

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 1

Introduction to FMO Theory

- General Bonding Considerations
- The H₂ Molecule Revisited (Again!)
- Donor & Acceptor Properties of Bonding & Antibonding States
- Hyperconjugation and "Negative" Hyperconjugation
- Anomeric and Related Effects

■ Reading Assignment for week:

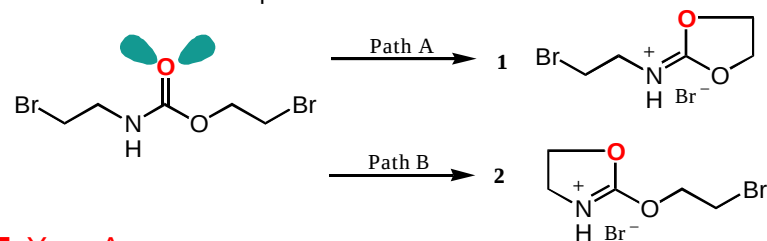
- A. Carey & Sundberg: **Part A**; Chapter 1
- B. Fleming, Chapter 1 & 2
- C. Fukui, *Acc. Chem. Res.* **1971**, *4*, 57.
- D. O. J. Curnow, *J. Chem. Ed.* **1998**, *75*, 910.
- E. J. I. Brauman, *Science*, **2002**, *295*, 2245.

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?



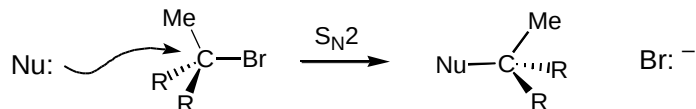
■ Your Answer

Universal Effects Governing Chemical Reactions

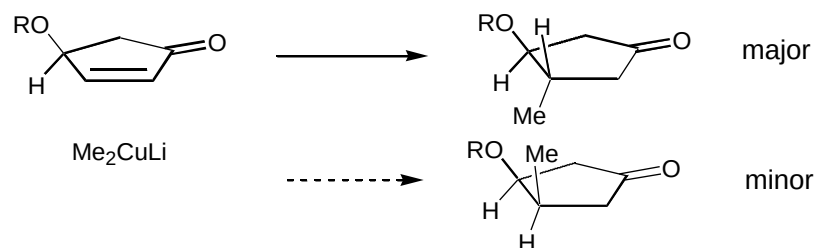
There are three:

■ Steric Effects

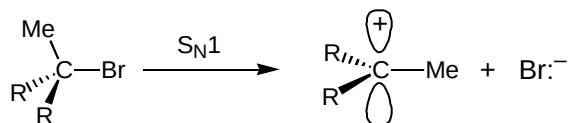
Nonbonding interactions (Van der Waals repulsion) between substituents within a molecule or between reacting molecules



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



■ Electronic Effects (Inductive Effects):

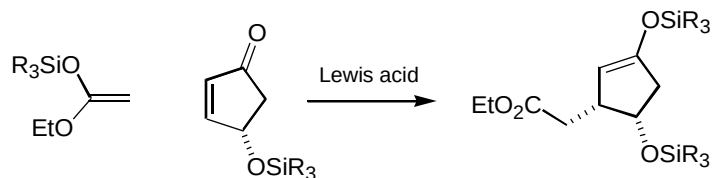


rate decreases as R becomes more electronegative

Inductive Effects: Through-bond polarization

Field Effects: Through-space polarization

Your thoughts on this transformation



Danishofsky, *JOC* **1991**, 56, 387

diastereoselection >94 : 6

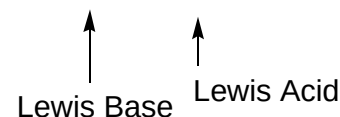
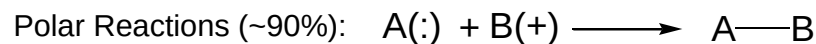
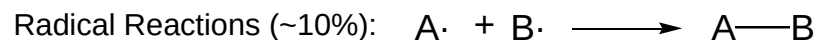
■ Stereoelectronic Effects

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

Fukui Postulate for reactions:

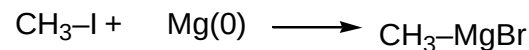
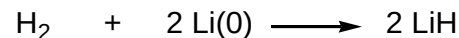
"During the course of chemical reactions, the interaction of the highest filled (HOMO) and lowest unfilled (antibonding) molecular orbital (LUMO) in reacting species is very important to the stabilization of the transition structure."

■ General Reaction Types



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

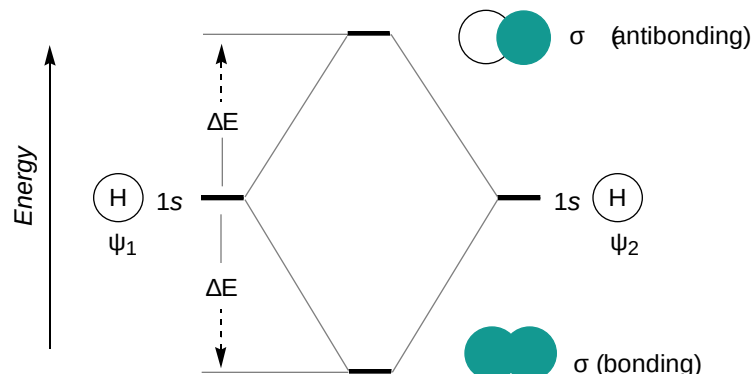
■ Examples to consider



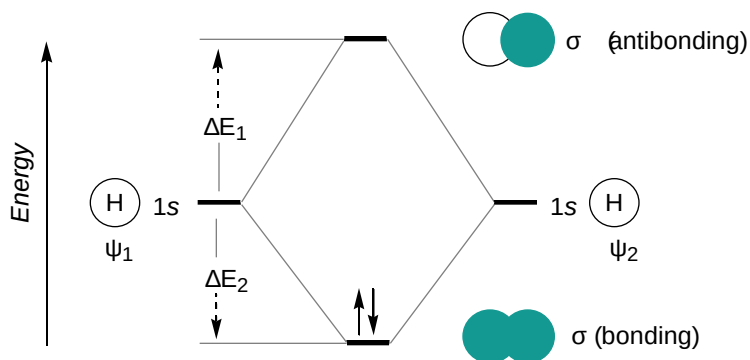
The H₂ Molecule (again!!)

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 ΔE₁ is greater than ΔE₂. 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):

$$\text{Bonding MO} \quad \sigma = C_1\psi_1 + C_2\psi_2$$

$$\text{Antibonding MO} \quad \sigma^* = C_1^*\psi_1 - C_2^*\psi_2$$

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

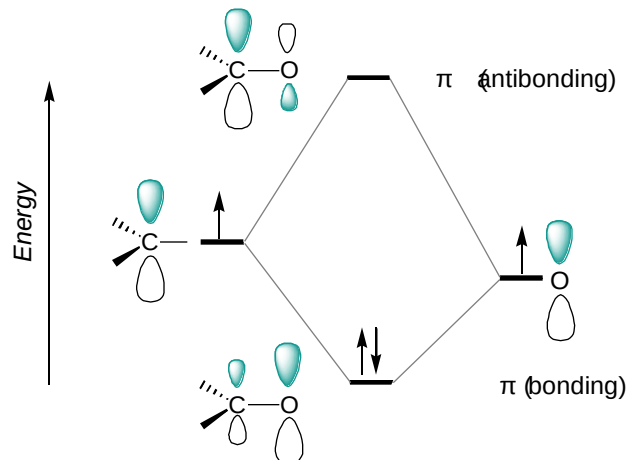
■ **Rule Three:** $(C_1)^2 + (C_2)^2 = 1$

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

■ **Rule Four:** $\text{bonding}(C_1)^2 + \text{antibonding}(C_1^*)^2 = 1$

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 (δE_{cov}) and an ionic contribution (δE_{ionic}).**

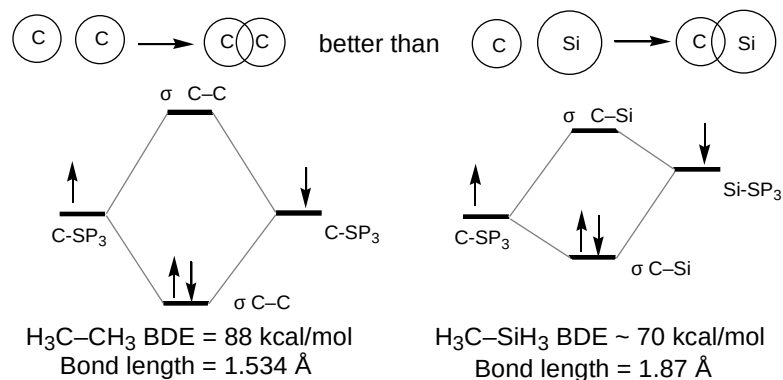
$$\text{Bond Energy (BDE)} = \delta E_{\text{covalent}} + \delta E_{\text{ionic}} \quad (\text{Fleming, page 27})$$

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.



This trend is even more dramatic with pi-bonds:

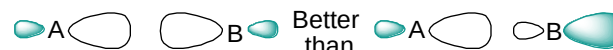
$$\pi \text{ C}-\text{C} = 65 \text{ kcal/mol} \quad \pi \text{ C}-\text{Si} = 36 \text{ kcal/mol} \quad \pi \text{ Si}-\text{Si} = 23 \text{ kcal/mol}$$

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

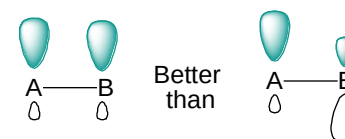
Formation of a weak bond will lead to a corresponding low-lying antibonding orbital. Such structures are reactive as both nucleophiles & electrophiles

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

For σ Bonds:



For π Bonds:



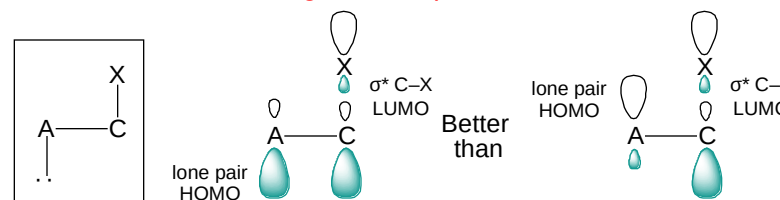
This is a simple notion with very important consequences. It surfaces in the delocalized bonding which occurs in the competing anti (favored) syn (disfavored) E2 elimination reactions. Review this situation.

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

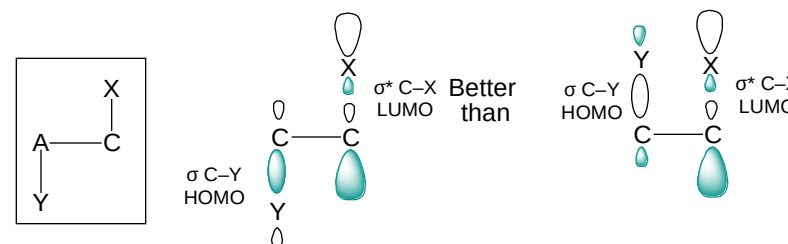
This is a corollary to the preceding generalization.

There are two common situations.

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

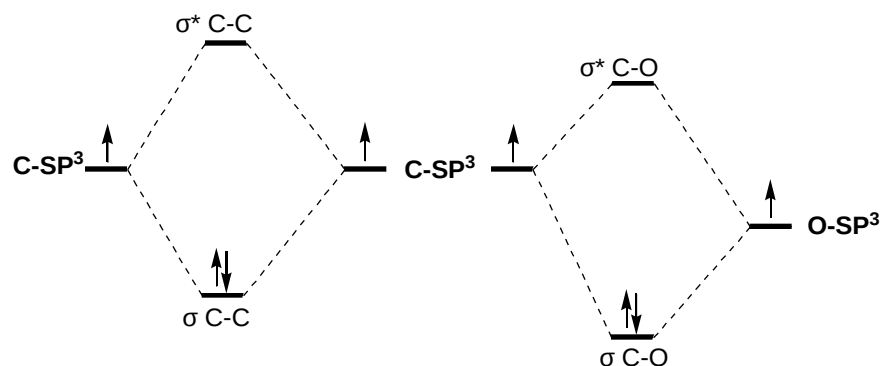


Case-2: Two anti sigma bonds



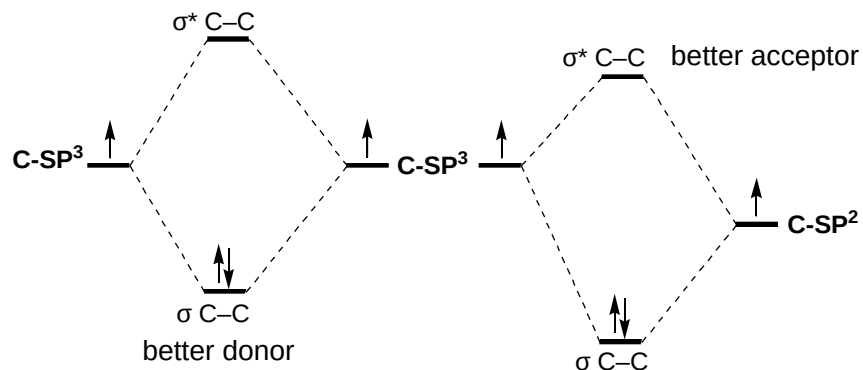
Donor Acceptor Properties of C-C & C-O Bonds

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

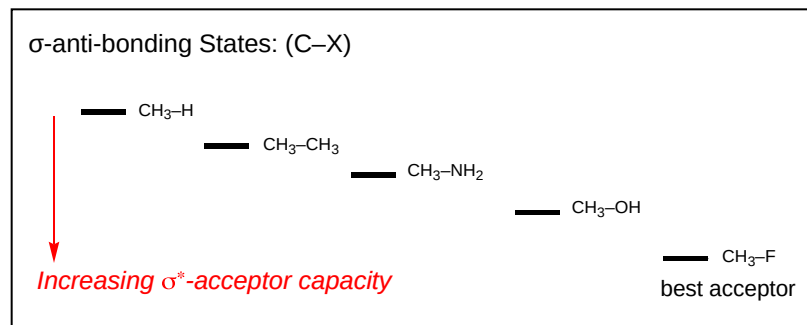
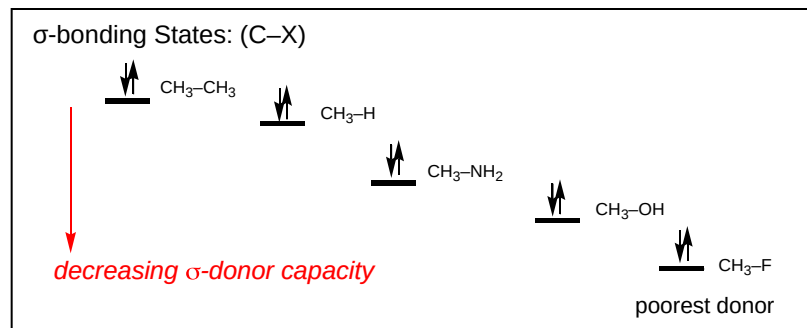
Donor Acceptor Properties of C_{SP^3} - C_{SP^3} & C_{SP^3} - C_{SP^2} Bonds

■ The greater electronegativity of C_{SP^2} lowers both the bonding & antibonding C-C states. Hence:

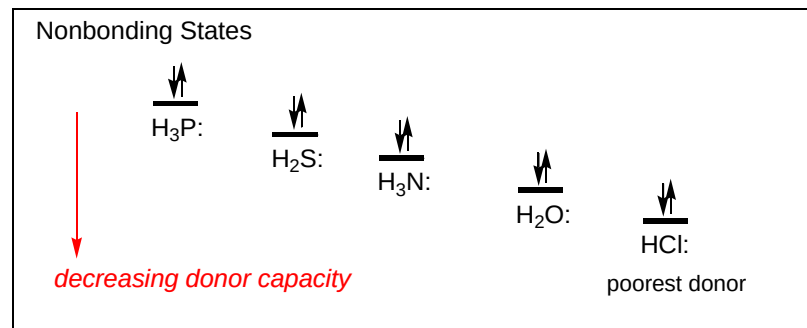
- σ C_{SP^3} - C_{SP^3} is a better donor orbital than σ C_{SP^3} - C_{SP^2}
- σ C_{SP^3} - C_{SP^2} is a better acceptor orbital than σ C_{SP^3} - C_{SP^3}

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 $X = C, N, O, F, \text{ \& H}$.

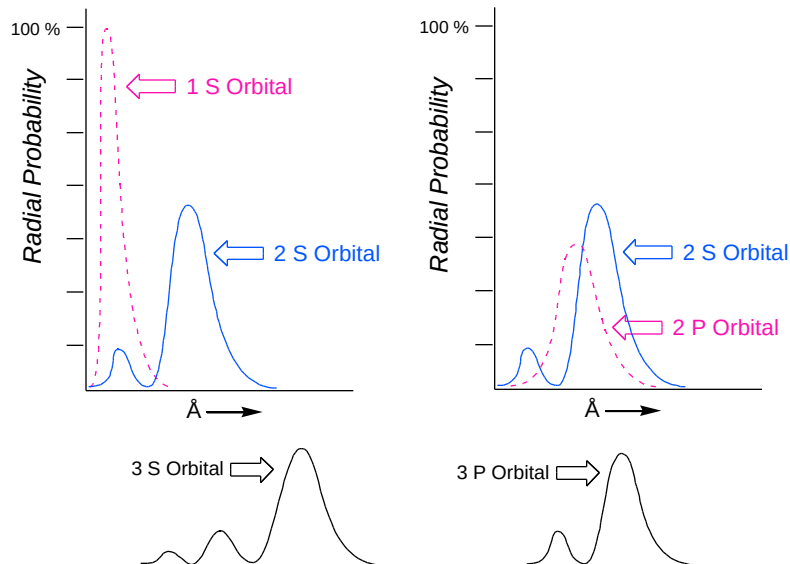


The following are trends for the energy levels of *nonbonding states* of several common molecules. Trend was established by photoelectron spectroscopy.



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.



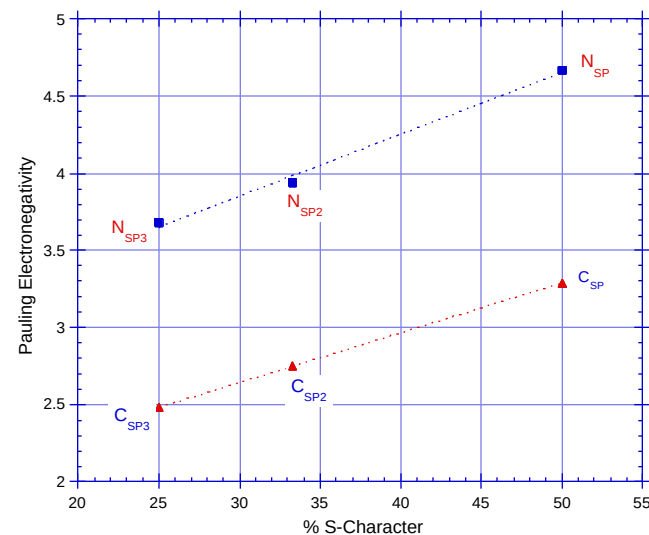
S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in S-states "see" a higher nuclear charge.

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

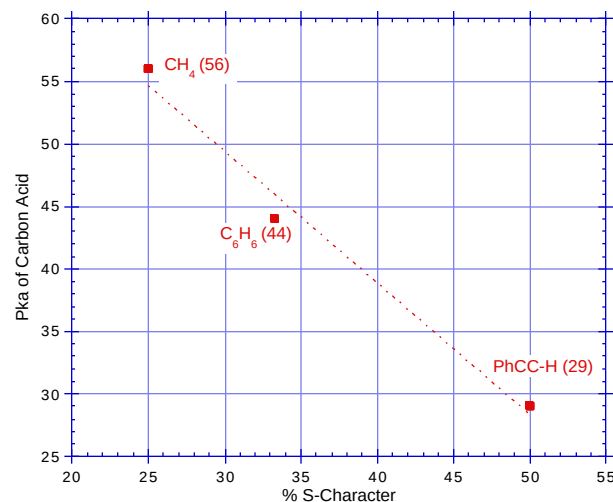


The above trend indicates that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

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

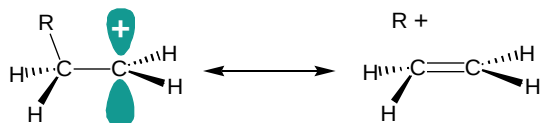


There is a direct relationship between %S character & hydrocarbon acidity



- 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.

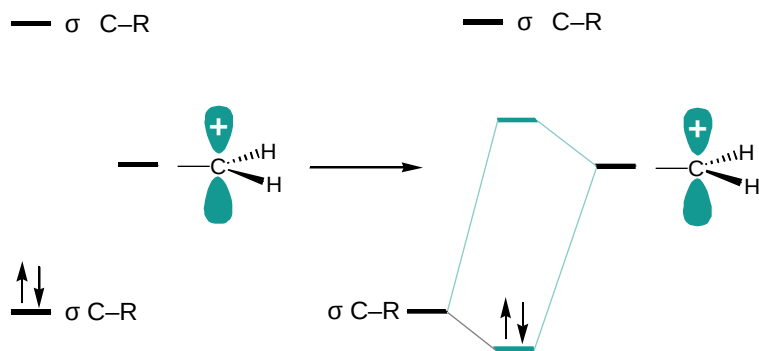


The graphic illustrates the fact that the C-R bonding electrons can "delocalize" to stabilize the electron deficient carbocationic center.

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



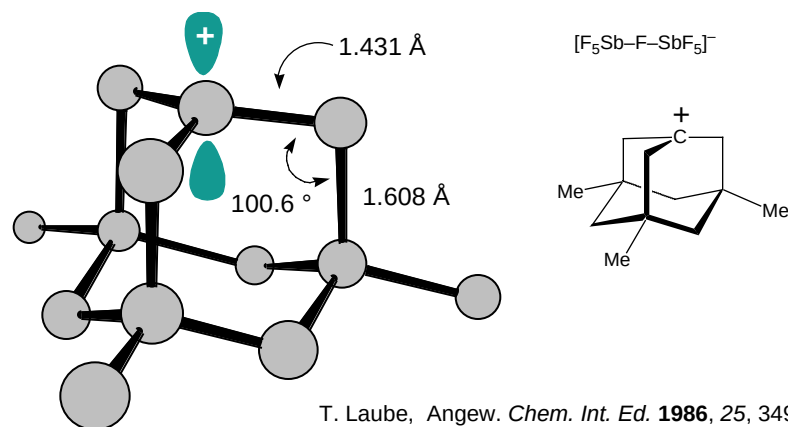
- Take a linear combination of σ C-R and CSP_2 p-orbital:

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

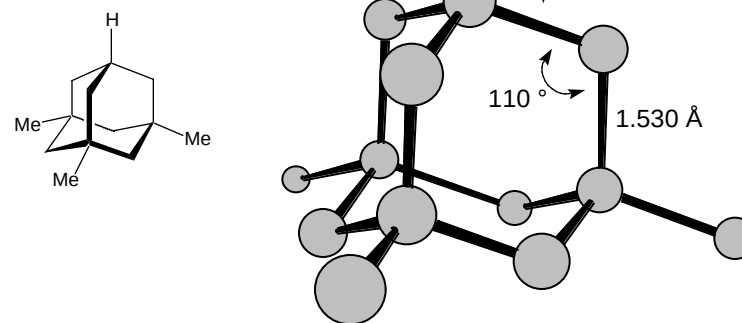
Physical Evidence for Hyperconjugation

- Bonds participating in the hyperconjugative interaction, e.g. C-R, will be lengthened while the $\text{C}(+)\text{-C}$ bond will be shortened.

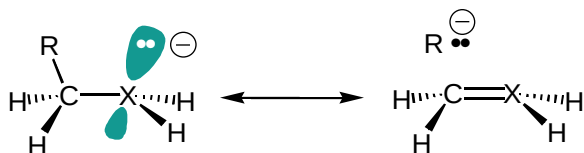
First X-ray Structure of an Aliphatic Carbocation



The Adamantane Reference (MM-2)



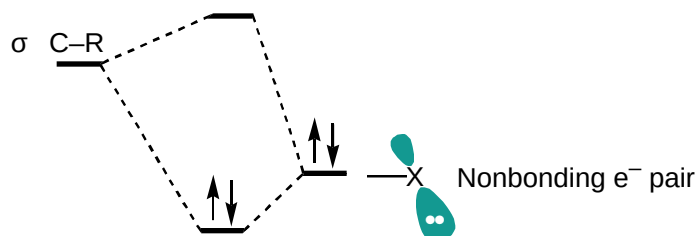
- Delocalization of nonbonding electron pairs into vicinal antibonding orbitals is also possible



This delocalization is referred to as "Negative" hyperconjugation

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

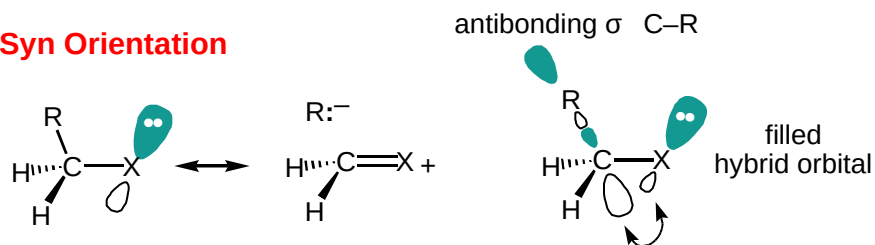
The Molecular Orbital Description



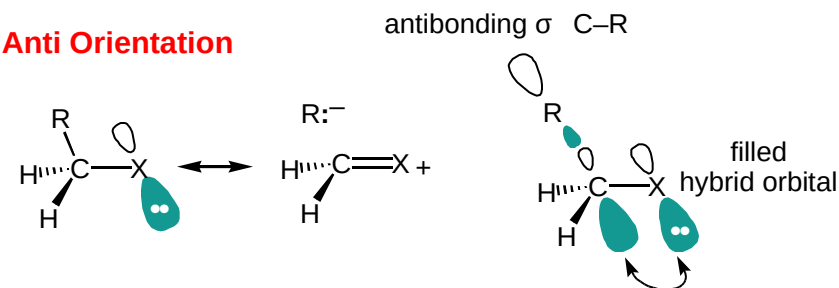
As the antibonding C-R orbital decreases in energy, the magnitude of this interaction will increase

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.

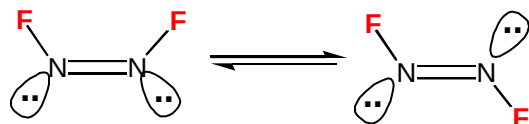
The Expected Structural Perturbations

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

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



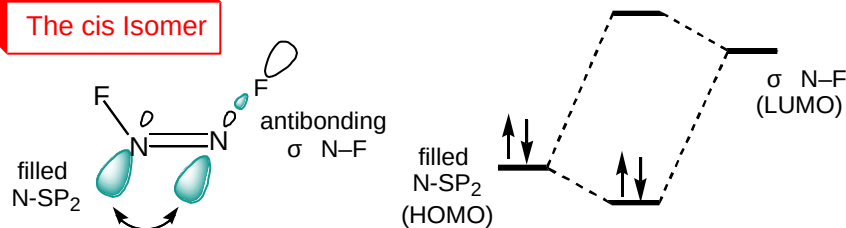
There are two logical reasons why the trans isomer should be more stable than the cis isomer.

- 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.

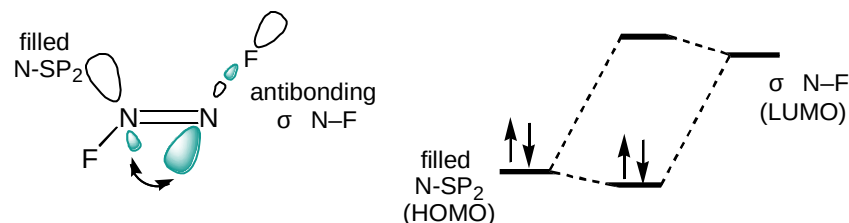
The cis Isomer



- 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.



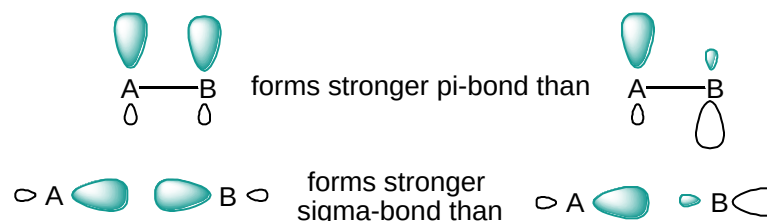
- In this geometry the "small lobe" of the filled N- SP_2 is required to overlap with the large lobe of the antibonding C–F orbital. Hence, when the new MO's are generated the new bonding orbital is not as stabilizing as for the cis isomer.

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

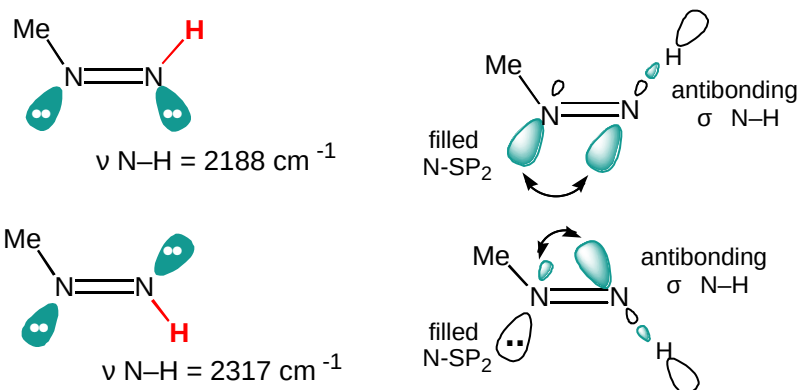
Orbital orientation is important for optimal orbital overlap.



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.

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.

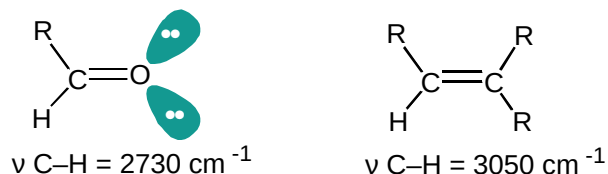


■ The low-frequency N–H shift in the cis isomer is a result of N–H bond weakening due to presence of the anti lone pair on the vicinal nitrogen which is interacting with the N–H antibonding orbital. Note that the orbital overlap is not nearly as good from the trans isomer

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

Aldehyde C–H Infrared Stretching Frequencies

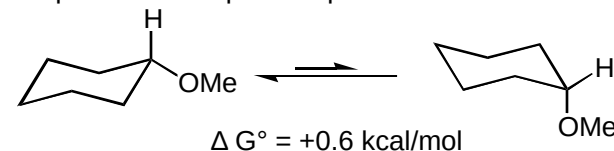
The IR C–H stretching frequency for aldehydes is lower than the closely related olefin C–H stretching frequency. For years this observation has gone unexplained.



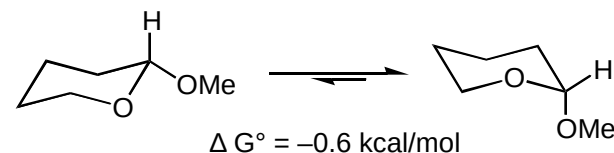
■ We now conclude that this is another example of the vicinal lone pair effect.

The Anomeric Effect

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

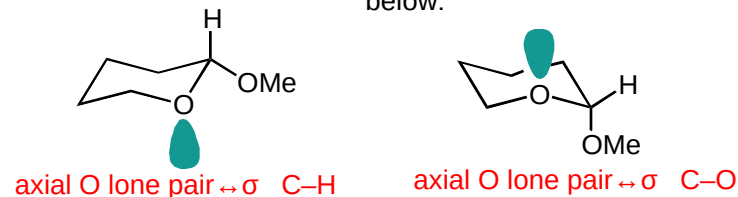


What is unexpected is that the closely related 2-methoxytetrahydropyran prefers the axial conformation:



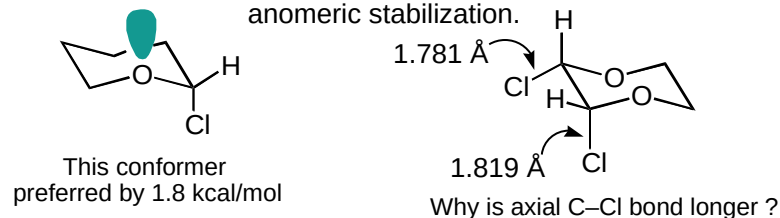
■ That effect which provides the stabilization of the axial OR conformer which overrides the inherent steric bias of the substituent is referred to as the anomeric effect.

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



■ 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.

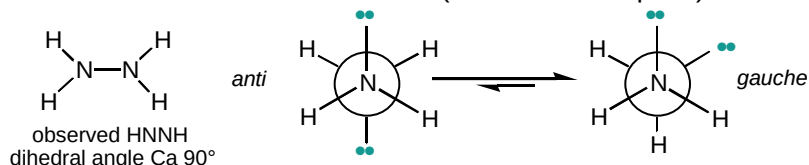


The interaction of filled orbitals with adjacent antibonding orbitals can have an ordering effect on the structure which will stabilize a particular conformation.

Here are several examples of such a phenomenon called the gauche effect:

Hydrazine

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

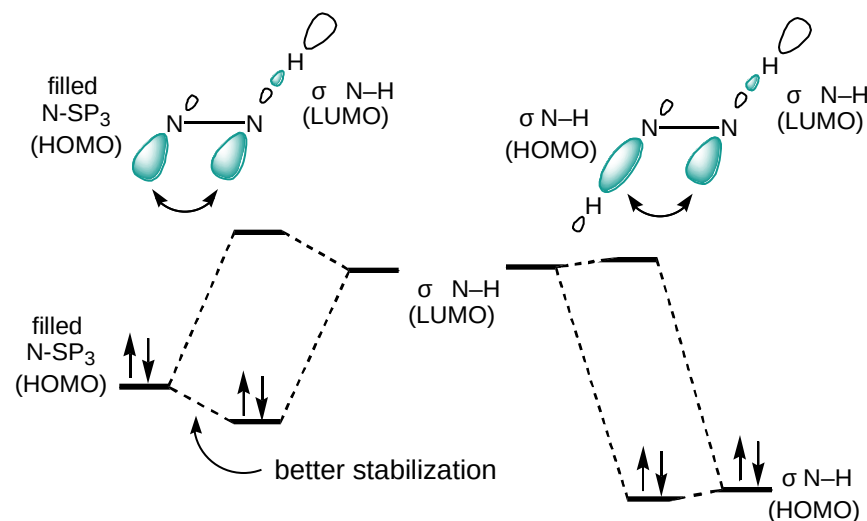


There is a logical reason why the anti isomer should be more stable than the gauche isomer. The nonbonding lone pair orbitals in the gauche isomer should be destabilizing due to electron-electron repulsion.

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 $\leftrightarrow$ σ^* N-H; (b) σ N-H $\leftrightarrow$ σ^* N-H



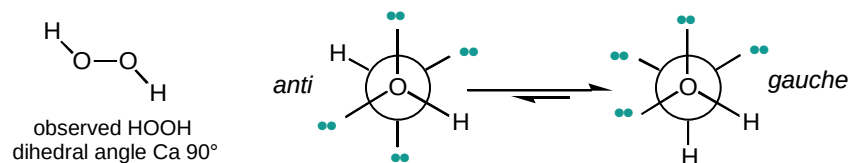
The closer in energy the HOMO and LUMO the better the resulting stabilization through delocalization.

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

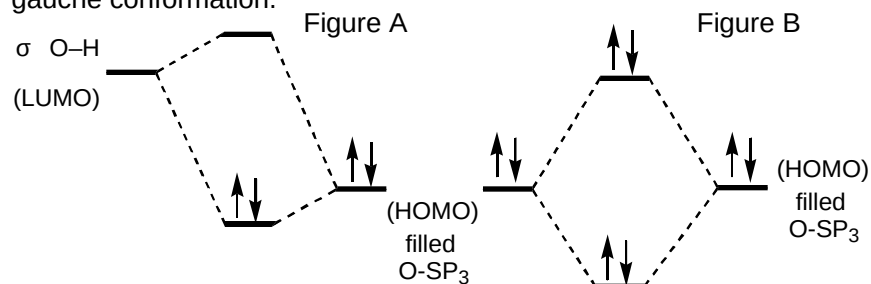
The trend observed for hydrazine holds for oxygen derivatives as well

Hydrogen peroxide

H₂O₂ can exist in either gauche or anti conformations (relative to hydrogens).
The gauche conformer is preferred.



- 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 $\text{XCH}_2\text{--OH}$ where $\text{X} = \text{OCH}_3$ 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 QVBM 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.

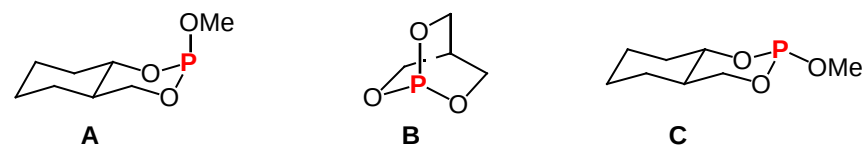
Juaristi, E. and G. Cuevas (1992). "Recent studies on the anomeric effect." *Tetrahedron* **48**: 5019.

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)

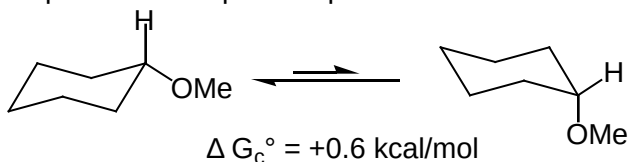
The three phosphites illustrated below exhibit a 750-fold span in reactivity with a test electrophile (eq 1) (Gorenstein, *JACS* **1984**, *106*, 7831).



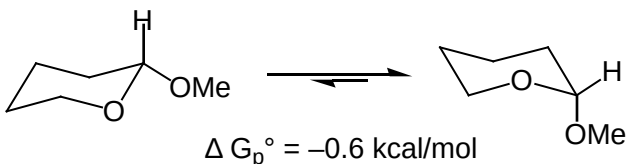
Rank the phosphites from the least to the most nucleophilic and provide a concise explanation for your predicted reactivity order.

The Anomeric Effect

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



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



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.

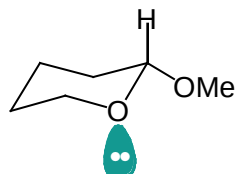
Let anomeric effect = A

$$\Delta G_p^\circ = \Delta G_c^\circ + A$$

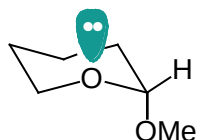
$$A = \Delta G_p^\circ - \Delta G_c^\circ$$

$$A = -0.6 \text{ kcal/mol} - 0.6 \text{ kcal/mol} = -1.2 \text{ kcal/mol}$$

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



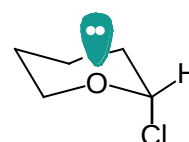
axial O lone pair $\leftrightarrow \sigma^* \text{ C-H}$



axial O lone pair $\leftrightarrow \sigma^* \text{ C-O}$

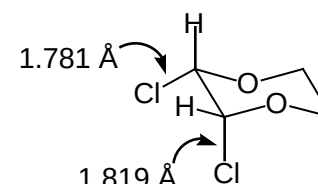
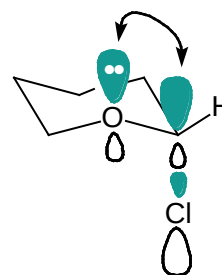
■ Since the antibonding C-O orbital is a better acceptor orbital than the antibonding C-H bond, the axial OMe conformer is better stabilized by this interaction which is worth ca. 1.2 kcal/mol.

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

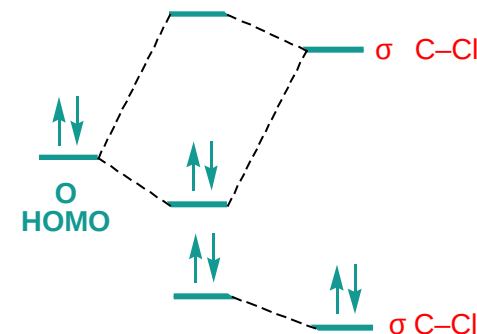


This conformer preferred by 1.8 kcal/mol

axial O lone pair $\leftrightarrow \sigma^* \text{ C-Cl}$

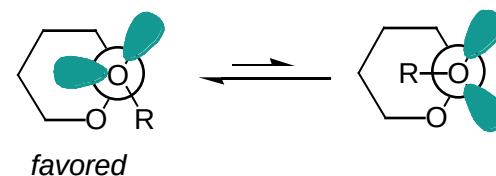
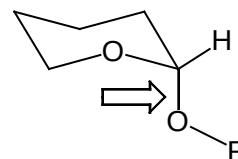


Why is axial C-Cl bond longer ?



The Exo-Anomeric Effect

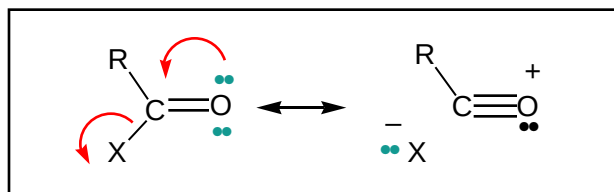
■ There is also a rotational bias that is imposed on the exocyclic C-OR bond where one of the oxygen lone pairs prefers to be anti to the ring sigma C-O bond



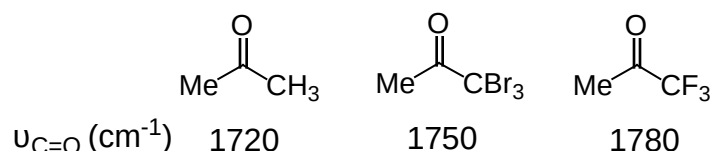
A. J. Kirby, *The Anomeric and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, 1983

E. Jurasti, G. Cuevas, *The Anomeric Effect*, CRC Press, 1995

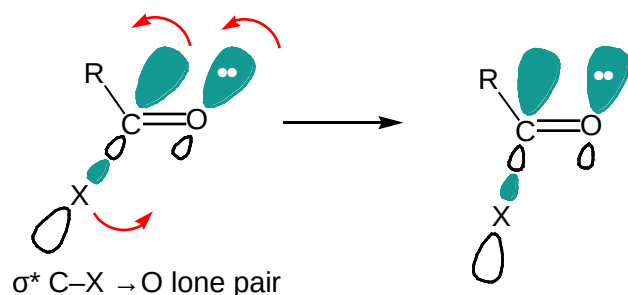
Do the following valence bond resonance structures have meaning?



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



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

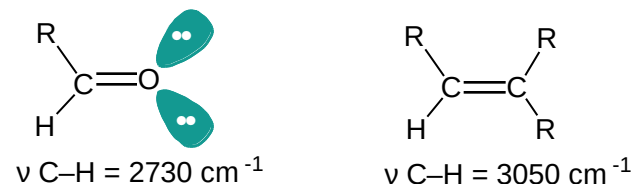


Evidence for this distortion has been obtained by X-ray crystallography

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

Aldehyde C-H Infrared Stretching Frequencies

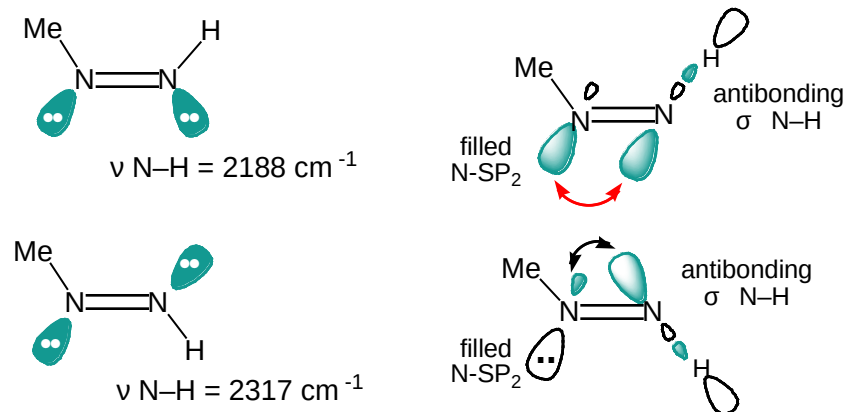
Prediction: The IR C-H stretching frequency for aldehydes is lower than the closely related olefin C-H stretching frequency. For years this observation has gone unexplained.



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.

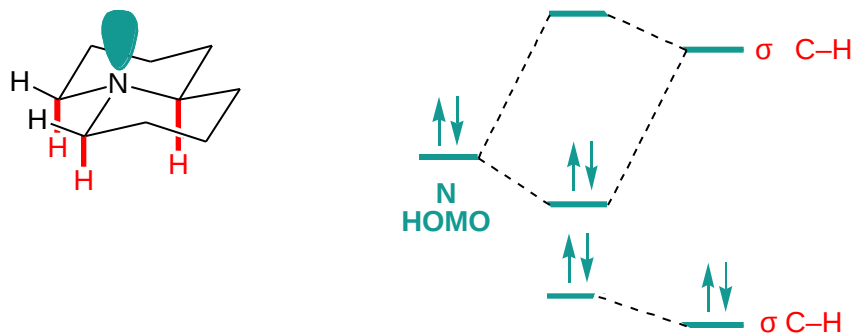
The N-H stretching frequency of cis-methyl diazene is 200 cm^{-1} lower than the trans isomer.



■ 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.

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–H₄, C–H₆, & C–H₁₀ 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

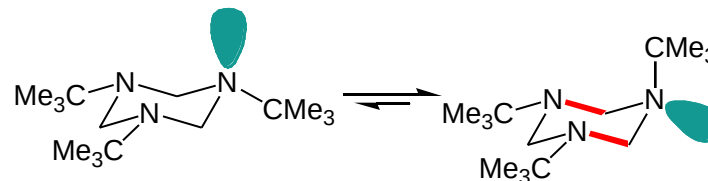
H₁₀ (axial): shifted furthest upfield

H₆, H₄: $\Delta\delta = \delta H_{\text{axial}} - \delta H_{\text{equatorial}} = -0.93 \text{ ppm}$

Protonation on nitrogen reduces $\Delta\delta$ to -0.5ppm

H. P. Hamlow et. al., *Tet. Lett.* **1964** 2553

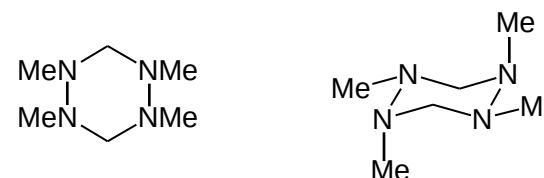
J. B. Lambert et. al., *JACS* **1967** 89 3761



$$\Delta G^\circ = -0.35 \text{ kcal/mol}$$

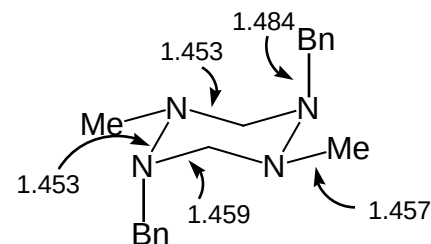
A. R. Katritzky et. al., *J. Chemm. Soc. B* **1970** 135

Favored Solution Structure (NMR)



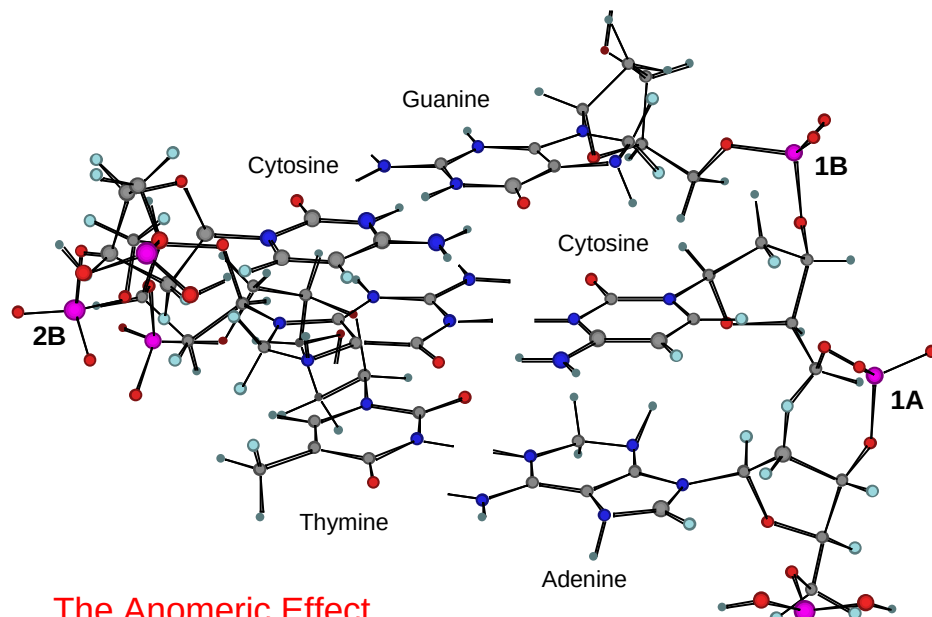
J. E. Anderson, J. D. Roberts, *JACS* **1967** 96 4186

Favored Solid State Structure (X-ray crystallography)



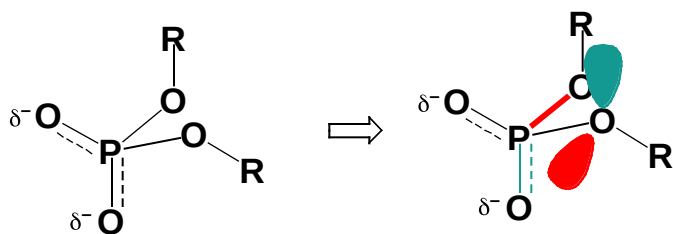
A. R. Katrizky et. al., *J. C. S. Perkin II* **1980** 1733

Calculated Structure of ACG–TGC Duplex

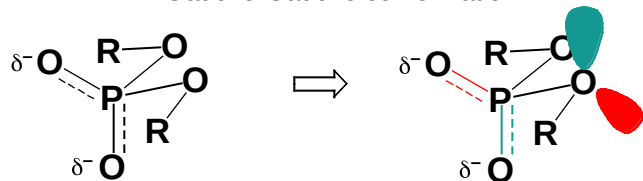


The Anomeric Effect

Acceptor orbital hierarchy: $\delta^* \text{P-OR}^* > \delta^* \text{P-O}^-$



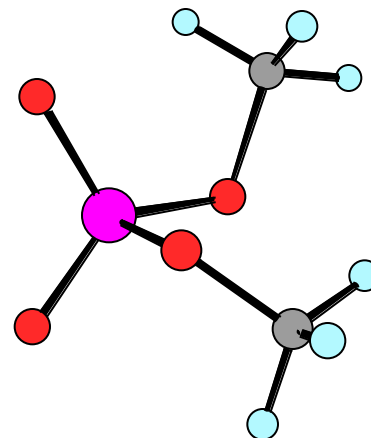
Gauche-Gauche conformation



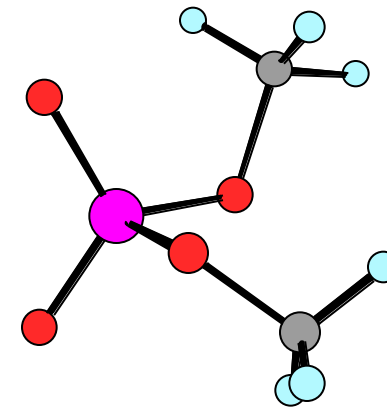
Anti-Anti conformation

Gauche-Gauche conformation affords a better donor-acceptor relationship

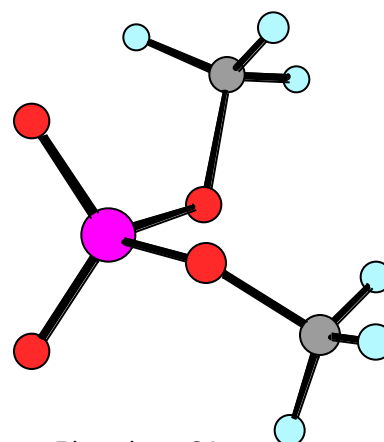
The Phospho-Diesters Excised from Crystal Structure



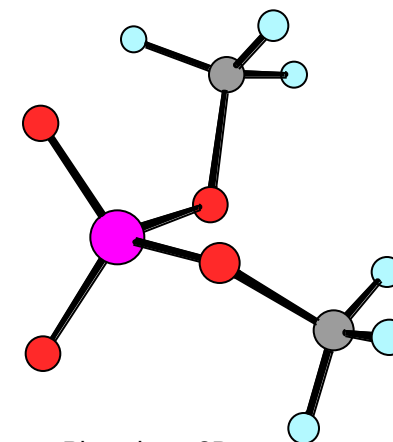
Phosphate-1A



Phosphate-1B



Phosphate-2A

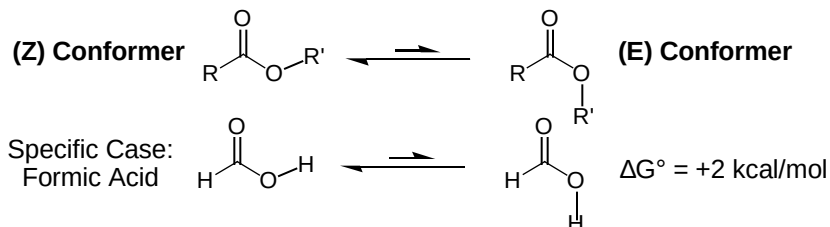


Phosphate-2B

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.

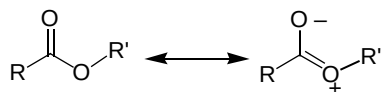
■ **Conformations:** There are 2 planar conformations.



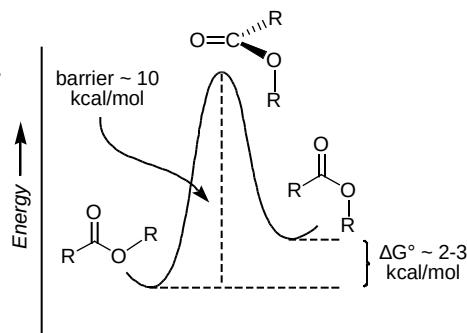
The (E) conformation of both acids and esters is less stable by 2-3 kcal/mol. If this equilibrium were governed only by steric effects one would predict that the (E) conformation of formic acid would be more stable (H smaller than =O). Since this is not the case, there are electronic effects which must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

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

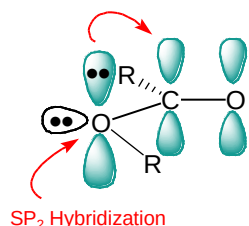
These resonance structures suggest hindered rotation about =C-OR bond. This is indeed observed:



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.

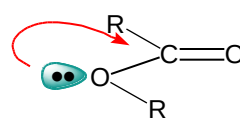


The filled oxygen p-orbital interacts with pi (and pi*) C=O to form a 3-centered 4-electron bonding system.

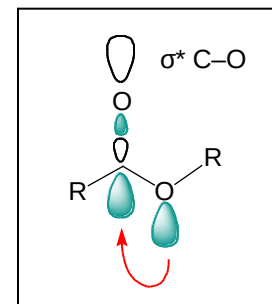
■ **Oxygen Hybridization:** Note that the alkyl oxygen is sp^2 . Rehybridization is driven by system to optimize pi-bonding.

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

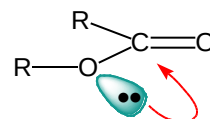
(Z) Conformer



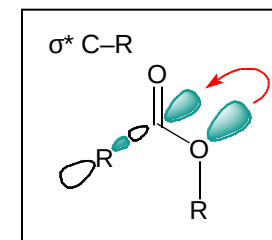
In the (Z) conformation this lone pair is aligned to overlap with $\sigma^* \text{C-O}$.



(E) Conformer



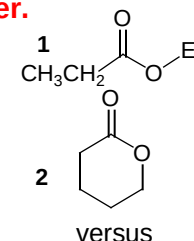
In the (E) conformation this lone pair is aligned to overlap with $\sigma^* \text{C-R}$.



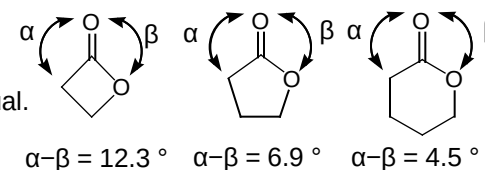
Since $\sigma^* \text{C-O}$ is a better acceptor than $\sigma^* \text{C-R}$ (where R is a carbon substituent) it follows that the (Z) conformation is stabilized by this interaction.

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:

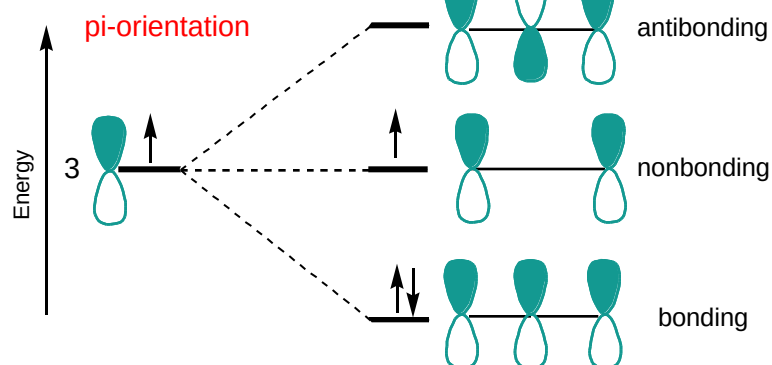


- Lactone **2** is significantly more susceptible to nucleophilic attack at the carbonyl carbon than **1**? Explain.
- Lactone **2** is significantly more prone to enolization than **1**? In fact the pK_a of **2** is ~25 while ester **1** is ~30 (DMSO). Explain.
- In 1985 Burgi, on carefully studying 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



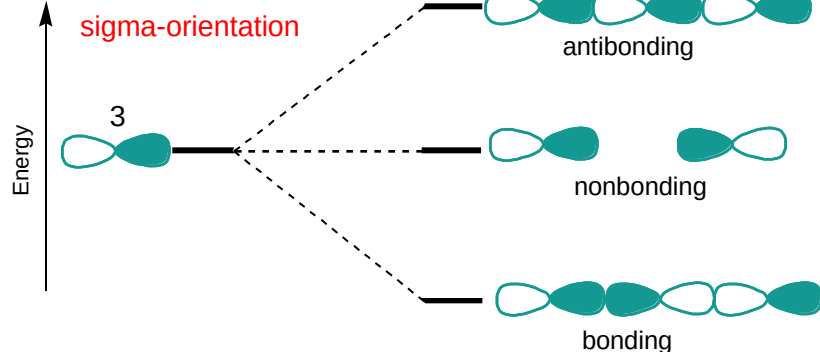
Note that the more nodes there are in the wave function, the higher its energy.

$\text{H}_2\text{C}=\text{CH}-\text{CH}_2^+$ **Allyl carbonium ion:** both pi-electrons in bonding state

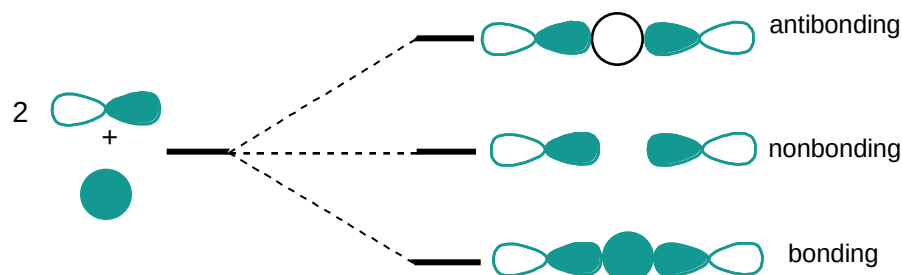
$\text{H}_2\text{C}=\text{CH}-\dot{\text{C}}\text{H}_2$ **Allyl Radical:** 2 electrons in bonding orbital plus one in nonbonding MO.

$\text{H}_2\text{C}=\text{CH}-\text{CH}_2^-$ **Allyl Carbanion:** 2 electrons in bonding orbital plus 2 in nonbonding MO.

Case 2: 3 p-Orbitals



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

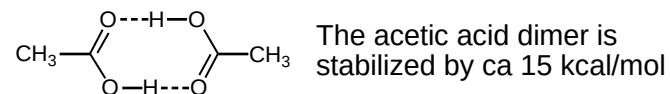


Case 4: 2 s-Orbitals; 1 p-orbital

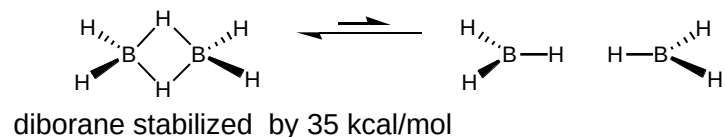
Do this as an exercise

Examples of three-center bonds in organic chemistry

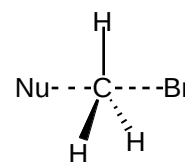
A. H-bonds: (3-center, 4 electron)



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



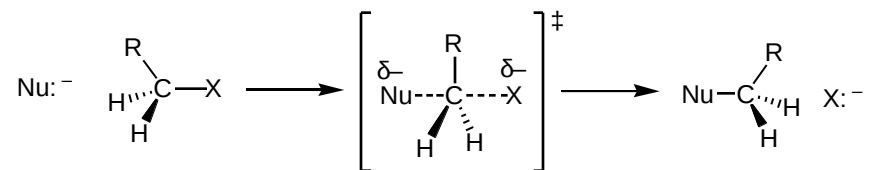
C. The $\text{S}_{\text{N}}2$ Transition state: (3-center, 4 electron)



The $\text{S}_{\text{N}}2$ transition state approximates a case 2 situation with a central carbon p-orbital

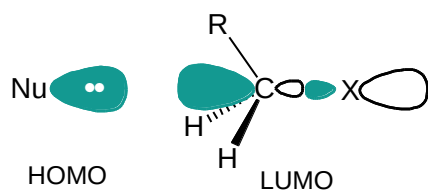
The three orbitals in reactant molecules used are:
 1 nonbonding MO from Nucleophile (2 electrons)
 1 bonding MO σ C-Br (2 electrons)
 1 antibonding MO σ^* C-Br

Why do S_N2 Reactions proceed with backside displacement?

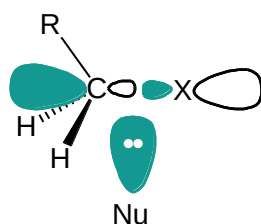


Given the fact that the LUMO on the electrophile is the C–X antibonding orbital, Nucleophilic attack could occur with either inversion or retention.

Inversion



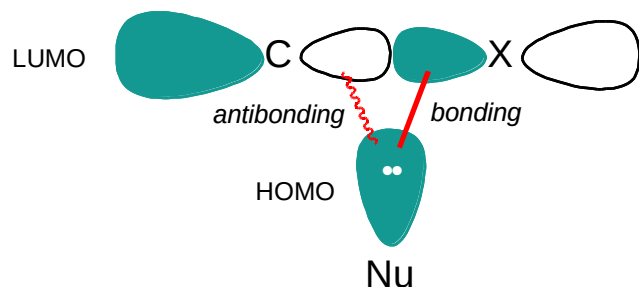
Retention



Constructive overlap between Nu & σ* C–X

Overlap from this geometry results in no net bonding interaction

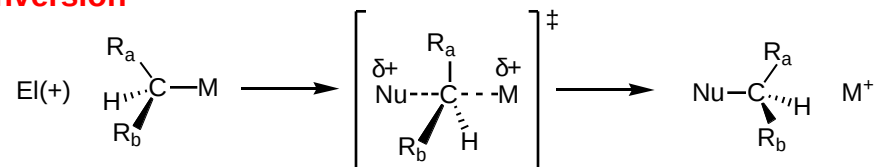
Expanded view of σ* C–X



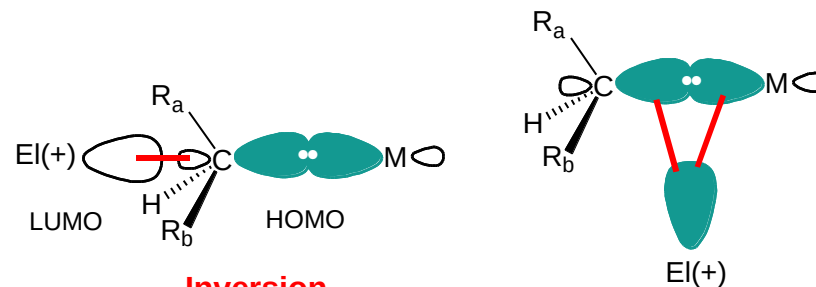
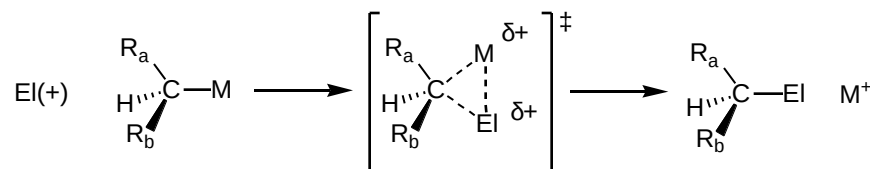
Fleming, page 75-76

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

Inversion



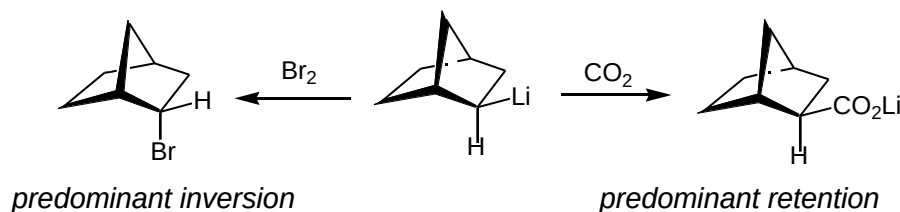
Retention



Inversion

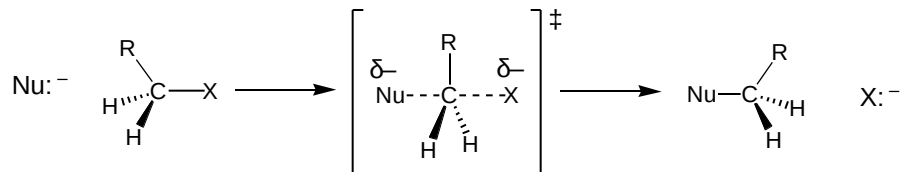
Retention

Examples

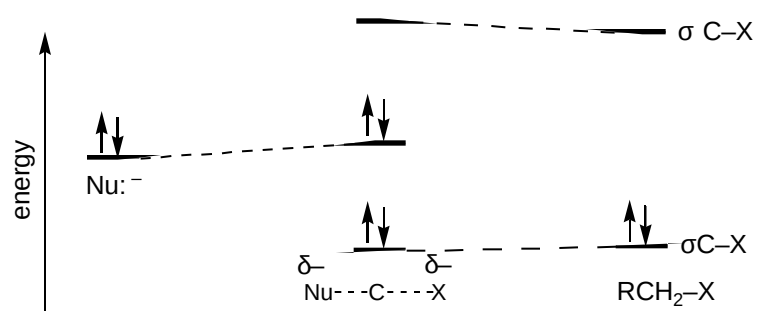


Stereochemistry frequently determined by electrophile structure

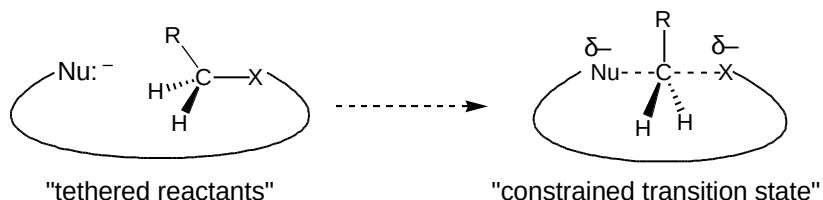
The reaction under discussion:



■ 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 σ C–X and σ C–X:

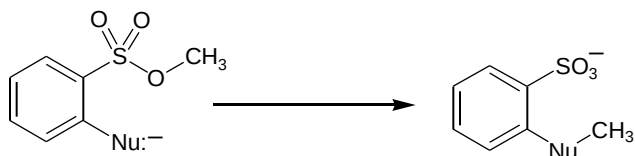


■ Experiments have been designed to probe inherent requirement for achieving a 180° Nu–C–X bond angle: Here both Nu and leaving group are constrained to be part of the same ring.



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

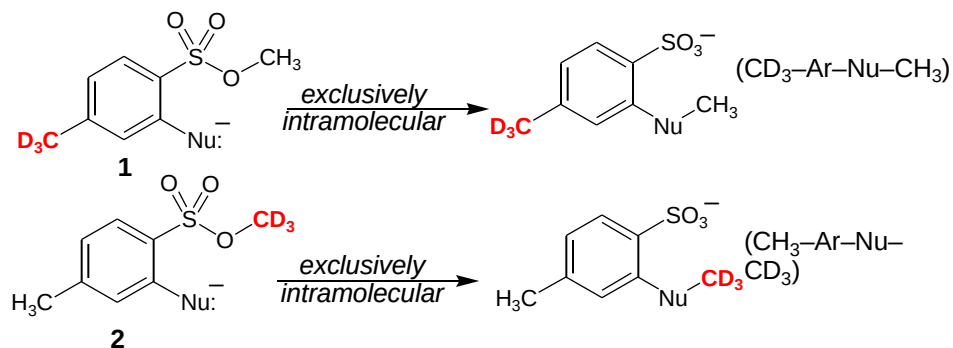
■ The reaction illustrated below proceeds exclusively through bimolecular pathway in contrast to the apparent availability of the intramolecular path.



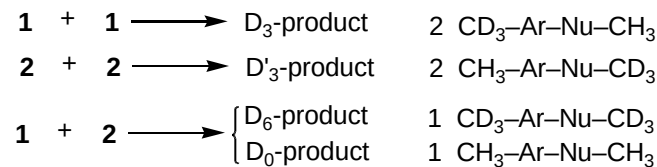
The use of isotope labels to probe mechanism.

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:



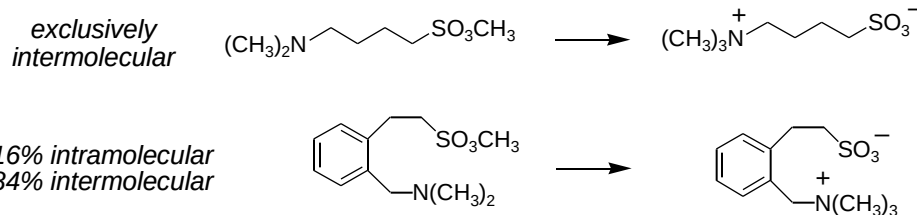
■ If the reaction was **exclusively intermolecular**, products would only contain differing amounts of D-label depending on which two partners underwent reaction. The deuterium content might be analyzed by mass spectrometry. Here are the possibilities:



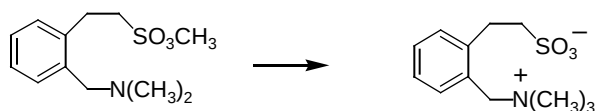
Hence, for the strictly intermolecular situation one should see the following ratios
D₀ : D₃ : D'₃ : D₆ = 1 : 2 : 2 : 1.

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

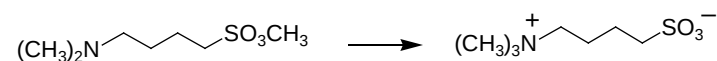
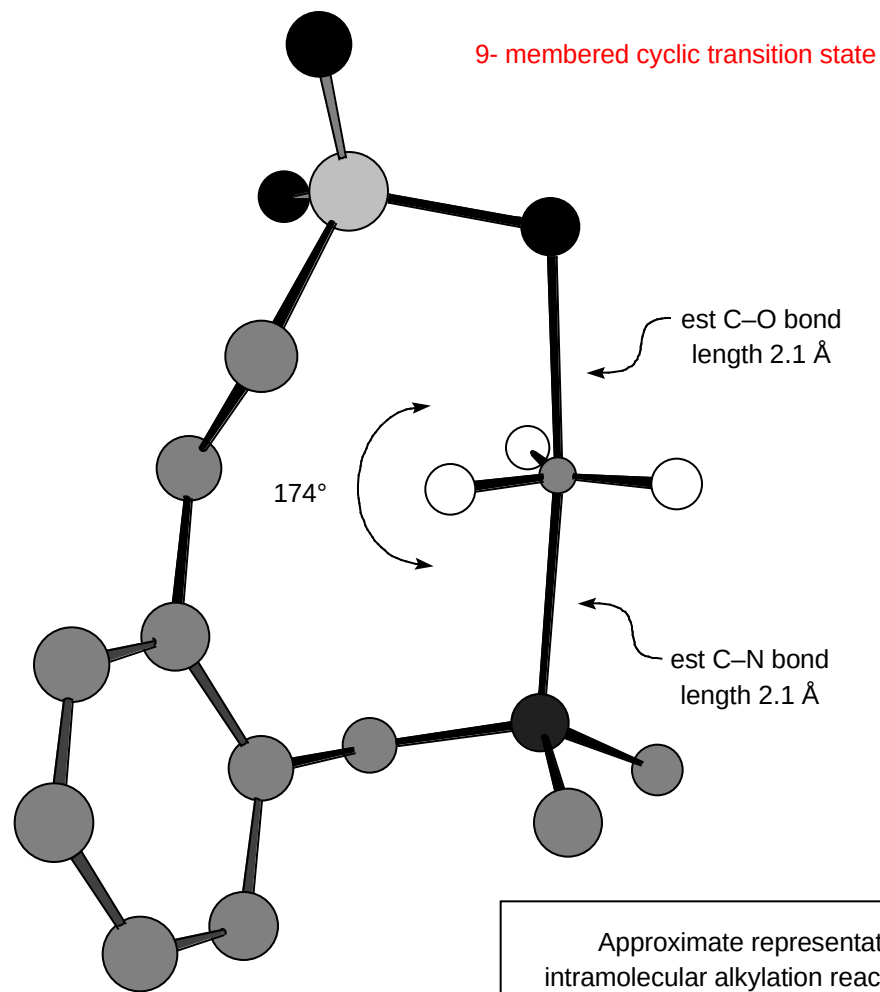
Other Cases:



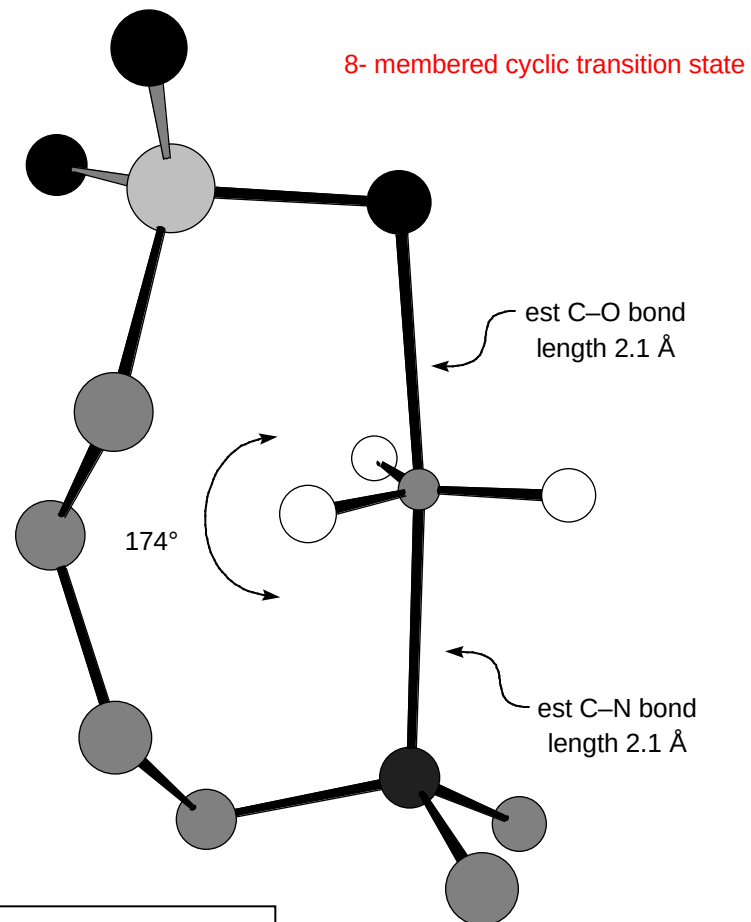
Hence, the Nu–C–X 180° transition state bond angle must be rigidly maintained for the reaction to take place.



16% intramolecular; 84% intermolecular

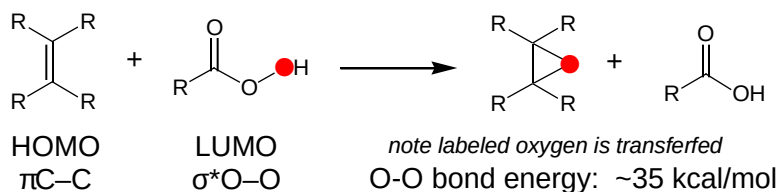


exclusively intermolecular

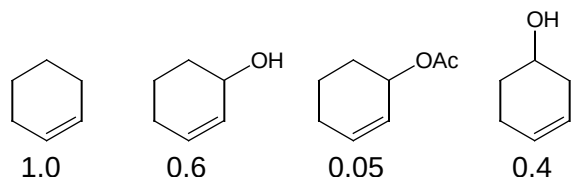


Approximate representation of the transition states of the intramolecular alkylation reactions. Transition state C-O and C-N bond lengths were estimated to be $1.5 \times (\text{C-X})$ bond length of 1.4 Å

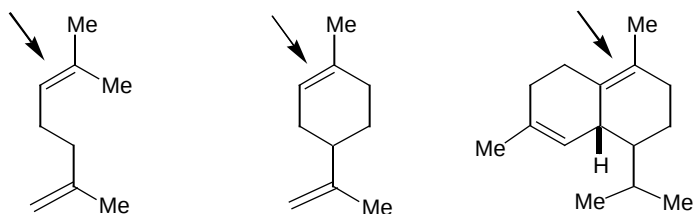
■ The General Reaction:



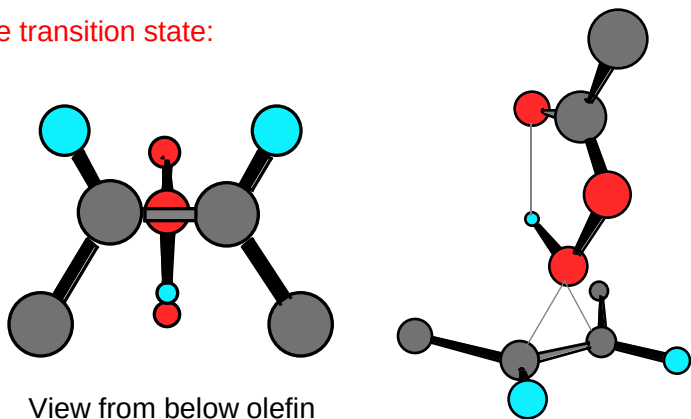
■ Reaction rates are governed by olefin nucleophilicity. The rates of epoxidation of the indicated olefin relative to cyclohexene are provided below:



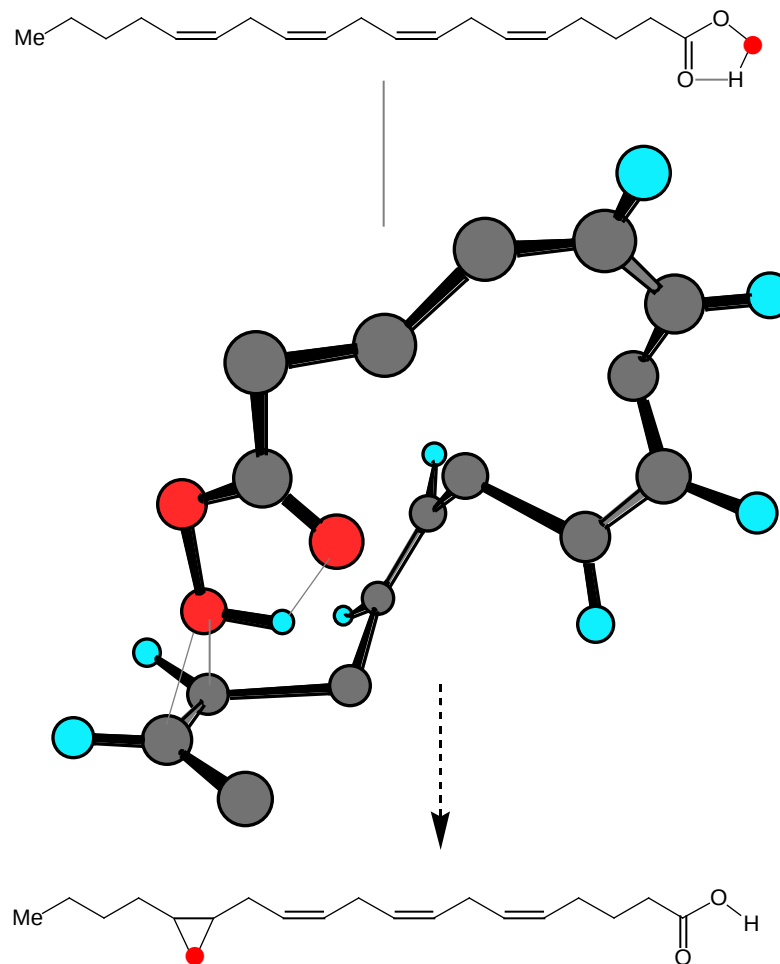
■ The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



■ The transition state:



Per-arachidonic acid Epoxidation

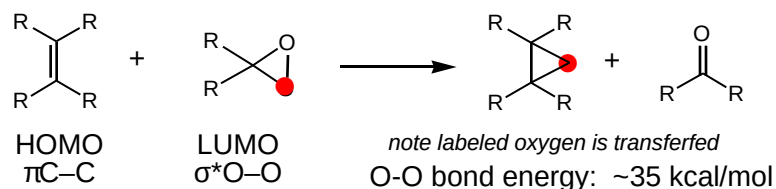


E. J. Corey, *JACS* **101**, 1586 (1979)

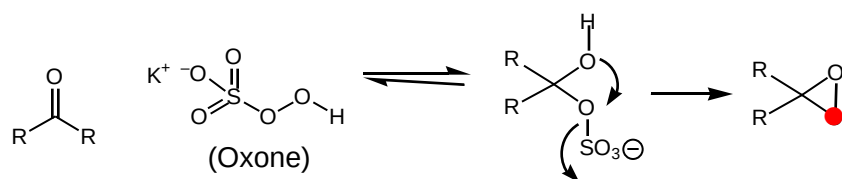
For a more detailed study see P. Beak, *JACS* **113**, 6281 (1991)

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

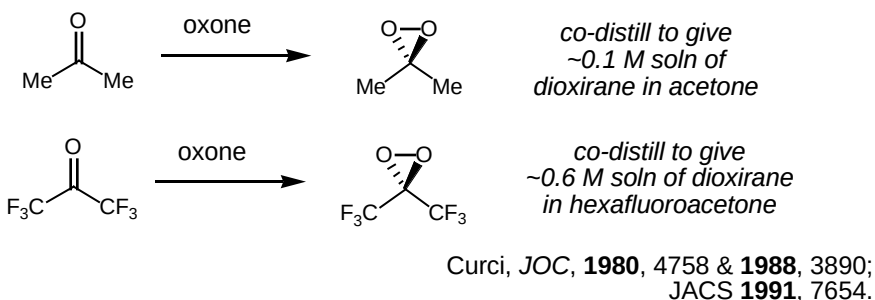
The General Reaction:



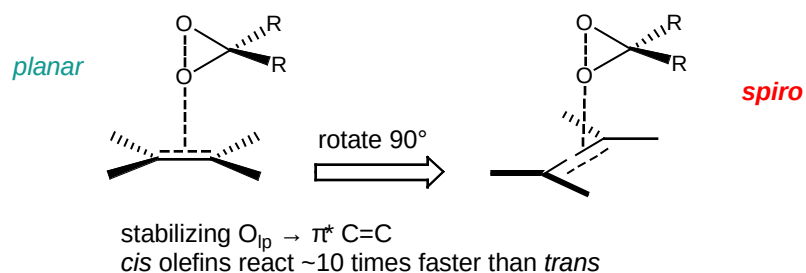
Synthesis of the Dioxirane Oxidant



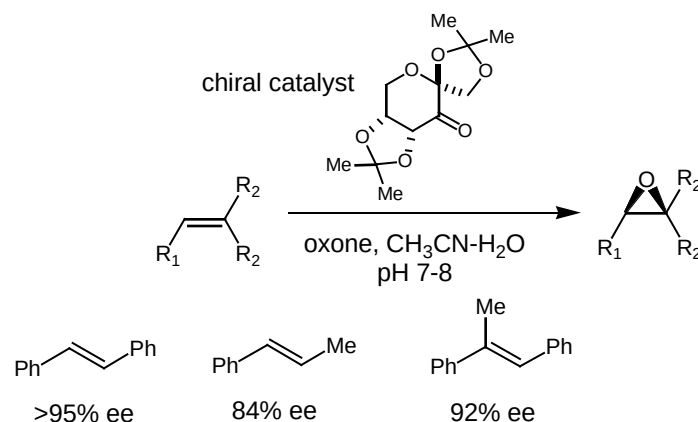
Synthetically Useful Dioxirane Synthesis



Transition State for the Dioxirane Mediated Olefin Epoxidation

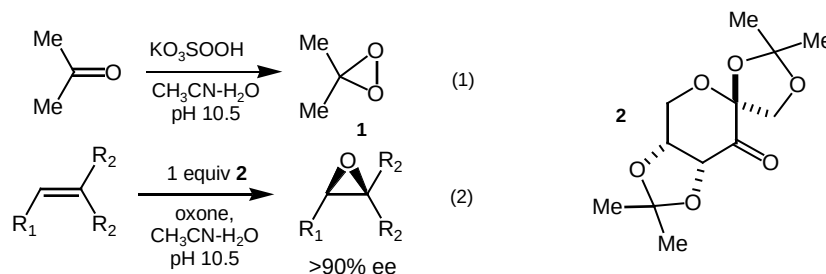
Houk, JACS, **1997**, 12982.

Asymmetric Epoxidation with Chiral Ketones

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

Question: First hour Exam 2000

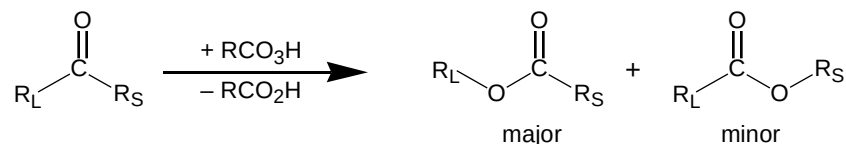
Question 4. (15 points). The useful epoxidation reagent dimethyldioxirane (**1**) may be prepared from "oxone" ($\text{K}_2\text{S}_2\text{O}_8$) and acetone (eq 1). In an extension of this epoxidation concept, Shi has described a family of chiral fructose-derived ketones such as **2** that, in the presence of "oxone", mediate the asymmetric epoxidation of di- and tri-substituted olefins with excellent enantioselectivities (>90% ee) (JACS **1997**, 119, 11224).



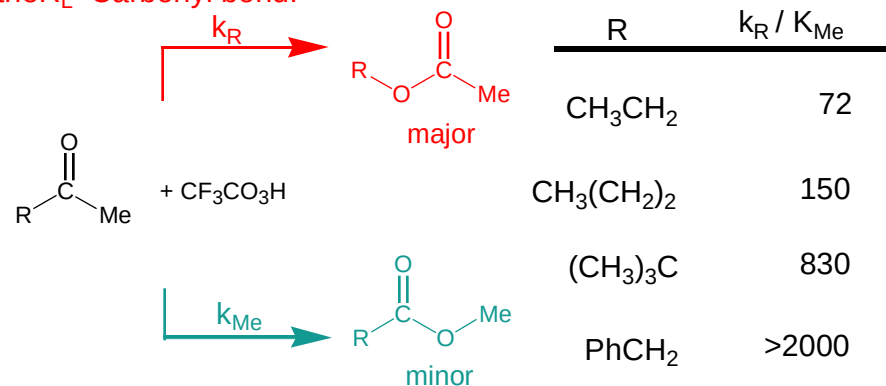
Part A (8 points). Provide a mechanism for the epoxidation of ethylene with dimethyldioxirane (**1**). Use three-dimensional representations, where relevant, to illustrate the *relative* stereochemical aspects of the oxygen transfer step. Clearly identify the frontier orbitals involved in the epoxidation.

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.

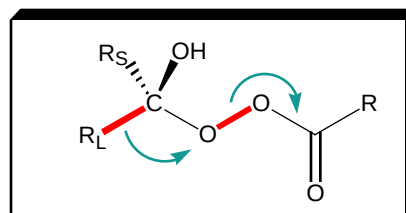
Let R_L and R_S be Sterically large and small substituents.



The major product is that wherein oxygen has been inserted into the R_1 -Carbonyl bond.



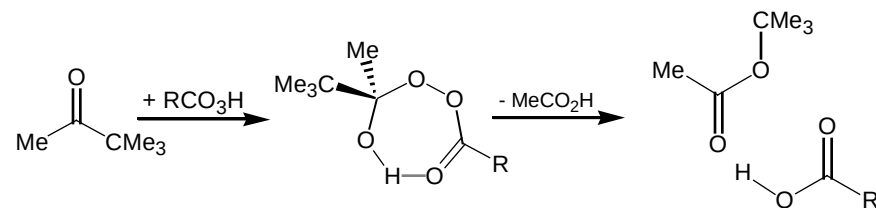
The Intermediate



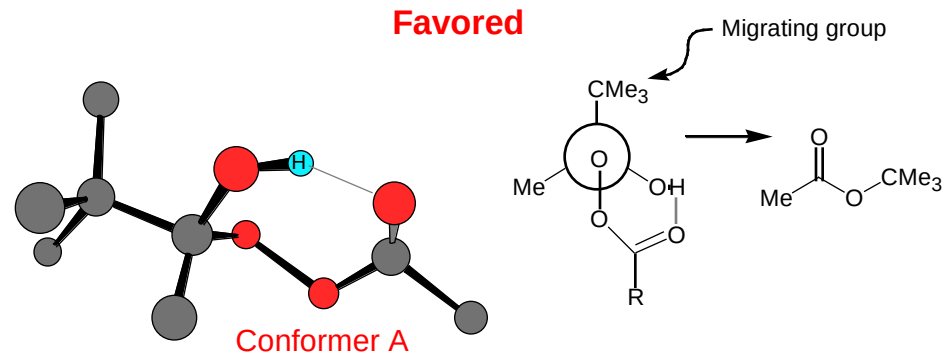
The important stereoelectronic components to this rearrangement:

1. The $R_L-C-O-O$ dihedral angle must be 180° due to the HOMO LUMO interaction $\sigma_{R_L-C} \leftrightarrow \sigma^*_{-O-O}$.
2. The $C-O-O-C'$ dihedral angle will be ca. 60° due to the gauche effect (O -lone pairs $\leftrightarrow \sigma^*_{-C-O}$).

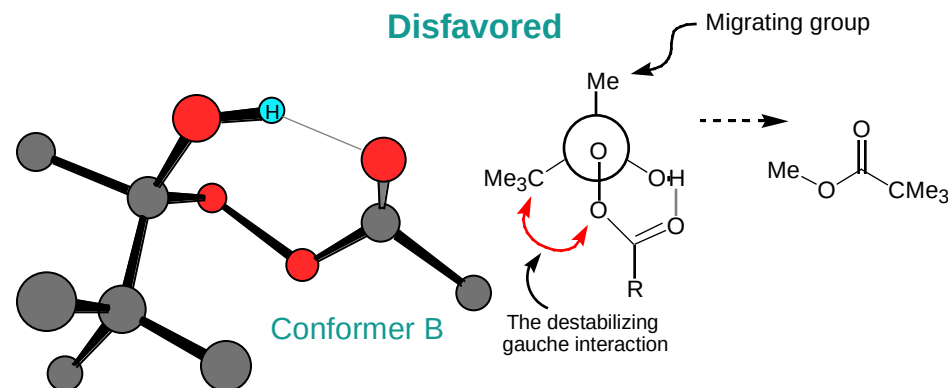
This gauche geometry is probably reinforced by intramolecular hydrogen bonding as illustrated on the opposite page:



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)

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)
<i>Hard</i>	<i>Hard</i>
H ₂ O, OH ⁻ , F ⁻	H ⁺ , Li ⁺ , Na ⁺ , K ⁺
CH ₃ CO ₂ ⁻ , PO ₄ ³⁻ , SO ₄ ²⁻	Be ²⁺ , Mg ²⁺ , Ca ²⁺
Cl ⁻ , CO ₃ ²⁻ , ClO ₄ ⁻ , NO ₃ ⁻	Al ³⁺ , Ga ³⁺
ROH, RO ⁻ , R ₂ O	Cr ³⁺ , Co ³⁺ , Fe ³⁺
NH ₃ , RNH ₂ , N ₂ H ₄	CH ₃ Sn ³⁺
	Si ⁴⁺ , Ti ⁴⁺
	Ce ³⁺ , Sn ⁴⁺
	(CH ₃) ₂ Sn 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)
<i>Borderline</i>	<i>Borderline</i>
C ₆ H ₅ NH ₂ , C ₅ H ₅ N, 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 ₃ C ⁺ , C ₆ H ₅ ⁺
<i>Soft</i>	<i>Soft</i>
R ₂ S, RSH, RS ⁻	Cu ⁺ , Ag ⁺ , Au ⁺ , Tl ⁺ , Hg ⁺
I ⁻ , SCN ⁻ , S ₂ O ₃ ²⁻	Pd ²⁺ , Cd ²⁺ , Pt ²⁺ , Hg ²⁺ , CH ₃ Hg ⁺ , Co(CN) ₅ ²⁻
R ₃ P, R ₃ As, (RO) ₃ P	Tl ³⁺ , Tl(CH ₃) ₃ , BH ₃
CN ⁻ , RNC, CO	RS ⁺ , RSe ⁺ , RTe ⁺
C ₂ H ₄ , C ₆ H ₆	I ⁺ , Br ⁺ , HO ⁺ , RO ⁺
H ⁻ , R ⁻	I ₂ , Br ₂ , ICN, etc.
	trinitrobenzene, etc.
	chloranil, quinones, etc.
	tetracyanoethylene, etc.
	O, Cl, Br, I, N, RO ⁻ , RO ₂ ⁻
	M ⁰ (metal atoms)
	bulk metals
	CH ₂ 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.

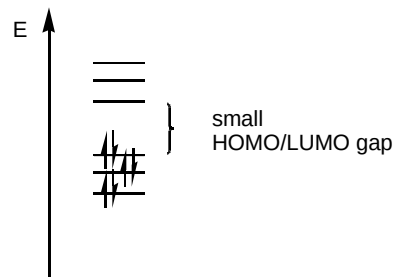
Soft Acids are usually uncharged and large (low charge density), they have an energy poor (low lying) LUMO (usually with large MO coefficient).

Hard Bases usually have a negative charge, small ion radii (high charge density), energy poor (low lying) HOMO.

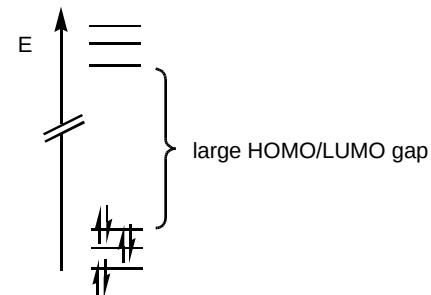
Soft Bases are usually uncharged and large (low charge density), energy rich (high lying) HOMO (usually with large MO coefficient).

Molecular Orbital Energies of an

idealized Soft Species

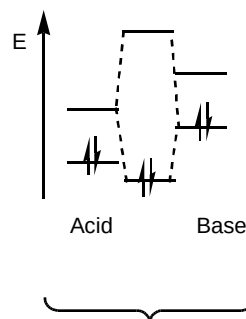


idealized Hard Species



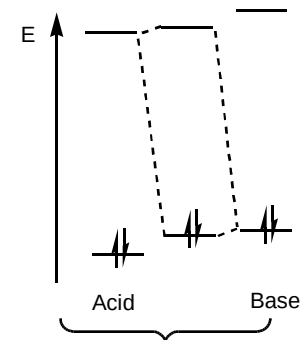
FMO-Theory for interaction:

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).

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

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 $\Delta E(\text{HOMO}_N/\text{LUMO}_E)$.
 formation of covalent bonds

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

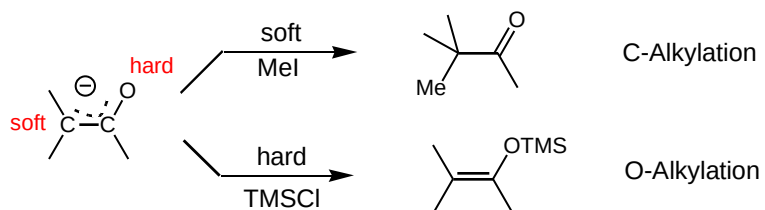
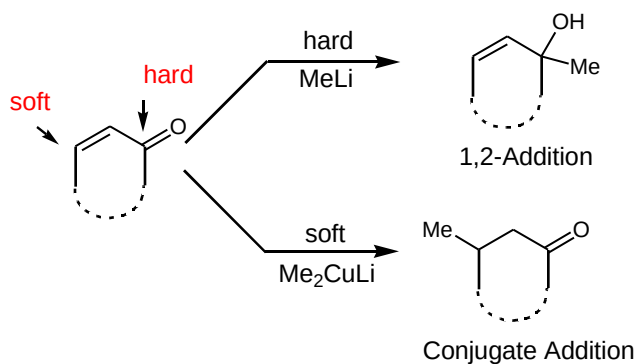
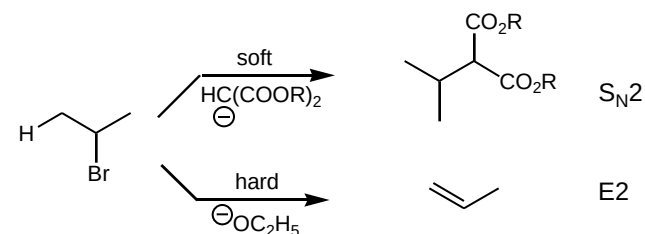
Hard-Soft Interactions: Neither energy term provides significant energy gain through interaction. Hence, Hard-Soft interactions are unfavorable.

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

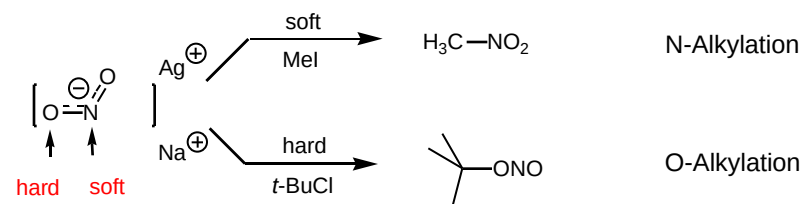
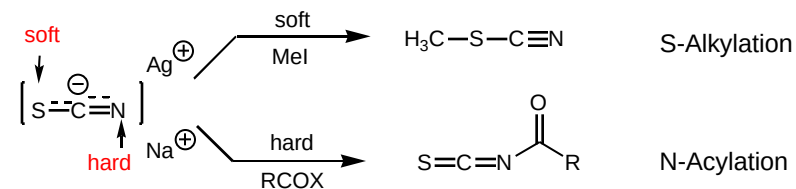
Nucleophile	HOMO E* (eV)		Electrophile	LUMO E* (eV)	
H ⁻	-7.37	↑ Soft ↓ Hard	Al ³⁺	6.01	↑ Hard ↓ Soft
I ⁻	-8.31		La ³⁺	4.51	
HS ⁻	-8.59		Ti ⁴⁺	4.35	
CN ⁻	-8.78		Be ²⁺	3.75	
Br ⁻	-9.22		Mg ²⁺	2.42	
Cl ⁻	-9.94		Ca ²⁺	2.33	
HO ⁻	-10.45		Fe ³⁺	2.22	
H ₂ O	-(10.73)		Sr ²⁺	2.21	
F ⁻	-12.18		Cr ³⁺	2.06	
			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	↓ Soft
			Ag ⁺	-2.82	
			Tl ³⁺	-3.37	
			Au ⁺	-4.35	
			Hg ²⁺	-4.64	

HSAB principle - Application to Chemoselectivity Issues

(a) Enolate Alkylation

(b) 1,2- vs. 1,4-addition to α,β -unsaturated carbonyl compounds(c) S_N2 vs E2

(d) Ambident Nucleophiles



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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 3

Stereoelectronic Effects-2

"Rules for Ring Closure: Baldwin's Rules"

Kirby, "Stereoelectronic Effects" Chapters 4, 5

Matthew D. Shair

Monday,
September 23, 2002

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.

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

The Primary Literature

Baldwin, J. *Chem. Soc., Chem. Comm.* **1976**, 734, 736.

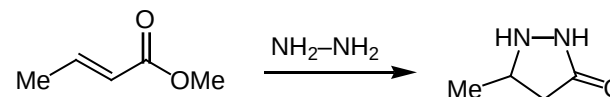
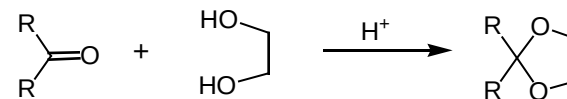
Baldwin, J. *Chem. Soc., Chem. Comm.* **1977** 323.

Baldwin, J. *Org. Chem.* **1977**, 42, 3846.

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

■ Problems of the Day

Propose mechanisms for the following reactions



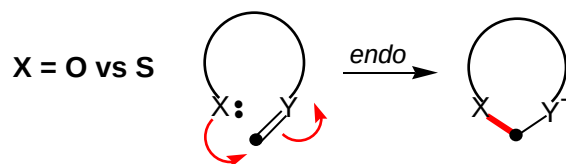
Ring Closure and Stereoelectronic Considerations An Examination of Baldwin's Rules

"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.

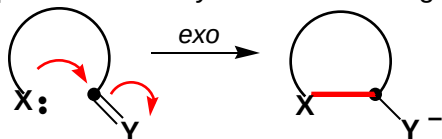


■ The "rules" do not apply to electrocyclic processes.

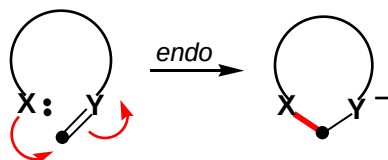
Nomenclature

Classes of Ring Closing Processes

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



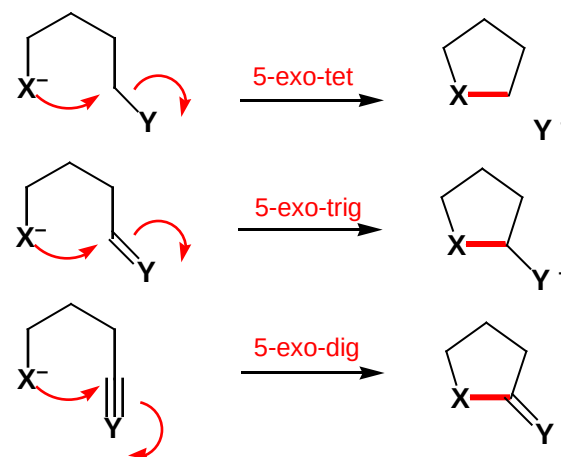
B. Endo-cyclization modes identified by the breaking bond being positioned endocyclic to the forming cycle.



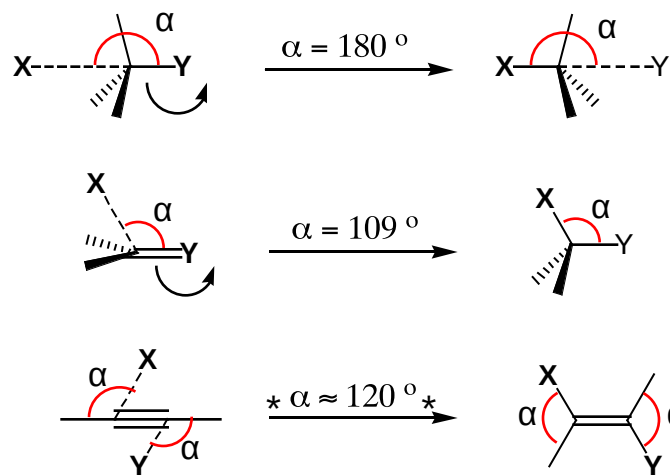
X = first-row element
N, O

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 formed ring**. For example:



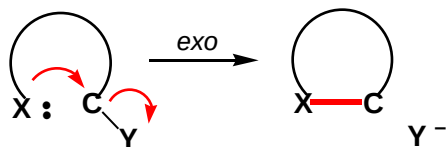
Required trajectories:



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

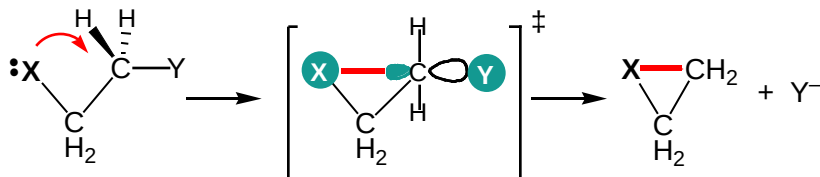
Tetrahedral Carbon

All **exo cyclization modes** are allowed: (**n-exo-tet**, $n = 3 \rightarrow$)



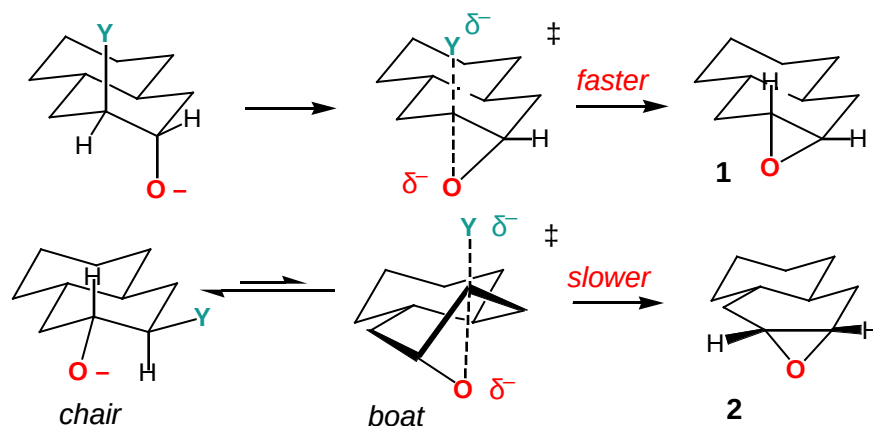
There are stereoelectronic issues to consider for **n-exo-tet** cyclizations

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:



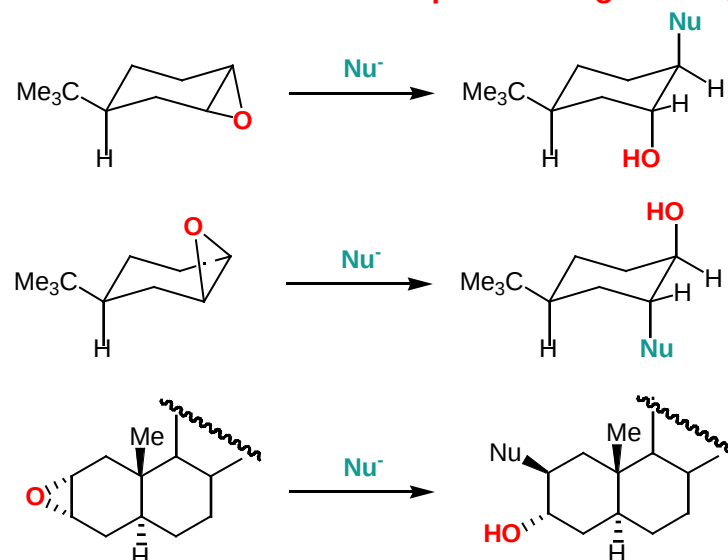
FÜRST-PLATTNER RULE

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 in the rates of ring closure.

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

Stereoelectronic Effects in Epoxide Ring Cleavage

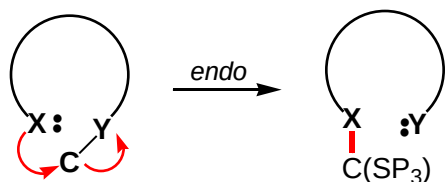


"The diaxial nucleophilic ring cleavage of epoxides"

For more information on epoxide cleavage see **Handout 03A**.

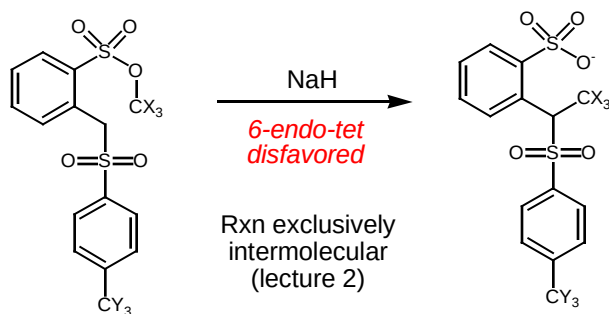
Tetrahedral Carbon

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

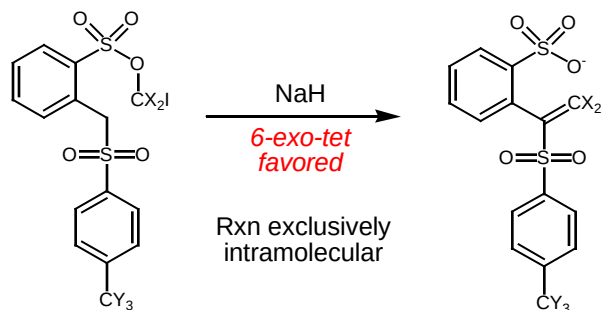


The stereoelectronic requirement for a **180° X–C–Y bond angle** is only met when the endo cyclization ring size reaches 9 or 10 members.

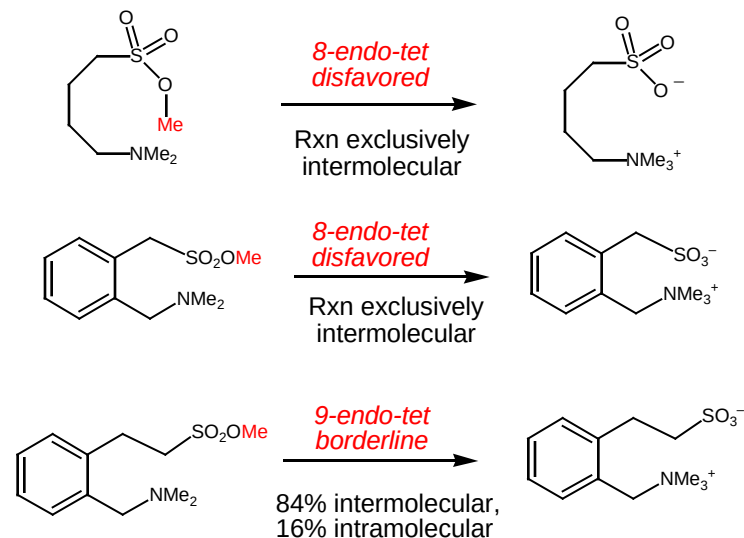
Case 1: Eschenmoser, *Helvetica Chim. Acta* **1970**, 53, 2059.



Cyclization exclusively intermolecular. However the exocyclic analog is exclusively intramolecular



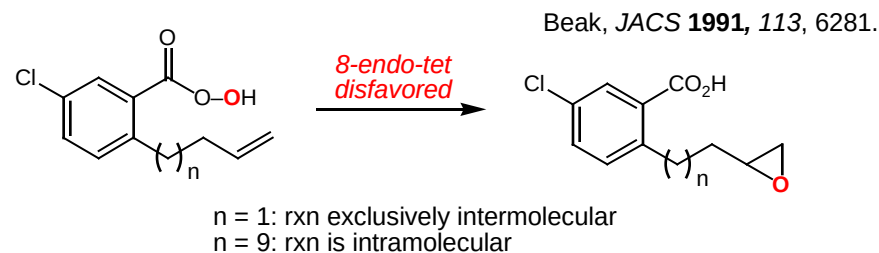
Case 2: King, *J.C.S. Chem. Comm.*, **1979**, 1140.



Conclusions

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

Intramolecular epoxidation has also been evaluated

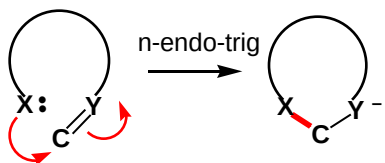


Beak states that the conclusions made with carbon substitution also hold for oxygen atom transfer.

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

Trigonal Carbon

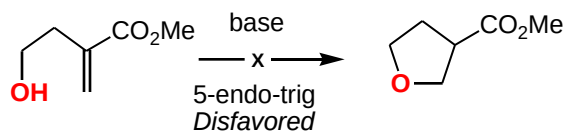
Endo cyclization modes that are disallowed
(3 to 5-endo-trig)



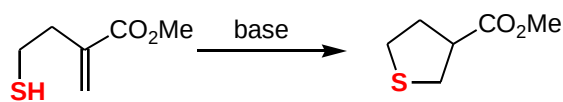
X = first-row element

The 5-endo-trig cyclization is a watershed case

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

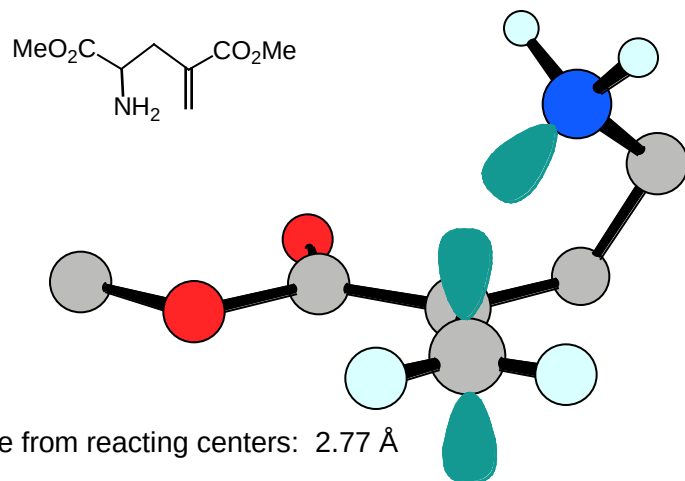
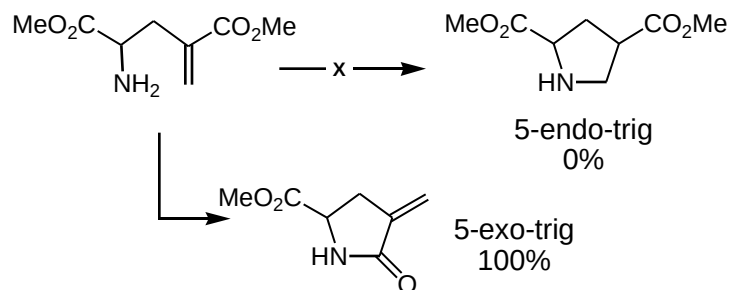


however

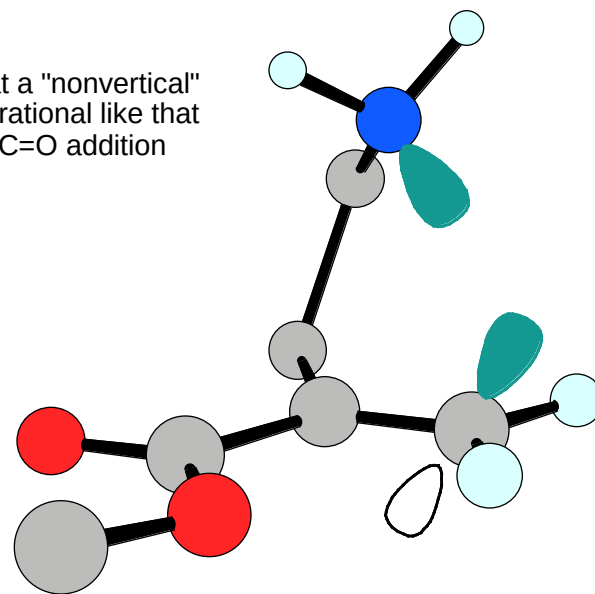


Second row atom relaxes the cyclization geometrical requirement

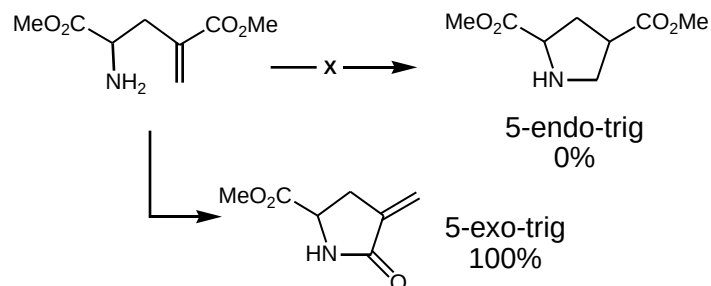
Case 2: Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 736.



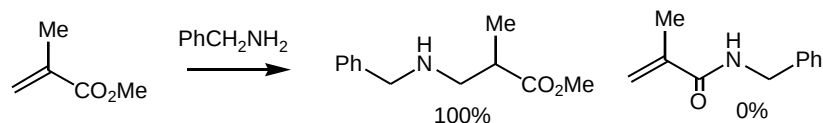
It is possible that a "nonvertical" trajectory is operational like that suspected in C=O addition



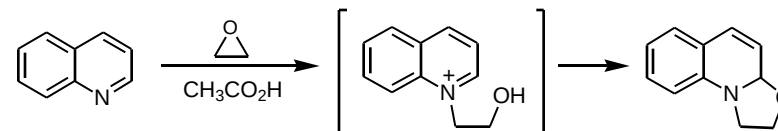
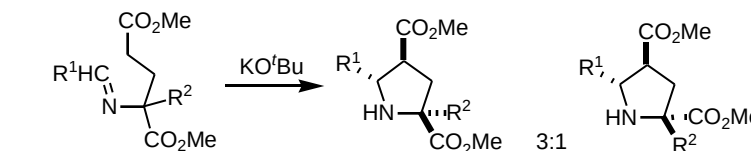
Case 2: continued...



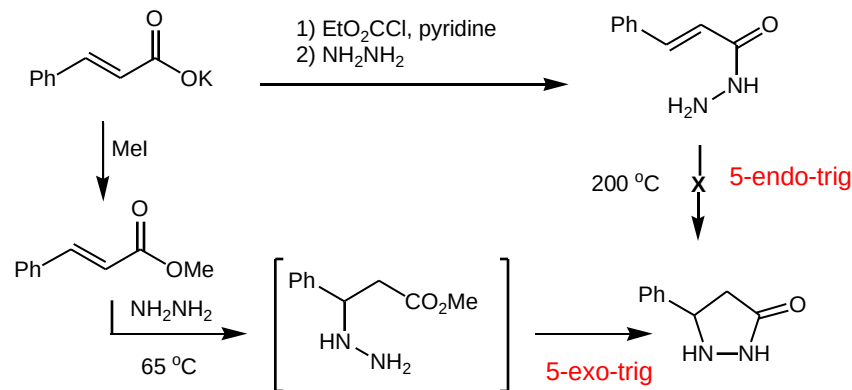
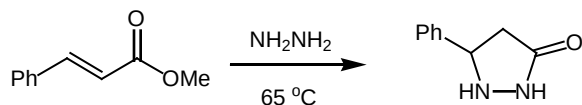
Control experiment: Intermolecular reaction favors conjugate addition.



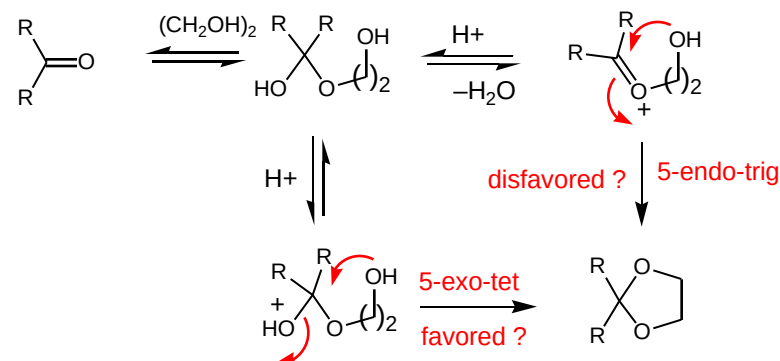
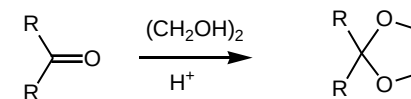
Apparent exceptions to disallowed 5-endo-trig cyclization process

Filer, *J. Am. Chem. Soc.* **1979**, *44*, 285.R¹ = aryl, R² = aryl, alkylGrigg, *J. Chem. Soc., Chem. Commun.* **1980**, 648.

Case 3:

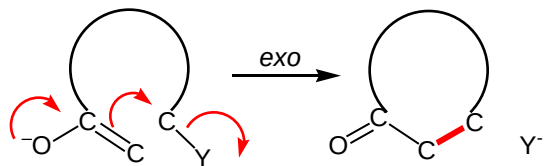


Does the illustrated ketalization process necessarily violate "the rules"?

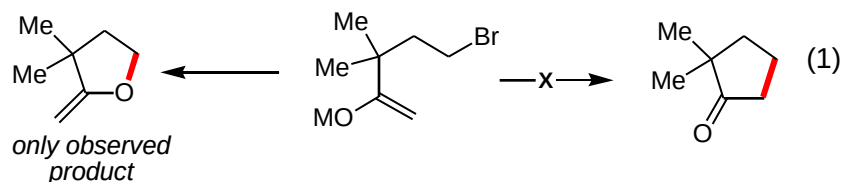


Johnson, C. D. (1993). "Stereochemical effects in the formation of 5- and 6-membered rings: the role of Baldwin's rules." *Acc. Chem. Res.* **26**: 476-82.

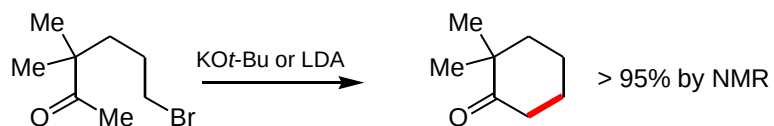
Trigonal Carbon: Exocyclic Enolate Alkylation



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

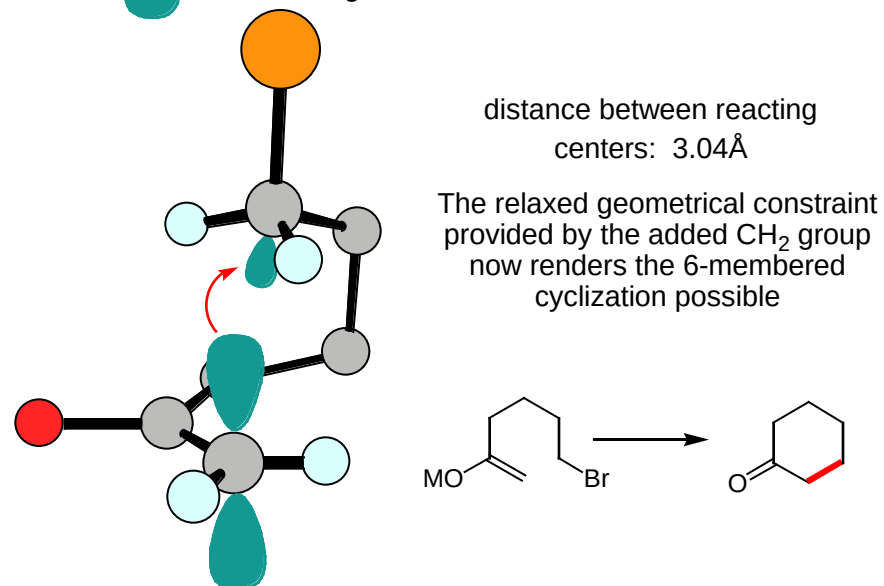
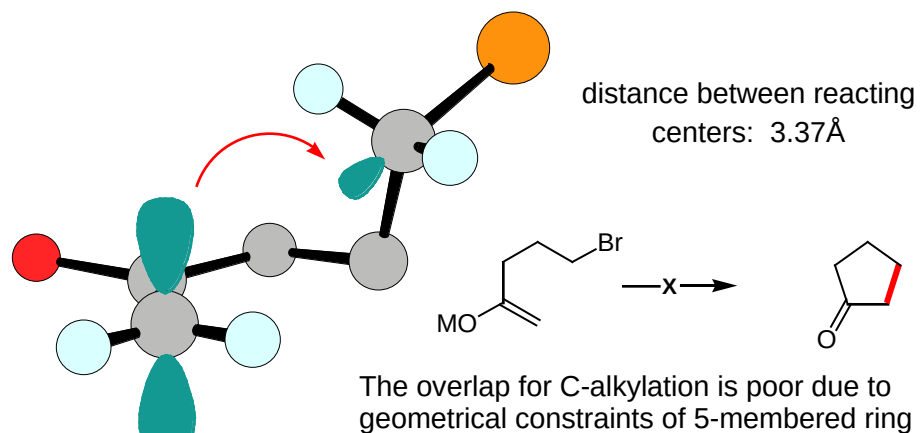
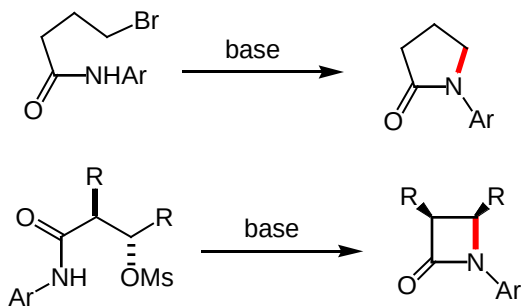


However:

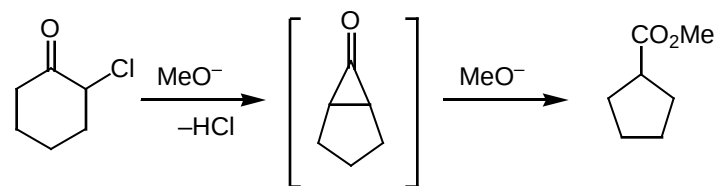


Baldwin, *J. Chem. Soc., Chem. Commun.* **1977**, 233.

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

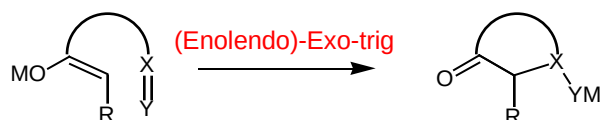


Favorskii Rearrangement (Carey, Pt B, pp 609-610)
Your thoughts on the mechanism

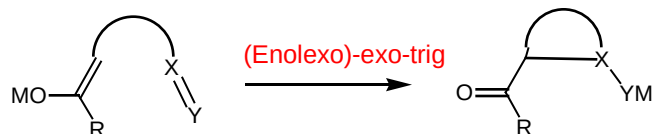


Trigonal Carbon: Intramolecular Aldol Condensations

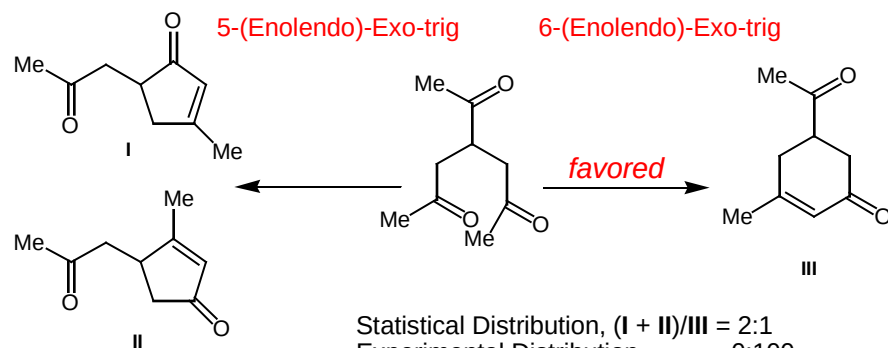
Baldwin, *Tetrahedron* **1982**, 38, 2939



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



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

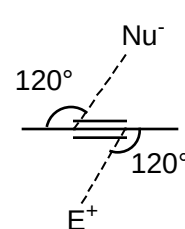


(KOH, MeOH, r.t., 5 min, 77% y.)

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

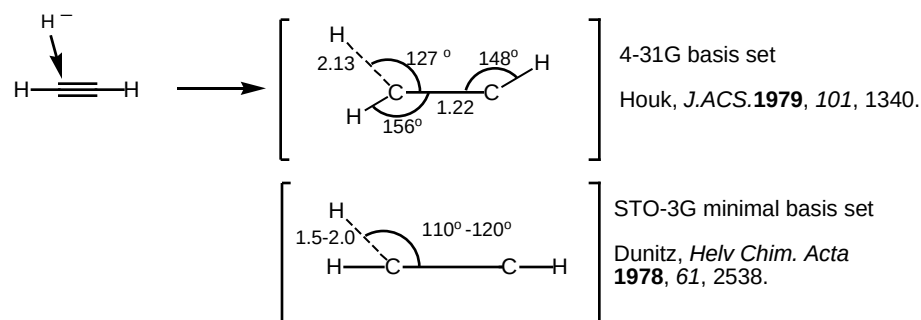
DIGONAL: Angle of approach for attack on triple bonds



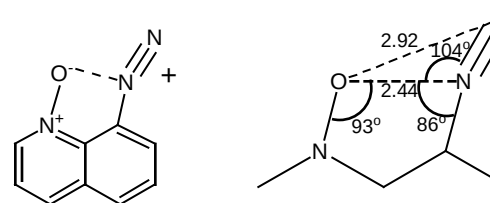
Baldwin:

- 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:



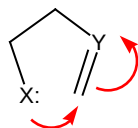
Crystal Structures do not support Baldwin



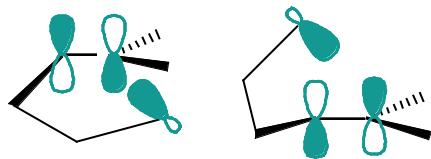
J. Dunitz and J. Wallis *J. C. S. Chem. Comm.* **1984**, 671.

Endo Digonal versus Endo Trigonal Cyclizations

5-endo-trig

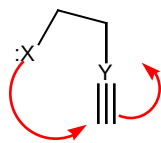


In-plane approach;
nucleophile lone pair is
orthogonal to π^*



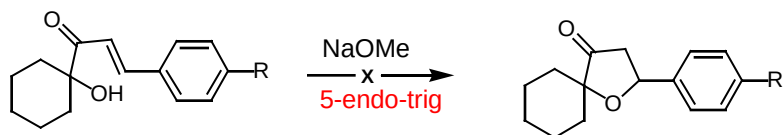
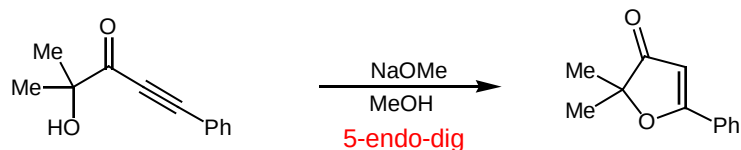
Out-of-plane approach;
nucleophile lone pair can't
achieve Bürgi-Dunitz angle

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

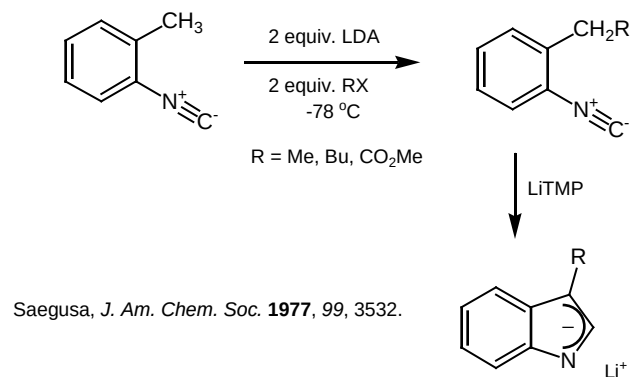
Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 736.

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

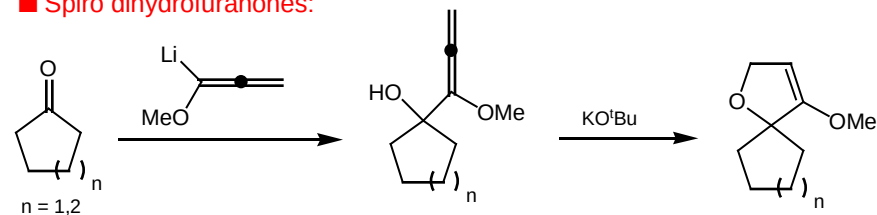
J. Am. Chem. Soc. **1983**, 105, 5090

J. Chem. Soc., Chem. Commun. **1982**, 36.

■ Indole synthesis:

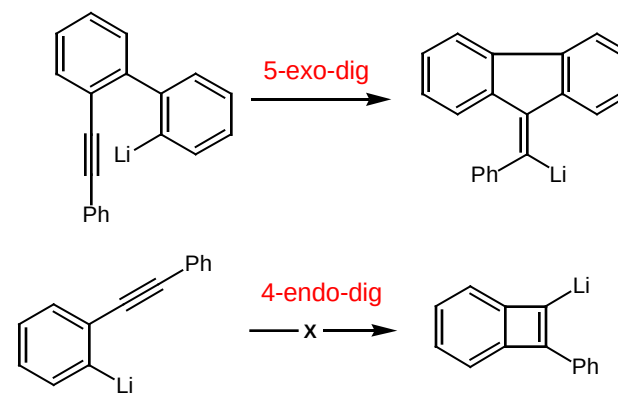


■ Spiro dihydrofuranones:

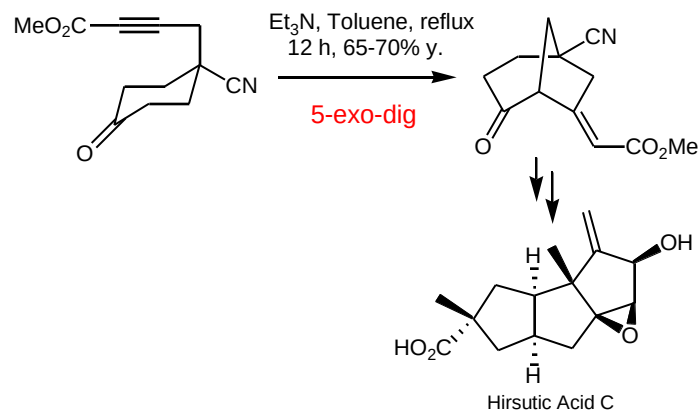


Developing negative charge on the central allenic carbon is
in the same plane as the OMe group

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

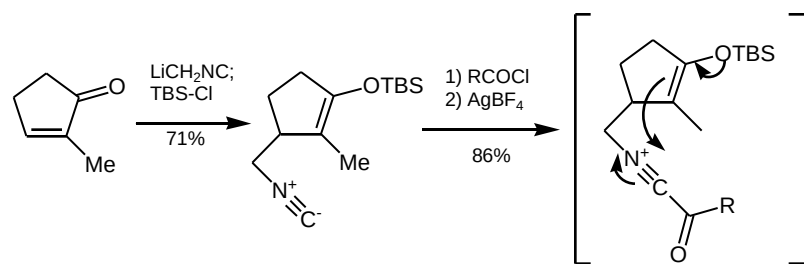
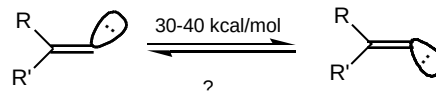


Digonal Cyclizations: Interesting Examples



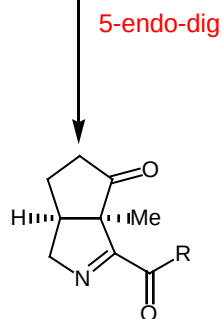
■ Trost, *J. Am. Chem. Soc.*, **1979**, *101*, 1284.

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



Works for varying ring sizes and R groups; acylnitrilium ion can also work as an electrophile 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	✓	✓	✗		✗	✓
4	✓	✓	✗		✗	✓
5	✓	✓	✓	✗	✗	✓
6	✓	✓	✓	✗	✓	✓
7	✓	✓	✓	✗	✓	✓

<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, VCH Verlagsgesellschaft: 369-404.

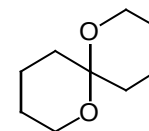
Kleinpeter, E. (1997). "Conformational Analysis of Saturated Six-Membered Oxygen-Containing Heterocyclic Rings." *Adv. Heterocycl. Chem.* **69**: 217-69.

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

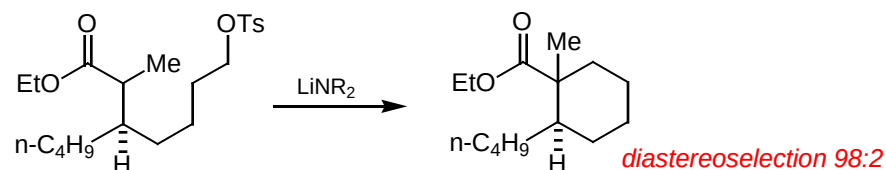
Bucourt, R. (1973). "The Torsion Angle Concept in Conformational Analysis." *Top. Stereochem.* **8**: 159.

■ Problems of the Day

Predict the most stable conformation of the indicated dioxospiran?



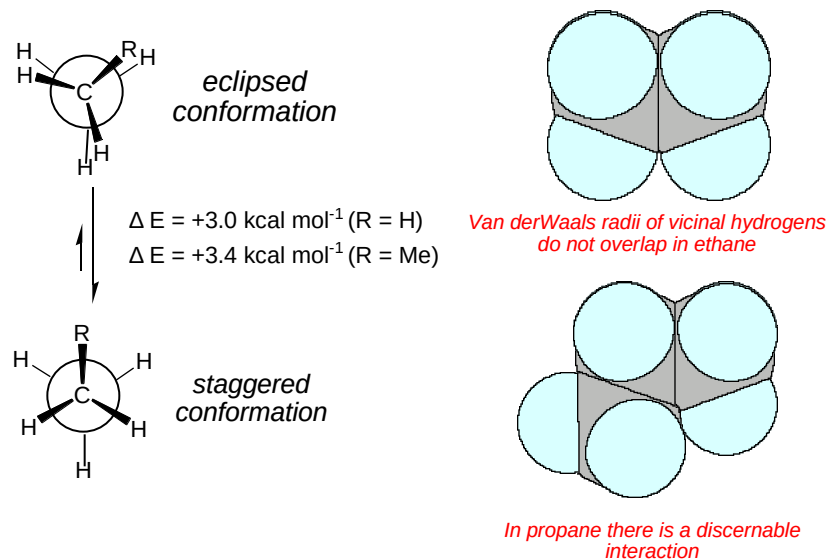
Can you predict the stereochemical outcome of this reaction?



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.



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

Incremental Contributions to the Barrier.

Structure	Eclipsed atoms	$\delta E \text{ (kcal mol}^{-1}\text{)}$
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

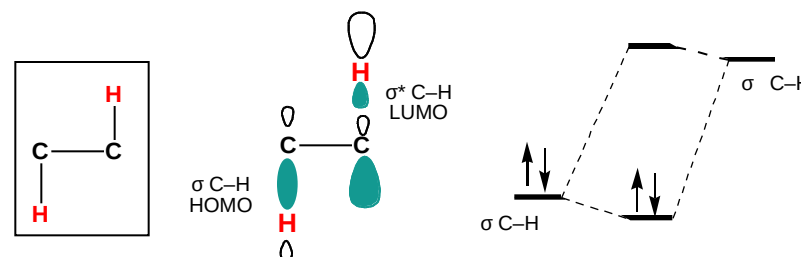
Ethane Rotational Barrier: The FMO View

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

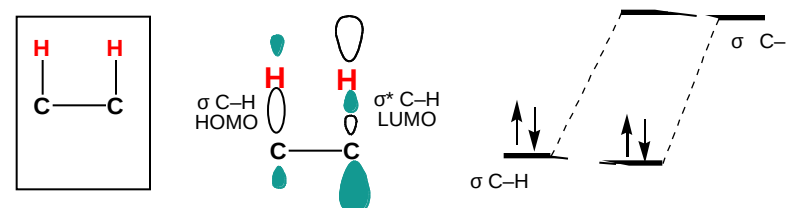
One can see from the space-filling models that the Van der Waals radii of the hydrogens do not overlap in the eclipsed ethane conformation. This makes the steric argument for the barrier untenable.

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



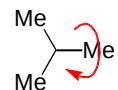
Following this argument one might conclude that:

■ 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

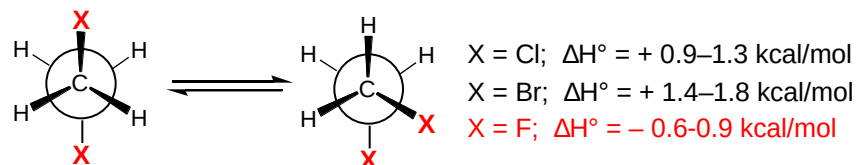
"A Simple Molecular Orbital Explanation for the Barrier to Internal Rotation in Ethane and Other Molecules"

J. P. Lowe, *JACS* **1970**, 92, 3799



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

The 1,2-Dihaloethanes



Observation: While the anti conformers are favored for $X = \text{Cl}, \text{Br}$, the gauche conformation is preferred for 1,2-difluoroethane. Explain.

Discuss with class the origin of the gauche stabilisation of the difluoro analog.

Relationship between ΔG and K_{eq} and pK_a

Recall that:

$$\Delta G^\circ = -RT \ln K$$

or

$$\Delta G^\circ = -2.3RT \log_{10} K$$

At 298 K: $2.3RT = 1.4 \text{ (}\Delta G \text{ in kcal Mol}^{-1}\text{)}$

$$\Delta G^\circ_{298} = -1.4 \log_{10} K_{eq}$$

Since $pK_{eq} = -\log_{10} K_{eq}$

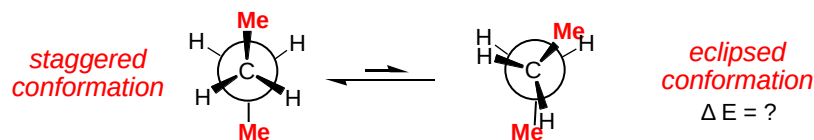
$$\Delta G^\circ_{298} = 1.4 pK_{eq}$$

Hence, pK is proportional to the free energy change

K_{eq}	pK_{eq}	ΔG°
1.0	0	0
10	-1	-1.4
100	-2	-2.8 kcal/mol

Butane

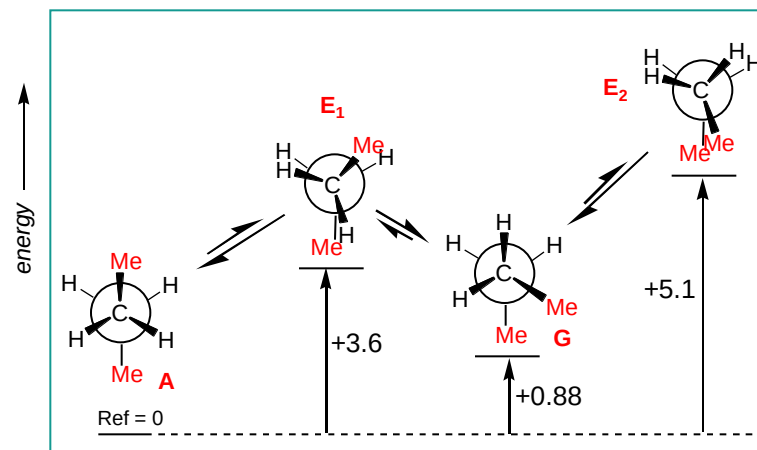
Using the eclipsing interactions extracted from propane & ethane we should be able to estimate all but one of the eclipsed butane conformations



Eclipsed atoms	$\delta E \text{ (kcal mol}^{-1}\text{)}$
1 (H ↔ H)	+1.0 kcal mol ⁻¹
2 (H ↔ Me)	+2.8 kcal mol ⁻¹
$\Delta E \text{ est} = 3.8 \text{ kcal mol}^{-1}$	

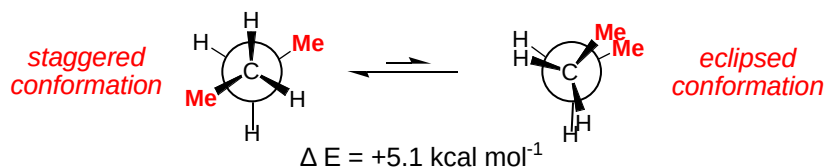
The estimated value of +3.8 agrees quite well with the value of +3.6 reported by Allinger (*J. Comp. Chem.* **1980**, *1*, 181-184)

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:

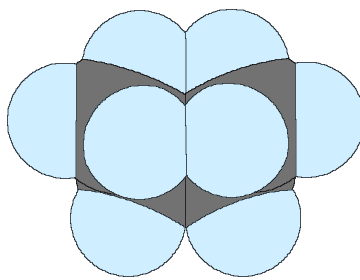


Let's extract out the magnitude of the Me–Me interaction

$$\begin{aligned}
 2 (\text{H} \leftrightarrow \text{H}) + 1 (\text{Me} \leftrightarrow \text{Me}) &= +5.1 \\
 1 (\text{Me} \leftrightarrow \text{Me}) &= +5.1 - 2 (\text{H} \leftrightarrow \text{H}) \\
 \mathbf{1 (\text{Me} \leftrightarrow \text{Me})} &= \mathbf{+3.1}
 \end{aligned}$$

Incremental Contributions to the Barrier.

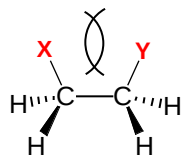
Eclipsed atoms	δE (kcal mol ⁻¹)
2 (H ↔ H)	+2.0
1 (Me ↔ Me)	+2.2



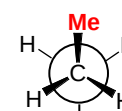
Eclipsed Butane conformation

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

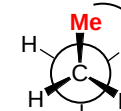
Hierarchy of Eclipsing Interactions

	X—Y	δE kcal mol ⁻¹
	H—H	+1.0
	H—Me	+1.4
	Me—Me	+3.1

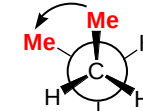
Nomenclature for staggered conformers:



trans or t
or (anti)



gauche(+) or g⁺



gauche(-) or g⁻

Conformer population at 298 K:

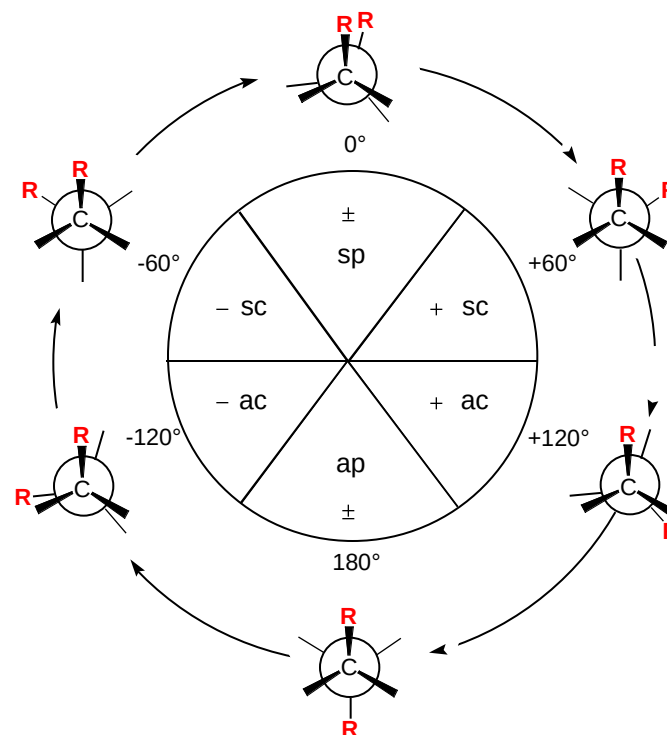
70%

15%

15%

General nomenclature for diastereomers resulting from rotation about a single bond

(Klyne, Prelog, *Experientia* 1960, 16, 521.)



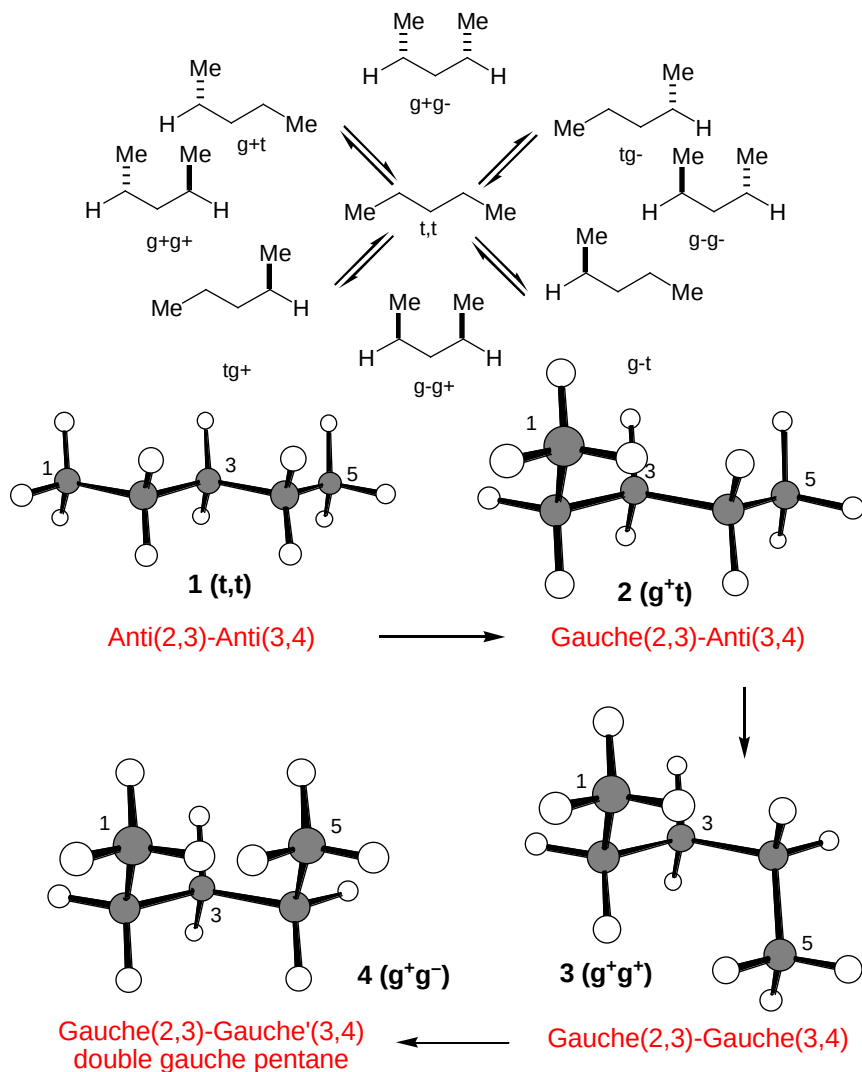
Energy Maxima $\longrightarrow$

Energy Minima $\dashrightarrow$

Torsion angle	Designation	Symbol	n-Butane Conformer
0 ± 30°	± syn periplanar	± sp	E ₂
+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 C₂-C₃ and C₃-C₄ bonds in either direction (+ or -):

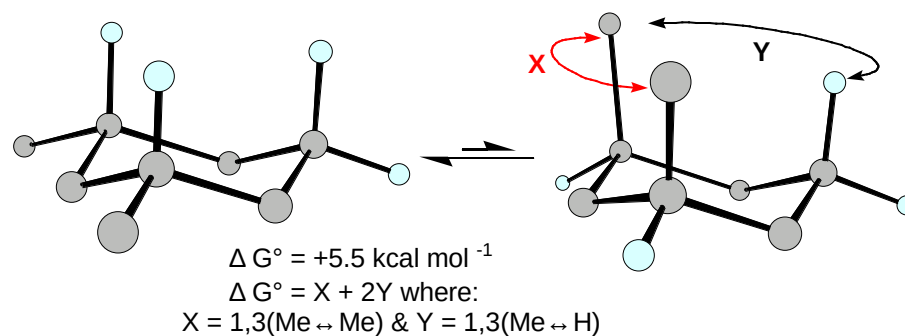


From prior discussion, you should be able to estimate energies of 2 & 3 (relative to 1). On the other hand, the least stable conformer 4 requires additional data before its relative energy can be evaluated.

The double-gauche pentane conformation

The new high-energy conformation: (g⁺g⁻)

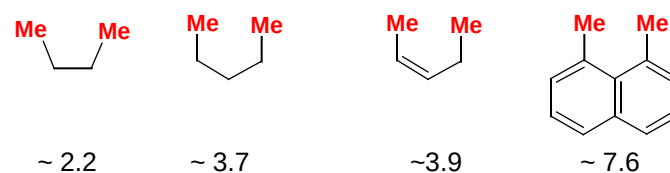
Estimate of 1,3-Dimethyl Eclipsing Interaction



$$1,3(\text{Me} \leftrightarrow \text{H}) = \text{Skew-butane} = 0.88 \text{ kcal mol}^{-1}$$

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

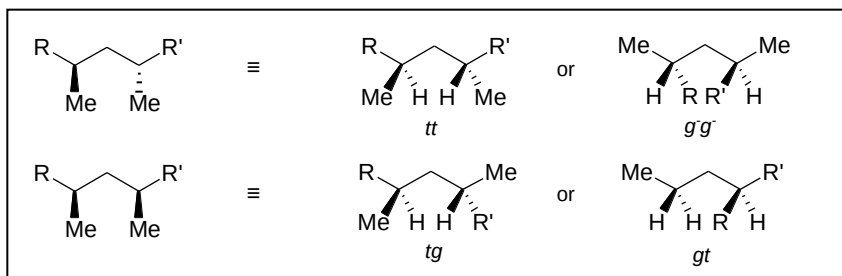
$$1,3(\text{Me} \leftrightarrow \text{Me}) = +3.7 \text{ kcal mol}^{-1}$$

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

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

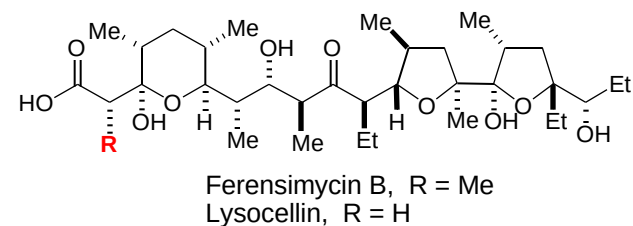
The syn-Pentane Interaction - Consequences

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



Lactol & Ketol Polyether Antibiotics

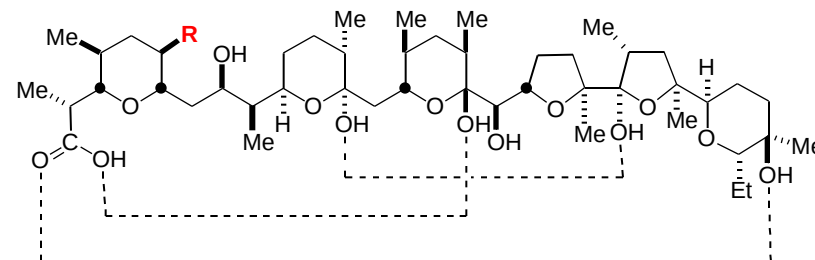
The conformation of these structures are strongly influenced by the acyclic stereocenters



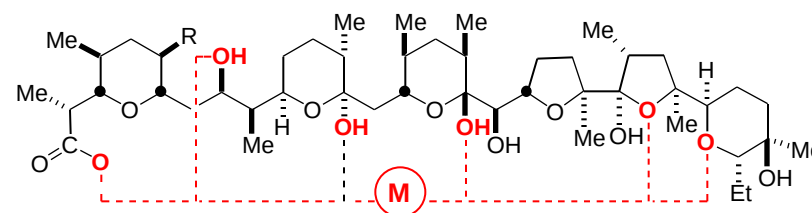
The conformation of these structures are strongly influenced by the acyclic stereocenters and internal H-bonding

Alborixin R = Me; X-206 R = H

Internal H-Bonding



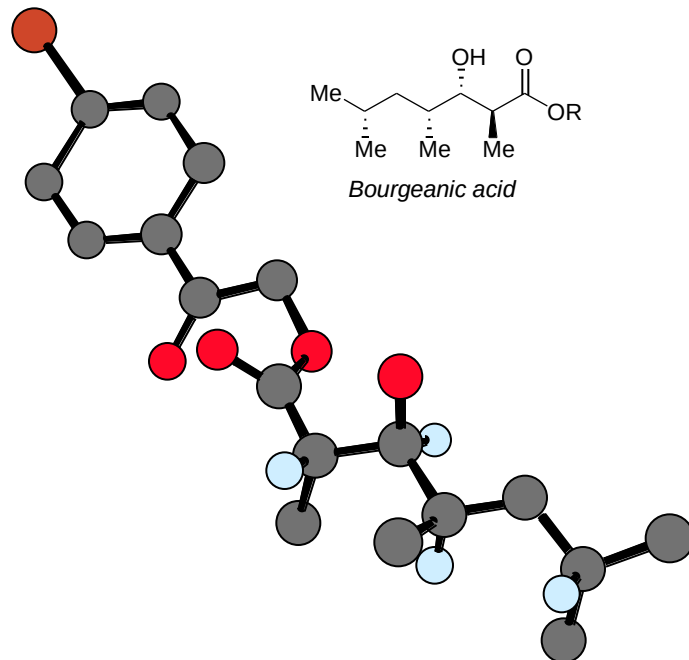
Metal ion ligation sites (M = Ag, K)



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

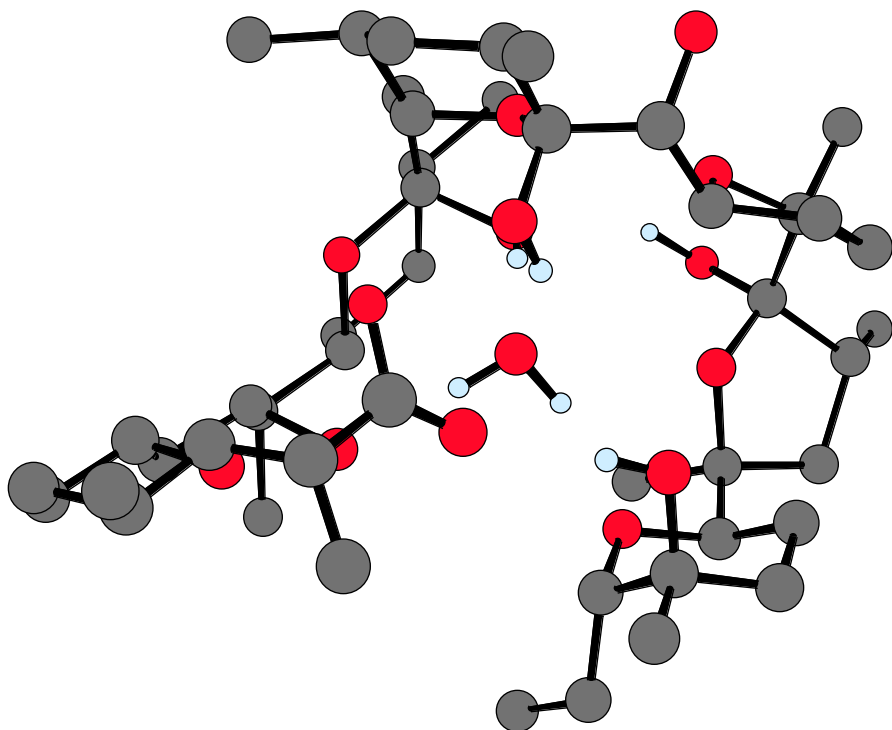
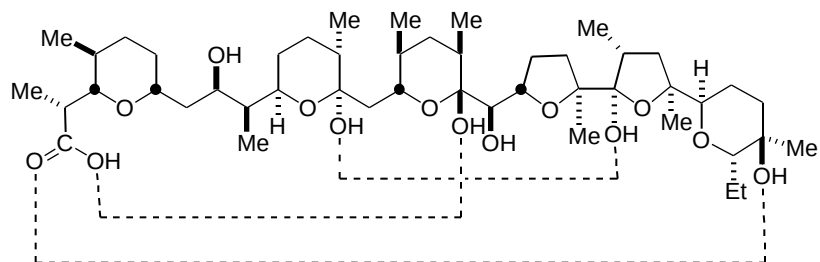
Consequences for the preferred conformation of polyketide natural products

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

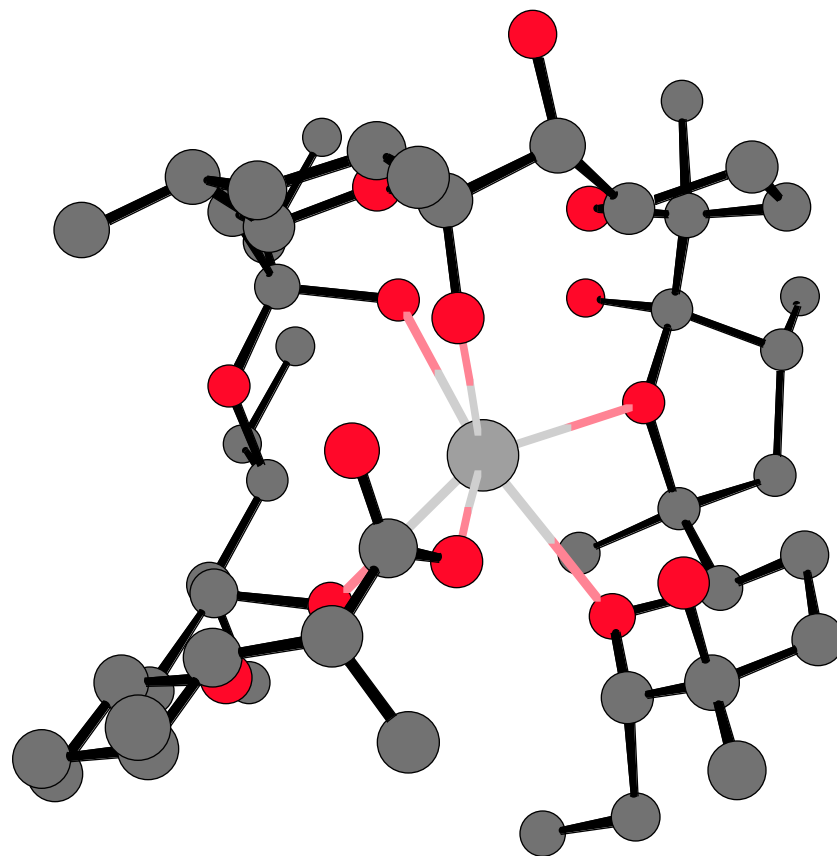
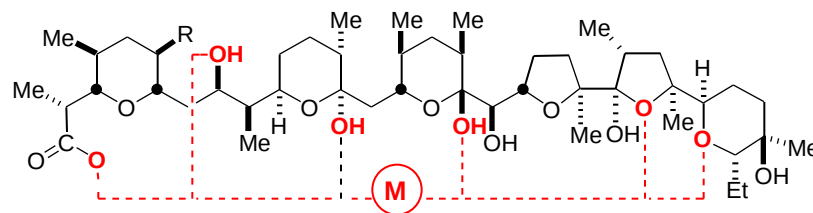


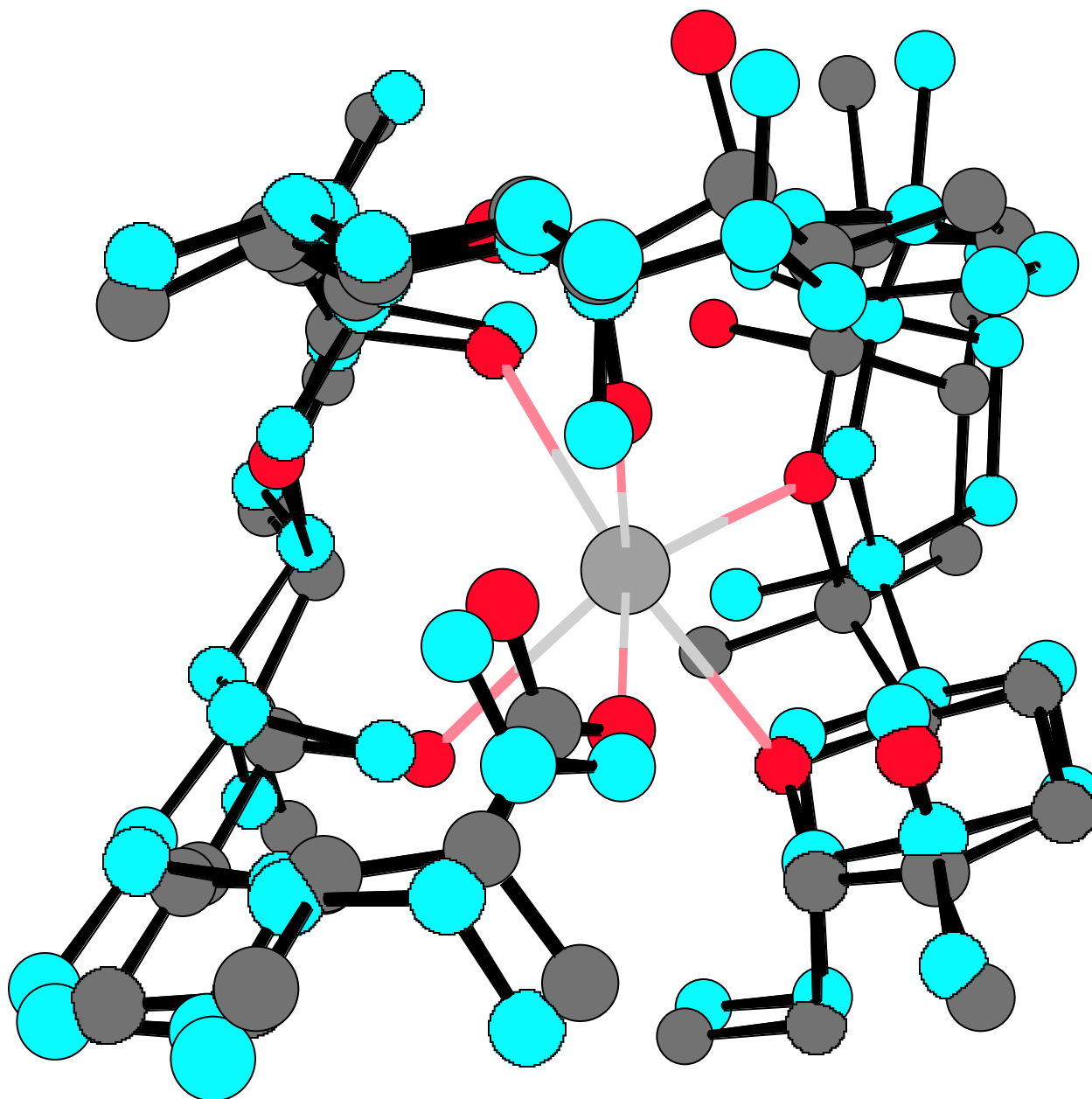
X-ray of Ionophore X-206 H₂O

Internal H-Bonding

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

Metal ion ligation sites (M = Ag, K)





<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

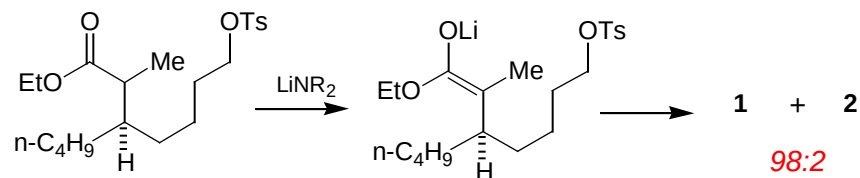
F. Weinhold, *Angew. Science* **2001**, 411, 539-541
"A New Twist on Molecular Shape"

Carl A. Morales

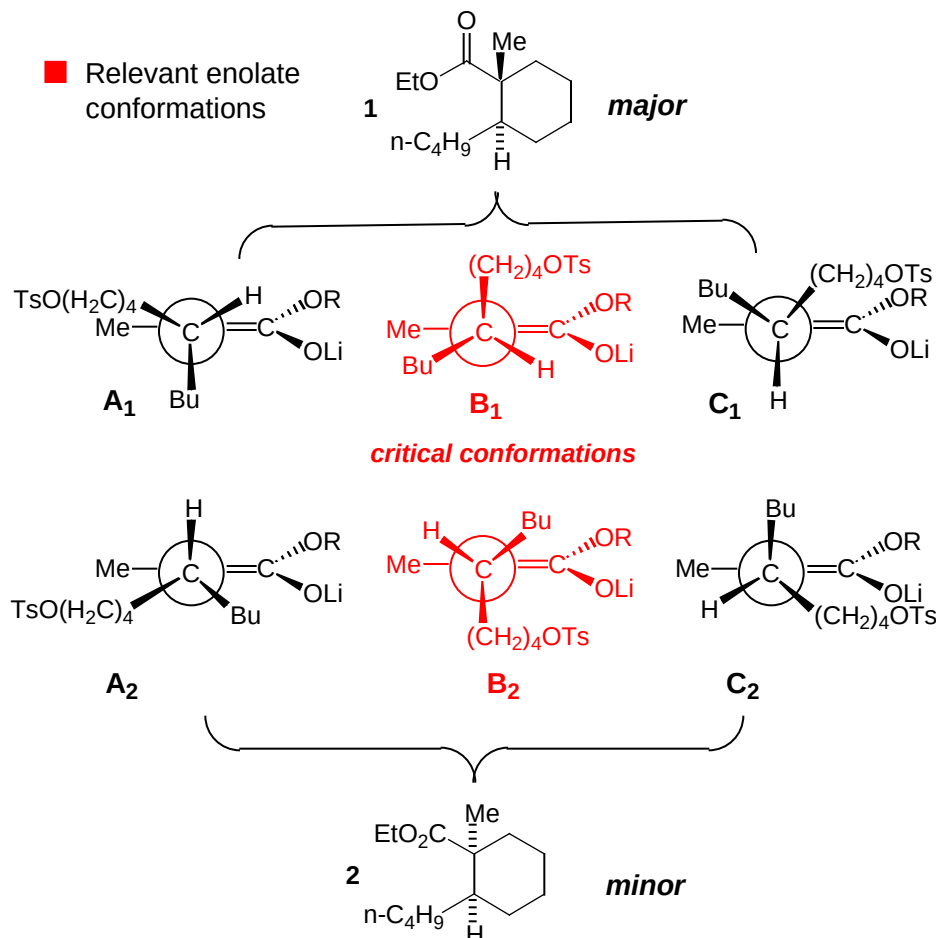
Friday,
 September 27, 2002

■ Problems of the Day: (To be discussed)

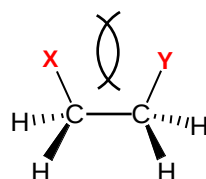
Can you predict the stereochemical outcome of this reaction?

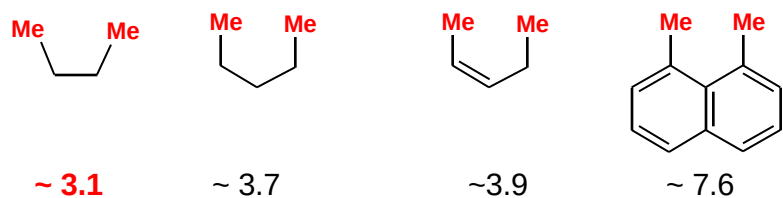


■ Relevant enolate conformations

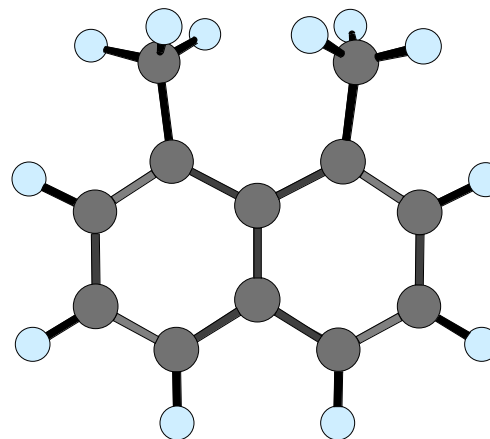


Hierarchy of Vicinal Eclipsing Interactions

	X—Y	δE 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

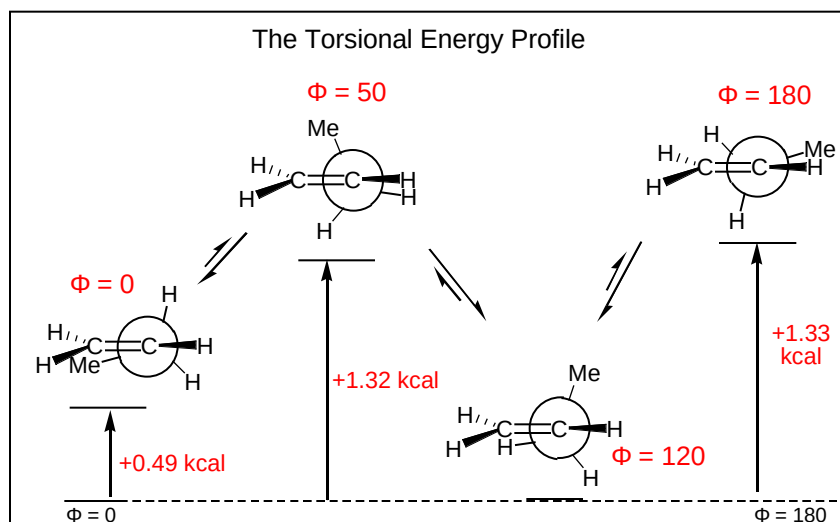
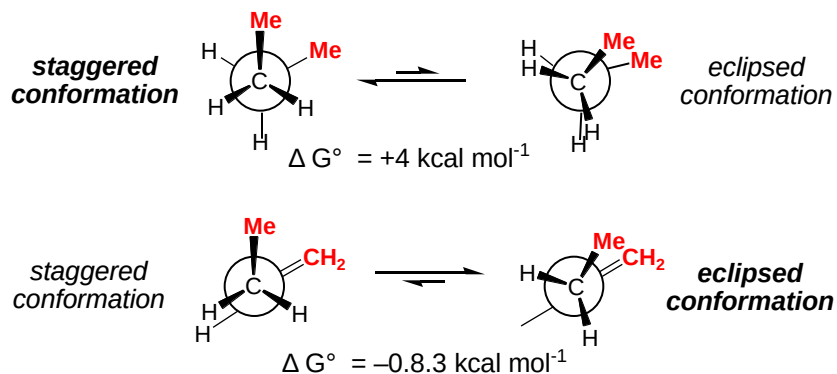
It may be concluded that in-plane 1,3(Me ↔ Me) interactions are Ca +4 kcal/mol while 1,2(Me ↔ Me) interactions are destabilizing by Ca +3 kcal/mol.



minimized structure

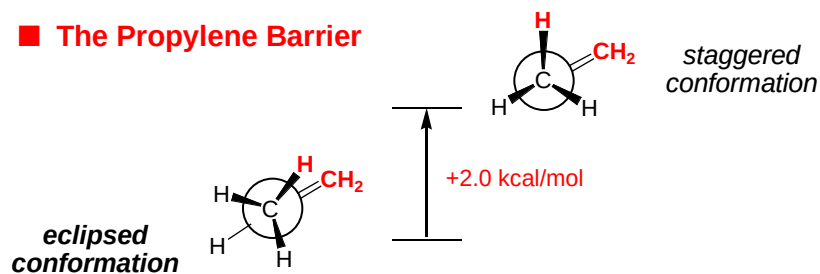
Simple olefins exhibit unusual conformational properties relative to their saturated counterparts

Butane versus 1-Butene

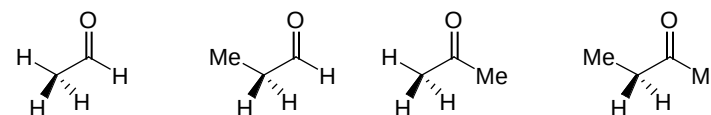


Conforms to *ab initio* (3-21G) values:
Wiberg, K. B.; Martin, E. J. *Am. Chem. Soc.* **1985**, *107*, 5035.

■ The Propylene Barrier

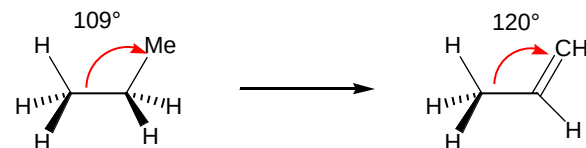


■ Acetaldehyde exhibits a similar conformational bias



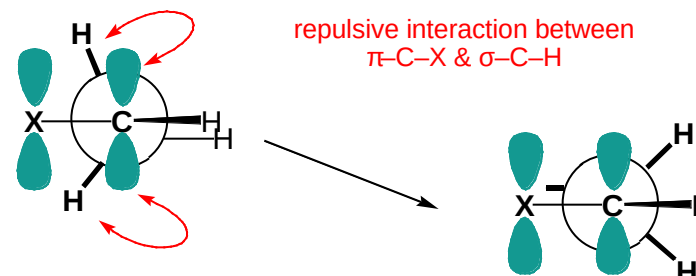
The low-energy conformation in each of above cases is eclipsed

Propane versus Propene



Hybridization change opens up the C-C-C bond angle

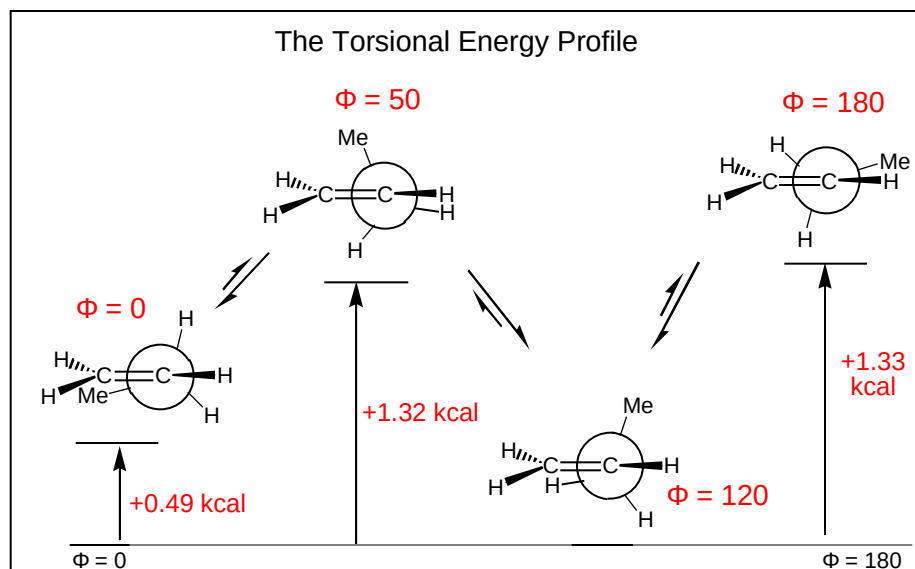
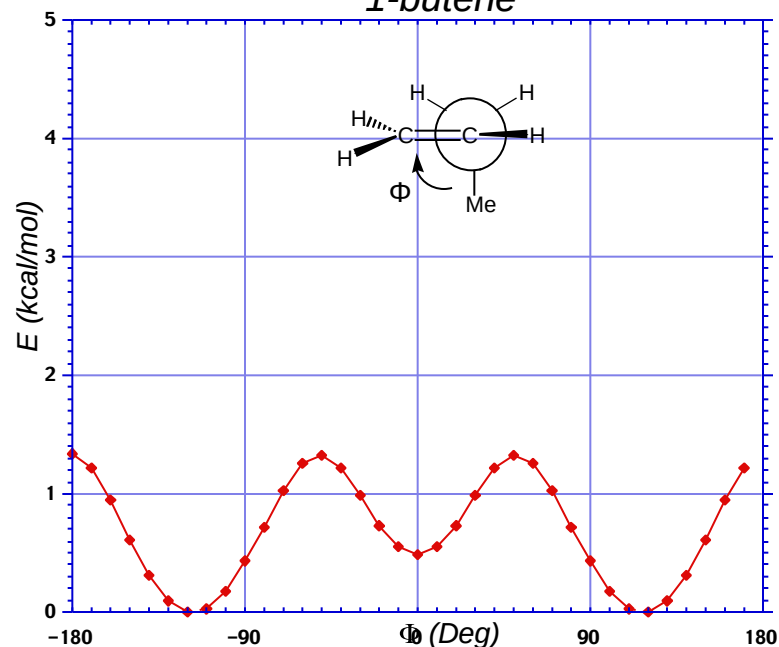
New destabilizing effect



K. Wiberg, *JACS* **1985**, *107*, 5035-5041

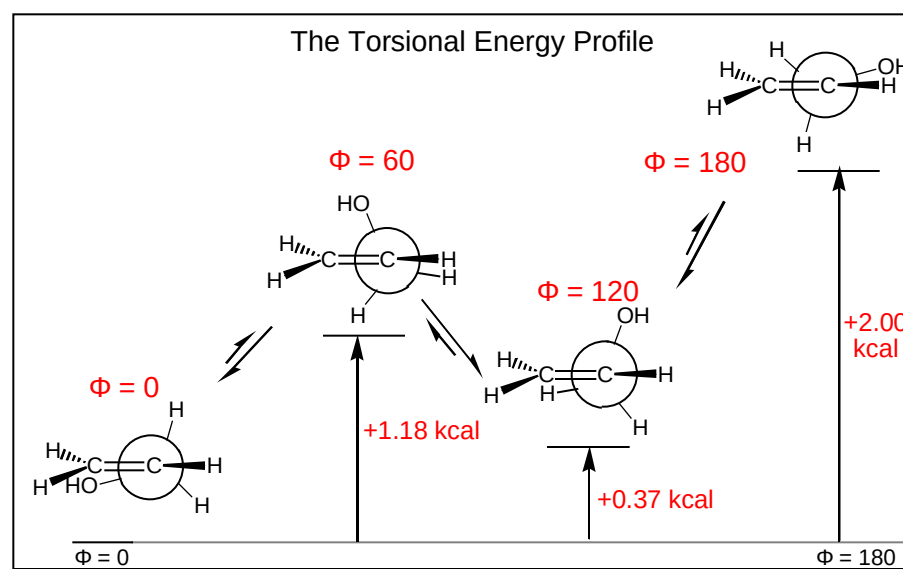
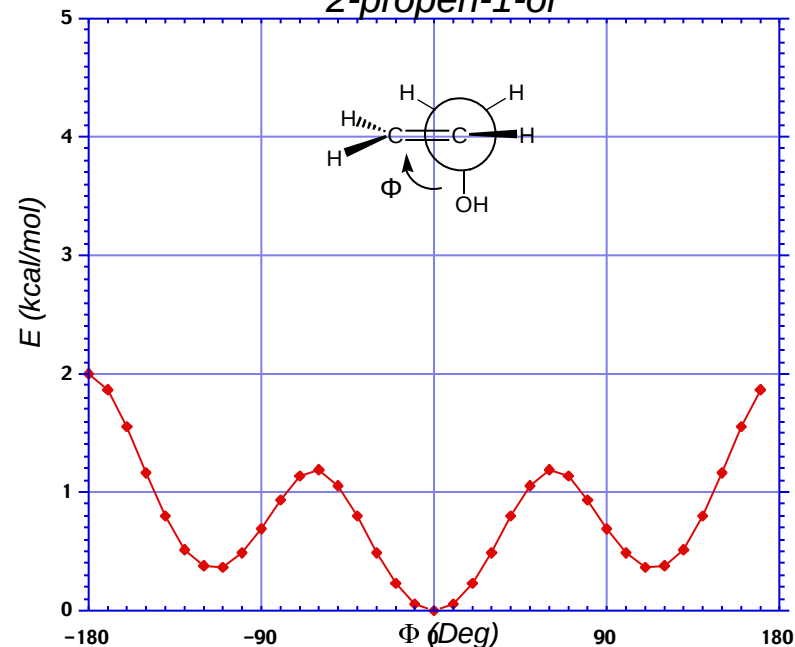
K. Houk, *JACS* **1987**, *109*, 6591-6600

1-butene

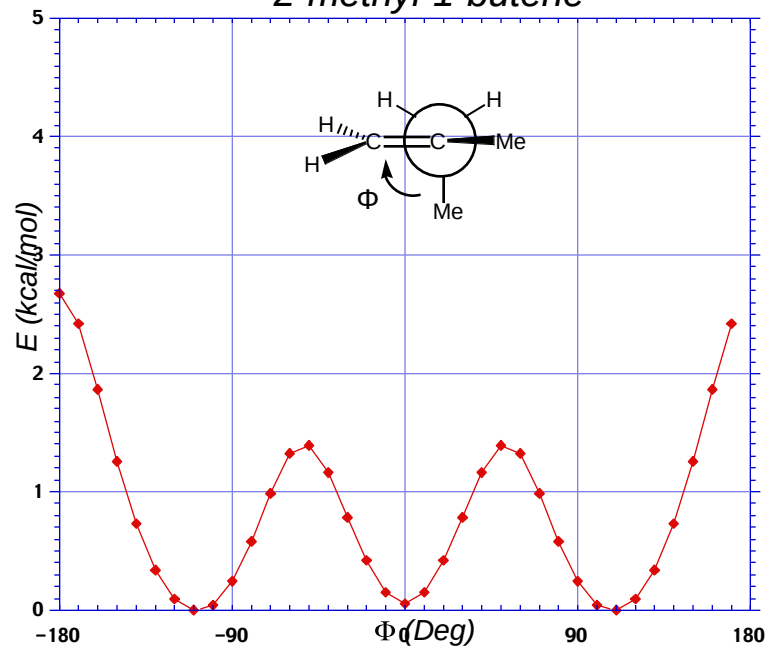


Conforms to *ab initio* (3-21G) values:
 Wiberg, K. B.; Martin, E. J. *Am. Chem. Soc.* **1985**, 107, 5035.

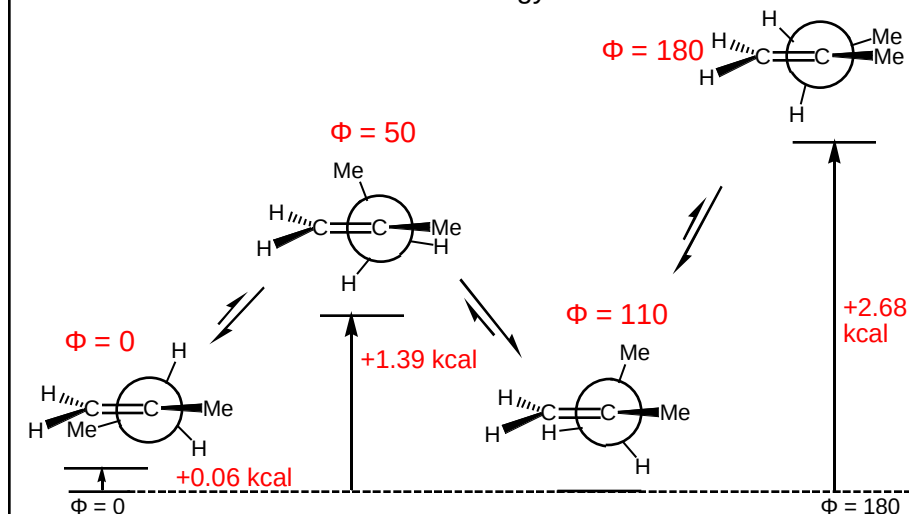
2-propen-1-ol



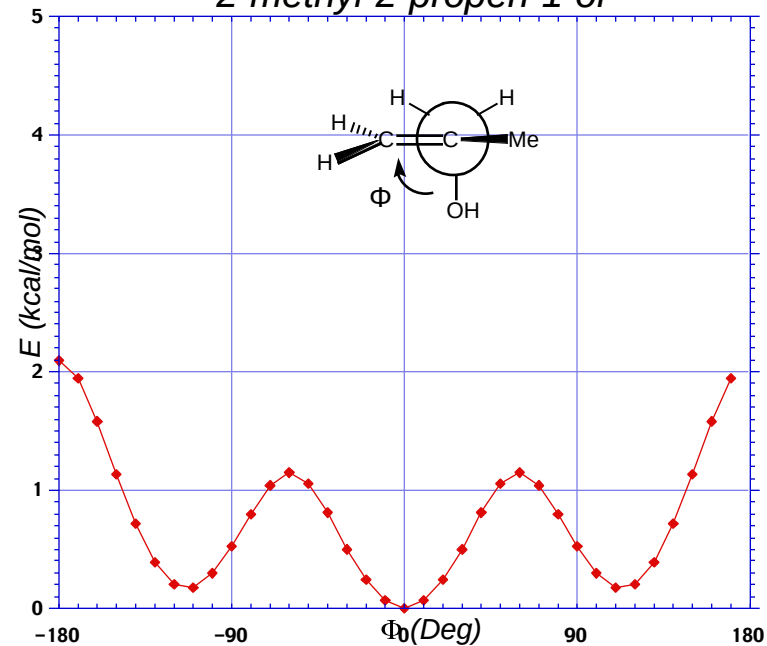
2-methyl-1-butene



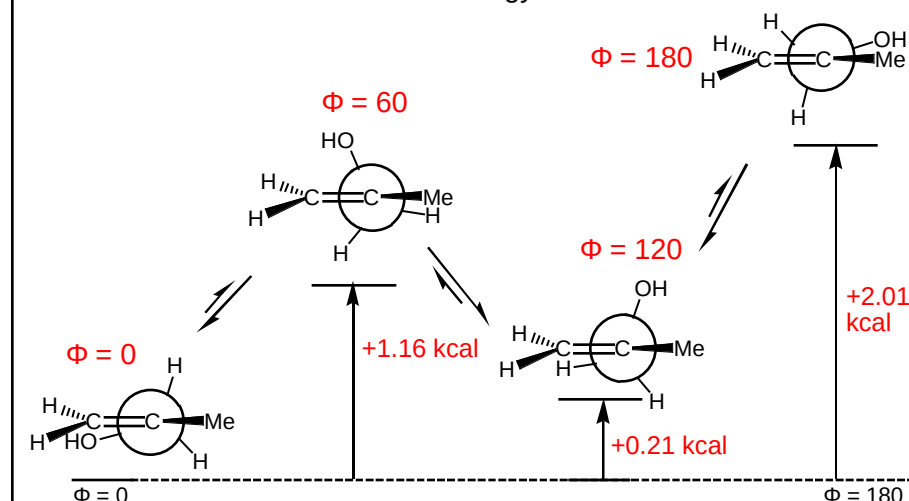
The Torsional Energy Profile

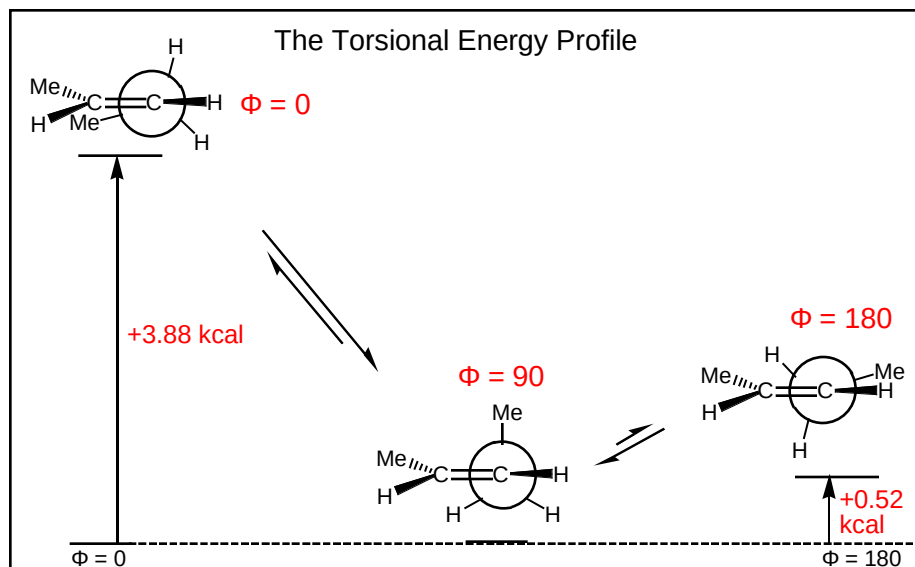
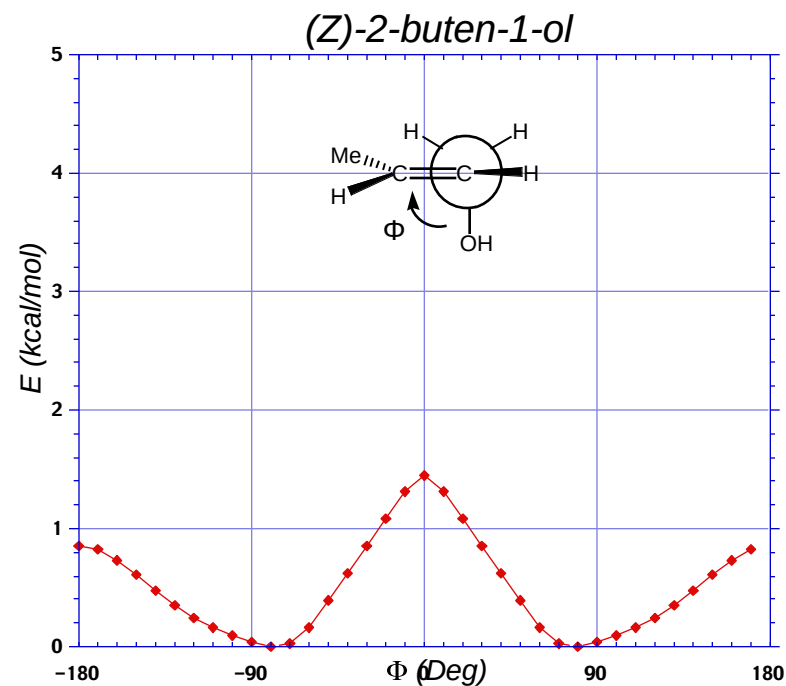
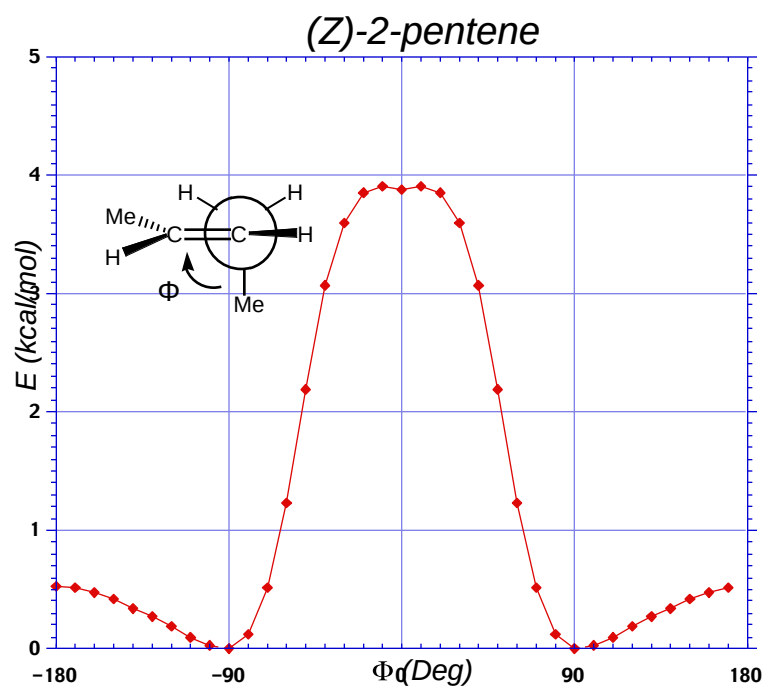


2-methyl-2-propen-1-ol

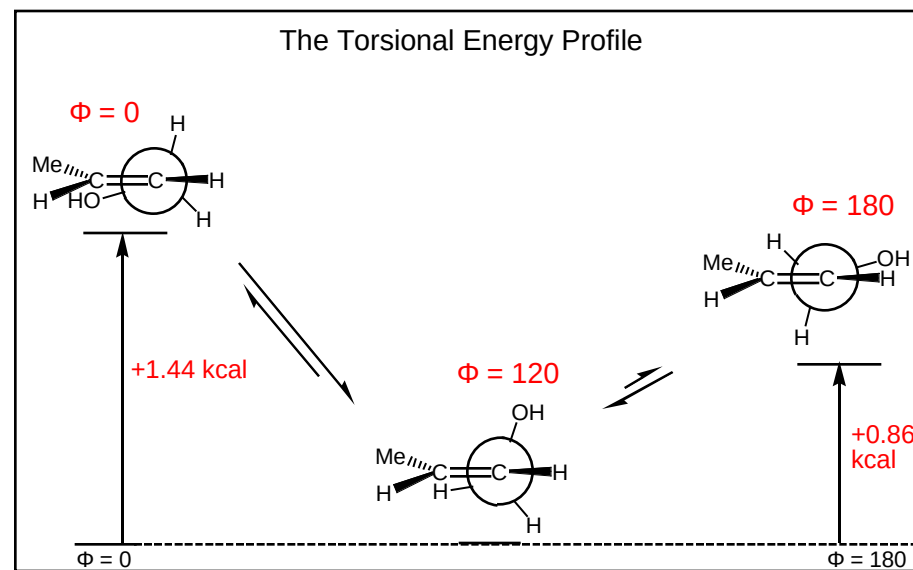


The Torsional Energy Profile

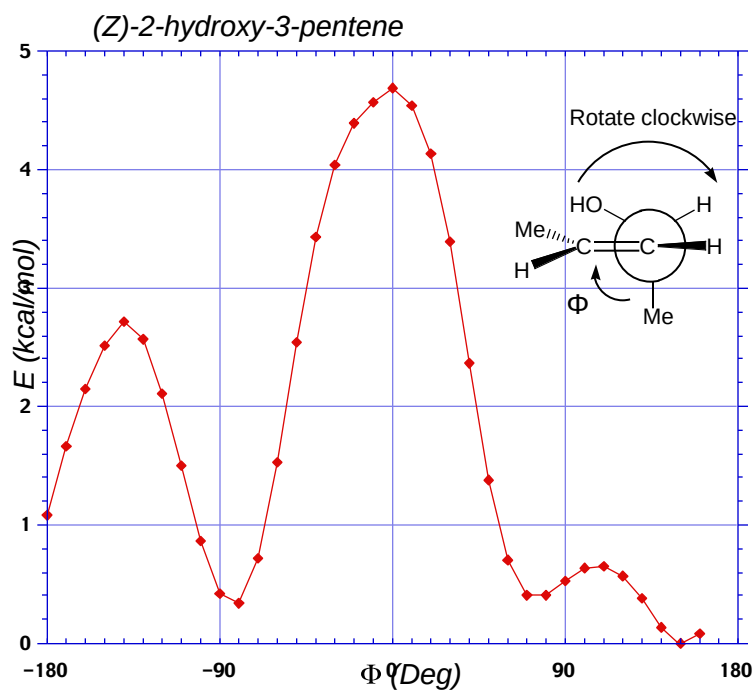




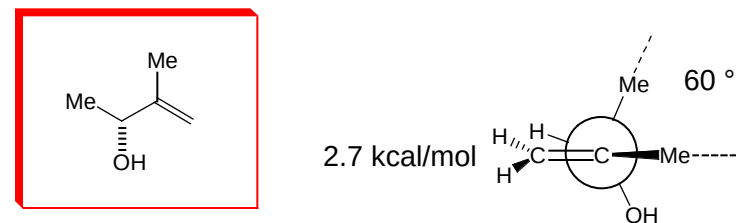
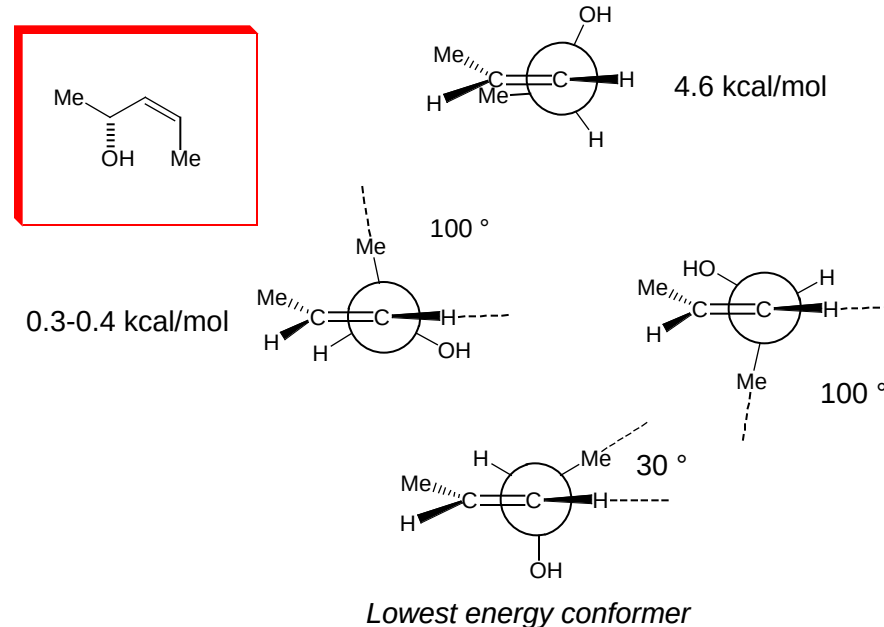
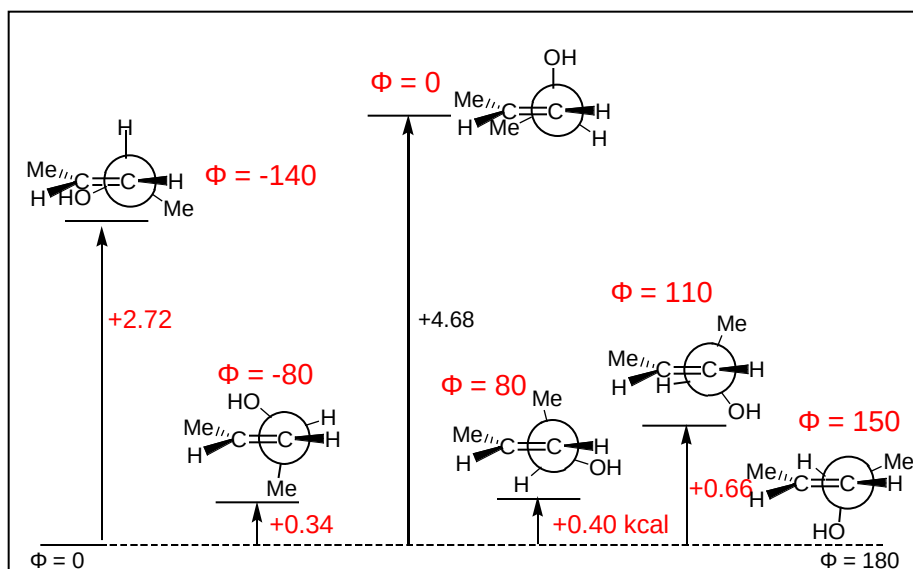
Values calculated using MM2 (molecular mechanics) force fields via the Macromodel multiconformation search.



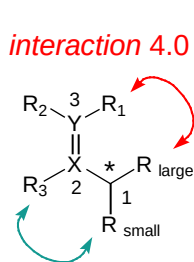
Review: Hoffman, R. W. *Chem. Rev.* **1989**, 89, 1841.



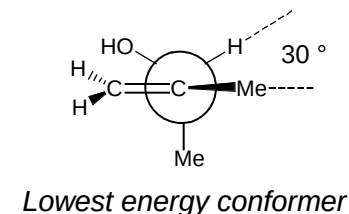
The Torsional Energy Profile

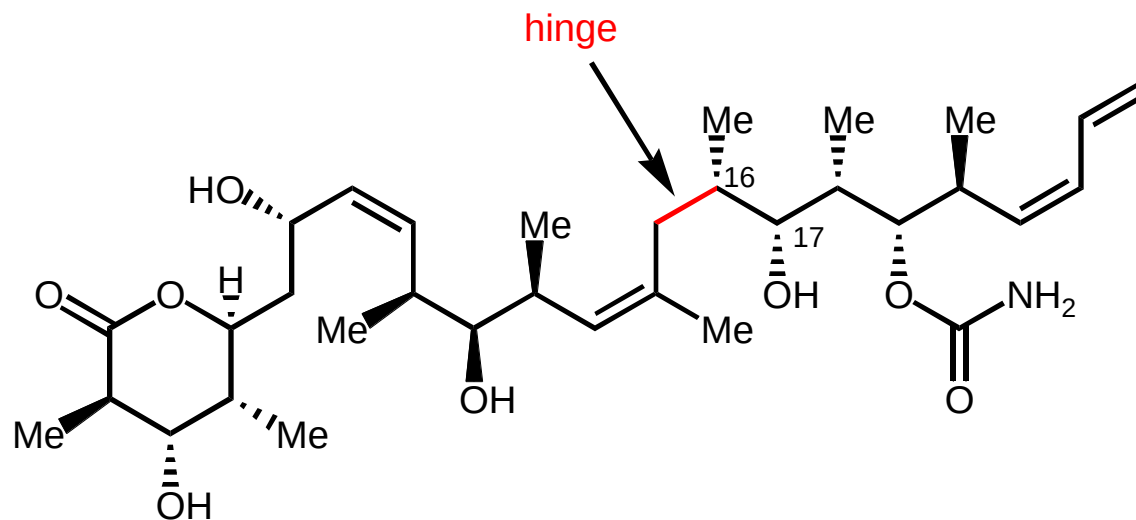


A(1,3) interaction 4.0 kcal/mol



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

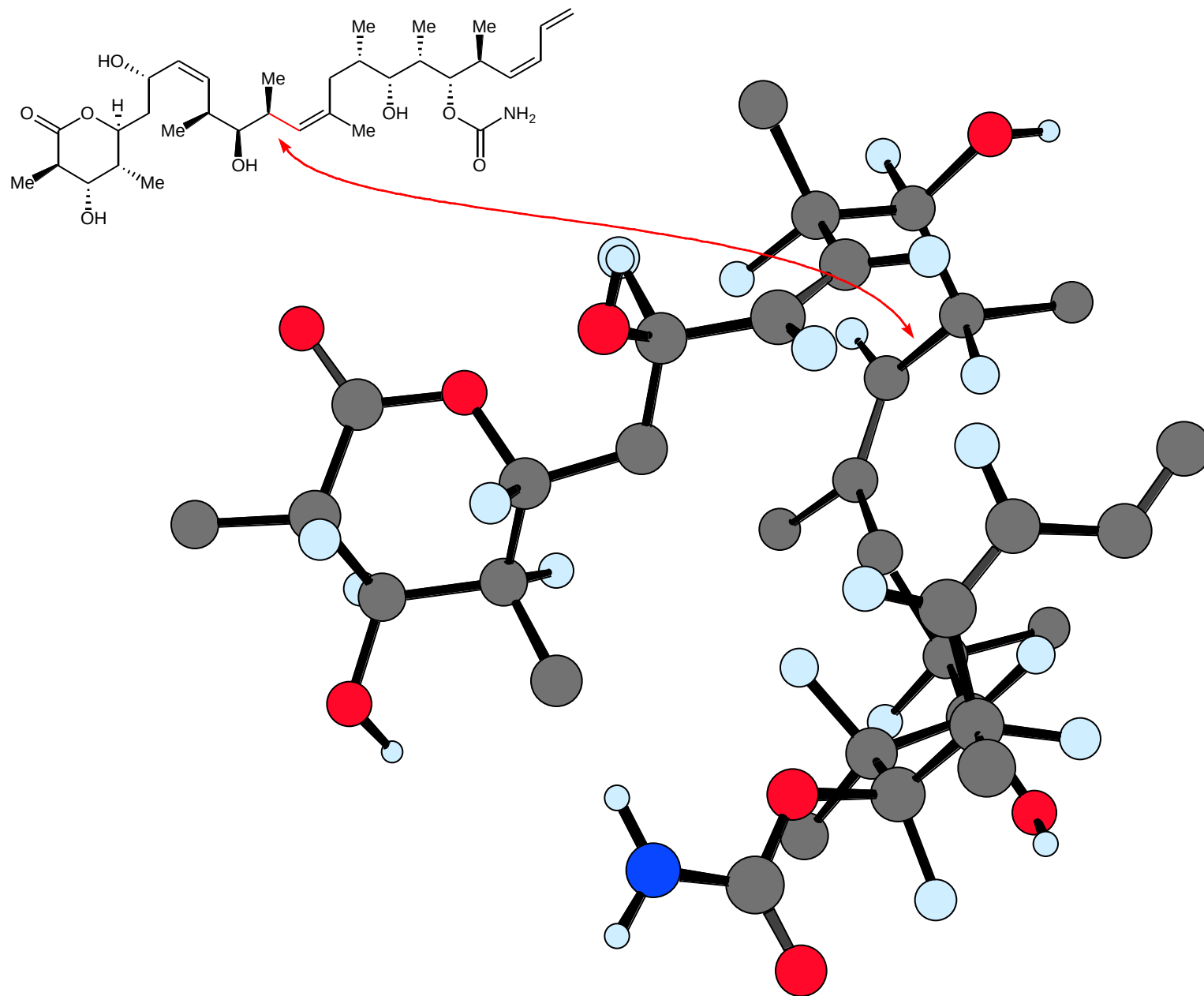


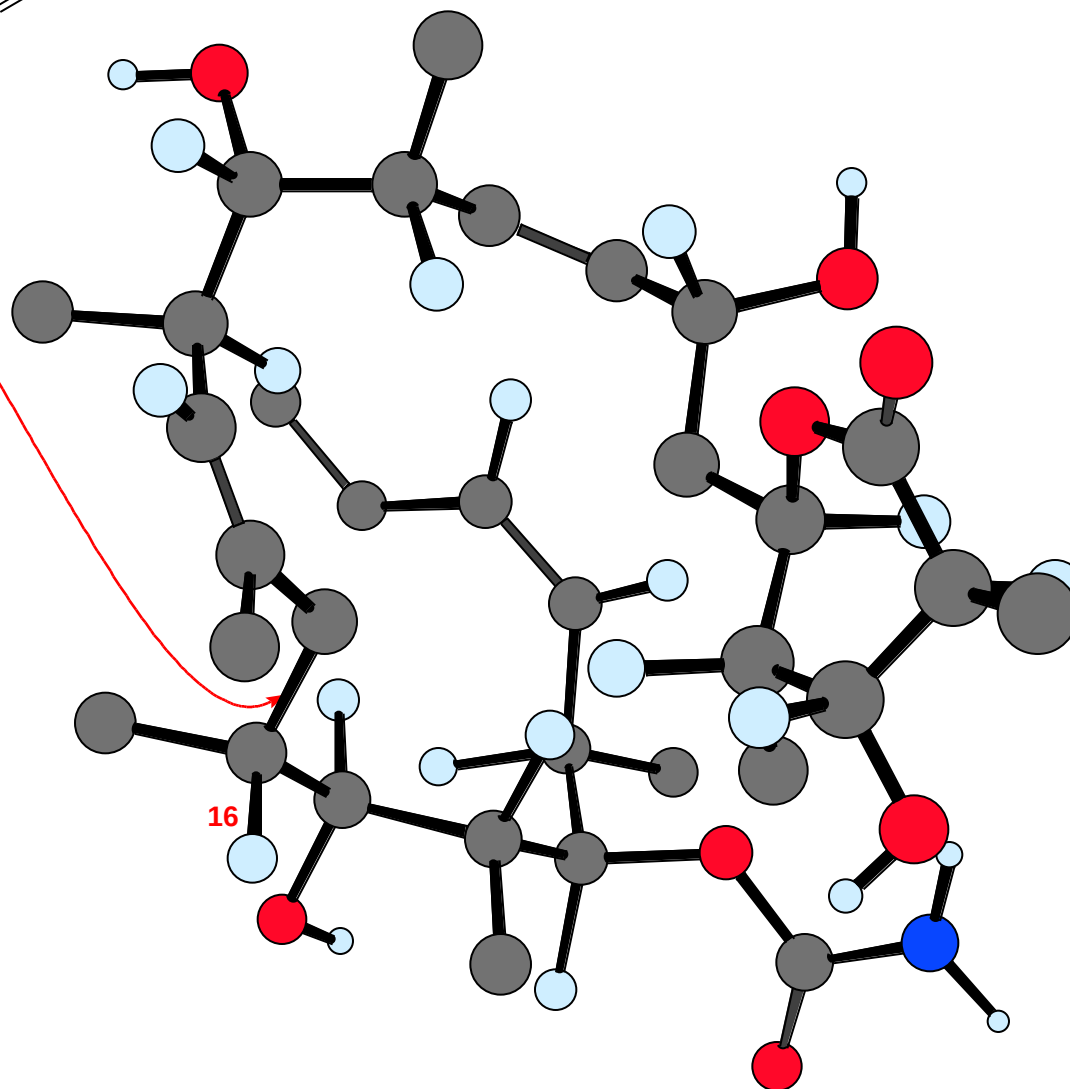
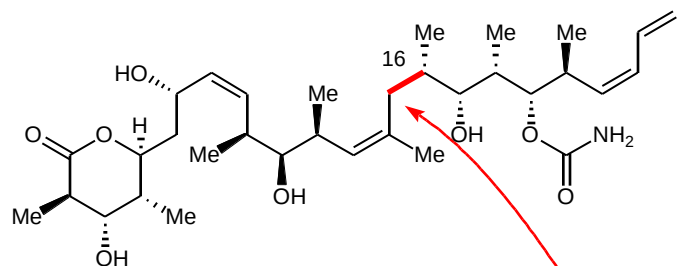


- immunosuppressive activity
- potent microtubule-stabilizing agent (antitumor activity similar to that of taxol)

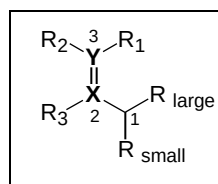
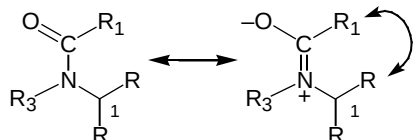
The epimers at C16 and C17 have no or almost no biological activity.

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

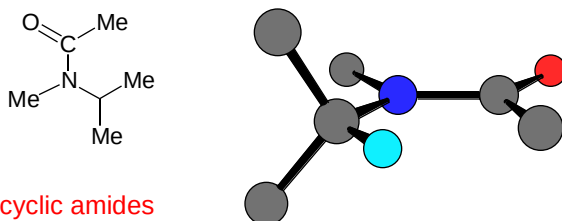




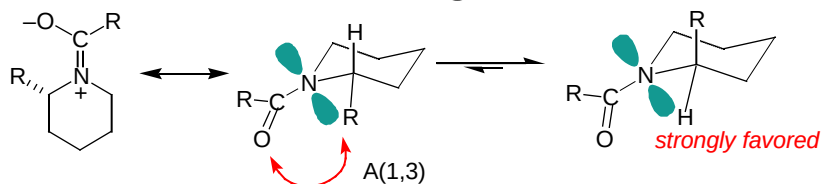
Consider the resonance structures of an amide:



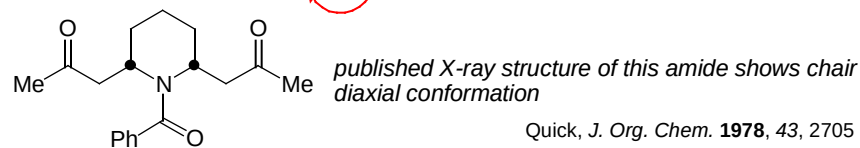
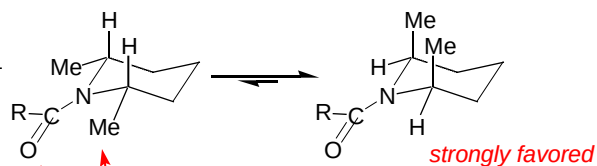
A(1,3) interactions between the "allylic substituent" and the R1 moiety will strongly influence the torsion angle between N & C1.



conformations of cyclic amides

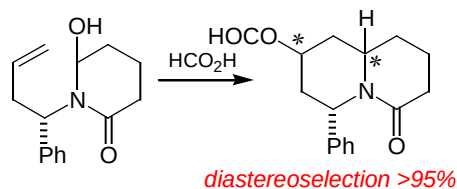


Chow
Can. J. Chem. **1968**, 46, 2821

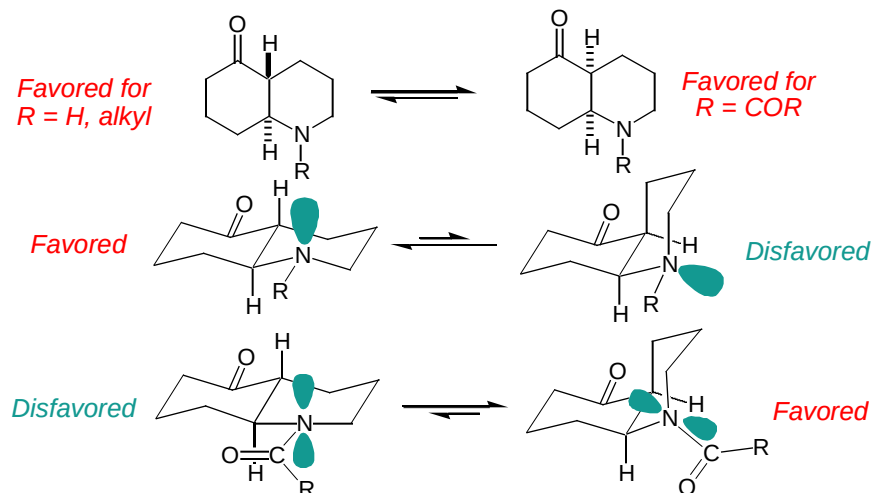


Problem: Predict the stereochemical outcome of this cyclization.

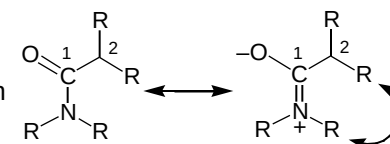
D. Hart, JACS **1980**, 102, 397



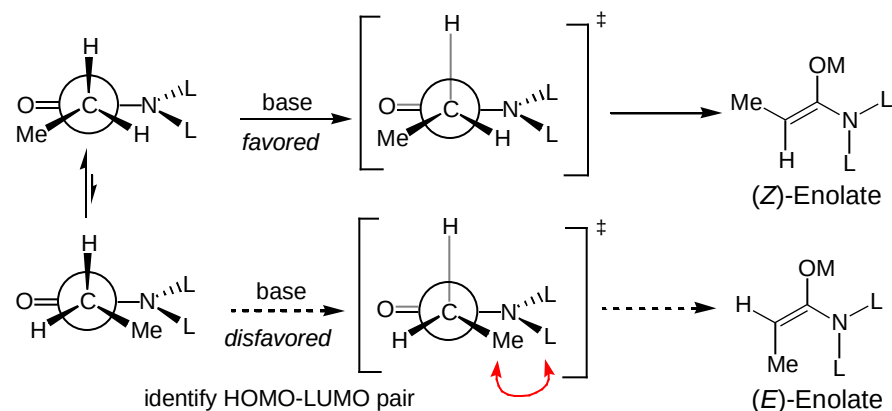
The selection of amide protecting group may be done with the knowledge that altered conformational preferences may result:



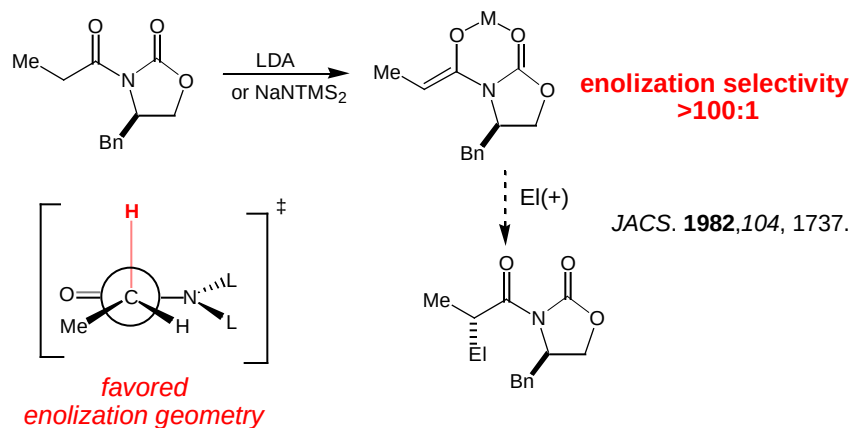
A(1,3) interaction between the C2 & amide substituents will strongly influence the torsion angle between C1 & C2.



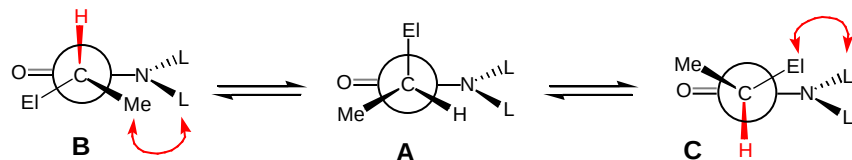
As a result, amides afford (Z) enolates under all conditions



A(1,3) Strain and Chiral Enolate Design

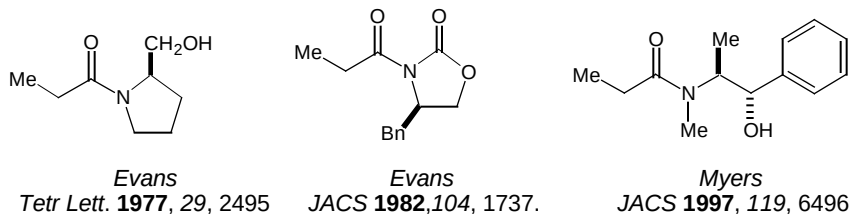


■ In the enolate alkylation process product epimerization is a serious problem. Allylic strain suppresses product enolization through the intervention of allylic strain

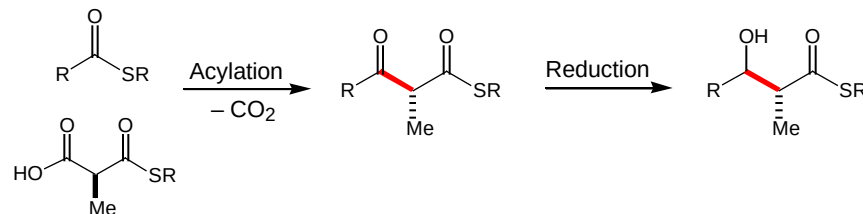


While conformers **B** and **C** meet the stereoelectronic requirement for enolization, they are much higher in energy than conformer **A**. Further, as deprotonation is initiated, A(1,3) destabilization contributes significantly to reducing the kinetic acidity of the system

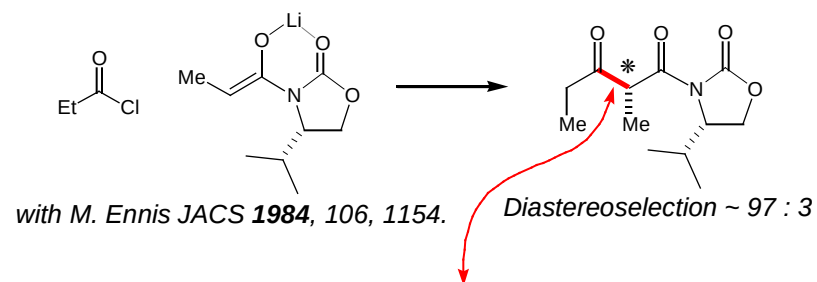
These allylic strain attributes are an integral part of the design criteria of chiral amide and imide-based enolate systems



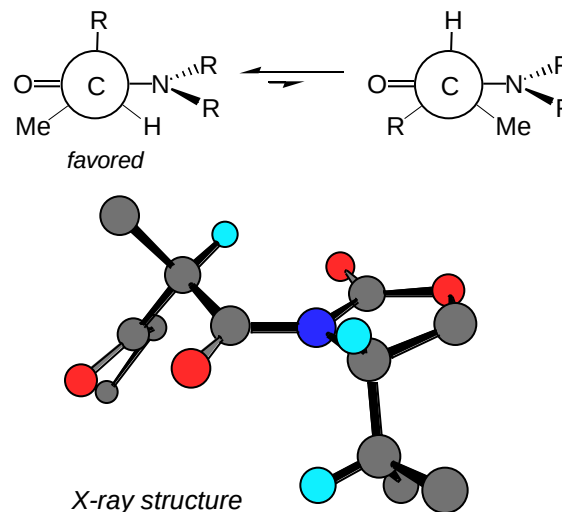
Polypropionate Biosynthesis: The Acylation Event

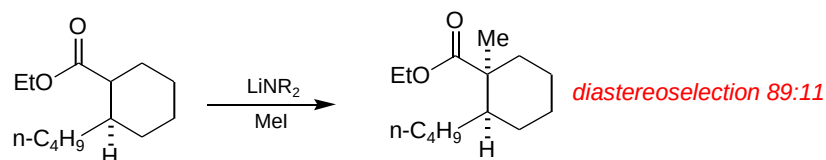
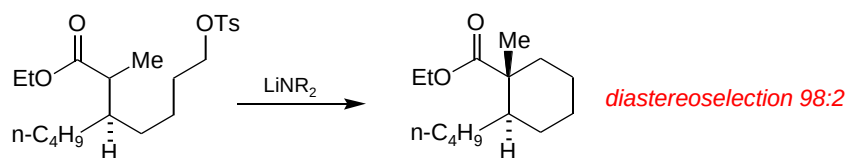


First laboratory analogue of the acylation event

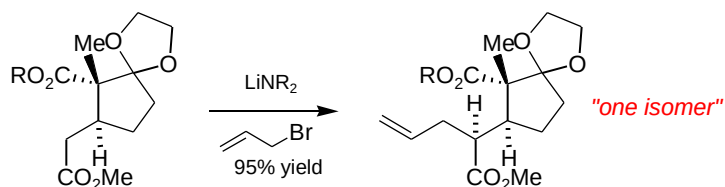


Why doesn't the acylation product rapidly epimerize at the exocyclic stereocenter??

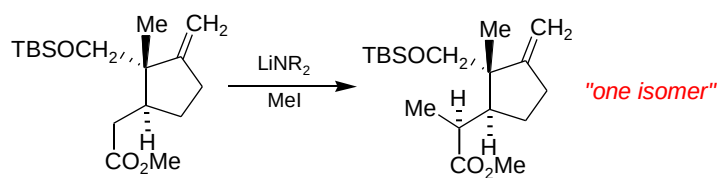




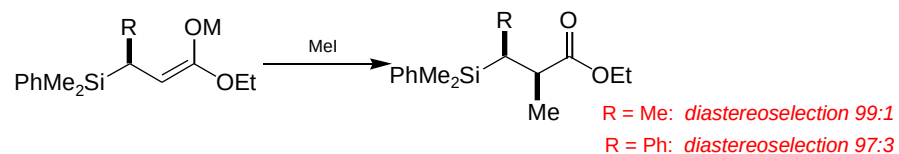
D. Kim & Co-workers, *Tetrahedron Lett.* **1986**, 27, 943.



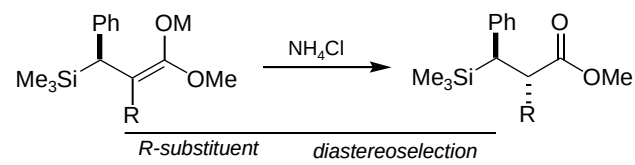
G. Stork & Co-workers, *Tetrahedron Lett.* **1987**, 28, 2088.



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



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



R = Me 87:13

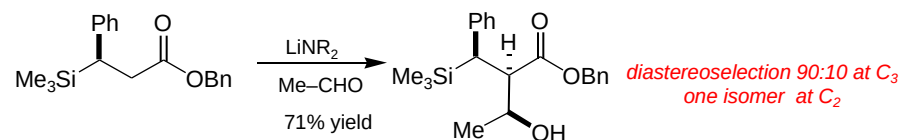
R = Et 80:20

R = CHMe₂ 40:60

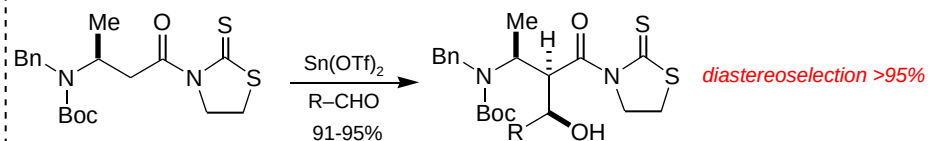
major diastereomer opposite to that shown

I. Fleming & Co-workers, *Chem. Commun.* **1985**, 318.

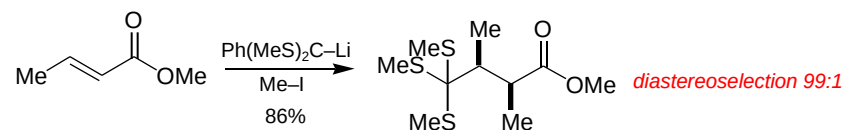
Y. Yamamoto & Co-workers, *Chem. Commun.* **1984**, 904.



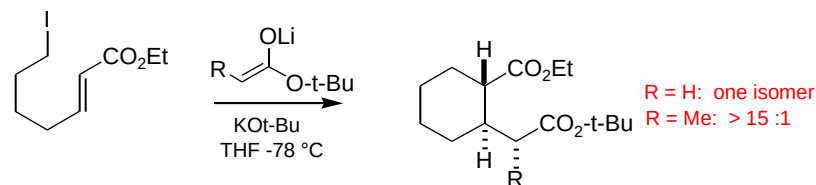
I. Fleming & Co-workers, *Chem. Commun.* **1986**, 1198.



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



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



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 $109^\circ 28'$
3	499.8	27.5	9.17	$24^\circ 44'$
4	656.1	26.3	6.58	$9^\circ 44'$
5	793.5	6.2	1.24	$0^\circ 44'$
6	944.8	0.1	0.02	$-5^\circ 16'$
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	

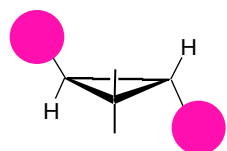
Eliel, E. L., Wilen, S. H. *Stereochemistry of Organic Compounds*
Chapter 11, John Wiley & Sons, 1994.

■ Baeyer "angle strain" is calculated from the deviation of the *planar* bond angles from the ideal tetrahedral bond angle.

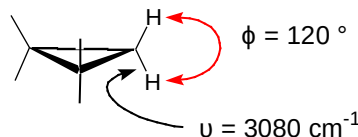
■ Discrepancies between calculated strain/ CH_2 and the "angle strain" results from puckering to minimize van der Waals or eclipsing torsional strain between vicinal hydrogens.

