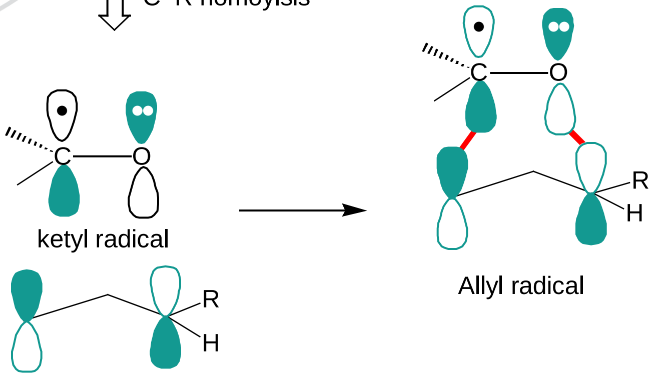


This 1,2-sigmatropic rearrangement is non-concerted

The Wittig Rearrangement [2,3]



C–R homoylsis



Allyl radical

Allyl radical

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 13

Pericyclic Reactions–3

- Introduction to Sigmatropic Rearrangements
- [2,3] Sigmatropic Rearrangements

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Fleming: Chapter 4
Thermal Pericyclic Reactions

Evans, *et al. Acc. Chem. Res.* **1974**, *7*, 149-155.

Matthew D. Shair

Wednesday,
October 16, 2002

Other Reading Material:

[2,3] Sigmatropic Rearrangements

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapter 4.6:

Nakai, T.; Mikami, K. *Org. React. (N.Y.)* **1994**, *46*, 105-209.

Hoffmann, *Angew. Chem. Int. Ed.* **1979**, *18*, 563-572 (Stereochemistry of)

Nakai, *Chem. Rev.* **1986**, *86*, 885-902 (Wittig Rearrangement)

Evans, *Accts. Chem. Res.* **1974**, *7*, 147-55 (Sulfoxide Rearrangement)

Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358-364 (Sulfur Ylilde Rearrangements)

[3,3] Sigmatropic Rearrangements

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
Chapter 7.2, Claisen

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)

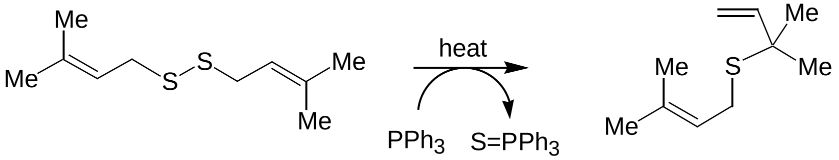
S. R. Wilson, *Organic Reactions* **1993**, *43*, 93 (oxy-Cope)

T. S. Ho, *Tandem Organic Reactions* **1992**, *Chapter 12* (Cope, Claisen)

Paquette, L. A. (1990). "Stereocontrolled construction of complex cyclic ketones by oxy-Cope rearrangement." Angew. Chem., Int. Ed. Engl. 29: 609.

Problems of the Day:

Provide a mechanism for this transformation.



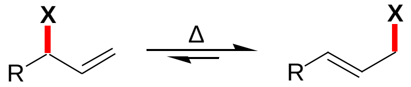
For study on this [2,3] rxn See Baldwin *JACS* **1971**, *93*, 6307

Sigmatropic Rearrangements-1

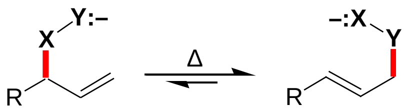
Sigmatropic rearrangements are those reactions in which a sigma bond (& associated substituent) interchanges termini on a conjugated pi system

■ Examples:

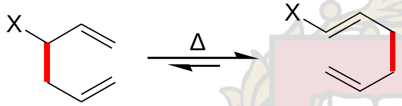
[1,3] Sigmatropic rearrangement



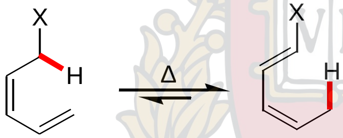
[2,3] Sigmatropic rearrangement



[3,3] Sigmatropic rearrangement



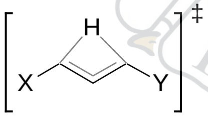
[1,5] Sigmatropic rearrangement



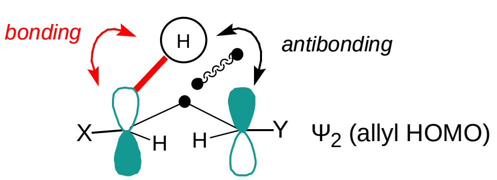
■ [1,3] Sigmatropic Rearrangements (H migration)

consider the 1,3-migration of H

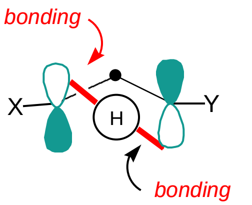
Consider the orbitals needed to contruct the transition state (TS).



■ Construct TS by uniting an allyl and H radical:



Suprafacial Geometry

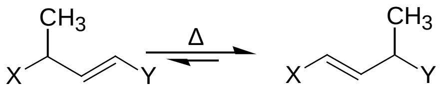


Antarafacial Geometry

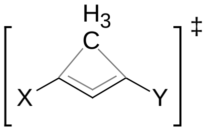
Bridging distance too great for antarafacial migration.

■ [1,3] Sigmatropic Rearrangements (C migration)

consider the 1,3-migration of Carbon

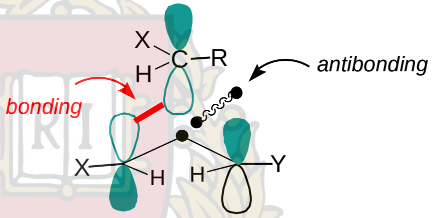


Consider the orbitals needed to contruct the transition state (TS).



❐ Construct TS by uniting an allyl and Me radicals:

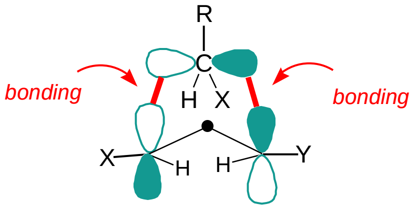
Retention at carbon



Suprafacial on allyl fragment

Sychronous bonding to both termini cannot be achieved from this geometry

Inversion at carbon



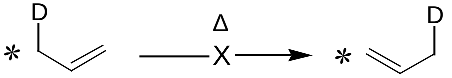
Suprafacial on allyl fragment

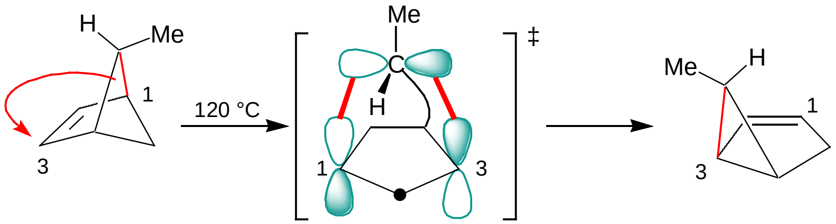
Sychronous bonding to both termini is possible from this geometry

❐ The stereochemical constraints on the suprafacial migration of carbon with inversion of configuration is highly disfavored on the basis of strain.

[1,3]-Sigmatropic rearrangements are not common

no observed scrambling of labels

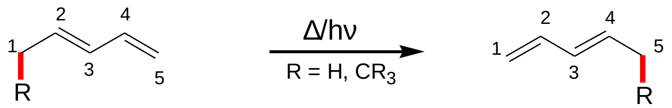




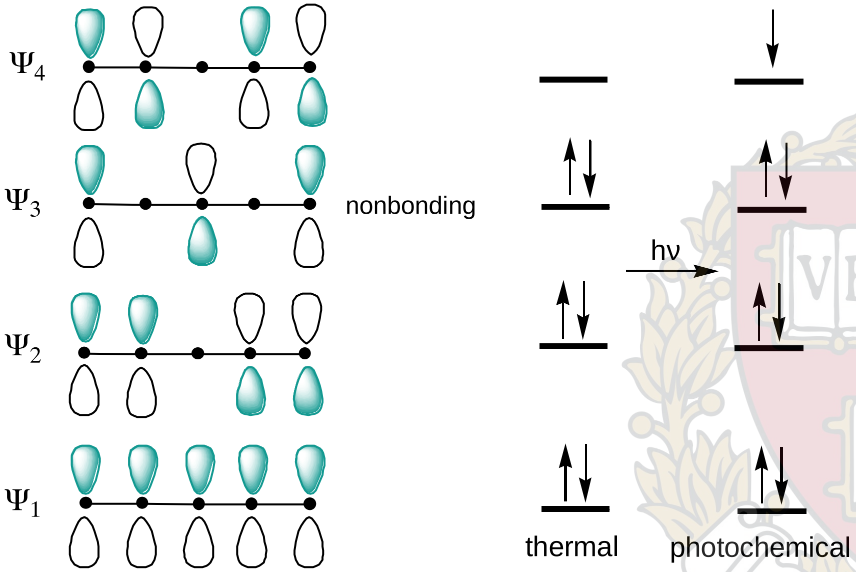
These rearrangements are only seen in systems that are highly strained, an attribute that lowers the activation for rearrangement.

Sigmatropic Rearrangements-2

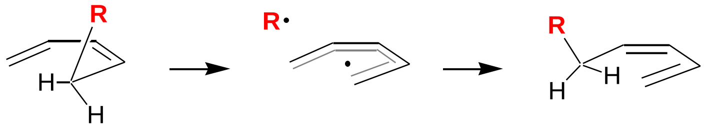
SIGMATROPIC REACTIONS - FMO-Analysis



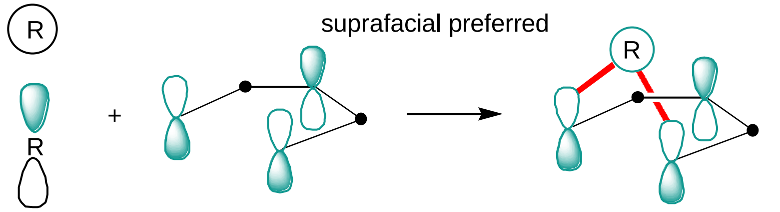
[1,5] Sigmatropic Rearrangements (H migration)



View as cycloadditon between following species:

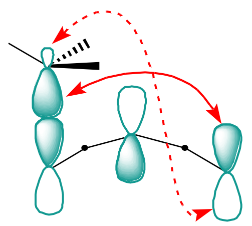


suprafacial preferred



either, or   pentadienyl radical Ψ_3 the transiton structure

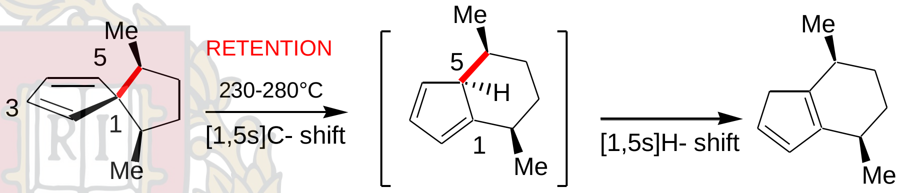
[1,5] Sigmatropic Rearrangements (C migration)



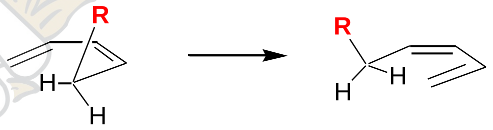
— [1s,5s] alkyl shift   RETENTION

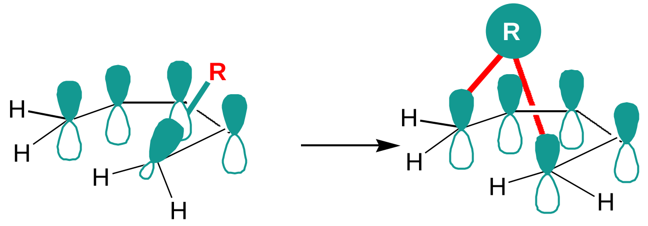
— [1a,5a] alkyl shift   INVERSION
disfavored

[1,5] (C migration): Stereochemical Evaluation



Dewar–Zimmerman Analysis: Retention





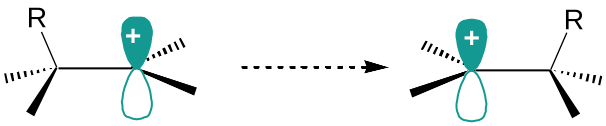
0 phase inversions   Huckel toplogy
6 electrons
therefore, allowed thermally

Sigmatropic Rearrangements: An Overview

[1,2] Sigmatropic Rearrangements: Carbon

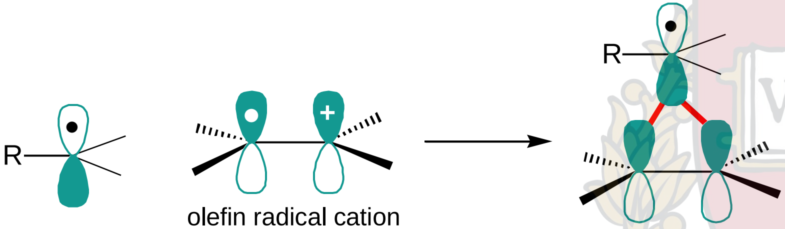
[1,2]-Sigmatropic rearrangements to cationic centers allowed.

Wagner-Meerwein Rearrangement



consider as cycloaddition

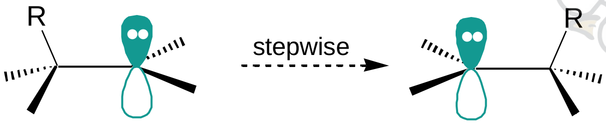
FMO analysis



olefin radical cation

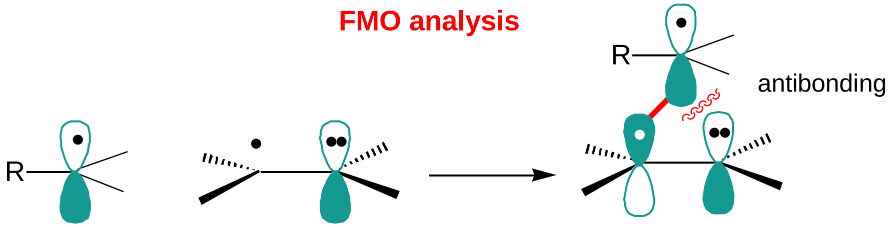
transition state

[1,2]-Sigmatropic rearr to carbanionic centers not observed



consider as cycloaddition

FMO analysis



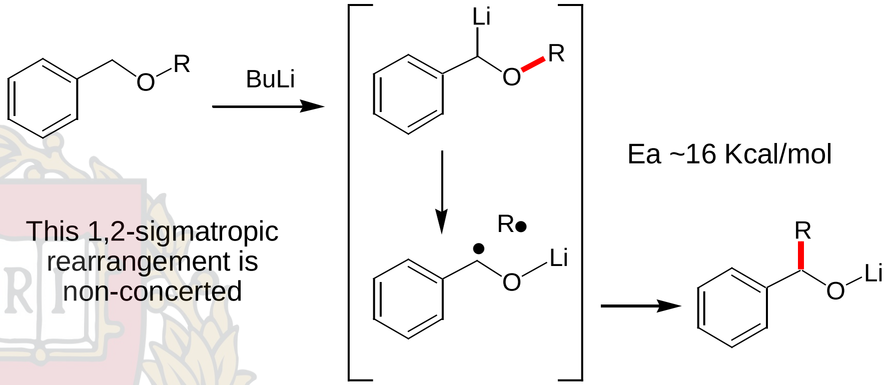
olefin radical anion

transition state

The Wittig Rearrangement [1,2]

"[2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis.", Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

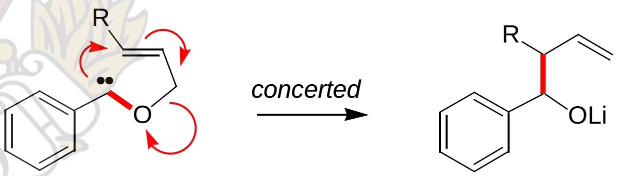
Marshall, J. A. *The Wittig Rearrangement*.; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 975.



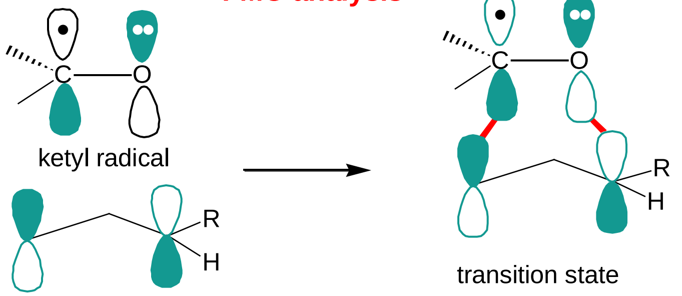
This 1,2-sigmatropic rearrangement is non-concerted

Ea ~16 Kcal/mol

The Wittig Rearrangement [2,3]



FMO analysis



ketyl radical

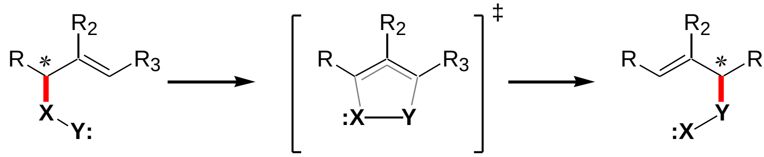
Allyl radical

transition state

The $\Delta\Delta G^{\ddagger}$ between concerted and non-concerted pathways can be quite small

[2,3] Sigmatropic Rearrangements

■ The basic process:



X & Y = permutations of C, N, O, S, Se, P; however X is usually a heteroatom

Attributes: Stereoselective olefin construction & chirality transfer

■ **Representative X-Y Pairs:**

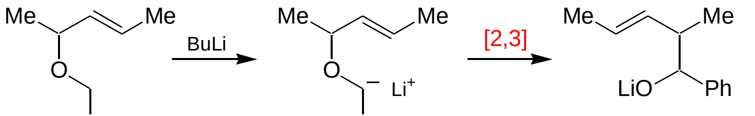
N–O (amine oxides)
S–C (sulfur ylids)
O–C (Wittig rearrangement)
N–C (nitrogen ylids)
S–S (disulfides)
S–P, S–N, S–O (sulfoxides)
O–P (phosphites)
N–N, Cl$^+$–C (haloium ylids)
P–C, C–C (homoallylic anions).

An important early paper: Baldwin, *J. Chem. Soc., Chem. Comm.* **1970**, 576

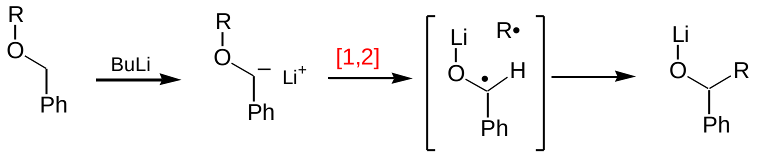
■ **General Reviews:**

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapter 4.6:
Nakai, T.; Mikami, K. *Org. React. (N.Y.)* **1994**, *46*, 105-209.
Hoffmann, *Angew. Chem. Int. Ed.* **1979**, *18*, 563-572 (Stereochemistry of)
Nakai, *Chem. Rev.* **1986**, *86*, 885-902 (Wittig Rearrangement)
Evans, *Accts. Chem. Res.* **1974**, *7*, 147-55 (sulfoxide Rearrangement)
Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358-364 (Sulfur Ylilde Rearrangements)

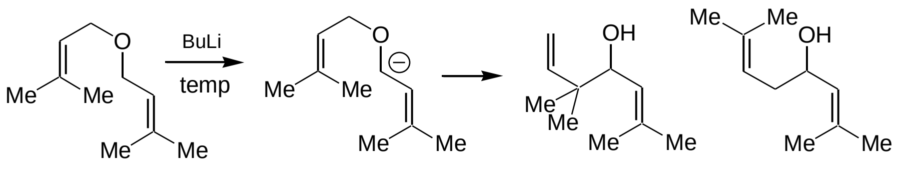
■ **X - O, Y = C; Wittig Rearrangement:**



Baldwin, *JACS* **1971**, *93*, 3556

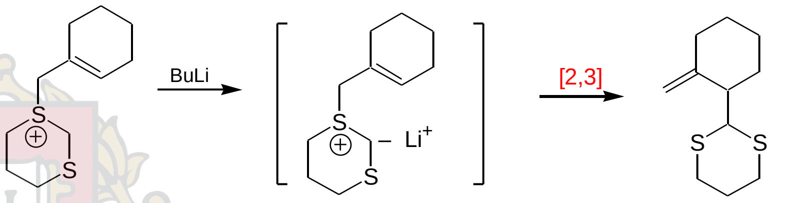


Garst, *JACS* **1976**, *98*, 1526



Rautenstrauch, *Chem Commun*. **1979**, 1970

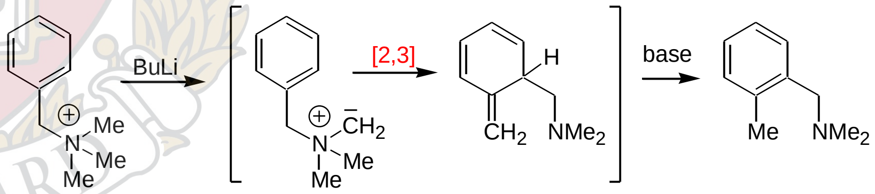
■ **X - S, Y = C; Sulfonium Ylide Rearrangement:**



Lythgoe, *Chem Commum* **1972**, 757

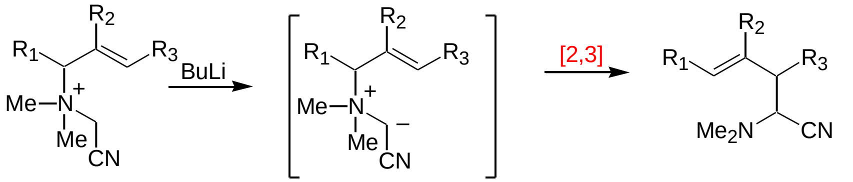
■ **X - N, Y = C; Ammonium Ylide Rearrangement:**

❐ **Sommelet-Hauser:**



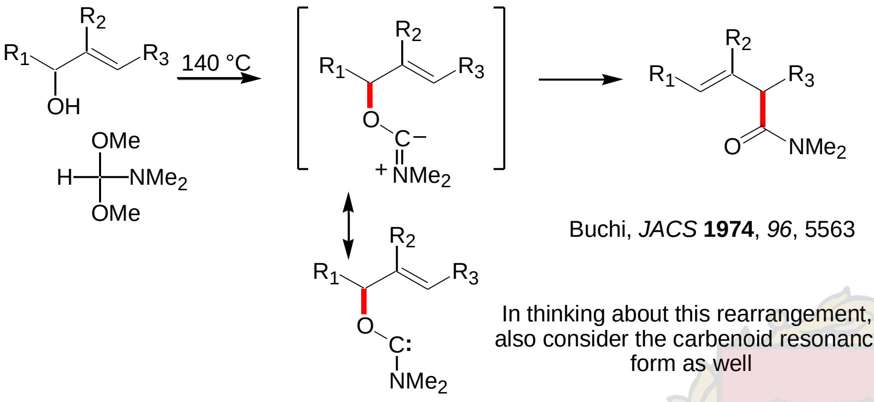
Review, Pines, *Org. Rxns* **1970**, *18*, 416

❐ **Modern versions of Stevens:**



Buchi, *JACS* **1974**, *96*, 7573
Mander, *JOC* **1973**, *38*, 2915
important extension lacking CN FG; Sato, *JACS* **1990**, *112*, 1999

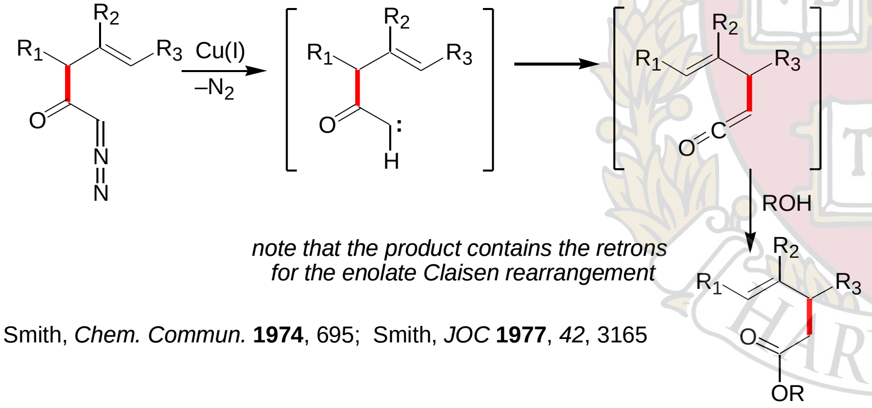
■ X - O, Y = C; Wittig-like Rearrangements



Buchi, *JACS* **1974**, *96*, 5563

In thinking about this rearrangement, also consider the carbenoid resonance form as well

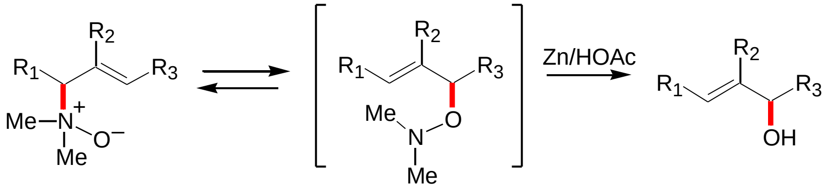
■ X - O, Y = C; An all-carbon Rearrangement



note that the product contains the retrons for the enolate Claisen rearrangement

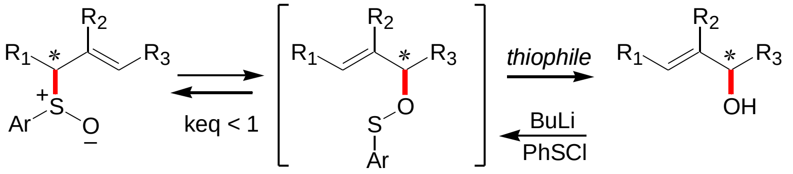
Smith, *Chem. Commun.* **1974**, 695; Smith, *JOC* **1977**, *42*, 3165

■ X - N, Y = O; Meisenheimer Rearrangement



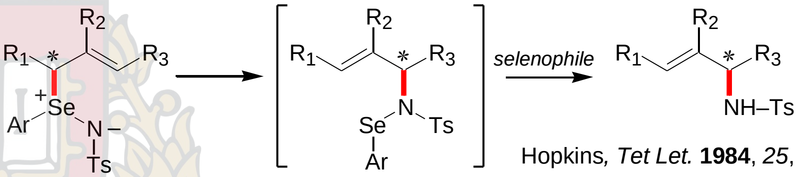
Tanabe, *Tet Let.* **1975**, 3005

■ X - S, Y = O; Sulfoxide Rearrangement



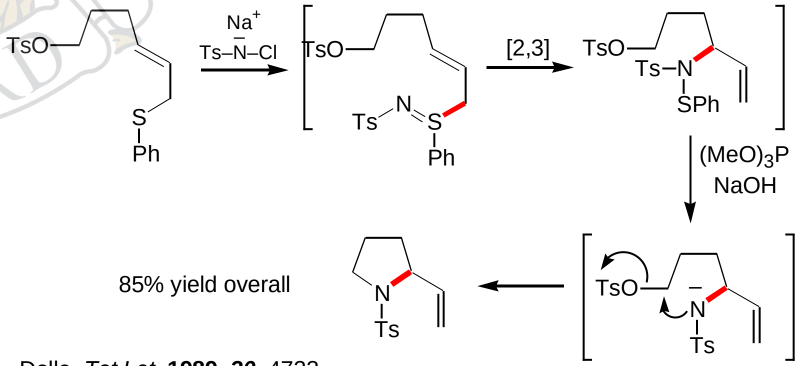
Evans, *Accts. Chem. Res.* **1974**, *7*, 147

■ X - Se, Y = N; Related Rearrangement



Hopkins, *Tet Let.* **1984**, *25*, 15
Hopkins, *JOC* **1984**, *49*, 3647
Hopkins, *JOC* **1985**, *50*, 417

■ X - S, Y = N; Related Rearrangement



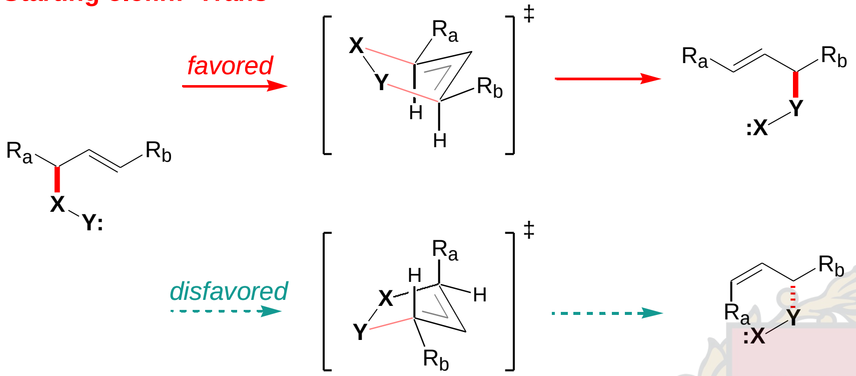
85% yield overall

Dolle, *Tet Let.* **1989**, ***30***, 4723

[2,3]-Sigmatropic Rearrangements: Olefin Geometry

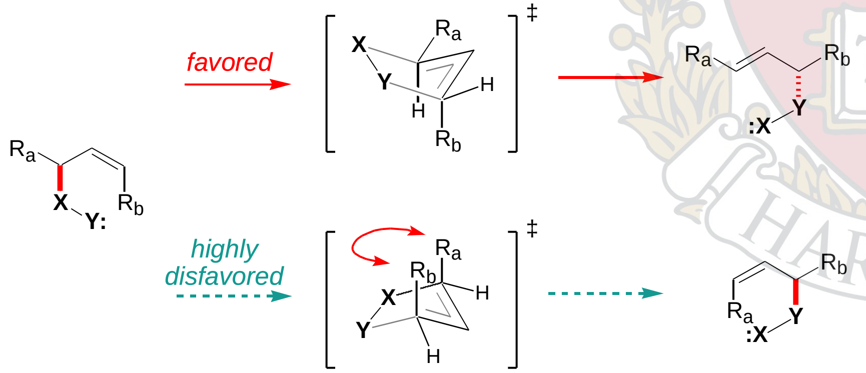
■ 1,2-Disubstitution: Good Trans Olefin Selectivity

Starting olefin: Trans



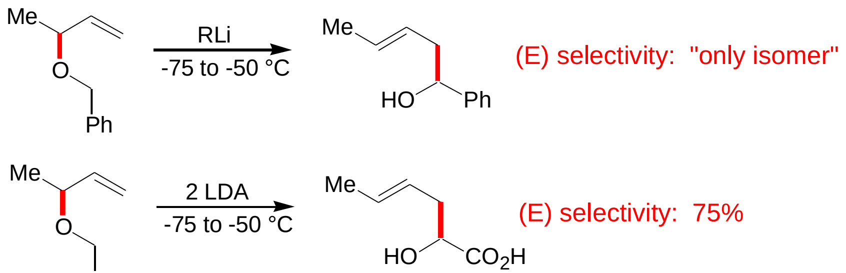
R_a & R_b prefer to orient in pseudo-equatorial positions during rearrangement; nevertheless, this is a delicately balanced situation

Starting olefin: Cis



Conclusions

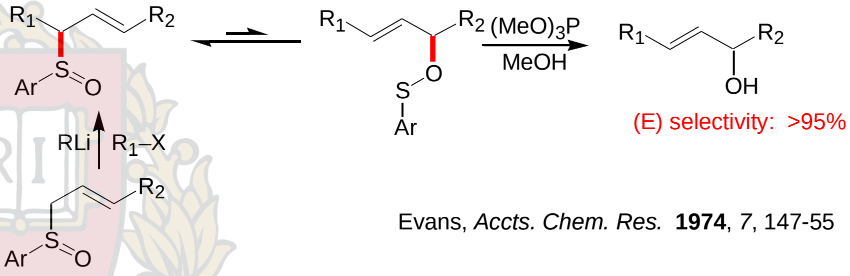
- ❑ Olefin geometry dictates sense of asymmetric induction in rearrangement
- ❑ (Z) Olefin rearrangements might exhibit higher levels of 1,3 induction
- ❑ Product olefin geometry can be either (E) or (Z) from (E) starting material
- ❑ Product olefin geometry will be (E) from (Z) starting material



(E) selectivity: "only isomer"

(E) selectivity: 75%

Nakai, *Tet. Lett* **1981**, *22*, 69

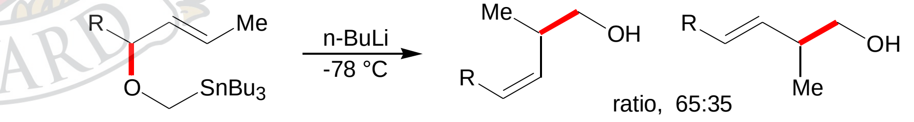


(E) selectivity: >95%

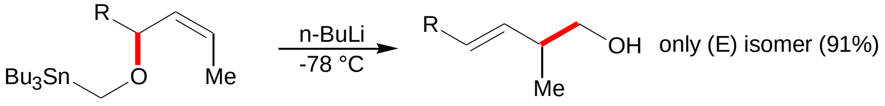
Evans, *Accts. Chem. Res.* **1974**, *7*, 147-55

The preceeding transition state models do not explain some of the results:

❑ Cis selectivity has been observed: Still JACS **1978**, *100*, 1927.



❑ However, Cis selectivity is dependent on starting olefin geometry



only (E) isomer (91%)

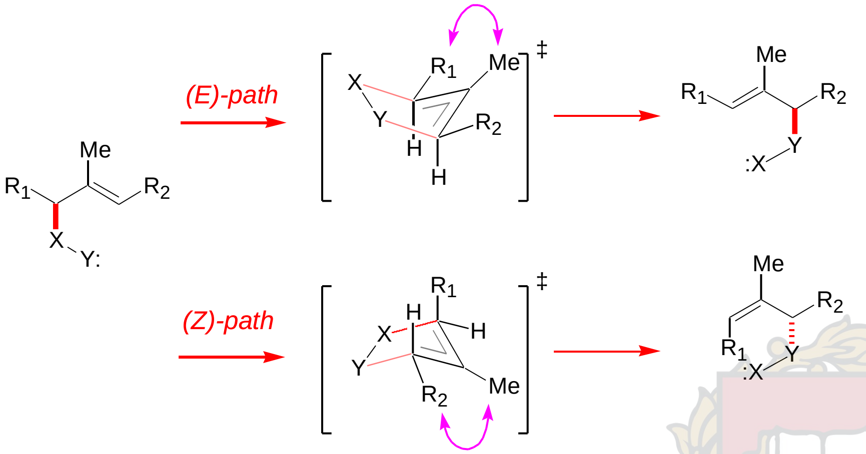
Several theoretical studies have been published: Good reading

Houk JOC **1991**, *56*, 5657 (Sulfur ylide transition states)

Houk JOC **1990**, *55*, 1421 (Wittig transition states)

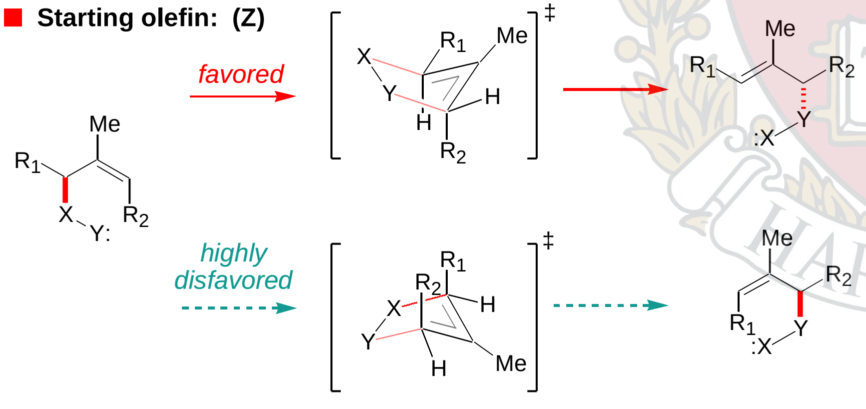
[2,3]-Sigmatropic Rearrangements: Olefin Geometry

■ Starting olefin: (E) Trisubstituted



R_1–Me interaction can destabilize the (E) transition state while (Z) TS might be destabilized by R_1 interactions with both X-Y and allyl moiety.

■ Starting olefin: (Z)



Conclusions

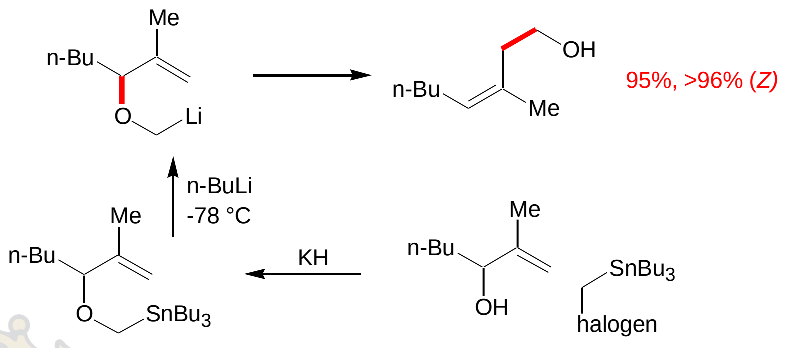
❏ Olefin geometry dictates sense of asymmetric induction in rearrangement

❏ (Z) Olefin rearrangements might exhibit higher levels of 1,3 induction

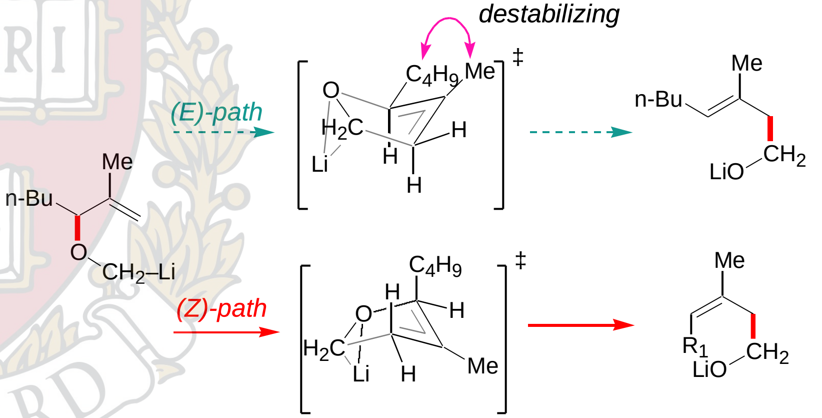
❏ Product olefin geometry can be either (E) or (Z) from (E) starting material

❏ Product olefin geometry will be (E) from (Z) starting material

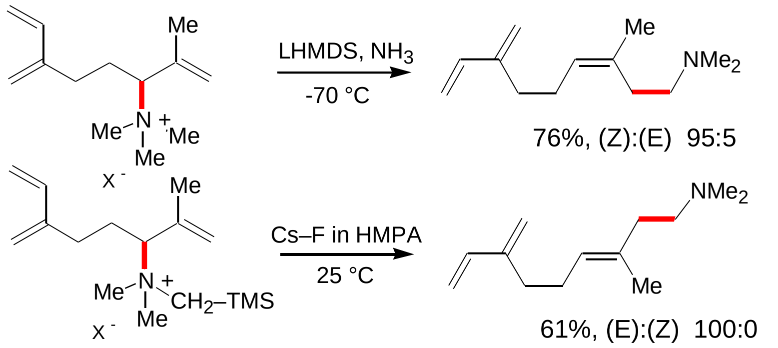
■ (Z) selectivity has been observed: Still JACS **1978**, *100*, 1927.



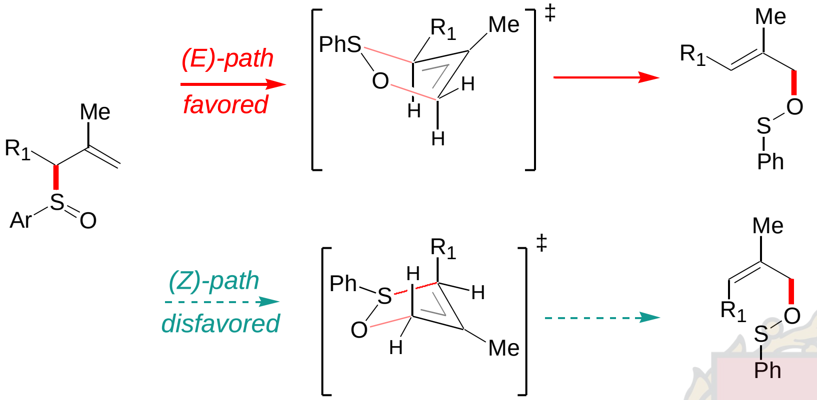
Still says that the TS is early, so that the 1,2 interactions in the TS are most important.

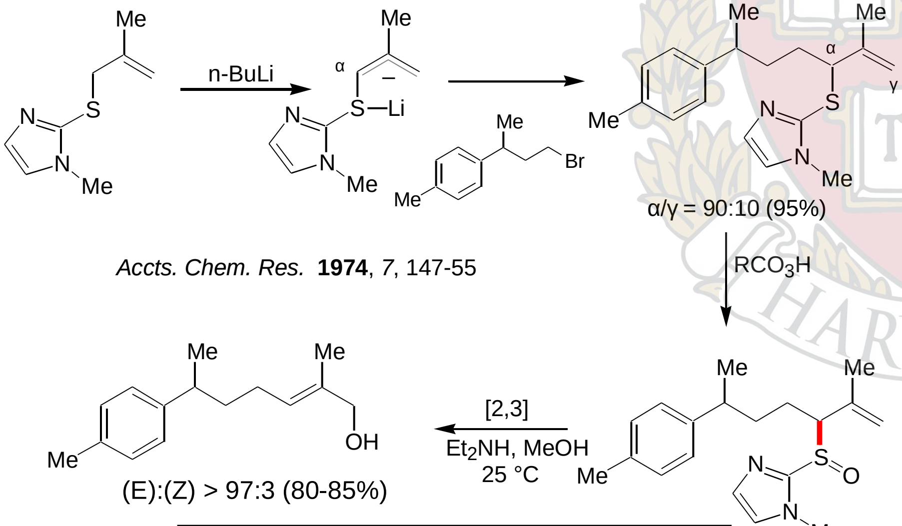


■ (Z) selectivity has also been observed by others: Sato JACS **1990**, *112*, 1999.



Trisubstituted olefins via [2,3]-rearrangement of sulfoxides:

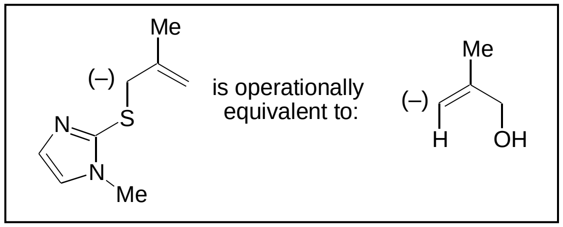




α/γ = 90:10 (95%)

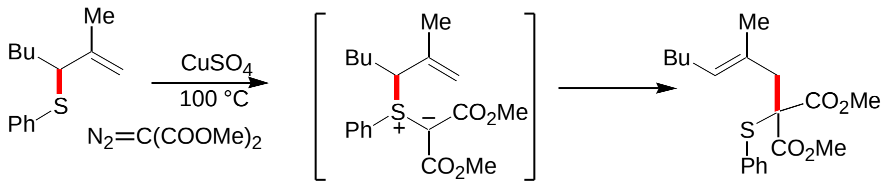
Accts. Chem. Res. **1974**, *7*, 147-55

(E):(Z) > 97:3 (80-85%)



is operationally equivalent to:

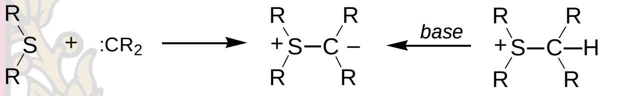
Trisubstituted olefins via [2,3]-rearrangement of sulfonium ylides:



Grieco, *JOC* **1973**, *38*, 2572

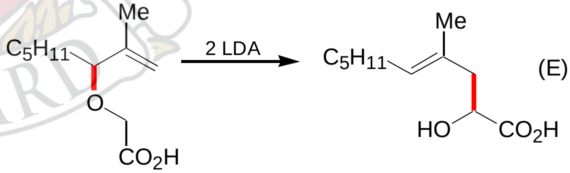
(E):(Z) > 90:10 (70%)

A general procedure for the direct synthesis of sulfur ylides:



pKa ~ 18 (DMSO

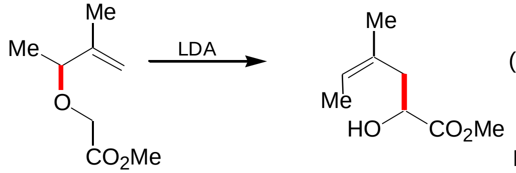
Trisubstituted olefins via Wittig [2,3]-rearrangement:



(E):(Z) > 95:5 (74%)

Nakai, *Tet Let* **1981**, *22*, 69

However, this reaction is not general:

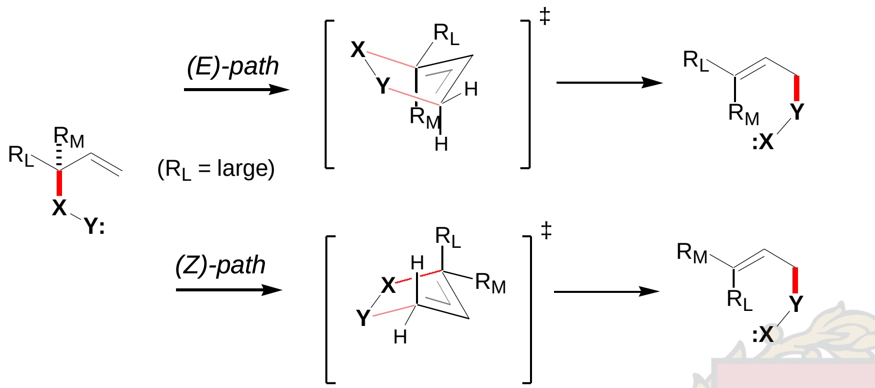


(E):(Z) 31:69

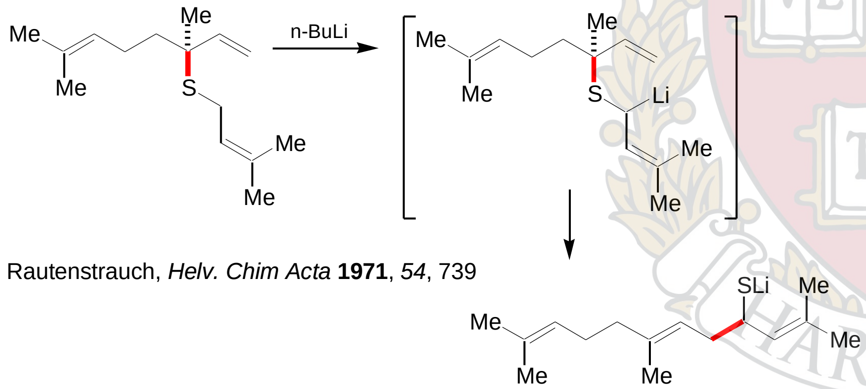
Nakai, *Tet Let* **1986**, *27*, 4511

[2,3]-Sigmatropic Rearrangements: Olefin Geometry

■ Trisubstituted olefins via [2,3]-rearrangement:

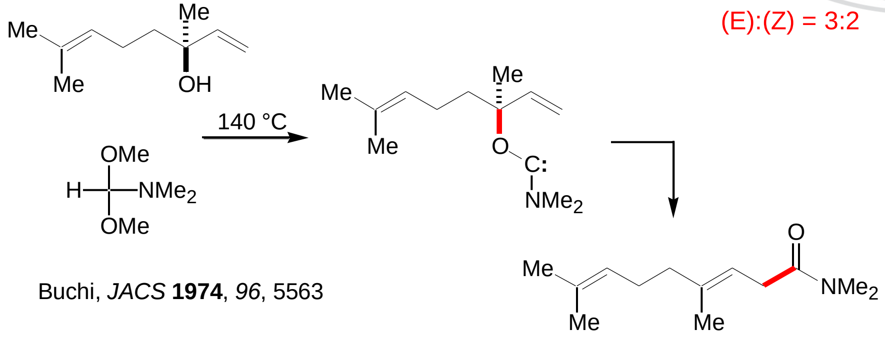


One might project that the (E) path will be moderately favored with selectivity depending on size difference between R_L & R_M



Rautenstrauch, *Helv. Chim Acta* **1971**, *54*, 739

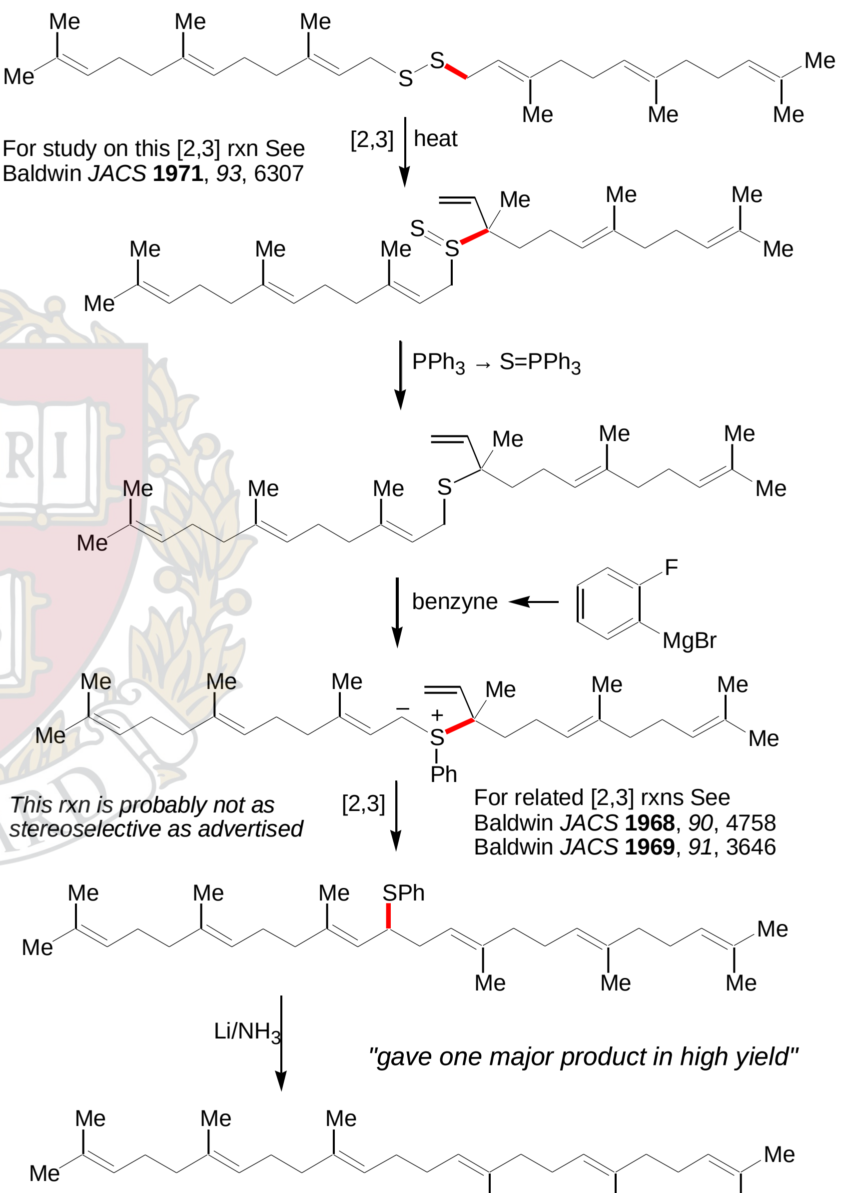
(E):(Z) = 3:2



Buchi, *JACS* **1974**, *96*, 5563

poorly selective

An elegant squalene synthesis **Ollis, *Chem. Commun* 1969, 99**



For study on this [2,3] rxn See Baldwin *JACS* **1971**, *93*, 6307

This rxn is probably not as stereoselective as advertised

For related [2,3] rxns See
Baldwin *JACS* **1968**, *90*, 4758
Baldwin *JACS* **1969**, *91*, 3646

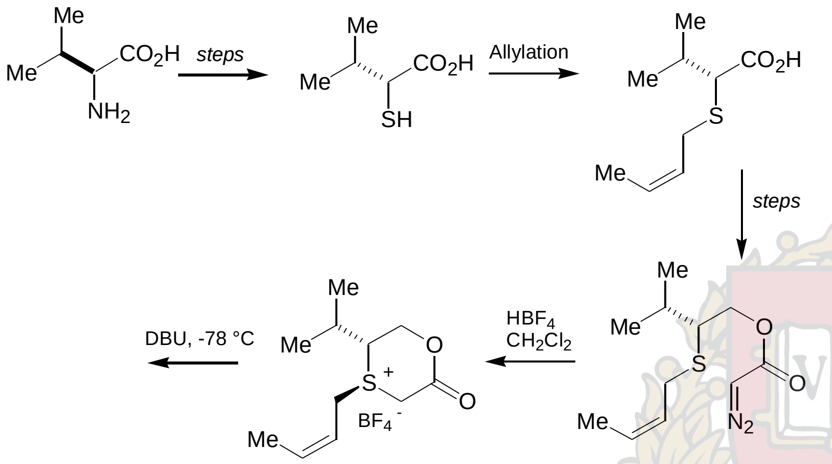
"gave one major product in high yield"

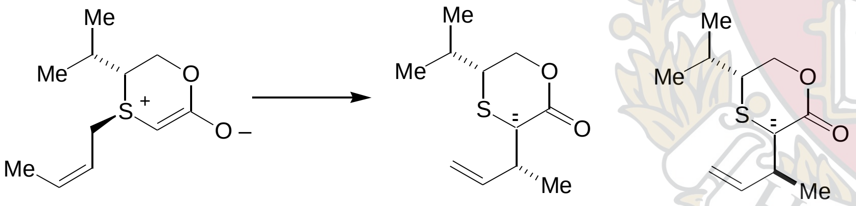
Squalene

[2,3]-Sigmatropic Rearrangements: Chirality Transfer

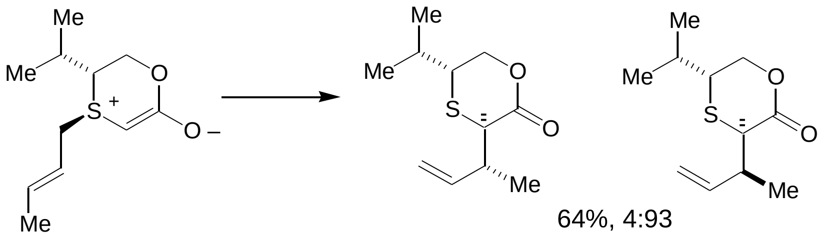
[2,3] Sulfur Ylide Rearrangement Using a Chiral Auxiliary

Kurth JOC **1990**, *55*, 2286 and TL **1991**, *32*, 335



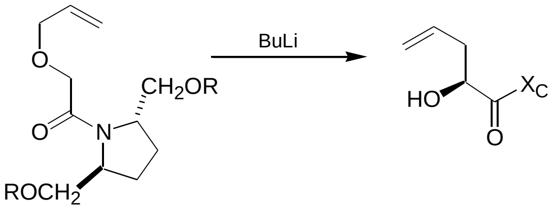


66%, 94:4

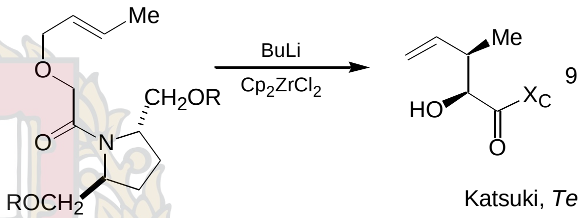


64%, 4:93

Chiral Auxiliaries can also be used in the Wittig Rearrangement



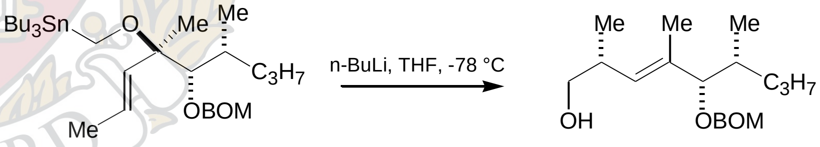
96% de (61%)



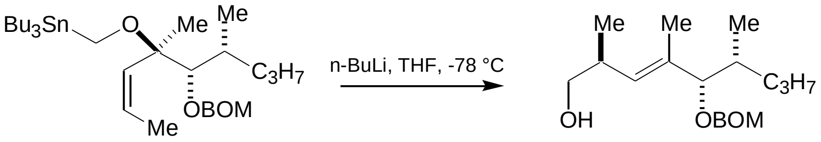
97% syn; 96% de (43%)

Katsuki, *Tet Lett* **1986**, *27*, 4577

Internal Relay of Stereochemistry in C–C Constructions



diastereoselection > 100:1 (57%)



Kallmerten TL **1988**, *29*, 6901.

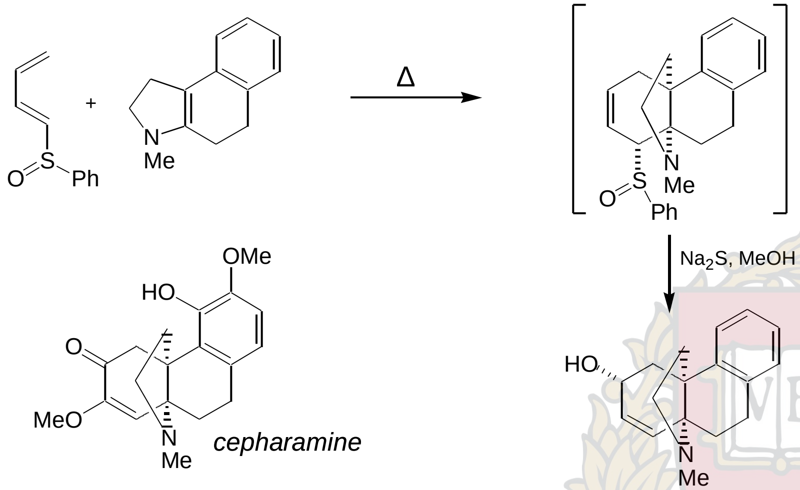
diastereoselection > 100:1 (64%)

See these papers for other applications

Kallmerten TL **1993**, *34*, 753.
Kallmerten TL **1993**, *34*, 749.
Kallmerten SynLet **1992**, 845.

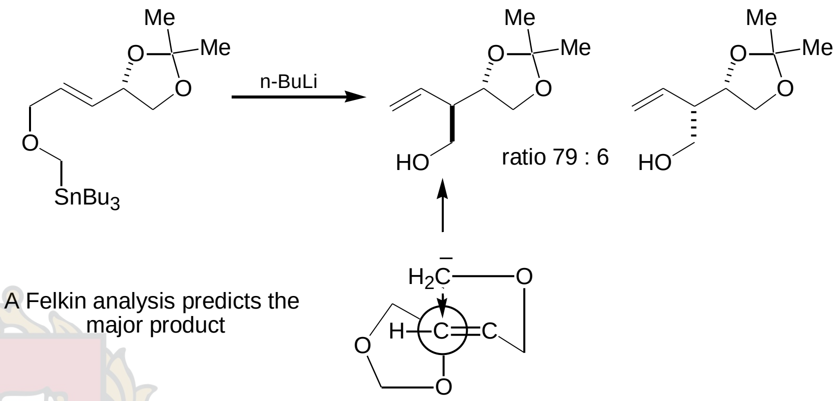
Internal Relay of Stereochemistry in C–O Constructions

Tandem [4+2] & [2,3] Process: Evans, Bryan, Sims *J. Am. Chem. Soc.* **1972**, 2891.



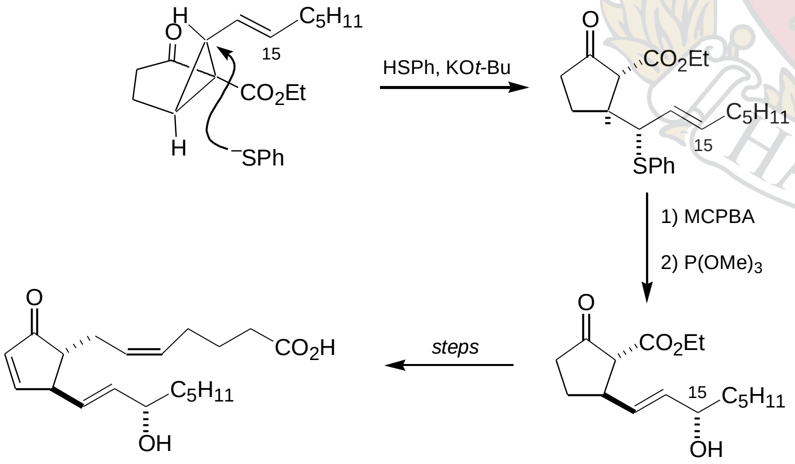
cepharamine

Cases where the chirality is exocyclic to the rearrangement



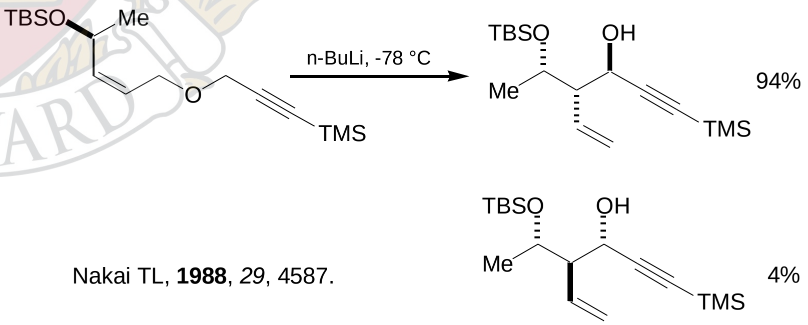
A Felkin analysis predicts the major product

Bruckner, *Angew. Chem. Int. Ed*. **1988**, *27*, 278



Taber *J. Am. Chem. Soc.* **1977**, *99*, 3513.
Kondo *Tet. Lett.* **1978**, 3927.

Allylic Ethers to Make Three Contiguous Stereocenters

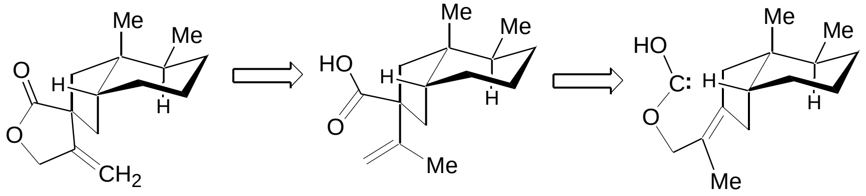


Nakai TL, **1988**, *29*, 4587.

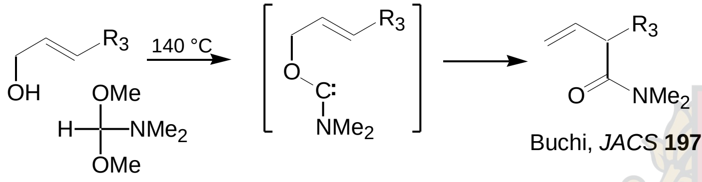
Can you rationalize the stereochemical outcome of this reaction?

[2,3]-Sigmatropic Rearrangements: Chirality Transfer

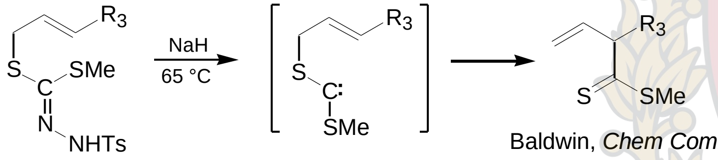
The Synthesis of Bakkenolide-A (*Evans JACS* **1977**, *99,* 5453)



- Candidate processes:

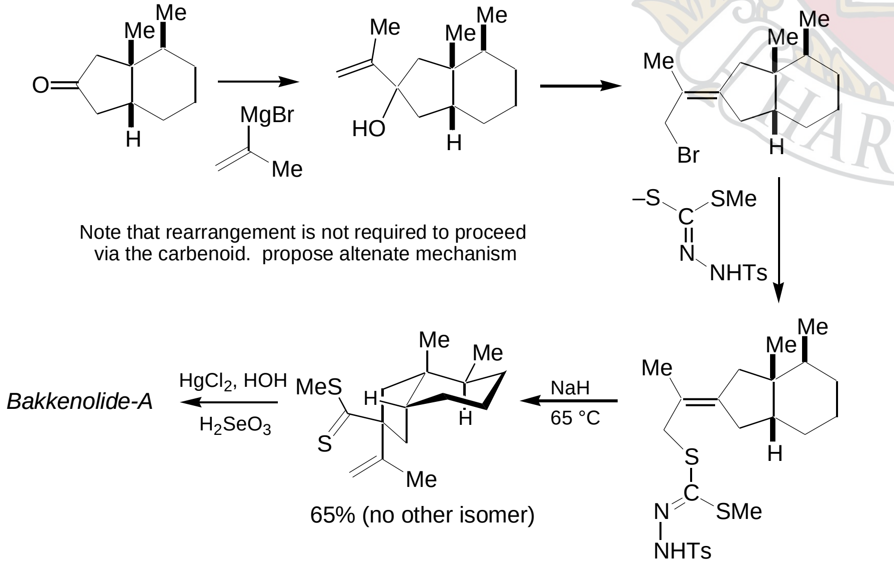


Buchi, *JACS* **1974**, *96*, 5563



Baldwin, *Chem Comm* **1972**, 354

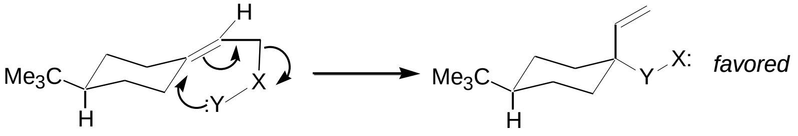
- The synthesis:

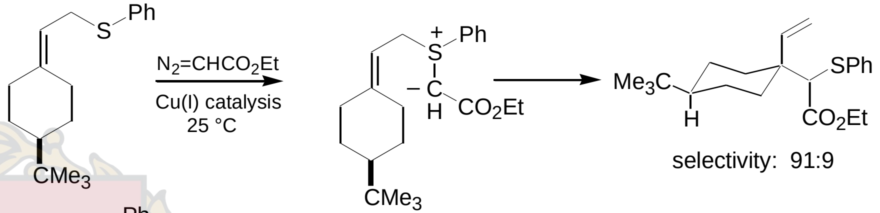


Note that rearrangement is not required to proceed via the carbenoid. propose altenate mechanism

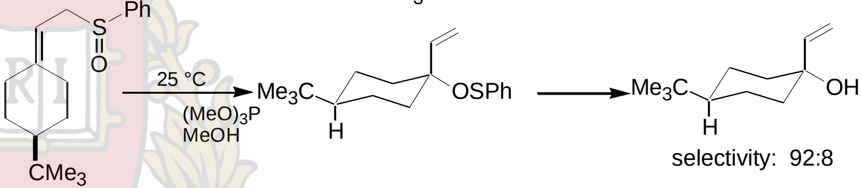
65% (no other isomer)

[2,3] Sigmatropic rearrangements respond to subtile steric effects



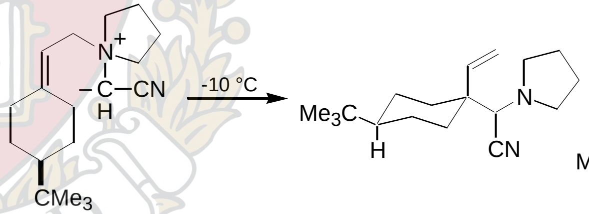


selectivity: 91:9



selectivity: 92:8

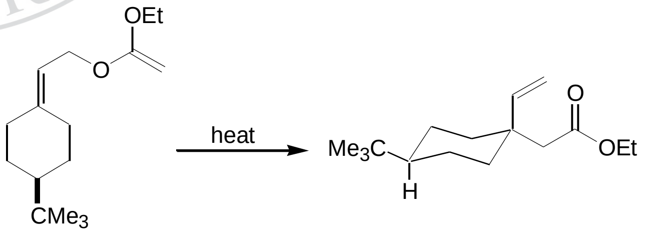
Evans, *JACS*, **1972**, *94*, 3672



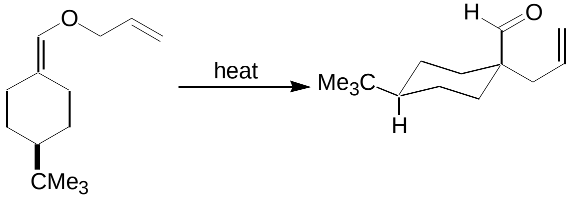
selectivity: 90:10

Mander, *JOC*, **1973**, *38*, 2915

- The comparison of analogous [2,3] & [3,3] rearrangements:



selectivity: 52:48



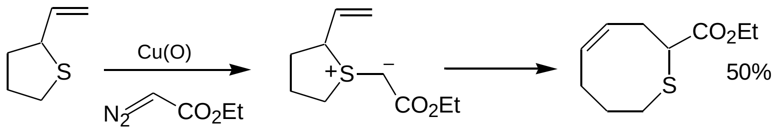
selectivity: 75:25

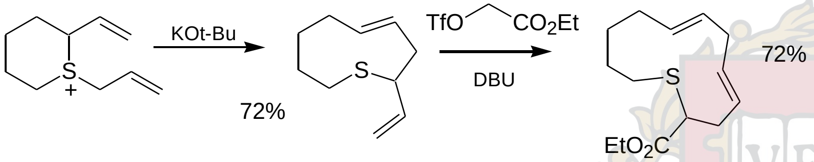
House, *JOC* **1975**, *40*, 86

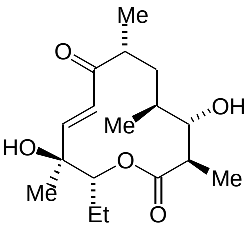
[2,3]-Sigmatropic Rearrangements: Ring Expansion & Contraction

Ring expansion reactions have been investigated

Methods based on sulfur ylides: (review) Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358



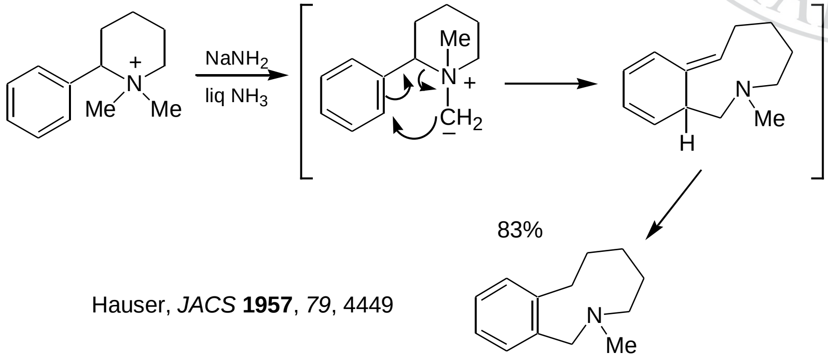




Methynolide has been synthesized by Vedejs using this ring-expansion methodology

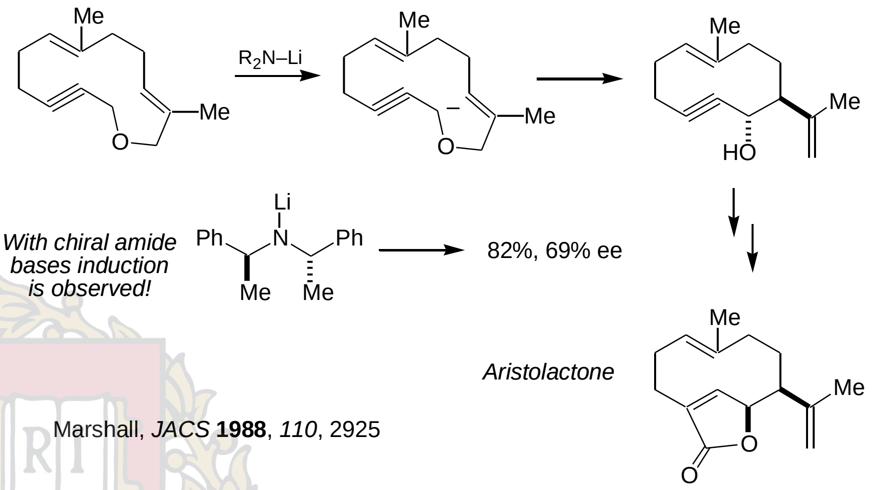
Vedejs, *JACS* **1989**, *111*, 8430

An early ring expansion using the Sommelet-Hauser Rearrangement



Hauser, *JACS* **1957**, *79*, 4449

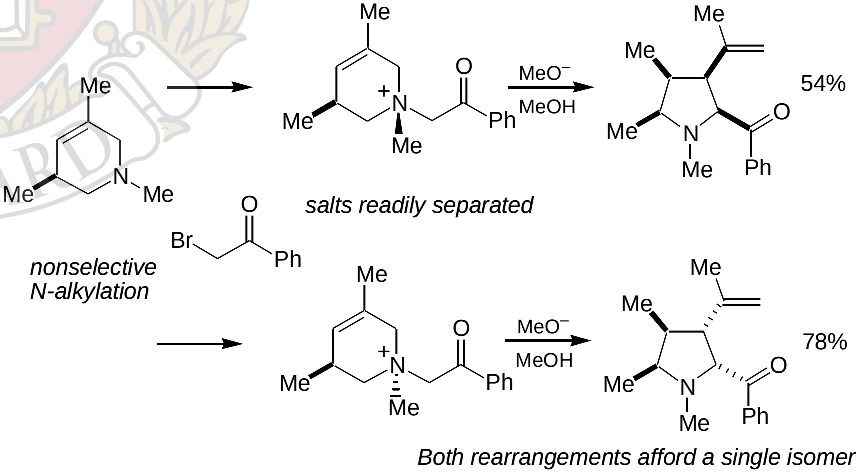
A ring contraction using the Wittig Rearrangement



With chiral amide bases induction is observed!

Marshall, *JACS* **1988**, *110*, 2925

A ring contraction using the Stevens Rearrangement



Both rearrangements afford a single isomer

Stevenson, *Tet. Lett* **1990**, *31*, 4351

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 14

Pericyclic Reactions–4

- [3,3] Sigmatropic Rearrangements: Introduction
- Cope Rearrangements & Variants
- Claisen Rearrangements & Variants

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Fleming: Chapter 4
Thermal Pericyclic Reactions

Matthew D. Shair

Monday,
October 21, 2002

Other Reading Material:

[3,3] Sigmatropic Rearrangements

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
Chapter 7.2, Claisen

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)

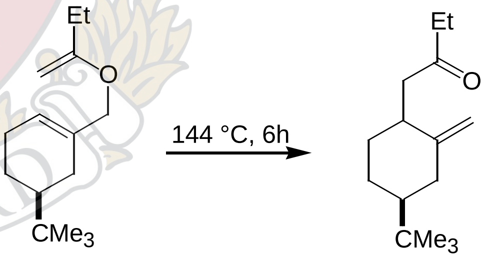
S. R. Wilson, *Organic Reactions* **1993**, *43*, 93 (oxy-Cope)

T. S. Ho, *Tandem Organic Reactions* **1992**, *Chapter 12* (Cope, Claisen)

Paquette, L. A. (1990). "Stereocontrolled construction of complex cyclic ketones by oxy-Cope rearrangement." Angew. Chem., Int. Ed. Engl. 29: 609.

Problems of the Day:

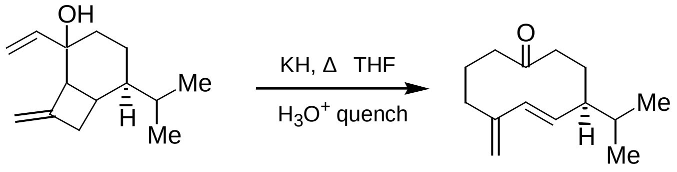
Predict the stereochemical outcome of this Claisen rearrangement



diastereoselection
>87:13

Ireland, *JOC* 1983, *48*, 1829

Provide a mechanism for the indicated transformation

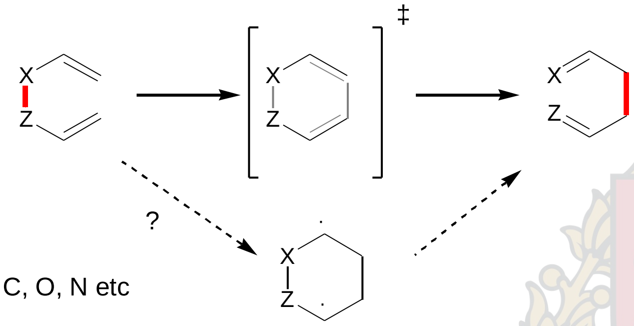


Schreiber, *JACS* **1984**, *106*, 4038

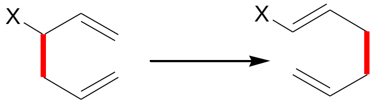
Introduction to [3, 3]-Sigmatropic Rearrangements

General Reviews:

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)
S. R. Wilson, *Organic Reactions* **1993**, *43*, 93 (oxy-Cope)
T. S. Ho, *Tandem Organic Reactions* **1992**, *Chapter 12* (Cope, Claisen)
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
Chapter 7.2, Claisen

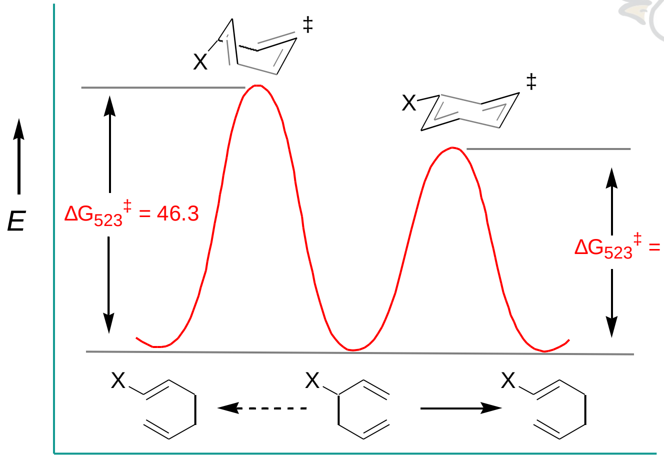


X & Z = C, O, N etc

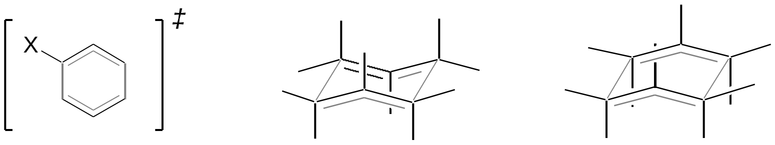

Cope Rearrangement, Ea = 33.5 kcal/mol


Claisen Rearrangement Ea = 30.6 kcal/mol

The Reaction Energetics Goldstein, *JACS* **1972**, *94*, 7147



The CopeTransition States



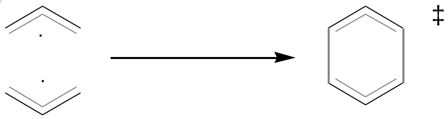
Relative Energy $\Delta\Delta G^{\ddagger}$: 0 + 5.8 kcal/mol

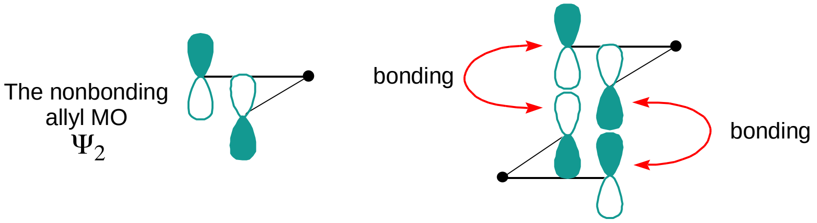
Relative Energy $\Delta G°$: 0 + 5.3 kcal/mol

The Boat and Chair geometries for these transition structures are well defined.

The FMO Analysis (Fleming page 101)

Bring two Allyl radicals together to access for a possible bonding interaction between termini.



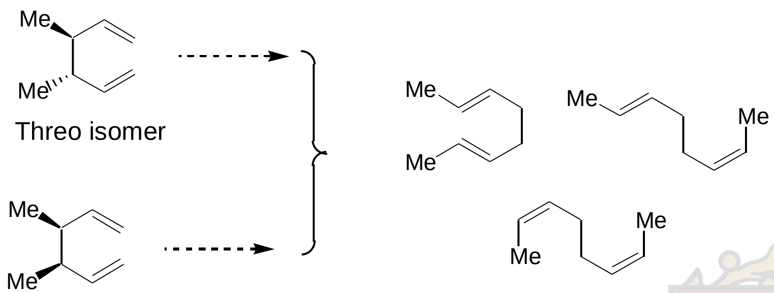


It is evident that synchronous bonding is possible in this rearrangement

The Doering–Roth Experiments

Doering & Roth *Tetrahedron* **18,** 67, (1962):

The Geometry of the transltion state (boat vs chair) can be analyzed via the rearrangement of substituted 1,5-dienes:

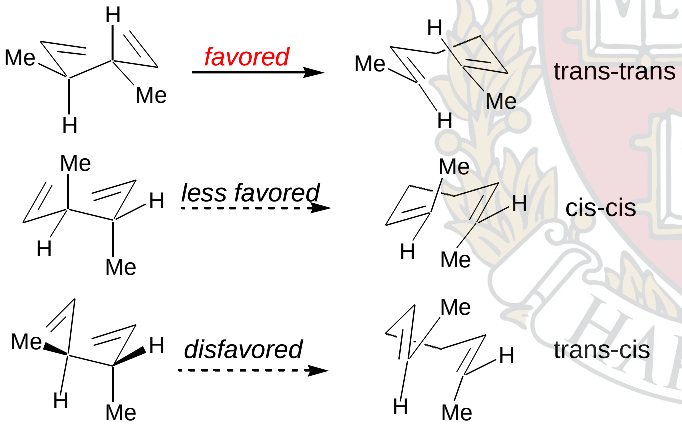


Threo isomer

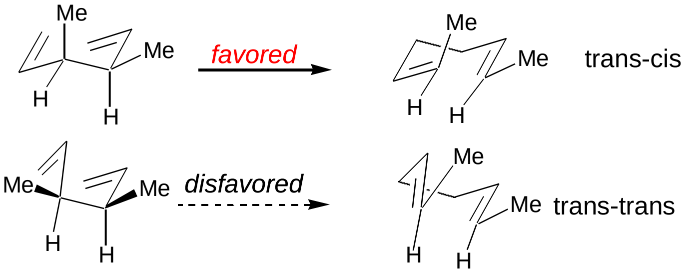
Meso isomer

- Measure product composition from rearrangement of each diene isomer

Predictions: *Threo isomer*

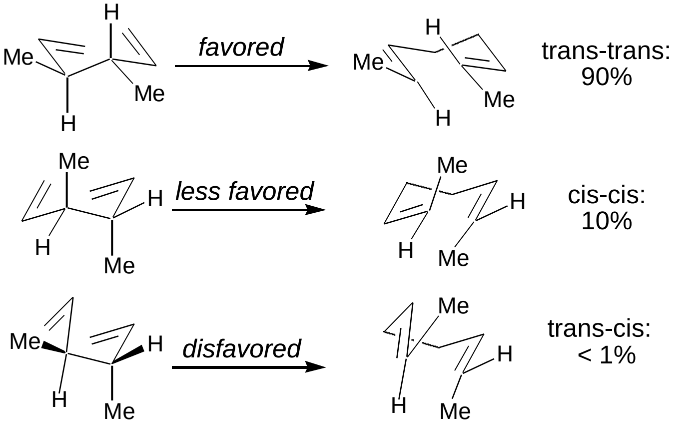


Predictions: *Meso isomer*

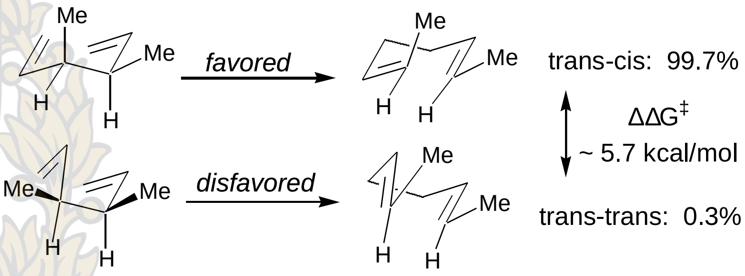


The Results

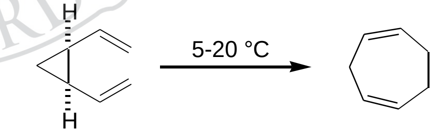
Results: *Threo isomer*



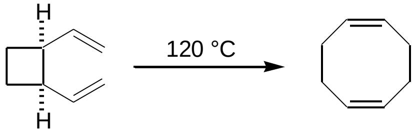
Results: *Meso isomer*



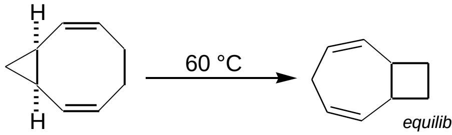
- Ring Strain can be employed to drive the Cope process:



Brown *Chem. Commun.* **1973**, 319



Vogel *Annalen* **1958**, *615*, 1

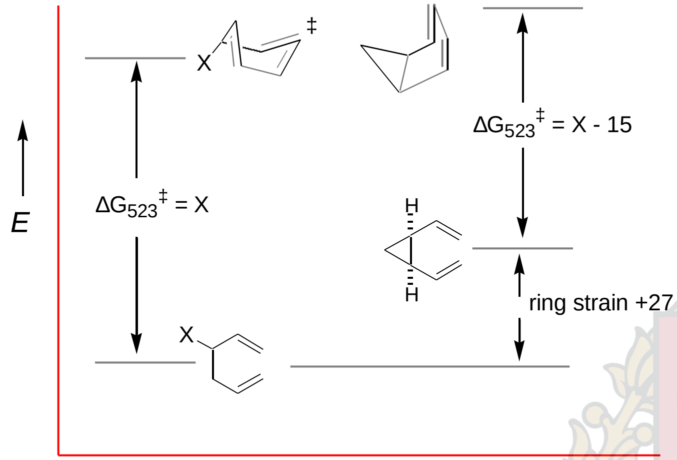


Reese *Chem. Commun.* **1970**, 1519

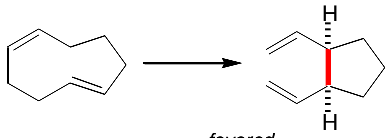
equilibrium stongly favors this isomer

Strain Accelerated-Cope Rearrangements

Cyclopropyl substitution is a ground state effect

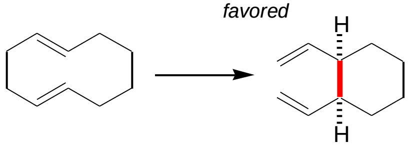


Position of Equilibrium dictated by ring strain issues:



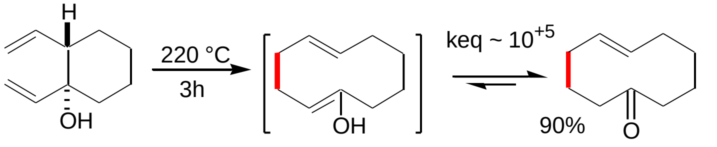
Vogel *Angew. Chem. Int. Ed.* **1963**, *2*, 739

favored



Wharton *J. Org. Chem.* **1973**, *38*, 4117

However, tautomerism can shift the equilibrium:



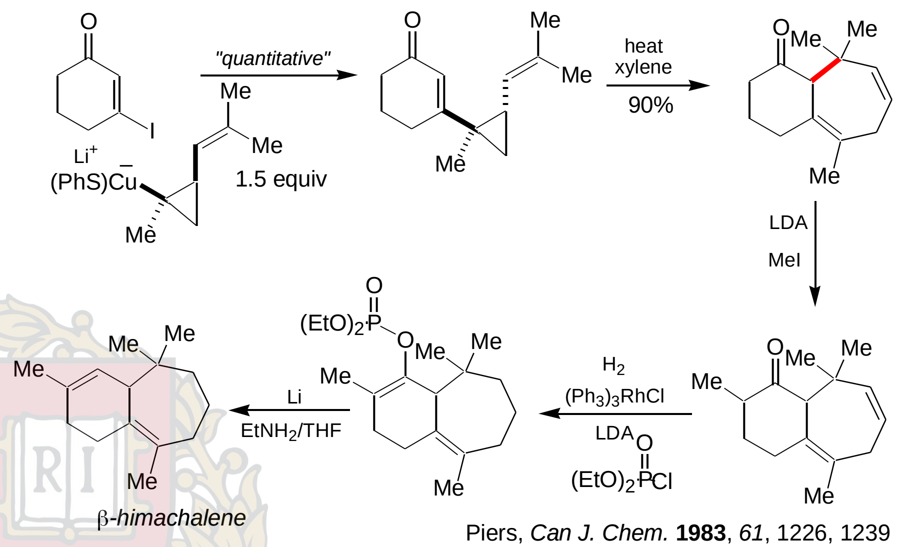
Marvell, *Tet. Lett.* **1970**, 509

keq ~ 10^{+5}

ΔG = 1.4(pKeq) = 1.4X(-5) = -7 kcal/mmol

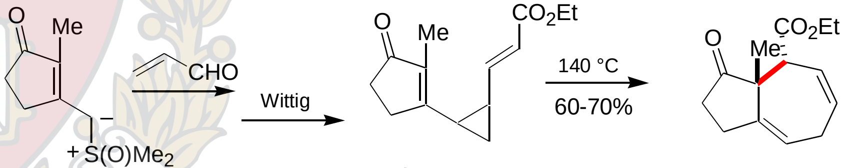
Energetically, how much does tautomerization give you?

Ring extension via divinylcyclopropane rearrangement



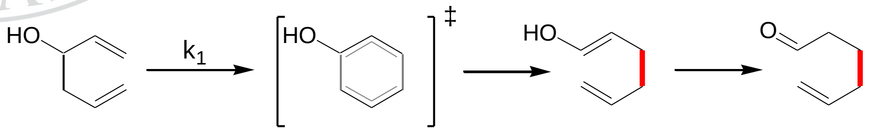
β-*himachalene*

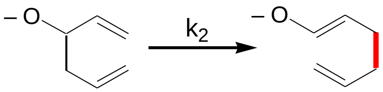
Piers, *Can J. Chem.* **1983**, *61*, 1226, 1239



Marino, *J. Org. Chem.* **1974**, *39*, 3175

Accelerated Cope Rearrangements





$$\boxed{\frac{k_2}{k_1} = 10^{+10} \longrightarrow 10^{+17}}$$

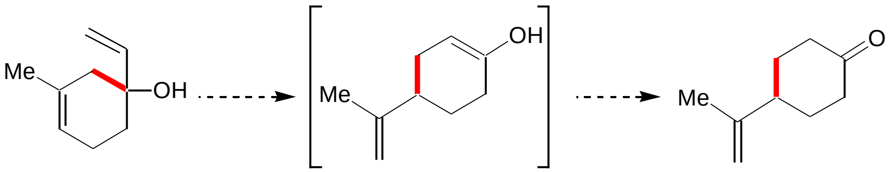
Evans, Golob, *JACS* **1975**, *97*, 4765.

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
"Recent applications of anionic oxy-Cope rearrangements."
Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971-14020

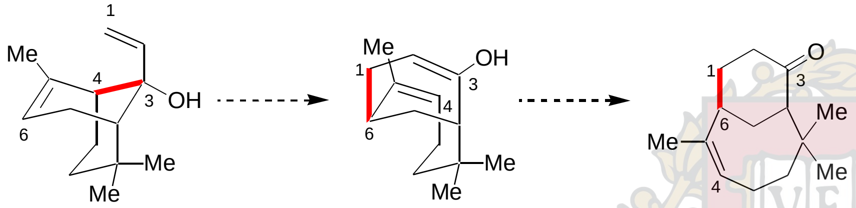
The Anionic Oxy-Cope Rearrangement

The Aborted Oxy-Cope Reaction (circa 1969)

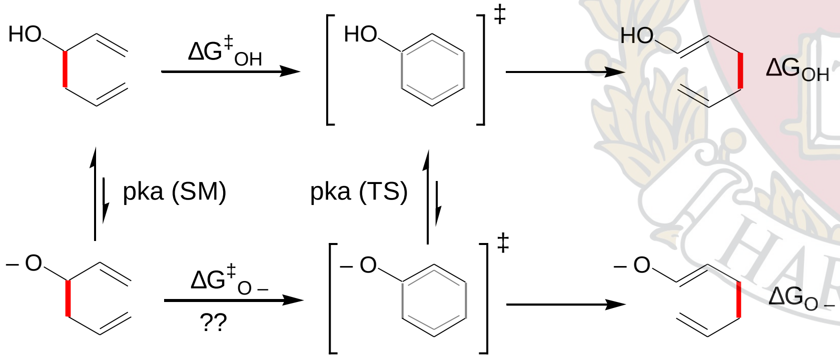
- *The basic reaction*



- *Actual case studied:*



Prediction of Substituent Effect (circa 1969)



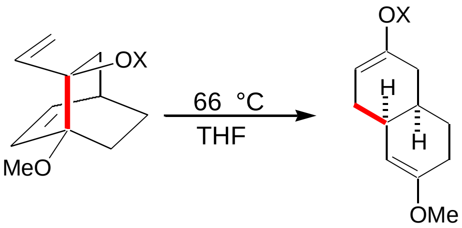
$$\boxed{\Delta G^{\ddagger}_{O-} = \Delta G^{\ddagger}_{OH} + 2.3RT\,[\,pka_{TS} - pka_{SM}]}$$

$\Delta G^{\ddagger}_{O-} = \Delta G^{\ddagger}_{OH} + 2.3RT\,[18 - 29]$ (in DMSO)

$\Delta G^{\ddagger}_{O-} = \Delta G^{\ddagger}_{OH} + 1.4\,[-11]$

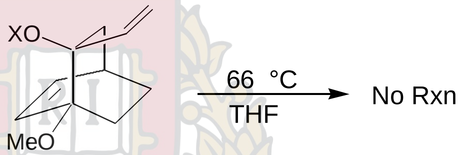
$\Delta G^{\ddagger}_{O-} = \Delta G^{\ddagger}_{OH} - 15$ kcal/mol at 298 K (in DMSO)

Documentation of Alkoxy Substituent Effect



	–OX	Half-life	
	–OH	(66 yrs)	66 °C
	–OLi	no rxn	
	–ONa	1.2 hrs	
	–OK	1.4 min	
	–OK	11 hrs	10 °C
(HMPT)	$–O^{-}\,{}^{+}K$	4.4 min	

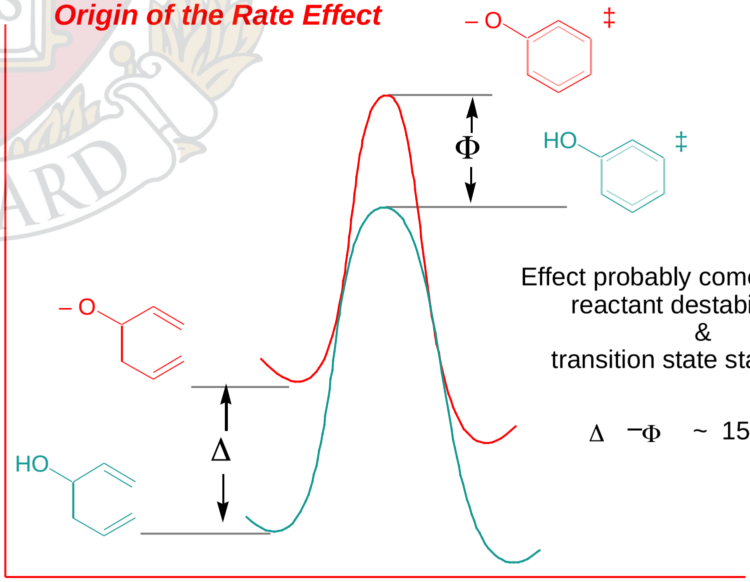
$\boxed{10^{+12}\text{ rate acceleration}}$



$$\boxed{\begin{aligned}\Delta\Delta G^{\ddagger}_{estimate} &= 15\text{ kca mol}^{-1}\\ \Delta\Delta G^{\ddagger}_{experiment} &= 13\text{ kca mol}^{-1}\end{aligned}}$$

with A. M. Golob, JACS. **1975**, *97*, 4765.

Origin of the Rate Effect



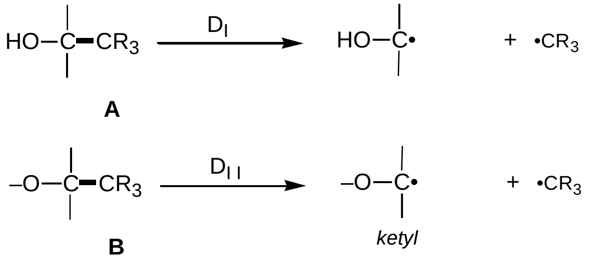
Effect probably comes from both
reactant destabilization
&
transition state stabilization

Δ −Φ ~ 15 kcal/mol

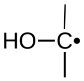
Maximal rates are observed under conditions where reactant is maximally destabilized

Anionic Substituent Effects: Bond Homolysis

Substituent Effects in Bond Homolysis



$D_I - D_{II} = 2.3\ RT[\text{pka}\ (\mathbf{A}) - \text{pka}\ (\mathbf{B})]$



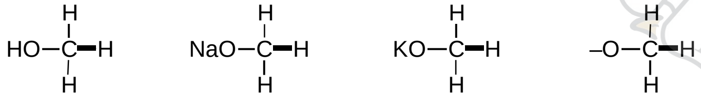
Acidities of these radicals are known in H_2O
Hayon, *Accts. Chem. Res.* **1974**, *7*, 114

(H_2O) pKa = 10.7   pKa = 9.2

In DMSO: ΔD = 2.3 RT[29 – pka 18] = ~ 15 kcal/mol

- Substituent Effect based on ab initio calculations

(Evans, Goddard, *JACS* **1979**, *101*, 1994)

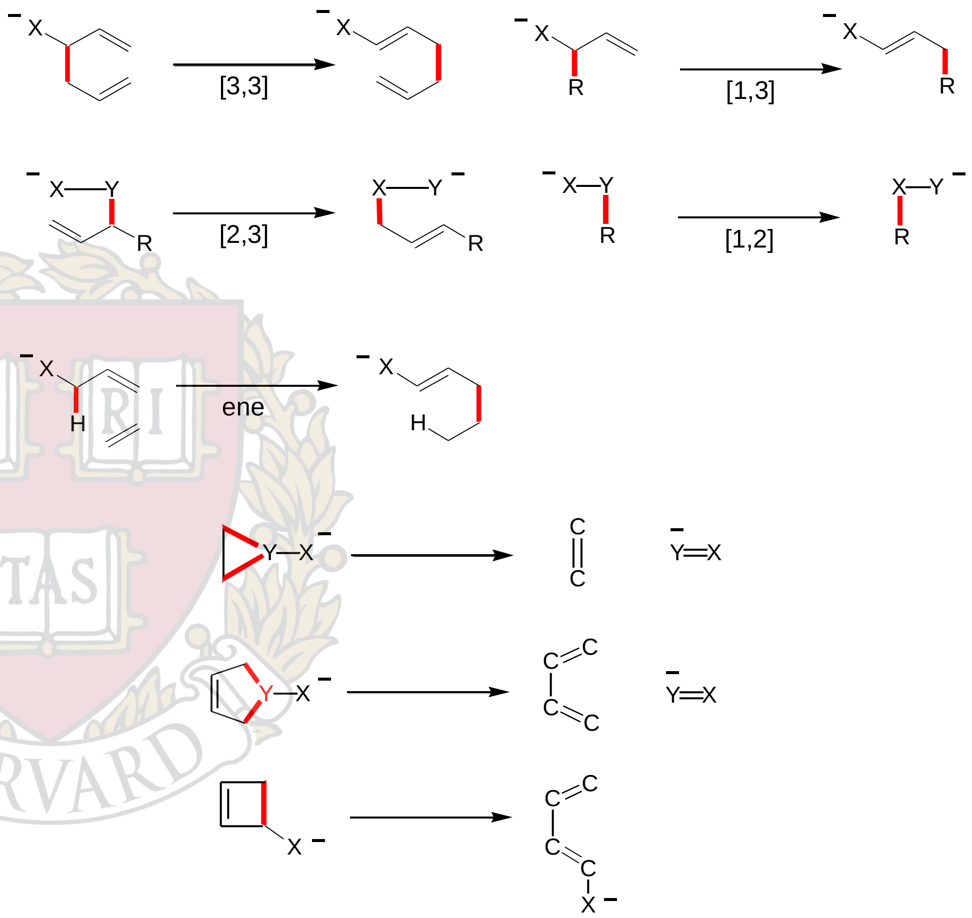


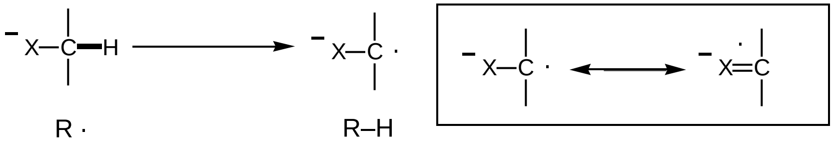
BDE = 90.7   BDE = 80.6   BDE = 79.0   BDE = 74.2
(BDE = 91.8 expt)

ΔD
+16.5 kcal/mol

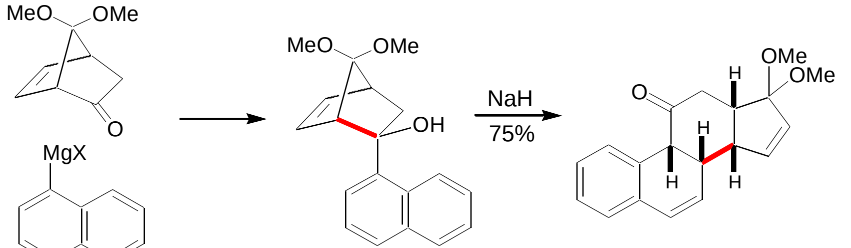
Related papers: Evans, Baillargeon, *Tet Lett.* **1978**, *36*, 3315, 3319

Substituent Effects in Molecular Rearrangements

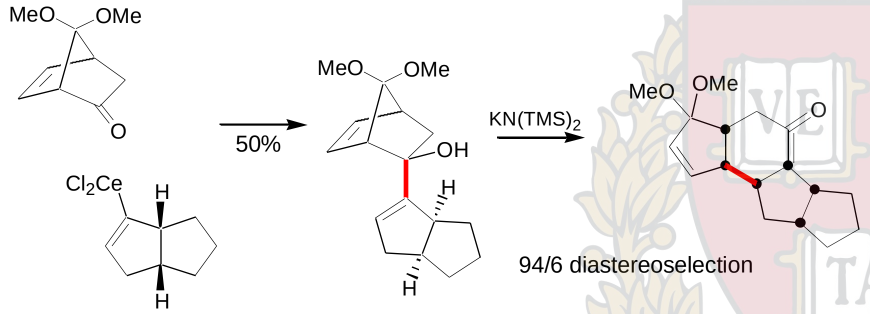




Anionic Oxy-Cope Rearrangement: Applications

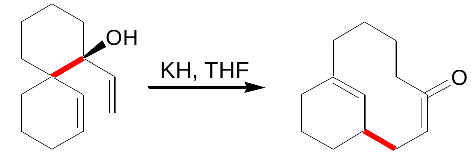


Jung, JACS **1978**, *100*, 4309
Jung, JACS **1980**, *102*, 2463

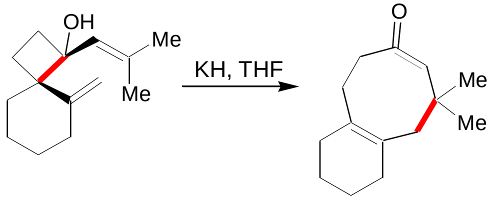


94/6 diastereoselection

Paquette, JACS **1988**, *110*, 879

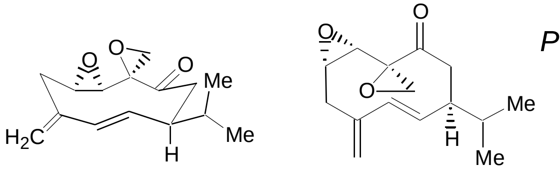


Levine, JOC **1981**, *46*, 2199

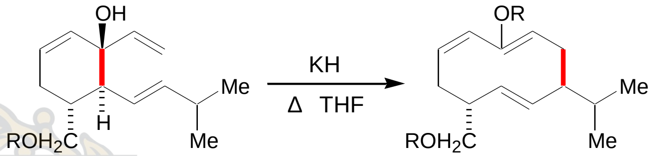


Gadwood, *JOC*, **1982**, *47*, 2268

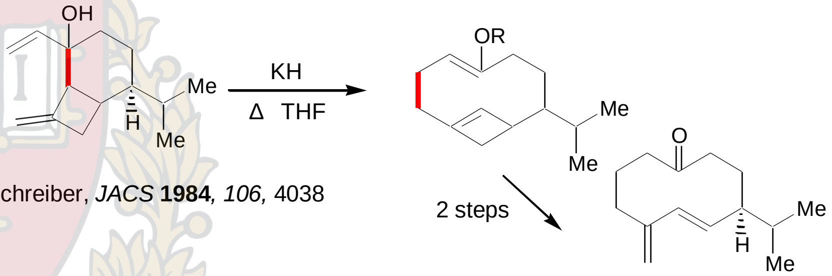
Periplanone-B Synthesis



200 µg from 75,000
virgin female cockroaches

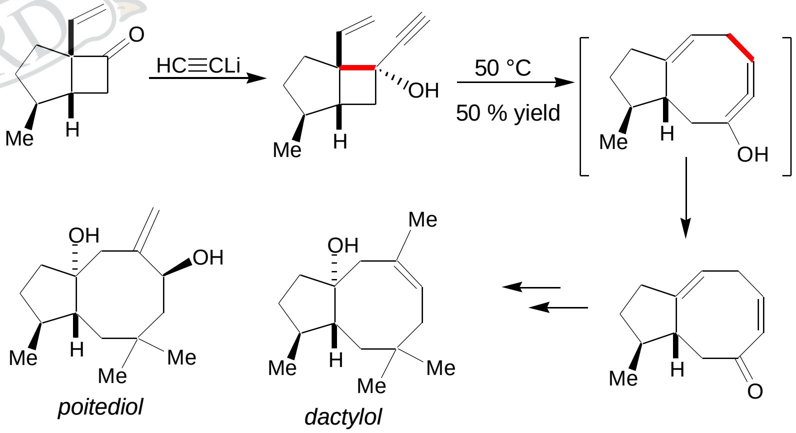


Still, *JACS* **1979**, *101*, 2493



Schreiber, *JACS* **1984**, *106*, 4038

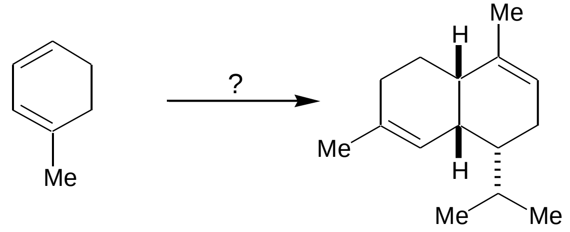
Gadwood, *JACS*, **1986**, *108*, 6343



poitediol
dactylol

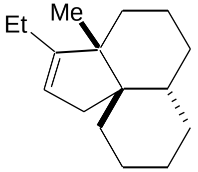
Oxy-Cope Problems

Propose a synthesis of α-amorphene using 1-methyl-1,3-cyclohexadiene.



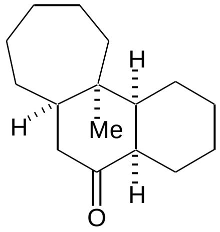
α-amorphene

Gregson, R. P.; Mirrington, R. N. *J. Chem. Soc., Chem. Commun.* **1973**, 598.



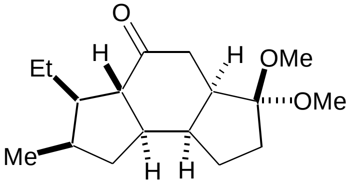
By incorporating a carbonyl group into this structure generate all possible oxy-Cope retrons.
Which is (are) the most reasonable?

Bérubé, G.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 4045.



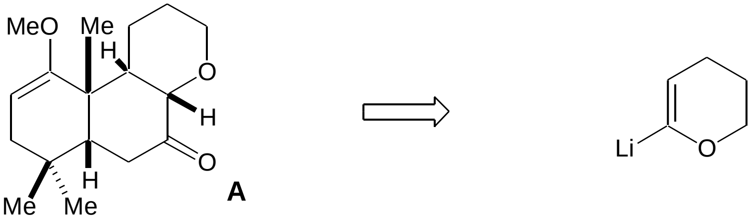
By incorporating a double bond into this structure generate all possible oxy-Cope retrons.
Which is (are) the most reasonable?

Ireland, et al. *J. Org. Chem.* **1981**, *46*, 4863.

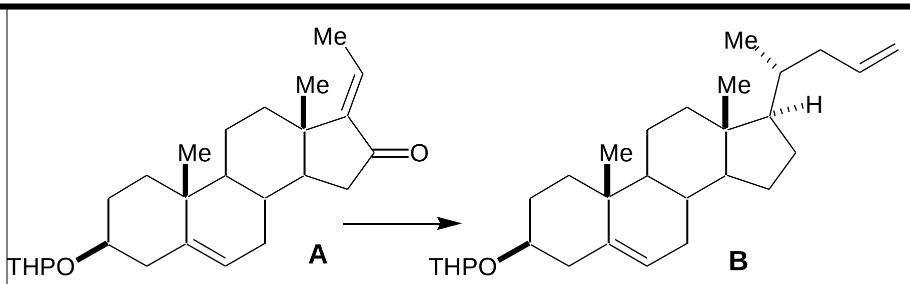


By incorporating a double bond into this structure generate all possible oxy-Cope retrons. Which is (are) the most reasonable?

Paquette, L. A. et al. *Tetrahedron Lett.* **1987**, *28*, 31.

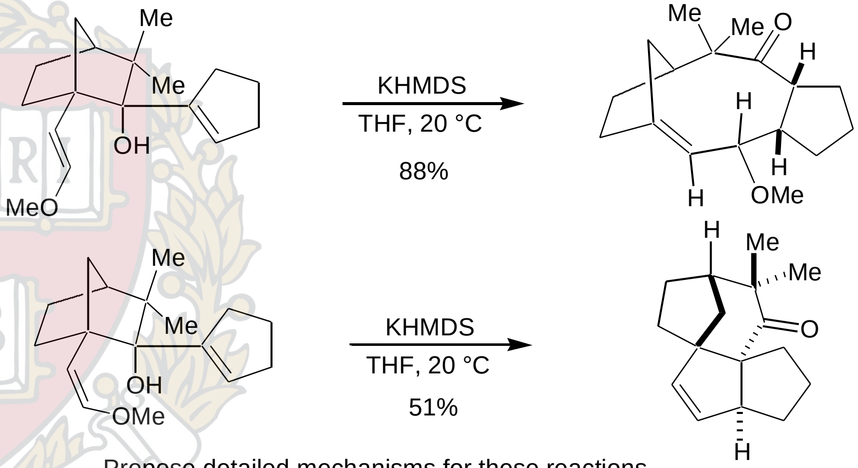


Propose a synthesis of **A** using the illustrated dihydropyran synthon.
Oplinger, J. A.; Paquette, L. A. *Tetrahedron Lett.* **1987**, *28*, 5441.



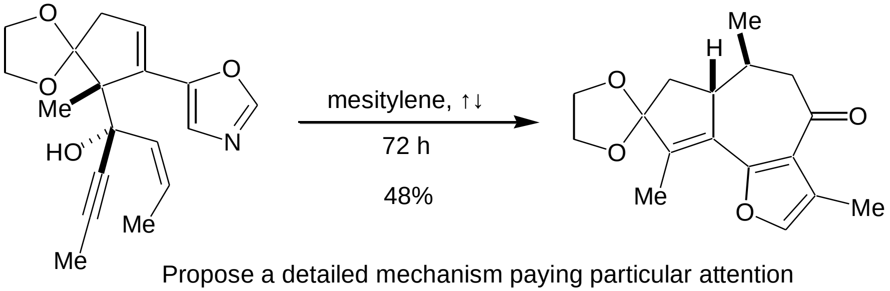
Propose a three step synthesis of **B** from **A**.

Koreeda, et al. *J. Org. Chem.* **1980**, *45*, 1172.



Propose detailed mechanisms for these reactions.
Rationalize the different behavior of these enol ether isomers.

Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331-2332.



Propose a detailed mechanism paying particular attention to issues of chemo- and stereoselectivity.

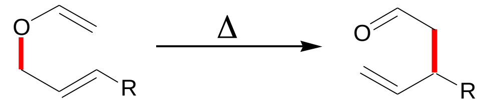
Jacobi, P. A.; Selnick, H. G. *J. Org. Chem.* **1990**, *55*, 202.

The Claisen Rearrangement

■ General Reviews:

S. J. Rhoades, *Organic Reactions* **1974**, *22*, 1 (Cope, Claisen)
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5, Ch 7.2
Ziegler, *Accts. Chem. Res.* **1977**, *10*, 227 (Claisen)
Bennett, *Synthesis* **1977**, 589 (Claisen)
Blechert, *Synthesis* **1989**, 71 (HeteroCope)
R. K. Hill, *Asymmetric Synthesis* vol 3, Ch 8, p503 (chirality transfer)
Ziegler, *Chem Rev.* **1989**, *89*, 1423 (Claisen)

■ The Reaction:



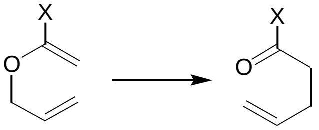
$\Delta H \sim -20$ kcal mol^{-1}

There is good thermodynamic driving force for this reaction.

Bonds Broken: C-C$_\pi$ (65 kcal mol^{-1}) & C-O$_\sigma$ (85 kcal mol^{-1})

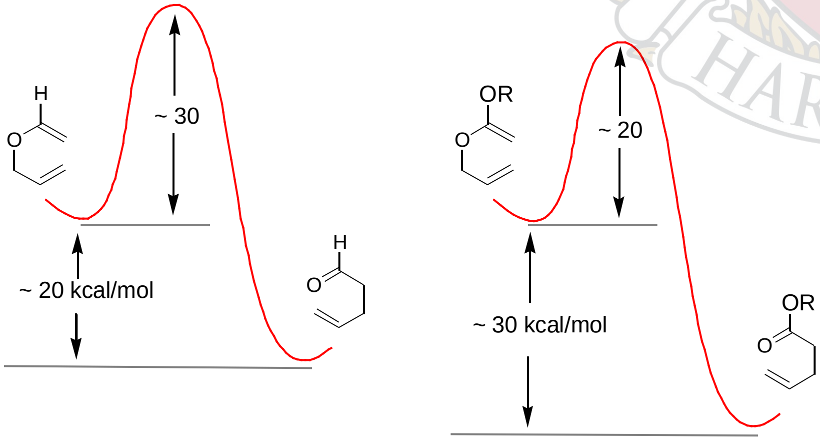
Bonds Made: C-O$_\pi$ (85 kcal mol^{-1}) and C-C$_\sigma$ (85 kcal mol-^{1})

■ Themodynamics of Claisen Variants:



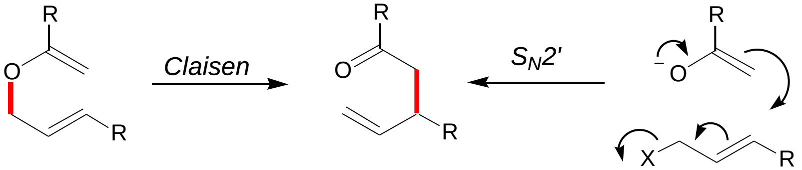
Substituent	ΔH (kcal mol$^{-1)}$
X = H	–16
X = OH	–31
X = NH$_2$	–30

(Benson estimates)

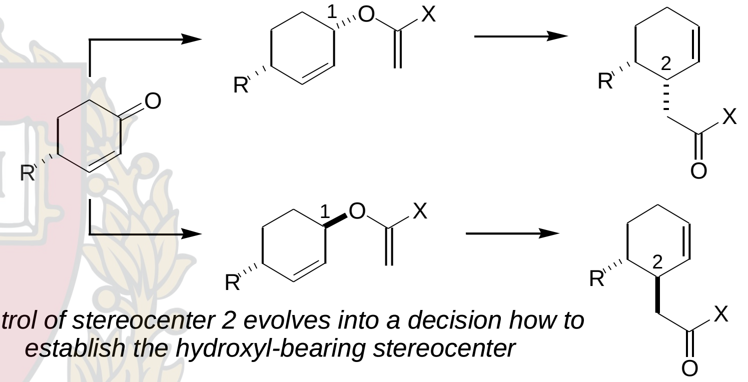


Heteroatom substitution at the indicated position increases exothermicity as well as reaction rate

Recognition Pattern for Organic Synthesis: An Enforced SN2'

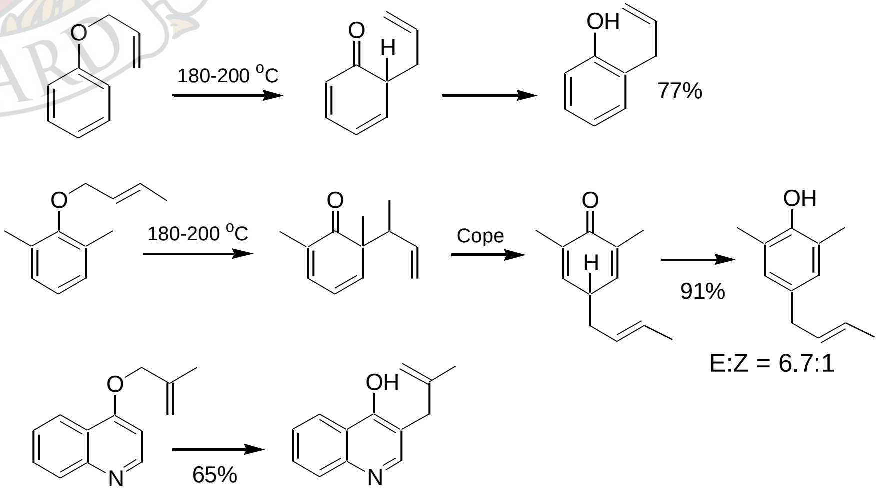


Stereochemical outcome is syn and controlled by hydroxyl stereocenter



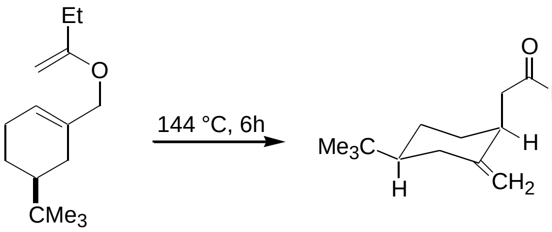
Control of stereocenter 2 evolves into a decision how to establish the hydroxyl-bearing stereocenter

Rearrangements of Aryl Allyl Ethers: Traditional Applications



Stereoelectronic & steric constraints

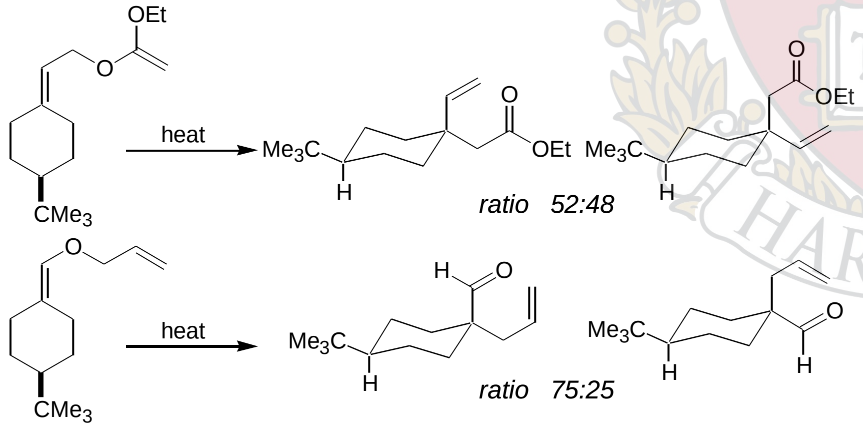
■ Endocyclic Olefins: Ireland, *JOC* 1983, *48*, 1829



diastereoselection >87:13

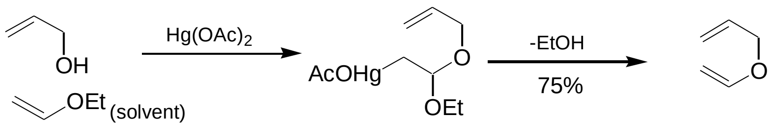
for endocyclic olefins, overlap between developing sigma and pi bonds required

■ Exocyclic Olefins: House, *JOC* 1975, *40*, 86

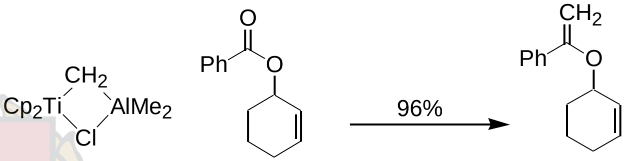


for exoocyclic olefins, overlap between developing sigma and pi bonds is equally good from either olefin diastereoface. In this instance, steric effects dominate & this system shows a modest preference for "equatorial attack." A related case is provided below.

Synthesis of Allyl Vinyl Ethers

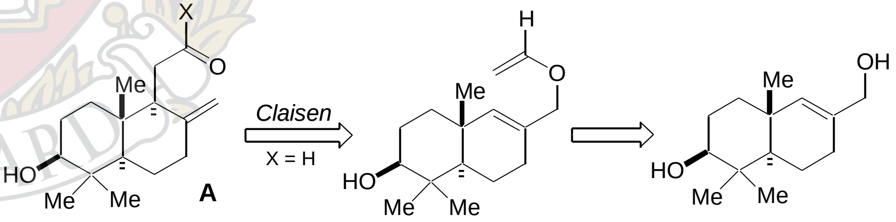


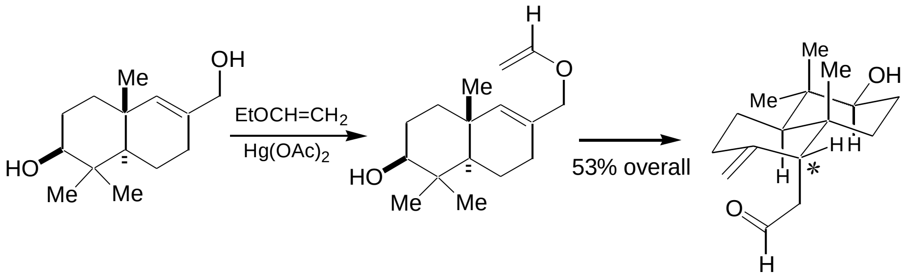
Watanabe, Conlon, *JACS* **1957**, *79*, 2828
Bronsted acids can also serve as catalysts



Use of Tebbe's Reagent: Evans, Grubbs, *J. Am. Chem. Soc.* **1980**, *102*, 3272.
(review) S. H. Pines, *Organic Reactions* **1993**, *43*, 1

■ The Ireland approach to the bicyclic acid A: *JOC* **1962**, *27*, 1118

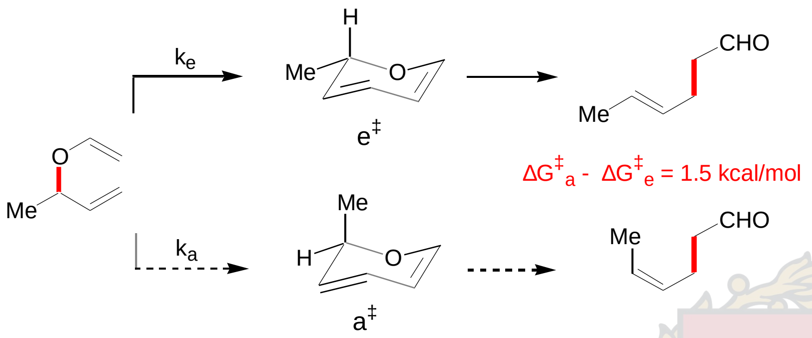




The new stereocenter (*) introduced via the rearrangement had the wrong configuration!

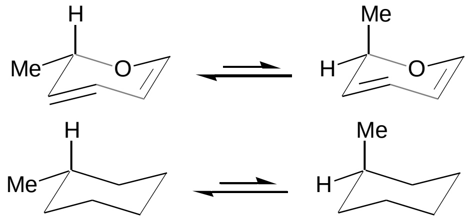
Claisen Rearrangement as vehicle for stereoselective olefin synthesis

Consider the following rearrangement:



$\Delta G^{\ddagger}_{a} - \Delta G^{\ddagger}_{e} = 1.5$ kcal/mol

Faulkner & Perrin (Tet. Lett. 2783 (1969) have made the correlation between $\Delta\Delta G^{\ddagger}$ for rearrangement & ΔG° for the corrresponding cyclohexane# equilibria:

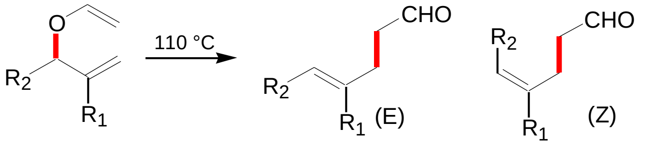


$\Delta\Delta G^{\ddagger} = +1.5$ kcal/mol

$\Delta G^{\circ} = +1.7$ kcal/mol

#Note: The A-value of 2-methyl-tetrahydropyran is +2.86 kcal/mol (Eliel pg 743)

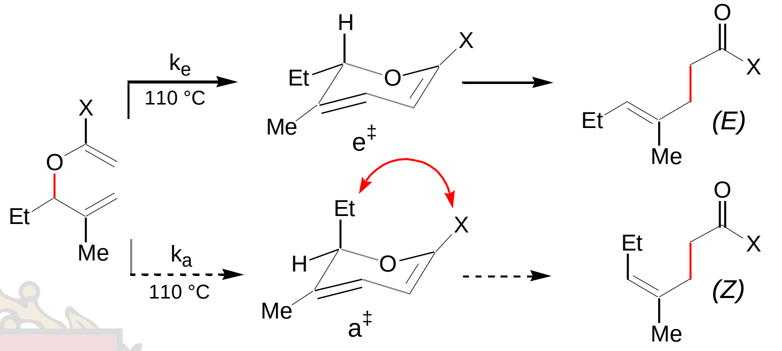
They then suggest that there is a good correlation between cyclohexane "A-values" & $\Delta\Delta G^{\ddagger}$ for the rearrangement process. Their case is fortified by the following expamples:



R_1	R_2	(E):(Z) found	(E):(Z) predicted
Me–	Et–	90:10	91:9
Me–	iPr–	93:07	94:6
Et–	Et–	90:10	91:9

Faulkner, *JACS* **1973**, *95*, 553

Faulkner suggests that the installation of other substituents on Claisen transition states will lead to enhanced reaction diastereoselection:

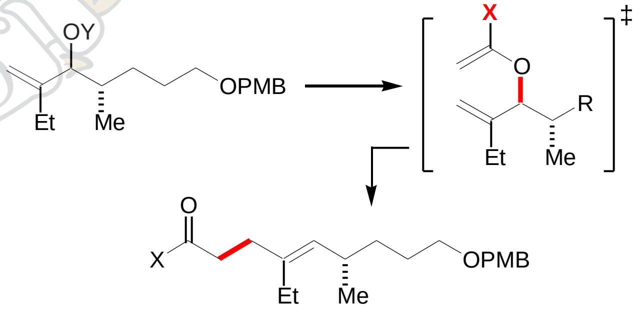


The $R_2 \leftrightarrow X$ interaction should destabilize a‡ as X gets progressively larger.

X	(E):(Z) found
H–	90:10
Me–	>99:1
MeO–	>99:1
Me_2N–	>98:2

Faulkner, *Tet Let* **1969**, 3243
Faulkner, *JACS* **1973**, *95*, 553
Johnson, *JACS* **1970**, *92*, 741

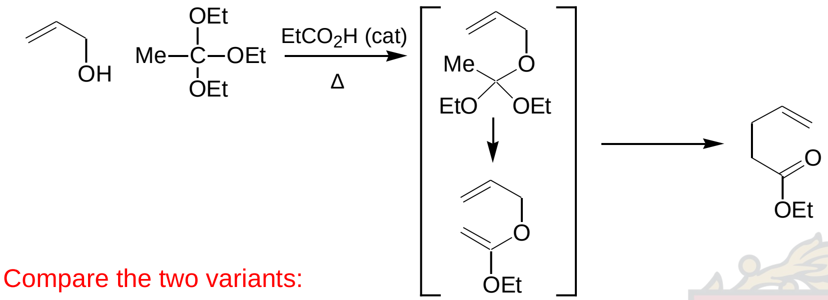
■ Another comparison: (DAE) M. DiMare, Ph. D. Harvard University, 1988



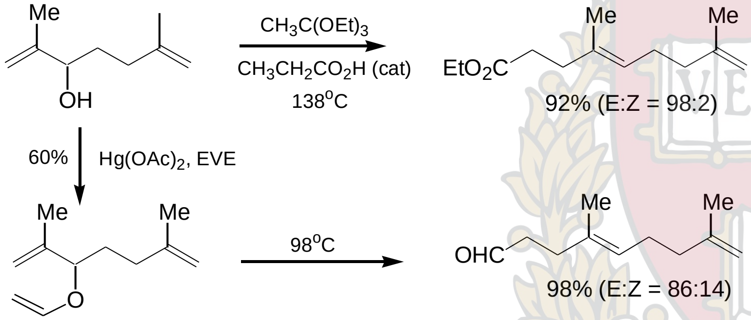
procedure	conditions	X	T, °C	(E):(Z) ratio
Y = Ac, Ireland	LDA, TMSCl	TMSO–	-78 → +55	97:3
Y = H, Johnson	$HC(OMe)_3, H^+$	MeO–	130	94:6
Y = H, Eschenmoser	$MeC(OMe)_2NMe_2$	Me_2N–	80	97.5:2.5

Johnson Orthoester Claisen

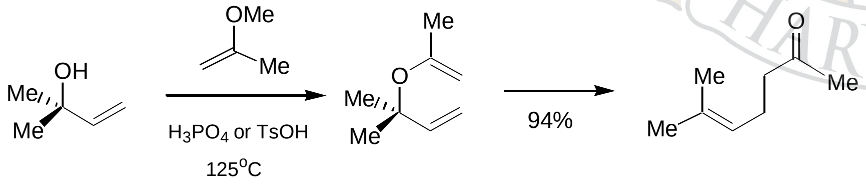
- Lead paper: Johnson, Faulkner, Peterson, *JACS* **1970**, *92*, 741

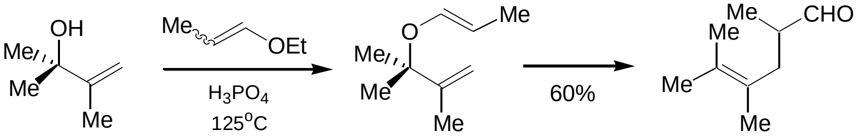


- Compare the two variants:



The Saucy Marbet Alternative

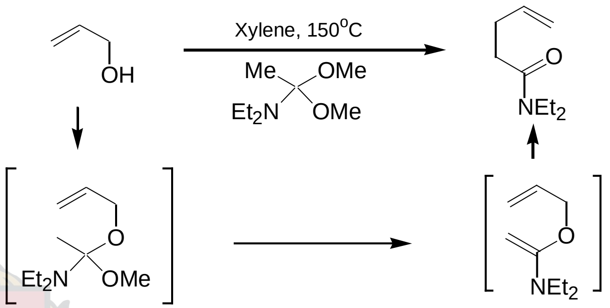


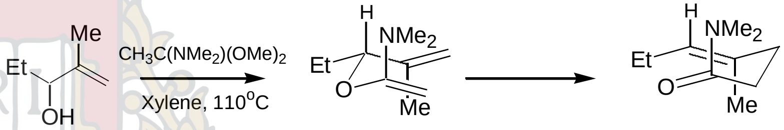


Saucy, Marbet, *Helv. Chim. Acta* **1967**, *50*, 2091,2095

Eschenmoser-Claisen

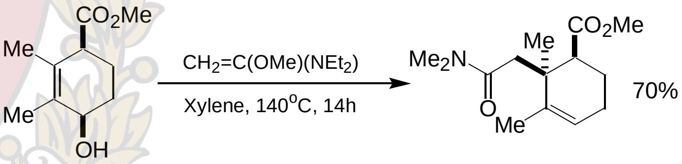
Eschenmoser, A. *Helv. Chem. Acta* **1964**, *47*, 2425; *Helv. Chim.Acta* **1969**, *52*, 1030.



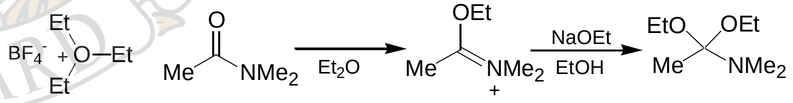


Faulkner and Peterson

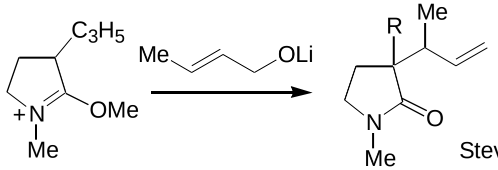
High yield, E:Z = 99:1



- Synthesis of Amide Acetals

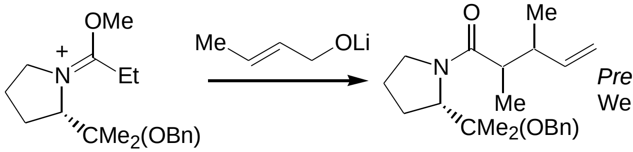


- Reactions to ponder:



diastereoselection 6:1
Predict the major diastereomer

Stevenson, *Tet. Let.* **1991**, *32*, 4199

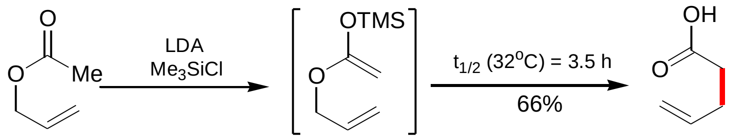


Predict the major diastereomer
Welch, *JACS* **1987**, *109*, 6716

Ireland-Enolate Claisen

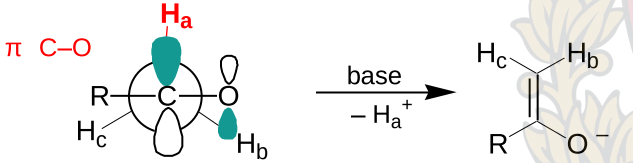
- Reviews Pereira, *Aldrichimica Acta* **1993**, *26*, 17-29 (Ireland-Claisen)
  Ireland, *Aldrichimica Acta* **1988**, *21*, 59-69 (Claisen-related)

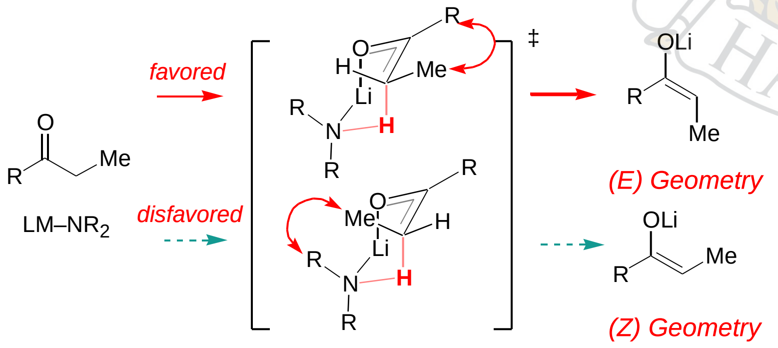
Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868



Enolization: Amide Bases

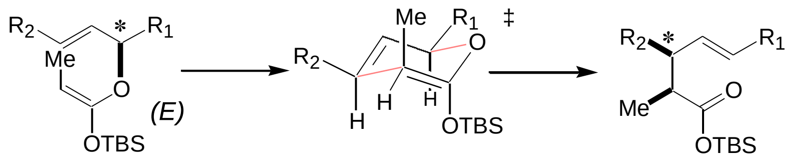
Stereoelectronic Requirements: The α-C-H bond must be able to overlap with π C–O

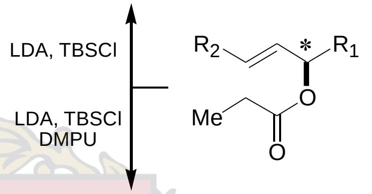


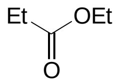


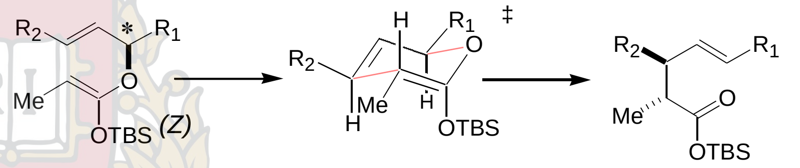
The Ireland Model (*JACS* **1976**, *98*, 2868)
Narula, Tetrahedron Lett. **1981**, *22*, 4119
more recent study: Ireland, *JOC* **1991**, *56*, 650

Substituted enolates afford an additional stereocenter





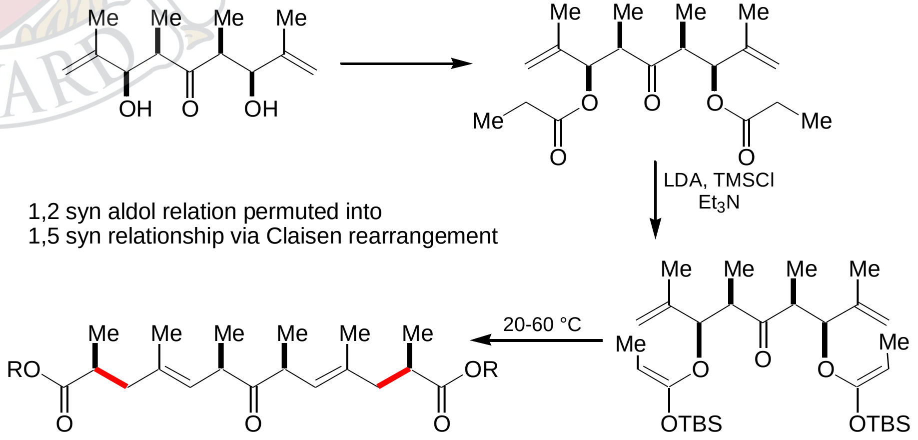
	conditions	*(E):(Z)*	*control*
	LDA, TBSCl	94:6	kinetic
	LDA, TBSCl DMPU	7:93	thermo



key study: Ireland, *JOC* **1991**, *56*, 650 and earlier cited papers

Double Claisen Rearrangements are also possible

Paterson, *Tet Lett* **1991**, *32*, 7601



1,2 syn aldol relation permuted into
1,5 syn relationship via Claisen rearrangement

63% yield (diastereoselection 86%)

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 15

Cycloaddition Reactions-1

- Introduction to Cycloaddition Reactions
- [2+2] Cycloaddition Reactions
- The Diels-Alder Reaction

Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Carey & Sundberg: **Part B**; Chapter 6
Cycloadditions, Unimolecular Rearrangements
Thermal Eliminations

Fleming: Chapter 4
Thermal Pericyclic Reactions

Matthew D. Shair

Wednesday,
October 23, 2002

Other Reading Material:

[2+2] Cycloaddiltion Reactions

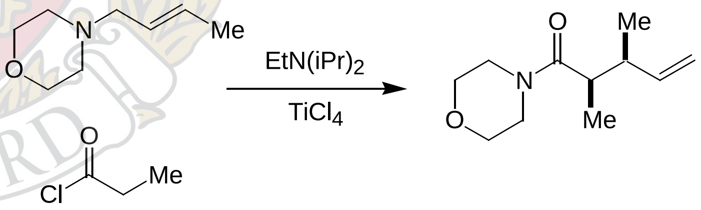
Tidwell, T. T. *Ketenes*, John Wiley and Sons, **1995**.
Ghosez, L.; Marchand-Brynaert, J. *Comprehensive Organic Synthesis*, Vol. 5, Pergamon, **1991**, p. 85-122.

The Diels-Alder Cycloaddition Reactions

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235 **(pdf)**

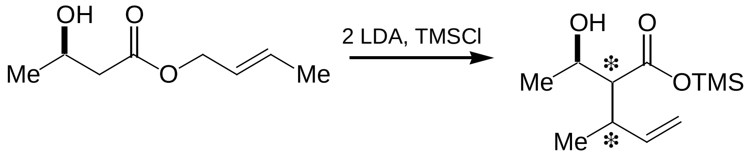
Problems of the Day:

Propose a mechanism for this transformation



MacMillan, *JACS* **1999**, *121*, 9726

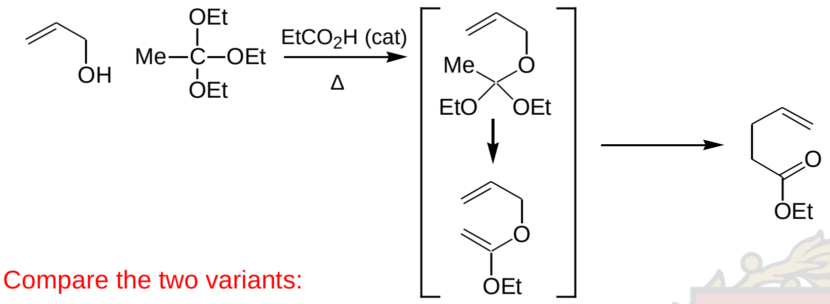
Predict the stereochemical outcome of this reaction



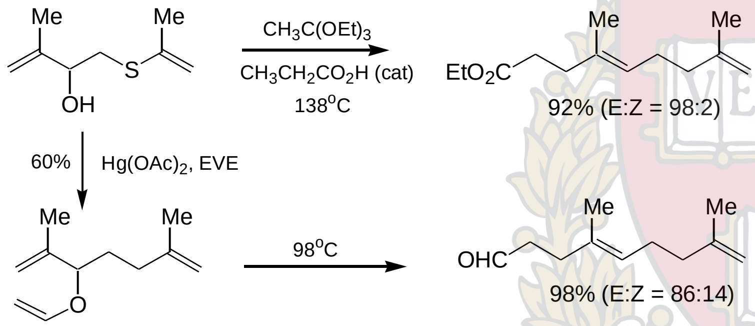
Kurth, *JOC* **1985**, *50*, 1840

Johnson Orthoester Claisen

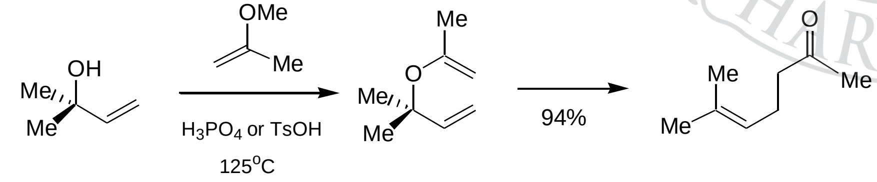
- Lead paper: Johnson, Faulkner, Peterson, *JACS* **1970**, *92*, 741

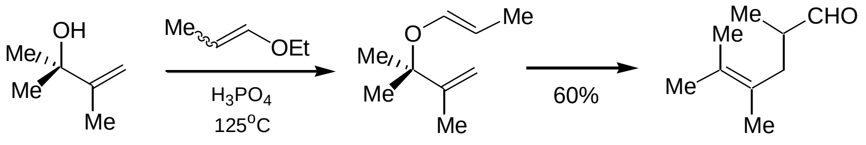


- Compare the two variants:



The Saucy Marbet Alternative

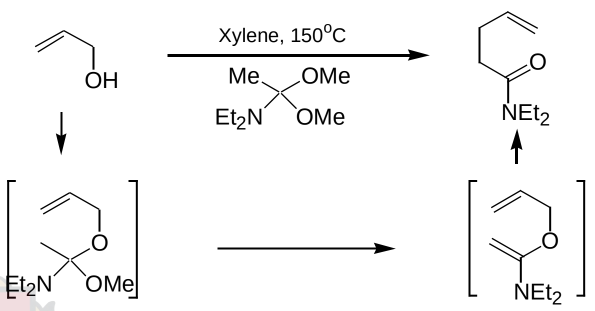


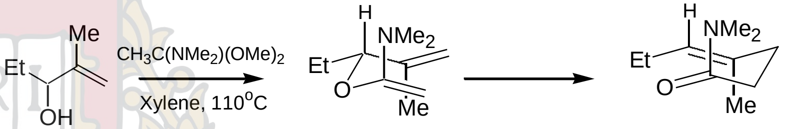


Saucy, Marbet, *Helv. Chim. Acta* **1967**, *50*, 2091,2095

Eschenmoser-Claisen

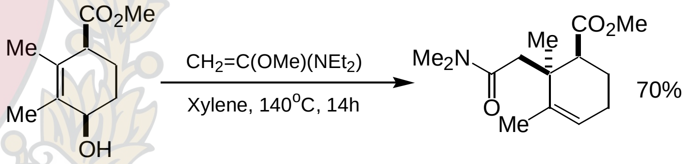
Eschenmoser, A. *Helv. Chem. Acta* **1964**, *47*, 2425; *Helv. Chim.Acta* **1969**, *52*, 1030.



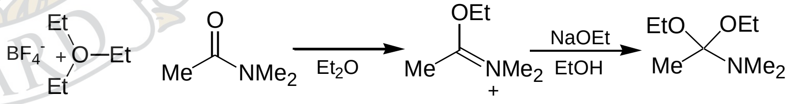


Faulkner and Peterson

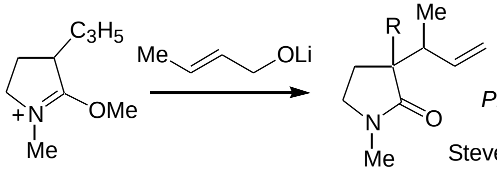
High yield, E:Z = 99:1



- Synthesis of Amide Acetals

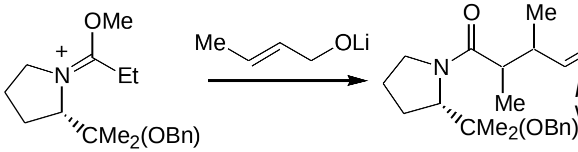


- Reactions to ponder:



diastereoselection 6:1
Predict the major diastereomer

Stevenson, *Tet. Let.* **1991**, *32*, 4199



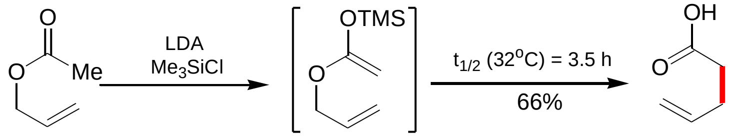
Predict the major diastereomer
Welch, *JACS* **1987**, *109*, 6716

Ireland Enolate Claisen Rearrangement

Ireland-Enolate Claisen

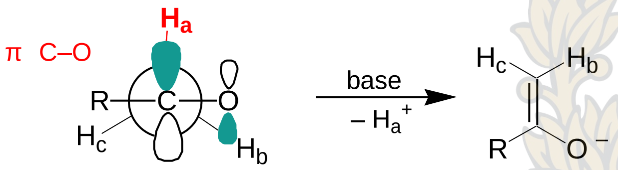
- **Reviews** Pereira, *Aldrichimica Acta* **1993**, *26*, 17-29 (Ireland-Claisen)
  Ireland, *Aldrichimica Acta* **1988**, *21*, 59-69 (Claisen-related)

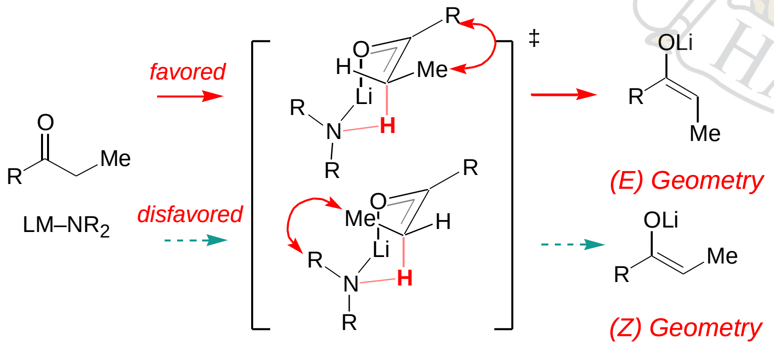
Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868



Enolization: Amide Bases

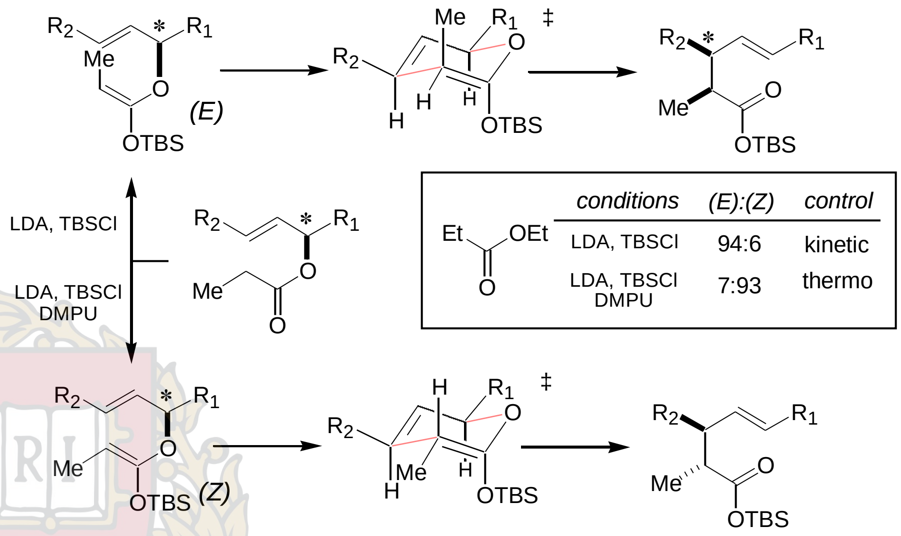
Stereoelectronic Requirements: The α-C-H bond must be able to overlap with π C–O





The Ireland Model (*JACS* **1976**, *98*, 2868)
Narula, Tetrahedron Lett. **1981**, *22*, 4119
more recent study: Ireland, *JOC* **1991**, *56*, 650

Substituted enolates afford an additional stereocenter

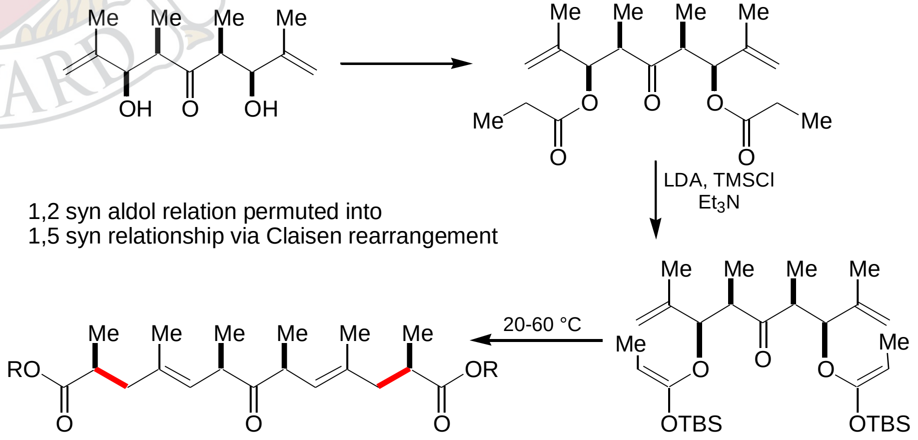


conditions	(E):(Z)	control
LDA, TBSCl	94:6	kinetic
LDA, TBSCl DMPU	7:93	thermo

key study: Ireland, *JOC* **1991**, *56*, 650 and earlier cited papers

Double Claisen Rearrangements are also possible

Paterson, *Tet Lett* **1991**, *32*, 7601

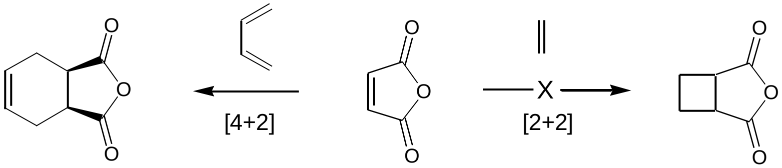


1,2 syn aldol relation permuted into
1,5 syn relationship via Claisen rearrangement

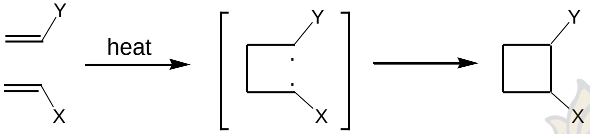
63% yield (diastereoselection 86%)

Cycloaddition Reactions-1

Why does maleic anhydride react easily with 1,3-butadiene, but not with ethylene? So what are the "rules"?



■ The related reaction of 2 ethylenes is nonconcerted: [2 + 2] cycloaddition

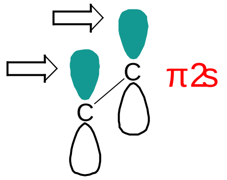


■ We also know that the photochemical variant is concerted

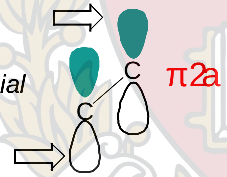
The frontier orbitals of the reacting species must have the proper symmetries

■ Nomenclature

suprafacial

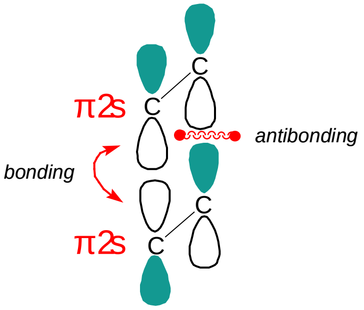


antarafacial

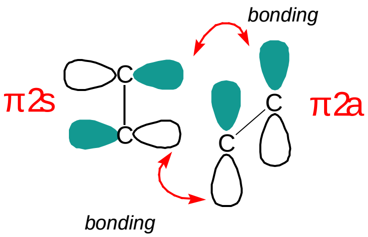


Using this nomenclature, the Diels-Alder reaction is a $\pi 4s + \pi 2s$ cycloaddition

■ Consider [2 + 2] cycloaddition: Thermal activation [$\pi 2s + \pi 2s$]

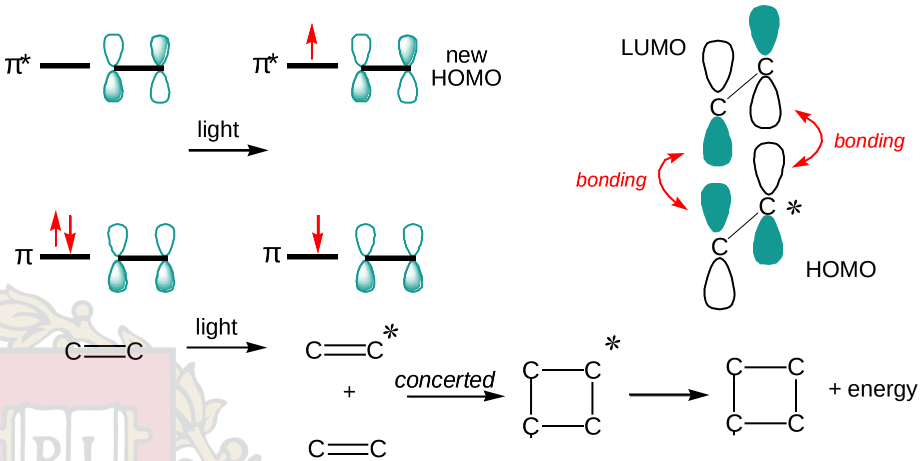


[$\pi 2s + \pi 2s$] "forbidden"

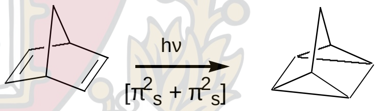


[$\pi 2s + \pi 2a$] "allowed"

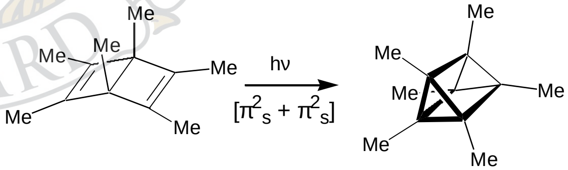
■ Consider [2 + 2] cycloaddition: Photochemical activation [$\pi 2s + \pi 2s$]



[2+2] Cycloaddition - Examples



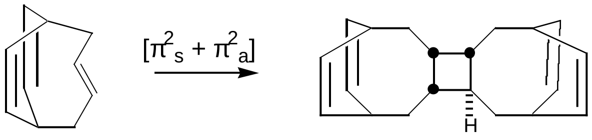
Quadricyclane Dauben, *Tet.* **1961**, *15*, 197.



Dewarbenzene-Derivative

Prismane-Der.

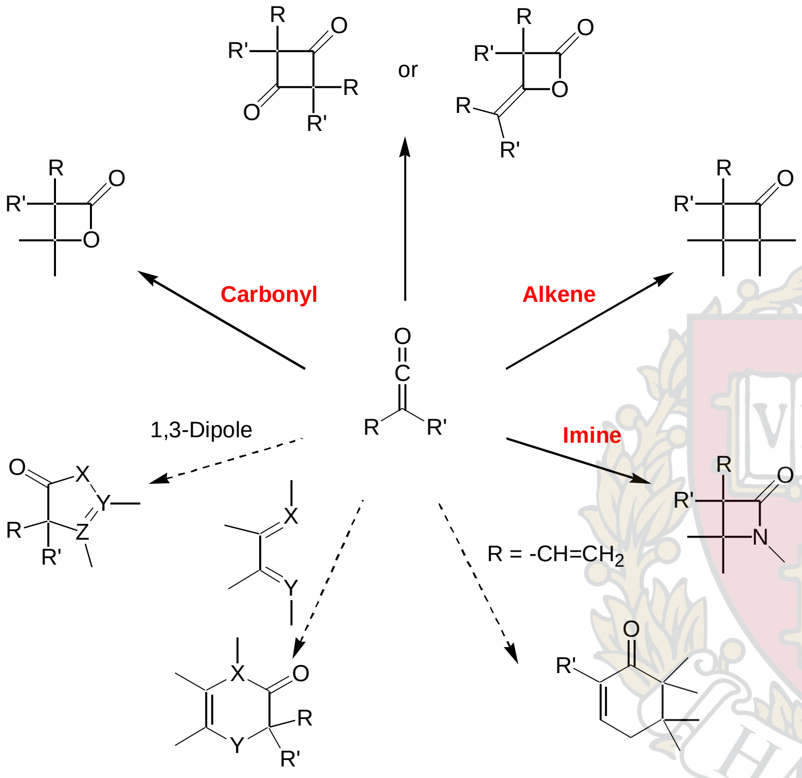
Schäfer, *AC* **1967**, *79*, 54.



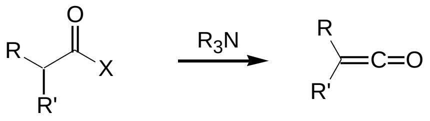
must be antarafical for indicated stereochem

TL **1967**, 4357, 4723.

Summary of Ketene Cycloadditions



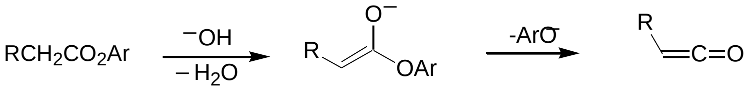
Ketene Preparation

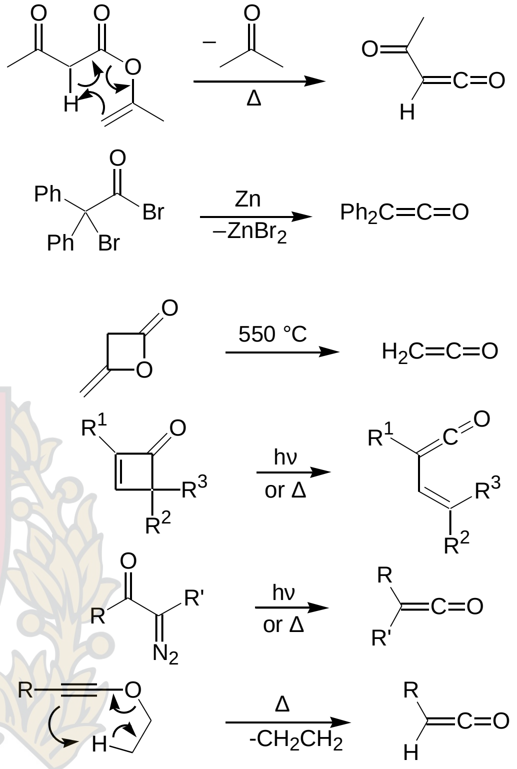


Staudinger Reaction (very general)

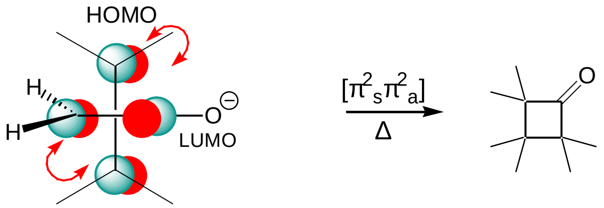
X = Cl, Ts, AcO, DCC, etc...

$(CH_3CO)_2O \xrightarrow{\Delta} H_2C{=}C{=}O + AcOH$

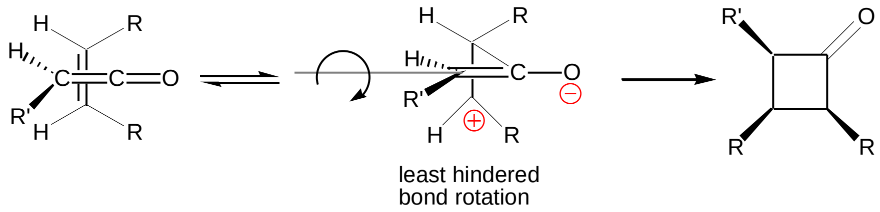




FMO Analysis



[2+2]: Stepwise Versus Concerted



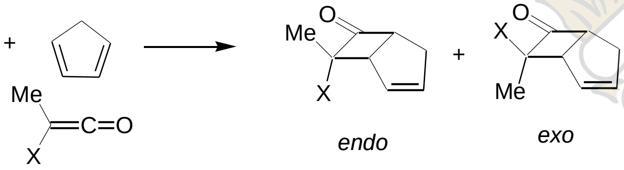
Stepwise

- Very large polar effects
- E olefins yield a mixture of *cis* and *trans* products
- Solvent effects observed, but it could merely be a ground state effect
- KIE seen for many reactions support stepwise mechanism
- Calculations (Wang and Houk) show a highly asynchronous transition state in the gas phase reaction
- All stereochemical outcomes can be rationalized assuming a stepwise mechanism

Concerted

- Ketenes add stereoselectively to Z alkenes
- Z olefins are much more reactive than E

Solvent Effects

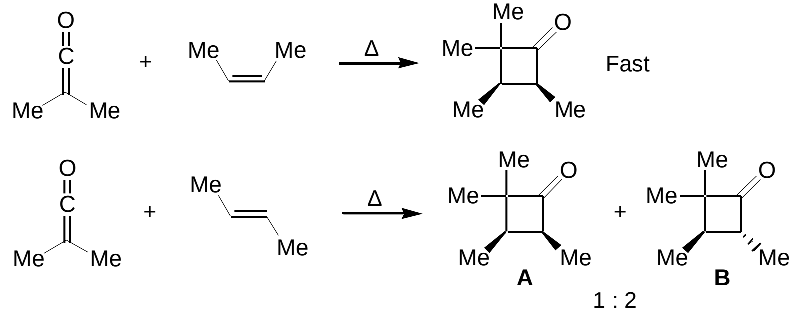


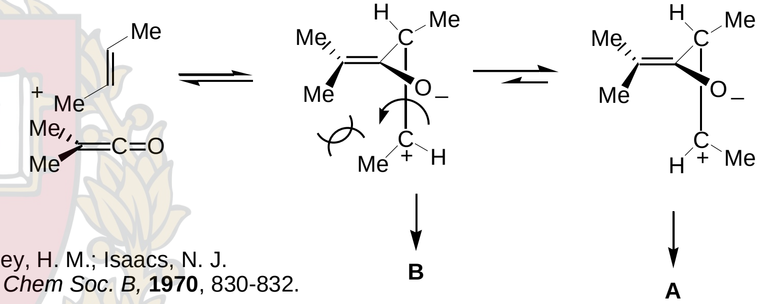
X	Solvent	*endo / exo*	X	Solvent	*endo / exo*
Cl	hexane	4.3 / 1	Br	hexane	0.71 / 1
Cl	Et_3N	2.2 / 1	Br	Et_3N	0.28 / 1
Cl	$CHCl_3$	1.6 / 1	Br	CH_3CN	0.14 / 1
Cl	CH_3CN	0.59 / 1			

- Solvent effects implicate a zwitterionic intermediate

Brady,et. al, *JACS* **1970**, *92*, 146-148.

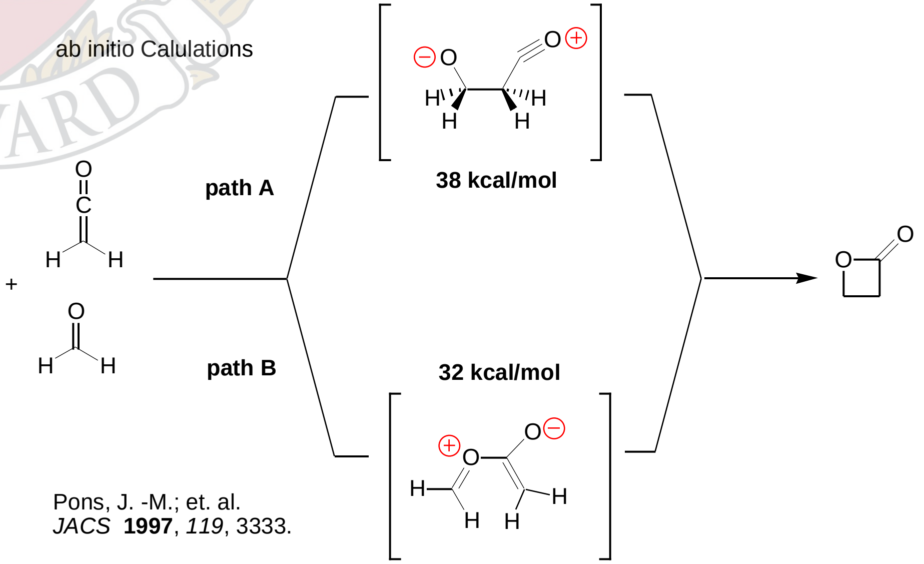
Ketene-Alkene [2+2]





Frey, H. M.; Isaacs, N. J.
J. Chem Soc. B, **1970**, 830-832.

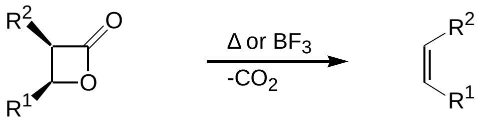
Ketenes + Aldehydes Afford β-Lactones

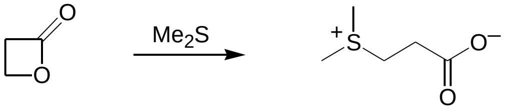


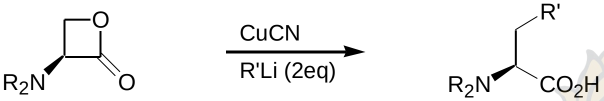
Pons, J. -M.; et. al.
JACS **1997**, *119*, 3333.

Cycloaddition Reactions-4

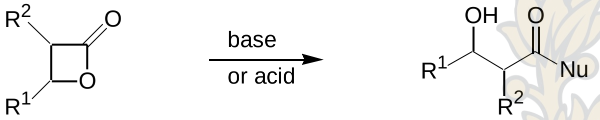
Transformations of β-Lactones





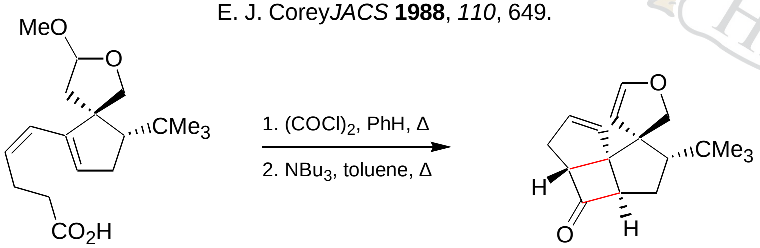


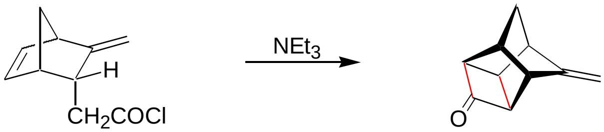
Arnold, L. D.; Drover, J. C. J.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *107*, 4649.



Nu = OH_2, ROH, R_2NH

Application in Natural Product Synthesis: Ginkolide B, E. J. Corey*JACS* **1988**, *110*, 649.

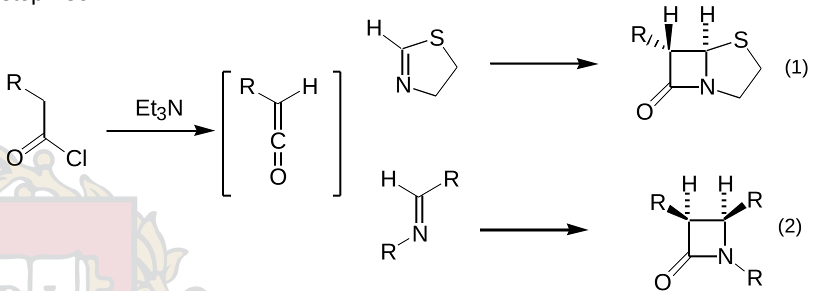




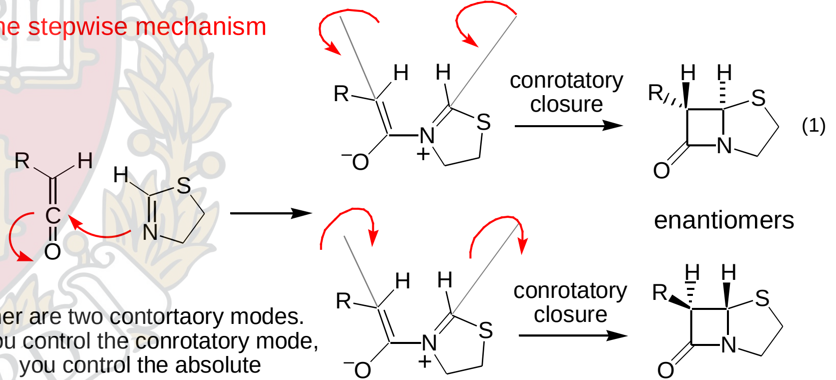
JOC **1982**, *47*, 3470.

The Staudinger Reaction

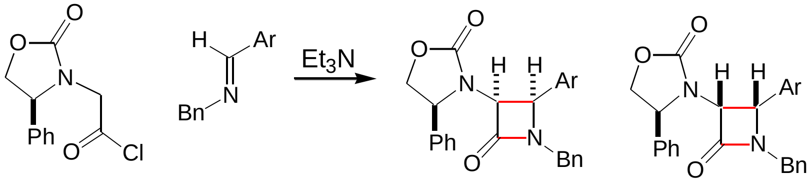
In this process, the illustrated ketene, generated *in situ* from an acid chloride, undergoes reaction with the indicated substrates to form β-lactams in a stereoselective process. When the azo-methine (RN=CHR) geometry in the reactant is (Z) the product stereochemistry is trans (eq 1). In a complementary fashion, the (E) imine affords the cis-substituted product (eq 2). While this transformatlion could be viewed as a [2s+2a] cycloaddition, it is felt that this reaction is stepwise.



■ The stepwise mechanism



Ther are two contortaory modes. If you control the conrotatory mode, you control the absolute stereochemistry of the reaction:



Evans, Sjogren*Tet. Lett.* **1985**, *26*, 3783, 3787.

See also Evans, Williams, *Tet. Lett*. **1988**, *29*, 5065.

diastereoselection > 95:5
80-90% yields

"[2+2] photocycloaddition/fragmentation strategies for the synthesis of natural and unnatural products.", Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003.

"Stereoselective intermolecular [2+2]-photocycloaddition reactions and their application in synthesis.", Bach, T. *Synthesis* **1998**, 683.

Articles and monographs of Significance

Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer
4.2 Heterodienophile Additions to Dienes, S. M. Weinreb
4.3 Heterodiene Additions, D. L. Boger
4.4 Intramolecular Diels-Alder Reactions, W. R. Roush
4.5 Retrogade Diels-Alder Reactions, R. W. Sweger, A. W. Czarnik

Intramolecular Diels-Alder Reactions, Org Rxns, Vol. 32, **1984**

Asymmetric Cycloaddition Reactions (Inter- & Intramolecular DA rxns)
Asymmetric Synthesis, Vol. 3 Morrison, J. D., Academic Press, **1984**

Hetero Diels-Alder Methodology in Organic Synthesis
Boger, D.L. and Weinreb, S.N., Academic Press, 1987

Natural Products Synthesis Through Pericyclic Reactions
Desimoni, Tacconi, Barco, Polini, ACS Monograph 180, 1983, Chapter 5,

Asymmetric Diels-Alder Reactions with Chiral Enoates as Dienophiles
Modern Synthetic Methods **1986**, Scheffold, Ed. Springer-Verlag,

Intramolecular Diels-Alder and Alder Ene Rxns, D. F. Taber, Springer-Verlag, **1984**

Synthetic Aspects of D-A Cycloadditions with Heterodienophiles
Weinreb, *Tetrahedron*, **1982**, *38*, 3087-3128

The Intramolecular DA Rxn: recent advances and synthetic applications
Fallis, *Can. J. Chem.*, **1984**, *62*, 183-234

Intramolecular [4 +2] & [3 + 2] Cycloadditions in Organic Synthesis
Oppolzer, *Angew. Chem. Int. Ed.*, **1977**, *16*, 10-23

Preparation & DA Reactions of Heterosubstituted 1, 3-Dienes
Petrzilka, *Synthesis*, **1981**, 753-786

DA Reactions of Azadienes
Boger, *Tetrahedron*, **1983**, *39*, 2869-2939

Silyloxydienes in Organic Synthesis
Danishefsky, *Acct. Chem. Res.*, **1981**, *14*, 400-406

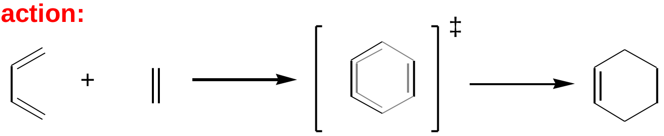
DA Reactions Part I: New Preparative Aspects
Sauer, *Angew. Chem. Int. Ed.*, **1966**, *5*, 211-230

DA Reactions Part II: The Reaction Mechanism
Sauer, *Angew. Chem. Int. Ed.*, **1967**, *6*, 16-33

Mechanistic Aspects of Diels-Alder Reactions: A Critical Survey
Sauer, *Angew. Chem. Int. Ed.*, **1980**, *19*, 779-807

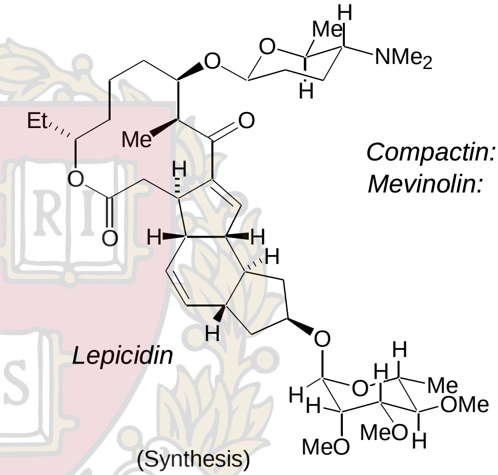
Retro-DA Strategy in Natural Products Synthesis
Ichihara, *Synthesis*, **1987**, 207-222

The Reaction:



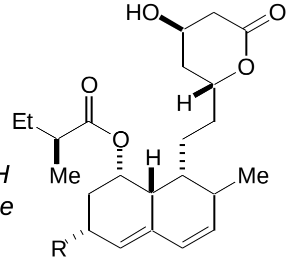
Representative natural products displaying the Diels-Alder retron:

These natural products could well have incorporated the DA rxn into their biosynthesis.



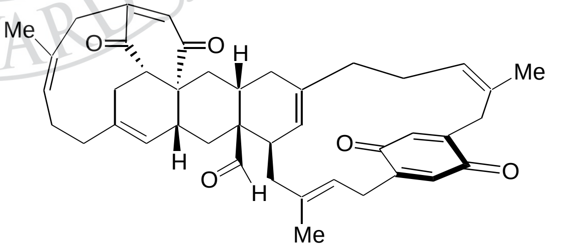
Lepicidin

(Synthesis)
Evans, *JACS*, **1993**, *115*, 4497



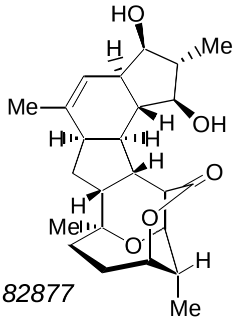
Compactin: R = H
Mevinolin: R = Me

(Biosynthesis) *JACS* **1985**, *107*, 3694
Clive, *JACS* **1988**, *110*, 6914
Kozikowski, *JOC* **1987**, *52*, 3541



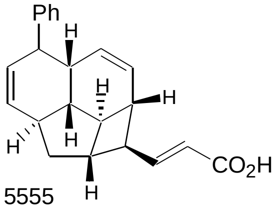
Longithorone A

(Synthesis)
Shair, *JACS,* **2002**, *124*, 773



FR182877

(Synthesis)
Sorensen, *JACS*, **2002**, *124*, 4552
Evans, *ACIE* **2002**, *41*, 1787



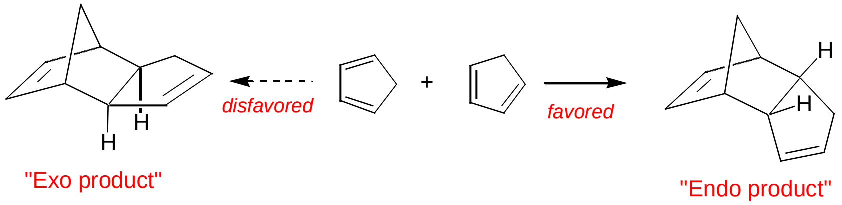
Endiandric Acid B

(Syntheses)
Nicolaou, *JACS* **1982**, *104*, 5555

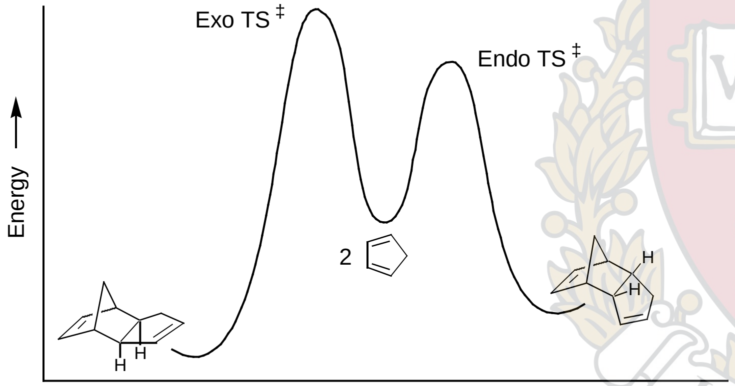
Diels-Alder Reaction-Orbital Symmetry Considerations

The Alder Endo Rule

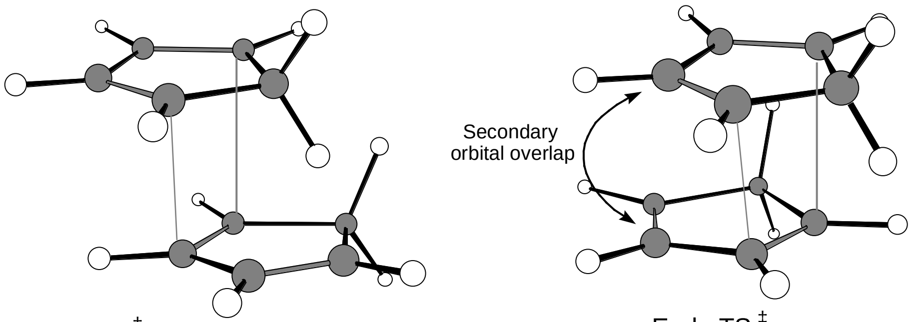
The following observation illustrates an example of the Alder Rule which will be defined below.



Observation: The endo Diels-Alder adduct is formed faster even though the exo product is more stable. There is thus some special stabilization in the transition state leading to the endo product which is lacking the exo transition state.



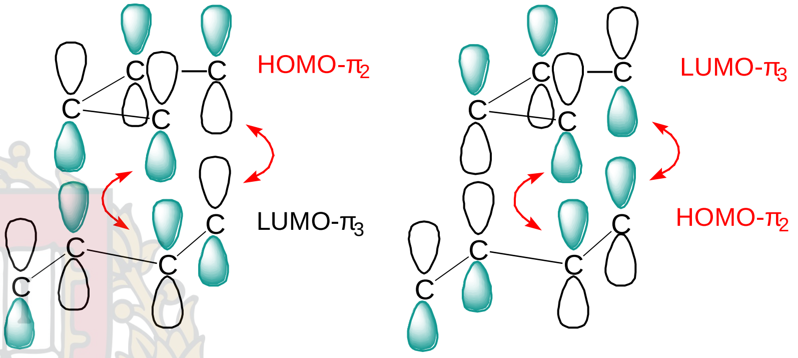
- Of the two possible transition states, the one having the "greatest accumulation of interacting double bonds will be preferred" (the Alder Endo Rule). Secondary orbital overlap is noted below.



Exo TS ‡ Endo TS ‡

Orbital Symmetry Considerations for Diels Alder Reaction

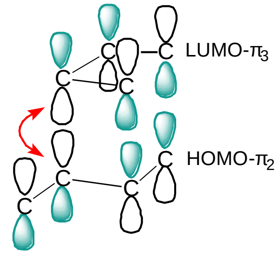
If the symmetries of the frontier MO's of reacting partners are "properly matched" the reaction is referred to as "symmetry-allowed". The Diels-Alder reaction is such a case. As illustrated, the HOMO and LUMO of both the diene and dienophile, which in this case are the same, will constructively overlap as indicated in formation of both sigma bonds.



- Primary orbital overlap leads directly to the formation of new chemical bonds.

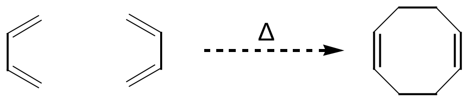
Frontier MO Explanation for the Endo Rule

- Secondary (transient) orbital overlap can also occcur in the stabilization of certain transition state geometries. Such a transient stabilizing interaction can occur in the endo, but not exo, transition state:

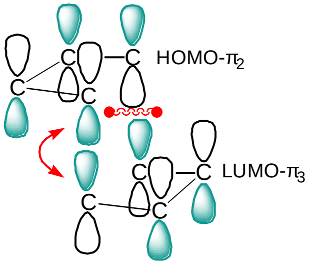


The Other Dimerization Possibility for Butadiene

Does the possibility for the following concerted dimerization exist?



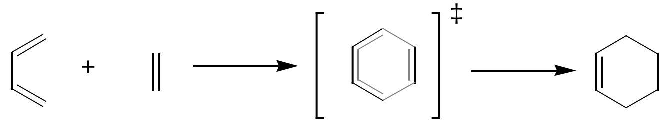
- Note that the termini only match at one end for the HOMO-LUMO pairing. Hence we say that the symmetry requirements for the reaction in question are not met. This does not mean that the reaction will not occur, only that the reaction will not be concerted. Such reactions are called "symmetry-forbidden".



Additional Reading: Lowry & Richardson,
Chapter 10, theory of Pericyclic Rxns pp 839-900

Diels-Alder Reaction: The Transition Structure

Transition State Modelling is Coming of Age

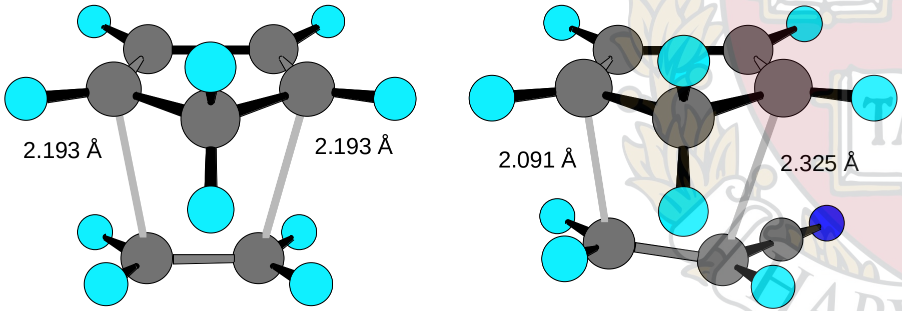


- The lengths of the forming C–C bonds are Ca. 1.5 times the normal bond distance. This factor comes out of the *ab initio* work of Jorgensen & Houk

leading references:
Jorgensen, *JACS* **1993**, *115*, 2936-2942
Houk, Jorgensen, *JACS* **1989**, *111*, 9172

Transition Structures of Hydrocarbon Pericyclic Reactions
Houk *Angew. chem. Int. Ed.* **1992**, *31*, 682-708

- Bond formation is not synchronus with substituted dienophiles (Jorgensen)



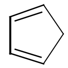
exptl { $\Delta H^{\ddagger}$ = 22.5 kcal/mol; $\Delta S^{\ddagger}$ = -32.1 eu

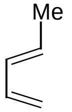
rel rate = 1

$\Delta H^{\ddagger}$ = 14.0 kcal/mol
$\Delta S^{\ddagger}$ = -38.3 eu

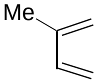
rel rate = 10^{+5}

- Diene Reactivity as measured against Maleic anhydride

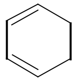

log k = 4.96

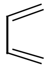


log k = 2.36



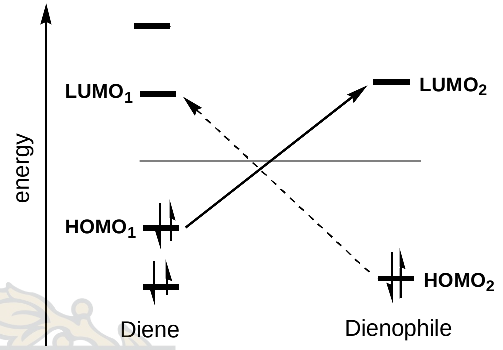
log k = 2.19


log k = 2.12


log k = 1.83

Sauer, *Angew. Chem. Int. Ed.*, **1980**, *19*, 779-807

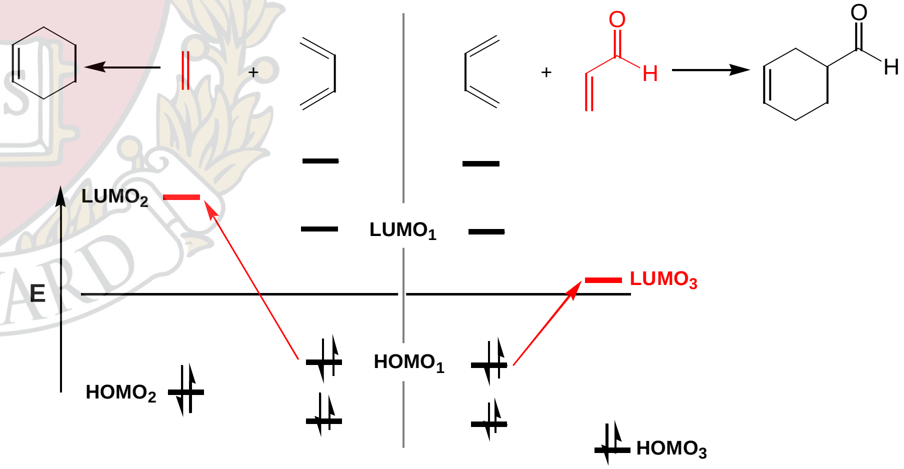
- Lewis Acid Catalysis of the reaction is possible: Yates & Eaton, *JACS* **1960**, *82*, 4436



The Critical Energy Difference:
E($LUMO_1$) - **E**($HOMO_2$)
or
E($LUMO_2$) - **E**($HOMO_1$)

- The closer the two orbitals are in energy, the better they interact
- As ΔE decreases for the relevant ground state FMOs, rxn rates increase

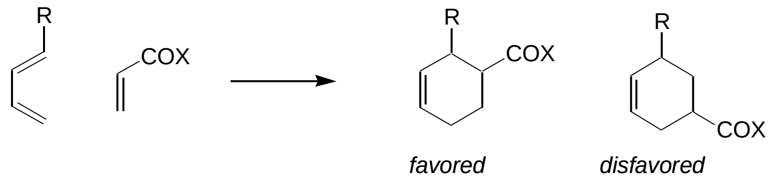
Ethylene & Butadiene Vs Butadiene & Acrolein



ΔE ($LUMO_3$-$HOMO_1$) < ΔE ($LUMO_2$-$HOMO_1$) ⟹ *Rate Acceleration*

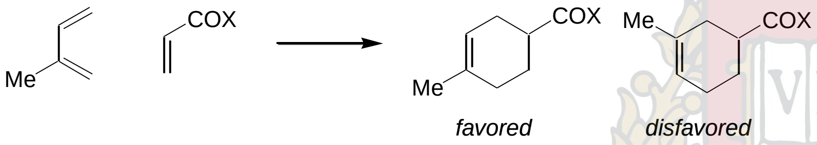
Lewis acid catalysis not only dramatically increases rates by ca 10^{+6} it also improves reaction regiochemistry & endo diastereoselectivity

Orientation of Reacting Partners



for R = CO_2H 100 : 00 @ 75 °C
X = OH 4.5 : 01 @ 100 °C

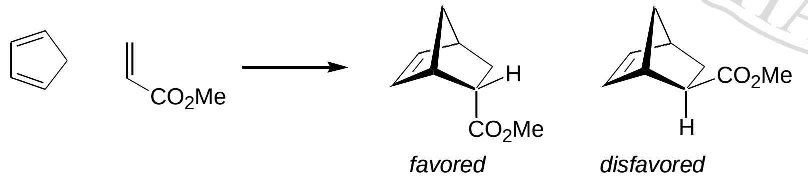
Lewis acid catalysis improves orientation



toluene, 120 °C	59 : 41
C_6H_6, $SnCl_4$, 25 °C	96 : 04

In general, 1-substituted dienes are more regioselective than their 2-substituted counterparts: Sauer, Angew. Chem. Int. Ed., ***1967****, 6, 16-33*

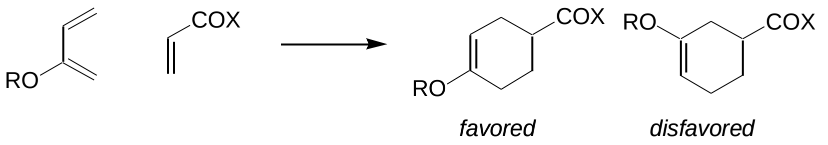
Lewis acid catalysis improves endo diastereoselection



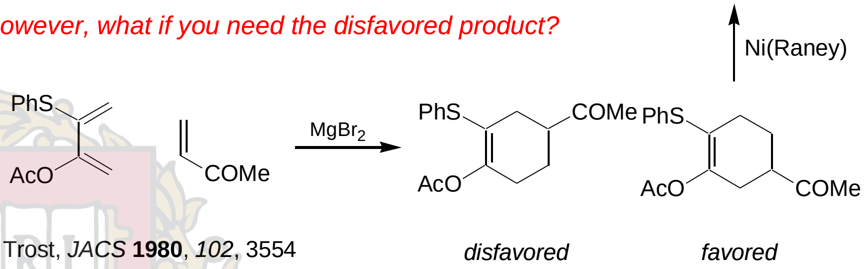
CH_2Cl_2, 0 °C	80 : 20
C_6H_6, $SnCl_4$, 25 °C	95 : 05

DA Reactions Part II: The Reaction Mechanism,
Sauer, *Angew. Chem. Int. Ed.*, **1967**, *6*, 16-33

Here is an interesting problem in reaction design

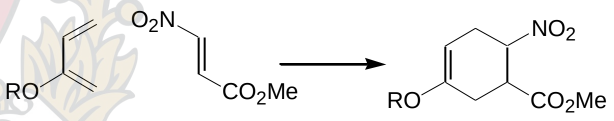


However, what if you need the disfavored product?