■ 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



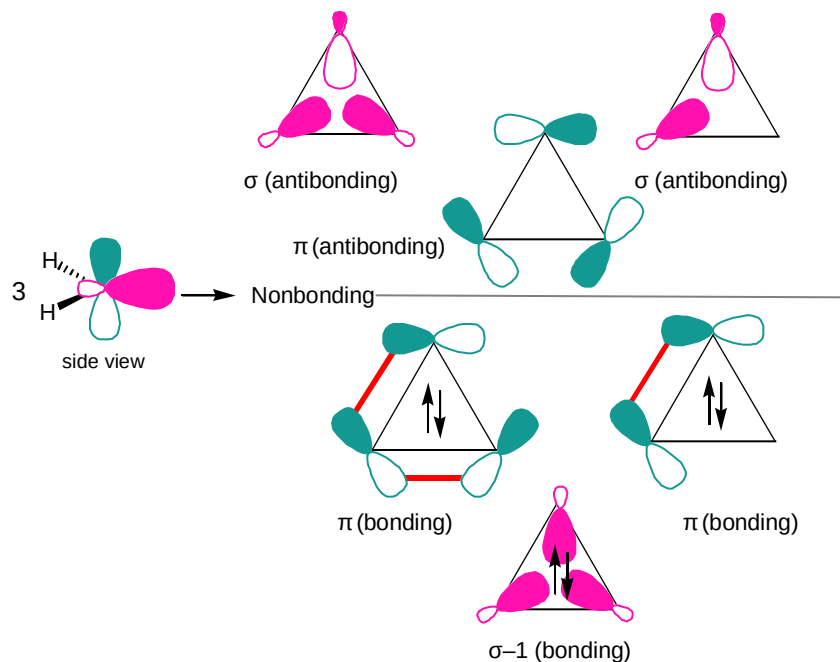
- Necessarily *planar*.
- Substituents are therefore eclipsed.
- Disubstitution prefers to be *trans*.



- Almost sp^2 , not sp^3

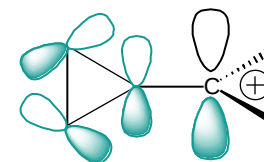
Walsh Model for Strained Rings:

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

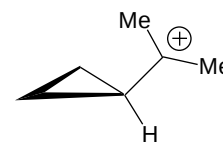


de Meijere, "Bonding Properties of Cyclopropane & their Chemical Characteristics"
Angew Chem. Int. Ed. **1979**, *18*, 809-826 (handout)

Carbocation Stabilization via Cyclopropylgroups

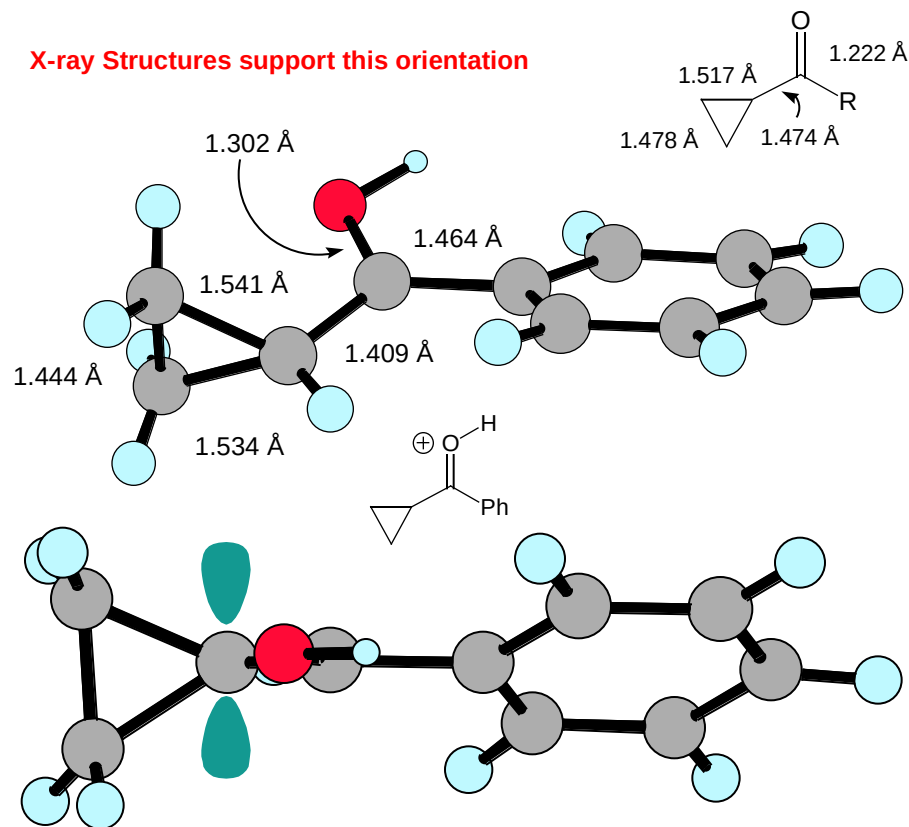


A rotational barrier of about 13.7 kcal/mol is observed in following example:



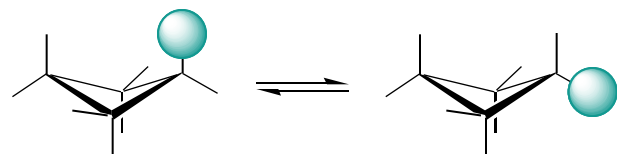
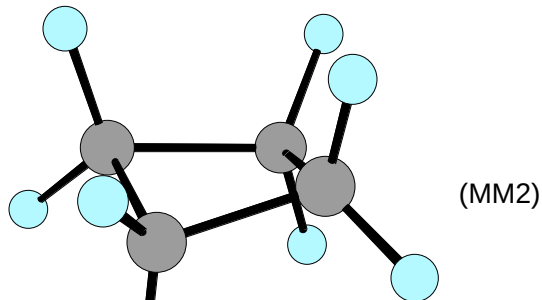
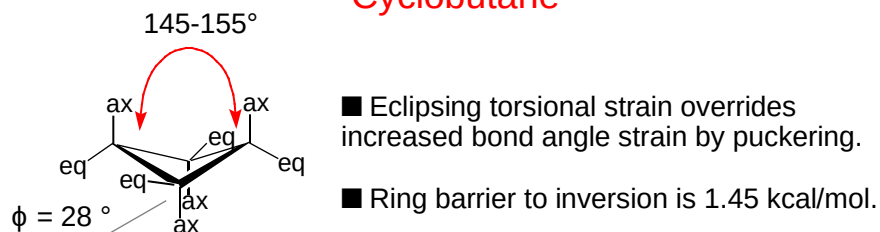
NMR in super acids
 $\delta(\text{CH}_3) = 2.6$ and 3.2 ppm

X-ray Structures support this orientation

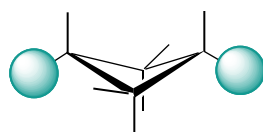


R. F. Childs, *JACS* **1986**, *108*, 1692

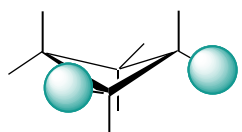
Cyclobutane



■ $\Delta G = 1$ kcal/mol favoring R = Me equatorial

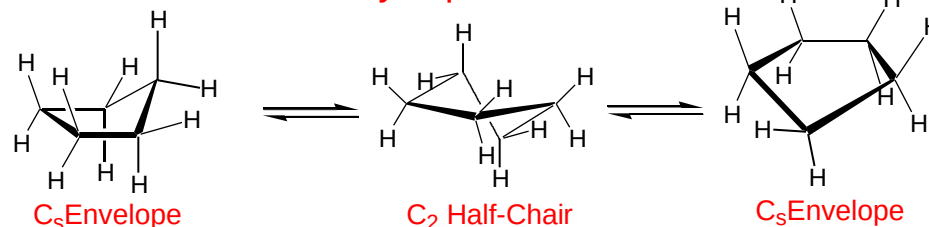


■ 1,3 Disubstitution prefers *cis* diequatorial to *trans* by 0.58 kcal/mol for di-bromo compd.



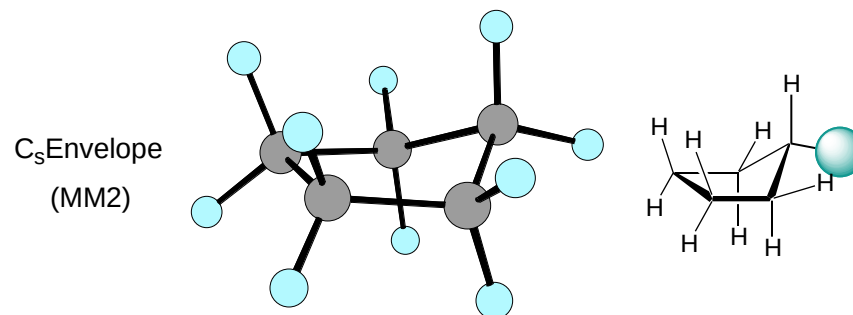
■ 1,2 Disubstitution prefers *trans* diequatorial to *cis* by 1.3 kcal/mol for diacid (roughly equivalent to the cyclohexyl analogue.)

Cyclopentane



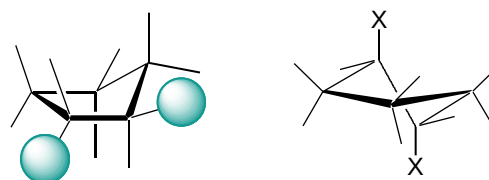
■ Two lowest energy conformations (10 envelope and 10 half chair conformations C_5 favored by only 0.5 kcal/mol) in rapid conformational flux (pseudorotation) which causes the molecule to appear to have a single out-of-plane atom "bulge" which rotates about the ring.

■ Since there is no "natural" conformation of cyclopentane, the ring conforms to minimize interactions of any substituents present.

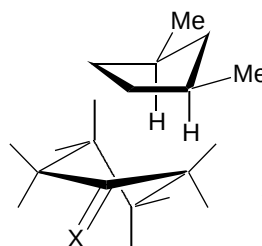


■ A single substituent prefers the equatorial position of the flap of the envelope (barrier ca. 3.4 kcal/mol, R = CH_3).

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



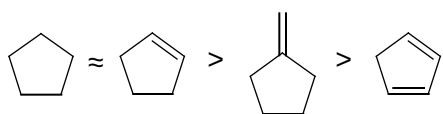
■ 1,3 Disubstitution: **Cis-1,3-dimethyl** cyclopentane 0.5 kcal/mol **more stable** than *trans*.



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

Methylenecyclopentane and Cyclopentene

Strain trends:

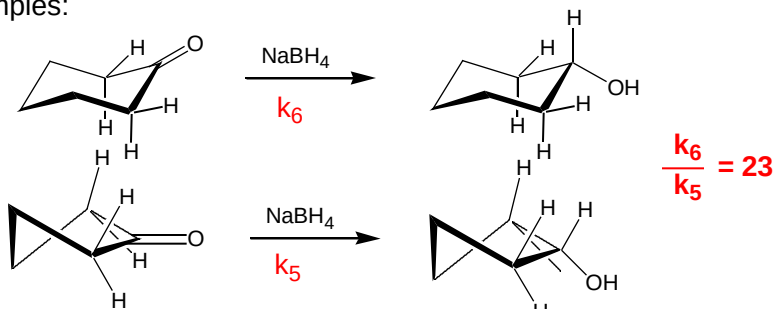


■ Decrease in eclipsing strain more than compensates for the increase in angle strain.

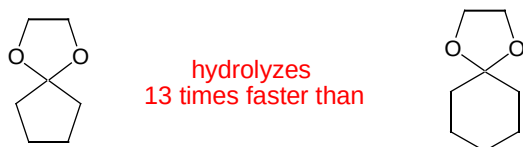
Relative to cyclohexane derivatives, those of cyclopentane prefer an sp^2 center in the ring to minimize eclipsing interactions.

"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.

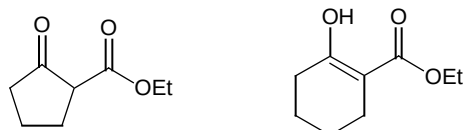
Examples:



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



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

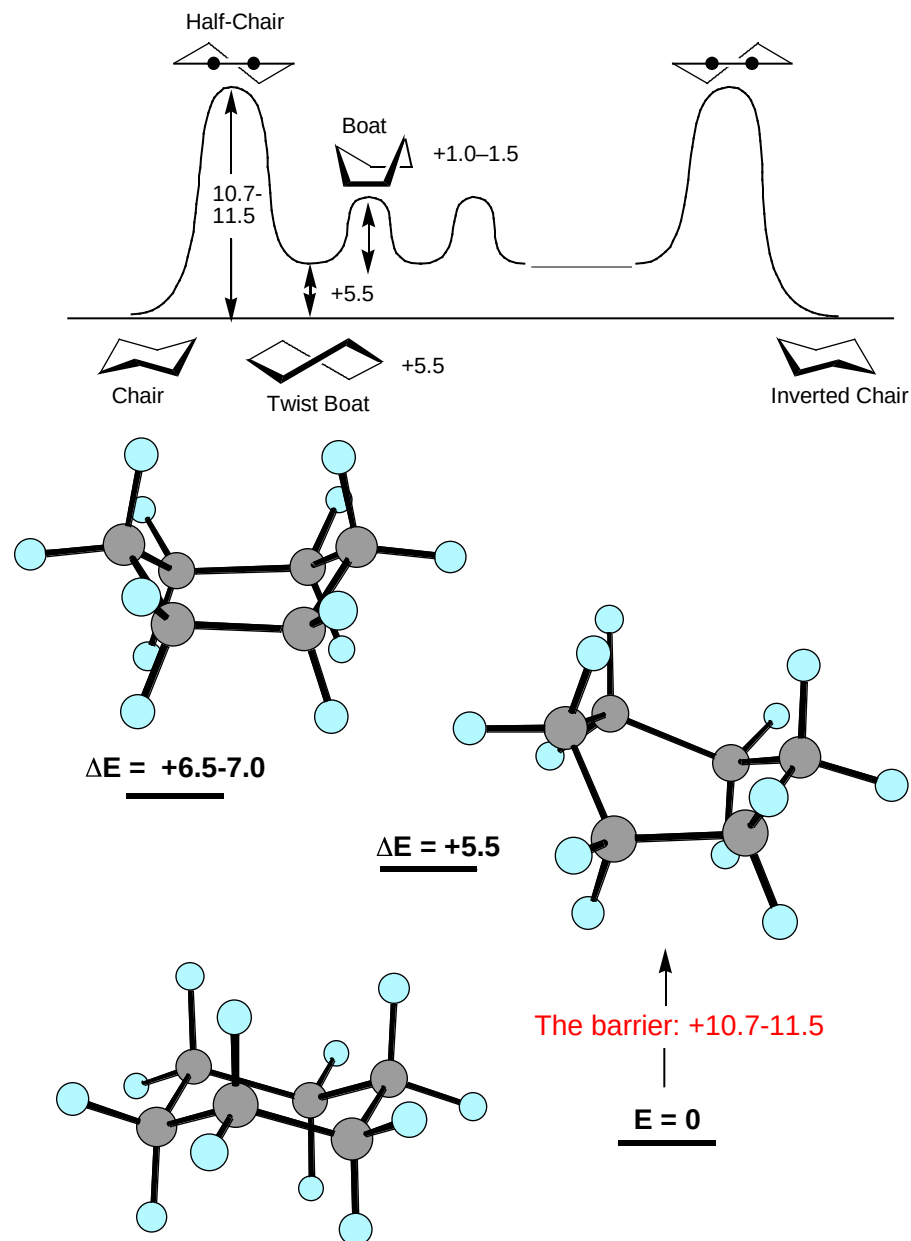


95.5:4.5 keto:enol

76:24 enol:keto

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

Cyclohexane Energy Profile (kcal/mol)



Monosubstituted Cyclohexanes: A Values



- Me - axial has **2 gauche butane interactions** more than Me-equatorial.
 Expected destabilization: $\approx 2(0.88) \text{ kcal/mol} = \sim 1.8 \text{ kcal/mol}$;
 Observed: 1.74 kcal/mol



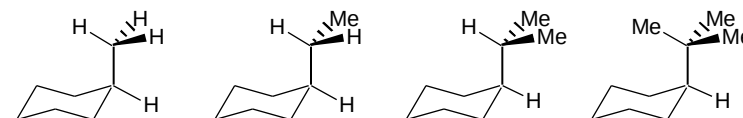
- The A-Value, or $-\Delta G^\circ$, is the preference of the substituent for the equatorial position.

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 ₂ CH 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≡CH	0.5	e
-C ₆ H ₅	2.9	d
-CN	0.15-0.25	a
-O ₂ CCH ₃	0.71	a
-CO ₂ H	1.35	c
-CO ₂ C ₂ H 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

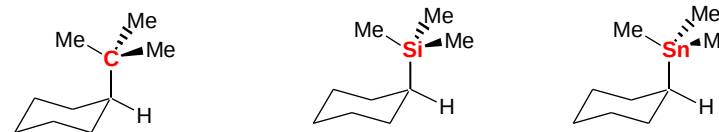
- a. F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.* **3**, 140 (1971).
 b. N. L. Allinger and L. A. Freiberg, *J. Org. Chem.* **31**, 804 (1966).
 c. J. A. Hirsch, *Top Stereochem.* **1**, 199 (1967).
 d. E. L. Eliel and M. Manoharan, *J. Org. Chem.* **46**, 1959 (1981).
 e. H. J. Schneider 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 $-\text{CMe}_3$ and $-\text{SiMe}_3$ substituents. While the $-\text{SiMe}_3$ substituent has a larger covalent radius, it has a smaller A-value:

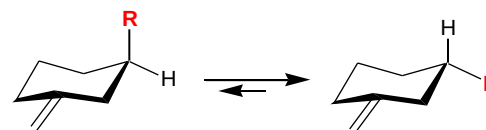


A-Value 4.5-5.0 2.5 1.1

Can you explain these observations?

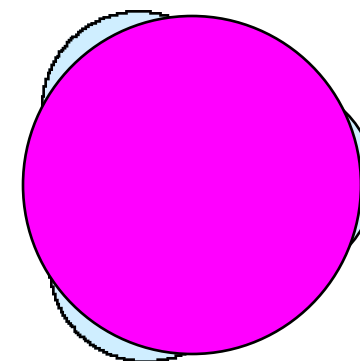
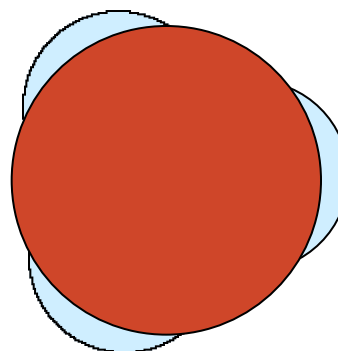
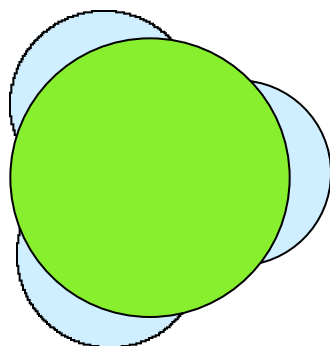
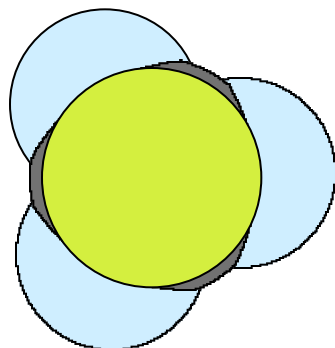
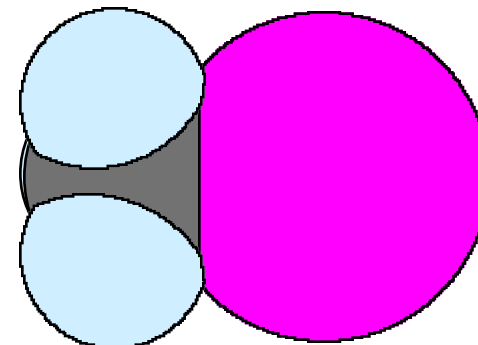
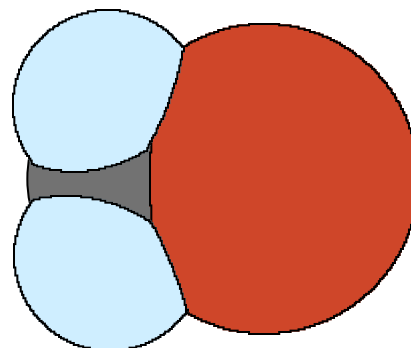
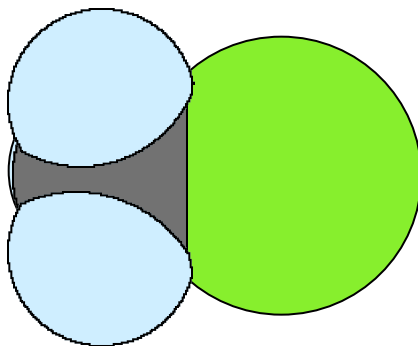
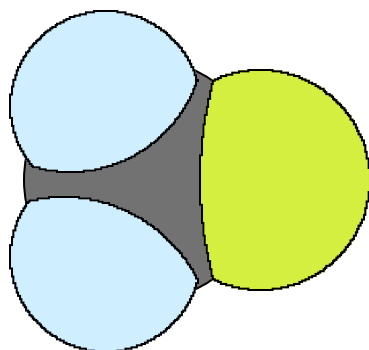
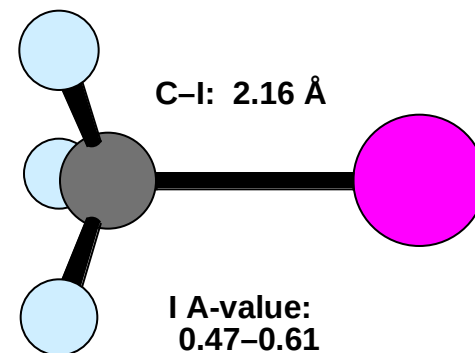
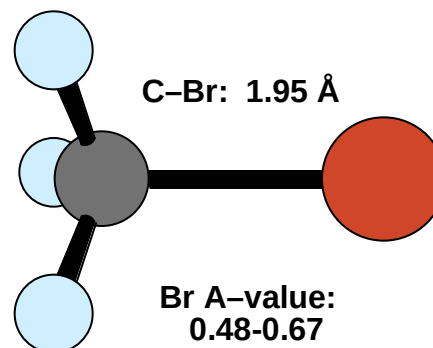
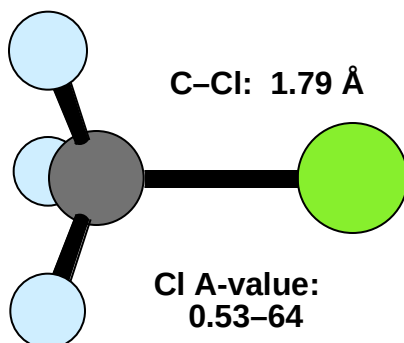
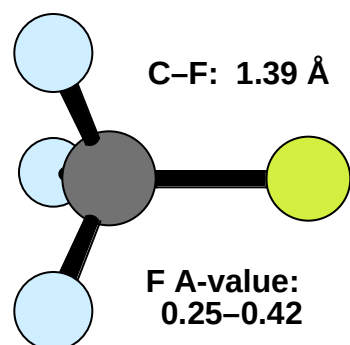
- The impact of double bonds on A-values:

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



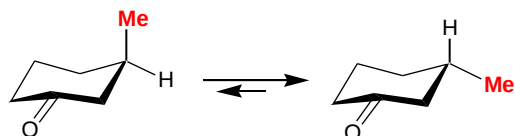
substituent	$-\Delta G^\circ$	A-value (cyclohexane)
R = Me	0.8	1.74
R = OMe	0.8	0.6
R = OAc	0.6	0.71

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.



The impact of trigonal Carbon

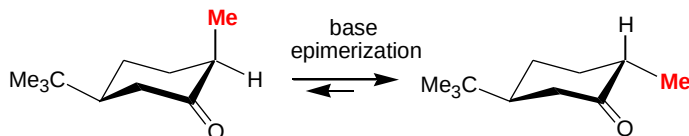
- Let's now compare look at the carbonyl analog in the 3-position



$$\Delta G^\circ = -1.36 \text{ kcal/mol}$$

versus -1.74 for cyclohexane

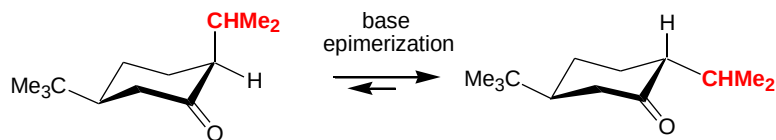
- Let's now compare look at the carbonyl analog in the 2-position



$$\Delta G^\circ = -1.56 \text{ kcal/mol}$$

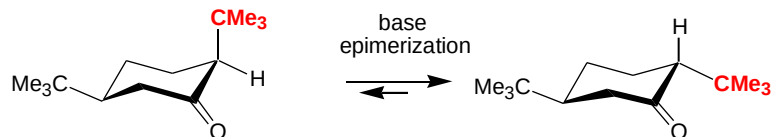
versus -1.74 for cyclohexane

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



$$\Delta G^\circ = -0.59 \text{ kcal/mol}$$

versus -2.15 for cyclohexane



$$\Delta G^\circ = -1.62 \text{ kcal/mol}$$

versus -5.0 for cyclohexane

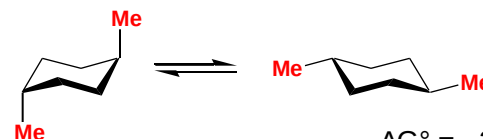
Polysubstituted Cyclohexane A Values

- 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.

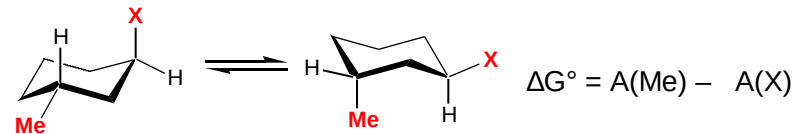


$$\Delta G^\circ = 0 \text{ kcal/mol}$$

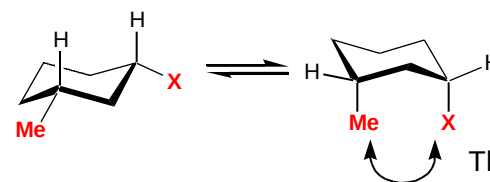


$$\Delta G^\circ = -2(1.74) = -3.48 \text{ kcal/mol}$$

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

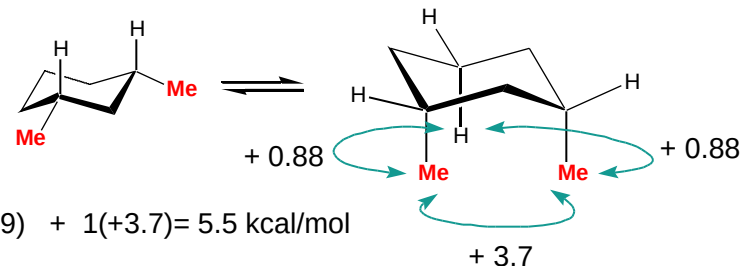


$$\Delta G^\circ = A(\text{Me}) - A(\text{X})$$



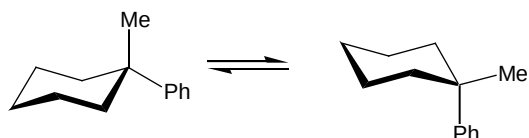
The new interaction!

For $\text{X} = \text{Me}$



$$\Delta G^\circ = 2(.9) + 1(3.7) = 5.5 \text{ kcal/mol}$$

Let's now consider geminal substitution



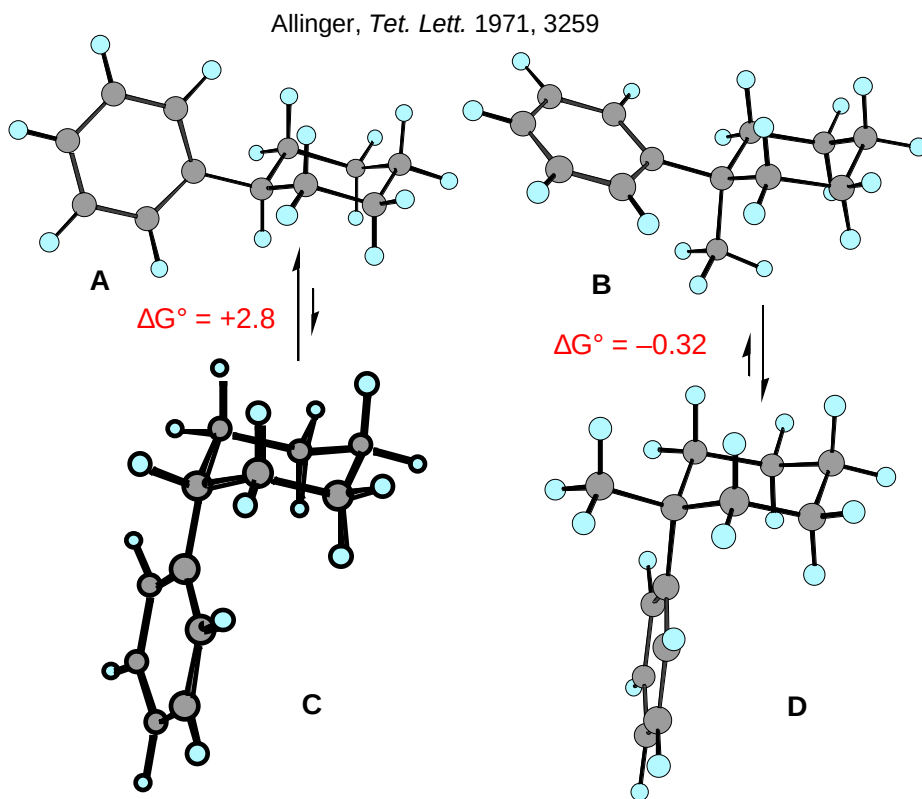
The prediction: $\Delta G^\circ = A(\text{Ph}) - A(\text{Me})$

$$\Delta G^\circ = +2.8 - 1.7 = +1.1 \text{ kcal/mol}$$

Observed:

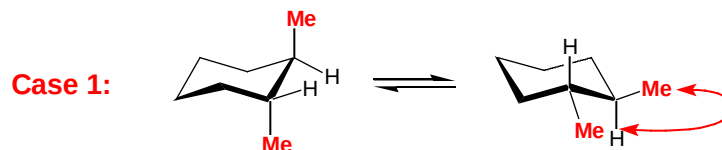
$$\Delta G^\circ = -0.32 \text{ kcal/mol}$$

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.



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

Let's now consider vicinal substitution



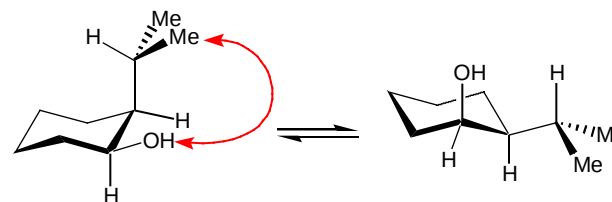
The prediction: $\Delta G^\circ = 1 \text{ gauche butane} - 2A(\text{Me})$

$$\Delta G^\circ = +0.88 - 2(1.74) = +2.6 \text{ kcal/mol}$$

Observed:

$$\Delta G^\circ = +2.74 \text{ kcal/mol}$$

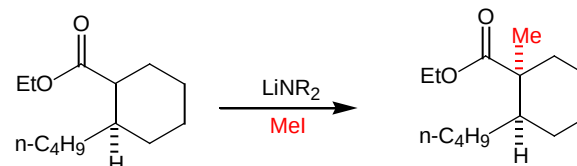
If the added gauche butane destabilization in the di-equatorial conformer had not been added, the estimate would have been off.

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?

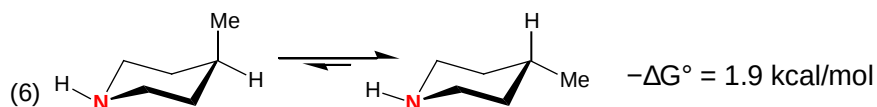
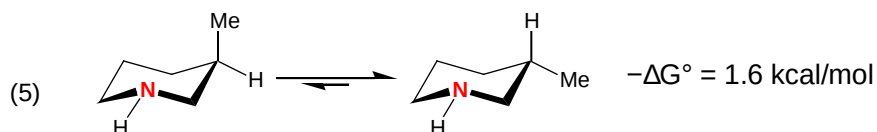
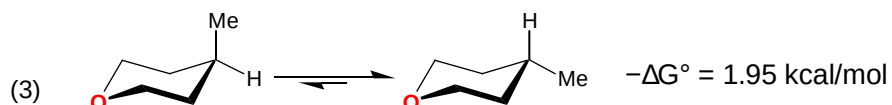
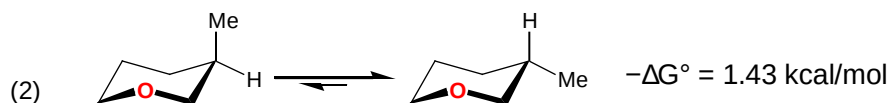
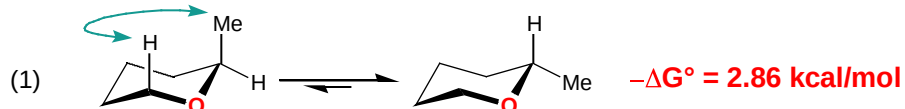
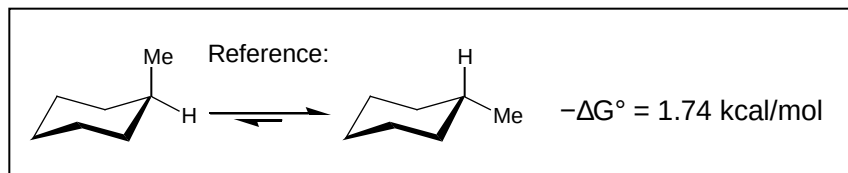


diastereoselection 89:11

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).

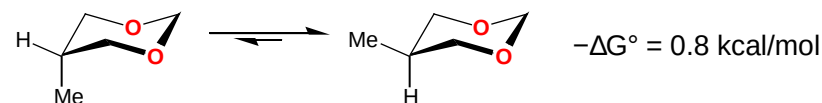
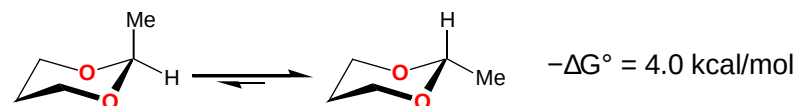


A-Values for N-Substituents in Piperidine

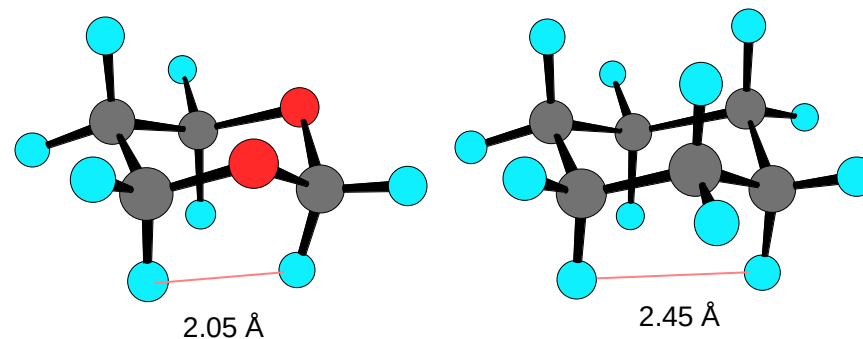


■ Hydrogen is "bigger" than the N-lone pair.

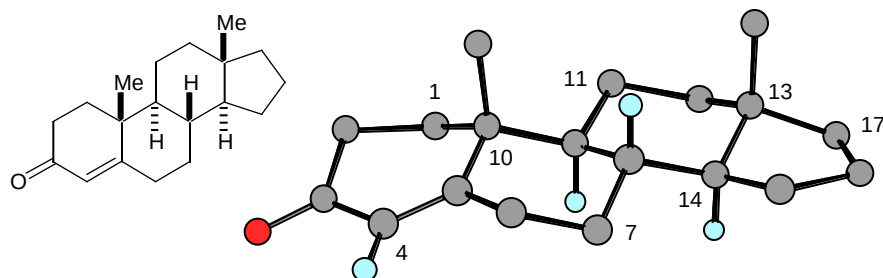
■ The A-value of N-substituents is slightly larger than the corresponding cyclohexane value. Rationalize



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

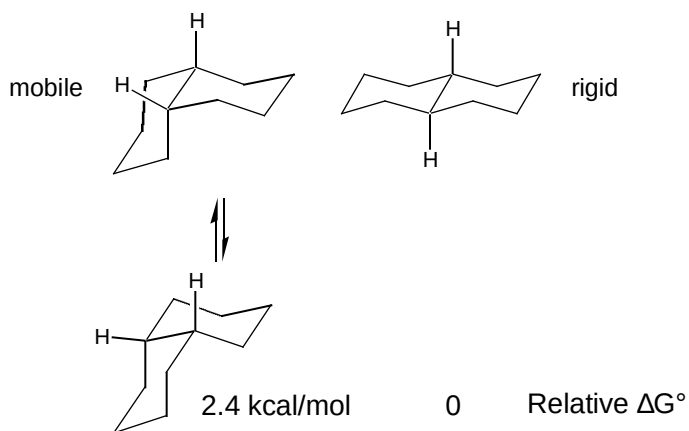


Conformations of Bicyclic Ring Systems

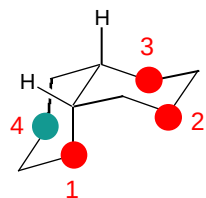


The steroid nucleus provided the stimulation for the development of conformational analysis, particularly of polycyclic ring systems. D. H. R. Barton was awarded a Nobel prize in 1969 for his contributions in this area.

Decalin Ring System (6/6)



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

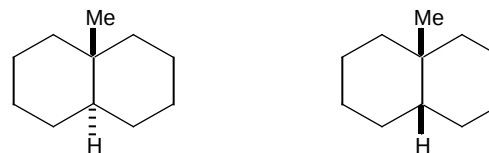


Gauche-butane interactions

C1 → C2
C1 → C3
C4 → C3

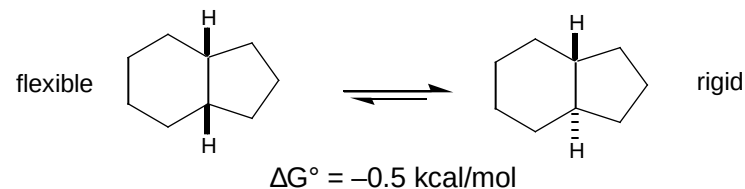
$$\Delta G^\circ(\text{est}) = 3(0.88) = 2.64 \text{ kcal/mol}$$

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



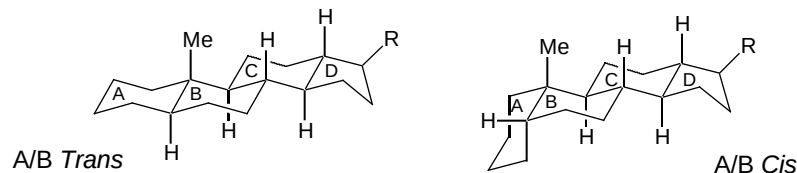
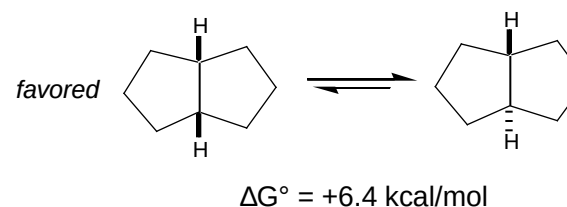
see Elier, p 780

Hydrindane Ring System (6/5)



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

The 5-5 Ring System

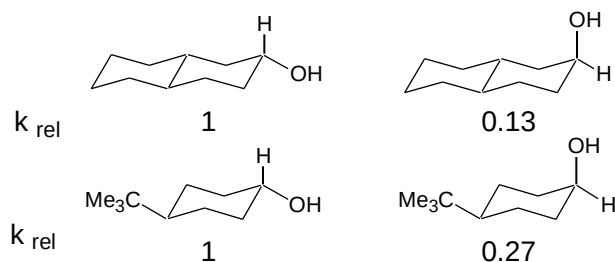


Rationalize the conformational flexibility of a *A/B Trans* vs. *A/B Cis* Steroid!

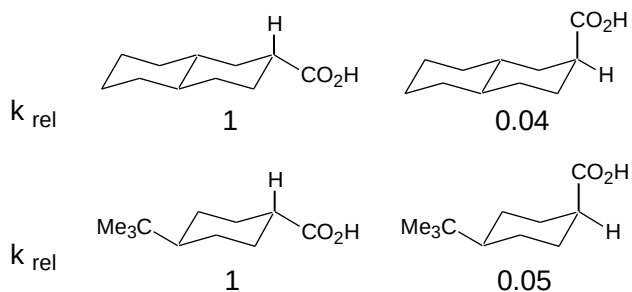
Different reactivity for axial and equatorial substituents

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

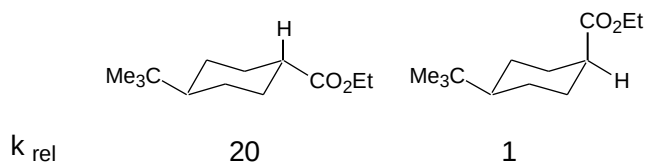
Acetylation with $\text{Ac}_2\text{O}/\text{Py}$



Acid-catalyzed esterification

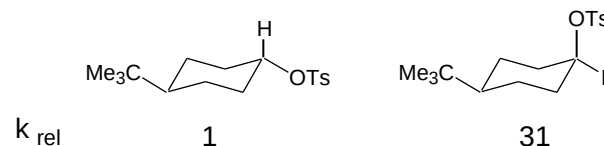


Ester Saponification



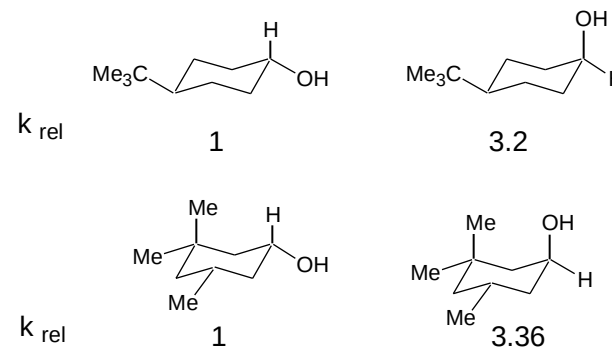
For a more detailed discussion of this topic see:
 Eliel, E. L., S. H. Wilen, et al. (1994). *Stereochemistry of Organic Compounds* pp 720-726

$\text{S}_{\text{N}}2$ Reactions (Displacement with Ph-S^-)



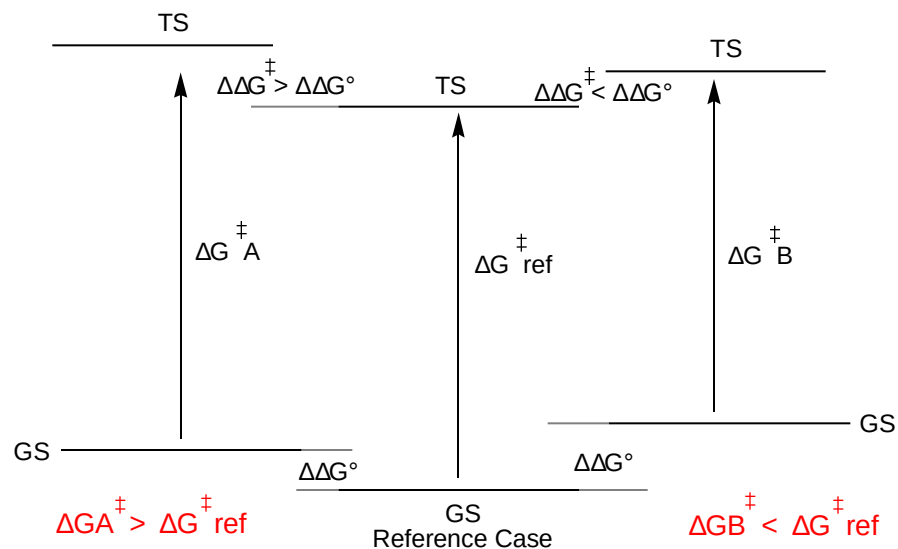
The axial diastereomer is not always slower reacting:

Alcohol Oxidation with Cr(6+)

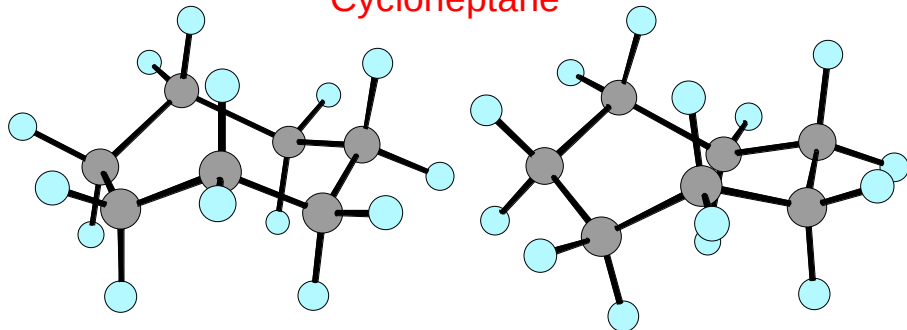


The rate-determining step is breakdown of the chromate ester. This is an apparent case of strain acceleration

Steric Hindrance and Steric Assistance

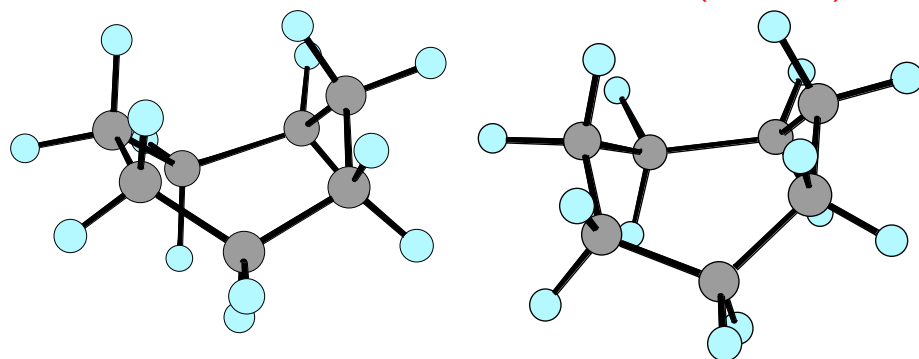


Cycloheptane



Chair (2.16 kcal/mol)

Twist-Chair (0 kcal/mol)



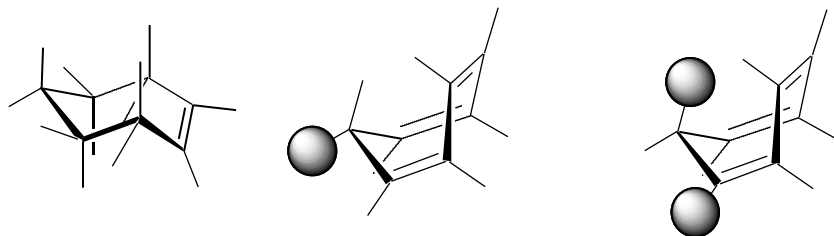
Boat (3.02 kcal/mol)

Twist-Boat (2.49 kcal/mol)

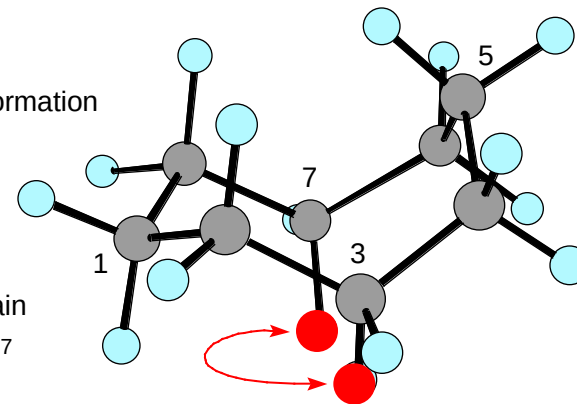
Hendrickson, J. B. *JACS* **1961**, 83, 4537.

See Eliel, page 762+

Olefins are preferentially orientated to eliminate eclipsing interactions.



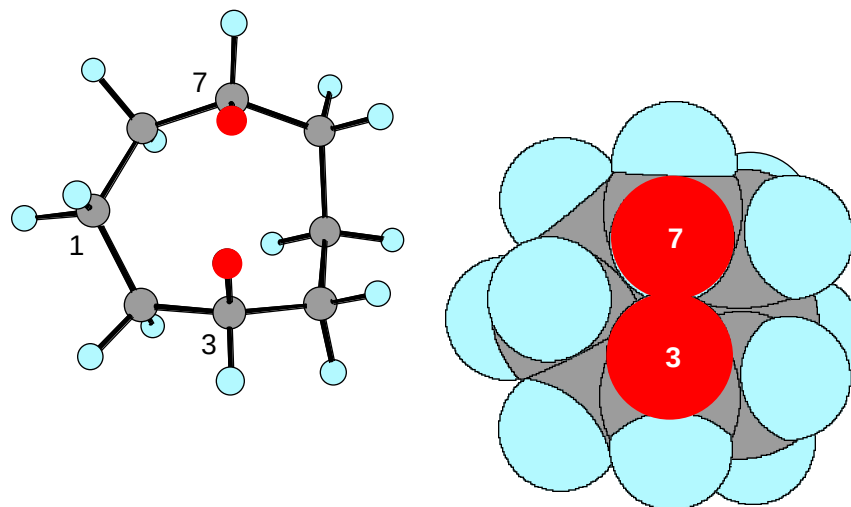
Cyclooctane

Chair-Boat
Lowest-energy conformationTransannular strain
between C₃ & C₇

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

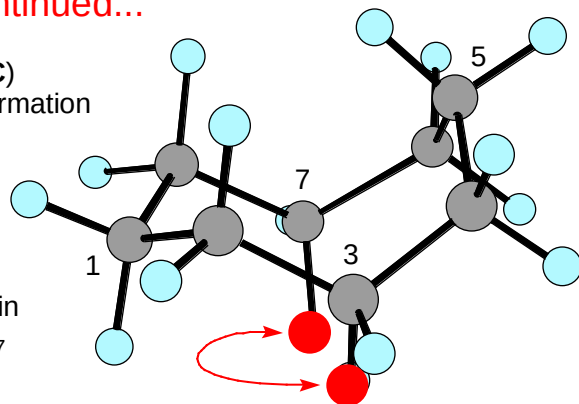
	Methyl position	1	2	3	4	5
ΔG	(pseudoeqatorial) (pseudoaxial) (kcal/mol)	1.8	2.8	>4.5	-0.3	6.1

Underside view of boat-chair C3 & C7 eclipsing interactions



Cyclooctane continued...

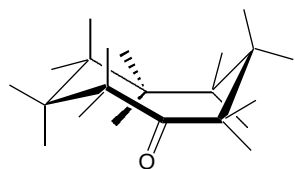
Chair-Boat (**BC**)
Lowest-energy conformation



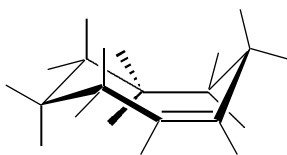
Transannular strain
between C₃ & C₇

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

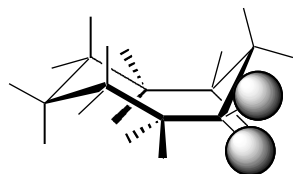
Cyclooctane derivatives



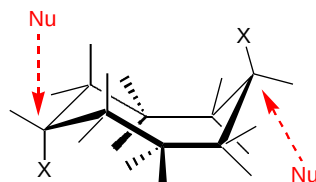
Carbonyl is positioned at C₃ or C₇



Olefin is positioned at C₃-C₄ or
C₆-C₇

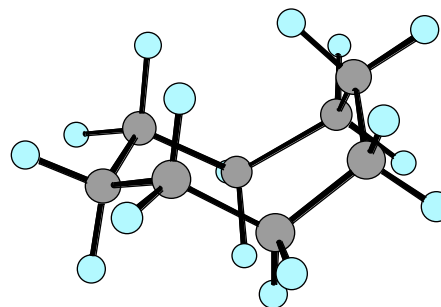


Disubstitution occurs at C₄ or C₆

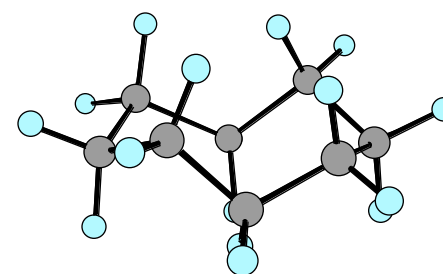


S_N2 occurs at C₁ and C₅

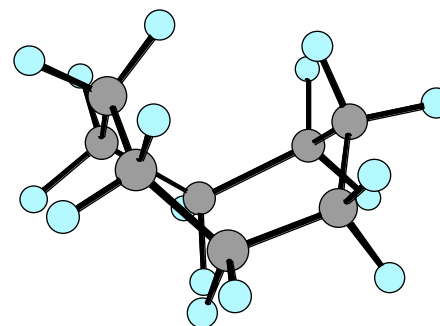
Still, W. C.; Galynker, I. *Tetrahedron* **1981**, 37, 1981.



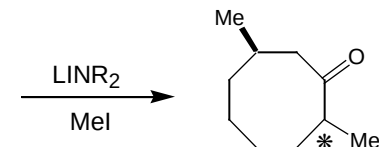
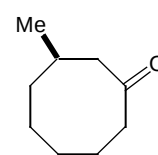
Chair-Boat (**CB**) conformation
reference structure



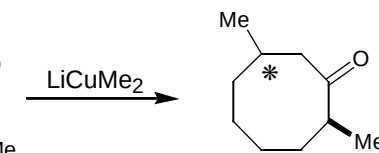
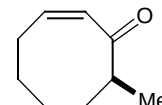
Chair-Chair (**CC**) conformation
(+1-1.6 kcal/mol)



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



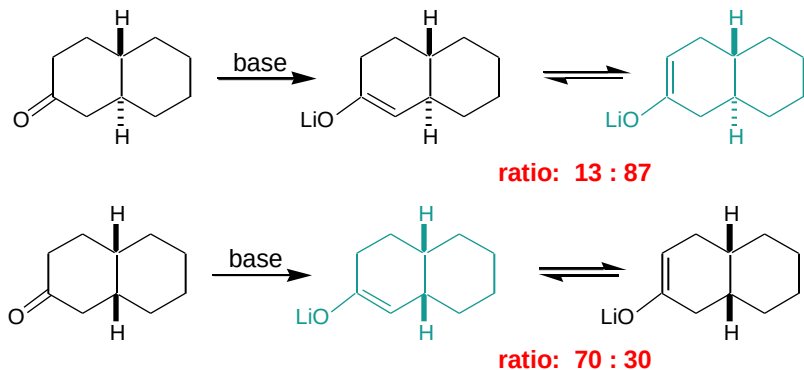
Predict
stereochemistry



Predict
stereochemistry

Observation:

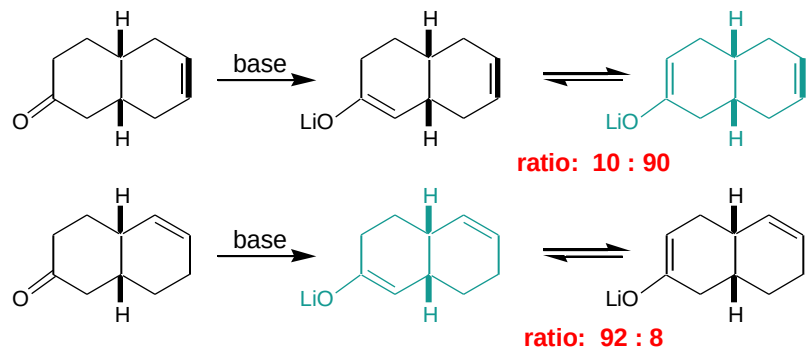
Relative enolate stability correlates to ring junction stereochemistry



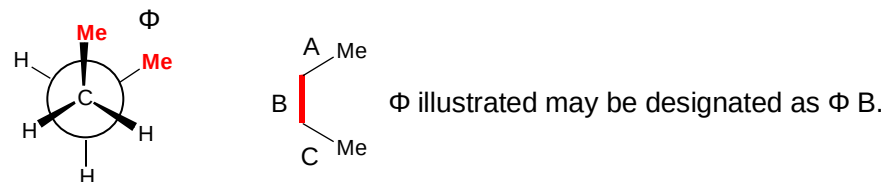
House, JOC 1965, 30, 1341

Observation:

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



How do we explain the experimental observations shown above?

Readings: Velluz et al, *Angew. Chemie, Int Ed.* 1965, 4, 181-270Let Φ be defined as the torsion or dihedral angle for butane

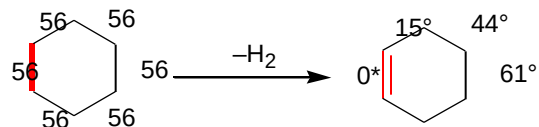
Let's now consider cyclohexane

	Perfect chair	real chair
	$\Phi = 60^\circ$	$\Phi = 56^\circ$
CCC	$109^\circ 28'$	111°

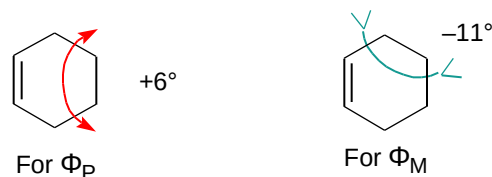
Given cyclohexane with an identified torsion angle Φ_R , if Φ_R either increases or decreases what effects in angle change are transmitted to Φ_O , Φ_M , and Φ_P ?

	$\Phi_R = 56^\circ$	$\Phi_R = 0^\circ$	$[\Delta]$
Φ_O	56	15	-41°
Φ_M	56	44	-11°
Φ_P	56	61	$+6^\circ$

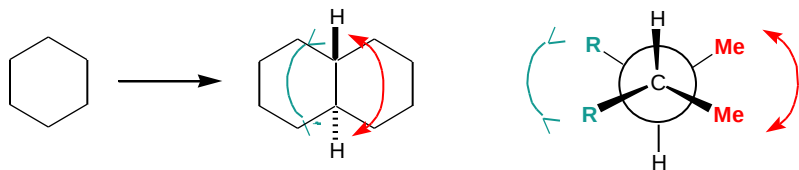
$[\Delta] = \Phi_R(0^\circ) - \Phi_R(56^\circ)$

Operation:

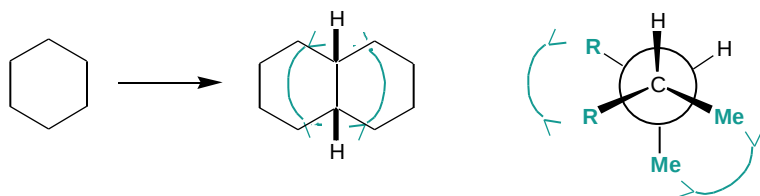
Hence, relative to cyclohexane, the following notation for torsion angle change may be denoted:



Operation:



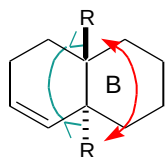
Operation:



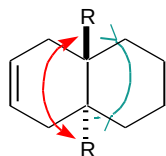
Simple Application: Reinforcing Torsional Effects



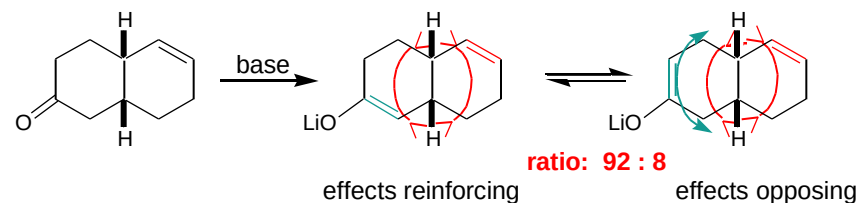
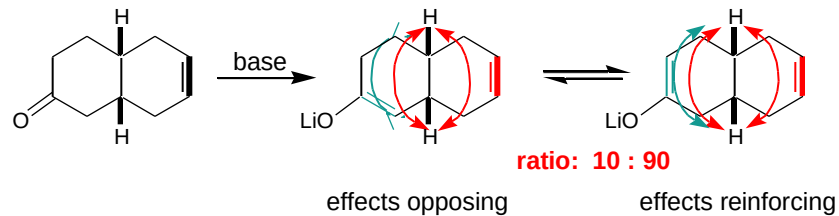
Which C=C bond isomer is more stable?



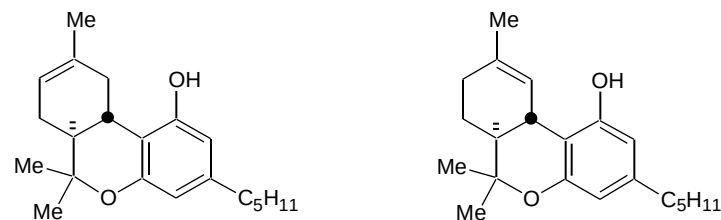
- 1) C=C will open up ring=B torsion angle
- 2) Ring B will resist increase in its ring fusion torsion angle
- 3) Therefore torsion effects are opposed



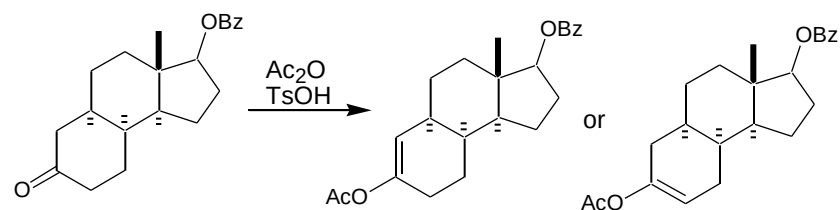
- 1) C=C will close down ring=B torsion angle
- 2) Ring B will accommodate decrease in its ring fusion torsion angle
- 3) Therefore torsion effects are reinforcing



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 & Description 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

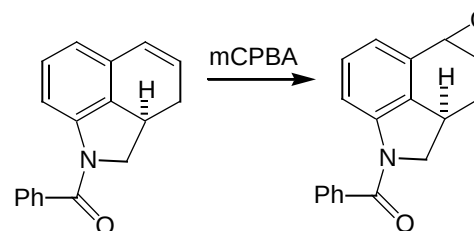
■ Other Reading Material

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

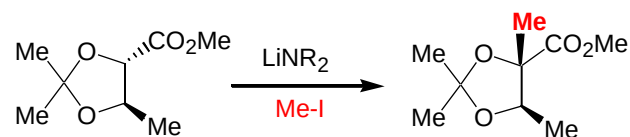
■ Problems of the Day: (To be discussed)

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



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

Rationalize the stereochemical outcome of this reaction.



diastereoselection is 8:1.

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

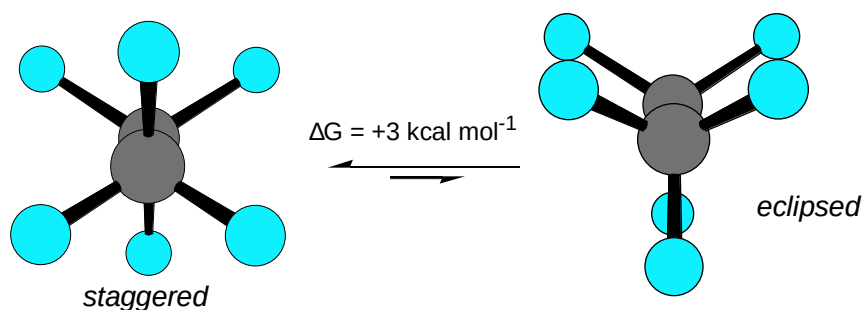
Torsional Effects

Torsional Strain: the resistance to rotation about a bond

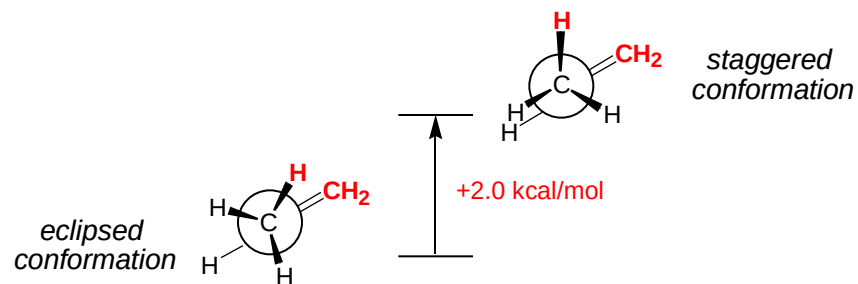
Torsional energy: the energy required to obtain rotation about a bond

Torsional Angle: also known as dihedral angle

Torsional steering: Stereoselectivity originating from transition state torsional energy considerations



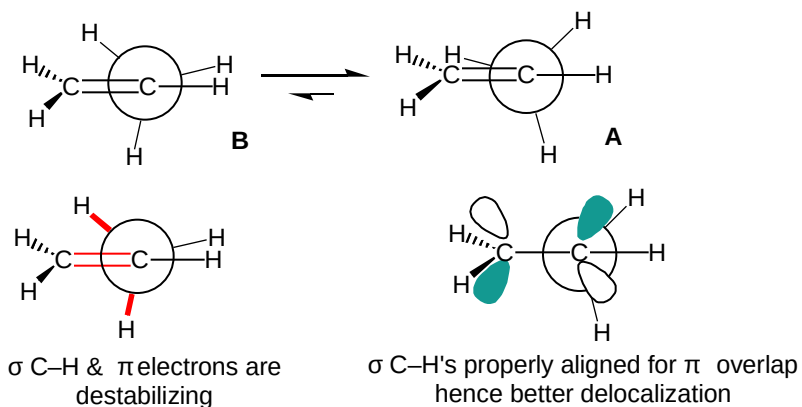
Torsional Strain (Pitzer Strain): Ethane



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

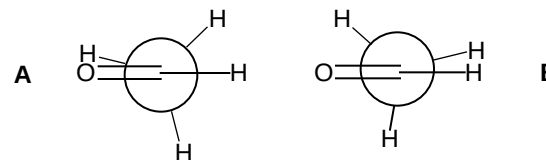
See Lecture 5 for previous discussion

Relevant Orbital Interactions:



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

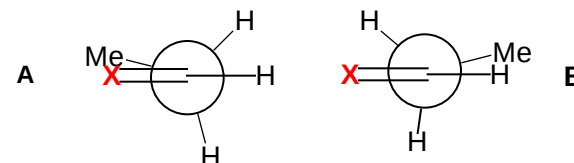
Conformational Preferences: Acetaldehyde



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

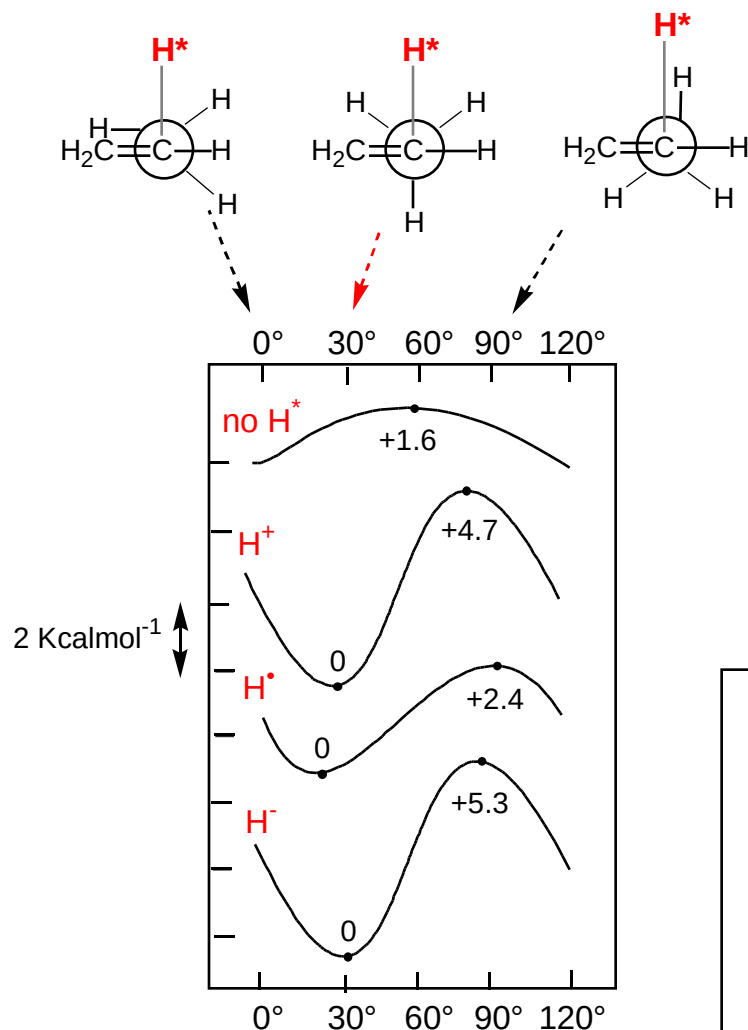
Houk, *JACS* **1983**, *105*, 5980-5988.

Conformational Preferences 1-Butene (X = CH₂); Propanal (X = O)



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

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

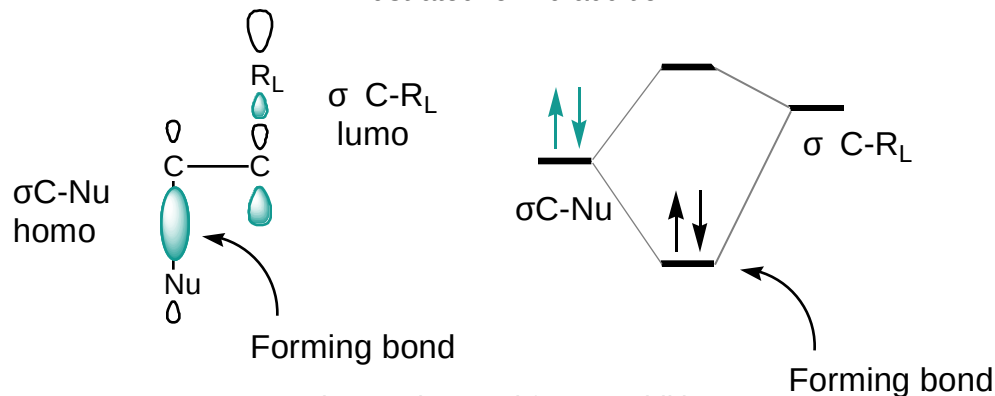


Houk, JACS **1981**, 103, 2438

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

Transition states

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

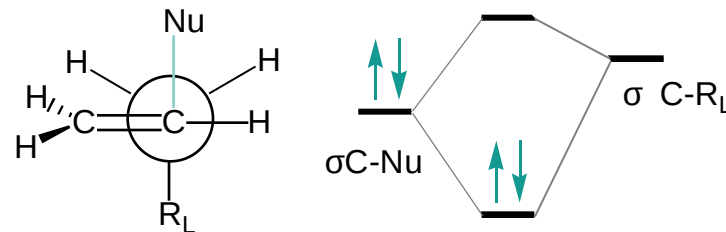


Same trends are observed for H^+ addition

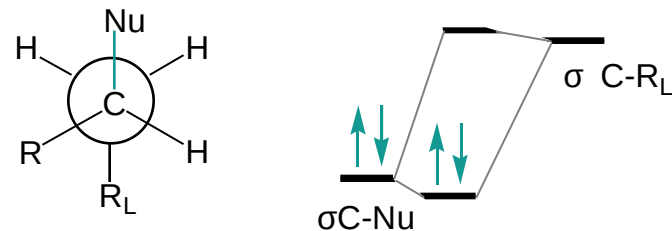
Houk, Science **1981**, 231, 1108-1117

"The Theory and Modeling of Stereoselective Organic Reactions"

Transition state

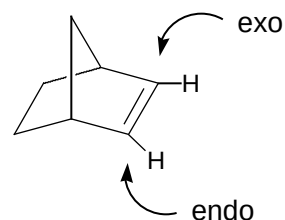


Ground state



■ 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

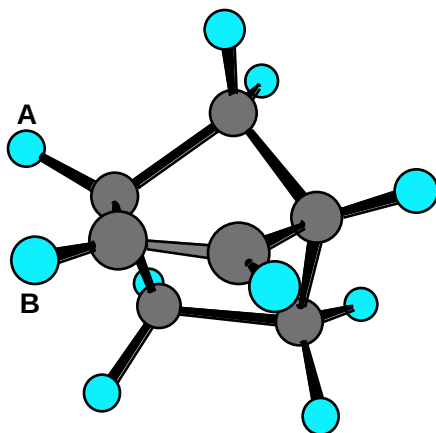
The Controversy over origin of high exoselectivities

Steric effects

Least nuclear motion

Orbital distortion

Schleyer: torsional steering

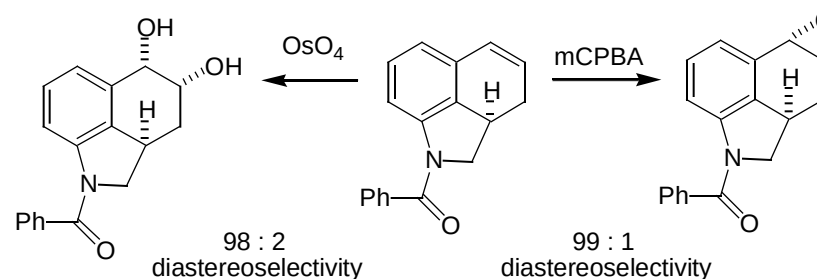


Schleyer, P. R. *J. Amer. Chem. Soc.* **1967**, 89, 701.

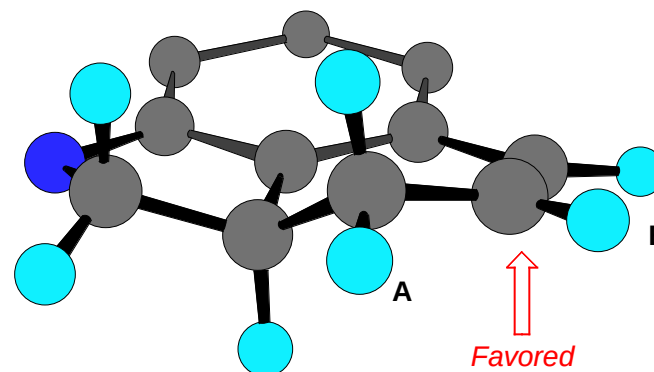
Addition from exo face avoids eclipsing A & B hydrogens
(better hyperconjugative stabilization of transition state)

■ Olefin Addition Reactions: Case two

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



Nitrogen protecting group does not affect selectivities

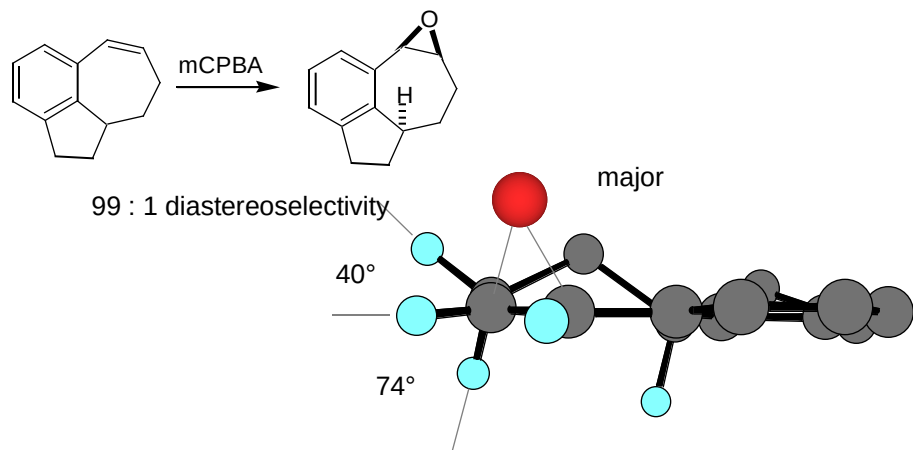
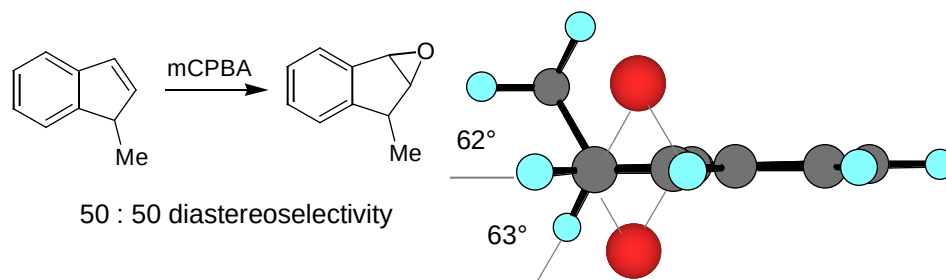
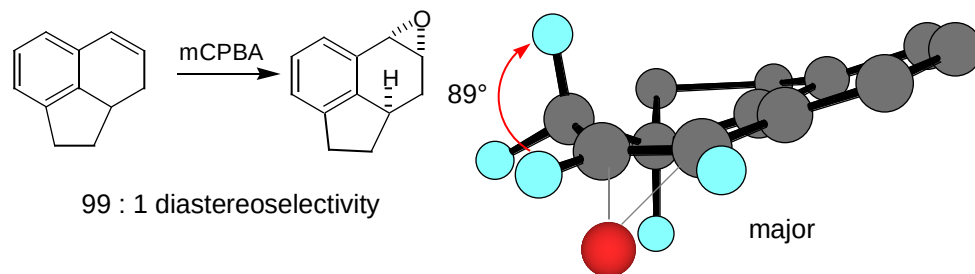


Martinelli, et.al. *Tett. Lett.* **1989**, 30, 3935

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.....

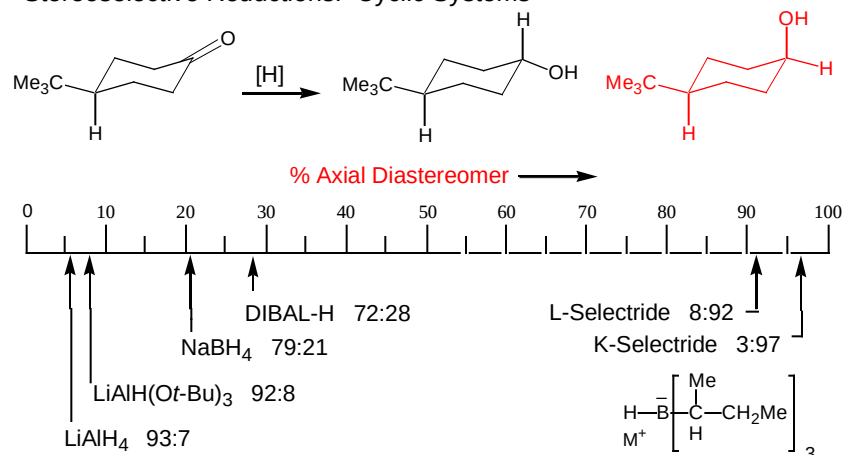
Martinelli: Torsional steering important in selectivity



**Authors propose that diastereoselection controlled by
TS torsional effects**

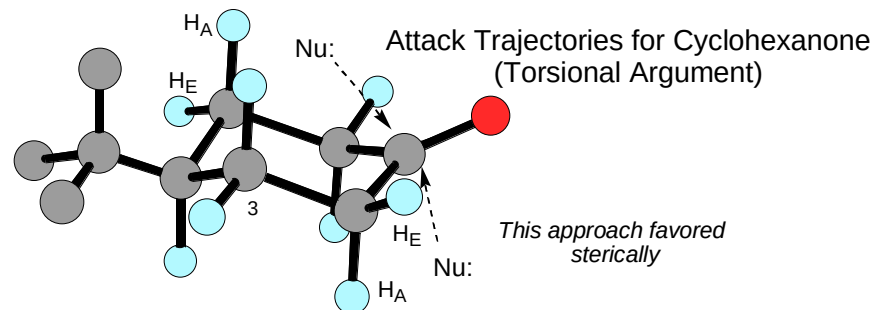
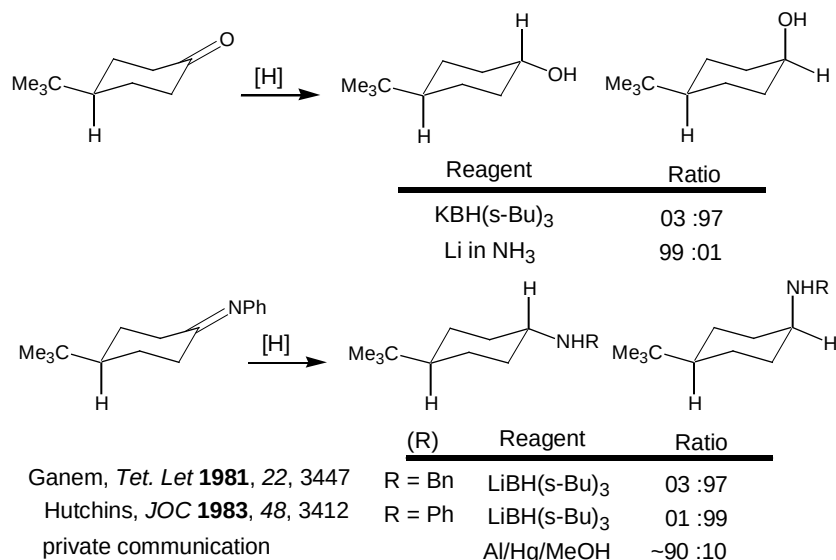
Martinelli & Houk, *J. Org. Chem.* **1994**, 59, 2204.

Stereoselective Reductions: Cyclic Systems

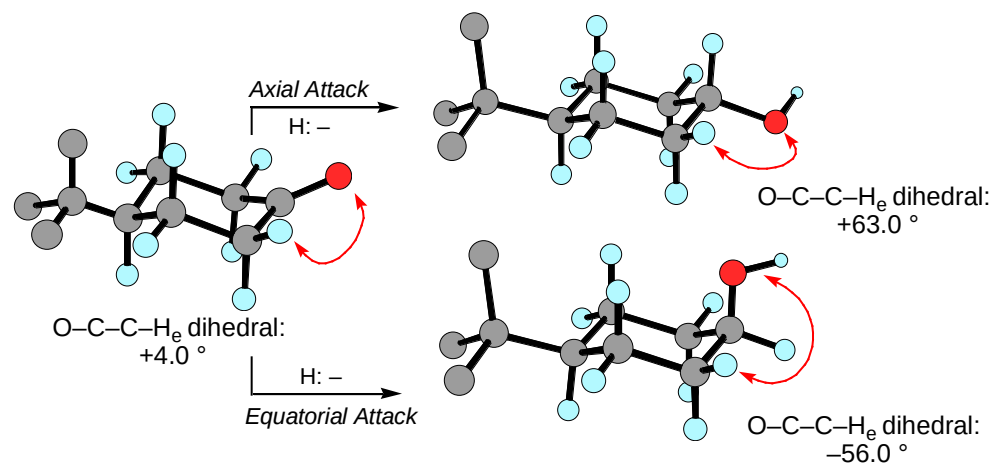


Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

The most stereoselective Reductions



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 hindrance 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.

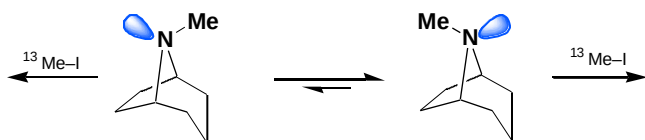
Prediction

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?

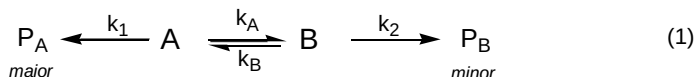
Consider the following example:



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.



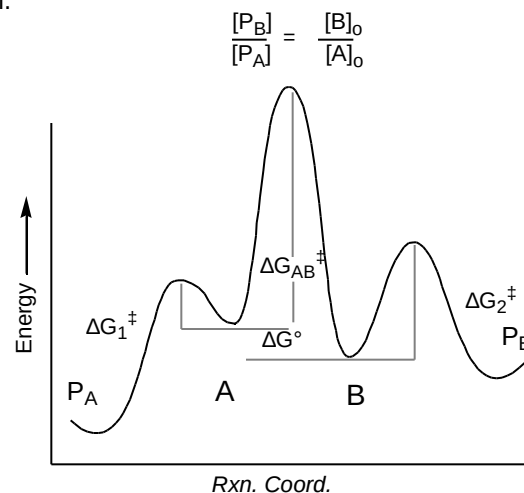
We'll consider two limiting cases:

- (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

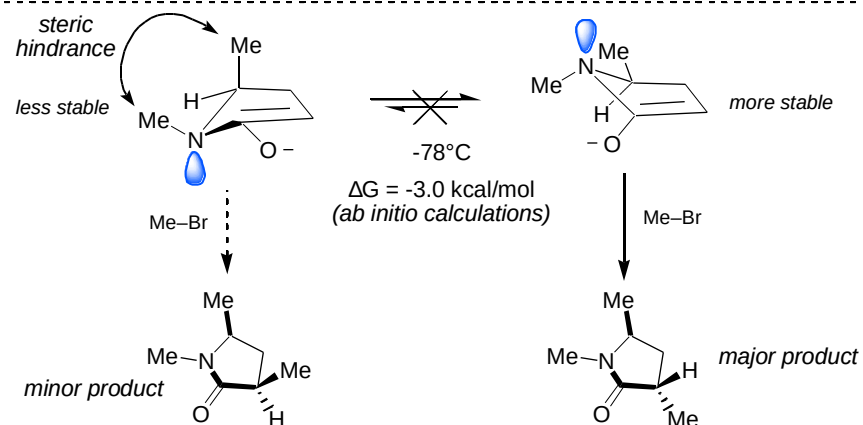
If the rates of conformational interconversion and reaction are comparable, the reactants are not in equilibrium during the course of the reaction and complex mathematical solutions are necessary. See Seeman, *Chem. Rev.* **1983**, 83 - 144 for analytical solutions.

Case 1: "Kinetic Quench"

k₁, k₂ >> 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.



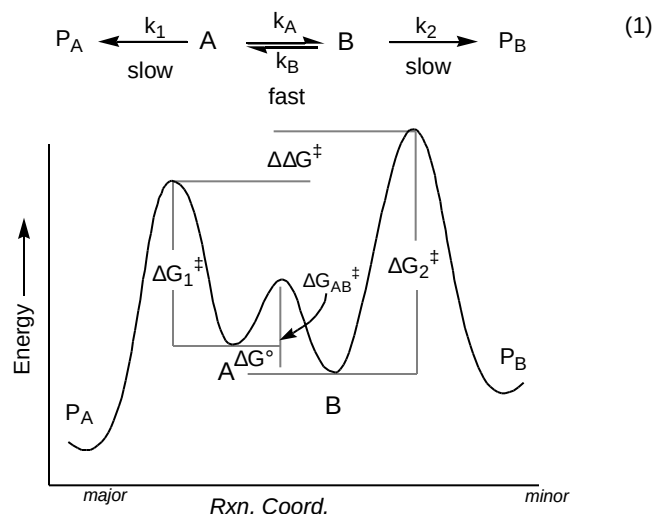
In this case, the product distribution depends solely on the initial ratio of the two conformers.



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

Case 2: Curtin-Hammett Conditions

$k_1, k_2 \ll k_A, k_B$: 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.

**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:

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

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

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

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 $\Delta G^\circ = -RT \ln K_{eq}$ or $K_{eq} = e^{-\Delta G^\circ/RT}$, $k_1 = e^{-\Delta G_1^\ddagger/RT}$, and $k_2 = e^{-\Delta G_2^\ddagger/RT}$. Substituting this into the above equation:

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

Combining terms:

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

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

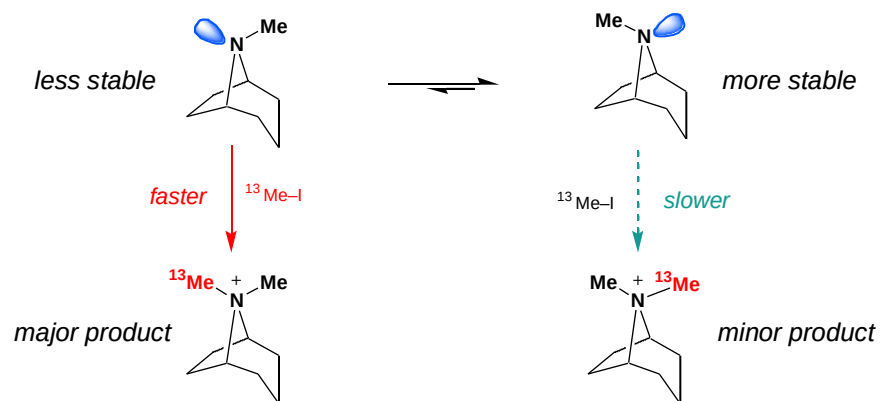
Curtin - Hammett Principle: The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.

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!

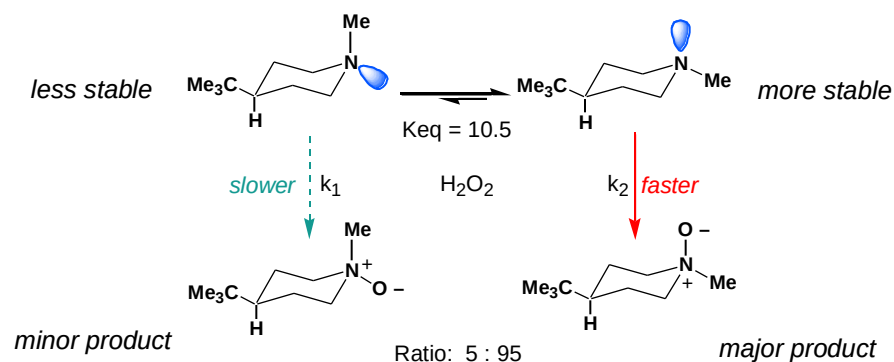
Tropane alkylation is a well-known example.



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

JOC 1974 319

Oxidation of piperidines:

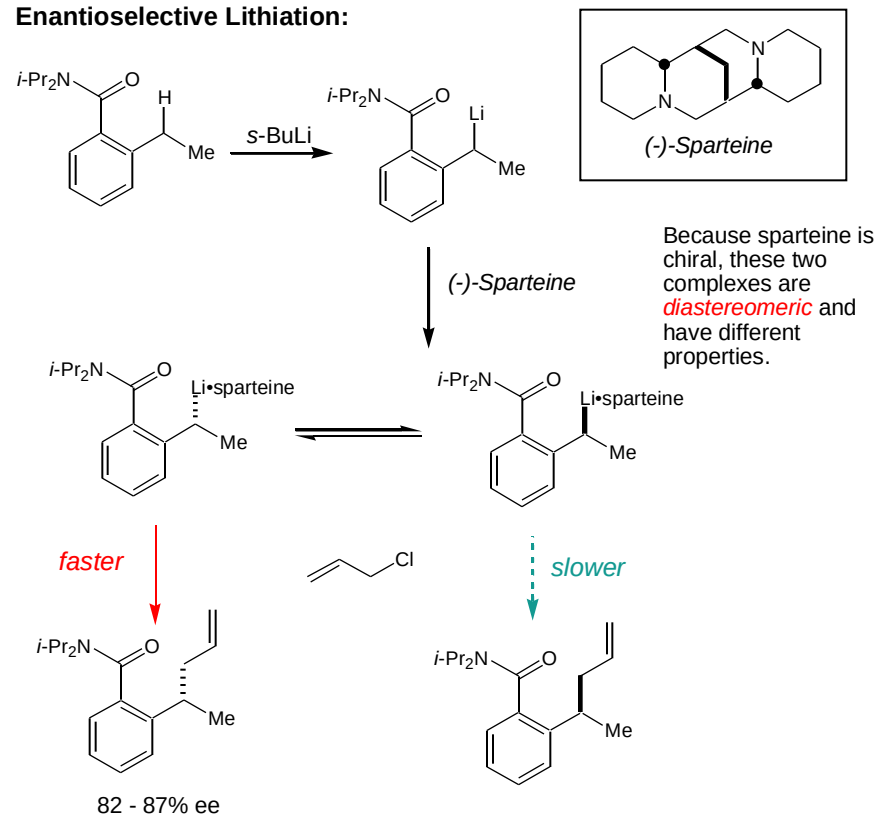


When the equilibrium constant is known, the Curtin-Hammett derivation can be used to calculate the relative rates of reaction of the two conformers. Substituting the above data into $[P_B]/[P_A] = k_2K/k_1$, the ratio $k_2/k_1 \sim 2$.

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

Tet. 1972 573
Tet. 1977 915

Enantioselective Lithiation:



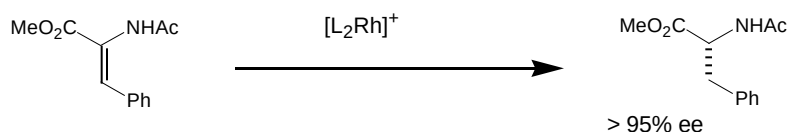
Enantioselectivities are the same, regardless of whether or not the starting material is chiral, even at low temperatures. Further, reaction in the absence of $(-)\text{-sparteine}$ results in racemic product.

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.

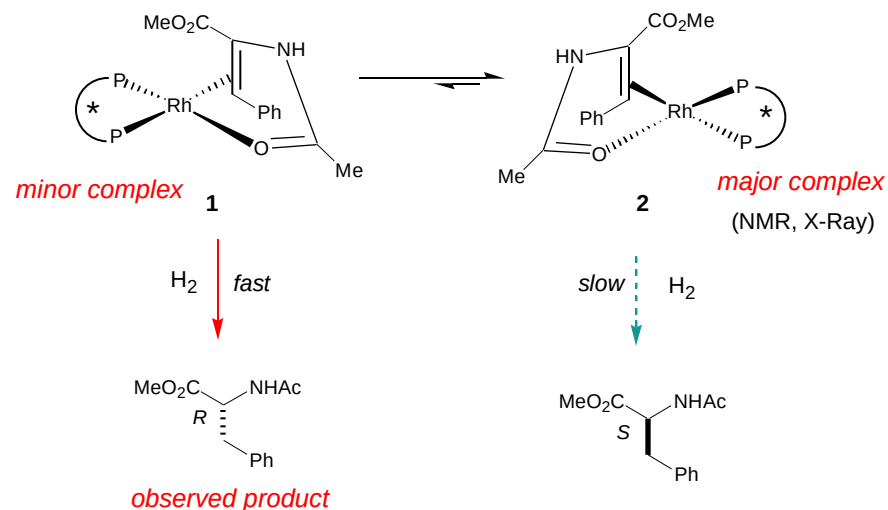
Beak, Acc. Chem. Res, 1996, 552

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)

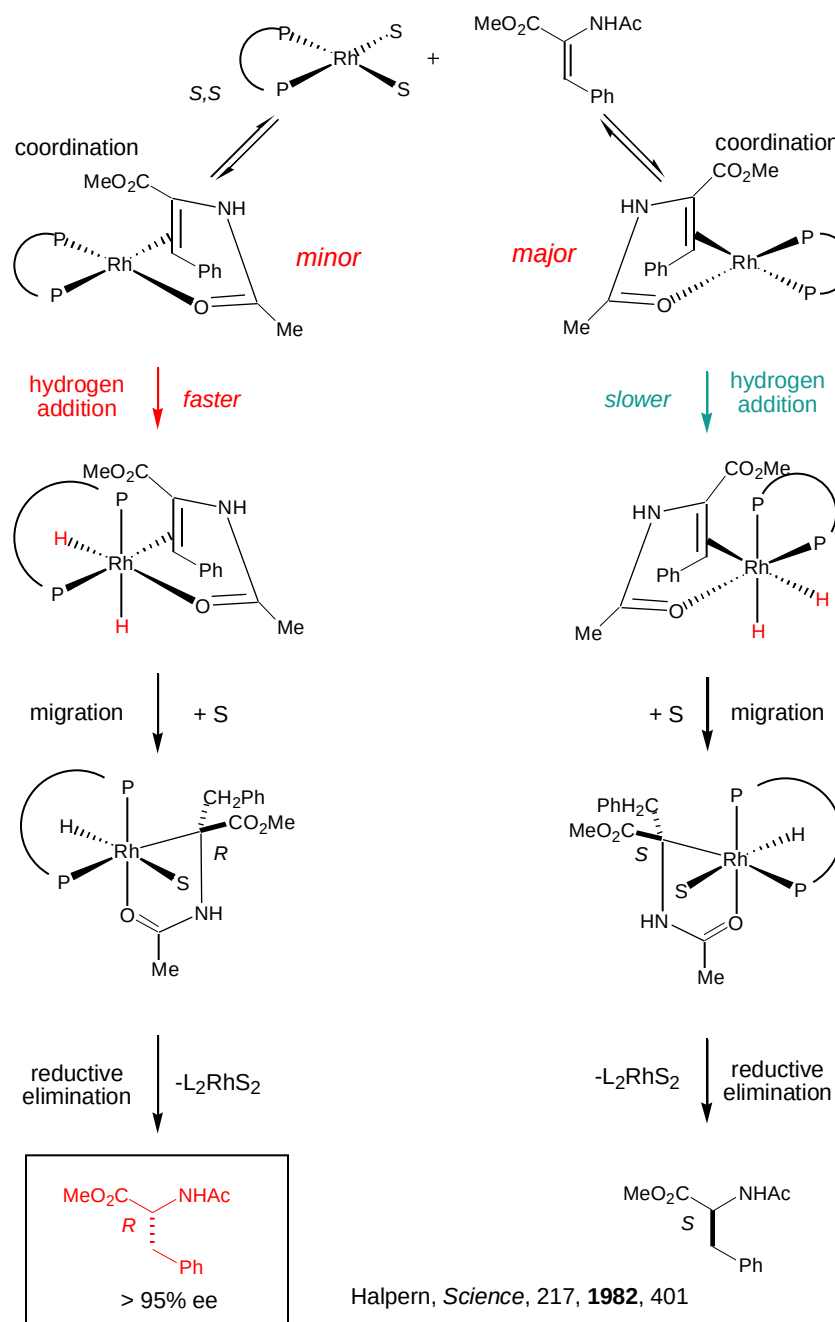
When a chiral ligand is used, there are two diastereomeric complexes which may be formed:



Observations:

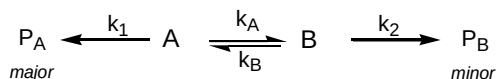
- Complex 2 is the only diastereomer observed for the catalyst-substrate complex (1H NMR, X-Ray crystallography) in the absence of hydrogen
- The enantioselectivity is strongly dependant on the pressure of H_2 , and degrades rapidly at higher hydrogen pressures
- The observed enantiomer is exclusively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

These observations may be explained using the Curtin - Hammett Principle

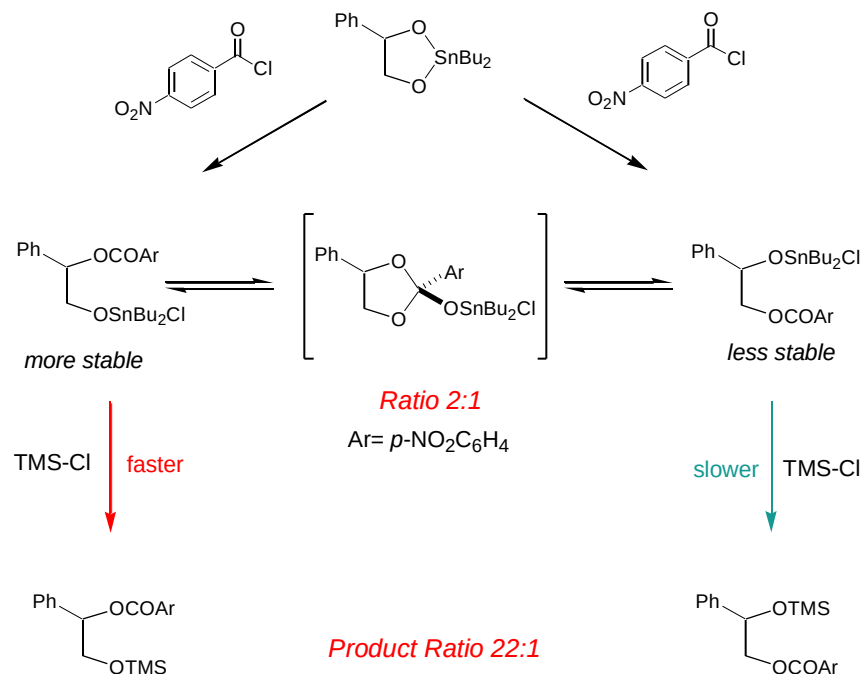


Halpern, Science, 217, 1982, 401

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



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 referred 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 Multiple Bonds"

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

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

Matthew D. Shair

Friday,
October 4, 2002

■ Other Reading Material

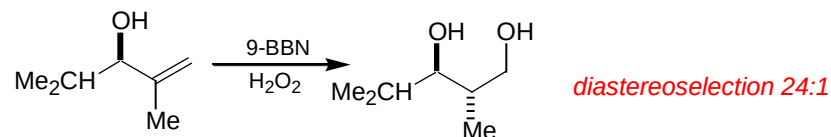
Smith, K. and A. Pelter (1991). Hydroboration of C=C and Alkynes. Comprehensive Organic Synthesis. B. M. Trost and I. Fleming. Oxford, Pergamon Press. 8: 703.

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.

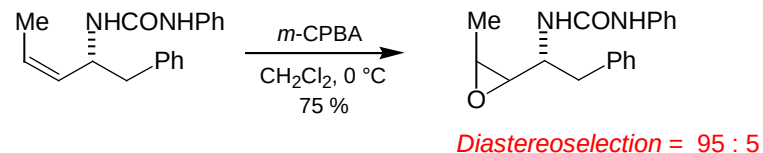
■ Problems of the Day: (To be discussed)

Rationalize the stereochemical outcome of this reaction



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

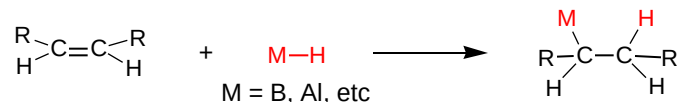
Predict the stereochemical outcome of this reaction



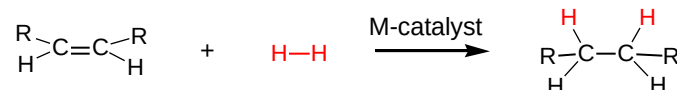
Roush, *J. Org. Chem.* **1987**, 52, 5127.

Representative Cis-Addition Processes

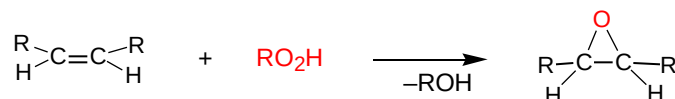
■ Hydrometallation



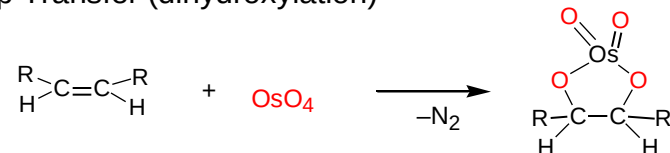
■ Hydrogenation



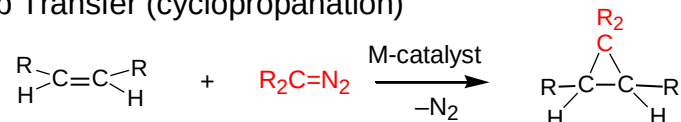
■ Group Transfer (epoxidation)



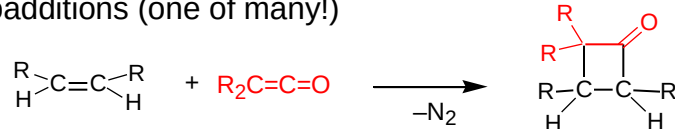
■ Group Transfer (dihydroxylation)



■ Group Transfer (cyclopropanation)



■ Cycloadditions (one of many!)



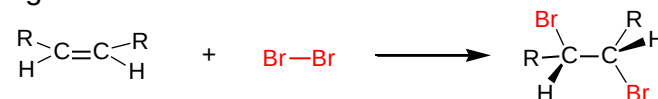
Attributes:

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

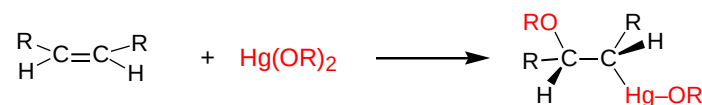
Intermediates *may* be involved in some of the indicated reactions

Representative Trans-Addition Processes

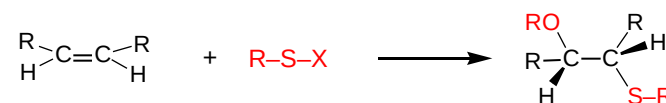
■ Halogenation



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



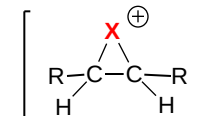
■ Oxy-sulfenation (M = S(II), Se(II))



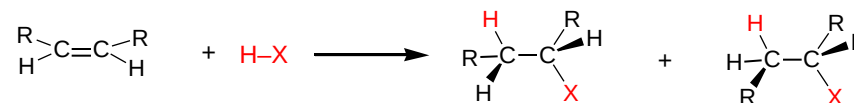
Attributes:

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

Olefin substitution may disrupt bridging



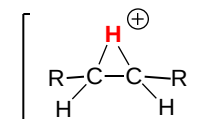
■ Addition of hydrogen halides



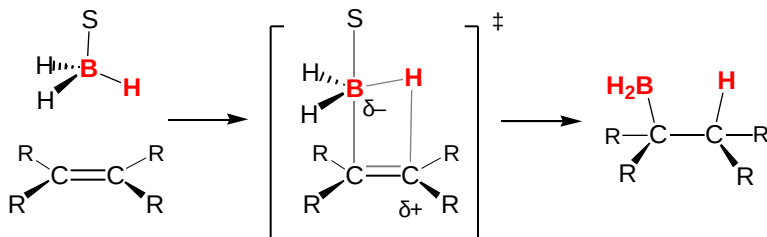
Attributes:

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

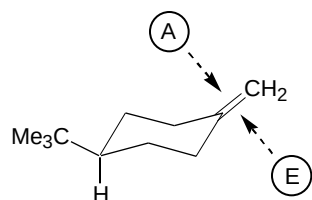
Olefin substitution, reaction conditions as well as halide type may disrupt bridging



■ The basic process

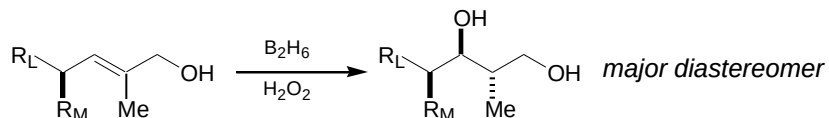


■ Response to steric effects: Here is a good calibration system:



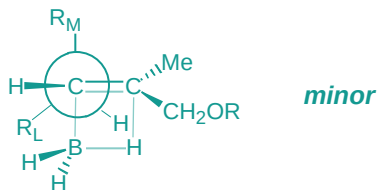
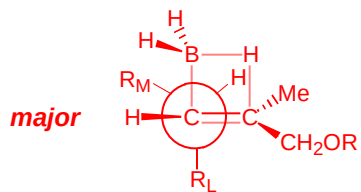
Oxidant	Ratio, A:E	Reference
MCPBA	69:31	JOC, 1967 , 32, 1363
BH ₃ , H ₂ O ₂	34:66	JOC, 1970 , 35, 2654

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



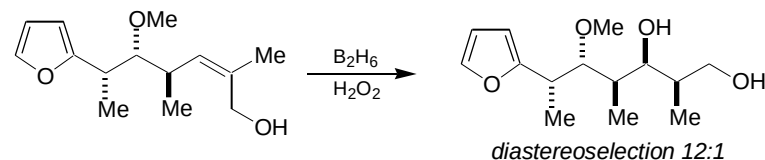
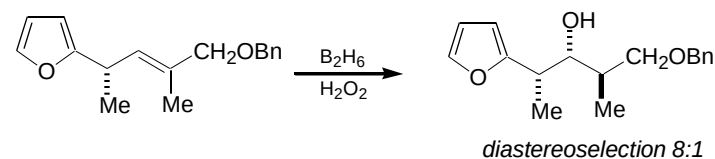
control elements

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

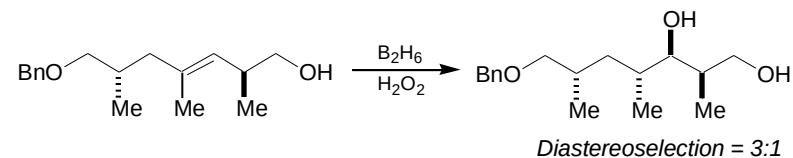


Houk, "Theoretical Studies of Stereoselective Hydroboration Reactions"
Tetrahedron **1984**, 40, 2257 (**Handout**)

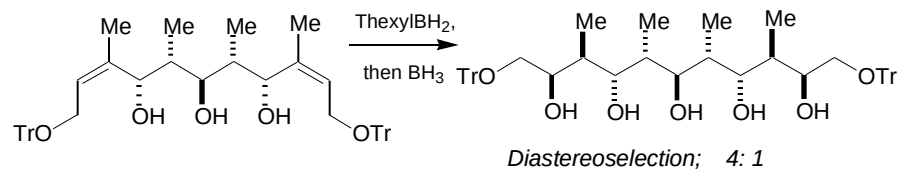
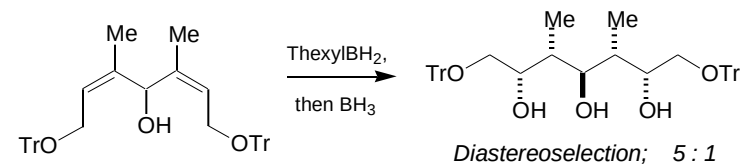
Hydroborations dominated by A(1,3) Strain



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

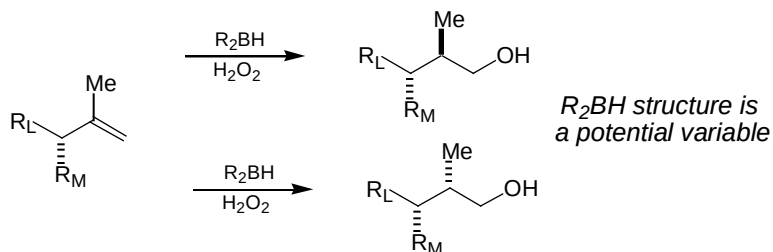


C. H. Heathcock et. al. *Tetrahedron Lett* **1984** 25 243.



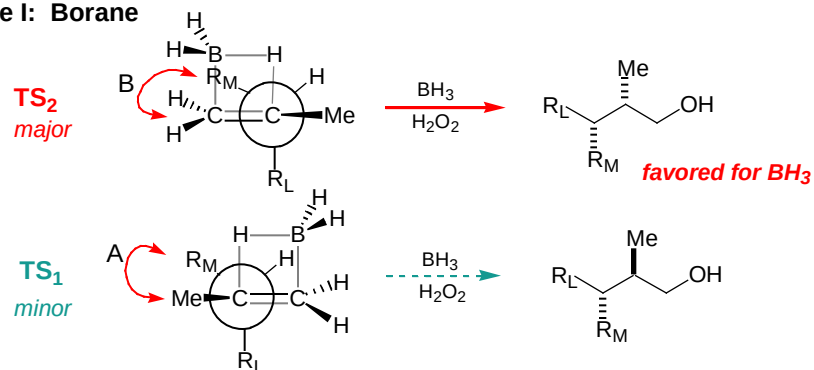
Still, W.C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, 105, 2487.

What about the following substitution pattern?

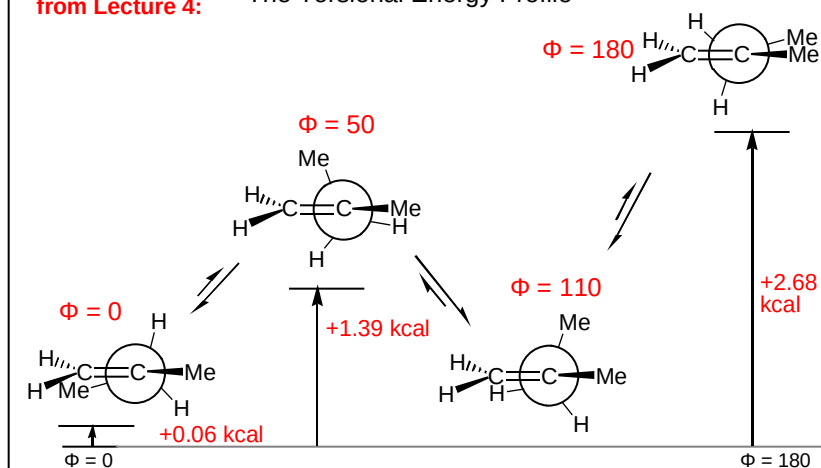


Houk's rules: Orient R_L anti-periplanar to incoming reagents to avoid TS eclipsing:

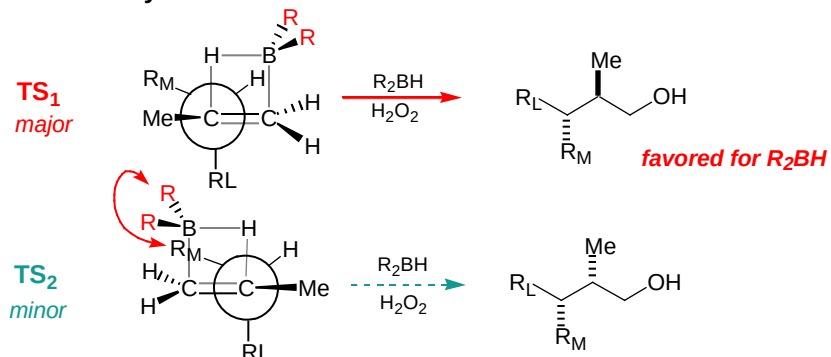
Case I: Borane



from Lecture 4: The Torsional Energy Profile



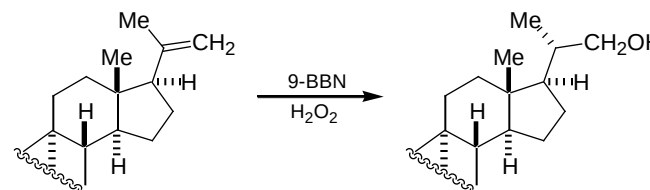
Case II: Dialkylboranes



Midland finds that TS_1 favored for R_2BH reagents, but $TS_1 \sim TS_2$ for BH_3

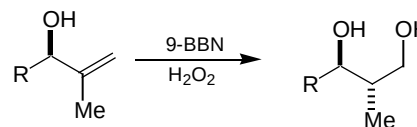
Others have found that TS_1 favored over TS_2 for BH_3

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

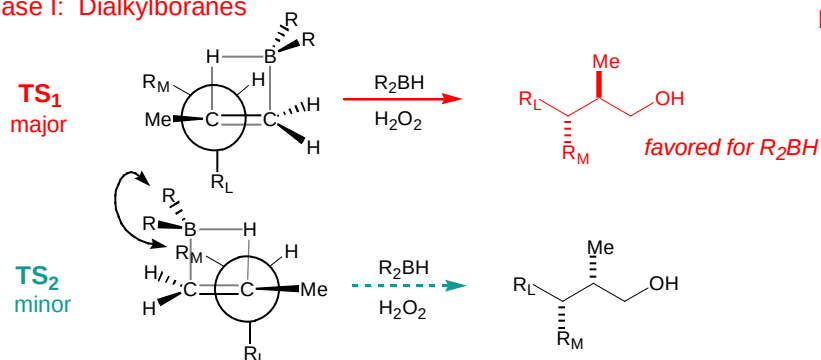


$R = n\text{-Bu}$: diastereoselection 11:1
 $R = CHMe_2$: diastereoselection 24:1

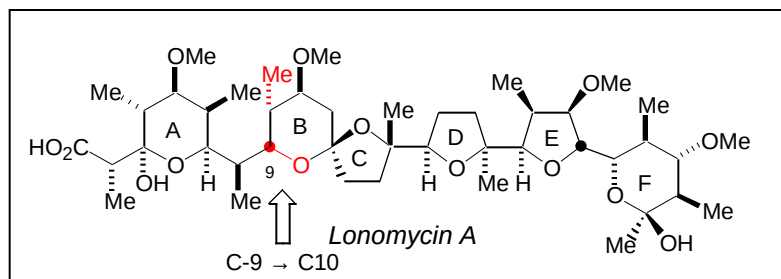
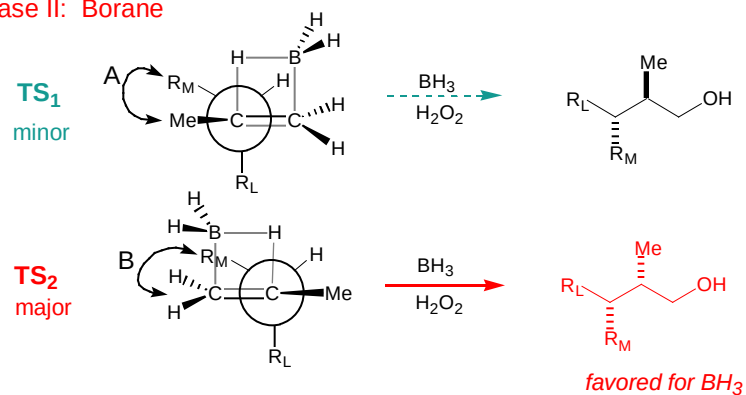
Model is consistent if you presume $HO = R_M$; $R = R_L$

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

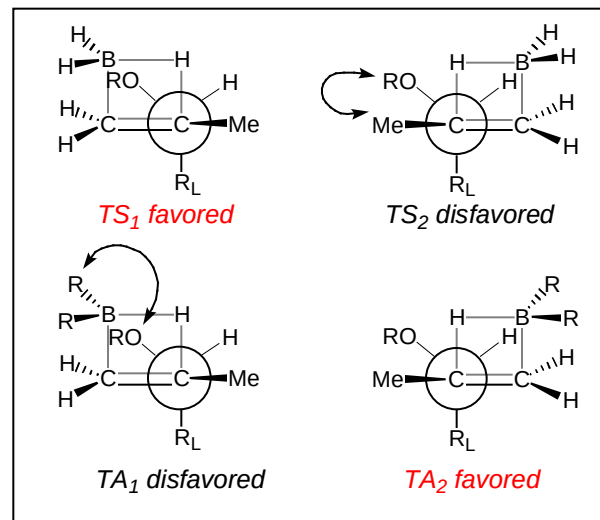
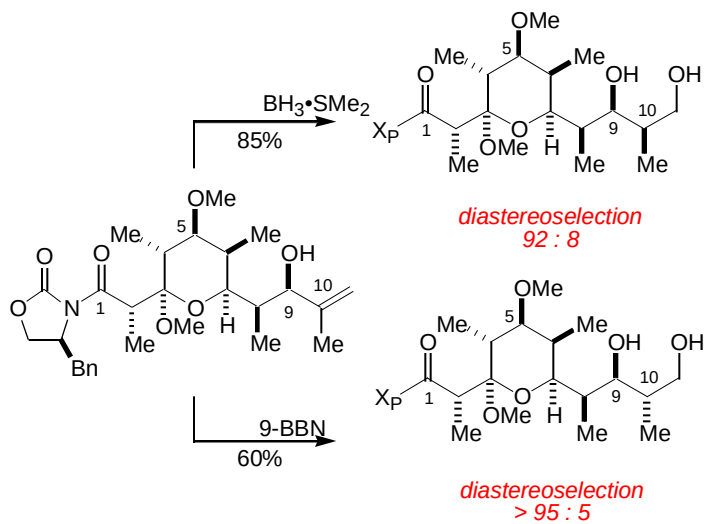
■ Case I: Dialkylboranes



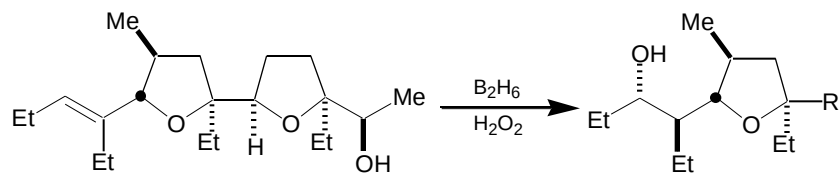
■ Case II: Borane



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

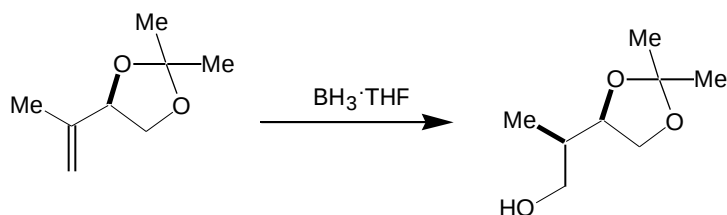


For each of the examples shown below, attempt to rationalize the stereochemical outcome of the reaction in terms of one of the models presented in the discussion.



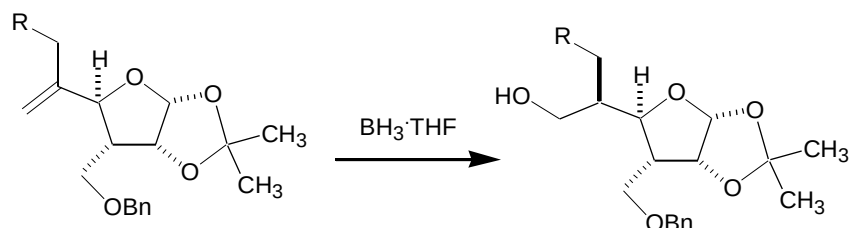
Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **1978**, *100*, 2933.

"one isomer"



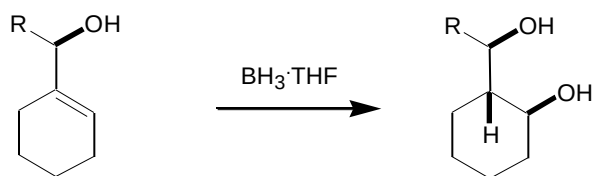
Mori, K.
Tetrahedron **1976**, *32*, 1979

diastereoselection 12:1



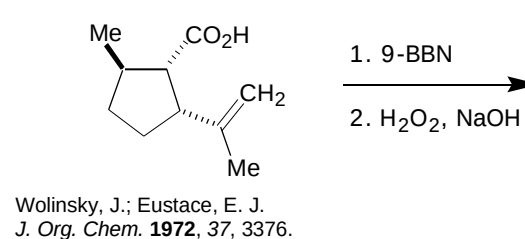
Oikawa et. al.
Tetrahedron Lett. **1983**, *19*, 1987.

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



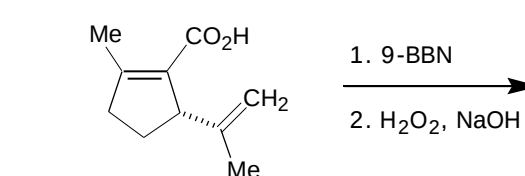
Birtwistle et. al.
Tetrahedron Lett. **1986**, *25*, 243.

$R = CH_3$; Diastereoselection = 6.7:1
 $R = isopropyl$ "One Compound"



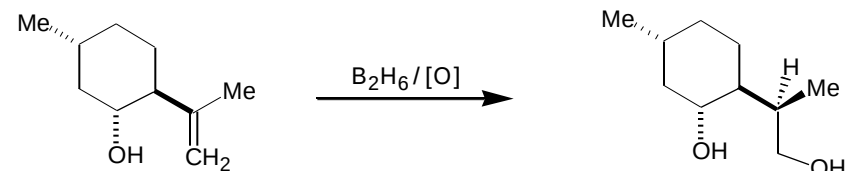
Wolinsky, J.; Eustace, E. J.
J. Org. Chem. **1972**, *37*, 3376.

Diastereoselection = 7:1

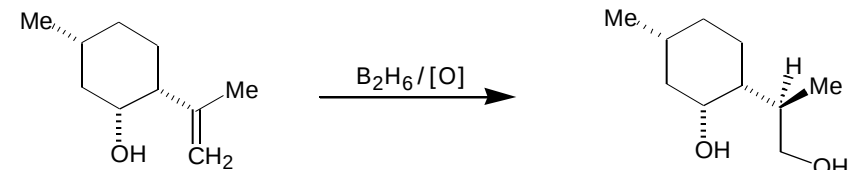


Wolinsky, J.; Nelson, D.
Tetrahedron. **1968**, *25*, 3767.

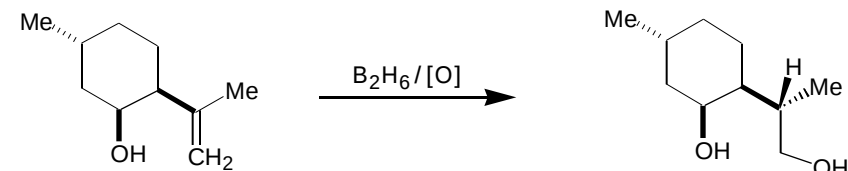
Diastereoselection = 10:1



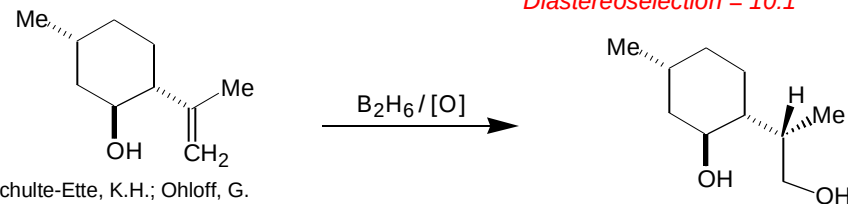
Diastereoselection = 19:1



Diastereoselection = 32:1

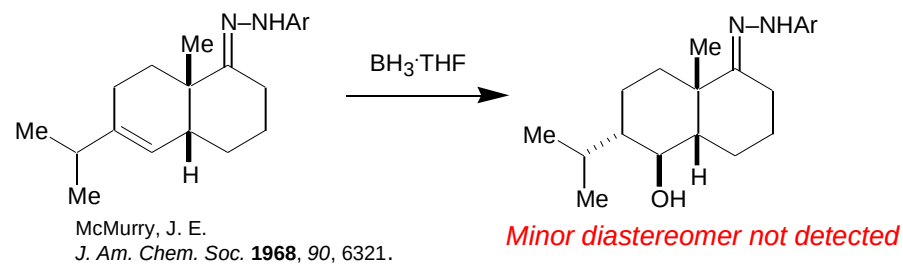
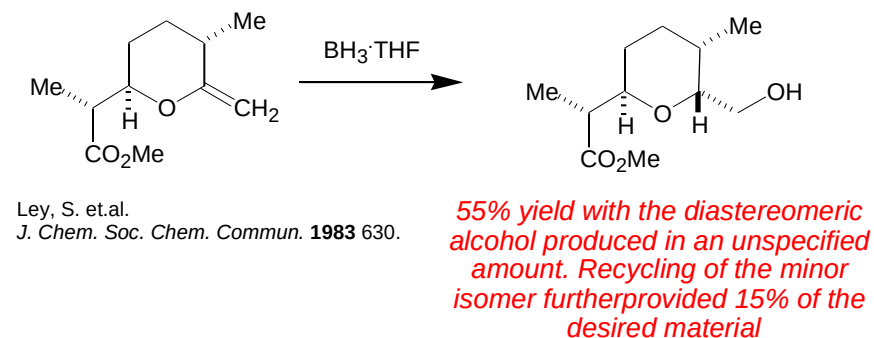
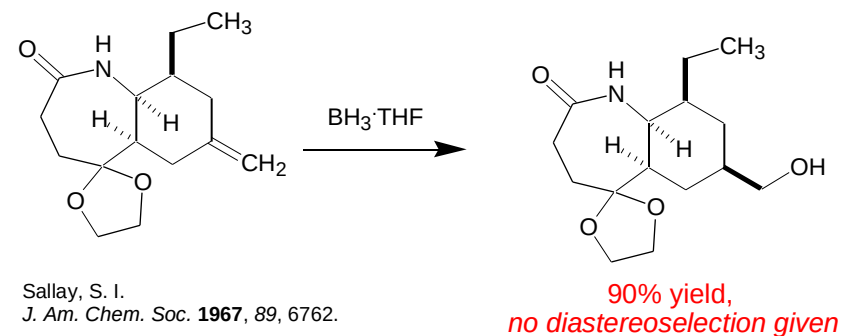
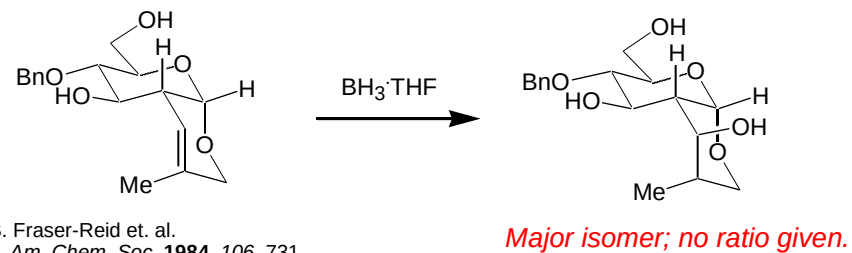
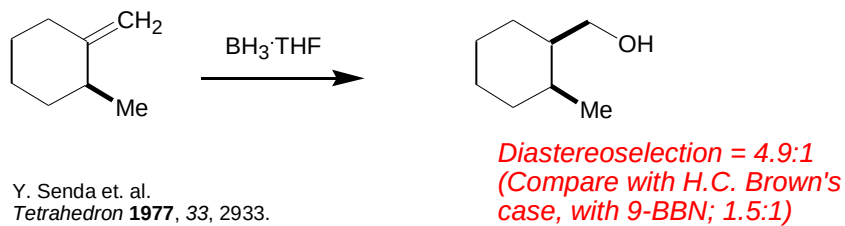
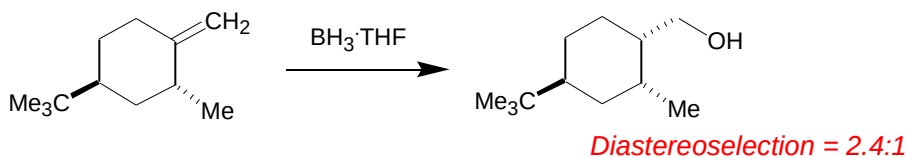
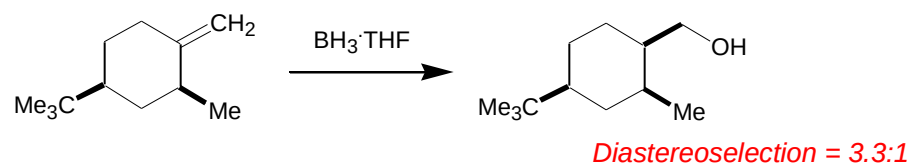
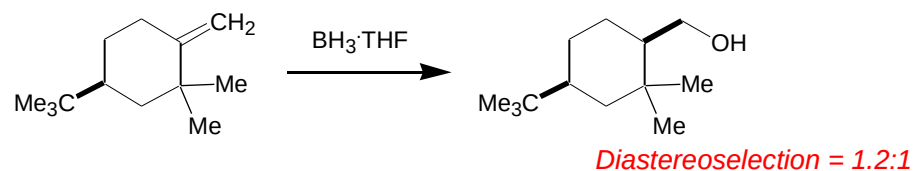
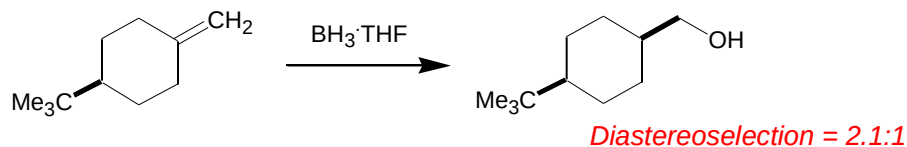


Diastereoselection = 10:1



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

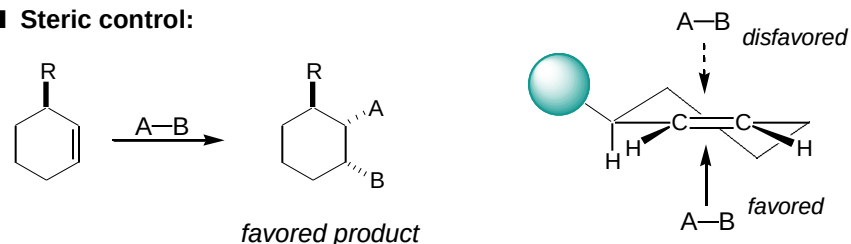
Diastereoselection = 4.6:1



Stereochemical Control Elements for all reactions

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

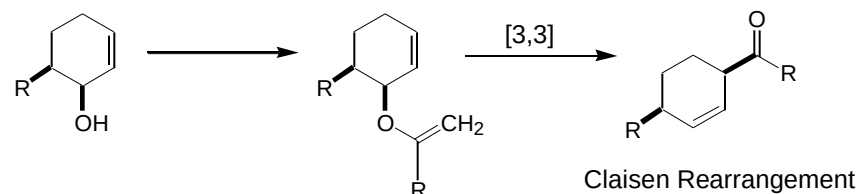
■ Steric control:



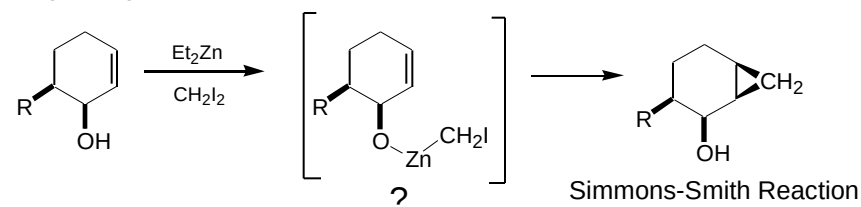
Nonbonding Interactions disfavor the syn diastereoface

Heteroatom-directed Reactions

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



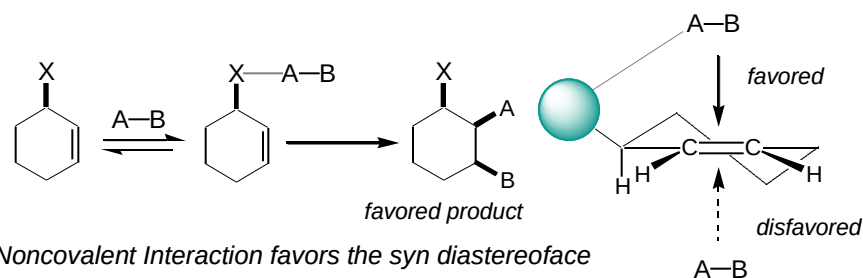
via Reagent Ligation



Directed Reactions

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

■ Associative Substrate-Reagent Interactions

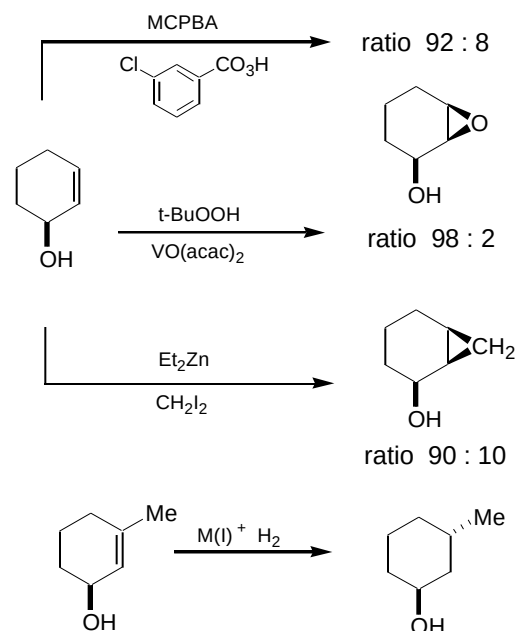


Noncovalent Interaction favors the syn diastereoface

Agenda

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

Hydroxyl-directed Reactions



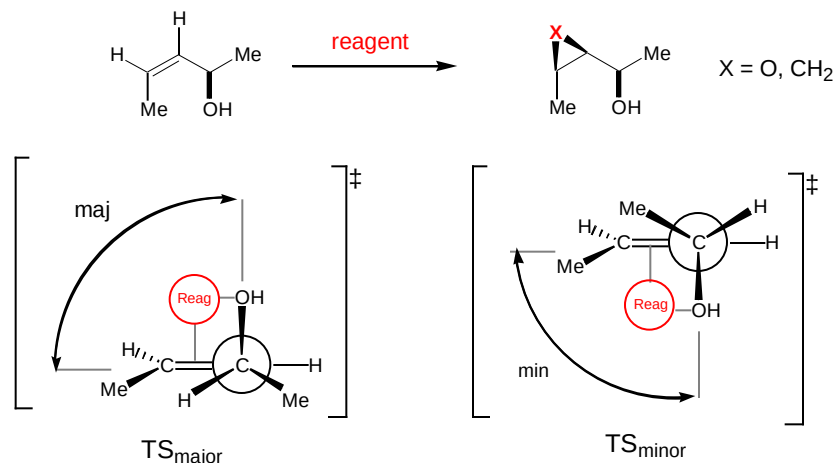
Henbest
J. Chem. Soc. 1958, (1957)

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 reactants

Reagent	Selectivity	Φ Estimate
t-BuO ₂ H, V ⁺⁵	71 : 29	~ 50 °
RCO ₃ H	95 : 5	~ 120 °
CH ₂ I ₂ , Zn-Cu	> 99 : 1	?

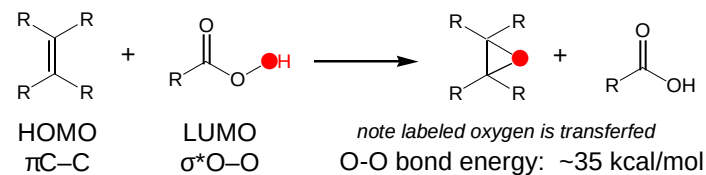
The transition state bite angles for the above reactions are either not known or have been only crudely estimated.

The "best guesses" are provided.

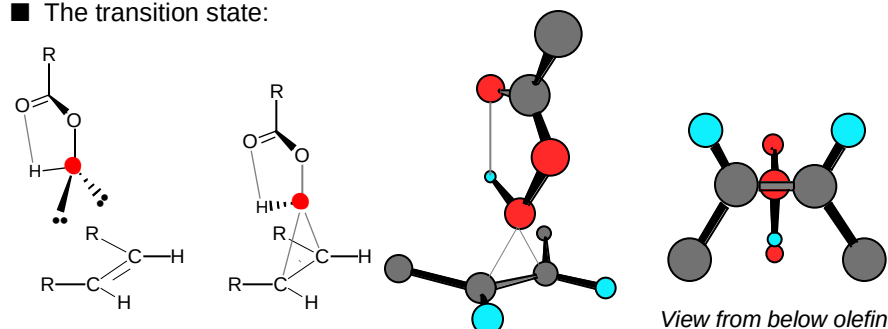
Peracid Epoxidation

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

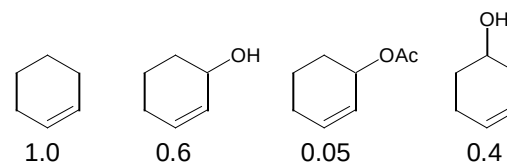
General Reaction:



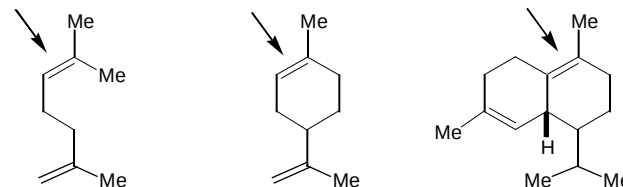
The transition state:



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

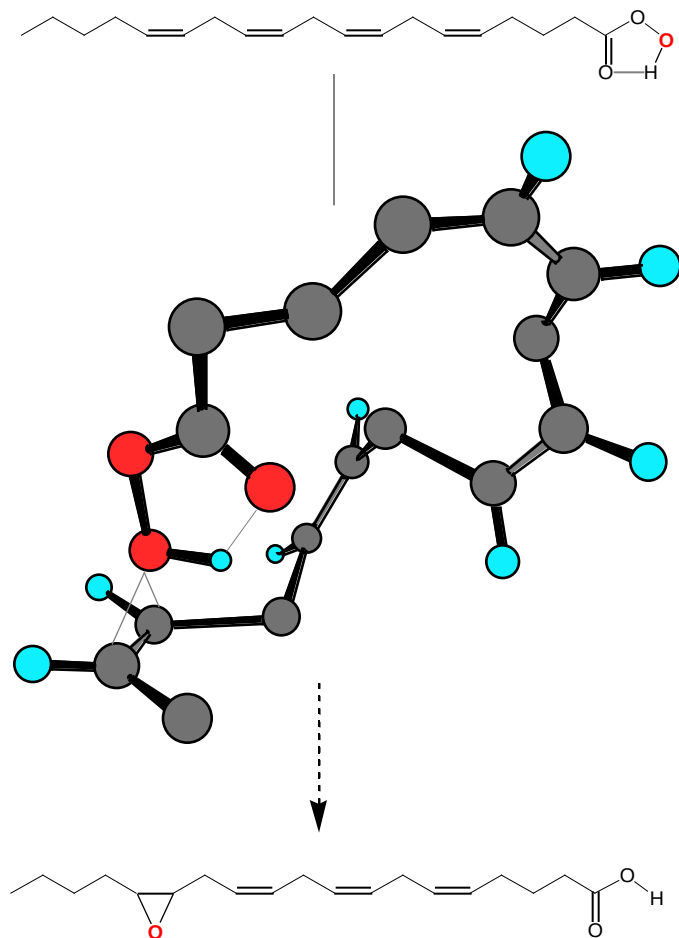


The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



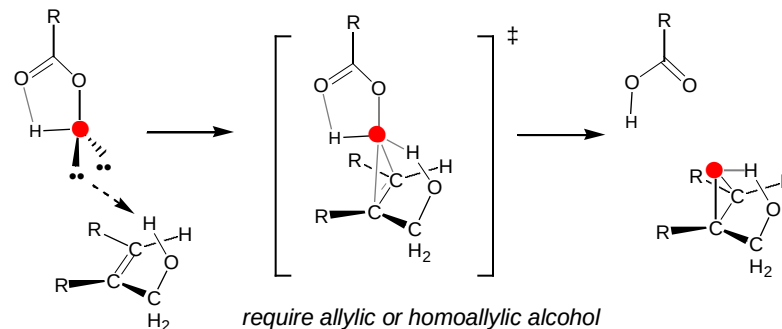
Stereoelectronic Implications of intramolecular Peracid Epoxidation

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

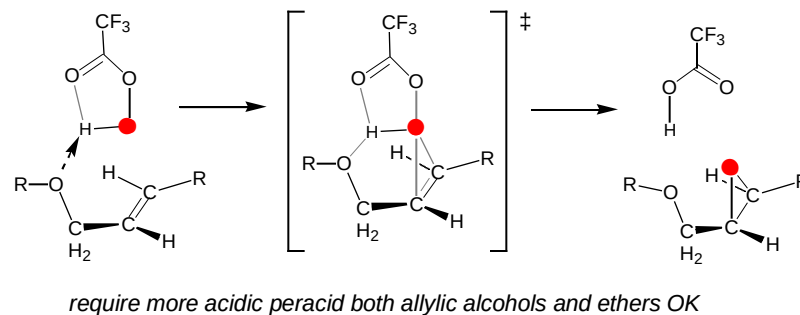


The Directed Peracid Epoxidation

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



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



	Syn : Anti (<i>m</i> -CPBA)		Syn : Anti (CF ₃ CO ₃ H)			Syn : Anti (<i>m</i> -CPBA)		Syn : Anti (CF ₃ CO ₃ H)	
	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

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)

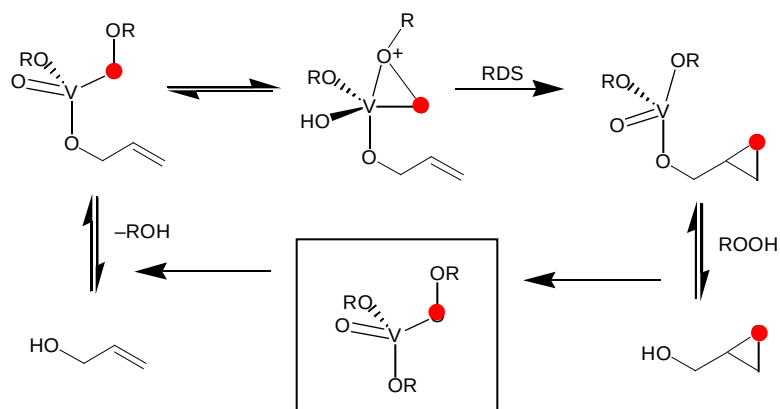
Epoxidation of Cyclic Homoallylic Alcohols

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.

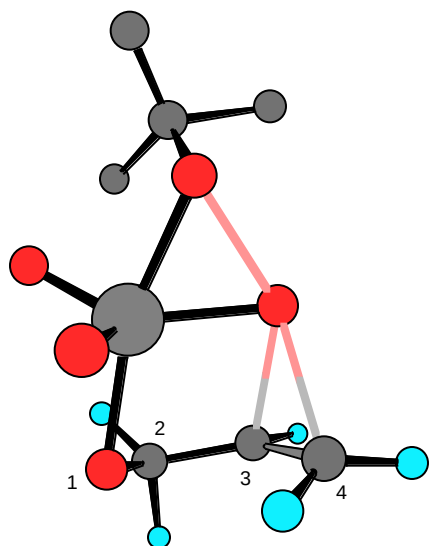
(Table 14, p1318, from the Evans, Hoveyda, Fu review article)

The Sharpless Epoxidation

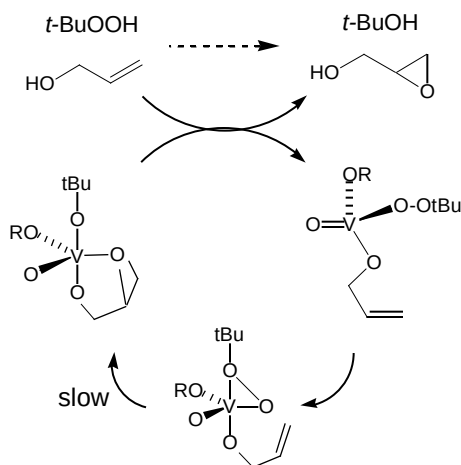


Aldrichimica Acta, 12, 63 (1979)

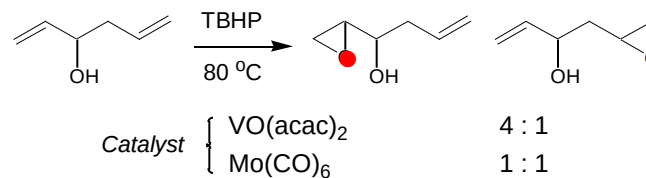
$O-C_2-C_3-C_4 = 41^\circ$
The Sharpless estimate: $\sim 50^\circ$



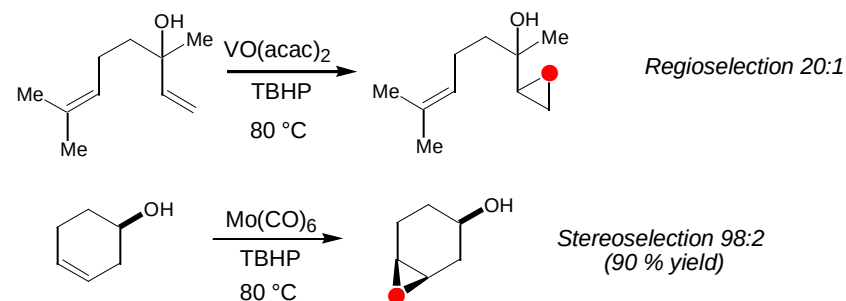
Chem 3D Transition State



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



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

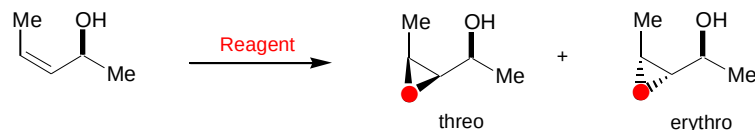


Relative Rates (Diastereoselectivities) for the Epoxidation of Cyclohexene Derivatives *JACS* **1973**, 95, 6136

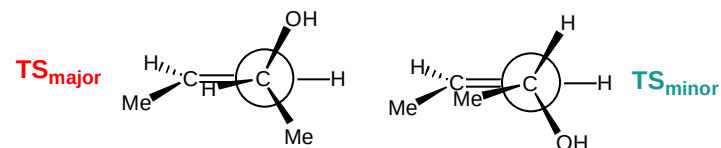
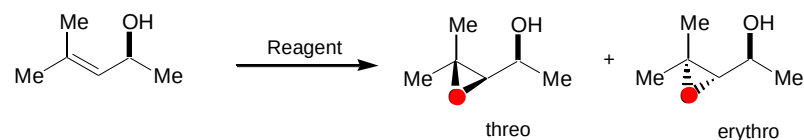
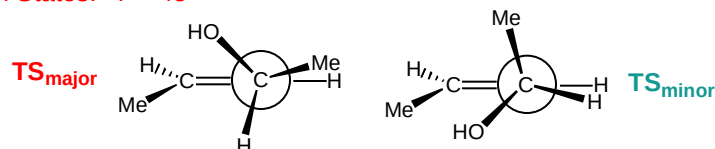
Substrate	$k_{\text{rel}}^{a,b}$ (diastereoselectivity ^c)		
	peracid	$\text{Mo}(\text{CO})_6$	$\text{VO}(\text{acac})_2$
	1.00	1.00	1.00
	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)
	0.046 (37 : 63)	0.07 (40 : 60)	--
	0.42 (60 : 40)	11.0 (98 : 2)	10.0 (98 : 2)

^{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:



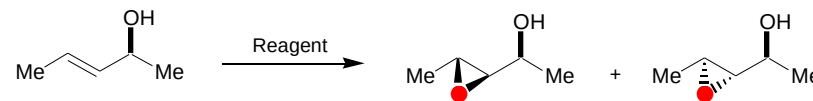
Φ Estimate	Reagent	Ratio
$\sim 120^\circ$	<i>m</i> -CPBA	95 : 5
40-50 °	<i>t</i> -BuOOH / VO(acac) ₂	71 : 29
	<i>t</i> -BuOOH / Mo(CO) ₆	84 : 16

■ RCO₃H Transition States: $\Phi \sim 120^\circ$ ■ V(+) Transition States: $\Phi \sim 45^\circ$ 

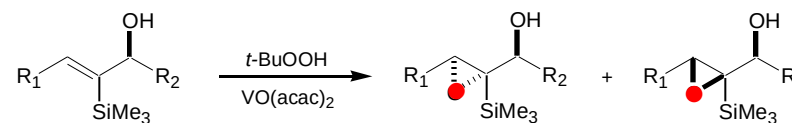
K. Oshima & Coworkers
Tetrahedron Lett. **1980**, 21, 1657, 4843.

Reagent	Ratio
<i>m</i> -CPBA	95 : 5
<i>t</i> -BuOOH / VO(acac) ₂	86 : 14
<i>t</i> -BuOOH / Mo(CO) ₆	95 : 5
<i>t</i> -BuOOH / (<i>t</i> -BuO) ₃ Al	100 : 0

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

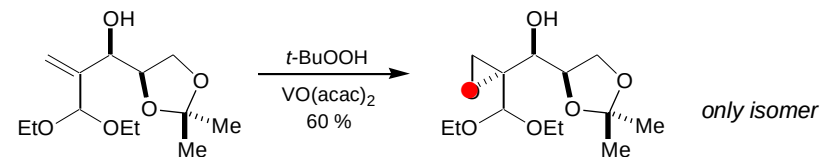
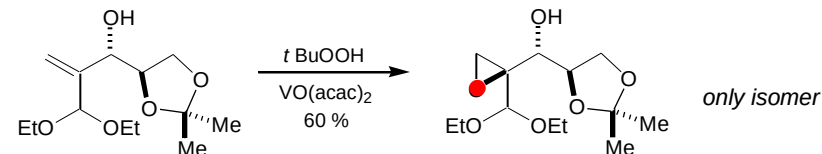


Reagent	Ratio
<i>m</i> -CPBA	64 : 36
<i>t</i> -BuOOH / VO(acac) ₂	29 : 71
<i>t</i> -BuOOH / Mo(CO) ₆	62 : 38
<i>t</i> -BuOOH / (<i>t</i> -BuO) ₃ Al	64 : 36

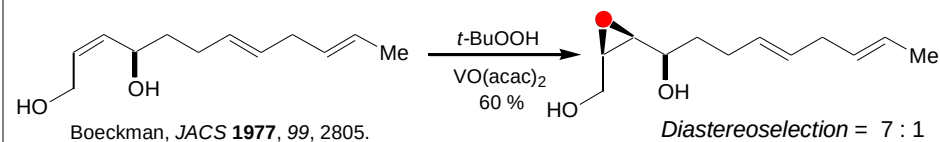


Oshima, *Tetrahedron Lett.* **1982**, 23, 3387.

R ₁	R ₂	Yield	Ratio
H	Bu	84 %	99 : 1
C ₅ H ₁₁	Me	70 %	99 : 1

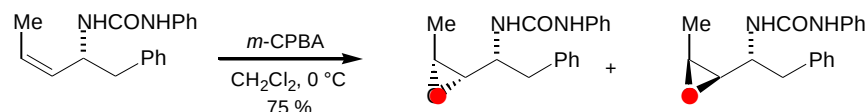


Depezay, *Tetrahedron Lett.* **1978**, 19, 2869.



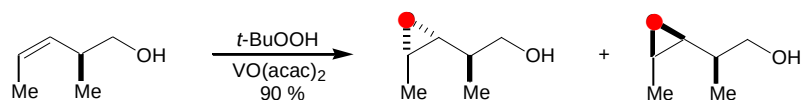
Boeckman, *JACS* **1977**, 99, 2805.

Diastereoselection = 7 : 1



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

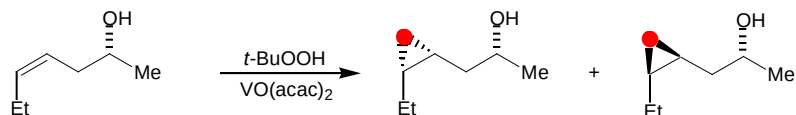
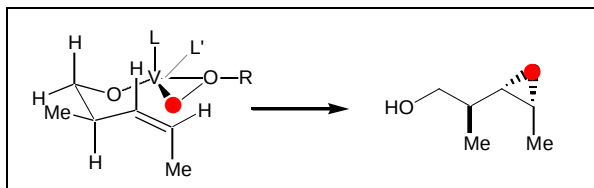
Diastereoselection = 95 : 5

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

Control Elements

A(1,3) Strain
Directed Rxn

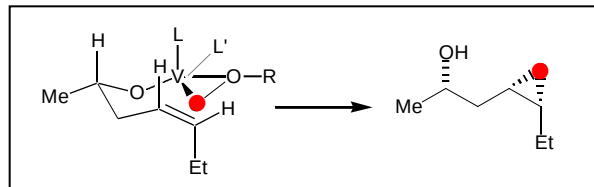
Diastereoselection > 400 : 1



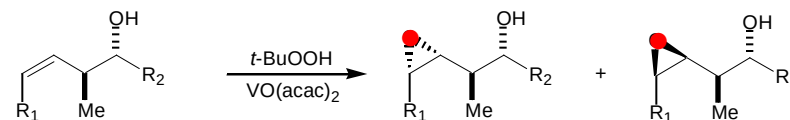
Diastereoselection 12 : 1

Control Elements

Directed Rxn

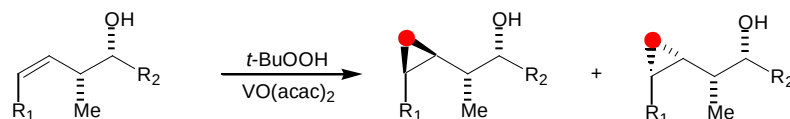


Anti diastereomer

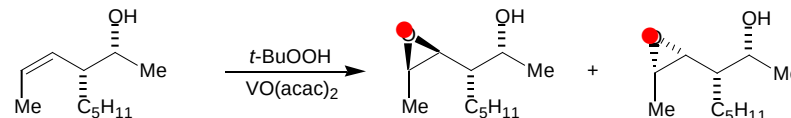


R ₁	R ₂	Yield	Ratio
C ₆ H ₁₃	Me	92 %	104 : 1
Me	<i>i</i> -Pr	97 %	> 400 : 1

Syn diastereomer



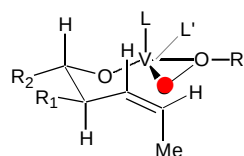
R ₁	R ₂	Yield	Ratio
C ₆ H ₁₃	Me	73 %	70 : 1
Me	Me	70 %	85 : 1
Me	C ₅ H ₁₁	81 %	16 : 1



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

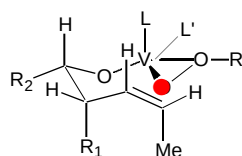
Diastereoselection = 211 : 1

Prediction



Anti diastereomer

Anti should be more
diastereoselective
than syn

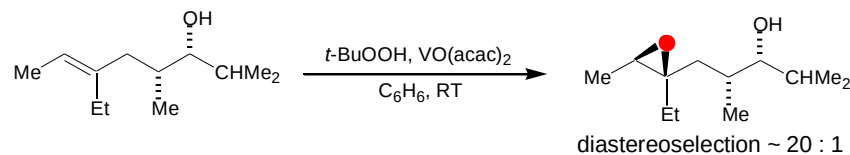
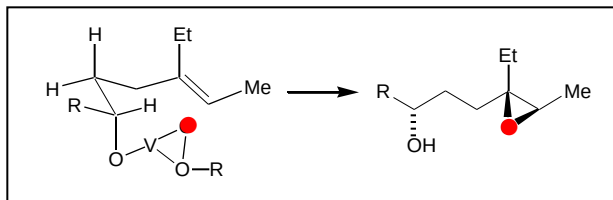
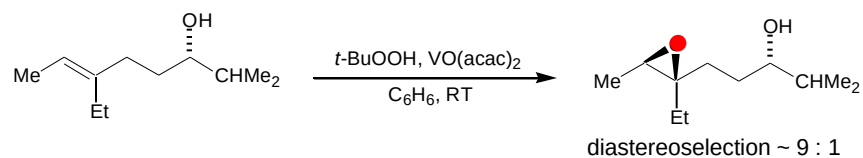
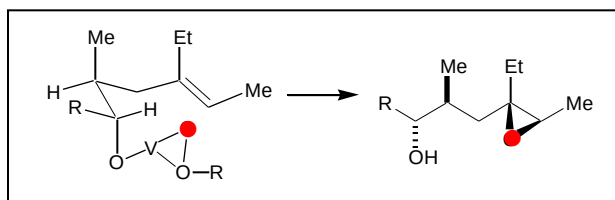
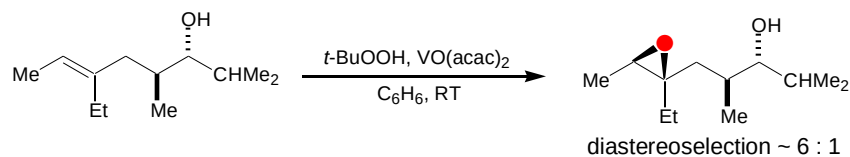
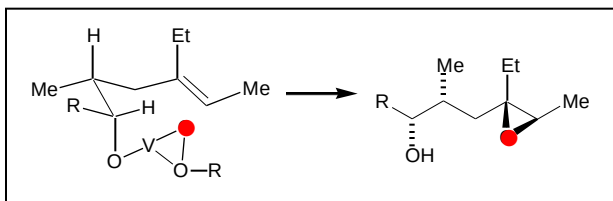


Syn diastereomer

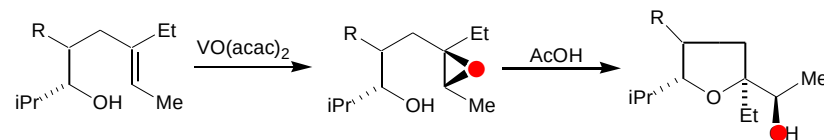
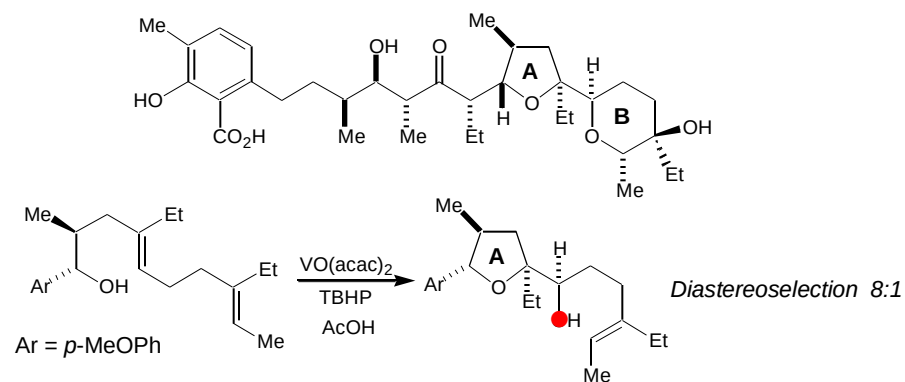
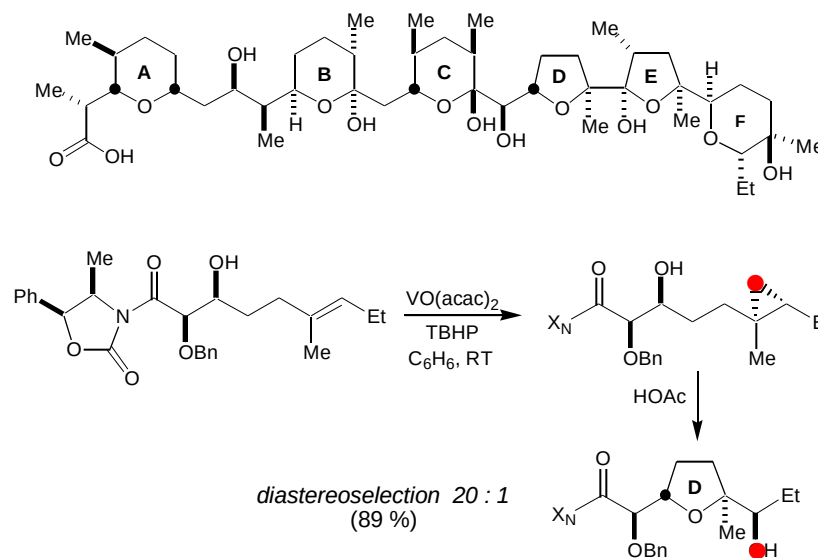
Epoxidation of Homoallylic Alcohols with TBHP, VO(acac)₂

Substrate	Product	Selectivity
		2 : 1
		4.6 : 1
		1.4 : 1

R = (CH₂)₇CO₂Me

Bishomoallylic Alcohols (Kishi, *Tet. Lett.* **1978**, *19*, 2741)2nd stereocenter
is reinforcing

Epoxidation & Cyclization of Bishomoallylic Alcohols

The Kishi Lasalocid Synthesis (*JACS* **1978**, *100*, 2933)Evans X-206 Synthesis *JACS* **1988**, *110*, 2506.

<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 Multiple 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

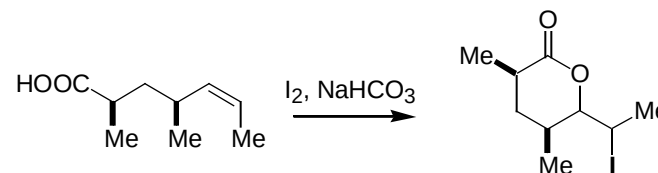
Takaya, H., T. Ohta, et al. (**1993**). Asymmetric Hydrogenation. *Catalytic Asymmetric Synthesis*. I. Ojima. New York, VCH: 1-39.

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.

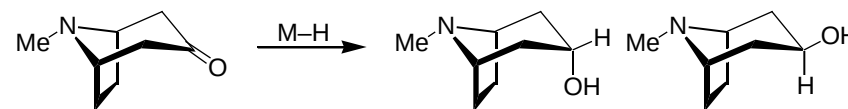


Kinetic Control: 3 eq. I_2 , MeCN, $NaHCO_3$, $0^\circ C$

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

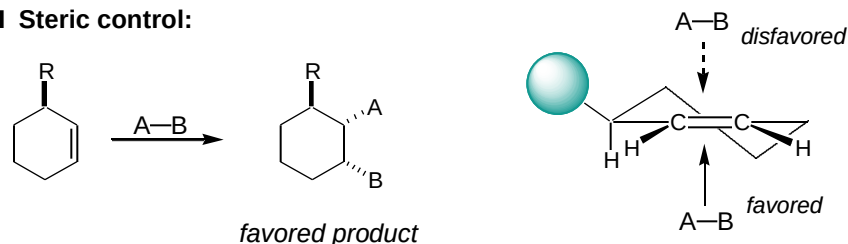
$LiAlH_4$

28 : 72

Stereochemical Control Elements for all reactions

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

■ Steric control:

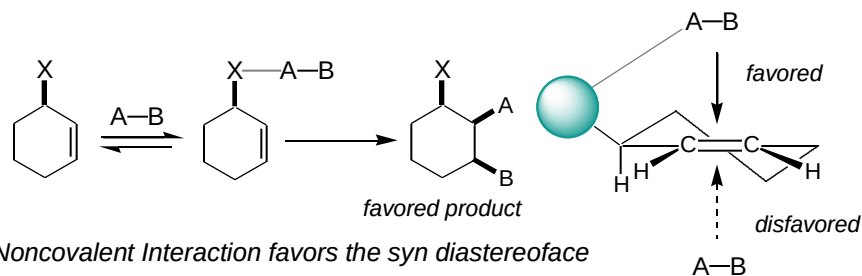


Nonbonding Interactions disfavor the syn diastereoface

Directed Reactions

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

■ Associative Substrate-Reagent Interactions



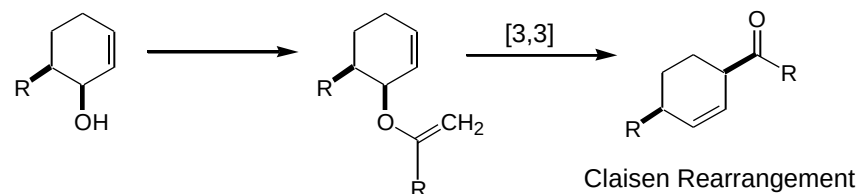
Noncovalent Interaction favors the syn diastereoface

Agenda

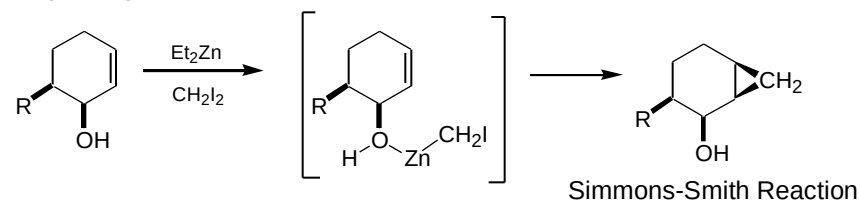
- Directed Oxidations
 - Epoxidation
 - Hydroboration
- Directed Reductions
 - Hydrogenation
 - Hydride reduction
- Directed C-C Bond Constructions

Heteroatom-directed Reactions

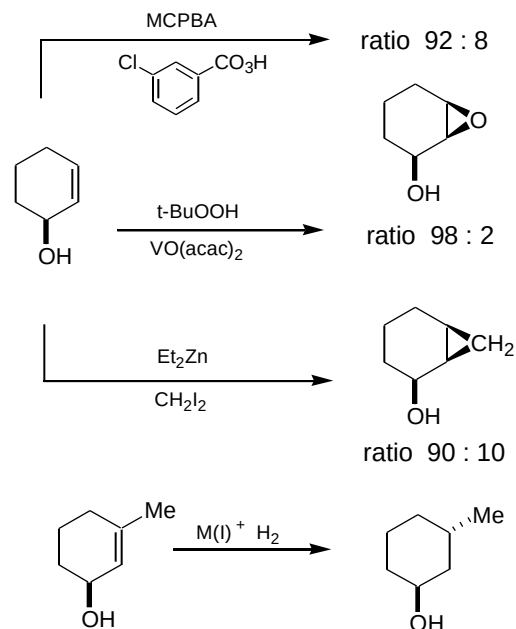
Mechanism-based: (HO & C=C must be allylic)



via Reagent Ligation



Hydroxyl-directed Reactions



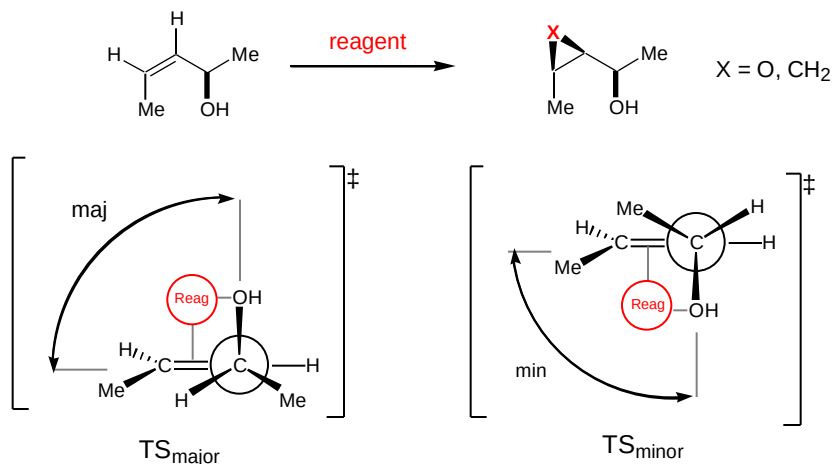
Henbest
J. Chem. Soc. 1958, (1957)

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 reagents

Reagent	Selectivity	Φ Estimate
t-BuO ₂ H, V ⁺⁵	71 : 29	~ 50 °
RCO ₃ H	95 : 5	~ 120 °
CH ₂ I ₂ , Zn-Cu	> 99 : 1	?

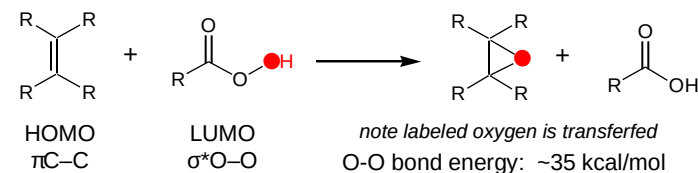
The transition state bite angles for the above reactions are either not known or have been only crudely estimated.

The "best guesses" are provided.

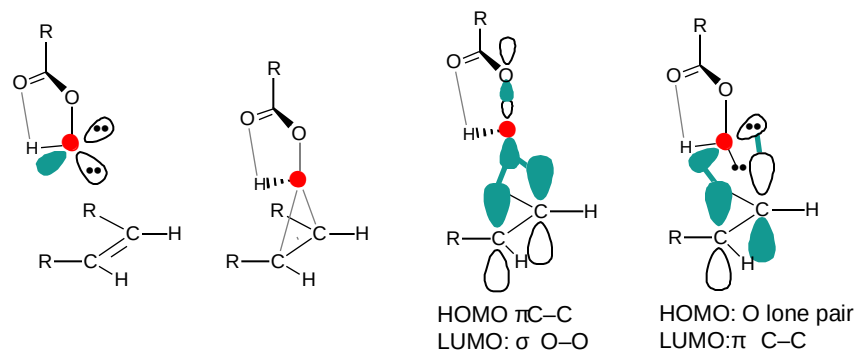
Peracid Epoxidation

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

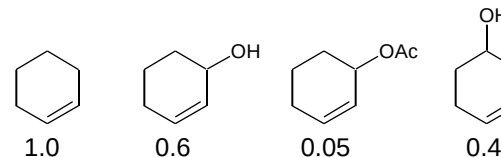
General Reaction:



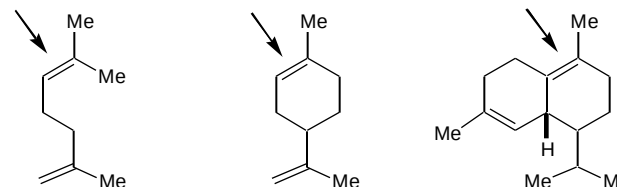
Transition state: What about lone pairs. [Consider ● to be Sp² hybridized].



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

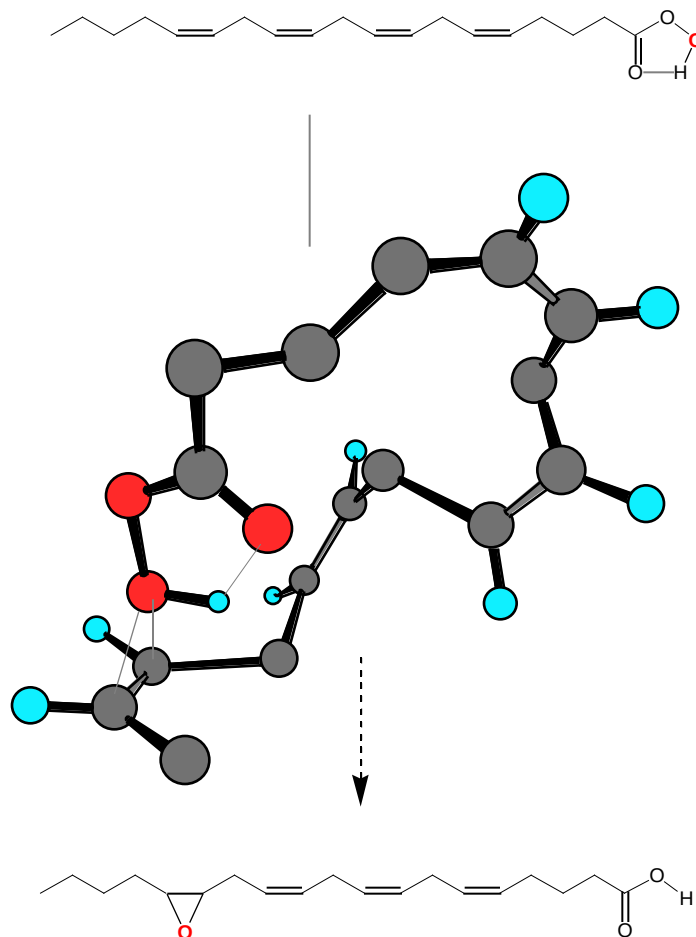


The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



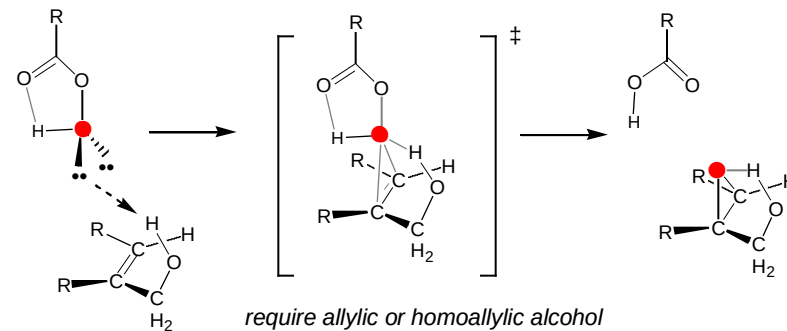
Stereoelectronic Implications of intramolecular Peracid Epoxidation

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

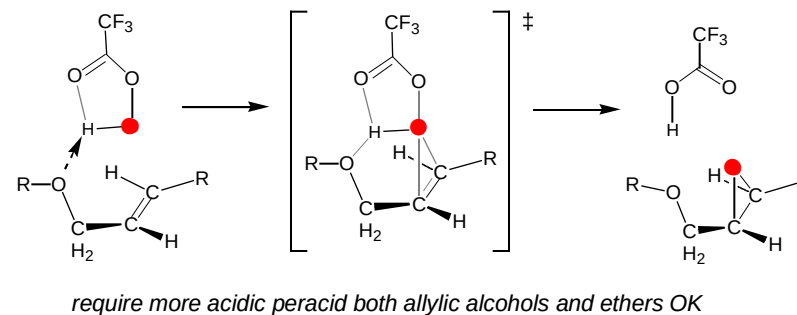


The Directed Peracid Epoxidation

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



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



	Syn : Anti (<i>m</i> -CPBA)	Syn : Anti (CF ₃ CO ₃ H)		Syn : Anti (<i>m</i> -CPBA)	Syn : Anti (CF ₃ CO ₃ H)
	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

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.

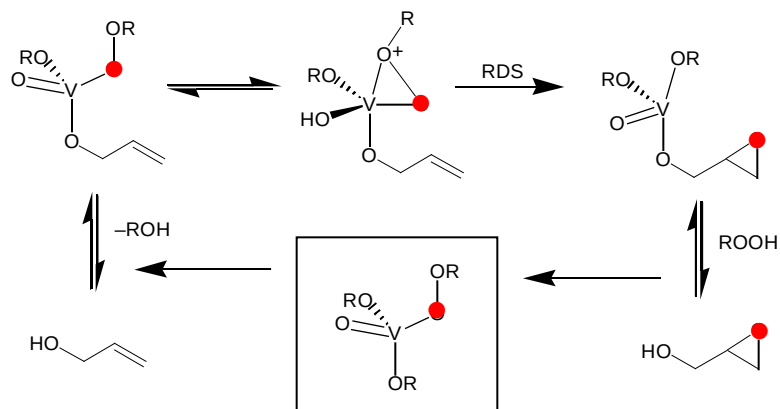
(Table 11, p1316, from the Evans, Hoveyda, Fu review article)

Epoxidation of Cyclic Homoallylic Alcohols

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

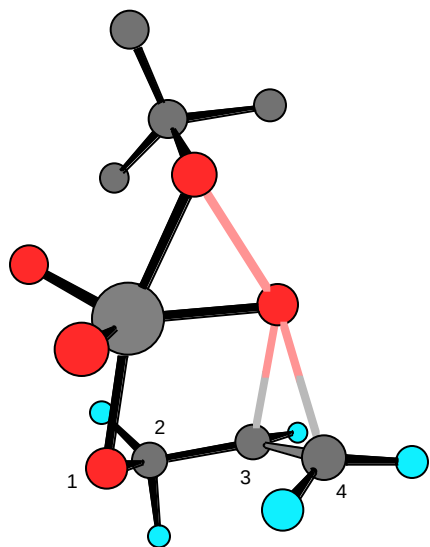
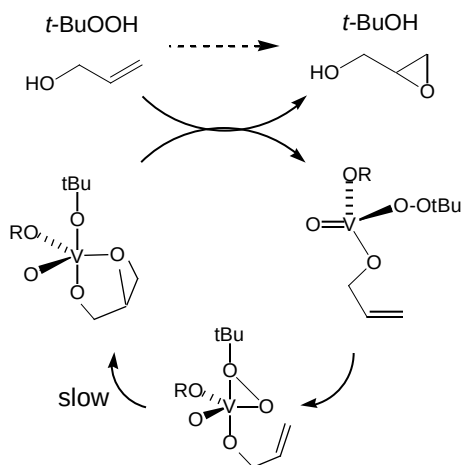
Conditions: Perbenzoic acid, or meta-chloroperbenzoic acid in benzene or cyclopentane.

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

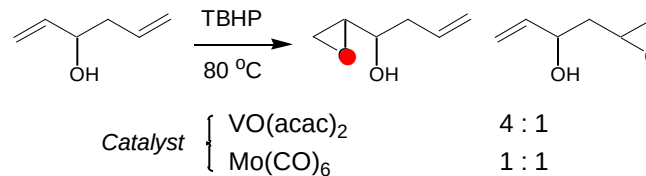
The Sharpless Epoxidation

Aldrichimica Acta, 12, 63 (1979)

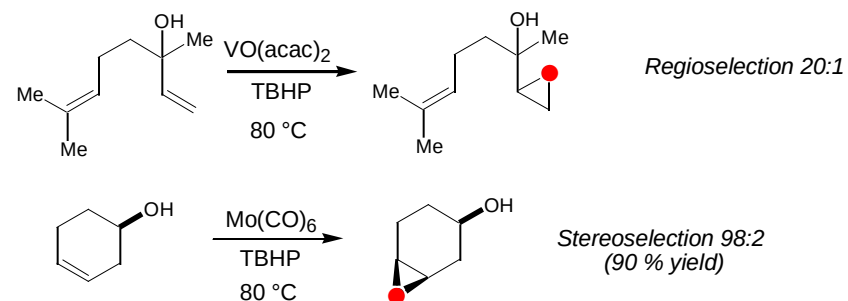
$O-C_2-C_3-C_4 = 41^\circ$
The Sharpless estimate: $\sim 50^\circ$

**Chem 3D Transition State**

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



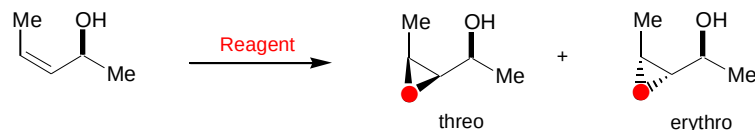
■ Next step: Sharpless, Michaelson *JACS* **1973**, 95, 6136

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

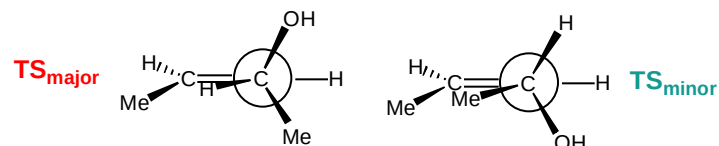
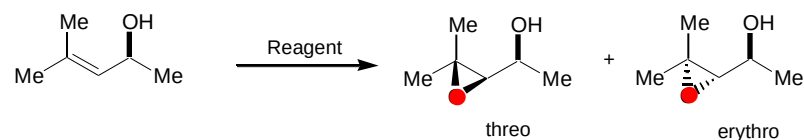
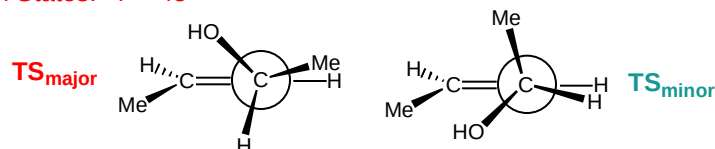
Substrate	$k_{rel}^{a,b}$ (diastereoselectivity ^c)		
	peracid	Mo(CO) ₆	VO(acac) ₂
	1.00	1.00	1.00
	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)
	0.046 (37 : 63)	0.07 (40 : 60)	--
	0.42 (60 : 40)	11.0 (98 : 2)	10.0 (98 : 2)

^{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:



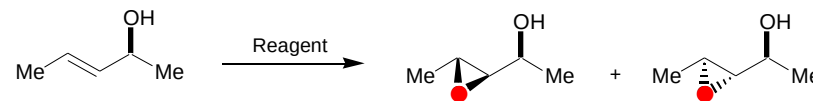
Φ Estimate	Reagent	Ratio
$\sim 120^\circ$	<i>m</i> -CPBA	95 : 5
40-50 °	<i>t</i> -BuOOH / VO(acac) ₂	71 : 29
	<i>t</i> -BuOOH / Mo(CO) ₆	84 : 16

■ RCO₃H Transition States: $\Phi \sim 120^\circ$ ■ V(+) Transition States: $\Phi \sim 45^\circ$ 

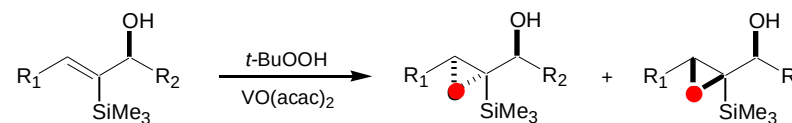
K. Oshima & Coworkers
Tetrahedron Lett. **1980**, 21, 1657, 4843.

Reagent	Ratio
<i>m</i> -CPBA	95 : 5
<i>t</i> -BuOOH / VO(acac) ₂	86 : 14
<i>t</i> -BuOOH / Mo(CO) ₆	95 : 5
<i>t</i> -BuOOH / (<i>t</i> -BuO) ₃ Al	100 : 0

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

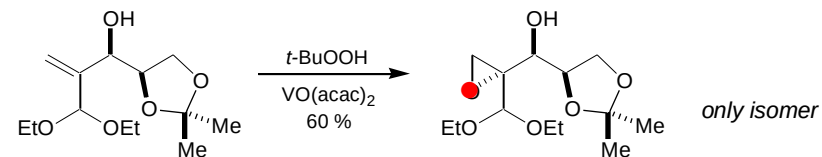
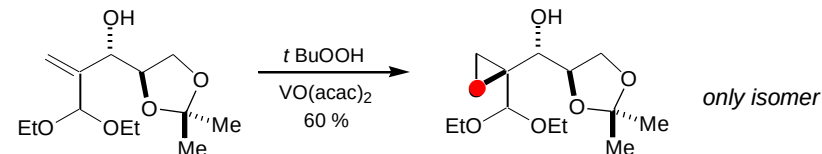


Reagent	Ratio
<i>m</i> -CPBA	64 : 36
<i>t</i> -BuOOH / VO(acac) ₂	29 : 71
<i>t</i> -BuOOH / Mo(CO) ₆	62 : 38
<i>t</i> -BuOOH / (<i>t</i> -BuO) ₃ Al	64 : 36

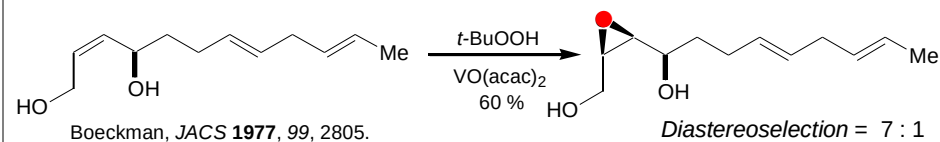


Oshima, *Tetrahedron Lett.* **1982**, 23, 3387.

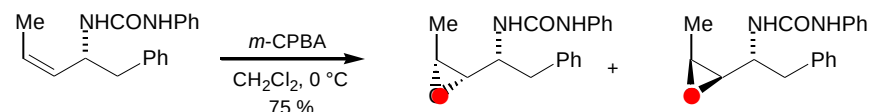
R ₁	R ₂	Yield	Ratio
H	Bu	84 %	99 : 1
C ₅ H ₁₁	Me	70 %	99 : 1



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

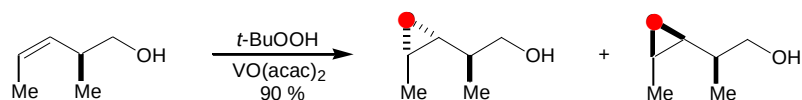


Boeckman, *JACS* **1977**, 99, 2805.



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

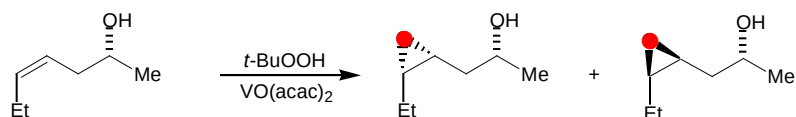
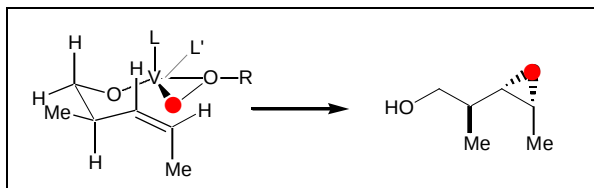
Diastereoselection = 95 : 5

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

Control Elements

A(1,3) Strain
Directed Rxn

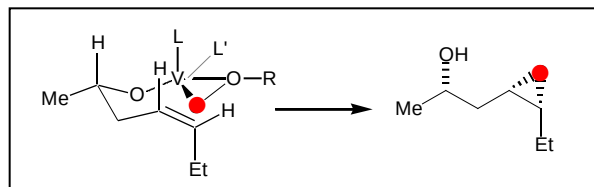
Diastereoselection > 400 : 1



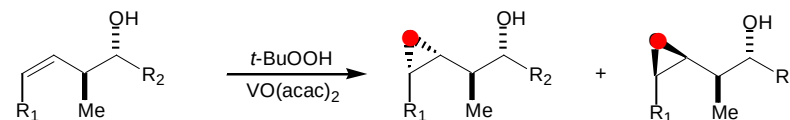
Diastereoselection 12 : 1

Control Elements

Directed Rxn

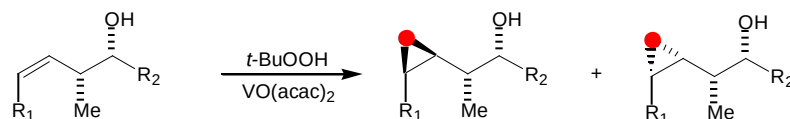


Anti diastereomer

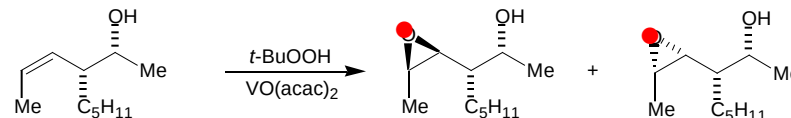


R ₁	R ₂	Yield	Ratio
C ₆ H ₁₃	Me	92 %	104 : 1
Me	<i>i</i> -Pr	97 %	> 400 : 1

Syn diastereomer



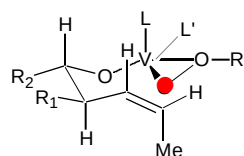
R ₁	R ₂	Yield	Ratio
C ₆ H ₁₃	Me	73 %	70 : 1
Me	Me	70 %	85 : 1
Me	C ₅ H ₁₁	81 %	16 : 1



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

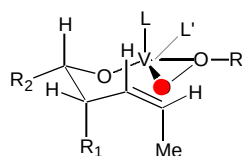
Diastereoselection = 211 : 1

Prediction



Anti diastereomer

Anti should be more
diastereoselective
than syn

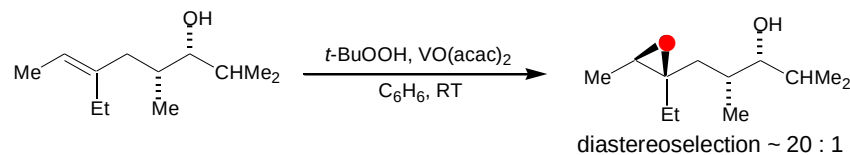
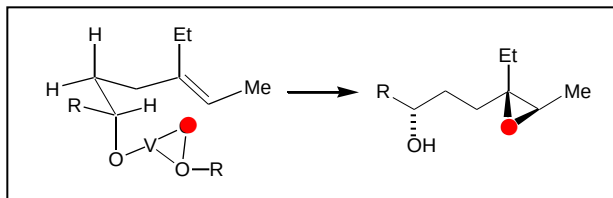
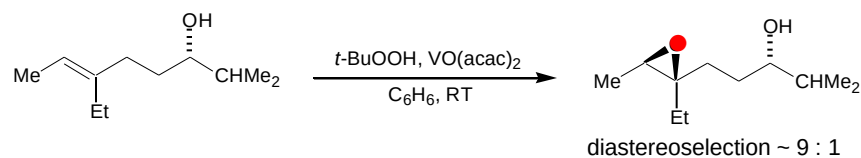
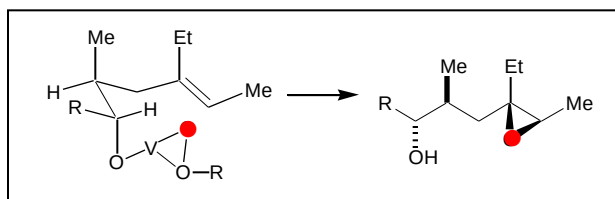
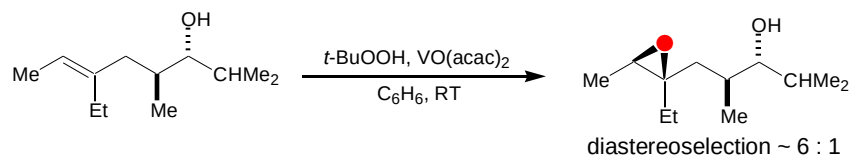
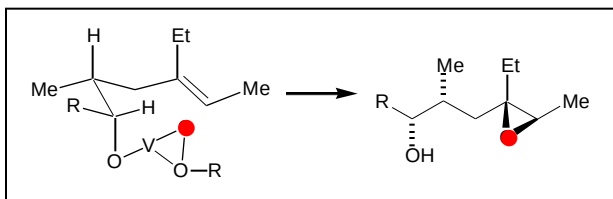


Syn diastereomer

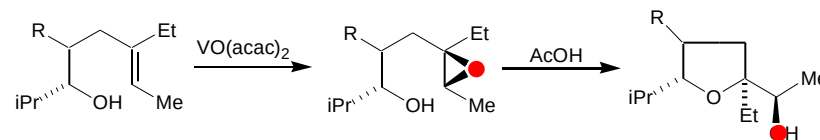
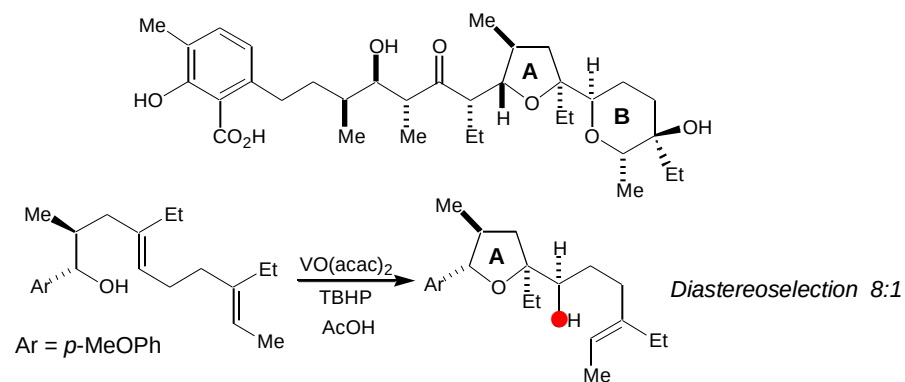
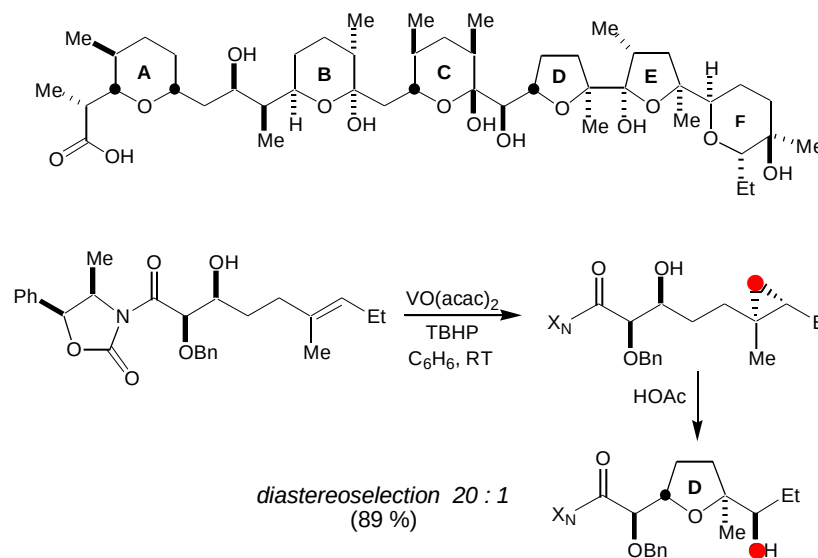
Epoxidation of Homoallylic Alcohols with TBHP, VO(acac)₂

Substrate	Product	Selectivity
		2 : 1
		4.6 : 1
		1.4 : 1

R = (CH₂)₇CO₂Me

Bishomoallylic Alcohols (Kishi, *Tet. Lett.* **1978**, *19*, 2741)2nd stereocenter
is reinforcing

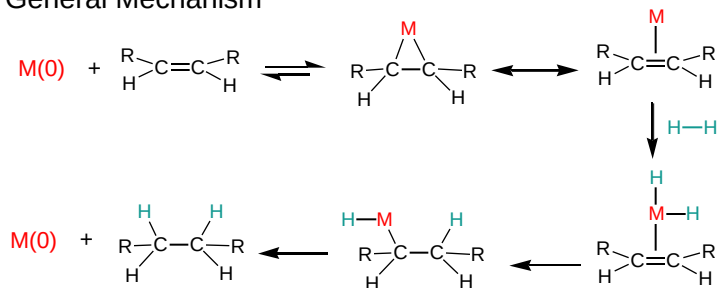
Epoxidation & Cyclization of Bishomoallylic Alcohols

The Kishi Lasalocid Synthesis (*JACS* **1978**, *100*, 2933)Evans X-206 Synthesis *JACS* **1988**, *110*, 2506.

The Hydrogenation Reaction

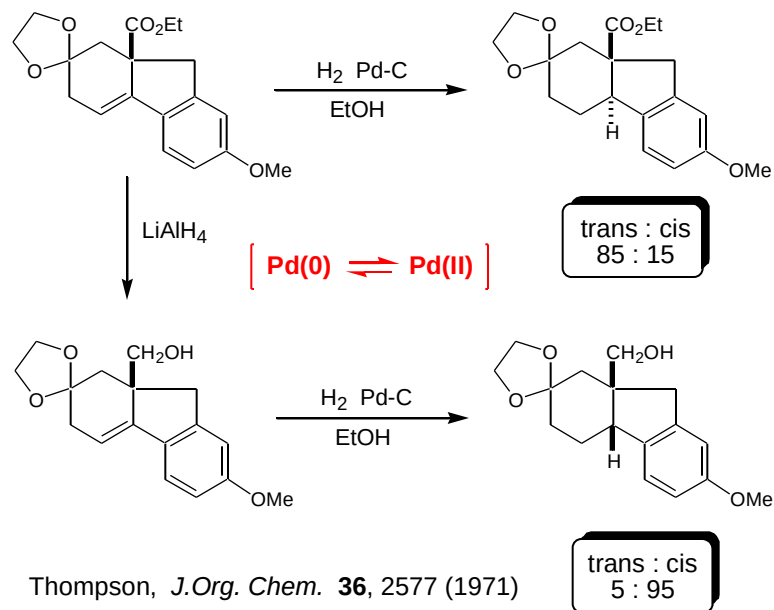
Relevant Review articles: J. M. Brown, *Angew. Chem. Int. Edit.* **26**, 190-203 (1987).

■ General Mechanism

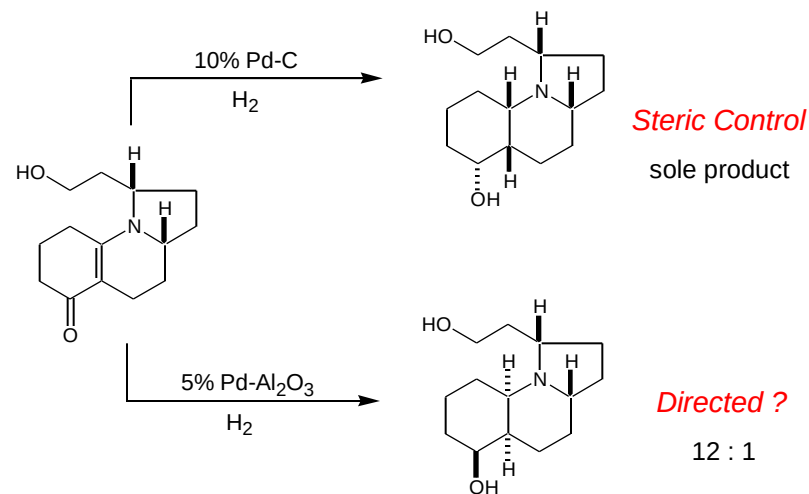
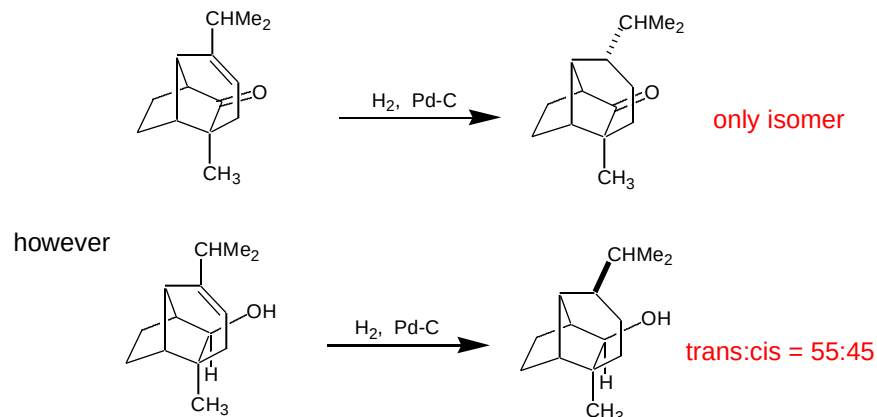


Historically, primary stereochemical control designed around analysis of steric environment in vicinity of $C=C$.

However, the influence of polar effects was documented

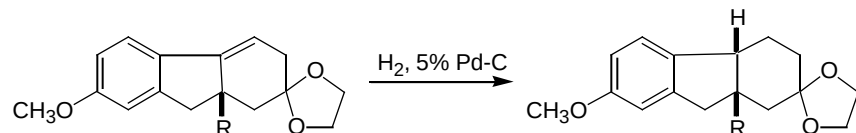


Polar functional groups may play a role in controlling the diastereoselectivity of the hydrogenation process; however, the control elements were not well-defined.



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

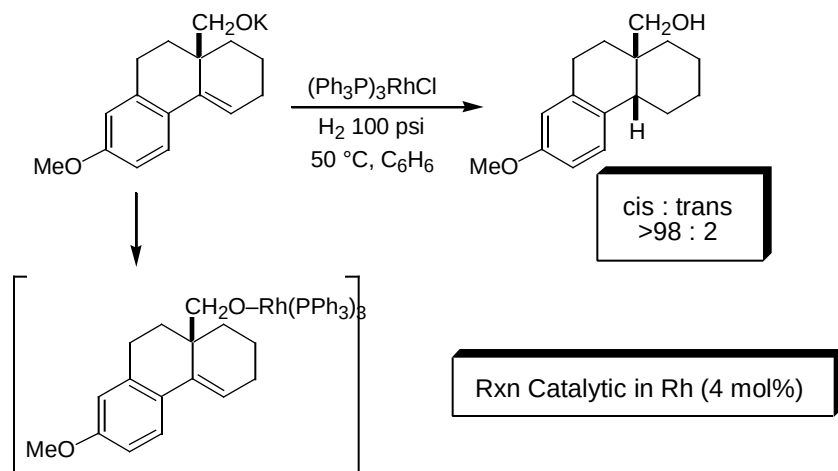
The first rational attempt to identify those FGs which will direct the reaction



R	cis : trans
CH ₂ OH	95 : 5
CHO	93 : 7
CN	75 : 25
COONa	55 : 45
COOH	18 : 82
COOMe	15 : 85
COMe	14 : 86
CONH ₂	10 : 90

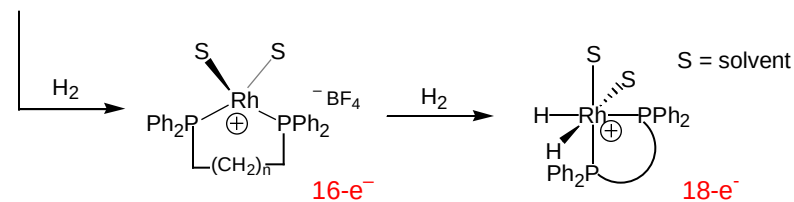
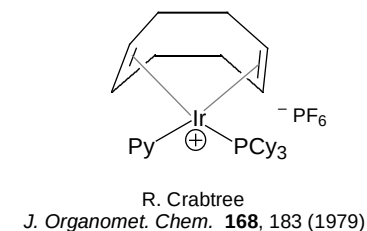
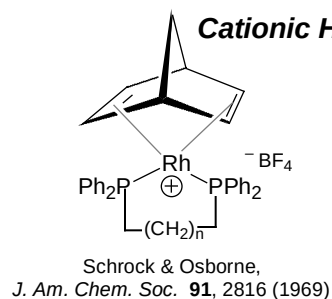
H. Thompson & Co-workers, *J. Am. Chem. Soc.* **95**, 838 (1973)

The first rational attempt to associate catalyst with substrate:



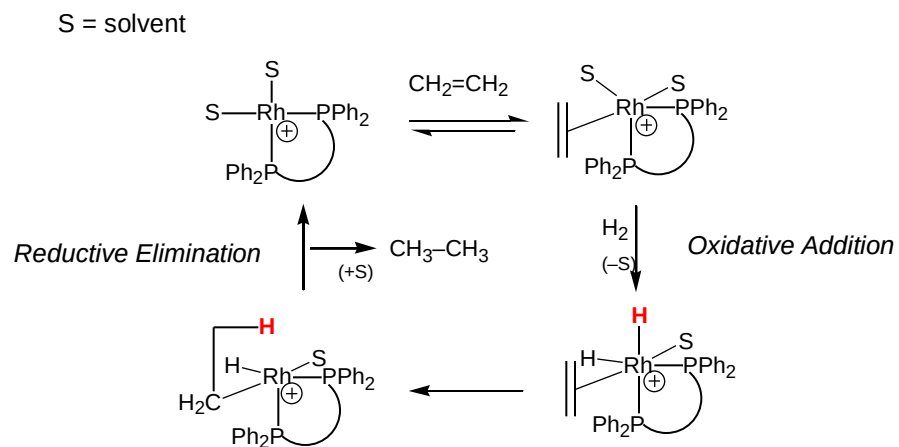
Thompson & Coworkers, *J. Am. Chem. Soc.* **97**, 6232 (1974)

Cationic Hydrogenation Catalysts

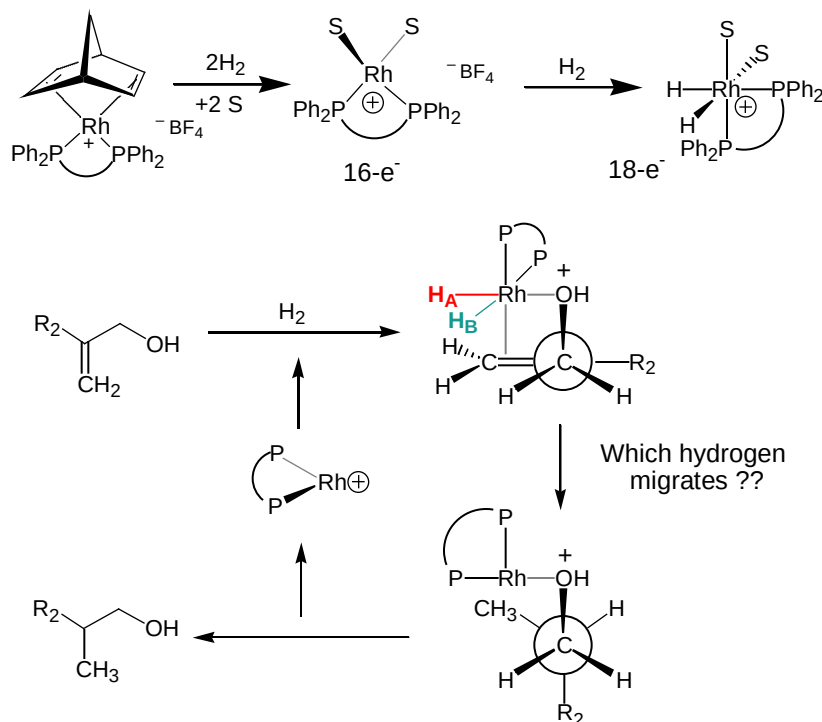


Rh(+I): d8

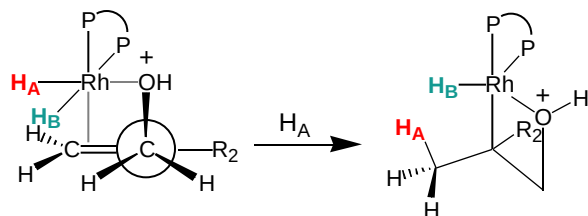
Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.



Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.

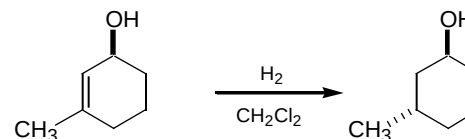


A potential stereoelectronic effect

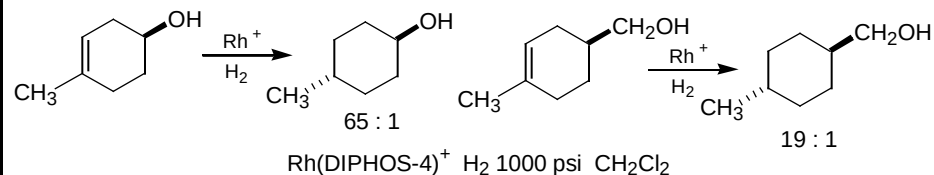


That H atom lying parallel to the π -system (H_A) should migrate preferentially if the dihydride is an intermediate.

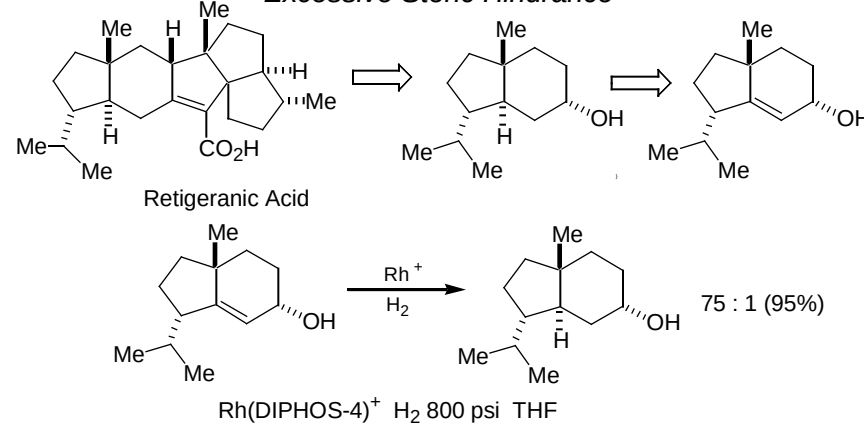
D. A. Evans & M. M. Morrissey *JACS* **106**, 3866 (1984)



Catalyst	Mol% Catalyst	H_2 Pressure	trans:cis (Yield)
$\text{Rh}(\text{DIPHOS-4})^+$	17.5	15 psi H_2	200 : 1 (89%)
	3.5	375 psi H_2	300 : 1 (95%)
$\text{Ir}(\text{pyr})\text{PCy}_3$	20.0	15 psi H_2	50 : 1 (82%)
	2.5	15 psi H_2	150 : 1 (85%)

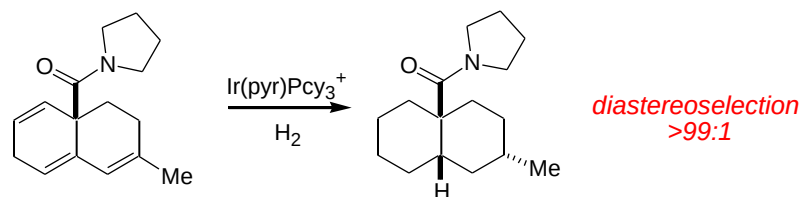
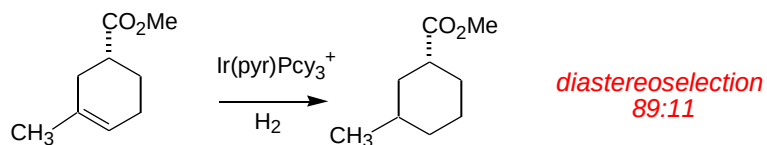
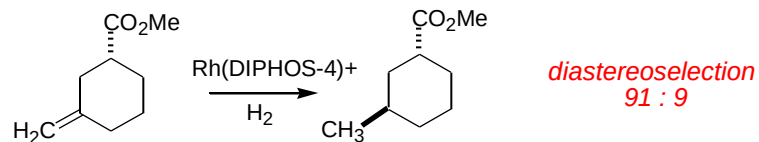


Excessive Steric Hindrance

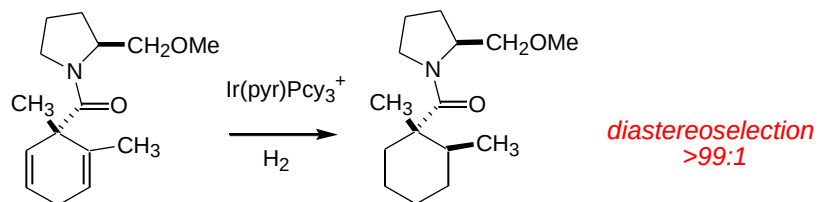
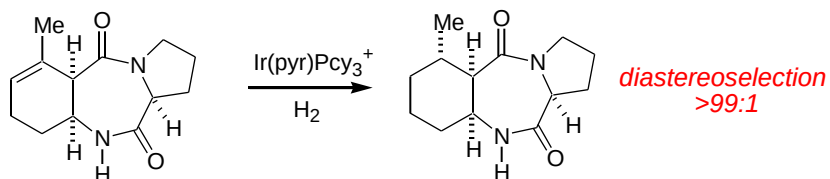


THF is important to success of rxn to buffer the Lewis acidity of the catalyst which causes elimination of ROH under normal conditions

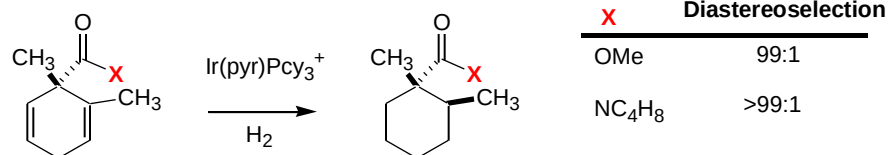
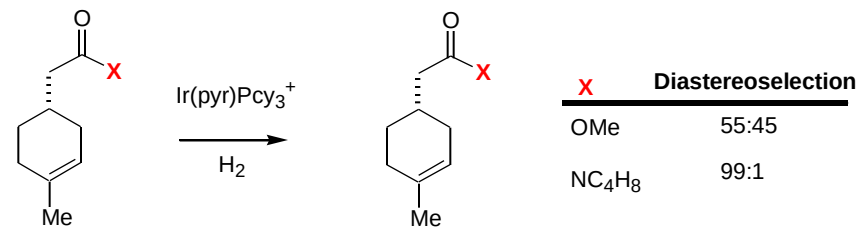
Polar functional groups other than OH may also direct the process



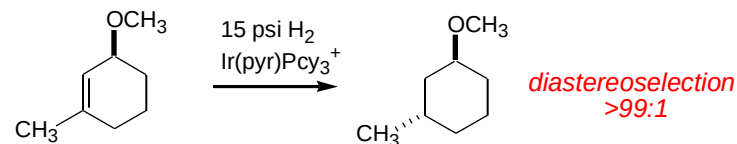
J.M. Brown and S.A. Hall, *J. Organomet. Chem.*, **1985**, 285, 333.



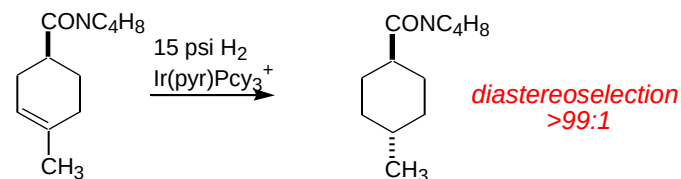
A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, 50, 5907.



A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, 50, 5907.

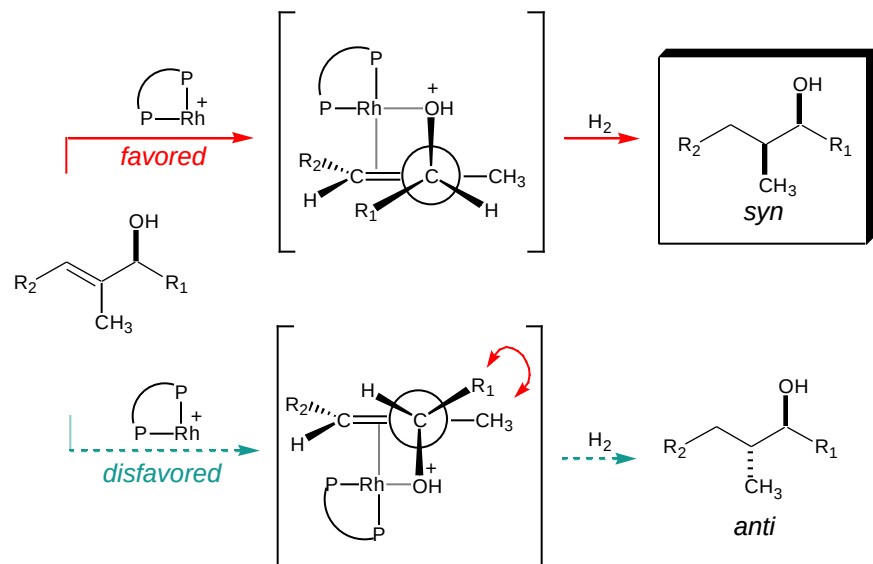
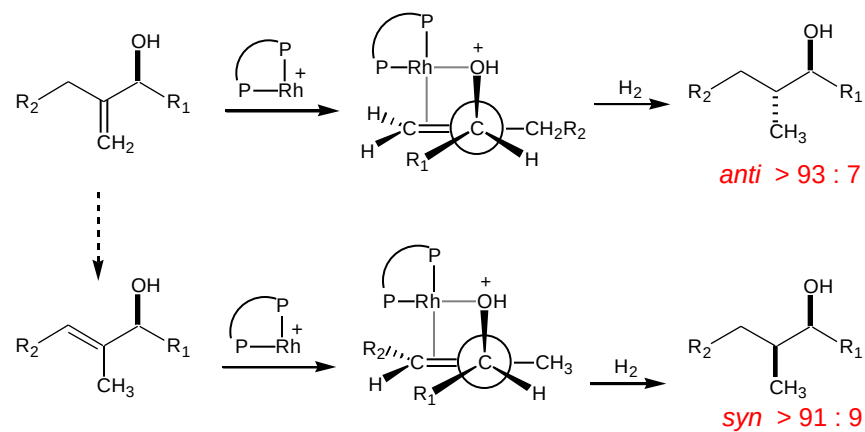
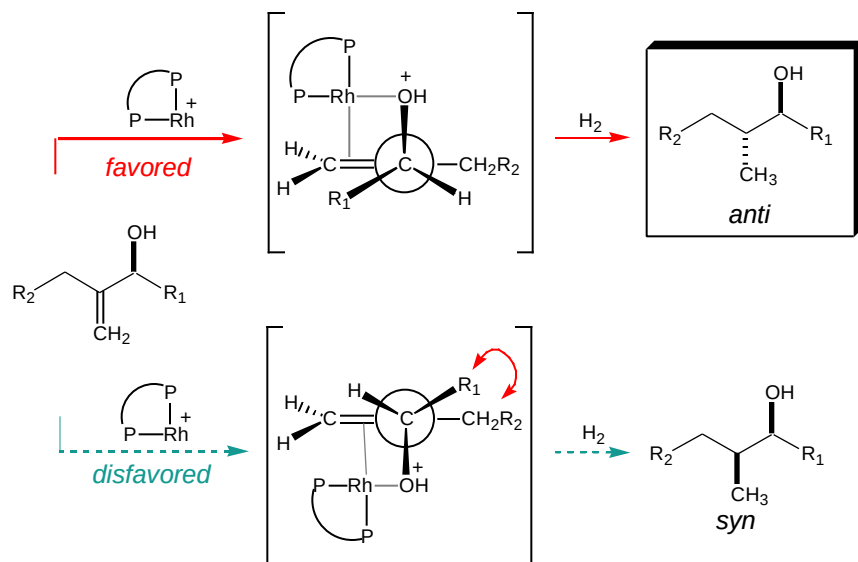
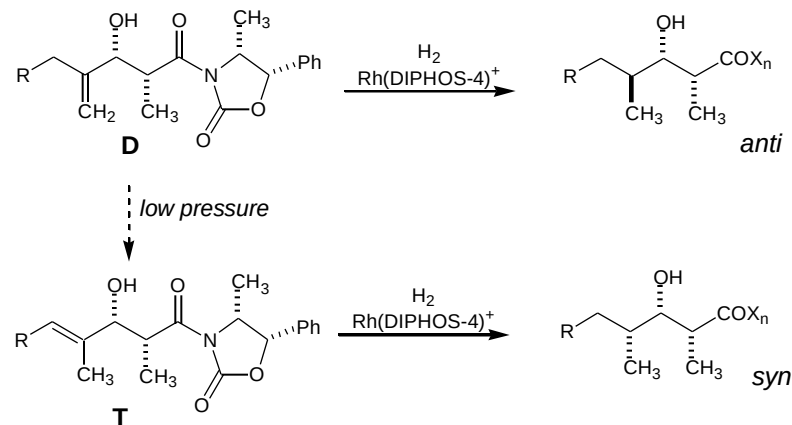


R.H. Crabtree and M.W. Davis, *J. Org. Chem.*, **1986**, 51, 2655.

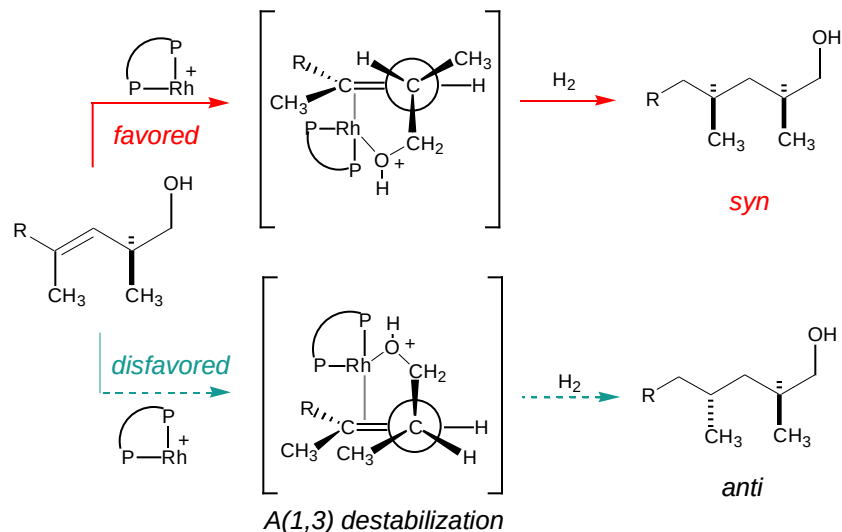


A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, 50, 5907.

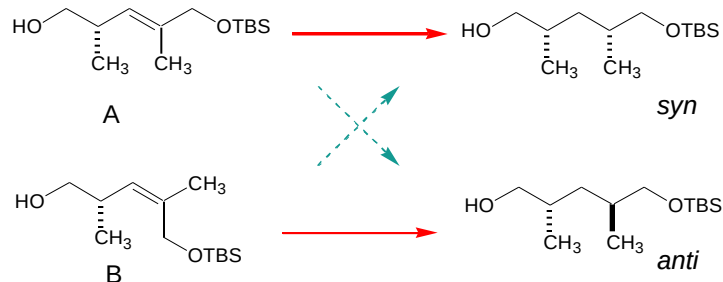
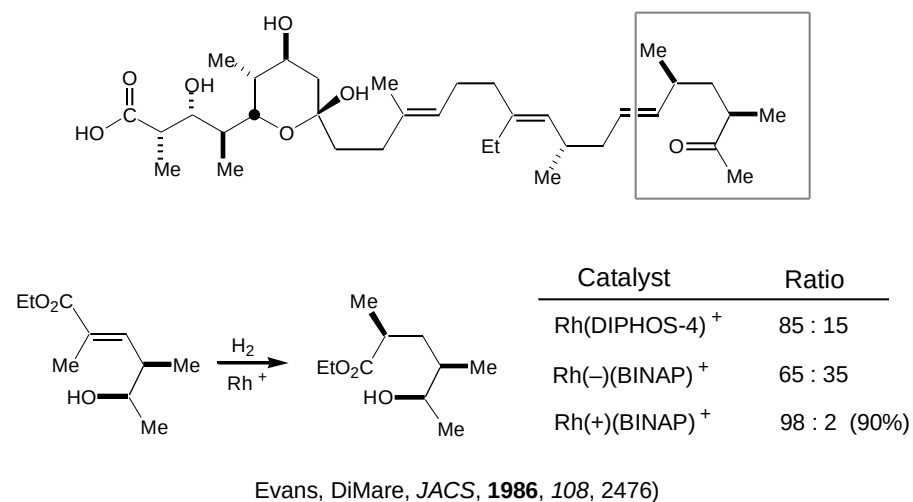
Acyclic Allylic Alcohols

D. A. Evans & M. M. Morrissey JACS **106**, 3866 (1984)

Anti : Syn Ratio			
Hydroxy-Olefin	15 psi H ₂	640 psi H ₂	
D {	R = CH ₃	25 : 75 (23%)	93 : 7
	R = (CH ₃) ₂ CH	52 : 48 (35%)	94 : 6
	R = Ph	71 : 29 (-)	93 : 7
T {	R = CH ₃	13 : 87 (6%)	9 : 91
	R = (CH ₃) ₂ CH	12 : 88 (8%)	8 : 92
	R = Ph	21 : 79 (-)	6 : 94

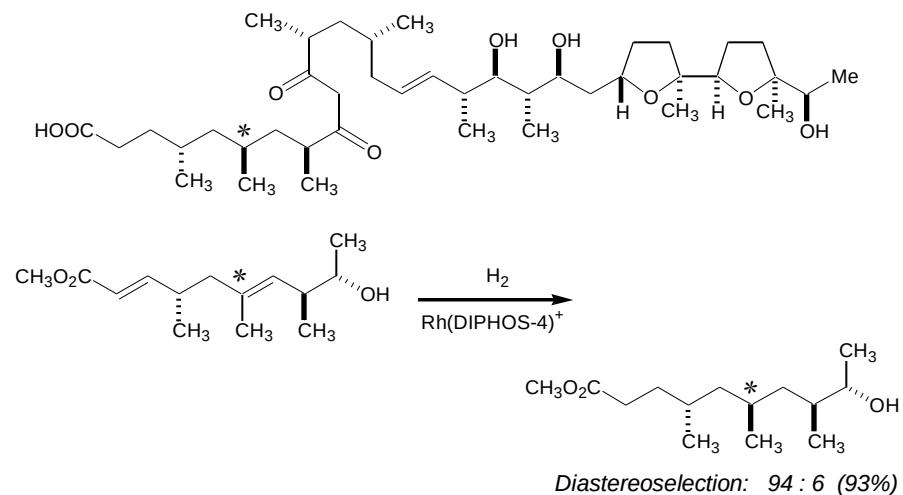
Homoallylic Alcohols Evans, Morrissey *Tetrahedron Lett.* **26** 6005 (1985)

The Premonensin Synthesis



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 Ionomycin Synthesis

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 Multiple 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

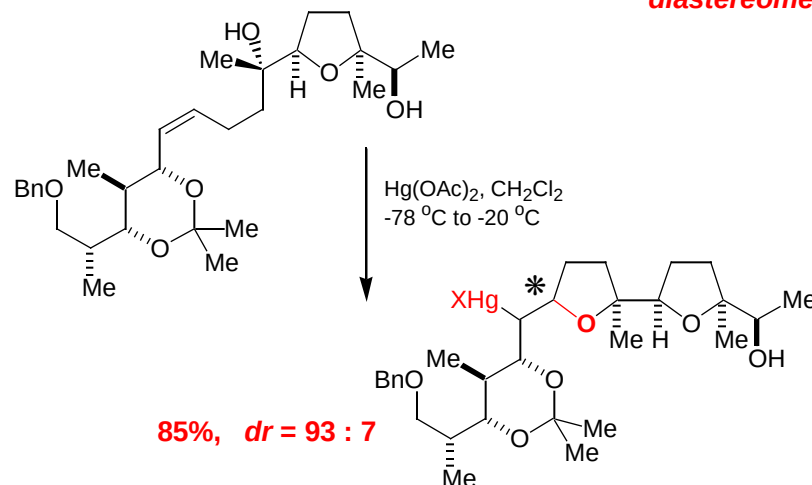
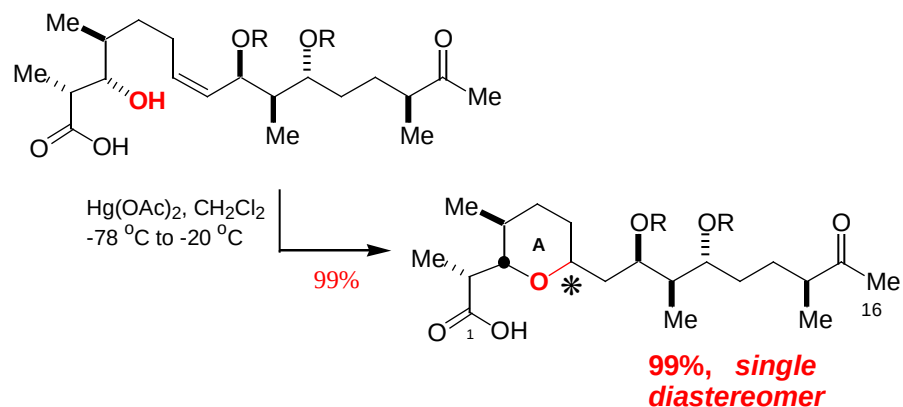
Bromonium Ions or β -Bromocarboxocations in Olefin Bromination. A Kinetic Approach to Product Selectivities

M-F. Ruasse, *Accts. Chem. Res.* **1990**, 23, 87 (**handout**)

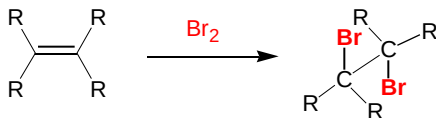
Investigation of the early Steps in Electrophilic Bromination through the Study of the Reaction of Sterically Encumbered Olefins

R. S. Brown, *Accts. Chem. Res.* **1997**, 30, 131 (**handout**)

■ Predict stereochemical outcome



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** .

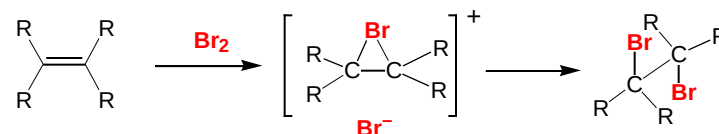
- Substituent Effects on Bromination Rates

Alkene	k_{rel}
$\text{CH}_2=\text{CH}_2$	1
$\text{CH}_3\text{CH}=\text{CH}_2$	61
$n\text{-PrCH}=\text{CH}_2$	70
$i\text{-PrCH}=\text{CH}_2$	57
$t\text{-BuCH}=\text{CH}_2$	27
$(\text{CH}_3)_2\text{C}=\text{CH}_2$	5470
$\text{cis-CH}_3\text{CH}=\text{CHCH}_3$	2620
$\text{trans-CH}_3\text{CH}=\text{CHCH}_3$	1700
$(\text{CH}_3)_2\text{C}=\text{CHCH}_3$	130,000
$(\text{CH}_3)_2\text{C}=\text{C}(\text{CH}_3)_2$	1,800,000

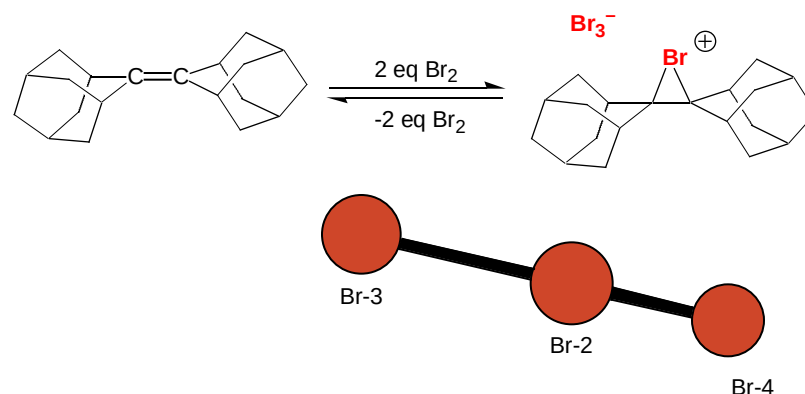
- Stereochemical outcome versus structure (Br_2 in HOAc @ 25°)

Alkene	% anti addition	Alkene	% anti addition
	100%		83%
	100%		63%
	73%		68%

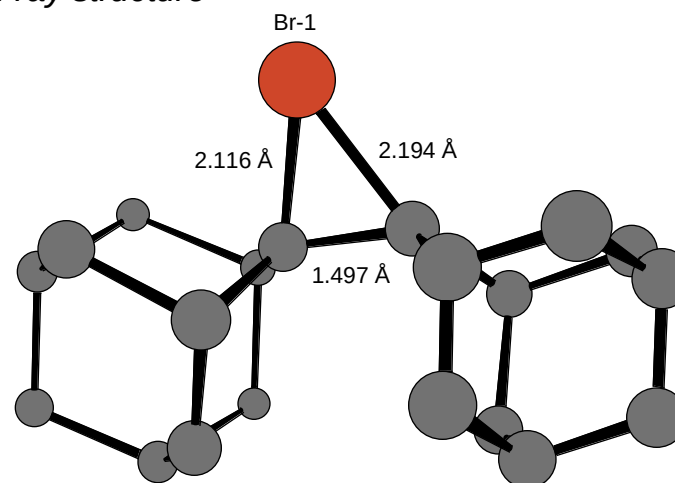
- Bromonium ion origin of the anti (trans) selectivity first suggested by Roberts, JACS **1937**, 59, 947



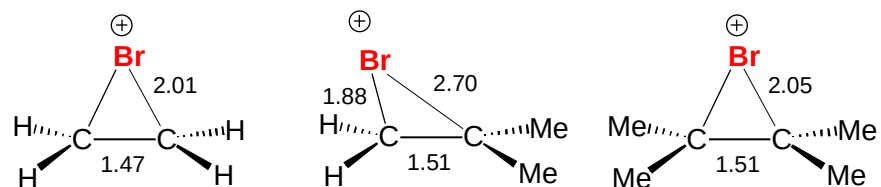
- First X-ray Structure of a bromonium ion: Brown, JACS **1985**, 107, 4504



X-ray structure



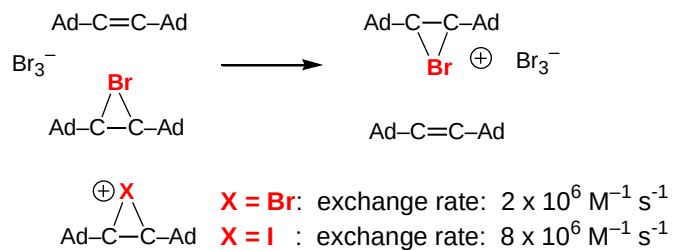
■ Calculated Geometries of Substituted Bromonium Ions
Ruasse, *Chem Commun.* **1990**, 898



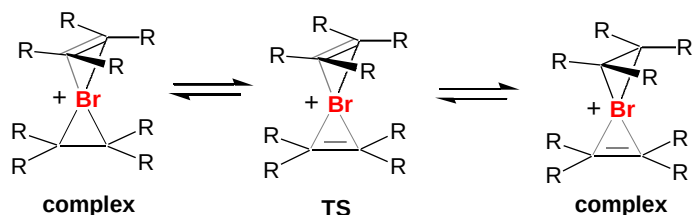
Note; the C-Br bond lengths in previous X-ray structure are 2.116 Å.

■ Bromonium Ions undergo fast exchange with olefins
Brown, *Accts. Chem. Res.* **1997**, 30, 131

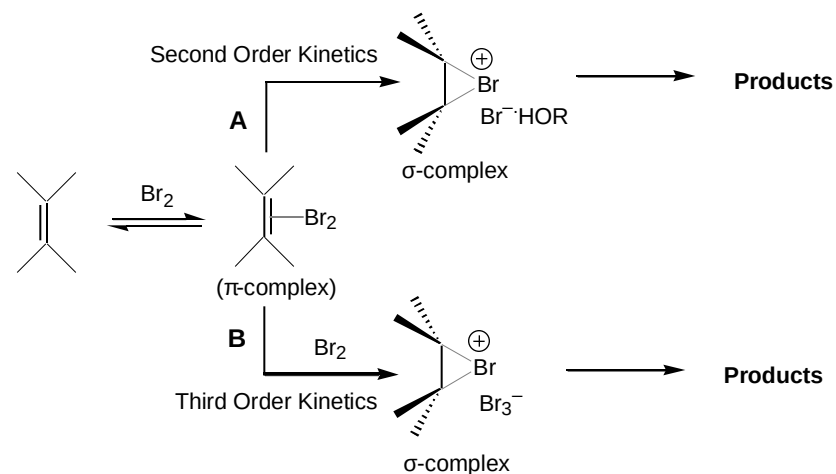
Unprecedented until 1991 (Bennet, *JACS* **1991**, 113, 8532)



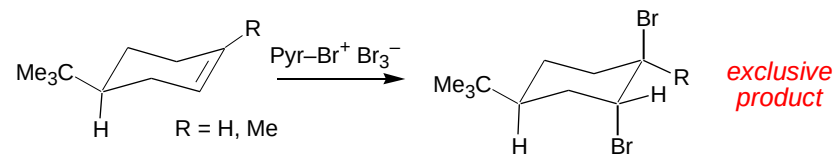
There is an intermediate in the halogen transfer (ab initio calcs):



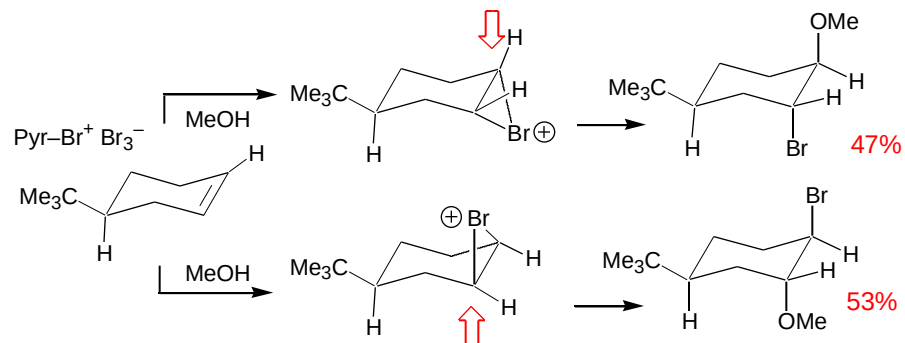
Overall Reaction Mechanism



Bromination of Cyclohexene Derivatives Pasto, *JACS* 1970, 92, 7480



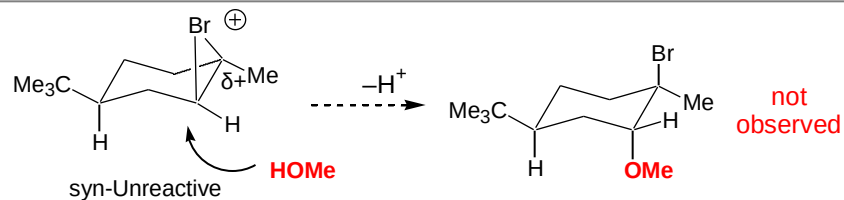
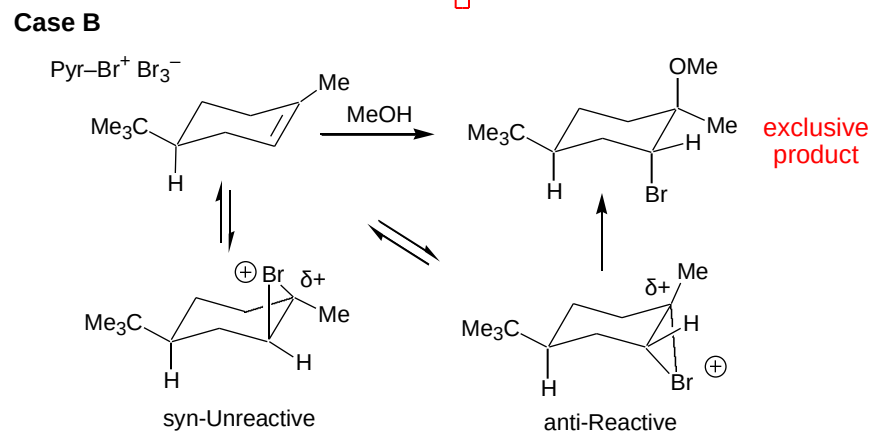
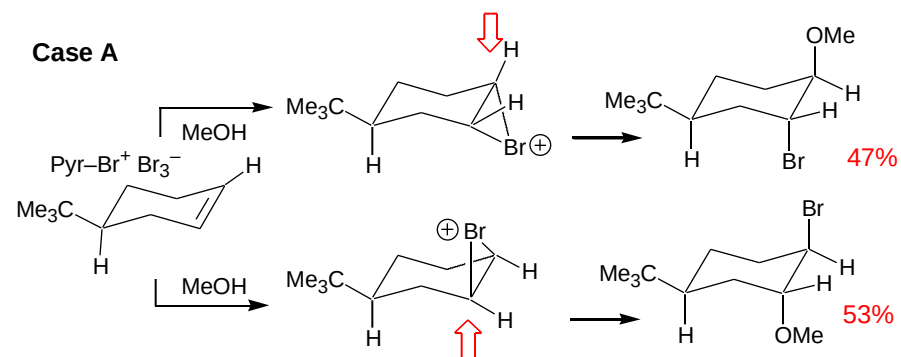
Di axial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening (**Lecture-3**).



It appears that bromine attack from both olefin faces occurs with near equal probability.

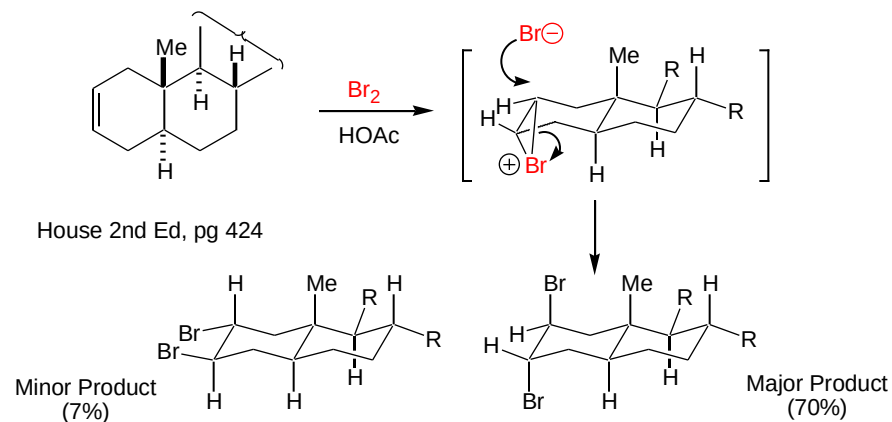
Bromination of Cyclohexene Derivatives Pasto, JACS 1970, 92, 7480

Di axial opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening. (Lecture-2)

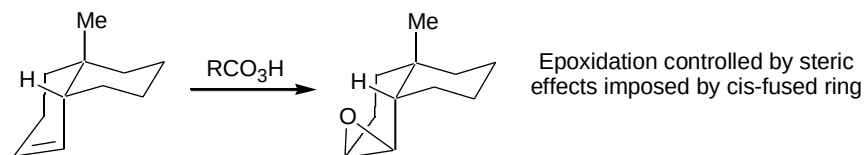


From Case **A**, one assumes that both bromonium ions are formed; however, for the syn isomer to react, ring opening must proceed against the polarization due to Methyl substituent.

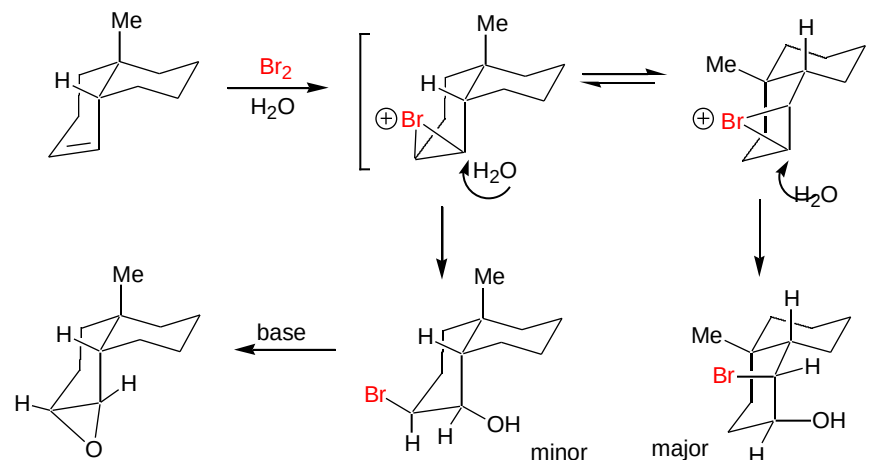
Representative Examples of Diastereoselective Bromination



How to generate either epoxide from a conformatinally biased olefin



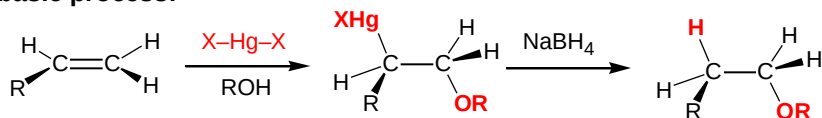
How do we construct the other epoxide diastereomer??



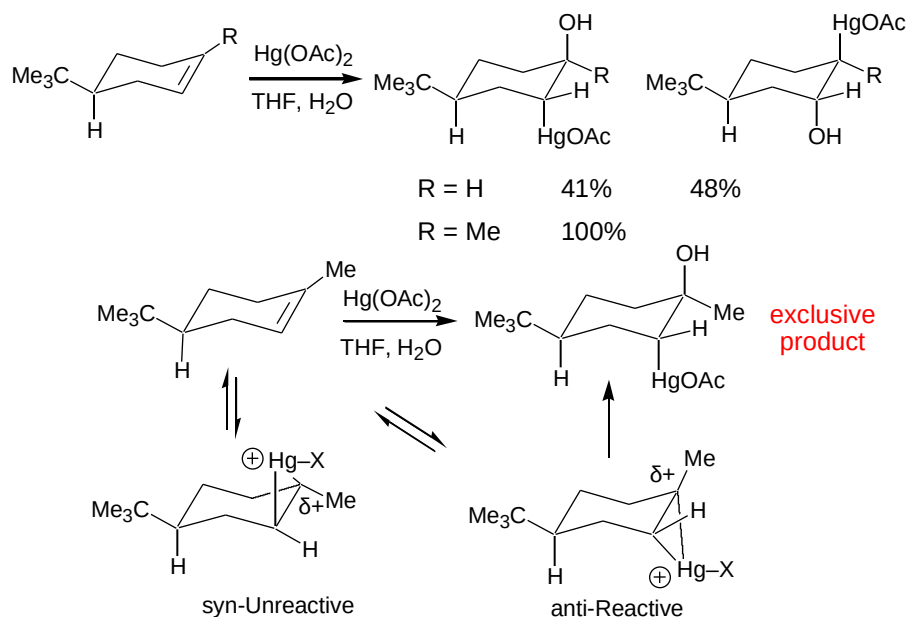
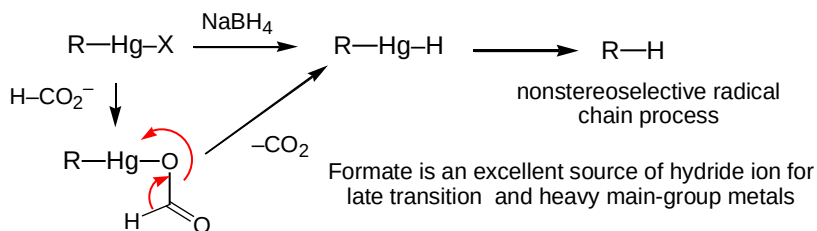
both bromohydrins afford same product

Oxymercuration Pasto, JACS 1970, 92, 7480

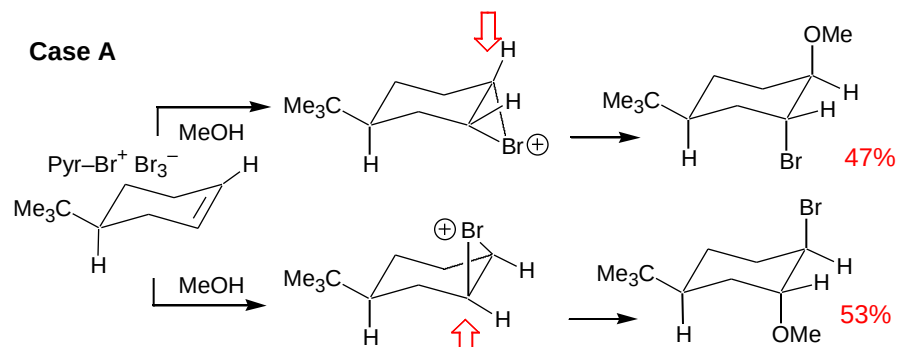
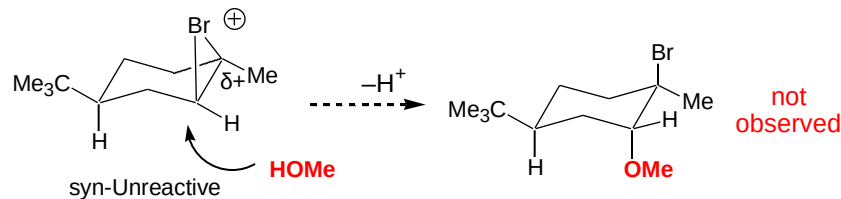
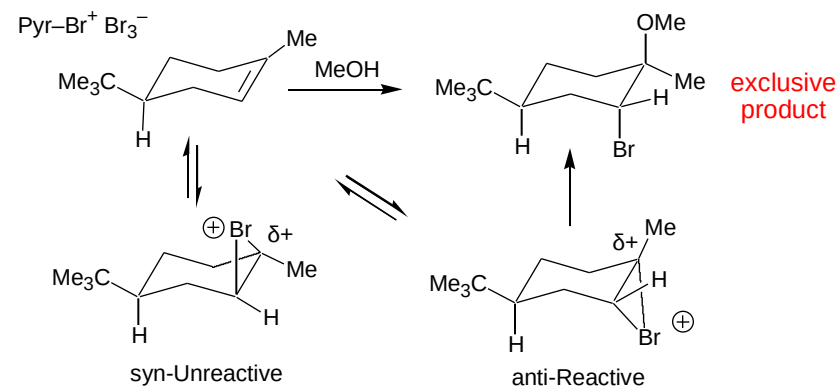
The basic process:



Kinetics: Halpern, JACS **1967**, 89, 6427 Reduction: Pasto, JACS **199**, 91, 719
 Overview: Brown, JOC **1981**, 46, 3810.

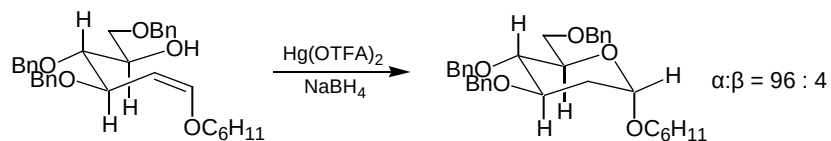
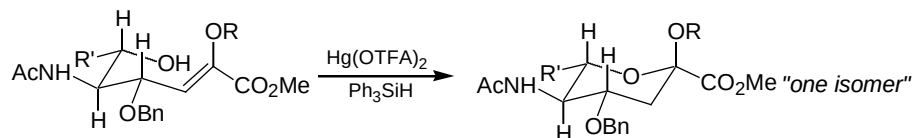
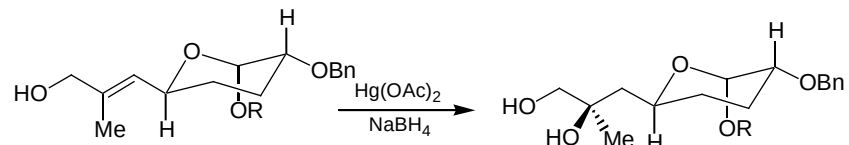
Oxy-Mercuration & bromination follow identical pathways (Pasto)**Reduction of the Hg-C bond****Bromination of Cyclohexene Derivatives** Pasto, JACS 1970, 92, 7480

Diastal opening of bromonium ions may be viewed as an extension of the Furst-Plattner Rule for epoxide ring opening. (Lecture-2)

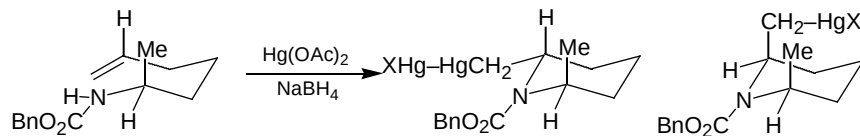
Case A**Case B**

From Case A, one assumes that both bromonium ions are formed; however, for the syn isomer to react, ring opening must proceed against the polarization due to Methyl substituent.

Diastereoselective ring closures via oxymercuration

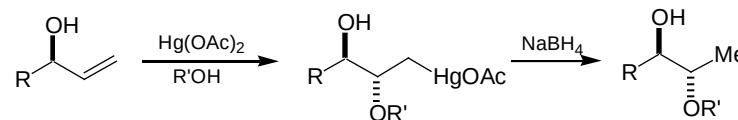
Mukaiyama, *Chem. Lett.* **1981**, 683Sinay, *Tet. Lett.* **1984**, 25, 3071Isobe, *Tet. Lett.* **1985**, 26, 5199

Kinetic vs Thermodynamic control:

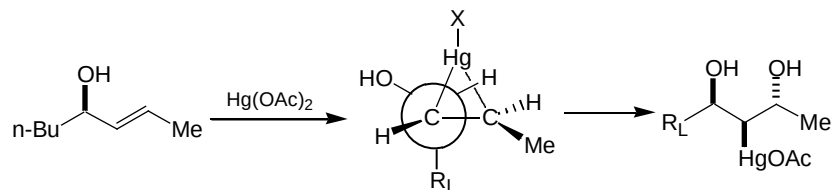
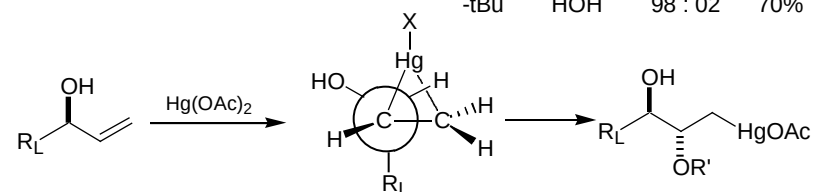
Harding, *JOC* **1984**, 49, 2838 $\text{Hg}(\text{OAc})_2$: short rxn times : 40 : 60 $\text{Hg}(\text{OTFA})_2$: longer rxn times : 2 : 98

With more electrophilic $\text{Hg}(\text{II})$ salt, more polar solvents, and longer rxn times, the rxn may be rendered reversible.

Acyclic allylic alcohols:

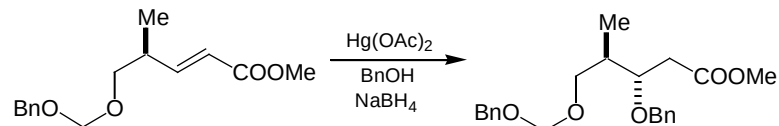
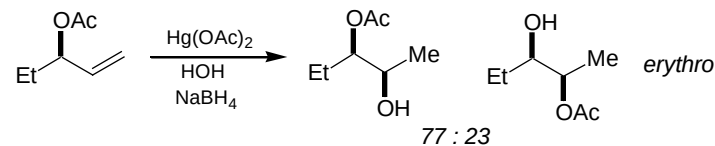
Giese, *Tet. Lett.* **1985**, 26, 1197

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%

Chamberlin, *Tetrahedron* **1984**, 40, 2297

syn:anti = 80 : 20

O-acetate participation will turn over the stereochemical course of the rxn

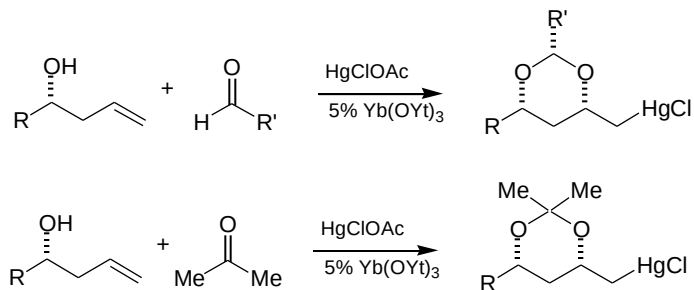
Seebach, *JACS* **1983**, 105, 7407

diastereoselection = 83 : 17 (79%)

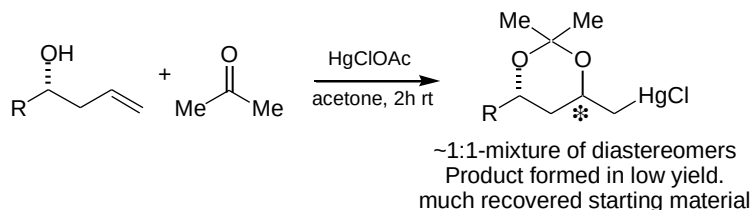
Oxymercuration via Hemiketals & Hemiacetals

J. L. Leighton et. al, *Org. Lett.* **2000**, 2, 3197-3199

■ General Reaction: diastereoselection >10:1

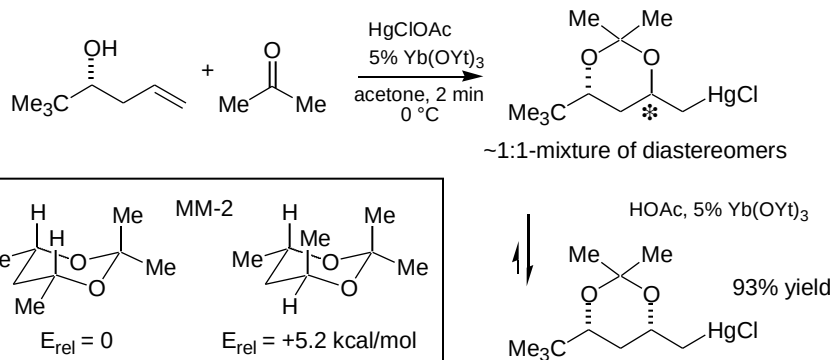


■ Mechanistic Observations:



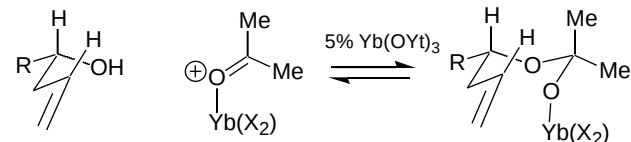
Lewis acid addends were surveyed. the logic for this step was two-fold:

- (A) Lewis acid would promote the formation of the putative hemiketal intermediate.
(B) Lewis acid would promote reversibility of the oxymercuration process

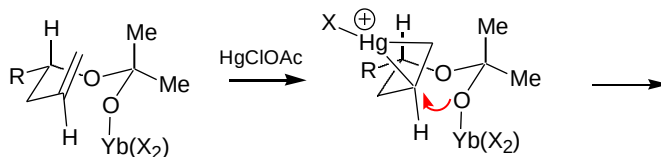
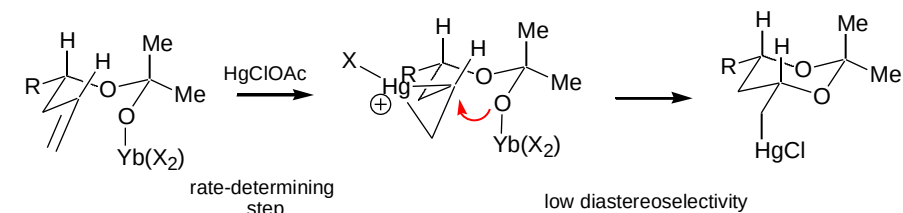


Proposed Mechanism

■ Lewis acid catalyzes formation of hemiketal

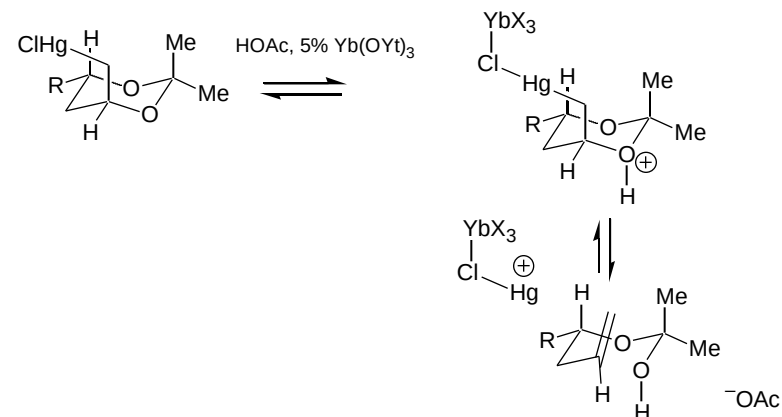


■ The Oxymercuration Step (Kinetic Phase)

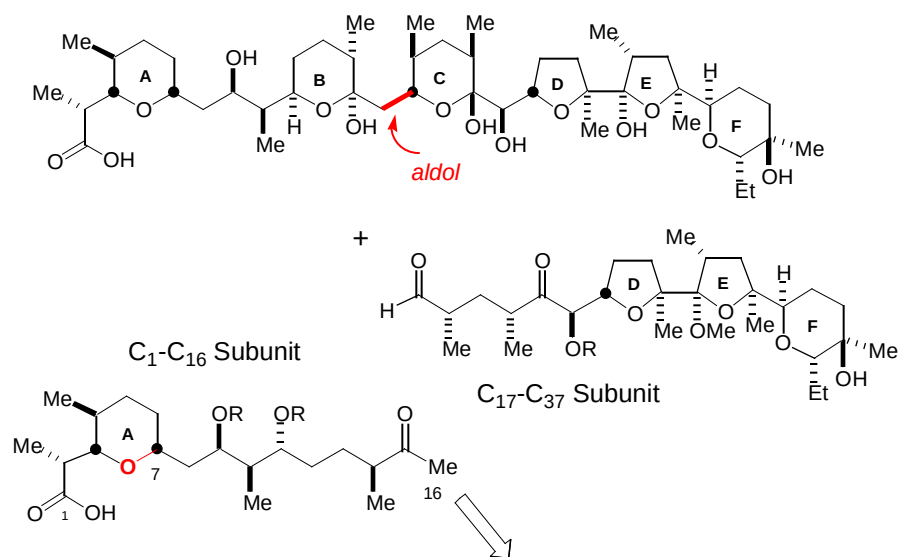


Leighton presumes that mercurium ion formation is rate-determining under kinetic conditions.

At higher temperatures and longer reaction times the products are shown to interconvert.

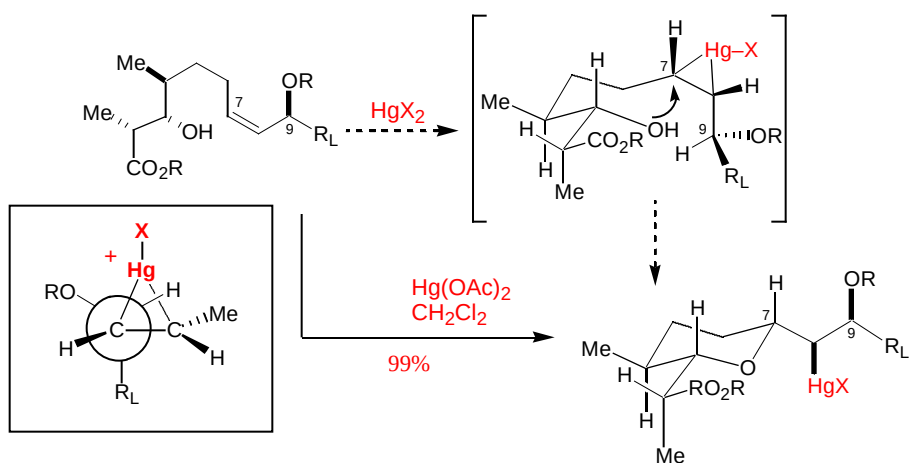


X-206 Synthesis (with S. Bender, JACS 1988, 110, 2506)

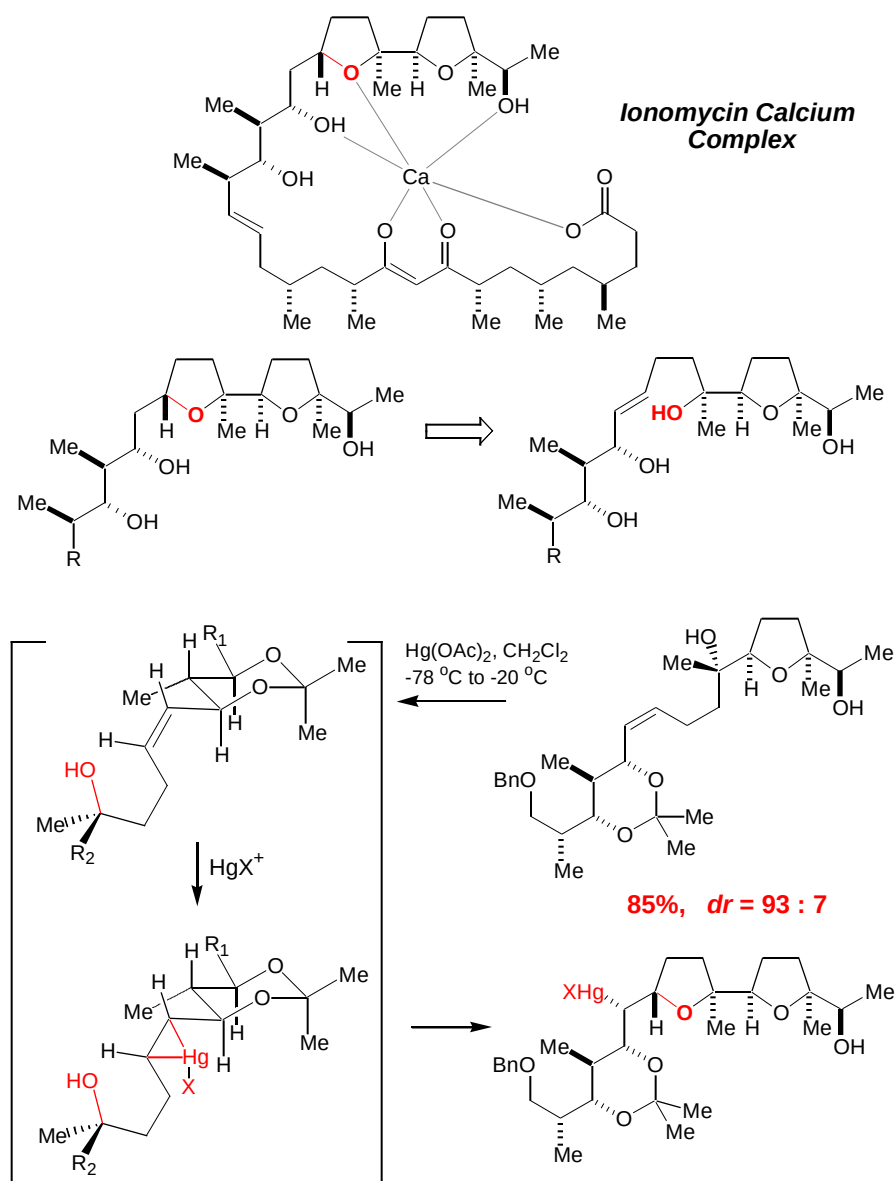


Assemblage strategy for Ring A:

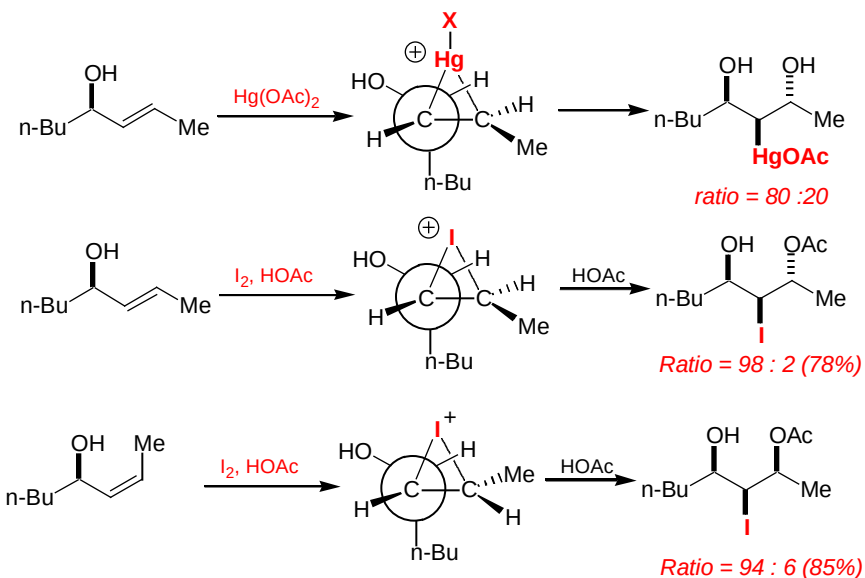
Predicted stereochemical outcome:



Lonomycin Synthesis (with Dow & Shih, JACS 1990, 112, 5290)



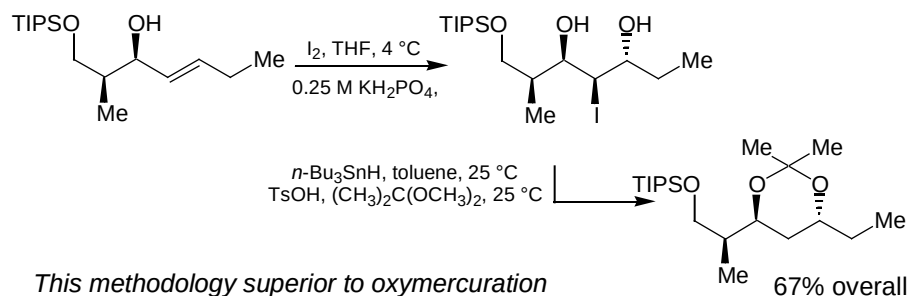
Other electrophilic olefin addition reactions afford the same stereochemical outcome



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)

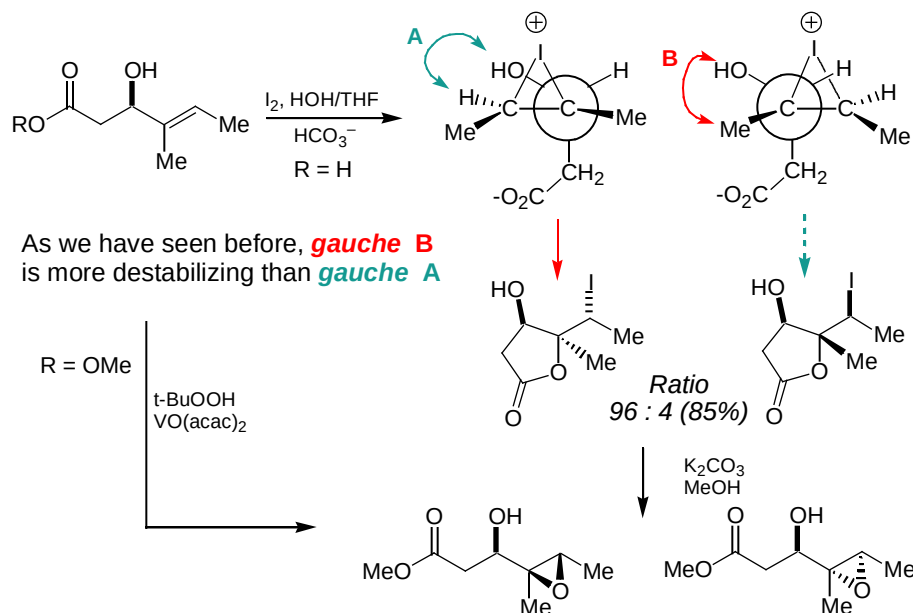


This methodology superior to oxymmercuration alternative which was evaluated first

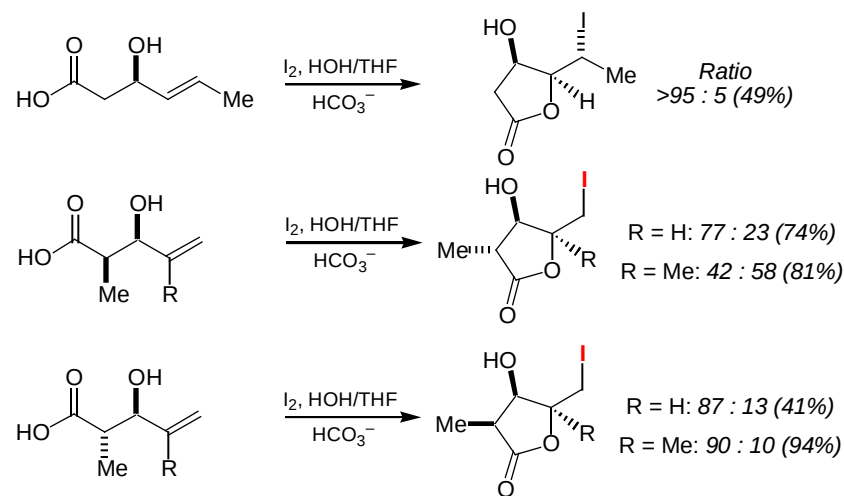
diastereoselection 96 : 4

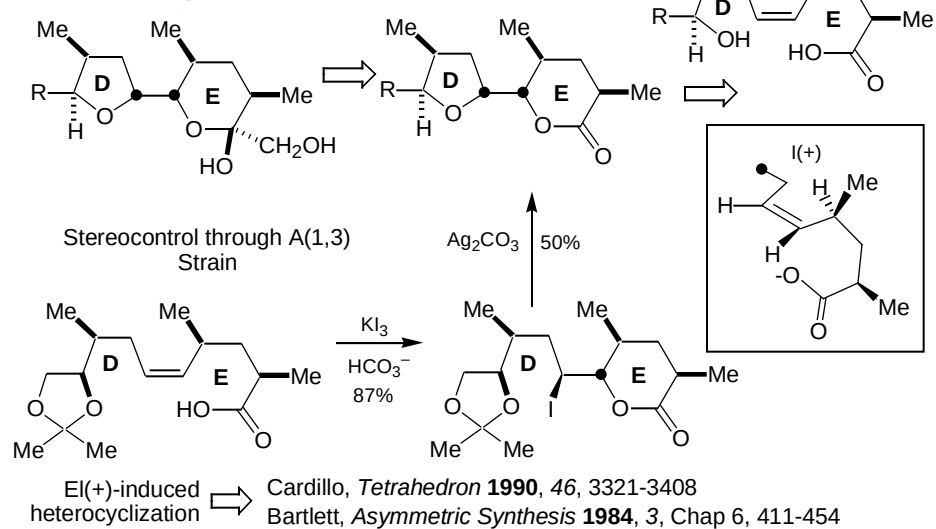
Iodine-induced lactonization is also highly stereoselective

■ Chamberlin (*JACS* **1983**, 105, 5819)

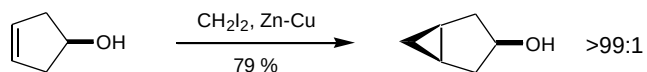


■ Other cases:



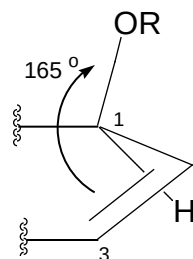
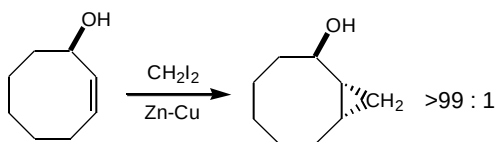
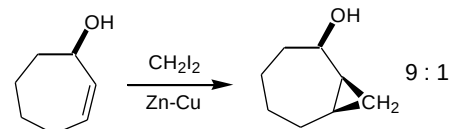
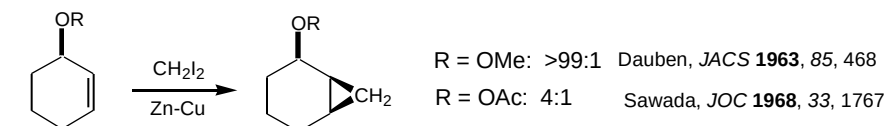


For a recent general review of the Simmons-Smith reaction see:
Charette & Beauchemin, *Organic Reactions*, **58**, 1-415 (2001)



S. Winstein, *JACS* **1959**, *81*, 6523; **1961**, *83*, 3235; **1969**, *91*, 6892

A large rate acceleration relative to simple olefins was observed.

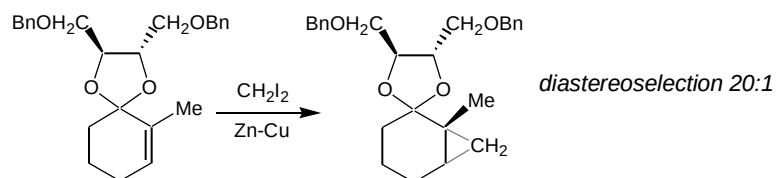


epoxidation also gives anti adduct

O-C₁-C₂-C₃ dihedral = 165 °

S. Winstein, *JACS*, **1969**, *91*, 6892

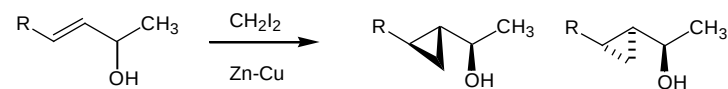
Absolute control of stereochemistry is possible through chiral ketal auxiliaries



Yamamoto, *JACS*, **1985**, *107*, 8254

Mash, *JACS*, **1985**, *107*, 8256

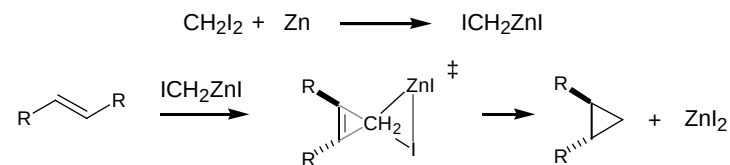
Yamamoto, *Tetrahedron*, **1986**, *42*, 6458



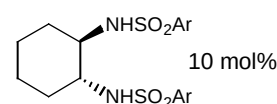
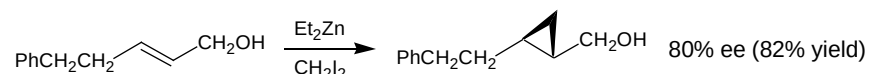
M. Pereyre and Co-workers
J. Chem. Res. (S) **1979**, 179

R	Ratio	
CH ₃	57	: 43
Et	64	: 36
tBu	67	: 33

The classical mechanism



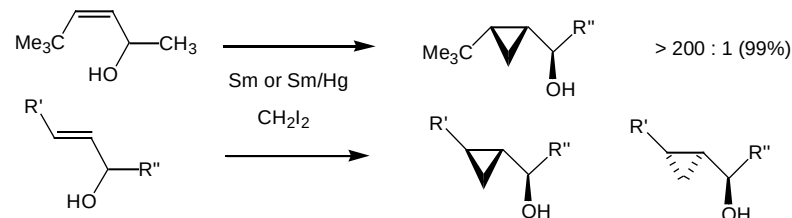
Enantioselective Simmons-Smith Variants: Kobayashi, *Tet. Let.* **1992**, *33*, 2575



These results suggest that the transition state might be binuclear.

Construct a reasonable transition structure which accommodates the data

Low-valent Samarium Variants: Molander, *JOC* **1987**, *52*, 3942

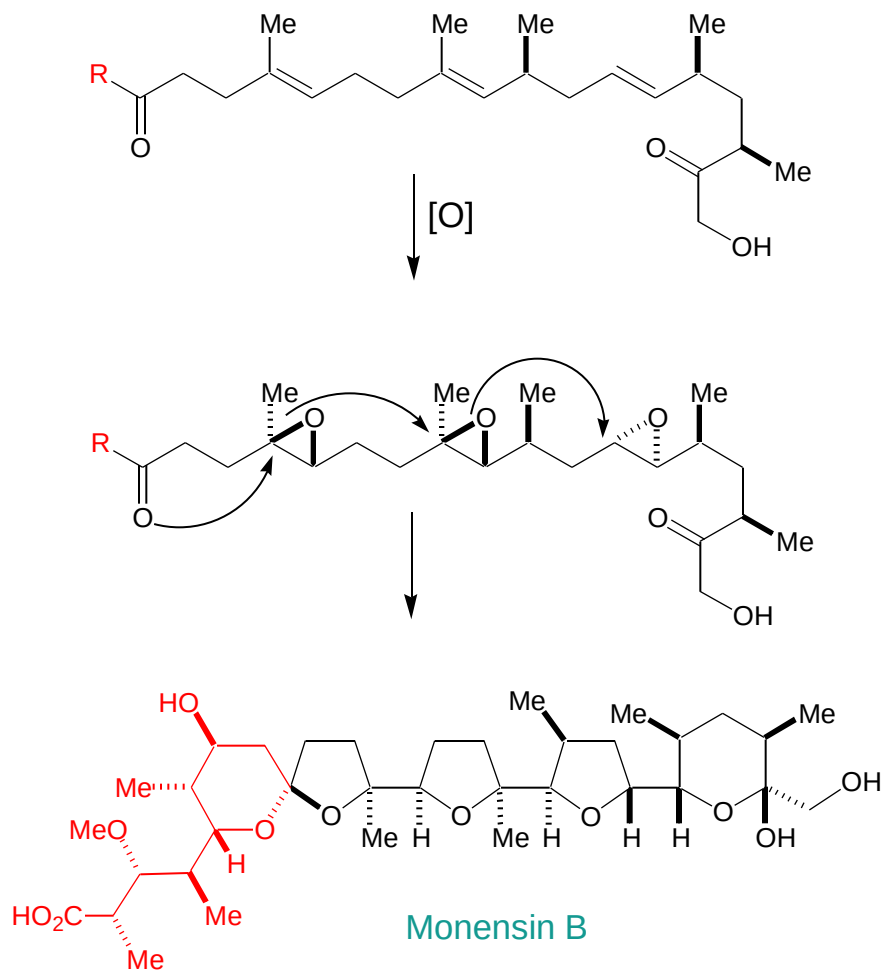


Isolated alkenes and homoallylic alcohols are inert to these reaction conditions.

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

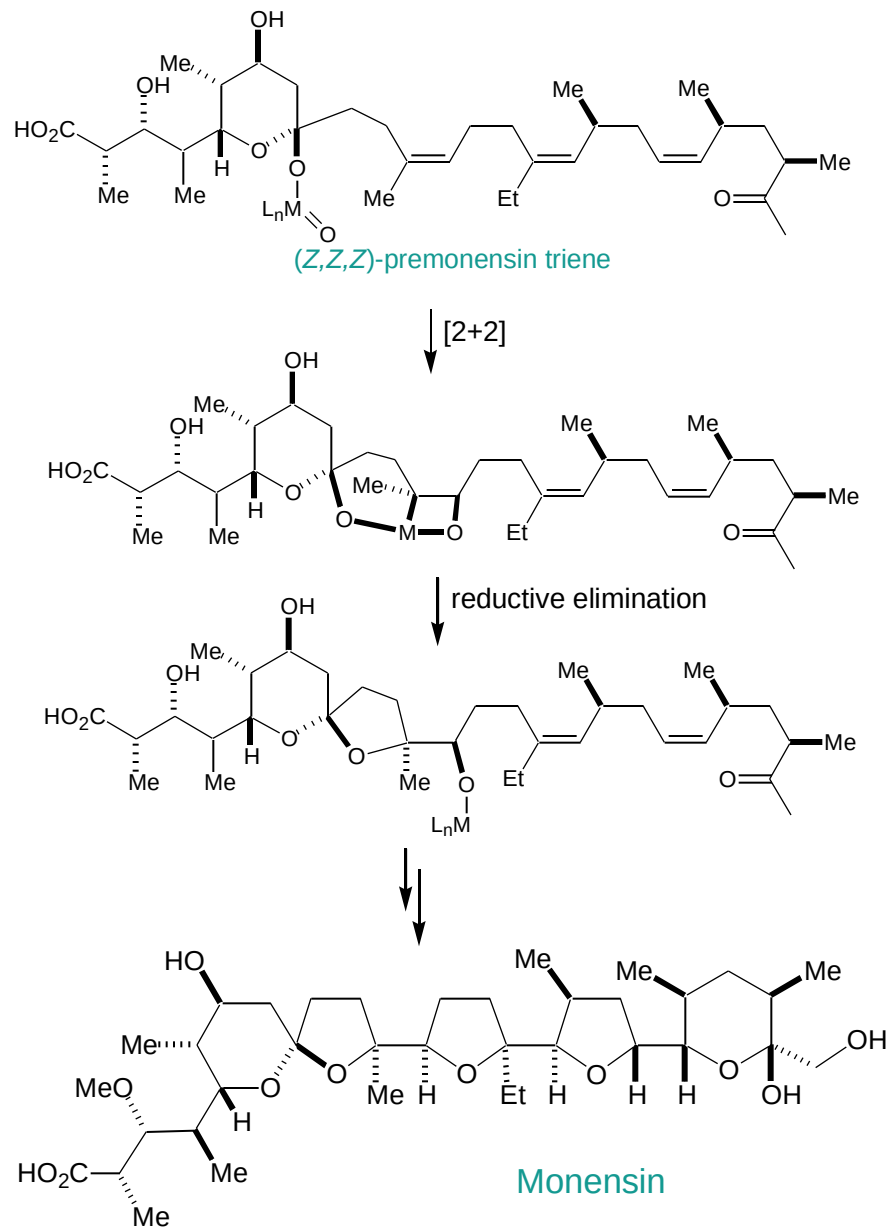
One plausible biosynthetic proposal for polyether natural products:



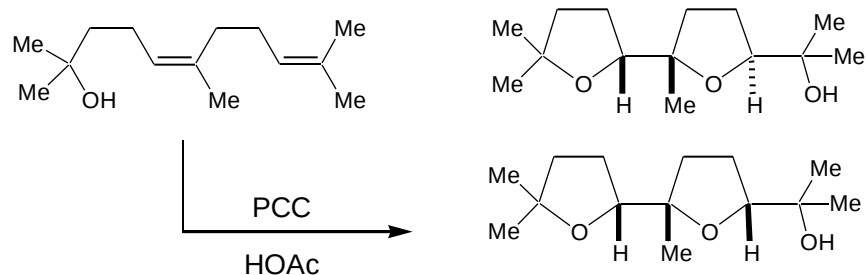
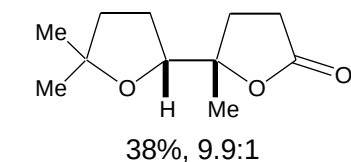
from lecture 7

Cane, D. E. *JACS*, **1983**, 105, 3394.
Cane, D. E. *JACS*, **1982**, 104, 7274.

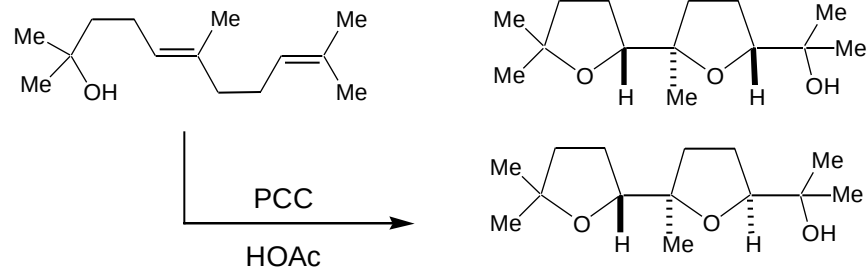
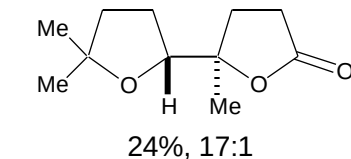
An alternate biosynthetic proposal:



Townsend, C. A.; Basak, A. *Tetrahedron*, **1991**, 47, 2591.

A biomimetic model for *syn*-oxidative polycyclization:9% combined, 11:1 (*trans*:*cis*)

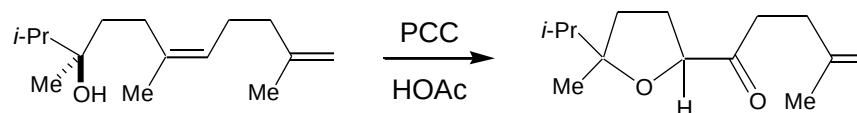
38%, 9.9:1

19% combined, 3.7:1 (*trans*:*cis*)

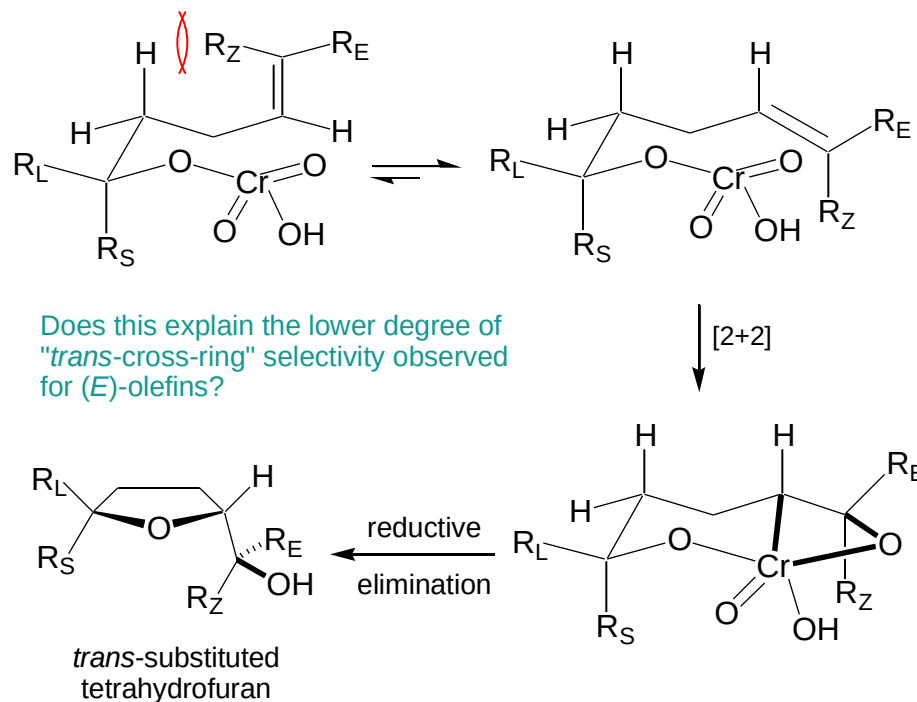
24%, 17:1

High *syn*-stereospecificity for tertiary alcohols

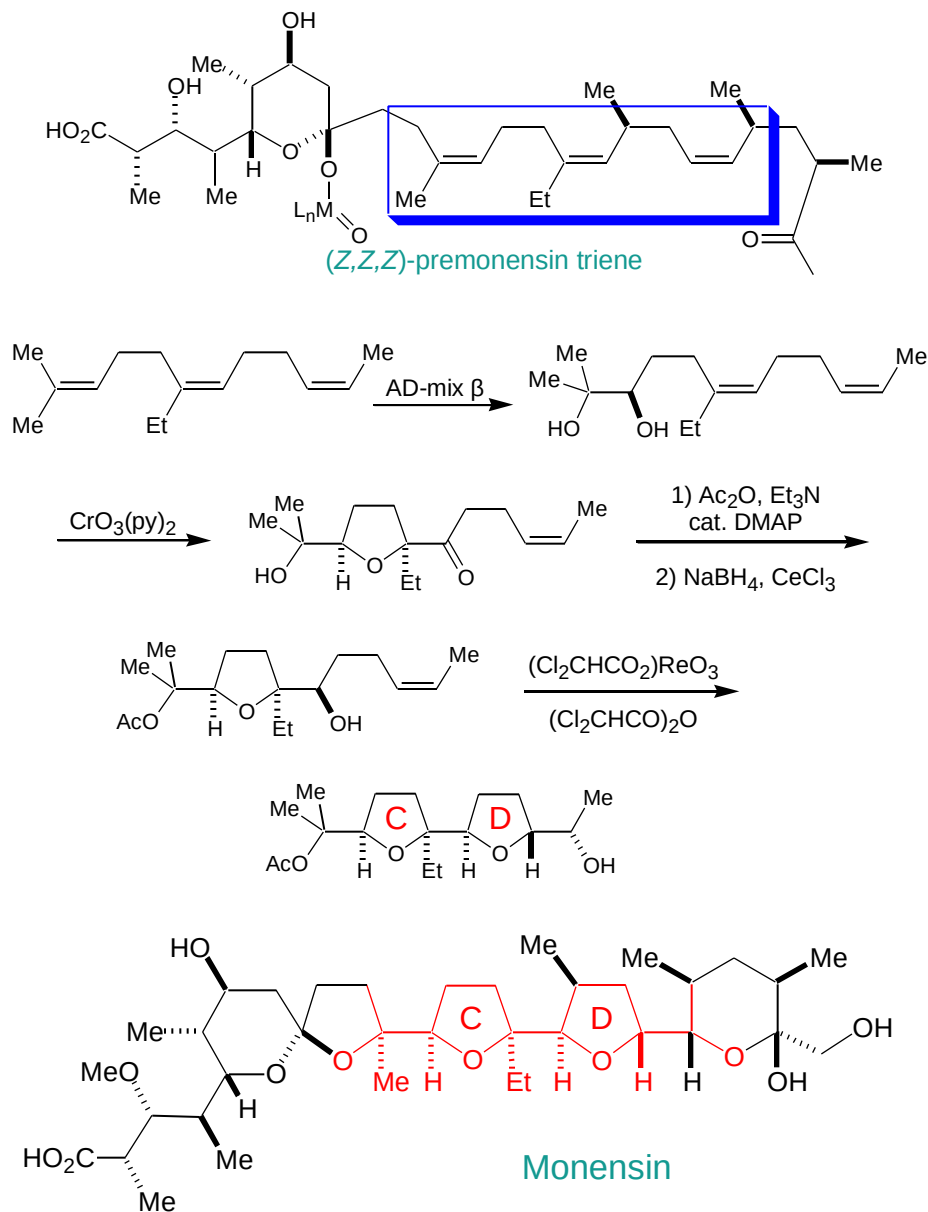
But for secondary alcohols...



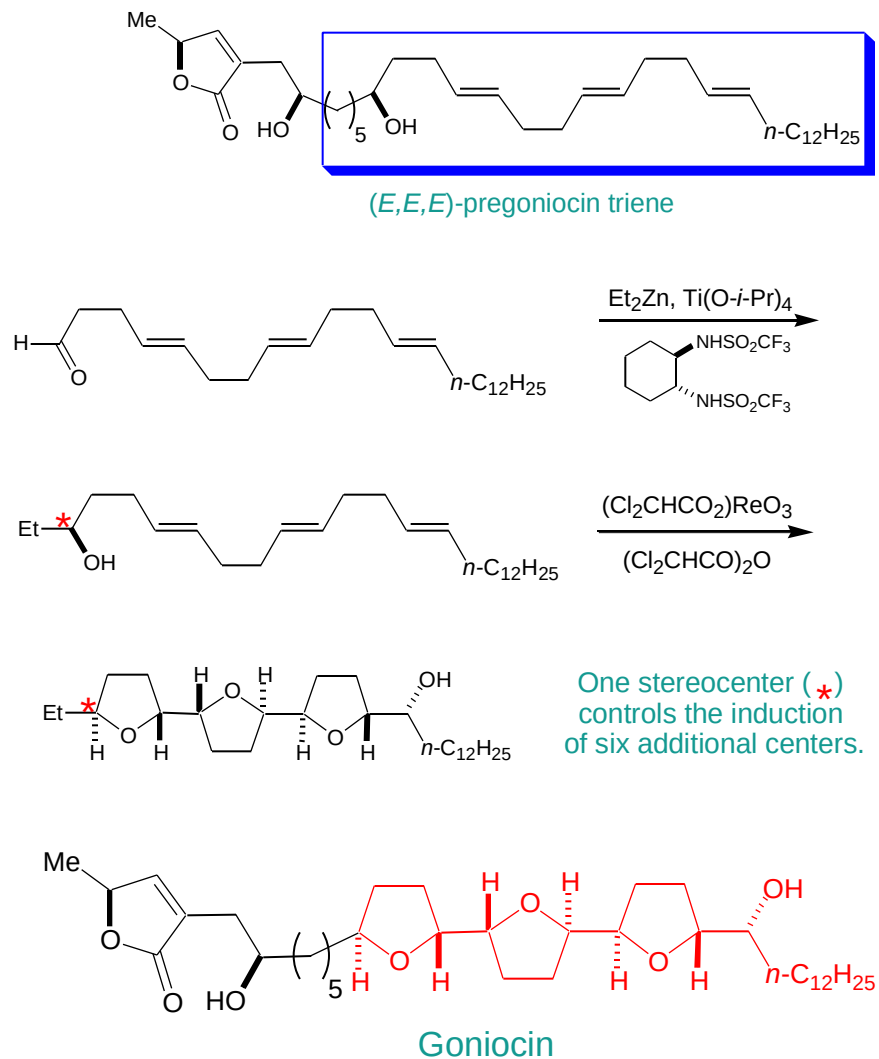
...simple oxidation occurs more rapidly than oxidative cyclization.

Conformational model for *syn*-oxidative cyclization:McDonald, F. E. JACS, **1994**, 116, 7921.

Application of the model for *syn*-oxidative polycyclization using an all (*Z*)-polyolefin:



Application of the model for *syn*-oxidative polycyclization on an all (*E*)-polyolefin:



<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

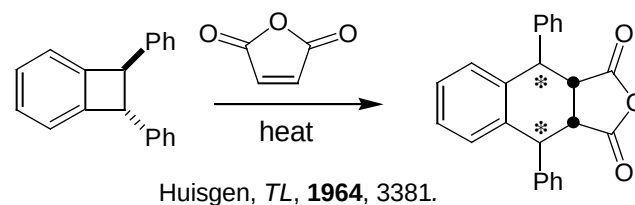
Friday,
October 11, 2002

■ Other Reading Material:

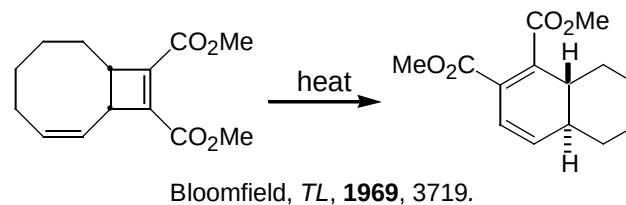
- Woodward-Hoffmann Theory
R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970.
- Frontier Molecular Orbital Theory
I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John-Wiley and Sons, New York, 1976.
- Dewar-Zimmerman Theory
T. H. Lowry 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.



Suggest a mechanism for the following reaction.



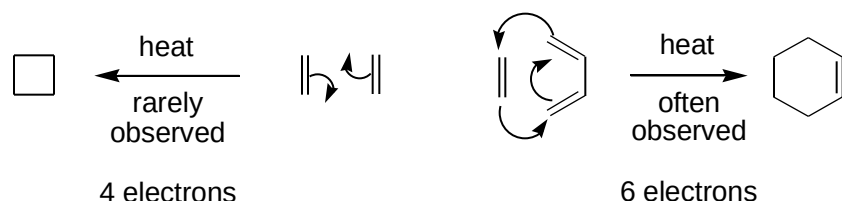
Pericyclic Reactions - Introduction/Definitions

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**.

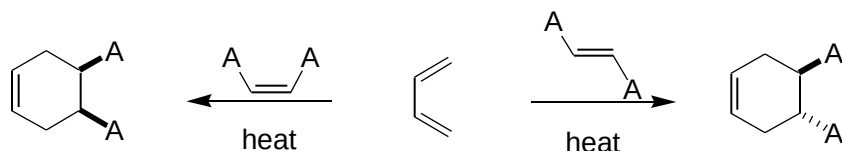
More precisely: The cyclic transition state must correspond to an arrangement of the **participating orbitals** which has to **maintain a bonding interaction** between the reaction components throughout the course of the reaction.

Some factors to consider in our analysis:

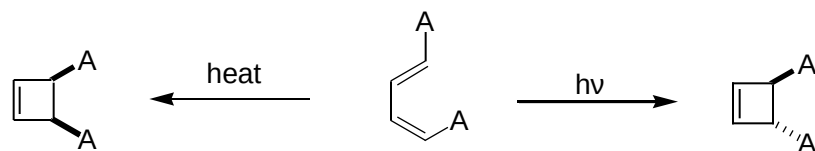
The number of electrons involved has a profound influence on reactivity:



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 is 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"

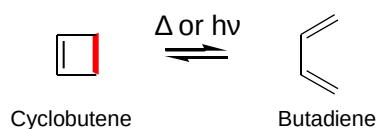
The Five Major Categories of Pericyclic Reactions

(1) ELECTROCYCLIC RING CLOSURE/RING OPENING:

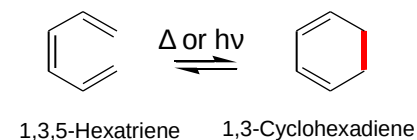
An electrocyclic ring closure is the creation of a new sigma bond at the expense of the terminal p orbitals of a conjugated pi system. There is a corresponding reorganization of the conjugated pi system. We usually classify the reaction according to the number of electrons involved.

Examples:

A 4 e⁻ electrocyclic reaction



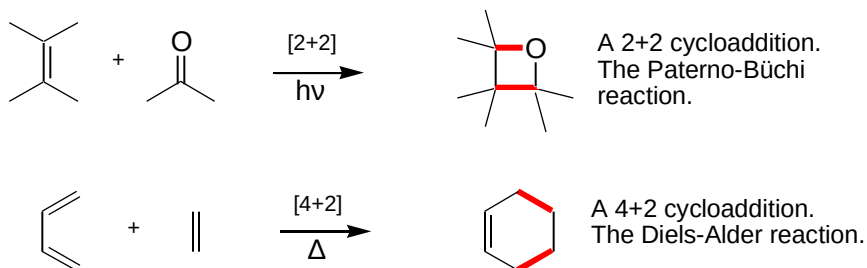
A 6 e⁻ electrocyclic reaction



(2) CYCLOADDITION REACTIONS/CYCLOREVERSION REACTIONS:

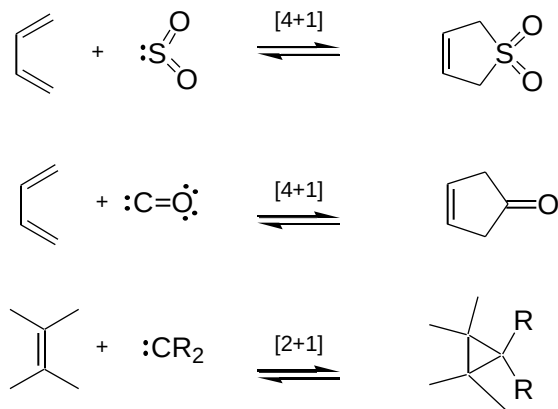
A cycloaddition reaction is the union of two smaller, independent pi systems. Sigma bonds are created at the expense of pi bonds. A cycloaddition can occur in an intramolecular sense, but it must be between two **independent** pi systems. Cycloaddition reactions are referred to as **[m + n]** additions 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:

**(3) CHELETROPIC REACTIONS:**

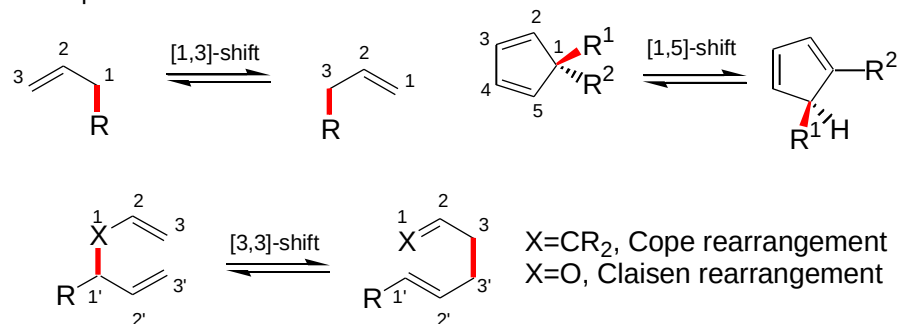
Cheletropic reactions are a special group of cycloaddition/cycloreversion reactions. Two bonds are formed or broken at a single atom. The nomenclature for cheletropic reactions is the same as for cycloadditions.

Examples:

**(4) SIGMATROPIC REARRANGEMENTS:**

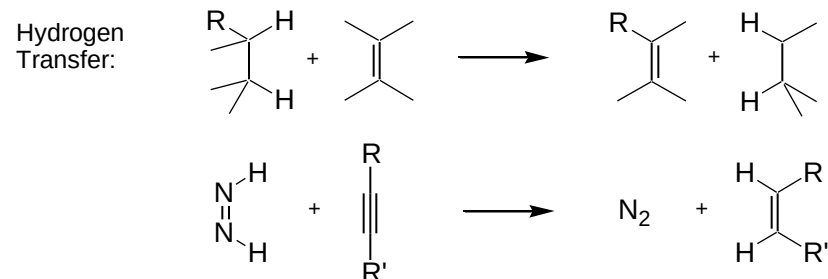
A sigmatropic rearrangement is the migration of a sigma bond from one position in a conjugated system to another position in the system, accompanied by reorganization of the connecting pi bonds. The number of pi and sigma bonds remains constant. The rearrangement is an **[m,n]** shift when the sigma bond migrates across **m** atoms of one system and **n** atoms of the second system.

Examples:

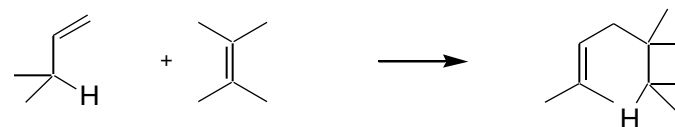
**(5) GROUP TRANSFER REACTIONS:**

In a group transfer reaction one or more groups get transferred to a second reaction partner.

Examples:



Ene Reaction:



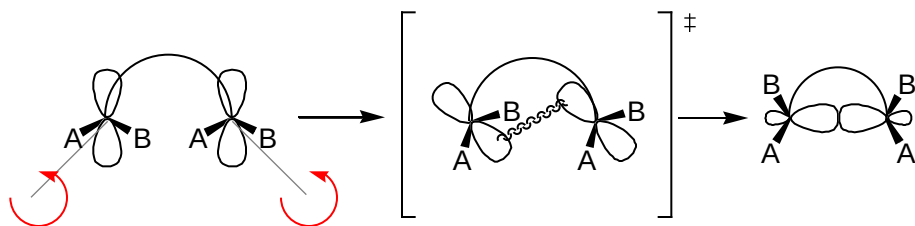
ELECTROCYCLIC RING CLOSURE/RING OPENING:

The Stereochemical issues:

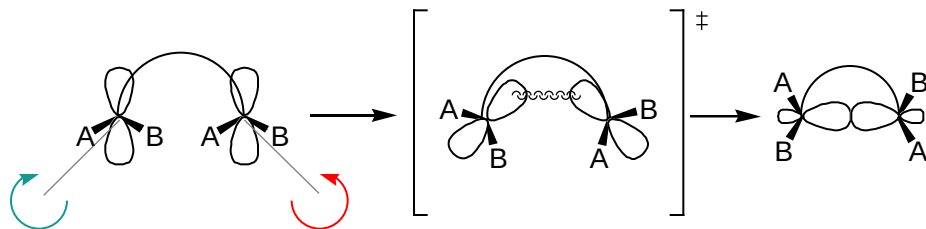
Ring closure can occur in two distinct ways. This has consequences with regard to:

- The orbital lobes that interact
- The disposition of substituents on the termini

Conrotatory Closure: The termini rotate in the **same direction**

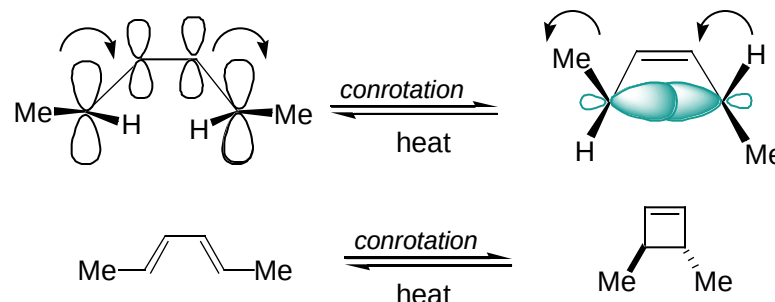


Disrotatory Closure: The termini rotate in **opposite directions**

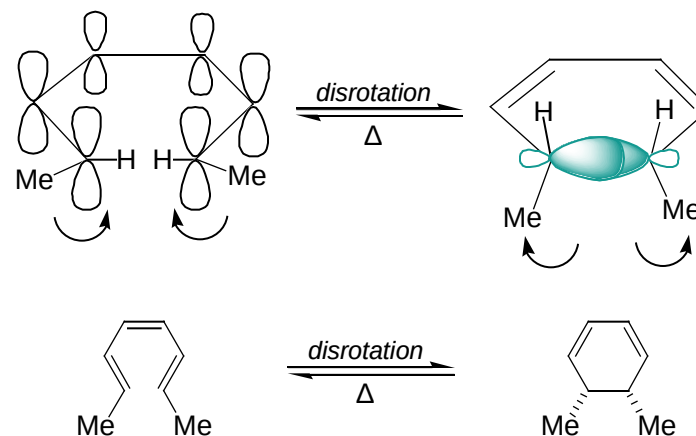
**Empirical Observations:**

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.)

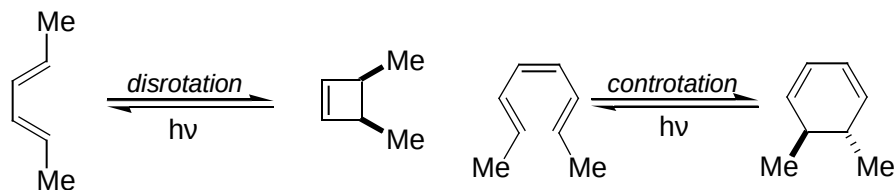
Butadiene to cyclobutene: A 4-electron ($4q$) system

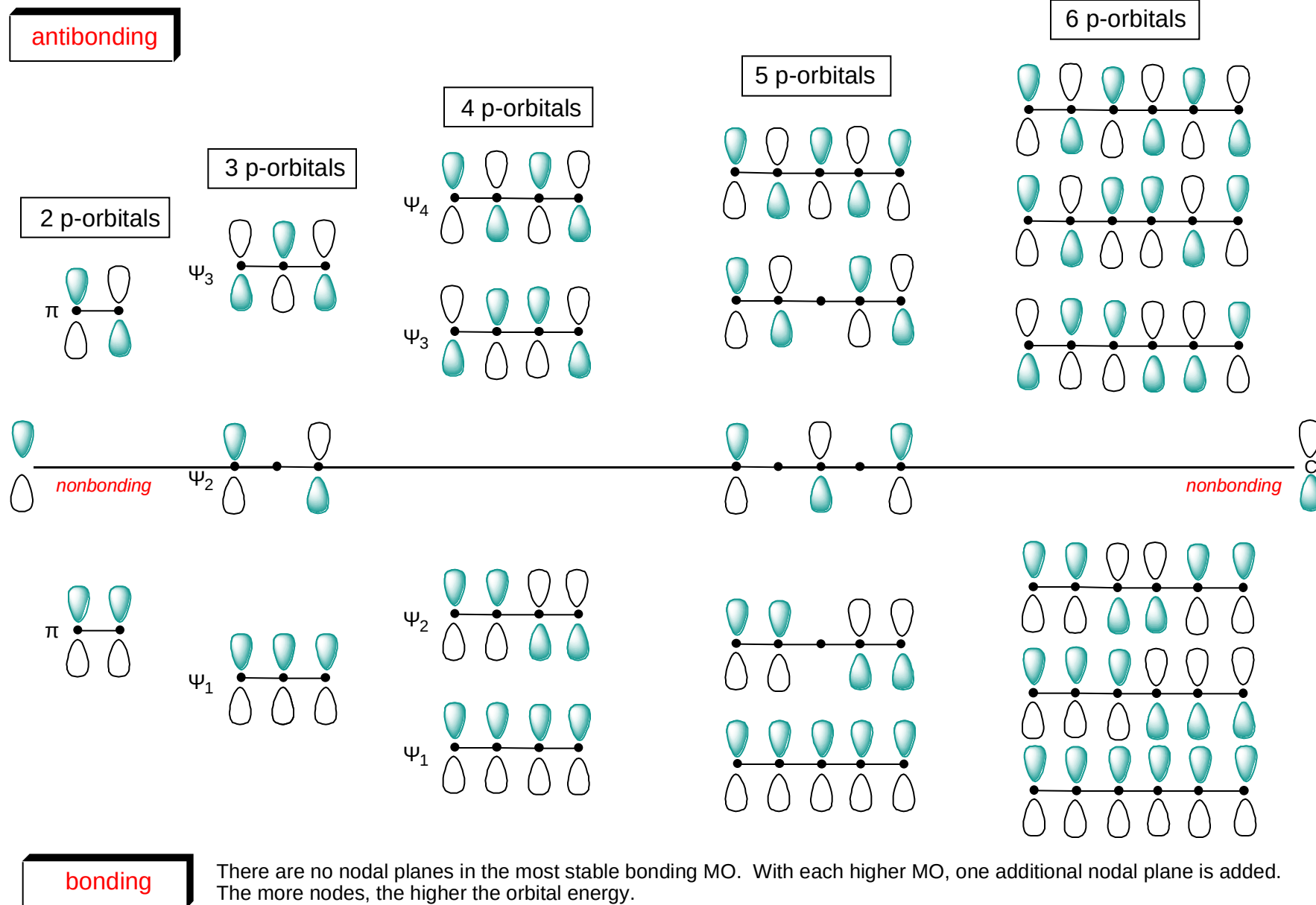


Hexatriene to cyclohexadiene: A 6-electron ($4q+2$) system



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.



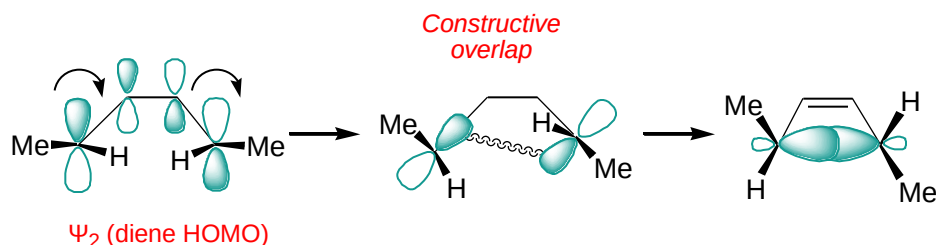


FMO Treatment of Electrocyclic reactions.

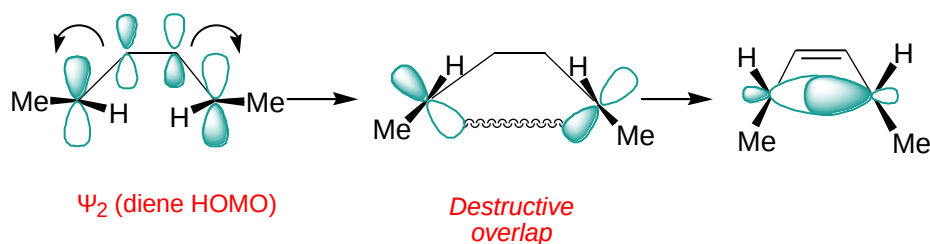
- Examine the interactions that occur in the HOMO as the reaction proceeds.
- If the overlap is constructive (i.e. of the same phase) then the reaction is "allowed."
- If the overlap is destructive (i.e. of different phases) then the reaction is "forbidden."

Thermal Activation:

Conrotatory Closure: (Allowed and observed)



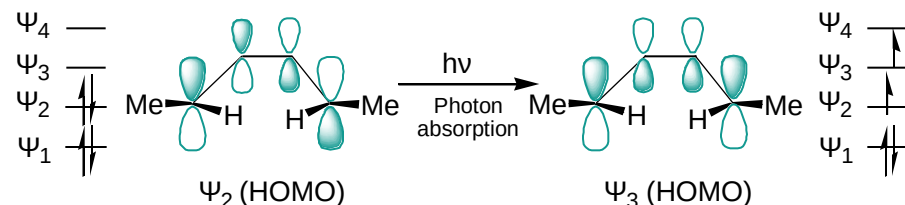
Disrotatory Closure: (Forbidden and not observed)



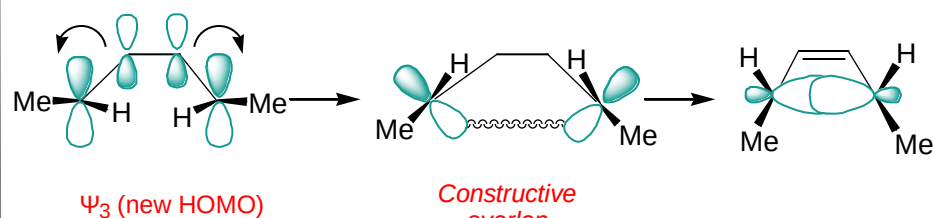
A similar analysis for the hexatriene system proves that under thermal conditions, disrotation is allowed and conrotation is forbidden.

Photochemical Activation:

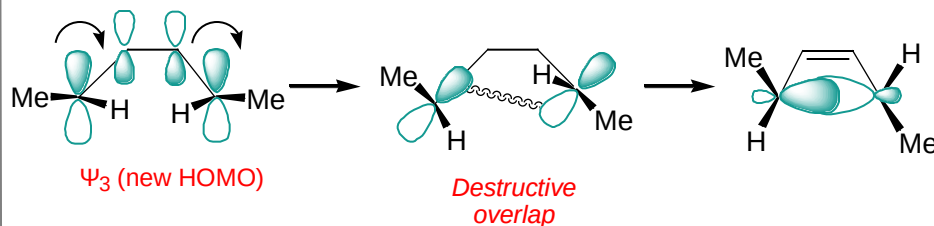
When light is used to initiate an electrocyclic reaction, an electron is excited from Ψ_2 to Ψ_3 . Treating Ψ_3 as the HOMO now shows that disrotatory closure is allowed and conrotatory closure is forbidden.



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 reversibility** says that if the reaction is allowed in one direction, it must be allowed in the other direction.

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.

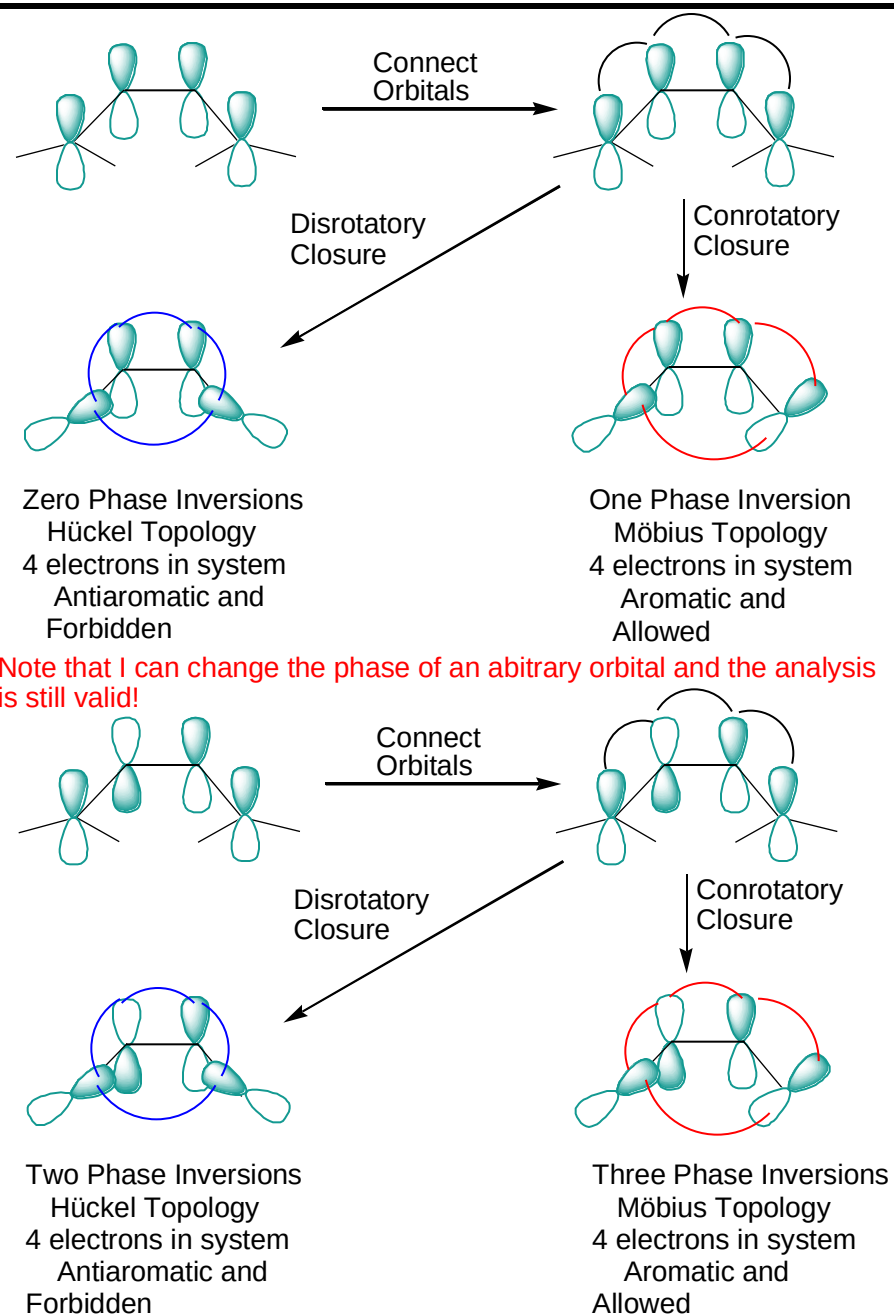
Using the Dewar-Zimmerman model:

- 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	$4q$	$4q + 2$

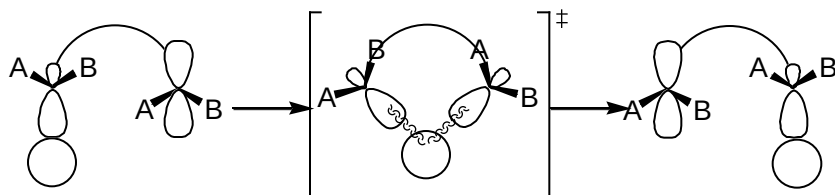
- If the transition state is **aromatic**, then the reaction will be allowed **thermally**. If the transition state is **antiaromatic**, then the reaction will be allowed **photochemically**.



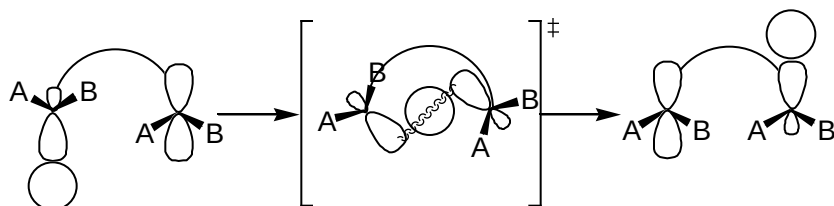
The Stereochemical issues:

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.

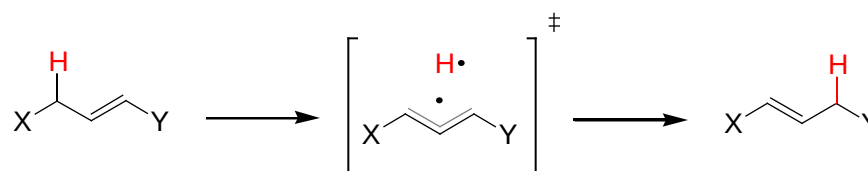
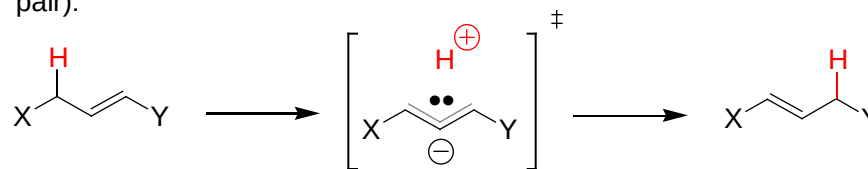
■ If the overlap is constructive at both termini then the reaction is allowed. If the overlap is destructive at either terminus then the reaction is forbidden.

■ If the migrating atom is carbon, then we can also entertain the possibility of the alkyl group migrating with inversion of configuration (antarafacial on the single atom).

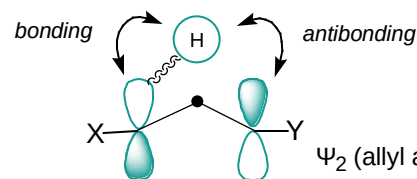
■ If the migrating atom is hydrogen, then it cannot migrate with inversion.

■ [1,3] Sigmatropic Rearrangements (H migration)

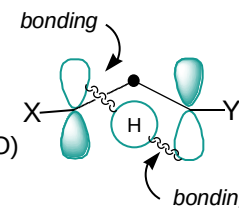
■ Construct TS by considering an allyl anion and the proton (or radical pair):



Proton 1S (LUMO)



Suprafacial Geometry



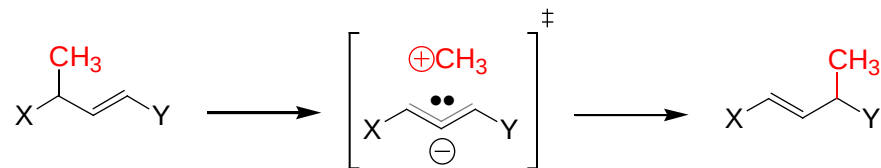
Antarafacial Geometry

■ 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.

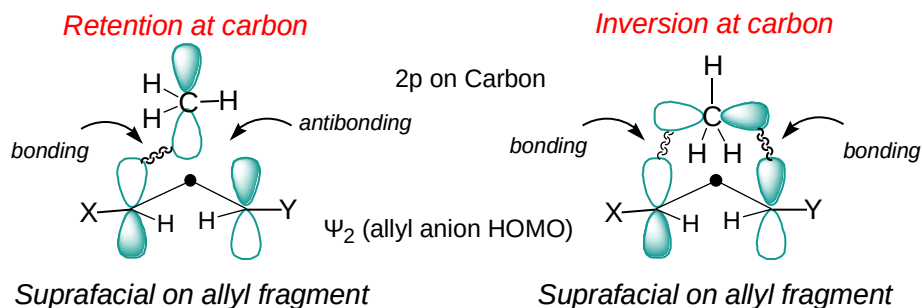
■ The suprafacial migration is forbidden and the bridging distance too great for the antarafacial migration. Hence, [1,3] hydrogen migrations are not observed under thermal conditions.

■ 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:



■ 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.

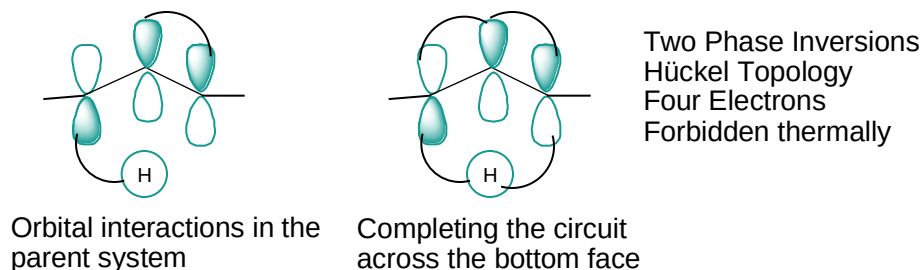
■ The stereochemical constraints on the migration of carbon with inversion of configuration is highly disfavored on the basis of strain. Such rearrangements are rare and usually only occur in highly strained systems.

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.

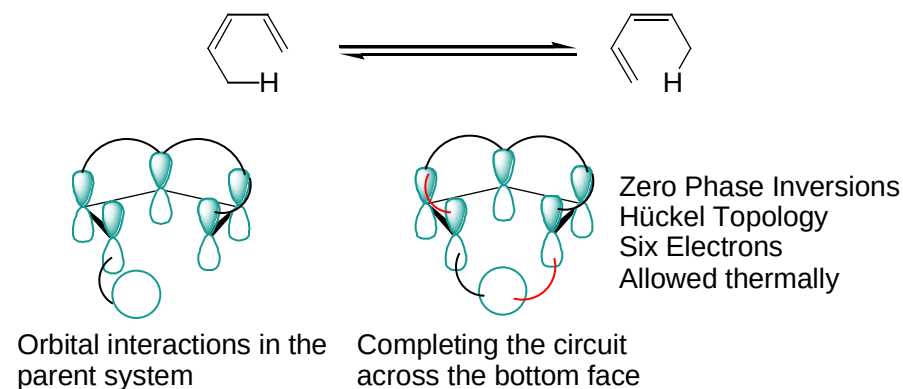
■ Sigmatropic Rearrangements: Dewar-Zimmerman

Dewar-Zimmerman also predicts the [1,3] suprafacial migration to be forbidden.

The basis set of s and p orbitals with arbitrary phase:

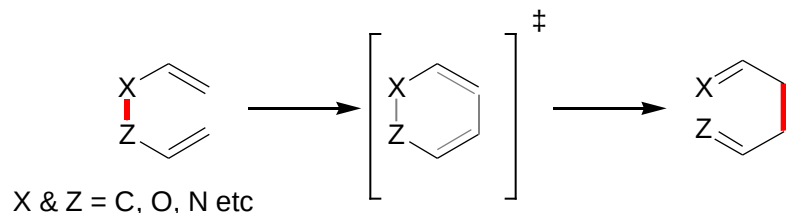


The [1,5] shift of a hydrogen atom across a diene.



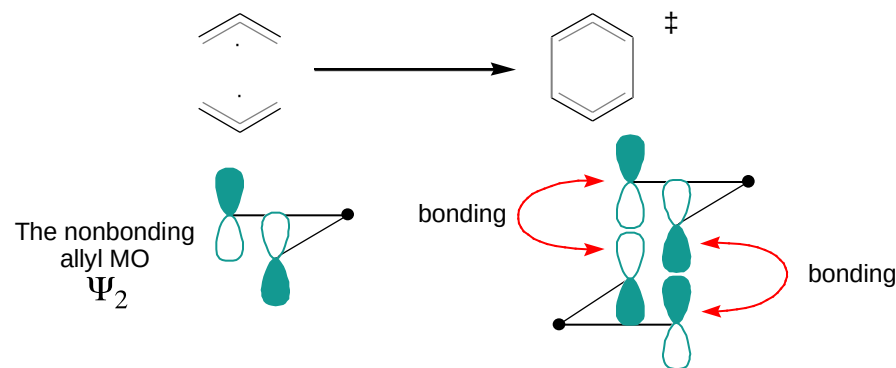
[3,3] Rearrangements:

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.

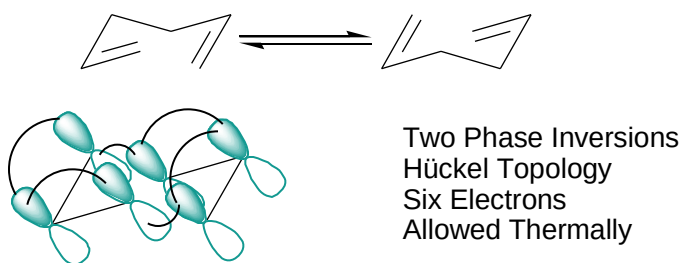


The FMO Analysis:

Bring two Allyl radicals together to access for a possible bonding interaction between termini.



The Dewar-Zimmerman Analysis:



■ 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, it's just a convenient way to rederive predictions without memorizing a table of selection rules.

An Example:

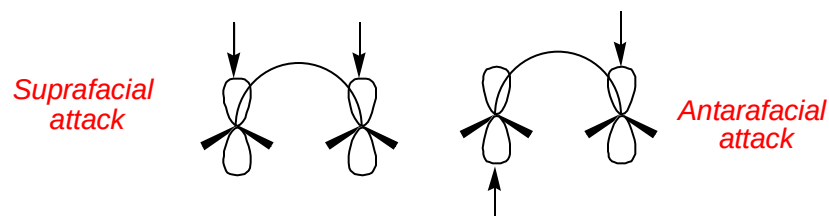
Take the [1,3] sigmatropic rearrangement of an alkyl group. We know this is forbidden under thermal conditions in a supra-supra manner, and so we make it the first entry in the table.

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?

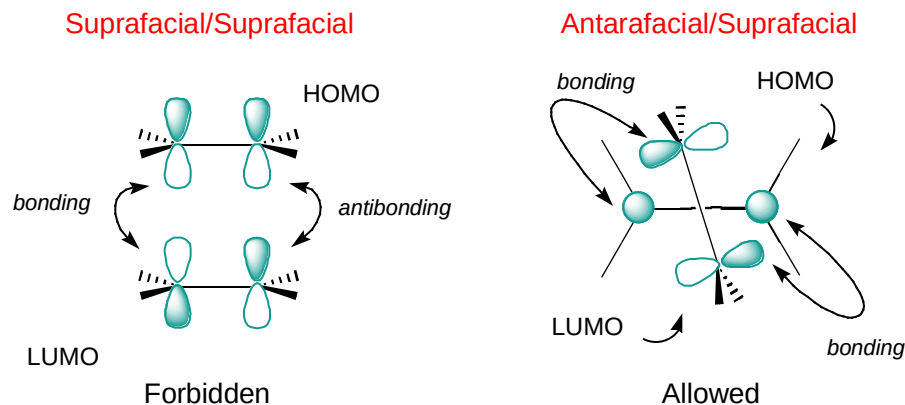
The Stereochemical issues:

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

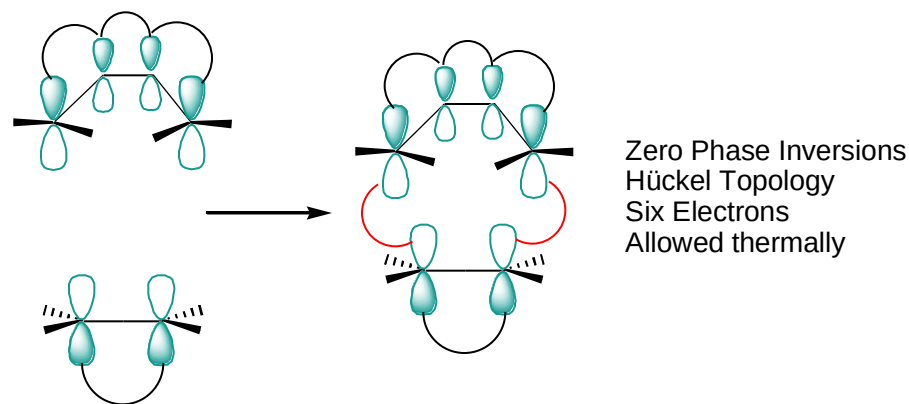
For the [2+2] cycloaddition two different geometries have to be considered.



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.



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

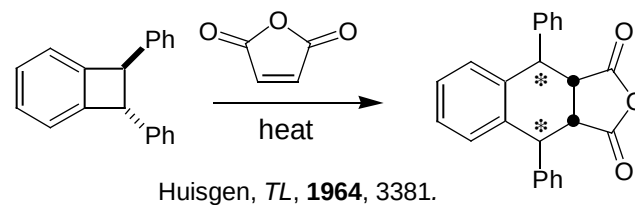
Monday,
Columbus Day,
October 14, 2002

■ Other Reading Material:

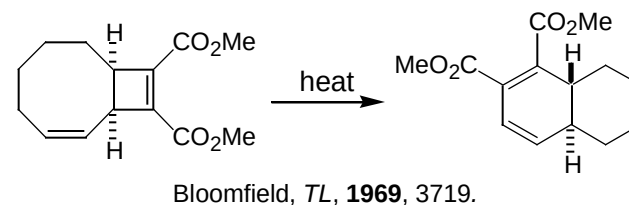
- Woodward-Hoffmann Theory
R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970.
- Frontier Molecular Orbital Theory
I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John-Wiley and Sons, New York, 1976.
- Dewar-Zimmerman Theory
T. H. Lowry 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.



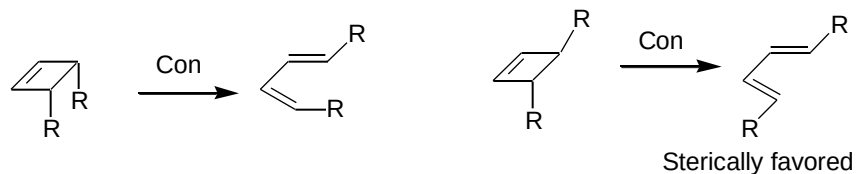
Suggest a mechanism for the following reaction.



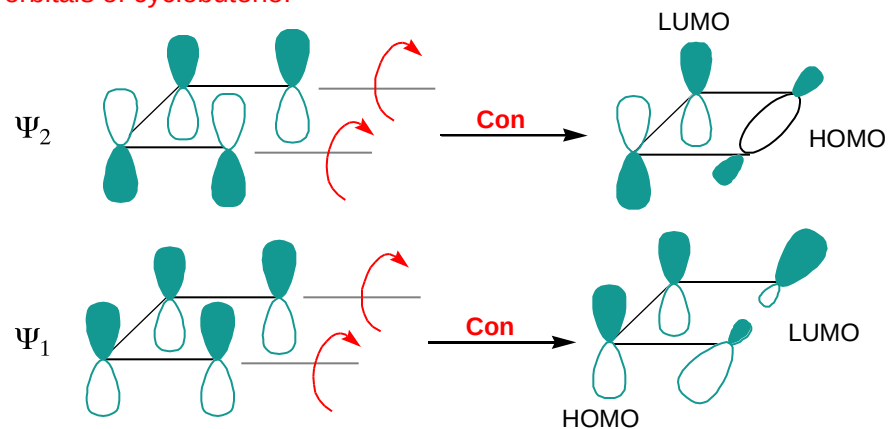
Electrocyclic Reaction - Selection Rules

	Ground State (Thermal process)	Excited State (Photochemical Process)
$4n \pi e^-$ ($n = 1, 2, \dots$)	conrotatory	disrotatory
$4n+2 \pi e^-$ ($n = 0, 1, 2, \dots$)	disrotatory	conrotatory

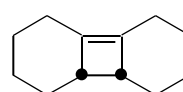
Examples	Ground State	Excited State
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory



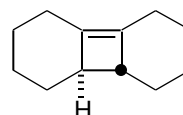
Controtation Ψ_1 and Ψ_2 on to the indicated bonding and anti-bonding orbitals of cyclobutene:



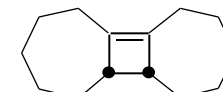
Activation Energy (kcal/mol)
for electrocyclic ring opening



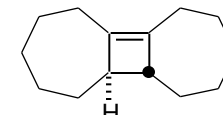
42



29

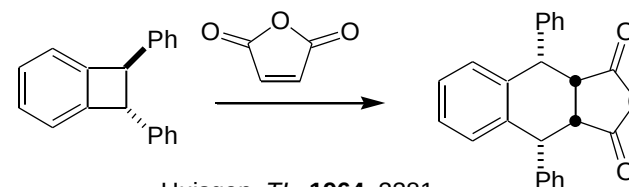
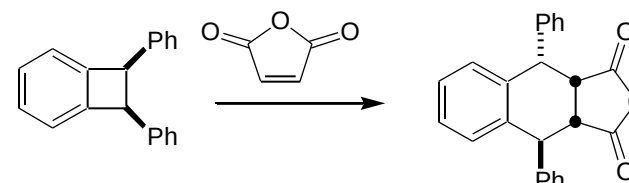


45



27

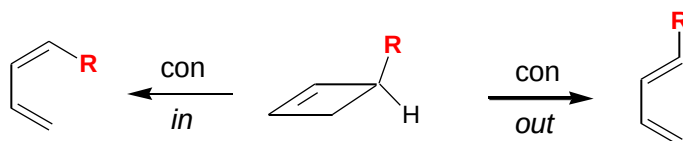
Criegee, *Chem. Ber.* **1968**, 101, 102.



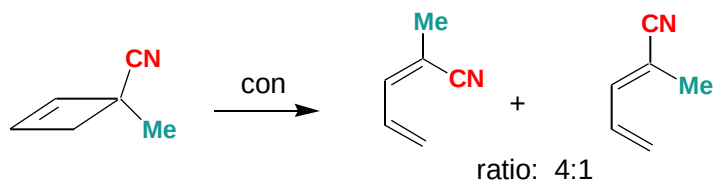
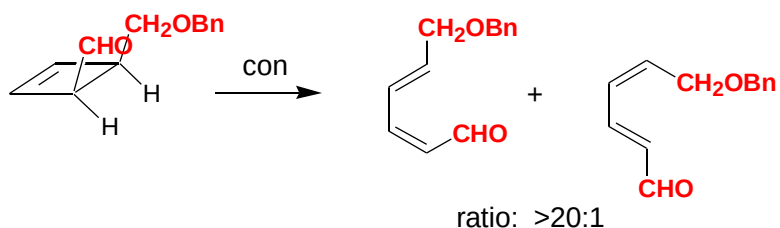
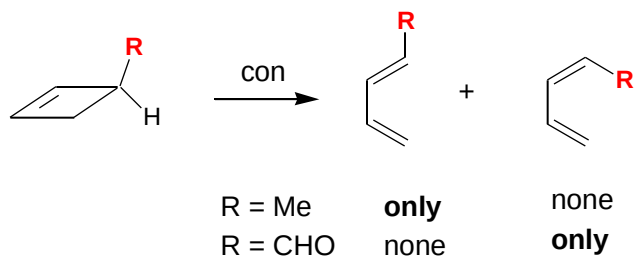
Huisgen, *TL*, **1964**, 3381.

Torquoselectivity is defined as the predisposition of a given R substituent for a given conrotatory motion

Houk et al. *Acc. Chem. Res.* **1996**, 29, 471

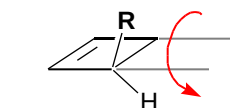
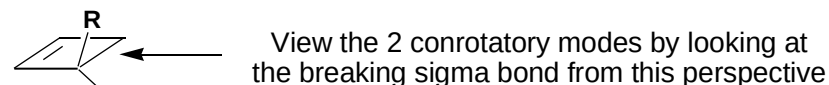


Examples: Donor substituents prefer con-out mode
Pi acceptor substituents prefer con-in mode

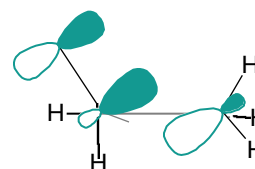


How do we explain?

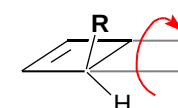
Donor substituents prefer con-out mode
Pi acceptor substituents prefer con-in mode



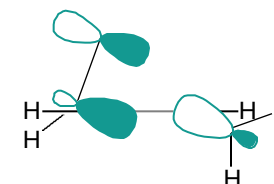
Outward Motion



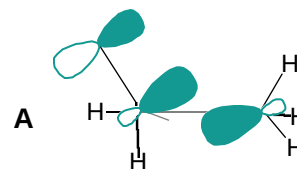
LUMO + p



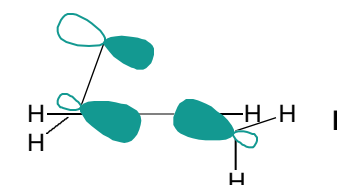
Inward Motion



LUMO + p



HOMO + p



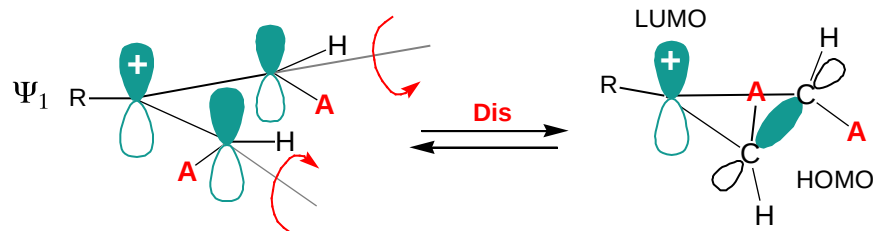
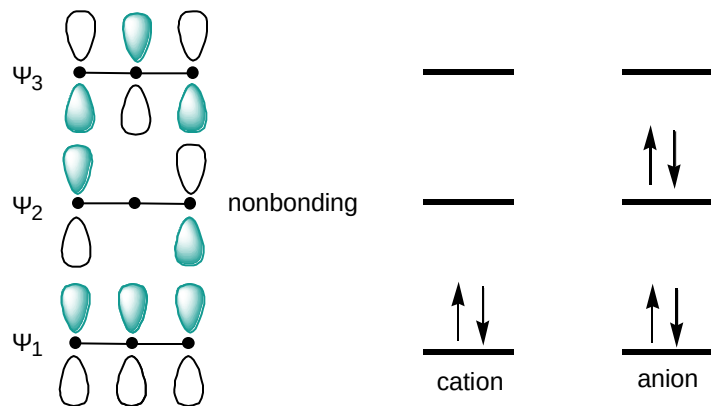
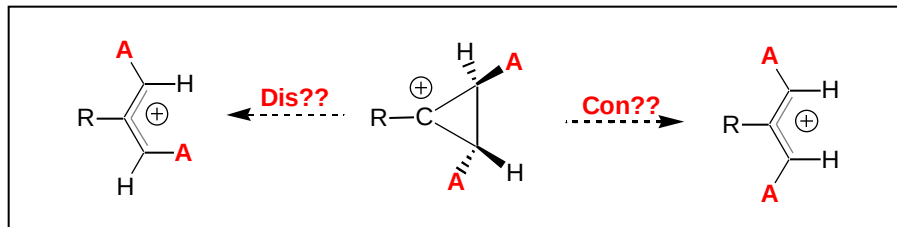
HOMO + p

destabilizing 4 electron
interaction for donor
substituents

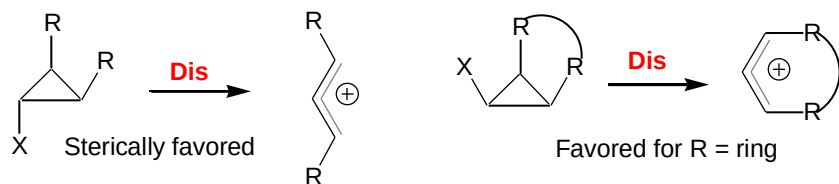
As conrotation begins the energy of the breaking sigma bond rises steeply. Hyperconjugation with a pi* orbital, while possible in both **A** & **B**, is better in **B**. (Houk)

stabilizing 2 electron
interaction for acceptor
substituents

Three-Atom Electrocyclizations (2 electrons)

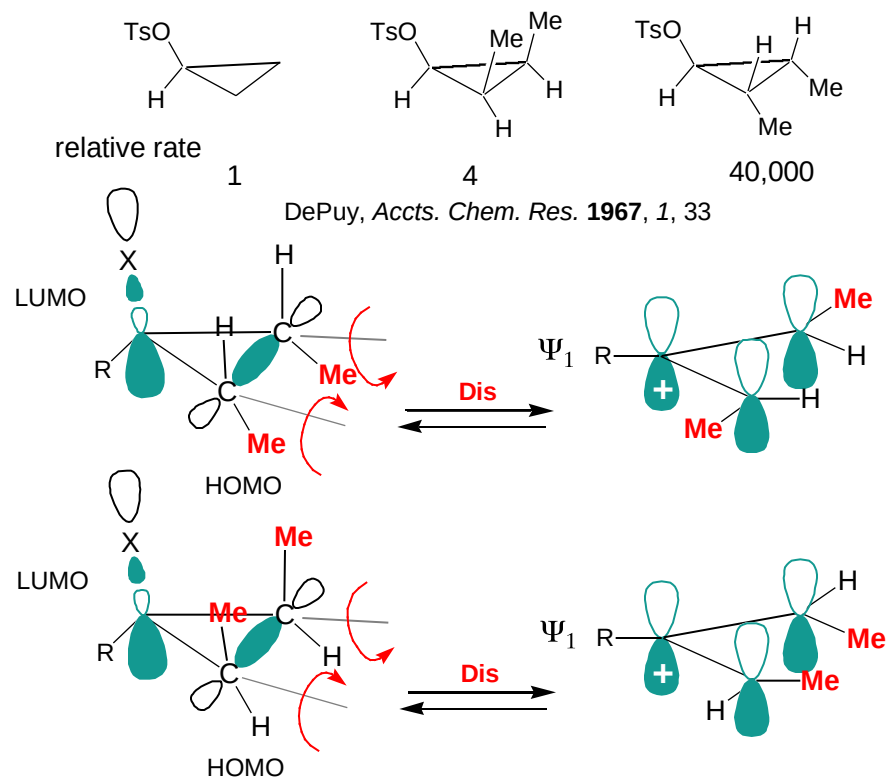
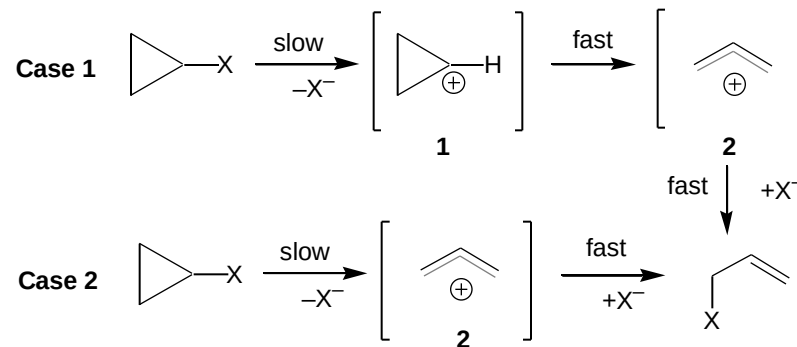


Note that there are two disrotatory modes

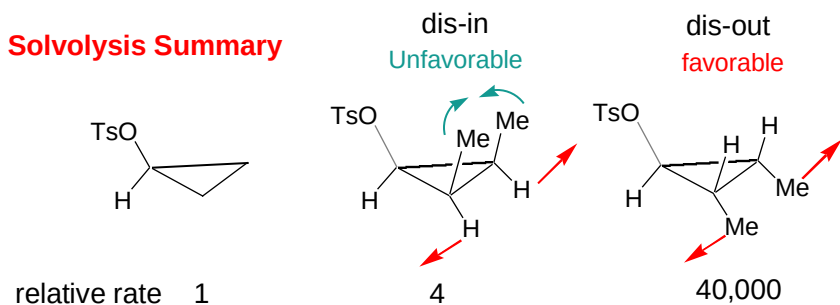


Solvolysis of Cyclopropyl Derivatives

Does solvolysis proceed via cation **1** followed by rearrangement to **2** (Case 1), or does it proceed directly to **2** (Case 2)?

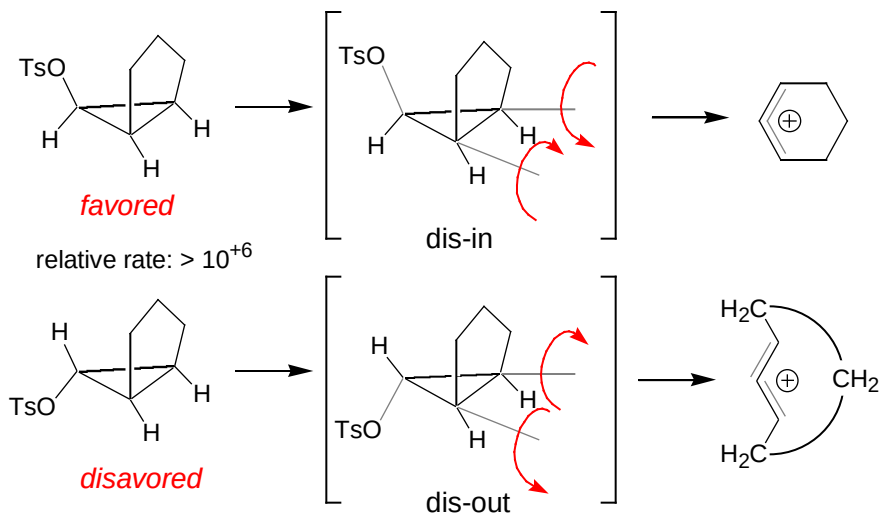


Solvolysis Summary

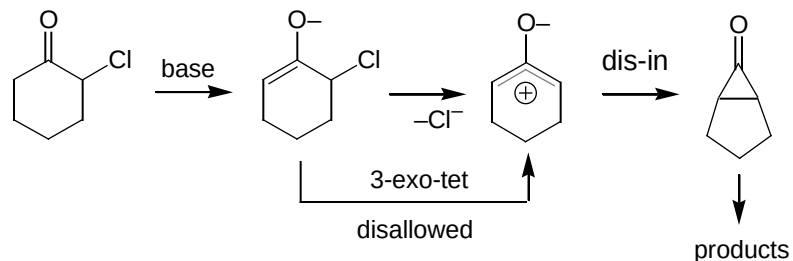


Ring-fused Cyclopropyl Systems

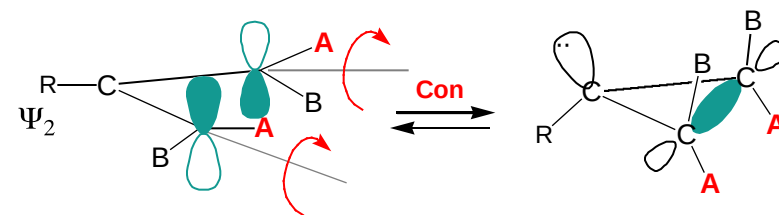
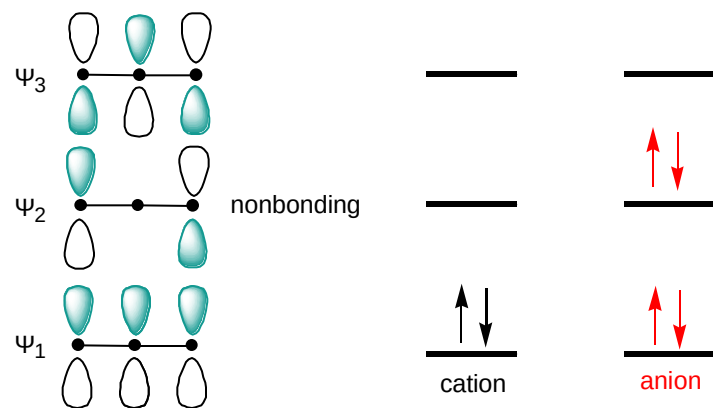
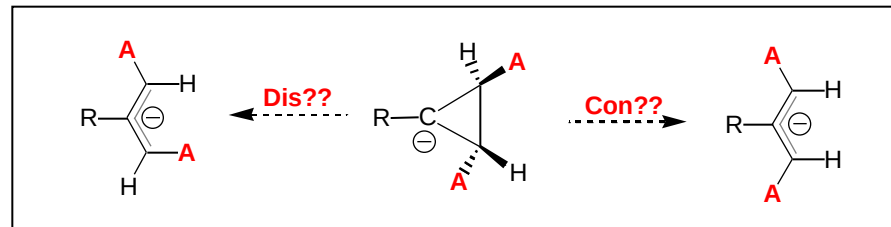
When the cis substituents on the cyclopropyl ring are tied together in a ring the following observations have been made



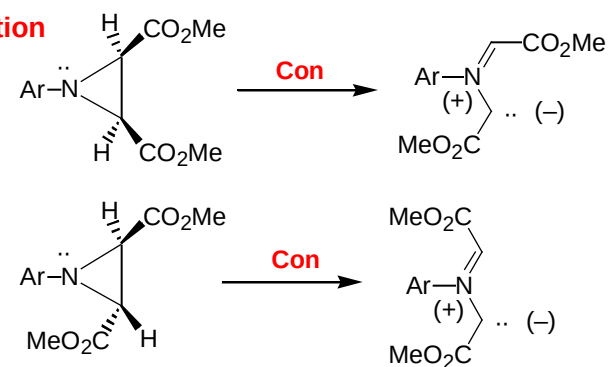
Revisiting the Favorski rearrangement: (Carey, Part A, pp 506-8)



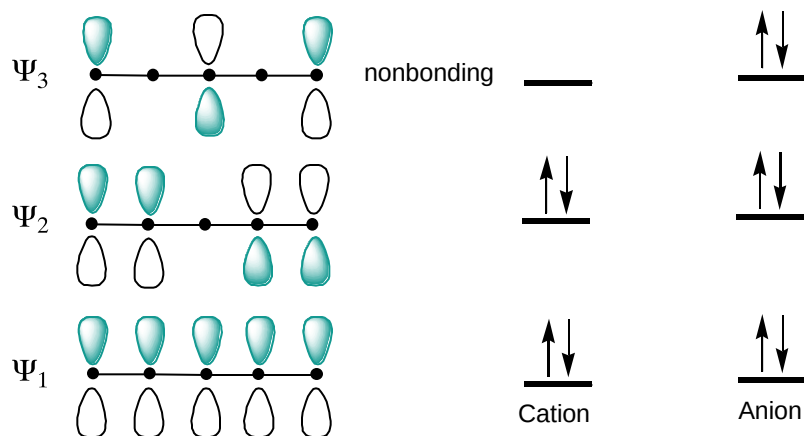
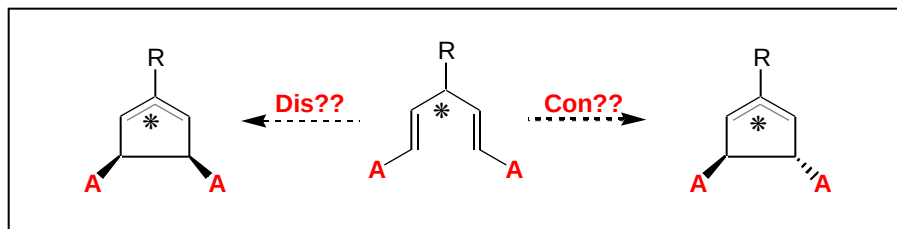
Three-Atom Electrocyclizations (4 electrons)



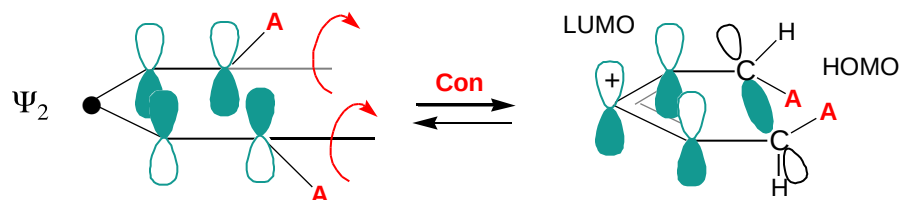
Observation



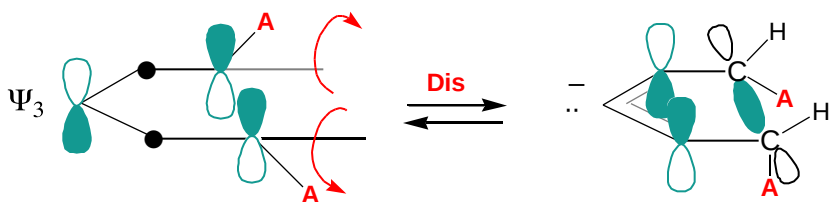
Five-Atom Electrocyclizations (4 electrons)



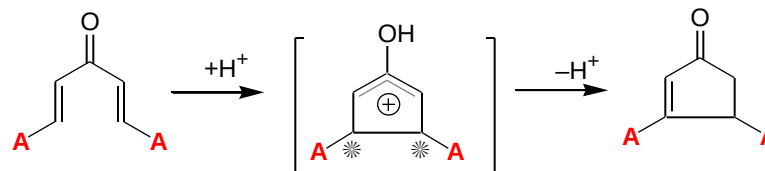
Pentadienyl Cation



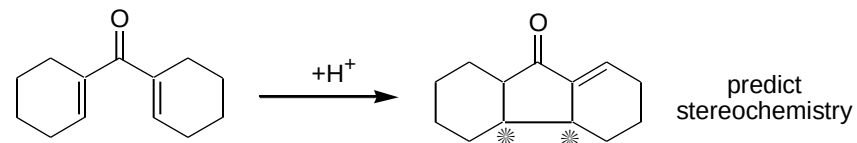
Pentadienyl Anion



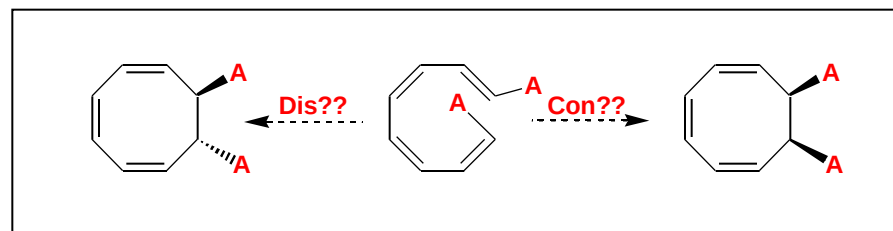
The Nazarov Reaction



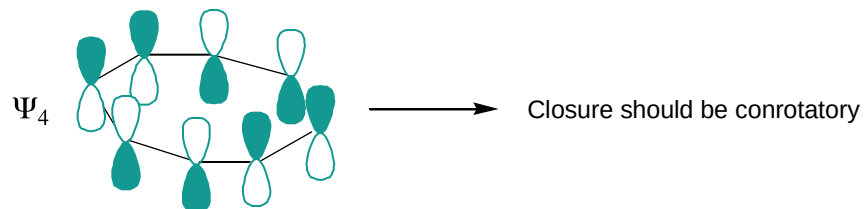
Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5; pp 751.



Eight-Atom Electrocyclizations (8 electrons)

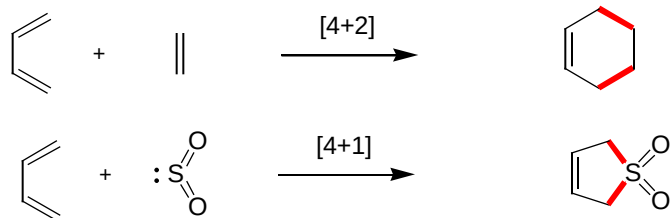


Let's use the "Ready" shortcut to find the homo: Nodes will appear at single bonds

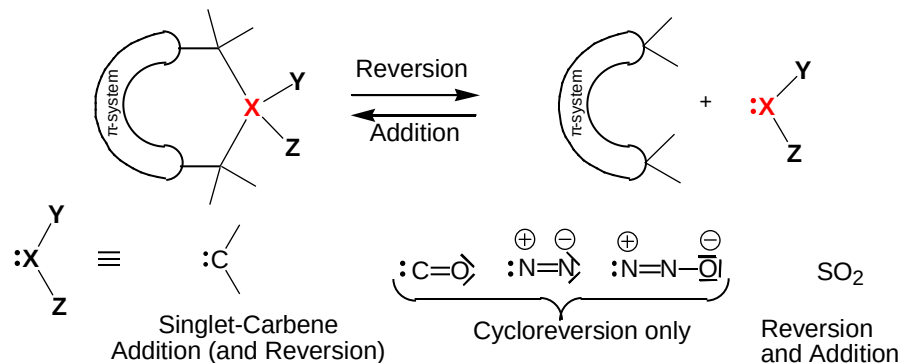


CHELETROPIC REACTIONS: $[n+1]$ Cycloadditions (or Cycloreversions)

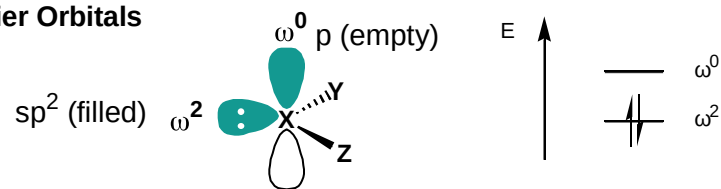
Concerted processes in which 2 σ -bonds are made (or broken) which terminate at a single atom.



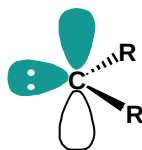
General



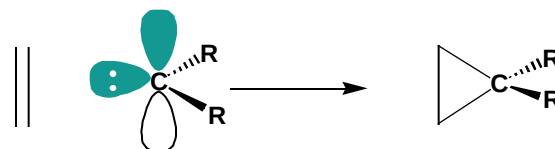
Frontier Orbitals



Question: what is orientation of carbene relative to attacking olefin??



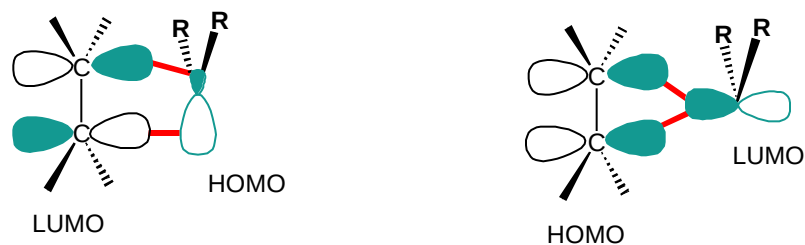
2 + 1 Cheletropic Reaction: Olefins + Singlet Carbene



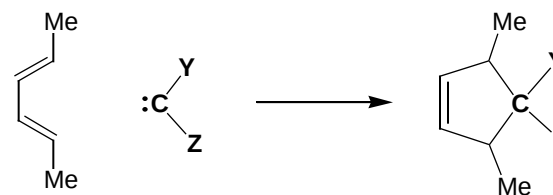
Linear Approach: 2 HOMO-LUMO Interactions



Nonlinear Approach: 2 HOMO-LUMO Interactions

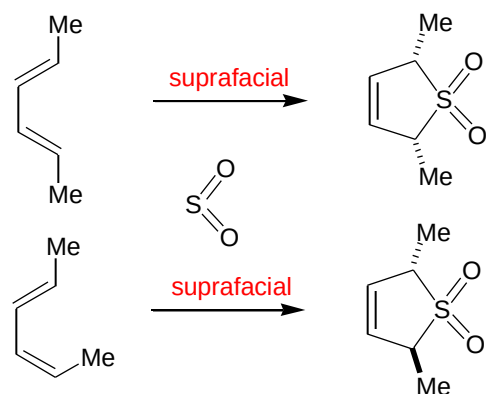
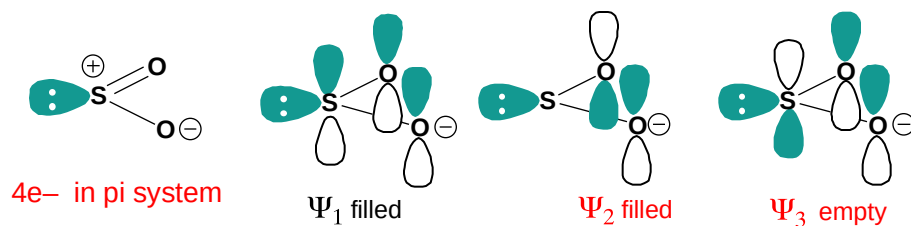


Carry out the analysis of the indicated hypothetical transformation

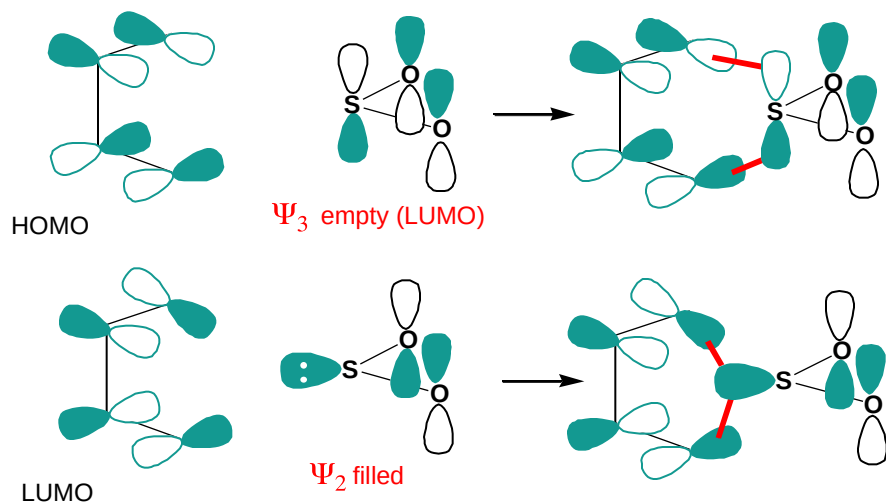


predict approach geometry of carbene

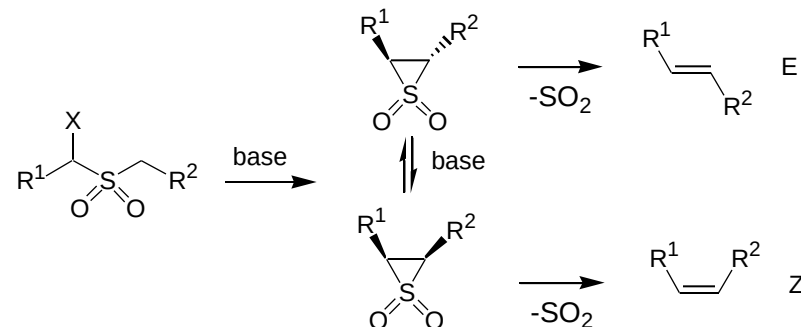
Let's now consider SO_2 as the one-atom component



reactions are:
stereospecific & reversible



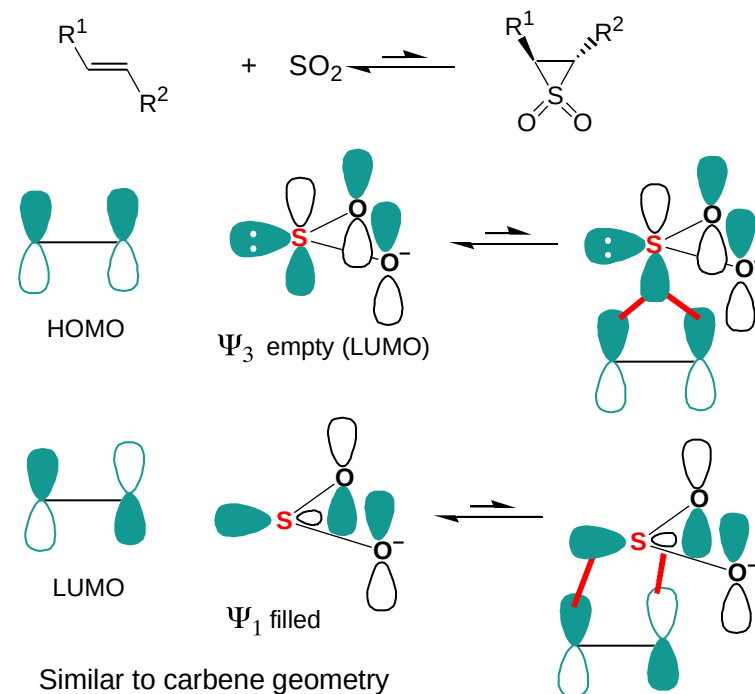
Key step in the Ramberg Bäcklund Rearrangement



Clough, J. M. *The Ramberg-Bäcklund Rearrangement*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 861.

"The Ramberg-Bäcklund Rearrangement.", Paquette, L. A. *Org. React. (N.Y.)* **1977**, 25, 1.

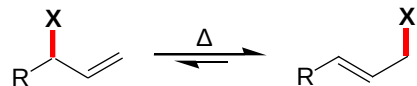
Analysis of the Suprafacial SO_2 Extrusion (nonlinear)



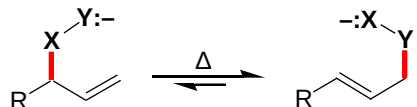
Sigmatropic rearrangements are those reactions in which a sigma bond (& associated substituent) interchanges termini on a conjugated pi system

Examples:

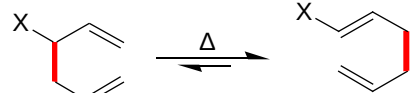
[1,3] Sigmatropic rearrangement



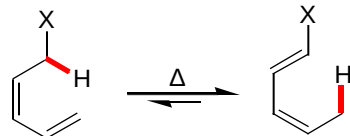
[2,3] Sigmatropic rearrangement



[3,3] Sigmatropic rearrangement

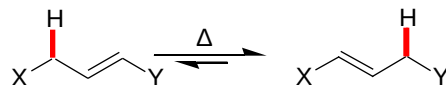


[1,5] Sigmatropic rearrangement

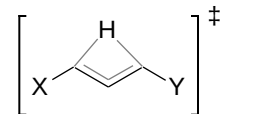


[1,3] Sigmatropic Rearrangements (H migration)

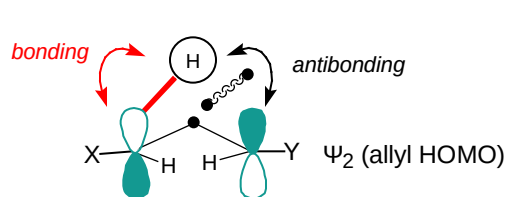
consider the 1,3-migration of H



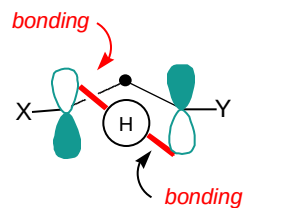
Consider the orbitals needed to construct the transition state (TS).



Construct TS by uniting an allyl and H radical:



Suprafacial Geometry

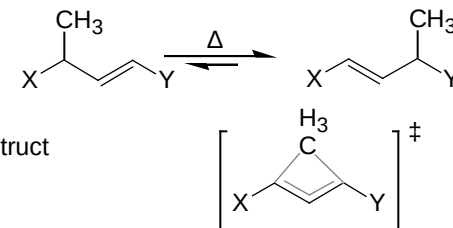


Antarafacial Geometry

Bridging distance too great for antarafacial migration.

[1,3] Sigmatropic Rearrangements (C migration)

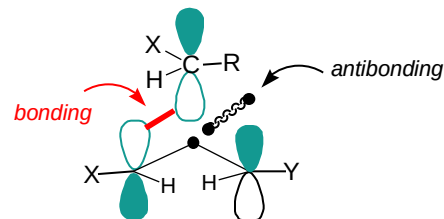
consider the 1,3-migration of Carbon



Consider the orbitals needed to construct the transition state (TS).

Construct TS by uniting an allyl and Me radicals:

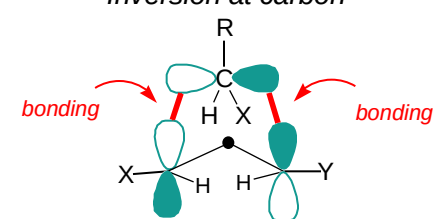
Retention at carbon



Suprafacial on allyl fragment

Synchronous bonding to both termini cannot be achieved from this geometry

Inversion at carbon

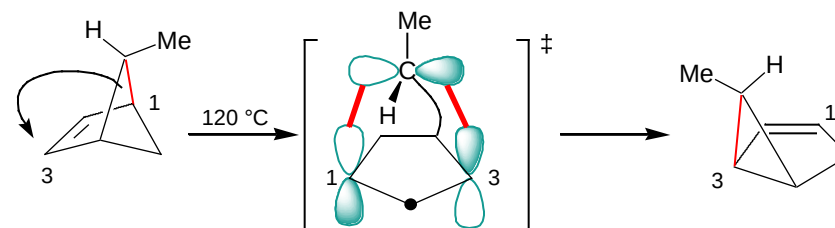
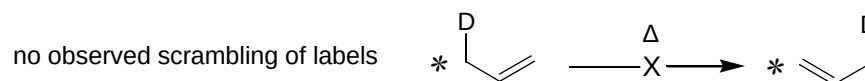


Suprafacial on allyl fragment

Synchronous bonding to both termini is possible from this geometry

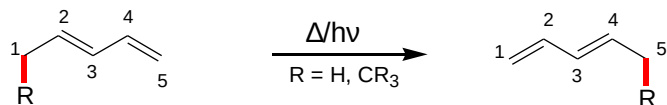
The stereochemical constraints on the suprafacial migration of carbon with inversion of configuration is highly disfavored on the basis of strain.

[1,3]-Sigmatropic rearrangements are not common

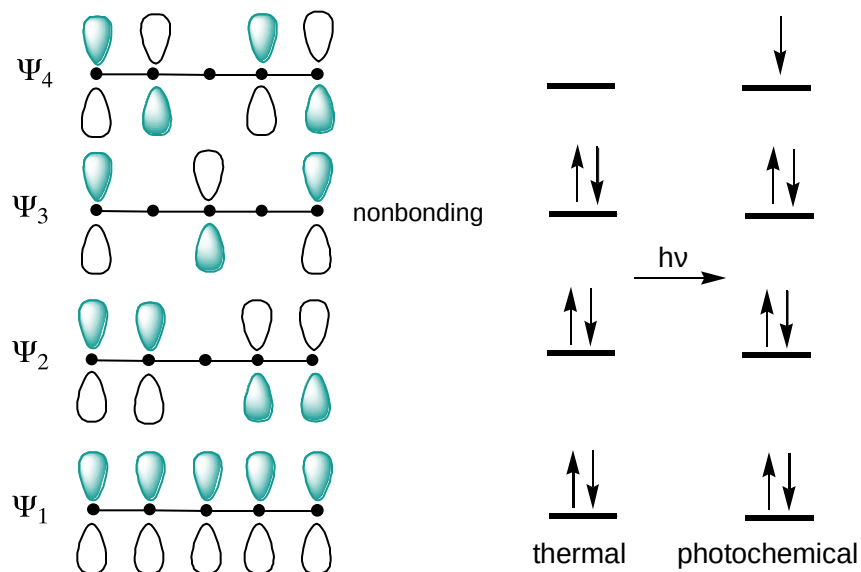


These rearrangements are only seen in systems that are highly strained, an attribute that lowers the activation for rearrangement.

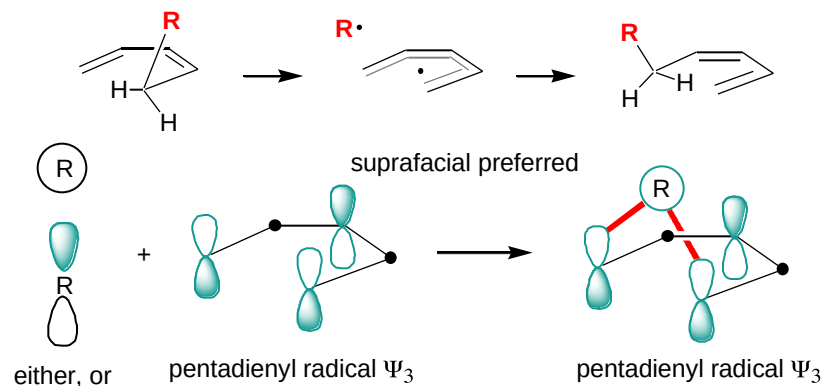
SIGMATROPIC REACTIONS - FMO-Analysis



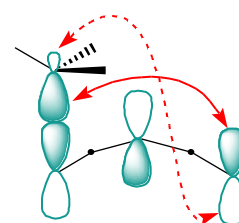
■ [1,5] Sigmatropic Rearrangements (H migration)



View as cycloaddition between following species:



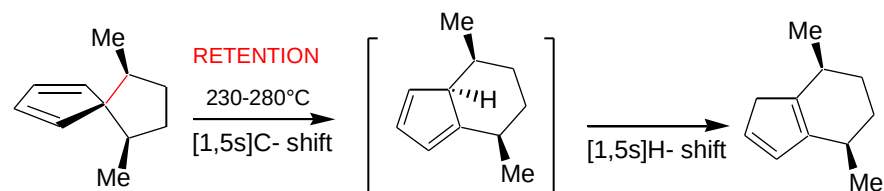
■ [1,5] Sigmatropic Rearrangements (C migration)



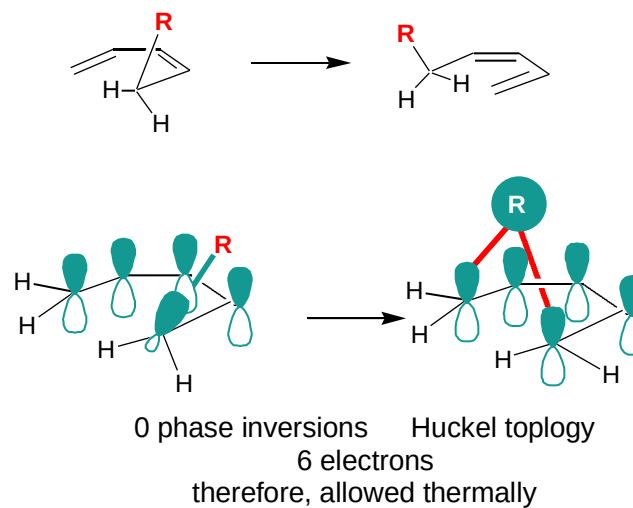
— [1s,5s] alkyl shift RETENTION

— [1a,5a] alkyl shift INVERSION
disfavored

■ [1,5] (C migration): Stereochemical Evaluation

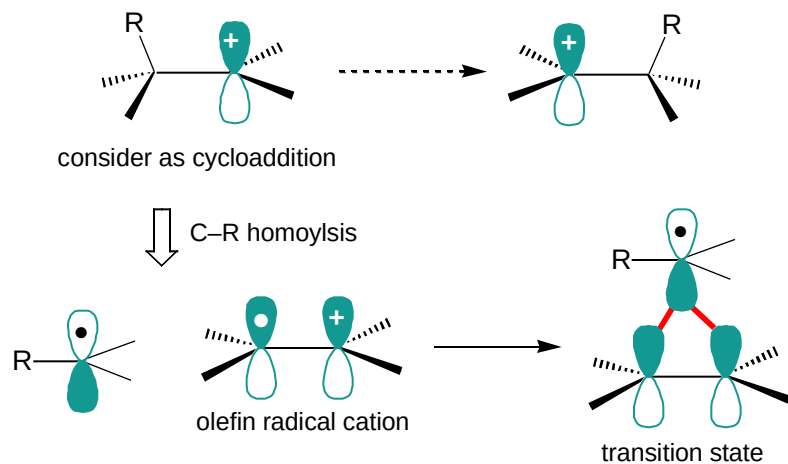


Dewar–Zimmerman Analysis: Retention

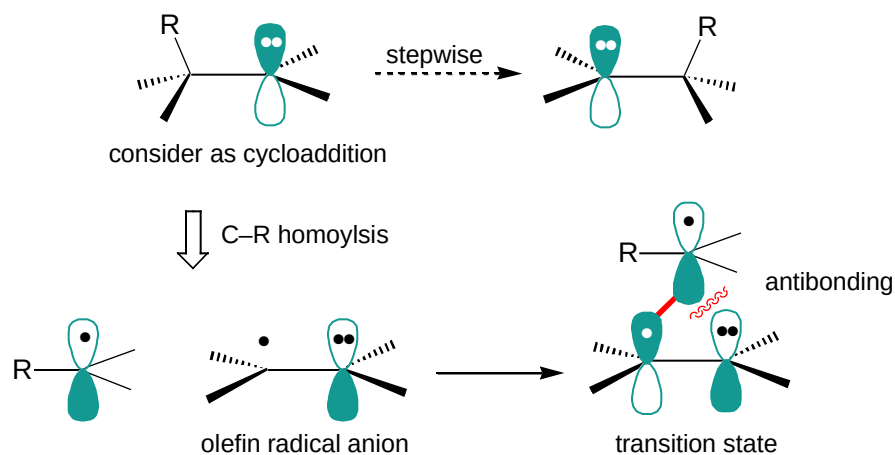


■ [1,2] Sigmatropic Rearrangements: Carbon

[1,2] Concerted sigmatropic rearrangements to cationic centers allowed



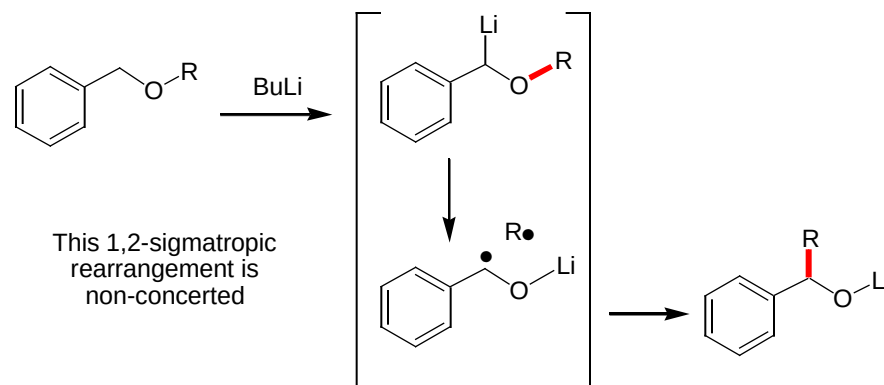
[1,2] Concerted sigmatropic rearrangements to carbanionic centers not observed



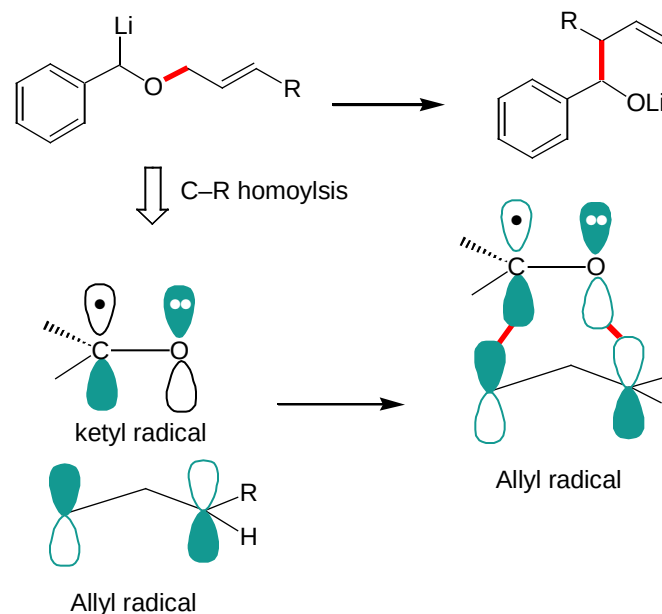
The Wittig Rearrangement [1,2]

"[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.



The Wittig Rearrangement [2,3]



<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 Ylide 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)

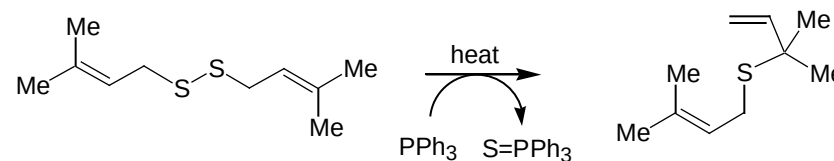
S. R. Wilson, *Organic Reactions* **1993**, 43, 93 (oxy-Cope)

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.

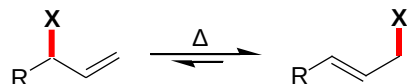


For study on this [2,3] rxn See Baldwin *JACS* **1971**, 93, 6307

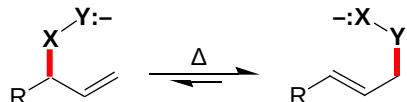
Sigmatropic rearrangements are those reactions in which a sigma bond (& associated substituent) interchanges termini on a conjugated pi system

■ **Examples:**

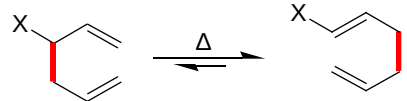
[1,3] Sigmatropic rearrangement



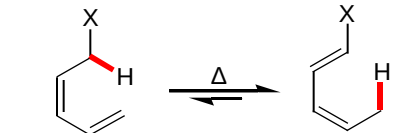
[2,3] Sigmatropic rearrangement



[3,3] Sigmatropic rearrangement

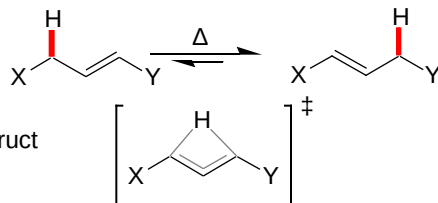


[1,5] Sigmatropic rearrangement



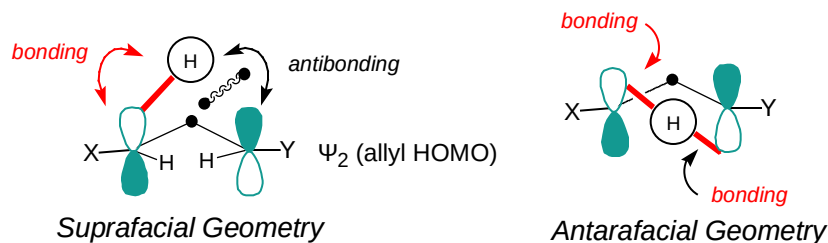
■ **[1,3] Sigmatropic Rearrangements (H migration)**

consider the 1,3-migration of H



Consider the orbitals needed to construct the transition state (TS).

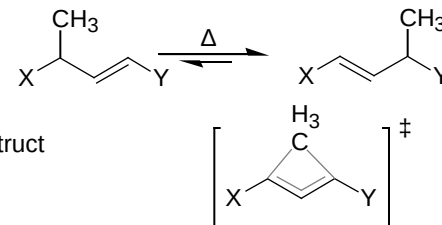
■ **Construct TS by uniting an allyl and H radical:**



Bridging distance too great for antarafacial migration.

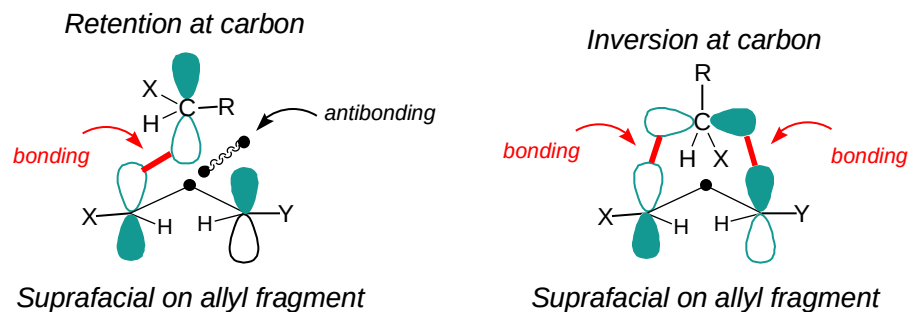
■ **[1,3] Sigmatropic Rearrangements (C migration)**

consider the 1,3-migration of Carbon



Consider the orbitals needed to construct the transition state (TS).

□ Construct TS by uniting an allyl and Me radicals:

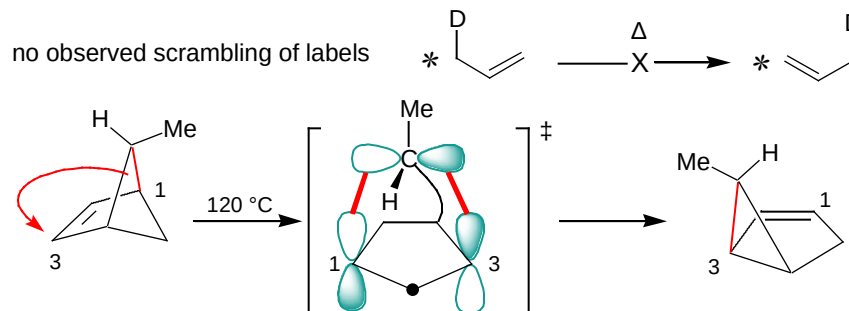


Synchronous bonding to both termini cannot be achieved from this geometry

Synchronous bonding to both termini is possible from this geometry

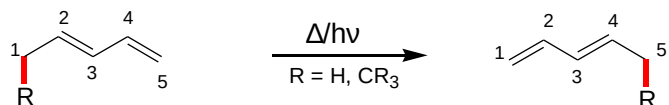
□ The stereochemical constraints on the suprafacial migration of carbon with inversion of configuration is highly disfavored on the basis of strain.

[1,3]-Sigmatropic rearrangements are not common

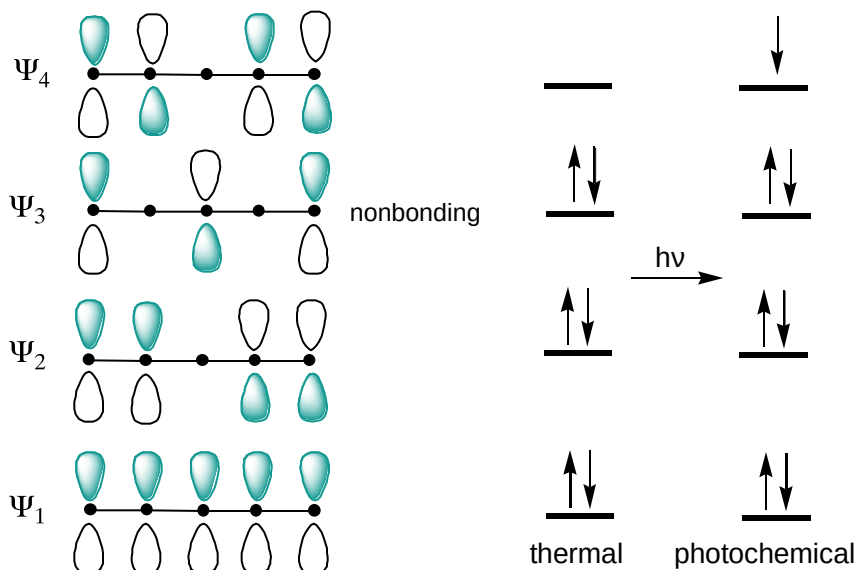


These rearrangements are only seen in systems that are highly strained, an attribute that lowers the activation for rearrangement.

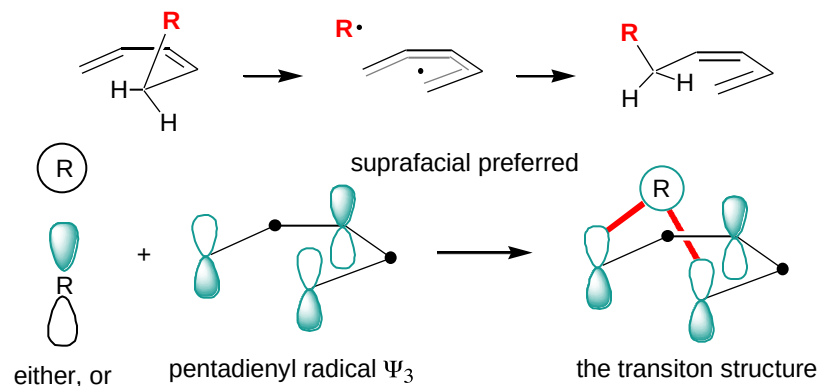
SIGMATROPIC REACTIONS - FMO-Analysis



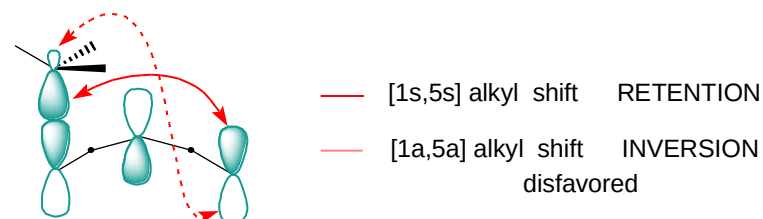
■ [1,5] Sigmatropic Rearrangements (H migration)



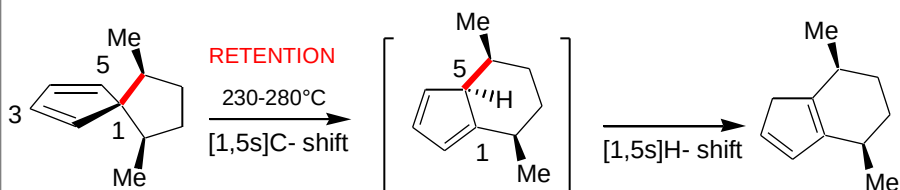
View as cycloaddition between following species:



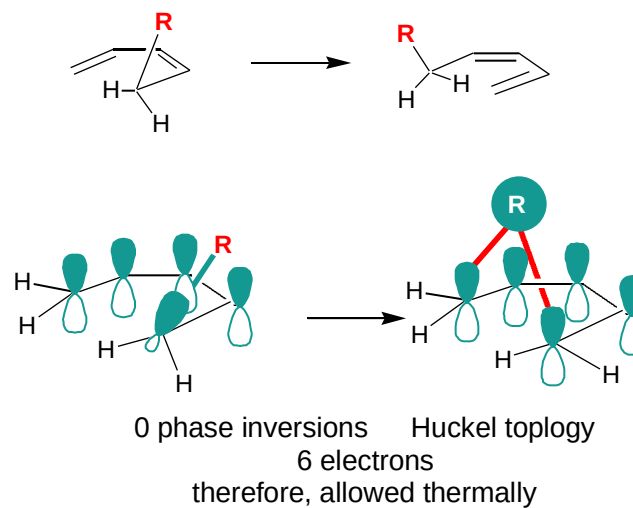
■ [1,5] Sigmatropic Rearrangements (C migration)

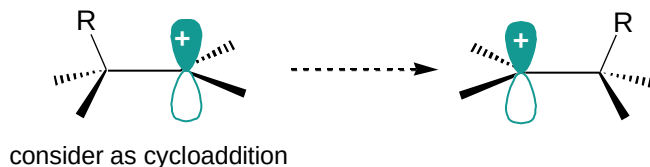
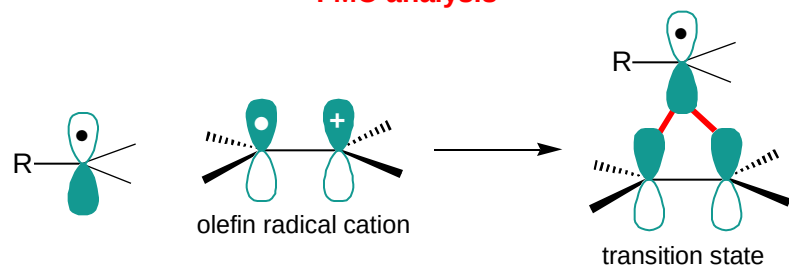
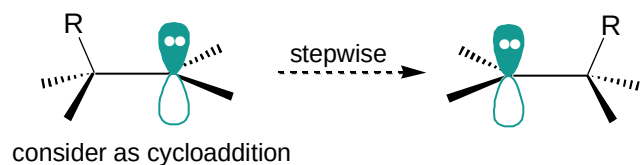
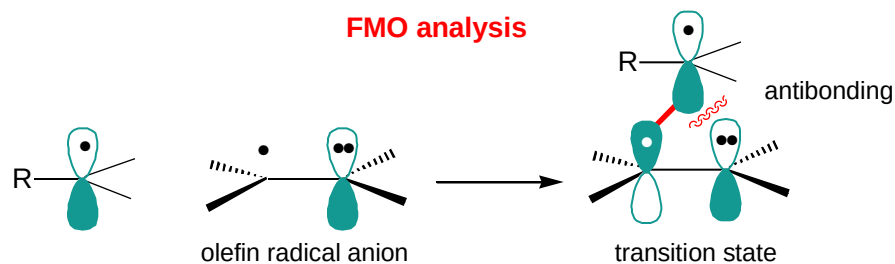


■ [1,5] (C migration): Stereochemical Evaluation



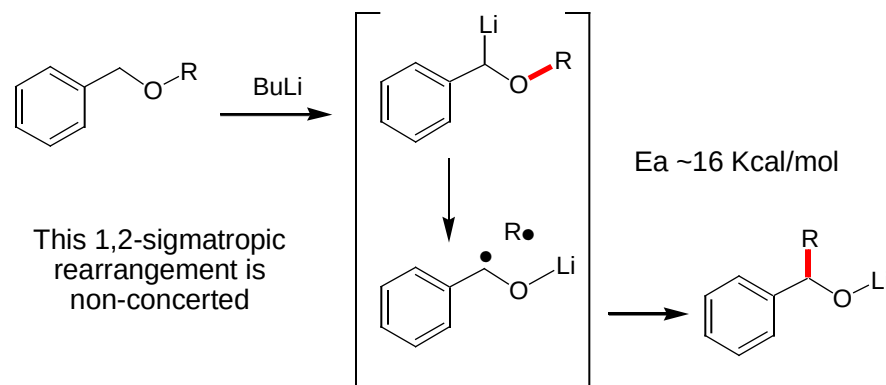
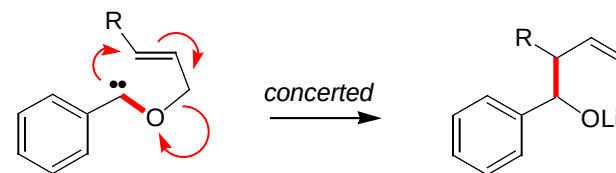
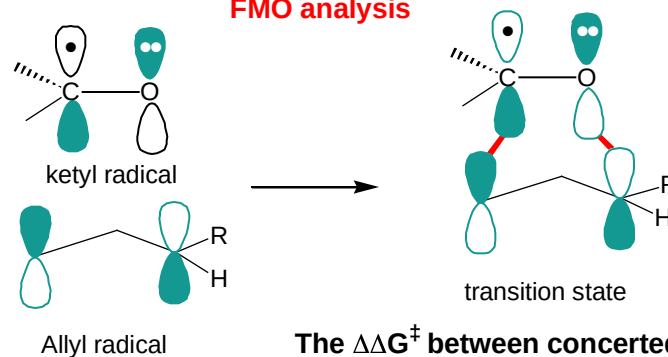
Dewar-Zimmerman Analysis: Retention



[1,2] Sigmatropic Rearrangements: Carbon**[1,2]-Sigmatropic rearrangements to cationic centers allowed.****Wagner-Meerwein Rearrangement****FMO analysis****[1,2]-Sigmatropic rearr to carbanionic centers not observed****FMO analysis****The Wittig Rearrangement [1,2]**

"[2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis.", Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, 86, 885.

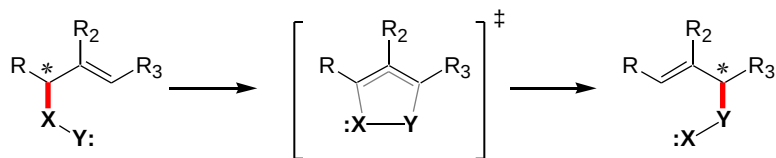
Marshall, J. A. *The Wittig Rearrangement*.; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 975.

**The Wittig Rearrangement [2,3]****FMO analysis**

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:

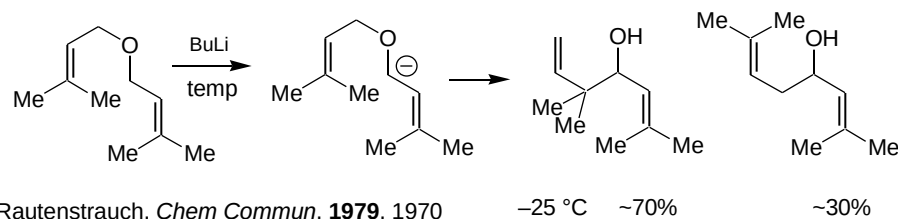
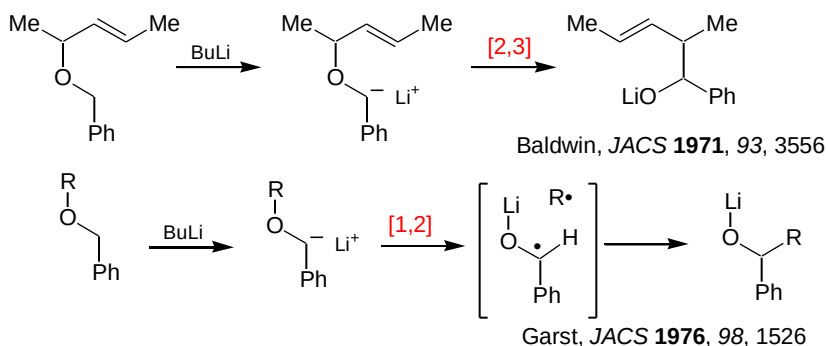
N-O (amine oxides)	S-P, S-N, S-O (sulfoxides)
S-C (sulfur ylids)	O-P (phosphites)
O-C (Wittig rearrangement)	N-N, Cl ⁺ -C (halonium ylids)
N-C (nitrogen ylids)	P-C, C-C (homoallylic anions).
S-S (disulfides)	

An important early paper: Baldwin, *J. Chem. Soc., Chem. Comm.* **1970**, 576

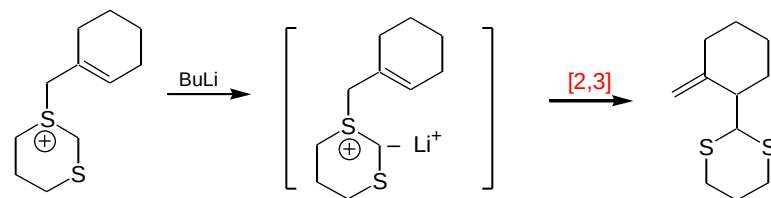
■ General Reviews:

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 Ylide Rearrangements)

■ X - O, Y = C; Wittig Rearrangement:



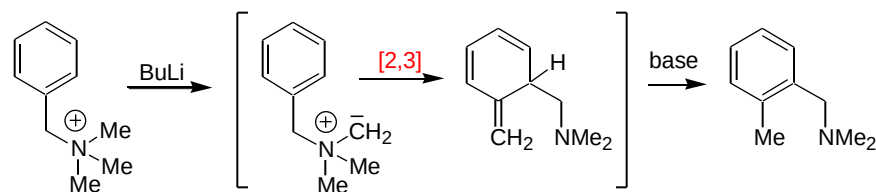
■ X - S, Y = C; Sulfonium Ylide Rearrangement:



Lythgoe, *Chem Commun* **1972**, 757

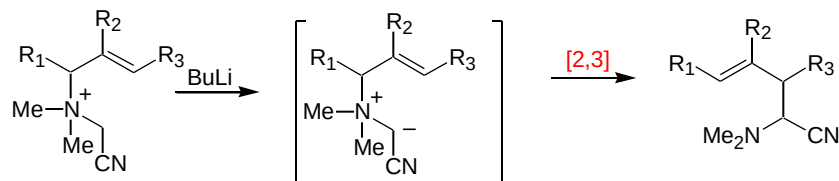
■ X - N, Y = C; Ammonium Ylide Rearrangement:

□ Sommelet-Hauser:



Review, Pines, *Org. Rxns* **1970**, 18, 416

□ Modern versions of Stevens:

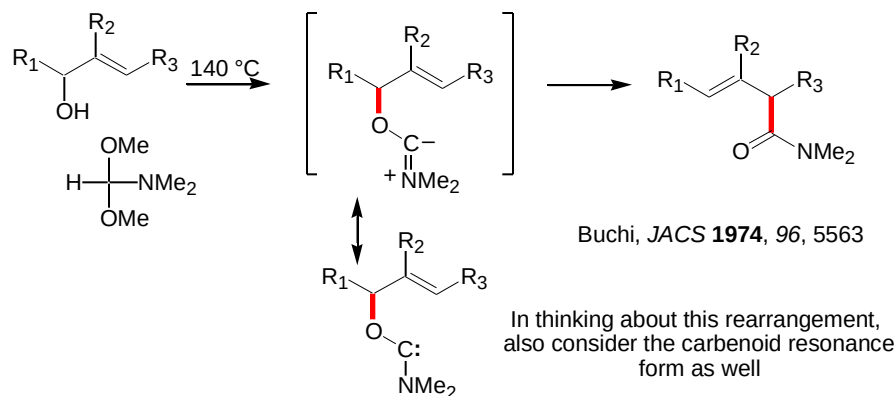


Buchi, *JACS* **1974**, 96, 7573

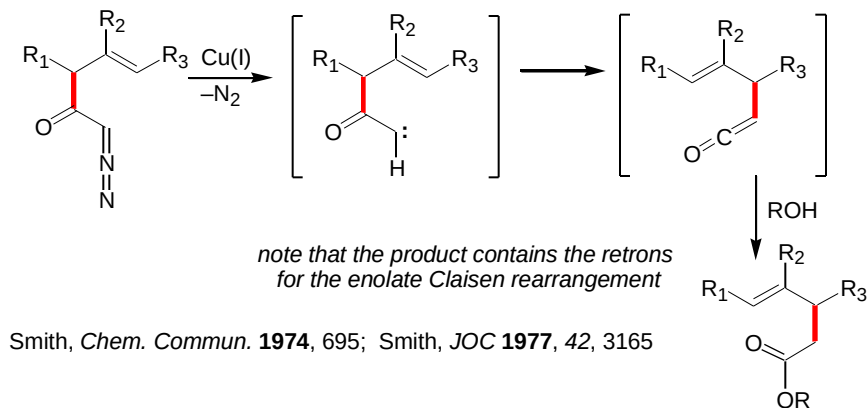
Mander, *JOC* **1973**, 38, 2915

important extension lacking CN FG; Sato, *JACS* **1990**, 112, 1999

■ X - O, Y = C; Wittig-like Rearrangements

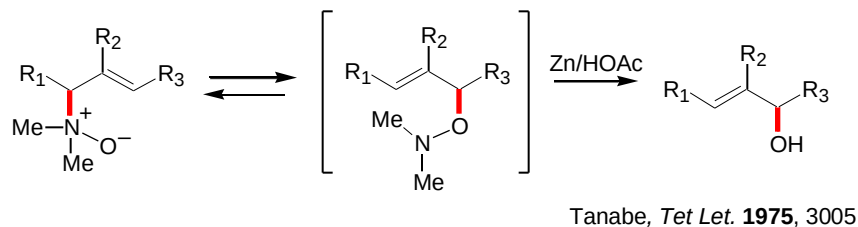


■ X - O, Y = C; An all-carbon Rearrangement

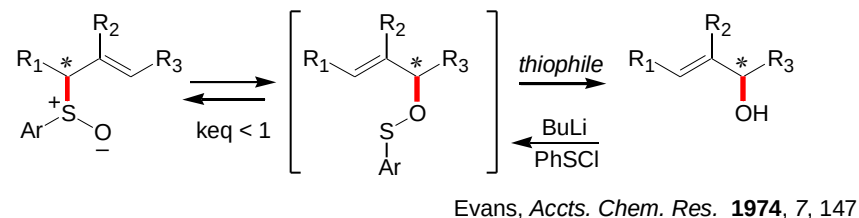


Smith, *Chem. Commun.* **1974**, 695; Smith, *JOC* **1977**, 42, 3165

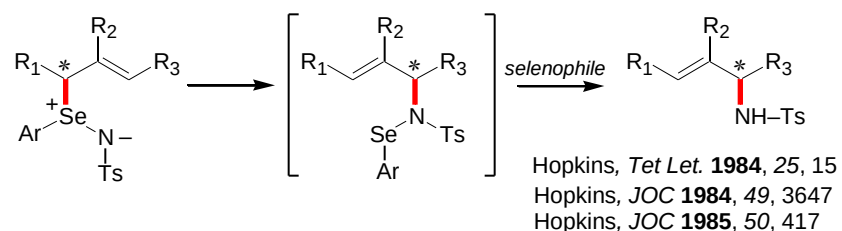
■ X - N, Y = O; Meisenheimer Rearrangement



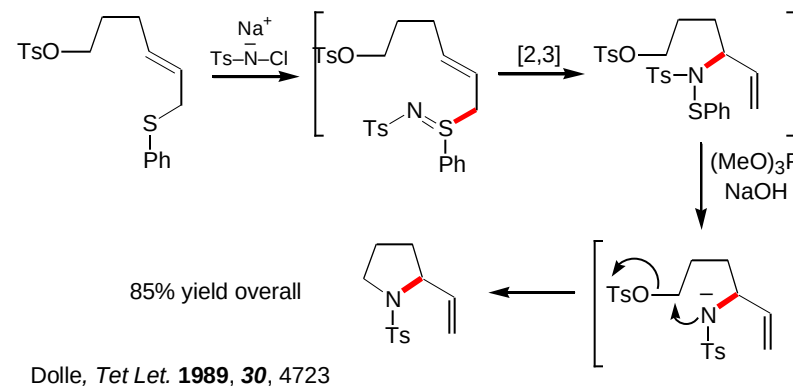
■ X - S, Y = O; Sulfoxide Rearrangement



■ X - Se, Y = N; Related Rearrangement

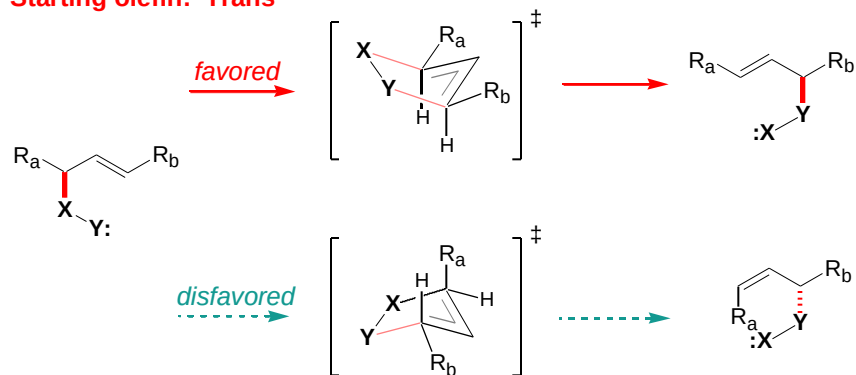


■ X - S, Y = N; Related Rearrangement



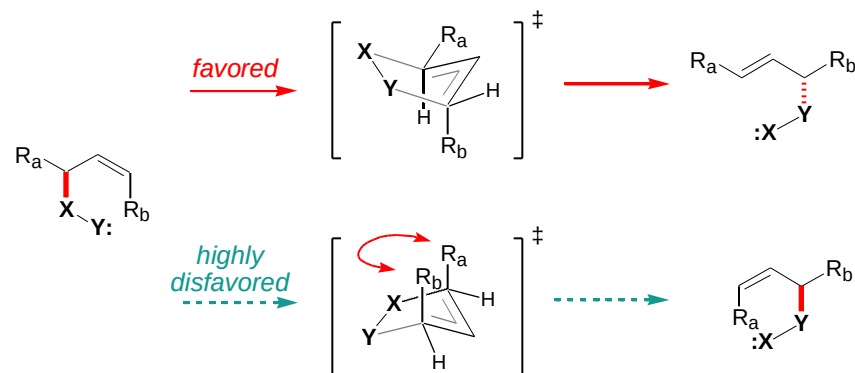
1,2-Disubstitution: Good Trans Olefin Selectivity

Starting olefin: Trans



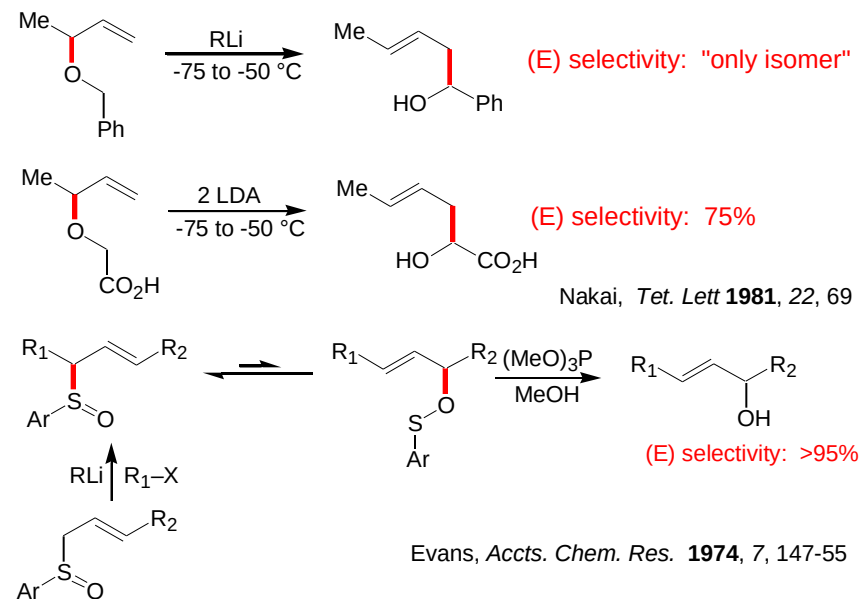
R_a & R_b prefer to orient in pseudo-equatorial positions during rearrangement; nevertheless, this is a delicately balanced situation

Starting olefin: Cis



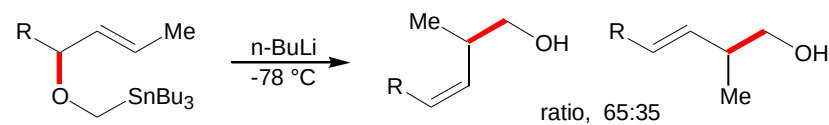
Conclusions

- ❑ 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

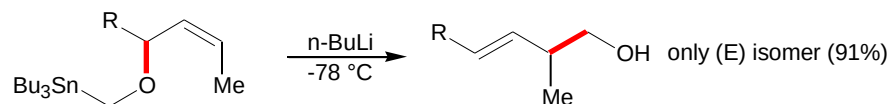


The preceding transition state models do not explain some of the results:

❑ Cis selectivity has been observed: Still *JACS* **1978**, 100, 1927.



❑ However, Cis selectivity is dependent on starting olefin geometry

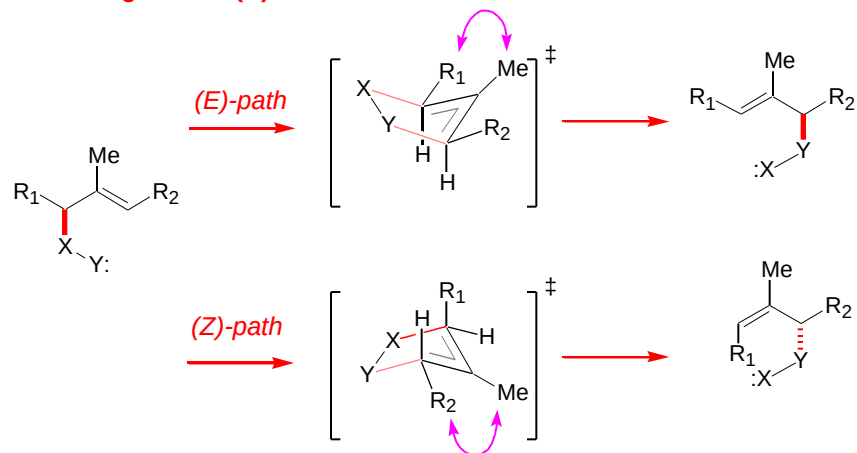


Several theoretical studies have been published: Good reading

Houk *JOC* **1991**, 56, 5657 (Sulfur ylide transition states)

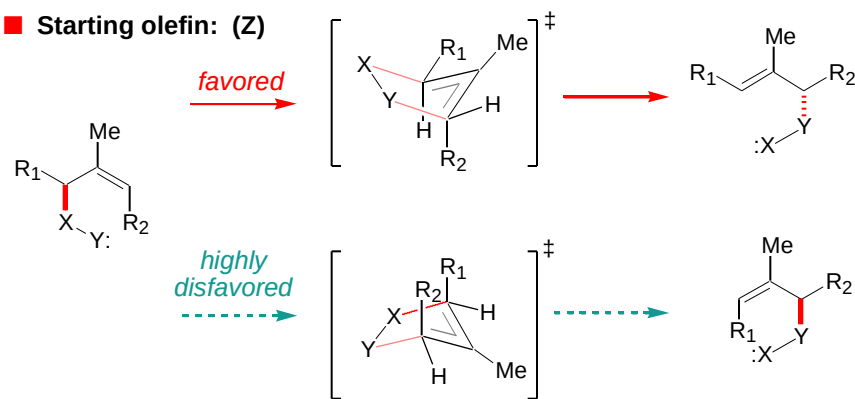
Houk *JOC* **1990**, 55, 1421 (Wittig transition states)

■ 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.

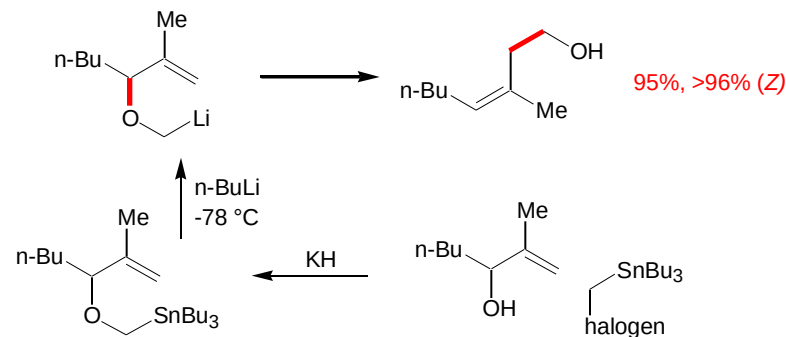
■ Starting olefin: (Z)



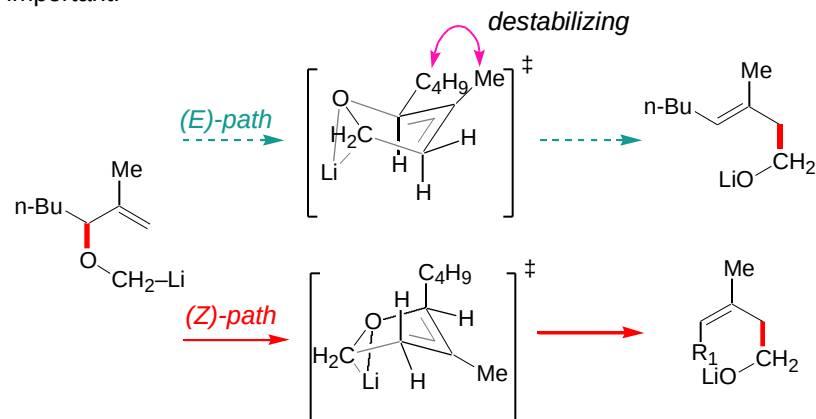
Conclusions

- 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

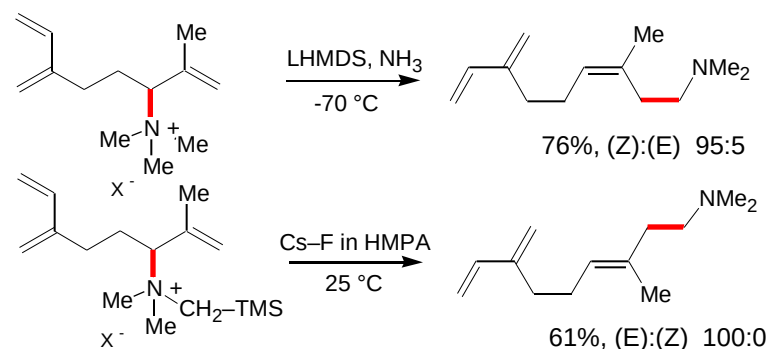
■ (Z) selectivity has been observed: Still JACS **1978**, *100*, 1927.



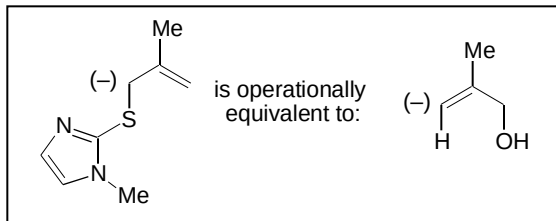
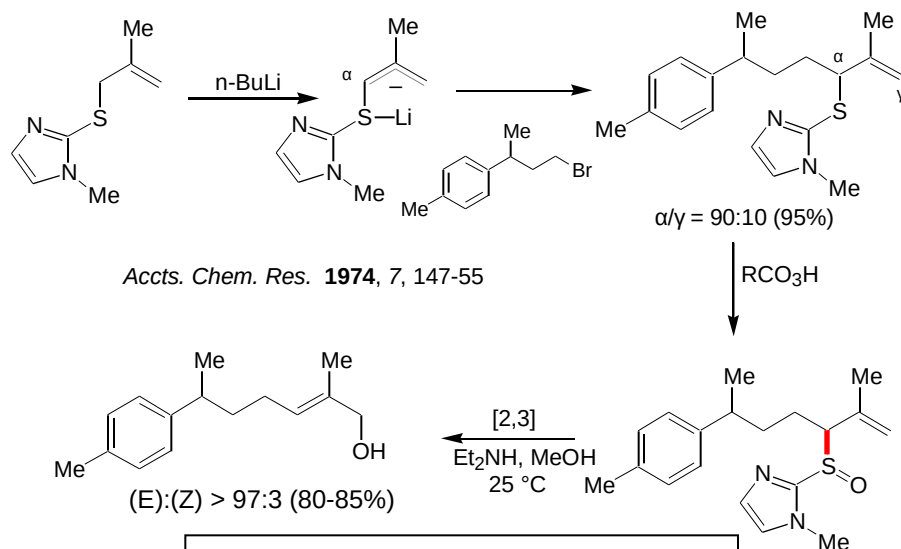
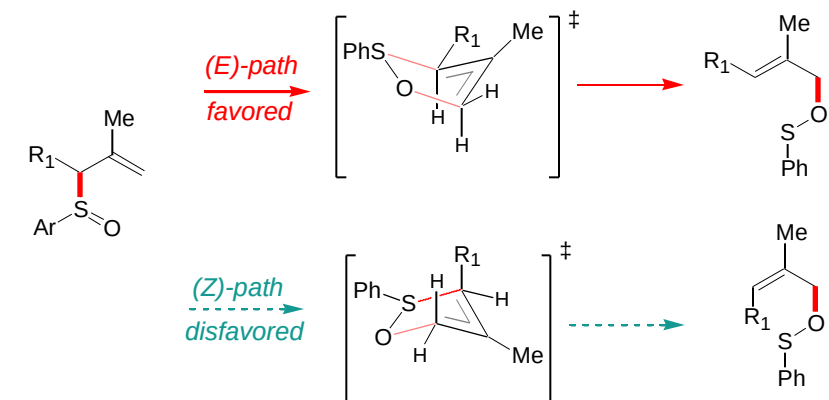
Still says that the TS is early, so that the 1,2 interactions in the TS are most important.



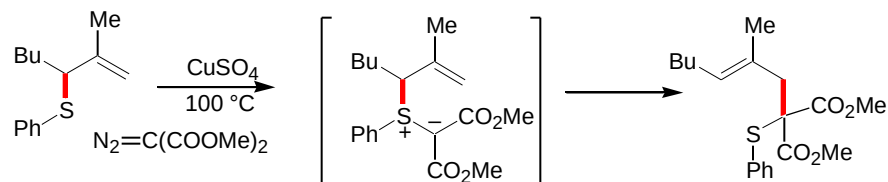
■ (Z) selectivity has also been observed by others: Sato JACS **1990**, *112*, 1999.



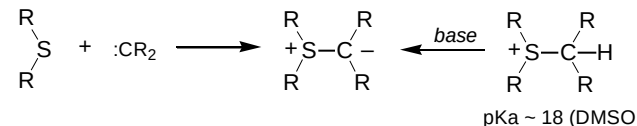
Trisubstituted olefins via [2,3]-rearrangement of sulfoxides:



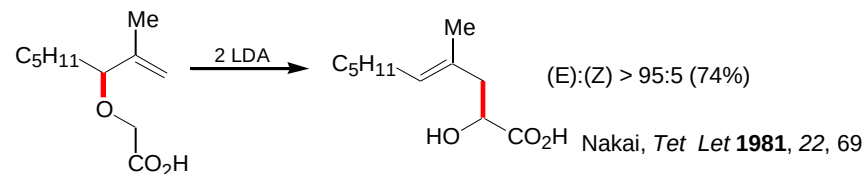
Trisubstituted olefins via [2,3]-rearrangement of sulfonium ylides:



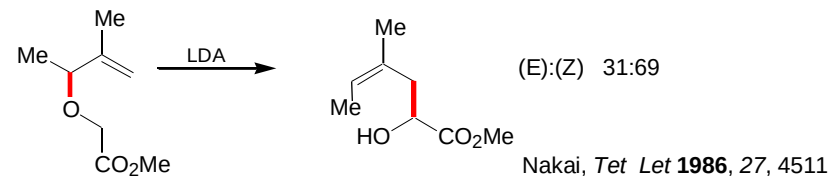
A general procedure for the direct synthesis of sulfur ylides:



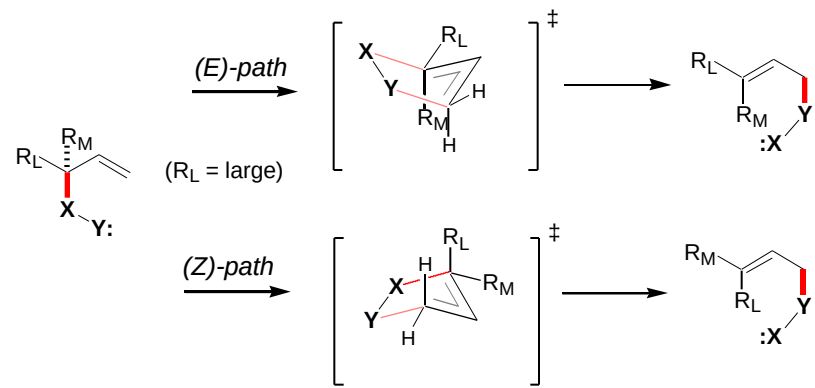
Trisubstituted olefins via Wittig [2,3]-rearrangement:



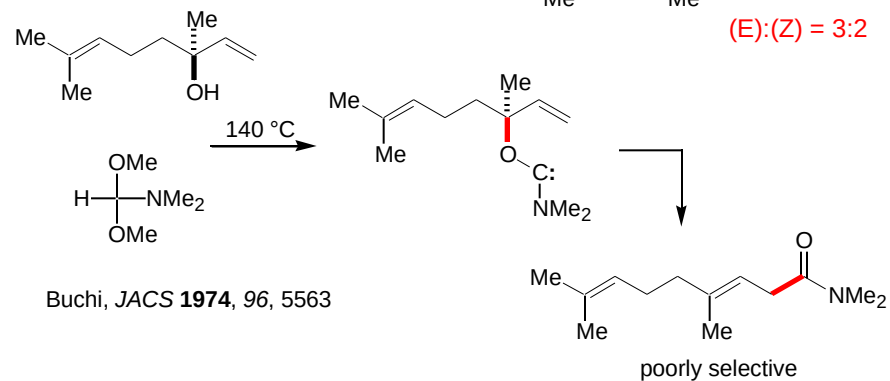
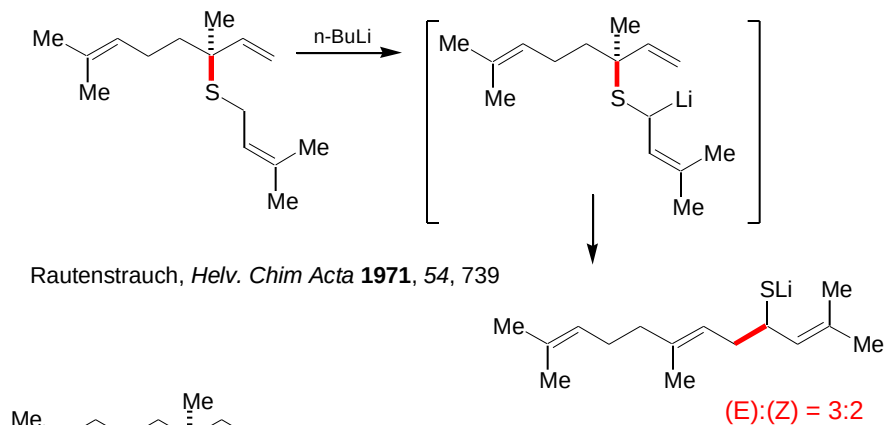
However, this reaction is not general:



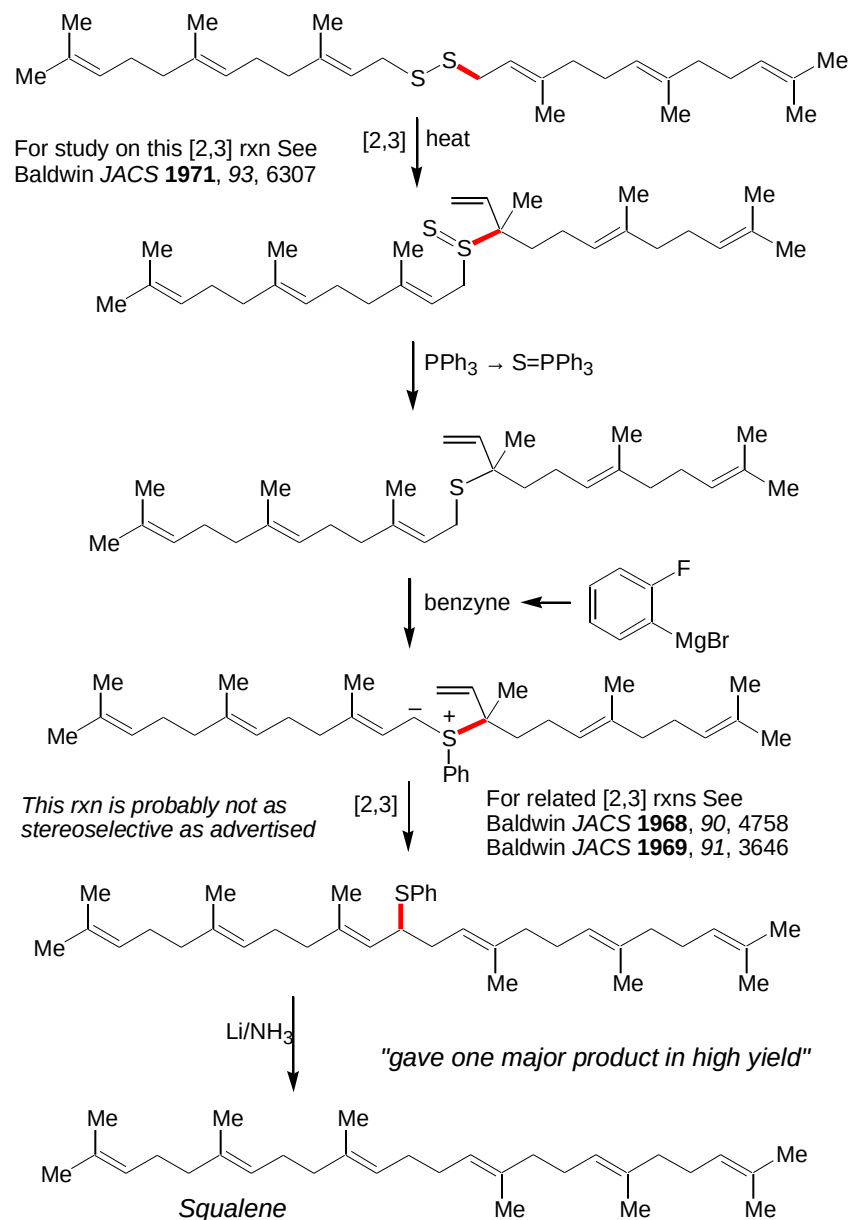
■ Trisubstituted olefins via [2,3]-rearrangement:

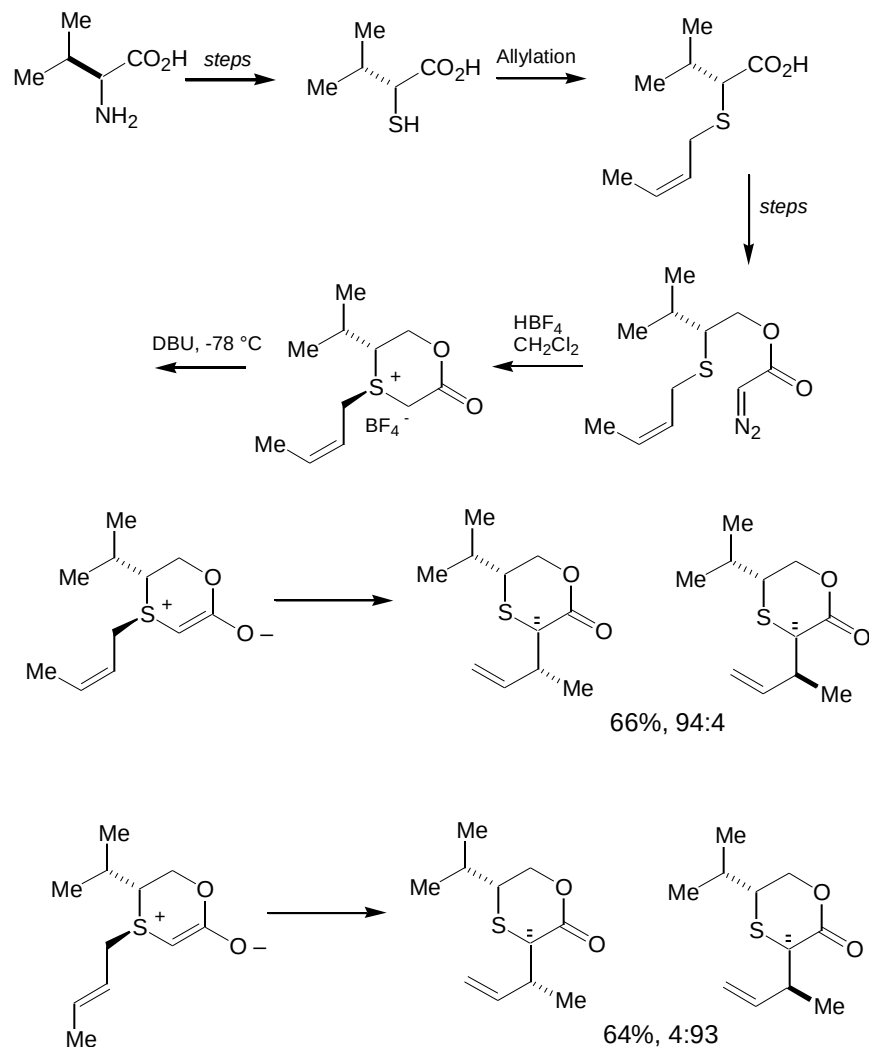
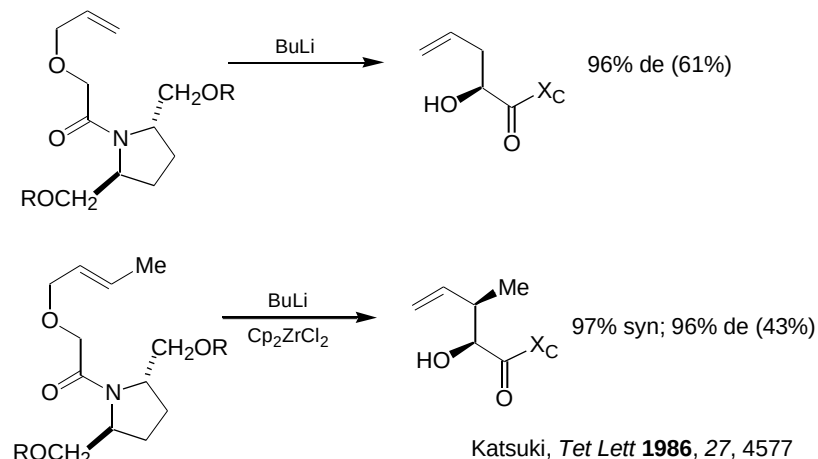
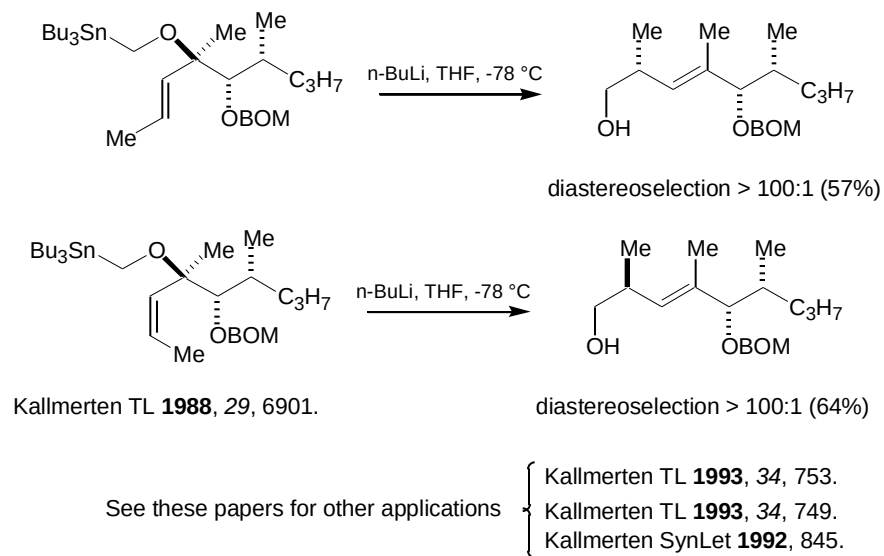


One might project that the (E) path will be moderately favored with selectivity depending on size difference between R_L & R_M

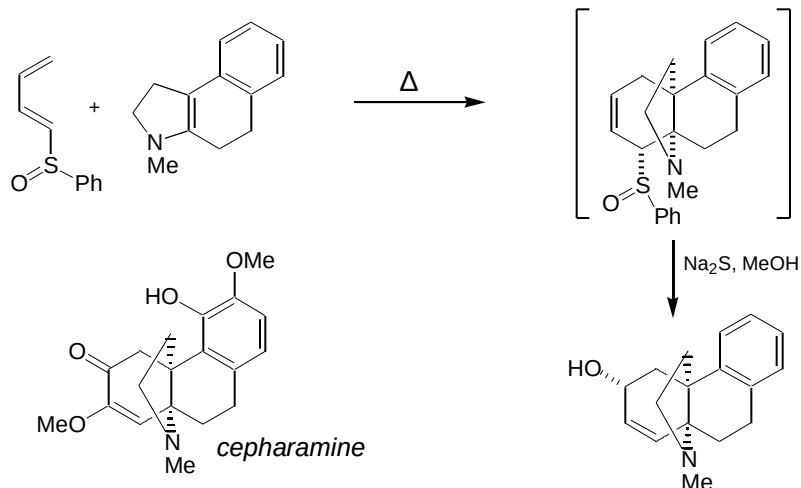


An elegant squalene synthesis Ollis, *Chem. Commun* **1969**, 99

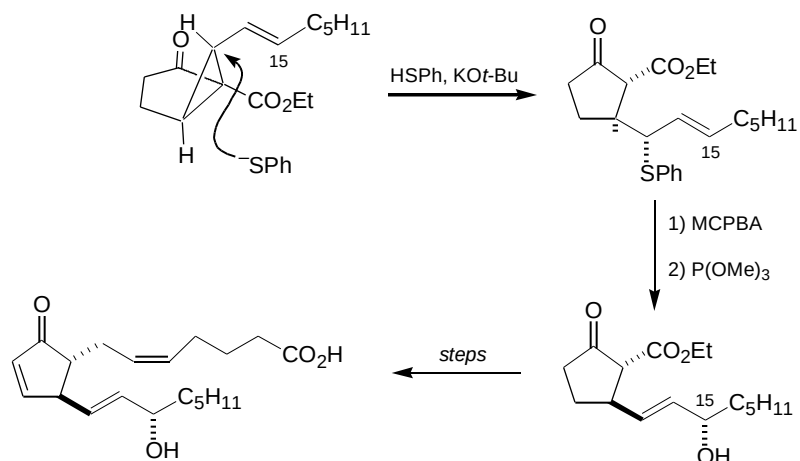
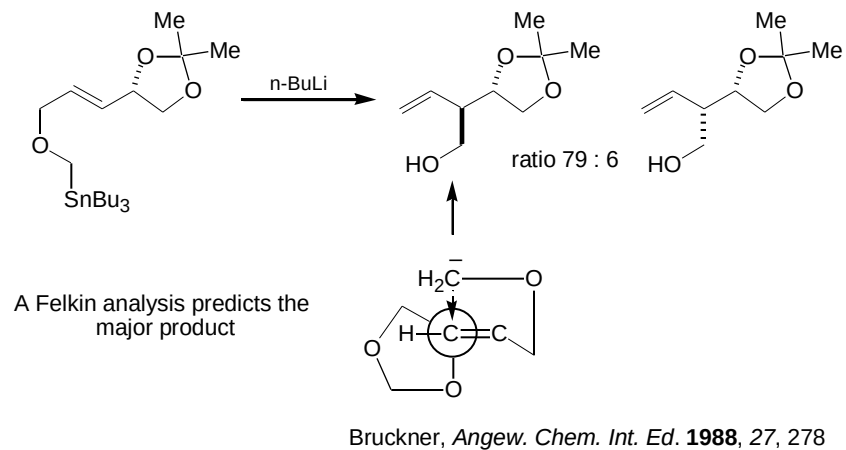


[2,3] Sulfur Ylide Rearrangement Using a Chiral AuxiliaryKurth JOC **1990**, 55, 2286 and TL **1991**, 32, 335**Chiral Auxiliaries can also be used in the Wittig Rearrangement****Internal Relay of Stereochemistry in C–C Constructions**

Internal Relay of Stereochemistry in C–O Constructions

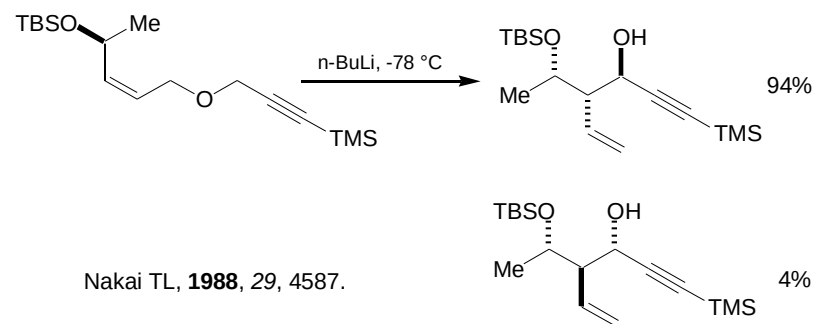
Tandem [4+2] & [2,3] Process: Evans, Bryan, Sims *J. Am. Chem. Soc.* **1972**, 2891.

Cases where the chirality is exocyclic to the rearrangement



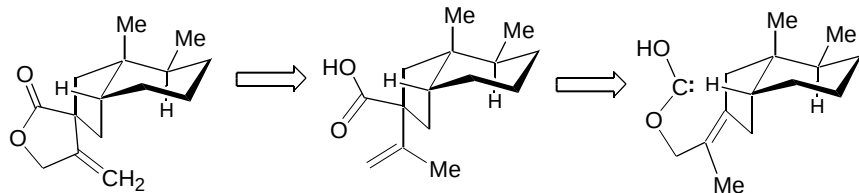
Taber *J. Am. Chem. Soc.* **1977**, 99, 3513.
Kondo *Tet. Lett.* **1978**, 3927.

Allylic Ethers to Make Three Contiguous Stereocenters

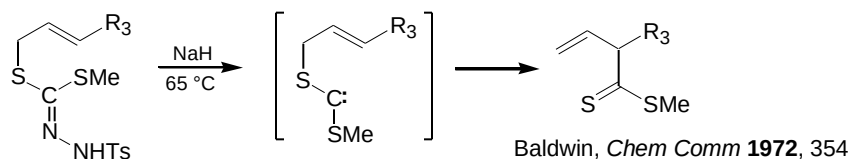
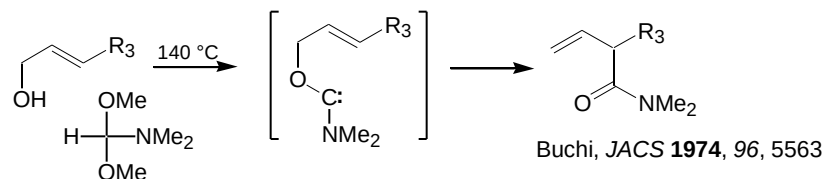


Can you rationalize the stereochemical outcome of this reaction?

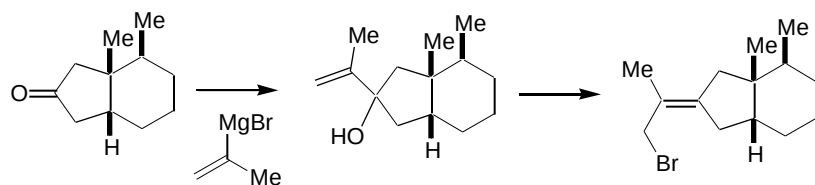
The Synthesis of Bakkenolide-A (Evans JACS **1977**, 99, 5453)



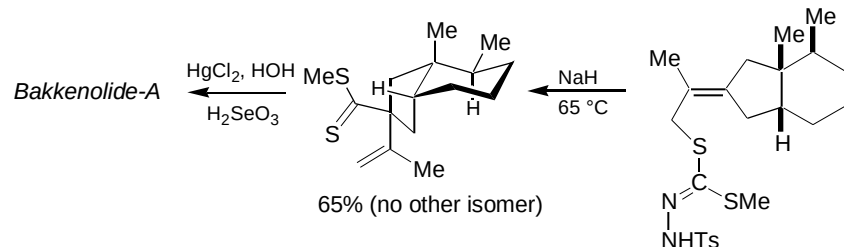
- Candidate processes:



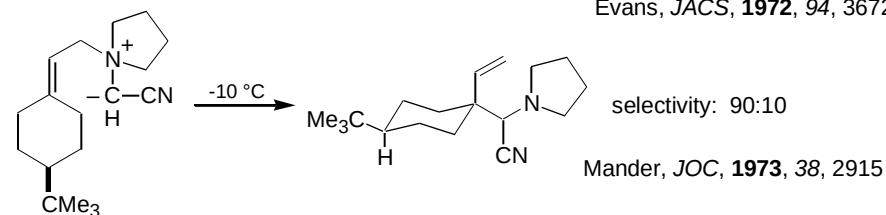
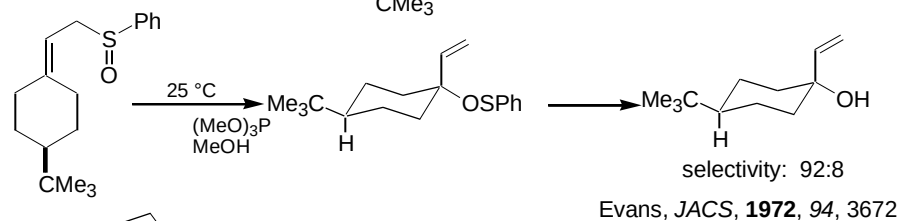
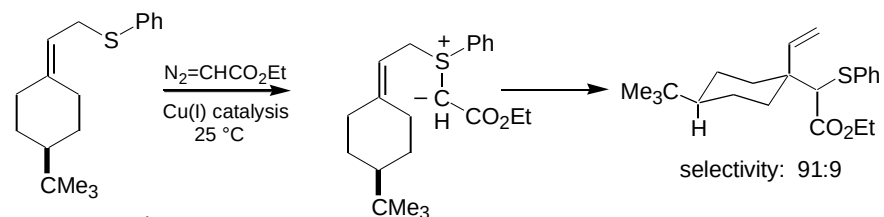
■ The synthesis:



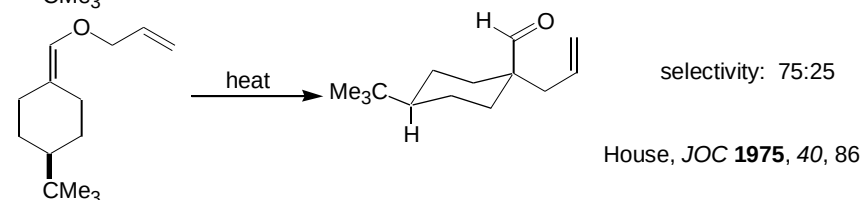
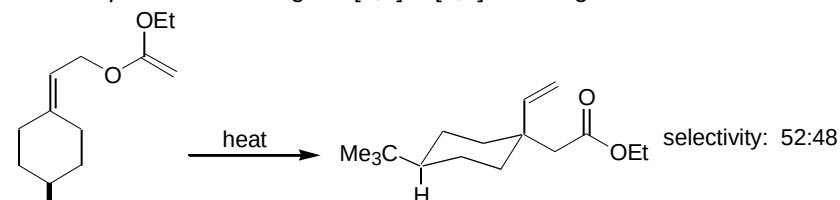
Note that rearrangement is not required to proceed via the carbenoid. propose alternate mechanism

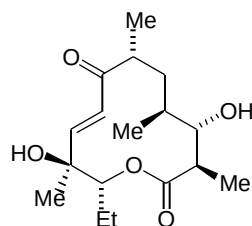
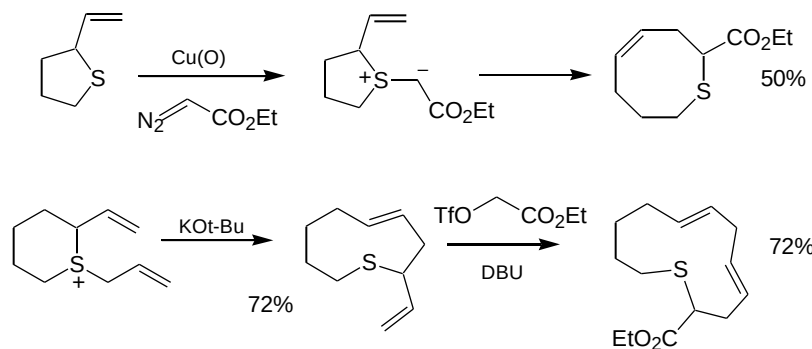
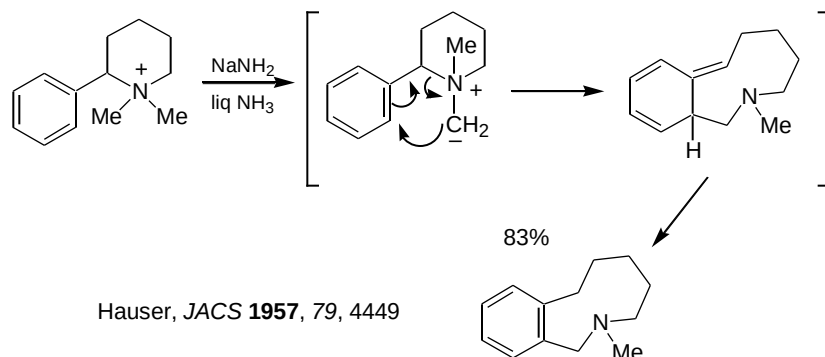
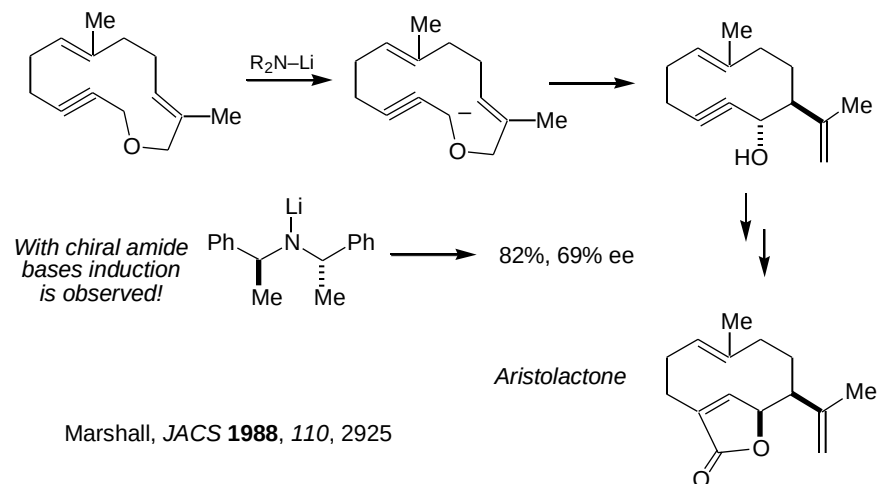
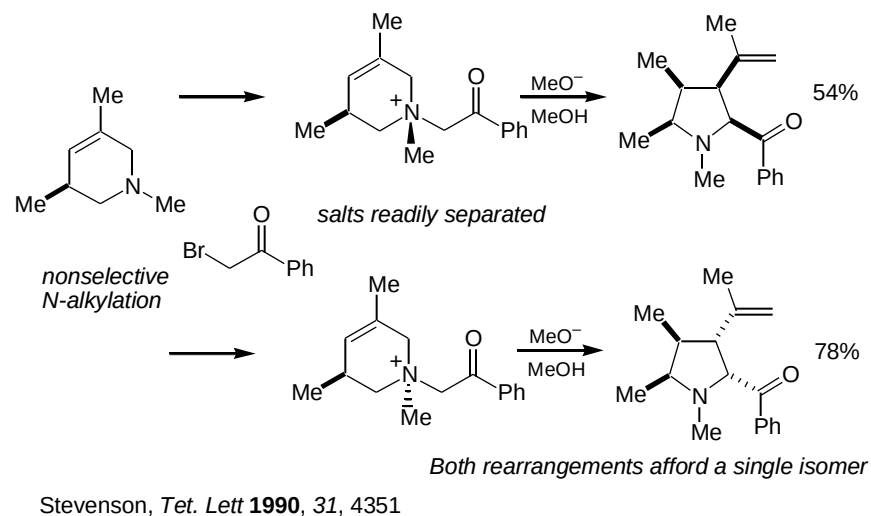


[2,3] Sigmatropic rearrangements respond to subtle steric effects



- The comparison of analogous [2,3] & [3,3] rearrangements:



Ring expansion reactions have been investigatedMethods based on sulfur ylides: (review) Vedejs, *Accts. Chem. Res.* **1984**, 17, 358Methynolide 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**Marshall, *JACS* **1988**, 110, 2925**A ring contraction using the Stevens Rearrangement**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)

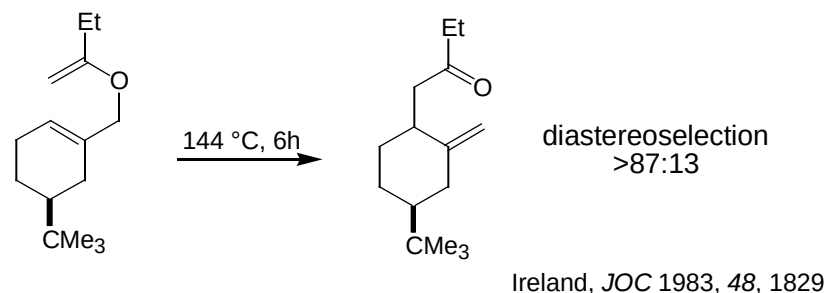
S. R. Wilson, *Organic Reactions* **1993**, 43, 93 (oxy-Cope)

T. S. Ho, *Tandem Organic Reactions* **1992**, Chapter 12 (Cope, Claisen)

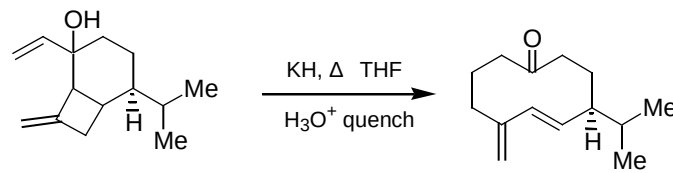
Paquette, L. A. (1990). "Stereocontrolled construction of complex cyclic ketones by oxy-Cope rearrangement." *Angew. Chem., Int. Ed. Engl.* 29: 609.

■ Problems of the Day:

Predict the stereochemical outcome of this Claisen rearrangement



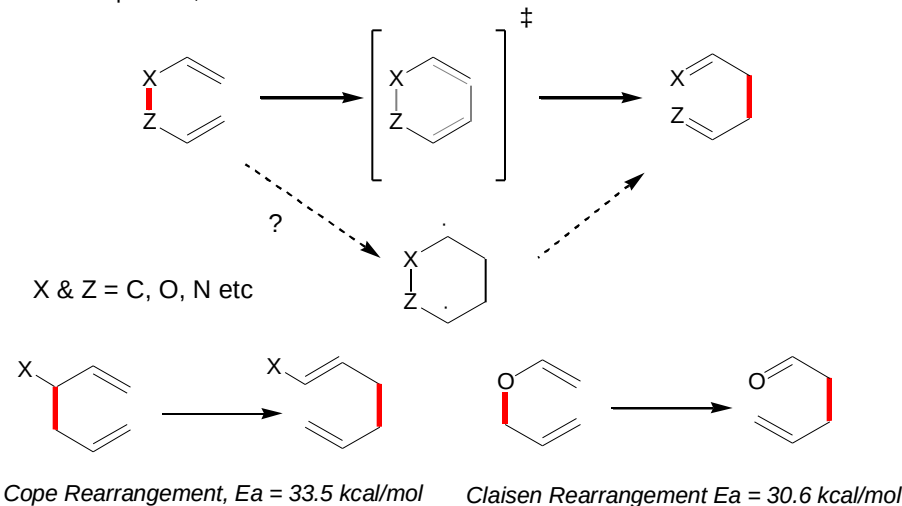
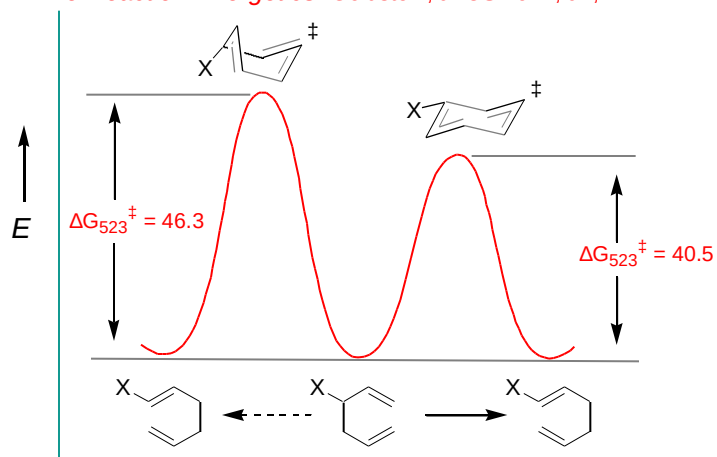
Provide a mechanism for the indicated transformation



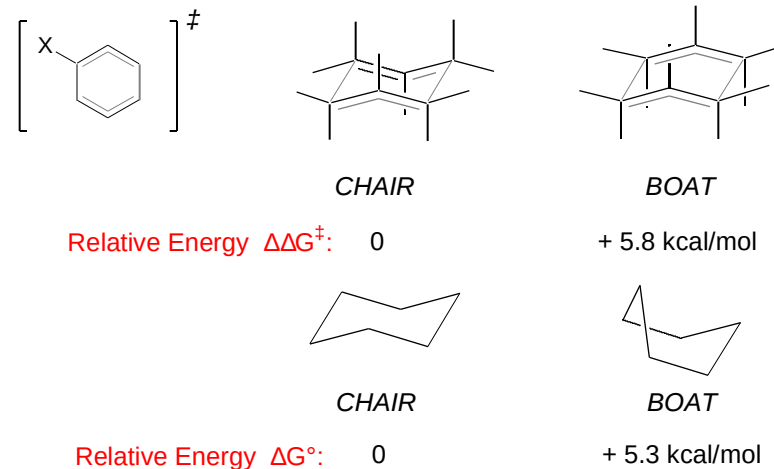
Schreiber, *JACS* **1984**, 106, 4038

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

The Reaction Energetics Goldstein, JACS **1972**, 94, 7147

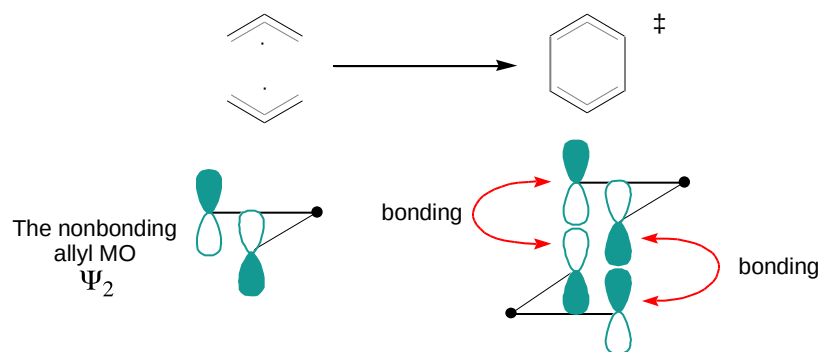
The Cope Transition States



The Boat and Chair geometries for these transition structures are well defined.