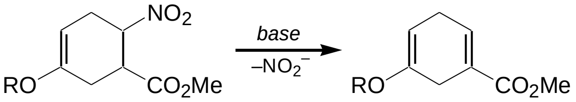
Trost, *JACS* **1980**, *102*, 3554

By employing a removable substituent, it is possible to access the normally disfavored product diastereomer

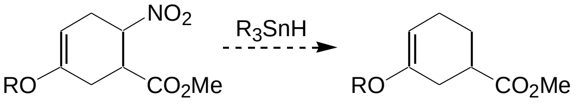


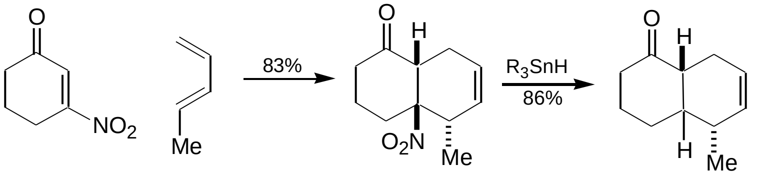
Danishefsky, *JACS* **1978**, *100*, 2918: The NO_2 FG completely dominates directivity

It then can be removed by elimination



or by reduction
Ono, *Tet.* **1985**, 4013

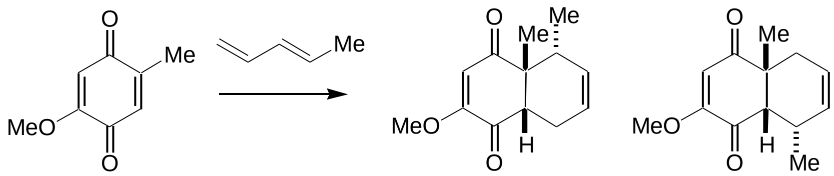




Ono, *Chem. Commun.* **1982**, 33-34

mixture of ring-fusion isomers

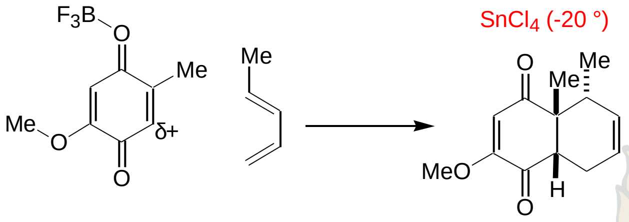
Instructive Issues of Regiocontrol with Quinone Dienophiles



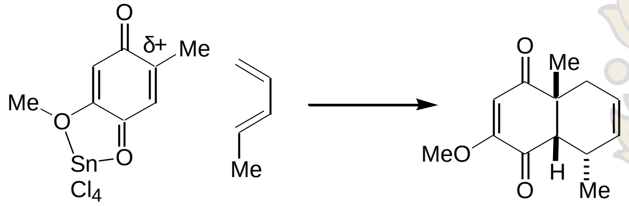
Orientation of Reacting Partners controlled by Lewis acid structure

Reusch *JOC* **1980**, *45*, 5013

Conditions	Ratio
thermal (100 °)	50 : 50
BF_3•OEt_2 (-20 °)	80 : 20
$SnCl_4$ (-20 °)	<5 : 95



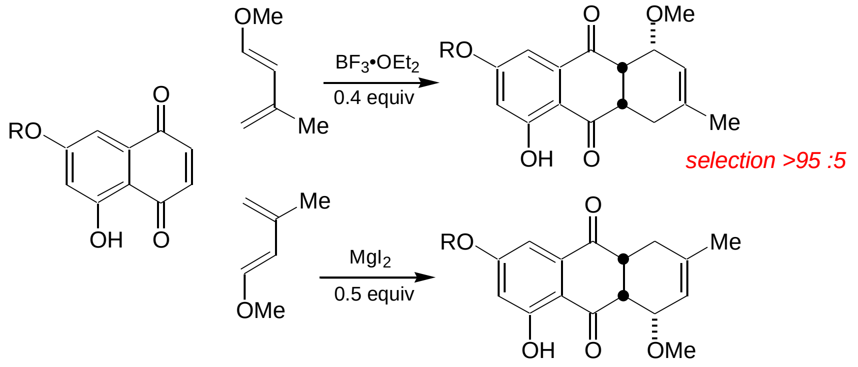
selection 80 : 20



selection >95 :5

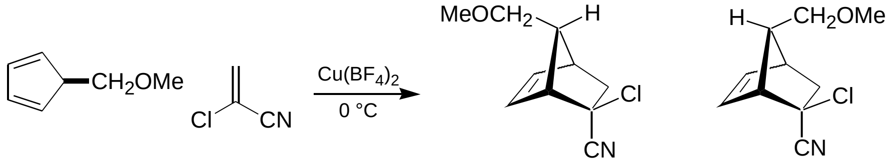
Similar results provided by Stoodley *Chem. Comm.* **1982**, 929

Kelly *Tet. Let.* **1978**, 4311



selection >95 :5

selection >95 :5



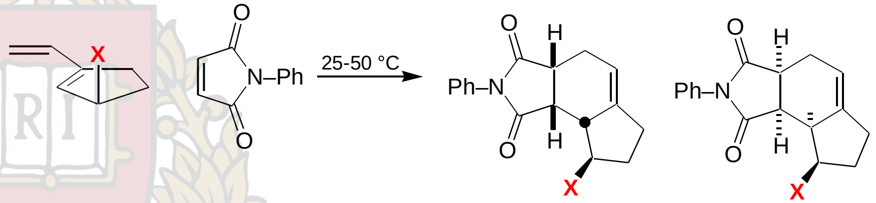
Corey, *JACS* **1969**, *91*, 5675

Ratio: 90 : 10

Diels-Alder Reactions with Chiral Dienes

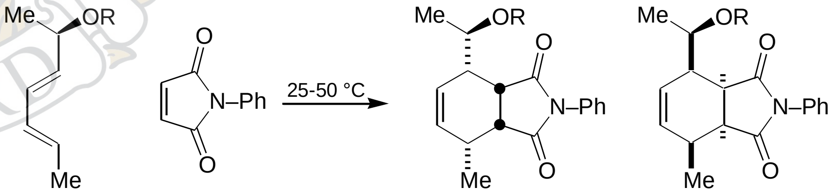
Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer, See page 347



X =	Ratio
–OH	36 : 64
–Me	83 : 17
–OMe	>97 : 3

Overman, *JACS* **1988**, *110*, 4625

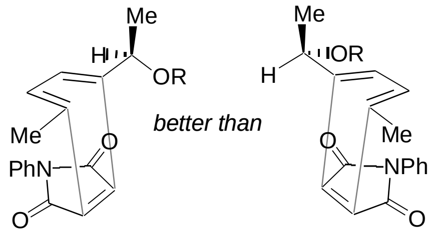


Franck, *Tet. Lett.* **1985**, *26*, 3187
Franck, *JACS* **1988**,*110*, 3257

R = Me: Ratio; 83 : 17
R = Me_3Si: Ratio; 88 : 12

Comments on the Transition State

- Avoid Eclipsing allylic substituents
- better donor (Me) anti to forming bond
- avoid gauche OR interaction



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 16

Cycloaddition Reactions-2

- The Diels-Alder Reaction

■ Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

Carey & Sundberg: **Part B**; Chapter 6
Cycloadditions, Unimolecular Rearrangements
Thermal Eliminations

Fleming: Chapter 4
Thermal Pericyclic Reactions

Matthew D. Shair

Friday
October 25, 2002

The Diels-Alder Cycloaddition Reactions

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235 **(pdf)**

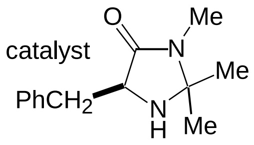
"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, J. S.; Evans, D. A. *Acc. Chem. Res*. **2000**, *33*, 325-335. **(pdf)**

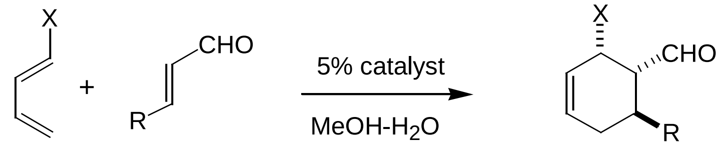
"New Strategies for Organic Catalysis: The first Highly Selective Organocatalytic Diels-alder Reaction", MacMillan, *JACS*, **2000**, 122, 4243. **(pdf)**

"New Strategies for Organic Catalysis: The first Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition", MacMillan, *JACS*, **2000**, 122, 4243. **(pdf)**

■ Problem of the Day:

Rationalize the sense of asymmetric induction for this Diels-Alder Reaction reported by MacMillan, *JACS*, **2000**, 122, 4243. **(pdf)**





Articles and monographs of Significance

Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

- 4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer
- 4.2 Heterodienophile Additions to Dienes, S. M. Weinreb
- 4.3 Heterodiene Additions, D. L. Boger
- 4.4 Intramolecular Diels-Alder Reactions, W. R. Roush
- 4.5 Retrogade Diels-Alder Reactions, R. W. Sweger, A. W. Czarnik

Intramolecular Diels-Alder Reactions, Org Rxns, Vol. 32, **1984**

Asymmetric Cycloaddition Reactions (Inter- & Intramolecular DA rxns)
Asymmetric Synthesis, Vol. 3 Morrison, J. D., Academic Press, **1984**

Hetero Diels-Alder Methodology in Organic Synthesis
Boger, D.L. and Weinreb, S.N., Academic Press, 1987

Natural Products Synthesis Through Pericyclic Reactions
Desimoni, Tacconi, Barco, Polini, ACS Monograph 180, 1983, Chapter 5,

Asymmetric Diels-Alder Reactions with Chiral Enoates as Dienophiles
Modern Synthetic Methods **1986**, Scheffold, Ed. Springer-Verlag,

Intramolecular Diels-Alder and Alder Ene Rxns, D. F. Taber, Springer-Verlag, **1984**

Synthetic Aspects of D-A Cycloadditions with Heterodienophiles
Weinreb, *Tetrahedron*, **1982**, *38*, 3087-3128

The Intramolecular DA Rxn: recent advances and synthetic applications
Fallis, *Can. J. Chem.*, **1984**, *62*, 183-234

Intramolecular [4 +2] & [3 + 2] Cycloadditions in Organic Synthesis
Oppolzer, *Angew. Chem. Int. Ed.*, **1977**, *16*, 10-23

Preparation & DA Reactions of Heterosubstituted 1, 3-Dienes
Petrzilka, *Synthesis*, **1981**, 753-786

DA Reactions of Azadienes
Boger, *Tetrahedron*, **1983**, *39*, 2869-2939

Silyloxydienes in Organic Synthesis
Danishefsky, *Acct. Chem. Res.*, **1981**, *14*, 400-406

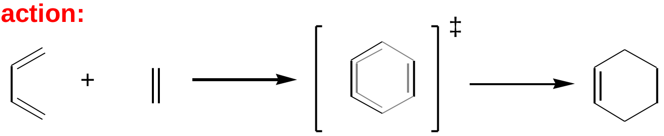
DA Reactions Part I: New Preparative Aspects
Sauer, *Angew. Chem. Int. Ed.*, **1966**, *5*, 211-230

DA Reactions Part II: The Reaction Mechanism
Sauer, *Angew. Chem. Int. Ed.*, **1967**, *6*, 16-33

Mechanistic Aspects of Diels-Alder Reactions: A Critical Survey
Sauer, *Angew. Chem. Int. Ed.*, **1980**, *19*, 779-807

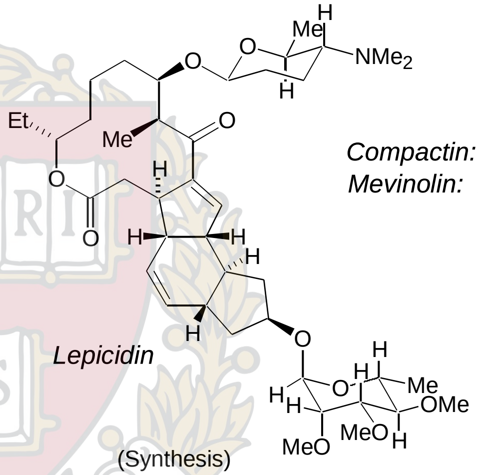
Retro-DA Strategy in Natural Products Synthesis
Ichihara, *Synthesis*, **1987**, 207-222

■ The Reaction:



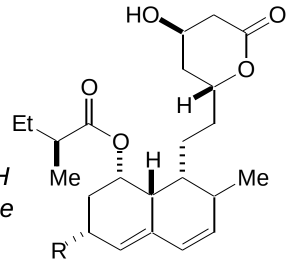
■ Representative natural products displaying the Diels-Alder retron:

These natural products could well have incorporated the DA rxn into their biosynthesis.



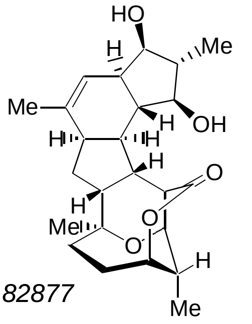
Lepicidin

(Synthesis)
Evans, *JACS*, **1993**, *115*, 4497



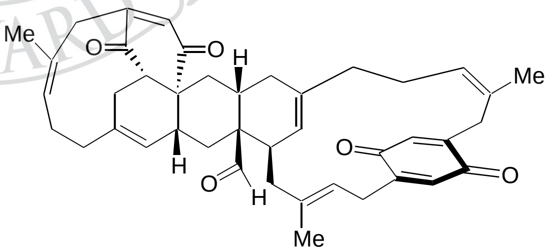
Compactin: R = H
Mevinolin: R = Me

(Biosynthesis) *JACS* **1985**, *107*, 3694
Clive, *JACS* **1988**, *110*, 6914
Kozikowski, *JOC* **1987**, *52*, 3541



FR182877

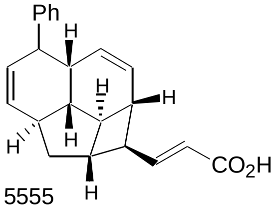
(Synthesis)
Sorensen, *JACS*, **2002**, *124*, 4552
Evans, *ACIE* **2002**, *41*, 1787



Longithorone A

(Synthesis)
Shair, *JACS,* **2002**, *124*, 773

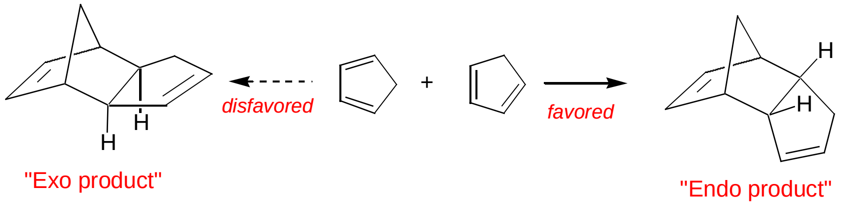
Endiandric Acid B



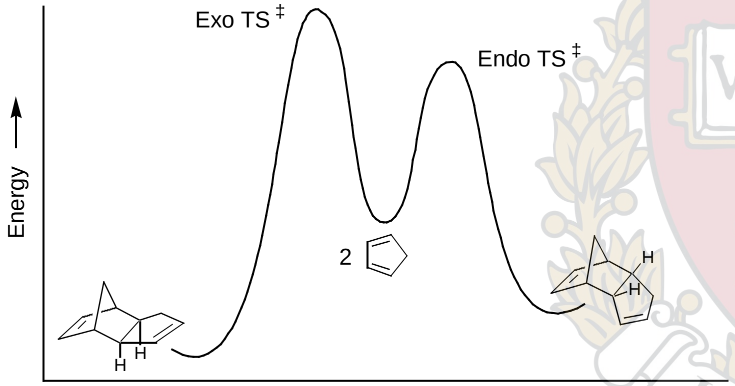
(Syntheses)
Nicolaou, *JACS* **1982**, *104*, 5555

The Alder Endo Rule

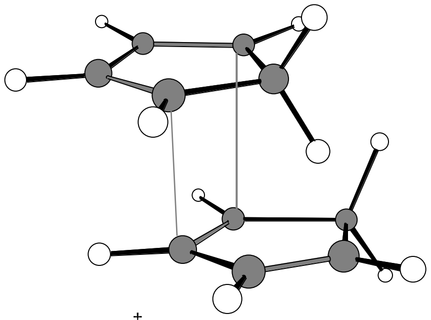
The following observation illustrates an example of the Alder Rule which will be defined below.

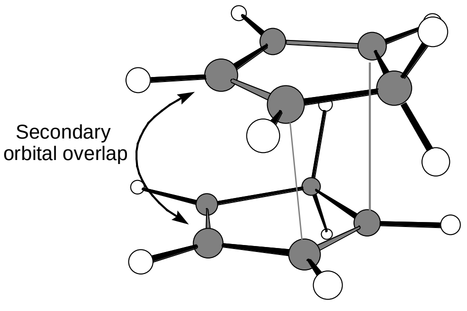


Observation: The endo Diels-Alder adduct is formed faster even though the exo product is more stable. There is thus some special stabilization in the transition state leading to the endo product which is lacking the exo transition state.



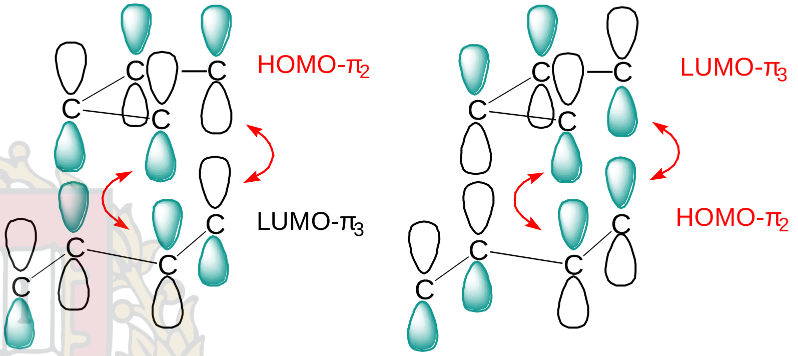
- Of the two possible transition states, the one having the "greatest accumulation of interacting double bonds will be preferred" (the Alder Endo Rule). Secondary orbital overlap is noted below.





Orbital Symmetry Considerations for Diels Alder Reaction

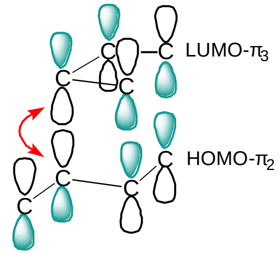
If the symmetries of the frontier MO's of reacting partners are "properly matched" the reaction is referred to as "symmetry-allowed". The Diels-Alder reaction is such a case. As illustrated, the HOMO and LUMO of both the diene and dienophile, which in this case are the same, will constructively overlap as indicated in formation of both sigma bonds.



- Primary orbital overlap leads directly to the formation of new chemical bonds.

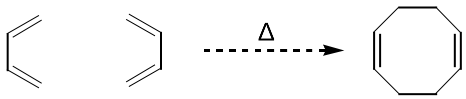
Frontier MO Explanation for the Endo Rule

- Secondary (transient) orbital overlap can also occcur in the stabilization of certain transition state geometries. Such a transient stabilizing interaction can occur in the endo, but not exo, transition state:

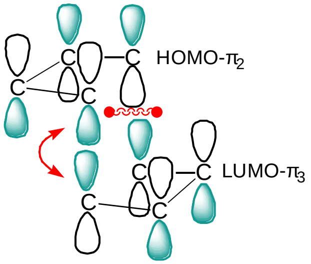


The Other Dimerization Possibility for Butadiene

Does the possibility for the following concerted dimerization exist?

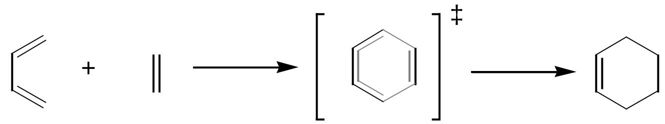


- Note that the termini only match at one end for the HOMO-LUMO pairing. Hence we say that the symmetry requirements for the reaction in question are not met. This does not mean that the reaction will not occur, only that the reaction will not be concerted. Such reactions are called "symmetry-forbidden".



Additional Reading: Lowry & Richardson, Chapter 10, theory of Pericyclic Rxns pp 839-900

Transition State Modelling is Coming of Age

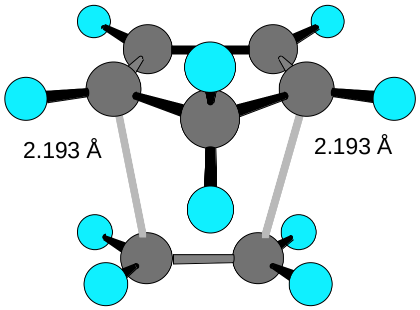


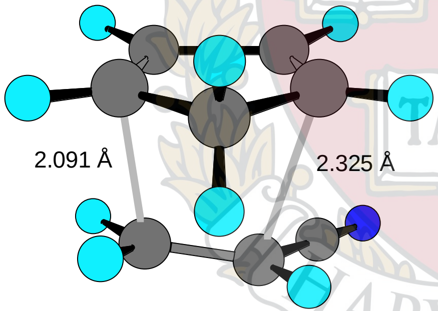
- The lengths of the forming C–C bonds are Ca. 1.5 times the normal bond distance. This factor comes out of the *ab initio* work of Jorgensen & Houk

leading references: Jorgensen, *JACS* **1993**, *115*, 2936-2942
Houk, Jorgensen, *JACS* **1989**, *111*, 9172

Transition Structures of Hydrocarbon Pericyclic Reactions
Houk *Angew. chem. Int. Ed.* **1992**, *31*, 682-708

- Bond formation is not synchronus with substituted dienophiles (Jorgensen)





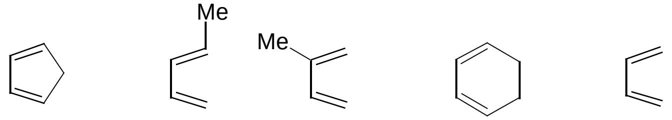
exptl $\left\{ \begin{array}{l} \Delta H^{\ddagger} = 22.5 \text{ kcal/mol} \\ \Delta S^{\ddagger} = -32.1 \text{ eu} \end{array} \right.$

rel rate = 1

$\Delta H^{\ddagger}$ = 14.0 kcal/mol
$\Delta S^{\ddagger}$ = -38.3 eu

rel rate = 10^{+5}

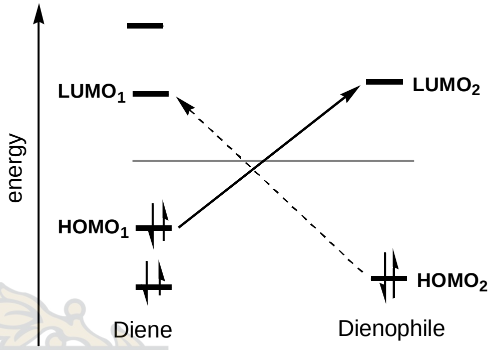
- Diene Reactivity as measured against Maleic anhydride



log k = 4.96 log k = 2.36 log k = 2.19 log k = 2.12 log k = 1.83

Sauer, *Angew. Chem. Int. Ed.*, **1980**, *19*, 779-807

- Lewis Acid Catalysis of the reaction is possible: Yates & Eaton, *JACS* **1960**, *82*, 4436

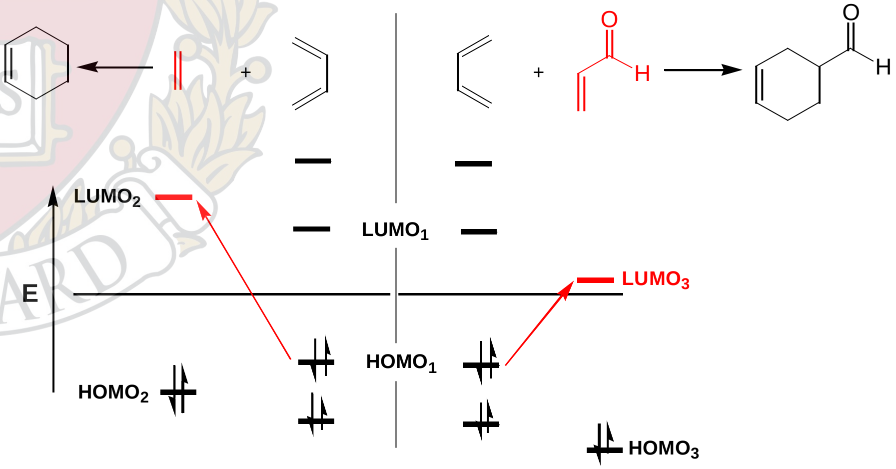


The Critical Energy Difference:

E(LUMO$_1$) - **E**(HOMO$_2$)
or
E(LUMO$_2$) - **E**(HOMO$_1$)

- The closer the two orbitals are in energy, the better they interact
- As ΔE decreases for the relevant ground state FMOs, rxn rates increase

Ethylene & Butadiene Vs Butadiene & Acrolein

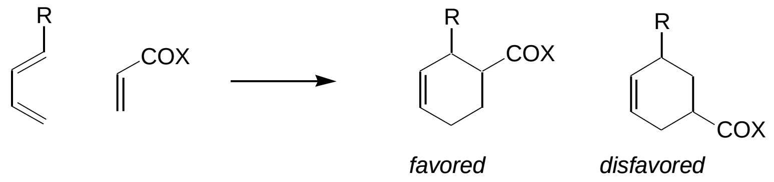


ΔE (LUMO$_3$-HOMO$_1$) < ΔE (LUMO$_2$-HOMO$_1$) $\Longrightarrow$ *Rate Acceleration*

Lewis acid catalysis not only dramatically increases rates by ca 10^{+6} it also improves reaction regiochemistry & endo diastereoselectivity

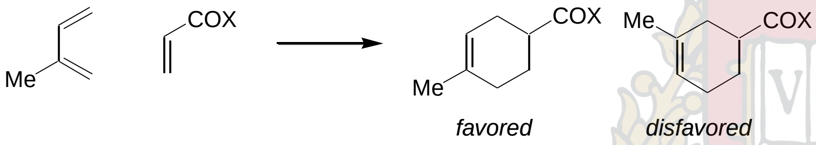
Diels-Alder Reaction: Regiochemistry

■ Orientation of Reacting Partners



for R = CO_2H, X = OH   100 : 00 @ 75 °C
4.5 : 01 @ 100 °C

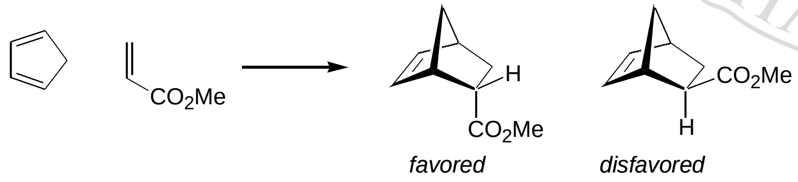
Lewis acid catalysis improves orientation



toluene, 120 °C	59 : 41
C_6H_6, $SnCl_4$, 25 °C	96 : 04

In general, 1-substituted dienes are more regioselective than their 2-substituted counterparts: *Sauer, Angew. Chem. Int. Ed.,* ***1967****, 6, 16-33*

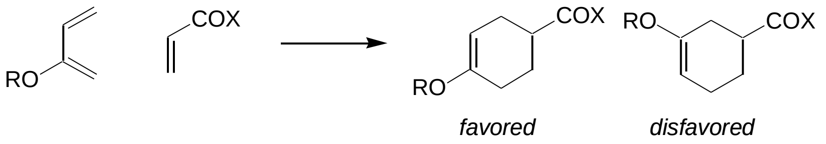
Lewis acid catalysis improves endo diastereoselection



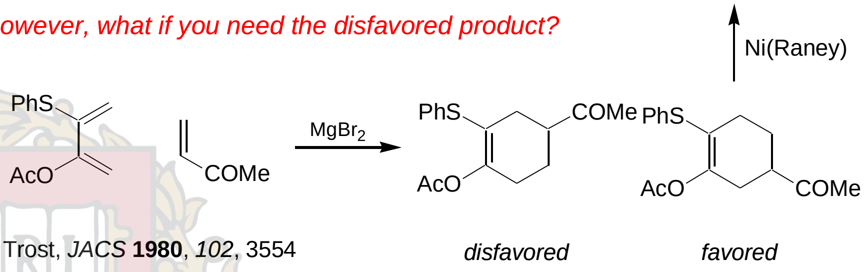
CH_2Cl_2, 0 °C	80 : 20
C_6H_6, $SnCl_4$, 25 °C	95 : 05

DA Reactions Part II: The Reaction Mechanism,
Sauer, *Angew. Chem. Int. Ed.*, **1967**, *6*, 16-33

Here is an interesting problem in reaction design

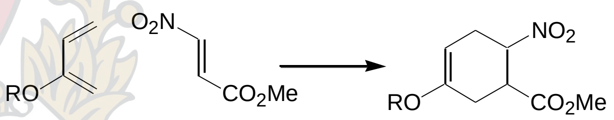


However, what if you need the disfavored product?



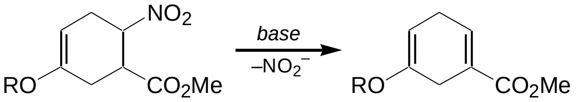
Trost, *JACS* **1980**, *102*, 3554

By employing a removable substituent, it is possible to access the normally disfavored product diastereomer

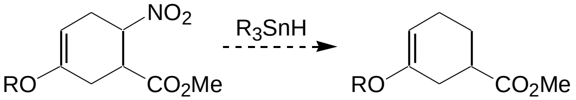


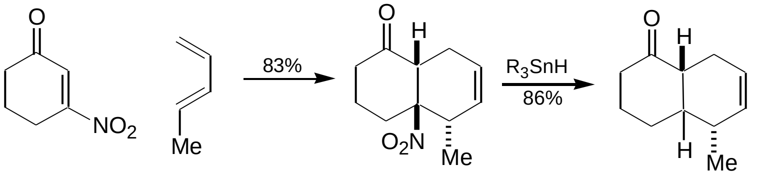
Danishefsky, *JACS* **1978**, *100*, 2918: The NO_2 FG completely dominates directivity

It then can be removed by elimination



or by reduction
Ono, *Tet.* **1985**, 4013

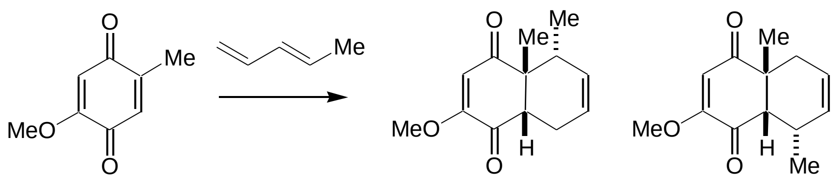




mixture of ring-fusion isomers

Ono, *Chem. Commun.* **1982**, 33-34

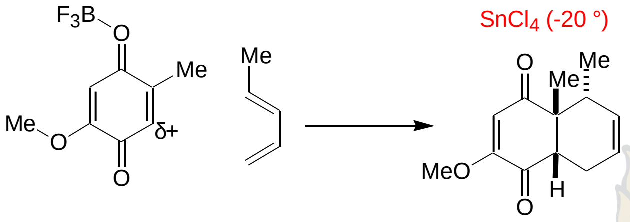
Instructive Issues of Regiocontrol with Quinone Dienophiles



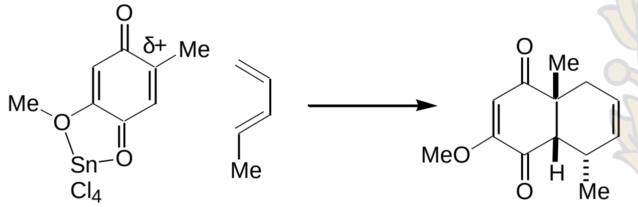
Orientation of Reacting Partners controlled by Lewis acid structure

Reusch *JOC* **1980**, *45*, 5013

Conditions	Ratio
thermal (100 °)	50 : 50
BF_3•OEt_2 (-20 °)	80 : 20
$SnCl_4$ (-20 °)	<5 : 95



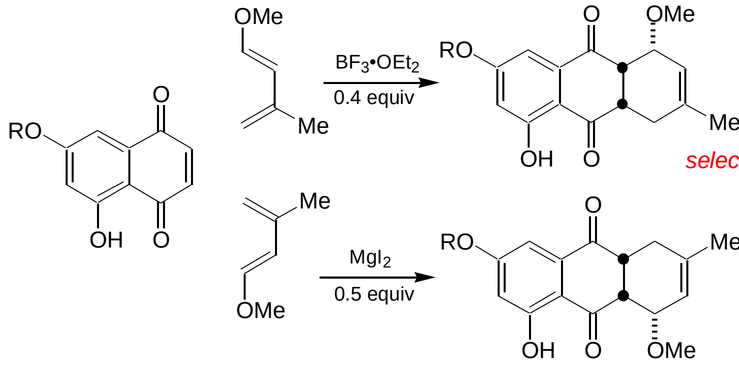
selection 80 : 20



selection >95 :5

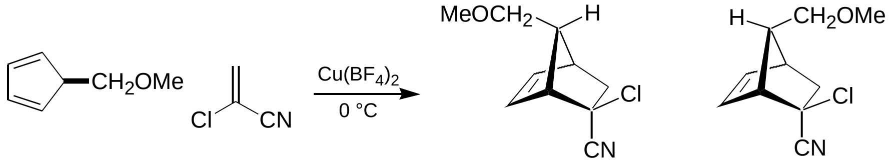
Similar results provided by Stoodley *Chem. Comm.* **1982**, 929

Kelly *Tet. Let.* **1978**, 4311



selection >95 :5

selection >95 :5



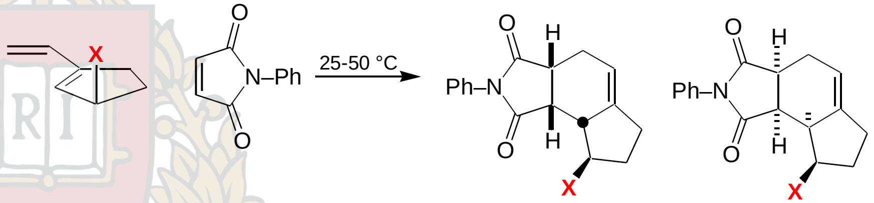
Corey, *JACS* **1969**, *91*, 5675

Ratio: 90 : 10

Diels-Alder Reactions with Chiral Dienes

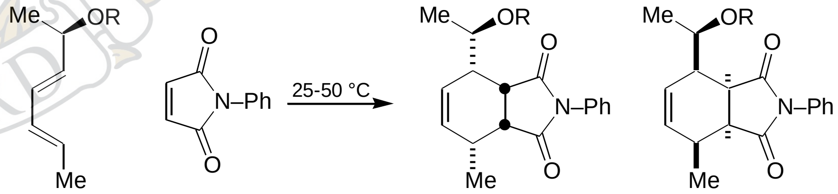
Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer, See page 347



Overman, *JACS* **1988**, *110*, 4625

X =	Ratio
–OH	36 : 64
–Me	83 : 17
–OMe	>97 : 3

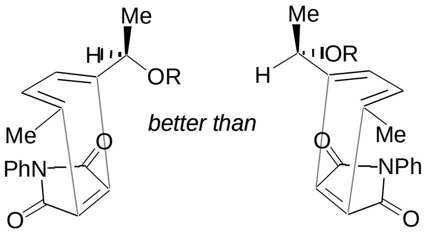


Franck, *Tet. Lett.* **1985**, *26*, 3187
Franck, *JACS* **1988**,*110*, 3257

R = Me: Ratio; 83 : 17
R = Me_3Si: Ratio; 88 : 12

Comments on the Transition State

- Avoid Eclipsing allylic substituents
- better donor (Me) anti to forming bond
- avoid gauche OR interaction

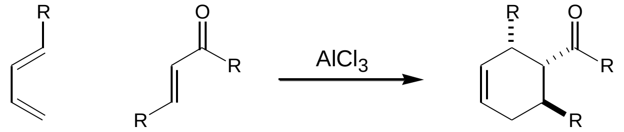


Representative Lewis Acid Catalyzed Processes

M. Santelli, J.-M. Pons, *Lewis Acids & Selectivity in Organic Synthesis*, CRC Press, New York, 1996

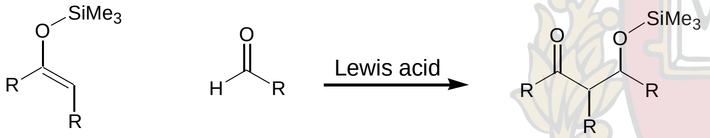
Schreiber, *Angew. Chem. Int. Ed. Eng.* **1990**, *29*, 256-272

- Diels-Alder Reaction Yates & Eaton, *JACS* **1960**, *82*, 4436



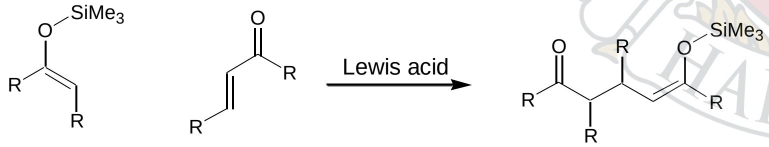
Lewis acid catalysis increases rates by ca 10^{+6}
& improves reaction regiochemistry & endo distereoselectivity

- Aldol Reaction:



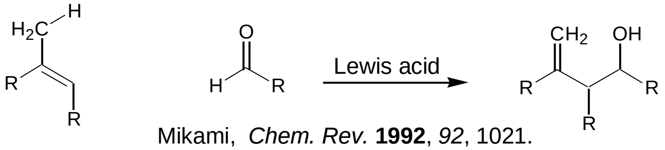
Mukaiyama, T. Org. React. (N.Y.) **1982**, *28*, 203.
Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357.

- Michael Reaction



Mukaiyama, *Chem. Lett* **1974**, 1223

- Carbonyl Ene Rxn

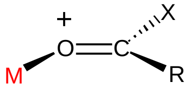


Mikami, *Chem. Rev.* **1992**, *92*, 1021.

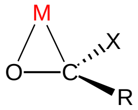
Common Stereochemical issues: Diastereoselectivity & Enantioselectivity

Lewis Acid Carbonyl Complexes

- Types of Lewis Acid-C=O Complexes (M = Lewis Acid)

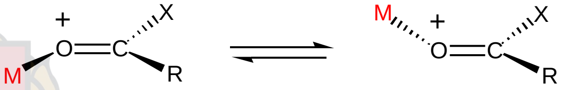


The η_1 Complex

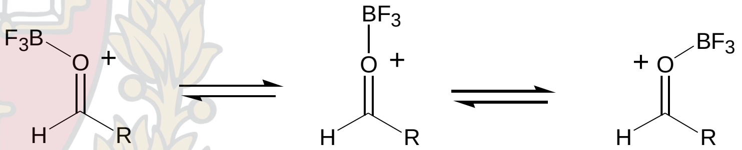


The η_2 Complex

- Conformations of η_1 Lewis Acid-C=O Complexes

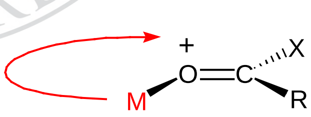


- Geometric Preferences for BF_3 Complexes (Santelli, page 5)

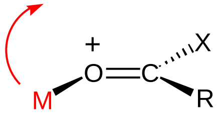


rel energy: 0 (kcal/mol) rel energy: +5.3 rel energy: +1.8

Changes in the C–O–M bond angle in the sigma plane do not require much destabilization. However distorations of the metal out of the sigma plane result in greater destabilization

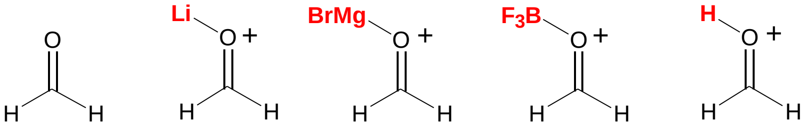


low-energy distortion



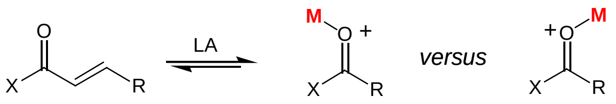
higher-energy distortion

Calculated Muliken Charges on Carbonyl Carbon (PM3)

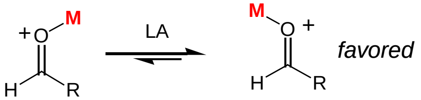


+0.29 +0.41 +0.43 +0.46 +0.47

- Well-defined Lewis acid-C=O Complex needed: Geometry of η_1 Complexes

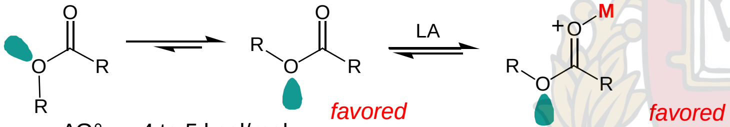


- Aldehydes: LA oriented anti to R moiety



The indicated geometry favored on steric grounds

- Esters: Lewis acid oriented anti to RO moiety

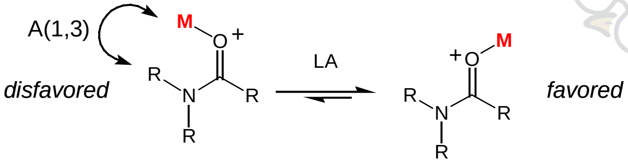


ΔG° ~ –4 to 5 kcal/mol

$\Delta G^{\ddagger}$ 10-13 kcal/mol

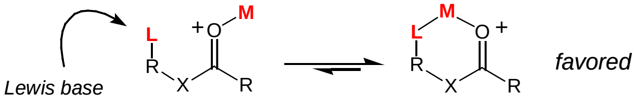
Oxygen-lone pair → σ* C–O interactions strongly stabilize the (Z) ester conformation. Such stabilzation should be expected to increase in LA-substrate complex.

- Amides: Lewis acid oriented anti to R_2N moiety



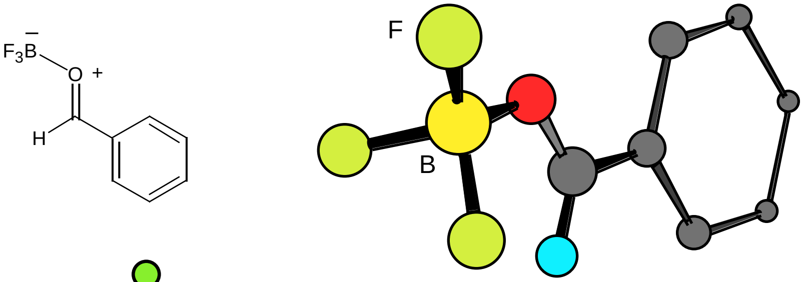
Allylic strain strongly disfavors Lewis acid complexation syn to the R_2N moiety

- Chelating Esters & Amides: Lewis acid can be bidentate coordinated

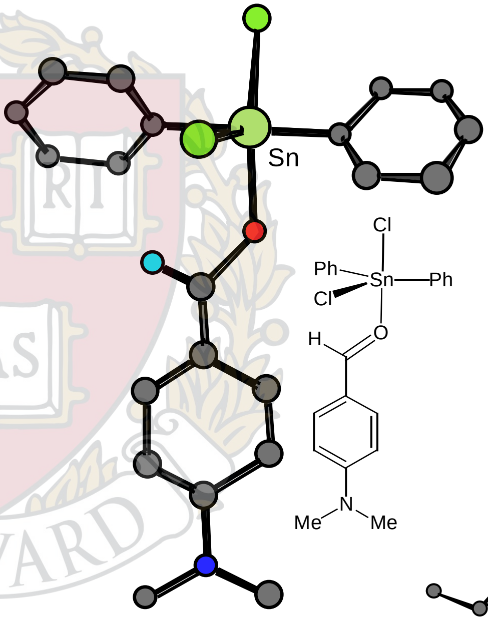


This situation is sometimes hard to predict

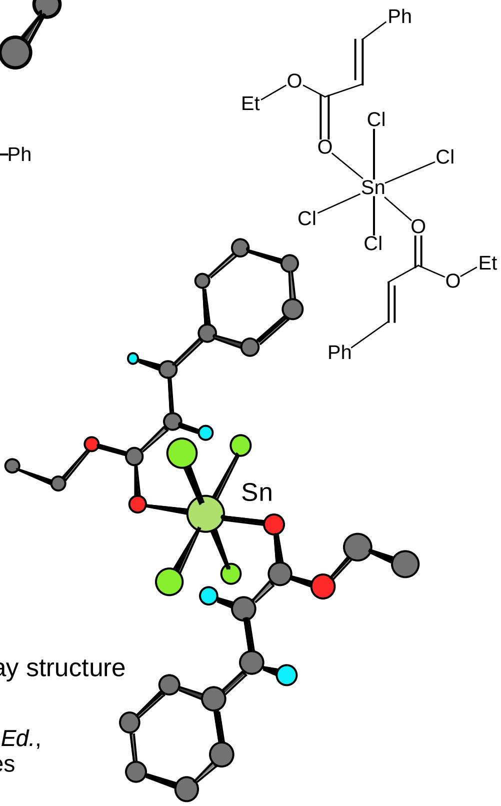
Representative η_1 Complexes & their X-ray Structuctures



X-ray structure



X-ray structure

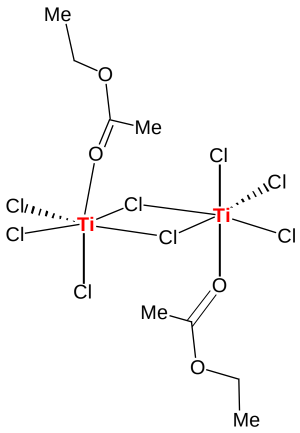


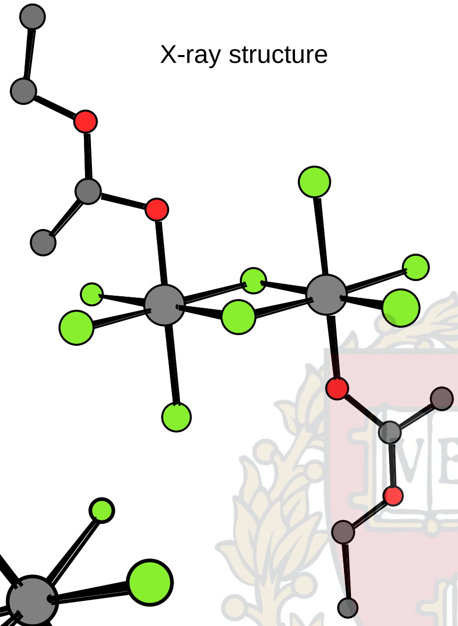
X-ray structure

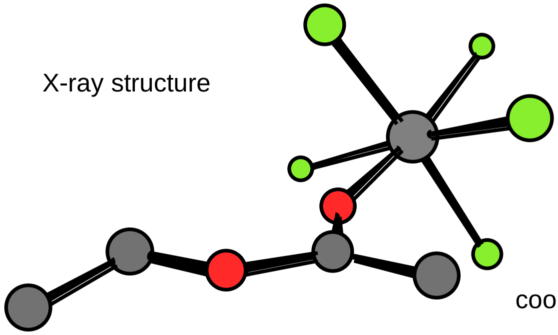
See Schreiber, *Angew. Chem. Int. Ed.*, **1990**, *29*, 256-272 for references

Lewis Acid–Carbonyl Complexes-3

Representative η_1–titanium complexes with organic compounds

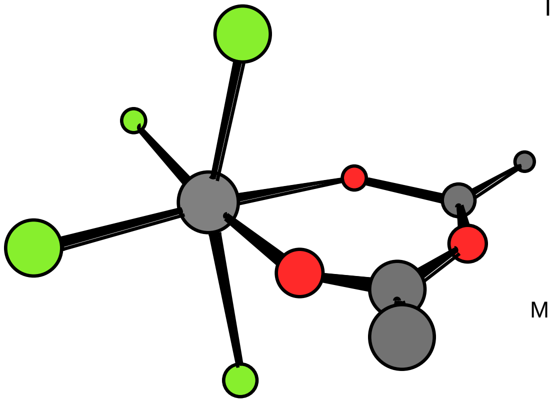


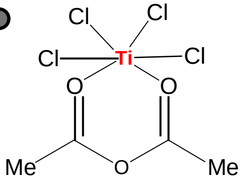

X-ray structure


X-ray structure

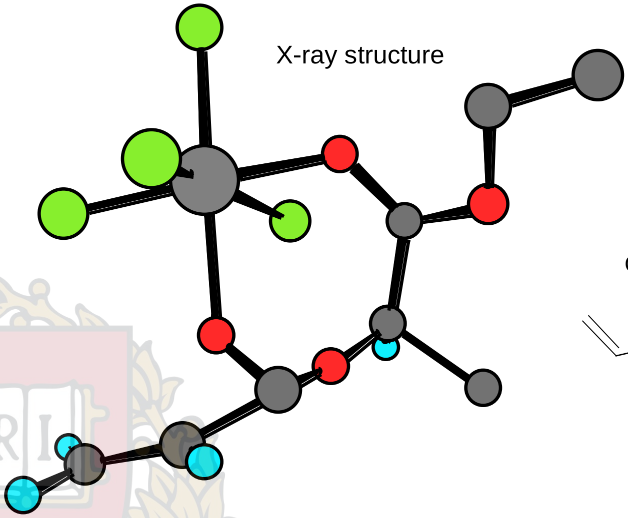
Side view of in-plane Ti coordination: Ti-O-C-C = 2.86°

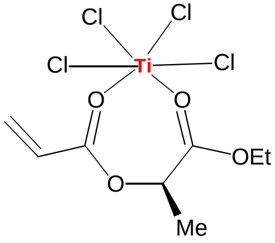
Ti–O–C angle = 152 °

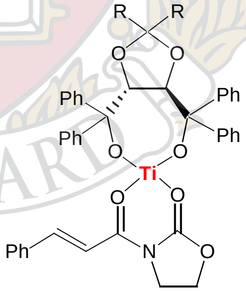


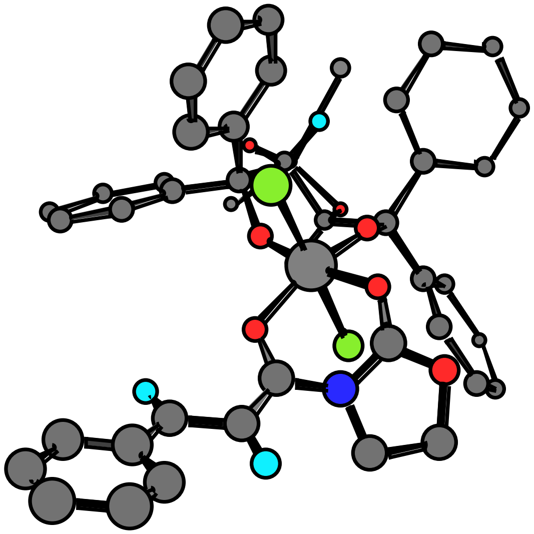


Representative η_1–titanium complexes with organic compounds


X-ray structure







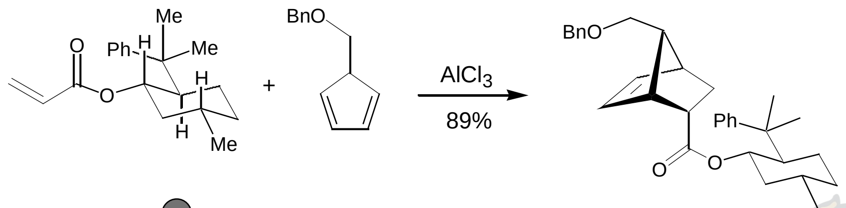
Narasaka *JACS*, **1989**, *111*, 5340

A. Jorgensen, *JACS*, **1995**, *117*, 4435

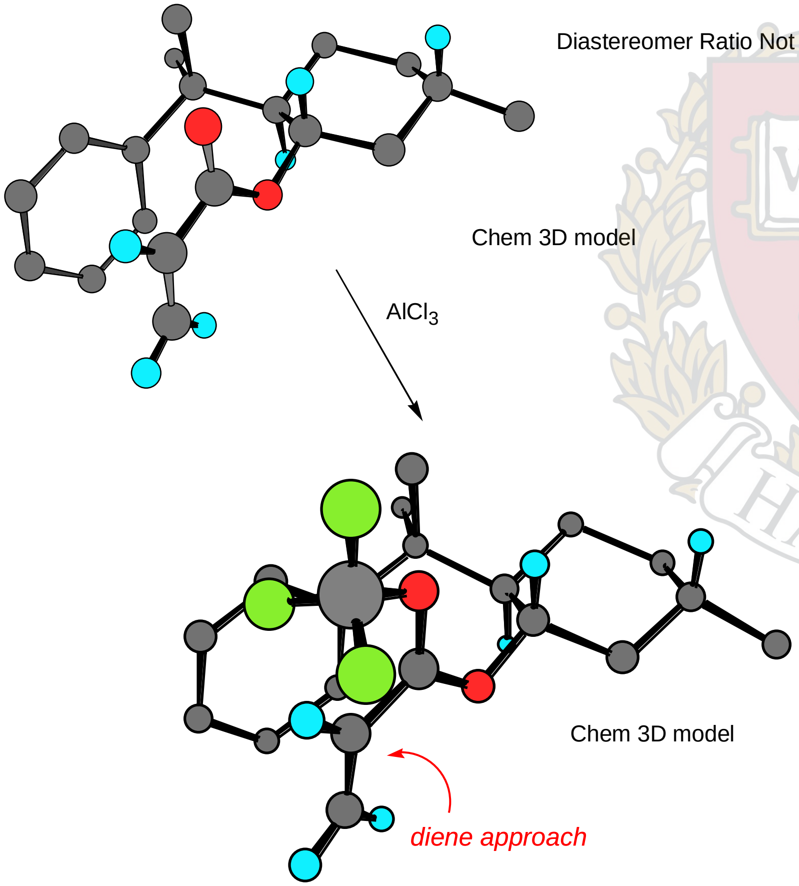
X-ray structure

Review: Oppolzer in *Comprehensive Organic Synthesis* **1992**,*Vol. 4*, 315-399.

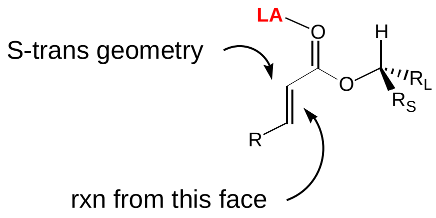
■ Ester-Type Chiral Auxiliaries Corey *JACS* **1975**, *97*, 6908.



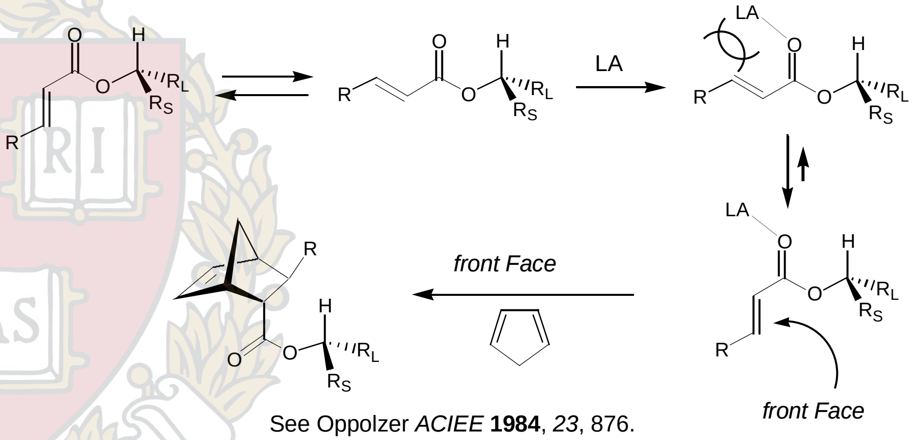
Diastereomer Ratio Not Given



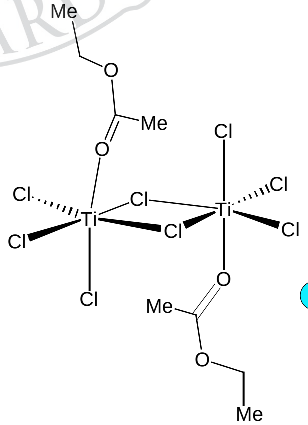
■ Non-Chelate Ester-Type Chiral Auxiliaries

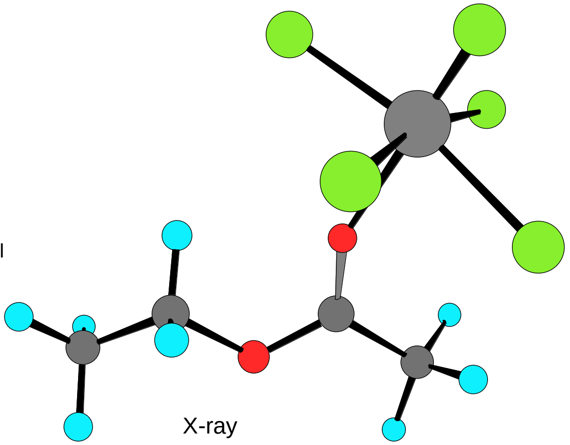


Lewis Acid-Ester Complex Conformation Dictates Diastereoselection



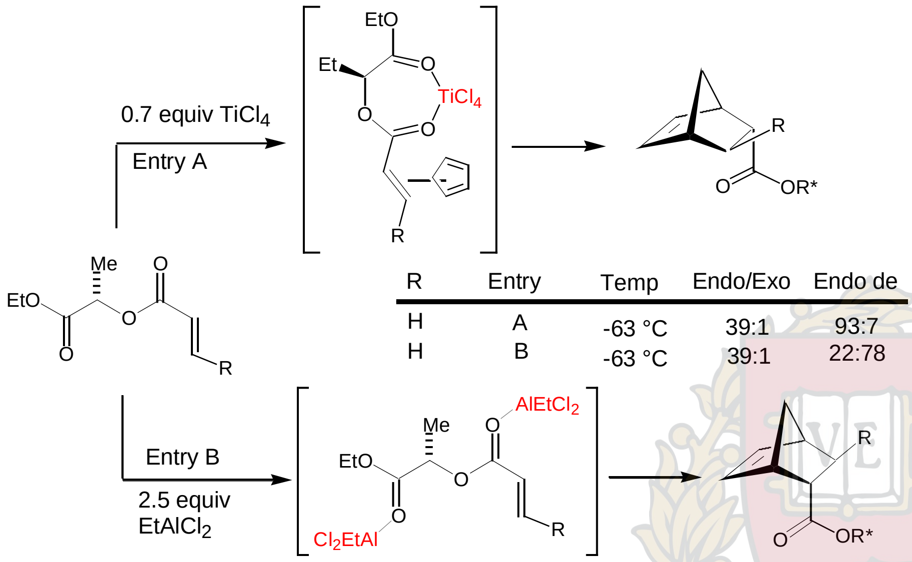
See Oppolzer *ACIEE* **1984**, *23*, 876.





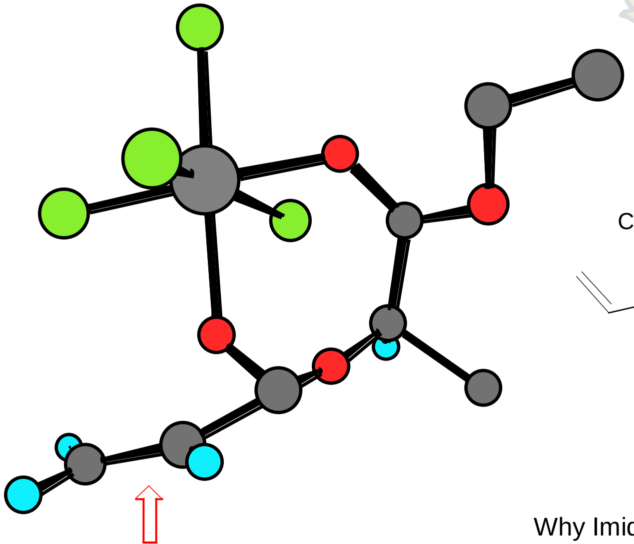
Chiral Auxiliary Controlled Diels-Alder Reactions-2

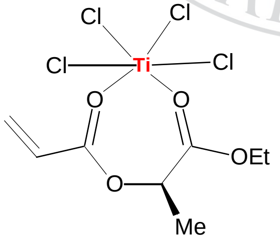
■ Ester-Type Chiral Auxiliaries: Chelating Dienophiles



R	Entry	Temp	Endo/Exo	Endo de
H	A	-63 °C	39:1	93:7
H	B	-63 °C	39:1	22:78

Helmchen *Tetrahedron Lett.* **1984**, *25*, 2191.
ACIEE **1985**, *24*, 112.
Tetrahedron Lett. **1985**, *26*, 3095.





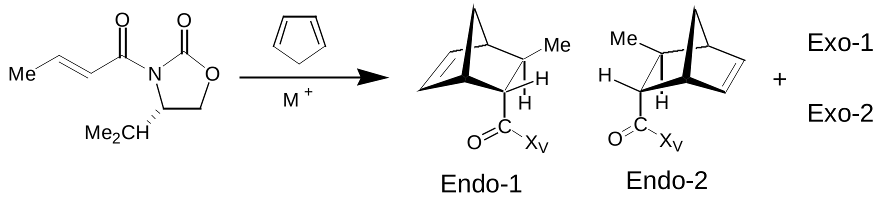
X-ray structure

Why Imide Dienophiles??
They are ~ 100-1000X more reactive

■ Chelating Imide-type Chiral Auxiliaries

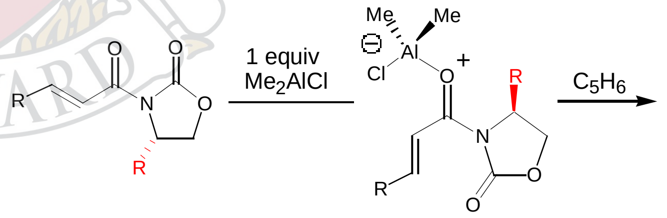
Evans *JACS*, **1984**, *106*, 4261.
Evans *JACS*, **1988**, *110*, 1238.

Metal ion Dependent Diastereoselection

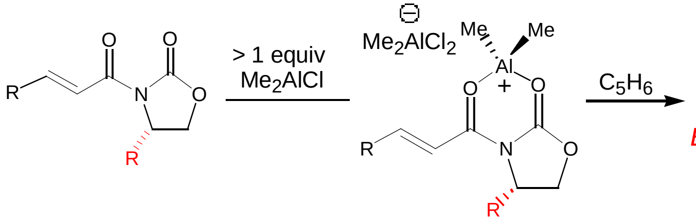


Lewis Acid (1.2 equiv)	Temp.	Endo-1 / Endo-2	Σ Endo / Exo
$SnCl_4$	25	2.7	92 : 8
$SnCl_4$	-78	3.1	93 : 7
$TiCl_4$	-78	2.6	91 : 9
$AlCl_3$	-78	1.5	80 : 20
Et_2AlCl	-78	15.7	>99 : 1
(0.7 equiv) Et_2AlCl	-78	4.4	92 : 8

Binding Mode Dictates Diastereoselectivity



1 Point Binding
⇩
Endo/Exo = 4 :1
Rel. Rate = 1



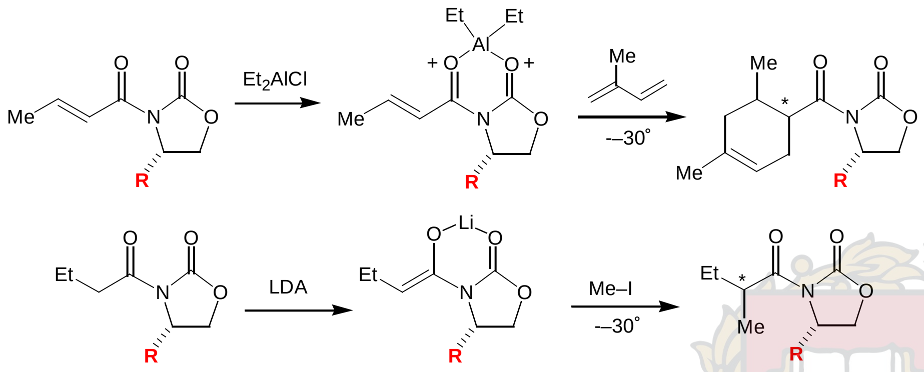
2 Point Binding
⇩
Endo/Exo = >20:1
Rel. Rate = 100

R = CH_2Ph much more stereoselective than R = $CHMe_2$

Chiral Auxiliary Controlled Diels-Alder Reactions-2

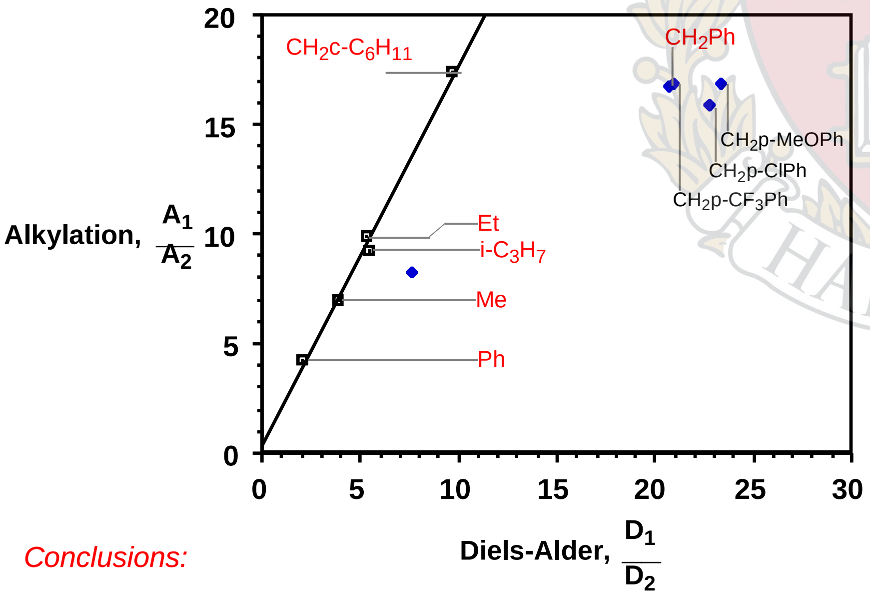
A Case for Π-Stacking: *Angew Chem, Int Ed.* **1987**, *26*, 1184

Compare the alkylation rxn which is dominated by steric effects with the DA rxn which may be controlled by both steric and electronic effects



$$\Delta\Delta G^{\ddagger} = 2.3\ RT\ \mathrm{Log}\ P_1/P_2$$

PLOT $\Delta\Delta G^{\ddagger}$ FOR EACH RXN AS A FUNCTION OF THE SUBST., R.

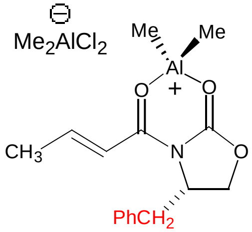


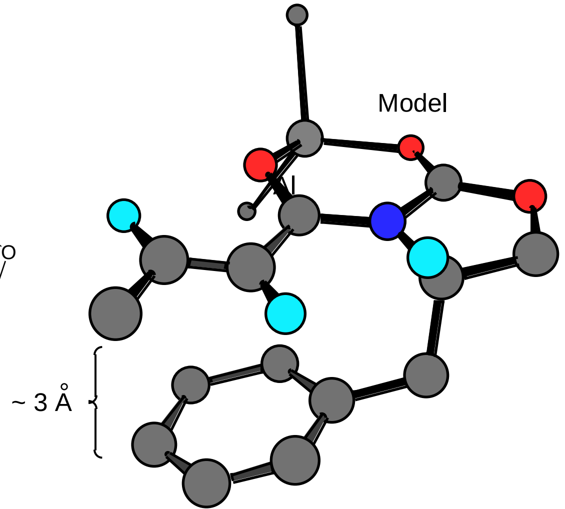
Conclusions:

Steric effects correlate well for the two reactions

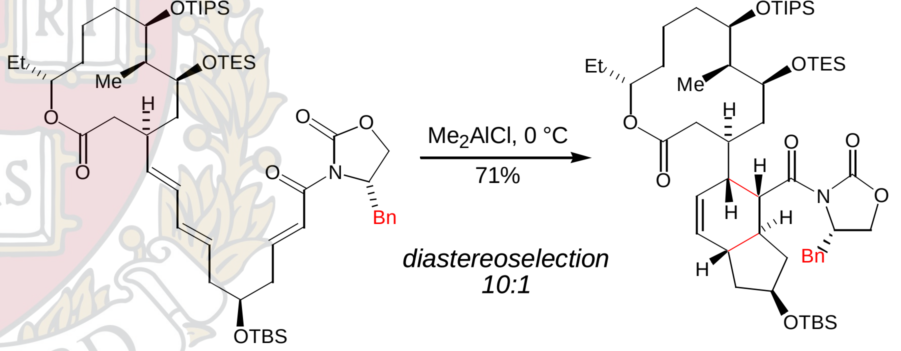
Added electronic effects from Bn group enhance facial bias

The Chiral Dienophile



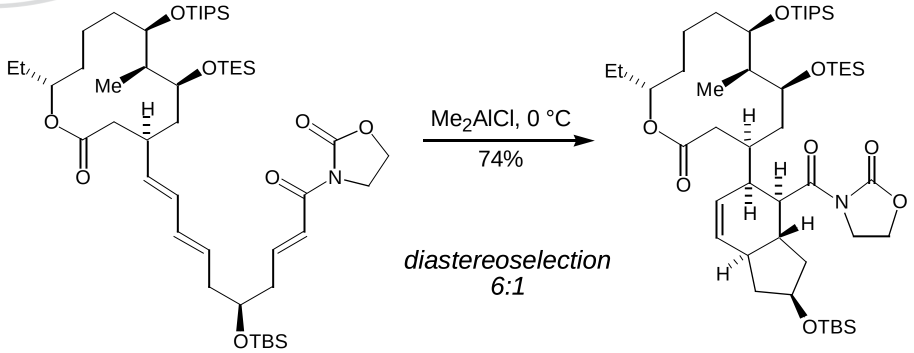


A Complex Application



diastereoselection 10:1

The control experiment with no chiral auxiliary:



diastereoselection 6:1

Lepicidin Synthesis, *JACS*, **1993**, *115*, 4497

The Diels-Alder Reaction: Enantioselective Catalysis

Articles and monographs of Significance

"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, 1999; Vol III, 1178-1235.

Review: Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007-1019

Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer
4.2 Heterodienophile Additions to Dienes, S. M. Weinreb
4.3 Heterodiene Additions, D. L. Boger
4.4 Intramolecular Diels-Alder Reactions, W. R. Roush
4.5 Retrogade Diels-Alder Reactions, R. W. Sweger, A. W. Czarnik

Catalytic Asymmetric Synthesis, I. Ojima, Ed. **1993**

Chapter 9, *Asymmetric Rxns with Chiral Lewis Acid Catalysts*

Chiral Lewis Acids in Catalytic Asymmetric Reactions
Narasaka, *Synthesis*, **1991**, 1-11

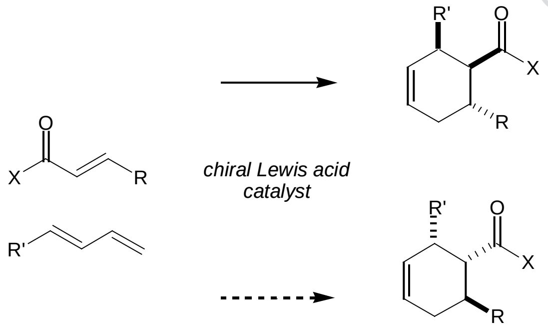
(Carbonyl-Lewis Acid Complexes)
Schreiber, *Angew. Chem. Int. Ed.*, **1990**, *29*, 256-272

Rotational barriers in Aldehydes & Ketones Coordinated to Neutral Lewis Acids
Wiberg, *JACS*, **1988**, *110*, 6642

Theoretical Studies on Conformations of Acrolein, Acrylic Acid, Methyl Acrylate & their Lewis Acid Complexes Houk, *JACS*, **1987**, *109*, 14-23

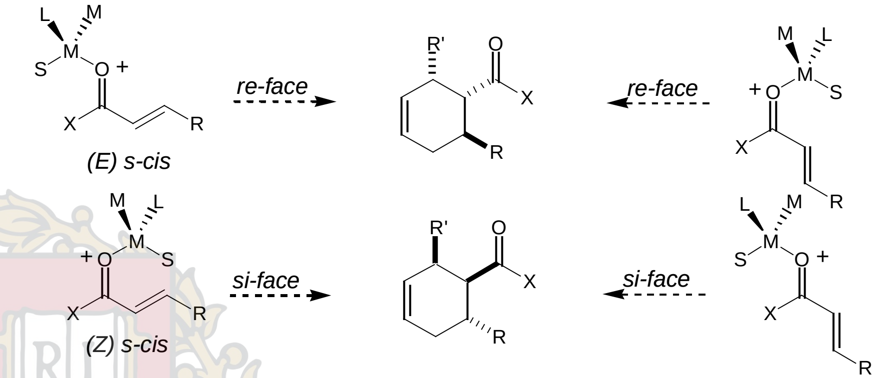
C_2 Symmetry and Asymmetric Induction, Whitesell, *Chem. Rev.*, **1989**, *89*, 1581-1590

The Design of Enantioselective Diels-Alder Catalysts



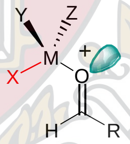
The conformation of the dienophile is also an issue

The S-cis versus S-trans dienophile conformation is is coupled to the geometry of the Lewis acid-dienophile complex & both issues determine face selection



Theoretical Studies on Conformations of Acrolein & Methyl Acrylate & their Lewis Acid Complexes
Houk, *JACS*, **1987**, *109*, 14-23

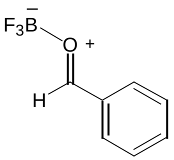
Stereoelectronic Effects (?) in Lewis acid-C=O Complexes

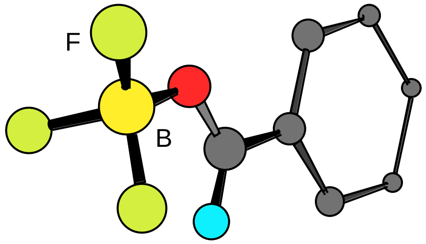


Let X be the most electronegative ligand in the Lewis acid

The stabilizing hyperconjugative interaction between the O-lone pair and σ* M–X will provide a stabilizing interaction for the illustrated conformation.
J. M. Goodman, *Tet. Lett*. **1992**, *33*, 7219

However, there is no evidence for this orienting effect in this X-ray structure reported by Reetz, *JACS*, **1986**, *108*, 2405



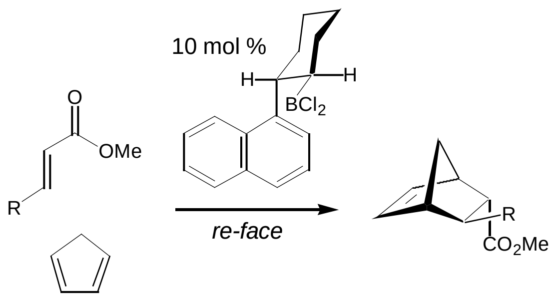


However pi-bonding to coordinated C=O-Al complexes has been reported
Barron, *JACS*, **1990**, *112*, 3446, *JACS*, **1990**, *112*, 2950

Theory predicts a small rotational barrier about B–O bond: Wiberg *JACS*, **1988**, *110*, 6642

The Diels-Alder Reaction: Enantioselective Catalysis-2

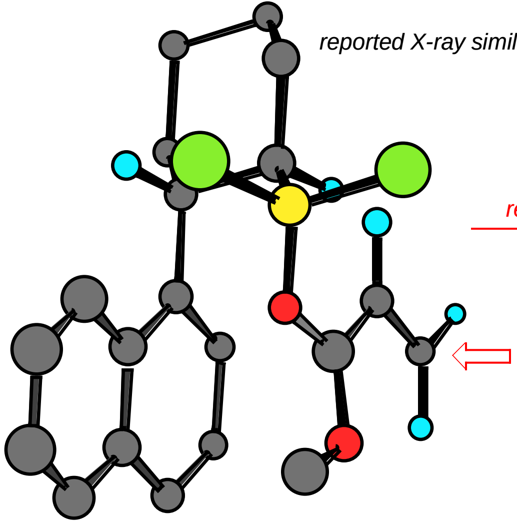
■ Boron-Based Catalysts: Hawkins *JACS* **1991**, *113*, 7794

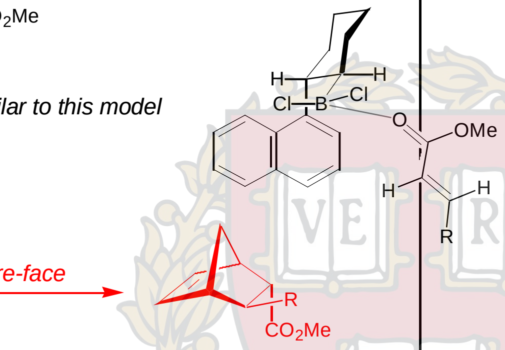


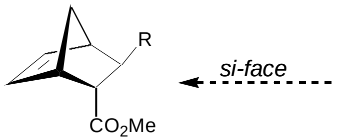
R	Temp (°C)	Endo ee
H	-78	97 %
Me	-20	91 %
CO$_2$Me	-78	92 %

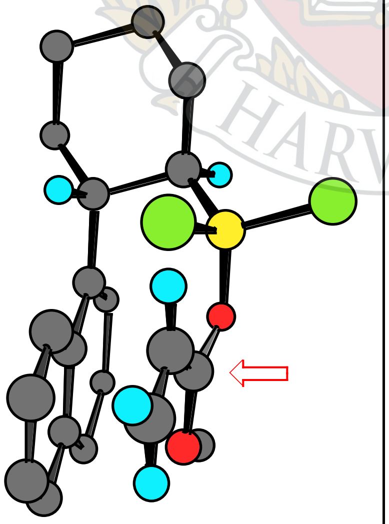
Endo/Exo Ratios not provided.

reported X-ray similar to this model



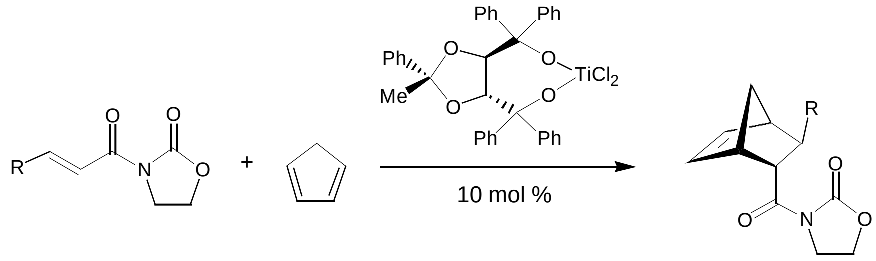




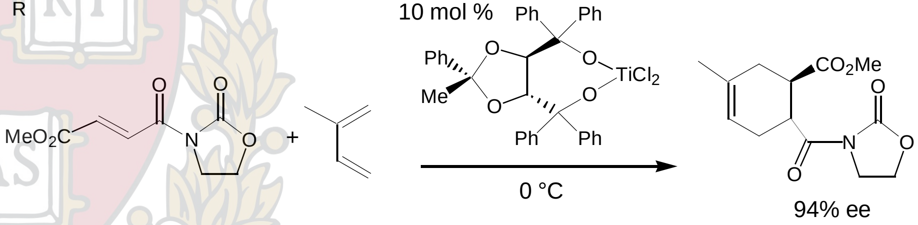


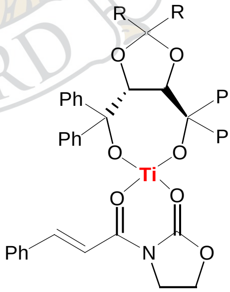
Chem 3D Models

■ Titanium-Based Catalysts: Narasaka *JACS* **1989**, *111*, 5340.

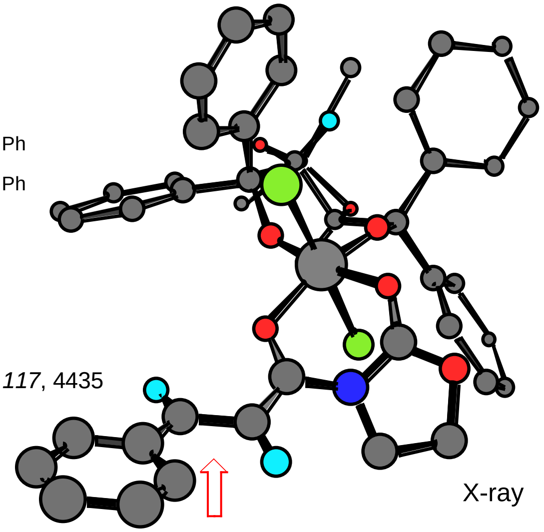


R	Temp (°C)	Endo/Exo	Endo ee
H	-40	96:4	64 %
Me	0	92:8	91 %
Ph	25	88:12	64 %



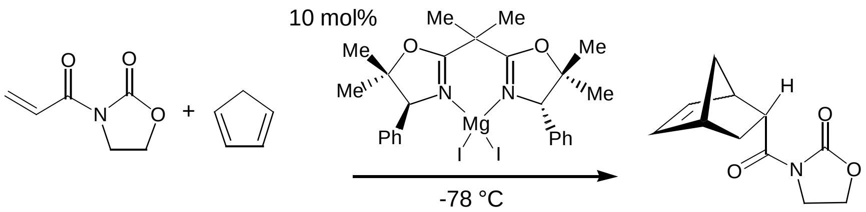


A. Jorgensen, *JACS*, **1995**, *117*, 4435



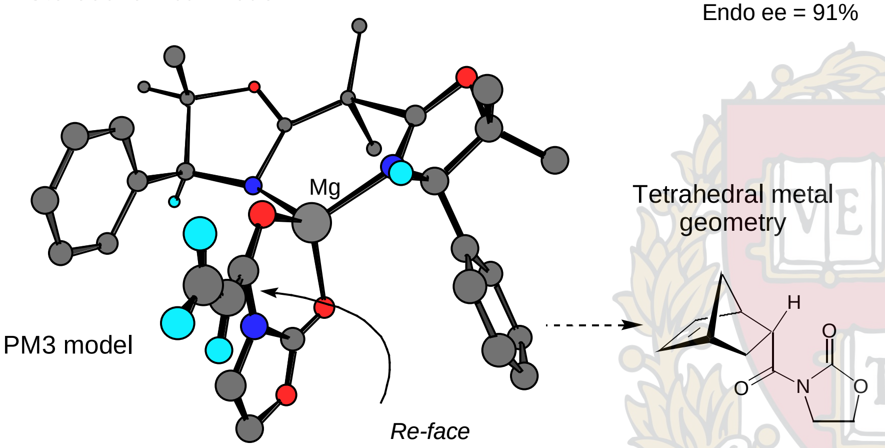
X-ray

■ Mg(2+)-Based Catalysts: Corey *Tetrahedron Lett*. **1992**, *33*, 6807.



Endo/Exo = 98:2
Endo ee = 91%

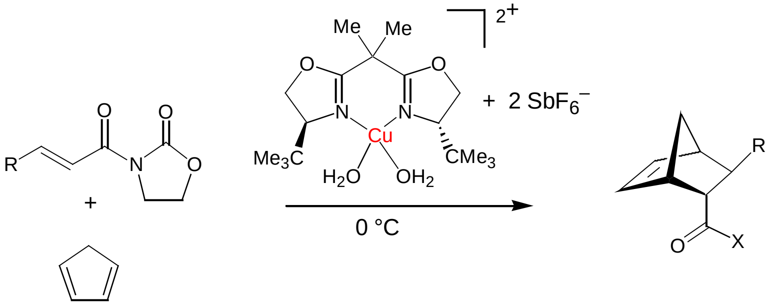
Stereochemical Model:

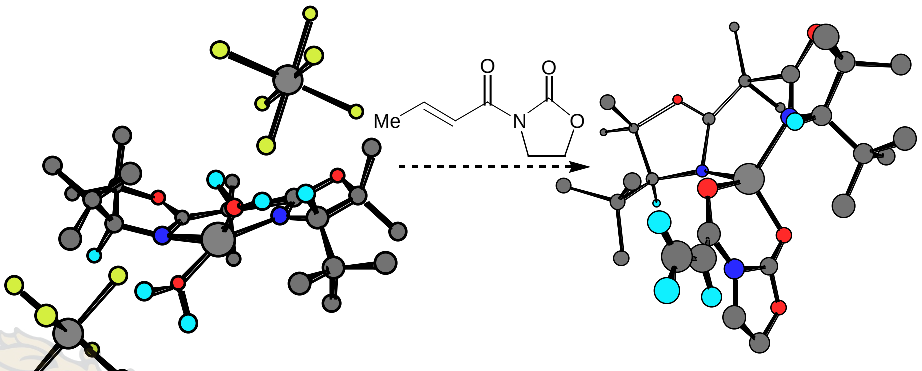


Limitations: Reactions limited to illustrated reaction

■ Cu(2+)-Based Catalysts:

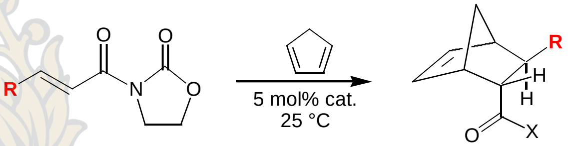
Evans, Miller, Lectka *JACS* **1993**, *115*, 6460.
Angew. Chem. Int. Engl. **1995**, *34*, 798-800.
JACS **1999**, *121*, 7559-7573.
JACS **1999**, *121*, 7582-7594



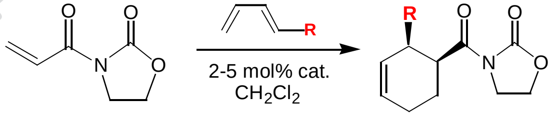


X-ray structure

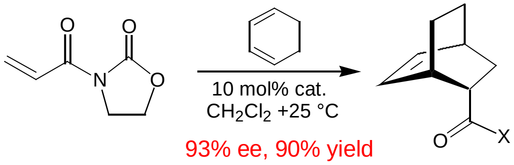
PM3 model



R	time	endo ee	yield
R = Me	8 h	96% ee	98%
R = Ph	8 h	96% ee	95%
R = Cl	8 h	94% ee	95%



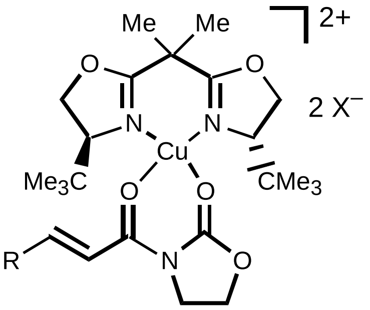
R	temp	endo ee	yield
R = Me	25 °C	94% ee	89%
R = Ph	-20 °C	97% ee	95%
R = OAc	0 °C	97% ee	100%



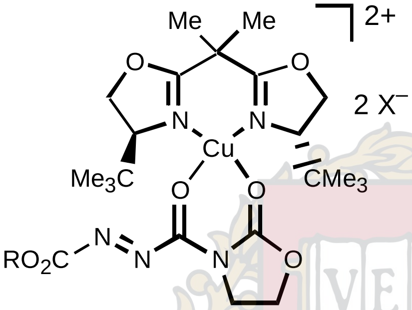
93% ee, 90% yield

Cu(box) and Cu(pybox) catalyst-substrate complexes implicated in enantioselective reactions.

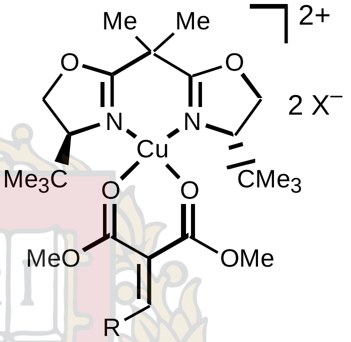
"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, Evans, *Acc. Chem. Res*. **2000**, *33*, 325-335. **(pdf)**



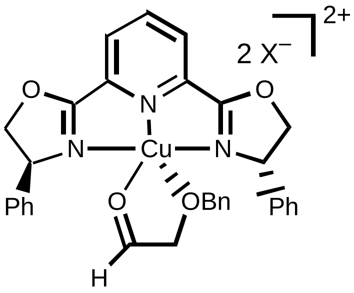
Cycloaddition Reactions
Michael Reactions



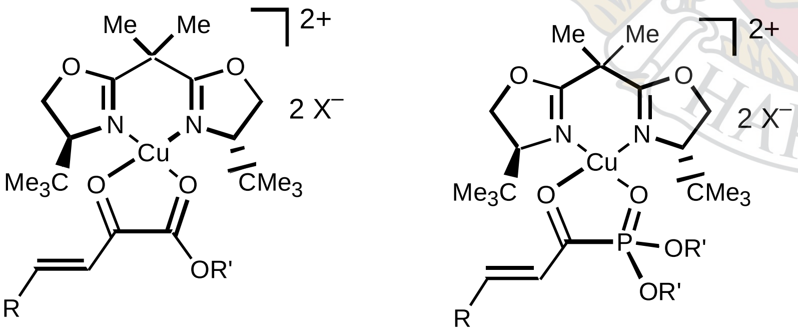
Enol Amination Reactons



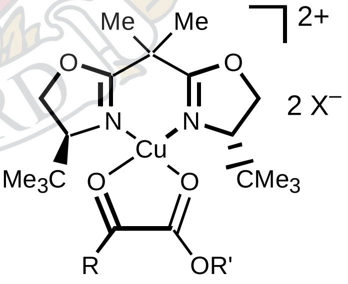
Michael Reactions



Aldol Reactions

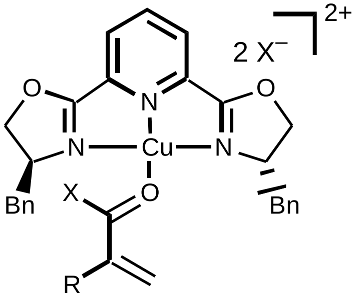


Hetero Diels-Alder Reactions



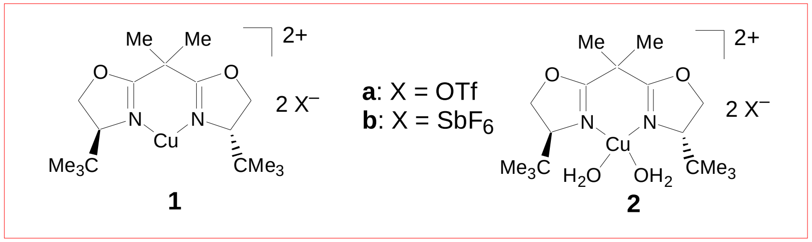
R = H, Cycloaddition Reactions
Ene Reactions

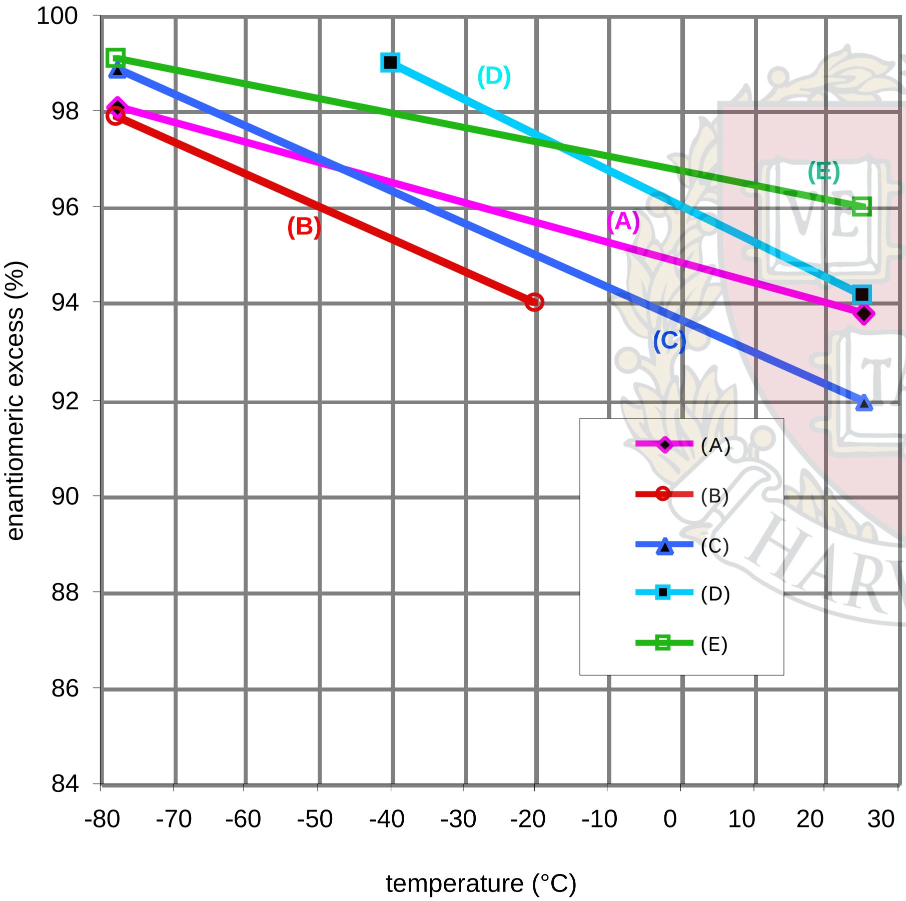
R = Alkyl, Cycloaddition Reactions
Aldol Reactions



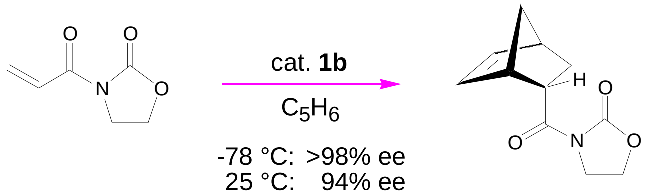
Diels-Alder Reactions

Temperature–Enantioselection Profile for [Cu((S,S)-t-Bu-box)](X)$_2$ Catalysts





(A)

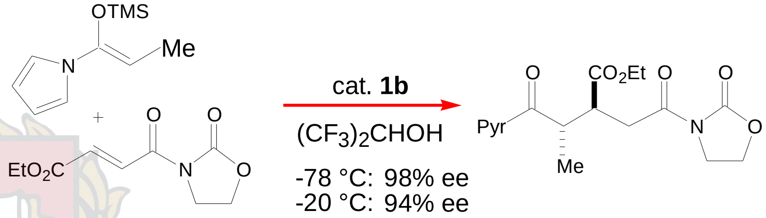


cat. **1b**

C_5H_6

-78 °C: >98% ee
25 °C: 94% ee

(B)

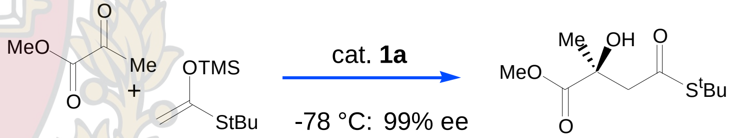


cat. **1b**

$(CF_3)_2CHOH$

-78 °C: 98% ee
-20 °C: 94% ee

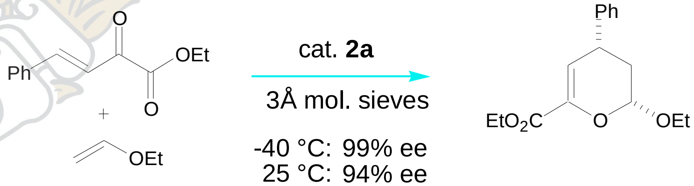
(C)



cat. **1a**

-78 °C: 99% ee
25 °C: 92% ee

(D)

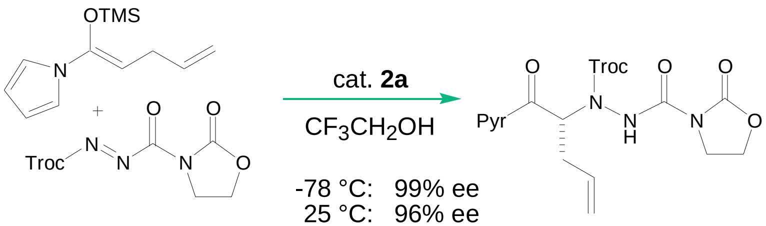


cat. **2a**

3Å mol. sieves

-40 °C: 99% ee
25 °C: 94% ee

(E)



cat. **2a**

CF_3CH_2OH

-78 °C: 99% ee
25 °C: 96% ee

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 17

Acid-Base Properties of Organic Molecules

- Bronsted Acidity Concepts in the Activation of Organic Structures
- Medium Effects on Bronsted Acidity
- Substituent & Hybridization Effects on Bronsted Acidity
- Kinetic & Thermodynamic Acidity of Ketones
- Kinetic Acidity: Carbon vs. Oxygen Acids
- Tabulation of Acid Dissociation Constants in DMSO

Reading Assignment for this Lecture:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

"Equilibrium acidities in DMSO Solution", F. G. Bordwell. *Acc. Chem. Res*. **1988**, *21*, 456-463.

Matthew D. Shair

Monday,
October 28, 2002

Articles on the Acidities of Organic Molecules

Lowry & Richardson: 3rd Edition, Chapter 3
Acids and Bases

"Equilibrium acidities in DMSO Solution", F. G. Bordwell. *Acc. Chem. Res*. **1988**, *21*, 456-463.

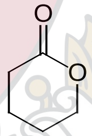
Here is a web site containing Brodwell pKa data

http://www.chem.wisc.edu/areas/reich/pkatable/index.htm

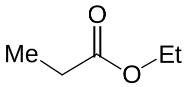
Problems of the Day:

Explain why **1** and **3** are ~4 pKa units more acidic than their acyclic counterparts **2** and **4**. (*J. Org. Chem.* **1994**, *59*, 6456)

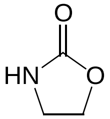
1



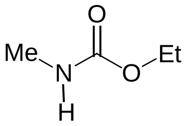
2



3

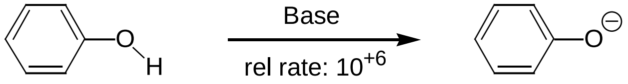


4

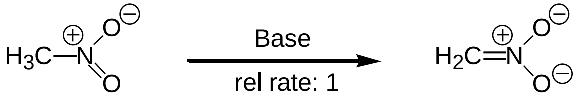


The thermodynamic acidities of phenol and nitromethane are both ~10; however, using a common base, phenol is deprotonated 10^{+6} times as fast. Rationalize

pKa(H_2O)
~10

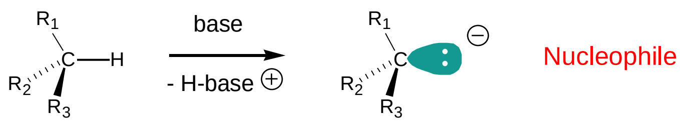


pKa(H_2O)
~10



Activation of Organic Molecules

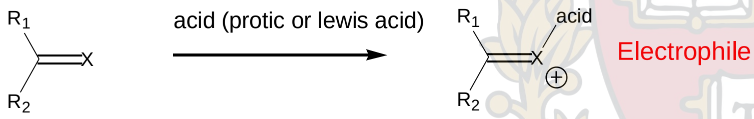
Base Activation



pK$_a$, describes quantitatively a molecule's propensity to act as an acid, i.e. to release a proton.

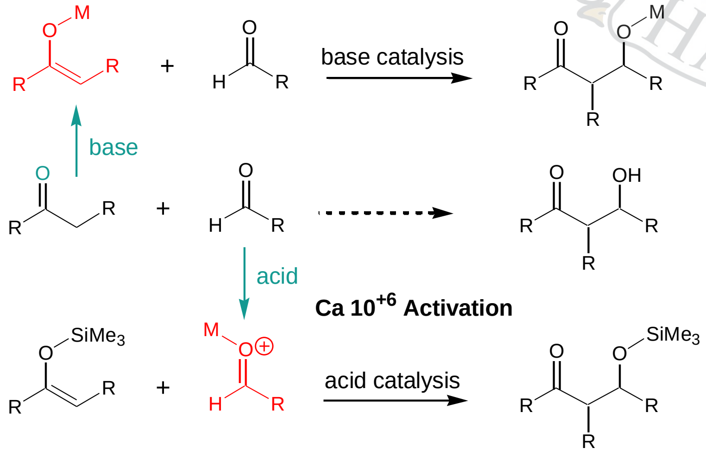
- Medium effects
- Structural effects (influence of substituents R_1)

Acid Activation



X = e.g. O, NR ...

The Aldol Example



Definition of Ka

Let H–X be any Bronsted acid. In water ionization takes place:

$$H{-}X + HOH \rightleftharpoons H_3O^+ + X{-}$$

where $$Keq = \frac{[H_3O^+]\,[X^-]}{[H{-}X]\,[HOH]}$$ where $[HOH] = 55.5\ mol\ L^{-1}$ (A)

Since [HOH] is, for all practical purposes, a constant value, the acid dissociation constant K_a is defined wilthout regard to this entity. e.g.

$$H{-}X \rightleftharpoons H^+ + X{-} \qquad \text{where } H^+ = H_3O^+$$

Hence $$K_a = \frac{[H^+]\,[X^-]}{[H{-}X]} \qquad \textbf{(B)}$$

From the above definitions, K_a is related to K_{eq} by the relation:

$$K_a(H{-}X) = 55.5\ K_{eq}(H{-}X) \qquad \textbf{(C)}$$

Autoionization of water

$$HOH + HOH \rightleftharpoons H_3O^+ + HO^-$$

$K_{eq} = 3.3 \times 10^{-18}$

From Eq C: $K_a = 55.5\ K_{eq} = 55.5(3.3 \times 10^{-18})$

Hence $K_a = 1.8 \times 10^{-16}$

Since pK$_a$ is defined in the following equation:

$$\mathbf{pK_a = -\log_{10} [K_a]}$$

The pK$_a$ of HOH is + 15.7

Keep in mind that the strongest base that can exist in water is HO^-.

Lets now calculate the acid dissociation constant for hydronium ion.

$$H_3O^+ + H_2O \rightleftharpoons H_3O^+ + H_2O$$

obviously: $K_{eq} = 1$

$K_a = [HOH] \times K_{eq}$ hence $K_a = 55.5$

$pK_a = -\log_{10} K_a = -1.7$

The strongest acid that can exist in water is H_3O^+.

The Gibbs Relationship

$$\Delta G° = - RT \ln K$$

or $$\Delta G° = – 2.3\ RT \log_{10} K$$

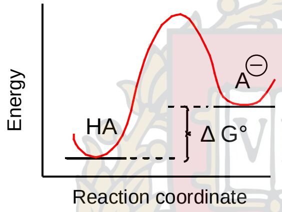
2.3 RT = 1.4
at T = 298 K
in kcal mol^{-1}

$$\Delta G°_{298} = - 1.4 \log_{10} K_{eq}$$

$$\boxed{\Delta G°_{298} = 1.4\ pK_{eq} \approx 1.4\ pK_a}$$ with $pK = – \log_{10} K$

Hence, pK_a is proportional to the free energy change

K_{eq}	pK_{eq}	$\Delta G°$
1	0	0
10	- 1	- 1.4
100	- 2	- 2.8 kcal/mol

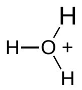
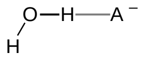
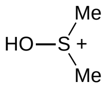


Medium Effects

Consider the ionization process:

$$H–A \; + \; \text{solvent} \rightleftharpoons A:^- \; + \; \text{solvent}(H^+)$$

In the ionization of an acid in solution, the acid donates a proton to the medium. The more basic the medium, the larger the dissociation equilibrium. The ability of the medium to stabilize the conjugate base also plays an important role in the promotion of ionization. Let us consider two solvents, HOH and DMSO and the performance of these solvents in the ionization process.

	The Protonated Solvent	Conjug. Base Stabiliz.
Water		
DMSO		No H-bonding Capacity

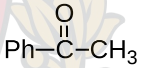
As shown above, although HOH can stabilize anions via H-bonding, DMSO cannot. Hence, a given acid will show a greater propensity to dissociate in HOH. As illustrated below the acidity constants of water in HOH, DMSO and in a vacuum dramatically reflect this trend.

Medium Effects on the pKa of HOH

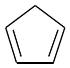
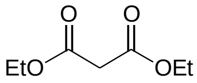
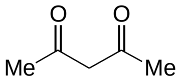
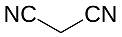
** The gas phase ionization of HOH is endothermic by 391 kcal/mol !!!

HOH pKa	Medium
15.7	HOH
31	DMSO
279 (est)**	Vacuum

Representative pKa Data

Substrate	DMSO	HOH	Δ pKa
HOH	31.2	15.7	15.5
HSH	14.7	7.0	7.7
MeOH	29.0	15.3	13.7
C_6H_5OH	18.0	9.9	8.1
$O_2N–CH_3$	17.2	10.0	7.2
 $Ph–\overset{O}{\overset{\|}{C}}–CH_3$	24.6	17	7.6

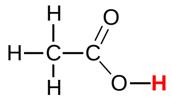
The change in pKa in going from water to DMSO is increasingly diminished as the conjugate base becomes resonance stabilized (Internal solvation!).

Substrate	DMSO	HOH	Δ pKa
	18.1	16.0	2.1
	16.4	13.3	3.1
	13.3	8.9	4.5
	11.1	11.2	0

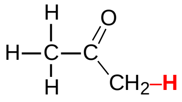
Acidity Trends for Carbonyl & Related Compounds

Substituent Effects

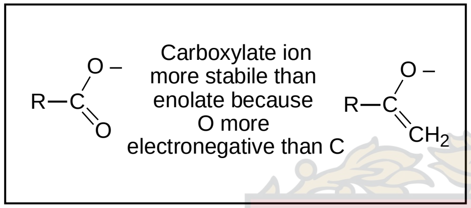
Electronegativity e.g. Compare Carboxylic Acids vs. Ketones



pK_A = 4.8
(DMSO)



pK_A ≈ 19
(DMSO)



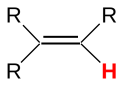
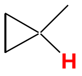
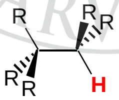
Carboxylate ion more stabile than enolate because O more electronegative than C

Hybridization - S-character of carbon hybridization

Remember:

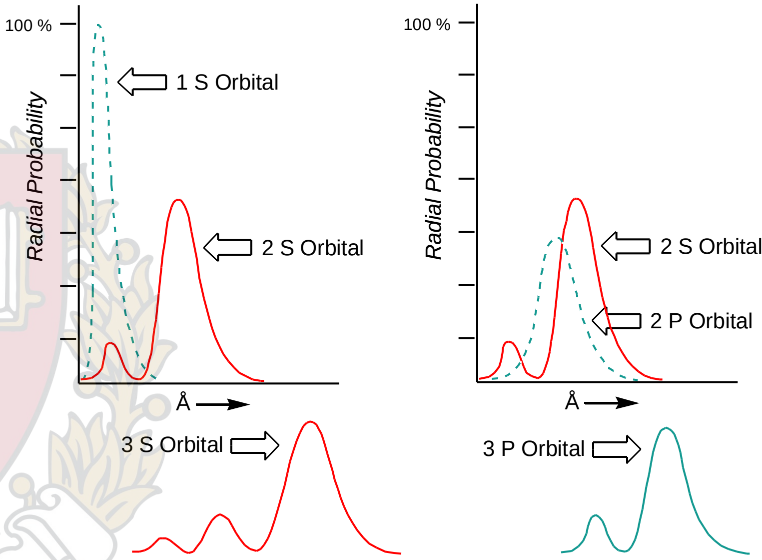
sp^3-orbitals	25% s-character
sp^2-orbitals	33% s-character
sp-orbitals	50% s-character

Carbon Acids

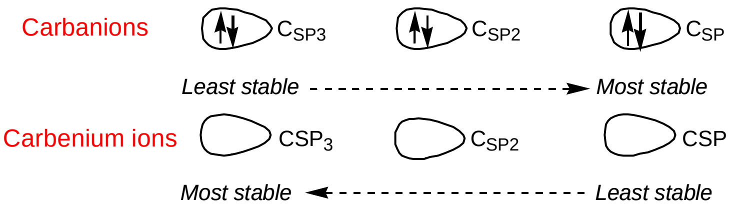
				
Hybridzation	sp	sp^2	≈ sp^2	sp^3
Bond Angle	180°	120°	≈ 120	109°
pK_a(DMSO)	23	32	≈ 39	50

Electrons in 2S states "see" a greater effective nuclear charge than electrons in 2P states.

This becomes apparent when the radial probability functions for S and P-states are examined: The radial probability functions for the hydrogen atom S & P states are shown below.



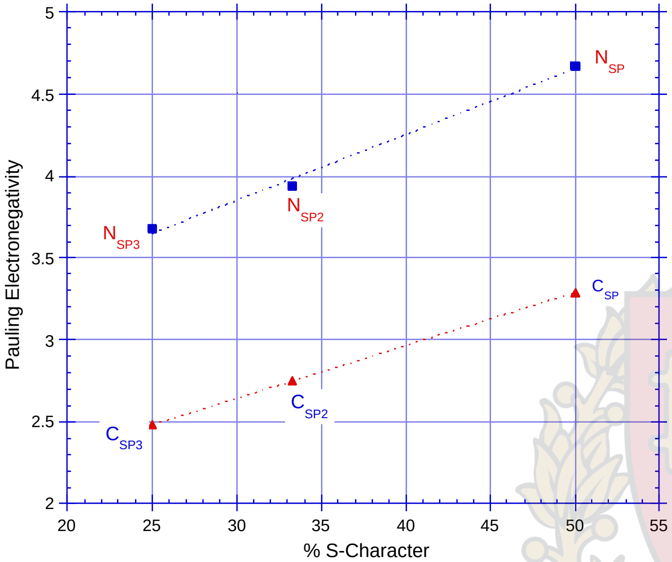
S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in s states see a higher nuclear charge. The above observation correctly implies that the stability of nonbonding electron pairs is directly proportional to the % of S-character in the doubly occupied orbital.



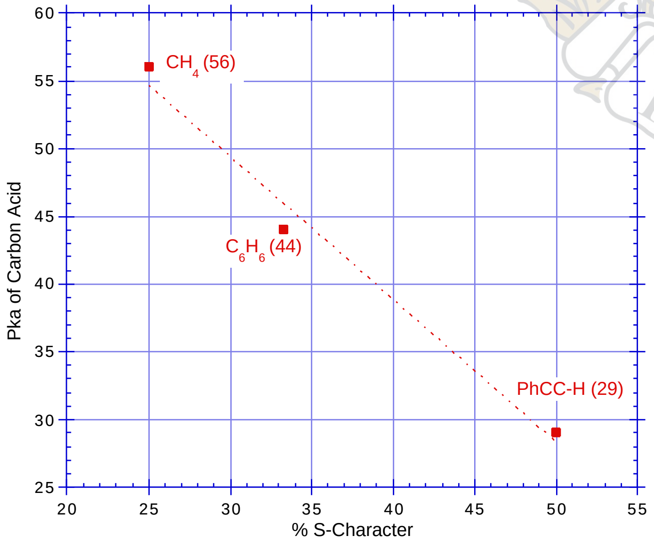
The above trends indicate that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

Hybridization vs Electronegativity

There is a linear relationship between %S character & Pauling electronegativity



There is a direct relationship between %S character & hydrocarbon acidity



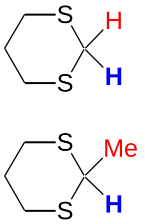
Substituent Effects

■ Alkyl Substituents on Localized Carbanions are Destabilizilng:

Steric hinderance of anion solvation

Compare: (*JACS* **1975**, *97*, 190)

	pK_A (DMSO)
$\underset{H}{PhSO_2\text{-}CH}\text{–}H$	29
$\underset{H}{PhSO_2\text{-}CH}\text{–}Me$	31



pK_A (DMSO)

31.1

38.3

■ Heteroatom-Substituents: - 1st row elements of periodic table

	pK_A (DMSO)	
$\underset{H}{PhSO_2\text{-}CH}\text{-}OCH_3$	30.7	Inductive Stabilization versus Lone Pair Repulsion (-I vs +M -Effect)
$\underset{H}{PhSO_2\text{-}CH}\text{-}OPh$	27.9	
$\underset{H}{PhSO_2\text{-}CH}\text{-}\overset{\oplus}{N}Me_3$	19.4	Inductive Stabilization

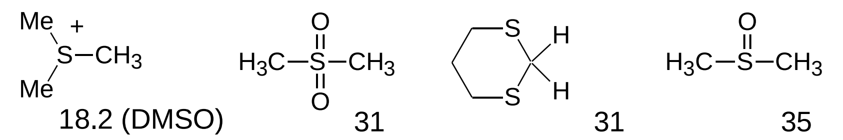
■ Heteroatom-Substituents: - 2nd row elements of periodic table

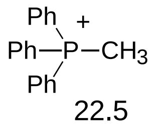
Strong carbanion stabilizing effect

	pK_A (DMSO)		pK_A (DMSO)
$\underset{H}{PhSO_2\text{-}CH}\text{-}H$	29	$\underset{H}{PhSO_2\text{-}CH}\text{-}SO_2Ph$	12.2
$\underset{H}{PhSO_2\text{-}CH}\text{-}SPh$	20.5	$\underset{H}{PhSO_2\text{-}CH}\text{-}PPh_2$	20.5

Acidity Trends for Carbonyl & Related Compounds

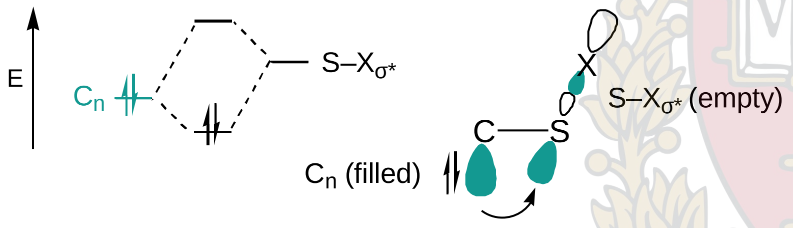
Carbanion Stabilization by 2rd–Row Atoms: SR, SO_2R, PR_3 etc





(*JACS* **1976**, *98*, 7498; *JACS* **1977**, *99*, 5633; *JACS* **1978**, *100*, 200).

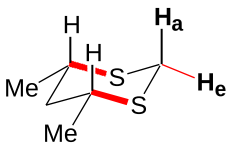
The accepted explanation for carbanion stabilization in 3rd row elements is delocalization into vicinal antibonding orbitals



This argument suggests a specific orientation requirement. This has been noted:

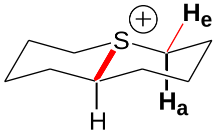
Anti (or syn) periplanar orientation of Carbanion-orbital and σ* orbital mandatory for efficient orbital overlap.

Rates for deprotonation with *n*-BuLi



$H_e : H_a = 8.6$

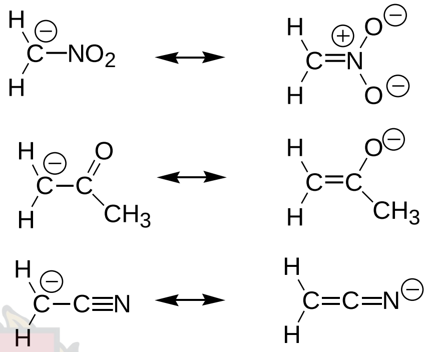
(*JACS* **1974**, *96*, 1811)



$H_e : H_a = 30$

(*JACS* **1978**, *100*, 200)

Conjugative Stabilization of Conjugate Base



17.2 pK_A (DMSO)

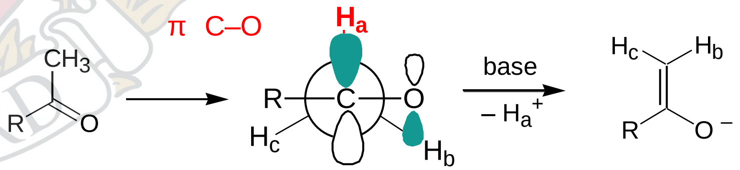
26.5

31.5

For efficient conjugative stabilization, rehybridization of carbanion orbital from n_{sp3} to n_p is required for efficient overlap with low-lying π*-orbital of stabilizing group. However, the cost of rehybridization must be considered.

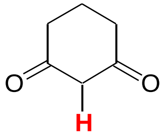
Stereoelectronic Requirement for Carbanion Overlap: Enolization of Carbonyl Compounds

Stereoelectronic Requirements: The α-C-H bond must be able to overlap with π C–O



pK_A

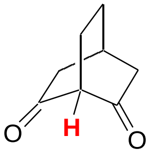
pK_A (DMSO)



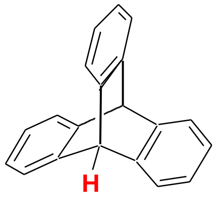
5.2

Ph_3C–**H**

31.5



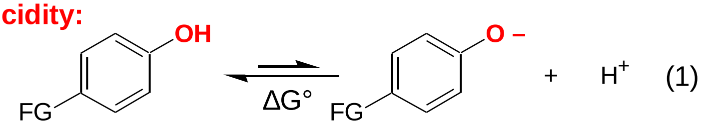
C-H acidity not detectable



47.7

Phenol Acidity: An Analysis of Resonance & Inductive Effects

■ Phenol Acidity:

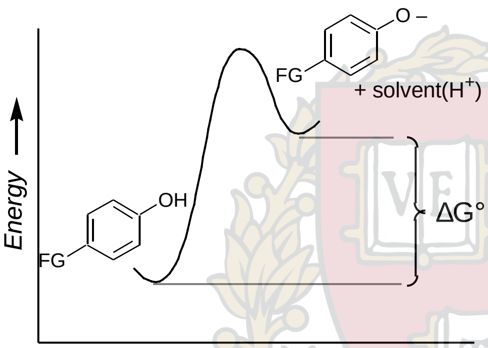


This topic has a number of take-home lessons. Most importantly, is is a useful construct on which to discuss the role of FG's in influencing the acidity of this oxygen acid.

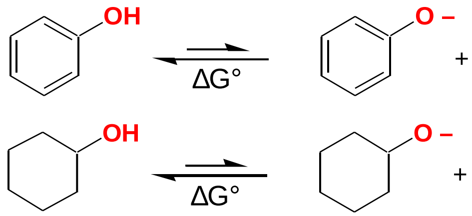
■ How does one analyze the impact of structure on pKa of a weak acid (pKa > 0) ?

■ The Approach:

For equilibria such as that presented above, analyze the effect of stabilizing (or destabilizing) interactions on the more energetic constituent which in this case is the conjugate base.



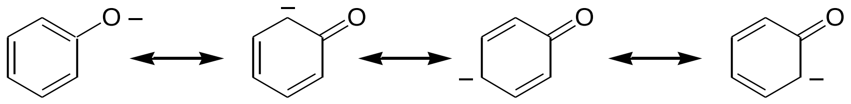
■ Why is phenol so much more acidic than cyclohexanol?



+ H^+ pKa (H_2O) = 10

+ H^+ pKa (H_2O) = 17

Loudon (pg 730): "The enhanced acidity of phenol is due largely to stabilization of its conjugate base by resonance."

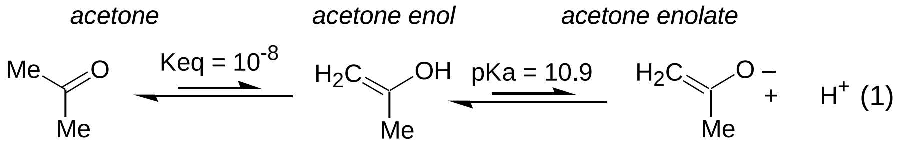


from previous discussion, $\Delta G^\circ_{298} = -1.4\ \mathrm{Log}_{10}\ \mathrm{Keq} = 1.4\ \mathrm{pKeq}$

$\Delta G^\circ\ (\mathrm{stab}) = 1.4(\mathrm{Pka}_{\mathrm{phenol}} - \mathrm{pKa}_{\mathrm{cyclohenanol}}) = 1.4(-7) = 9.8$ kcal/mol

■ Is the benzene ring somehow special. i.e "larger resonance space."

■ Acetone enol:



The surprising facts is that the acetone enol has nearly the same pKa as phenol. Hence, the answer to the above question is no!

■ How important are inductive effects in the stabilization of $C_6H_5O^-$?

Consider the following general oxygen acid X–OH where X can only stabilize the conjugate base through induction:

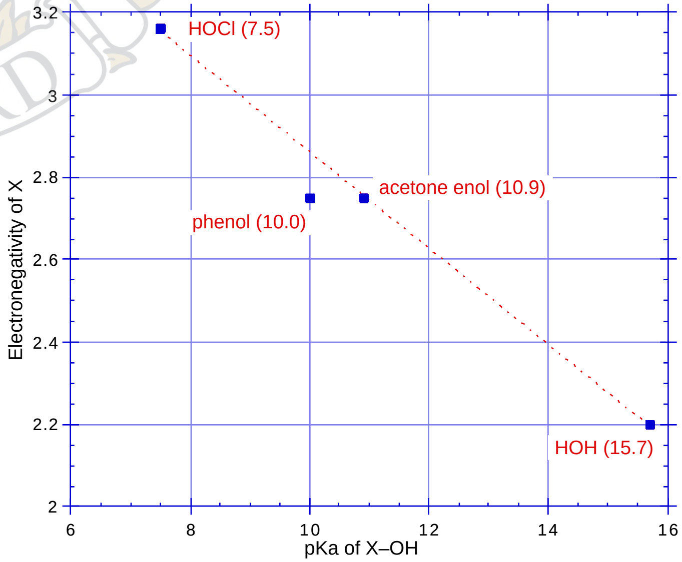
$$\text{X—OH} \rightleftharpoons \text{X—O}^- + H^+$$

As the electronegativity of X increases the acidity of X–OH increases.

X—OH	pKa(H_2O)
CH_3—OH	15.5
CF_3CH_2—OH	12.4
Cl—OH	7.5

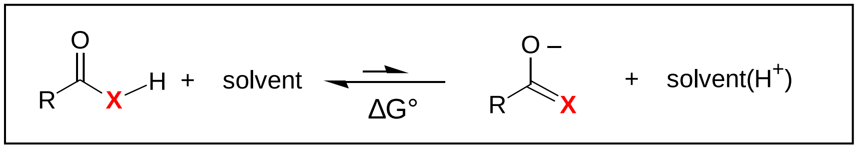
If you take the calculated electronegativity of an SP_2 carbon (2.75) you can see that there is a linear correlation between the electronegativity of X and the pKa of X–OH.

This argument suggests that the acidity of acetone enol is largely due to inductive stabilization, not resonance.



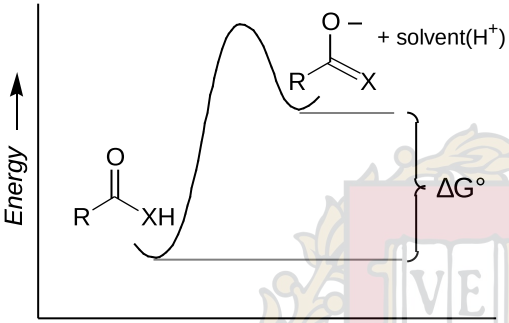
Weak Acids: Impact of Structure on Acidity

The General Reaction: Ionization of a weak acid (pKa ≤ 0)



Variables:
X = O (carboxylic acid)
X = NH (amide)
X = CH_2 (Ketone/ester)

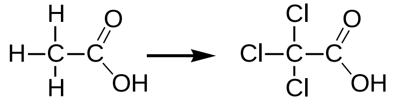
R = CR_3
R = OR
R = NR_2



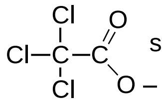
- The Question: How does one analyze the impact of structure on pKa ?
- The Approach:

For equilibria such as that presented above, analyze the effect of stabilizing (or destabilizing) interactions on the more energetic constituent which in this case is the conjugate base.

Case I: Carboxylic Acids: Inductive Effects

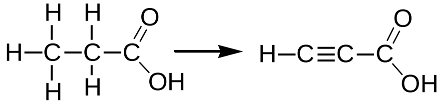


pKa = 4.8 pKa = 0.6

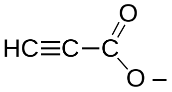


Carboxylate ion stabilized by increased electron-withdrawing CCl_3 group.

Case II: Carboxylic Acids: Inductive Effects & Carbon Hybridization

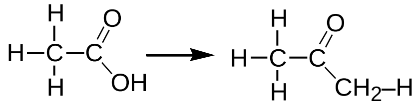


pKa = 4.9 pKa = 1.9

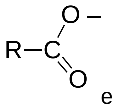


Carboxylate ion stabilized by increased electron-withdrawing SP-hybridized carbon

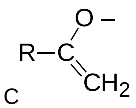
Case III: Carboxylic Acids vs Ketones:



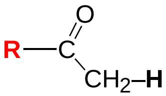
pKa = 4.8 pKa ~ 19



Carboxylate ion more stabile than enolate because O more electronegative than C



Case IV: Carboxylic Acids, Esters, Amides & Ketones:

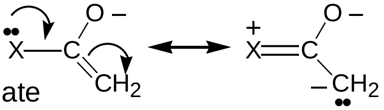


pKa ~ 26 pKa ~ 30 pKa ~ 34 pKa > 34 < 40

The Analysis:

In this series of compounds, there are two variables to consider:

- Inductive Effect: OEt > Me_2N > H_3C but (O–?)
- Resonance Effect:

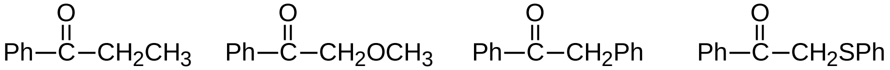


The degree to which substituent X: "contributes" electron density into enolate represents a destabilizing interaction:

Trend: O– > Me_2N > OEt

- Resonance donation dominates inductive electron withdrawal as indicated by the data.

Substituents on the α-carbon: Stabilization by either resonance, induction, or both is observed:



$Ph-\overset{O}{\overset{\|}{C}}-CH_2CH_3$ pKa = 24.4

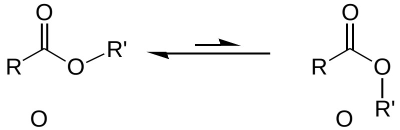
$Ph-\overset{O}{\overset{\|}{C}}-CH_2OCH_3$ pKa = 22.9

$Ph-\overset{O}{\overset{\|}{C}}-CH_2Ph$ pKa = 17.7

$Ph-\overset{O}{\overset{\|}{C}}-CH_2SPh$ pKa = 17.1

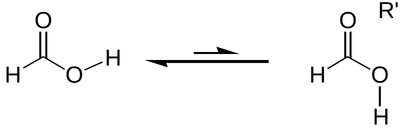
Conformations: There are 2 planar conformations.

(Z) Conformer



(E) Conformer

Specific Case:
Formic Acid

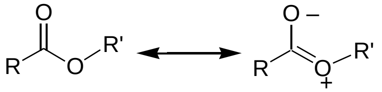


ΔG° = +2 kcal/mol

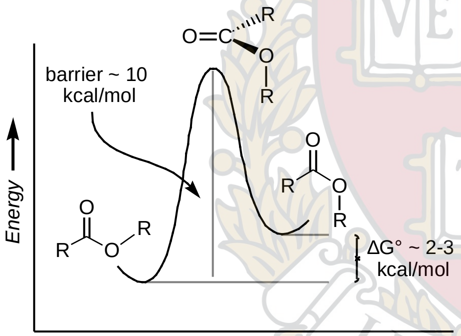
The (E) conformation of both acids and esters is less stable by 2-3 kcal/mol. If this equilibrium were governed only by steric effects one would predict that the (E) conformation of formic acid would be more stable (H smaller than =O). Since this is not the case, there are electronic effects which must also be considered. These effects will be introduced shortly.

Rotational Barriers: There is hindered rotation about the =C–OR bond.

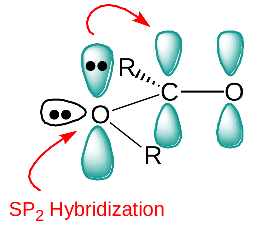
These resonance structures suggest hindered rotation about =C–OR bond. This is indeed observed:



Rotational barriers are ~ 10 kcal/mol This is a measure of the strength of the pi bond.



Lone Pair Conjugation: The oxygen lone pairs conjugate with the C=O.

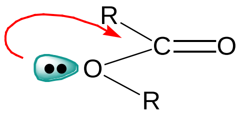


The filled oxygen p-orbital interacts with pi (and pi*) C=O to form a 3-centered 4-electron bonding system.

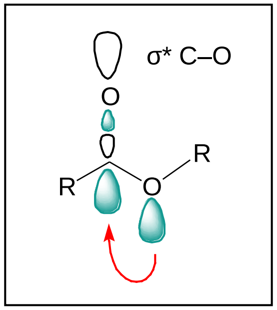
Oxygen Hybridization: Note that the alkyl oxygen is Sp2. Rehybridization is driven by system to optimize pi-bonding.

Hyperconjugation: Let us now focus on the oxygen lone pair in the hybrid orbital lying in the sigma framework of the C=O plane.

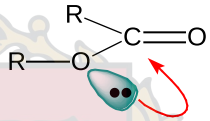
(Z) Conformer



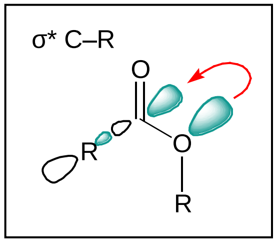
In the (Z) conformation this lone pair is aligned to overlap with σ* C–O.



(E) Conformer



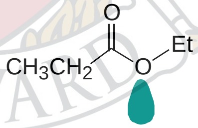
In the (E) conformation this lone pair is aligned to overlap with σ* C–R.



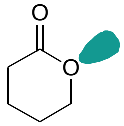
Since σ* C–O is a better acceptor than σ* C–R (where R is a carbon substituent) it follows that the (Z) conformation is stabilized by this interaction.

Lone pair orientation & Impact on pKa (DMSO)

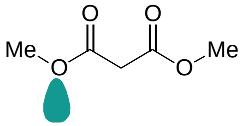
See Bordwell, *J. Org. Chem.* **1994,** *59*, 6456-6458



pKa ~ 30

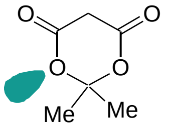


pKa = 25.2

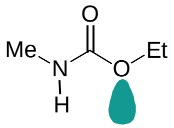


pKa = 15.9

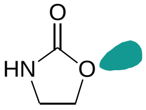
Meldrum's Acid



pKa = 7.3



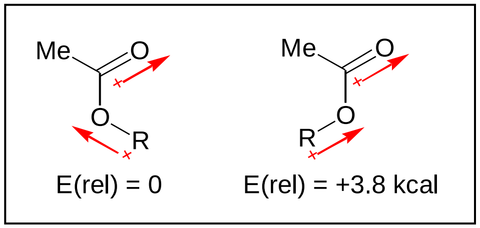
pKa = 24.5



pKa = 20.6

Houk, *JACS* **1988**, *110*, 1870
supports the dipole argument

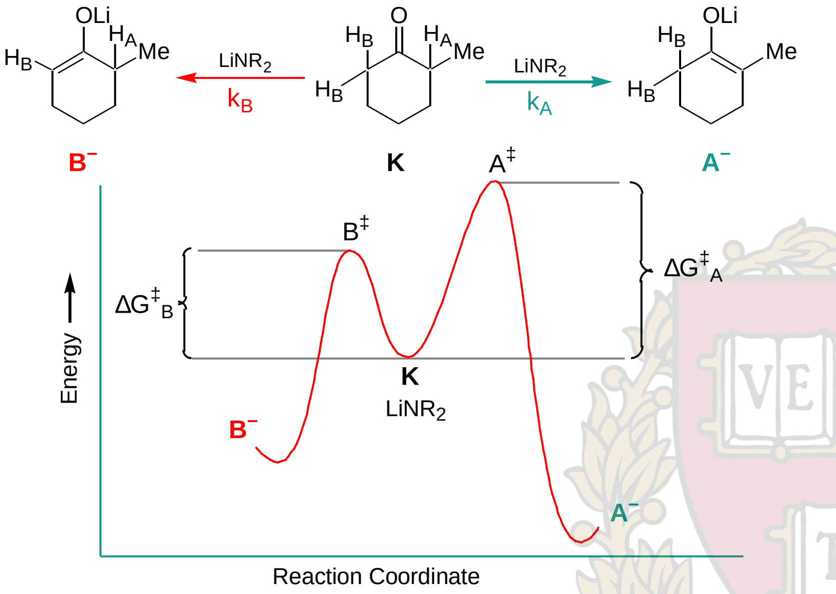
Is this a dipole effect? See Bordwell



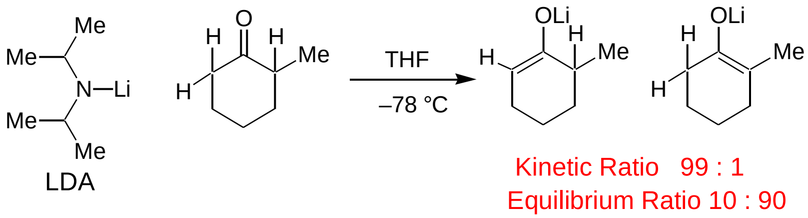
Kinetic & Thermodynamic Acidity of Ketones

■ Kinetic Acidity: Rates of proton removal

Consider enolization of the illustrated ketone under non-equilibrating conditions:

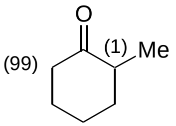


Kinetic acidity refers to the rate of proton removal. e.g. k_A vs k_B. For example, in reading the above energy diagram you would say that H_A has a lower kinetic acidity than H_B. As such, the structure of the base (hindered vs unhindered) employed plays a role in determining the magnitude of k_A and k_B. For the case shown above, $\Delta G^‡_A$ will increase more than $\Delta G^‡_B$ as the base becomes more hindered since the proton H_A resides in a more sterically hindered environment. The example shown below shows the high level of selectivity which may be achieved with the sterically hindered base lithium diisopropylamide (LDA).

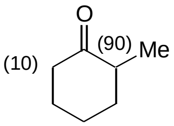


Kinetic Ratio 99 : 1
Equilibrium Ratio 10 : 90

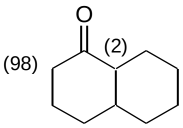
Kinetic & Equilibrium Ratios of Enolates Resulting from Enolization with LDA & Subsequent Equilibration



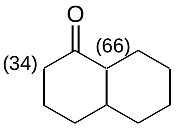
Kinetic Ratios



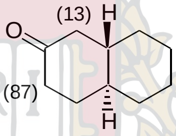
Equilibrium Ratios



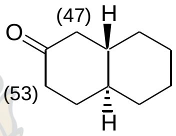
Kinetic Ratios



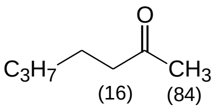
Equilibrium Ratios



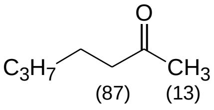
Kinetic Ratios



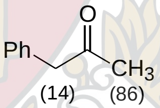
Equilibrium Ratios



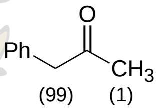
Kinetic Ratios



Equilibrium Ratios



Kinetic Ratios



Equilibrium Ratios

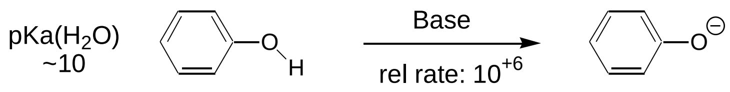
■ Note that alkyl substitution stabilizes the enolate (Why??). This effect shows up in the equilibrium ratios shown above.

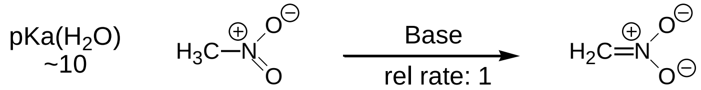
■ Hence, enolization under "kinetic control with LDA allows you to produce the less-substituted enolate while subsequent equilibration by simply heating the enolate mixture allows equilibration to the more substituted enolate.

Kinetic Acidity: Carbon versus Oxygen Acids

■ Kinetic Acidity

Observation: The thermodynamic acidities of phenol and nitromethane are both approximately 10; however, using a common base, phenol is deprotonated 10^{+6} times as fast.

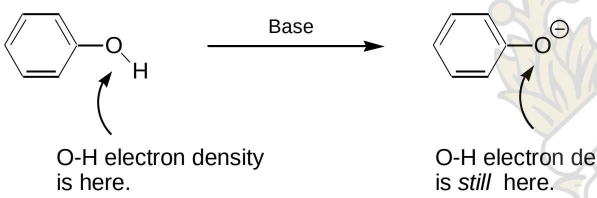


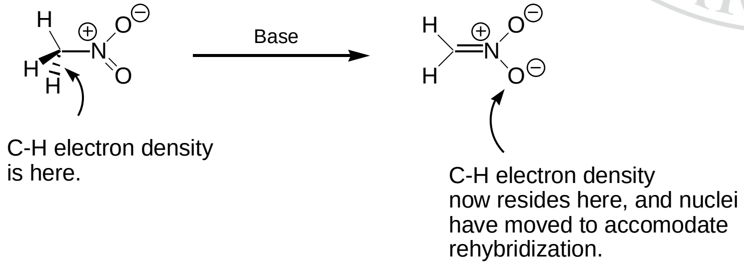


Proton transfers from C-H Bonds are slow.

■ Why???

Most carbon acids are stabilized by resonance. Hence significant structural reorganization must accompany deprotonation.

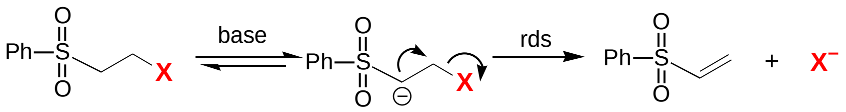


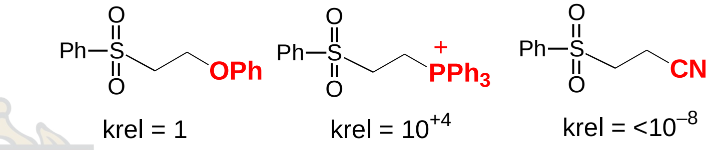


The greater the structural reorganization during deprotonation, the lower the kinetic acidity

■ Kinetic Acidity vs. Leaving Group Ability: E1cb Elimination Reactions

Stirling, *Chem. Commun.* **1975**, 940



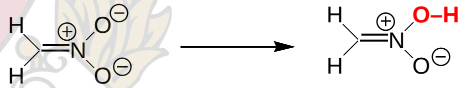


krel = 1 | krel = 10^{+4} | krel = $<10^{-8}$

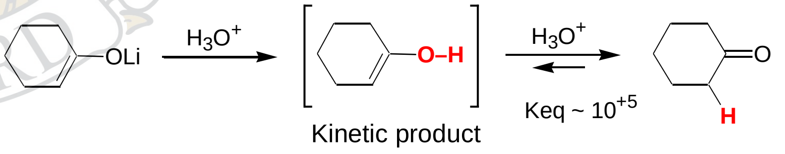
pKa HX | 10 | 0 | 9.5

The greater the structural reorganization of the leaving group during E1cb elimination, the slower the rate of elimination.

■ Protonation of Conjugate bases



Kinetic product



Kinetic product

Jack Hine: Least Motion Principle (*Adv. Phys. Org. Chem*. **1977**, *15*, 1)
Lowry & Richardson, 3rd Edition, pp 205-206

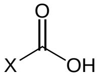
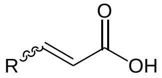
Those elementary reactions that involve the least change in atomic posiitons will be favored

pKa's of Inorganic and Oxo-Acids

INORGANIC ACIDS

Substrate	pKa H_2O	(DMSO)
H_2O	15.7	(32)
H_3O^+	-1.7	
H_2S	7.00	
HBr	-9.00	(0.9)
HCl	-8.0	(1.8)
HF	3.17	(15)
HOCl	7.5	
$HClO_4$	-10	
HCN	9.4	(12.9)
HN_3	4.72	(7.9)
HSCN	4.00	
H_2SO_3	1.9, 7.21	
H_2SO_4	-3.0, 1.99	
H_3PO_4	2.12, 7.21, 12.32	
HNO_3	-1.3	
HNO_2	3.29	
H_2CrO_4	-0.98, 6.50	
CH_3SO_3H	-2.6	(1.6)
CF_3SO_3H	-14	(0.3)
NH_4Cl	9.24	
$B(OH)_3$	9.23	
HOOH	11.6	

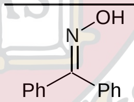
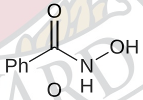
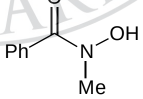
CARBOXYLIC ACIDS

Substrate	pKa H_2O	(DMSO)
		
X= CH_3	4.76	(12.3)
CH_2NO_2	1.68	
CH_2F	2.66	
CH_2Cl	2.86	
CH_2Br	2.86	
CH_2I	3.12	
$CHCl_2$	1.29	
CCl_3	0.65	
CF_3	-0.25	
H	3.77	
HO	3.6, 10.3	
C_6H_5	4.2	(11.1)
o-$O_2NC_6H_4$	2.17	
m-$O_2NC_6H_4$	2.45	
p-$O_2NC_6H_4$	3.44	
o-ClC_6H_4	2.94	
m-ClC_6H_4	3.83	
p-ClC_6H_4	3.99	
o-$(CH_3)_3N^+C_6H_4$	1.37	
p-$(CH_3)_3N^+C_6H_4$	3.43	
p-$OMeC_6H_4$	4.47	
		
R= H	4.25	
trans-CO_2H	3.02, 4.38	
cis-CO_2H	1.92, 6.23	

ALCOHOLS

Substrate	pKa H_2O	(DMSO)
	15.7	(31.2)
	15.54	(27.9)
	16.5	(29.3)
t-BuOH	17	(29.4)
c-hex_3COH	24	
	12.5	(23.5)
$(CF_3)_2CHOH$		(17.9)
C_6H_5OH	9.95	(18.0)
m-$O_2NC_6H_4OH$	8.35	
p-$O_2NC_6H_4OH$	7.14	(10.8)
p-$OMeC_6H_4OH$	10.20	(19.1)
2-napthol		(17.1)

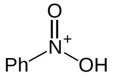
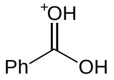
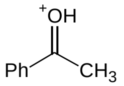
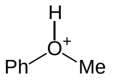
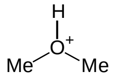
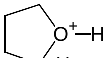
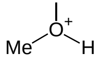
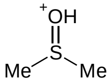
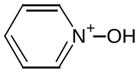
OXIMES & HYDROXAMIC ACIDS

Substrate	pKa H_2O	(DMSO)
	11.3	(20.1)
	8.88	(13.7)
		(18.5)

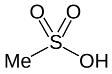
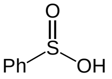
PEROXIDES

Substrate	pKa H_2O	(DMSO)
MeOOH	11.5	
CH_3CO_3H	8.2	

PROTONATED SPECIES

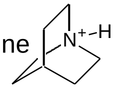
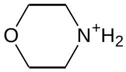
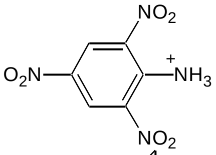
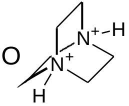
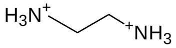
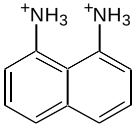
Substrate	pKa H_2O	(DMSO)
	-12.4	
	-7.8	
	-6.2	
	-6.5	
	-3.8	
	-2.05	
	-2.2	
	-1.8	
	0.79	

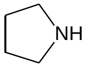
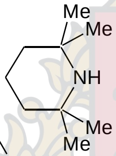
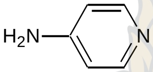
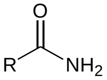
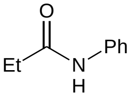
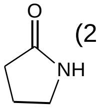
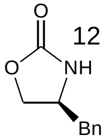
SULFINIC & SULFONIC ACIDS

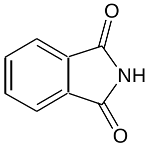
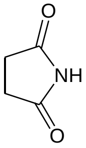
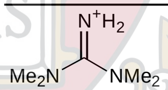
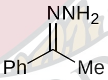
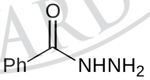
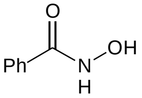
Substrate	pKa H_2O	(DMSO)
	-2.6	
	2.1	

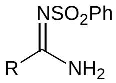
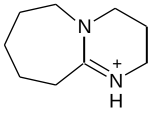
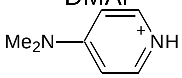
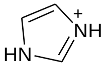
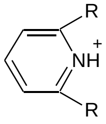
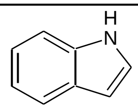
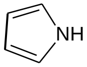
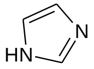
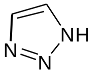
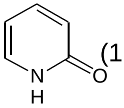
*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

pKa's of Nitrogen Acids

Substrate	pKa H_2O	(DMSO)
PROTONATED NITROGEN		
N^+H_4	9.2	(10.5)
EtN^+H_3	10.6	
$i\text{-}Pr_2N^+H_2$	11.05	
Et_3N^+H	10.75	(9.00)
PhN^+H_3	4.6	(3.6)
$PhN^+(Me)_2H$	5.20	(2.50)
$Ph_2N^+H_2$	0.78	
2-napthal-N^+H_3	4.16	
$H_2NN^+H_3$	8.12	
HON^+H_3	5.96	
Quinuclidine 	11.0	(9.80)
Morpholine 	8.36	
N-Me morpholine	7.38	
	-9.3	
DABCO 	2.97, 8.82	(2.97, 8.93)
	6.90, 9.95	
Proton Sponge 	-9.0, 12.0	(--, 7.50)
$PhCN^+H$	-10	

Substrate	pKa H_2O	(DMSO)
AMINES		
HN_3	4.7	(7.9)
NH_3	38	(41)
$i\text{-}Pr_2NH$	(36 THF))	
TMS_2NH	26(THF)	(30)
$PhNH_2$		(30.6)
Ph_2NH		(25.0)
$NCNH_2$		(16.9)
		(44)
TMP 		(37)
		(26.5)
AMIDES & CARBAMATES		
		
R= H		(23.5)
CH_3	15.1	(25.5)
Ph		(23.3)
CF_3		(17.2)
NH_2 (urea)		(26.9)
OEt		(24.8)
		(21.6)
		(24.1)
	12	(20.5)

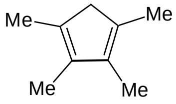
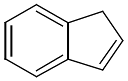
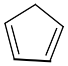
Substrate	pKa H_2O	(DMSO)
IMIDES		
	8.30	
		(14.7)
Ac_2NH		(17.9)
SULFONAMIDE		
$MeSO_2NH_2$		(17.5)
$PhSO_2NH_2$		(16.1)
$CF_3SO_2NH_2$	6.3	(9.7)
$MeSO_2NHPh$		(12.9)
GUANIDINIUM, HYRDAZONES,- IDES, & -INES		
		(13.6)
		(21.6)
		(18.9)
$PhSO_2NHNH_2$		(17.2)
PhNHNHPh		(26.1)
HYDROXAMIC ACID		
	8.88 (NH)	(13.7)

Substrate	pKa H_2O	(DMSO)
AMIDINES		
		
R= Me		(17.3)
Ph		(15.0)
PROTONATED HETEROCYCLES		
DBU 	(12) (estimate)	
DMAP 	9.2	
	6.95	
		
R= H (PPTS)	5.21	(3.4)
t-Bu	4.95	(0.90)
Me	6.75	(4.46)
Cl, H	0.72	
HETEROCYCLES		
		(20.95)
		(23.0)
		(18.6)
1,2,3 triazole 		(13.9)
		(17.0)

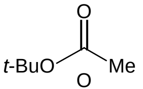
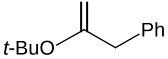
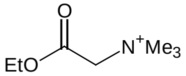
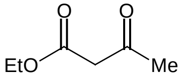
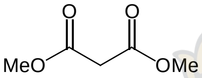
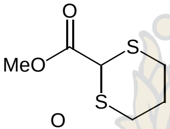
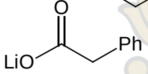
*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

pKa's of CH bonds in Hydrocarbons and Carbonyl Compounds

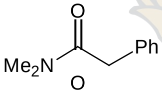
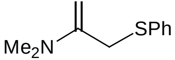
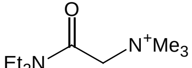
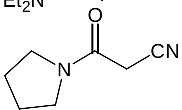
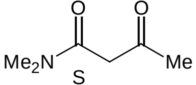
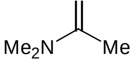
HYDROCARBONS

Substrate	pKa H_2O	(DMSO)
$(Me)_3CH$	53	
$(Me)_2CH_2$	51	
$CH_2=CH_2$	50	
CH_4	48	(56)
	46	
$CH_2=CHCH_3$	43	(44)
PhH	43	
$PhCH_3$	41	(43)
Ph_2CH_2	33.5	(32.2)
Ph_3CH	31.5	(30.6)
HCCH	24	
PhCCH	23	(28.8)
$XC_6H_4CH_3$		
X= *p*-CN		(30.8)
p-NO_2		(20.4)
p-COPh		(26.9)
 Me Me Me Me		(26.1)
	20	(20.1)
	15	(18.0)
H_2	~36	

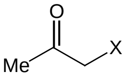
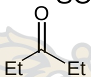
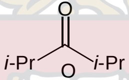
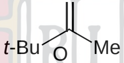
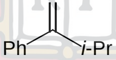
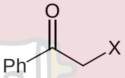
ESTERS

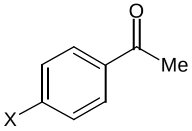
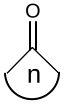
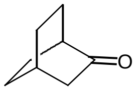
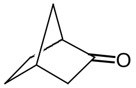
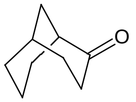
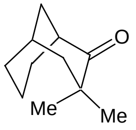
Substrate	pKa H_2O	(DMSO)
 *t*-BuO, Me	24.5	(30.3)
 *t*-BuO, Ph		(23.6)
 EtO, N^+Me_3		(20.0)
 EtO, Me	11	(14.2)
 MeO, OMe	13	(15.7)
 MeO, S, S		(20.9)
 LiO, Ph		[30.2 (THF)]

AMIDES

Substrate	pKa H_2O	(DMSO)
 Me_2N, Ph		(26.6)
 Me_2N, SPh		(25.9)
 Et_2N, N^+Me_3		(24.9)
 N, CN		(17.2)
 Me_2N, Me		(18.2)
 Me_2N, Me		(25.7)

KETONES

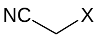
Substrate	pKa H_2O	(DMSO)
 Me, X		
X= H		(26.5)
Ph		(19.8)
SPh		(18.7)
$COCH_3$	9	(13.3)
SO_2Ph		(15.1)
 Et, Et	19-20	(27.1)
 *i*-Pr, *i*-Pr		(28.3)
 *t*-Bu, Me		(27.7)
 Ph, *i*-Pr		(26.3)
 Ph, X		
X= H		(24.7)
CH_3		(24.4)
Ph		(17.7)
$COCH_3$		(12.7)
COPh		(13.3)
CO_2Et		(22.7)
CN		(10.2)
F		(21.6)
OMe		(22.85)
OPh		(21.1)
SPh		(16.9)
SePh		(18.6)
NPh_2		(20.3)
N^+Me_3		(14.6)
NO_2		(7.7)
SO_2Ph		(11.4)

Substrate	pKa H_2O	(DMSO)
 X, Me		
X= H		(24.7)
OMe		(25.7)
NMe_2		(27.5)
Br		(23.8)
CN		(22.0)
 n		
n= 4		(25.1)
5		(25.8)
6		(26.4)
7		(27.7)
8		(27.4)
		(28.1)
		(29.0)
		(25.5)
 Me, Me		(32.4)

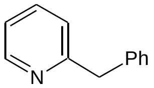
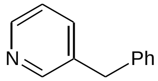
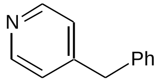
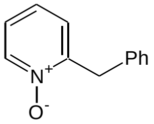
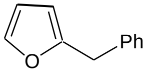
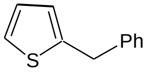
*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

pKa's of CH bonds at Nitrile, Heteroaromatic, and Sulfur Substituted Carbon

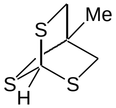
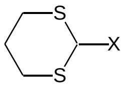
NITRILES

Substrate	pKa H_2O	(DMSO)
		
X= H		(31.3)
CH_3		(32.5)
Ph		(21.9)
COPh		(10.2)
$CONR_2$		(17.1)
CO_2Et		(13.1)
CN	11	(11.1)
OPh		(28.1)
N^+Me_3		(20.6)
SPh		(20.8)
SO_2Ph		(12.0)

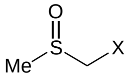
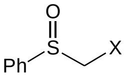
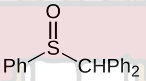
HETERO-AROMATICS

Substrate	pKa H_2O	(DMSO)
		(28.2)
		(30.1)
		(26.7)
		(25.2)
		(30.2)
		(30.0)

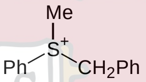
SULFIDES

Substrate	pKa H_2O	(DMSO)
$PhSCH_2X$		
X= Ph		(30.8)
CN		(20.8)
$COCH_3$		(18.7)
COPh		(16.9)
NO_2		(11.8)
SPh		(30.8)
SO_2Ph		(20.3)
SO_2CF_3		(11.0)
$POPh_2$		(24.9)
$MeSCH_2SO_2Ph$		(23.4)
$PhSCHPh_2$		(26.7)
$(PhS)_3CH$		(22.8)
$(PrS)_3CH$		(31.3)
		(30.5)
$(PhS)_2CHPh$		(23.0)
		
X= Ph		(30.7)
CO_2Me		(20.8)
CN		(19.1)
$RSCH_2CN$		
R= Me		(24.3)
Et		(24.0)
i-Pr		(23.6)
t-Bu		(22.9)
$PhSCH=CHCH_2SPh$		(26.3)
BuSH	10-11	(17.0)
PhSH	≈7	(10.3)

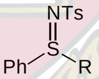
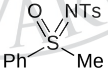
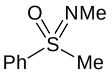
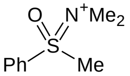
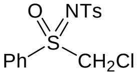
SULFOXIDES

Substrate	pKa H_2O	(DMSO)
		
X= H		(35.1)
Ph		(29.0)
SPh		(29.0)
		
X= H		(33)
Ph		(27.2)
SOPh		(18.2)
		(24.5)

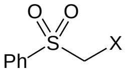
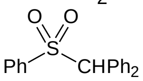
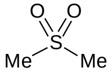
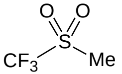
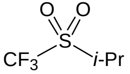
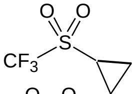
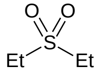
SULFONIUM

Substrate	pKa H_2O	(DMSO)
$Me_3S^+=O$		(18.2)
		(16.3)

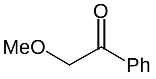
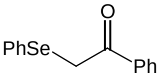
SULFIMIDES & SULFOXIMINES

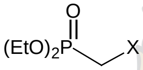
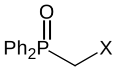
Substrate	pKa H_2O	(DMSO)
		
R= Me		(27.6)
i-Pr		(30.7)
		(24.5)
		(33)
		(14.4)
		(20.7)

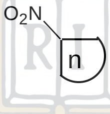
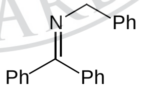
SULFONES

Substrate	pKa H_2O	(DMSO)
		
X= H		(29.0)
CH_3		(31.0)
t-Bu		(31.2)
Ph		(23.4)
$CH=CH_2$		(22.5)
$CH=CHPh$		(20.2)
CCH		(22.1)
CCPh		(17.8)
COPh		(11.4)
COMe		(12.5)
OPh		(27.9)
N^+Me_3		(19.4)
CN		(12.0)
NO_2		(7.1)
SMe		(23.5)
SPh		(20.5)
SO_2Ph		(12.2)
PPh_2		(20.2)
		(22.3)
		(31.1)
		(18.8)
		(21.8)
		(26.6)
		(32.8)
$(PhSO_2)_2CH_2Me$		(14.3)

*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

Substrate	pKa H_2O	(DMSO)
ETHERS		
CH_3OPh		(49)
$MeOCH_2SO_2Ph$		(30.7)
$PhOCH_2SO_2Ph$		(27.9)
$PhOCH_2CN$		(28.1)
		(21.1)
SELENIDES		
		(18.6)
$PhSeCHPh_2$		(27.5)
$(PhSe)_2CH_2$		(31.3)
$PhSeCH_2Ph$		(31.0)
$PhSeCH=CHCH_2SePh$		(27.2)
AMMONIUM		
$Me_3N^+CH_2X$		
X= CN		(20.6)
SO_2Ph		(19.4)
COPh		(14.6)
CO_2Et		(20.6)
$CONEt_2$		(24.9)

Substrate	pKa H_2O	(DMSO)
PHOSPHONIUM		
P^+H_4	-14	
MeP^+H_3	2.7	
Et_3P^+H	9.1	
$Ph_3P^+CH_3$		(22.4)
Ph_3P^+*i*-Pr		(21.2)
$Ph_3P^+CH_2COPh$		(6.2)
$Ph_3P^+CH_2CN$		(7.0)
PHOSPONATES & PHOSPHINE OXIDES		
		
X= Ph		(27.6)
CN		(16.4)
CO_2Et		(18.6)
Cl		(26.2)
$SiMe_3$		(28.8)
		
X= SPh		(24.9)
CN		(16.9)
PHOSPHINES		
$Ph_2PCH_2PPh_2$		(29.9)
$Ph_2PCH_2SO_2Ph$		(20.3)

Substrate	pKa H_2O	(DMSO)
NITRO		
RNO_2		
R= CH_3	$\approx$10	(17.2)
CH_2Me		(16.7)
$CHMe_2$		(16.9)
CH_2Ph		(12.2)
CH_2Bn		(16.2)
CH_2SPh		(11.8)
CH_2SO_2Ph		(7.1)
CH_2COPh		(7.7)
		
n= 3		(26.9)
4		(17.8)
5		(16.0)
6		(17.9)
7		(15.8)
IMINES		
		(24.3)

Oxime ethers are ~ 10 pka units less acidic than their ketone counterparts
Streitwieser, JOC 1991, 56, 1989

REFERENCES

DMSO:

JACS 97, 7007 (1975)
JACS 97, 7160 (1975)
JACS 97, 442 (1975)
JACS 105, 6188 (1983)
JOC 41, 1883 (1976)
JOC 41, 1885 (1976)
JOC 41, 2786 (1976)
JOC 41, 2508 (1976)
JOC 42, 1817 (1977)
JOC 42, 321 (1977)
JOC 42, 326 (1977)
JOC 43, 3113 (1978)
JOC 43, 3095 (1978)
JOC 43, 1764 (1978)
JOC 45, 3325 (1980)
JOC 45, 3305 (1980)
JOC 45, 3884 (1980)
JOC 46, 4327 (1981)
JOC 46, 632 (1981)
JOC 47, 3224 (1982)
JOC 47, 2504 (1982)
Acc. Chem. Res. 21, 456 (1988)
Unpublished results of F. Bordwell

Water:

Advanced Org. Chem., 3rd Ed.
J. March (1985)
Unpublished results of W. P. Jencks

THF:

JACS 110, 5705 (1988)

*Values <0 for H_2O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

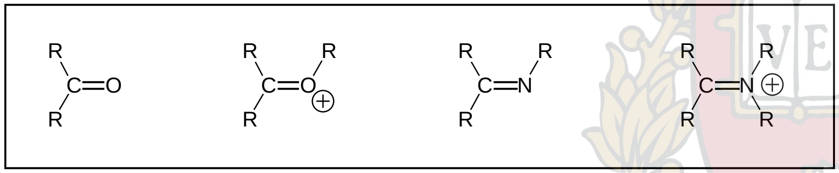
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 18

Carbonyl and Azomethine Electrophiles-1



- Reactivity Trends
- C=X Stereoelectronic Effects
- Carbonyl Addition: Theoretical Models
- The Felkin-Anh-Eisenstein Model for C=O Addition
- Diastereoselective Ketone Reduction

■ Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

Matthew D. Shair

Wednesday,
October 30, 2002

Additional Reading Material Provided

Additions to 5- & 6-Membered oxocarbenium Ions:

Woerpel etal. *JACS* **1999**, *121*, 12208.
Woerpel etal. *JACS* **2000**, *122*, 168.

"Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein *Nouv. J. Chem.* **1977**, *1*, 61-70.

■ Relevant Dunitz Articles

"Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group", *JACS* **1973**, *95*, 5065.

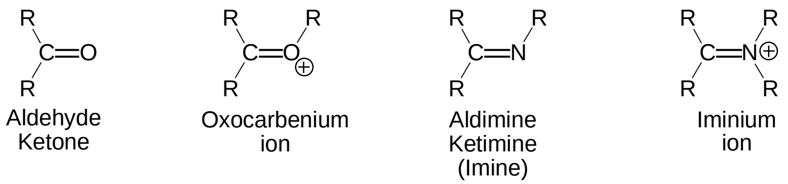
"Stereochemistry of Reaction Paths at Carbonyl Centers", *Tetrahedron* **1974**, *30*, 1563

"From Crystal Statics to Chemical Dynamics", *Accounts Chem. Research* **1983**, *16*, 153.

"Stereochemistry of Reaction Paths as Determined from Crystal Structure Data. A Relationship Between Structure and Energy.", Burgi, H.-B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460.

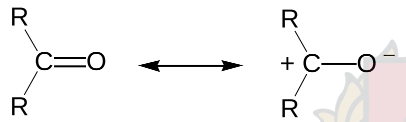
C=X Electrophiles: Carbonyls, Imines & Their Conjugate Acids

The Set of Functional Groups:

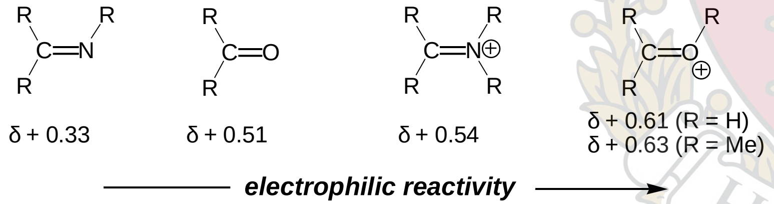


These functional groups are among the most versatile sources of electrophilic carbon in both synthesis and biosynthesis. The ensuing discussion is aimed at providing a more advanced discussion of this topic.

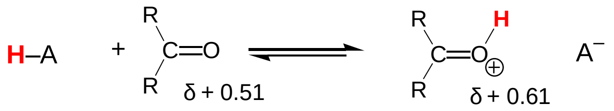
C=X Polarization



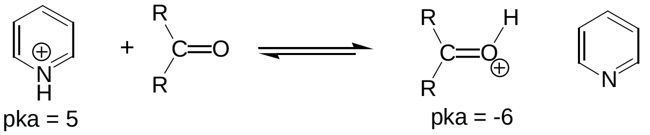
Partial Charge: As the familiar polar resonance structure above indicates, the carbonyl carbon supports a partial positive charge due to the polarization of the sigma and pi system by the more electronegative heteroatom. The partial charges for this family of functional groups derived from molecular orbital calclulations (ab initio, 3-21(G)*, HF) are illustrated below:



Proton Activation of C=X Functional groups



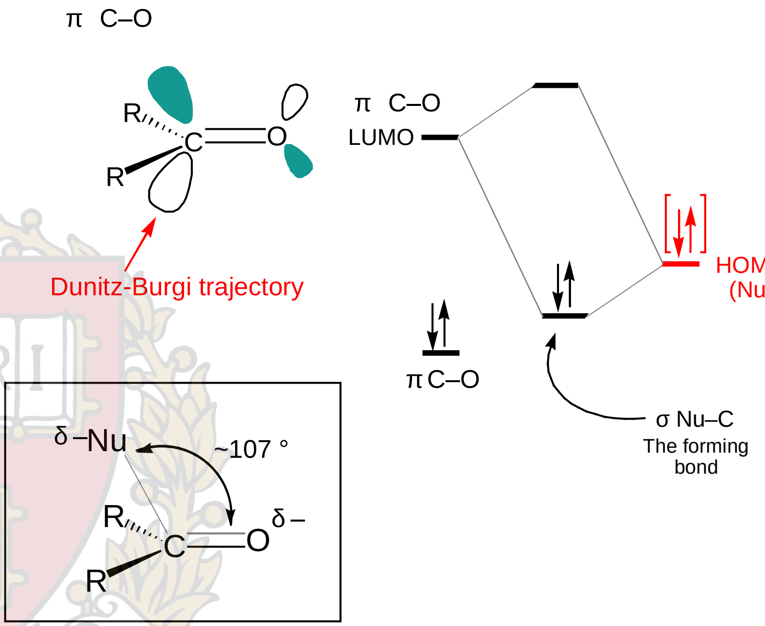
The electrophilic potential of the C=O FG may be greatly increased by either Lewis acid coordination of by protonation. The magnitude of this increase in reactivity is ~ 10^{+6}. Among the weakest Bronsted acids that may be used for C=O actilvation (ketalization) is pyridinium ion (pKa = 5). Hence, the Keq below, while quite low, is still functional.



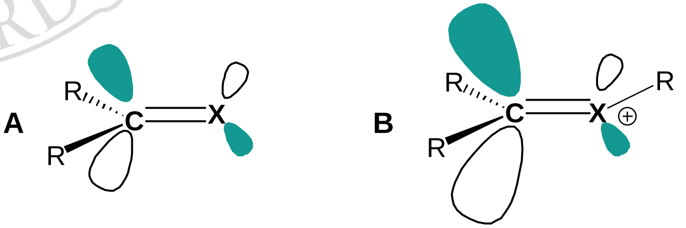
Keq ~ 10^{-11}

Stereoelectronic Considerations for C=O Addition

LUMO is π C–O; HOMO Provided by Nu:



What about C=X vs C=X-R(+)?



The LUMO coefficient on carbon for **B** will be considerably larger than for **A**. Does this mean that there is a lower constraint on the approach angle for the attacking nucleophile? There is no experimental proof for this question; however, it is worthy of consideration

What was the basis for the Dunitz-Burgi analysis?

The Dunitz-Burgi Trajectory for C=O Addition

■ Relevant Dunitz Articles

"Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group", *JACS* **1973**, *95*, 5065.

"Stereochemistry of Reaction Paths at Carbonyl Centers", *Tetrahedron* **1974**, *30*, 1563

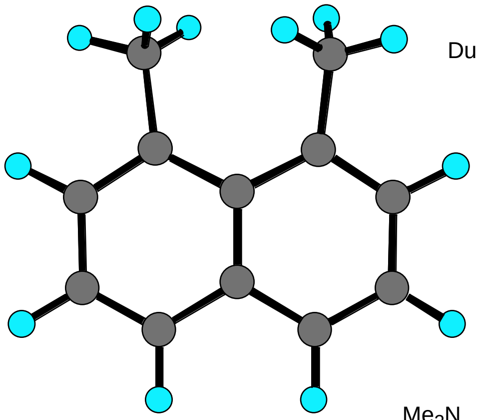
"From Crystal Statics to Chemical Dynamics", *Accounts Chem. Research* **1983**, *16*, 153.

"Stereochemistry of Reaction Paths as Determined from Crystal Structure Data. A Relationship Between Structure and Energy.", Burgi, H.-B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460.

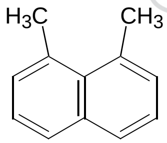
■ Dunitz Method of Analysis

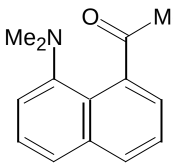
A series of organic structures containing both C=O and Nu FG's disposed in a geometry for mutual interaction were designed. These structures positioned the interacting FGs an increasingly closer distances. The X-ray structures of these structures were determined to ascertain the direction of C=O distortion. The two families of structures that were evaluated are shown below.

1,8-Disubstituted Naphthalenes. Substituents located at these positions are strongly interacting as illustrated by the MM2 minimized di-methyl-naphthalene structure shown below.

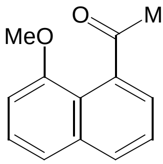


Dunitz, *Helv. Chem. Acta* **1978**, *61*, 2783

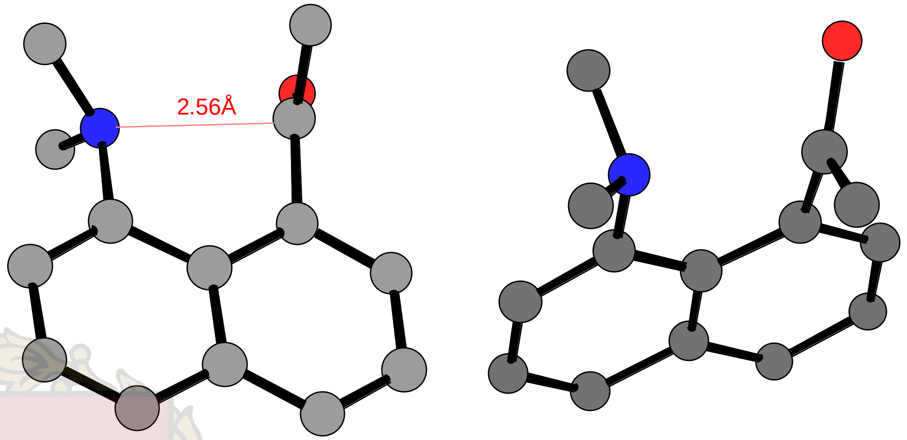




A (shown)

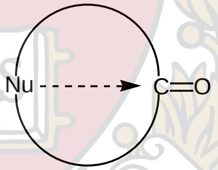


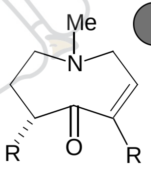
B



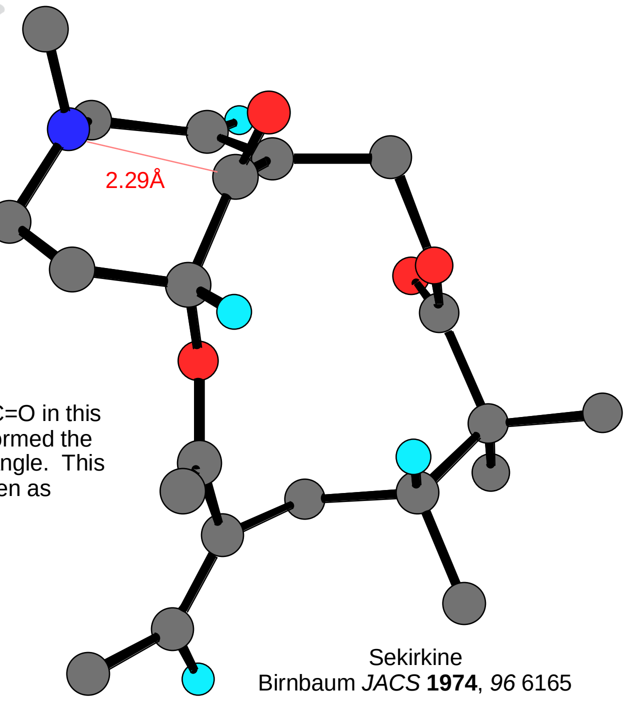
In this structure (**A**), at 2.56Å the C=O is starting to pyramidalize

Cyclic aminoketones. Medium-ring ketones of various ring sizes were analyzed for the interaction of amine an C=O FGs. One example is shown below.





Analysis of distortion of C=O in this and related structures formed the basis of the 107° attack angle. This value should be taken as approximate.



Sekirkine
Birnbaum *JACS* **1974**, *96* 6165

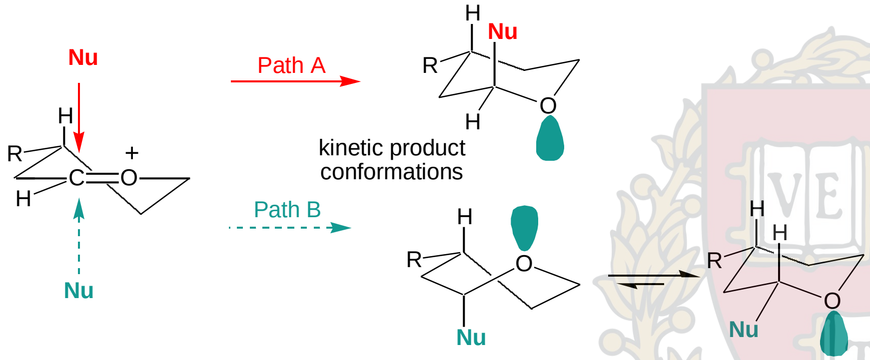
Stereoelectronic Effects in the Addition to Iminium and Oxo-carbenium Ions

■ Pivotal Articles

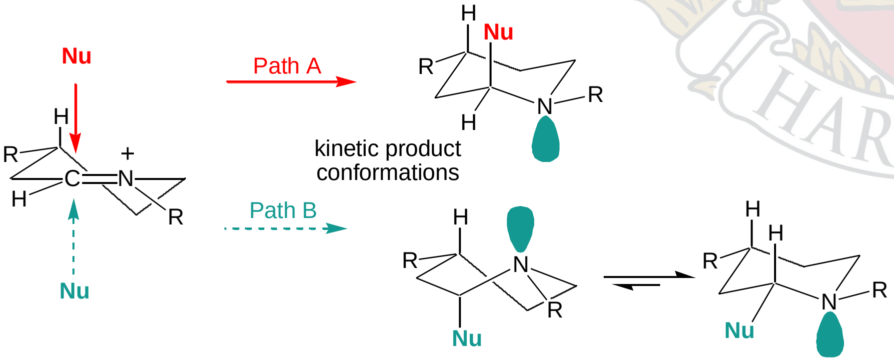
R. V. Stevens in
"Strategies and Tactics in Organic Synthesis", Vol. 1.
On the Stereochemistry of Nucleophilic Additions to Tetrahydropyridinium Salts: a Powerful Heuristic Principle for the Stereorationale Design of Alkaloid Synthesis.;
Lindberg, T., Ed.; Academic Press, 1984;

Eliel etal. , *JACS* **1969**, *91*, 536
Kishi etal. , *JACS* **1982**, *104*, 4976-8

■ The Proposal for Oxo-carbenium Ions (Eliel, Kishi)

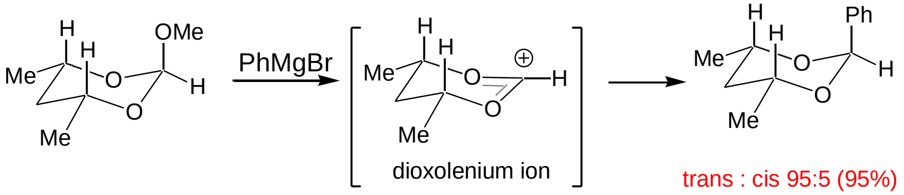


■ The Proposal for Iminium Ions (Stevens)



It was proposed that chair-axial addition would be preferred as a consequence of the intervention of a transition state anomeric effect (Path A). Attack through Path B would necessitate the generation of the twist-boat kinetic product conformation thus destabilizing attack from the equatorial diastereoface. While Stevens espoused this concept for iminium ions in the late 70's, his untimely death at the age of 42 significantly delayed his cited publication.

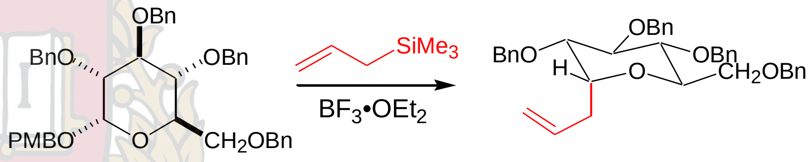
■ An early example from Eliel; *JACS* 1969, *91*, 536



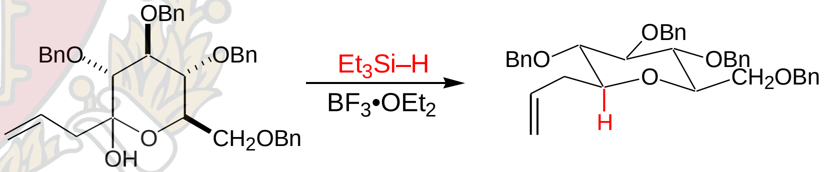
trans : cis 95:5 (95%)

Eliel was the first to attibute stereoelectronic factors to the addition of nucleophiles to cyclic oxo-carbenium ions.

■ Kishi Examples; *JACS* 1982, *104*, 4976-8



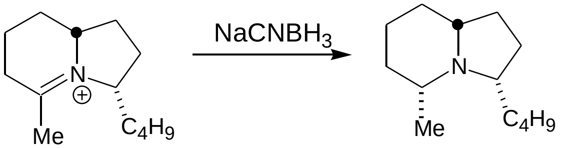
stereoselection 10:1 (55%)



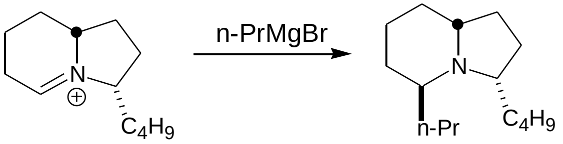
stereoselection 10:1 (55%)

Chair-axial attack on oxo-carbenium ion occurs for both carbon and hydride nucleophiles

■ Iminium Ions (Stevens) *cited reference*

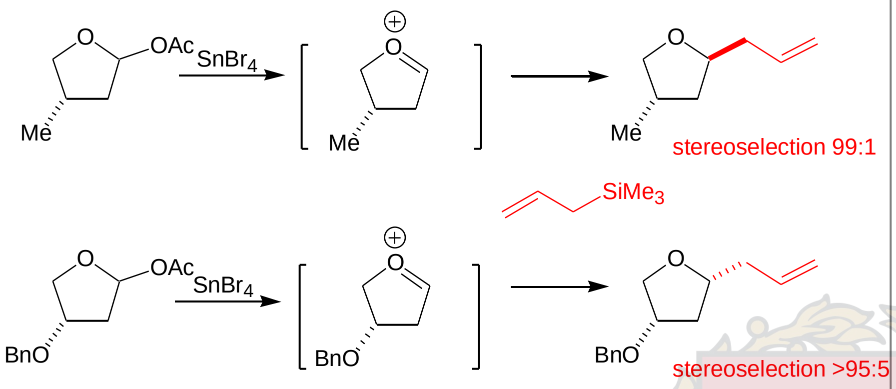


only one stereoisomer



Stereoelectronic Effects in the Addition to Iminium and Oxo-carbenium Ions

5-Membered oxocarbenium Ions: Woerpel etal. *JACS* 1999, 121, 12208.

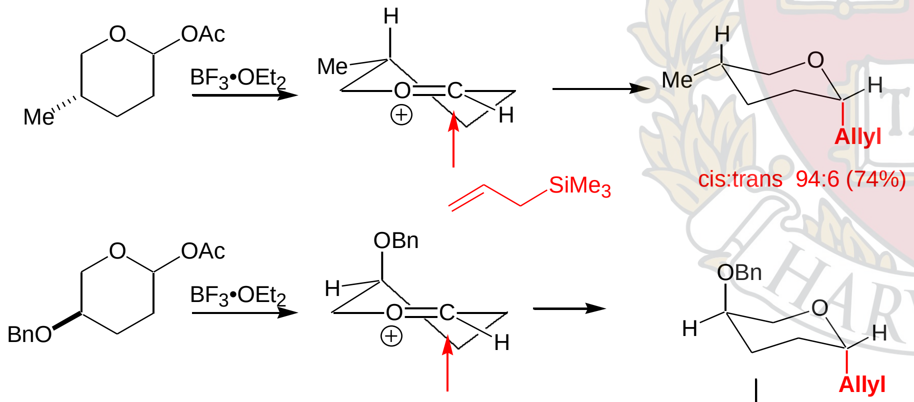


stereoselection 99:1

stereoselection >95:5

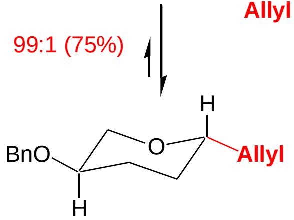
These cases provide dramatic evidence for the importance of electrostatic effects in controlling face selecticity.

6-Membered oxocarbenium Ions: Woerpel etal. *JACS* 2000, 122, 168.



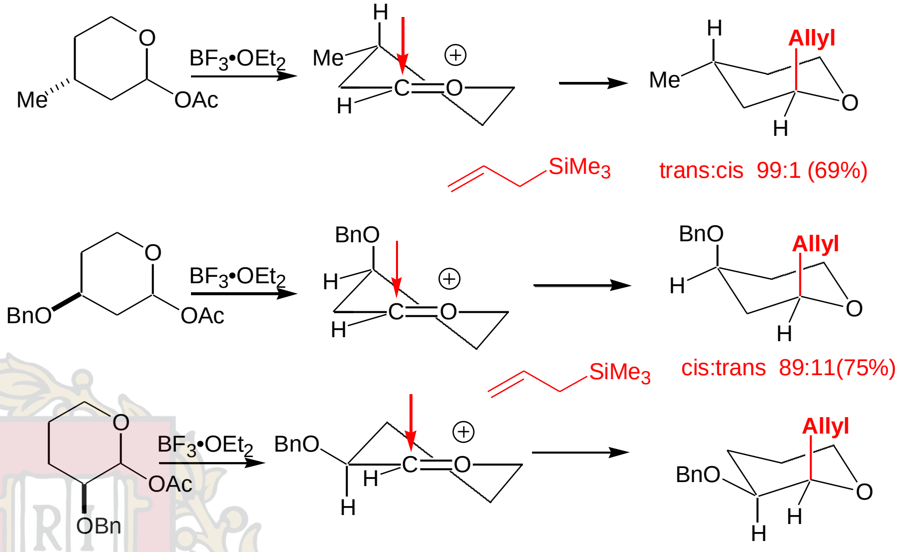
cis:trans 94:6 (74%)

trans:cis 99:1 (75%)



This analysis presumes that only pseudo-chair transition states need be considered.

Woerpel's model states that axial attack from the most stable chair conformer predicts the major product.



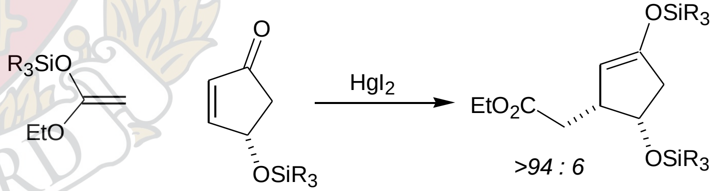
trans:cis 99:1 (69%)

cis:trans 89:11(75%)

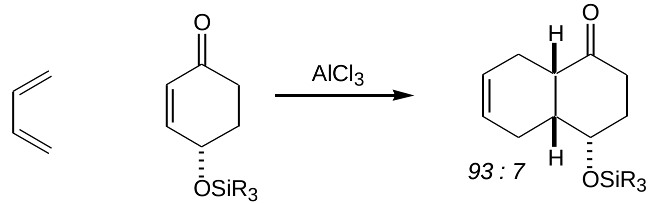
cis:trans 83:17(84%)

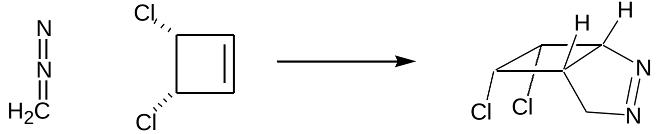
These cases provide dramatic evidence for the importance of electrostatic effects in controlling face selecticity.

Are the preceding addition reactions somehow related to the apparently contrasteric reactions shown below??



JOC **1991**, *56*, 387





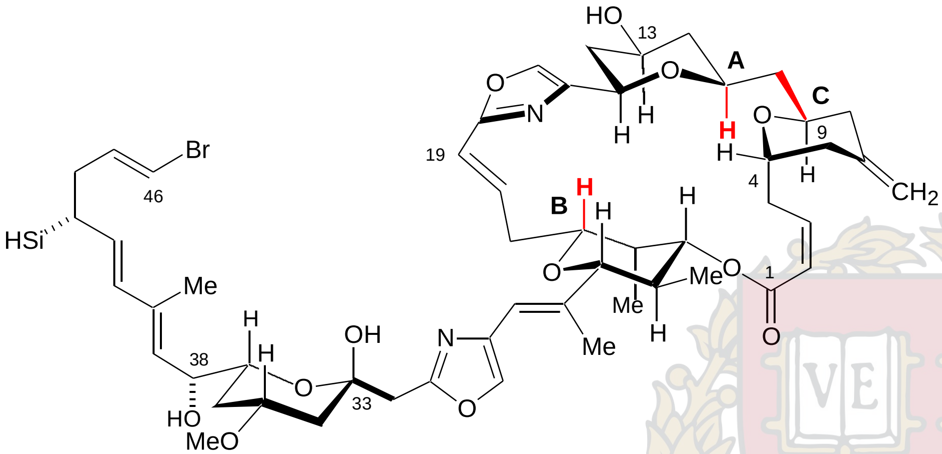
exclusive adduct

Tet. Lett. **1988**, *29*, 6593

Diastereoselective Oxocarbenium Ion Additions in the Phorboxazole Synthesis

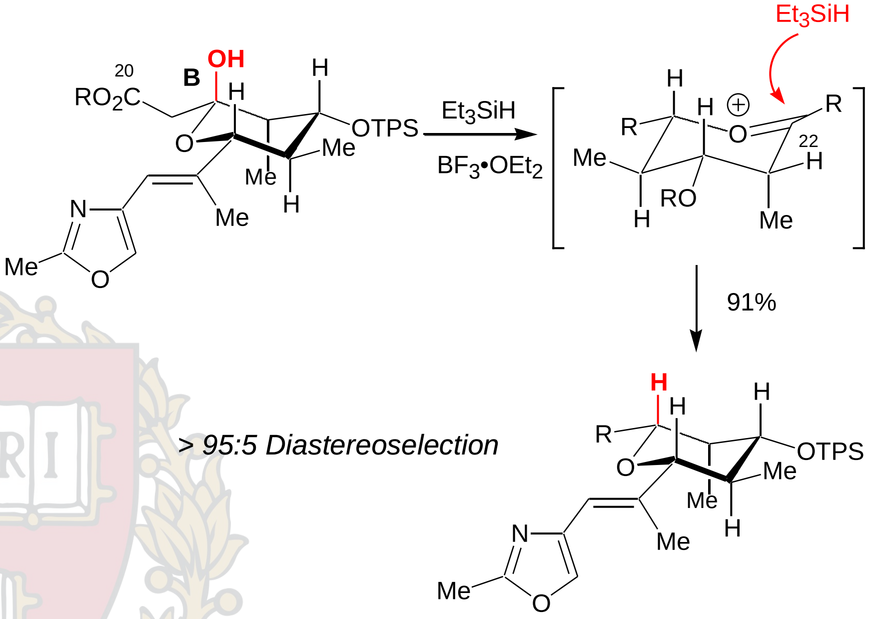
Phorboxazole B

Evans, Fitch, Smith, Cee, *JACS* ***2000****, 122, 10033*



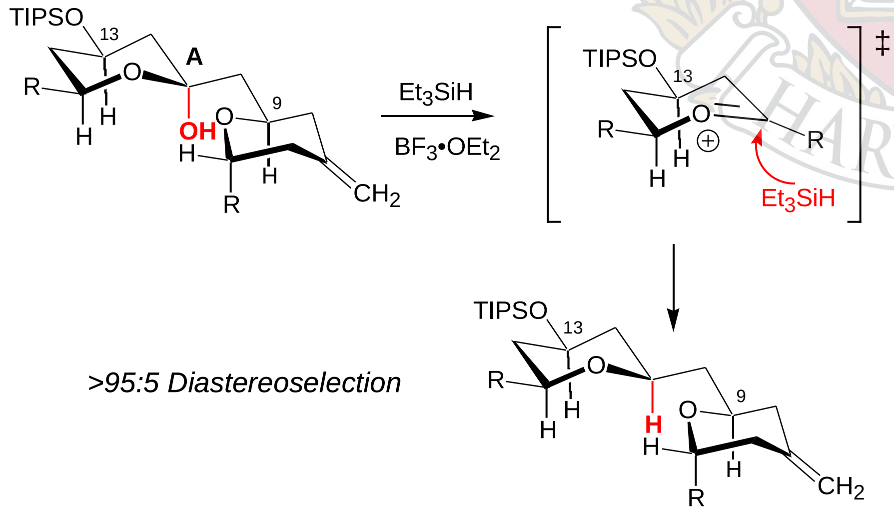
Stereochemical analogies:
Kishi et. al.: *JACS* **1982**, *104*, 4976-8

B: The C-22 Reduction



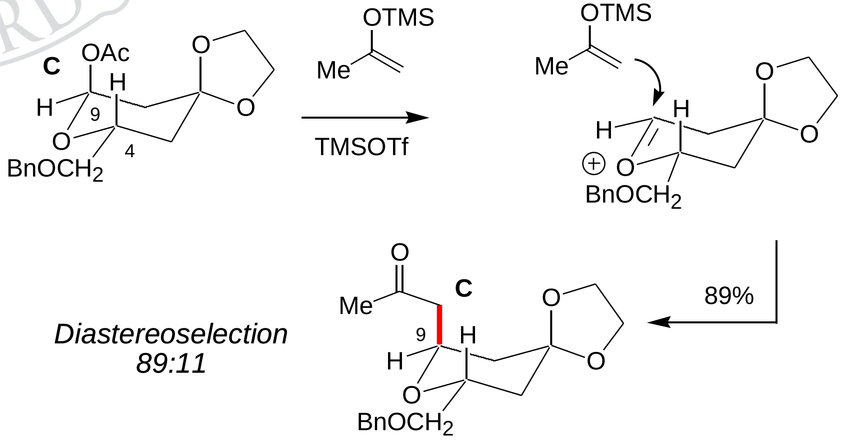
> 95:5 Diastereoselection

A: The C-11 Reduction



>95:5 Diastereoselection

C: The C-9 C–C Bond Construction



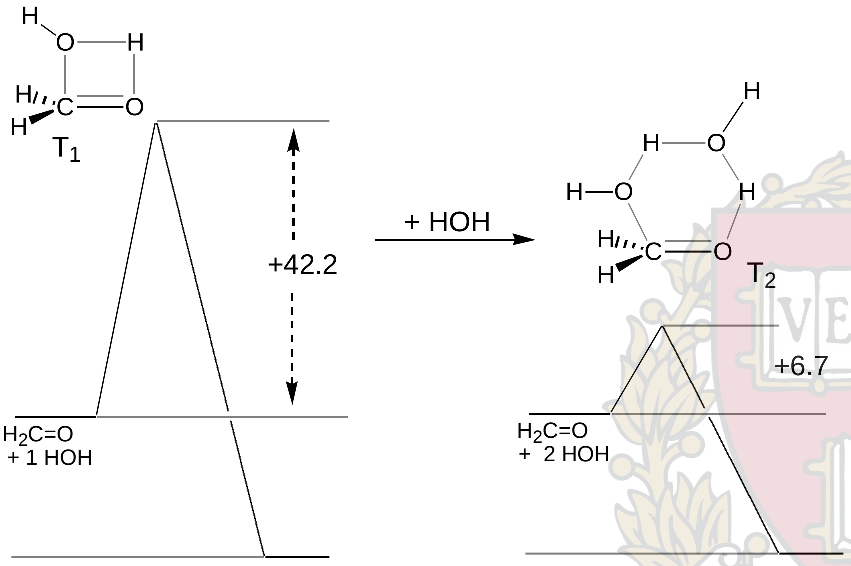
Diastereoselection
89:11

Carbonyl Addition Reactions: Transition State Geometry

4- vs 6-Membered Transition Structures for C=O Addition

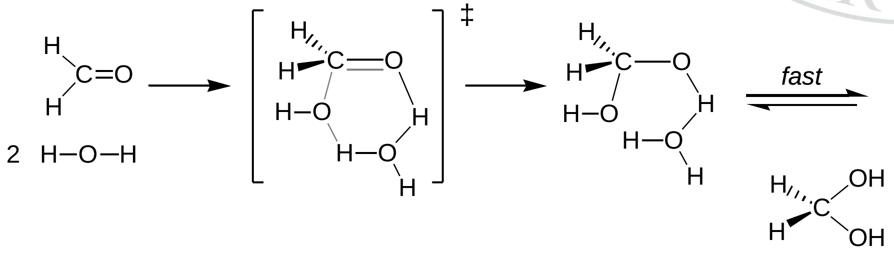
Consider carbonyl hydration:

$H_2C=O$ + n HOH $\longrightarrow$ $H_2C(-OH)_2$ + (n-1) HOH



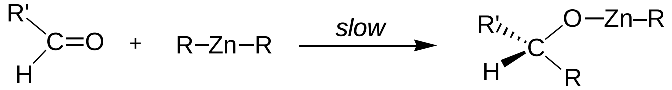
Schowen *J. Am. Chem. Soc*. **105**, 31, (1983).

Overall Process:

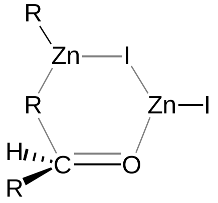


Transiton structure T$_2$ determined to be ~40 kcal/mol more stable than transition structure T$_1$.

Do these results relate to "real" reactions? Yes!



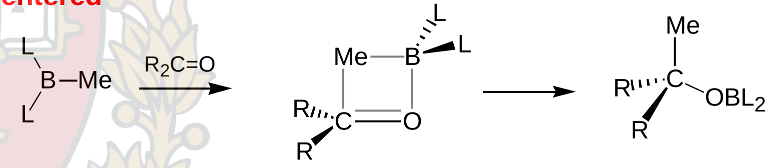
Observation: catalytic amounts of ZnI_2 dramatically catalyze addition process.



The bimetallic transition state

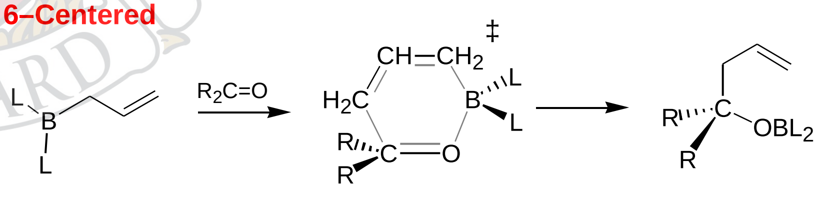
4– Versus 6–Center Transition States for Boron

4-Centered



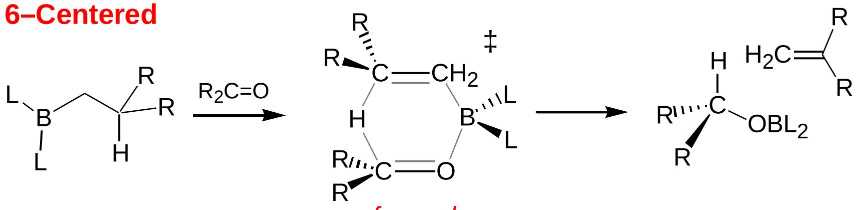
disfavored : rxn does not proceed!)