The FMO Analysis (Fleming page 101)

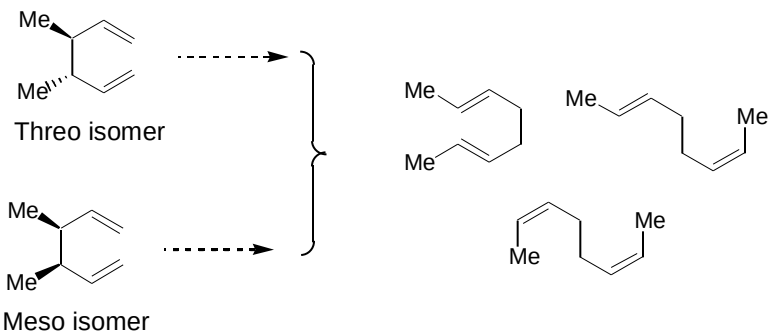
Bring two Allyl radicals together to access for a possible bonding interaction between termini.



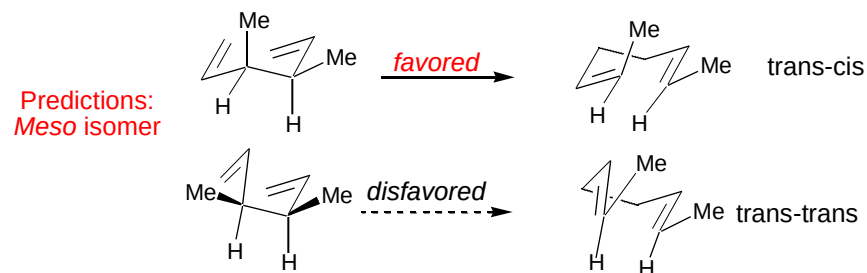
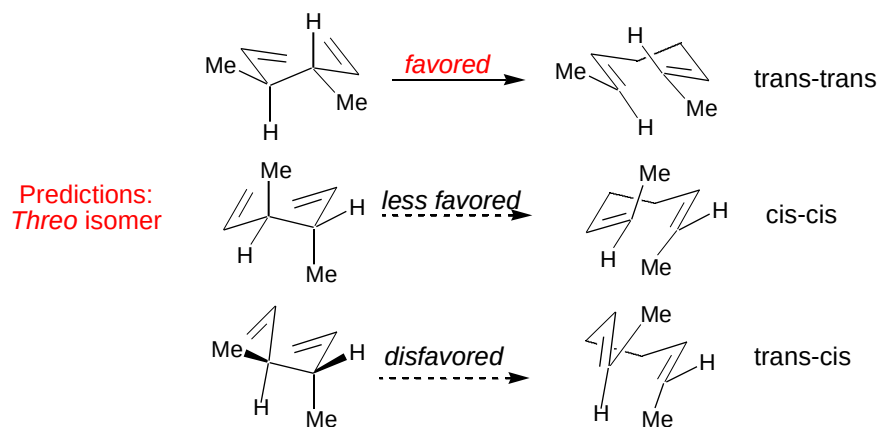
It is evident that synchronous bonding is possible in this rearrangement

Doering & Roth *Tetrahedron* **18**, 67, (1962):

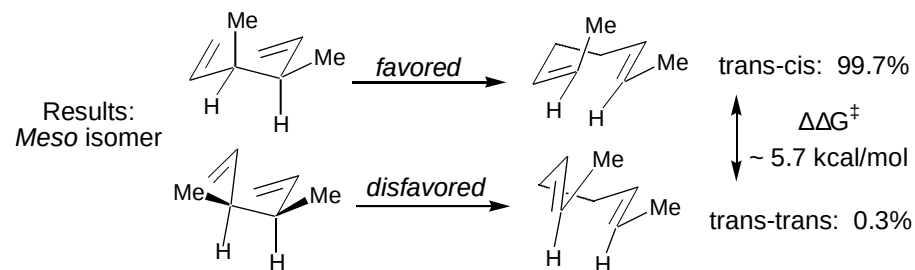
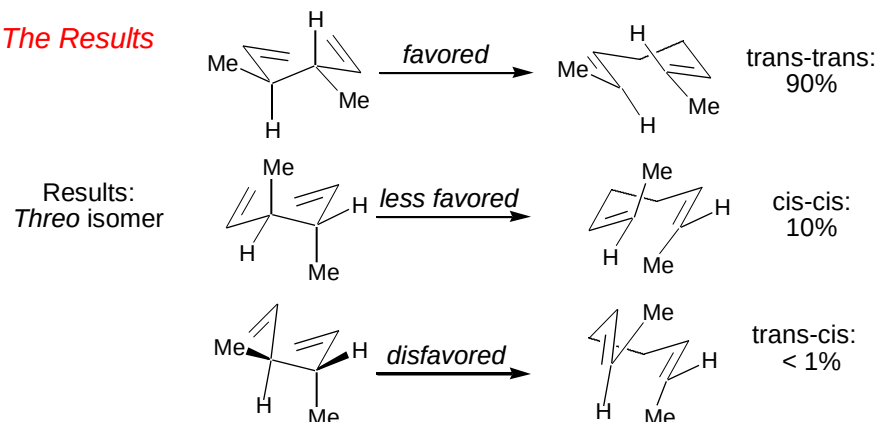
The Geometry of the transition state (boat vs chair) can be analyzed via the rearrangement of substituted 1,5-dienes:



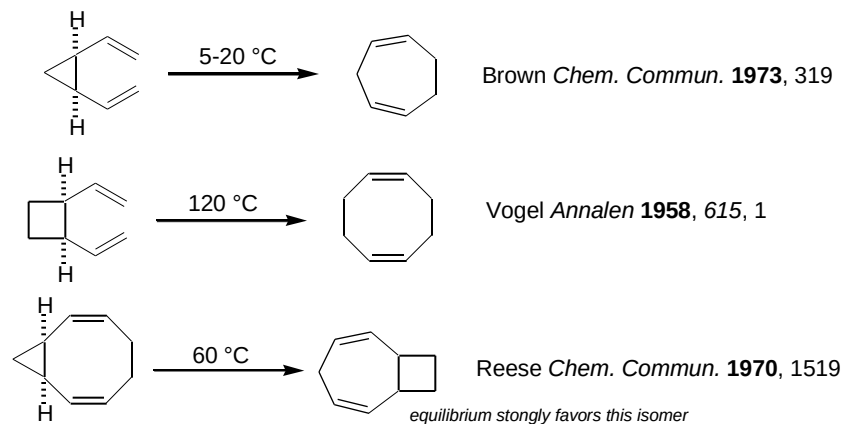
■ Measure product composition from rearrangement of each diene isomer



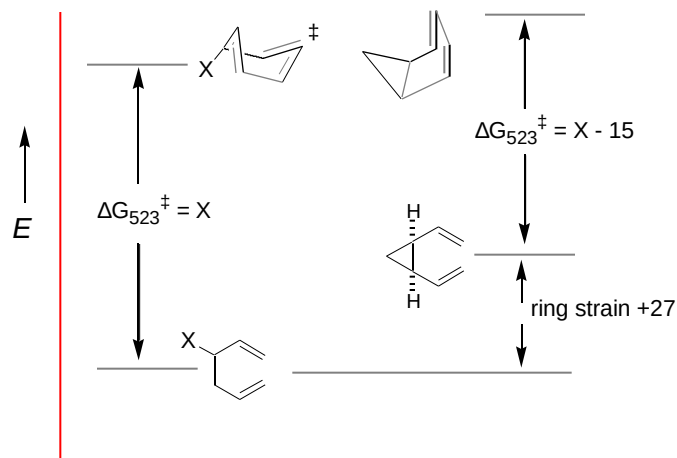
The Results



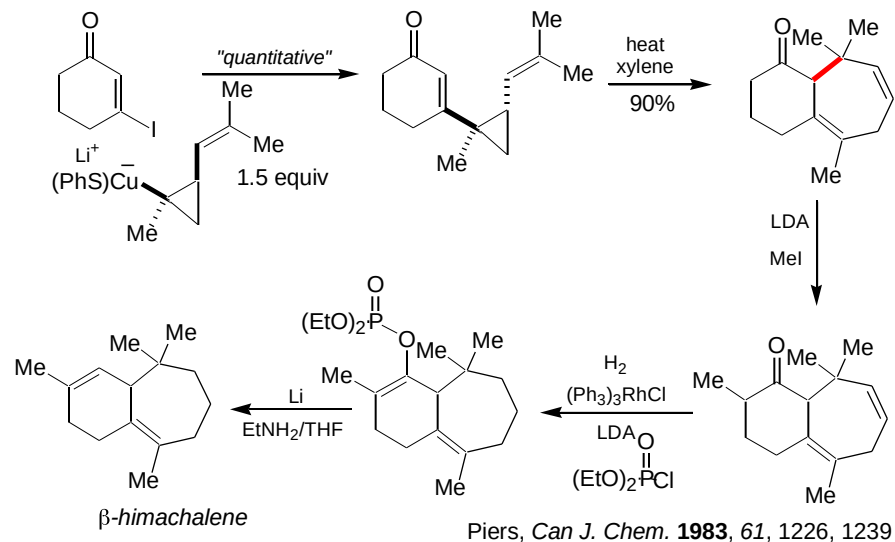
■ Ring Strain can be employed to drive the Cope process:



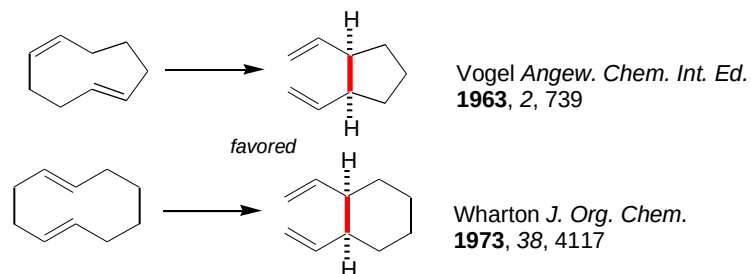
Cyclopropyl substitution is a ground state effect



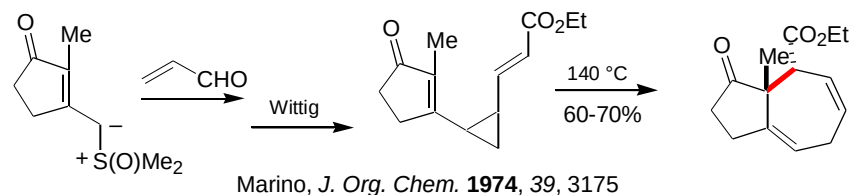
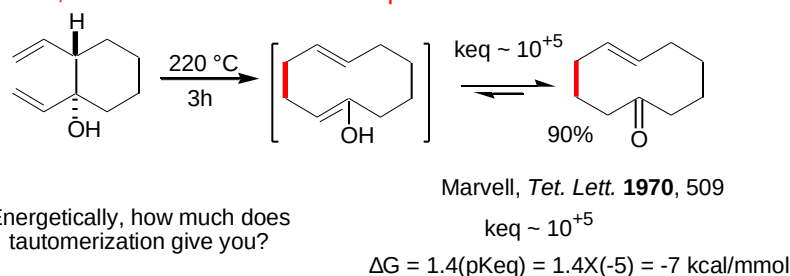
Ring extension via divinylcyclopropane rearrangement



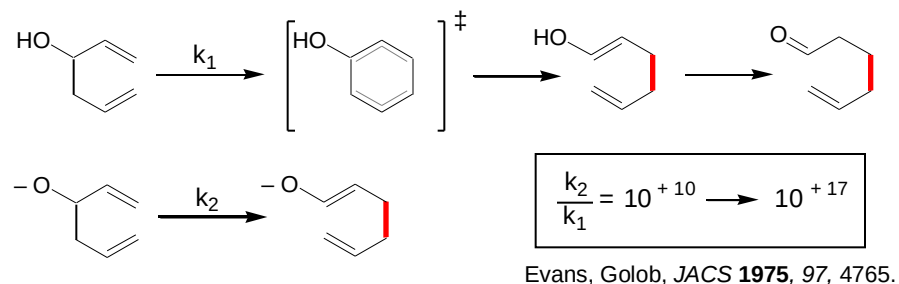
Position of Equilibrium dictated by ring strain issues:



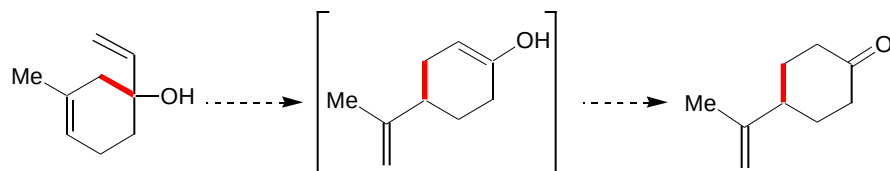
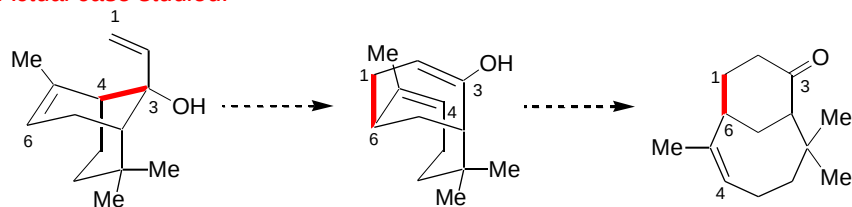
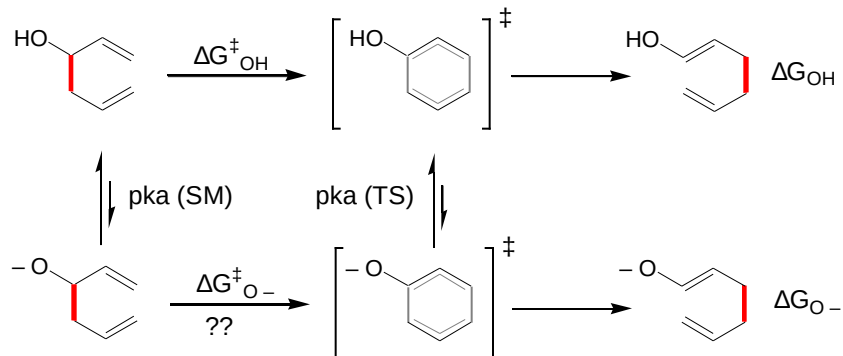
However, tautomerism can shift the equilibrium:



Accelerated Cope Rearrangements



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

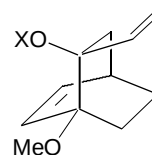
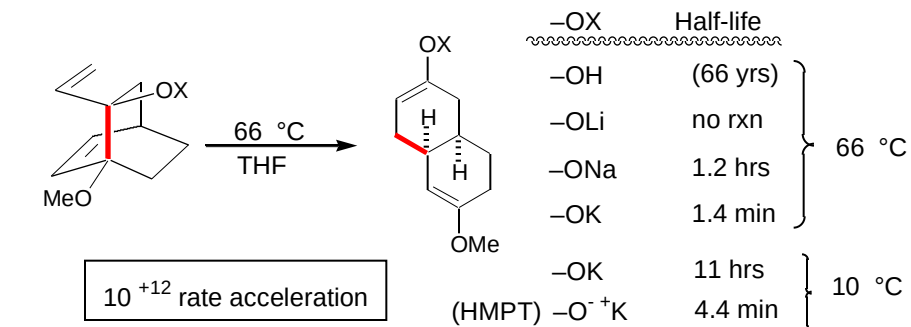
The Aborted Oxy-Cope Reaction (circa 1969)■ **The basic reaction**■ **Actual case studied:****Prediction of Substituent Effect (circa 1969)**

$$\Delta G_{O-}^{\ddagger} = \Delta G_{OH}^{\ddagger} + 2.3RT [pK_{a\text{ TS}} - pK_{a\text{ SM}}]$$

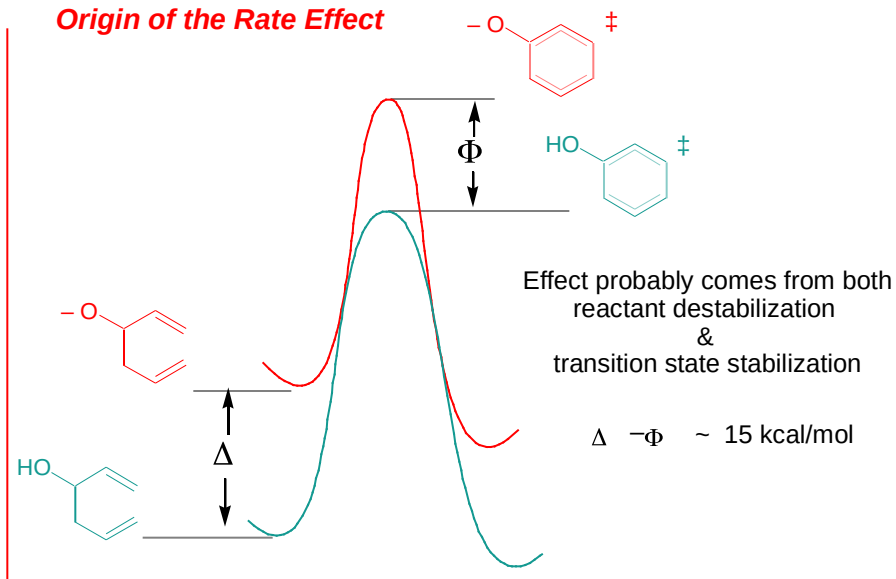
$$\Delta G_{O-}^{\ddagger} = \Delta G_{OH}^{\ddagger} + 2.3RT [18 - 29] \text{ (in DMSO)}$$

$$\Delta G_{O-}^{\ddagger} = \Delta G_{OH}^{\ddagger} + 1.4 [-11]$$

$$\Delta G_{O-}^{\ddagger} = \Delta G_{OH}^{\ddagger} - 15 \text{ kcal/mol at 298 K (in DMSO)}$$

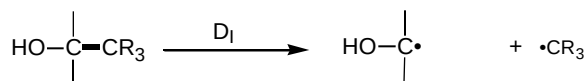
Documentation of Alkoxy Substituent Effect

with A. M. Golob, JACS. 1975, 97, 4765.

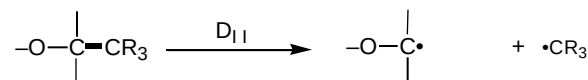
Origin of the Rate Effect

Maximal rates are observed under conditions where reactant is maximally destabilized

Substituent Effects in Bond Homolysis



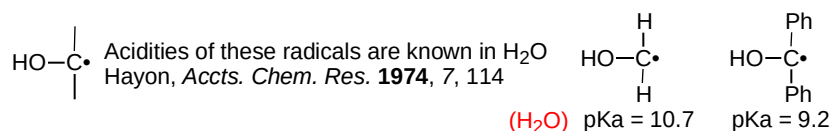
A



B

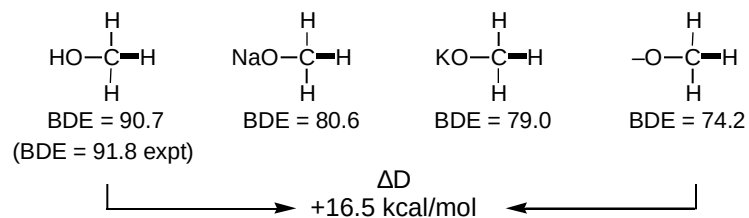
ketyl

$$D_I - D_{II} = 2.3 RT[\text{pKa}(\text{A}) - \text{pKa}(\text{B})]$$

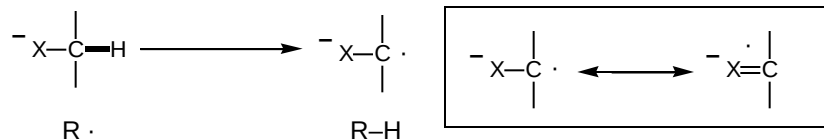
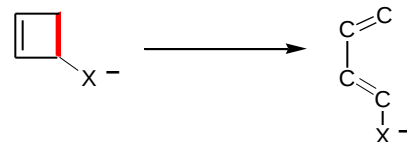
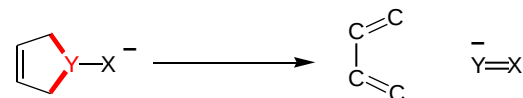
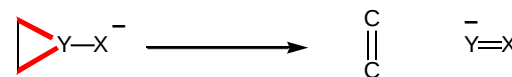
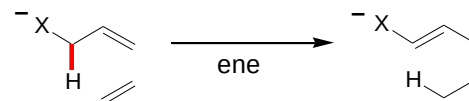
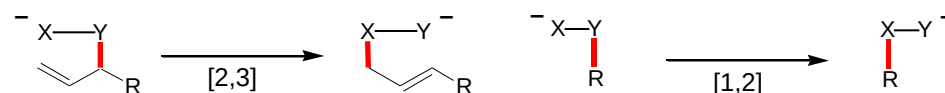
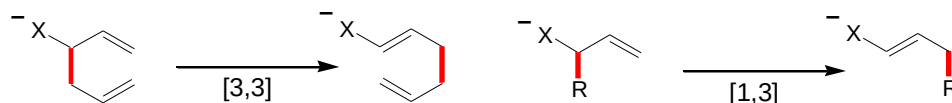


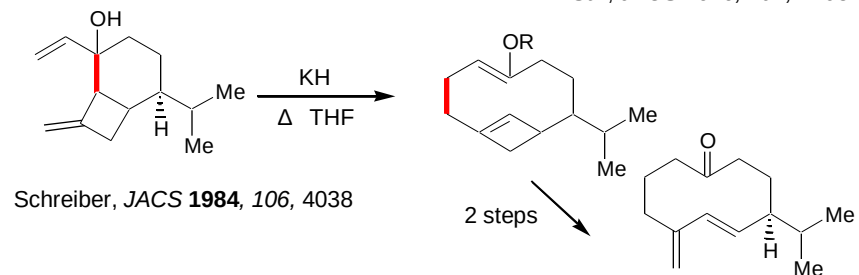
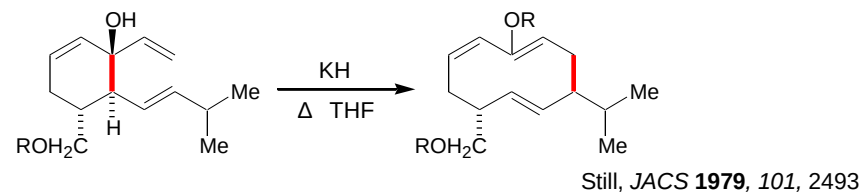
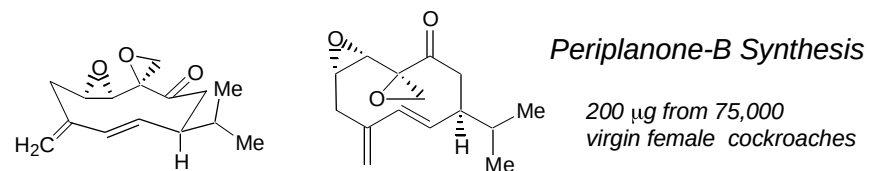
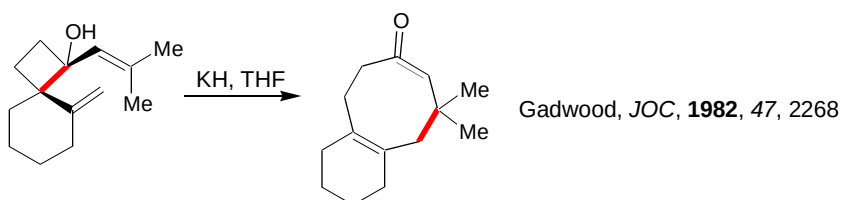
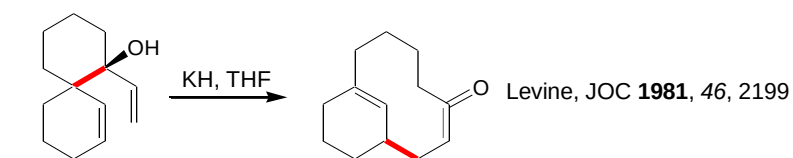
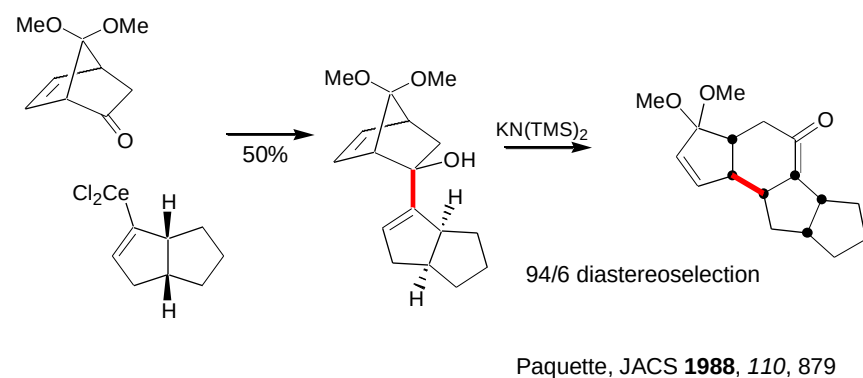
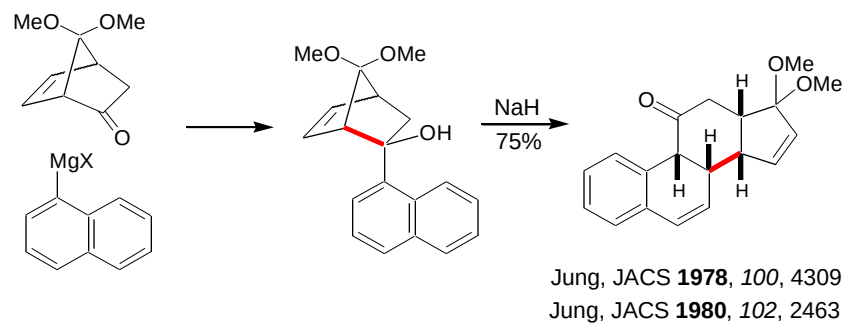
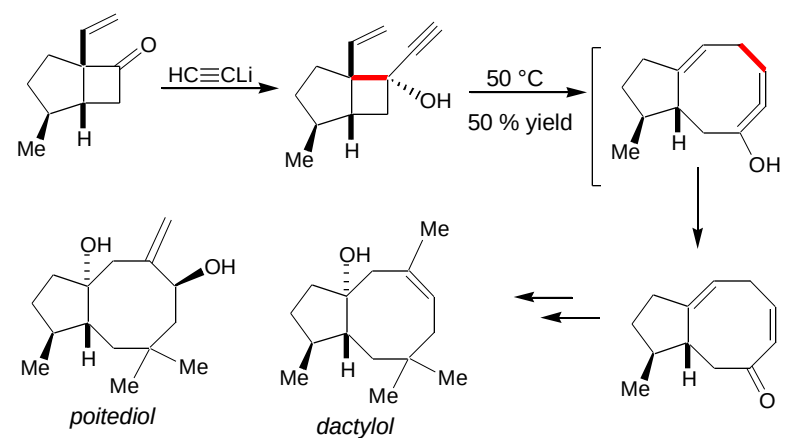
In DMSO: $\Delta D = 2.3 RT[29 - \text{pKa} 18] = \sim 15 \text{ kcal/mol}$

Substituent Effect based on ab initio calculations

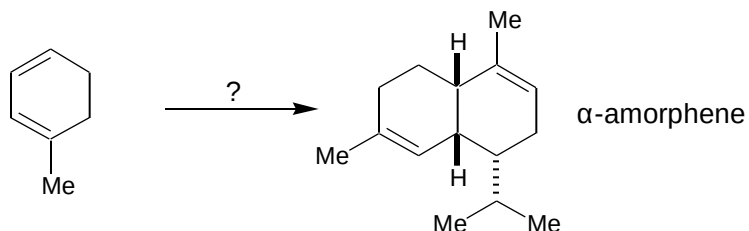
(Evans, Goddard, *JACS* **1979**, 101, 1994)Related papers: Evans, Baillargeon, *Tet Lett.* **1978**, 36, 3315, 3319

Substituent Effects in Molecular Rearrangements

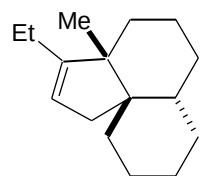


Gadwood, JACS, **1986**, *108*, 6343

Propose a synthesis of α -amorphene using 1-methyl-1,3-cyclohexadiene.

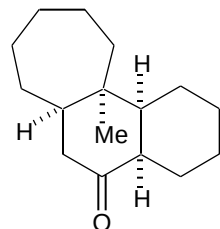


Gregson, R. P.; Mirrington, R. N. *J. Chem. Soc., Chem. Commun.* **1973**, 598.



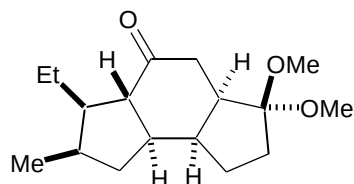
By incorporating a carbonyl group into this structure generate all possible oxy-Cope retrons. Which is (are) the most reasonable?

Bérubé, G.; Fallis, A. G. *Tetrahedron Lett.* **1989**, 30, 4045.



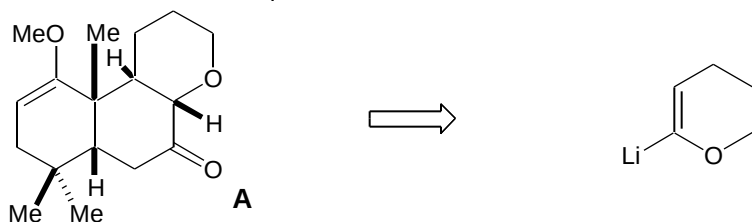
By incorporating a double bond into this structure generate all possible oxy-Cope retrons. Which is (are) the most reasonable?

Ireland, et al. *J. Org. Chem.* **1981**, 46, 4863.



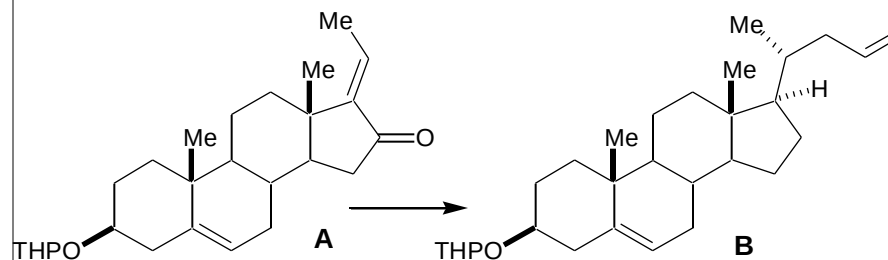
By incorporating a double bond into this structure generate all possible oxy-Cope retrons. Which is (are) the most reasonable?

Paquette, L. A. et al. *Tetrahedron Lett.* **1987**, 28, 31.



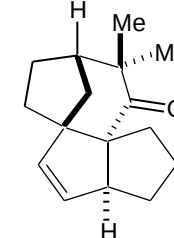
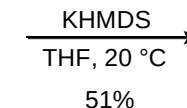
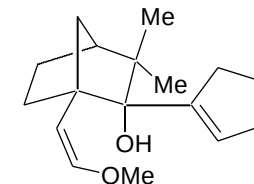
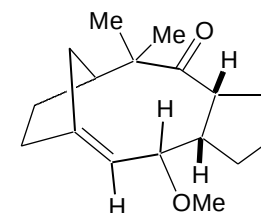
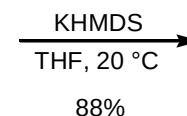
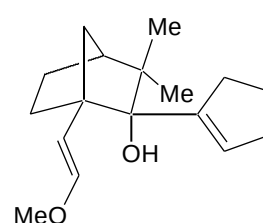
Propose a synthesis of **A** using the illustrated dihydropyran synthon.

Oplinger, J. A.; Paquette, L. A. *Tetrahedron Lett.* **1987**, 28, 5441.



Propose a three step synthesis of **B** from **A**.

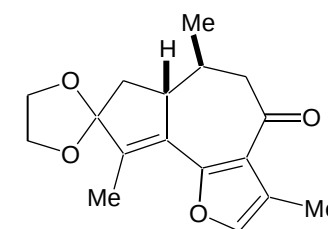
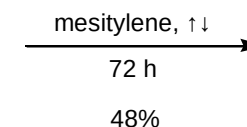
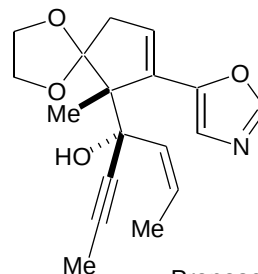
Koreeda, et al. *J. Org. Chem.* **1980**, 45, 1172.



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.



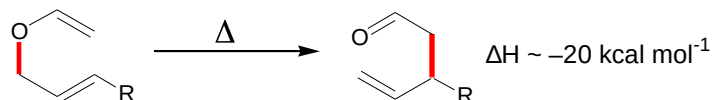
Propose a detailed mechanism paying particular attention to issues of chemo- and stereoselectivity.

Jacobi, P. A.; Selnick, H. G. *J. Org. Chem.* **1990**, 55, 202.

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:

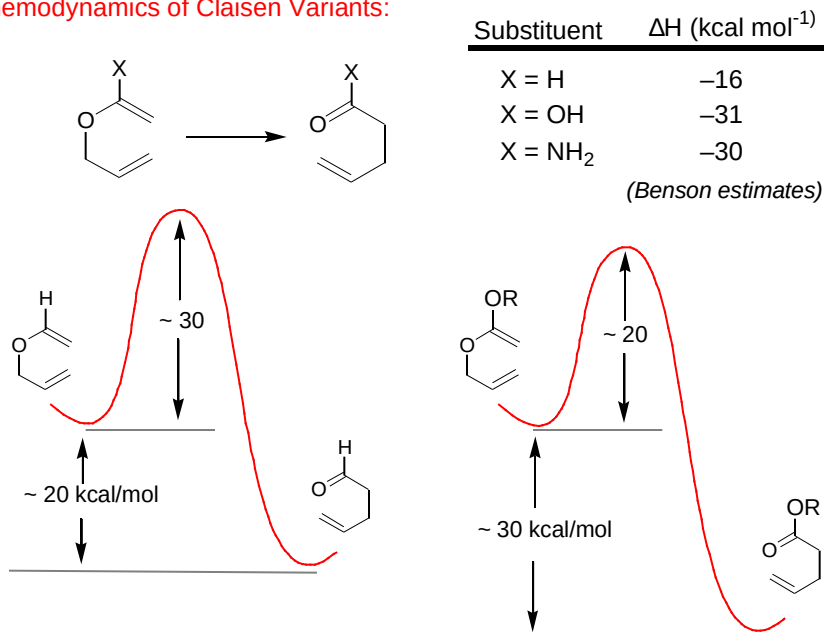


There is good thermodynamic driving force for this reaction.

Bonds Broken: C-C π (65 kcal mol⁻¹) & C-O σ (85 kcal mol⁻¹)

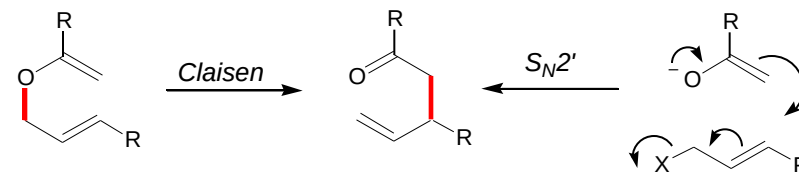
Bonds Made: C-O π (85 kcal mol⁻¹) and C-C σ (85 kcal mol⁻¹)

Thermodynamics of Claisen Variants:

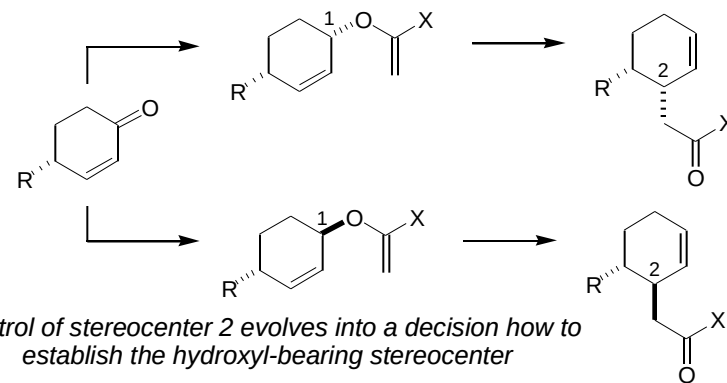


Heteroatom substitution at the indicated position increases exothermicity as well as reaction rate

Recognition Pattern for Organic Synthesis: An Enforced S_N2'

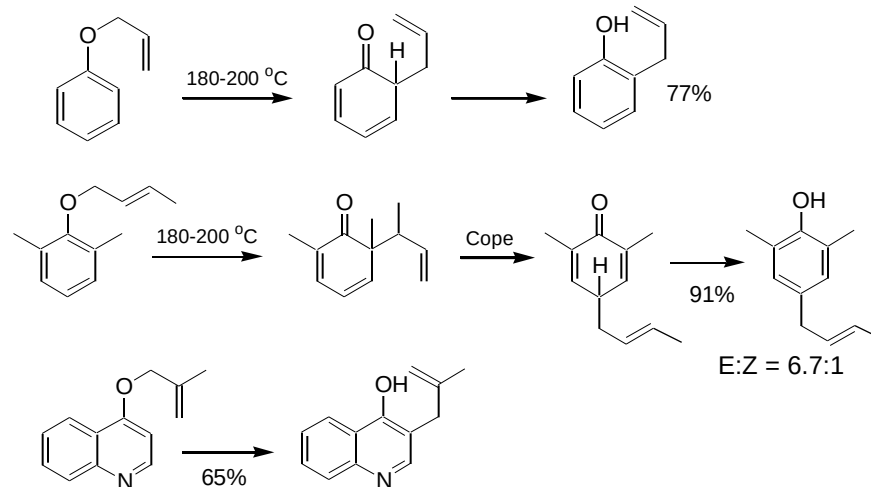


Stereochemical outcome is syn and controlled by hydroxyl stereocenter



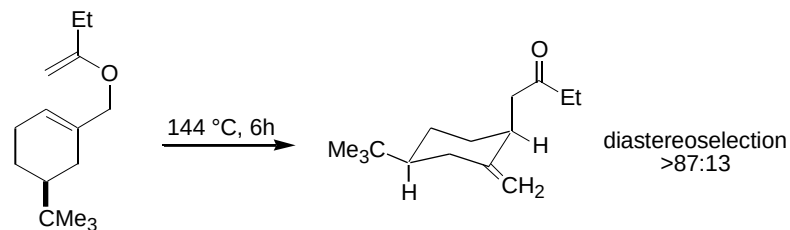
Control of stereocenter 2 evolves into a decision how to establish the hydroxyl-bearing stereocenter

Rearrangements of Aryl Allyl Ethers: Traditional Applications



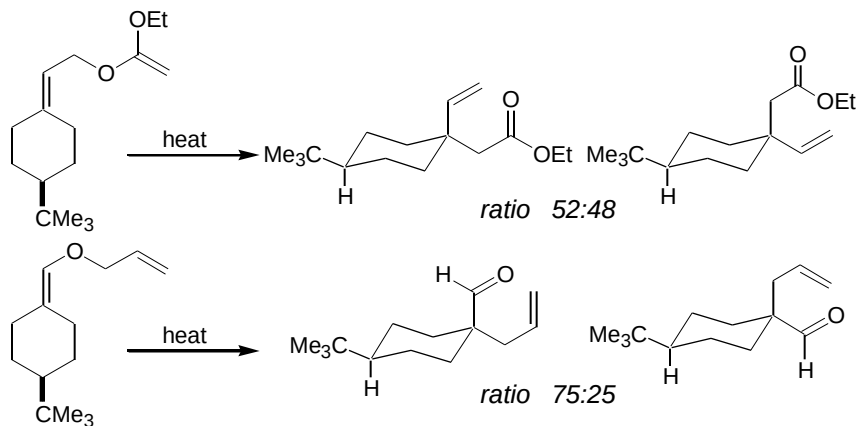
Stereoelectronic & steric constraints

■ Endocyclic Olefins: Ireland, JOC 1983, 48, 1829



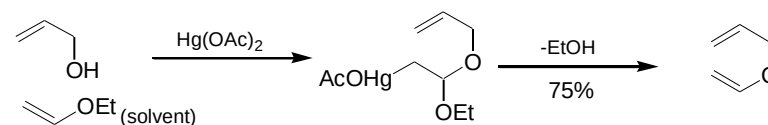
for endocyclic olefins, overlap between developing sigma and pi bonds required

■ Exocyclic Olefins: House, JOC 1975, 40, 86

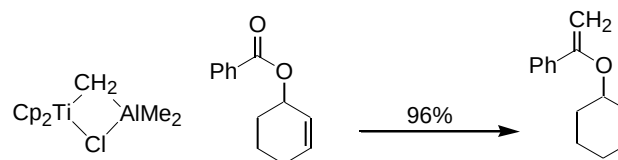


for exocyclic olefins, overlap between developing sigma and pi bonds is equally good from either olefin diastereoface. In this instance, steric effects dominate & this system shows a modest preference for "equatorial attack." A related case is provided below.

Synthesis of Allyl Vinyl Ethers

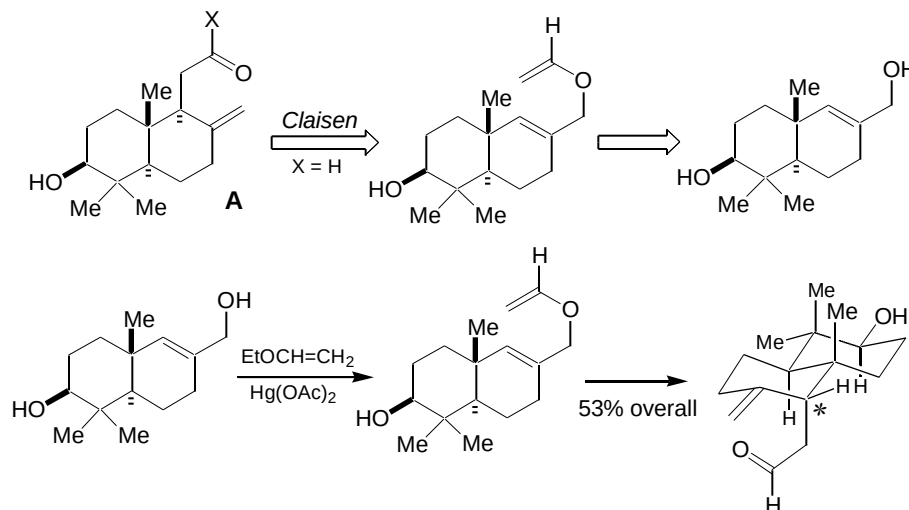


Watanabe, Conlon, JACS **1957**, 79, 2828
Bronsted acids can also serve as catalysts



Use of Tebbe's Reagent: Evans, Grubbs, *J. Am. Chem. Soc.* **1980**, 102, 3272.
(review) S. H. Pines, *Organic Reactions* **1993**, 43, 1

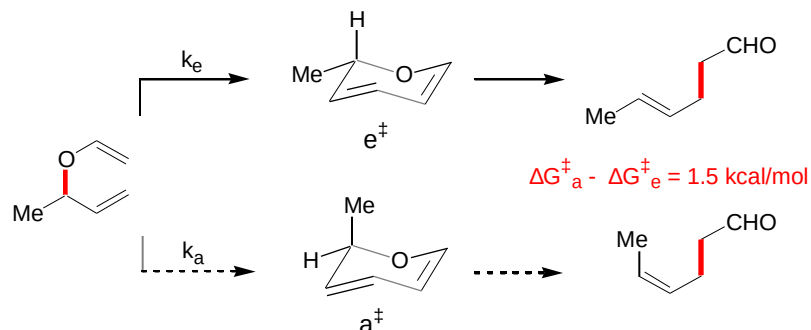
■ The Ireland approach to the bicyclic acid A: JOC 1962, 27, 1118



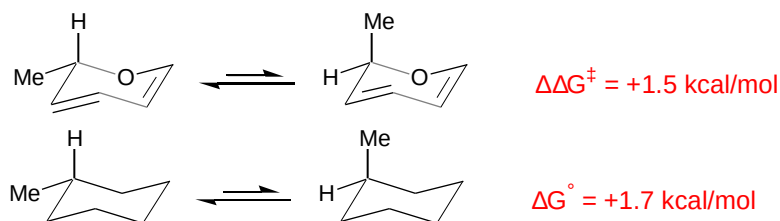
The new stereocenter (*) introduced via the rearrangement had the wrong configuration!

Claisen Rearrangement as vehicle for stereoselective olefin synthesis

Consider the following rearrangement:

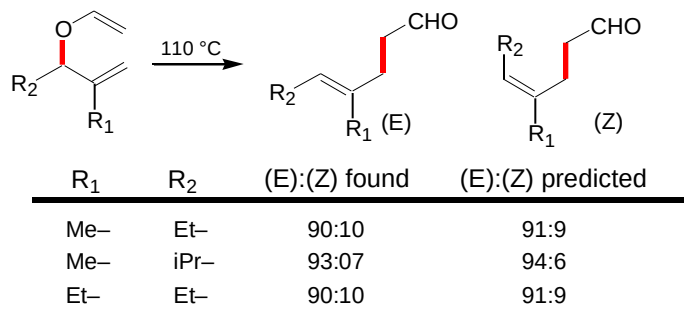


Faulkner & Perrin (Tet. Lett. 2783 (1969) have made the correlation between $\Delta\Delta G^\ddagger$ for rearrangement & ΔG° for the corresponding cyclohexane[#] equilibria:



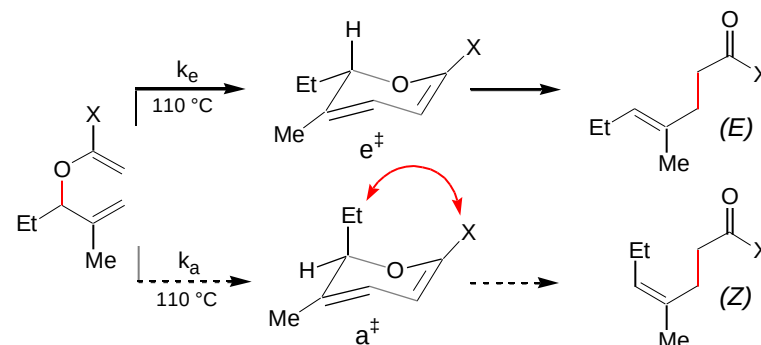
[#]Note: The A-value of 2-methyl-tetrahydropyran is +2.86 kcal/mol (Eliel pg 743)

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 examples:



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 $a^\ddagger$ as X gets progressively larger.

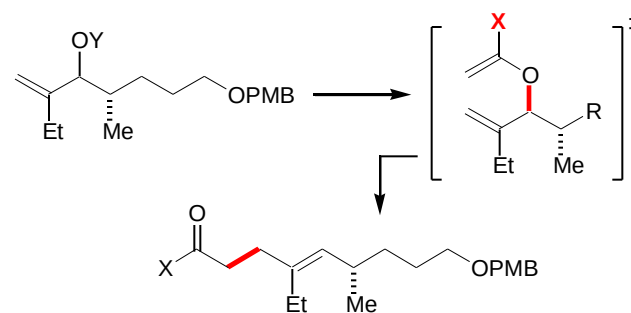
X	(E):(Z) found
H-	90:10
Me-	>99:1
MeO-	>99:1
Me ₂ N-	>98:2

Faulkner, *Tet Let* **1969**, 3243

Faulkner, *JACS* **1973**, 95, 553

Johnson, *JACS* **1970**, 92, 741

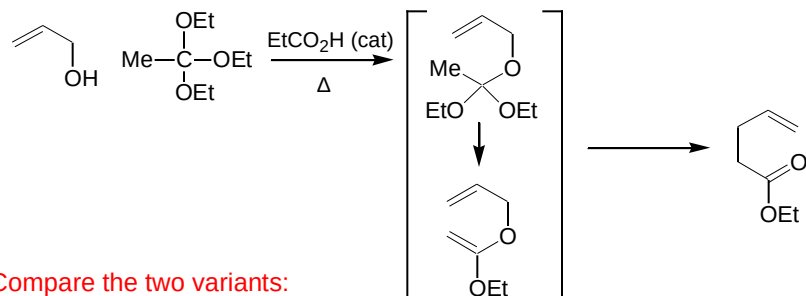
■ Another comparison: (DAE) M. DiMare, Ph. D. Harvard University, 1988



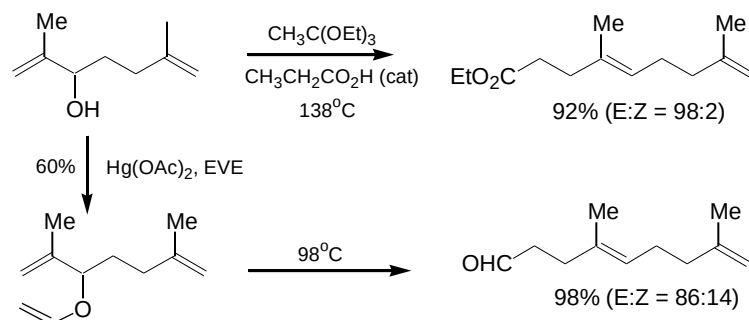
procedure	conditions	X	T, °C	(E):(Z) ratio
Y = Ac, Ireland	LDA, TMSCl	TMSO-	-78 → +55	97:3
Y = H, Johnson	HC(OMe) ₃ , H ⁺	MeO-	130	94:6
Y = H, Eschenmoser	MeC(OMe) ₂ NMe ₂	Me ₂ N-	80	97.5:2.5

Johnson Orthoester Claisen

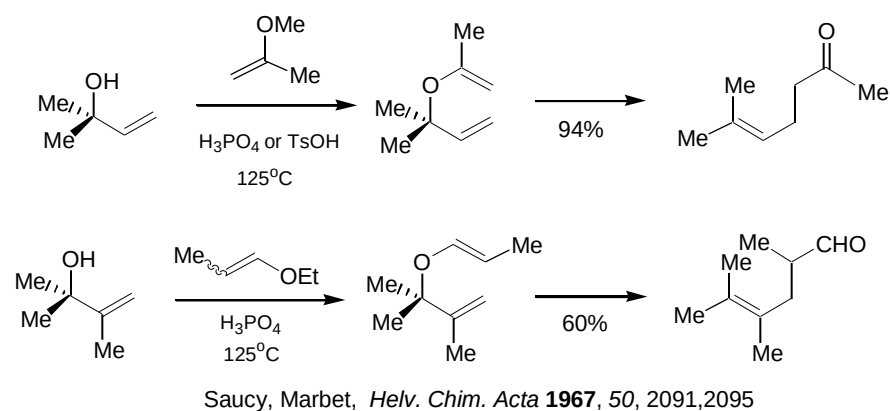
■ Lead paper: Johnson, Faulkner, Peterson, JACS **1970**, 92, 741



■ Compare the two variants:

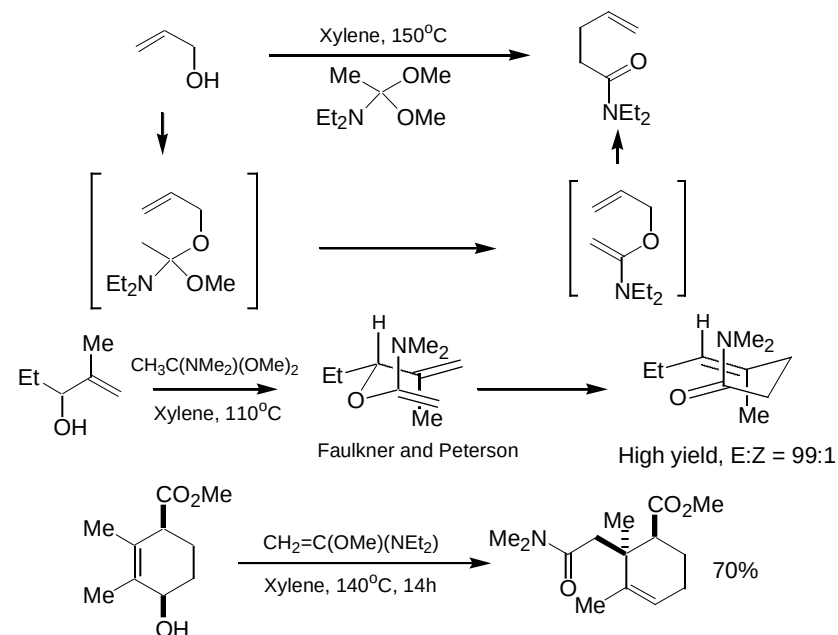


The Saucy Marbet Alternative

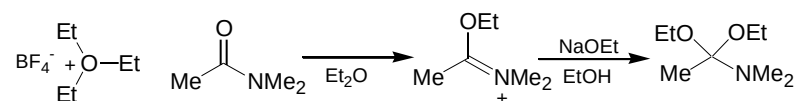


Eschenmoser-Claisen

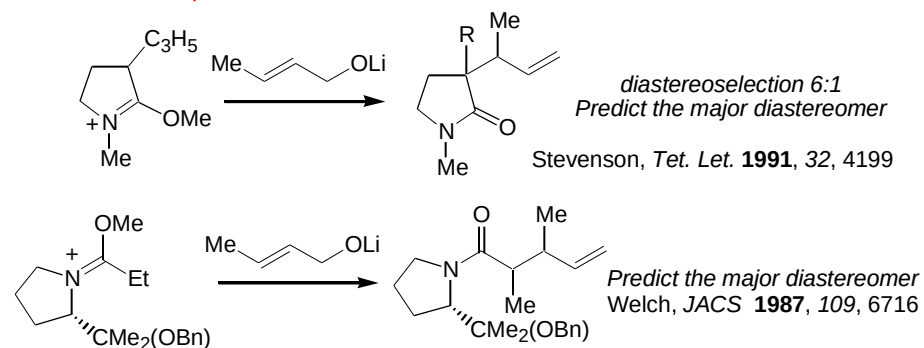
Eschenmoser, A. *Helv. Chem. Acta* **1964**, 47, 2425; *Helv. Chim. Acta* **1969**, 52, 1030.



■ Synthesis of Amide Acetals



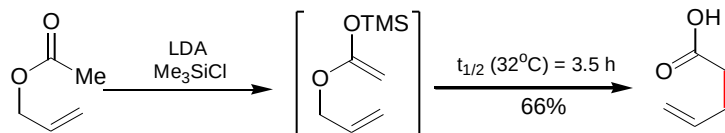
■ Reactions to ponder:



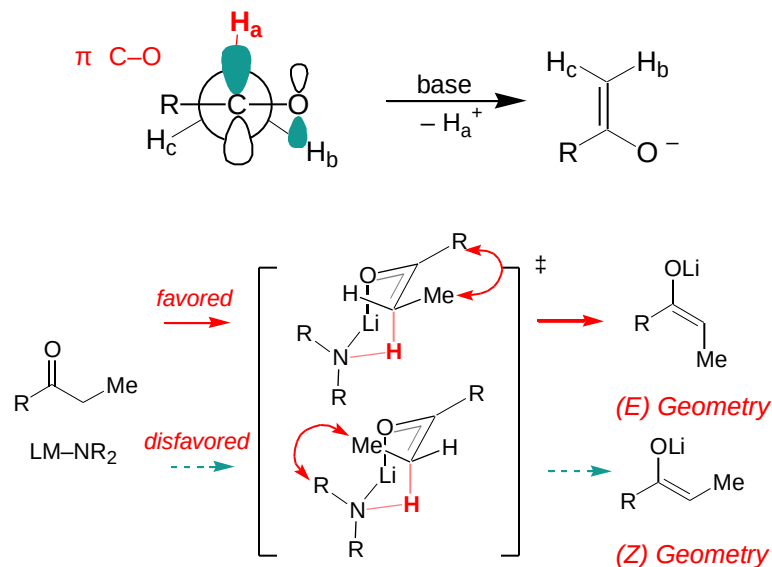
Ireland-Enolate Claisen

- Reviews Pereira, *Aldrichimica Acta* **1993**, 26, 17-29 (Ireland-Claisen)
 Ireland, *Aldrichimica Acta* **1988**, 21, 59-69 (Claisen-related)

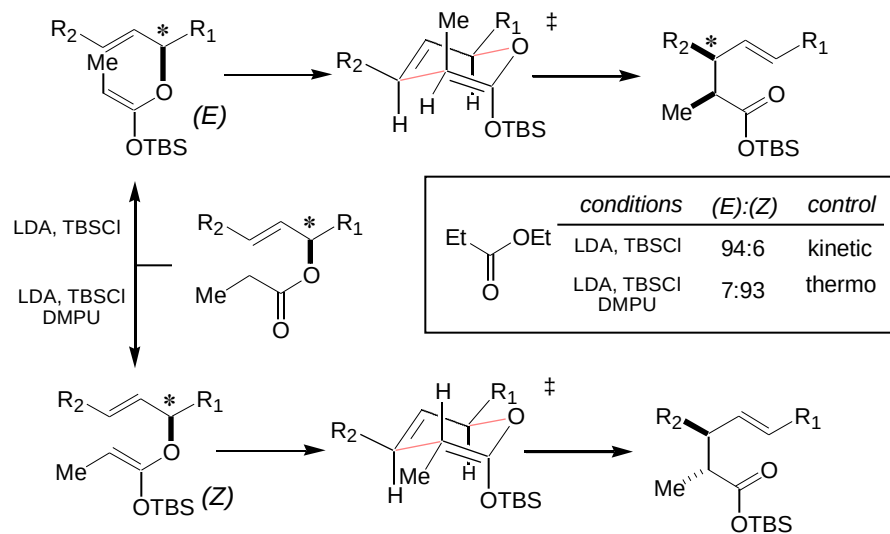
Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, 98, 2868

**Enolization: Amide Bases**

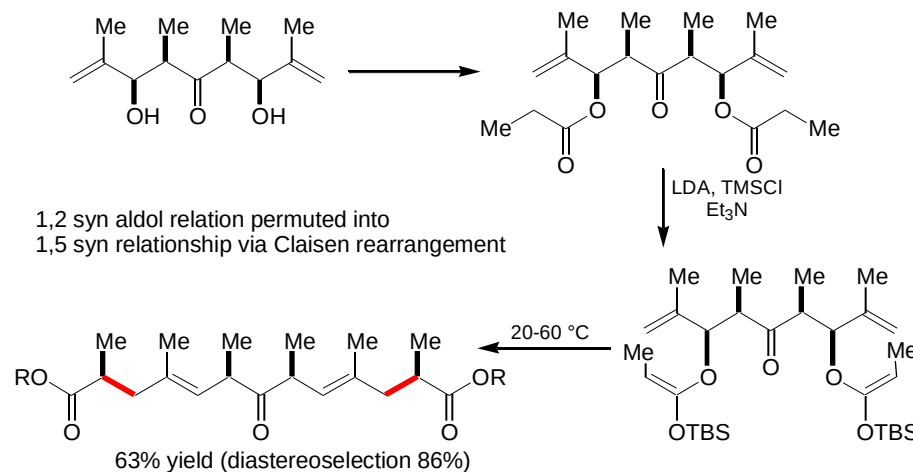
Stereoelectronic Requirements: The α -C-H bond must be able to overlap with π C=O



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**Double Claisen Rearrangements are also possible**

Paterson, *Tet Lett* **1991**, 32, 7601



<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] Cycloaddition Reactions

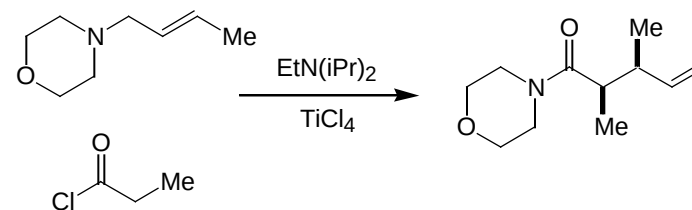
Tidwell, T. T. *Ketenes*, John Wiley and Sons, **1995**.
Ghosez, L.; Marchand-Brynaert, J. *Comprehensive Organic Synthesis*, Vol. 5, Pergamon, **1991**, p. 85-122.

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](#))

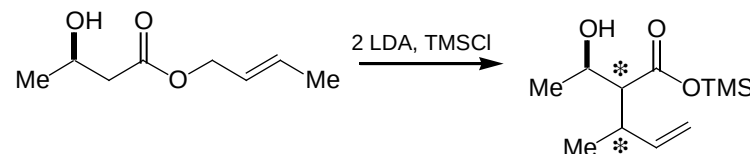
■ Problems of the Day:

Propose a mechanism for this transformation



MacMillan, *JACS* **1999**, 121, 9726

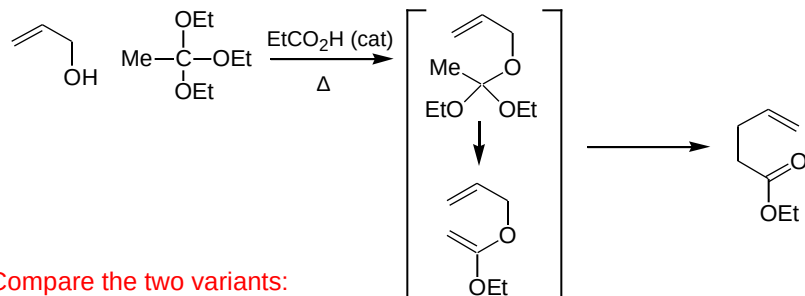
Predict the stereochemical outcome of this reaction



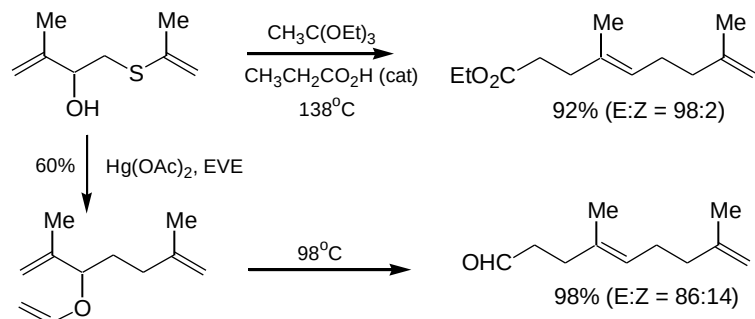
Kurth, *JOC* **1985**, 50, 1840

Johnson Orthoester Claisen

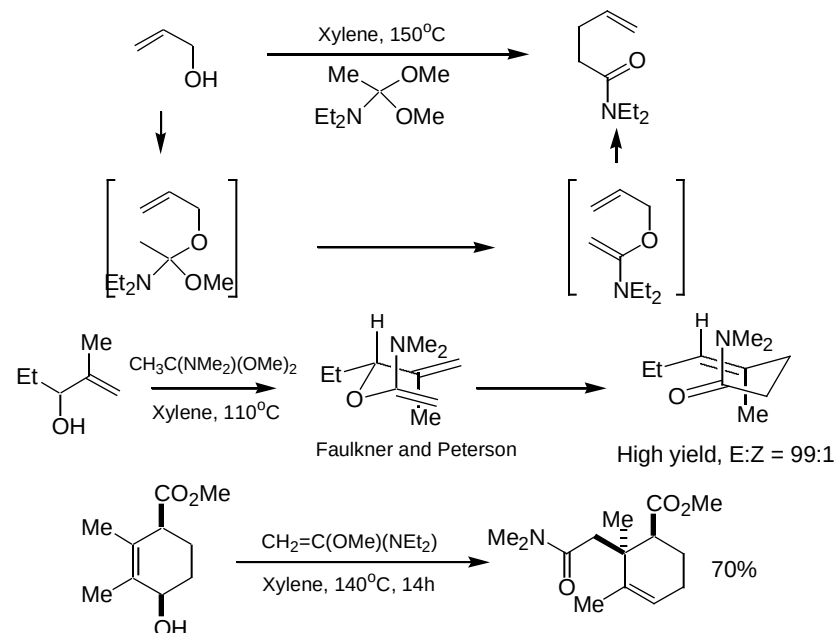
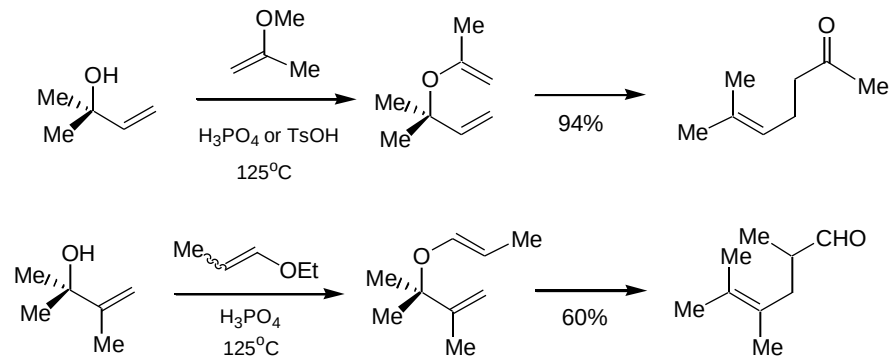
■ Lead paper: Johnson, Faulkner, Peterson, JACS **1970**, 92, 741



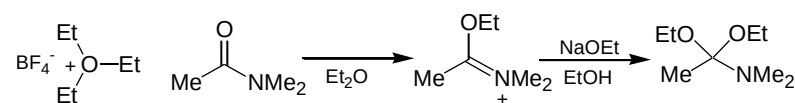
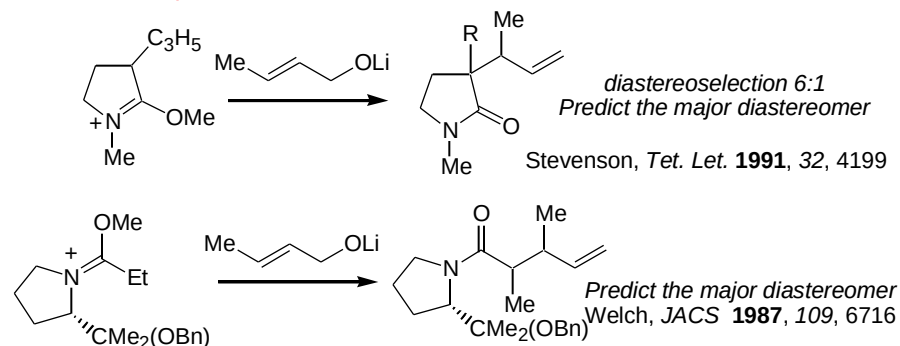
■ Compare the two variants:

**Eschenmoser-Claisen**

Eschenmoser, A. *Helv. Chem. Acta* **1964**, 47, 2425; *Helv. Chim. Acta* **1969**, 52, 1030.

**The Saucy Marbet Alternative**

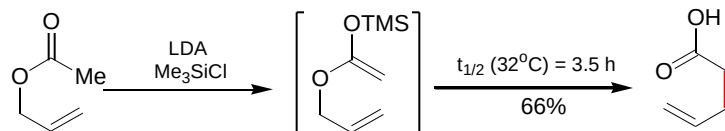
Saucy, Marbet, *Helv. Chim. Acta* **1967**, 50, 2091, 2095

Synthesis of Amide Acetals**Reactions to ponder:**

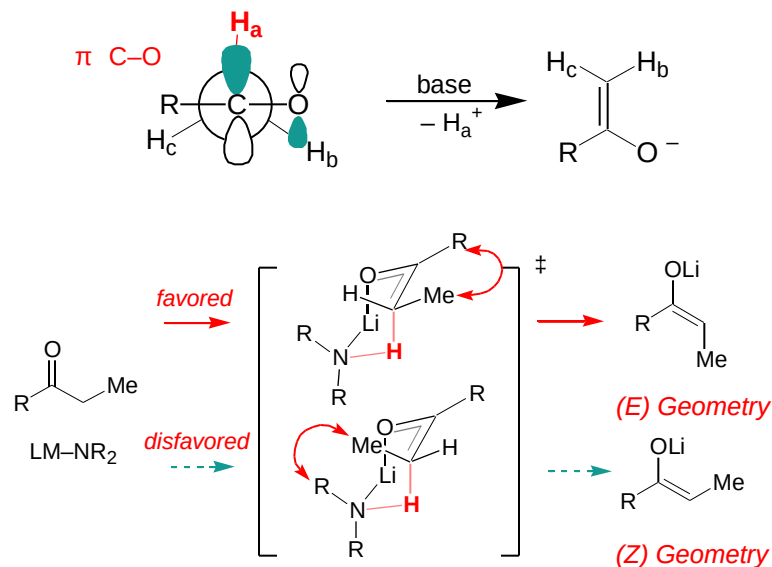
Ireland-Enolate Claisen

- Reviews Pereira, *Aldrichimica Acta* **1993**, 26, 17-29 (Ireland-Claisen)
 Ireland, *Aldrichimica Acta* **1988**, 21, 59-69 (Claisen-related)

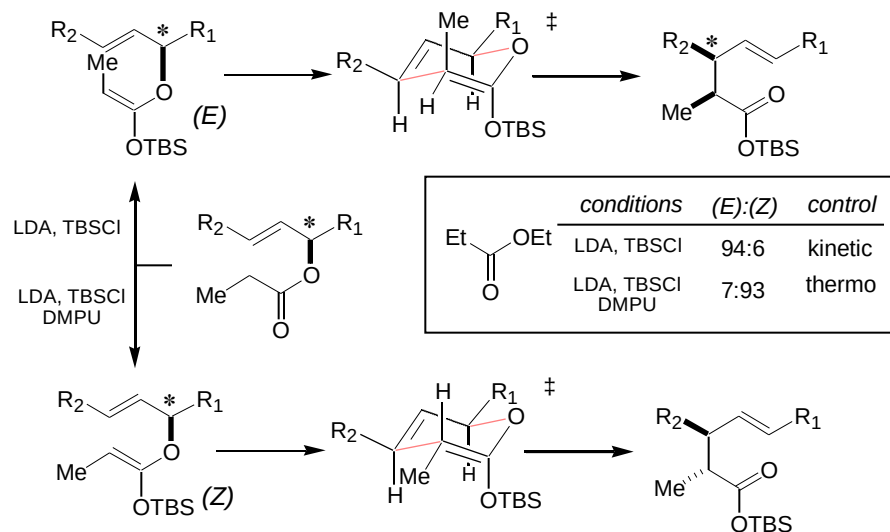
Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, 98, 2868

**Enolization: Amide Bases**

Stereoelectronic Requirements: The α -C-H bond must be able to overlap with π C=O



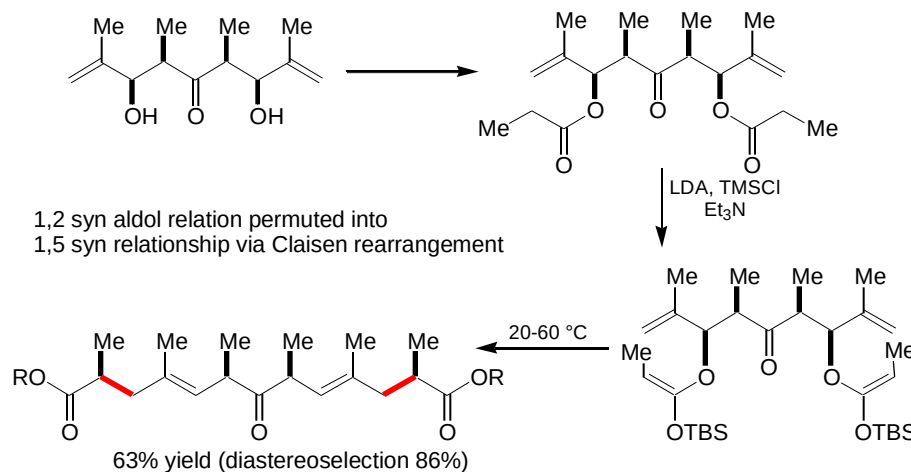
The Ireland Model (*JACS* **1976**, 98, 2868)
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 more recent study: Ireland, *JOC* **1991**, 56, 650

Substituted enolates afford an additional stereocenter

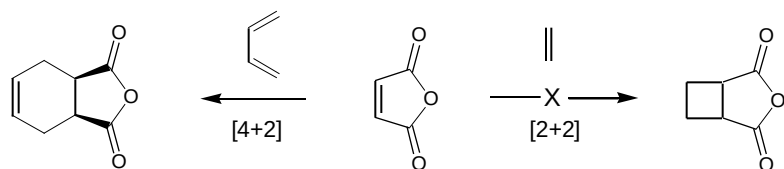
key study: Ireland, *JOC* **1991**, 56, 650 and earlier cited papers

Double Claisen Rearrangements are also possible

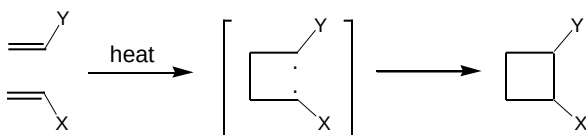
Paterson, *Tet Lett* **1991**, 32, 7601



Why does maleic anhydride react easily with 1,3-butadiene, but not with ethylene? So what are the "rules"?



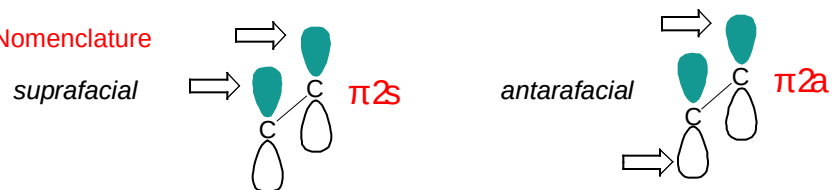
■ The related reaction of 2 ethylenes is nonconcerted: $[2+2]$ cycloaddition



■ We also know that the photochemical variant is concerted

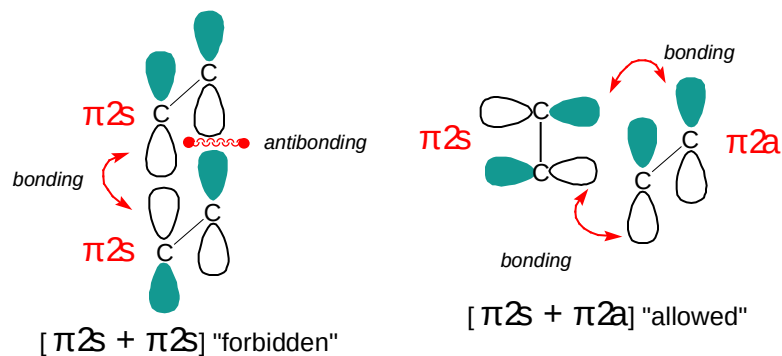
The frontier orbitals of the reacting species must have the proper symmetries

■ Nomenclature

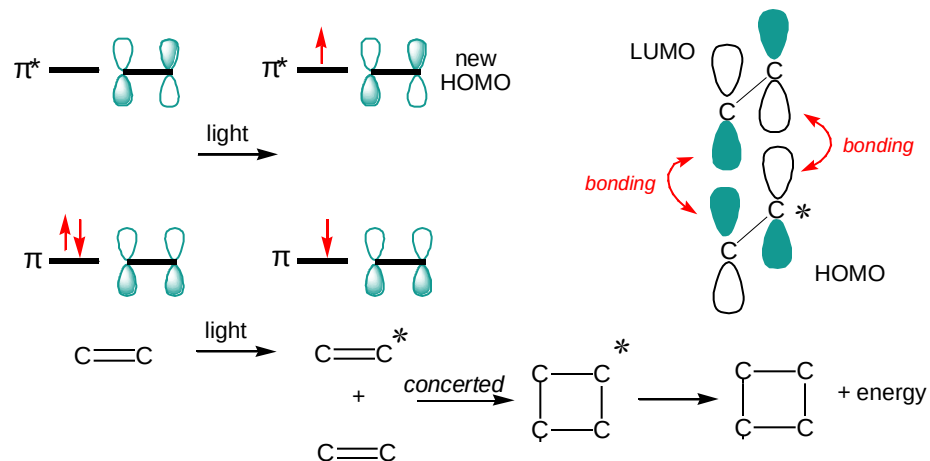


Using this nomenclature, the Diels-Alder reaction is a $\pi_{4s} + \pi_{2s}$ cycloaddition

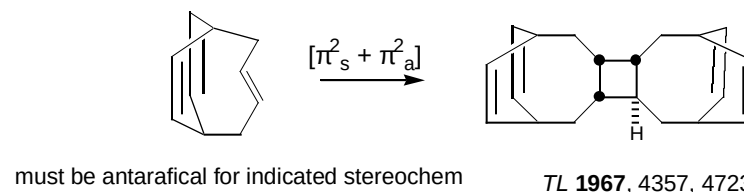
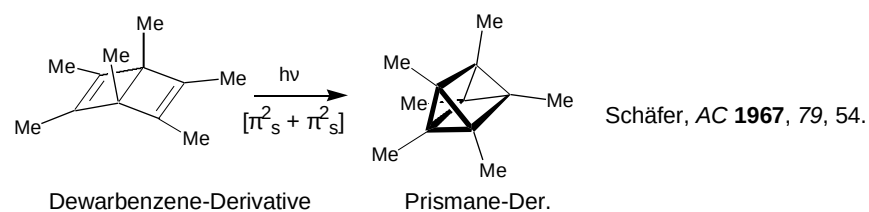
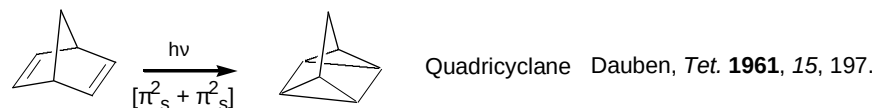
■ Consider $[2+2]$ cycloaddition: Thermal activation $[\pi_{2s} + \pi_{2s}]$



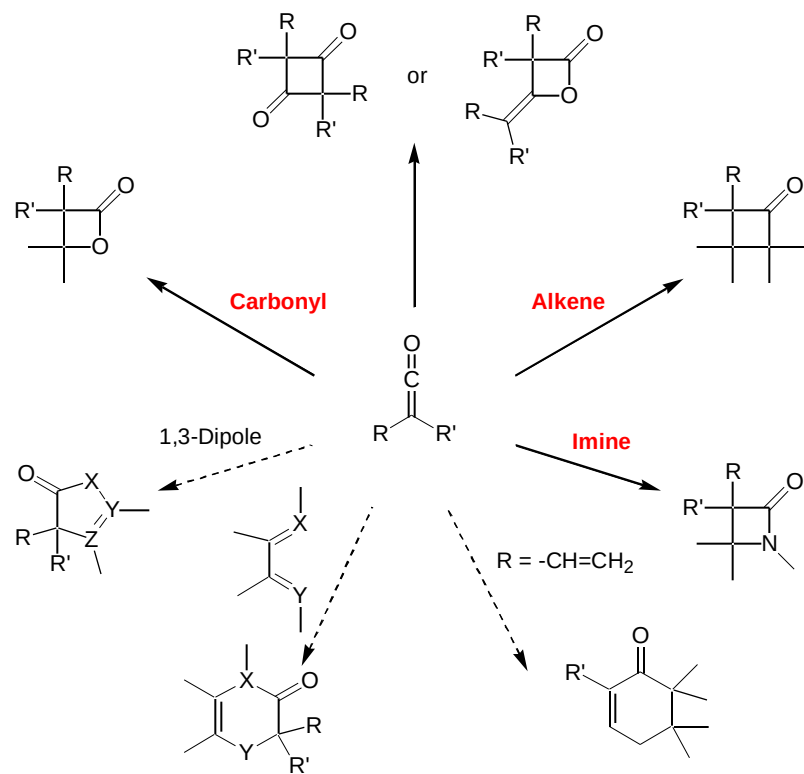
■ Consider $[2+2]$ cycloaddition: Photochemical activation $[\pi_{2s} + \pi_{2s}]$



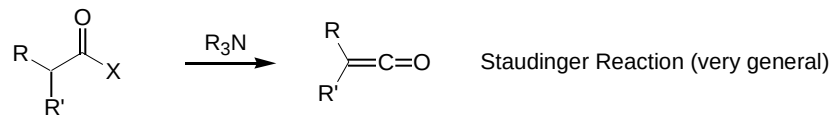
$[2+2]$ Cycloaddition - Examples



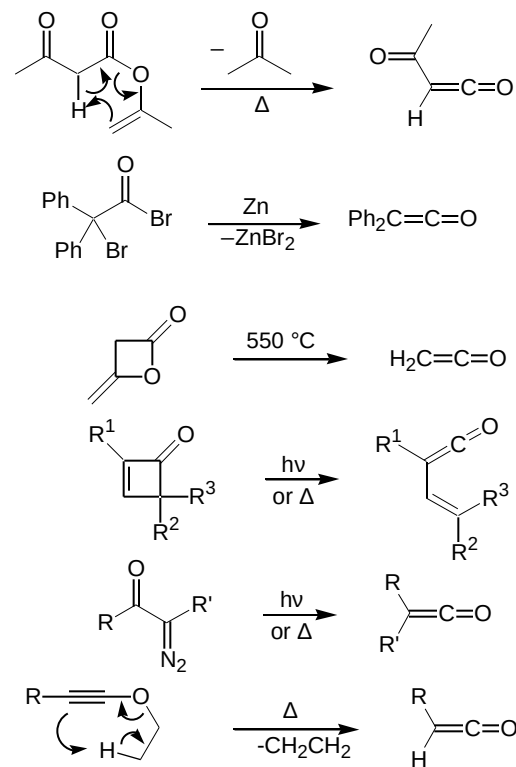
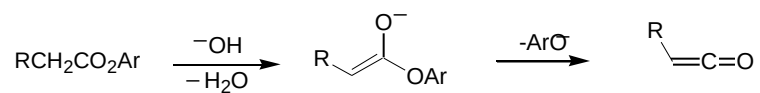
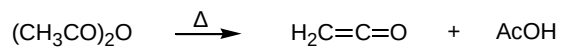
Summary of Ketene Cycloadditions



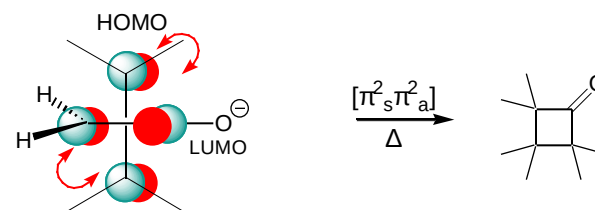
Ketene Preparation

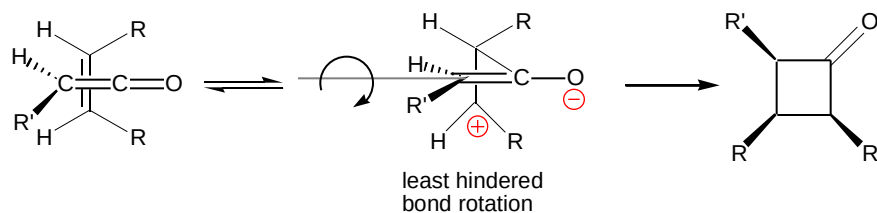


X = Cl, Ts, AcO, DCC, etc...



FMO Analysis

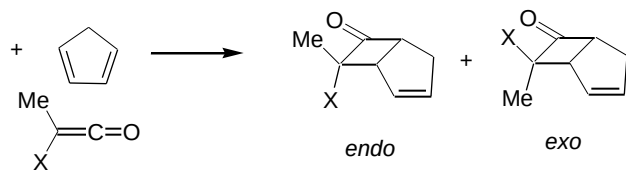


[2+2]: Stepwise Versus Concerted**Stepwise**

- 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

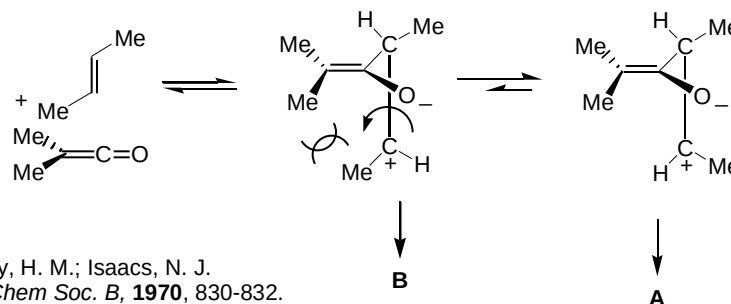
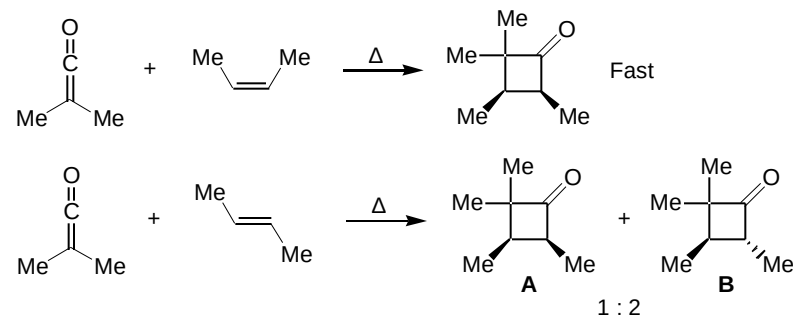
Concerted

- Ketenes add stereoselectively to Z alkenes
- Z olefins are much more reactive than E

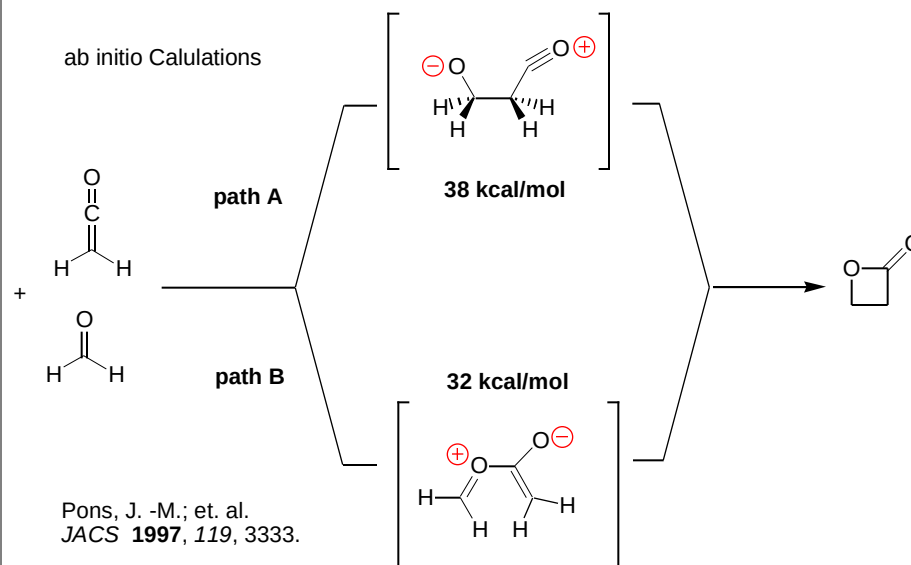
Solvent Effects

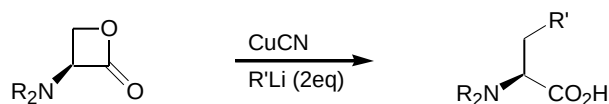
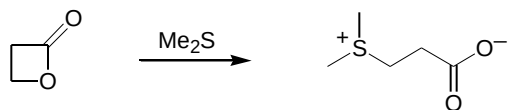
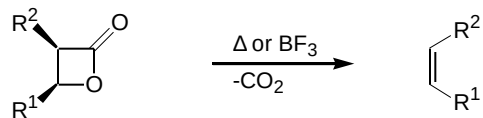
X	Solvent	<i>endo</i> / <i>exo</i>	X	Solvent	<i>endo</i> / <i>exo</i>
Cl	hexane	4.3 / 1	Br	hexane	0.71 / 1
Cl	Et ₃ N	2.2 / 1	Br	Et ₃ N	0.28 / 1
Cl	CHCl ₃	1.6 / 1	Br	CH ₃ CN	0.14 / 1
Cl	CH ₃ CN	0.59 / 1			

- Solvent effects implicate a zwitterionic intermediate
Brady, et. al, JACS **1970**, 92, 146-148.

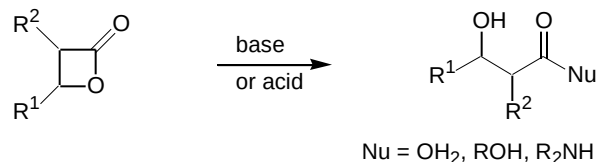
Ketene-Alkene [2+2]

Frey, H. M.; Isaacs, N. J.
J. Chem Soc. B, **1970**, 830-832.

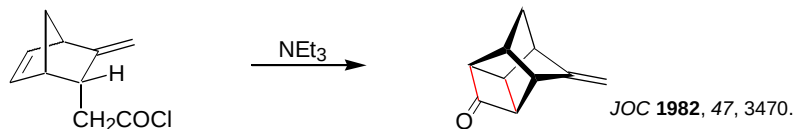
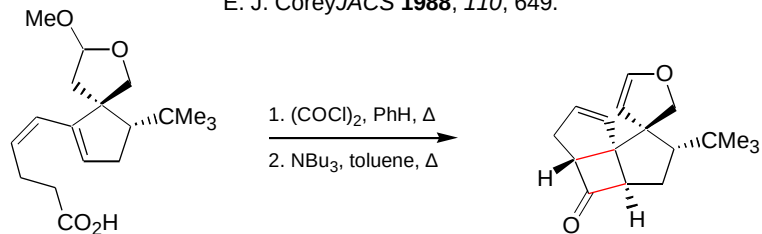
Ketenes + Aldehydes Afford β -Lactones

Transformations of β -Lactones

Arnold, L. D.; Drover, J. C. J.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *107*, 4649.



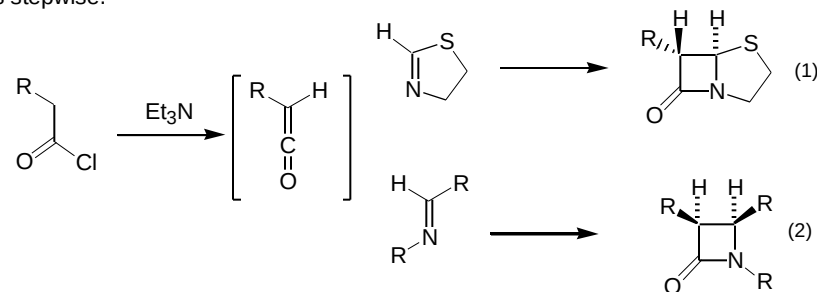
Application in Natural Product Synthesis: Ginkgolide B,
E. J. Corey *JACS* **1988**, *110*, 649.



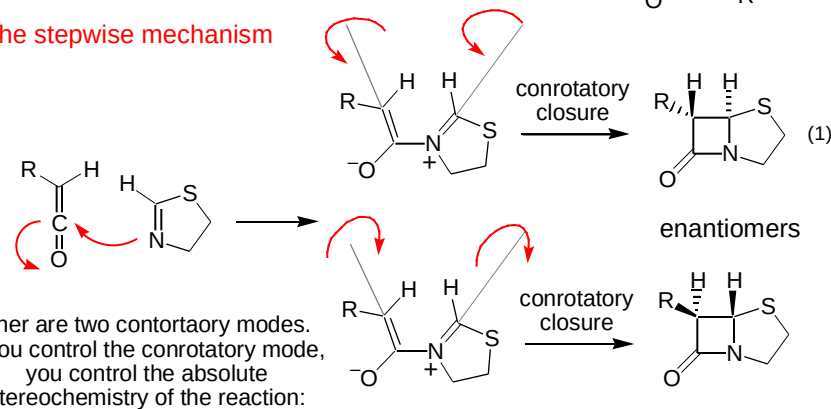
JOC **1982**, *47*, 3470.

The Staudinger Reaction

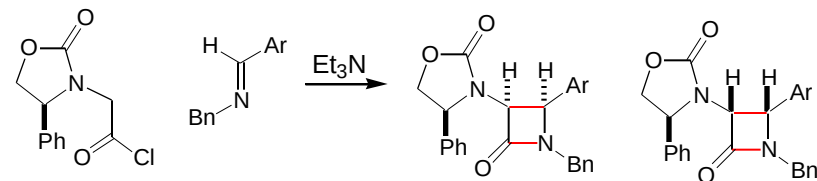
In this process, the illustrated ketene, generated *in situ* from an acid chloride, undergoes reaction with the indicated azo substrates to form β -lactams in a stereoselective process. When the azo-methine ($\text{RN}=\text{CHR}$) geometry in the reactant is (Z) the product stereochemistry is trans (eq 1). In a complementary fashion, the (E) imine affords the cis-substituted product (eq 2). While this transformation could be viewed as a $[2s+2a]$ cycloaddition, it is felt that this reaction is stepwise.



The stepwise mechanism



There are two conrotatory 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 Retrograde 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
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Preparation & DA Reactions of Heterosubstituted 1, 3-Dienes
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DA Reactions of Azadienes
 Boger, *Tetrahedron*, **1983**, 39, 2869-2939

Silyloxydienes in Organic Synthesis
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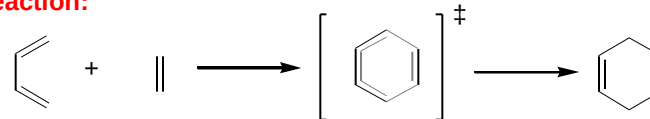
DA Reactions Part I: New Preparative Aspects
 Sauer, *Angew. Chem. Int. Ed.*, **1966**, 5, 211-230

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

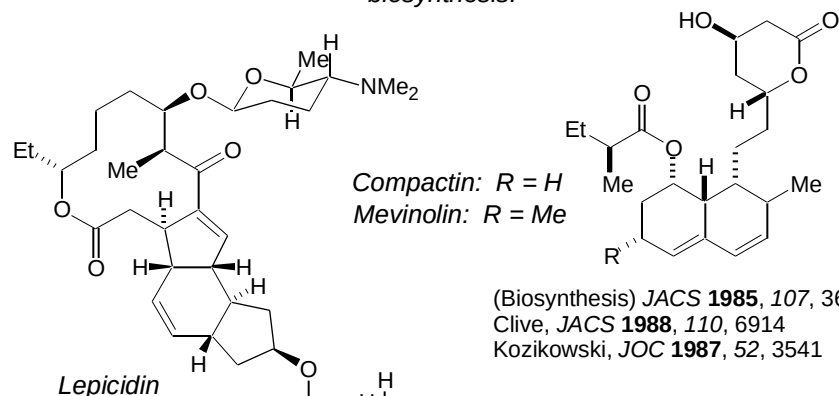
Retro-DA Strategy in Natural Products Synthesis
 Ichihara, *Synthesis*, **1987**, 207-222

■ The Reaction:

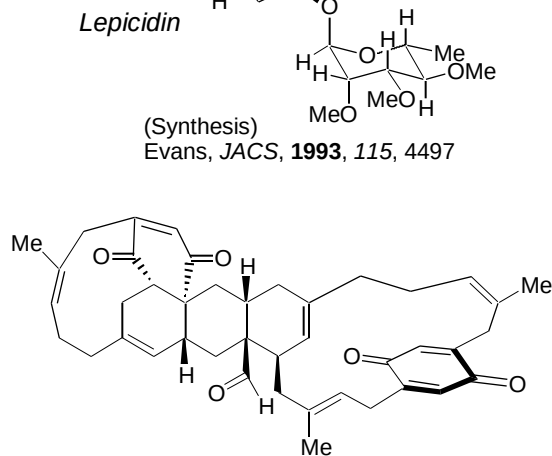


■ Representative natural products displaying the Diels-Alder retron:

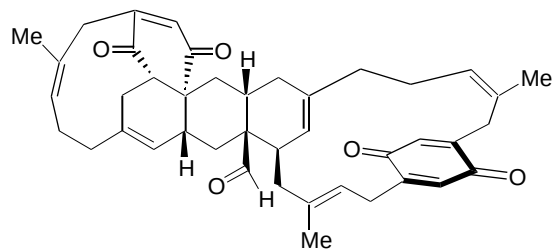
These natural products could well have incorporated the DA rxn into their biosynthesis.



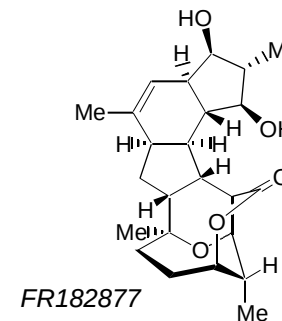
(Biosynthesis) *JACS* **1985**, 107, 3694
 Clive, *JACS* **1988**, 110, 6914
 Kozikowski, *JOC* **1987**, 52, 3541



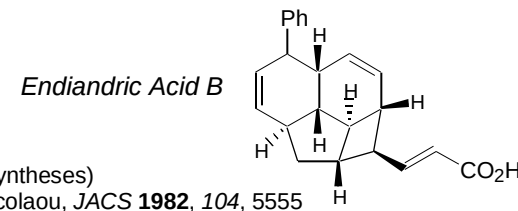
(Synthesis)
 Evans, *JACS*, **1993**, 115, 4497



(Synthesis)
 Shair, *JACS*, **2002**, 124, 773



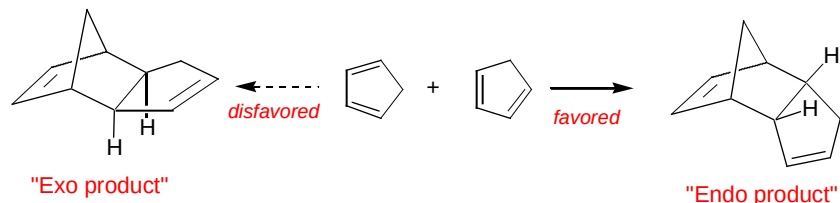
(Synthesis)
 Sorensen, *JACS*, **2002**, 124, 4552
 Evans, *ACIE* **2002**, 41, 1787



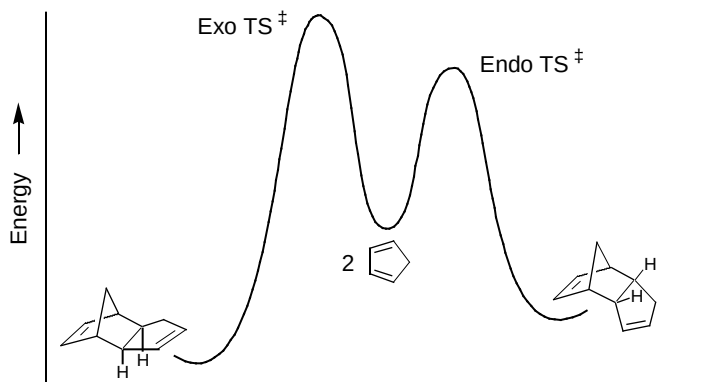
(Syntheses)
 Nicolaou, *JACS* **1982**, 104, 5555

The Alder Endo Rule

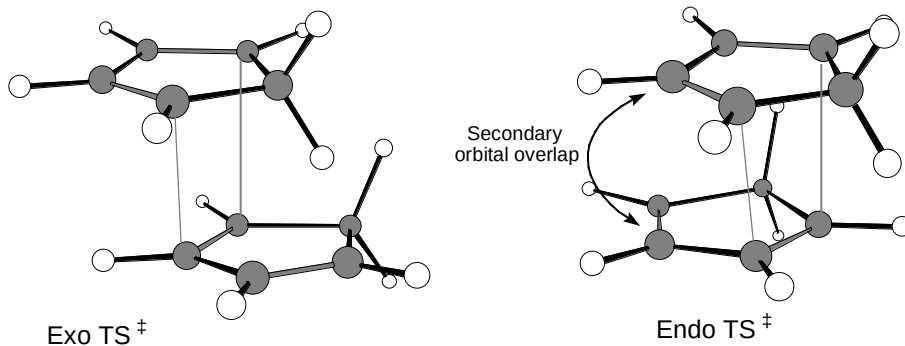
The following observation illustrates an example of the Alder Rule which will be defined below.



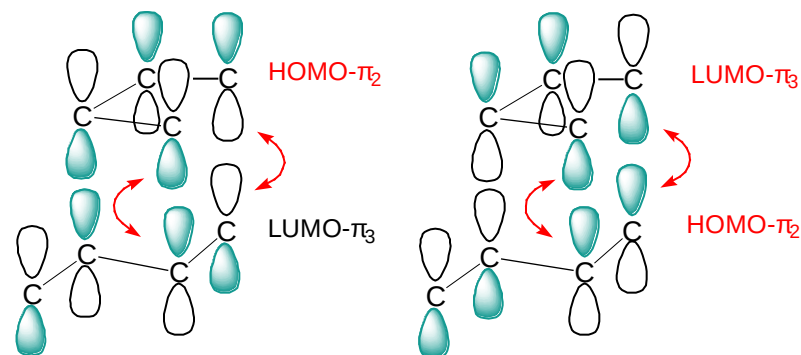
Observation: The endo Diels-Alder adduct is formed faster even though the exo product is more stable. There is thus some special stabilization in the transition state leading to the endo product which is lacking the exo transition state.



■ 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**

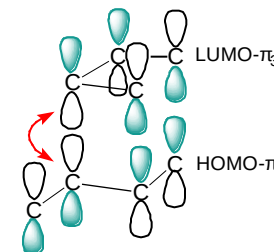
If the symmetries of the frontier MO's of reacting partners are "properly matched" the reaction is referred to as "symmetry-allowed". The Diels-Alder reaction is such a case. As illustrated, the HOMO and LUMO of both the diene and dienophile, which in this case are the same, will constructively overlap as indicated in formation of both sigma bonds.



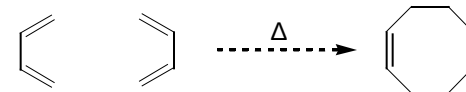
■ Primary orbital overlap leads directly to the formation of new chemical bonds.

Frontier MO Explanation for the Endo Rule

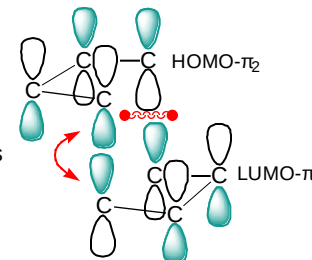
■ Secondary (transient) orbital overlap can also occur in the stabilization of certain transition state geometries. Such a transient stabilizing interaction can occur in the endo, but not exo, transition state:

**The Other Dimerization Possibility for Butadiene**

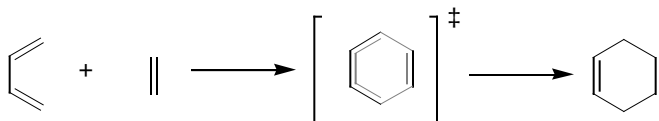
Does the possibility for the following concerted dimerization exist?



■ 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

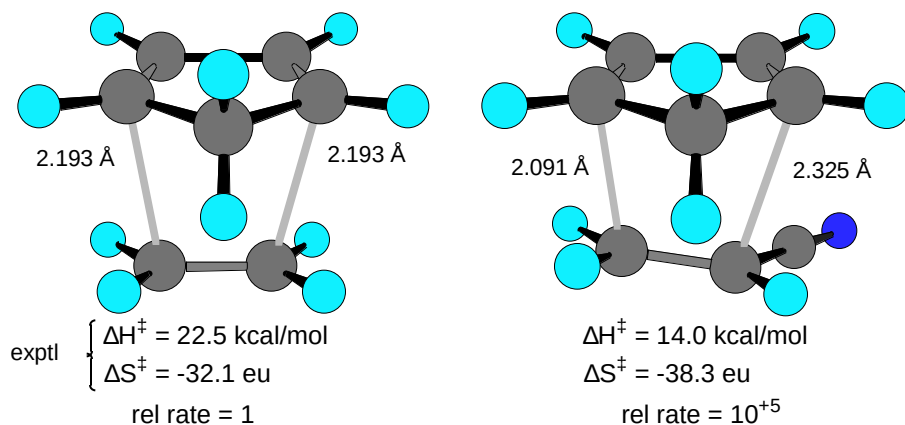
Transition State Modelling is Coming of Age

- 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

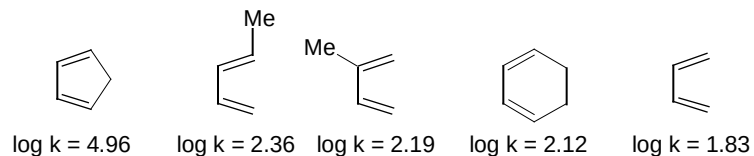
leading references: Jorgensen, JACS **1993**, 115, 2936-2942
 Houk, Jorgensen, JACS **1989**, 111, 9172

Transition Structures of Hydrocarbon Pericyclic Reactions
 Houk Angew. chem. Int. Ed. **1992**, 31, 682-708

- Bond formation is not synchronus with substituted dienophiles (Jorgensen)

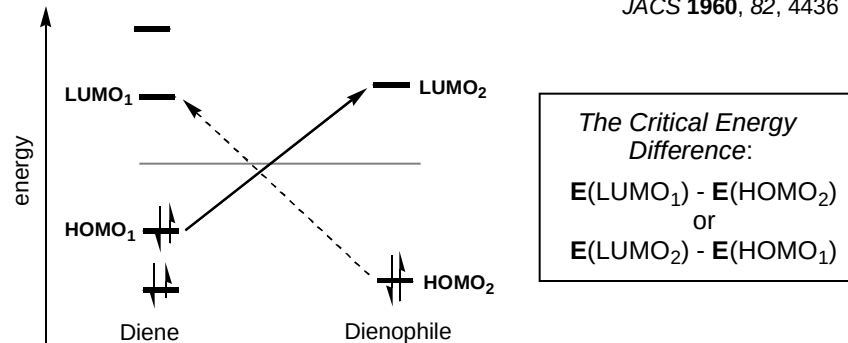


- Diene Reactivity as measured against Maleic anhydride

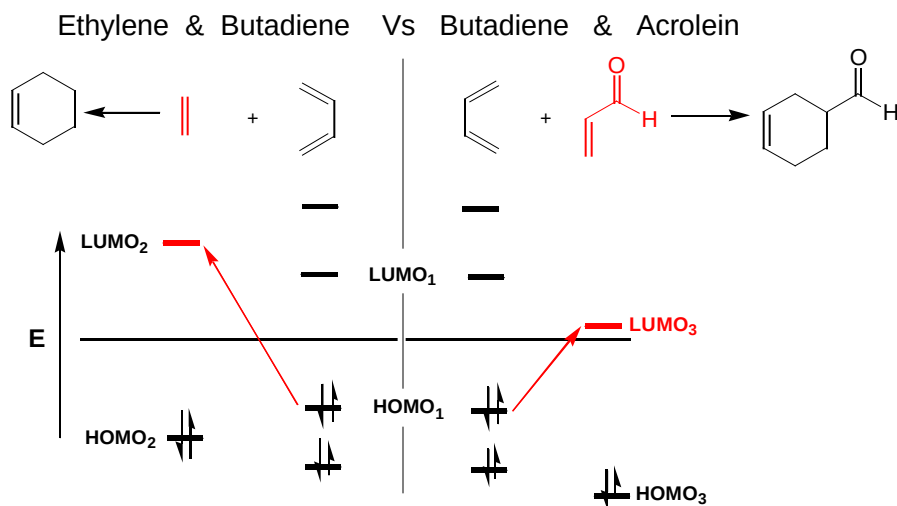


Sauer, Angew. Chem. Int. Ed., **1980**, 19, 779-807

- Lewis Acid Catalysis of the reaction is possible: Yates & Eaton, JACS **1960**, 82, 4436

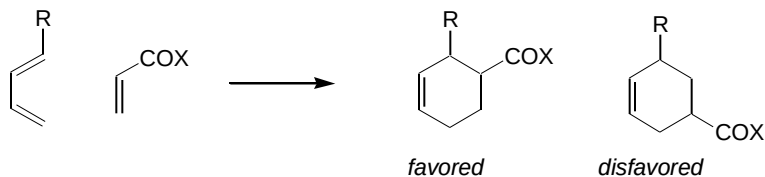


- The closer the two orbitals are in energy, the better they interact
- As ΔE decreases for the relevant ground state FMOs, rxn rates increase



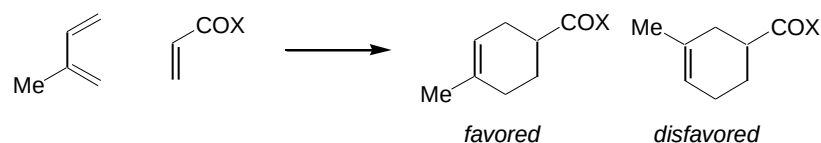
Lewis acid catalysis not only dramatically increases rates by ca 10^{+6} it also improves reaction regiochemistry & endo diastereoselectivity

Orientation of Reacting Partners



for R = CO₂H 100 : 00 @ 75 °C
 X = OH 4.5 : 01 @ 100 °C

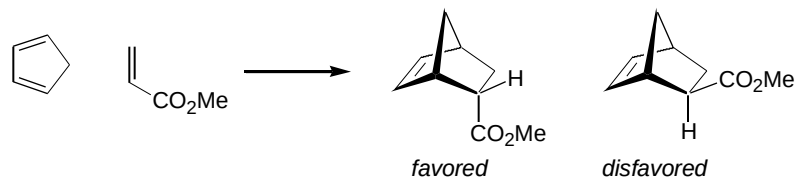
Lewis acid catalysis improves orientation



toluene, 120 °C 59 : 41
 C₆H₆, SnCl₄, 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

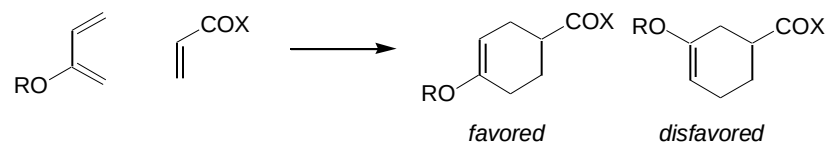
Lewis acid catalysis improves endo diastereoselection



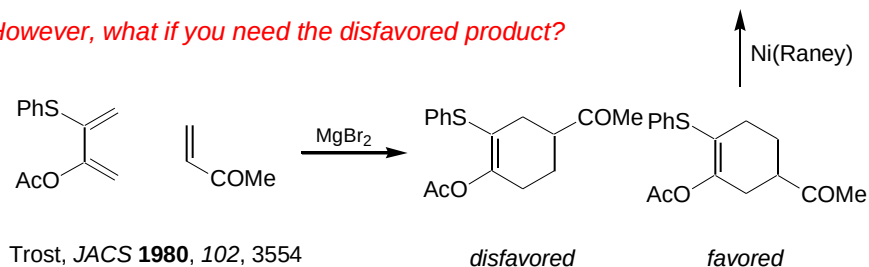
CH₂Cl₂, 0 °C 80 : 20
 C₆H₆, SnCl₄, 25 °C 95 : 05

DA Reactions Part II: The Reaction Mechanism,
 Sauer, Angew. Chem. Int. Ed., **1967**, 6, 16-33

Here is an interesting problem in reaction design

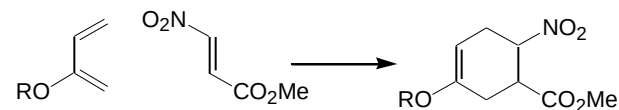


However, what if you need the disfavored product?

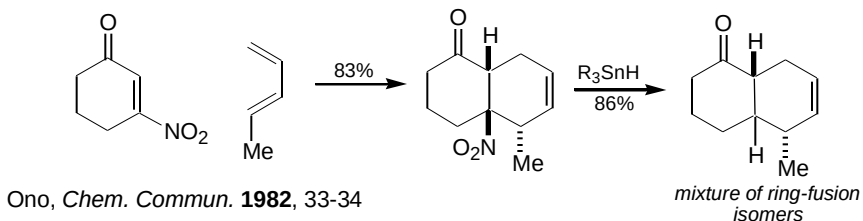
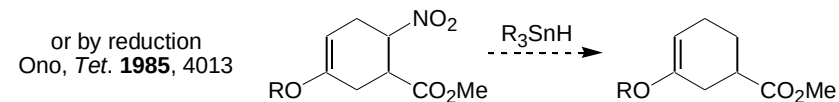
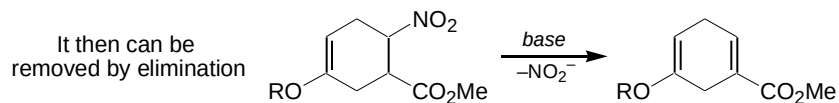


Trost, JACS **1980**, 102, 3554

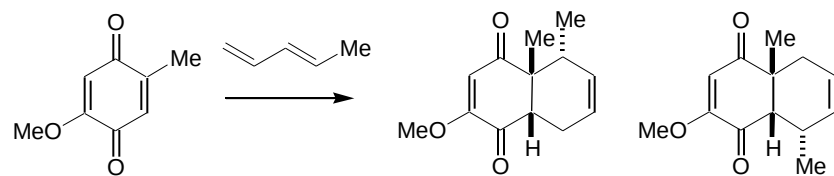
By employing a removable substituent, it is possible to access the normally disfavored product diastereomer



Danishefsky, JACS **1978**, 100, 2918: The NO₂ FG completely dominates directivity



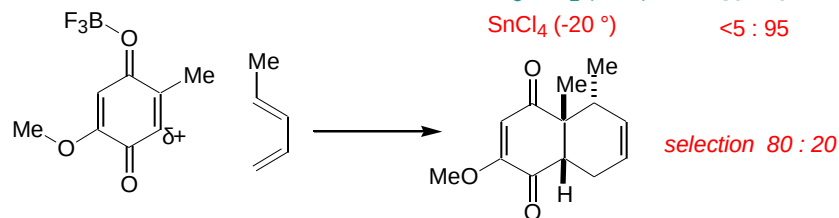
Ono, Chem. Commun. **1982**, 33-34

Instructive Issues of Regiocontrol with Quinone Dienophiles

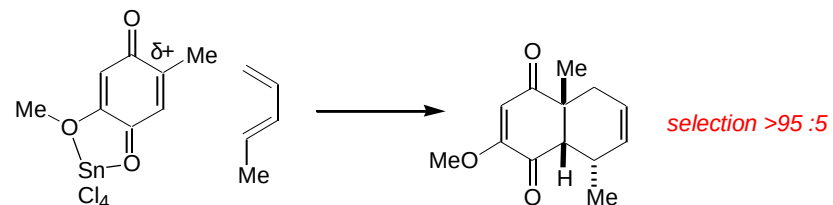
Orientation of Reacting Partners
controlled by Lewis acid structure

Reusch JOC **1980**, 45, 5013

Conditions	Ratio
thermal (100 °)	50 : 50
$\text{BF}_3 \cdot \text{OEt}_2$ (-20 °)	80 : 20
SnCl_4 (-20 °)	<5 : 95



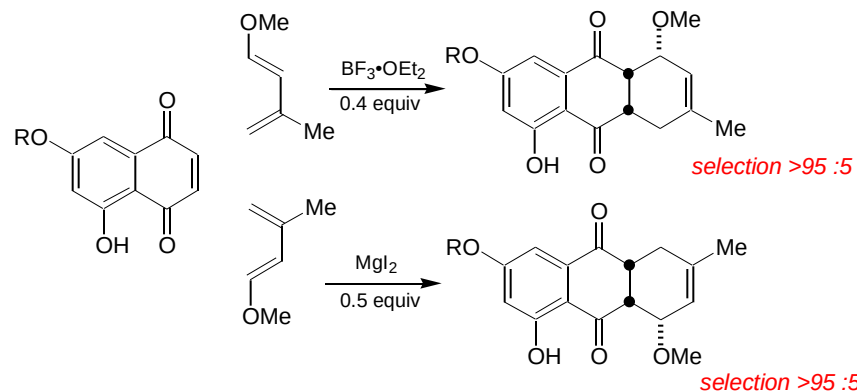
selection 80 : 20



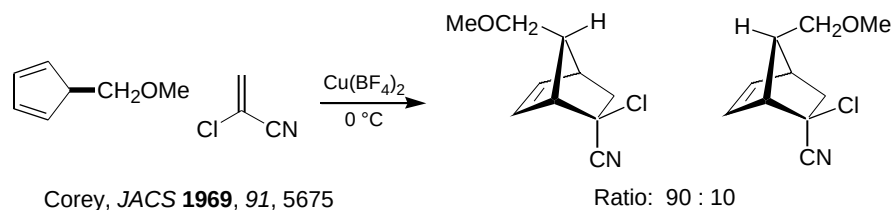
selection >95 : 5

Similar results provided by Stoodley Chem. Comm. **1982**, 929

Kelly Tet. Let. **1978**, 4311



selection >95 : 5



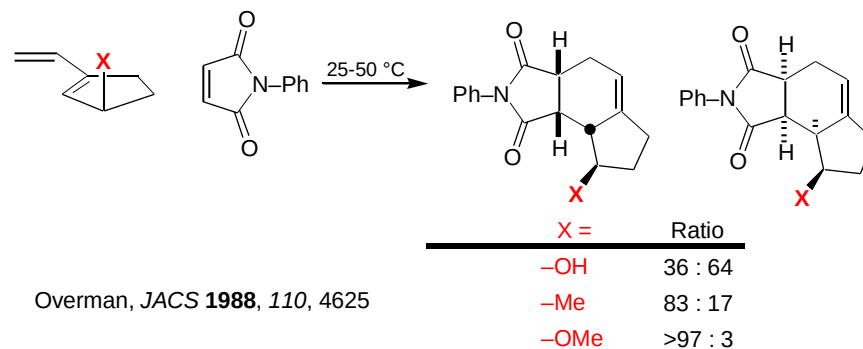
Corey, JACS **1969**, 91, 5675

Ratio: 90 : 10

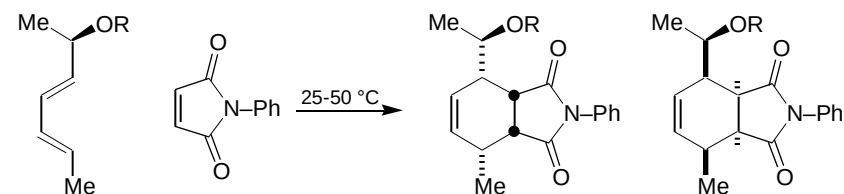
Diels-Alder Reactions with Chiral Dienes

Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer, See page 347



Overman, JACS **1988**, 110, 4625



Franck, Tet. Lett. **1985**, 26, 3187

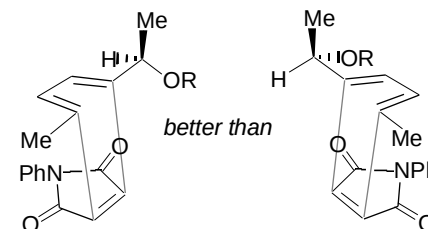
Franck, JACS **1988**, 110, 3257

R = Me: Ratio; 83 : 17

R = Me₃Si: 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](#))

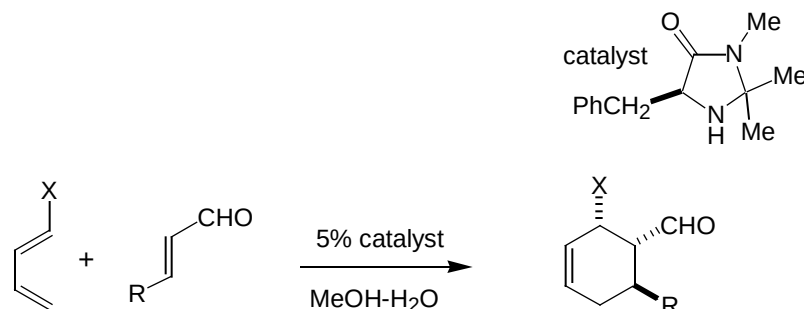
"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, 33, 325-335. ([pdf](#))

"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
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- 4.3 Heterodiene Additions, D. L. Boger
- 4.4 Intramolecular Diels-Alder Reactions, W. R. Roush
- 4.5 Retrograde 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**

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The Intramolecular DA Rxn: recent advances and synthetic applications
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 Boger, *Tetrahedron*, **1983**, 39, 2869-2939

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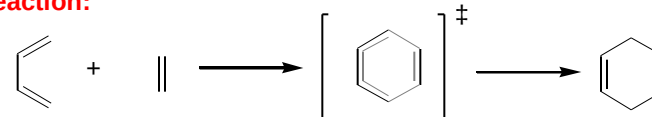
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 Sauer, *Angew. Chem. Int. Ed.*, **1967**, 6, 16-33

Mechanistic Aspects of Diels-Alder Reactions: A Critical Survey
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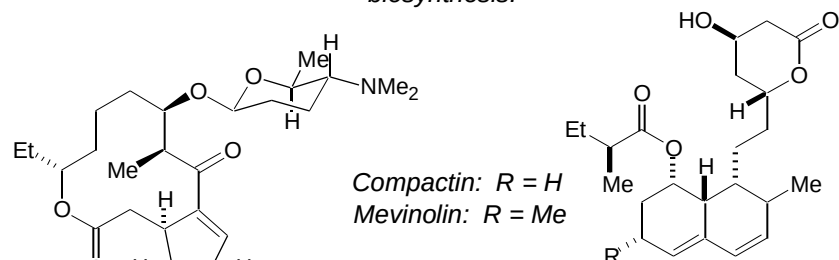
Retro-DA Strategy in Natural Products Synthesis
 Ichihara, *Synthesis*, **1987**, 207-222

■ The Reaction:

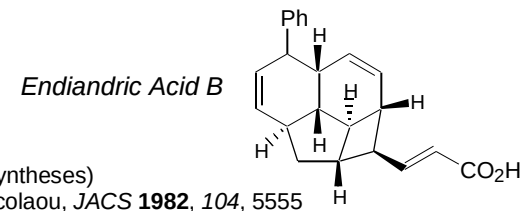
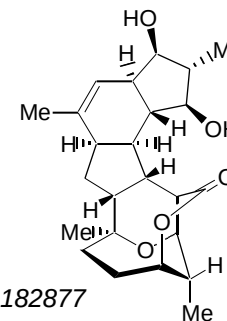
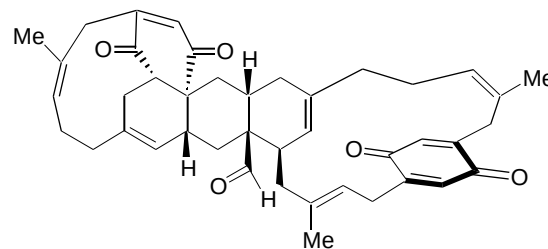
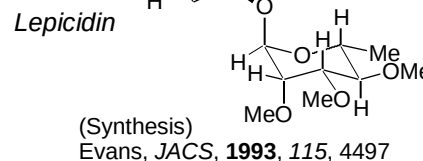


■ Representative natural products displaying the Diels-Alder retron:

These natural products could well have incorporated the DA rxn into their biosynthesis.

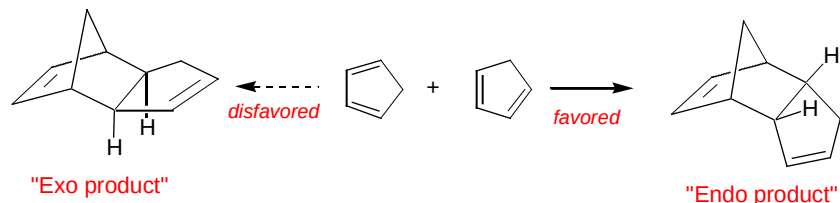


(Biosynthesis) *JACS* **1985**, 107, 3694
 Clive, *JACS* **1988**, 110, 6914
 Kozikowski, *JOC* **1987**, 52, 3541

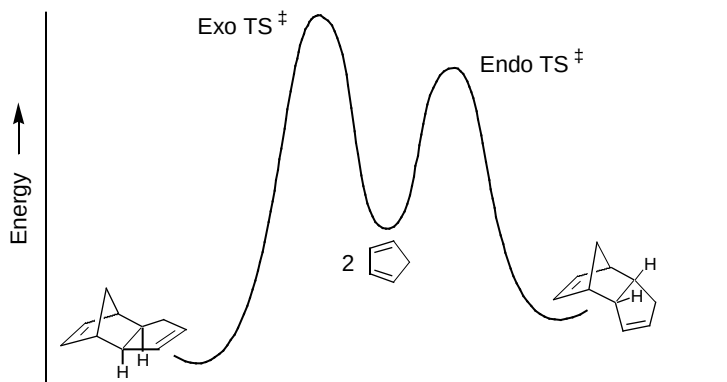


The Alder Endo Rule

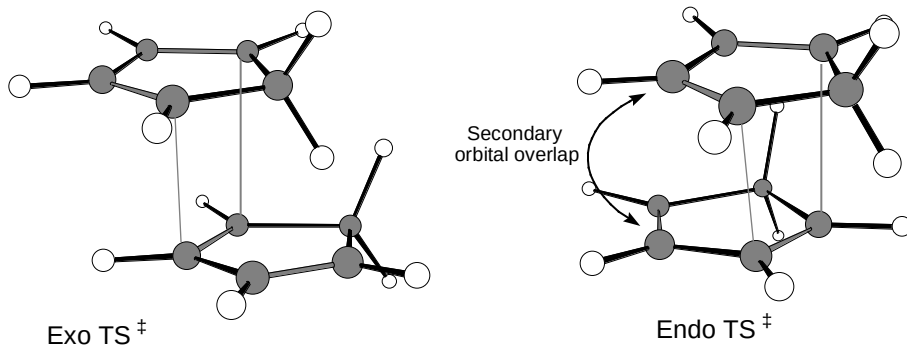
The following observation illustrates an example of the Alder Rule which will be defined below.



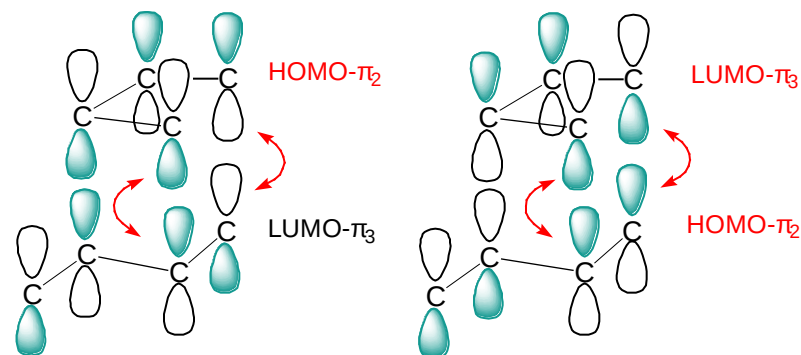
Observation: The endo Diels-Alder adduct is formed faster even though the exo product is more stable. There is thus some special stabilization in the transition state leading to the endo product which is lacking the exo transition state.



■ 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**

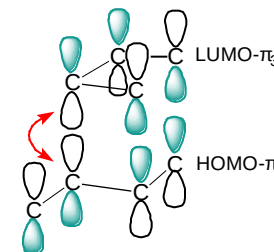
If the symmetries of the frontier MO's of reacting partners are "properly matched" the reaction is referred to as "symmetry-allowed". The Diels-Alder reaction is such a case. As illustrated, the HOMO and LUMO of both the diene and dienophile, which in this case are the same, will constructively overlap as indicated in formation of both sigma bonds.



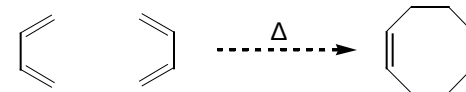
■ Primary orbital overlap leads directly to the formation of new chemical bonds.

Frontier MO Explanation for the Endo Rule

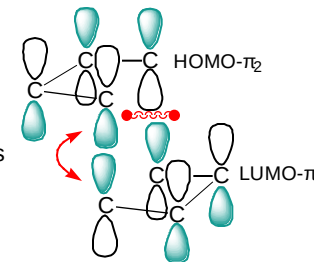
■ Secondary (transient) orbital overlap can also occur in the stabilization of certain transition state geometries. Such a transient stabilizing interaction can occur in the endo, but not exo, transition state:

**The Other Dimerization Possibility for Butadiene**

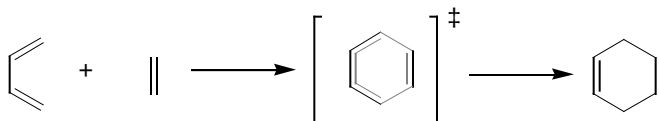
Does the possibility for the following concerted dimerization exist?



■ 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

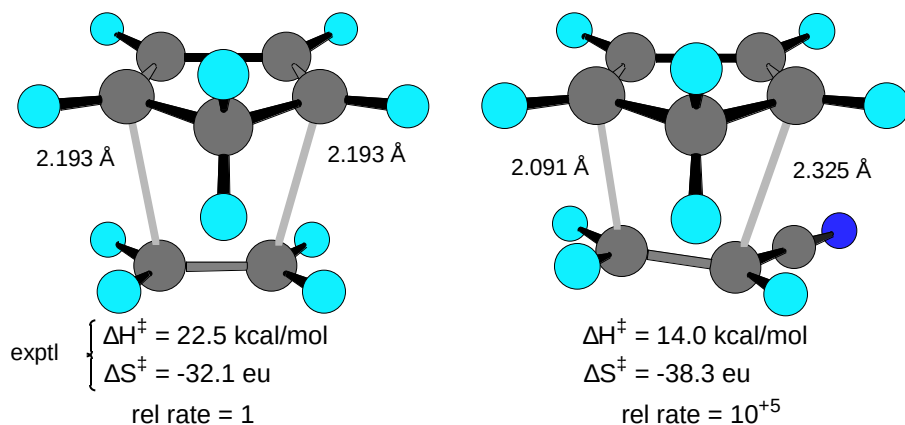
Transition State Modelling is Coming of Age

- 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

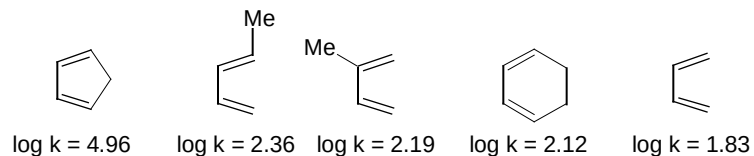
leading references: Jorgensen, JACS **1993**, 115, 2936-2942
 Houk, Jorgensen, JACS **1989**, 111, 9172

Transition Structures of Hydrocarbon Pericyclic Reactions
 Houk Angew. chem. Int. Ed. **1992**, 31, 682-708

- Bond formation is not synchronus with substituted dienophiles (Jorgensen)

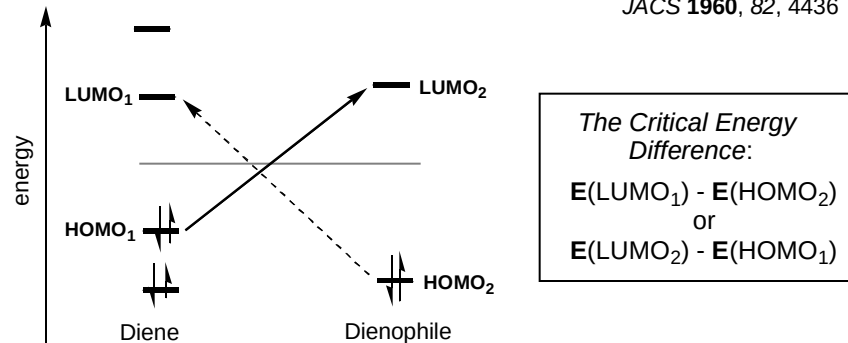


- Diene Reactivity as measured against Maleic anhydride

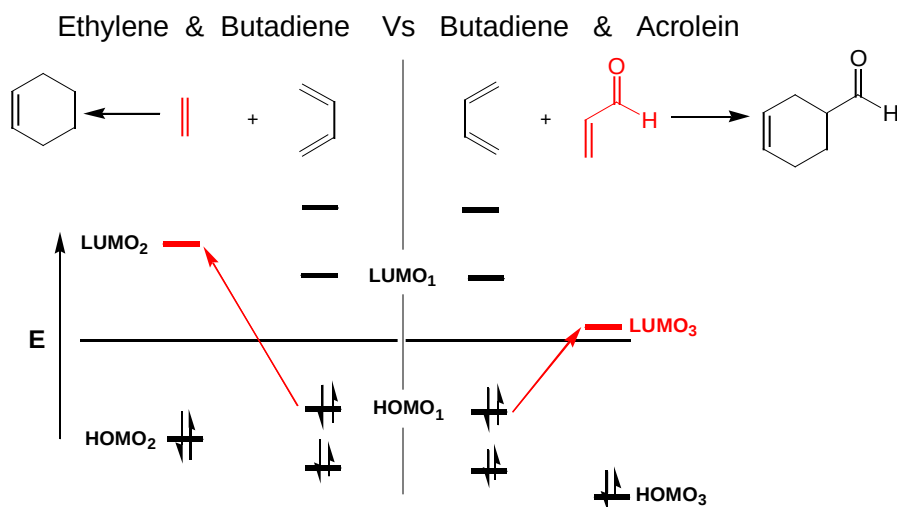


Sauer, Angew. Chem. Int. Ed., **1980**, 19, 779-807

- Lewis Acid Catalysis of the reaction is possible: Yates & Eaton, JACS **1960**, 82, 4436



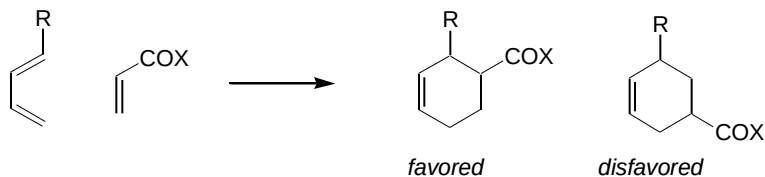
- The closer the two orbitals are in energy, the better they interact
- As ΔE decreases for the relevant ground state FMOs, rxn rates increase



$$\Delta E (\text{LUMO}_3\text{-HOMO}_1) < \Delta E (\text{LUMO}_2\text{-HOMO}_1) \Rightarrow \text{Rate Acceleration}$$

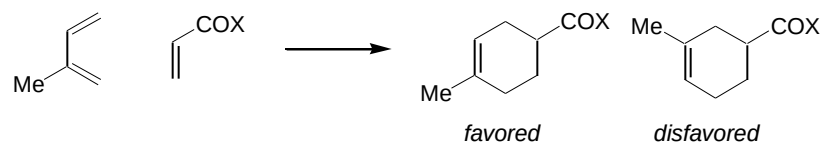
Lewis acid catalysis not only dramatically increases rates by ca 10^{+6} it also improves reaction regiochemistry & endo diastereoselectivity

Orientation of Reacting Partners



for R = CO₂H 100 : 00 @ 75 °C
 X = OH 4.5 : 01 @ 100 °C

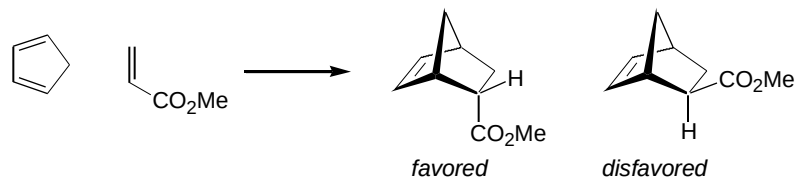
Lewis acid catalysis improves orientation



toluene, 120 °C 59 : 41
 C₆H₆, SnCl₄, 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

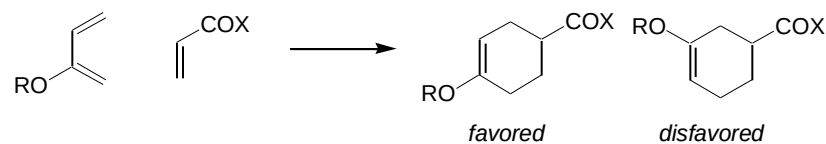
Lewis acid catalysis improves endo diastereoselection



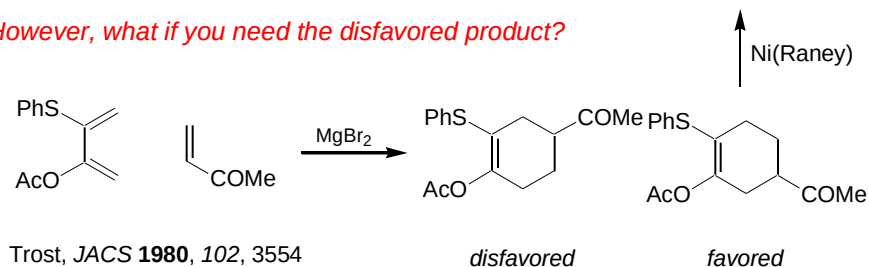
CH₂Cl₂, 0 °C 80 : 20
 C₆H₆, SnCl₄, 25 °C 95 : 05

DA Reactions Part II: The Reaction Mechanism,
 Sauer, Angew. Chem. Int. Ed., **1967**, 6, 16-33

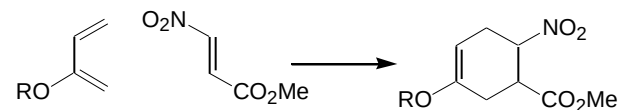
Here is an interesting problem in reaction design



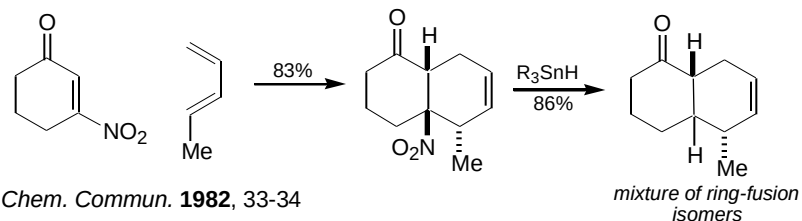
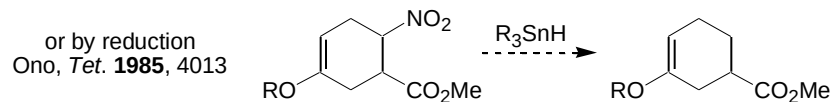
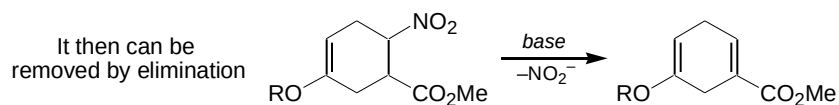
However, what if you need the disfavored product?



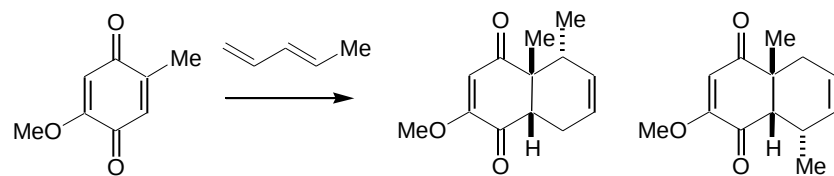
By employing a removable substituent, it is possible to access the normally disfavored product diastereomer



Danishefsky, JACS **1978**, 100, 2918: The NO₂ FG completely dominates directivity

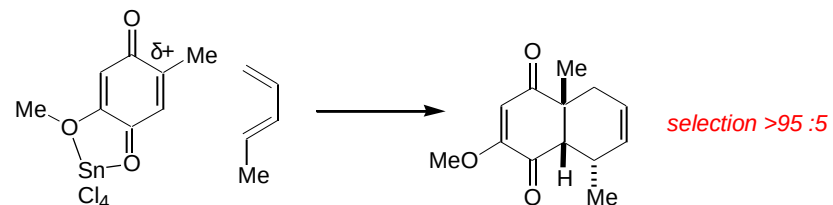
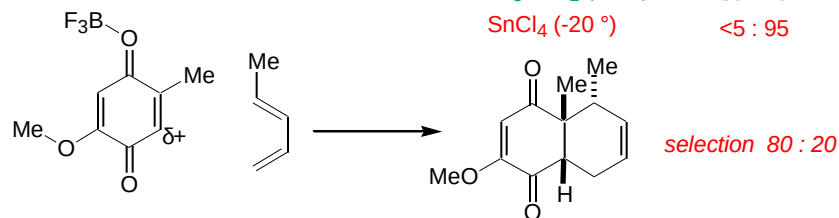


Ono, Chem. Commun. **1982**, 33-34

Instructive Issues of Regiocontrol with Quinone Dienophiles

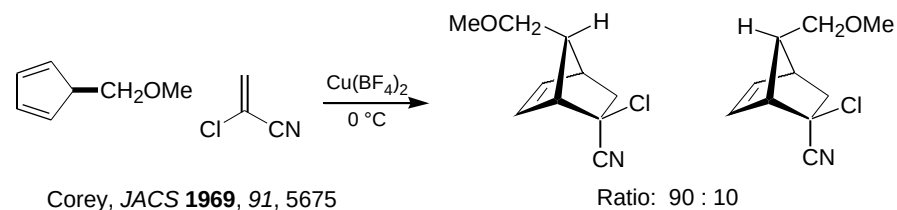
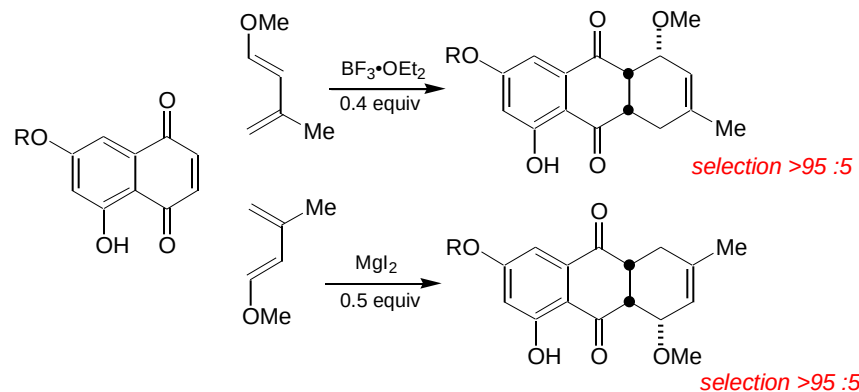
Orientation of Reacting Partners
controlled by Lewis acid structure

Reusch JOC **1980**, 45, 5013



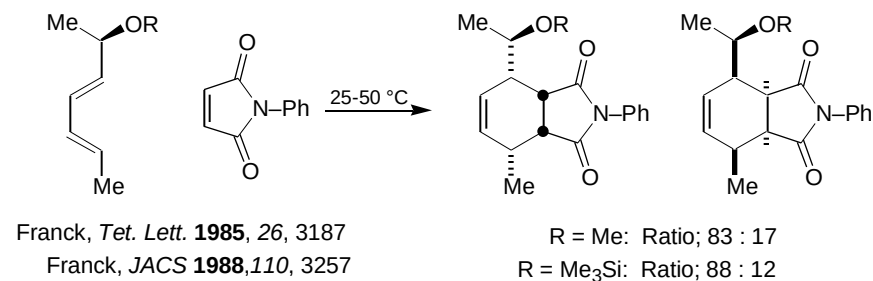
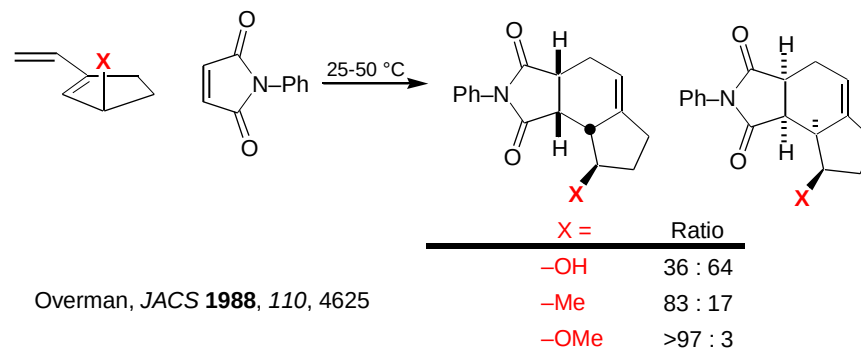
Similar results provided by Stoodley Chem. Comm. **1982**, 929

Kelly Tet. Let. **1978**, 4311

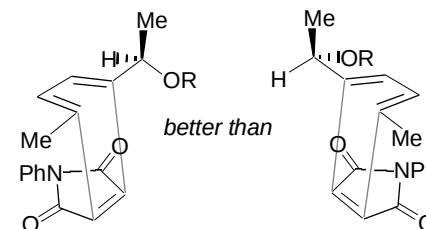
*Diels-Alder Reactions with Chiral Dienes*

Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer, See page 347

*Comments on the Transition State*

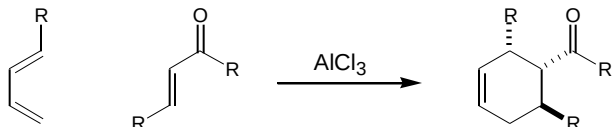
- Avoid Eclipsing allylic substituents
- better donor (Me) anti to forming bond
- avoid gauche OR interaction



Representative Lewis Acid Catalyzed Processes

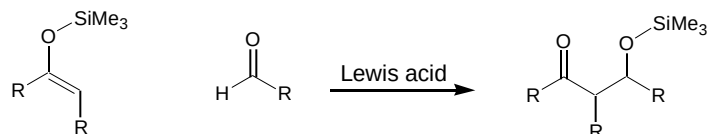
M. Santelli, J.-M. Pons, *Lewis Acids & Selectivity in Organic Synthesis*, CRC Press, New York, 1996

Schreiber, *Angew. Chem. Int. Ed. Eng.* **1990**, 29, 256-272

■ Diels-Alder Reaction Yates & Eaton, *JACS* **1960**, 82, 4436

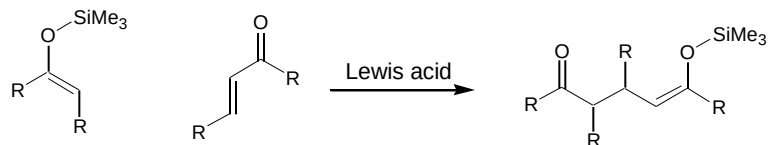
Lewis acid catalysis increases rates by ca 10^{+6}
& improves reaction regiochemistry & endo distereoselectivity

■ Aldol Reaction:



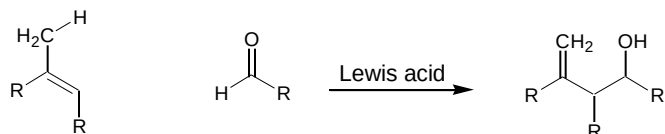
Mukaiyama, T. *Org. React.* (N.Y.) **1982**, 28, 203.
Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, 9, 357.

■ Michael Reaction



Mukaiyama, *Chem. Lett* **1974**, 1223

■ Carbonyl Ene Rxn

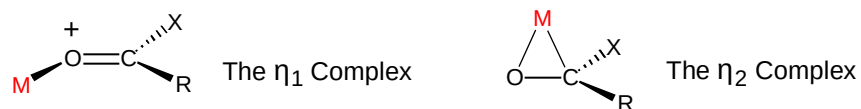
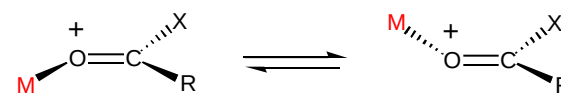
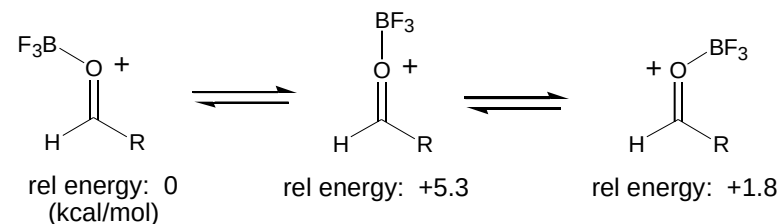


Mikami, *Chem. Rev.* **1992**, 92, 1021.

Common Stereochemical issues: Diastereoselectivity & Enantioselectivity

Lewis Acid Carbonyl Complexes

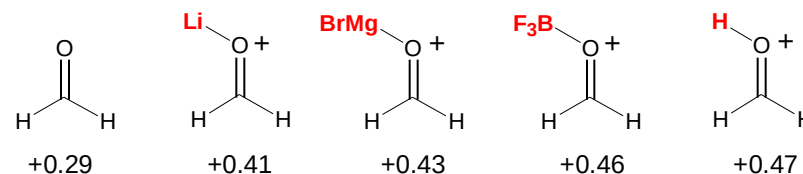
■ Types of Lewis Acid-C=O Complexes (M = Lewis Acid)

■ Conformations of η_1 Lewis Acid-C=O Complexes■ Geometric Preferences for BF_3 Complexes (Santelli, page 5)

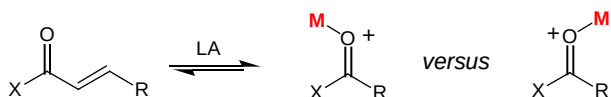
Changes in the C-O-M bond angle in the sigma plane do not require much destabilization. However distortions of the metal out of the sigma plane result in greater destabilization



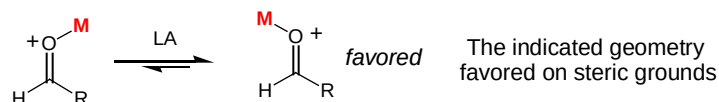
Calculated Mulliken Charges on Carbonyl Carbon (PM3)



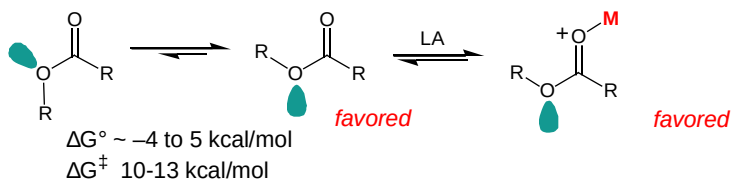
- Well-defined Lewis acid-C=O Complex needed: Geometry of η_1 Complexes



- Aldehydes: LA oriented anti to R moiety

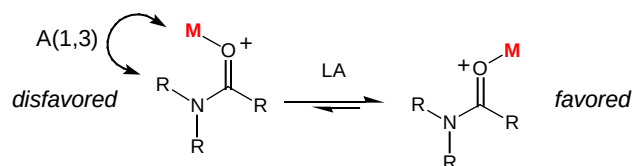


- Esters: Lewis acid oriented anti to RO moiety



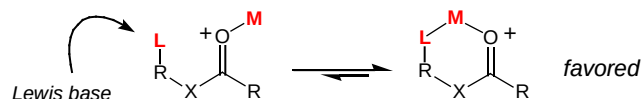
Oxygen-lone pair $\rightarrow \sigma^*$ C–O interactions strongly stabilize the (Z) ester conformation. Such stabilization should be expected to increase in LA-substrate complex.

- Amides: Lewis acid oriented anti to R_2N moiety



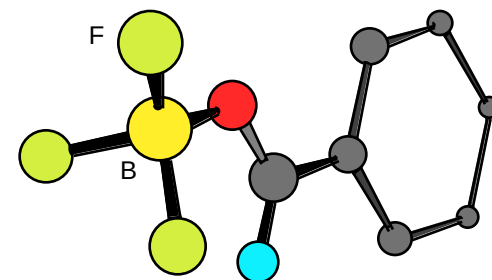
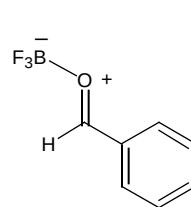
Allylic strain strongly disfavors Lewis acid complexation syn to the R_2N moiety

- Chelating Esters & Amides: Lewis acid can be bidentate coordinated

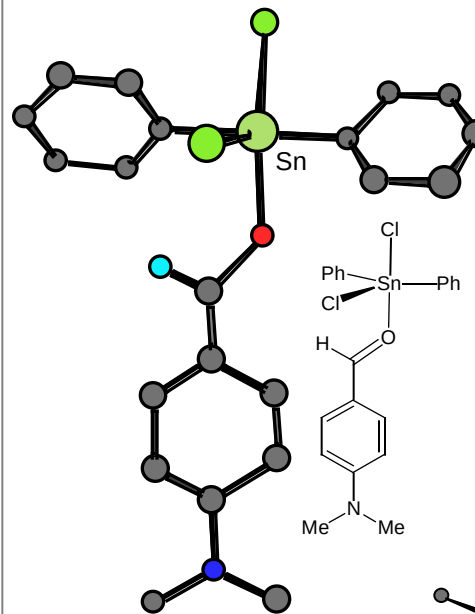


This situation is sometimes hard to predict

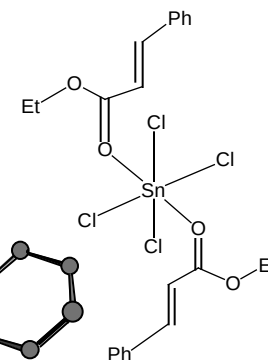
Representative η_1 Complexes & their X-ray Structures



X-ray structure

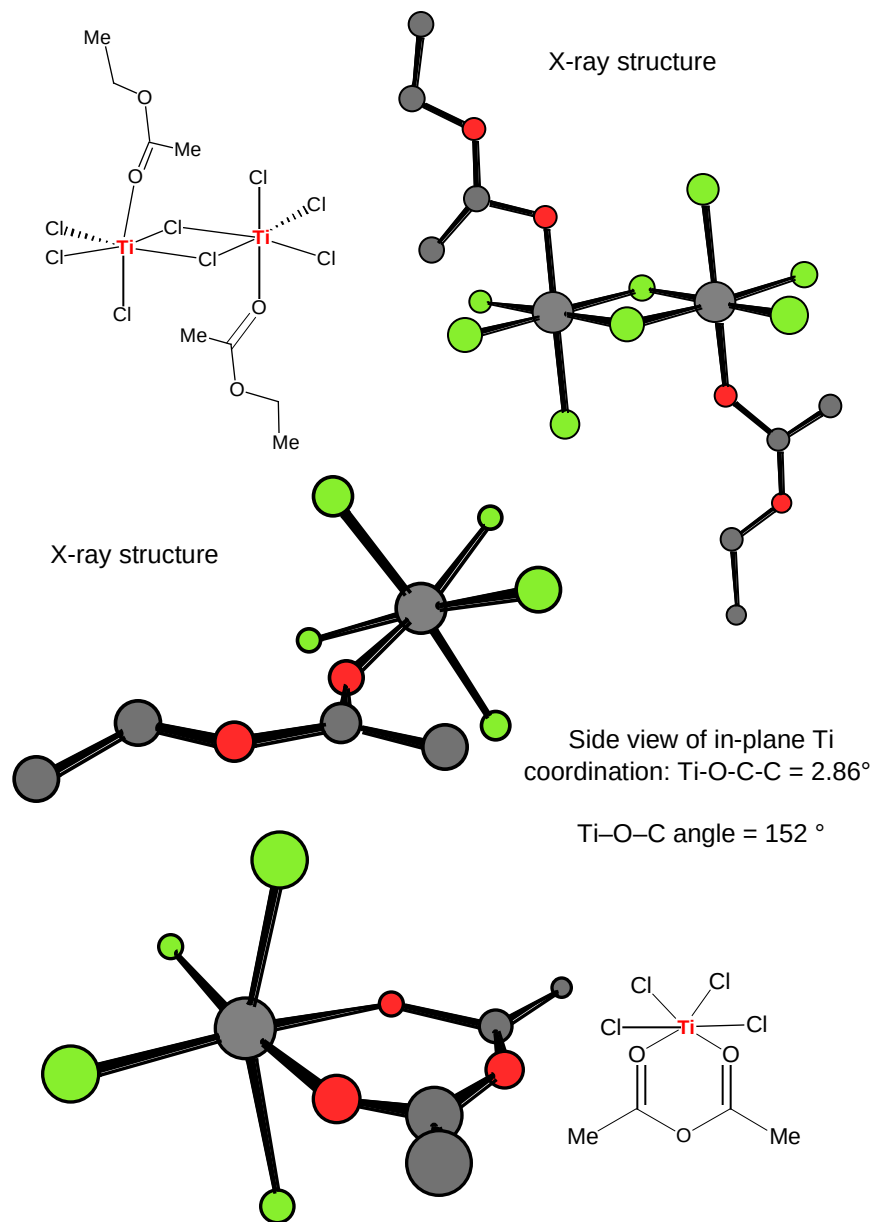
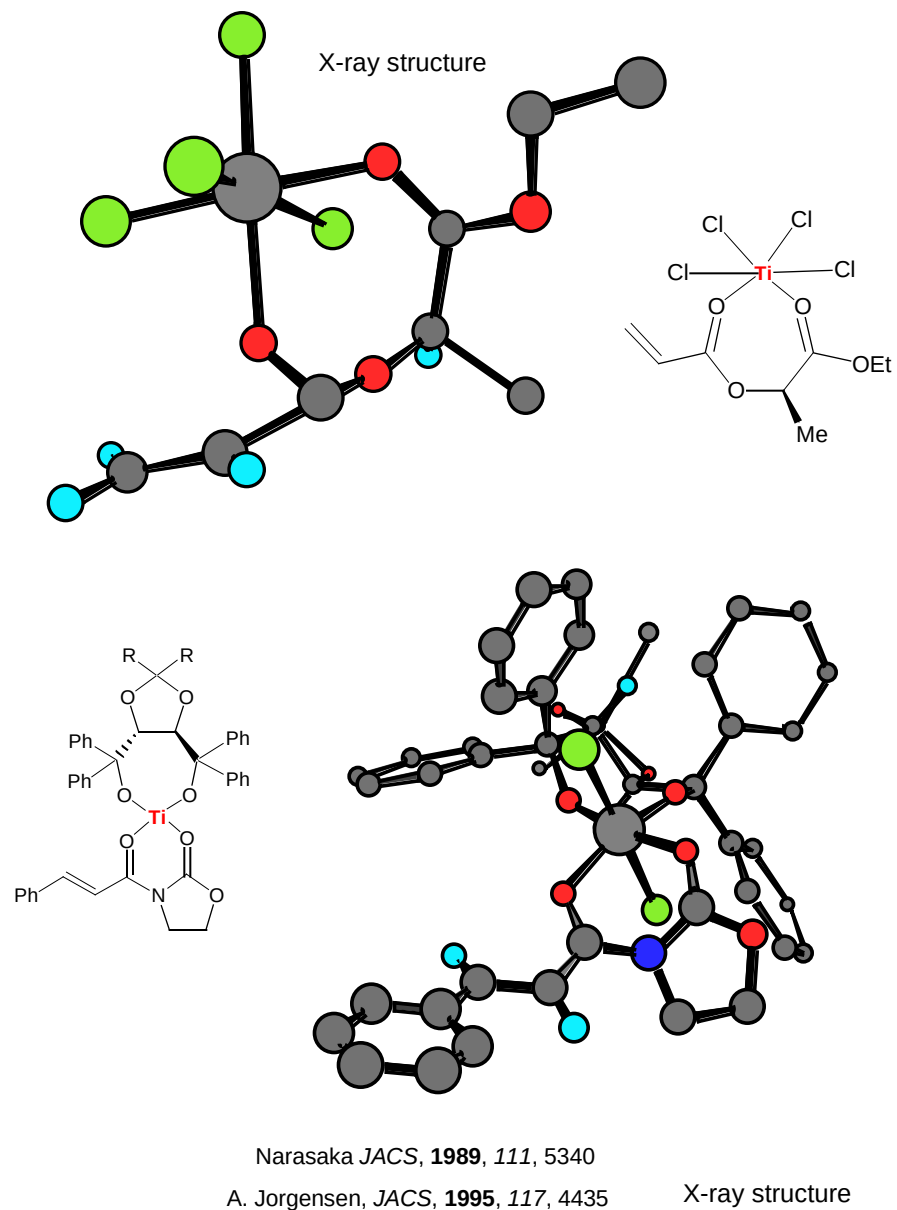


X-ray structure



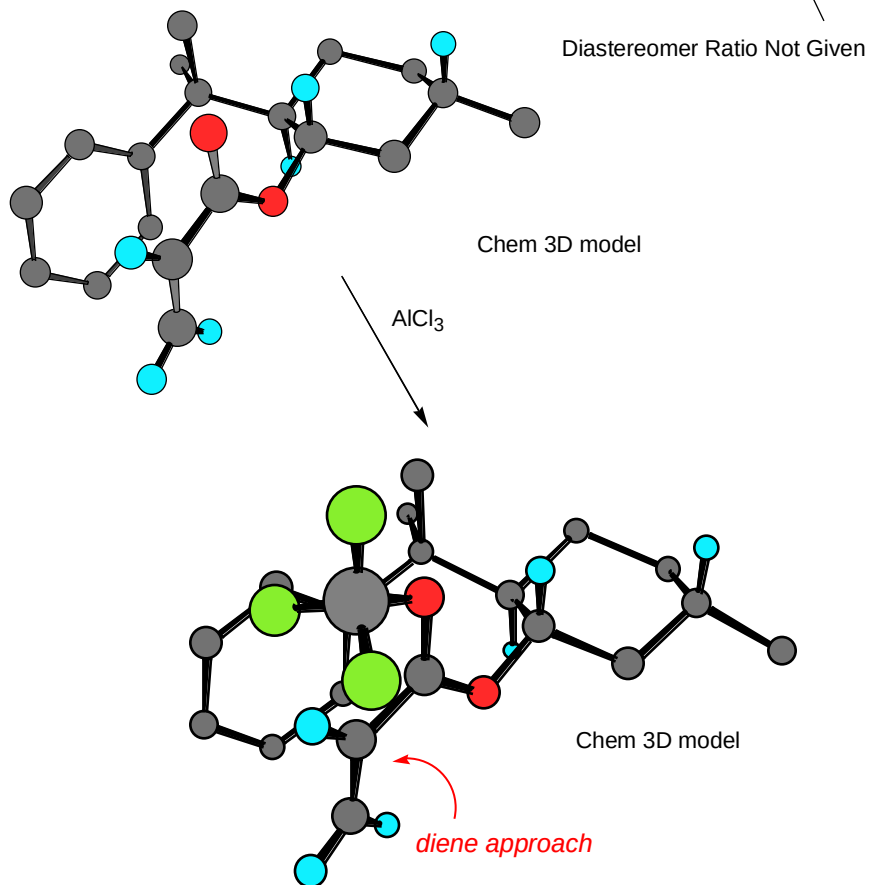
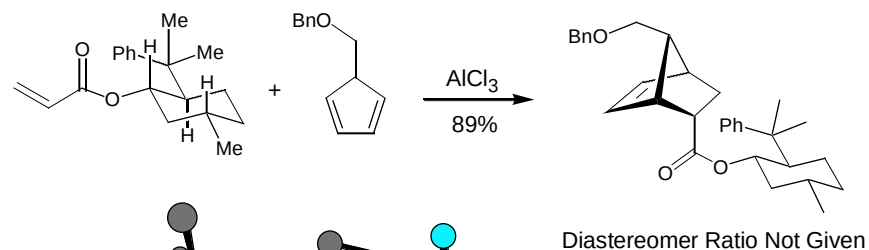
X-ray structure

See Schreiber, *Angew. Chem. Int. Ed.*,
 1990, 29, 256-272 for references

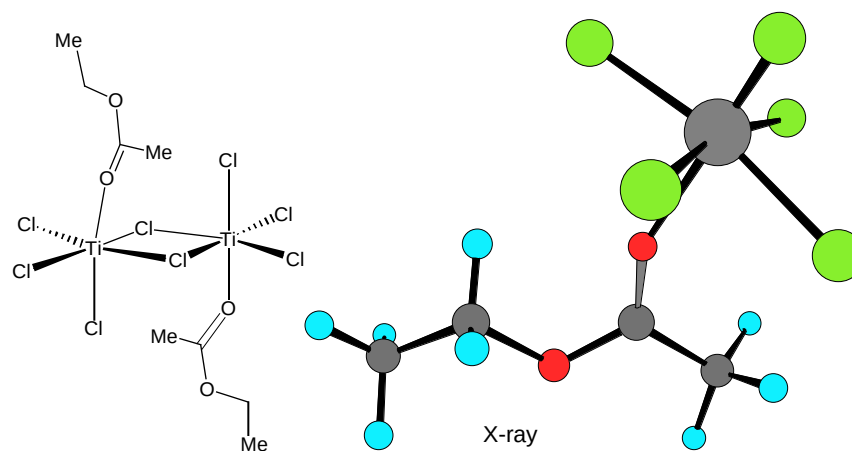
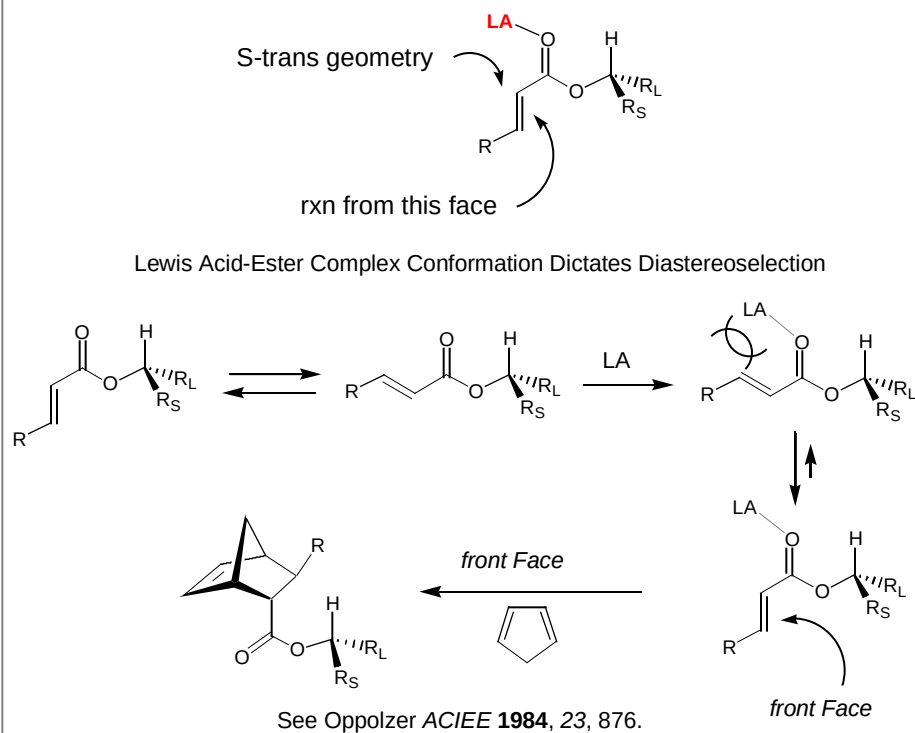
Representative η_1 -titanium complexes with organic compoundsRepresentative η_1 -titanium complexes with organic compounds

Review: Oppolzer in *Comprehensive Organic Synthesis* **1992**, Vol. 4, 315-399.

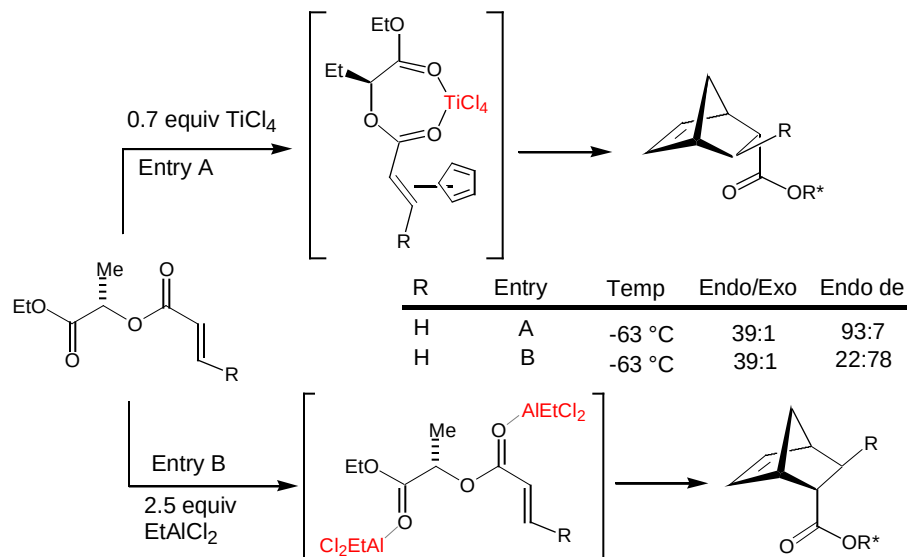
■ **Ester-Type Chiral Auxiliaries** Corey *JACS* **1975**, 97, 6908.



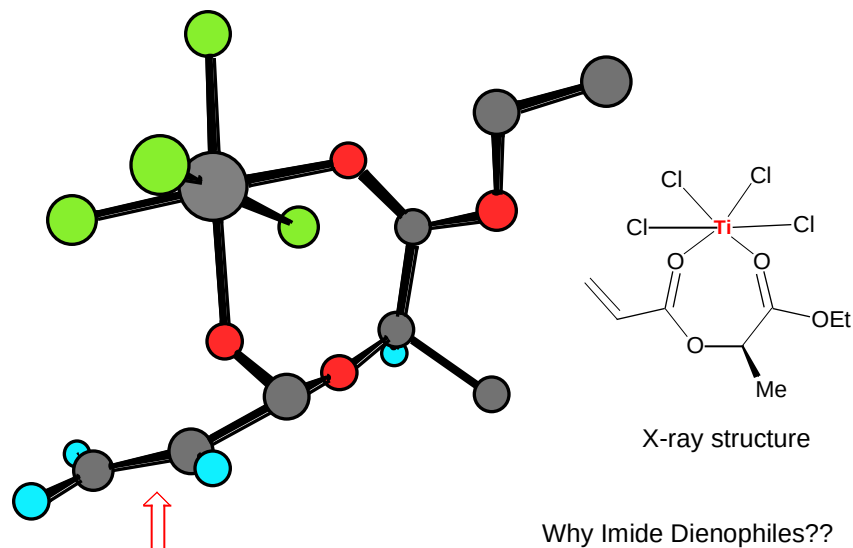
■ **Non-Chelate Ester-Type Chiral Auxiliaries**



■ Ester-Type Chiral Auxiliaries: Chelating Dienophiles



Helmchen *Tetrahedron Lett.* **1984**, 25, 2191.
 ACIEE **1985**, 24, 112.
Tetrahedron Lett. **1985**, 26, 3095.



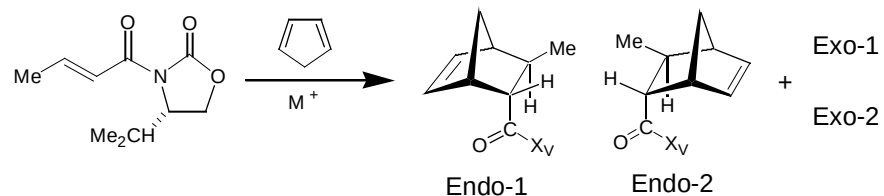
Why Imide Dienophiles??
 They are ~ 100-1000X more reactive

■ Chelating Imide-type Chiral Auxiliaries

Evans *JACS*, **1984**, 106, 4261.

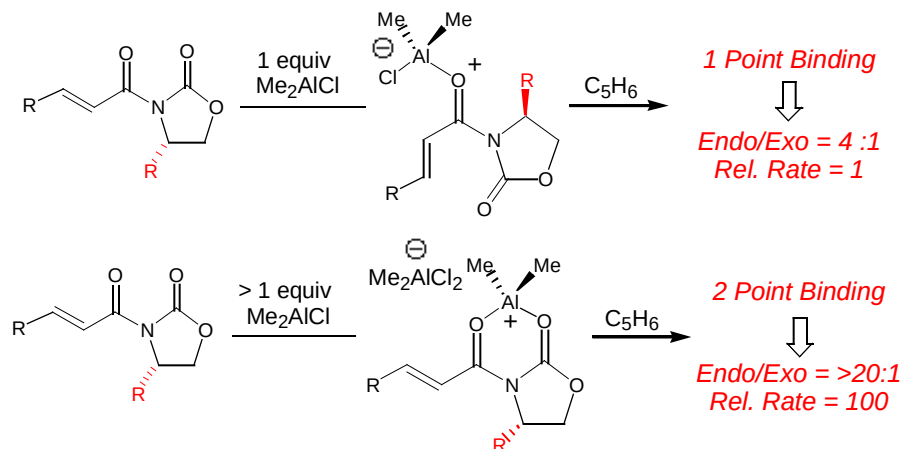
Evans *JACS*, **1988**, 110, 1238.

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

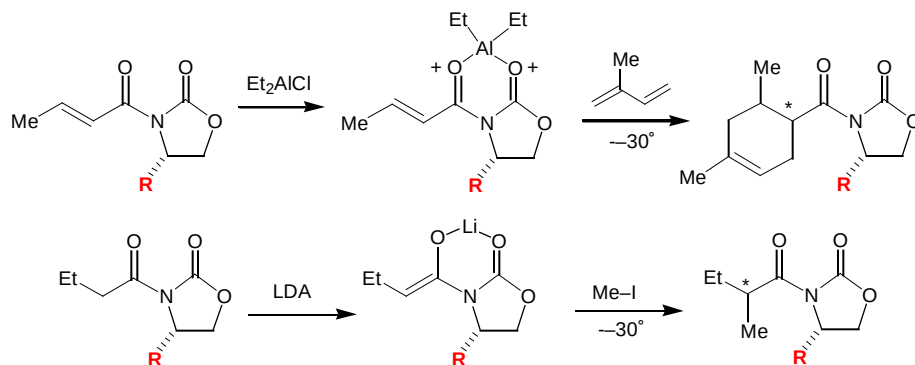
Binding Mode Dictates Diastereoselectivity



R = CH_2Ph much more stereoselective than R = CHMe_2

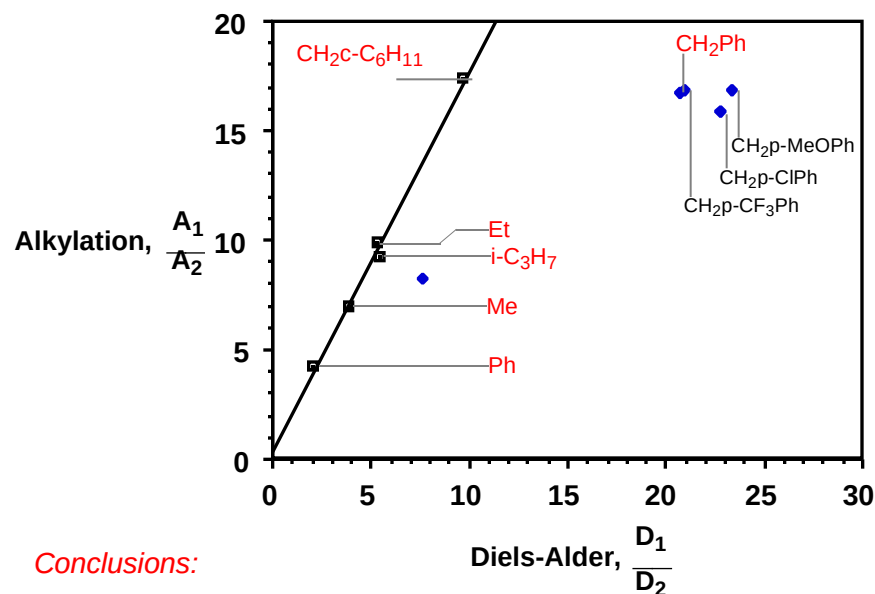
A Case for π -Stacking: *Angew Chem, Int Ed.* **1987**, 26, 1184

Compare the alkylation rxn which is dominated by steric effects with the DA rxn which may be controlled by both steric and electronic effects



$$\Delta\Delta G^\ddagger = 2.3 RT \log P_1/P_2$$

PLOT $\Delta\Delta G^\ddagger$ FOR EACH RXN AS A FUNCTION OF THE SUBST., R.

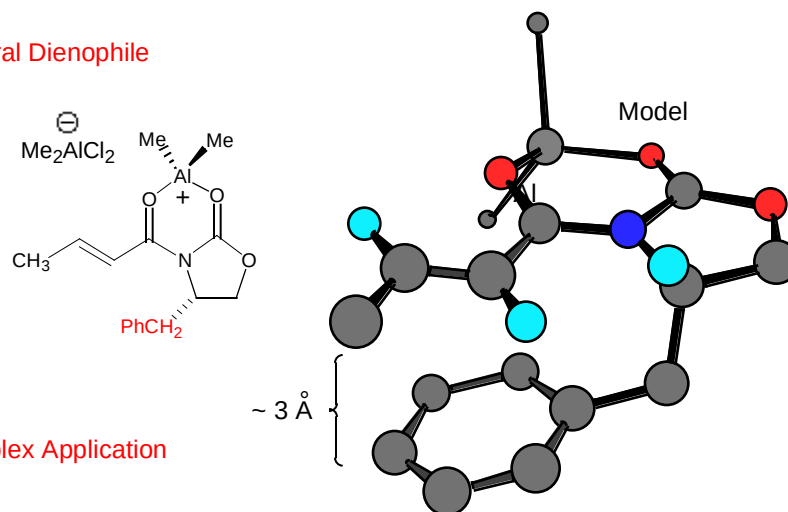


Conclusions:

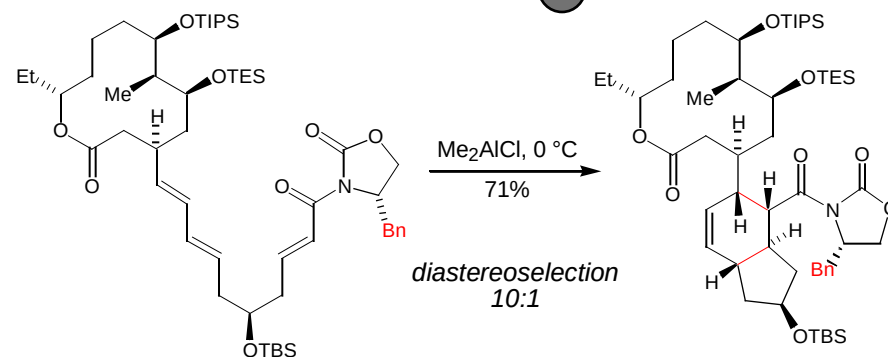
Steric effects correlate well for the two reactions

Added electronic effects from Bn group enhance facial bias

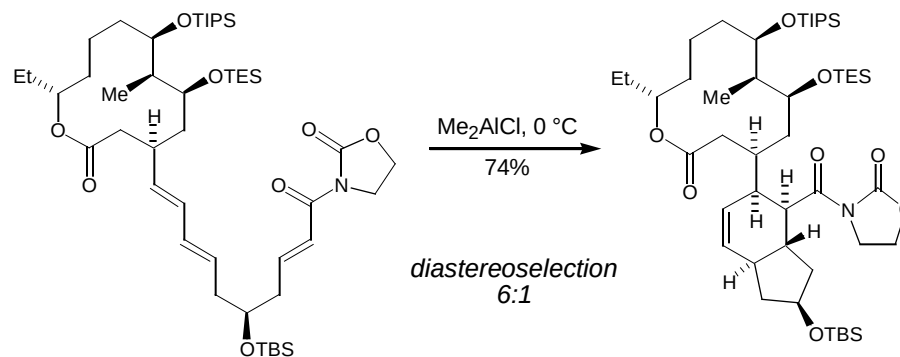
The Chiral Dienophile



A Complex Application



The control experiment with no chiral auxiliary:



Lepicidin Synthesis, *JACS*, **1993**, 115, 4497

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 Retrograde 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)

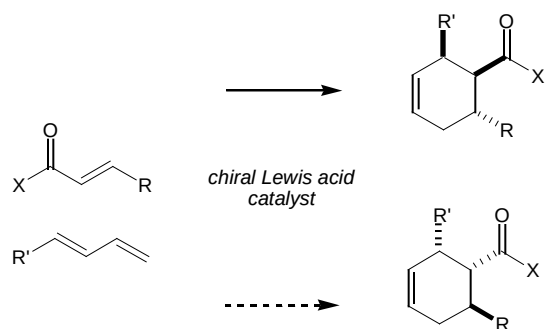
Schreiber, *Angew. Chem. Int. Ed.*, **1990**, 29, 256-272

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

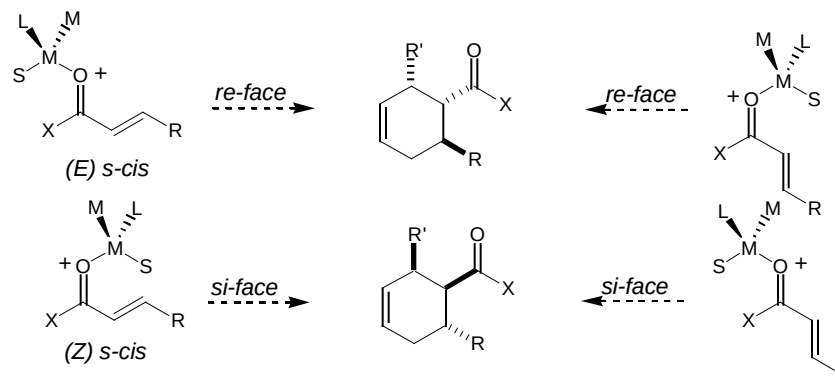
C₂ Symmetry and Asymmetric Induction, Whitesell, *Chem. Rev.*, **1989**, 89, 1581-1590

The Design of Enantioselective Diels-Alder Catalysts



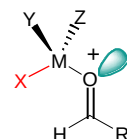
The conformation of the dienophile is also an issue

The S-cis versus S-trans dienophile conformation is 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

Stereochemical Effects (?) in Lewis acid-C=O Complexes

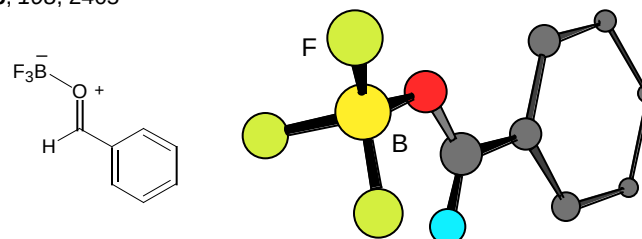


Let X be the most electronegative ligand in the Lewis acid

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

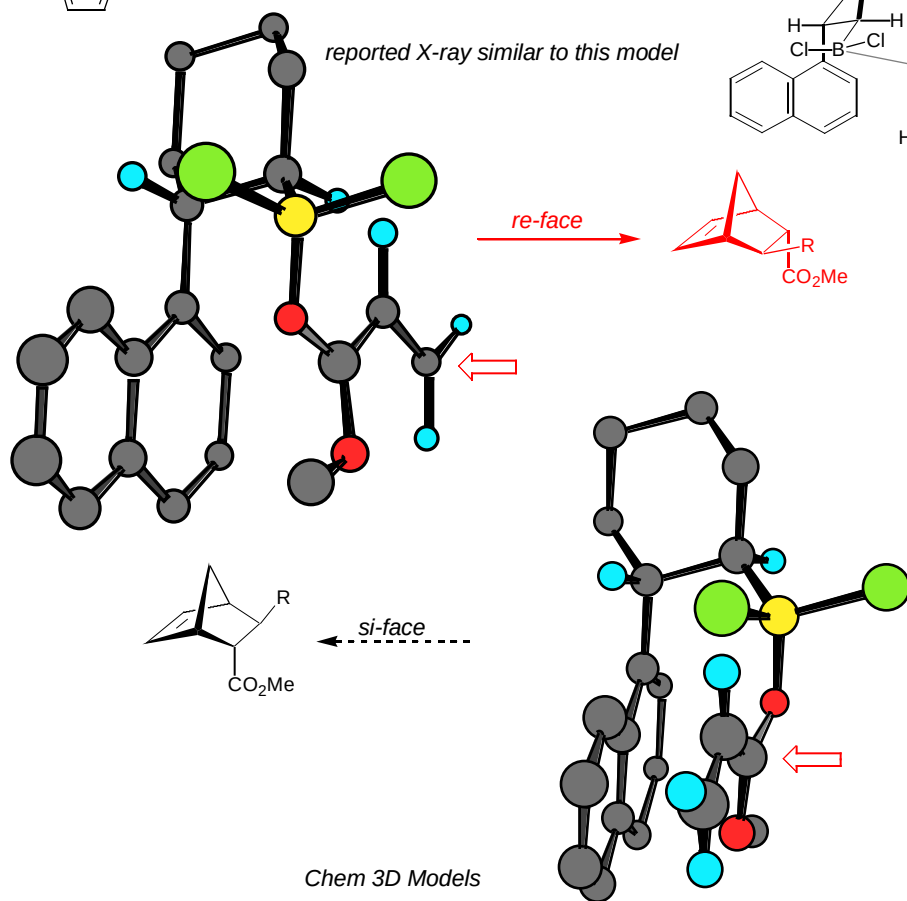
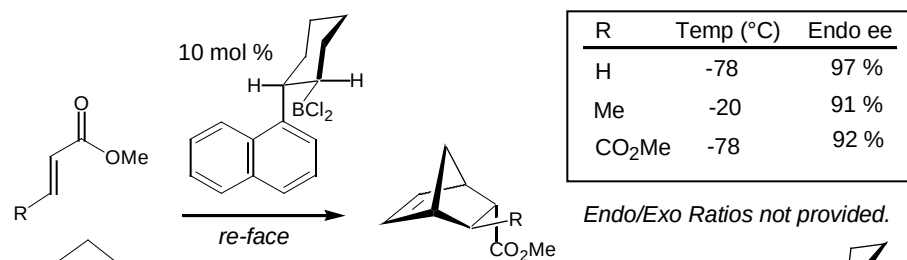
However, there is no evidence for this orienting effect in this X-ray structure reported by Reetz, *JACS*, **1986**, 108, 2405



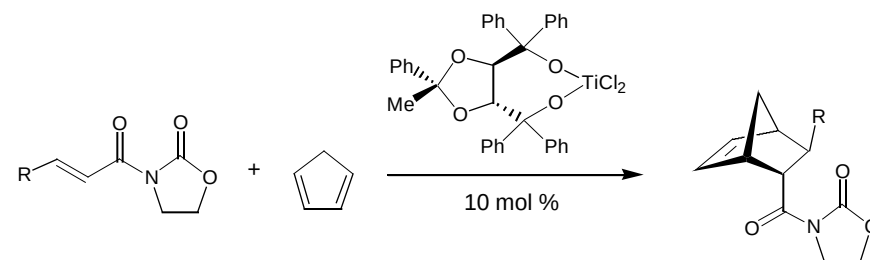
However pi-bonding to coordinated C=O-Al complexes has been reported
Barron, *JACS*, **1990**, 112, 3446, *JACS*, **1990**, 112, 2950

Theory predicts a small rotational barrier about B-O bond: Wiberg *JACS*, **1988**, 110, 6642

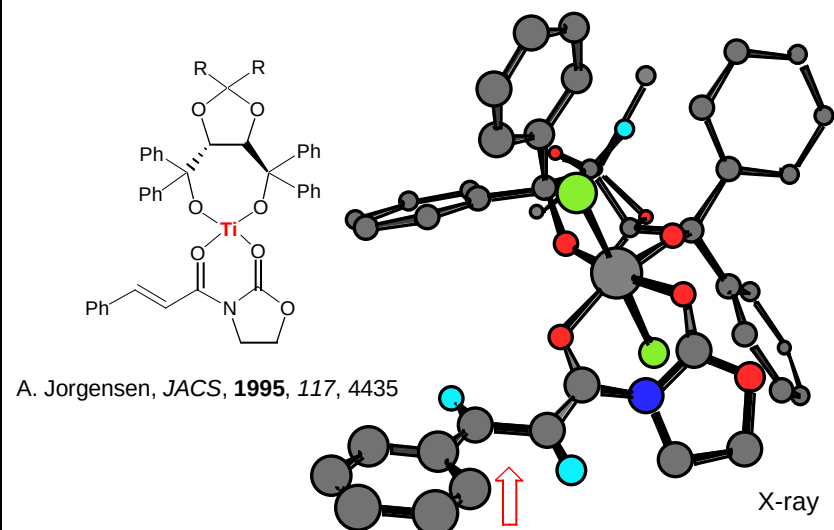
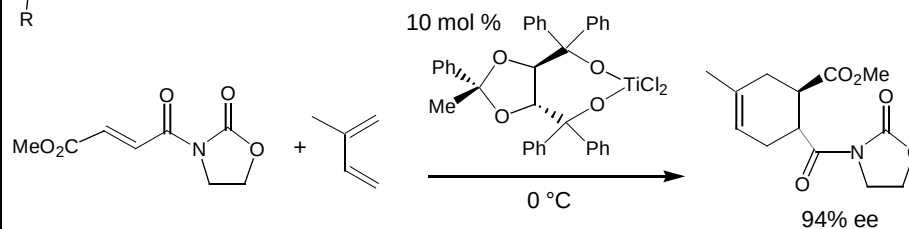
■ Boron-Based Catalysts: Hawkins JACS 1991, 113, 7794



■ Titanium-Based Catalysts: Narasaka JACS 1989, 111, 5340.

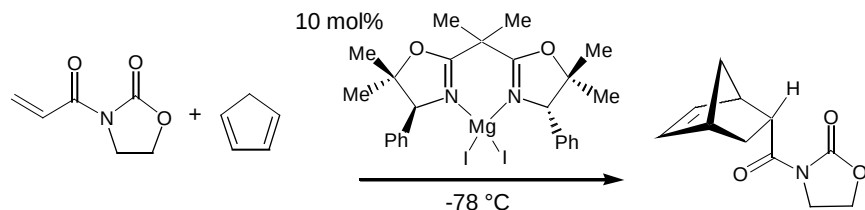


R	Temp (°C)	Endo/Exo	Endo ee
H	-40	96:4	64 %
Me	0	92:8	91 %
Ph	25	88:12	64 %

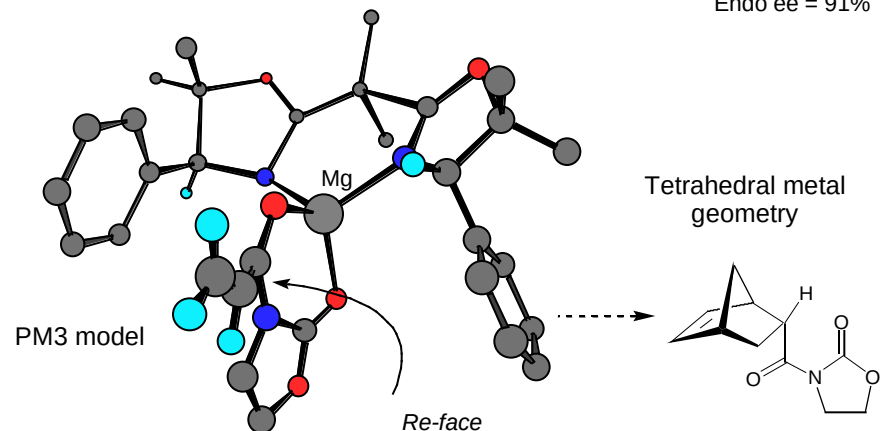


A. Jorgensen, JACS, 1995, 117, 4435

■ **Mg(2+)-Based Catalysts:** Corey *Tetrahedron Lett.* **1992**, 33, 6807.



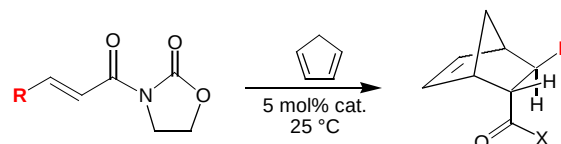
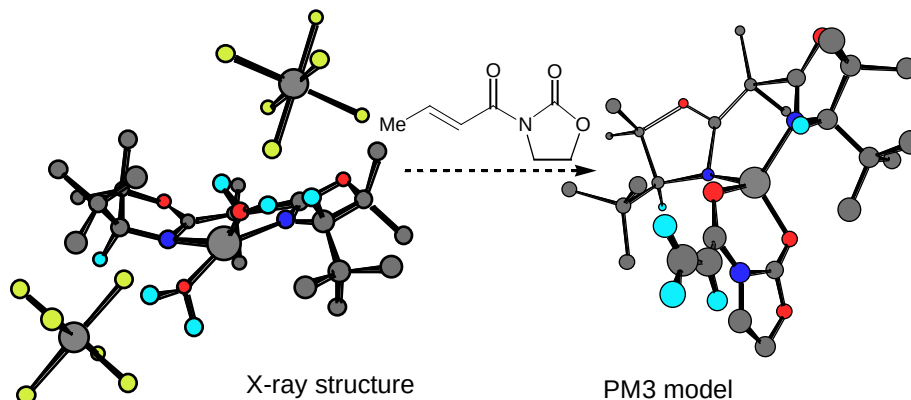
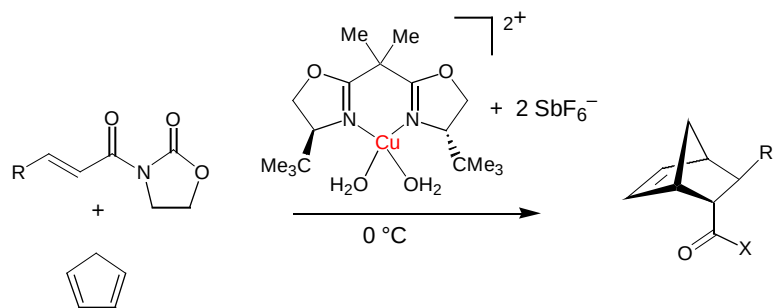
Stereochemical Model:



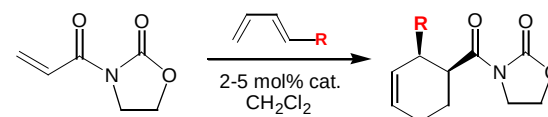
Limitations: Reactions limited to illustrated reaction

■ **Cu(2+)-Based Catalysts:**

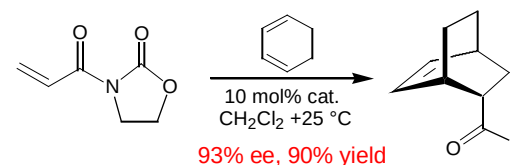
Evans, Miller, Lectka *JACS* **1993**, 115, 6460.
Angew. Chem. Int. Engl. **1995**, 34, 798-800.
JACS **1999**, 121, 7559-7573.
JACS **1999**, 121, 7582-7594



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%

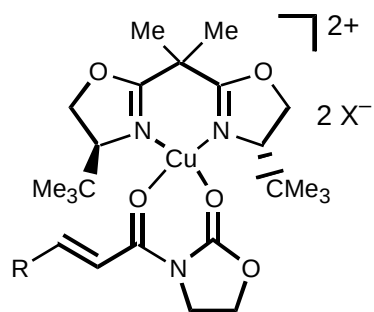


R	temp	endo ee	yield
R = Me	25 °C	94% ee	89%
R = Ph	-20 °C	97% ee	95%
R = OAc	0 °C	97% ee	100%

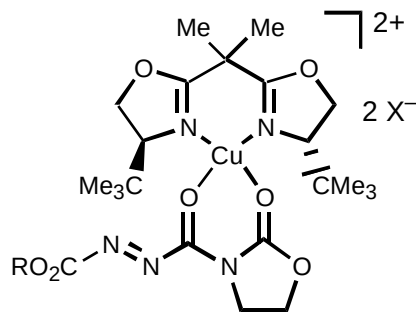


Cu(box) and Cu(pybox) catalyst-substrate complexes implicated in enantioselective reactions.

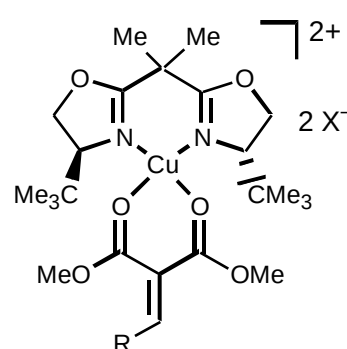
"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, Evans, *Acc. Chem. Res.* **2000**, 33, 325-335. (pdf)



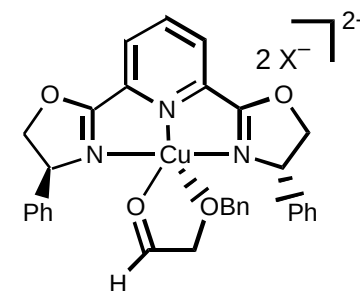
Cycloaddition Reactions
Michael Reactions



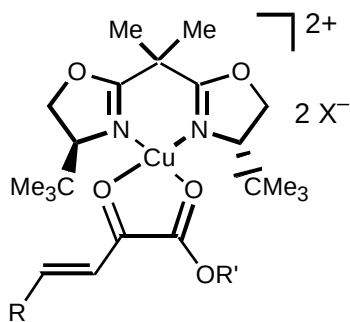
Enol Amination Reactions



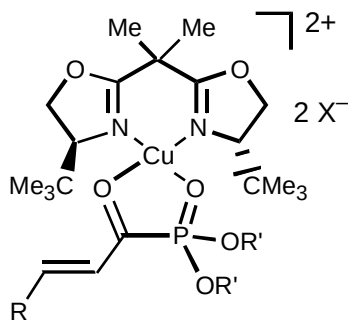
Michael Reactions



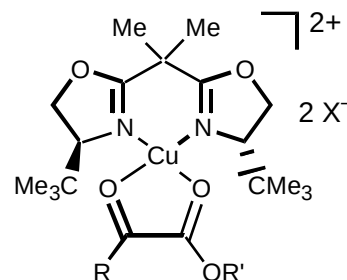
Aldol Reactions



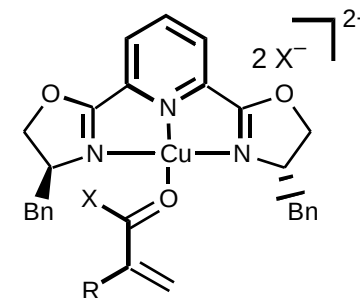
Hetero Diels-Alder Reactions



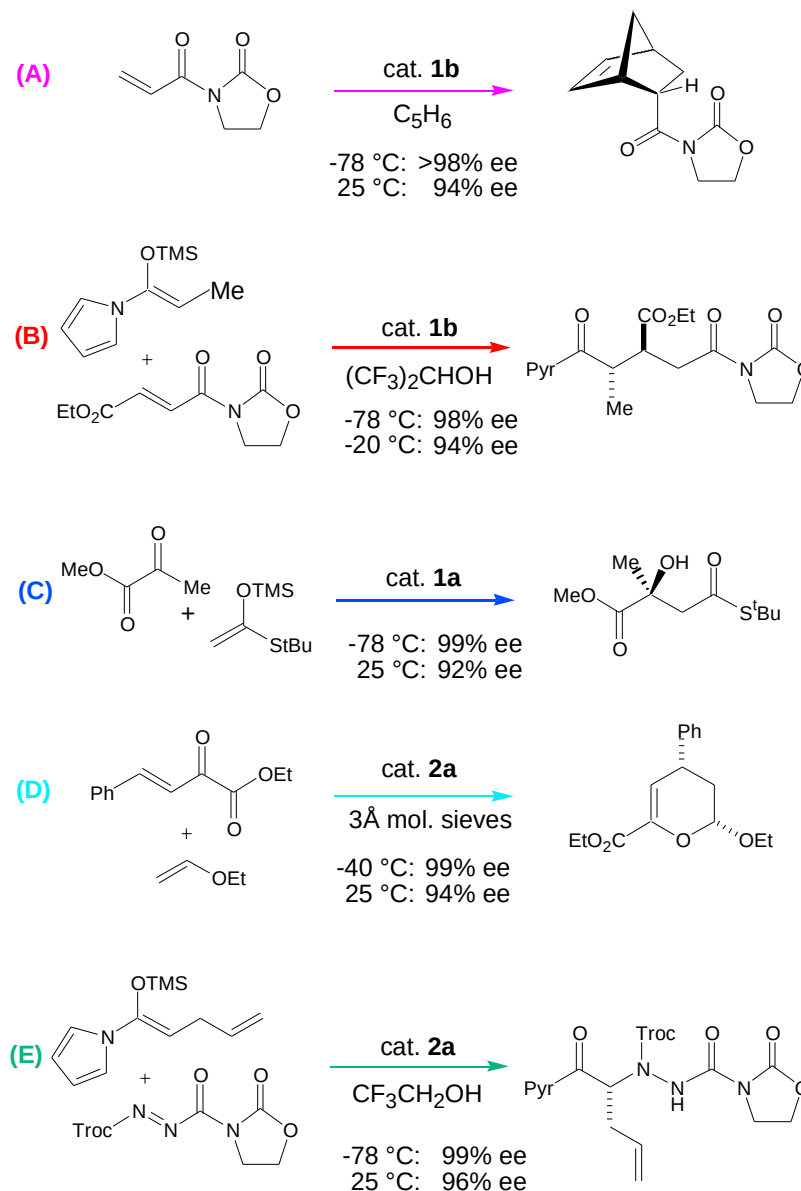
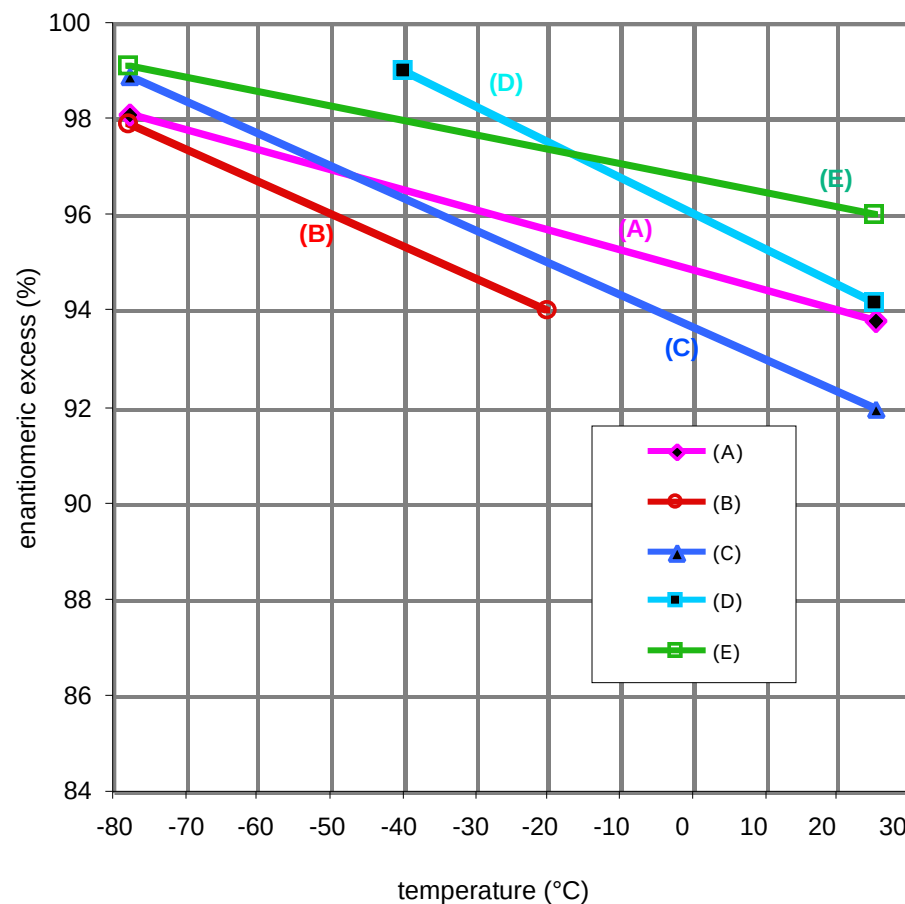
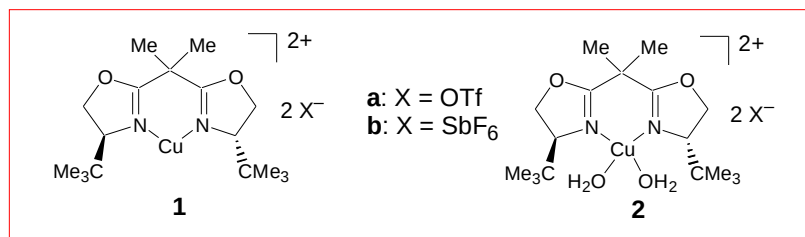
$R = H$, Cycloaddition Reactions
Ene Reactions



$R = Alkyl$, Cycloaddition Reactions
Aldol Reactions



Diels-Alder Reactions



<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

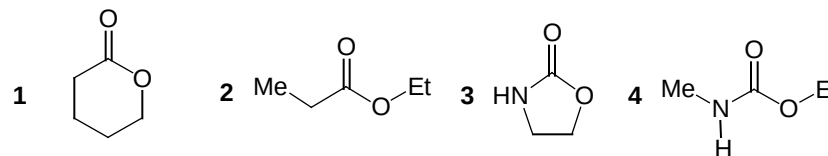
"Equilibrium acidities in DMSO Solution", F. G. Bordwell.
Acc. Chem. Res. **1988**, 21, 456-463.

Here is a web site containing Bordwell pKa data

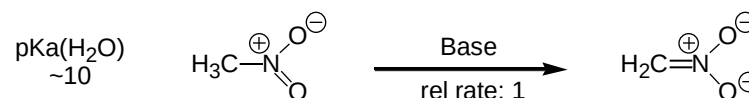
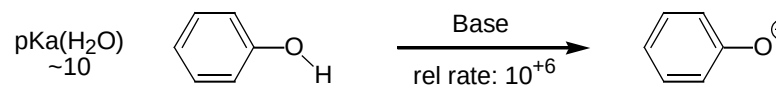
<http://www.chem.wisc.edu/areas/reich/pkatable/index.htm>

■ 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)

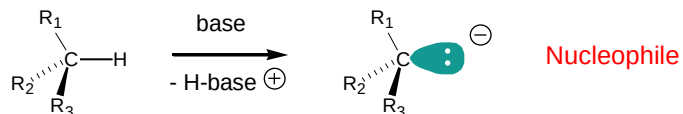


The thermodynamic acidities of phenol and nitromethane are both ~10; however, using a common base, phenol is deprotonated 10^{+6} times as fast. Rationalize



Activation of Organic Molecules

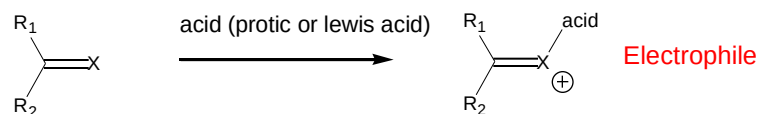
■ Base Activation



pK_a , describes quantitatively a molecule's propensity to act as an acid, i.e. to release a proton.

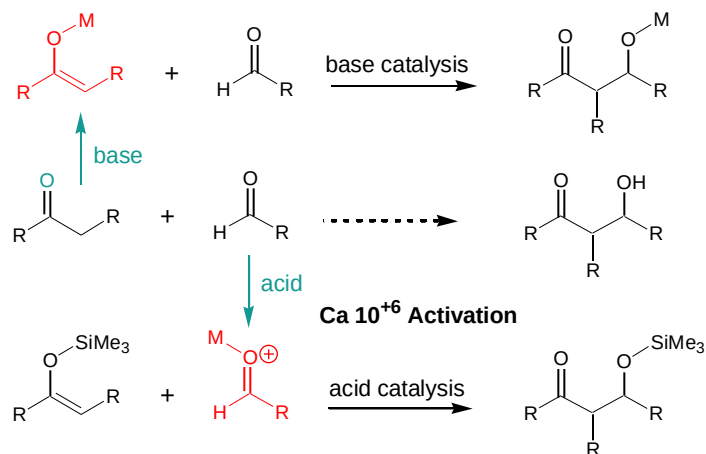
- Medium effects
- Structural effects (influence of substituents R_1)

■ Acid Activation

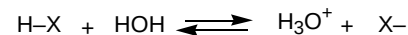


$\text{X} = \text{e.g. O, NR} \dots$

■ The Aldol Example

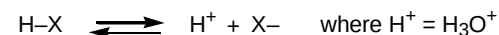
■ Definition of K_a

Let H-X be any Bronsted acid. In water ionization takes place:



where $K_{eq} = \frac{[\text{H}_3\text{O}^+][\text{X}^-]}{[\text{H-X}][\text{HOH}]}$ where $[\text{HOH}] = 55.5 \text{ mol L}^{-1}$ (A)

Since $[\text{HOH}]$ is, for all practical purposes, a constant value, the acid dissociation constant K_a is defined without regard to this entity. e.g.



Hence $K_a = \frac{[\text{H}^+][\text{X}^-]}{[\text{H-X}]} \quad \text{(B)}$

From the above definitions, K_a is related to K_{eq} by the relation:

$$K_a(\text{H-X}) = 55.5 K_{eq}(\text{H-X}) \quad \text{(C)}$$

■ Autoionization of water



$$K_{eq} = 3.3 \times 10^{-18}$$

From Eq C: $K_a = 55.5 K_{eq} = 55.5(3.3 \times 10^{-18})$

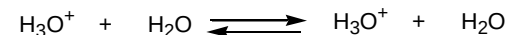
Hence $K_a = 1.8 \times 10^{-16}$

Since pK_a is defined in the following equation:

$$\text{pK}_a = -\log_{10} [K_a] \quad \text{The } \text{pK}_a \text{ of HOH is } +15.7$$

Keep in mind that the strongest base that can exist in water is HO^- .

Lets now calculate the acid dissociation constant for hydronium ion.



obviously: $K_{eq} = 1$

$$K_a = [\text{HOH}] \times K_{eq} \quad \text{hence } K_a = 55.5$$

$$\text{pK}_a = -\log_{10} K_a = -1.7$$

The strongest acid that can exist in water is H_3O^+ .

■ The Gibbs Relationship

$$\Delta G^\circ = -RT \ln K$$

$$\text{or } \Delta G^\circ = -2.3 RT \log_{10} K$$

$$\Delta G^\circ_{298} = -1.4 \log_{10} K_{\text{eq}}$$

$$2.3 RT = 1.4$$

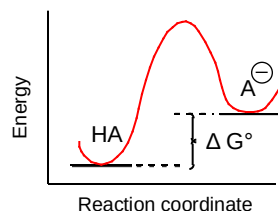
$$\text{at } T = 298 \text{ K}$$

$$\text{in kcal mol}^{-1}$$

$$\Delta G^\circ_{298} = 1.4 \text{ p}K_{\text{eq}} \approx 1.4 \text{ p}K_{\text{a}} \quad \text{with } \text{p}K = -\log_{10} K$$

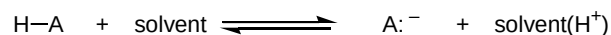
Hence, $\text{p}K_{\text{a}}$ is proportional to the free energy change

K_{eq}	$\text{p}K_{\text{eq}}$	ΔG°
1	0	0
10	-1	-1.4
100	-2	-2.8 kcal/mol



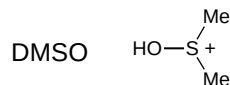
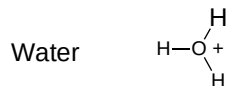
■ Medium Effects

Consider the ionization process:

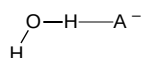


In the ionization of an acid in solution, the acid donates a proton to the medium. The more basic the medium, the larger the dissociation equilibrium. The ability of the medium to stabilize the conjugate base also plays an important role in the promotion of ionization. Let us consider two solvents, HOH and DMSO and the performance of these solvents in the ionization process.

The Protonated Solvent



Conjug. Base Stabiliz.



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

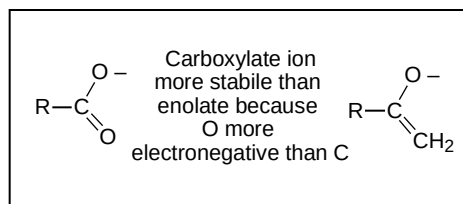
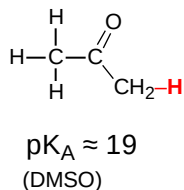
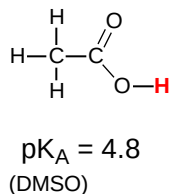
■ Representative pKa Data

Substrate	DMSO	HOH	$\Delta \text{p}K_{\text{a}}$
HOH	31.2	15.7	15.5
HSH	14.7	7.0	7.7
MeOH	29.0	15.3	13.7
C ₆ H ₅ OH	18.0	9.9	8.1
O ₂ N-CH ₃	17.2	10.0	7.2
Ph-C(=O)-CH ₃	24.6	17	7.6

The change in $\text{p}K_{\text{a}}$ in going from water to DMSO is increasingly diminished as the conjugate base becomes resonance stabilized (Internal solvation!).

Substrate	DMSO	HOH	$\Delta \text{p}K_{\text{a}}$
	18.1	16.0	2.1
	16.4	13.3	3.1
	13.3	8.9	4.5
NC-CH ₂ -CN	11.1	11.2	0

Substituent Effects

Electronegativity e.g. Compare Carboxylic Acids vs. Ketones**Hybridization** - S-character of carbon hybridization

Remember:

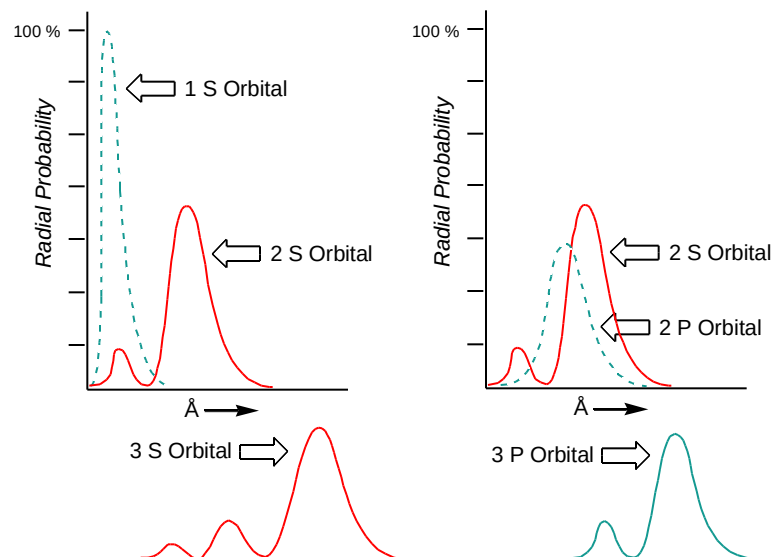
sp^3 -orbitals 25% s-character
 sp^2 -orbitals 33% s-character
 sp -orbitals 50% s-character

Carbon Acids

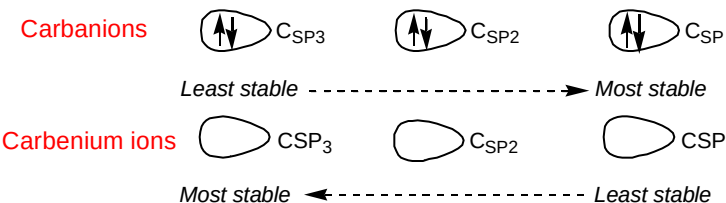
	$\text{R}-\text{C}\equiv\text{H}$	$\text{R}_2\text{C}=\text{CH}_2$	$\text{R}_2\text{CH}-\text{CH}_3$	R_3CH
Hybridization	sp	sp^2	$\approx \text{sp}^2$	sp^3
Bond Angle	180°	120°	$\approx 120^\circ$	109°
$\text{pK}_\text{a}(\text{DMSO})$	23	32	≈ 39	50

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.



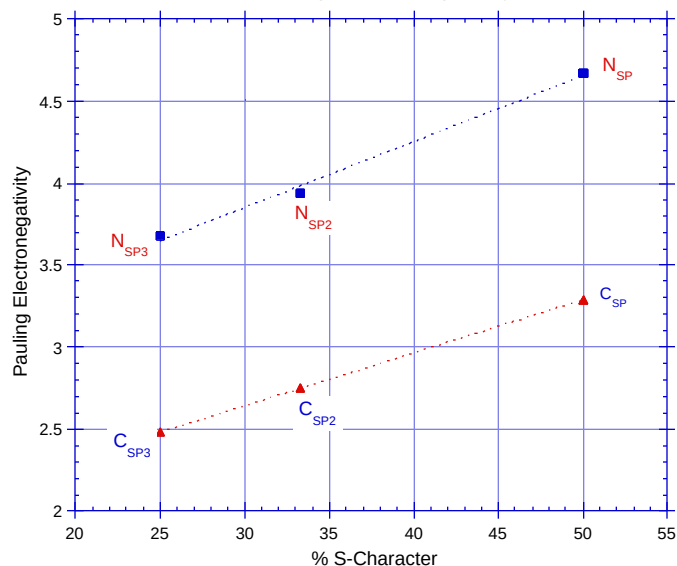
S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in s states see a higher nuclear charge. The above observation correctly implies that the stability of nonbonding electron pairs is directly proportional to the % of S-character in the doubly occupied orbital.



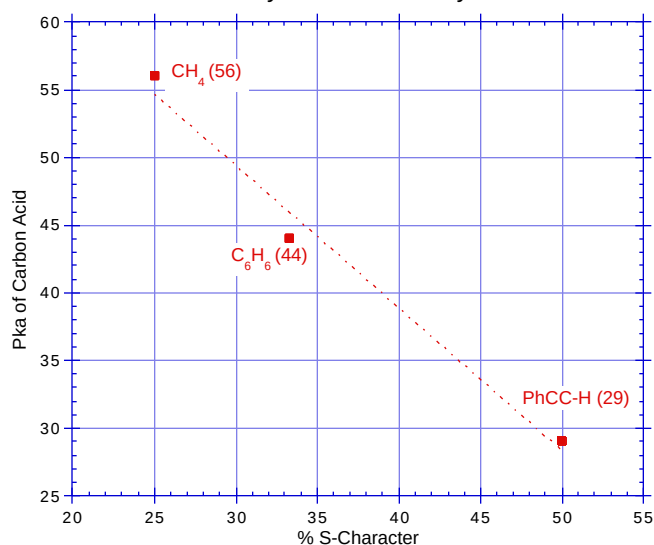
The above trends indicate that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

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 Destabilizing:**

Steric hinderance of anion solvation

Compare:

(JACS **1975**, 97, 190)

	pK _A (DMSO)		pK _A (DMSO)
PhSO ₂ -CH ₂ -H	29		31.1
PhSO ₂ -CH ₂ -Me	31		38.3

Heteroatom-Substituents: - 1st row elements of periodic table

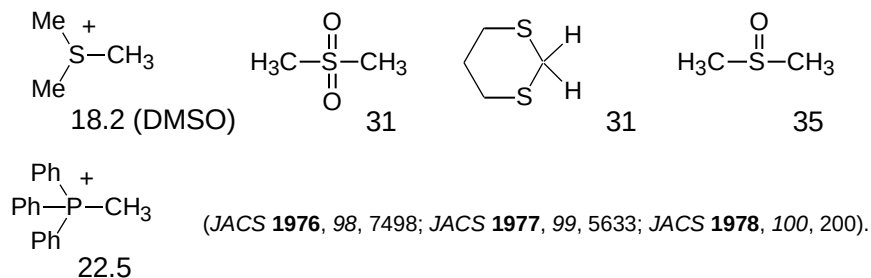
	pK _A (DMSO)	
PhSO ₂ -CH ₂ -OCH ₃	30.7	Inductive Stabilization versus Lone Pair Repulsion (-I vs +M -Effect)
PhSO ₂ -CH ₂ -OPh	27.9	
PhSO ₂ -CH ⁺ -NMe ₃	19.4	Inductive Stabilization

Heteroatom-Substituents: - 2nd row elements of periodic table

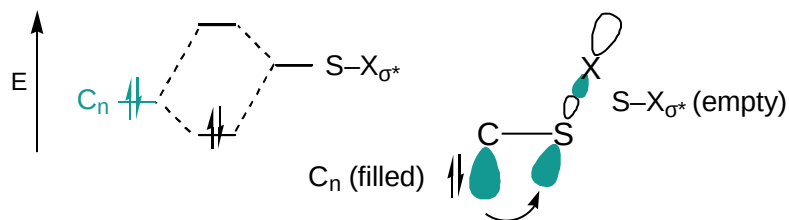
Strong carbanion stabilizing effect

	pK _A (DMSO)		pK _A (DMSO)
PhSO ₂ -CH ₂ -H	29	PhSO ₂ -CH ₂ -SO ₂ Ph	12.2
PhSO ₂ -CH ₂ -SPh	20.5	PhSO ₂ -CH ₂ -PPh ₂	20.5

■ Carbanion Stabilization by 2nd-Row Atoms: SR, SO₂R, PR₃ etc

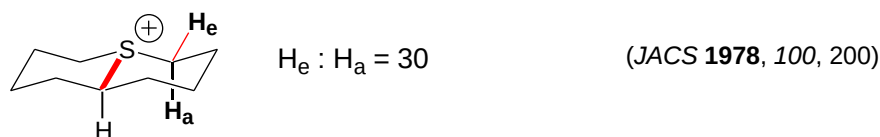
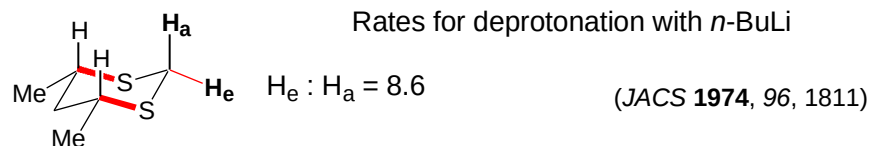


The accepted explanation for carbanion stabilization in 3rd row elements is delocalization into vicinal antibonding orbitals

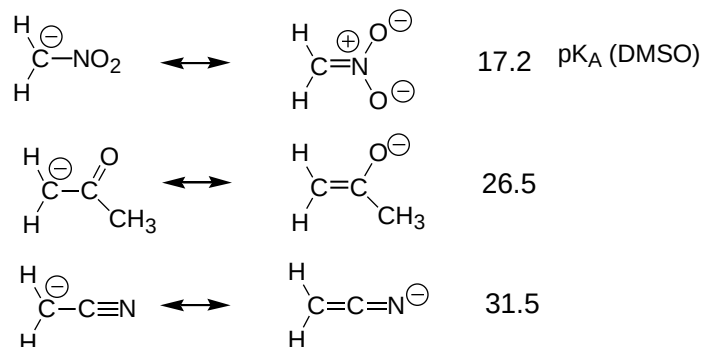


This argument suggests a specific orientation requirement.
This has been noted:

Anti (or syn) periplanar orientation of Carbanion-orbital and σ^* orbital mandatory for efficient orbital overlap.



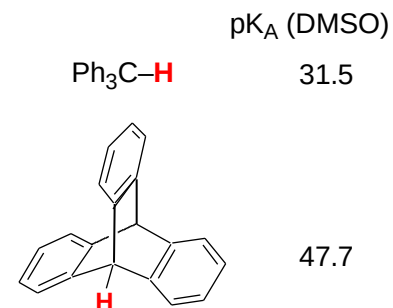
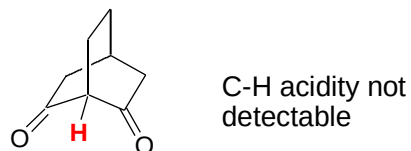
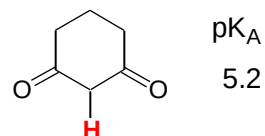
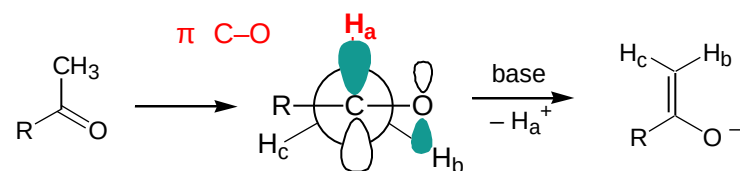
■ Conjugative Stabilization of Conjugate Base



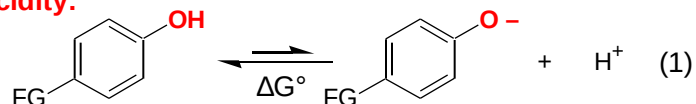
For efficient conjugative stabilization, rehybridization of carbanion orbital from n_{sp^3} to n_{p} is required for efficient overlap with low-lying π^* -orbital of stabilizing group. However, the cost of rehybridization must be considered.

■ 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



Phenol Acidity:

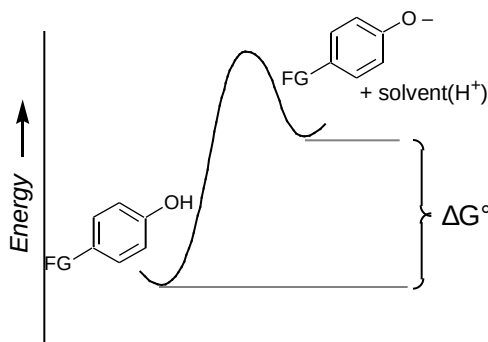


This topic has a number of take-home lessons. Most importantly, is is a useful construct on which to discuss the role of FG's in influencing the acidity of this oxygen acid.

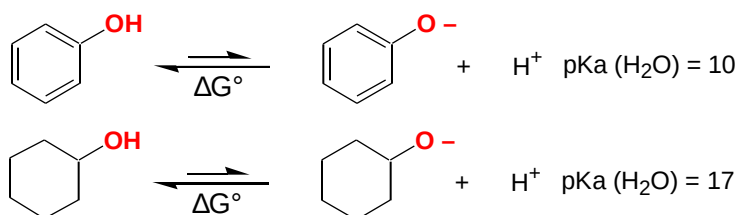
How does one analyze the impact of structure on pKa of a weak acid (pKa > 0) ?

The Approach:

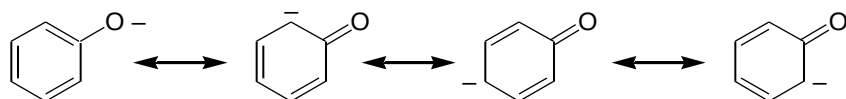
For equilibria such as that presented above, analyze the effect of stabilizing (or destabilizing) interactions on the more energetic constituent which in this case is the conjugate base.



Why is phenol so much more acidic than cyclohexanol?



Loudon (pg 730): "The enhanced acidity of phenol is due largely to stabilization of its conjugate base by resonance."

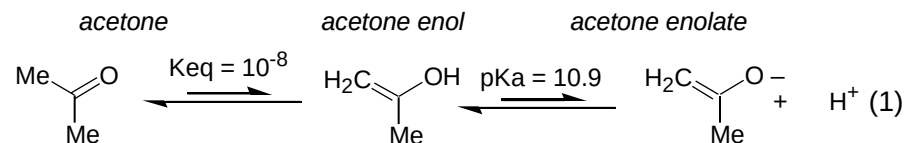


from previous discussion, $\Delta G^\circ_{298} = -1.4 \log_{10} K_{eq} = 1.4 \text{ pK}_{eq}$

$$\Delta G^\circ (\text{stab}) = 1.4(\text{pK}_{a\text{phenol}} - \text{pK}_{a\text{cyclohexanol}}) = 1.4(-7) = 9.8 \text{ kcal/mol}$$

Is the benzene ring somehow special. i.e "larger resonance space."

Acetone enol:



The surprising fact 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 $\text{C}_6\text{H}_5\text{O}^-$?

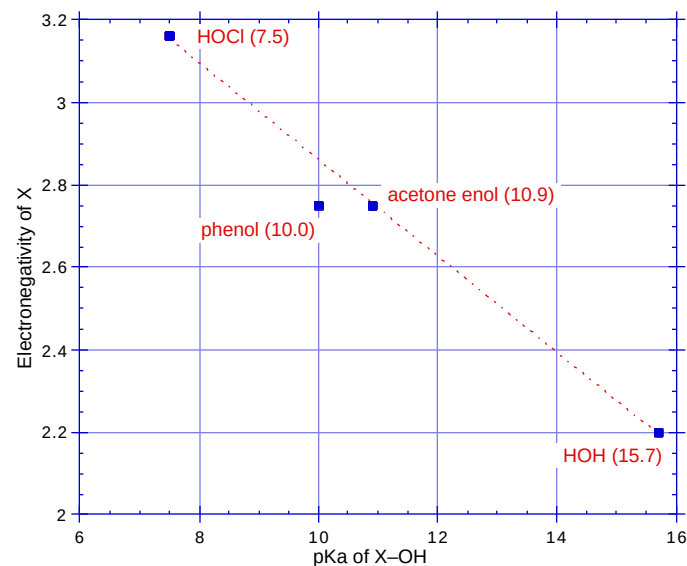
Consider the following general oxygen acid X-OH where X can only stabilize the conjugate base through induction:

X-OH	X-O ⁻ + H ⁺	X-OH	pKa(H ₂ O)
CH ₃ -OH		CH ₃ -OH	15.5
CF ₃ CH ₂ -OH		CF ₃ CH ₂ -OH	12.4
Cl-OH		Cl-OH	7.5

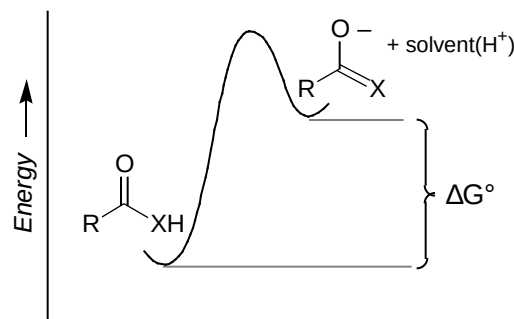
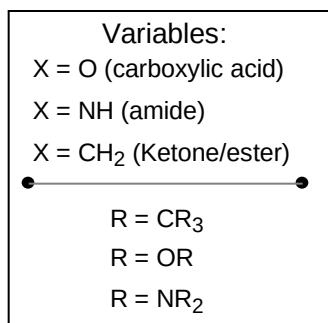
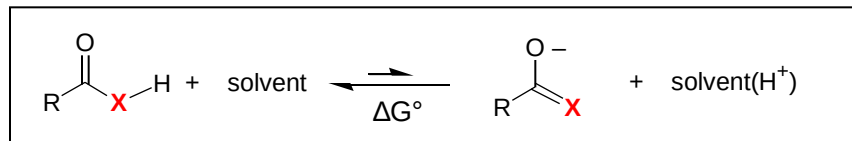
As the electronegativity of X increases the acidity of X-OH increases.

If you take the calculated electronegativity of an SP₂ 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.



■ The General Reaction: Ionization of a weak acid ($pK_a \leq 0$)

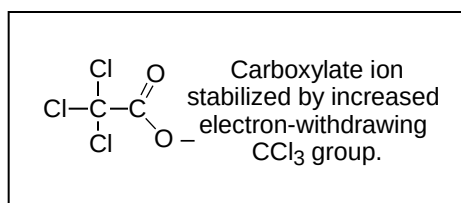
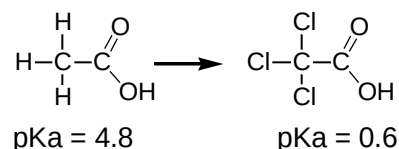


■ The Question: How does one analyze the impact of structure on pK_a ?

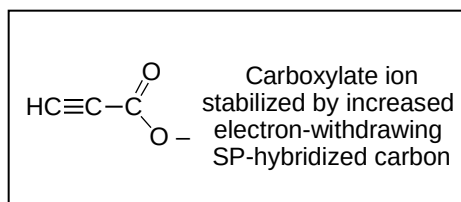
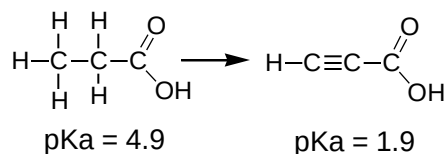
■ The Approach:

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.

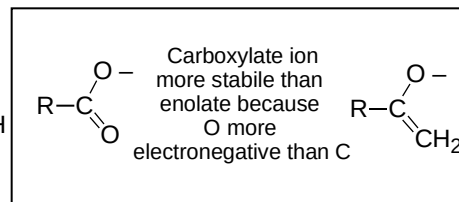
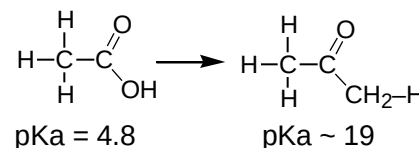
Case I: Carboxylic Acids: Inductive Effects



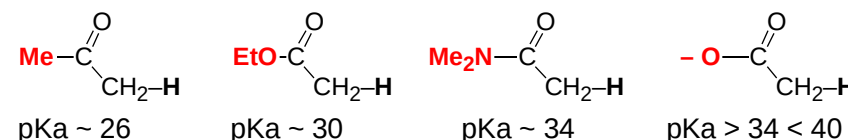
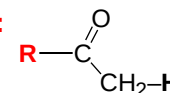
Case II: Carboxylic Acids: Inductive Effects & Carbon Hybridization



Case III: Carboxylic Acids vs Ketones:



Case IV: Carboxylic Acids, Esters, Amides & Ketones:



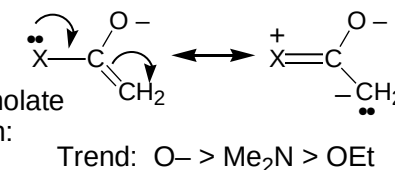
The Analysis:

In this series of compounds, there are two variables to consider:

■ Inductive Effect: $OEt > Me_2N > H_3C$ but (O-?)

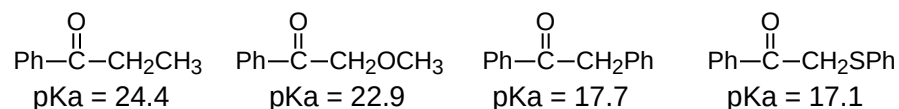
■ Resonance Effect:

The degree to which substituent X: "contributes" electron density into enolate represents a destabilizing interaction:

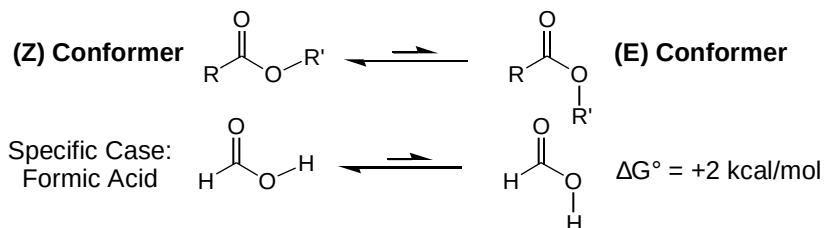


■ Resonance donation dominates inductive electron withdrawal as indicated by the data.

Substituents on the α -carbon: Stabilization by either resonance, induction, or both is observed:



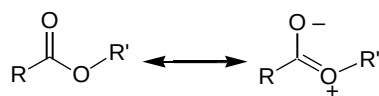
■ **Conformations:** There are 2 planar conformations.



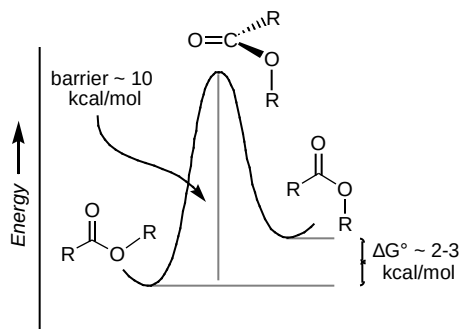
The (E) conformation of both acids and esters is less stable by 2-3 kcal/mol. If this equilibrium were governed only by steric effects one would predict that the (E) conformation of formic acid would be more stable (H smaller than =O). Since this is not the case, there are electronic effects which must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

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

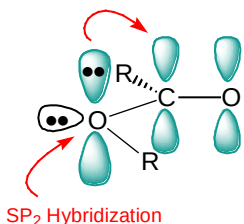
These resonance structures suggest hindered rotation about =C-OR bond. This is indeed observed:



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.

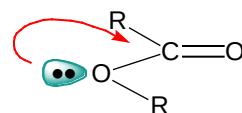


The filled oxygen p-orbital interacts with pi (and pi*) C=O to form a 3-centered 4-electron bonding system.

■ **Oxygen Hybridization:** Note that the alkyl oxygen is sp^2 . Rehybridization is driven by system to optimize pi-bonding.

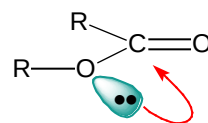
■ **Hyperconjugation:** Let us now focus on the oxygen lone pair in the hybrid orbital lying in the sigma framework of the C=O plane.

(Z) Conformer



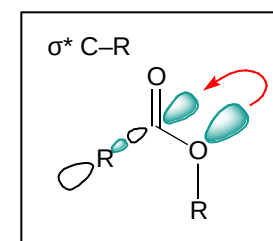
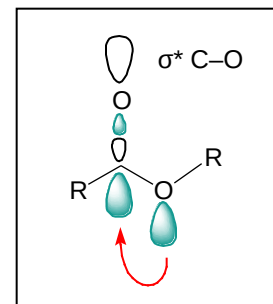
In the (Z) conformation this lone pair is aligned to overlap with $\sigma^* \text{C-O}$.

(E) Conformer



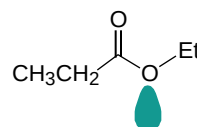
In the (E) conformation this lone pair is aligned to overlap with $\sigma^* \text{C-R}$.

Since $\sigma^* \text{C-O}$ is a better acceptor than $\sigma^* \text{C-R}$ (where R is a carbon substituent) it follows that the (Z) conformation is stabilized by this interaction.

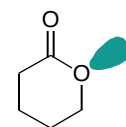


Lone pair orientation & Impact on pKa (DMSO)

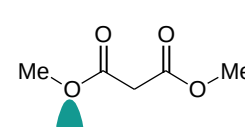
See Bordwell, *J. Org. Chem.* **1994**, 59, 6456-6458



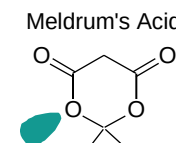
pKa ~ 30



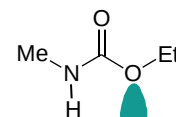
pKa = 25.2



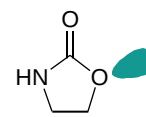
pKa = 15.9



pKa = 7.3

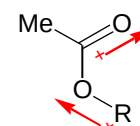


pKa = 24.5

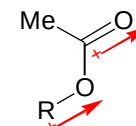


pKa = 20.6

Is this a dipole effect? See Bordwell



$E(\text{rel}) = 0$

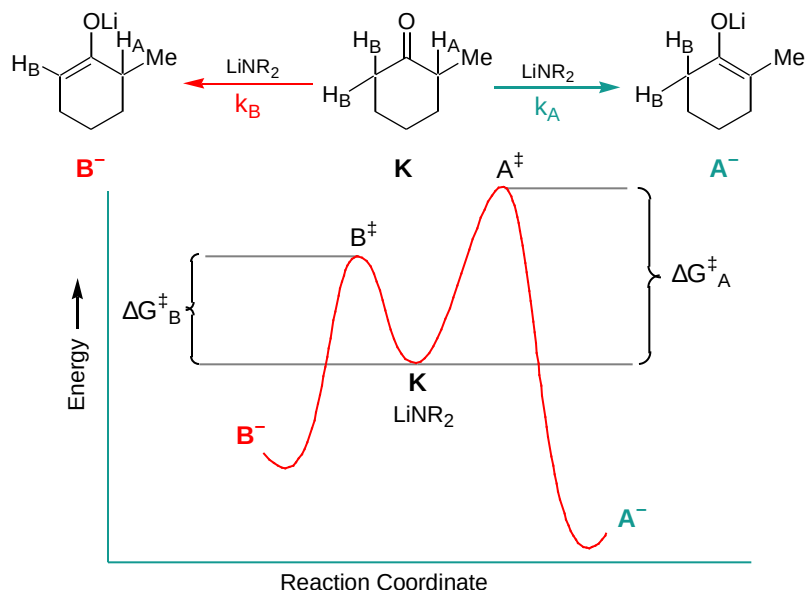


$E(\text{rel}) = +3.8 \text{ kcal}$

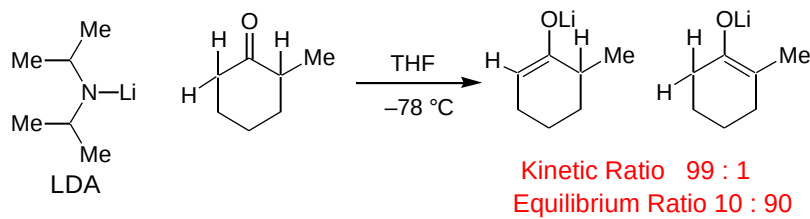
Houk, *JACS* **1988**, 110, 1870 supports the dipole argument

■ Kinetic Acidity: Rates of proton removal

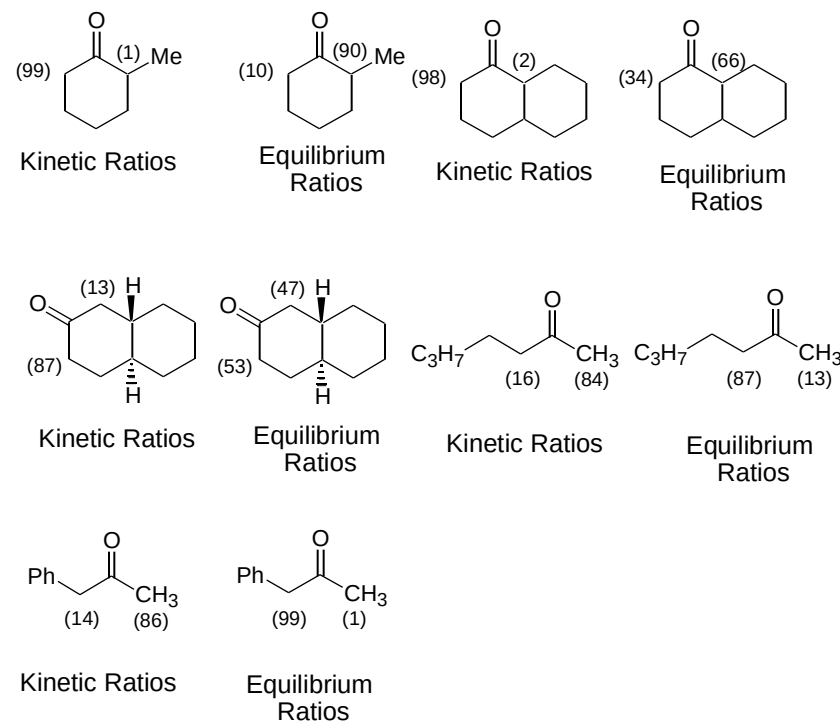
Consider enolization of the illustrated ketone under non-equilibrating conditions:



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, $\Delta G^\ddagger_A$ will increase more than $\Delta G^\ddagger_B$ 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 & Equilibrium Ratios of Enolates Resulting from Enolization with LDA & Subsequent Equilibration

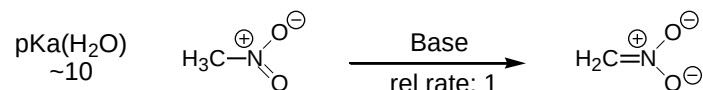
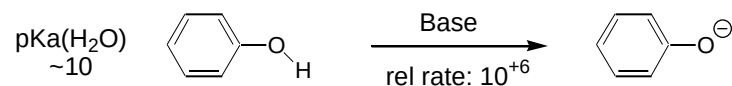


■ Note that alkyl substitution stabilizes the enolate (Why??). This effect shows up in the equilibrium ratios shown above.

■ 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

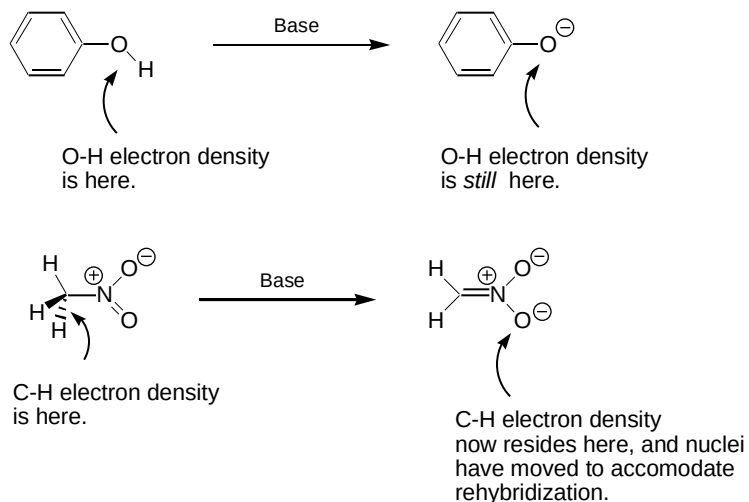
Observation: The thermodynamic acidities of phenol and nitromethane are both approximately 10; however, using a common base, phenol is deprotonated 10^{+6} times as fast.



Proton transfers from C-H Bonds are slow.

Why???

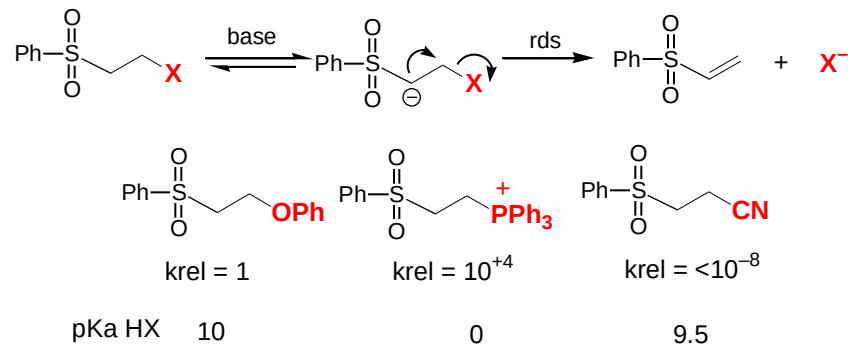
Most carbon acids are stabilized by resonance. Hence significant structural reorganization must accompany deprotonation.



The greater the structural reorganization during deprotonation, the lower the kinetic acidity

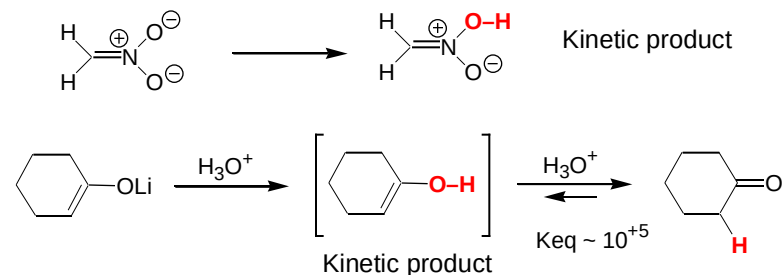
Kinetic Acidity vs. Leaving Group Ability: E1cb Elimination Reactions

Stirling, *Chem. Commun.* **1975**, 940



The greater the structural reorganization of the leaving group during E1cb elimination, the slower the rate of elimination.

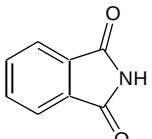
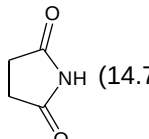
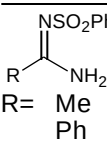
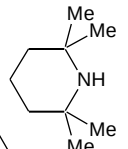
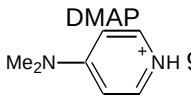
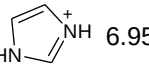
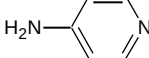
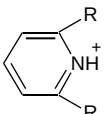
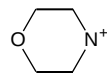
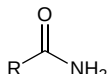
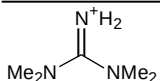
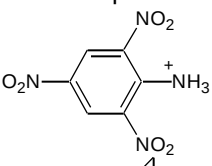
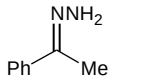
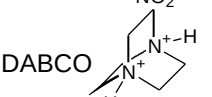
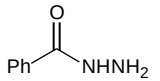
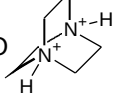
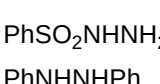
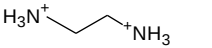
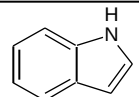
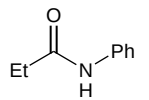
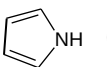
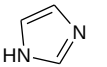
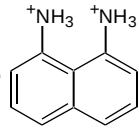
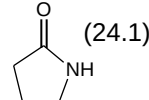
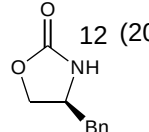
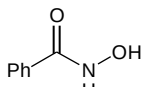
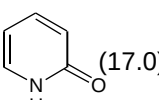
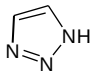
Protonation of Conjugate bases



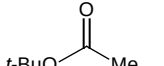
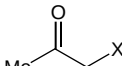
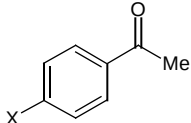
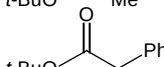
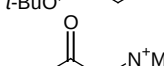
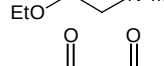
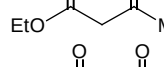
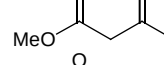
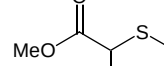
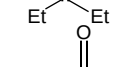
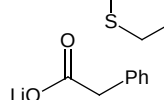
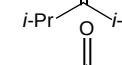
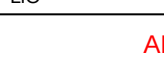
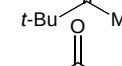
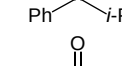
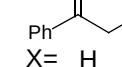
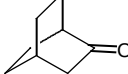
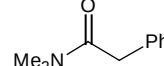
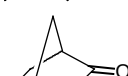
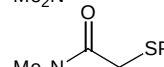
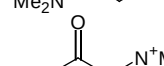
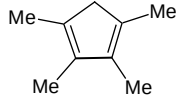
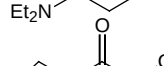
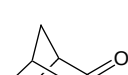
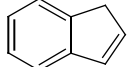
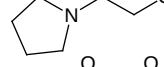
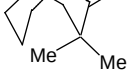
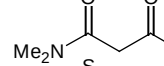
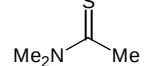
Jack Hine: Least Motion Principle (*Adv. Phys. Org. Chem.* **1977**, 15, 1)
 Lowry & Richardson, 3rd Edition, pp 205-206

Those elementary reactions that involve the least change in atomic positions will be favored

*Values <0 for H₂O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

Substrate	pKa	H ₂ O	(DMSO)	Substrate	pKa	H ₂ O	(DMSO)	Substrate	pKa	H ₂ O	(DMSO)	Substrate	pKa	H ₂ O	(DMSO)
PROTONATED NITROGEN				AMINES				IMIDES				AMIDINES			
N ⁺ H ₄	9.2	(10.5)		HN ₃	4.7	(7.9)			8.30		(14.7)				
EtN ⁺ H ₃	10.6			NH ₃	38	(41)						R= Me	(17.3)		
<i>i</i> -Pr ₂ N ⁺ H ₂	11.05			<i>i</i> -Pr ₂ NH	(36 THF))							R= Ph	(15.0)		
Et ₃ N ⁺ H	10.75	(9.00)		TMS ₂ NH	26(THF)	(30)		Ac ₂ NH		(17.9)					
PhN ⁺ H ₃	4.6	(3.6)		PhNH ₂		(30.6)						PROTONATED HETEROCYCLES			
PhN ⁺ (Me) ₂ H	5.20	(2.50)		Ph ₂ NH		(25.0)						DBU	(12)	(estimate)	
Ph ₂ N ⁺ H ₂	0.78			NCNH ₂		(16.9)		SULFONAMIDE							
2-napthal-N ⁺ H ₃	4.16					(44)		MeSO ₂ NH ₂		(17.5)					
H ₂ NN ⁺ H ₃	8.12			TMP		(37)		PhSO ₂ NH ₂		(16.1)			9.2		6.95
HON ⁺ H ₃	5.96					(26.5)		CF ₃ SO ₂ NH ₂	6.3	(9.7)					
Quinuclidine	11.0	(9.80)		AMIDES & CARBAMATES					MeSO ₂ NHPh	(12.9)					
Morpholine		N ⁺ H ₂ 8.36						GUANIDINIUM, HYDRAZONES, -IDES, & -INES							
N-Me morpholine	7.38			R= H		(23.5)				(13.6)		R= H (PPTS)	5.21	(3.4)	
	-9.3			CH ₃	15.1	(25.5)				(21.6)		<i>t</i> -Bu	4.95	(0.90)	
				Ph		(23.3)				(18.9)		Me	6.75	(4.46)	
DABCO		2.97, 8.82 (2.97, 8.93)		CF ₃		(17.2)				(17.2)		Cl, H	0.72		
	6.90, 9.95			NH ₂ (urea)		(26.9)		PhSO ₂ NHNH ₂		(26.1)		HETEROCYCLES			
				OEt		(24.8)		PhNHNHPh						(20.95)	
						(21.6)							(23.0)		(18.6)
Proton Sponge		-9.0, 12.0 (--, 7.50)			(24.1)			HYDROXAMIC ACID							
PhCN ⁺ H	-10				12	(20.5)			8.88 (NH)	(13.7)			(17.0)	1,2,3 triazole	
													(13.9)		

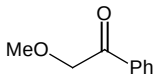
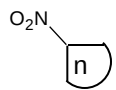
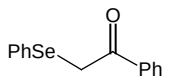
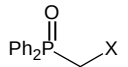
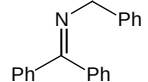
*Values <0 for H₂O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

Substrate	pKa	H ₂ O (DMSO)	Substrate	pKa	H ₂ O (DMSO)	Substrate	pKa	H ₂ O (DMSO)	Substrate	pKa	H ₂ O (DMSO)
HYDROCARBONS			ESTERS			KETONES					
(Me) ₃ CH	53			24.5	(30.3)						
(Me) ₂ CH ₂	51				(23.6)	X= H		(26.5)	X= H		(24.7)
CH ₂ =CH ₂	50				(20.0)	Ph		(19.8)	OMe		(25.7)
CH ₄	48	(56)			(20.0)	SPh		(18.7)	NMe ₂		(27.5)
	46			11	(14.2)	COCH ₃	9	(13.3)	Br		(23.8)
CH ₂ =CHCH ₃	43	(44)		13	(15.7)	SO ₂ Ph		(15.1)	CN		(22.0)
PhH	43						19-20	(27.1)			
PhCH ₃	41	(43)			(20.9)			(28.3)	n= 4		(25.1)
Ph ₂ CH ₂	33.5	(32.2)			[30.2 (THF)]			(27.7)	5		(25.8)
Ph ₃ CH	31.5	(30.6)						(26.3)	6		(26.4)
HCCH	24								7		(27.7)
PhCCH	23	(28.8)				X= H		(24.7)	8		(27.4)
XC ₆ H ₄ CH ₃			AMIDES			CH ₃		(24.4)			(28.1)
X= <i>p</i> -CN		(30.8)			(26.6)	Ph		(17.7)			(29.0)
<i>p</i> -NO ₂		(20.4)			(25.9)	COCH ₃		(12.7)			(25.5)
<i>p</i> -COPh		(26.9)			(24.9)	COPh		(13.3)			
		(26.1)				CO ₂ Et		(22.7)			
	20	(20.1)			(17.2)	CN		(10.2)			
	15	(18.0)			(18.2)	F		(21.6)			
H ₂	~36				(25.7)	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 ₂ Ph		(11.4)			

*Values <0 for H₂O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

Substrate	pKa	H ₂ O (DMSO)	Substrate	pKa	H ₂ O (DMSO)	Substrate	pKa	H ₂ O (DMSO)	Substrate	pKa	H ₂ O (DMSO)
NITRILES			SULFIDES			SULFOXIDES			SULFONES		
NC-CH ₂ -X			PhSCH ₂ X								
X= H		(31.3)	X= Ph		(30.8)	X=		(35.1)	X= H		(29.0)
CH ₃		(32.5)	CN		(20.8)	Ph		(29.0)	CH ₃		(31.0)
Ph		(21.9)	COCH ₃		(18.7)	SPh		(29.0)	<i>t</i> -Bu		(31.2)
COPh		(10.2)	COPh		(16.9)				Ph		(23.4)
CONR ₂		(17.1)	NO ₂		(11.8)				CH=CH ₂		(22.5)
CO ₂ Et		(13.1)	SPh		(30.8)	X=		(33)	CH=CHPh		(20.2)
CN	11	(11.1)	SO ₂ Ph		(20.3)	H		(27.2)	CCH		(22.1)
OPh		(28.1)	SO ₂ CF ₃		(11.0)	Ph		(18.2)	CCPh		(17.8)
N ⁺ Me ₃		(20.6)	POPh ₂		(24.9)	SOPh			COPh		(11.4)
SPh		(20.8)						(24.5)	COMe		(12.5)
SO ₂ Ph		(12.0)	MeSCH ₂ SO ₂ Ph		(23.4)				OPh		(27.9)
			PhSCHPh ₂		(26.7)	SULFONIUM			N ⁺ Me ₃		(19.4)
			(PhS) ₃ CH		(22.8)	Me ₃ S ⁺ =O		(18.2)	CN		(12.0)
			(PrS) ₃ CH		(31.3)			(16.3)	NO ₂		(7.1)
					(30.5)	SULFIMIDES & SULFOXIMINES			SMe		(23.5)
			(PhS) ₂ CHPh		(23.0)				SPh		(20.5)
						R= Me		(27.6)	SO ₂ Ph		(12.2)
			X= Ph		(30.7)	<i>i</i> -Pr		(30.7)	PPh ₂		(20.2)
			CO ₂ Me		(20.8)			(24.5)			(22.3)
			CN		(19.1)			(33)			(31.1)
			RSCH ₂ CN								(18.8)
			R= Me		(24.3)			(14.4)			(21.8)
			Et		(24.0)						(26.6)
			<i>i</i> -Pr		(23.6)			(20.7)			(32.8)
			<i>t</i> -Bu		(22.9)				(PhSO ₂) ₂ CH ₂ Me		(14.3)
			PhSCH=CHCH ₂ SPh		(26.3)						
			BuSH	10-11	(17.0)						
			PhSH	≈7	(10.3)						
HETERO-AROMATICS											
		(28.2)									
		(30.1)									
		(26.7)									
		(25.2)									
		(30.2)									
		(30.0)									

*Values <0 for H₂O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

Substrate	pKa	H ₂ O (DMSO)	Substrate	pKa	H ₂ O (DMSO)	Substrate	pKa	H ₂ O (DMSO)	REFERENCES
ETHERS			PHOSPHONIUM			NITRO			DMSO:
CH ₃ OPh	(49)		P ⁺ H ₄	-14		RNO ₂			
MeOCH ₂ SO ₂ Ph	(30.7)		MeP ⁺ H ₃	2.7		R= CH ₃	≈10	(17.2)	JACS 97, 7007 (1975)
PhOCH ₂ SO ₂ Ph	(27.9)		Et ₃ P ⁺ H	9.1		CH ₂ Me		(16.7)	JACS 97, 7160 (1975)
PhOCH ₂ CN	(28.1)		Ph ₃ P ⁺ CH ₃	(22.4)		CHMe ₂		(16.9)	JACS 97, 442 (1975)
	(21.1)		Ph ₃ P ⁺ <i>i</i> -Pr	(21.2)		CH ₂ Ph		(12.2)	JACS 105, 6188 (1983)
			Ph ₃ P ⁺ CH ₂ COPh	(6.2)		CH ₂ Bn		(16.2)	JOC 41, 1883 (1976)
			Ph ₃ P ⁺ CH ₂ CN	(7.0)		CH ₂ SPh		(11.8)	JOC 41, 1885 (1976)
						CH ₂ SO ₂ Ph		(7.1)	JOC 41, 2786 (1976)
						CH ₂ COPh		(7.7)	JOC 41, 2508 (1976)
SELENIDES			PHOSPONATES & PHOSPHINE OXIDES						JOC 42, 1817 (1977)
	(18.6)		(EtO) ₂ P(=O)CH ₂ X			n= 3		(26.9)	JOC 42, 321 (1977)
PhSeCHPh ₂	(27.5)		X= Ph	(27.6)		4		(17.8)	JOC 42, 326 (1977)
(PhSe) ₂ CH ₂	(31.3)		CN	(16.4)		5		(16.0)	JOC 43, 3113 (1978)
PhSeCH ₂ Ph	(31.0)		CO ₂ Et	(18.6)		6		(17.9)	JOC 43, 3095 (1978)
PhSeCH=CHCH ₂ SePh	(27.2)		Cl	(26.2)		7		(15.8)	JOC 43, 1764 (1978)
			SiMe ₃	(28.8)					JOC 45, 3325 (1980)
									JOC 45, 3305 (1980)
AMMONIUM			X= SPh	(24.9)					JOC 45, 3884 (1980)
Me ₃ N ⁺ CH ₂ X			CN	(16.9)					JOC 46, 4327 (1981)
X= CN	(20.6)								JOC 46, 632 (1981)
SO ₂ Ph	(19.4)		PHOSPHINES					(24.3)	JOC 47, 3224 (1982)
COPh	(14.6)		Ph ₂ PCH ₂ PPh ₂	(29.9)					JOC 47, 2504 (1982)
CO ₂ Et	(20.6)		Ph ₂ PCH ₂ SO ₂ Ph	(20.3)					Acc. Chem. Res. 21, 456 (1988)
CONEt ₂	(24.9)								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 H₂O and DMSO, and values >14 for water and >35 for DMSO were extrapolated using various methods.

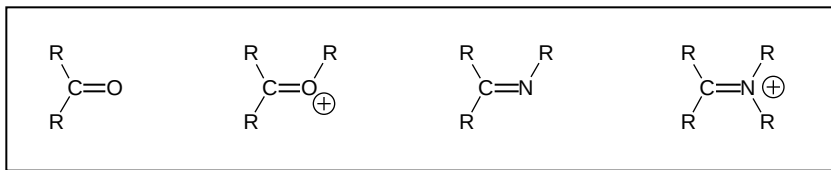
<http://www.courses.fas.harvard.edu/~chem206/>

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 et al. *JACS* **1999**, *121*, 12208.

Woerpel et al. *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

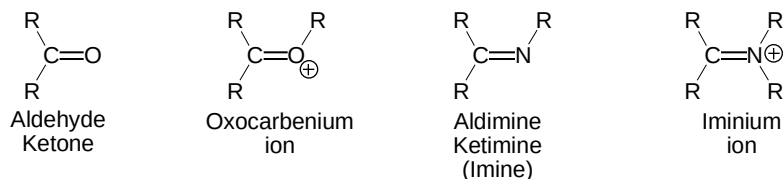
"Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group", *JACS* **1973**, *95*, 5065.

"Stereochemistry of Reaction Paths at Carbonyl Centers",
Tetrahedron **1974**, *30*, 1563

"From Crystal Statics to Chemical Dynamics", *Accounts Chem. Research* **1983**, *16*, 153.

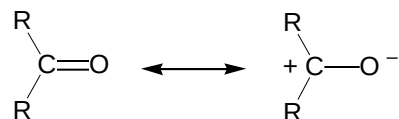
"Stereochemistry of Reaction Paths as Determined from Crystal Structure Data. A Relationship Between Structure and Energy.",
Burgi, H.-B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460.

■ The Set of Functional Groups:

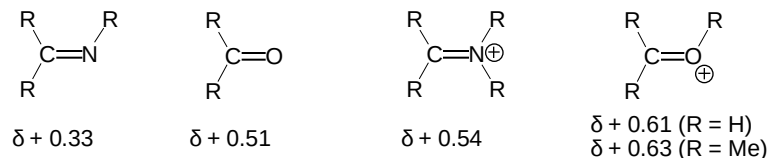


These functional groups are among the most versatile sources of electrophilic carbon in both synthesis and biosynthesis. The ensuing discussion is aimed at providing a more advanced discussion of this topic.

■ C=X Polarization

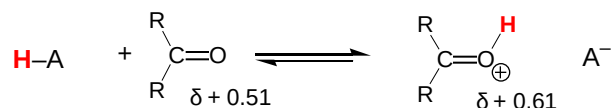


Partial Charge: As the familiar polar resonance structure above indicates, the carbonyl carbon supports a partial positive charge due to the polarization of the sigma and pi system by the more electronegative heteroatom. The partial charges for this family of functional groups derived from molecular orbital calculations (ab initio, 3-21(G)*, HF) are illustrated below:

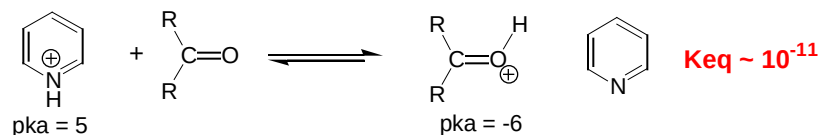


————— **electrophilic reactivity** —————>

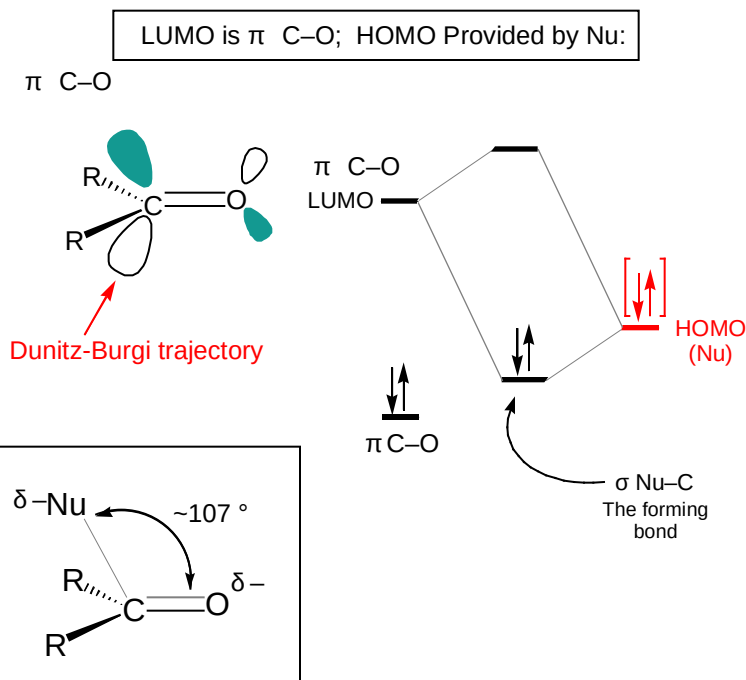
■ Proton Activation of C=X Functional groups



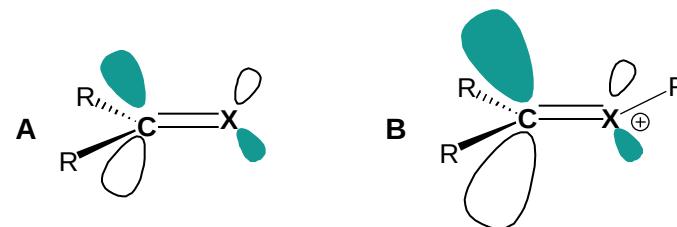
The electrophilic potential of the C=O FG may be greatly increased by either Lewis acid coordination or by protonation. The magnitude of this increase in reactivity is $\sim 10^{+6}$. Among the weakest Brønsted acids that may be used for C=O activation (ketalization) is pyridinium ion (pKa = 5). Hence, the Keq below, while quite low, is still functional.



Stereoelectronic Considerations for C=O Addition



■ 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?

■ 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

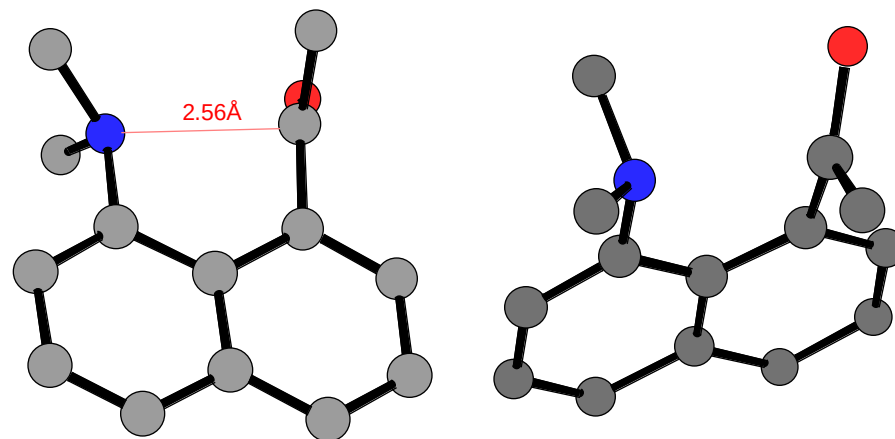
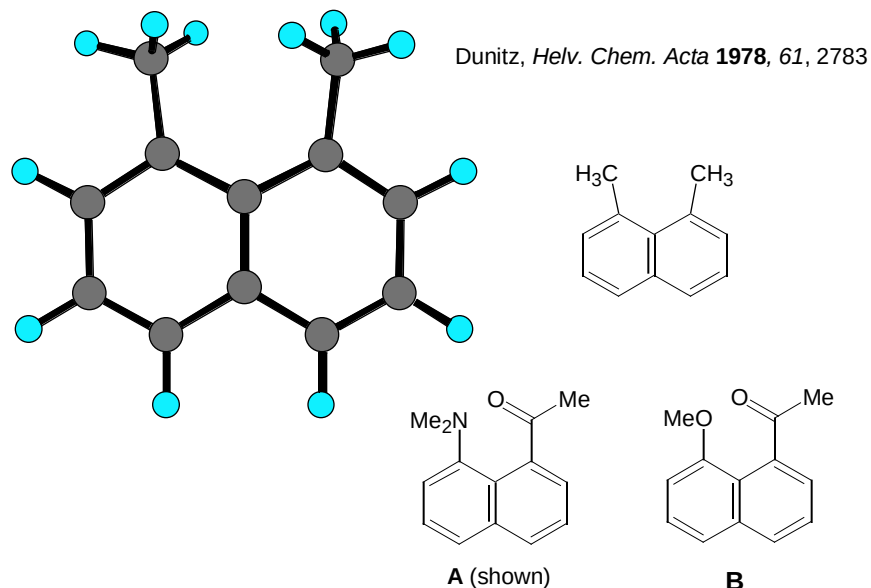
"From Crystal Statics to Chemical Dynamics", *Accounts Chem. Research* **1983**, 16, 153.

"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

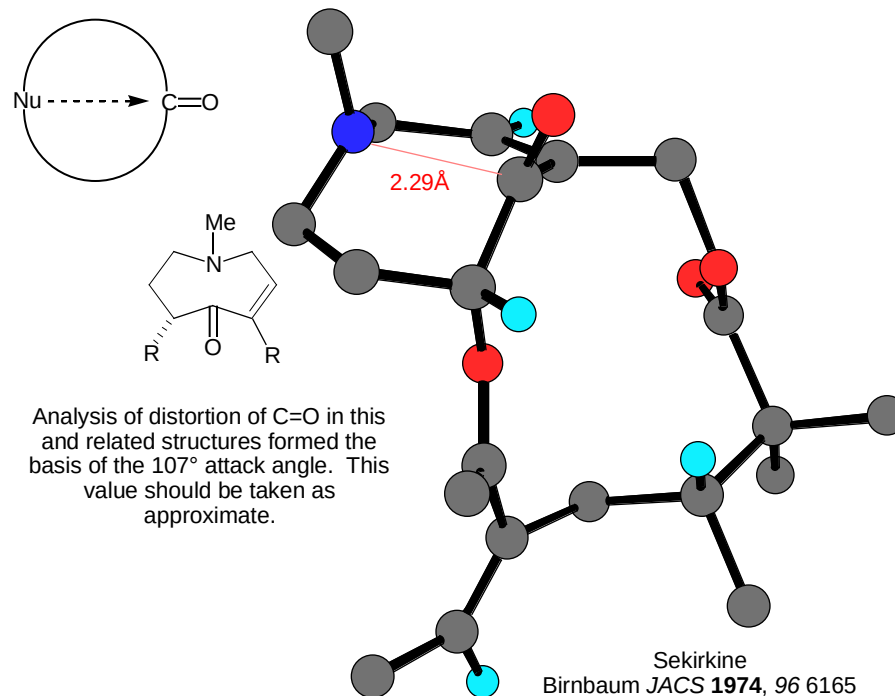
A series of organic structures containing both C=O and Nu FG's disposed in a geometry for mutual interaction were designed. These structures positioned the interacting FGs an increasingly closer distances. The X-ray structures of these structures were determined to ascertain the direction of C=O distortion. 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.



In this structure (A), at 2.56 Å the C=O is starting to pyramidalize

Cyclic aminoketones. Medium-ring ketones of various ring sizes were analyzed for the interaction of amine and C=O FGs. One example is shown below.

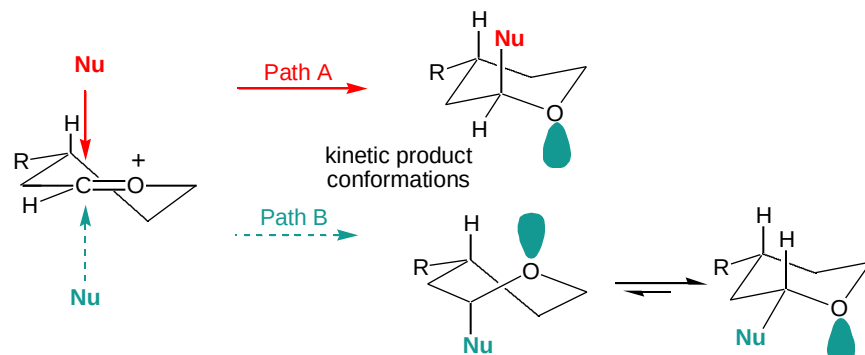


■ Pivotal Articles

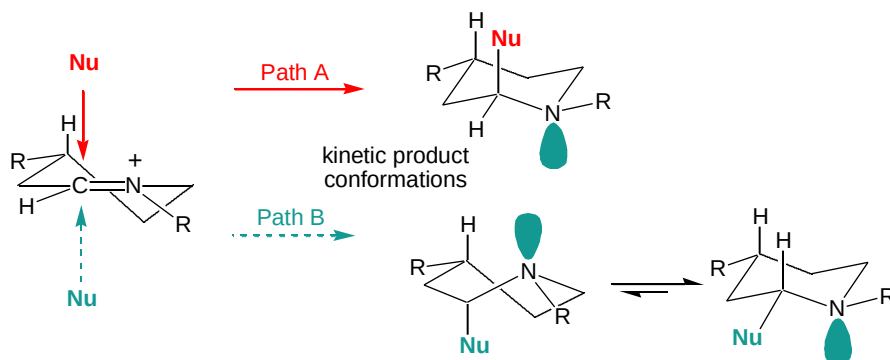
R. V. Stevens in
 "Strategies and Tactics in Organic Synthesis", Vol. 1.
On the Stereochemistry of Nucleophilic Additions to Tetrahydropyridinium Salts: a Powerful Heuristic Principle for the Stereoselective Design of Alkaloid Synthesis.;
 Lindberg, T., Ed.; Academic Press, 1984;

Eliel et al. , JACS **1969**, *91*, 536
 Kishi et al. , JACS **1982**, *104*, 4976-8

■ The Proposal for Oxo-carbenium Ions (Eliel, Kishi)

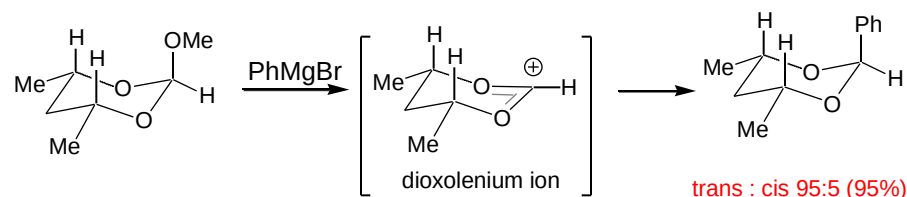


■ The Proposal for Iminium Ions (Stevens)



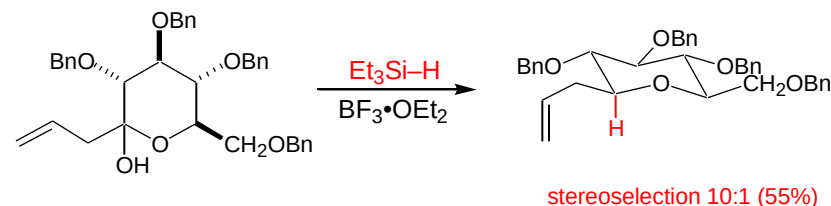
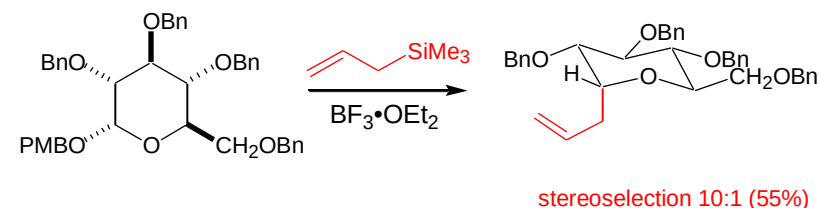
It was proposed that chair-axial addition would be preferred as a consequence of the intervention of a transition state anomeric effect (Path A). Attack through Path B would necessitate the generation of the twist-boat kinetic product conformation thus destabilizing attack from the equatorial diastereoface. 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



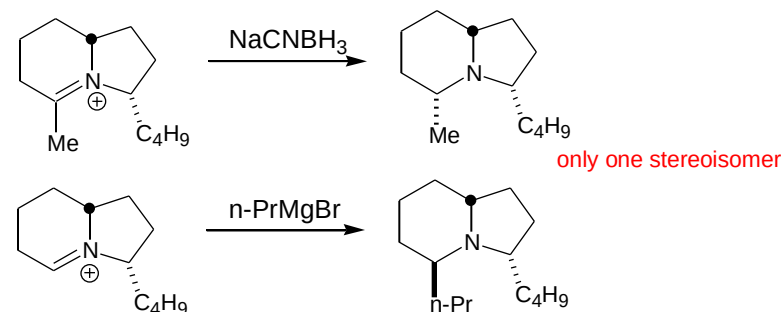
Eliel was the first to attribute stereoelectronic factors to the addition of nucleophiles to cyclic oxo-carbenium ions.

■ Kishi Examples; JACS 1982, 104, 4976-8

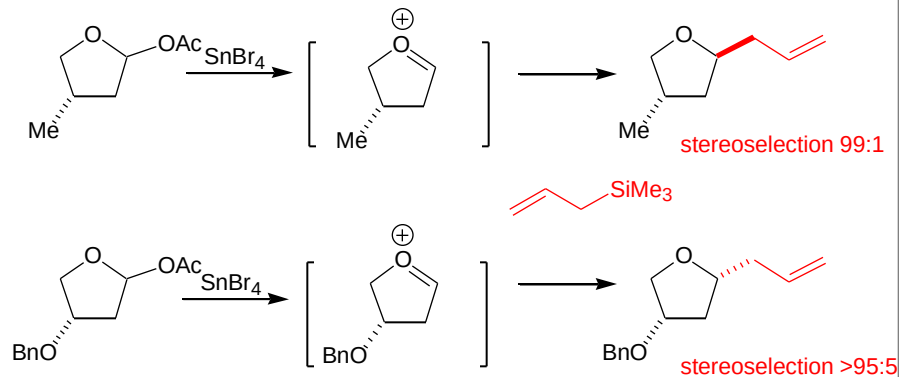


Chair-axial attack on oxo-carbenium ion occurs for both carbon and hydride nucleophiles

■ Iminium Ions (Stevens) cited reference

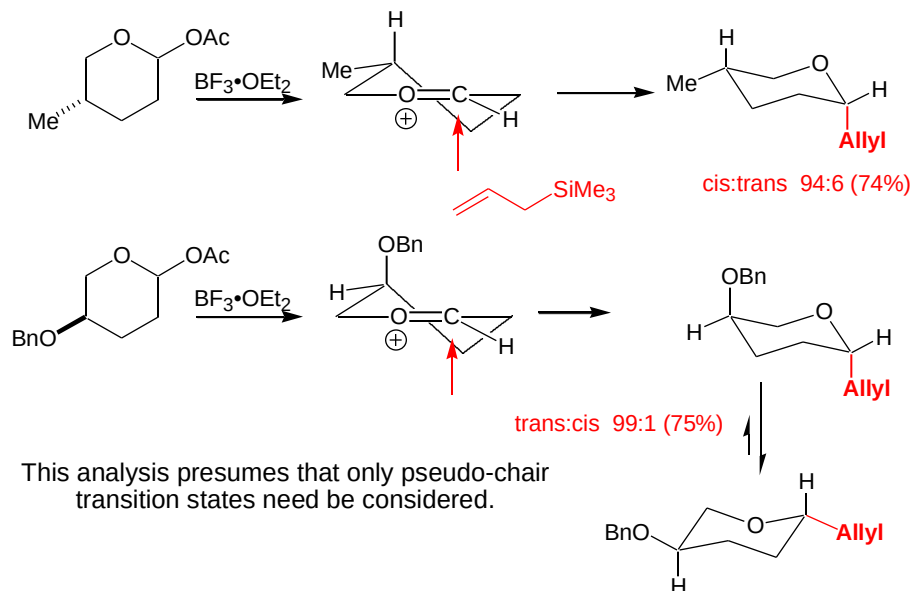


5-Membered oxocarbenium Ions: Woerpel et al. JACS 1999, 121, 12208.



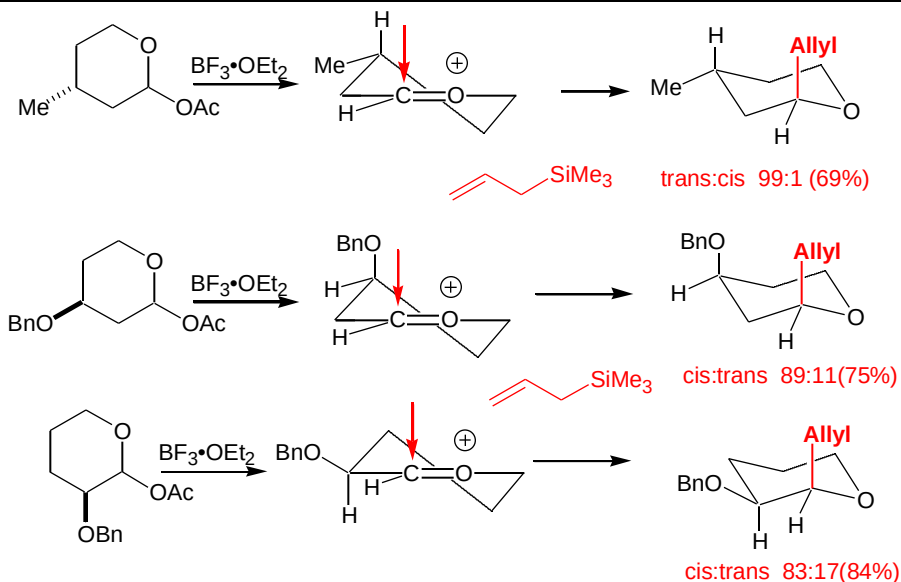
These cases provide dramatic evidence for the importance of electrostatic effects in controlling face selectivity.

6-Membered oxocarbenium Ions: Woerpel et al. JACS 2000, 122, 168.



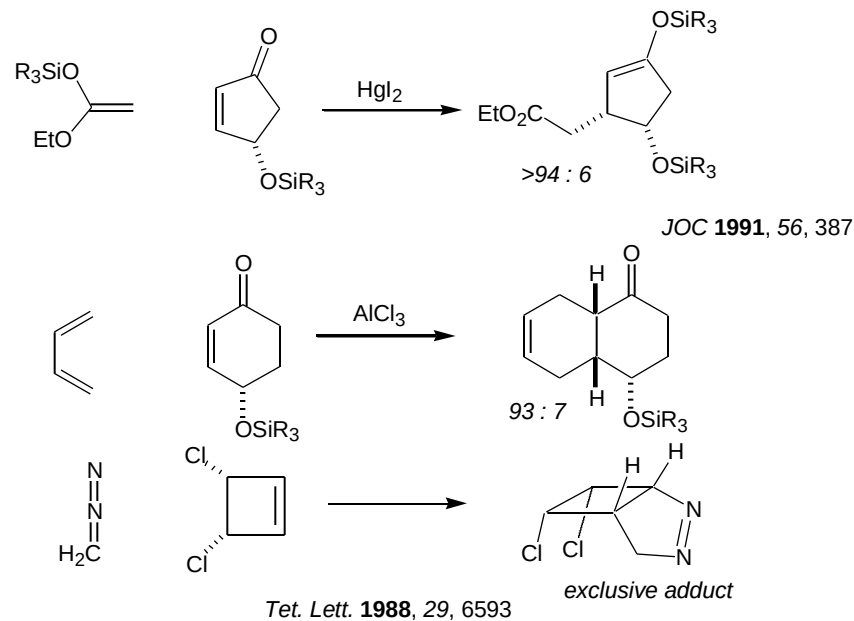
This analysis presumes that only pseudo-chair transition states need be considered.

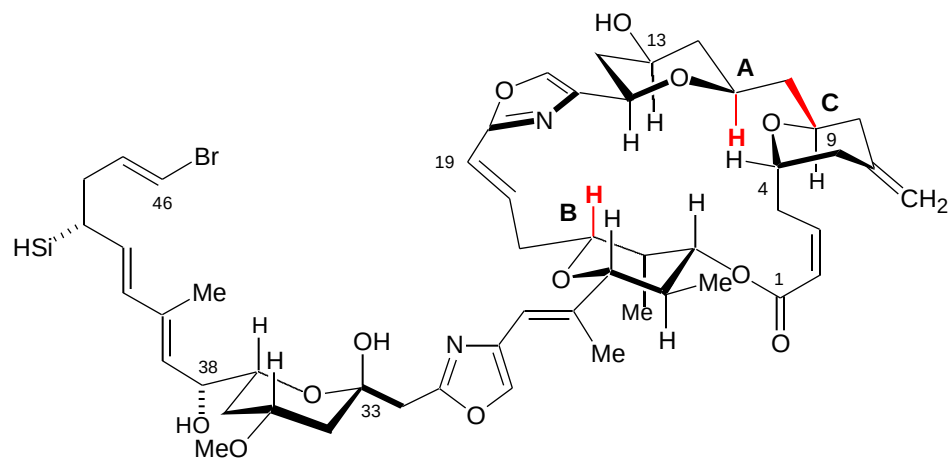
Woerpel's model states that axial attack from the most stable chair conformer predicts the major product.



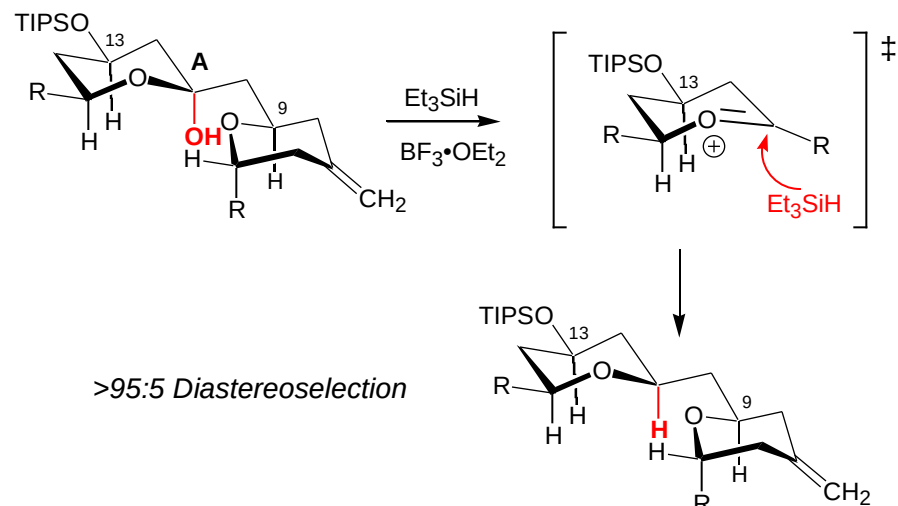
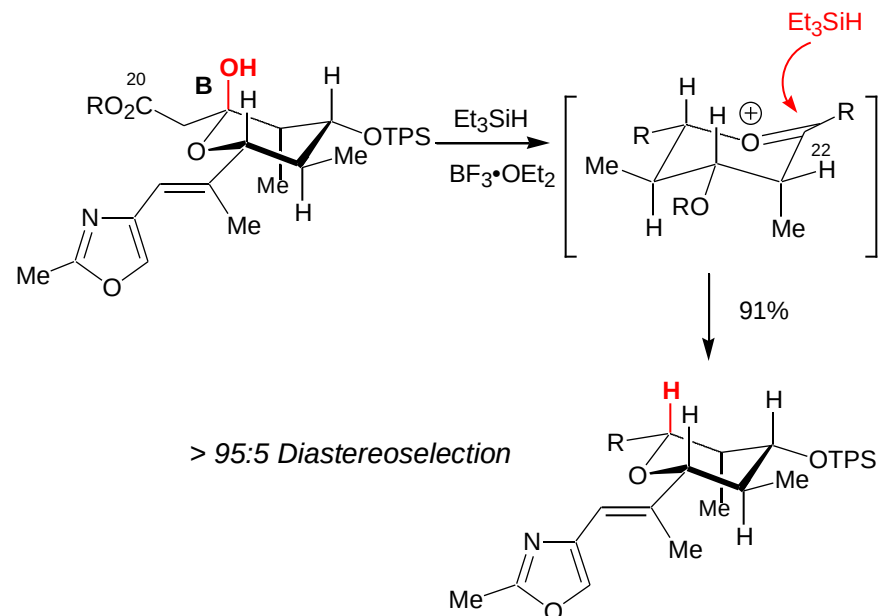
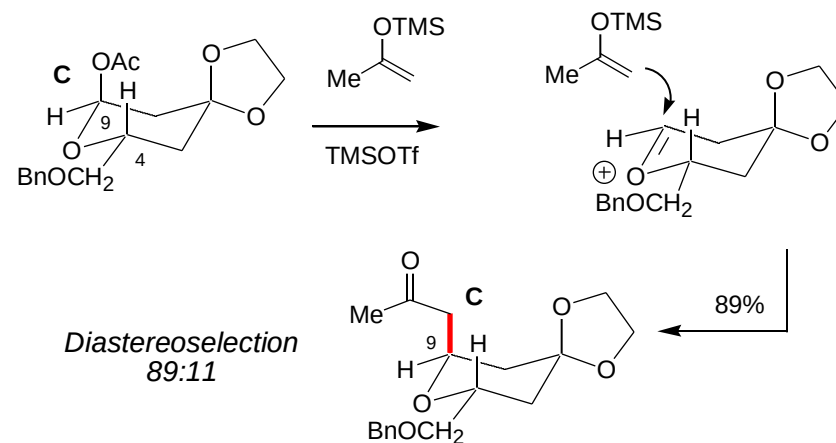
These cases provide dramatic evidence for the importance of electrostatic effects in controlling face selectivity.

Are the preceding addition reactions somehow related to the apparently contrasteric reactions shown below??



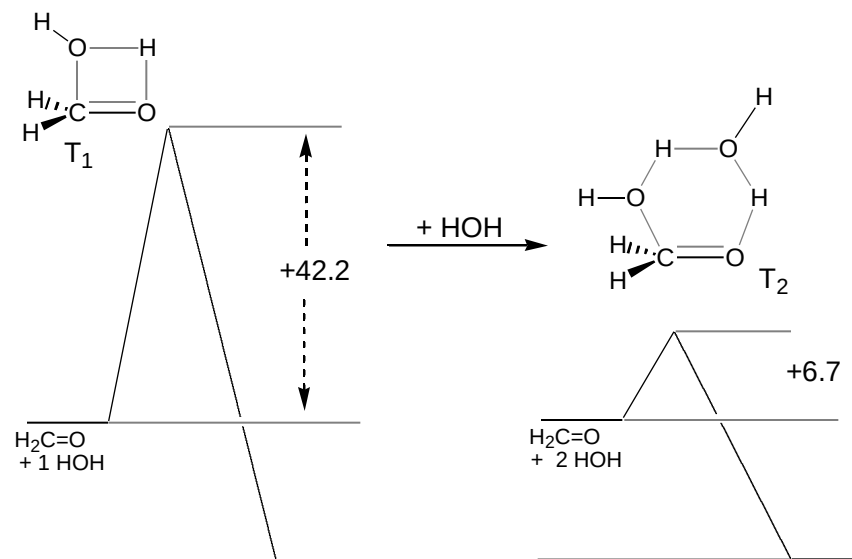
Phorboxazole BEvans, Fitch, Smith, Cee, *JACS* **2000**, *122*, 10033

Stereochemical analogies:
Kishi et. al.: *JACS* **1982**, *104*, 4976-8

A: The C-11 Reduction**B: The C-22 Reduction****C: The C-9 C-C Bond Construction**

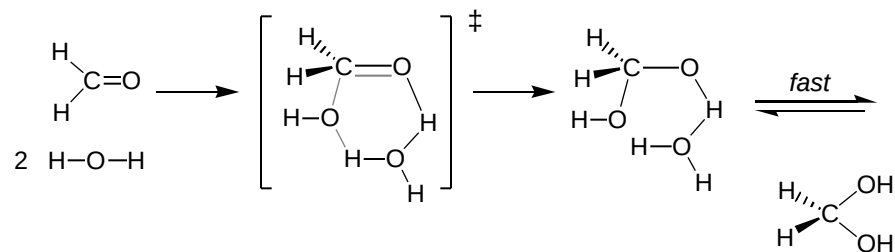
■ 4- vs 6-Membered Transition Structures for C=O Addition

Consider carbonyl hydration:



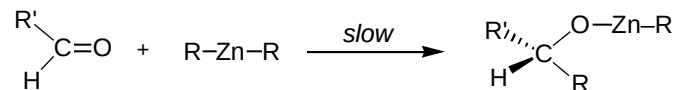
Schowen J. Am. Chem. Soc. **105**, 31, (1983).

Overall Process:

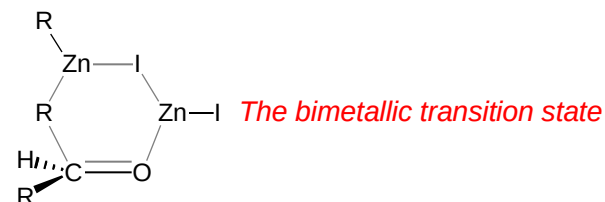


Transition structure T_2 determined to be ~ 40 kcal/mol more stable than transition structure T_1 .

■ Do these results relate to "real" reactions? Yes!

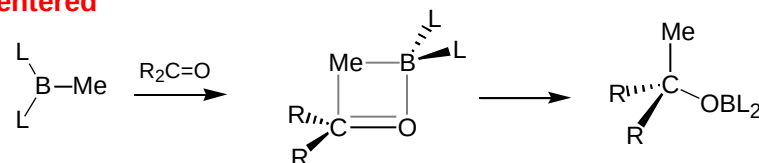


Observation: catalytic amounts of ZnI_2 dramatically catalyze addition process.



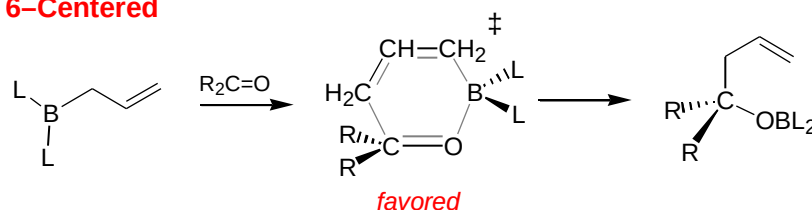
■ 4- Versus 6-Center Transition States for Boron

4-Centered

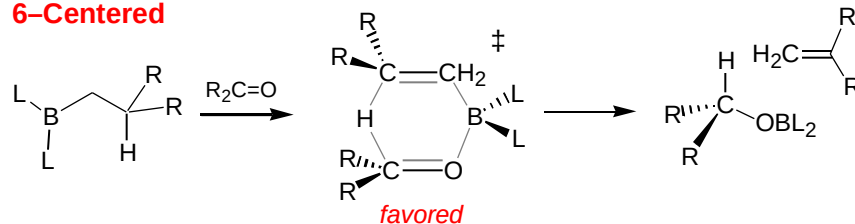


disfavored : rxn does not proceed!

6-Centered

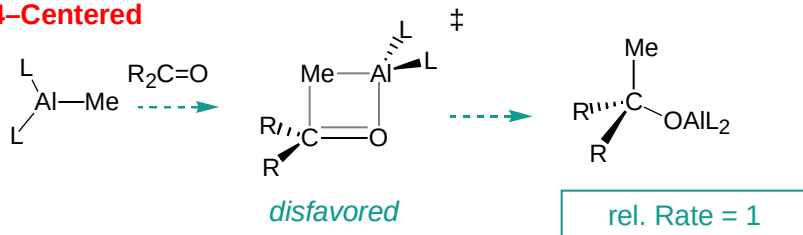


6-Centered

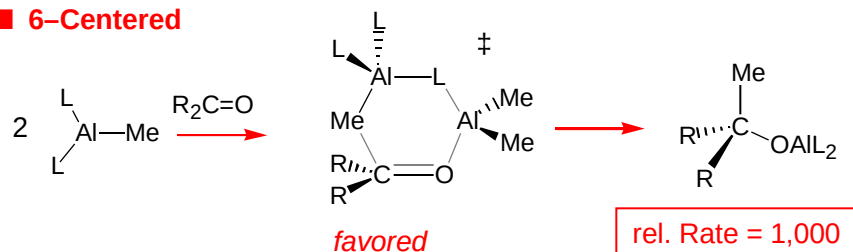


Carbonyl Addition: 4- Versus 6-Center Transition States for Aluminum

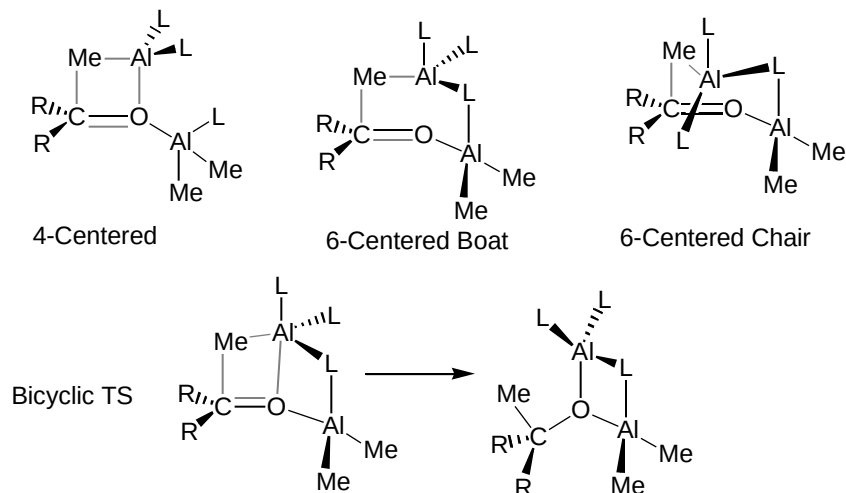
4-Centered



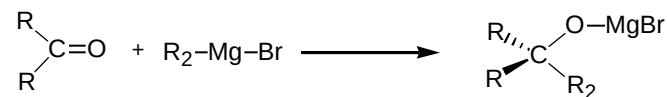
6-Centered



Bimetallic Transition States

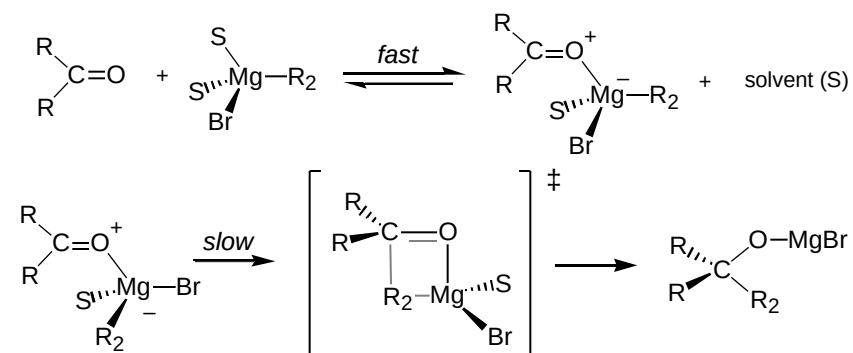
Ashby JOC **1977**, 42, 425

Grignard Reagents:

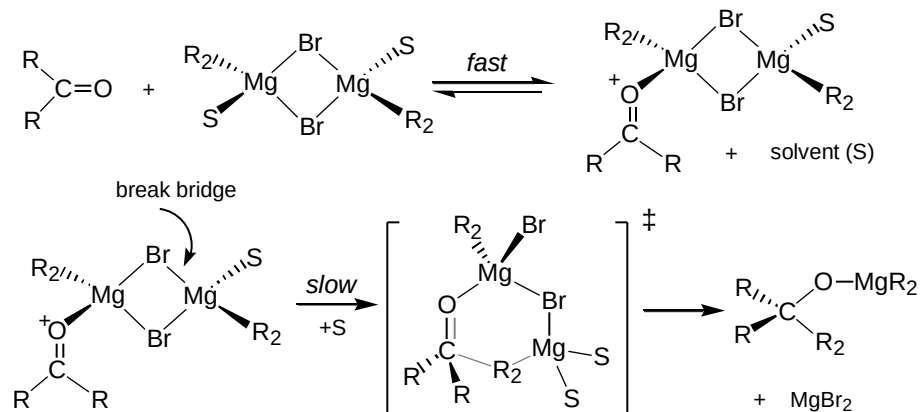


The molecularity and transition structure for this reaction have not been carefully elucidated. The fact that the Grignard reagent is not a single species in solution greatly complicates the kinetic analysis.

Monometallic (Mononuclear) Mechanism:

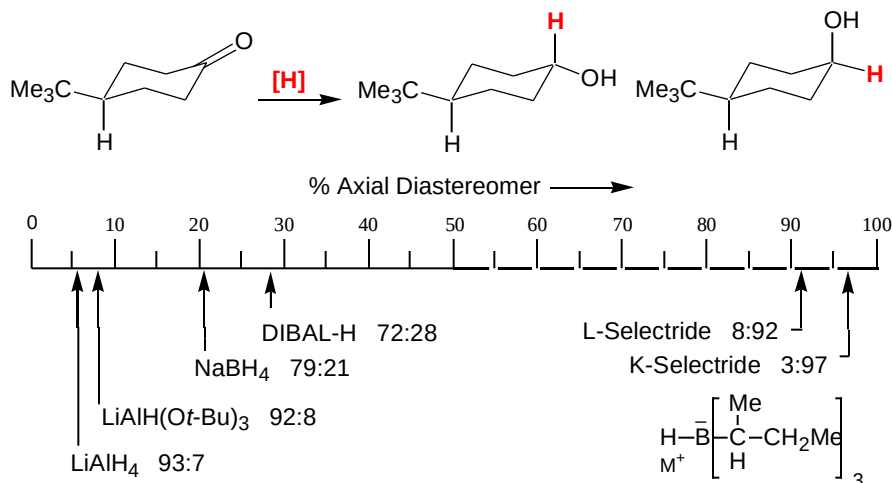


Bimetallic (Binuclear) Mechanism: The more probable situation.



The 6-membered geometry for transferring the R_2 ligand from the metal to the C=O is far less strained.

Product Development & Steric Approach Control:

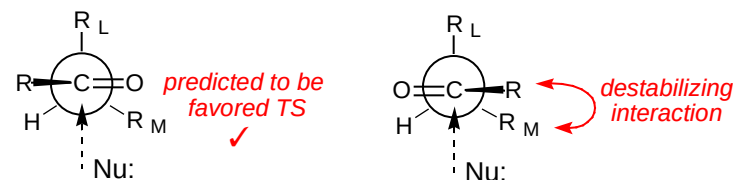
Dauben, JACS **1956**, 78, 2579

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

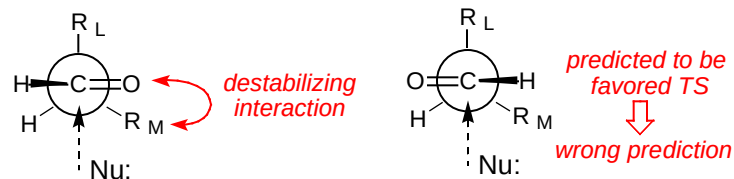
Assumption: Hindered reagents react through more highly developed transition states than unhindered reagents

Assumptions in Felkin Model:

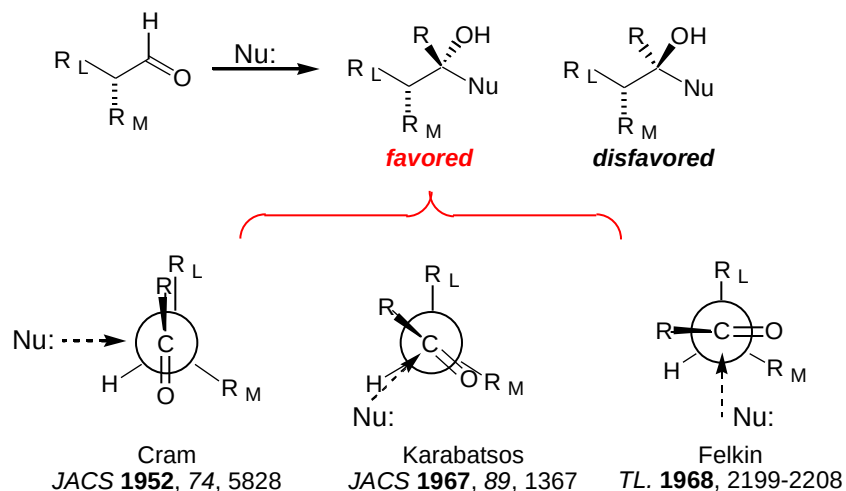
- Transition states are all reactant-like rather than product-like.
- Torsional strain considerations are dominant. Staggered TS conformations preferred
- The principal steric interactions are between Nu & R.



The flaw in the Felkin model: A problem with aldehydes!!

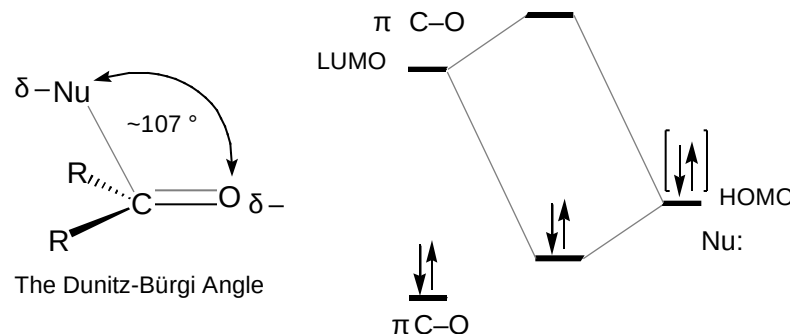


Carbonyl Addition: Evolution of Acyclic Models



Stereoelectronic Effect:

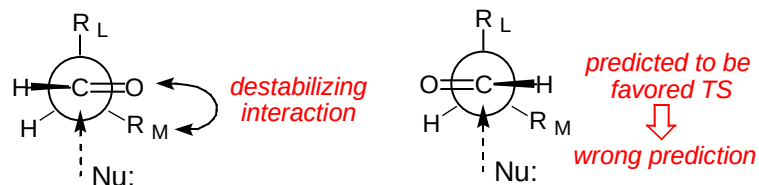
The HOMO-LUMO interaction dictates the following reaction geometry:



attack angle greater than 90°; estimates place it in the 100-110° range

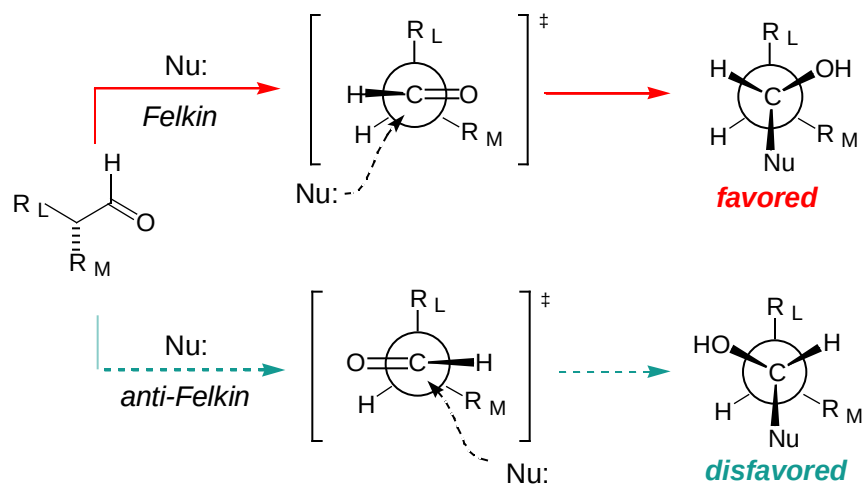
Burgi, Dunitz, Acc. Chem. Res. **1983**, 16, 153-161

The flaw in the Felkin model: A problem with aldehydes!!



Anh & Eisenstein *Nouveau 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 stabilize the transition state.

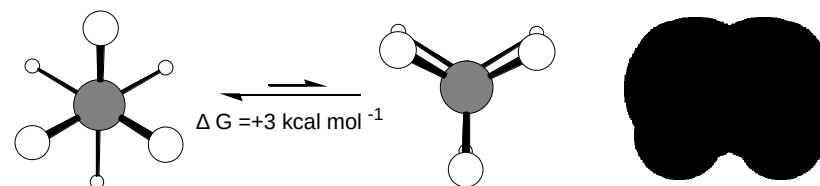
Theoretical Support for Staggered Transition states

Houk, *JACS* **1982**, *104*, 7162-6

Houk, *Science* **1986**, *231*, 1108-17

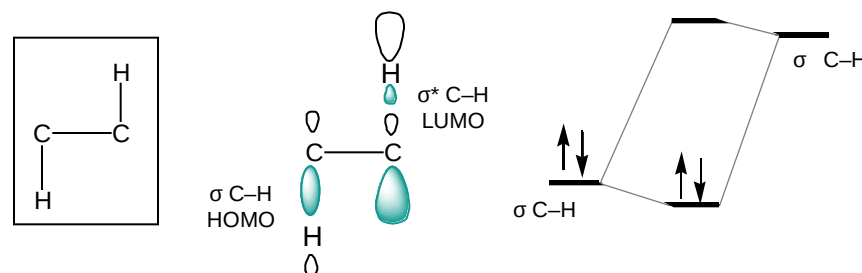
Houk: "The tendency for the staggering of partially formed vicinal bonds is greater than for fully formed bonds"

Lets begin with ground state effects: Ethane Rotational Barrier

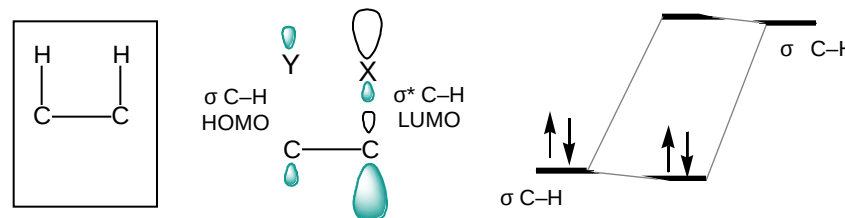


One explanation for the rotational barrier in ethane is that better overlap is achieved in the staggered conformation than in the eclipsed conformation.

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



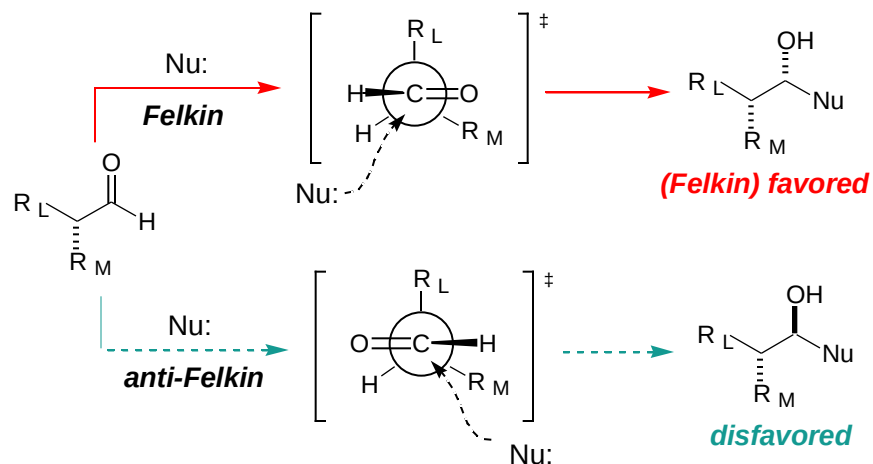
In the eclipsed conformation there are 3 syn-periplanar C–H Bonds



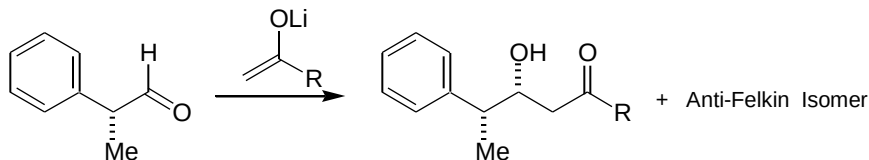
Following this argument one might conclude that:

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

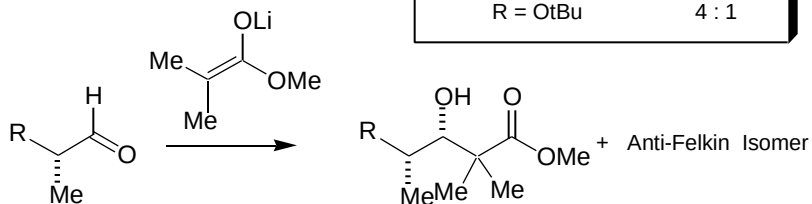
Addition of Enolate & Enol Nucleophiles

**Trend-1:**

For Li enolates, increased steric hindrance at enolate carbon results in enhanced selectivity



L. Flippin & Co-workers,
Tetrahedron Lett. **1985**, 26, 973.

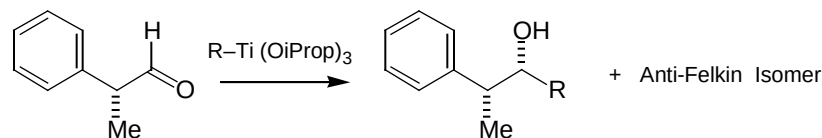
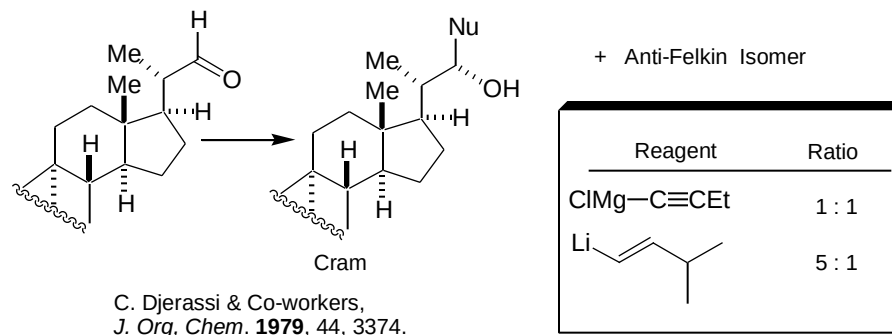


L. Flippin & Co-workers,
Tetrahedron Lett. **1985**, 26, 973.

Enolate (R)	Ratio
R = Me	3 : 1
R = OtBu	4 : 1

Ketone (R)	Ratio
R = Ph	>200 : 1
R = c-C ₆ H ₁₁	9 : 1

■ This trend carries over to organometallic reagents as well



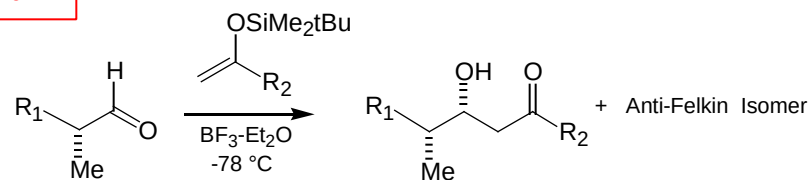
M. Reetz & Co-workers,
Angew. Chem. Int. Ed. **1982**, 21, 135.

(R-MgX gives Ca 3:1 ratios)

R-Titanium	Ratio
R = Me	>90 : 10
R = n-Bu	>90 : 10

Trend-2:

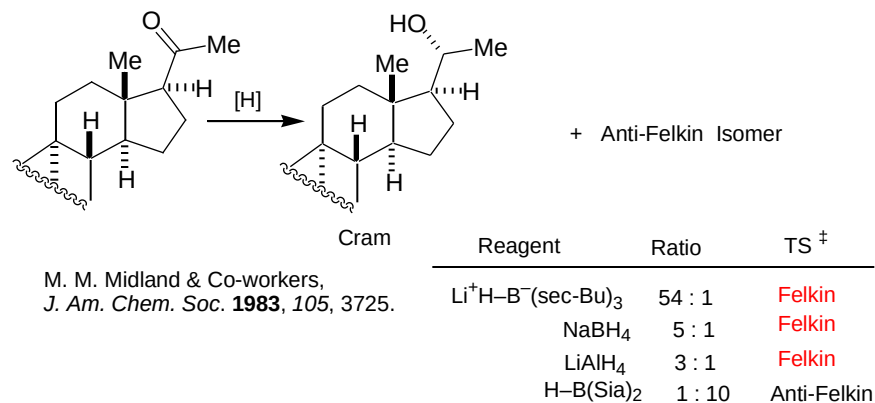
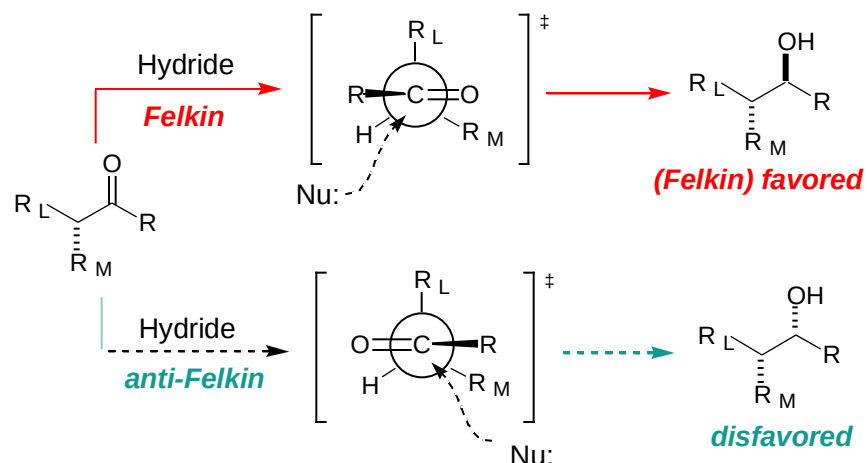
Lewis acid catalyzed rxns are more diastereoselective



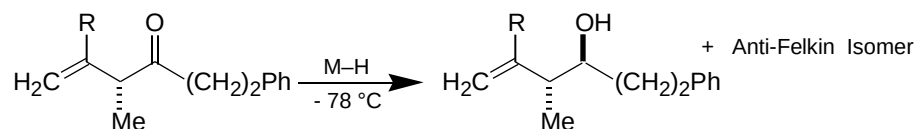
Ketone (R ₁)	Enolate (R ₂)	Ratio	Ratio Li enolate
R = Ph	R = Me	10 : 1	3 : 1
R = Ph	R = t-Bu	24 : 1	
R = Ph	R = OMe	15 : 1	
R = Ph	R = Ot-Bu	36 : 1	4 : 1
R = c-C ₆ H ₁₁	R = Ot-Bu	16 : 1	

C. Heathcock & L. Flippin *J. Am. Chem. Soc.* **1983**, 105, 1667.

Addition of Hydride Nucleophiles

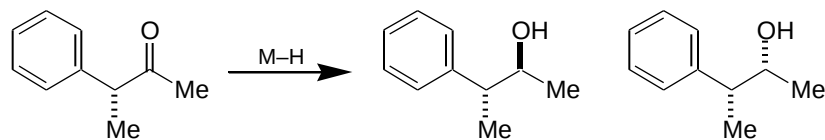


Note: Borane reducing agents do not follow the normal trend



G. Tsuchihashi & Co-workers,
Tetrahedron Lett. **1984**, 25, 2479.

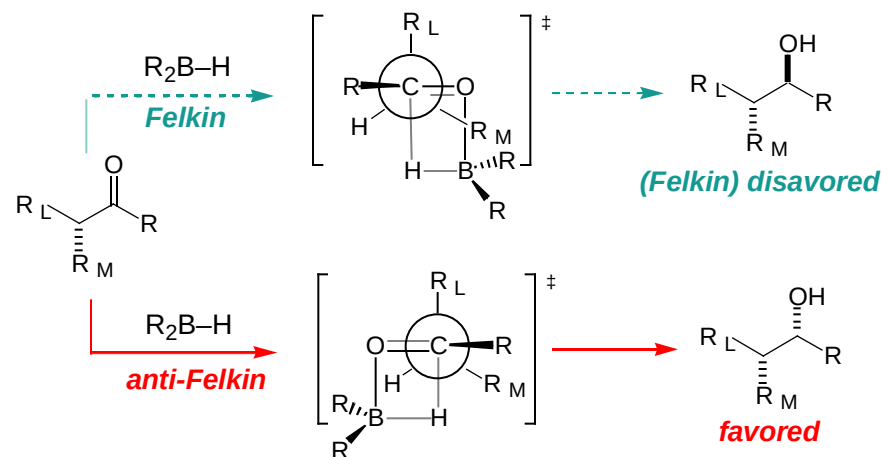
Ketone (R)	Reagent	Ratio
R = H	Li ⁺ H-B ⁻ (sec-Bu) ₃	96 : 4
R = H	DIBAL	47 : 53
R = Me	Li ⁺ H-B ⁻ (sec-Bu) ₃	>99 : 1
R = Me	DIBAL	88 : 12



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



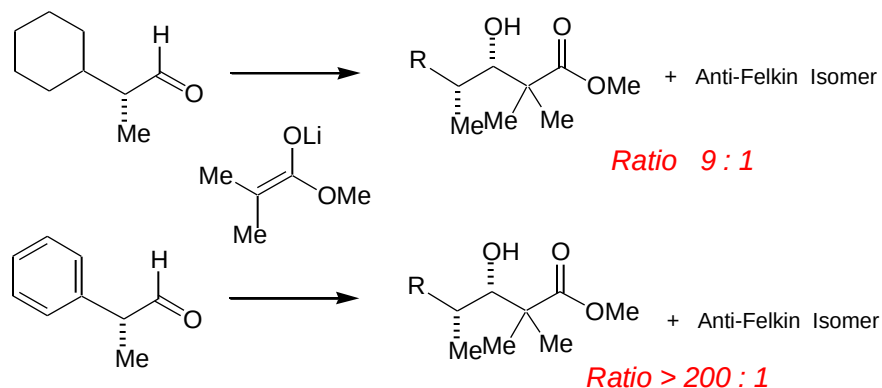
Nonspherical nucleophiles are unreliable in the Felkin Analysis

Exercise: Draw the analogous bis(R₂BH)₂ transition structures

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.

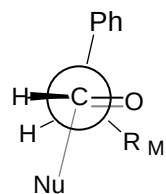


The molecular volume occupied by cyclohexyl is acknowledged to be larger than that for phenyl. Because of shape phenyl "can get out of the way."

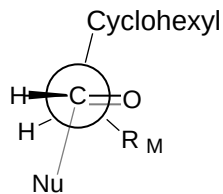
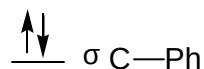
Anh-Eisenstein Explanation based on HOMO-LUMO Analysis:

"Best acceptor σ^* orbital is oriented anti periplanar to forming bond."

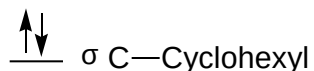
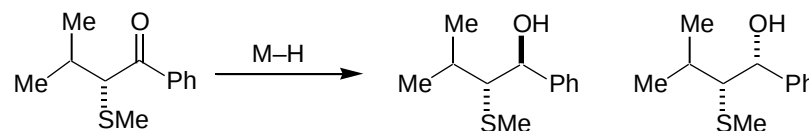
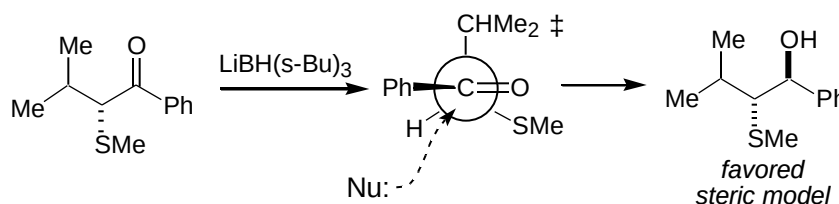
$\sigma_{C_{SP^3}-C_{SP^2}}$ is lower in energy than $\sigma_{C_{SP^3}-C_{SP^3}}$ bond.



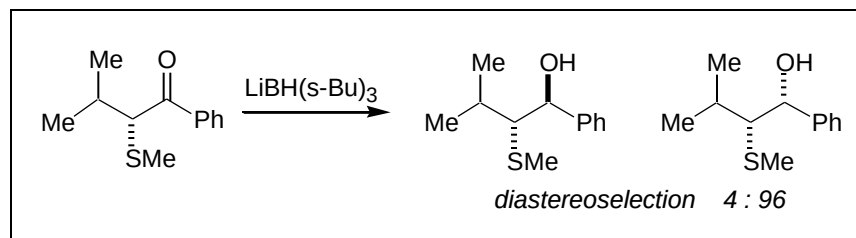
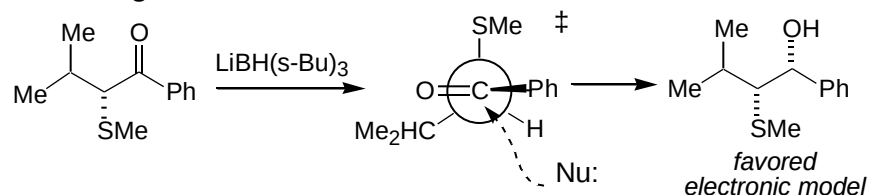
σ_{C-Ph}



$\sigma_{C-Cyclohexyl}$

A Second Case Study: Shimagaki *Tetrahedron Lett.* 1984, 25, 4775Dominant Steric Effects: $CHMe_2$ larger than SMe

Dominant Electronic Effects: SMe provides better acceptor antibonding orbital



If this analysis is correct, the electronic contributions to transition state stabilization dominate nonbonding destabilization

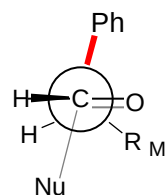
Is this another case where we are ignoring electrostatic effects?

Are there cases not handled by the Anh-Eisenstein Model?

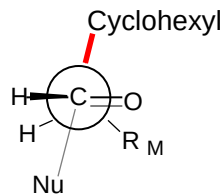
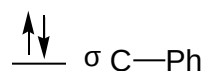
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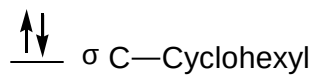
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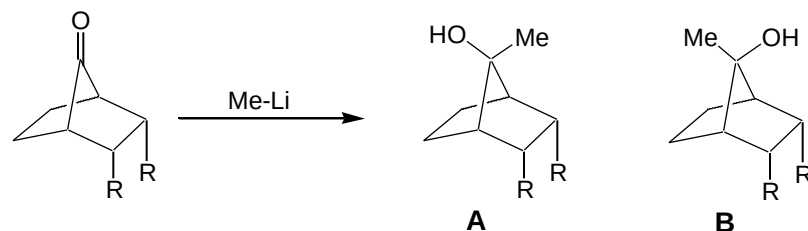
σ C—Ph



σ C—Cyclohexyl



Felkin-Anh analysis predicts **B** for R = electronegative substituent.



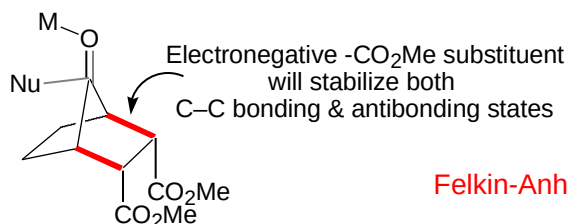
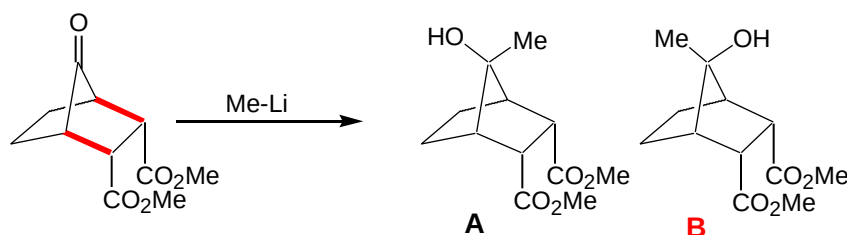
(Felkin-Anh Prediction)

G. Mehta, *JACS* **1990**, 112, 6140

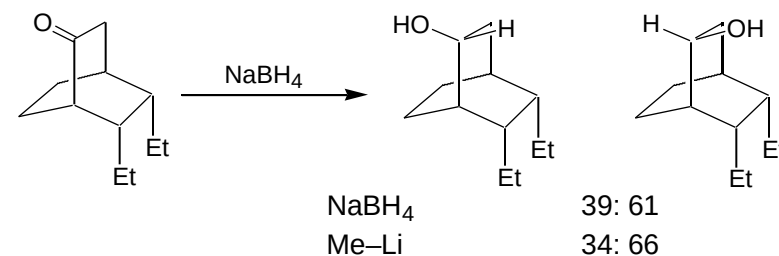
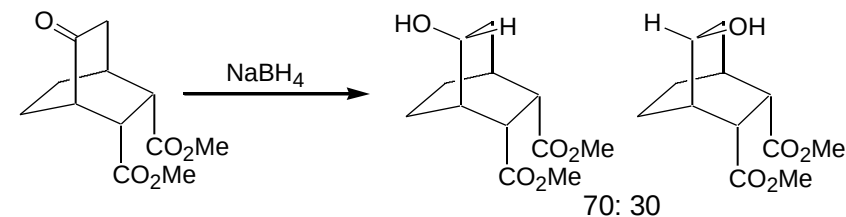
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$-\text{CH}=\text{CH}_2$	27:73
$-\text{CH}_2\text{CH}_3$	17:83

Felkin-Anh analysis predicts the wrong product!

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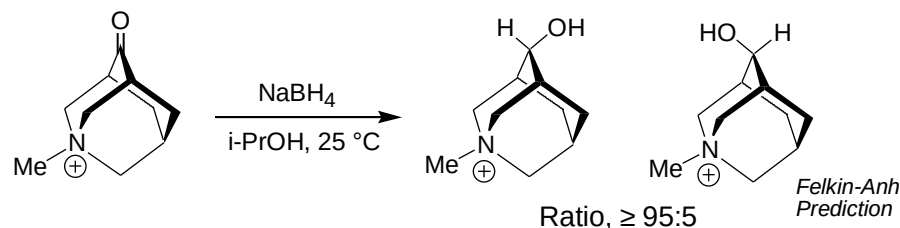
Felkin-Anh analysis predicts B



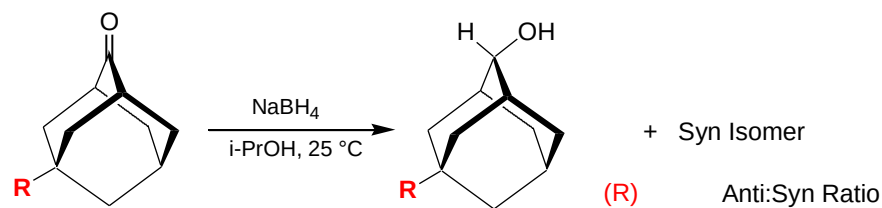
G. Mehta, *Chem. Commun.* **1992**, 1711-2:

"These results can be reconciled in terms of the Cieplak model."

Case II: The Le Noble Examples Le Noble, JACS 1992, 114, 1916

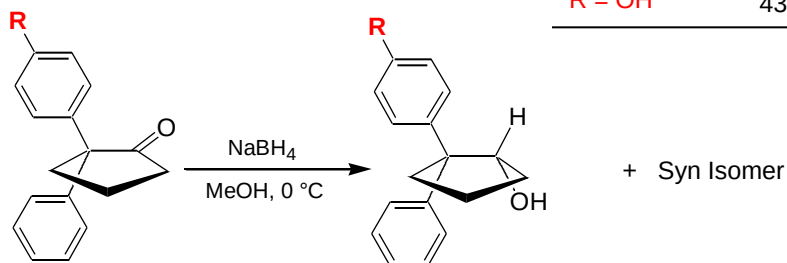


Pyramidally distorted C=O ruled out from inspection of X-ray structures.



Le Noble, J. Org. Chem. 1989, 54, 3836

R = F	62:38
R = CO ₂ Me	61:39
R = SiMe ₃	45:55
R = OH	43:57



Halterman, JACS 1990, 112, 6690

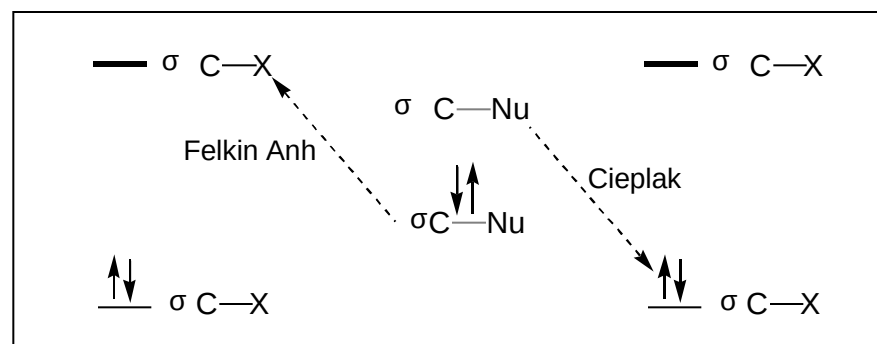
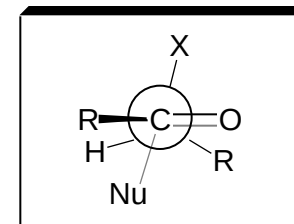
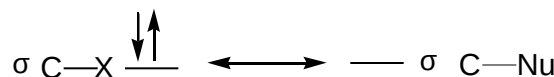
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Cieplak Model for C=O Addition

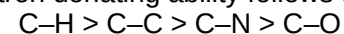
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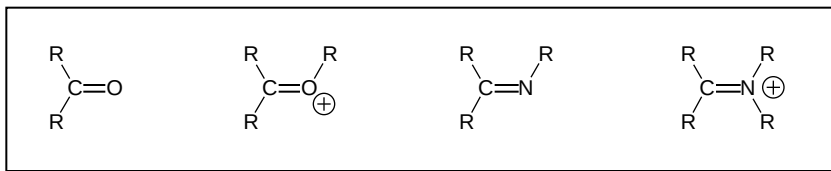
The management

<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 et al. *JACS* **1999**, *121*, 12208.

Woerpel et al. *JACS* **2000**, *122*, 168.

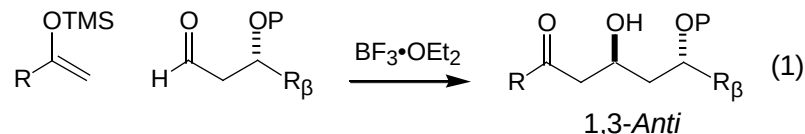
"Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein
Nouv. J. Chem. **1977**, *1*, 61-70.

"Structural, mechanistic, and theoretical aspects of chelation controlled carbonyl addition reactions." Reetz, *Acc. Chem. Res.* **1993** *26*: 462. (pdf)

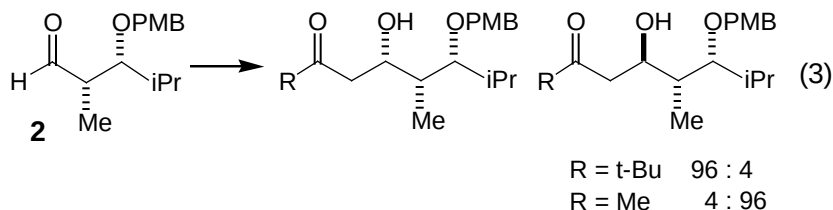
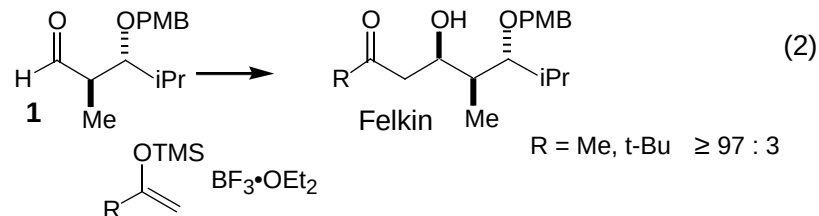
"A Stereochemical Model for Merged 1,2- and 1,3-Asymmetric Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes." Evans, et. al. *JACS* **1996**, *118*, 4322-4343. (pdf)

■ A problem

Construct a model for the addition process in eq 1 using the principles learned thus far in the course.



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)

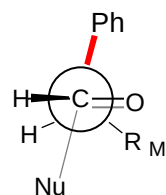


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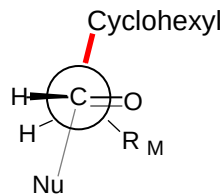
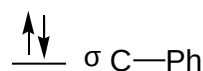
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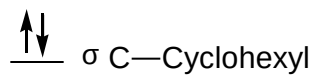
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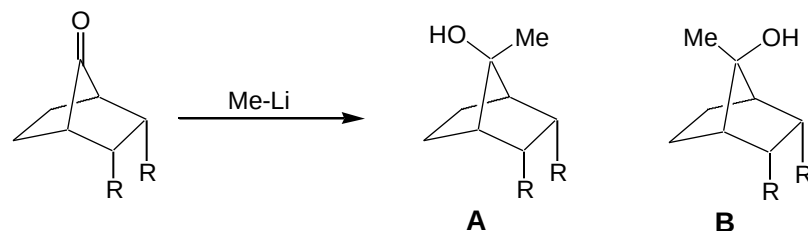
σ C—Ph



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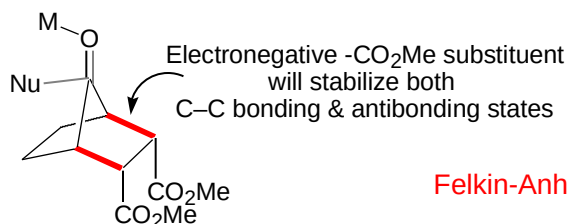
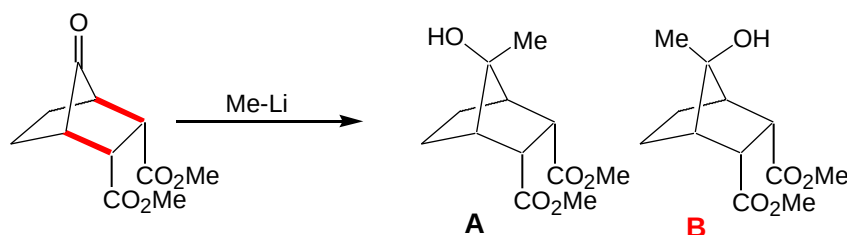
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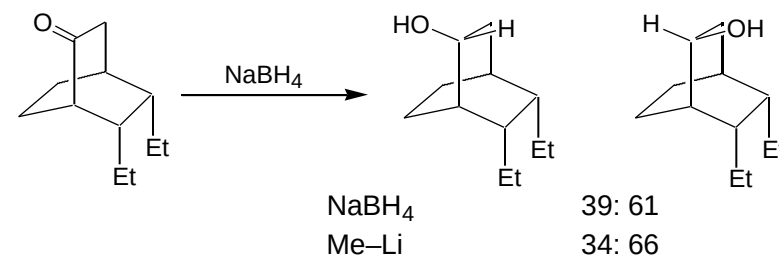
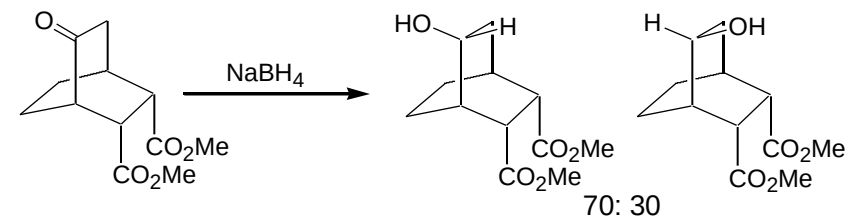
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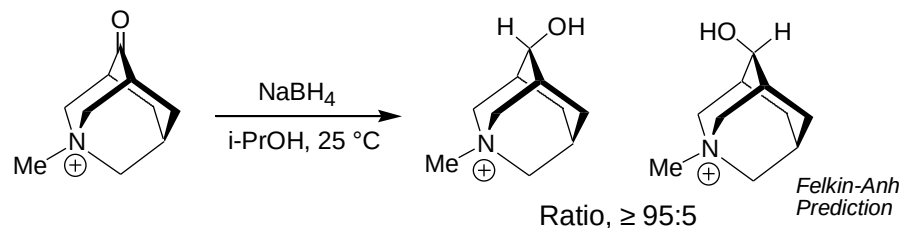


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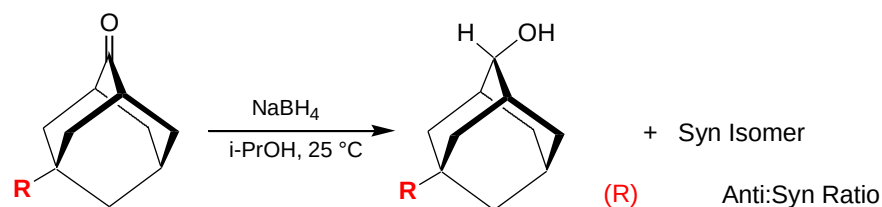


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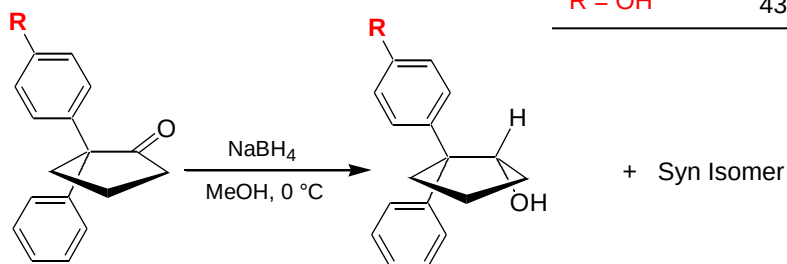
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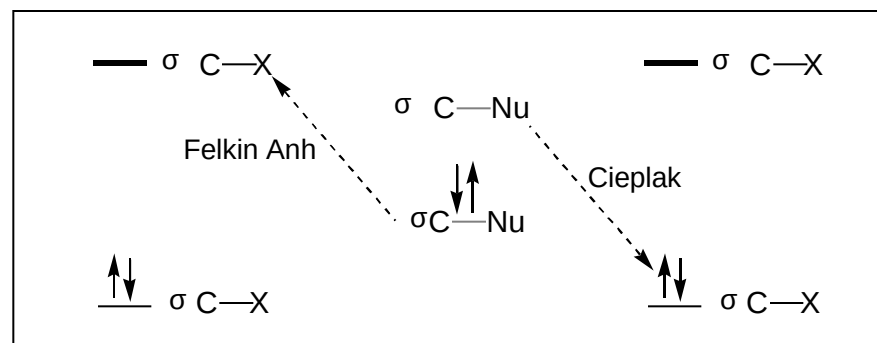
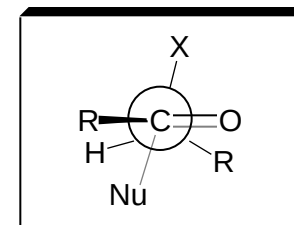
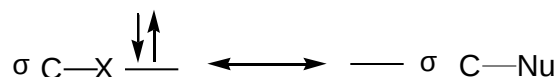
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Cieplak Model for C=O Addition

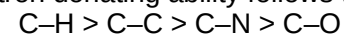
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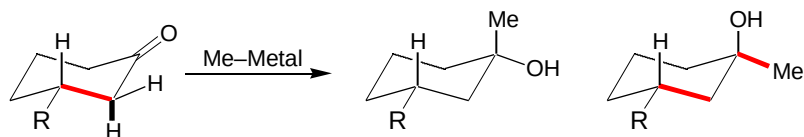
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"Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct."

The management

Observation As R becomes more electronegative, percentage of axial attack increases.



(R) Substituent	% Axial Attack	
	Me-Li	Me ₂ Cu-Li
R = H	21%	6%
R = C ₆ F ₅	34%	21%
R = CF ₃	50%	42%

Felkin-Anh predicts opposite trend.

Cieplak argument consistent with results.

The Frenking Position:

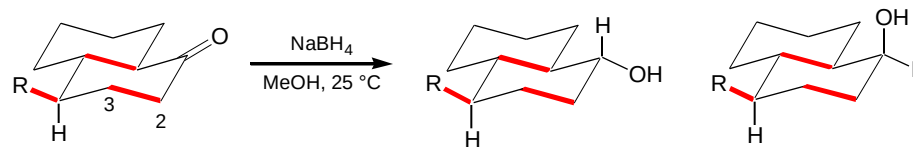
- Cieplak stabilizing interaction is "dubious." Why not stabilize the forming sigma bond?
- Enhanced rate of axial Nu attack on cyclohexanone is caused by better electrostatic interactions of the ketone with the attacking reagent and not by torsional considerations.
- Nonequivalence of the $\pi^*C=O$ LUMO with a greater extension on the axial face dictates stereoselection (Klein, 1973).

"Since interactions between the $\pi C=O$ & $\pi C=C$ 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

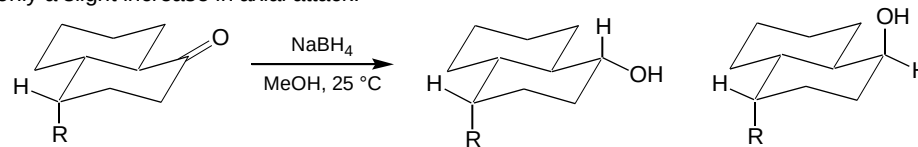
Houk: Electrostatic rather than covalent considerations may be dominant.

"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."

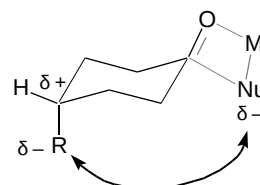


(R) Substituent	Product Ratio
R = OAc	83:17
R = Cl	88:12

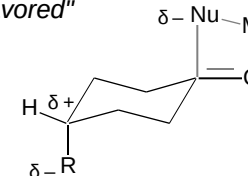
"Exactly the opposite is observed."

Axial 4-substituents favor axial attack for electrostatic reasons:

"Disfavored"



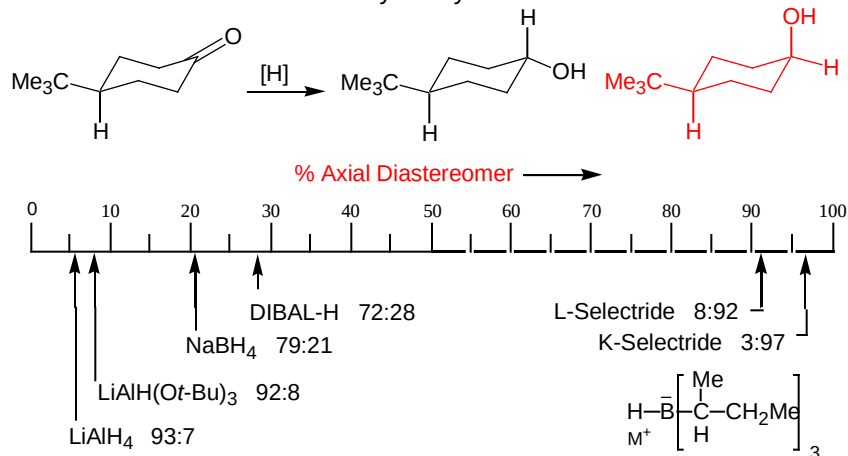
"Favored"



(DAE: Bimetallic transition states were not considered)

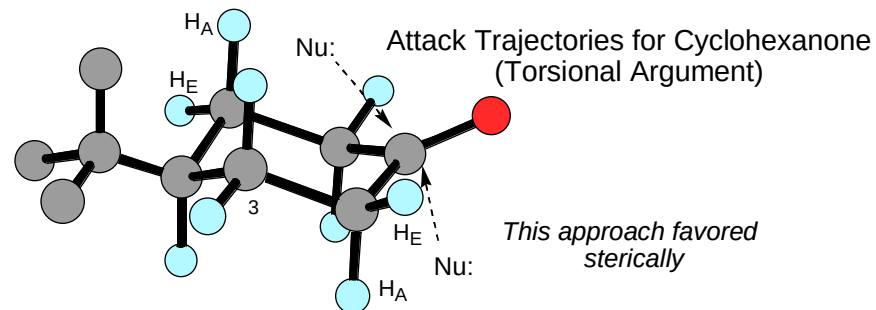
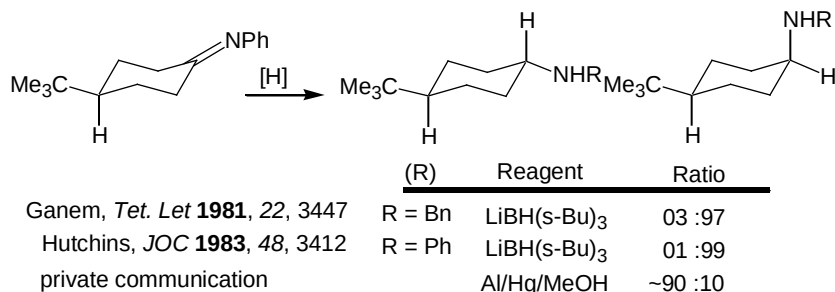
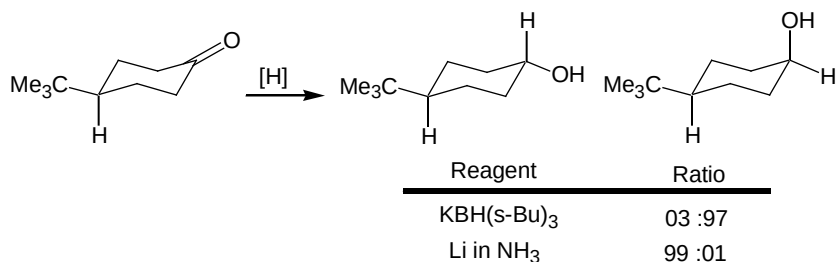
K. Houk & Co-workers, *J. Am. Chem. Soc.* **1991**, 113, 5018

Stereoselective Reductions: Cyclic Systems

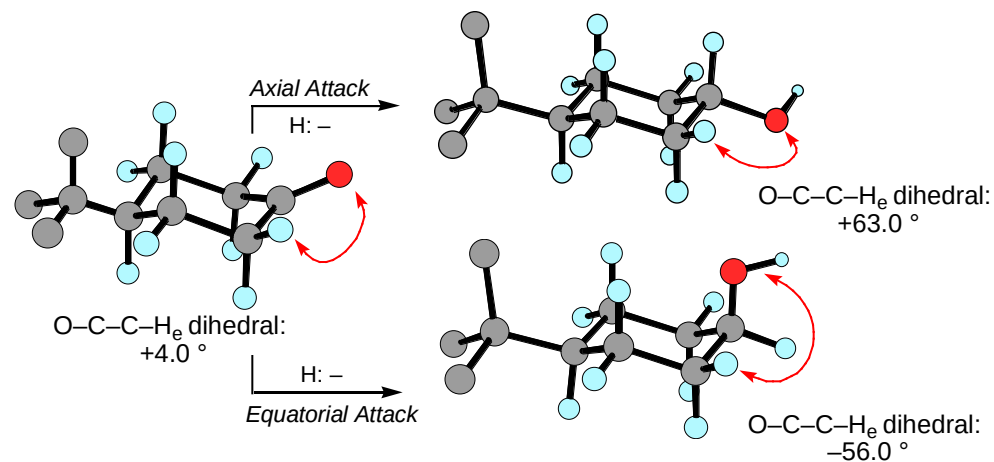


Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

The most stereoselective Reductions



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 hindrance 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

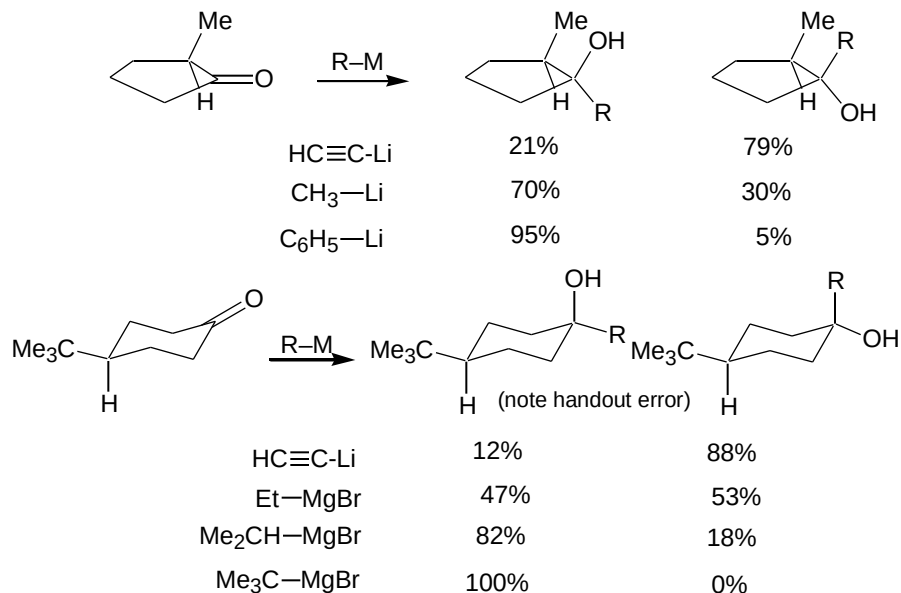
For "small" hydride reagents such as LiAlH₄, torsional effects are felt to be dominant and this explains the predisposition for axial attack.

Prediction

For "large" hydride reagents such as H-BR₄, steric effects now are dominant and this explains the predisposition for equatorial attack.

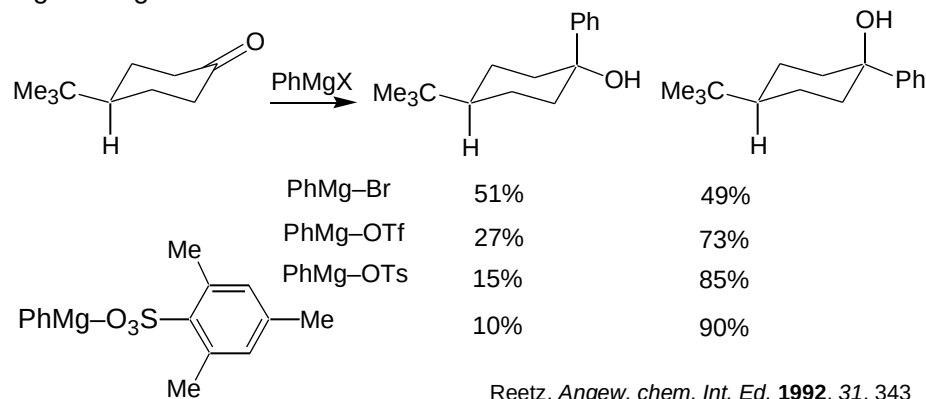
Stereoselective Organometallic Addition reactions:

As the cases below indicate, reaction diastereoselection is strongly coupled to the steric requirements of the organometallic reagent

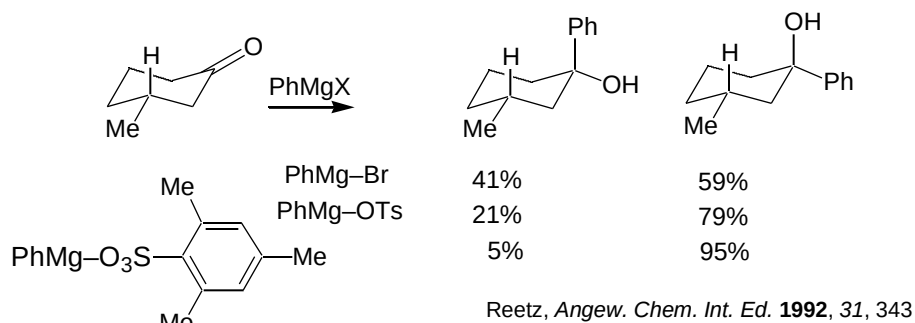


Ashby, *Chem. Rev.* **1975**, 75, 521

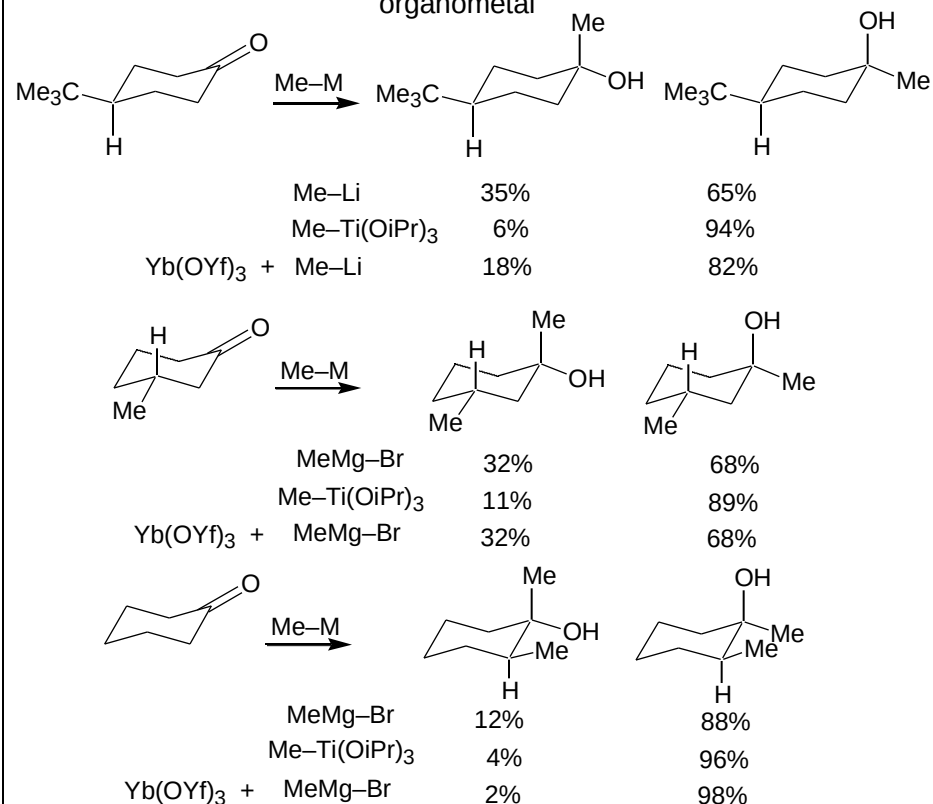
One can enhance C=O face selectivity by modifying the ligands on a given organometal.



Reetz, *Angew. chem. Int. Ed.* **1992**, 31, 343



One can also enhance C=O face selectivity by changing the organometal

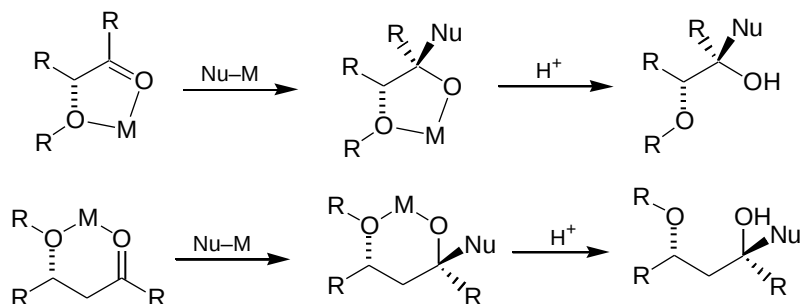


(Yb) Molander, *J. Org. Chem.* **1990**, 55, 4990

(Ti) Reetz, *Tetrahedron* **1986**, 42, 2931

(Mn) Reetz, *Tet. Let.* **1992**, 33, 6963

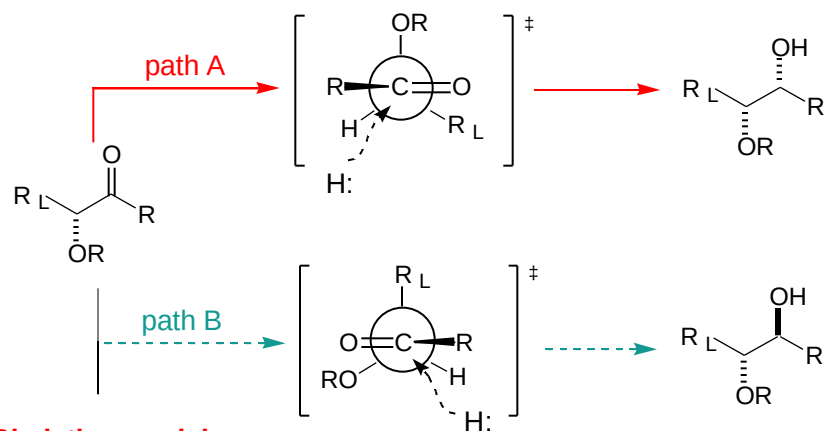
Chelate organization provides a powerful control element in carbonyl addition reactions



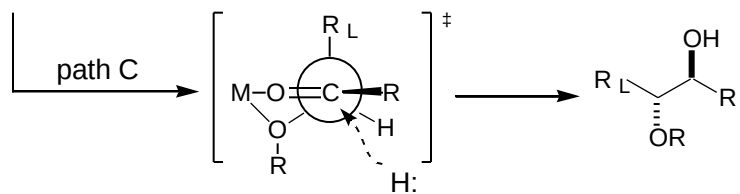
Reviews

Reetz, *Accs. Chem. Res.* **1993**, 26, 462-468 (pdf)
 Reetz, *Angew. Chem. Int. Ed.* **1984**, 23, 556-569

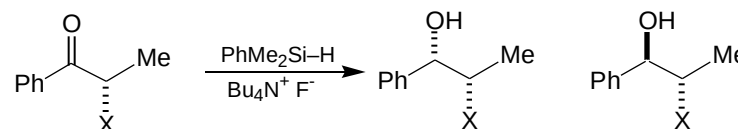
Lets begin with the hydride reductions of alkoxy ketones



Chelation model



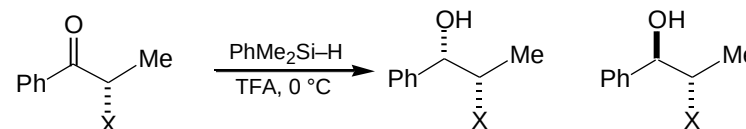
Lets begin with a case where chelation is precluded: (Path A)



Let $R_L = X$
 in the Ahn-Eisenstein model

T. Hiyama & Co-workers,
J. Am. Chem. Soc. **1984**, 106, 4629.

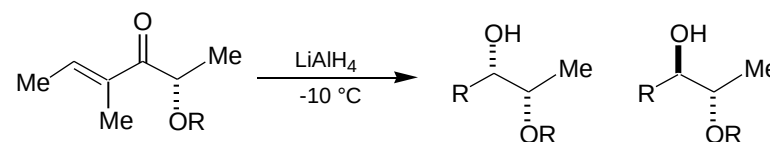
Substituent (X)	Ratio
X = NMe ₂	>99 : 1
X = OAc	95 : 5
X = OCOPh	96 : 4



H-bonding Chelate Model

T. Hiyama & Co-workers,
J. Am. Chem. Soc. **1984**, 106, 4629.

Substituent (X)	Ratio
X = NHCO ₂ Et	<1 : 99
X = OCOPh	7 : 93



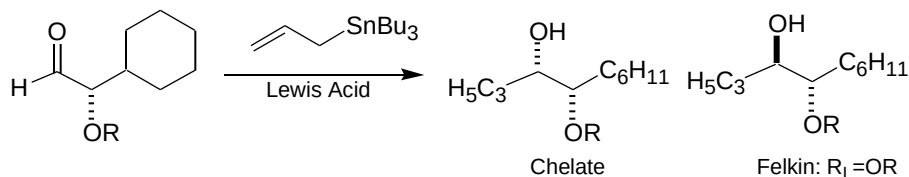
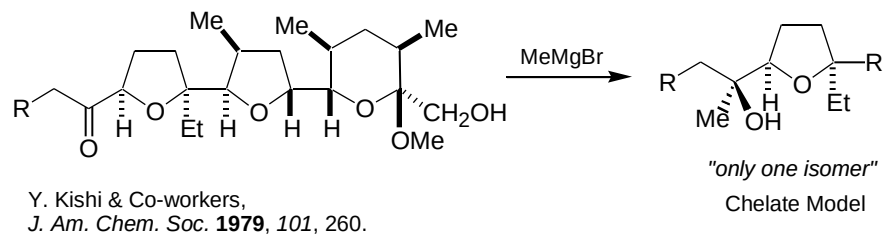
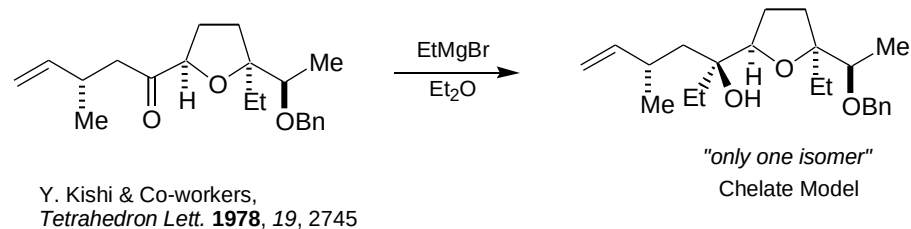
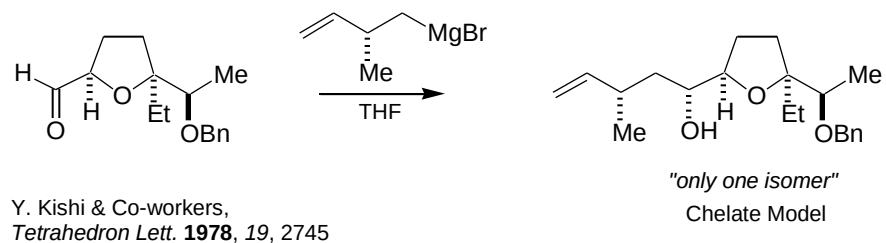
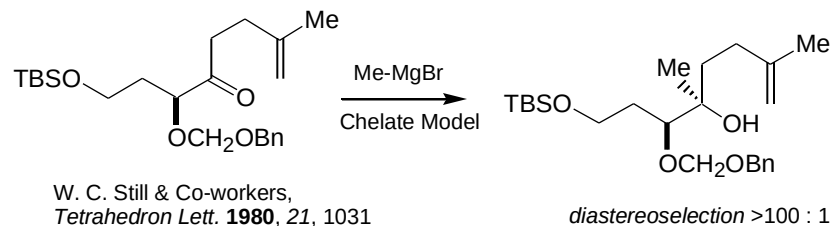
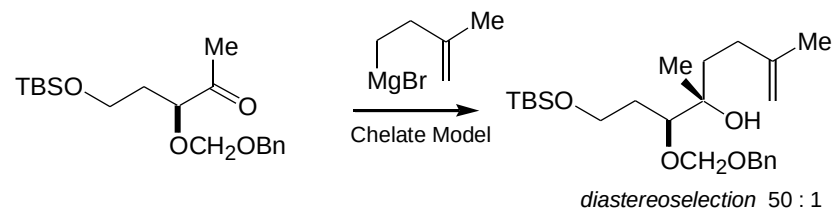
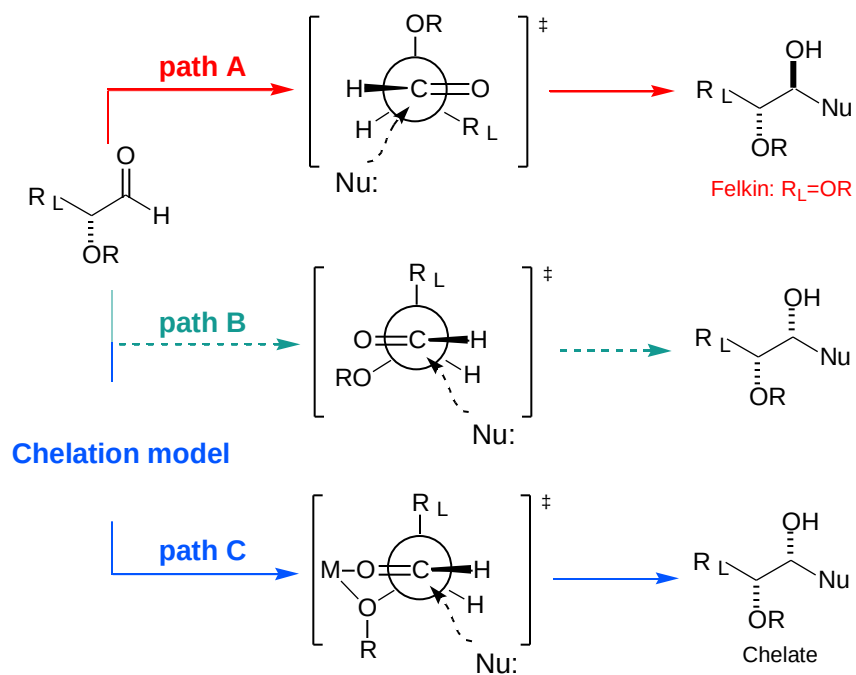
Overman
Tet Lett. **1982**, 23, 2355

(OR)	Solv.	Ratio	Model
R = CH ₂ OBn	THF	30 : 70	Chelate
R = CH ₂ OBn	Et ₂ O	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 SiPh₂(t)Bu group prevents chelation.

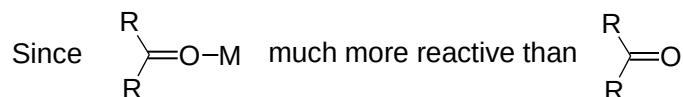
Addition of Carbon Nucleophiles



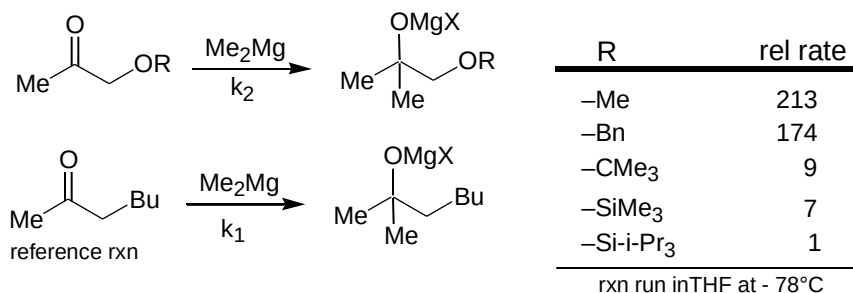
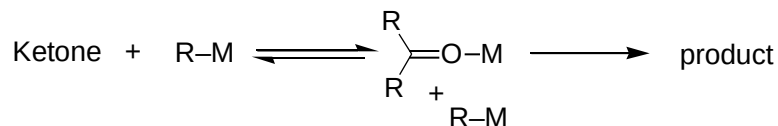
(OR)	Acid	Solv.	Ratio
R = CH ₂ OBn	MgBr ₂	THF (0°)	20 : 80
R = CH ₂ OBn	MgBr ₂	CH ₂ Cl ₂ (-20°)	>99 : 1
R = CH ₂ OBn	TiCl ₄	CH ₂ Cl ₂ (-78°)	>99 : 1
R = SiMe ₂ (t)Bu	BF ₃ -Et ₂ O	CH ₂ Cl ₂ (-78°)	5 : 95

G. Keck & Co-workers, *Tetrahedron Lett.* **1984**, 25, 265

Kinetic Evidence for Chelate-Controlled C=O Addition

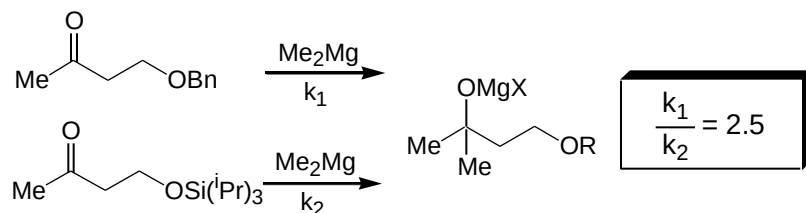


Substrates which can participate in C=O chelation will be more reactive since the effective concentration of chelated intermediate will be higher.

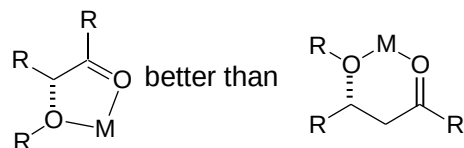


Eliel, Frye, JACS **1992**, 114, 1778-84 (read)

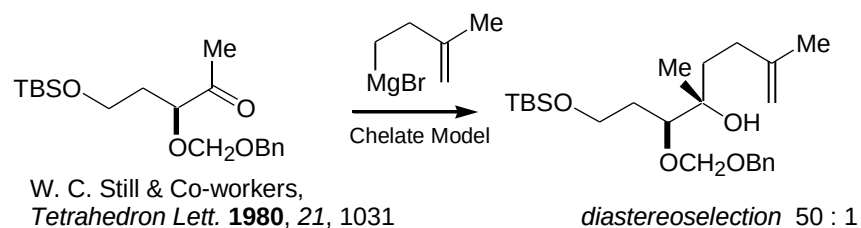
However, these trends are not transmitted strongly to β -chelation



Hence, organization through



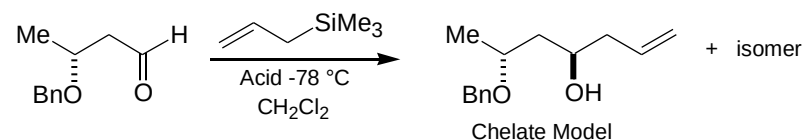
Alpha-Versus Beta-Chelation



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 ₂ Cl ₂	90 : 10

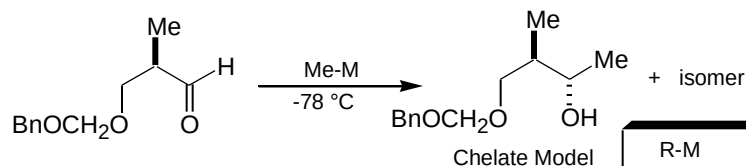


M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, 25, 729.

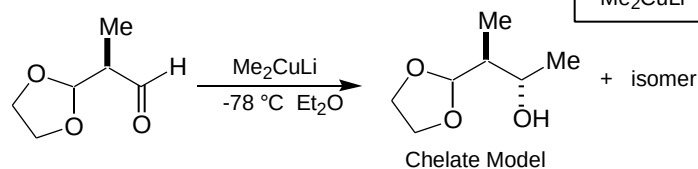
Acid	Ratio
TiCl ₄	95 : 5
SnCl ₄	95 : 5
BF ₃ -OEt ₂	85 : 15

- Note that beta chelation can be developed as a control element by varying solvent & Nu.
- Note BF_3 gives "apparent" chelate control

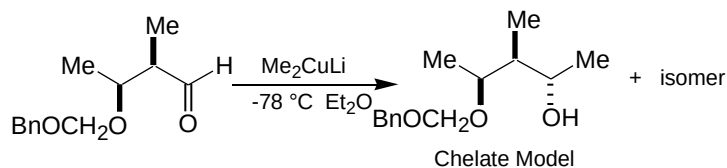
Beta Chelation with Organometals



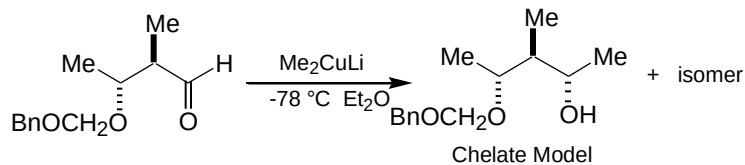
R-M	Ratio
MeMgBr	50 : 50
Me ₂ CuLi	97 : 3



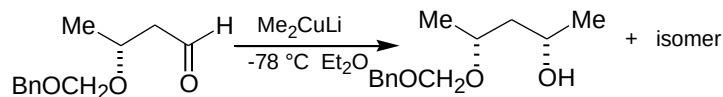
diastereoselection > 95 : 5



diastereoselection > 95 : 5

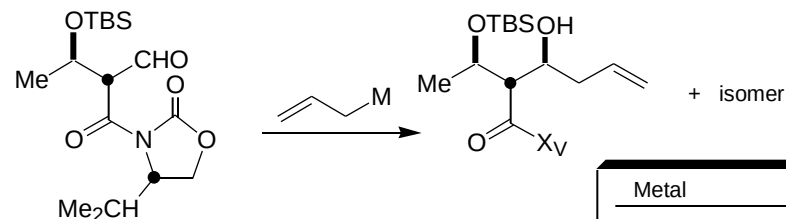


diastereoselection 70 : 30



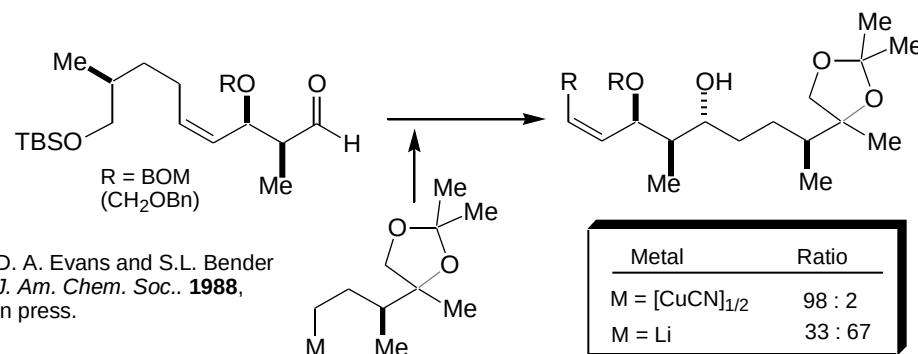
diastereoselection 50 : 50

W.C. Still & Co-workers,
Tetrahedron Lett. **1980**, 21, 1035.



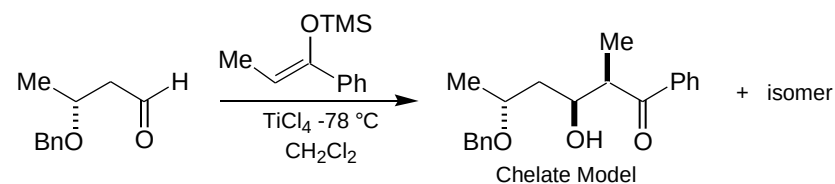
D. A. Evans & E. Sjogren
Tetrahedron Lett. **1986**, 27, 4961.

Metal	Ratio
M = MgCl	70 : 30
M = ZnCl	97 : 3



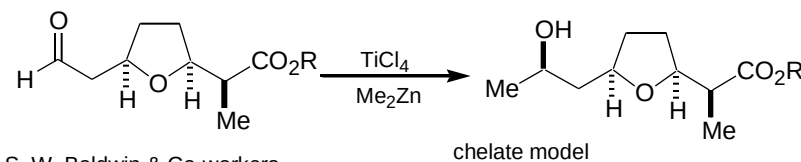
D. A. Evans and S.L. Bender
J. Am. Chem. Soc. **1988**,
in press.

Metal	Ratio
M = [CuCN] _{1/2}	98 : 2
M = Li	33 : 67



diastereoselection >92 %

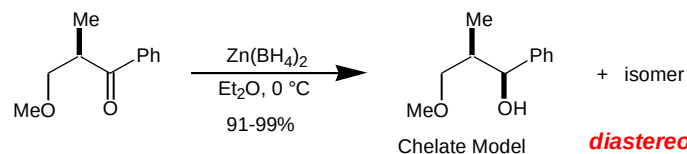
M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, 25, 729.



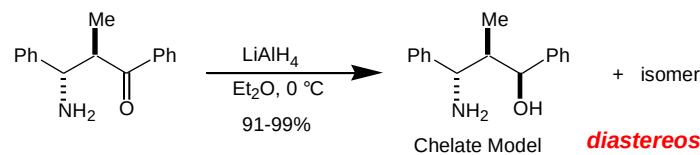
S. W. Baldwin & Co-workers
J. Org. Chem. **1987**, 52, 320.

diastereoselection 96 : 4

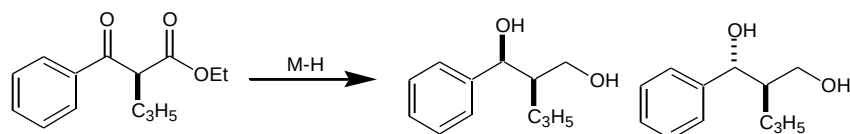
Beta Chelate-Controlled Reduction



T. Oishi & Co-workers
Chem. Pharm. Bull. **1984**, 32, 1411.

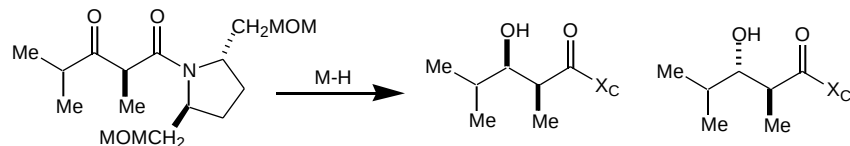


J. Barluenga & Co-workers
J. Org. Chem. **1985**, 50, 4052.



G. R. Brown & Co-workers
Chem. Commun. **1985**, 455.

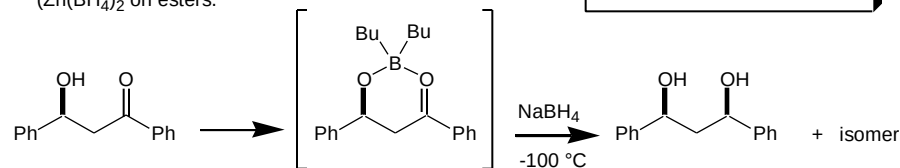
M-H	Ratio
Zn(BH ₄) ₂ Et ₂ O	100 : 0
LiAlH ₄ THF	0 : 100



M. Yamaguchi & Co-workers
Tetrahedron Lett. **1985**, 26, 4643.

T. Oishi & Co-workers
Tetrahedron Lett. **1980**, 21, 1641
(Zn(BH₄)₂ on esters.)

M-H	Ratio
Zn(BH ₄) ₂ Et ₂ O	100 : 0
KBH ₃ H THF	0 : 100

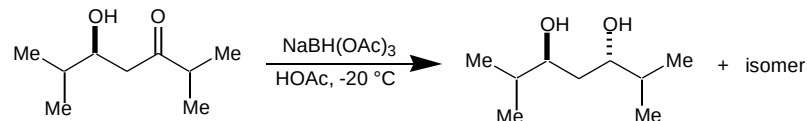
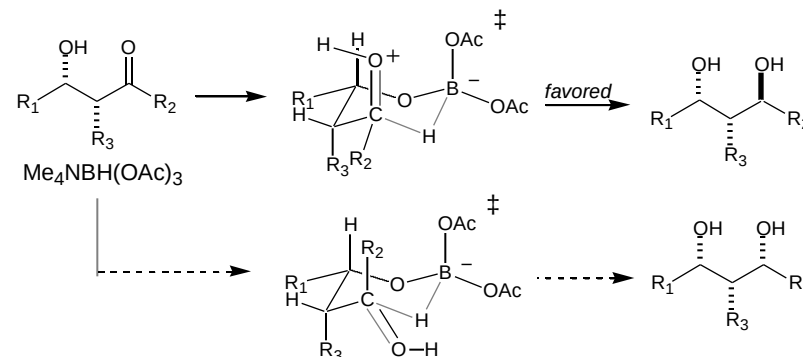


K. Narasaka & Co-workers
Chem. Lett. **1980**, 1415.

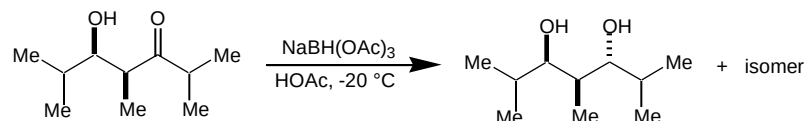
diastereoselection 96 : 4

Directed reductions of β-hydroxyketones

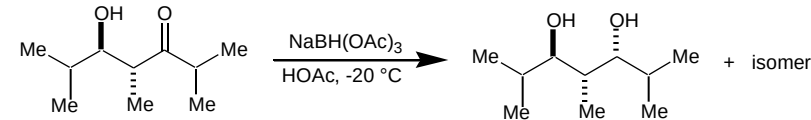
Evans, Chapman, Carreira, *JACS* **110**, 3560 (1988)



diastereoselection 96 : 4

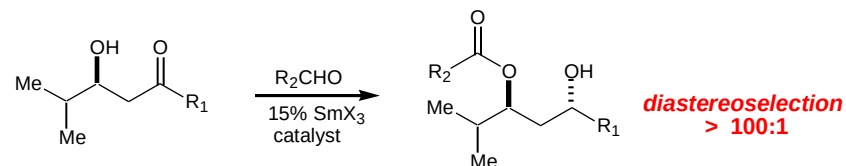


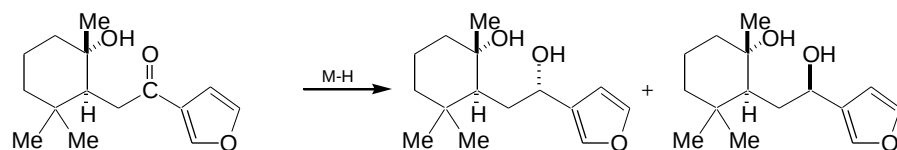
diastereoselection 98 : 2



diastereoselection 98 : 2

Propose a mechanism for this highly diastereoselective transformation,
Evans, Hoveyda *JACS* **112**, 6447 (1990)

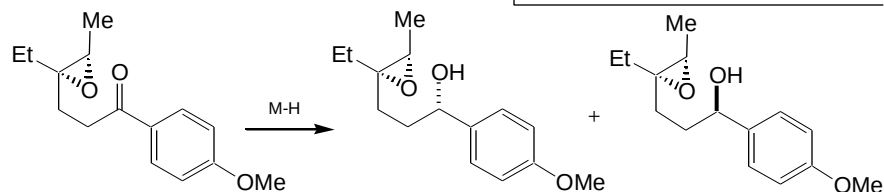




Temp. & Solvent not specified in this study
in first three cases

R. Baker & Co-workers
Chem. Commun. **1984**, 74

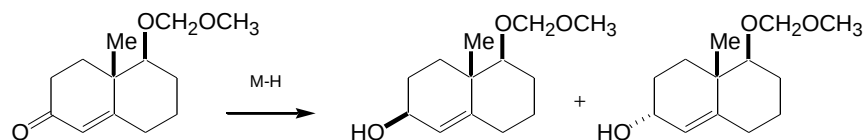
Reagent	Ratio
Li-AlH ₄	40 : 60
Na-BH ₄	50 : 50
Zn-BH ₄	60 : 40
Li-BHEt ₃ , (THF, -78°C)	100 : 0



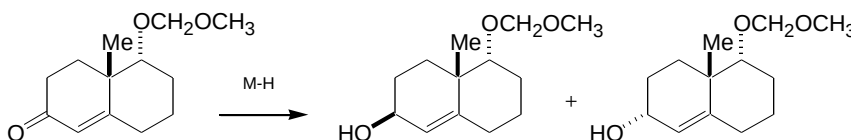
Y. Kishi & Co-workers
Tetrahedron Lett. **1978**, 2741.

* di-2-(o-toluidinomethyl)pyrrolidine

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

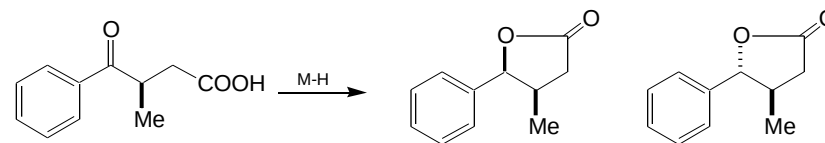


Li-BH(R) ₃ ,	73 : 27
LiAlH ₄	76 : 24



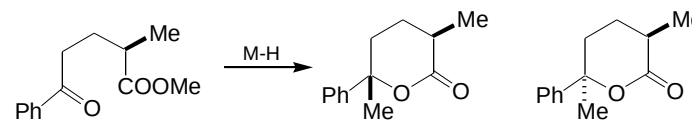
W. G. Dauben & Co-workers
Tetrahedron Lett. **1978**, 2741.

Li-BH(R) ₃ ,	28 : 72
LiAlH ₄	72 : 28



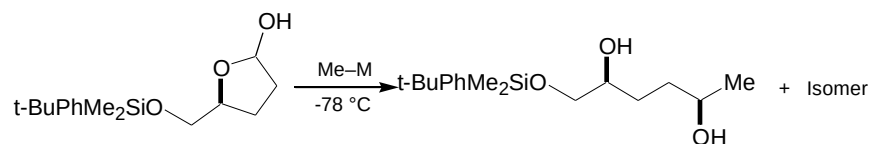
R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

Reagent	Ratio
NaBH ₂ (OR) ₂	50 : 50
NaBH ₄	70 : 30
DIBAL (2.4 equiv)	95 : 5
DIBAL (2.4 equiv) with ZnCl ₂	99 : 1



R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

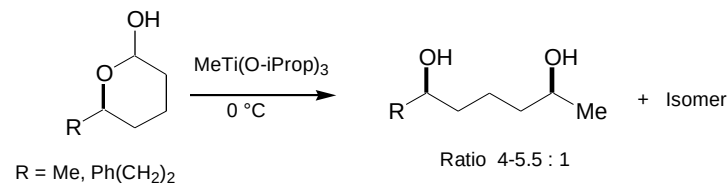
Solvent	Ratio
THF	50 : 50
C ₆ H ₆	70 : 30



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



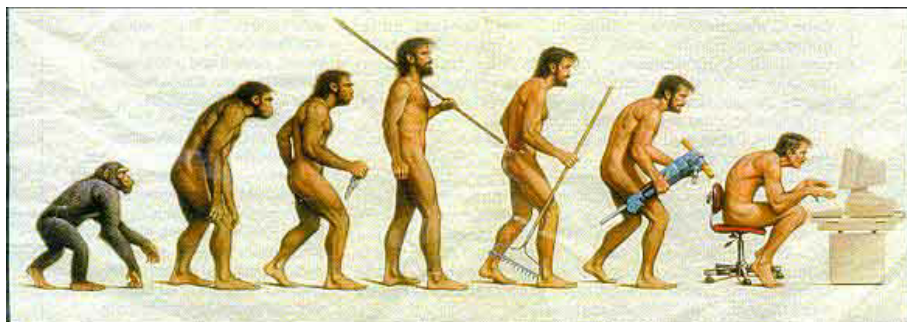
<http://www.courses.fas.harvard.edu/~chem206/>

Chemistry 206

Advanced Organic Chemistry

Lecture Number 20

The Evolution of Models for Carbonyl Addition



Fischer Cornforth Anh/Eisenstein Tomoda
Cram Felkin Cieplak

- 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

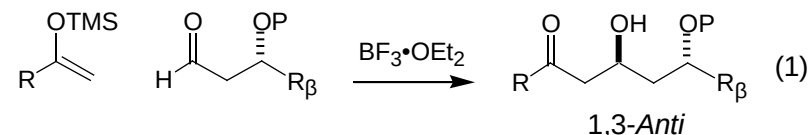
Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 556-569

Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*;
Prentice Hall Inc.: **1971**

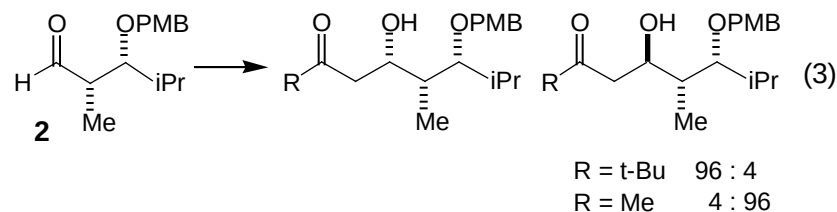
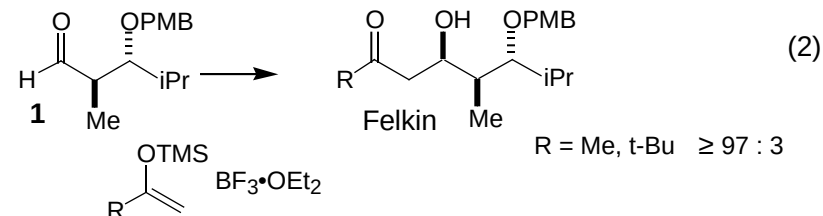
Wipf, P.; Kim, Y. J. *Am. Chem. Soc.* **1994**, 116, 11678-11688, ref. 1-5, 7

■ A problem

Construct a model for the addition process in eq 1 using the principles learned thus far in the course.

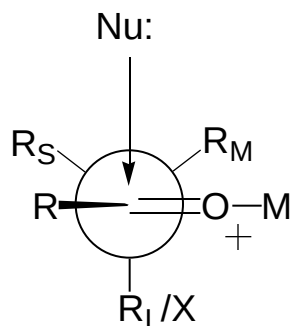


Aldehydes **1** & **2** contain 2 stereocenters, each of which may influence the course of the addition process. For **1**, the reaction is Felkin selective for all enolsilanes; however, for **2**, this is not the case. Explain. For the answer see: Evans, *JACS* **1996**, 118, 4322. ([pdf](#))



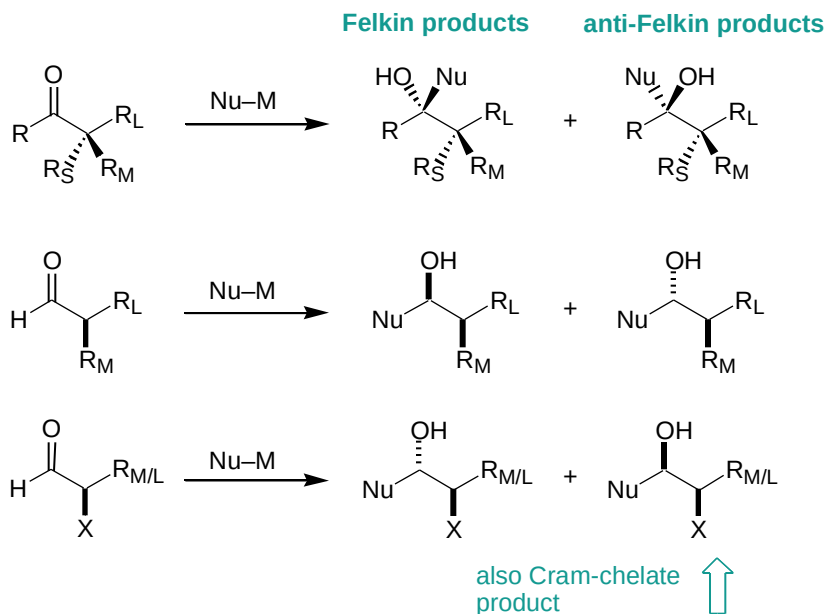
Definition of Terms

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

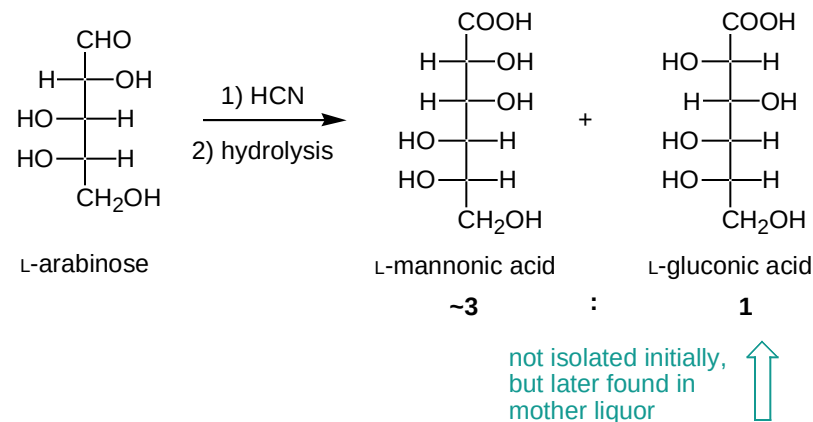


Felkin-Anh model

Examples:



Fischer, and the Dawn of Asymmetric Induction

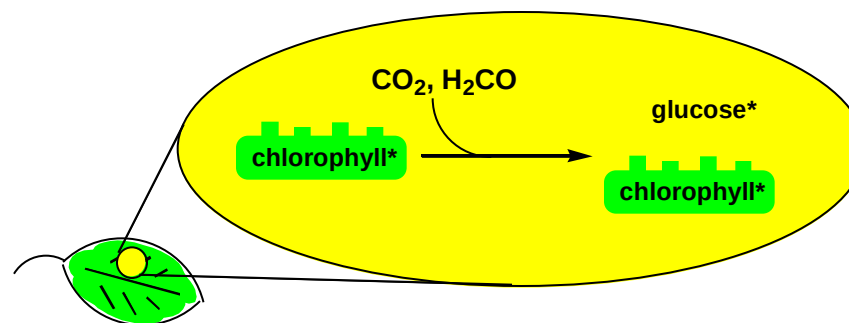


"To my knowledge these observations furnish the first definitive evidence that further synthesis with asymmetric systems proceeds in an asymmetric manner."

-Emil Fischer, 1894

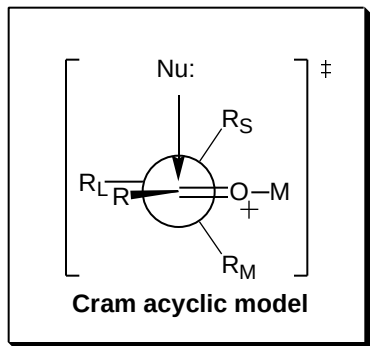
Fischer, E. *Ber.* **1890**, 23, 2611
Fischer, E. *Ber.* **1894**, 27, 3189

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

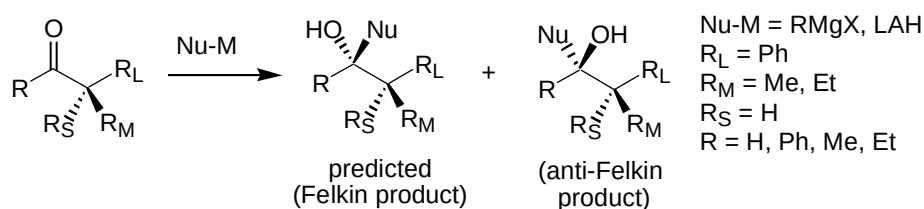
Don Cram: 1952



Cram'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."

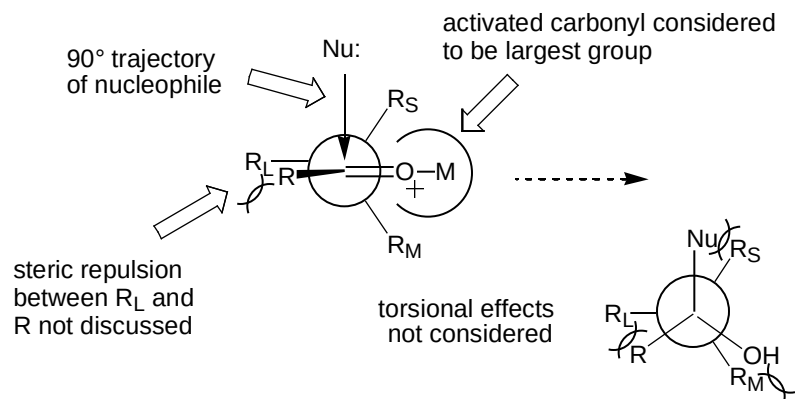
Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, 74, 5828

Basis for Model

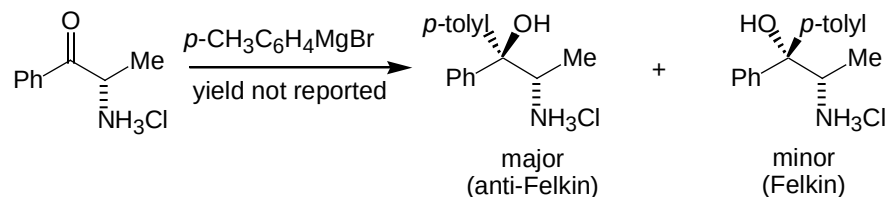


selectivities ranging from 2:1 to >4:1, favoring Felkin product

Features and Liabilities



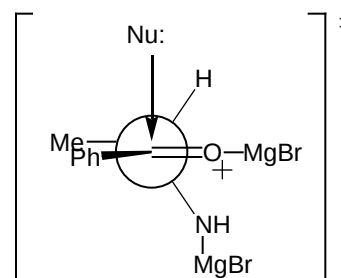
Among the 27 cited reactions whose stereoselection is "predicted" by Cram's acyclic rule:



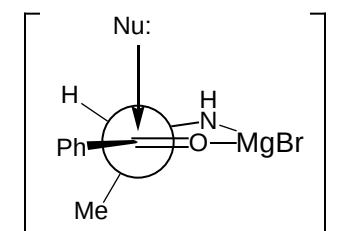
Curtin, D. Y.; Pollak, P. I. *J. Am. Chem. Soc.* **1951**, 73, 992

Ranking of steric bulk of α -substituents is somewhat arbitrary:
 $\text{Me} > \text{NH}_3\text{Cl}$ 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

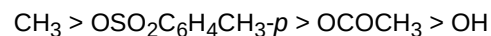
Bottom Line

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

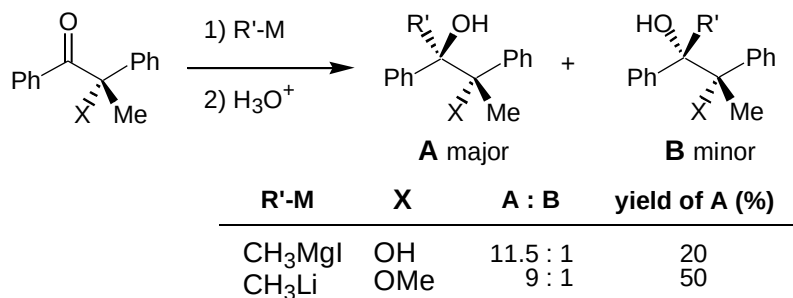
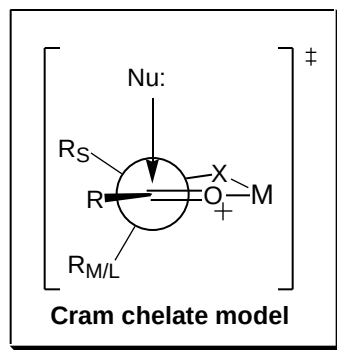
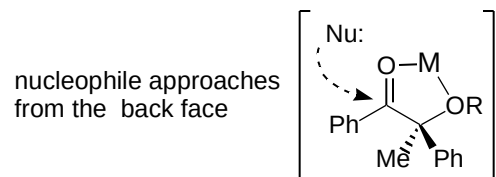
Don Cram: 1959

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.



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



- expects groups OH, OR, OAc, NR₂, 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."

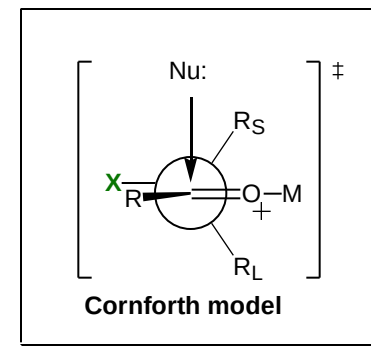
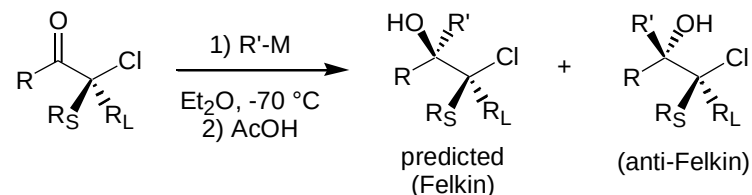
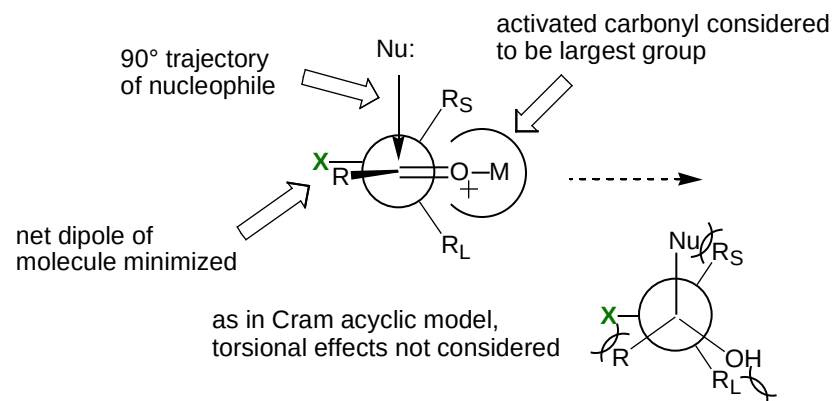
Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, 81, 2748

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

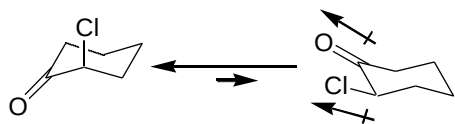
- a modification of Cram's rule for electronegative, non-chelating α -substituents X

**Additions to α -Chloro Carbonyls****Features**

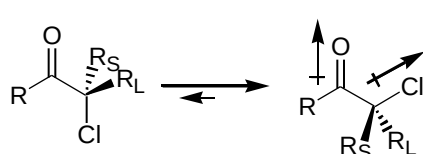
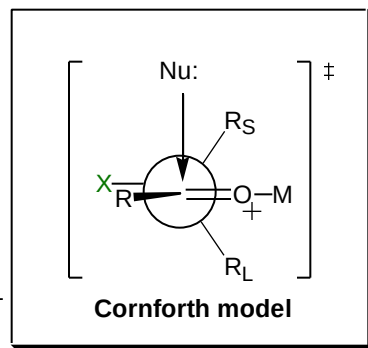
Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112

Cornforth: Rationalization and Evidence

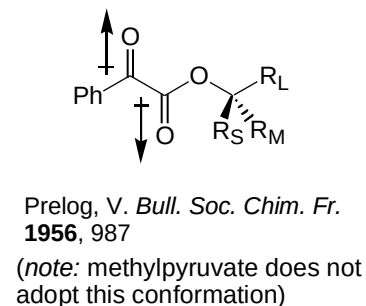
Support and Contradiction for Dipole Minimization



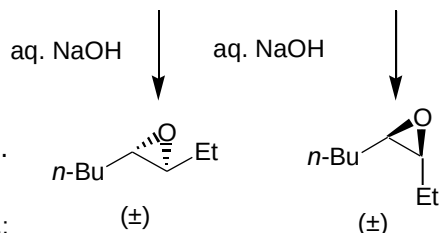
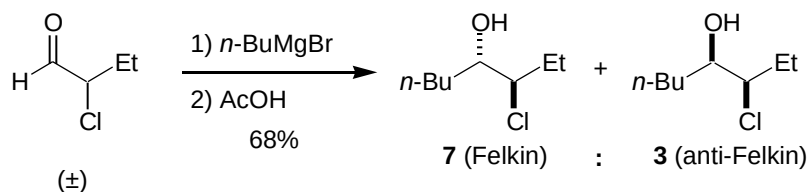
Corey, E. J. *J. Am. Chem. Soc.* **1953**, 75, 2301
 Corey, E. J.; Burke, H. J. *ibid.* **1955**, 77, 5418



Bellamy, L. J.; Thomas, L. C.; Williams, R. L. *J. Chem. Soc.* **1956**, 3704
 Bellamy, L. J.; Williams, R. L. *ibid.* **1957**, 4294



Chlorohydrin Synthesis

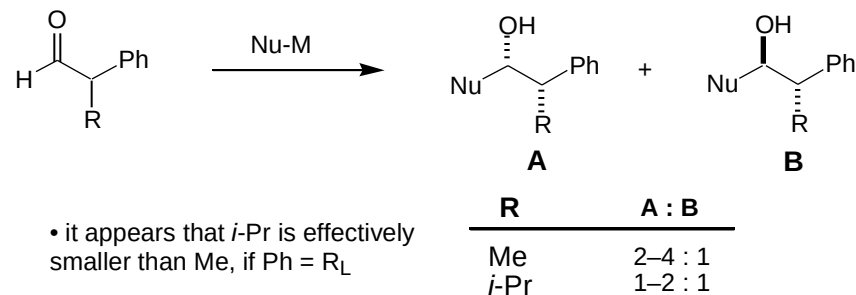


These were known products.

Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112

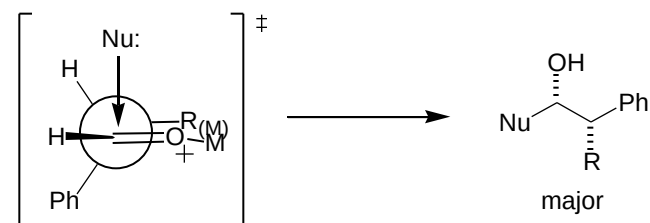
Karabatsos: 1967

Given Cram's acyclic model, Karabatsos is surprised by the following selectivities:



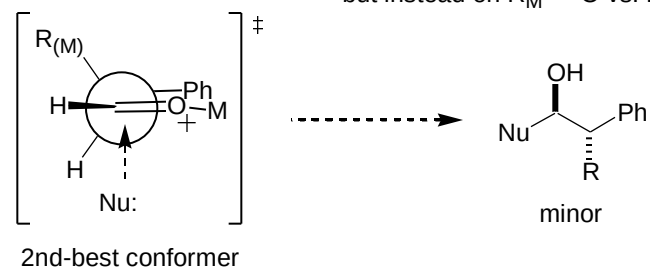
• it appears that *i*-Pr is effectively smaller than Me, if Ph = R_L

Karabatsos' explanation: Cram transition states are incorrect

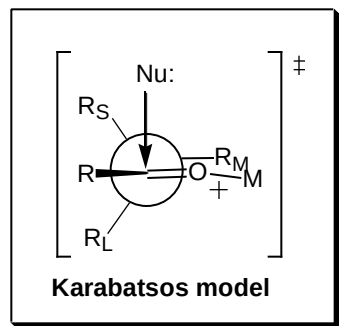


Karabatsos model

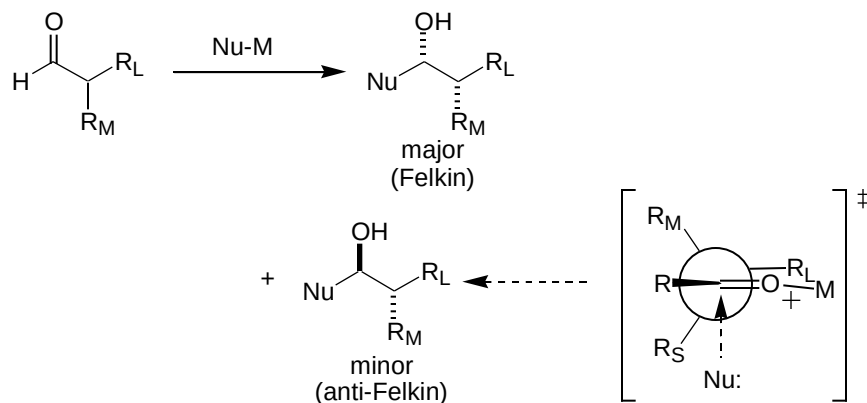
Compared Interaction	ΔΔH°
Me ↔ O – Ph ↔ O	0.6 kcal/mol
<i>i</i> -Pr ↔ O – Ph ↔ O	0.2 kcal/mol
• ratios depend not on Nu ↔ H and Nu ↔ R _M , but instead on R _M ↔ O vs. R _L ↔ O	



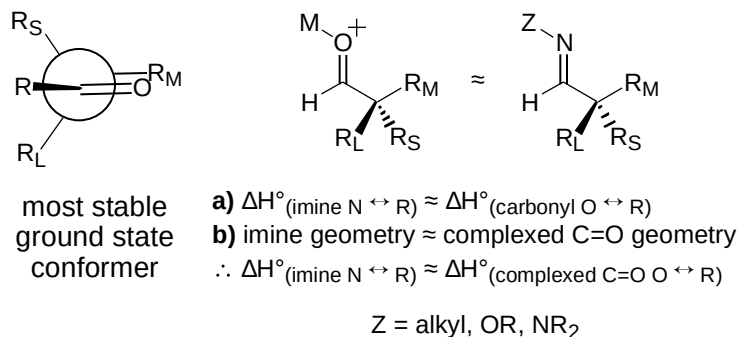
Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, 89, 1367



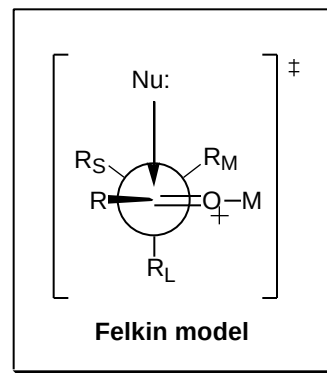
- energy difference ($\Delta\Delta H^\circ$) between interactions of $R_M \leftrightarrow O$ and $R_L \leftrightarrow O$ determines product ratio
- reactant-like transition state
- model based on most stable ground-state conformation
- energy differences between major and minor conformations are <1 kcal/mol



Rationalizations



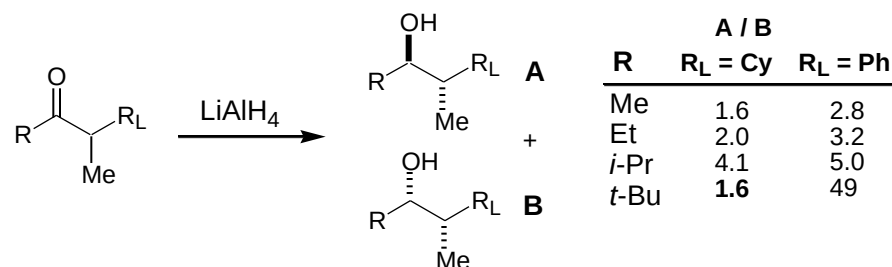
Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, 89, 1367



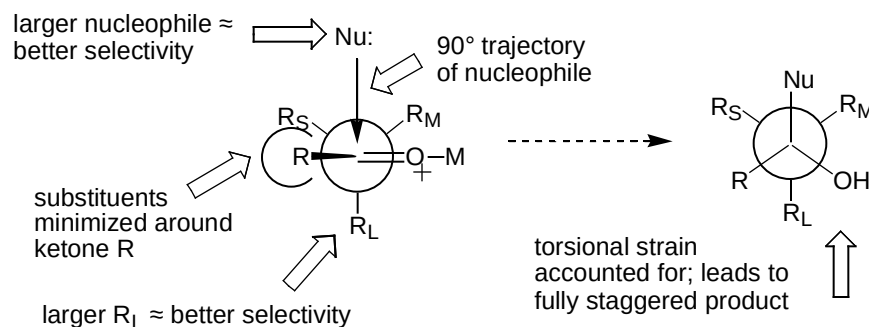
Felkin: 1968

- "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



Features

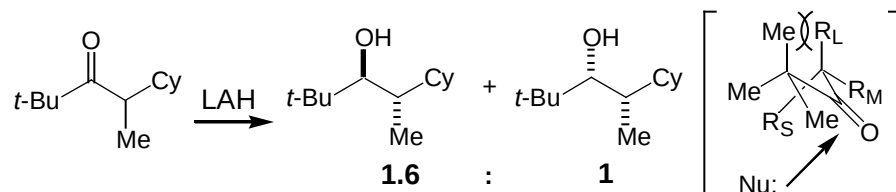


Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 18, 2199

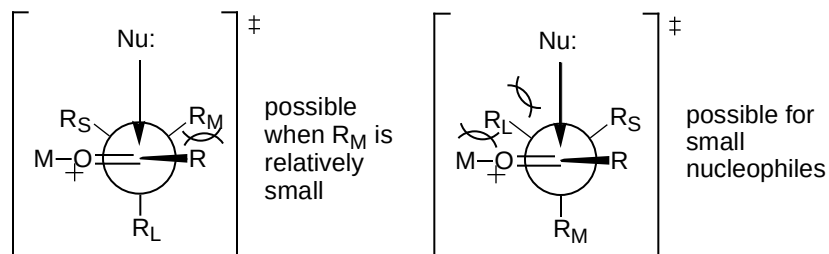
Felkin: Accounting for Less Selective Reactions

1) The *t*-butyl ketone case

- with α -branching, in any staggered conformation, *syn*-pentane is impossible to avoid

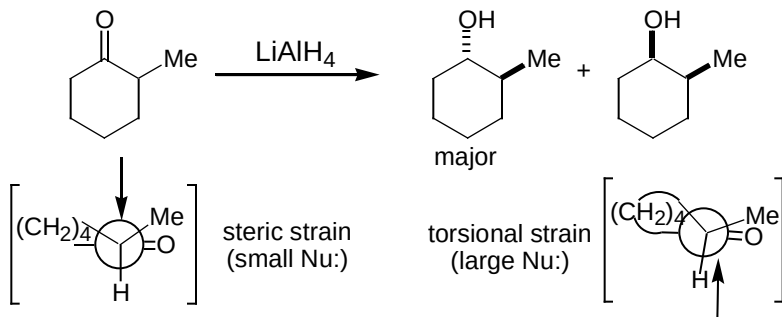


2) Transition states for minor products (does not consider conformers with R_L next to R)



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

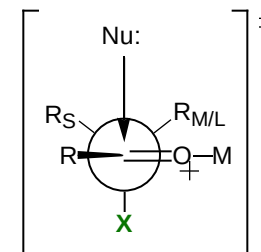


Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 18, 2199; 2205

Weaknesses in Felkin's Argument

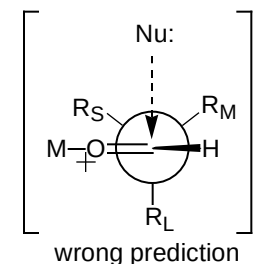
1) Polar effect

- main repulsion to minimize between Nu and electronegative group X -- no justification given



2) Breakdown for aldehydes

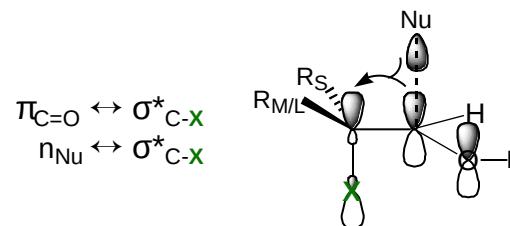
- without ketone R, important steric interaction removed: would predict R_M to be next to H rather than carbonyl



Anh's Solutions

1) Antiperiplanar effect

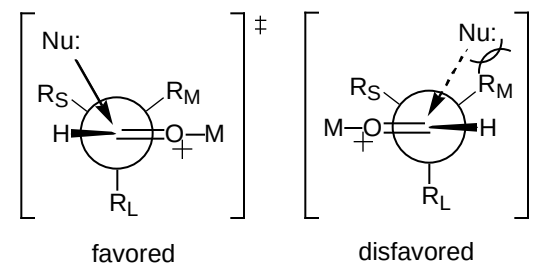
- best acceptor σ^* orbital aligned parallel to π and π^* orbitals of carbonyl; stabilization of incoming anion



2) Non-perpendicular attack

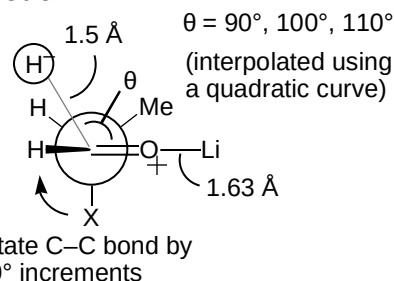
- incorporation of the Bürgi-Dunitz trajectory

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



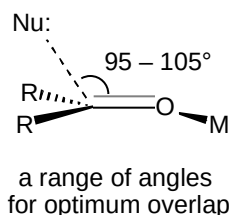
Anh's Calculated Transition State Energies

The model:

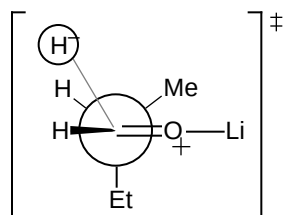


STO-3G *ab initio* method (low level)

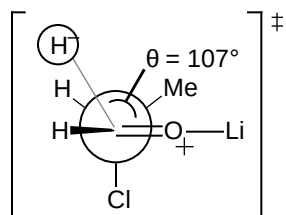
Non-perpendicular attack



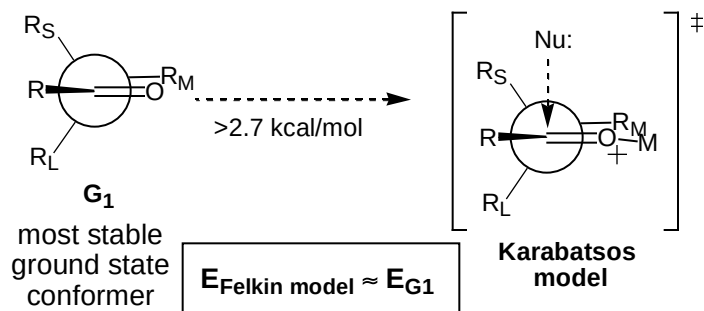
Lowest energy transition states:



2-methylbutanal
(Felkin-Anh model)



2-chloropropanal
(Felkin-Anh polar model)

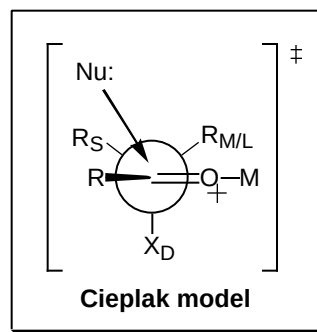


Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155

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

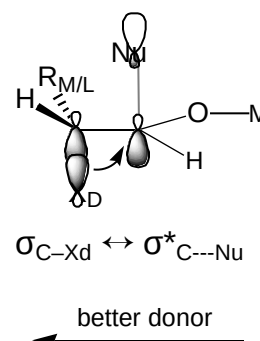
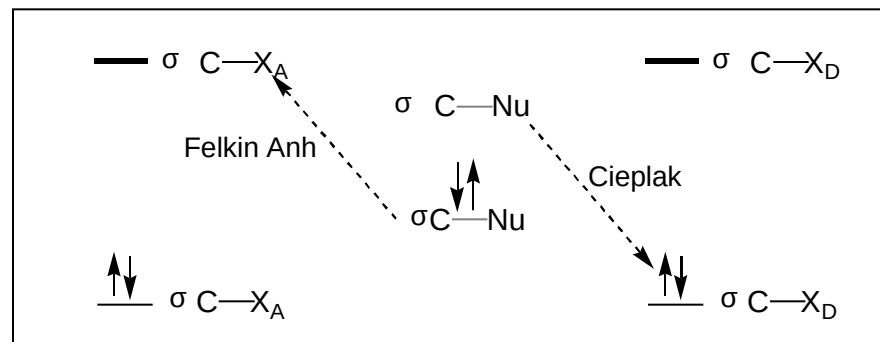


- similar to Anh-Eisenstein modification of the Felkin model: stabilization of nucleophile via antiperiplanar C-X_D bond

- 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



"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."

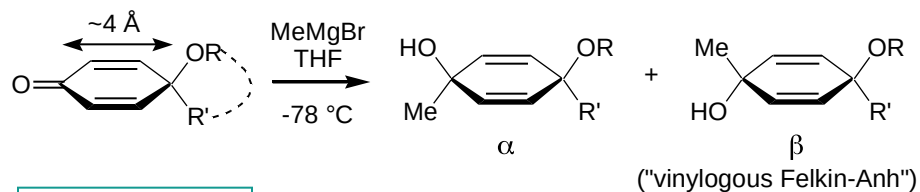
- DAE

C-H > C-C > C-N > C-O
(Houk disputes the ordering of C-H, C-C)

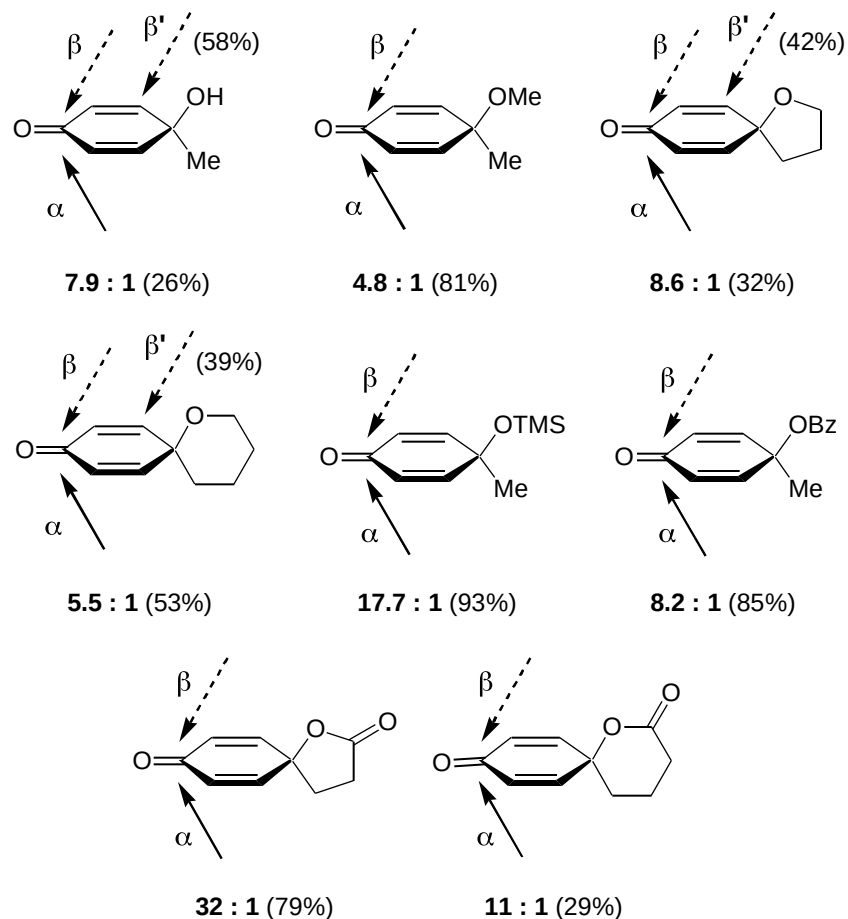
Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, 103, 4540;

Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, 111, 8447

4,4-Disubstituted Cyclohexadienones: Experimental Data



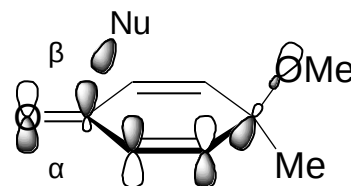
KEY: α : β (yield)



Wipf Seeking an Explanation

Stereoelectronic effect?

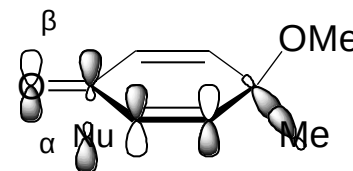
Neither vinylogous Felkin nor vinylogous Cieplak sufficiently explains or predicts selectivity.



"vinylogous Anh-Eisenstein" model

LUMO of enone has phase inversion due to double bond between carbonyl and donor/acceptor orbital

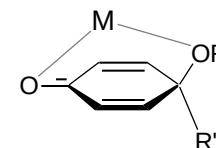
- stabilizing HOMO of nucleophile
- predicts β attack -- wrong product!



"vinylogous Cieplak" model

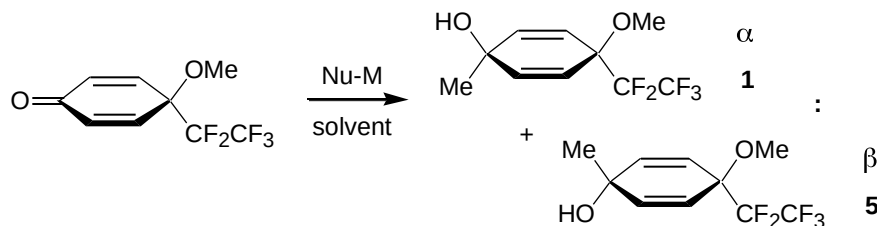
- stabilizing σ* of the incipient bond
- predicts α attack, but no qualitative correlation between ratio of isomers and σ energy of donor C-C bonds

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!

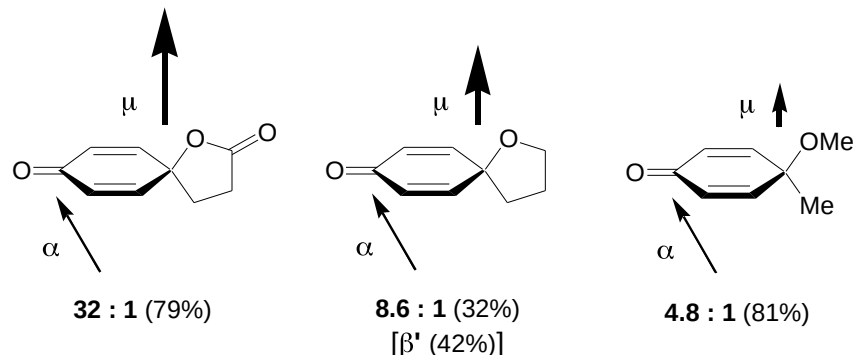


Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678

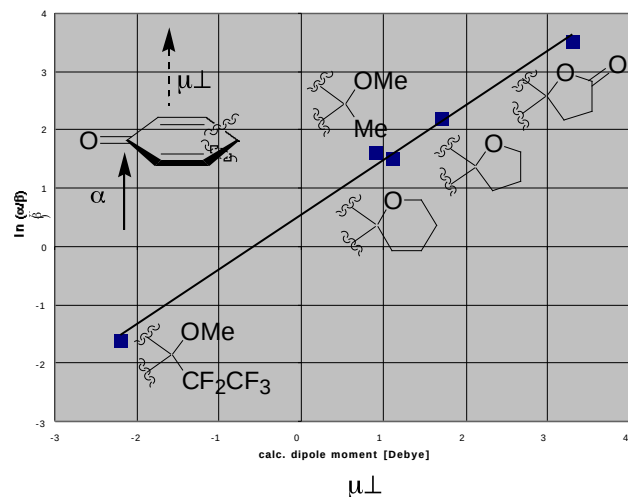
Wipf, P.; Jung, J-K. *Chem. Rev.* **1999**, *99*, 1469

Quantitative Correlation Between Facial Selectivity and Dipole Moment

Qualitative Assessment

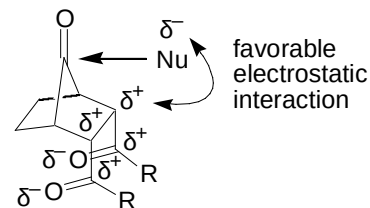
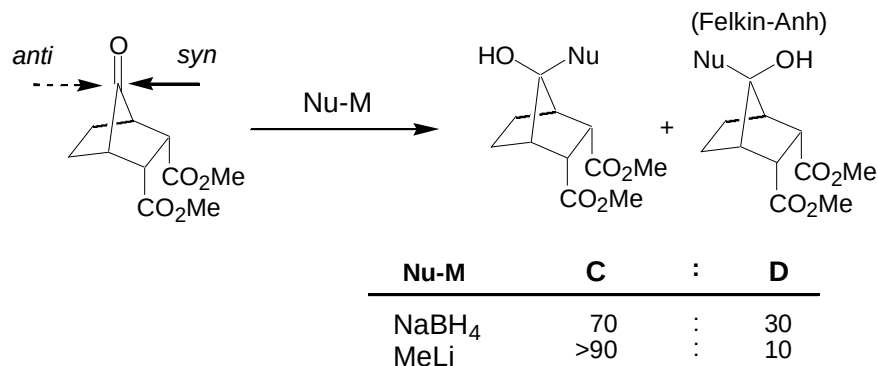
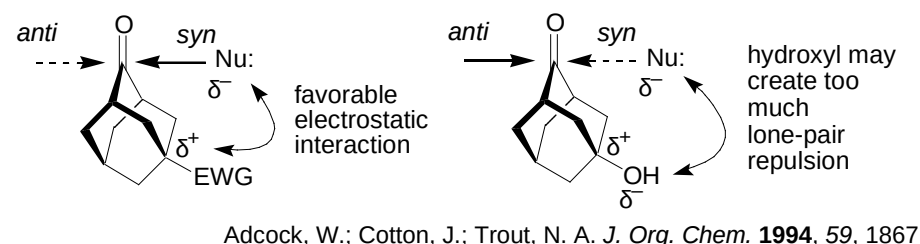
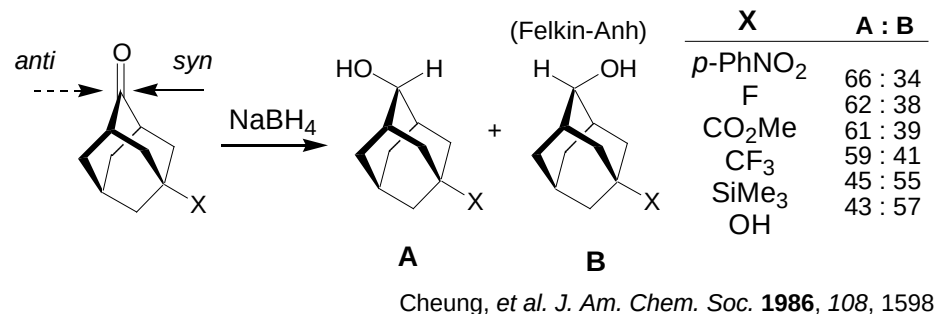


Dipole Moment Calculations

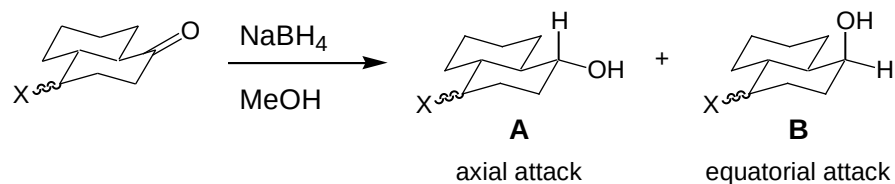


- calculated dipole moments of five representative dienones using SPARTAN
- linear correlation between perpendicular vector of dipole moment and natural log of facial selectivity
- validity of ground-state dipole moment: complexed carbonyl should affect dipoles of all dienone substrates in same manner
- approach of nucleophile toward positive end of dipole favored

An Electrostatic Take on Some Controversial Cases



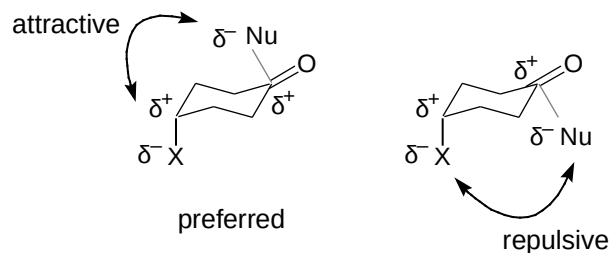
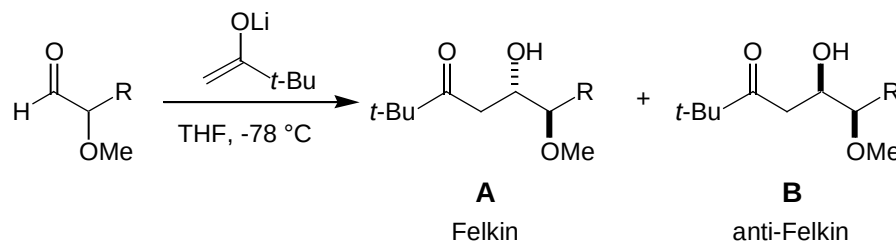
- Mehta, G.; Khan, F. A. *J. Am. Chem. S.* **1990**, 112, 6140
 Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, 114, 10638
 Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, 58, 1734

Houk: Axial Effect

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:

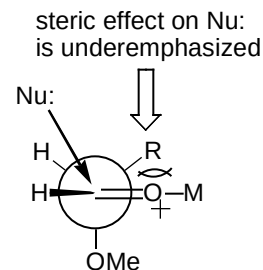
a remote electrostatic effect

**Heathcock: α -Alkoxy Lithium Aldol**

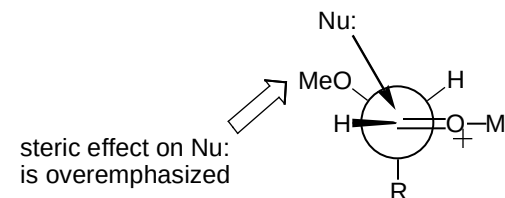
"Quite simply, we believe our data show that the Anh-Eisenstein hypothesis is only partly correct."

R	A : B
Me	58 : 42
Et	76 : 24
<i>i</i> -Pr	92 : 08
Ph	83 : 17
<i>t</i> -Bu	93 : 07

Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353

**Felkin-Anh polar model**

- Would expect some erosion of selectivity as size of R increases -- observe just the opposite!

**electrostatic model**

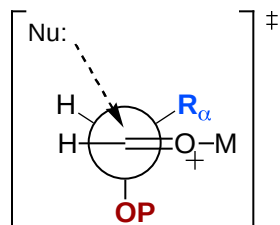
- As R is anti to incoming nucleophile, increasing size of R should not erode selectivity
- As R gets larger, conformation may be more "locked" in the above conformer

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

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.

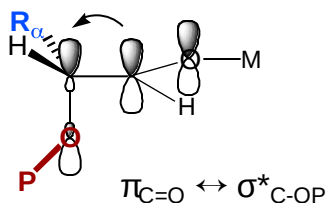
Are Felkin-selective reactions of α -heteroatom aldehydes going through the Felkin-Anh transition state?

Felkin-Anh model



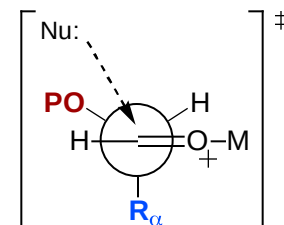
- leads directly to staggered conformation, Felkin product

- best acceptor σ^* orbital aligned parallel to π and π^* orbitals of carbonyl: hyperconjugative stabilization



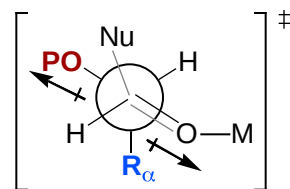
- assumes a covalent transition state in which FMO stabilization dominates

electrostatic model



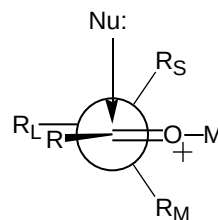
- leads directly to staggered conformation, Felkin product

- dipoles of carbonyl and α -C-O are minimized, with increasing stabilization as pyramidalization occurs at the reactive center

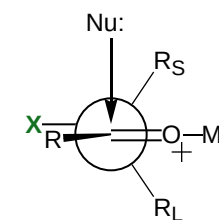


- assumes a more ionic transition state in which coulombic interactions dominate
- larger π^* coefficient on C of oxocarbenium species may enable a wider range of angles for nucleophilic trajectory

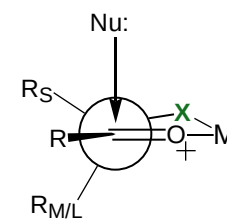
Models Proposed for 1,2-Asymmetric Induction



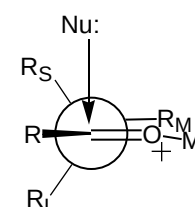
Cram acyclic model (1952)
steric



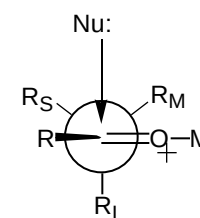
Cornforth model (1959)
electrostatic



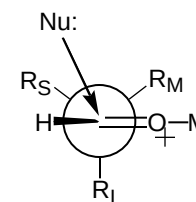
Cram rigid model (1959)
chelation



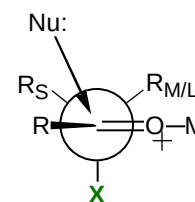
Karabatsos model (1967)
ground-state, steric



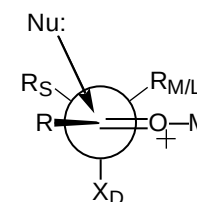
Felkin model (1968)
steric, torsional



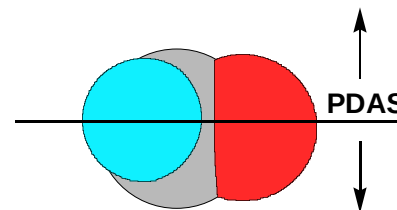
Felkin-Anh model (1977)
steric, torsional, Bürgi-Dunitz



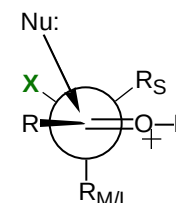
Felkin-Anh polar model (1977)
electronic, torsional, Bürgi-Dunitz



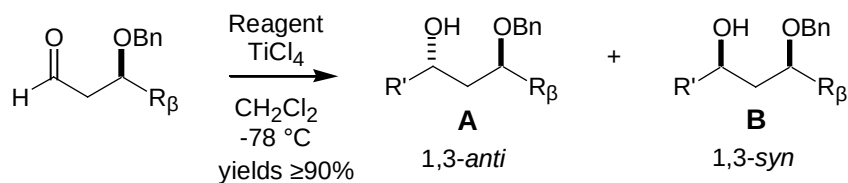
Cieplak model (1981)
electronic, torsional, Bürgi-Dunitz



Tomoda EFOE model (1997)
ground-state, steric, electronic



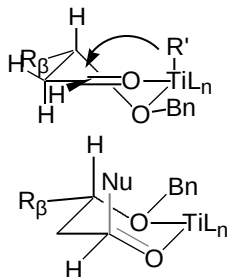
electrostatic model (2001)
electrostatic, torsional, Bürgi-Dunitz

Reetz: Chelation in β -Alkoxy Aldehydes

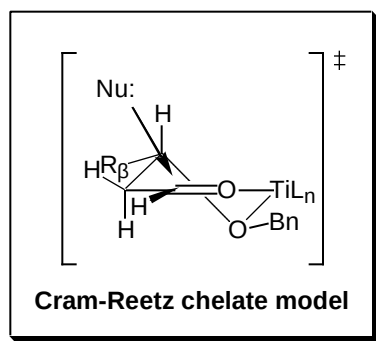
Reagent	R_β	R'	A : B
	Me		95 : 05
	Me		95 : 05
$n\text{-Bu}_2\text{Zn}$	Me	$n\text{-Bu}$	90 : 10
	$n\text{-Bu}$		95 : 5
	$n\text{-Bu}$		99 : 01

RMgX , RLi , and R_2CuLi fail to give high chelation selectivities for β -alkoxy aldehydes.

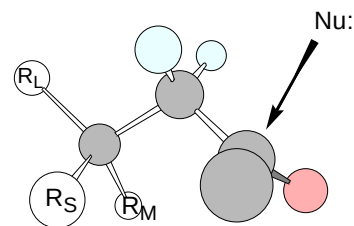
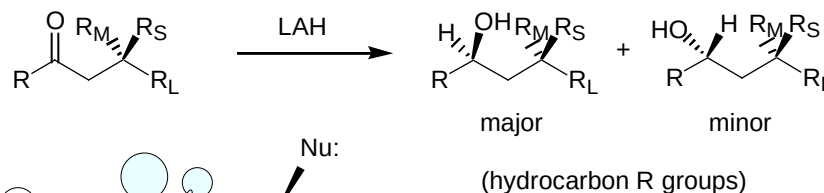
Reetz proposes possible transmetalation event of nucleophile: internal delivery.



- leads to a chair-like intermediate



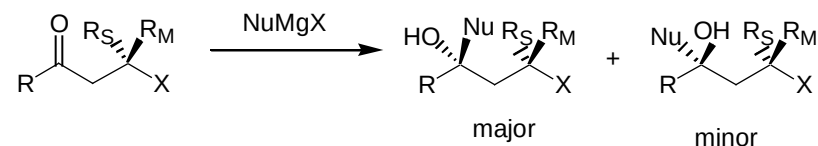
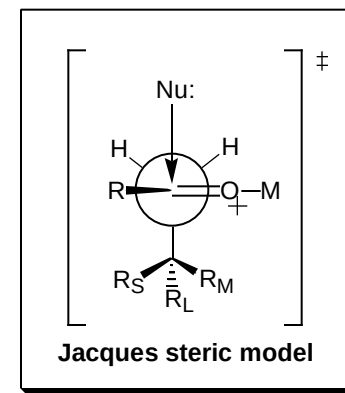
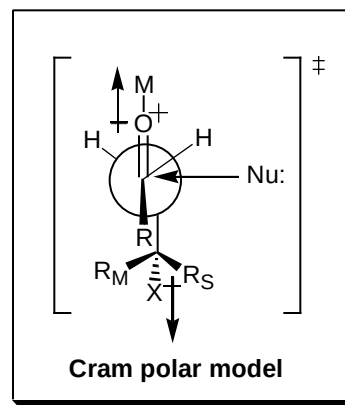
Reetz, M. T.; Jung, A. J. *Am. Chem. Soc.* **1983**, 105, 4833

1,3-Asymmetric Induction: Open-Chain Models

3-D depiction of Jacques model

- rationalization similar to Felkin: minimization of $\text{R} \leftrightarrow \beta\text{-R}$ steric interactions

Brienne, M-J.; Ouannès, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1968**, 3, 1036

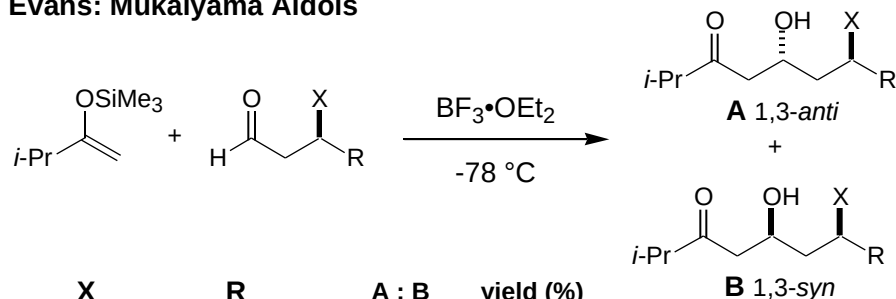


- an adaptation of the Cram steric model, with the key feature being dipole minimization of electronegative substituent X and carbonyl

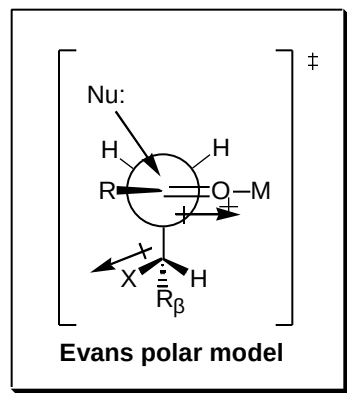
Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, 90, 4011, 4019

1,3-Asymmetric Induction: Open-Chain Models

Evans: Mukaiyama Aldols

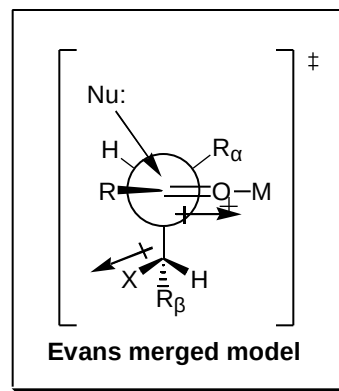


X	R	A : B	yield (%)
OPMB	<i>i</i> -Pr	92 : 08	91
OTBS	<i>i</i> -Pr	80 : 20	84
OPMB	CH ₂ CH ₂ Ph	81 : 19	87
OTBS	CH ₂ CH ₂ Ph	73 : 27	90
OAc	CH ₂ CH ₂ Ph	43 : 57	79
Cl	CH ₂ CH ₂ Ph	83 : 17	84
Me	C(Me) ₂ CHCH ₂	58 : 42	88

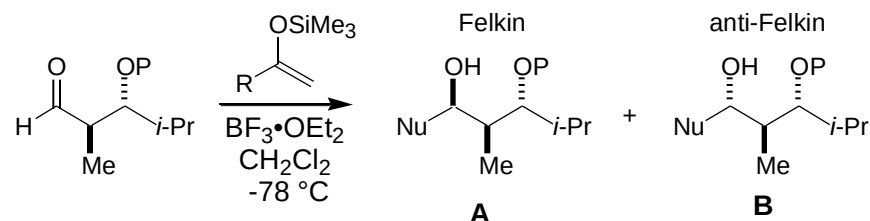


- staggered to avoid torsional strain
- dipoles of C_β-X and carbonyl minimized
- non-perpendicular nucleophile trajectory

Evans Merged Model for 1,2- and 1,3-Asymmetric Induction



- 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)

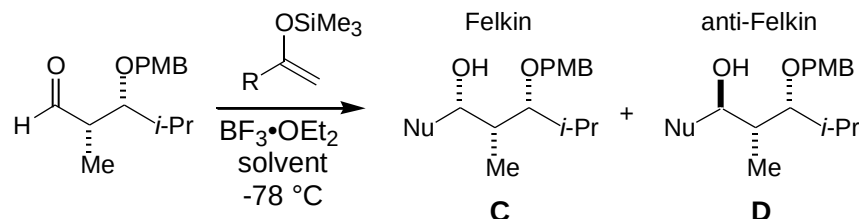
R	P = PMB A : B	yield (%)	P = TBS A : B	yield (%)
<i>t</i> -Bu	99 : 01	94	99 : 01	93
<i>i</i> -Pr	98 : 02	98	95 : 05	88
Me	97 : 03	86	71 : 29	92

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

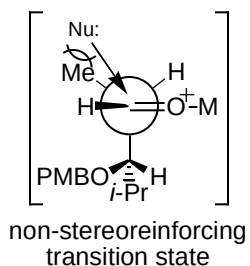
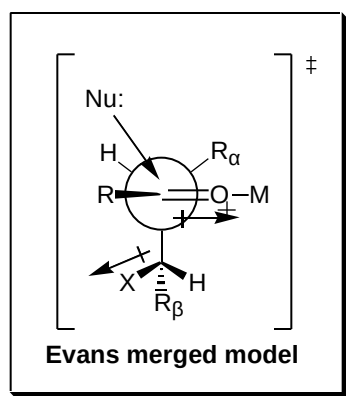
Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, 117, 6619
 Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, 118, 4322

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 ₂ Cl ₂	yield (%)	C : D toluene	yield (%)
<i>t</i> -Bu	96 : 04	89	88 : 12	75
<i>i</i> -Pr	56 : 44	98	32 : 68	86
Me	17 : 83	82	06 : 94	92

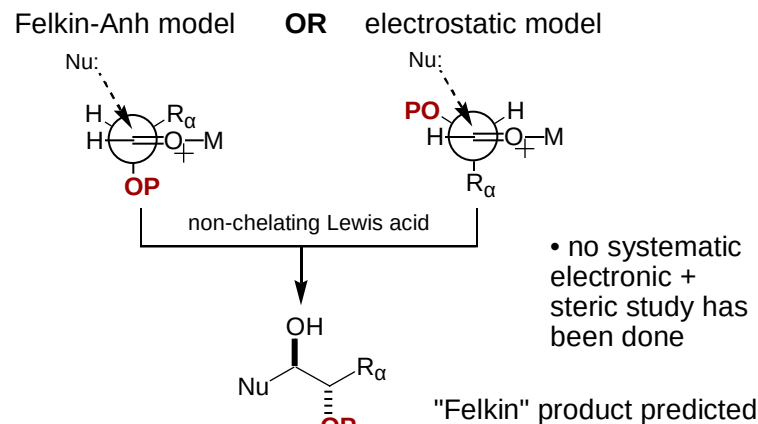


- with a small nucleophile, β -stereocenter becomes the dominant control element

- 1,3-induction is enhanced in nonpolar media

Integration of α - and β -Alkoxy Aldehyde Models in Non-chelating Systems

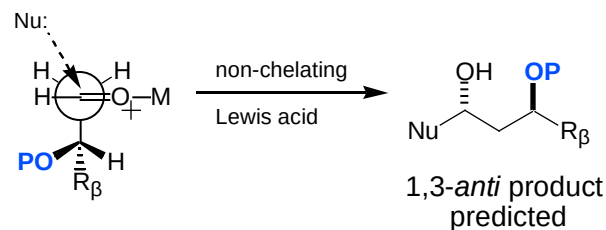
For α -alkoxy aldehydes:



- no systematic electronic + steric study has been done

For β -alkoxy aldehydes:

Evans model

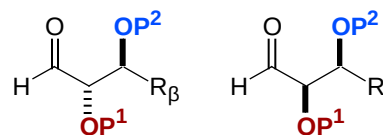


- under non-chelating conditions, 1,3-*anti* selectivity is observed

Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, 35, 8537-8540

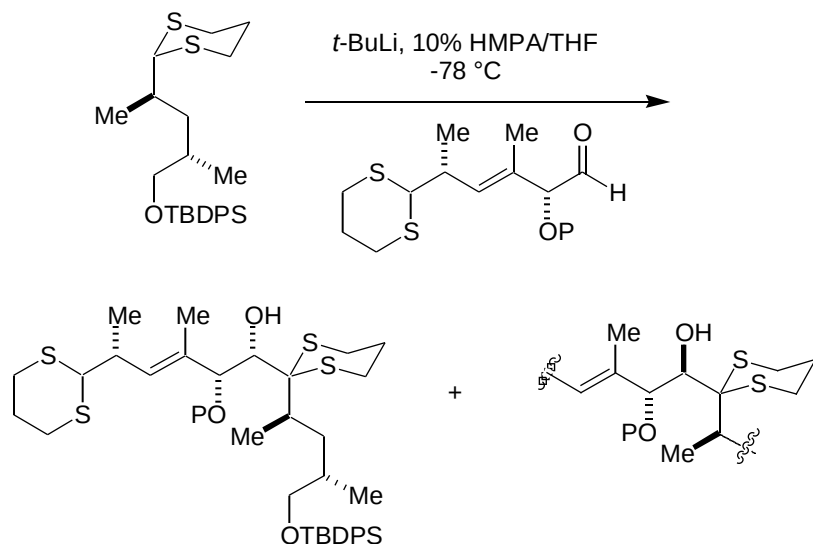
For α,β -bisalkoxy aldehydes:

Which is stereoreinforcing, *anti* or *syn*?

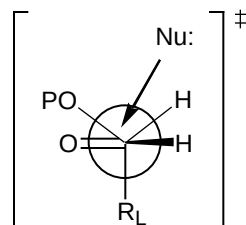


How does the α -alkoxy substituent affect the conformation of the β -stereocenter?

Smith: Rapamycin

A
anti-FelkinB
Felkin

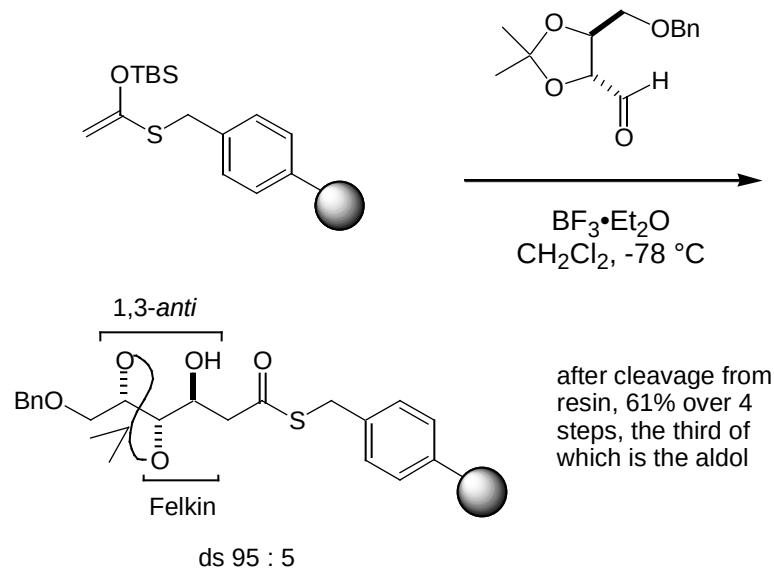
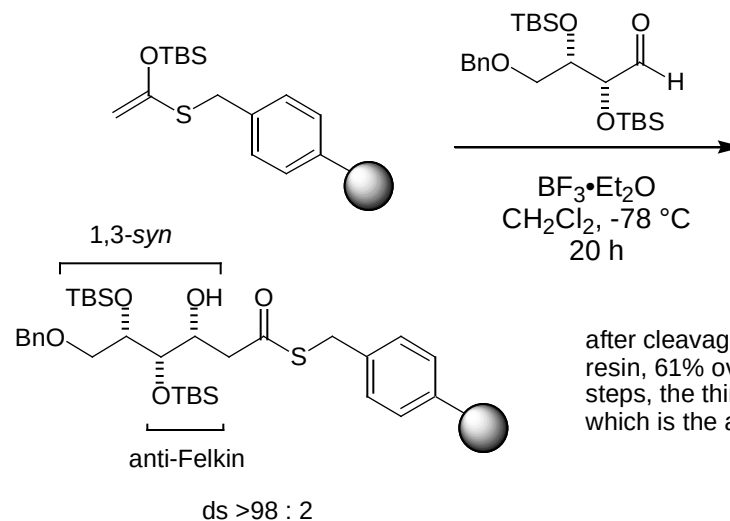
P	A : B	yield (%)
MOM	2 : 1	32
TBS	5 : 1	75
TBDPS	>20 : 1	60



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



Kobayashi, S.; Wakabayashi, T.; Yasuda, M. *J. Org. Chem.* **1998**, *63*, 4868

- 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**)

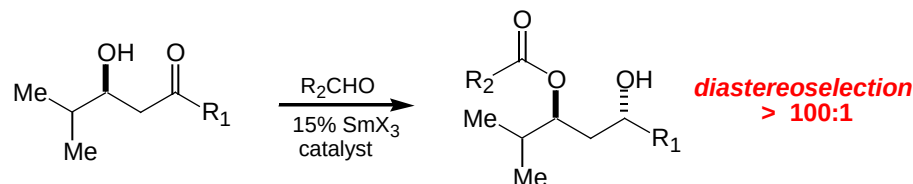
Enantioselective Carbonyl Addition (R_2Zn): Noyori Angew. Chem. Int Ed. **1991**, 30, 49-69 (**handout**)

Matthew D. Shair

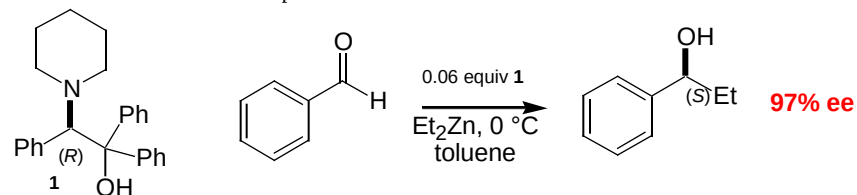
Wednesday,
November 6, 2002

■ Problems:

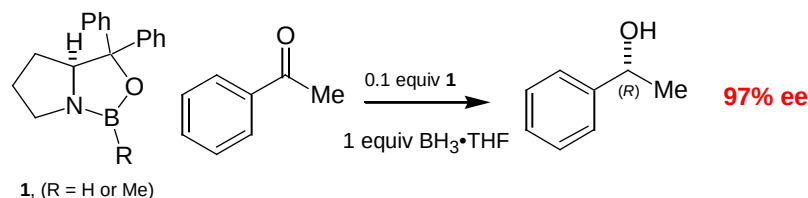
Propose a mechanism for this highly diastereoselective transformation, Evans, Hoveyda JACS **112**, 6447 (1990)



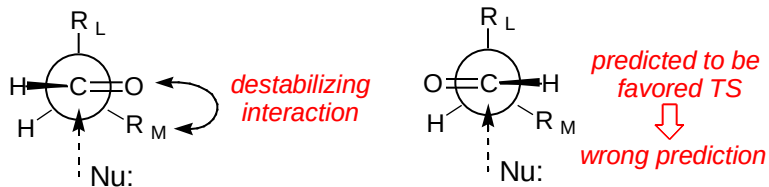
Cume Question, 2000: Chiral amino alcohol **1** efficiently mediates the addition of diethylzinc to aromatic aldehydes. While a number of other amino alcohols are also effective in controlling the absolute course of the addition process, this amino alcohol has been the focus of a recent computational 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.



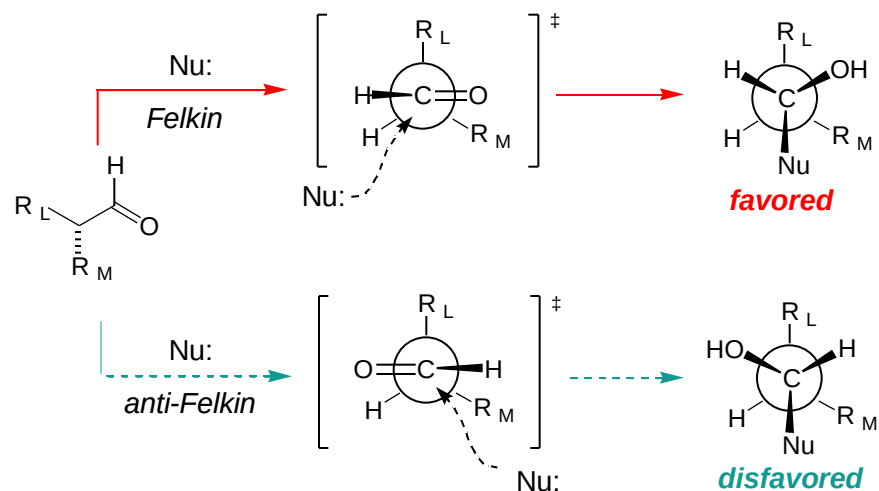
Cume Question, 2000: Corey's introduction of chiral oxazaborolidine catalysts **1** in the borane-mediated enantioselective reduction of ketones represents an important advance in asymmetric synthesis (Corey & Helal, *Angew. Chem. Int. Ed.* **1998**, 37, 1986-2012). Provide a detailed mechanism for the overall transformation. Use 3-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.



The flaw in the Felkin model: A problem with aldehydes!!



Anh & Eisenstein *Nouvea 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 $\pi^*C=O$ will stabilize the transition state.