6–Centered



favored

6–Centered

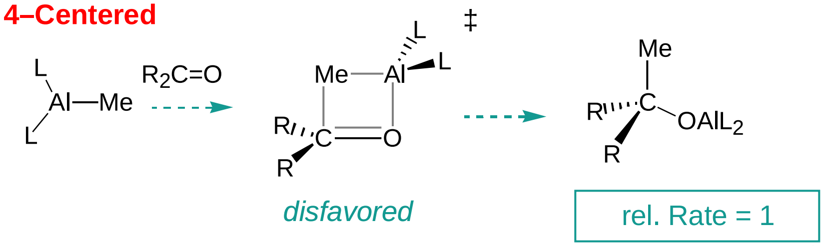


favored

Carbonyl Addition Reactions: Transition State Geometry

Carbonyl Addition: 4– Versus 6–Center Transition States for Aluminum

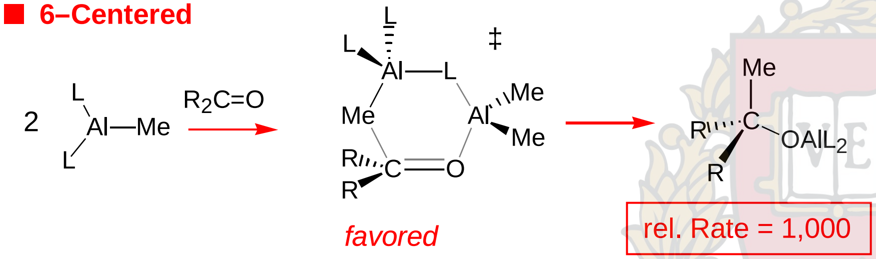
■ 4–Centered



disfavored

rel. Rate = 1

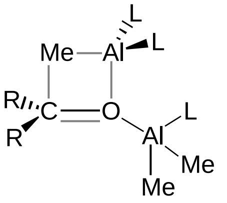
■ 6–Centered



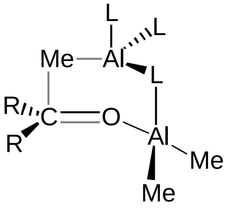
favored

rel. Rate = 1,000

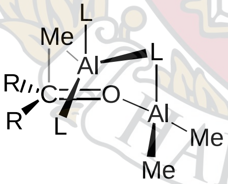
■ Bimetallic Transition States



4-Centered

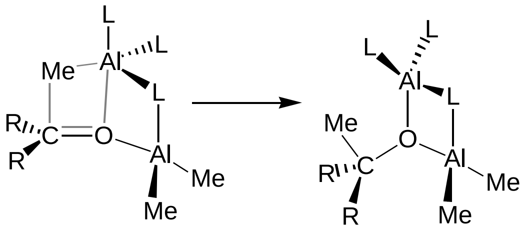


6-Centered Boat



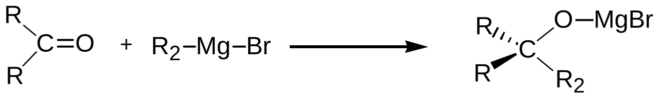
6-Centered Chair

Bicyclic TS



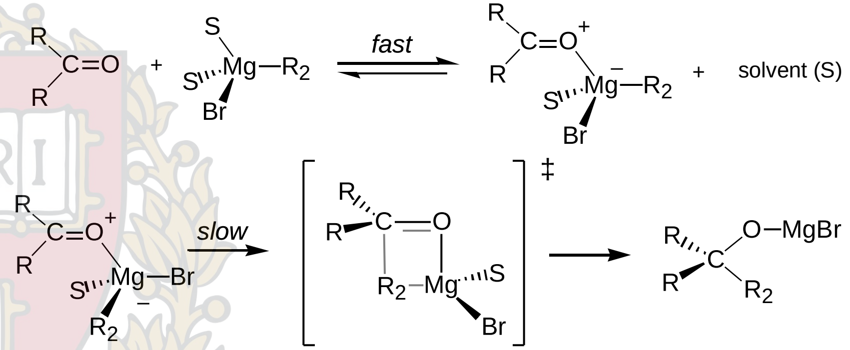
Ashby *JOC* **1977**, *42*, 425

■ Grignard Reagents:

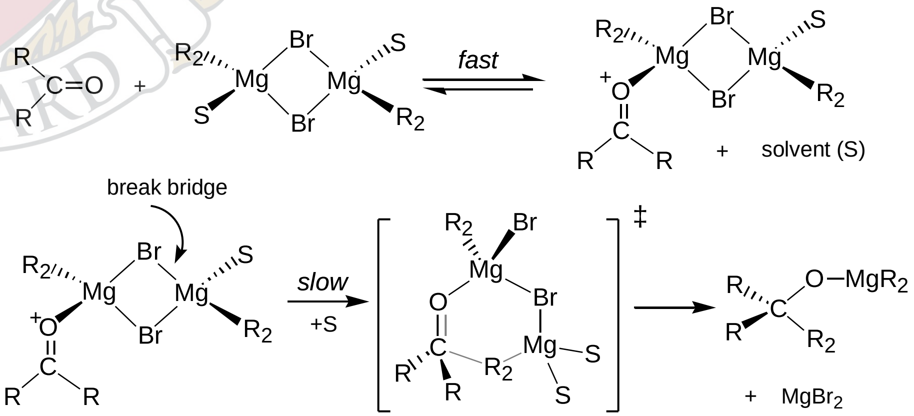


The molecularity and transition structure for this reaction have not been carefully elucidated. The fact that the Grignard reagent is not a single species in solution greatly complicates the kinetic analysis.

■ Monometallic (Mononuclear) Mechanism:



■ Bimetallic (Binuclear) Mechanism: The more probable situation.

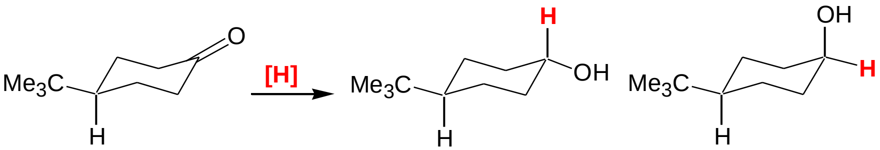


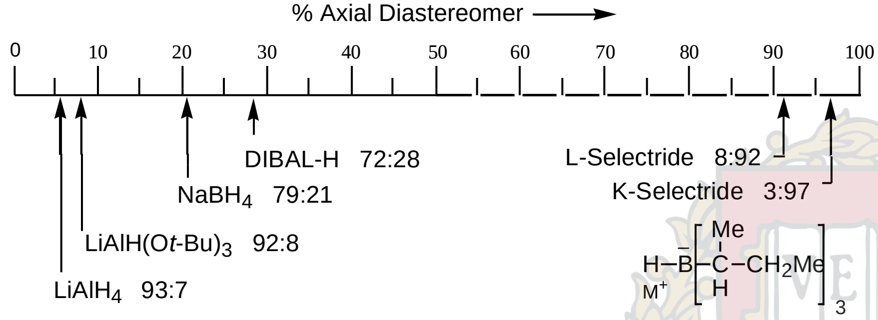
The 6-membered geometry for transferring the R_2 ligand from the metal to the C=O is far less strained.

Evolution of a Model for C=O Addition

■ Product Development & Steric Approach Control:

Dauben, *JACS* **1956**, *78*, 2579



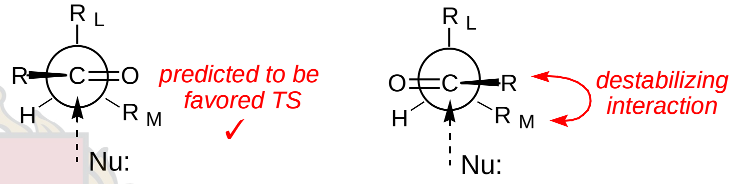


Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

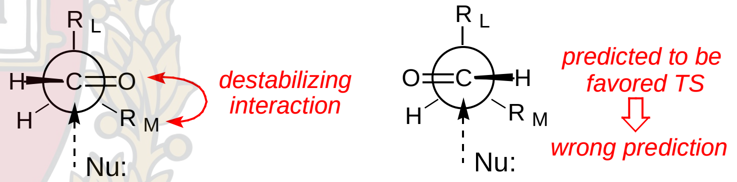
Assumption: Hindered reagents react through more highly developed transition states than unhindered reagents

Assumptions in Felkin Model:

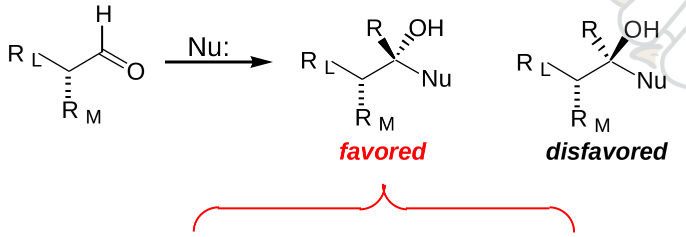
- ■ Transition states are all reactant-like rather than product-like.
- ■ Torsional strain considerations are dominant.
  Staggered TS conformations preferred
- ■ The principal steric interactions are between Nu & R.

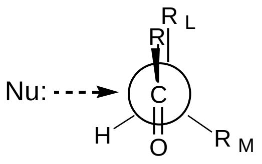


The flaw in the Felkin model: A problem with aldehydes!!

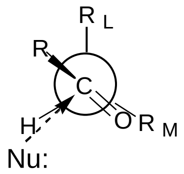


Carbonyl Addition: Evolution of Acyclic Models

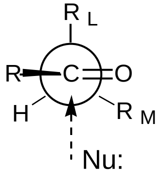




Cram
JACS **1952**, *74*, 5828



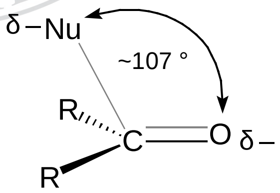
Karabatsos
JACS **1967**, *89*, 1367



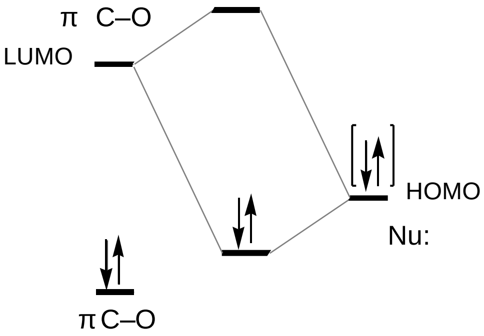
Felkin
TL. **1968**, 2199-2208

Stereoelectronic Effect:

The HOMO-LUMO interaction dictates the following reaction geometry:



The Dunitz-Bürgi Angle

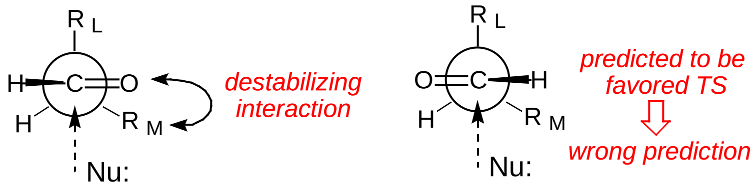


attack angle greater than 90 °; estimates place it in the 100-110 ° range

Burgi, Dunitz, *Acc. Chem. Res.* **1983**, *16*, 153-161

The Felkin-Anh Eisenstein Model

The flaw in the Felkin model: A problem with aldehydes!!



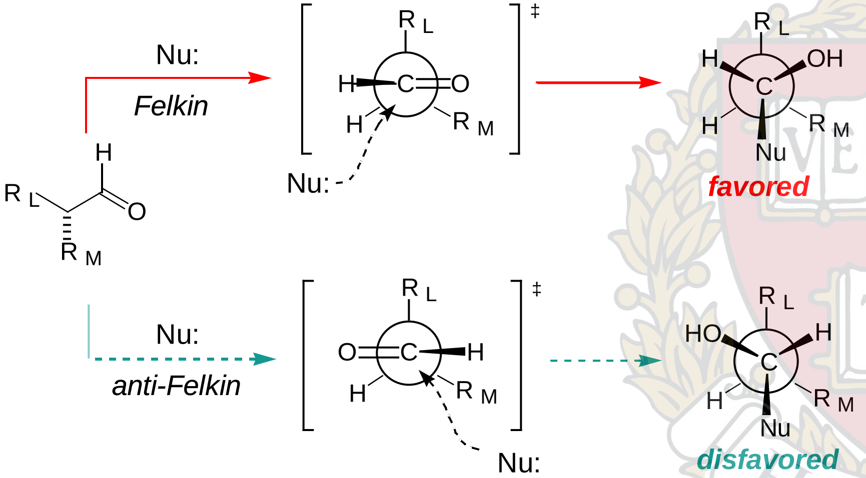
destabilizing interaction

predicted to be favored TS

⇩

wrong prediction

Anh & Eisenstein *Noveau J. Chim.* **1977**, *1*, 61-70
Anh *Topics in Current Chemistry.* **1980**, ***No 88***, 146-162



New Additions to Felkin Model:

- ■ Dunitz-Bürgi C=O–Nu orientation applied to Felkin model.

- ■ The antiperiplanar effect:

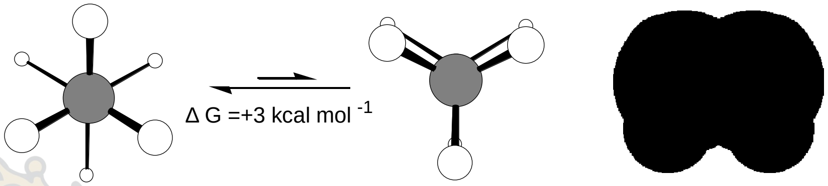
Hyperconjugative interactions between C-R_L which will lower π*C=O will stablize the transition state.

Theoretical Support for Staggered Transition states

Houk, *JACS* **1982**, *104*, 7162-6
Houk, *Science* **1986**, *231*, 1108-17

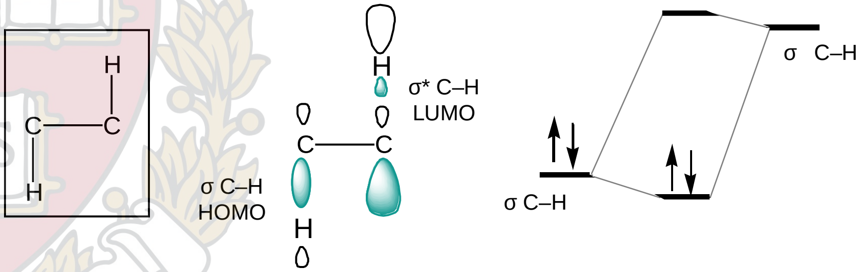
Houk: "The tendency for the staggering of partially formed vicinal bonds is greater than for fully formed bonds"

Lets begin with ground state effects: Ethane Rotational Barrier

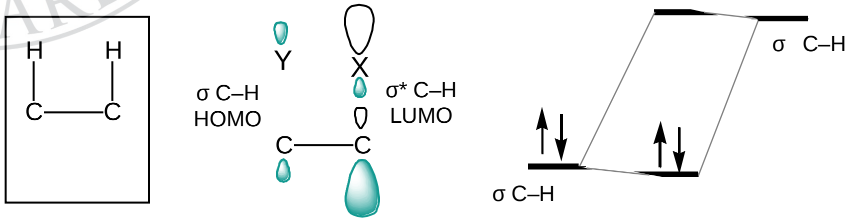


One explanation for the rotational barrier in ethane is that better overlap is achieved in the staggered conformation than in the eclipsed conformation.

In the staggered conformation there are 3 anti-periplanar C–H Bonds



In the eclipsed conformation there are 3 syn-periplanar C–H Bonds

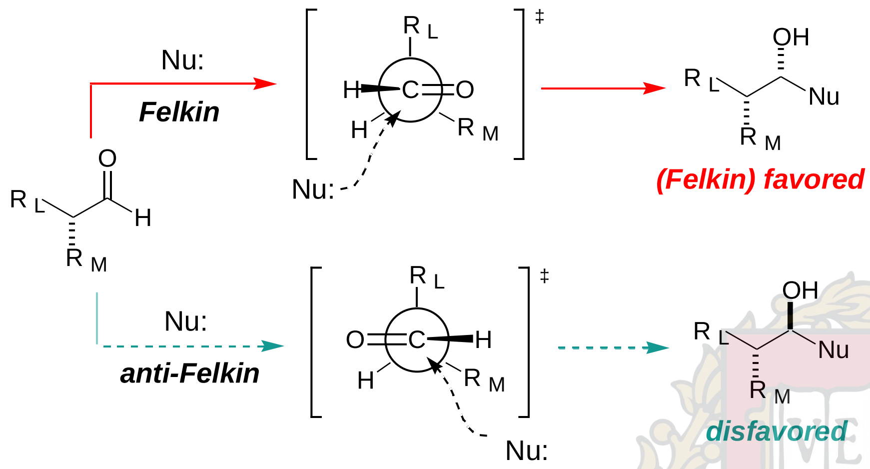


Following this argument one might conclude that:

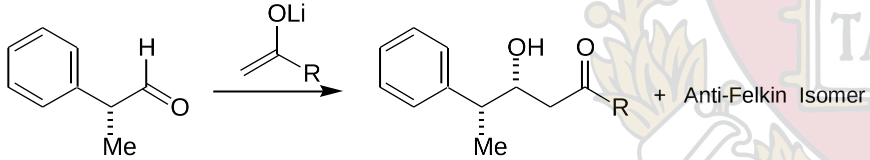
- ■ The staggered conformer has a better orbital match between bonding and antibonding states.
- ■ The staggered conformer can form more delocalized molecular orbitals.

The Felkin-Anh Eisenstein Model: Verification

Addition of Enolate & Enol Nucleophiles

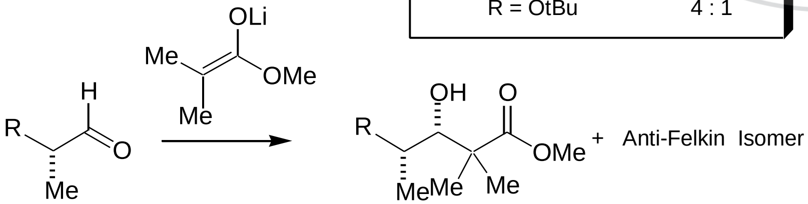


Trend-1: For Li enolates, increased steric hindrance at enolate carbon results in enhanced selectivity



L. Flippin & Co-workers, *Tetrahedron Lett.*. **1985**, *26*, 973.

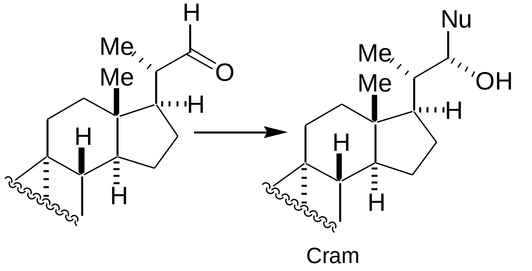
Enolate (R)	Ratio
R = Me	3 : 1
R = OtBu	4 : 1



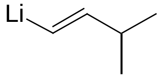
L. Flippin & Co-workers, *Tetrahedron Lett.*. **1985**, *26*, 973.

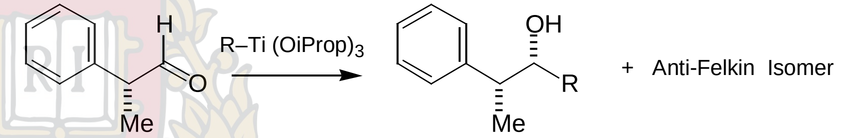
Ketone (R)	Ratio
R = Ph	>200 : 1
R = c-C_6H_{11}	9 : 1

This trend carries over to organometallic reagents as well



C. Djerassi & Co-workers, *J. Org, Chem*. **1979**, 44, 3374.

Reagent	Ratio
ClMg—C≡CEt	1 : 1
Li 	5 : 1

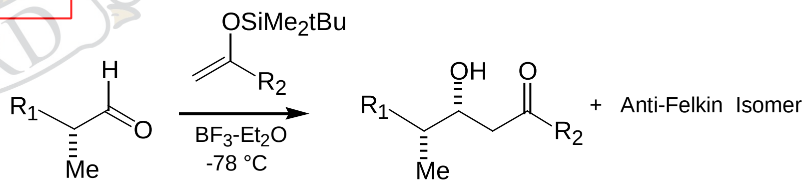


M. Reetz & Co-workers, *Angew Chemie Int. Ed.*. **1982**, *21*, 135.

R-Titanium	Ratio
R = Me	>90 : 10
R = n-Bu	>90 : 10

(R–MgX gives Ca 3:1 ratios)

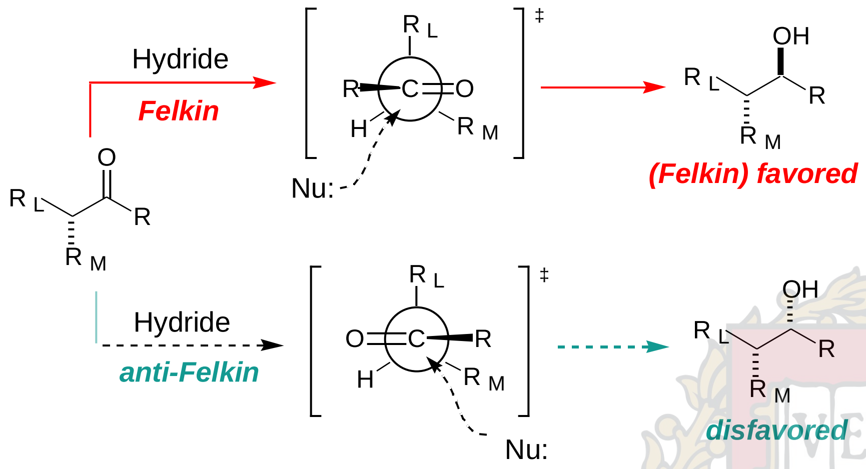
Trend-2: **Lewis acid catalyzed rxns are more diastereoselective**

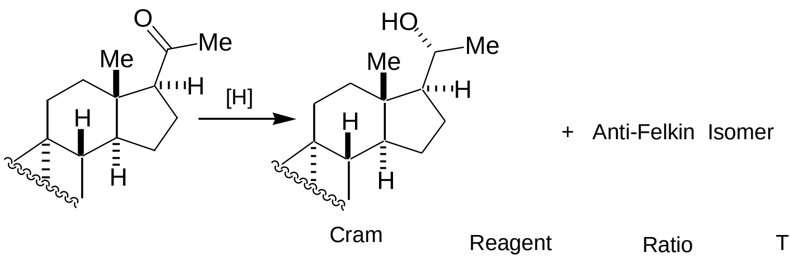


Ketone (R_1)	Enolate (R_2)	Ratio	Ratio Li enolate
R = Ph	R = Me	10 : 1	3 : 1
R = Ph	R = t-Bu	24 : 1	
R = Ph	R = OMe	15 : 1	
R = Ph	R = Ot-Bu	36 : 1	4 : 1
R = c-C_6H_{11}	R = Ot-Bu	16 : 1	

C. Heathcock & L. Flippin *J. Am. Chem. Soc.* **1983**, *105*, 1667.

Addition of Hydride Nucleophiles

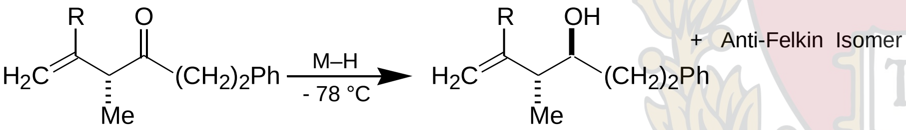




M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725.

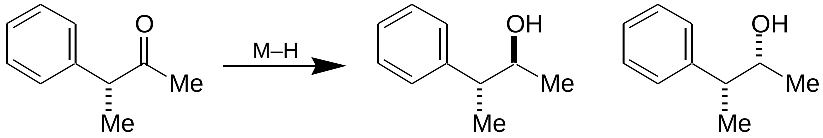
Reagent	Ratio	TS ‡
Li$^+$H–B$^-$(sec-Bu)$_3$	54 : 1	Felkin
NaBH$_4$	5 : 1	Felkin
LiAlH$_4$	3 : 1	Felkin
H–B(Sia)$_2$	1 : 10	Anti-Felkin

Note: Borane reducing agents do not follow the normal trend



G. Tsuchihashi & Co-workers,
Tetrahedron Lett. **1984**, *25*, 2479.

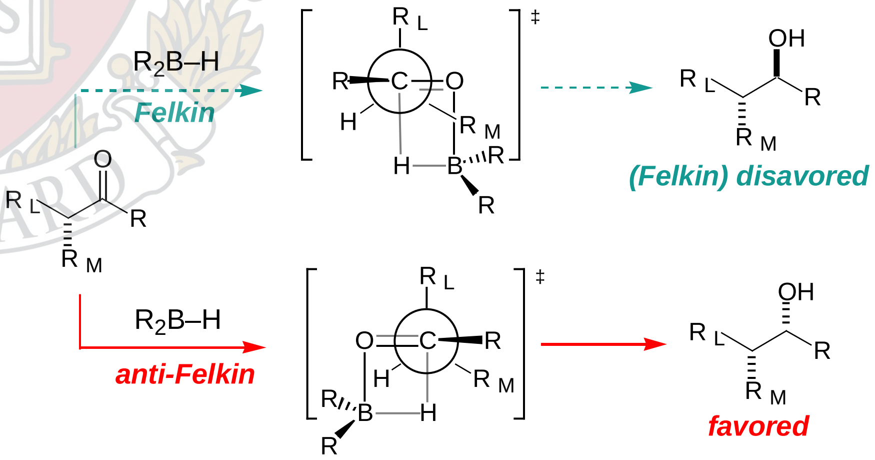
Ketone (R)	Reagent	Ratio
R = H	Li$^+$H–B$^-$(sec-Bu)$_3$	96 : 4
R = H	DIBAL	47 : 53
R = Me	Li$^+$H–B$^-$(sec-Bu)$_3$	>99 : 1
R = Me	DIBAL	88 : 12



M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725.

Reagent	Ratio	TS ‡
Li$^+$H–B$^-$(sec-Bu)$_3$	22 : 1	Felkin
H–B(Sia)$_2$	1 : 4	Anti-Felkin

Transition States for C=O-Borane Reductions



Nonspherical nucleophiles are unreliable in the Felkin Analysis

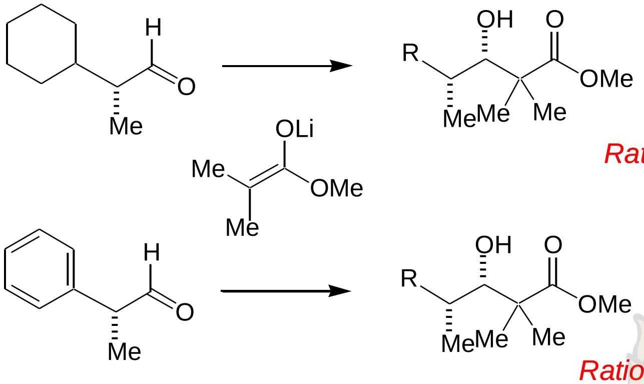
Exercise: Draw the analogous bis(R$_2$BH)$_2$ transition structures

The Felkin-Anh Eisenstein Model: Electronic Effects

Are there electronic effects in the reaction?

Several cases have already been presented which may be relevant

L. Flippin & Co-workers, *Tetrahedron Lett.*. **1985**, *26*, 973.



\+ Anti-Felkin Isomer

Ratio 9 : 1

\+ Anti-Felkin Isomer

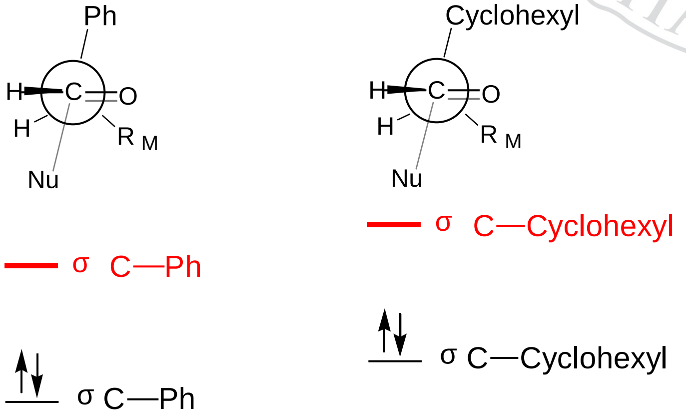
Ratio > 200 : 1

The molecular volume occupied by cyclohexyl acknowledged to be larger than that for phenyl. Because of shape phenyl "can get out of the way."

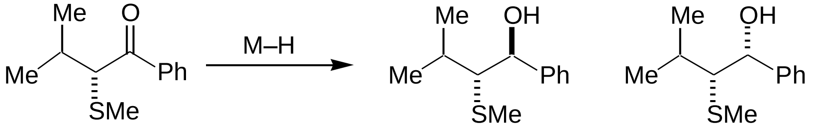
Anh-Eisenstein Explanation based on HOMO-LUMO Analysis:

"Best acceptor σ* orbital is oriented anti periplanar to forming bond."

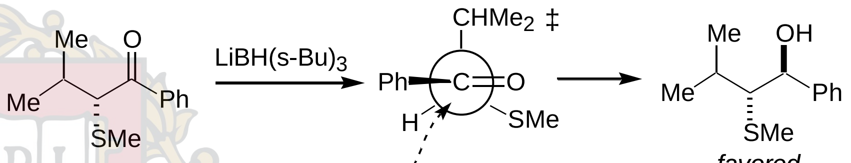
σ C_{SP3}–C_{SP2} is lower in energy than σ C_{SP3}–C_{SP3} bond.



A Second Case Study: Shimagaki *Tetrahedron Lett.* 1984, *25*, 4775

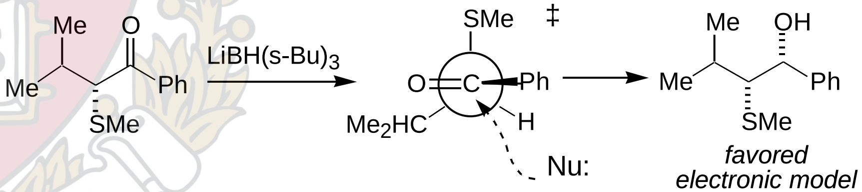


- **Dominant Steric Effects: $CHMe_2$ larger than SMe**

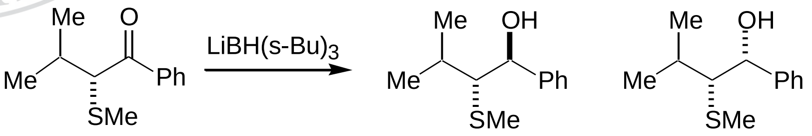


favored steric model

- **Dominant Electronic Effects: SMe provides better acceptor antibonding orbital**



favored electronic model



diastereoselection 4 : 96

If this analysis is correct, the electronic contributions to transition state stabilization dominate nonbonding destabilization

Is this another case where we are ignoring electrostatic effects?

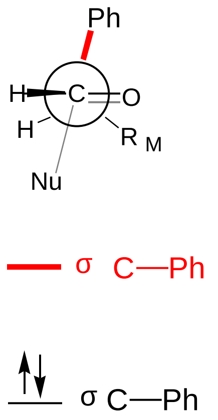
The Felkin-Anh Eisenstein Model: A Breakdown

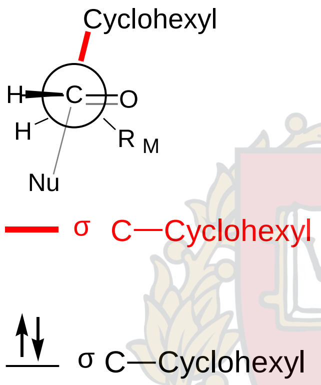
Are there cases not handled by the Anh-Eisenstein Model?

Anh-Eisenstein:

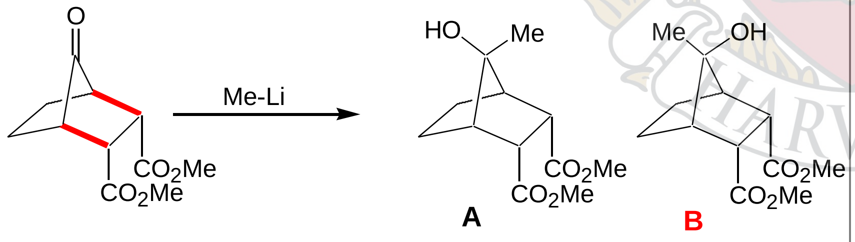
"Best acceptor σ* orbital is oriented anti periplanar to forming bond."

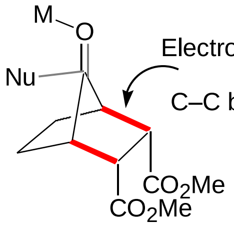
σ C_{SP3}–C_{SP2} is lower in energy than σ C_{SP3}–C_{SP3} bond.





Case I:



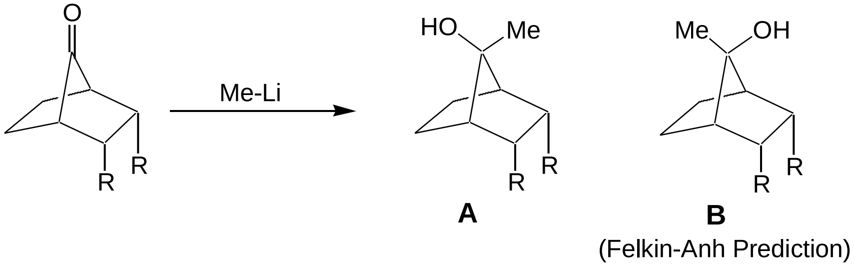


Electronegative -CO_2Me substituent will stabilize both C–C bonding & antibonding states

⇩

Felkin-Anh analysis predicts **B**

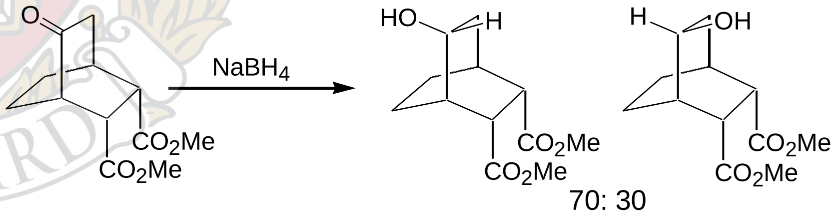
Felkin-Anh analysis predicts **B** for R = electronegative substituent.

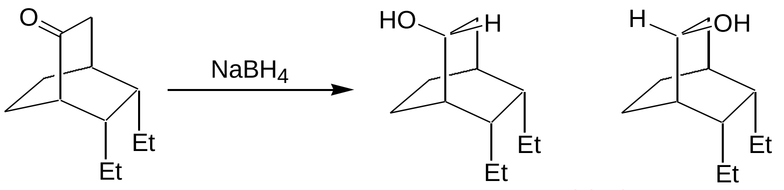


G. Mehta, *JACS* **1990**, *112*, 6140

(R) Substituent	A/B Ratio
$-\overset{O}{\overset{\|\|}{C}}-OMe$	>90:10
$-CH_2OMe$	34:66
$-CH{=}CH_2$	27:73
$-CH_2{-}CH_3$	17:83

Felkin-Anh analysis predicts the wrong product!





$NaBH_4$ 39: 61

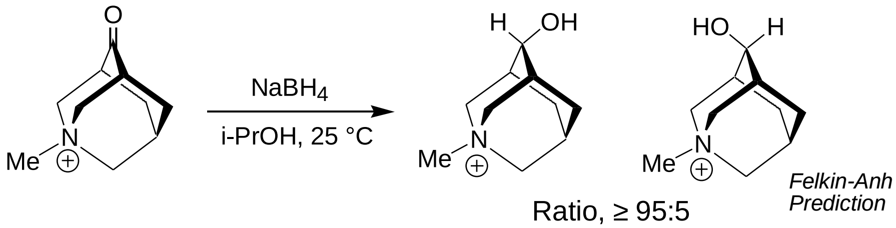
Me–Li 34: 66

G. Mehta, *Chem. Commun.* **1992**, 1711-2:

"These results can be reconciled in terms of the Cieplak model."

The Felkin-Anh Eisenstein Model: A Breakdown

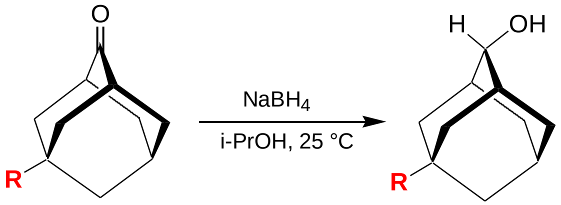
Case II: The Le Noble Examples Le Noble, *JACS* 1992, *114*, 1916



Felkin-Anh Prediction

Ratio, ≥ 95:5

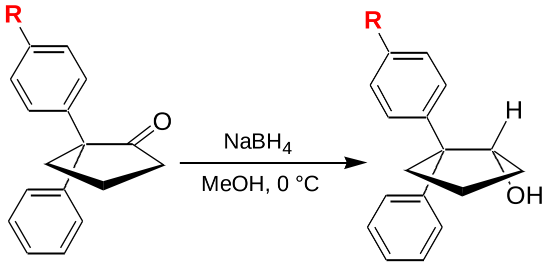
Pyramidally distorted C=O ruled out from inspection of X-ray structures.



\+ Syn Isomer

(R)	Anti:Syn Ratio
R = F	62:38
R = CO_2Me	61:39
R = $SiMe_3$	45:55
R = OH	43:57

Le Noble, *J. Org. Chem*. **1989**, *54*, 3836



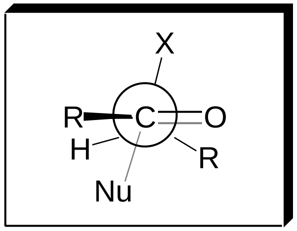
\+ Syn Isomer

(R)	Anti:Syn Ratio
R = NO_2	79:21
R = Cl	63:37
R = OMe	43:57
R = NH_2	36:64

Halterman, *JACS* **1990**, *112*, 6690

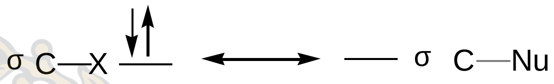
Cieplak Model for C=O Addition

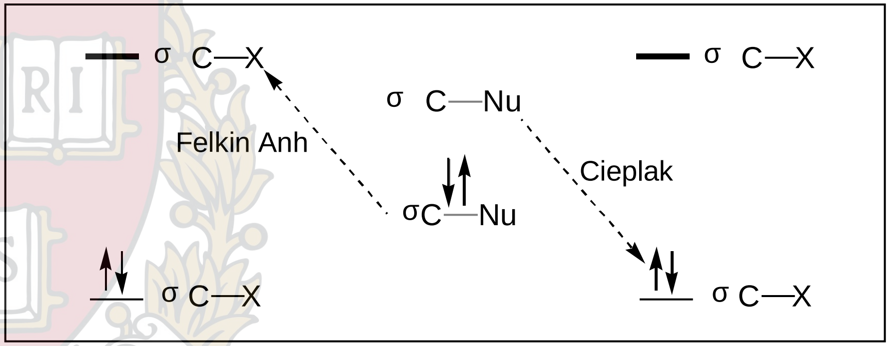
Cieplak, *JACS* **1981**,*103*, 4540; Cieplak/Johnson, *JACS* **1989**, *111*, 8447



Point A: TS is stabilized by antiperiplanar allylic bond, but....

Point B: Nature of the stabilizing secondary orbital interactions differ:





Point C: C–X Electron donating ability follows the order:
C–H > C–C > C–N > C–O
(Houk disputes the ordering of C–H, C–C)

Point D: Importance of torsional effects
(Felkin, Anh, Houk, Padden-Row) disputed.

"Structures are stabilized by stabilizing their highest energy filled states. This is one of the fundamendal assumptions in frontier molecular orbital theory. The Cieplak hypothesis is nonsense."

"Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct."

The management

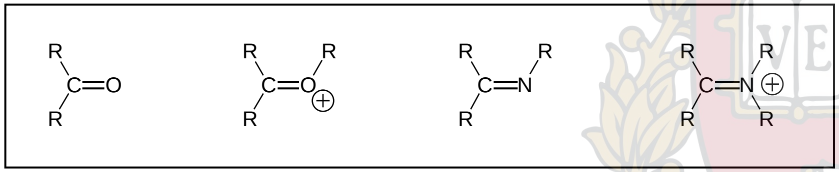
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 19

Carbonyl and Azomethine Electrophiles-2



- Breakdown in the Felkin-Anh Model
- Cyclohexanone Revisited
- Diastereoselective Additions to Cyclic Ketones
- Chelate Controlled Carbonyl Additions

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

Matthew D. Shair

Friday,
November 1, 2002

Assigned Journal Articles

Additions to 5- & 6-Membered oxocarbenium Ions:

Woerpel etal. *JACS* **1999**, *121*, 12208.
Woerpel etal. *JACS* **2000**, *122*, 168.

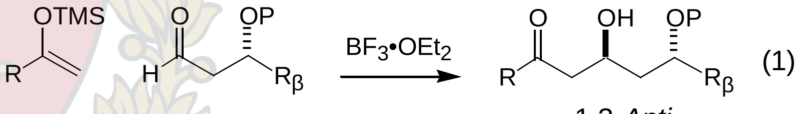
"Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein *Nouv. J. Chem.* **1977**, *1*, 61-70.

"Structural, mechanistic, and theoretical aspects of chelation controlled carbonyl addition reactions."Reetz, Acc. Chem. Res. **1993** *26*: 462. **(pdf)**

"A Stereochemical Model for Merged 1,2- and 1,3-Asymmetric Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes." Evans, et. al. *JACS* **1996**, *118*, 4322-4343. **(pdf)**

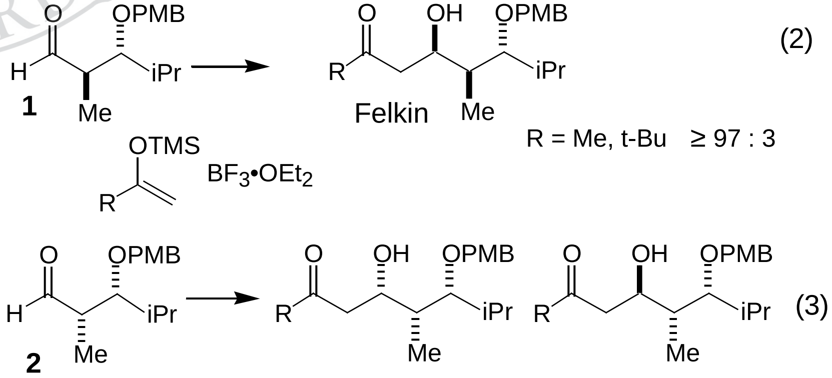
A problem

Construct a model for the addition process in eq 1 using the principles learned thus far in the course.



1,3-*Anti*

Aldehydes **1** & **2** contain 2 stereocenters, each of which may influence the course of the addition process. For **1**, the reaction is Felkin selective for all enolsilanes; however, for **2**, this is not the case. Explain. For the answer see: Evans, *JACS* **1996**, *118*, 4322. **(pdf)**



R = Me, t-Bu ≥ 97 : 3

R = t-Bu 96 : 4
R = Me 4 : 96

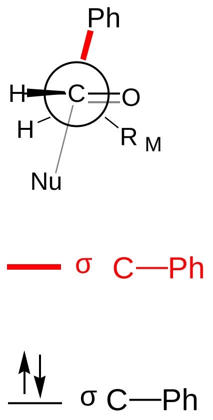
The Felkin-Anh Eisenstein Model: A Breakdown

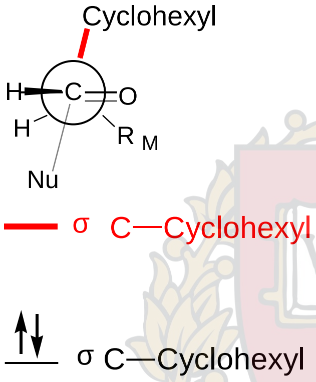
Are there cases not handled by the Anh-Eisenstein Model?

Anh-Eisenstein:

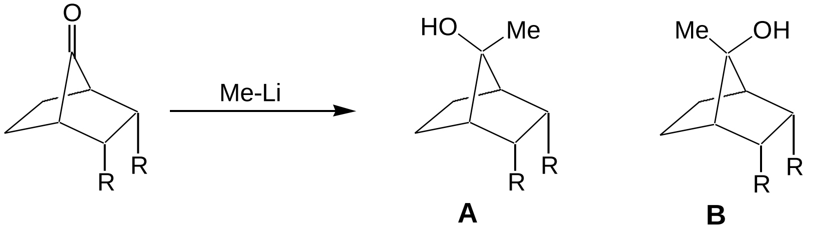
"Best acceptor σ* orbital is oriented anti periplanar to forming bond."

σ C_{SP3}–C_{SP2} is lower in energy than σ C_{SP3}–C_{SP3} bond.





Felkin-Anh analysis predicts **B** for R = electronegative substituent.



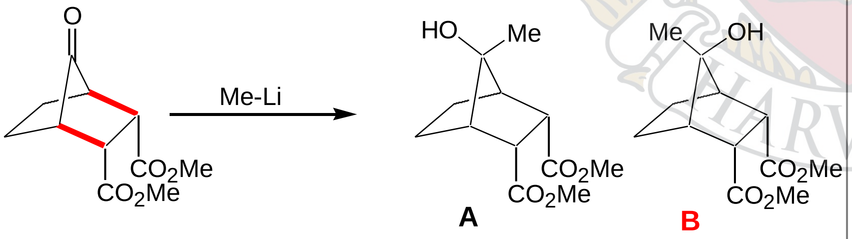
(Felkin-Anh Prediction)

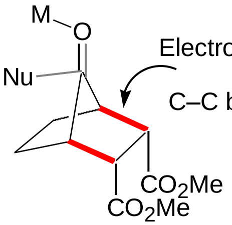
G. Mehta, *JACS* **1990**, *112*, 6140

(R) Substituent	A/B Ratio
$-\overset{O}{\overset{\|}{C}}-OMe$	>90:10
$-CH_2OMe$	34:66
$-CH=CH_2$	27:73
$-CH_2-CH_3$	17:83

Felkin-Anh analysis predicts the wrong product!

Case I:

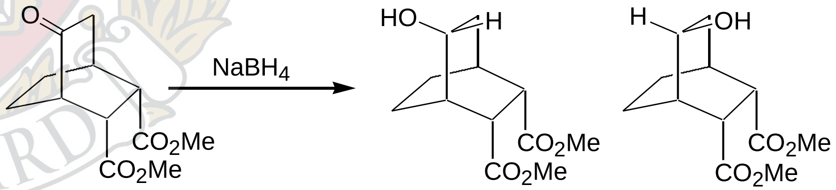




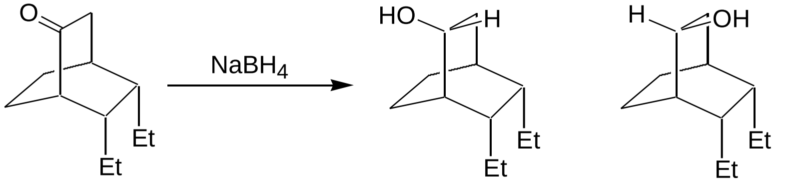
Electronegative -CO_2Me substituent will stabilize both C–C bonding & antibonding states

⇓

Felkin-Anh analysis predicts **B**



70: 30

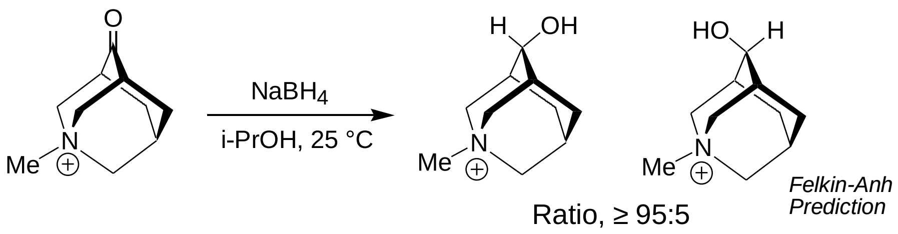


$NaBH_4$	39: 61
Me–Li	34: 66

G. Mehta, *Chem. Commun.* **1992**, 1711-2:

"These results can be reconciled in terms of the Cieplak model."

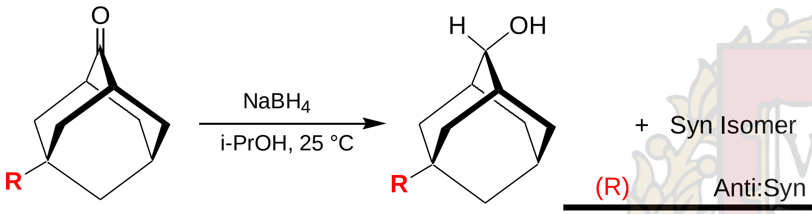
Case II: The Le Noble Examples Le Noble, *JACS* 1992, *114*, 1916



Ratio, ≥ 95:5

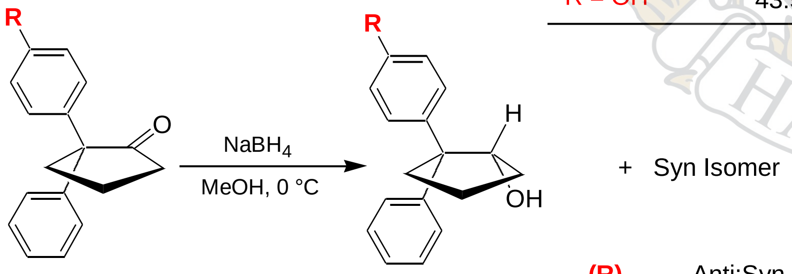
Felkin-Anh Prediction

Pyramidally distorted C=O ruled out from inspection of X-ray structures.



(R)	Anti:Syn Ratio
R = F	62:38
R = CO_2Me	61:39
R = $SiMe_3$	45:55
R = OH	43:57

Le Noble, *J. Org. Chem*. **1989**, *54*, 3836

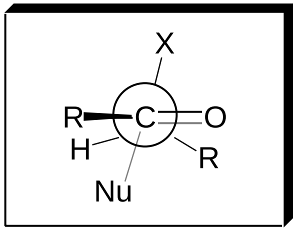


(R)	Anti:Syn Ratio
R = NO_2	79:21
R = Cl	63:37
R = OMe	43:57
R = NH_2	36:64

Halterman, *JACS* **1990**, *112*, 6690

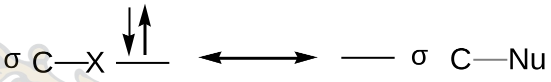
Cieplak Model for C=O Addition

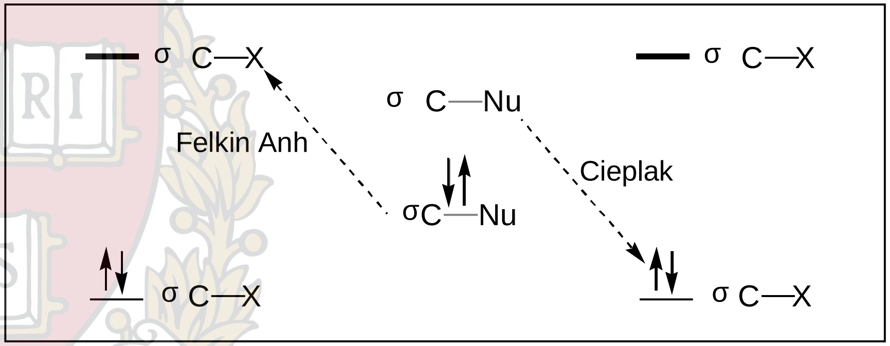
Cieplak, *JACS* **1981**,*103*, 4540; Cieplak/Johnson, *JACS* **1989**, *111*, 8447



Point A: TS is stabilized by antiperiplanar allylic bond, but....

Point B: Nature of the stabilizing secondary orbital interactions differ:





Point C: C–X Electron donating ability follows the order:
C–H > C–C > C–N > C–O
(Houk disputes the ordering of C–H, C–C)

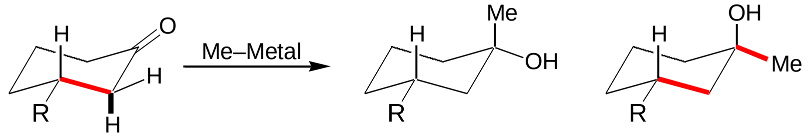
Point D: Importance of torsional effects
(Felkin, Anh, Houk, Padden-Row) disputed.

"Structures are stabilized by stabilizing their highest energy filled states. This is one of the fundamendal assumptions in frontier molecular orbital theory. The Cieplak hypothesis is nonsense."

"Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct."

The management

Observation As R becomes more electronegative, percentage of axial attack increases.



(R) Substituent	% Axial Attack	
	Me-Li	Me_2Cu-Li
R = H	21%	6%
R = C_6F_5	34%	21%
R = CF_3	50%	42%

Felkin-Anh predicts opposite trend.

Cieplak argument consistent with results.

The Frenking Position:

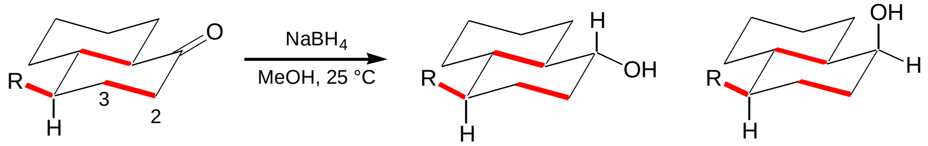
- Cieplak stabilizing interaction is "dubious." Why not stabilize the forming sigma bond?
- Enhanced rate of axial Nu attack on cyclohexanone is caused by better electrostatic interactions of the ketone with the attacking reagent and not by torsional considerations.
- Nonequivalence of the π*C=O LUMO with a greater extension on the axial face dictates stereoselection (Klein, 1973).

"Since interactions between the π C=O & π C=O and the bonding & anti-bonding (β) C–H & (β) C–C orbitals are all symmetry allowed, it is difficult to predict a priori which interactions are dominant without carrying out quantum mechanical calculations."

Frenking & Reetz, *Angew. Chem*. Int. Ed. **1991**, *30*, 1146

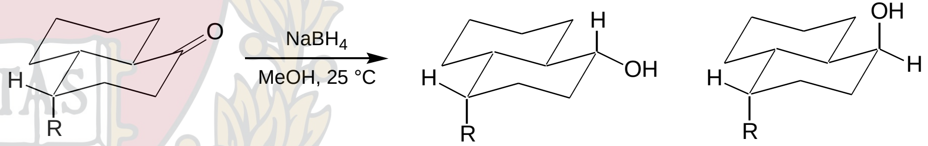
Houk: Electrostatic rather than covalent considerations may be dominant.

"Equatorial electronegative substituents should interact more strongly with the C(2-3) and C(9-10) bonds than axial substituents."



(R) Substituent	Product Ratio
R = H	60:40
R = OAc	71:29
R = Cl	71:29

"If nucleophilic addition occurs anti to the better donor bond (Cieplak), the equatorial isomers should have considerably more axial attack than the parent while the axial isomers should have only a slight increase in axial attack."



(R) Substituent	Product Ratio
R = OAc	83:17
R = Cl	88:12

"Exactly the opposite is observed."

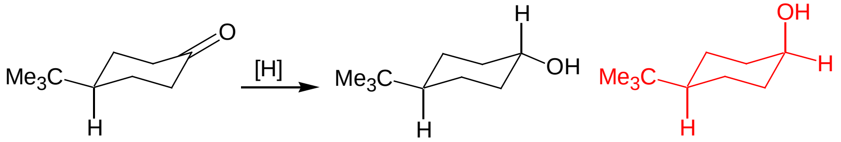
Axial 4-substituents favor axial attack for electrostatic reasons:

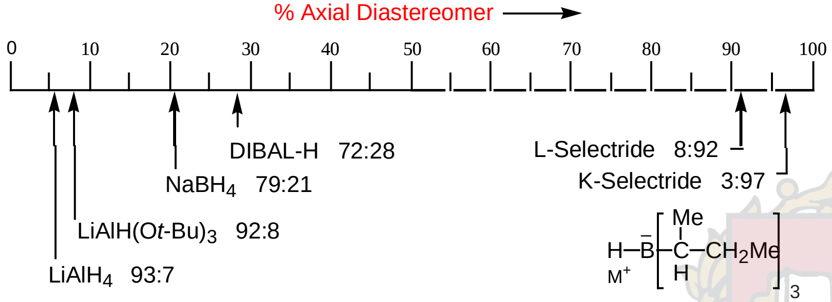
"Disfavored" *"Favored"*

(DAE: Bimetallic transition states were not considered)

K. Houk & Co-workers, *J. Am. Chem. Soc*. **1991**, *113*, 5018

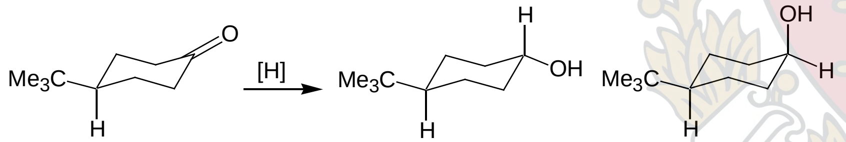
Stereoselective Reductions: Cyclic Systems



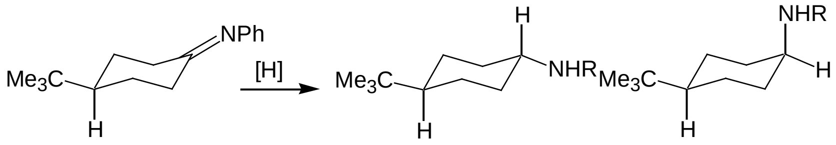


Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

The most stereoselective Reductions



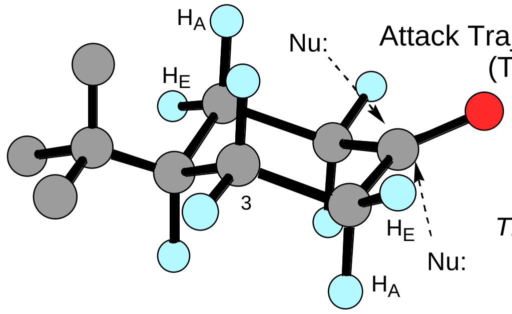
Reagent	Ratio
KBH(s-Bu)$_3$	03 :97
Li in NH$_3$	99 :01



(R)	Reagent	Ratio
R = Bn	LiBH(s-Bu)$_3$	03 :97
R = Ph	LiBH(s-Bu)$_3$	01 :99
	Al/Hg/MeOH	~90 :10

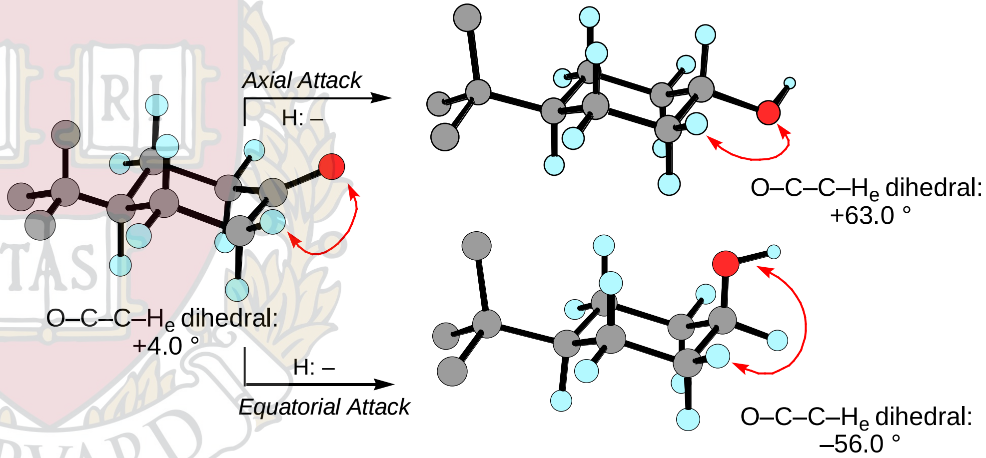
Ganem, *Tet. Let* **1981**, *22*, 3447
Hutchins, *JOC* **1983**, *48*, 3412
private communication

Attack Trajectories for Cyclohexanone
(Torsional Argument)



This approach favored sterically

The steric hindrance encountered by Nu-attack from the axial C=O face by the axial ring substituents (hydrogens in this case) at the 3-positions is more severe than the steric hinderance encountered from Nu-attack from the equatorial C=O face.



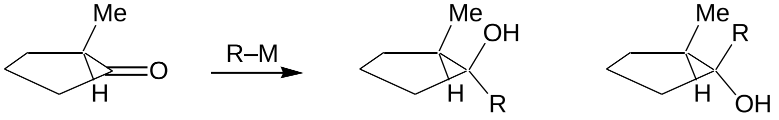
The Issues Associated with the Reduction Process

Steric Effects:	Attack across equatorial C=O face sterically more favorable.
Torsional Effects:	However, attack across the axial face of the C=O group avoids development of eclipsing interactions in the transition state. (Note the dihedral angle sign changes between reactants & products shown above). These "torsional effects" favor axial attack.
Prediction	For "small" hydride reagents such as LiAlH$_4$, torsional effects are felt to be dominant and this explains the predisposition for axial attack.
Prediction	For "large" hydride reagents such as H–BR$_4$, steric effects now are dominant and this explains the predisposition for equatorial attack.

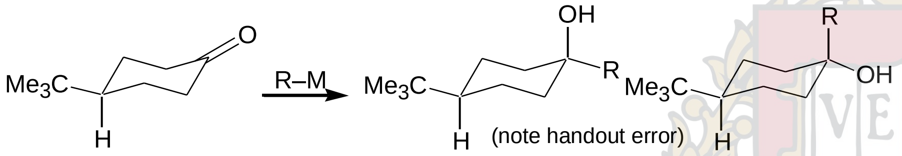
Cyclohexanone Addition Reactions: Nucleophilic Addition

Stereoselective Organometallic Addition reactions:

As the cases below indicate, reaction diastereoselection is strongly coupled to the steric requirements of the organometallic reagent



HC≡C-Li	21%	79%
CH_3—Li	70%	30%
C_6H_5—Li	95%	5%

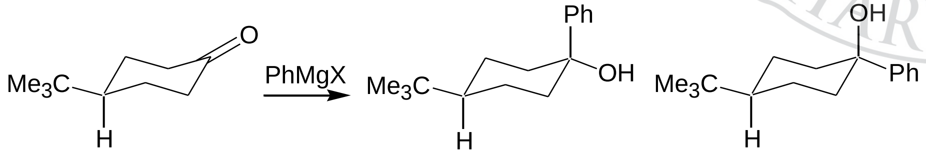


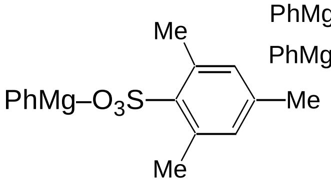
(note handout error)

HC≡C-Li	12%	88%
Et—MgBr	47%	53%
Me_2CH—MgBr	82%	18%
Me_3C—MgBr	100%	0%

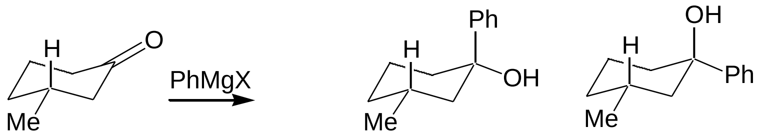
Ashby, *Chem. Rev.* **1975**, *75*, 521

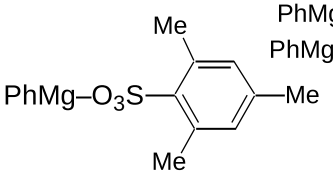
One can enhance C=O face selectivity by modifying the ligands on a given organometal.



PhMg–Br	51%	49%
PhMg–OTf	27%	73%
PhMg–OTs	15%	85%
	10%	90%

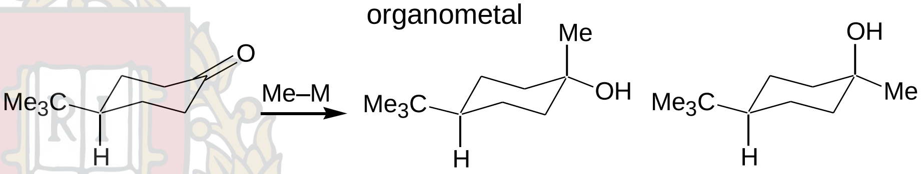
Reetz, *Angew. chem. Int. Ed.* **1992**, *31*, 343



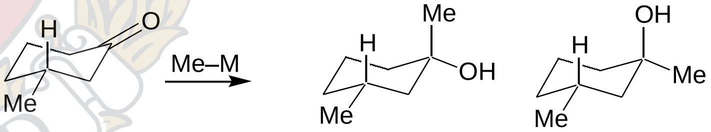
PhMg–Br	41%	59%
PhMg–OTs	21%	79%
	5%	95%

Reetz, *Angew. Chem. Int. Ed.* **1992**, *31*, 343

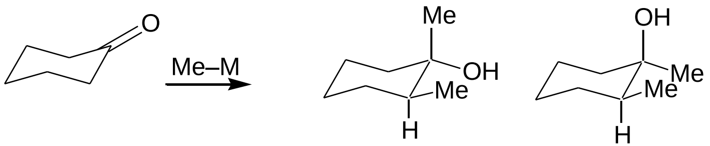
One can also enhance C=O face selectivity by changing the organometal



Me–Li	35%	65%
Me–Ti(OiPr)$_3$	6%	94%
Yb(OYf)$_3$ + Me–Li	18%	82%



MeMg–Br	32%	68%
Me–Ti(OiPr)$_3$	11%	89%
Yb(OYf)$_3$ + MeMg–Br	32%	68%



MeMg–Br	12%	88%
Me–Ti(OiPr)$_3$	4%	96%
Yb(OYf)$_3$ + MeMg–Br	2%	98%

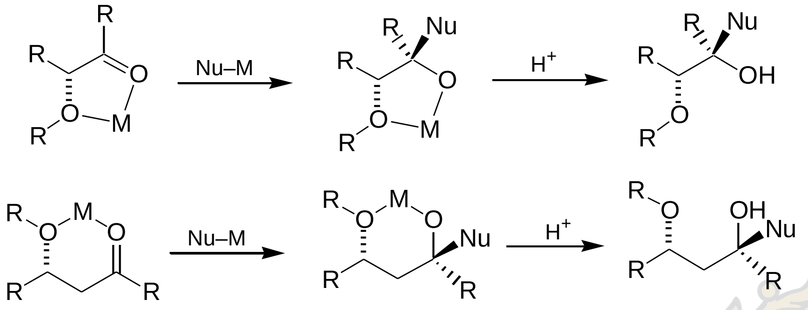
(Yb) Molander, *J. Org. Chem.* **1990**, *55*, 4990

(Ti) Reetz, *Tetrahedron* **1986**, *42*, 2931

(Mn) Reetz, *Tet. Let.* **1992**, *33*, 6963

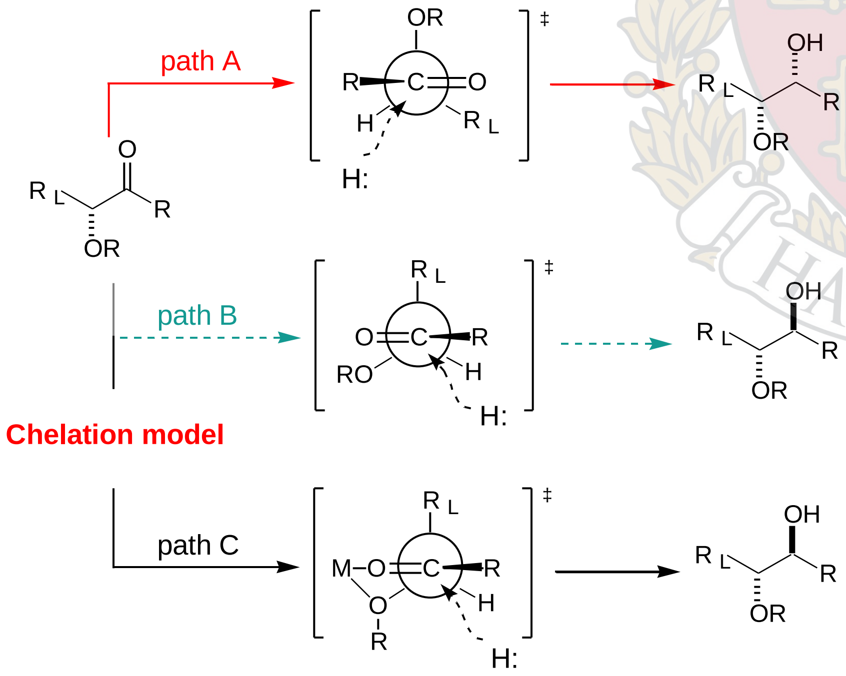
Carbonyl Addition Reactions: Chelate Organization

Chelate organization provides a powerful control element in carbonyl addition reactions

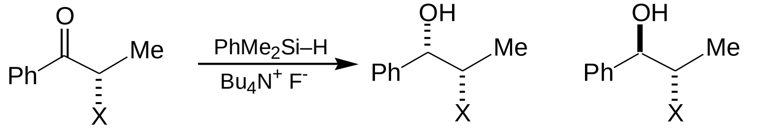


Reviews Reetz, *Accts. Chem. Res*. **1993**, *26*, 462-468 **(pdf)**
Reetz, *Angew. Chem. Int. Ed*. **1984**, *23*, 556-569

Lets begin with the hydride reductions of alkoxy ketones



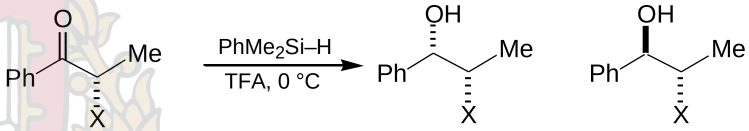
Lets begin with a case where chelation is precluded: (Path A)



Let R_L = X
in the Ahn-Eisenstein model

T. Hiyama & Co-workers,
J. Am. Chem. Soc. **1984**, *106*, 4629.

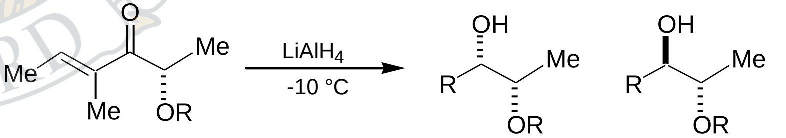
Substituent (X)	Ratio
X = NMe_2	>99 : 1
X = OAc	95 : 5
X = OCOPh	96 : 4



H-bonding Chelate Model

T. Hiyama & Co-workers,
J. Am. Chem. Soc. **1984**, *106*, 4629.

Substituent (X)	Ratio
X = $NHCO_2Et$	<1 : 99
X = OCOPh	7 : 93



Overman
Tet Lett. **1982**, *23*, *2355*

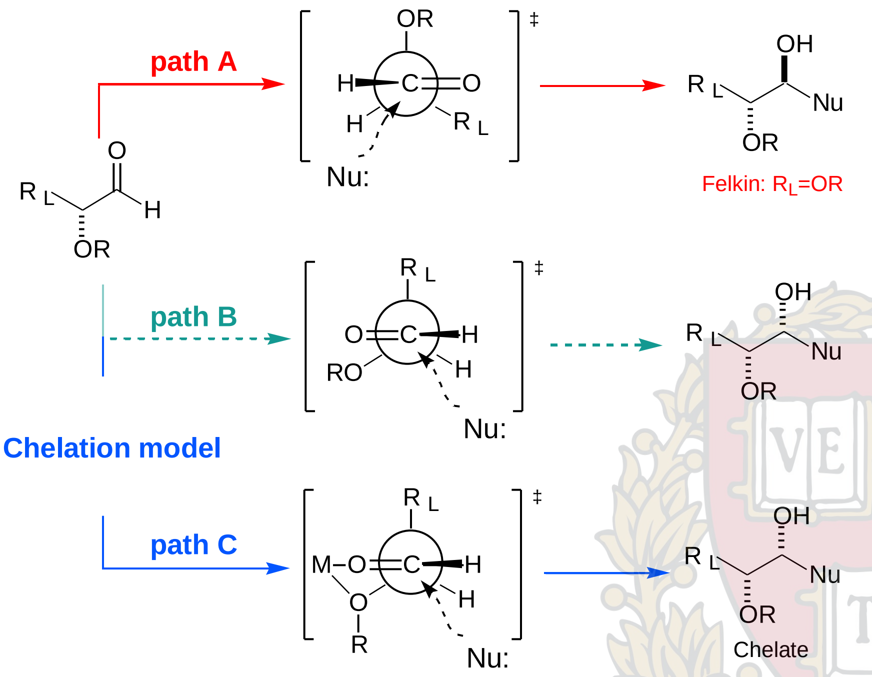
(OR)	Solv.	Ratio	Model
R = CH_2OBn	THF	30 : 70	Chelate
R = CH_2OBn	Et_2O	2 : 98	Chelate
R = $SiPh_2(t)Bu$	THF	95 : 5	Cram: R_L=OR

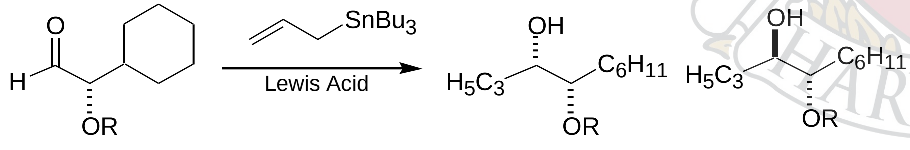
Degree of chelate organization may be regulated by choice of solvent and protecting group.

Note that $SiPh_2(t)Bu$ group prevents chelation.

Carbonyl Addition Reactions: Chelate Organization

Addition of Carbon Nucleopiles



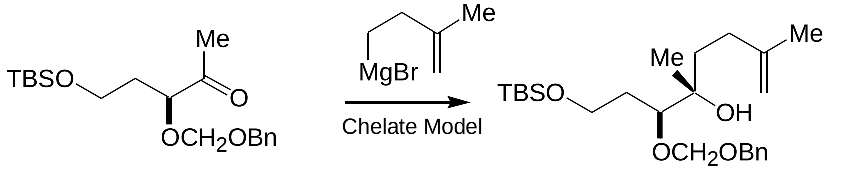


Chelate

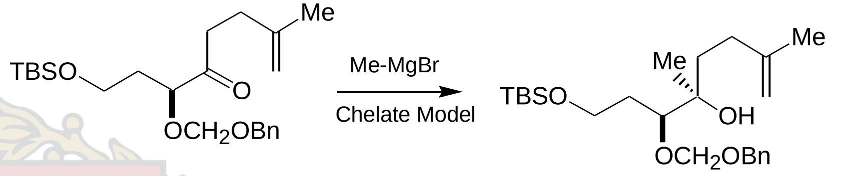
Felkin: R_L=OR

(OR)	Acid	Solv.	Ratio
R = CH_2OBn	$MgBr_2$	THF (0°)	20 : 80
R = CH_2OBn	$MgBr_2$	CH_2Cl_2 (-20°)	>99 : 1
R = CH_2OBn	$TiCl_4$	CH_2Cl_2 (-78°)	>99 : 1
R = $SiMe_2$(t)Bu	BF_3-Et_2O	CH_2Cl_2 (-78°)	5 : 95

G. Keck & Co-workers, *Tetrahedron Lett.* **1984**, *25*, 265

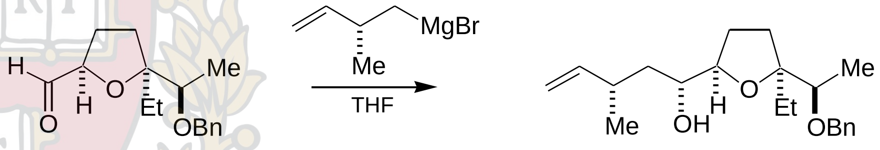


diastereoselection 50 : 1



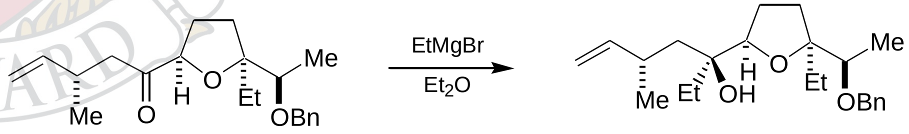
W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1031

diastereoselection >100 : 1



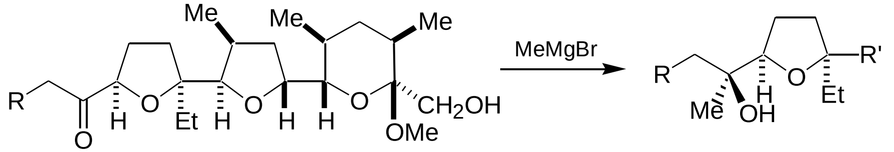
Y. Kishi & Co-workers,
Tetrahedron Lett. **1978**, *19*, 2745

"only one isomer"
Chelate Model



Y. Kishi & Co-workers,
Tetrahedron Lett. **1978**, *19*, 2745

"only one isomer"
Chelate Model

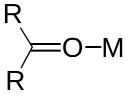
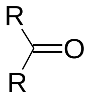


Y. Kishi & Co-workers,
J. Am. Chem. Soc. **1979**, *101*, 260.

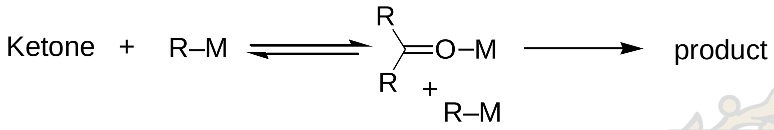
"only one isomer"
Chelate Model

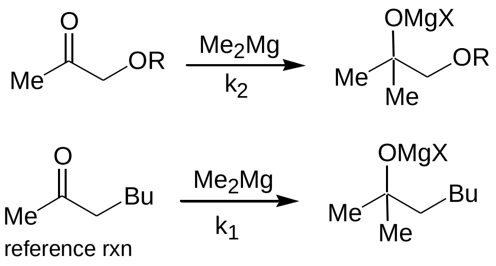
Carbonyl Addition Reactions: Chelate Organization

Kinetic Evidence for Chelate-Controlled C=O Additon

Since  much more reactive than 

Substrates which can participate in C=O chelation will be more reactive since the effective concentration of chelated intermediate will be higher.



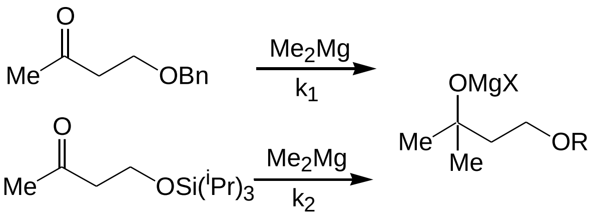


R	rel rate
–Me	213
–Bn	174
–CMe$_3$	9
–SiMe$_3$	7
–Si-i-Pr$_3$	1

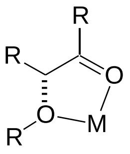
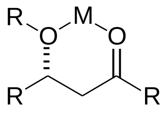
rxn run inTHF at - 78°C

Eliel, Frye, *JACS* **1992**, *114*, 1778-84 (read)

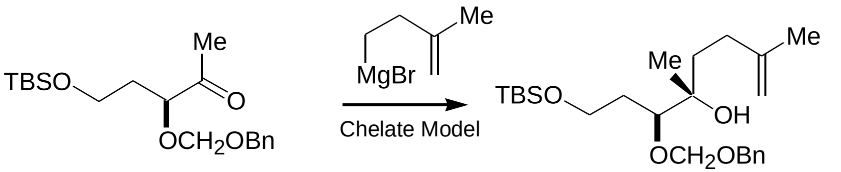
However, these trends are not transmitted strongly to β-chelation



$$\boxed{\frac{k_1}{k_2} = 2.5}$$

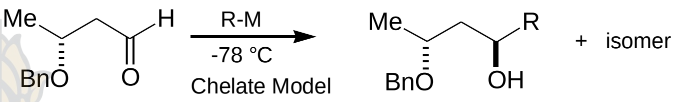
Hence, organization through  better than 

Alpha–Versus Beta-Chelation



W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1031

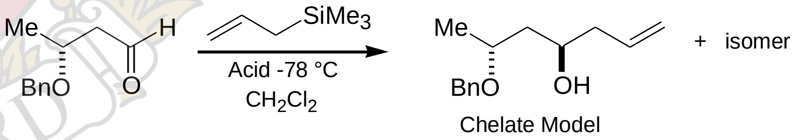
diastereoselection 50 : 1



M. T. Reetz & Co-workers
J. Am. Chem. Soc.. **1983**, 105, 4833.

R-M	Solv.	Ratio
Me-MgCl	THF	40 : 60
Me-TiCl$_3$	CH$_2$Cl$_2$	90 : 10

Other nucleophiles reported

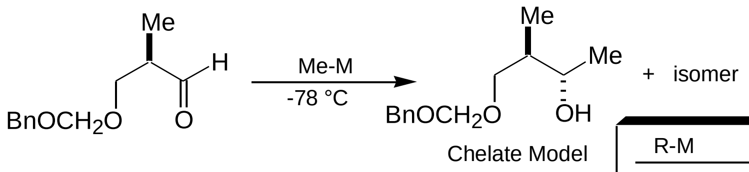


M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, *25*, 729.

Acid	Ratio
TiCl$_4$	95 : 5
SnCl$_4$	95 : 5
BF$_3$-OEt$_2$	85 : 15

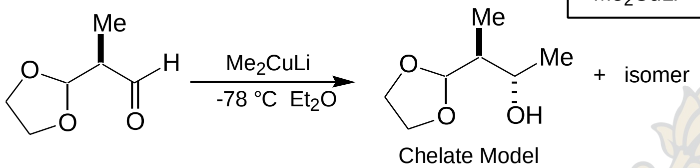
- Note that beta chelation can be developed as a control element by varying solvent & Nu.
- Note BF$_3$ gives "apparent" chelate control

Beta Chelation with Organometals



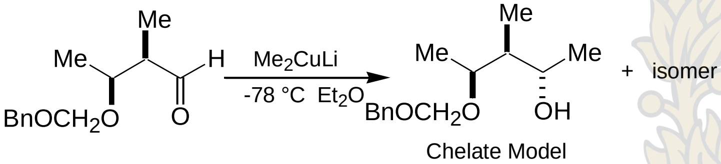
Chelate Model

R-M	Ratio
MeMgBr	50 : 50
Me_2CuLi	97 : 3



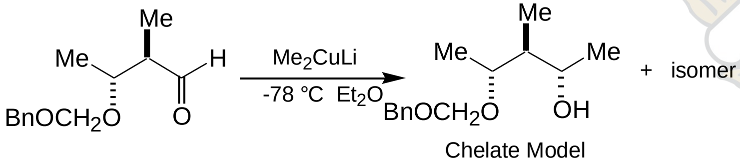
Chelate Model

diastereoselection > 95 : 5



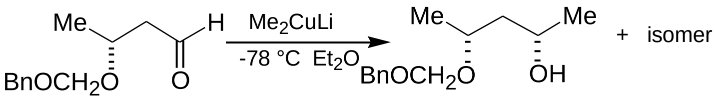
Chelate Model

diastereoselection > 95 : 5



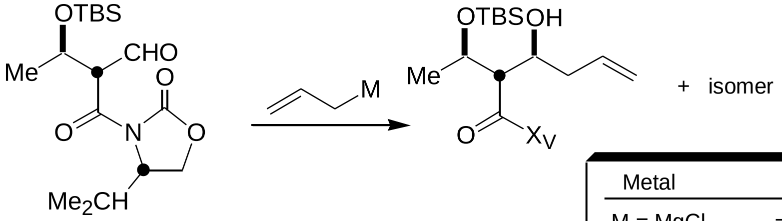
Chelate Model

diastereoselection 70 : 30



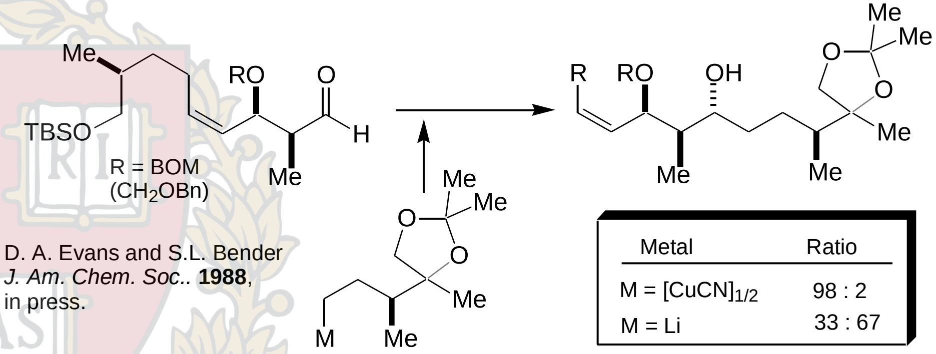
diastereoselection 50 : 50

W.C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1035.



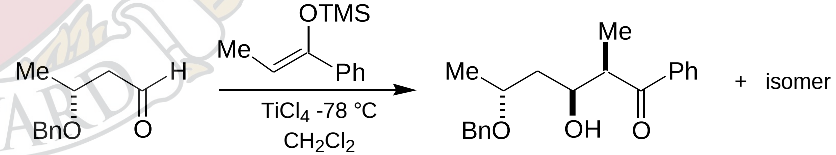
D. A. Evans & E. Sjogren
Tetrahedron Lett. **1986**, *27*, 4961.

Metal	Ratio
M = MgCl	70 : 30
M = ZnCl	97 : 3



D. A. Evans and S.L. Bender
J. Am. Chem. Soc.. **1988**,
in press.

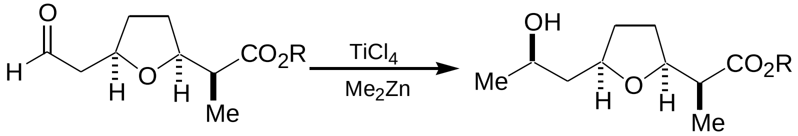
Metal	Ratio
M = $[CuCN]_{1/2}$	98 : 2
M = Li	33 : 67



Chelate Model

M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, *25*, 729.

diastereoselection >92 %

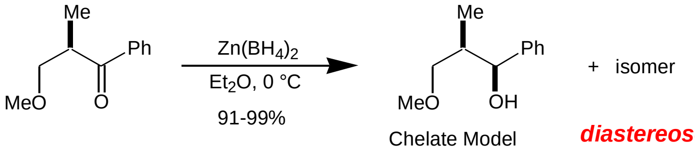


chelate model

S. W. Baldwin & Co-workers
J. Org. Chem. **1987**, *52*, 320.

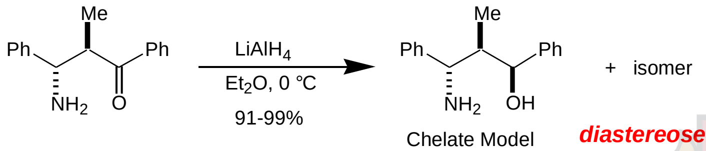
diastereoselection 96 : 4

Beta Chelate-Controlled Reduction



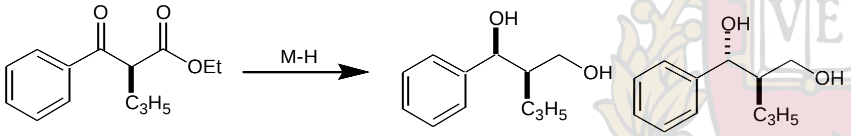
diastereoselection 97 : 3

T. Oishi & Co-workers
Chem. Pharm Bull. **1984**, *32*, 1411.



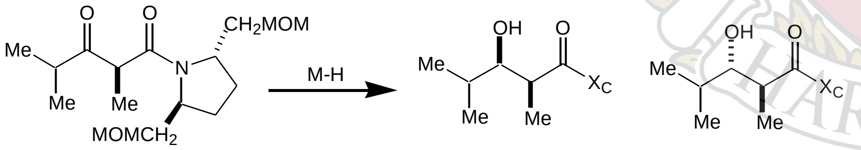
diastereoselection 88 : 12

J. Barluenga & Co-workers
J. Org. Chem. **1985**, *50*, 4052.



G. R. Brown & Co-workers
Chem. Commun. **1985**, 455.

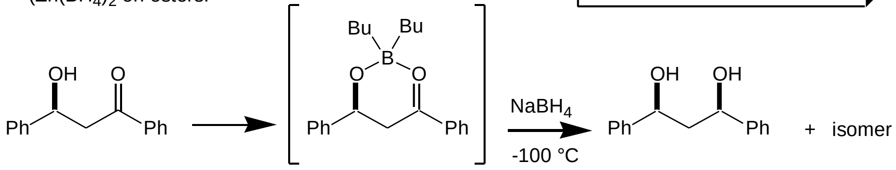
M-H	Ratio
$Zn(BH_4)_2$ Et_2O	100 : 0
$LiAlH_4$ THF	0 : 100



M. Yamaguchi & Co-workers
Tetrahedron Lett. **1985**, *26*, 4643.

T. Oishi & Co-workers
Tetrahedron Lett. **1980**, *21*, 1641
($Zn(BH_4)_2$ on esters).

M-H	Ratio
$Zn(BH_4)_2$ Et_2O	100 : 0
KBH_3H THF	0 : 100

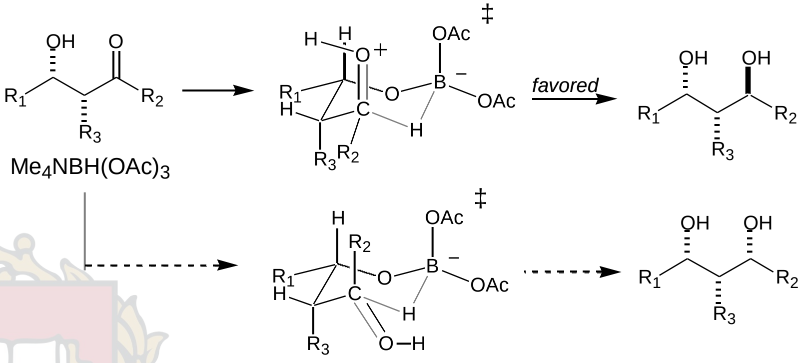


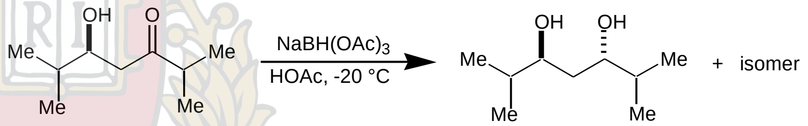
K. Narasaka & Co-workers
Chem. Lett. **1980**, 1415.

diastereoselection 96 : 4

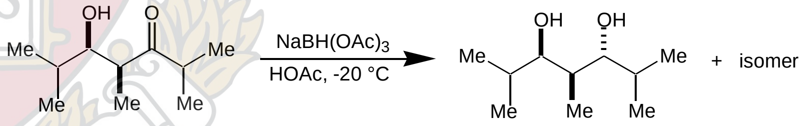
Directed reductions of β-hydroxyketones

Evans, Chapman, Carreira, JACS **110**, 3560 (1988)

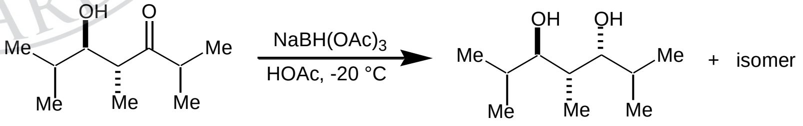




diastereoselection 96 : 4

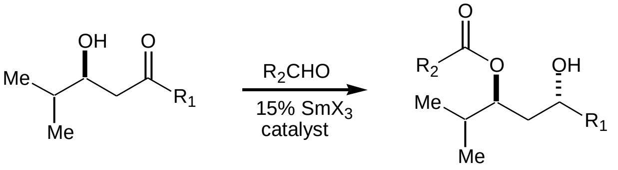


diastereoselection 98 : 2



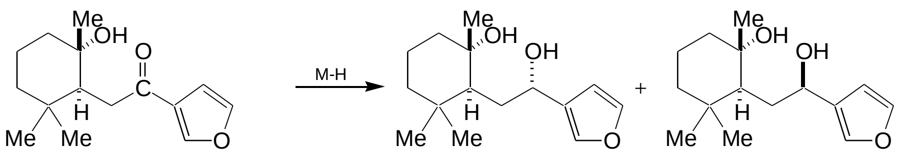
diastereoselection 98 : 2

Propose a mechanism for tihs highly diastereoselective transformation,
Evans, Hoveyda JACS **112**, 6447 (1990)



diastereoselection > 100:1

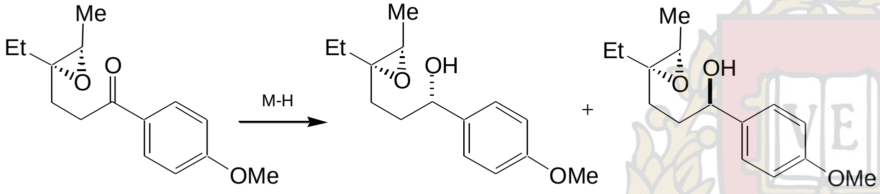
Remote Heteroatom Effects in Carbonyl Addition



Temp. & Solvent not specified in this study in first three cases

R. Baker & Co-workers
Chem. Commun. **1984,** 74

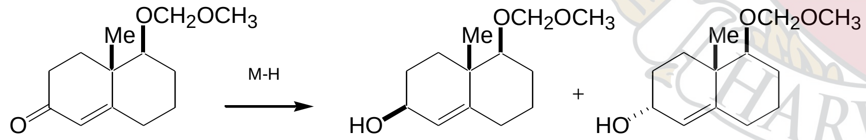
Reagent	Ratio
Li-AlH$_4$	40 : 60
Na-BH$_4$	50 : 50
Zn-BH$_4$	60 : 40
Li-BHEt$_3$, (THF, -78˚C)	100 : 0



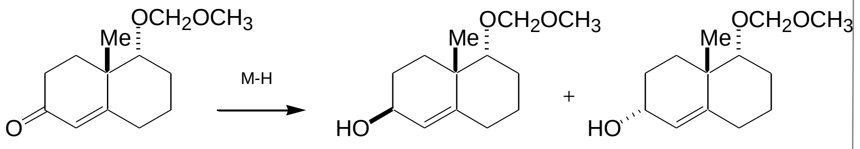
Y. Kishi & Co-workers
Tetrahedron Lett. **1978**, 2741.

Li-BH(R)$_3$, Et$_2$O, 25˚C	1 : 1
LiAlH$_4$, Et$_2$O, 25˚C	3 : 1
LiAlH$_4$-diamine,* -78˚C	11 : 1

** di-2-(o-toluidinomethyl)pyrrolidine*

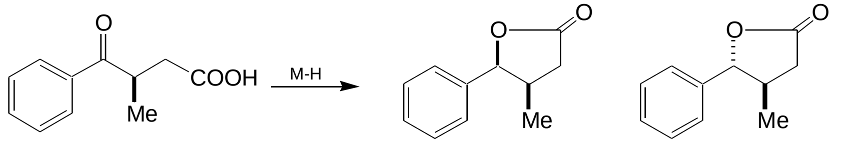


Li-BH(R)$_3$,	73 : 27
LiAlH$_4$	76 : 24



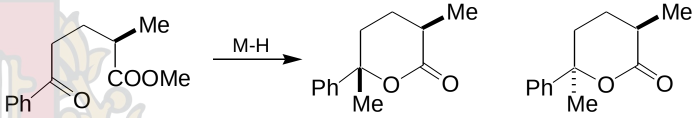
Li-BH(R)$_3$,	28 : 72
LiAlH$_4$	72 : 28

W. G. Dauben & Co-workers
Tetrahedron Lett. **1978**, 2741.



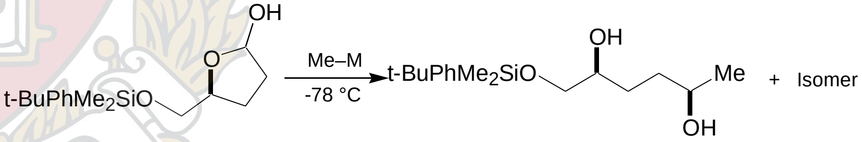
R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

Reagent	Ratio
NaBH$_2$(OR)$_2$	50 : 50
NaBH$_4$	70 : 30
DIBAL (2.4 equiv)	95 : 5
DIBAL (2.4 equiv) with ZnCl2	99 : 1



R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

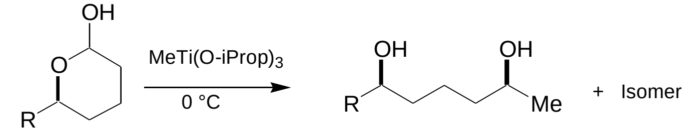
Solvent	Ratio
THF	50 : 50
C$_6$H$_6$	70 : 30



67-87% yields

G. Tsuchihashi & Co-workers
Tetrahedron Lett. **1987**,*28*, 6335.

Reagent	Solvent	Ratio
MeLi	Et$_2$O	1.7 : 1
MeMgBr	THF	1.3 : 1
Me$_3$Al	CH$_2$Cl$_2$	1.1 : 1
MeTiCl$_3$	CH$_2$Cl$_2$	8.4 : 1
MeTi(O-iProp)$_3$	CH$_2$Cl$_2$	12 : 1



R = Me, Ph(CH$_2$)$_2$

Ratio 4-5.5 : 1

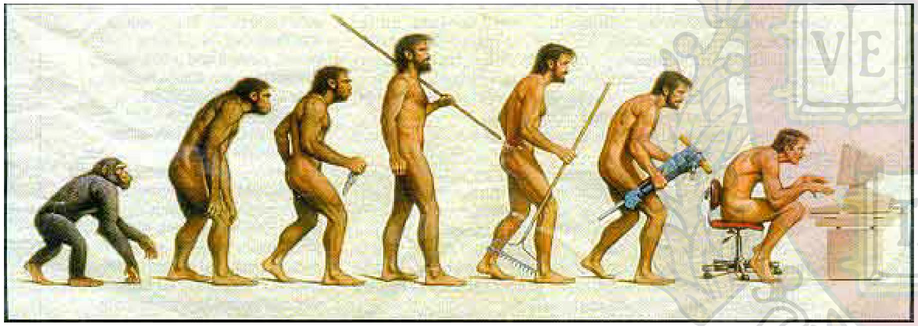
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 20

The Evolution of Models for Carbonyl Addition



Fischer Cram Cornforth Felkin Anh/Eisenstein Cieplak Tomoda

- 1,2-Asymmetric Induction Models
- 1,3-Asymmetric Induction Models
- Merged 1,2- and 1,3-Asymmetric Induction
- Unpredicted, highly selective carbonyl additions

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Matthew D. Shair

Monday,
November 4, 2002

Useful Reviews

Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191-1223

Gung, B. W. *Tetrahedron* **1996**, *52*, 5263-5301

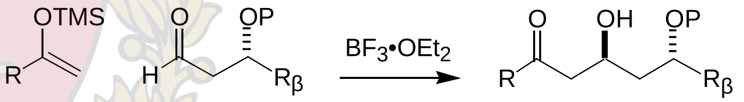
Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803-2894

Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556-569

Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*;
Prentice Hall Inc.: **1971**
Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678-11688, ref. 1-5, 7

A problem

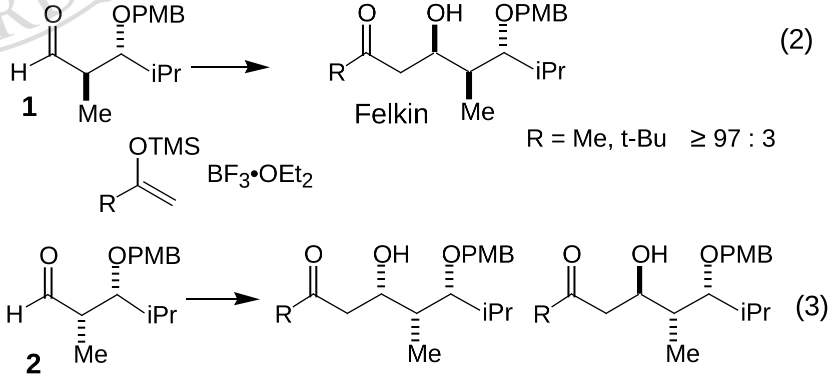
Construct a model for the addition process in eq 1 using the principles learned thus far in the course.



(1)

1,3-*Anti*

Aldehydes **1** & **2** contain 2 stereocenters, each of which may influence the course of the addition process. For **1**, the reaction is Felkin selective for all enolsilanes; however, for **2**, this is not the case. Explain. For the answer see: Evans, *JACS* **1996**, *118*, 4322. **(pdf)**



(2)

1

Felkin

R = Me, t-Bu ≥ 97 : 3

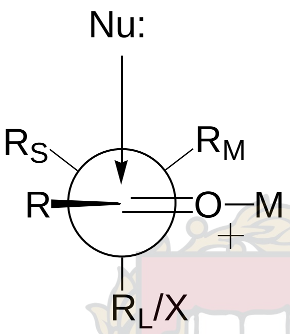
(3)

2

R = t-Bu 96 : 4
R = Me 4 : 96

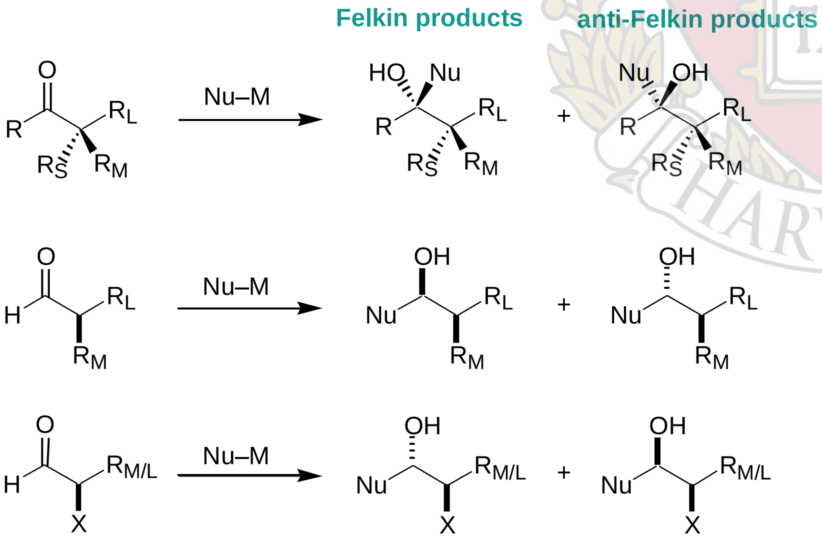
Definition of Terms

Felkin product = commonly accepted term for the major carbonyl addition product predicted by the Felkin-Anh model; also predicted by Cram and Karabatsos for steric cases, Cornforth for α-heteroatom (non-chelating) cases



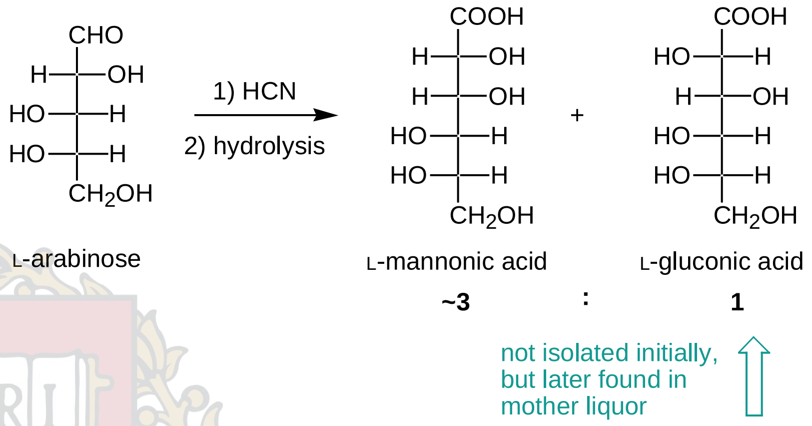
Felkin-Anh model

Examples:



also Cram-chelate product

Fischer, and the Dawn of Asymmetric Induction



L-arabinose

L-mannonic acid **~3** : **1** L-gluconic acid

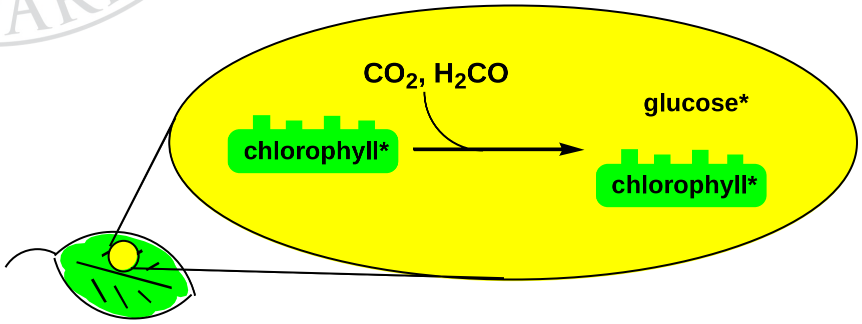
not isolated initially, but later found in mother liquor

"To my knowledge these observations furnish the first definitive evidence that further synthesis with asymmetric systems proceeds in an asymmetric manner."

-Emil Fischer, 1894

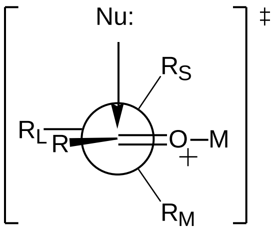
Fischer, E. *Ber.* **1890**, *23*, 2611
Fischer, E. *Ber.* **1894**, *27*, 3189

Assimilation in nature: propagation of asymmetry from one chiral molecule to another



Fischer, E. *Ber.* **1894**, *27*, 3189
Freudenberg, K. *Adv. in Carbohydrate Chem.* **1966**, *21*, 1

Don Cram: 1952

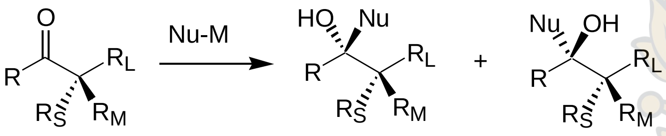


Cram acyclic model

Cram's Rule: "In reactions of the following type, that diastereomer will predominate which would be formed by the approach of the entering group from the *least hindered side* of the double bond when the rotational conformation of the C–C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric center."

Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828

Basis for Model



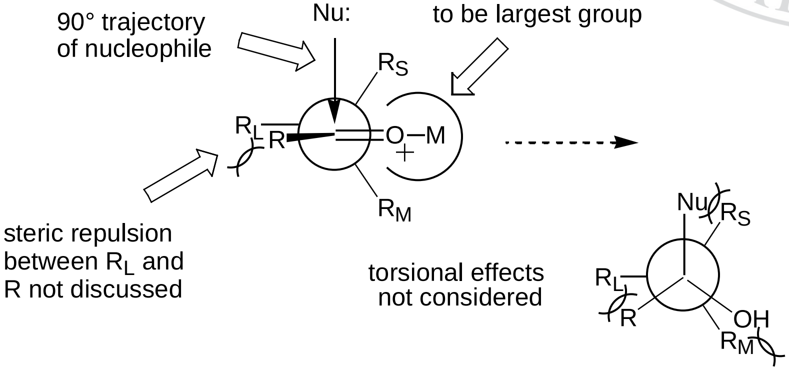
predicted (Felkin product)

(anti-Felkin product)

Nu-M = RMgX, LAH
R_L = Ph
R_M = Me, Et
R_S = H
R = H, Ph, Me, Et

selectivities ranging from 2:1 to >4:1, favoring Felkin product

Features and Liabilities



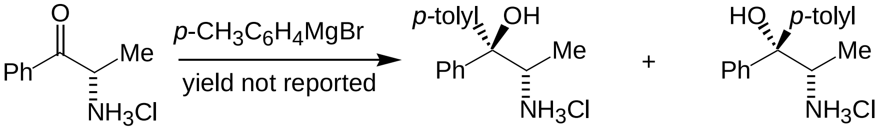
90° trajectory of nucleophile

activated carbonyl considered to be largest group

steric repulsion between R_L and R not discussed

torsional effects not considered

Among the 27 cited reactions whose stereoselection is "predicted" by Cram's acyclic rule:



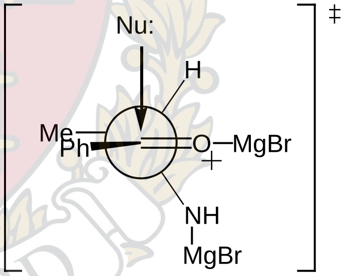
major (anti-Felkin)

minor (Felkin)

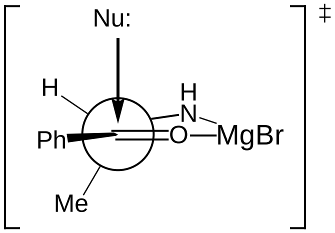
Curtin, D. Y.; Pollak, P. I. *J. Am. Chem. Soc.* **1951**, *73*, 992

Ranking of steric bulk of α-substituents is somewhat arbitrary: Me > NH_3Cl due to the amino group's formation of a non-rigid "more adaptable" ion pair

one proposed transition state:



in the end, a suggestion of a chelate . . .



■ Possible Pitfalls

- Low or unreported yields may result in misleading selectivities
- Model based on qualitative assessment of steric bulk

■ Bottom Line

Cram's acyclic model is a convenient mnemonic that predicts Felkin products in α-alkyl or aryl aldehydes or ketones.

Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828

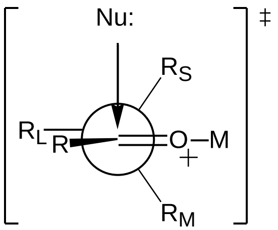
Don Cram: 1959

Methyl has greater *effective bulk* than OH; Cram cites "A-values" of Winstein, who compares the relative tendency of groups to occupy the equatorial position on a cyclohexane ring.

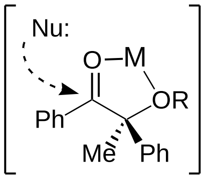
$CH_3 > OSO_2C_6H_4CH_3\text{-}p > OCOCH_3 > OH$

The acyclic model would predict the opposite product in the case of an α-heteroatom -- a new model is needed!

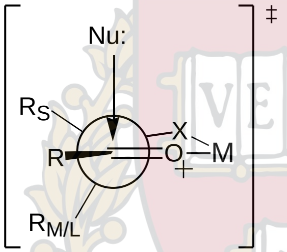
Winstein, S.; Holmes, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562



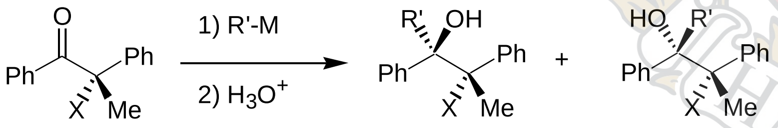
Cram acyclic model



nucleophile approaches from the back face



Cram chelate model



A major **B** minor

R'-M	X	A : B	yield of A (%)
CH_3MgI	OH	11.5 : 1	20
CH_3Li	OMe	9 : 1	50

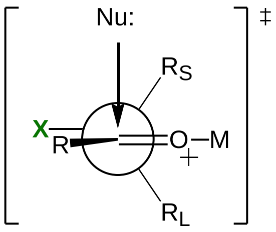
- expects groups OH, OR, OAc, NR_2, NHAc to chelate

"The open-chain model applies to systems which contain only groups attached to asymmetric carbon of the starting material which are incapable of complexing with organometallic reagents."

Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748

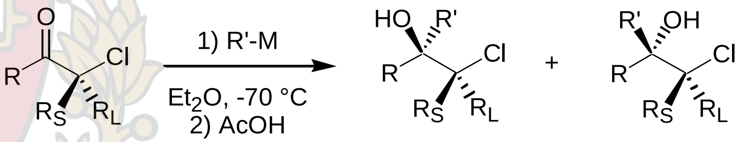
Cornforth: 1959

- argument based on importance of polarization in transition state, and evidence of selectivity in α-chlorocyclohexanone additions
- ". . . where the dipoles are antiparallel, the polarization of the carbonyl group would be easiest," thereby lowering transition state energy
- a modification of Cram's rule for electronegative, non-chelating α-substituents X



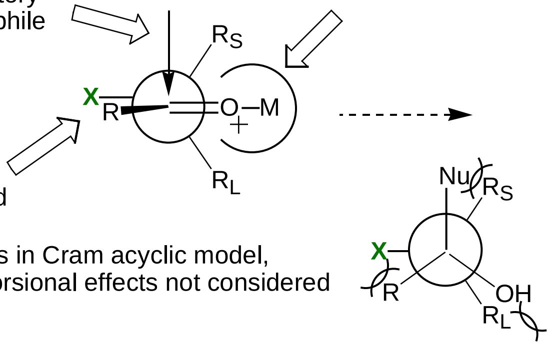
Cornforth model

Additions to α-Chloro Carbonyls



predicted (Felkin) (anti-Felkin)

Features



90° trajectory of nucleophile

activated carbonyl considered to be largest group

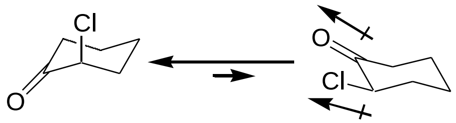
net dipole of molecule minimized

as in Cram acyclic model, torsional effects not considered

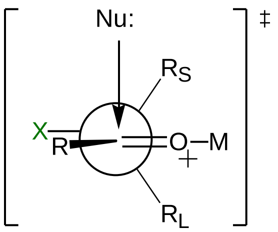
Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112

Cornforth: Rationalization and Evidence

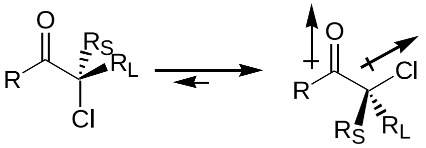
Support and Contradiction for Dipole Minimization



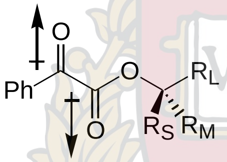
Corey, E. J. *J. Am. Chem. Soc.* **1953**, *75*, 2301
Corey, E. J.; Burke, H. J. *ibid.* **1955**, *77*, 5418



Cornforth model



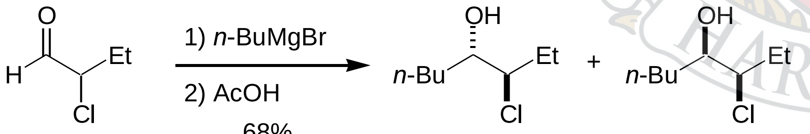
Bellamy, L. J.; Thomas, L. C.; Williams, R. L. *J. Chem. Soc.* **1956**, 3704
Bellamy, L. J.; Williams, R. L. *ibid.* **1957**, 4294



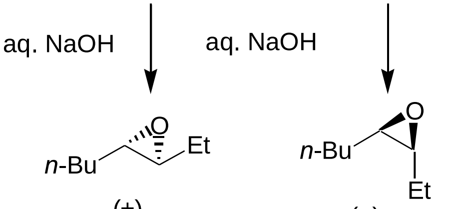
Prelog, V. *Bull. Soc. Chim. Fr.* **1956**, 987

(*note:* methylpyruvate does not adopt this conformation)

Chlorohydrin Synthesis



(±) **7** (Felkin) : **3** (anti-Felkin)



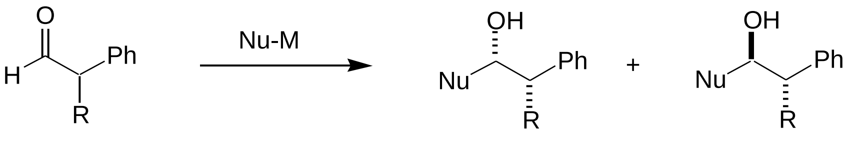
These were known products.

(±) (±)

Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112

Karabatsos: 1967

Given Cram's acyclic model, Karabatsos is surprised by the following selectivities:

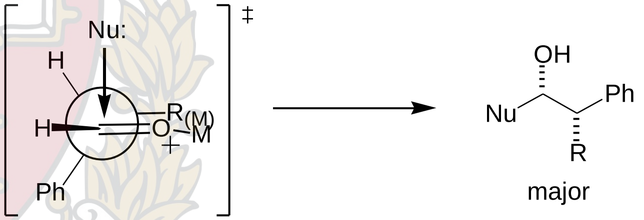


A **B**

- it appears that *i*-Pr is effectively smaller than Me, if Ph = R_L

R	A : B
Me	2–4 : 1
i-Pr	1–2 : 1

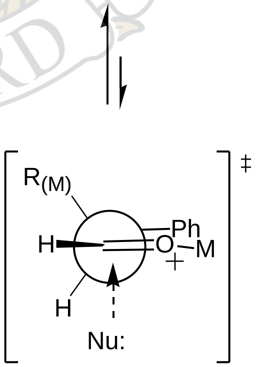
Karabatsos' explanation: Cram transition states are incorrect



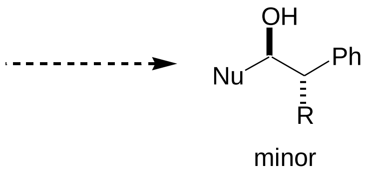
Karabatsos model

Compared Interaction	**ΔΔH°**
Me ↔ O – Ph ↔ O	0.6 kcal/mol
i-Pr ↔ O – Ph ↔ O	0.2 kcal/mol

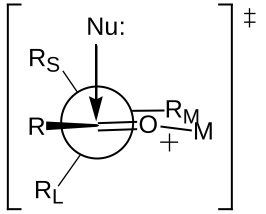
- ratios depend not on Nu ↔ H and Nu ↔ R_M, but instead on R_M ↔ O vs. R_L ↔ O



2nd-best conformer

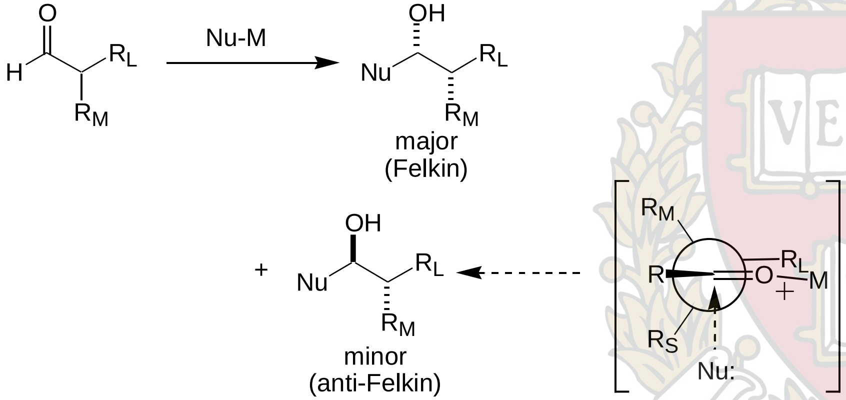


Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367

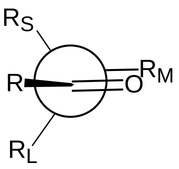


Karabatsos model

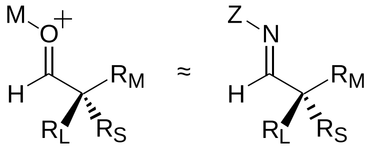
- energy difference ($\Delta\Delta H°$) between interactions of $R_M \leftrightarrow$ O and $R_L \leftrightarrow$ O determines product ratio
- reactant-like transition state
- model based on most stable ground-state conformation
- energy differences between major and minor conformations are <1 kcal/mol



Rationalizations



most stable ground state conformer



a) $\Delta H°_{\text{(imine N} \leftrightarrow \text{R)}} \approx \Delta H°_{\text{(carbonyl O} \leftrightarrow \text{R)}}$

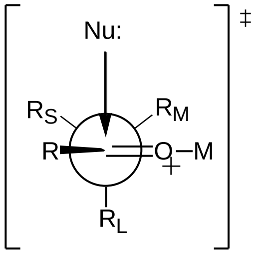
b) imine geometry ≈ complexed C=O geometry

$\therefore \Delta H°_{\text{(imine N} \leftrightarrow \text{R)}} \approx \Delta H°_{\text{(complexed C=O O} \leftrightarrow \text{R)}}$

Z = alkyl, OR, NR_2

Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367

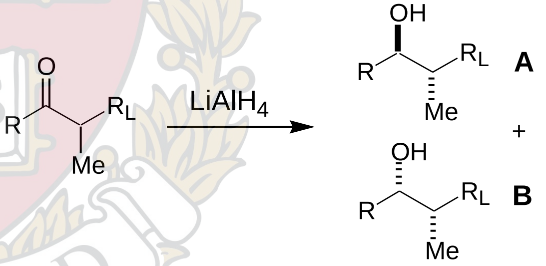
Felkin: 1968



Felkin model

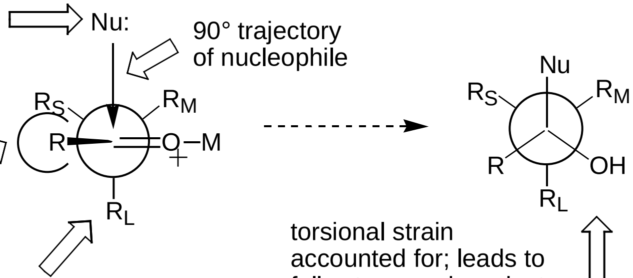
- "reactant-like" transition state
- assumption of torsional strain in partially formed or broken bonds: first fully staggered acyclic model
- substituents minimized around R; leads to inconsistency in aldehyde substrates
  → see DAE Chem 206 Lecture Notes (2000), 18-08
- polar effect: maximize separation between incoming anionic nucleophile and electronegative α-substituent (R_S, R_M, or R_L)

Reduction of α-Methyl Ketones



R	A / B R_L = Cy	R_L = Ph
Me	1.6	2.8
Et	2.0	3.2
i-Pr	4.1	5.0
t-Bu	**1.6**	49

Features



larger nucleophile ≈ better selectivity

90° trajectory of nucleophile

substituents minimized around ketone R

larger R_L ≈ better selectivity

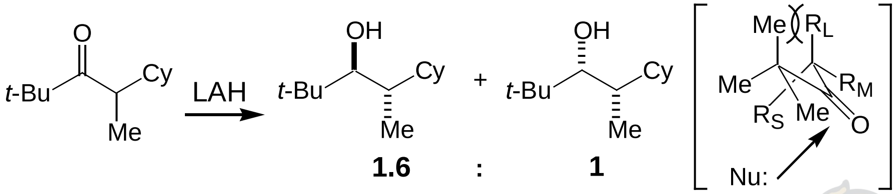
torsional strain accounted for; leads to fully staggered product

Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199

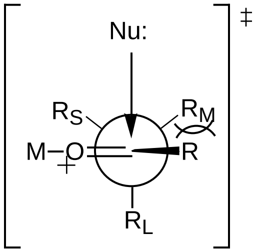
Felkin: Accounting for Less Selective Reactions

1) The *t*-butyl ketone case

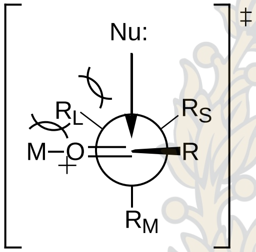
- with α-branching, in any staggered conformation, *syn*-pentane is impossible to avoid



2) Transition states for minor products (does not consider conformers with R_L next to R)



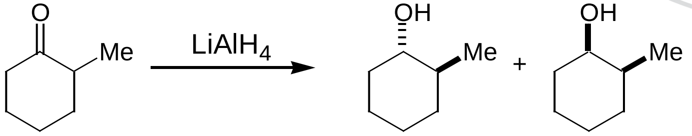
possible when R_M is relatively small



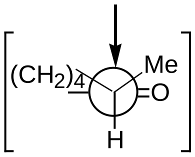
possible for small nucleophiles

3) 2-methylcyclohexanone

- cannot adopt Felkin-type conformation; still considered as a reactant-like transition state
- selectivity based on competition between torsional strain and steric strain

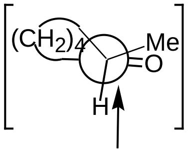


major



steric strain (small Nu:)

torsional strain (large Nu:)

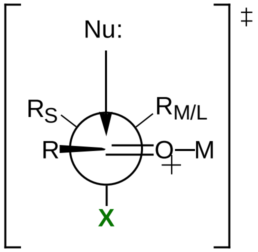


Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199; 2205

Weaknesses in Felkin's Argument

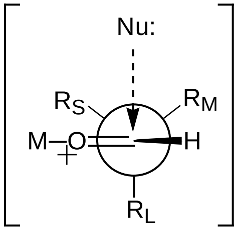
1) Polar effect

- main repulsion to minimize between Nu and electronegative group X -- no justification given



2) Breakdown for aldehydes

- without ketone R, important steric interaction removed: would predict R_M to be next to H rather than carbonyl



wrong prediction

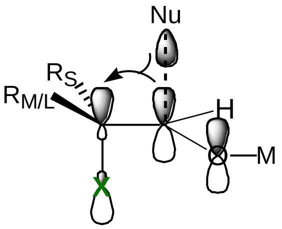
Anh's Solutions

1) Antiperiplanar effect

- best acceptor σ* orbital aligned parallel to π and π* orbitals of carbonyl; stabilization of incoming anion

$\pi_{C=O} \leftrightarrow \sigma^*_{C\text{-}X}$

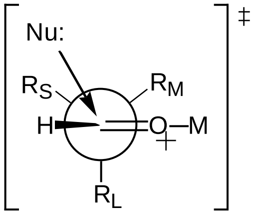
$n_{Nu} \leftrightarrow \sigma^*_{C\text{-}X}$



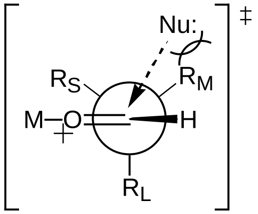
2) Non-perpendicular attack

- incorporation of the Bürgi-Dunitz trajectory

Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61
Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065
Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563



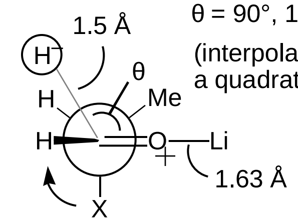
favored



disfavored

Anh's Calculated Transition State Energies

The model:

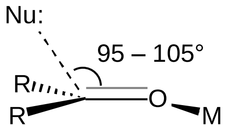


θ = 90°, 100°, 110°
(interpolated using a quadratic curve)

rotate C–C bond by 30° increments

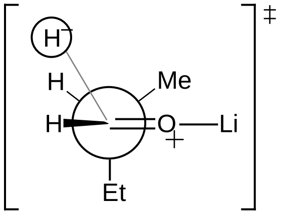
STO-3G *ab initio* method (low level)

Non-perpendicular attack

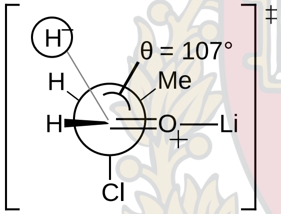


a range of angles for optimum overlap

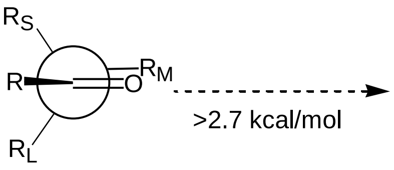
Lowest energy transition states:



2-methylbutanal (Felkin-Anh model)



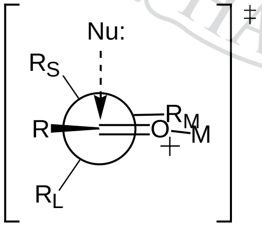
2-chloropropanal (Felkin-Anh polar model)



G_1

most stable ground state conformer

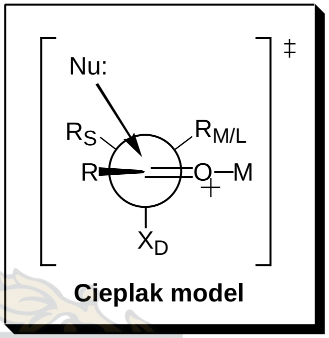
$$\boxed{E_{\text{Felkin model}} \approx E_{G1}}$$



Karabatsos model

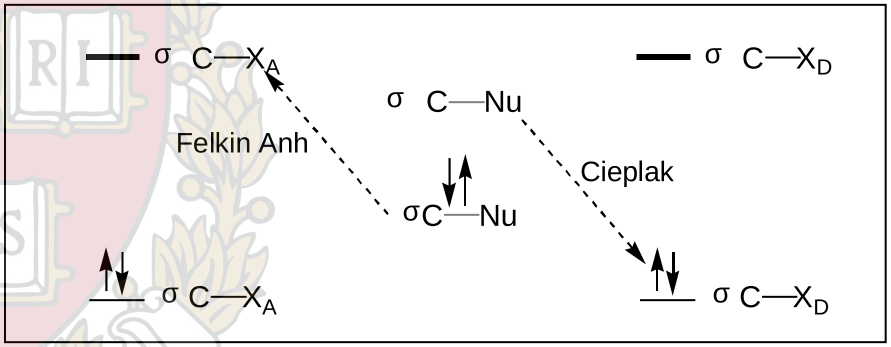
Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155
Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61
Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 146

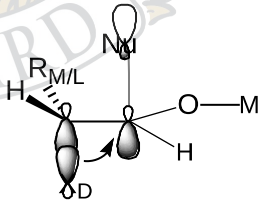
Cieplak Model for Carbonyl Addition



Cieplak model

- similar to Anh-Eisenstein modification of the Felkin model: stabilization of nucleophile via antiperiplanar C–X_D bond
- assumes an electron-poor transition state: aligns best donor C–X_D *anti* to incoming nucleophile to stabilize σ* of forming bond
- a model generated to explain unexpected selectivities
- importance of torsional effects (Felkin, Anh, Houk, Paddon-Row) disputed





$$\sigma_{C\text{–}Xd} \leftrightarrow \sigma^*_{C\text{---}Nu}$$

← better donor

C–H > C–C > C–N > C–O
(Houk disputes the ordering of C–H, C–C)

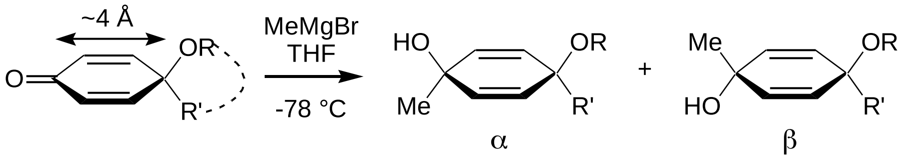
"Structures are stabilized by stabilizing their highest energy filled states. This is one of the fundamental assumptions in frontier molecular orbital theory. The Cieplak hypothesis is nonsense."

"Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct."

- *DAE*

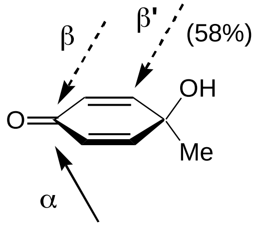
Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540;
Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447

4,4-Disubstituted Cyclohexadienones: Experimental Data

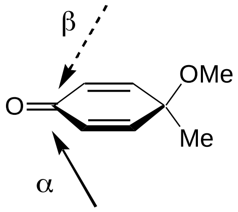


("vinylogous Felkin-Anh")

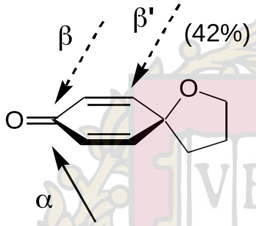
KEY: α : β (yield)



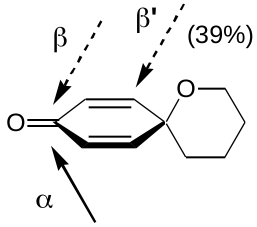
7.9 : 1 (26%)



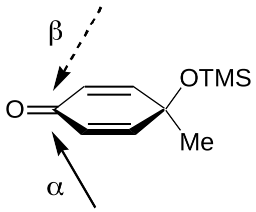
4.8 : 1 (81%)



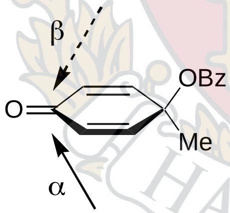
8.6 : 1 (32%)



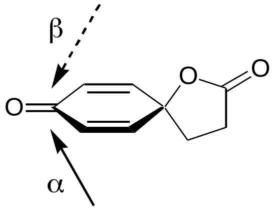
5.5 : 1 (53%)



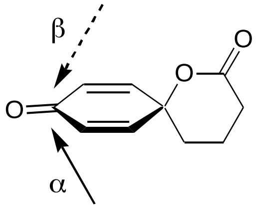
17.7 : 1 (93%)



8.2 : 1 (85%)



32 : 1 (79%)

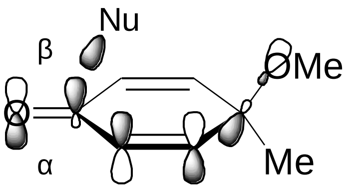


11 : 1 (29%)

Wipf Seeking an Explanation

Stereoelectronic effect?

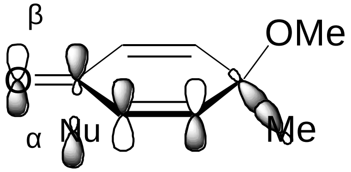
Neither vinylogous Felkin nor vinylogous Cieplak sufficiently explains or predicts selectivity.



"vinylogous Anh-Eisenstein" model

LUMO of enone has phase inversion due to double bond between carbonyl and donor/acceptor orbital

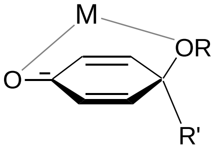
- stabilizing HOMO of nucleophile
- predicts β attack -- wrong product!



"vinylogous Cieplak" model

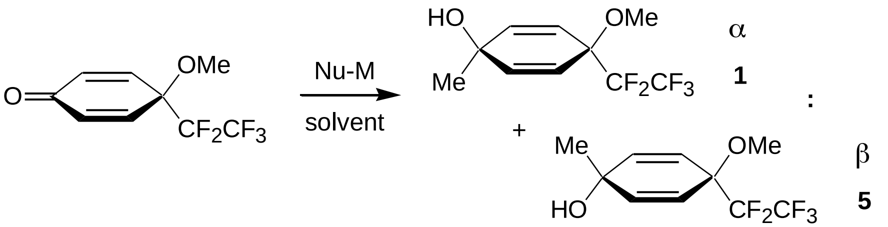
- stabilizing σ* of the incipient bond
- predicts α attack, but no qualitative correlation between ratio of isomers and σ energy of donor C–C bonds

Chelate shielding of the β face is not likely, since 1,4-addition, when it does occur, is β-selective.



Electrostatic effect?

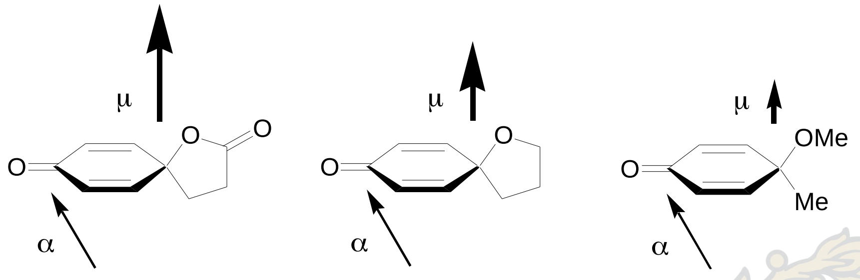
Substrate with inverted dipole exhibits good β selectivity!



Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678
Wipf, P.; Jung, J-K. *Chem. Rev.* **1999**, *99*, 1469

Quantitative Correlation Between Facial Selectivity and Dipole Moment

Qualitative Assessment

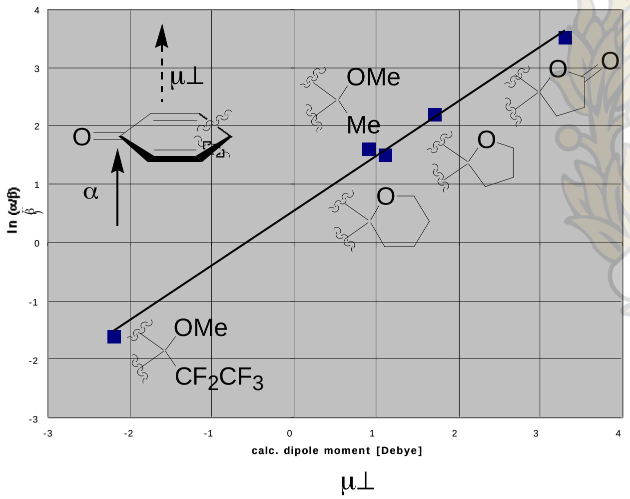


32 : 1 (79%)

8.6 : 1 (32%)
[β' (42%)]

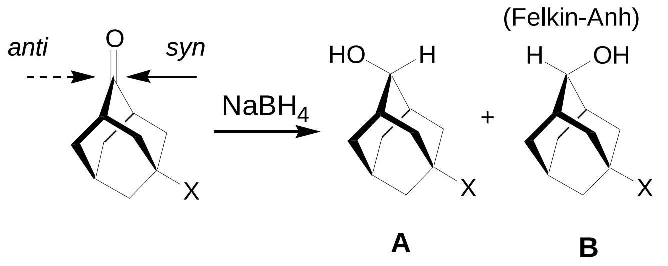
4.8 : 1 (81%)

Dipole Moment Calculations



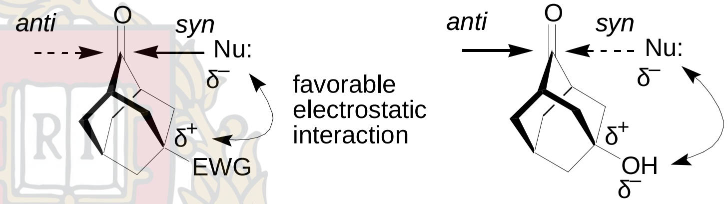
- calculated dipole moments of five representative dienones using SPARTAN
- linear correlation between perpendicular vector of dipole moment and natural log of facial selectivity
- validity of ground-state dipole moment: complexed carbonyl should affect dipoles of all dienone substrates in same manner
- approach of nucleophile toward positive end of dipole favored

An Electrostatic Take on Some Controversial Cases



X	A : B
p-PhNO$_2$	66 : 34
F	62 : 38
CO$_2$Me	61 : 39
CF$_3$	59 : 41
SiMe$_3$	45 : 55
OH	43 : 57

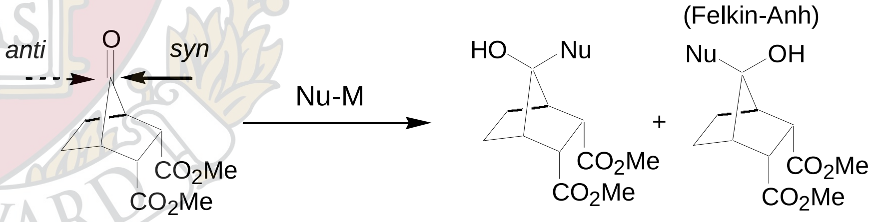
Cheung, *et al. J. Am. Chem. Soc.* **1986**, *108*, 1598



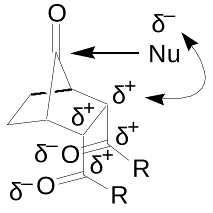
favorable electrostatic interaction

hydroxyl may create too much lone-pair repulsion

Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867



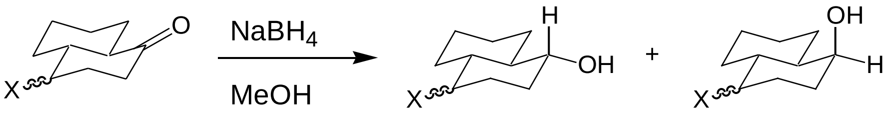
Nu-M	C	:	D
NaBH$_4$	70	:	30
MeLi	>90	:	10



favorable electrostatic interaction

Mehta, G.; Khan, F. A. *J. Am. Chem. S*, **1990**, *112*, 6140
Paddon-Row, M. N.; Wu, Y-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638
Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734

Houk: Axial Effect



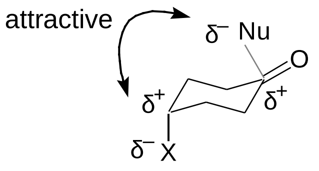
A axial attack

B equatorial attack

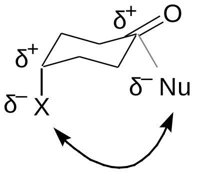
X	A : B
H	60 : 40
eq OH	61 : 39
eq OAc	71 : 29
eq Br	66 : 34
eq Cl	71 : 29
ax OH	85 : 15
ax OAc	83 : 17
ax Cl	88 : 12
ax F	87 : 13

Rationalization:

a remote electrostatic effect



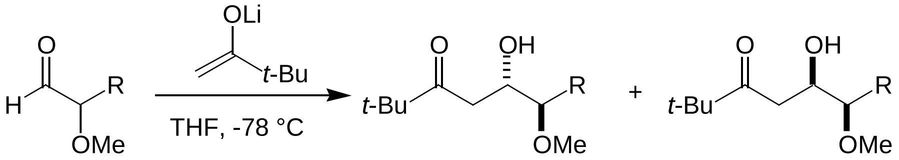
preferred



repulsive

Wu, Y-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018
Paddon-Row, M. N.; Wu, Y-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638

Heathcock: α-Alkoxy Lithium Aldol



A Felkin

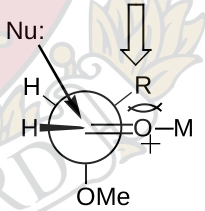
B anti-Felkin

"Quite simply, we believe our data show that the Anh-Eisenstein hypothesis is only partly correct."

R	A : B
Me	58 : 42
Et	76 : 24
i-Pr	92 : 08
Ph	83 : 17
t-Bu	93 : 07

Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353

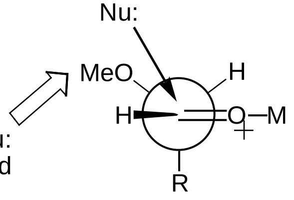
steric effect on Nu: is underemphasized



Felkin-Anh polar model

- Would expect some erosion of selectivity as size of R increases -- observe just the opposite!

steric effect on Nu: is overemphasized



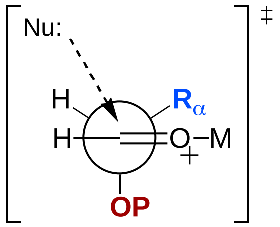
electrostatic model

- As R is anti to incoming nucleophile, increasing size of R should not erode selectivity
- As R gets larger, conformation may be more "locked" in the above conformer

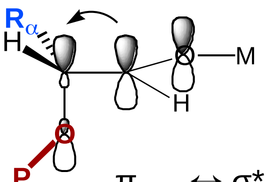
In both models, the stereoelectronic or electrostatic control element is not consistently dominant!
Both the size and the electronic properties of the α-substituents must be considered.

Are Felkin-selective reactions of α-heteroatom aldehydes going through the Felkin-Anh transition state?

Felkin-Anh model



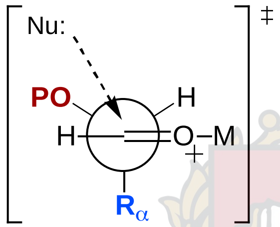
- leads directly to staggered conformation, Felkin product
- best acceptor σ* orbital aligned parallel to π and π* orbitals of carbonyl: hyperconjugative stabilization



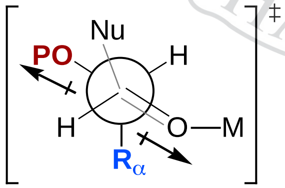
$\pi_{C=O} \leftrightarrow \sigma^*_{C\text{-}OP}$

- assumes a covalent transition state in which FMO stabilization dominates

electrostatic model

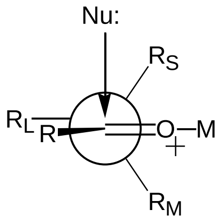


- leads directly to staggered conformation, Felkin product
- dipoles of carbonyl and α-C-O are minimized, with increasing stabilization as pyramidalization occurs at the reactive center

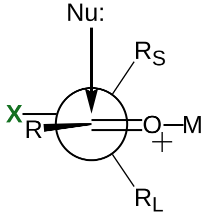


- assumes a more ionic transition state in which coulombic interactions dominate
- larger π* coefficient on C of oxocarbenium species may enable a wider range of angles for nucleophilic trajectory

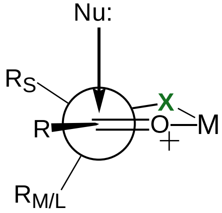
Models Proposed for 1,2-Asymmetric Induction



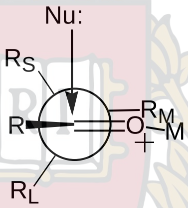
Cram acyclic model (1952)
steric



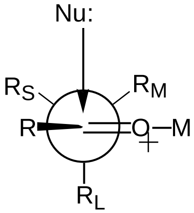
Cornforth model (1959)
electrostatic



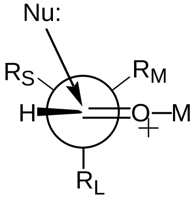
Cram rigid model (1959)
chelation



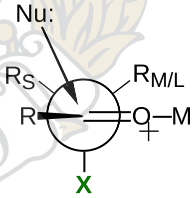
Karabatsos model (1967)
ground-state, steric



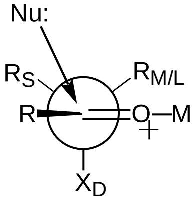
Felkin model (1968)
steric, torsional



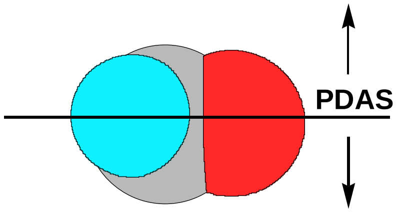
Felkin-Anh model (1977)
steric, torsional, Bürgi-Dunitz



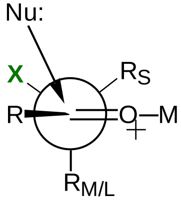
Felkin-Anh polar model (1977)
electronic, torsional, Bürgi-Dunitz



Cieplak model (1981)
electronic, torsional, Bürgi-Dunitz

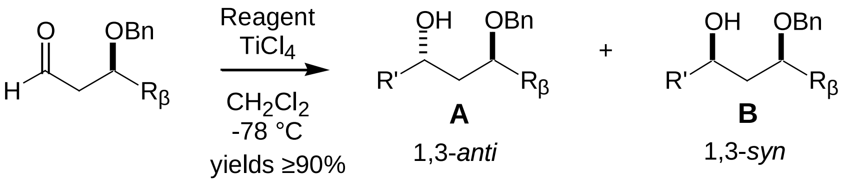


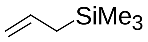
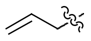
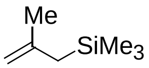
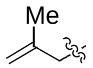
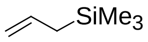
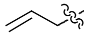
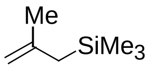
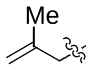
Tomoda EFOE model (1997)
ground-state, steric, electronic



electrostatic model (2001)
electrostatic, torsional, Bürgi-Dunitz

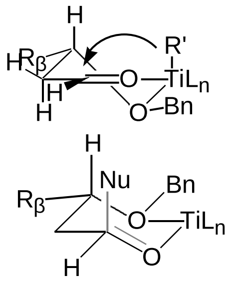
Reetz: Chelation in β-Alkoxy Aldehydes



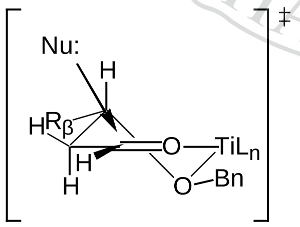
Reagent	R_β	R'	A : B
 $SiMe_3$	Me		95 : 05
 Me $SiMe_3$	Me	 Me	95 : 05
n-Bu_2Zn	Me	*n*-Bu	90 : 10
 $SiMe_3$	*n*-Bu		95 : 5
 Me $SiMe_3$	*n*-Bu	 Me	99 : 01

RMgX, RLi, and R_2CuLi fail to give high chelation selectivities for β-alkoxy aldehydes.

Reetz proposes possible transmetallation event of nucleophile: internal delivery.



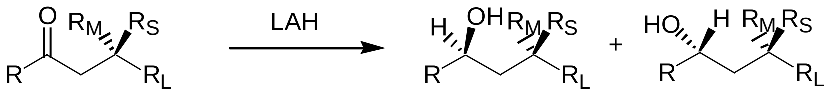
- leads to a chair-like intermediate



Cram-Reetz chelate model

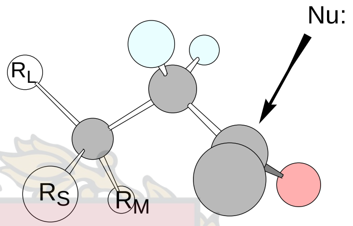
Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833

1,3-Asymmetric Induction: Open-Chain Models



major minor

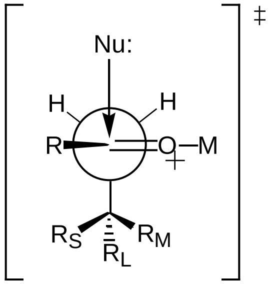
(hydrocarbon R groups)



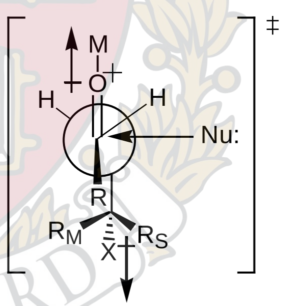
3-D depiction of Jacques model

- rationalization similar to Felkin: minimization of R ↔ β-R steric interactions

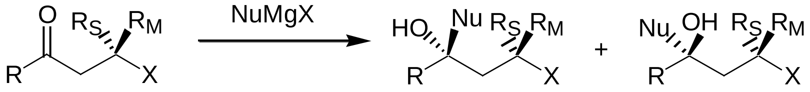
Brienne, M-J.; Ouannès, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1968**, *3*, 1036



Jacques steric model



Cram polar model



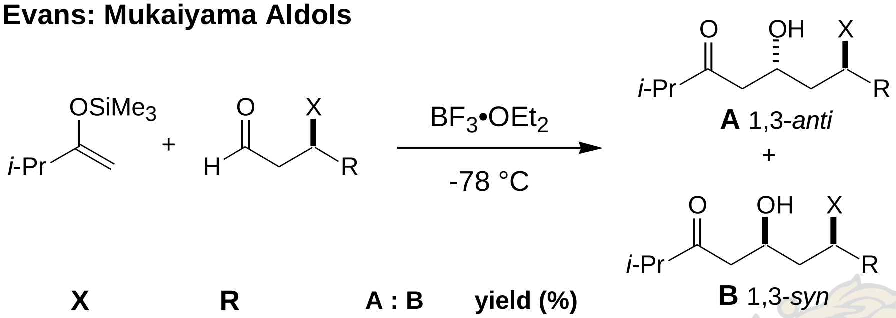
major minor

- an adaptation of the Cram steric model, with the key feature being dipole minimization of electronegative substituent X and carbonyl

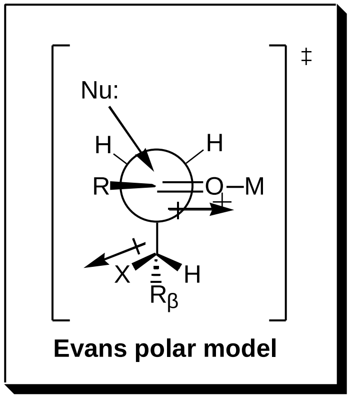
Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011, 4019

1,3-Asymmetric Induction: Open-Chain Models

Evans: Mukaiyama Aldols



X	R	A : B	yield (%)
OPMB	*i*-Pr	92 : 08	91
OTBS	*i*-Pr	80 : 20	84
OPMB	CH_2CH_2Ph	81 : 19	87
OTBS	CH_2CH_2Ph	73 : 27	90
OAc	CH_2CH_2Ph	43 : 57	79
Cl	CH_2CH_2Ph	83 : 17	84
Me	$C(Me_2)CHCH_2$	58 : 42	88

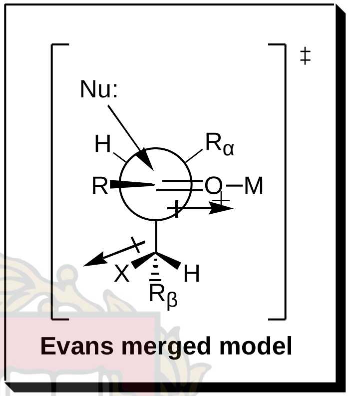


Evans polar model

- staggered to avoid torsional strain
- dipoles of C_β–X and carbonyl minimized
- non-perpendicular nucleophile trajectory

Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537
Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *116*, 4322
See also: Bonini, C.; Esposito, V.; D'Auria, M.; Righi, G. *Tetrahedron* **1997**, *53*, 13419

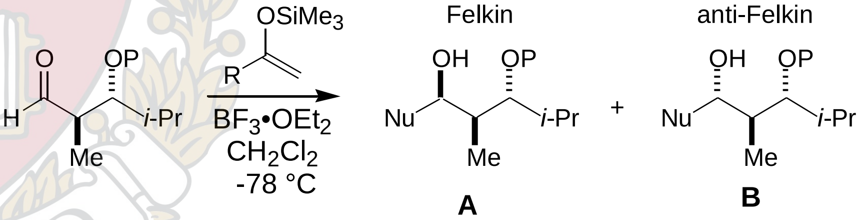
Evans Merged Model for 1,2- and 1,3-Asymmetric Induction



Evans merged model

- for non-chelating conditions
- a merger of the Felkin-Anh (1,2) model and the Evans polar (1,3) model
  - minimized dipole moment
  - non-perpendicular trajectory
  - R_L *anti* to incoming nucleophile
- predicts 1,2-Felkin control and 1,3-*anti*

The stereoreinforcing case (Felkin and 1,3-*anti* induction coincide)

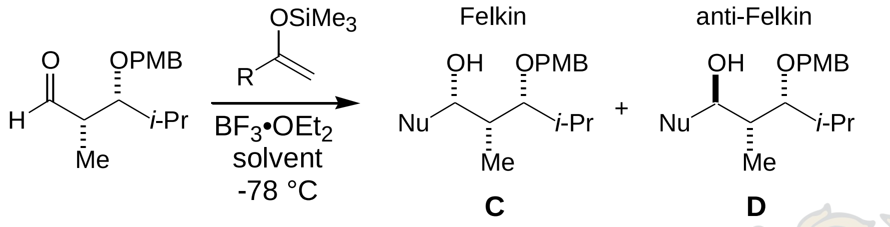


R	P = PMB A : B	yield (%)	P = TBS A : B	yield (%)
t-Bu	99 : 01	94	99 : 01	93
i-Pr	98 : 02	98	95 : 05	88
Me	97 : 03	86	71 : 29	92

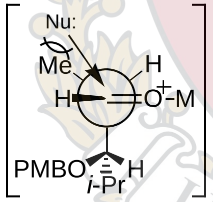
Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619
Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322

Evans Merged Model for 1,2- and 1,3-Asymmetric Induction

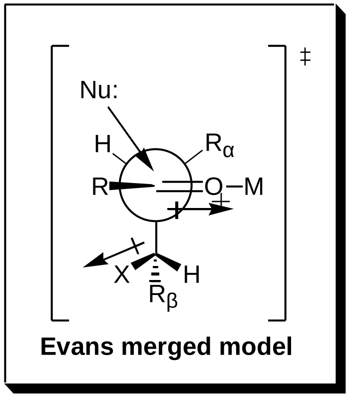
The non-stereoreinforcing case: Felkin control opposes 1,3-stereocontrol



R	C : D CH_2Cl_2	yield (%)	C : D toluene	yield (%)
t-Bu	96 : 04	89	88 : 12	75
i-Pr	56 : 44	98	32 : 68	86
Me	17 : 83	82	06 : 94	92



non-stereoreinforcing transition state

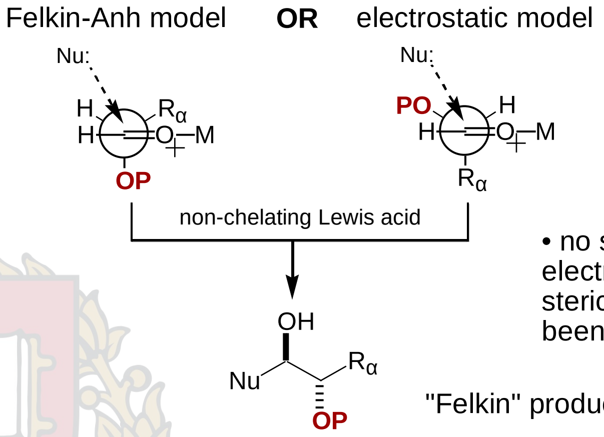


Evans merged model

- with a small nucleophile, β-stereocenter becomes the dominant control element
- 1,3-induction is enhanced in nonpolar media

Integration of α- and β-Alkoxy Aldehyde Models in Non-chelating Systems

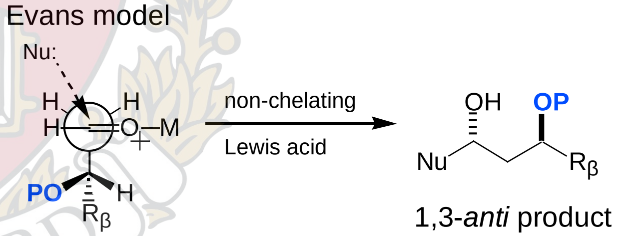
For α-alkoxy aldehydes:



- no systematic electronic + steric study has been done

"Felkin" product predicted

For β-alkoxy aldehydes:



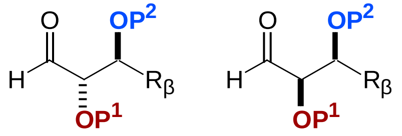
1,3-*anti* product predicted

- under non-chelating conditions, 1,3-*anti* selectivity is observed

Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537-8540

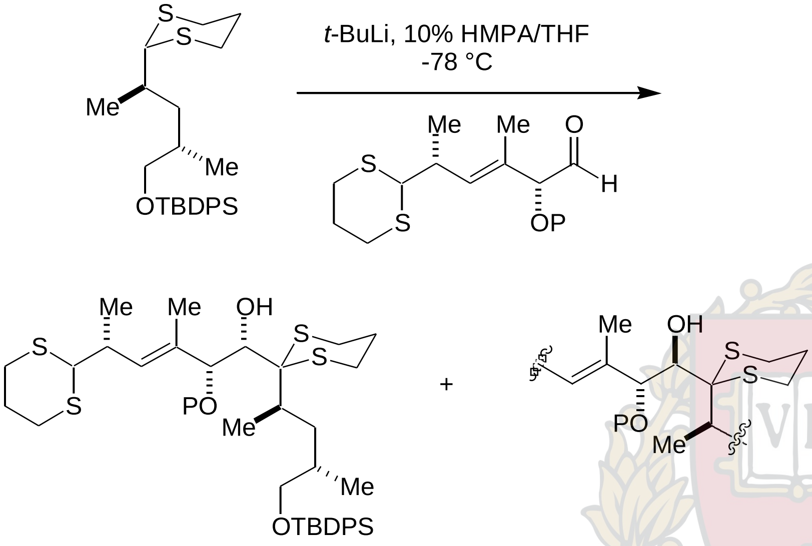
For α,β-bisalkoxy aldehydes:

Which is stereoreinforcing, *anti* or *syn*?



How does the α-alkoxy substituent affect the conformation of the β-stereocenter?

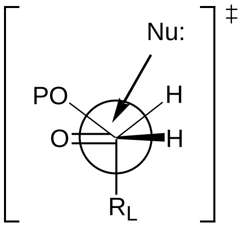
Smith: Rapamycin



A
anti-Felkin

B
Felkin

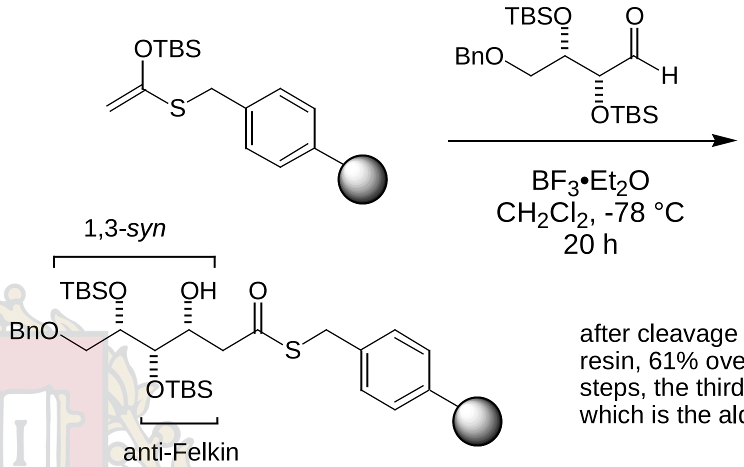
P	A : B	yield (%)
MOM	2 : 1	32
TBS	5 : 1	75
TBDPS	>20 : 1	60



suggested as reactive conformer

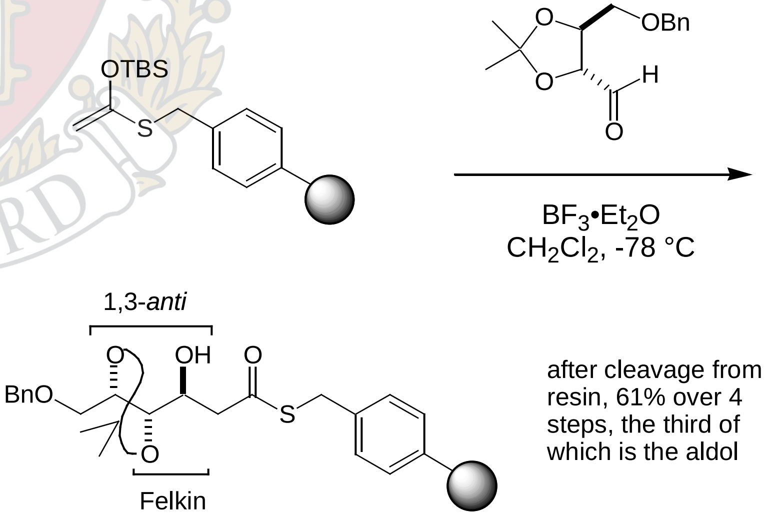
Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947

Kobayashi: Monosaccharide Derivatives on the Solid Phase



ds >98 : 2

after cleavage from resin, 61% over 4 steps, the third of which is the aldol



ds 95 : 5

after cleavage from resin, 61% over 4 steps, the third of which is the aldol

Kobayashi, S.; Wakabayashi, T.; Yasuda, M. *J. Org. Chem.* **1998**, *63*, 4868

Conclusions

- Nucleophilic additions to α-heteroatom-substituted carbonyl compounds are highly sensitive to solvent, nature and size of nucleophile, nature and size of protecting group, and size of other α-substituent.

- While the Felkin-Anh model has withstood the test of time for hydrocarbon α-substituents, the numerous exceptions to the electronic model have sparked a flurry of new explanations, beginning with Cieplak in 1981. The debate continues, between steric, torsional, electronic, and electrostatic effects.

- Judging by the Smith and Kobayashi results, as well as many others, it remains a challenge to predict the stereochemical outcome of addition to α- and β-heteroatom-substituted carbonyl compounds. It may be that more than one model is operational in a single system.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 21

Enantioselective Carbonyl Addition

- Enantioselective addition of R_2Zn to aldehydes
- Enantioselective Reduction of Ketones & Imines

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 8
Reactions of Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

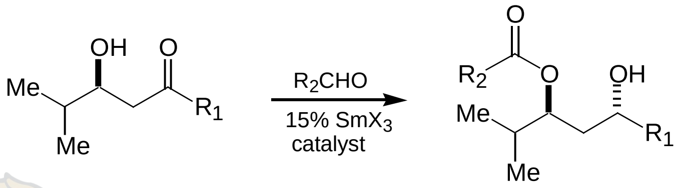
Carbonyl Addn: Felkin Control: Evans, *JACS* **1996**, *118*, 4322 **(handout)**
Carbonyl Additon: Chelate Control: Evans *JACS* **2001**, ASAP **(handout)**
Enantioselective Carbonyl Reduction: Corey *Angew. Chem. Int Ed*. **1998**, *37*, 1986-2012 **(handout)**
Enantioselective Carbonyl Addition (R_2Zn): Noyori *Angew. Chem. Int Ed*. **1991**, *30*, 49-69 **(handout)**

Matthew D. Shair

Wednesday,
November 6, 2002

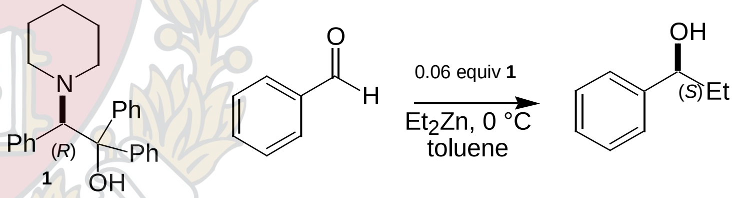
Problems:

Propose a mechanism for tihs highly diastereoselective transformation, Evans, Hoveyda JACS **112**, 6447 (1990)



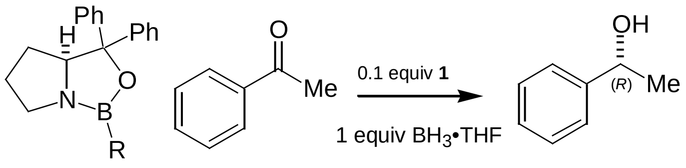
diastereoselection > 100:1

Cume Question, 2000: Chiral amino alcohol **1** efficiently mediates the addition of diethylzinc to aromatic aldehydes. While a number of other amino alcohols are also effective in controlling the absolute course of the addition process, this amino alcohol has been the focus of a recent computational investigation that addresses the preferred transition state geometry for this addition process (Pericas, et al. *J. Org. Chem*. **2000**, *65*, 7303 and references cited therein). It should be noted that, while **1** is not the actual catalyst, it is modified under the reaction conditions to the competent catalytic agent. Provide a detailed mechanism for the overall transformation. Use 3-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.



97% ee

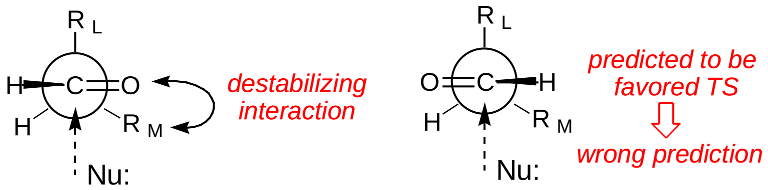
Cume Question, 2000: Corey's introduction of chiral oxazaborolidine catalysts **1** in the borane-mediated enantioselective reduction of ketones represents an important advance in asymmetric synthesis (Corey & Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012). Provide a detailed mechanism for the overall transformation. Use 3-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.



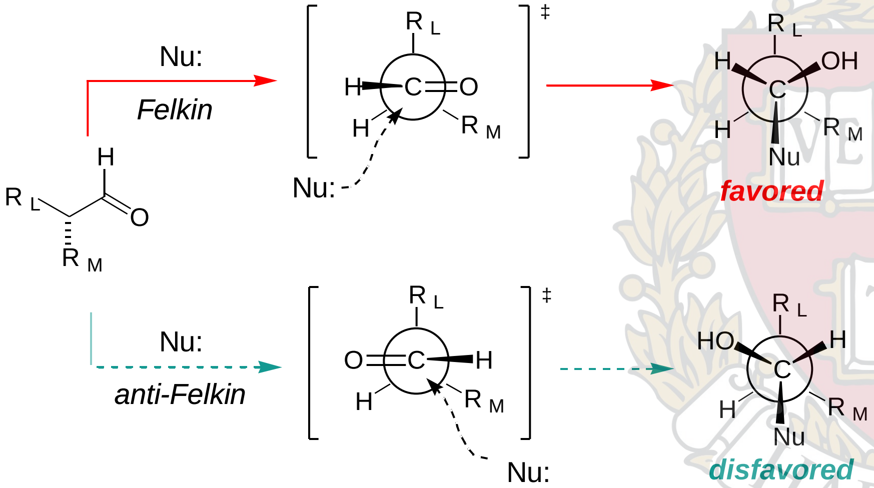
1, (R = H or Me)

97% ee

The flaw in the Felkin model: A problem with aldehydes!!



Anh & Eisenstein *Noveau J. Chim.* **1977**, *1*, 61-70
Anh *Topics in Current Chemistry.* **1980**, ***No 88***, 146-162



New Additions to Felkin Model:

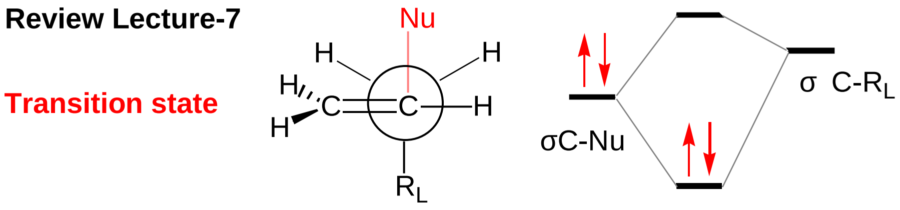
- Dunitz-Bürgi C=O–Nu orientation applied to Felkin model.
- The antiperiplanar effect:
Hyperconjugative interactions between C-R_L which will lower π*C=O will stablize the transition state.

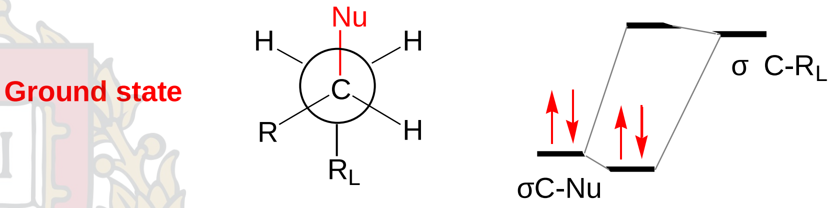
Theoretical Support for Staggered Transition states

Houk, *JACS* **1982**, *104*, 7162-6
Houk, *Science* **1986**, *231*, 1108-17

Houk: "Torsional effects in transition states are more important than in ground states"

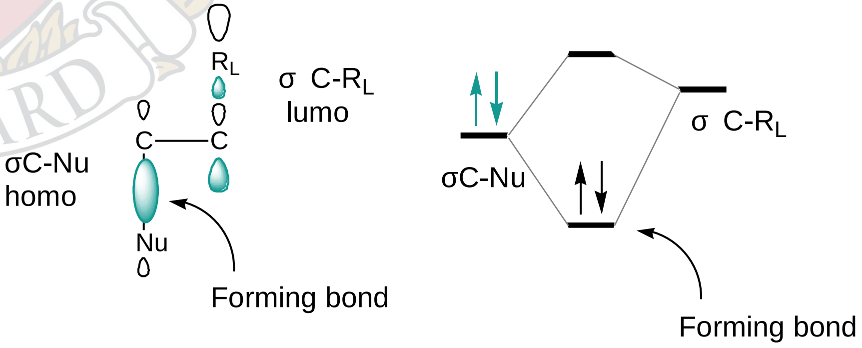
Review Lecture-7





Transition states

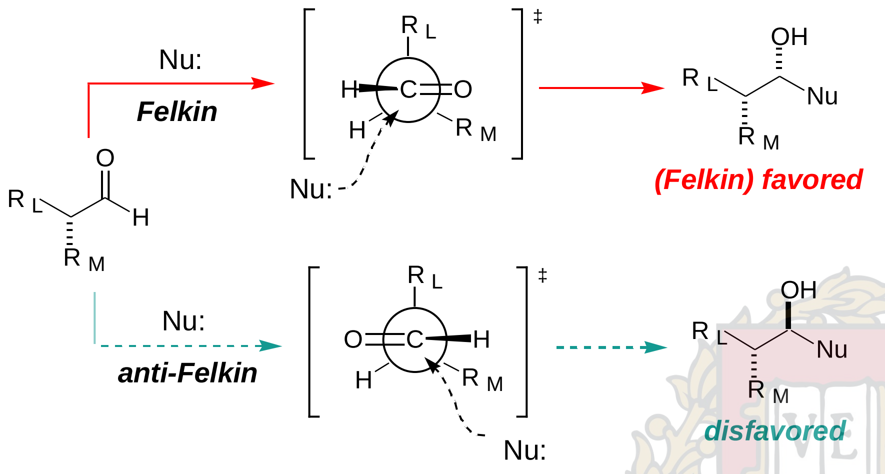
H-radical and H-anion: antiperiplanar σ C–R orbital stabilized the TS illustrated for Nu addition



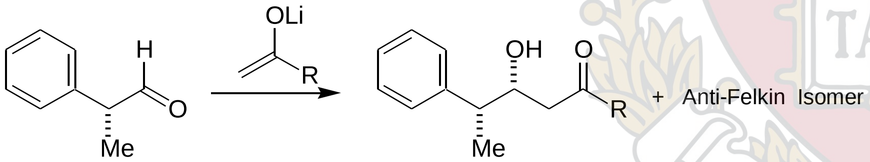
Houk, *Science* **1981**, *231*, 1108-1117
"The Theory and Modeling of Stereoselective Organic Reactions"

The Felkin-Anh Eisenstein Model: Verification

Addition of Enolate & Enol Nucleophiles

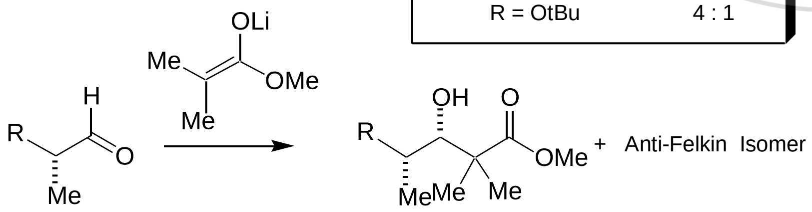


Trend-1: For Li enolates, increased steric hindrance at enolate carbon results in enhanced selectivity



L. Flippin & Co-workers,
Tetrahedron Lett.. **1985**, *26*, 973.

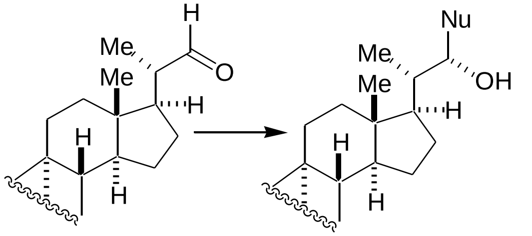
Enolate (R)	Ratio
R = Me	3 : 1
R = OtBu	4 : 1



L. Flippin & Co-workers,
Tetrahedron Lett.. **1985**, *26*, 973.

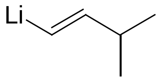
Ketone (R)	Ratio
R = Ph	>200 : 1
R = c-C_6H_{11}	9 : 1

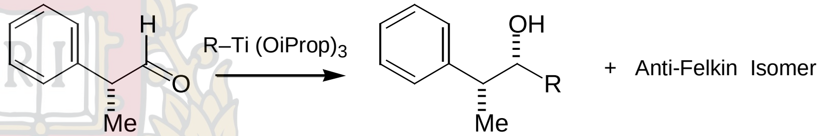
■ This trend carries over to organometallic reagents as well



Cram

C. Djerassi & Co-workers,
J. Org, Chem. **1979**, 44, 3374.

Reagent	Ratio
ClMg—C≡CEt	1 : 1
Li 	5 : 1

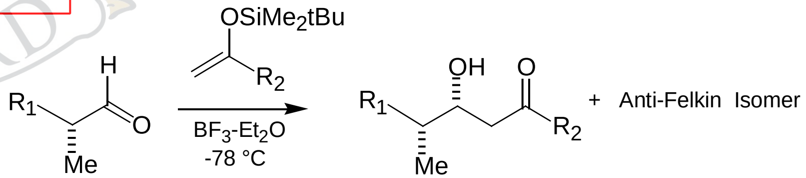


M. Reetz & Co-workers,
Angew Chemie Int. Ed.. **1982**, *21*, 135.

(R–MgX gives Ca 3:1 ratios)

R-Titanium	Ratio
R = Me	>90 : 10
R = n-Bu	>90 : 10

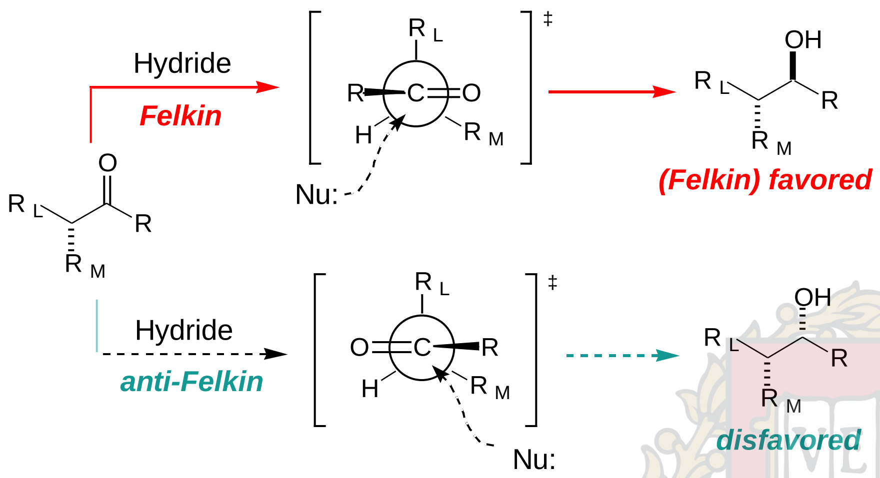
Trend-2: **Lewis acid catalyzed rxns are more diastereoselective**

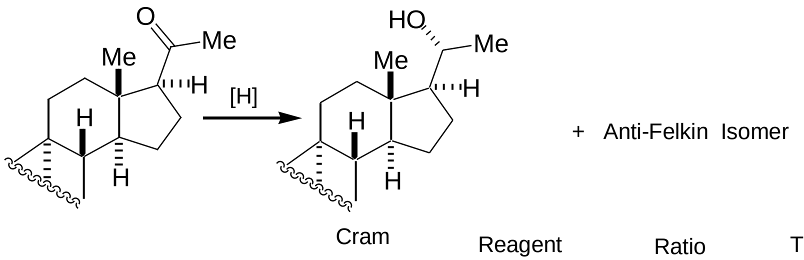


Ketone (R_1)	Enolate (R_2)	Ratio	Ratio Li enolate
R = Ph	R = Me	10 : 1	3 : 1
R = Ph	R = t-Bu	24 : 1	
R = Ph	R = OMe	15 : 1	
R = Ph	R = Ot-Bu	36 : 1	4 : 1
R = c-C_6H_{11}	R = Ot-Bu	16 : 1	

C. Heathcock & L. Flippin *J. Am. Chem. Soc.* **1983**, *105*, 1667.

Addition of Hydride Nucleophiles

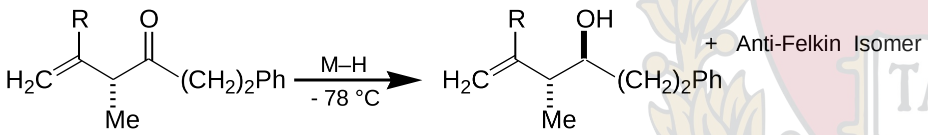




M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725.

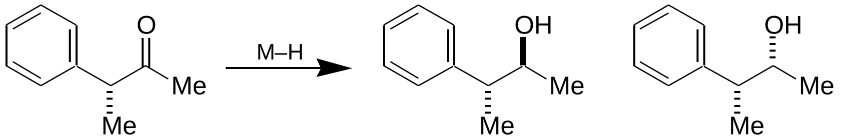
Reagent	Ratio	TS ‡
$Li^+H–B^-(sec\text{-}Bu)_3$	54 : 1	Felkin
$NaBH_4$	5 : 1	Felkin
$LiAlH_4$	3 : 1	Felkin
$H–B(Sia)_2$	1 : 10	Anti-Felkin

Note: Borane reducing agents do not follow the normal trend



G. Tsuchihashi & Co-workers,
Tetrahedron Lett. **1984**, *25*, 2479.

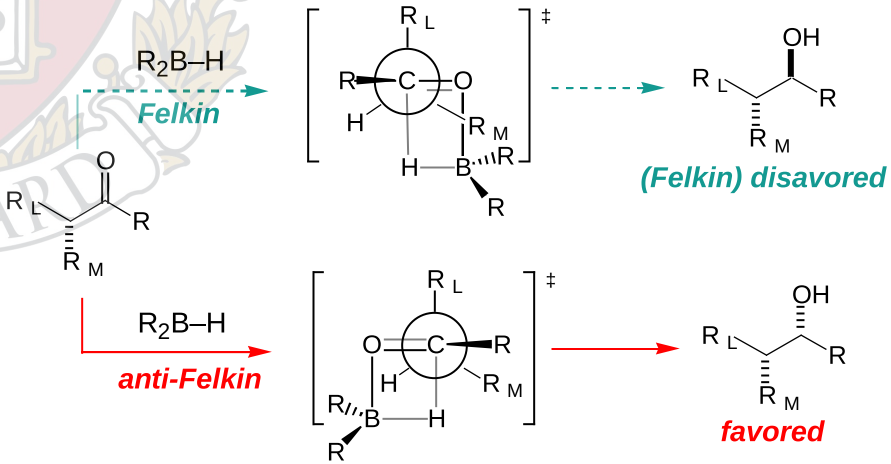
Ketone (R)	Reagent	Ratio
R = H	$Li^+H–B^-(sec\text{-}Bu)_3$	96 : 4
R = H	DIBAL	47 : 53
R = Me	$Li^+H–B^-(sec\text{-}Bu)_3$	>99 : 1
R = Me	DIBAL	88 : 12



M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, *105*, 3725.

Reagent	Ratio	TS ‡
$Li^+H–B^-(sec\text{-}Bu)_3$	22 : 1	Felkin
$H–B(Sia)_2$	1 : 4	Anti-Felkin

Transition States for C=O-Borane Reductions

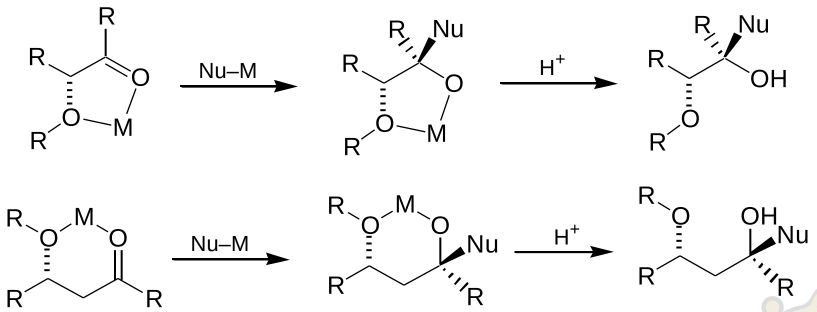


Nonspherical nucleophiles are unreliable in the Felkin Analysis

Exercise: Draw the analogous bis$(R_2BH)_2$ transition structures

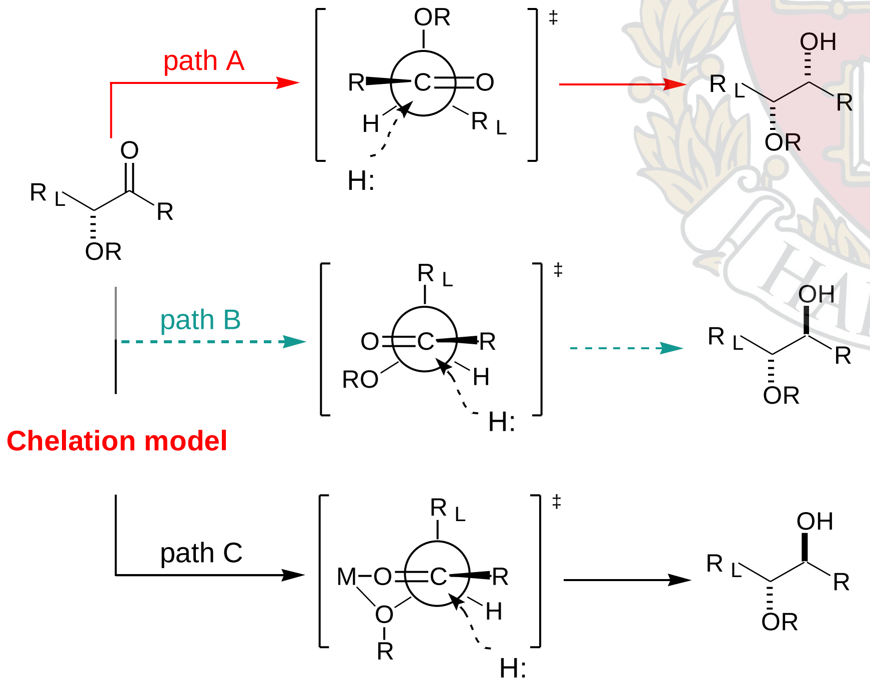
Review hydroboration discussion in Lecture-8

Chelate organization provides a powerful control element in carbonyl addition reactions

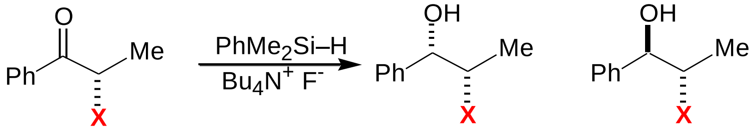


Reviews Reetz, *Accts. Chem. Res.* **1993**, *26*, 462-468 **(pdf)**
Reetz, *Angew. Chem. Int. Ed*. **1984**, *23*, 556-569

Lets begin with the hydride reductions of alkoxy ketones



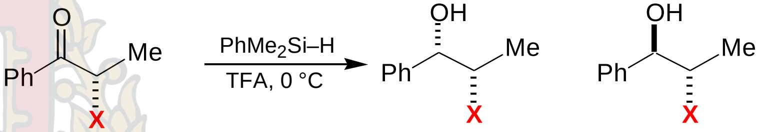
Lets begin with a case where chelation is precluded: (Path A)



Let R_L = X
in the Ahn-Eisenstein model

T. Hiyama & Co-workers,
J. Am. Chem. Soc. **1984**, *106*, 4629.

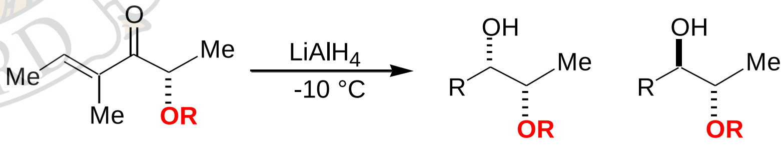
Substituent (X)	Ratio
X = NMe_2	>99 : 1
X = OAc	95 : 5
X = OCOPh	96 : 4



H-bonding Chelate Model

T. Hiyama & Co-workers,
J. Am. Chem. Soc. **1984**, *106*, 4629.

Substituent (X)	Ratio
X = $NHCO_2Et$	<1 : 99
X = OCOPh	7 : 93



Overman
Tet Lett. **1982**, *23*, 2355

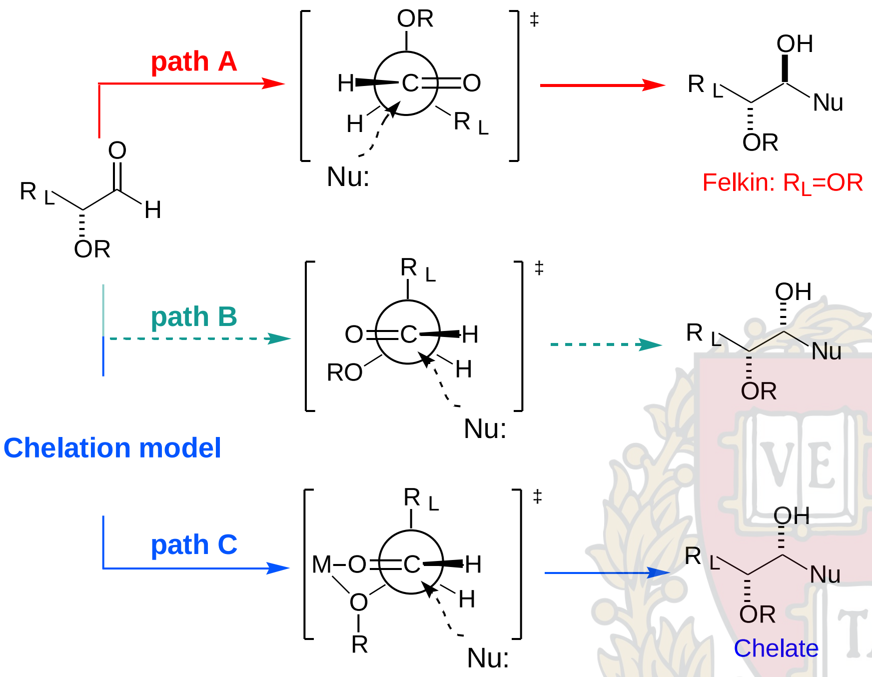
(OR)	Solv.	Ratio	Model
R = CH_2OBn	THF	30 : 70	Chelate
R = CH_2OBn	Et_2O	2 : 98	Chelate
R = $SiPh_2$(t)Bu	THF	95 : 5	Cram: R_L=OR

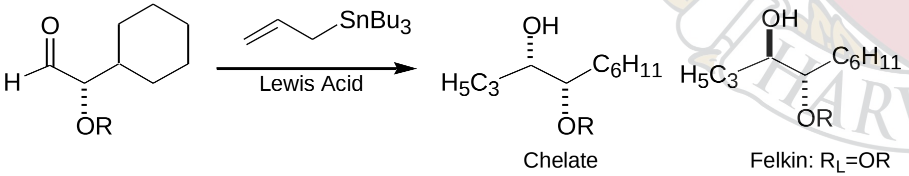
Degree of chelate organization may be regulated by choice of solvent and protecting group. Note that $SiPh_2$(t)Bu group prevents chelation for most Lewis acids. There are dramatic exceptions However:

Carbonyl Additon: Chelate Control: Evans *JACS* **2001**, ASAP **(handout)**

Carbonyl Addition Reactions: Chelate Organization

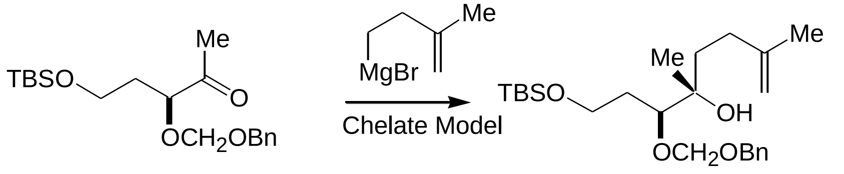
Addition of Carbon Nucleopiles



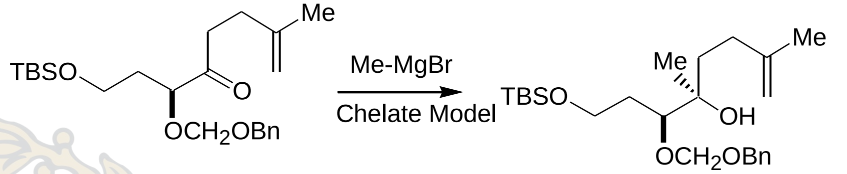


(OR)	Acid	Solv.	Ratio
R = CH_2OBn	$MgBr_2$	THF (0°)	20 : 80
R = CH_2OBn	$MgBr_2$	CH_2Cl_2 (-20°)	>99 : 1
R = CH_2OBn	$TiCl_4$	CH_2Cl_2 (-78°)	>99 : 1
R = $SiMe_2$(t)Bu	BF_3-Et_2O	CH_2Cl_2 (-78°)	5 : 95

G. Keck & Co-workers, *Tetrahedron Lett.* **1984**, *25*, 265

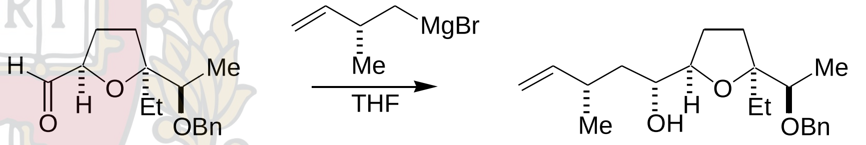


diastereoselection 50 : 1



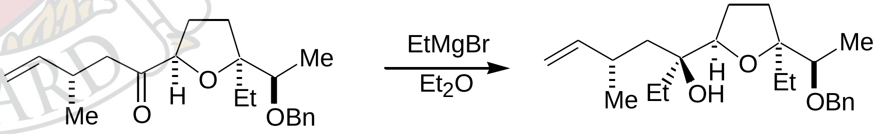
W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1031

diastereoselection >100 : 1



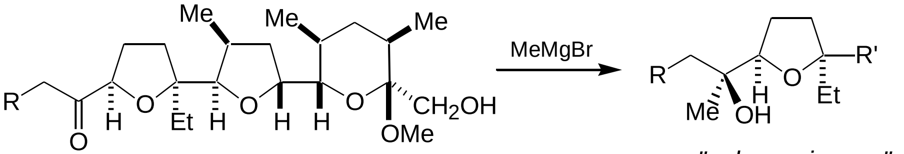
"only one isomer"
Chelate Model

Y. Kishi & Co-workers,
Tetrahedron Lett. **1978**, *19*, 2745



"only one isomer"
Chelate Model

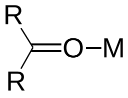
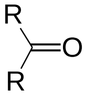
Y. Kishi & Co-workers,
Tetrahedron Lett. **1978**, *19*, 2745



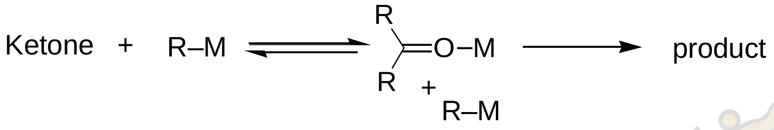
"only one isomer"
Chelate Model

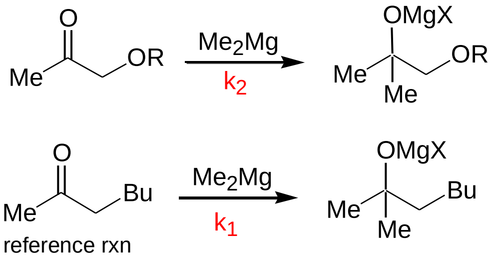
Y. Kishi & Co-workers,
J. Am. Chem. Soc. **1979**, *101*, 260.