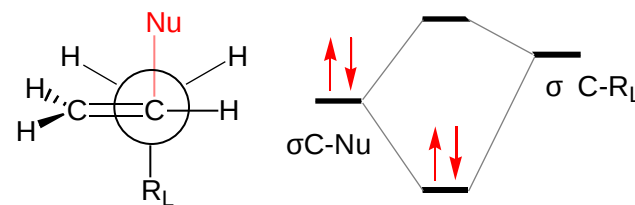
Theoretical Support for Staggered Transition states

Houk, *JACS* **1982**, 104, 7162-6
 Houk, *Science* **1986**, 231, 1108-17

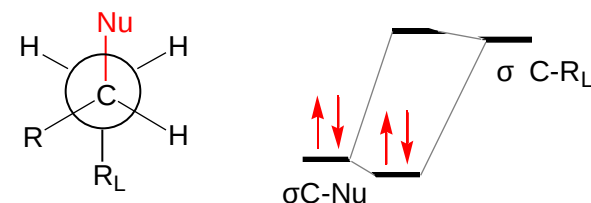
Houk: "Torsional effects in transition states are more important than in ground states"

Review Lecture-7

Transition state

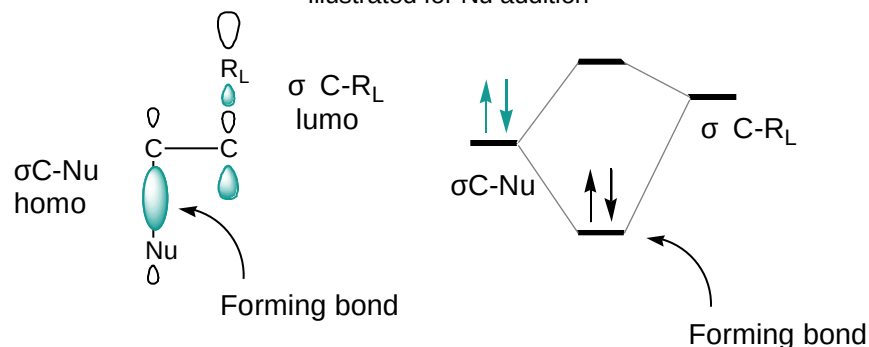


Ground state



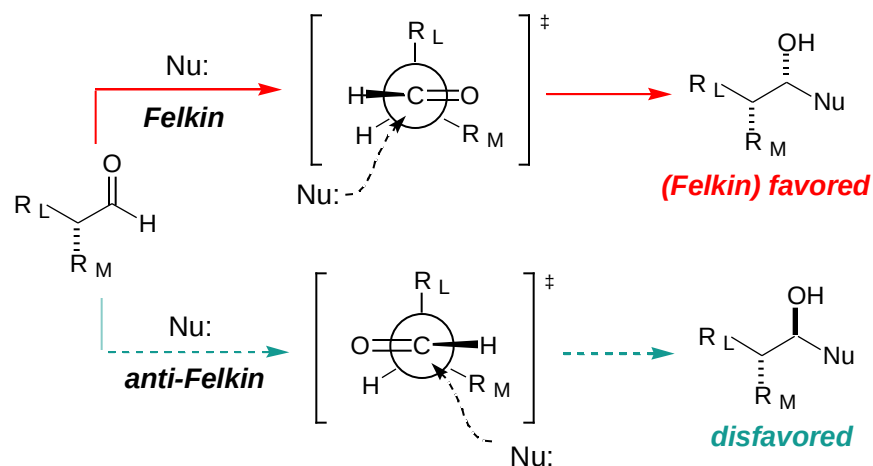
Transition states

H-radical and H-anion: antiperiplanar $\sigma C-R$ orbital stabilized the TS illustrated for Nu addition

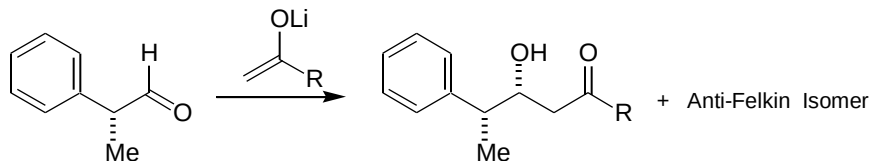


Houk, *Science* **1981**, 231, 1108-1117
 "The Theory and Modeling of Stereoselective Organic Reactions"

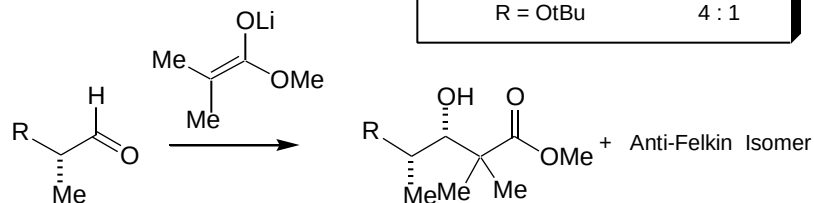
Addition of Enolate & Enol Nucleophiles

**Trend-1:**

For Li enolates, increased steric hindrance at enolate carbon results in enhanced selectivity



L. Flippin & Co-workers,
Tetrahedron Lett. **1985**, 26, 973.

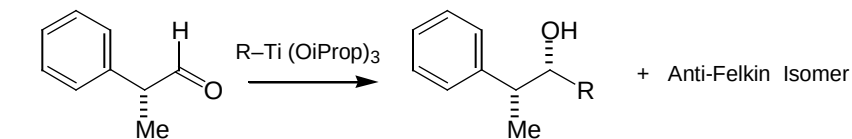
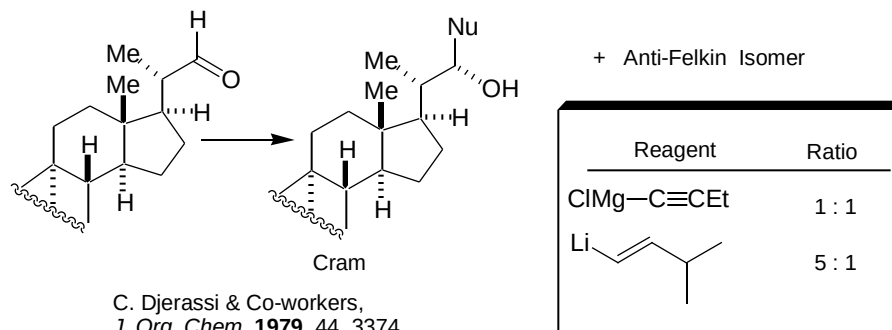


L. Flippin & Co-workers,
Tetrahedron Lett. **1985**, 26, 973.

Enolate (R)	Ratio
R = Me	3 : 1
R = OtBu	4 : 1

Ketone (R)	Ratio
R = Ph	>200 : 1
R = c-C ₆ H ₁₁	9 : 1

■ This trend carries over to organometallic reagents as well



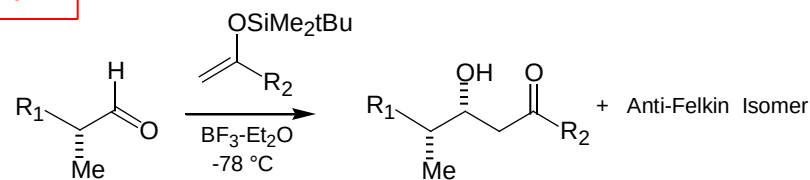
M. Reetz & Co-workers,
Angew Chemie Int. Ed. **1982**, 21, 135.

(R-MgX gives Ca 3:1 ratios)

R-Titanium	Ratio
R = Me	>90 : 10
R = n-Bu	>90 : 10

Trend-2:

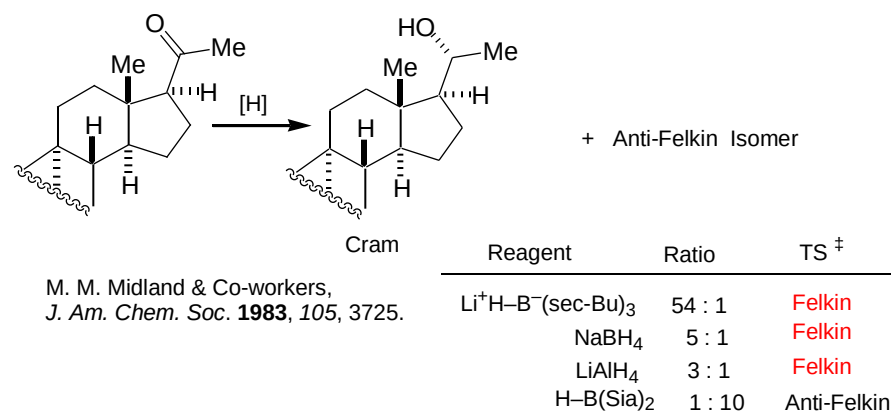
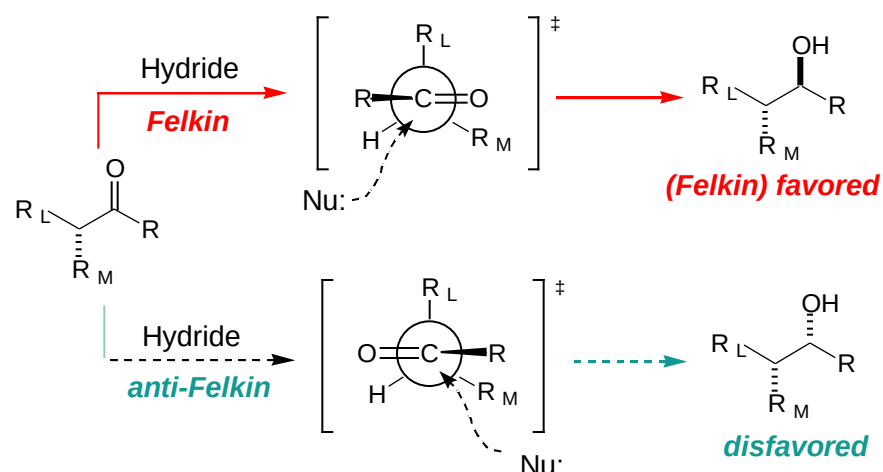
Lewis acid catalyzed rxns are more diastereoselective



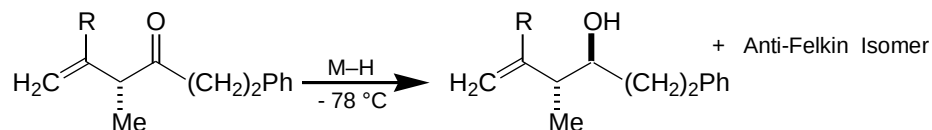
Ketone (R ₁)	Enolate (R ₂)	Ratio	Ratio Li enolate
R = Ph	R = Me	10 : 1	3 : 1
R = Ph	R = t-Bu	24 : 1	
R = Ph	R = OMe	15 : 1	
R = Ph	R = Ot-Bu	36 : 1	4 : 1
R = c-C ₆ H ₁₁	R = Ot-Bu	16 : 1	

C. Heathcock & L. Flippin *J. Am. Chem. Soc.* **1983**, 105, 1667.

Addition of Hydride Nucleophiles

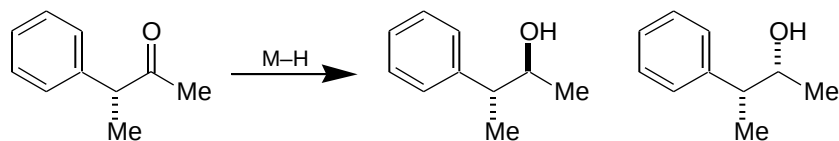


Note: Borane reducing agents do not follow the normal trend



G. Tsuchihashi & Co-workers,
Tetrahedron Lett. **1984**, 25, 2479.

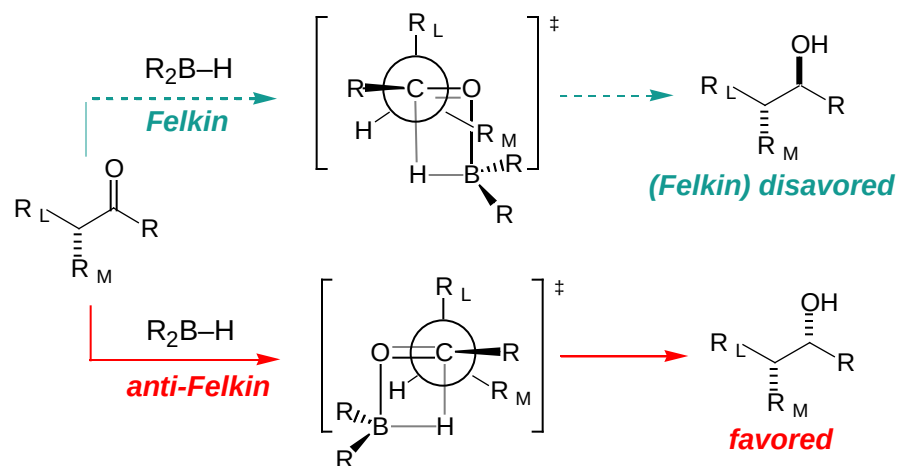
Ketone (R)	Reagent	Ratio
R = H	$\text{Li}^+\text{H}-\text{B}^-(\text{sec-Bu})_3$	96 : 4
R = H	DIBAL	47 : 53
R = Me	$\text{Li}^+\text{H}-\text{B}^-(\text{sec-Bu})_3$	>99 : 1
R = Me	DIBAL	88 : 12



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

Reagent	Ratio	TS ‡
$\text{Li}^+\text{H}-\text{B}^-(\text{sec-Bu})_3$	22 : 1	Felkin
$\text{H}-\text{B}(\text{Sia})_2$	1 : 4	Anti-Felkin

Transition States for C=O-Borane Reductions

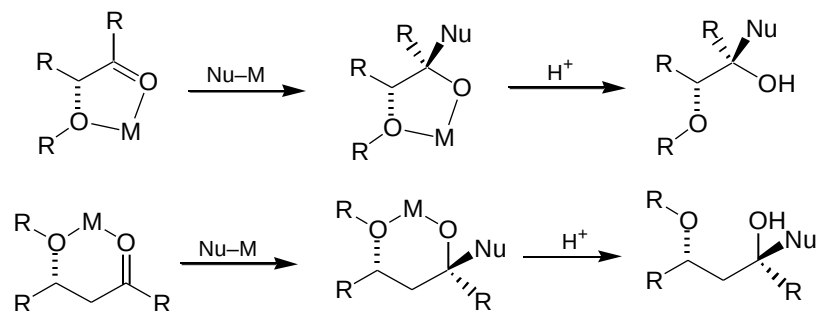


Nonspherical nucleophiles are unreliable in the Felkin Analysis

Exercise: Draw the analogous bis(R_2BH)₂ transition structures

Review hydroboration discussion in Lecture-8

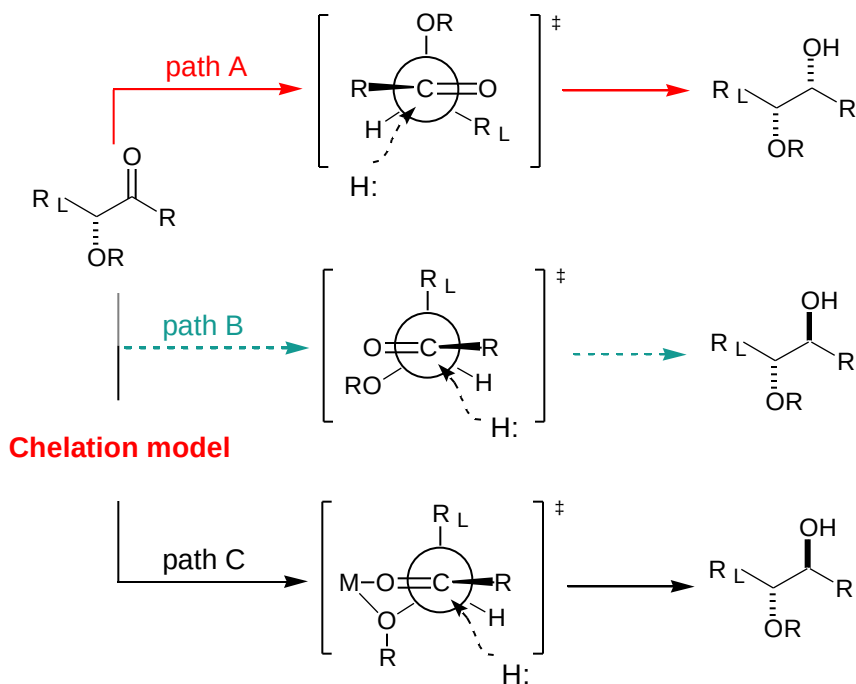
Chelate organization provides a powerful control element in carbonyl addition reactions



Reviews

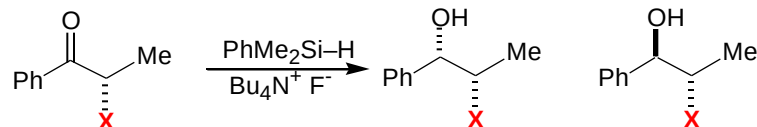
Reetz, *Accts. Chem. Res.* **1993**, 26, 462-468 (pdf)
 Reetz, *Angew. Chem. Int. Ed.* **1984**, 23, 556-569

Lets begin with the hydride reductions of alkoxy ketones



Chelation model

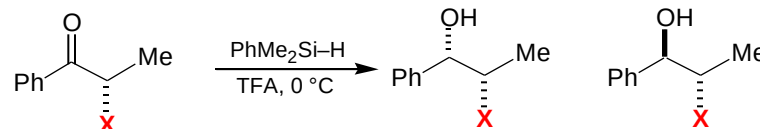
Lets begin with a case where chelation is precluded: (Path A)



Let $R_L = X$
 in the Ahn-Eisenstein model

T. Hiyama & Co-workers,
J. Am. Chem. Soc. **1984**, 106, 4629.

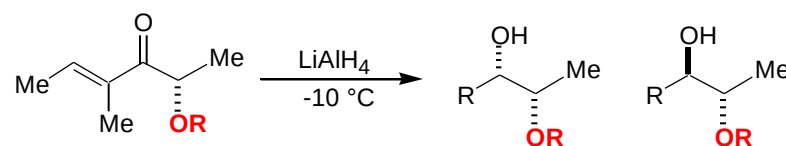
Substituent (X)	Ratio
X = NMe ₂	>99 : 1
X = OAc	95 : 5
X = OCOPh	96 : 4



H-bonding Chelate Model

T. Hiyama & Co-workers,
J. Am. Chem. Soc. **1984**, 106, 4629.

Substituent (X)	Ratio
X = NHCO ₂ Et	<1 : 99
X = OCOPh	7 : 93



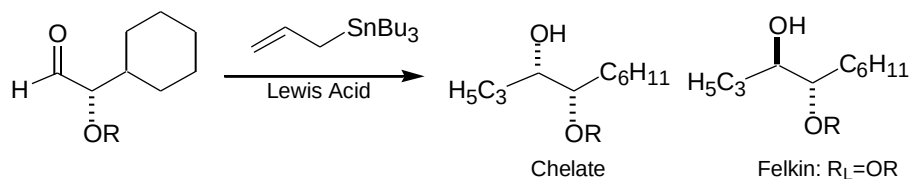
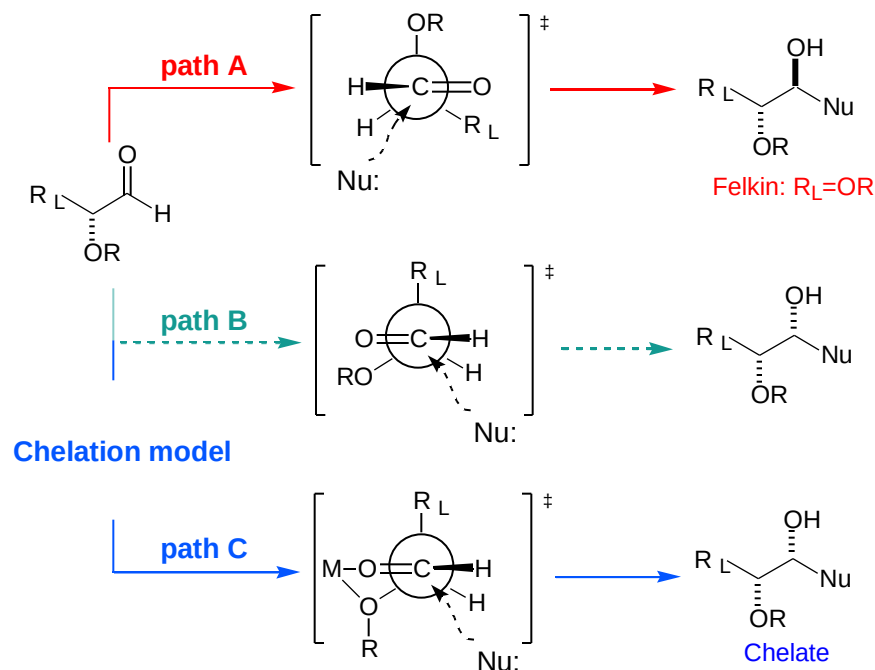
Overman
Tet Lett. **1982**, 23, 2355

(OR)	Solv.	Ratio	Model
R = CH ₂ OBn	THF	30 : 70	Chelate
R = CH ₂ OBn	Et ₂ O	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 SiPh₂(t)Bu group prevents chelation for most Lewis acids. There are dramatic exceptions However:

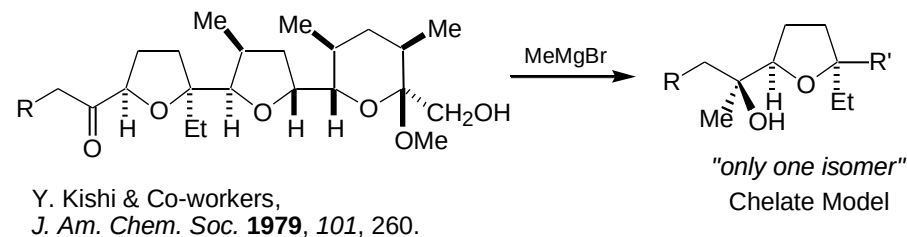
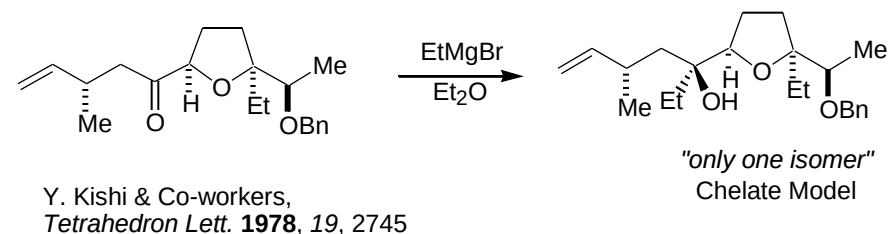
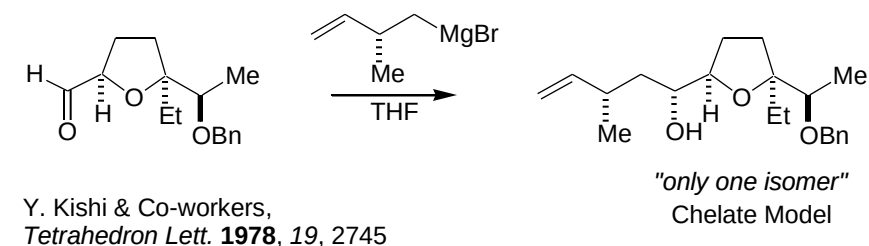
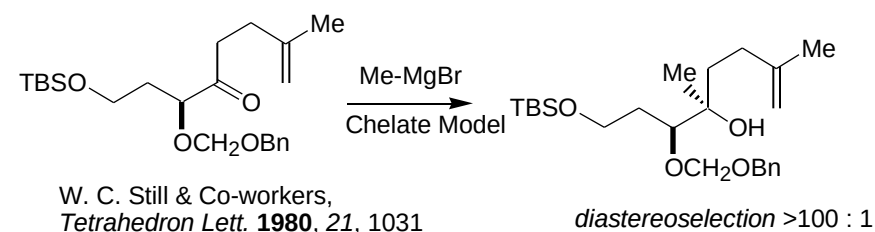
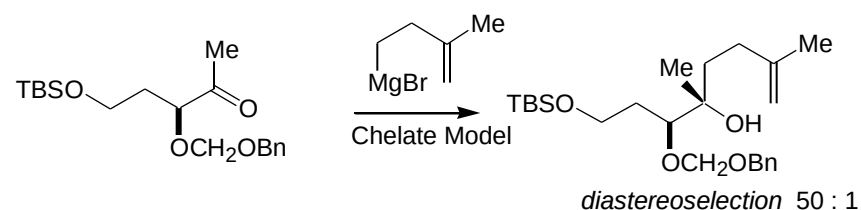
Carbonyl Additon: Chelate Control: Evans *JACS* **2001**, ASAP (handout)

Addition of Carbon Nucleopiles

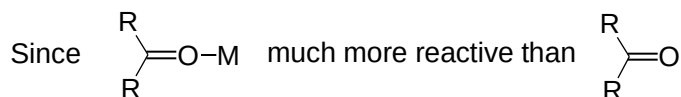


(OR)	Acid	Solv.	Ratio
R = CH ₂ OBn	MgBr ₂	THF (0°)	20 : 80
R = CH ₂ OBn	MgBr ₂	CH ₂ Cl ₂ (-20°)	>99 : 1
R = CH ₂ OBn	TiCl ₄	CH ₂ Cl ₂ (-78°)	>99 : 1
R = SiMe ₂ (t)Bu	BF ₃ -Et ₂ O	CH ₂ Cl ₂ (-78°)	5 : 95

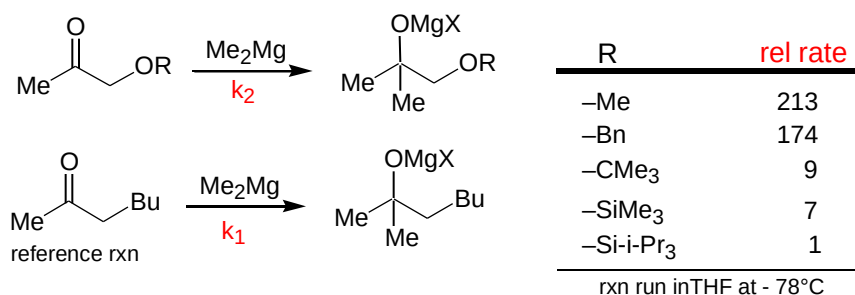
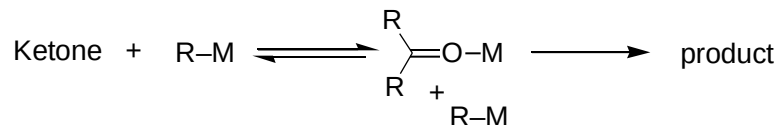
G. Keck & Co-workers, *Tetrahedron Lett.* **1984**, 25, 265



Kinetic Evidence for Chelate-Controlled C=O Addition

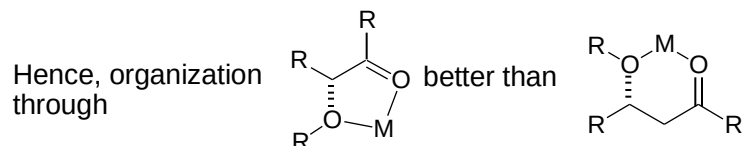
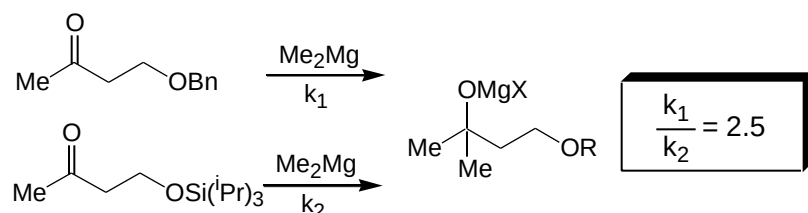


Substrates which can participate in C=O chelation will be more reactive since the effective concentration of chelated intermediate will be higher.

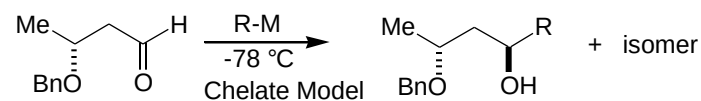
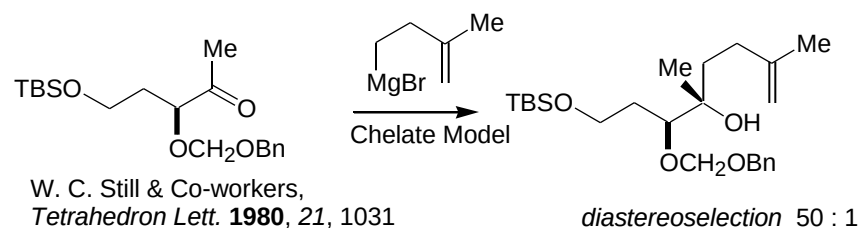


Eliel, Frye, *JACS* **1992**, *114*, 1778-84 (read)

However, these trends are not transmitted strongly to β -chelation



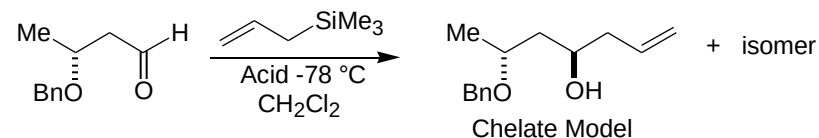
Alpha-Versus Beta-Chelation



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 ₂ Cl ₂	90 : 10



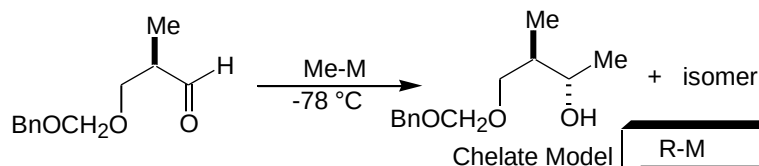
M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, *25*, 729.

Acid	Ratio
TiCl ₄	95 : 5
SnCl ₄	95 : 5
BF ₃ -OEt ₂	85 : 15

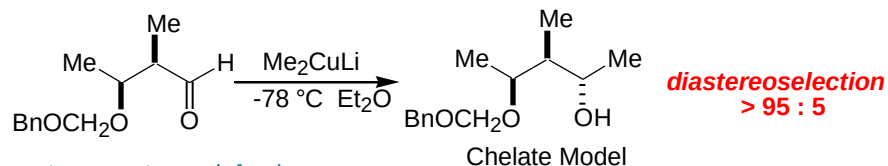
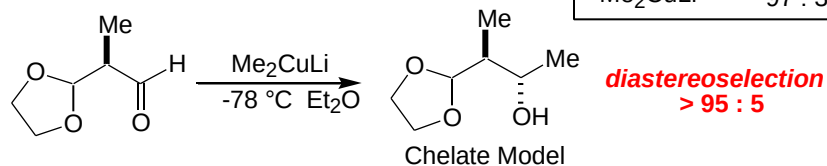
■ Note that beta chelation can be developed as a control element by varying solvent & Nu.

■ Note BF_3 gives "apparent" chelate control

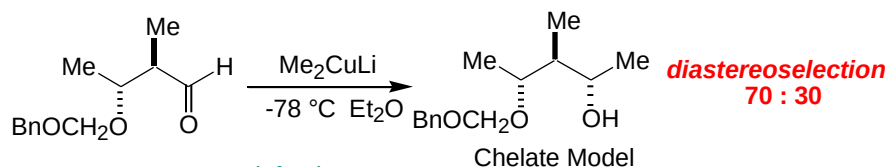
Beta Chelation with Organometals



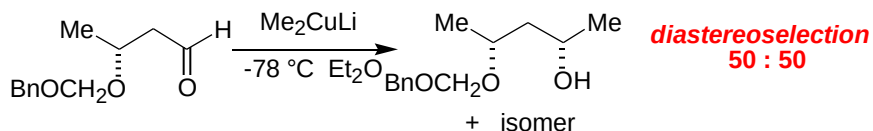
R-M	Ratio
MeMgBr	50 : 50
Me ₂ CuLi	97 : 3



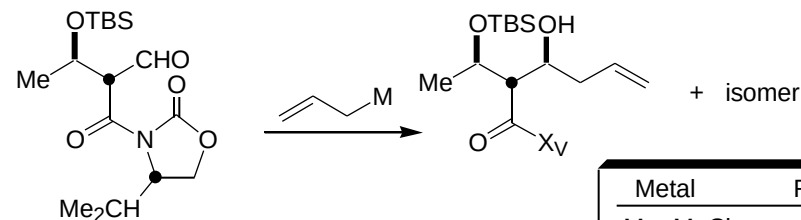
stereocenters reinforcing



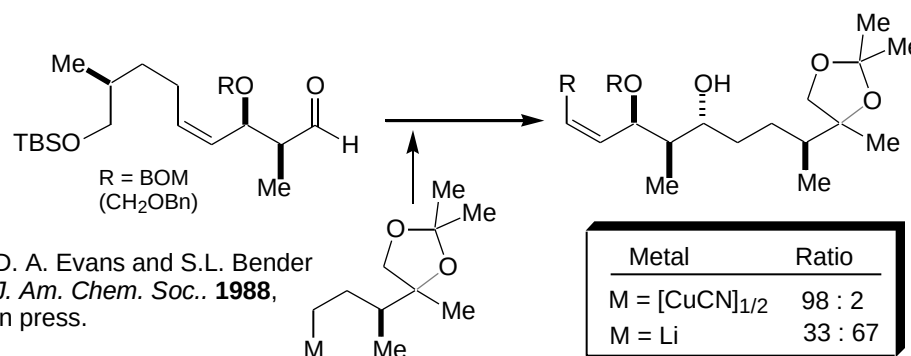
stereocenters non-reinforcing

W.C. Still & Co-workers,
Tetrahedron Lett. **1980**, 21, 1035.

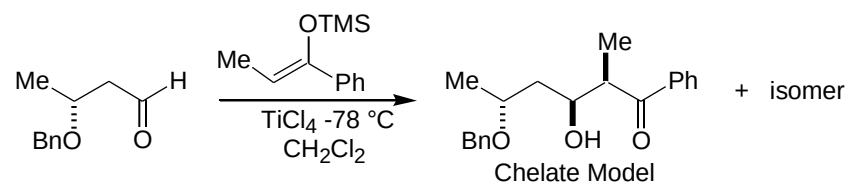
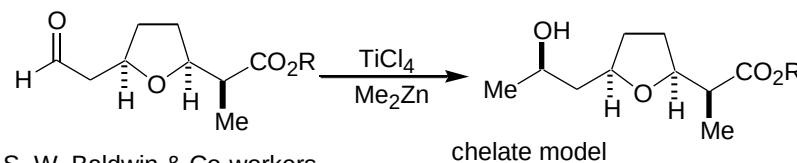
Carbonyl Addition: Chelate Control: Evans JACS 2001, ASAP (handout)

D. A. Evans & E. Sjogren
Tetrahedron Lett. **1986**, 27, 4961.

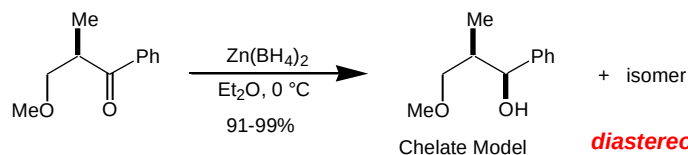
Metal	Ratio
M = MgCl	70 : 30
M = ZnCl	97 : 3

D. A. Evans and S.L. Bender
J. Am. Chem. Soc. **1988**,
in press.

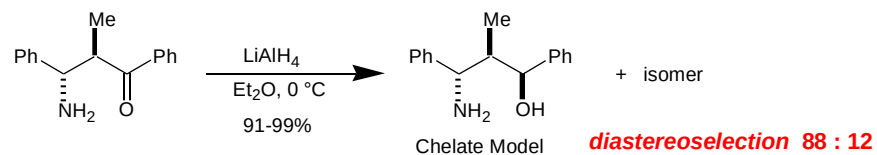
Metal	Ratio
M = [CuCN] _{1/2}	98 : 2
M = Li	33 : 67

M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, 25, 729.**diastereoselection >92 %**S. W. Baldwin & Co-workers
J. Org. Chem. **1987**, 52, 320.**diastereoselection 96 : 4**

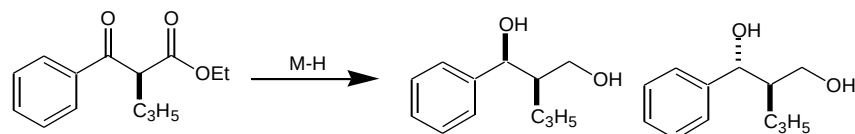
Beta Chelate-Controlled Reduction



T. Oishi & Co-workers
Chem. Pharm. Bull. **1984**, 32, 1411.

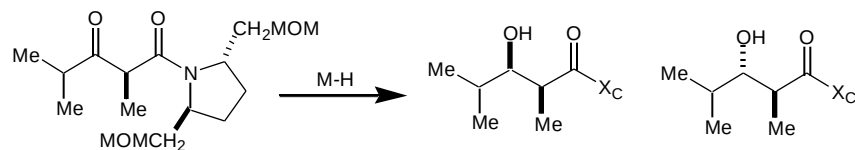


J. Barluenga & Co-workers
J. Org. Chem. **1985**, 50, 4052.



G. R. Brown & Co-workers
Chem. Commun. **1985**, 455.

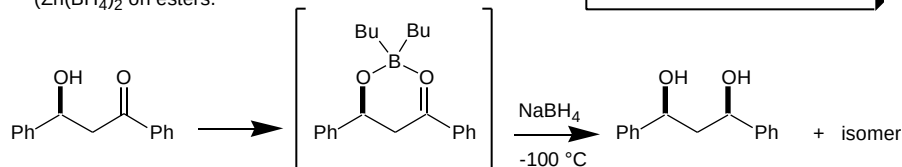
M-H	Ratio
Zn(BH ₄) ₂ Et ₂ O	100 : 0
LiAlH ₄ THF	0 : 100



M. Yamaguchi & Co-workers
Tetrahedron Lett. **1985**, 26, 4643.

T. Oishi & Co-workers
Tetrahedron Lett. **1980**, 21, 1641
(Zn(BH₄)₂ on esters.)

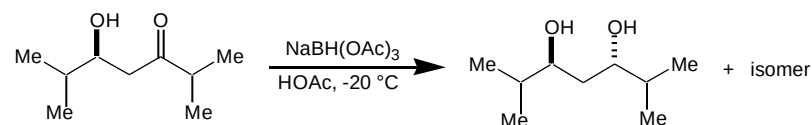
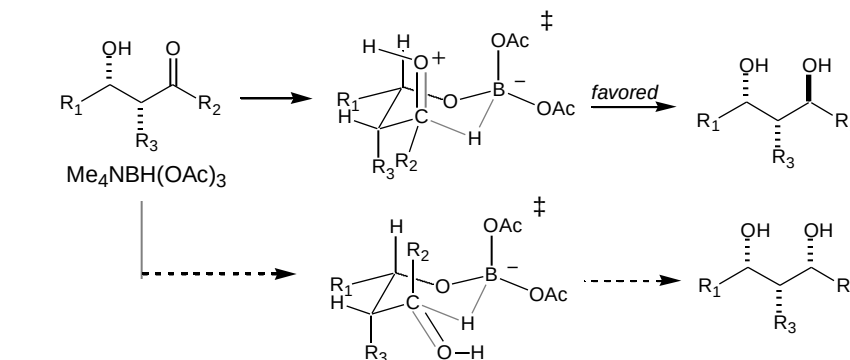
M-H	Ratio
Zn(BH ₄) ₂ Et ₂ O	100 : 0
KBH ₃ H THF	0 : 100



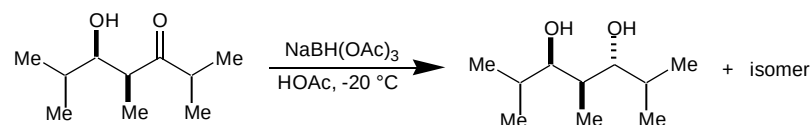
K. Narasaka & Co-workers
Chem. Lett. **1980**, 1415.

Directed reductions of β-hydroxyketones

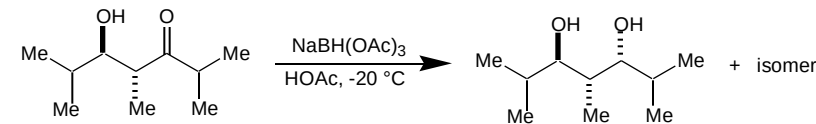
Evans, Chapman, Carreira, *JACS* **110**, 3560 (1988)



diastereoselection 96 : 4

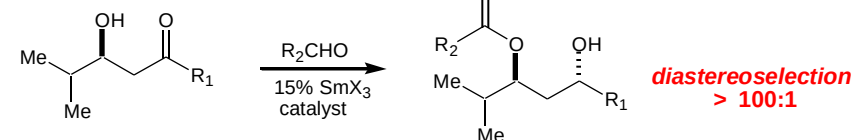


diastereoselection 98 : 2

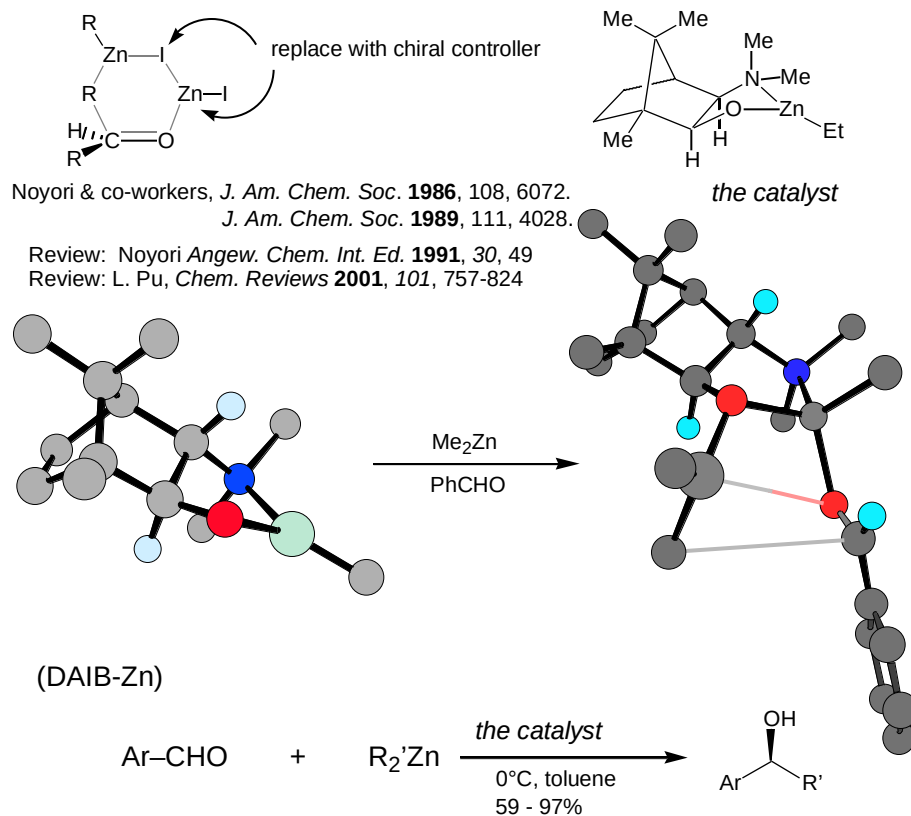


diastereoselection 98 : 2

Propose a mechanism for this highly diastereoselective transformation,
Evans, Hoveyda *JACS* **112**, 6447 (1990)



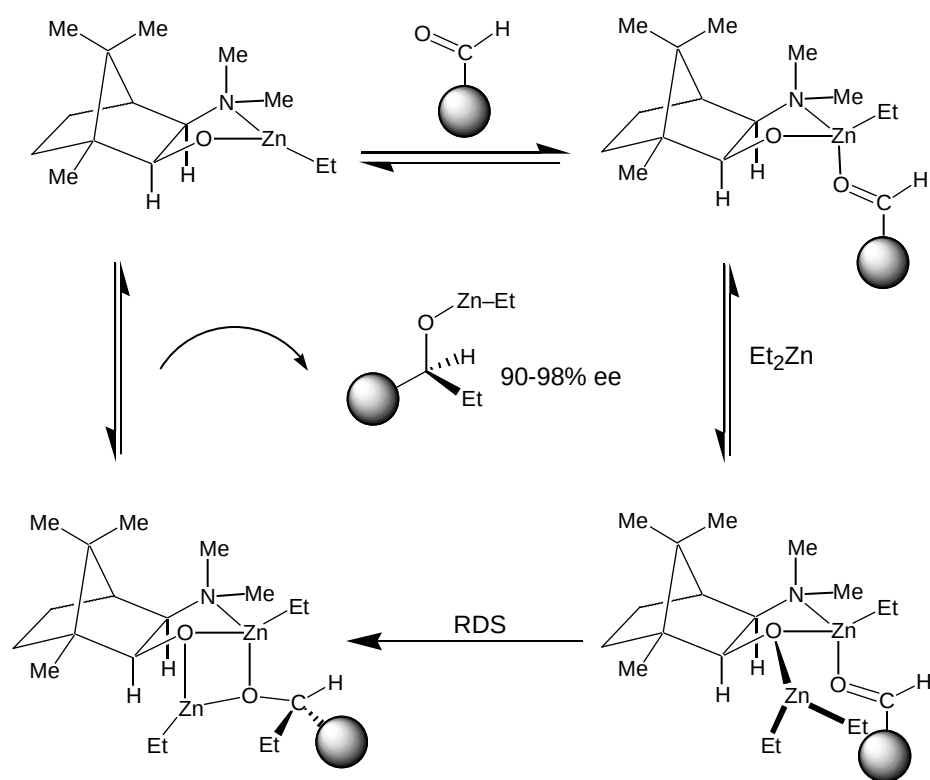
Catalytic Asymmetric Carbonyl Addition



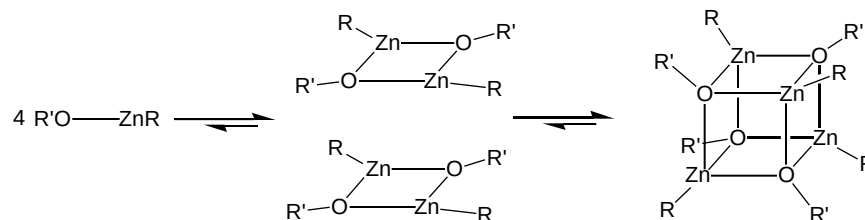
C ₆ H ₅ CHO	Et ₂ Zn	98% e.e.
"	Me ₂ Zn	91% e.e.
p-ClC ₆ H ₄ CHO	Et ₂ Zn	93% e.e.
p-MeOC ₆ H ₄ CHO	Et ₂ Zn	93% e.e.
Cinnamyl	Et ₂ Zn	96% e.e.
PhCH ₂ CH ₂ CHO	Et ₂ Zn	90% e.e.
n-C ₆ H ₁₃ CHO	Et ₂ Zn	61% e.e.

- 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

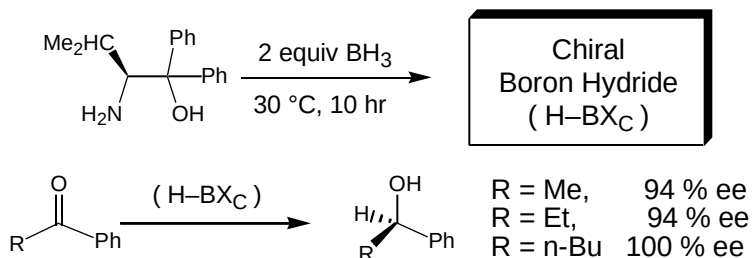


■ Product is taken out of the picture by aggregation

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

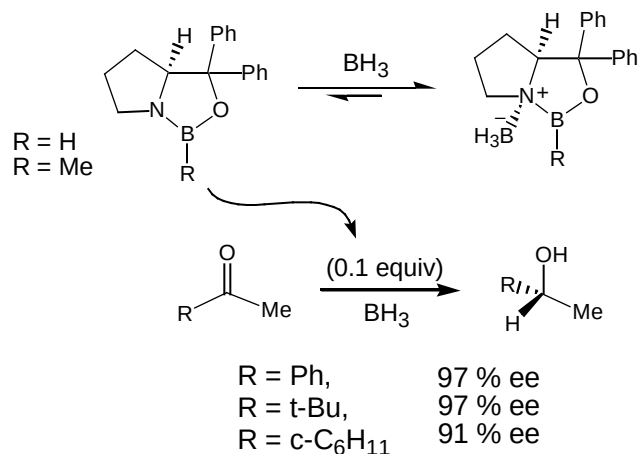


Itsuno, *Chem. Commun.* **1983**, 469

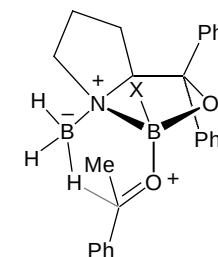
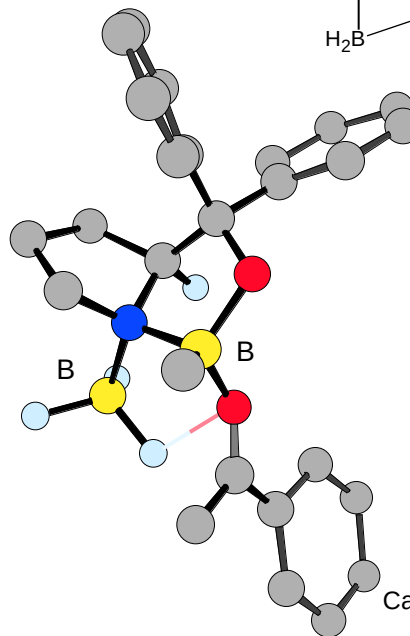
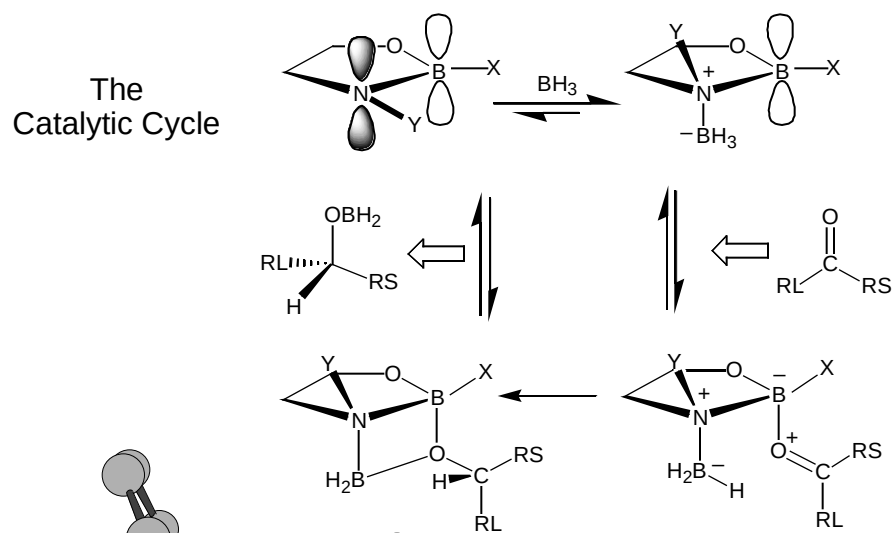
Itsuno, *J. Org. Chem.* **1984**, 49, 555

Itsuno, *J. Chem. Soc. Perkin Trans I.* **1985**, 2615

■ The Catalytic Process: Corey, 1987



But how does it really work ?



Corey, *JACS* **1987**, 109, 5551

Corey, *JACS* **1987**, 109, 7925

Corey, *JOC* **1988**, 53, 2861

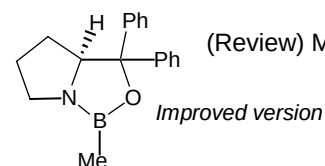
Catalyst X-ray, Corey, *Tet. Let* **1992**, 33, 3429

Mathre, *JOC* **1993**, 58, 2880

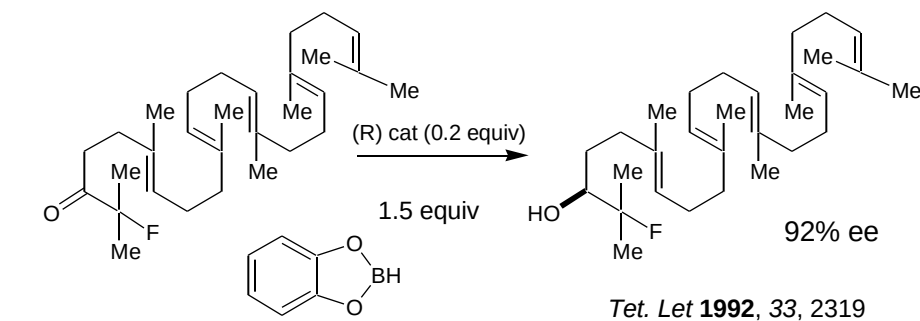
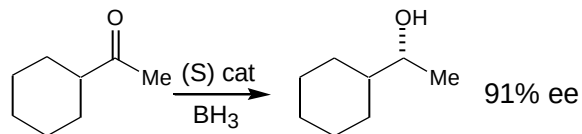
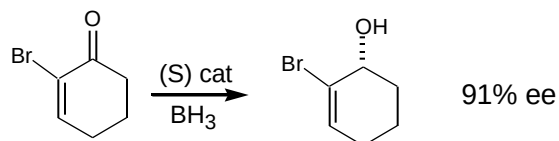
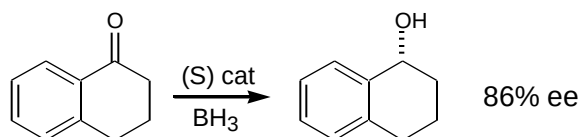
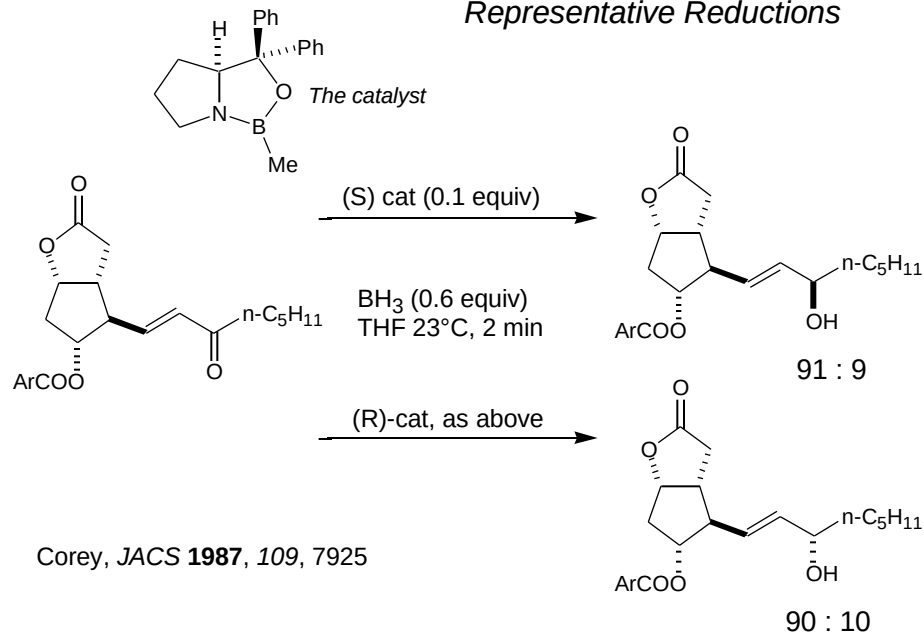
catalyst prep: Mathre, *JOC* **1993**, 58, 799

Mathre, *JOC* **1991**, 56, 751

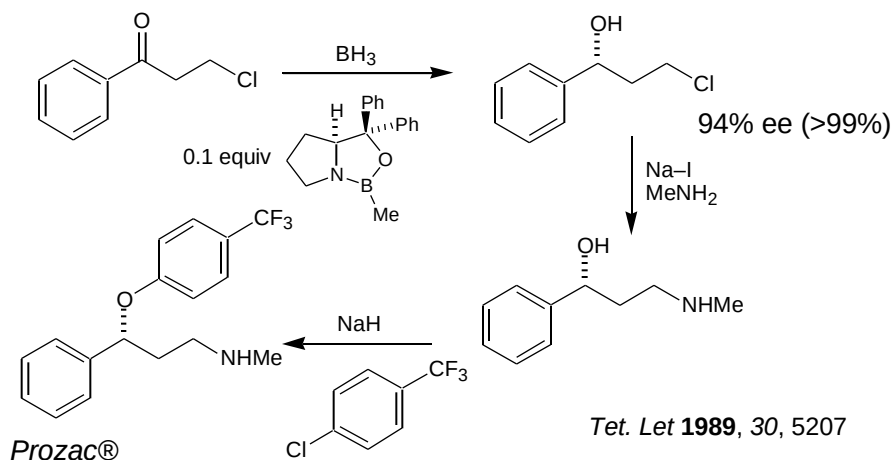
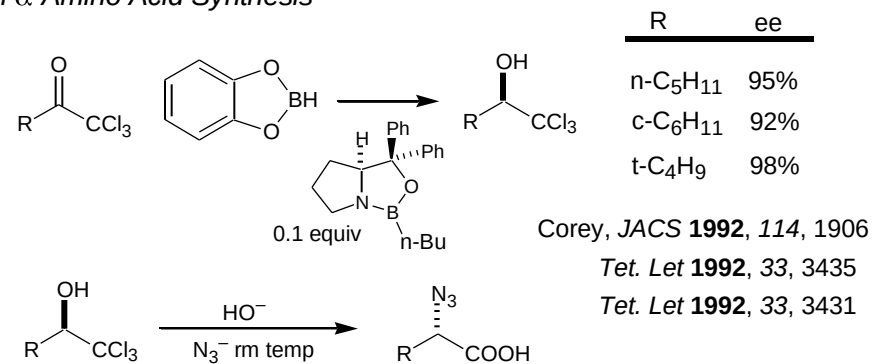
(Review) Martens, *Tetrahedron Asymmetry* **1992**, 3, 1475



Representative Reductions



Fluoxetine (Prozac®) Synthesis

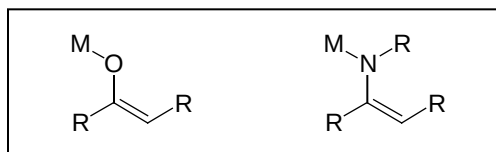
An α -Amino Acid Synthesis

<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).

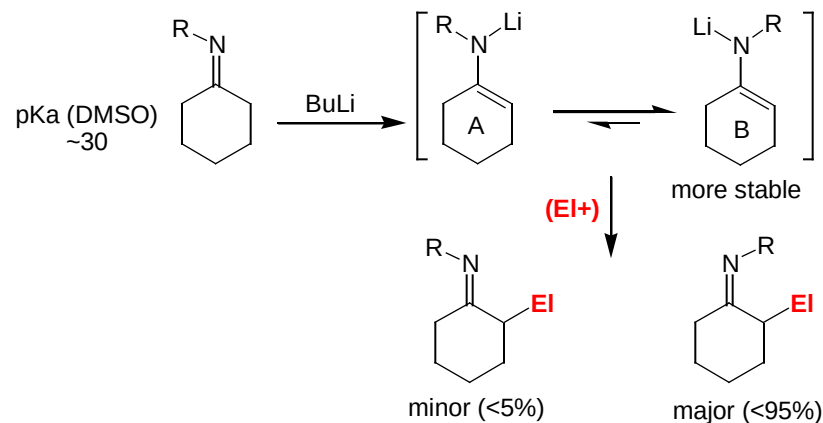
The Reactions of Dianions of Carboxylic Acids and Ester Enolates". N. Petragnani and M. Yonashiro *Synthesis*, 521 (1982).

"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".

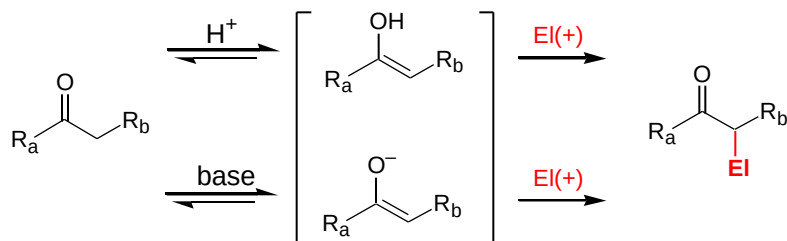
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983).

"Stereoselective Alkylation Reactions of Chiral Metal Enolates". D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984).

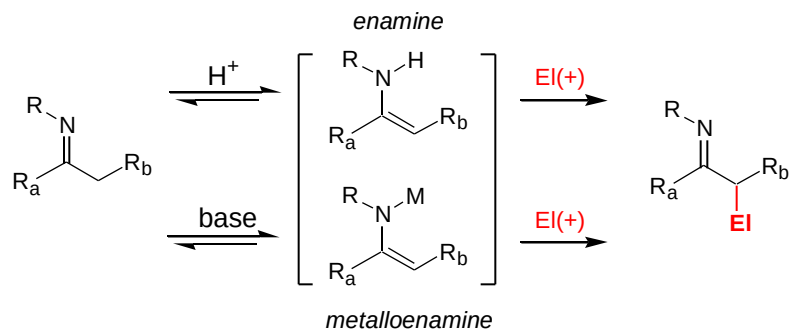
"Generation of Simple Enols in Solution". B. Capon, B.-Z. Guo, F. C. Kwok, A. K. Siddhanta, and C. Zucco *Acc. Chem. Res.* **21**, 121 (1988).

"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.



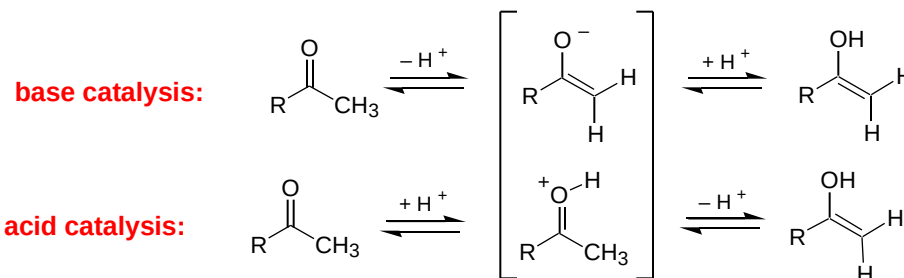
Enamines & metalloenamines, their nitrogen counterparts, are equally important.



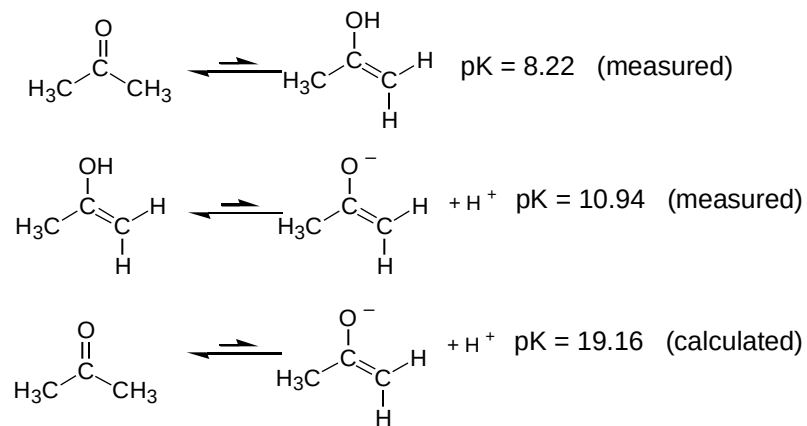
Tautomers: Structural isomers generated as a consequence of the 1,3-shift of a proton adjacent to a X=Y bond. for example:



Keto-Enol Tautomers: Tautomerism may be catalyzed by either acids or bases:



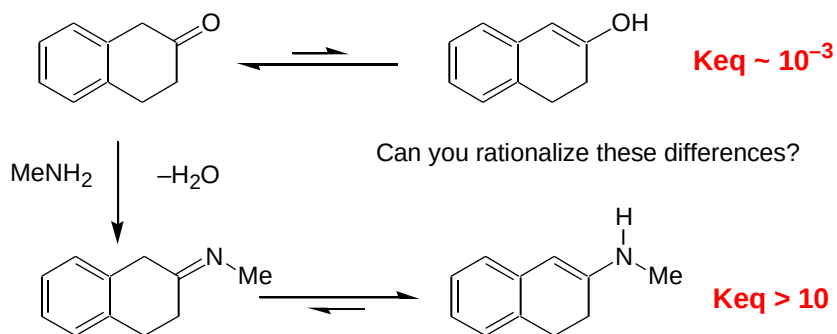
Acidity of Keto and Enol Tautomers: Consider Acetone:



Kresge, *JACS* **1984**, *106*, 460

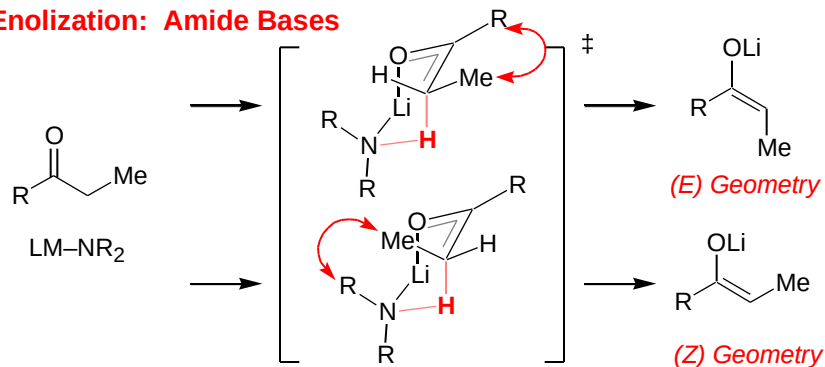
On the origin of the acidity of enols: Wiberg, *JACS* **1996**, *118*, 8291-8299

Tautomeric Equilibria: Ketones vs. Imines



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



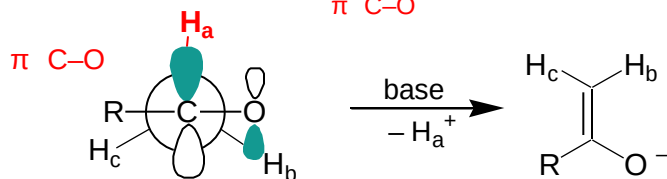
The Ireland Model (*J. Am. Chem. Soc.* **1976**, 98, 2868)

Narula, *Tetrahedron Lett.* **1981**, 22, 4119

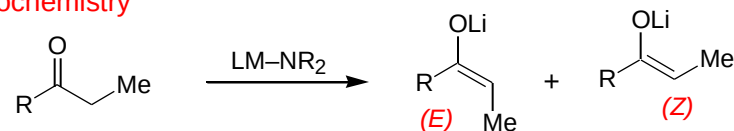
more recent study: Ireland, *JOC* **1991**, 56, 650

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



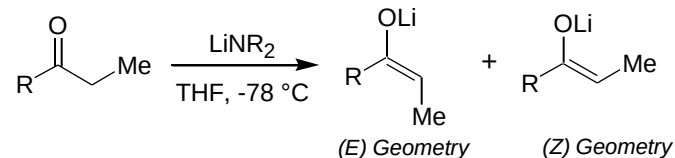
Stereochemistry



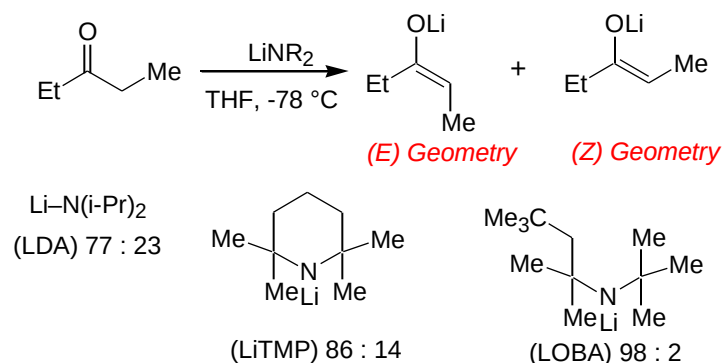
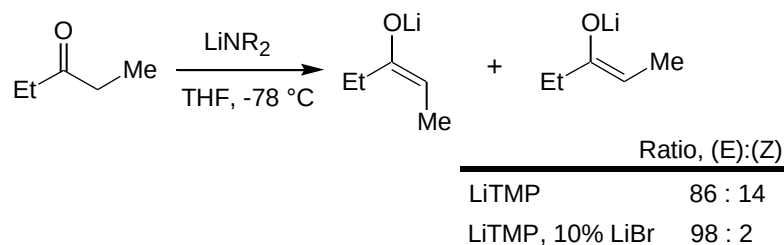
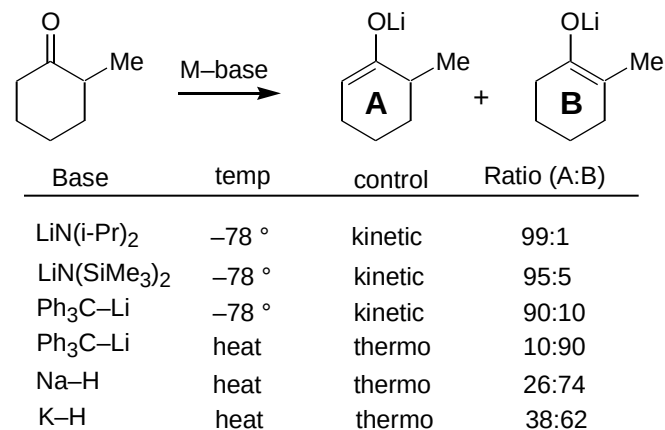
Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe, O-t-Bu	95 : 5
LDA (THF)	-S-t-Bu	95 : 5
LDA (THF)	-Et	77 : 23
LDA (THF)	-CHMe ₂	40 : 60
LDA (THF)	-CMe ₃	0 : 100
LDA (THF)	-C ₆ H ₅	0 : 100
LDA (THF)	-NEt ₂	0 : 100
s-BuLi (THF)	-NEt ₂	25 : 75

Solvent

Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe	95 : 5
LDA (THF, HMPA)	-OMe	16 : 84

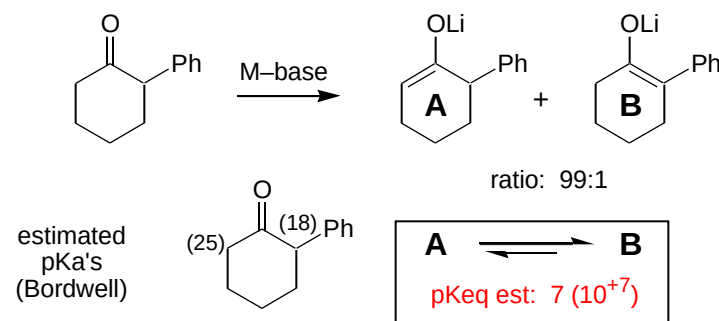
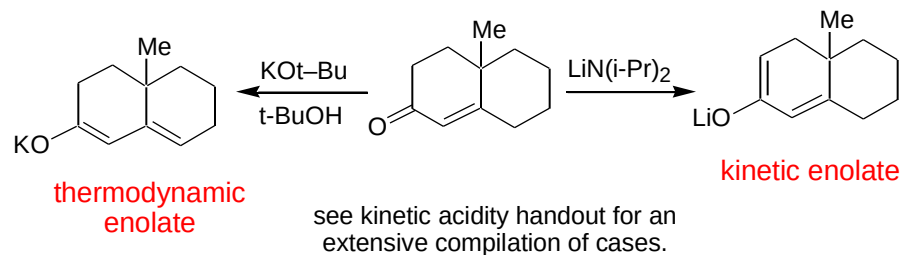
Base Structure Masamune (*J. Am. Chem. Soc.* **1982**, 104, 5526)

Base	R = Et, (E):(Z)	R = Cy, (E):(Z)
Li-N(i-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 ₂ Ph) ₂	0 : 100	0 : 100
at equilibrium	16 : 84	—

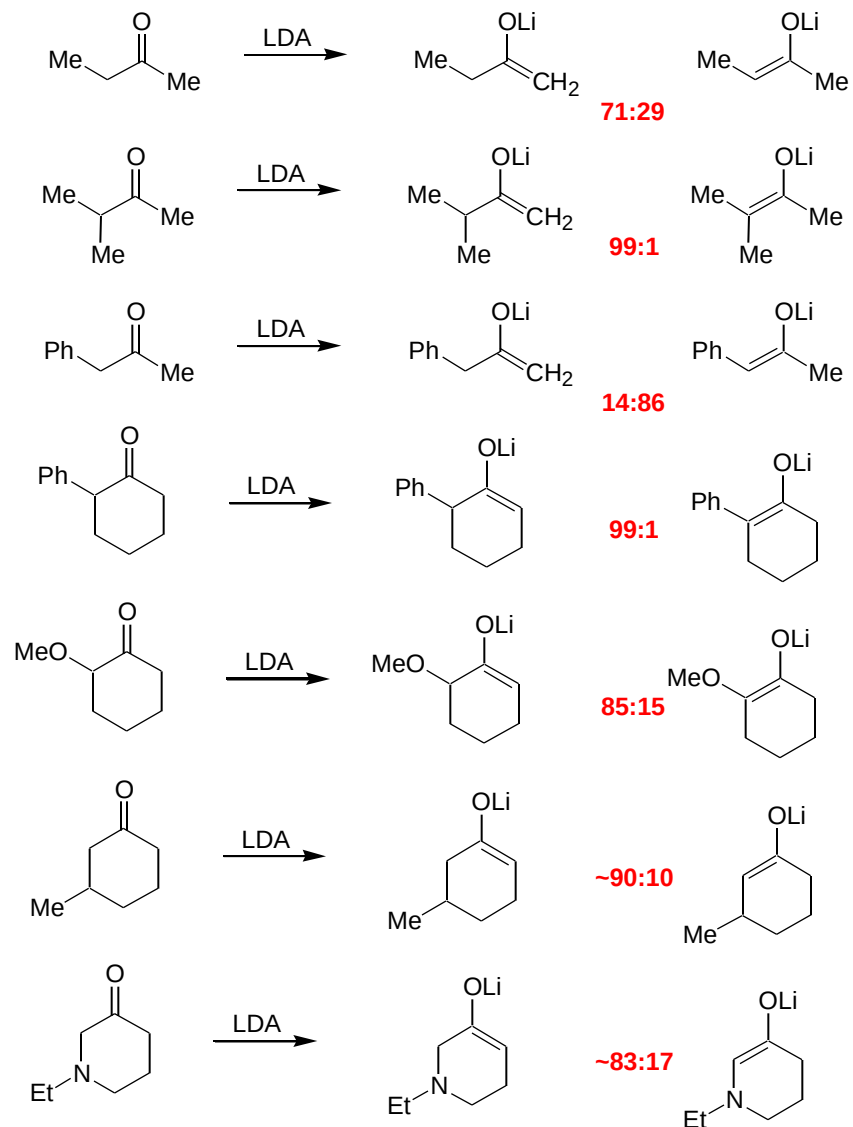
Base Structure Corey & Co-workers, *Tetrahedron Lett.* **1984**, 25, 491, 495
Lithium Halide Effects Collum (*J. Am. Chem. Soc.* **1991**, 113, 9572)
 Collum (*J. Am. Chem. Soc.* **1991**, 113, 9575)
 Collum (*J. Am. Chem. Soc.* **1991**, 113, 5053)

 For the latest in the series of Collum papers see: *JACS* **2000**, 122, 2452-2458
Regioselective Enolization

A: Alkyl groups stabilize metal enolate

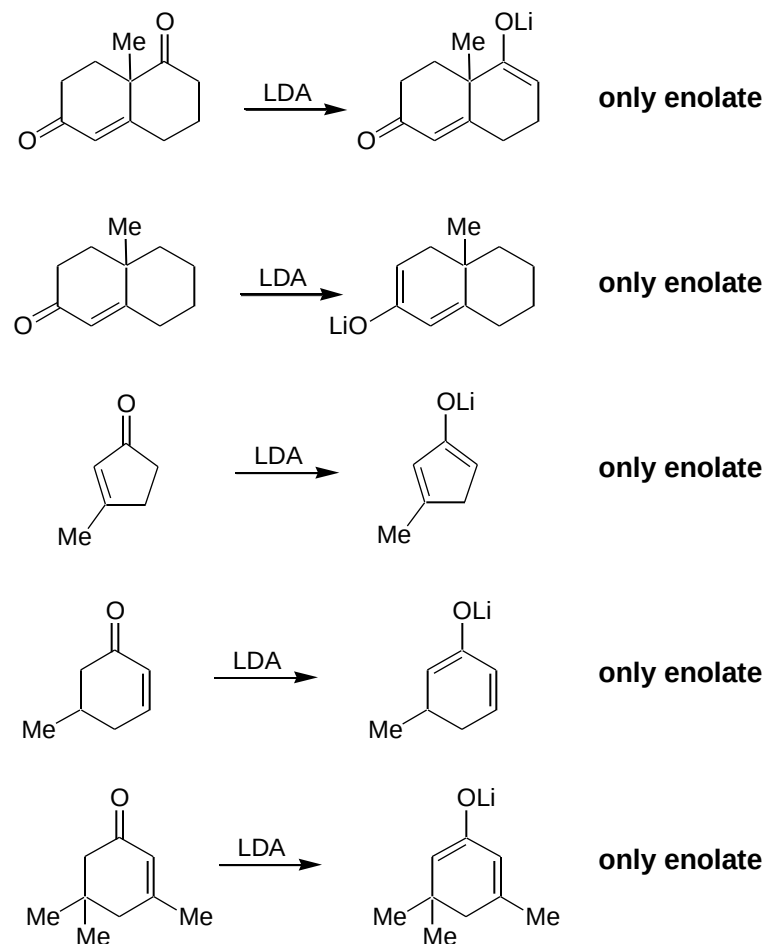
A: As M-O bond becomes more ionic A is attenuated

Kinetic Selection sensitive to structure**Unsaturated Ketones**

Kinetic Selection sensitive to structure

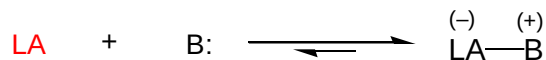


Kinetic Selection in Enolization of Unsaturated Ketones

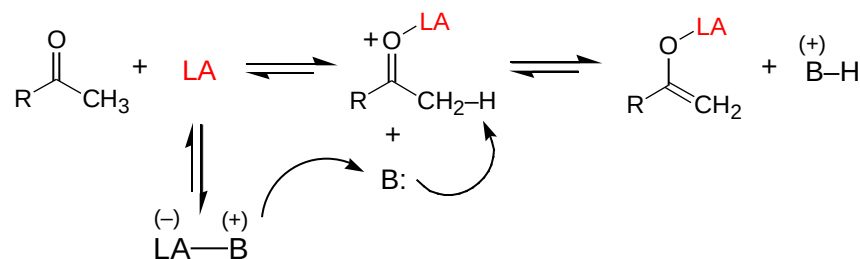


Strategy

Choose Lewis Acid (LA) which can reversibly associate with amine base (B:).



This system has the potential to enolize carbonyl functional groups:



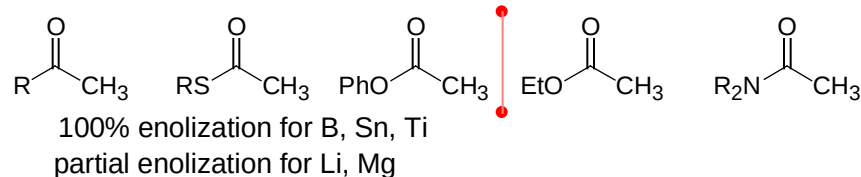
Useful Lewis Acid Pairs

Complexation

-OTf = -OSO₂CF₃

MgBr ₂ + NEt ₃	Reversible	
Li-X + NR ₃	Reversible	
Sn(OTf) ₂ + NR ₃	Reversible (Et ₃ N, EtNi-Pr ₂)	
R ₂ B-OTf + NR ₃	Reversible (Et ₃ N, EtNi-Pr ₂)	
R ₂ BCl + NR ₃	Reversible (Et ₃ N, EtNi-Pr ₂)	
PhBCl ₂ + NR ₃	Reversible (Et ₃ N, EtNi-Pr ₂)	
TiCl ₄ + NR ₃	Irreversible (Et ₃ N, EtNi-Pr ₂)	
i-PrOTiCl ₃ + NR ₃	Reversible (Et ₃ N, EtNi-Pr ₂)	
(i-PrO) ₂ TiCl ₂ + NR ₃	Reversible (Et ₃ N, EtNi-Pr ₂)	
(i-PrO) ₃ TiCl + NR ₃	Reversible (Et ₃ N, EtNi-Pr ₂)	

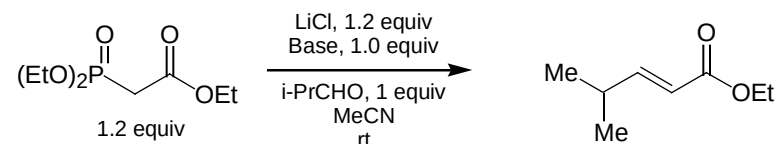
All of the above systems will enolize simple ketones to some extent.



Lithium Enolates

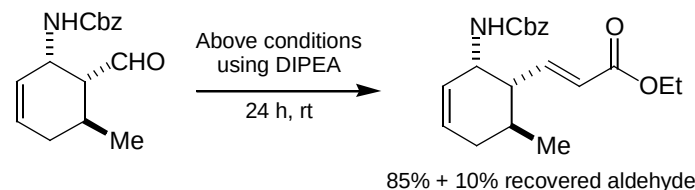
Roush & Masamune, Tet. Lett. 1984, 25, 2183-2186

Horner-Wadsworth-Emmons Reaction.



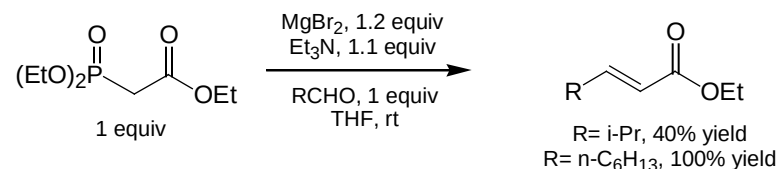
pKa 19.2 (DMSO), K⁺ counterion
pKa 12.2 (Diglyme), Li⁺ counterion

Base = DBU, 5 min, 99%, >50:1 E:Z
Base = DIPEA, 7 h, 97%, >50:1 E:Z



Conventional methods of deprotonation (NaH) resulted in epimerization (Overman JACS **1978**, 5179).

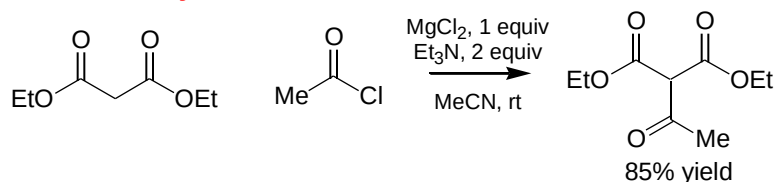
Rathke, Nowak J. Org. Chem. **1985**, 50, 2624-2626.



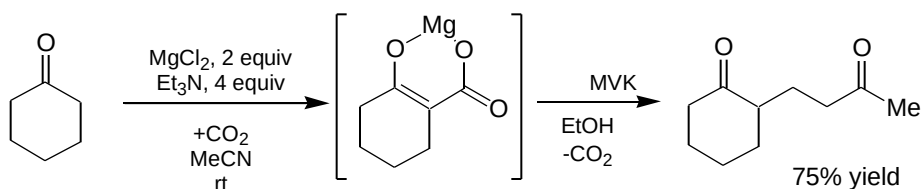
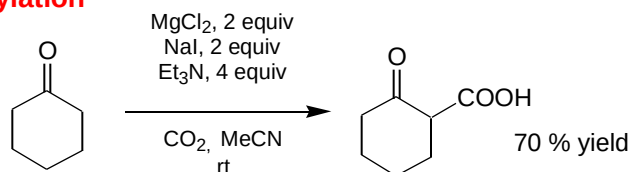
Magnesium Enolates

Rathke *J. Org. Chem.* **1985**, 50, 2622-2624.
J. Org. Chem. **1985**, 50, 4877-4879.
Syn. Comm. **1986**, 16, 1133-1139.

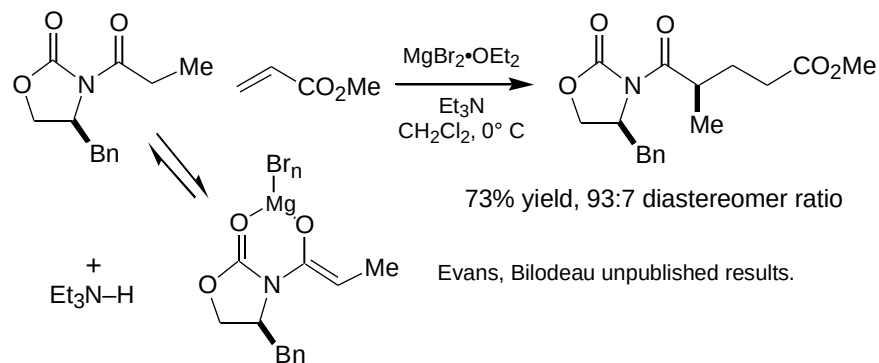
Diethylmalonate acylations



Ketone Carboxylation



Michael reaction

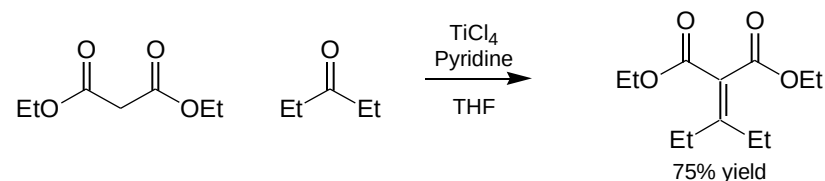


Deuterium quench indicates 25% enolization of *N*-propionyloxazolidinone

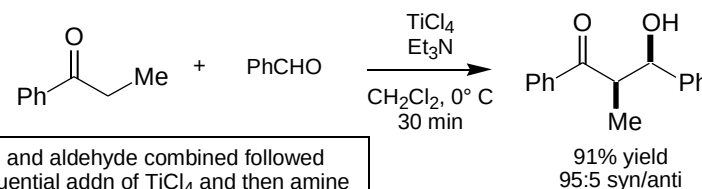
Titanium Enolates

The Early Literature

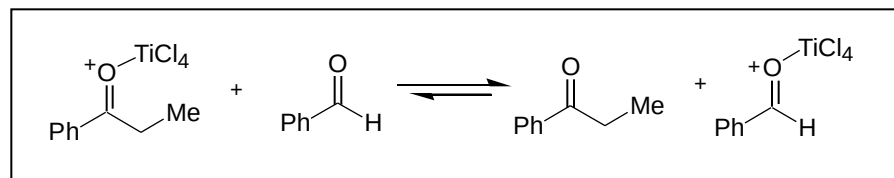
Lehnert, W. *Tetrahedron Lett.* **1970**, 4723-4724.



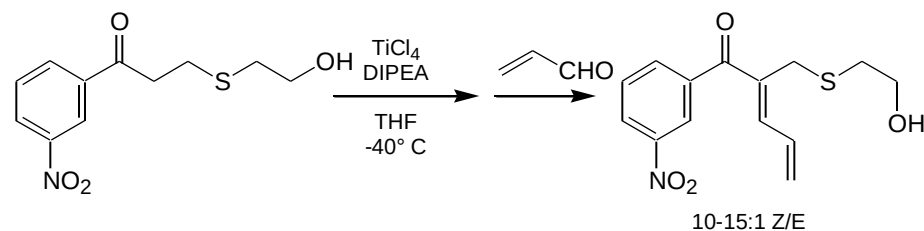
Harrison, C. R. *Tetrahedron Lett.* **1987**, 28, 4135-4138.



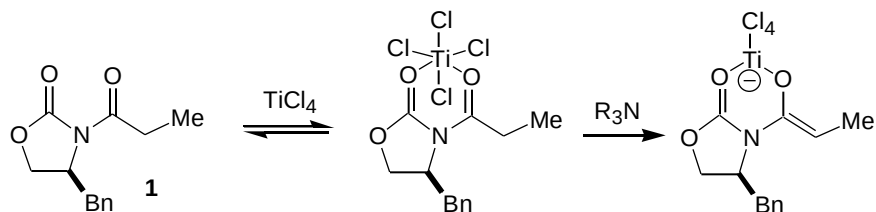
Ketone and aldehyde combined followed by sequential addn of TiCl₄ and then amine



Brocchini, Eberle, Lawton *J. Am. Chem. Soc.* **1988**, 110, 5211-5212.



Titanium Enolates



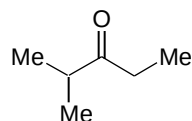
- Enolization process not responsive to tertiary amine structure
- DIPEA, Et₃N, N-Ethylpiperidine all suitable bases.
- DBU and tetramethylguanidine do not provide enolate.
- CH₂Cl₂ is the only suitable solvent for these enolizations.

N-Propionyloxazolidone (1)

Lewis Acid	% Enolization
TiCl ₄	100
<i>i</i> -PrOTiCl ₃	100
TiCl ₄ •2THF	80
(<i>i</i> -PrO) ₂ TiCl ₂	70
(<i>i</i> -PrO) ₃ TiCl	~10

Ethylisopropylketone

Lewis Acid	% Enolization
TiCl ₄	100
<i>i</i> -PrOTiCl ₃	80
(<i>i</i> -PrO) ₂ TiCl ₂	50



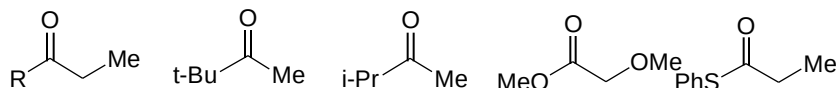
- Order of addition of reagents is important for TiCl₄.



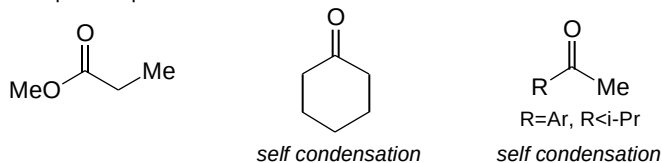
- Order of addition of reagents is not important for *i*-PrOTiCl₃ or (*i*-PrO)₂TiCl₂.



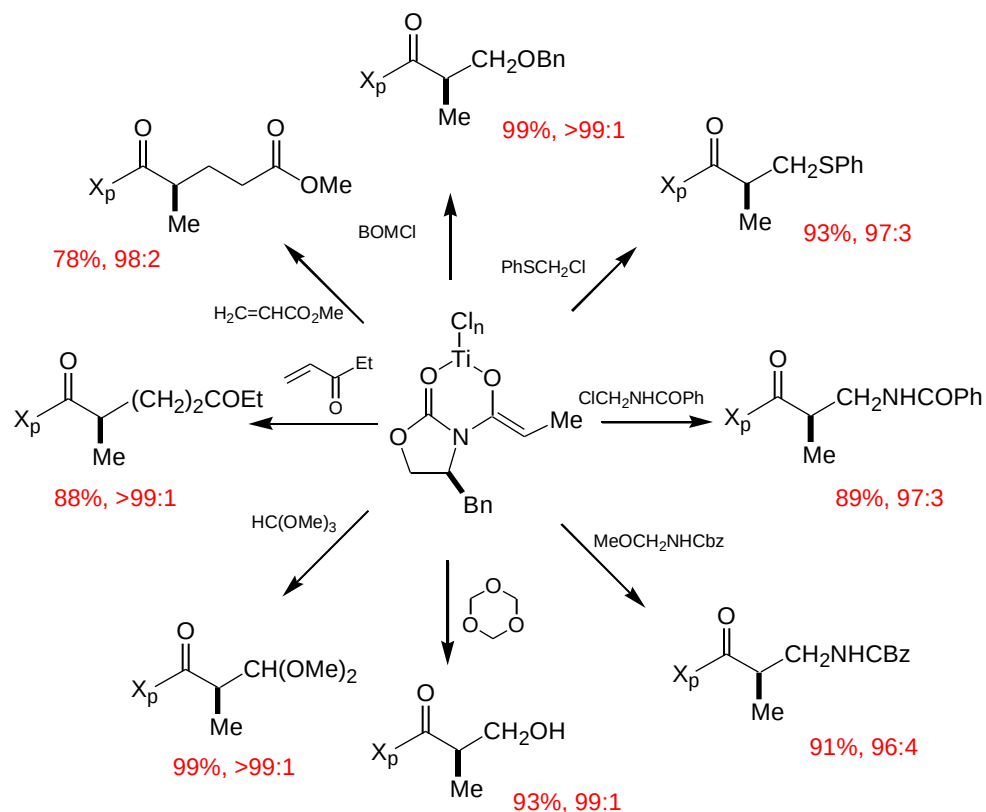
- Enolizable substrates:



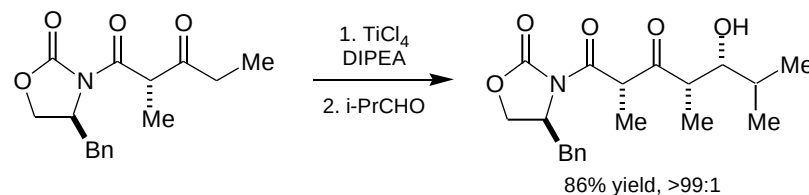
- Substrates Which present problems:



Reactions with Representative Electrophiles



J. Am. Chem. Soc. **1990**, *112*, 8215-8216.; *J. Org. Chem.* **1991**, *56*, 5750-5752.



Evans, Clark, Metternich, Novack, Sheppard *J. Am. Chem. Soc.* **1990**, *112*, 866.

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.

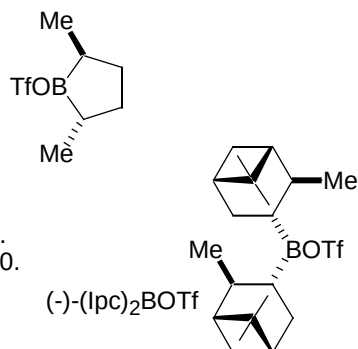
Evans, Vogel, Nelson *J. Am. Chem. Soc.* **1979**, 101, 6120.
 Evans, Nelson, Vogel, Taber *J. Am. Chem. Soc.* **1981**, 103, 3099-3111.
 Evans, Bartroli, Shih *J. Am. Chem. Soc.* **1981**, 103, 2127.
 Masamune, S. et. al. *Tetrahedron Lett.* **1979**, 2225, 2229, 3937.
 Masamune, S. et. al. *J. Am. 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.

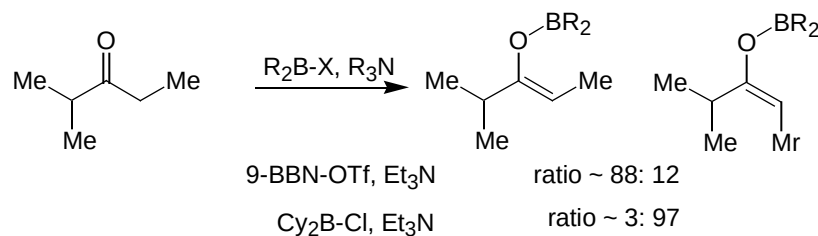
Tetrahedron **1990**, 46, 4663-4684.
Tetrahedron Lett. **1989**, 30, 997-1000.
Tetrahedron Lett. **1986**, 27, 4787-4790.



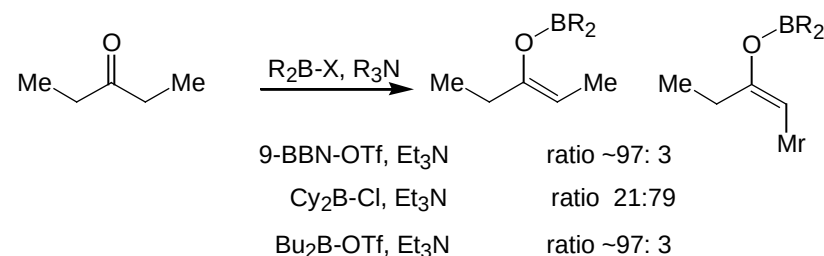
Enolate Stereochemistry

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.

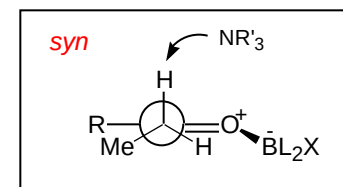
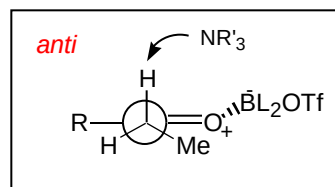
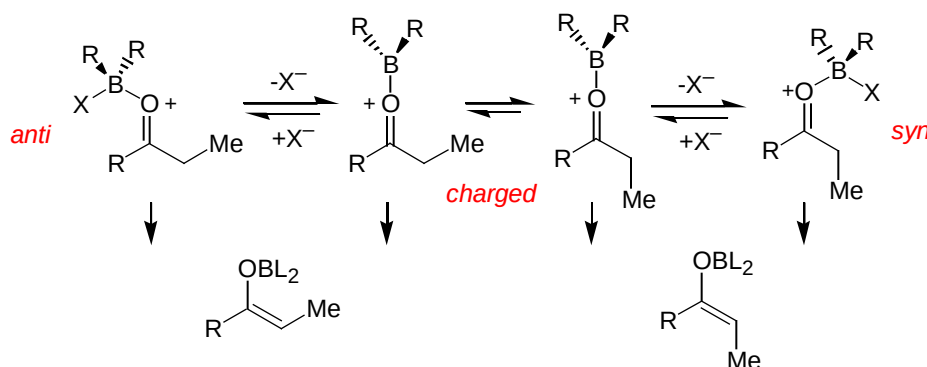


Brown, *J. Org. Chem.* **1993**, 58, 147-153



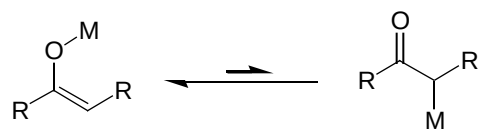
Borane and lutidine or DIPEA form 1:1 complex with L_2B-OTf . Complexation reversible as enolization will occur upon addition of ketone. Less hindered nitrogen bases - pyridine, Dabco, DBU, irreversibly complex with L_2B-OTf .

The Ketone-Boron Complexes as enolate precursors:



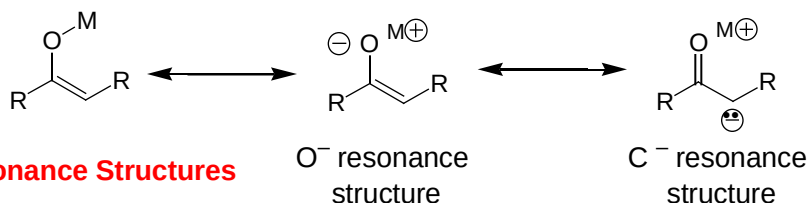
Cy_2BCl -ketone complex may deprotonate through syn complex

R_2BOTf -ketone complex may deprotonate through charged complex with (Z) preference

Metal Tautomerism

For alkali metal enolates ($M = \text{Li, Na, K etc.}$) 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

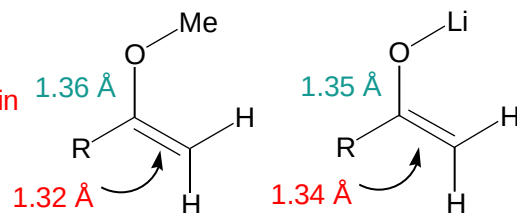
For certain metal enolates from heavy metals such as $M = \text{Hg}^{+2}$ the C-metal tautomer is sometimes favored.

Resonance Structures

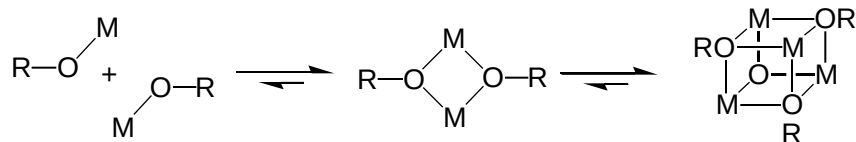
Since enolates usually function as carbon nucleophiles, it is therefore of some interest to assess the relative importance of the illustrated contributing polar resonance structures. Within the last decade good X-ray crystal structures of a number of metal enolates have been obtained.

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.

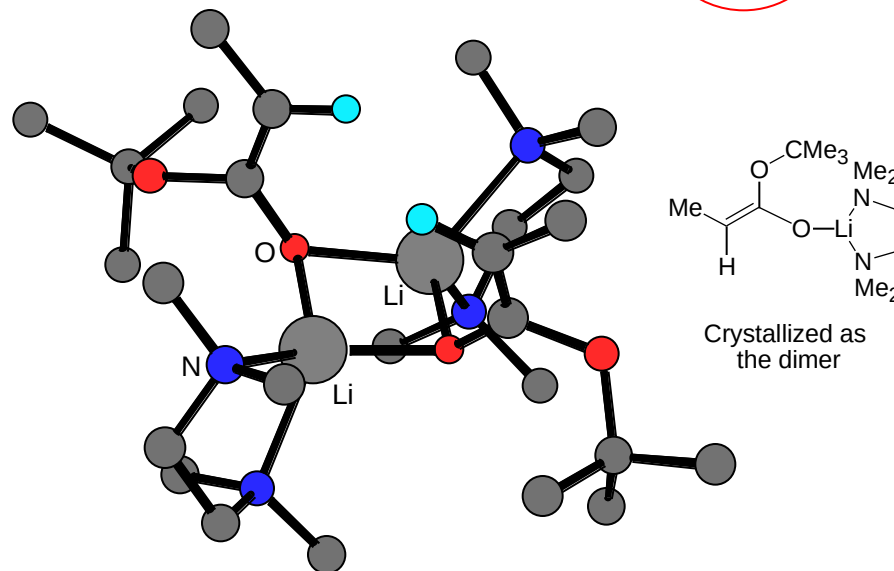
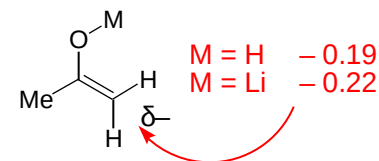
The prediction stated above does hold, but the net change in the C–C bond length is < 2 % !



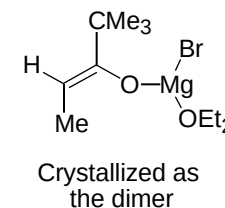
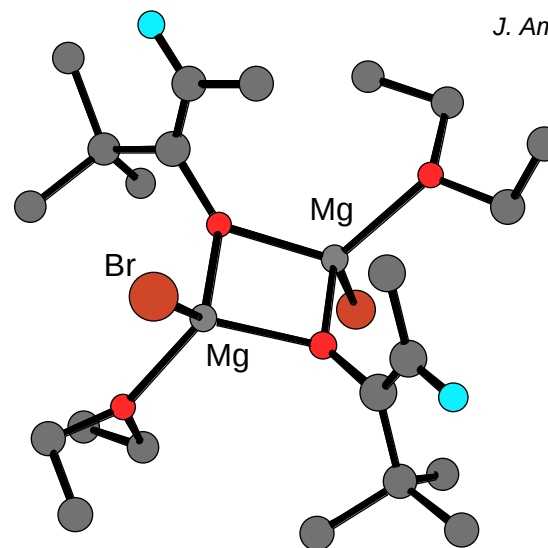
In solution and in the solid state metal enolates have a strong tendency to aggregate into dimers and tetramers to satisfy metal solvation requirements.



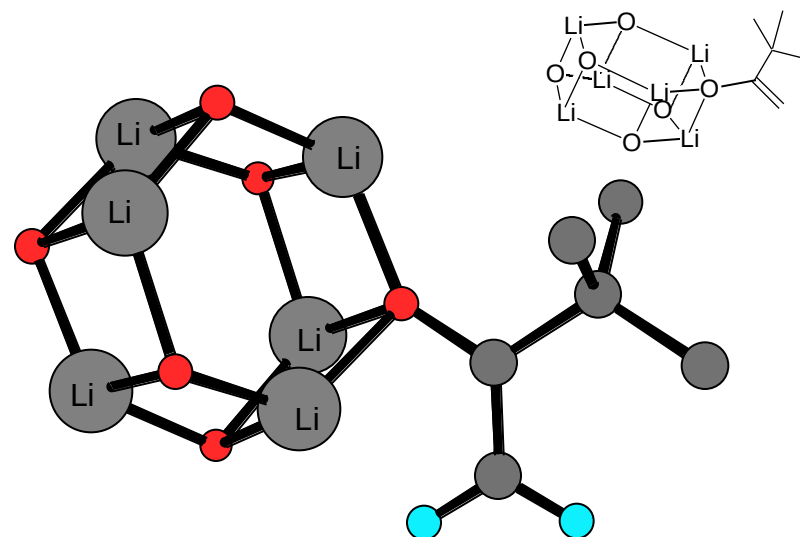
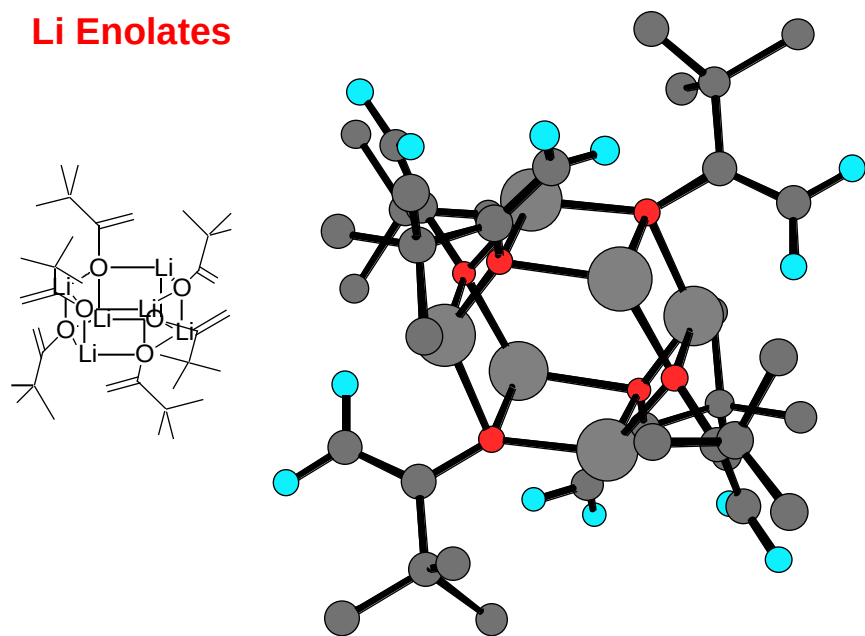
Ab initio calculations (Spartan) indicate that the partial negative charge on the alpha carbon is ~ -0.22 for the Li enolate



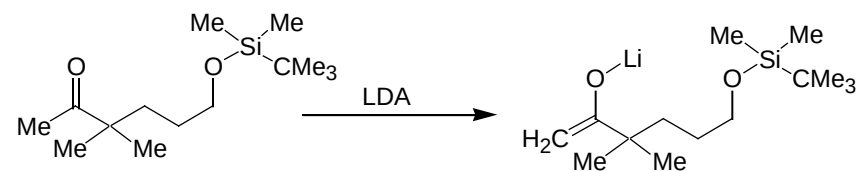
Seebach & co-workers,
J. Am. Chem. Soc. **1985**, 107, 5403.



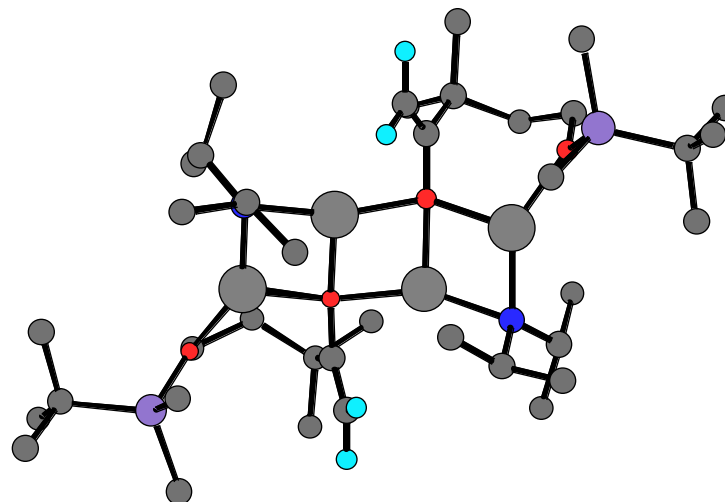
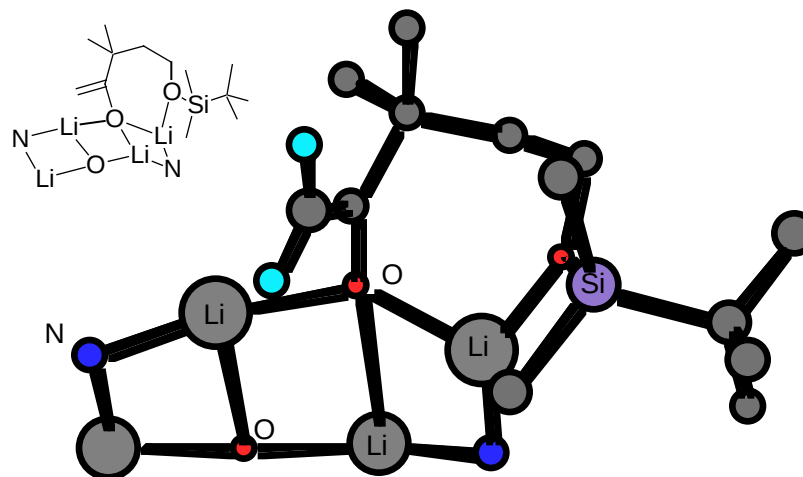
Li Enolates

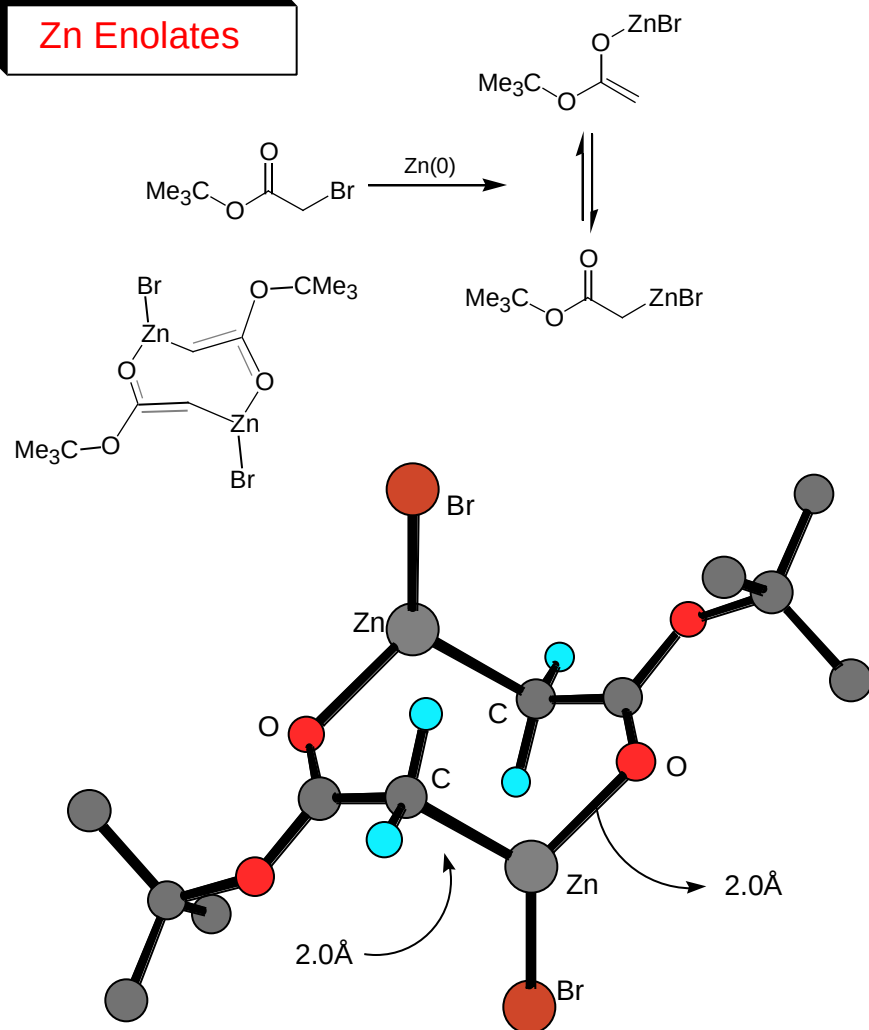


Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462-468.



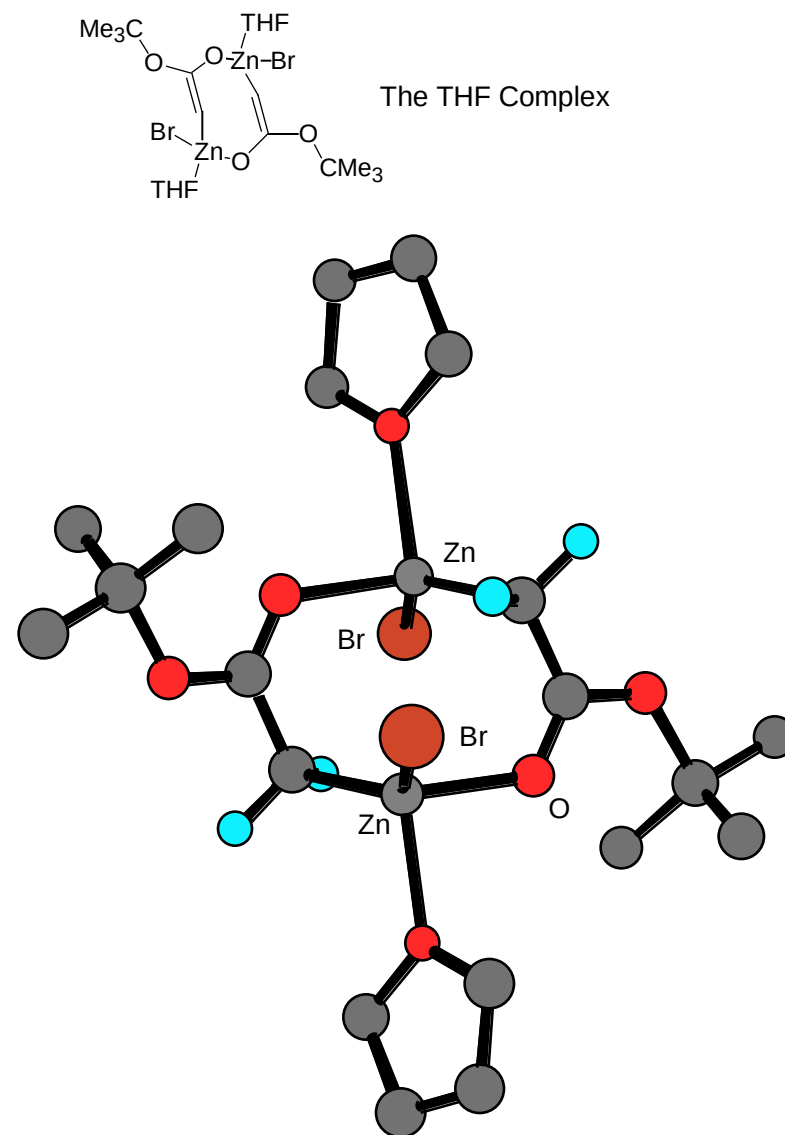
Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539-5541.



Zn Enolates

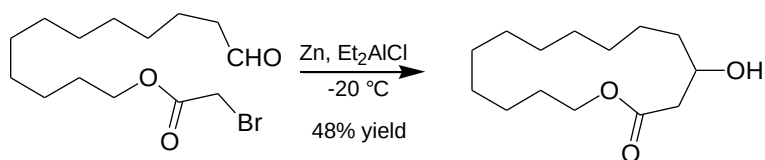
Dekker, J.; Boersma, J.; van der Kerk, G. J. M. *J. Chem. Soc. Chem. Commun.* **1983**, 553.

Dekker, J.; Budzelaar, J.; Boersma, J.; van der Kerk, G. J. M. *Organometallics* **1984**, 3, 1403.

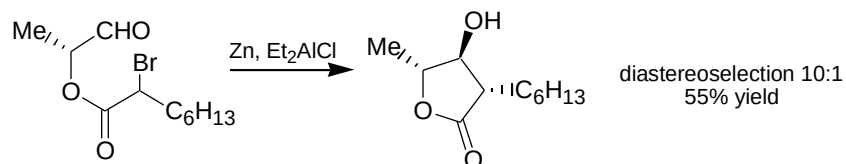


The "Classical" Reformatsky Process

Review: *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.8, pp 277-299

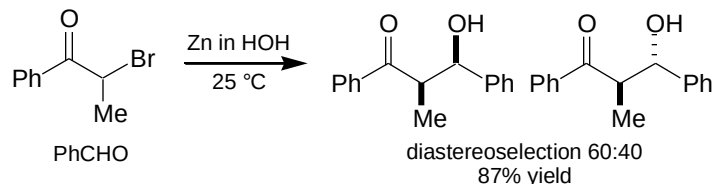


H. Nozaki & Co-workers, *J. Am. Chem. Soc.* **197**, 99, 7705 Both cyclic and acyclic cases studied (11 cases).



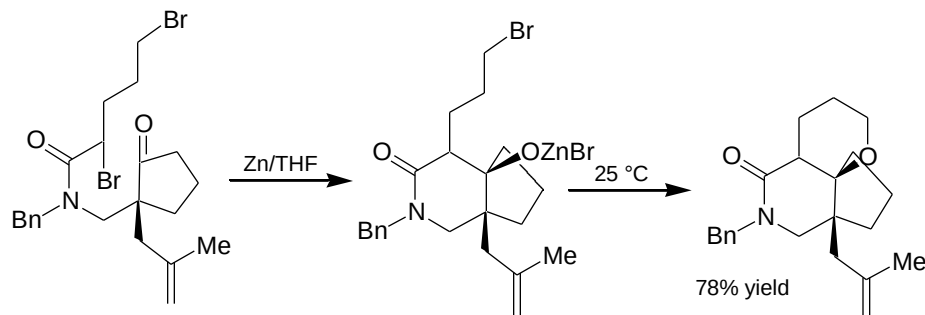
T. Nishida & Co-workers, *Tetrahedron* **1991**, 47, 6623.

Based on the Nozaki recipe *JACS* **1977**, 99, 7705



T. H. Chan & Co-workers, *Chem. Commun.* **1990**, 505.

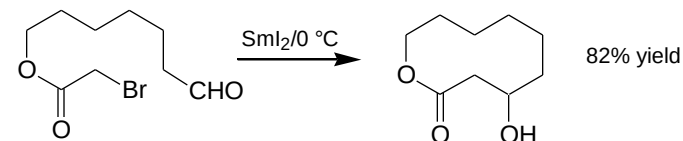
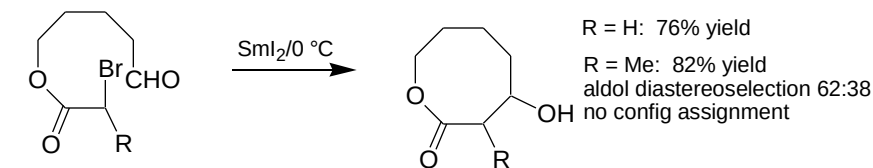
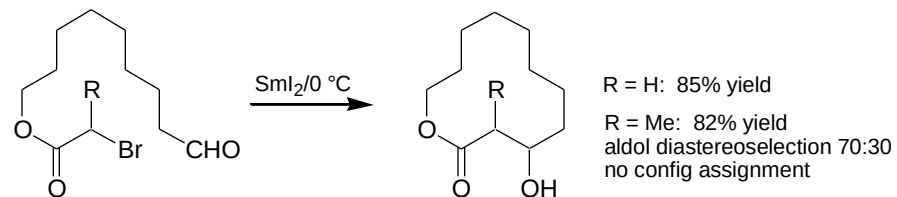
Rxns carried out in water with either activated Zn or Sn . 19 cases reported.



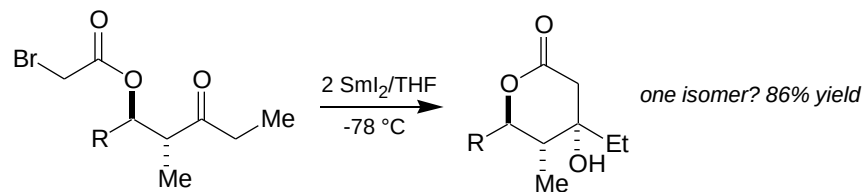
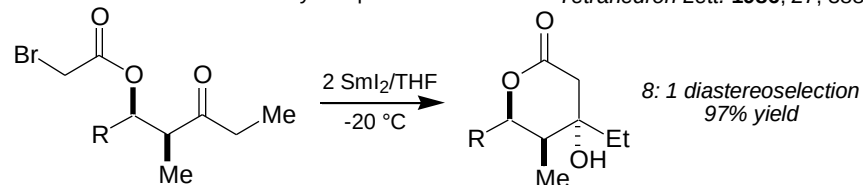
C. H. Heathcock & Co-workers, *J. Org. Chem.* **1987**, 52, 5745.

The Samarium(II) Variant

Summary of SmI_2 chemistry: Sonderquist, *Aldrichimica Acta* **1991**, 24, 15

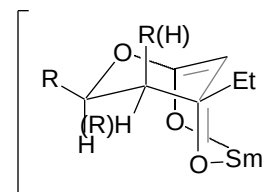


Good entry into prior literature T. Tabushi & Co-workers, *Tetrahedron Lett.* **1986**, 27, 3889.

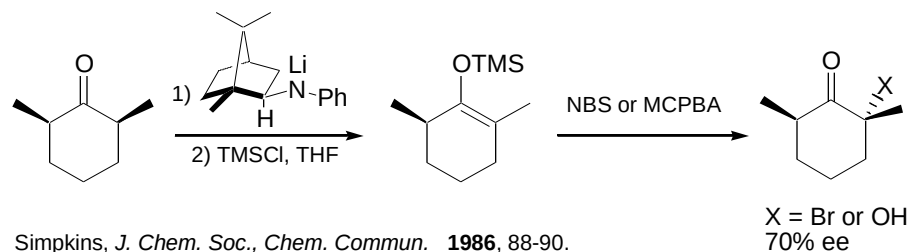


G. A. Molander & Co-workers, *J. Am. Chem. Soc.* **1987**, 109, 6556.

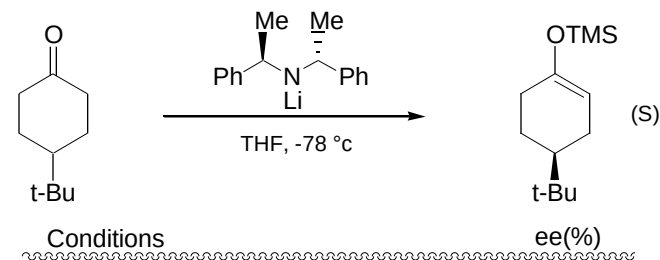
Proposed Transition structure



Asymmetric Deprotonation of Meso Ketones

Simpkins, *J. Chem. Soc., Chem. Commun.* **1986**, 88-90.

The Effects of Additives on Induction

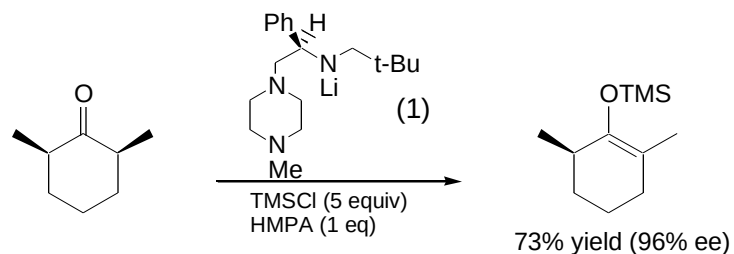
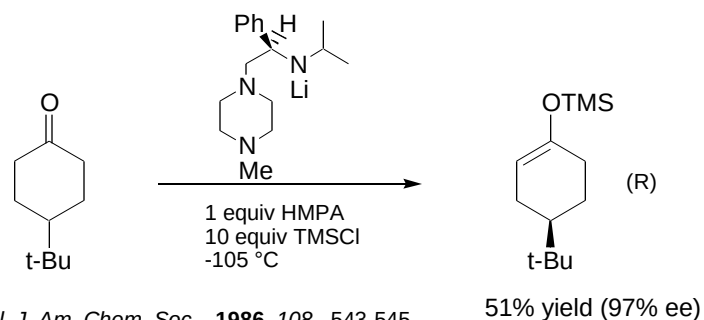


Internal quench with TMSCl 69

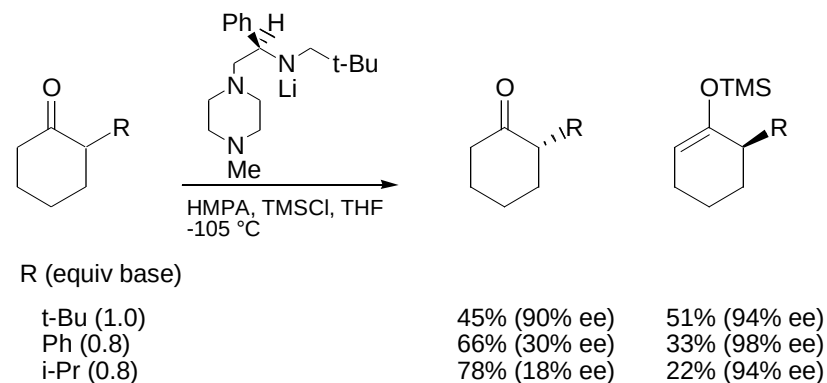
External quench of TMSCl 23

Reaction run with 0.5 equiv of LiCl (rel. to amide), then quenched with TMSCl 83

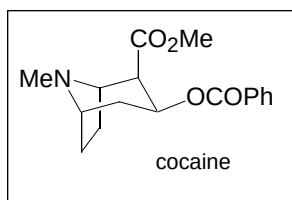
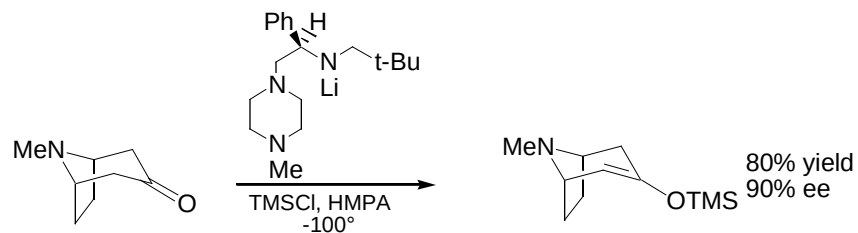
Does a change in aggregation state inhibit racemization of the initial Li enolate?

Simpkins and Cousins, *Tetrahedron Lett.* **1989**, 30, 7241-7244
Simpkins and Bunn, *J. Org. Chem.* **1993**, 58, 533-534.With an *in situ* quench:Koga, et al *Heterocycles* **1990**, 30, 307-318.Koga, et al *J. Am. Chem. Soc.* **1986**, 108, 543-545.

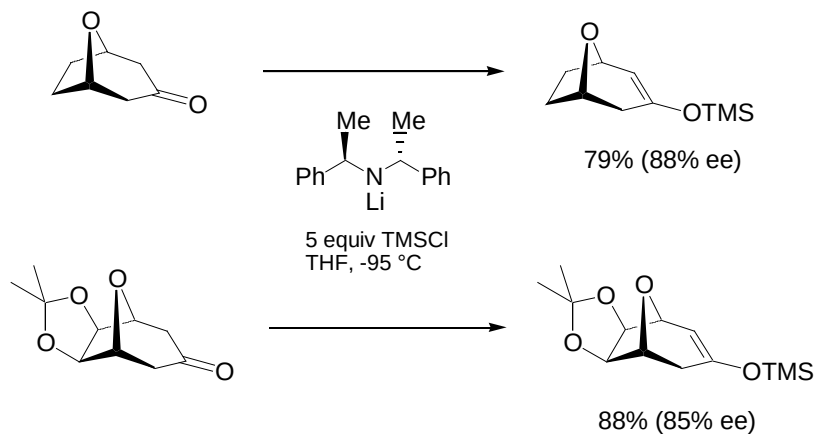
Kinetic Resolution of Ketones

Koga, et al *Tetrahedron Lett.* **1989**, 30, 6537-6540.

Other cyclic ketones can be used as substrates. See:
Cox and Simpkins, *Tetrahedron: Asymmetry* **1991**, 2, 1-26.

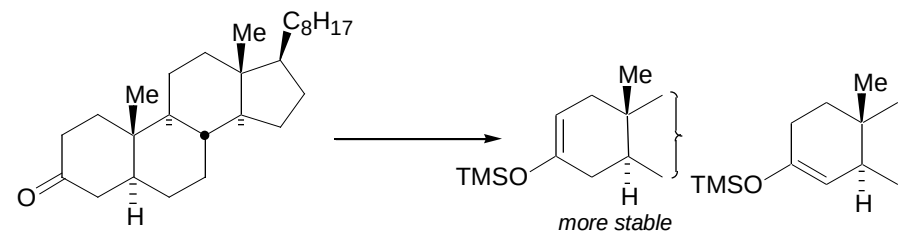


Momose, et al *Chem. Pharm. Bull.* **1990**, 38, 2072-2074

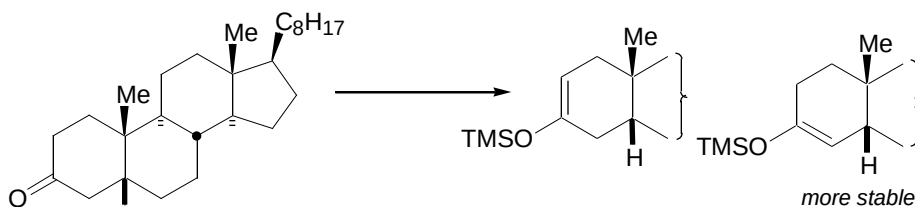


Simpkins, et al *Tetrahedron* **1993**, 49, 207-218.

Regioselective Deprotonation of Unsymmetrical Ketones

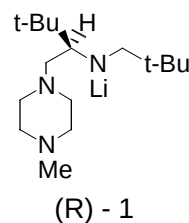


Conditions		Ratio	
(TMS) ₂ NH, TMSI	Thermodynamic	90	10
LDA	Kinetic	78	22
(R) - 1	Kinetic	2	98
(S) - 1	Kinetic	>98	<2



Conditions		Ratio	
(TMS) ₂ NH, 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.



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.

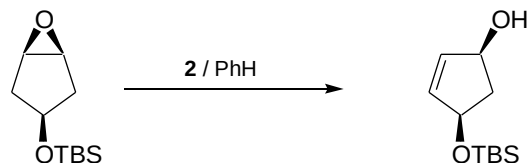
Ring opening of meso epoxides

Conditions	Yield (%)	ee(%)	Ref.	
 1 THF, reflux	65	31 (R)	1	
 2 THF, 0°	77	92 (S) <i>this number has been challenged</i>	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.

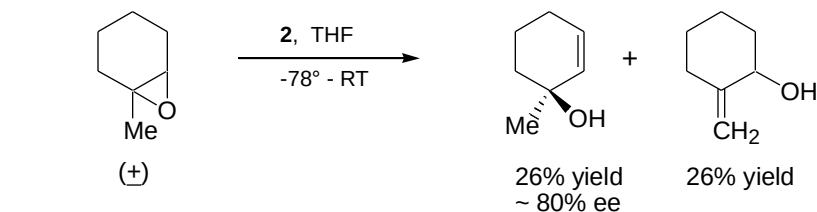
² Asami, *Chem. Lett.* **1984**, 289-832.

³ Asami and Kiriara, *Chem. Lett.* **1987**, 389-392.

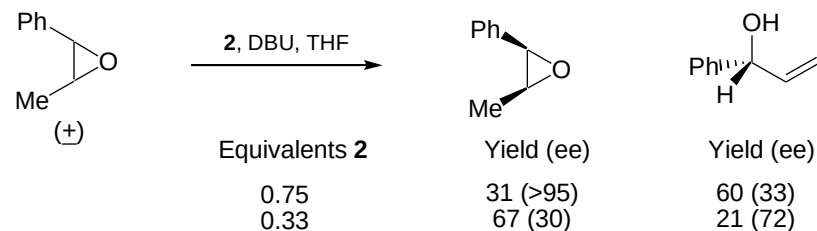


92% yield (90% ee - rotation) - Asami, *Tetrahedron Lett.* **1985**, 26, 5803-5806.
 73% yield (76% ee - Mosher) - Hendrie and Leonard, *Tetrahedron* **1987**, 43, 3289-3294.

Kinetic Resolution of Racemic Epoxides

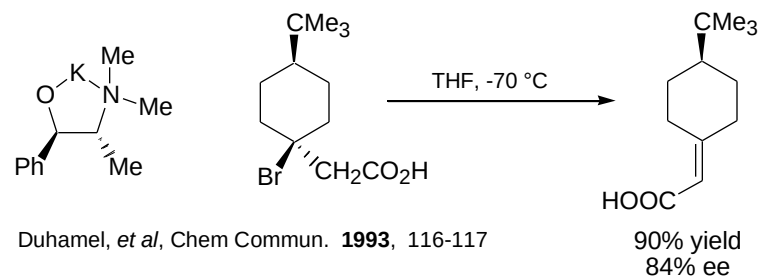
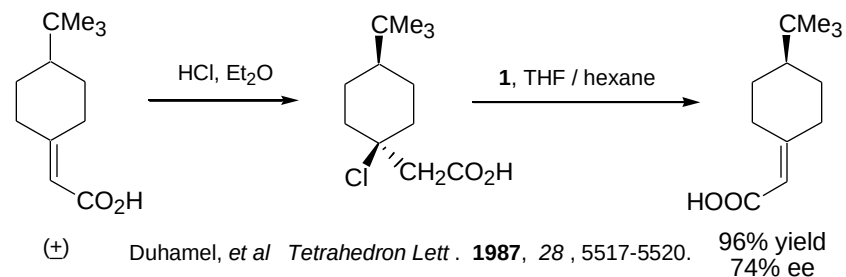


Mori, *Tetrahedron* **1987**, 43, 2249-2254. Aggregation pheromone of the Douglas Fir Beetle



Asami and Kanemaki, *Tetrahedron Lett.* **1989**, 30, 2125-2128.

Asymmetric Eliminations

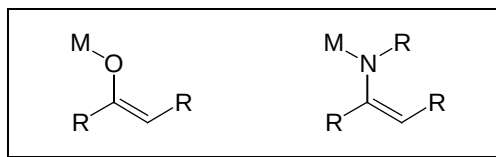


<http://www.courses.fas.harvard.edu/~chem206/>

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).

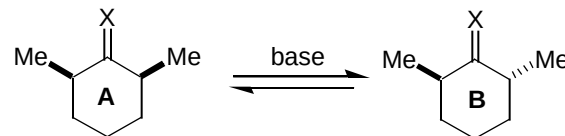
The Reactions of Dianions of Carboxylic Acids and Ester Enolates". N. Petragnani and M. Yonashiro *Synthesis*, 521 (1982).

"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).

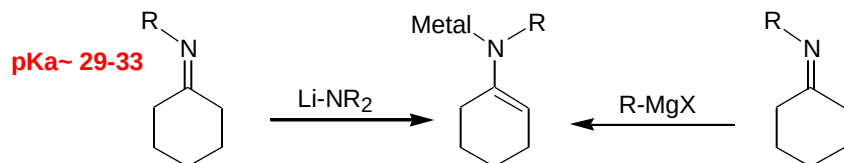
"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Chiang, Kresge, and Tang *JACS* **106**, 460 (1984).

Explain why **A** is favored for X = O while **B** is favored for X = NNHR



■ Metalloenamines:

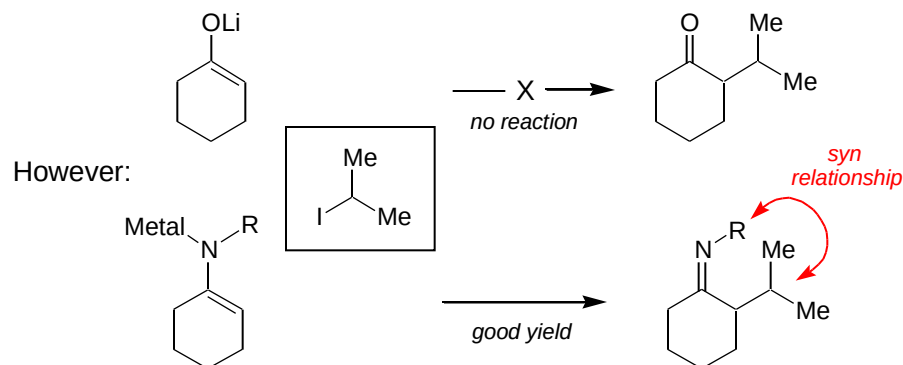
Imines may be transformed into their conjugate bases (enolate counterparts) with strong bases:



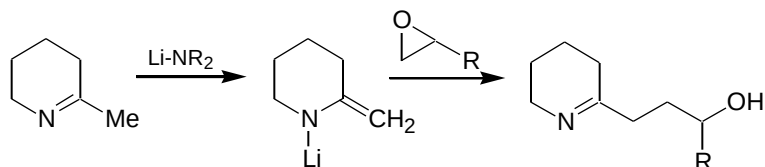
The usual bases employed are either lithium amides (LDA) or Grignard reagents. Note that Grignard reagents do not add to the C=N pi-bond due to the reduced dipole. With this functional group, deprotonation is observed to be the preferred reaction.

■ 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----->

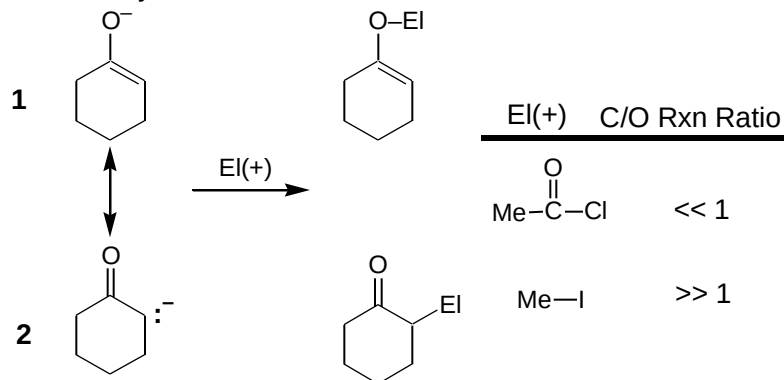
Nucleophile \ Electrophile	$\text{C}=\text{C}^-\text{NR}$	$\text{C}=\text{C}^-\text{O}^-$	$\text{C}=\text{C}^-\text{NR}_2$	$\text{C}=\text{C}^-\text{OMe}$
Br_2, O_3	+	+	+	+
H_3O^+	+	+	+	+
$\text{R}-\text{C}(=\text{O})-\text{Cl}$	+	+	+	
$\text{R}-\text{C}(=\text{O})-\text{H}$	+	+	+	
$\text{R}-\text{C}(=\text{O})-\text{R}$	+	+		
$\text{Me}-\text{I}$	+	+		
$\text{R}-\text{C}(=\text{O})-\text{OR}$	+	+		
$\text{H}_2\text{C}-\text{O}-\text{CH}_2$	+			
$\text{Me}_2\text{CH}-\text{I}$	+			
$\text{R}-\text{C}(=\text{O})-\text{NR}_2$				

Decreasing Electrophilicity----->

■ Nature uses enamines, "stabilized" enolates, and enol derivatives in C-C bond constructions extensively.

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:



■ 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."

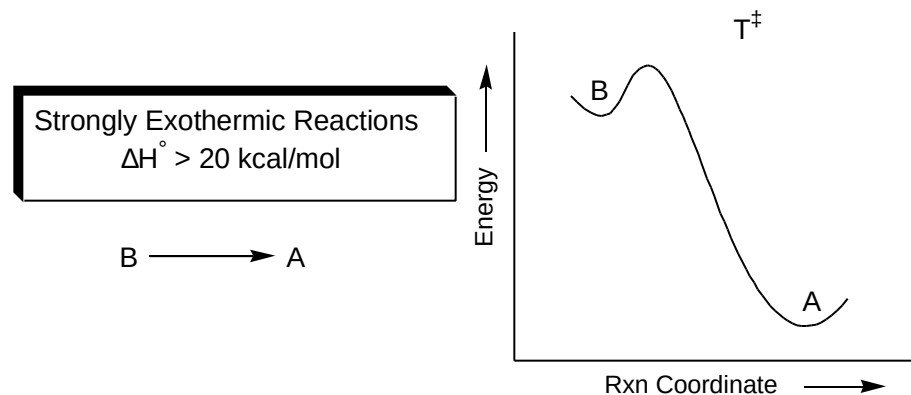
See Hine in *Advances in Phys. Org. Chem.* 1977, 15, 1-61

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.



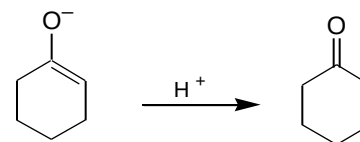
Hammond Postulate

"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.

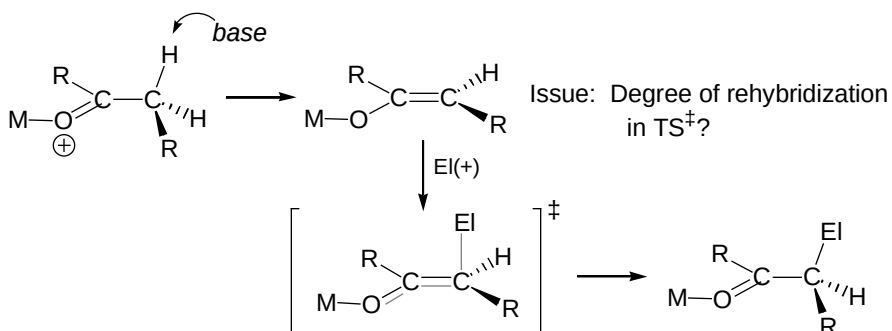


Review

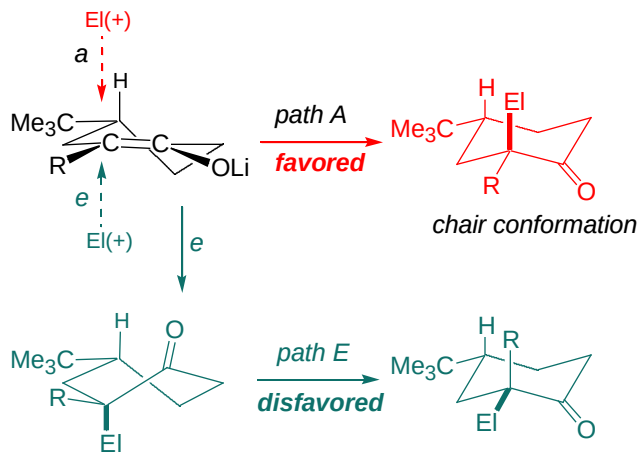
Evans, D. A. *Stereoselective Alkylation Reactions of Chiral Metal Enolates*; Morrison, J. D., Ed.; AP: New York, 1984; Vol. 3, pp 1-110.

Stereoelectronic Issues

- Enolization: Breaking C-H bond must overlap with π C-O in TS[‡]
- Alkylation: Forming C-EI bond must overlap with π C-O in TS[‡]



■ Cyclohexanone Enolate:

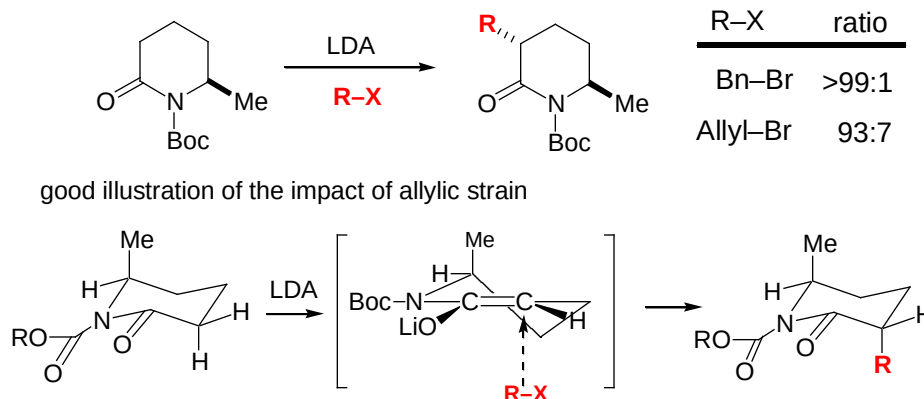
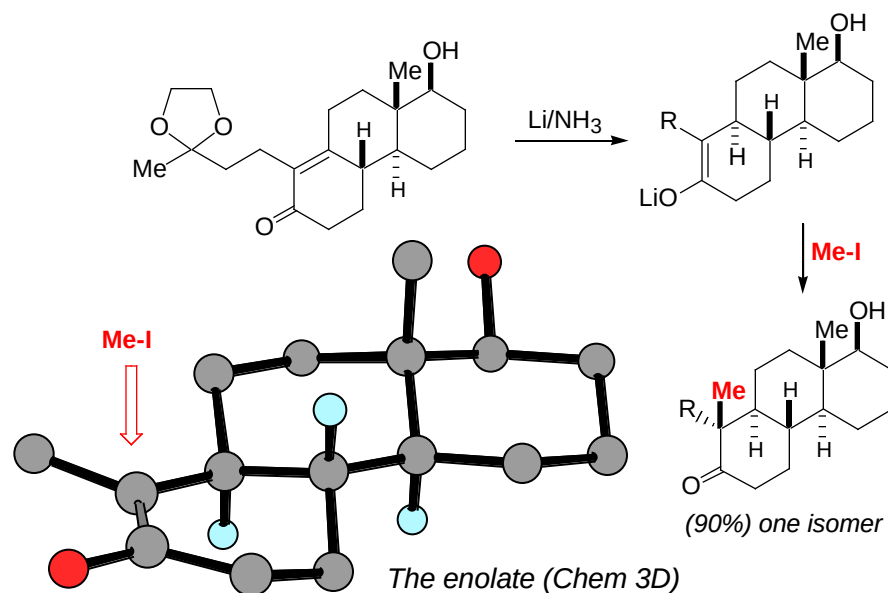


Metal	R-substituent	Electrophile	Ratio, a:e
Li	Me	CD ₃ I	70:30
Li	CO ₂ Me	Me-I	83:17

Chair vs boat geometries not strongly reflected in diastereomeric TS[‡]s. The transition states is early and enolate-like.

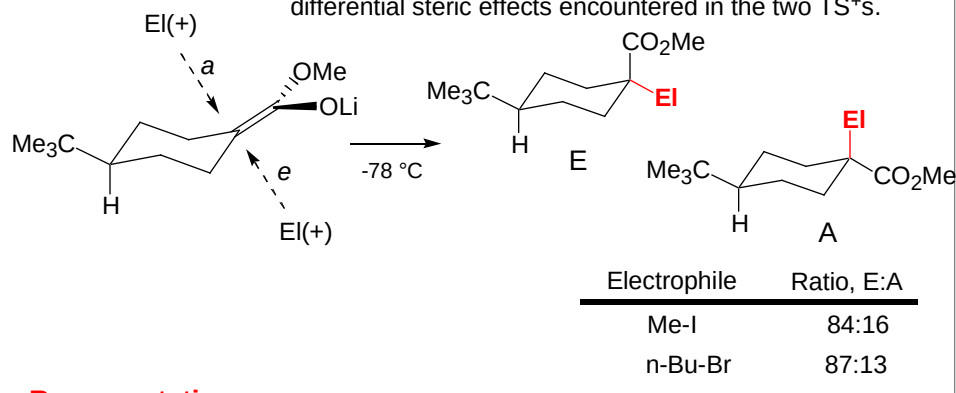
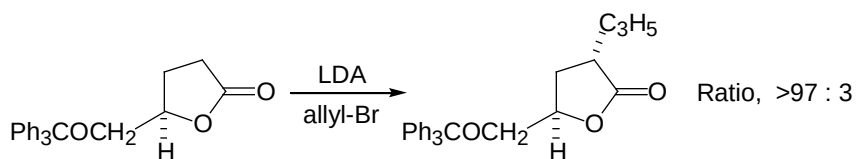
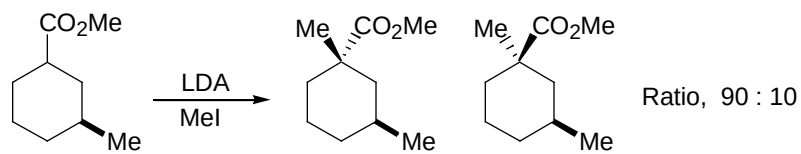
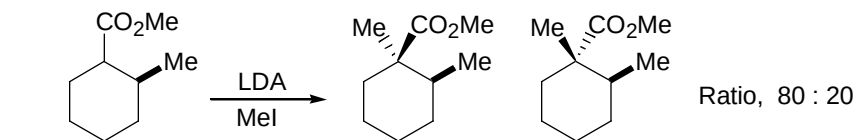
Examples where stereoelectronic factors are dominant

Pilli, *Tetrahedron*, **1999**, 55, 13321

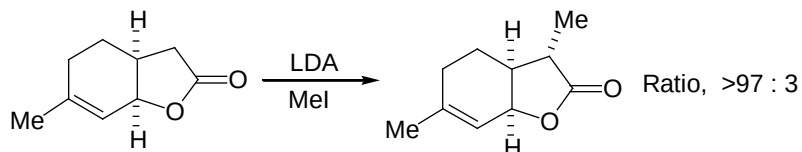
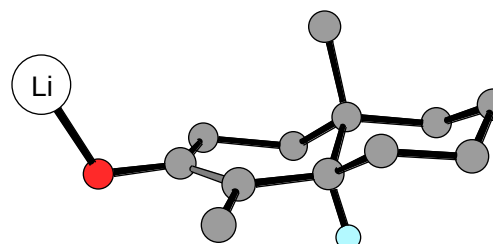
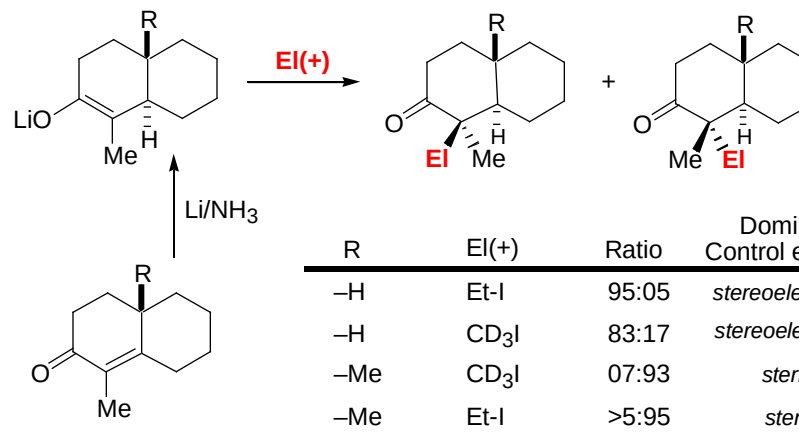
The C₁₉ Angular Methyl Group in the steroid nucleus

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.

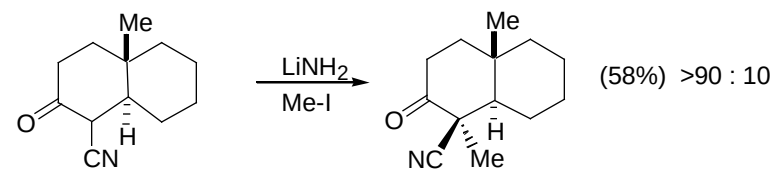
**Representative cases**

diastereoselectivity depends strongly on O-protecting group

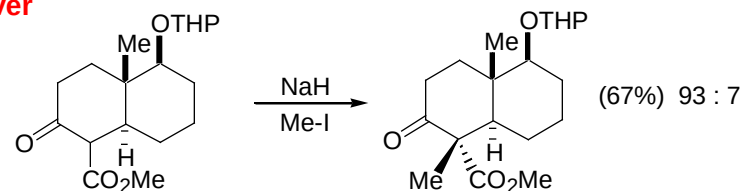
**Cases with Opposed steric & electronic effects**

The enolate R = Me
(Chem 3D)

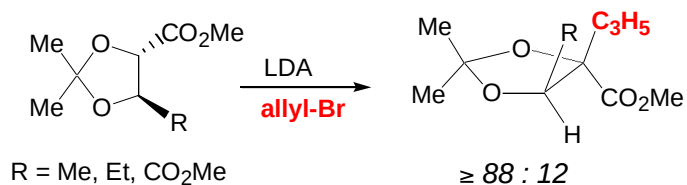
Based on above data, this case is reasonable:



However



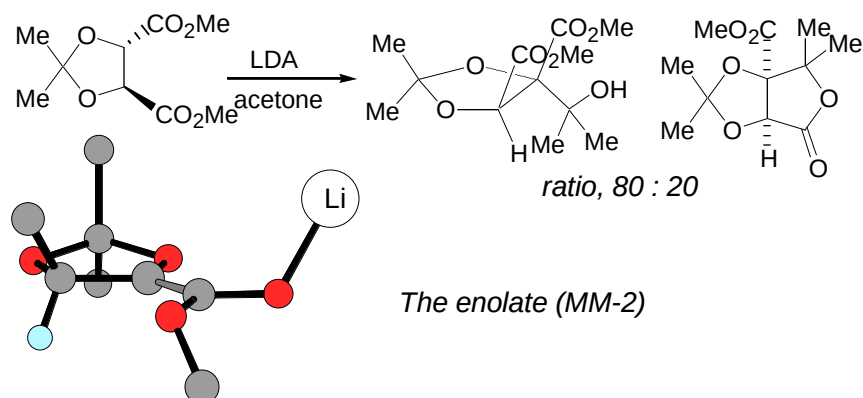
Cases which do not appear to give the expected product based on the analysis of steric effects



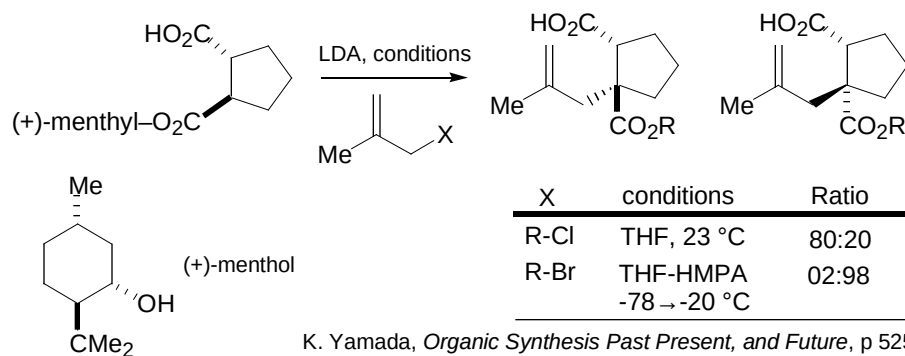
Seebach, *Angew. Chem. Int. Ed* **1981**, 20, 1030

Ladner, *Angew. Chem. Int. Ed* **1982**, 21, 449

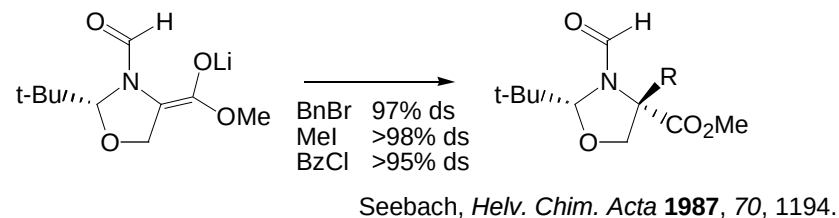
■ However:



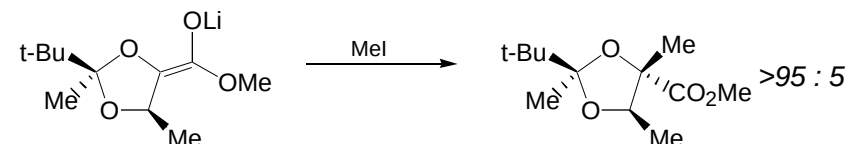
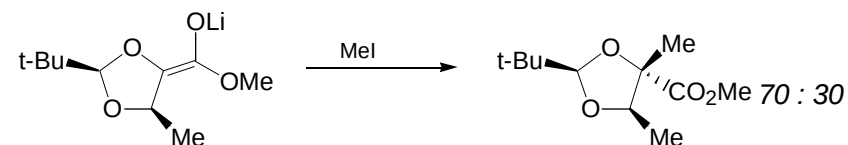
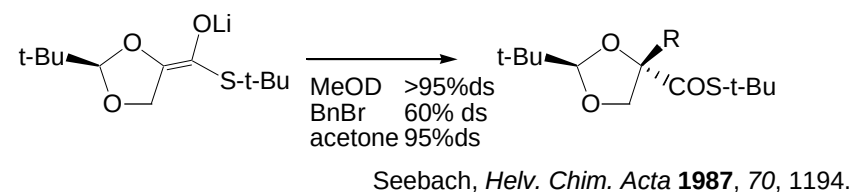
Here is another example of a contra-steric alkylation



Sterically Expected Results:

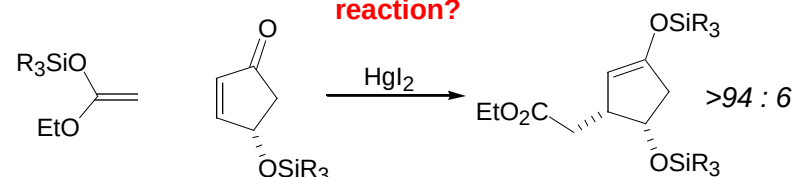


Contra-steric relatives:



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?



Danishefsky *J. Org. Chem.* **1991**, 56, 387

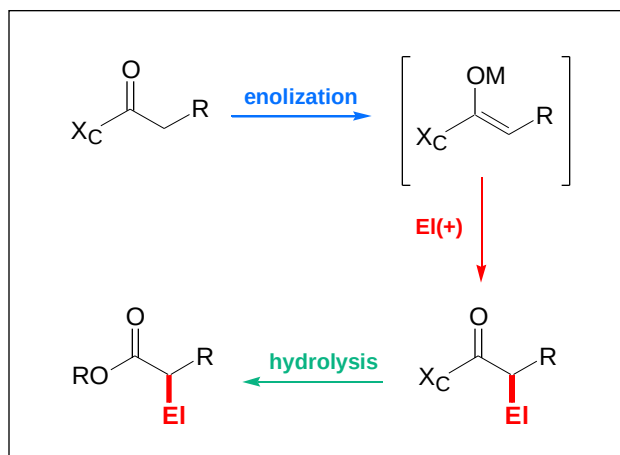
Chiral Enolate Design Requirements Circa 1978

Overall enantioselection will be the sum total of the defects introduced through:

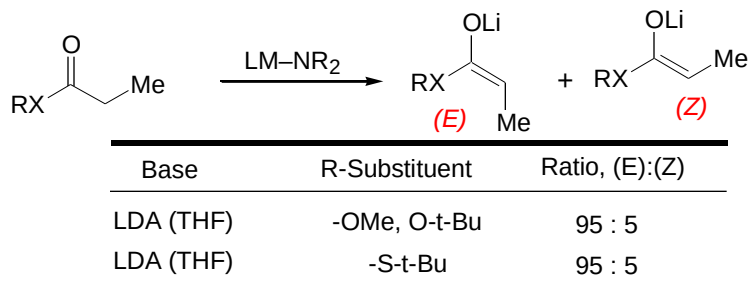
■ Enolization selectivity

■ Enolate-electrophile face selectivity

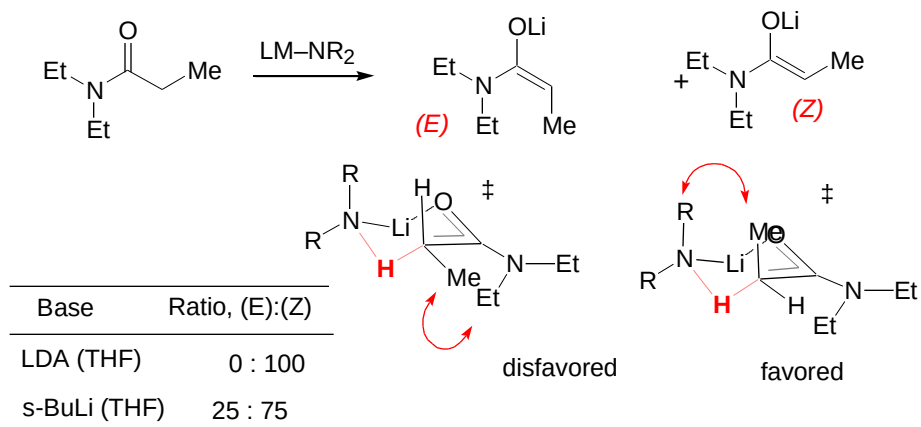
■ Racemization attendant with X_C removal



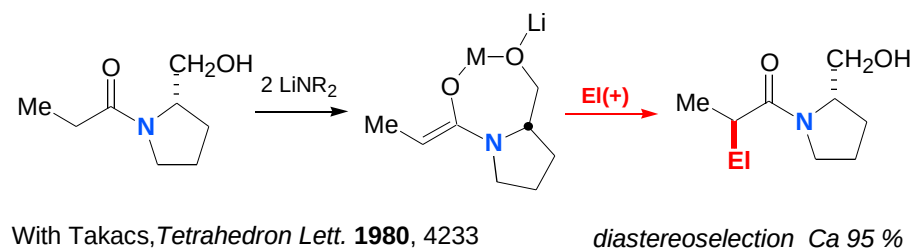
■ Enolization selectivity: Ester-based chiral controllers X_C limited by enolization selectivity (Lecture 22)



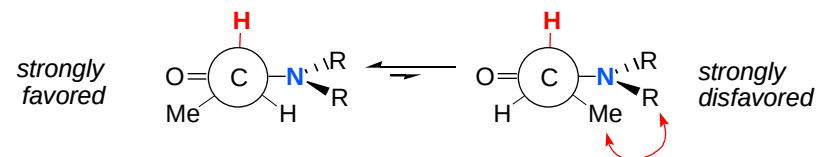
■ Enolization selectivity: Amide-based controllers X_C limited by enolization selectivity (Lecture 22)



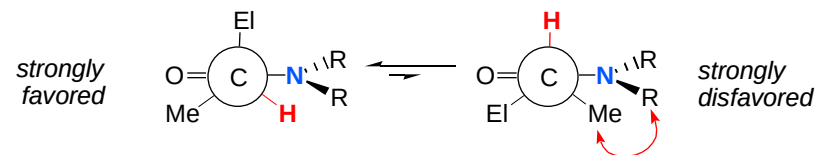
■ Amide Based Chiral Auxiliaries



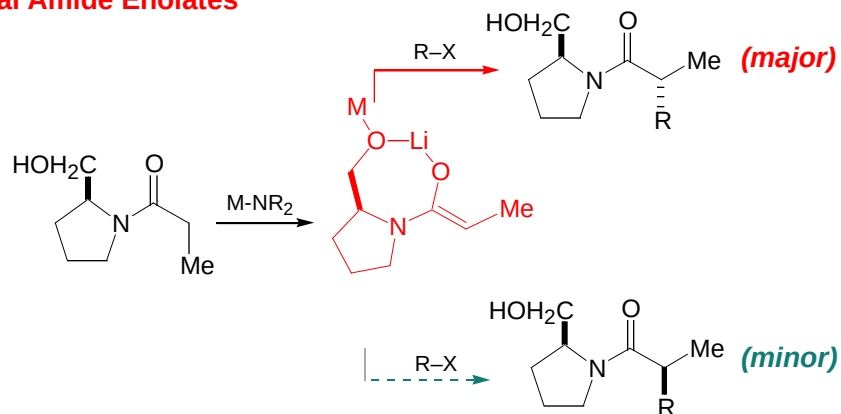
Allylic Strain controls Enolate Geometry:



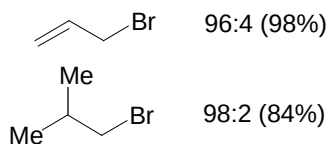
Allylic Strain Prevents Product Enolization:



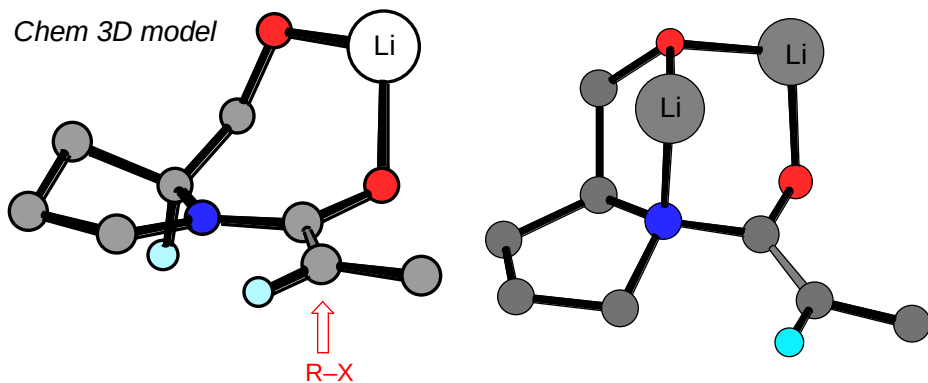
Chiral Amide Enolates



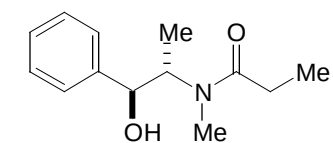
Evans, Takacs,
Tet. Lett. **1980**, 21, 4233-4236



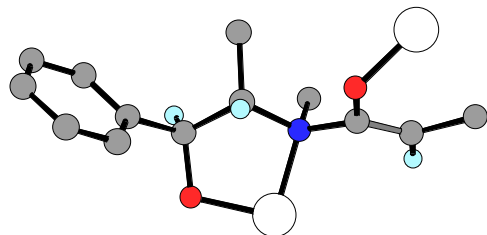
Chem 3D model



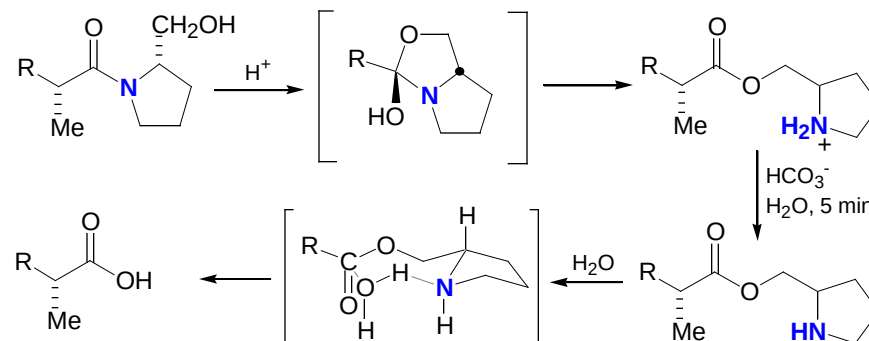
The nature of enolate chelation is ambiguous. Nitrogen chelation is a real possibility.



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



Amide Hydrolysis

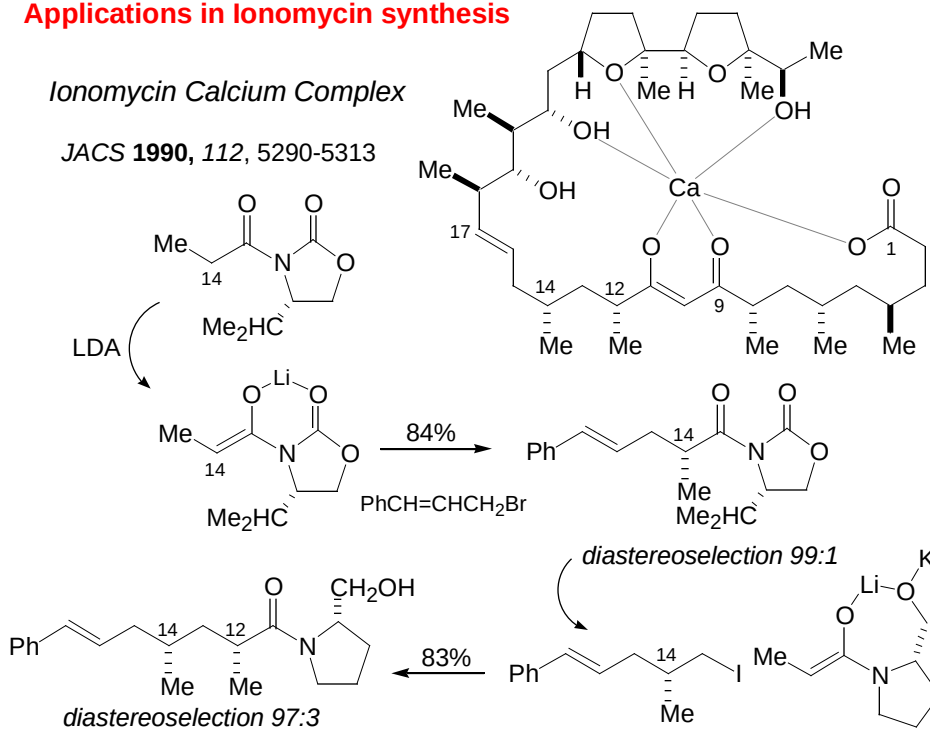


intramolecular general base catalysis

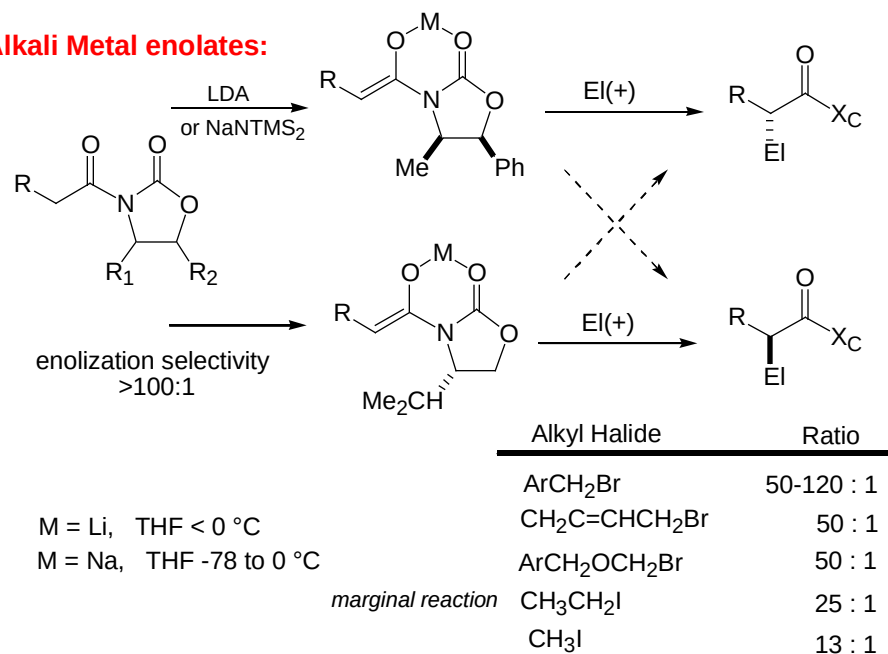
Applications in Ionomycin synthesis

Ionomycin Calcium Complex

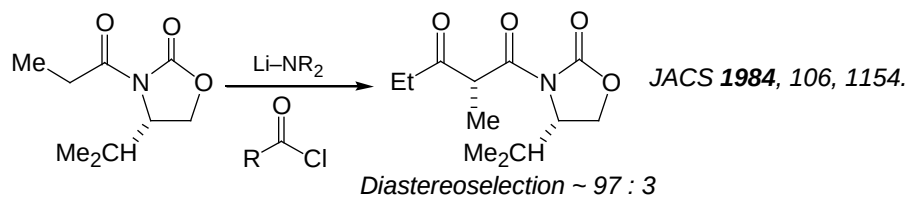
JACS **1990**, 112, 5290-5313



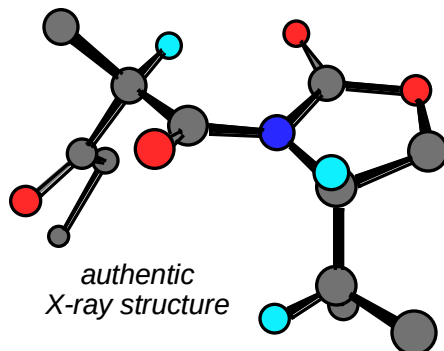
Alkali Metal enolates:



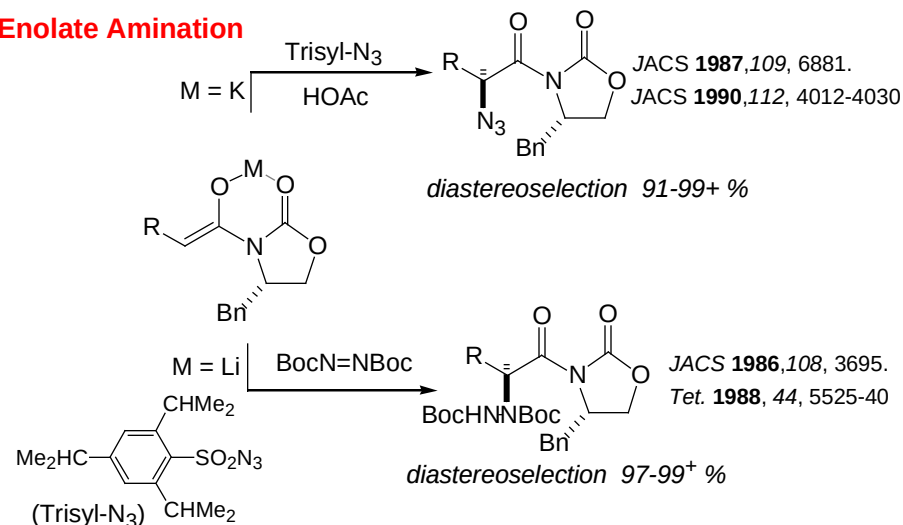
Enolate Acylation



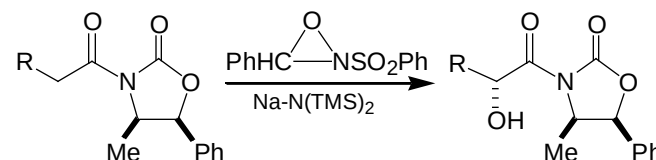
New stereocenter not lost through enolization



Enolate Amination



Enolate Hydroxylation



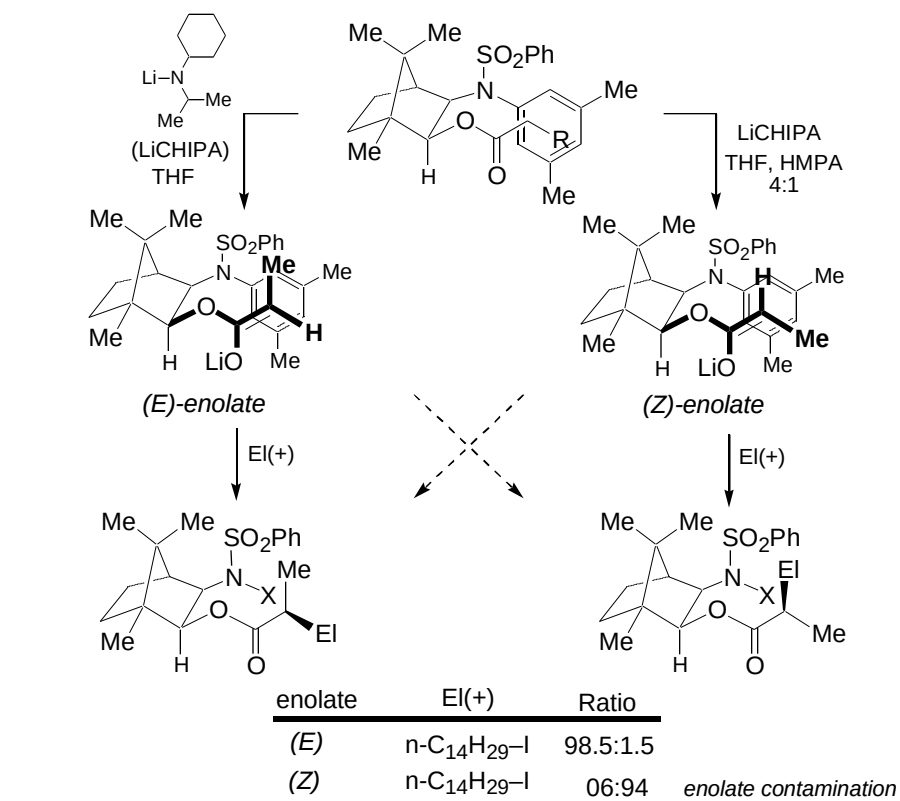
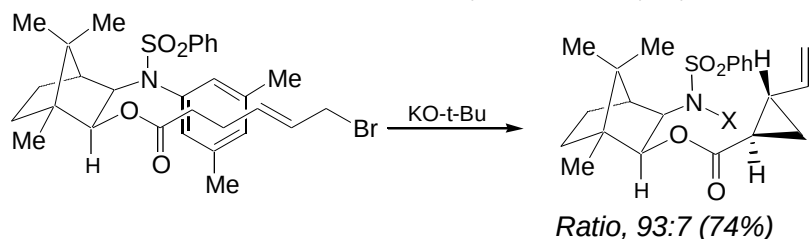
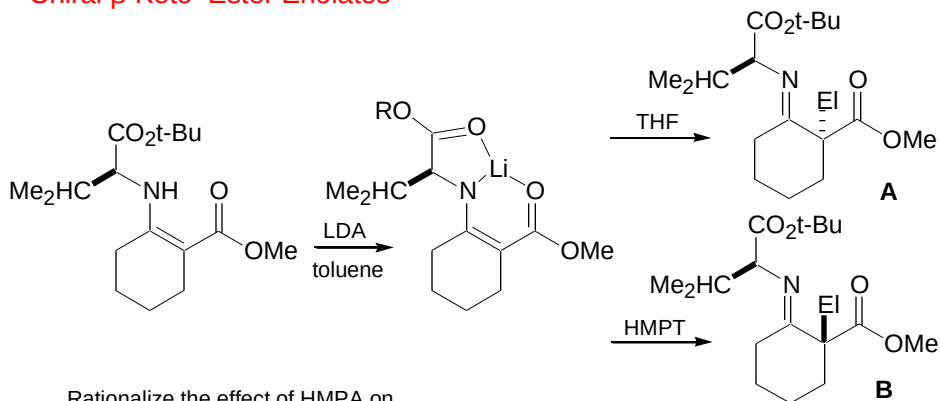
Na enolate is required.
Why?

Imide (R)	Ratio	Yield *
PhCH ₂ -	94 : 6	86 %
CH ₂ =CHCH ₂ -	95 : 5	91 %
MeO ₂ CCH ₂ CH ₂ CH ₂ -	96 : 4	68 %
Ph-	90 : 10	77 %
Me ₃ C-	>99 : 1	94 %

JACS. 1985, 107, 4346.

For all indicated rxns, as the R on the enolate grp increases in size enolate-EI face selectivity increases. Explain.

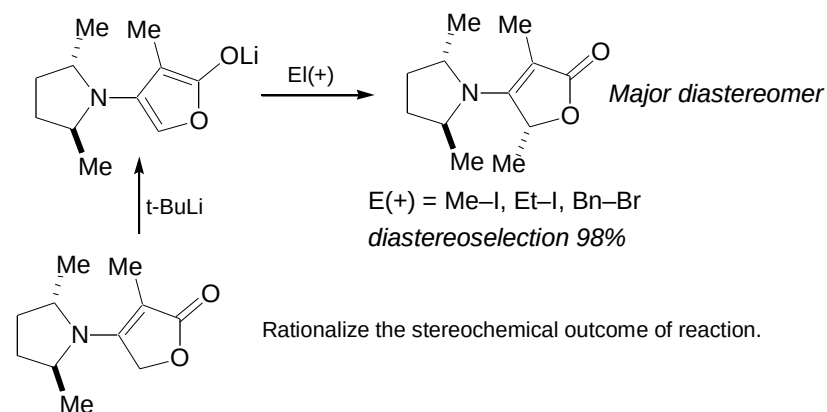
Chiral Ester Enolates

Helmchen, *Angew. Chem. Int.Ed.* **1981**, 20, 207-208Helmchen, *Angew. Chem. Int.Ed.* **1984**, 23, 60-61Helmchen, *Tet. Lett.* **1983**, 24, 1235-1238Helmchen, *Tet. Lett.* **1983**, 24, 3213-3216Helmchen, *Tet. Lett.* **1985**, 26, 3319-3322Chiral β -Keto Ester Enolates

Rationalize the effect of HMPA on the stereochemical outcome of reaction.

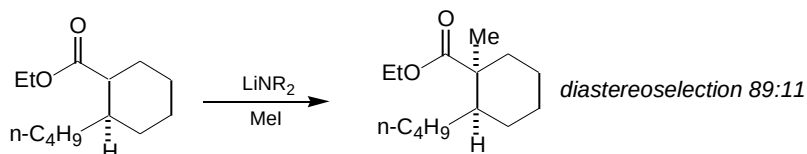
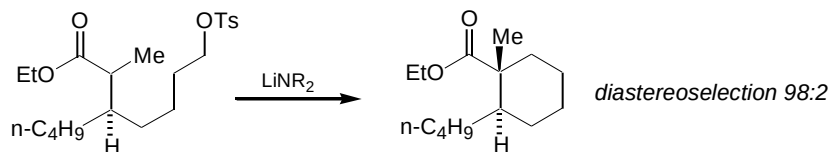
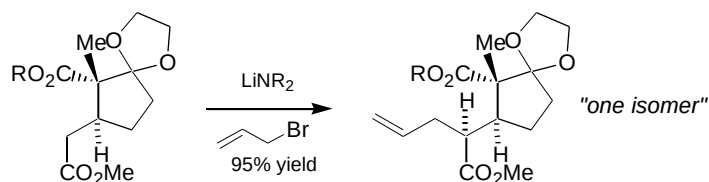
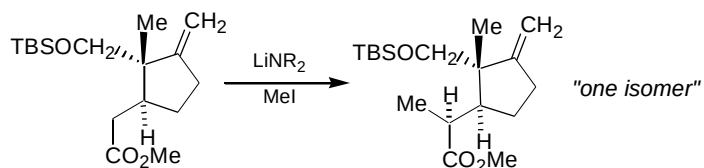
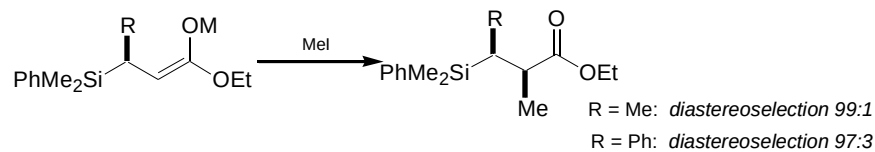
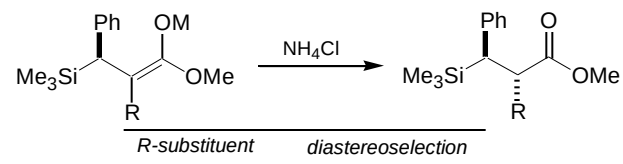
Koga, *JACS* **1984**, 106, 2718-2719

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

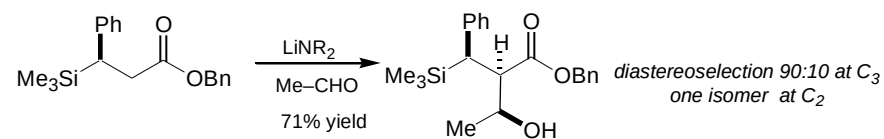
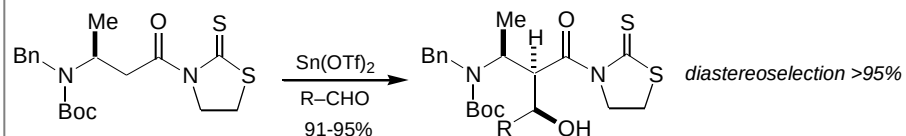
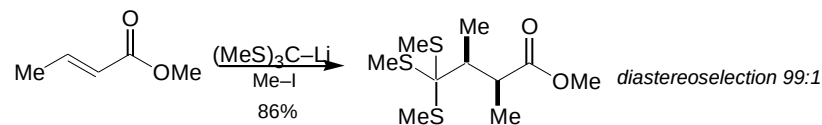
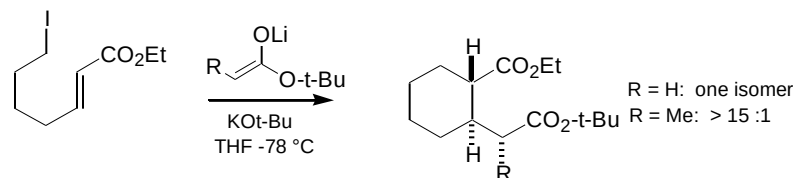
Rationalize the stereochemical outcome of reaction.

Schlessinger, *Tet. Lett.* **1988**, 29, 1489-1492

D. Kim & Co-workers, *Tetrahedron Lett.* **1986**, 27, 943.G. Stork & Co-workers, *Tetrahedron Lett.* **1987**, 28, 2088.T. Money & Co-workers, *Chem. Commun.* **1986**, 288.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.I. Fleming & Co-workers, *Chem. Commun.* **1986**, 1198.T. Mukaiyama & Co-workers, *Chem. Letters* **1986**, 637K. Koga & Co-workers, *Tetrahedron Letters* **1985**, 26, 3031.Y. Yamaguchi & Co-workers, *Tetrahedron Letters* **1985**, 26, 1723.

■ **Seminal Paper:** Stork & Dowd, *JACS*, **1963**, 85, 2178-2180

■ **Reviews:**

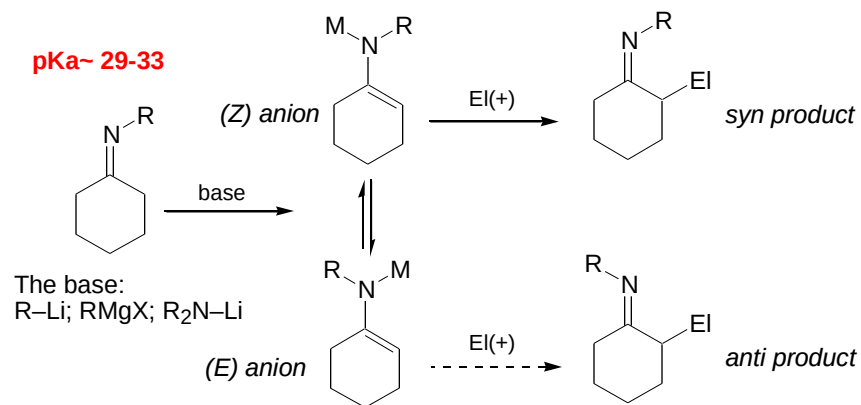
Martin in *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.16, pp 475-502

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:**



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

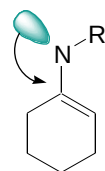
■ **Solid State & Solution Structure:**

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

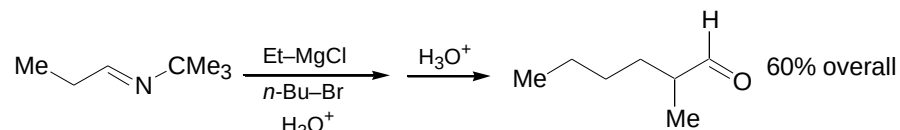
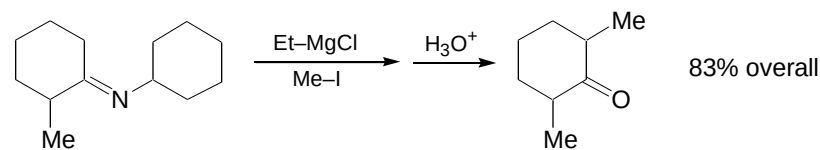
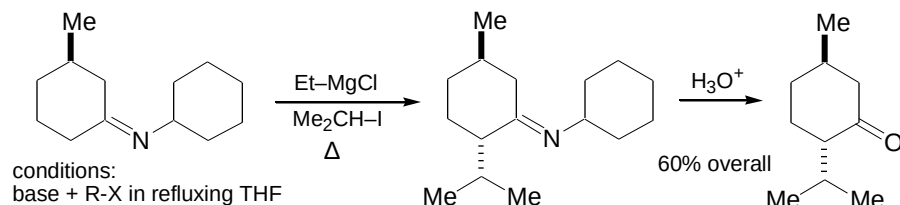
■ **Geometry Rationalization:**



nonbonding N-lone pair may be stabilized by delocalization into antibonding orbital of C=C.

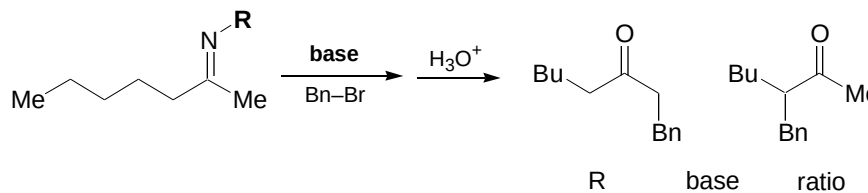
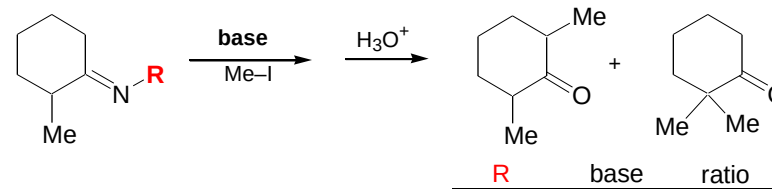
Remember, (Z) geometry also favored for enol ethers

■ **Representative Reactions:**



Stork & Dowd, *JACS*, **1963**, 85, 2178-2180

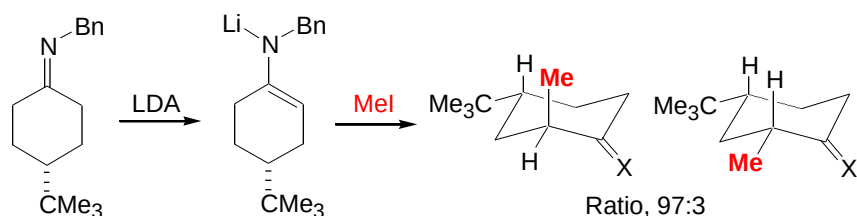
■ **Nature of N-substituent, base, and solvent additive can play a role in deprotonation regioselectivity:** Hosomi, *JACS*, 1982, 104, 2081-2082



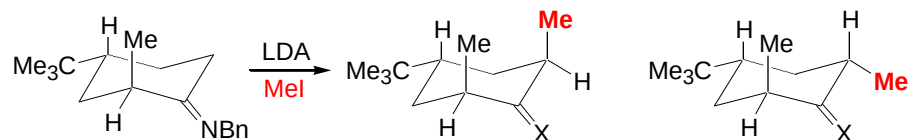
+ 1 equiv HMPA

-cyclohexyl	s-BuLi	74:26
-cyclohexyl	s-BuLi	100:0

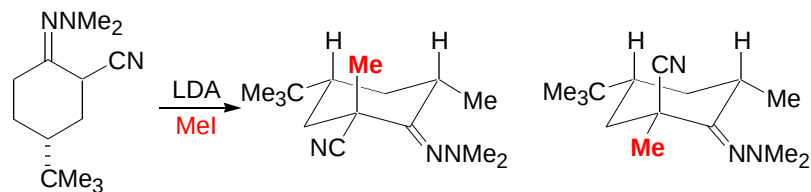
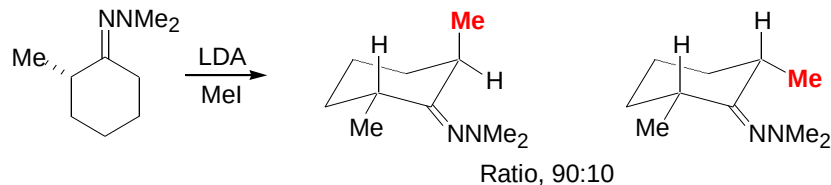
Stereochemical Issues:

Fraser, JACS **1978**, 100, 7999

Tendency for axial-chair alkylation is significantly greater than for ketones

Fraser, JACS **1978**, 100, 7999

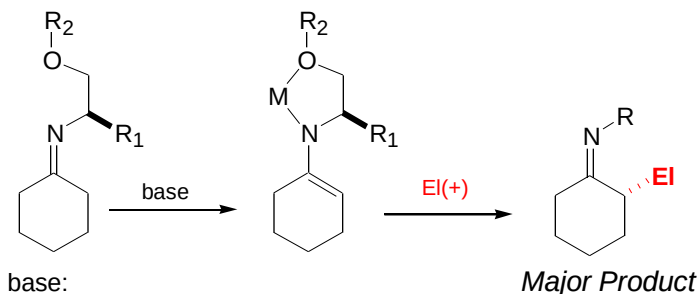
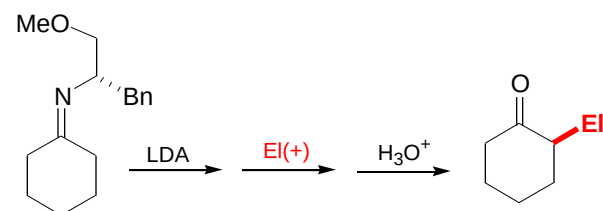
X	Ratio
X = N-Bn	94:06
X = O	60:40

Collum, JACS **1984**, 106, 4865-4869

Chiral Metalloenamines:

early papers: { Meyers, J. Am. Chem. Soc **1976**, 98, 3032
Whitesell, J. Org. Chem. **1978**, 42, 377-378

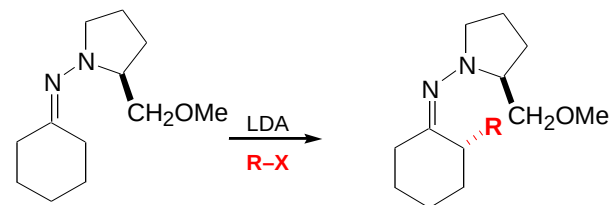
full papers: { Meyers, J. Org. Chem **1978**, 43, 892
Meyers, J. Am. Chem. Soc **1981**, 103, 3081
Meyers, J. Am. Chem. Soc **1981**, 103, 3088

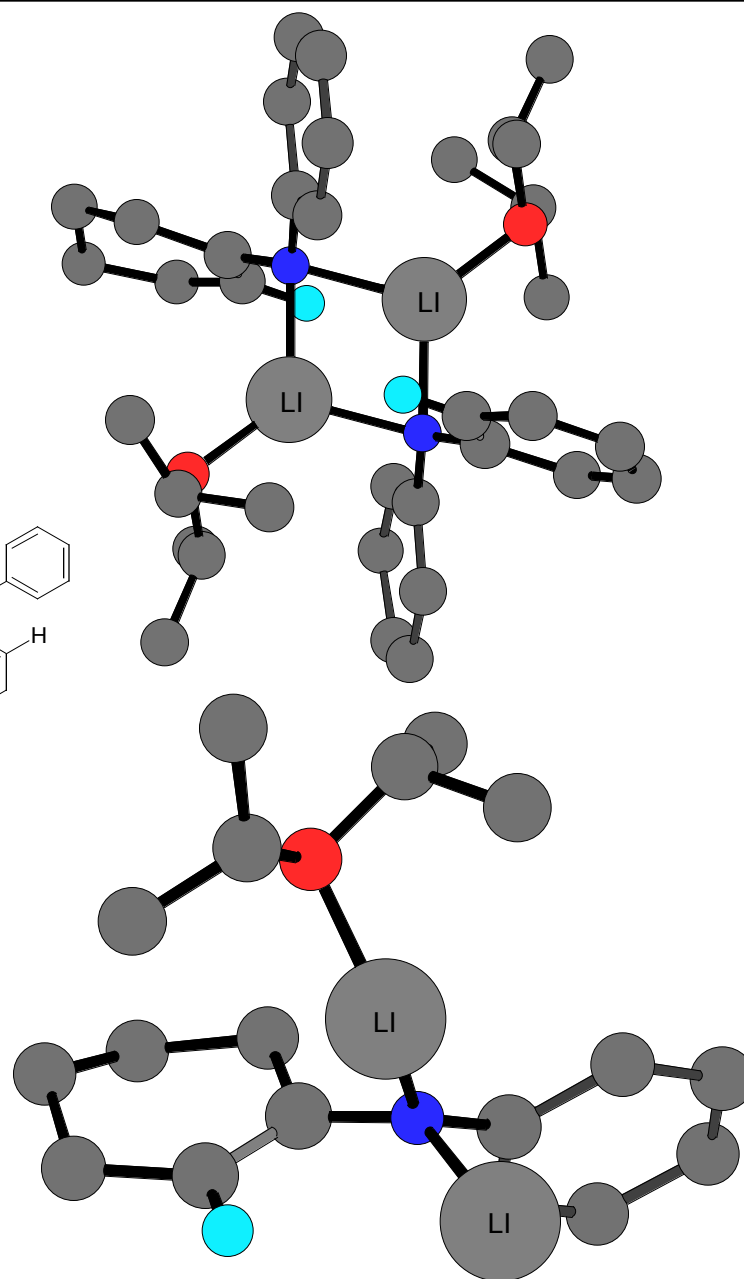
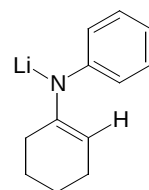
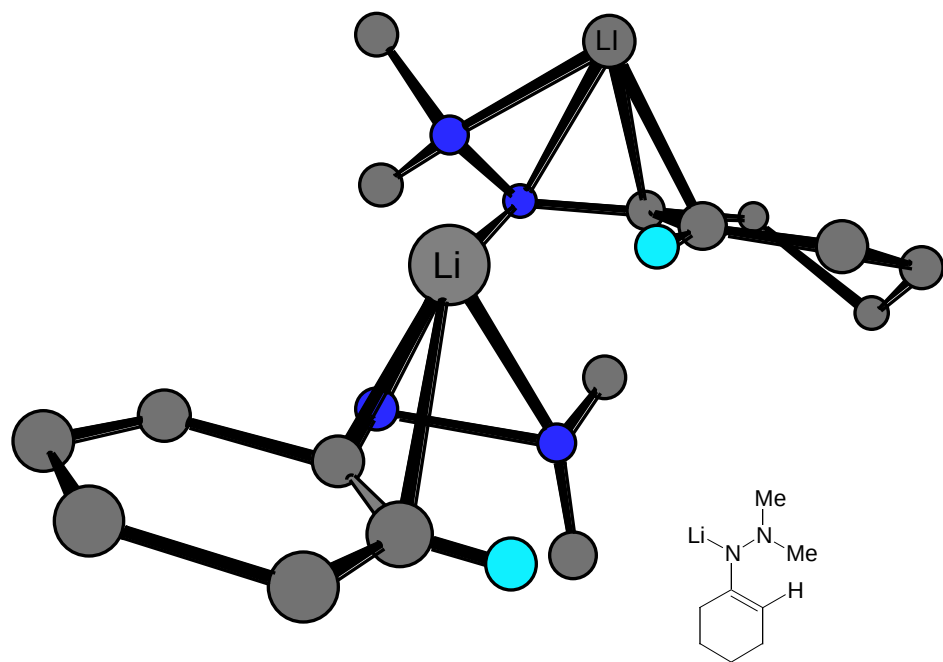
The base:
R-Li; RMgX; R₂N-Li

R-X	ee
Me-I	87
Et-I	94
n-Pr-I	99

Meyers, J. Am. Chem. Soc **1981**, 103, 3081

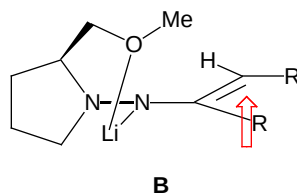
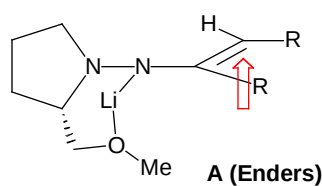
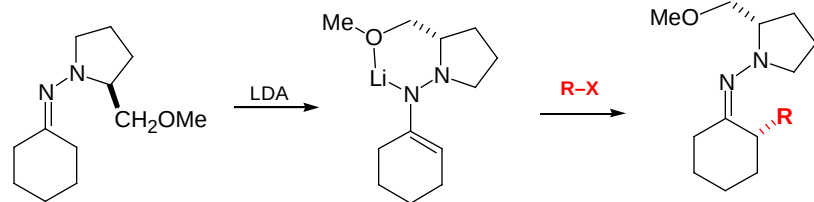
Chiral Metallated Hydrazones

Enders in *Asymmetric Synthesis*, **1984**; Vol 3, Chapter 4, pp 275-339

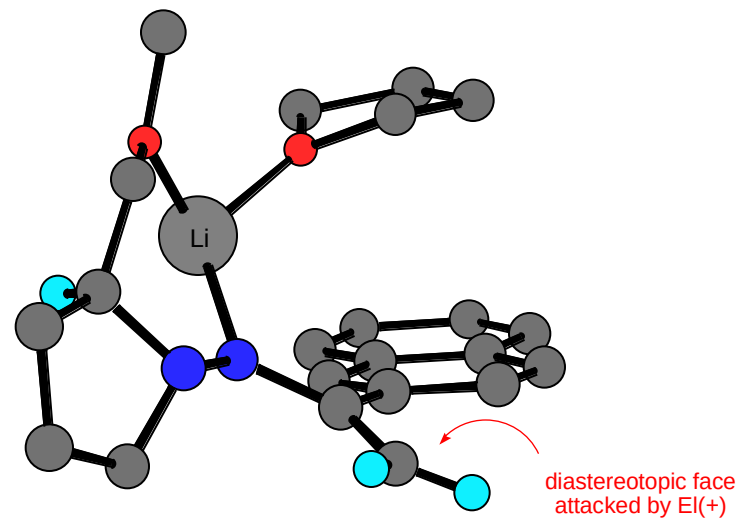
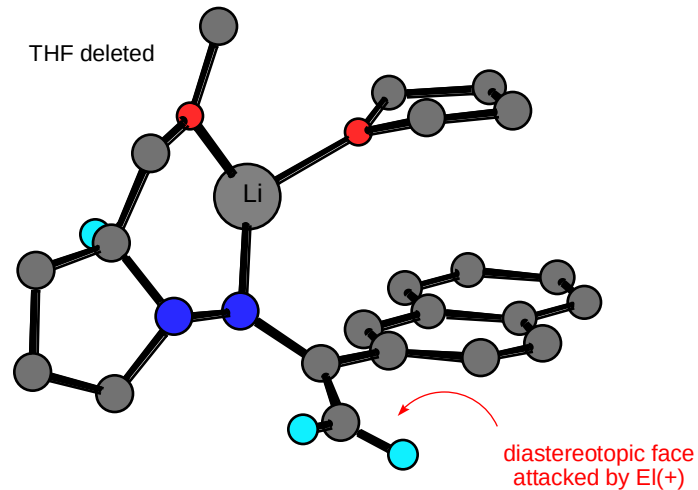


Collum & Clardy, JACS **1984**, 106, 4865

Chiral Metallated Hydrazones



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.

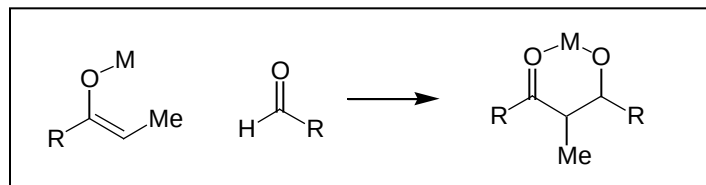
<http://www.courses.fas.harvard.edu/~chem206/>

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 Reactions 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.

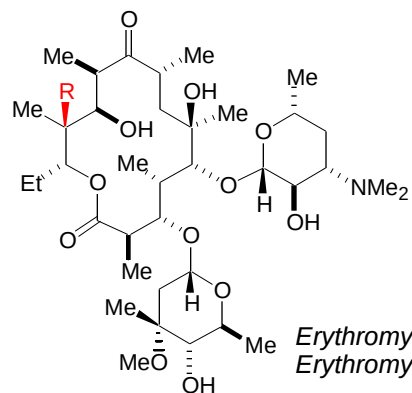
Franklin, A. S. and I. Paterson (**1994**). "Recent Developments in Asymmetric Aldol Methodology." *Contemporary Organic Synthesis* 1: 317-338.

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."

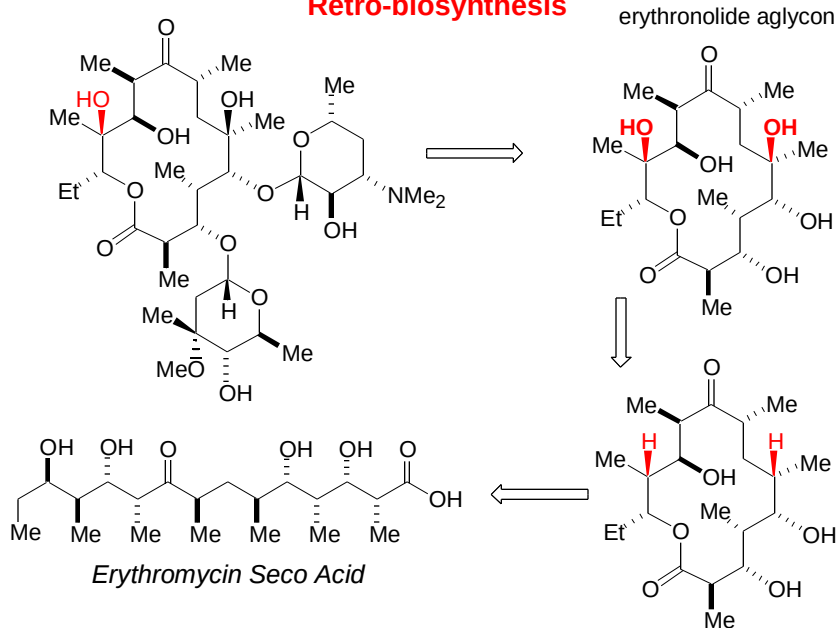


J. W. Cornforth

"That Outpost of Empire, Australia
Produces some Curious Mammalia
The Kangaroo Rat
The Blood-sucking Bat
and Aurthur J. Birch, inter alia."

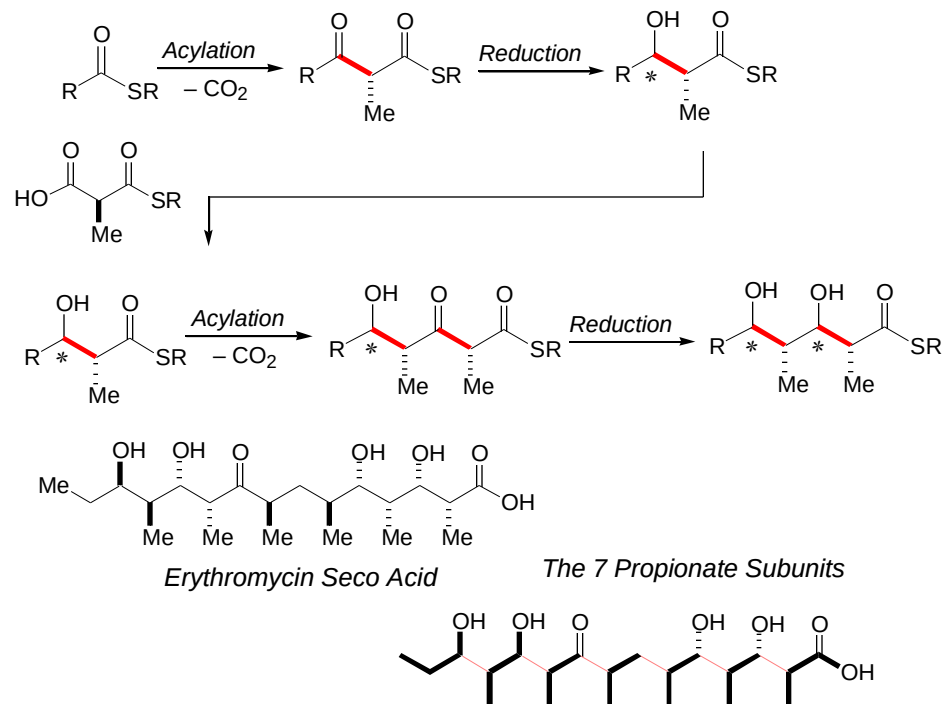
Erythromycin A, R = OH
Erythromycin B, R = H

Retro-biosynthesis



Recent overview: Staunton, *Angew. Chem. Int. Edit.* **1991**, 30, 1302-1306

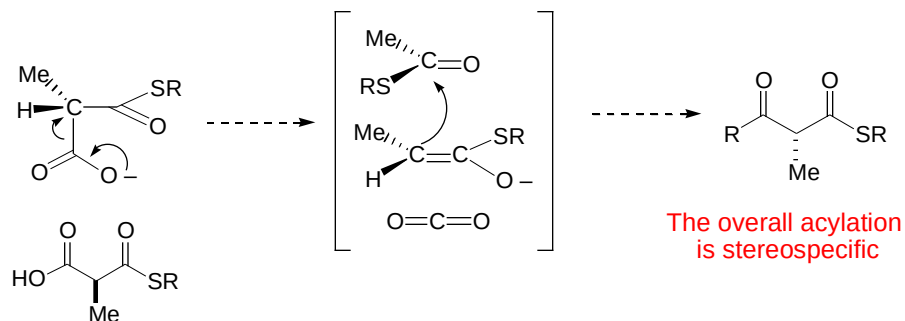
Polypropionate Biosynthesis: The Elementary Steps



The Acylation Event

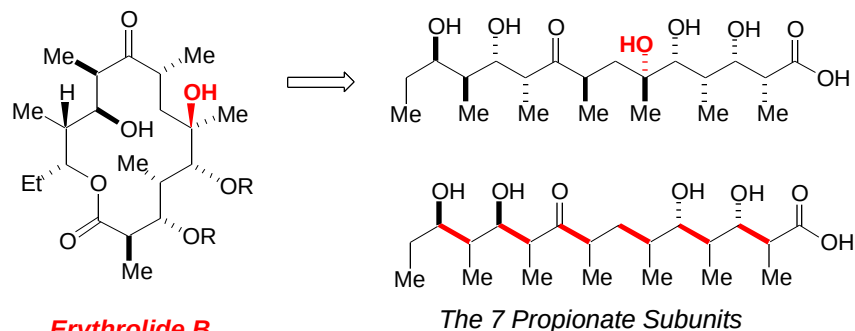
Decarboxylation-Acylation could either be stepwise (Option A) or concerted (Option B).

The stepwise Option

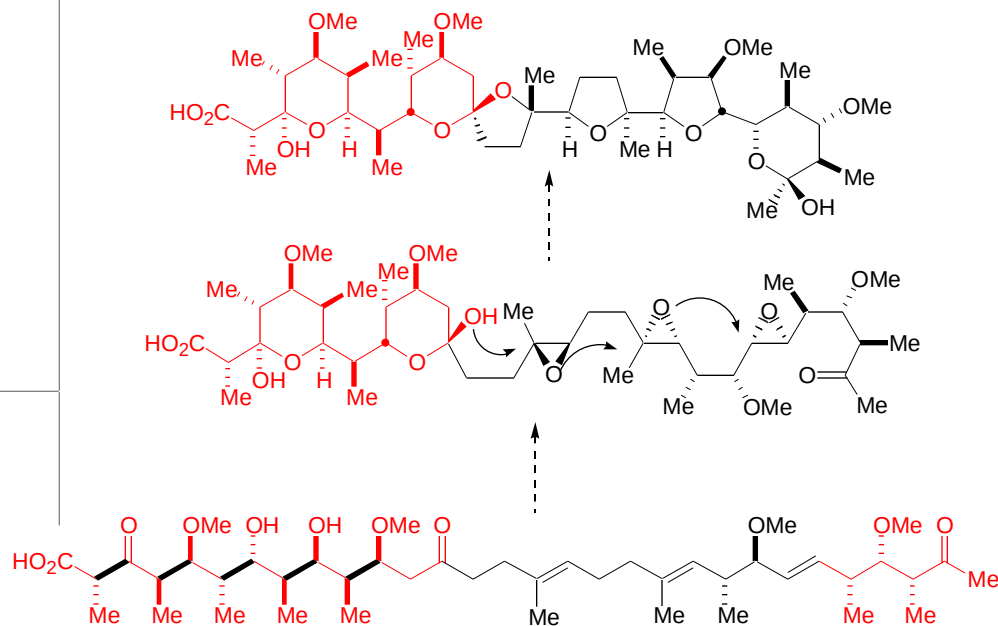


See Lecture 23; page 23-08 for first laboratory example

Polypropionate & Polyacetate Biosynthesis: Develop a Laboratory Simulation

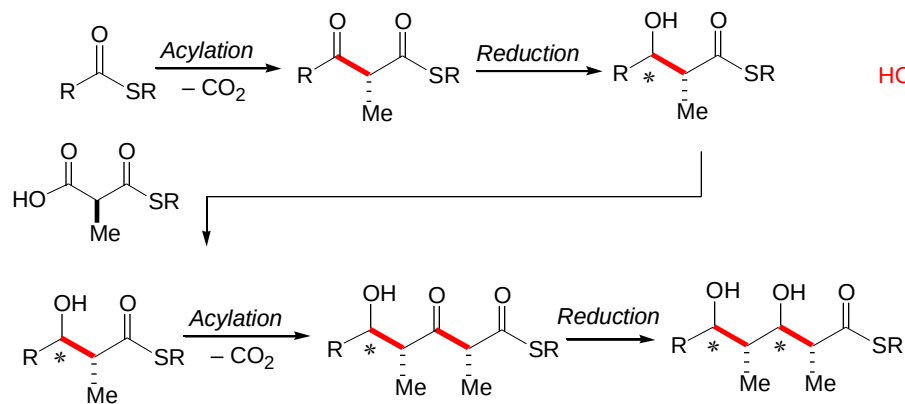


Latter Stages of Lonomycin Biosynthesis

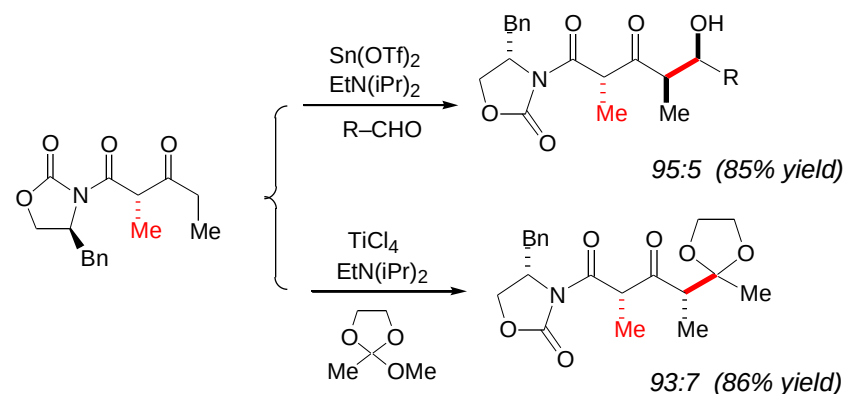
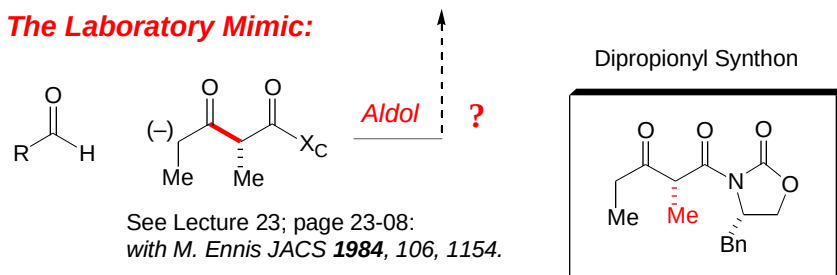


Cane, Celmer, Westley JACS **1983**, 105, 3594

Polypropionate Biosynthesis: The Elementary Steps



The Laboratory Mimic:



with Ratz, Huff, & Sheppard, JACS **1995**, 117, 3448

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

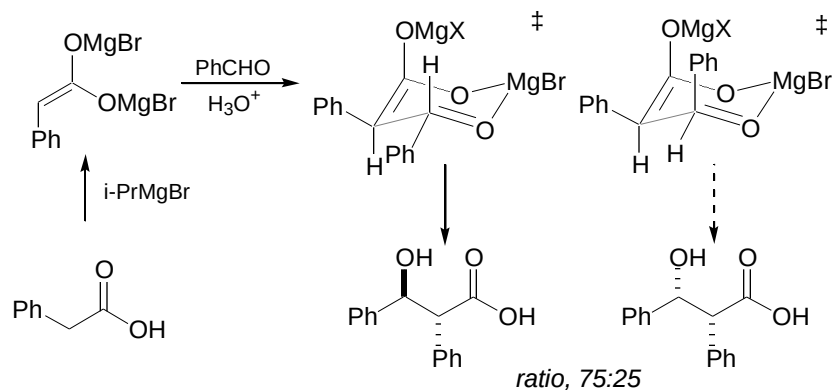
Comprehensive Organic Synthesis, **1991**; Vol 2

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



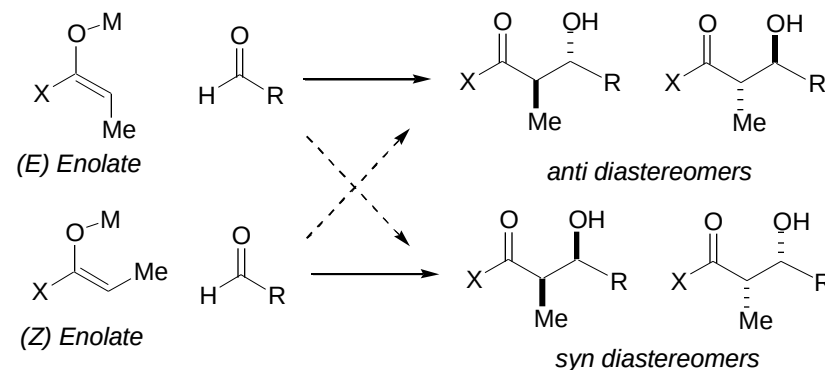
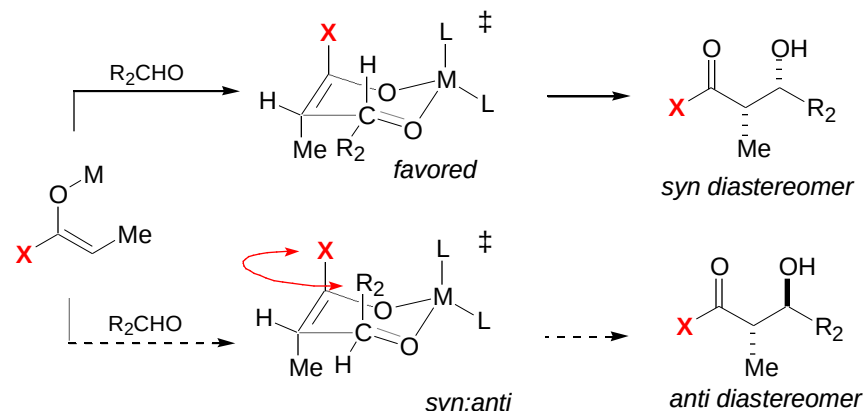
Zimmerman recognized that diastereoselection should be a function of the relative sizes of the substituents on the carbonyl component.

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.

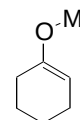
Zimmerman, *J. Am. Chem. Soc.* **1956**, 79, 1920

DuBois 1965-67: Rough correlation between enolate structure & product stereochemistry for alkali and alkaline earth enolates

**Zimmerman-Traxler Model for (Z) Enolates**

X = CMe ₃	M = Li	> 98 : 2	Heathcock 1977
	M = MgBr	> 95 : 5	DuBois 1972

X = C₆H₅ M = Li 80 : 20

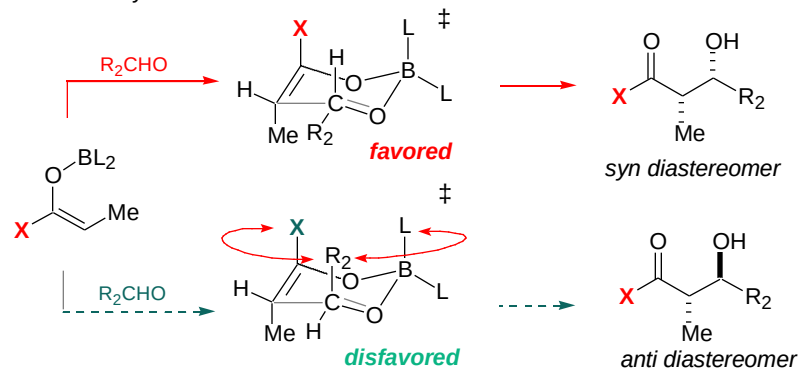
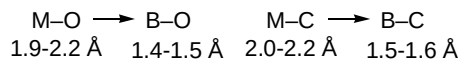


M = Li 48 : 52
 M = AlEt₂ 50 : 50 House 1971

Stereocontrol optimal for "large" X; the reaction is not general.

Why Boron?

To tighten up the transition state.
Design TS where control can come
exclusively from metal center



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	Evans, Masamune, 1979-81
	M = BBu ₂	> 97 : 3	

	M = Li	48 : 52	House 1971	Evans/masamune, 1979-81
	M = AlEt ₂	50 : 50	Yamamoto 1977	
	M = BBu ₂	33 : 67 (ether)		
	M = BBu ₂	17 : 83 (pentane)		
	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

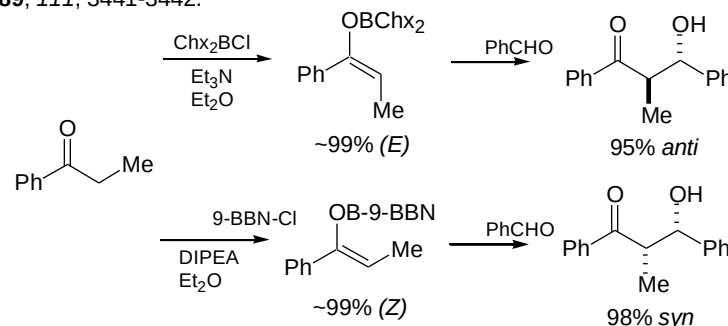
Masamune, *Tet. Lett* **1979**, 1665, 2225, 2229, 3937

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. *JACS* **1989**, 111, 3441-3442.

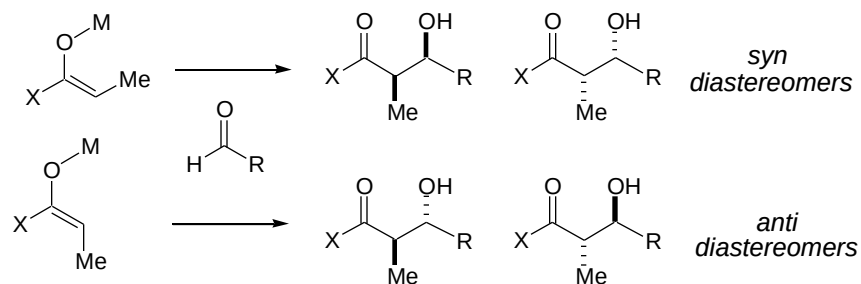
Dialkylboron chlorides (Brown)
J. Org. Chem. **1992**, 57, 499-504.
J. Org. Chem. **1992**, 57, 2716-2721.
J. Org. Chem. **1992**, 57, 3767-3772.
J. Org. Chem. **1993**, 58, 147-153.

JACS **1989**, 111, 3441-3442.

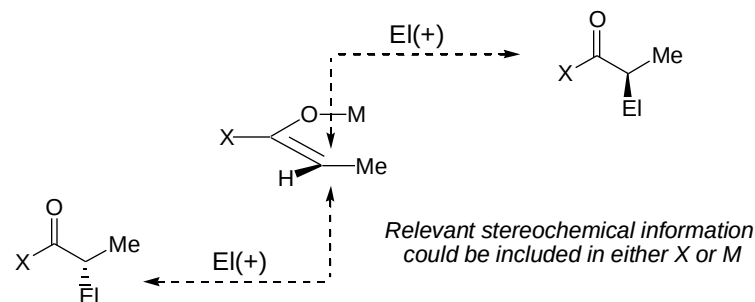


It appears that there is not a great difference in aldol diastereoselectivity

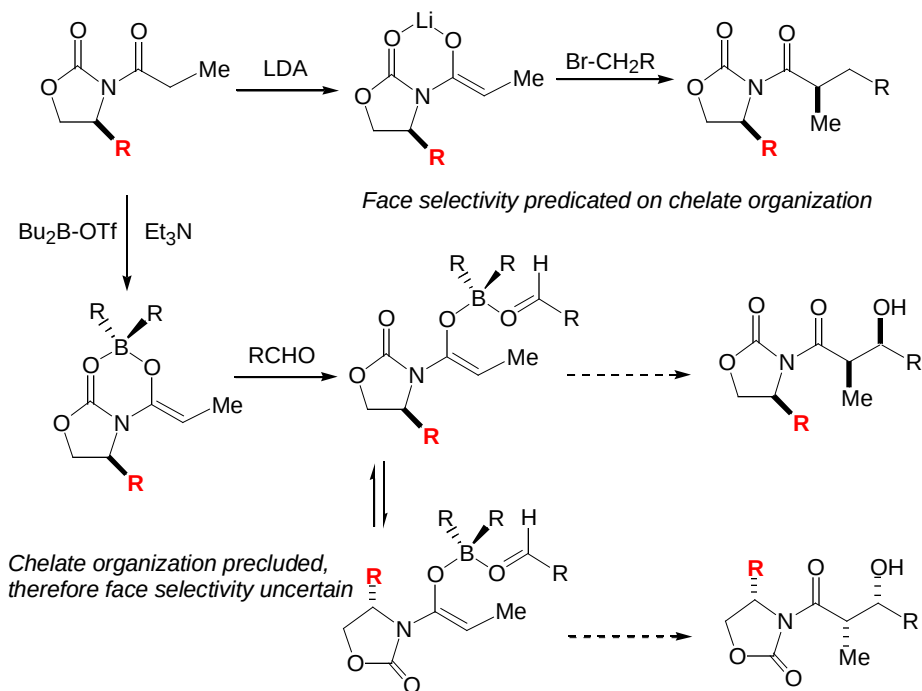
Dissection of the Aldol Problem: Selection of one enantioface



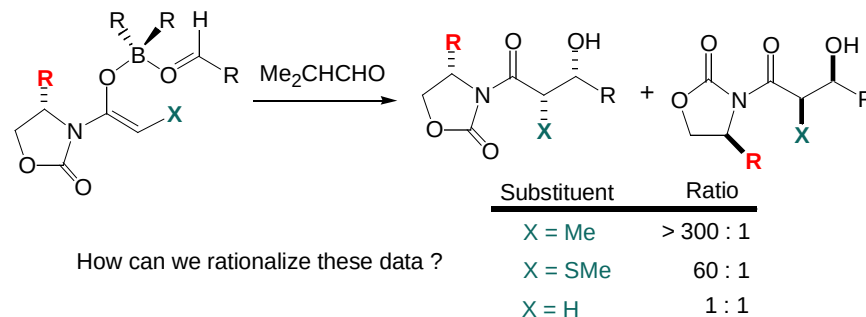
Control attack on the two enolate enantiofaces



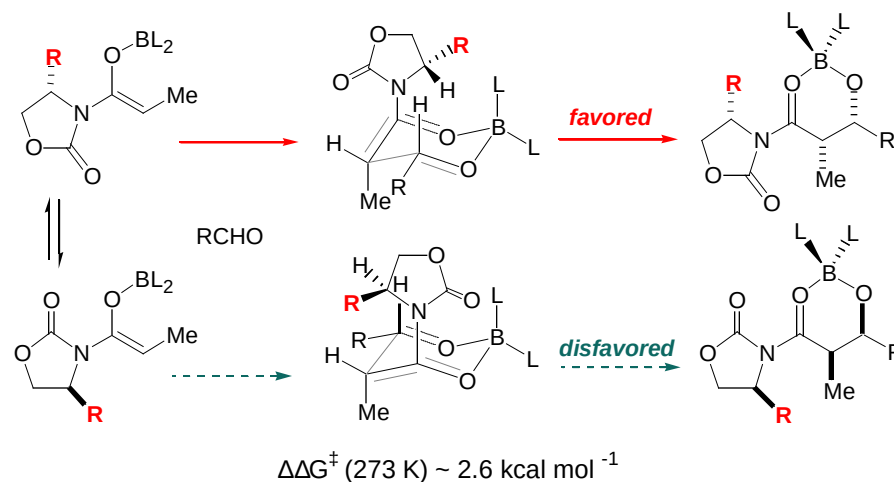
Imide Enolates: The problem of enolate face selectivity



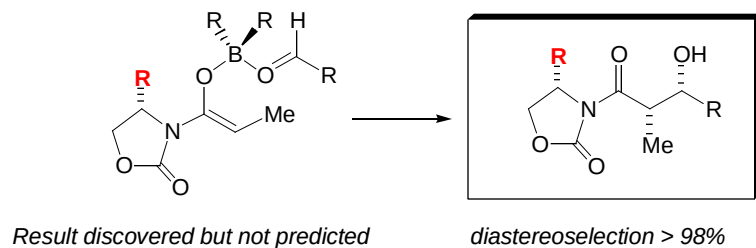
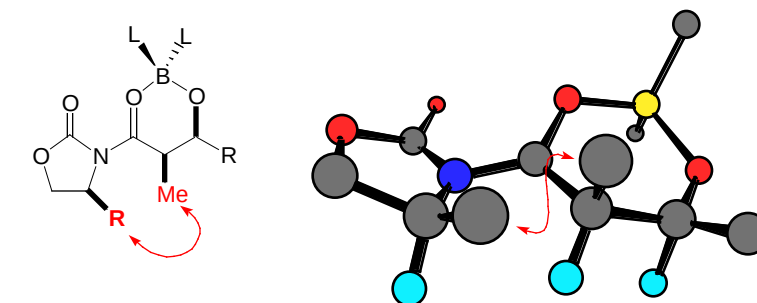
The Alpha substituent, X, plays pivotal role in aldol diastereoselection



Model for Asymmetric Induction (unpublished)



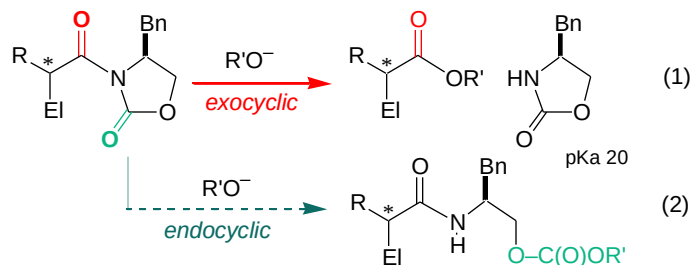
The aldol reaction selects for the opposite enolate diastereoface

J. Am. Chem. Soc **1981**, 103, 212-2129

disfavored product diastereomer: The destabilizing interaction?