Kinetic Evidence for Chelate-Controlled C=O Additon

Since  much more reactive than 

Substrates which can participate in C=O chelation will be more reactive since the effective concentration of chelated intermediate will be higher.



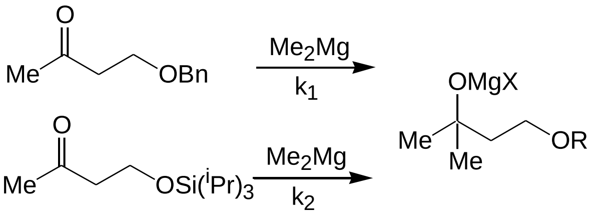


R	rel rate
–Me	213
–Bn	174
–CMe_3	9
–$SiMe_3$	7
–Si-i-Pr_3	1

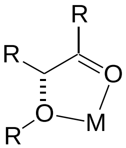
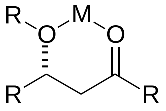
rxn run inTHF at - 78°C

Eliel, Frye, *JACS* **1992**, *114*, 1778-84 (read)

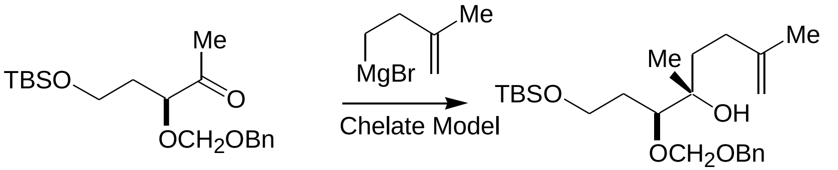
However, these trends are not transmitted strongly to β-chelation



$$\frac{k_1}{k_2} = 2.5$$

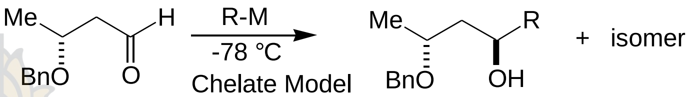
Hence, organization through  better than 

Alpha–Versus Beta-Chelation



W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1031

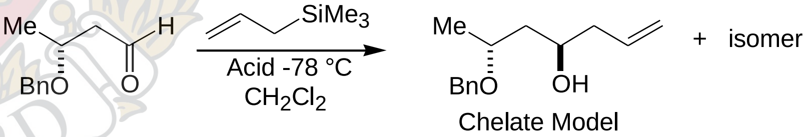
diastereoselection 50 : 1



M. T. Reetz & Co-workers
J. Am. Chem. Soc.. **1983**, 105, 4833.

Other nucleophiles reported

R-M	Solv.	Ratio
Me-MgCl	THF	40 : 60
Me-$TiCl_3$	CH_2Cl_2	90 : 10

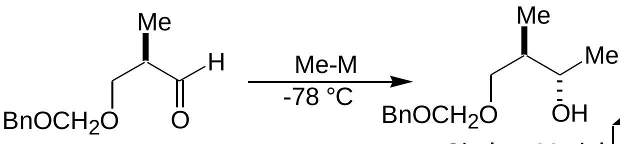


M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, *25*, 729.

Acid	Ratio
$TiCl_4$	95 : 5
$SnCl_4$	95 : 5
BF_3-OEt_2	85 : 15

- Note that beta chelation can be developed as a control element by varying solvent & Nu.
- Note BF_3 gives "apparent" chelate control

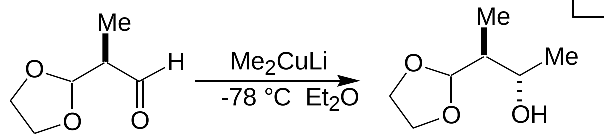
Beta Chelation with Organometals



+ isomer

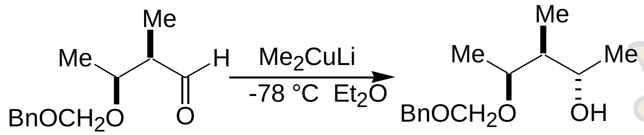
Chelate Model

R-M	Ratio
MeMgBr	50 : 50
Me_2CuLi	97 : 3



Chelate Model

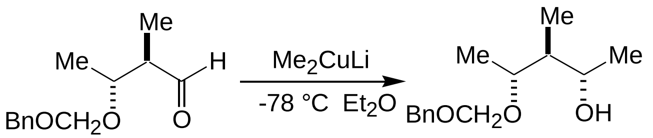
diastereoselection
> 95 : 5



Chelate Model

diastereoselection
> 95 : 5

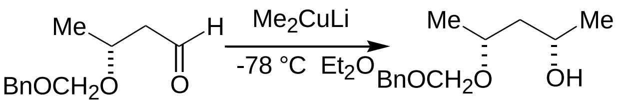
stereocenters reinforcing



Chelate Model

diastereoselection
70 : 30

stereocenters non-reinforcing

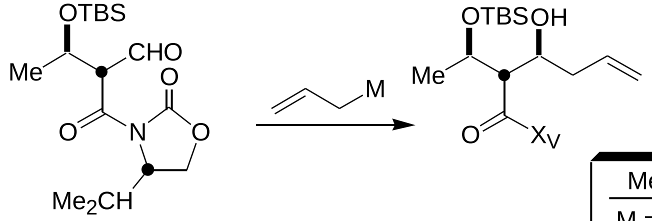


+ isomer

diastereoselection
50 : 50

W.C. Still & Co-workers,
Tetrahedron Lett. **1980**, *21*, 1035.

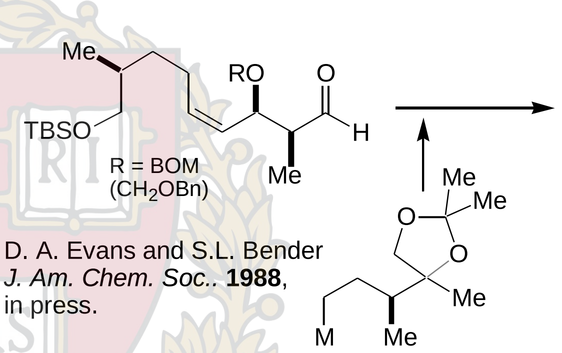
Carbonyl Additon: Chelate Control: Evans *JACS* **2001**, ASAP **(handout)**

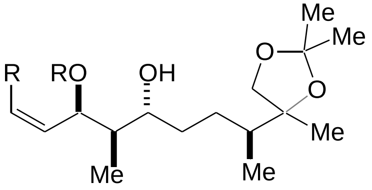


+ isomer

Metal	Ratio
M = MgCl	70 : 30
M = ZnCl	97 : 3

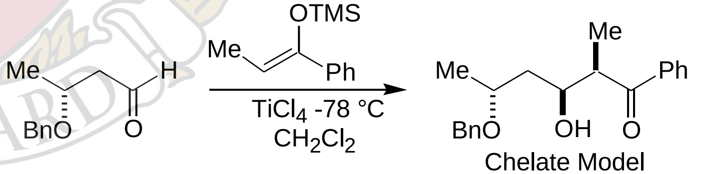
D. A. Evans & E. Sjogren
Tetrahedron Lett. **1986**, *27*, 4961.





D. A. Evans and S.L. Bender
J. Am. Chem. Soc.. **1988**,
in press.

Metal	Ratio
M = $[CuCN]_{1/2}$	98 : 2
M = Li	33 : 67

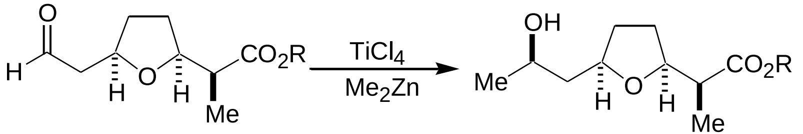


+ isomer

Chelate Model

M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, *25*, 729.

diastereoselection >92 %

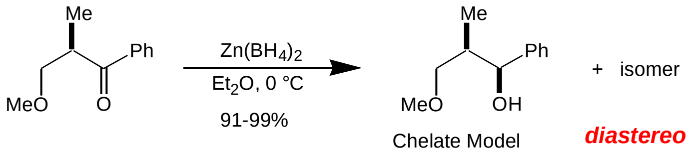


chelate model

S. W. Baldwin & Co-workers
J. Org. Chem. **1987**, *52*, 320.

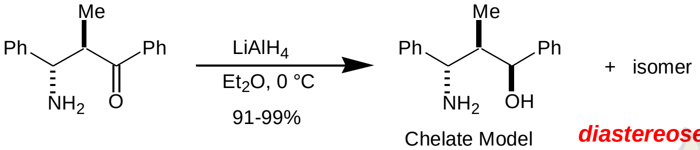
diastereoselection 96 : 4

Beta Chelate-Controlled Reduction



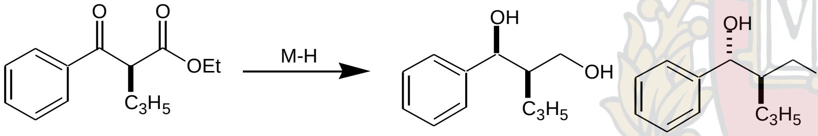
diastereoselection 97 : 3

T. Oishi & Co-workers
Chem. Pharm Bull. **1984**, *32*, 1411.



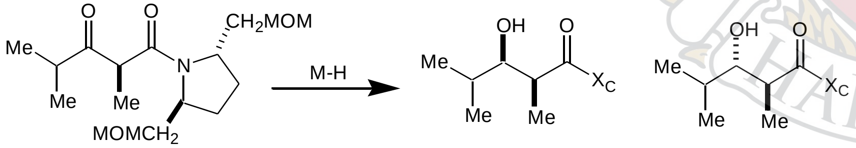
diastereoselection 88 : 12

J. Barluenga & Co-workers
J. Org. Chem. **1985**, *50*, 4052.



G. R. Brown & Co-workers
Chem. Commun. **1985**, 455.

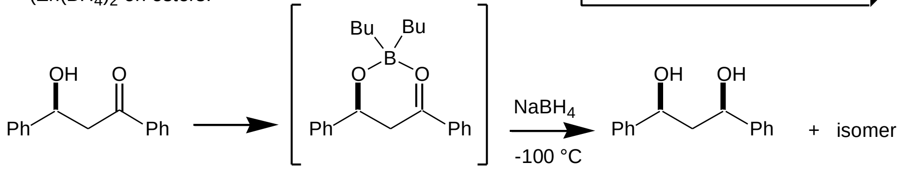
M-H	Ratio
$Zn(BH_4)_2$ Et_2O	100 : 0
$LiAlH_4$ THF	0 : 100



M. Yamaguchi & Co-workers
Tetrahedron Lett. **1985**, *26*, 4643.

T. Oishi & Co-workers
Tetrahedron Lett. **1980**, *21*, 1641
($Zn(BH_4)_2$ on esters.

M-H	Ratio
$Zn(BH_4)_2$ Et_2O	100 : 0
KBH_3H THF	0 : 100

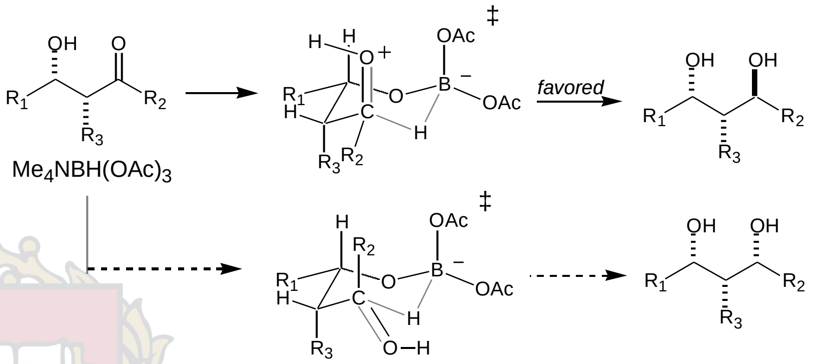


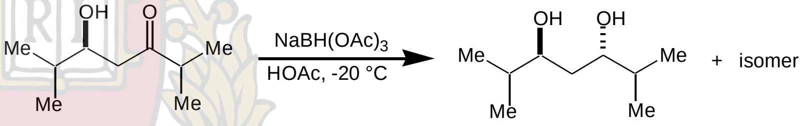
K. Narasaka & Co-workers
Chem. Lett. **1980**, 1415.

diastereoselection 96 : 4

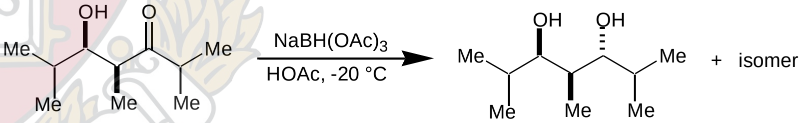
Directed reductions of β-hydroxyketones

Evans, Chapman, Carreira, JACS **110**, 3560 (1988)

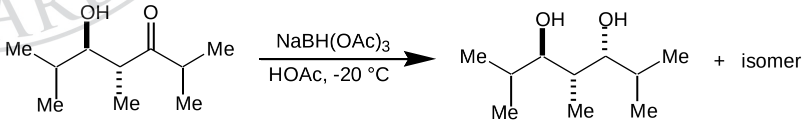




diastereoselection 96 : 4

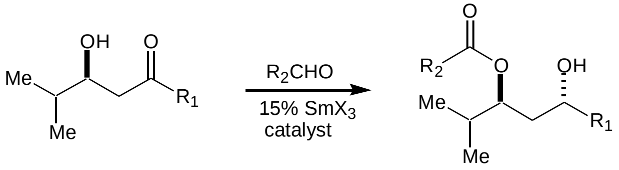


diastereoselection 98 : 2



diastereoselection 98 : 2

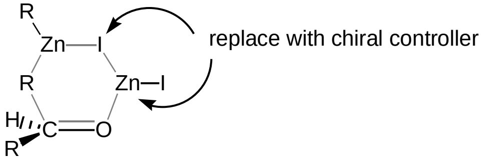
Propose a mechanism for tihs highly diastereoselective transformation, Evans, Hoveyda JACS **112**, 6447 (1990)

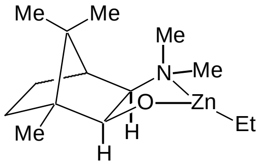


diastereoselection
> 100:1

Enantioselective C=O Addition: Noyori Catalyst

Catalytic Asymmetric Carbonyl Addition

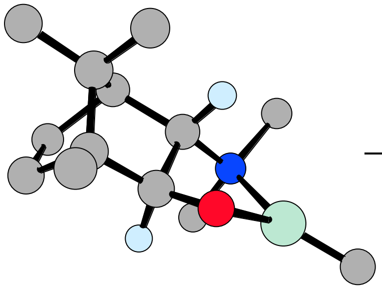




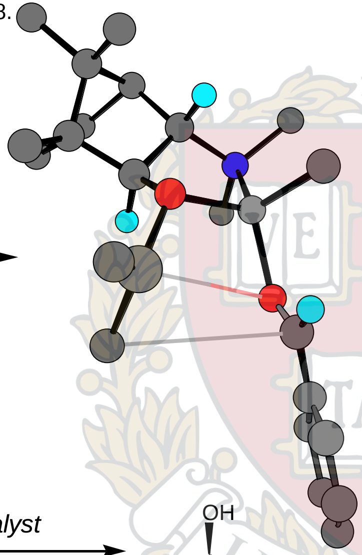
the catalyst

Noyori & co-workers, *J. Am. Chem. Soc.* **1986**, 108, 6072.
J. Am. Chem. Soc. **1989**, 111, 4028.

Review: Noyori *Angew. Chem. Int. Ed.* **1991**, *30*, 49
Review: L. Pu, *Chem. Reviews* **2001**, *101*, 757-824

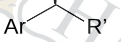


$\xrightarrow[\text{PhCHO}]{Me_2Zn}$



(DAIB-Zn)

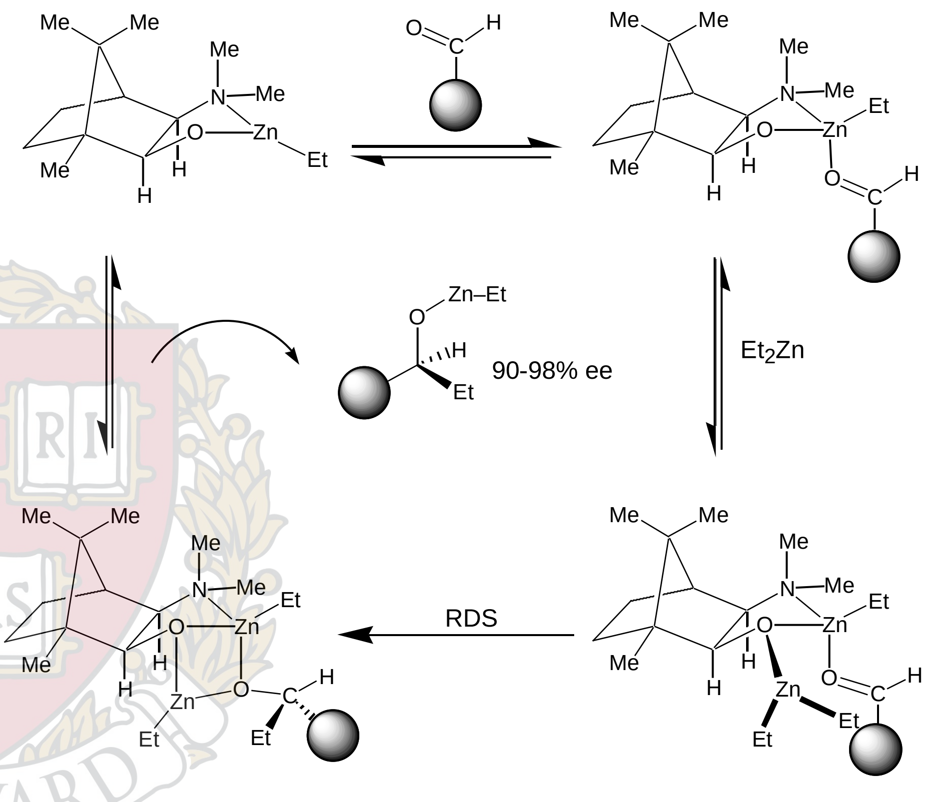
Ar–CHO + R_2'Zn $\xrightarrow[\text{0°C, toluene; 59 - 97\%}]{\text{the catalyst}}$



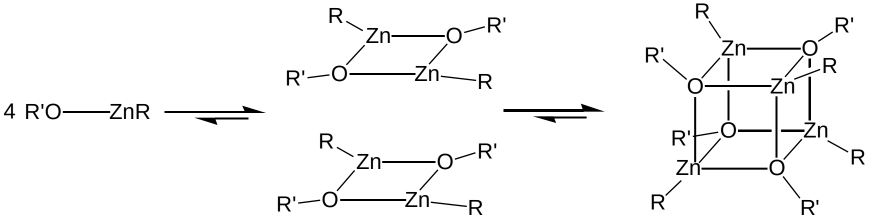
C_6H_5CHO	Et_2Zn	98% e.e.
"	Me_2Zn	91% e.e.
p-ClC_6H_4CHO	Et_2Zn	93% e.e.
p-$MeOC_6H_4CHO$	Et_2Zn	93% e.e.
Cinnamyl	Et_2Zn	96% e.e.
$PhCH_2CH_2CHO$	Et_2Zn	90% e.e.
n-$C_6H_{13}CHO$	Et_2Zn	61% e.e.

- *The method is catalytic in aminoalcohol.*
- *Two zinc species per aldehyde are involved in the alkylation step.*

The Catalytic Cycle



- *Catalyst must be sterically hindered so that association is precluded*



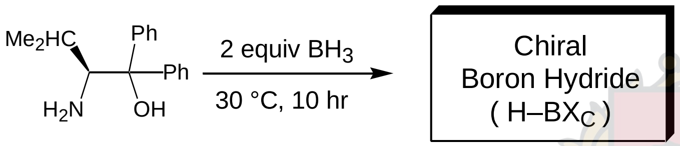
- *Product is taken out of the picture by aggregation*

Enantioselective C=O Addition: Corey-Itsuno Catalyst

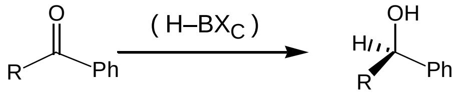
Discovery of a Catalytic Process

Recent Review: Corey, E. J. and C. J. Helal (**1998**). "Reduction of carbonyl compounds with chiral oxazaborolidine catalysts: A new paradigm for enantioselective catalysis and a powerful new synthetic method." Angew. Chem., Int. Ed. Engl. **37**(15): 1987-2012.

- The Stoichiometric Process: Itsuno, 1983-1985



Chiral
Boron Hydride
(H–BX$_C$)



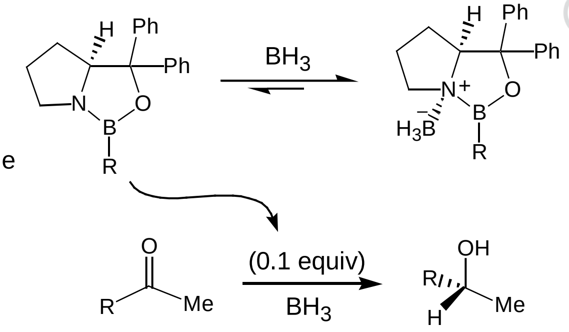
R = Me, 94 % ee
R = Et, 94 % ee
R = n-Bu 100 % ee

Itsuno, *Chem. Commun*. **1983**, 469

Itsuno, *J. Org. Chem.* **1984**, 49, 555

Itsuno, *J. Chem. Soc. Perkin Trans I*. **1985**, 2615

- The Catalytic Process: Corey, 1987

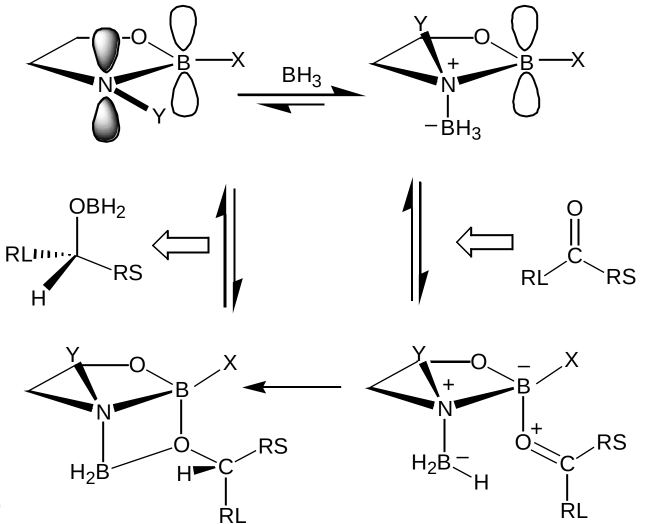


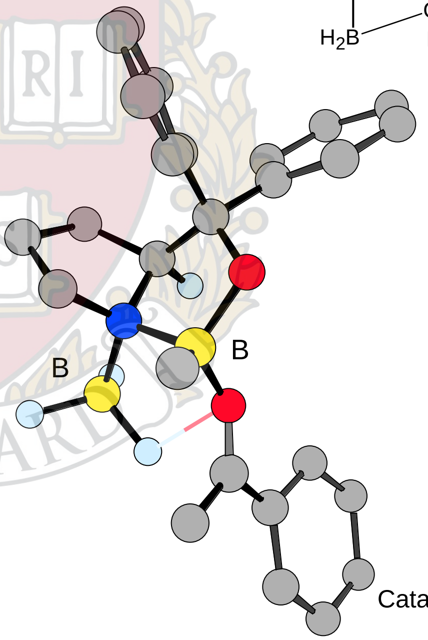
R = H
R = Me

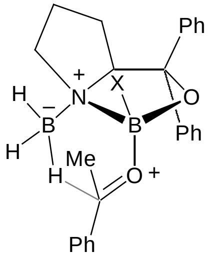
R = Ph, 97 % ee
R = t-Bu, 97 % ee
R = c-C$_6$H$_{11}$ 91 % ee

But how does it really work ?

The
Catalytic Cycle







Corey, *JACS* **1987**, *109*, 5551

Corey, *JACS* **1987**, *109*, 7925

Corey, *JOC* **1988**, *53*, 2861

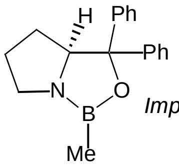
Catalyst X-ray, Corey, *Tet. Let* **1992**, *33*, 3429

Mathre, *JOC* **1993**, *58*, 2880

catalyst prep: Mathre, *JOC* **1993**, *58*, 799

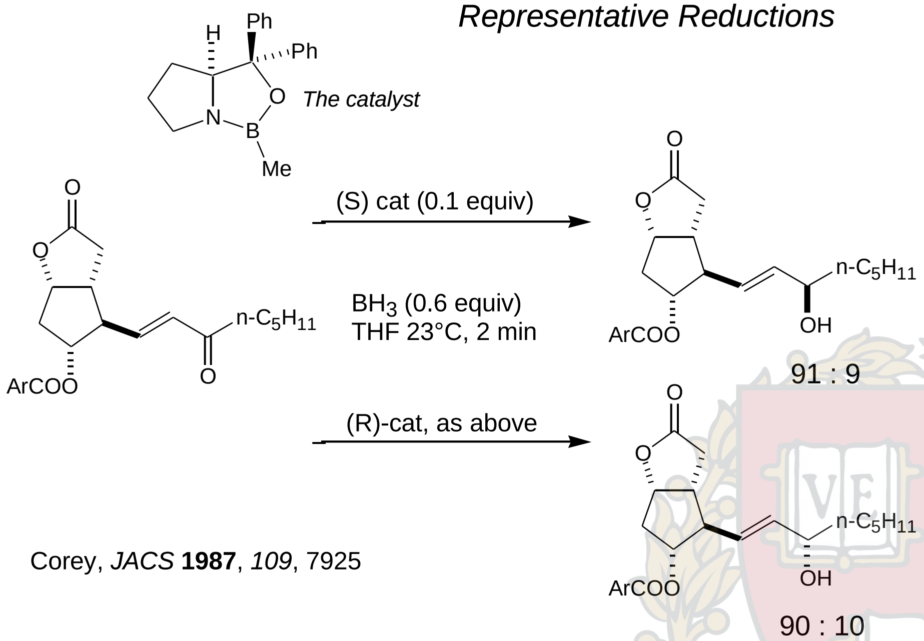
Mathre, *JOC* **1991**, *56*, 751

(Review) Martens, *Tertrahedron Asymmetry* **1992**, *3*, 1475

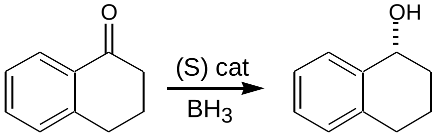


Improved version

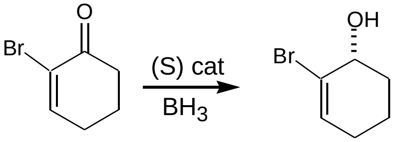
Representative Reductions



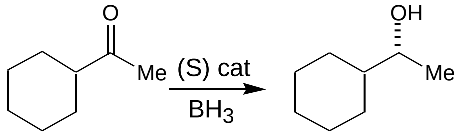
Corey, *JACS* **1987**, *109*, 7925



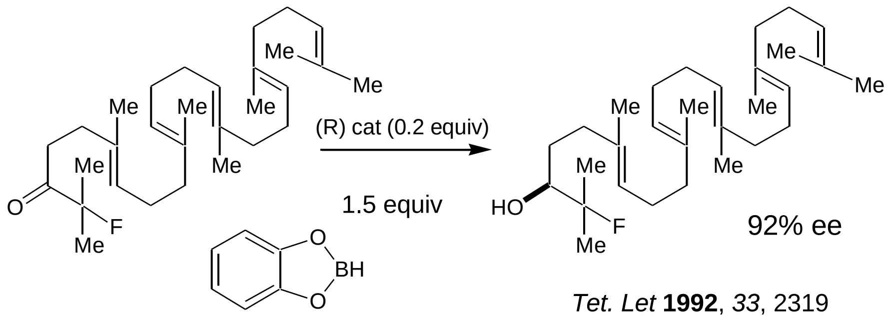
86% ee



91% ee



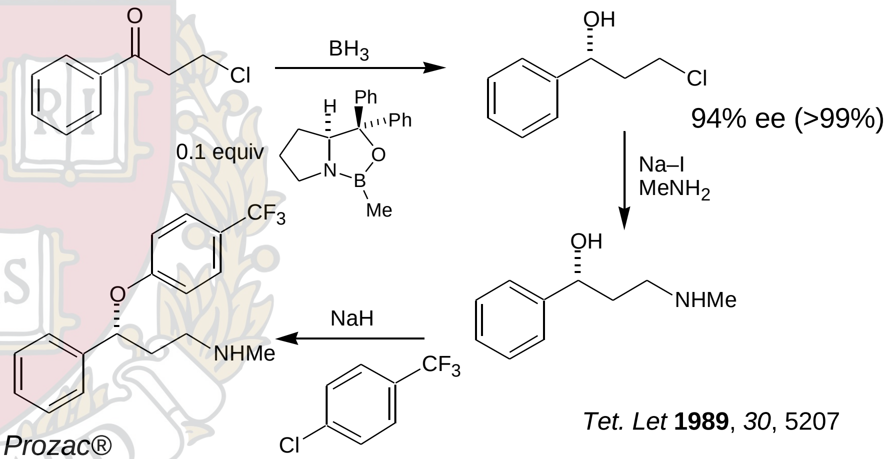
91% ee



92% ee

Tet. Let **1992**, *33*, 2319

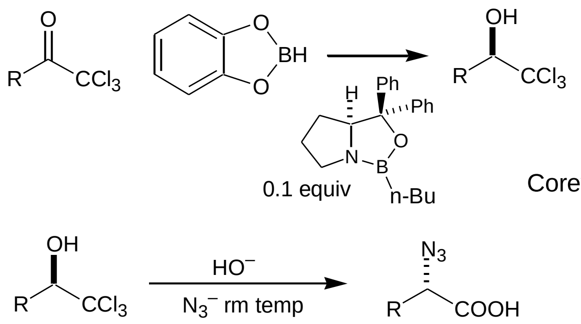
Fluoxetine (Prozac®) Synthesis



94% ee (>99%)

Tet. Let **1989**, *30*, 5207

An α-Amino Acid Synthesis



R	ee
$n\text{-}C_5H_{11}$	95%
$c\text{-}C_6H_{11}$	92%
$t\text{-}C_4H_9$	98%

Corey, *JACS* **1992**, *114*, 1906
Tet. Let **1992**, *33*, 3435
Tet. Let **1992**, *33*, 3431

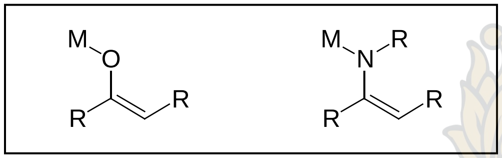
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 22

Enolates & Metalloenamines-1



- Tautomerism in C=O and C=NR Systems
- C=O Enolization with Metal Amide Bases
- C=O Enolization: Kinetic Acidities
- Mild Methods for Enolate Generation
- Enolate Structure: A Survey of X-ray Structures
- Metallo-Enamine X-ray Structures

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Matthew D. Shair

Friday,
November 8, 2002

Assigned Journal Articles

"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures".
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983). **(handout)**

"Stereoselective Alkylation Reactions of Chiral Metal Enolates".
D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984). **(handout)**

Other Useful References

"Recent Advances in Dianion Chemistry". C. M. Thompson and D. L. C. Green *Tetrahedron*, **47**, 4223 (1991).

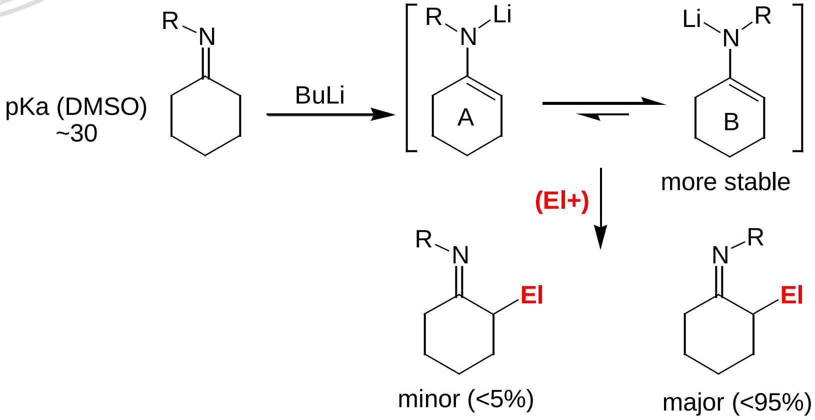
The Reactions of Dianions of Carboxylic Acids and Ester Enolates". N. Petragnani and M. Yonashiro *Synthesis*, 521 (1982).

"Generation of Simple Enols in Solution". Capon, Guo, Kwok, Siddhanta, and Zucco *Acc. Chem. Res*. **21**, 121 (1988).

"Keto-Enol Equilibrium Constants of Simple Monofunctional Aldehydes and Ketones in Aqueous Solution". Keeffe, Kresge, and Schepp *JACS*, 112, 4862 (1990).

"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Chiang, Kresge, and Tang *JACS* **106**, 460 (1984).

Rationalize why metalloenamine B is more stable than A.



Important References

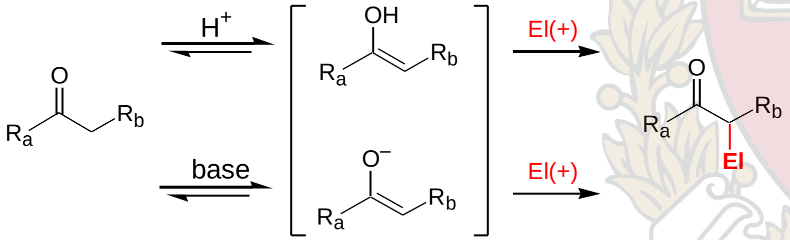
"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures".
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983).

"Stereoselective Alkylation Reactions of Chiral Metal Enolates". D. A. Evans
Asymmetric Synthesis, **3**, 1 (1984).

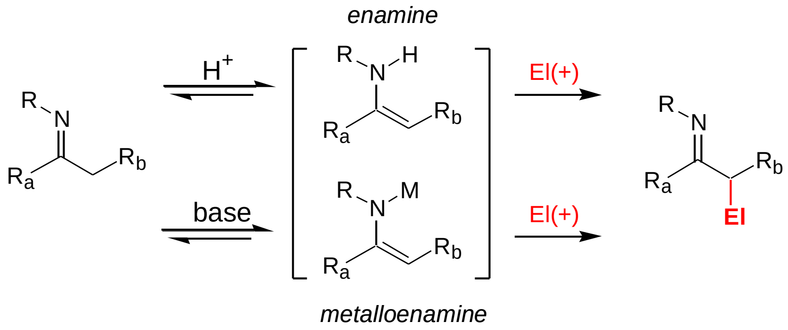
"Generation of Simple Enols in Solution". B. Capon, B.-Z. Guo, F. C. Kwok, A. K. Siddhanta, and C. Zucco *Acc. Chem. Res.* **21**, 121 (1988).

"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Y. Chiang, A. J. Kresge, and Y. S. Tang *J. Am. Chem. Soc.* **106**, 460 (1984).

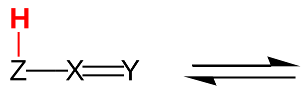
Enols & Enolates are the most important nucleophiles in organic & biological chemistry.



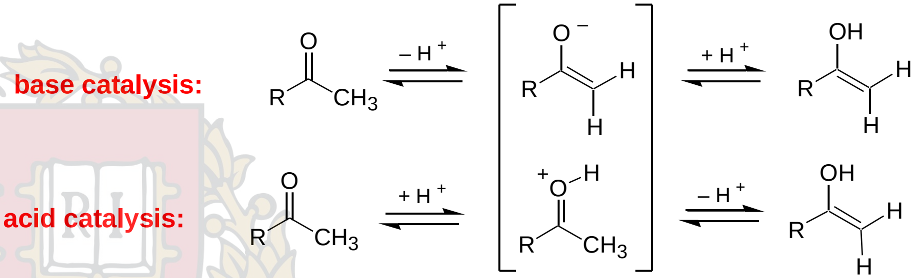
Enamines & metalloenamines, their nitrogen counterparts, are equally important.



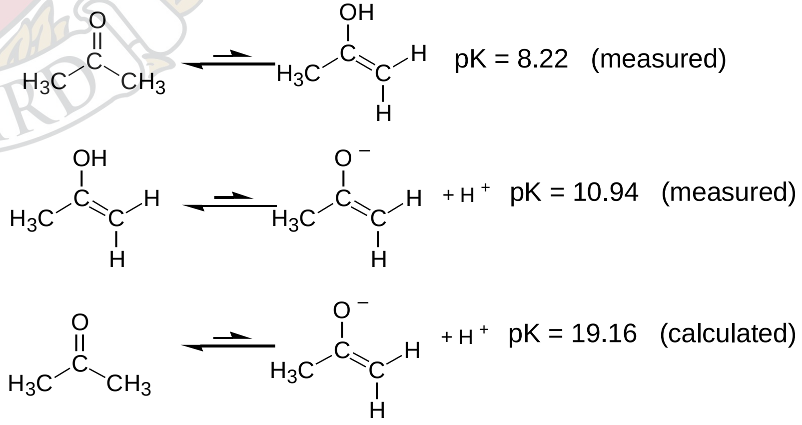
Tautomers: Structural isomers generated as a consequence of the 1,3-shift of a proton adjacent to a X=Y bond. for example:



Keto-Enol Tautomers: Tautomerism may be catalyzed by either acids or bases:



Acidity of Keto and Enol Tautomers: Consider Acetone:

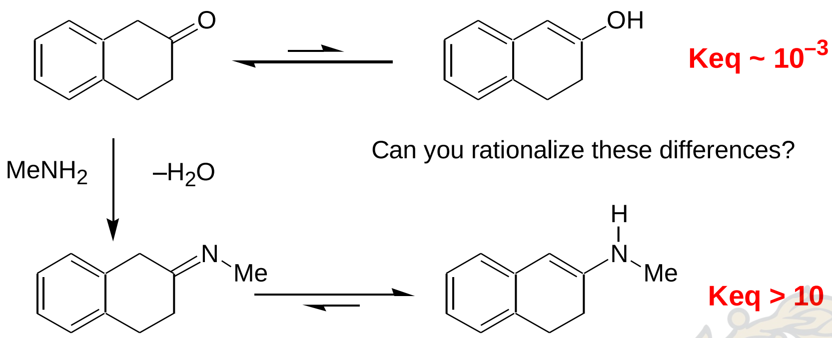


Kresge, *JACS* **1984**, *106*, 460

On the origin of the acidity of enols: Wiberg, *JACS* **1996**, *118*, 8291-8299

Enolization with Metal Amides bases

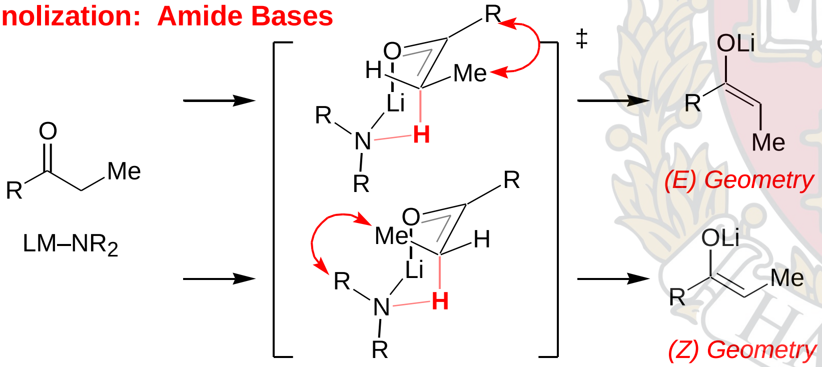
Tautomeric Equilibria: Ketones vs. Imines



Can you rationalize these differences?

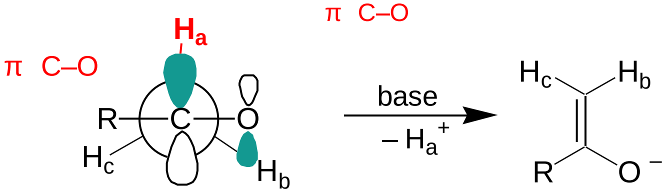
The enamine content in an analogous imine is invariably higher than its carbonyl counterpart. In the case above, ring conjugation now stabilizes the enamine tautomer as the major tautomer in solution.

Enolization: Amide Bases

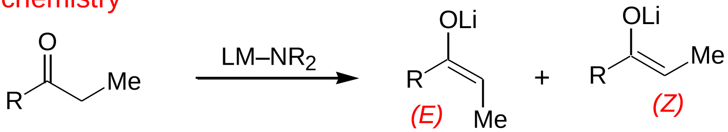


The Ireland Model (*J. Am. Chem. Soc*. **1976**, *98*, 2868)
Narula, Tetrahedron Lett. **1981**, *22*, 4119
more recent study: Ireland, *JOC* **1991**, *56*, 650
For the latest word on this subject see: Xie, *JOC* 1997, *62*, 7516-9

Stereoelectronic Requirements: The α-C-H bond must be able to overlap with π C–O



Stereochemistry



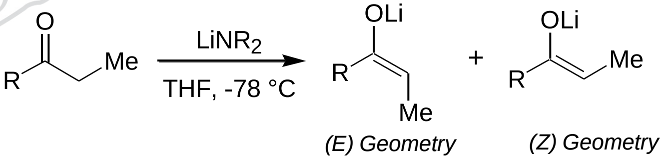
Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe, O-t-Bu	95 : 5
LDA (THF)	-S-t-Bu	95 : 5
LDA (THF)	-Et	77 : 23
LDA (THF)	$-CHMe_2$	40 : 60
LDA (THF)	$-CMe_3$	0 : 100
LDA (THF)	$-C_6H_5$	0 : 100
LDA (THF)	$-NEt_2$	0 : 100
s-BuLi (THF)	$-NEt_2$	25 : 75

Solvent

Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe	95 : 5
LDA (THF, HMPA)	-OMe	16 : 84

Base Structure

Masamune (*J. Am. Chem. Soc.* **1982**, *104*, 5526)

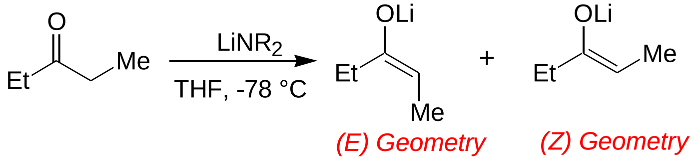


Base	R = Et, (E):(Z)	R = Cy, (E):(Z)
$Li–N(i\text{-}Pr)_2$	70 : 30	39 : 61
$Li–N(SiMe_3)_2$	30 : 70	15 : 85
$Li–N(SiEt_3)_2$	1 : 99	4 : 96
$Li–N(SiMe_2Ph)_2$	0 : 100	0 : 100
at equilibrium	16 : 84	—

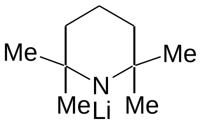
Enolization with Metal Amides bases

Base Structure

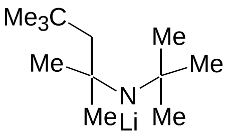
Corey & Co-workers, *Tetrahedron Lett.* **1984**, *25*, 491, 495



Li–N(i-Pr)$_2$
(LDA) 77 : 23



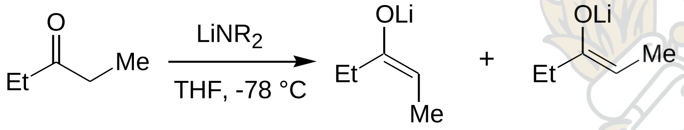
(LiTMP) 86 : 14



(LOBA) 98 : 2

Lithium Halide Effects

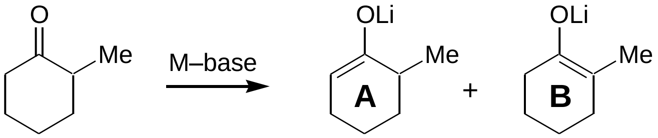
Collum (*J. Am. Chem. Soc*. **1991**, *113*, 9572)
Collum (*J. Am. Chem. Soc*. **1991**, *113*, 9575)
Collum (*J. Am. Chem. Soc*. **1991**, *113*, 5053)



	Ratio, (E):(Z)
LiTMP	86 : 14
LiTMP, 10% LiBr	98 : 2

For the latest in the series of Column papers see: *JACS* **2000**, *122*, 2452-2458

Regioselective Enolization

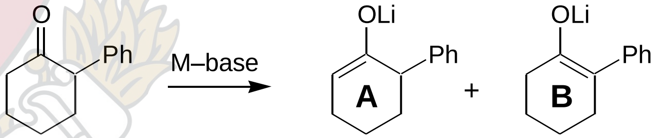


Base	temp	control	Ratio (A:B)
LiN(i-Pr)$_2$	–78 °	kinetic	99:1
LiN(SiMe$_3$)$_2$	–78 °	kinetic	95:5
Ph$_3$C–Li	–78 °	kinetic	90:10
Ph$_3$C–Li	heat	thermo	10:90
Na–H	heat	thermo	26:74
K–H	heat	thermo	38:62

A: Alkyl groups stabilize metal enolate

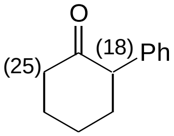
A: As M–O bond becomes more ionic A is attenuated

Kinetic Selection sensitive to structure



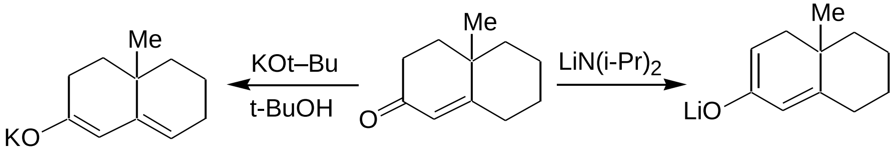
ratio: 99:1

estimated
pKa's
(Bordwell)



A $\rightleftharpoons$ **B**
pKeq est: 7 (10^{+7})

Unsaturated Ketones



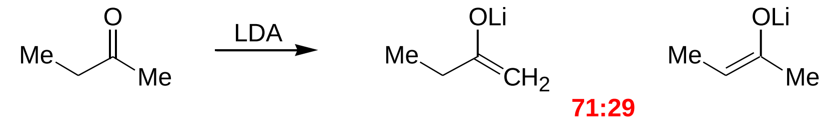
thermodynamic
enolate

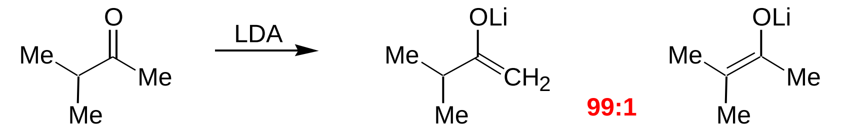
kinetic enolate

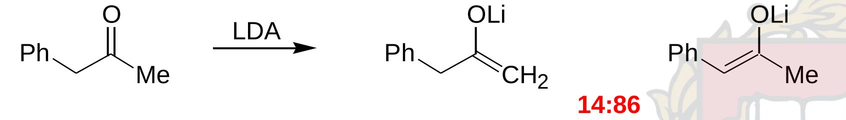
see kinetic acidity handout for an
extensive compilation of cases.

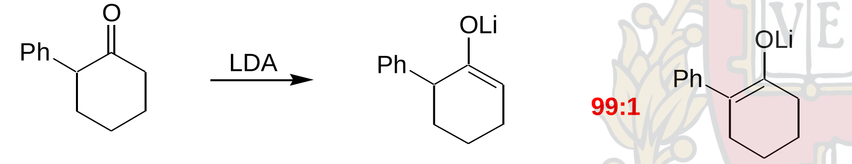
Enolization with Metal Amides bases

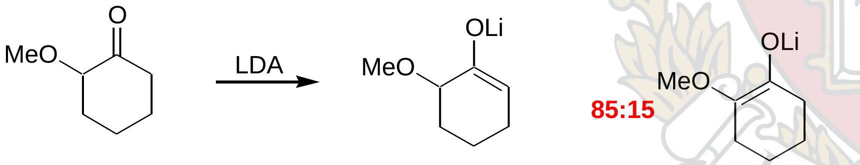
Kinetic Selection sensitive to structure

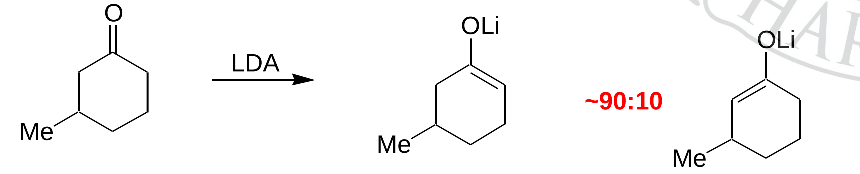

71:29

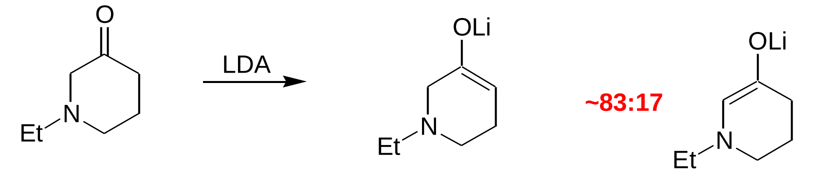

99:1


14:86

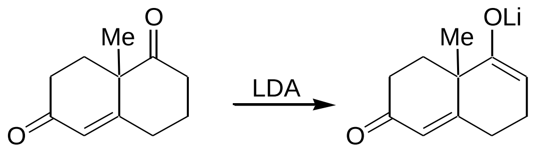

99:1

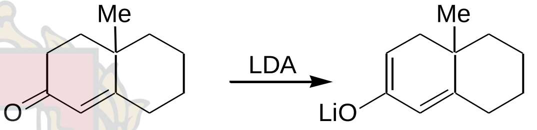

85:15

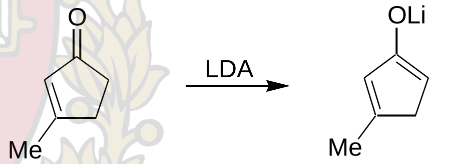

~90:10

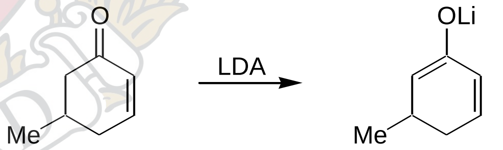

~83:17

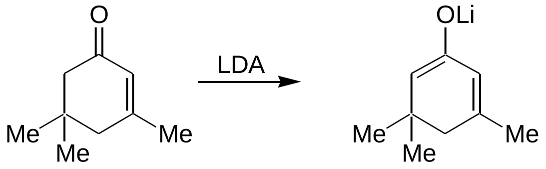
Kinetic Selection in Enolization of Unsaturated Ketones


only enolate


only enolate


only enolate


only enolate


only enolate

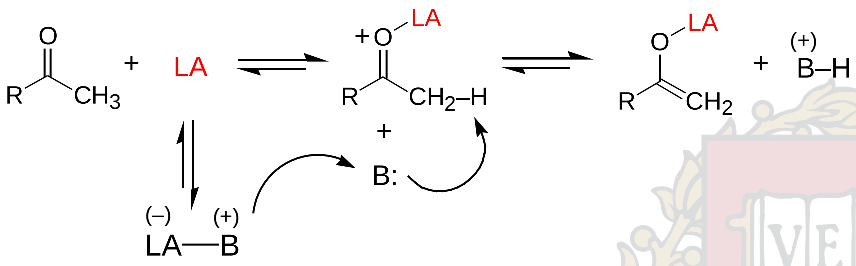
Design of Soft Enolization Systems

Strategy

Choose Lewis Acid (LA) which can reversibly associate with amine base (B:).

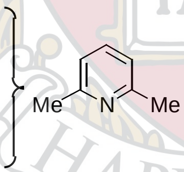
$$\text{LA} + \text{B:} \rightleftharpoons \overset{(-)}{\text{LA}}\text{—}\overset{(+)}{\text{B}}$$

This system has the potential to enolize carbonyl functional groups:

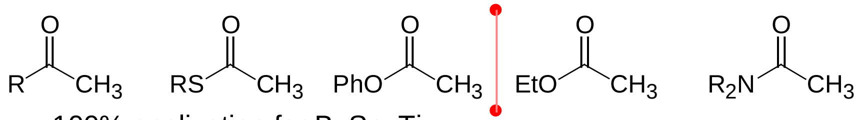


-OTf = - OSO_2CF_3

Useful Lewis Acid Pairs	Complexation
$MgBr_2$ + NEt_3	Reversible
Li–X + NR_3	Reversible
$Sn(OTf)_2$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$R_2B\text{-}OTf$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
R_2BCl + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$PhBCl_2$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$TiCl_4$ + NR_3	Irreversible (Et_3N, $EtNi\text{-}Pr_2$)
$i\text{-}PrOTiCl_3$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$(i\text{-}PrO)_2TiCl_2$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)
$(i\text{-}PrO)_3TiCl$ + NR_3	Reversible (Et_3N, $EtNi\text{-}Pr_2$)



All of the above systems will enolize simple ketones to some extent.

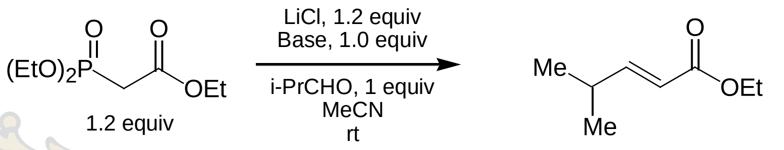


100% enolization for B, Sn, Ti
partial enolization for Li, Mg

Lithium Enolates

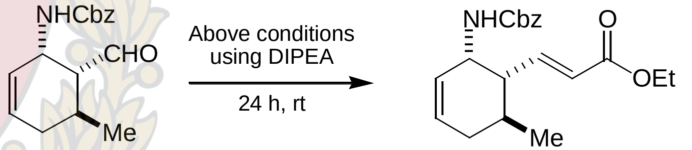
Roush & Masamune, Tet. Lett. 1984, 25, 2183-2186

Horner-Wadsworth-Emmons Reaction.



pKa 19.2 (DMSO), K^+ counterion
pKa 12.2 (Diglyme), Li^+ counterion

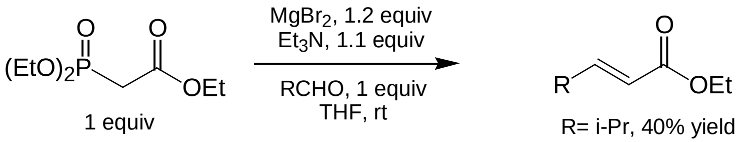
Base = DBU, 5 min, 99%, >50:1 E:Z
Base = DIPEA, 7 h, 97%, >50:1 E:Z



85% + 10% recovered aldehyde

Conventional methods of deprotonation (NaH) resulted in epimerization (Overman *JACS* **1978**, 5179).

Rathke, Nowak *J. Org. Chem.* **1985**, *50*, 2624-2626.

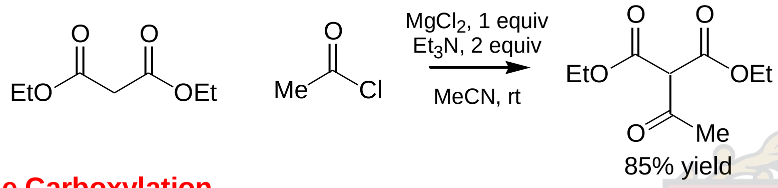


R= i-Pr, 40% yield
R= n-C_6H_{13}, 100% yield

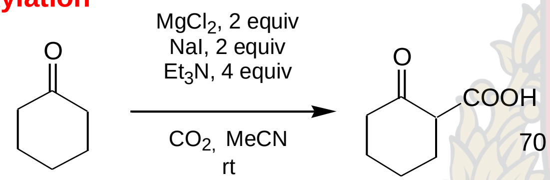
Magnesium Enolates

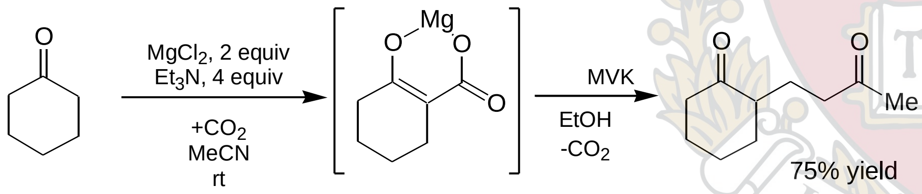
Rathke *J. Org. Chem.* **1985**, *50*, 2622-2624.
J. Org. Chem. **1985**, *50*, 4877-4879.
Syn. Comm. **1986**, *16*, 1133-1139.

Diethylmalonate acylations

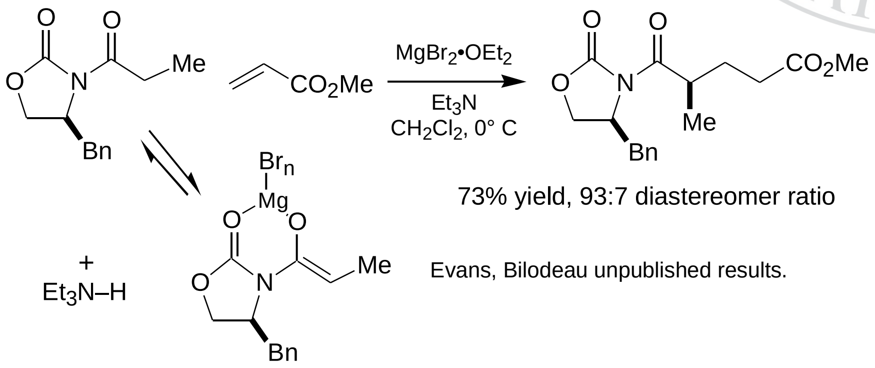


Ketone Carboxylation





Michael reaction



73% yield, 93:7 diastereomer ratio

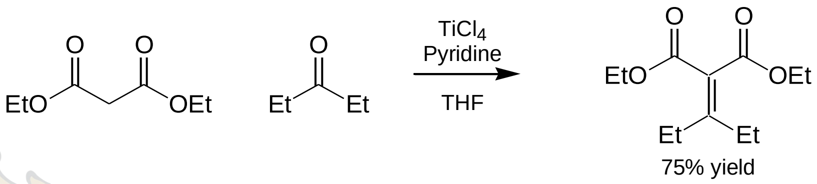
Evans, Bilodeau unpublished results.

Deuterium quench indicates 25% enolization of *N*-propionyloxazolidinone

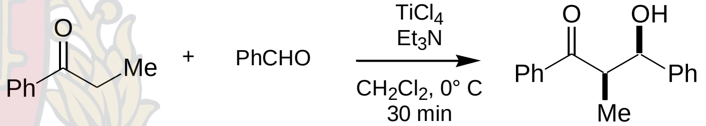
Titanium Enolates

The Early Literature

Lehnert, W. *Tetrahedron Lett.* 1970, 4723-4724.

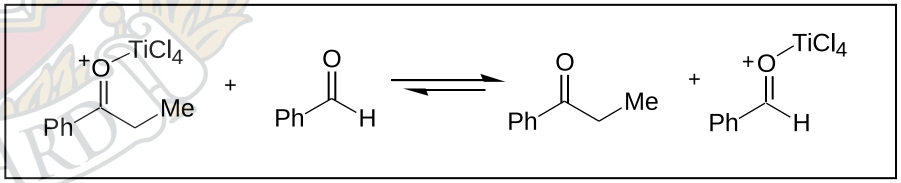


Harrison, C. R. *Tetrahedron Lett.* 1987, *28*, 4135-4138.

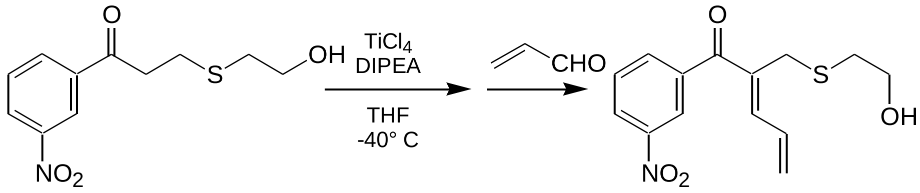


91% yield
95:5 syn/anti

Ketone and aldehyde combined followed by sequential addn of TiCl$_4$ and then amine

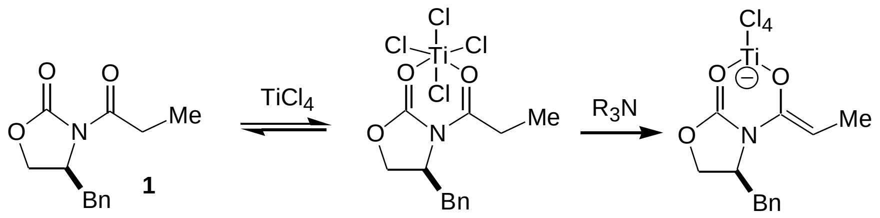


Brocchini, Eberle, Lawton *J. Am. Chem. Soc.* 1988, *110*, 5211-5212.



10-15:1 Z/E

Titanium Enolates



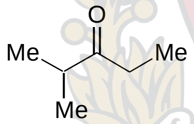
- Enolization process not responsive to tertiary amine structure
- DIPEA, Et_3N, N-Ethylpiperidine all suitable bases.
- DBU and tetramethylguanidine do not provide enolate.
- CH_2Cl_2 is the only suitable solvent for these enolizations.

N-Propionyloxazolidone (**1**)

Lewis Acid	% Enolization
$TiCl_4$	100
i-$PrOTiCl_3$	100
$TiCl_4$•2THF	80
(*i*-PrO)$_2$$TiCl_2$	70
(*i*-PrO)$_3$TiCl	~10

Ethylisopropylketone

Lewis Acid	% Enolization
$TiCl_4$	100
i-$PrOTiCl_3$	80
(*i*-PrO)$_2$$TiCl_2$	50



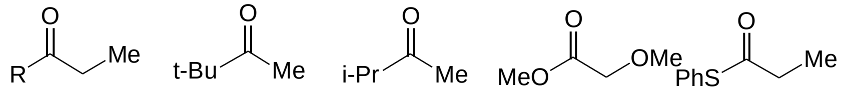
- Order of addition of reagents is important for $TiCl_4$.

R_3N + $TiCl_4$ $\longrightarrow$ $R_3\overset{+}{N}-\overset{-}{Ti}Cl_4$ Irreversible Complexation

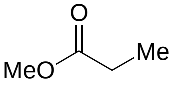
- Order of addition of reagents is not important for *i*-$PrOTiCl_3$ or (*i*-PrO)$_2$$TiCl_2$.

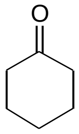
R_3N + *i*-$PrOTiCl_3$ $\rightleftharpoons$ $R_3\overset{+}{N}-\overset{-}{Ti}Cl_3(OiPr)$ Reversible Complexation

- Enolizable substrates:

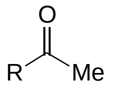


- Substrates Which present problems:





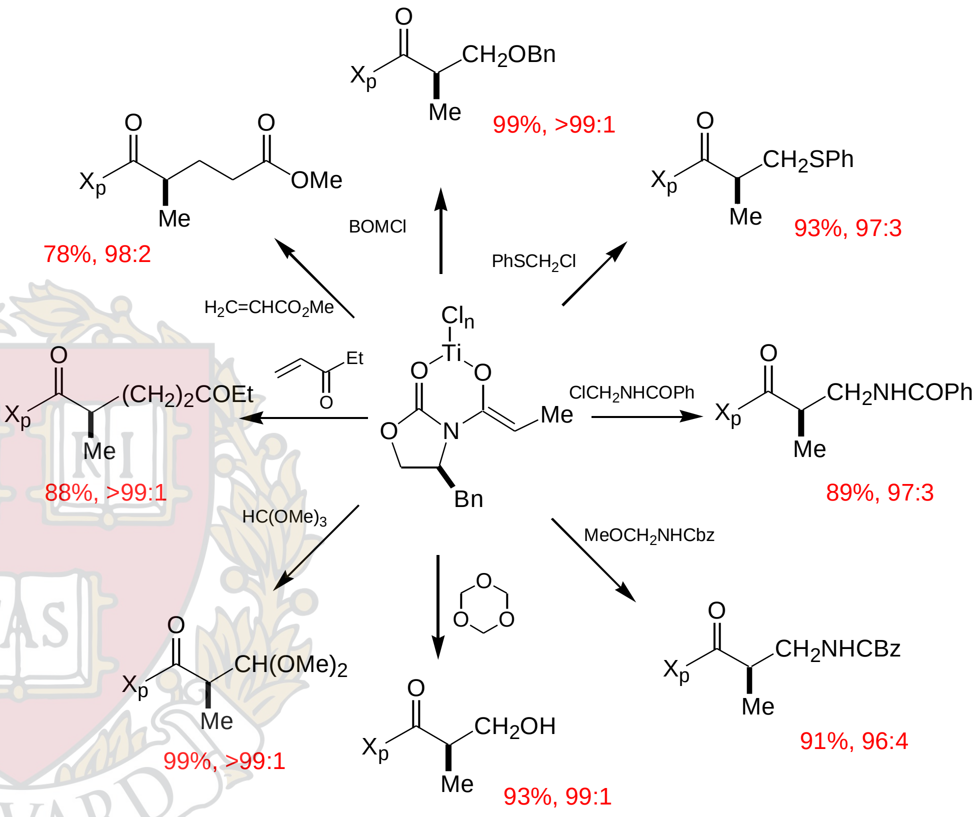
self condensation



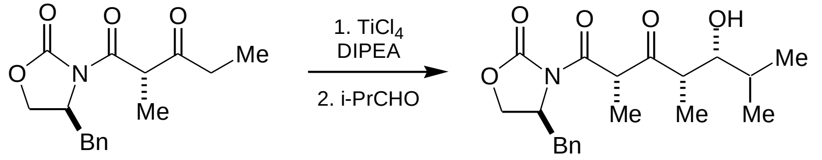
R=Ar, R<i-Pr

self condensation

Reactions with Representative Electrophiles



J. Am. Chem. Soc. **1990**, *112*, 8215-8216.; *J. Org. Chem.* **1991**, *56*, 5750-5752.



86% yield, >99:1

Evans, Clark, Metternich, Novack, Sheppard *J. Am. Chem. Soc.* **1990**, *112*, 866.

A Survey of 'Soft' Enolization Techniques: Boron Enolates-1

Dialkylboron Triflates

Di-n-butylboron triflate

Mukaiyama, Inoue *Chem. Lett.* **1976**, 559-562.
Bull. Chem. Soc. Jpn. **1980**, *53*, 174-178.

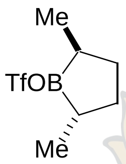
Enolizes ketones with 2,6-lutidine or DIPEA in ethereal solvents.

Diastereoselective Aldol Reactions of Boron Enolates.

Evans, Vogel, Nelson *J. Am. Chem. Soc.* **1979**, *101*, 6120.
Evans, Nelson, Vogel, Taber *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111.
Evans, Bartroli, Shih *J. Am. Chem. Soc.* **1981**, *103*, 2127.
Masamune, S. et. al. *Tetrahedron Lett.* **1979**, 2225, 2229, 3937.
Masamune, S. et. al. *J. Am Chem. Soc.* **1981**, *103*, 1566-1568.

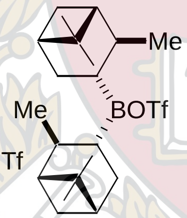
Chiral dialkylboron triflates

Masamune, Sato, Kim, Wollmann
J. Am. Chem. Soc. **1986**, *108*, 8279-8281.



Paterson, I. et. al.

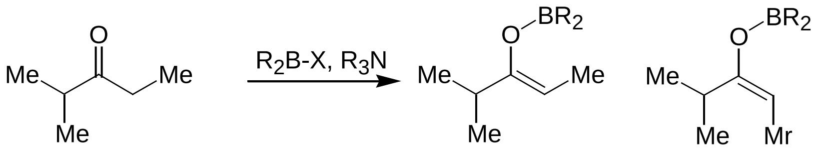
Tetrahedron **1990**, *46*, 4663-4684.
Tetrahedron Lett. **1989**, *30*, 997-1000.
Tetrahedron Lett. **1986**, *27*, 4787-4790.



(-)-(Ipc)$_2$BOTf

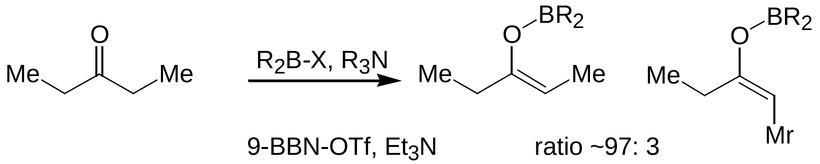
Enolate Stereochemistry

Evans, Nelson, Vogel, Taber *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111.
Goodman, *Tetrahedron Lett.* **1992**, *33*, 7219.
Enolization Model: Paterson, *Tetrahedron Lett.* **1992**, *33*, 7223.



9-BBN-OTf, Et$_3$N	ratio ~ 88: 12
Cy$_2$B-Cl, Et$_3$N	ratio ~ 3: 97

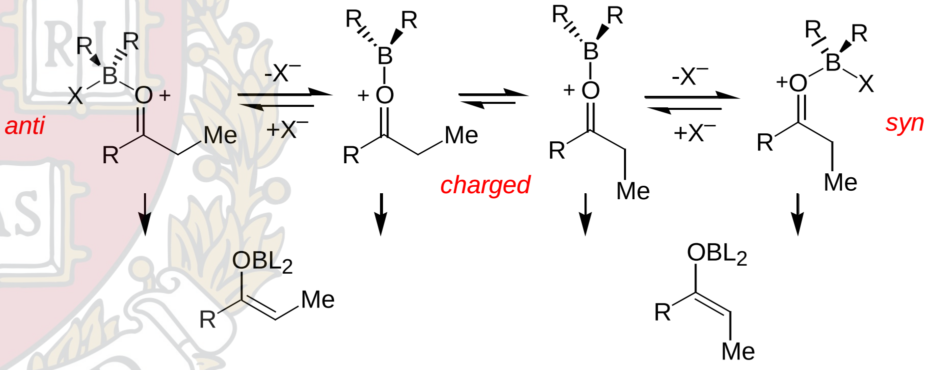
Brown, *J. Org. Chem.* **1993**, *58*, 147-153

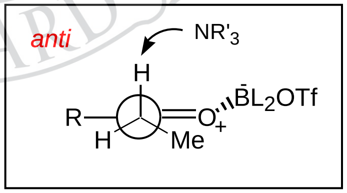


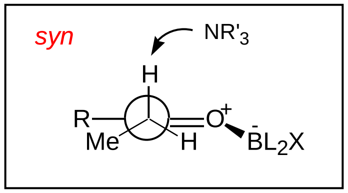
9-BBN-OTf, Et$_3$N	ratio ~97: 3
Cy$_2$B-Cl, Et$_3$N	ratio 21:79
Bu$_2$B-OTf, Et$_3$N	ratio ~97: 3

Borane and lutidine or DIPEA form 1:1 complex with L$_2$B-OTf. Complexation reversible as enolization will occur upon addition of ketone. Less hindered nitrogen bases - pyridine, Dabco, DBU, irreversibly complex with L$_2$B-OTf.

The Ketone-Boron Complexes as enolate precursors:





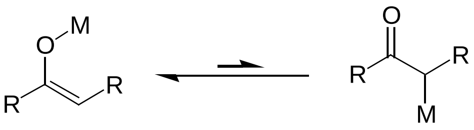


Cy$_2$BCl-ketone complex may deprotonate through syn complex

R$_2$BOTf-ketone complex may deprotonate through charged complex with (Z) preference

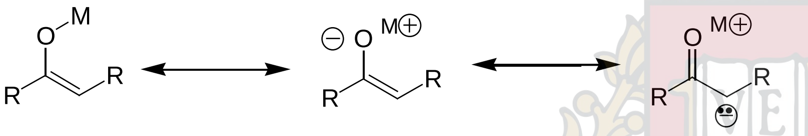
Enolate Structures from X-ray Diffraction

Metal Tautomerism



For alkali metal enolates (M = Li, Na, K etc.) the O-metal tautomer is strongly favored. This generalization holds for most alkaline earth enolates (Mg^{+2}) as well. These are the generally useful enolate nucleophiles

For certain metal enolates from heavy metals such as M = Hg^{+2} the C-metal tautomer is sometimes favored.



Resonance Structures

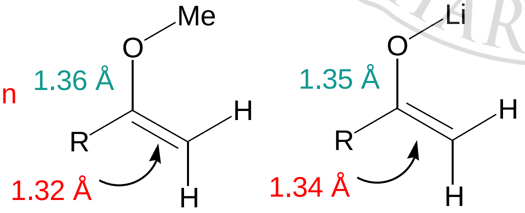
O^- resonance structure

C^- resonance structure

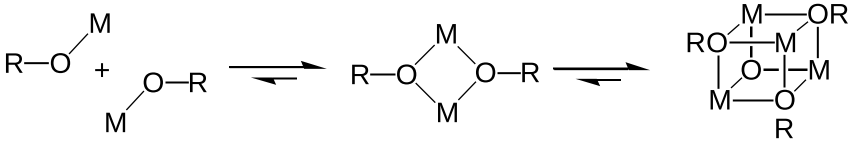
Since enolates usually function as carbon nucleophiles, it is therefore of some interest to assess the relative importance of the illustrated contributing polar resonance structures. Within the last decade good X-ray crystal structures of a number of metal enolates have been obtained.

One would predict that as the relative importance of the C^- structure increases, the C–O bond would shorten and the C–C bond would lengthen.

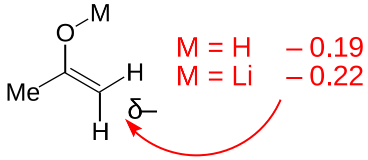
The prediction stated above does hold, but the net change in the C–C bond length is < 2 % !

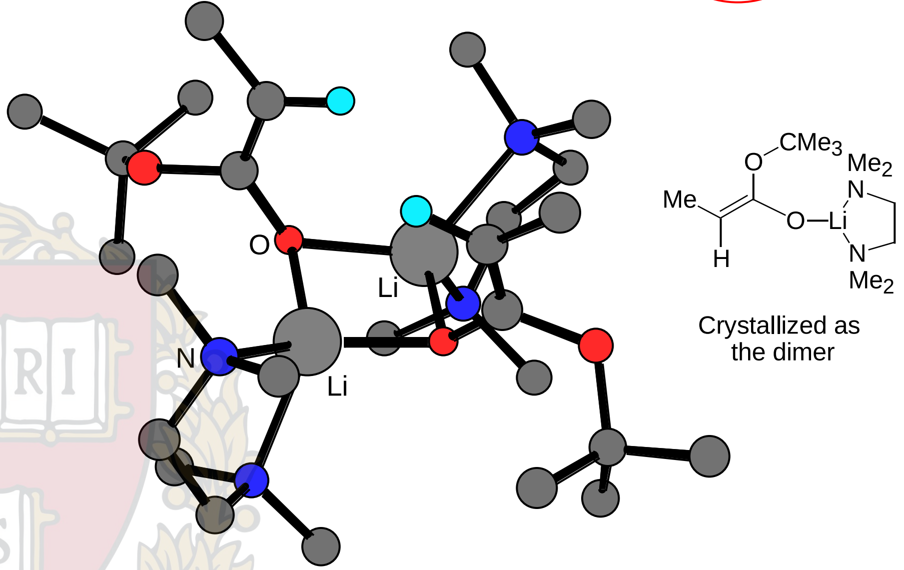


In solution and in the solid state metal enolates have a strong tendency to aggregate into dimers and tetramers to satisfy metal solvation requirements.



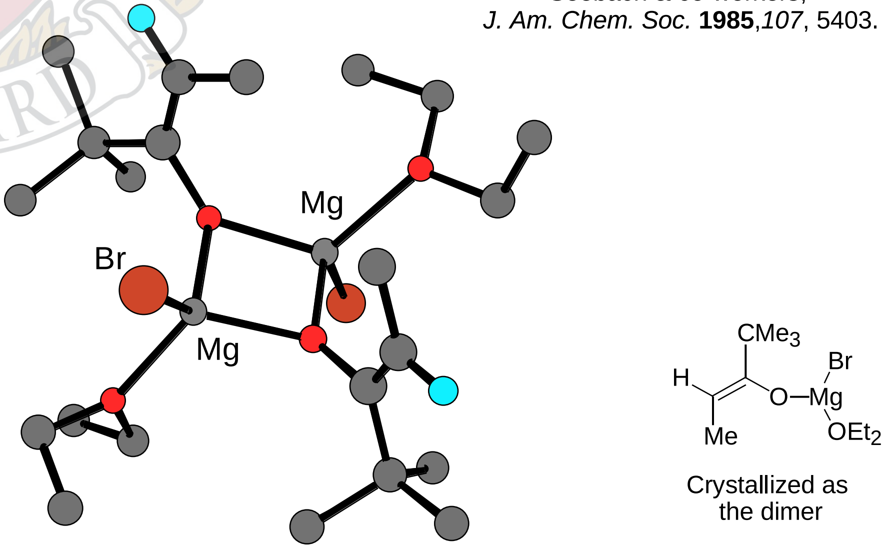
Ab initio calculations (Spartan) indicate that the partial negatilve charge on the alpha carbon is ~ – 0.22 for the Li enolate





Crystallized as the dimer

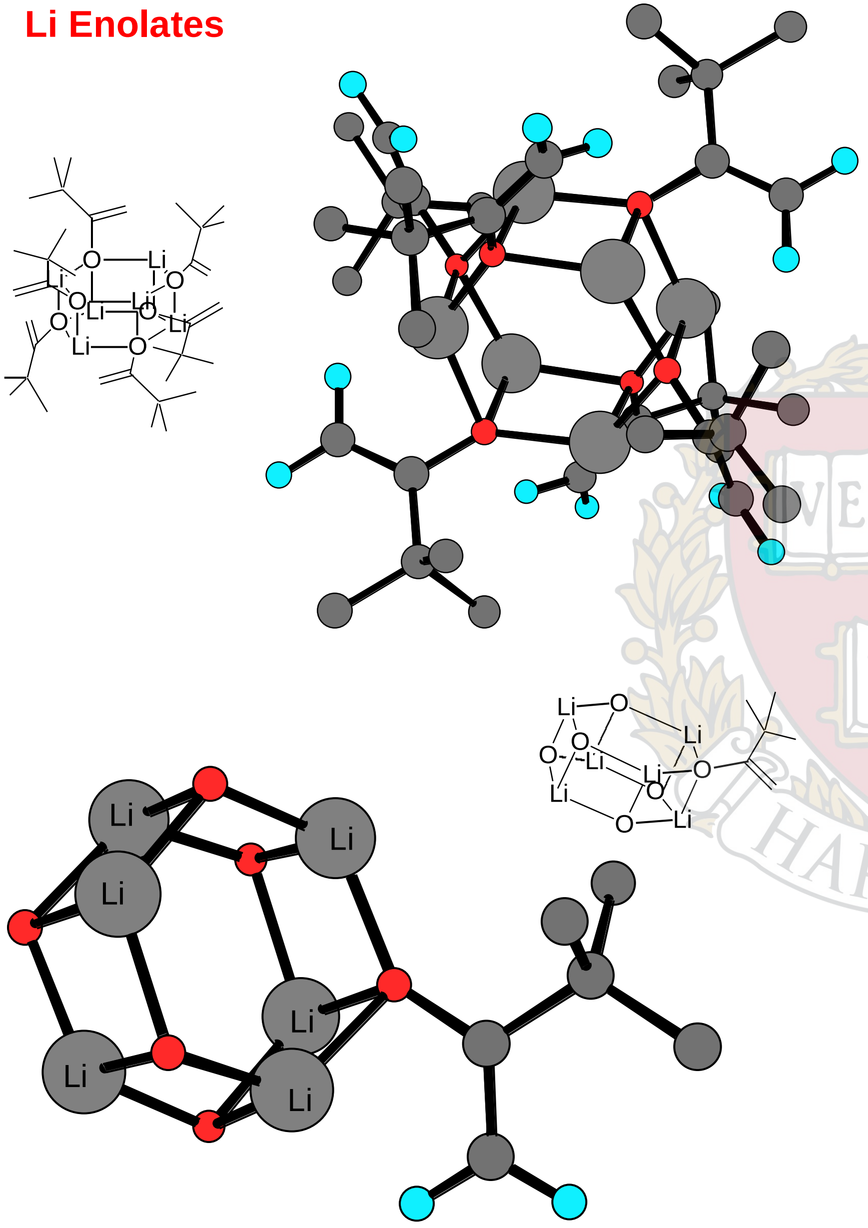
Seebach & co-workers,
J. Am. Chem. Soc. **1985**,*107*, 5403.



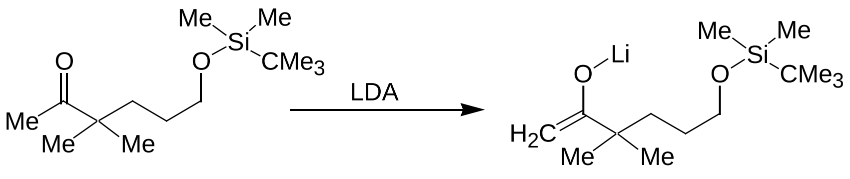
Crystallized as the dimer

Enolate Structures: Lithiun Enolates

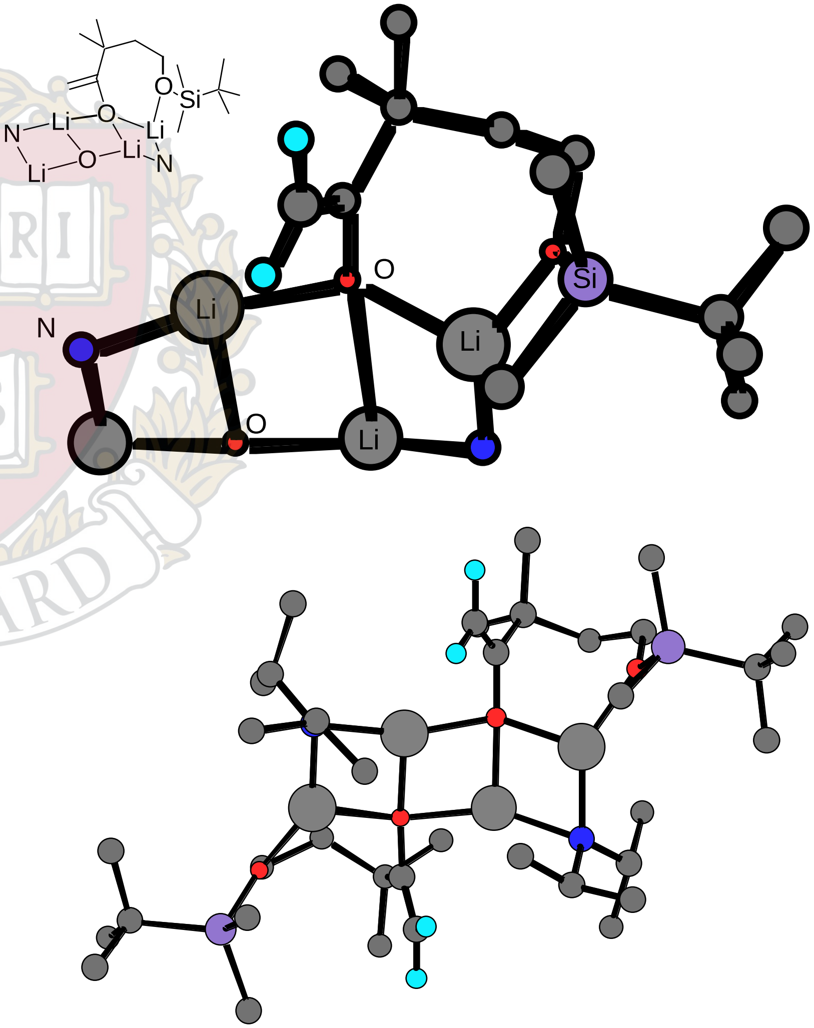
Li Enolates



Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462-468.

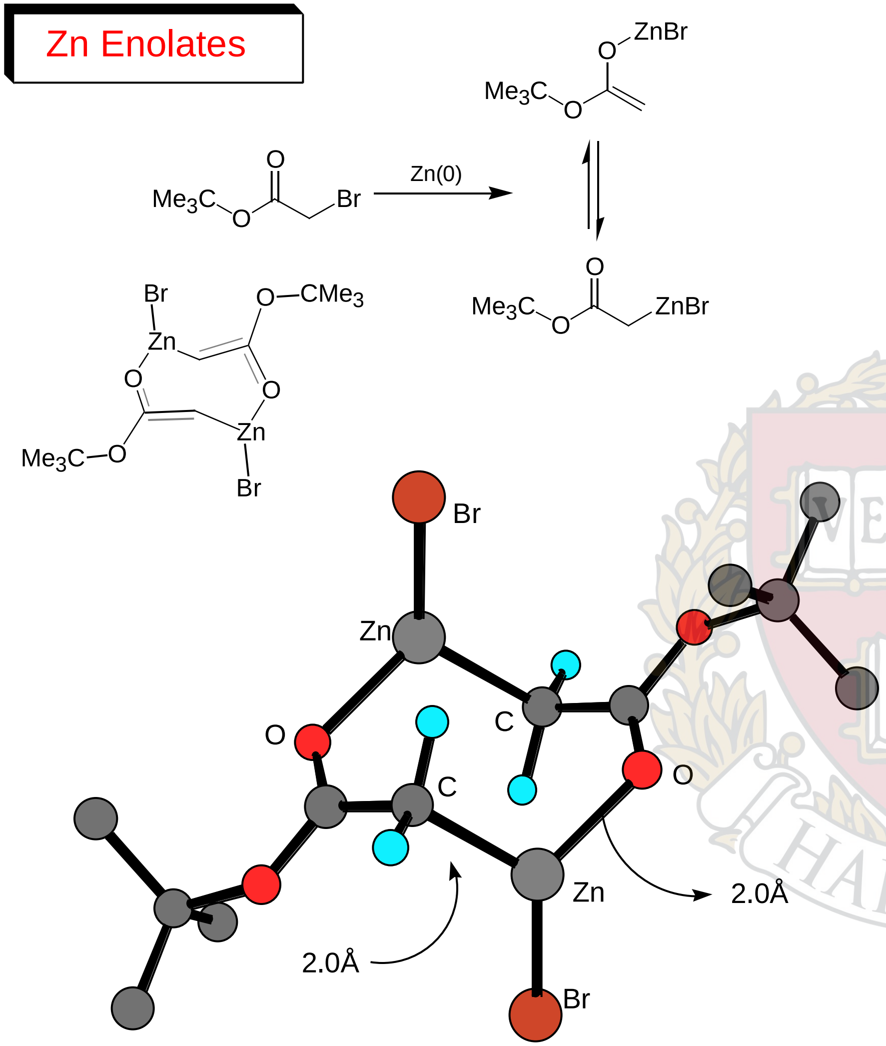


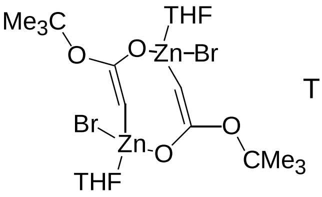
Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539-5541.



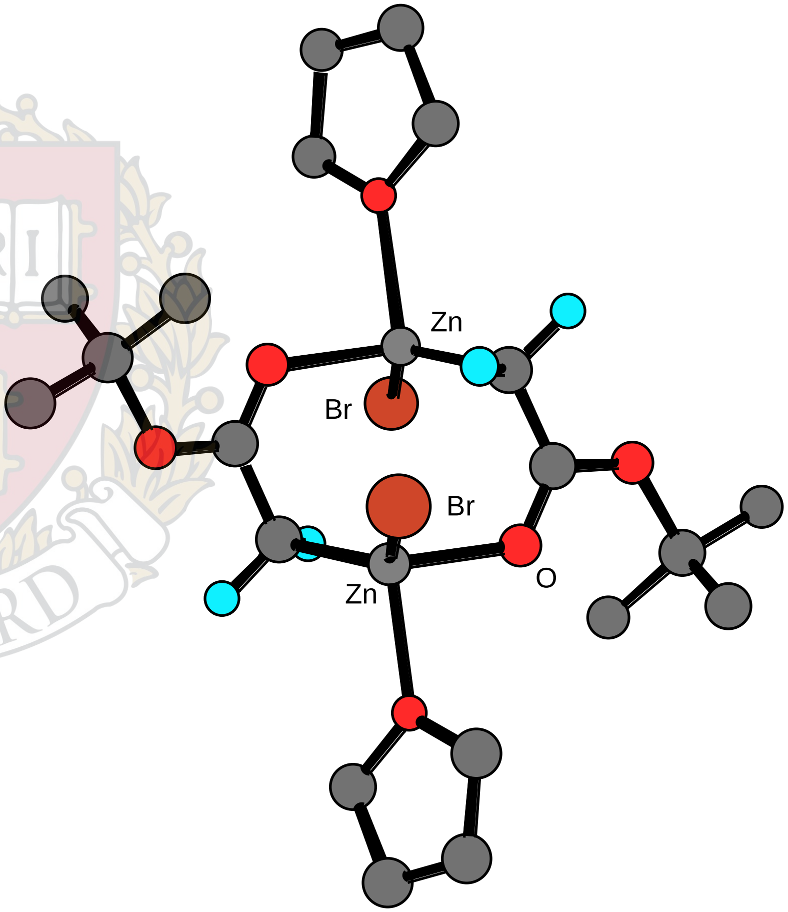
Enolate Structures: The Reformatsky Reagent

Zn Enolates





The THF Complex

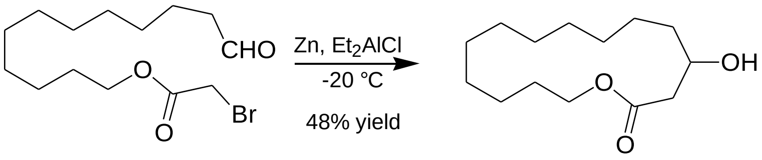


Dekker, J.; Boersma, J.; van der Kerk,
G. J. M. *J. Chem. Soc. Chem. Commun.* **1983**, 553.

Dekker, J.; Budzelaar, J.; Boersma, J.; van der Kerk, G. J. M.
Organometallics **1984**, *3*, 1403.

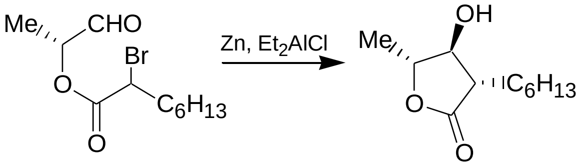
The "Classical" Reformatsky Process

Review: *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.8, pp 277-299



H. Nozaki & Co-workers,
J. Am. Chem. Soc. **197**, *99*, 7705

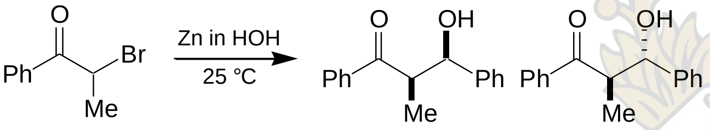
Both cyclic and acyclic cases studied (11 cases).



diastereoselection 10:1
55% yield

T. Nishida & Co-workers,
Tetrahedron **1991**, *47*, 6623.

Based on the Nozaki recipe *JACS* **1977**, *99*, 7705

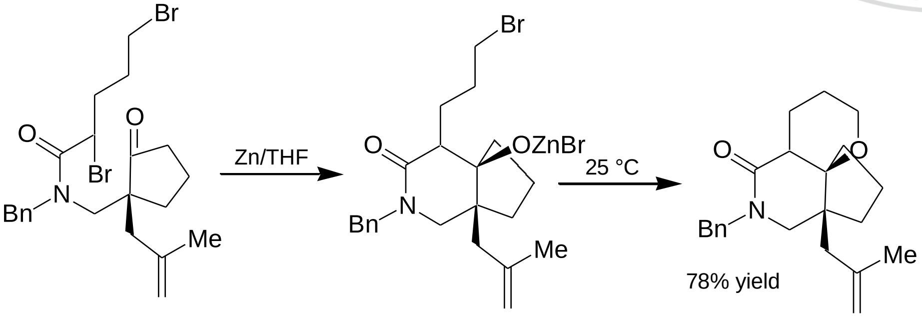


PhCHO

diastereoselection 60:40
87% yield

T. H. Chan & Co-workers,
Chem. Commun. **1990**, 505.

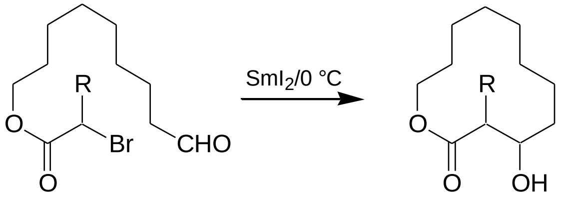
Rxns carried out in water with either activated Zn or Sn.
19 cases reported.



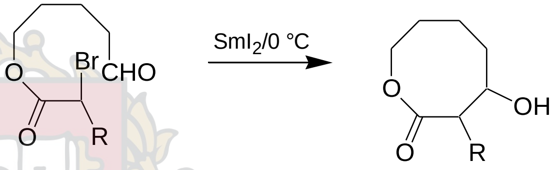
C. H. Heathcock & Co-workers,
J. Org. Chem. **1987**, *52*, 5745.

The Samarium(II) Variant

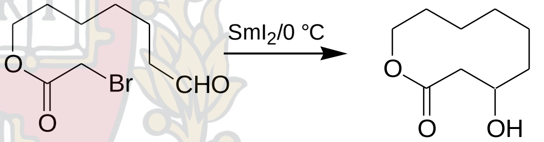
Summary of SmI_2 chemistry: Sonderquist, *Aldrichimica Acta* **1991**, *24*, 15



R = H: 85% yield
R = Me: 82% yield
aldol diastereoselection 70:30
no config assignment



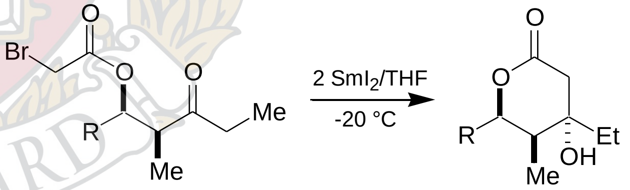
R = H: 76% yield
R = Me: 82% yield
aldol diastereoselection 62:38
no config assignment



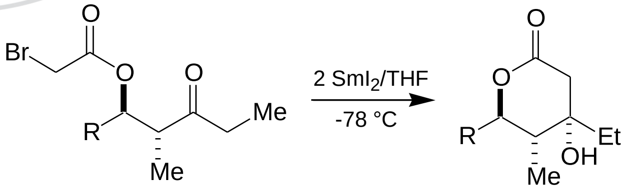
82% yield

Good entry into prior literature

T. Tabushi & Co-workers,
Tetrahedron Lett. **1986**, *27*, 3889.



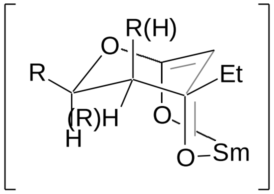
8: 1 diastereoselection
97% yield



one isomer? 86% yield

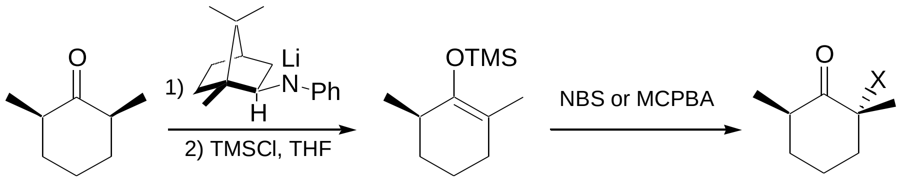
G. A. Molander & Co-workers,
J. Am. Chem. Soc. **1987**, *109*, 6556.

Proposed Transition structure



Chiral Amide Bases: Deprotonation of Ketones

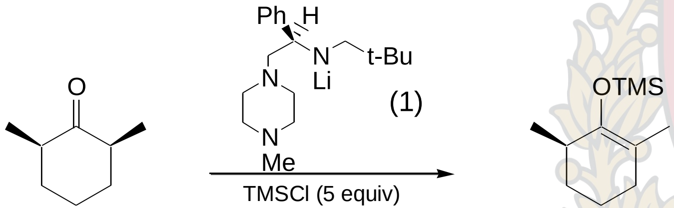
Asymmetric Deprotonation of Meso Ketones



X = Br or OH
70% ee

Simpkins, *J. Chem. Soc., Chem. Commun.* **1986**, 88-90.

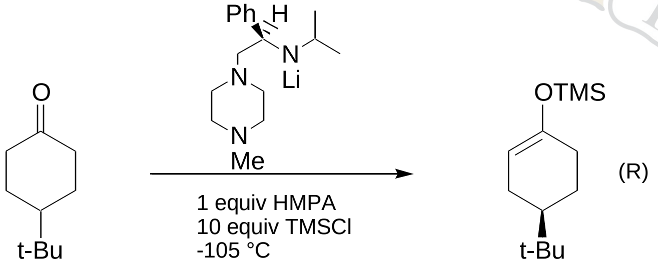
With an *in situ* quench:



(1)

73% yield (96% ee)

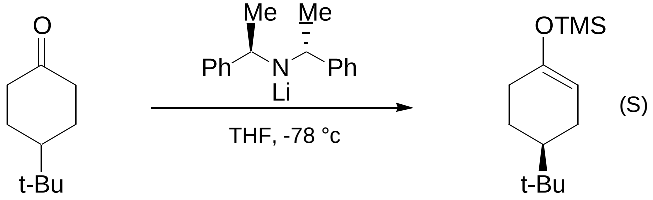
Koga, *et al* *Heterocycles* **1990**, *30* , 307-318.



51% yield (97% ee)

Koga, *et al* *J. Am. Chem. Soc* . **1986**, *108* , 543-545.

The Effects of Additives on Induction

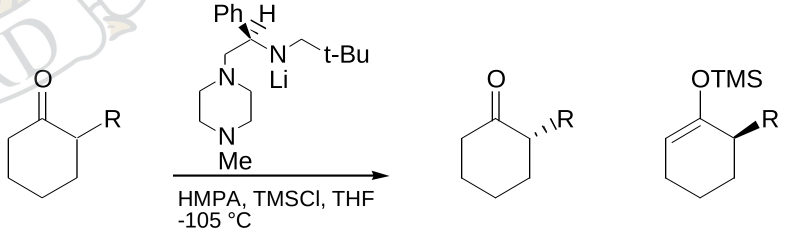


Conditions	ee(%)
Internal quench with TMSCl	69
External quench of TMSCl	23
Reaction run with 0.5 equiv of LiCl (rel. to amide), then quenched with TMSCl	83

Does a change in aggregation state inhibit racemization of the initial Li enolate?

Simpkins and Cousins, *Tetrahedron Lett* . **1989**, *30* , 7241-7244
Simpkins and Bunn, *J. Org. Chem* . **1993**, *58* , 533-534.

Kinetic Resolution of Ketones

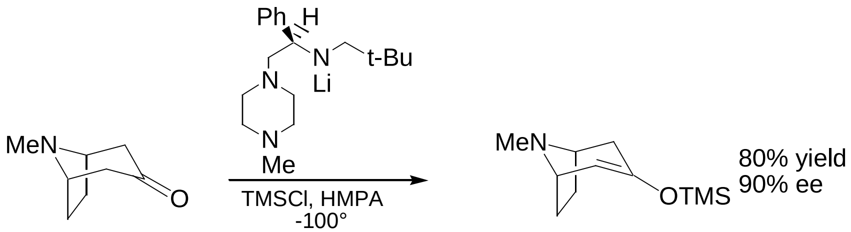


R (equiv base)		
t-Bu (1.0)	45% (90% ee)	51% (94% ee)
Ph (0.8)	66% (30% ee)	33% (98% ee)
i-Pr (0.8)	78% (18% ee)	22% (94% ee)

Koga, *et al* *Tetrahedron Lett* . **1989**, *30*, 6537-6540.

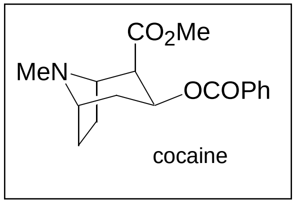
Chiral Amide Bases: Other Ketonic Substrates

Other cyclic ketones can be used as substrates.See:
Cox and Simpkins, *Tetrahedron: Asymmetry* **1991**, *2*, 1-26.



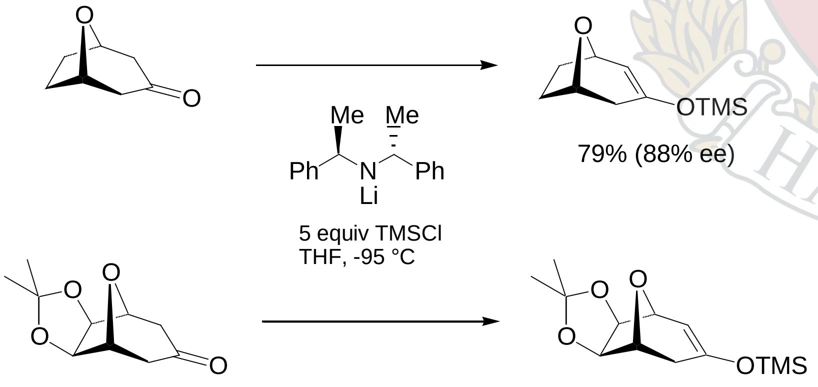
TMSCl, HMPA
-100°

80% yield
90% ee



cocaine

Momose, *et. al* *Chem. Pharm. Bull* . **1990**, *38* , 2072-2074



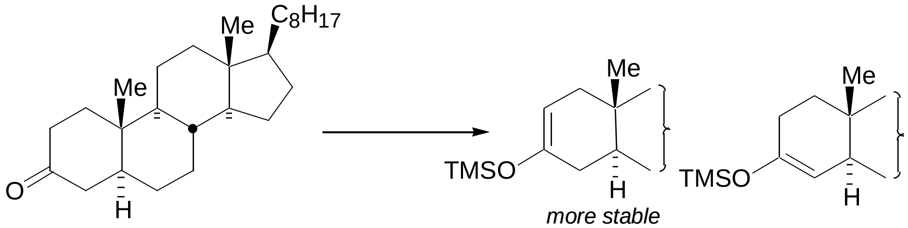
79% (88% ee)

5 equiv TMSCl
THF, -95 °C

88% (85% ee)

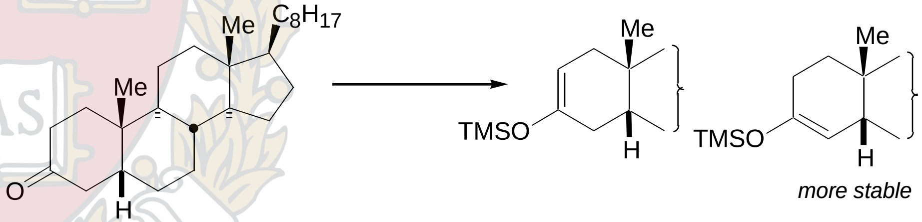
Simpkins, *et al* *Tetrahedron* **1993**, *49* , 207-218.

■ Regioselective Deprotonation of Unsymmetrical Ketones



more stable

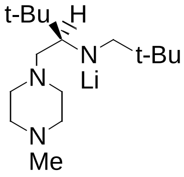
Conditions		Ratio	
$(TMS)_2NH$, TMSI	Thermodynamic	90	10
LDA	Kinetic	78	22
(R) - **1**	Kinetic	2	98
(S) - **1**	Kinetic	>98	<2



more stable

Conditions		Ratio	
$(TMS)_2NH$, TMSI	Thermodynamic	7	93
LDA	Kinetic	16	84
(R) - **1**	Kinetic	96	4
(S) - **1**	Kinetic	<2	>98

Koga, *et al* *Tetrahedron: Asymmetry* **1990**, *1* , 295-298.

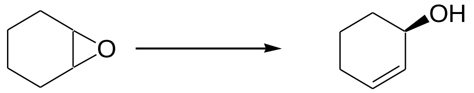


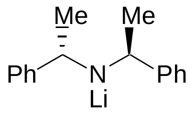
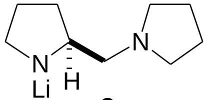
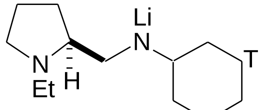
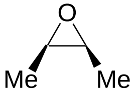
(R) - 1

Chiral Amide Bases: Epoxide Opening and Eliminations

Reviews:
Cox and Simpkins, *Tetrahedron: Asymmetry* **1991**, *2*, 1-26.
Simpkins, *Pure Appl. Chem.* **1996**, *68*, 691-694.
Simpkins, In Advanced Asymmetric Synthesis;
Stephenson, G. R., Ed.; Chapman & Hall: London, U.K., 1996; pp 111-125.

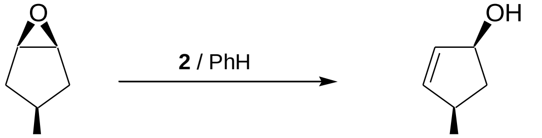
Ring opening of meso epoxides



Conditions		Yield (%)	ee(%)	Ref.
 1	THF, reflux	65	31 (R)	1
 2	THF, 0°	77	92 (S) *this number has been challenged*	2
 3	THF, HMPA, 0°	80	78 (R)	3
 + 3	THF, HMPA, 0°	58	62 (R)	3

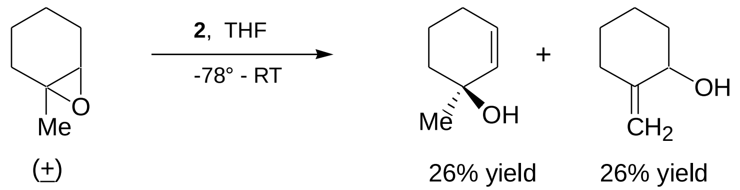
---

[1] Whitesell and Felman, *J. Org. Chem* . **1980**, *45*, 755-756.
[2] Asami, *Chem. Lett* . **1984**, 289-832.
[3] Asami and Kirihara, *Chem. Lett* . **1987**, 389-392.



92% yield (90% ee - rotation) - Asami, *Tetrahedron Lett* . **1985**, *26* , 5803-5806.
73% yield (76% ee -Mosher) - Hendrie and Leonard, *Tetrahedron* **1987**, *43* , 3289-3294.

Kinetic Resolution of Racemic Epoxides

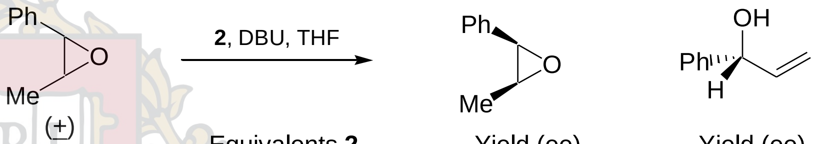


26% yield
~ 80% ee

26% yield

Mori, *Tetrahedron* **1987**, *43* , 2249-2254.

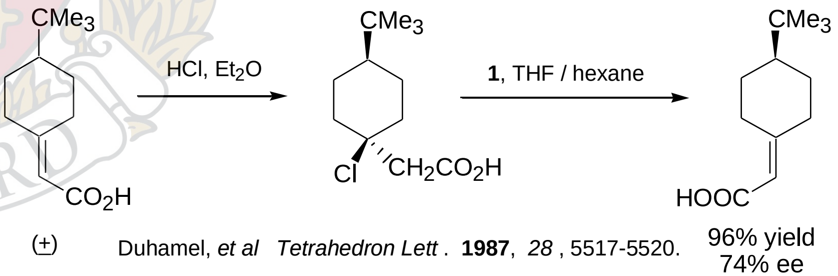
Aggregation pheremone
of the Douglas Fir Beetle



Equivalents **2**	Yield (ee)	Yield (ee)
0.75	31 (>95)	60 (33)
0.33	67 (30)	21 (72)

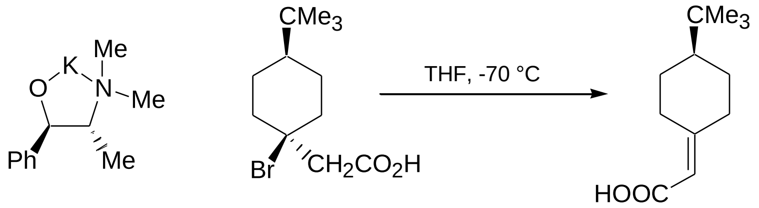
Asami and Kanemaki, *Tetrahedron Lett* . **1989**, *30*, 2125-2128.

Asymmetric Eliminations



Duhamel, *et al* *Tetrahedron Lett* . **1987**, *28* , 5517-5520.

96% yield
74% ee



Duhamel, *et al*, Chem Commun. **1993**, 116-117

90% yield
84% ee

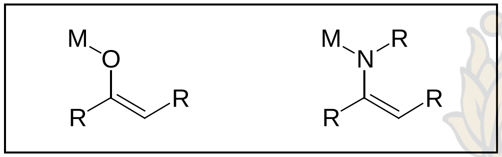
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 23

Enolates & Metalloenamines-2



- Introduction and General Trends
- Enolate Alkylation: Electronic & Steric Control Elements
- Enolate Alkylation: Unusual Cases
- Chiral Amide Enolates
- Chiral Ester Enolates
- Chiral Imide Enolates
- Chiral Metalloenamines

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Matthew D. Shair

Monday,
November 11, 2002

Assigned Journal Articles

"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures".
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983). **(handout)**

"Stereoselective Alkylation Reactions of Chiral Metal Enolates".
D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984). **(handout)**

Other Useful References

"Advances in Asymmetric Enolate Methodology" Arya, Qin, *Tetrahedron* **2000**, *56*, 917-947 **(pdf)**

"Recent Advances in Dianion Chemistry". C. M. Thompson and D. L. C. Green *Tetrahedron*, **47**, 4223 (1991).

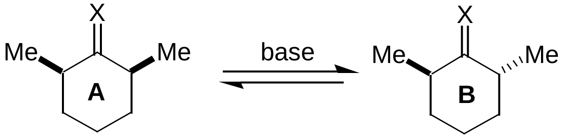
The Reactions of Dianions of Carboxylic Acids and Ester Enolates". N. Petragnani and M. Yonashiro *Synthesis*, 521 (1982).

"Generation of Simple Enols in Solution". Capon, Guo, Kwok, Siddhanta, and Zucco *Acc. Chem. Res*. **21**, 121 (1988).

"Keto-Enol Equilibrium Constants of Simple Monofunctional Aldehydes and Ketones in Aqueous Solution". Keeffe, Kresge, and Schepp *JACS*, 112, 4862 (1990).

"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Chiang, Kresge, and Tang *JACS* **106**, 460 (1984).

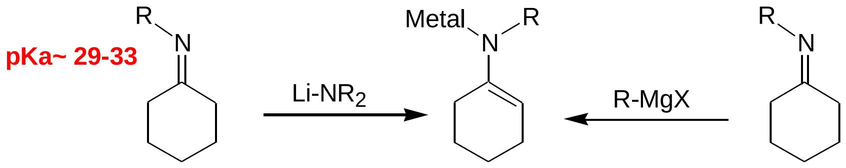
Explain why **A** is favored for X = O while **B** is favored for X = NNHR



Enols, Enolates, Enamines & Metalloenamines: Reactivity Hierarchy

■ Metalloenamines:

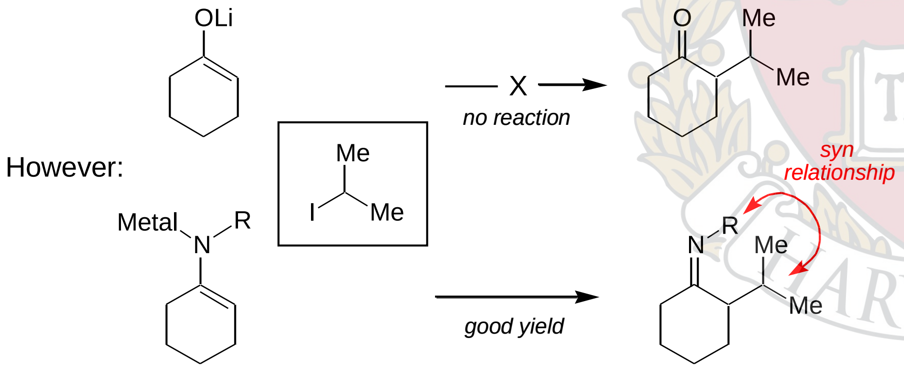
Imines may be transformed into their conjugate bases (enolate counterparts) with strong bases:



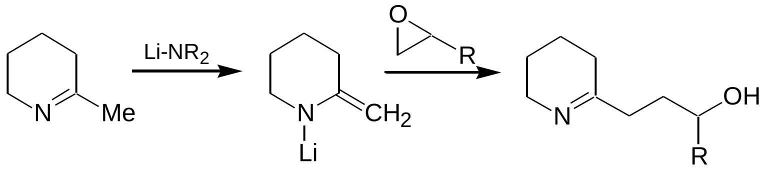
The usual bases employed are either lithium amides (LDA) or Grignard reagents. Note that Grignard reagents do not add to the C=N pi-bond due to the reduced dipole. With this functional group, deprotonation is observed to be the preferred reaction.

■ When to use a metalloenamine:

Metalloenamines are significantly more nucleophilic than ketone or aldehyde enolates. They are used when less reactive electrophiles are under consideration. For example:

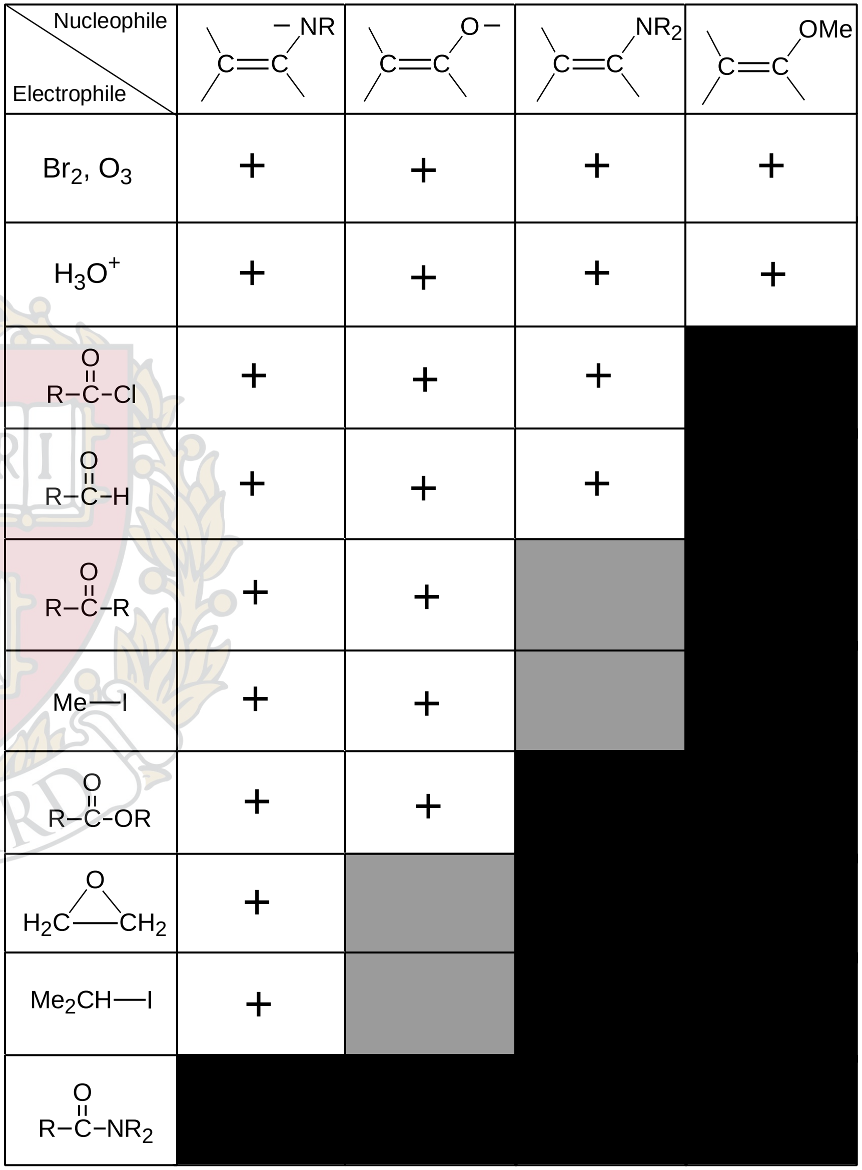


Metalloenamines are reactive enough to open epoxides in good yield. Ketone enolates are only marginally reactive enough for this family of electrophiles.



Decreasing Nucleophilicity - - - - - - ➤

Decreasing Electrophilicity - - - - ➤



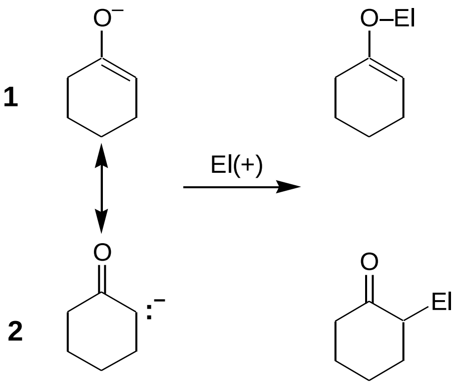
Nucleophile / Electrophile	$C=C-NR^-$	$C=C-O^-$	$C=C-NR_2$	$C=C-OMe$
Br_2, O_3	+	+	+	+
H_3O^+	+	+	+	+
$R-C(=O)-Cl$	+	+	+	■
$R-C(=O)-H$	+	+	+	■
$R-C(=O)-R$	+	+	▨	■
$Me-I$	+	+	▨	■
$R-C(=O)-OR$	+	+	■	■
H_2C-CH_2 (O)	+	▨	■	■
Me_2CH-I	+	▨	■	■
$R-C(=O)-NR_2$	■	■	■	■

■ Nature uses enamines, "stabilized" enolates, and enol derivatives in C–C bond constructions extensively.

C versus O Enolate Reactivity & the Hammond Postulate

Question: Why do we generally show enolates reacting with electrophiles at carbon as opposed to oxygen ?? Let's begin the the discussion with an observation:

■ "As electrophile reactivity increases, the percentage of reaction at the enolate oxygen increases." For example, consider the reactions of cyclohexanone enolate with the two electrophiles, methyl iodide and the much more reactive acetyl chloride:



El(+)	C/O Rxn Ratio
$Me-\overset{O}{\overset{\|}{C}}-Cl$	<< 1
Me—I	>> 1

■ The very reactive acid chloride gives almost exclusively the O-acylation product while the less reactive methyl iodide affords the alternate C-alkylation product.

These results may be understood in the context of qualitative statements made by Hammond (**The Hammond Postulate**) and Hine (**The Principle of Least Motion**)

The Principle of Least Motion:
"As reactions become more exothermic, the favored reaction becomes that path which results in the least structural (electronic) reorganization."

See Hine in Advances in Phys. Org. Chem. 1977, 15, 1-61

Since the X-ray data clearly support the picture that resonance structure **1** best represents the enolate structure, highly reactive electrophiles will favor O-attack according to Hine's generalization.

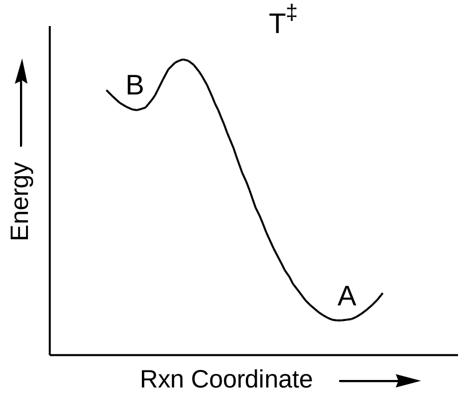
The Hammond Postulate is also relevant to this issue and is broadly used to make qualitative statements about transition state structure.

Hammond, *JACS* **1955**, *77*, 334

■ In attempting to grasp the Hammond Postulate, let's consider two extreme reactions, one which is strongly endothermic and one which is strongly exothermic.

Strongly Exothermic Reactions
$\Delta H^\circ > 20$ kcal/mol

B ⟶ A

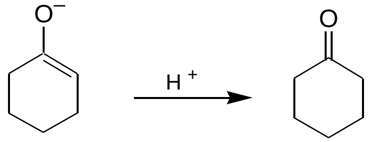


Hammond Postulate
"For strongly exothermic reactions, the transition state $T^\ddagger$ looks like reactant(s) e.g. B."

■ As applied to the enolate-electrophile reaction, for very exothermic reactions, e.g. the reaction with acetyl chloride, the transition state for the process will involve little enolate structural reorganization. Hence in this instance the electrophile heads for the site of highest electron density

Carey & Sundberg: **Part A**; Chapter 4, pp217-220
for discussion of Hammond's Postulate

Based upon the above discussion draw a detailed mechanism for the protonation of cyclohexanone enolate.

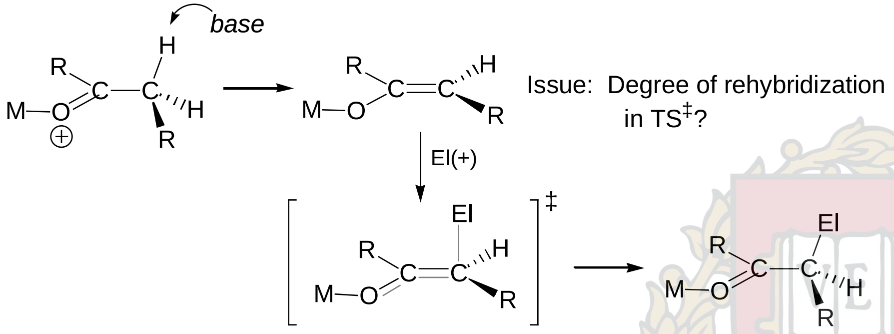


Enolate Alkylation: Stereoelectronic Control Elements

Review Evans, D. A. *Stereoselective Alkylation Reactions of Chiral Metal Enolates.*; Morrison, J. D., Ed.; AP: New York, 1984; Vol. 3, pp 1-110.

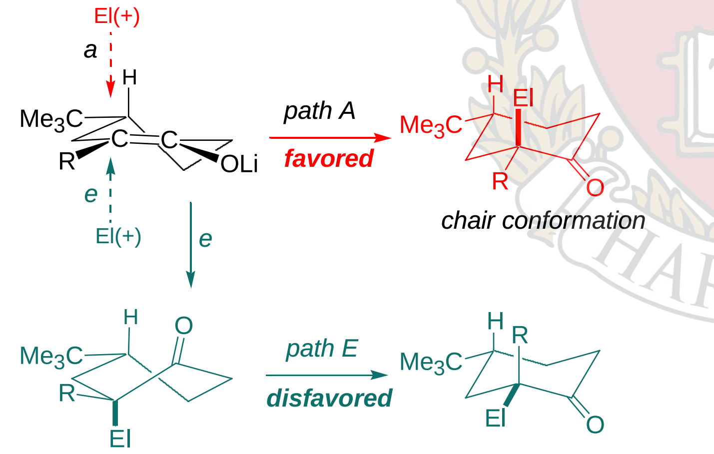
Stereoelectronic Issues

- Enolization: Breaking C–H bond must overlap with π C–O in TS‡
- Alkylation: Forming C–El bond must overlap with π C–O in TS‡



Issue: Degree of rehybridization in TS‡?

Cyclohexanone Enolate:

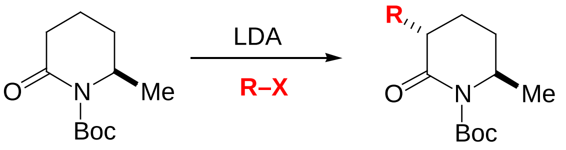


Metal	R-substituent	Electrophile	Ratio, a:e
Li	Me	CD_3I	70:30
Li	CO_2Me	Me-I	83:17

Chair vs boat geometries not stongly reflected in diastereomeric TS‡s. The transition states is early and enolate-like.

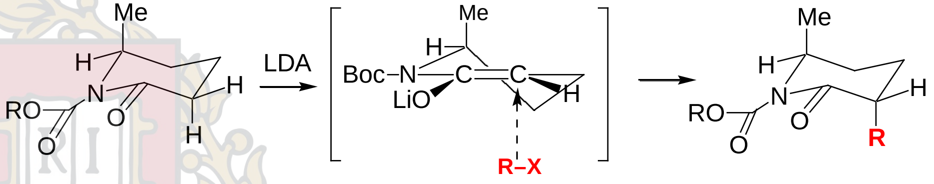
Examples where stereoelectronic factors are dominant

Pilli, *Tetrahedron*, **1999**, *55*, 13321

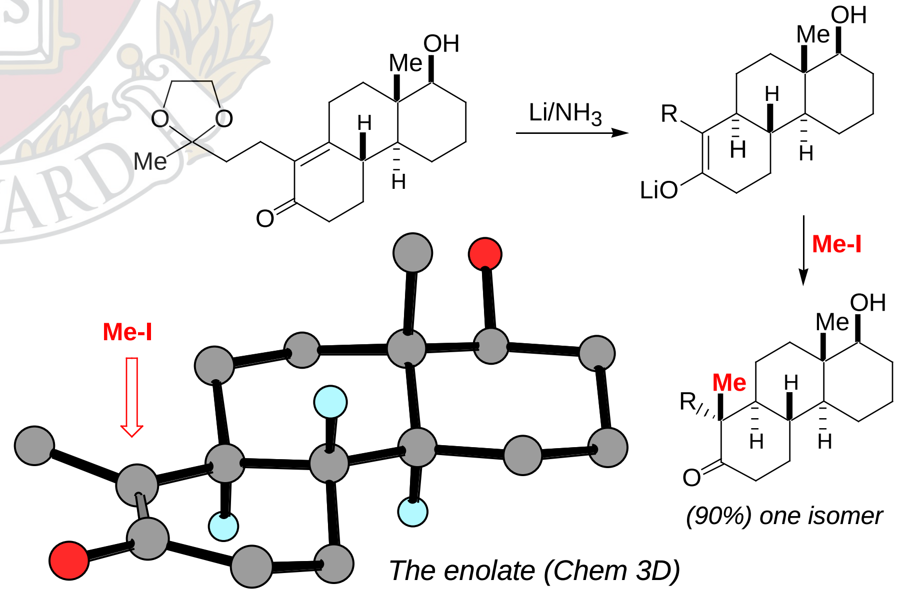


R–X	ratio
Bn–Br	>99:1
Allyl–Br	93:7

good illustration of the impact of allylic strain



The C_{19} Angular Methyl Group in the steroid nucleus

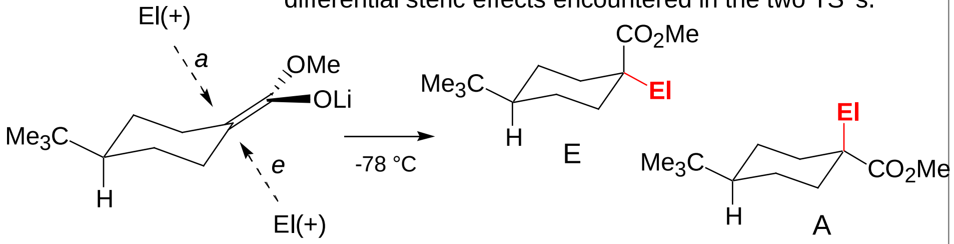


(90%) one isomer

The enolate (Chem 3D)

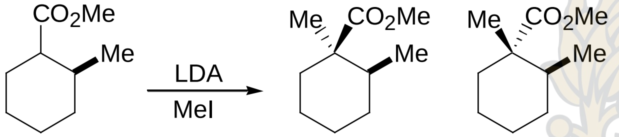
Steric Effects

In this case, both e and a paths are stereoelectronically equivalent. Diastereoselectivity is now determined by the differential steric effects encountered in the two TS‡s.

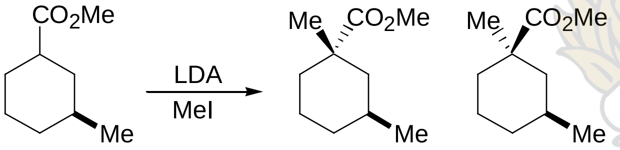


Electrophile	Ratio, E:A
Me-I	84:16
n-Bu-Br	87:13

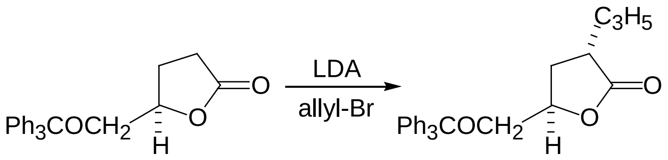
Representative cases



Ratio, 80 : 20

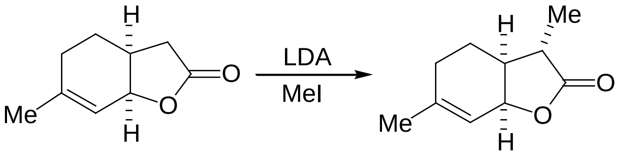


Ratio, 90 : 10



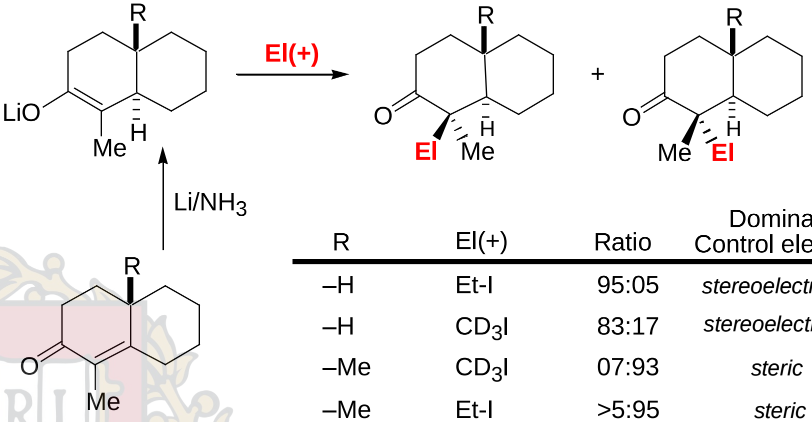
Ratio, >97 : 3

diastereoselectivity depends stongly on O-protecting group

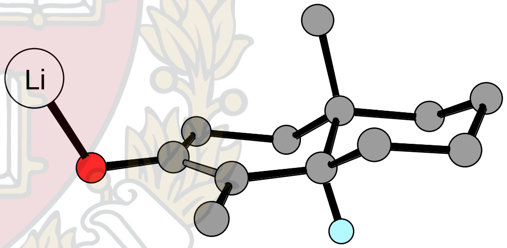


Ratio, >97 : 3

Cases with Opposed steric & electronic effects

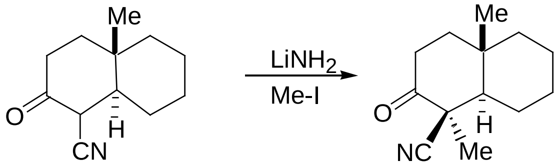


R	El(+)	Ratio	Dominant Control element
–H	Et-I	95:05	*stereoelectronic*
–H	CD_3I	83:17	*stereoelectronic*
–Me	CD_3I	07:93	*steric*
–Me	Et-I	>5:95	*steric*



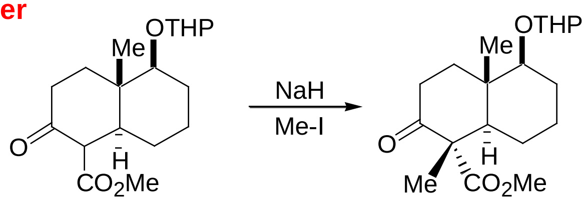
The enolate R = Me (Chem 3D)

Based on above data, this case is reasonable:



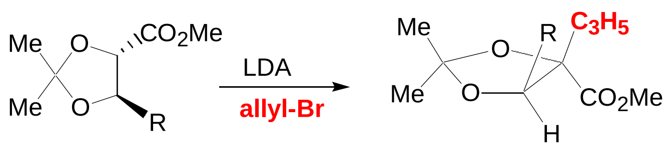
(58%) >90 : 10

However



(67%) 93 : 7

Cases which do not appear to give the expected product based on the analysis of steric effects



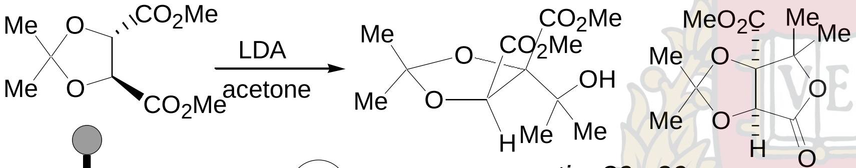
R = Me, Et, CO_2Me

≥ *88 : 12*

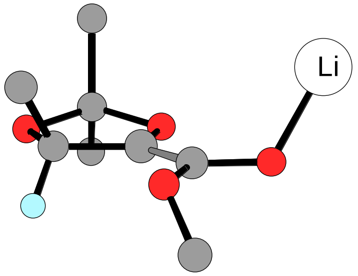
Seebach, *Angew. Chem. Int. Ed* **1981**, *20*, 1030

Ladner, *Angew. Chem. Int. Ed* **1982**, *21*, 449

■ However:

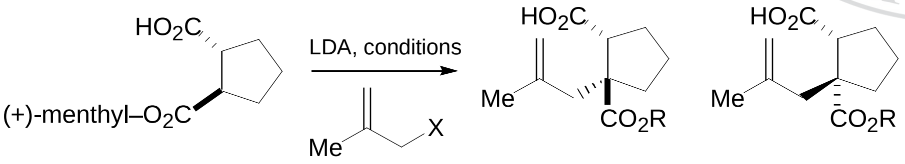


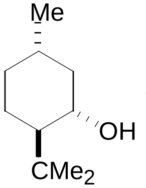
ratio, 80 : 20



The enolate (MM-2)

Here is another example of a contrasteric alkylation



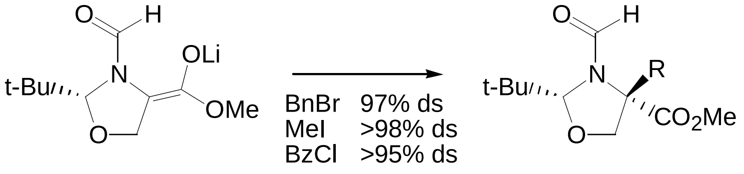


(+)-menthol

X	conditions	Ratio
R-Cl	THF, 23 °C	80:20
R-Br	THF-HMPA -78 → -20 °C	02:98

K. Yamada, *Organic Synthesis Past Present, and Future*, p 525

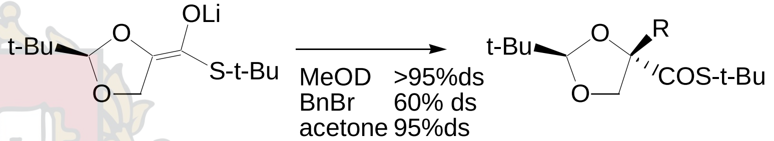
Sterically Expected Results:



BnBr	97% ds
MeI	>98% ds
BzCl	>95% ds

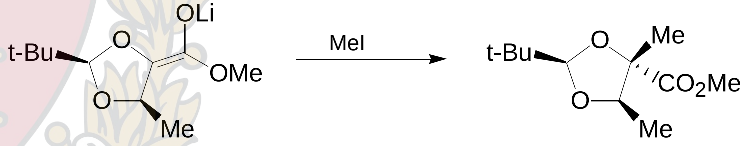
Seebach, *Helv. Chim. Acta* **1987**, *70*, 1194.

Contrasteric relatives:

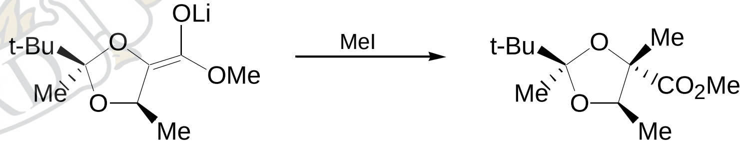


MeOD	>95%ds
BnBr	60% ds
acetone	95%ds

Seebach, *Helv. Chim. Acta* **1987**, *70*, 1194.



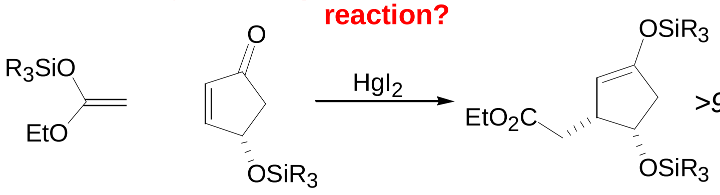
70 : 30



>95 : 5

Ladner, *Chem. Ber.* **1983**, *116*, 3413-3426.

Those factors defining olefin face selection are currently being defined: Would you have predicted the outcome of the following reaction?



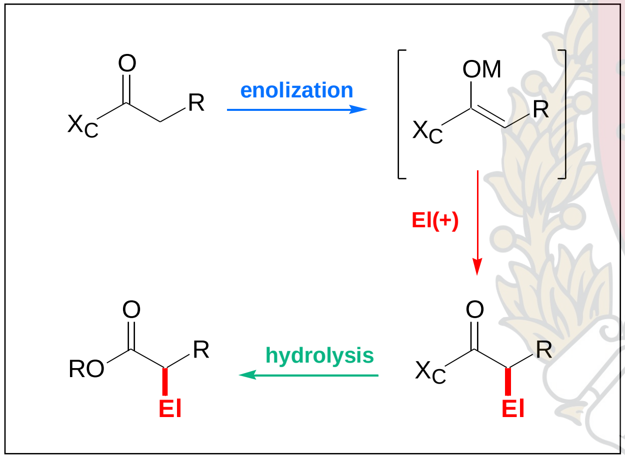
>94 : 6

Danishefsky *J. Org. Chem.* **1991**, *56*, 387

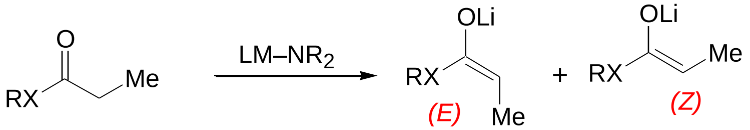
Chiral Enolate Design Requirements Circa 1978

Overall enantioselection will be the sum total of the defects introduced through:

- **Enolization selectivity**
- **Enolate-electrophile face selectivity**
- **Racemization attendant with X_c removal**

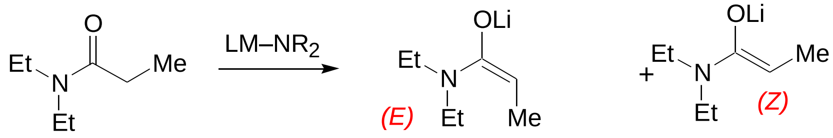


- **Enolization selectivity:** Ester-based chiral controllers X_C limited by enolization selectivity (Lecture 22)

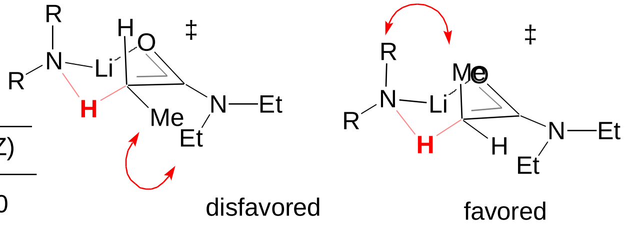


Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe, O-t-Bu	95 : 5
LDA (THF)	-S-t-Bu	95 : 5

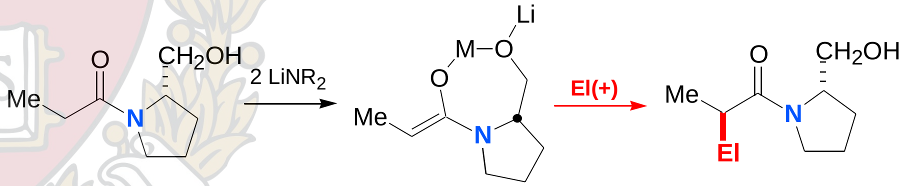
- **Enolization selectivity:** Amide-based controllers X_C limited by enolization selectivity (Lecture 22)



Base	Ratio, (E):(Z)
LDA (THF)	0 : 100
s-BuLi (THF)	25 : 75



- **Amide Based Chiral Auxiliaries**

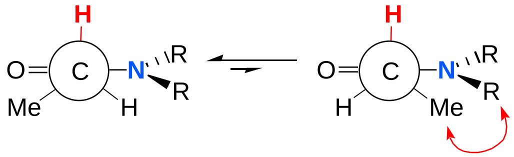


With Takacs,*Tetrahedron Lett.* **1980**, 4233

diastereoselection Ca 95 %

Allylic Strain controls Enolate Geometry:

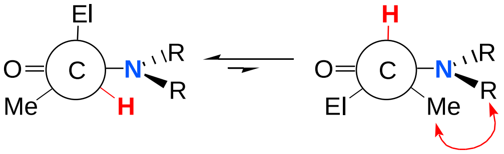
strongly favored



strongly disfavored

Allylic Strain Prevents Product Enolization:

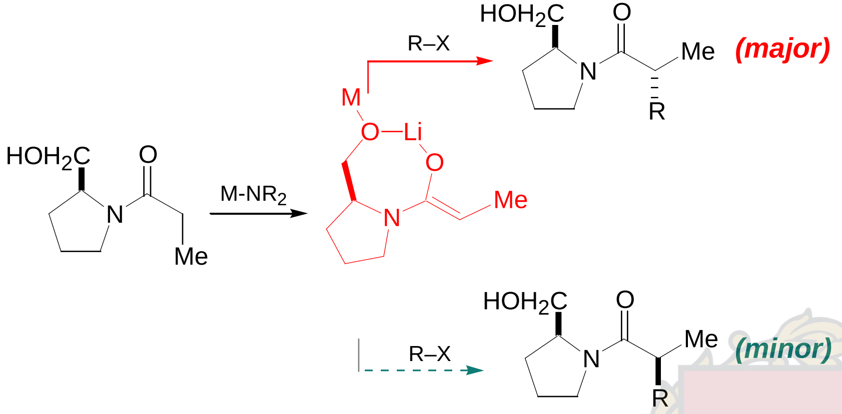
strongly favored



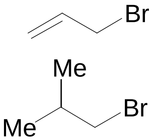
strongly disfavored

Enolate Alkylation: Chiral Amide Enolates

Chiral Amide Enolates



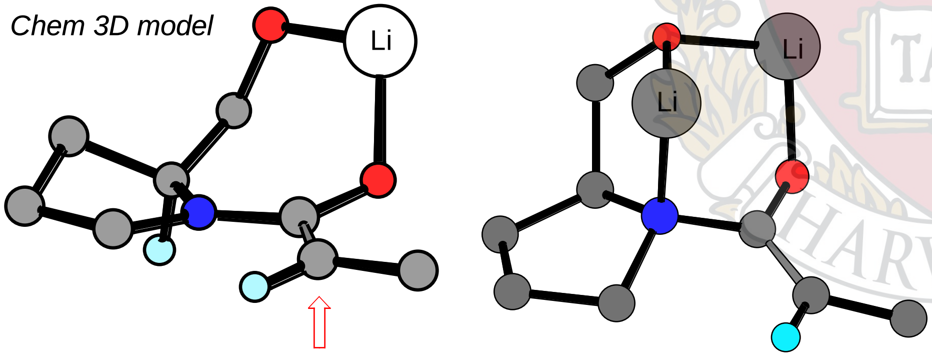
Evans, Takacs,
Tet. Lett. **1980**, *21*, 4233-4236



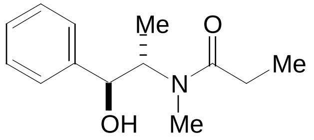
96:4 (98%)

98:2 (84%)

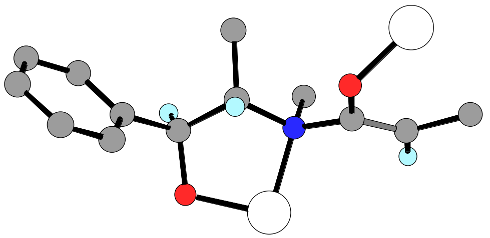
Chem 3D model



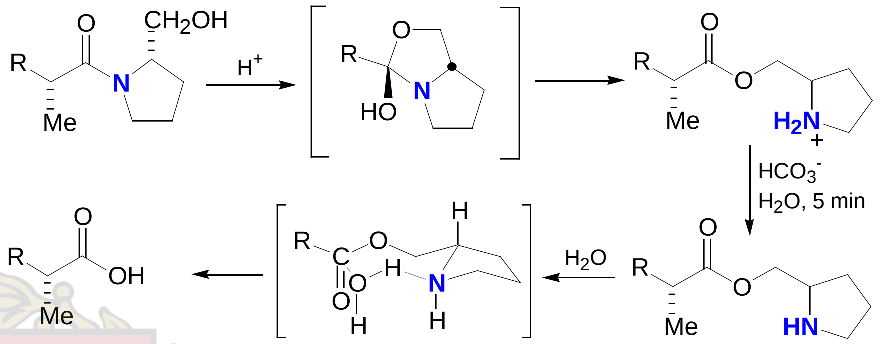
The nature of enolate chelation is ambiguous. Nitrogen chelation is a real possibility.



Myers, *JACS* **1997**, *119*, 6496



Amide Hydrolysis

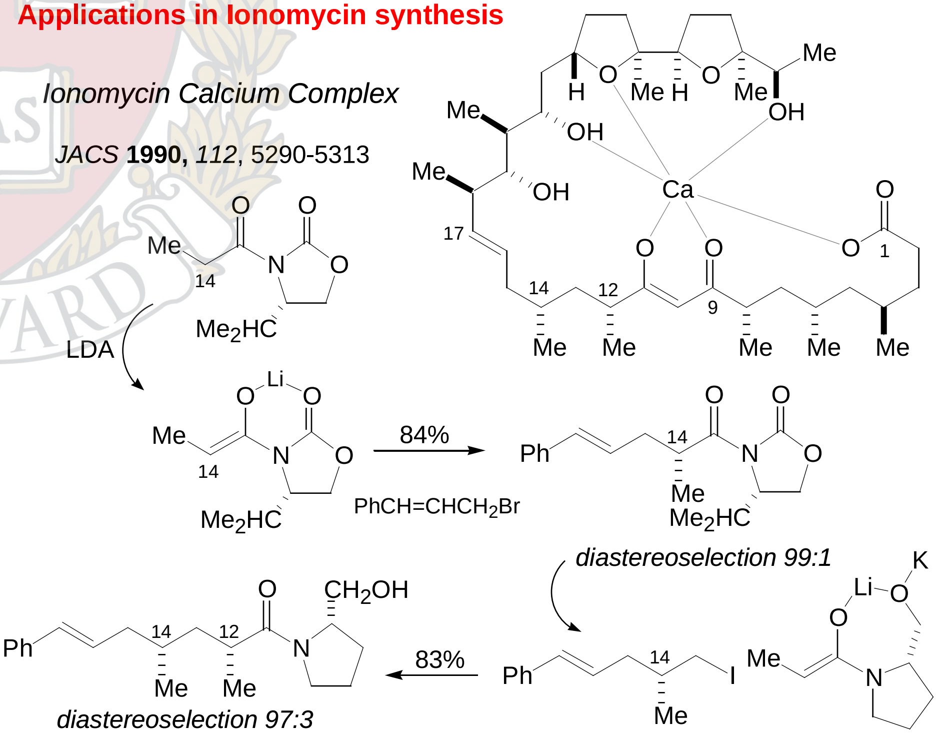


intramoleclar general base catalysis

Applications in Ionomycin synthesis

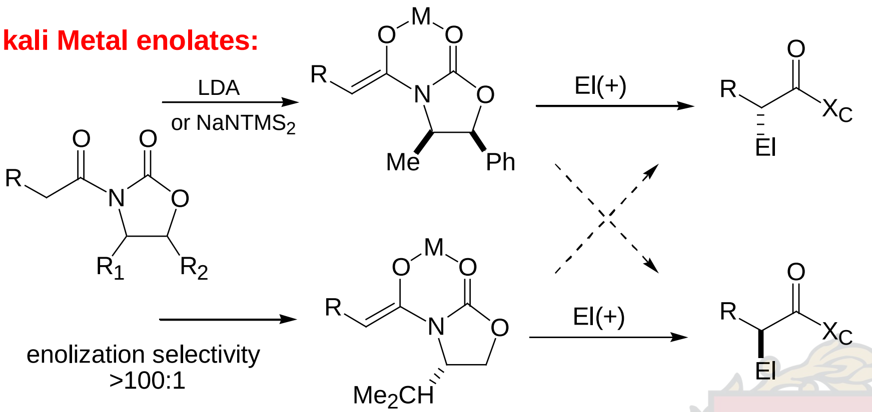
Ionomycin Calcium Complex

JACS **1990**, *112*, 5290-5313



Enolate Alkylation: Chiral Imide Enolates

Alkali Metal enolates:



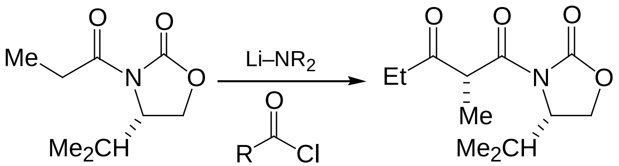
enolization selectivity >100:1

M = Li, THF < 0 °C
M = Na, THF -78 to 0 °C

	Alkyl Halide	Ratio
	$ArCH_2Br$	50-120 : 1
	$CH_2C{=}CHCH_2Br$	50 : 1
	$ArCH_2OCH_2Br$	50 : 1
marginal reaction	CH_3CH_2I	25 : 1
	CH_3I	13 : 1

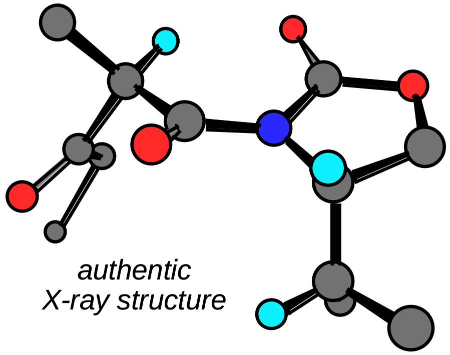
JACS. **1982**,*104*, 1737.

Enolate Acylation



JACS ***1984****, 106, 1154.*

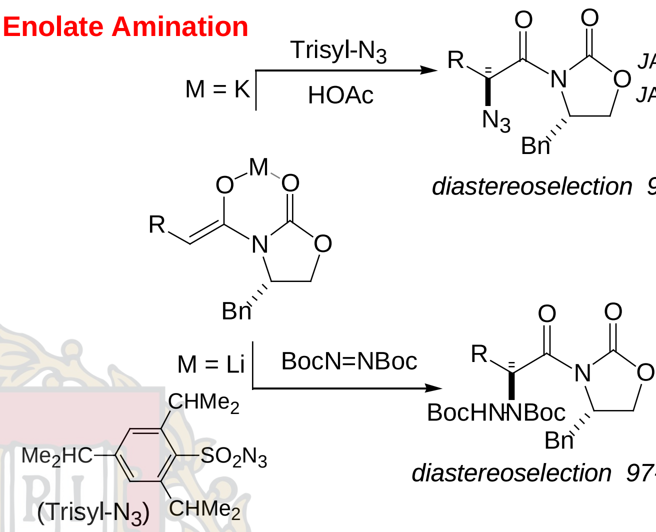
Diastereoselection ~ 97 : 3



New stereocenter not lost through enolization

authentic X-ray structure

Enolate Amination



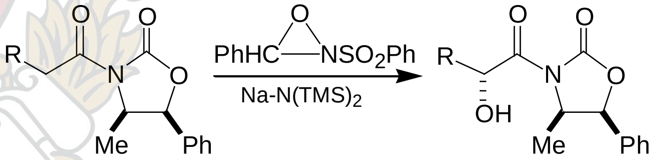
JACS **1987**,*109*, 6881.
JACS **1990**,*112*, 4012-4030

diastereoselection 91-99+ %

JACS **1986**,*108*, 3695.
Tet. **1988**, *44*, 5525-40

diastereoselection 97-99$^+$ %

Enolate Hydroxylation



Na enolate is required. Why?

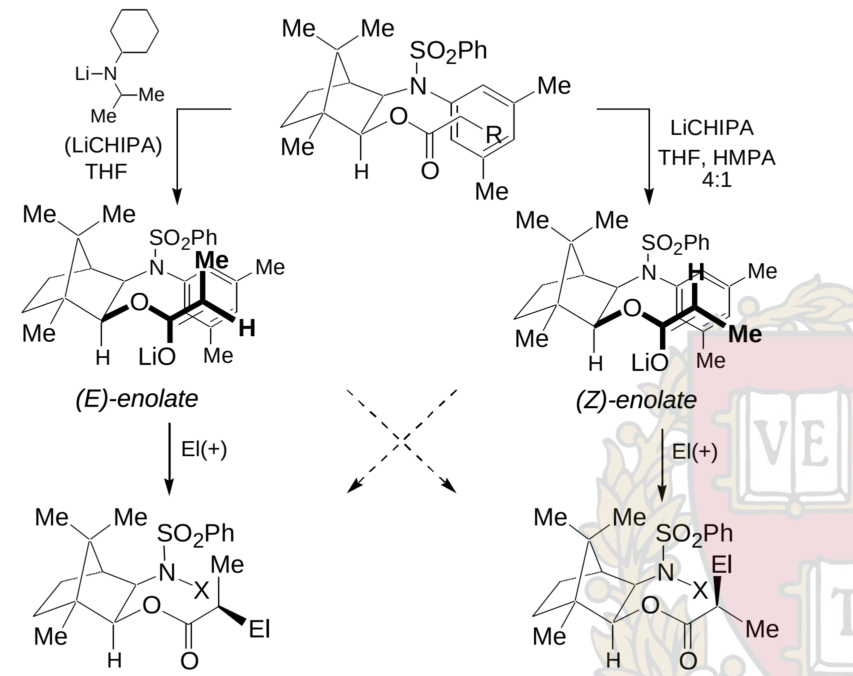
Imide (R)	Ratio	Yield *
$PhCH_2$-	94 : 6	86 %
$CH_2{=}CHCH_2$-	95 : 5	91 %
$MeO_2CCH_2CH_2CH_2$-	96 : 4	68 %
Ph-	90 : 10	77 %
Me_3C-	>99 : 1	94 %

JACS. **1985**,*107*, 4346.

For all indicated rxns, as the R on the enolate grp increases in size enolate-El face selectivity increases. Explain.

Chiral Ester Enolates

Helmchen, *Angew. Chem. Int.Ed.* **1981**, *20*, 207-208



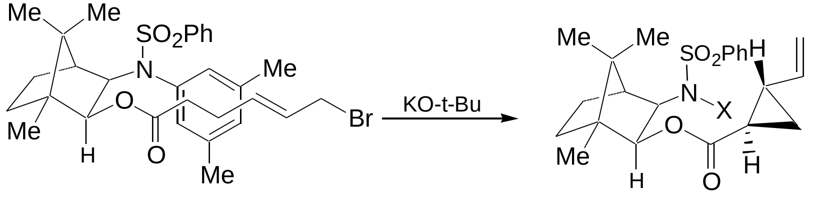
enolate	El(+)	Ratio
(E)	n-$C_{14}H_{29}$–I	98.5:1.5
(Z)	n-$C_{14}H_{29}$–I	06:94

enolate contamination

Helmchen, *Angew. Chem. Int.Ed.* **1984**, *23*, 60-61

Helmchen, *Tet. Lett.* **1983**, *24*, 1235-1238

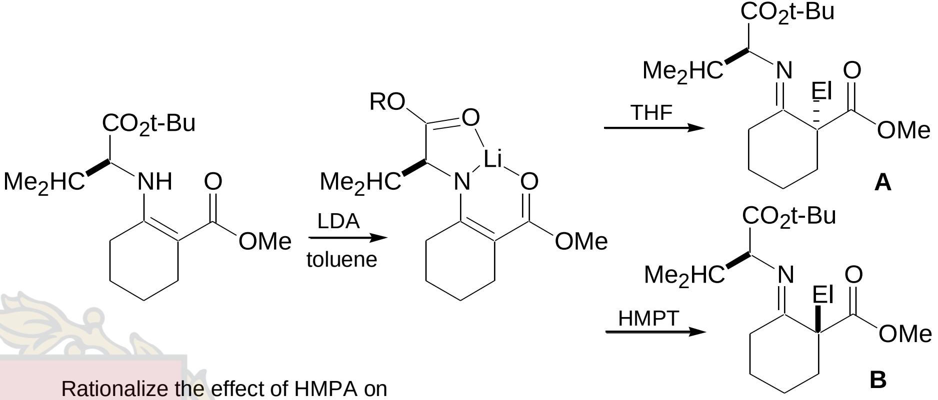
Helmchen, *Tet. Lett.* **1983**, *24*, 3213-3216



Ratio, 93:7 (74%)

Helmchen, *Tet. Lett.* **1985**, *26*, 3319-3322

Chiral β-Keto Ester Enolates

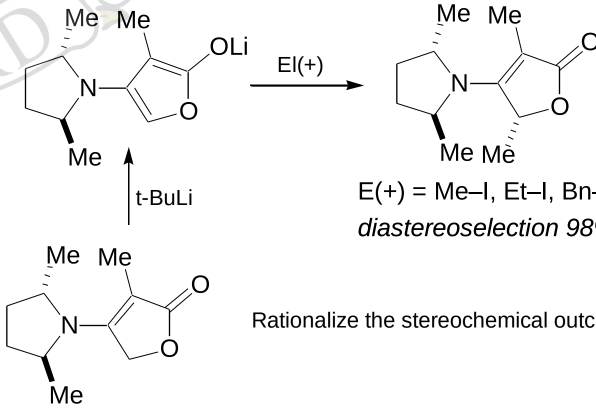


Rationalize the effect of HMPA on the stereochemical outcome of reaction.

Koga, *JACS* **1984**, *106*, 2718-2719

El(+)	addend	Yield	Ratio (A:B)
Me–I	THF	63%	96:04
Me–I	HMPT	57%	01:99
Bn-Br	THF	48%	99:01
Bn-Br	HMPT	77%	15:85

Chiral β-Keto Ester Dienolates



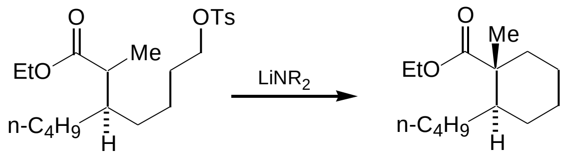
Major diastereomer

E(+) = Me–I, Et–I, Bn–Br

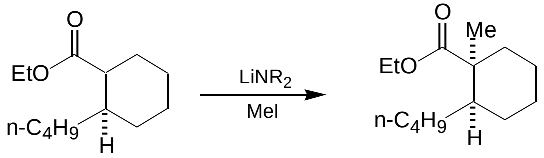
diastereoselection 98%

Rationalize the stereochemical outcome of reaction.

Schlessinger, *Tet. Lett.* **1988**, *29*, 1489-1492

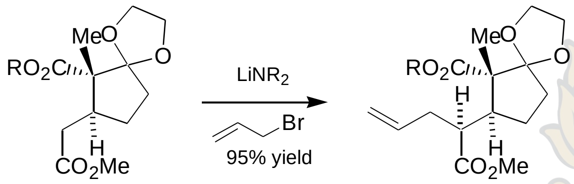


diastereoselection 98:2



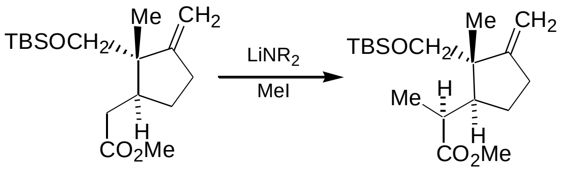
diastereoselection 89:11

D. Kim & Co-workers, *Tetrahedron Lett*. **1986**, *27*, 943.



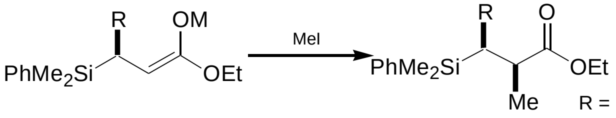
"one isomer"

G. Stork & Co-workers, *Tetrahedron Lett*. **1987**, *28*, 2088.



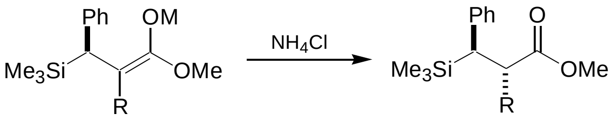
"one isomer"

T. Money & Co-workers, *Chem. Commun*. **1986**, 288.



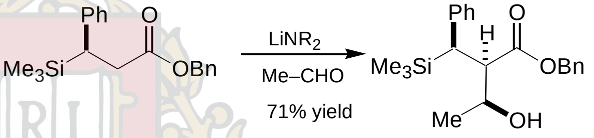
R = Me: *diastereoselection 99:1*
R = Ph: *diastereoselection 97:3*

I. Fleming & Co-workers, *Chem. Commun*. **1984**, 28.



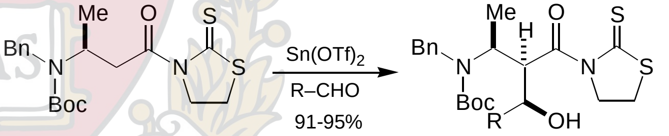
R-substituent	*diastereoselection*
R = Me	87:13
R = Et	80:20
R = CHMe$_2$	40:60 major diastereomer opposite to that shown

I. Fleming & Co-workers, *Chem. Commun*. **1985**, 318.
Y. Yamamoto & Co-workers, *Chem. Commun*. **1984**, 904.



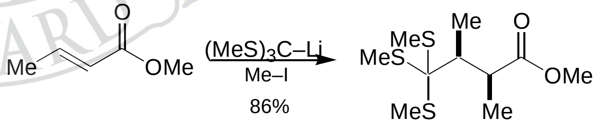
diastereoselection 90:10 at C$_3$
one isomer at C$_2$

I. Fleming & Co-workers, *Chem. Commun*. **1986**, 1198.



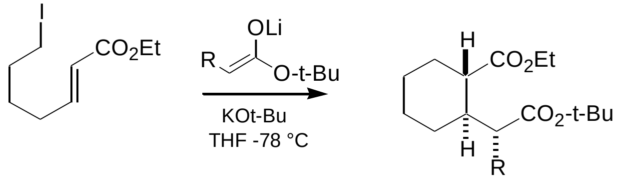
diastereoselection >95%

T. Mukaiyama & Co-workers, *Chem. Letters* **1986**, 637



diastereoselection 99:1

K. Koga & Co-workers, *Tetrahedron Letters* **1985**, *26*, 3031.



R = H: one isomer
R = Me: > 15 :1

Y. Yamaguchi & Co-workers, *Tetrahedron Letters* **1985**, *26*,1723.

Metalloenamines-1

Seminal Paper: Stork & Dowd, *JACS*, **1963**, *85*, 2178-2180

Reviews:

Martin in *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.16, pp 475-502

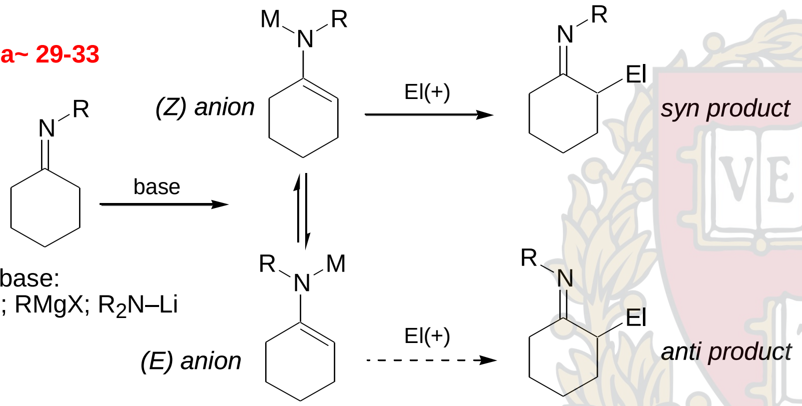
Whitesell *Synthesis*, **1983**, 517-535

Bregbreiter in *Asymmetric Synthesis*, **1983**; Vol 2, Chapter 9, pp 243-273

Enders in *Asymmetric Synthesis*, **1984**; Vol 3, Chapter 4, pp 275-339

Generation & Structure:

pKa~ 29-33



The base:
R–Li; RMgX; R_2N–Li

Acidity Measurements: (Streitwiser, *JOC* **1991**, *56*, 1989; Fraser, *ibid*. **1985**, *50*, 3234):

Kinetic product geometry strongly favors the *syn* isomer (>99%) (Fraser)

Fraser, *JACS* ***1978***, *100*, 7999
Fraser, *Chem. Commun.* ***1979***, 47

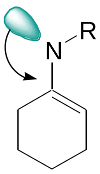
Solid State & Solution Structure:

X-ray structure reveals the following:

- ❐ Anion geometry is (Z)
- ❐ For M = Li, anion is delocalized rather than localized as pictured

Collum, *JACS* ***1984***, *106*, 4865-4869
Collum, *JACS* ***1985***, *107*, 2078-2082
Collum, *JACS* ***1986***, *108*, 3415-3422
Collum, *JACS* ***1993***, *115*, 789-790

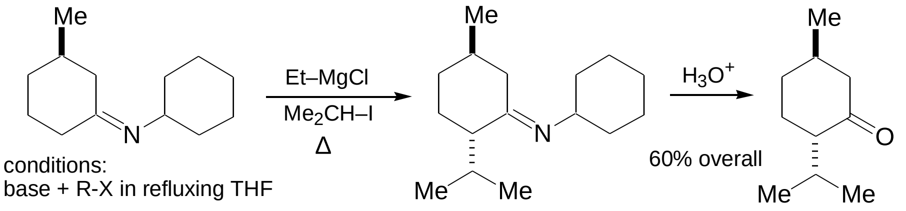
Geometry Rationalization:



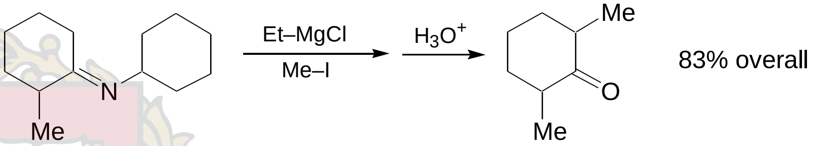
nonbonding N-lone pair may be stabilized by delocalizatin into antibonding orbital of C=C.

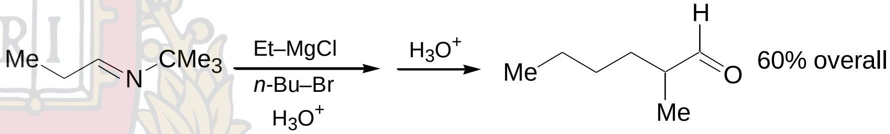
Remember, (Z) geometry also favored for enol ethers

Representative Reactions:



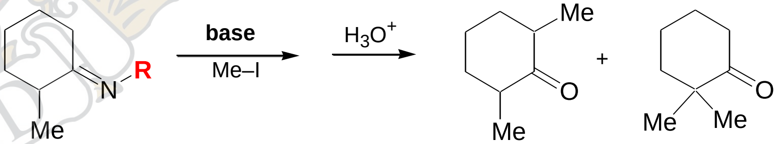
conditions:
base + R-X in refluxing THF



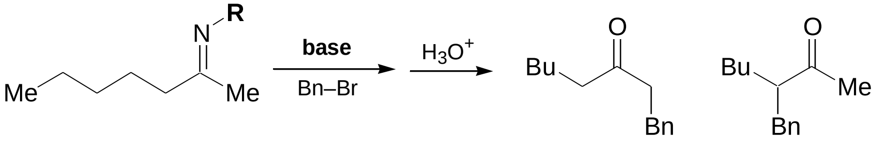


Stork & Dowd, *JACS*, **1963**, *85*, 2178-2180

- Nature of N-substituent, base, and solvent additive can play a role in deprotonation regioselectivity: Hosomi, JACS, 1982, 104, 2081-2082



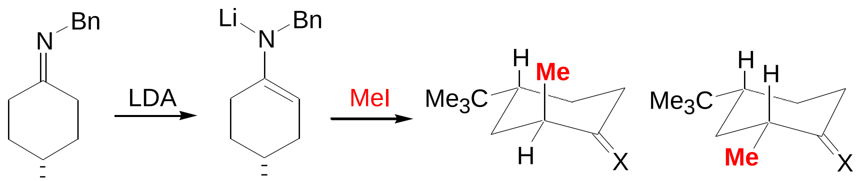
R	base	ratio
–cyclohexyl	*s*-BuLi	10:90
–NMe_2	*s*-BuLi	100:0



	R	base	ratio
	–cyclohexyl	*s*-BuLi	74:26
+ 1 equiv HMPA →	–cyclohexyl	*s*-BuLi	100:0

Metalloenamines-2

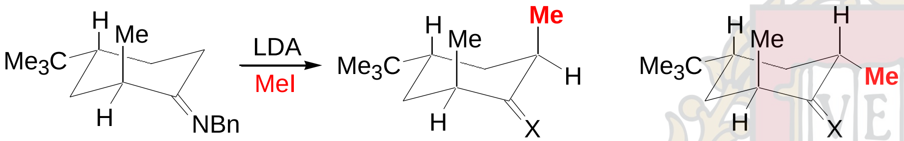
Stereoelectronic Issues:



Ratio, 97:3

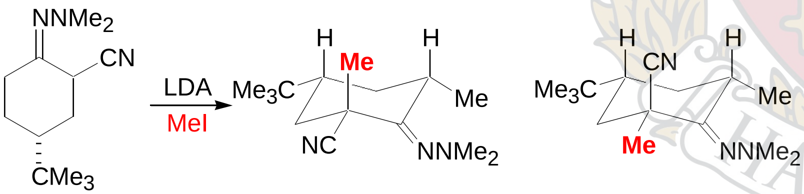
Fraser, *JACS* **1978**, *100*, 7999

Tendency for axial-chair alkylation is significantly greater that for ketones

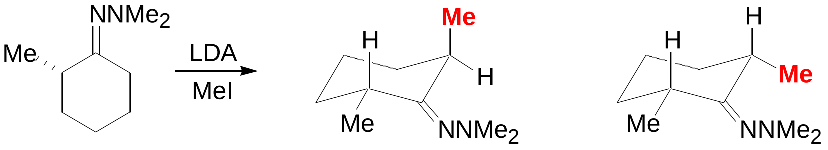


Fraser, *JACS* **1978**, *100*, 7999

X	Ratio
X = N-Bn	94:06
X = O	60:40



Collum, *JACS* **1984**, *106*, 4865-4869

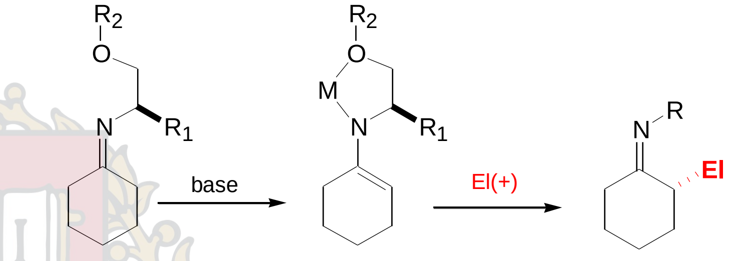


Ratio, 90:10

Chiral Metalloenamines:

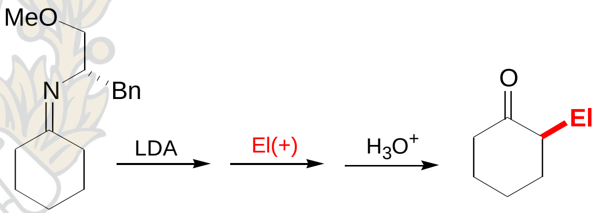
early papers:
- Meyers, *J. Am. Chem. Soc* **1976**, *98*, 3032
- Whitesell, *J. Org. Chem.* **1978**, *42*, 377-378

full papers:
- Meyers, *J. Org. Chem* **1978**, *43*, 892
- Meyers, *J. Am. Chem. Soc* **1981**, *103*, 3081
- Meyers, *J. Am. Chem. Soc* **1981**, *103*, 3088



Major Product

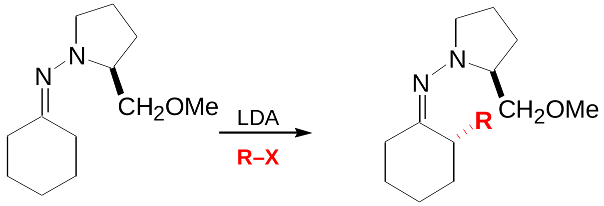
The base:
R–Li; RMgX; R_2N–Li



Meyers, *J. Am. Chem. Soc* **1981**, *103*, 3081

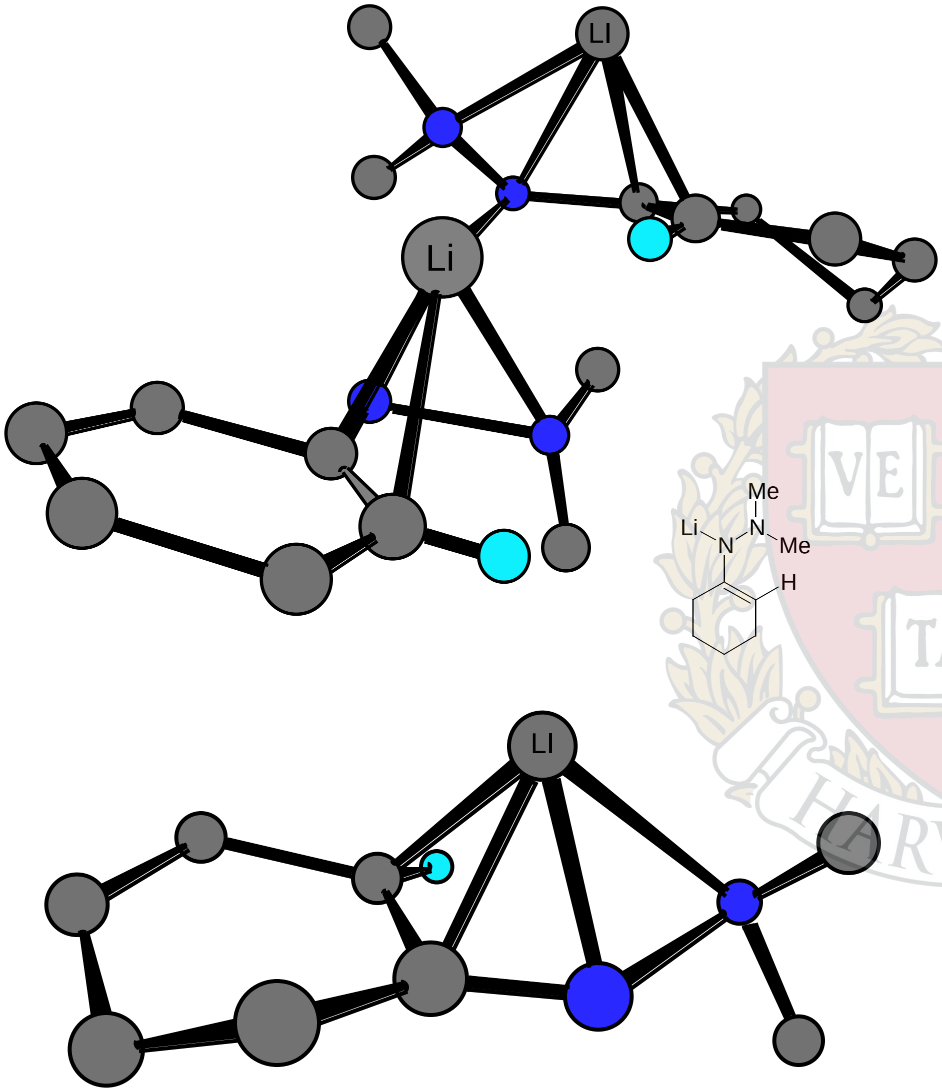
R–X	ee
Me–I	87
Et–I	94
n-Pr–I	99

Chiral Metallated Hydrazones

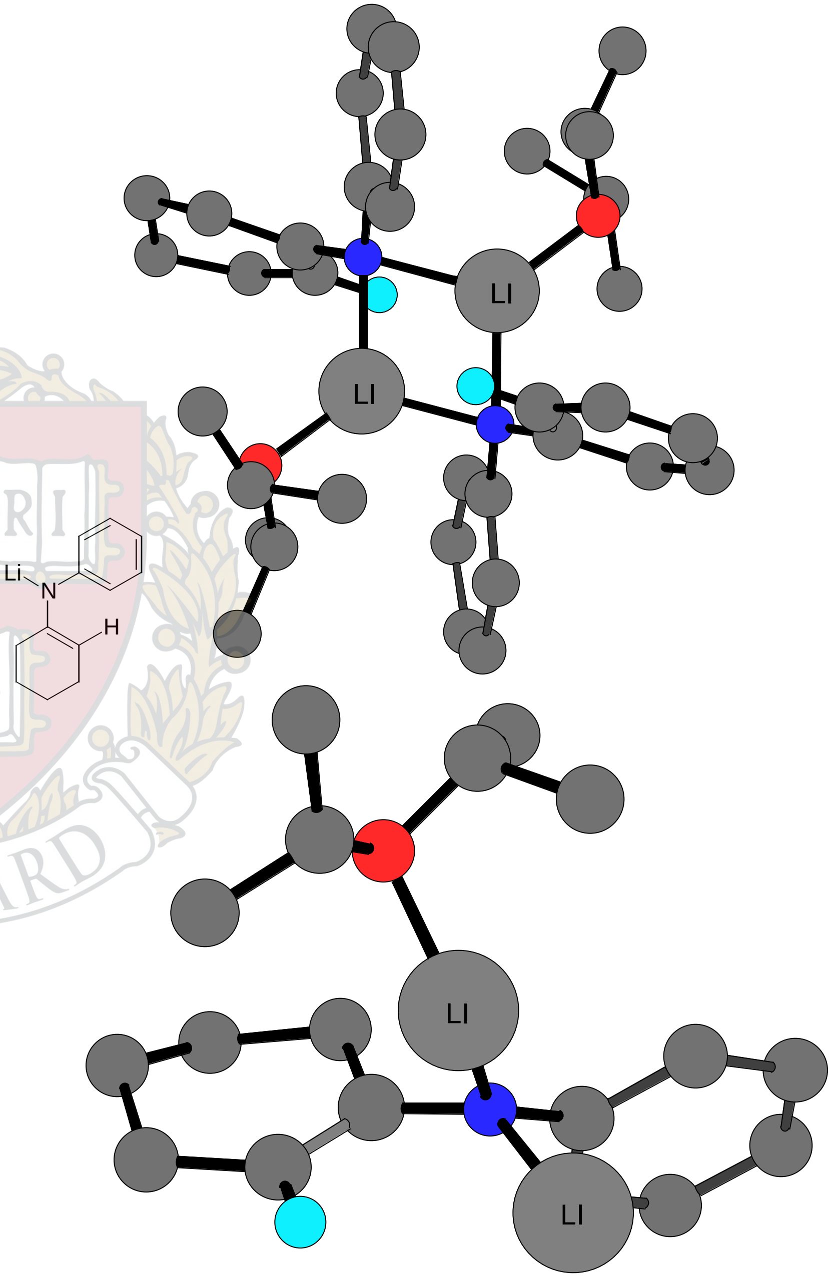


Enders in *Asymmetric Synthesis*, **1984**; Vol 3, Chapter 4, pp 275-339

Metalloenamine X-ray Structures

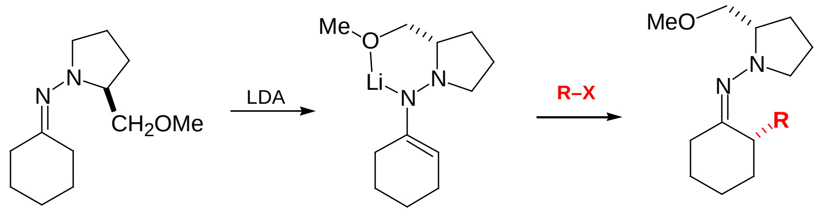


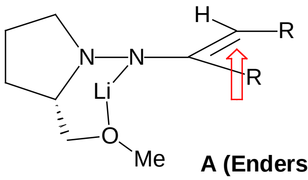
Collum & Clardy, *JACS* **1984**, *106*, 4865



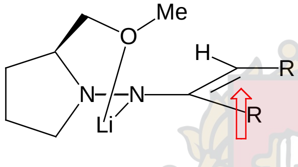
SAMP-Metalloenamine X-ray Structure

Chiral Metallated Hydrazones



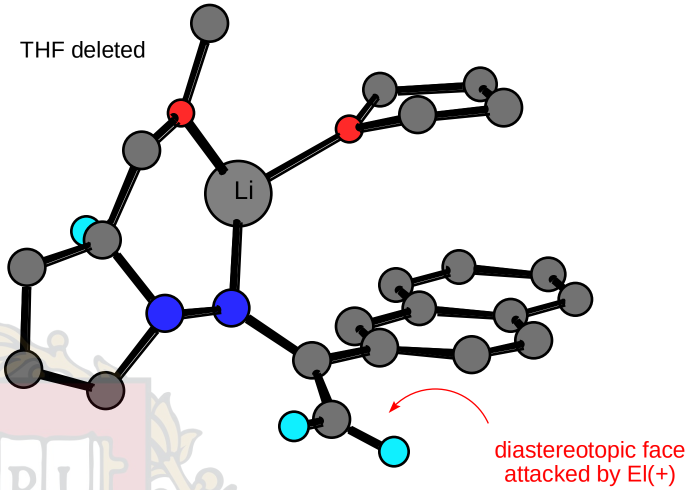


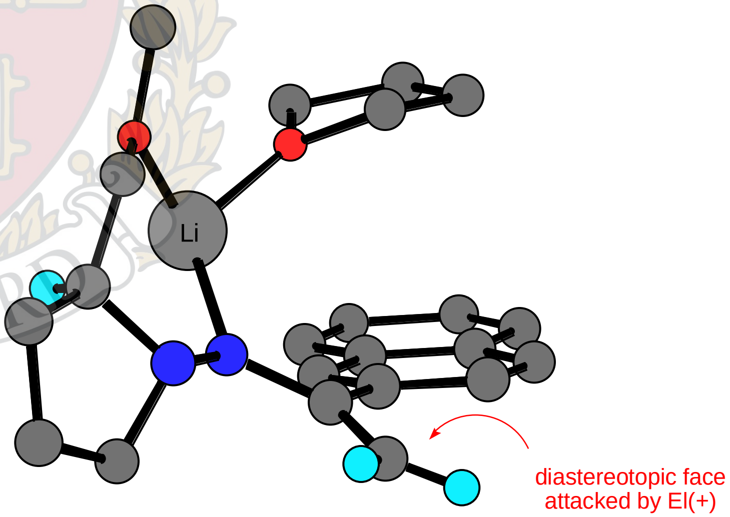
A (Enders)



B

Which of the reactive chelate conformations are we to begin our analysis from?





For a review of this methodology see Enders, D. in *Asymmetric Synthesis*.; Morrison, J. D., Ed.; AP: New York, **1984**; Vol. **3**, p 275-339.

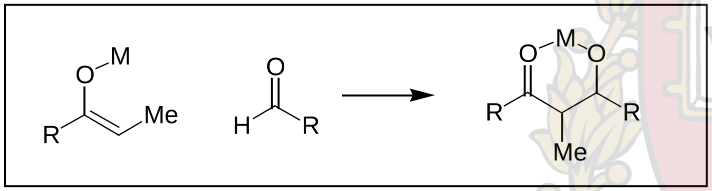
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 24

The Aldol Reaction–1



- Polyketide Biosynthesis
- Historical Perspective on the Aldol Reaction
- Aldol Diastereoselectivity
- Enolate Diastereoface Selectivity
- Absolute Control in the Aldol Process

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Matthew D. Shair

Wednesday,
November 13, 2002

Assigned Reading

Stereoselective Aldol Reactionsw in the Synthesis of Polyketide natural Products, I. Paterson et al. in Modern Carbonyl Chemistry, pp 249-297, J. Otera, Ed. Wiley VCH, **2000 CCB Library**

Ager, D. J., I. Prakash, et al. (**1997**). “Chiral oxazolidinones in asymmetric synthesis.” Aldrichimica Acta 30(1): 3-12

Other Useful References

Evans, D. A., J. V. Nelson, et al. (**1982**). “Stereoselective Aldol Condensations.” Top. Stereochem. 13: 1.

Heathcock, C. H. (**1984**). The Aldol Addition Reaction. Asymmetric Synthesis. Stereodifferentiating Reactions, Part B. J. D. Morrison. New York, AP. 3: 111.

Oppolzer, W. (**1987**). “Camphor Derivatives as Chiral Auxiliaries in Asymmetric Synthesis.” Tetrahedron **43**: 1969.

Heathcock, C. H. (**1991**). The Aldol Reaction: Acid and General Base Catalysis. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 133.

Heathcock, C. H. (**1991**). The Aldol Reaction: Group I and Group II Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 181.

Kim, B. M., S. F. Williams, et al. (**1991**). The Aldol Reaction: Group III Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 239.

Franklin, A. S. and I. Paterson (**1994**). “Recent Developments in Asymmetric Aldol Methodology.” Contemporary Organic Synthesis 1: 317-338.

Cowden, C. J. and I. Paterson (**1997**). “Asymmetric aldol reactions using boron enolates.” Org. React. (N.Y.) 51: 1-200.

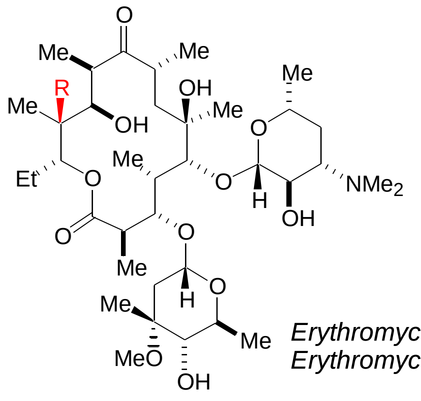
Nelson, S. G. (**1998**). “Catalyzed enantioselective aldol additions of latent enolate equivalents.” Tetrahedron: Asymmetry 9(3): 357-389.

Mahrwald, R. (**1999**). “Diastereoselection in Lewis-acid-mediated aldol additions.” Chem. Rev. 99(5): 1095-1120.

"Nature, it seems, is an organic chemist having some predilection for the aldol and related condensations."

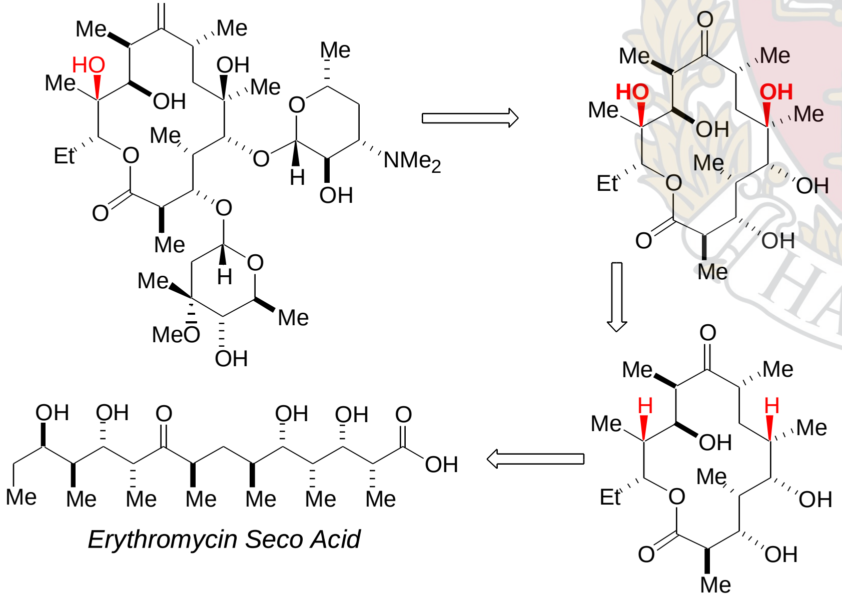
J. W. Cornforth

"That Outpost of Empire, Australia
Produces some Curious Mammalia
The Kangaroo Rat
The Blood-sucking Bat
and Aurthur J. Birch, inter alia."



Erythromycin A, R = OH
Erythromycin B, R = H

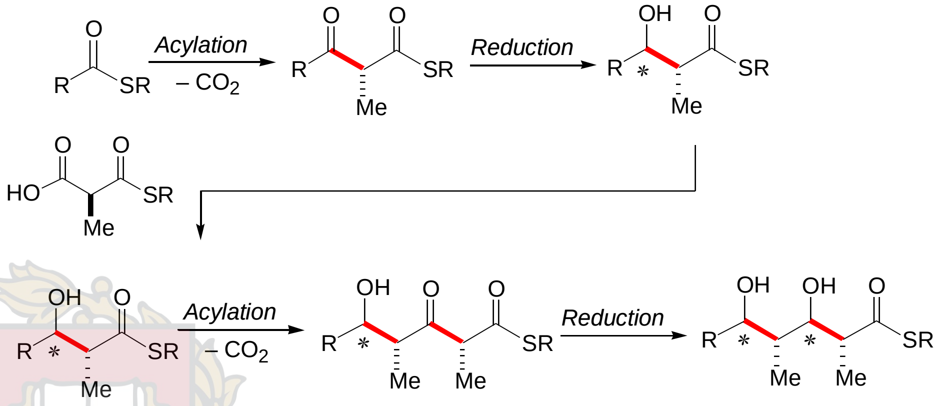
Retro-biosynthesis

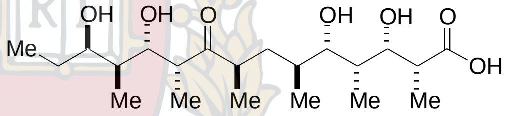


Erythromycin Seco Acid

Recent overview: Staunton, *Angew. Chem. Int. Edit.* **1991**, *30*, 1302-1306

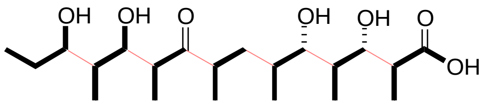
Polypropionate Biosynthesis: The Elementary Steps





Erythromycin Seco Acid

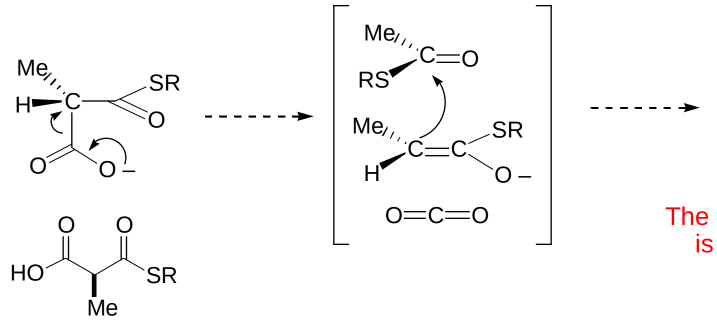
The 7 Propionate Subunits



The Acylation Event

Decarboxylation-Acylation could either be stepwise (Option A) or concerted (Option B).

The stepwise Option

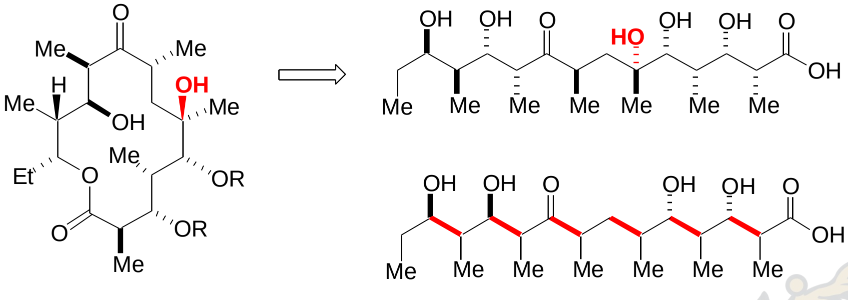


The overall acylation is stereospecific

See Lecture 23; page 23-08 for first laboratory example

Polypropionate Biosynthesis: A Laboratory Simulation

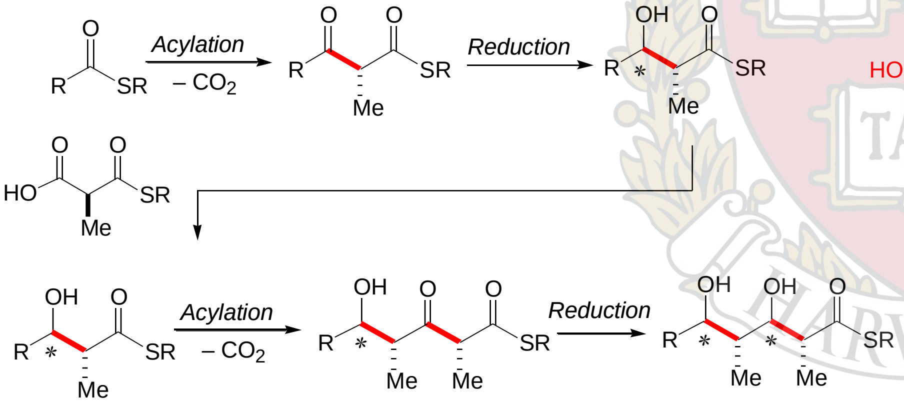
Polypropionate & Polyacetate Biosynthesis: Develop a Laboratory Simulation



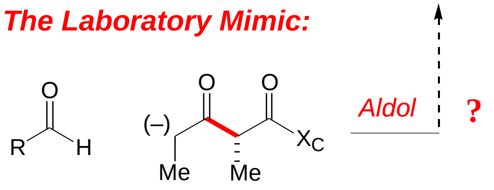
Erythrolide B

The 7 Propionate Subunits

Polypropionate Biosynthesis: The Elementary Steps

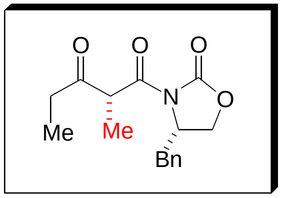


The Laboratory Mimic:

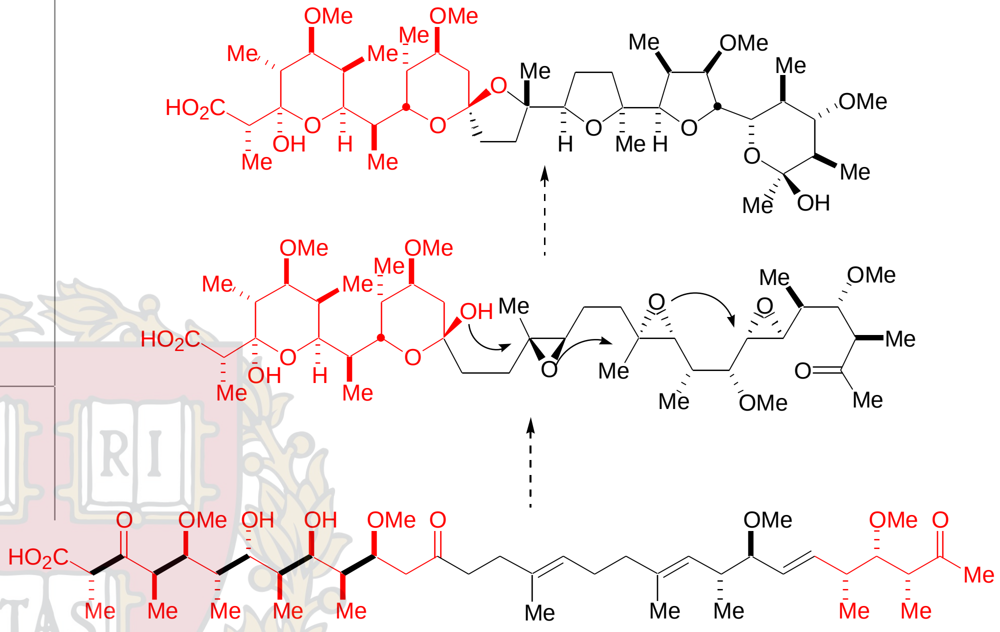


See Lecture 23; page 23-08:
*with M. Ennis JACS **1984**, 106, 1154.*

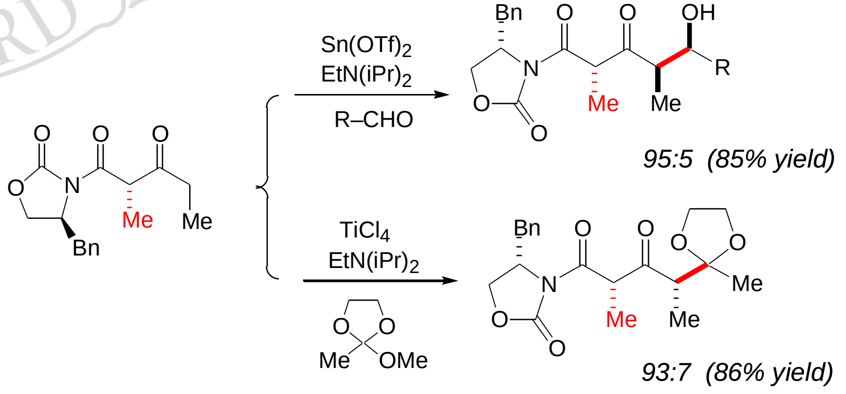
Dipropionyl Synthon



Latter Stages of Lonomycin Biosynthesis



Cane, Celmer, Westley *JACS* **1983**, *105*, 3594



with Ratz, Huff, & Sheppard, *JACS* **1995**, *117*, 3448

The Aldol Reaction: Early Contributions

General Reviews of the Aldol Literature:

Mukaiyama in *Organic Reactions*, **1982**; Vol 28, pp 203-331
Evans in *Topics in Stereochemistry*, **1982**; Vol 13, pp 1-115
Heathcock in *Asymmetric Synthesis*, **1984**; Vol 3, pp 111-212

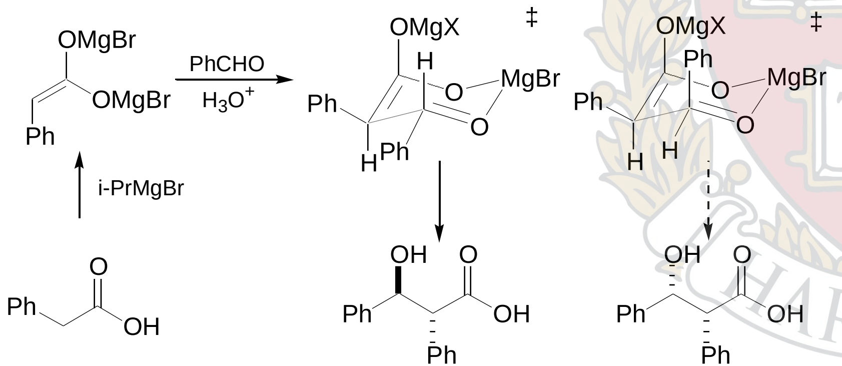
Comprehensive Organic Synthesis, **1991**; Vol 2

Group I & II metal enolates: Heathcock; Chapter 1.6, pp 181
Group III metal enolates: Masamune; Chapter 1.7, pp 239
Transition metal enolates: Paterson; Chapter 1.9, pp 301

Control relative stereochemical relationships

Zimmerman 1957:

Proposed chair-like geometry for the Ivanov Reaction



ratio, 75:25

Zimmerman recognized that diastereoselection should be a function of the relative sizes of the substituents on the carbonyl component.

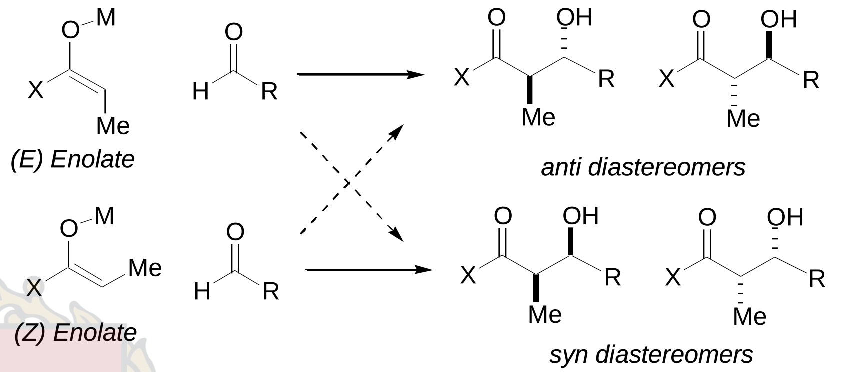
He also speculated on the role that the metal center might play in controlling the process.

The only flaw in the study was that he failed to determine whether the aldol adducts were stable to the reaction conditions.

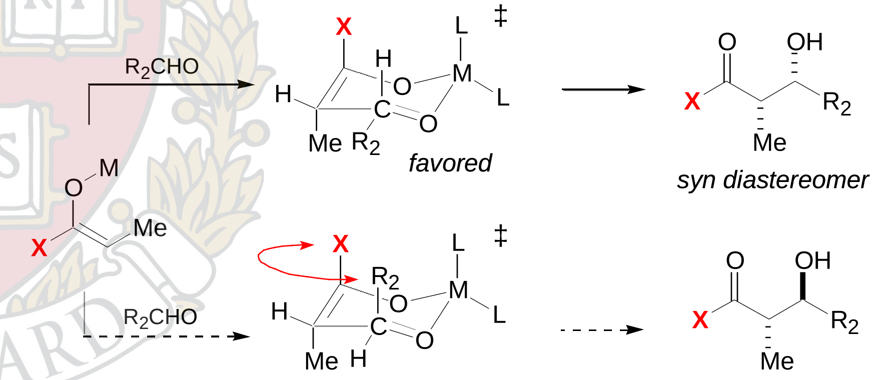
Zimmerman, *J. Am. Chem. Soc* ***1956***, *79*, 1920

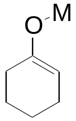
DuBois 1965-67:

Rough correlation between enolate stucture & product stereochemistry for alkali and alkaline earth enolates



Zimmerman-Traxler Model for *(Z)* Enolates



		syn:anti	
X = CMe_3	M = Li	> 98 : 2	Heathcock 1977
	M = MgBr	> 95 : 5	DuBois 1972
X = C_6H_5	M = Li	80 : 20	
	M = Li	48 : 52	
	M = $AlEt_2$	50 : 50	House 1971

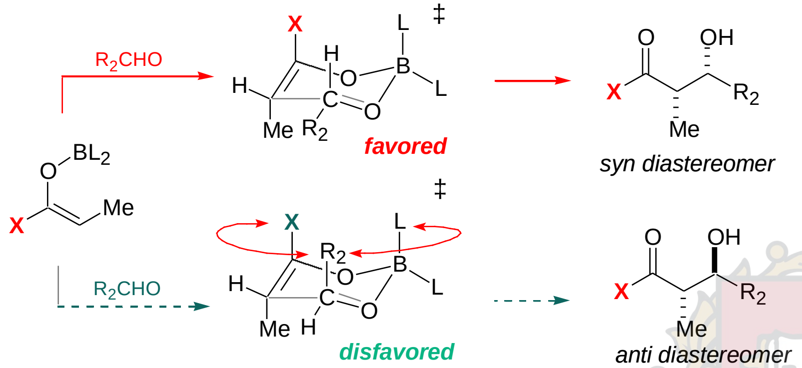
Stereocontrol optimal for "large" X; the reaction is not general.

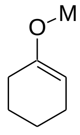
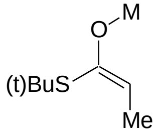
The Aldol Reaction: Boron Enolates

Why Boron?

To tighten up the transition state.
Design TS where control can come
exclusively from metal center

M–O → B–O   M–C → B–C
1.9-2.2 Å   1.4-1.5 Å   2.0-2.2 Å   1.5-1.6 Å



	M	syn:anti	
X = CMe$_3$	M = Li	> 98 : 2	Heathcock 1977
	M = MgBr	> 95 : 5	DuBois 1972
	M = BBu$_2$	> 97 : 3	DuBois 1972
X = C$_6$H$_5$	M = Li	80 : 20	Evans, Masamune, 1979-81
	M = BBu$_2$	> 97 : 3	
X = Et	M = Li	80 : 20	
	M = BBu$_2$	> 97 : 3	
	M = Li	48 : 52	House 1971
	M = AlEt$_2$	50 : 50	Yamamoto 1977
	M = BBu$_2$	33 : 67 (ether)	
	M = BBu$_2$	17 : 83 (pentane)	Evans/masamune, 1979-81
	M = BCy(thex)	6 : 94 (CH$_2$Cl$_2$)	
	M = B(Cyp)$_2$	<5 : 95 (pentane)	

Evans et al. *JACS **1979**, 101,* 6120-6123; *JACS **1981**, 103,* 3099-3111

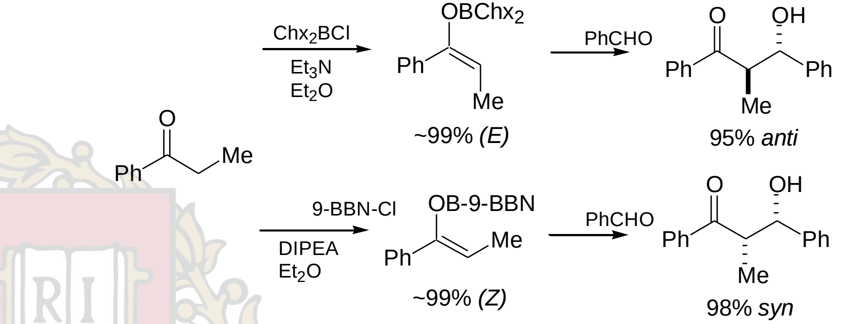
Masamune, *Tet. Lett **1979**,* 1665, 2225, 2229, 3937

Are (E) enolates intrinsically less diastereoselective?

Now that there are good methods for preparing (E) enolates, it appears that both enolate geometries are nearly equivalent.

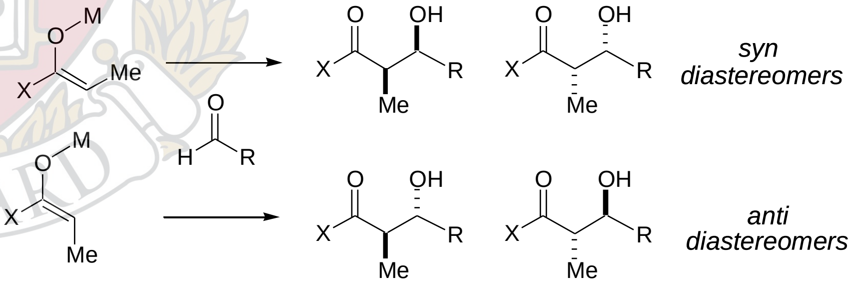
Dialkylboron chlorides (Brown)
JACS. **1989**, *111*, 3441-3442.
J. Org. Chem. **1992**, *57*, 499-504.
J. Org. Chem. **1992**, *57*, 2716-2721.
J. Org. Chem. **1992**, *57*, 3767-3772.
J. Org. Chem. **1993**, *58*, 147-153.

JACS. **1989**, *111*, 3441-3442.

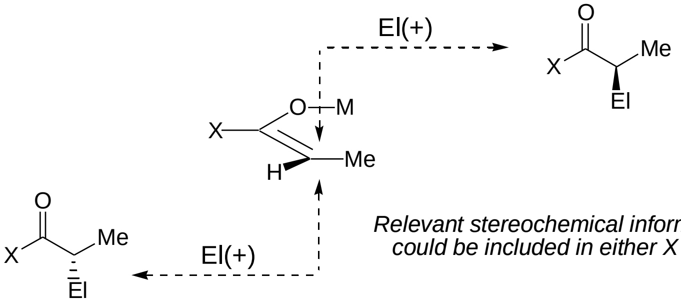


It appears that there is not a great difference in aldol diastereoselectivity

Dissection of the Aldol Problem: Selection of one enantioface



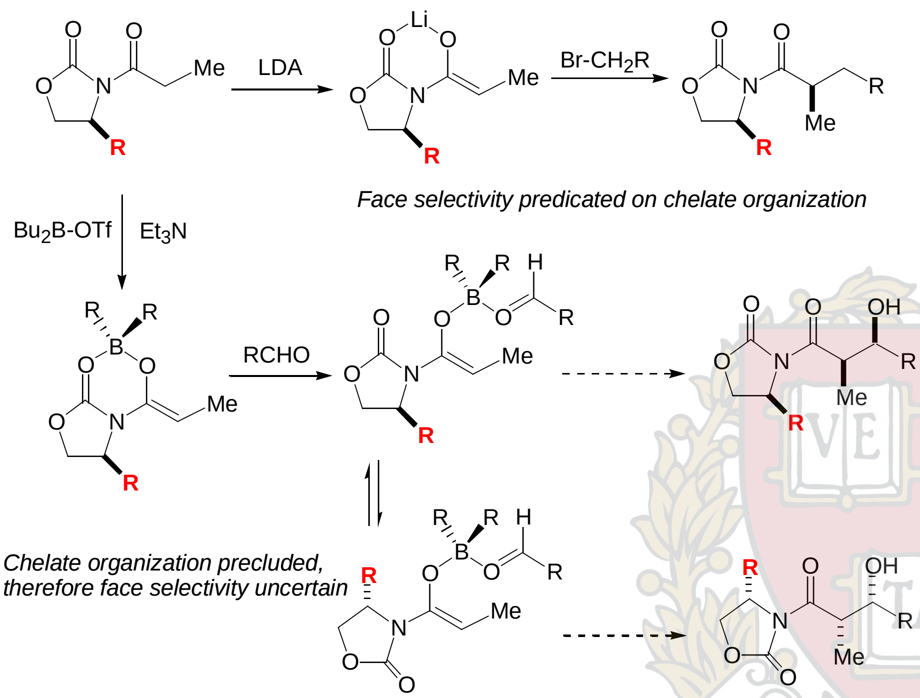
Control attack on the two enolate enantiofaces



Relevant stereochemical information could be included in either X or M

The Aldol Reaction: Boron Imide Enolates

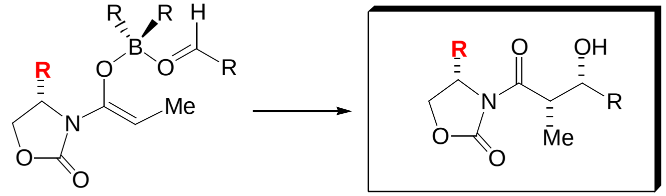
Imide Enolates: The problem of enolate face selectivity



Face selectivity predicated on chelate organization

Chelate organization precluded, therefore face selectivity uncertain

The aldol reaction selects for the opposite enolate diastereoface

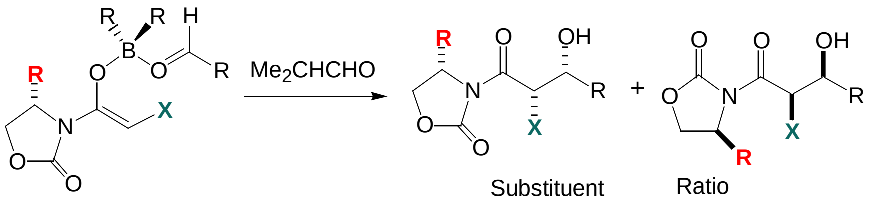


Result discovered but not predicted

diastereoselection > 98%

J. Am. Chem. Soc **1981**, *103*, 212-2129

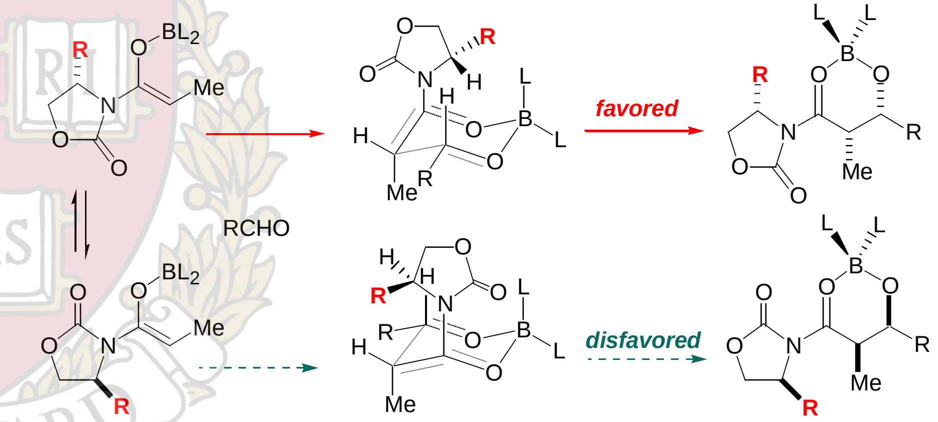
The Alpha substituent, X, plays pivotal role in aldol diastereoselection



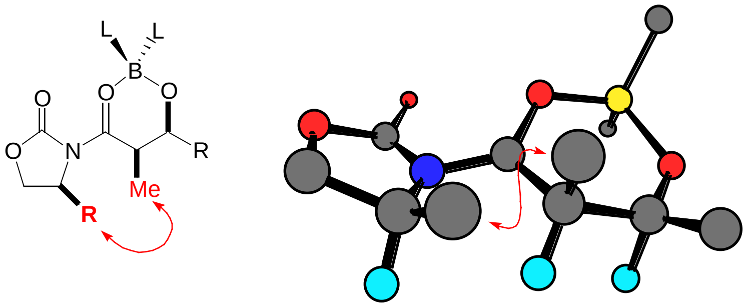
Substituent	Ratio
X = Me	> 300 : 1
X = SMe	60 : 1
X = H	1 : 1

How can we rationalize these data ?

Model for Asymmetric Induction (unpublished)



$\Delta\Delta G^{\ddagger}$ (273 K) ~ 2.6 kcal mol $^{-1}$

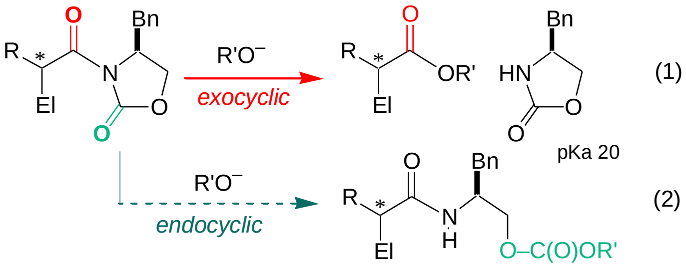


disfavored product diastereomer: The destabilizing interaction?

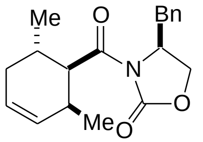
The Aldol Reaction: Imide Transformations

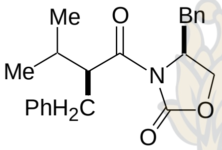
Imide Hydrolysis

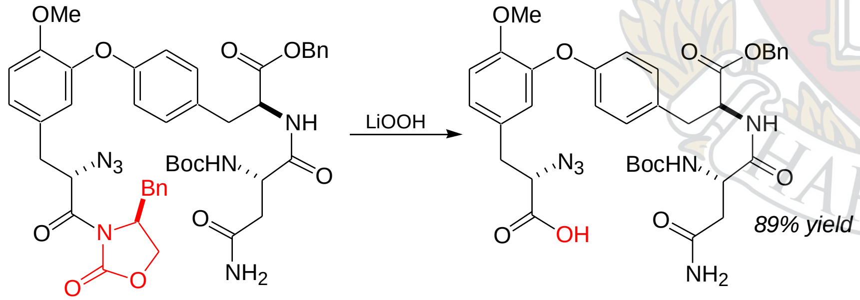
Imides may suffer attack at either of the two C=O functions (eq 1, eq 2)



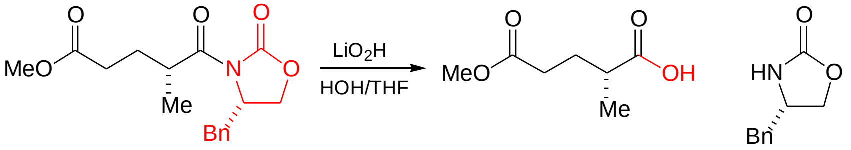
Product distribution a function of attacking nucleophile (*Tet. Lett.* **1987**, *28*, 6141)

Substrate	Reagent	Exo:Endo Ratio
	LiOH	0 : 100
	LiOOH	76 : 16

Substrate	Reagent	Exo:Endo Ratio
	LiOH	06 : 89
	LiOOH	96 : 04



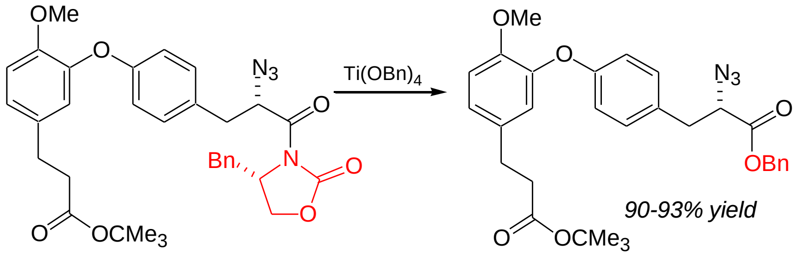
(OF-4949 Synthesis) JACS **1989**, *111*, 1063



M. Bilodeau, unpublished results

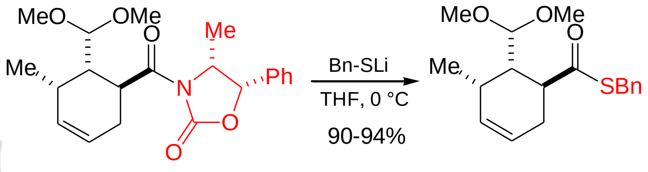
complete hydroytic selectivity possible

Trans-esterification

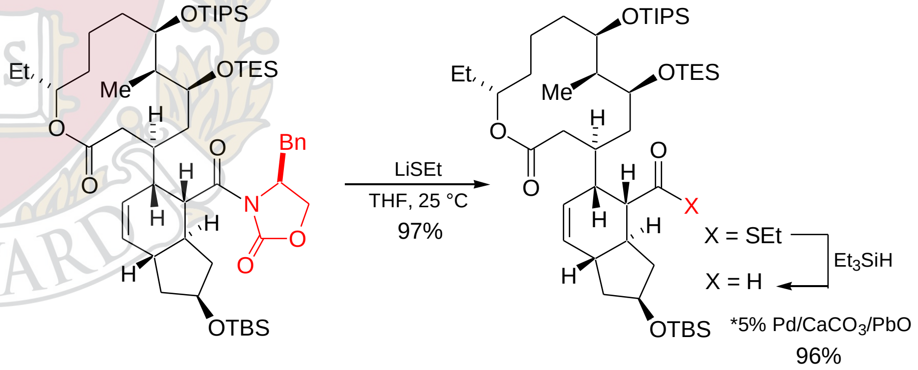


*(OF-4949 Synthesis) JACS***1989**, *111*, 1063

Trans-thioesterification:



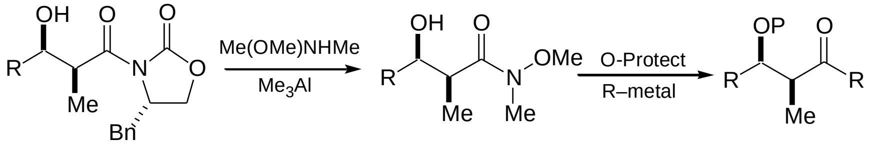
Damon, *Tet. Lett.* **1990**, *31*, 2849-2852



(Lepicidin Synthesis) J. Am. Chem. Soc **1993**, *115*, 4497-4513

$RCOSR \longrightarrow RCHO$ Fukuyama, *J. Am. Chem. Soc* **1990**, *112*, 7050-7051

Transamination to Weinreb Amides (see Handout 23A)

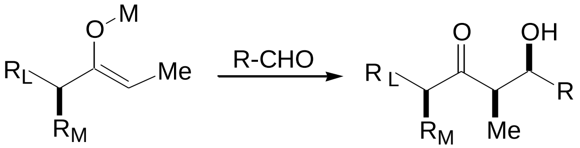


for recent examples see, *J. Am. Chem. Soc* **1992**, *114*, 9434-9453

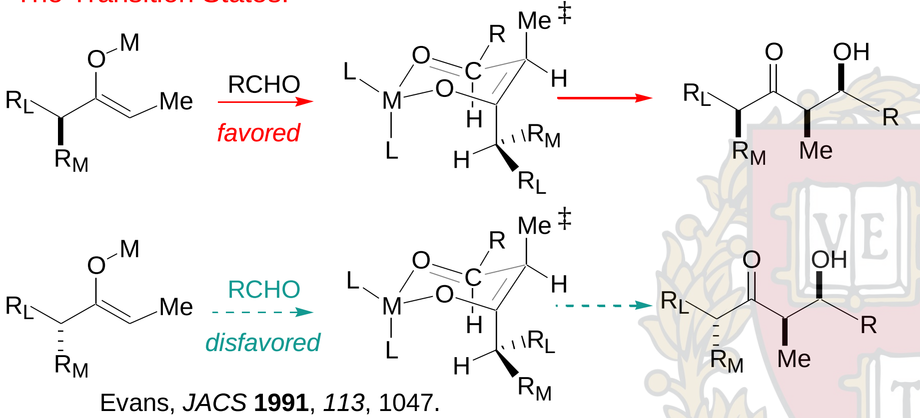
The Aldol Reaction: Syn Aldol Rxns of Chiral Ethyl Ketones

General Reaction for Syn Aldols: M = B, Ti

M = B, Ti

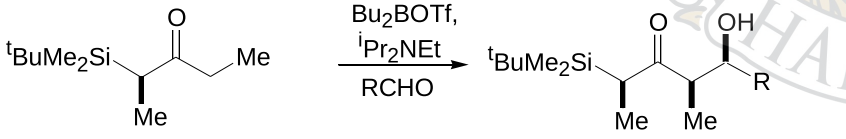


The Transition States:



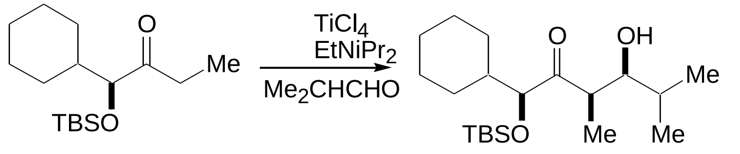
Evans, *JACS* **1991**, *113*, 1047.

Examples:



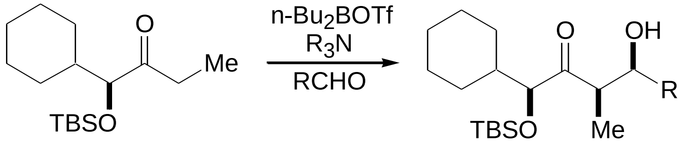
Enders *ACIEE* **1988**, *27*, 581.

Diastereoselection = 96-98%



Evans, *JACS* **1991**, *113*, 1047.

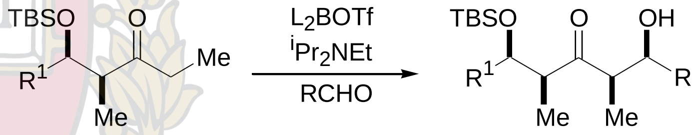
Diastereoselection: 99:1 (81%)



TBS = $SiMe_2{}^tBu$

R	Diastereoselection
Ph	97:3
Et	98:2
$BnOCH_2CH_2$	96:4
Me_2CH	>99:<1

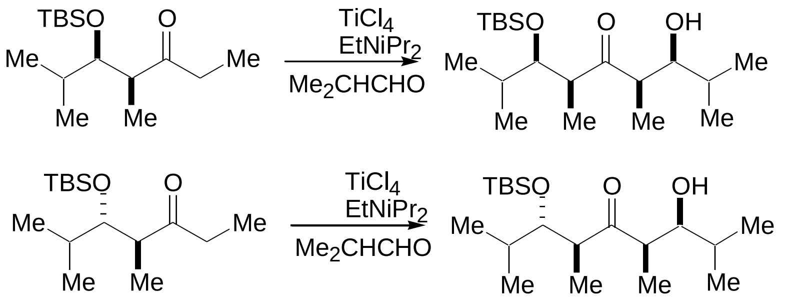
Masamune, *JACS* **1981**, *103*, 1566.



This system does not give a completely clean (Z) enolate

L	Diastereoselection
Bu	63:37 - 84:16
9-BBN	83:17 - 85:15
(-)-Ipc	72:28
(+)-Ipc	91:9 - 94:6

Paterson, McClure, *Tet.Lett.* **1987**, *28*, 1229.

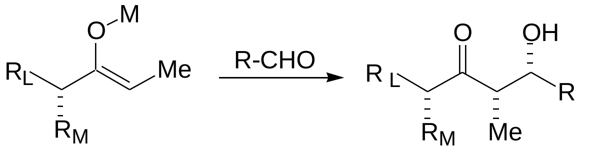


Evans, *JACS* **1991**, *113*, 1047.

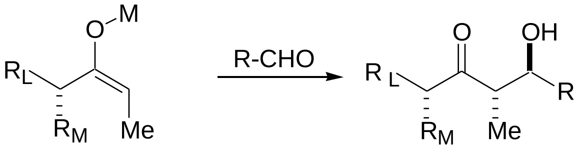
Diastereoselection: 95:5 (80-90%)

The Aldol Reaction: Anti Aldol Rxns of Chiral Ethyl Ketones

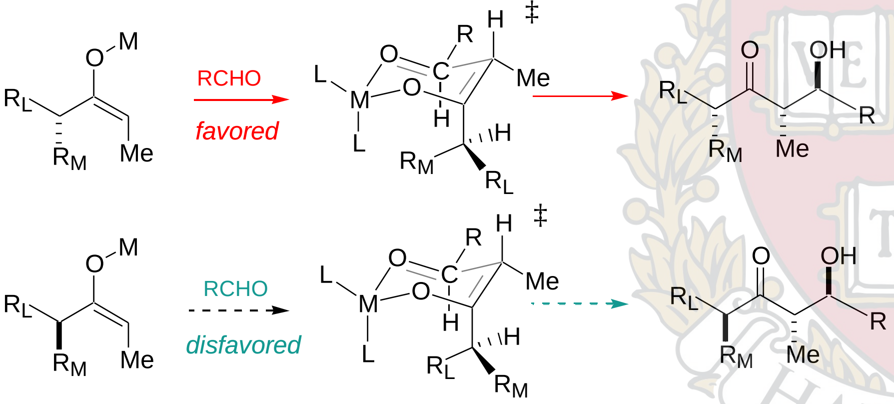
General Reaction
for
Syn Aldols:



General Reaction
for
Anti Aldols:

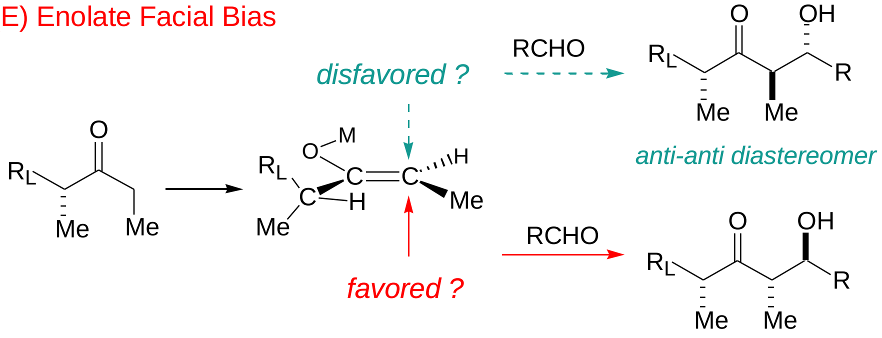


The Transition States:



Evans, *JACS* **1991**, *113*, 1047.

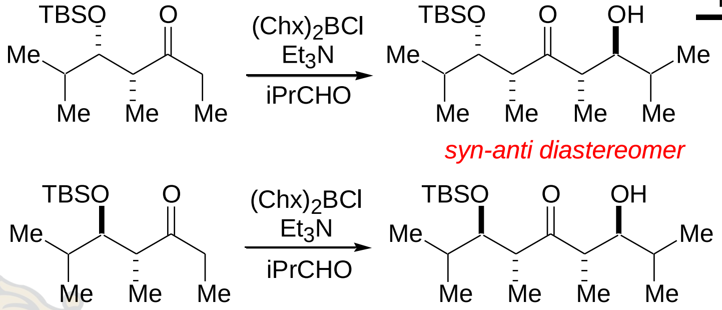
(E) Enolate Facial Bias



anti-anti diastereomer

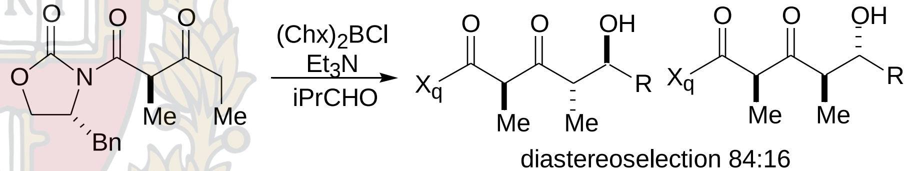
syn-anti diastereomer

Examples:



Diastereoselection major : Σ others
94:6 (90%)
96:4 (75%)

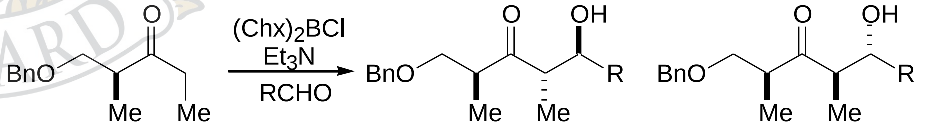
However, the preceding precedent does not extend to these systems:



diastereoselection 84:16

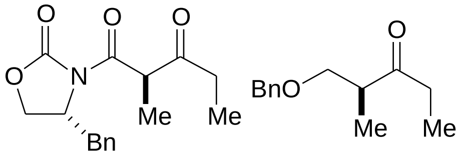
D. A. Evans, H. P. Ng, J. S. Clark, D. L. Rieger *Tetrahedron*, **1992**, *48*, 2127-2142.

An analogous case:



diastereoselection 95:5

I. Patterson, J. M. Goodman, M. Isaka *Tetrahedron Lett*. **1989**, *30*, 7121-7124.

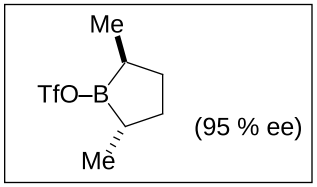


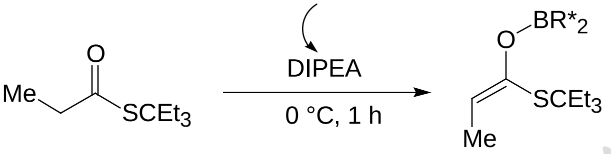
These enolates do not comply with steric analysis: → electronic effects?

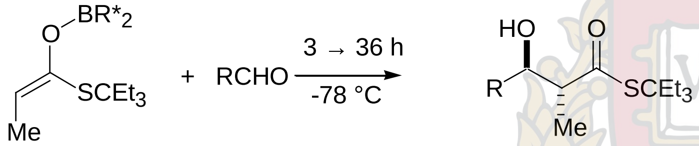
Tetrahedron, **1992**, *48*, 2127-2142.

The Aldol Reaction: Metal-Centered Chirality

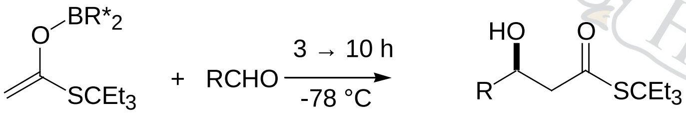
Masamune, Sato, Kim, Wollmann *J. Am. Chem. Soc.* **1986**, *108*, 8279-8281.







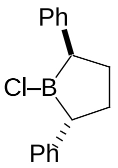
RCHO	Yield, %	anti/syn	ee % (corrected)
n-PrCHO	91	33:1	93 (98)
i-PrCHO	85	30:1	95 (99)
t-BuCHO	95	30:1	96 (99.9)
c-C_6H_{11}CHO	82	32:1	93 (98)
PhCHO	(71)	33:1	96 (99.8)

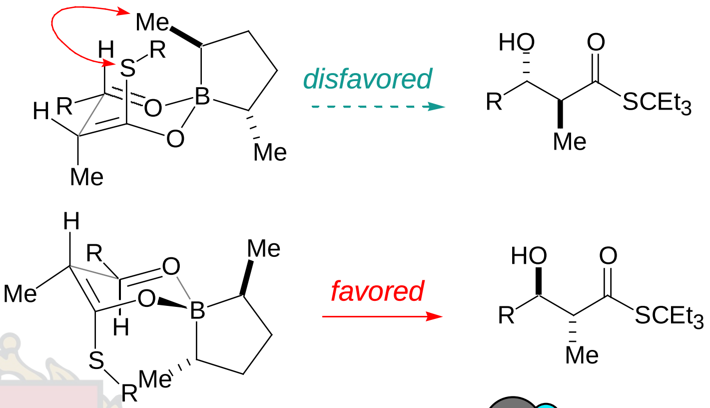


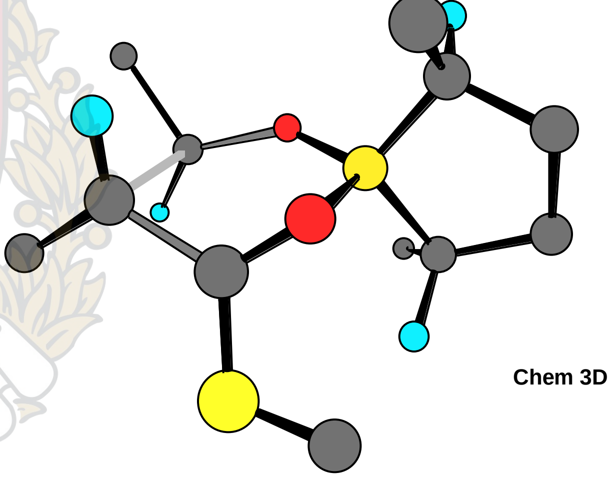
RCHO	Yield, %	ee % (corrected)
n-PrCHO	82	87 (91)
i-PrCHO	81	87 (92)
t-BuCHO	71	94 (98)
c-C_6H_{11}CHO	95	86 (90)
PhCHO	78	88 (92)

See analogous study by Reetz

Reetz *Tetrahedron Lett.* **1986**, 4721



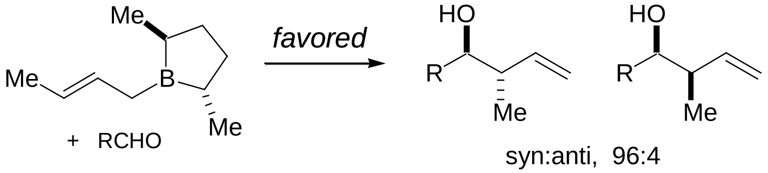




Chem 3D

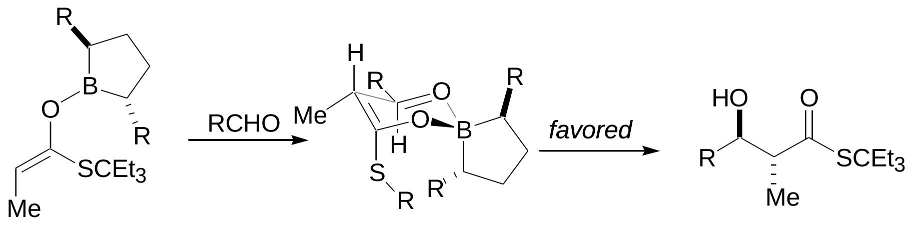
Analogous Carbonyl Allylation

Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, *52*, 4831

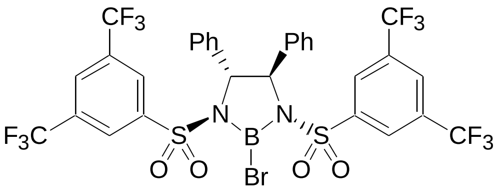


syn:anti, 96:4
enantioselection: 95-97%

Masamune-Reetz Analogy:



Metal-Based Chiral Auxilliary:



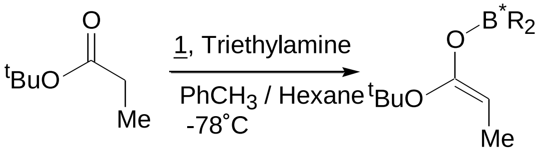
1

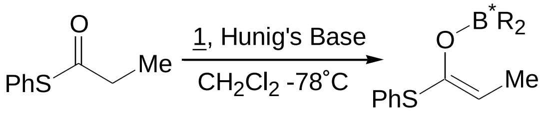
References:
(Corey) JACS. **1989**,*111*, 5494
(Corey) JACS. **1990**,*112*, 4977
(Corey) TL. **1991**,*32*, 2857
(Corey) TL. **1993**,*34*, 1737.

Does this reagent perform in accord with the Masamune-Reetz analogy?
Note: The sulfonamide nitrogens are pseudo-tetrahedral

Enolization:

Either enolate geometry possible with proper choice of base, solvent, and substrate.

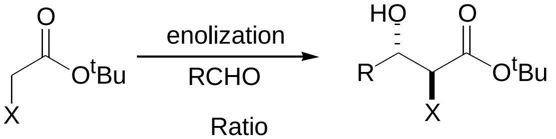




A mechanistic proposal for enolization control is presented in paper

(Corey) JACS. **1989**,*111*, 5494

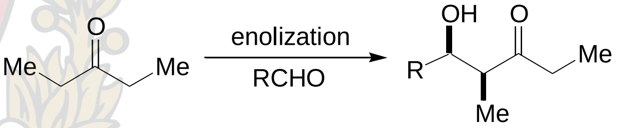
Chiral Anti Aldol Reaction: *JACS* **1990**,*112*, 4977; *TL* **1991**,*32*, 2857.



(R)	(X)	Ratio syn:anti	% ee	Yield
Ph-	Me	2 : 98	94	93 %
chex-	Me	6 : 94	75	82 %

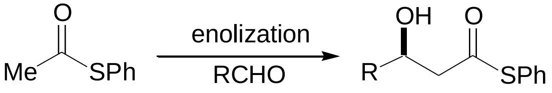
(R)	(X)	Ratio syn:anti	% ee	Yield
Ph-	Br	2 : 98	96	86 %
chex-	Br	2 : 98	91	65 %

Chiral Syn Aldol Reaction *JACS* **1989**,*111*, 5494.



(R)	Ratio syn:anti	% ee	Yield
Ph-	94 : 6	97	86 %
Me$_2$CH-	98 : 2	95	91 %
MeCH$_2$-	>98 : 2	>98	68 %

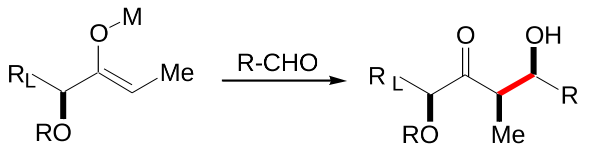
Chiral Acetate Aldol Reaction *JACS* **1989**,*111*, 5494.



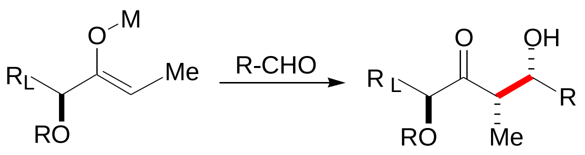
(R)	% ee	Yield
Ph-	91	84 %
Me$_2$CH-	83	82 %

The Aldol Reaction: Chelate vs Steric Control

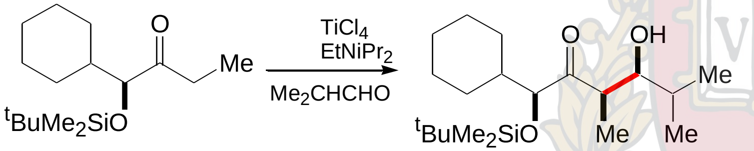
Reference Rxn



Chelate-Organized Variant

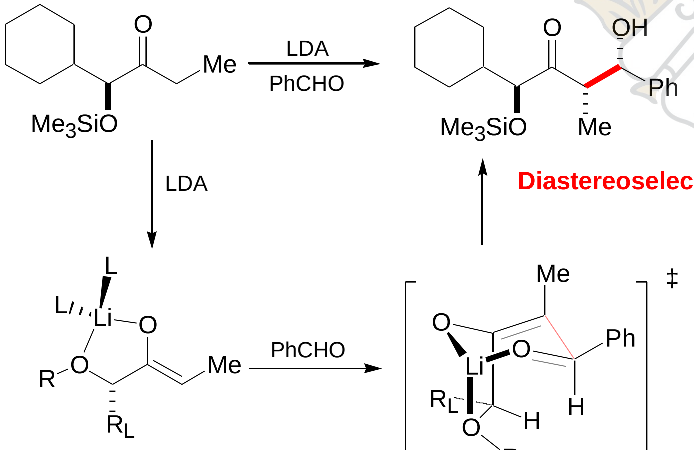


Nonchelate Reaction



Masamune, *JACS* **1981**, *103*, 1566 (boron enolate)
Evans, *JACS* **1991**, *113*, 1047 (titanium enolate)

Diastereoselection: 99:1

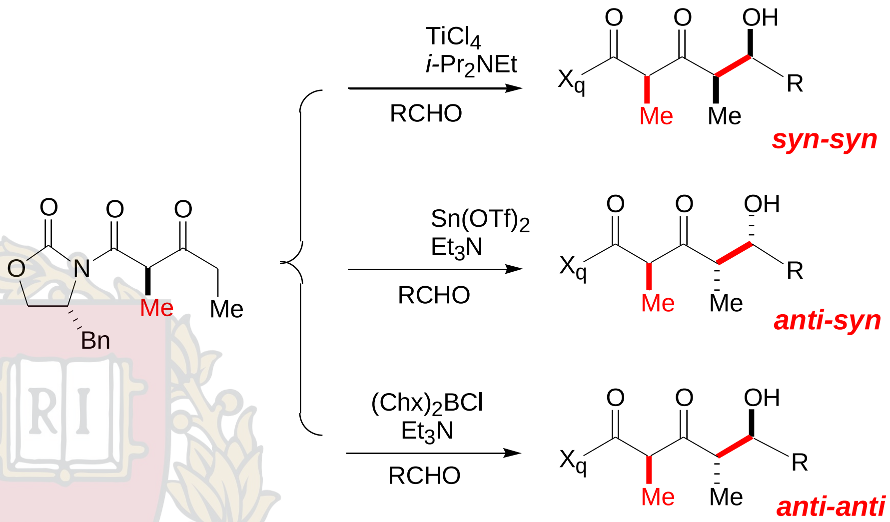


Diastereoselection: 90:10

Chelation possible for R = Bn, TMS
but marginal for TBS

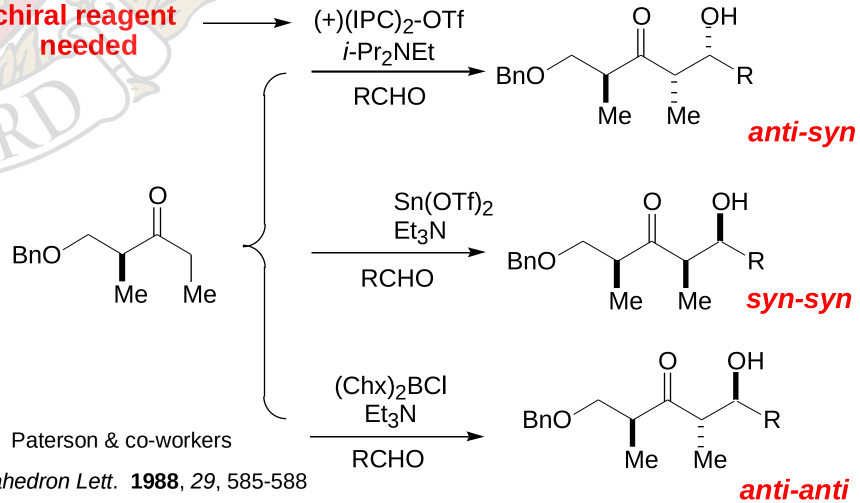
Thorton, *Tet. Let.* **1990**, *31*, 6001

Complimentary aldol reactions may be obtained by changing metal as well as enolate geometry



JACS, **1990**, *112*, 866; *Tetrahedron*, **1992**, *48*, 2127-2142.

chiral reagent needed



Paterson & co-workers

Tetrahedron Lett. **1988**, *29*, 585-588
Tetrahedron Lett. **1989**, *30*, 7121-7124
Tetrahedron Lett. **1992**, *33*, 4233-4236

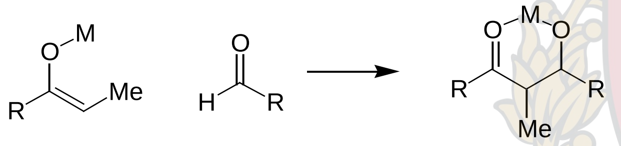
http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 25

The Aldol Reaction–2



- (E) & (Z) Enolates: Felkin Selectivity
- Double Stereodifferentiating Aldol Reactions
- The Mukaiyama Aldol Reaction Variant
- Allylmetal Nucleophiles as Enolate Synthons

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Matthew D. Shair

Friday,
November 15, 2002

Assigned Reading

Stereoselective Aldol Reactionsw in the Synthesis of Polyketide natural Products, I. Paterson et al. in Modern Carbonyl Chemistry, pp 249-297, J. Otera, Ed. Wiley VCH, **2000** **(handout)**

W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157. **(handout)**

Other Useful References

Evans, D. A., J. V. Nelson, et al. (**1982**). “Stereoselective Aldol Condensations.” Top. Stereochem. 13: 1.

Heathcock, C. H. (**1984**). The Aldol Addition Reaction. Asymmetric Synthesis. Stereodifferentiating Reactions, Part B. J. D. Morrison. New York, AP. 3: 111.

Oppolzer, W. (**1987**). “Camphor Derivatives as Chiral Auxiliaries in Asymmetric Synthesis.” Tetrahedron **43**: 1969.

Heathcock, C. H. (**1991**). The Aldol Reaction: Acid and General Base Catalysis. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 133.

Heathcock, C. H. (**1991**). The Aldol Reaction: Group I and Group II Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 181.

Kim, B. M., S. F. Williams, et al. (**1991**). The Aldol Reaction: Group III Enolates. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 239.

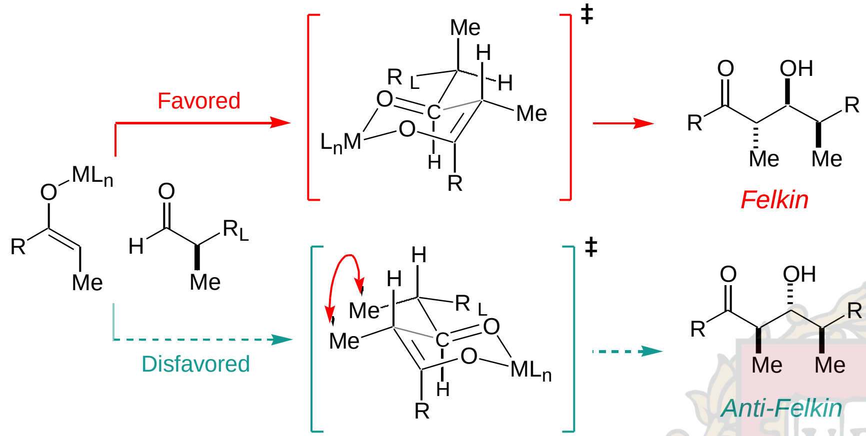
Franklin, A. S. and I. Paterson (**1994**). “Recent Developments in Asymmetric Aldol Methodology.” Contemporary Organic Synthesis 1: 317-338.

Cowden, C. J. and I. Paterson (**1997**). “Asymmetric aldol reactions using boron enolates.” Org. React. (N.Y.) 51: 1-200.

Nelson, S. G. (**1998**). “Catalyzed enantioselective aldol additions of latent enolate equivalents.” Tetrahedron: Asymmetry 9(3): 357-389.

Mahrwald, R. (**1999**). “Diastereoselection in Lewis-acid-mediated aldol additions.” Chem. Rev. 99(5): 1095-1120.

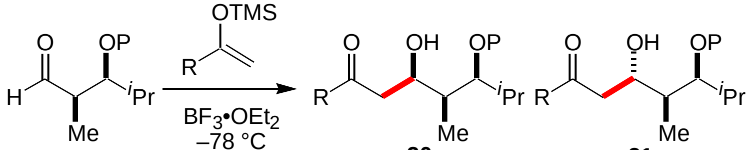
(E) Enolates Exhibit Felkin Aldehyde Diastereoface Selection



- ■ The illustrated syn-pentane interaction disfavors the anti-Felkin pathway.

Evans, Nelson, Taber, *Topics in Stereochemistry* **1982,** *13*, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157.

The Non-Reinforcing syn- RCHO is the most Interesting Dependence of the Selectivity of Felkin-controlled Reactions on Nu Size



19 P = PMB
6 P = TBS

20 Felkin/1,3-*syn*

21 *anti*-Felkin/1,3-*anti*

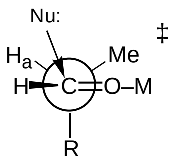
α-substituent dominates for Large Nu

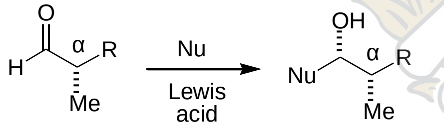
β-substituent dominates for small Nu

	P = PMB	P = TBS
R	**20 : 21**	**20 : 21**
t-Bu	96 : 04	94 : 06
i-Pr	56 : 44	75 : 25
Me	17 : 83	40 : 60

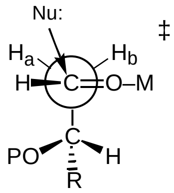
Background Information: The influence of β-OR substituents on RCHO

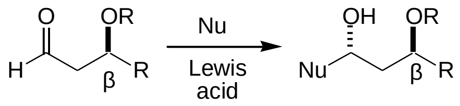
Evans, *JACS* **1996**, *118*, 4322-4343





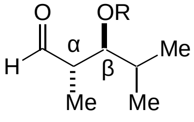
Felkin Selecton



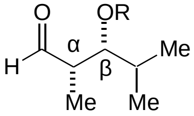


1,3-selection

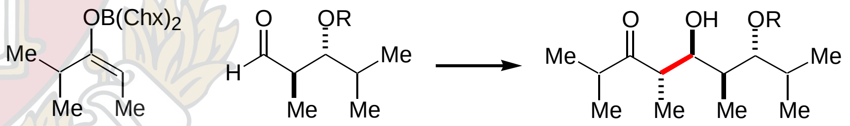
Therefore, one might conclude that:



stereocenters reinforcing



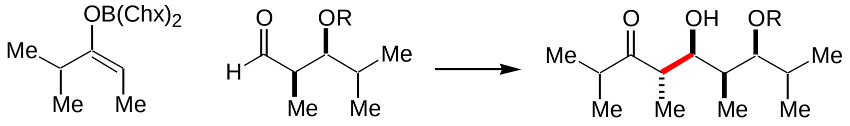
stereocenters non-reinforcing



both centers reinforcing

Felkin

	major : Σ minors	
R = TBS	99 : 1	(77% yield)
R = PMB	93 : 7	(84% yield)



centers non-reinforcing

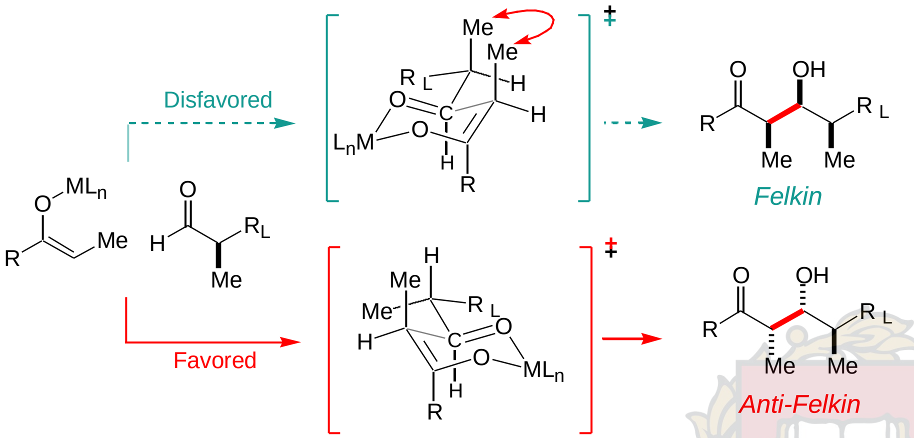
Felkin

	major : Σ minors	
R = TBS	94 : 6	(79% yield)
R = PMB	74 : 26	(82% yield)

Achiral (*E*) enolates preferentially add to the Felkin diastereoface
High *anti*:*syn* diastereoselectivity (≥ 97 : 3) is observed in all cases

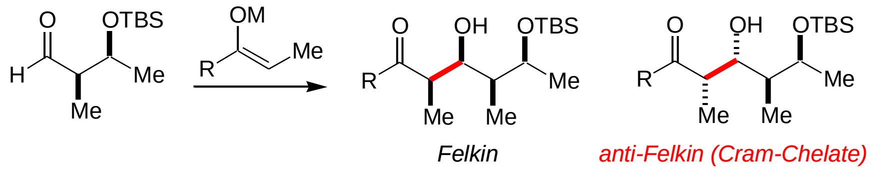
Evans etal. *JACS* ***1995***, *117*, 9073

(Z) Enolates Exhibit Anti-Felkin Aldehyde Diastereoface Selection

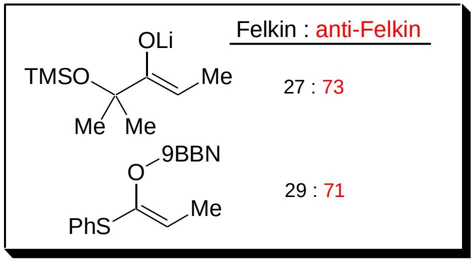


The illustrated syn-pentane interaction disfavors the Felkin pathway.

Evans, Nelson, Taber, *Topics in Stereochemistry* **1982,** *13*, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151-4157.



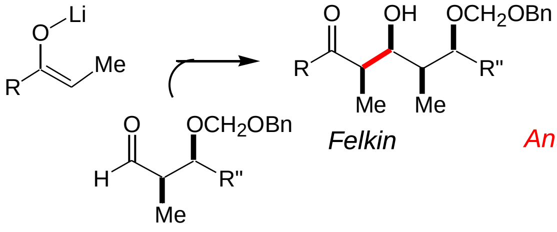
D. W. Brooks & Co-workers
Tetrahedron Lett. **1982**, *23*, 4991-4994.

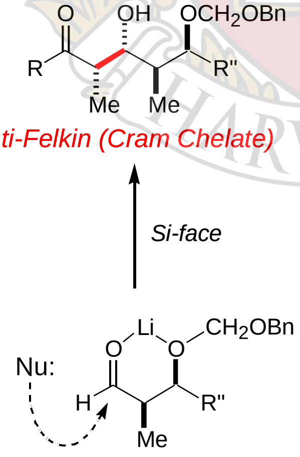


Felkin : anti-Felkin
27 : 73
29 : 71

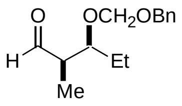
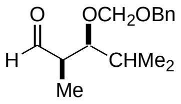
- The bulky OTBS group disfavors chelation. (see Keck, *JACS* **1986**, *108*, 3847.)
- The boron and lithium enolates display nearly equal levels of anti-Felkin selectivity.

An Early study rationalized results through chelated transition states:

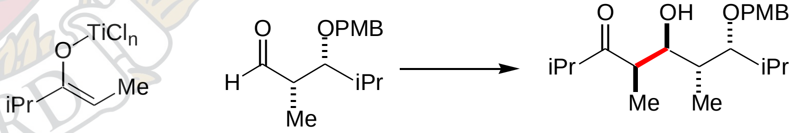




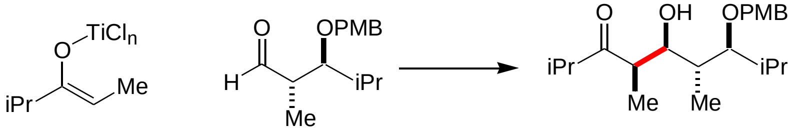
Masamune
JACS ***1982****, 104,* 5526

(R)	(R")	Felkin : Anti-Felkin
Et		17 : 83
C_6H_{11}		10 : 90
Et		13 : 87
C_6H_{11}		8 : 92

Titanium enolates exhibit the same trend



anti-Felkin : Felkin 77 : 23 (78%)

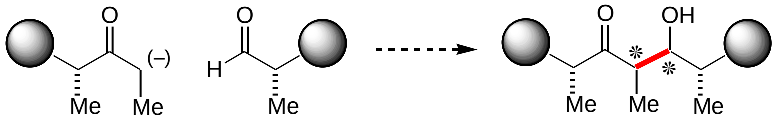


anti-Felkin : Felkin 56 : 44 (84%)

Evans etal. *JACS* ***1995****, 117,* 9073

Double Stereodifferentiating Bond Constructions-1

Double Stereodifferentiating Aldol Bond Constructions



Stereochemical Control Elements

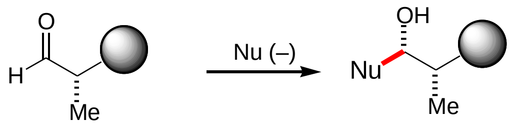
Enolate geometry

⇩

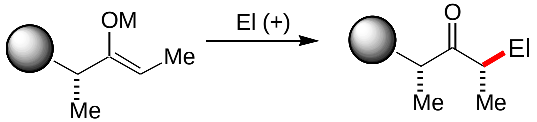
Enolate facial bias ⇨ Product Stereochemistry ⇦ Aldehyde facial bias

The Issue: Can one reliably take the diastereoselectivites of the individual reaction partners and use this information in the illustrated extrapolation:

The model reactions:

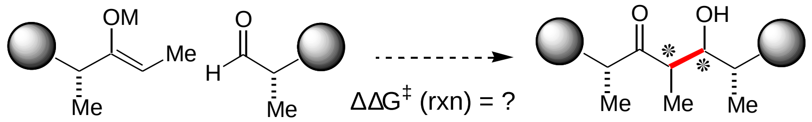


$\Delta\Delta G^{\ddagger}$ (aldehyde)



$\Delta\Delta G^{\ddagger}$ (enolate)

The extrapolation:

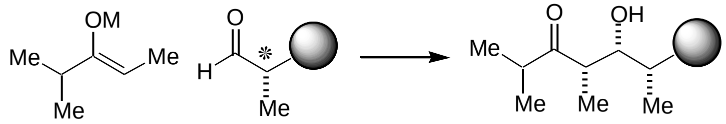


$\Delta\Delta G^{\ddagger}$ (rxn) = ?

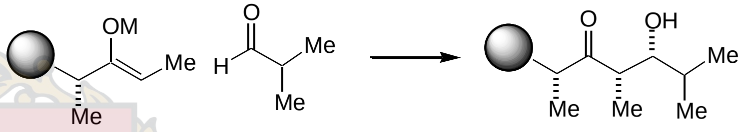
Masamune, *Angew. Chem. Int. Ed.* **1985**, *24*, 1-76

Matched reactant pair: Stereo-induction from both partners reinforcing

The reference reactions:

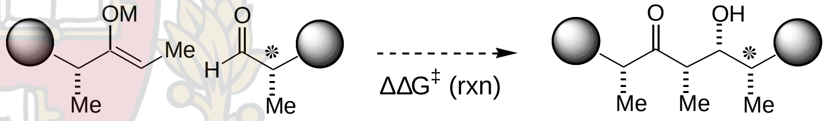


[aldehyde prod ratio] = 10/1



[enolate prod ratio] = 10/1

- The double stereodifferentiating situation: Stereoselectivity?



$\Delta\Delta G^{\ddagger}$ (rxn)

- The assumption: (Masamune, Heathcock)

It is presumed that useful information can be obtained from related achiral enolate & RCHO addition reactions and that the free energy contributions will be additive:

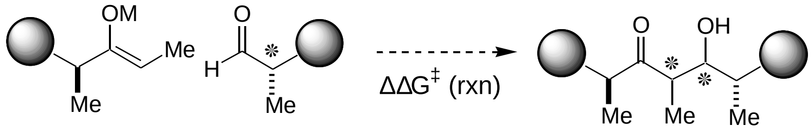
$$\Delta\Delta G^{\ddagger}\text{ (Rxn)} \sim \Delta\Delta G^{\ddagger}\text{ (enolate)} + \Delta\Delta G^{\ddagger}\text{ (RCHO)}$$

log [Product ratio] ~ log [enolate ratio] + log [aldehyde ratio]

[Product ratio] ~ [enolate prod ratio] x [aldehyde prod ratio]

- Hence, for the case at hand: [Product ratio] ~ [10] x [10] ~ 100

Mismatched reactant pair: Stereo-induction from partners nonreinforcing

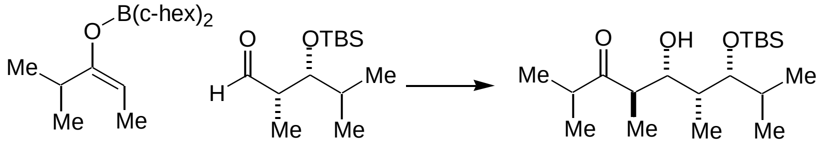


$\Delta\Delta G^{\ddagger}$ (rxn)

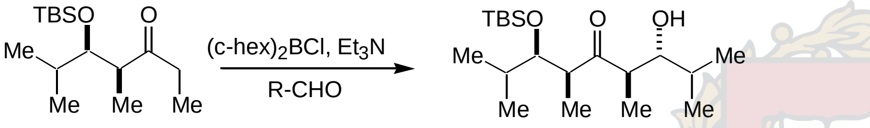
$$\Delta\Delta G^{\ddagger}\text{ (Rxn)} \sim \Delta\Delta G^{\ddagger}\text{ (enolate)} - \Delta\Delta G^{\ddagger}\text{ (RCHO)}$$

The Masamune-Heathcock generalizations hold to a point:

(E)-Boron Enolates: The reference reactions

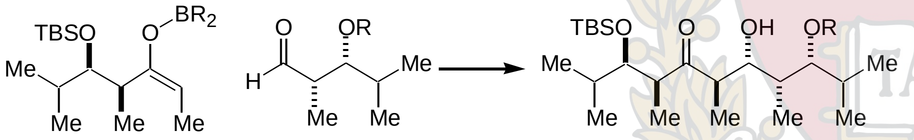


diastereoselection 94 : 6



diastereoselection 96 : 4

(E)-Boron Enolates: The matched cases

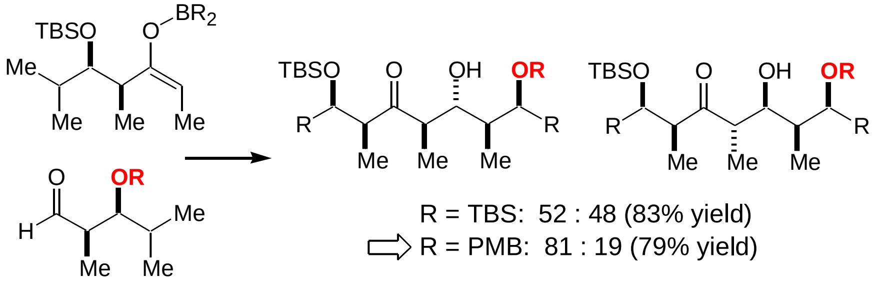


diastereoselection: anti : Σ others

R = TBS: >99 : 1 (85% yield)

R = PMB: >99 : 1 (84% yield)

(E)-Boron Enolates: The mismatched cases

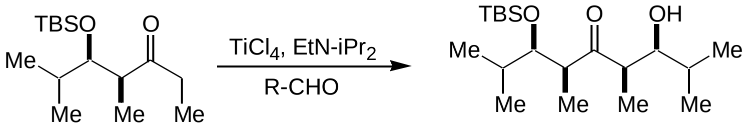


R = TBS: 52 : 48 (83% yield)

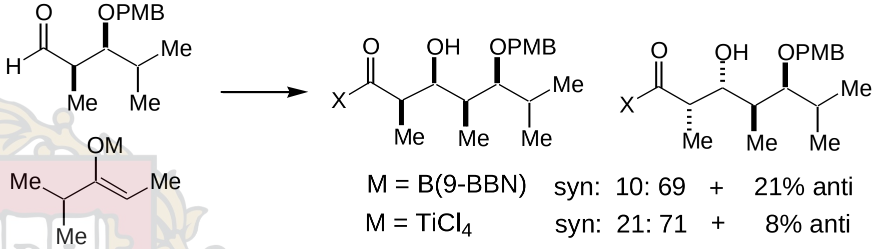
⇨ R = PMB: 81 : 19 (79% yield)

β-center on RCHO can play a significant role in this marginal situation

(Z)-Titanium Enolates: The reference reactions



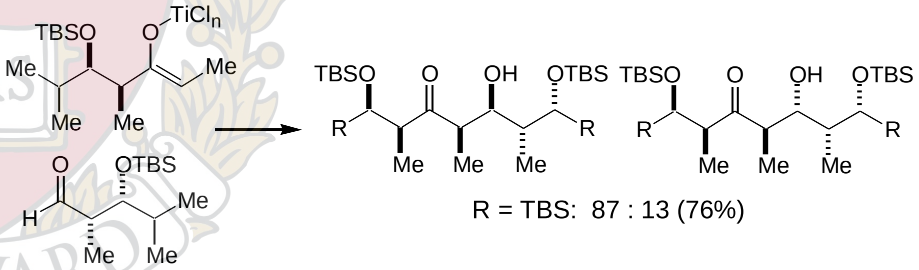
diastereoselection 96 : 4



M = B(9-BBN) syn: 10: 69 + 21% anti

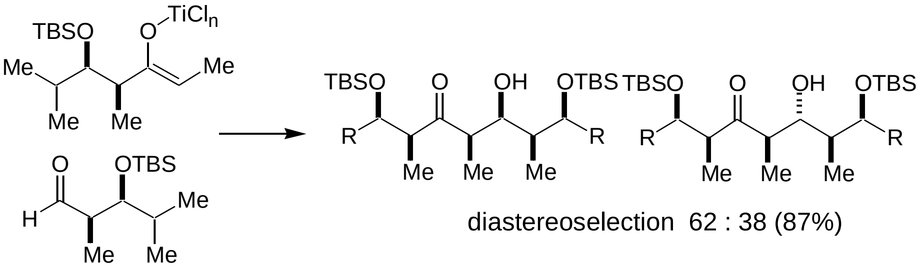
M = $TiCl_4$ syn: 21: 71 + 8% anti

(Z)-Titanium Enolates: The matched cases



R = TBS: 87 : 13 (76%)

(Z)-Titanium Enolates: The mismatched cases

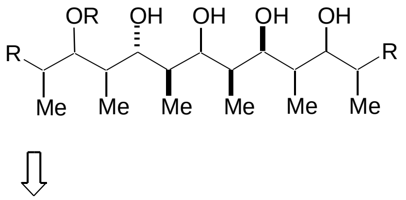


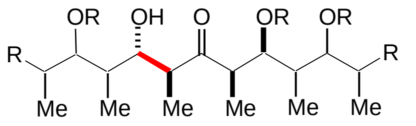
diastereoselection 62 : 38 (87%)

"Double Stereodifferentiating Aldol Reactions. The Documentation of "Partially Matched" Aldol Bond Constructions". Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *JACS* **1995**, *117*, 9073-9074.

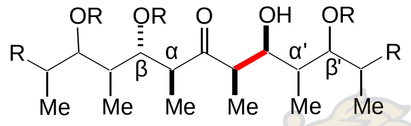
Synthesis of Polyketide chains

Given a polyprpionate chain of alternating Me & OH substitutents, select a disconnection point sectioning the fragments into subunits of comparable complexity by adding C=O as illustrated.



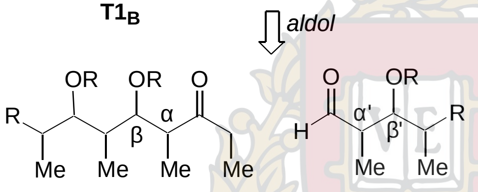


$T1_A$



$T1_B$

Focusing on the =O FG, there are 2 1st-order aldol disconnections highlighted. Let's proceed forward with **$T1_B$**. Carry out the dissconnection to subunits **2_K** and **2_A**.



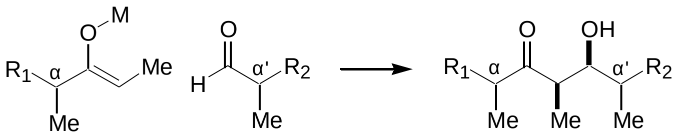
2_K

α center important
β center ignore

2_A

Both centers important

For substituted enolate and enolsilane-based processes, there are at least three identifiable **stereochemical determinants** that influence reaction diastereoselectivity (eq 1). Two of these determinants are associated with the local chirality of the individual reaction partners. For example, enolate (enolsilane) chirality influences the absolute stereochemistry of the forming methyl-bearing stereocenter, and in a similar fashion, aldehyde chirality controls the absolute stereochemical outcome of the incipient hydroxyl-bearing stereocenter. The third determinant, the pericyclic transition state, imposes a relative stereochemical relationship between the developing stereocenters. This important control element is present in the aldol reactions of metal enolates (M = BR_2, TiX_3, Li, etc.), but is absent in the Lewis acid catalyzed (Mukaiyama) enolsilanes aldol variants that proceed via open transition states.

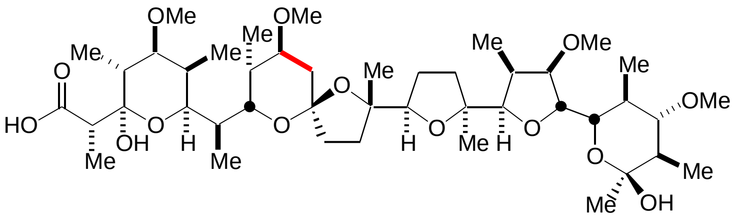


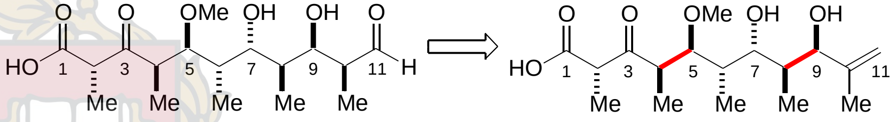
(1)

Stereochemical Determinants	M = BR_2	M = SiR_3
enolate facial bias	✔	✔
aldehyde facial bias	✔	✔
pericyclic transition state	✔	✘

The Lonomycin Synthesis: An example of polypropionate assembage

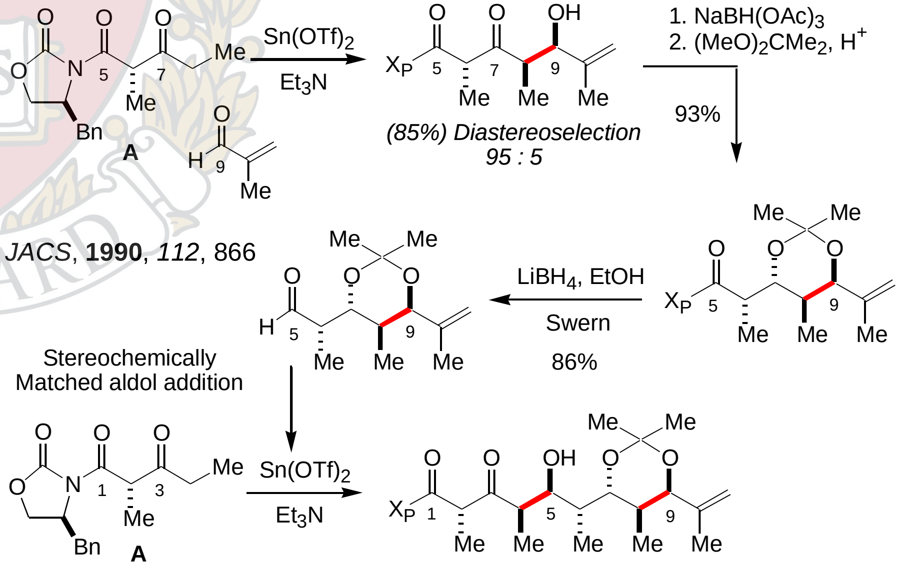
Evans, Ratz, Huff, Sheppard *JACS* **1995**, *117*, 3448





BH_3 Transform: See Lecture No. 8

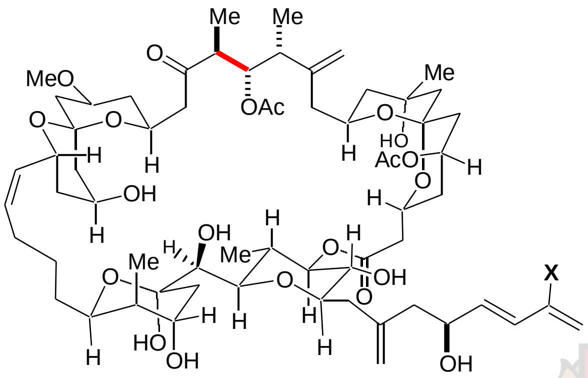
C_1–C_{11} Assemblage



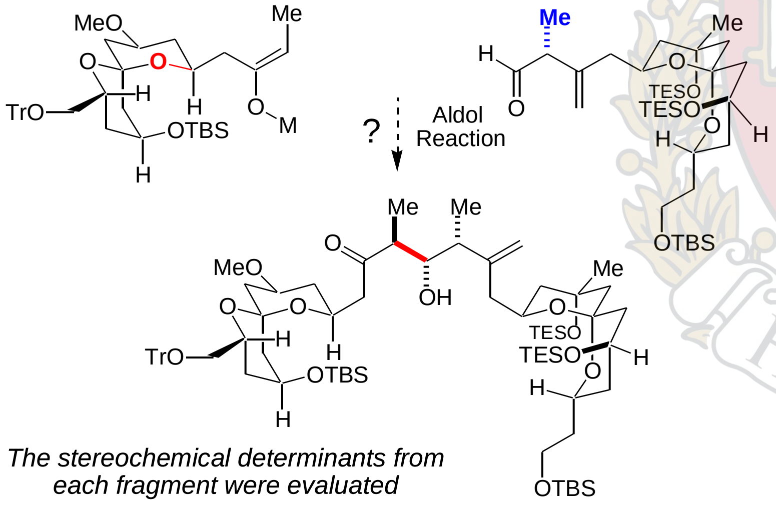
Anti-Felkin Adduct Diastereoselection >95 : 5 (86%)

The $Sn(OTf)_2$ aldol reaction of A: seethis lecture + *JACS*, **1990**, *112*, 866

The Altohyrtin Synthesis: An example of polypropionate assembage

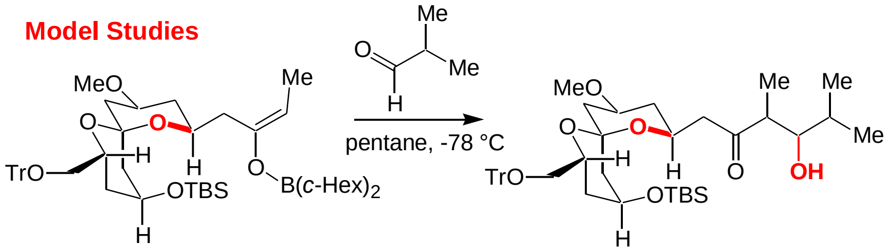


Evans, Trotter, Coleman, Côté, Dias, Rajapakse, *Tetrahedron* **1999**, *55*, 8671-8726.



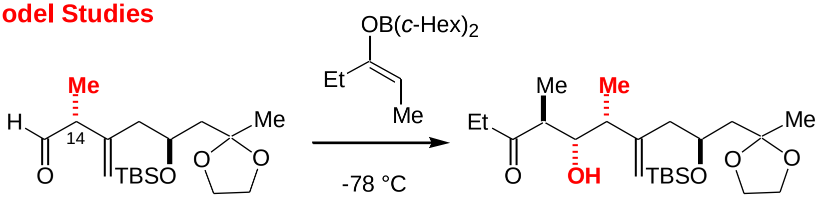
The stereochemical determinants from each fragment were evaluated

Model Studies



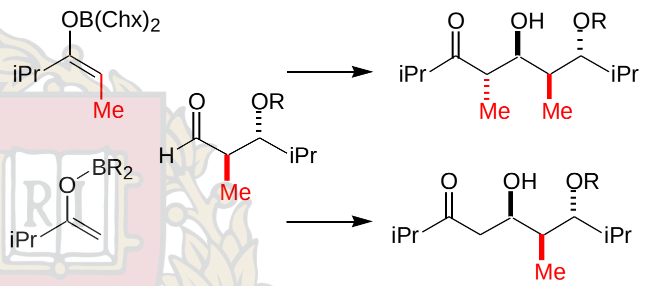
2:1 mixture of diastereomers

Model Studies



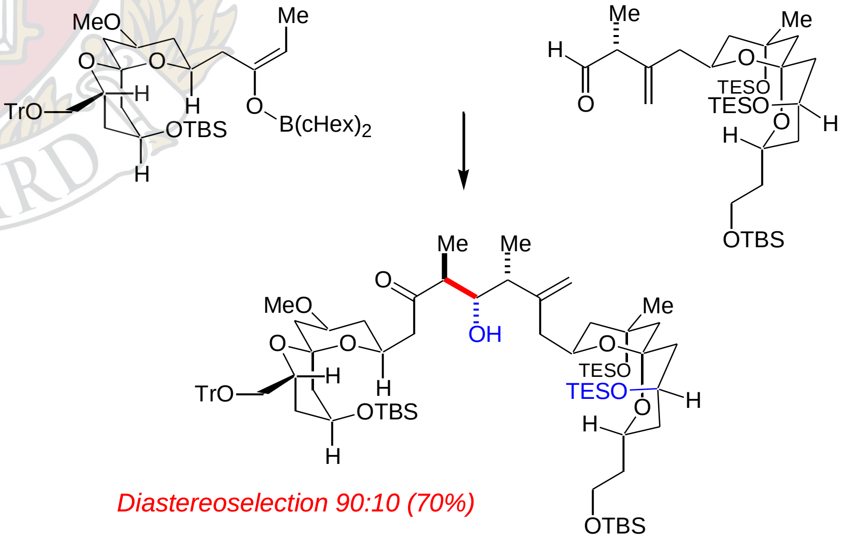
Diastereoselection 97:3

Background



	major : Σ others
R = TBS	99 : 1
R = PMB	93 : 7
R = PMB	69:31

The Aldol Fragment Coupling

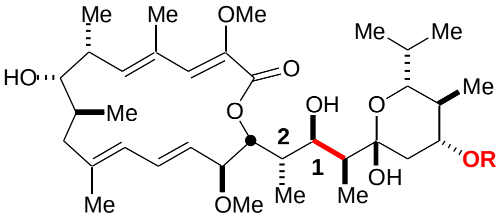


Diastereoselection 90:10 (70%)

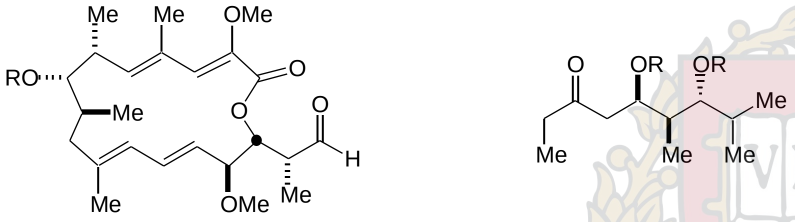
Bafilomycin A_1 Synthesis: An example of polypropionate assembage

Evans, Calter, *Tetrahedron Lett.* **1993**, 34, 6871

Bafilomycin A_1



Critical Aldol Disconnection



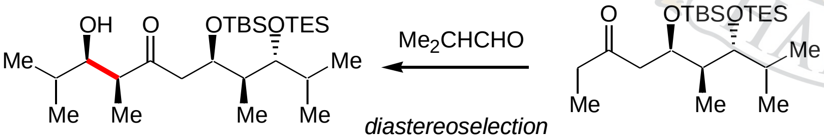
Required: Syn aldol addition

Aldehyde Fragment: Target contains syn aldol retron witth anti-Felkin relationship at 1 & 2

Enolate Fragment: Can the needed enolate facial bias be built into the reaction??

Aldol Model Studies

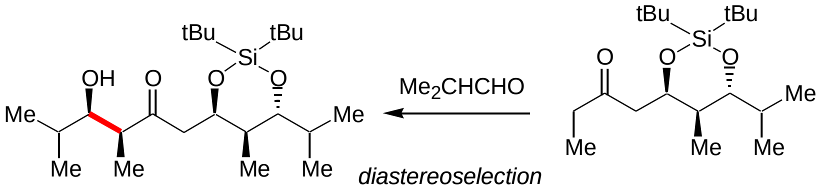
Enolization Conditions: $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, -78°C.



Me_2CHCHO

diastereoselection 62:38 [9]

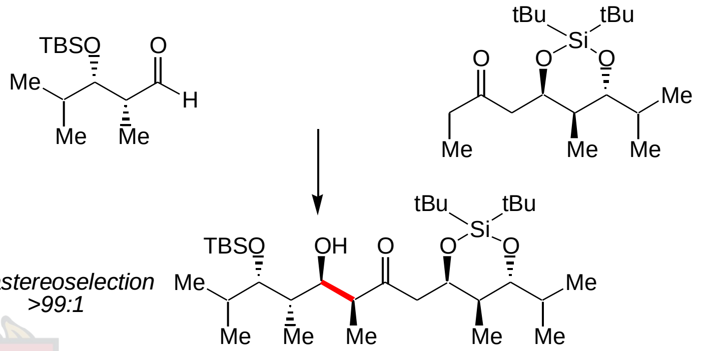
The Critical Observation



Me_2CHCHO

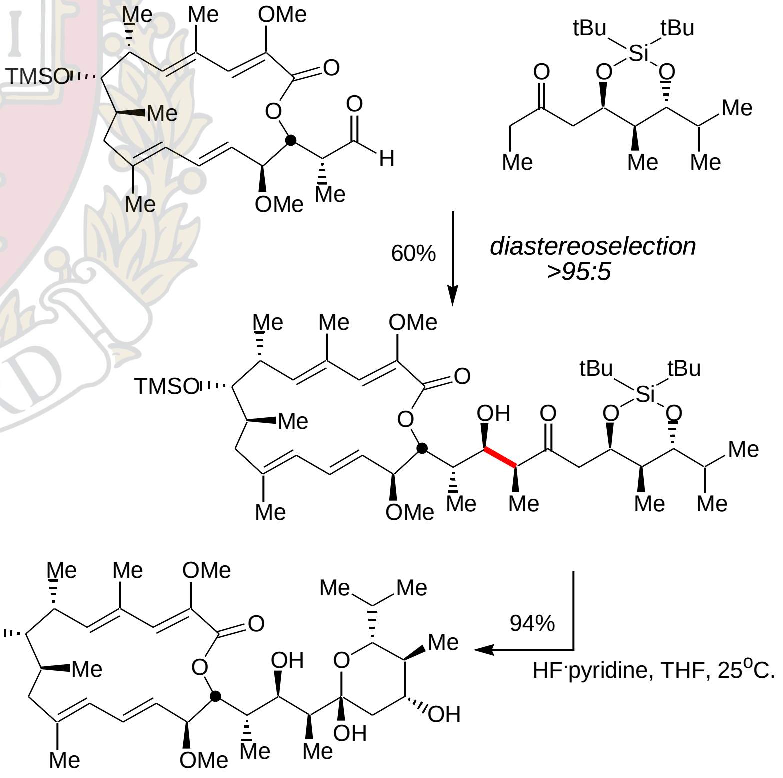
diastereoselection >99:1

Enolization Conditions: $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, -78°C.



diastereoselection >99:1

Critical Aldol Disconnection



60%

diastereoselection >95:5

94%

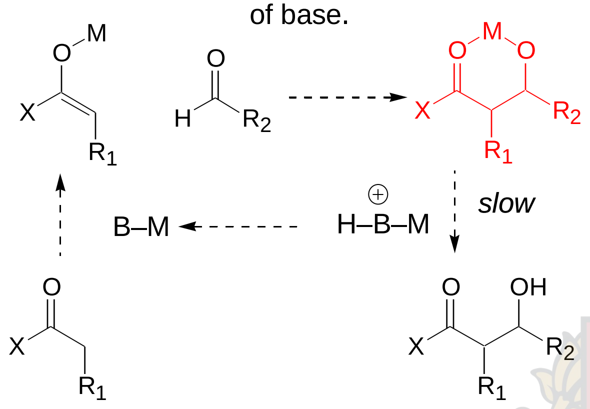
HF·pyridine, THF, 25°C.

Bafilomycin A_1

The Mukayama Aldol Reaction-1

Type I Aldol Reaction: Metal Aldol Process

This reaction may be run with either a stoichiometric or catalytic amount of base.

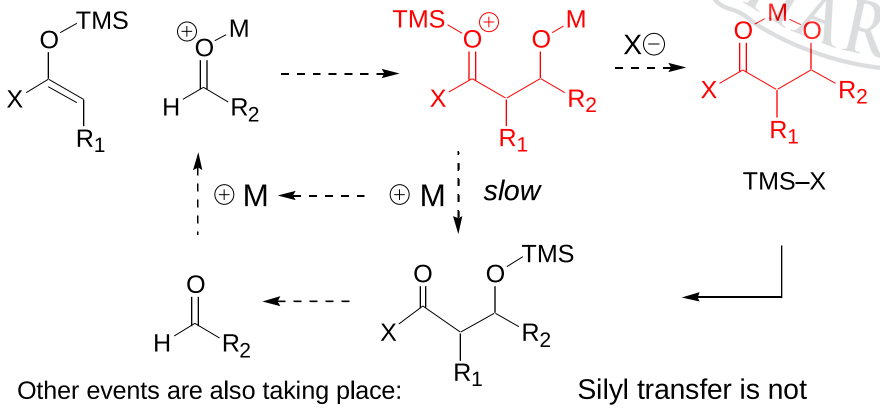


Catalytic Version: Slow step in the catalytic variant is protonation of the intermediate metal aldolate

Type II Aldol Reaction: Mukaiyama Aldol Process

This reaction may be run with either a stoichiometric or catalytic amount of Lewis acid.

The minimalist mechanism: MX = Lewis acid



Other events are also taking place:
Carreira *Tet. Lett* **1994**, *35*, 4323

Silyl transfer is not necessarily intramolecular

Recent Reviews

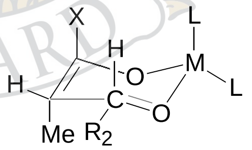
R. Mahrwald, *Diatereoselection in Lewis Acid Mediated Aldol Additions*, *Chem. Rev.* **1999**, *99*, 1095-1120

S. G. Nelson, *Catalyzed enantioselective aldol additions of latent enolate equivalents Tetrahedron: Asymmetry* **1998**, *9*, 357-389.

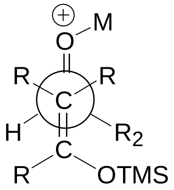
Mukaiyama Aldol Reaction, E. Carreira In Comprehensive Asymmetric Catalysis, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 998-1059.

Reaction Mechanism: "Closed" versus "Open" Transition States

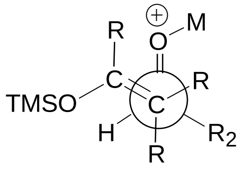
The Mukaiyama aldol reaction proceeds through an "open" transition state. The two illustrated competing TS orientations do not differ significantly in energy. For most reactions in this family there is not a good understanding of reactans-pair orientation. There is a prevalent view that the anti-periplanar TS is favored on the basis of electrostatic effects.



Metal aldolate TS
"Closed"



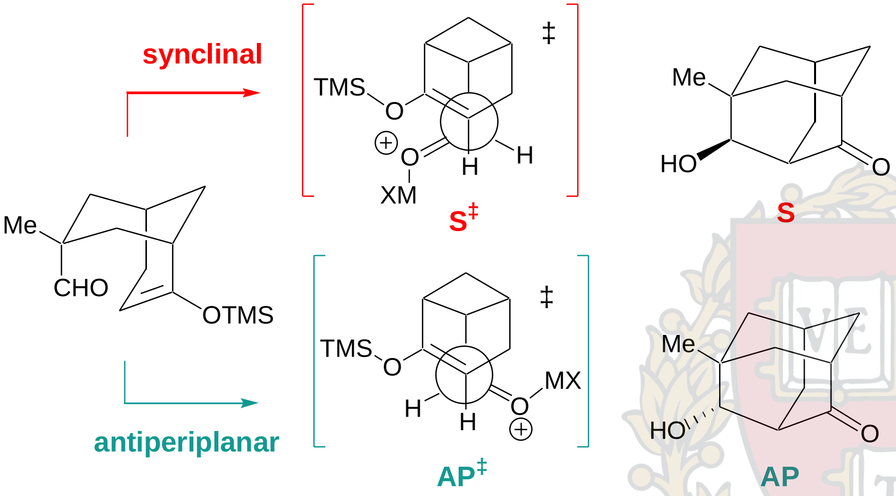
anti-periplanar TS
"Open"



synclinal TS
"Open"

The Mukayama Aldol Reaction-2

Denmark has designed a nice substrate to distinguish between synclinal and anntiperiplanat transition states:
Denmark, *J. Org. Chem.* **1994**, *59*, 707-709

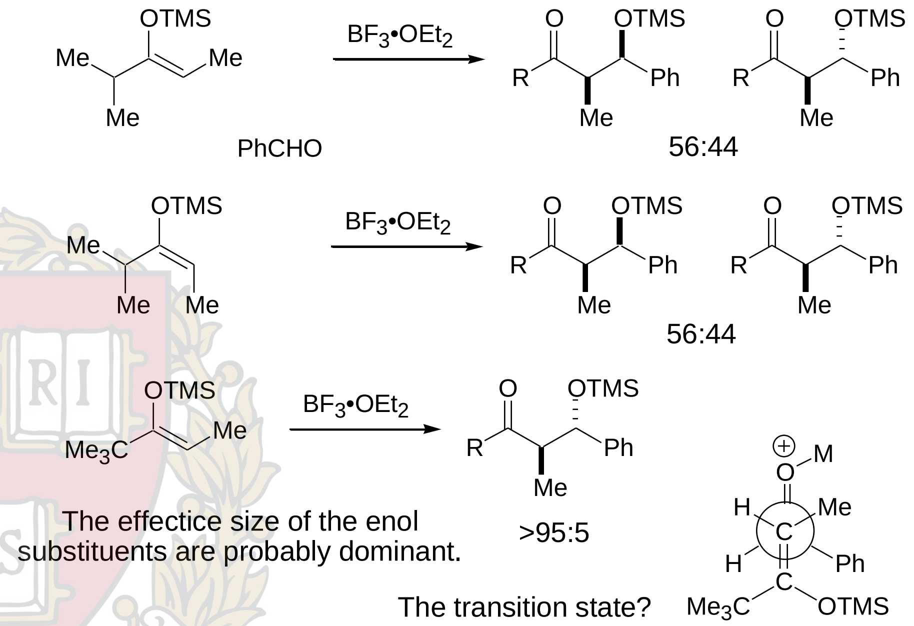


Lewis Acid	syn:anti
$TiCl_4$	21:79
$SnCl_4$	18:82
$BF_3•OEt_2$	29:71
$TrClO_4$	27:73
$SnCl_2$	78:22

conclusion: there is a modestpreference for the antiperiplanar TS

Syn-Anti Aldol Diastereoselection

Heathcock: *J. Org. Chem* **1986**, *51*, 3027



The effectice size of the enol substituents are probably dominant.

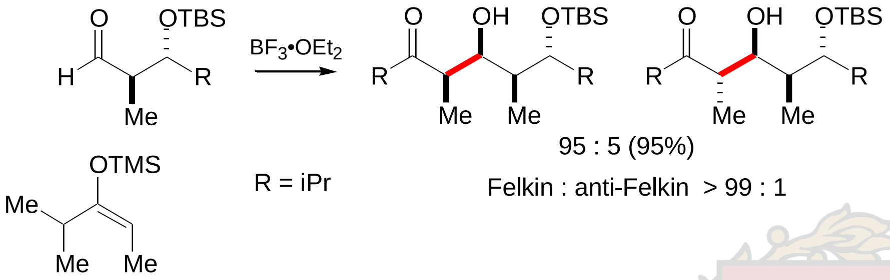
The transition state?

These reactions "exhibit little simple diastereoselection except in special cases."....Heathcock

The Mukayama Aldol Reaction-3

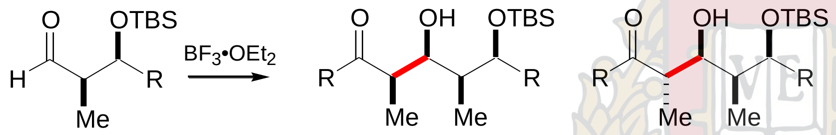
Merged Syn-Anti & Felkin Diastereoselection

Evans: *JACS* **1995**, *117*, 9598



95 : 5 (95%)

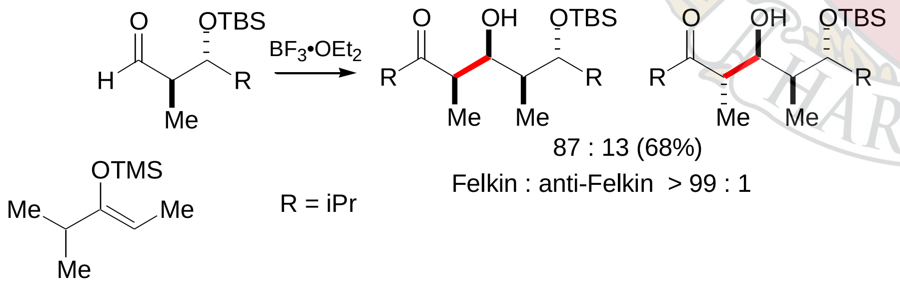
Felkin : anti-Felkin > 99 : 1



70 : 30 (89%)

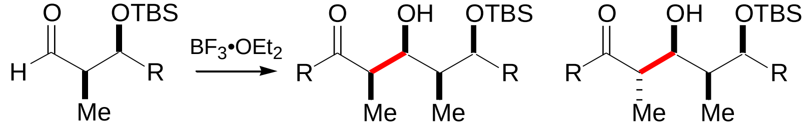
Felkin : anti-Felkin 99 : 1

Conclusions:
Moderate to Good syn diastereoselectlion
Excellent Felkin diastereoselectlion



87 : 13 (68%)

Felkin : anti-Felkin > 99 : 1

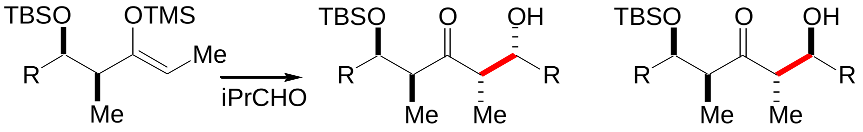


91 : 9 (75%)

Felkin : anti-Felkin 87 : 13

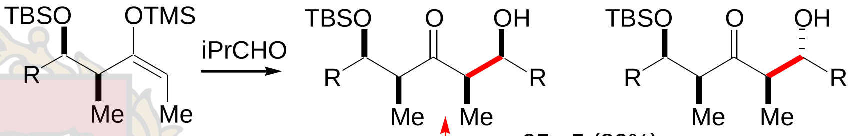
Conclusions:
Moderate to Good syn diastereoselectlion
Excellent Felkin diastereoselectlion

Enolslane Face Selection



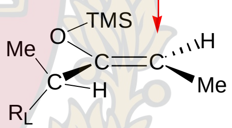
R = iPr

59 : 41 (82%)
Enolsilane Face Selectivity 95 : 5



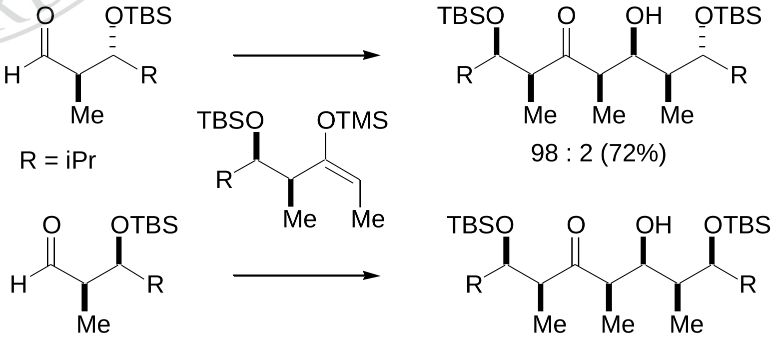
95 : 5 (80%)
Enolsilane Face Selectivity 90 : 10

favored



A(1-3) control is good for the
(E) enolsilane

Double Stereodifferentiating *Syn* Aldol Rxns with Enolsilanes



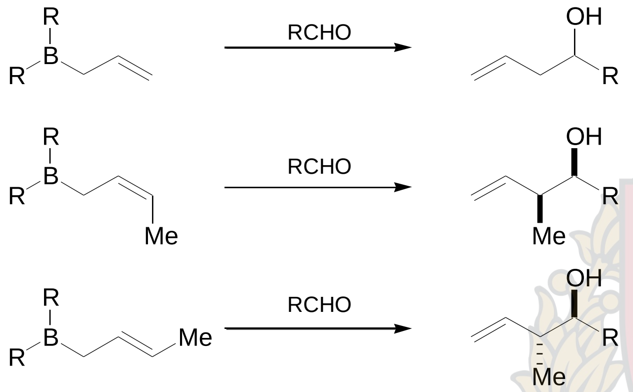
98 : 2 (72%)

98 : 2 (83%)

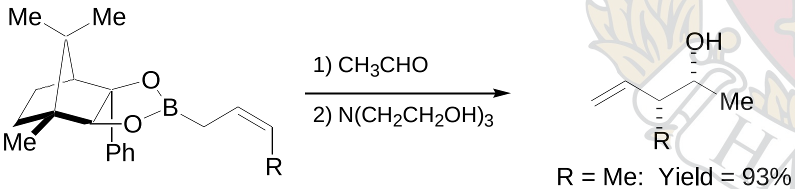
Allyl and Crotylmetal Species–1 : Boron

■ General Reviews of Allyl Metal Reagents:
Comprehensive Organic Synthesis, **1991**;Vol. 2.

The General Reactions



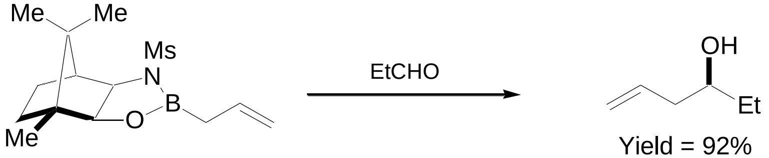
The Hoffman Chiral Allylboronic Esters



R = Me: Yield = 93%
ee = 60-70%

R = H: Yield = 92%
ee = 65%

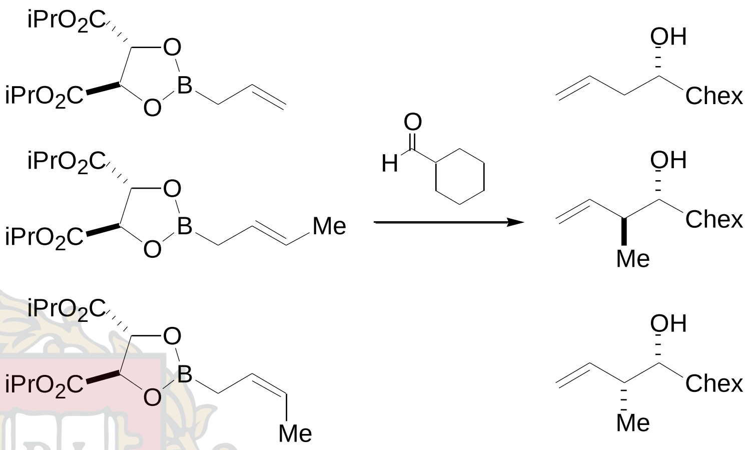
R. Hoffman *Tetrahedron Lett*. **1979**, 4653-4656.
ACIEE, **1978**, *17*, 768-769.



Yield = 92%
ee = 92%

M. Reetz *Chem. Ind. (London)* **1988**, 663-664.

The Tartrate-derived Allylboronic Esters

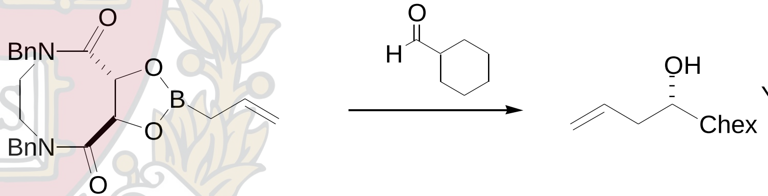


Yield = 72%
ee = 87%

Yield = 100%
ee = 91%

Yield = 90%
ee = 83%

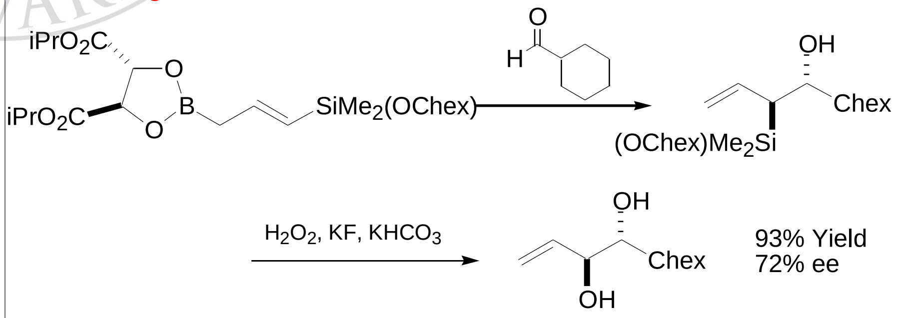
W. Roush, *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.
Tetrahedron Lett. **1988**, *29*, 5579-5582.



Yield = 40%
ee = 97%

W. Roush, *J. Am. Chem. Soc.* **1988**, *110*, 3979-3982.

A Reagent for the Generation of Anti-1,2-Diols

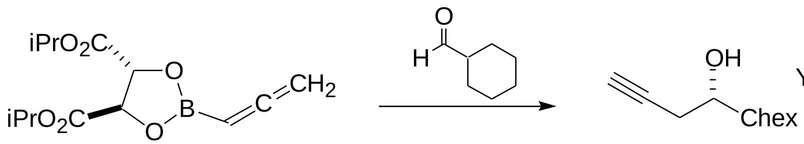


93% Yield
72% ee

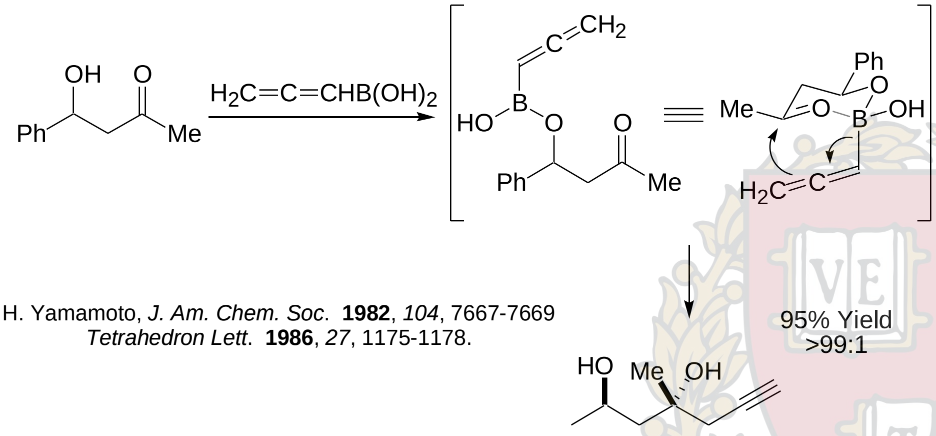
W. Roush, *Tetrahedron Lett*. **1990**, *31*, 7563-7566.

Allyl and Crotylmetal Species–2 : Boron

■ Allenylboronic Esters: Tartrate-derived Controllers and Internal Delivery



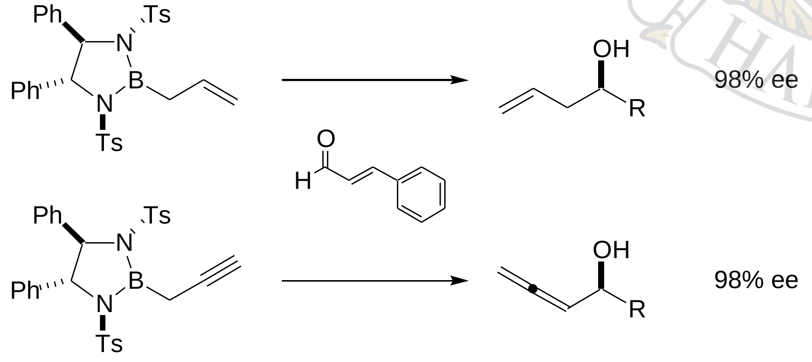
Yield = 56%
ee = 92%



95% Yield
>99:1

H. Yamamoto, *J. Am. Chem. Soc.* **1982**, *104*, 7667-7669
Tetrahedron Lett. **1986**, *27*, 1175-1178.

■ The Corey Stein Controller

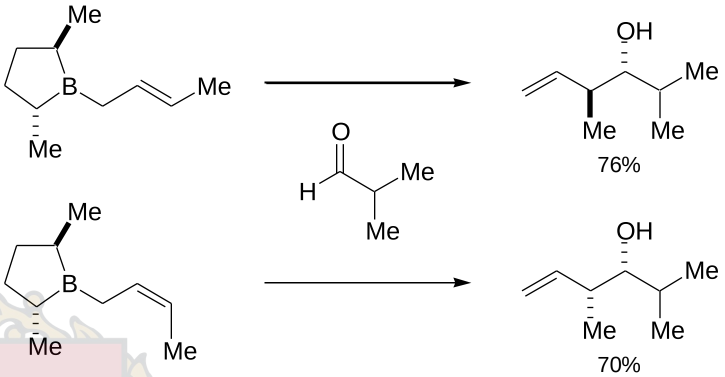


98% ee

98% ee

E. J. Corey, *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.
J. Am. Chem. Soc. **1990**, *112*, 878-879.

■ The Masamune Borolane

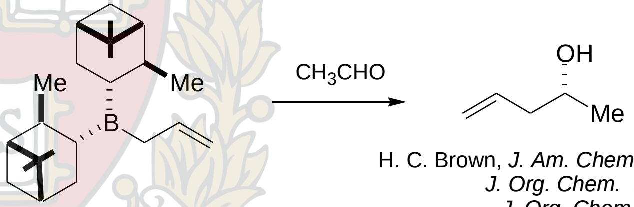


96:4
97% ee

96:4
93% ee

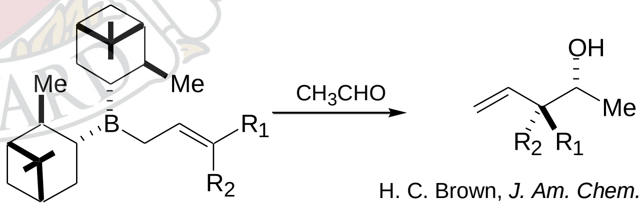
S. Masamune, *J. Org. Chem.* **1987**, *52*, 4831-4832.

■ The Brown IPC Controller



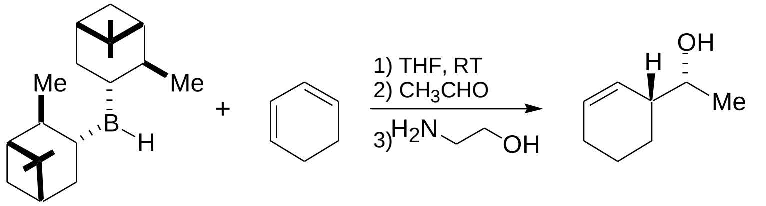
> 99% ee

H. C. Brown, *J. Am. Chem. Soc.* **1983**, *105*, 2092-2093.
J. Org. Chem. **1991**, *56*, 401-404.
J. Org. Chem. **1992**, *57*, 6614.



R$_1$ = Me, R$_2$ = H: ee = 90%
R$_1$ = H, R$_2$ = Me: ee = 90%
R$_1$ = H, R$_2$ = OMe: ee = 90%

H. C. Brown, *J. Am. Chem. Soc.* **1988**, *110*, 1535-1538.
See also: *Tetrahedron Lett.* **1990**, *31*, 455-458.

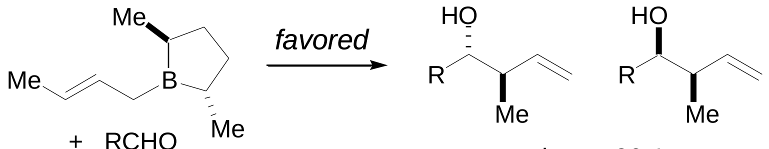


ee = 94%

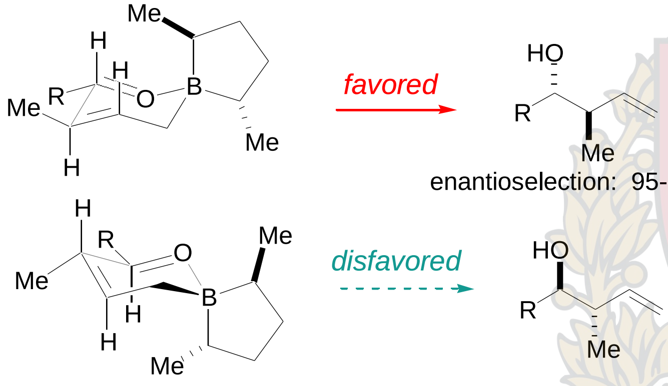
H. C. Brown, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2633.

The Allylboron Reagents Add to Carbonyl Compounds via a Zimmerman-Traxler Transition State

Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, *52*, 4831

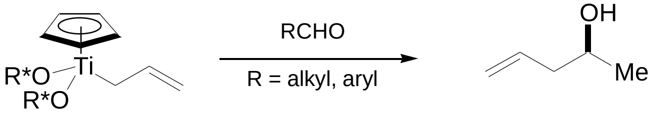


anti:syn, 96:4



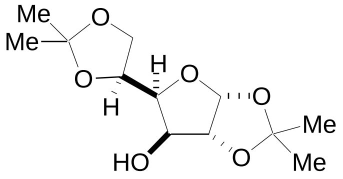
enantioselection: 95-97%

An Enantioselective Allyltitanium Reagent



ee = 85 - 94%

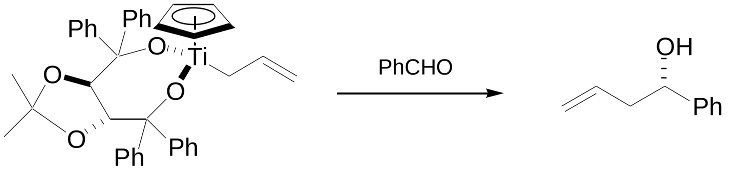
R*OH =



M. Riediker, R. Duthaler, *ACIEE*, **1989**, *28*, 494-495.
In *Organic Synthesis via Organometallics*, **1991**, 285-309.
J. Am. Chem. Soc. **1992**, *114*, 2321-2336.

Duthaler *Chem. Rev.* **1992**, *92*, 807

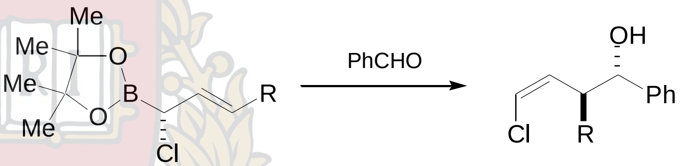
Another Enantioselective Allyltitanium Reagent



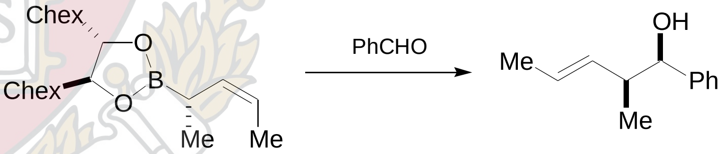
95% ee

R. Duthaler, *J. Am. Chem. Soc.* **1992**, *114*, 2321-2336.

Chiral α-Substituted Allyl Metal Reagents: Boron

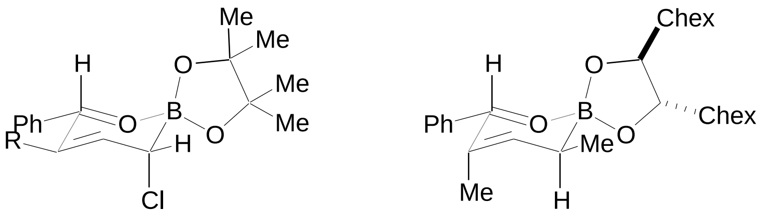


R = H: 92% ee
R = Me: 98% ee



68% Yield
99% ee

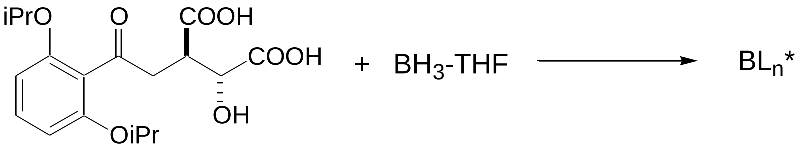
R. Hoffman, *Chem. Ber*. **1986**, *119*, 2013-2024.
Chem. Ber. **1988**, *121*, 1501-1507.
ACIEE, **1986**, *25*, 1028-1030.

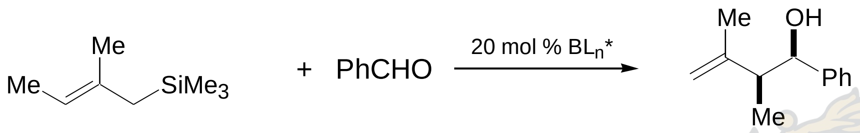


The favored transition states

Allyl and Crotylmetal Species–4: Catalytic Systems

■ Three Catalytic Asymmetric Allylations of Aldehydes are Known

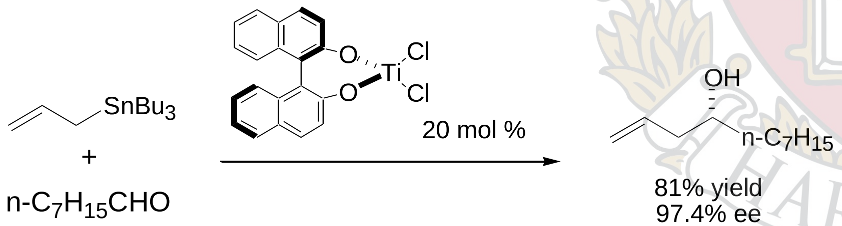




E/Z = 61/39

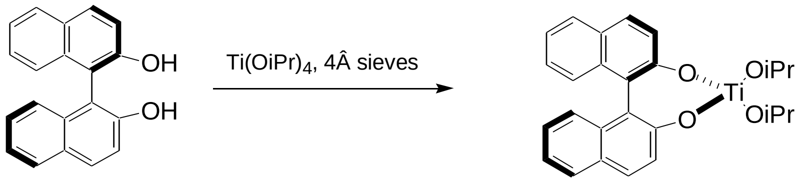
63% yield
90% ee

H. Yamamoto, *Synlett* **1991**, 561-562.

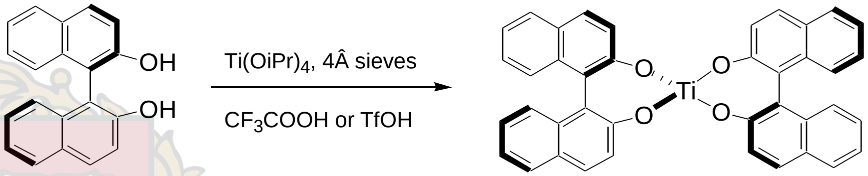


81% yield
97.4% ee

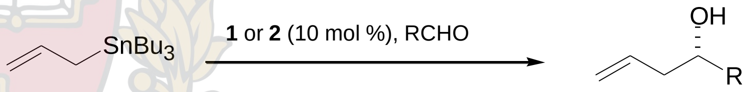
E. Tagliavini, A. Umani-Ronchi *J. Am. Chem. Soc*. **1993**, *115*, 7001-7002.

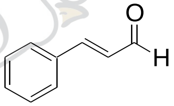


1



2



R	Catalyst	Yield (%)	ee (%)
Ph	**1**	88	95
	2	98	92
Chex	**1**	66	94
	2	95	92
 	**1**	42	89
	2	78	77

G. Keck *J. Am. Chem. Soc*. **1993**, *115*, 8467-8468.

■ Many Other Metals Have Been Employed in the Allylation Reaction ...

Pb: S. Torii, *Chem. Lett*. **1986**, 1461-1462.
Mo: J. Faller, *Tetrahedron Lett*. **1991**, *32*, 1271-1274.
Cr: Y. Kishi, *Tetrahedron Lett*. **1982**, *23*, 2343-2346.
P. Knochel, *J. Org. Chem*. **1992**, *57*, 6384-6386.
Sb: Y. Butsugan, *Tetrahedron Lett*. **1987**, *28*, 3707-3708.
Mn: T. Hiyama, *Organometallics*, **1982**, *1*, 1249-1251.
Zn: T. Shono, *Chem. Lett*. **1990**, 449-452.
Ba: H. Yamamoto, *J. Am. Chem. Soc*. **1991**, *113*, 8955-8956.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 26

Ambiphilic Functional Groups-1
Nitro and Diazo Groups

- Historical Perspective
- Charge Affinity Patterns
- Functional Group Classification Scheme
- The Chemistry of the $–NO_2$ Group
- The Chemistry of the $–N_2$ Group

Reading Assignment for this Week:

"An Organizational Scheme for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships."
D. A. Evans *Unpublished manuscript* (Lecture 26A, pdf)

"Methods of Reactivity Umpolung."
D. Seebach *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

"Nitroaliphatic Compounds–Ideal Intermediates in Organic Synthesis'" Seebach, D. et. al, *Chimia*, **1979**, *33*, 1-18.

"Synthetic Applications of α-Diazocarbonyl Compounds"
Krista Beaver, Evans Group Seminar (Lecture 26B, pdf)

Matthew D. Shair

Monday,
November 18, 2002

Papers of Historical Interest:

"Arthur Lapworth: The Genesis of Reaction Mechanism."
M. Saltzman *J. Chem. Ed.* **1972**, *49*, 750.

"A Theoretical Derivation of the Principle of Induced Alternate Polarities."
A. Lapworth *J. Chem. Soc.* **1922**, *121*, 416.

"The Electron Theory of Valence as Applied to Organic Compounds."
J. Steiglitz *J. Am. Chem. Soc.* **1922**, *44*, 1293.

Monographs:

Hase, T. A. "Umpoled Synthons. A Survey of Sources and Uses in Synthesis".; John Wiley & Sons, Inc.: New York, 1987.

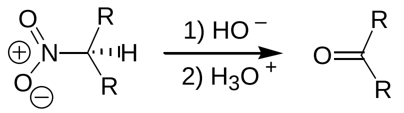
Ho, T.-L. "Polarity Control for Synthesis"; John Wiley & Sons, Inc.: New York, 1991.

Ono, N., "The Nitro Group in Organic Synthesis", Wiley-VCH, 2001

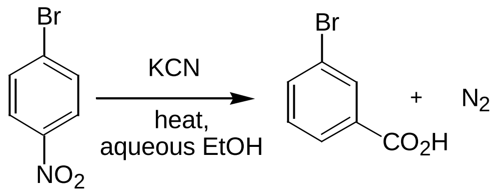
Several Interesting Problems

Provide a mechanism for the Nef reaction

Nef Reaction



Cume Question: The **von Richter** reaction is illustrated in the accompanying equation. Please provide a plausible mechanism for this transformation taking into account the following observations. (a) If ^{15}N-labeled KCN is used, the N_2 formed is half labeled; (b) 3-bromo-benzonitrile does not form 3-bromo-benzoic acid under the reaction conditions.



Ambiphilic Functional Groups

Required Reading:

"An Organizational Scheme for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships."
D. A. Evans *Unpublished manuscript.*

"Methods of Reactivity Umpolung."
D. Seebach *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

"Nitroaliphatic Compounds–Ideal Intermediates in Organic Synthesis'"
Seebach, D. et. al, *Chimia*, **1979**, *33*, 1-18.

Papers of Historical Interest:

"Arthur Lapworth: The Genesis of Reaction Mechanism."
M. Saltzman *J. Chem. Ed.* **1972**, *49*, 750.

"A Theoretical Derivation of the Principle of Induced Alternate Polarities."
A. Lapworth *J. Chem. Soc.* **1922**, *121*, 416.

"The Electron Theory of Valence as Applied to Organic Compounds."
J. Steiglitz *J. Am. Chem. Soc.* **1922**, *44*, 1293.

"Displacement of Aliphatic Nitro Groups by Carbon & Heteroatom Nucleophiles." R. Tamura, A. Kamimura, N. Ono *Synthesis* **1991**, 423.

"Functionalized Nitroalkanes as Useful Reagents for Alkyl Anion Synthons." G. Rosini, R. Ballini *Synthesis* **1988**, 833.

"Conjugated Nitroalkenes: Versatile Intermediates in Organic Synthesis."
A. G. M. Barrett, G. G. Graboski *Chem. Rev.* **1986**, *86*, 751.

Monographs:

Hase, T. A. "Umpoled Synthons. A Survey of Sources and Uses in Synthesis".; John Wiley & Sons, Inc.: New York, 1987.

Ho, T.-L. "Polarity Control for Synthesis"; John Wiley & Sons, Inc.: New York, 1991.

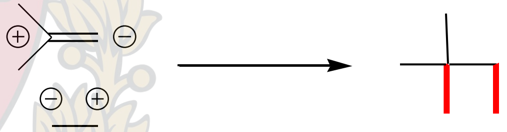
Arthur Lapworth (1872–1941)

Lapworth was among the first to understand and conceptualize the effect of heteroatomic substituents on the reactivity of individual carbon centers, and how this effect is propagated through the carbon framework of organic molecules.

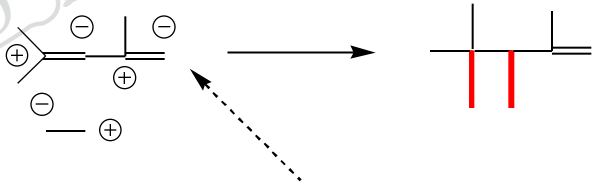
Lapworth's Theory of Alternating Polarities:

"Latent Polarities of Atoms and Mechanism of Reaction, with Special Reference to Carbonyl Compounds."
A. Lapworth *Mem. Manchester. Lit. Phil. Soc.* **1920**, *64 (3)*, 1.

"The addition of electrolytes to the carbonyl compound invariably proceeded as if the carbon were more positive than the oxygen atom, and invariably selected the negative ion; for example:"



"The extension of the influence of the directing, or "key atom," over a long range seems to require for its fullest display the presence of double bonds, and usually in conjugated positions...."



The "key atom" is the one with the most electronegative character, in this case the carbonyl oxygen.

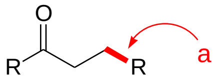
anionoid/cationoid - - - - - - - - - - -► nucleophilic/electrophilic

The Lapworth polarity designations can be used to form the basis of a functional group classification scheme.

Reactivity Patterns of Functional Groups: Charge Affinity Patterns

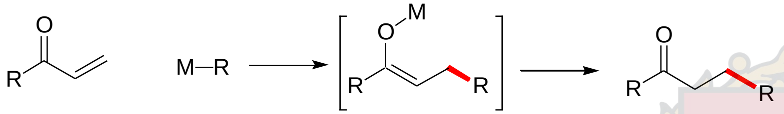
- Polar rxns form the basis set of bond constructions in synthesis
- Generalizations on conferred site reactivity will therefore be important

Given this target

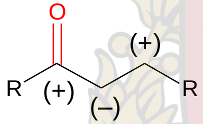


and the desire to form this bond

The functional group =O "dictates" the following bond construction



- Conferred site reactivity of =O



Charge Affinity Patterns

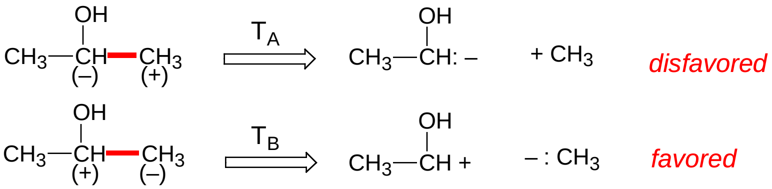
- Use the descriptors (+) and (–) to denote the polar disconnections shown.

$\overset{(-)}{A}\text{—}\overset{(+)}{B} \Longrightarrow A:^- \quad B^+$

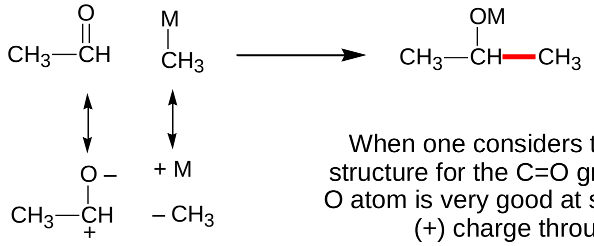
$\overset{(+)}{A}\text{—}\overset{(-)}{B} \Longrightarrow A:^+ \quad B:^-$

- In the transforms illustrated above, symbols (+) & (–) are used to denote the particular polar transform illustrated.
In the present case there is NO INTRINSIC BIAS in favoring one transform over the other.

Let's now add an OH functional group (FG) to propane at C-2 and see whether one creates a bias in the favoring of one or the other transforms:

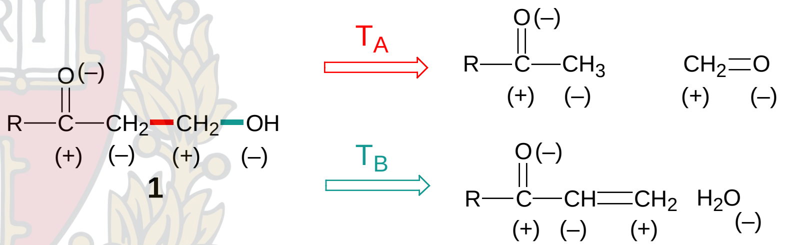


- The actual reaction associated with this transform is the addition of organometals to carbonyl substrates.



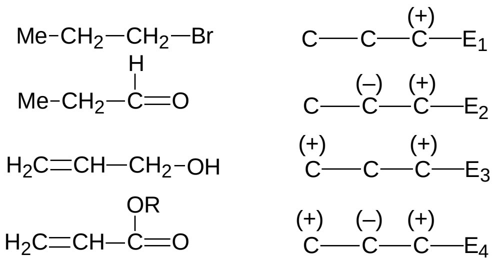
When one considers the polar resonance structure for the C=O group it is clear that an O atom is very good at stabilizing an adjacent (+) charge through resonance.

- Consider polar disconnections of the illustrated β-hydroxy ketone **1**:

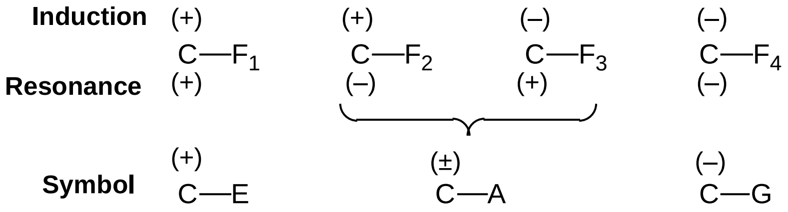


It is evident that the heteroatom functional groups, =O and -OH, strongly bias the indicated polar disconnections.

Charge Affinity Patterns of Common Functional Groups



Functional groups activate the carbon skeleton at the point of attachment by either induction & resonance.



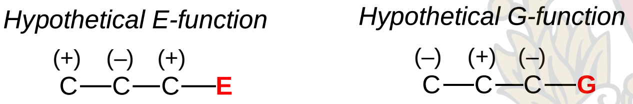
$$\begin{array}{lcccc} \textbf{Induction} & (+) & (+) & (-) & (-) \\ & C{-}F_1 & C{-}F_2 & C{-}F_3 & C{-}F_4 \\ \textbf{Resonance} & (+) & (-) & (+) & (-) \\ \textbf{Symbol} & \overset{(+)}{C{-}E} & \multicolumn{2}{c}{\overset{(\pm)}{C{-}A}} & \overset{(-)}{C{-}G} \end{array}$$

E = electrophilic at the point of attachment
A = ambiphilic at the pont of attachment
G = nucleophilic at the point of attachment

For simplicity, we will designate three FG classes according to the designations provided above.

E & G-Functions:

To organize activating functions into common categories it is worthwhile to define "hypothetical" functional groups E, and G, having the charge affinity patterns denoted below.



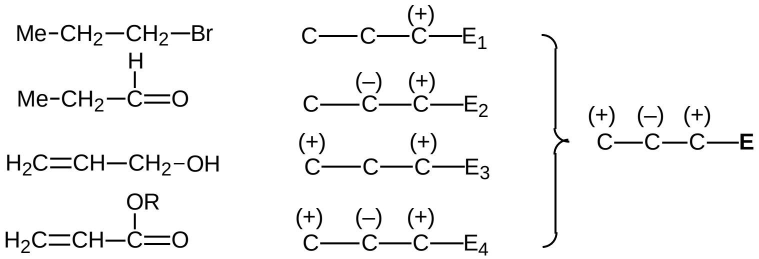
Hypothetical E-function $\overset{(+)}{C}{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}\mathbf{E}$

Hypothetical G-function $\overset{(-)}{C}{-}\overset{(+)}{C}{-}\overset{(-)}{C}{-}\mathbf{G}$

Given the appropriate oxidation state of the carbon skeleton, such functional groups confer the indicated polar site reactivity patterns toward both electrophiles and nucleophiles.

Any FG that conforms either to the ideal charge affinity parrern or a sub-pattern thereof will thus be classified as either an E- or G-function.

Representative E-functions:



$Me{-}CH_2{-}CH_2{-}Br$ $\quad C{-}C{-}\overset{(+)}{C}{-}E_1$

$Me{-}CH_2{-}\overset{H}{C}{=}O$ $\quad C{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}E_2$

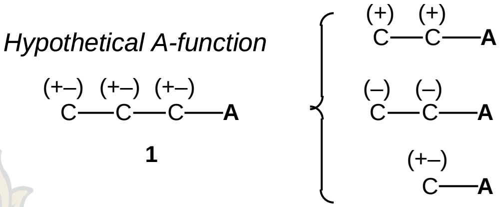
$H_2C{=}CH{-}CH_2{-}OH$ $\quad \overset{(+)}{C}{-}C{-}\overset{(+)}{C}{-}E_3$

$H_2C{=}CH{-}\overset{OR}{C}{=}O$ $\quad \overset{(+)}{C}{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}E_4$

$$\overset{(+)}{C}{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}\mathbf{E}$$

A-Functions:

A 3rd hypothetical FG, designated as A, may be defined that has an unbiased charge affinity pattern as in **1**. Such an idealized FG's activates all sites to both nucleophilic and electrophilic reactions, and as such include those functions classifies as either E– or G–. The importance of introducing this third class designation is that it includes those functional groups having non-alternate charge affinity patterns such as **2–4**.



Hypothetical A-function $\overset{(+-)}{C}{-}\overset{(+-)}{C}{-}\overset{(+-)}{C}{-}\mathbf{A}$ **1**

$\overset{(+)}{C}{-}\overset{(+)}{C}{-}\mathbf{A}$ **2**

$\overset{(-)}{C}{-}\overset{(-)}{C}{-}\mathbf{A}$ **3**

$\overset{(+-)}{C}{-}\mathbf{A}$ **4**

FG-Classification Rules

In the proposed classification scheme the following rules followed in the assignment of class designation of a given FG.

- 🟥 Activating functions are to be considered as heteroatoms appended to or included within the carbon skeleton.
- 🟥 Activating functions are inspected and classified according to their observed polar site reactivities.
- 🟥 Since proton removal and addition processes are frequently an integral aspect of FG activation, the FG, its conjugate acid or base, and its proton tautomers are considered together in determining its class designation.
- 🟥 The oxidation state of the FG is deemphasized since this is a subordinate strategic consideration.

Common E-Functions: Symbol: $\overset{(+)}{C}{-}E$

$-OR$ $\quad =O$

$-NR_2$ $\quad =NR$

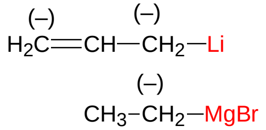
$-X$, X = halogen

exception: $\equiv O$
exception: $\equiv N$

Also consider all combinations of of above FGs; e.g =O + OR

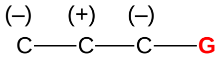
Common G-Functions: Symbol: (–)C—G

Typical G-class functions are the Group I-IV metals whose reactivity patterns, falls into a subset of the idealized G-FG **5**.



$\overset{(-)}{H_2C}=CH-\overset{(-)}{CH_2}-Li$

$CH_3-\overset{(-)}{CH_2}-MgBr$



$\overset{(-)}{C}-\overset{(+)}{C}-\overset{(-)}{C}-G$

5

Common A-Functions: Symbol: (±)C—A

A-functions are usually more structurally complex FGs composed of polyatomic assemblages of nitrogen, oxygen and their heavier Group V and VI relatives (P, As, S, Se).

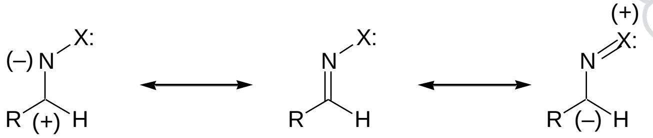
Typical A-functions, classified by inspection, are provided below

$-NO_2$ $=NOR$ $=NNR_2$ $=\underset{+}{N}(O)R$ $=N_2$ $\equiv N$

$-SR$ $-S(O)R$ $-\underset{+}{SO_2}R$ $-SR_2$

$-PR_2$ $-P(O)R_2$ $-PR_3$

■ These FG's are capable of conferring both (+) and (–) at point of attachment.



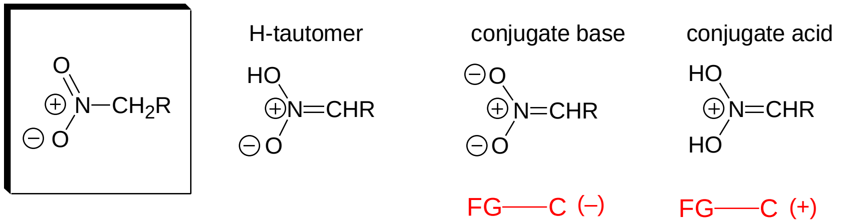
X = OR, NR_2

Remarkably, the dual electronic properties of oximes were first discussed by Lapworth in 1924 before the modern concepts of valence bond resonance were developed.

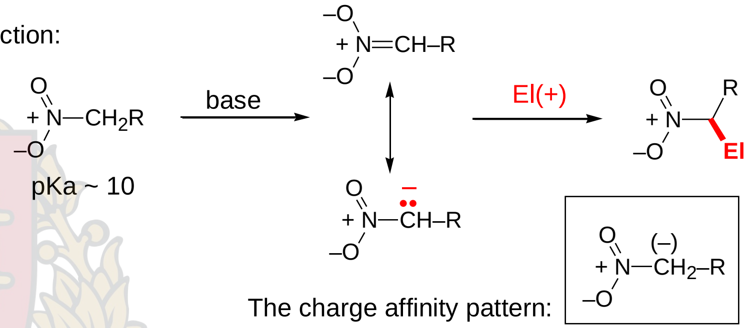
Lapworth, A. *Chemistry and Industry* **1924**, *43*, 1294-1295.

The Nitro Functional Group

As an example, the class designation of the nitro function is determined by an evaluation of the parent function, its nitronic acid tautomer, as well as conjugate acid and base.

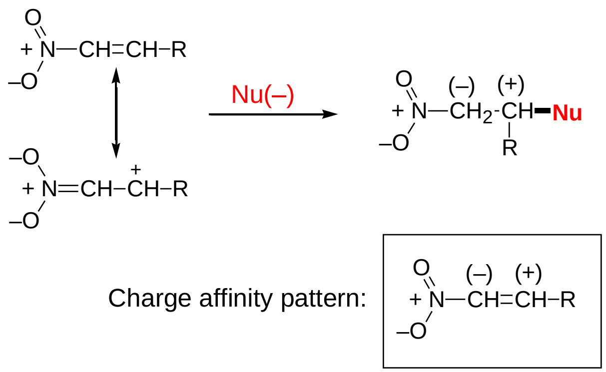


The Reaction:

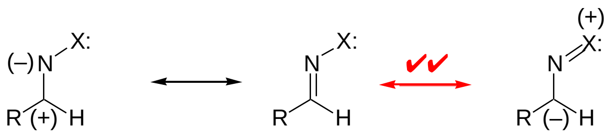


■ This reactivity pattern may be extended via conjugation:

The Reaction:



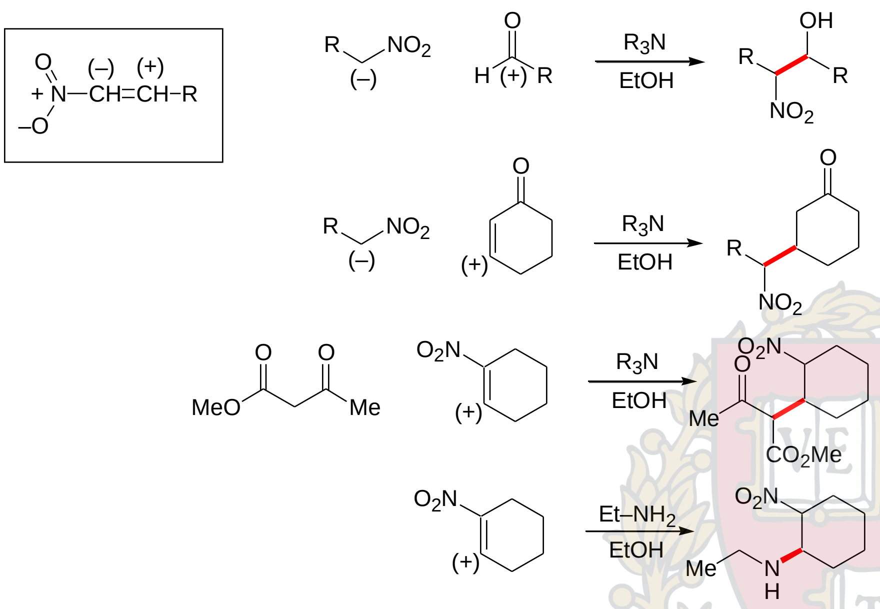
■ The resonance feature which has been exploited:



X = OR, NR_2

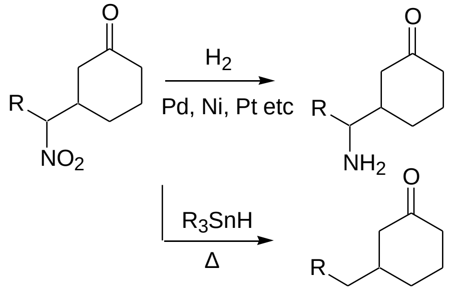
Charge Affinity Patterns and the Nitro Functional Group

Some Reactions of the Nitro Functional Group



Important Transformations of the -NO$_2$ Functional Group

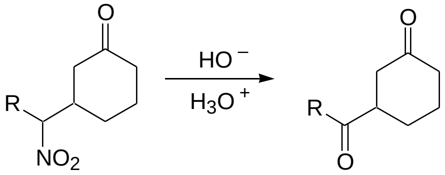
- **Reduction:**



rxn is quite facile

Ono, N.; Kaji, A. *Synthesis* **1986**, 693.

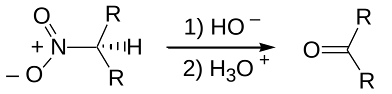
- Nef Reaction:



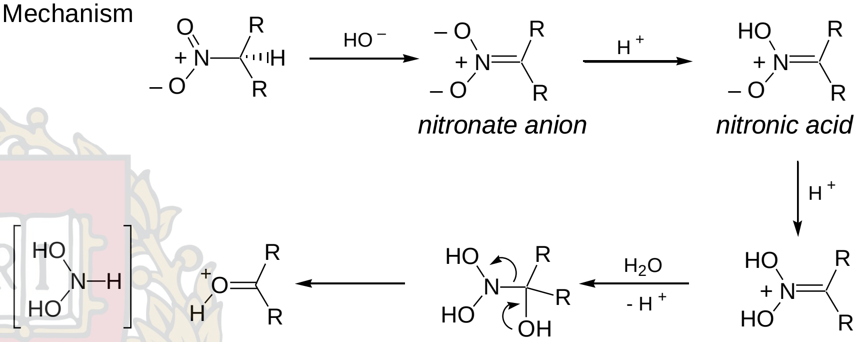
Pinnick, *Org. Reactions* **1990**, *38*, 655

The Nef Reaction

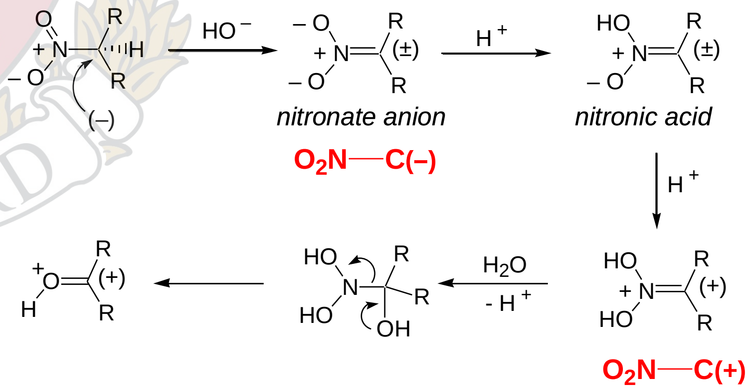
- **Overall Transformation:**



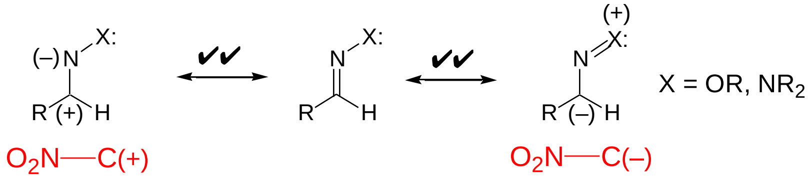
- Mechanism



The charge affinity patterns represented

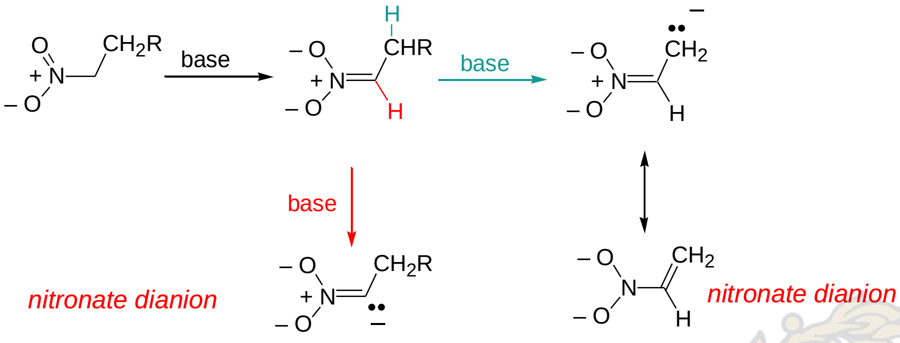


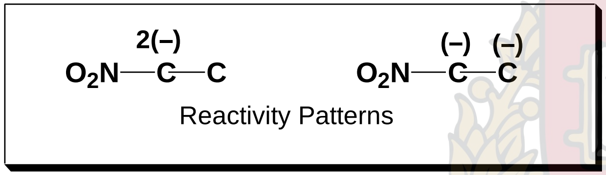
- **The resonance features which have been exploited:**



X = OR, NR$_2$

Other Nonalternate Behavior of –NO_2 FG

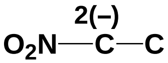


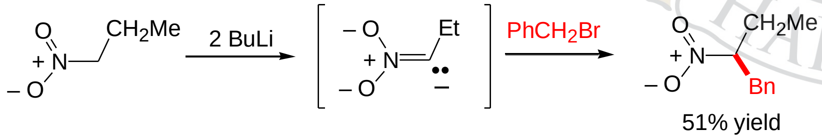

$$O_2N\text{—}\overset{2(-)}{C}\text{—}C \qquad O_2N\text{—}\overset{(-)}{C}\text{—}\overset{(-)}{C}$$

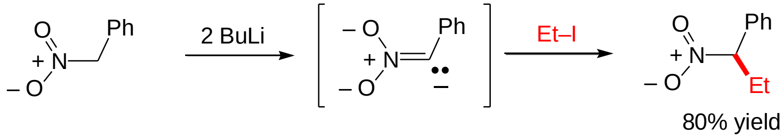
Reactivity Patterns

Seebach et. al. *Tetrahedron Lett.* **1977**, 1161-1164

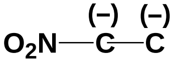
Representative examples:

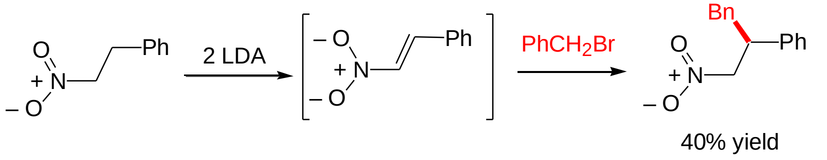

$$O_2N\text{—}\overset{2(-)}{C}\text{—}C$$

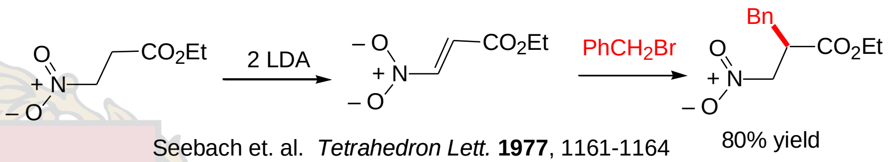




Representative examples:


$$O_2N\text{—}\overset{(-)}{C}\text{—}\overset{(-)}{C}$$





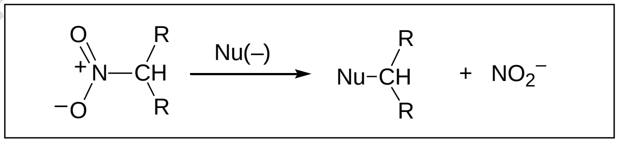
Seebach et. al. *Tetrahedron Lett.* **1977**, 1161-1164

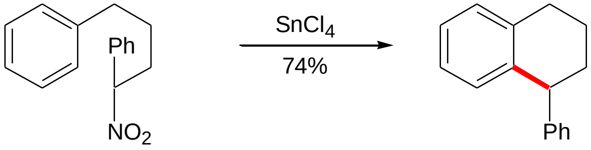
–NO_2 As a Leaving Group

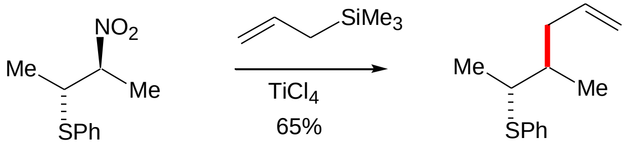
Review: Tamura et. al. *Synthesis* **1991**, 423-434.

"Nitroaliphatic Compounds–Ideal Intermediates in Organic Synthesis"'
Seebach, D. etal, *Chimia*, **1979**, *33*, 1-18

Representative examples: O_2N—C(+)

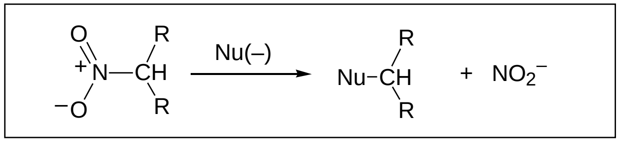


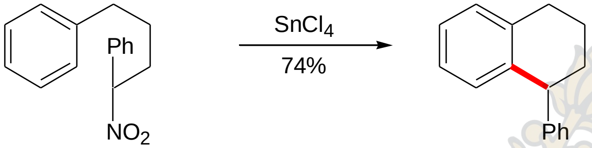


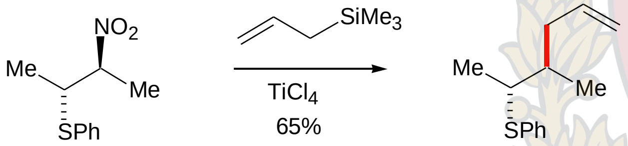


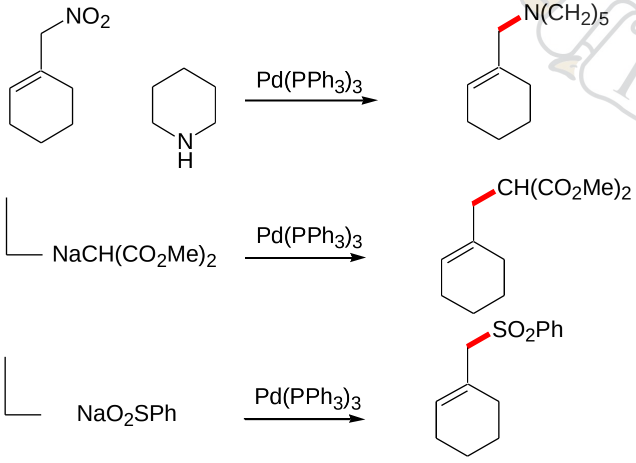
–NO_2 As a Leaving Group

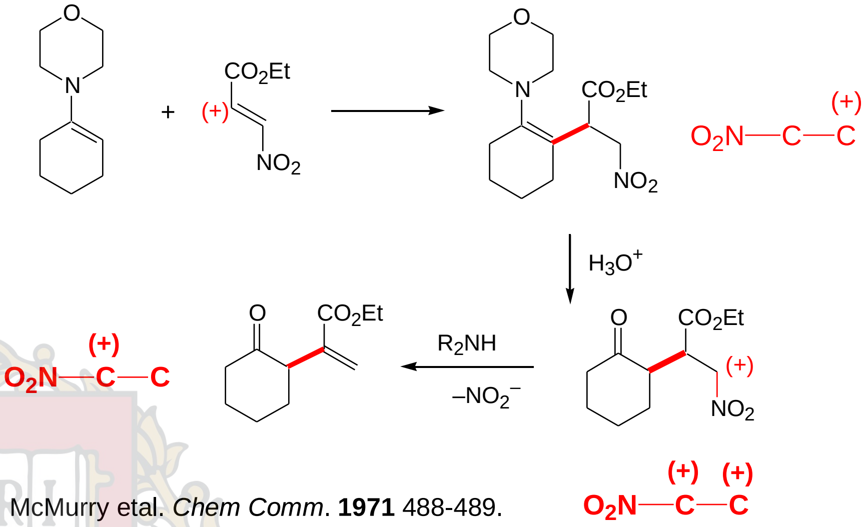
Representative examples: **O_2N—C (+)**



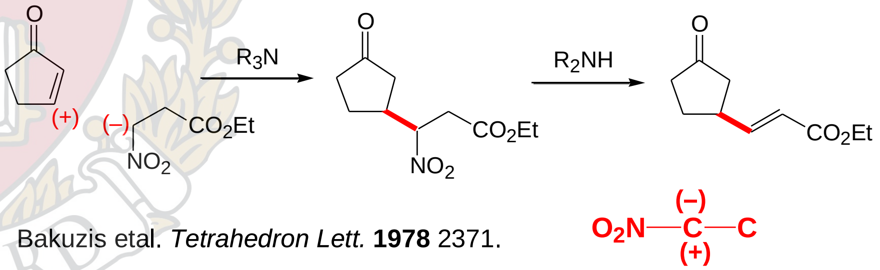




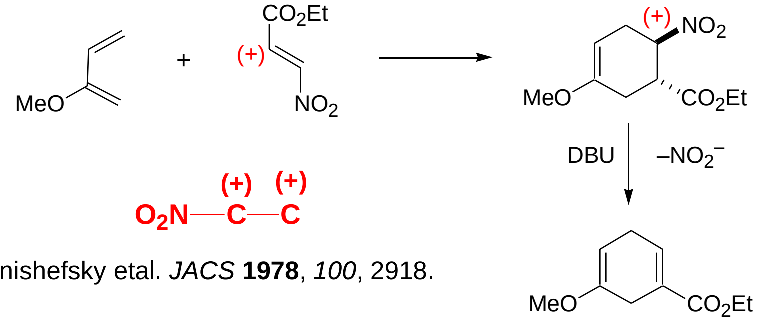




McMurry etal. *Chem Comm*. **1971** 488-489.



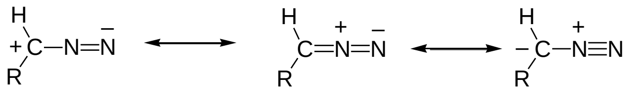
Bakuzis etal. *Tetrahedron Lett.* **1978** 2371.



Danishefsky etal. *JACS* **1978**, *100*, 2918.

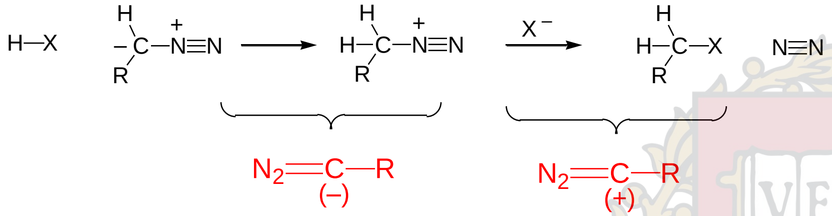
Other Functional Groups with Non-alternate Reactivity Patterns

The Diazo Functional Group



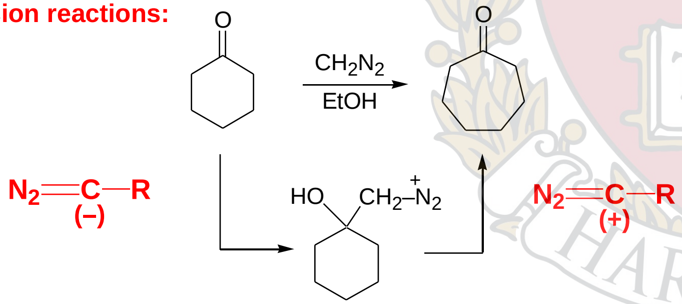
- Both (+) and (–) reactivity patterns suggested by resonance structures

- Rxns with acids:



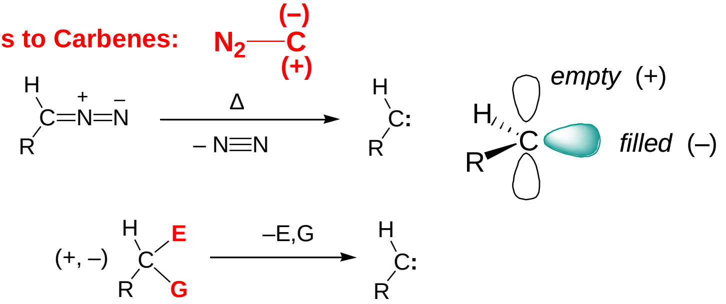
- **Initiating reactivity is (–); subsequent reactivity is (+)**

- **Ring expansion reactions:**



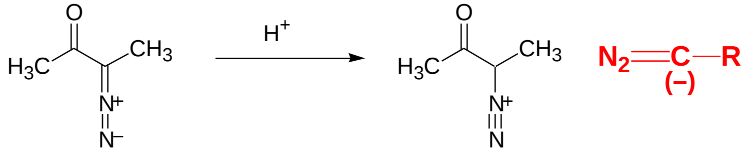
Restriction: Starting ketone must be more reactive than product ketone

- **Precursors to Carbenes:**



Acid Catalyzed Reactions of Diazo Compounds

Review: Smith, Tet. 1981 2407

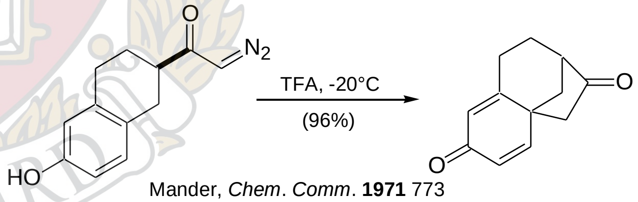


Diazocarbonyl *Diazonium*

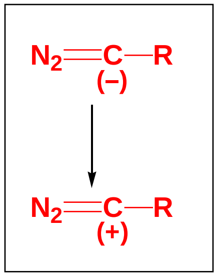
Common acids include BF_3•OEt_2, HBF_4, TFA, etc.

Mechanism of activation is unclear for both Lewis and protic acids; activation may occur by protonation on C or O

Acid-Catalyzed Reactions

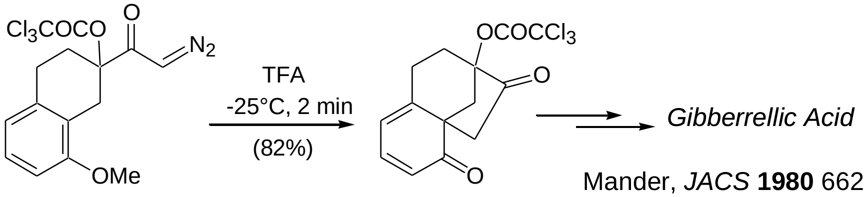


Mander, *Chem*. *Comm*. **1971** 773
Tet., **1991** 134



"Having become familiar with the peculiarities of diazoketone chemistry while preparing [other compounds] (and, I might add, inured to handling uncomfortably large quantites of diazomethane), it occurred to us that we might be able to substitute a diazo group for bromine."

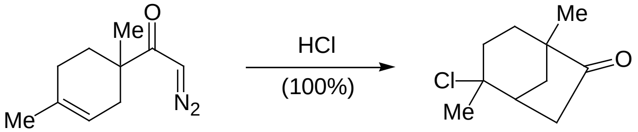
Lewis Mander



Mander, *JACS* **1980** 6626

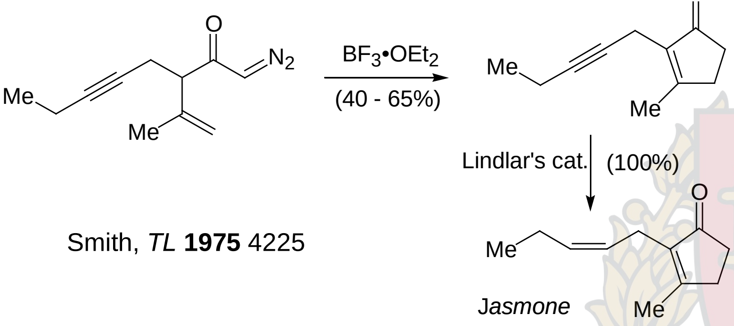
More Acid Catalysis

Olefins as nucleophiles:



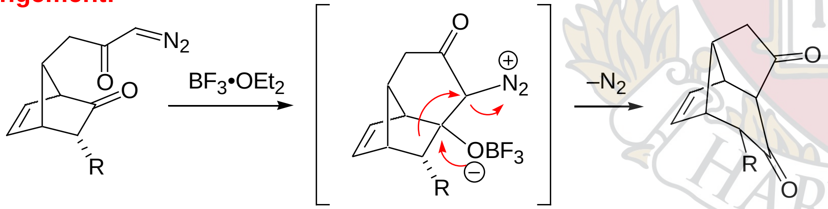
Mander

Smith's cyclopentenone annulation:



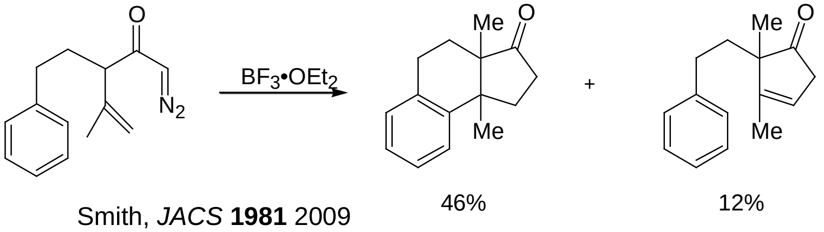
Smith, *TL* **1975** 4225

Rearrangement:



Mander, *Aust. J. Chem.* **1979** 1975

Polyene cyclizations:



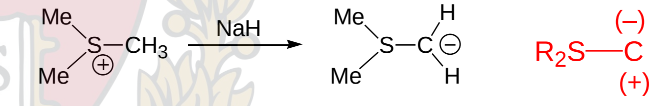
Smith, *JACS* **1981** 2009

Sulfur Functional Groups

Simpkins, N. S. *Sulfones in Organic Synthesis.*; Pergamon, 1993.

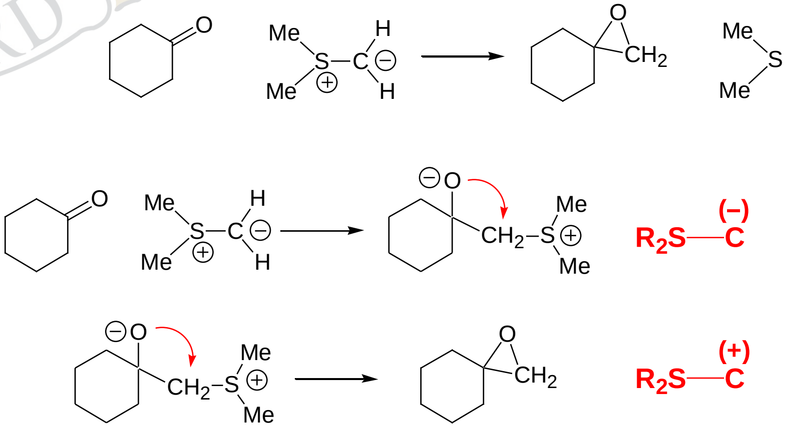
		pKa (DMSO)	
			← CH_4
CH_3-S-CH_3	Sulfide	(45)	pKa (~56)
			← NH_3
$CH_3-\overset{O}{\overset{\|}{S}}-CH_3$	Sulfoxide	~35	pKa (~41)
$CH_3-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-CH_3$	Sulfone	~ 31	← HOH pKa 31
$CH_3-\overset{CH_3}{\underset{\oplus}{S}}-CH_3$	Sulfonium Salt	~ 18	

(same acidity as phenol)



Reactivity Pattern Nonalternate

■ Reactions with carbonyl compnds



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 27

Ambiphilic Functional Groups–2
Sulfur-Based Activating Groups

- Sulfur-Ylides
- Sulfur-Stabilized Carbanions: Structure
- Sulfone-Based Transformations
- Pummerer Rearrangement

Reading Assignment for this Week:

Carey & Sundberg: **Part A**; Chapter 7
Carbanions & Other Nucleophilic Carbon Species

Carey & Sundberg: **Part B**; Chapter 2
Reactions of Carbon Nucleophiles with Carbonyl Compounds

"Chemical Chameleons: Organosulfones as Synthetic Building Blocks"
B. M. Trost, *Bull. chem. Soc. Japan,* **1988**, *61*, 107-124 **(handout)**

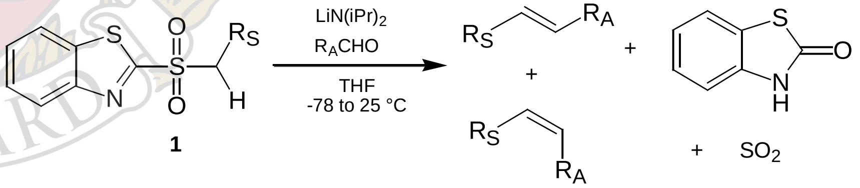
Matthew D. Shair

Wednesday,
November 20, 2002

Relevant Background Reading

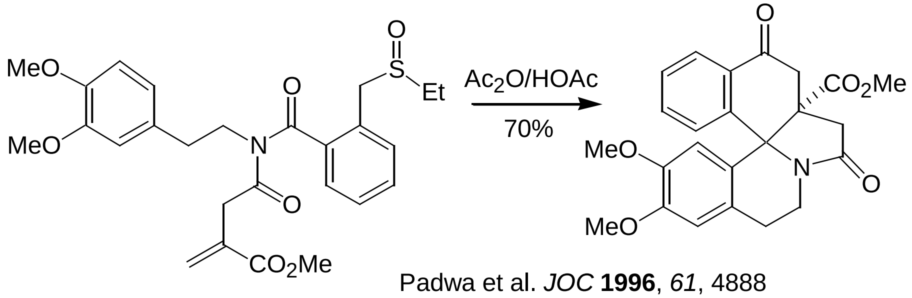
General:	Simpkins, N.S. *Sulphones in Organic Synthesis*, Pergamon Press, New York, 1993.
General:	Magnus, P.D. *Tetrahedron* **1977**, *33*, 2019.
Julia:	Kocienski, P.J. *Chem. Ind.(London)* **1981**, 548.
Electrophilic Properties:	Trost, B.M. *Bull.Chem. Soc. Jpn.* **1988**, *61*, 107.
SO_2 Extrusion:	Vogtle, F.; Rossa, L. *ACIEE* **1979**, *18*, 515.
Ramberg-Bäcklund Rxn:	Paquette, L.A. *Org. Reactions* **1977**, *25*, 1.
Triflones:	Hendrickson, J.B. *Org. Prep. Proc. Int.* **1977**, 175.
Sulfoximides:	Johnson, C.R. *Tetrahedron* **1984**, *40*, 1225

Cume Question, 1998: The stereoselective construction of trans olefins through carbanion-mediated condensation processes has still not been rendered general. One transformation that may be used in certain circumstances is the "one-step" Julia transformation illustrated below. Provide a mechanism for this transformation.



1

The cruel mechanistic problems that you should be prepared for in Chem 206

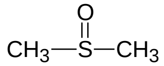
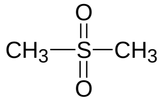
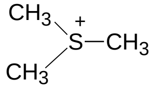


Padwa et al. *JOC* **1996**, *61*, 4888

Relevant Background Reading

General:	Simpkins, N.S. *Sulphones in Organic Synthesis*, Pergamon Press, New York, 1993.
General:	Magnus, P.D. *Tetrahedron* **1977**, *33*, 2019.
Julia:	Kocienski, P.J. *Chem. Ind.(London)* **1981**, 548.
Electrophilic Properties:	Trost, B.M. *Bull.Chem. Soc. Jpn.* **1988**, *61*, 107.
SO_2 Extrusion:	Vogtle, F.; Rossa, L. *ACIEE* **1979**, *18*, 515.
Ramberg-Bäcklund Rxn:	Paquette, L.A. *Org. Reactions* **1977**, *25*, 1.
Triflones:	Hendrickson, J.B. *Org. Prep. Proc. Int.* **1977**, 175.
Sulfoximides:	Johnson, C.R. *Tetrahedron* **1984**, *40*, 1225

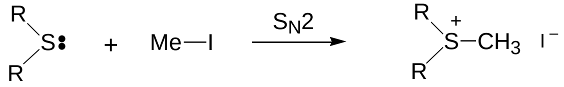
Acidities of Sulfur-based Functional Groups

		pKa (DMSO)	
			← CH_4 pKa (~56)
$CH_3{-}S{-}CH_3$	Sulfide	(45)	
			← NH_3 pKa (~41)
 $CH_3{-}\overset{O}{\overset{\|}{S}}{-}CH_3$	Sulfoxide	~35	
 $CH_3{-}\overset{O}{\overset{\|}{\underset{\underset{O}{\|}}{S}}}{-}CH_3$	Sulfone	~ 31	← HOH pKa 31
	Sulfonium Salt	~ 18	

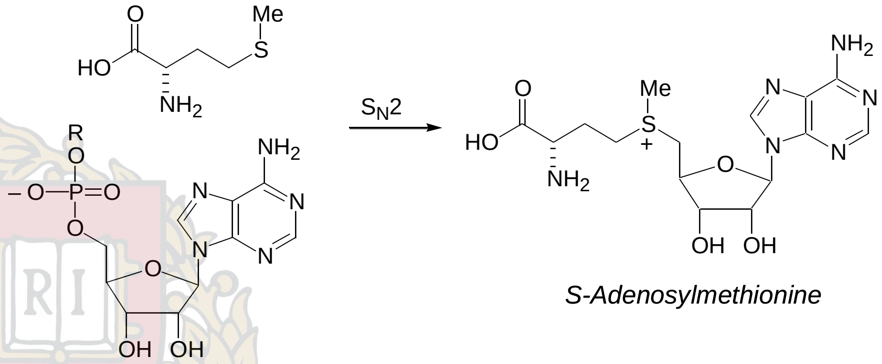
Bordwell, F. G.; Zhang, X.-M. *Acc. Chem. Res.* **1993**, *26*, 510-17.

Reactions of Sulfonium Ylids

Synthesis:

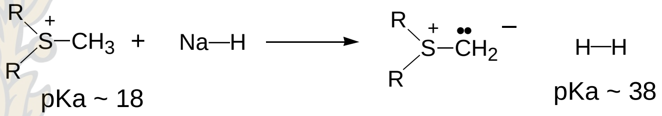


Sulfonium Salt: pKa ~ 18

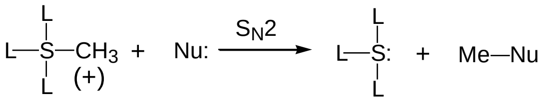


S-Adenosylmethionine

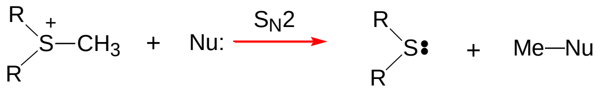
Deprotonation:



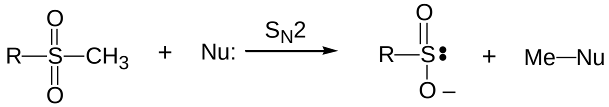
Leaving Group Potential: R_2S—C(+)



Excellent LG

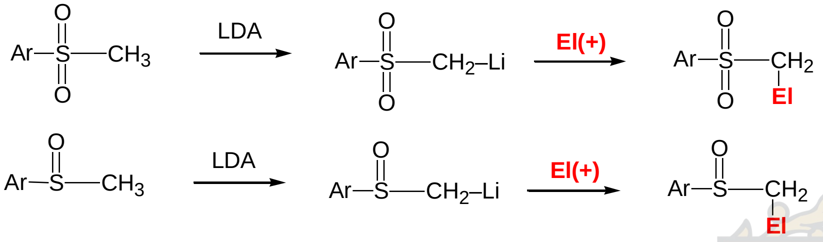


Good LG



Sulfone- & Sulfoxide Based Carbanions: Structure

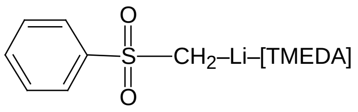
- Sulfone- and sulfoxide-stabilized carbanions are extremely useful carbon nucleophiles in organic synthesis.

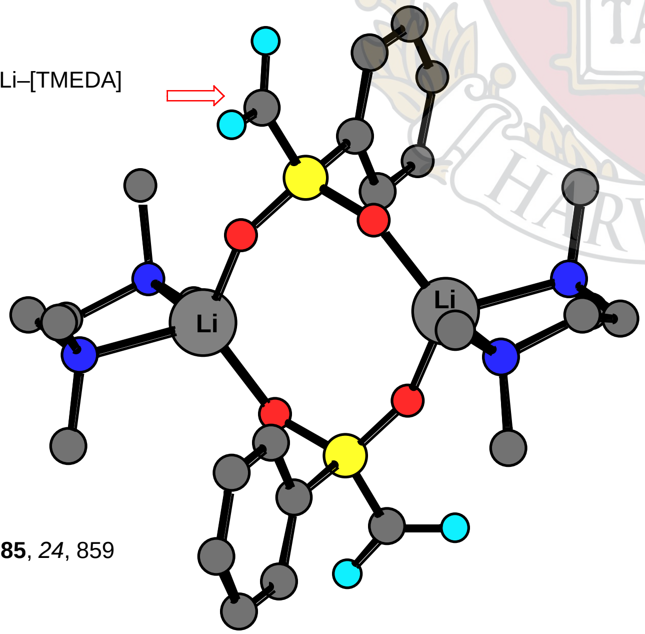


However, until recently little information was available on the solid state structures of these species:

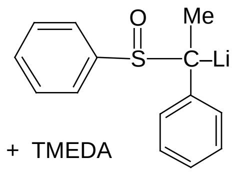
"The Structure of Lithium Coumpounds of Sulfones, Sulfoximides, Sulfoxides, Thioethers, 1,3 Dithianes, Nitriles, Nitro Compounds, and Hydrazones." Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

Here are several examples taken from the Boche review:

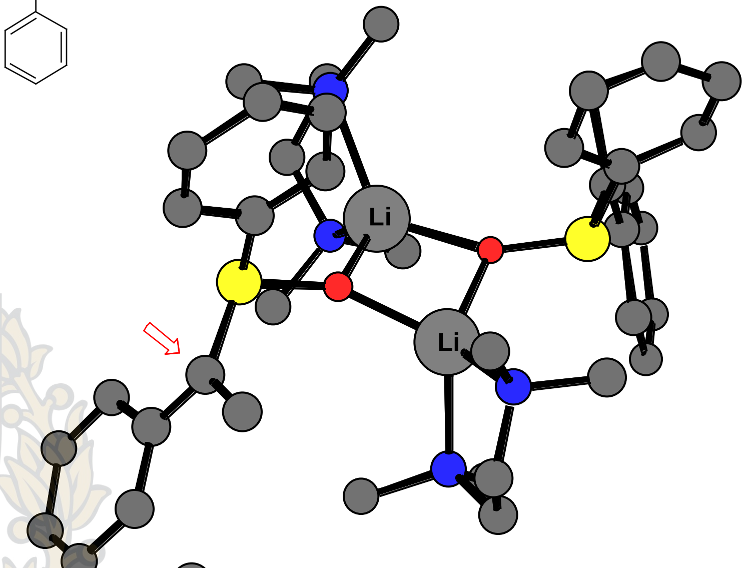


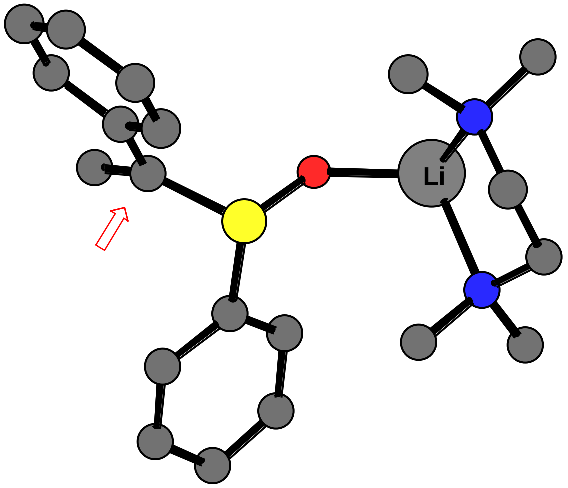


Gais, etal.
Angew. Chem. Int. Ed. **1985**, *24*, 859



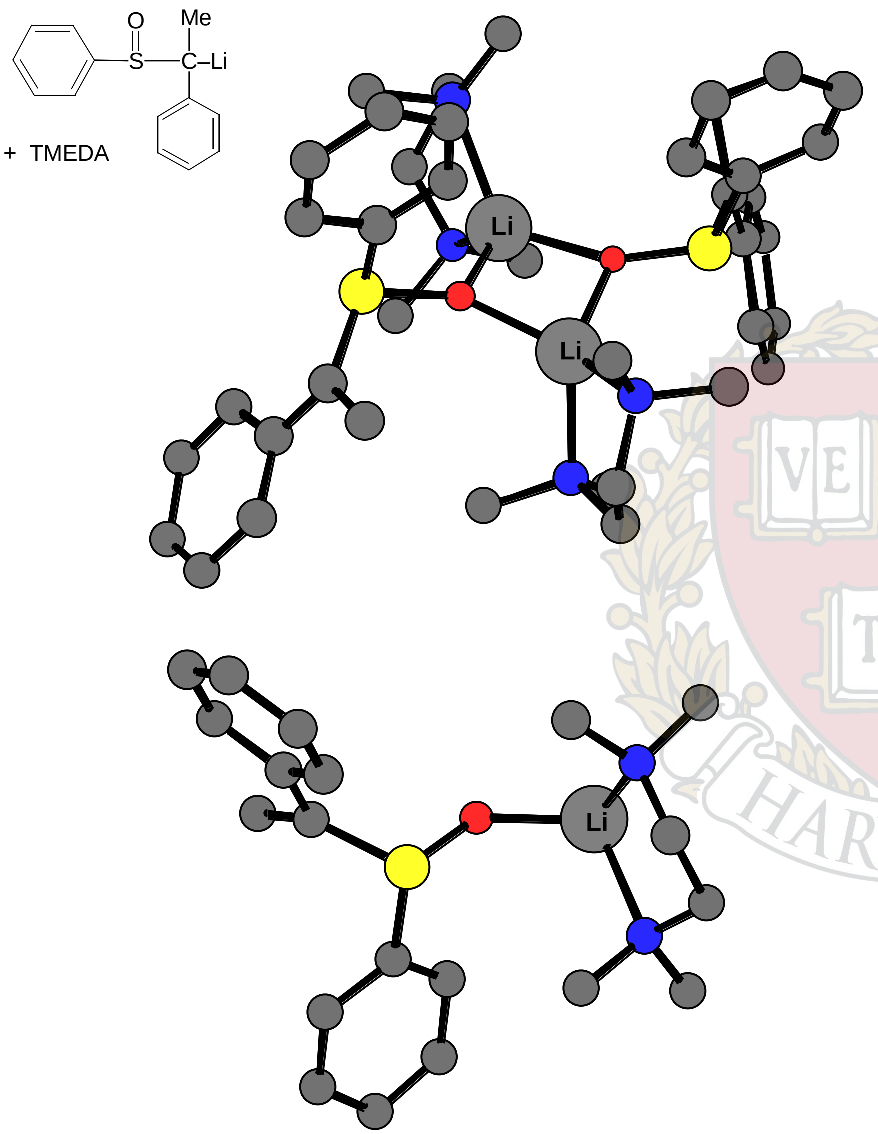
Boche, etal. *Angew. Chem. Int. Ed.* **1986**, *25*, 1101



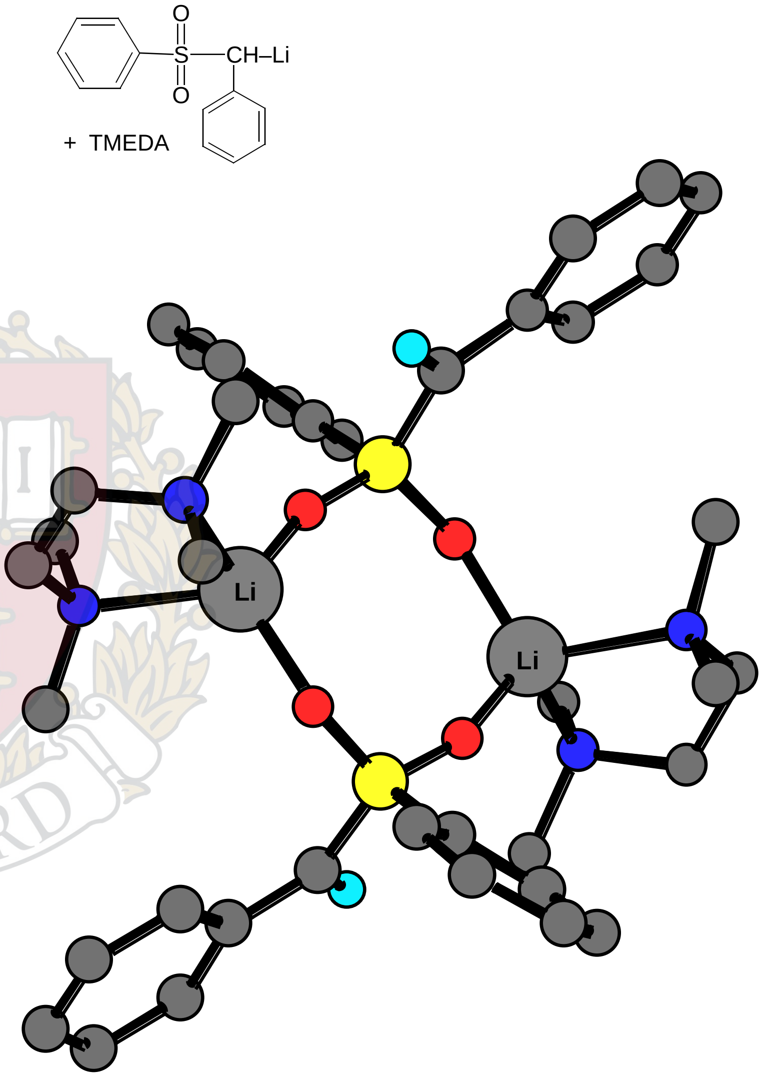


- The Li counterions are not associated with the charged carbon.
- The carbanions are largely trigonal.

X-ray Structures of Phenylsulfinyl Carbanions

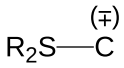


Boche, etal. *Angew. Chem. Int. Ed.* **1986**, *25*, 1101



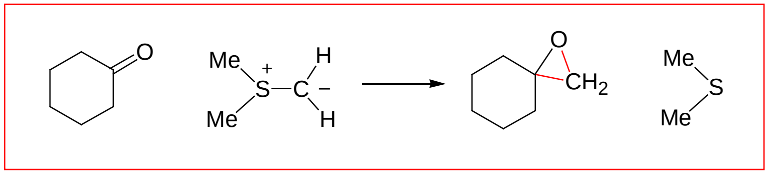
Boche, etal. *Angew. Chem. Int. Ed.* **1985**, *24*, 573

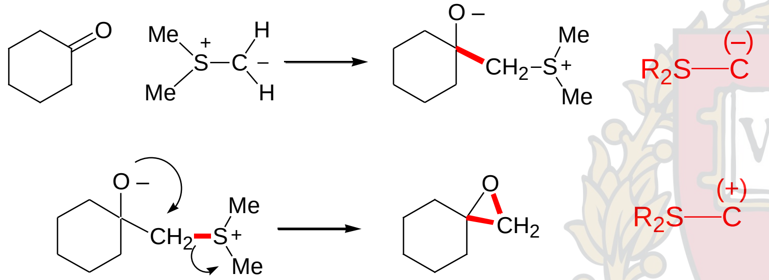
Reactions with ketones:



$R_2S—\overset{(\mp)}{C}$

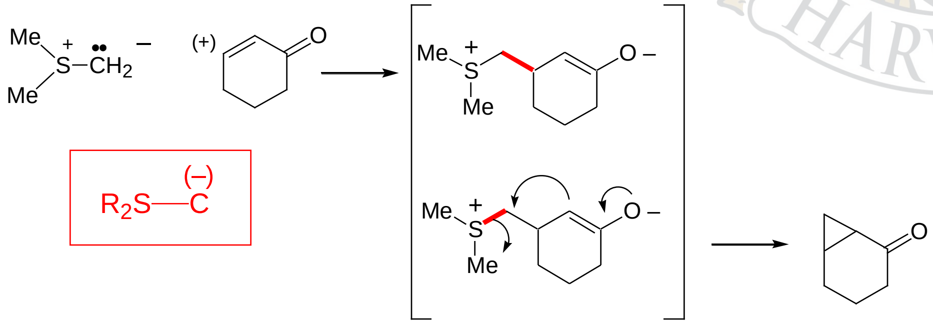
Reactivity Pattern: Nonalternate



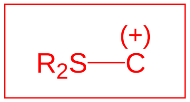


"Twenty-five Years of Dimethylsulfoxonium Methylide (Corey's Reagent).", Gololobov, Y. G.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609.

Reactions of Sulfonium Ylids: Conjugate Addition



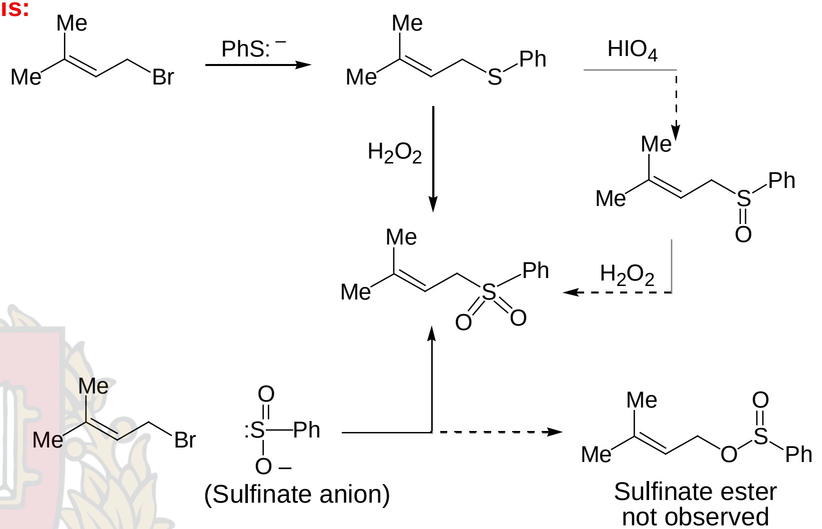
Nonalternate reactivity pattern revealed in consecutive reactions



$R_2S—\overset{(+)}{C}$

Reactions of Sulfones

Synthesis:

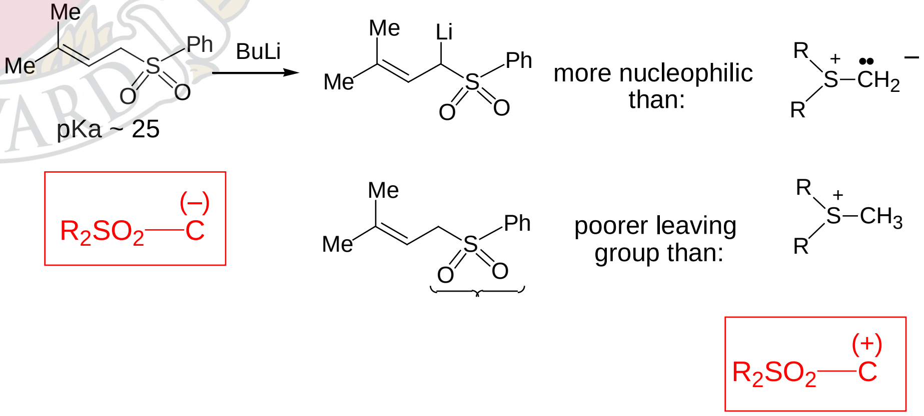


(Sulfinate anion)

Sulfinate ester
not observed

Good review article: Magnus, *Tetrahedron* **1977**, *33*, 2019-2045.