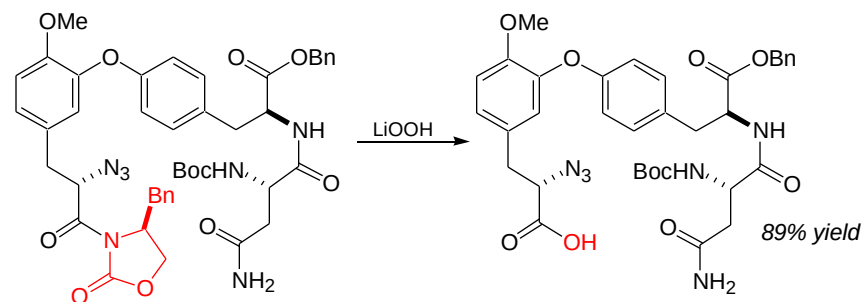
Imide Hydrolysis

Imides may suffer attack at either of the two C=O functions (eq 1, eq 2)

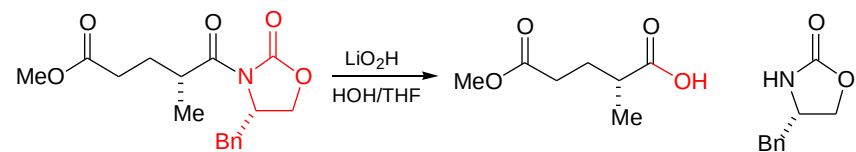


Product distribution a function of attacking nucleophile (*Tet. Lett.* **1987**, 28, 6141)

Substrate	Reagent	Exo:Endo Ratio	Substrate	Reagent	Exo:Endo Ratio
	LiOH	0 : 100		LiOH	06 : 89
	LiOOH	76 : 16		LiOOH	96 : 04



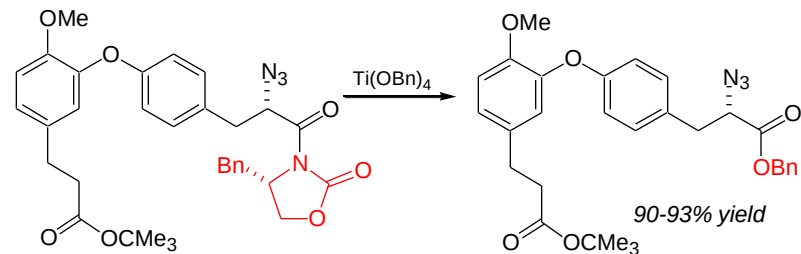
(OF-4949 Synthesis) *JACS* **1989**, 111, 1063



M. Bilodeau, unpublished results

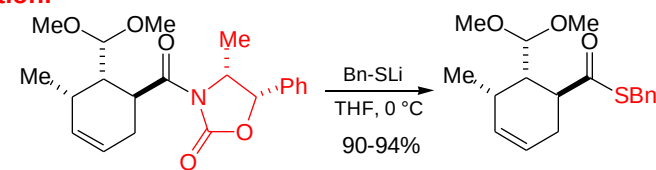
complete hydrolytic selectivity possible

Trans-esterification

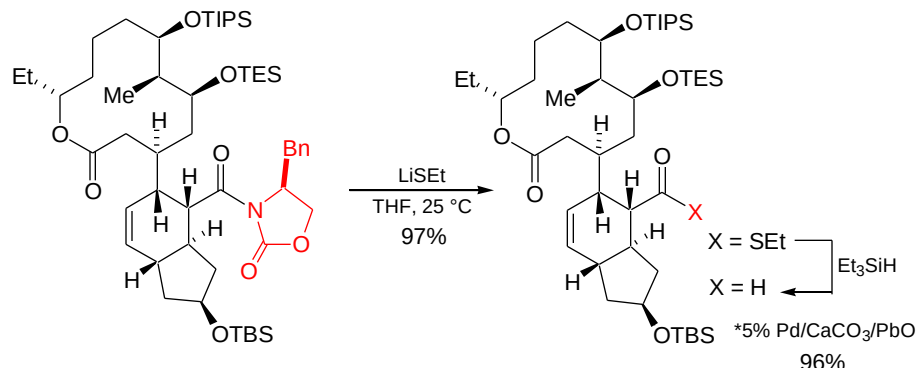


(OF-4949 Synthesis) *JACS* **1989**, 111, 1063

Trans-thioesterification:



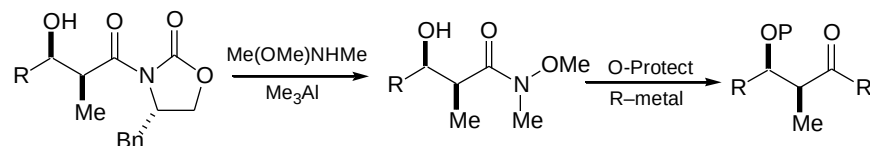
Damon, *Tet. Lett.* **1990**, 31, 2849-2852



(Lepicidin Synthesis) *J. Am. Chem. Soc.* **1993**, 115, 4497-4513

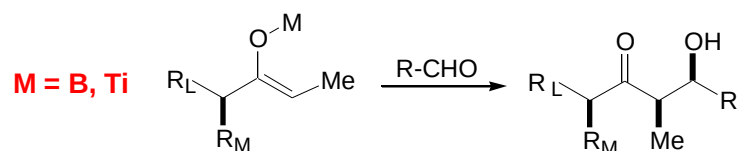
RCOSR $\rightarrow$ RCHO Fukuyama, *J. Am. Chem. Soc.* **1990**, 112, 7050-7051

Transamination to Weinreb Amides (see Handout 23A)

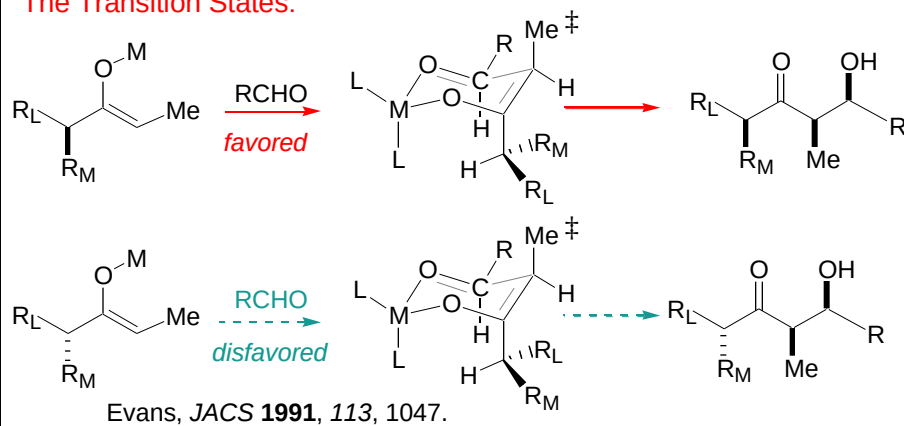


for recent examples see, *J. Am. Chem. Soc.* **1992**, 114, 9434-9453

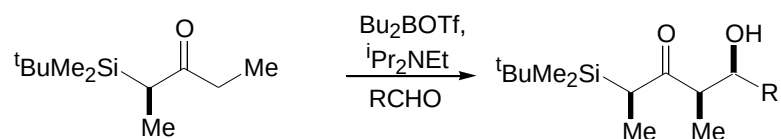
General Reaction for Syn Aldols: M = B, Ti



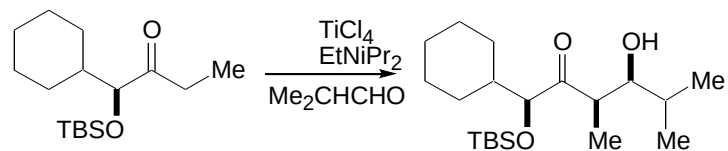
The Transition States:



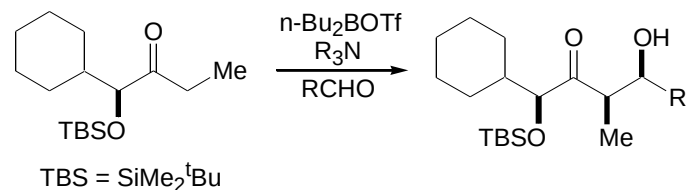
Examples:

Enders ACIEE **1988**, 27, 581.

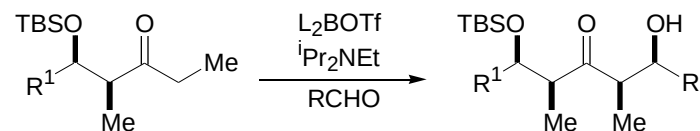
Diastereoselection = 96-98%

Evans, JACS **1991**, 113, 1047.

Diastereoselection: 99:1 (81%)

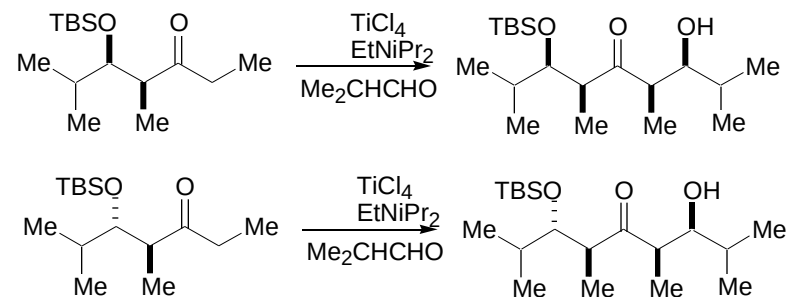
Masamune, JACS **1981**, 103, 1566.

R	Diastereoselection
Ph	97:3
Et	98:2
BnOCH ₂ CH ₂	96:4
Me ₂ CH	>99:<1

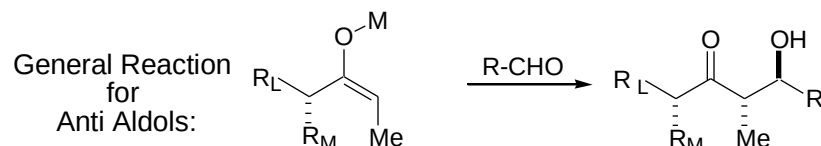
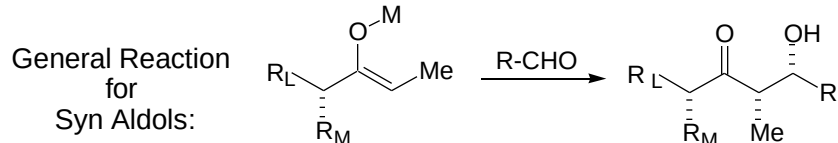


This system does not give a completely clean (Z) enolate

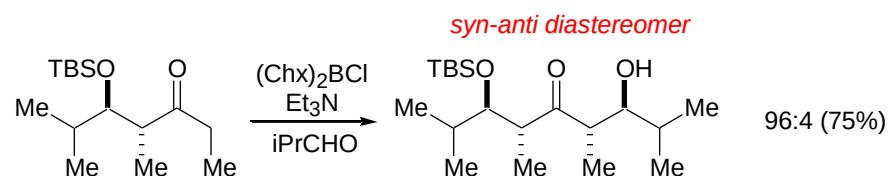
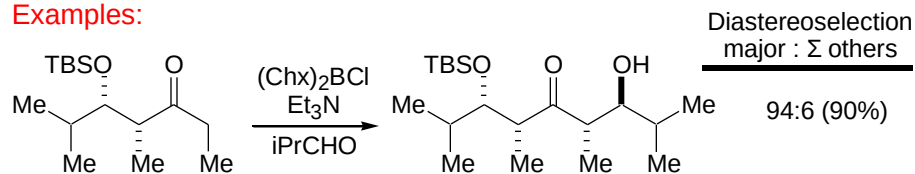
L	Diastereoselection
Bu	63:37 - 84:16
9-BBN	83:17 - 85:15
(-)-lpc	72:28
(+)-lpc	91:9 - 94:6

Paterson, McClure, Tet.Lett. **1987**, 28, 1229.Evans, JACS **1991**, 113, 1047.

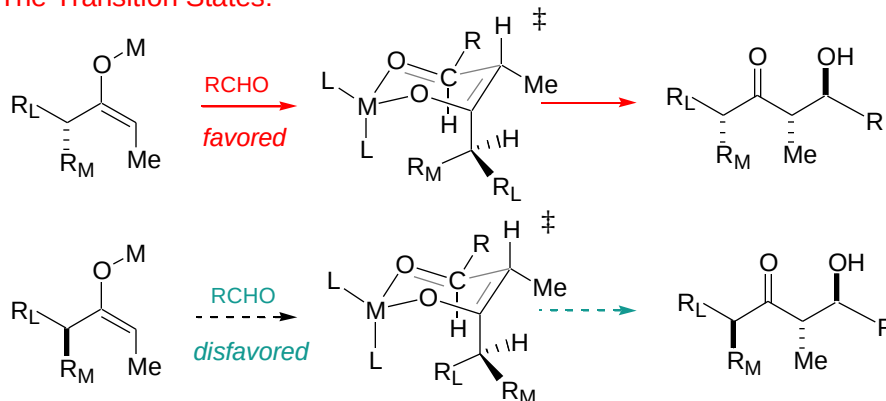
Diastereoselection: 95:5 (80-90%)



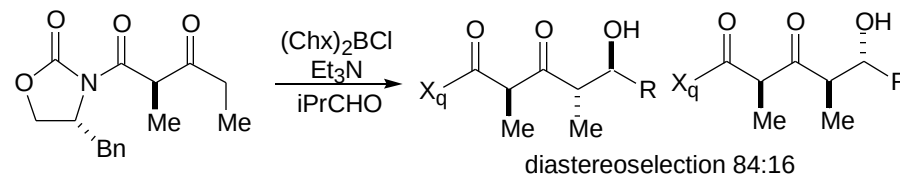
Examples:



The Transition States:

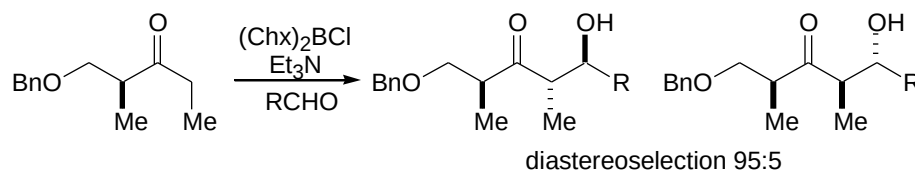


However, the preceding precedent does not extend to these systems:



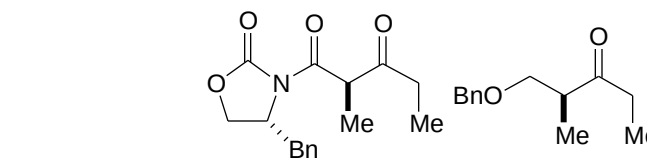
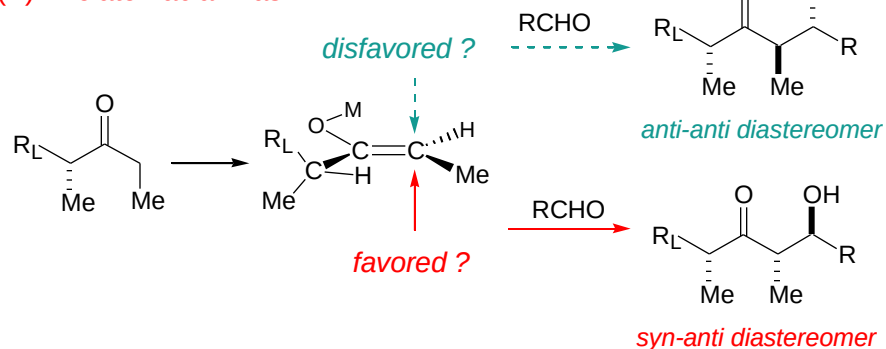
D. A. Evans, H. P. Ng, J. S. Clark, D. L. Rieger *Tetrahedron*, **1992**, 48, 2127-2142.

An analogous case:



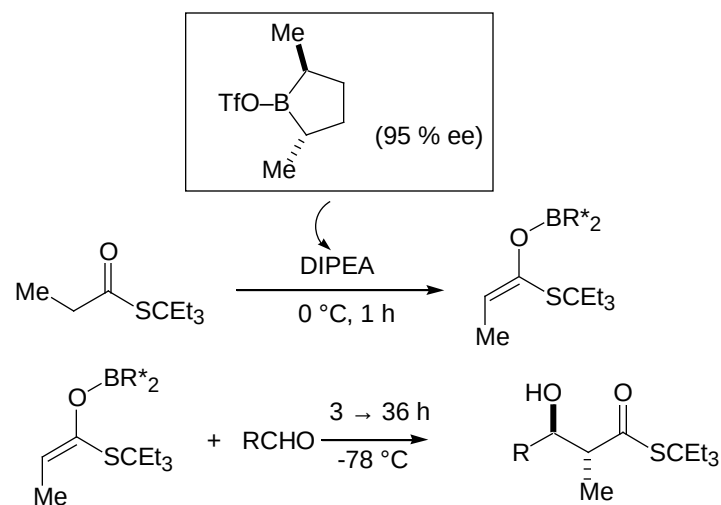
I. Patterson, J. M. Goodman, M. Isaka *Tetrahedron Lett.* **1989**, 30, 7121-7124.

(E) Enolate Facial Bias

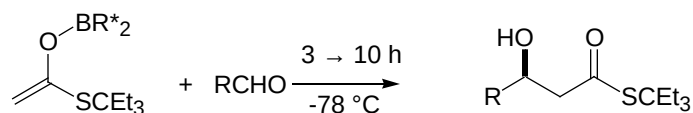


These enolates do not comply with steric analysis: $\rightarrow$ electronic effects?

Tetrahedron, **1992**, 48, 2127-2142.

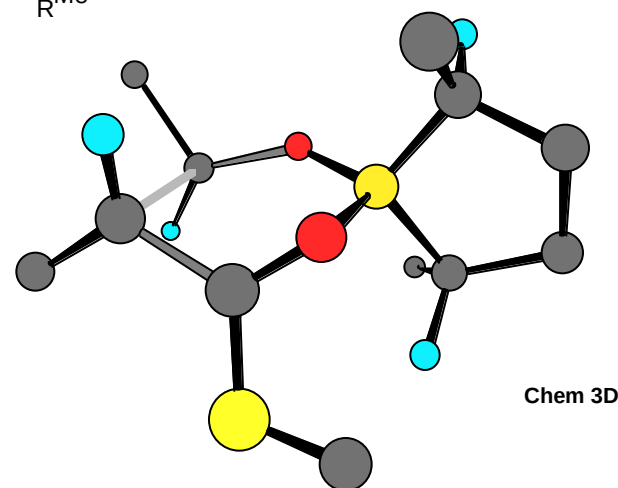
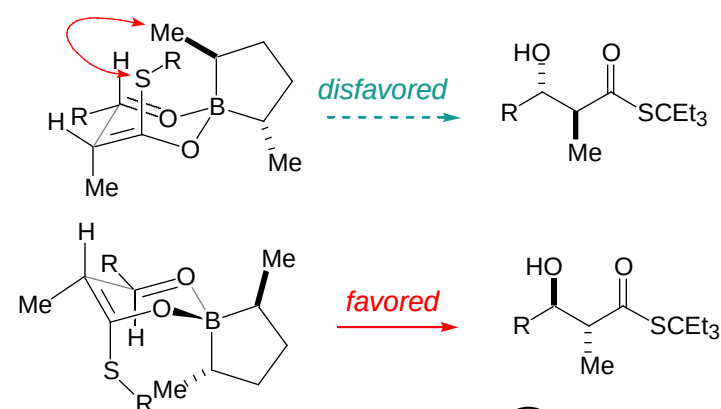
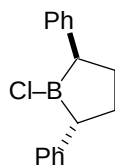
Masamune, Sato, Kim, Wollmann *J. Am. Chem. Soc.* **1986**, 108, 8279-8281.

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 ₆ H ₁₁ CHO	87	32:1	93 (98)
PhCHO (71)	71	33:1	96 (99.8)

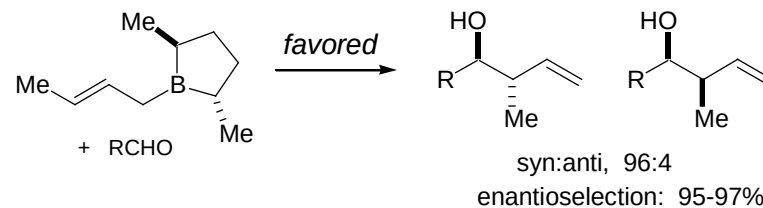


RCHO	Yield, %	ee % (corrected)
n-PrCHO	82	87 (91)
i-PrCHO	81	87 (92)
t-BuCHO	71	94 (98)
c-C ₆ H ₁₁ CHO	95	86 (90)
PhCHO	78	88 (92)

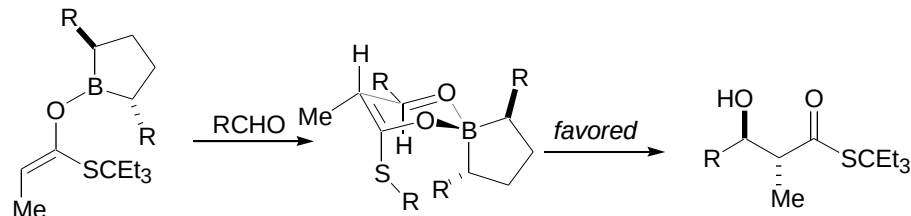
See analogous study by Reetz

Reetz *Tetrahedron Lett.* **1986**, 4721

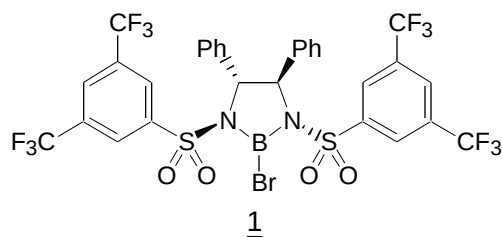
Analogous Carbonyl Allylation

Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, 52, 4831

Masamune-Reetz Analogy:



Metal-Based Chiral Auxilliary:

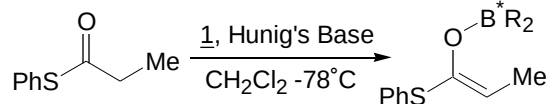
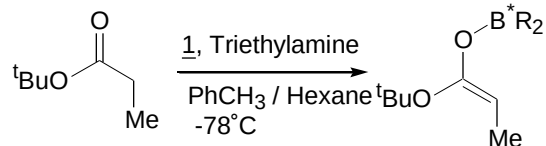


References:
 (Corey) JACS. **1989**,111, 5494
 (Corey) JACS. **1990**,112, 4977
 (Corey) TL. **1991**,32, 2857
 (Corey) TL. **1993**,34, 1737.

Does this reagent perform in accord with the Masamune-Reetz analogy?
 Note: The sulfonamide nitrogens are pseudo-tetrahedral

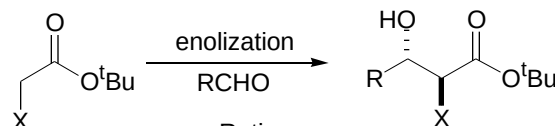
Enolization:

Either enolate geometry possible with proper choice of base, solvent, and substrate.



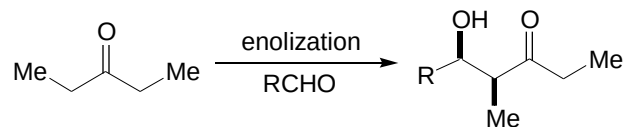
A mechanistic proposal for enolization control is presented in paper

(Corey) JACS. **1989**,111, 5494

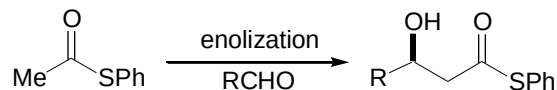
Chiral Anti Aldol Reaction: JACS **1990**,112, 4977; TL **1991**,32, 2857.

(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 %

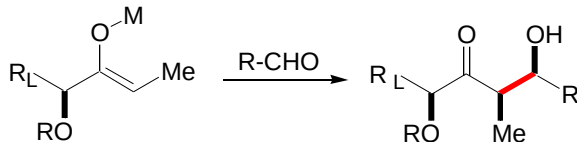
Chiral Syn Aldol Reaction JACS **1989**,111, 5494.

(R)	Ratio syn:anti	% ee	Yield
Ph-	94 : 6	97	86 %
Me ₂ CH-	98 : 2	95	91 %
MeCH ₂ -	>98 : 2	>98	68 %

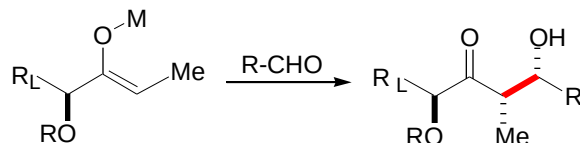
Chiral Acetate Aldol Reaction JACS **1989**,111, 5494.

(R)	% ee	Yield
Ph-	91	84 %
Me ₂ CH-	83	82 %

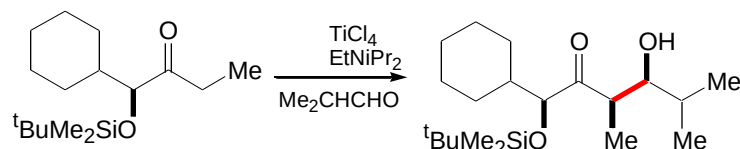
Reference Rxn



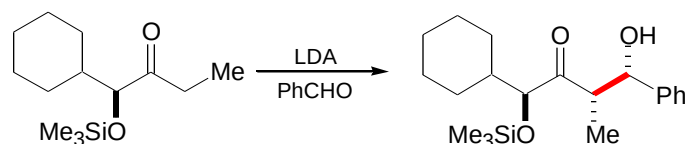
Chelate-Organized Variant



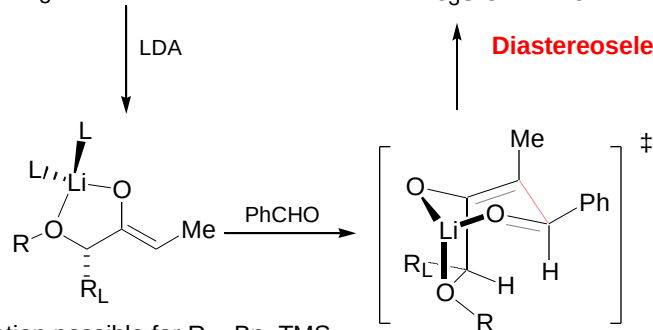
Nonchelate Reaction

Masamune, *JACS* **1981**, 103, 1566 (boron enolate)Evans, *JACS* **1991**, 113, 1047 (titanium enolate)

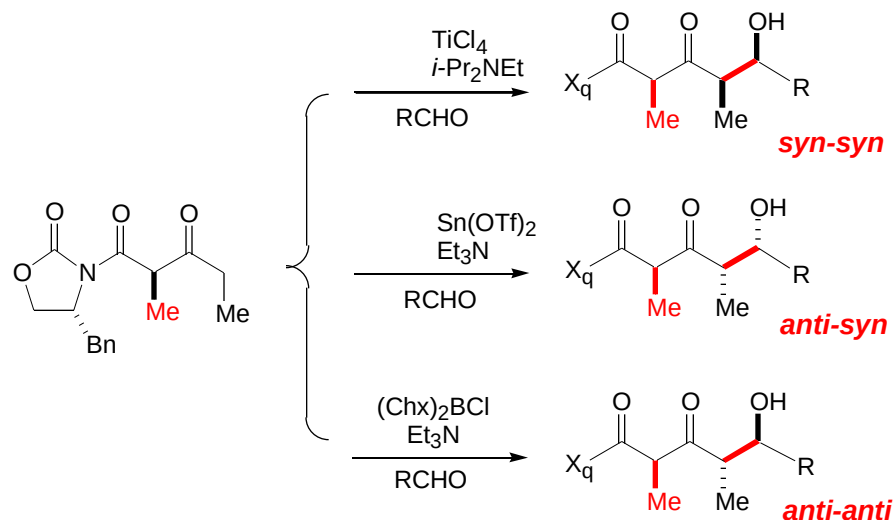
Diastereoselection: 99:1



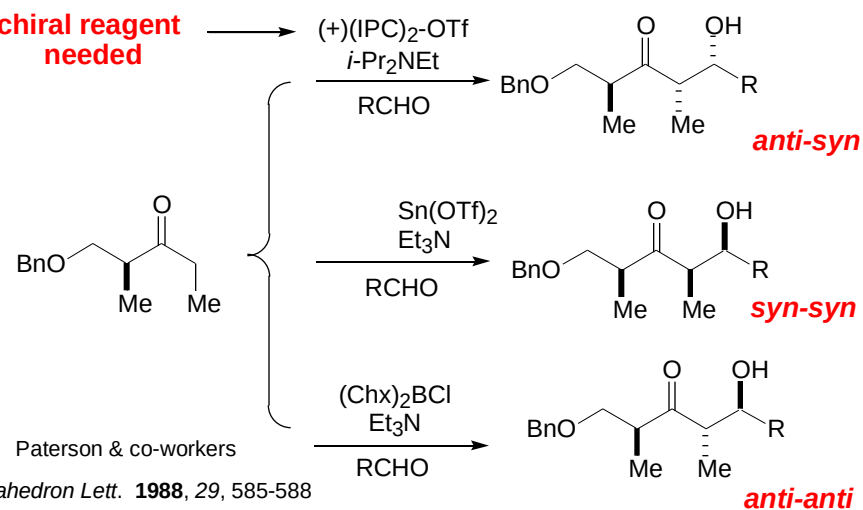
Diastereoselection: 90:10

Chelation possible for R = Bn, TMS
but marginal for TBSThorton, *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

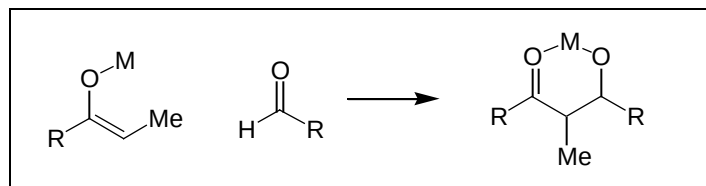
<http://www.courses.fas.harvard.edu/~chem206/>

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 Reactions 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.

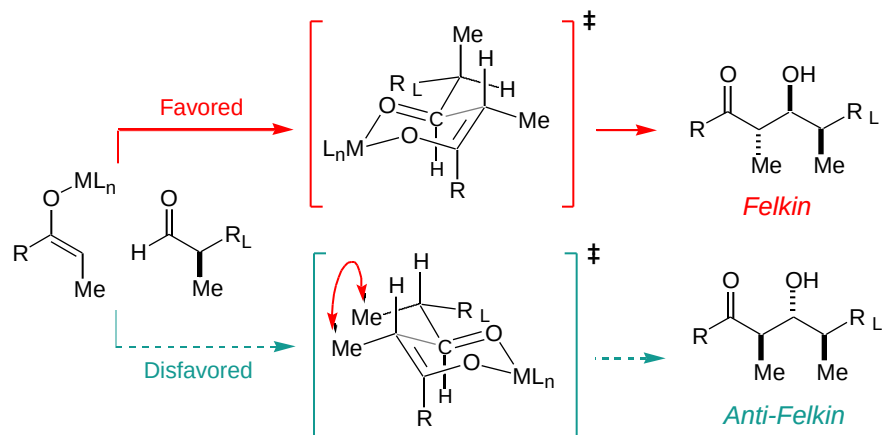
Kim, B. M., S. F. Williams, et al. (**1991**). The Aldol Reaction: Group III Enolates. *Comprehensive Organic Synthesis.* B. M. Trost and I. Fleming. Oxford, Pergamon Press. 2: 239.

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.

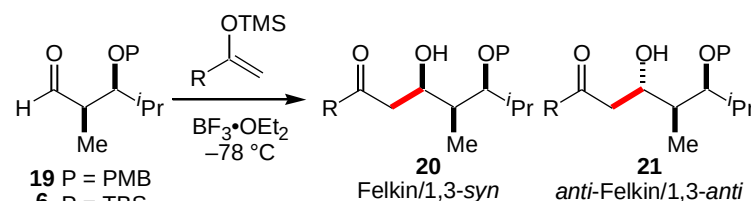
Mahrwald, R. (**1999**). "Diastereoselection in Lewis-acid-mediated aldol additions." *Chem. Rev.* 99(5): 1095-1120.

(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


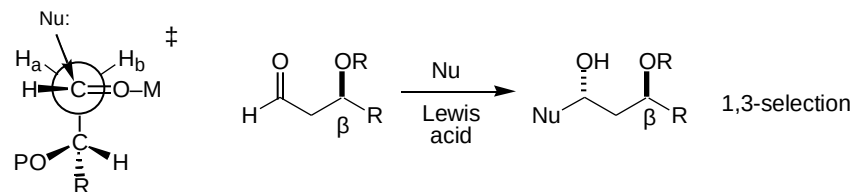
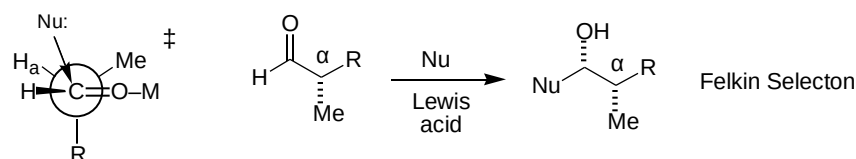
	P = PMB	P = TBS
R	20 : 21	20 : 21
t-Bu	96 : 04	94 : 06
i-Pr	56 : 44	75 : 25
Me	17 : 83	40 : 60

α -substituent dominates for Large Nu

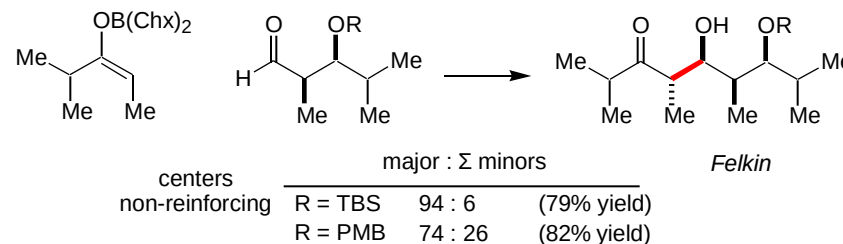
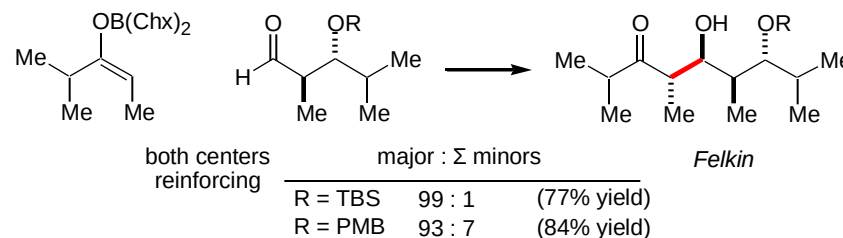
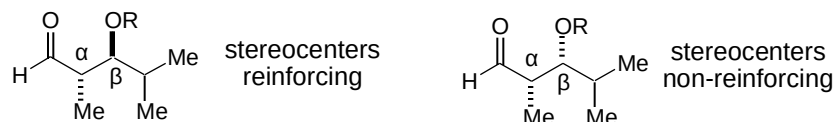
β -substituent dominates for small Nu

Background Information: The influence of β -OR substituents on RCHO

Evans, *JACS* **1996**, 118, 4322-4343

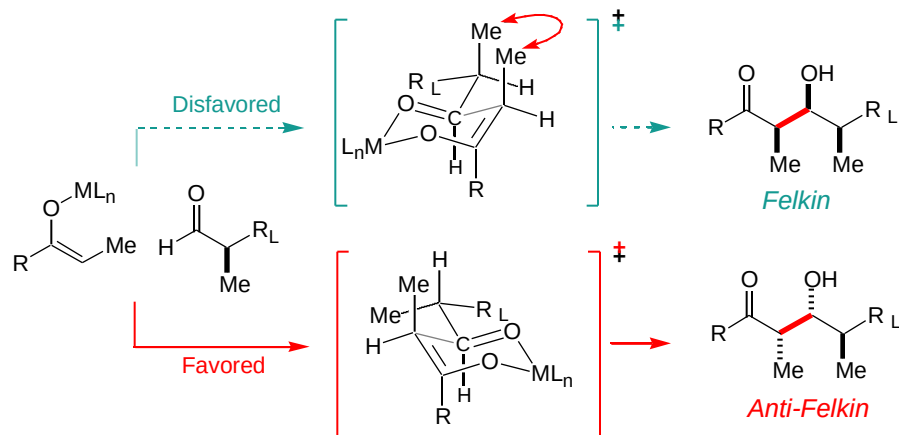


Therefore, one might conclude that:



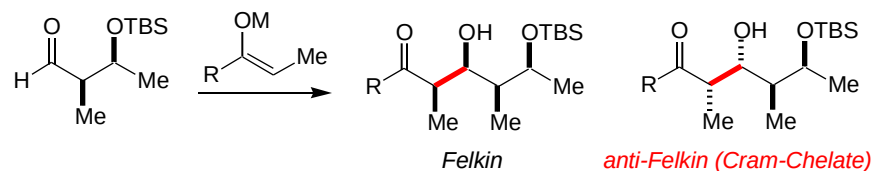
Achiral (E) enolates preferentially add to the Felkin diastereoface
High anti:syn diastereoselectivity ($\geq 97 : 3$) is observed in all cases

Evans et al. *JACS* **1995**, 117, 9073

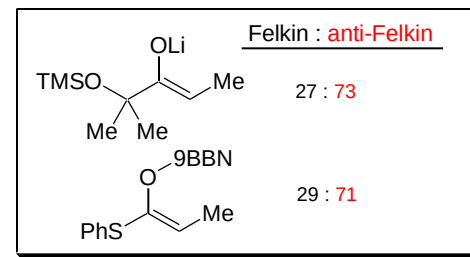
(Z) Enolates Exhibit Anti-Felkin Aldehyde Diastereoface Selection

The illustrated syn-pentane interaction disfavors the Felkin pathway.

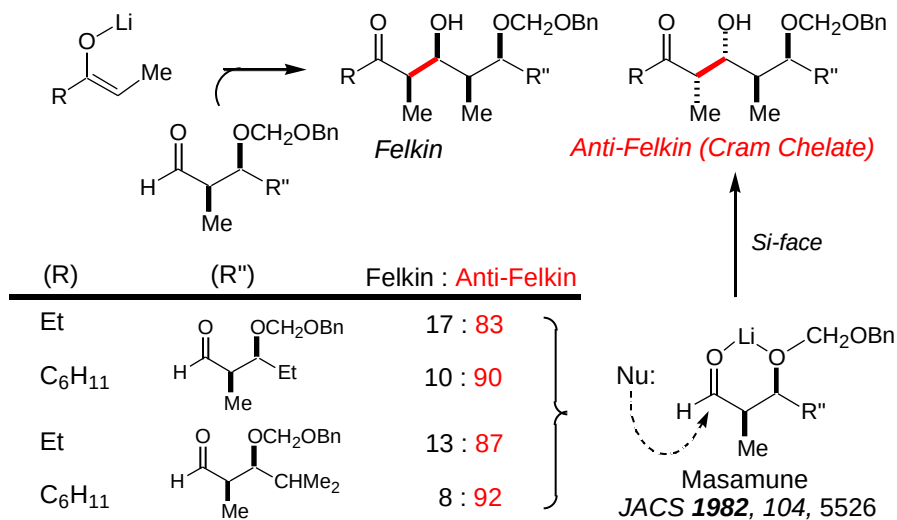
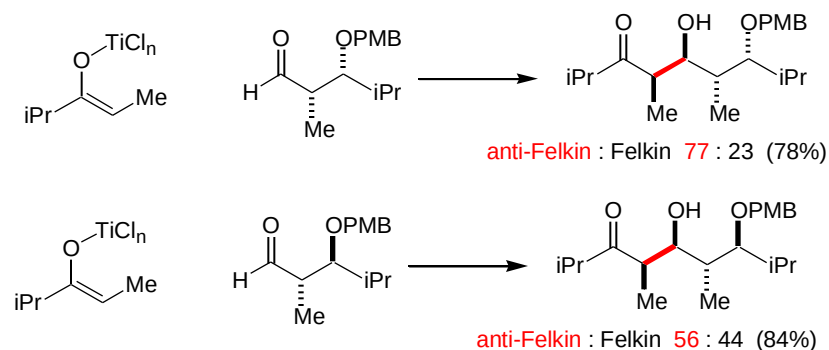
Evans, Nelson, Taber, *Topics in Stereochemistry* **1982**, 13, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, 56, 4151-4157.



D. W. Brooks & Co-workers
Tetrahedron Lett. **1982**, 23, 4991-4994.

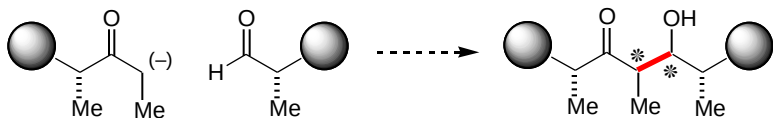


- The bulky OTBS group disfavors chelation. (see Keck, *JACS* **1986**, 108, 3847.)
- The boron and lithium enolates display nearly equal levels of anti-Felkin selectivity.

An Early study rationalized results through chelated transition states:**Titanium enolates exhibit the same trend**

Evans et al. *JACS* **1995**, 117, 9073

Double Stereodifferentiating Aldol Bond Constructions



Stereochemical Control Elements

Enolate geometry

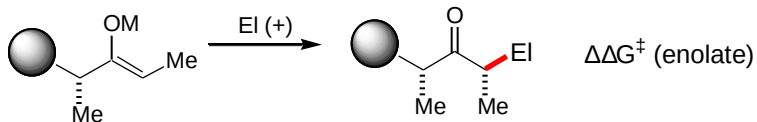
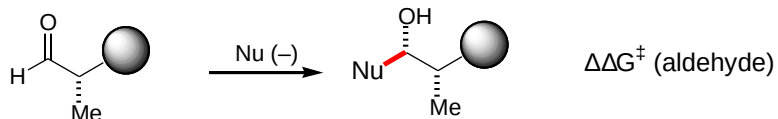


Product

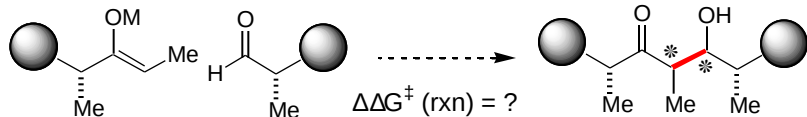
Enolate facial bias $\Rightarrow$ Stereochemistry $\Leftarrow$ Aldehyde facial bias

The Issue: Can one reliably take the diastereoselectivities of the individual reaction partners and use this information in the illustrated extrapolation:

The model reactions:

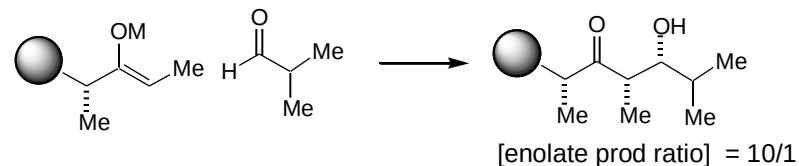
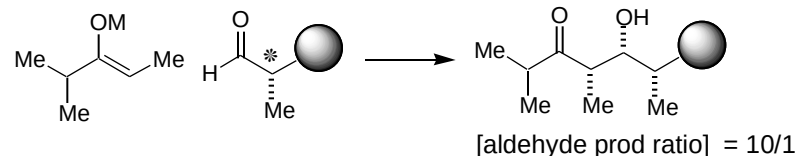


The extrapolation:

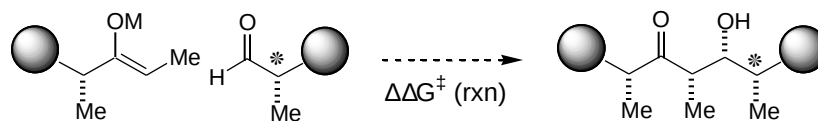
Masamune, *Angew. Chem. Int. Ed.* **1985**, 24, 1-76

Matched reactant pair: Stereo-induction from both partners reinforcing

The reference reactions:



The double stereodifferentiating situation: Stereoselectivity?



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:

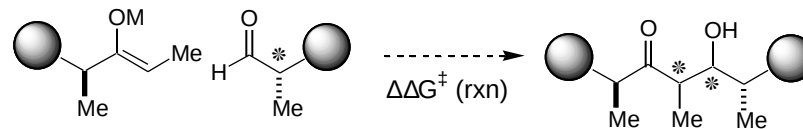
$$\Delta\Delta G^\ddagger (\text{Rxn}) \sim \Delta\Delta G^\ddagger (\text{enolate}) + \Delta\Delta G^\ddagger (\text{RCHO})$$

$$\log [\text{Product ratio}] \sim \log [\text{enolate ratio}] + \log [\text{aldehyde ratio}]$$

$$[\text{Product ratio}] \sim [\text{enolate prod ratio}] \times [\text{aldehyde prod ratio}]$$

Hence, for the case at hand: [Product ratio] $\sim$ [10] $\times$ [10] $\sim$ 100

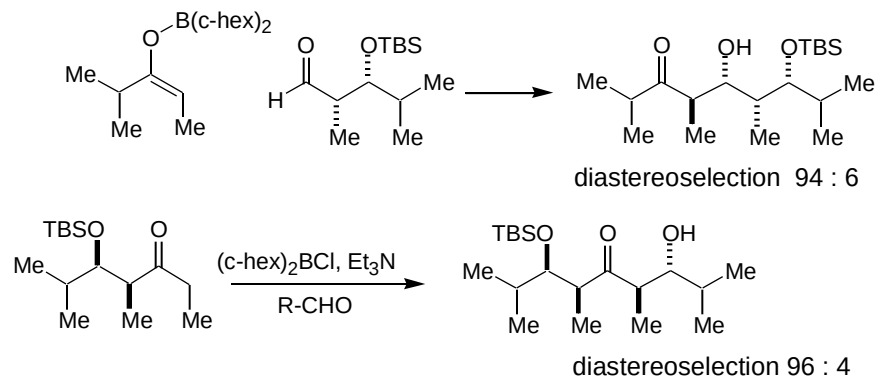
Mismatched reactant pair: Stereo-induction from partners nonreinforcing



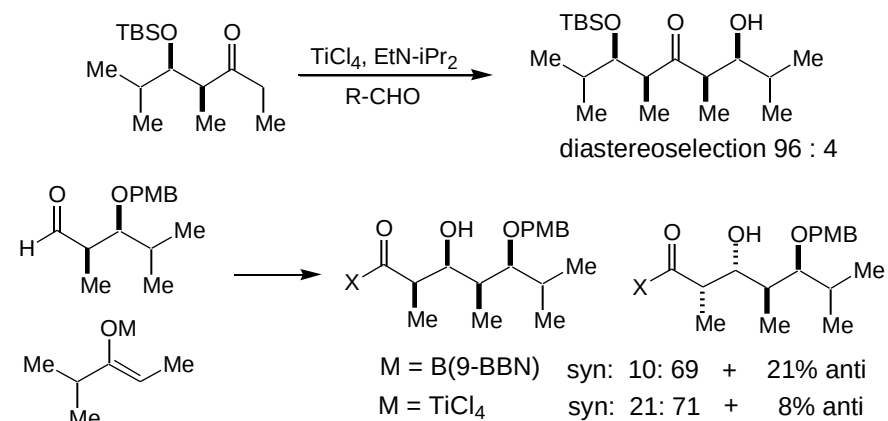
$$\Delta\Delta G^\ddagger (\text{Rxn}) \sim \Delta\Delta G^\ddagger (\text{enolate}) - \Delta\Delta G^\ddagger (\text{RCHO})$$

The Masamune-Heathcock generalizations hold to a point:

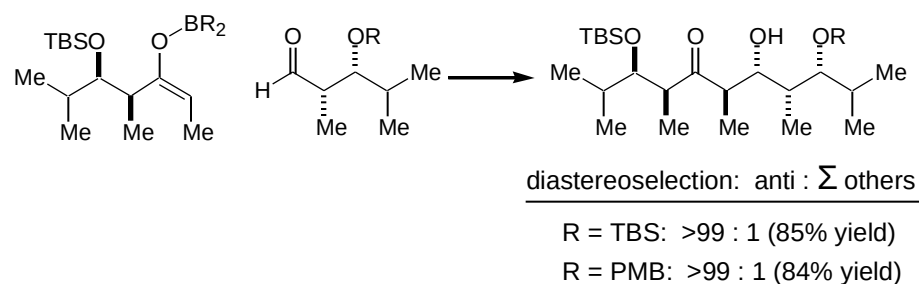
(E)-Boron Enolates: The reference reactions



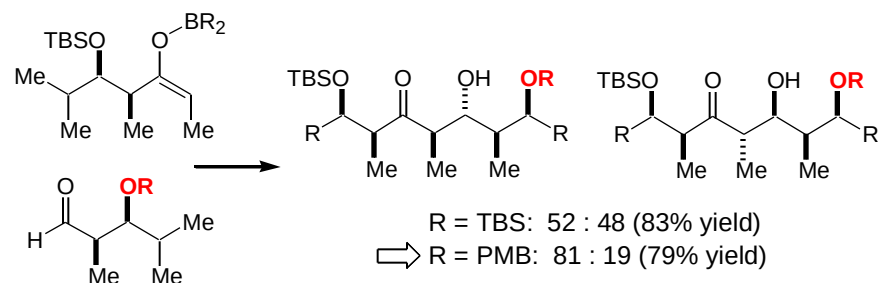
(Z)-Titanium Enolates: The reference reactions



(E)-Boron Enolates: The matched cases

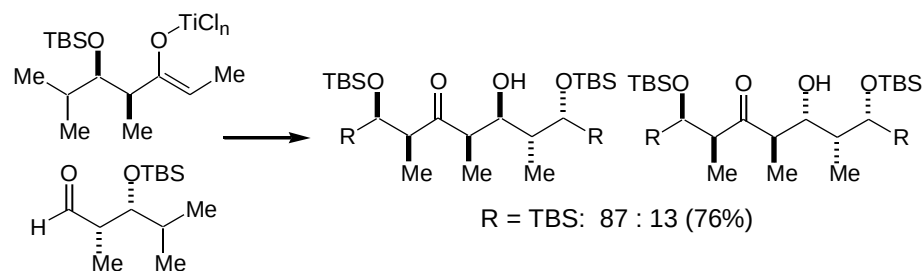


(E)-Boron Enolates: The mismatched cases

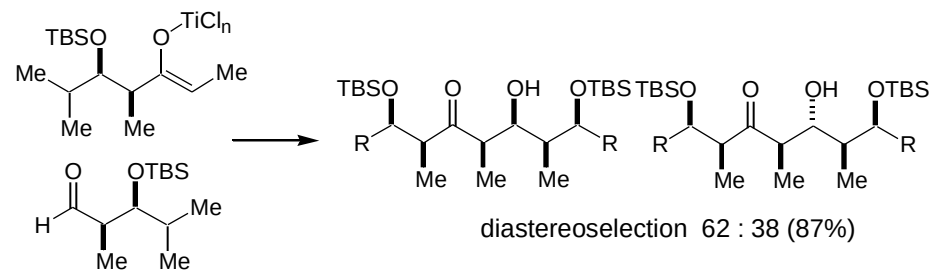


β -center on RCHO can play a significant role in this marginal situation

(Z)-Titanium Enolates: The matched cases



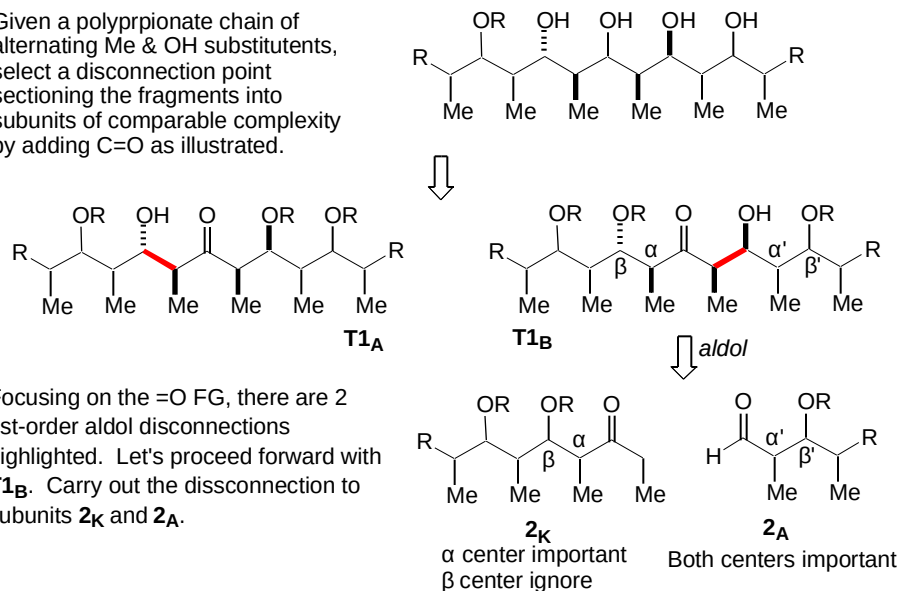
(Z)-Titanium Enolates: The mismatched cases



"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.

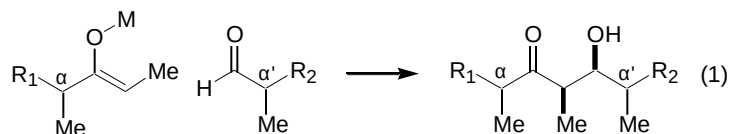
Synthesis of Polyketide chains

Given a polypropionate chain of alternating Me & OH substituents, select a disconnection point sectioning the fragments into subunits of comparable complexity by adding C=O as illustrated.



Focusing on the =O FG, there are 2 1st-order aldol disconnections highlighted. Let's proceed forward with **T1_B**. Carry out the disconnection to subunits **2_K** and **2_A**.

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.

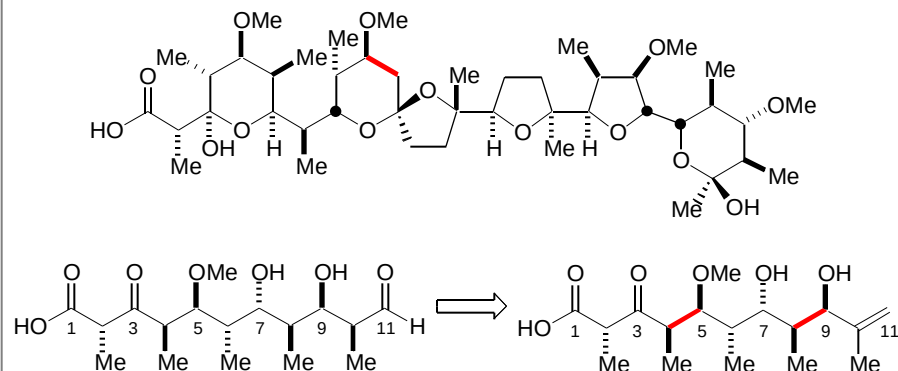


Stereochemical Determinants

	$M = BR_2$	$M = SiR_3$
enolate facial bias	✓	✓
aldehyde facial bias	✓	✓
pericyclic transition state	✓	✗

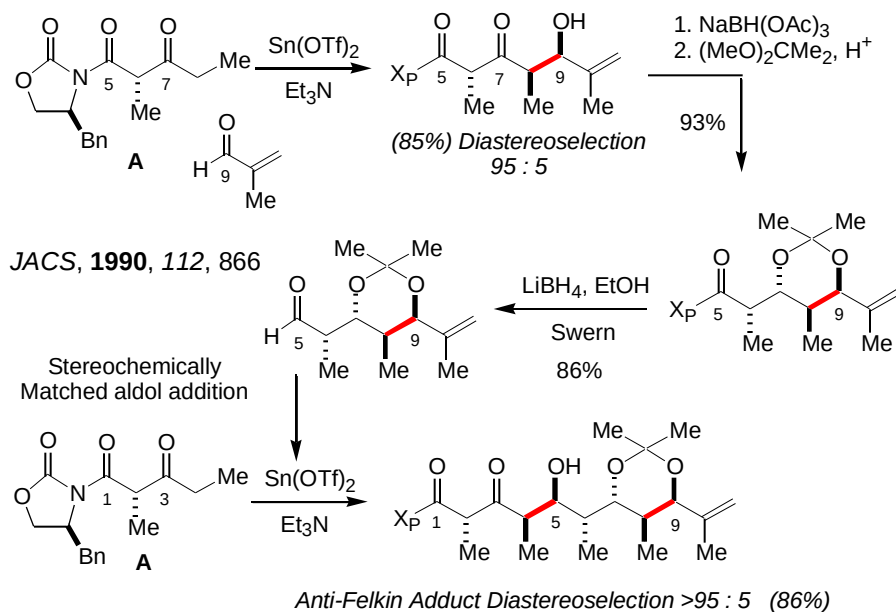
The Lonomycin Synthesis: An example of polypropionate assemblage

Evans, Ratz, Huff, Sheppard JACS **1995**, 117, 3448

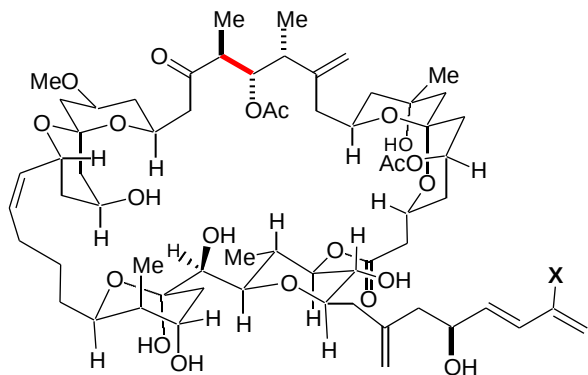


BH₃ Transform: See Lecture No. 8

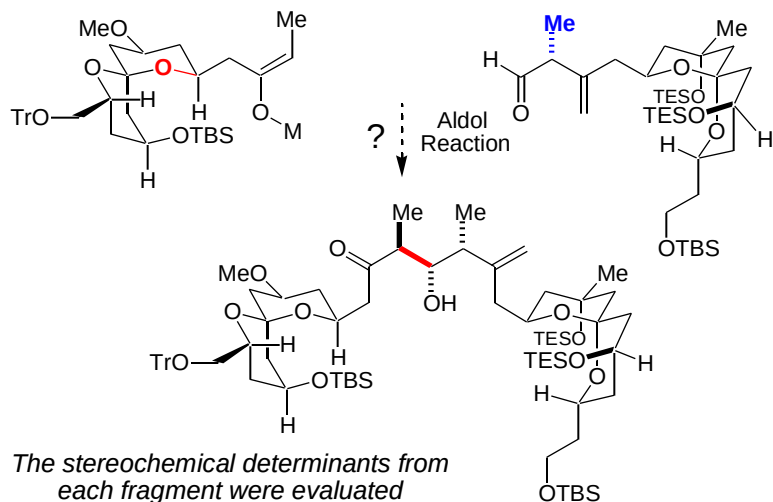
C₁–C₁₁ Assemblage



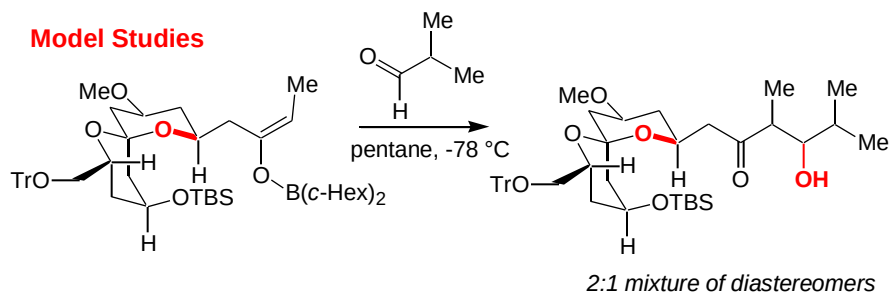
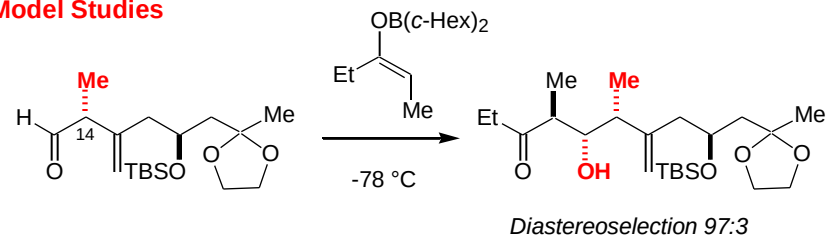
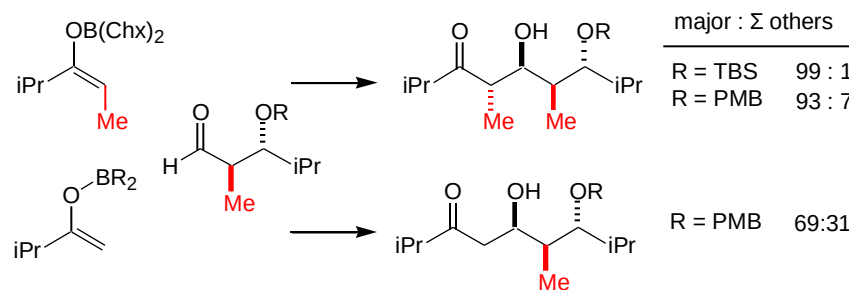
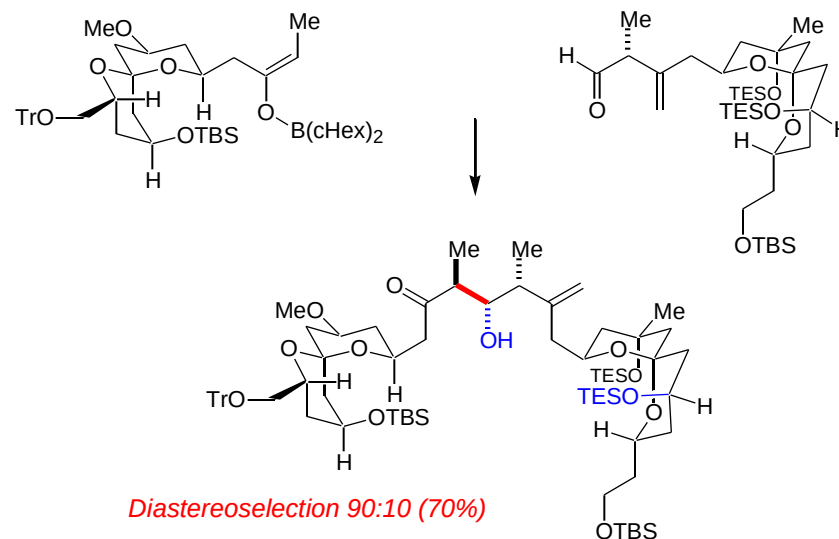
The Sn(OTf)₂ aldol reaction of A: see this lecture + JACS, **1990**, 112, 866

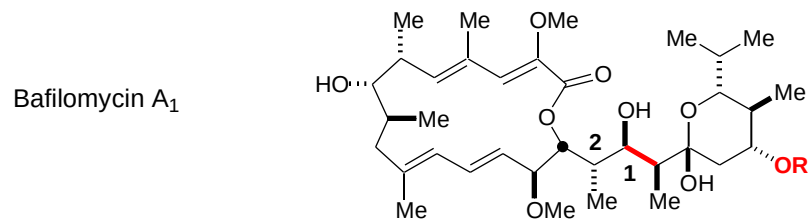
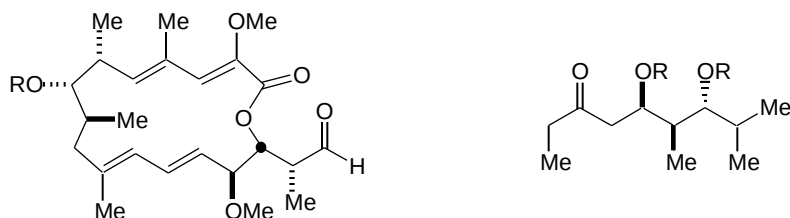
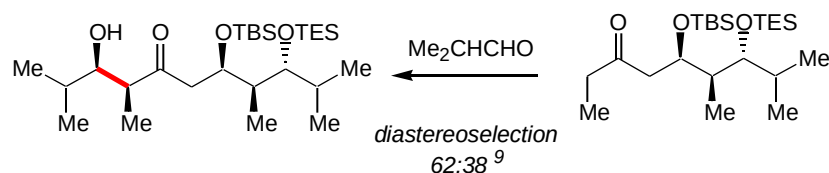
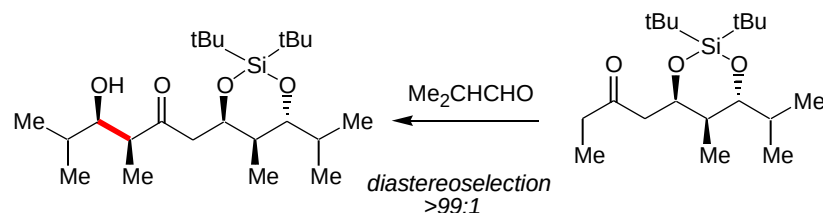
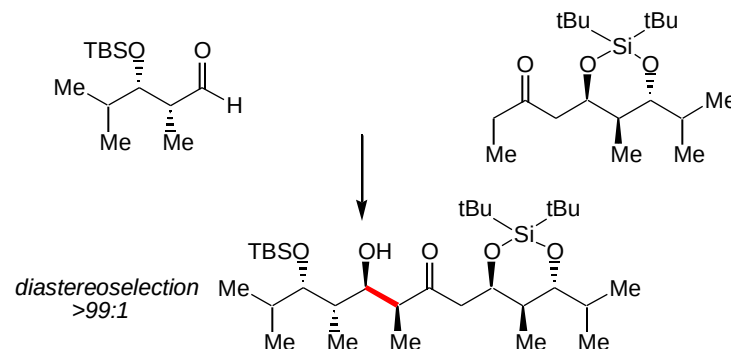
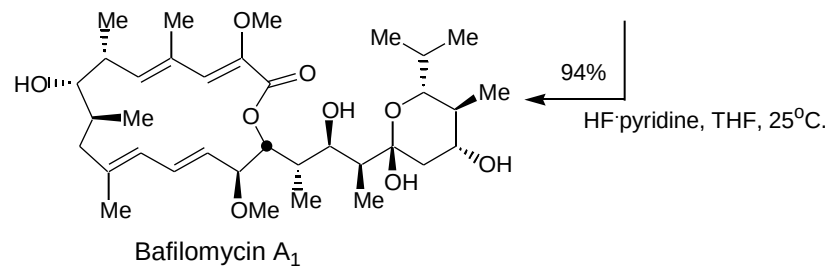
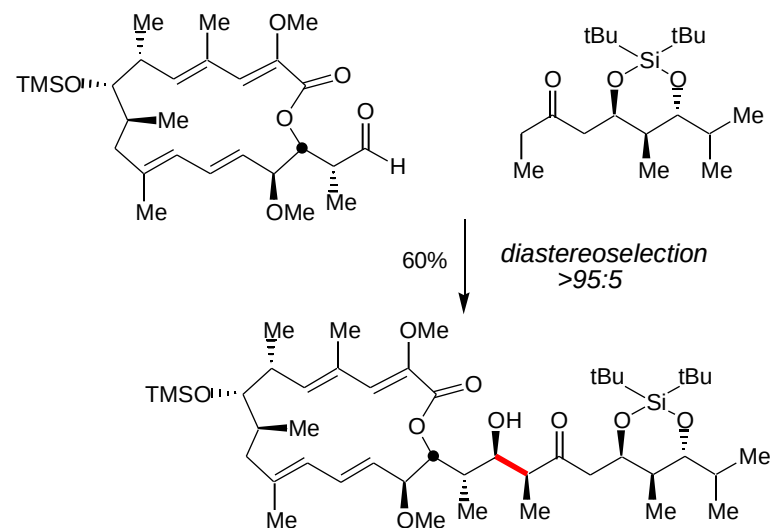
The Althoyrtin Synthesis: An example of polypropionate assemblage

Evans, Trotter, Coleman, Côté, Dias, Rajapakse, *Tetrahedron* **1999**, 55, 8671-8726.



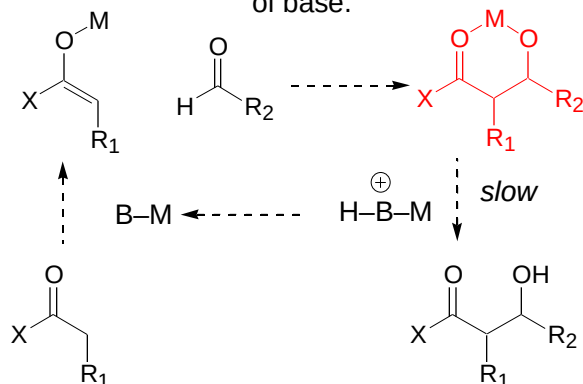
The stereochemical determinants from each fragment were evaluated

Model Studies**Model Studies****Background****The Aldol Fragment Coupling**

Bafilomycin A₁ Synthesis: An example of polypropionate assemblageEvans, Calter, *Tetrahedron Lett.* **1993**, 34, 6871**Critical Aldol Disconnection****Required:** Syn aldol addition**Aldehyde Fragment:** Target contains syn aldol retron with anti-Felkin relationship at 1 & 2**Enolate Fragment:** Can the needed enolate facial bias be built into the reaction??**Aldol Model Studies** Enolization Conditions: PhBCl₂, *i*-Pr₂NEt, CH₂Cl₂, -78°C.**The Critical Observation**Enolization Conditions: PhBCl₂, *i*-Pr₂NEt, CH₂Cl₂, -78°C.**Critical Aldol Disconnection**

Type I Aldol Reaction: Metal Aldol Process

This reaction may be run with either a stoichiometric or catalytic amount of base.

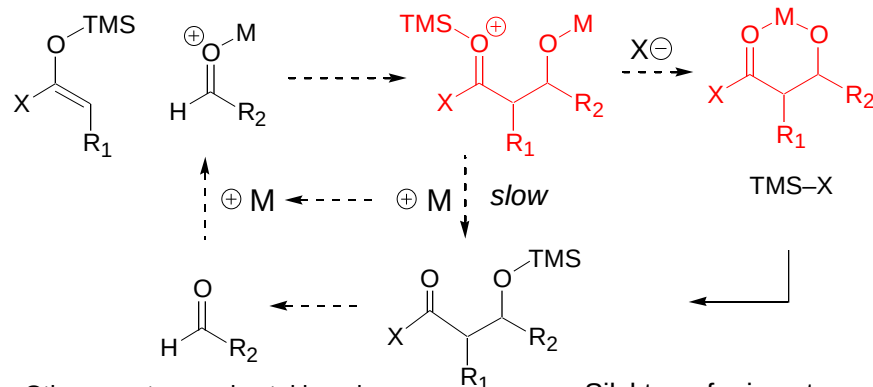


Catalytic Version: Slow step in the catalytic variant is protonation of the intermediate metal aldolate

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: $\text{MX} = \text{Lewis acid}$



Other events are also taking place:
Carreira *Tet. Lett* **1994**, 35, 4323

Silyl transfer is not necessarily intramolecular

Recent Reviews

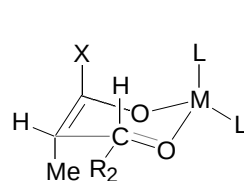
R. Mahrwald, *Diatereoselection in Lewis Acid Mediated Aldol Additions*, *Chem. Rev.* **1999**, 99, 1095-1120

S. G. Nelson, *Catalyzed enantioselective aldol additions of latent enolate equivalents* *Tetrahedron: Asymmetry* **1998**, 9, 357-389.

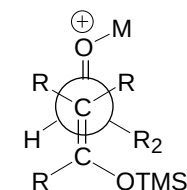
Mukaiyama Aldol Reaction, E. Carreira In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 998-1059.

Reaction Mechanism: "Closed" versus "Open" Transition States

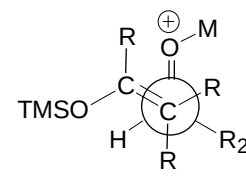
The Mukaiyama aldol reaction proceeds through an "open" transition state. The two illustrated competing TS orientations do not differ significantly in energy. For most reactions in this family there is not a good understanding of reactants-pair orientation. There is a prevalent view that the anti-periplanar TS is favored on the basis of electrostatic effects.



Metal aldolate TS
"Closed"

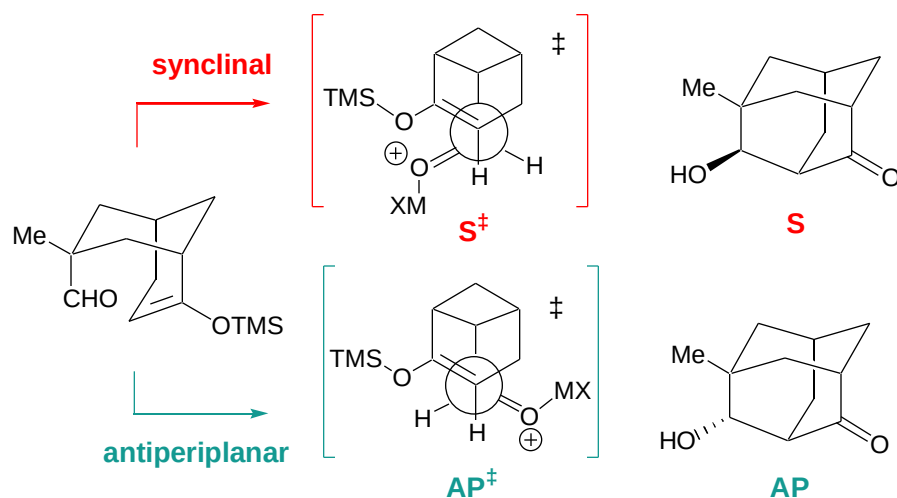


anti-periplanar TS
"Open"



synclinal TS
"Open"

Denmark has designed a nice substrate to distinguish between synclinal and antiperiplanar transition states:
Denmark, *J. Org. Chem.* **1994**, 59, 707-709

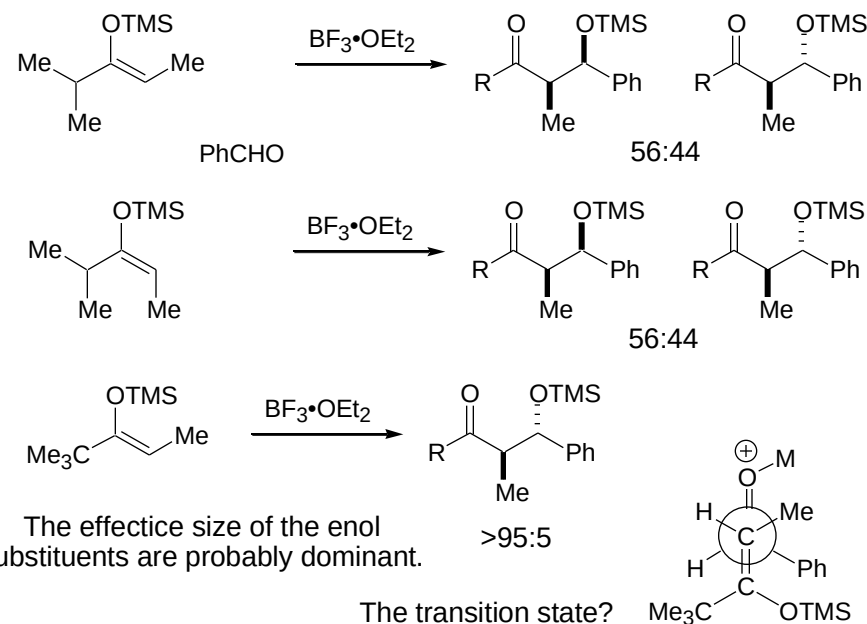


Lewis Acid	syn:anti
TiCl ₄	21:79
SnCl ₄	18:82
BF ₃ •OEt ₂	29:71
TrClO ₄	27:73
SnCl ₂	78:22

conclusion: there is a modest preference for the antiperiplanar TS

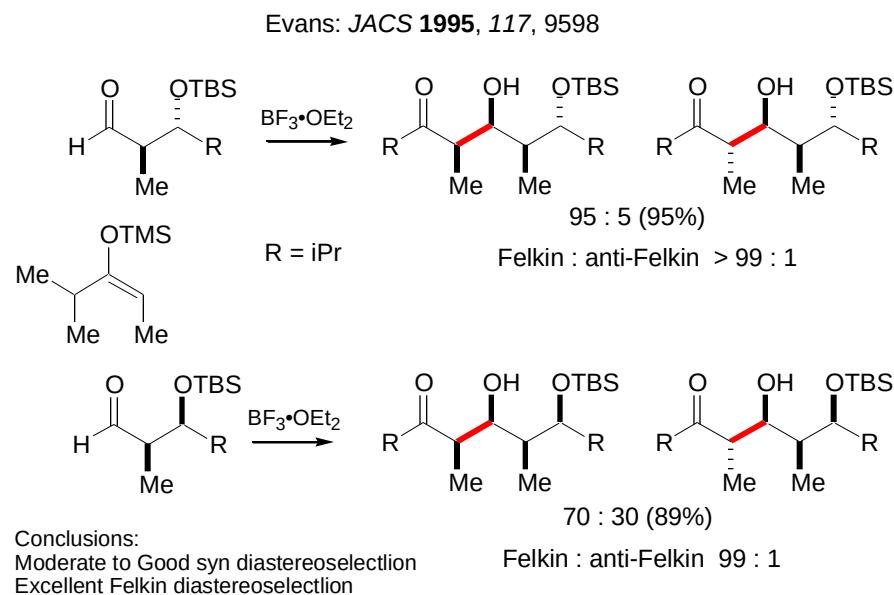
Syn-Anti Aldol Diastereoselection

Heathcock: *J. Org. Chem.* **1986**, 51, 3027

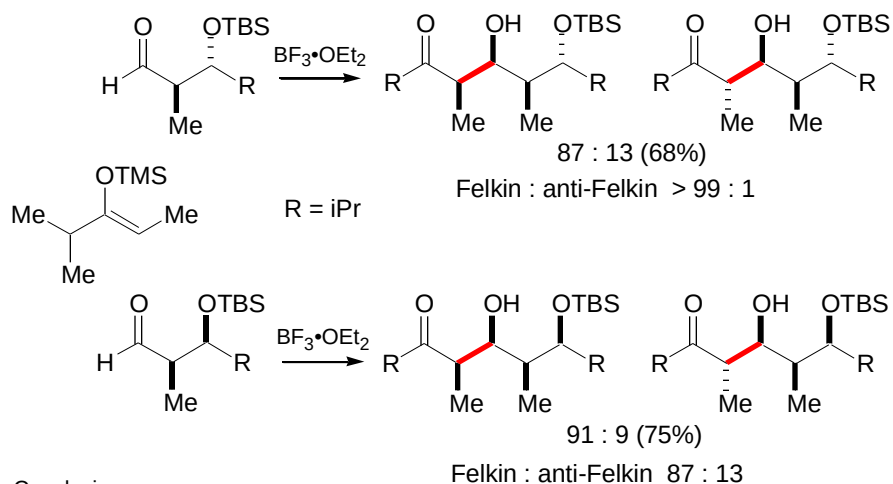
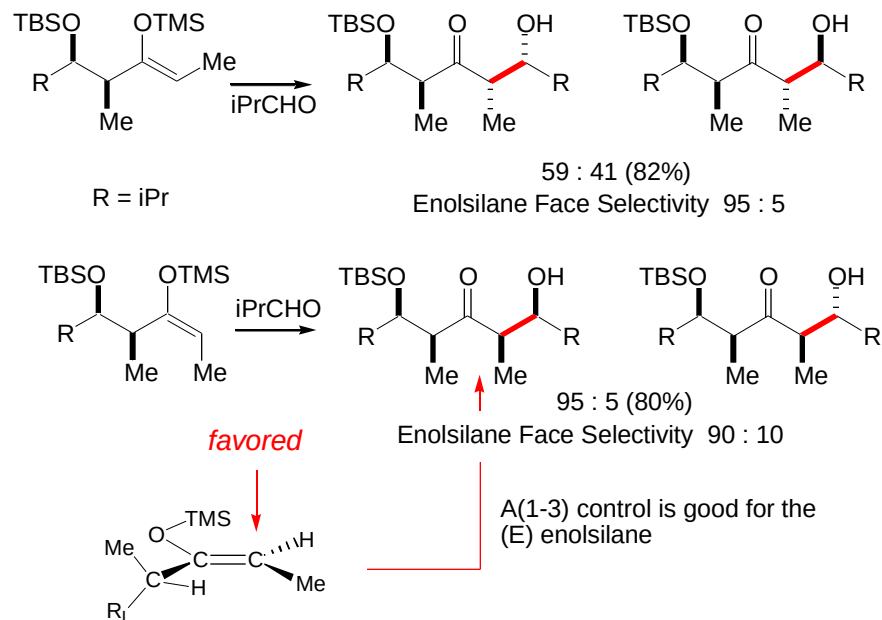


These reactions "exhibit little simple diastereoselection except in special cases.".....Heathcock

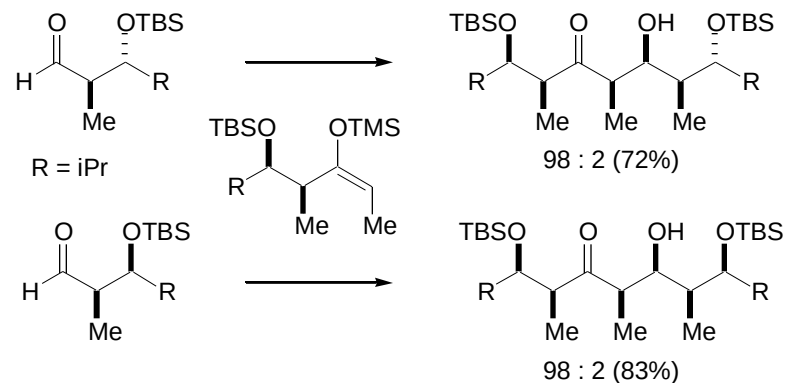
Merged Syn-Anti & Felkin Diastereoselection



Enolsilane Face Selection

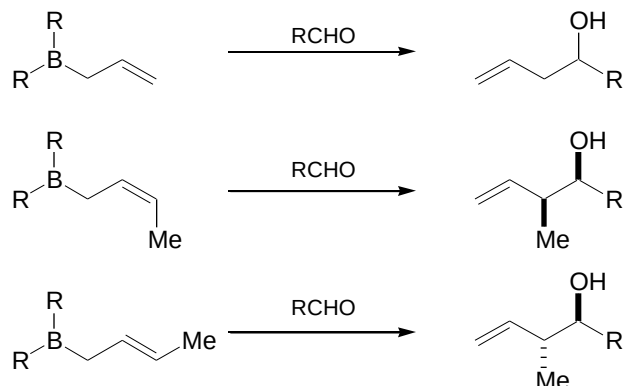


Double Stereodifferentiating Syn Aldol Rxns with Enolsilanes

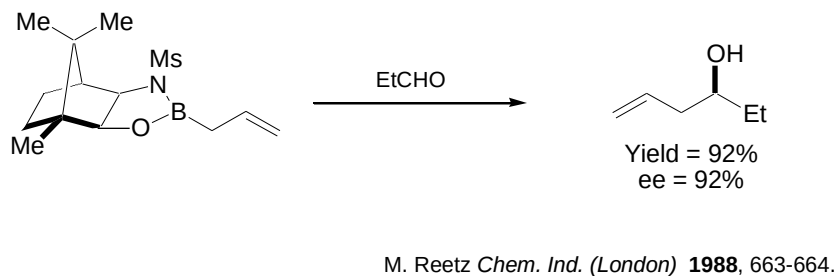
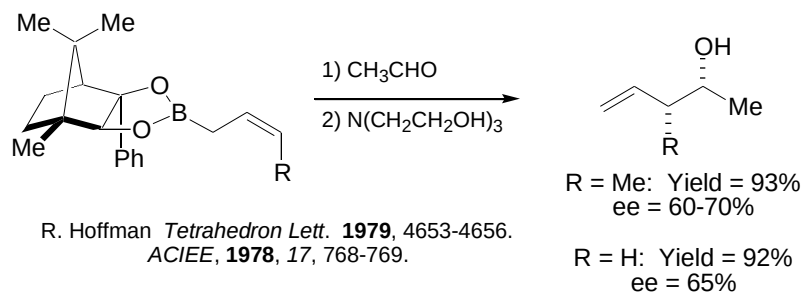


■ General Reviews of Allyl Metal Reagents:
Comprehensive Organic Synthesis, **1991**; Vol. 2.

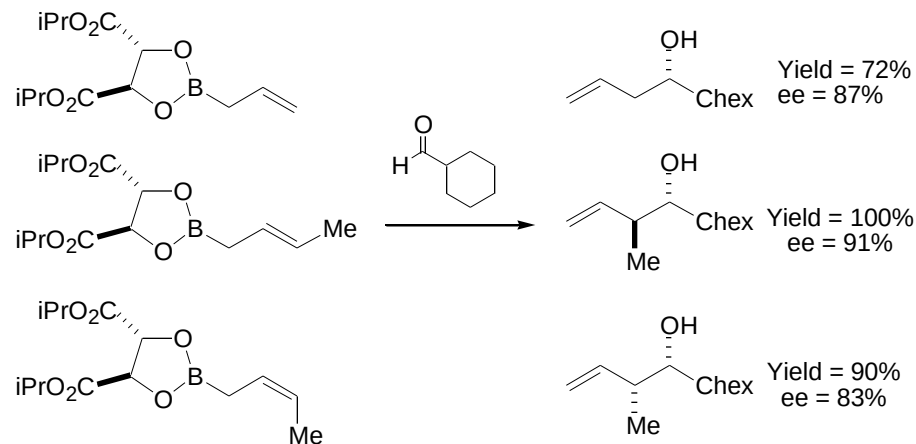
■ The General Reactions



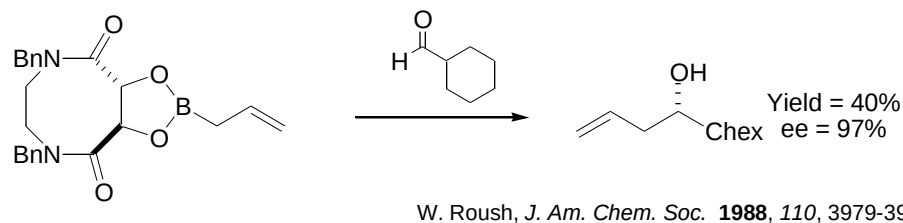
■ The Hoffman Chiral Allylboronic Esters



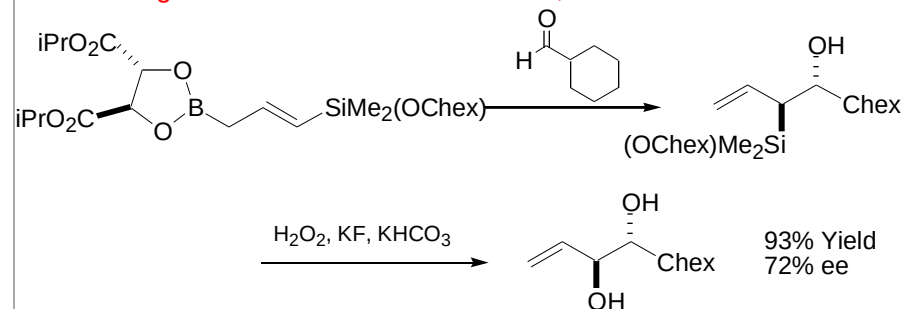
■ The Tartrate-derived Allylboronic Esters



W. Roush, *J. Am. Chem. Soc.* **1985**, 107, 8186-8190.
Tetrahedron Lett. **1988**, 29, 5579-5582.

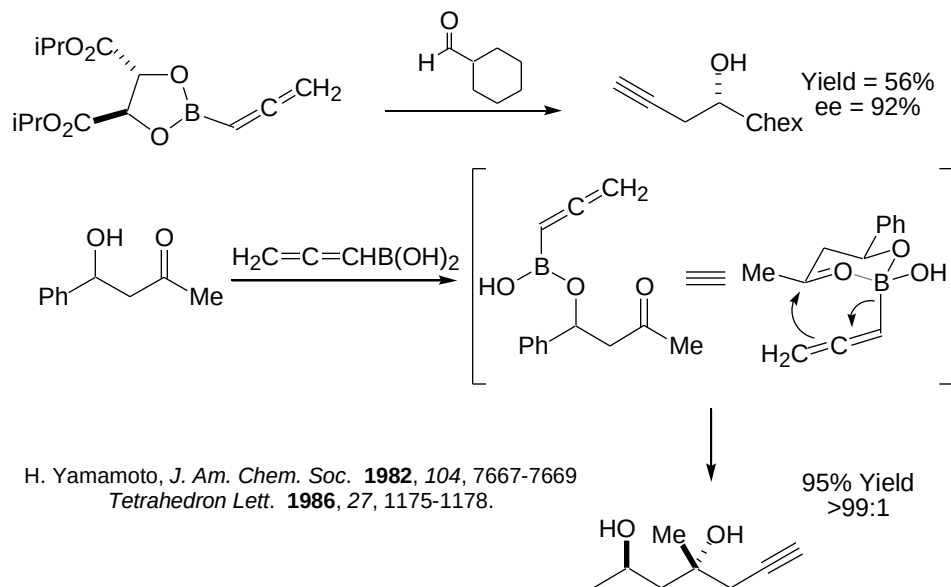


■ A Reagent for the Generation of Anti-1,2-Diols



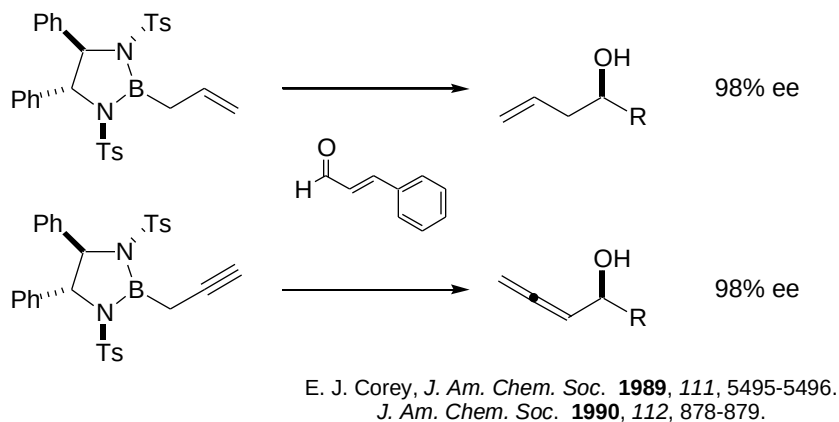
W. Roush, *Tetrahedron Lett.* **1990**, 31, 7563-7566.

■ Allenylboronic Esters: Tartrate-derived Controllers and Internal Delivery



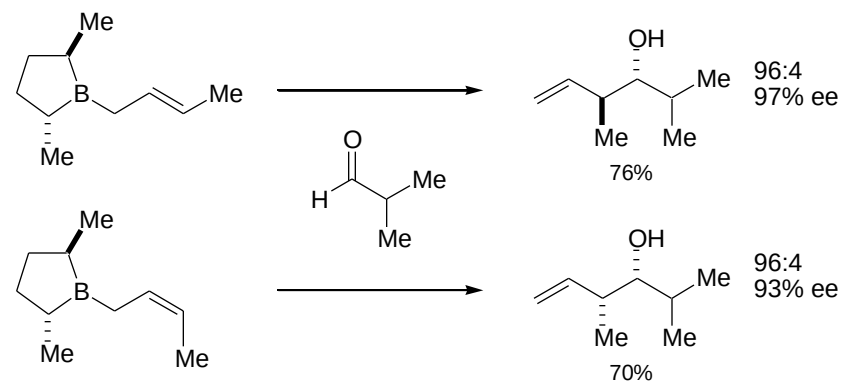
H. Yamamoto, *J. Am. Chem. Soc.* **1982**, *104*, 7667-7669
Tetrahedron Lett. **1986**, *27*, 1175-1178.

■ The Corey Stein Controller



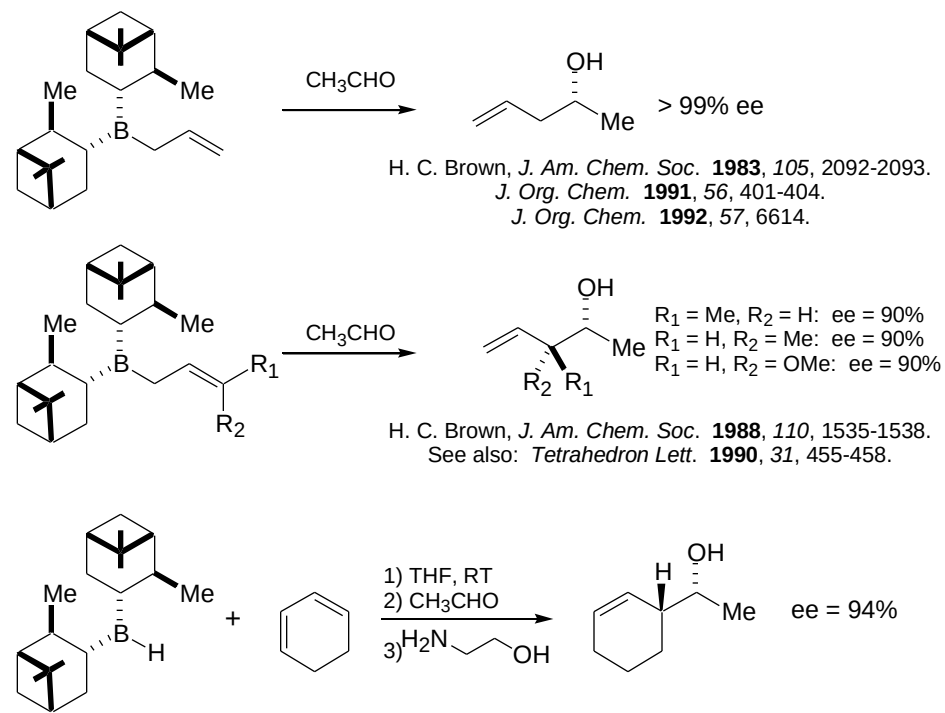
E. J. Corey, *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.
J. Am. Chem. Soc. **1990**, *112*, 878-879.

■ The Masamune Borolane



S. Masamune, *J. Org. Chem.* **1987**, 52, 4831-4832.

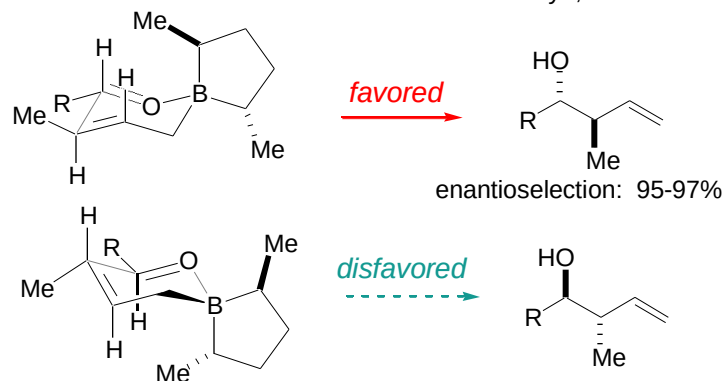
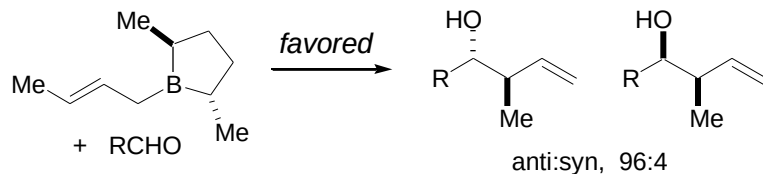
■ The Brown IPC Controller



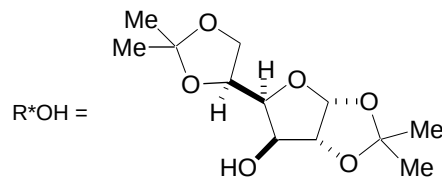
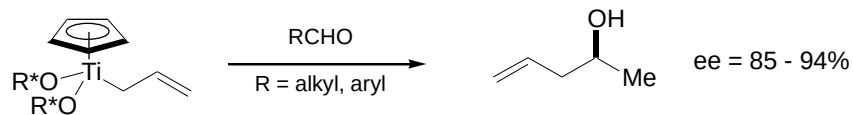
H. C. Brown, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2633.

The Allylboron Reagents Add to Carbonyl Compounds via a Zimmerman-Traxler Transition State

Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, 52, 4831



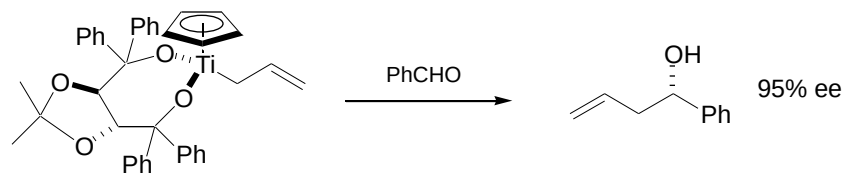
An Enantioselective Allyltitanium Reagent



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.

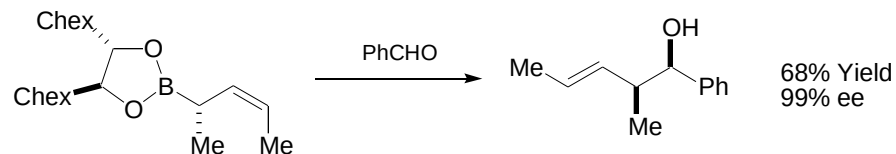
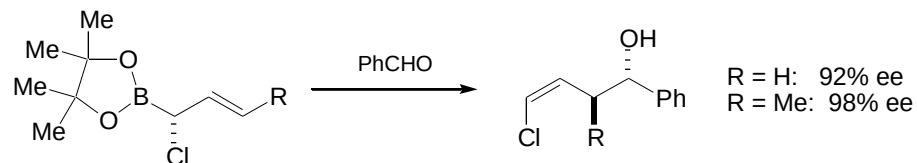
Duthaler *Chem. Rev.* **1992**, 92, 807

Another Enantioselective Allyltitanium Reagent

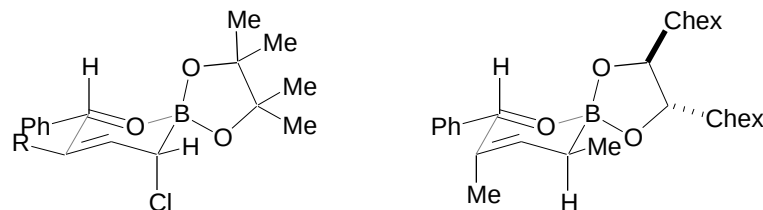


R. Duthaler, *J. Am. Chem. Soc.* **1992**, 114, 2321-2336.

Chiral α -Substituted Allyl Metal Reagents: Boron

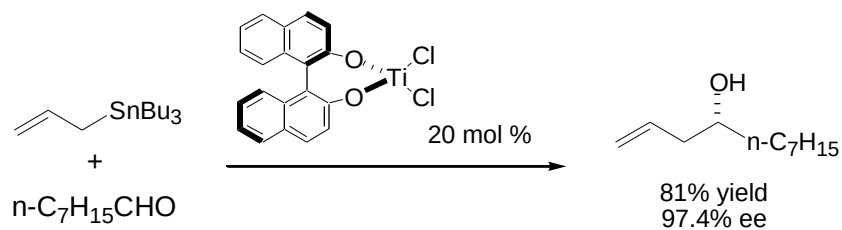
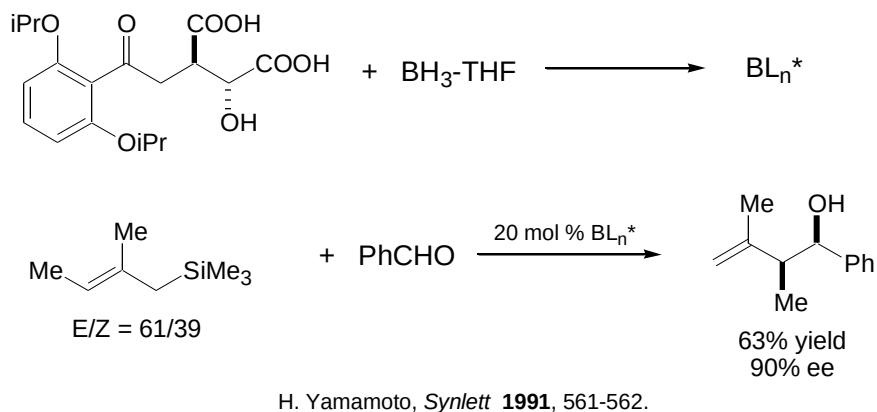


R. Hoffman, *Chem. Ber.* **1986**, 119, 2013-2024.
Chem. Ber. **1988**, 121, 1501-1507.
ACIEE, **1986**, 25, 1028-1030.

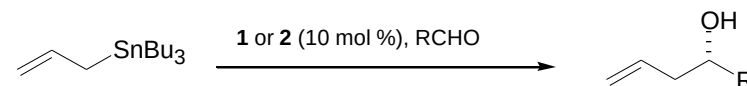
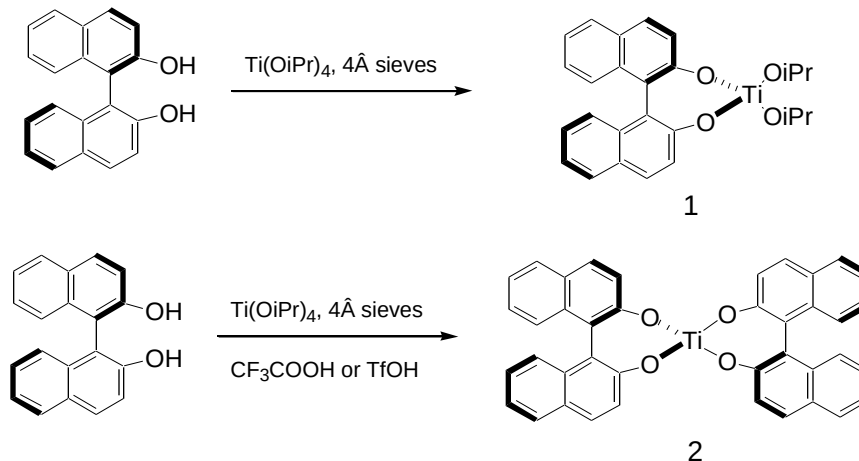


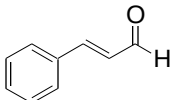
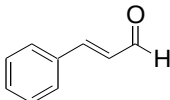
The favored transition states

■ Three Catalytic Asymmetric Allylations of Aldehydes are Known



E. Tagliavini, A. Umani-Ronchi *J. Am. Chem. Soc.* **1993**, *115*, 7001-7002.



R	Catalyst	Yield (%)	ee (%)
Ph	1	88	95
Ph	2	98	92
Chex	1	66	94
Chex	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 $-\text{NO}_2$ Group
- The Chemistry of the $-\text{N}_2$ 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. "Unpoled Synthons. A Survey of Sources and Uses in Synthesis"; John Wiley & Sons, Inc.: New York, 1987.

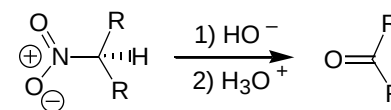
Ho, T.-L. "Polarity Control for Synthesis"; John Wiley & Sons, Inc.: New York, 1991.

Ono, N., "The Nitro Group in Organic Synthesis", Wiley-VCH, 2001

Several Interesting Problems

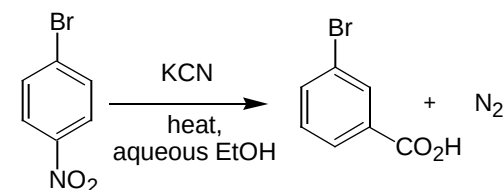
Provide a mechanism for the Nef reaction

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.



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.

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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)

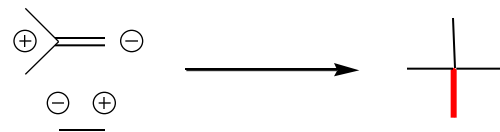
Lapworth was among the first to understand and conceptualize the effect of heteroatomic substituents on the reactivity of individual carbon centers, and how this effect is propagated through the carbon framework of organic molecules.

Lapworth's Theory of Alternating Polarities:

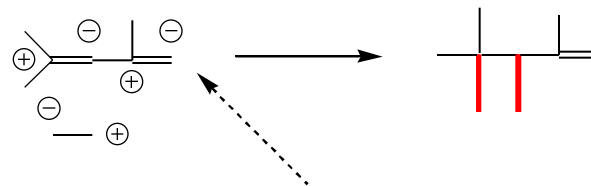
"Latent Polarities of Atoms and Mechanism of Reaction, with Special Reference to Carbonyl Compounds."

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...."

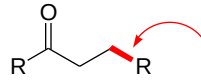


The "key atom" is the one with the most electronegative character, in this case the carbonyl oxygen.

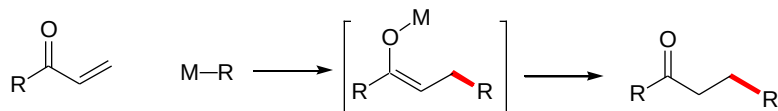
anionoid/cationoid -----> nucleophilic/electrophilic

The Lapworth polarity designations can be used to form the basis of a functional group classification scheme.

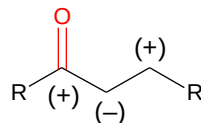
- Polar rxns form the basis set of bond constructions in synthesis
- Generalizations on conferred site reactivity will therefore be important

Given this target  and the desire to form this bond

The functional group =O "dictates" the following bond construction



- Conferred site reactivity of =O



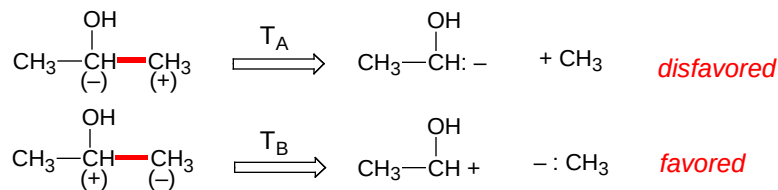
Charge Affinity Patterns

- Use the descriptors (+) and (-) to denote the polar disconnections shown.

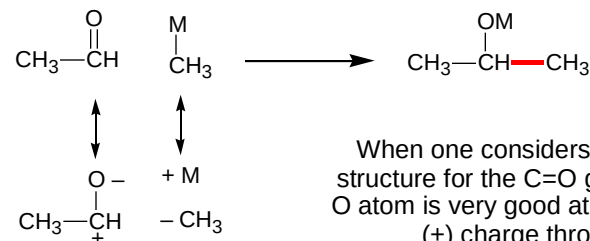


- In the transforms illustrated above, symbols (+) & (-) are used to denote the particular polar transform illustrated. In the present case there is NO INTRINSIC BIAS in favoring one transform over the other.

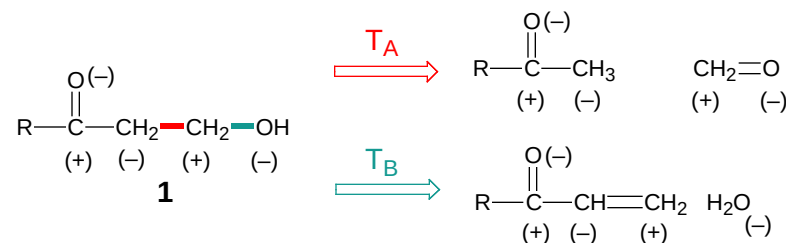
Let's now add an OH functional group (FG) to propane at C-2 and see whether one creates a bias in the favoring of one or the other transforms:



- The actual reaction associated with this transform is the addition of organometals to carbonyl substrates.

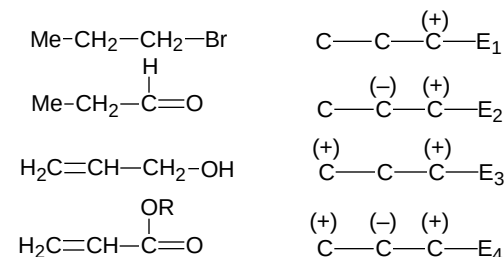


- Consider polar disconnections of the illustrated β -hydroxy ketone **1**:

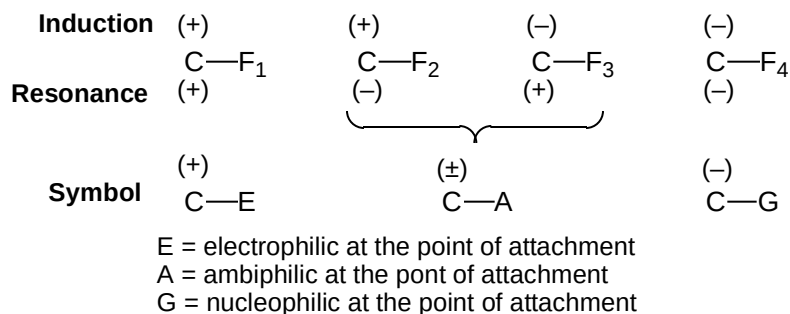


It is evident that the heteroatom functional groups, =O and -OH, strongly bias the indicated polar disconnections.

Charge Affinity Patterns of Common Functional Groups



Functional groups activate the carbon skeleton at the point of attachment by either induction & resonance.

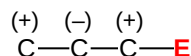


For simplicity, we will designate three FG classes according to the designations provided above.

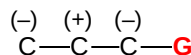
E & G-Functions:

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



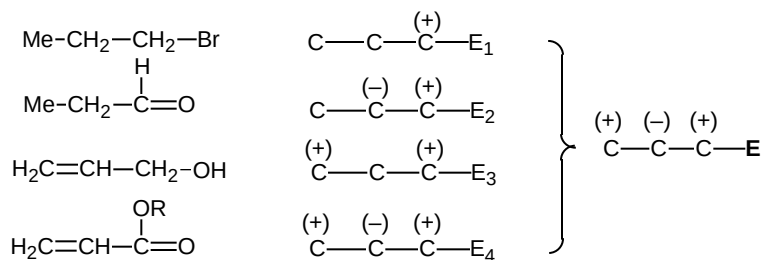
Hypothetical G-function



Given the appropriate oxidation state of the carbon skeleton, such functional groups confer the indicated polar site reactivity patterns toward both electrophiles and nucleophiles.

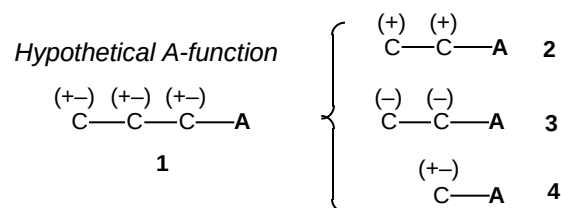
Any FG that conforms either to the ideal charge affinity pattern or a sub-pattern thereof will thus be classified as either an E- or G-function.

Representative E-functions:



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 classified 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.

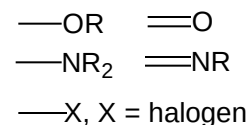


FG-Classification Rules

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: (+)C—E



exception: ≡O
exception: ≡N

Also consider all combinations of of above FGs; e.g =O + OR

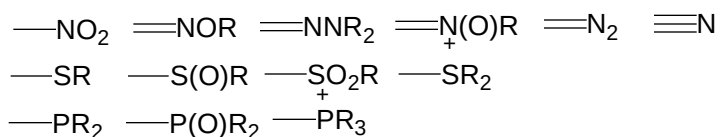
Common G-Functions: Symbol: $(-)\text{C}-\text{G}$

Typical G-class functions are the Group I-IV metals whose reactivity patterns, falls into a subset of the idealized G-FG 5.

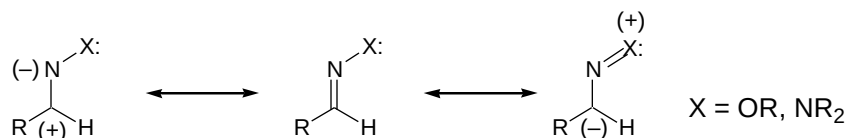
**Common A-Functions: Symbol: $(\pm)\text{C}-\text{A}$**

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



■ These FG's are capable of conferring both (+) and (−) at point of attachment.

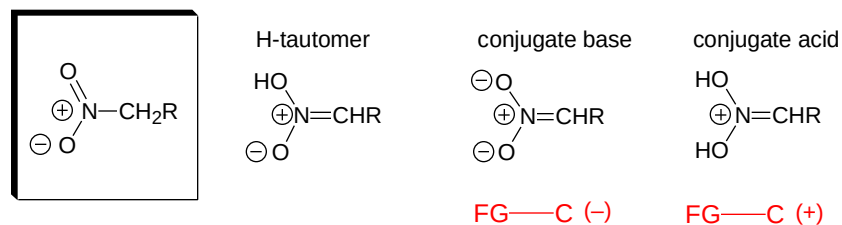


Remarkably, the dual electronic properties of oximes were first discussed by Lapworth in 1924 before the modern concepts of valence bond resonance were developed.

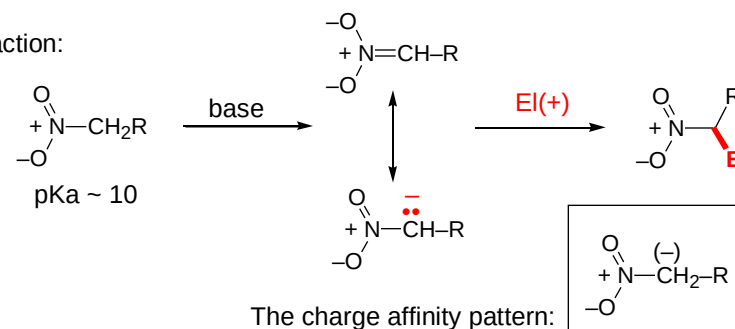
Lapworth, A. *Chemistry and Industry* **1924**, 43, 1294-1295.

The Nitro Functional Group

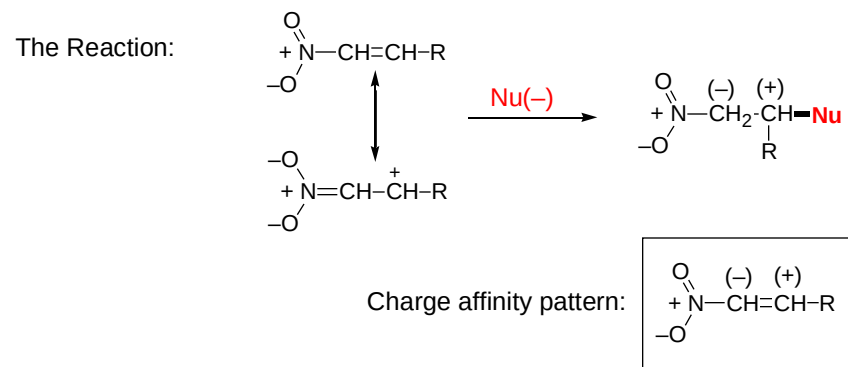
As an example, the class designation of the nitro function is determined by an evaluation of the parent function, its nitronic acid tautomer, as well as conjugate acid and base.



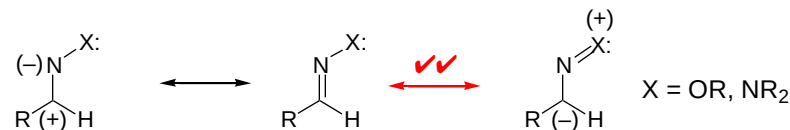
The Reaction:



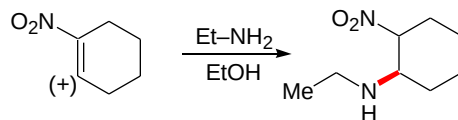
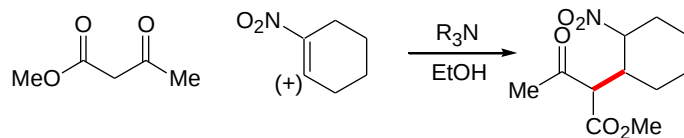
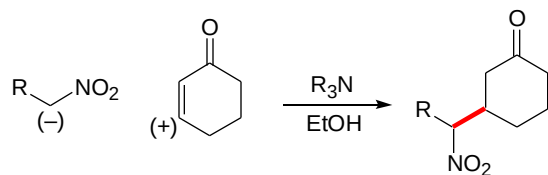
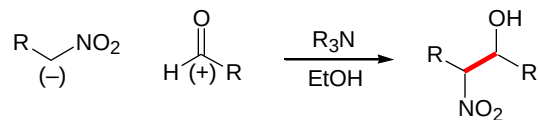
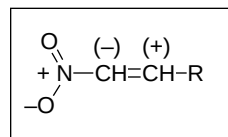
■ This reactivity pattern may be extended via conjugation:



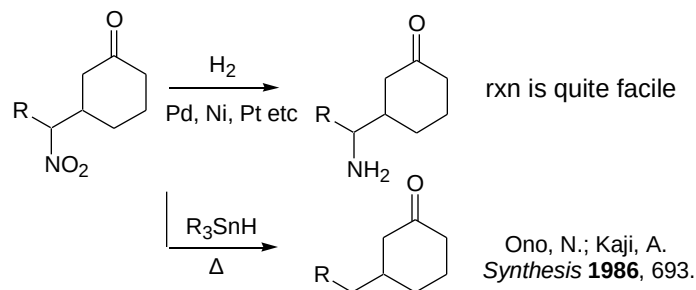
■ The resonance feature which has been exploited:



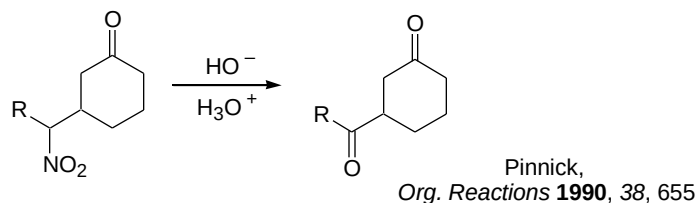
Some Reactions of the Nitro Functional Group

Important Transformations of the -NO₂ Functional Group

Reduction:

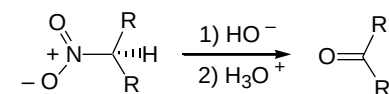


Nef Reaction:

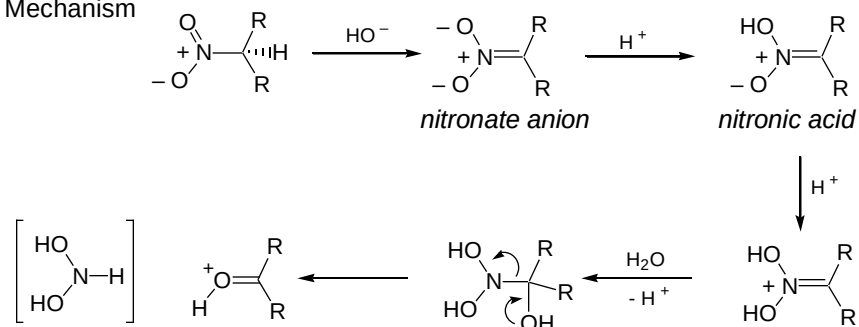


The Nef Reaction

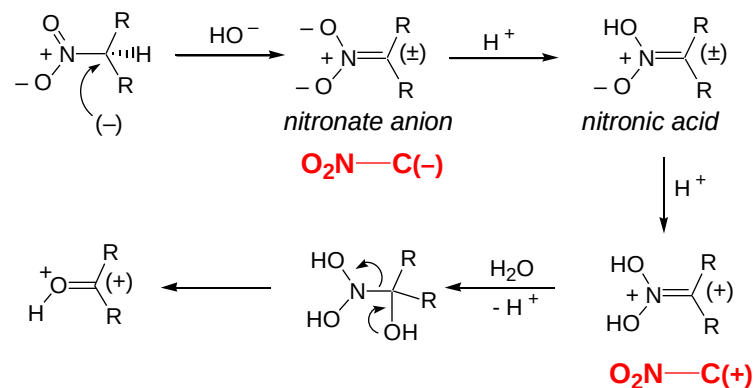
Overall Transformation:



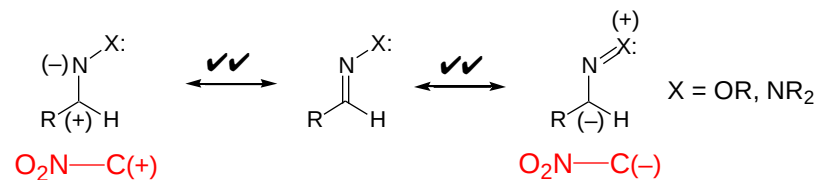
Mechanism

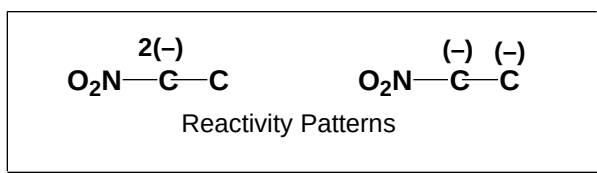
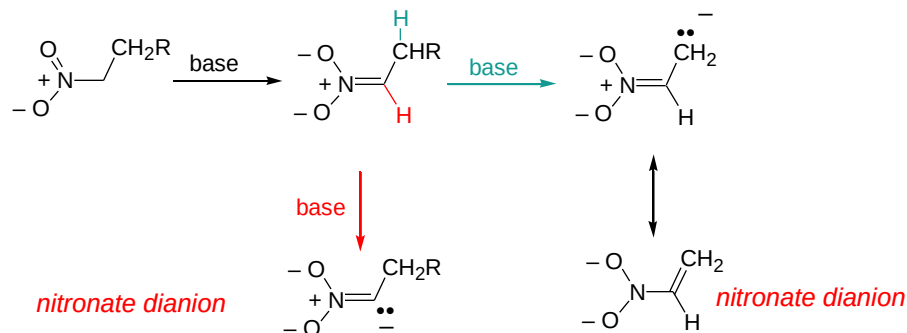
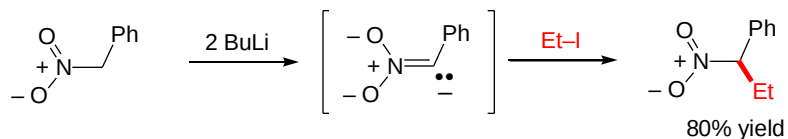
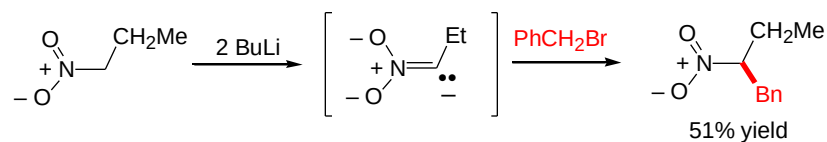
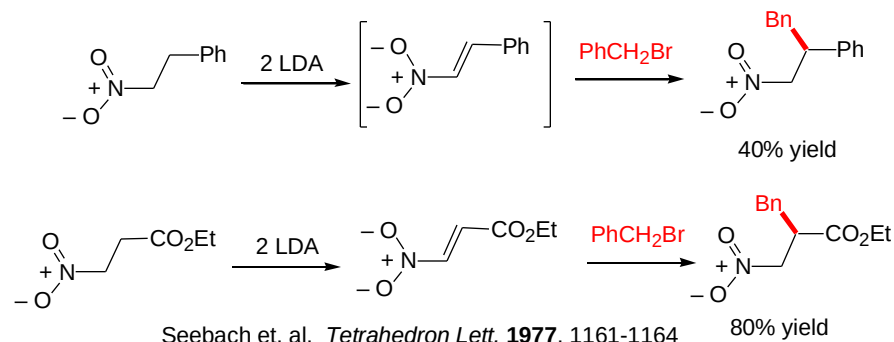
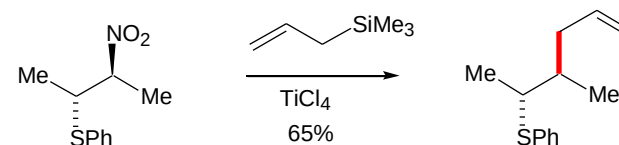
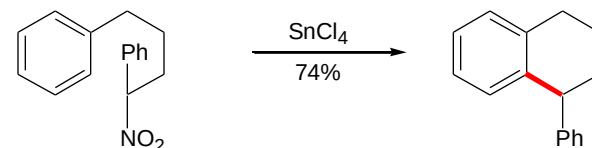
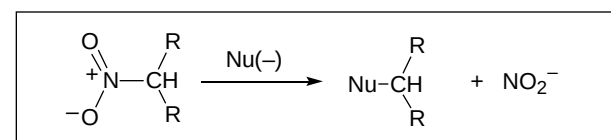


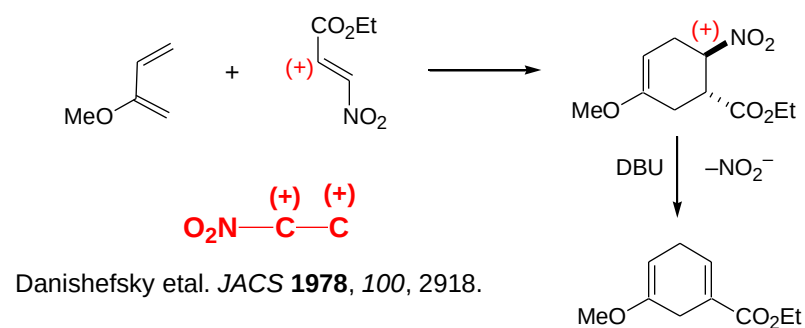
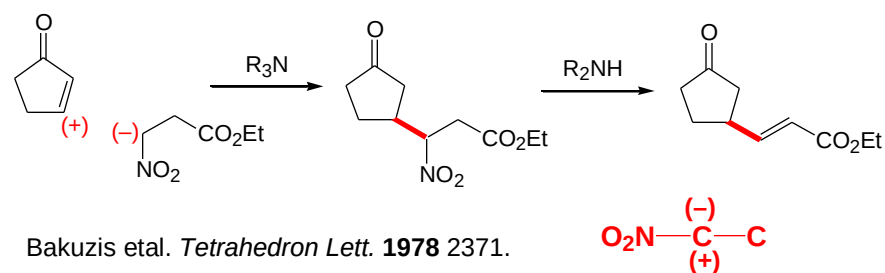
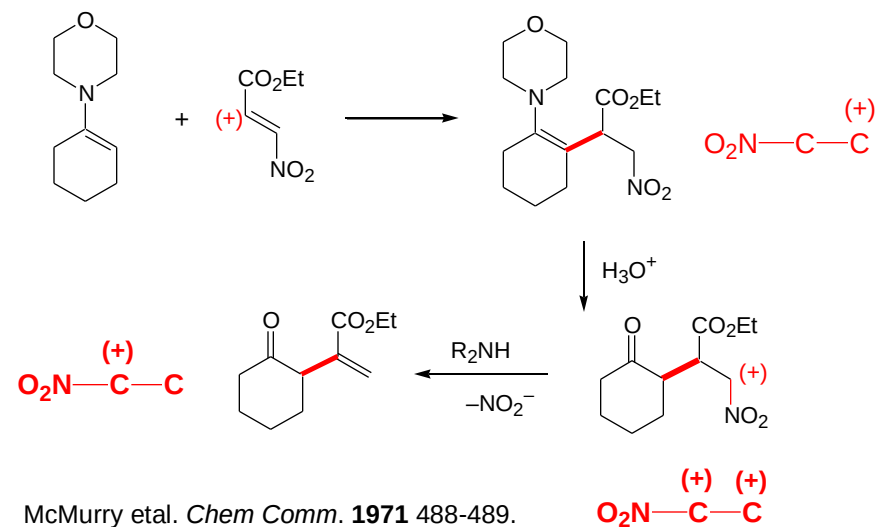
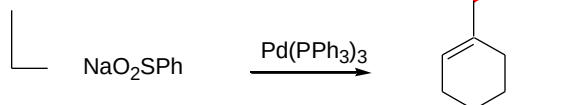
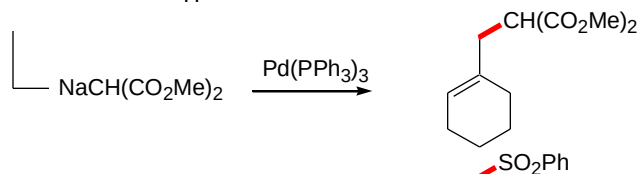
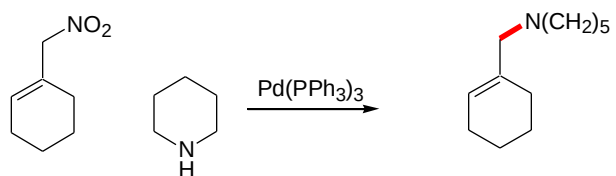
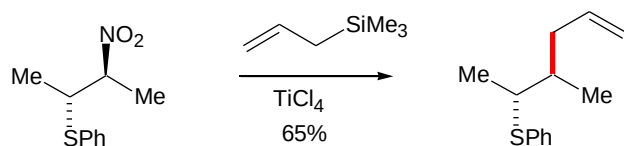
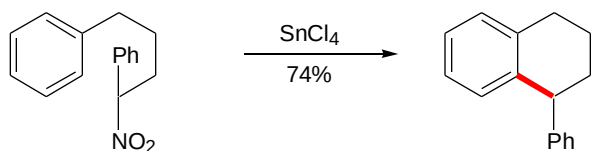
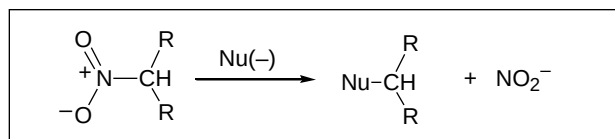
The charge affinity patterns represented



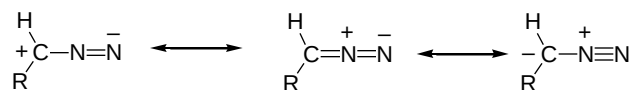
The resonance features which have been exploited:



Other Nonalternate Behavior of $-\text{NO}_2$ FGSeebach et. al. *Tetrahedron Lett.* **1977**, 1161-1164Representative examples: $\text{O}_2\text{N}-\overset{2(-)}{\text{C}}-\text{C}$ Representative examples: $\text{O}_2\text{N}-\overset{(-)}{\text{C}}-\overset{(-)}{\text{C}}$ Seebach et. al. *Tetrahedron Lett.* **1977**, 1161-1164 $-\text{NO}_2$ As a Leaving GroupReview: Tamura et. al. *Synthesis* **1991**, 423-434."Nitroaliphatic Compounds—Ideal Intermediates in Organic Synthesis"
Seebach, D. et al, *Chimia*, **1979**, 33, 1-18Representative examples: $\text{O}_2\text{N}-\text{C}(+)$ 

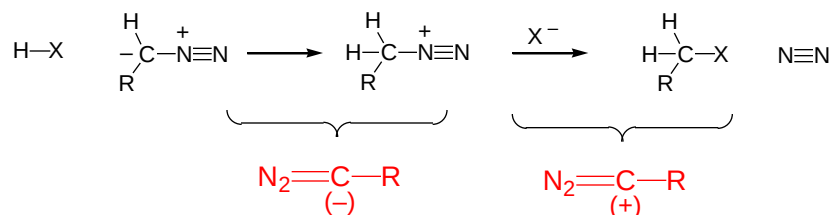
-NO₂ As a Leaving Group***Representative examples: O₂N—C(+)*** 

The Diazo Functional Group



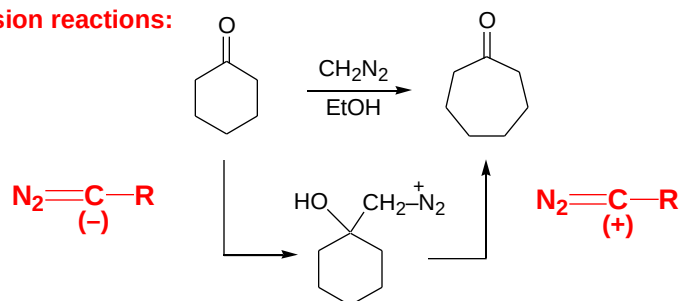
■ Both (+) and (-) reactivity patterns suggested by resonance structures

■ Rxns with acids:



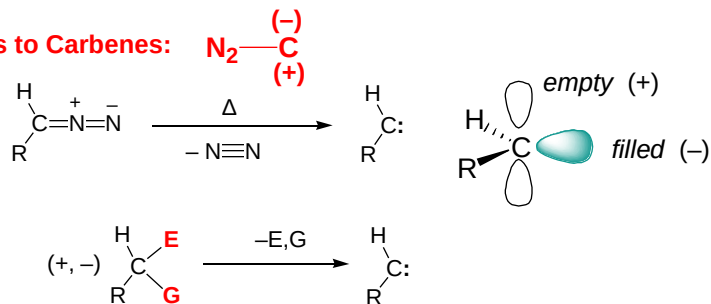
■ Initiating reactivity is (-); subsequent reactivity is (+)

■ Ring expansion reactions:



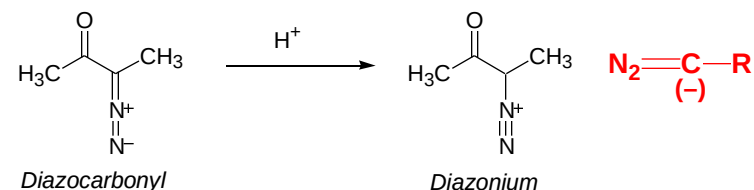
Restriction: Starting ketone must be more reactive than product ketone

■ Precursors to Carbenes: $\text{N}_2=\text{C} \quad \begin{array}{l} (-) \\ (+) \end{array}$



Acid Catalyzed Reactions of Diazo Compounds

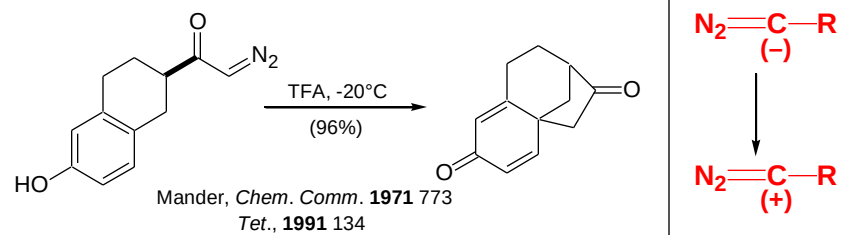
Review: Smith, Tet. 1981 2407



Common acids include $\text{BF}_3 \cdot \text{OEt}_2$, HBF_4 , TFA, etc.

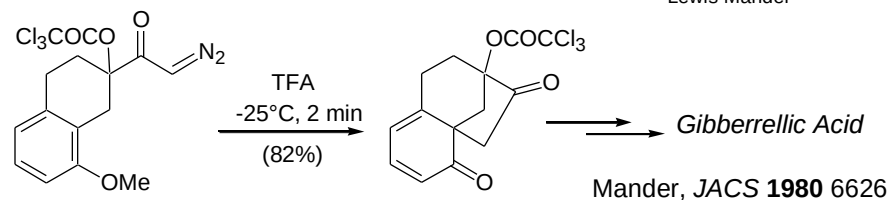
Mechanism of activation is unclear for both Lewis and protic acids; activation may occur by protonation on C or O

Acid-Catalyzed Reactions



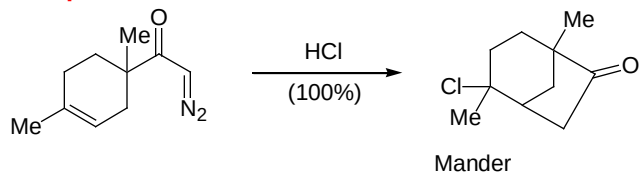
"Having become familiar with the peculiarities of diazoketone chemistry while preparing [other compounds] (and, I might add, inured to handling uncomfortably large quantities of diazomethane), it occurred to us that we might be able to substitute a diazo group for bromine."

Lewis Mander

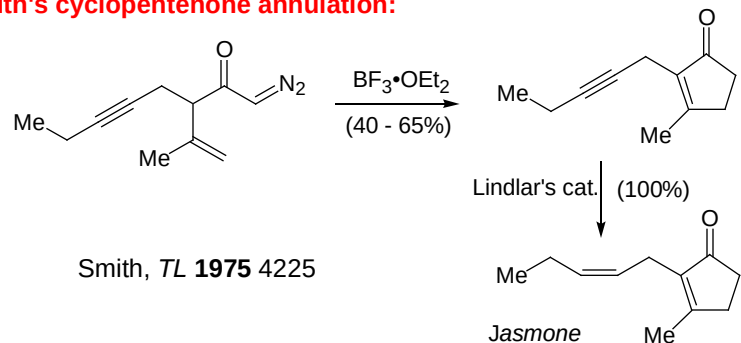


More Acid Catalysis

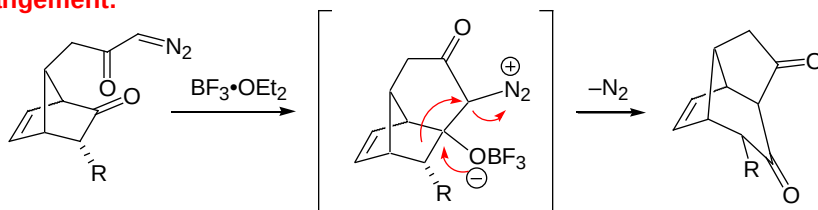
Olefins as nucleophiles:



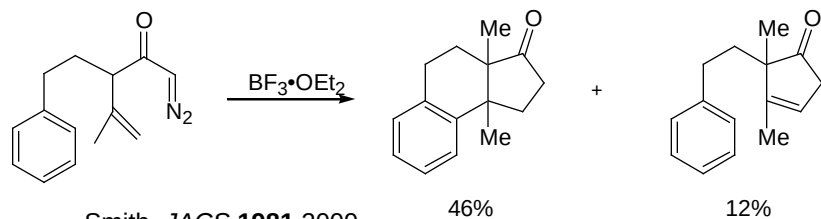
Smith's cyclopentenone annulation:

Smith, *TL* **1975** 4225

Rearrangement:

Mander, *Aust. J. Chem.* **1979** 1975

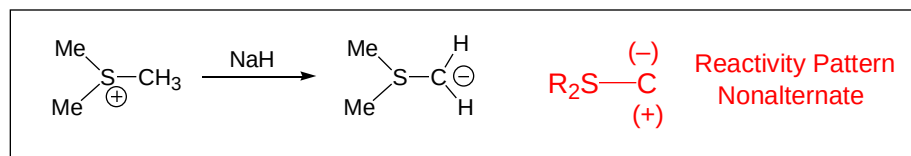
Polyene cyclizations:

Smith, *JACS* **1981** 2009

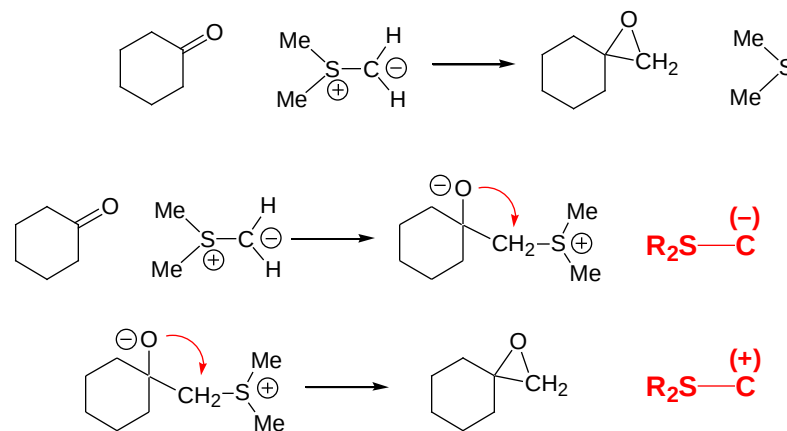
Sulfur Functional Groups

Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon, 1993.

		pKa (DMSO)	
$\text{CH}_3-\text{S}-\text{CH}_3$	Sulfide	(45)	$\leftarrow \text{CH}_4$ pKa (~56)
$\text{CH}_3-\text{S}(=\text{O})-\text{CH}_3$	Sulfoxide	~35	$\leftarrow \text{NH}_3$ pKa (~41)
$\text{CH}_3-\text{S}(=\text{O})_2-\text{CH}_3$	Sulfone	~31	$\leftarrow \text{HOH}$ pKa 31
$\text{CH}_3-\text{S}^+(\text{CH}_3)_2$	Sulfonium Salt	~18	
		(same acidity as phenol)	



Reactions with carbonyl compounds



<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.

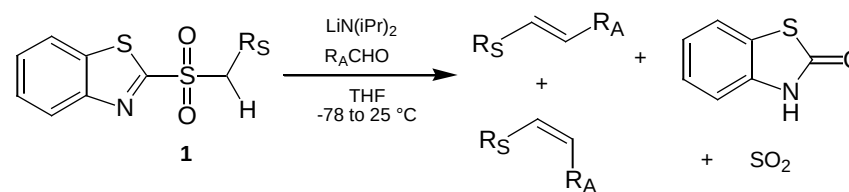
SO₂ Extrusion: Vogtle, F.; Rossa, L. *ACIEE* **1979**, 18, 515.

Ramberg-Bäcklund Rxn: Paquette, L.A. *Org. Reactions* **1977**, 25, 1.

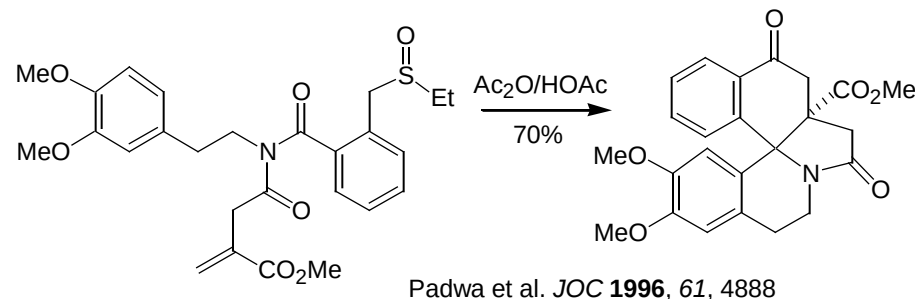
Triflones: Hendrickson, J.B. *Org. Prep. Proc. Int.* **1977**, 175.

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.

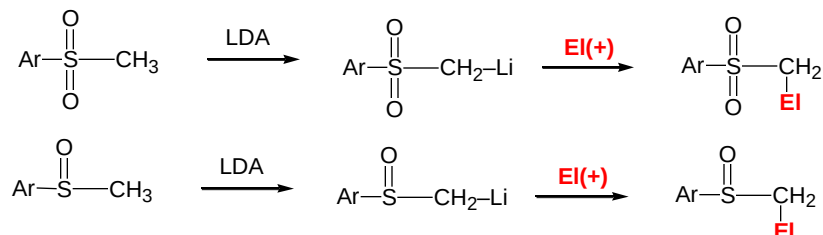


The cruel mechanistic problems that you should be prepared for in Chem 206



Sulfone- & Sulfoxide Based Carbanions: Structure

- Sulfone- and sulfoxide-stabilized carbanions are extremely useful carbon nucleophiles in organic synthesis.

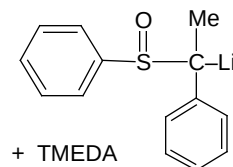
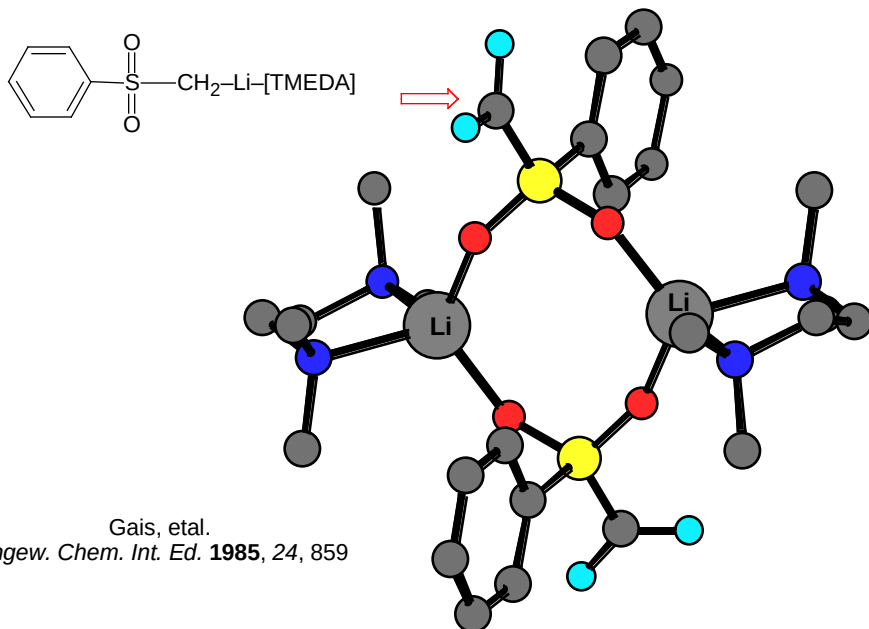


However, until recently little information was available on the solid state structures of these species:

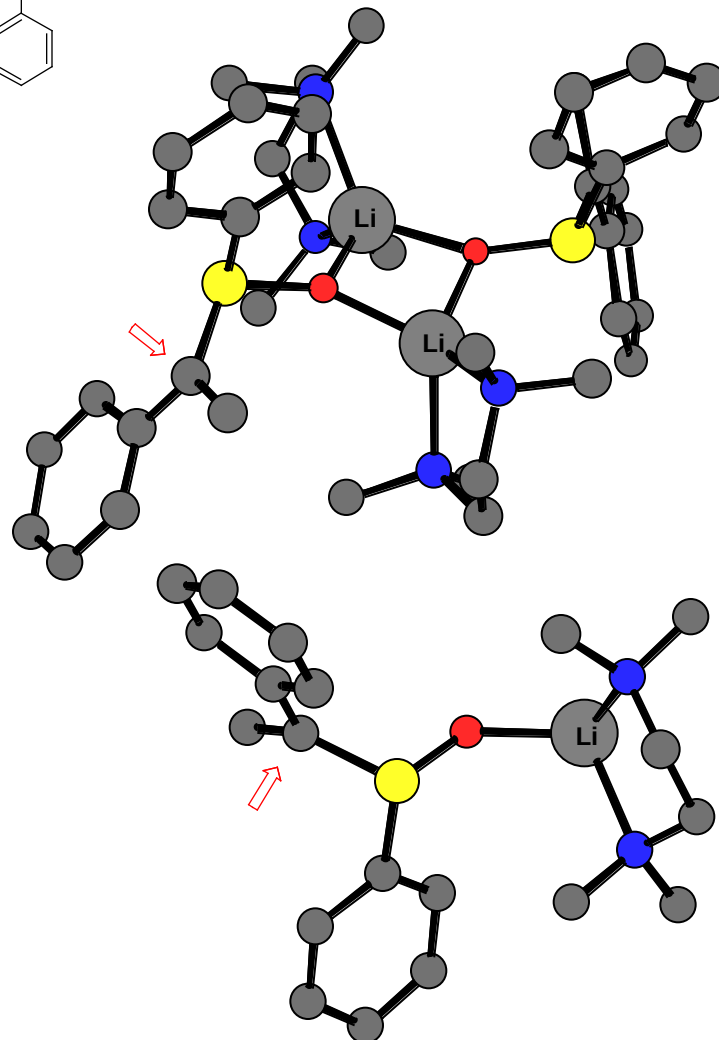
"The Structure of Lithium Compounds of Sulfones, Sulfoximides, Sulfoxides, Thioethers, 1,3 Dithianes, Nitriles, Nitro Compounds, and Hydrazones."

Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

Here are several examples taken from the Boche review:

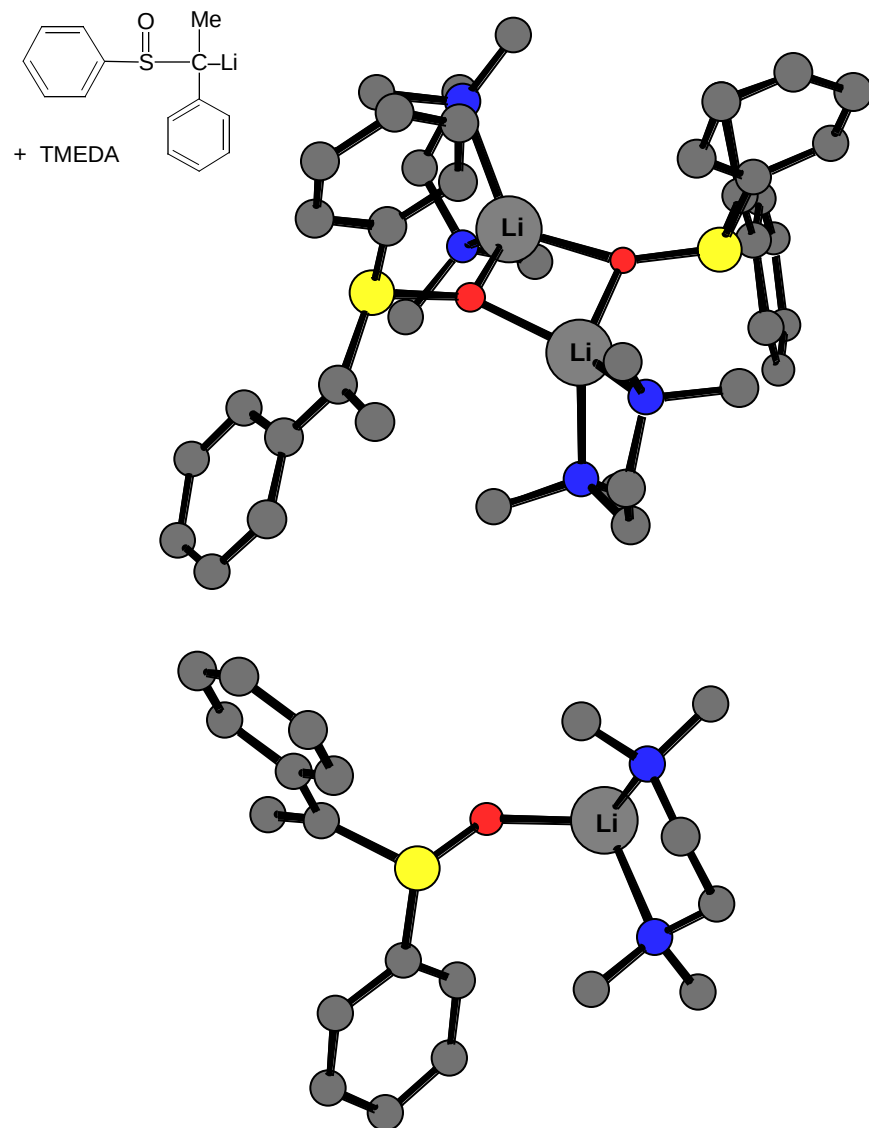


Boche, et al. *Angew. Chem. Int. Ed.* **1986**, *25*, 1101

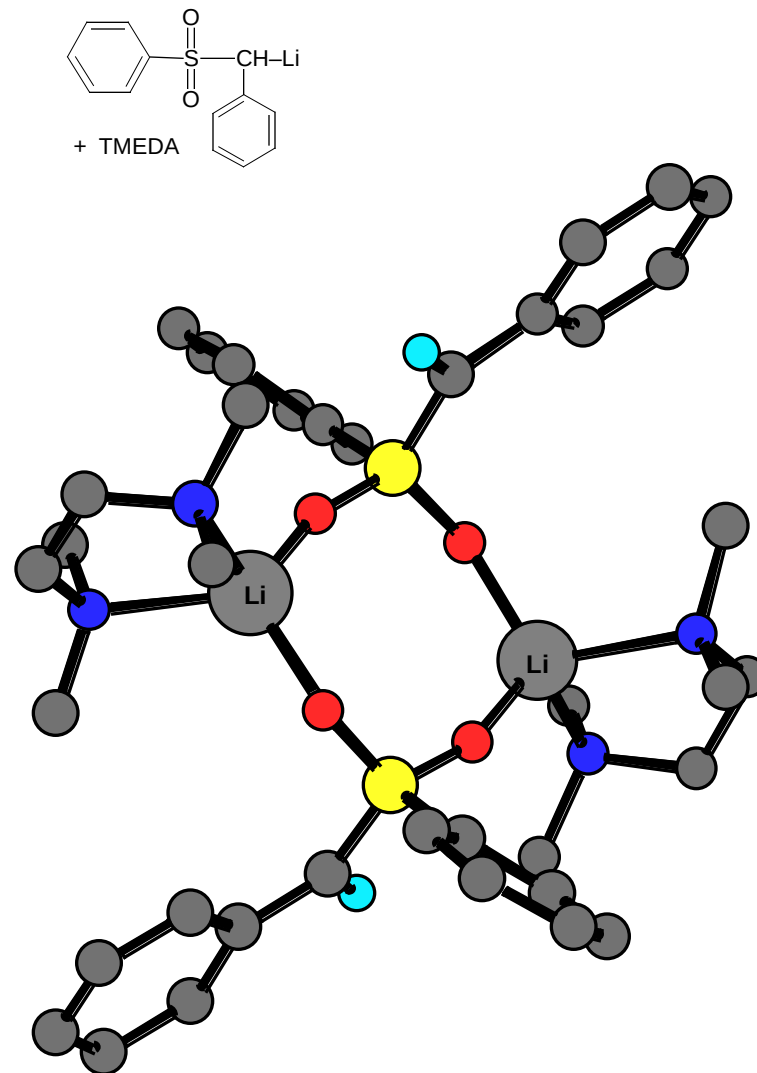


■ The Li counterions are not associated with the charged carbon.

■ The carbanions are largely trigonal.



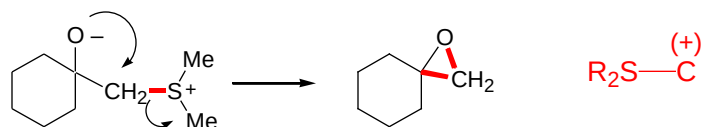
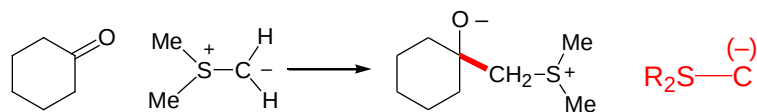
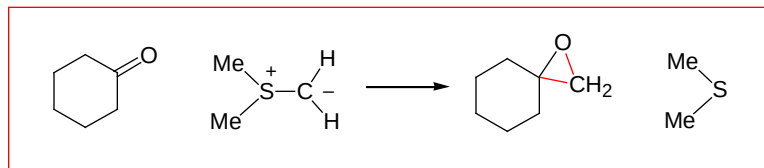
Boche, etal. *Angew. Chem. Int. Ed.* **1986**, 25, 1101



Boche, etal. *Angew. Chem. Int. Ed.* **1985**, 24, 573

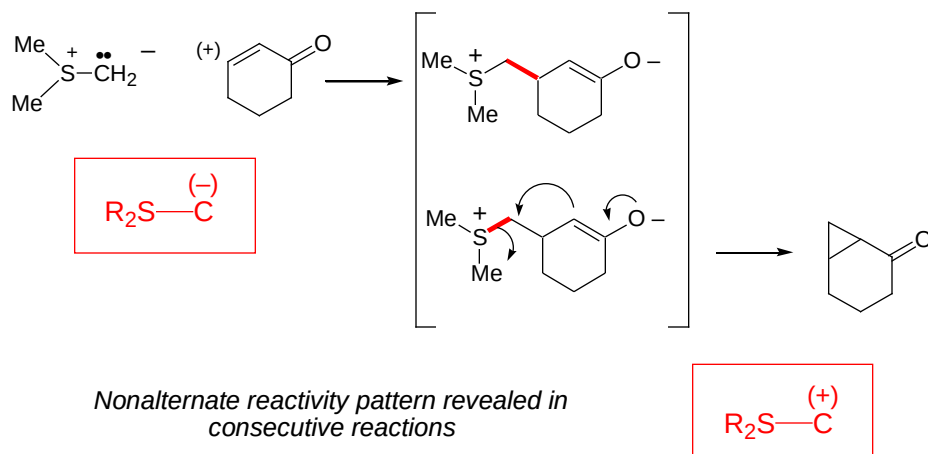
■ Reactions with ketones:

$R_2S-C^{\oplus}$ Reactivity Pattern: Nonalternate



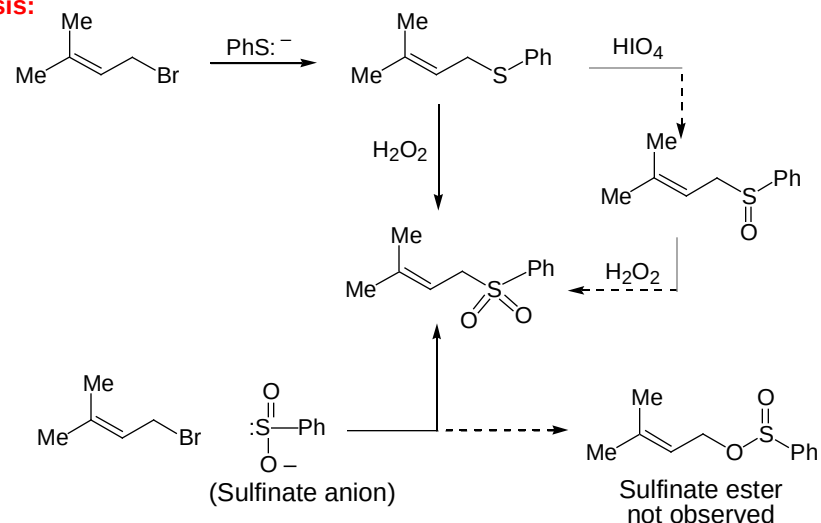
"Twenty-five Years of Dimethylsulfoxonium Methylide (Corey's Reagent).", Gololobov, Y. G.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, 43, 2609.

Reactions of Sulfonium Ylids: Conjugate Addition

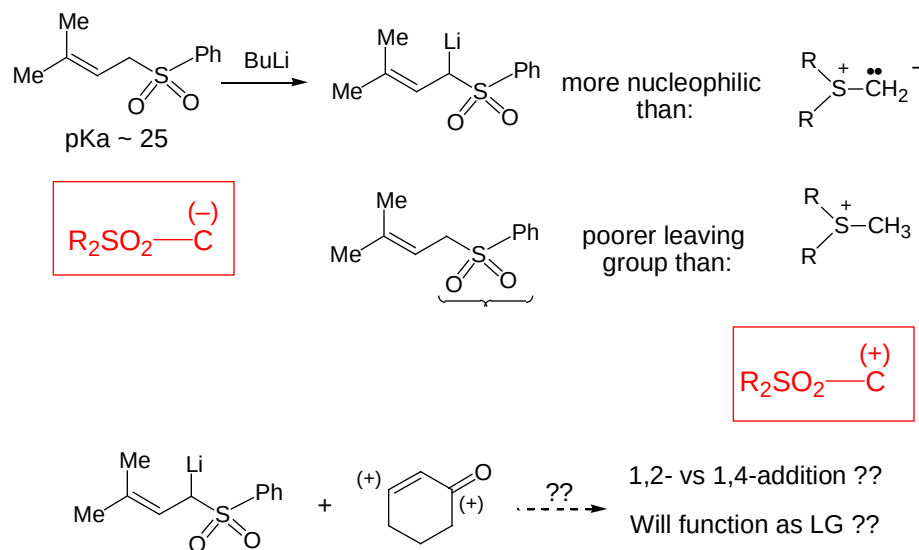


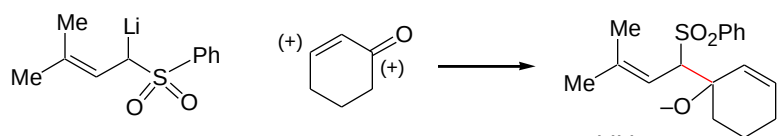
Reactions of Sulfones

Synthesis:

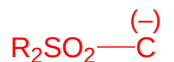


Reactions of Sulfones



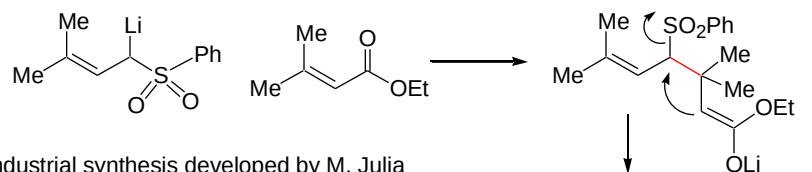


1,2-addition

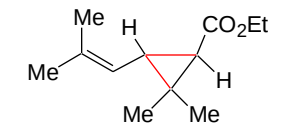
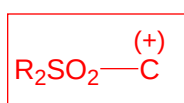
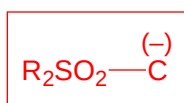


Alkoxide not sufficiently nucleophilic to displace PhSO_2^- anion.

However!!

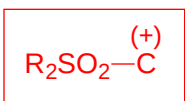
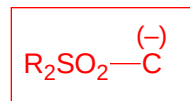
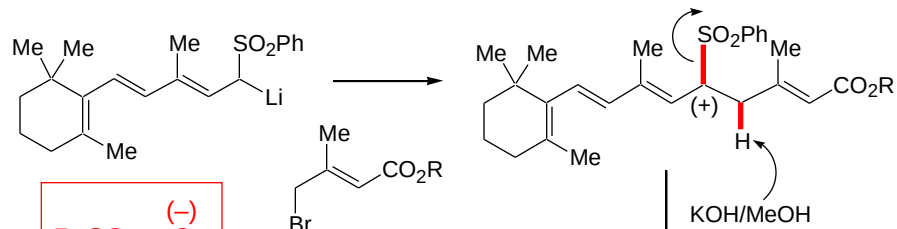


Industrial synthesis developed by M. Julia

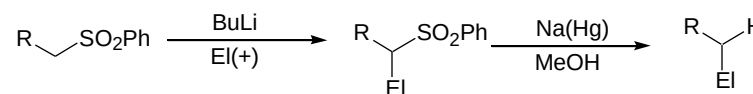


trans chrysanthemic acid

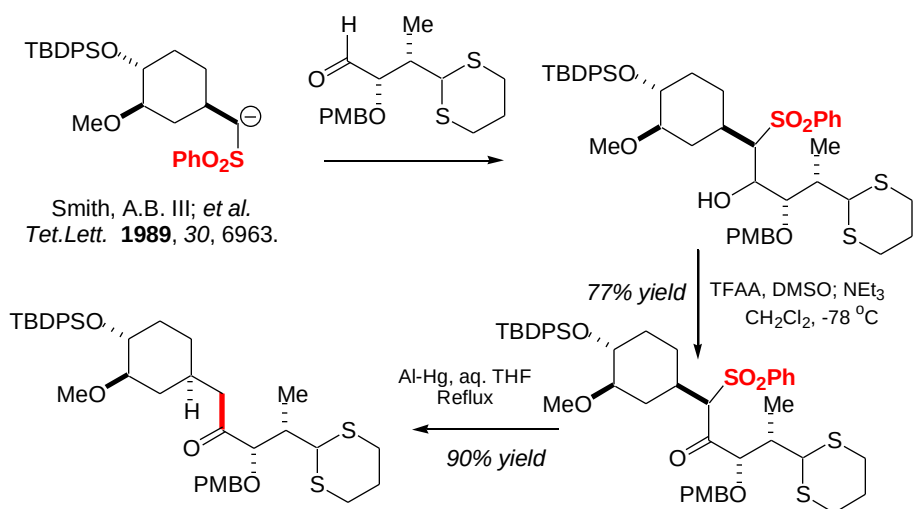
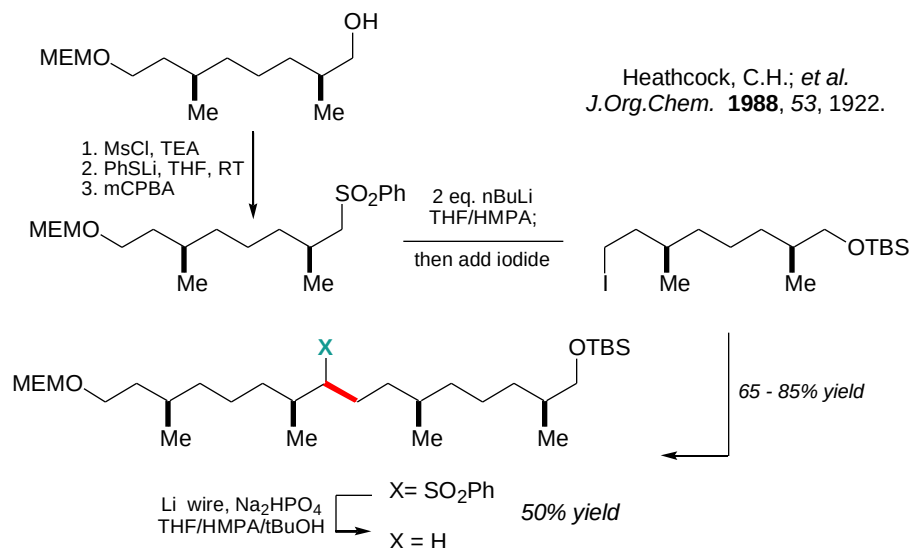
Synthesis of Vitamin A: Julia & Co-workers, *Bull. Soc. Chim. Fr.* **1985**, 130



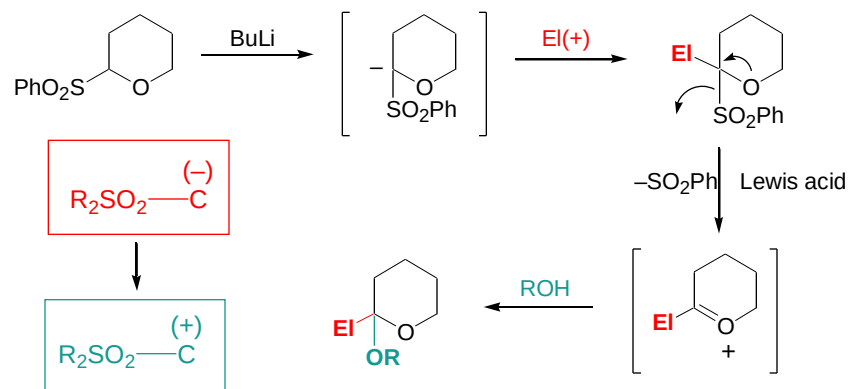
The Sulfone group may also be readily removed reductively:



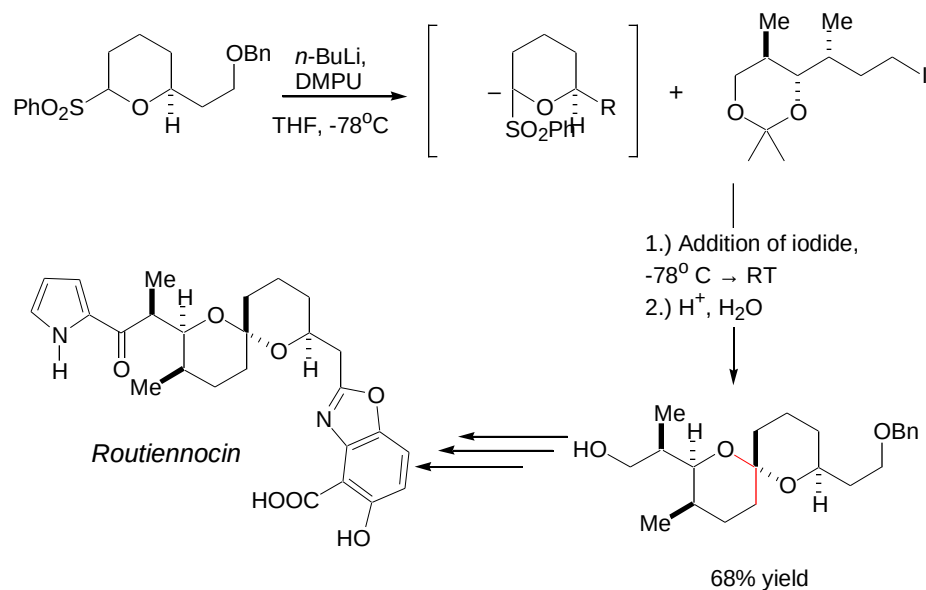
Fragment Coupling with Sulfonyl Carbanions



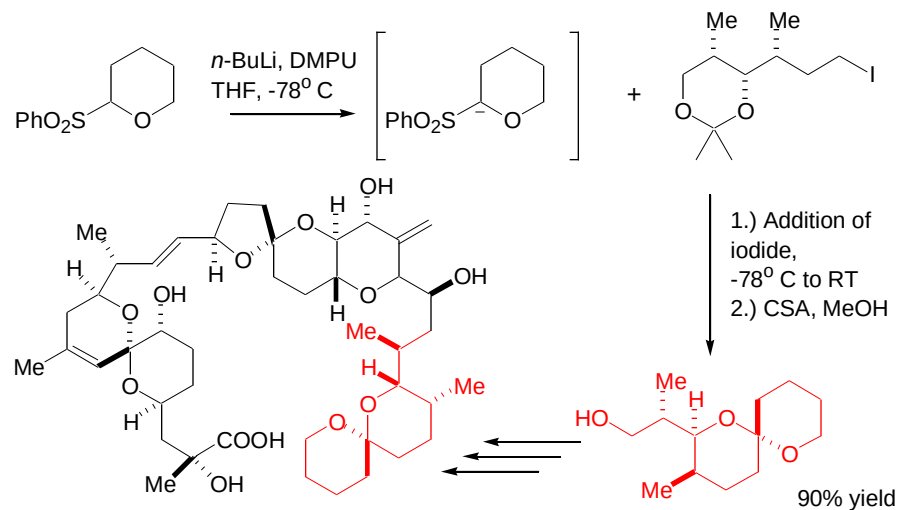
Functionalization of cyclic Ethers

Ley et al, *Synlett*, **1992**, 395; Ley et. al, *Tetrahedron*, **1992**, 48, 7899

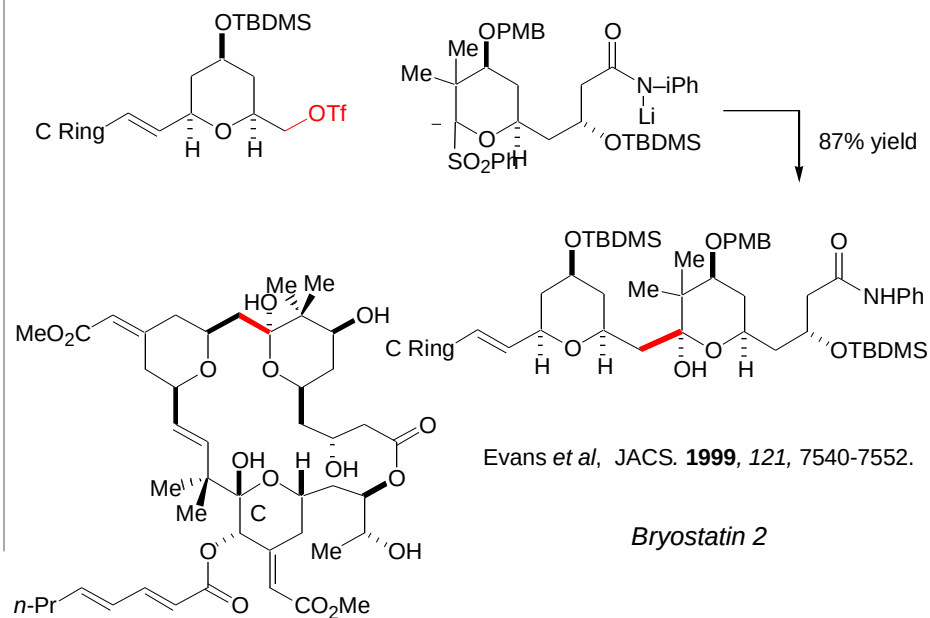
Total Synthesis of Routiennocin (CP-61,405)



Total synthesis of Okadaic Acid

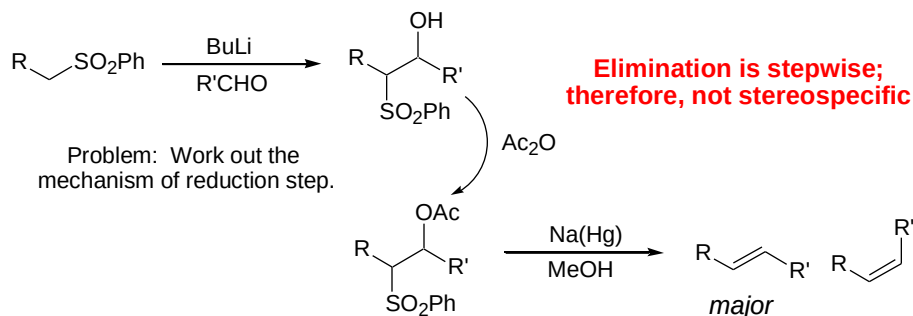
Ley et al, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3907.

Total synthesis of Bryostatin 2

Evans et al, *JACS*. **1999**, 121, 7540-7552.

Bryostatin 2

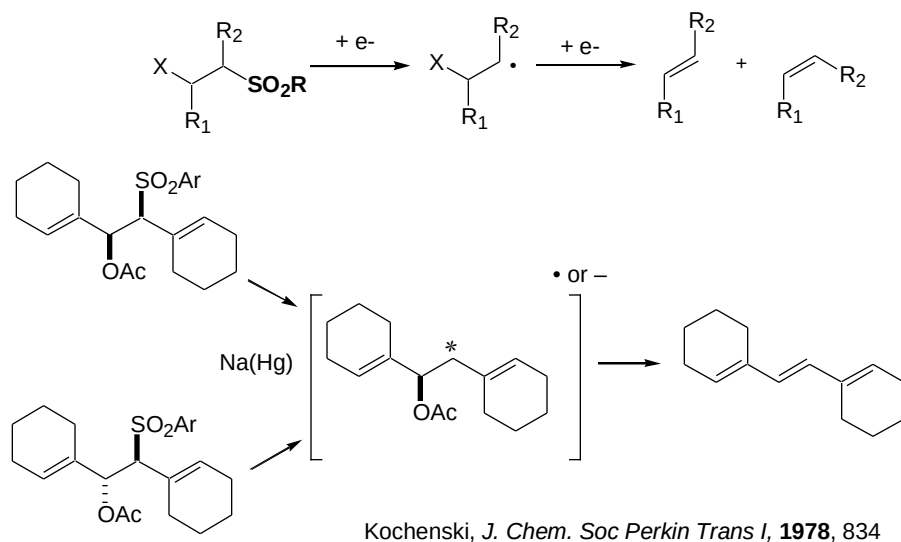
Julia Trans Olefin Synthesis:



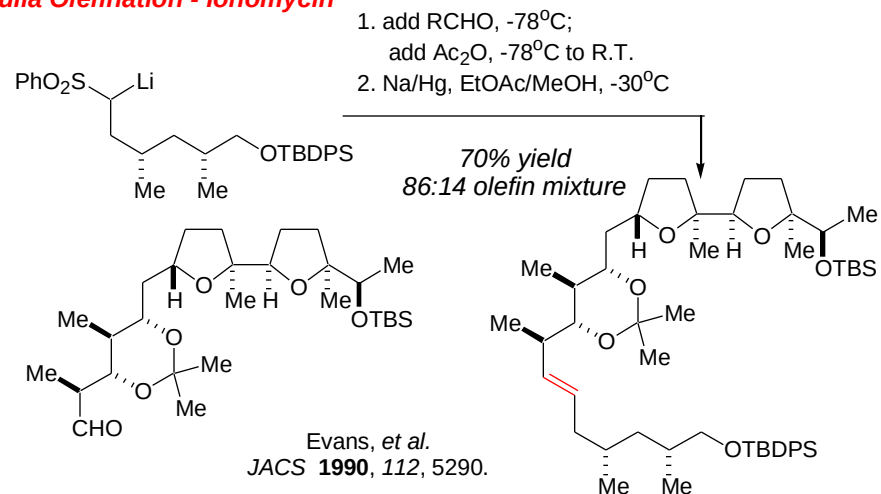
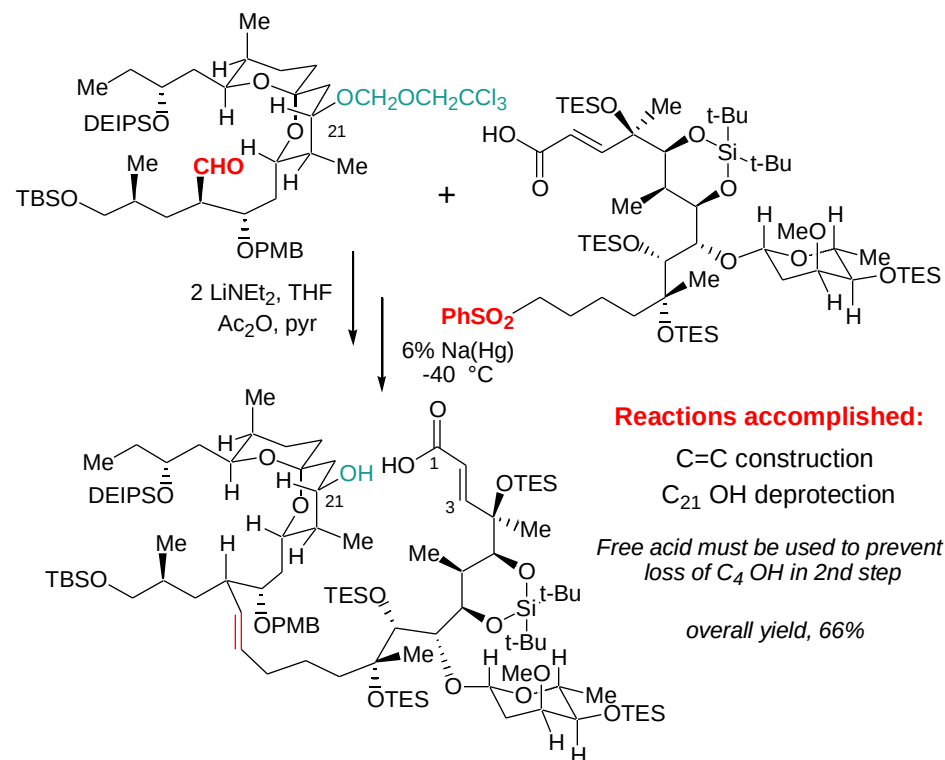
Good sulfone review: Trost, *Bull Chem. Soc. Japan*, **1988**, 61, 107-124.

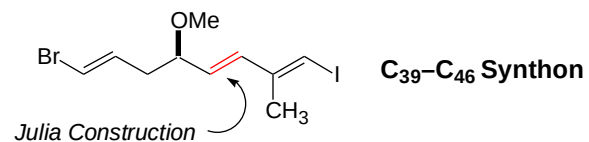
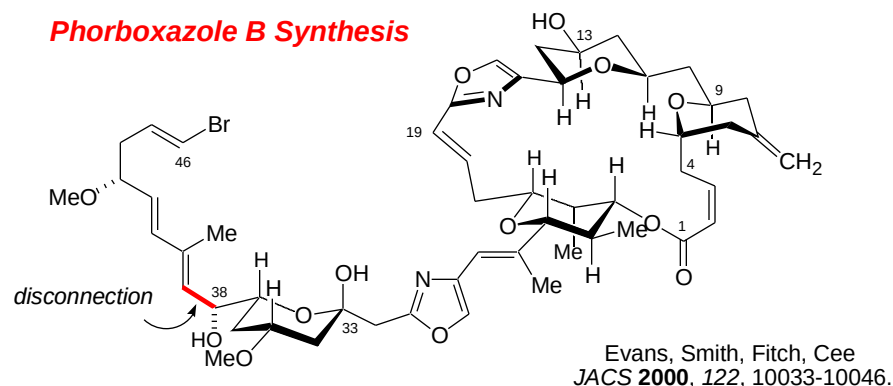
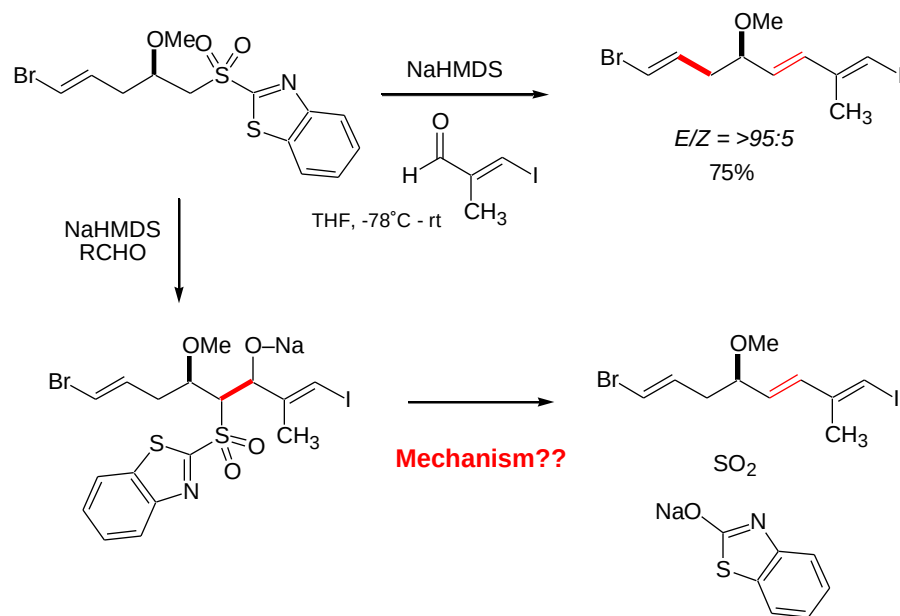
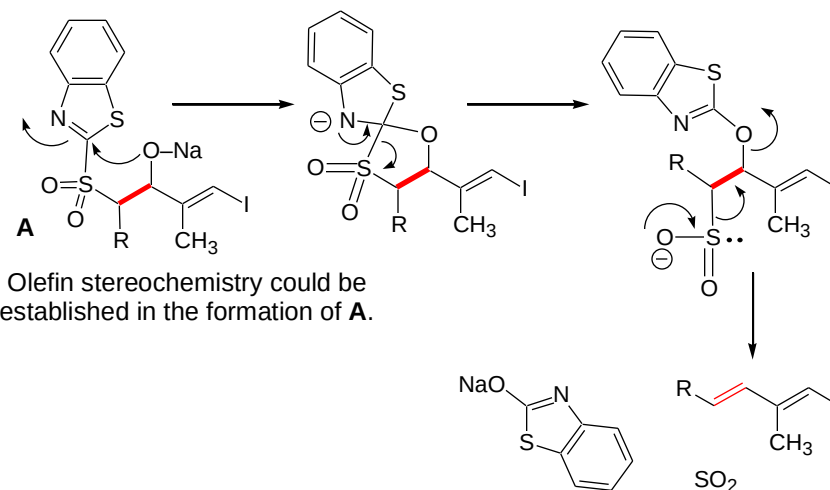
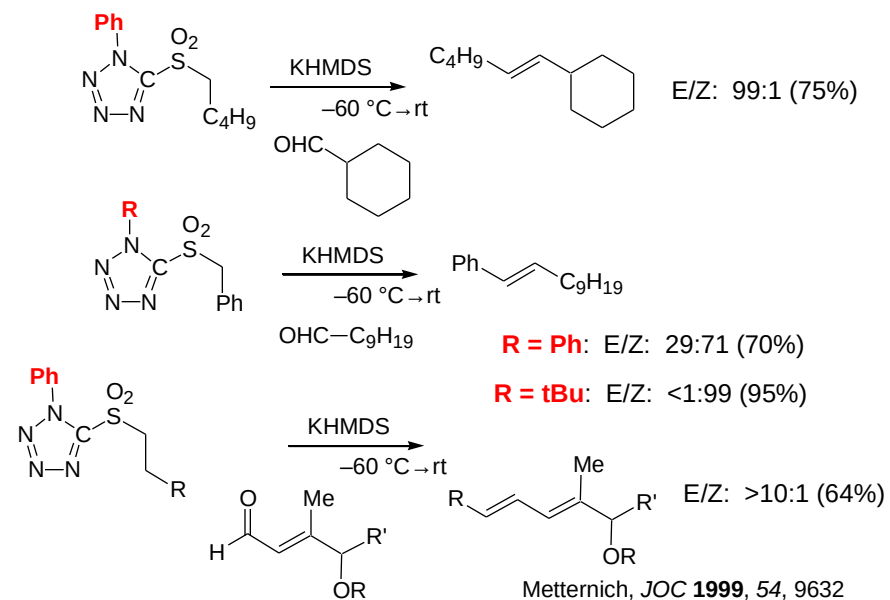
Review: Kocienski et al. *Phosphorus & Sulfur* **1985**, 24, 97-127

The reduction step is not stereospecific



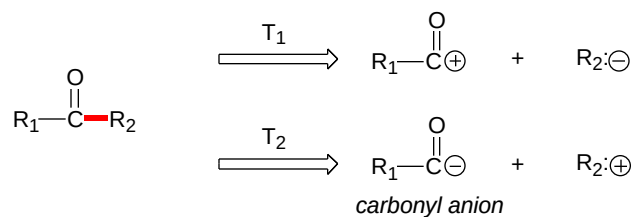
Julia Olefination - Ionomycin

Cytovaricin Synthesis: *JACS* **1990**, 112, 7001

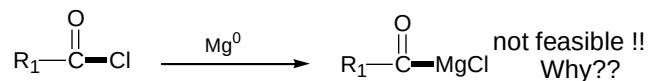
Phorboxazole B Synthesis**The Mechanism:****Recent Modifications of the Julia Process:**Kocienski, *SynLett* **2000**, 3, 365-366.

Carbonyl Anions: A useful Reversed Polarity Equivalent

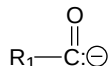
Consider the two possible polar disconnections of the C–R₂ bond of the ketone shown below:



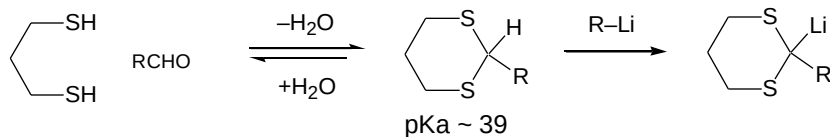
Carbonyl anions are not normally accessible via aldehyde deprotonation.



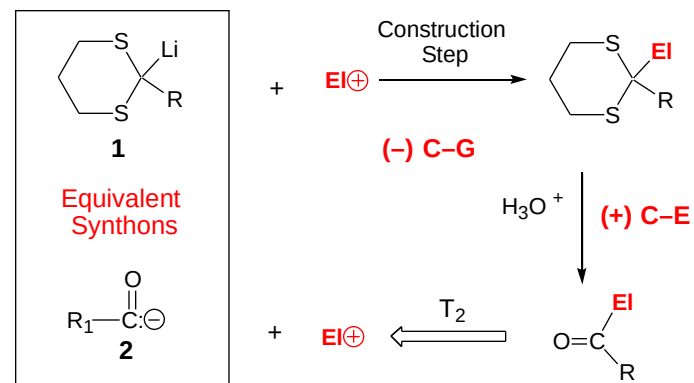
Operational equivalents to the carbonyl anion are useful in synthesis



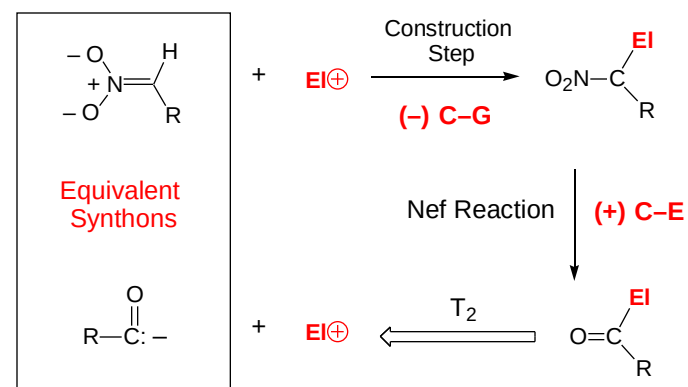
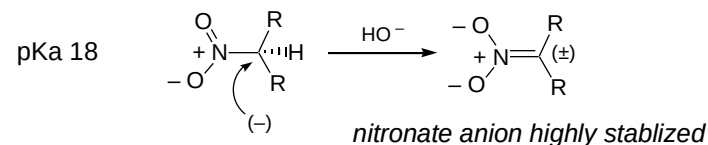
1,3-Dithianes as Carbonyl Anion Equivalents

Reactivity Patterns: $(\text{RS})_2\text{-C}(+)$
$$(\text{RS})_2\text{-C}(-)$$

The overall set of reactions which establishes the equivalency of the hypothetical carbonyl anion **1** and its equivalent synthon **2** is shown below:

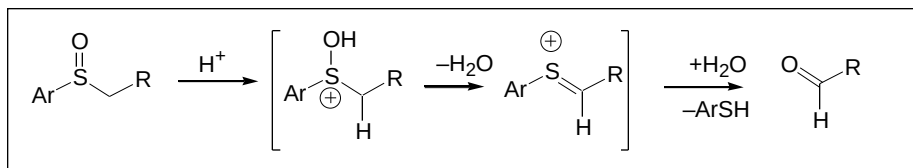


Nitronate Anions are also useful Carbonyl Anions

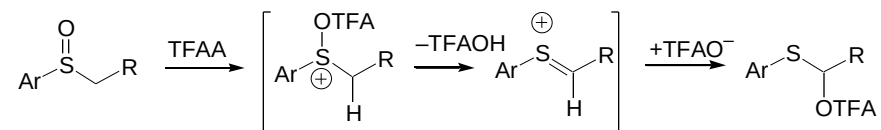


*Dithianes anions highly nucleophilic (indiscriminate):
Nitronate anions highly discriminating*

Basic Transformation:



The Pummerer Rearrangement facilitates the transformation of a sulfinyl $\rightarrow$ 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.

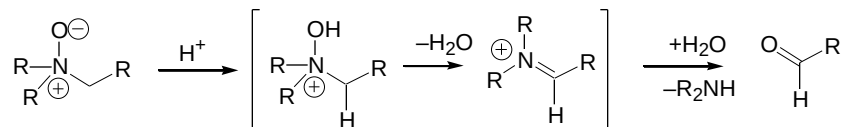
Grierson, and Husson (1991). Polonovski- and Pummerer-type Reactions and the Nef Reaction. *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 6: 909.

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.

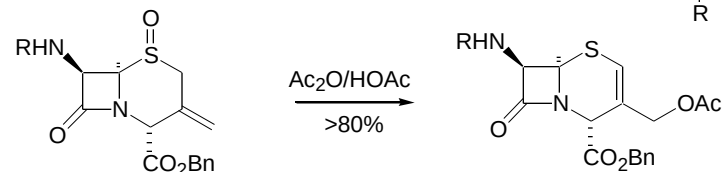
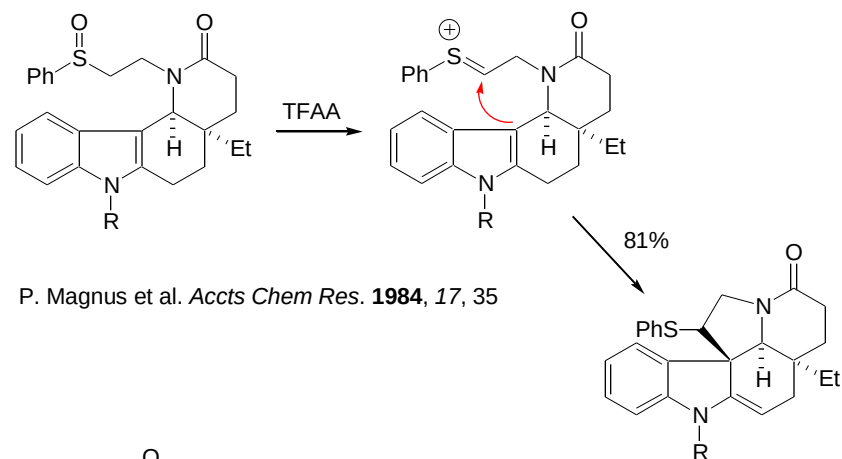
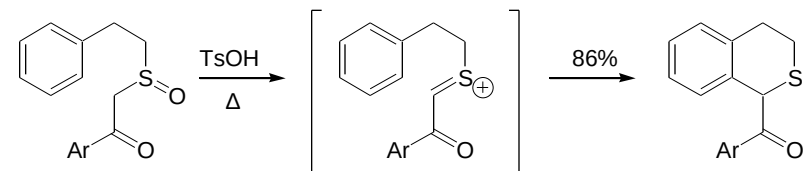
Kita, Y. and N. Shibata (1996). "Asymmetric pummerer-type reactions induced by O-silylated ketene acetals." *Synlett*(4): 289-296.

The Related Polonovski Reaction:

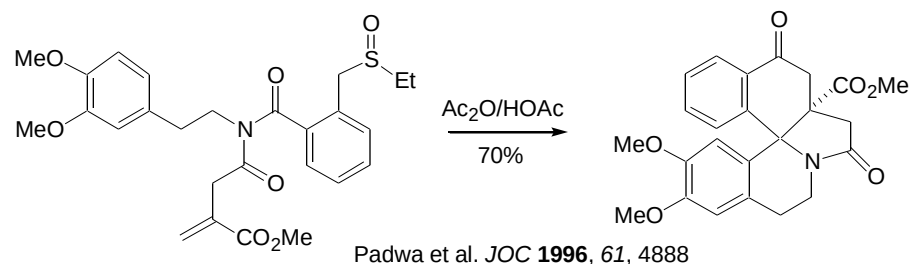


Regioselectivity: Depends on the relative kinetic acidity of the α protons

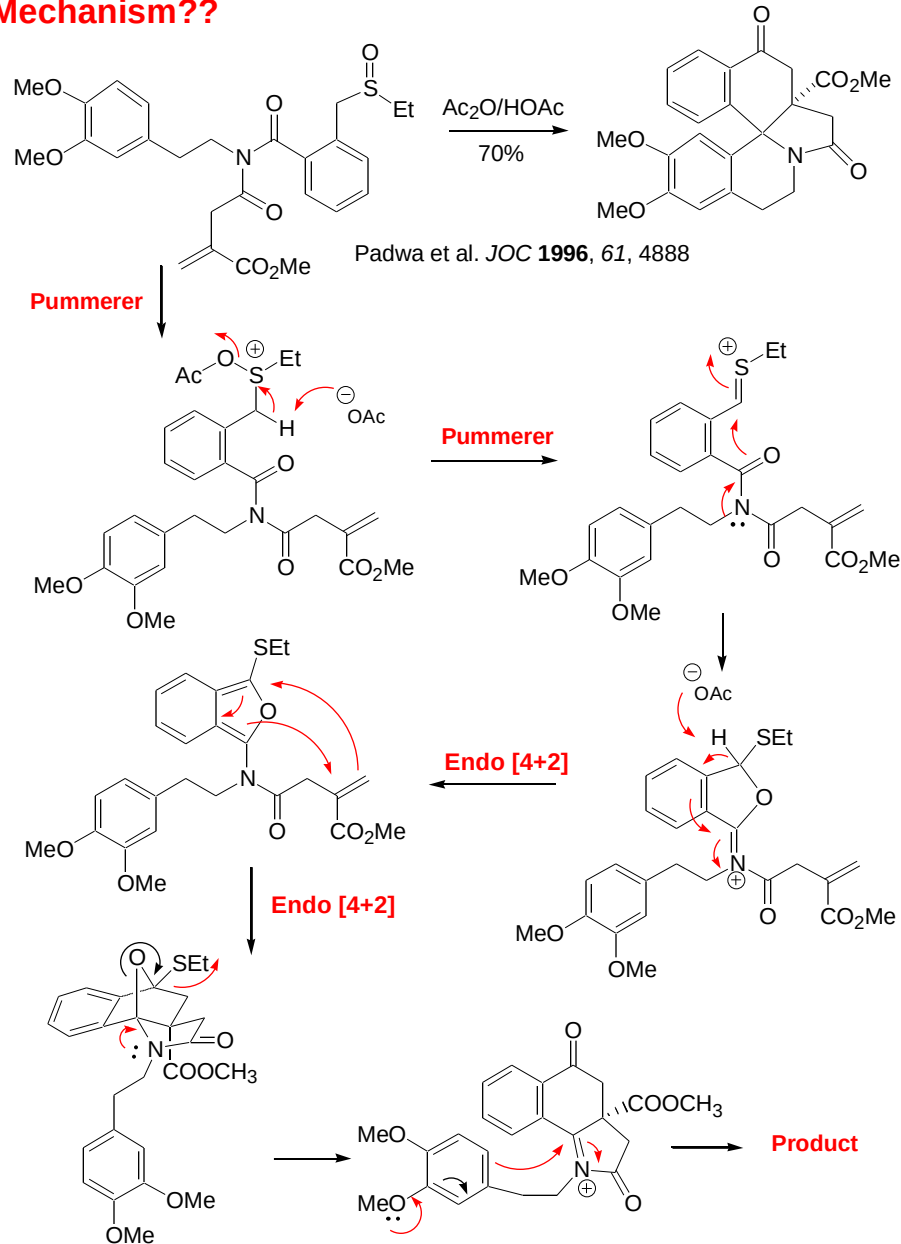
Transformations Mediated by the Pummer Rearrangement



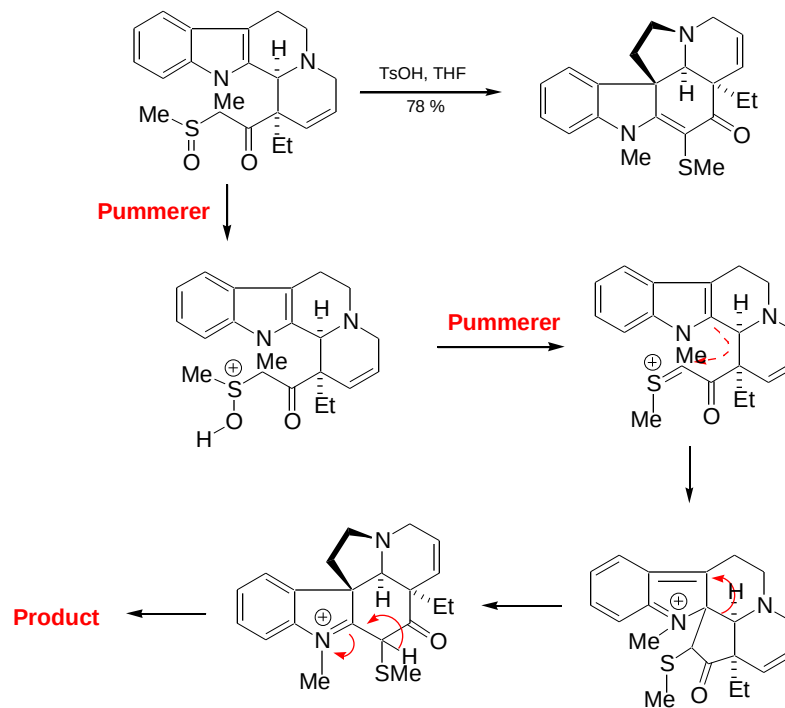
The cruel mechanistic problems that you should be prepared for in Chem 206



Mechanism??



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 arylsulfonyl-hydrazones." *Org. Reactions* **1990**, 39: 1. (**handout**)

Wolff-Kishner & Related Reactions: Hutchins, (1991). "Reduction of C=X to CH₂ 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 CH₂ 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.

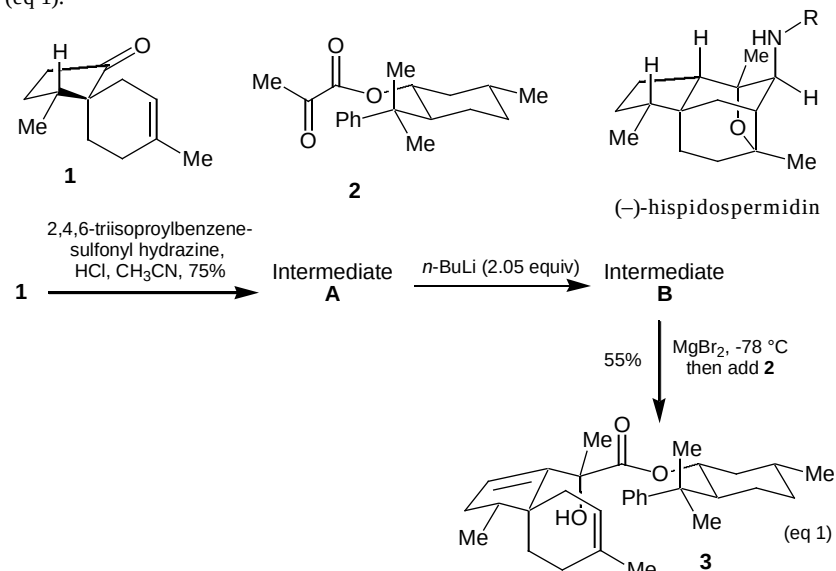
Addington, R. M. and A. G. M. Barrett (1983). "Recent Applications of the Shapiro Reaction." *Acc. Chem. Res.* 16: 55.

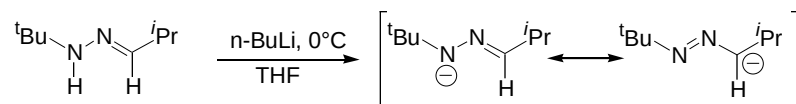
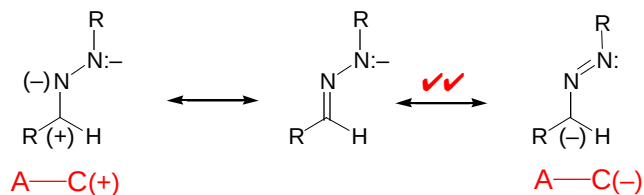
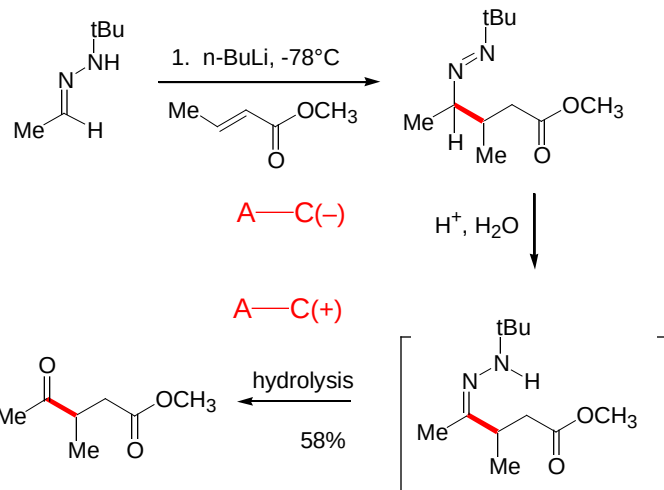
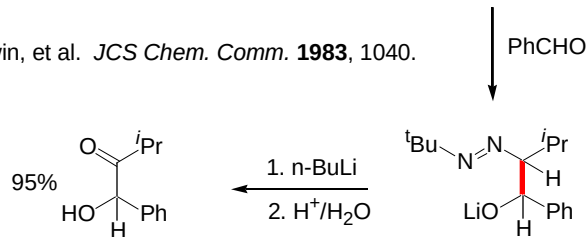
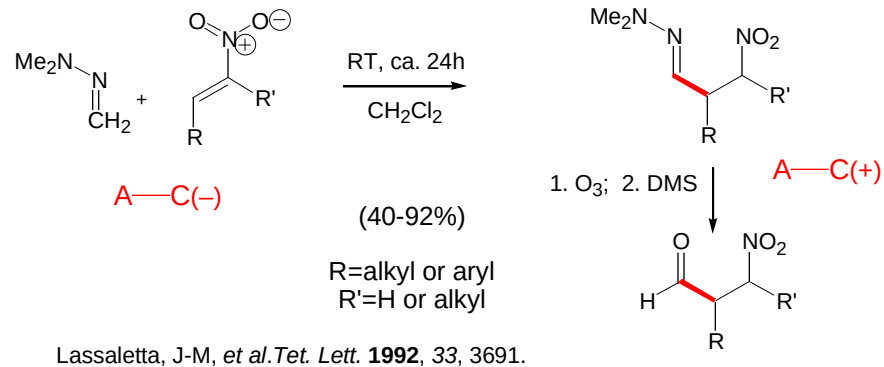
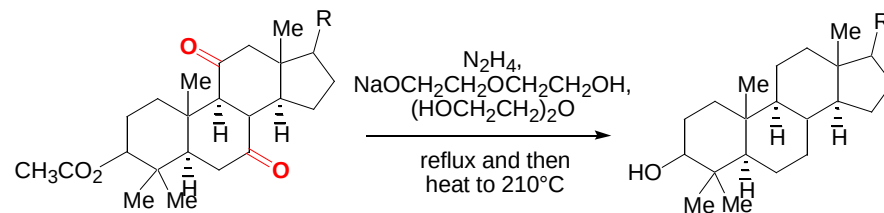
Chamberlin, and Bloom (1990). "Lithioalkenes from arylsulfonyl-hydrazones." *Org. React.* (N.Y.) 39: 1.

Bergbreiter, and Momongan (1991). "Hydrazone Anions". *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 2: 503.

Cume Question, November, 2000

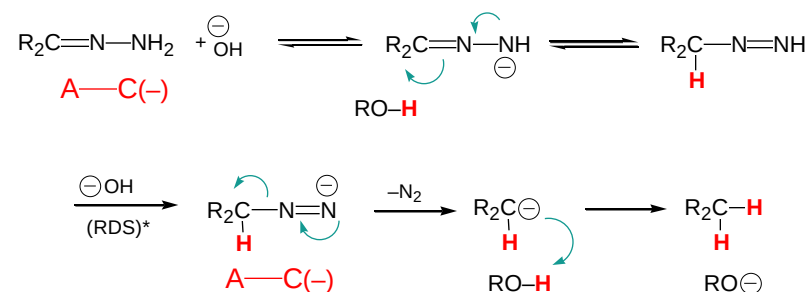
Sorensen and coworkers recently reported the synthesis of (–)-hispidospermidin (Sorensen *JACS*. **2000**, 122, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was used in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).

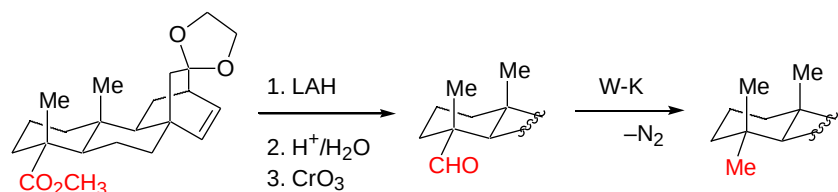
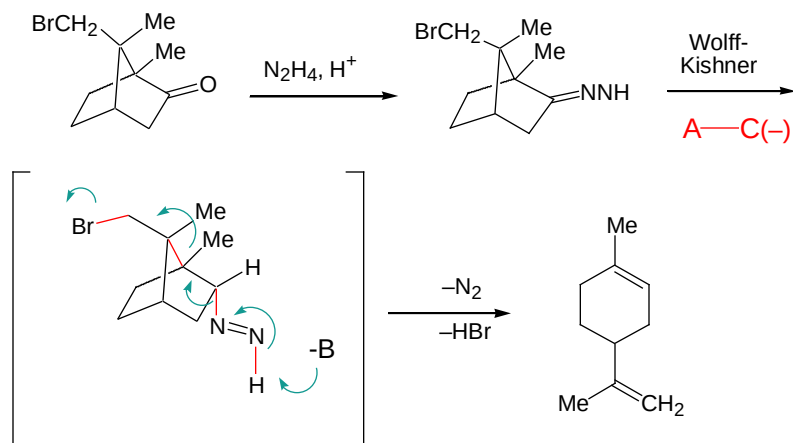
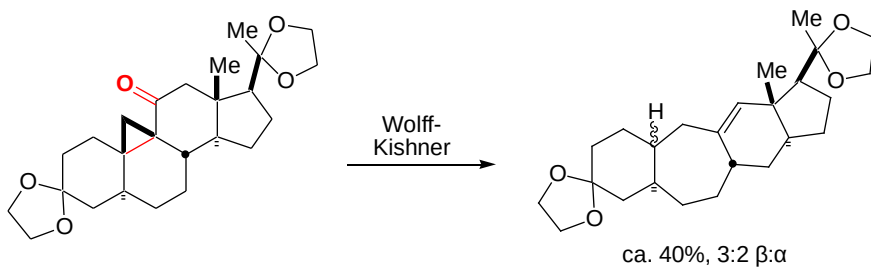
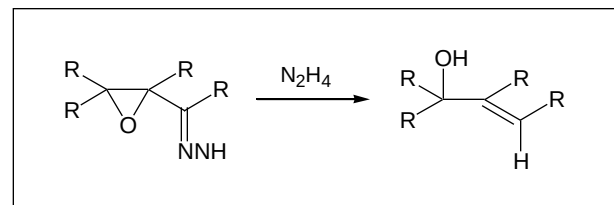
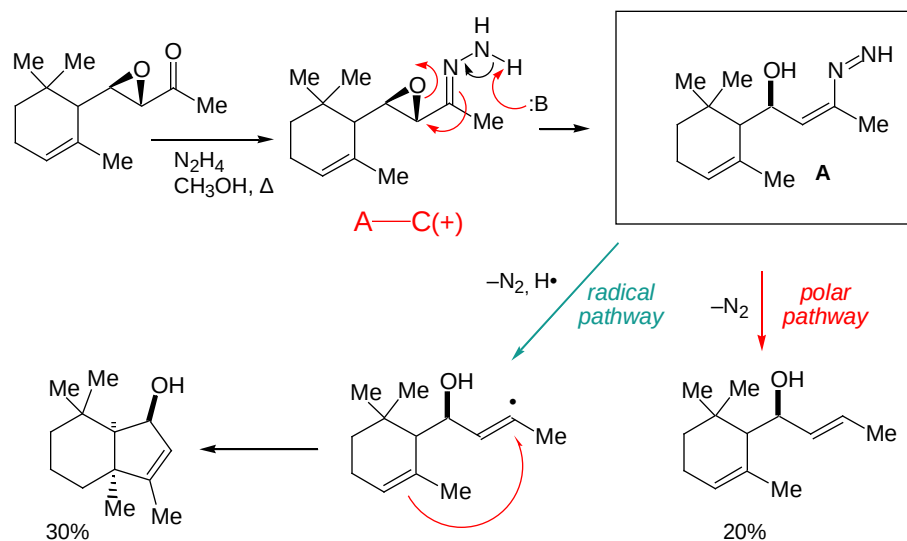
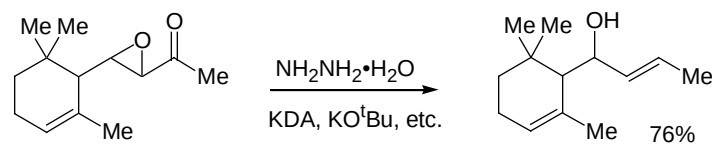


Hydrazone Anions: A useful Reversed Polarity EquivalentJ. E. Baldwin, et al. *JCS Chem. Comm.* **1983**, 1040.J. E. Baldwin, et al. *JCS Chem. Comm.* **1984**, 1095.**Wolff-Kishner Reduction Procedures**Barton, D. H. R., Ives, D. A. J., and Thomas, B. R. *J. Chem. Soc.* **1955**, 2056.

For particularly 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

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.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:**

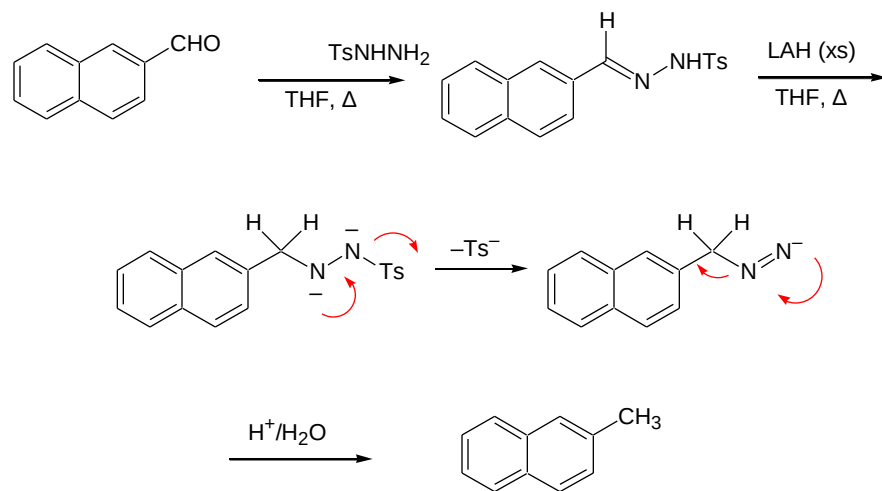
For stable hydrazones, strongly basic conditions favor the ionic pathway.

C. Dupuy, J. L. Luche *Tetrahedron Lett.* **1989**, 44, 3437.

Tosylhydrazones – Better Than Hydrazones

Tosylhydrazones are isolable, stable, and easily prepared.

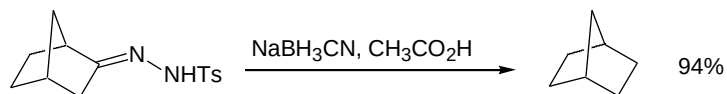
The presence of the tosyl leaving group strongly biases the system towards polar reaction pathways under hydridic reducing conditions.



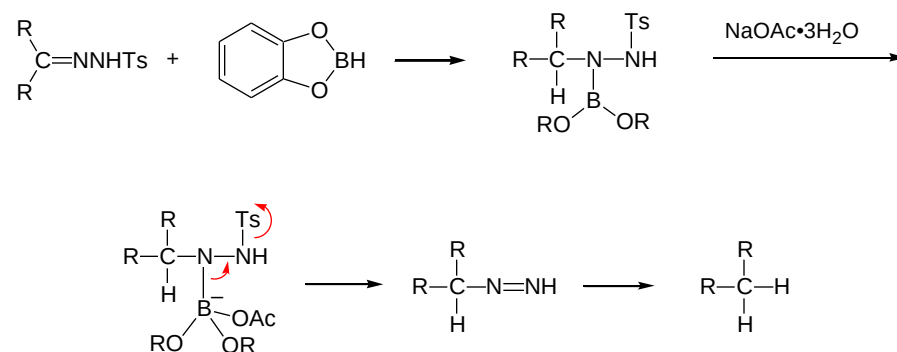
L. Caglioti, M. Magi *Tetrahedron* **1963**, 19, 1127.

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.

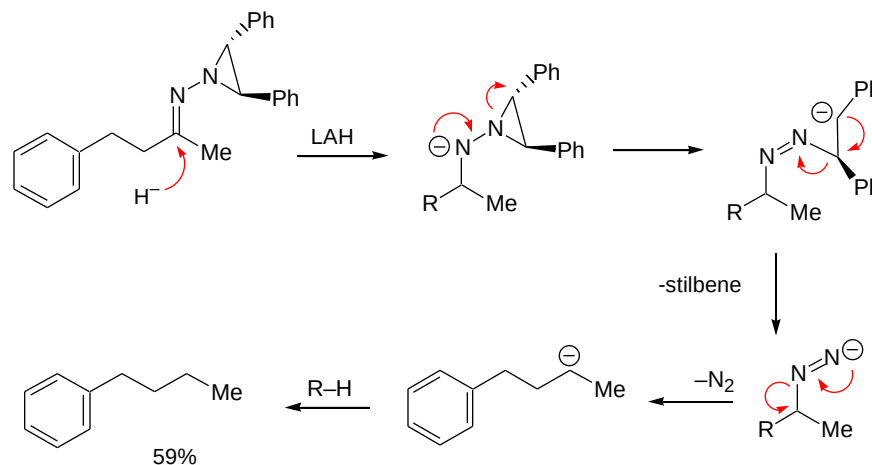


R. O. Hutchins, et al. *JACS* **1973**, 95, 3662.



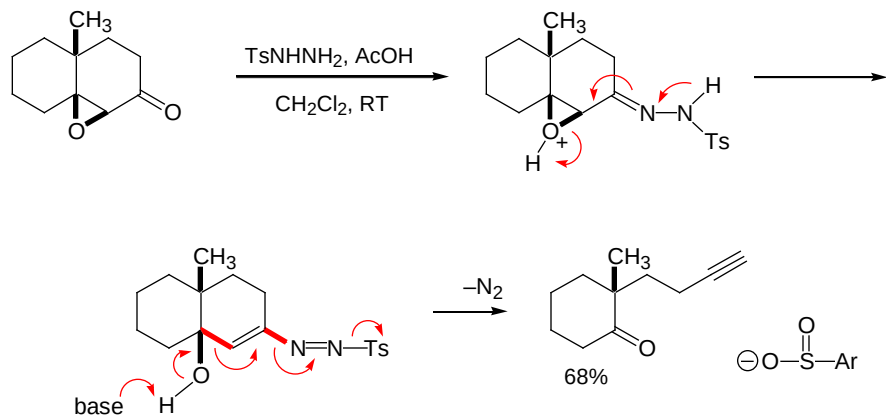
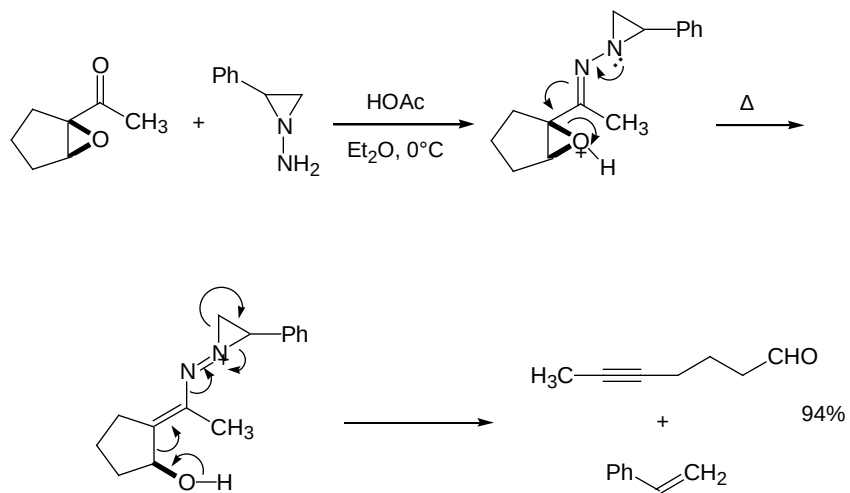
G. W. Kabalka, et al. *J. Org. Chem.* **1975**, 40, 1834.

Another Interesting Leaving Group

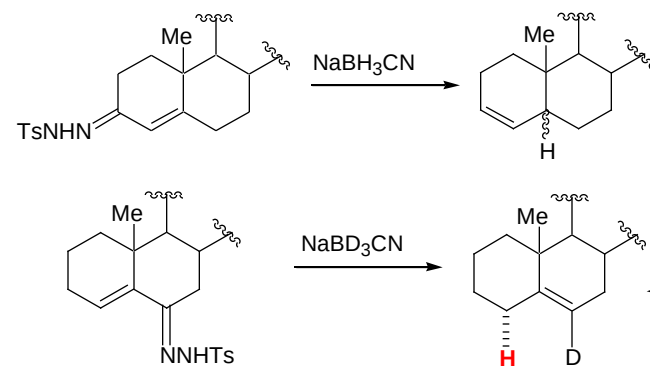
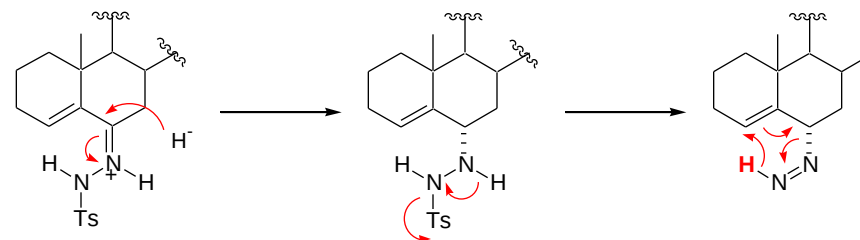


A. R. Chamberlin, et al. *Tetrahedron Lett.* **1991**, 32, 1691.

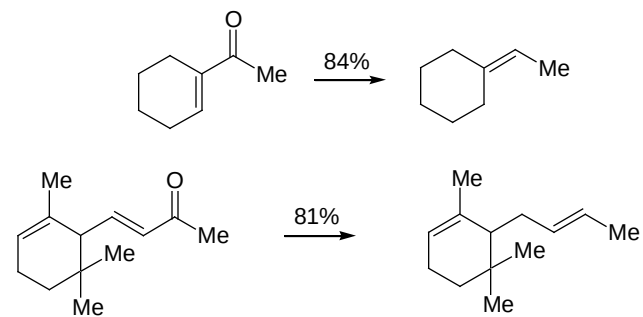
The Eschenmoser–Tanabe Fragmentation

A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, 50, 708.A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, 50, 2108.

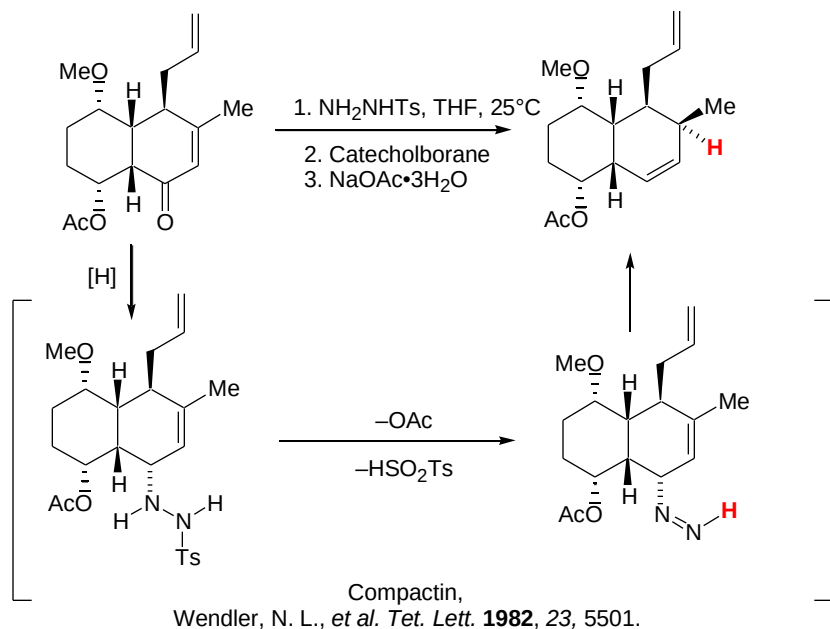
Tosylhydrazone Reductions: The Alkene Walk

C. Djerassi, et al. *JACS* **1976**, 98, 2275.

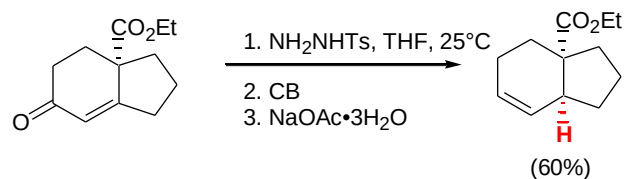
This has been developed into a reliable reduction

16 cases reported: Hutchins, et al. *JOC* **1975**, 40, 923

Alkene Walk: Syntheses

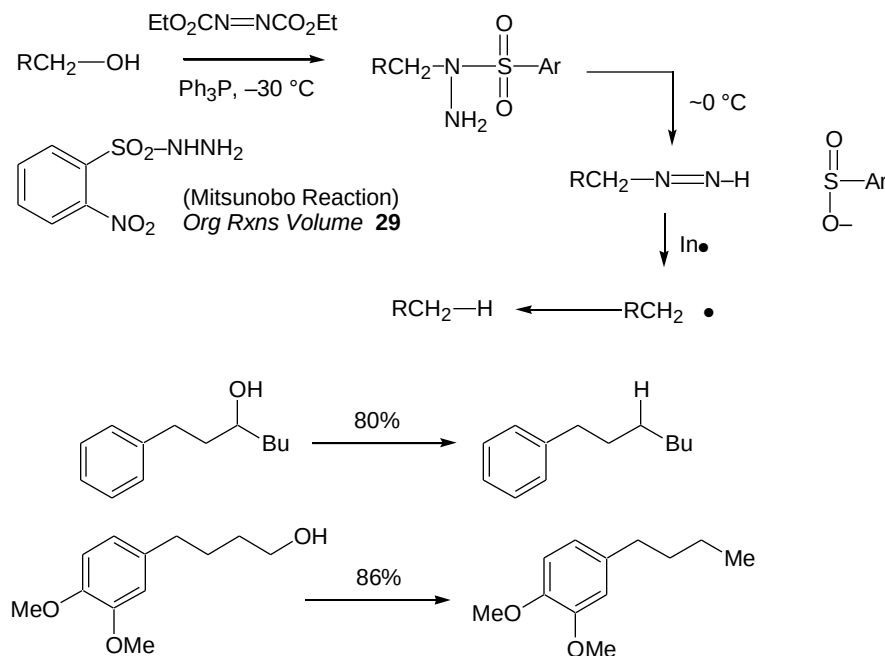


The stereochemical course of the hydrazone reduction may be stereospecifically transferred via the 1, 3-rearrangement

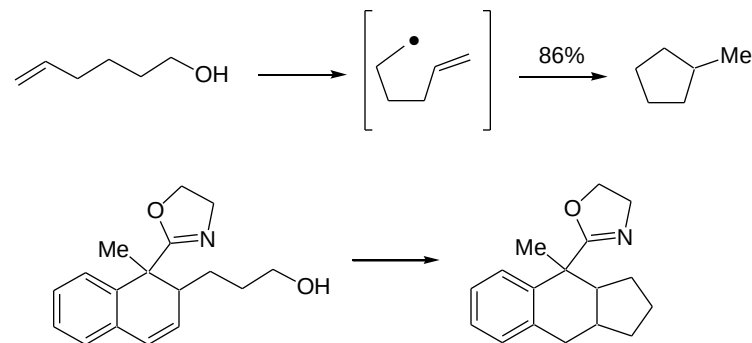


Topiramate,
 Maryanoff, B. E., *et al. Tet. Lett.* **1992**, 33, 5009.

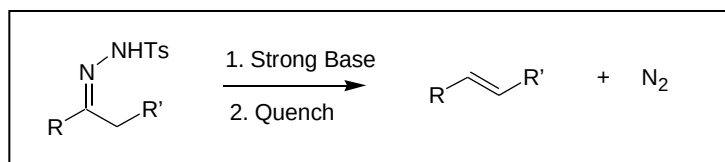
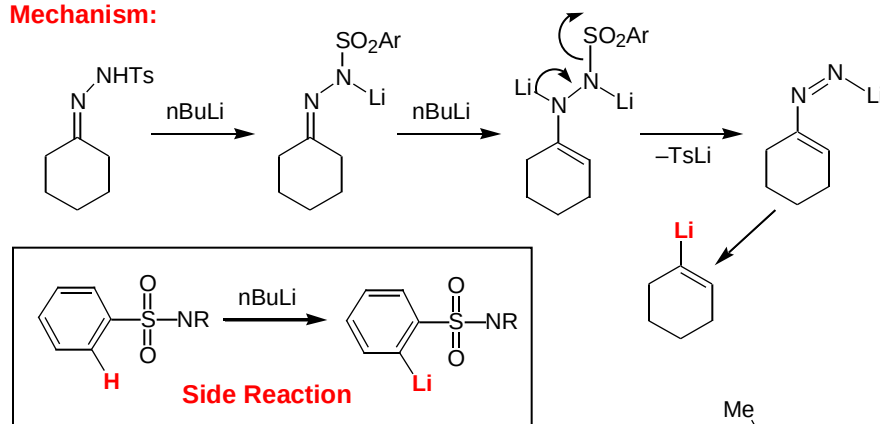
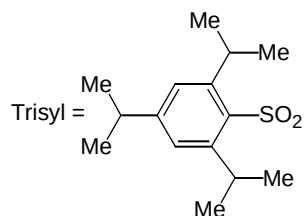
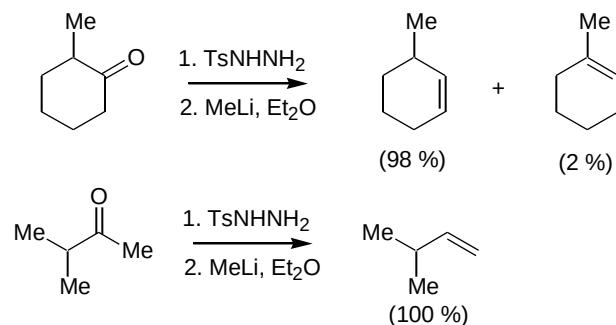
Sulfonylhydrazone Reductions: Alcohol Deoxygenation



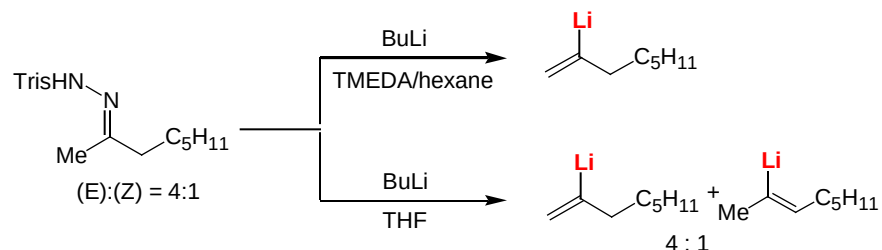
The intervention of radicals has been implicated (again):



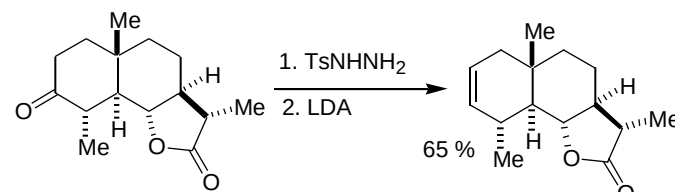
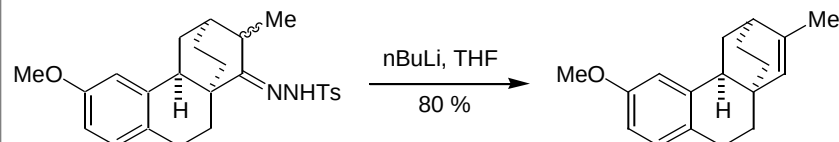
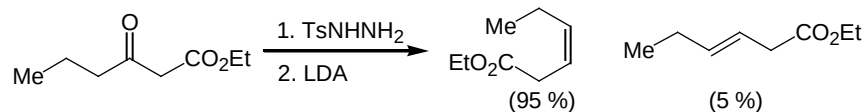
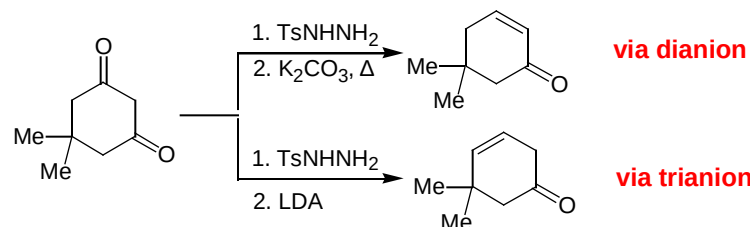
10 cases reported: A. Myers, *et al. JACS* **1997**, 119, 8572.

**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).**Regiochemistry**

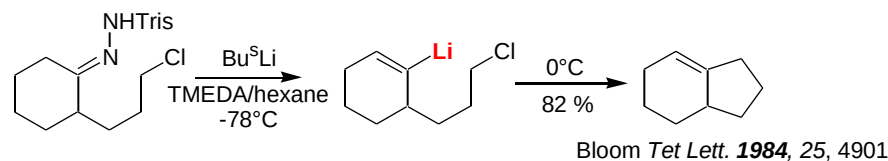
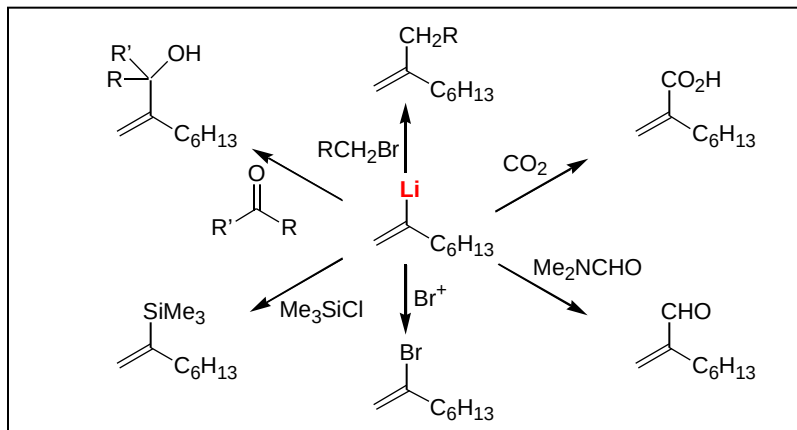
Deprotonation of the monoanion occurs predominantly at the kinetically more acidic site giving after elimination the less substituted alkene product.