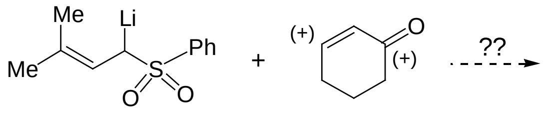
Reactions of Sulfones



pKa ~ 25

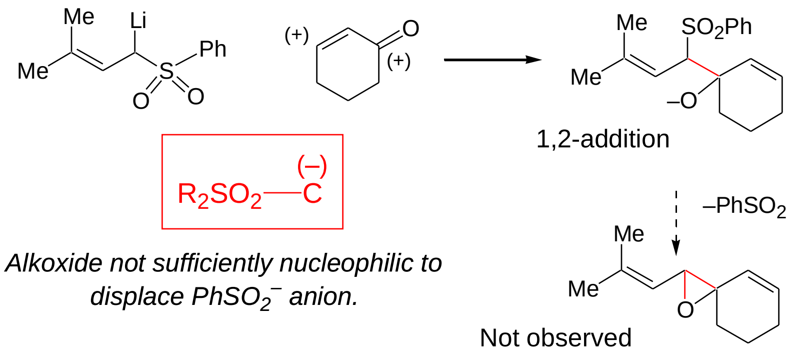
more nucleophilic than:

poorer leaving group than:



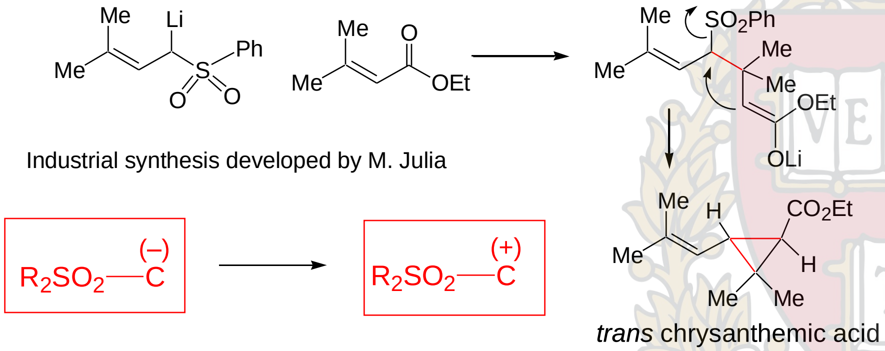
1,2- vs 1,4-addition ??

Will function as LG ??



Alkoxide not sufficiently nucleophilic to displace $PhSO_2^-$ anion.

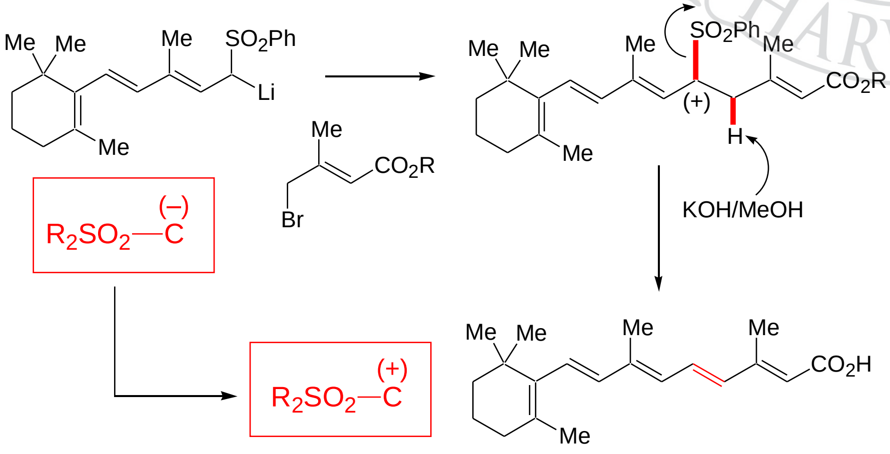
However!!



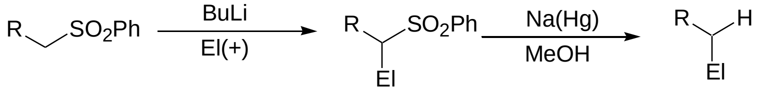
trans chrysanthemic acid

Industrial synthesis developed by M. Julia

Synthesis of Vitamin A: Julia & Co-workers, *Bull. Soc. Chim. Fr.* **1985**, 130

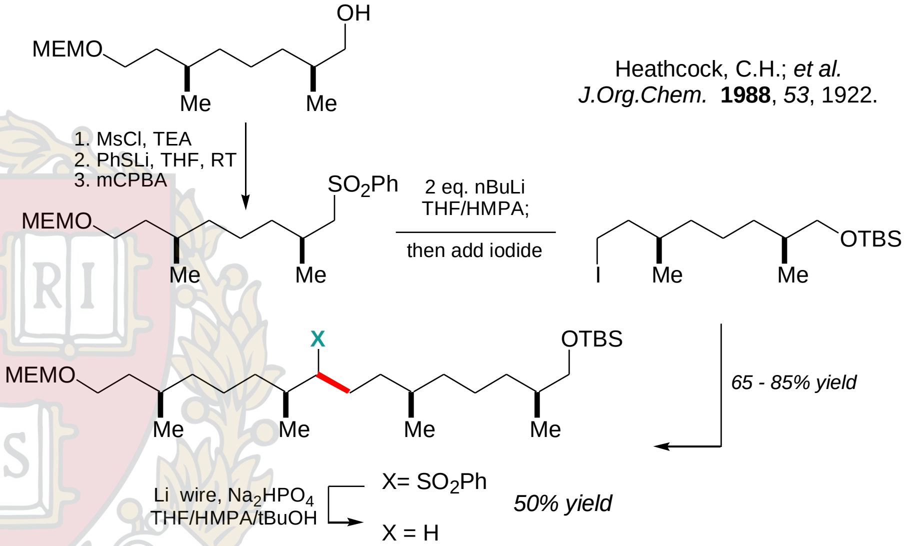


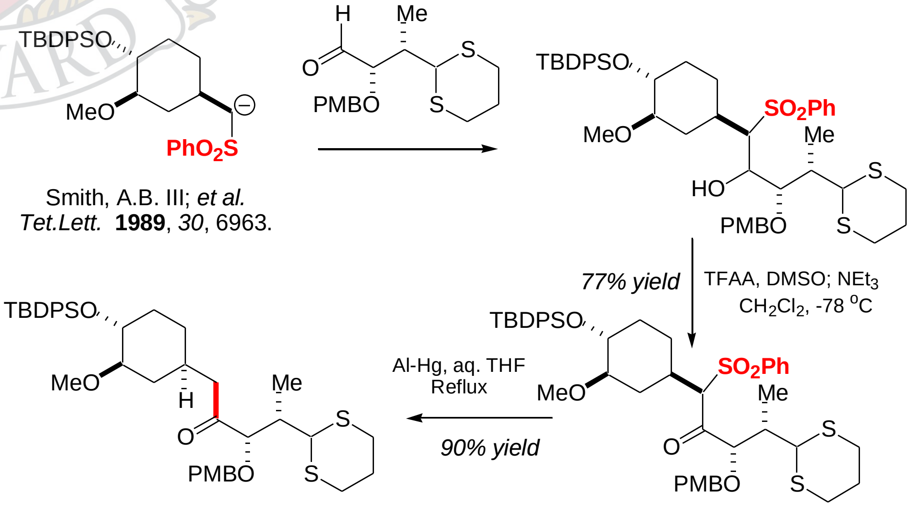
The Sulfone group may also be readily removed reductively:



Fragment Coupling with Sulfonyl Carbanions

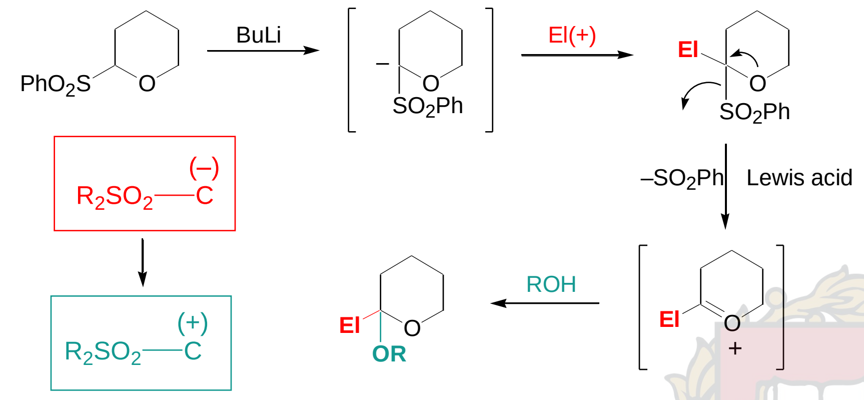
Heathcock, C.H.; *et al.*
J.Org.Chem. **1988**, *53*, 1922.





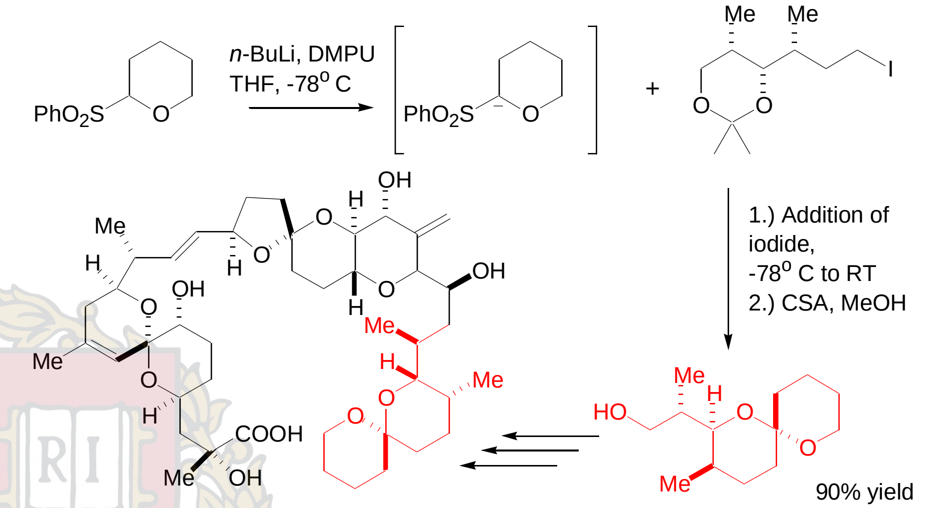
Smith, A.B. III; *et al.*
Tet.Lett. **1989**, *30*, 6963.

Functionalization of cyclic Ethers



Ley *et al*, *Synlett*, **1992**, 395; Ley *et. al*, *Tetrahedron*, **1992**, *48*, 7899

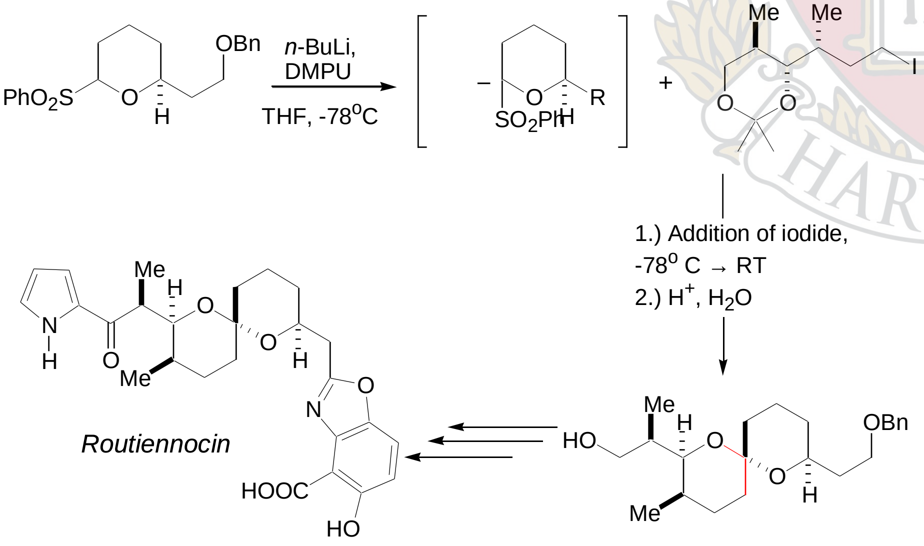
Total synthesis of Okadaic Acid



90% yield

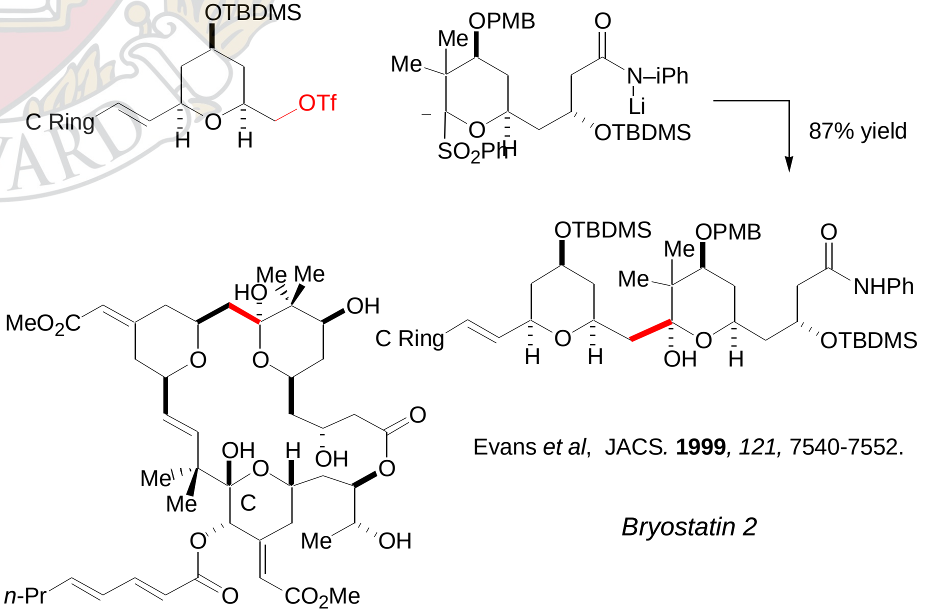
Ley *et al, J. Chem. Soc., Perkin Trans. 1*, **1998**, 3907.

Total Synthesis of Routiennocin (CP-61,405)



68% yield

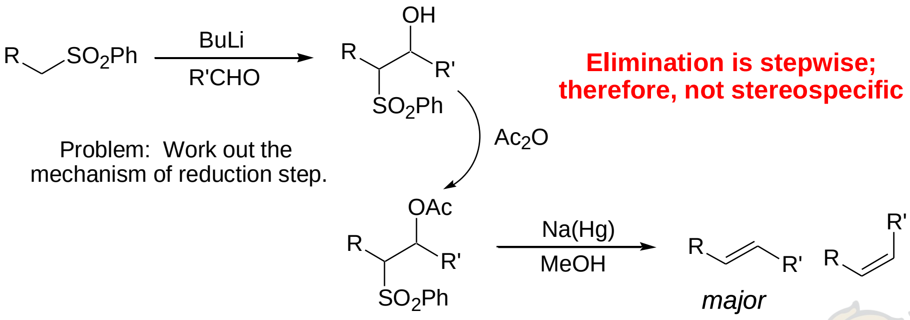
Total synthesis of Bryostatin 2



Evans *et al*, JACS. **1999**, *121*, 7540-7552.

Bryostatin 2

Julia Trans Olefin Synthesis:



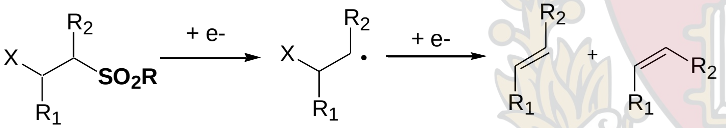
Elimination is stepwise; therefore, not stereospecific

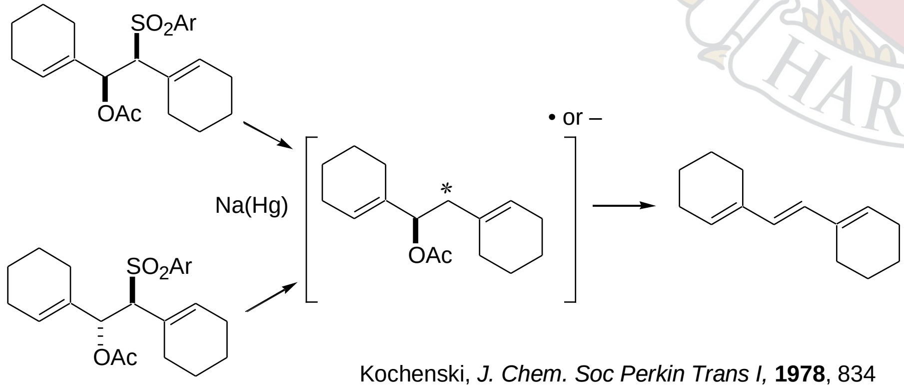
Problem: Work out the mechanism of reduction step.

Good sulfone review: Trost, *Bull Chem. Soc. Japan*, **1988**, *61*, 107-124.

Review: Kocienski etal. *Phosphorus & Sulfur* **1985**, *24*, 97-127

The reduction step is not stereosecific



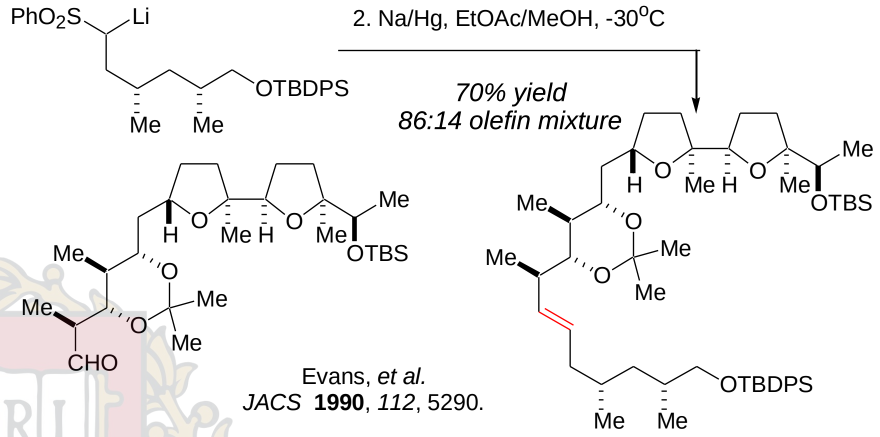


Kochenski, *J. Chem. Soc Perkin Trans I*, **1978**, 834

Julia Olefination - Ionomycin

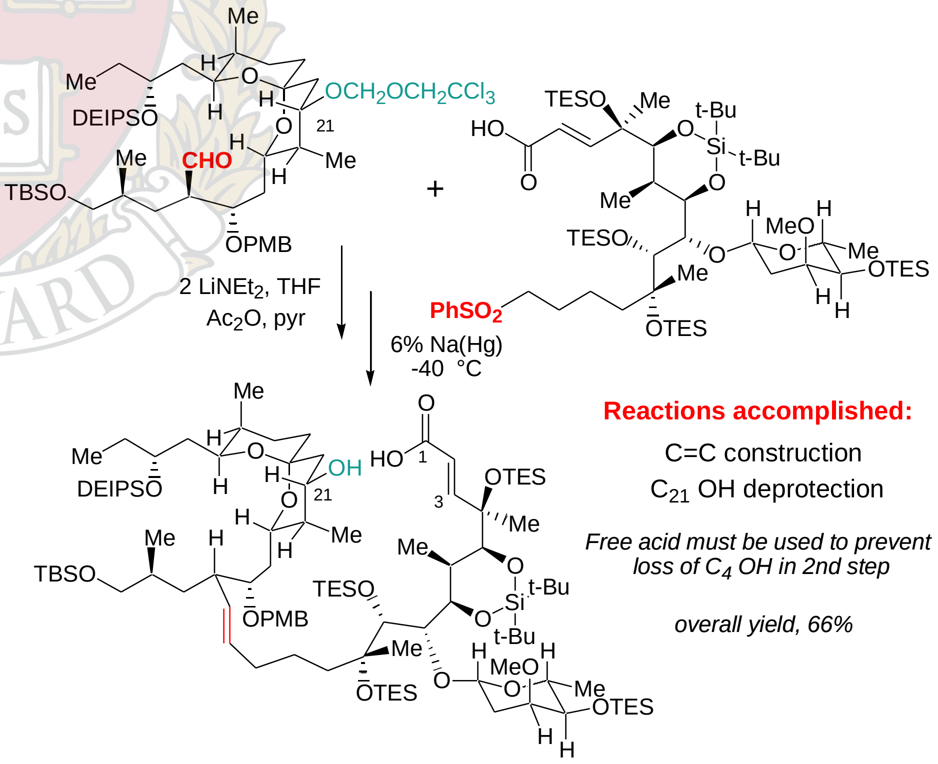
1. add RCHO, -78°C;
   add Ac$_2$O, -78°C to R.T.
2. Na/Hg, EtOAc/MeOH, -30°C

70% yield
86:14 olefin mixture



Evans, *et al.*
JACS **1990**, *112*, 5290.

Cytovaricin Synthesis: *JACS* 1990, *112*, 7001



Reactions accomplished:

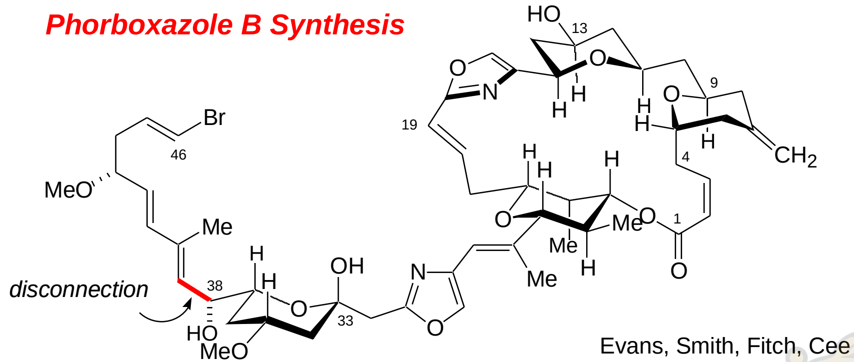
C=C construction

C_{21} OH deprotection

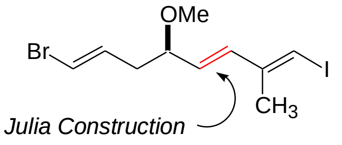
Free acid must be used to prevent loss of C_4 OH in 2nd step

overall yield, 66%

Phorboxazole B Synthesis

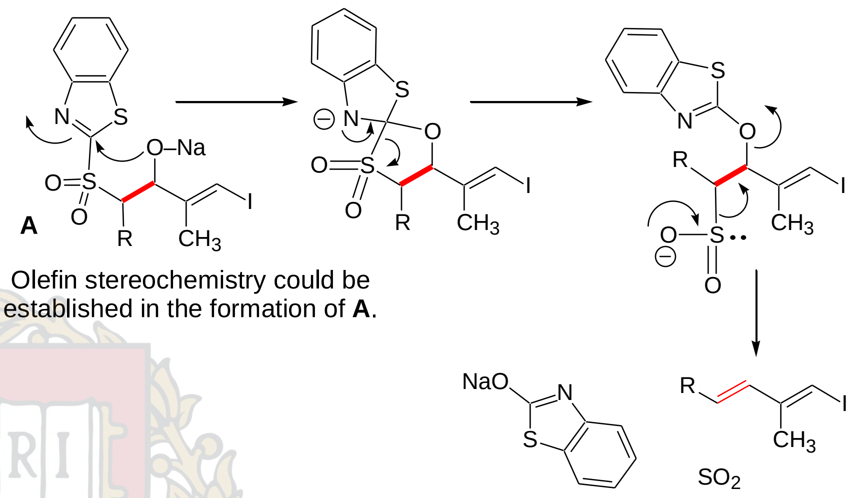


Evans, Smith, Fitch, Cee
JACS **2000**, *122*, 10033-10046.

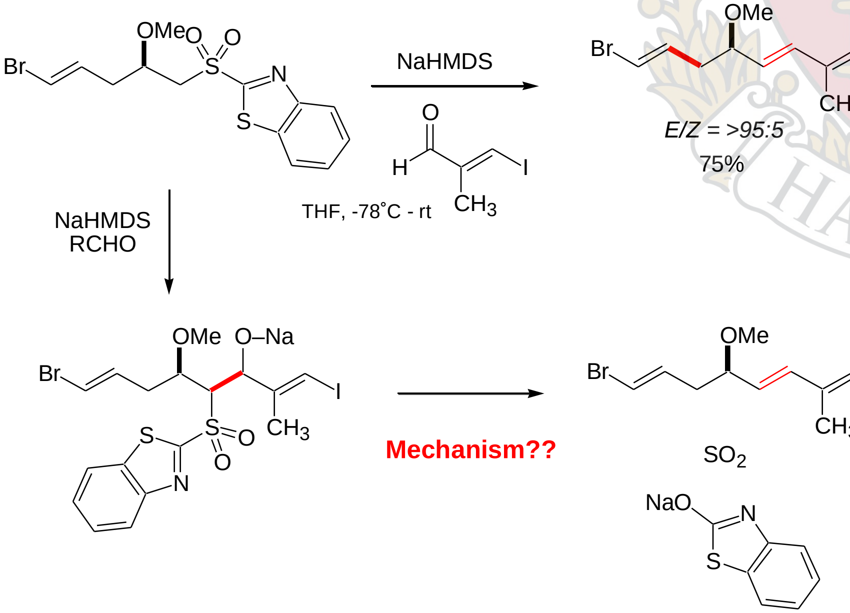


C_{39}–C_{46} Synthon

The Mechanism:

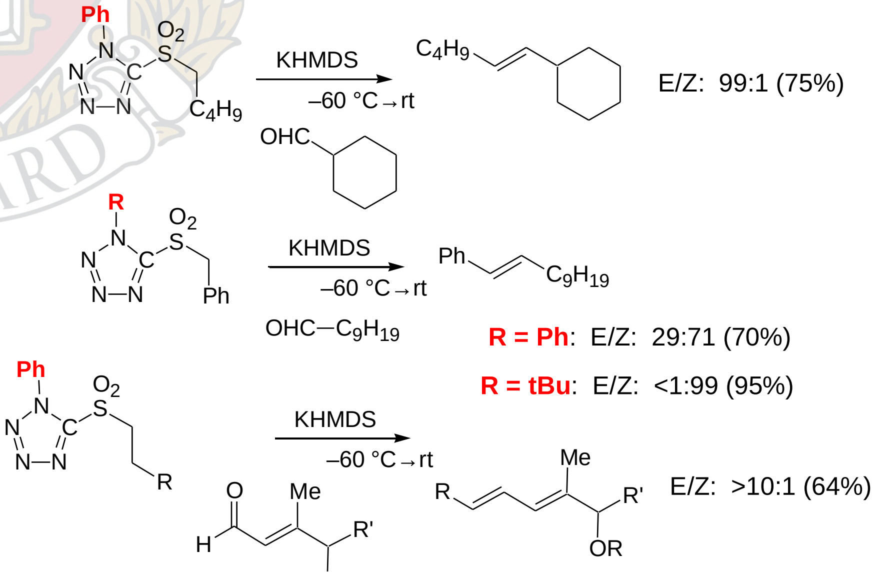


Olefin stereochemistry could be established in the formation of **A**.



Recent Modifications of the Julia Process:

Kocienski, *SynLett* **2000**, *3*, 365-366.



E/Z: 99:1 (75%)

R = Ph: E/Z: 29:71 (70%)

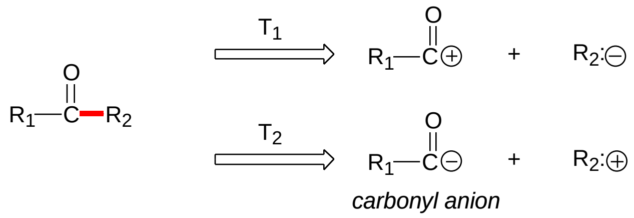
R = tBu: E/Z: <1:99 (95%)

E/Z: >10:1 (64%)

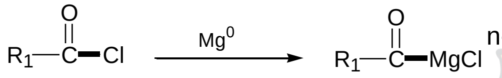
Metternich, *JOC* **1999**, *54*, 9632

Carbonyl Anions: A useful Reversed Polarity Equivalent

Consider the two possible polar disconnections of the C–R_2 bond of the ketone shown below:

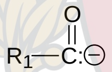


Carbonyl anions are not normally accessible via aldehyde deprotonation

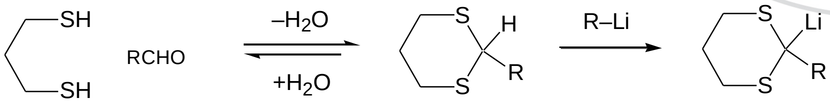


not feasible !!
Why??

Operational equivalents to the carbonyl anion are useful in synthesis



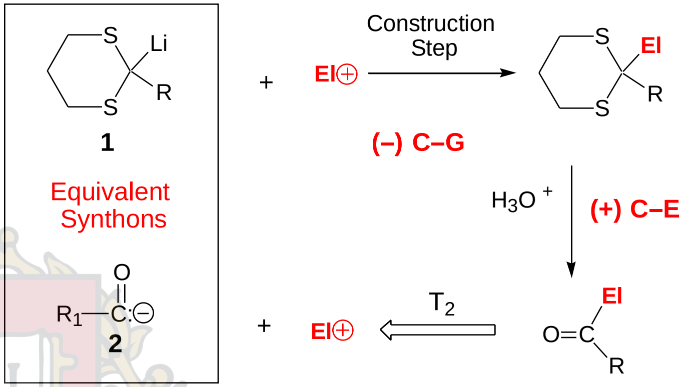
1,3-Dithianes as Carbonyl Anion Equivalents



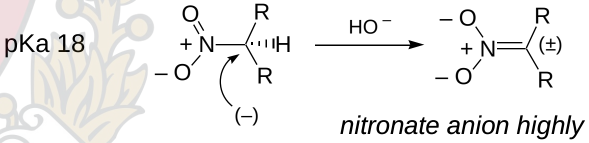
pKa ~ 39

Reactivity Patterns: $(RS)_2$–C(+) $(RS)_2$–C(–)

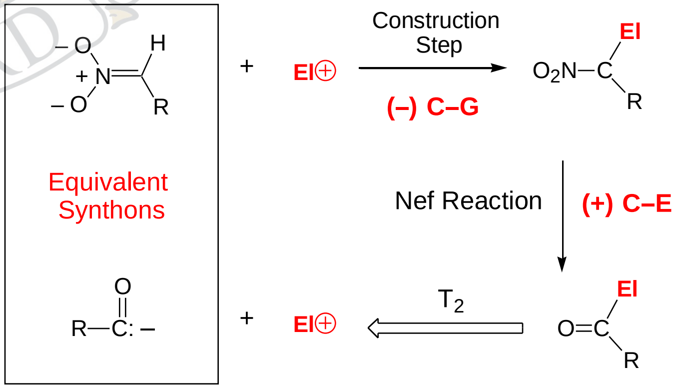
The overall set of reactions which establishes the equivalency of the hypothetical carbonyl anion **1** and its equivalent synthon **2** is shown below:



Nitronate Anions are also useful Carbonyl Anions

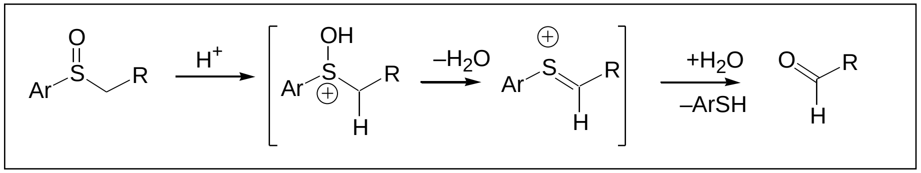


nitronate anion highly stablized

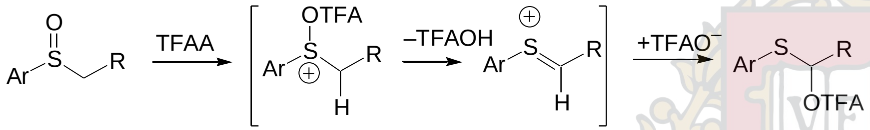


Dithianes anions highly nucleophilic (indiscriminate):
Nitonate anions higly discriminating

Basic Transformation:



The Pummerer Rearrangement facilitates the transformation of a sulfinyl → aldehyde transformation. The rearrangement may be initiated by either a Bronsted acid or an anhydride such as trifluoroacetic anhydride (TFAA). With the latter reagent, the transformation occurs at room temperature.



Leading References

De Lucchi, Miotti, et al. (1991). “The Pummerer reaction of sulfinyl compounds.” *Organic Reactions* **1991**, *40*: 157.

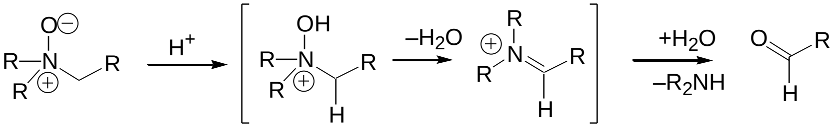
Grierson, and Husson (**1991**). Polonovski- and Pummerer-type Reactions and the Nef Reaction. *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. *6*: 909.

Padwa, A., D. E. Gunn, et al. “Application of the Pummerer reaction toward the synthesis of complex carbocycles and heterocycles.” *Synthesis* **1997** 1353-1377.

Carreno, “Applications of sulfoxides to asymmetric synthesis of biologically active compounds.” Chem. Reviews **1995** *95*, 1717-1760.

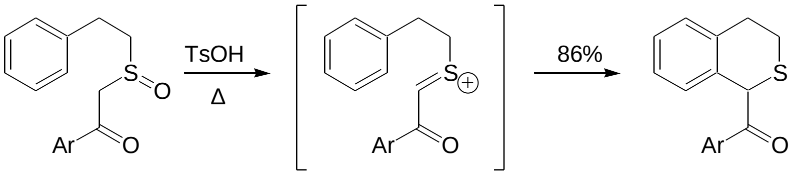
Kita, Y. and N. Shibata (1996). “Asymmetric pummerer-type reactions induced by O-silylated ketene acetals.” Synlett(4): 289-296.

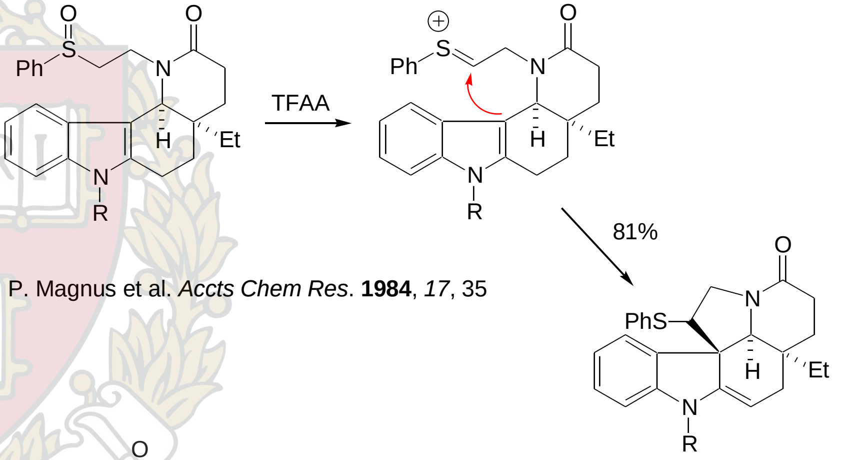
The Related Polonovski Reaction:



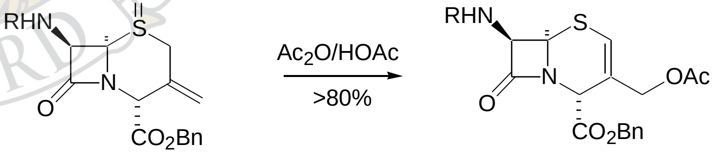
Regioselectivfity: *Depends on the relative kinetic acidy of the α protons*

Transformations Mediated by the Pummer Rearrangement

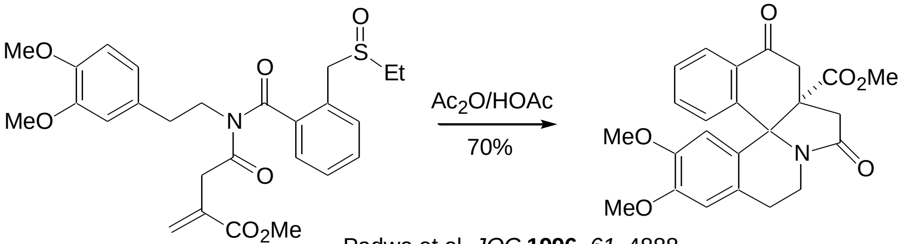




P. Magnus et al. *Accts Chem Res*. **1984**, *17*, 35

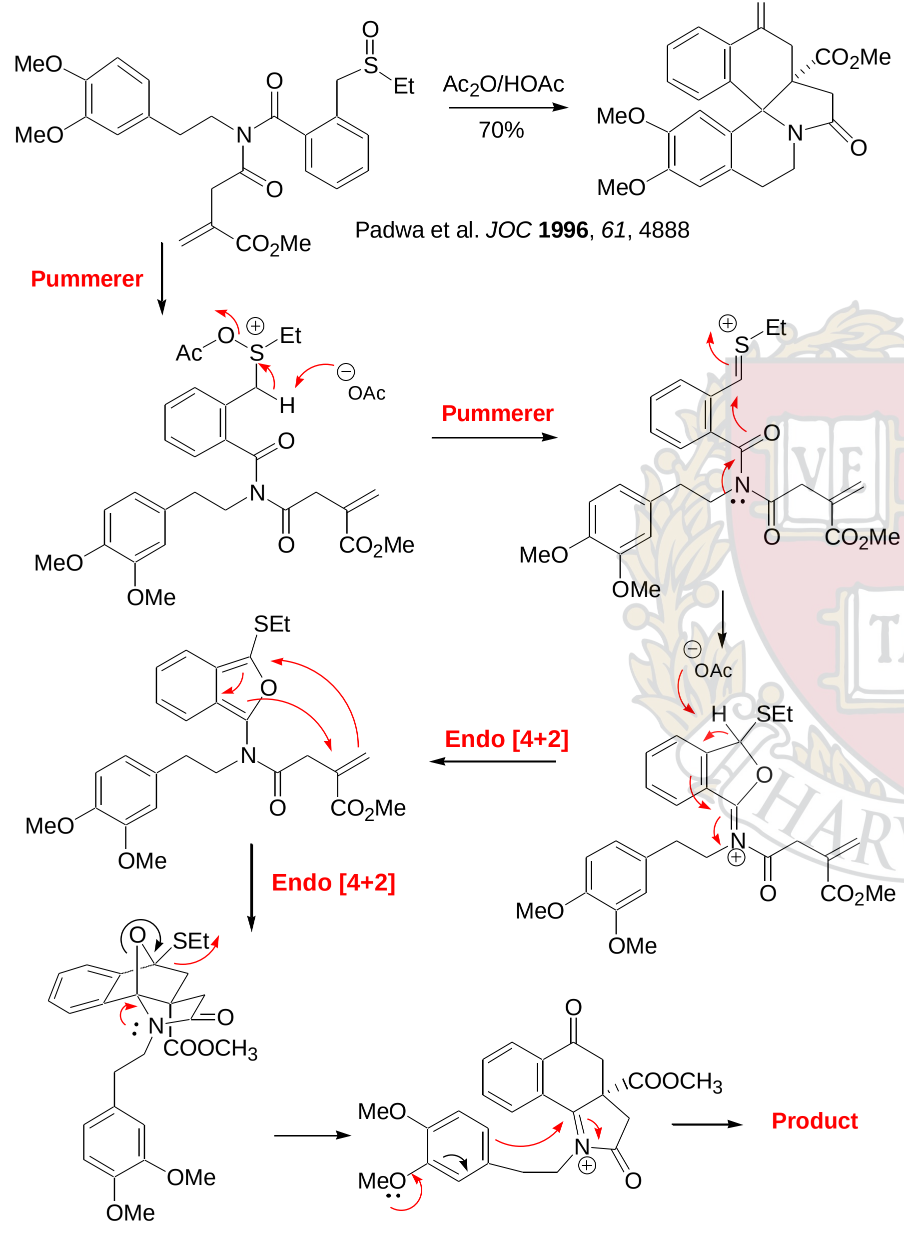


The cruel mechanistic problems that you should be prepared for in Chem 206



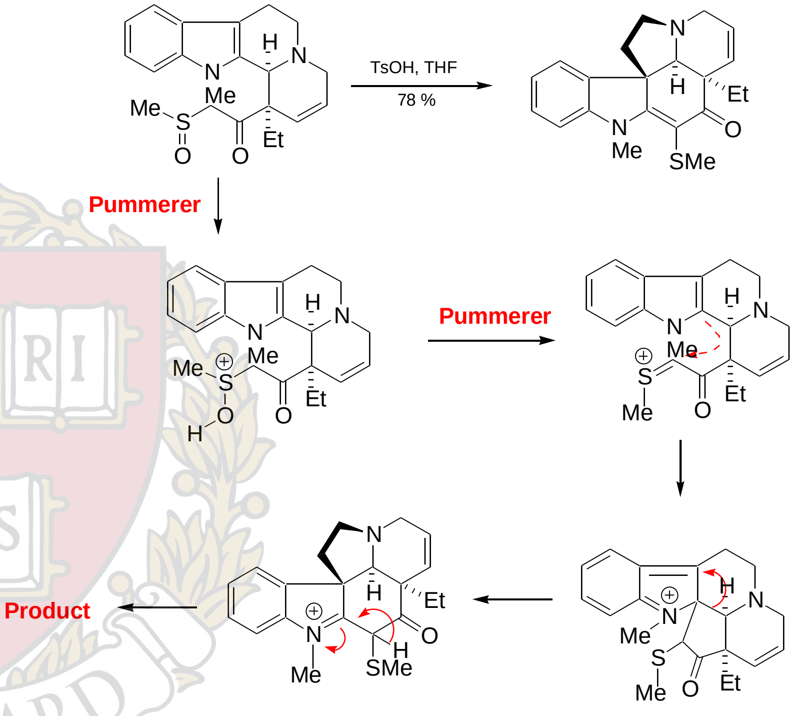
Padwa et al. *JOC* **1996**, *61*, 4888

Mechanism??



Padwa et al. *JOC* **1996**, *61*, 4888

Exam 3, 2000: Question 5 (11 points). An interesting rearrangement which also results in the construction of this same ring system (Question 4) has been reported by Langlois & coworkers (*J.Org. Chem.* **1985** , *50* , 961). This rearrangement is illustrated below. Provide a mechanism for this transformation.



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 28

Ambiphilic Functional Groups–3 Hydrazone-Based Transformations

- Wolff-Kischner Reduction
- Wharton Rearrangement
- Eschenmoser-Tanabe Fragmentation
- Reduction of Tosyl Hydrazones: "The Alkene Walk"
- Tosyl Hydrazone-Based Fragment Coupling
- The Shapiro Reaction
- Bamford-Stevens Reaction

Reading Assignment for this Week:

Shapiro Reaction: Chamberlin, and Bloom. "Lithioalkenes from arylsulphonyl-hydrazones." *Org. Reactions* **1990**, 39: 1. **(handout)**

Wolff-Kishner & Related Reactions: Hutchins, (**1991**). "Reduction of C=X to CH_2 by Wolff-Kishner and Other Hydrazone Methods". *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 8: 327. **(in library)**

Matthew D. Shair

Monday,
November 25, 2002

Relevant Background Reading

Hutchins, R. O. (**1991**). "Reduction of C=X to CH_2 by Wolff-Kishner and Other Hydrazone Methods". *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 8: 327.

Shapiro, R. H. (**1976**). "Alkenes from Tosylhydrazones." *Org. React.* (N.Y.) 23: 405.

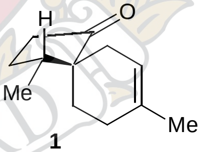
Addlington, R. M. and A. G. M. Barrett (**1983**). "Recent Applications of the Shapiro Reaction." *Acc. Chem. Res*. 16: 55.

Chamberlin, and Bloom (**1990**). "Lithioalkenes from arylsulphonyl-hydrazones." Org. React. (N.Y.) 39: 1.

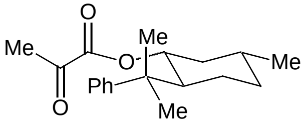
Bergbreiter, and Momongan (**1991**). "Hydrazone Anions". *Comprehensive Organic Synthesis.* Trost and Fleming. Oxford, Pergamon Press. 2: 503.

Cume Question, November, 2000

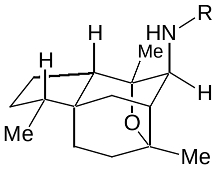
Sorensen and coworkers recently reported the synthesis of (–)-hispidospermidin (Sorensen *JACS*. **2000**, *122*, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was use in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



1



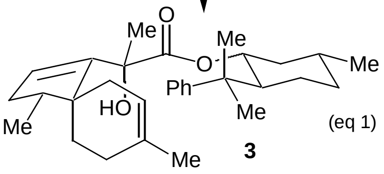
2



(–)-hispidospermidin

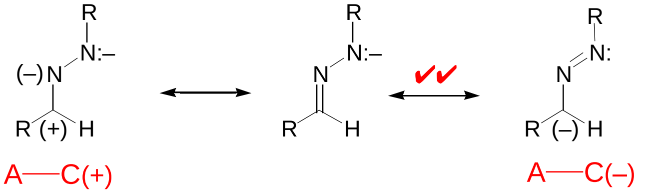
1 $\xrightarrow{\text{2,4,6-triisoproylbenzene-sulfonyl hydrazine, HCl, } CH_3CN\text{, 75\%}}$ Intermediate **A** $\xrightarrow{n\text{-BuLi (2.05 equiv)}}$ Intermediate **B**

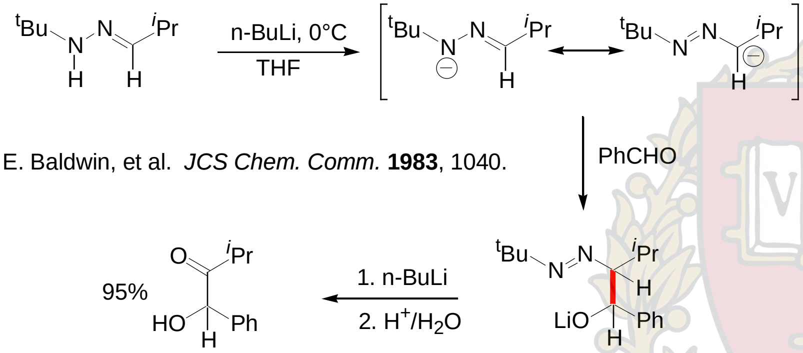
$\downarrow$ 55%, $MgBr_2$, -78 °C then add **2**



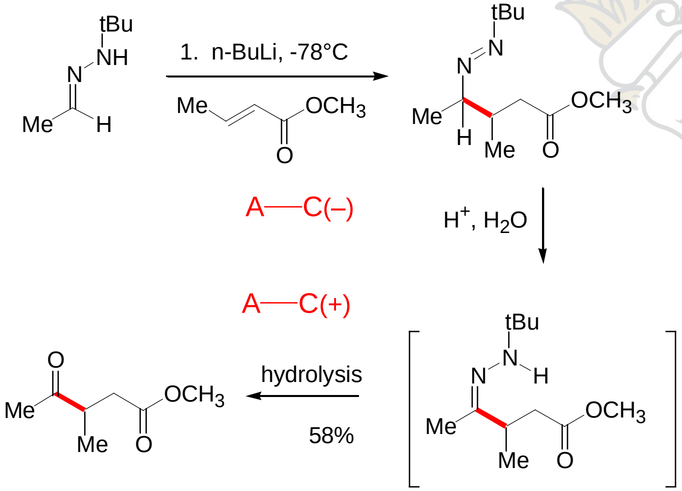
3 (eq 1)

Hydrazone Anions: A useful Reversed Polarity Equivalent

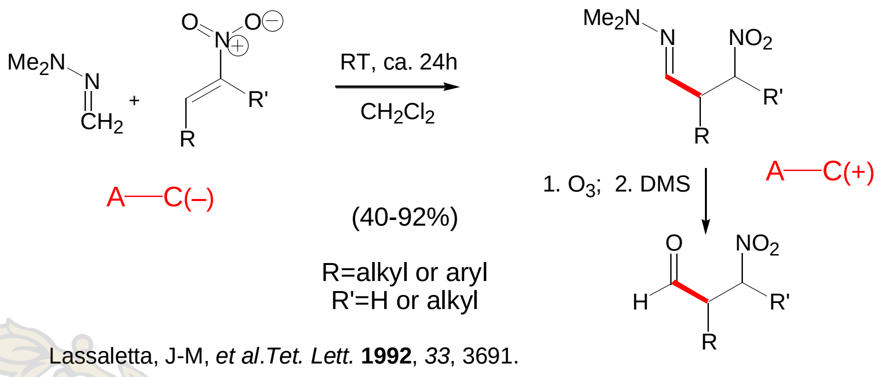




J. E. Baldwin, et al. *JCS Chem. Comm.* **1983**, 1040.

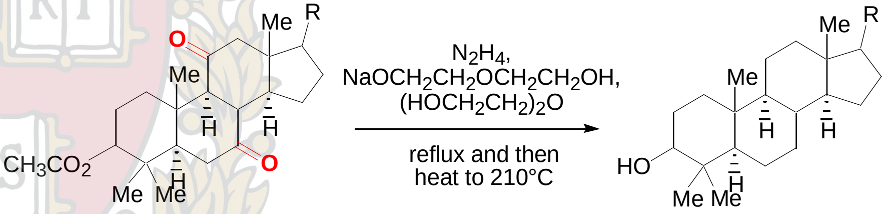


J. E. Baldwin, et al. *JCS Chem. Comm.* **1984**, 1095.



Lassaletta, J-M, *et al.Tet. Lett.* **1992**, *33*, 3691.

Wolff-Kishner Reduction Procedures

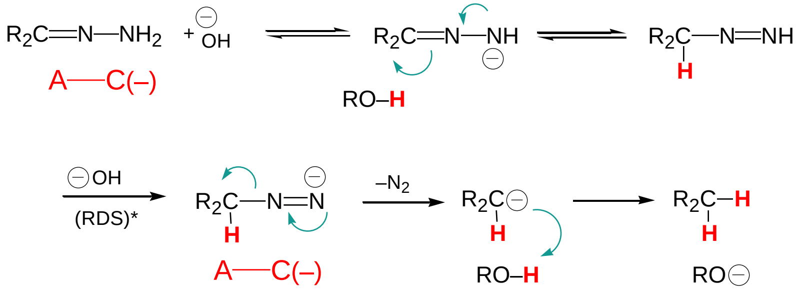


Barton, D. H. R., Ives, D. A. J., and Thomas, B. R. *J. Chem. Soc.* **1955**, 2056.

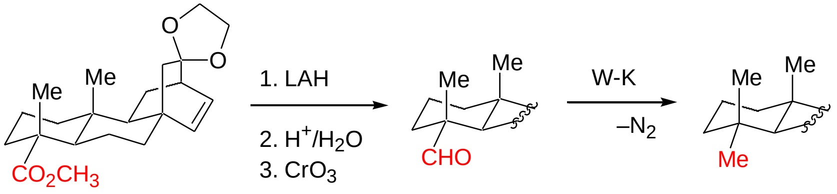
For particulary hindered ketones: anhydrous hydrazine or formation of hydrazone under acid catalysis (hydrazine/hydrazine dihydrochloride), then basify.

Under these forcing conditions, saponification, epimerization, and methyl ether cleavage can occur.

Mechanism

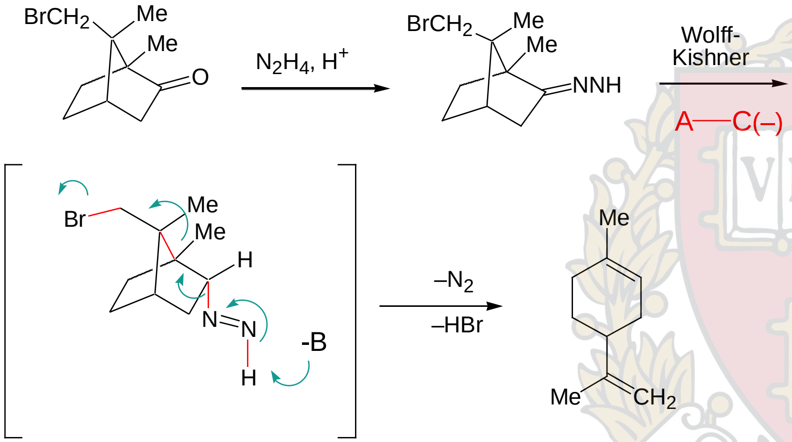


Hydrazone Transformations-2

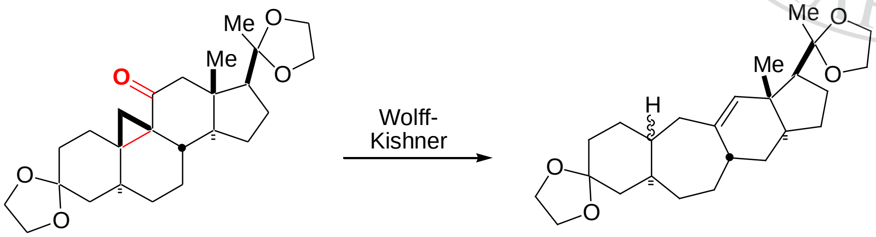


L. H. Zalkow, N. N. Girotra *J. Org. Chem.* **1964**, *29*, 1299.

Elimination of α-Leaving Groups



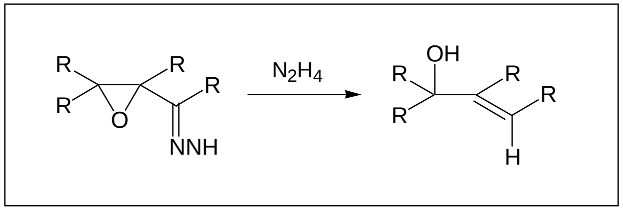
D. H. Gusyafson, W. F. Erman *J. Org. Chem.* **1965**, *30*, 1665.



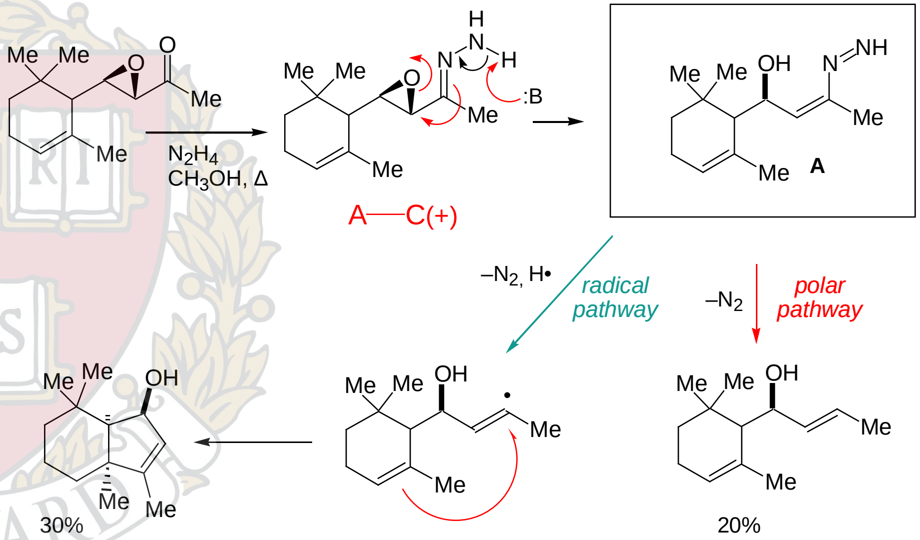
ca. 40%, 3:2 β:α

S. M. Kupchan *JACS* **1967**, *89*, 6327.

The Wharton Rearrangement

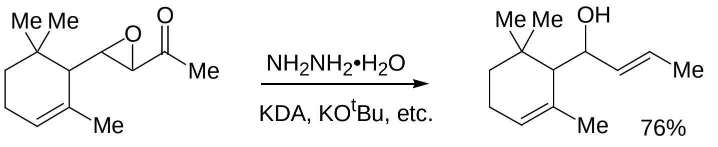


This example illustrates the 2 possible modes for the decomposition of **A**.



G. Stork et al. *JACS* **1977**, *99,* 7067.

Some procedural improvements:



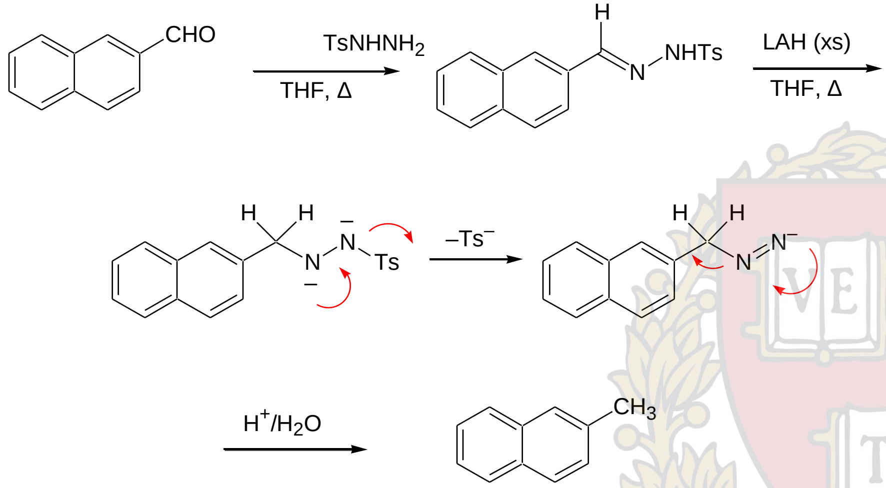
For stable hydrazones, strongly basic conditions favor the ionic pathway.

C. Dupuy, J. L. Luche *Tetrahedron Lett.* **1989**, *44,* 3437.

Tosylhydrazones – Better Than Hydrazones

Tosylhydrazones are isolable, stable, and easily prepared.

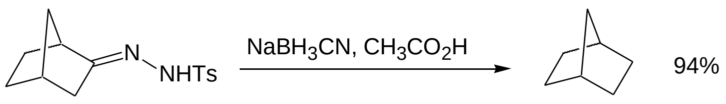
The presence of the tosyl leaving group strongly biases the system towards polar reaction pathways under hydridic reducing conditions.



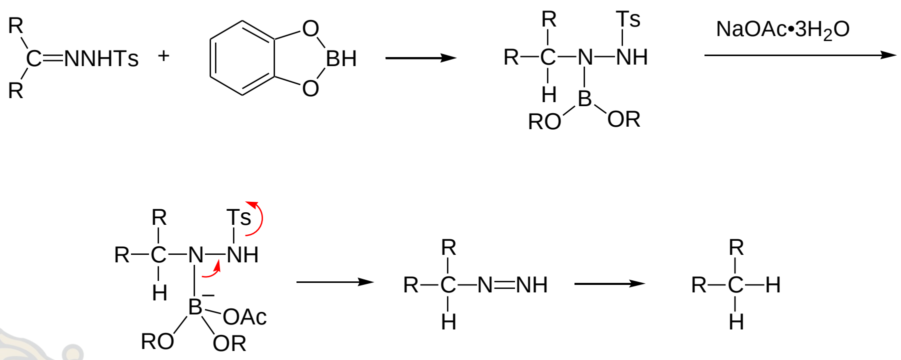
L. Caglioti, M. Magi *Tetrahedron* **1963**, *19*, 1127.

Further Refinements

Very mild reduction with $NaBH_3CN$ under slightly acidic conditions (pH 4-5).
No reduction in the absence of acid; carbonyl, nitro, nitrile FGs unaffected.
Aromatic, sterically hindered carbonyls very poor substrates.

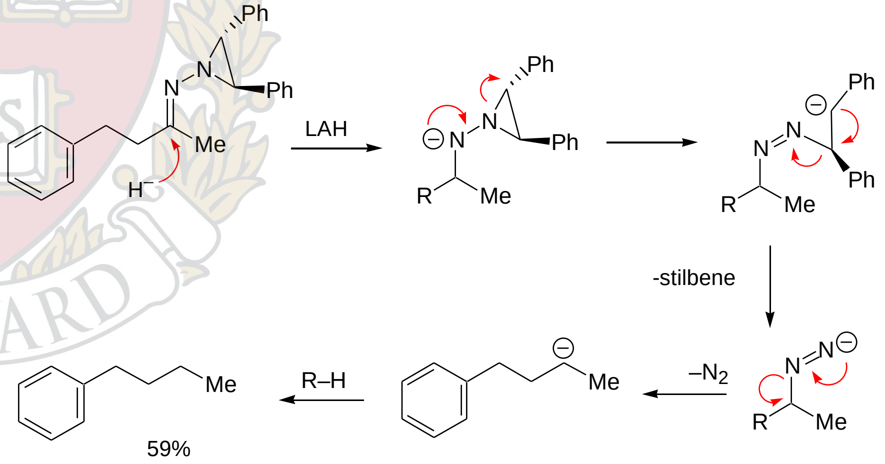


R. O. Hutchins, et al. *JACS* **1973**, *95,* 3662.



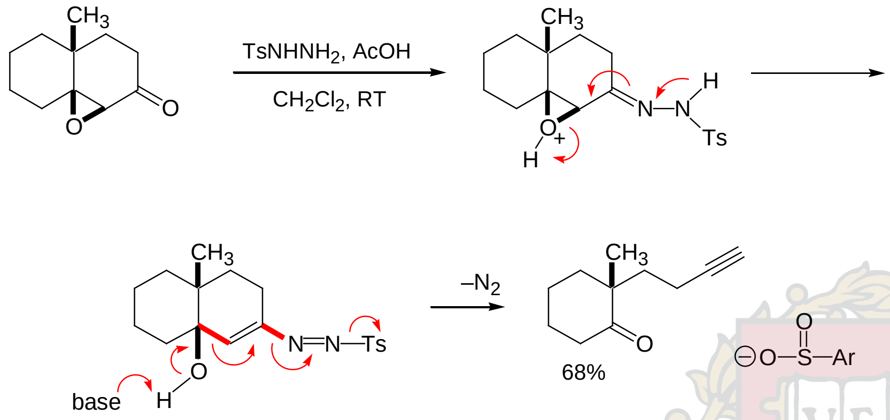
G. W. Kabalka, et al. *J. Org. Chem.* **1975**, *40,* 1834.

Another Interesting Leaving Group

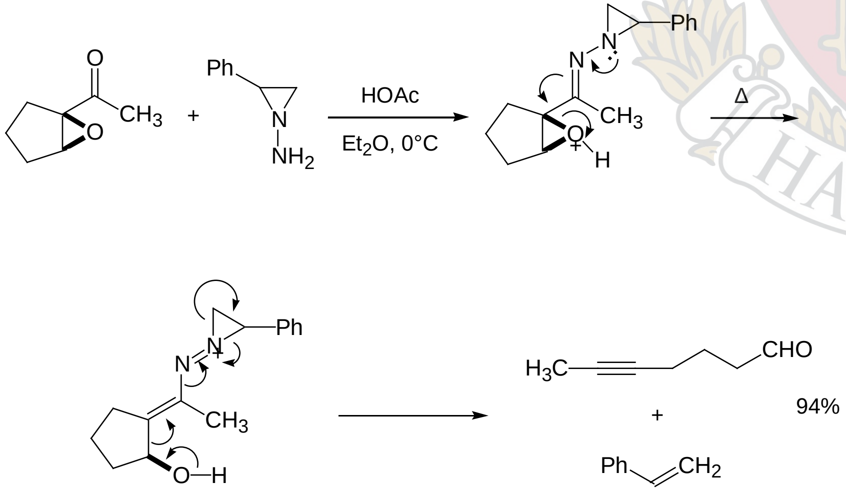


A. R. Chamberlin, et al. *Tetrahedron Lett.* **1991**, *32,* 1691.

The Eschenmoser–Tanabe Fragmentation

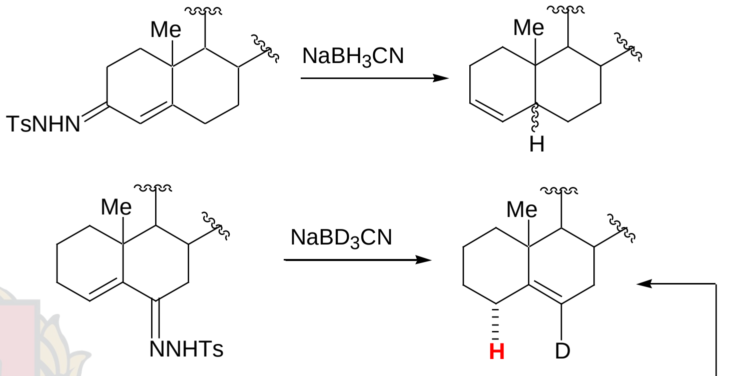


A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, *50,* 708.

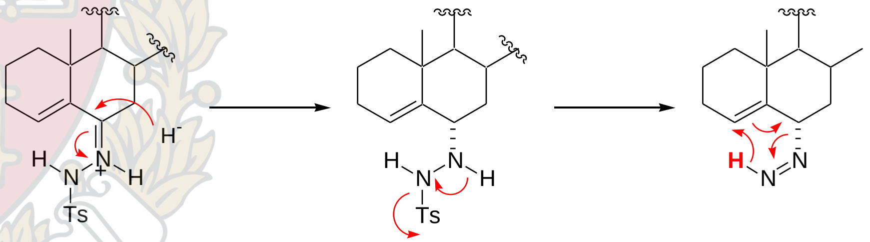


A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, *50,* 2108.

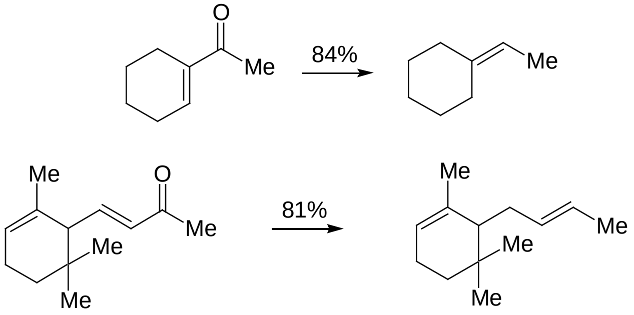
Tosylhydrazone Reductions: The Alkene Walk



C. Djerassi, et al. *JACS* **1976**, *98,* 2275.

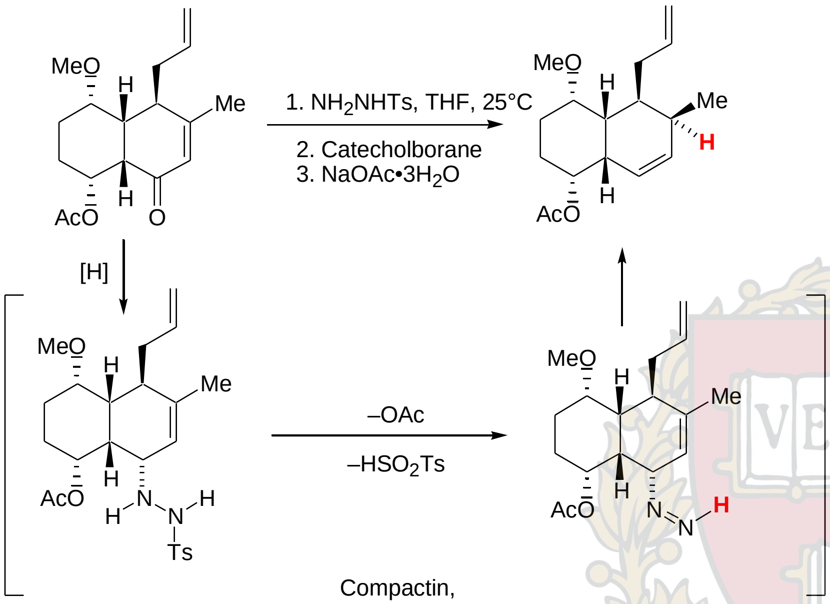


This has been developed into a reliable reduction



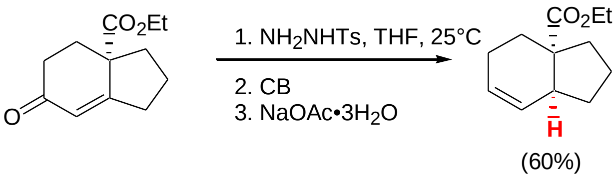
16 cases reported: Hutchins, et al. *JOC* **1975**, *40,* 923

Alkene Walk: Syntheses



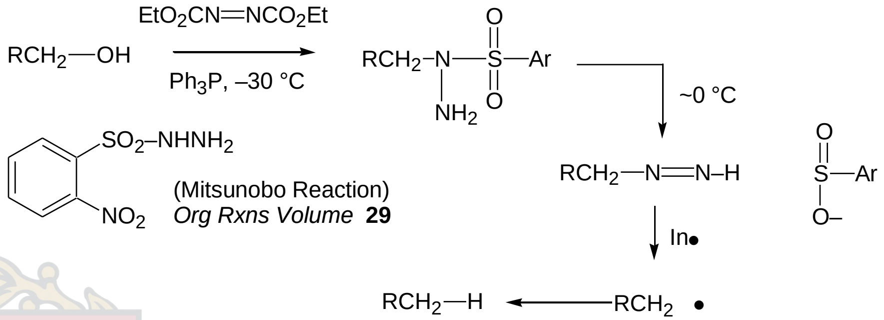
Compactin,
Wendler, N. L., *et al. Tet. Lett.* **1982**, *23*, 5501.

The stereochemical course of the hydrazone reduction may be stereospecifically transferred via the 1, 3-rearrangement

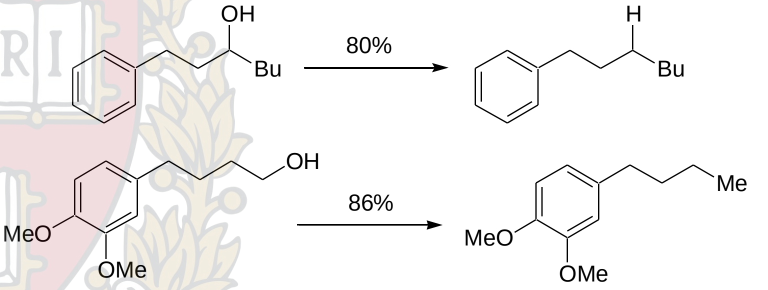


Topiramate,
Maryanoff, B. E., *et al. Tet. Lett.* **1992**, *33*, 5009.

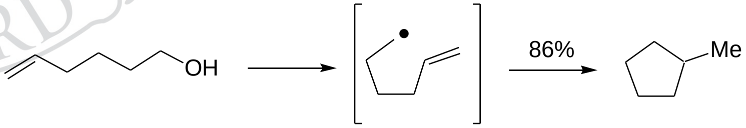
Sulfonylhydrazone Reductions: Alcohol Deoxygenation

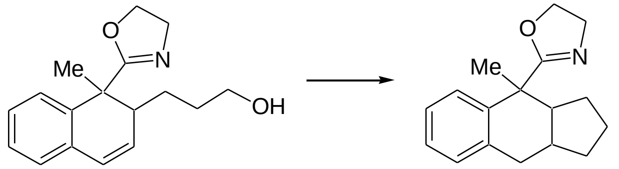


(Mitsunobo Reaction)
Org Rxns Volume **29**



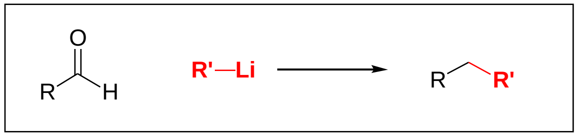
The intervention of radicals has been implicated (again):

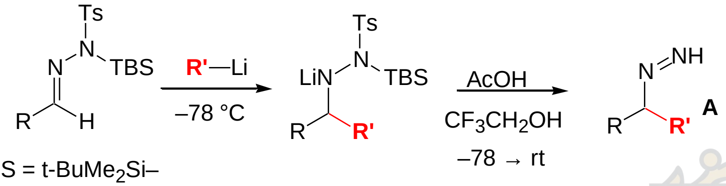




10 cases reported: A. Myers, et al. *JACS* **1997**, *119*, 8572.

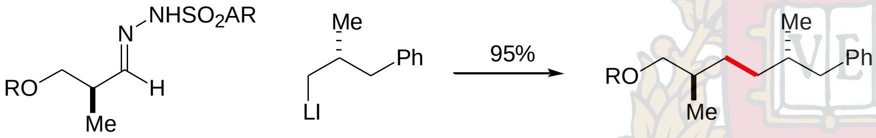
Tosylhydrazone-Based Fragment Coupling





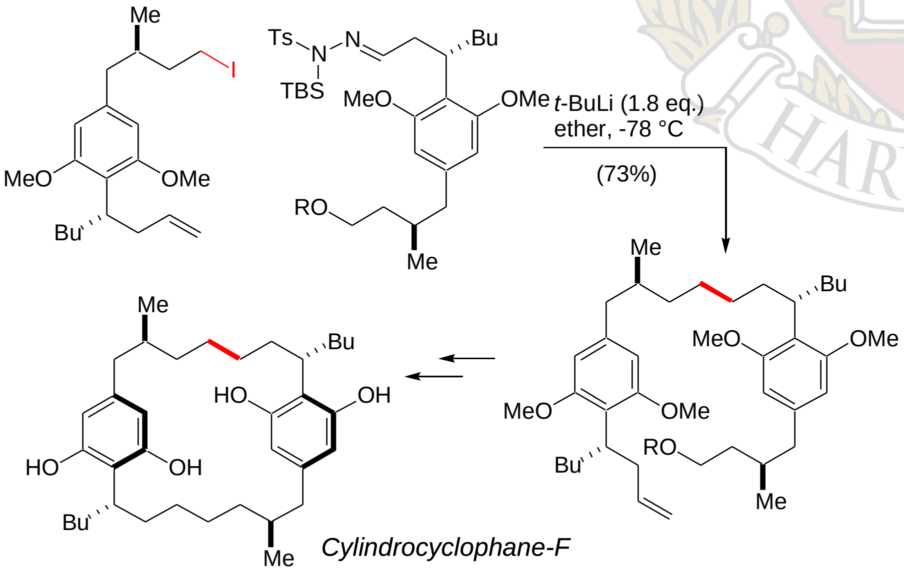
TBS = t-BuMe$_2$Si–

The monoalkyl azene **A** decomposes via a radical pathway



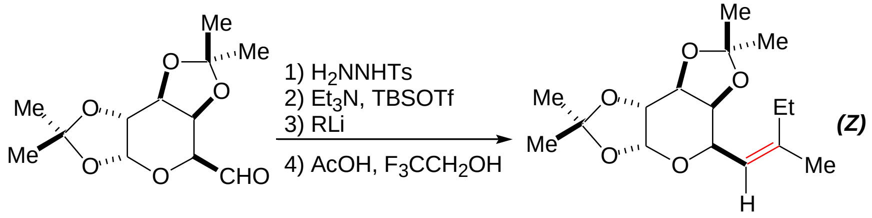
16 cases reported: A. G. Myers etal. *JACS*, **1998**, *120*, 8891.

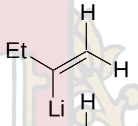
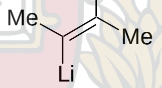
A Complex Application: A. Smith etal. *JACS* **1999**, *121*, 7423

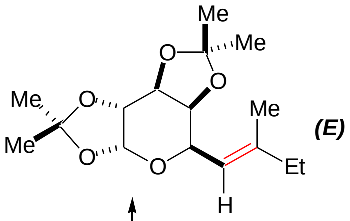


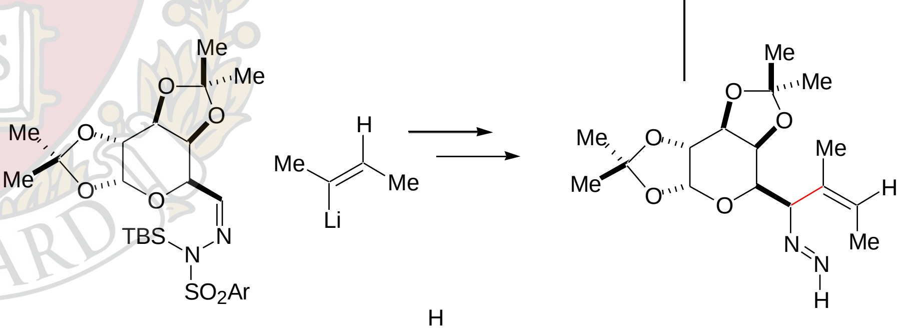
Stereoselective Construction of Trisubstituted Olefins

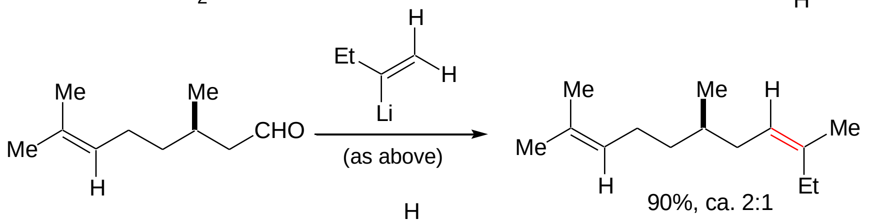
A. G. Myers, P. J. Kukkola *JACS*, **1990**, *112*, 8208.

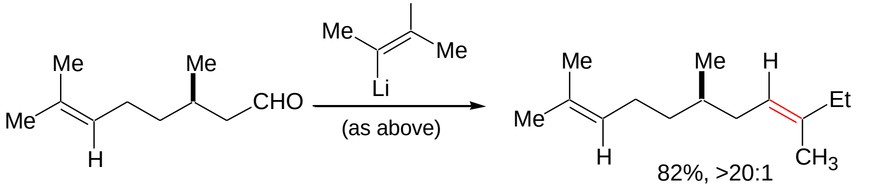


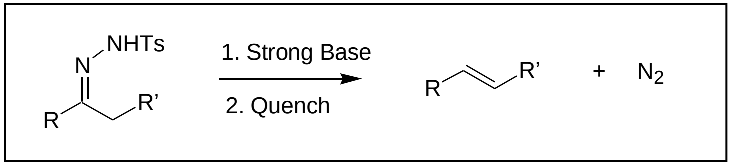
RLi	Ratio ***Z:E***	Yield
	50:50	79%
	<5:95	81%







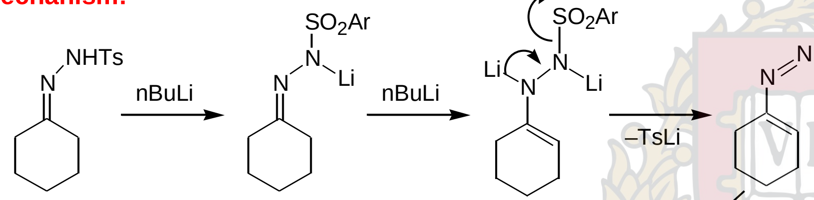


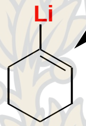


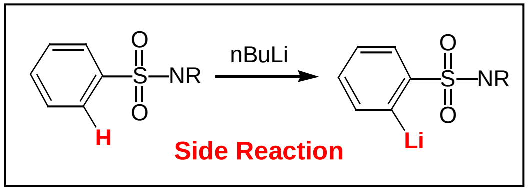
General Reviews:

Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapters 4.3 .
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapters 4.6.
Shapiro, *Organic Reactions* **1976**, Vol 23, pp 405-507.

Mechanism:

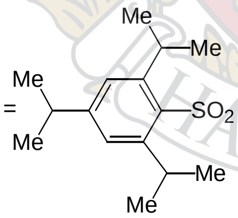




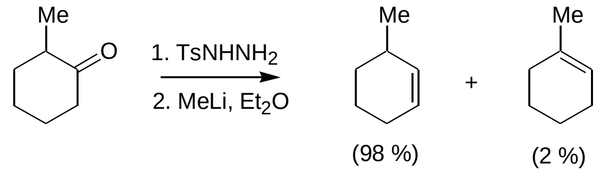


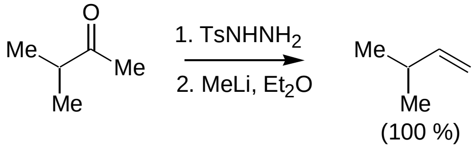
the Triisopropylsulfonyl (Trisyl) group is used (Roberts *Tet. Let.* **1981**, *22*, 4895).

Trisyl =

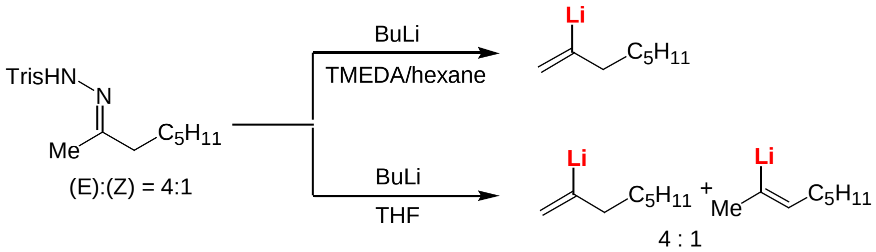


Regiochemistry



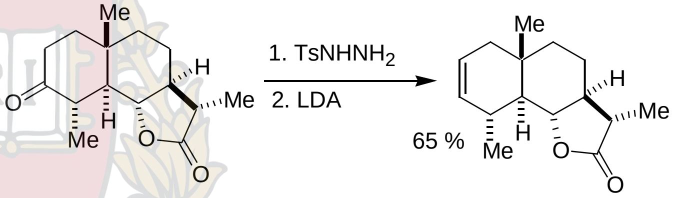


Deprotonation of the monoanion occurs predominantly at the kinetically more acidic site giving after elimination the less substituted alkene product.

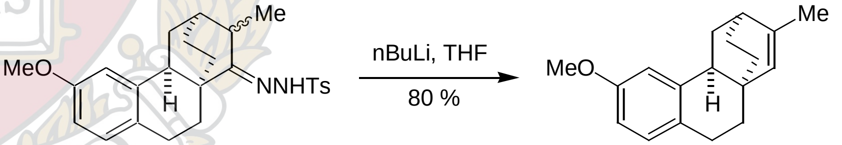


In THF solution regiochemical ratios generally reflect the starting hydrazone geometries

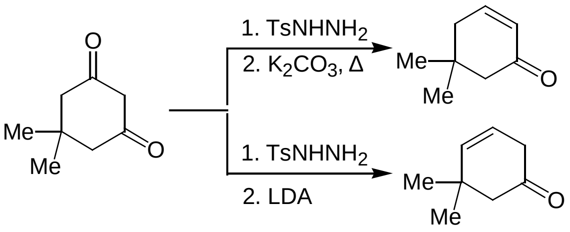
Bond *J. Org. Chem.* **1978**, *43,* 154.



Grieco *J. Org. Chem.* **1977**, *42*, 1717.

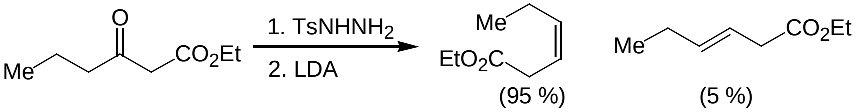


Nemoto *et. al. JCS, Perkin Trans. 1* **1985**, 927.

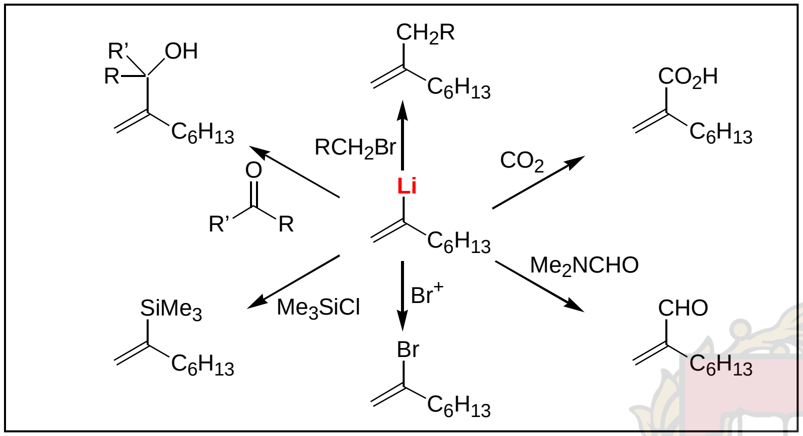


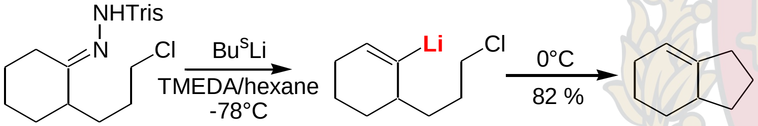
via dianion

via trianion



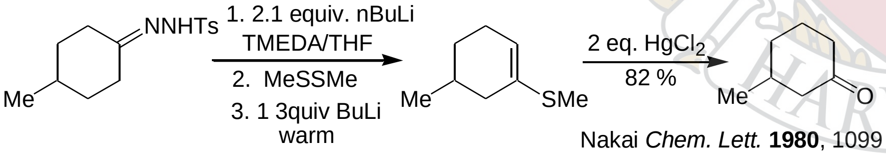
Trapping of the intermediate alkenyllithium





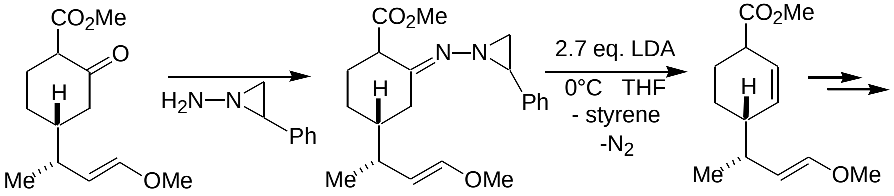
Bloom *Tet Lett.* ***1984***, *25*, 4901

Carbonyl Transposition

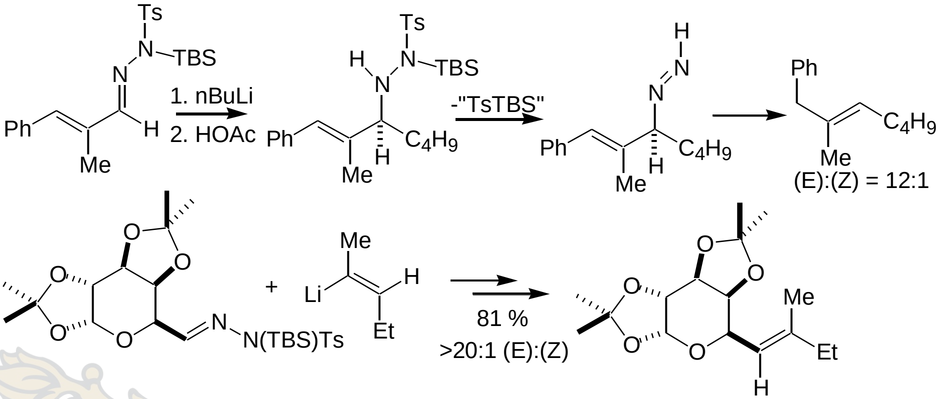


Nakai *Chem. Lett.* **1980**, 1099

Shapiro alternatives

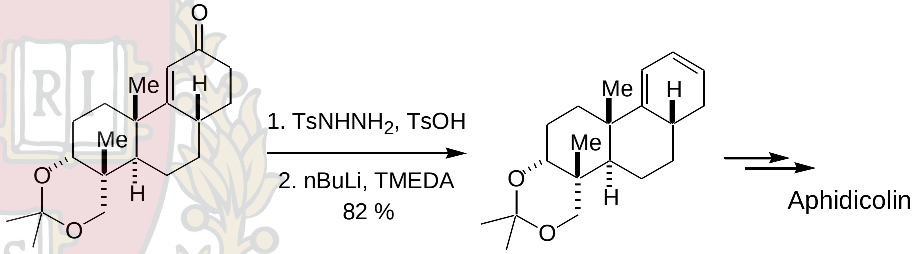


(Juvabione) Evans *J. Am. Chem. Soc.* **1980**, *102*, 774

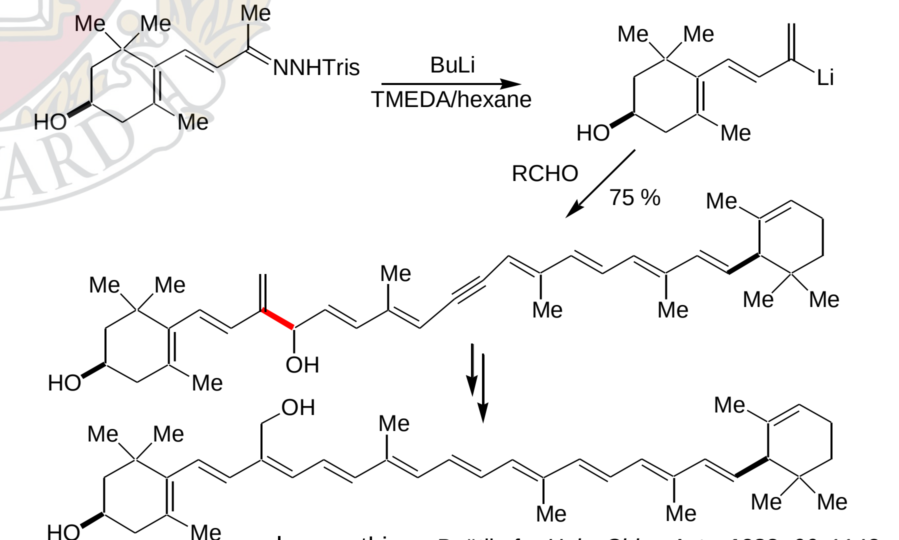


Myers, *J. Am. Chem. Soc.* **1990**, *112*, 8208

Applications



van Tamelen *J. Am. Chem. Soc.* **1983**, *105*, 142.

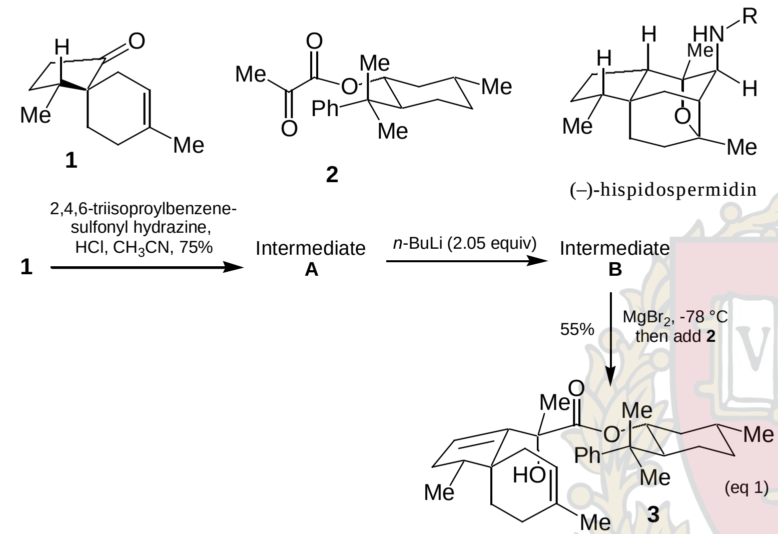


Baütikofer *Helv. Chim. Acta.* **1983**, *66*, 1148

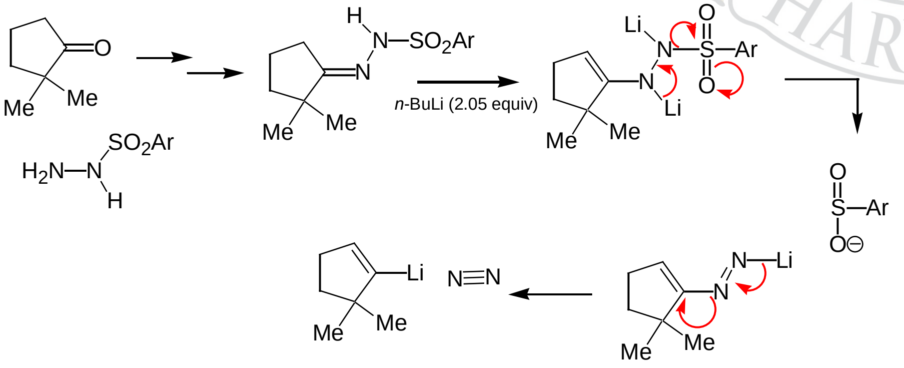
A Recent Aplication of the Shapiro Reaction

Cume Question, November, 2000

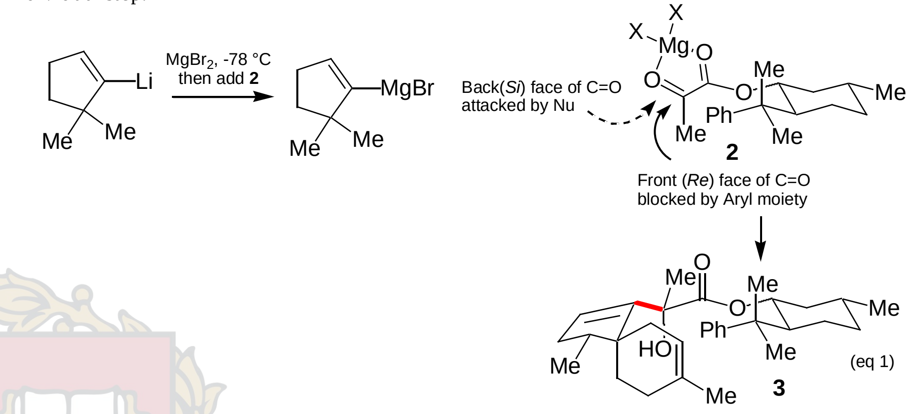
Sorensen and coworkers recently reported the synthesis of (–)-hispidospermidin (Sorensen *JACS*. **2000**, *122*, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was use in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



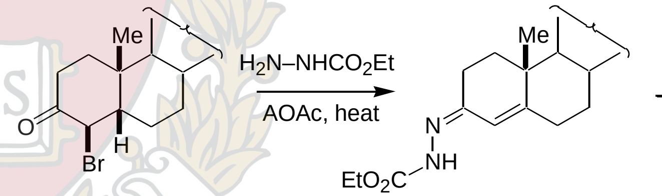
Part A (8 points). Provide a mechanism for the **Shapiro Reaction** of **1** to intermediate **B** in the space below. Feel free to use a simplified analog of **1** such as 2,2-dimethylcyclopentanone to answer this question.

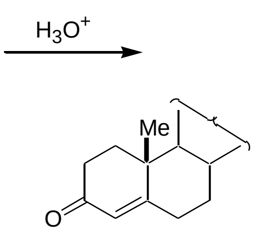


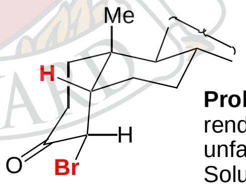
Part B (7 points). Provide a mechanism for the **transformation** of intermediate **B** to the illustrated product **3**. Use 3-dimensional representations to illustrate the stereochemical aspects of this individual step.



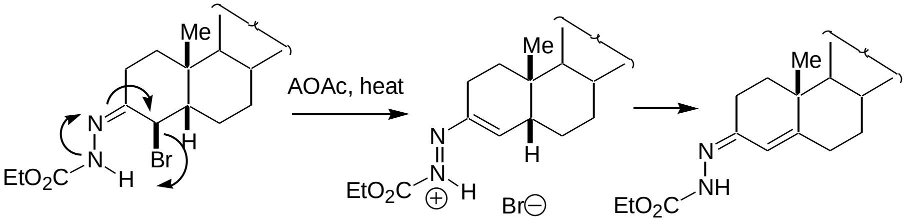
Mattox-Kendall Dehydrohalogenation (Paquette, *Reagents*, Vol 5, p 3509)





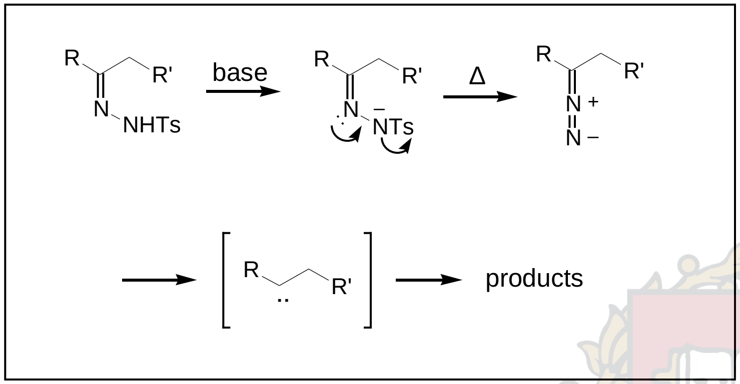


Problem: The syn relationship between Br and H renders the direct dehydrohalogenation with base unfavorable (relative to other potential reactions. Solution; proceed via the hydrazone.

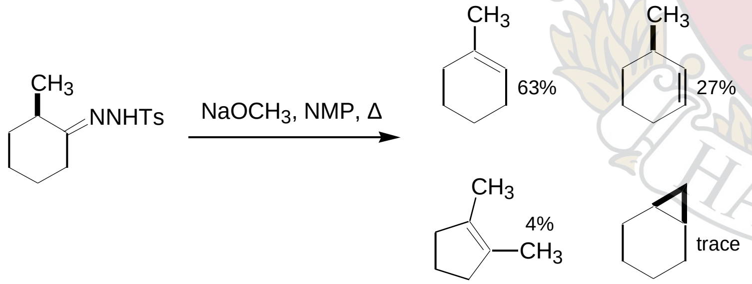


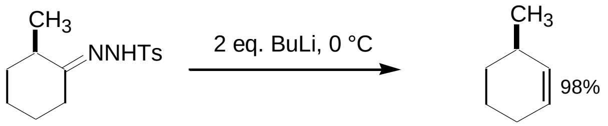
tautomerization

An Alternate Decomposition Pathway for Tosyl Hydrazones

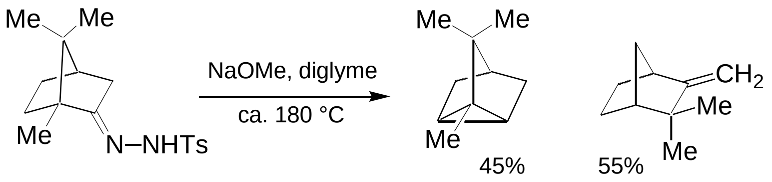


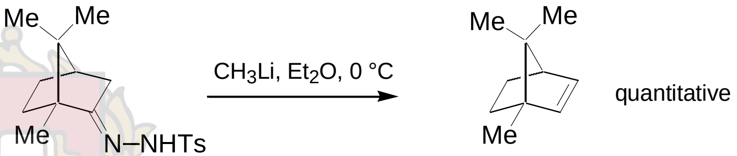
Bamford-Stevens vs. Shapiro



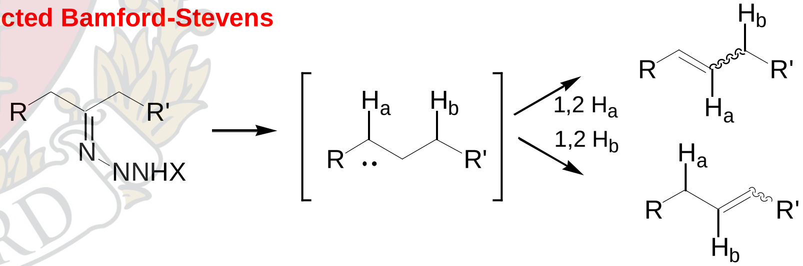


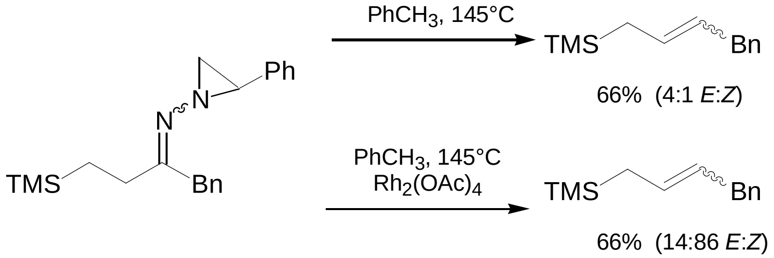
R. H. Shapiro *Org. React.* **1976**, *23*, 405.





Directed Bamford-Stevens





T. K. Sarkar, et al. *JCS Chem. Comm.* **1992**, 1184.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 29

Ambiphilic Functional Groups–4

- Construction of Consonant & Dissonant FG Relationships
- Charge Affinity Inversion Operators

Pummerer Reviews

"Application of the Pummerer reaction toward the synthesis of complex carbocycles and heterocycles.", Padwa, A.; Gunn, D. E.; Osterhout, M. H. *Synthesis* **1997**, 1353-1377.

"Asymmetric pummerer-type reactions induced by O-silylated ketene acetals.", Kita, Y.; Shibata, N. *Synlett* **1996**, 289-296.

Grierson, D. S.; Husson, H.-P. *Polonovski- and Pummerer-type Reactions and the Nef Reaction.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 6, pp 909.

"The Pummerer reaction of sulfinyl compounds.", De Lucchi, O.; Miotti, U.; Modena, G. *Org. React. (N.Y.)* **1991**, *40*, 157.

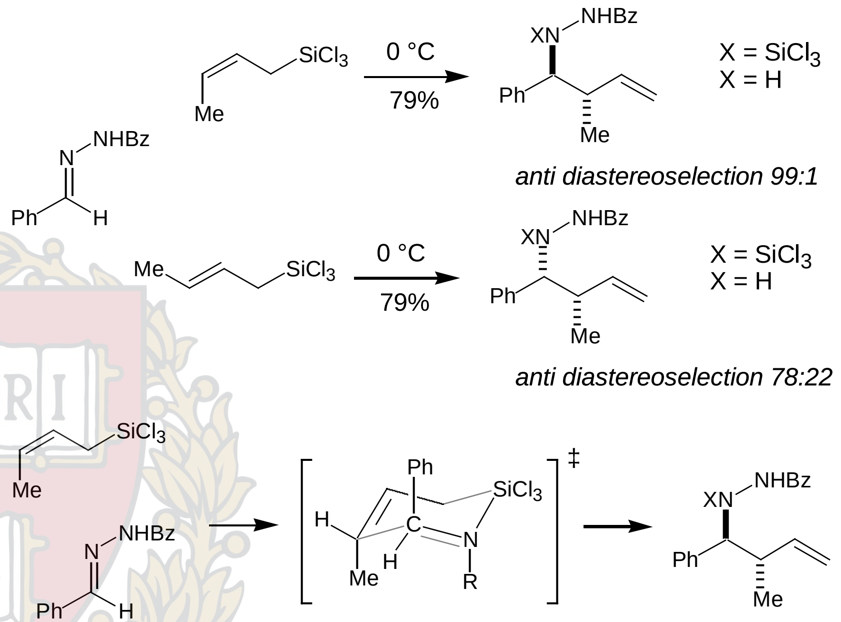
"Applications of sulfoxides to asymmetric synthesis of biologically active compounds.", Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717-1760.

Matthew D. Shair

Monday,
December 2, 2002

The Imine Aldol Reaction: New Information

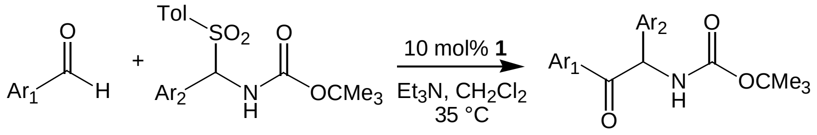
A recent relevant paper: Kobayashi, *JACS* **2001**, *123*, 9493-9499

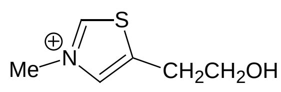


anti diastereoselection 99:1

anti diastereoselection 78:22

Cume Question, Fall 2001. The reaction illustrated below was recently reported by Murry and co-workers from the Merck Process Group (*JACS* **2001**, *123*, 9696-9697). Provide a mechanism for this transformation.





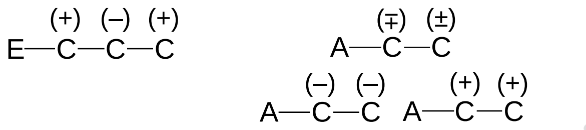
1 (used as catalyst)

Classification of Functional Groups

Each substituent attached to carbon activates that carbon toward a polar reaction by either resonance or induction or both.

	F_1—C	F_2—C	F_3—C	F_4—C
Induction	(+)	(+)	(–)	(–)
Resonance	(+)	(–)	(+)	(–)
Symbol	E—C (+)	A—C (±)		G—C (–)

Charge Affinity Patterns



$\mathrm{E{-}\overset{(+)}{C}{-}\overset{(-)}{C}{-}\overset{(+)}{C}}$ $\mathrm{A{-}\overset{(\mp)}{C}{-}\overset{(\pm)}{C}}$ $\mathrm{G{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}\overset{(-)}{C}}$

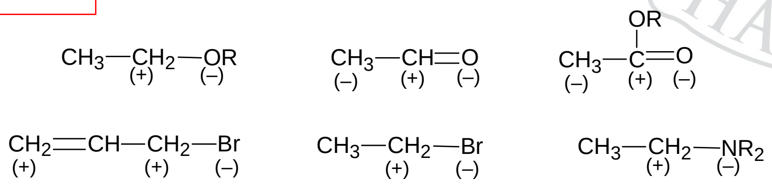
$\mathrm{A{-}\overset{(-)}{C}{-}\overset{(-)}{C}}$ $\mathrm{A{-}\overset{(+)}{C}{-}\overset{(+)}{C}}$

Real functional groups are assigned to a class designation by inspection of the chemistry of that FG, along with that of its conjugate acid and conjugate base

Charge affinities of real functional groups form a subset of the ideal FG classes.

E-Functions

$\mathrm{E{-}\overset{(+)}{C}{-}\overset{(-)}{C}{-}\overset{(+)}{C}}$

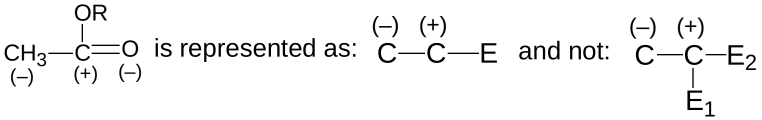


$\mathrm{CH_3{-}\underset{(+)}{CH_2}{-}\underset{(-)}{OR}}$ $\mathrm{\underset{(-)}{CH_3}{-}\underset{(+)}{CH}{=}\underset{(-)}{O}}$ $\mathrm{\underset{(-)}{CH_3}{-}\overset{OR}{\underset{(+)}{C}}{=}\underset{(-)}{O}}$

$\mathrm{\underset{(+)}{CH_2}{=}CH{-}\underset{(+)}{CH_2}{-}\underset{(-)}{Br}}$ $\mathrm{CH_3{-}\underset{(+)}{CH_2}{-}\underset{(-)}{Br}}$ $\mathrm{CH_3{-}\underset{(+)}{CH_2}{-}\underset{(-)}{NR_2}}$

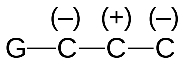
- Note that the issue of oxidation state in not explicitly incorporated. This issue is subordinate to that of defining site reactivity.

For example,



$\mathrm{\underset{(-)}{CH_3}{-}\overset{OR}{\underset{(+)}{C}}{=}\underset{(-)}{O}}$ is represented as: $\mathrm{\overset{(-)}{C}{-}\overset{(+)}{C}{-}E}$ and not: $\mathrm{\overset{(-)}{C}{-}\overset{(+)}{\underset{E_1}{C}}{-}E_2}$

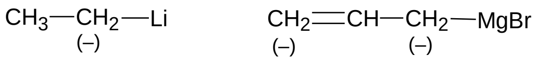
G-Functions



$\mathrm{G{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}\overset{(-)}{C}}$

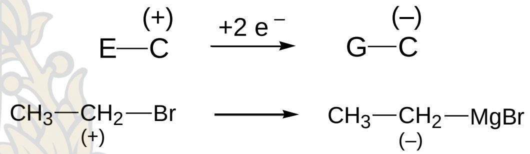
- Those ideal FGs which create nucleophilic carbon at point of attachment.
- Exhibit strictly alternate charge affinity patterns.

These are your metallic FGs such as Li, Mg, etc.



$\mathrm{CH_3{-}\underset{(-)}{CH_2}{-}Li}$ $\mathrm{\underset{(-)}{CH_2}{=}CH{-}\underset{(-)}{CH_2}{-}MgBr}$

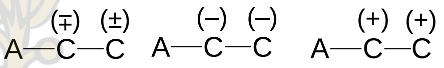
- Note that a 2-electron reduction (or oxidation) will transform an E-Class FG to a G-Class FG.



$\mathrm{E{-}\overset{(+)}{C}} \xrightarrow{+2\,e^-} \mathrm{G{-}\overset{(-)}{C}}$

$\mathrm{CH_3{-}\underset{(+)}{CH_2}{-}Br} \longrightarrow \mathrm{CH_3{-}\underset{(-)}{CH_2}{-}MgBr}$

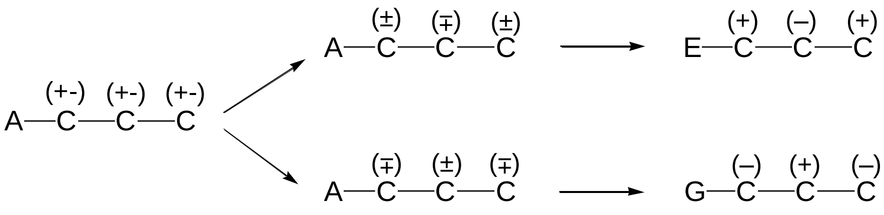
A-Functions



$\mathrm{A{-}\overset{(\mp)}{C}{-}\overset{(\pm)}{C}}$ $\mathrm{A{-}\overset{(-)}{C}{-}\overset{(-)}{C}}$ $\mathrm{A{-}\overset{(+)}{C}{-}\overset{(+)}{C}}$

- All sites activated equally for electrophilic & nucleophilic reactivity.
- Those ideal FGs which exhibit nonalternate polar site reactivity are included.

One might visualize a process wherein A-functions are gradually polarized towards either E– or G– behavior in response to changes in inductive and resonance effects.



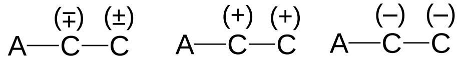
$\mathrm{A{-}\overset{(+-)}{C}{-}\overset{(+-)}{C}{-}\overset{(+-)}{C}} \nearrow \mathrm{A{-}\overset{(\pm)}{C}{-}\overset{(\mp)}{C}{-}\overset{(\pm)}{C}} \longrightarrow \mathrm{E{-}\overset{(+)}{C}{-}\overset{(-)}{C}{-}\overset{(+)}{C}}$

$\mathrm{A{-}\overset{(+-)}{C}{-}\overset{(+-)}{C}{-}\overset{(+-)}{C}} \searrow \mathrm{A{-}\overset{(\mp)}{C}{-}\overset{(\pm)}{C}{-}\overset{(\mp)}{C}} \longrightarrow \mathrm{G{-}\overset{(-)}{C}{-}\overset{(+)}{C}{-}\overset{(-)}{C}}$

A-functions are some of the most useful FGs in organic synthesis because of the unique reactivity provided.

A-Functions: Real Examples

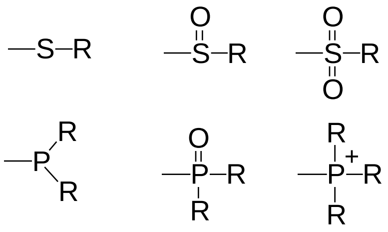
A-Functions


$A-\overset{(\mp)}{C}-\overset{(\pm)}{C}$ $A-\overset{(+)}{C}-\overset{(+)}{C}$ $A-\overset{(-)}{C}-\overset{(-)}{C}$

- A-functions are composed of polyatomic arrangements of N & O.

—NO_2 =NOH =NNR_2 —N=NR_2 =N(O)R =N=N ≡N

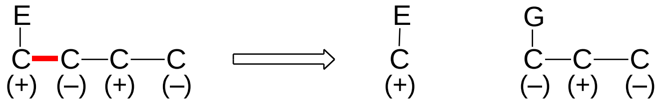
- A-functions are composed of second-row elements such **S** and **P**.



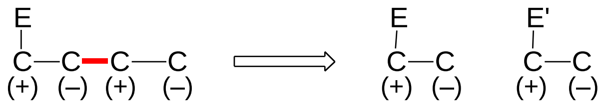
- Functional groups derived from many of the transition elements

Synthesis of Targets containing E-Functions

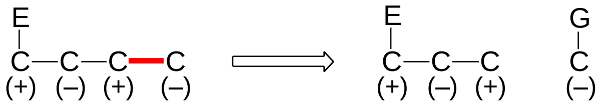
Transforms utilizing target E-function in synthesis plan given highest priority.



G–FG lost
in construction



E'–FG lost
in construction

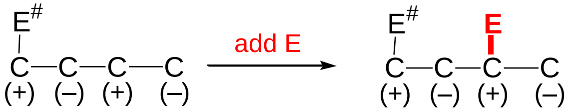


G–FG lost
in construction

Given the resident E-function, the charge affinity pattern dictates the nature of the polar coupling process and thus functional groups to be employed in synthesis.

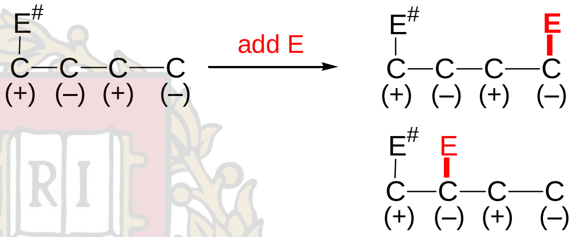
Classification of Pairwise Difunctional Relationships

Consider the paired relationships of E-functions. There are two relationships.



Charge affinity patterns
are "matched."

Pairwise relationship is "consonant".



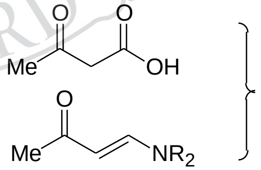
Charge affinity patterns
are "unmatched."

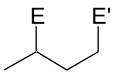
Pairwise relationship is "dissonant".

Consonant & dissonant relationships may be established with E-E, E-G, or G-G pairings.

Most target structures are composed of E-functions.

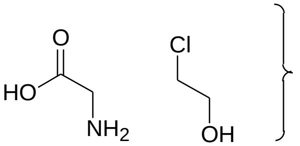
Representative difunctional relationships

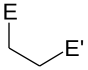




symbolic representation

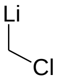
Classification: 1,3-C





symbolic representation

Classification: 1,2-D

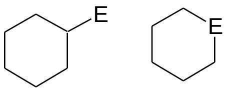


symbolic representation

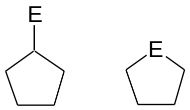
Classification: 1,1-D

Classification of Pairwise Difunctional Relationships

- A single FG residing either in or appended to a cycle may establish a FG relationship with itself.



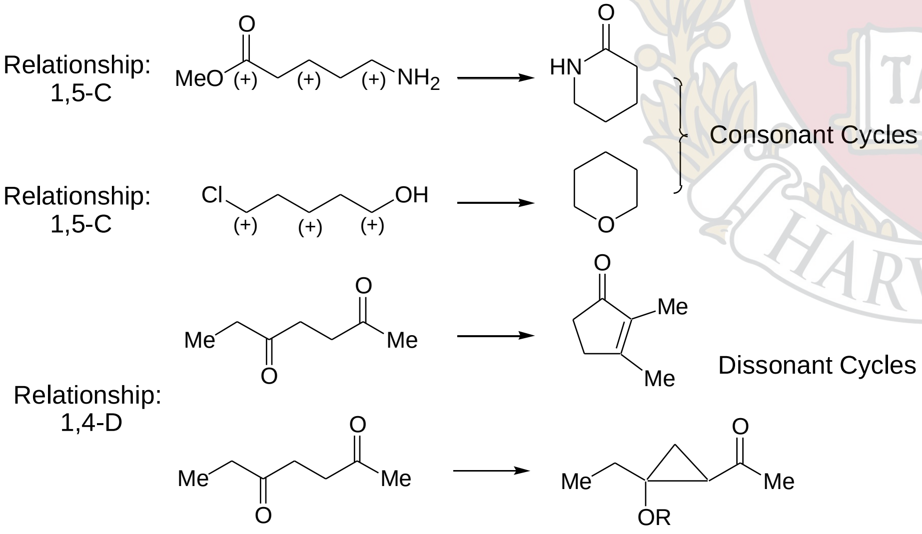
Consonant cycles



Dissonant cycles

Consonant & Dissonant Relationships: Path-Cycle Interconversions

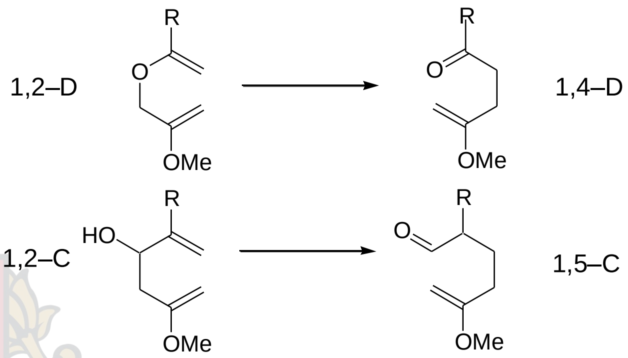
Linear molecules may be transformed into cycles & vice-versa:



Path-cycle interconversions such as those illustrated permute, but do not eliminate the relationship. i.e. D-bond paths are transformed into D-cycles.

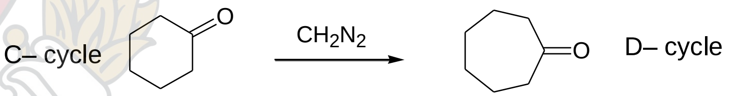
Pairwise Relationships: Path-Path Interconversions via Sigmatropic Rearrangements

[3,3] Sigmatropic Rearrangements:

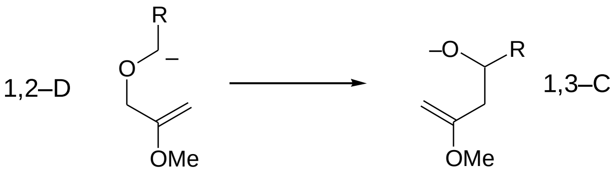


- For these rearrangements, C → C', D → D' but C → D not possible

[1,2] Sigmatropic Rearrangements:



[2,3] Sigmatropic Rearrangements:



General Rule For [m,n] Sigmatropic Rearrangements:

When the sum of m+n is even, the FG relationship is maintained, e.g. C → C'
When the sum of integers is odd, the FG relationship is changed, e.g. C → D

Pairwise Relationships in Inorganic Reagents

■ E-functions in their most stable oxidation states (HO^-, NH_3, Cl^-) are represented as E(–).

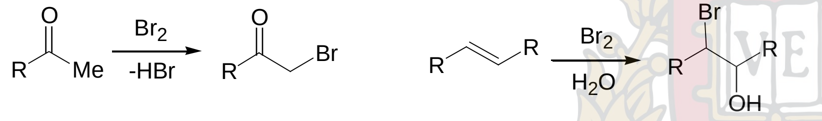
There exist an important family of reagents which have E-FGs directly coupled:

E–E Reagents

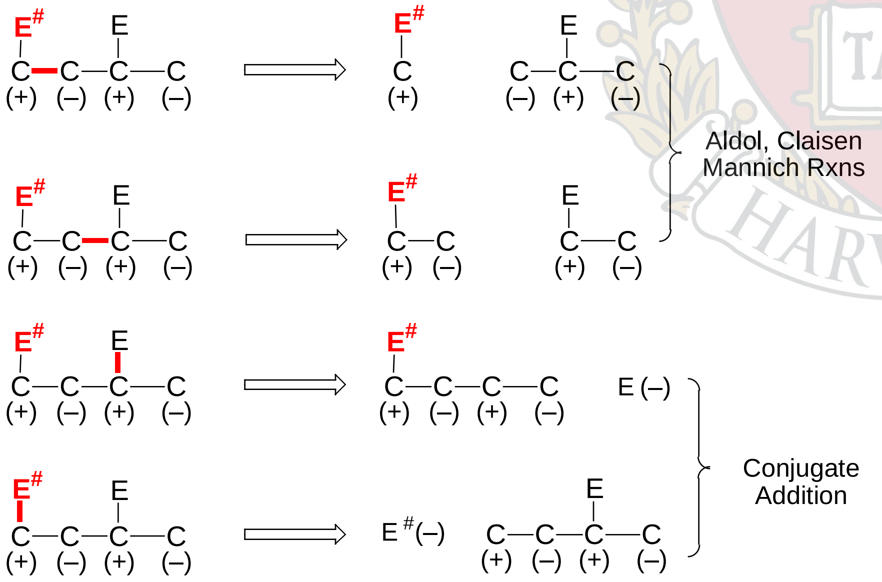
$Br—Br$ $HO—NH_2$
$HO—OH$ $H_2N—NH_2$

In each of these reagents there is a 0,0-D relationship

These reagents are used to construct D-Relationships:



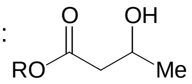
Synthesis of Targets containing Consonant Pairwise Relationships



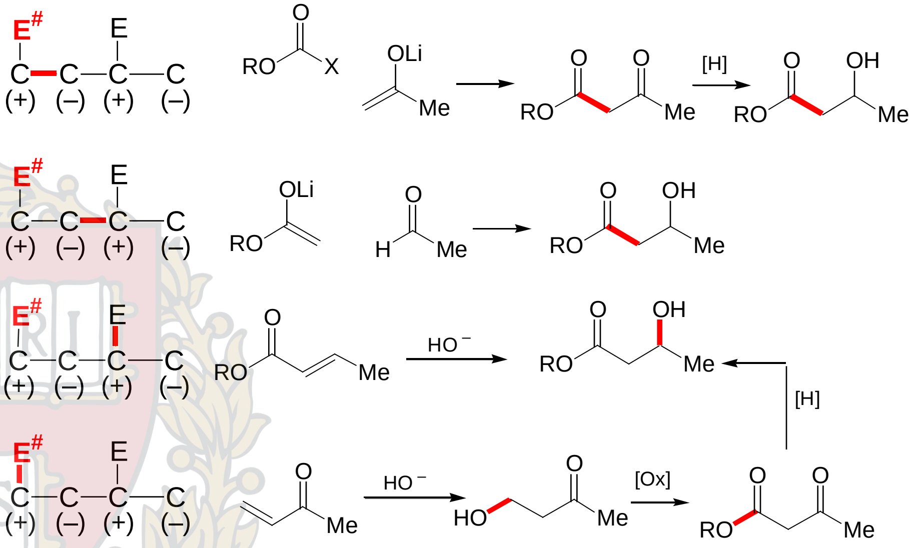
Consonant difunctional relationships can be constructed from just the functions illustrated & polar bond constructions.

A Specific Case

Target structure:



Step I: There are 4 bonds interconnecting E & E'. Hence generate the 4 transforms leading to mono-functional precursors:

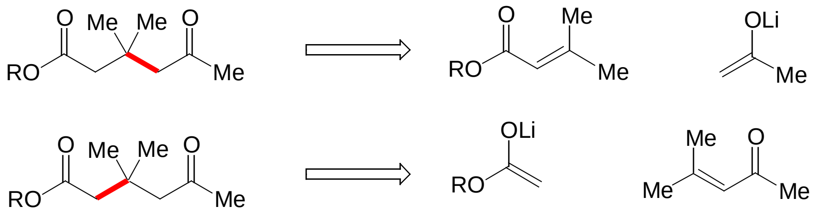


Step II: Evaluate the efficiency of the 4 plausible routes to the target from available precursors.

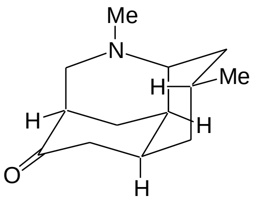
Given the oxidation state in the target, the second synthesis looks the best and the fourth looks the worst.

The Constraint of Quaternary Centers

If a quaternary center occurs along the consonant bond path, one is limited to bond constructions on either side of that restriction

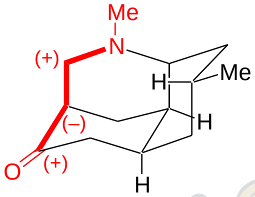


Quaternary Centers & Bridgehead Restrictions

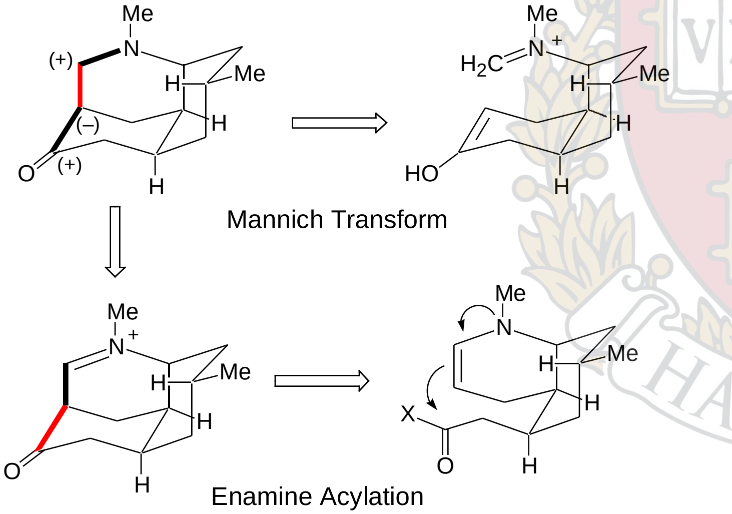


Lucidulene Synthesis: *JACS* **94**, 4779 (1972)

Focus on the shortest consonant bond path:



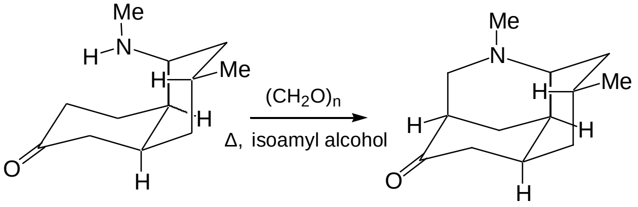
The two permitted bond constructions along illustrated bond path flank the bridgehead carbon



Mannich Transform

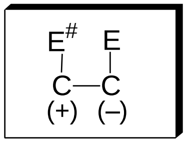
Enamine Acylation

Option Selected:

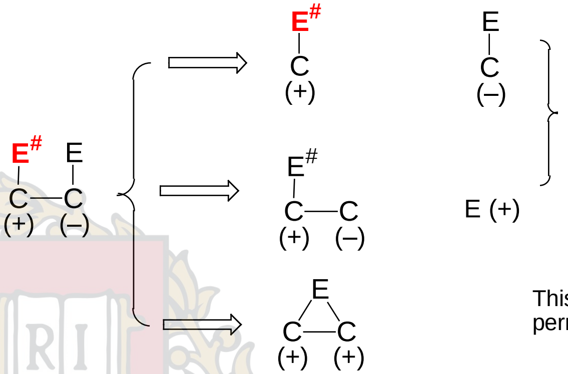


- Corrolary: π-conjugation cannot be extended through bridgehead or quaternary centers

Synthesis of Dissonant Pairwise Relationlships



The pairwise relationship is "unmatched"; hence, the illustrated E-functions cannot be used exclusively to construct the bond path. Let's consider the simplest case: a 1,2-D relationship.



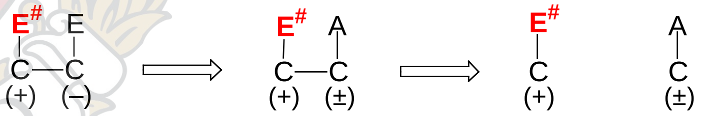
Resident E-functions do not provide required charge affininty pattern for coupling

This transform defined a path-cycle permutation of the D-relationship

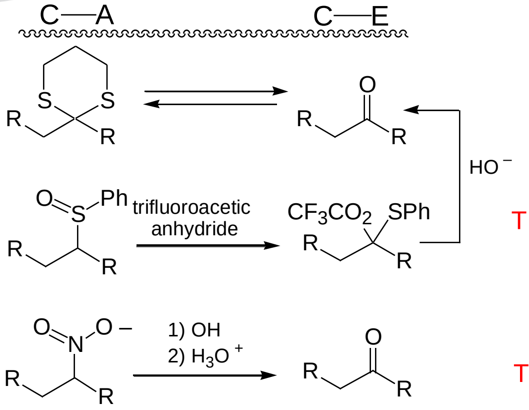
In the illustrated polar disconnections, one of the fragments may exploit the charge affinity pattern of the resident FG while the other may not.

Hence dissonant pairwise relationships may not be constructed via just the functions present in the target.

Dissonant Pairwise Relationlships via A-Functions



In implementing this strategy you must know all important **1,1-A↔E FG transformations.**



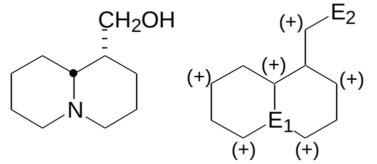
The Pummerer Rearrangement

"The Pummerer reaction of sulfinyl compounds.", De Lucchi, etal. *Org. Reactions* **1991**, *40*, 157.

The Nef Reaction

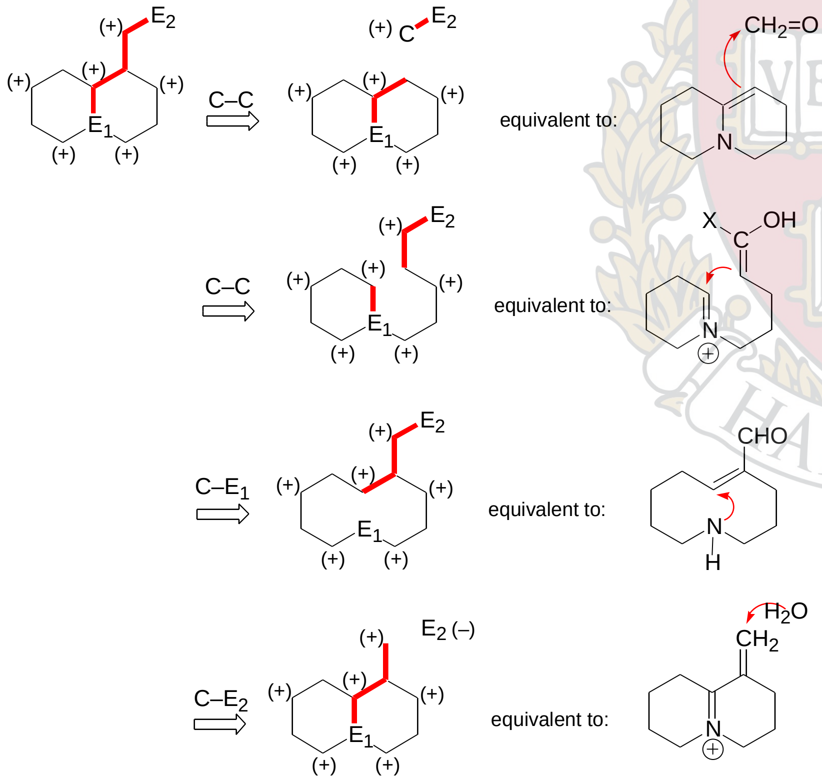
Bond path analysis of simple alkaloids

lupinine

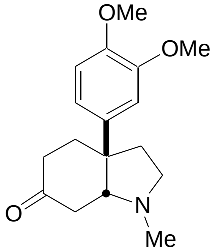


Every complex polyfunctional molecule may be analyzed structurally in terms of its individual consonant or dissonant construction paths or cycles. For example, in the alkaloid lupinine all possible construction paths interconnecting E1 and E2 are consonant. Consonant paths within the polyatomic framework define seams in the structure that may be constructed using aldol and related processes.

Begin the disconnection process by focusing on the shortest consonant bond path. In this case, there are 4 bonds, hence 4 disconnections.



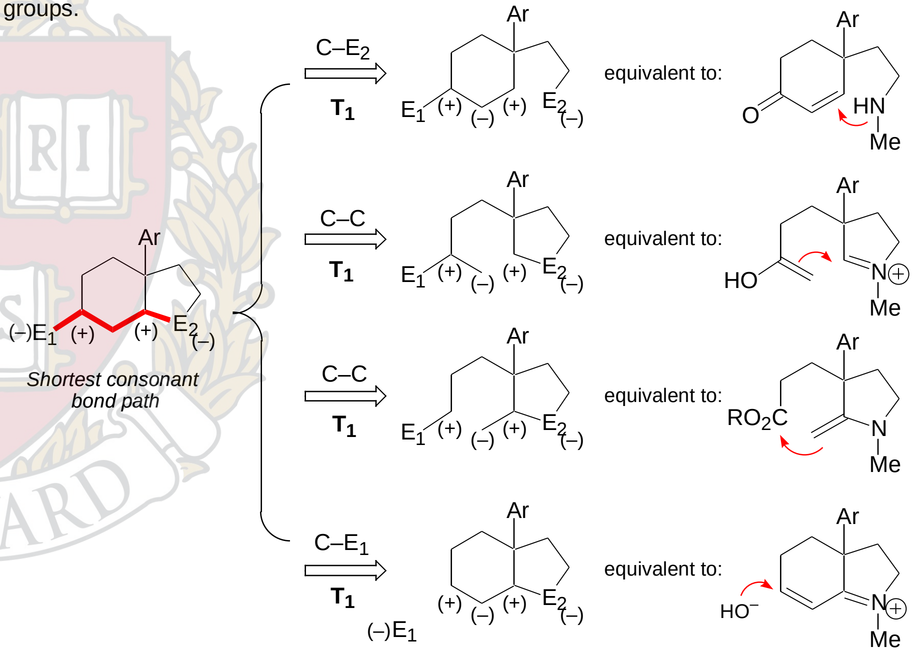
Note that oxidation states of precursors is not yet considered.



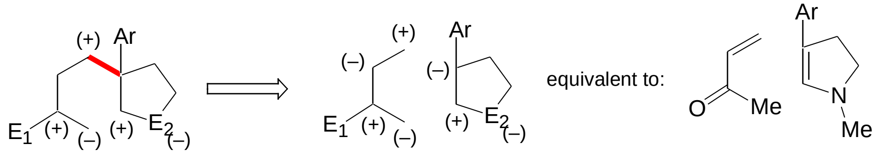
Mesembrine

Curphey, T. J.; Kim, H. L. *Tetrahedron Lett*. **1968**, 1441.
Keely, S. L.; Tahk, F. C. *JACS*. **1968**, *90*, 5584.
Stevens, R. V.; Wentland, M. P. *JACS* **1968**, *90*, 5580
Shamma, M.; Rodrigues, H. R. *Tetrahedron* **1968**, *24*, 6583

In the analysis of potential routes to structures like **mesembrine** , identify the shortest consonant bond path and then proceed to carry out all polar disconnections along that bond path. Since there four bonds interconnecting =O and N (E1 and E2), there will be four associated transforms which one may execute using the illustrated functional groups.



Now consider further analysis of T_1: Again, select the shortest E_1-E_2 bond path and disconnect next to quaternary center. Dissonant element is localized in 5-membered enamine

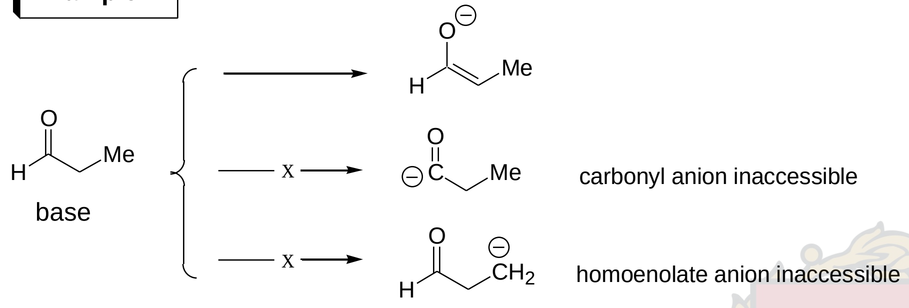


Handouts

Keely, S. L.; Tahk, F. C. *JACS*. **1968**, *90*, 5584.
Stevens, R. V.; Wentland, M. P. *JACS* **1968**, *90*, 5580

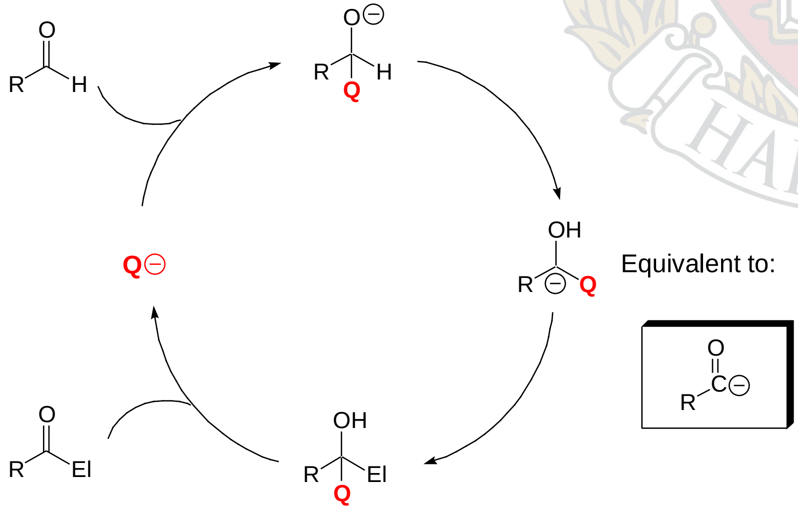
Inaccessible Reactivity Modes in Carbonyl Deprotonation

Example:

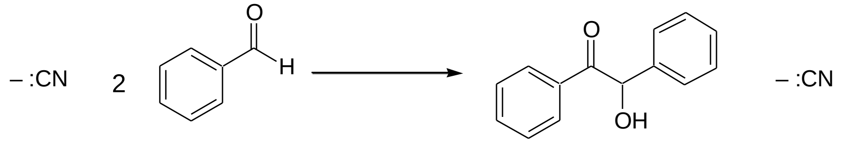


Can one design "catalysts" which will provide access to carbonyl anion equivalents in situ??

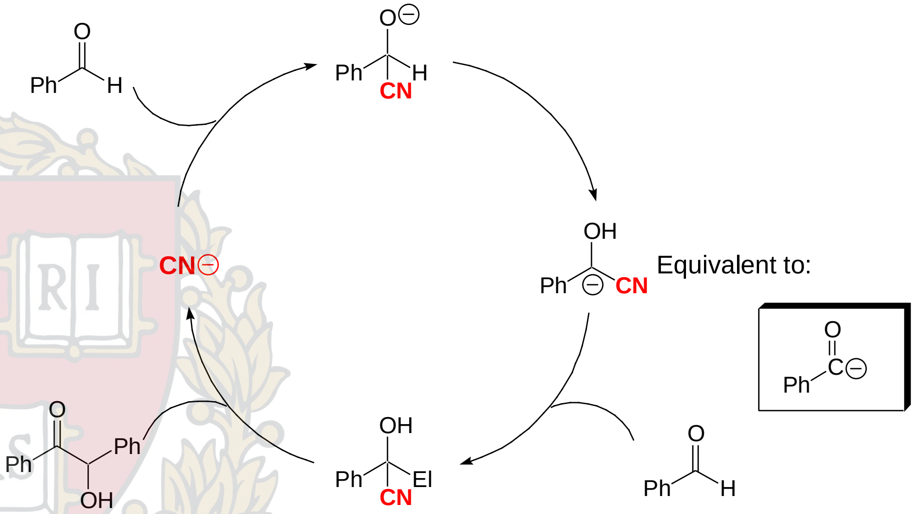
Let Q – be such a catalyst, we will call it an "inversion operator"



The Benzoin Condensation



- Cyanide ion is such a "catalyst"



How do we classify the ≡N functional group?

- Hydrogen cyanide is a fairly good Bronsted acid (pKa$_{HOH}$ 9.5)

$$\mathrm{H{-}C{\equiv}N} \rightleftharpoons \mathrm{H^+} + \mathrm{{-}\,{:}C{\equiv}N} \qquad \overset{(-)}{\mathrm{C}}\!-\!\mathrm{G}$$

- Acetonitrile can be attacked be nucleophiles:

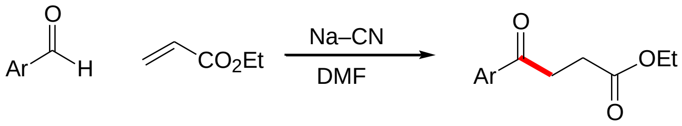
$$\mathrm{Me{-}C{\equiv}N} \xrightarrow{\mathrm{Nu{:}\ -}} \mathrm{Me{-}}\overset{\mathrm{N^{-}}}{\overset{\|}{\mathrm{C}}}\mathrm{{-}Nu} \qquad \overset{(+)}{\mathrm{C}}\!-\!\mathrm{E}$$

- Acetonitrile can be deprotonated by strong bases (pKa $_{DMSO}$ ~ 30)

$$\mathrm{Me{-}C{\equiv}N} \rightleftharpoons \mathrm{H^+} + \mathrm{H_2\bar{C}{-}C{\equiv}N} \qquad \overset{(-)}{\mathrm{C}}\!-\!\overset{(+)}{\mathrm{C}}\!-\!\mathrm{E}$$

Cyanide-based Carbonyl Anion Equivalents

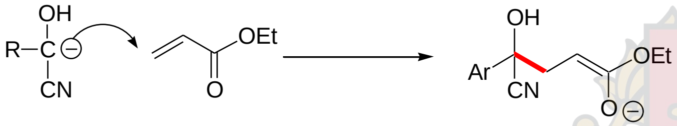
- Extensions of the Benzoin condensation concept are possible in some instances:



44% yield

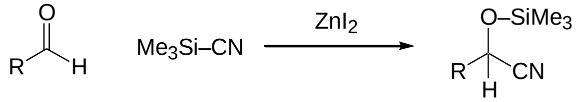
The C–C Bond Construction

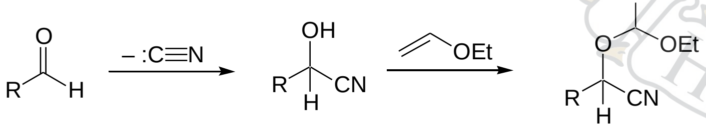
Stetter, *Org. Reactions* **1991**, *40*, 407.



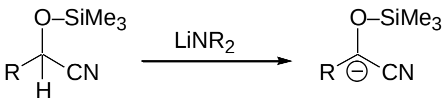
- The in situ use of cyanide ion as an inversion operator is limited. Greater generality may be achieved by multistep alternatives:

Aldehyde Derivatization Step

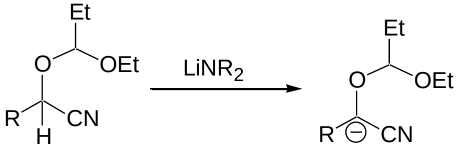




Substrate Deprotonation Step



Deprotonation possible only for R = Ar due to Si migration.

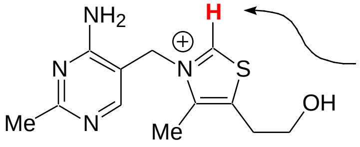


Deprotonation possible for All R groups

G. Stork *JACS* **93**, 5286 (1971)

Thiazolium Salts: Nature's Inversion Operators

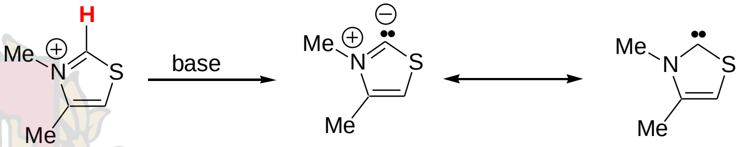
Reactions equivalent to the benzoin are catalyzed by biological co-factors to make (and break) dissonant difunctional heteroatom-heteroaton relationships



The thiamine cofactor

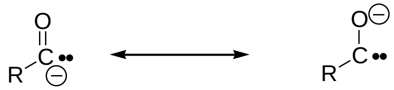
The pka of this proton has been the subject of considerable study. The current estimates are that the value falls in the range of 16-20 but this number is not firm.

F. G. Bordwell *JACS* **113**, 985, (1991)



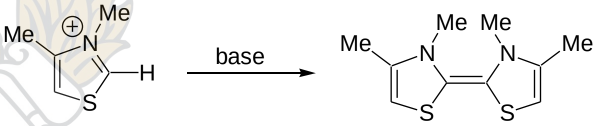
1

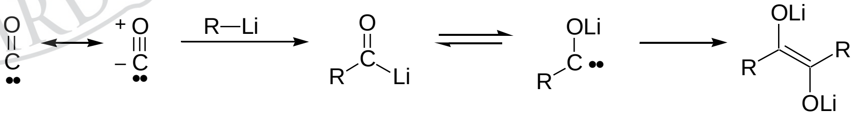
Carbonyl anions might be similarly stabilized



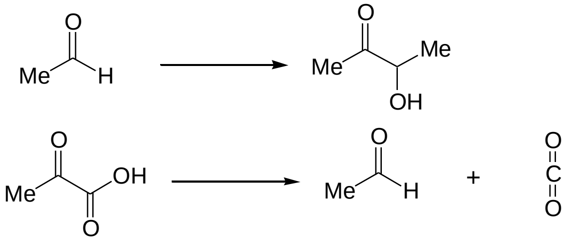
2

In the absence of electrophiles **1** & **2** dimerize as would be expected for carbene reactivity.



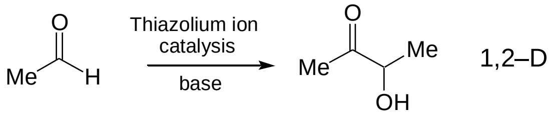


Reactions catalyzed by thiamine

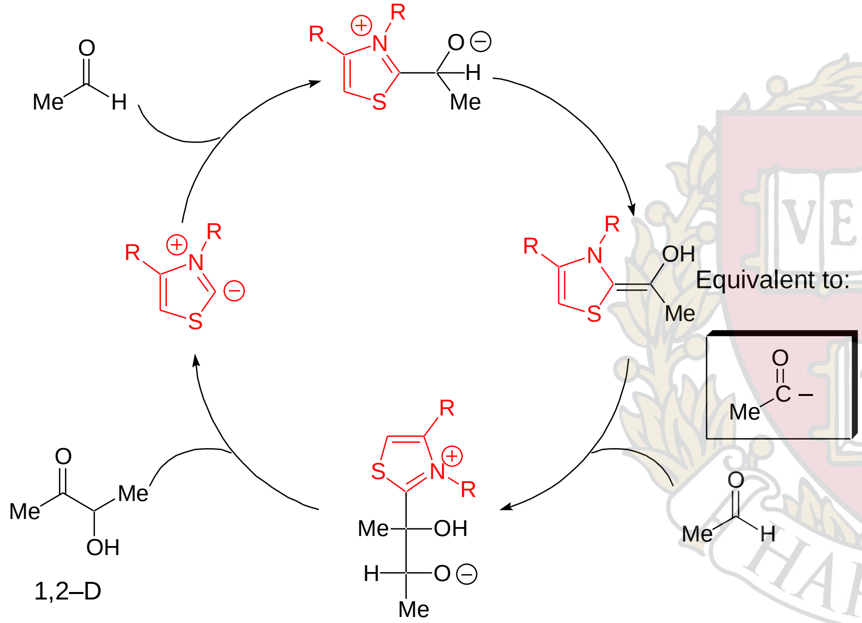


Aldehyde dimerization by Thiazolium Salts

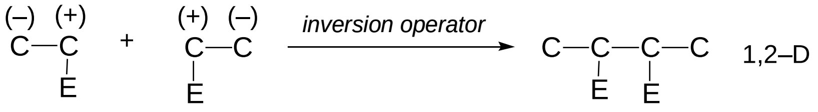
The Reaction



The Catalytic Cycle



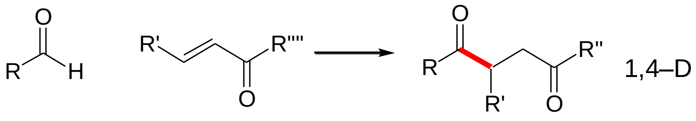
■ Hence dissonant relationships may made from E-functions if "inversion operator" is employed



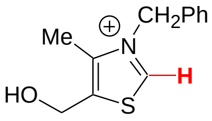
■ The is a fundamental strategy for handling the formation and cleavage of D-relationships in nature.

Cataylzed Michael Reactions byThiazolium Salts

The Reaction

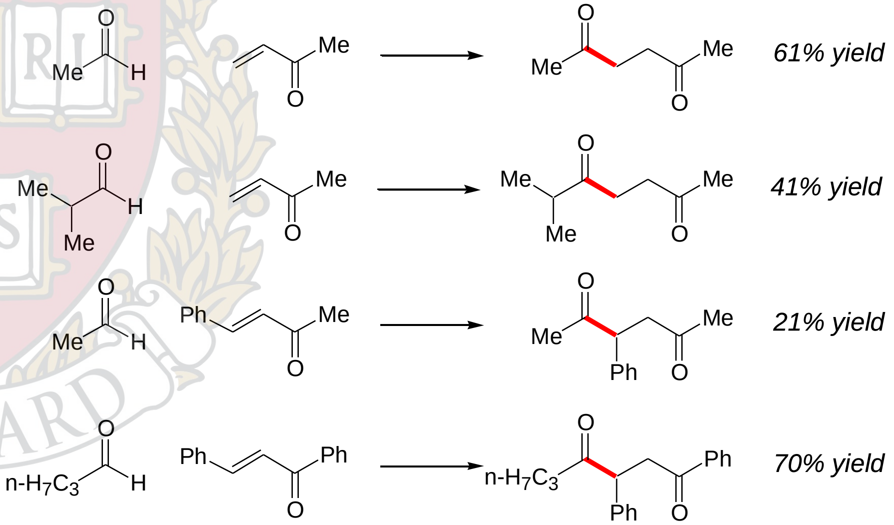


The Catalyst:

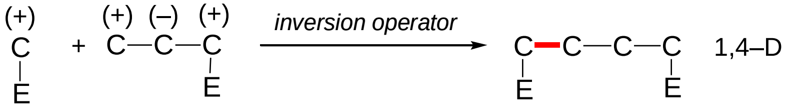


The Conditions:
0.1 equiv catalyst, Et_3N or NaOAc,
EtOH or DMF at 60-80 °C

Examples: "The catalyzed nucleophilic addition of aldehydes to electrophilic double bonds.", Stetter, H.; Kuhlmann, H. *Org. Reactions* **1991**, *40*, 407.



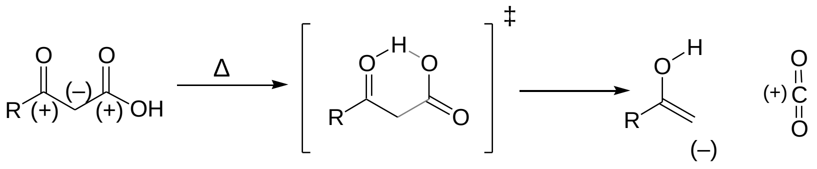
■ 1,4-D relationships may also be made from E-functions if "inversion operator" is employed.



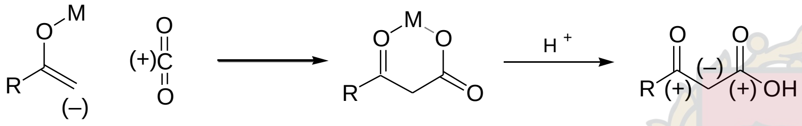
■ There is no analogue to this reaction in nature.

Decarboxylation Catalyzed by Thiazolium Salts

- Background: Decarboxylation from consonant difunctional relationships is facile:

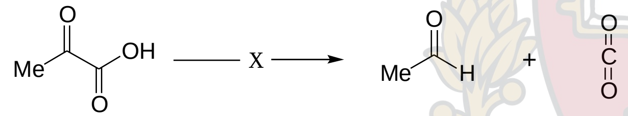


- The reverse processe can be achieved under basic conditions:

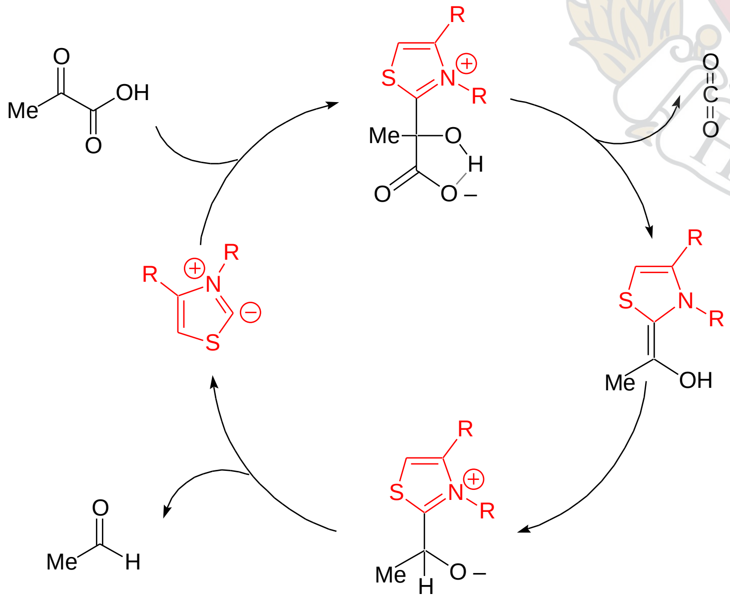


- Such consonant relationships may be readily made (and broken) via the resident functional groups. The analog reactions for dissonant relationships not possible.

For example:



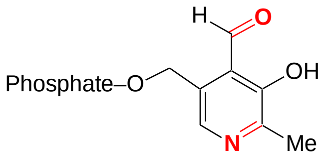
- Nature uses inversion operators to break such 1,2-D relationships



Design Attributes of Inversion Operators

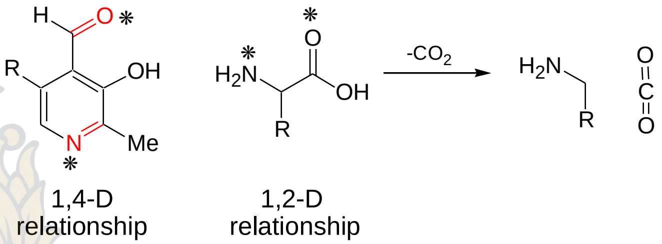
Inversion operators are constructed from A-functions or molecules containing D-relationships.

The pyridoxal Co-factor (Vitamin B_6)

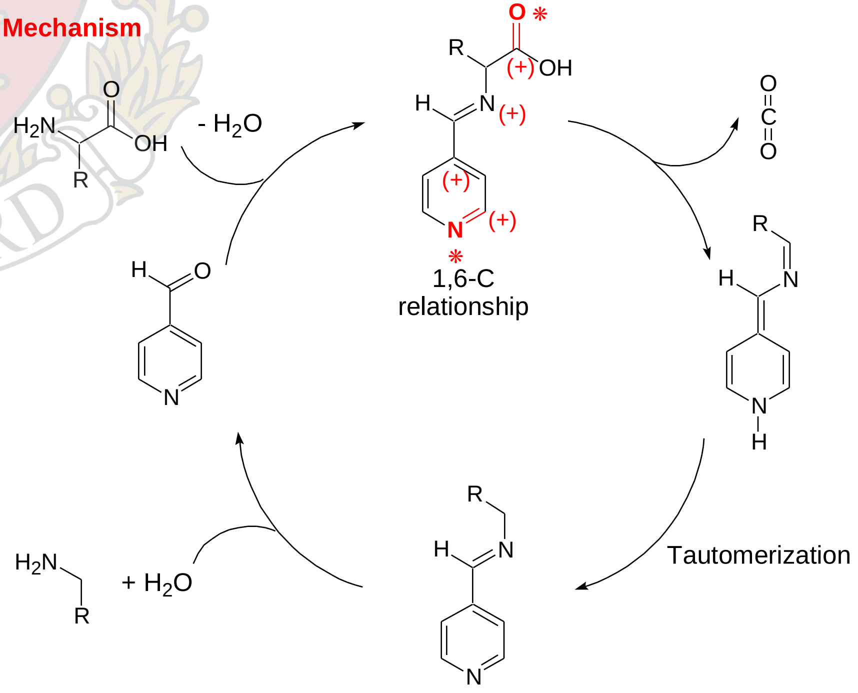


The critical difunctional relationlship is that between =O & =N. This is a 1,4-D relationship

The Reaction



The Mechanism



http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 30

Introduction to Carbonium Ions

- Carbocation Stabilization
- Carbocation Structures by X-ray Crystallography
- Vinyl & Allyl Carbonium Ions

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed.
Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

Laube (**1995**). “X-Ray Crystal Structures of Carbocations Stabilized by Bridging or Hyperconjugation.” *Acc. Chem. Res. 28*,: 399 **(pdf)**

Olah, G. A. (**1995**). “My search for carbocations and their role in chemistry (Nobel lecture).” *Angew. Chem., Int. Ed. Engl.* **34**, 1393-1405. **(CCB library)**

Olah, G. A. (**2001**). “100 Years of Carbocations and their Significance in Chemistry.” *J. Org. Chem.* **2001**, *66*, 5944-5957. **(pdf)**

Matthew D. Shair

Wednesday,
December 4, 2002

Other Relevant Background Reading

March, *Advanced Organic Chemistry*, 4th Ed. Chapter 5, pp165-174.

Lowery & Richardson, *Mech. & Theory in Org, Chem.*, 3rd Ed. pp 383-412.

Arnett, Hoeflich, Schriver in *Reactive Intermediates* **Vol 3**, Wiley, 1985, Chapter 5, p 189.

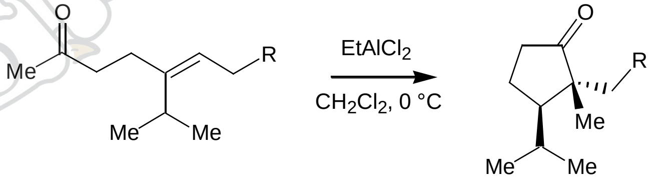
Saunders, M. and H. A. Jimenez-Vazquez (**1991**). “Recent studies of carbocations.” Chem. Rev. 91: 375.

Stang, P. J. (**1978**). “Vinyl Triflate Chemistry: Unsaturated Cations and Carbenes.” Acc. Chem. Res. 11: 107.

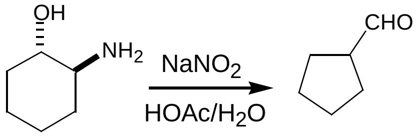
Olah, G. A. and G. Rasul (**1997**). “Chemistry in superacids .26. From Kekule's tetravalent methane to five-, six- and seven-coordinate protonated methanes.” Acc. Chem. Res. 30(6): 245-250.

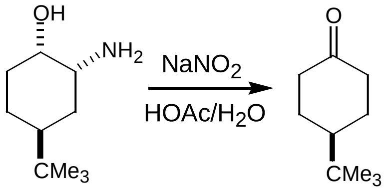
Walling, C. (**1983**). “An Innocent Bystander Looks at the 2-Norbornyl Cation.” Acc. Chem. Res. 16: 448.

Qumulative Exam Question Fall, 2001. The reaction illustrated below was recently reported by Snider and co-workers (*Org. Lett.* **2001**, *123*, 569-572). Provide a mechanism for this transformation. Where stereochemical issues are present, provide clear three dimensional drawings to support your answer.



Carey & Sundberg-A, p 337: Provide mechanisms for the following reactions.

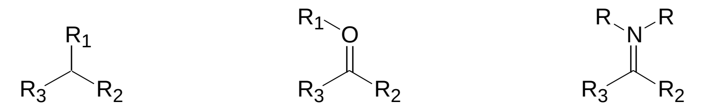




Carbocations: Stability

Carbocation Subclasses

Carbon-substituted **Heteroatom–stabilized**



$R–R_3$ = alkyl or aryl $R–R_3$ = alkyl or aryl $R–R_3$ = alkyl or aryl

The following discussion will focus on carbocations unsubstitutred with heteroatoms

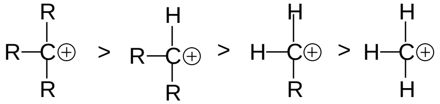
Classical vs nonclassical carbonium ions

open trivalent | hyperconjugation no bridging | unsymmetrical bridging | symmetrical bridging

classical increasing nonclassical character → **nonclassical**

Stability: Stabilization via alkyl substituents (hyperconjugation)

Order of carbocation stability: 3°>2°>1°



Due to increasing number of substituents capable of hyperconjugation

The relative stabilities of various carbocations can be measured in the gas phase by their affinity for hydride ion.

$$R^{\oplus} + H^{\ominus} \longrightarrow R–H + HI$$

Hydride Affinity = –ΔG°

ΔHI increases → C(+) stability decreases

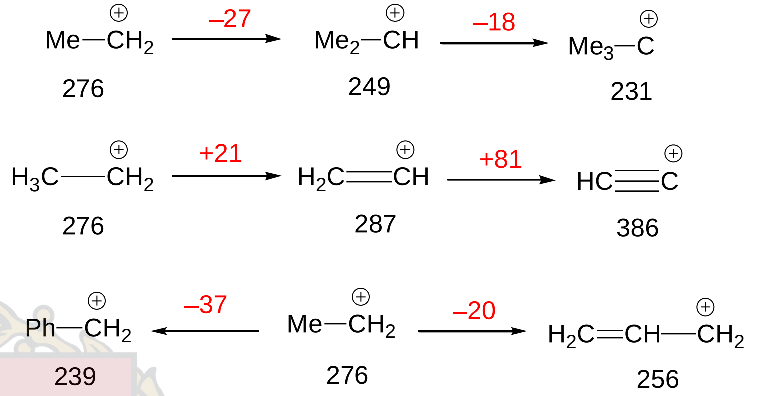
Note: As S-character increases, cation stability decreases due to more electronegative carbon.

J. Beauchamp, *J. Am. Chem. Soc.* **1984**, *106*, 3917.

	Hydride ion affinities
CH_3^+	314
$CH_3CH_2^+$	276
$(CH_3)_2CH^+$	249
$(CH_3)_3C^+$	231
$H_2C{=}CH^+$	287
$H–C{\equiv}C^+$	386
$PhCH_2^+$	239

Carey & Sundberg–**A**, pp 276-

Hydride ion affinities (HI)

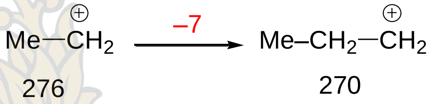


$$\underset{276}{Me–\overset{\oplus}{C}H_2} \xrightarrow{-27} \underset{249}{Me_2–\overset{\oplus}{C}H} \xrightarrow{-18} \underset{231}{Me_3–\overset{\oplus}{C}}$$

$$\underset{276}{H_3C–\overset{\oplus}{C}H_2} \xrightarrow{+21} \underset{287}{H_2C{=}\overset{\oplus}{C}H} \xrightarrow{+81} \underset{386}{HC{\equiv}\overset{\oplus}{C}}$$

$$\underset{239}{Ph–\overset{\oplus}{C}H_2} \xleftarrow{-37} \underset{276}{Me–\overset{\oplus}{C}H_2} \xrightarrow{-20} \underset{256}{H_2C{=}CH–\overset{\oplus}{C}H_2}$$

The effect of beta substituents: Rationalize



$$\underset{276}{Me–\overset{\oplus}{C}H_2} \xrightarrow{-7} \underset{270}{Me–CH_2–\overset{\oplus}{C}H_2}$$

Hydride ion affinities versus Rates of Solvolysis

	$PhCH_2$–Br	CH=CH–CH_2–Br	Me_2CH–Br
rel rate	100	52	0.7
HI	239	256	249
Δ-HI	0	+17	+10

Relative Solvolysis rates in 80% EtOH, 80 °C

A. Streitwieser, *Solvolytic Displacement Reactions*, p75

Conclusion:
Gas phase stabilities do not always correlate with rates of solvolysis

Carbocation Stability: The pK_{R+} value

Definition: $R^+ + H_2O \rightleftharpoons ROH + H^+$

$$K_{R+} = \frac{a_{ROH}\ a_{H+}}{a_{R+}\ a_{H2O}}$$

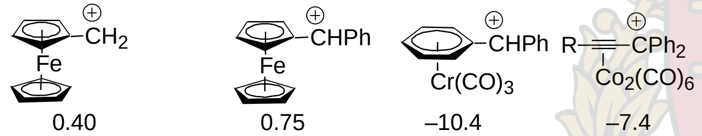
a = activity

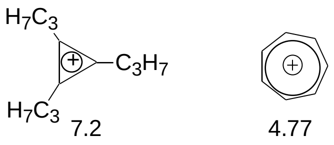
$$\boxed{pK_{R+} = -\log K_{R+}}$$

Carey & Sundberg, A, p 277

Table: **pK_{R+} values of some selected carbenium salts**

$(4\text{-MeO-}C_6H_4)_3C^{\oplus}$	$Ph_3C^{\oplus}$	$(3\text{-Cl-}C_6H_4)_3C^{\oplus}$	$Ph_2\overset{\oplus}{C}H$
0.82	– 6.63	– 11.0	– 13.3





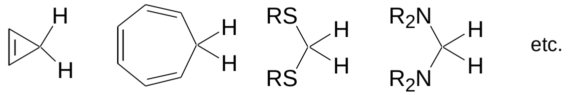
Carey & Sundberg, A, pp 276-

Carbocation Generation

Hydride abstraction from neutral precursors

$$\boxed{R_3C{-}H \ + \ \text{Lewis-Acid} \longrightarrow R_3C^{\oplus}}$$

$R_3C{-}H$ =



Lewis-Acid: $Ph_3\overset{\oplus}{C}\ \overset{\ominus}{B}F_4$, BF_3, PCl_5

Removal of an energy-poor anion from a neutral precursor via Lewis Acids

$$\boxed{R_3C{-}X \ + \ \textbf{LA} \longrightarrow R_3C^{\oplus} \ + \ LA{-}X^{\ominus}}$$

LA: Ag , $AlCl_3$, $SnCl_4$, $SbCl_5$, **SbF_5**, BF_3, $FeCl_3$, $ZnCl_2$, PCl_3, PCl_5, $POCl_3$ ...

X: F, Cl, Br, I, OR

Acidic dehydratization of *secondary* and *tertiary* alcohols

$$\boxed{R_3C{-}OH \ + \ H{-}X \xrightarrow{-H_2O} R_3C^{\oplus} \ + \ X^{\ominus}}$$

R: Aryl + other charge stabilizing substituents

X: SO_4^{2-}, ClO_4^-, FSO_3^-, $CF_3SO_3^-$

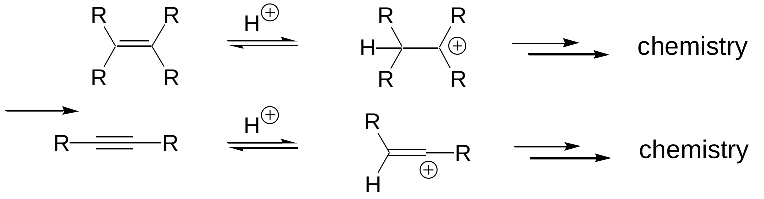
From neutral precursors via heterolytic dissociation (solvolysis) - First step in S_N1 or E1 reactions

$$R_3C{-}X \xrightarrow{\text{solvent}} R_3C^{\oplus} \ + \ X^{\ominus}$$

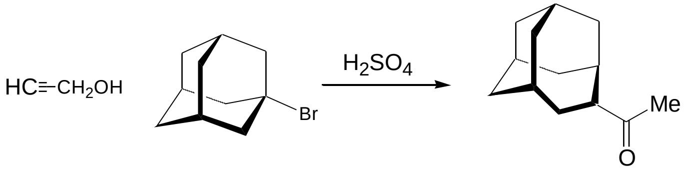
Ability of X to function as a leaving group:

$-N_2^+ > -OSO_2R' > -OPO(OR')_2 > -I \geq -Br > Cl > OH_2^+$ ...

Addition of electrophiles to π-systems

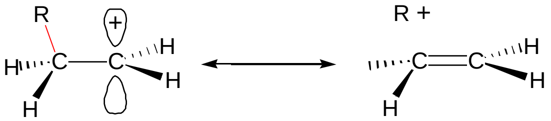


Provide a Mechanism of this transformation



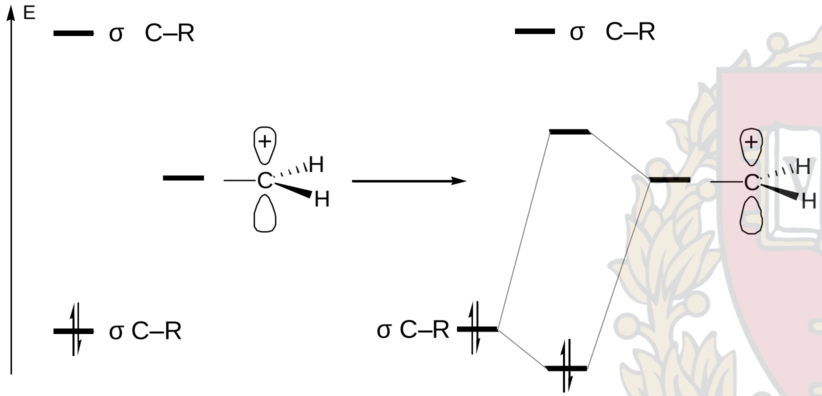
J.C.S.,CC **1971**, 556

Carbocation Stabilization Through Hyperconjugation



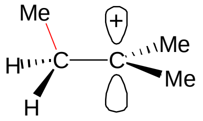
■ FMO Description

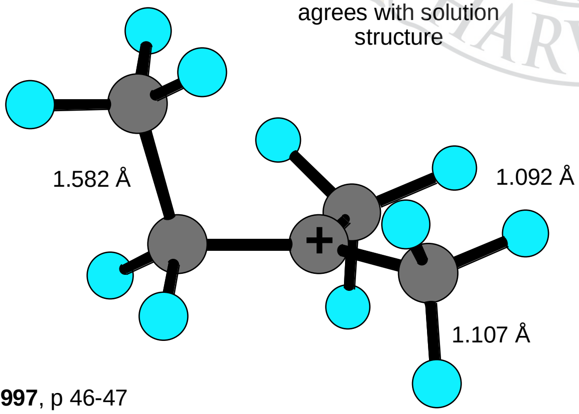
Take linear combination of σ C–R (filled) and C p_z-orbital (empty):



Syn-planar orientation between interacting orbitals

C–H versus C–C Hyperconjugation: The t-Pentyl Cation





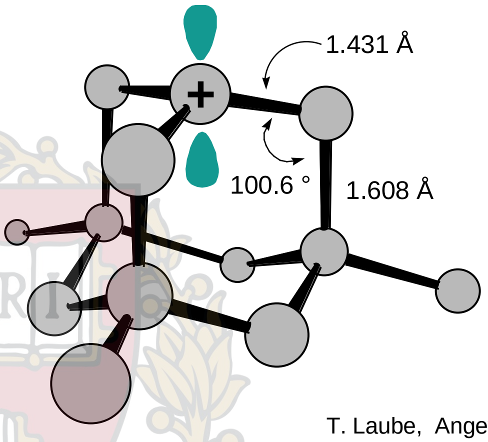
Calculated carbocation agrees with solution structure

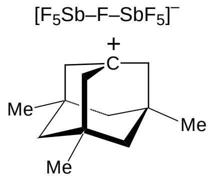
R. P von Schleyer in
Stable Carbocation Chemistry, **1997**, p 46-47

Physical Evidence for Hyperconjugation: The Adamantyl Cation

Bonds participating in the hyperconjugative interaction, e.g C–R, will be lengthened while the C(+)–C bond will be shortened.

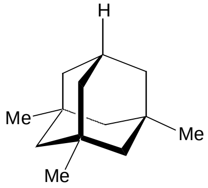
First X-ray Structure of an Aliphatic Carbocation

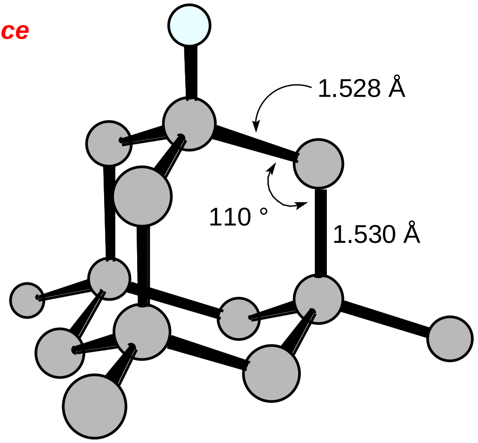




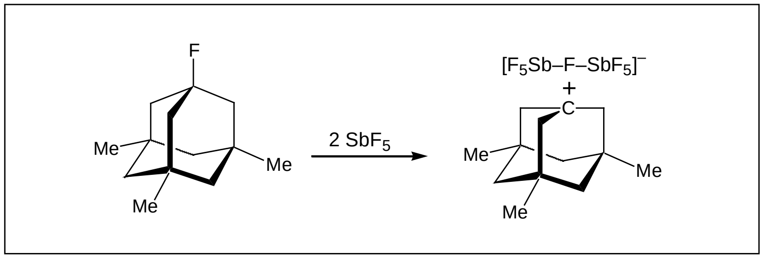
T. Laube, Angew. *Chem. Int. Ed.* **1986**, *25*, 349

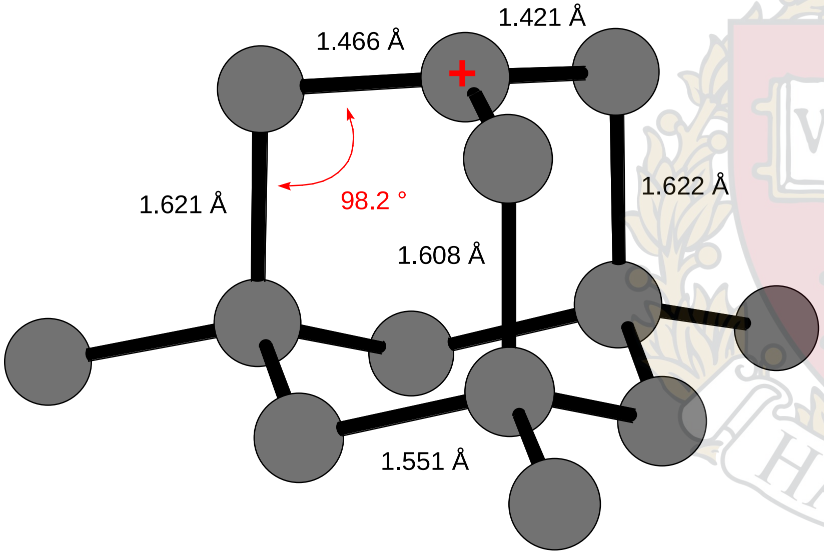
The Adamantane Reference (MM-2)





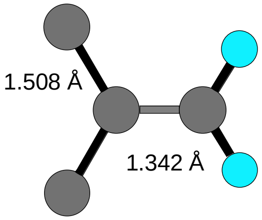
Carbocations: Structure

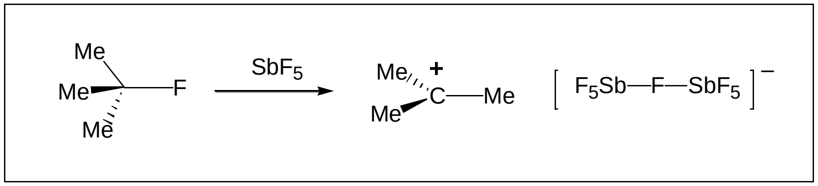


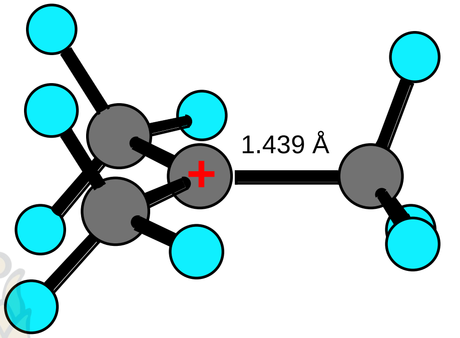


T. Laube, Angew. *Chem. Int. Ed.* **1986**, *25*, 349

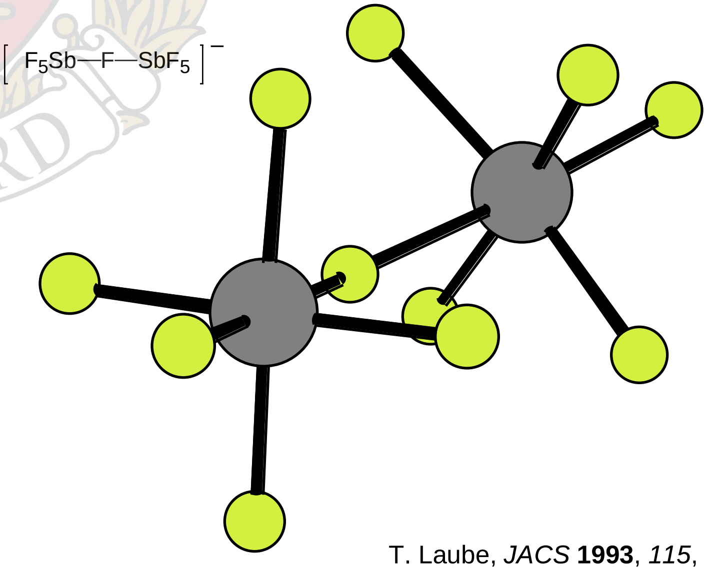
reference structure:
CSP3–Csp2 bond length



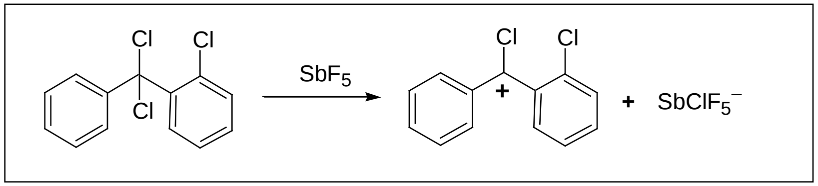


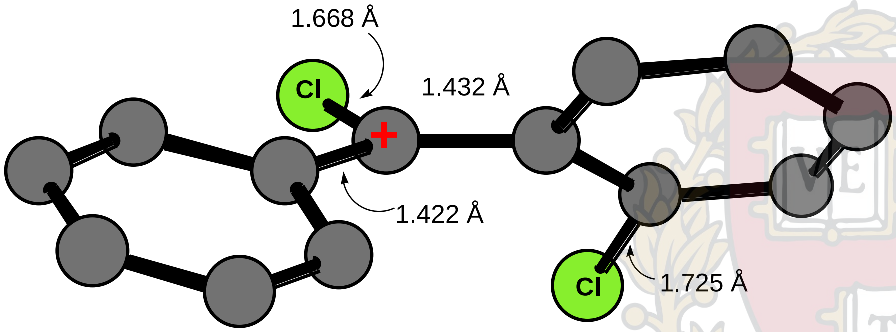


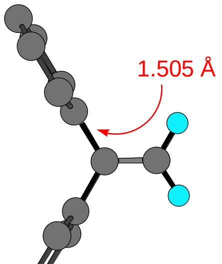
C–C$_1$: 1.439 Å
C–C$_2$: 1.446 Å
C–C$_3$: 1.442 Å



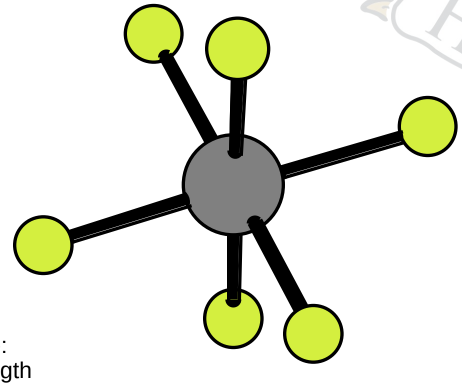
T. Laube, *JACS* **1993**, *115*, 7240

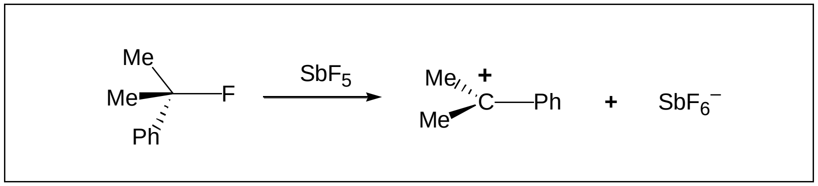


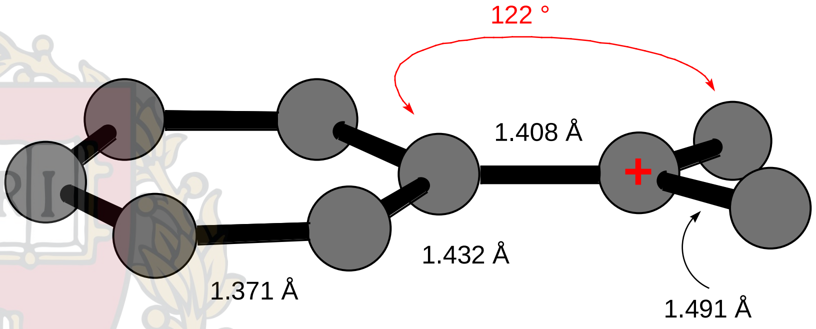


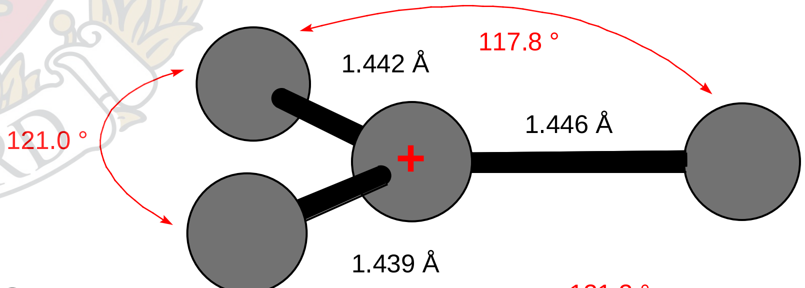


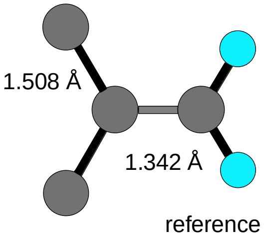
reference structure:
CSP$_2$–Csp$_2$ bond length







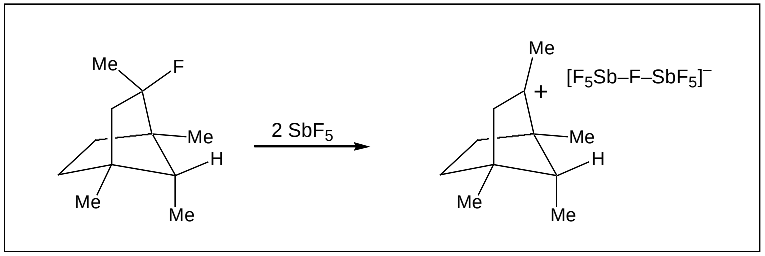




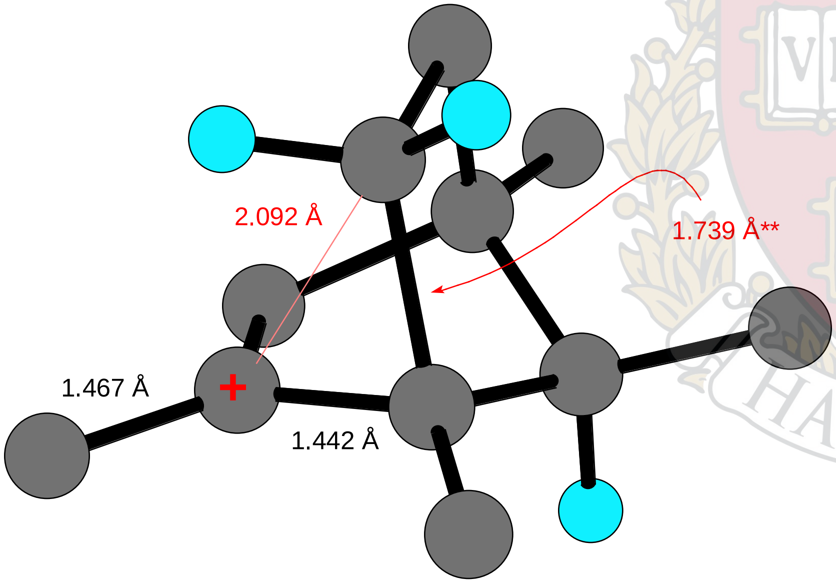
reference structure:
CSP$_3$–Csp$_2$ bond length

T. Laube, *JACS* **1993**, *115*, 7240

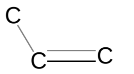
Carbonium Ion X-ray Structures: Bridged Carbocations



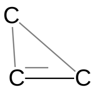
T. Laube, Angew. *Chem. Int. Ed.* **1987**, *26*, 560



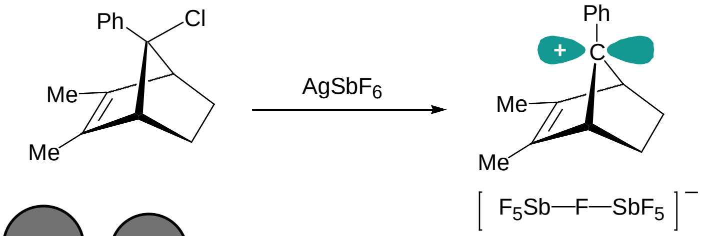
**One of the longest documented C–C bond lengths.

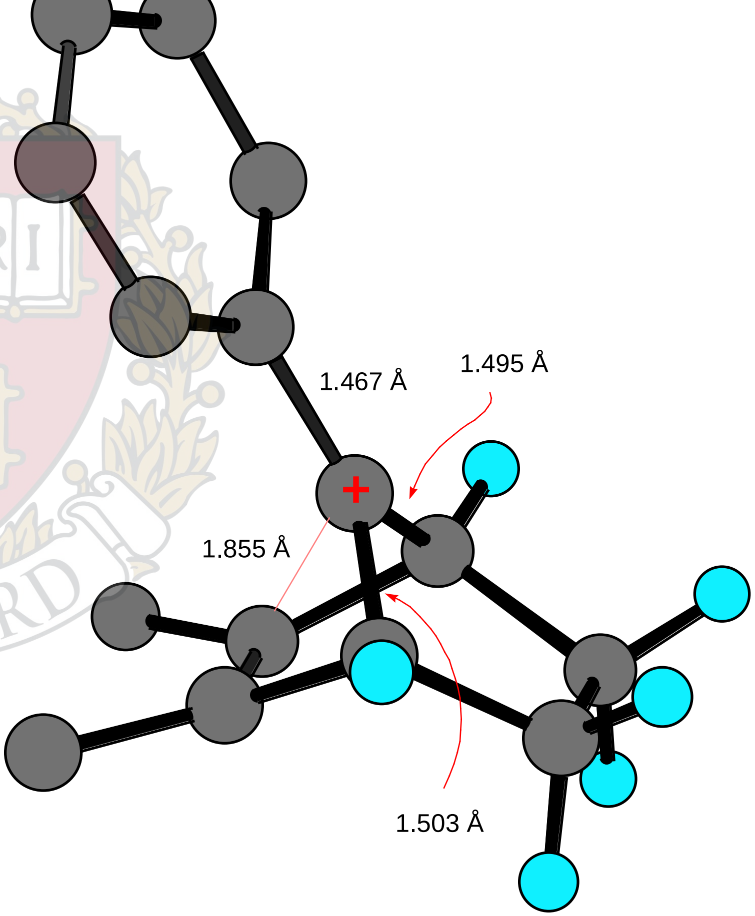


hyperconjugation
no bridging



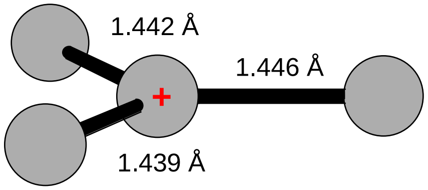
unsymmetrical
bridging



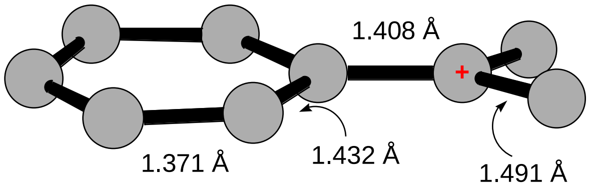


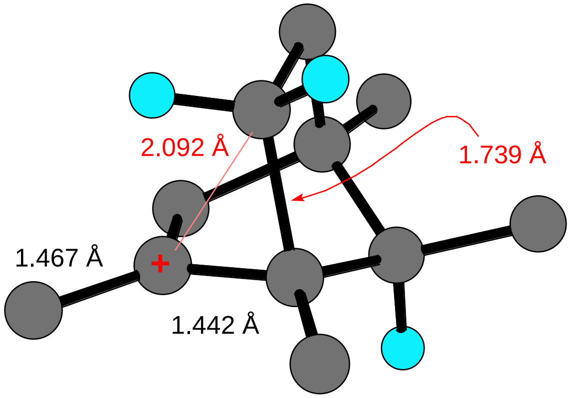
T. Laube, *JACS* **1989**, *111*, 9224

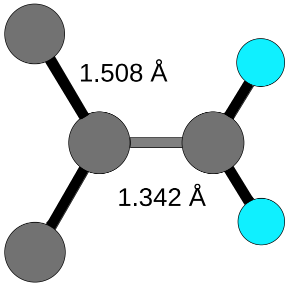
Carbonium Ion X-ray Structures: A Summary

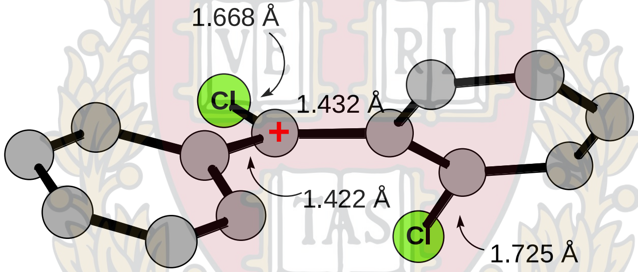


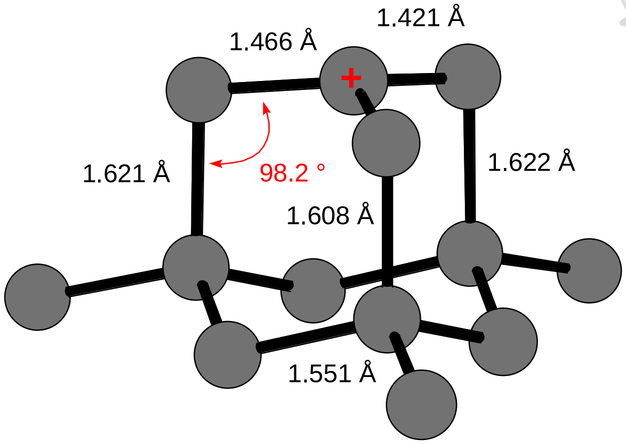
(ref 1.513 Å)Ph–C(Me)=CH2

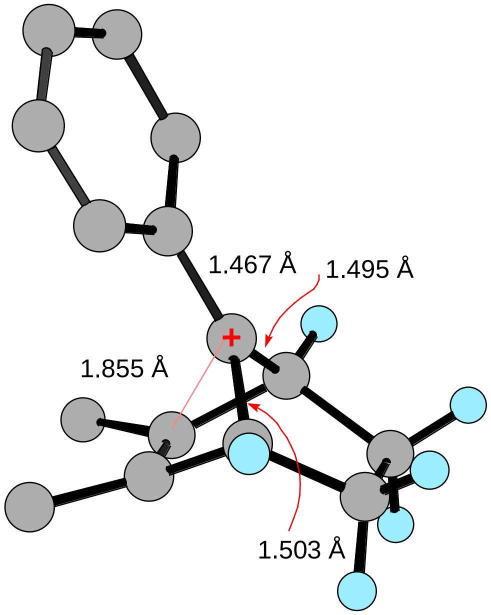




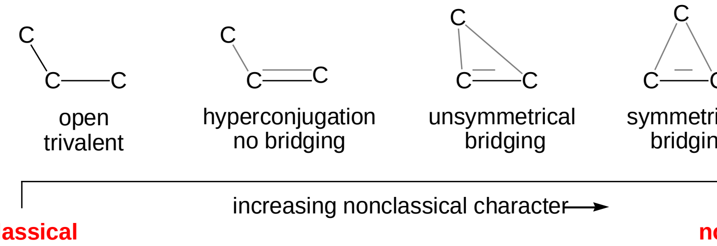








Nomenclature: classical vs nonclassical



open trivalent

hyperconjugation no bridging

unsymmetrical bridging

symmetrical bridging

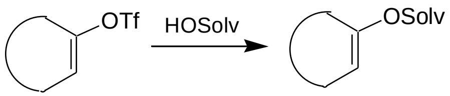
increasing nonclassical character→

classical

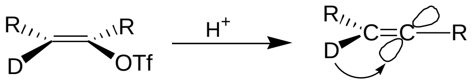
nonclassical

Vinyl & Phenyl Cations: Highly Unstable

Evidence suggests that vinyl cations are linear.



As ring size decreases, the rate of hydrolysis also diminishes. Implying that the formation of the linear vinyl cation is disfavored due to increasing ring strain.



Hyperconjugation

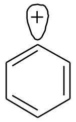
A secondary kinetic isotope effect was measured to be $K_H/K_D = 1.5$ (quite large) indicating strong hyperconjugation and an orientation of the vacant p orbital as shown above.

P. J. Stang *J. Am. Chem Soc.* **1971**, *93*, 1513; P. J. Stang *J.C.S. PT II* **1977,** 1486.

Hydride ion affinities (HI)

$$\underset{276}{\mathrm{H_3C{-}\overset{\oplus}{C}H_2}} \xrightarrow{+21} \underset{287}{\mathrm{H_2C{=}\overset{\oplus}{C}H}} \xrightarrow{+81} \underset{386}{\mathrm{HC{\equiv}\overset{\oplus}{C}}}$$

$$\underset{287}{\mathrm{H_2C{=}\overset{\oplus}{C}H}} \xrightarrow{+11}$$



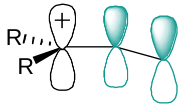
298

Phenyl Cations

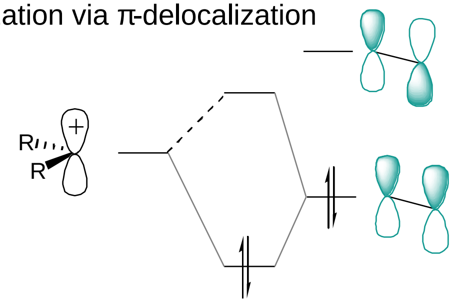
The ring geometry opposes rehybridization (top) so the vacant orbital retains sp^2 character. Additionally, the empty orbital lies in the nodal plane of the ring, effectively prohibiting conjugative stabilization.

Allyl & Benzyl Carbocations

Carbocation Stabilization via π-delocalization



allyl cation



■ Stabilization by Phenyl-groups

The Benzyl cation is as stable as a t-Butylcation. This is shown in the subsequent isodesmic equations:

	ΔH^0_r [kcal/mol]
$\mathrm{(CH_3)_3\overset{\oplus}{C} + PhCH_3 \rightleftharpoons (CH_3)_3CH + Ph\overset{\oplus}{C}H_2}$	3.8
$\mathrm{(CH_3)_3\overset{\oplus}{C} + PhCH_2Cl \rightleftharpoons (CH_3)_3CCl + Ph\overset{\oplus}{C}H_2}$	- 0.8

Hydride ion affinities (HI)

$$\underset{239}{\mathrm{Ph{-}\overset{\oplus}{C}H_2}} \xrightarrow{-8} \underset{231}{\mathrm{Me_3{-}\overset{\oplus}{C}}}$$

Hydride ion affinities versus Rates of Solvolysis

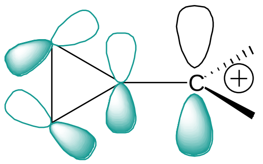
	$\mathrm{PhCH_2}$–Br	$\mathrm{Me_2CH}$–Br	$\mathrm{CH{=}CH{-}CH_2}$–Br
	100	0.7	52
HI	239	249	256
Δ-HI	0	+10	+17

Relative Solvolysis rates in 80% EtOH, 80 °C

A. Streitwieser, *Solvolytic Displacement Reactions*, p75

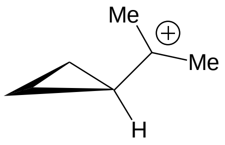
Cyclopropyl-carbinyl Carbocations

Carbocation Stabilization via Cyclopropylgroups



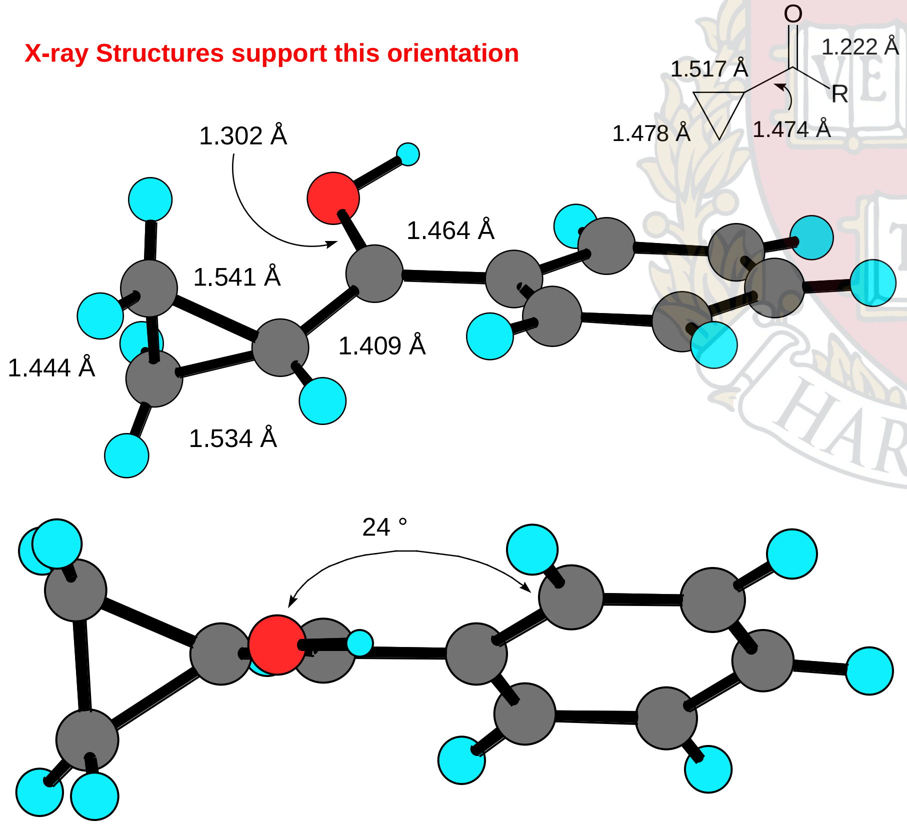
See Lecture 5, slide 5-05 for discussion of Walsh orbitals

A rotational barrier of about 13.7 kcal/mol is observed in following example:



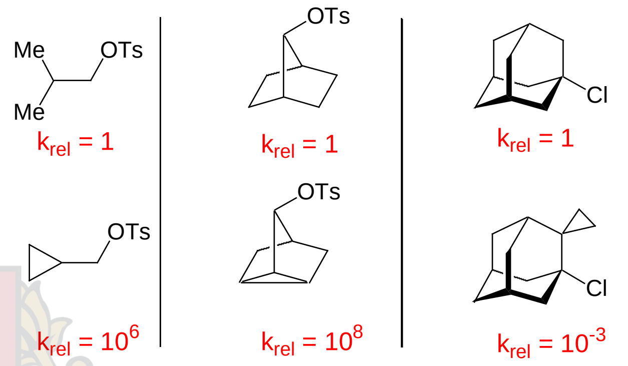
NMR in super acids
δ(CH_3) = 2.6 and 3.2 ppm

X-ray Structures support this orientation

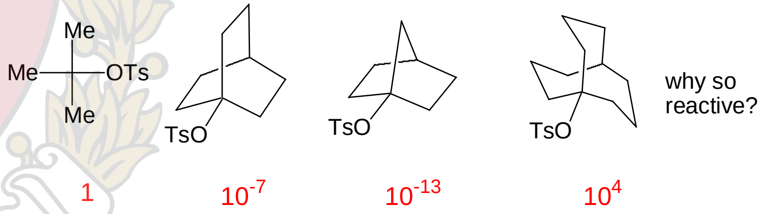


R. F. Childs, *JACS* **1986**, *108*, 1692

Solvolysis rates represent the extend of that cyclopropyl orbital overlap contributing to the stabiliziation of the carbenium ion which is involved as a reactive intermediate:



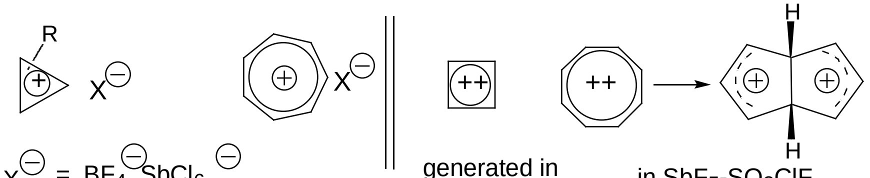
Bridgehead Carbocations



Bridgehead carbocations are highly disfavored due to a strain increase in achieving planarity. Systems with the greatest strain increase upon passing from ground state to transition state react slowest.

Carbocation Stabilization - Aromaticity

Some Hückel aromatic cations (4n+2) π-electrons are isolable as salts with non-nucleophilic anions.



$X^{\ominus}$ = $BF_4^{\ominus}$, $SbCl_6^{\ominus}$

stable, isolable salts

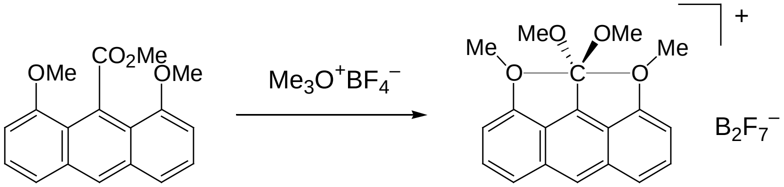
generated in SbF_5-SO_3

in SbF_5-SO_2ClF

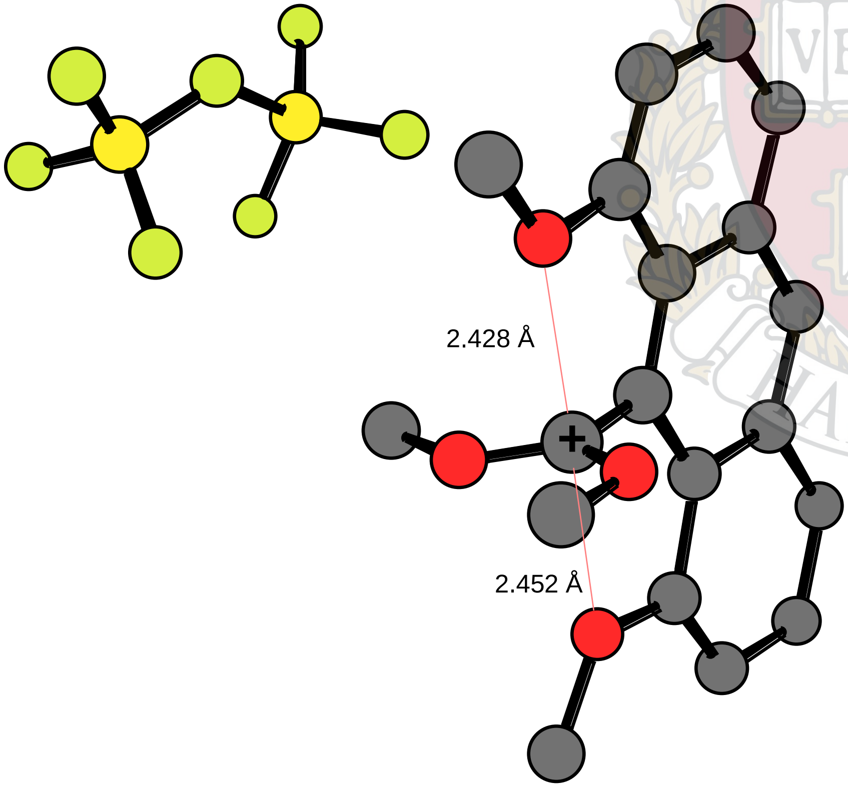
A Stable Hypervalent Carbon Compound ?

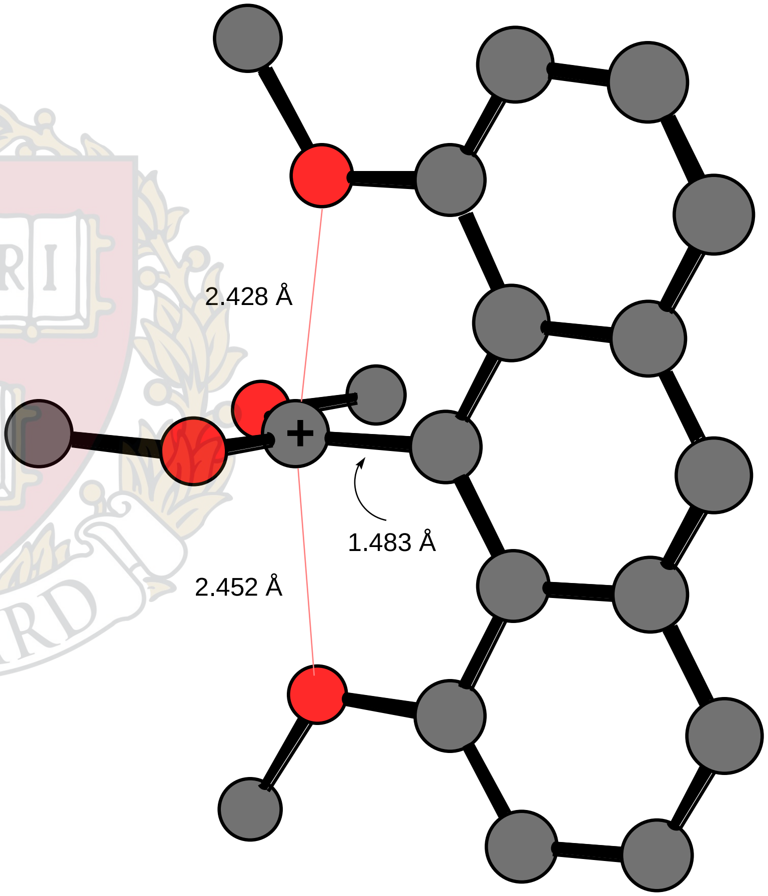
"The Synthesis and Isolation of Stable Hypervalent Carbon Compound (10-C-5) Bearing a 1,8-Dimethoxyanthrecene Ligand"

Akibe, et al. *JACS* **1999**, *121*, 10644-10645



"The relevant C–O distances are longer than a covalent C–O bond (1.43 Å) but shorter than the sum of the van der Waals radii (3.25 Å)."



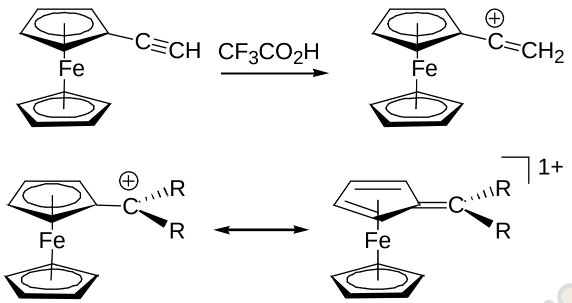


For a recent monograph on hypervalent Compounds see:
"Chemistry of Hypervalent Compounds", K. Akiba, Wiley-VGH, 1999

Transition Metal-Stablized Carbocations-1

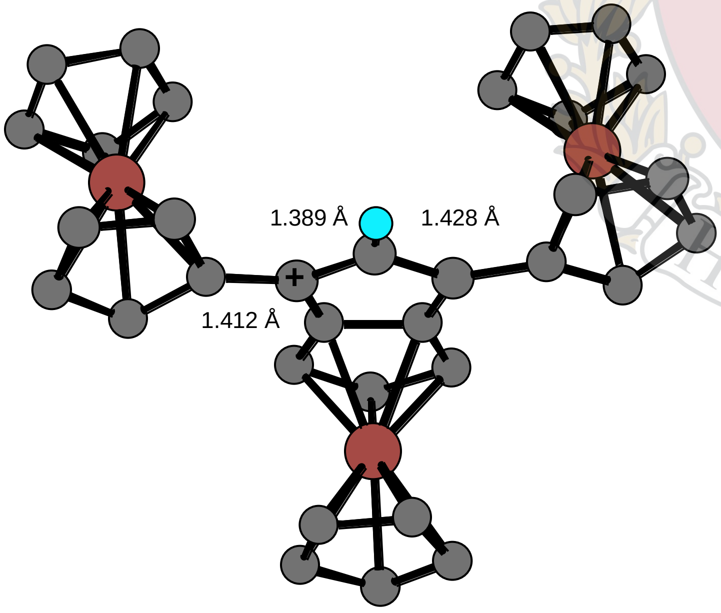
Carbocation Stabilization - d(π) stabilization via Transition metal Fragments

- Transition metal not bound directly to carbenium ion: **Ferrocenes**

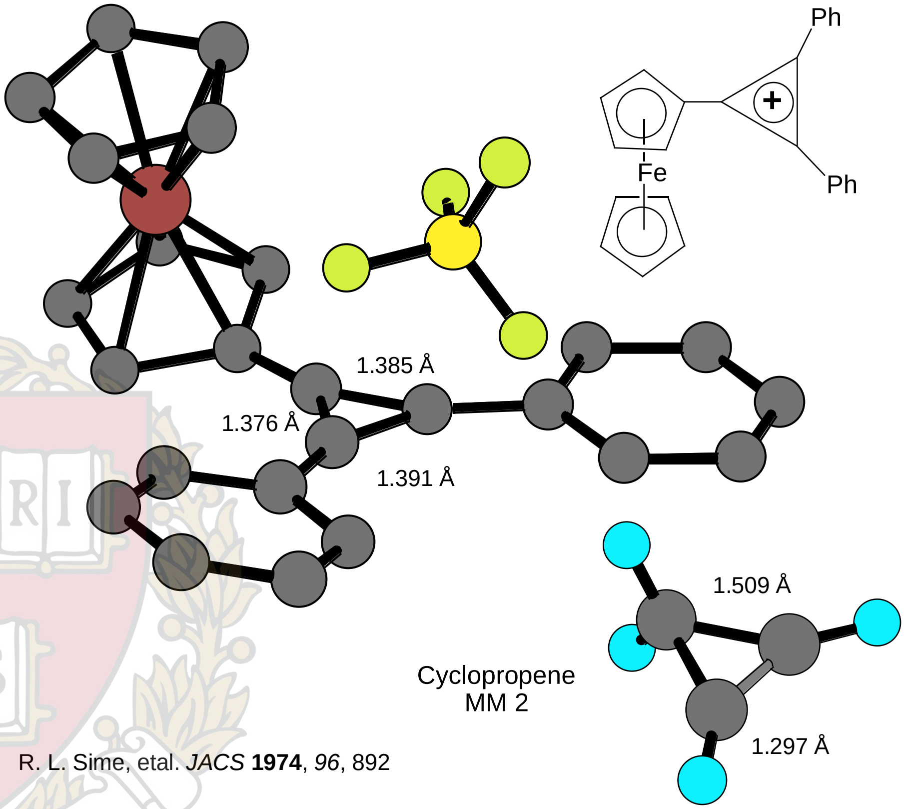


stable in CF_3COOH

an important resonance contribution



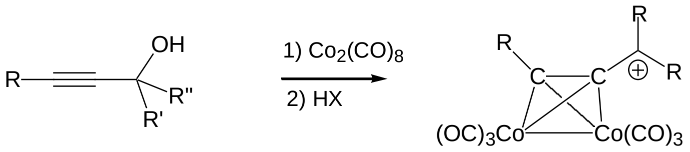
J. Lukasser, etal. *Organometallics* **1995**, *14*, 5566-5578



Cyclopropene
MM 2

R. L. Sime, etal. *JACS* **1974**, *96*, 892

- Transition metal not bound directly to carbenium ion: **Colbalt-Acetylenes**

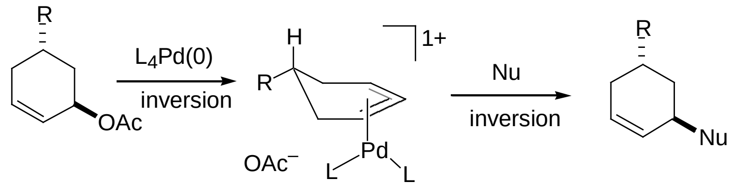


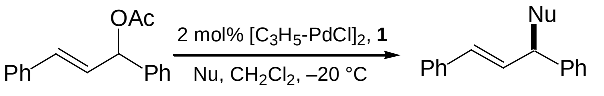
isolable,
basis of the Nicholas reaction

See Houk etal. *JACS* **1999**, *121*, 3596-3606

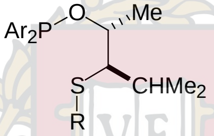
Carbocation Stabilization - d(π) stabilization via Transition metal Fragments

Transition metals bound to carbenium ions: π–Allyl Pd(II) Complexes

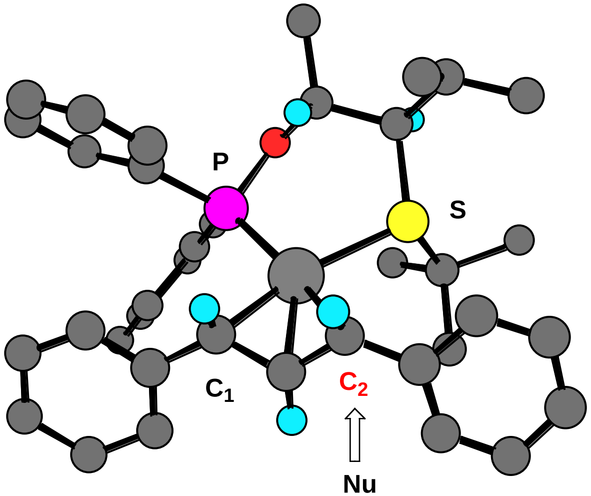




Nu = $CH(CO_2Me)_2$	98% ee
Nu = BnNH	95% ee

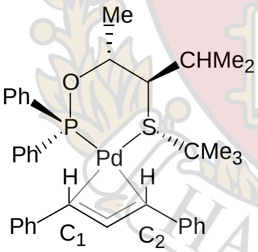


1a Ar = Ph



Pd-C_1, 2.16Å

Pd-C_2, 2.28Å

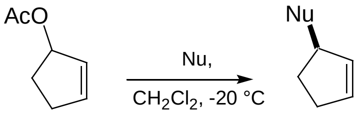
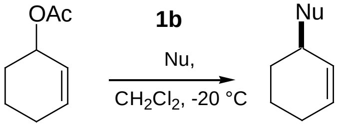
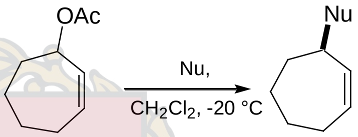
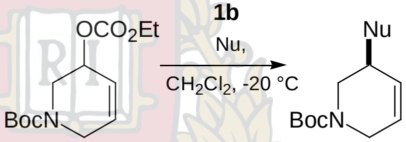


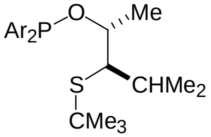
Selected Bond Lengths:

Pd-C_1, 2.16Å; Pd-C_2, 2.28Å

Pd-P, 2.29 Å; Pd-S, 2.38 Å

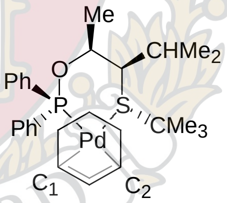
Evans, Campos,Tedrow, Michael, Gagné,
JACS **2000**, *122*, 7905

	Nu = $CH(CO_2Me)_2$	Nu = BnNH
	94% ee	91% ee
	94% ee	91% ee
	96% ee	97% ee
	94% ee	94% ee



1b, Ar = α-naphthyl

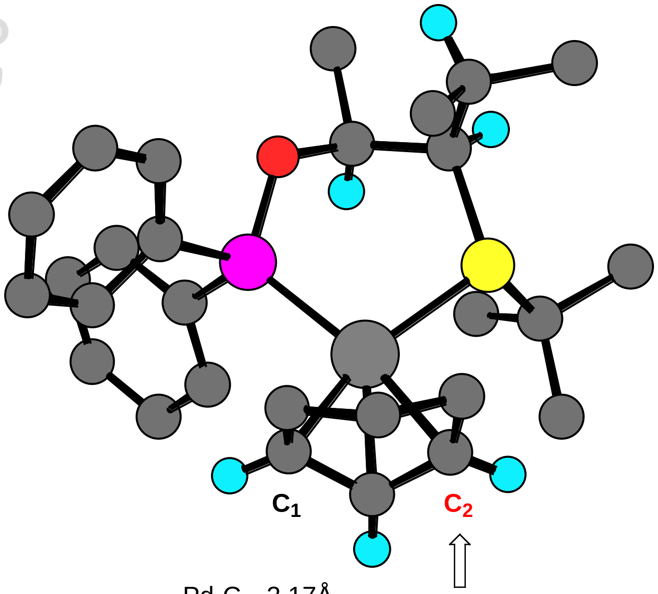
conditions: 2 mol% $[C_3H_5\text{-}PdCl]_2$, **2b**



Selected Bond Lengths:

Pd-C_1, 2.17Å; Pd-C_2, 2.26Å

Pd-P, 2.25 Å; Pd-S, 2.36 Å



Pd-C_1, 2.17Å

Pd-C_2, 2.26Å

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 31

Introduction to Carbonium Ions–2

- Allyl- & Vinylsilanes: The β-Silicon Effect
- Carbonium Ion Rearrangements

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed.
Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

Walling, C. (**1983**). “An Innocent Bystander Looks at the 2-Norbornyl Cation.” *Acc. Chem. Res. 16*: 448. **(handout)**

Birladeanu (**2000**). “The Story of the Wagner-Meerwein Rearrangement.” *J. Chem. Ed. 77*: 858. **(handout)**

Lambert, (**1999**). “The β effect of silicon and related manifestations of σ conjugation.” *Acc. Chem. Res. 32*, 183-190. **(handout)**

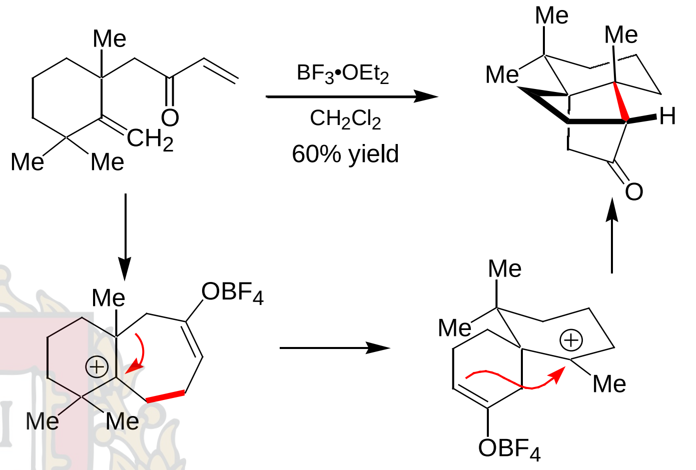
Other Relevant Background Reading

Saunders, M. and H. A. Jimenez-Vazquez (**1991**). “Recent studies of carbocations.” Chem. Rev. 91: 375.

Matthew D. Shair

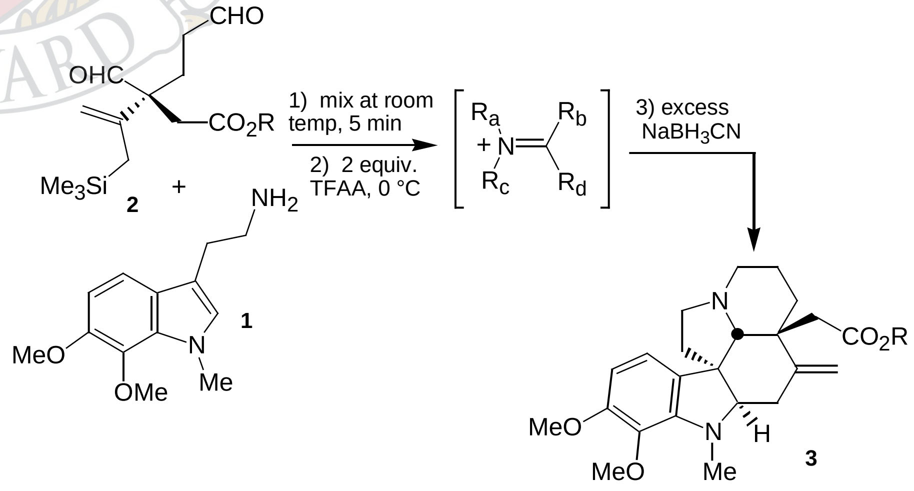
Friday,
December 6, 2002

Here is a typical carbonium ion question that you should be able to handle by the end of the course. Write out a mechanism for the following transformation.



A. Srikrishna, *Chem Commun* **1994**, 2259

Question 13. Final Exam, 1999. During Corey's synthesis of Aspidophytine (*JACS*, **1999**, *121*, 6771), the pivotal intermediate **3** was assembled by the union of **1** and **2** under the specified conditions. Provide a mechanism for this single-pot transformation.

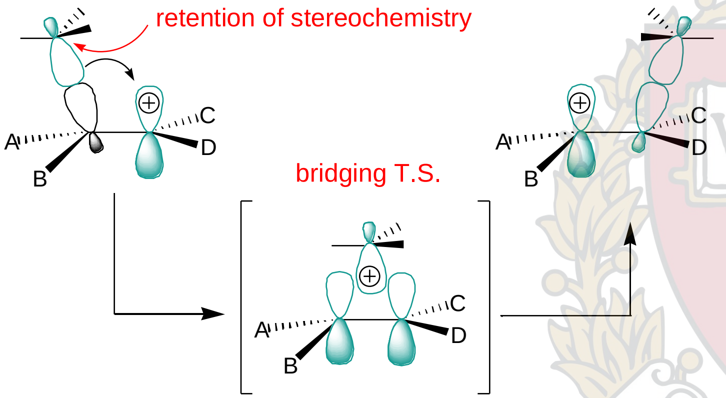


Carbocation [1,2] Sigmatropic Rearrangements

1,2 Sigmatropic shifts are the most commonly encountered cationic rearrangements. When either an **alkyl** substituent or a **hydride** is involved, the term **Wagner-Meerwein shift** is employed to identify this class of rearrangments.

Birladeanu (**2000**). "The Story of the Wagner-Meerwein Rearrangement." J. Chem. Ed. 77: 858. **(handout)**

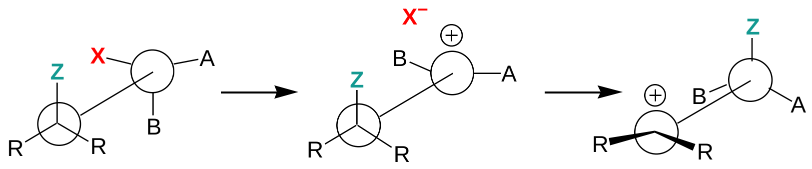
Stereoelectronic requirement for migration....



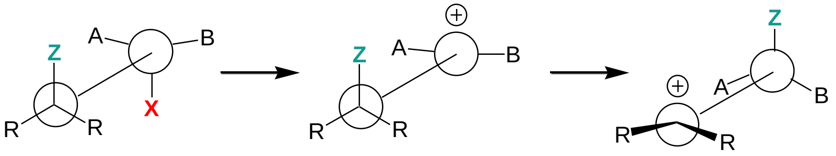
2-electron Huckel transition state

Long-lived Carbocations: X departs before Z moves.

In the most stable ground state conformation, if the relationship between the migrating group (Z) and the leaving group (X) is **gauche**, usually **retention** is observed in the migration terminus.



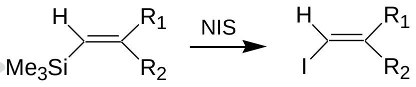
In the most stable ground state conformation, if the relationship between the migrating group (Z) and the leaving group (X) is **anti**, usually **inversion** is observed in the migration terminus.



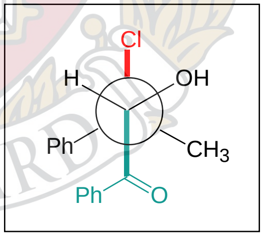
These observations can be ascribed to the **principle of least motion**: "...those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."

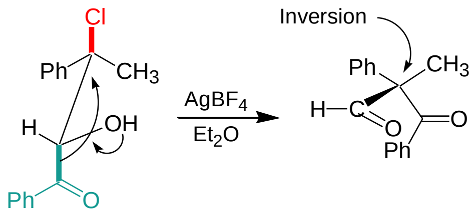
O. S. Tee *JACS* **1969**, *91*, 7144

Principle of least motion in action:



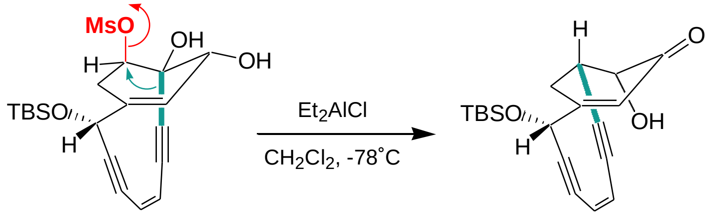
Migration attends ionization





R. Bach *J. Am. Chem. Soc.* **1979**, *101*, 3118

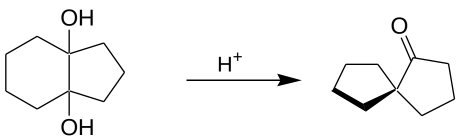
If **migration accompanies ionization**, the migration terminus will be **inverted**. Overlap between the σ C-C (migration origin) and the σ* C-X (migration terminus) will be maximized in an **antiperiplanar** arrangement.

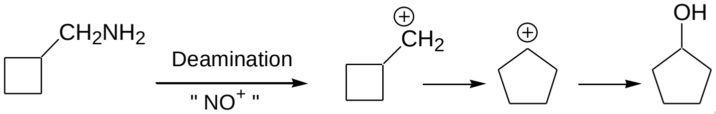


S. L. Schreiber et al *Tetrahedron Lett.* **1989**, *30*, 3765.

Carbocation [1,2] Sigmatropic Rearrangements

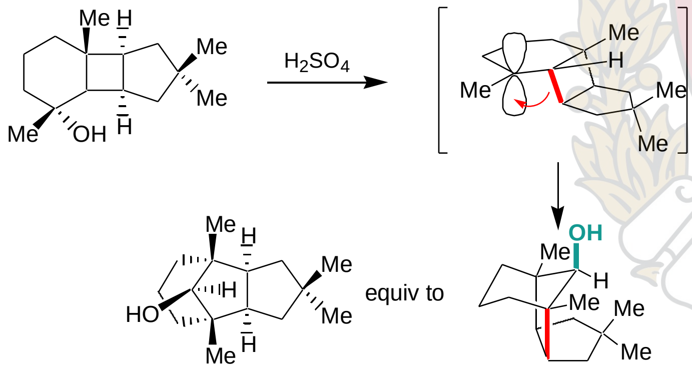
Pinacol rearrangement (vicinal diol): Driving force is the gen. of C=O





Demjanov-rearrangement (Driving force: relief of ring strain)

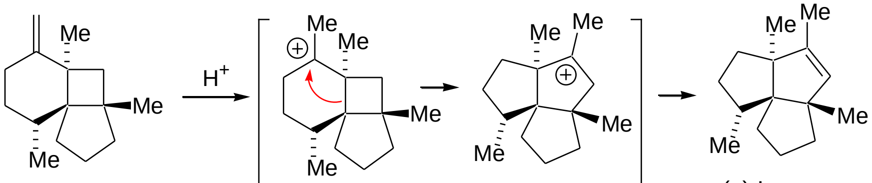
Wagner-Meerwein Rearrangements: Application in Total Synthesis



E. J. Corey *J. Am. Chem. Soc.* **1964**, *86*, 1652.

α-caryophyllene alcohol

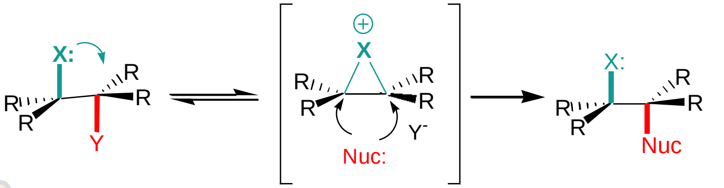
Synthesis of (±)-Isocomene: Pirrung, *JACS* **1979**, 7130; *1981*, 82.



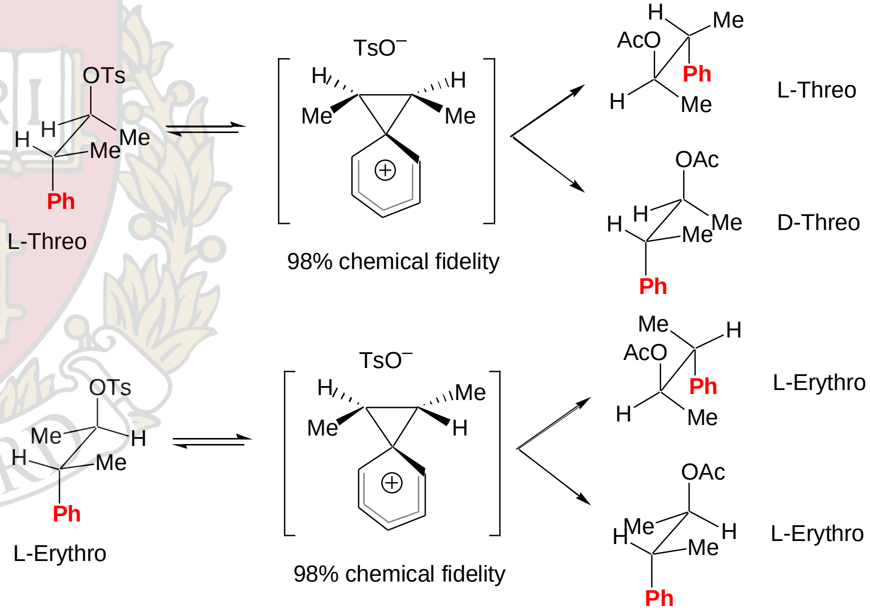
(±)-Isocumene

Carbocations: Neighboring Group Participation

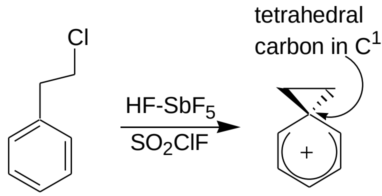
- Groups with accessable electron density (heteroatoms, arenes) and the correct stereoelectronic orientation (anti-periplanar) can "assist" in the ionization of a leaving group.



The Cram Phenonium Ion Experiments: Cram, *JACS* **1949**, *71*, 3865



Physical Evidence for Neighboring Group Participation



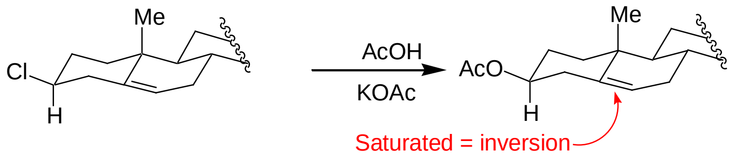
tetrahedral carbon in C^{13} NMR (68.8 ppm)

Phenonium ion
G. Olah *JACS* **1976**, *98*, 6784.

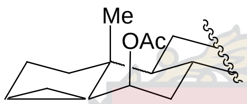
See Lowry & Richardson, pp 434-439 for discussion of this controversy

"Nonclassical" carbonium Ions

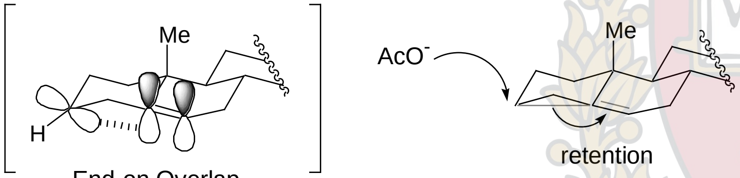
Introduction



- Solvolysis of 3-β-cholesteryl chloride with acetate ion proceeds with complete retention Additionally, the β-Cl solvolyzed at an enhanced rate vs. the α-Cl. Under certain conditions, the cholesteryl *i*-acetate is obtained.



cholesteryl *i*-acetate

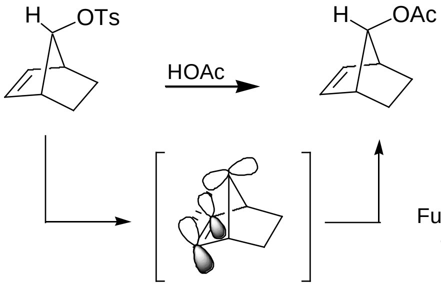


End-on Overlap

- These results have been attributed to an end-on overlap between the filled *p* orbital of the double bond and the vacant *p* orbital of the cation in a σ-type of interaction. This type of stabilization (a 3 center-2 electron bond) results in what are referred to as **"nonclassical carbonium ions"**.

C. Shoppee *J. Chem. Soc.* **1946**, 1147S. Winstein *J. Am. Chem. Soc.* **1954**, *76*, 18

The Norbornenyl Example

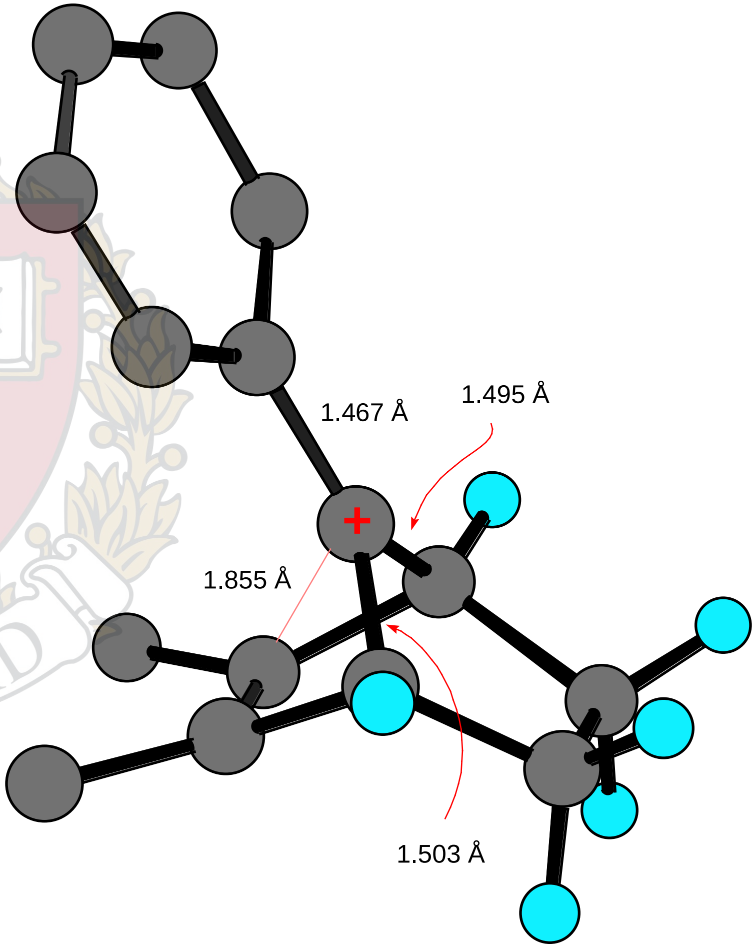


end-on overlap

Full retention & 10^{11} times faster hydrolysis than saturated system

- In the norbonenyl system, both *p* orbitals of the double bond can stabilize the vacant *p* orbital in an end-on orientation.

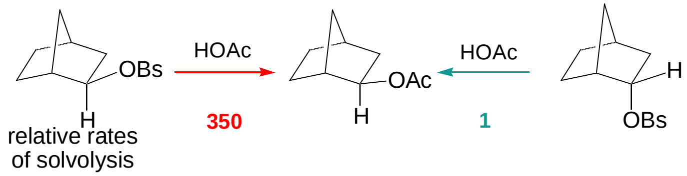
Physical Evidence of Nonclassical Carbonium Ion



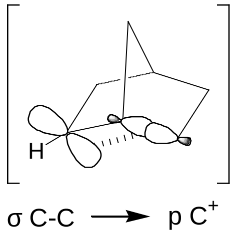
T. Laube, *JACS* **1989**, *111*, 9224

The 2-Norbornyl Cation

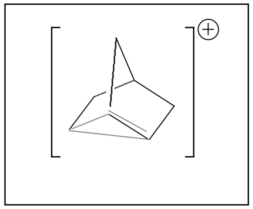
"An Innocent Bystander Looks at the 2-Norbornyl Cation"
Walling, C. *Acc. Chem. Res.* **1983**, *16*, 448.

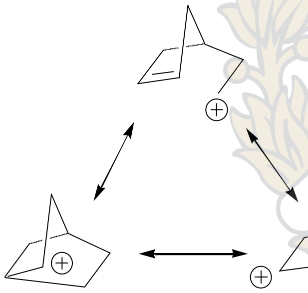


How do we explain the rate difference and stereochemical result?



Stabilization of the 2-norbornyl cation is provided by interaction with the C1-C6 bonding σ orbital in an end-on orientation



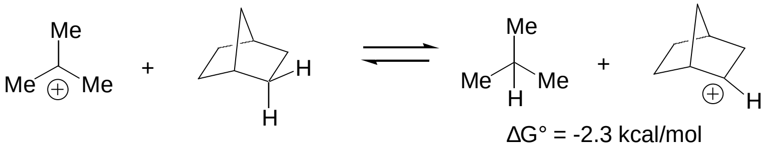


Resonance representation of norbornyl cation

Winstein: The delocalized structure is the lowest energy structure

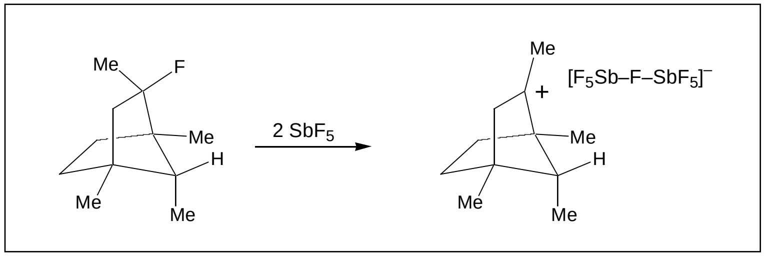
Brown: Delocalized structure is the transiltion state separating localized ions

Ion Equilibrium Experiments: Field & Soloman, *JACS* **1976**, *98*, 1567

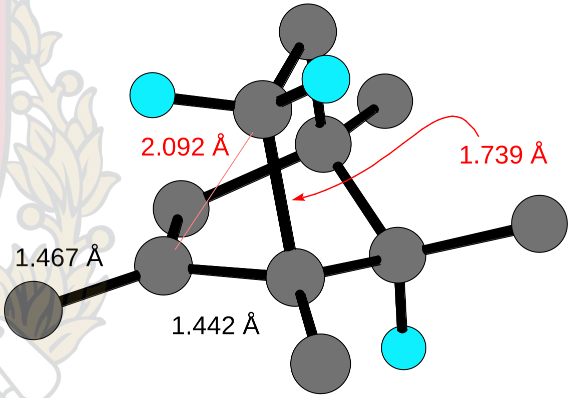


ΔG° = -2.3 kcal/mol

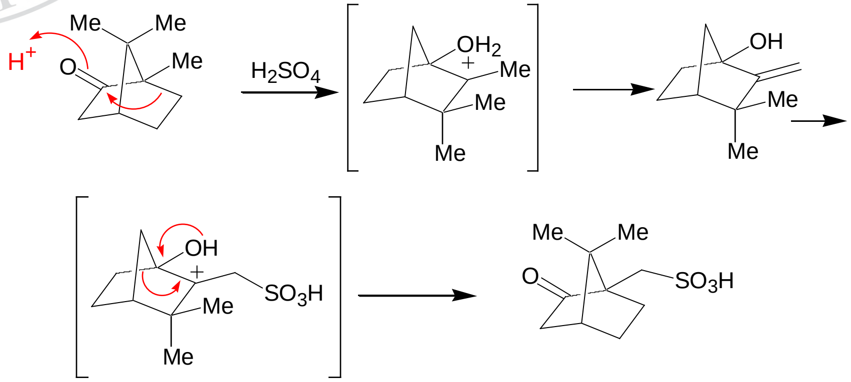
"Nonclassical" carbonium Ions: The Facts!



T. Laube, Angew. *Chem. Int. Ed.* **1987**, *26*, 560



Functionalization of Camphor

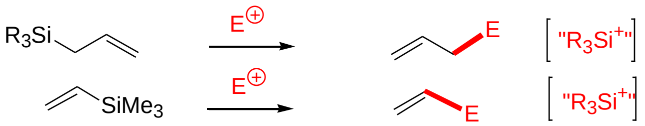


Allyl- & Vinylsilanes: The β-Silicon Effect

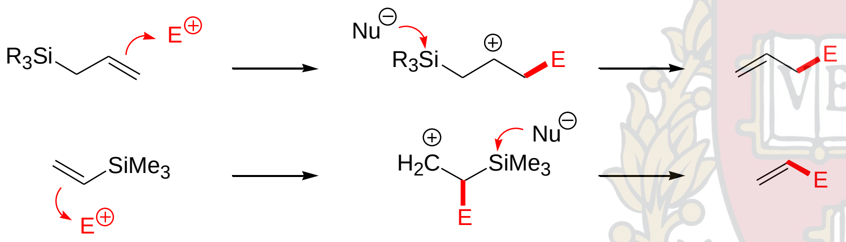
References: Lambert *Acc. Chem. Res.* **1999**, *32*, 183-190
Lambert, *JACS* **1990**, *112*, 8120; **1996**, *118*, 7867.
Fleming, *Organic Reactions* **1989**, *37*, 54.
Fleming, *Chem. Rev.*, **1997**, 2063.

Allyl– & Vinylsilanes react with electrophiles

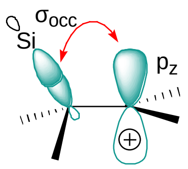
(trapped by solution Nu)



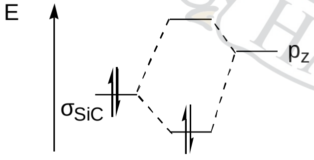
Mechanism - the simple picture: β-Silicon stabilizes carbocation



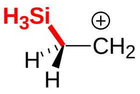
β-Silicon Effect: the origin of regioselectivity



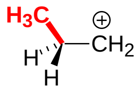
$\sigma_{Si–C}$ → p_z empty



A



versus

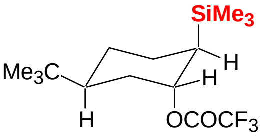


B

Calculation: A more stable than B by 38 kcal/mol.

Jorgensen *JACS* **1985**, *107*, 1496.

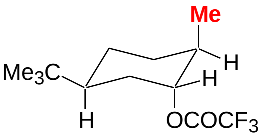
Magnitude of the β-Silicon Effect



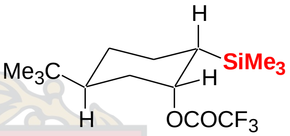
1

Solvolysis (CF_3CH_2OH)

$\frac{k_1}{k_2}$ = 2.4 x 10^{+12}



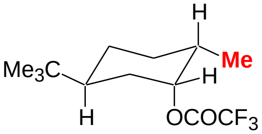
2



3

Solvolysis (CF_3CH_2OH)

$\frac{k_3}{k_4}$ = 4 x 10^{+4}

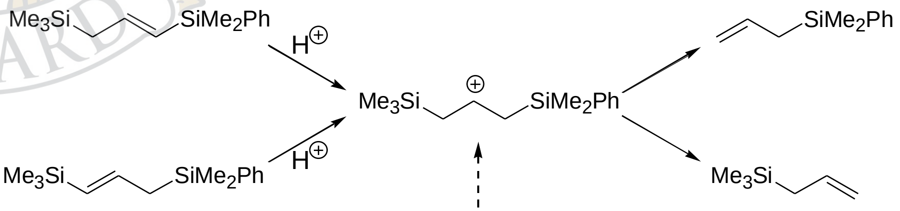


4

"These figures established the β-effect as one of the kinetically strongest in organic chemistry": J. Lambert

Data provide no distinction between open and bridged intermediates

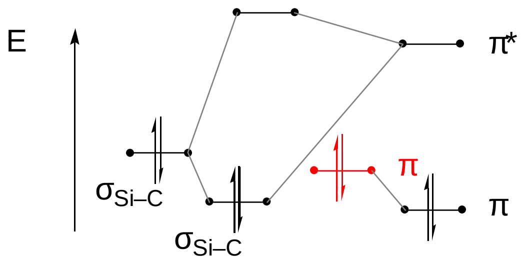
Proof for a stepwise mechanism provided the following protodesilylation experiment:



both silanes yield the same product mixture. Hence, the reaction proceeds most likely via a common intermediate, a carbeniumion

General: Allylsilanes are more nucleophilic than alkenes

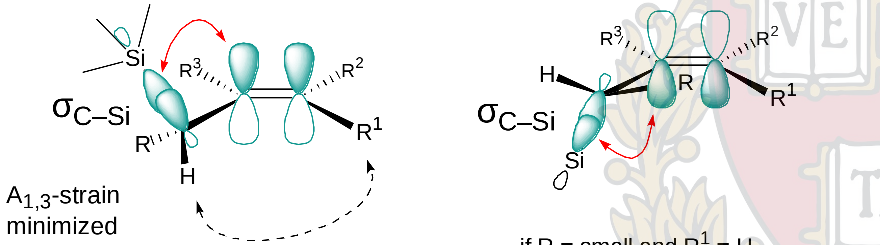
⇨ HOMO is higher in energy due to ***negative hyperconjugation***



$\pi\ (\pi^*) \longleftrightarrow \sigma_{C-Si}$

Houk, *JACS* **1982**, *104*, 7162.

Electrophile Addition - Stereoelectronics

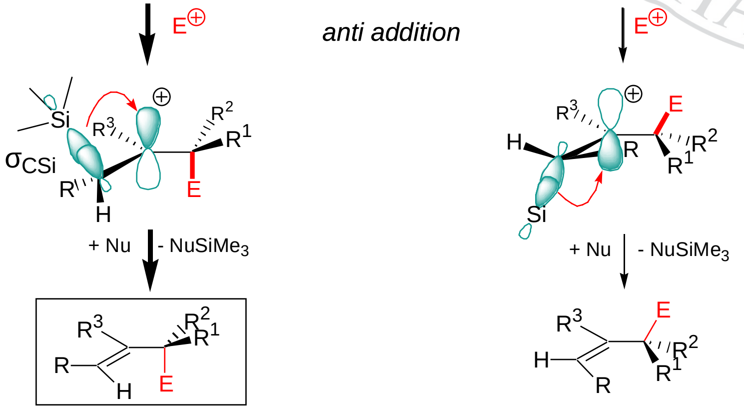


$A_{1,3}$-strain minimized

if R = medium size to large and/or $R^1 \neq H$ major product arises via this reactive conformation

if R = small and R^1 = H a reaction pathway via this reactive conformation could compete

anti addition



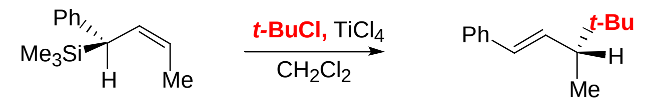
major (trans)

minor (cis)

The stereochemical consequences for the major product are:

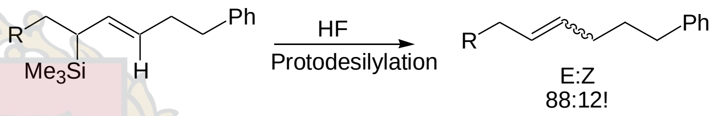
❒ trans-alkene:
❒ anti-addition of E^+ with respect to SiR_3

Examples:



JACS **1982**, *104*, 4962.

But



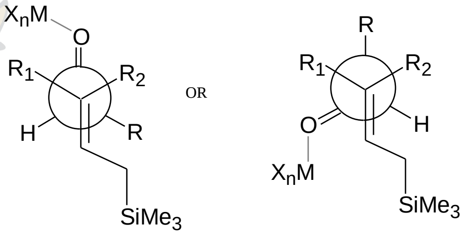
E:Z
88:12!

Eschenmoser, *Helv. Chim. Acta* **1979**, *62*, 1922.

Carbonyl Addition of Allylsilanes: Open Transition States

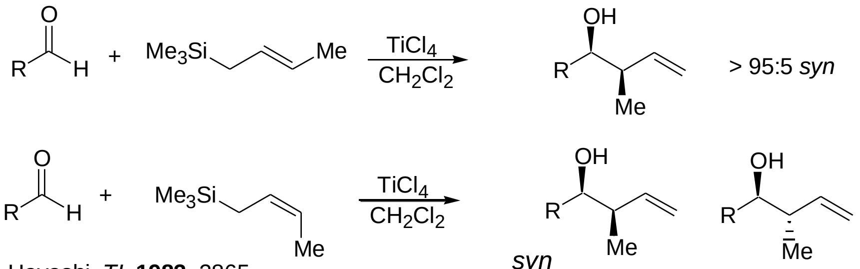
Me_3Si– is not sufficiently Lewis acidic to activate C=O through pre-association; however $(RO)_2MeSi$– is Lewis acidic enough to activate C=O through pre-association. These allylsilanes add to RCHO througl closed transition states

Antiperiplanar TS



Synclinal TS

Calculations by Houk et al. show that the relative energy differences between the antiperiplanar and and synclinal transition states are negligible. Both the antiperiplanar and synclinal models predict a ***syn*** selectivity for the newly formed stereogenic centers.



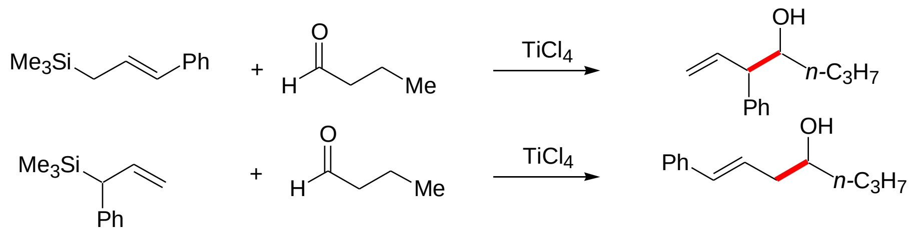
> 95:5 *syn*

Hayashi, *TL* **1983**, 2865.

syn

ca. 65 : 35

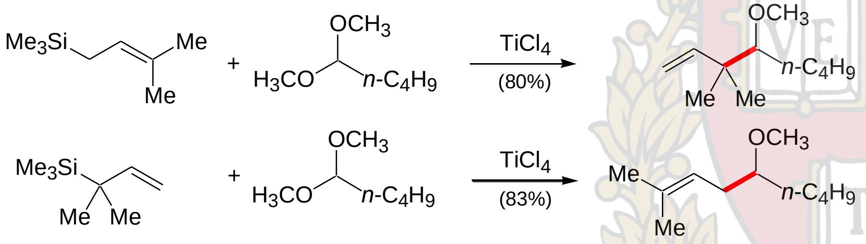
Allylsilanes add to aldehydes and acetals under Lewis acid promotion



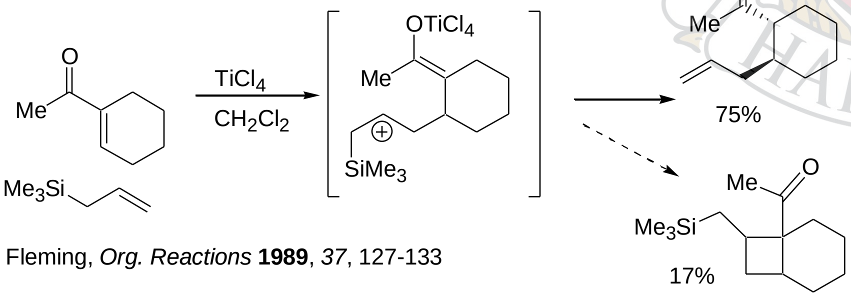
regioselectivity: Allyl inversion

Felkin Selectivity also holds with this class of nucleophiles

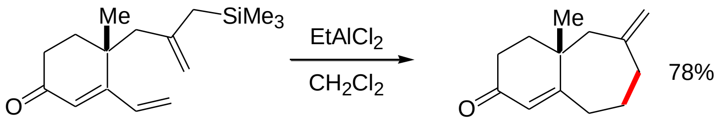
Acetals can be used as well



The Sakurai Reaction (Enone Conjugate Addition)



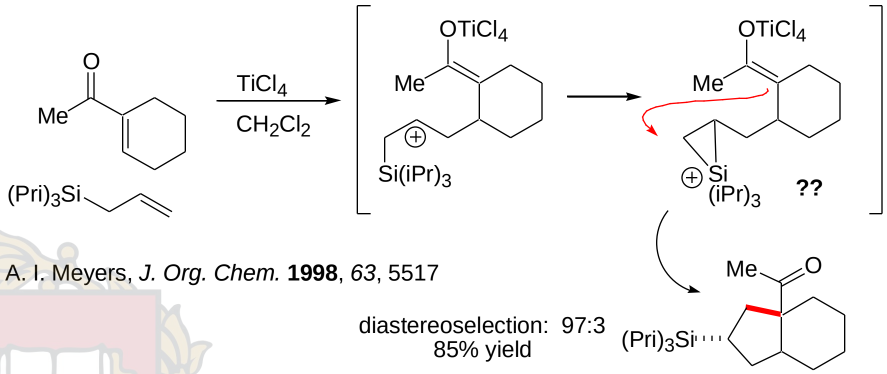
Fleming, *Org. Reactions* **1989**, *37*, 127-133



Majetich, *Tetrahedron* **1987**, *43*, 5621

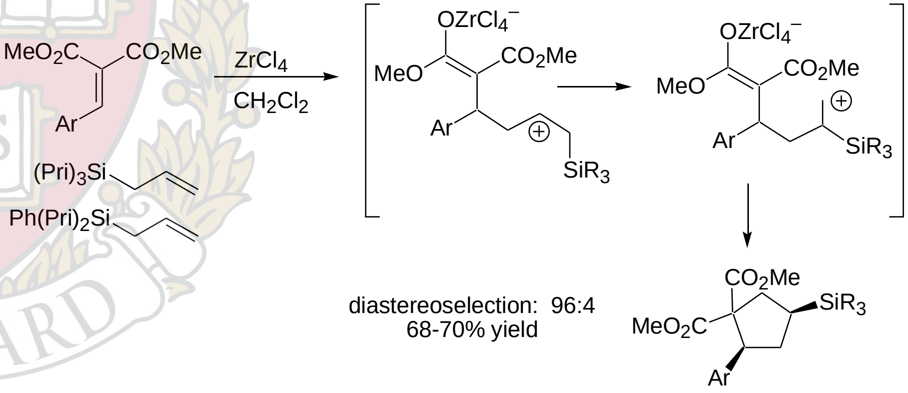
Reactions Proceedilng through Silicon-Migration

Si migration may be promoted by using hindered Si substituents



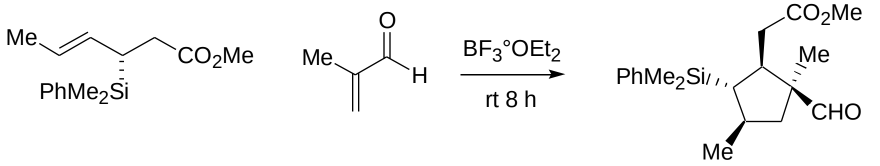
A. I. Meyers, *J. Org. Chem.* **1998**, *63*, 5517

diastereoselection: 97:3
85% yield



diastereoselection: 96:4
68-70% yield

Can you work out the mechanism??



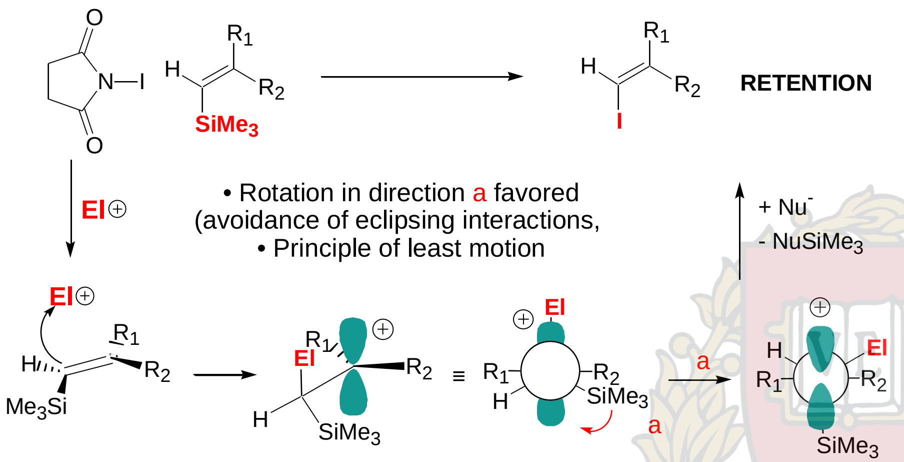
diastereoselection: >30:1
93% yield

Panek, *J. Org. Chem.* **1993**, *58*, 2345

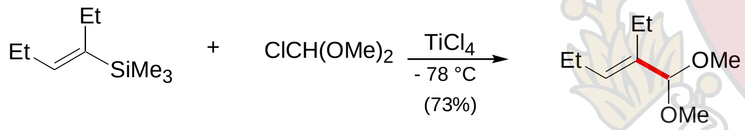
Stereochemistry of Electrophile Addition to Vinylsilanes

Vinyl/Allylsilanes in Organic Synthesis - Selected Examples

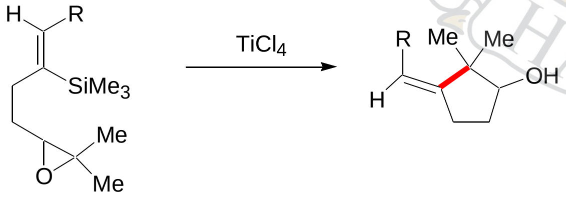
Fleming, *Org. Reactions* **1989**, *37*, 54.



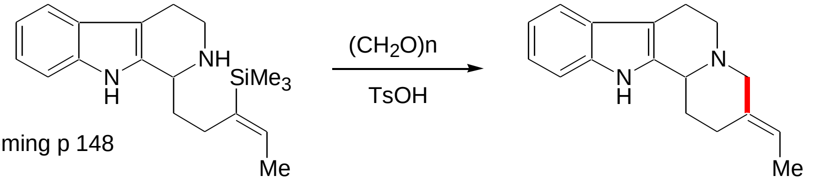
- Rotation in direction a favored
(avoidance of eclipsing interactions,
- Principle of least motion



Fleming p 289

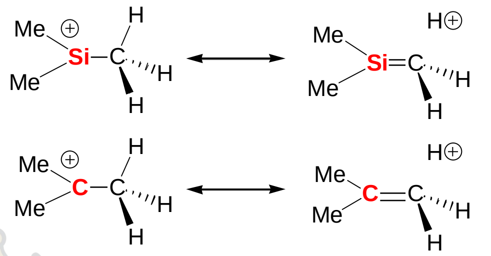


Fleming p 148



Summary Statements

1. Me_3C+ is more stable than Me_3Si+ in spite of the fact that Si is less electronegative than C.



C–Si bond length: 1.87 Å

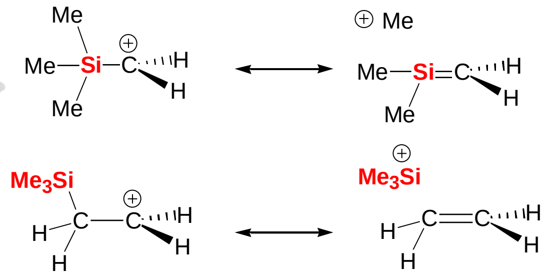
C–C bond length: 1.54 Å

C–Si hyperconjugation is less pronounced than the anaologous C–C hyperconjugation do to the impact of the longer C–Si bond lengths.

2. Carbonium ions α to Si are less stabilized than carbonium ions β to Si.

C(+) α to silicon

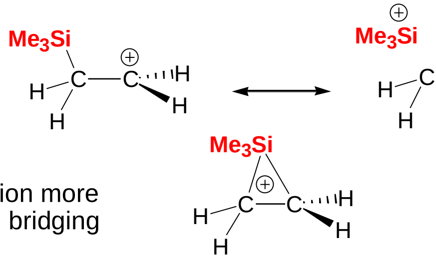
C(+) β to silicon



C–Si hyperconjugation is less pronounced than the anaologous C–C hyperconjugation do to the impact of the longer C–Si bond lengths.

3. According to Lambert, silicon has a propensity to stabilize β carbonium ion via hyperconjugation (vertical stabilization) rather than bridging (nonvertical stabilization.

C(+) β to silicon

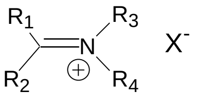


hyperconjugation more important than bridging

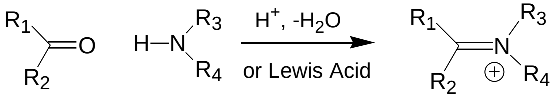
4. Silicon has a lower propensity to undergo Wagner-Meerwein like rearrangements than carbon.

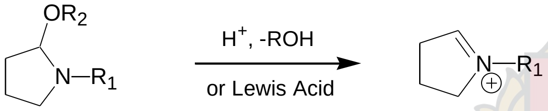
Stabilized Cations: Iminium-Ions 1

Iminium Ions

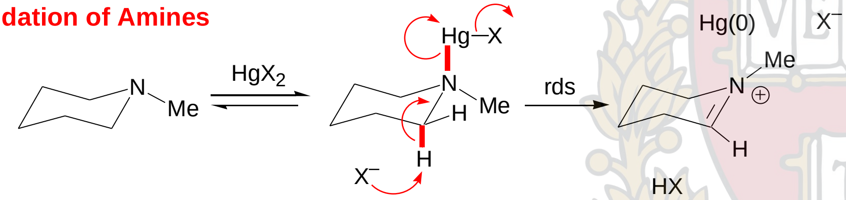


Common Methods of Generation:

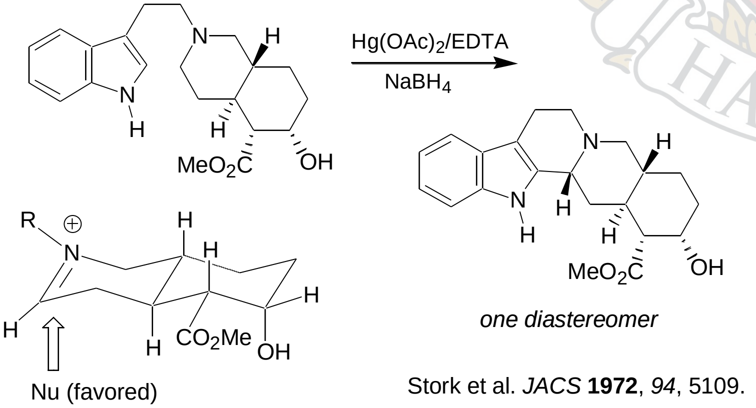




Oxidation of Amines

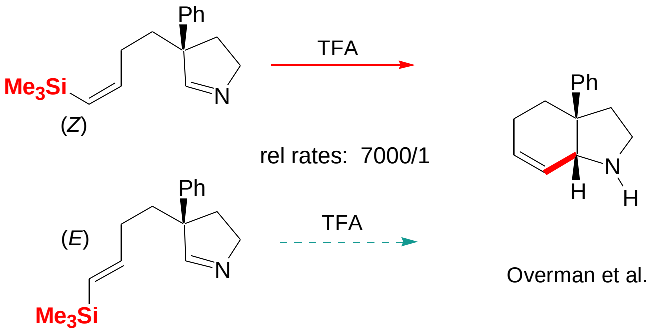


Stereoelectronic Effects on Nu Addition to Iminium Ions

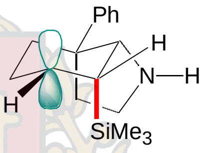


Stork et al. *JACS* **1972**, *94*, 5109.

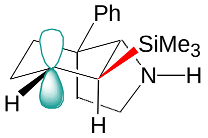
C=N Stereoelectronic Effects: Lecture 19



Overman et al. *TL* **1984**, *25*, 5739.

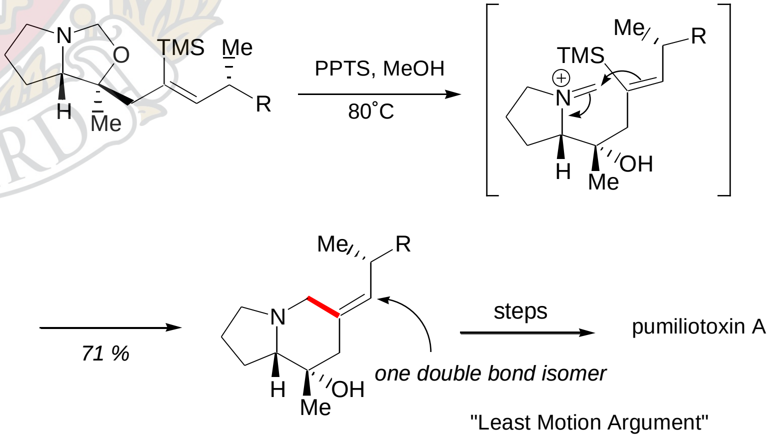


(Z) vinylsilane)



(*E) vinylsilane*)

Only in the case of the (Z) vinylsilane is the emerging p orbital coplanar with C-Si bond. Full stabilization of the empty orbital cannot occur with the (E) vinylsilane.....hence the rate difference.



Overman et al. *JOC* **1989**, *54*, 2591.

For additional related transformations see Aza-Cope Handout , Lecture 11

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 32

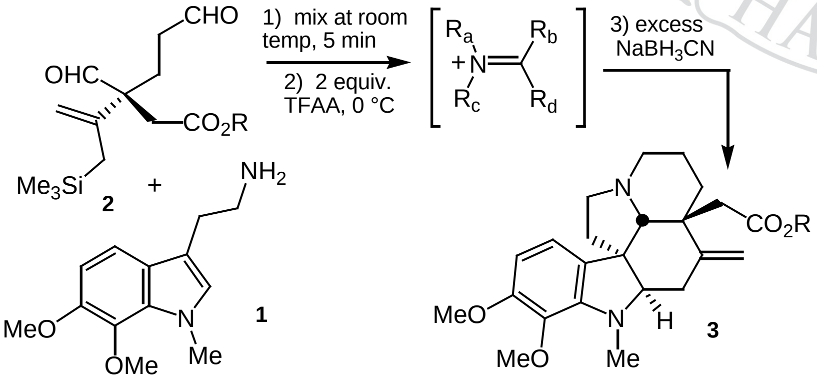
Introduction to Carbonium Ions–3

- Stabilized Carbocations: Iminium Ions ($C{=}NR_2(+)$)
- Stabilized Carbocations: Oxo–Carbenium Ions ($C{=}OR(+)$)
- Stabilized Carbocations: Addition & Rearrangements

Reading Assignment for this Lecture:

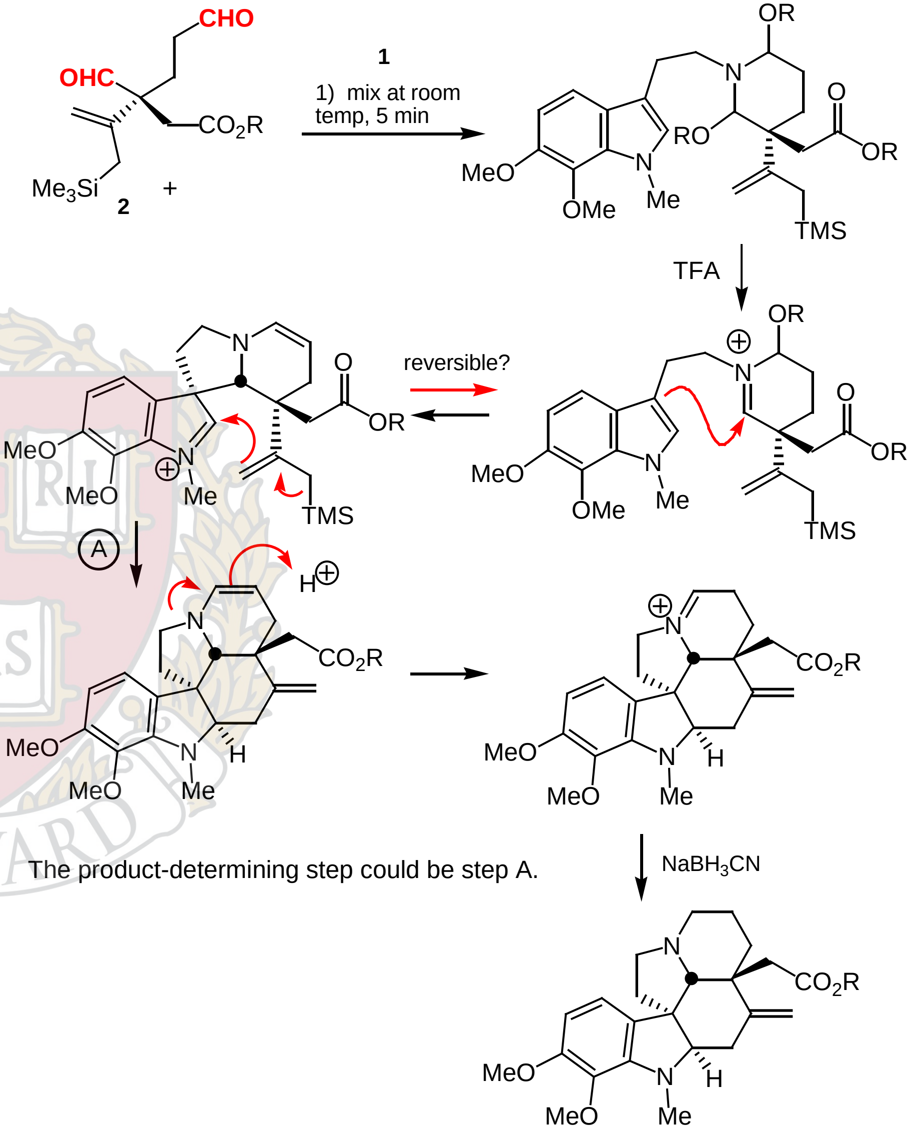
Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed.
Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

Question 13. Final Exam, 1999. During Corey's recent synthesis of Aspidophytine (*JACS*, **1999**, *121*, 6771), the pivotal intermediate **3** was assembled by the union of **1** and **2** under the specified conditions. Provide a mechanism for this single-pot transformation.



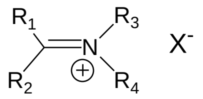
Matthew D. Shair

Monday,
December 9 , 2002

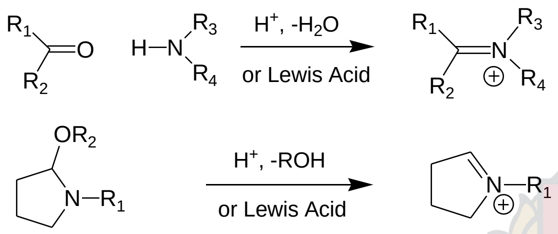


The product-determining step could be step A.

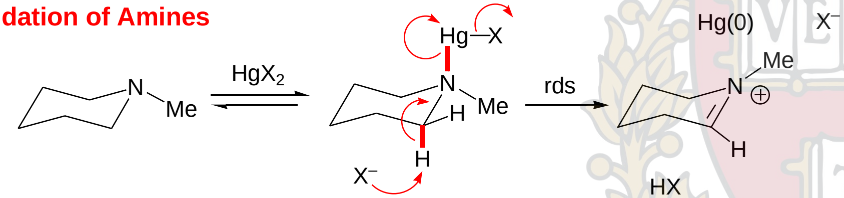
Iminium Ions



Common Methods of Generation:

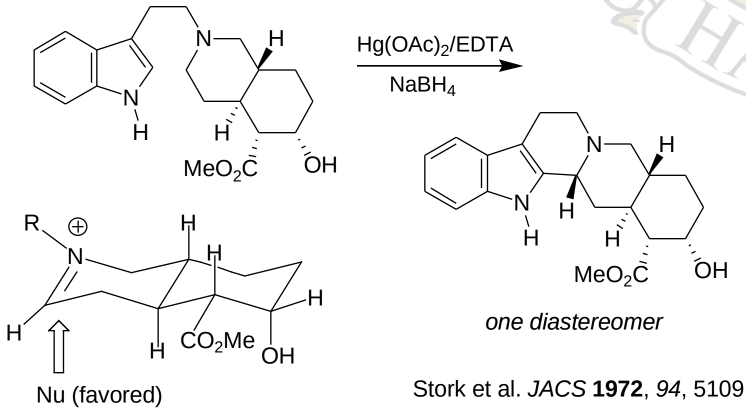


Oxidation of Amines



Related to Polonovski & Pummerer Reactions: Lecture 27

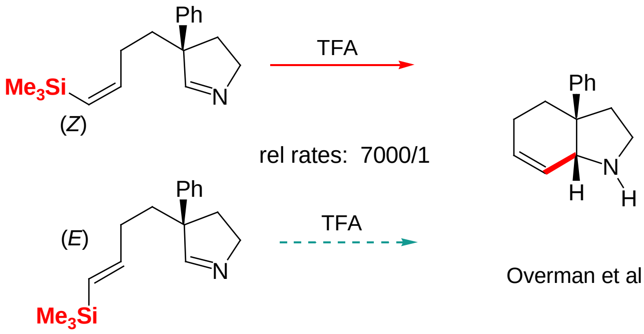
Stereoelectronic Effects on Nu Addition to Iminium Ions



one diastereomer

Stork et al. *JACS* **1972**, *94*, 5109.

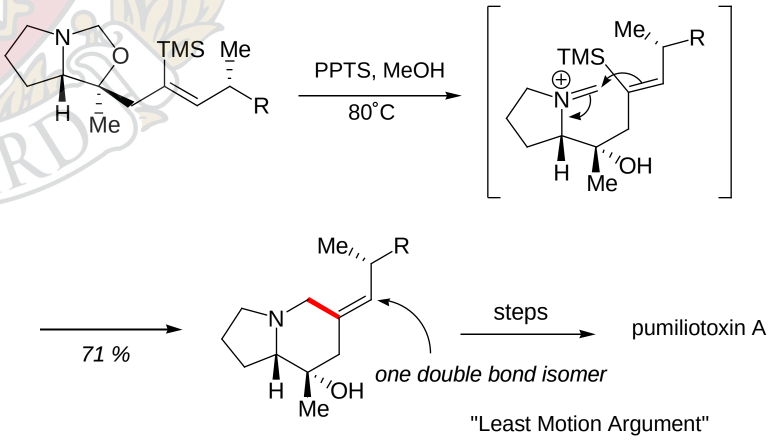
C=N Stereoelectronic Effects: Lecture 19



Overman et al. *TL* **1984**, *25*, 5739.

(*Z*) *vinylsilane*) (*E*) *vinylsilane*)

Only in the case of the (Z) vinylsilane is the emerging p orbital coplanar with C-Si bond. Full stabilization of the empty orbital cannot occur with the (E) vinylsilane.....hence the rate difference.



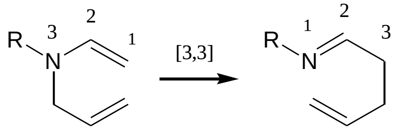
Overman et al. *JOC* **1989**, *54*, 2591.

Review:

Heimgartner, H. In "Iminium Salts in Organic Chemistry"; Bohme, H., Viehe, H., Eds.; Wiley: New York, 1979; Part 2, pp 655-732.

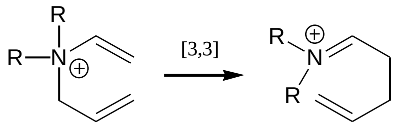
The 3-aza-Cope Rearrangement:

Neutral Variant:



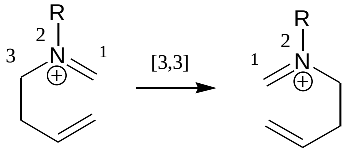
Exothermic as written by ~7-10kcal/mole.

Ammonium Variant:



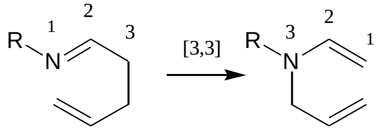
Even more exothermic than the neutral version, since enamine lacks resonance and iminium salt has stronger p-Bond than imine does.

2-aza-Cope Rearrangement:



In the simplest case, degenerate. Steric effects, conjugation, or selective trapping of a particular isomer, will drive equilibrium. As with the 3-aza-Cope, the cationic version proceeds under much milder conditions.

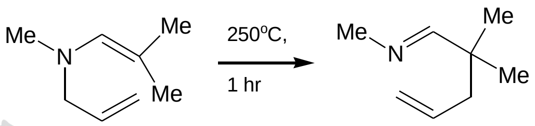
1-aza-Cope Rearrangement:



The 3-aza-Cope rearrangement can be driven in reverse by judicious choice of substrates(i.e., incorporating the imine into a strained ring or by making R an acyl group).

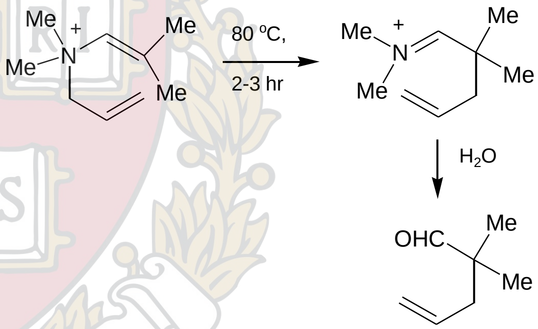
The 3-aza-Cope Rearrangement

First Neutral Case: Hill TL **1967**, 1421.



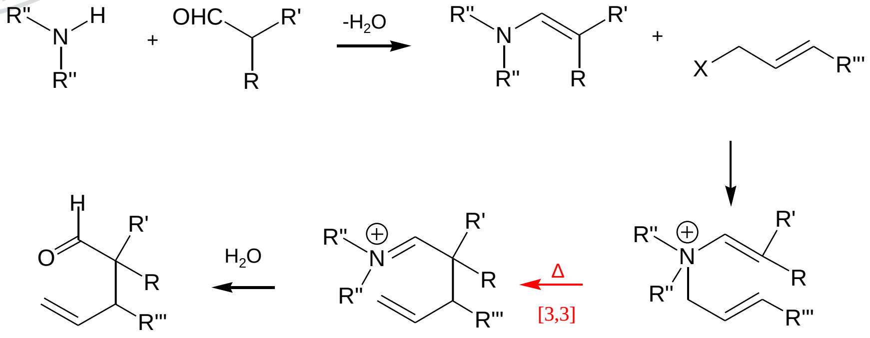
"Practically quantitative", no real yields given.

First Cationic Case: Elkik *Compt. Rend.* **1968**, *267*, 623.



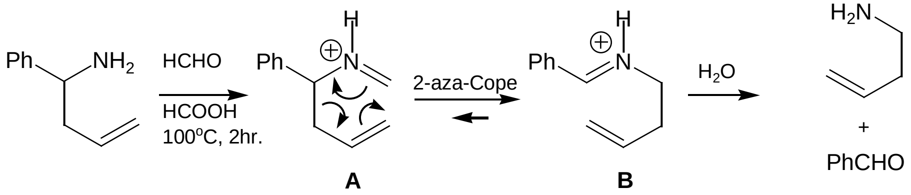
No yields given.

Good way to allylate aldehydes: Opitz *Angew. Chem.* **1960**, *72*, 169.



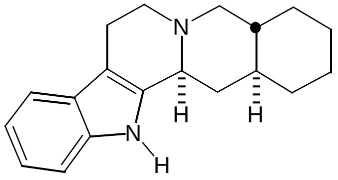
The 2-aza-Cope Rearrangement

First Reported Case: Horowitz JACS 1950, *72*, 1518.

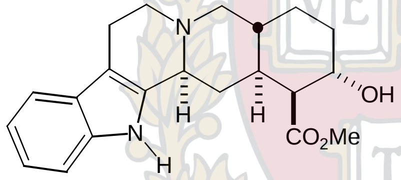


Equilibrium between **A** and **B** driven towards **B** by conjugation of iminium double bond to the aromatic ring in **B**.

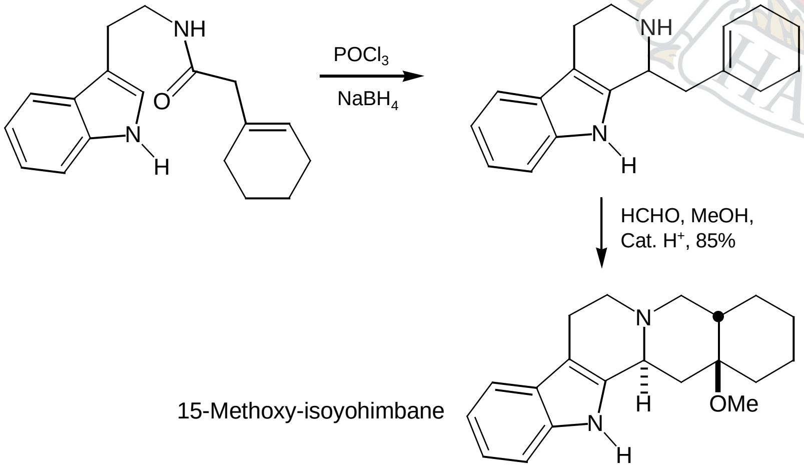
Application to Yohimbine Analog Synthesis: Winterfeldt *Chem. ber.* **1968**, *101*, 2938.



Yohimbane

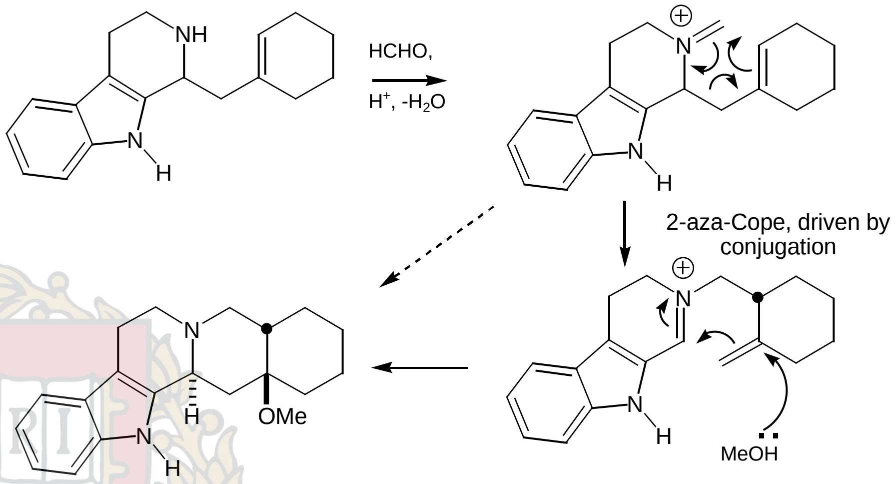


Yohimbine



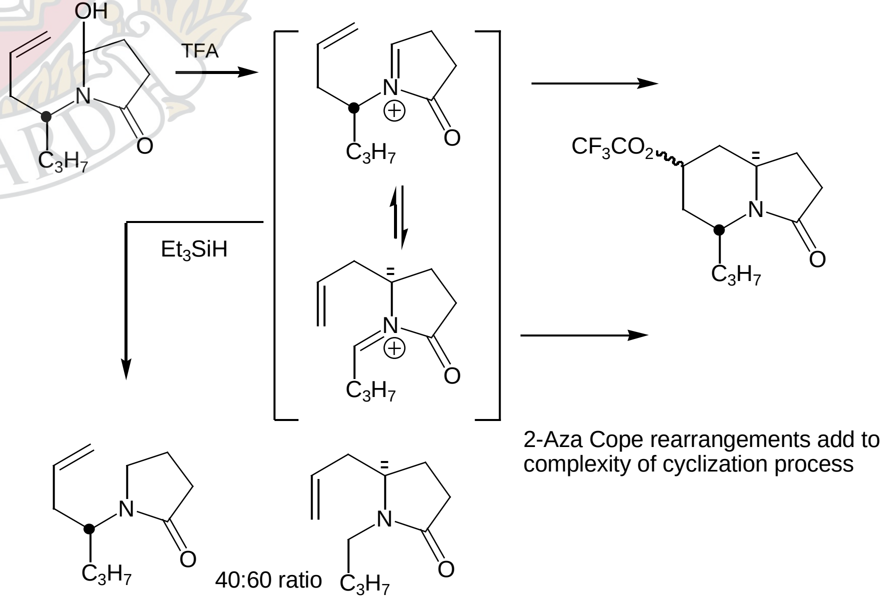
15-Methoxy-isoyohimbane

Mechanism for Yohimbane Analog Formation:



*N-Acyliminium Ion Rearrangements: Hart JOC **1985**, 50, 235.*

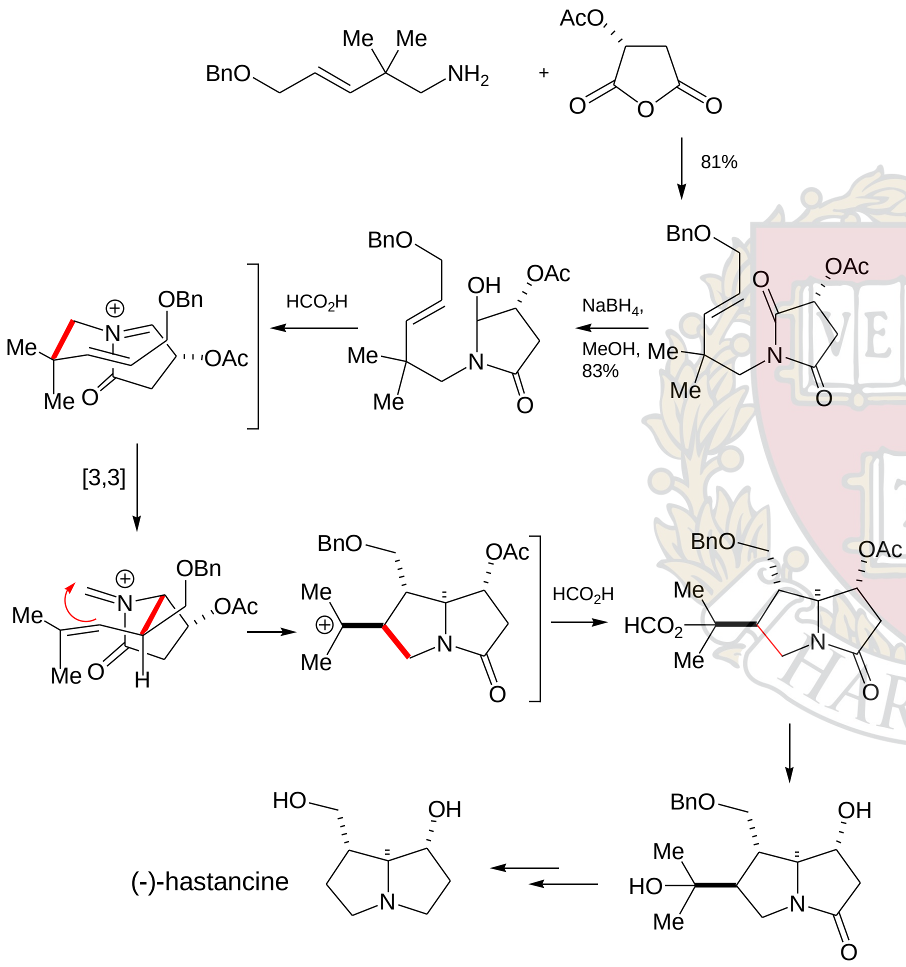
Hart observed an unusual product while trapping the intermediates of N-acyliminium olefin cyclizations.

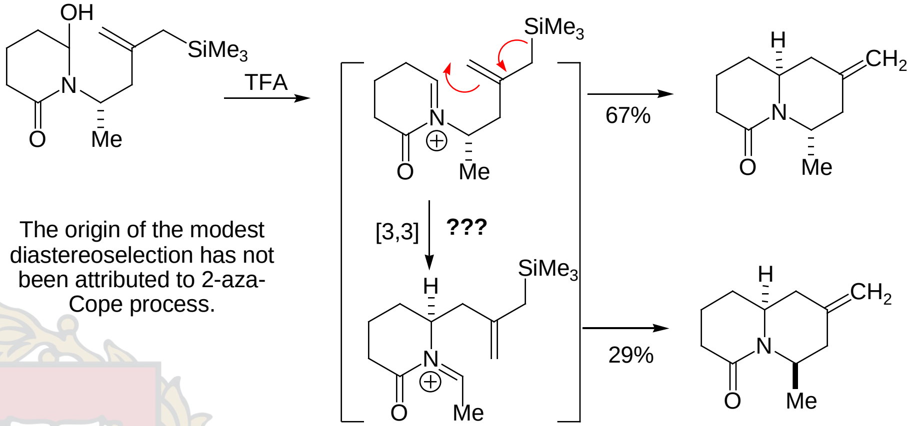


2-Aza Cope rearrangements add to complexity of cyclization process

N-Acyliminium Ion Rearrangements

*Synthesis of (-)-hastanecine: Hart JOC **1985**, 50, 235.*

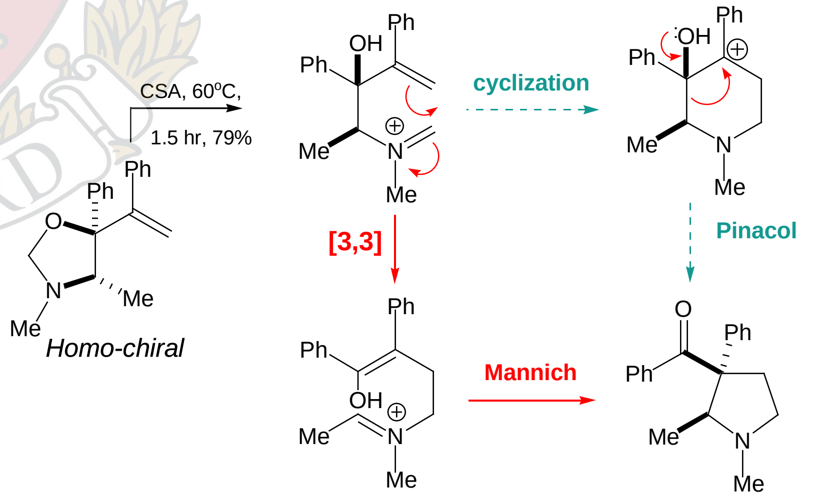




The origin of the modest diastereoselection has not been attributed to 2-aza-Cope process.

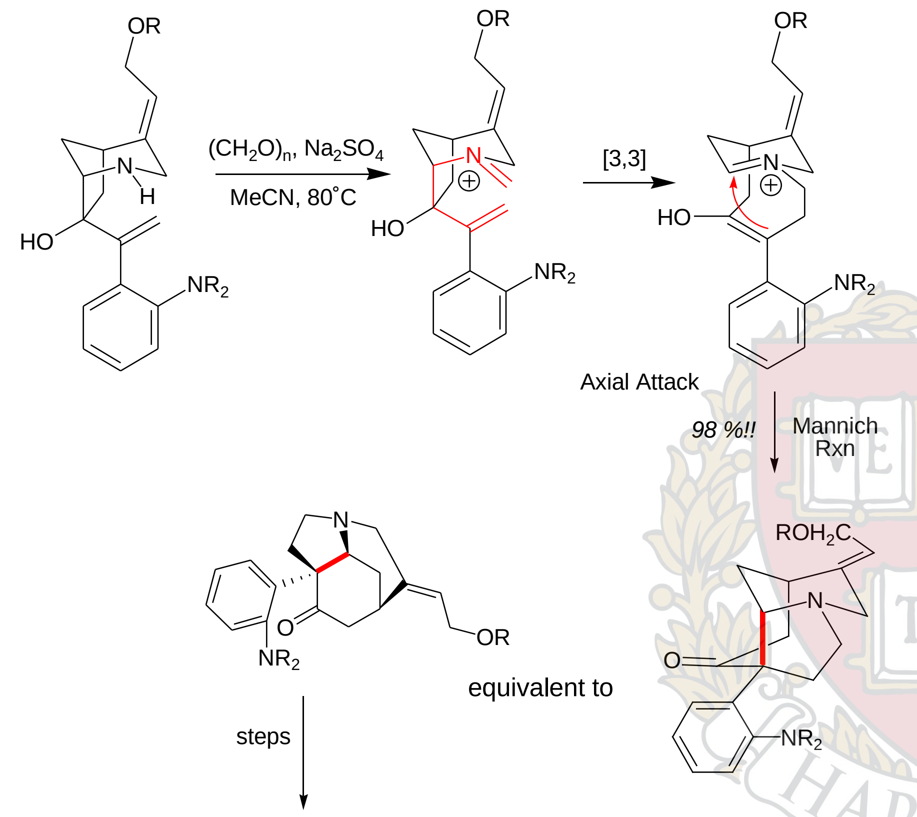
Gelas-Mailhe, *Tet. Lett*, **1992**, *33*, 73

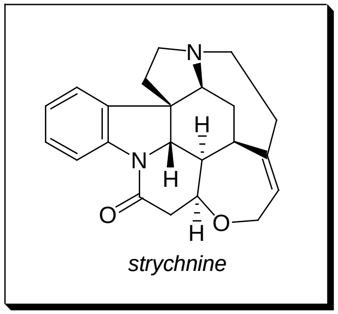
Competing 2-Aza-Cope and Pinacol Rearrangements: Which Dominates??



Conclusion: 2-aza-Cope rearrangements afford a low-barrier to competing processes

2-Aza-Cope-Mannich sequence:

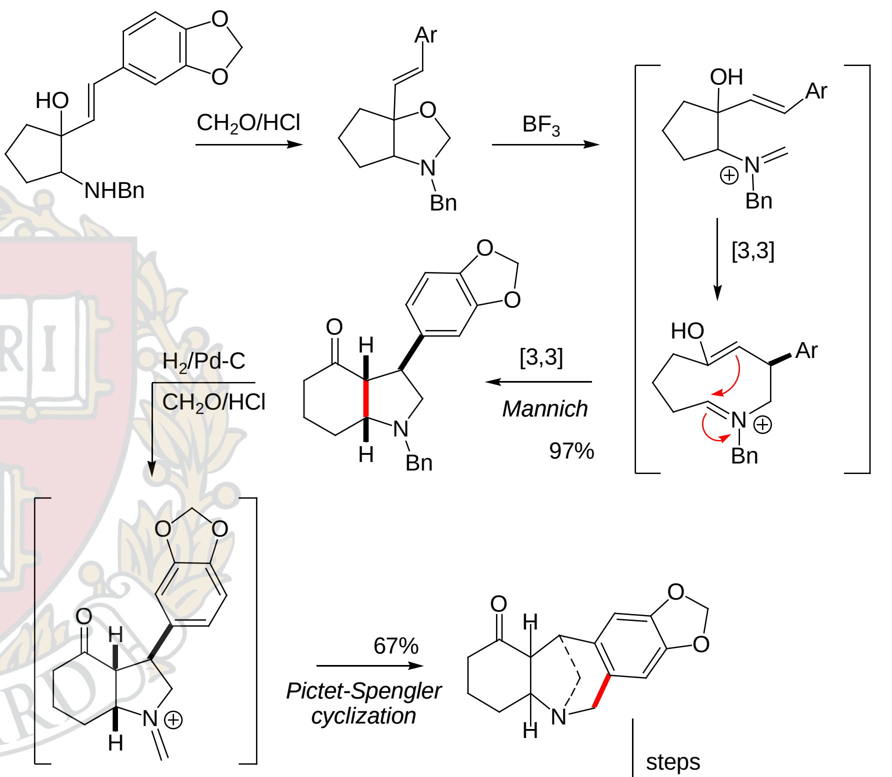


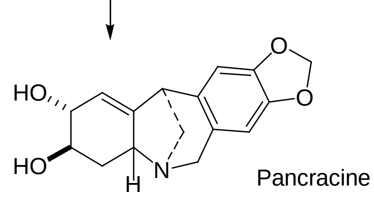


strychnine

Overman et al. *JACS* **1995**, *117*, 5776.

Another aza-Cope-Mannich sequence:





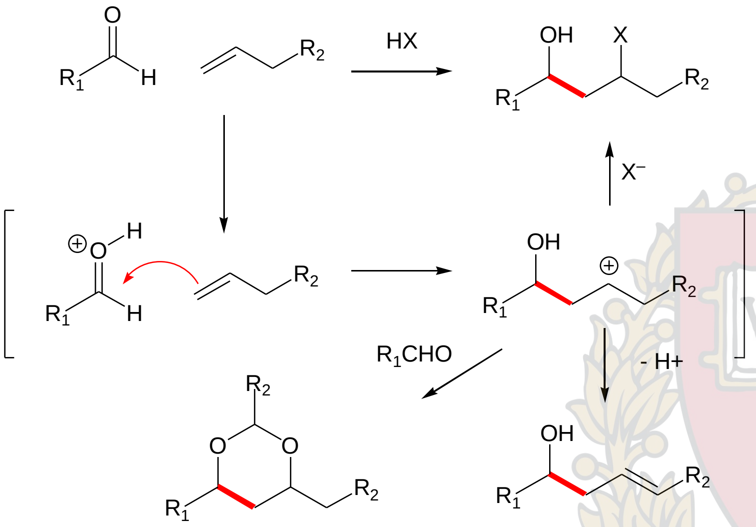
Pancracine

Overman et al. *JOC* **1991**, *56*, 5005

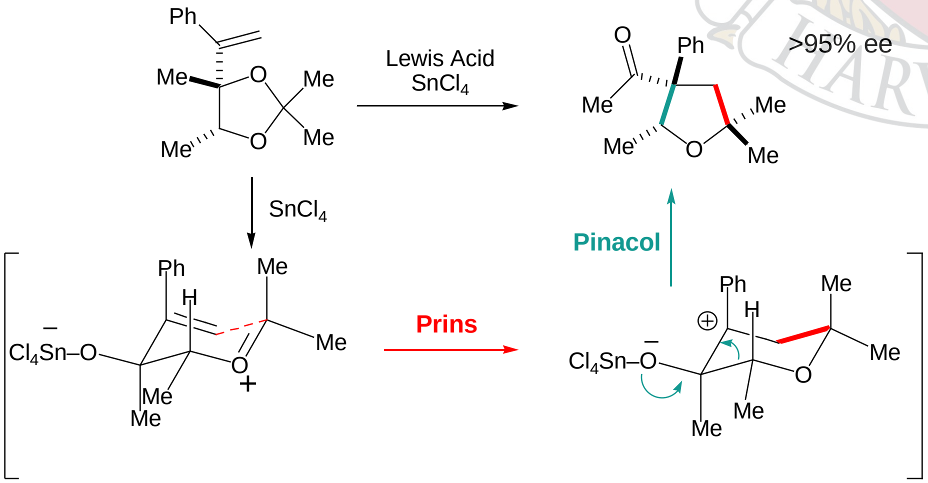
References

Prins reaction: Adams, D.R.; Bhaynagar, S. D. *Synthesis* **1977**, 661
Prins & carbonyl ene reactions: Snider, *Comprehensive Organic Synthesis*, **1991**, *Vol. 2*

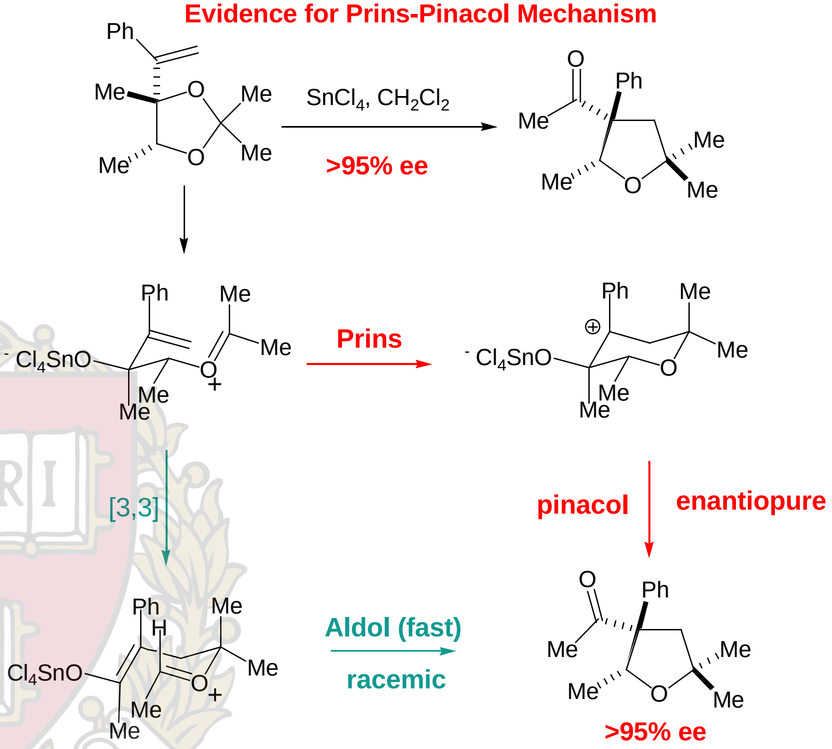
The Prins Process:



The Prins-Pinacol Variant:

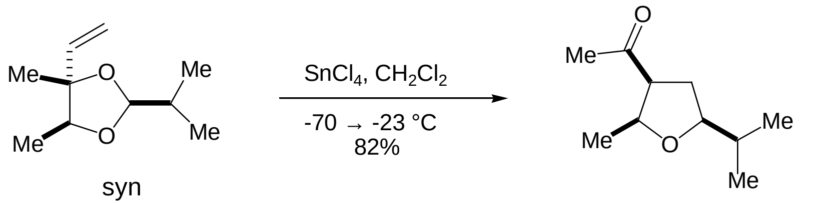


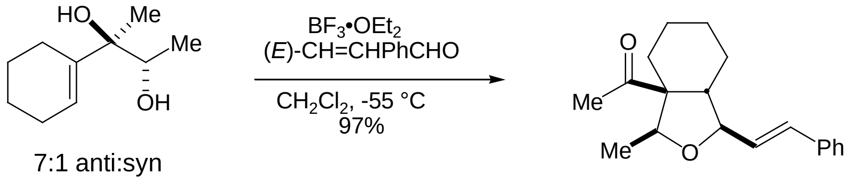
Evidence for Prins-Pinacol Mechanism



If a [3,3] rearrangement were intervening, the product would be racemic.
Overman, *JACS* **2000**, *122*, 8672
Overman, *Org Lett* **2001**, *3*, 1225

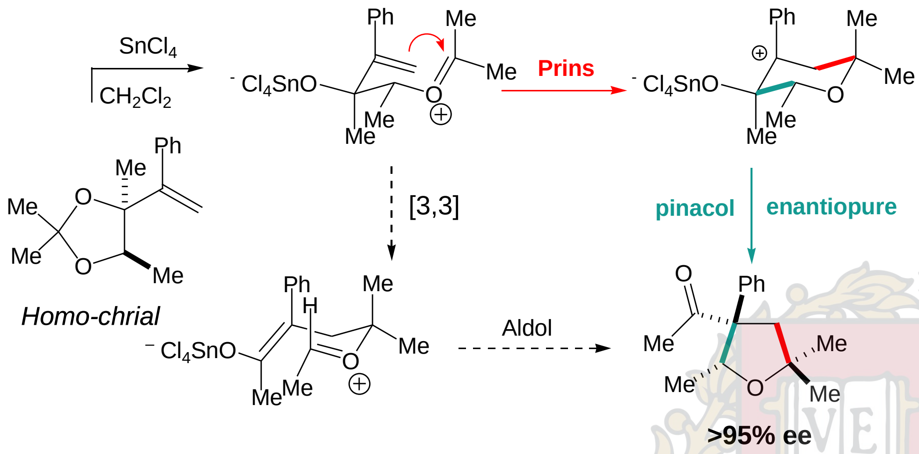
Examples of Stereoselective THF Formation





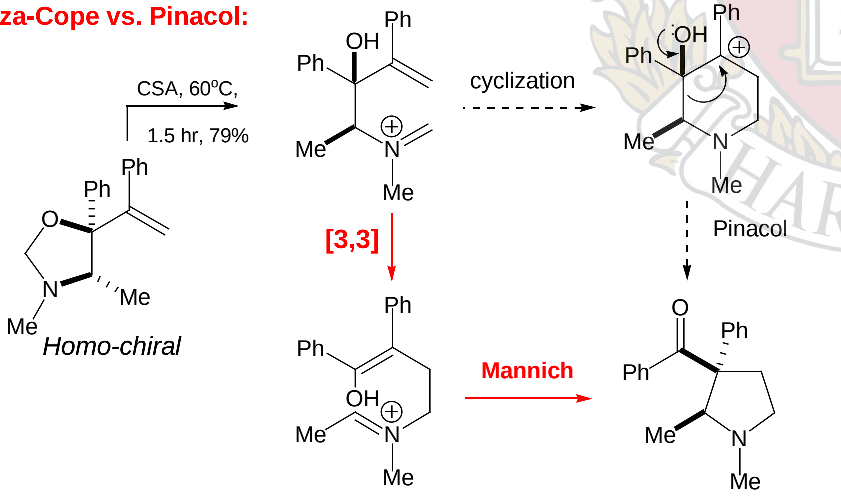
The Prins-Pinacol Reaction

Prins-Pinacol Mechanism



Prins cyclization faster than [3,3] rearrngement

2-aza-Cope vs. Pinacol:



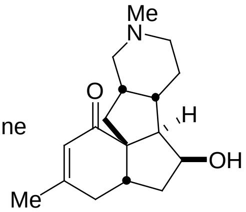
racemic product

[3,3] rearrngement faster than Mannich cyclization

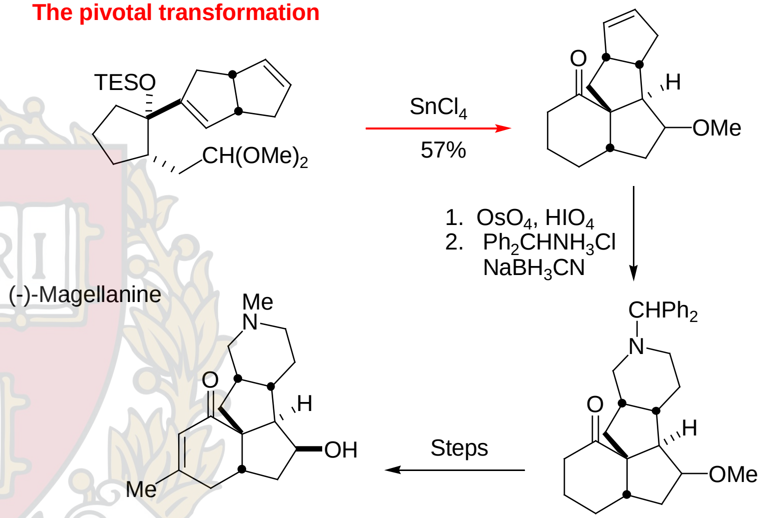
Overman: Magellanine Synthesis

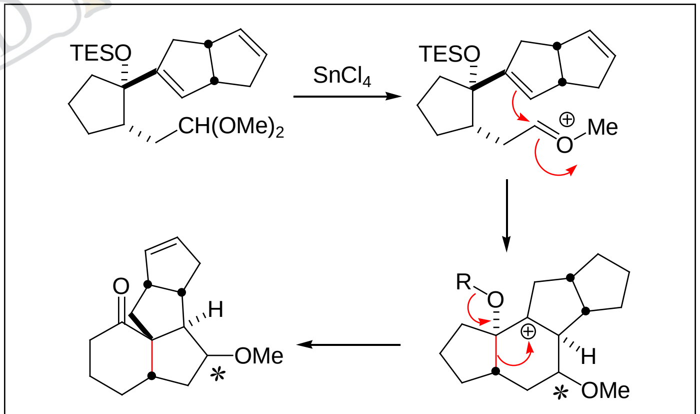
JACS, **1993**, *115*, 2992

(-)-Magellanine



The pivotal transformation



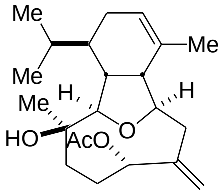


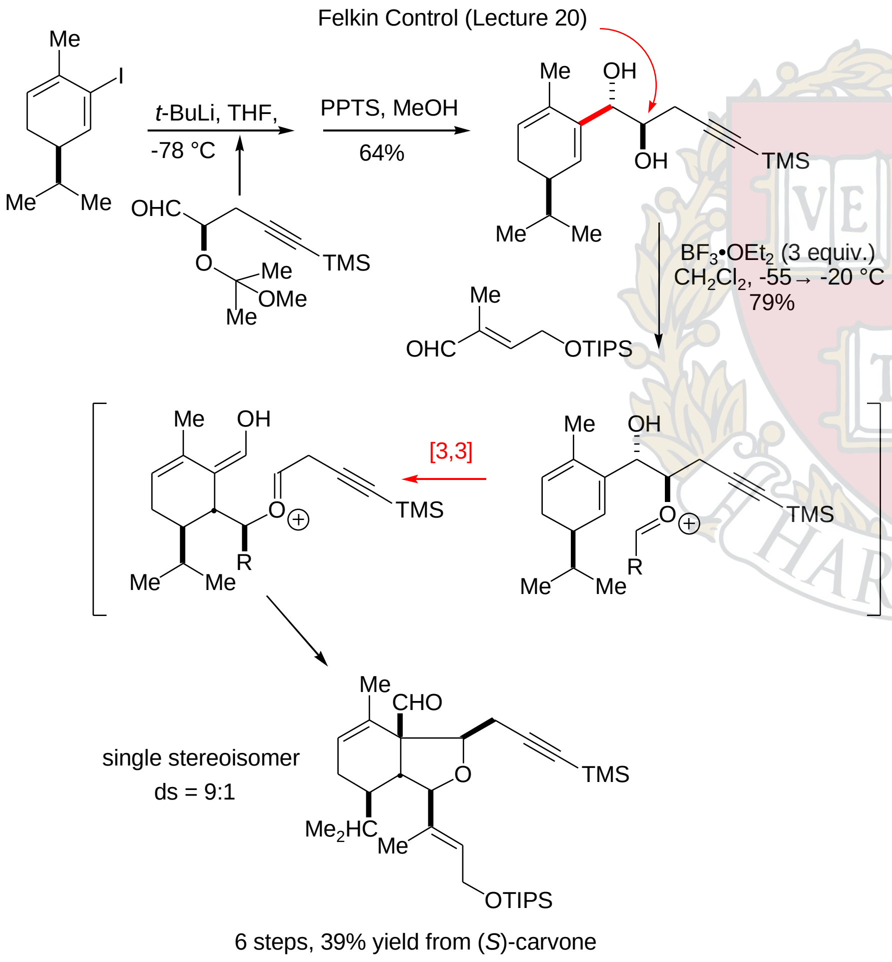
* mixture of diastereomers

Overman Synthesis of a Eunicellin Diterpene

Overman & MacMillan JACS, **1995**, *117,* 10391

(-)-7-Deacetoxy-alcyoninacetate



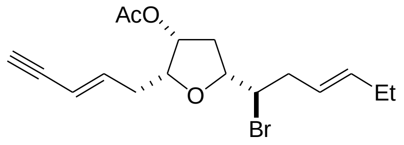


single stereoisomer
ds = 9:1

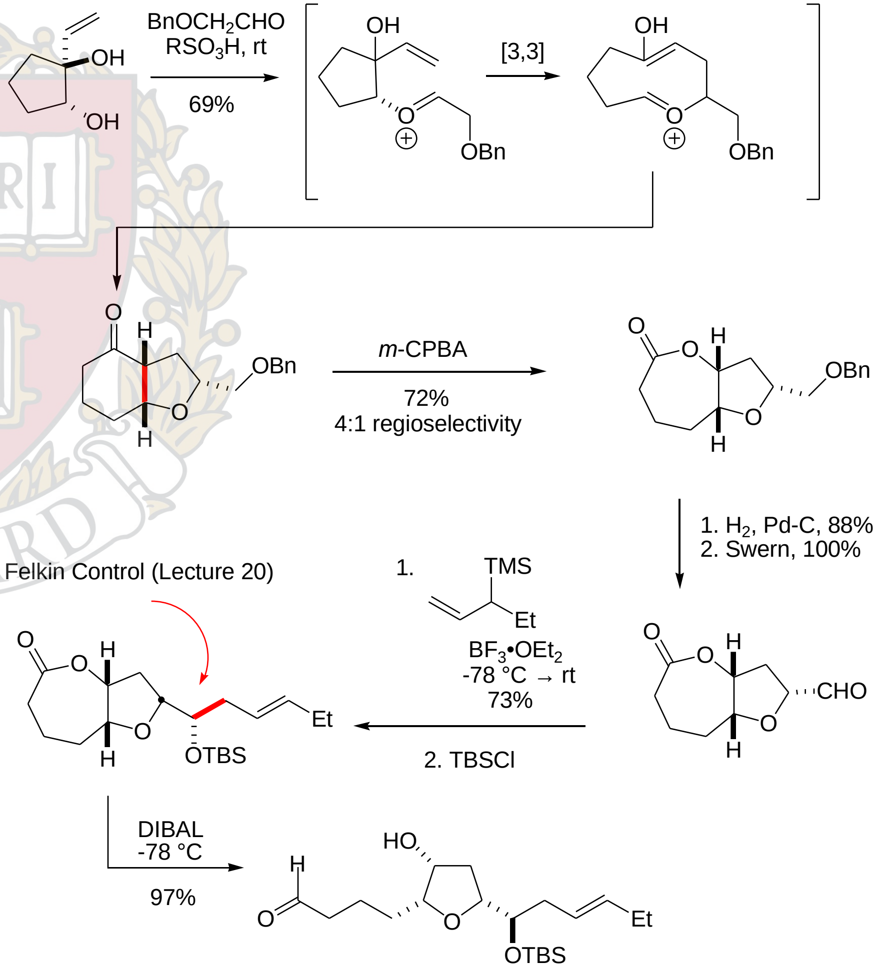
6 steps, 39% yield from (*S*)-carvone

Overman: Synthesis of *trans*-Kumausyne

JACS, **1991**, *113,* 5378



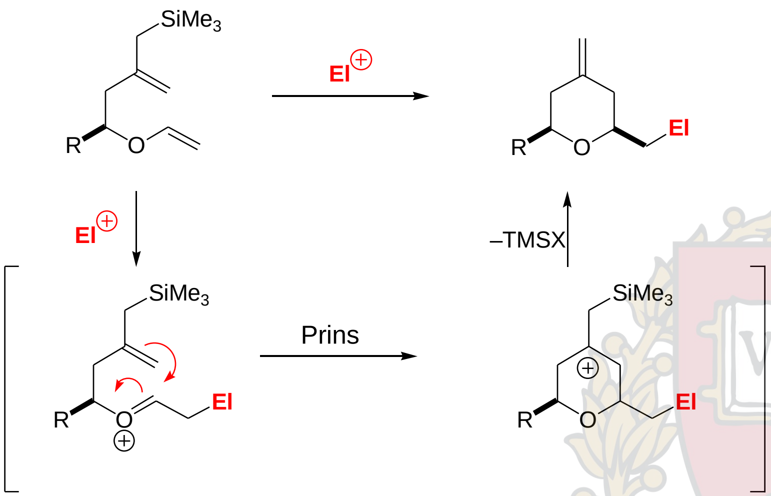
trans-Kumausyne



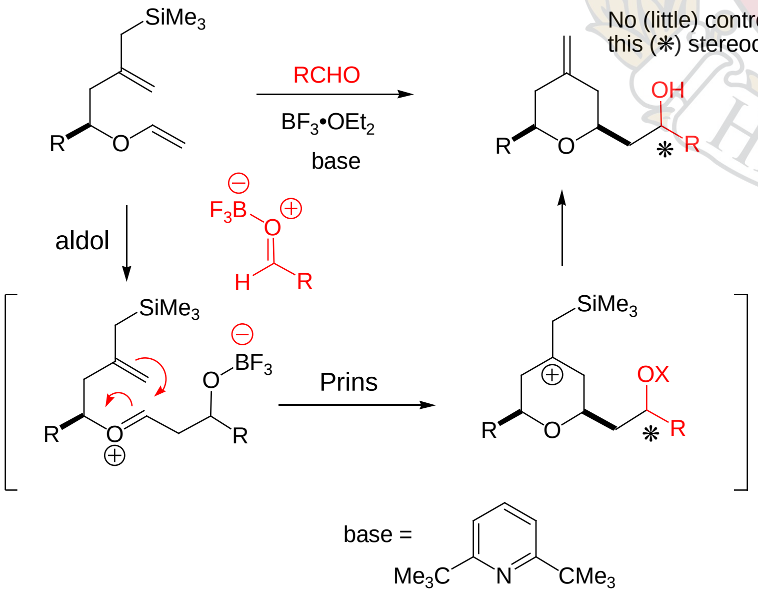
Mukaiyama Aldol–Prins Cascade

Rychnovsky JACS, **2001**, *123,* 8420

The Basic Process

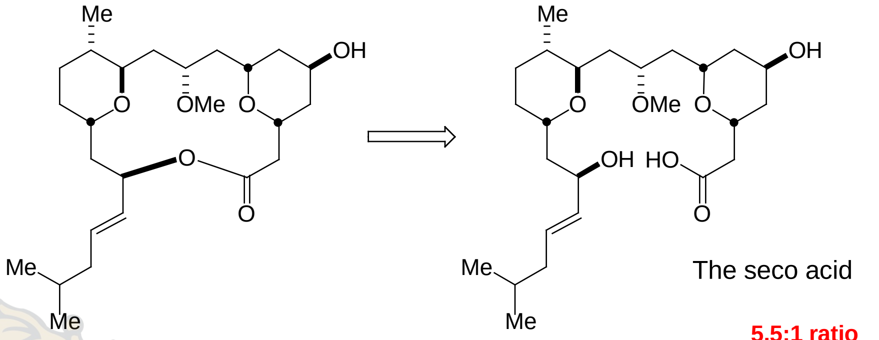


Let El(+) = Lewis acid activated RCHO



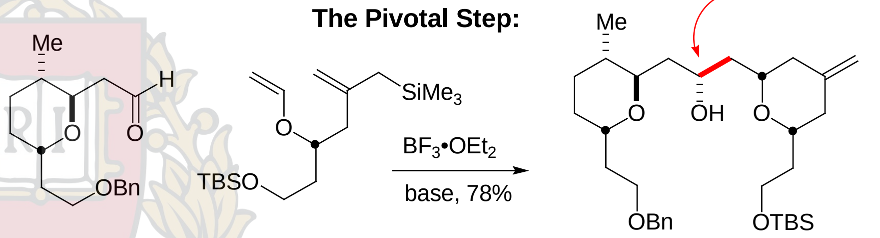
No (little) control over this (✱) stereocenter

Application to Leucasandrolide

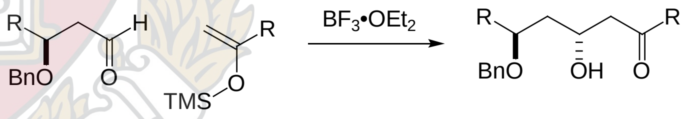


The seco acid

The Pivotal Step:



Control of hydroxyl center: see Lecture 20

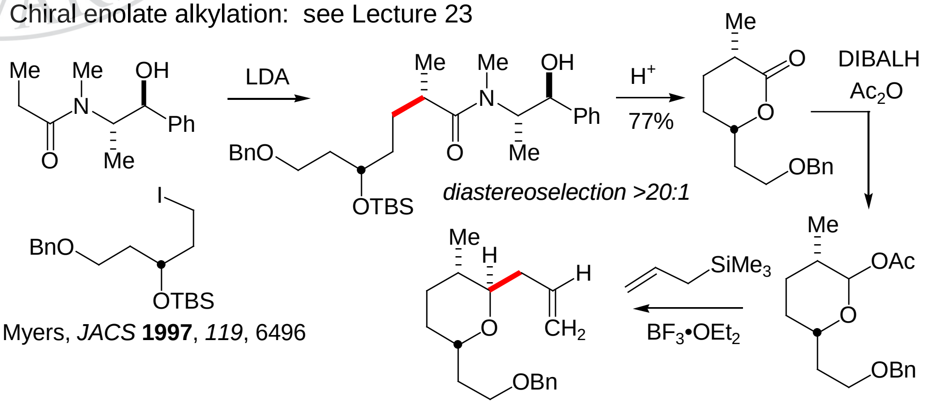


anti selection: ~5–8:1

Evans et al., *JACS* **1996**, *116*, 4322

Aldehyde Synthesis

Chiral enolate alkylation: see Lecture 23



diastereoselection >20:1

Myers, *JACS* **1997**, *119*, 6496

cyclic oxo-carbenium ion addition: see Lecture 19

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 33

Introduction to Organosilicon Chemistry

- Silicon Bonding Considerations
- The Silicon–Proton Analogy
- C=O Addition of Organosilanes
- Sigmatropic Rearrangements of Organosilanes
- Anionic (Brook) Rearrangements
- Peterson Olefination Reaction
- Survey of Silicon (and related) Protecting Groups

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part B Chapter 9, " C–C Bond Forming Rxns of Boron, Silicon & Tin", 595–680.

Fleming, I.; Barbero, A.; Walter, D. "Stereochemical control in organic synthesis using silicon-containing compounds." *Chem. Rev*. **1997**, *97*, 2063-2192. (**Web**)

Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, *57*, 2065-2084 (**handout**)

Masse, C. E.; Panek, J. S. "Diastereoselective reactions of chiral allyl- and allenylsilanes with activated C-X pi-bonds." *Chem. Rev.* **1995**, *95*, 1293-1316.

Ager, D. J. "The Peterson olefination reaction." *Org. Reactions* **1990**, *38*, 1-224

Colvin, E. "Silicon in Organic Synthesis," *Butterworths*, **1981**

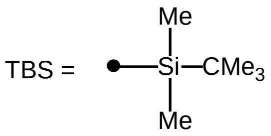
Bois, et al. "SiliconTethered Reactions" *Chem. Rev*. **1995**, *95*, 1253-1277. (**Handout**)

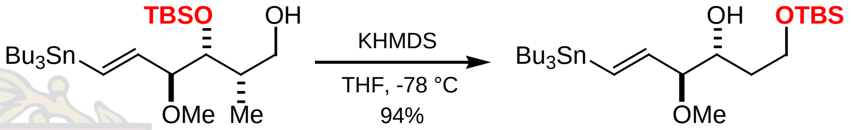
Matthew D. Shair

Wednesday,
December 11, 2002

Problems to Contemplate

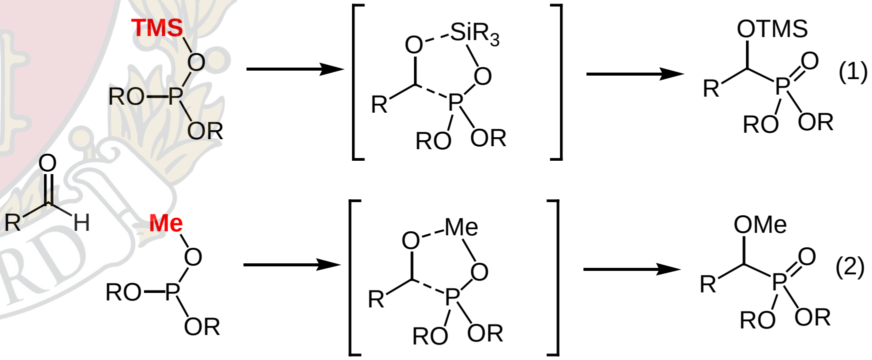
Explain what drives this rearrangement.



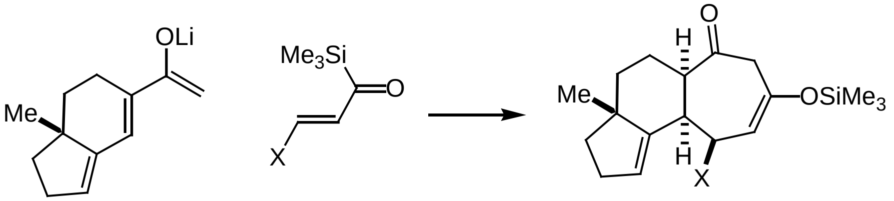


Calter, M. A. Ph. D. Thesis, Harvard University, 1993.

The C=O addition illustrated in eq 1 proceeds while the carbon analogue (eq 2) does not. Explain



Provide a mechanism for the indicated transformation



Takeda, *Org. Lett*, **2000**, *2*, 903-1905

Bonding Considerations: Carbon vs Silicon

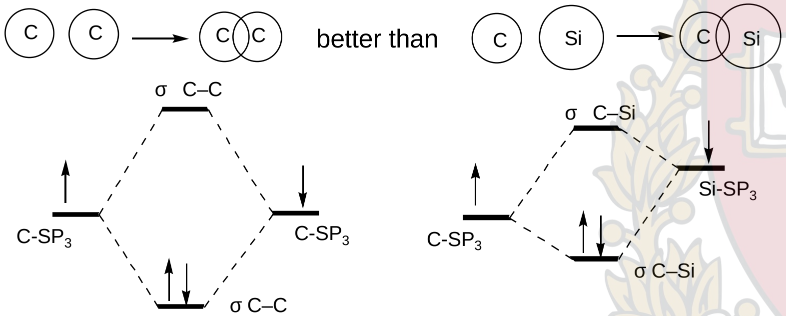
Average Bond dissociation eneregies (Kcal/mol)

C–C	C–Si	Si–Si	C–F	Si–F	C–O	Si–O
83	76	53	116	135	86	108

C–H	Si–H
83	76

Average Bond Lengths (Å)

C–C	C–Si	C–O	Si–O
1.54	1.87	1.43	1.66



$H_3C{-}CH_3$ BDE = 83 kcal/mol

Bond length = 1.534 Å

$H_3C{-}SiH_3$ BDE ~ 76 kcal/mol

Bond length = 1.87 Å

This trend is even more dramatic with pi-bonds:

π C–C = 65 kcal/mol   π C–Si = 36 kcal/mol   π Si–Si = 23 kcal/mol

$$\boxed{\overset{\delta-}{C}{-\!\!-}\overset{\delta+}{Si}}$$

Group IV Electronegativities (Pauling)

Carbon	Silicon	Germanium	Tin	Lead
2.55	1.90	2.01	1.96	2.33

+2 Oxidation state becones increasingly more stable →

Hypervalent 5-Coordinate Silicon Compounds

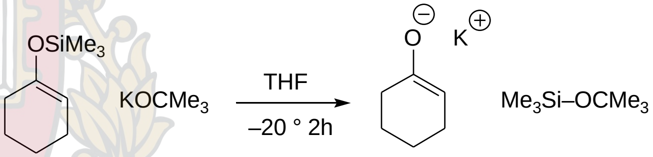
Akiba, "Chemistry of hypervalent Compounds" Wiley-VCH, Chapters 4-5, 1999

Penta-coordinate silicates are commonly observed

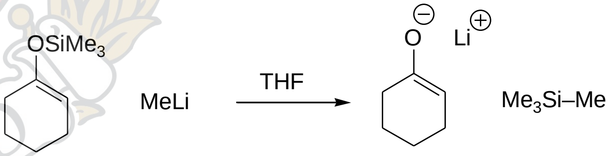
$\overset{\ominus}{MeSiF_4}\ \overset{\oplus}{NEt_4}$ $\overset{\ominus}{Ph_3SiF_2}\ \overset{\oplus}{NR_4}$

Nucleophilic substitution at Silicon

$$RO{-}SiMe_3 \xrightarrow{F^{\ominus}} RO^{\ominus} + F{-}SiMe_3$$

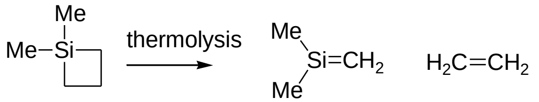


Duhamel et al. *J. Org. Chem.* **1996**, *61*, 2232

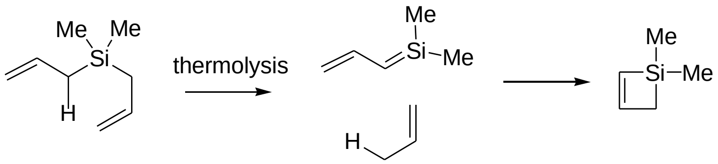


Stork et al. *JACS.* **1968**, *90*, 4462, 4464

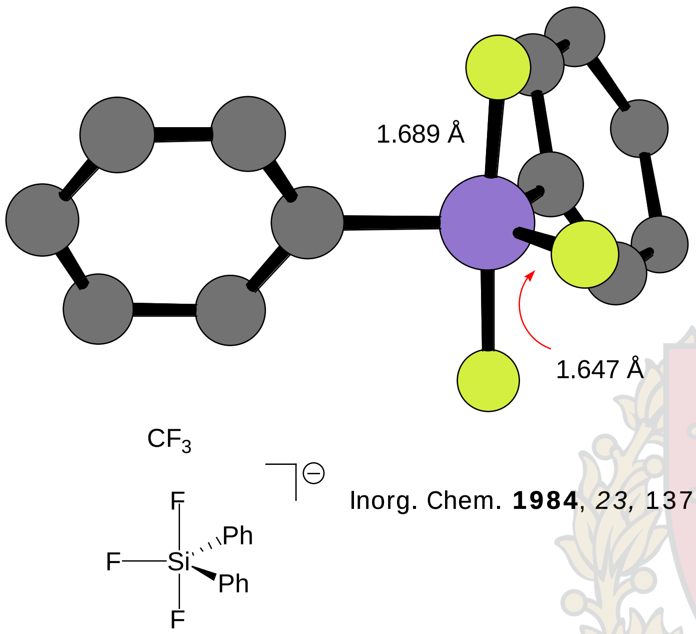
Thermal Rearrangements One may readily access divalent intermediates



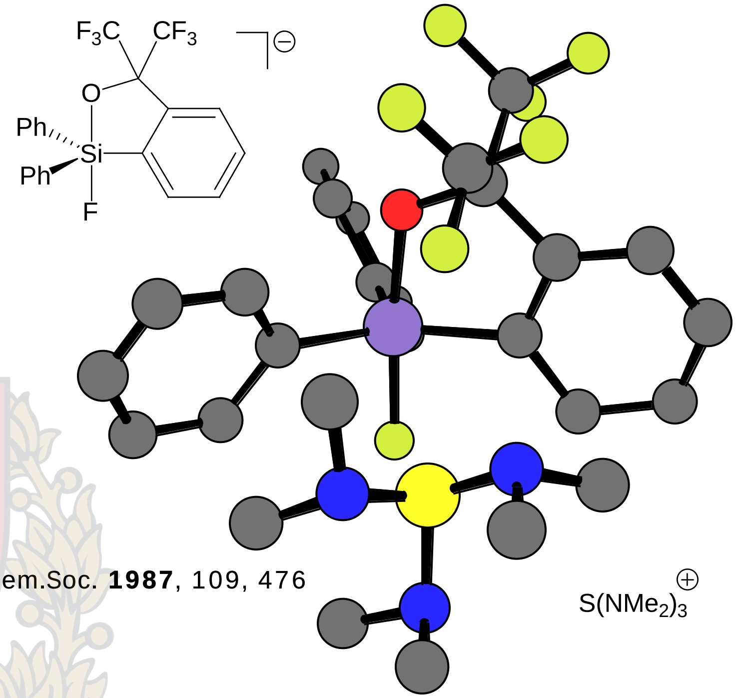
Colvin, pp 7-9



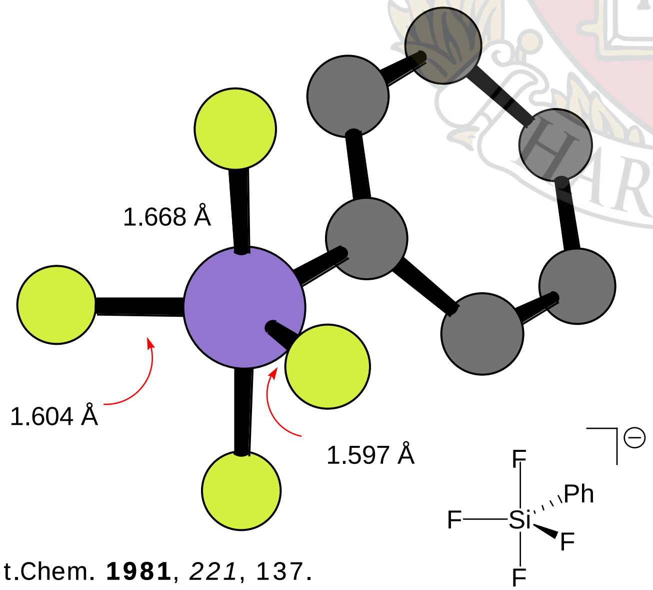
Hypervalent Silicon Ate-Complexes



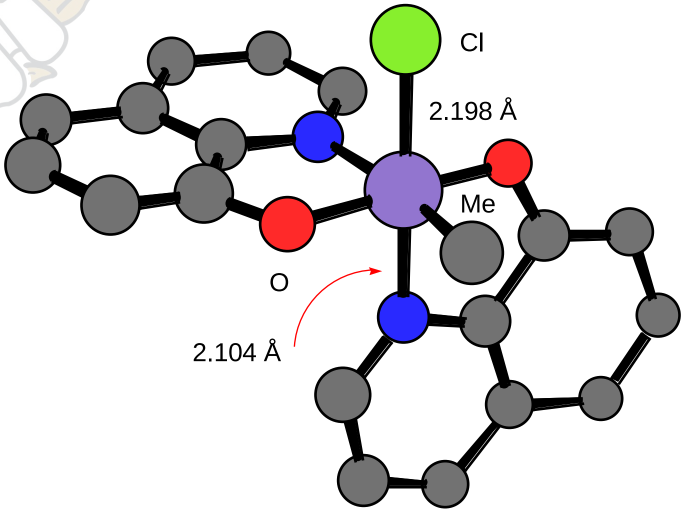
Inorg. Chem. **1984**, *23*, 1378



J. Am. Chem.Soc. **1987**, 109, 476



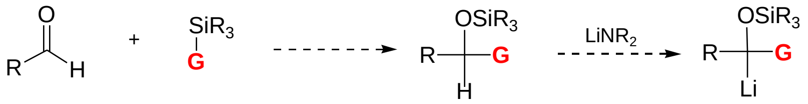
J. Organomet.Chem. **1981**, *221*, 137.



Acta Crystallogr. Sect. C **1984**, *40*, 476

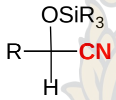
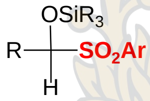
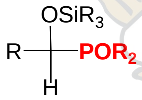
Carbonyl addition Reactions

1970 DAE Objective: *Develop a reagent that will transform aldehydes into protected cyanohydrins in one step*

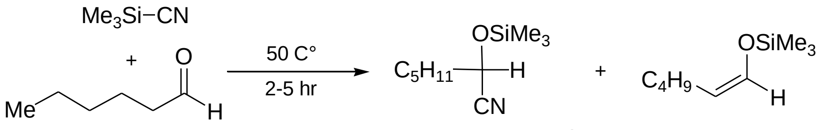


G = carbanion-stabilizing FG

Carbonyl Anion Equivalent

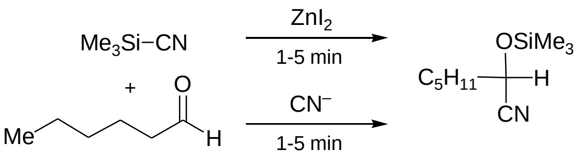
R_3Si—**G** Candidates	Carbonyl Adducts
R_3Si—**CN**	
R_3Si—**OSO_2Ar**	
R_3Si—**OPR_2**	

Thermal C=O addition of TMSCN is not a clean reaction



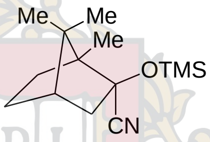
ratio: 65:35

The prospect of catalysis was investigated

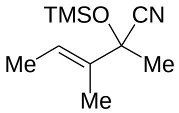


reaction was instaneous and quantiltative

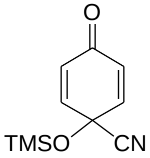
Principle established that normally inaccessible cyanohydrin derivatives may now be accessed



>95% yield
(ZnI_2 catalysis)



92% yield
only 1,2-addition
(ZnI_2 catalysis)

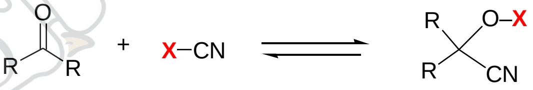


>95% yield
only 1,2-addition
(CN^- catalysis)

with Truesdale, Carroll, *Chem Commun.* **1973**, 55; *J. Org. Chem..* **1974**, *39*, 914
Tetrahedron Lett **1973**, 4929 (first discussion of Nu catalysis)

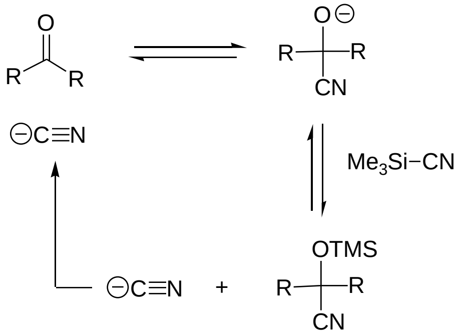
"The Silicon Advantage"

From the preceding case, it is clear that ΔH_{Si} is more exothermic than ΔH_H

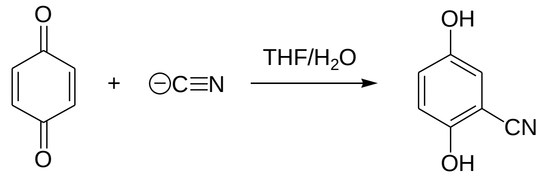


$\Delta H_{Si} > \Delta H_H$

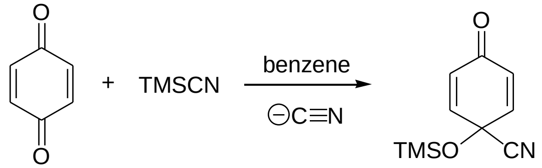
Nucleophilic Catalysis



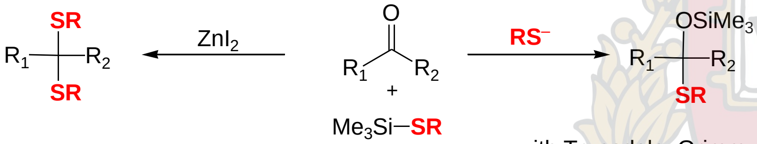
Explain the following observations



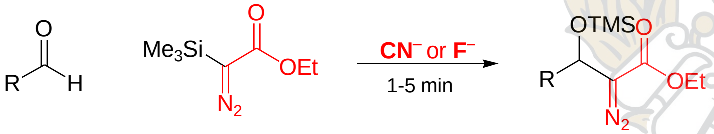
1-4 addition



1-2 addition

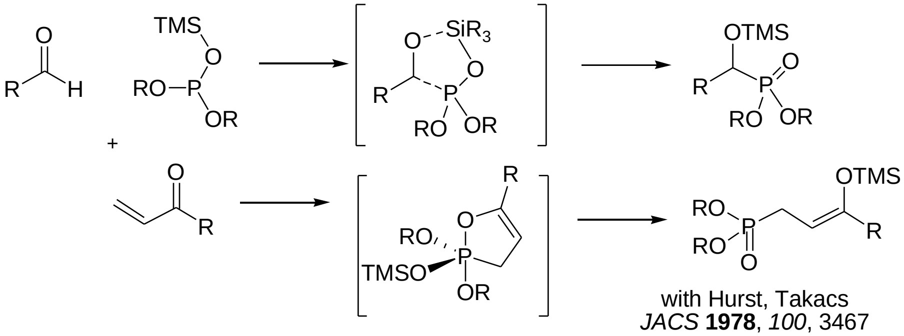


with Truesdale, Grimm, Nesbitt,
JACS **1975**, *97*, 3229
JACS **1977**, *99*, 5009



with Truesdale, Grimm
JOC **1976**, *41*, 3335

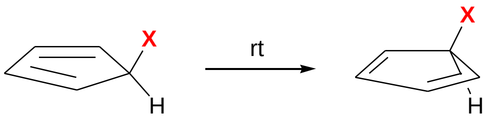
Non-catalyzed processes may also occur if a proper geometry for atom transfer can be achieved



with Hurst, Takacs
JACS **1978**, *100*, 3467

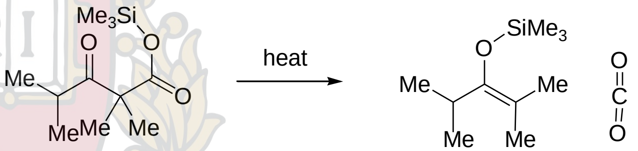
"The Proton–Silicon Correlation"

- Organosilanes undergo carbonyl addition processes in direct analogy with their proton counterparts but with an attendant greater exothermicity.
- Organosilanes undergo a range of thermal rearrangements processes in direct analogy with their proton counterparts.

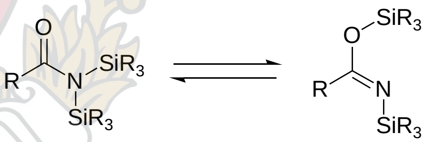


k(Si) =10^{+6} K(H)

A. J. Ashe III, *JACS* **1970**. *92*, 1233



Colvin, pp 37-8



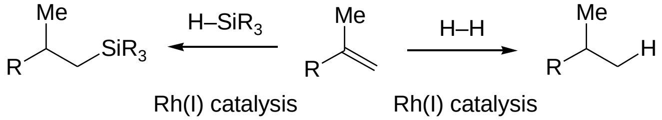
ΔG* 15-22kcal/mol

Si transfer is intramolecular

Yoder et al., *JACS* **1974**. *96*, 4283

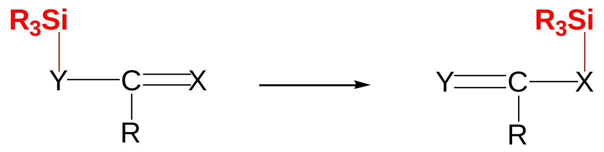
$$Me_3Si{-}C{\equiv}N \rightleftharpoons C{\equiv}N{-}SiMe_3$$

- Organosilicon hydrides undergo transition metal catalyzed hydrosilylation processes in direct analogy with normal hydrogenation reactions

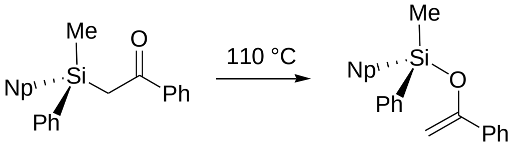


"Hydrosilylation of C–C Bonds". T. Hayashi In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol I, 319-332.

[1,3]-Sigmatropic Rearrangements



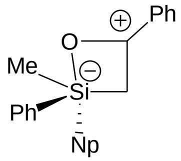
Y = C; X = O



Complete retention of Si stereochemistry was noted.

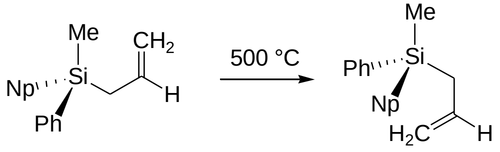
Ea = 28 kcal/mol

A. G. Brook *Accts. Chem. Research* **1974**, *7*, 77-84



Brook speculates that a hypervalent Si intermediate might be involved in the rearrangement.

Y = C; X = C



Inversion of Si stereochemistry was noted.

Ea = 48 kcal/mol

H. Kwart et al., *JACS* **1973**. *95*, 8678

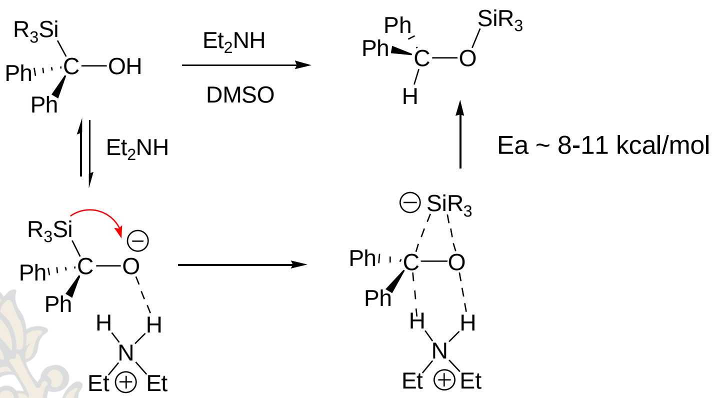
Theoretical calculations lead to the conclusion that the concerted [1,3] sigmatropic rearrangement with ***retention*** of Si-configuration should represent the lower energy pathway.

Yamabe, *JACS* **1997**, *119*, 808

At the present time these rearrangements are not well studied,

"The Brook Rearrangement(s)"

A. G. Brook *Accts. Chem. Research* **1974**, *7*, 77-84

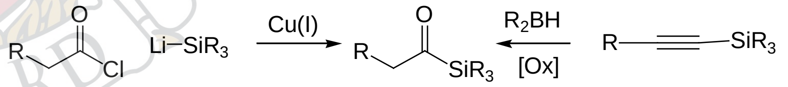


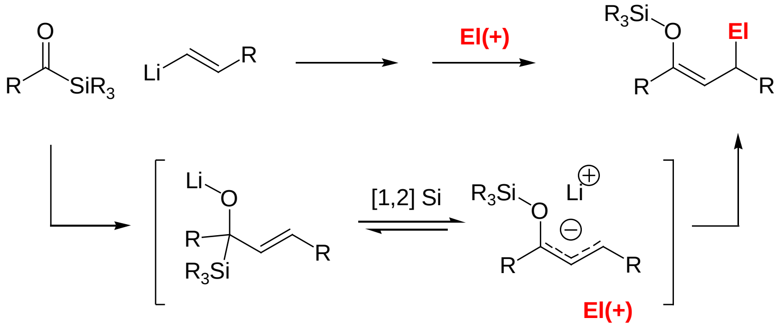
Brook has documented that **retention** at Silicon & **inversion** at Carbon occur.

Transformations Involving the Brook Rearrangement

Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, *57*, 2065-2084

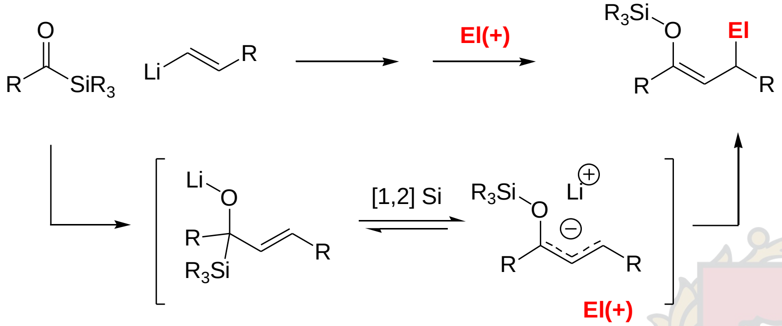
Acylsilanes

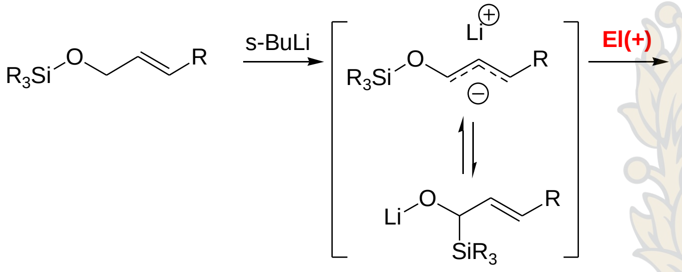


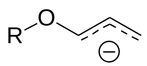


Transformations Involving the Brook Rearrangement

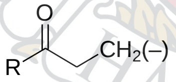
Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, *57*, 2065-2084







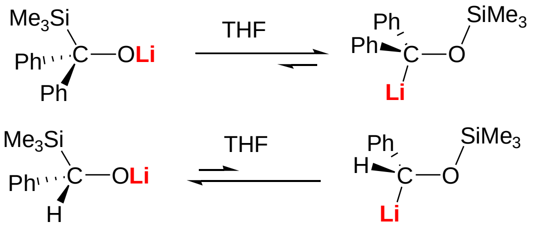
These reagents are useful homoenolate anion equivalents



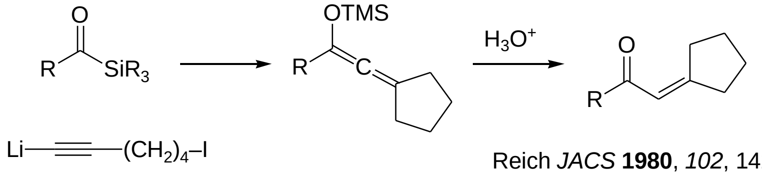
"Metalated Allylic Ethers as Homoenolate Anion Equivalents".
Evans, D. A.; Andrews, G. C.; Buckwalter, B. *JACS* **1974**, *96*, 5560.
Si–Variant: Still & MacDonald *JACS* **1974**, *96*, 5561

Brook Equilibrium

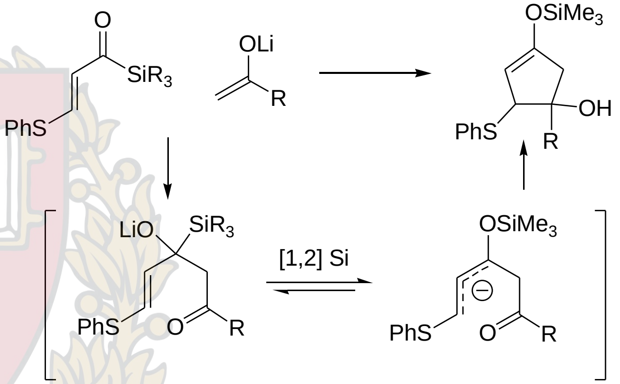
Reich *JACS* **1980**, *102*, 1423 (see footnote 8)



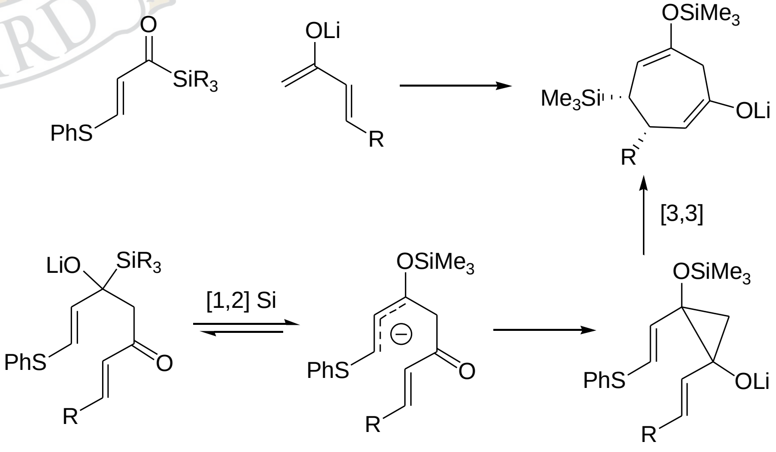
Intramolecular alkylations may be carried out:



Reich *JACS* **1980**, *102*, 1423

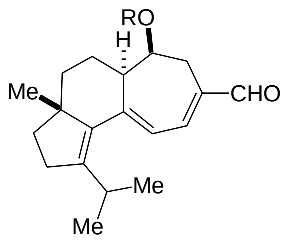


Takeda *JACS* **1993**, *115*, 9351; *Synlett* **1994**, 178; *SynLett* **1997**, 255

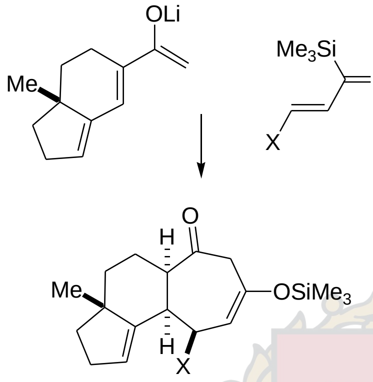


Tetrahedron **2001**, *57*, 2065-2084, footnote 16

The natural product target:



The key reaction



Takeda, *Org. Lett*, **2000**, *2*, 903-1905

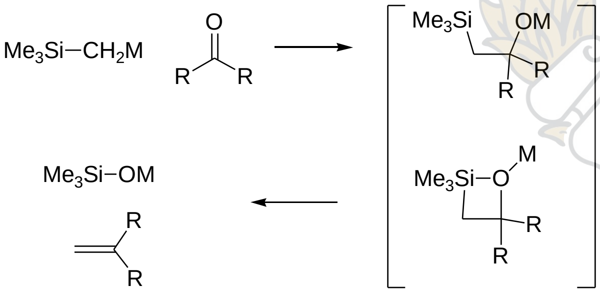
The Peterson Olefination Reaction

Ager, D. J. "The Peterson olefination reaction."
Org. Reactions **1990**, *38*, 1-224

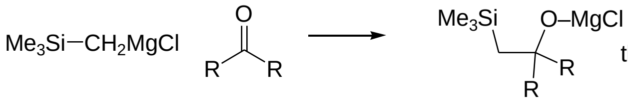
The key paper: Peterson, J. Org. chem. 1968, 33, 780-784

It was Peterson's intent to find a silicon analog to the Wittig rxn.
The reaction concept is outlined below:

C	**N**
Si	**P**

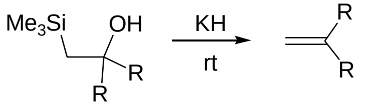


Magnesium alkoxides: Stable

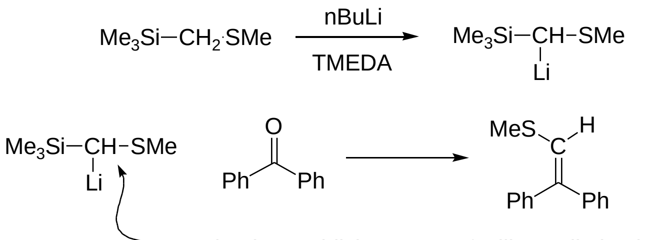


these adducts are quite stable

Na & K alkoxides: Eliminate



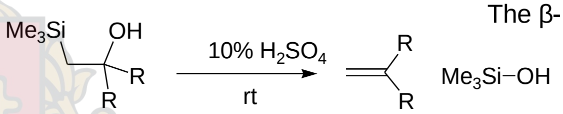
Me_3Si-OK (Na)



carbanion-stabiizing groups facilitate elimination

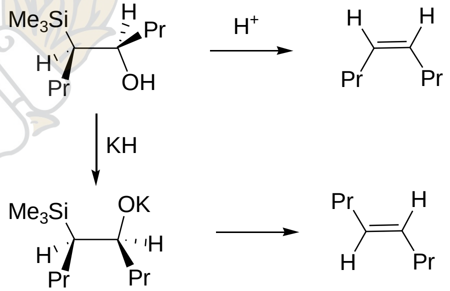
Elimination could also be effected with dilute acid

The β-Effect (lecture 31)



analogy provided by Whitmore et al. *JACS* **1947**, *69*, 1551

Mechanistic aspects of Beta-OH Elimination



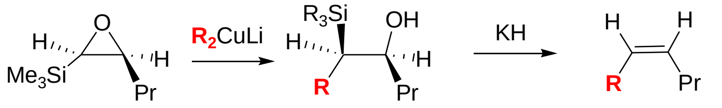
Anti Elimination

The β-Effect (lecture 31)

Syn Elimination

Hudrlik et al. *JACS* **1975**, *97*, 1464

Colvin chapter 12, pp 141

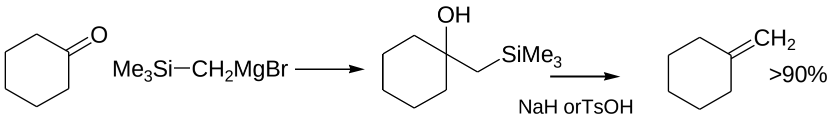


reaction is stereospecific

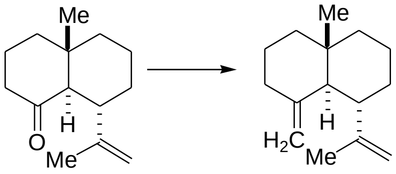
note site of nu attack. Why?

The Peterson Olefination Reaction

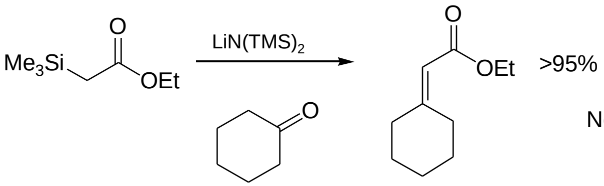
Simple Examples: Taken from Organic Rxns review



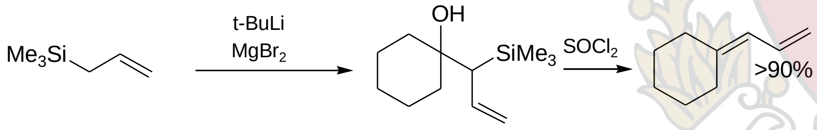
This reagent is better that $H_2C=PPh_3$ for hindered ketones



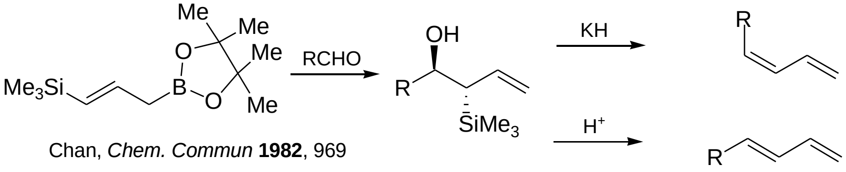
Boeckman, *Tet. Lett* **1973**, 3437



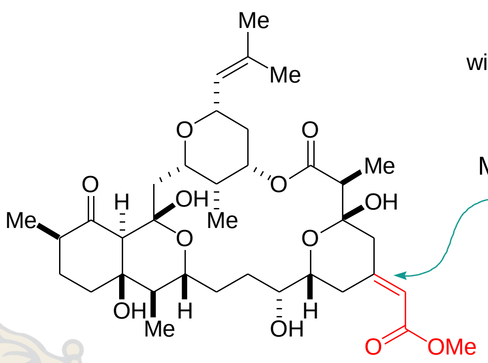
Nozaki, *JACS* **1974**, *96*, 1620



Chan, *Tet. Lett* **1978**, 2383



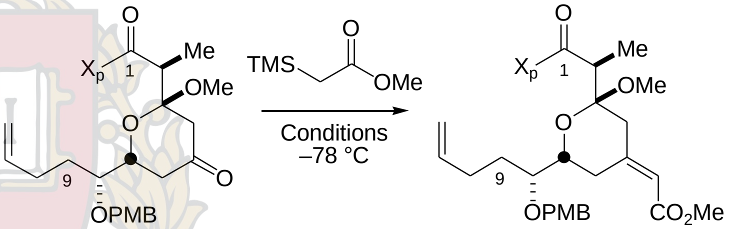
Chan, *Chem. Commun* **1982**, 969



Miyakolide **(+)-1**

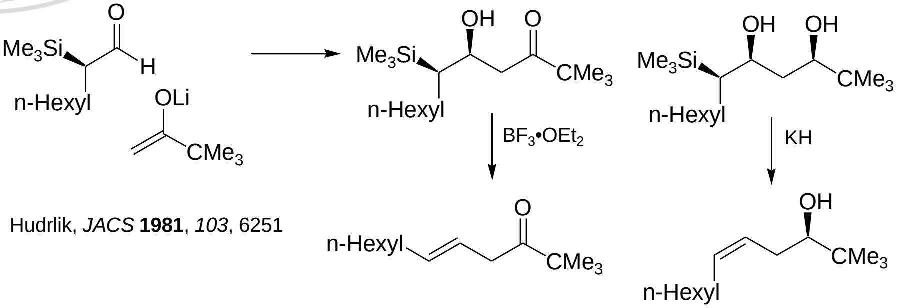
with Ripin, Halstead, and Campos
JACS **1999**, *121*, 6816-6826.

Miyakolide presents an interesting olefin geometry challenge

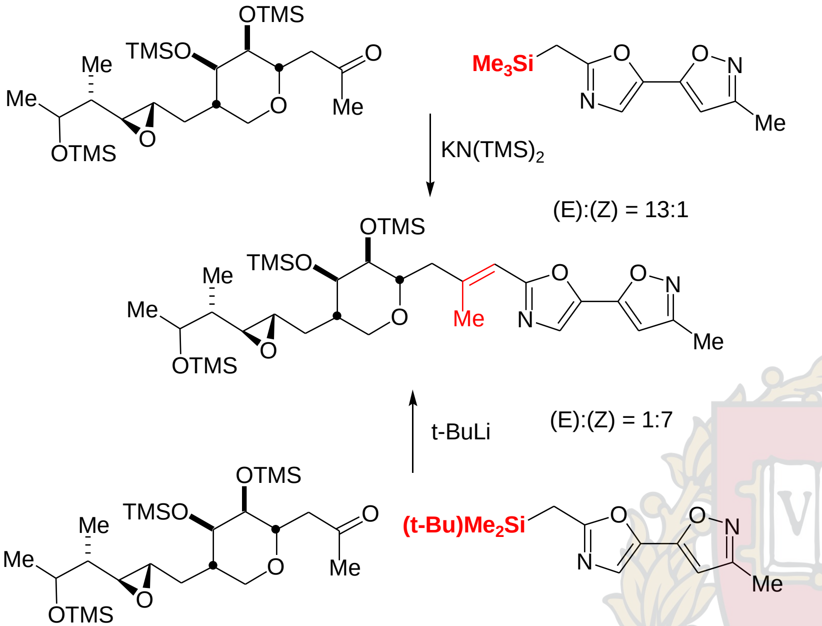


19-E

entry	base	solvent	*E* : *Z*
1	**LDA**	**THF**	**73 : 27**
2	NaHMDS	THF	18 : 82
3	LDA	Et_2O	66 : 33
4	LDA	PhMe	66 : 33



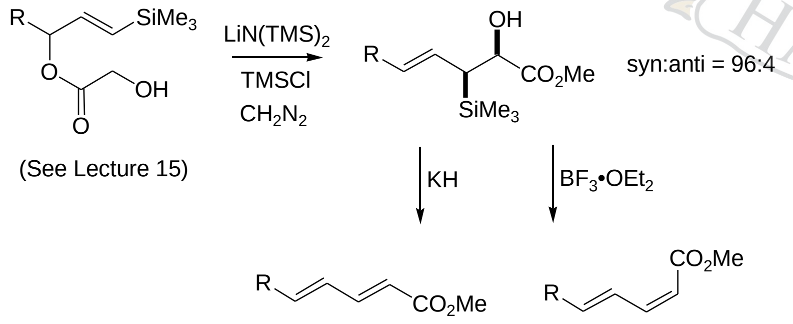
Hudrlik, *JACS* **1981**, *103*, 6251



Bell et al. *Tetrahedron* **1994**, *50*, 6643

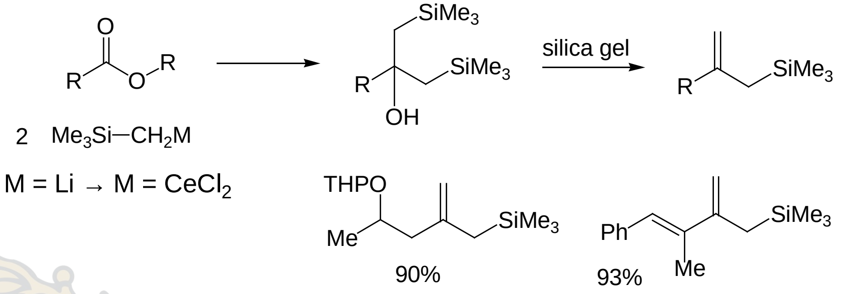
Reaction may be altered significantly with an attendant chenge in stereoselection

Ireland Enolate Claisen Coupled to Peterson Olefination

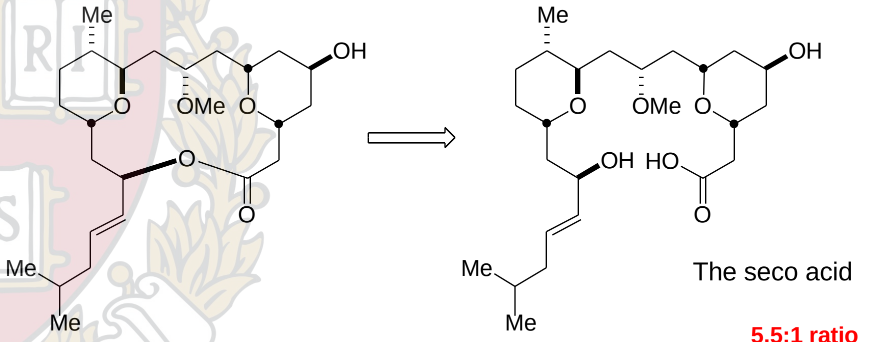


Sato et al. *Chem. Lett* **1986**, 1553

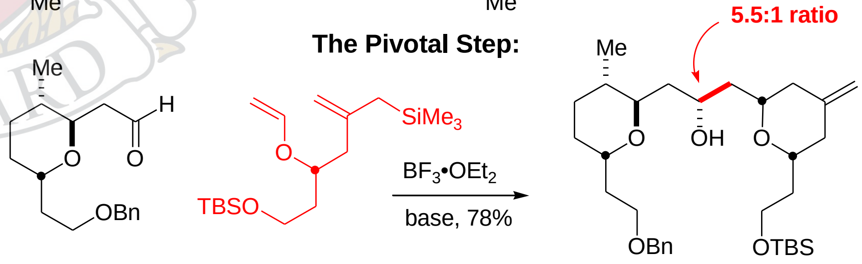
Bunnelle-Peterson Allylsilane Synthesis

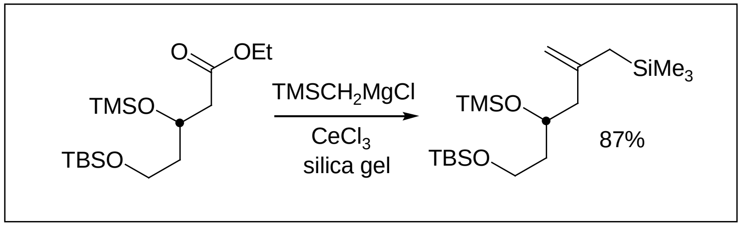


Application to Leucasandrolide: *Rychnovsky JACS*, **2001**, *123*, 8420

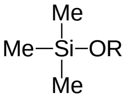


The Pivotal Step:





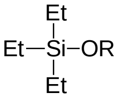
Silyl Ethers:



$\mathrm{Me{-}\overset{Me}{\underset{Me}{Si}}{-}OR}$

trimethylsilyl

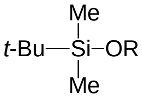
(TMS)



$\mathrm{Et{-}\overset{Et}{\underset{Et}{Si}}{-}OR}$

triethylsilyl

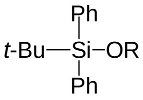
(TES)



$\mathrm{\textit{t}\text{-}Bu{-}\overset{Me}{\underset{Me}{Si}}{-}OR}$

tert-butyldimethylsilyl

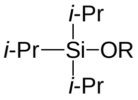
(TBS or TBDMS)



$\mathrm{\textit{t}\text{-}Bu{-}\overset{Ph}{\underset{Ph}{Si}}{-}OR}$

tert-butyldiphenylsilyl

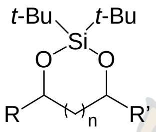
(TBDPS)



$\mathrm{\textit{i}\text{-}Pr{-}\overset{\textit{i}\text{-}Pr}{\underset{\textit{i}\text{-}Pr}{Si}}{-}OR}$

triisopropylsilyl

(TIPS)



di-*tert*-butyldimethylsilylene

(DTBS)

Formation:

By far the two most common methods:

$$\mathrm{R{-}OH} \xrightarrow[\text{DMF, R.T.}]{\mathrm{R_3Si\text{-}Cl}\text{, imidazole}} \mathrm{R{-}OSiR_3}$$

2 equiv of imidazole are required relative to R_3SiCl.

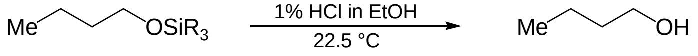
Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

$$\mathrm{R{-}OH} \xrightarrow[\mathrm{CH_2Cl_2}\text{, 0 °C}]{\mathrm{R_3Si\text{-}OTf}\text{, 2,6-lutidine}} \mathrm{R{-}OSiR_3}$$

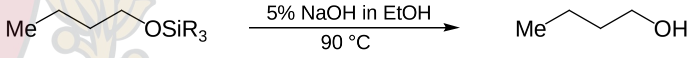
Corey, E. J. et al., *Tetrahedron Lett.* **1981**, *22*, 3455.

Relative stabilities:

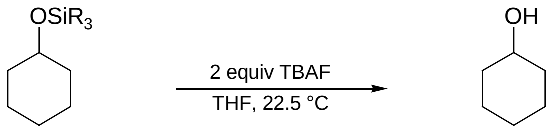
TES ~10^2 times more stable to acidic hydrolysis than TMS
TBS ~10^4 times more stable to acidic hydrolysis than TMS



SiR_3	Half-life
TBS	< 1 min
TIPS	18 min
TBDPS	244 min



SiR_3	Half-life
TBS	1 h
TIPS	14 h
TBDPS	< 4 h

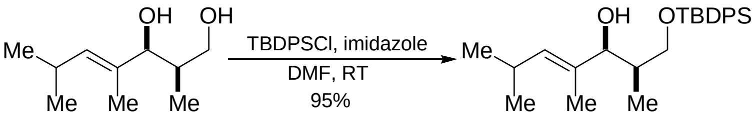


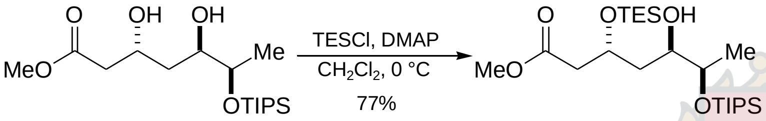
SiR_3	Half-life
TBS	76 min
TIPS	137 min

Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797-4798.

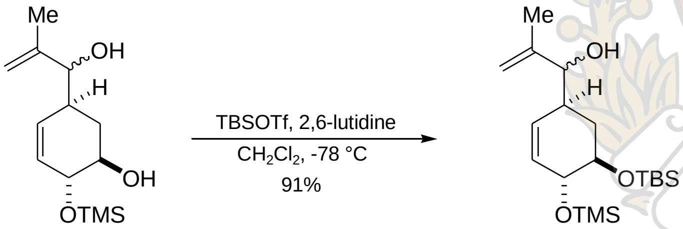
ROH Protecting Groups-2

Selective Protection:

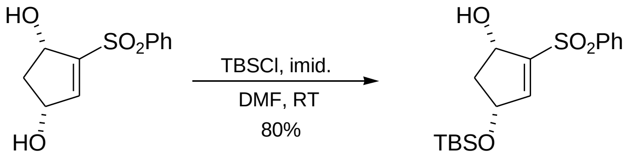




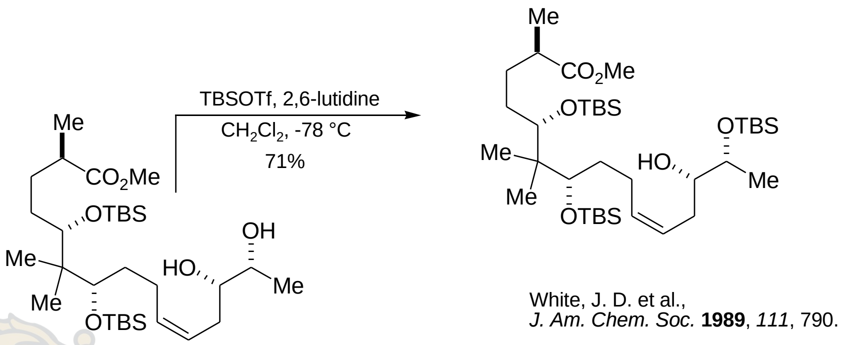
Evans et al.JACS **1999**, *121*, 7540-7552.



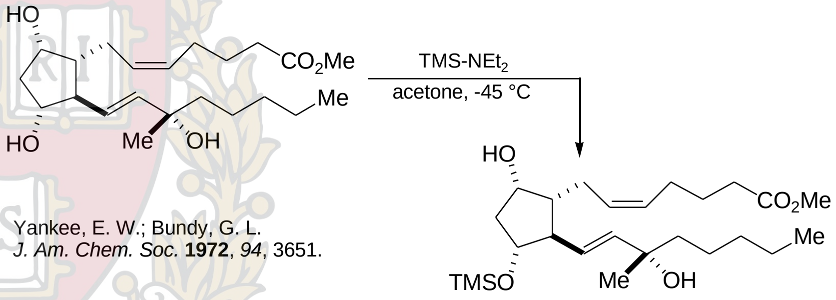
Askin, D.; Angst, D.; Danishefsky, S. *J. Org. Chem.* **1987**, *52*, 622.



Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2108.

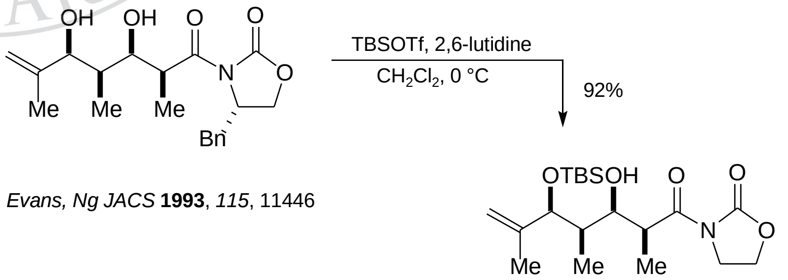


White, J. D. et al.,
J. Am. Chem. Soc. **1989**, *111*, 790.



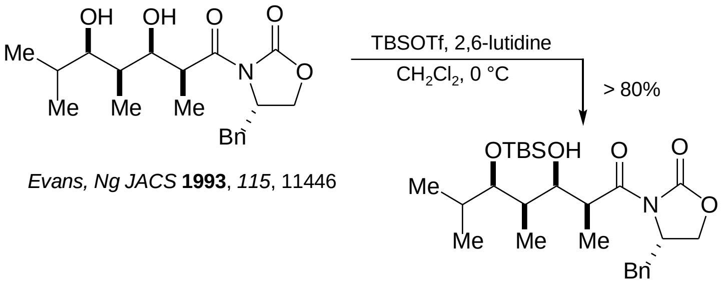
Yankee, E. W.; Bundy, G. L.
J. Am. Chem. Soc. **1972**, *94*, 3651.

TMS-NEt_2 has been reported to selectively protect equatorial alcohols in the presence of axial alcohols:
Weisz, I. et al. *Acta. Chim. Acad. Sci. Hung.* **1968**, *58*, 189.

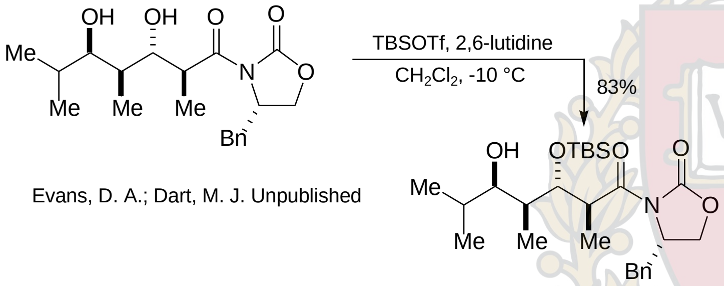


Evans, Ng JACS **1993**, *115*, 11446

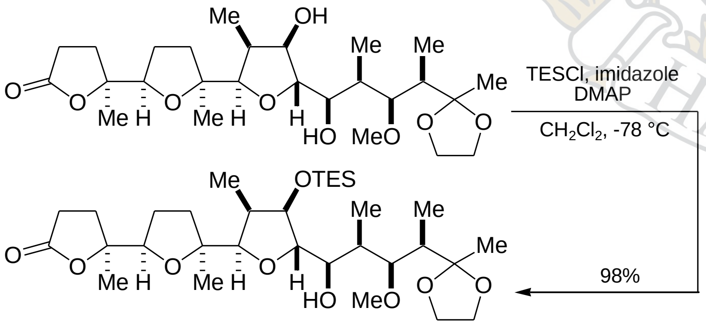
Selective Protection:



Evans, Ng JACS ***1993***, *115*, 11446

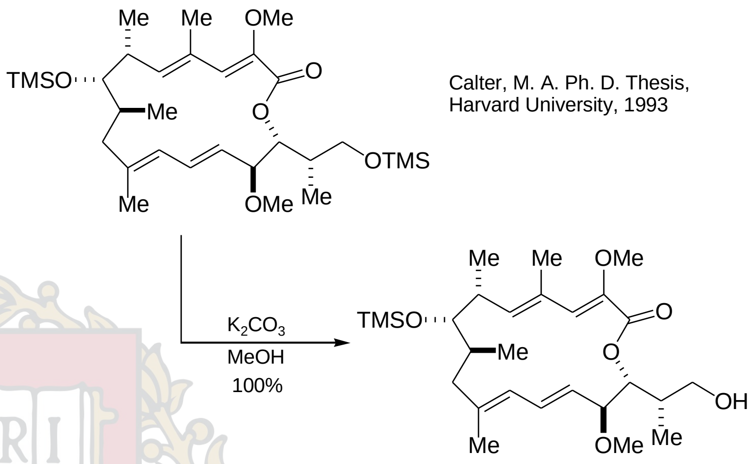


Evans, D. A.; Dart, M. J. Unpublished

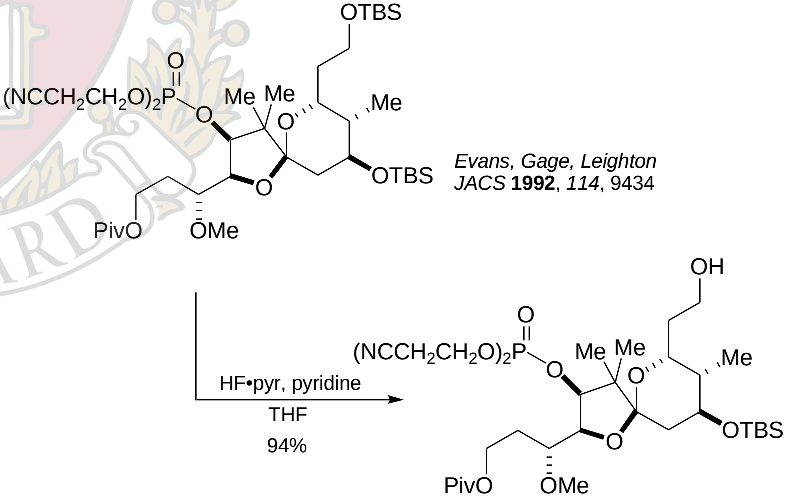


Evans, Ratz JACS ***1995***, *117*, 3448

Selective Deprotection:

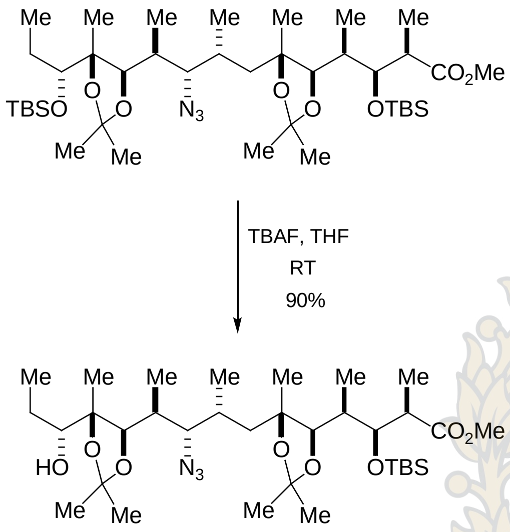


Calter, M. A. Ph. D. Thesis, Harvard University, 1993

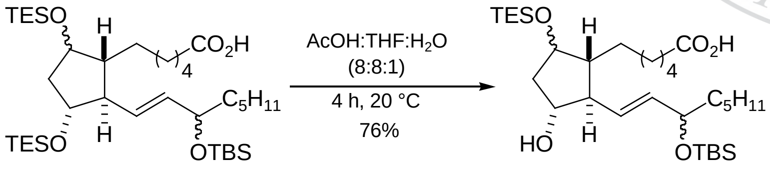


Evans, Gage, Leighton JACS ***1992***, *114*, 9434

Selective Deprotection:

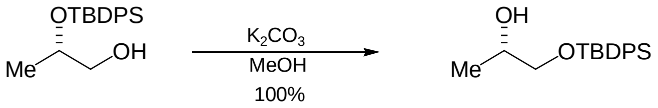


Nakaba, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 2219, 2223.



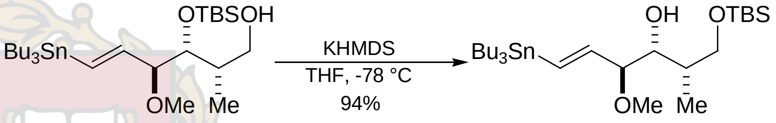
Hart, T. W.; Metcalfe, D. A.; Scheinmann, F.
J. Chem. Soc., Chem. ommun. **1979**, 156.

1,2-Migration:

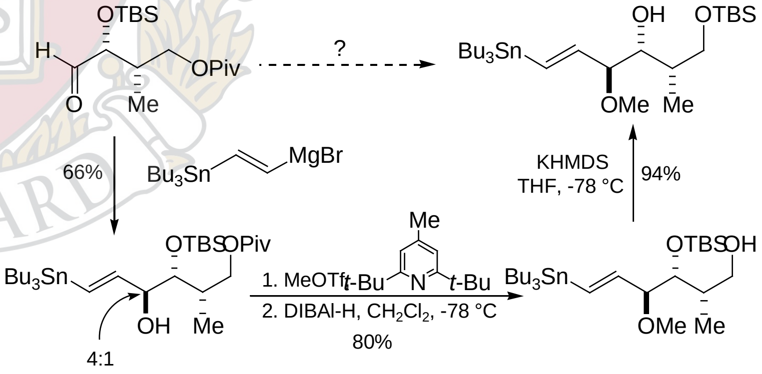


Mulzer, J.; Schollhorn, B. *Angew. Chem., Int. Ed. Eng.* **1990**, *29*, 431-432.

1,3-Migration:



Calter, M. A. Ph. D. Thesis, Harvard University, 1993.



Calter, M. A. Ph. D. Thesis, Harvard University, 1993.

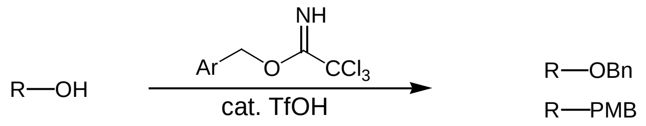
ROH Protecting Groups

Principle Methods for Benzylation of Alcohols:

1.

$$R{-}OH \xrightarrow[\text{2. BnBr/PMBBr}]{\text{1. NaH, DMF, 0 °C}} \begin{matrix} R{-}OBn \\ R{-}PMB \end{matrix}$$

2.



Ar = Ph: CH_2Cl_2

Ar = 4-MeO-Ph: Et_2O

Ar = Ph:	Iversen, T.; Bundle, K. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.
Ar = 4-MeO-Ph:	Yonemitsu, O. et al., *Tetrahedron Lett.* **1988**, *29*, 4139.

3.

$$R{-}OH \xrightarrow[\text{2. BnBr, }N\text{-methylimidazole}]{\text{1. }(Bu_3Sn)_2O\text{, PhMe, }\uparrow\downarrow} R{-}OBn$$

Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *J. Org. Chem.* **1989**, *54*, 465.

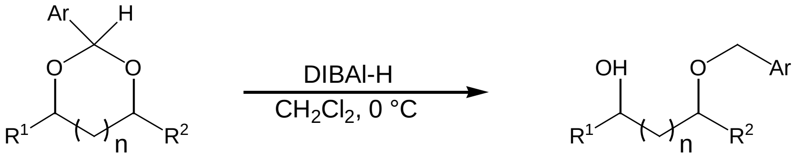
Review: David, S.; Hanessian, S. *Tetrahedron*, **1985**, *41*, 643-663.

4.

$$R{-}OH \xrightarrow[\text{DMF}]{Ag_2O\text{, BnBr}} R{-}OBn$$

Van Hijfte, L.; Little, R. D. *J. Org. Chem.* **1985**, *50*, 3940.

Via Benzylidene Acetal:



Takano, S. et al., *Synthesis* **1986**, 811-817.

Principle Methods for Deprotection:

1. Hydrogenation

$$R{-}OBn \xrightarrow[\text{EtOH/EtOAc/AcOH}]{\text{10\% Pd on C, }H_2} R{-}OH$$

See Greene, p. 49.

2. Transfer Hydrogenation

$$R{-}OBn \xrightarrow[\text{Hydrogen Source}]{\text{10\% Pd on C}} R{-}OH$$

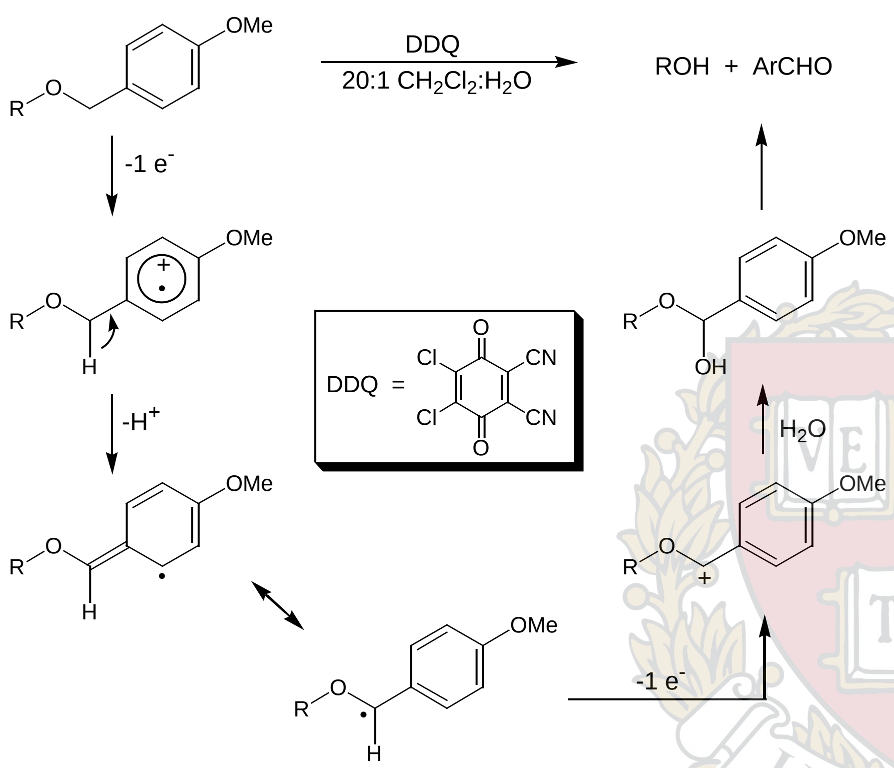
Hydrogen Source	Ref.
Cyclohexene	*Synthesis* **1981**, 396.
Cyclohexadiene	*J. Org. Chem.* **1978**, *43*, 4194.
HCO_2H	*J. Org. Chem.* **1979**, *44*, 3442.
i-PrOH	*Tetrahedron Lett.* **1986**, *27*, 2497

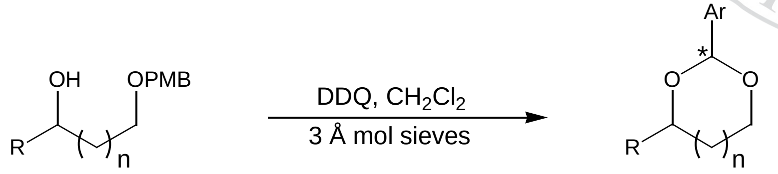
3. Lewis Acids

$$R{-}OBn \longrightarrow R{-}OH$$

Reagents	Ref.
$BF_3{\bullet}OEt_2$, EtSH	*Tetrahedron Lett.* **1989**, *30*, 5713.
1. BCl_3, -78 °C to 0 °C. 2. MeOH, -78 °C.	*J. Am. Chem. Soc.* **1989**, *111*, 1923.
TMSBr, C_6H_5SMe	*Chem. Pharm. Bull.* **1987**, *35*, 3880.

PMB Deprotection:



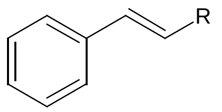


Yonemitsu, O. et al., *Tetrahedron* **1986**, *42*, 3021.

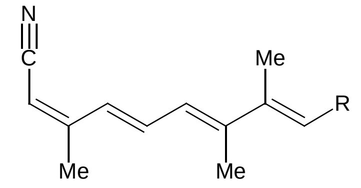
Other Oxidants: NBS, Br$_2$, CAN ((NH$_4$)$_2$Ce(NO$_3$)$_6$).

Acta Chem. Scand. Ser. B, **1984**, *B38*, 419.
J. Chem. Soc., Perkin Trans. I, **1984**, 2371.

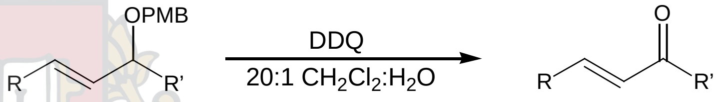
DDQ is incompatible with:



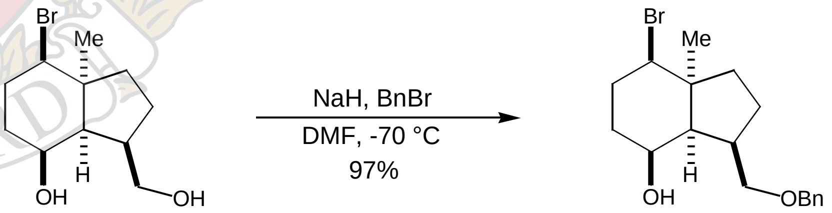
styryl



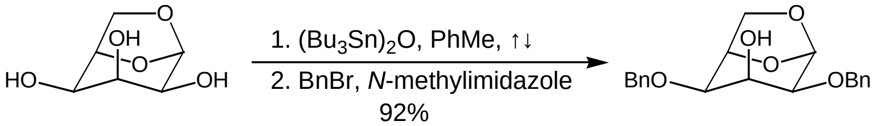
extended conjugated polyenes



Selective Benzylation:

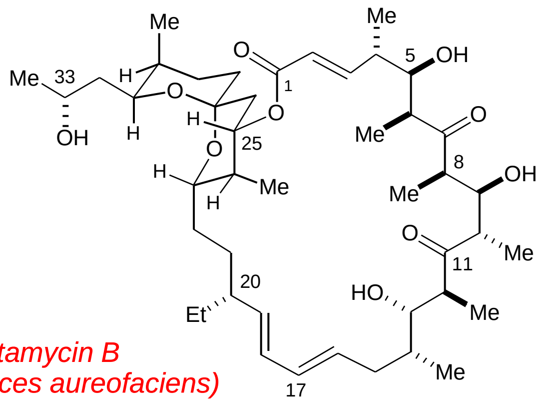


Fukuzawa, A. et al. *Tetrahedron Lett.* **1987**, *28*, 4303.



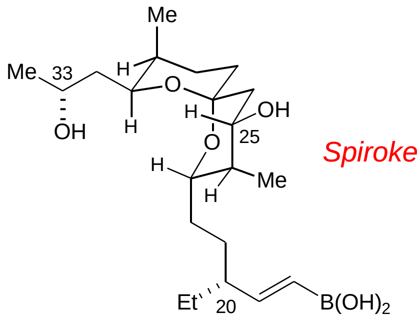
Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *J. Org. Chem.* **1989**, *54*, 465.

ROH Protecting Groups

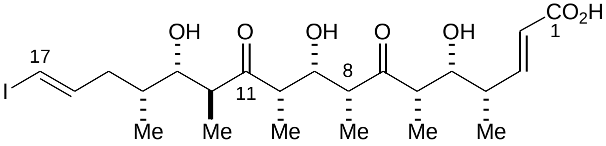


Rutamycin B
(Streptomyces aureofaciens)

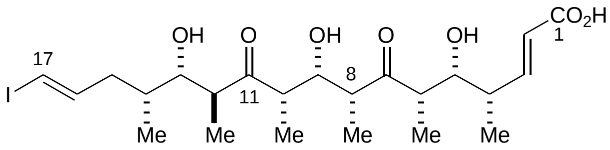
Ng, H. P. Ph. D. Thesis,
Harvard University, 1993

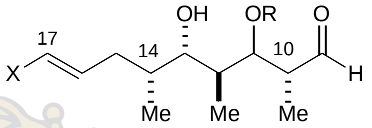


Spiroketal Fragment

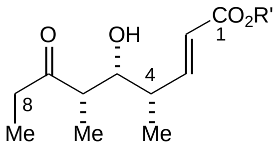


Polypropionate Fragment

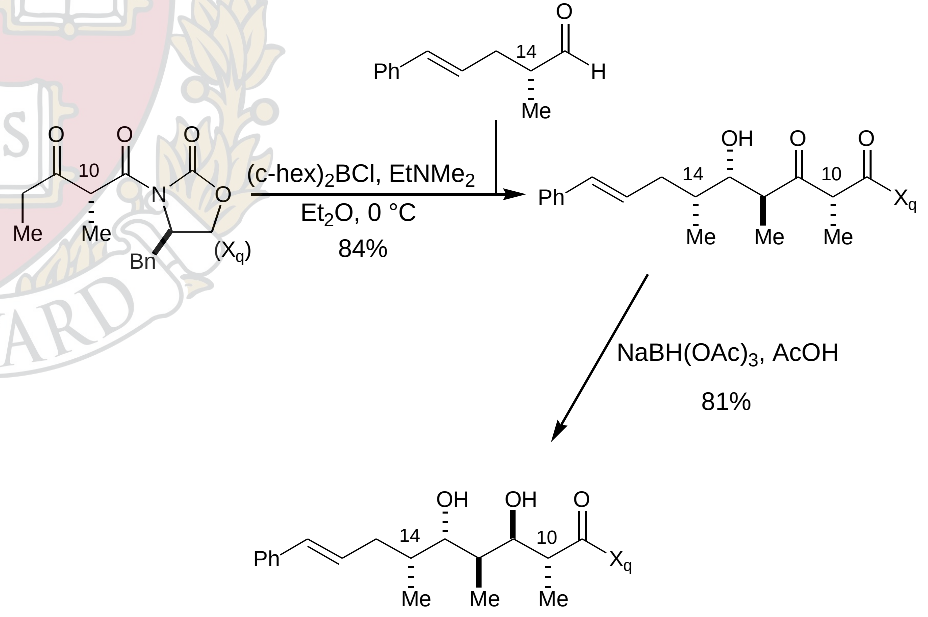




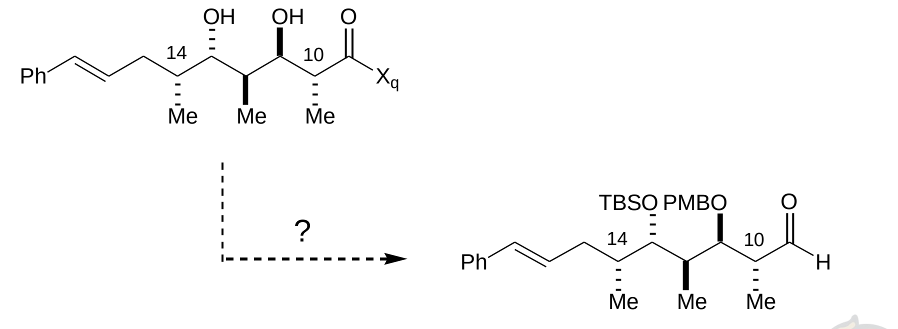
C_9-C_{17} Subunit



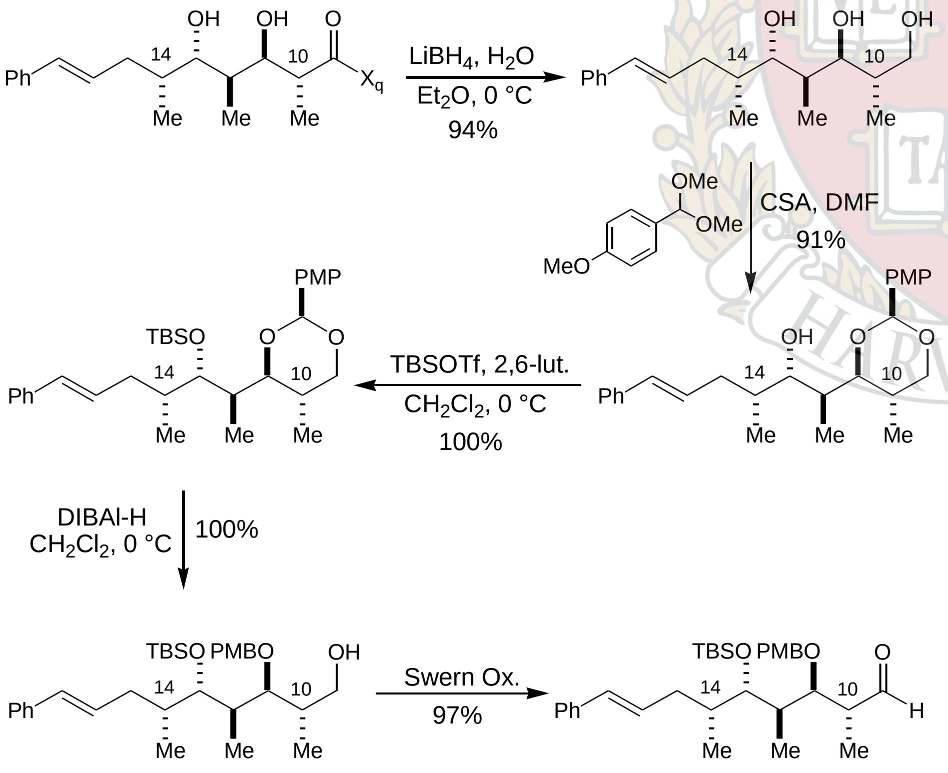
C_1-C_8 Subunit

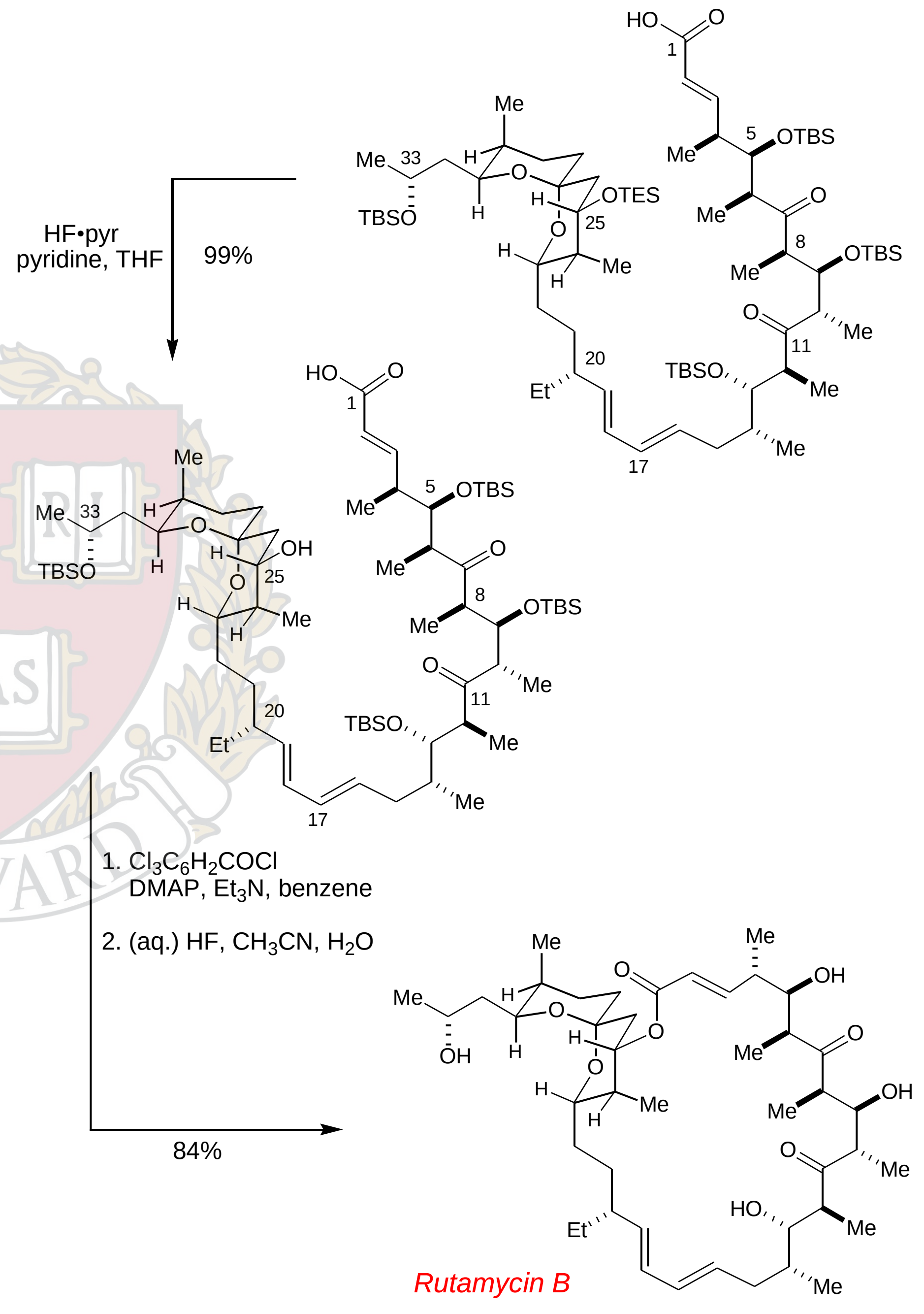


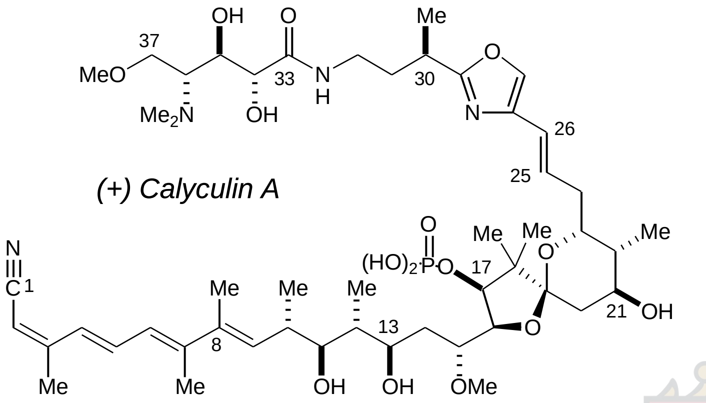
ROH Protecting Groups



Selective silylation was unsuccessful.

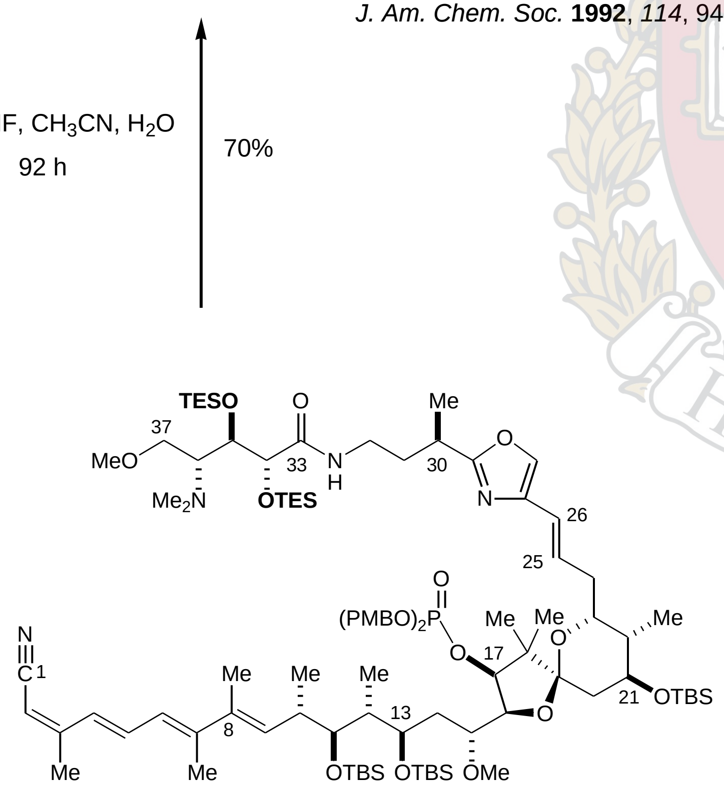


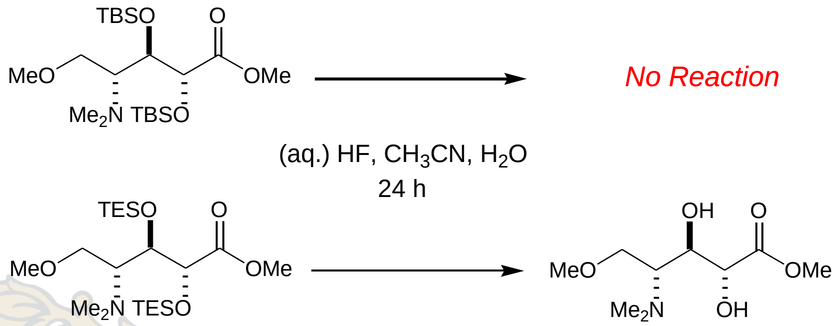




(+) Calyculin A

Evans, D. A.; Gage, J. R.; Leighton, J. L.
J. Am. Chem. Soc. **1992**, *114*, 9434-9453.

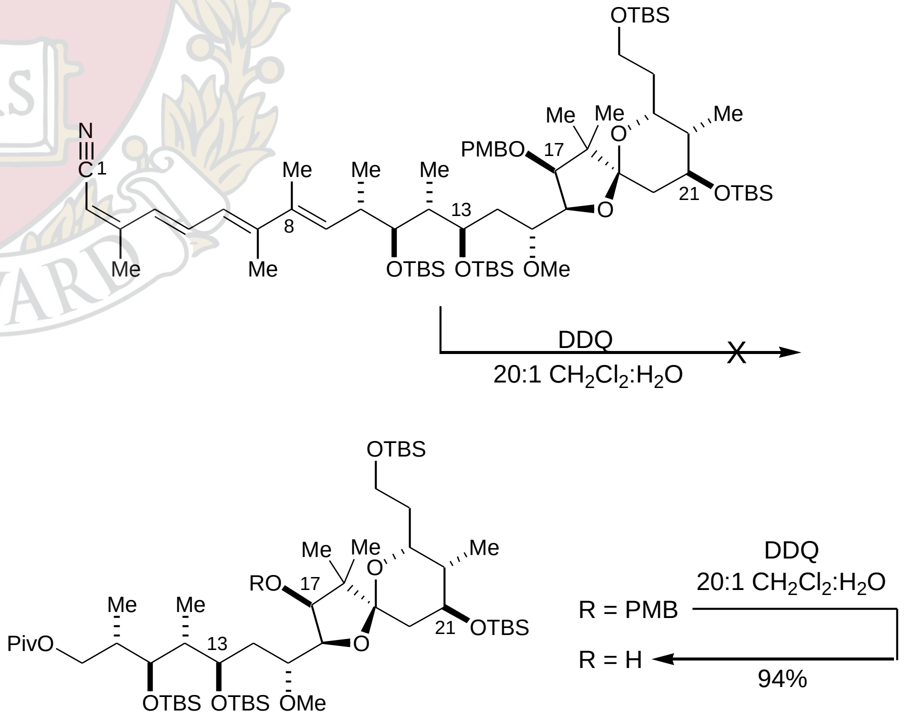

(aq.) HF, CH_3CN, H_2O
92 h
70%



No Reaction

(aq.) HF, CH_3CN, H_2O
24 h

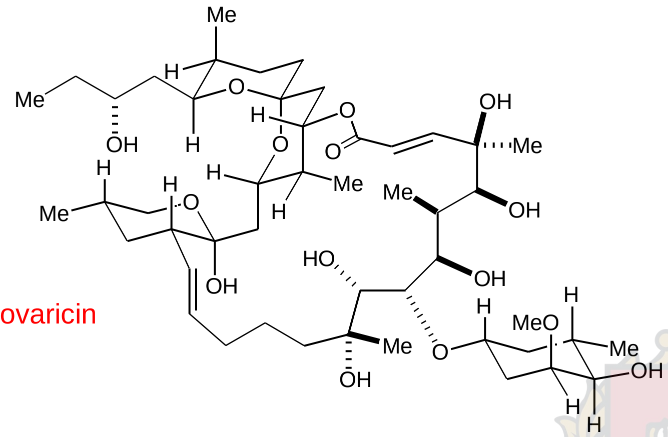
After protonation of the amine, coulombic repulsion insulates against formation of another cationic site in the vicinity.



DDQ
20:1 CH_2Cl_2:H_2O

R = PMB
R = H
DDQ
20:1 CH_2Cl_2:H_2O
94%

ROH Protecting Groups

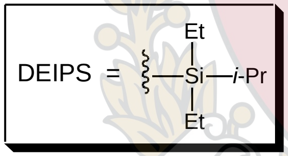


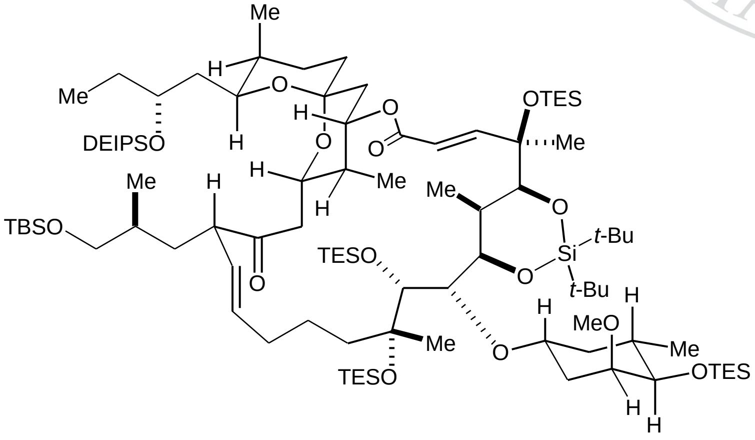
Cytovaricin

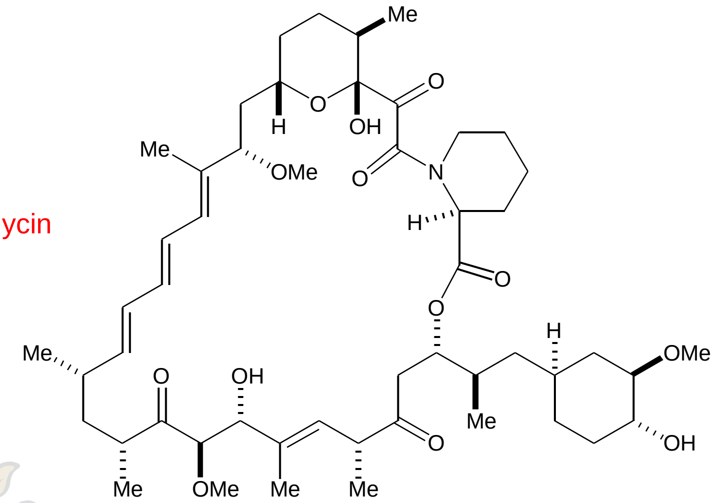
Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J.
J. Am. Chem. Soc. **1990**, *112*, 7001-7031.

HF•pyr, pyridine
THF, RT

74%





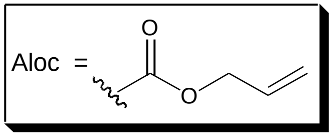


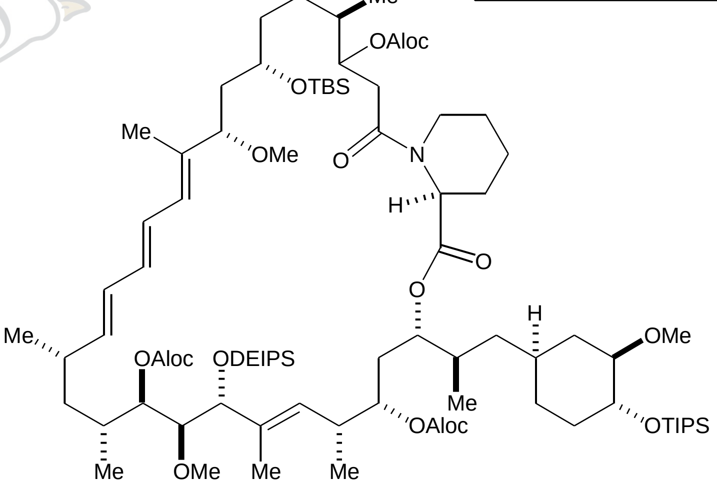
Rapamycin

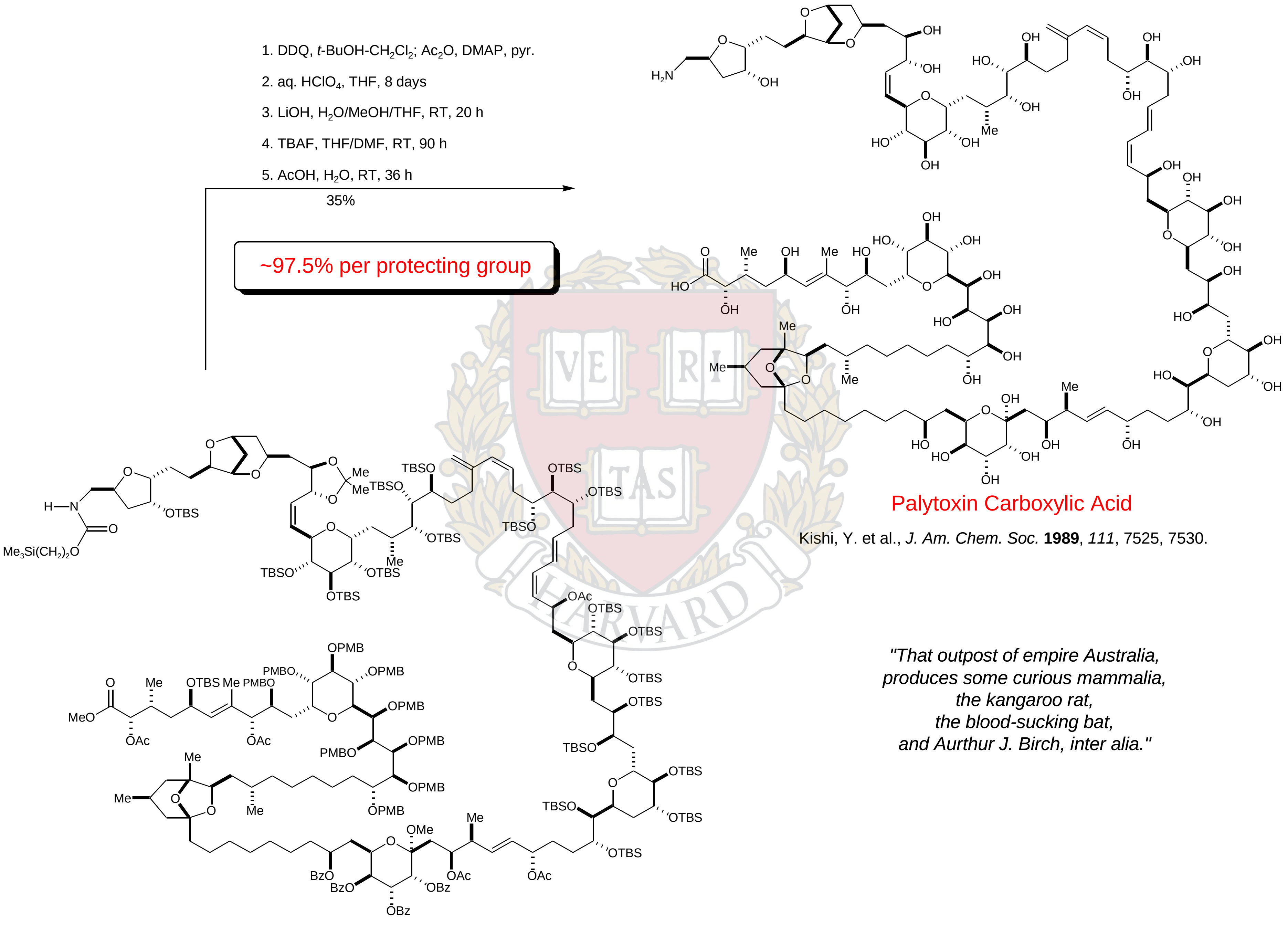
Romo, D.; Meyer, S. D.;
Johnson, D. D.; Schreiber, S. L.
J. Am. Chem. Soc. **1993**, *115*, 7906-7907.

1. $Pd(Ph_3P)_4$, HCO_2NH_4, THF
2. Dess-Martin Periodinane
3. HF•pyr, pyridine, THF

30% overall







1. DDQ, *t*-BuOH-CH$_2$Cl$_2$; Ac$_2$O, DMAP, pyr.
2. aq. HClO$_4$, THF, 8 days
3. LiOH, H$_2$O/MeOH/THF, RT, 20 h
4. TBAF, THF/DMF, RT, 90 h
5. AcOH, H$_2$O, RT, 36 h

35%

~97.5% per protecting group

Palytoxin Carboxylic Acid

Kishi, Y. et al., *J. Am. Chem. Soc.* **1989**, *111*, 7525, 7530.

"That outpost of empire Australia,
produces some curious mammalia,
the kangaroo rat,
the blood-sucking bat,
and Aurthur J. Birch, inter alia."

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 34

Introduction to Carbenes & Carbenoids-1

- Carbene Structure & Electronics
- Methods for Generating Carbenes
- Simmons-Smith Reaction
- Carbene-Olefin Insertions
- Carbene Rearrangements

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part B Chapter 9, " C–C Bond Forming Rxns of Boron, Silicon & Tin", 595–680.

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part B Chapter 10, "Reactions Involving Highly Reactive Electron-Deficient Intermediates", 595–680.

Lecture 09A Simmons-Smith Reaction: Enantioselective Variants
Lecture 26B Synthetic Applications of α-Diazocarbonyl Compounds

Ligand Effects on the Chemoselectivity of Transition Metal Catalyzed Rxns of α-diazocarbonyl Compnds" Padwa et al.Angew Chem Int Ed. **1994**, *33*, 1797

Chiral DirhodiumCarboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta*. **1996**, *29*, 3

"Stable Carbenes–Illusion or reality"? Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674

Matthew D. Shair

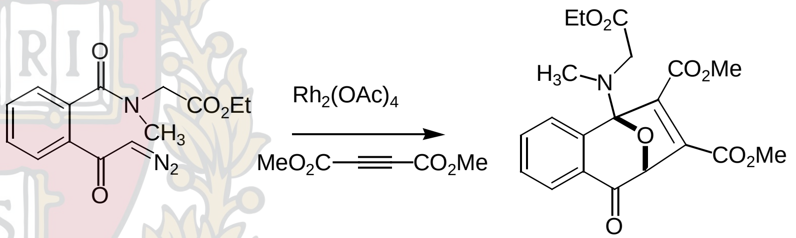
Friday,
December 13 , 2002

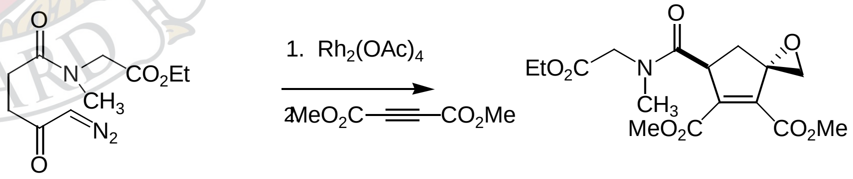
Useful References to the Carbene Literature

Books:
Modern Catalytic methods for Organic Synthesis with Diazo Compounds; M. P. Doyle, Wiley, 1998.

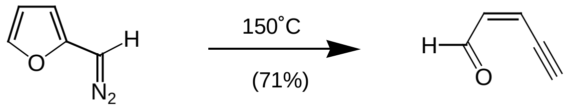
Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

Provide a mechanism for the following transformations.





JACS **1990** 2037



Mandatory Reading:

Doyle, *Chem Rev.* **1988,** *86*, 919.
Kodadek, *Science*, **1992**, *256*, 1544.

Recent Review Article:
Chemistry of Diazocarbonyls: McKervey et al. *Chem Rev*. **1994**, *94*, 1091.

Books:
Modern Catalytic methods for Organic Synthesis with Diazo Compounds; M. P. Doyle, Wiley, 1998.

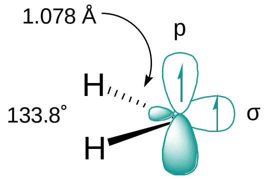
Carbenes and Nitrenes in "Reactive Molecules: The Neutral Reactive Intermediates in Organic Chemistry", Wentrup, C. W. 1984, Wiley, p. 162.

Rearrangements of Carbenes and Nitrenes in Rearrangements in Ground & Excited States, Academic Press, DeMayo ed., Jones, W. M. 1980, p. 95.

Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

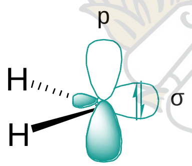
Carbenes: Electronic Structure

Carbene Configuration: Triplet vs. Singlet



Triplet (two unpaired e$^-$)

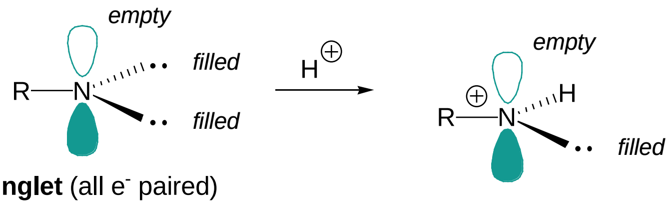
Often has **radical**-like character



Singlet (all e$^-$ paired)

Often has **electrophilic** or **nucleophilic** character: **A**-type (**Ambiphilic**)

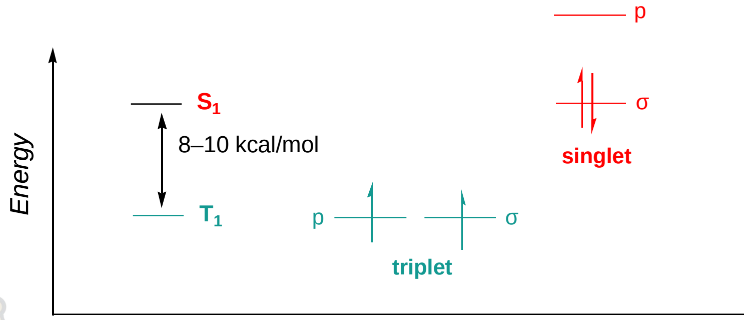
Nitrene



Singlet (all e$^-$ paired)

Nitrenium ion

Carbene Configuration: Triplet vs. Singlet



Due to electron repulsion, there is an energy cost in pairing both electrons in the σ orbital. If a **small energy difference** between the σ and p orbitals exists, the electrons will remain **unpaired (triplet)**. If a **large gap** exists between the σ and p orbitals the electrons will **pair** in the σ orbital (**singlet**).

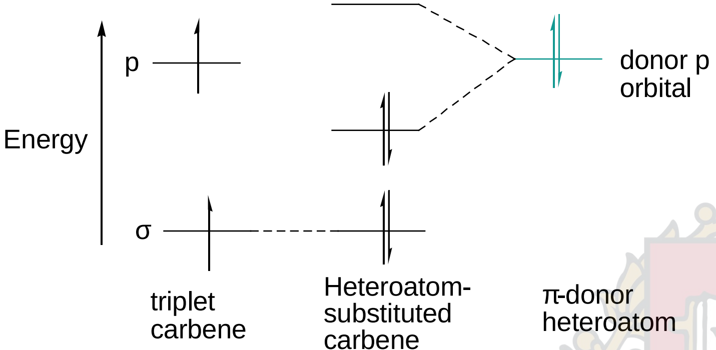
the History of the Singlet-Triplet Gap

Year	Method	Author	HCH Angle	Grnd State	S–T Splitting kcal/mol
1932	Qual.	Muliken	90-100°	*singlet*	—
1947	Thermochem	Walsh	180°	*triplet*	*small*
1957	Qual. QM	Gallup	160°	*triplet*	30
1969	Ab initio	Harrison	138°	*triplet*	>33
1971	Kinetics	Hase	—	*triplet*	8–9
1971	SCF	Pople	132°	*triplet*	19
1974	MINDO	Dewar	134°	*triplet*	8.7
1976	Expt	Lineberger	138°	*triplet*	19.5
1976	An Initio	Schaeffer	—	*triplet*	19.7
1978	**Expt**	**Zare**	**---**	***triplet***	**8.1**
1982	**Expt**	**Haydon**	**---**	***triplet***	**8.5**

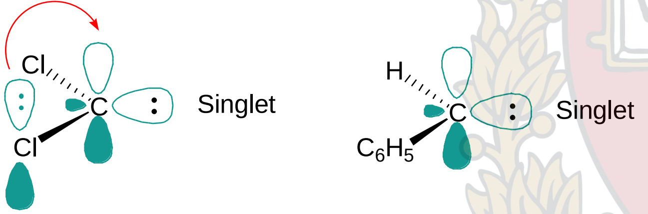
(Wentrup)

Heteroatom-Substituted Carbenes: Singlets

The p orbital of carbenes substituted with **p-donor atoms** (N, O, halogen) is raised high enough in energy to make the pairing of the electrons in the σ orbital energetically favorable. As a result, these carbenes are often in the **singlet** state.

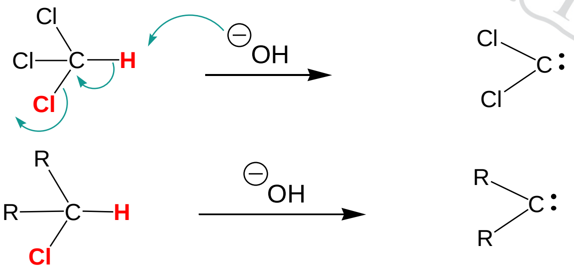


Examples:

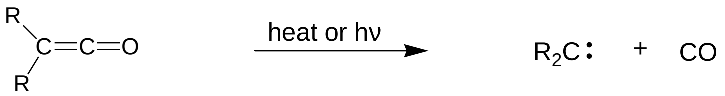


Methods of Synthesis

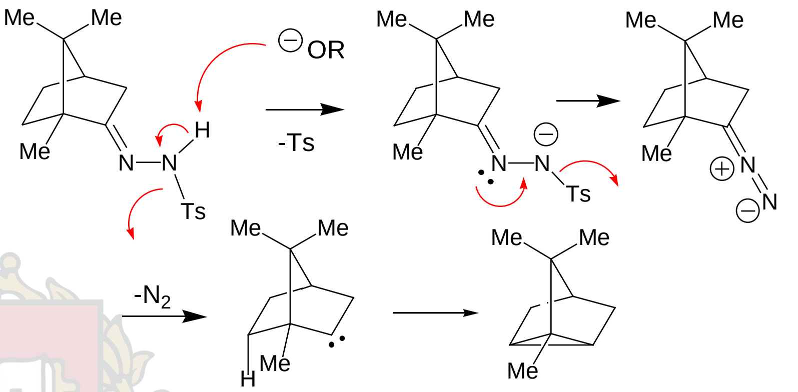
Alkyl Halides:



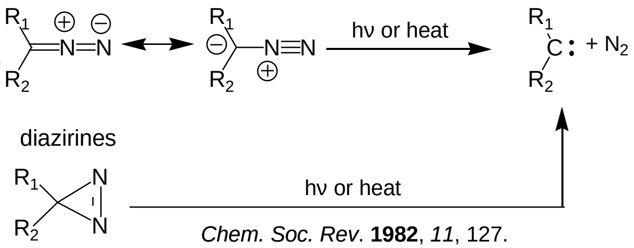
ketenes



Bamford-Stevens Reaction: See Lecture 28 on Hydrazones
Shapiro *Org. Rxns.* **1976**, *23*, 405.

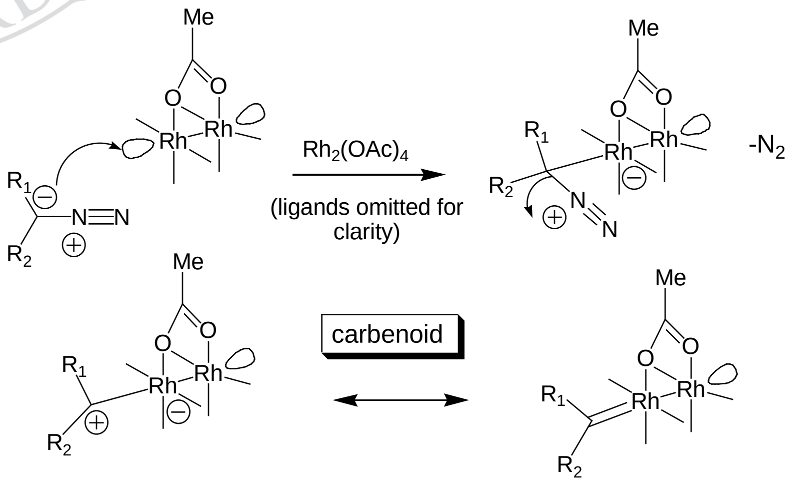


diazo compounds



Chem. Soc. Rev. **1982**, *11*, 127.

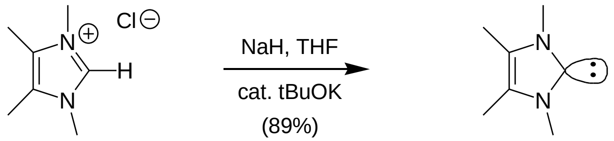
metal-catalyzed decomposition Doyle *Chem Rev*. **1988**, *86*, 919.



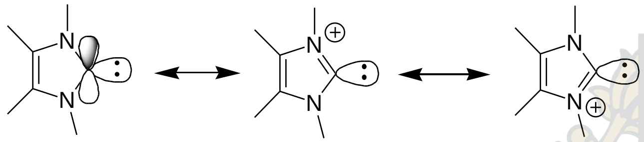
Carbenes: Structure and Generation

"Stable Carbenes"

"Stable Carbenes–Illusion or reality"?
Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674



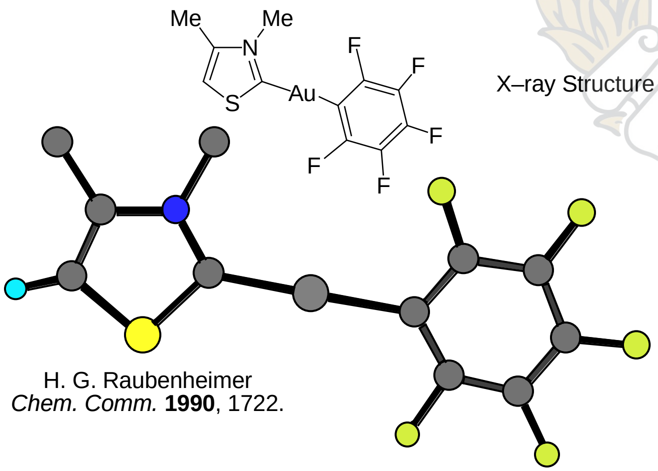
Arduengo et al. *J. Am. Chem. Soc.* **1991**, *113*, 361; **1992**, *114*, 5530.
Arduengo et al. *J. Am. Chem. Soc.* **1994**, *116*, 6812, Neutron diffraction study:



Arduengo argues that these resonance structures are not players based on electron distribution from neutron diffraction.

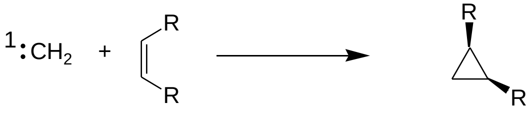
These are nucleophilic carbenes which display high stability.

For reviews on the subject, see:
Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 725.
Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674.

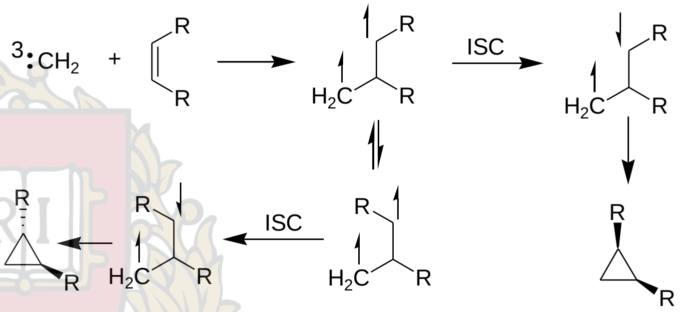


H. G. Raubenheimer
Chem. Comm. **1990**, 1722.

Cyclopropanation The Skell Rule:



Singlet carbenes add to olefins **stereospecifically**;

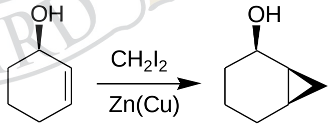


Triplet carbenes add **non-stereospecifically**

Skell and Woodworth *JACS*, **1956**, *78*, 4496.

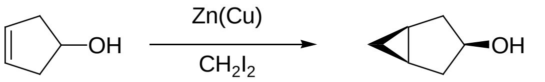
Simmons-Smith Cyclopropanation (See Tedrow hanndout 09B)

Simmons, H.; Smith, R. *J. Am. Chem. Soc.*, **1958**, *80*, 5323.



>99:1 diastereoselectivity

The intermediate organometallic reagent: I–CH$_2$–Zn–I

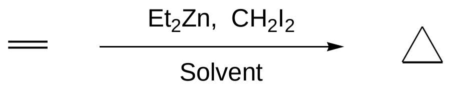


150:1 cis : trans 75% yield

Winstein & Sonnenberg, *JACS* **1961**, *91*, 3235

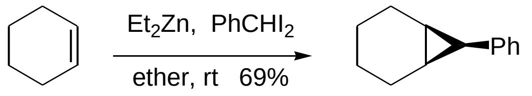
The Furakawa Simmons-Smith Variant

For a recent general review of the Simmons-Smith reaction see: Charette & Beauchemin, *Organic Reactions*, **58**, 1-415 (2001)



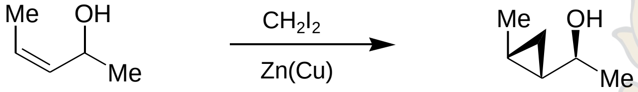
$$\text{Et–Zn–Et} + \text{I–CH}_2\text{–I} \rightleftharpoons 2\ \text{I–CH}_2\text{–Zn–Et}$$

Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron,* **1968,** *24,* 53
Furukawa, J.; Kawabata, N.; Fujita, T. *Tetrahedron,* **1970,** *26,* 243

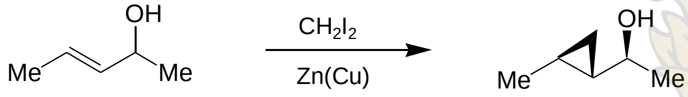


syn : anti
94 : 6

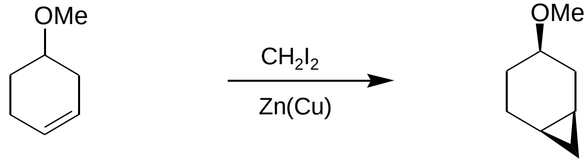
Hydroxyl directivity is a powerful atribute of the S–S Rxn



>99:1 diastereoselectivity

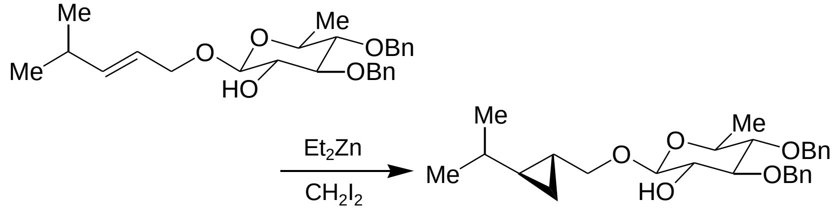


no diastereoselectivity



>99:1 diastereoselectivity

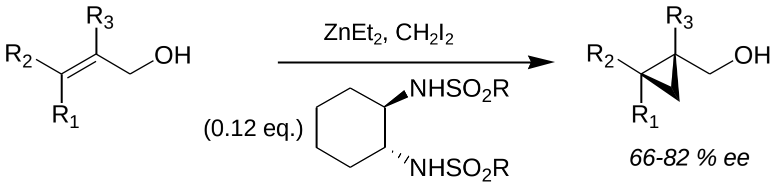
For an review of the directed Simmons-Smith, see:
with A. Hoveyda and G. Fu *Chem. Rev.* **1993**, *93*, 1307.



Charette, A. B. *JACS* **1991**, *113*, 8166.

>50 : 1 diastereoselection

Catalytic Asymmetric Cyclopropanation:

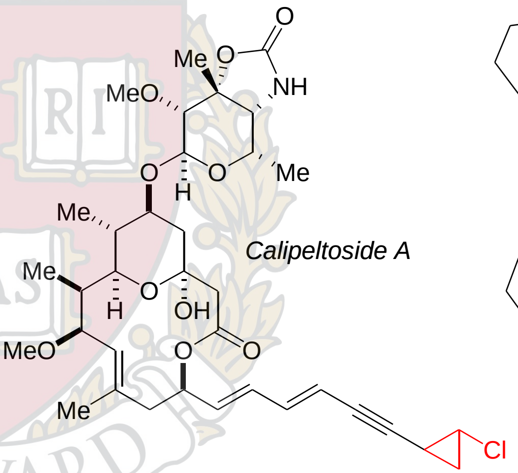


66-82 % ee

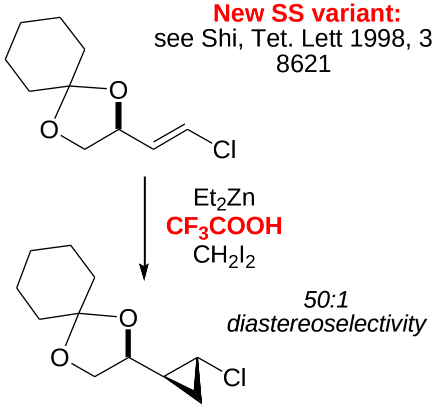
Kobayashi, et al. *Tetrahedron Lett*. **1994**, *35*, 7045.

For a Lewis Acid catalyzed process in which the rate of the catalyzed process is faster than the uncatalyzed, see: Charette, A. B. *JACS* **1995**, *117*, 11367.

Applications in Synthesis



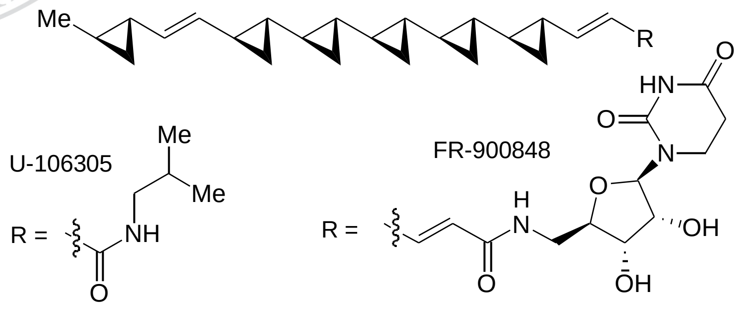
Calipeltoside A



New SS variant:
see Shi, Tet. Lett 1998, 39, 8621

50:1 diastereoselectivity

with Burch
Org. Lett. **2001**, *3*, 503



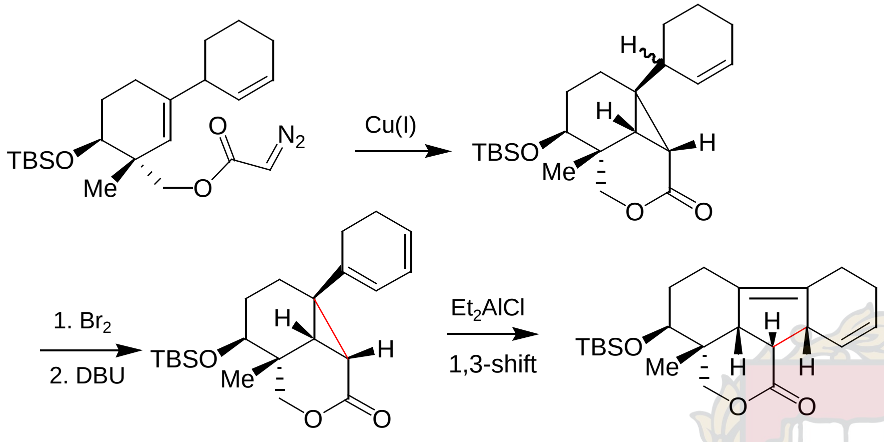
Charrette, A. B.; *J. Am. Chem. Soc.* **1996**, *118*, 10327.

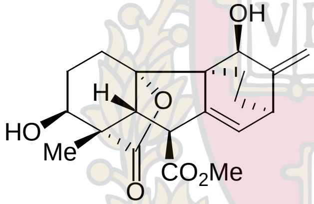
Falck *J. Am. Chem. Soc.* **1996**, *118*, 6096.

Barrett, *JOC*, **1996**, *61*, 3280.

Carbenoids: Cyclopropanation

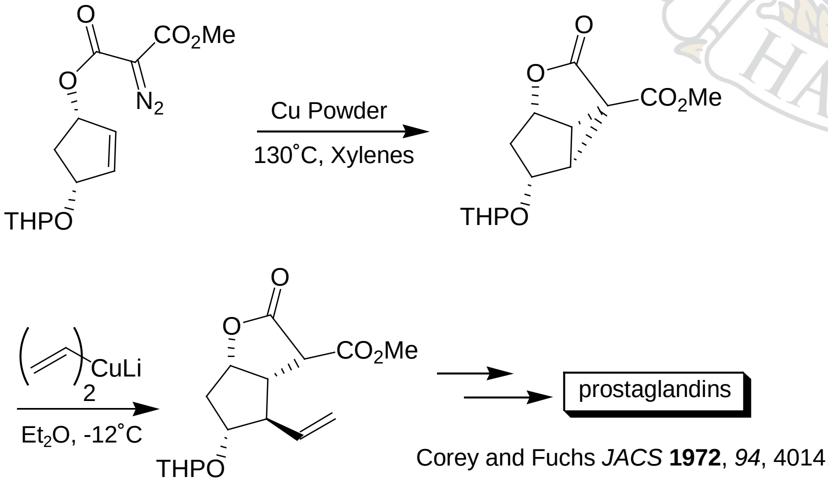
Synthetic Applications





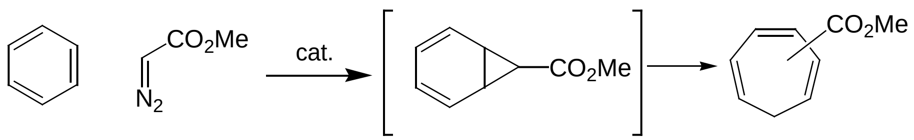
Antheridic Acid

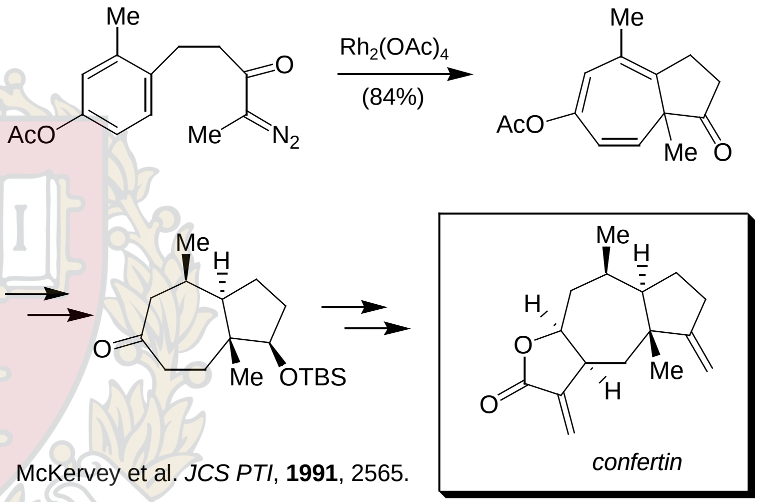
Corey & Myers *JACS* **1985**, *107*, 5574.



Corey and Fuchs *JACS* **1972**, *94*, 4014.

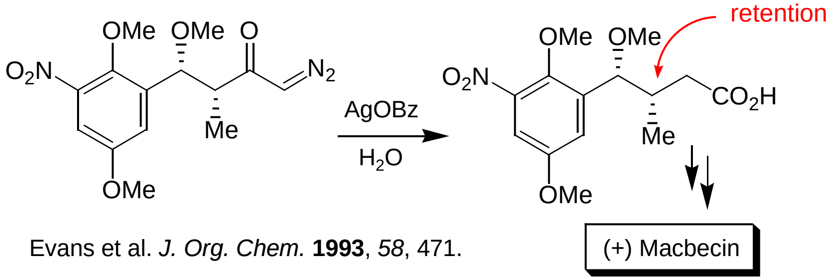
Buchner Reaction





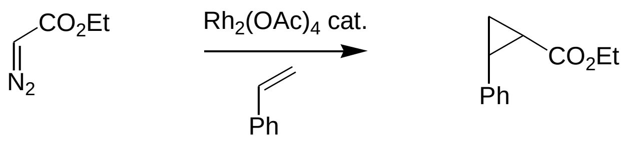
McKervey et al. *JCS PTI*, **1991**, 2565.

Wolff Rearrangement



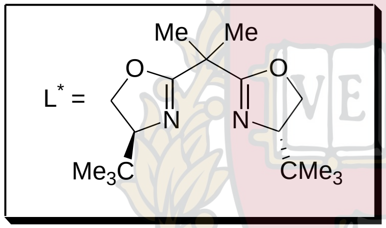
Evans et al. *J. Org. Chem.* **1993**, *58*, 471.

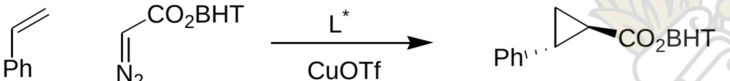
Carbenes: Enantioselective Cyclopropanation



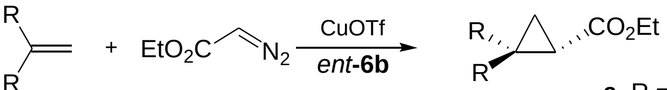
** For a detailed mechanistic study which provides supporting evidence for the intermediacy of a Rh carbene, see: Kodakek, *Science*, **1992**, *256*, 1544.

Catalytic Asymmetric Variants: Chiral Cu(I) Complexes





99% ee
94:6 trans/cis

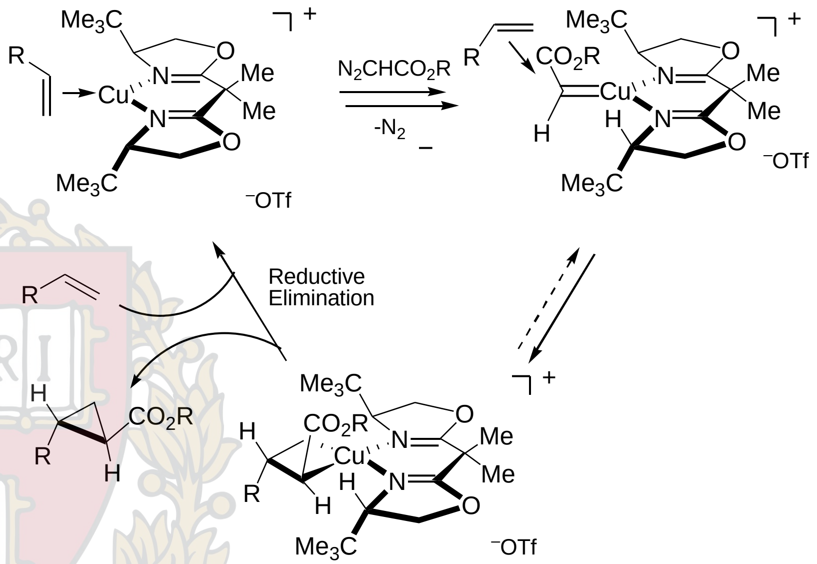


a, R = Ph, >99% ee
b, R = Me, >99% ee

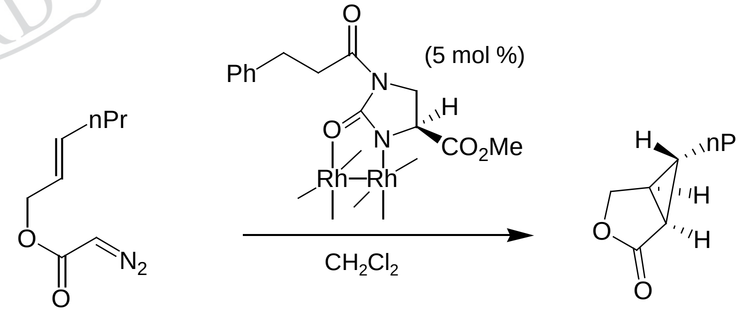
Evans, et al. *J. Am. Chem. Soc.* **1991**, *113*, 726.

Mechanism

There is no definitive evidence for metal-catalyzed cyclopropanation and the possibility that metallacyclobutane intermediates are involved cannot be ruled out.



Catalytic Asymmetric Variants:Chiral Rh(II) Complexes

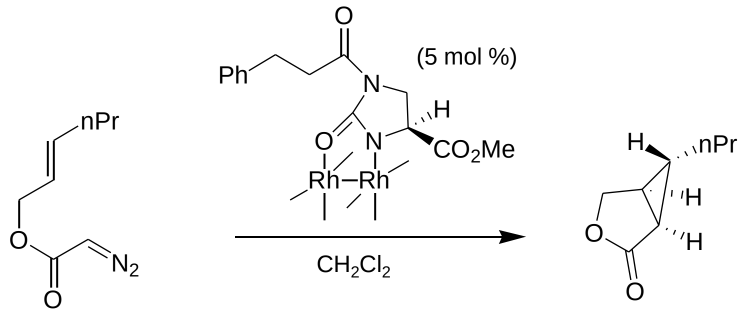


Doyle et al. *Tetrahedron Lett.* **1995**, *36*, 7579.

95% ee

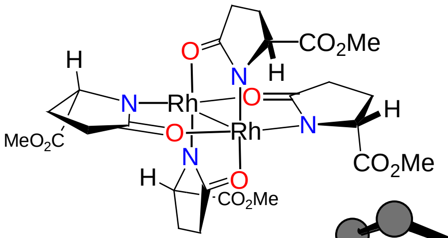
How do these complexes really work??

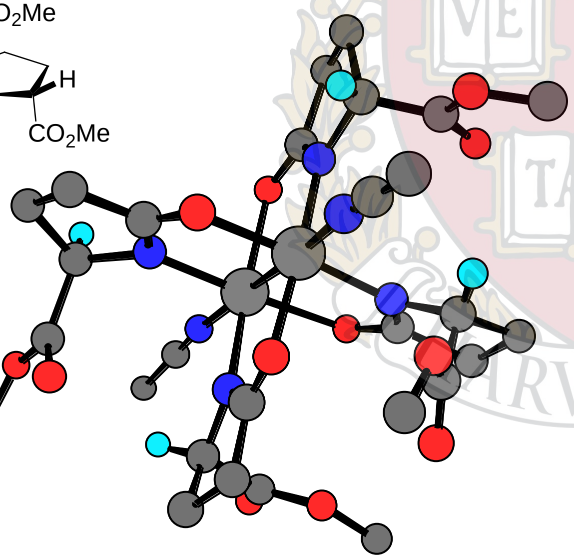
Catalytic Asymmetric Variants:Chiral Rh(II) Complexes



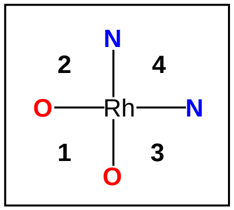
95% ee

Doyle et al. *Tetrahedron Lett.* **1995**, *36*, 7579.





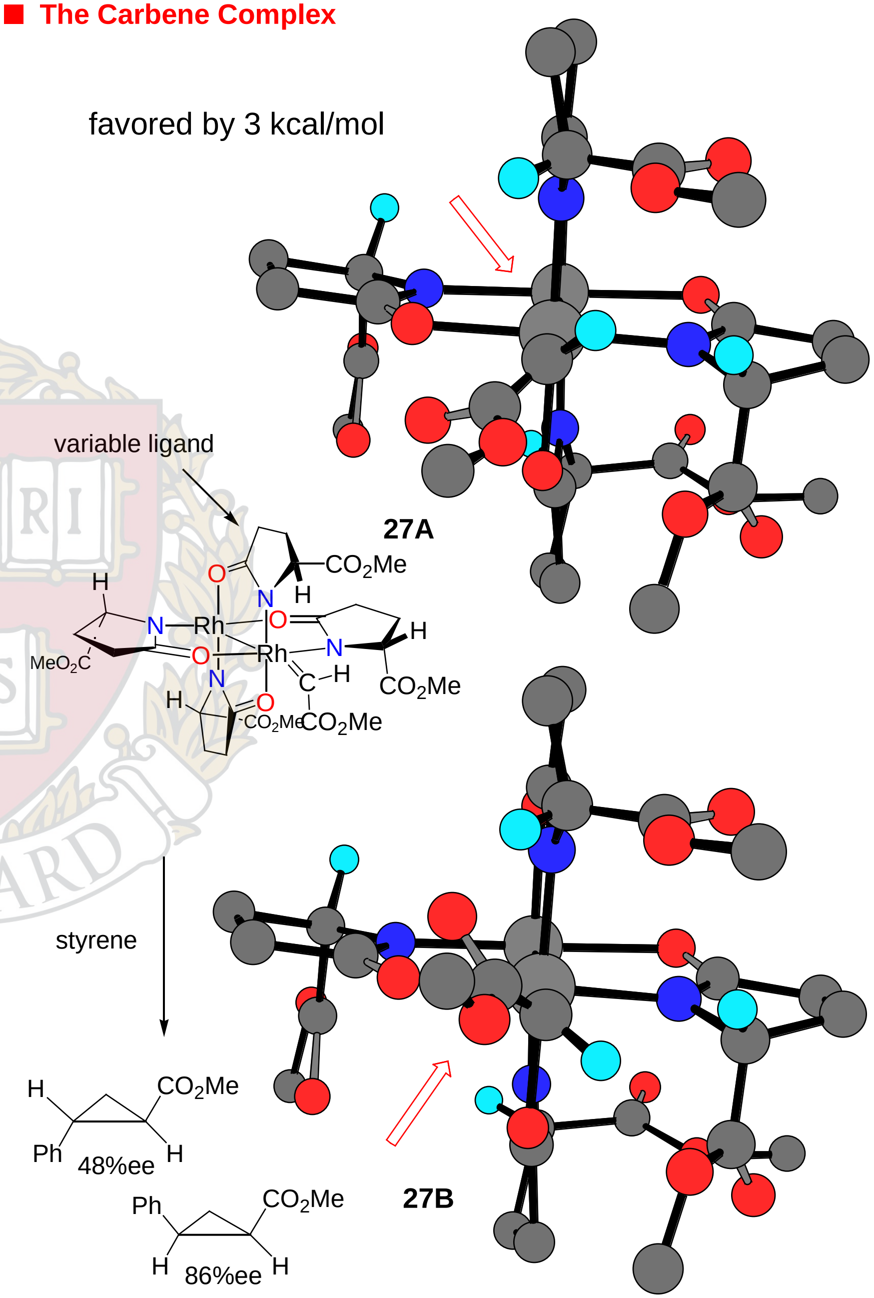
Note N–O trans influence



Numbers designate increasing steric
hindrance in each quadrant

Doyle, *JACS* **1993**, *115*, 9968

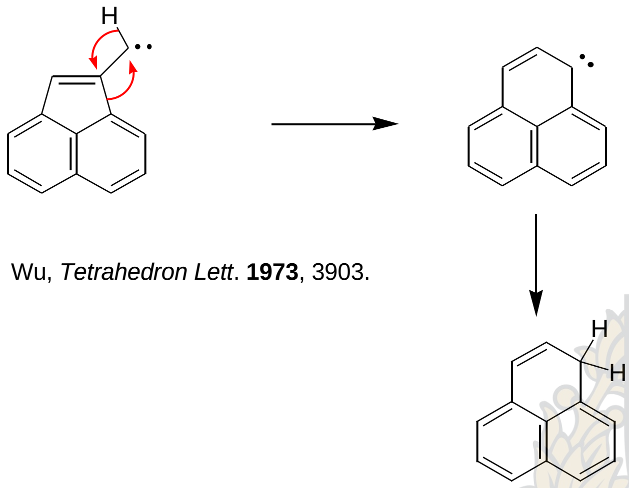
The Carbene Complex



27A

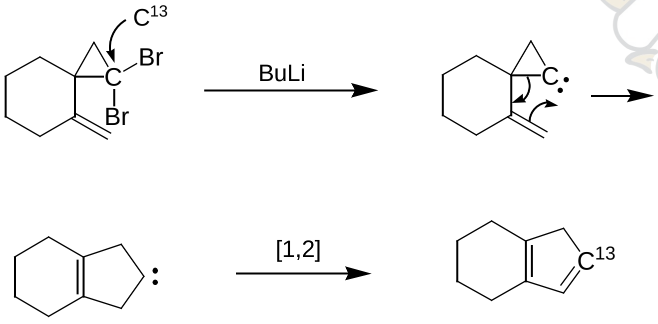
27B

Carbene-Carbene Rearrangements



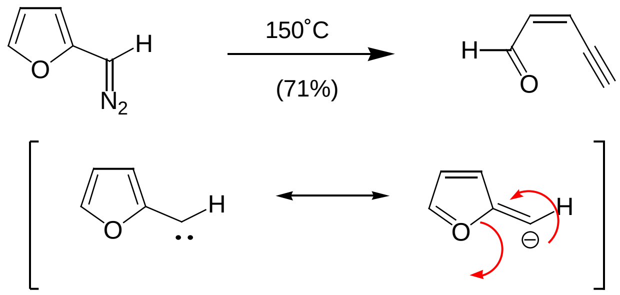
Wu, *Tetrahedron Lett*. **1973**, 3903.

Skattebol Rearrangement

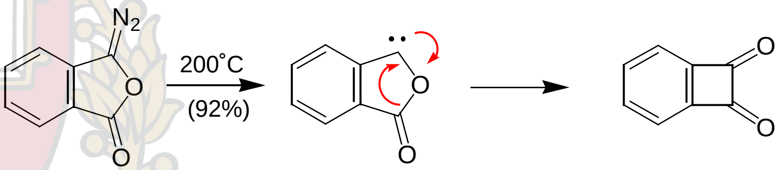


Tetrahedron Lett. **1973**, 2283.

Other Rearrangements



Schecter, *J. Am. Chem. Soc.* **1971**, *93*, 5940.

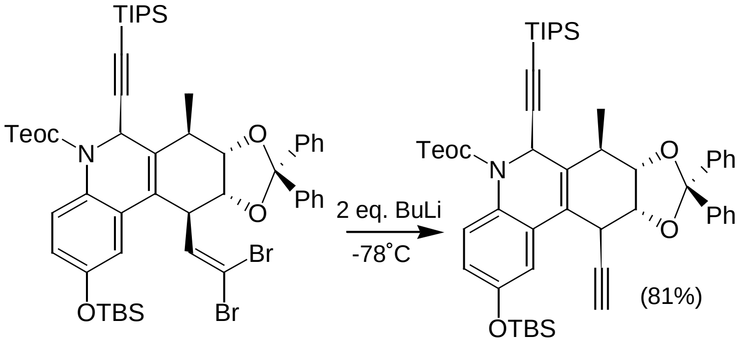


Sammes, *Chem. Comm*. **1975**, 328.

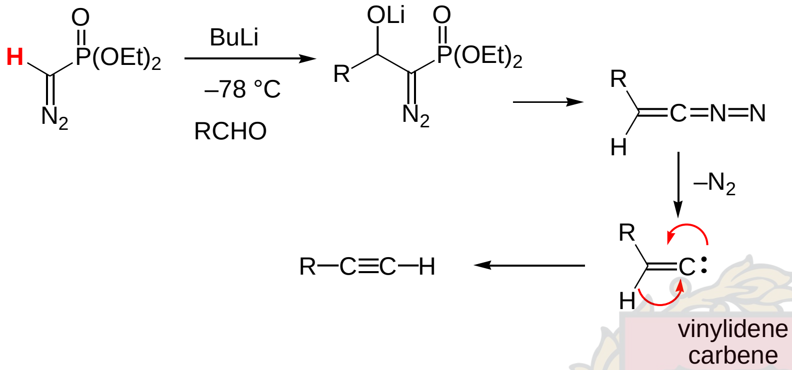
Vinylidenes

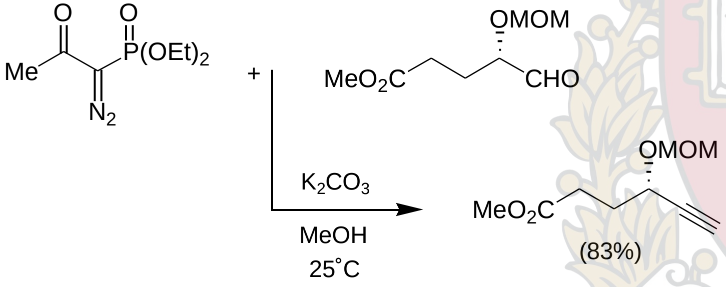
Corey-Fuchs:

Danishefsky et al.
J. Am. Chem. Soc. **1996**, *118*, 9509.

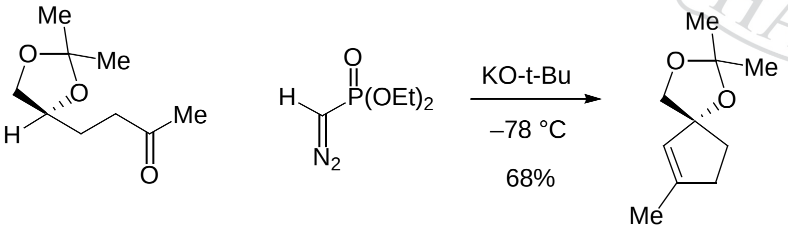


Carbene Rearrangements

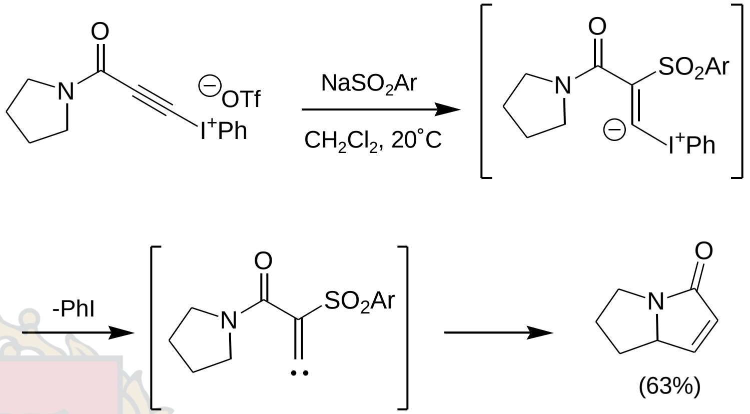




Bestmann, et al. *Synlett* **1996**, 521.

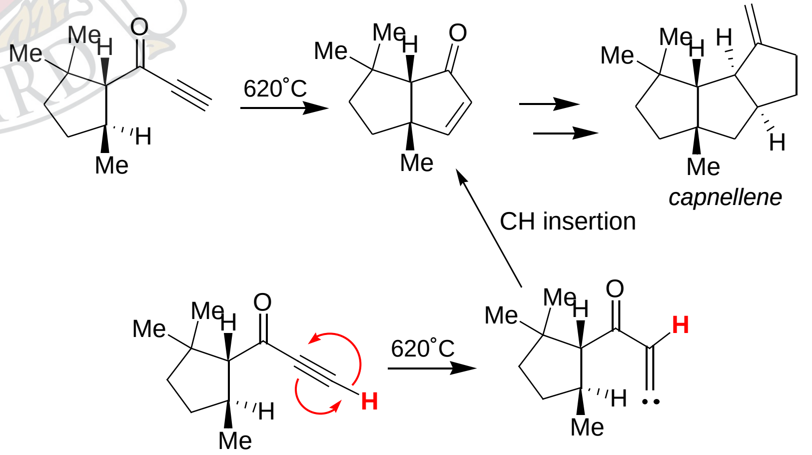


Gilbert, *JOC* **1983**, *48*, 5251

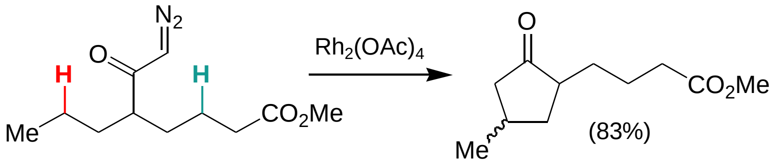


Stang et al. *J. Am. Chem. Soc.* **1994**, *116*, 93.

carbene intermediates are accessible at high temperatures, more later!

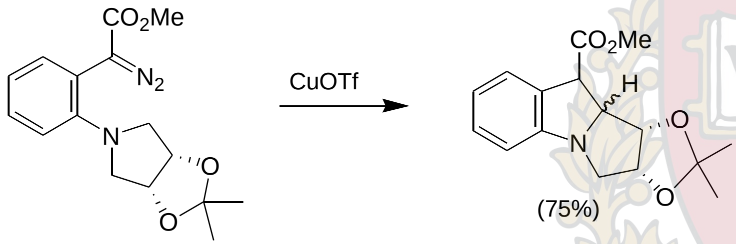


C–H Insertions continued...



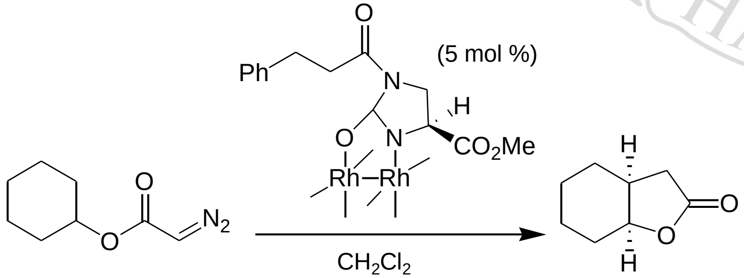
Electrophilic carbenes are very sensitive to electronic effects

Stork *Tetrahedron Lett.* **1988**, *29*, 2283.



Sulikowski, *J. Org. Chem*. **1995**, *60*, 2326.

Enantioselective C-H Insertion

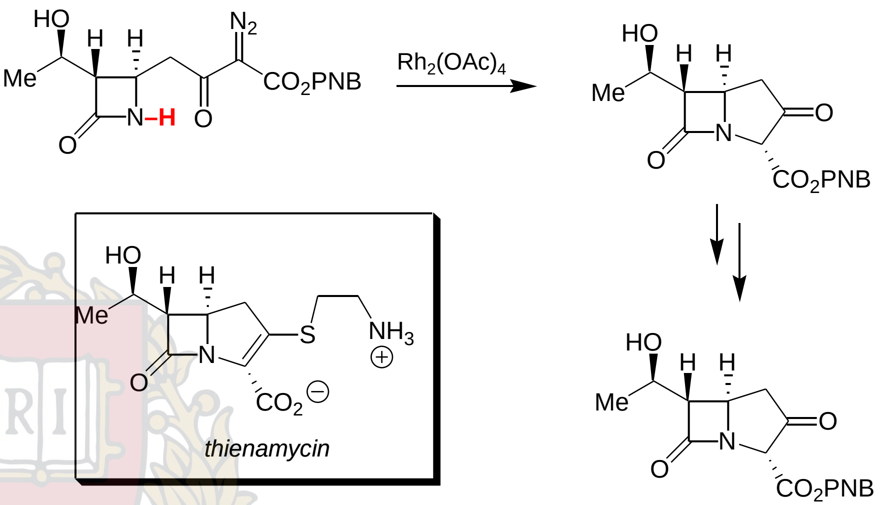


Doyle, *JACS* **1994**, *116*, 4507

99%, 97% ee

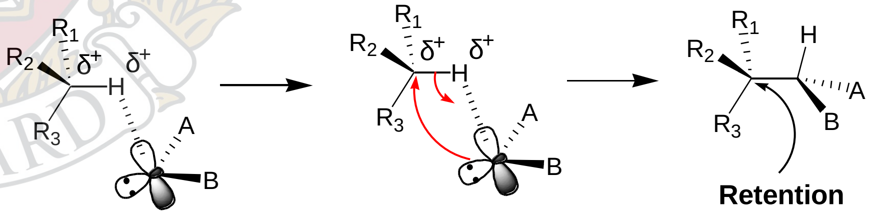
Chiral DirhodiumCarboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta*. **1996**, *29*, 3

N–H Insertions are also possible...

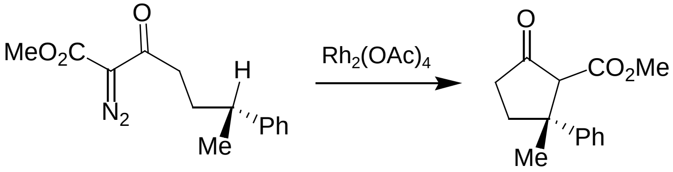


Salzmann, *JACS*, **1980**, *102*, 6163.

Insertions (X-H): Stereochemical outcome

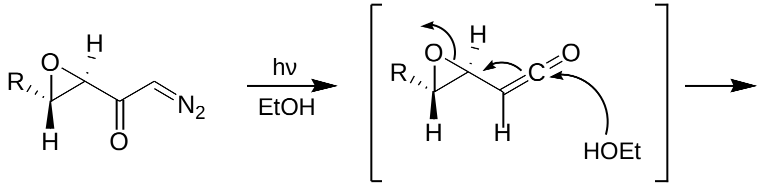


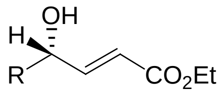
Retention



Taber *JACS*, **1996**, *107*, 196.

Ring Opening

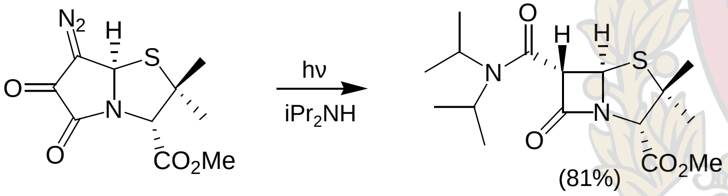




(88%

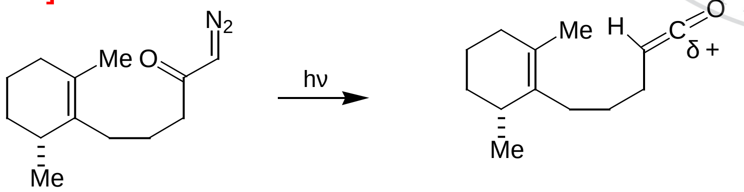
Tetrahedron Lett. **1990**, *31*, 6589.

Ring Contraction

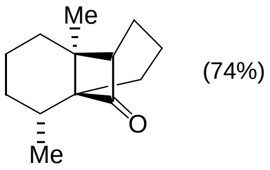


Moore et al. *J. Org. Chem.* **1983**, *48*, 3365.

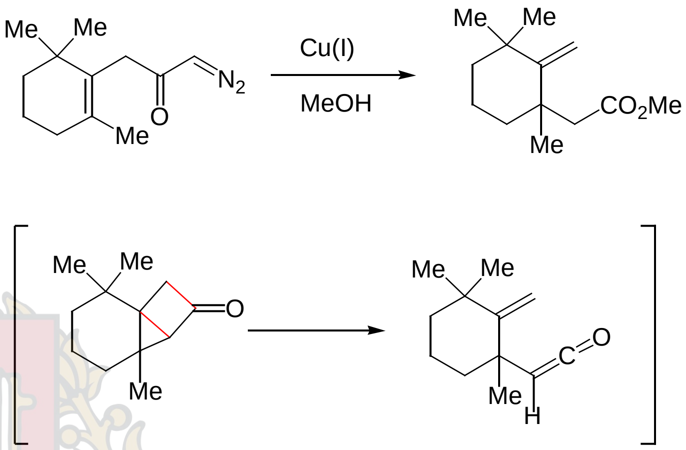
Wolff-[2+2]



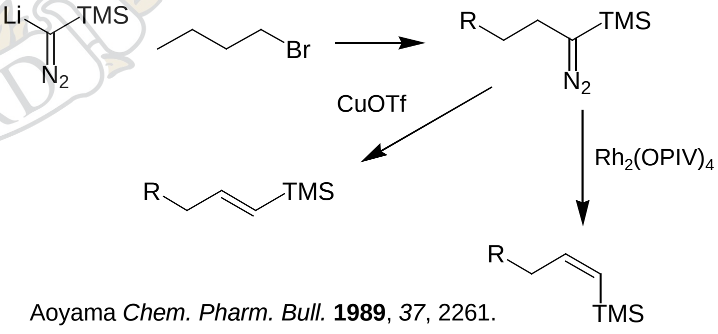
J. Org. Chem. **1980**, *45*, 2708.



Vinylolgous Wolff Rearrangement Doyle pp520-521



[1,2]-Rearrangements



Aoyama *Chem. Pharm. Bull.* **1989**, *37*, 2261.

http://www.courses.fas.harvard.edu/~chem206/

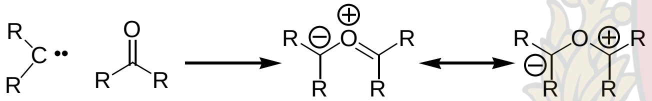
Chemistry 206

Advanced Organic Chemistry

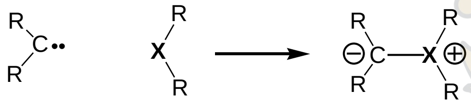
Lecture Number 35

Introduction to Carbenes & Carbenoids-2

- Thermally Induced Carbene Rearrangements
- Carbonyl Ylides and their Reactions



- Oxonium & Sulfonium Ylides and their Reactions



Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part B Chapter 10, "Reactiona Involving Highly Reactive Electron-Deficient Intermediates", 263-350 .

Lecture 09A Simmons-Smith Reaction: Enantioselective Variants
Lecture 26B Synthetic Applications of α-Diazocarbonyl Compounds
Lecture 35A The Use of Fischer Carbenes in Organic Synthesis
Lecture 35B The Synthetic Applications of Carbonyl Ylides

Matthew D. Shair

Monday,
December 16 , 2002

Useful References to the Carbene Literature

Recent Review Article:
Chemistry of Diazocarbonyls: McKervey et al. *Chem Rev*. **1994**, *94*, 1091.

Books:
Modern Catalytic methods for Organic Synthesis with Diazo Compounds; M. P. Doyle, Wiley, 1998.

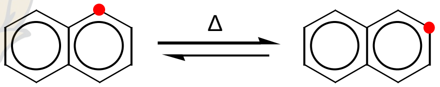
Carbenes and Nitrenes in "Reactive Molecules: The Neutral Reactive Intermediates in Organic Chemistry", Wentrup, C. W. 1984, Wiley, p. 162.

Rearrangements of Carbenes and Nitrenes in Rearrangements in Ground & Excited States, Academic Press, DeMayo ed., Jones, W. M. 1980, p. 95.

Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

The Automerization of Naphthalene (The Cume Question from Hell!)

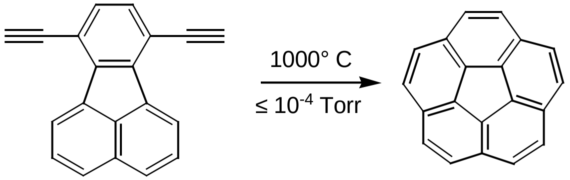
Rationalize



α–^{13}C-labeled $C_{10}H_8$ is isomerized into β–^{13}C-labeled $C_{10}H_8$ at 1035 °C

L. T. Scott, *JACS* **1991**, *113*, 9692.

Provide a Mechanism for this Transformation

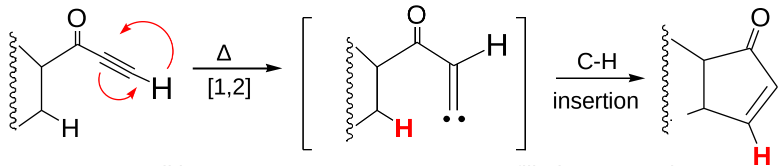


Corannulene 10%

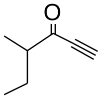
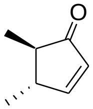
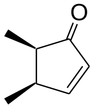
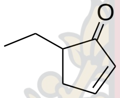
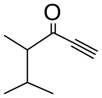
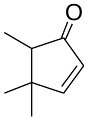
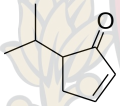
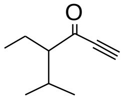
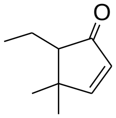
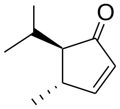
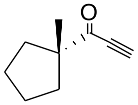
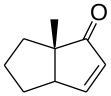
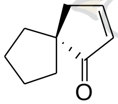
Scott, L.T., et. al., *JACS* **113** 7082 (1991)

Carbenes are Accessible via Sigmatropic Rearrangement

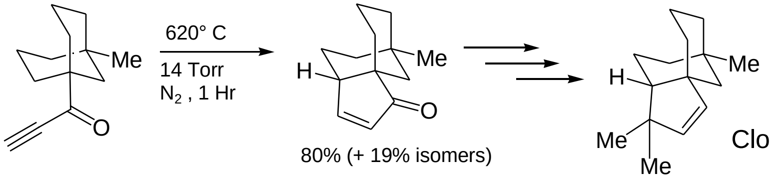
[1,2] Shifts: Alpha-Alkynone Cyclizations



Conditions: 620° C, 12-16 Torr, Quartz filled Quartz Tube

S.M.	3°	2°	1°	Recovery
	–	 60  22	 18	80%
	 87	–	 13	78%
	 54	 46	–	89%
	–	 92	 8	90%

Karpf, M., Dreiding, A., *Helv. Chim. Acta.* **65** 13 (1982)



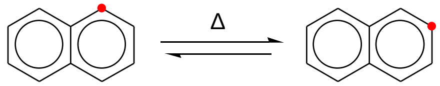
80% (+ 19% isomers)

Clovene

Karpf, M., Dreiding, A.S., *Helv. Chim. Acta.* **67** 1963 (1984)

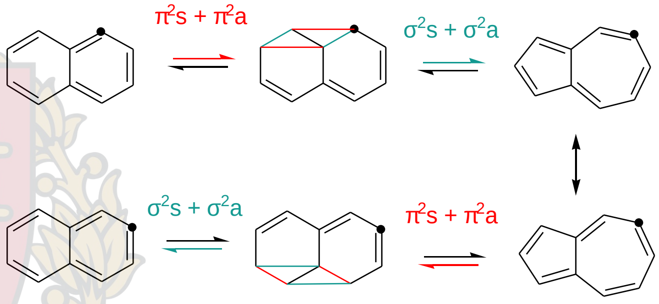
The Automerization of Naphthalene (The Cume Question from Hell!)

Rationalize



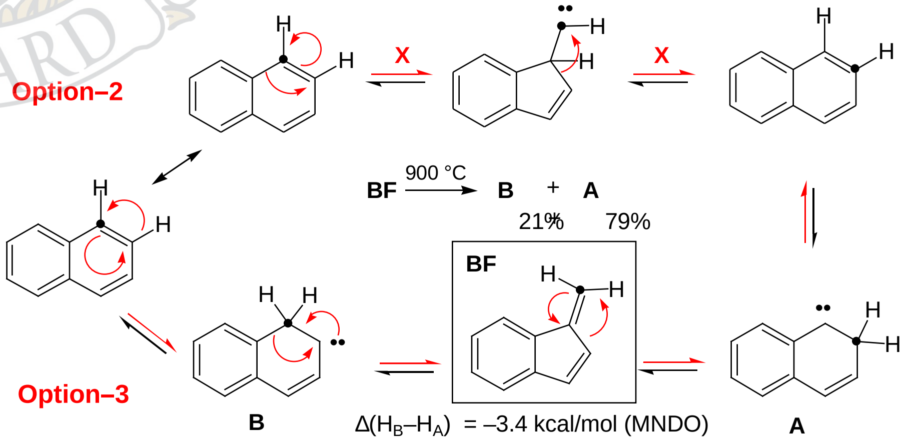
α–^{13}C-labeled $C_{10}H_8$ is isomerized into β–^{13}C-labeled $C_{10}H_8$ at 1035 °C

Mechanism-1: L. T. Scott, *JACS* **1977**, *99*, 4506;



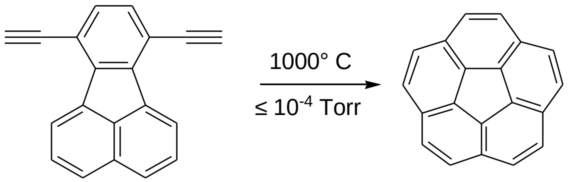
- For the azulene–naphthalene Isomerization: ΔG° = –30.7 kcal/mol (298K)
- The Activation energy for the isomerization: ΔG$^{\pm}$ = +86 kcal/mol

Mechanism-2,3: L. T. Scott, *JACS* **1991**, *113*, 9692.



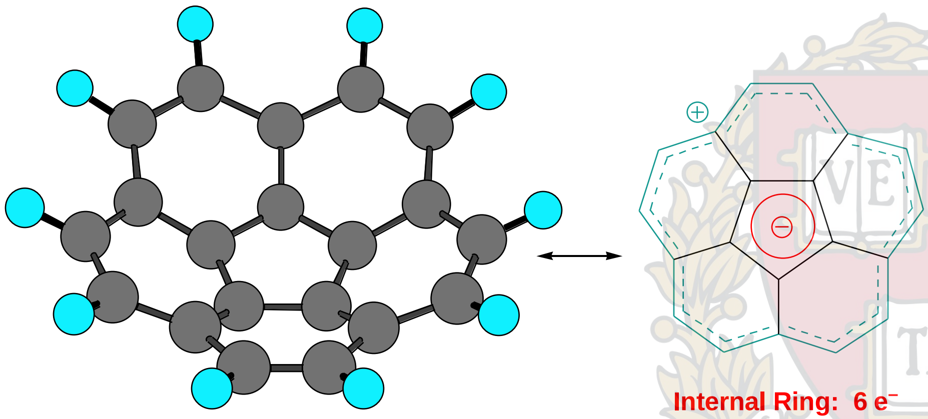
Δ(H_B–H_A) = –3.4 kcal/mol (MNDO)

Provide a Mechanism for this Transformation



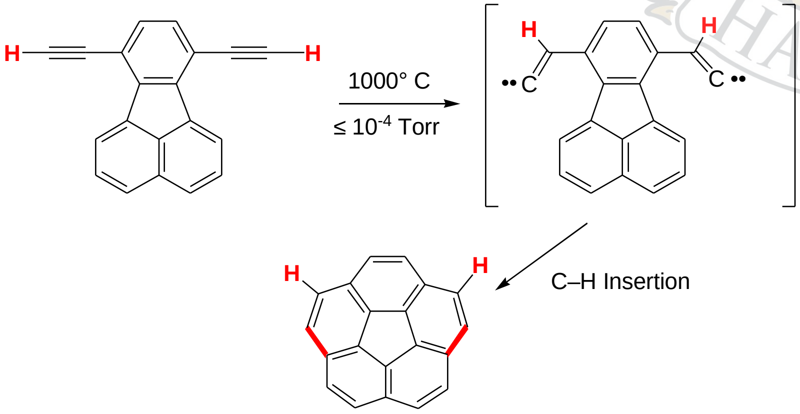
Corannulene 10%

Scott, L.T., et. al., *JACS* **113** 7082 (1991)



Internal Ring: 6 e⁻

External Ring: 14 e⁻



Carbenes: Reaction with Heteroatoms

Suggested Reading

Houk and Wu *J. Org. Chem.* **1991**, *56*, 5657.

Padwa and Hornbuckle *Chem. Rev.* **1991**, *91*, 263.

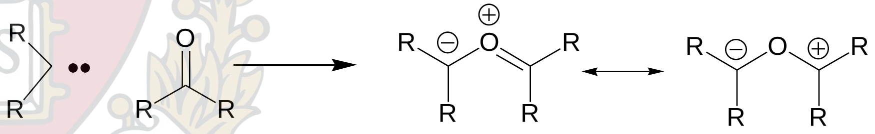
Review Articles

Padwa and Krumpe *Tetrahedron* **1992**, *48*, 5385.

Hoffman, R. W. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 563.

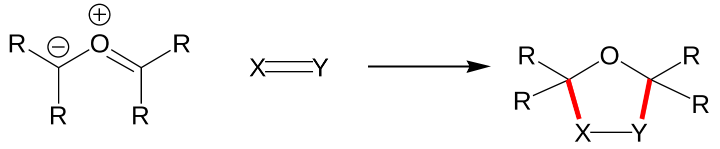
McKervey et al. *Chem. Rev.* **1994**, *94*, 1091.

Ylide Formation by the Interaction of Carbeneoids with Carbonyl Lone Pairs



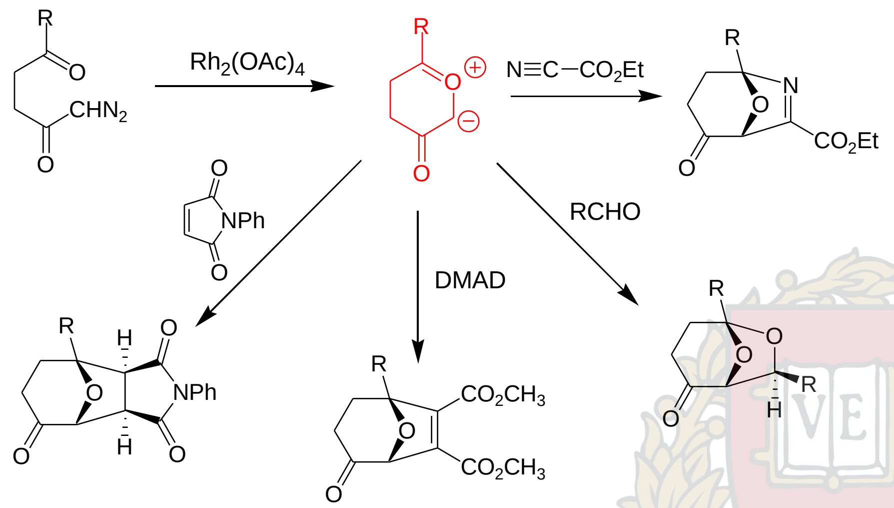
Generally, the carbene precursor of choice is a diazoalkane or, more frequently, an α-diazocarbonyl reagent. These can be decomposed via thermolysis or photolysis. However, the most common method involves catalytic amounts of transition metals, such as copper or rhodium.

Dipolar Cycloaddition



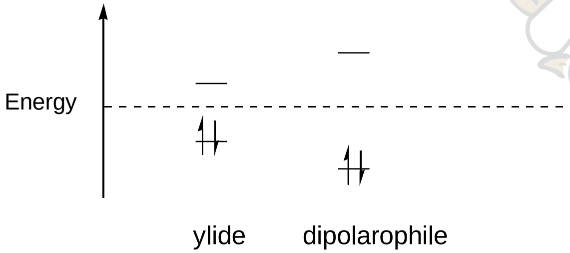
Carbonyl Ylids: Dipolar Cycloaddition

Tandem Intramolecular Cyclization–Intermolecular Cycloaddition

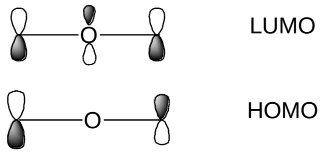


Dipolar-Dipolarophile Cycloadditions: HOMO–LUMO Energies

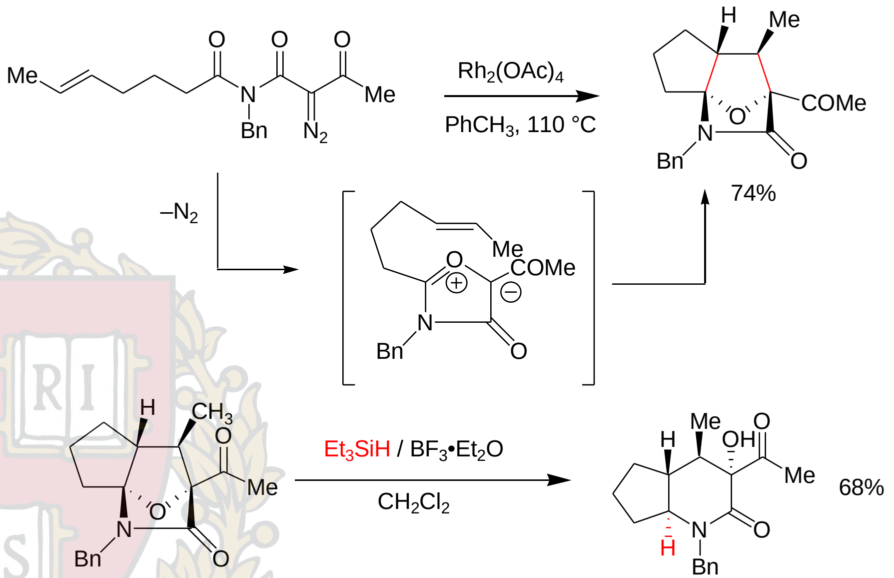
Carbonyl Ylides have very small HOMO-LUMO gaps



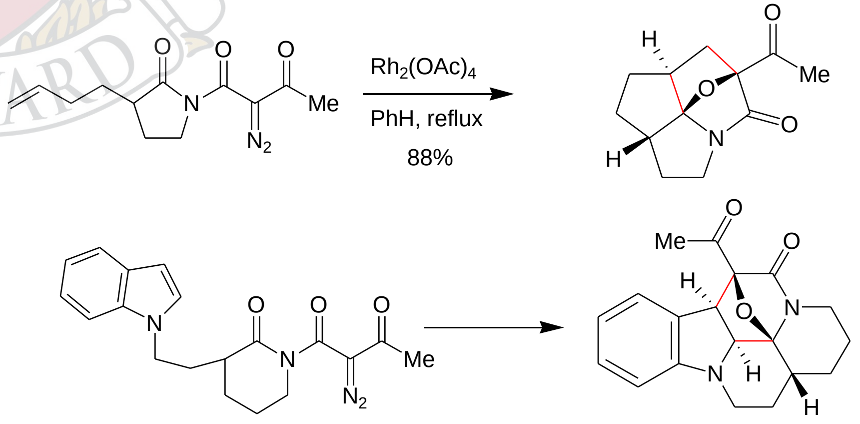
Therefore, either raising the dipolarophile HOMO (electron-donating substituents) or lowering the LUMO (electron-withdrawing) will accelerate the reaction.



Reactions of Diazoimides: [3+2] addition



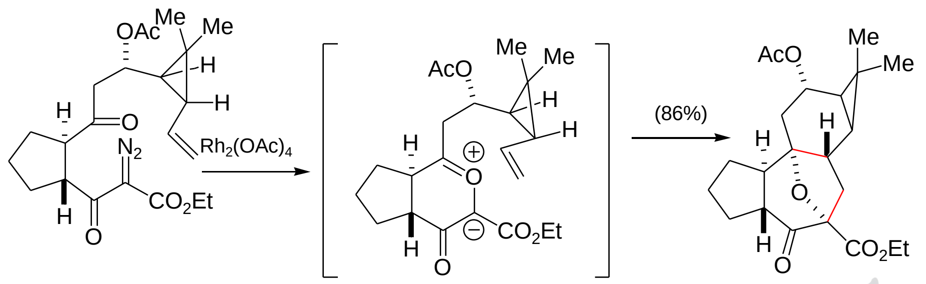
Maier, M. E.; Evertz, K. *Tetrahedron Lett*. **1988**, *29*, 1677-1680.



"high yield"

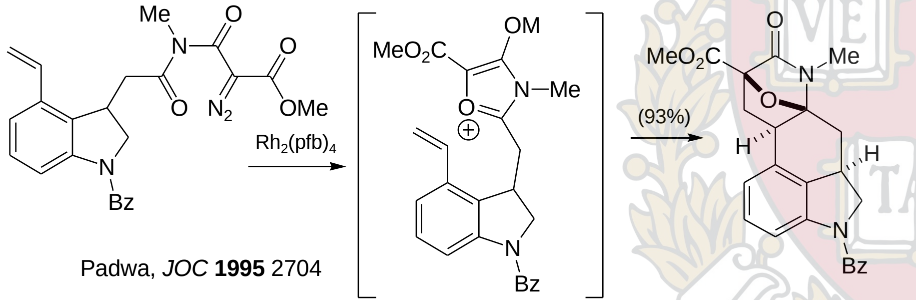
Padwa et. al. *Tetrahedron Lett*. **1992**, *33*, 4731-4734.

Dipolar Cycloadditions: Carbonyl Ylides



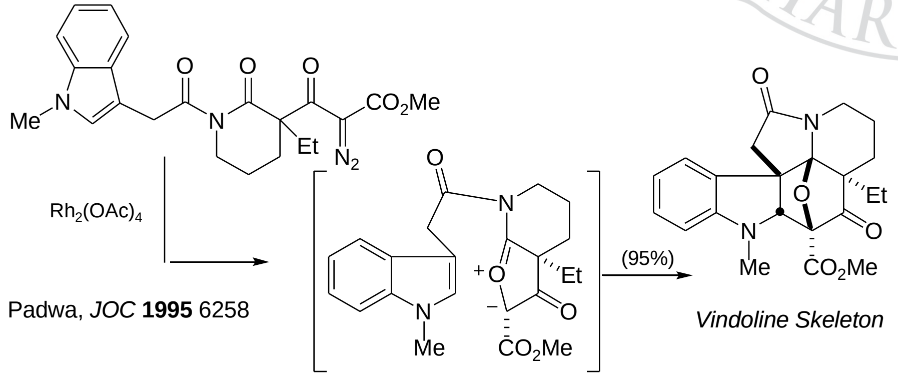
Dauben, *JOC* **1993** 7635

Tigilane Skeleton



Padwa, *JOC* **1995** 2704

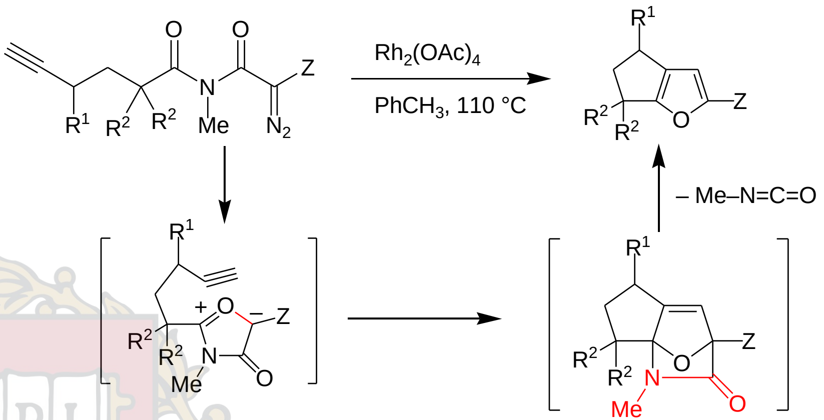
Lysergic Acid Skeleton



Padwa, *JOC* **1995** 6258

Vindoline Skeleton

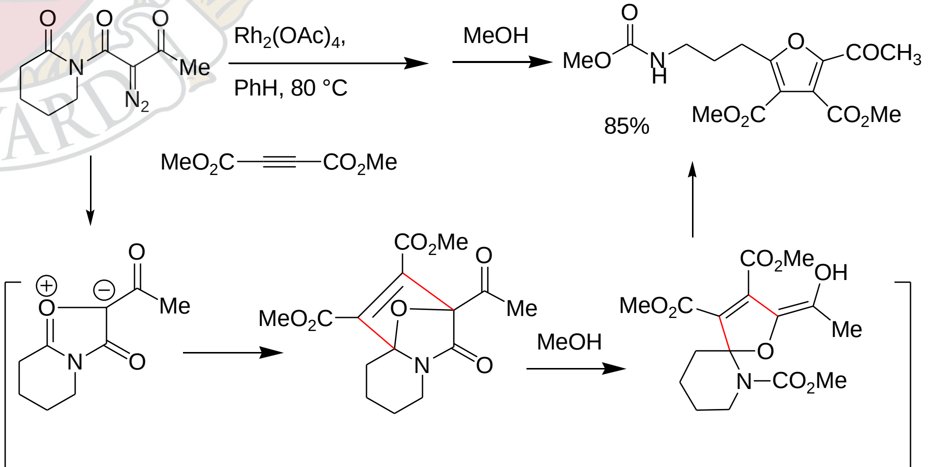
Reactions of Diazoimides: [3+2] addition – [4+2] retroaddition



R^1 = H, OBn
R^2 = H, Me
Z = COMe, CO$_2$Me

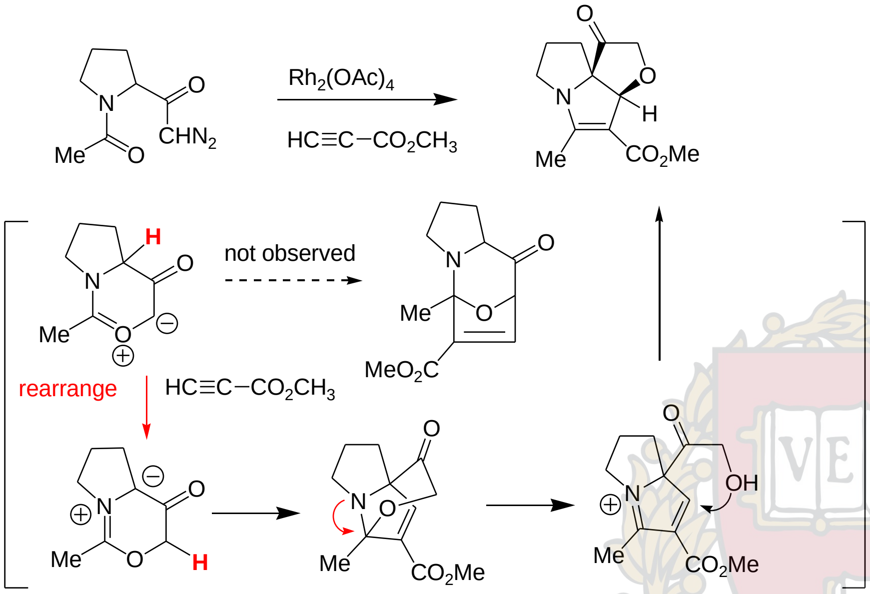
Yields = 44-63%

Maier, M. E.; Schöffling, B. *Chem. Ber*. **1989**, *122*, 1081-1087.



Padwa, A.; Hertzog, D. L.; Chinn, R. L. *Tetrahedron Lett*. **1989**, *30*, 4077-4080.

The Carbonyl Ylide - Azomethine "Dipole Cascade"

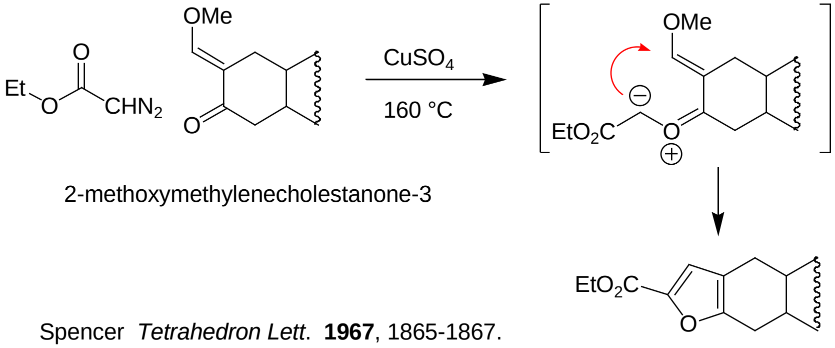


The 1,3-proton shift is catalyzed by trace amounts of water. Azomethine ylide formation requires a proton at the tertiary center.

Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc*. **1989**, *111*, 6451-6452.
Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc*. **1992**, *114*, 593-601.

The Synthesis of Furans

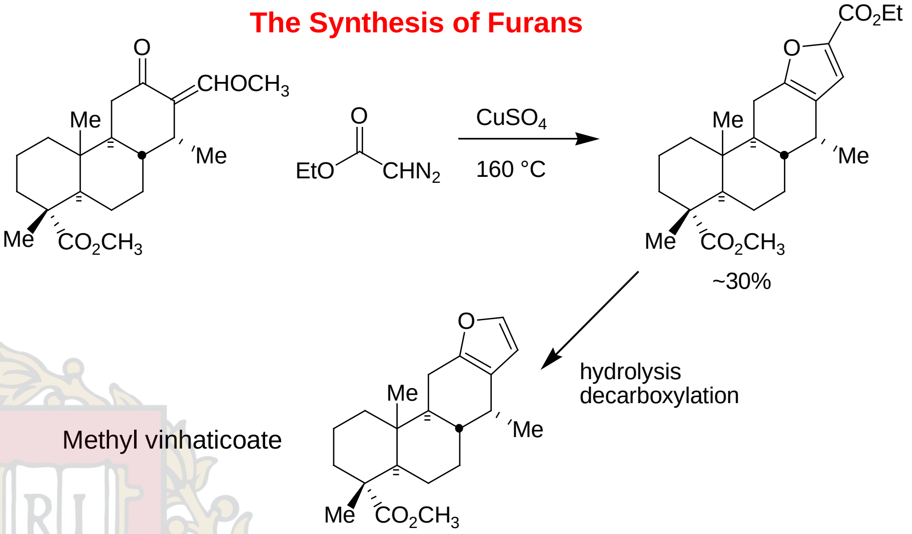
Intermolecular addition to α,β-unsaturated carbonyls



2-methoxymethylenecholestanone-3

Spencer *Tetrahedron Lett*. **1967**, 1865-1867.

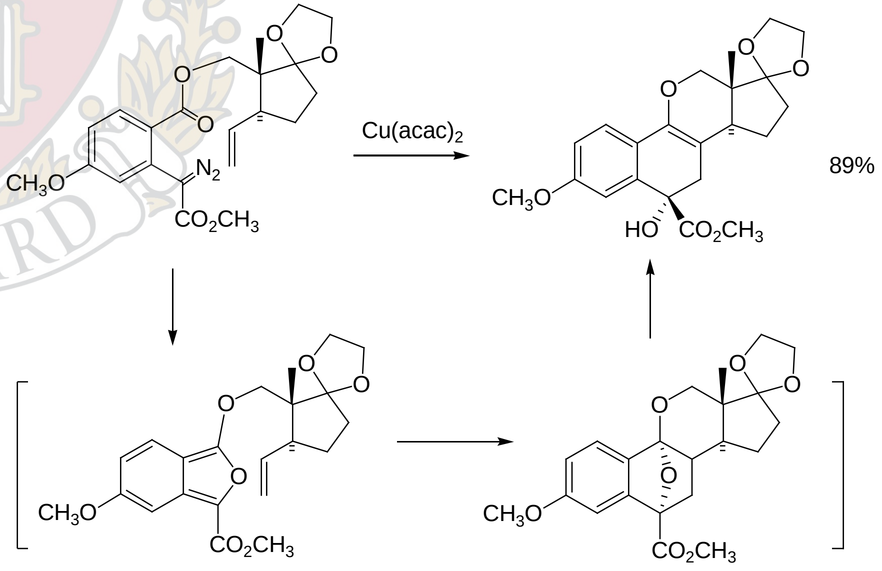
The Synthesis of Furans



Methyl vinhaticoate

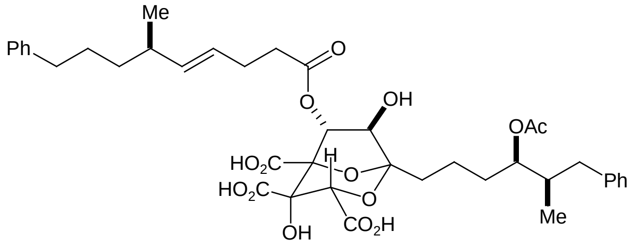
Spencer, T. A., *et. al*. *JACS* **1967**, *89*, 5497.

Can you propose a rational mechanism for this transformation?

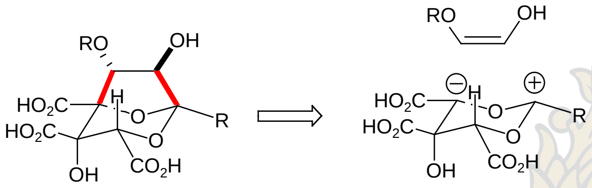


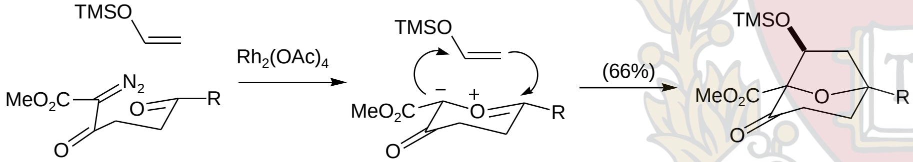
Hildebrandt, *Tetrahedron Lett*. **1988**, *29*, 2045-2046.

Application of Carbonyl Ylids to the Synthesis of Zaragozic acid:



C=O Ylid Transforms

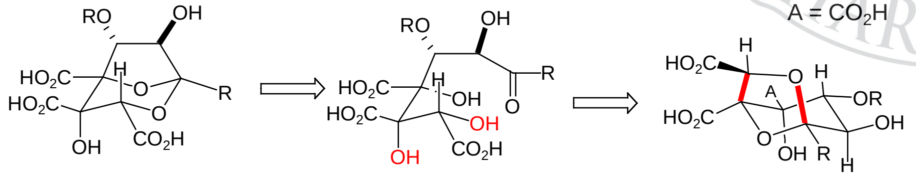




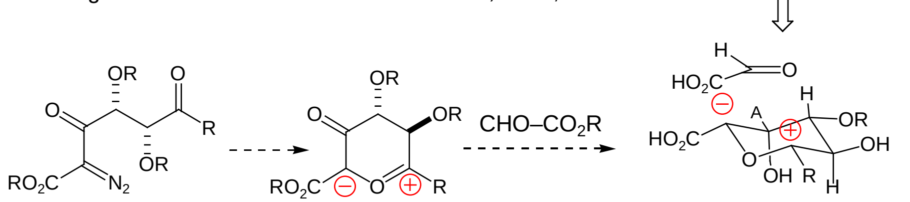
Merck, *TL* **1994** 9185

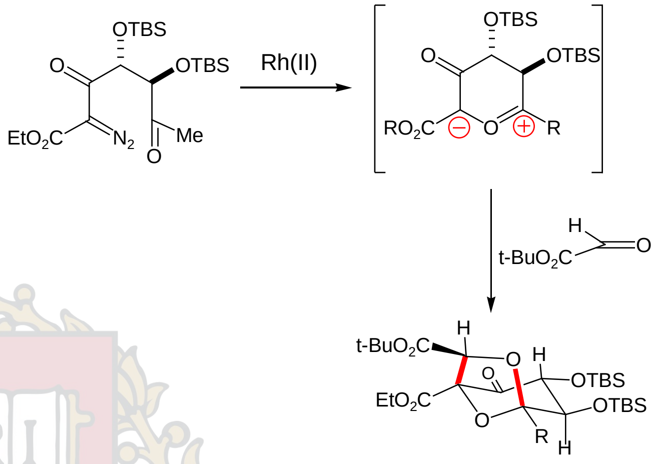
Zaragozic Acid Skeleton

A = CO_2H



Hodgson et al. *J. Chem. Soc. Perkin Trans I*, **2000**, 3432





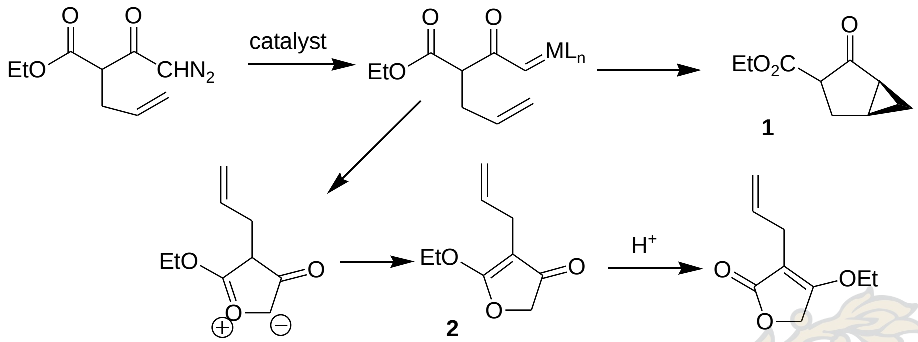
58% yield

Sir John Cornforth:

If you are anxious for over-exposure,
to prepublication disclosure,
to good food and good drink,
without leisure to think,
try IUPAC symposia."

Carbene Heteroatom Transformations: Ylid Formation

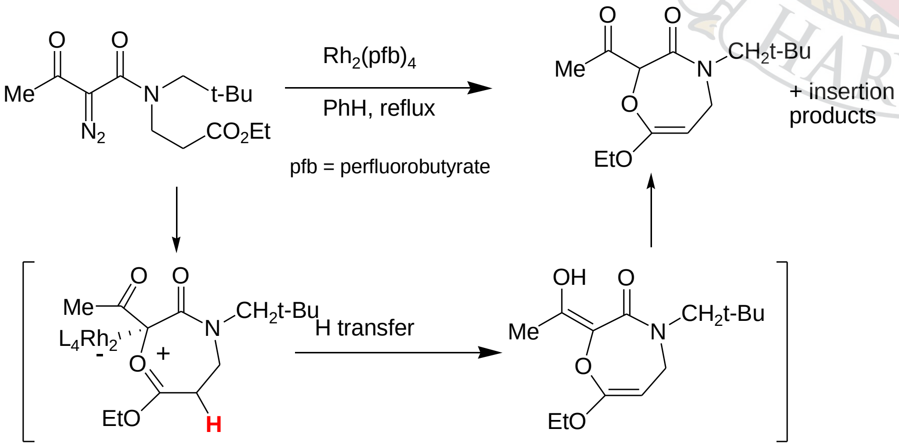
Ylid Formation versus Cyclopropanation



catalyst	Temp (°C)	%1	%2
$Pd_2Cl_2(C_3H_5)_2$	RT	53	3
$Cu(PhCOCHCOMe)_2$	80	50	13
$(MeO)_3PCuI$	RT	3	35
$Rh_2(OAc)_4$	RT	**1**	**58**
None	80	15	54

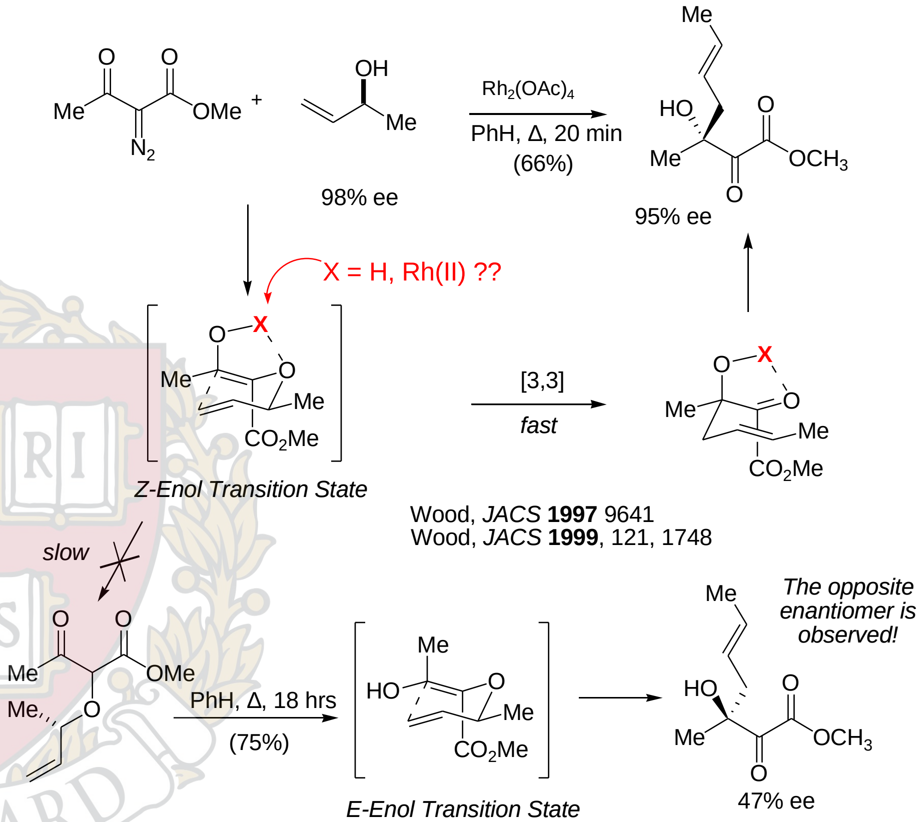
it is evident that these are reactions of metal carbenoids

Bien, S.; Gillon, A.; Kohen, S. *J. Chem. Soc. Perkin Trans. I.* **1976**, 489-492



Doyle, M. P., *et al.* *J. Org. Chem.* **1991**, *56*, 820-829.
Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397.

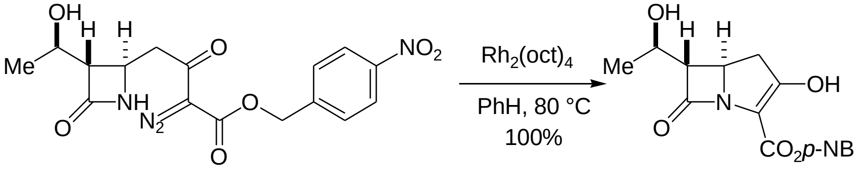
Tandem O-H Insertion/Claisen Rearrangement

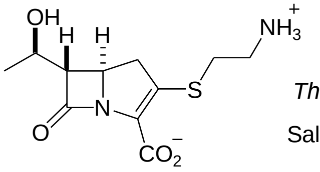


The opposite enantiomer is observed!

Wood, *JACS* **1997** 9641
Wood, *JACS* **1999**, 121, 1748

Merck Thienamycin Process

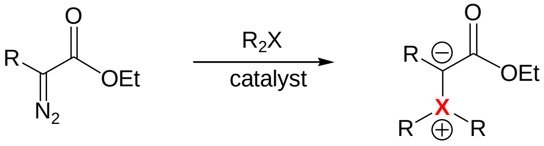




Thienamycin

Salzmann, *JACS* **1980** 6161

Ylide Formation

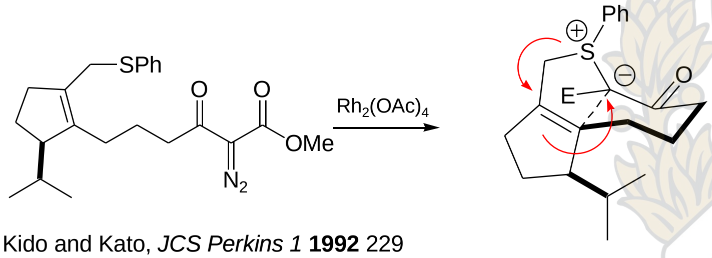


Reviews: Padwa, *Chem. Rev.* **1991** 263
Padwa, *Chem. Rev*. **1996** 223
Barnes, Evening Seminar, March 16, 1993

X is generally S, O or N and can be sp^2 or sp^3 hybridized

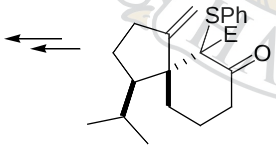
Ylides often undergo sigmatropic rearrangements or cycloadditions

[2,3]-Sigmatropic rearrangement:

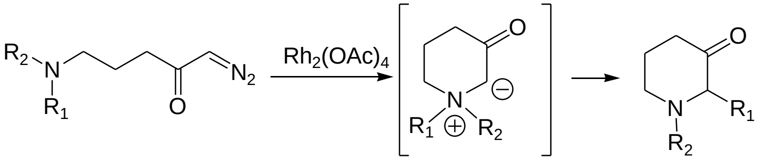


Kido and Kato, *JCS Perkins 1* **1992** 229

Acorenone B



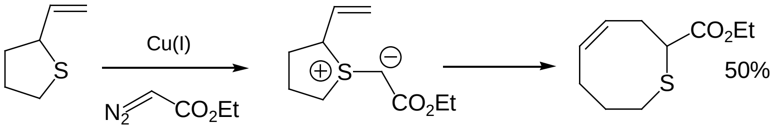
Stevens Rearrangement ([1,2] alkyl shift):

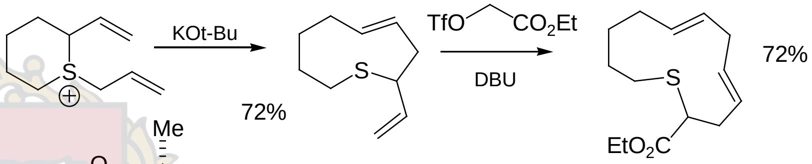


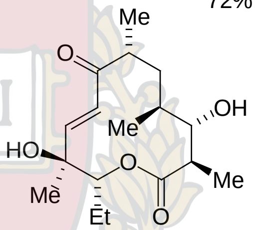
West, *JACS* **1993** 1177

Ring expansion reactions have been investigated

Methods based on sulfur ylides: (review) Vedejs, *Accts. Chem. Res*. **1984**, *17*, 358

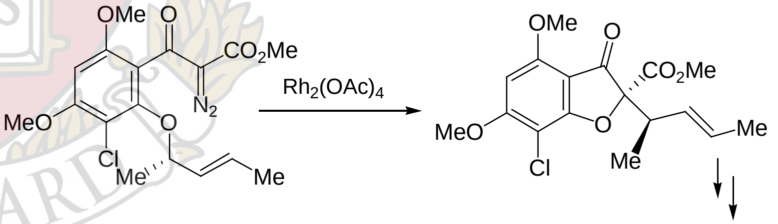




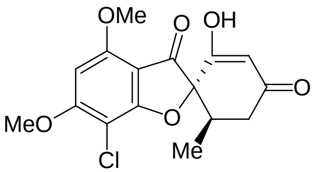


Methynolide has been synthesized by Vedejs using this ring-expansion methodology

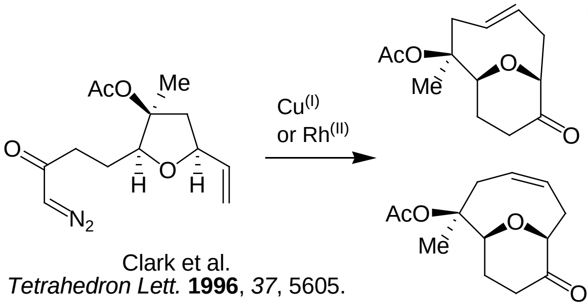
Vedejs, *JACS* **1989**, *111*, 8430



Pirrung et al *JACS*, **1991**, *113*, 8561.



griseofulvin



Clark et al.
Tetrahedron Lett. **1996**, *37*, 5605.

http://www.courses.fas.harvard.edu/~chem206/

Chemistry 206

Advanced Organic Chemistry

Lecture Number 36

Introduction to Photochemistry

- Introduction to Electronic Excitation
- Franck-Condon Principle, Jabolonski Diagram
- Photochemistry of Olefins and Dienes
- Photochemistry of Carbonyl Compounds
- Norrish Type-I & II Processes
- Paterno-Büchi Reaction
- [2 + 2] Photocycloaddition of Olefins

Reading Assignment for this Lecture:

Carey, and Sundberg, *Advanced Organic Chemistry*, Part A fourth Edition, Chepter 13, "Photochemistry", pp 743-789

"Stereoselective intermolecular [2+2]-photocycloaddition reactions and their application in synthesis.", Bach, T. *Synthesis* **1998**, 683-703. **(handout)**

"[2+2] photocycloaddition/fragmentation strategies for the synthesis of natural and unnatural products.", Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003-2020. **(handout)**

Matthew D. Shair

Friday,
December 20, 2002

Worthwhile General Reviews

"New insights into an old mechanism: [2 + 2] photocycloaddition of enones to alkenes.", Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev*. **1993**, *93*, 3.

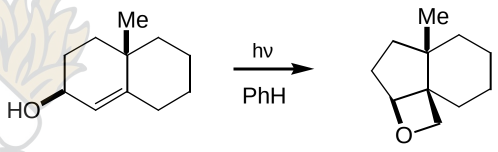
"Stereoselective intermolecular [2+2]-photocycloaddition reactions and their application in synthesis.", Bach, T. *Synthesis* **1998**, 683-703.

"[2+2] photocycloaddition/fragmentation strategies for the synthesis of natural and unnatural products.", Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003-2020.

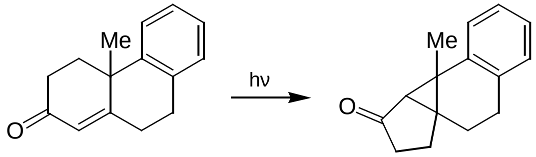
"Synthetic Applications of Intramolecular Enone-Olefin Photocycloadditions.", Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453.

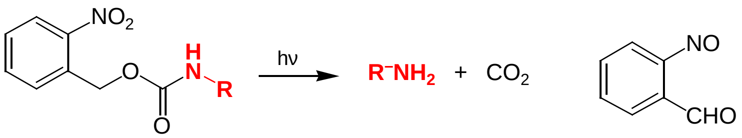
"The meta photocycloaddition of arenes to alkenes.", Cornelisse,*Chem. Rev*. **1993**, *93*, 615.

Chem 206, 1999 Final Exam Question. Provide a mechanism for the following transformation that explains the observed stereochemistry (Marshall, *JOC*, **1971**, 214).



Mechanism??





The above reaction forms the basis of a photo-labile protecting gtroup strategy for amines and alcohols

Background Reading

Carey, and Sundberg, *Advanced Organic Chemistry*, Parts A
Third Edition, Chepter 13, "Photochemistry", pp 729-765

Worthwhile General Reviews

"New insights into an old mechanism: [2 + 2] photocycloaddition of enones to alkenes.", Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev*. **1993**, *93*, 3.

"Stereoselective intermolecular [2+2]-photocycloaddition reactions and their application in synthesis.", Bach, T. *Synthesis* **1998**, 683-703.

"[2+2] photocycloaddition/fragmentation strategies for the synthesis of natural and unnatural products.", Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003-2020.

"Synthetic Applications of Intramolecular Enone-Olefin Photocycloadditions.", Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453.

"The meta photocycloaddition of arenes to alkenes.", Cornelisse, J. *Chem. Rev*. **1993**, *93*, 615.

■ Important Regions of the Electromagnetic Spectrum

Basic Types	Information	Energy Range
Ultraviolet-Visible	**Electronic States**	**40-140 kcal/mol**
Infrared	Functional Groups	2-12 kcal/mol
NMR	H & C Connectivity	10^{-5}–10^{-6} kcal/mol

■ Light-induced electron excitation

Electrons are excited to higher energy levels when a molecule absorbs a photon of energy equal to the energy difference between the ground-state electronic level and the excited state electronic level.

$$E = h\nu = \frac{h\,c}{\lambda}$$

for λ = 200 nm: E = 143 kcal

for λ = 700 nm: E = 40.9 kcal

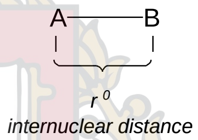
Knowing the absorption wavelength in nm, you can calculate the the energy

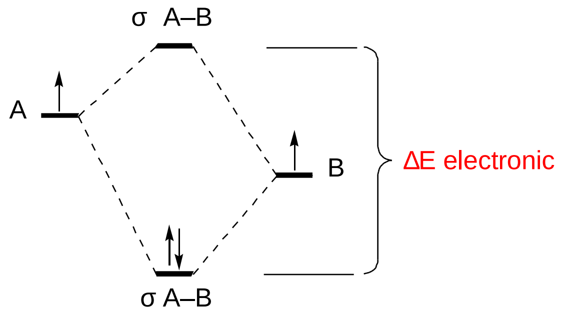
$$\boxed{E\ (\text{kcal/mol}) = \frac{2.86 \times 10^{+4}}{\lambda(\text{ in nm})}}$$

for λ = 200 nm: E = 143 kcal

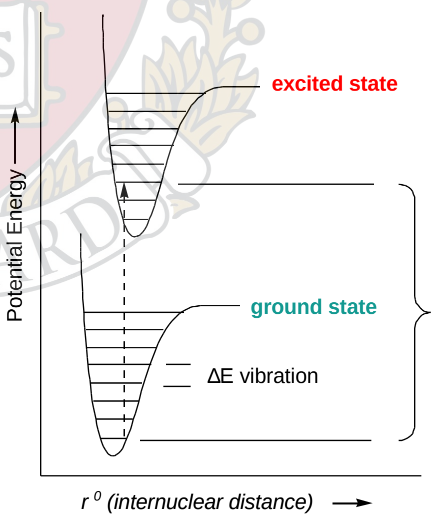
for λ = 700 nm: E = 40.9 kcal

Consider a simple diatomic molecule **A–B**





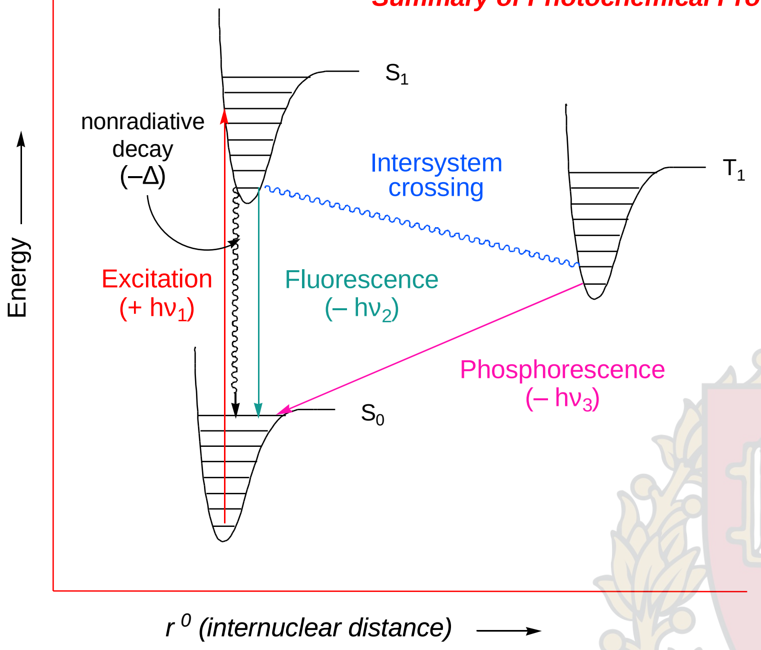
■ Morse Curve



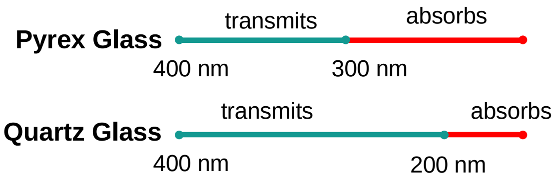
Time scale: electron excitation: 10^{-15} s
Time scale: nuclei movement: 10^{-12} s

■ **Franck-Condon Principle:** Upon light-induced electronic excitation, only the electrons are reorganized; the heavier nuclei stay in their ground-state geometry. (**Vertical Transitions**)

Summary of Photochemical Processes



Substrates	Absorption max (nm)
Simple alkenes	190–200
Acyclic dienes	220–250
Cyclioc dienes	250–270
Styrenes	270–300
Saturated ketones	270–280
Unsaturated ketones	310–330
Aromatic ketones (aldehydes)	280–300
Aromatic compounds	250–280



Hg lamp ⟶ 254 nm, 313 nm, 366 nm

Selection Rules

Not all excitations/transitions are allowed (have high probability):

(a) Spin-forbidden: Transitions between states of different multiplicity M

$M = 2S + 1$ $S = \Sigma s$

M: multiplicity
S: total spin
s: spin of a single electron (±1/2)

Spins Paired: Singlet State: $S = \Sigma s = (+1/2 \; -1/2) = 0$

Spins Unpaired: Triplet State: $S = \Sigma s = (+1/2 \; +1/2) = 1$

$\mathbf{S_0} \longrightarrow \mathbf{S_1}$ **or** $\mathbf{S_2}$ **allowed**

$\mathbf{S_0} \not\longrightarrow \mathbf{T_1}$ **forbidden**

(b) **Space-forbidden**: transitions between orbitals which do not overlap.

vacuum UV only (ΔE large) $\sigma \longrightarrow \sigma$ } allowed

UV(VIS) { $\pi \longrightarrow \pi^*$ } allowed

UV(VIS) { $n \longrightarrow \pi^*$ forbidden (Does not mean impossible. Implies only that probability for that particular transition is low.)

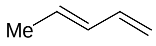
■ Sensitizer: e.g. acetophenone, benzophenone

Small ΔE between S_0 & S_1. Facile excitation into S_1 followed by ISC into T_1. Interaction with substrate:

$$\text{Substrate } (S_0) + \text{Sens. } (T_1) \longrightarrow \text{Substrate } (T_1) + \text{Sens. } (S_0)$$

Substrate reacts *via* T_1 excited state.

■ Triplet-Quencher: e.g. O_2, piperylene



Reacts immediately with molecules in T_1 excited state, depopulate T_1

$$\text{Quencher } (S_0) + \text{Substrate } (T_1) \longrightarrow \text{Quencher } (T_1) + \text{Substrate } (S_0)$$

Substrate reacts *via* S_1 excited state.

Jablonski Diagram

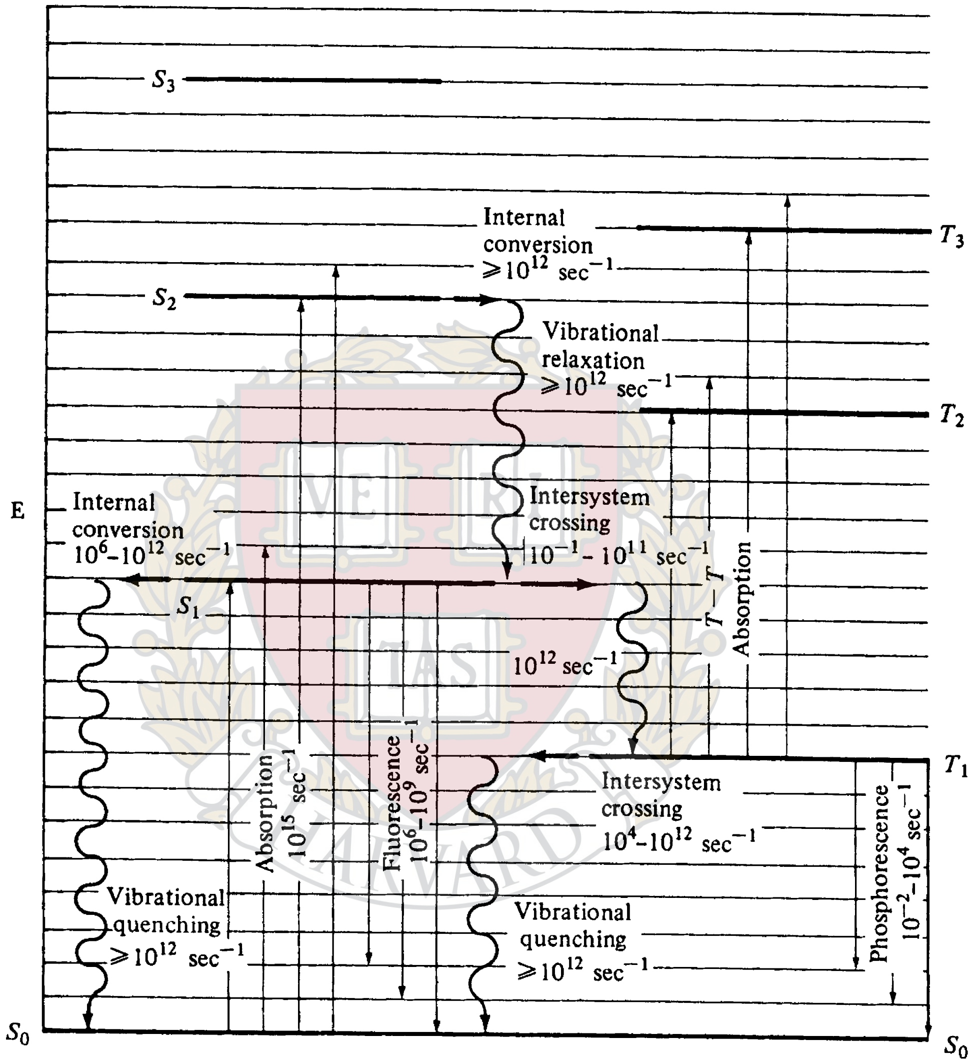


Figure 12.2 Jablonski diagram. Energy levels of excited states of a polyatomic molecule. The lowest vibrational energy levels of a state are indicated by thick horizontal lines; other horizontal lines represent associated vibrational levels. Vertical straight lines represent radiative transitions, wavy lines nonradiative transitions. The orders of magnitude of the first-order rate constants for the various processes are indicated. From Cundall, R. B.; Gilbert, A. "Photochemistry." Thomas Nelson: London, 1970. Reproduced by permission of Thomas Nelson and Sons Limited.

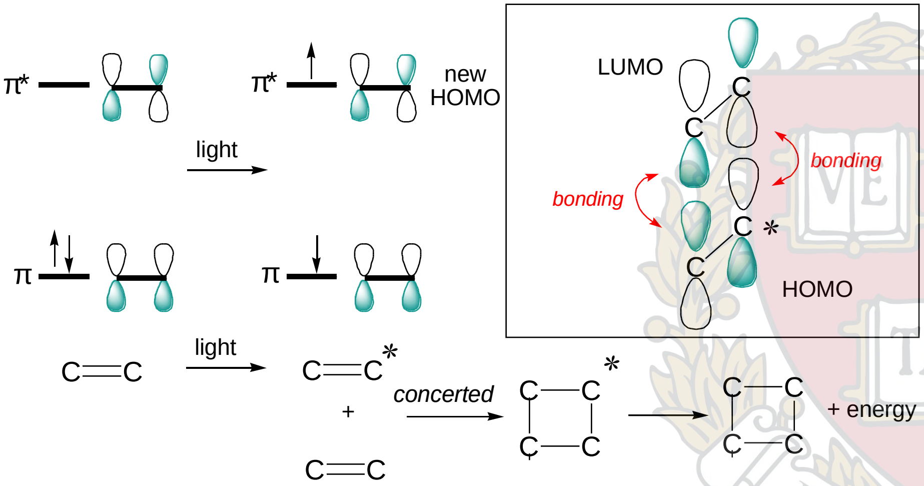
Photochemical Reactions

Frontier MO Description

Fleming, I. "Frontier Orbitals and Organic Chemical Reactions", Chapter 6, "Photochemical Reactions"

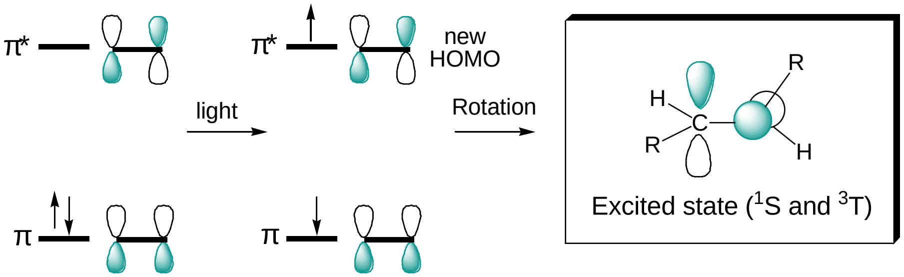
Reactions of Olefins

Consider [2 + 2] cycloaddition: Photochemical activation

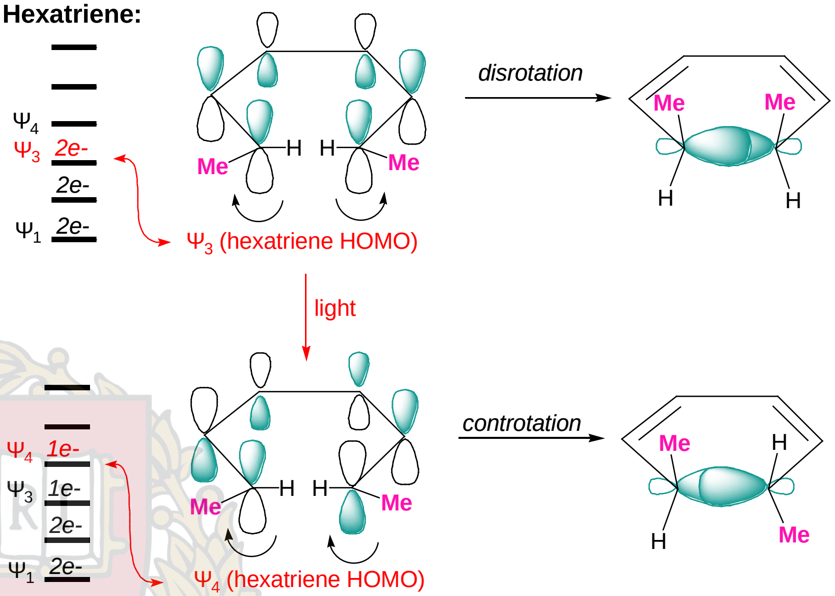


The [2 + 2] cycloaddition of two olefins exhibits the option of being concerted if one of the olefins reacts out of its photochemically excited state.

Excited State Geometry

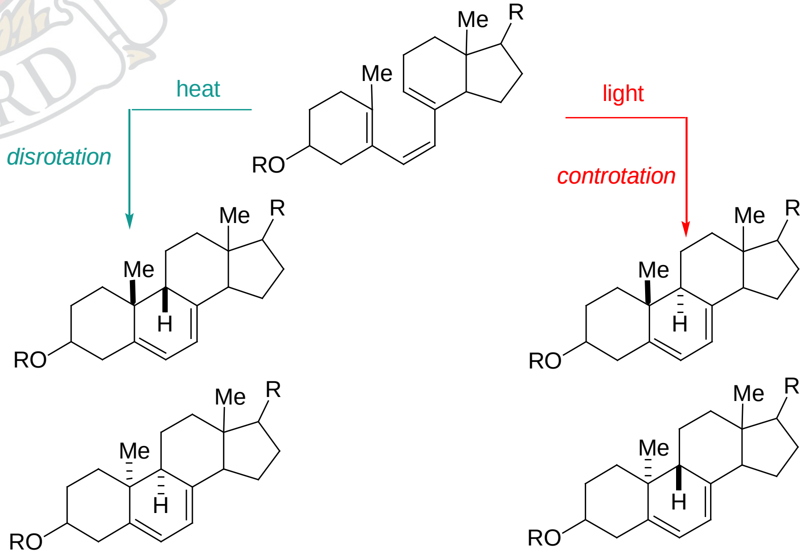


Hexatriene:



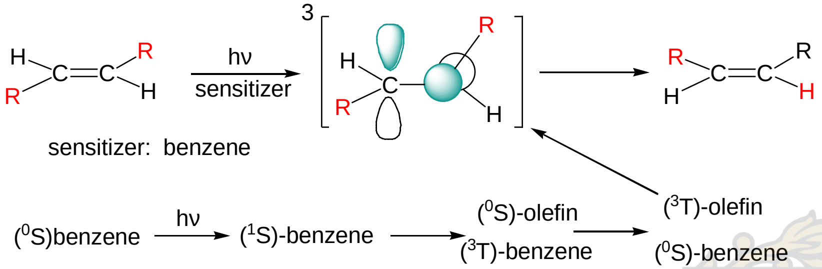
The rotatory motion of ring closure may be reversed by photo-activation

One of the first cases where heat and light induced electrocyclizations followed different pathways.
Havinga, *Tetrahedron*, **1961**, *16*, 146.

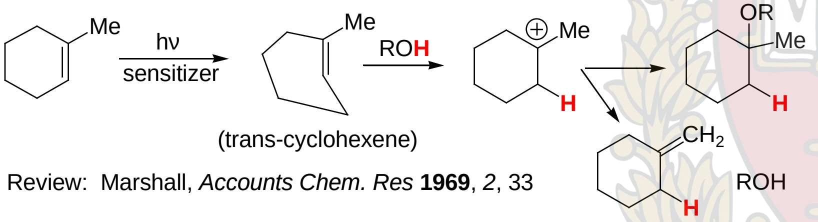


Cis–Trans Isomerization

Cis & trans olefins may be interconverted by either direct or sensitized irradiation



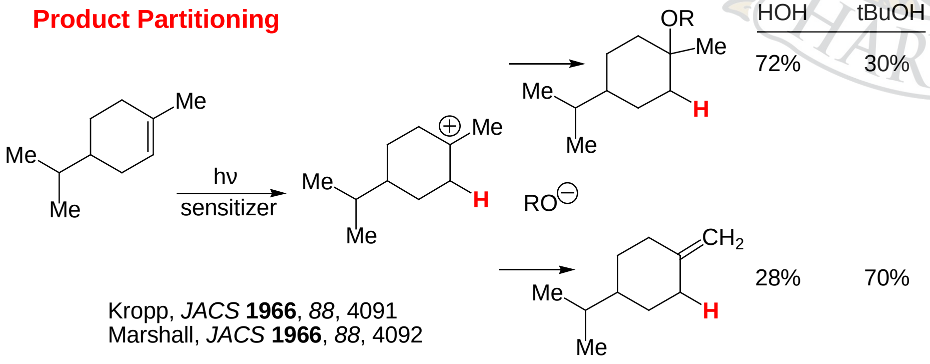
Sensitized Photohydration



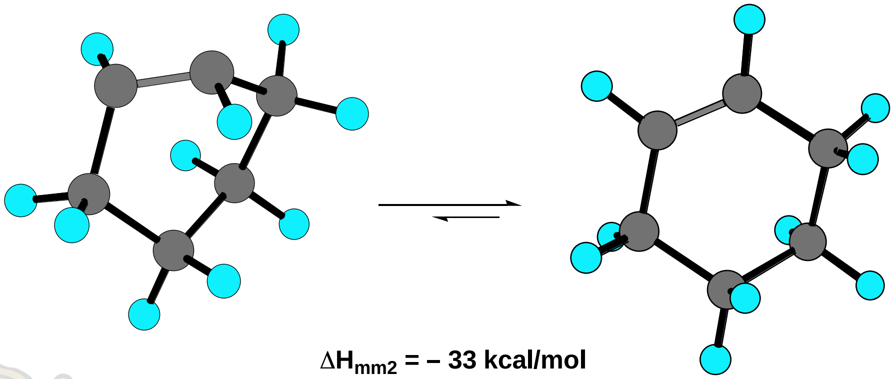
Review: Marshall, *Accounts Chem. Res* **1969**, *2*, 33

Ground state trans cyclohexene is now sufficiently basic to deprotonate alcohols

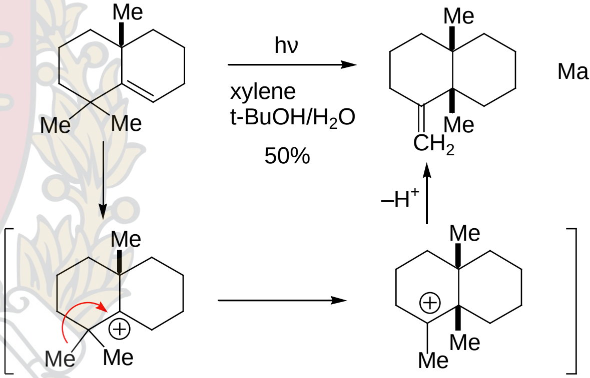
Product Partitioning



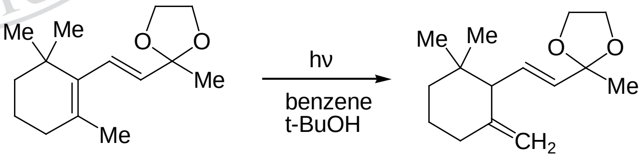
Kropp, *JACS* **1966**, *88*, 4091
Marshall, *JACS* **1966**, *88*, 4092



ΔH_{mm2} = – 33 kcal/mol

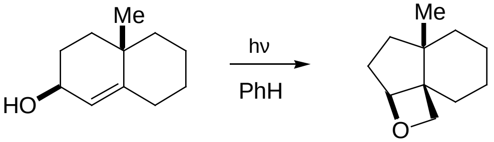


Marshall



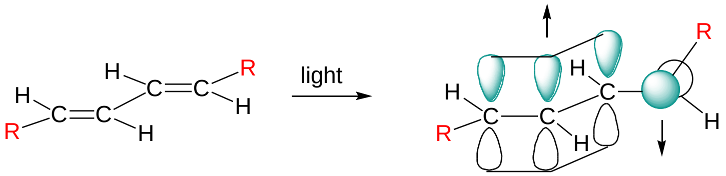
85% yield

Evans et. al. unpublished results, 1972

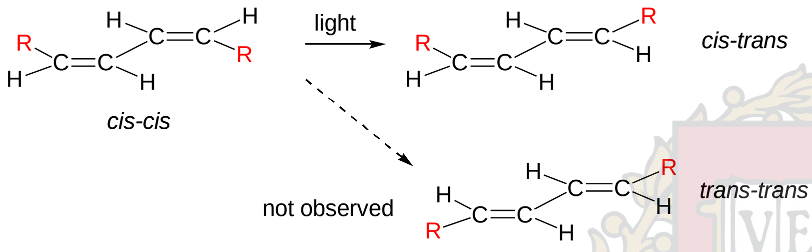


(Marshall, *JOC*, **1971**, 214).

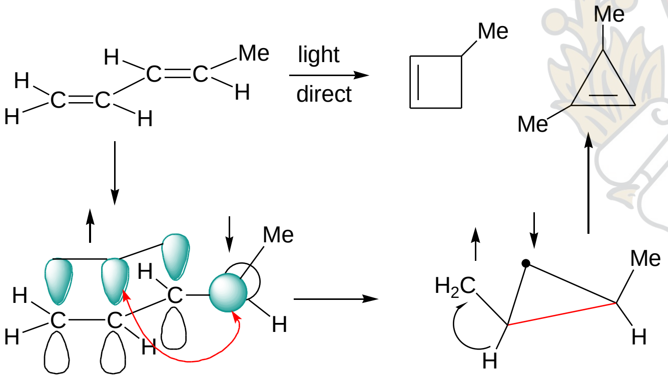
Excited State Geometry of Dienes

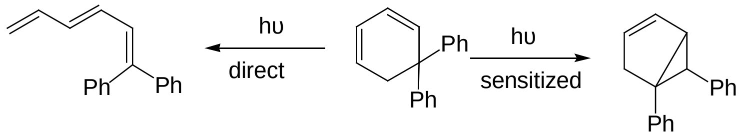


Allylmethylene diradical



Explain why trans-trans isomer is not observed in this photosiomerization





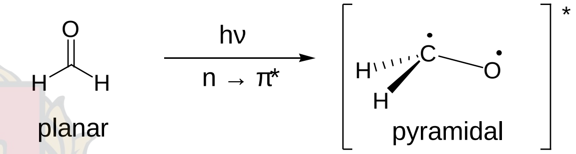
Rationalize the course of the sensitized transformation

Photochemistry of Carbonyl Compounds

Photochemical excitation of carbonyl group: n → π*

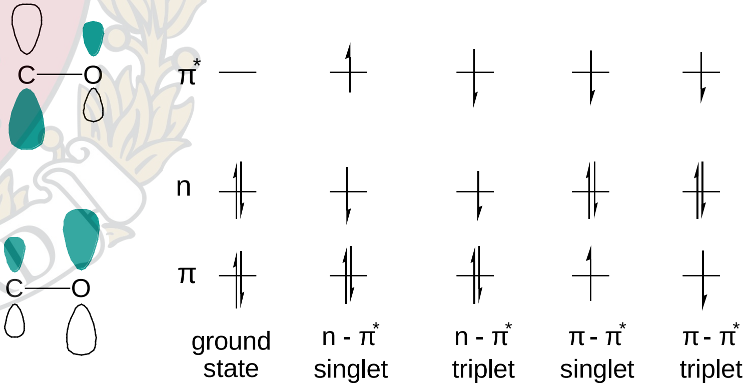
S^1 80–85 kcal/mol

T^1 75–80 kcal/mol



dipole: 2.34D

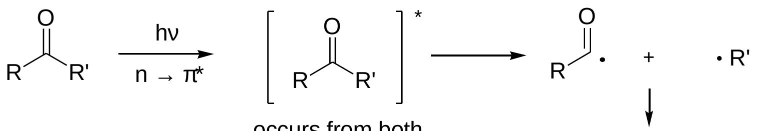
dipole: 1.56D



Note the diradical character of the excited states. Photochemically excited carbonyl compounds undergo many of the reactions typical of radical species.

Norrish-type I reactions (α-cleavage)

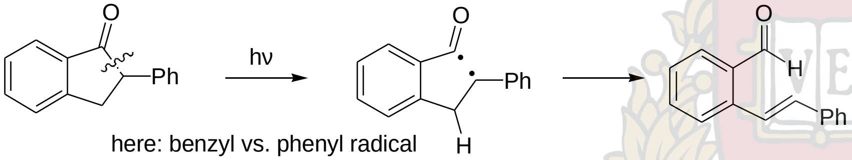
Barton, *JACS* **1985**, *107*, 3607.



occurs from both S^1 and T^1

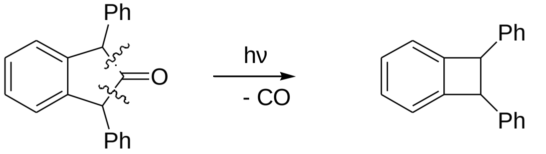
Σ products (decarbonylation, recombination, disproportionation)

Regioselectivity of bond cleavage: Depends on relative stability of the two radicals formed.



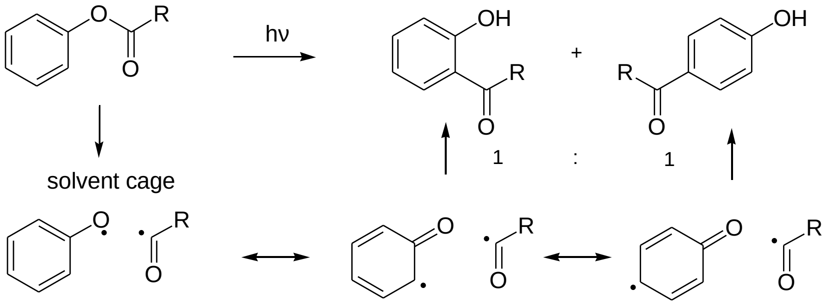
here: benzyl vs. phenyl radical

Reaction occurs readily if stabilized radicals are formed.



Quinkert, *TL* **1963**, 1863.

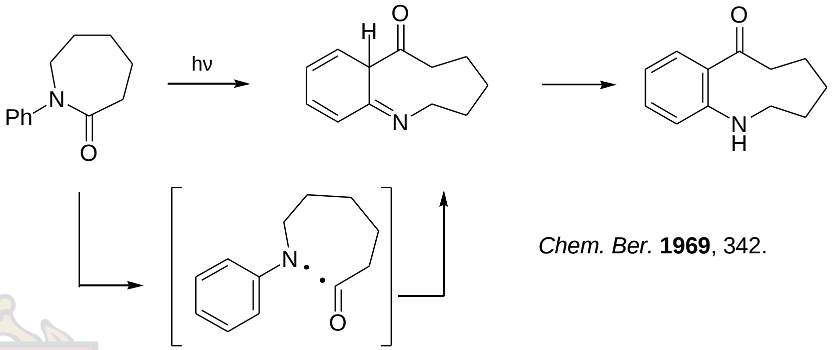
C/O and C/N bond cleavage: Photo–Fries rearrangement



solvent cage

phenoxy radical (resonance stabilized)

C/N bond cleavage: Aza–Fries rearrangement

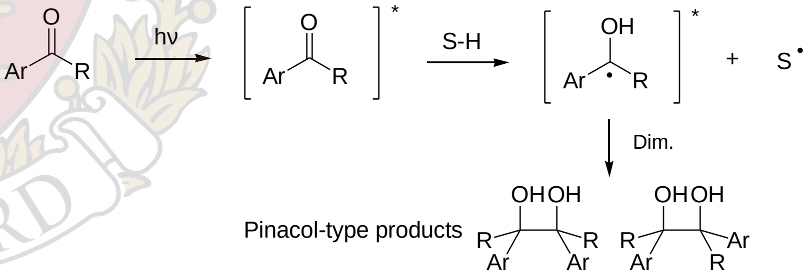


Chem. Ber. **1969**, 342.

Norrish-type II reactions *Acc. Chem. Res.* **1971**, *4*, 168.

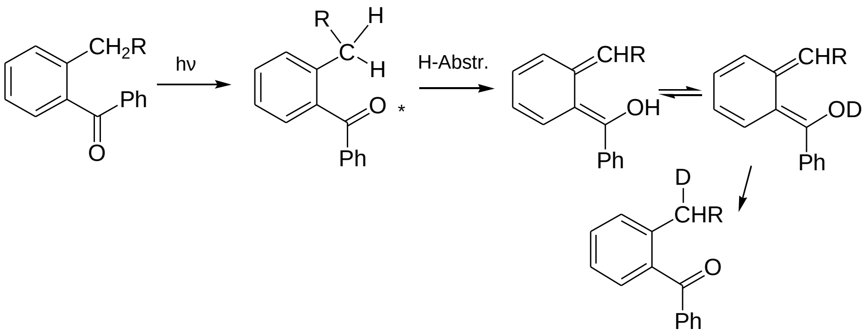
Photo-excitation of carbonyl is followed by hydrogen atom abstraction.

Intermolecular (Reaction with solvent)



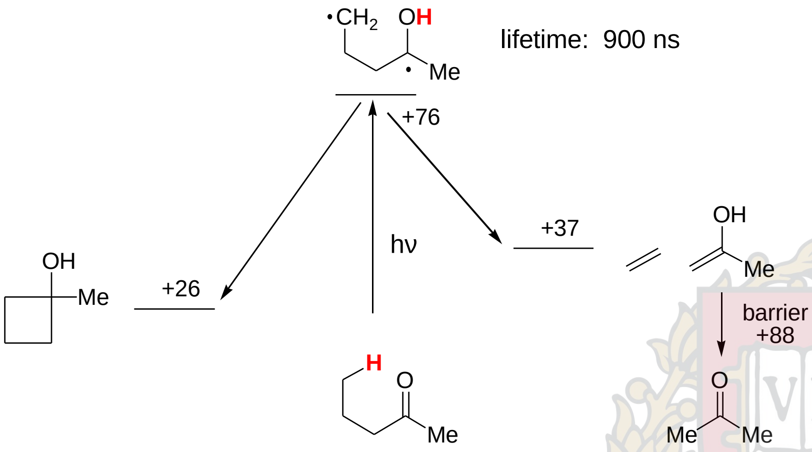
Pinacol-type products

Intramolecular (a) Photoenolization



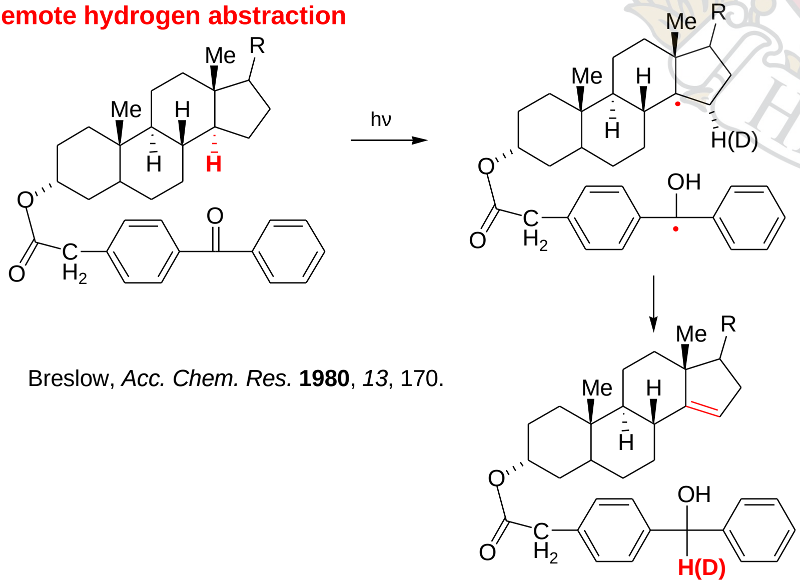
Norrish-type II reactions continued...gamma H Abstraction

"Femptosecond Dynamics of Norrish Type-II Reaction: Nonconcerted Hydrogen Transfer and Diradical Intermediiacy", Zewail et. al., *Angew. Chemie, Int. Ed.* **2000**, *39*, 260



- Rxn may take place out of either singlet or triplet state
- Fragmentation to enol is favored entropically
- The decomposition of the diradical is essentially barrierless
- Fragmentation to enol is favored entropically
- Fagmentation similar to McLafferty Rearrangement in mass spectroscopy

Remote hydrogen abstraction

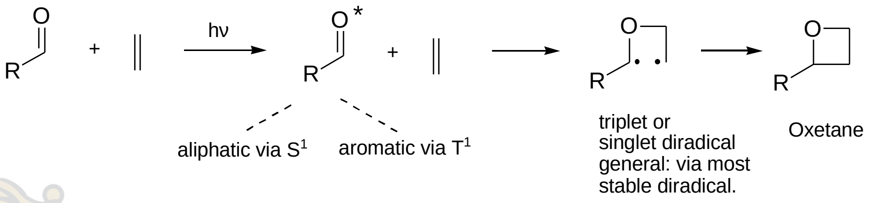


Breslow, *Acc. Chem. Res.* **1980**, *13*, 170.

Paterno-Büchi Reaction

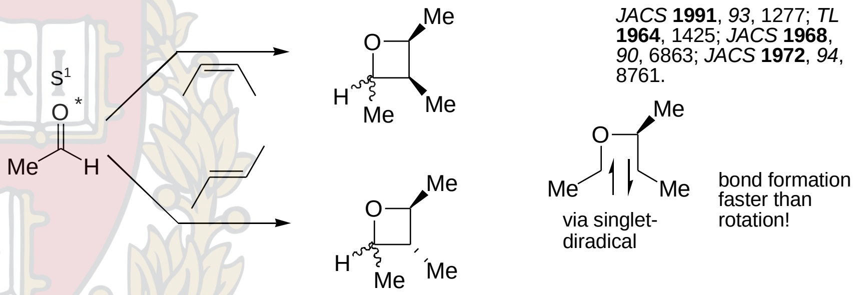
Reviews: Scharf, ACIEE **1991**, *30*, 477; Ynoue, *Chem. Rev.* **1992**, *92*, 741.

Photochemical [2+2] cycloaddition of ketones/aldehydes with olefins:
The general reaction:



With some aliphatic aldehydes stereospecific reactions have been observed:

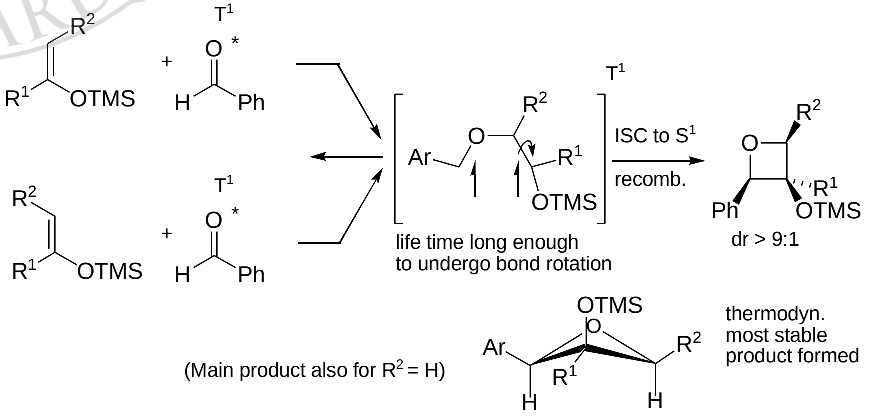
JACS **1991**, *93*, 1277; *TL* **1964**, 1425; *JACS* **1968**, *90*, 6863; *JACS* **1972**, *94*, 8761.



Aromatic aldehydes/ketones show stereo-convergent behavior:

(a) simple diastereoselectivity

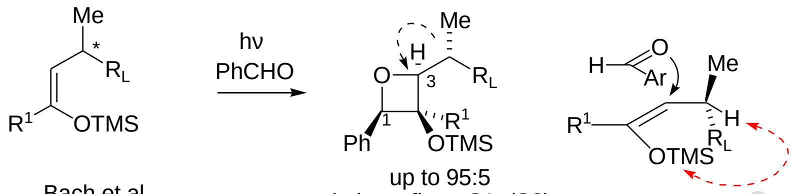
T. Bach, *Liebigs Ann.* **1997**, 1627.



Paterno-Büchi Reaction conbtinued....

Induced facial diastereoselectivity

controls rel. config.

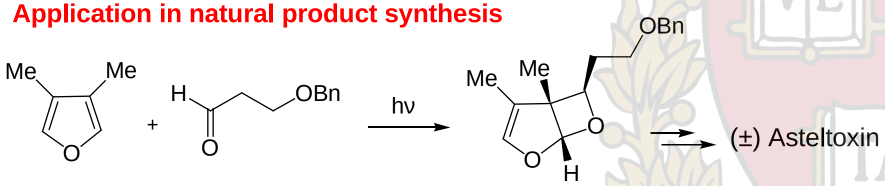


Bach et al.

up to 95:5
(rel. config. atC1–/C3)

$A^{1,3}$ minimized

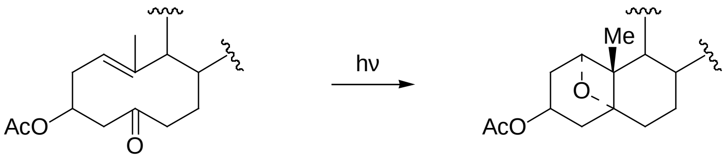
Application in natural product synthesis



head to head, exo

Schreiber, *JACS* **1984**, *106*, 4186; *Science* **1985**, 857; *JACS*, **1983**, *105*, 660.

Transannular reaction



"Stereoselective intermolecular [2+2]-photocycloaddition reactions and their application in synthesis.", Bach, T. *Synthesis* **1998**, 683-703.

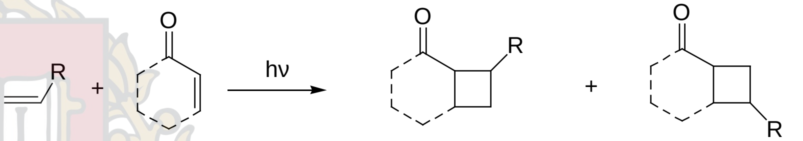
Photocycloaddition of Enones

"New insights into an old mechanism: [2 + 2] photocycloaddition of enones to alkenes.", Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3.

"[2+2] photocycloaddition/fragmentation strategies for the synthesis of natural and unnatural products.", Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003-2020.

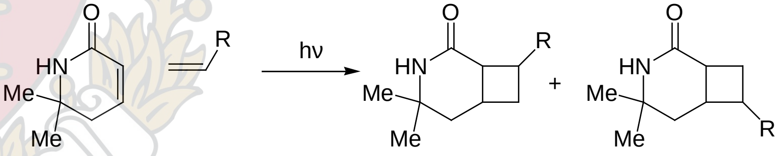
"Synthetic Applications of Intramolecular Enone-Olefin Photocycloadditions.", Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453.

Reaction Regiochemistry



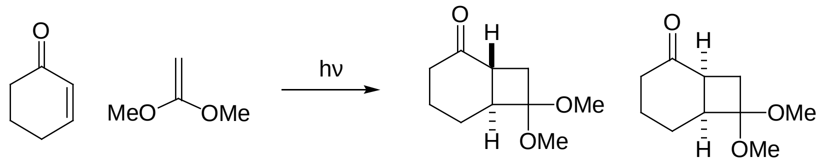
head-to-head (HH) head-to-tail (HT)

Favored: R = EWG **Favored: R = Donor**



R = CN	82 : 18
R = OEt	05 : 95

Ring Fusion Stereochemistry



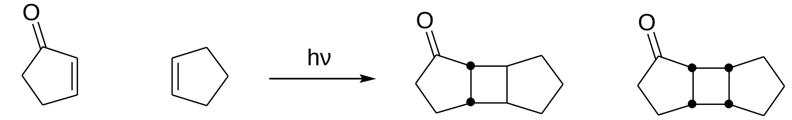
49% 21%

+ 6% other products

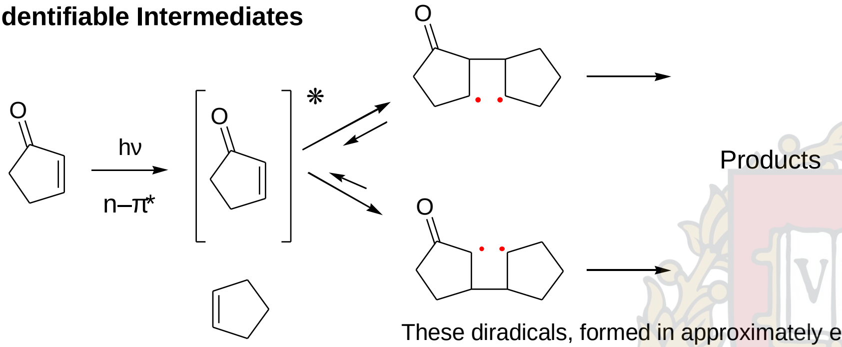
It is hard to rationalize the trans ring fusion stereochemistry through the intervention of a 1,4-diradical

Corey *JACS* **1964**, *86*, 485

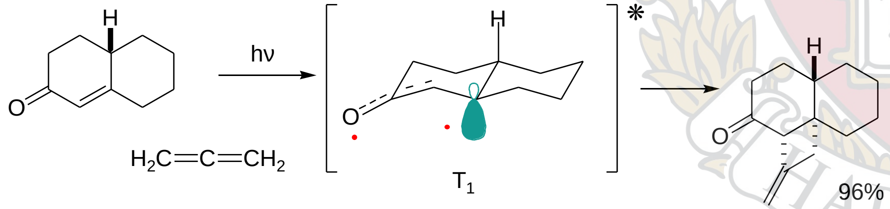
Photocycloaddition of Enones continued.....



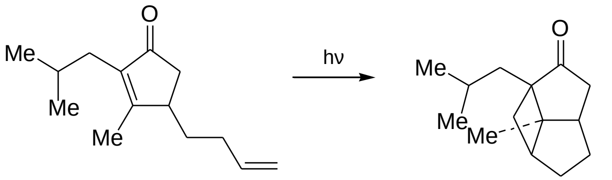
Identifiable Intermediates



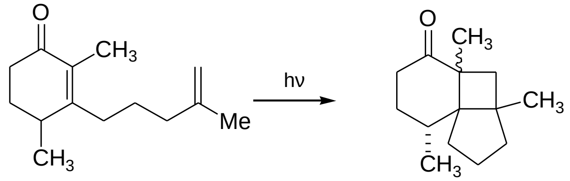
These diradicals, formed in approximately equal amounts, partition to products and reactants



- Intramolecular reactions work nicely



Heathcock, *JOC* **1985**, *50*, 4135.

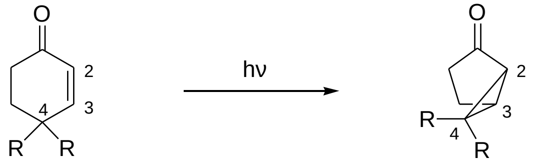


Oppolzer, *JACS* **1978**, *100*, 2583.

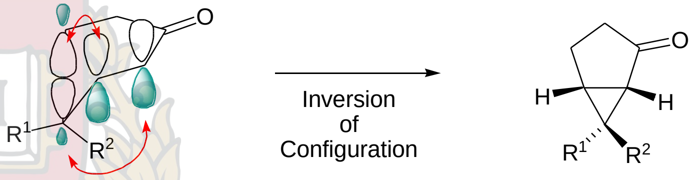
Photochemical Rearrangement of 4,4-Dialkyl-Substituted Cyclohexenones

Review: Schuster in "Rearrangements in Ground and Excited States", Vol. 3, de Mayo (Ed.), Academic Press, NY **1980**, Chapter 17.

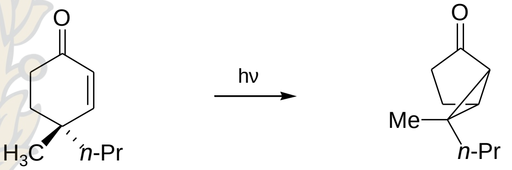
The reaction:



- Reaction is stereospecific
- can be described as a concerted $[\pi^2{}_a\sigma^2{}_a]$ CA



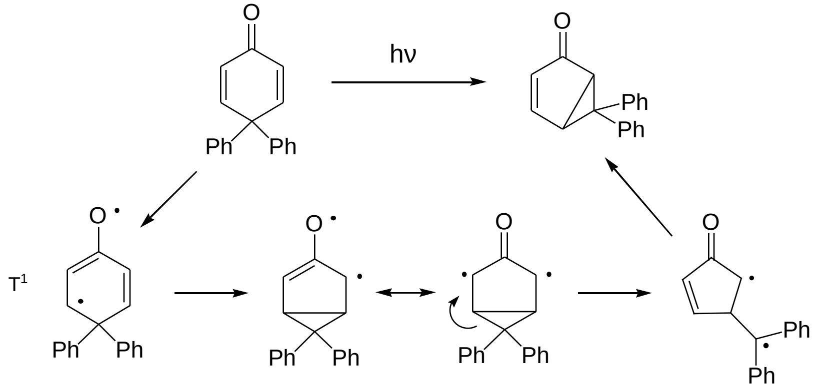
Example



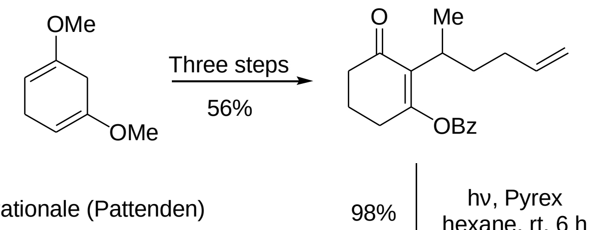
- for R^1, R^2 = Aryl non-concerted mechanisms compete

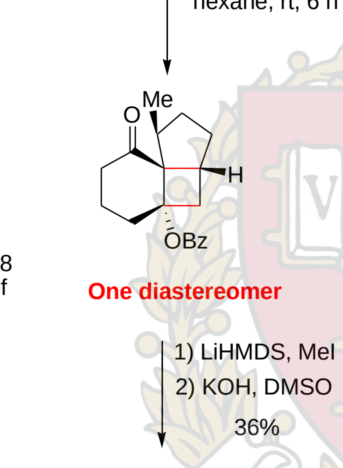
Cyclohexadienone Rearrangement

Zimmerman, *ACIEE* **1969**, *8*, 1; *Acc. Chem. Res.* **1978**, *11*, 65; de Mayo, Chapter 18.

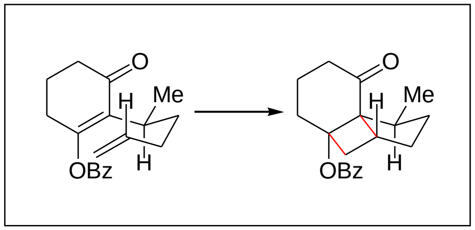


(±)-Epiprecapnelladiene

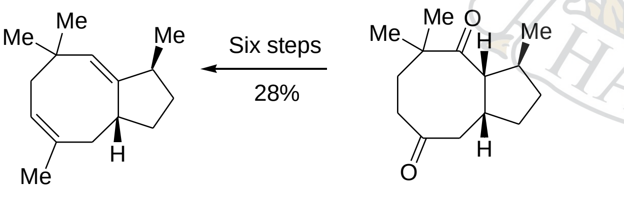




Stereochemical rationale (Pattenden)



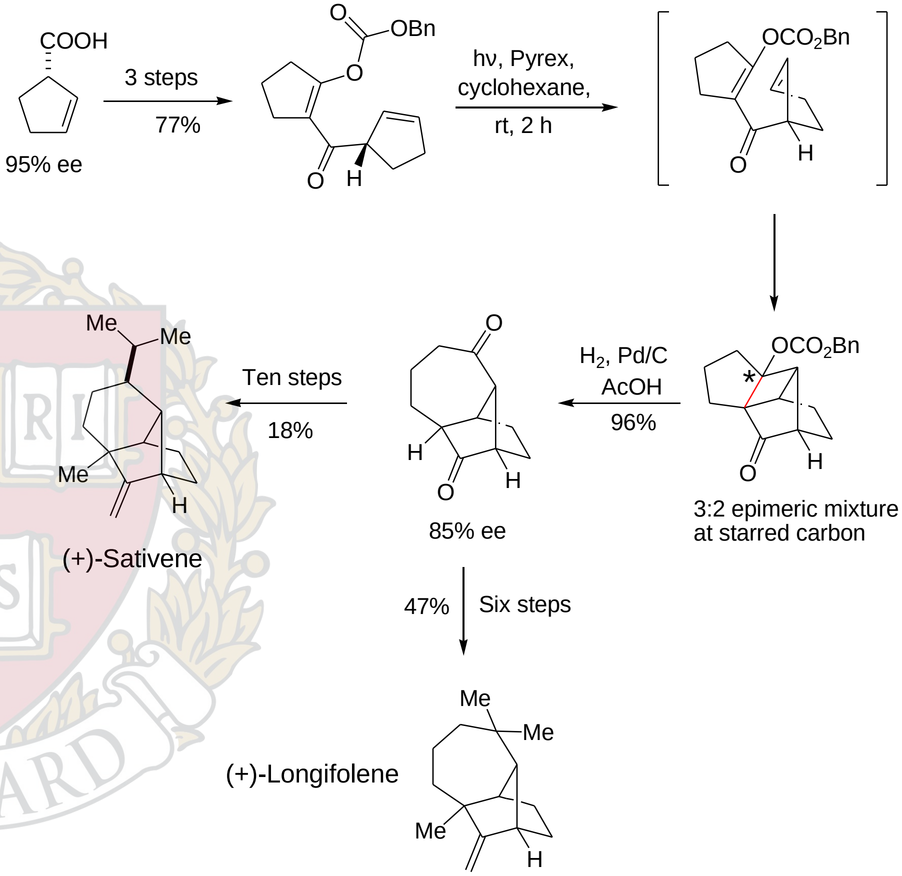
Irradiation of the enol acetate resulted in a 92:8 mixture, presumably due to the smaller size of the acetate versus benzoate.



Epiprecapnelladiene

Pattenden, G., *et al. J. Chem. Soc., Chem. Comm.* **1980**, 1195.
Pattenden, G., *et al. J. Chem. Soc., Perkin Trans. I* **1983**, 1913.

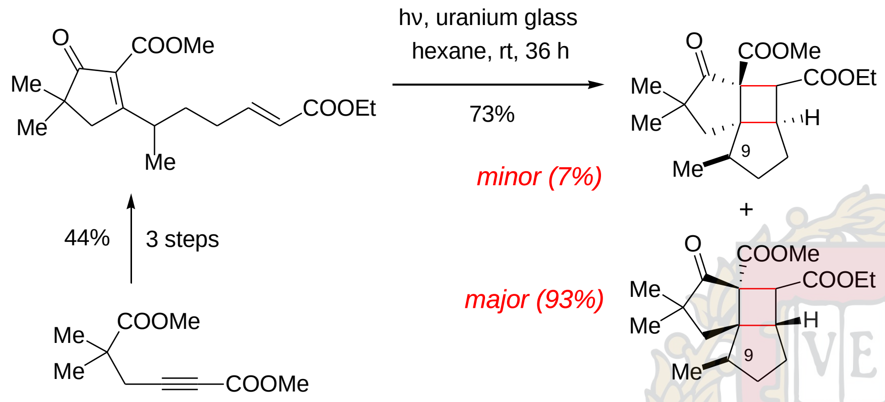
(+)-Longifolene and (+)-Sativene



Oppolzer, W., *et al. J. Am. Chem. Soc.* **1978**, *100,* 2583.
Oppolzer, W., *et al. Helv. Chim. Acta.* **1984**, *67*, 1154.

[2+2] Photocycloaddiltion: Synthetic Applications

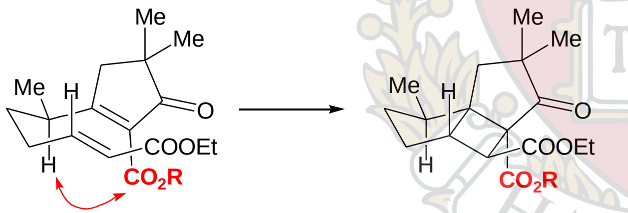
(±)-Pentalenene, (±)-Pentalenic Acid & (±)-Deoxypentalenic Acid from a Common Precursor



R	C-9 dr
Me	13:1
Et	17:1
i-Pr	>20:1

Varying the size of the indicated alkyl group influenced the stereoselectivity

Stereochemical rationale (Crimmins)

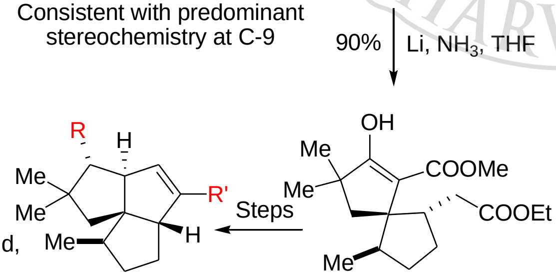


Consistent with predominant stereochemistry at C-9

R=H, R'=Me, Pentalenene, nine steps, 27%

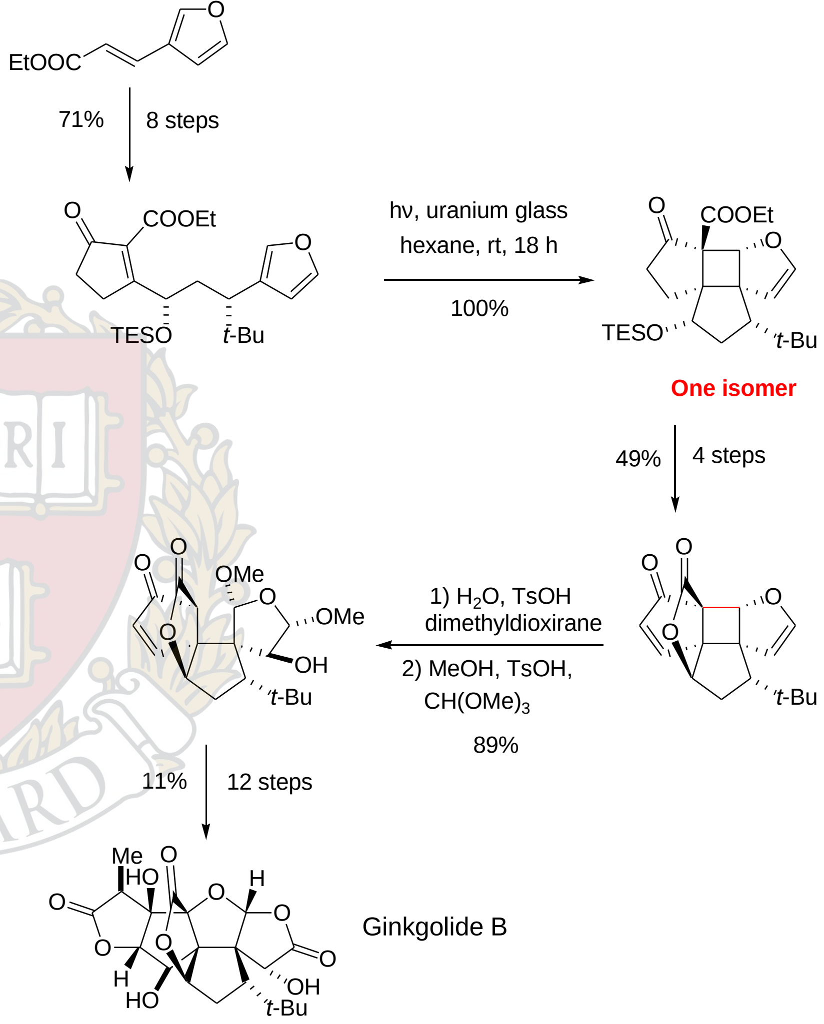
R=OH, R'=COOH, Pentalenic acid, eight steps, 42%

R=H, R'=COOH, Deoxypentalenic acid, eleven steps, 22%

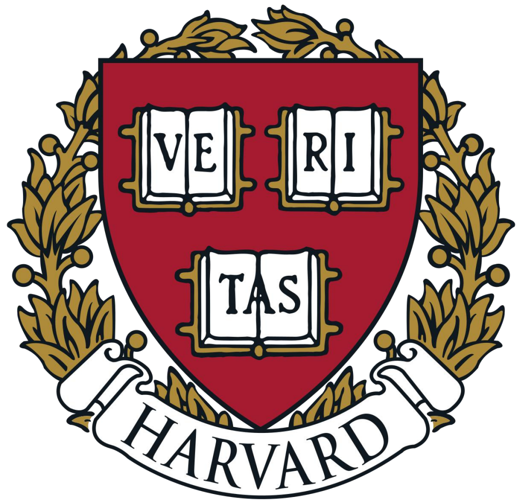


Crimmins, M.T., *et al. J. Org. Chem.* **1984**, *49,* 2076.
Crimmins, M.T., *et al. J. Am. Chem. Soc.* **1986**, *108,* 800.

(±)-Ginkgolide B



Crimmins, M.T. *et al. J. Am. Chem. Soc.* **1999**, *121*, 10249.
Crimmins, M.T. *et al. Tetrahedron Lett.* **1989**, *30*, 5997.


VE RI
TAS
HARVARD