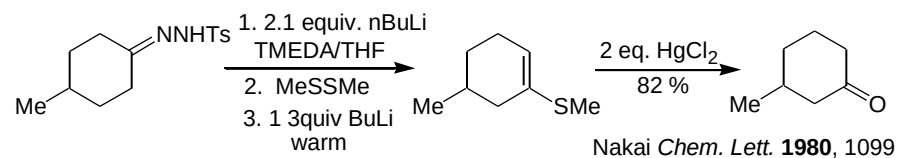
In THF solution regiochemical ratios generally reflect the starting hydrazone geometries

Bond *J. Org. Chem.* **1978**, 43, 154.Grieco *J. Org. Chem.* **1977**, 42, 1717.Nemoto *et. al. JCS, Perkin Trans. 1* **1985**, 927.

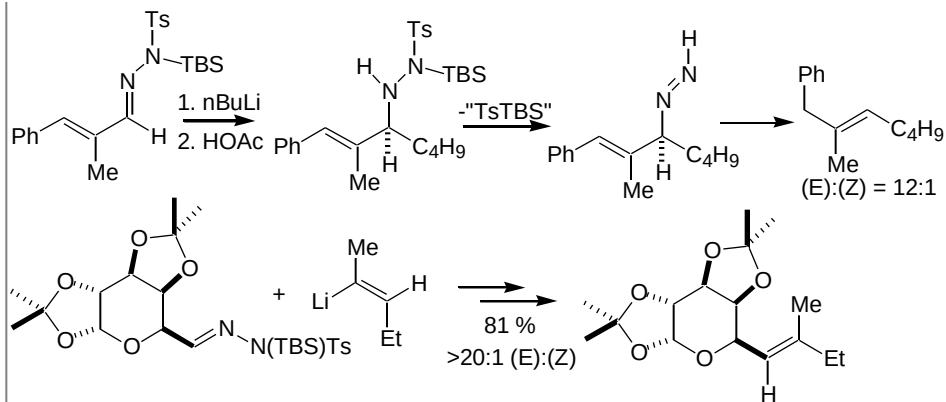
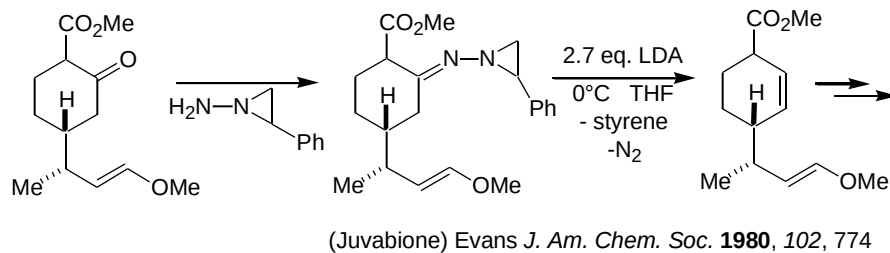
Trapping of the intermediate alkenyllithium



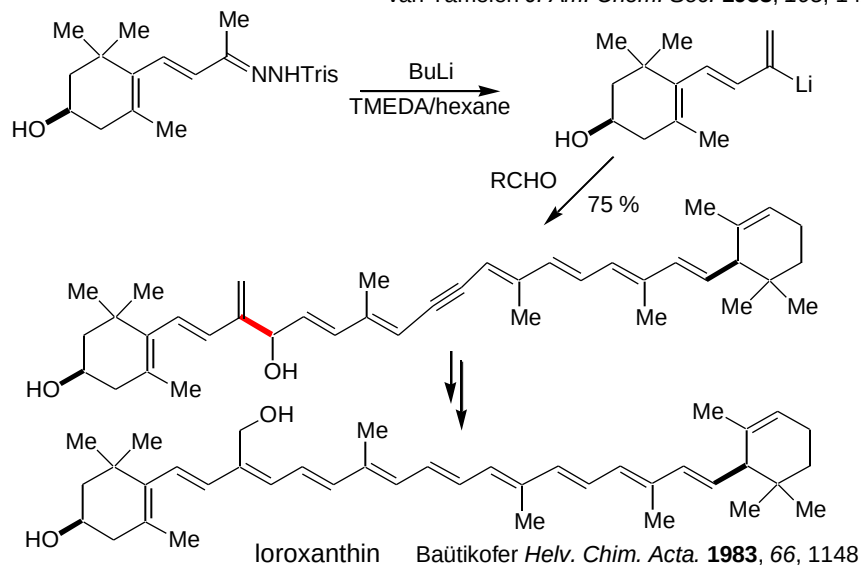
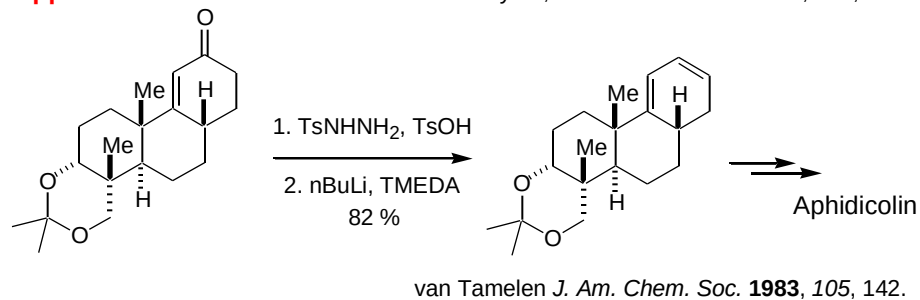
Carbonyl Transposition



Shapiro alternatives



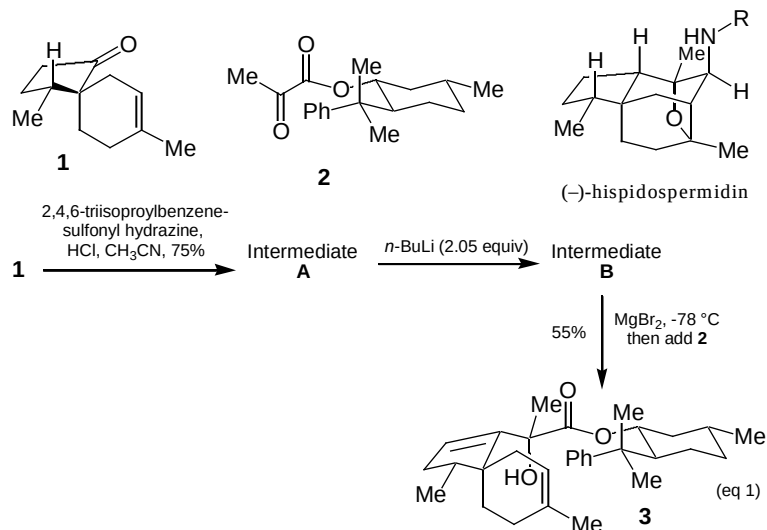
Applications



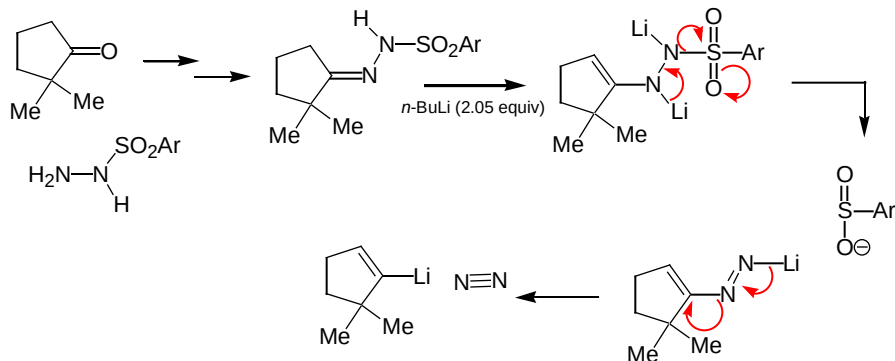
A Recent Application of the Shapiro Reaction

Cume Question, November, 2000

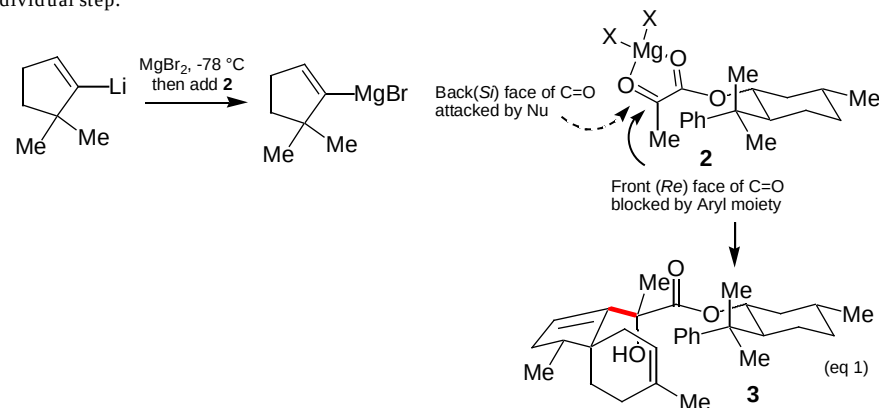
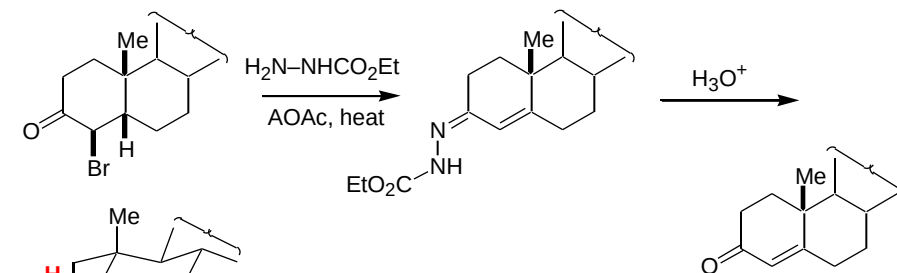
Sorensen and coworkers recently reported the synthesis of (-)-hispidospermidin (Sorensen *JACS*, 2000, 122, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was used in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



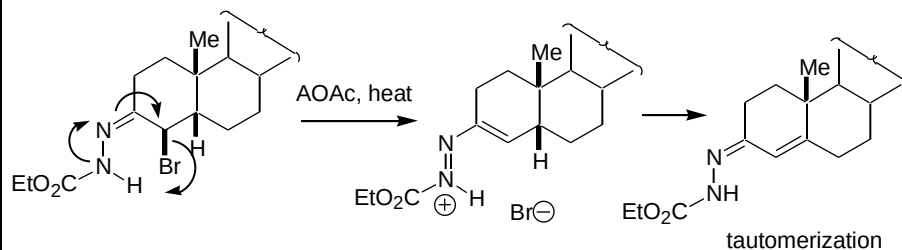
Part A (8 points). Provide a mechanism for the **Shapiro Reaction** of **1** to intermediate **B** in the space below. Feel free to use a simplified analog of **1** such as 2,2-dimethylcyclopentanone to answer this question.



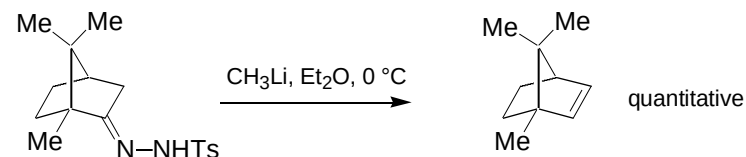
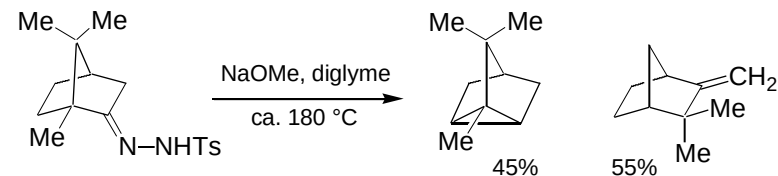
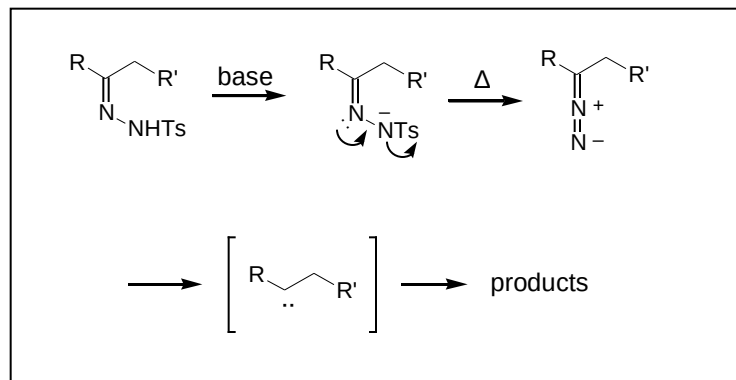
Part B (7 points). Provide a mechanism for the **transformation** of intermediate **B** to the illustrated product **3**. Use 3-dimensional representations to illustrate the stereochemical aspects of this individual step.

Mattox-Kendall Dehydrohalogenation (Paquette, *Reagents*, Vol 5, p 3509)

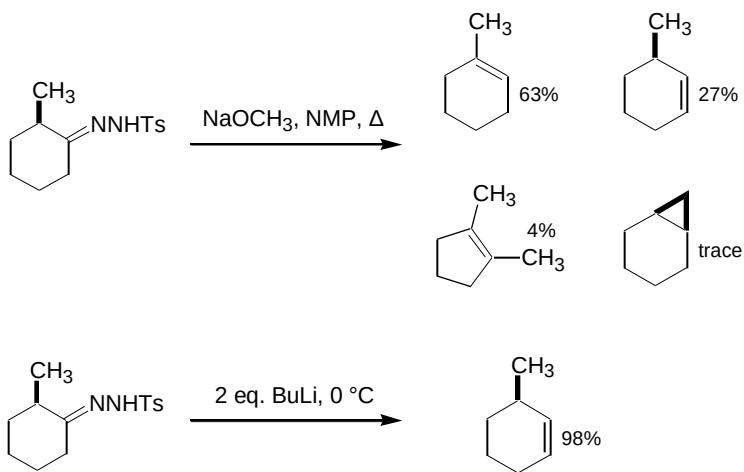
Problem: The syn relationship between Br and H renders the direct dehydrohalogenation with base unfavorable (relative to other potential reactions). Solution; proceed via the hydrazone.



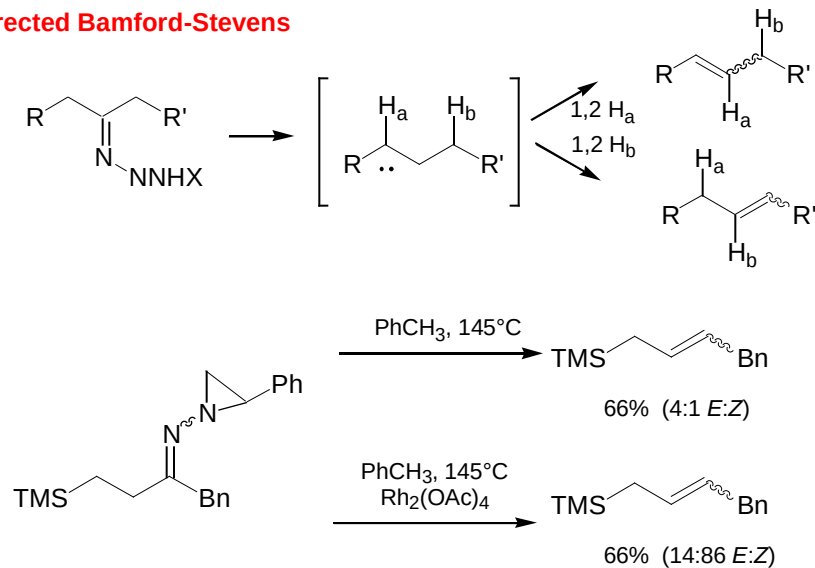
An Alternate Decomposition Pathway for Tosyl Hydrazones



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.

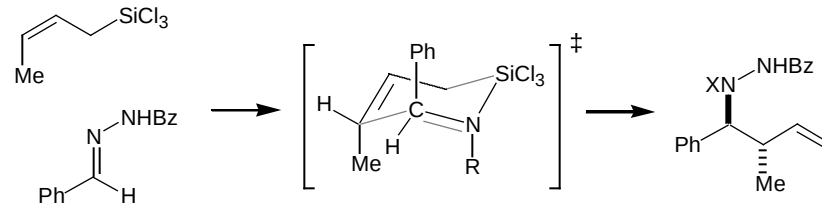
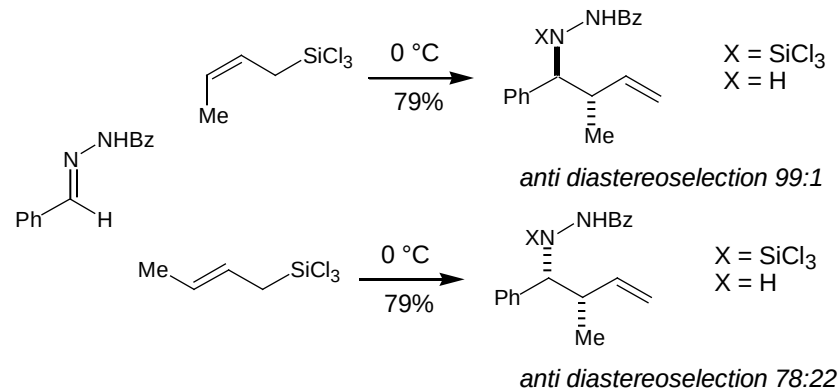
"Applications of sulfoxides to asymmetric synthesis of biologically active compounds.", Carreno, M. C. *Chem. Rev.* **1995**, 95, 1717-1760.

Matthew D. Shair

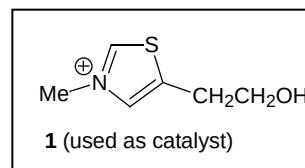
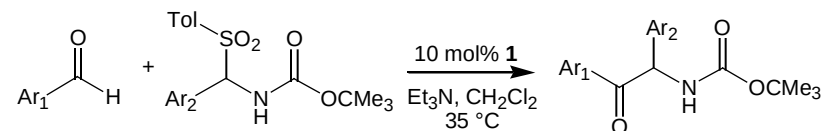
Monday,
December 2, 2002

The Imine Aldol Reaction: New Information

A recent relevant paper: Kobayashi, *JACS* **2001**, 123, 9493-9499

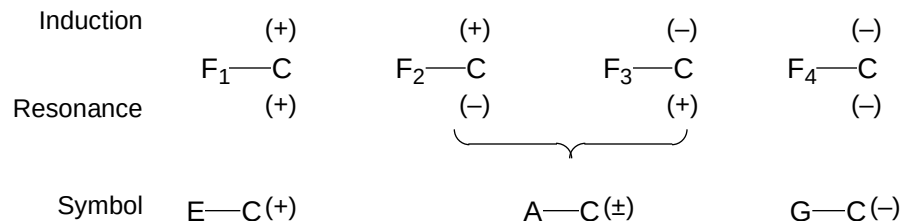
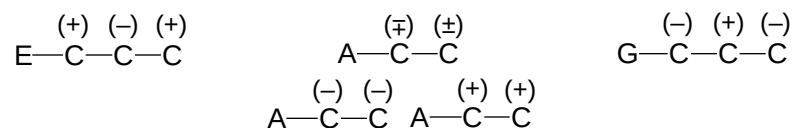


Cume Question, Fall 2001. The reaction illustrated below was recently reported by Murry and co-workers from the Merck Process Group (*JACS* **2001**, 123, 9696-9697). Provide a mechanism for this transformation.



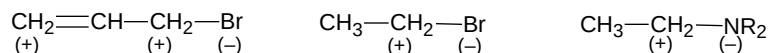
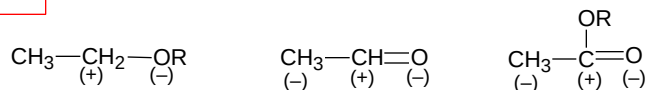
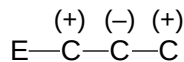
Classification of Functional Groups

Each substituent attached to carbon activates that carbon toward a polar reaction by either resonance or induction or both.

**Charge Affinity Patterns**

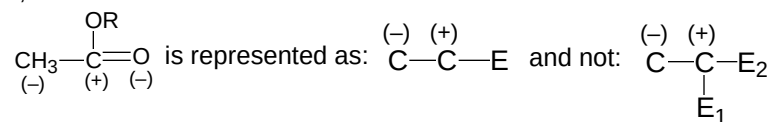
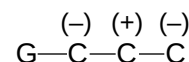
Real functional groups are assigned to a class designation by inspection of the chemistry of that FG, along with that of its conjugate acid and conjugate base

Charge affinities of real functional groups form a subset of the ideal FG classes.

E-Functions

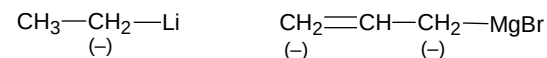
- Note that the issue of oxidation state is not explicitly incorporated. This issue is subordinate to that of defining site reactivity.

For example,

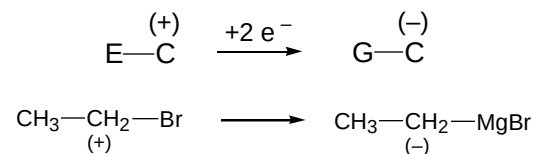
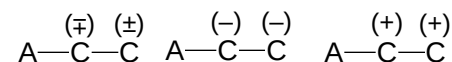
**G-Functions**

- 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.

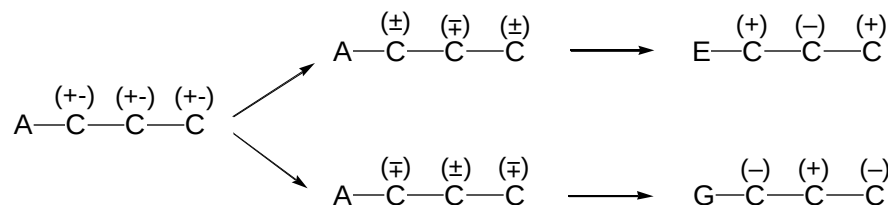


- Note that a 2-electron reduction (or oxidation) will transform an E-Class FG to a G-Class FG.

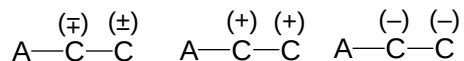
**A-Functions**

- All sites activated equally for electrophilic & nucleophilic reactivity.
- Those ideal FGs which exhibit nonalternate polar site reactivity are included.

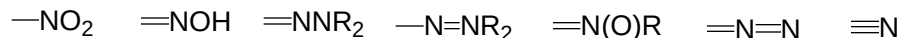
One might visualize a process wherein A-functions are gradually polarized towards either E- or G- behavior in response to changes in inductive and resonance effects.



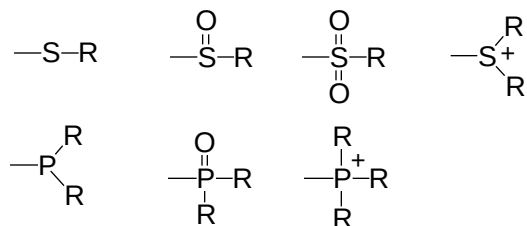
A-functions are some of the most useful FGs in organic synthesis because of the unique reactivity provided.

A-Functions: Real Examples**A-Functions**

■ A-functions are composed of polyatomic arrangements of N & O.



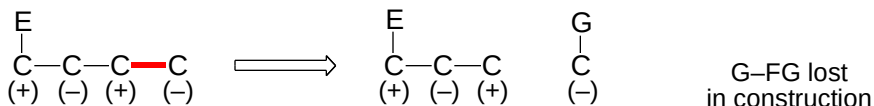
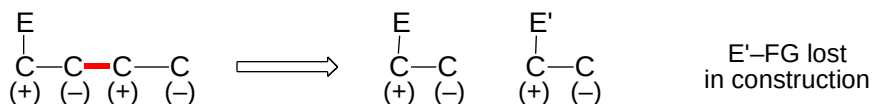
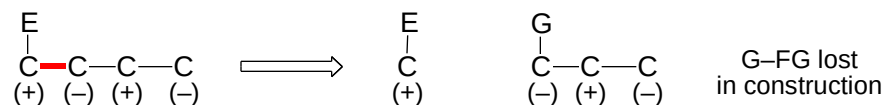
■ A-functions are composed of second-row elements such **S** and **P**.



■ Functional groups derived from many of the transition elements

Synthesis of Targets containing E-Functions

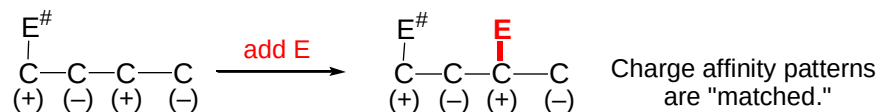
Transforms utilizing target E-function in synthesis plan given highest priority.



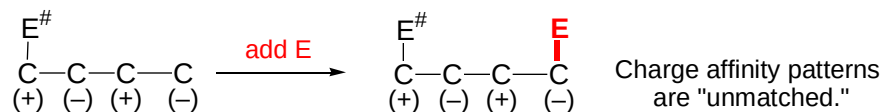
Given the resident E-function, the charge affinity pattern dictates the nature of the polar coupling process and thus functional groups to be employed in synthesis.

Classification of Pairwise Difunctional Relationships

Consider the paired relationships of E-functions. There are two relationships.



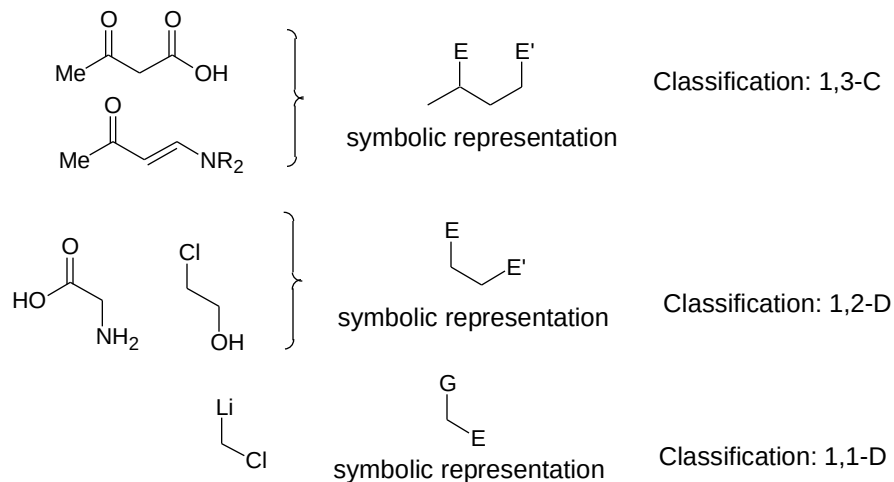
Pairwise relationship is "consonant".



Pairwise relationship is "dissonant".

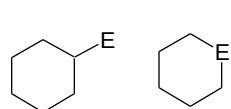
Consonant & dissonant relationships may be established with E-E, E-G, or G-G pairings.

Most target structures are composed of E-functions.

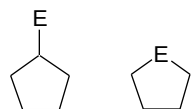
Representative difunctional relationships

Classification of Pairwise Difunctional Relationships

- A single FG residing either in or appended to a cycle may establish a FG relationship with itself.



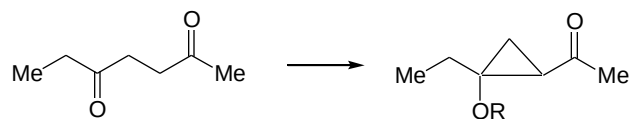
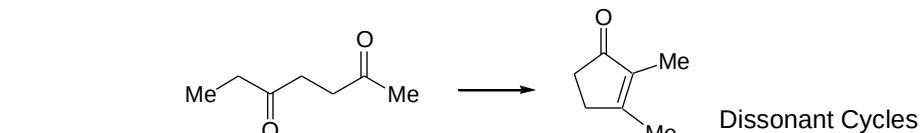
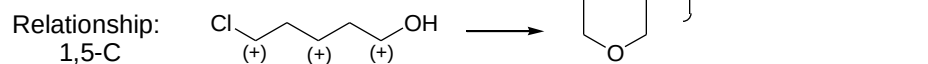
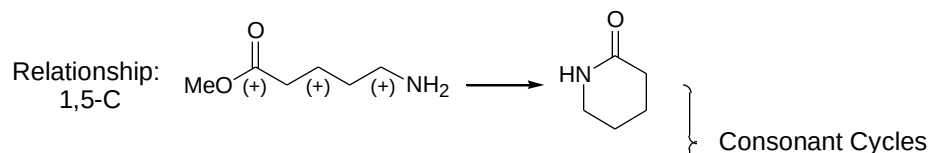
Consonant cycles



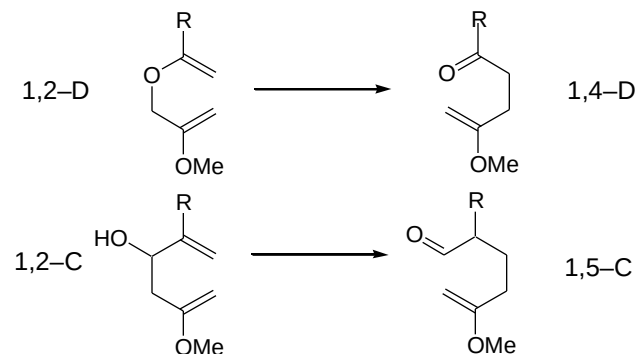
Dissonant cycles

**Consonant & Dissonant Relationships:
Path-Cycle Interconversions**

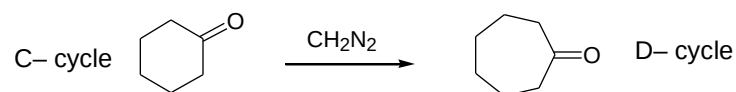
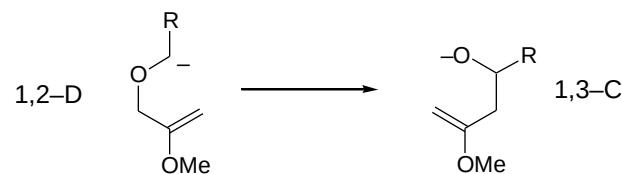
Linear molecules may be transformed into cycles & vice-versa:



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, $C \rightarrow C'$, $D \rightarrow D'$ but $C \rightarrow D$ not possible

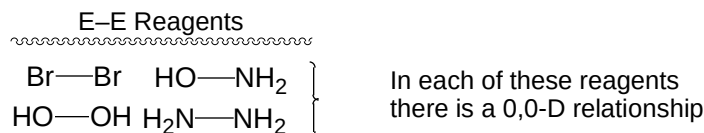
[1,2] Sigmatropic Rearrangements:**[2,3] Sigmatropic Rearrangements:****General Rule For [m,n] Sigmatropic Rearrangements:**

When the sum of $m+n$ is even, the FG relationship is maintained, e.g. $C \rightarrow C'$
 When the sum of integers is odd, the FG relationship is changed, e.g. $C \rightarrow D$

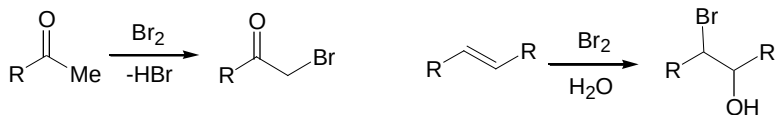
Pairwise Relationships in Inorganic Reagents

- E-functions in their most stable oxidation states (HO^- , NH_3 , Cl^-) are represented as $\text{E}(-)$.

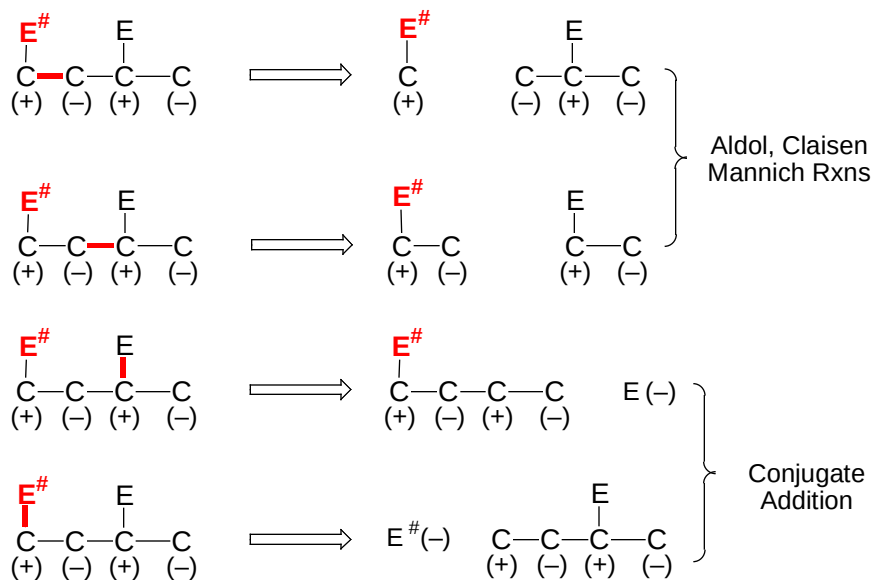
There exist an important family of reagents which have E-FGs directly coupled:



These reagents are used to construct D-Relationships:

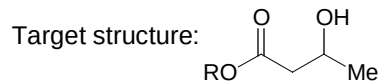


Synthesis of Targets containing Consonant Pairwise Relationships

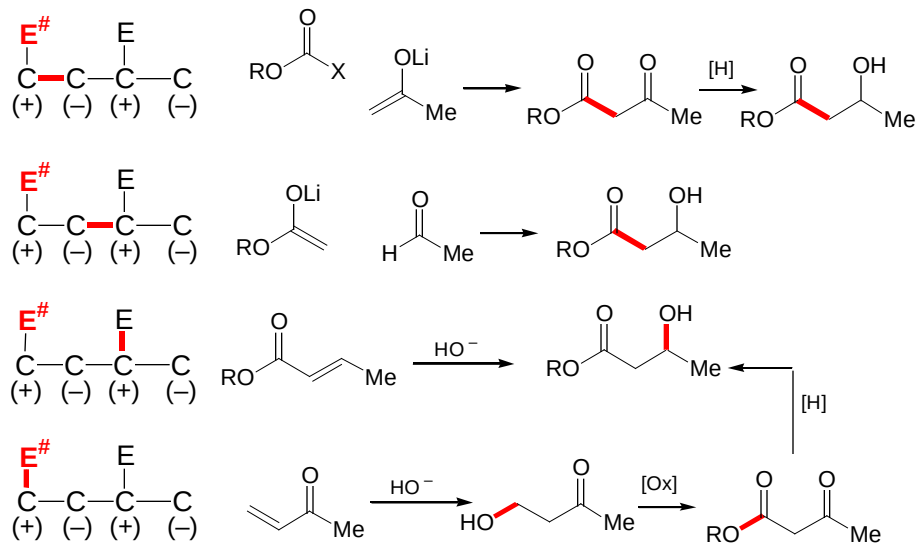


Consonant difunctional relationships can be constructed from just the functions illustrated & polar bond constructions.

A Specific Case



Step I: There are 4 bonds interconnecting E & E'. Hence generate the 4 transforms leading to mono-functional precursors:

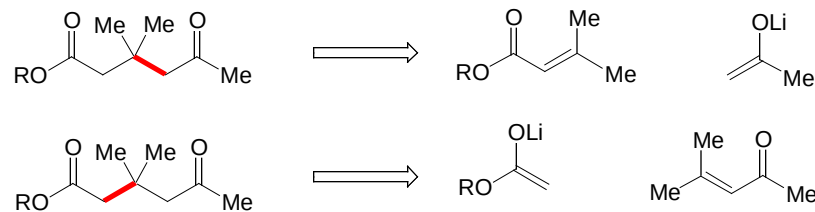


Step II: Evaluate the efficiency of the 4 plausible routes to the target from available precursors.

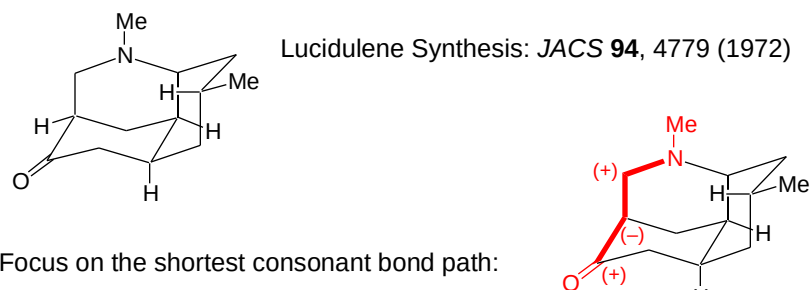
Given the oxidation state in the target, the second synthesis looks the best and the fourth looks the worst.

The Constraint of Quaternary Centers

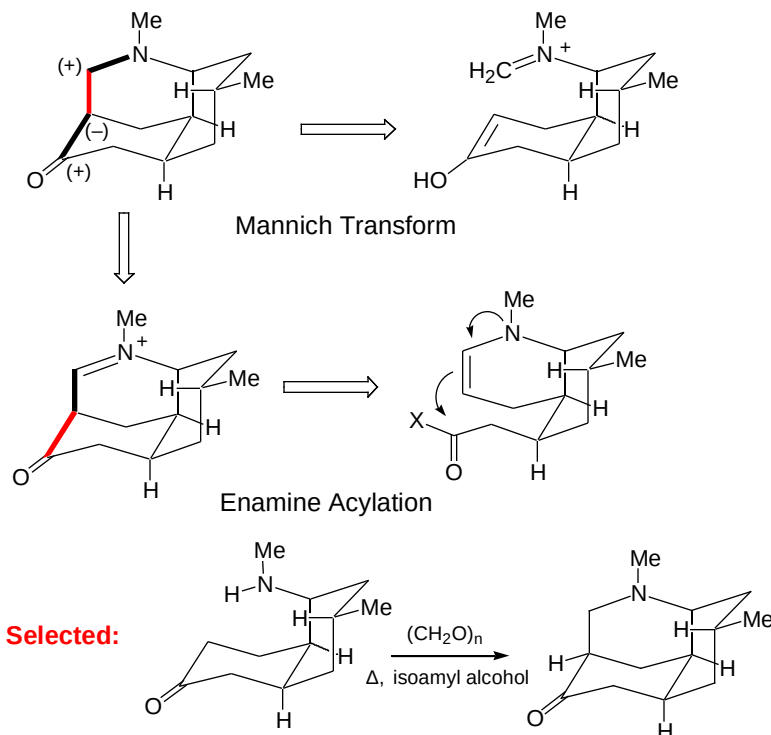
If a quaternary center occurs along the consonant bond path, one is limited to bond constructions on either side of that restriction



Quaternary Centers & Bridgehead Restrictions



The two permitted bond constructions along illustrated bond path flank the bridgehead carbon

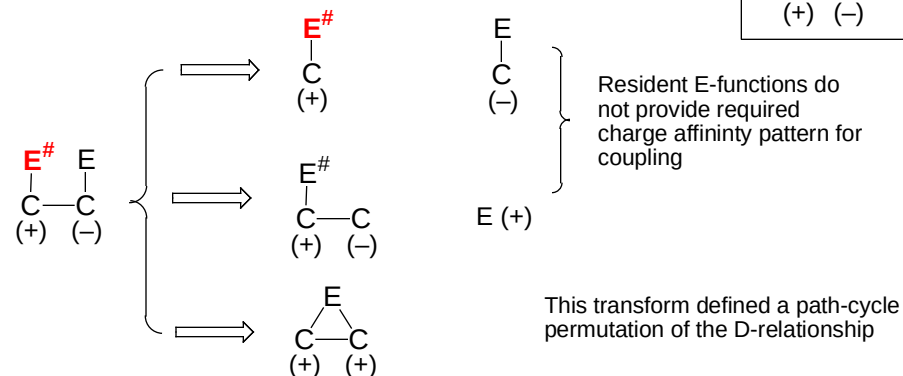


Option Selected:

■ Corollary: π -conjugation cannot be extended through bridgehead or quaternary centers

Synthesis of Dissonant Pairwise Relationships

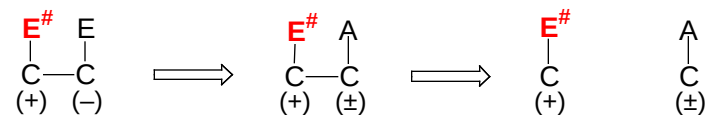
The pairwise relationship is "unmatched"; hence, the illustrated E-functions cannot be used exclusively to construct the bond path. Let's consider the simplest case: a 1,2-D relationship.



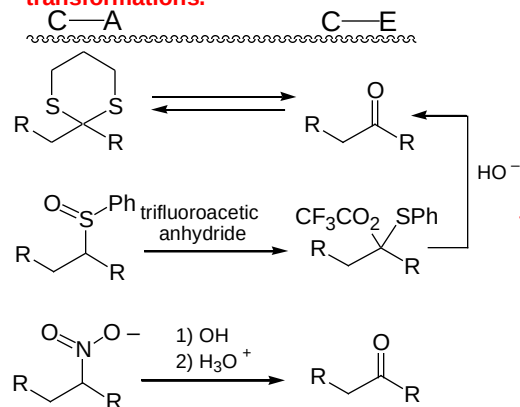
In the illustrated polar disconnections, one of the fragments may exploit the charge affinity pattern of the resident FG while the other may not.

Hence dissonant pairwise relationships may not be constructed via just the functions present in the target.

Dissonant Pairwise Relationships via A-Functions



In implementing this strategy you must know all important **1,1-A $\leftrightarrow$ E FG transformations**.

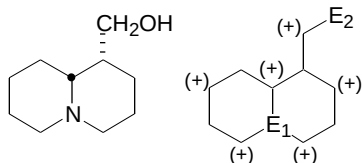


The Pummerer Rearrangement
"The Pummerer reaction of sulfinyl compounds.", De Lucchi, et al. *Org. Reactions* **1991**, 40, 157.

The Nef Reaction

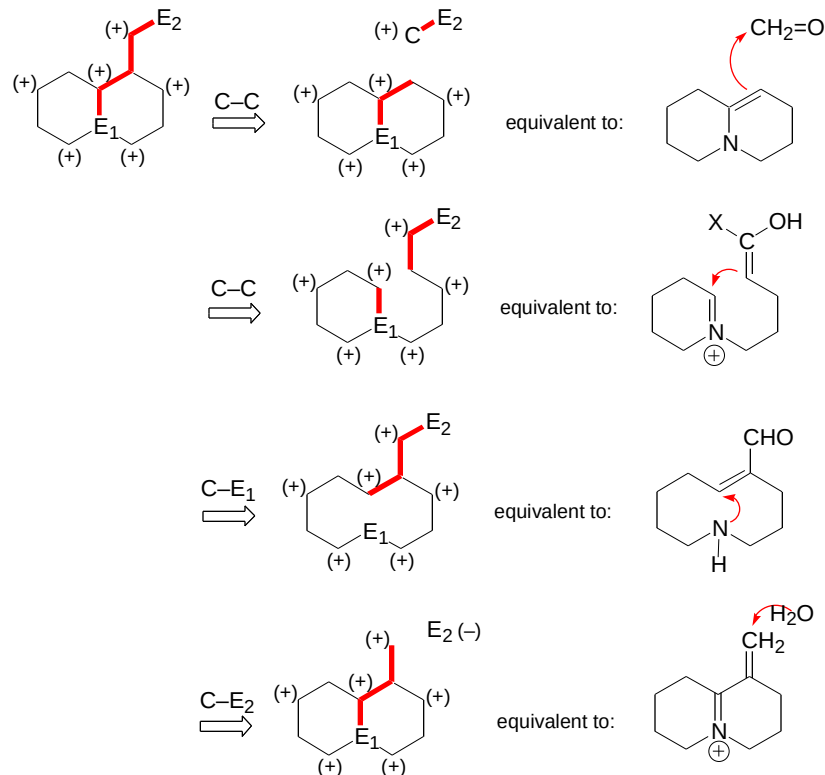
Bond path analysis of simple alkaloids

lupinine



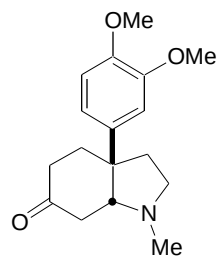
Every complex polyfunctional molecule may be analyzed structurally in terms of its individual consonant or dissonant construction paths or cycles. For example, in the alkaloid lupinine all possible construction paths interconnecting E1 and E2 are consonant. Consonant paths within the polyatomic framework 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



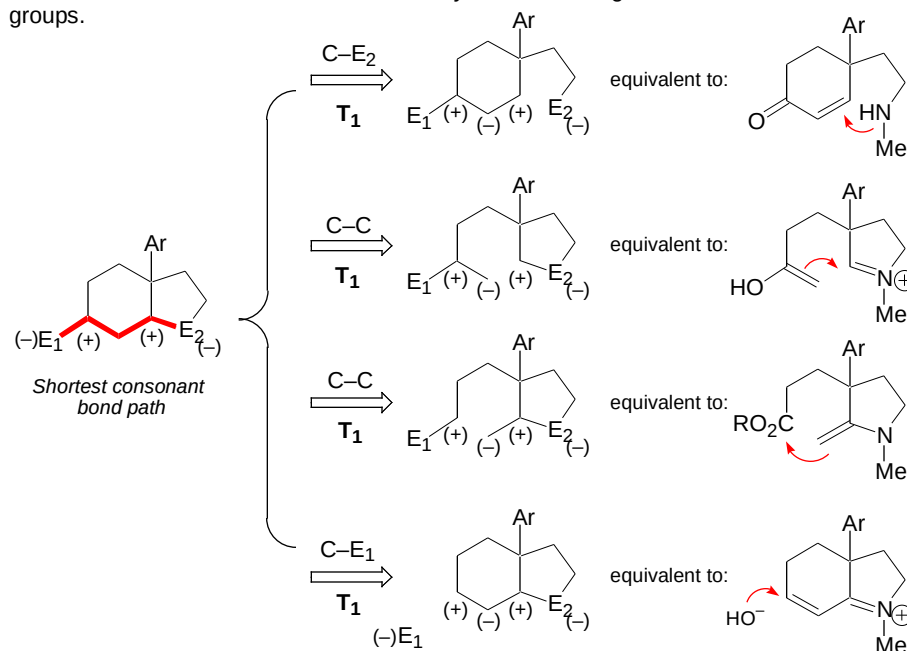
Curphey, T. J.; Kim, H. L. *Tetrahedron Lett.* **1968**, 1441.

Keely, S. L.; Tahk, F. C. *JACS.* **1968**, 90, 5584.

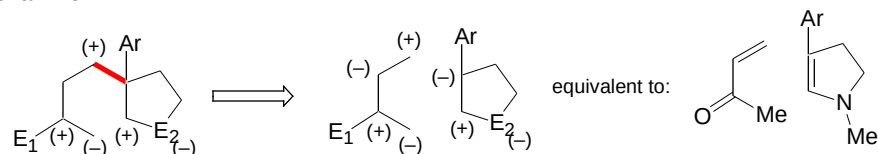
Stevens, R. V.; Wentland, M. P. *JACS* **1968**, 90, 5580

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 **T1**: Again, select the shortest E1-E2 bond path and disconnect next to quaternary center. Dissonant element is localized in 5-membered enamine



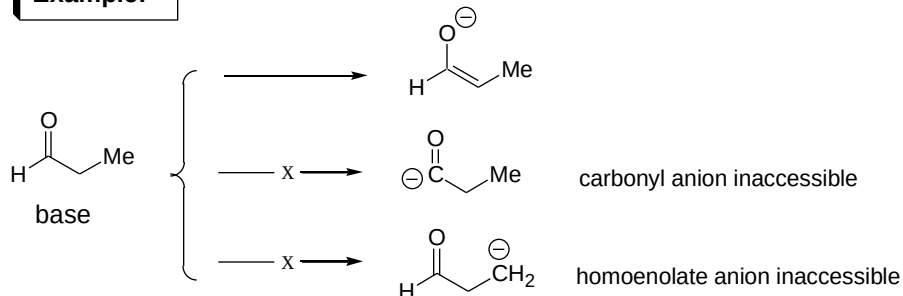
Handouts

Keely, S. L.; Tahk, F. C. *JACS.* **1968**, 90, 5584.

Stevens, R. V.; Wentland, M. P. *JACS* **1968**, 90, 5580

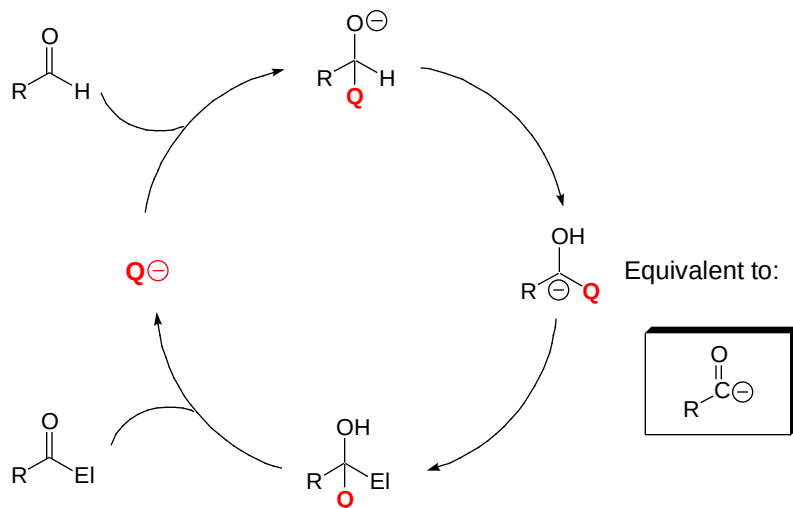
Inaccessible Reactivity Modes in Carbonyl Deprotonation

Example:

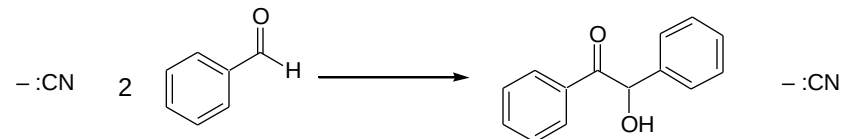


Can one design "catalysts" which will provide access to carbonyl anion equivalents in situ??

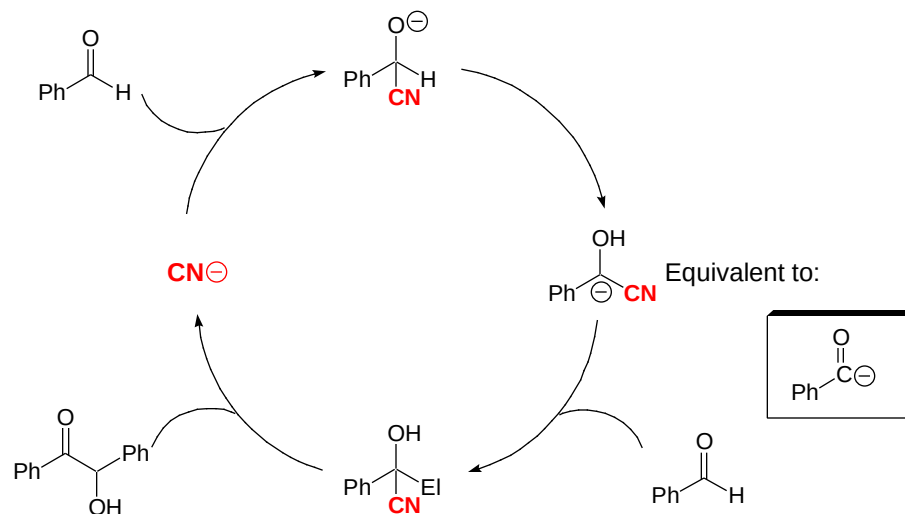
Let Q – be such a catalyst, we will call it an "inversion operator"



The Benzoin Condensation

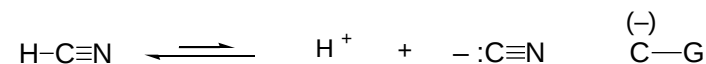


■ Cyanide ion is such a "catalyst"



How do we classify the $\equiv\text{N}$ functional group?

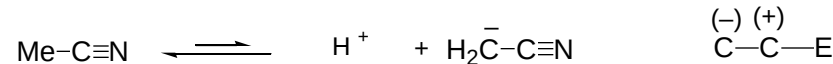
■ Hydrogen cyanide is a fairly good Bronsted acid ($\text{pK}_{\text{a}_{\text{HOH}}} 9.5$)



■ Acetonitrile can be attacked by nucleophiles:



■ Acetonitrile can be deprotonated by strong bases ($\text{pK}_{\text{a}_{\text{DMSO}}} \sim 30$)



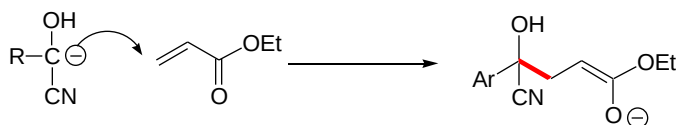
Cyanide-based Carbonyl Anion Equivalents

- Extensions of the Benzoin condensation concept are possible in some instances:



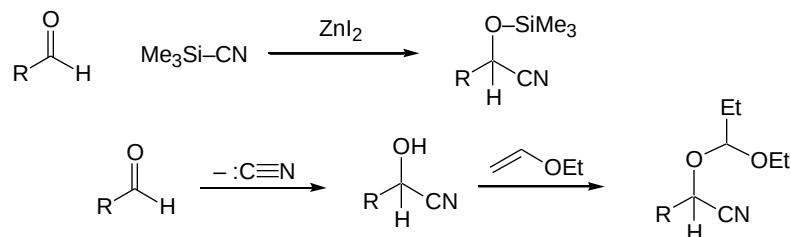
The C-C Bond Construction

Stetter, *Org. Reactions* **1991**, 40, 407.

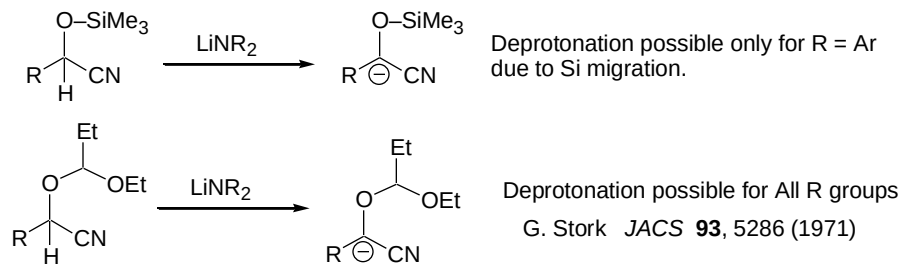


- The in situ use of cyanide ion as an inversion operator is limited. Greater generality may be achieved by multistep alternatives:

Aldehyde Derivatization Step

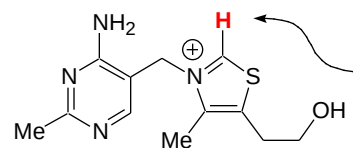


Substrate Deprotonation Step



Thiazolium Salts: Nature's Inversion Operators

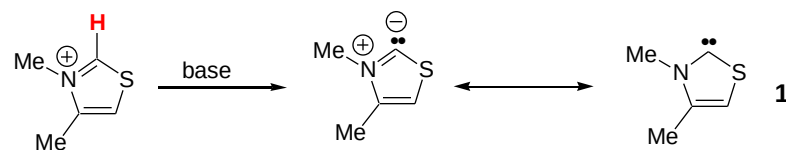
Reactions equivalent to the benzoin are catalyzed by biological co-factors to make (and break) dissonant difunctional heteroatom-heteroatom relationships



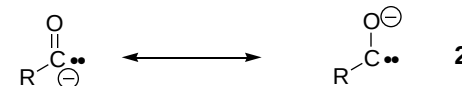
The thiamine cofactor

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.

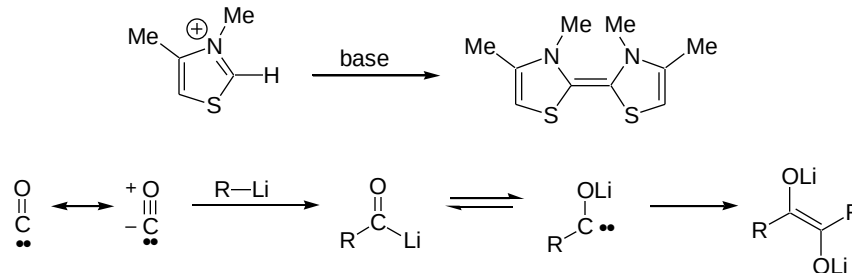
F. G. Bordwell *JACS* **113**, 985, (1991)



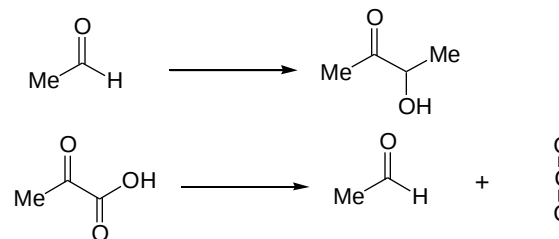
Carbonyl anions might be similarly stabilized



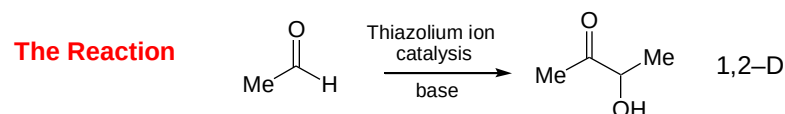
In the absence of electrophiles **1** & **2** dimerize as would be expected for carbene reactivity.



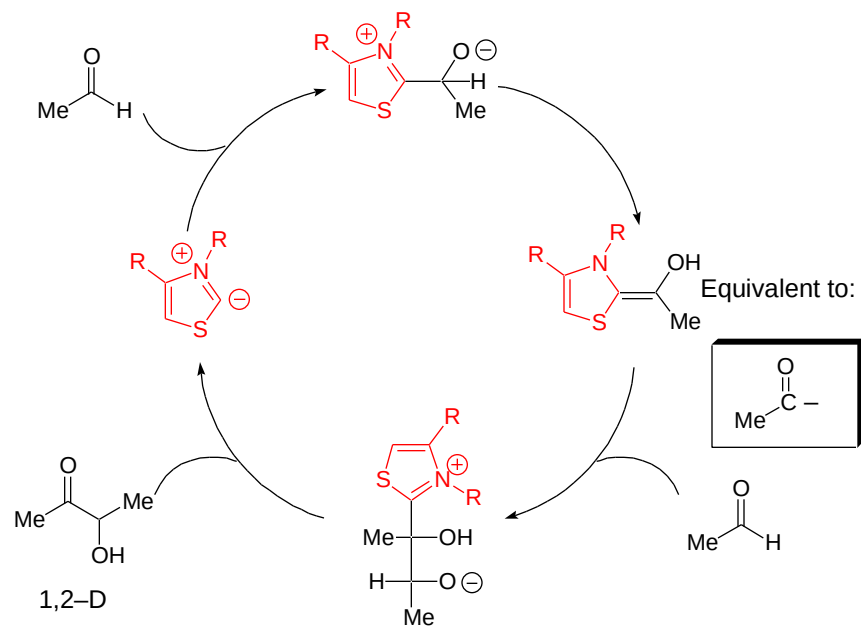
Reactions catalyzed by thiamine



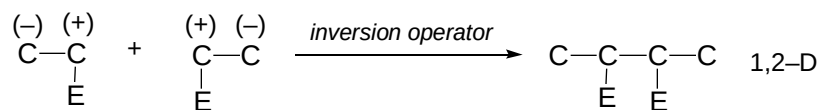
Aldehyde dimerization by Thiazolium Salts



The Catalytic Cycle

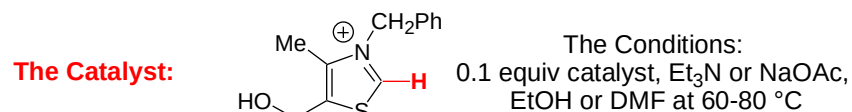
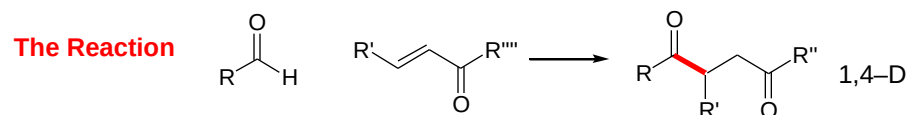


■ Hence dissonant relationships may be made from E-functions if "inversion operator" is employed

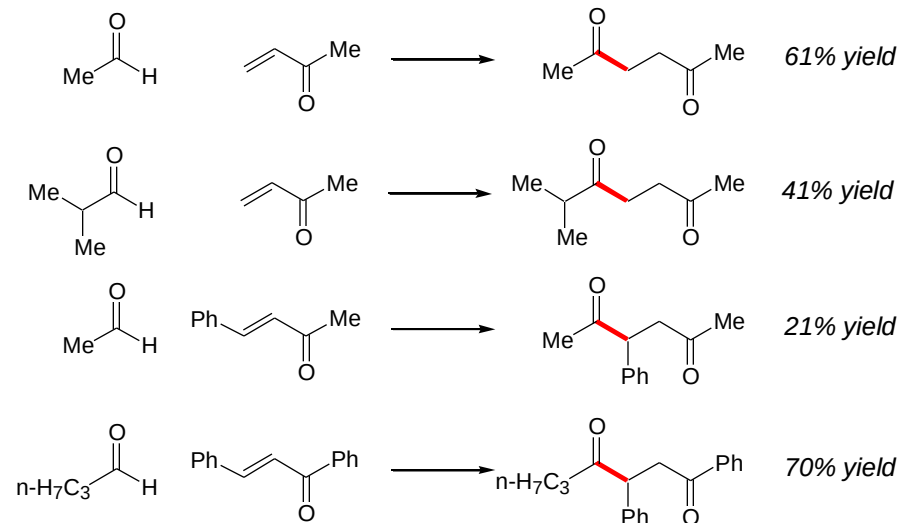


■ The is a fundamental strategy for handling the formation and cleavage of D-relationships in nature.

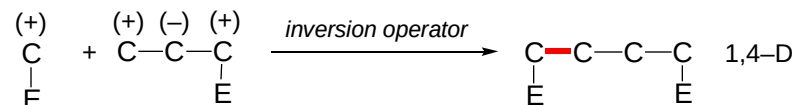
Catalyzed Michael Reactions by Thiazolium Salts



Examples: "The catalyzed nucleophilic addition of aldehydes to electrophilic double bonds.", Stetter, H.; Kuhlmann, H. *Org. Reactions* **1991**, 40, 407.



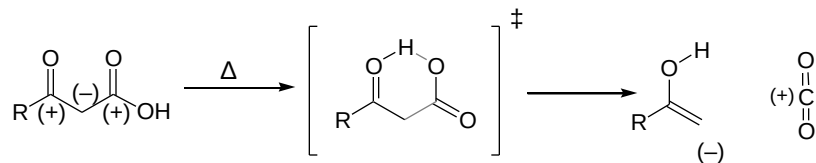
■ 1,4-D relationships may also be made from E-functions if "inversion operator" is employed.



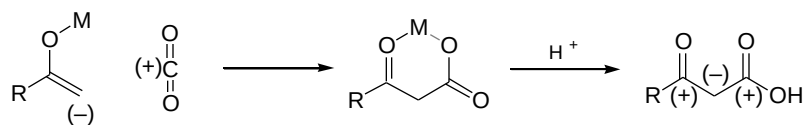
■ There is no analogue to this reaction in nature.

Decarboxylation Catalyzed by Thiazolium Salts

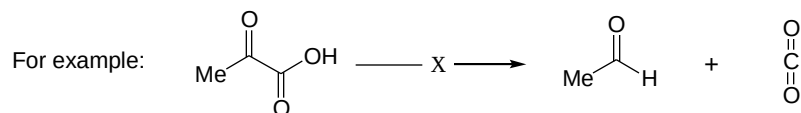
- Background: Decarboxylation from consonant difunctional relationships is facile:



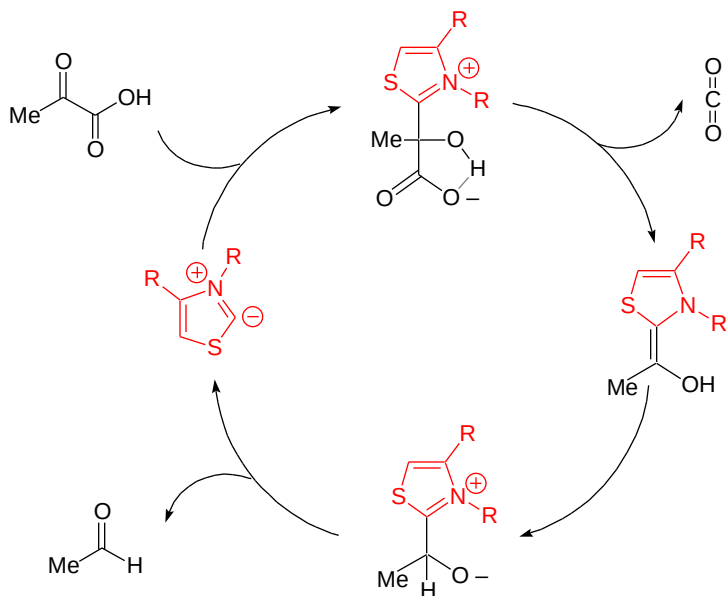
- The reverse process can be achieved under basic conditions:



- Such consonant relationships may be readily made (and broken) via the resident functional groups. The analog reactions for dissonant relationships not possible.

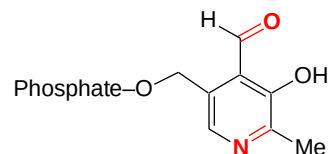


- Nature uses inversion operators to break such 1,2-D relationships

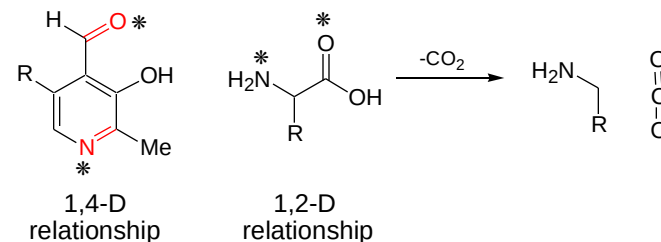
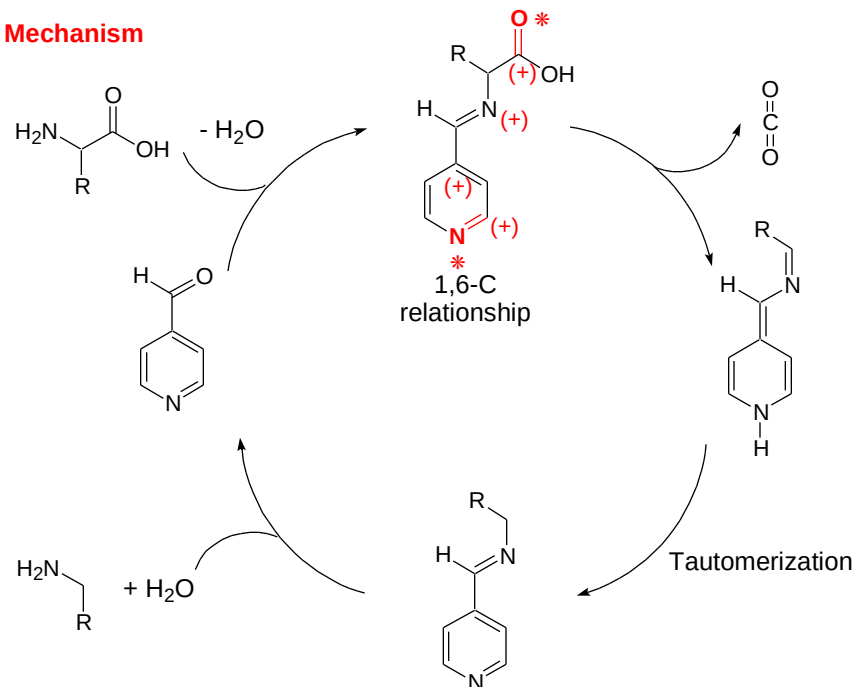
**Design Attributes of Inversion Operators**

Inversion operators are constructed from A-functions or molecules containing D-relationships.

The pyridoxal Co-factor (Vitamin B₆)



The critical difunctional relationship 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, Hoefflich, Schriver in *Reactive Intermediates Vol 3*, Wiley, 1985, Chapter 5, p 189.

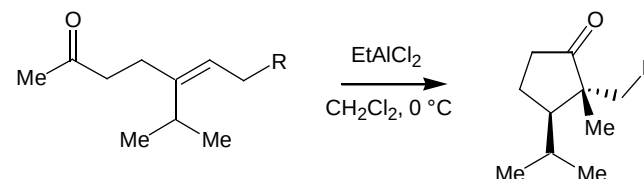
Saunders, M. and H. A. Jimenez-Vazquez (1991). "Recent studies of carbocations." *Chem. Rev.* 91: 375.

Stang, P. J. (1978). "Vinyl Triflate Chemistry: Unsaturated Cations and Carbenes." *Acc. Chem. Res.* 11: 107.

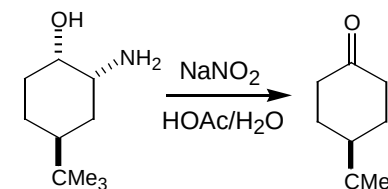
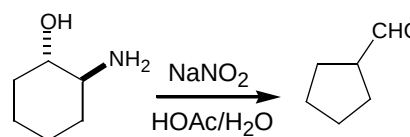
Olah, G. A. and G. Rasul (1997). "Chemistry in superacids .26. From Kekule's tetravalent methane to five-, six- and seven-coordinate protonated methanes." *Acc. Chem. Res.* 30(6): 245-250.

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.

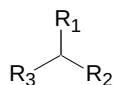


Carey & Sundberg-A, p 337: Provide mechanisms for the following reactions.

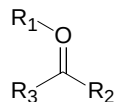
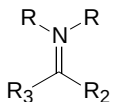


Carbocation Subclasses

Carbon-substituted

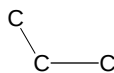
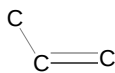
R-R₃ = alkyl or aryl

Heteroatom-stabilized

R-R₃ = alkyl or arylR-R₃ = alkyl or aryl

The following discussion will focus on carbocations unsubstituted with heteroatoms

Classical vs nonclassical carbonium ions

open
trivalenthyperconjugation
no bridgingunsymmetrical
bridgingsymmetrical
bridging

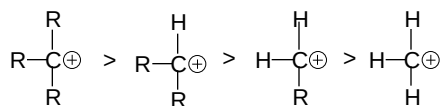
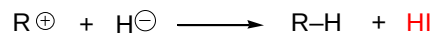
increasing nonclassical character →

classical

nonclassical

Stability: Stabilization via alkyl substituents (hyperconjugation)

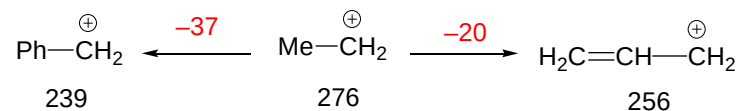
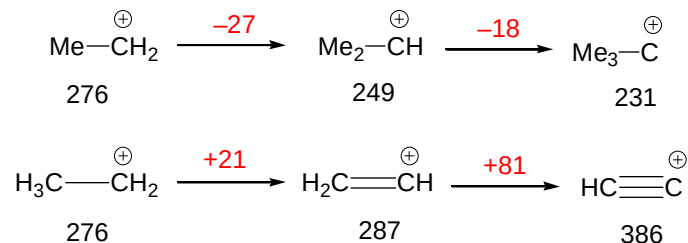
Order of carbocation stability: 3° > 2° > 1°

Due to increasing number of substituents
capable of hyperconjugationThe relative stabilities of various carbocations
can be measured in the gas phase by their
affinity for hydride ion.Hydride Affinity = $-\Delta G^\circ$ ΔHI increases → C(+) stability decreasesNote: As s-character increases, cation stability
decreases due to more electronegative carbon.J. Beauchamp, *J. Am. Chem. Soc.* **1984**, 106, 3917.

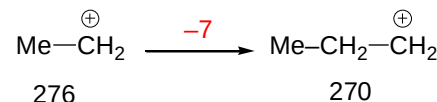
	Hydride ion affinities
CH_3^+	314
CH_3CH_2^+	276
$(\text{CH}_3)_2\text{CH}^+$	249
$(\text{CH}_3)_3\text{C}^+$	231
$\text{H}_2\text{C}=\text{CH}^+$	287
$\text{H}-\text{C}\equiv\text{C}^+$	386
PhCH_2^+	239

Carey & Sundberg-A, pp 276-

Hydride ion affinities (HI)



The effect of beta substituents: Rationalize



Hydride ion affinities versus Rates of Solvolysis

	$\text{PhCH}_2\text{-Br}$	$\text{CH}=\text{CH}-\text{CH}_2\text{-Br}$	$\text{Me}_2\text{CH-Br}$
rel rate	100	52	0.7
HI	239	256	249
ΔHI	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

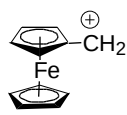
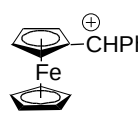
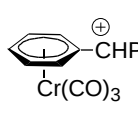
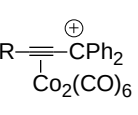
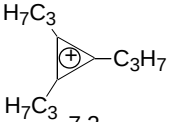
Definition: $R^+ + H_2O \rightleftharpoons ROH + H^+$

$$K_{R^+} = \frac{a_{ROH}}{a_{R^+}} \frac{a_{H^+}}{a_{H_2O}} \quad a = \text{activity}$$

$$pK_{R^+} = -\log K_{R^+}$$

Carey & Sundberg, A, p 277

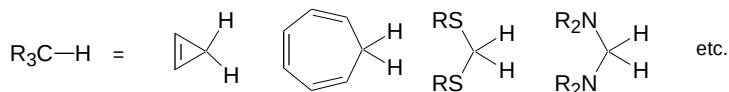
Table: pK_{R^+} values of some selected carbenium salts

$(4\text{-MeO-C}_6\text{H}_4)_3\text{C}^+$ 0.82	Ph_3C^+ - 6.63	$(3\text{-Cl-C}_6\text{H}_4)_3\text{C}^+$ - 11.0	Ph_2CH^+ - 13.3
 0.40	 0.75	 -10.4	 -7.4
 7.2	 4.77		

Carey & Sundberg, A, pp 276-

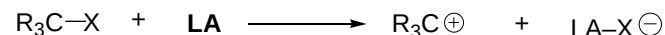
Carbocation Generation

Hydride abstraction from neutral precursors



Lewis-Acid: $\text{Ph}_3\text{C}^+\text{BF}_4^-$, BF_3 , PCl_5

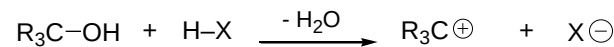
Removal of an energy-poor anion from a neutral precursor via Lewis Acids



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

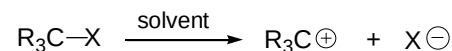
Acidic dehydration of secondary and tertiary alcohols



R: Aryl + other charge stabilizing substituents

X: SO_4^{2-} , ClO_4^- , FSO_3^- , CF_3SO_3^-

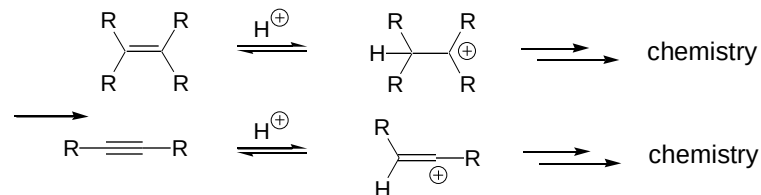
From neutral precursors via heterolytic dissociation (solvolysis) - First step in S_N1 or $E1$ reactions



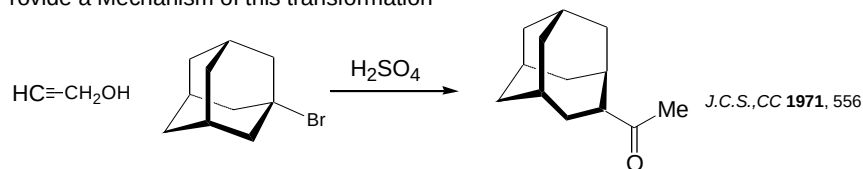
Ability of X to function as a leaving group:

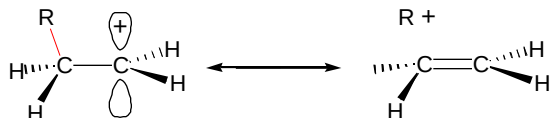
$-\text{N}_2^+ > -\text{OSO}_2\text{R}' > -\text{OPO}(\text{OR}')_2 > -\text{I} \geq -\text{Br} > \text{Cl} > \text{OH}_2^+ \dots$

Addition of electrophiles to π -systems

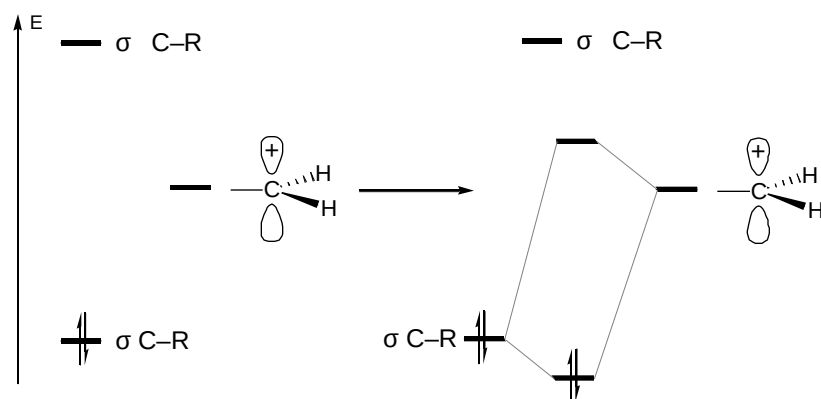


Provide a Mechanism of this transformation

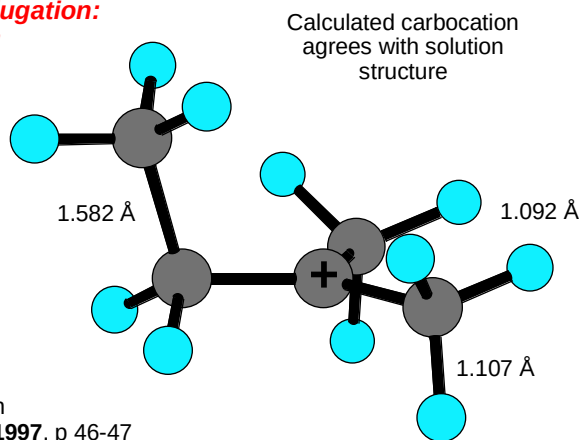
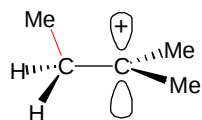


Carbocation Stabilization Through Hyperconjugation**FMO Description**

Take linear combination of σ C-R (filled) and C p_z -orbital (empty):



Syn-planar orientation between interacting orbitals

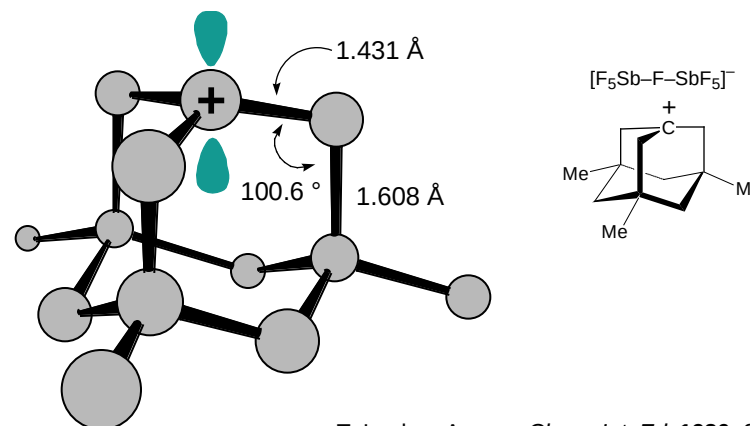
**C-H versus C-C Hyperconjugation:
The *t*-Pentyl Cation**

Calculated carbocation agrees with solution structure

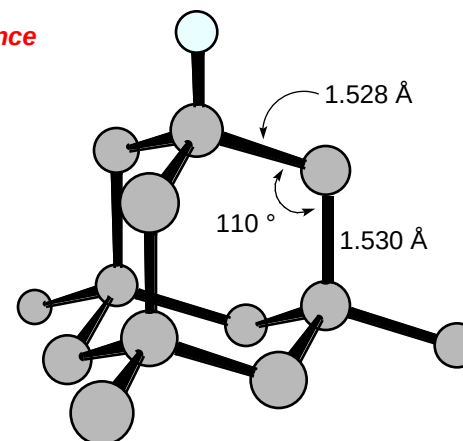
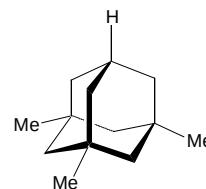
R. P von Schleyer in
Stable Carbocation Chemistry, 1997, p 46-47

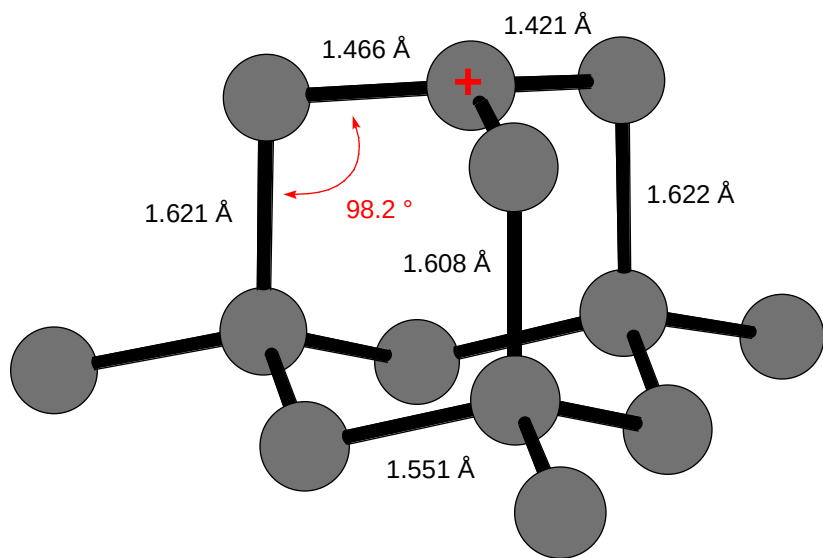
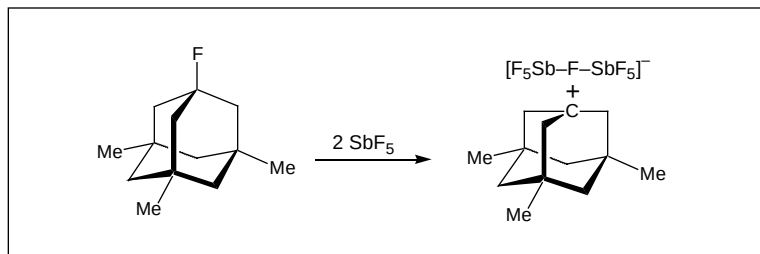
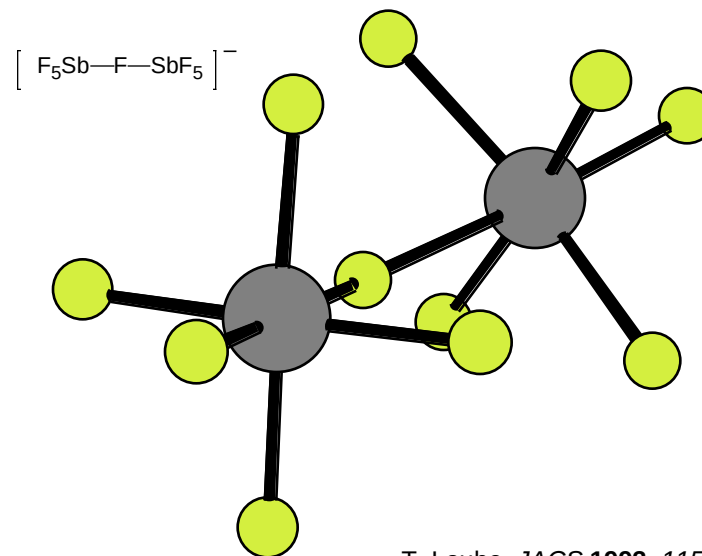
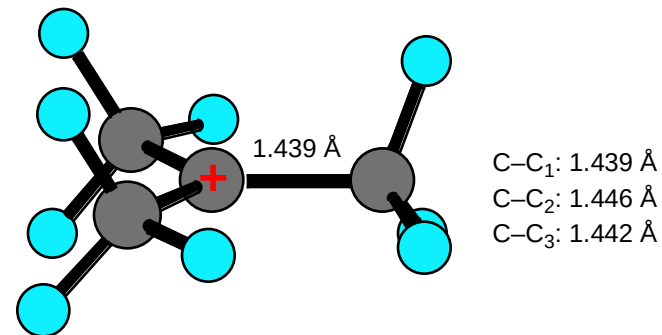
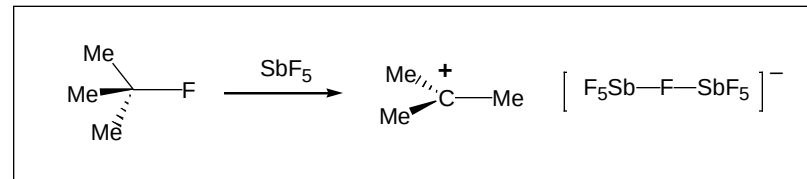
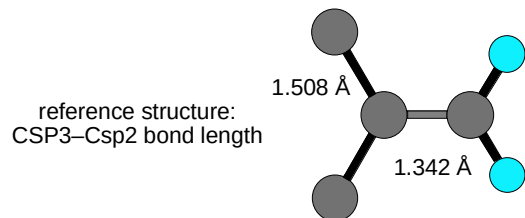
Physical Evidence for Hyperconjugation: The Adamantyl Cation

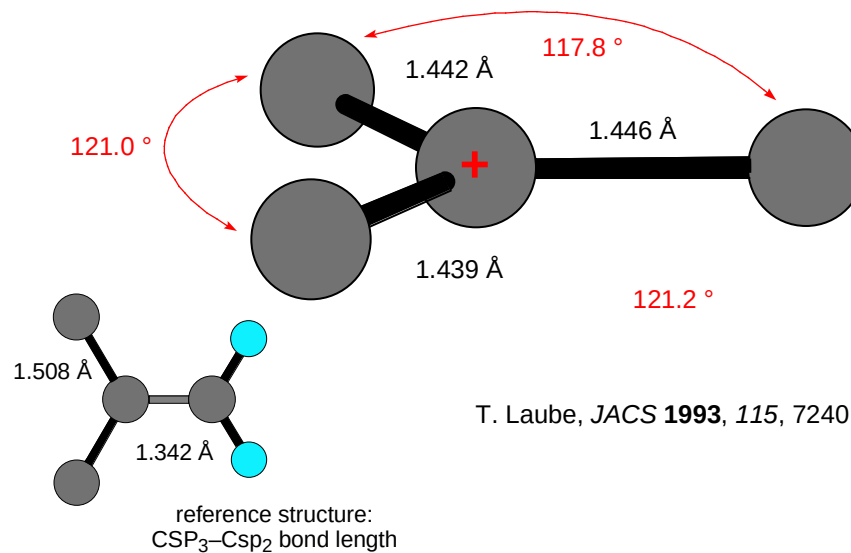
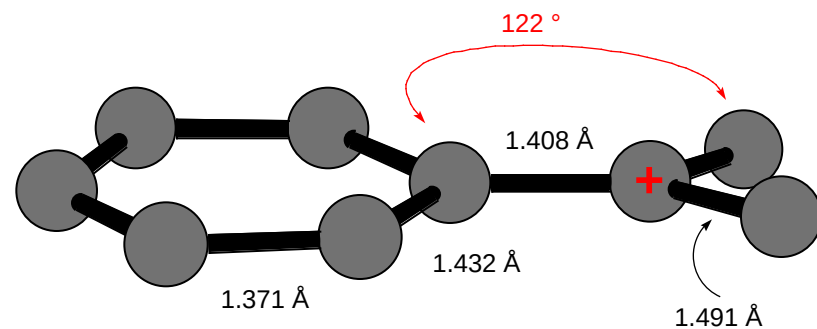
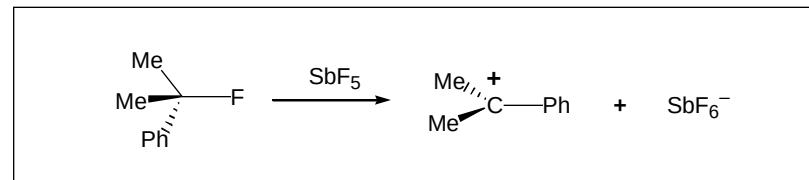
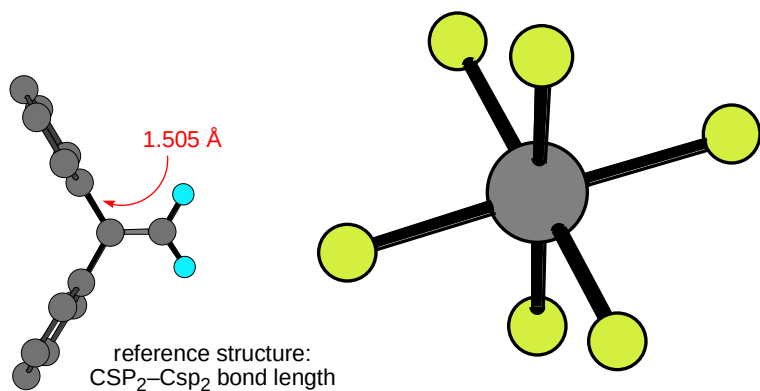
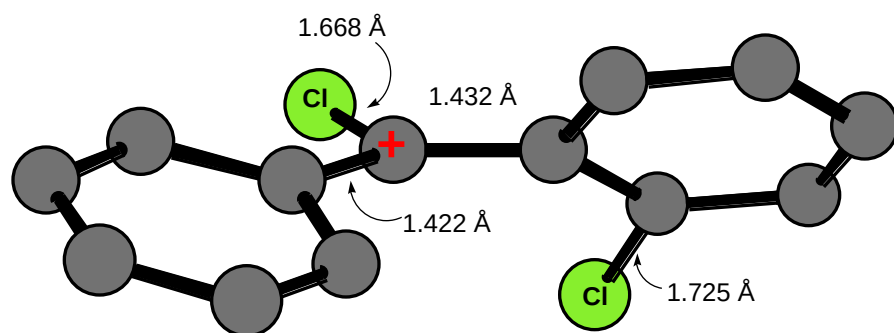
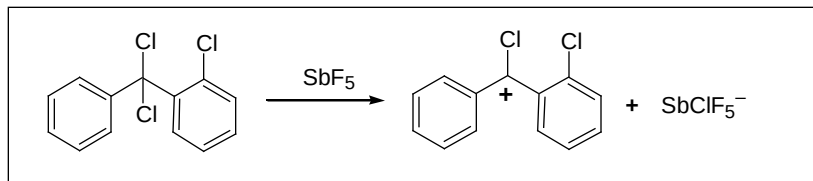
Bonds participating in the hyperconjugative interaction, e.g C-R, will be lengthened while the C(+)-C bond will be shortened.

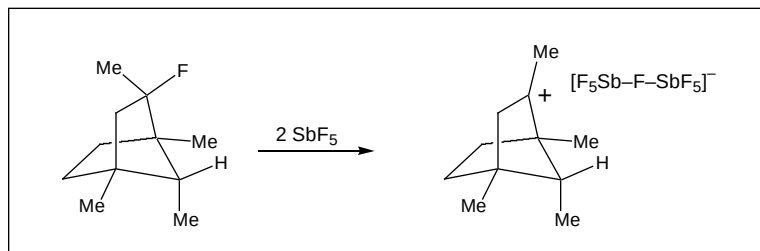
First X-ray Structure of an Aliphatic Carbocation

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

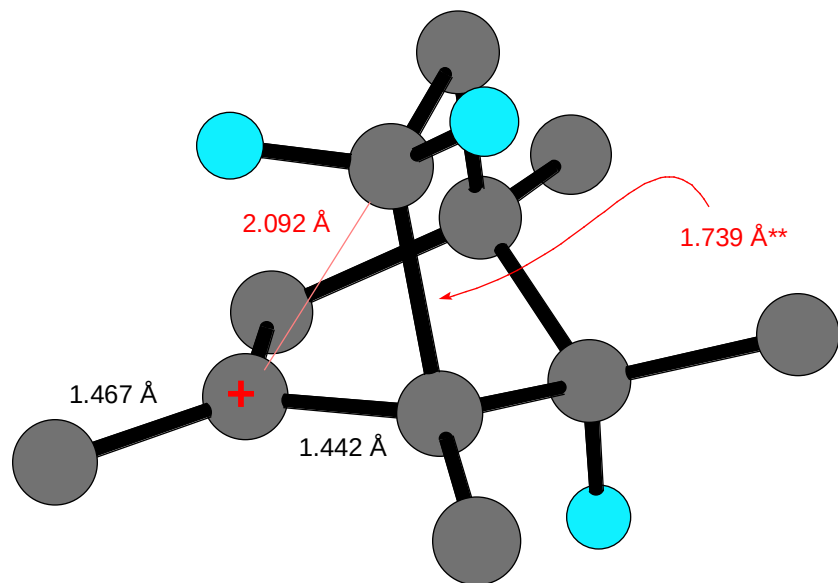
**The Adamantane Reference
(MM-2)**

T. Laube, *Angew. Chem. Int. Ed.* **1986**, 25, 349T. Laube, *JACS* **1993**, 115, 7240

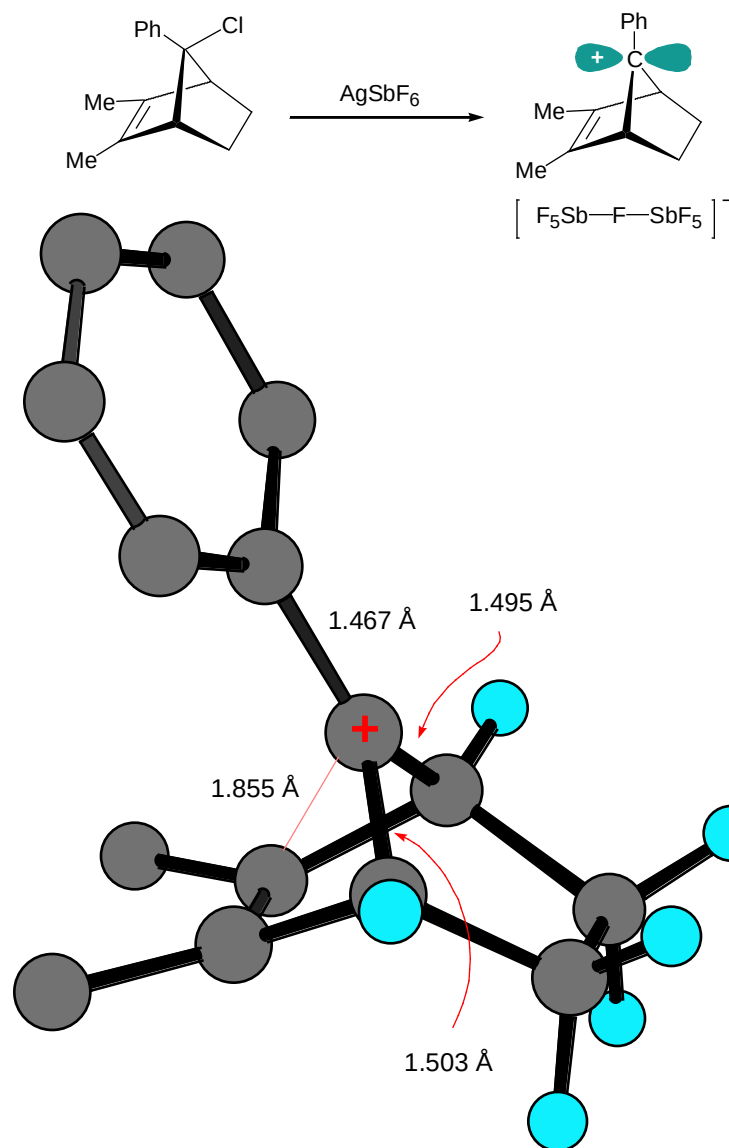
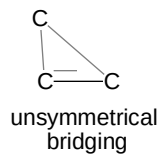
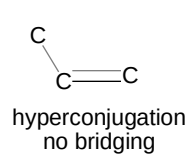
T. Laube, JACS **1993**, 115, 7240



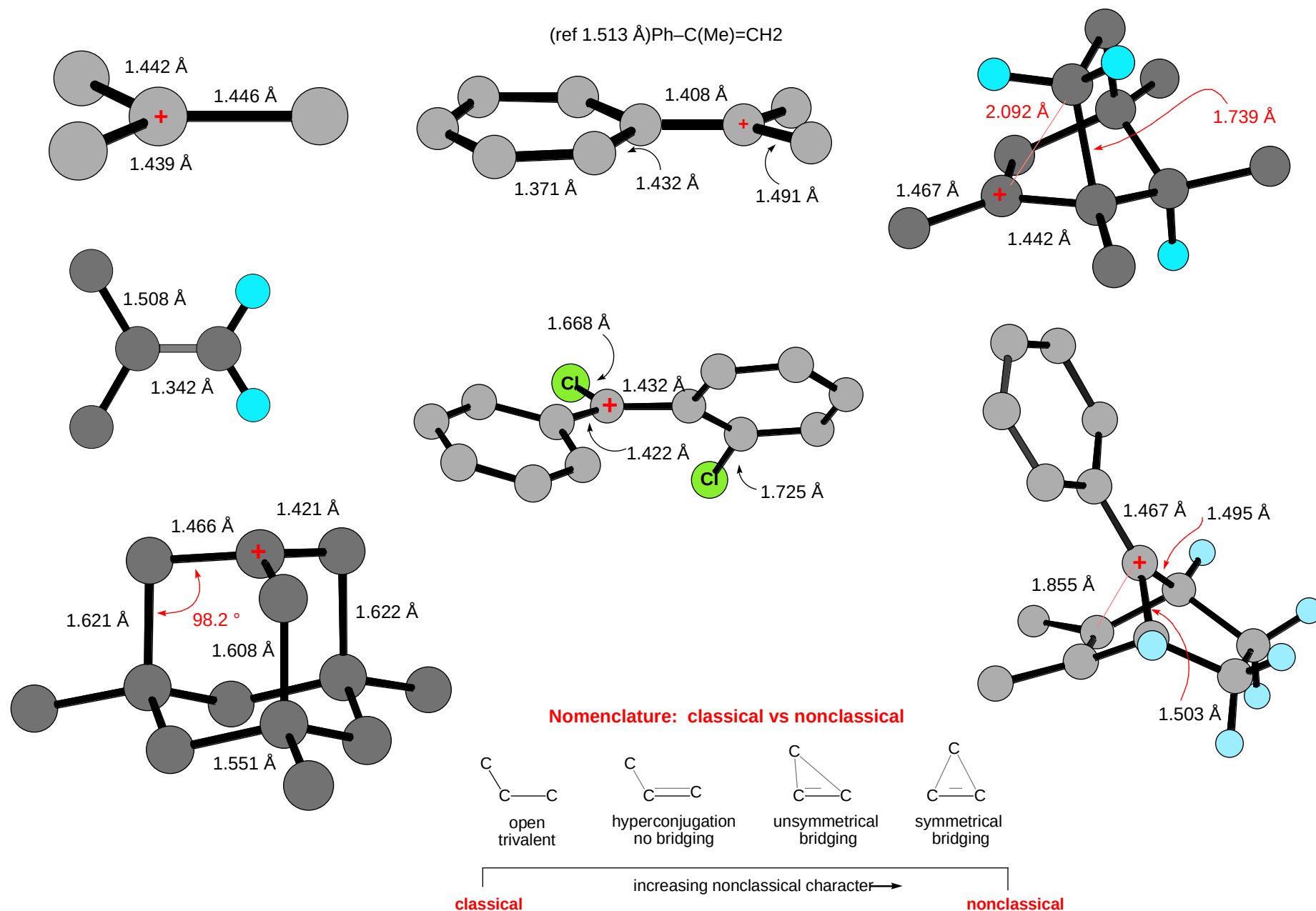
T. Laube, *Angew. Chem. Int. Ed.* **1987**, 26, 560



**One of the longest documented C-C bond lengths.

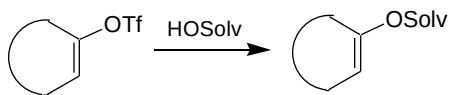


T. Laube, *JACS* **1989**, 111, 9224

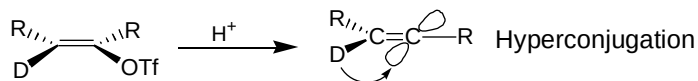


Vinyl & Phenyl Cations: Highly Unstable

Evidence suggests that vinyl cations are linear.



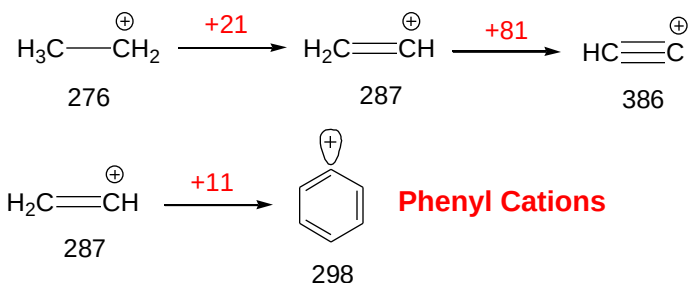
As ring size decreases, the rate of hydrolysis also diminishes. Implying that the formation of the linear vinyl cation is disfavored due to increasing ring strain.



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.

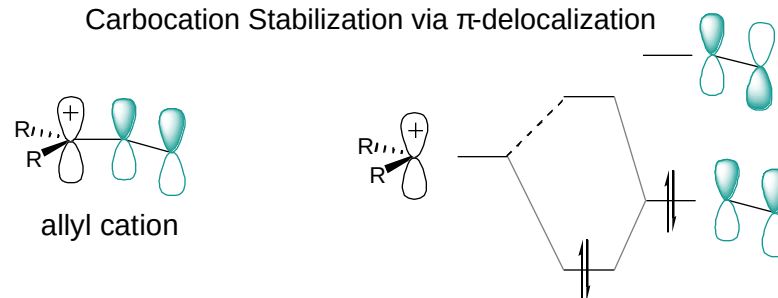
Hydride ion affinities (HI)



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.

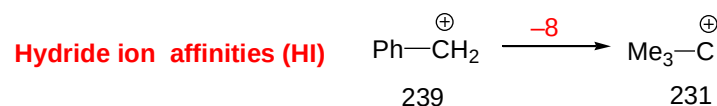
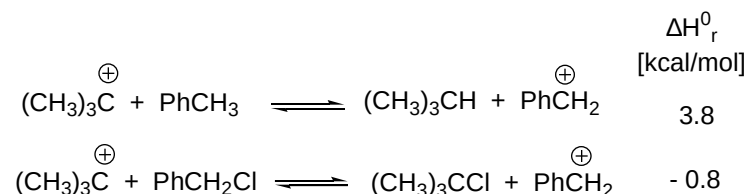
Allyl & Benzyl Carbocations

Carbocation Stabilization via π -delocalization



Stabilization by Phenyl-groups

The Benzyl cation is as stable as a t-Butylcation. This is shown in the subsequent isodesmic equations:



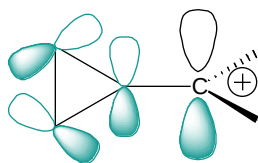
Hydride ion affinities versus Rates of Solvolysis

	PhCH ₂ -Br	Me ₂ CH-Br	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

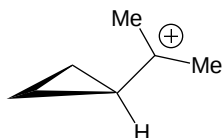
A. Streitwieser, *Solvolytic Displacement Reactions*, p75

Carbocation Stabilization via Cyclopropylgroups



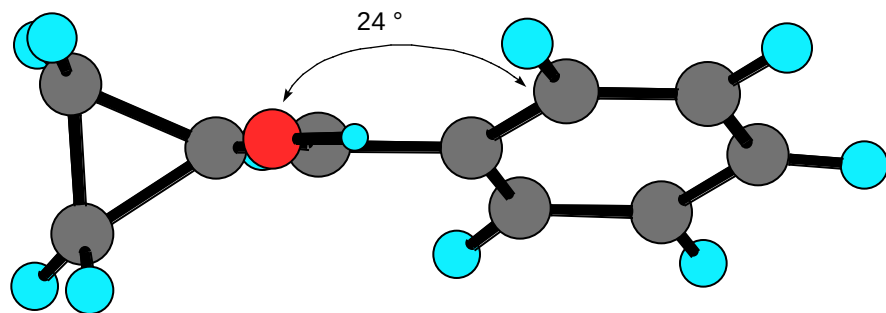
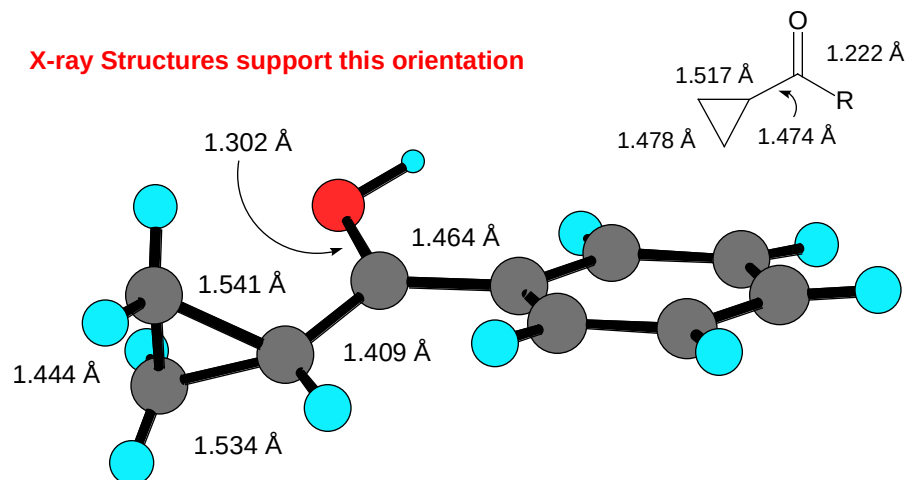
See Lecture 5, slide 5-05 for discussion of Walsh orbitals

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



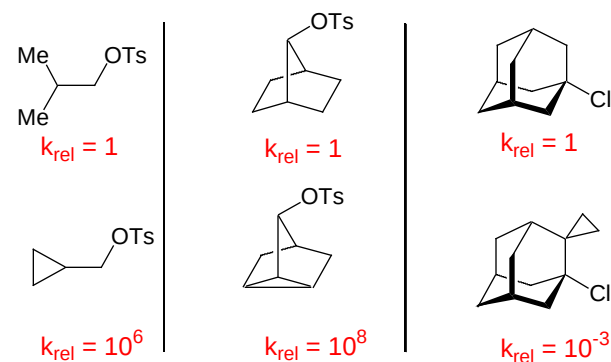
NMR in super acids
 $\delta(\text{CH}_3) = 2.6$ and 3.2 ppm

X-ray Structures support this orientation

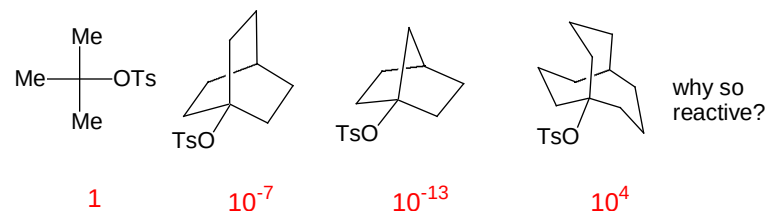


R. F. Childs, JACS **1986**, 108, 1692

Solvolysis rates represent the extent of that cyclopropyl orbital overlap contributing to the stabilization of the carbenium ion which is involved as a reactive intermediate:



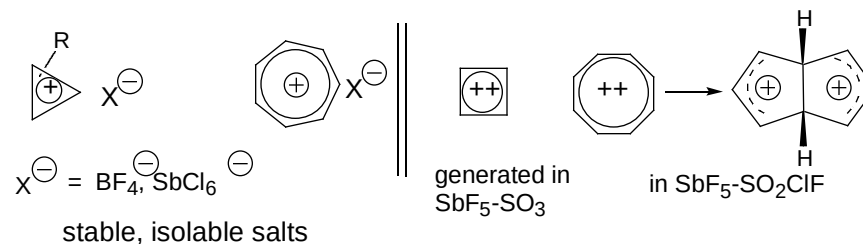
Bridgehead Carbocations



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.

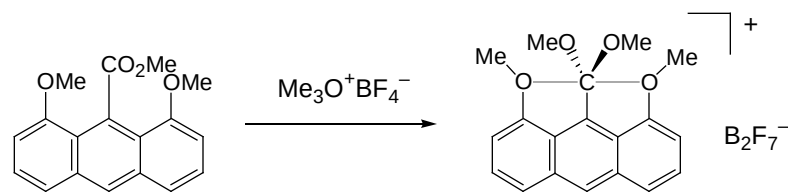
Carbocation Stabilization - Aromaticity

Some Hückel aromatic cations ($4n+2$) π -electrons are isolable as salts with non-nucleophilic anions.

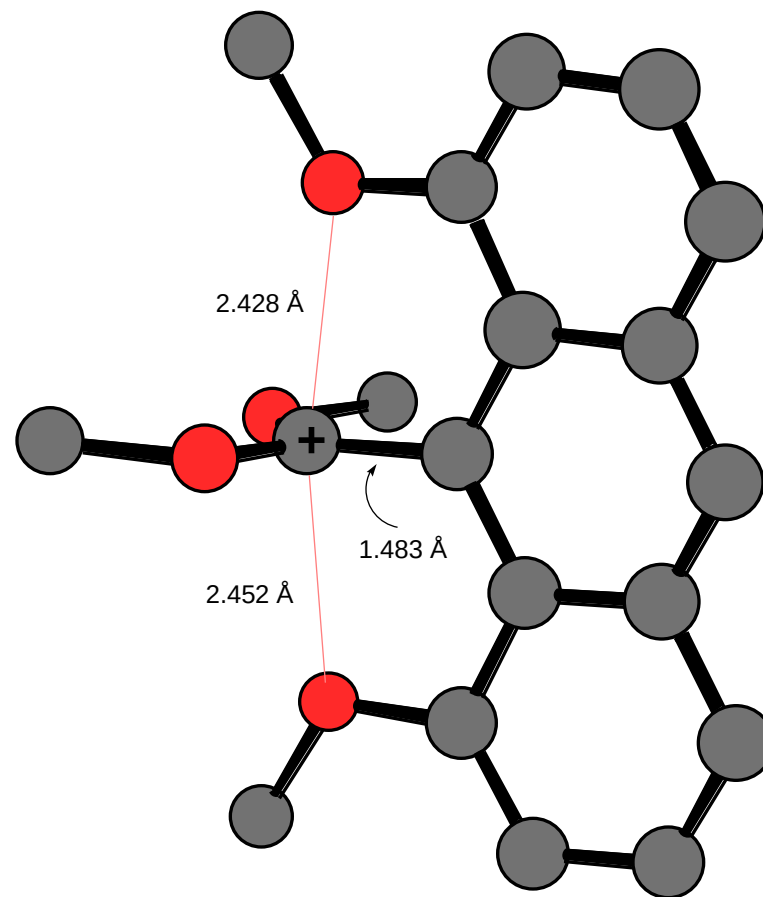
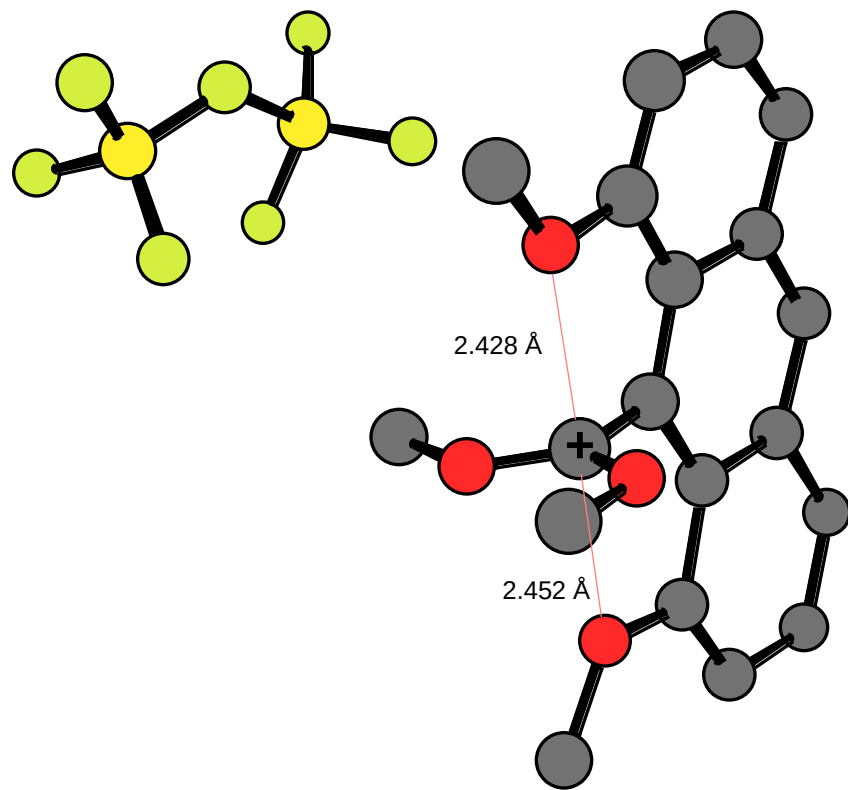


"The Synthesis and Isolation of Stable Hypervalent Carbon Compound (10-C-5) Bearing a 1,8-Dimethoxyanthracene Ligand"

Akiba, et al. *JACS* **1999**, *121*, 10644-10645



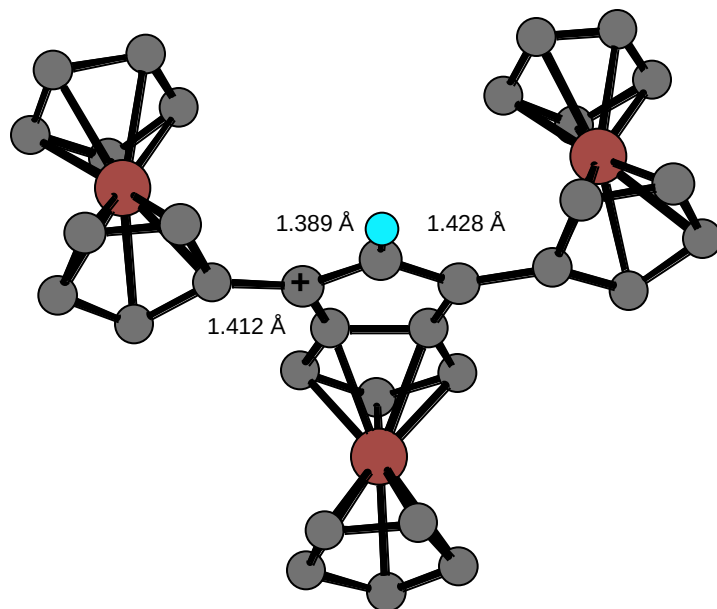
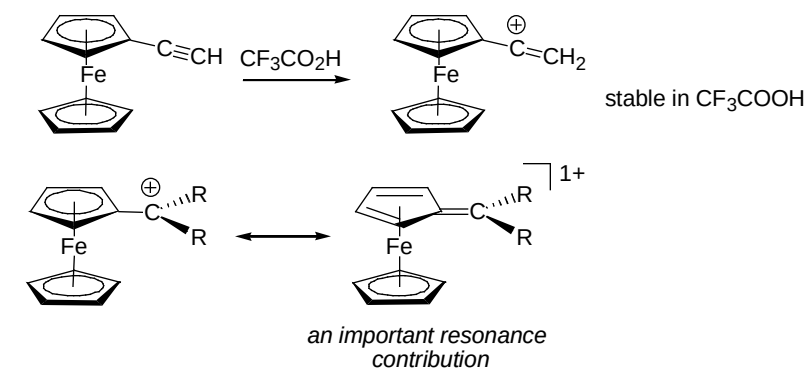
"The relevant C–O distances are longer than a covalent C–O bond (1.43 Å) but shorter than the sum of the van der Waals radii (3.25 Å)."



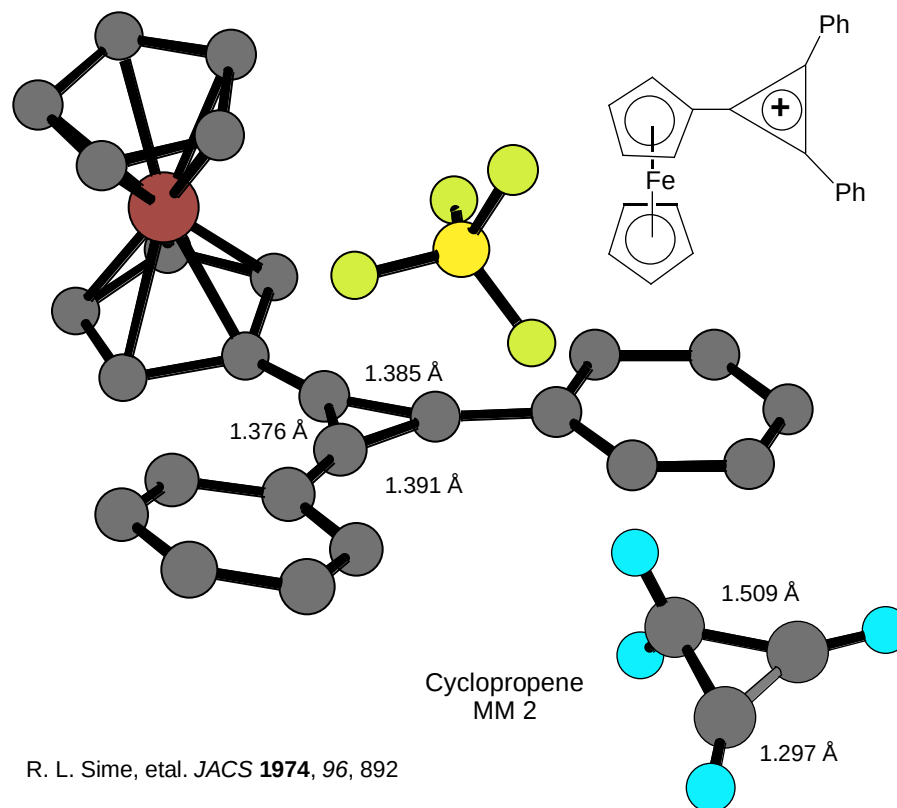
For a recent monograph on hypervalent Compounds see:
"Chemistry of Hypervalent Compounds", K. Akiba, Wiley-VGH, 1999

Carbocation Stabilization - $d(\pi)$ stabilization via Transition metal Fragments

Transition metal not bound directly to carbenium ion: **Ferrocenes**

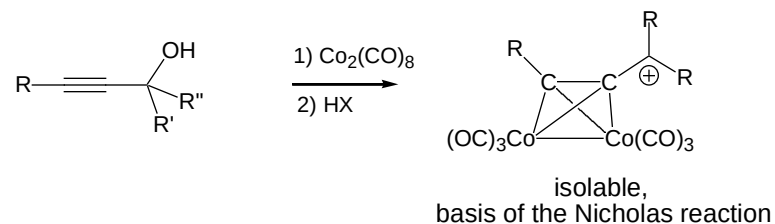


J. Lukasser, et al. *Organometallics* **1995**, 14, 5566-5578



R. L. Sime, et al. *JACS* **1974**, 96, 892

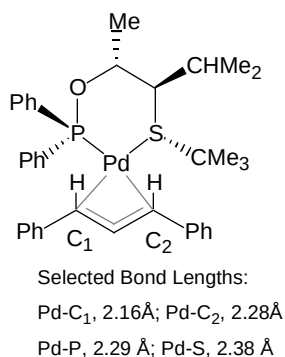
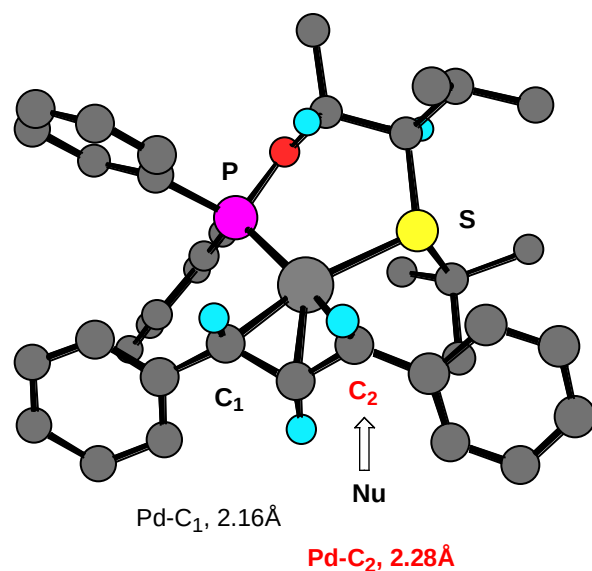
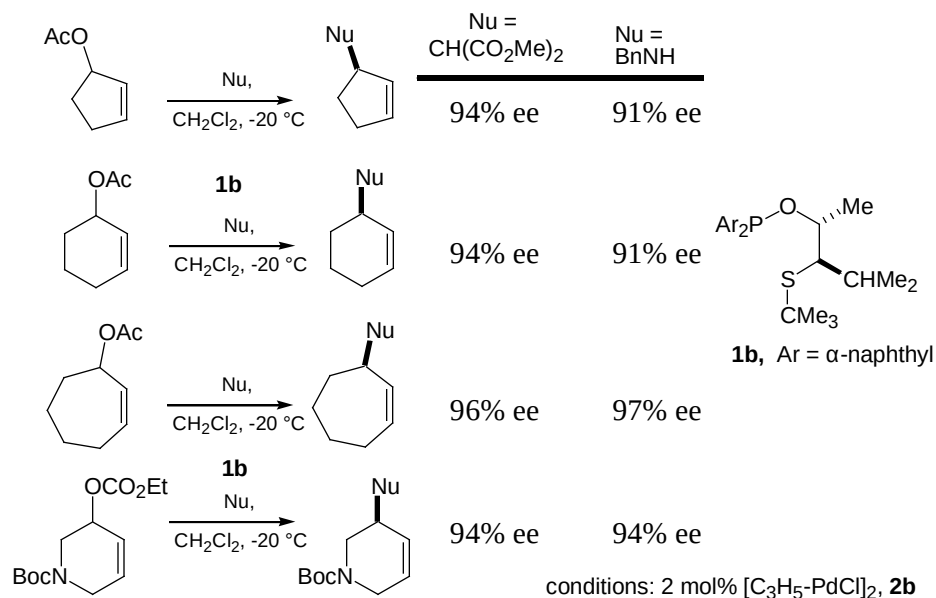
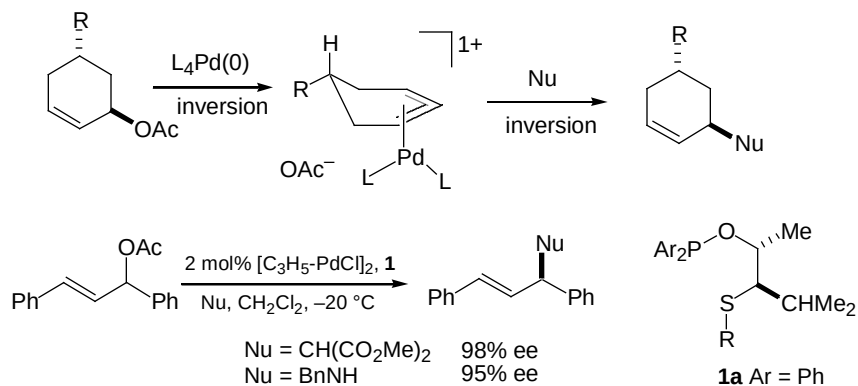
Transition metal not bound directly to carbenium ion: **Cobalt-Acetylenes**



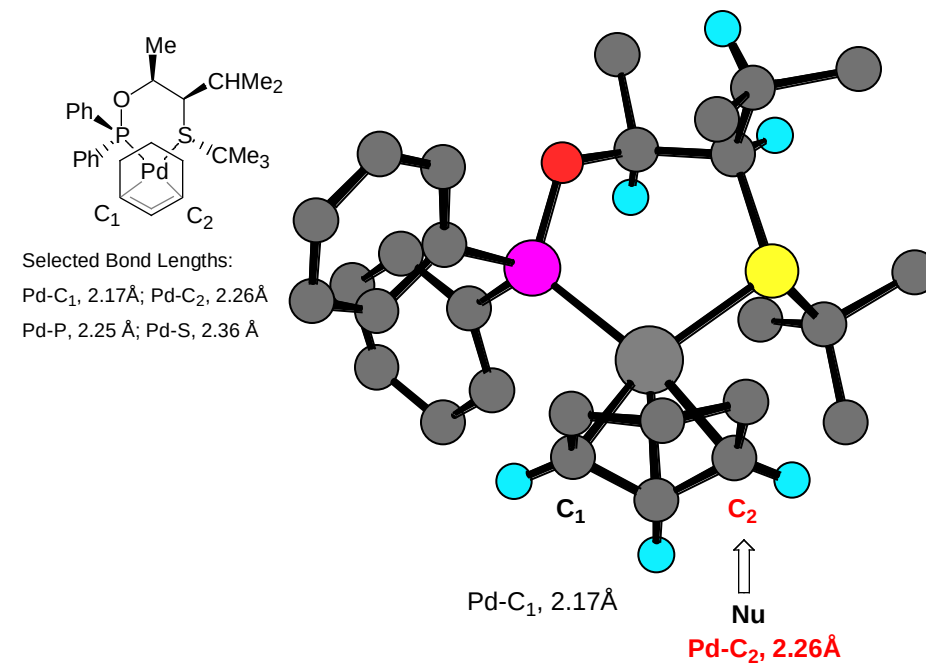
See Houk et al. *JACS* **1999**, 121, 3596-3606

**Carbocation Stabilization - $d(\pi)$ stabilization
via Transition metal Fragments**

Transition metals bound to carbenium ions: π -Allyl Pd(II) Complexes



Evans, Campos, Tedrow, Michael, Gagné,
JACS 2000, 122, 7905



<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)

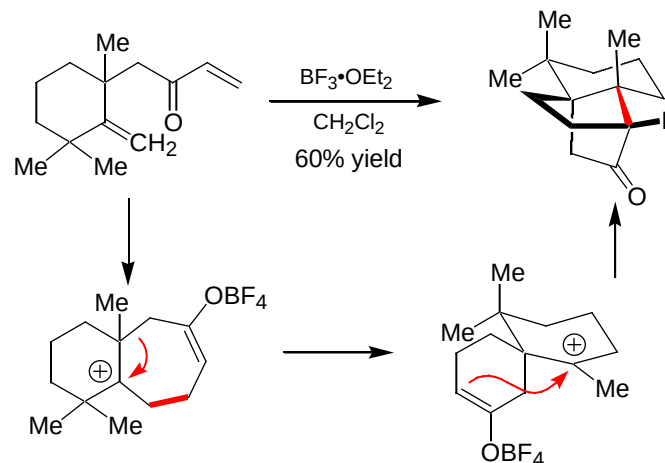
Other Relevant Background Reading

Saunders, M. and H. A. Jimenez-Vazquez (1991). "Recent studies of carbocations." *Chem. Rev.* 91: 375.

Matthew D. Shair

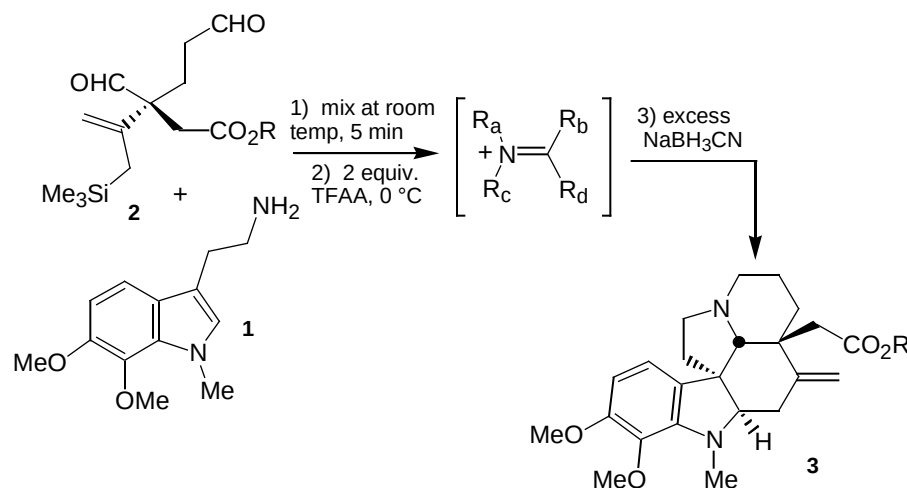
Friday,
December 6, 2002

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.

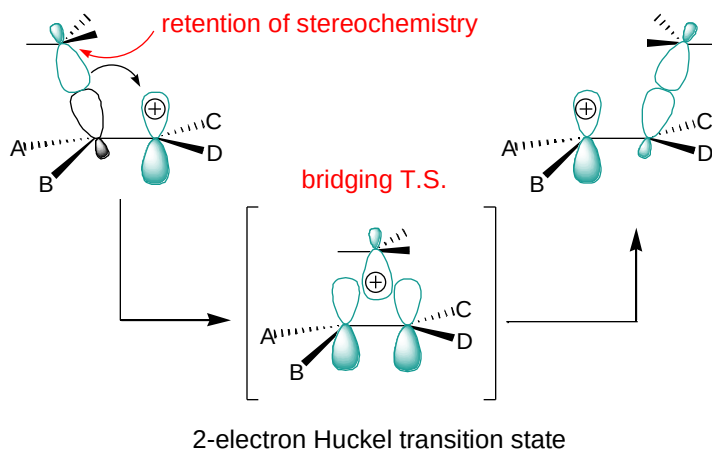


Carbocation [1,2] Sigmatropic Rearrangements

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 rearrangements.

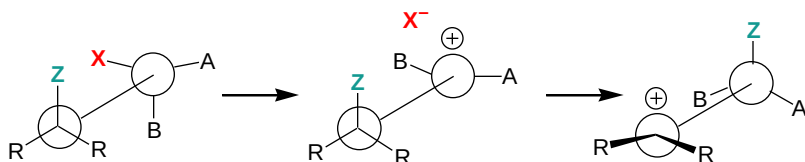
Birladeanu (2000). "The Story of the Wagner-Meerwein Rearrangement." J. Chem. Ed. 77: 858. (**handout**)

Stereoelectronic requirement for migration....

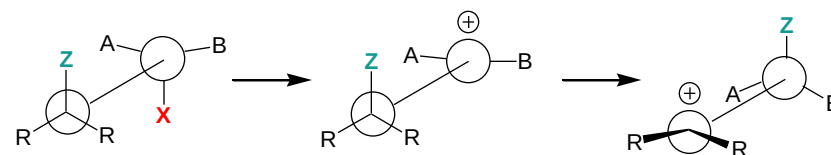


Long-lived Carbocations: X departs before Z moves.

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.



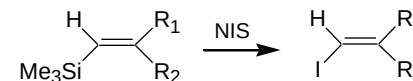
In the most stable ground state conformation, if the relationship between the migrating group (Z) and the leaving group (X) is **anti**, usually **inversion** is observed in the migration terminus.



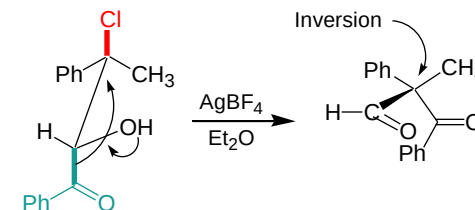
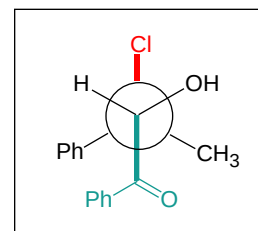
These observations can be ascribed to the **principle of least motion**: "...those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."

O. S. Tee JACS **1969**, 91, 7144

Principle of least motion in action:

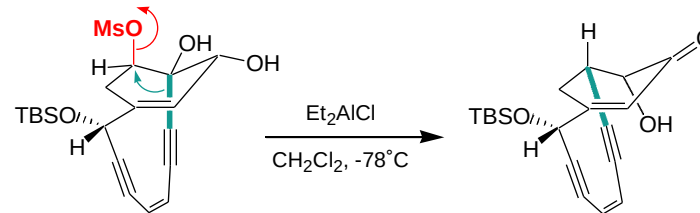


Migration attends ionization



R. Bach J. Am. Chem. Soc. **1979**, 101, 3118

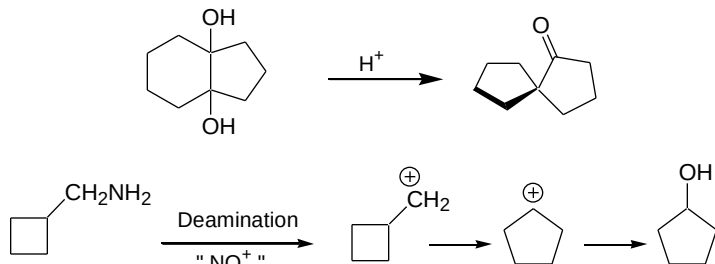
If **migration accompanies ionization**, the migration terminus will be **inverted**. Overlap between the σ C-C (migration origin) and the σ^* C-X (migration terminus) will be maximized in an **antiperiplanar** arrangement.



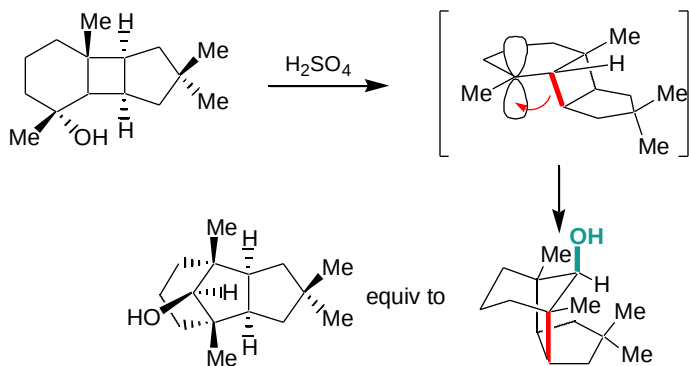
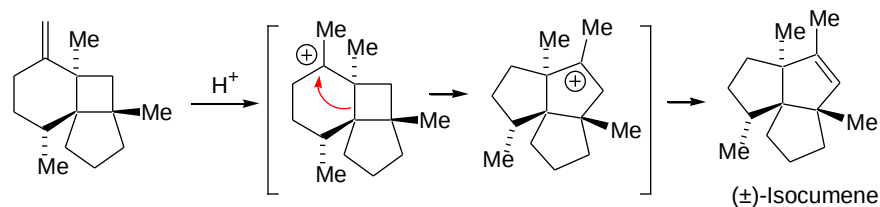
S. L. Schreiber et al Tetrahedron Lett. **1989**, 30, 3765.

Carbocation [1,2] Sigmatropic Rearrangements

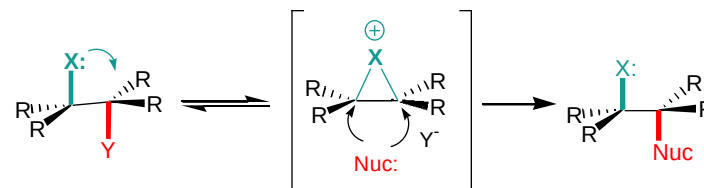
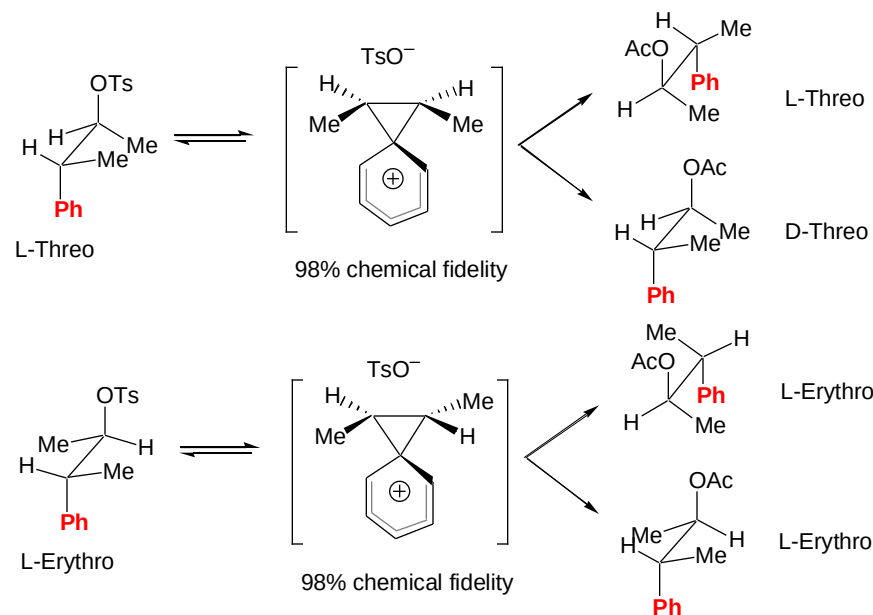
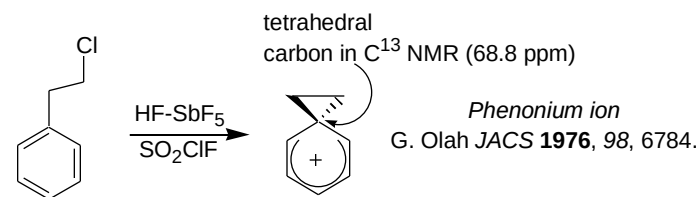
Pinacol rearrangement (vicinal diol): Driving force is the gen. of C=O



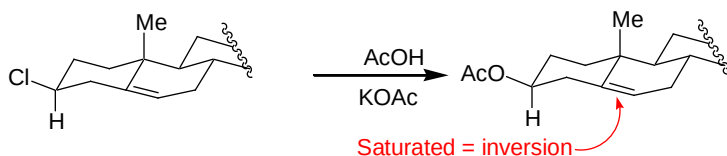
Demjanov-rearrangement (Driving force: relief of ring strain)

Wagner-Meerwein Rearrangements: Application in Total SynthesisE. J. Corey *J. Am. Chem. Soc.* **1964**, 86, 1652. α -caryophyllene alcohol**Synthesis of ($\pm$)-Isocomene:** Pirrung, *JACS* **1979**, 7130; 1981, 82.**Carbocations: Neighboring Group Participation**

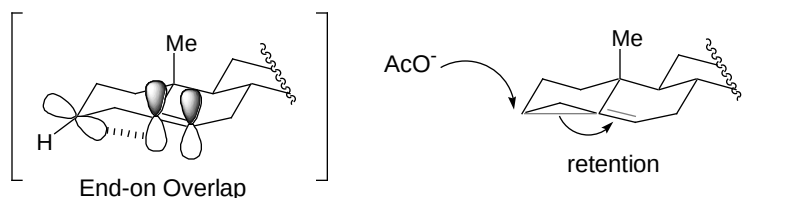
- Groups with accessible electron density (heteroatoms, arenes) and the correct stereoelectronic orientation (anti-periplanar) can "assist" in the ionization of a leaving group.

**The Cram Phenonium Ion Experiments:** Cram, *JACS* **1949**, 71, 3865**Physical Evidence for Neighboring Group Participation**

See Lowry & Richardson, pp 434-439 for discussion of this controversy

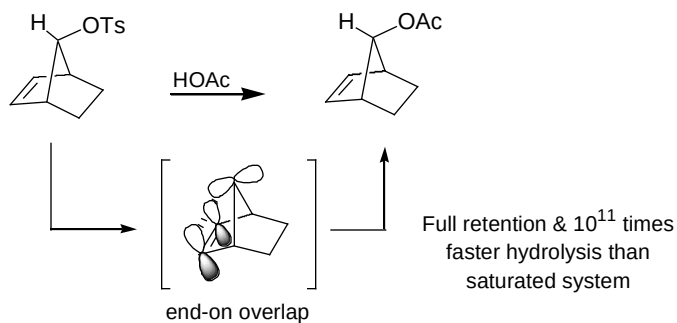
"Nonclassical" carbonium ions**Introduction**

- 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.

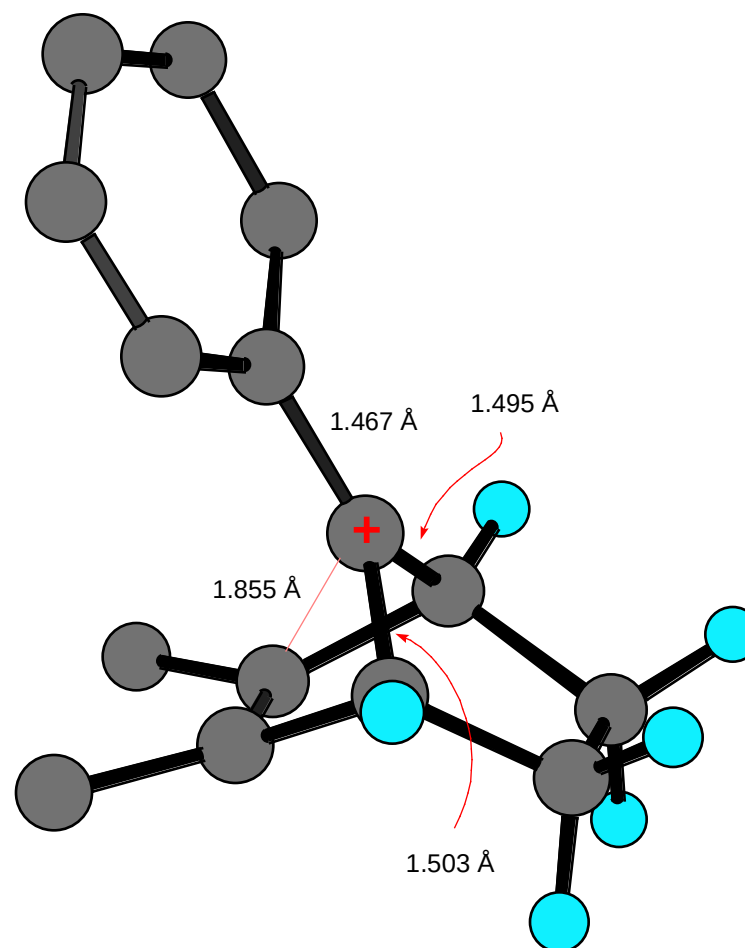


- These results have been attributed to an end-on overlap between the filled p orbital of the double bond and the vacant p orbital of the cation in a σ -type of interaction. This type of stabilization (a 3 center-2 electron bond) results in what are referred to as **"nonclassical carbonium ions"**.

C. Shoppee *J. Chem. Soc.* **1946**, 1147S. Winstein *J. Am. Chem. Soc.* **1954**, 76, 18

The Norbornenyl Example

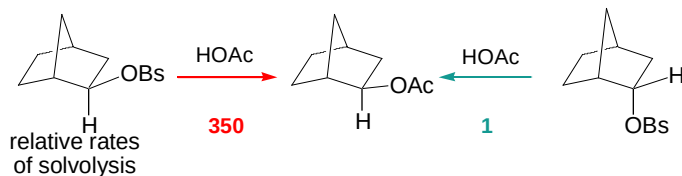
- In the norbornenyl system, both p orbitals of the double bond can stabilize the vacant p orbital in an end-on orientation.

Physical Evidence of Nonclassical Carbonium Ion

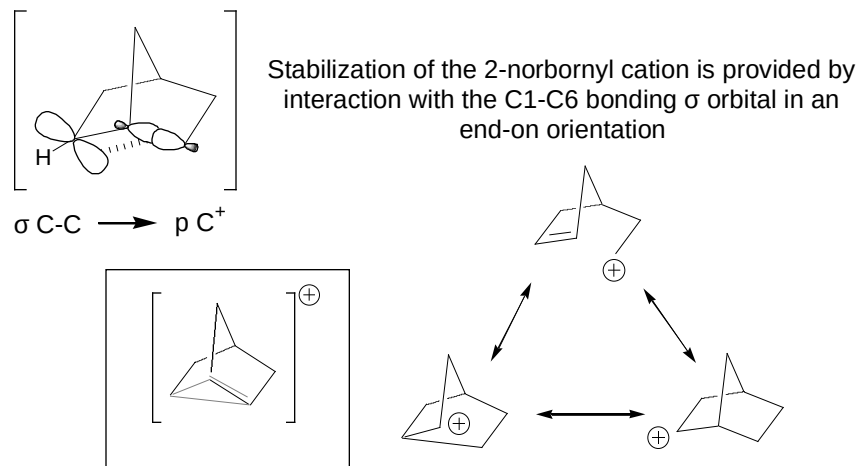
T. Laube, *JACS* **1989**, 111, 9224

The 2-Norbornyl Cation

"An Innocent Bystander Looks at the 2-Norbornyl Cation"
Walling, C. *Acc. Chem. Res.* **1983**, 16, 448.



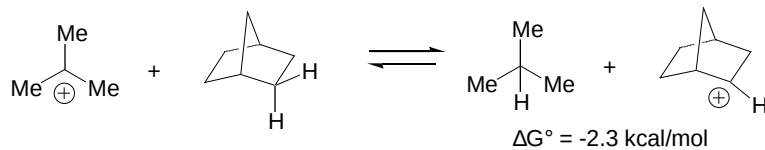
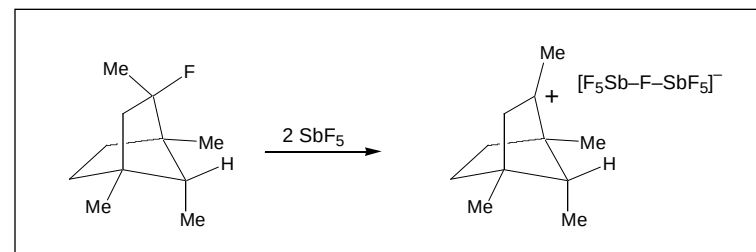
How do we explain the rate difference and stereochemical result?



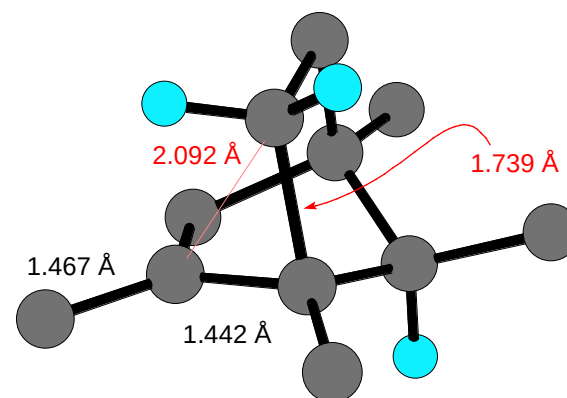
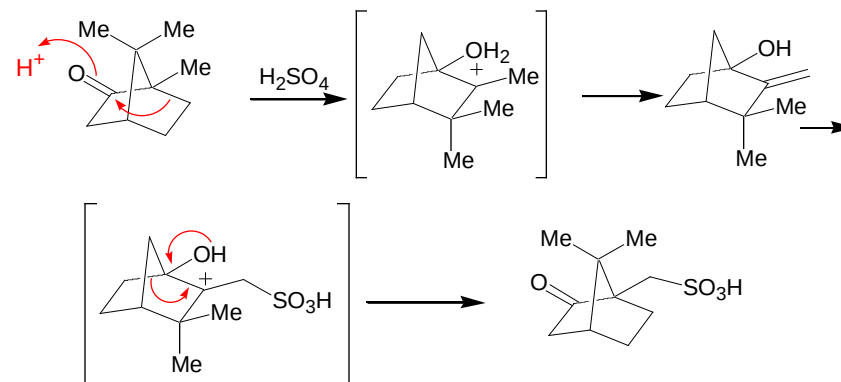
Winstein: The delocalized structure is the lowest energy structure

Brown: Delocalized structure is the transition state separating localized ions

Ion Equilibrium Experiments: Field & Soloman, *JACS* **1976**, 98, 1567

**"Nonclassical" carbonium ions: The Facts!**

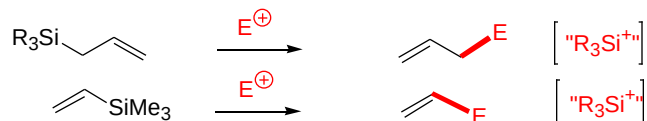
T. Laube, *Angew. Chem. Int. Ed.* **1987**, 26, 560

**Functionalization of Camphor**

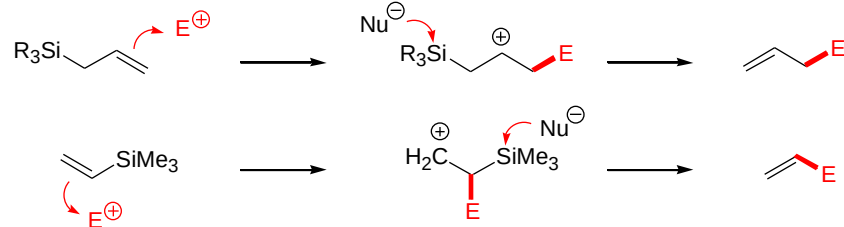
References: Lambert *Acc. Chem. Res.* **1999**, 32, 183-190
 Lambert, JACS **1990**, 112, 8120; **1996**, 118, 7867.
 Fleming, *Organic Reactions* **1989**, 37, 54.
 Fleming, *Chem. Rev.*, **1997**, 2063.

Allyl- & Vinylsilanes react with electrophiles

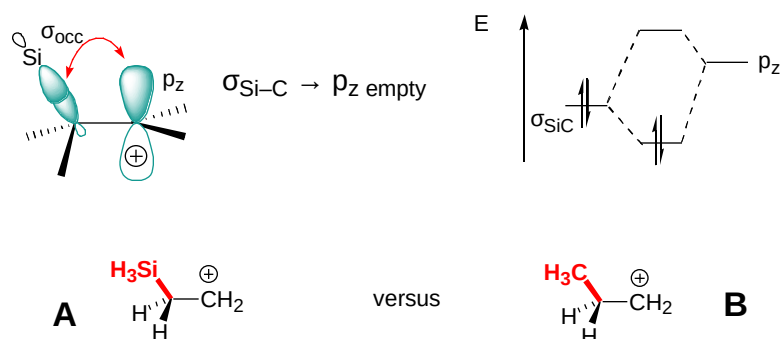
(trapped by solution Nu)



Mechanism - the simple picture: β -Silicon stabilizes carbocation



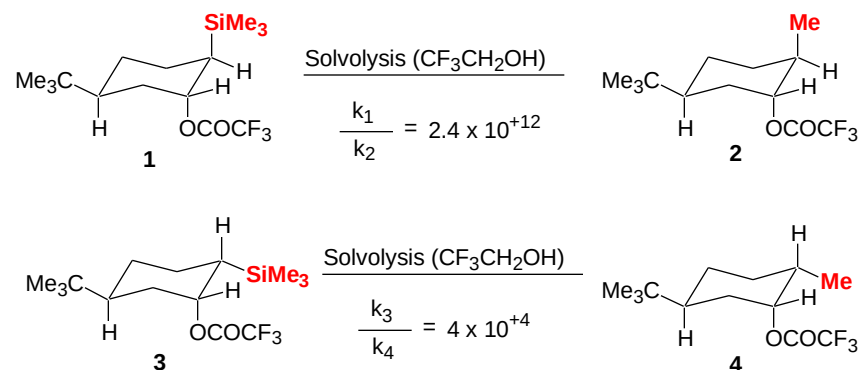
β -Silicon Effect: the origin of regioselectivity



Calculation: A more stable than B by 38 kcal/mol.

Jorgensen JACS **1985**, 107, 1496.

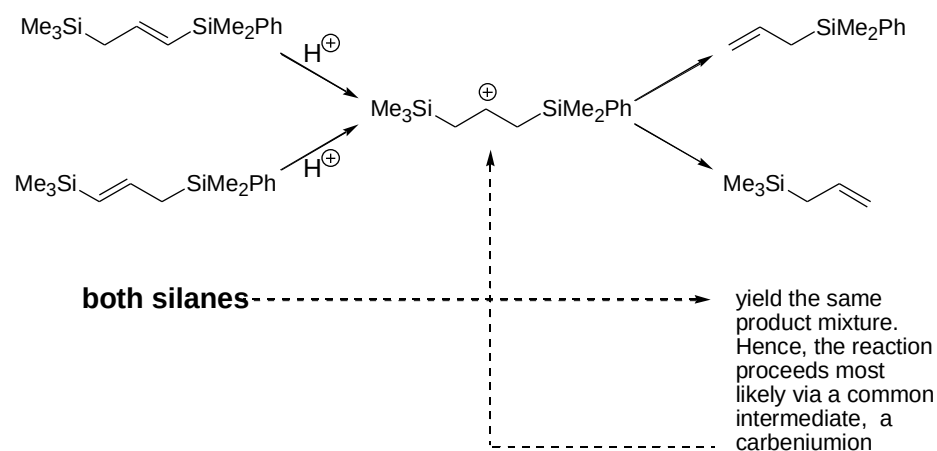
Magnitude of the β -Silicon Effect



"These figures established the β -effect as one of the kinetically strongest in organic chemistry": J. Lambert

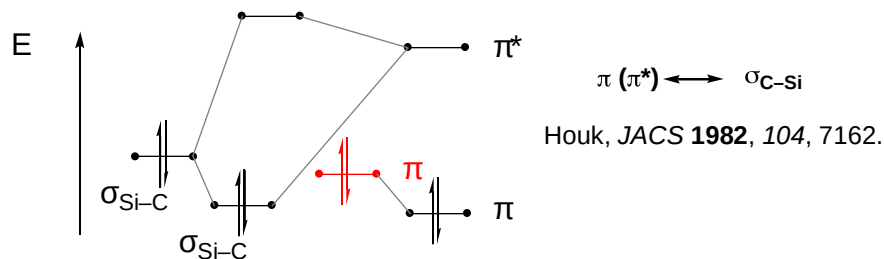
Data provide no distinction between open and bridged intermediates

Proof for a stepwise mechanism provided the following protodesilylation experiment:

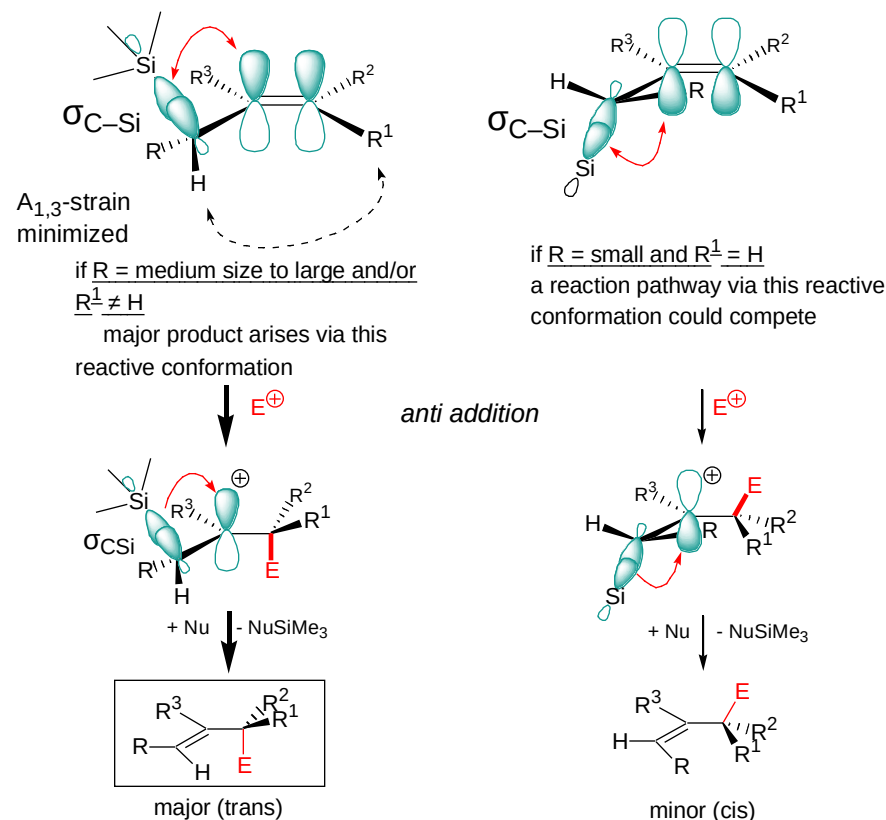


General: Allylsilanes are more nucleophilic than alkenes

$\Rightarrow$ HOMO is higher in energy due to **negative hyperconjugation**



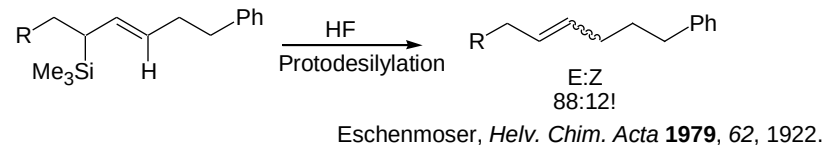
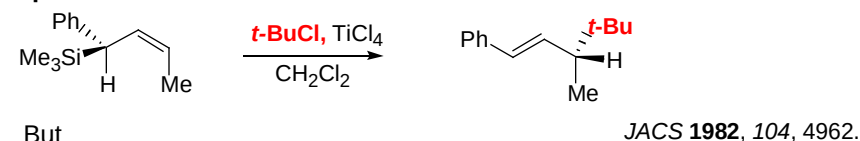
Electrophile Addition - Stereoelectronics



The stereochemical consequences for the major product are:

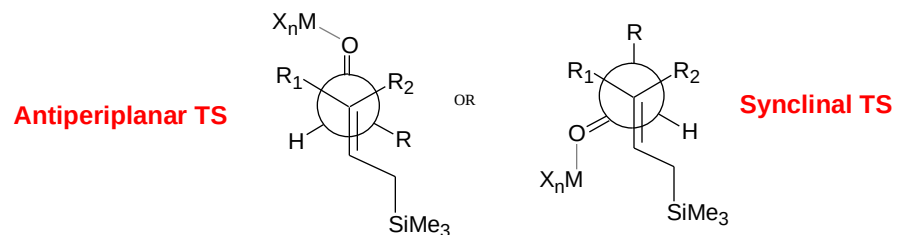
- ☐ trans-alkene:
- ☐ anti-addition of E^+ with respect to SiR₃

Examples:

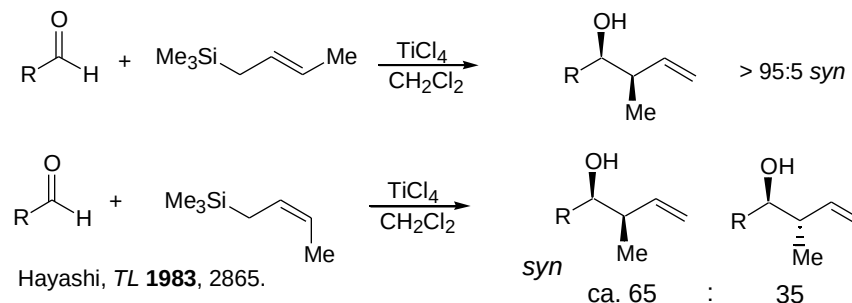


Carbonyl Addition of Allylsilanes: Open Transition States

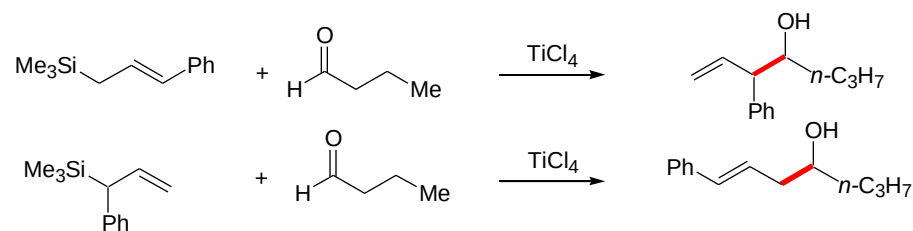
Me₃Si- is not sufficiently Lewis acidic to activate C=O through pre-association; however (RO)₂MeSi- is Lewis acidic enough to activate C=O through pre-association. These allylsilanes add to RCHO through closed transition states



Calculations by Houk et al. show that the relative energy differences between the antiperiplanar and synclinal transition states are negligible. Both the antiperiplanar and synclinal models predict a **syn** selectivity for the newly formed stereogenic centers.



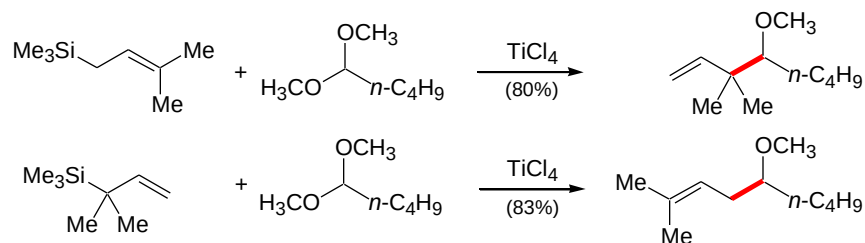
Allylsilanes add to aldehydes and acetals under Lewis acid promotion



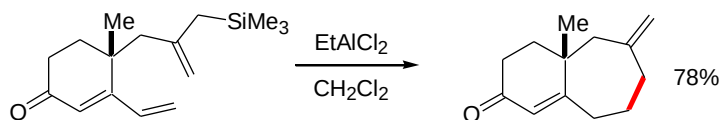
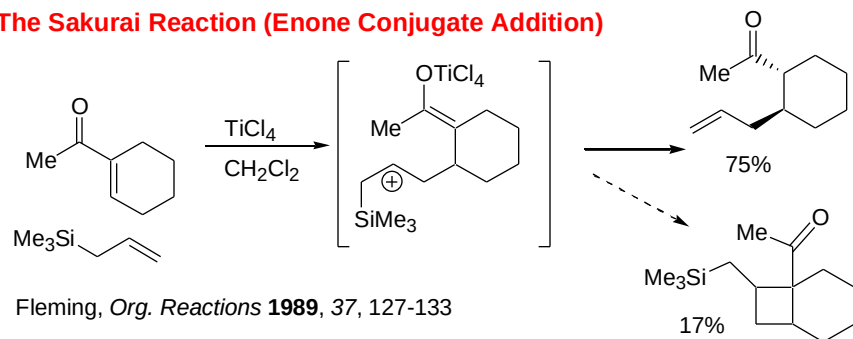
regioselectivity: Allyl inversion

Felkin Selectivity also holds with this class of nucleophiles

Acetals can be used as well



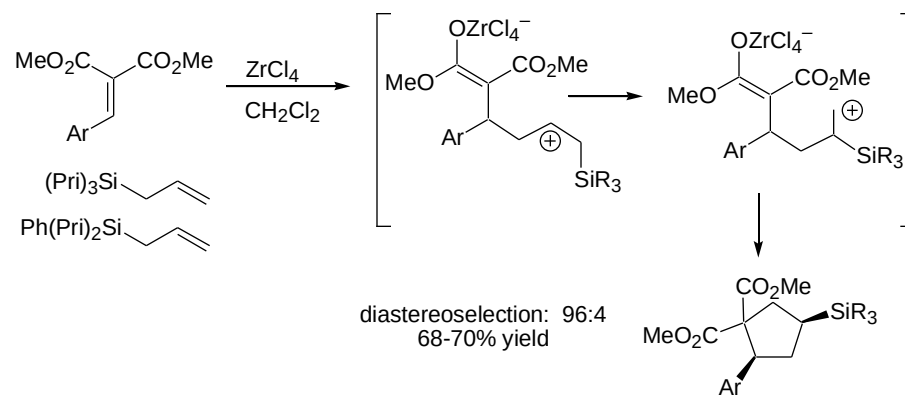
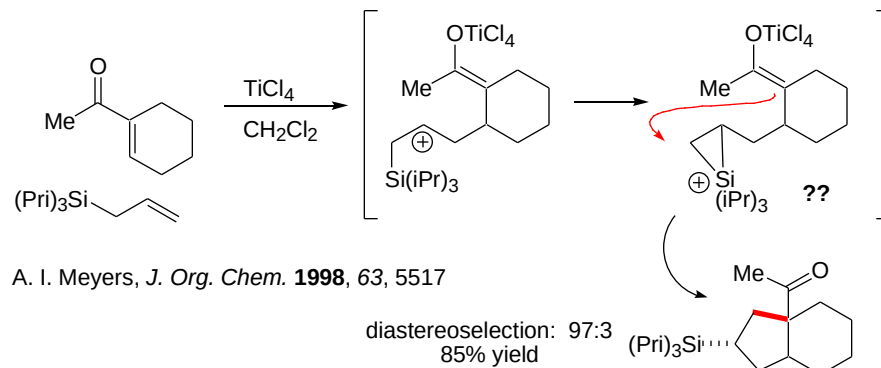
The Sakurai Reaction (Enone Conjugate Addition)



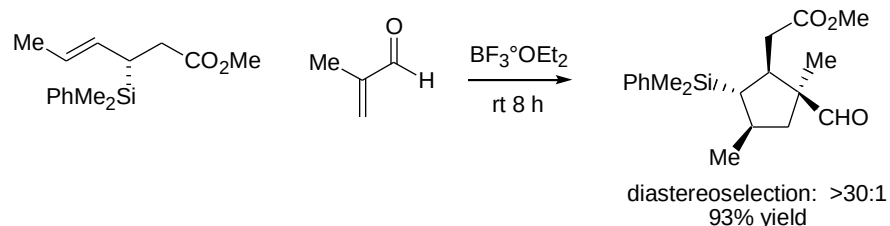
Majetich, *Tetrahedron* **1987**, 43, 5621

Reactions Proceeding through Silicon-Migration

Si migration may be promoted by using hindered Si substituents



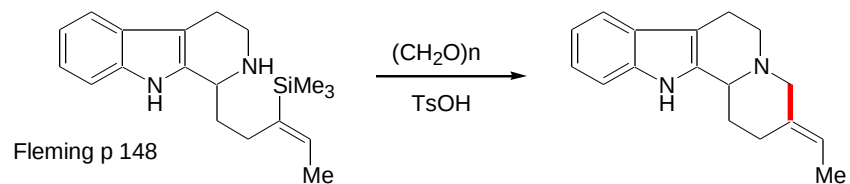
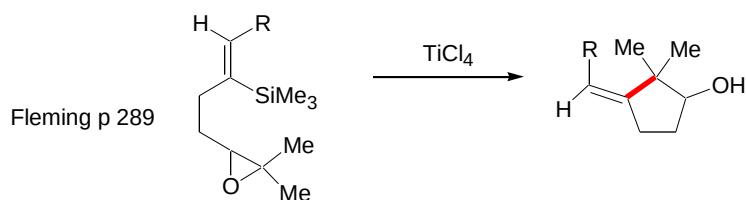
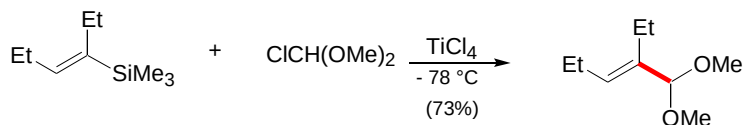
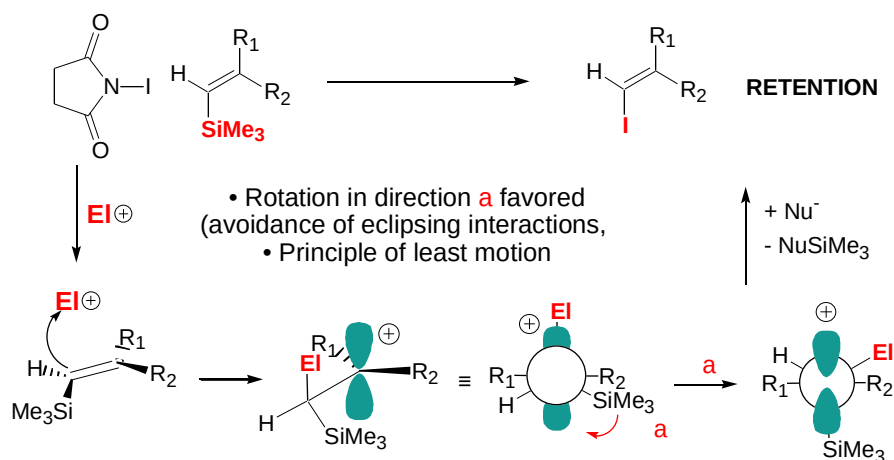
Can you work out the mechanism??



Panek, *J. Org. Chem.* **1993**, 58, 2345

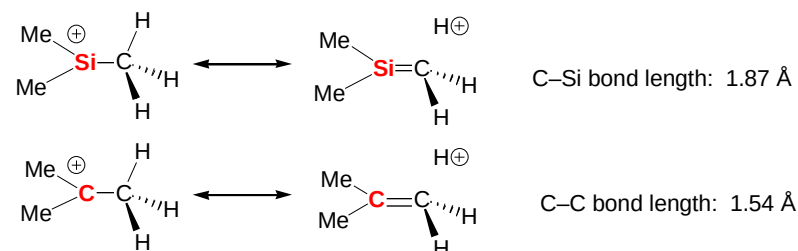
Stereochemistry of Electrophile Addition to Vinylsilanes

Vinyl/Allylsilanes in Organic Synthesis - Selected Examples

Fleming, *Org. Reactions* 1989, 37, 54.

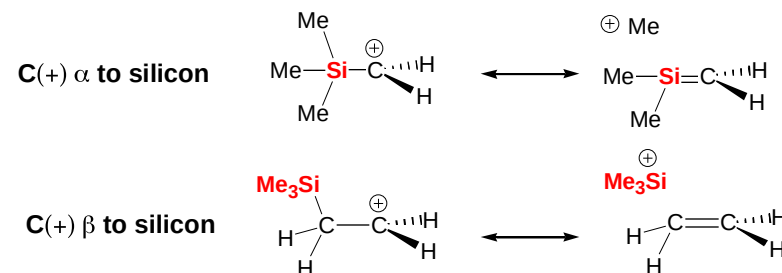
Summary Statements

1. Me_3C^+ is more stable than Me_3Si^+ in spite of the fact that Si is less electronegative than C.



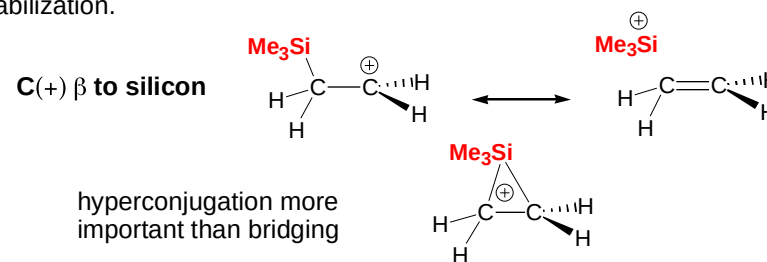
C-Si hyperconjugation is less pronounced than the analogous C-C hyperconjugation due to the impact of the longer C-Si bond lengths.

2. Carbonium ions α to Si are less stabilized than carbonium ions β to Si.



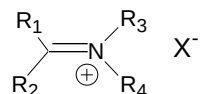
C-Si hyperconjugation is less pronounced than the analogous C-C hyperconjugation due to the impact of the longer C-Si bond lengths.

3. According to Lambert, silicon has a propensity to stabilize β carbonium ion via hyperconjugation (vertical stabilization) rather than bridging (nonvertical stabilization).

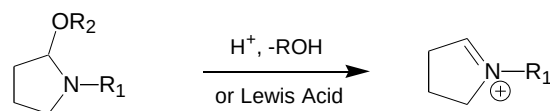
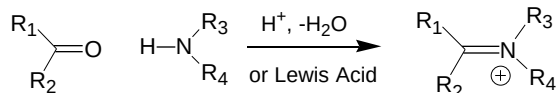


4. Silicon has a lower propensity to undergo Wagner-Meerwein like rearrangements than carbon.

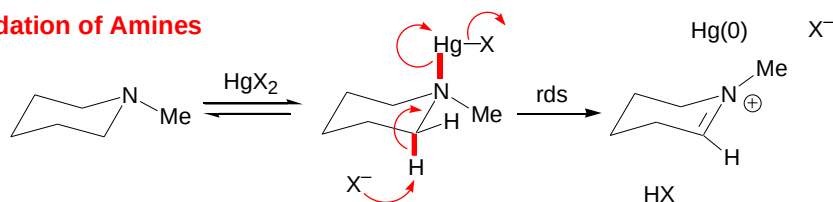
Iminium Ions



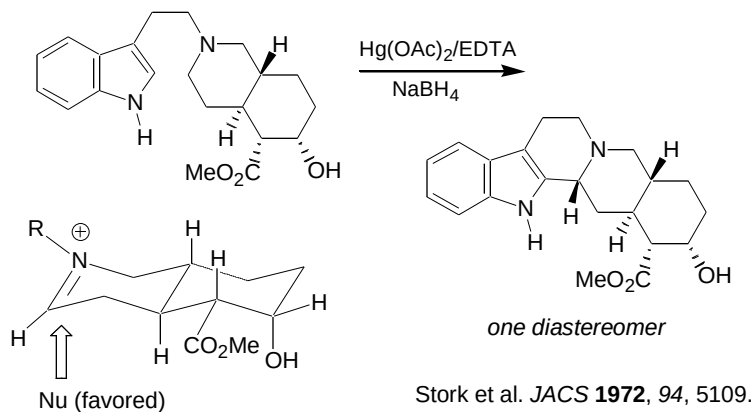
Common Methods of Generation:



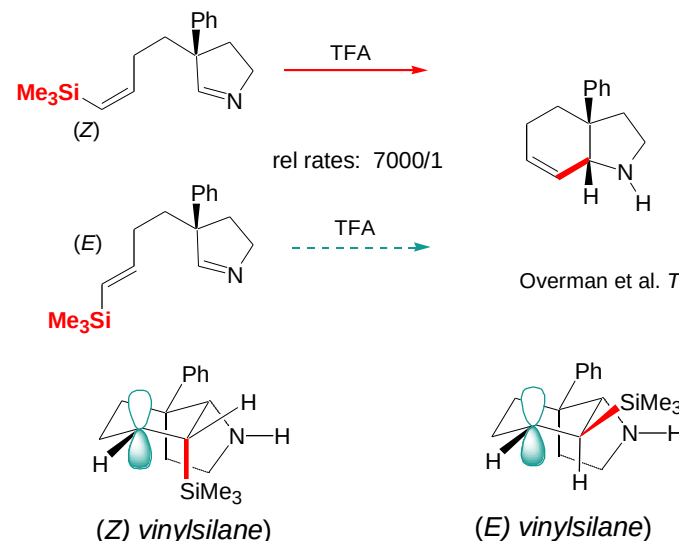
Oxidation of Amines



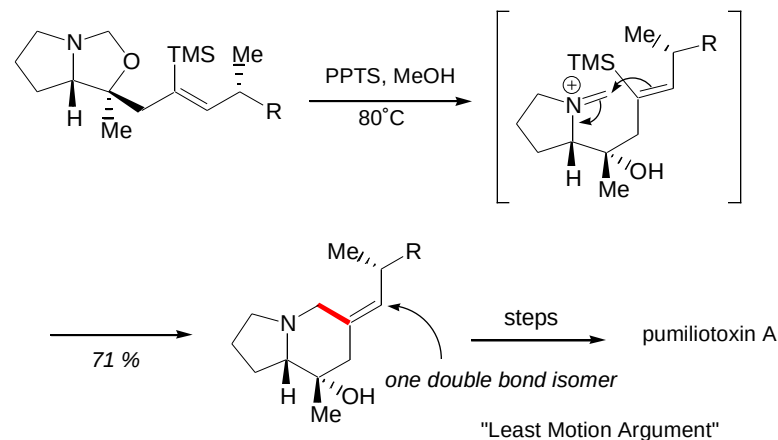
Stereoelectronic Effects on Nu Addition to Iminium Ions



C=N Stereoelectronic Effects: Lecture 19



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

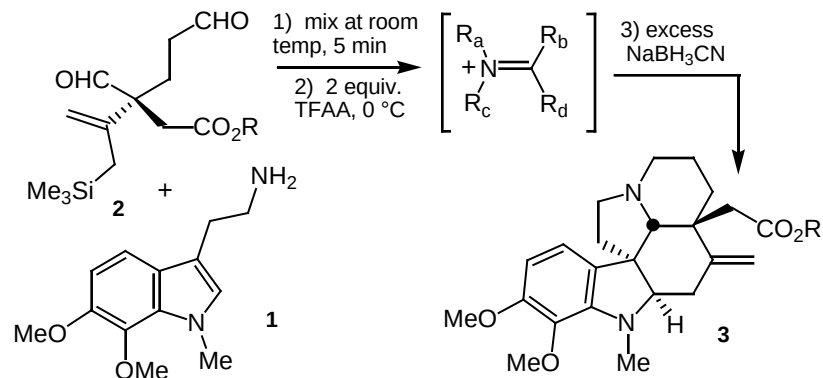
Introduction to Carbonium Ions–3

- Stabilized Carbocations: Iminium Ions ($C=NR_2^{+}$)
- Stabilized Carbocations: Oxo–Carbenium Ions ($C=OR^{+}$)
- Stabilized Carbocations: Addition & Rearrangements

Reading Assignment for this Lecture:

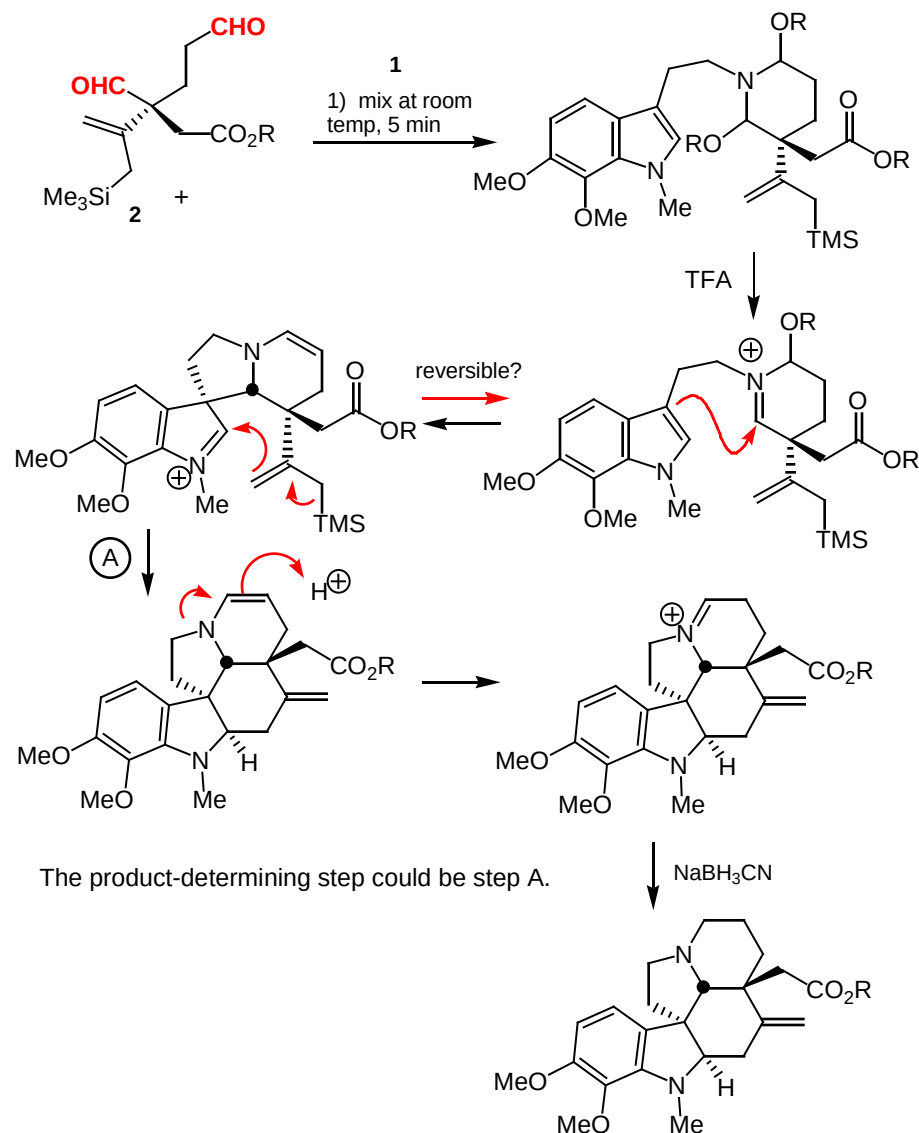
Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed.
Part A Chapter 5, "Nucleophilic Substitution", 263-350 .

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.

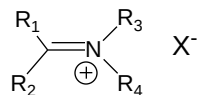


Matthew D. Shair

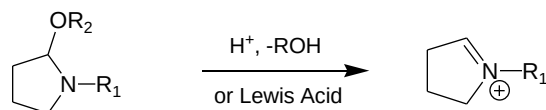
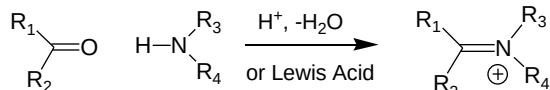
Monday,
December 9, 2002



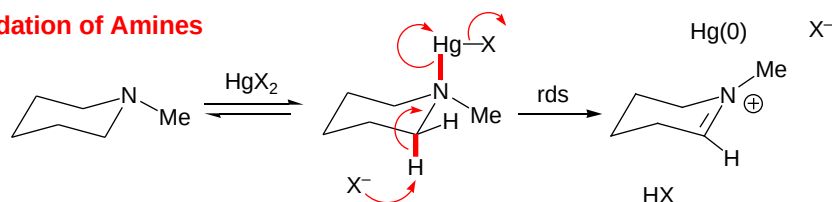
Iminium Ions



Common Methods of Generation:

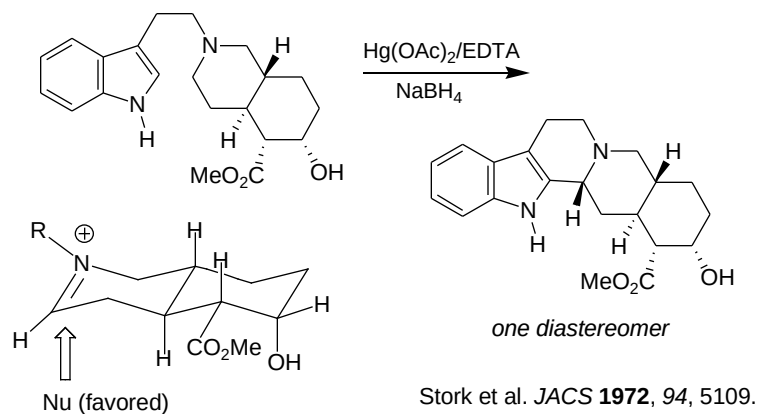


Oxidation of Amines

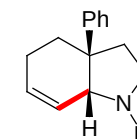
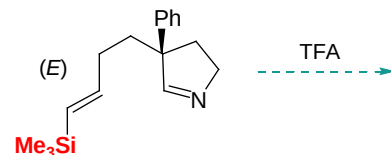
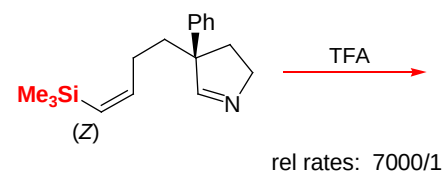
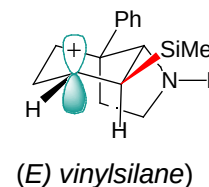
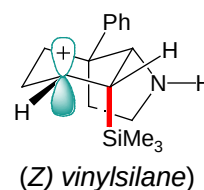


Related to Polonovski & Pummerer Reactions: Lecture 27

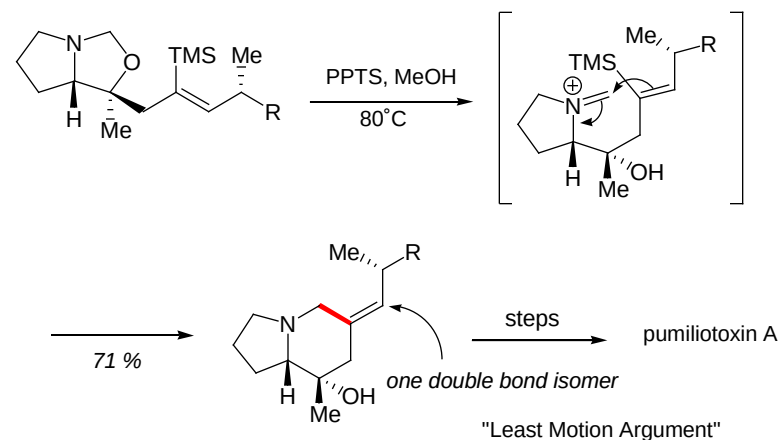
Stereoelectronic Effects on Nu Addition to Iminium Ions



C=N Stereoelectronic Effects: Lecture 19

Overman et al. TL **1984**, 25, 5739.

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.

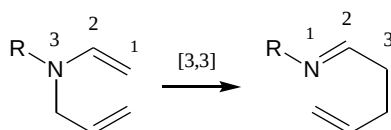
Overman et al. JOC **1989**, 54, 2591.

Review:

Heimgartner, H. In "Iminium Salts in Organic Chemistry"; Bohme, H., Viehe, H., Eds.; Wiley: New York, 1979; Part 2, pp 655-732.

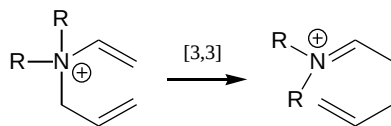
The 3-aza-Cope Rearrangement:

Neutral Variant:



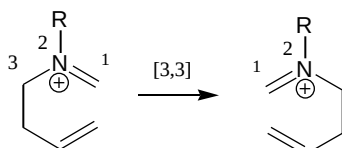
Exothermic as written by $\sim 7\text{-}10\text{ kcal/mole}$.

Ammonium Variant:



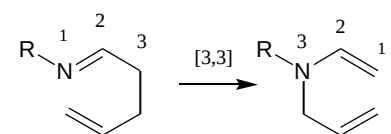
Even more exothermic than the neutral version, since enamine lacks resonance and iminium salt has stronger p-Bond than imine does.

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.

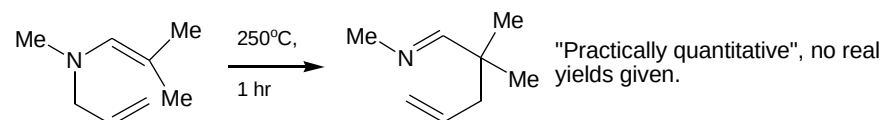
1-aza-Cope Rearrangement:



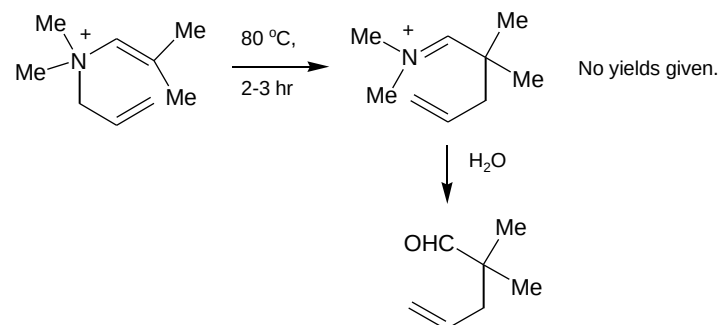
The 3-aza-Cope rearrangement can be driven in reverse by judicious choice of substrates (i.e., incorporating the imine into a strained ring or by making R an acyl group).

The 3-aza-Cope Rearrangement

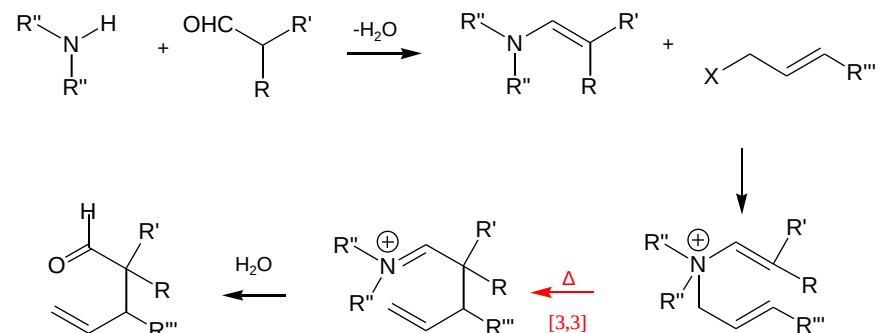
First Neutral Case: Hill TL **1967**, 1421.



First Cationic Case: Elkik *Compt. Rend.* **1968**, 267, 623.

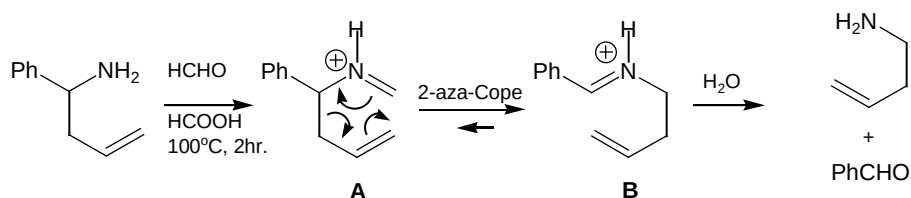


Good way to allylate aldehydes: Opitz *Angew. Chem.* **1960**, 72, 169.



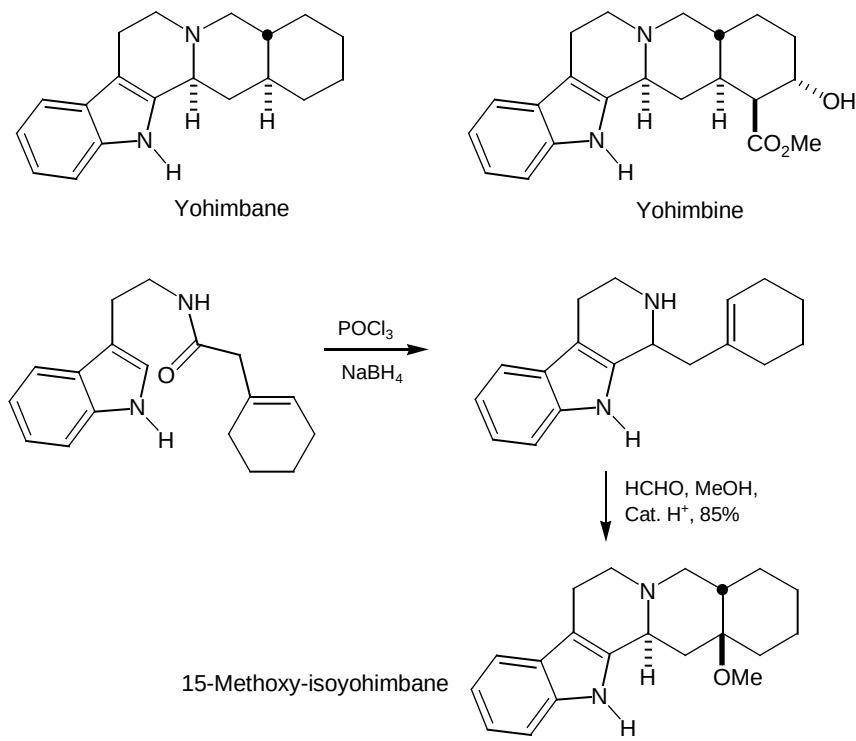
The 2-aza-Cope Rearrangement

First Reported Case: Horowitz JACS 1950, 72, 1518.

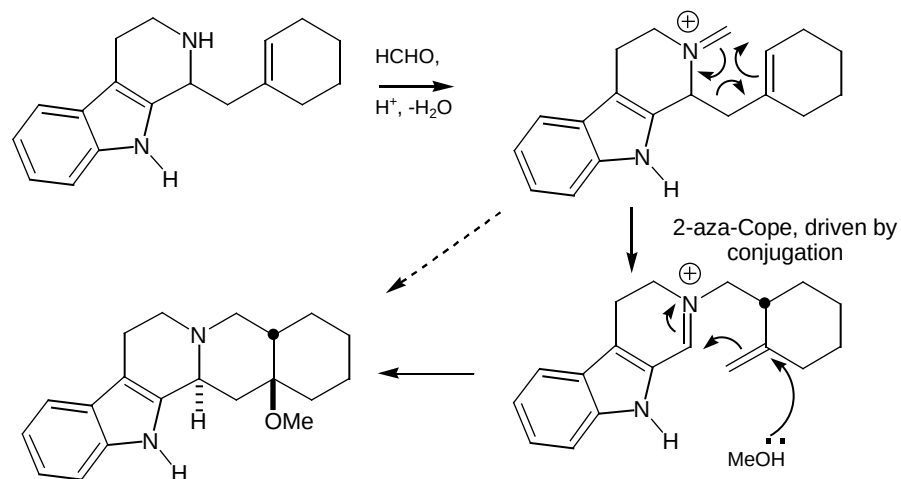


Equilibrium between **A** and **B** driven towards **B** by conjugation of iminium double bond to the aromatic ring in **B**.

Application to Yohimbine Analog Synthesis: Winterfeldt *Chem. ber.* **1968**, 101, 2938.

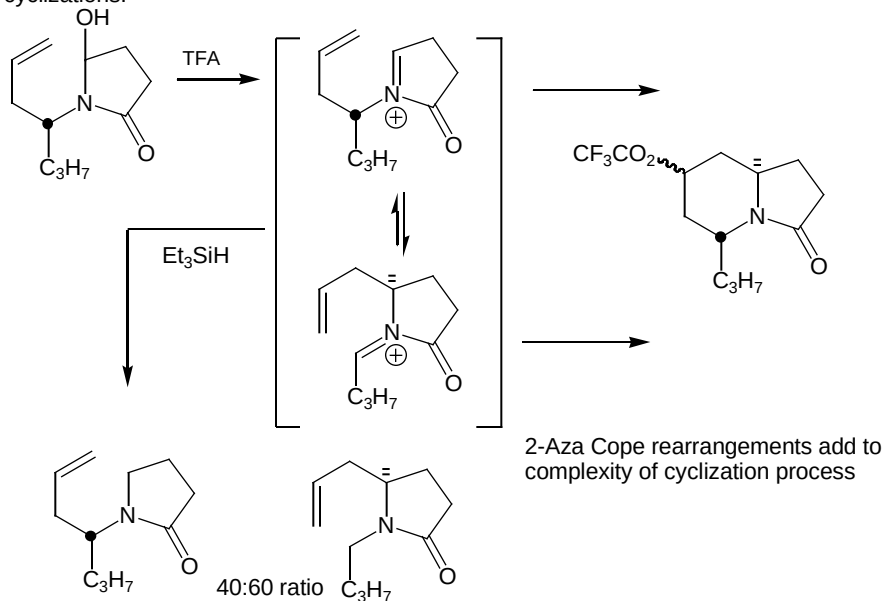


Mechanism for Yohimbane Analog Formation:



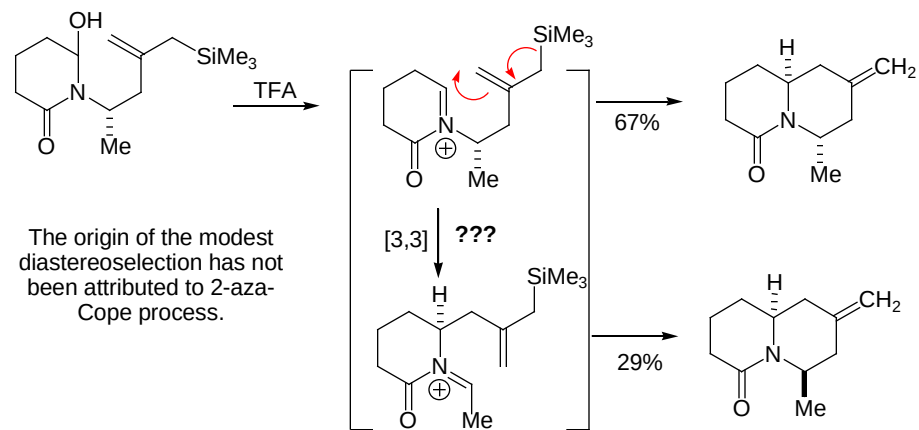
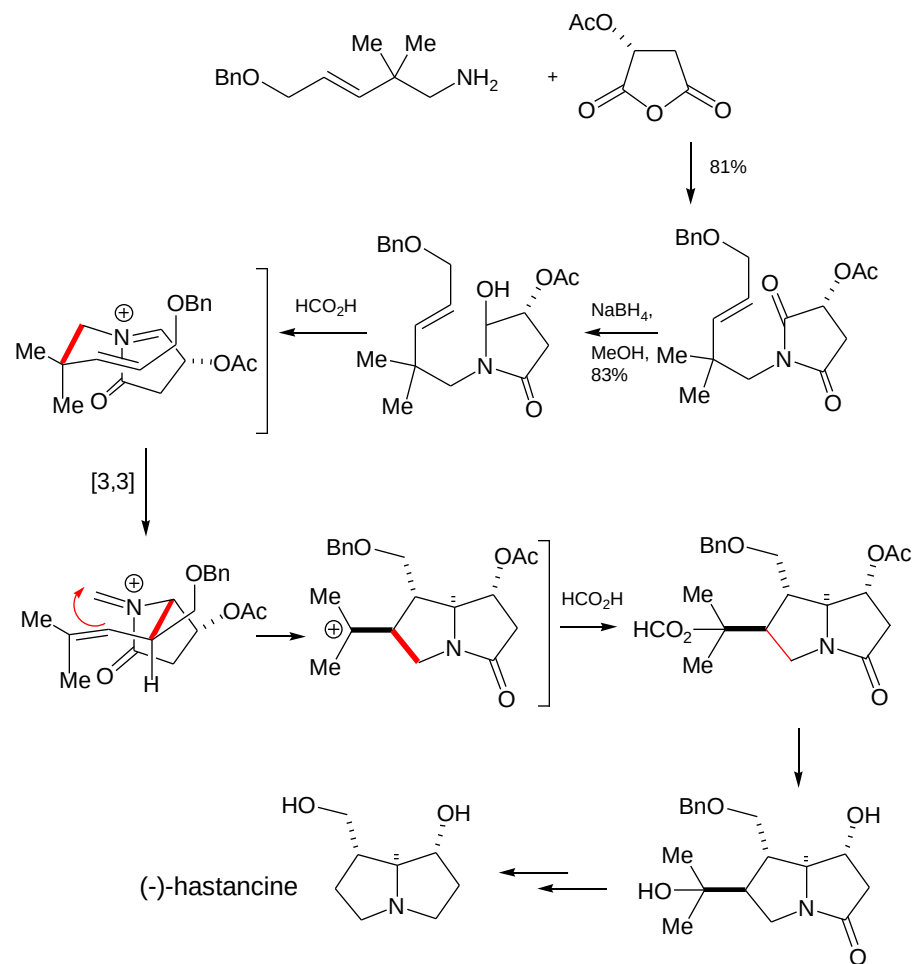
N-Acyliminium Ion Rearrangements: Hart *JOC* **1985**, 50, 235.

Hart observed an unusual product while trapping the intermediates of *N*-acyliminium olefin cyclizations.



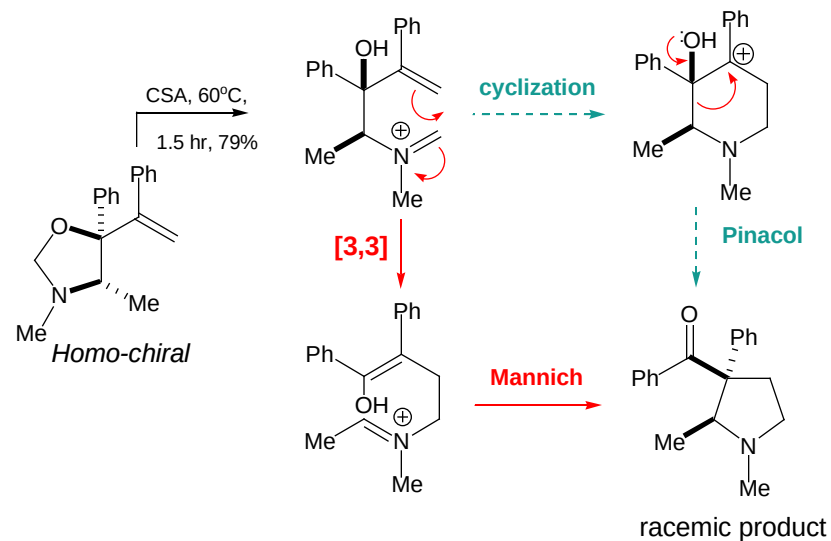
N-Acyliminium Ion Rearrangements

Synthesis of (-)-hastanecine: Hart JOC **1985**, 50, 235.

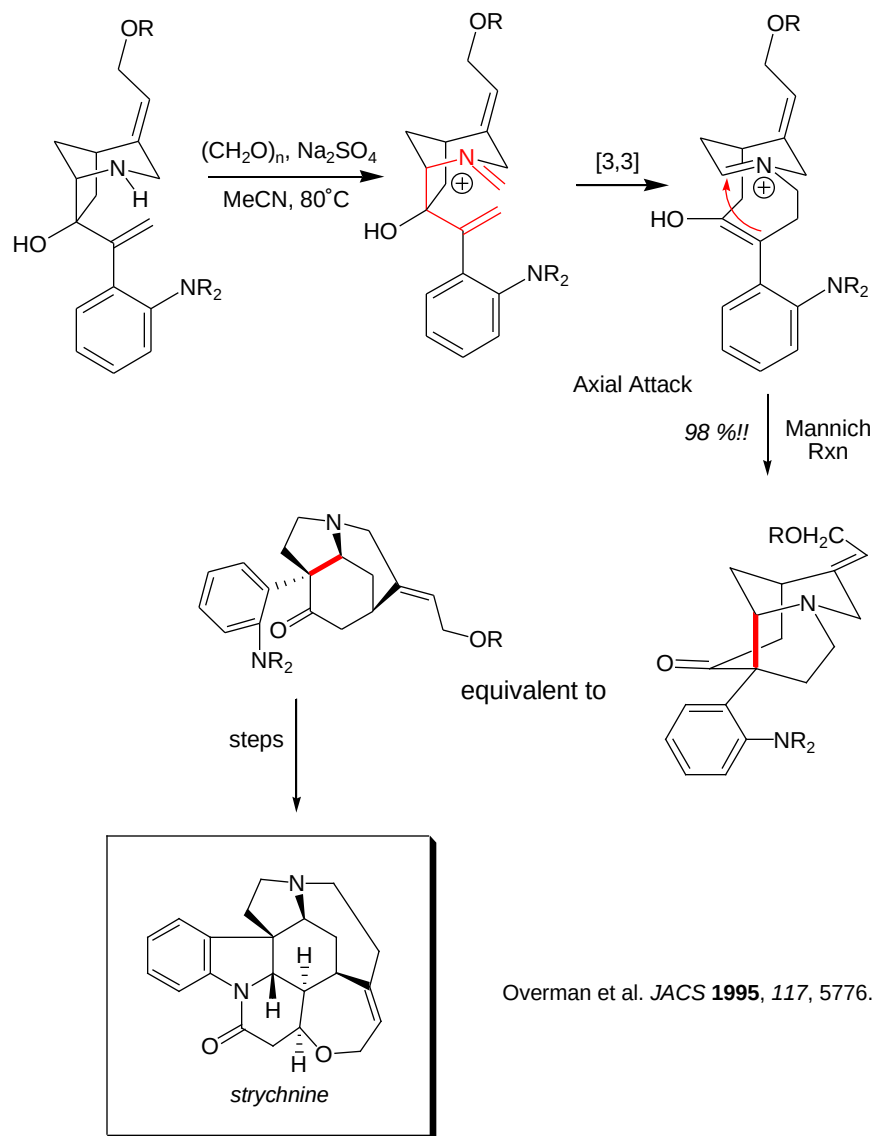
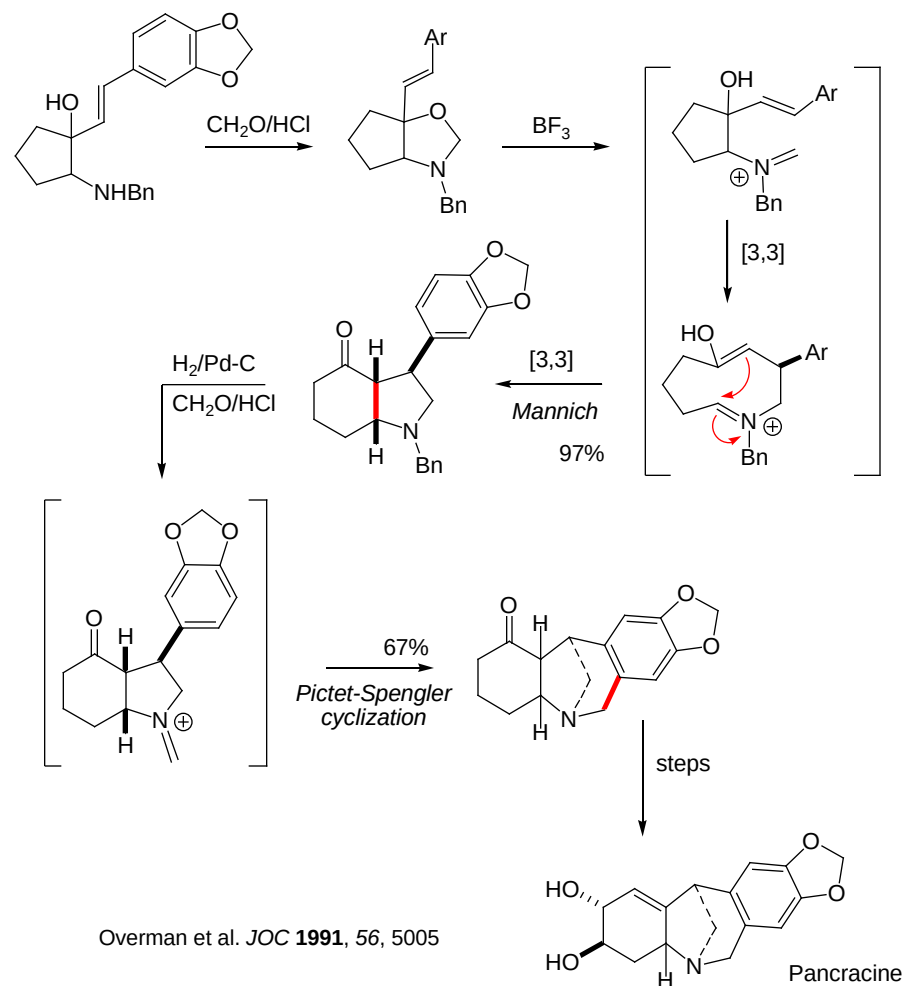


The origin of the modest diastereoselection has not been attributed to 2-aza-Cope process.

Gelas-Mailhe, *Tet. Lett.*, **1992**, 33, 73

Competing 2-Aza-Cope and Pinacol Rearrangements: Which Dominates??

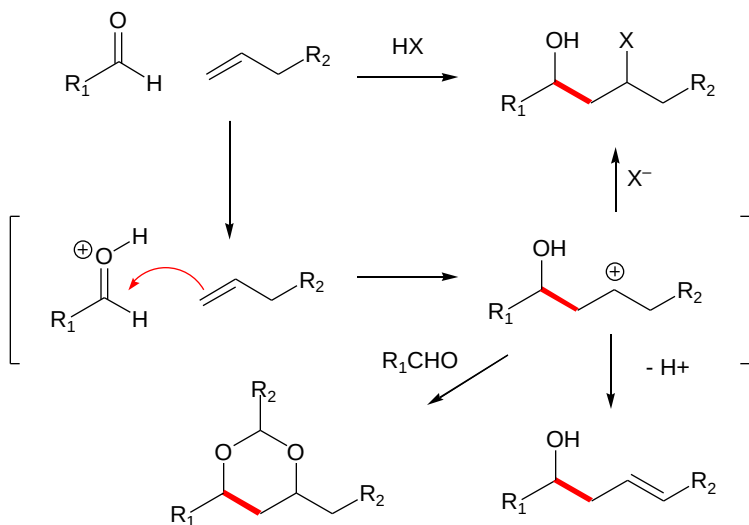
Conclusion: 2-aza-Cope rearrangements afford a low-barrier to competing processes

2-Aza-Cope-Mannich sequence:**Another aza-Cope-Mannich sequence:**

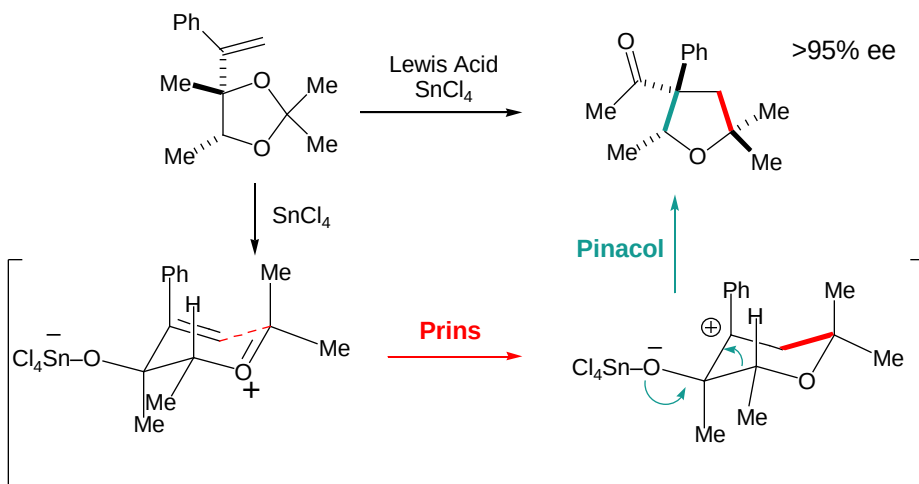
References

Prins reaction: Adams, D.R.; Bhaynagar, S. D. *Synthesis* **1977**, 661.
 Prins & carbonyl ene reactions: Snider, *Comprehensive Organic Synthesis*, **1991**, Vol. 2

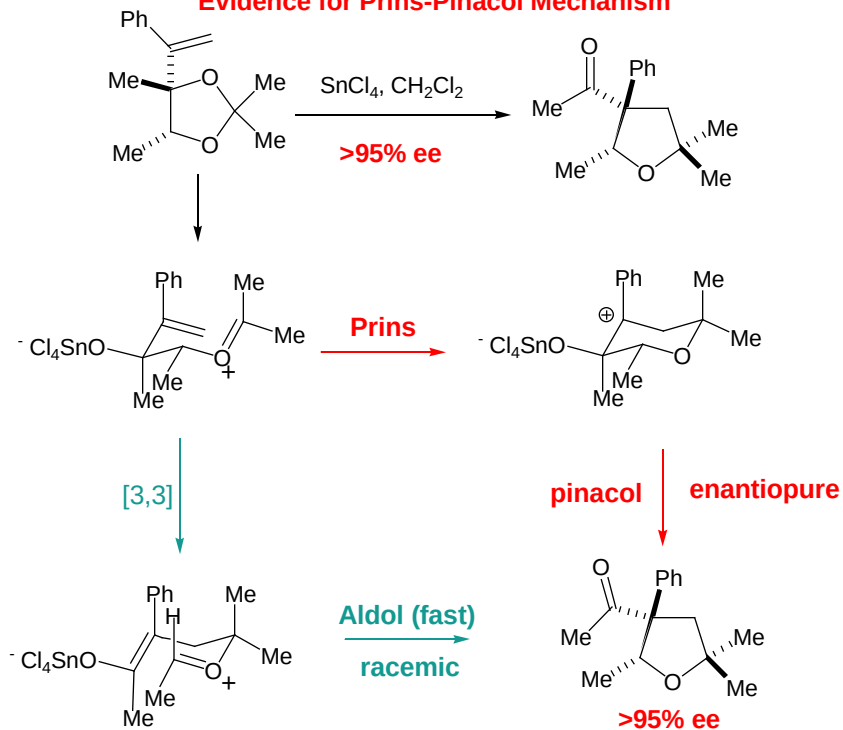
The Prins Process:



The Prins-Pinacol Variant:

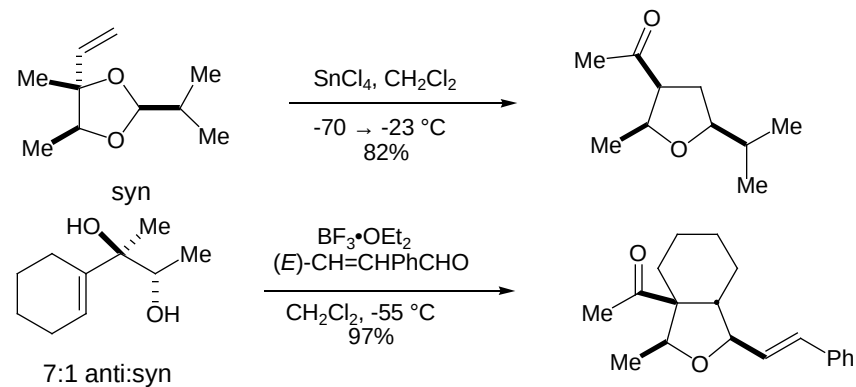


Evidence for Prins-Pinacol Mechanism

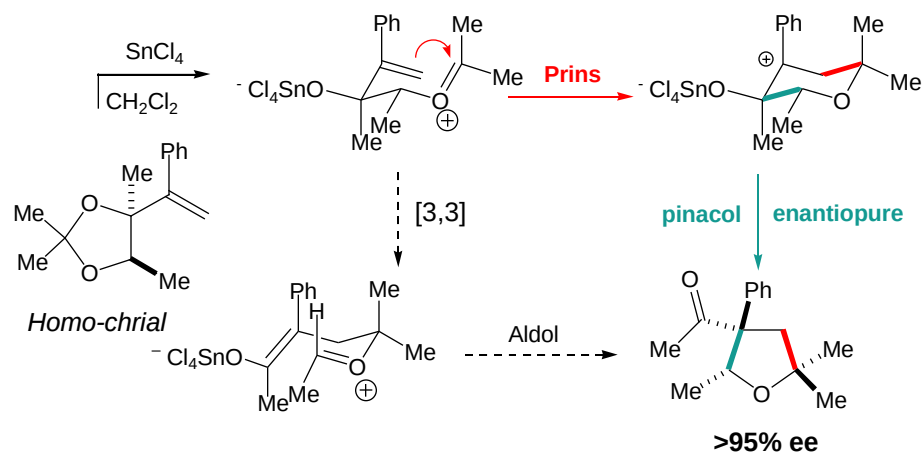


If a [3,3] rearrangement were intervening, the product would be racemic.
 Overman, *JACS* **2000**, 122, 8672
 Overman, *Org Lett* **2001**, 3, 1225

Examples of Stereoselective THF Formation



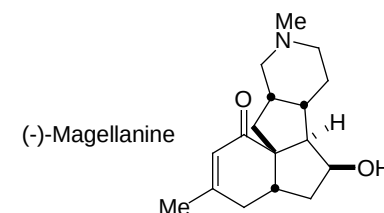
Prins-Pinacol Mechanism



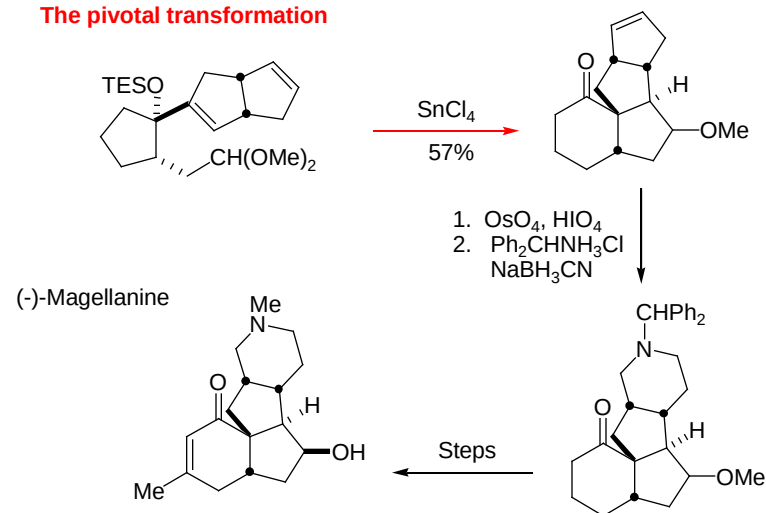
Prins cyclization faster than [3,3] rearrangement

Overman: Magellanine Synthesis

JACS, 1993, 115, 2992

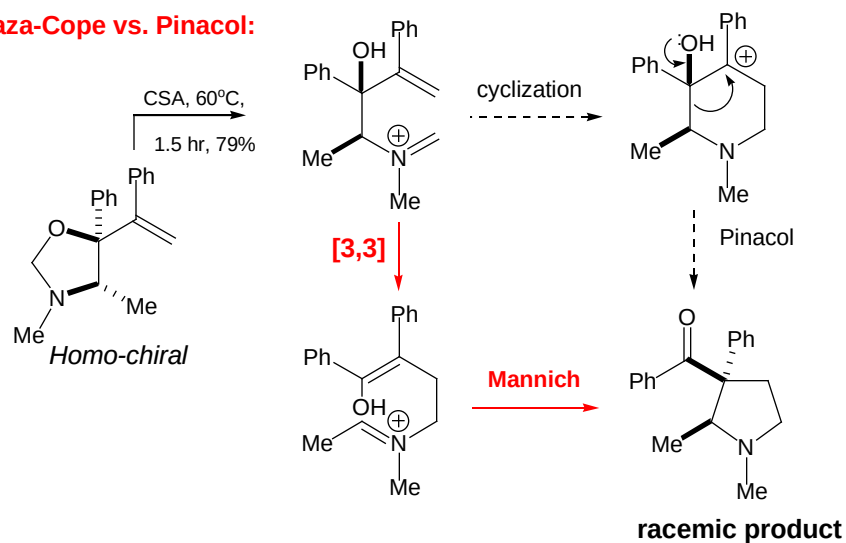


The pivotal transformation

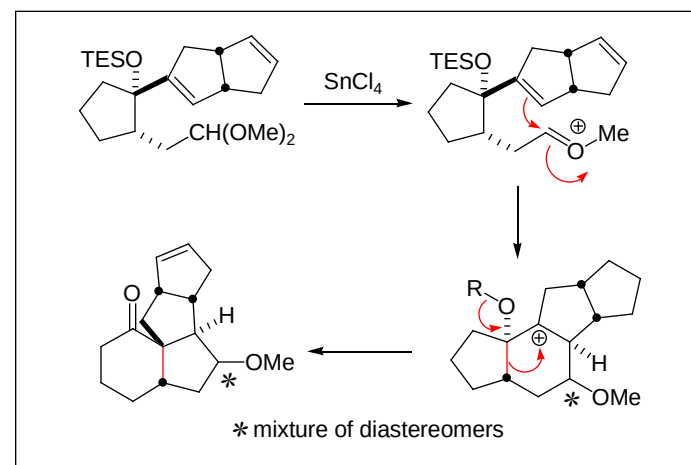


(-)-Magellanine

2-aza-Cope vs. Pinacol:



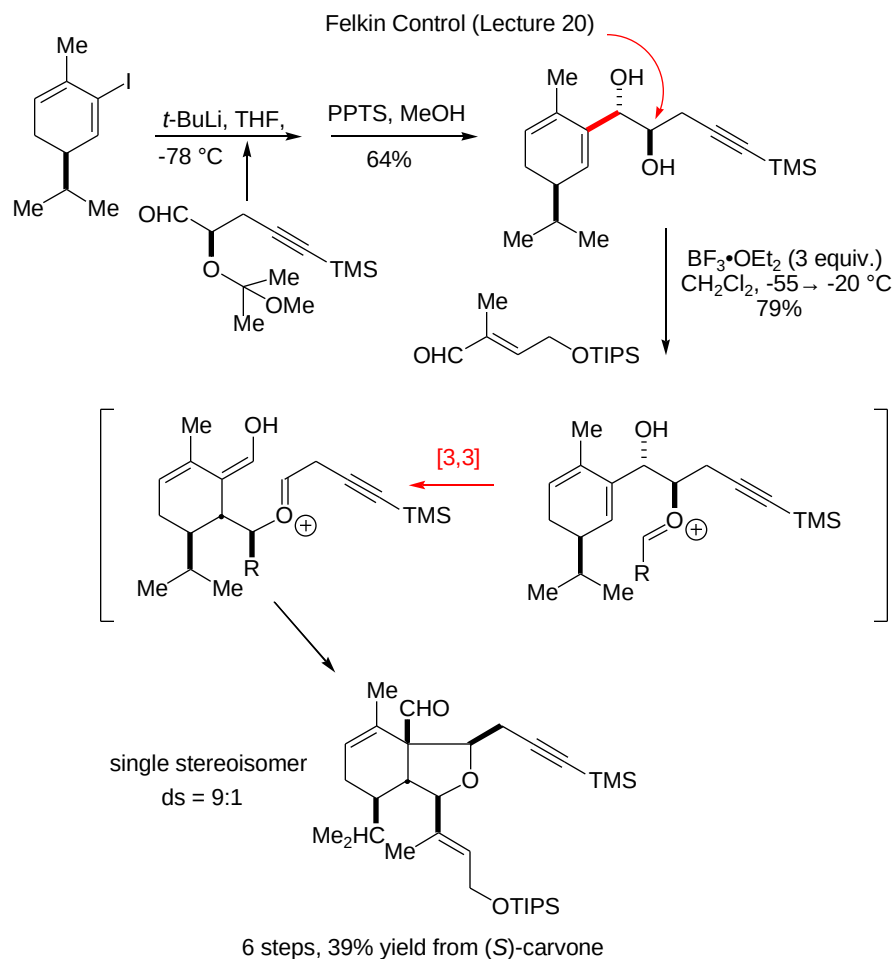
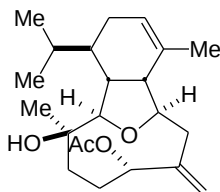
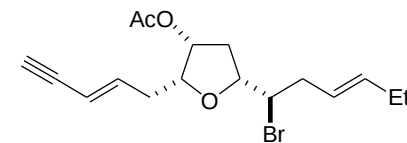
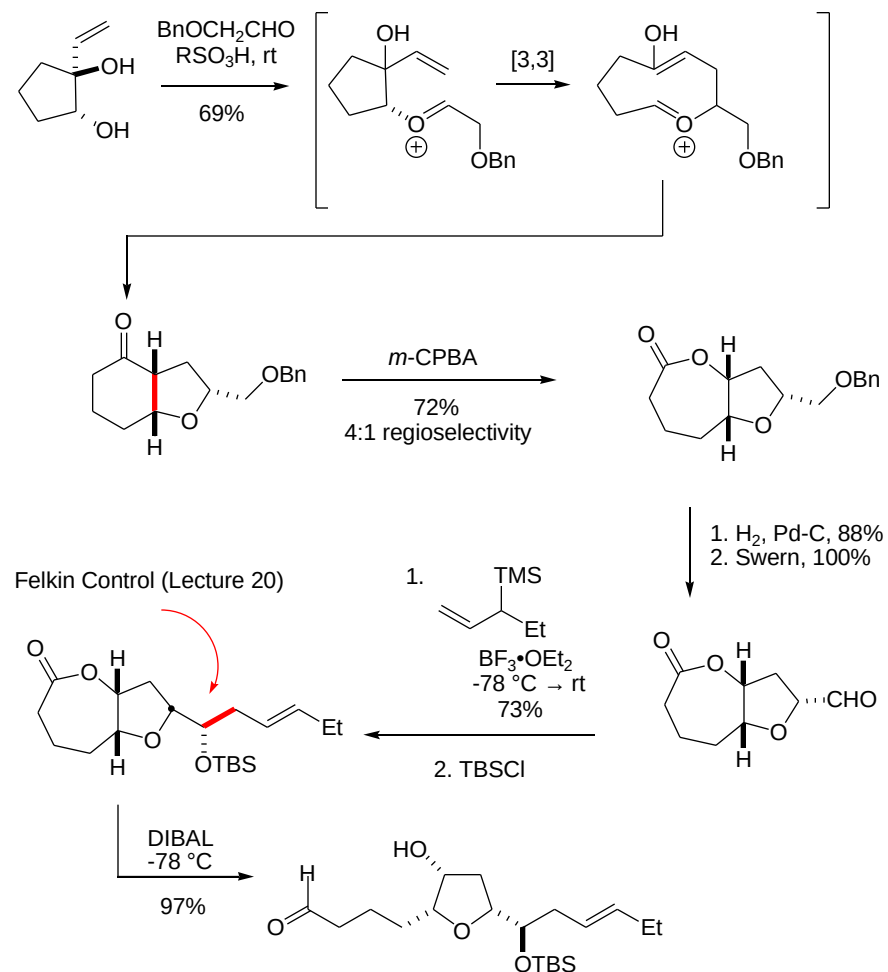
[3,3] rearrangement faster than Mannich cyclization



Overman Synthesis of a Eunicellin Diterpene

Overman & MacMillan JACS, **1995**, 117, 10391

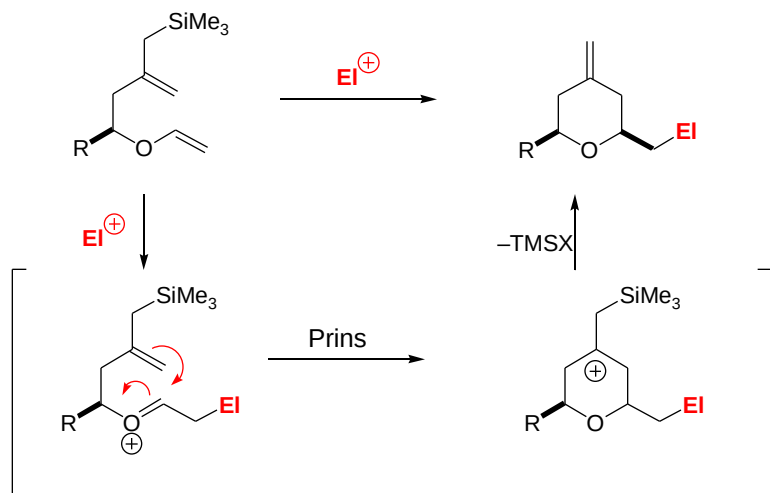
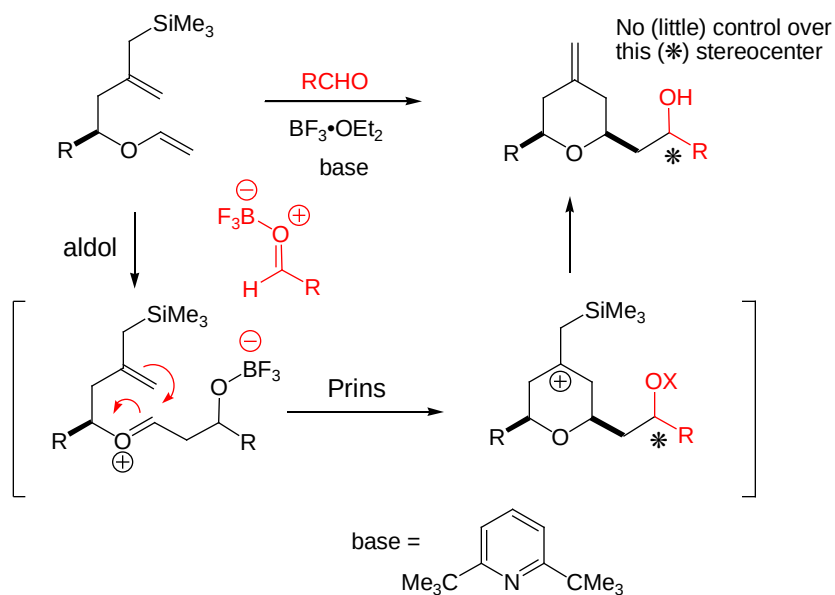
(-)-7-Deacetoxy-alcyoninacetate

Overman: Synthesis of *trans*-KumausyneJACS, **1991**, 113, 5378*trans*-Kumausyne

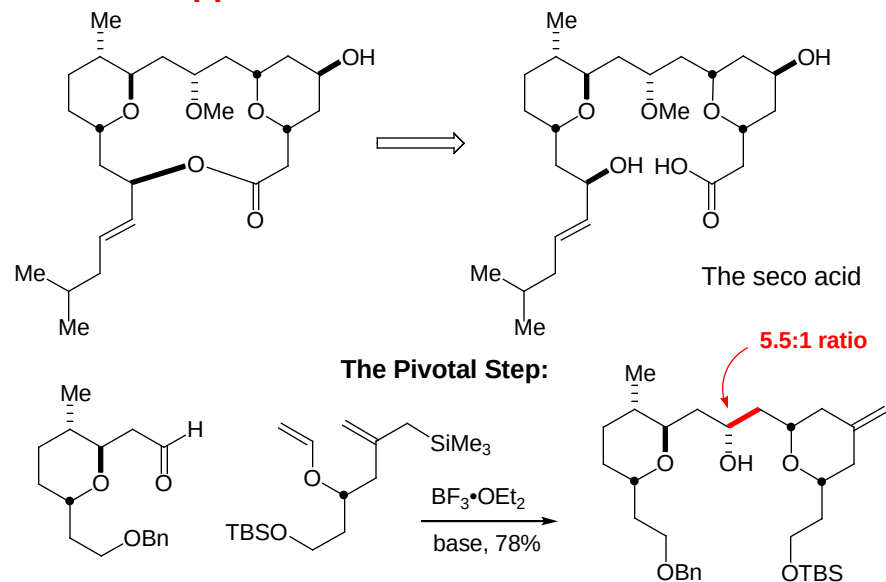
Mukaiyama Aldol-Prins Cascade

Rychnovsky JACS, 2001, 123, 8420

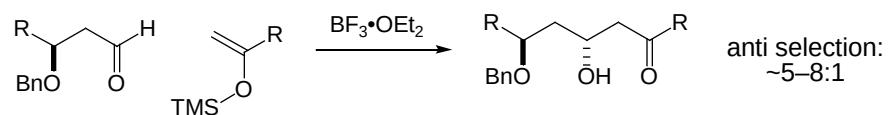
The Basic Process

Let EI^+ = Lewis acid activated RCHO

Application to Leucasandrolide



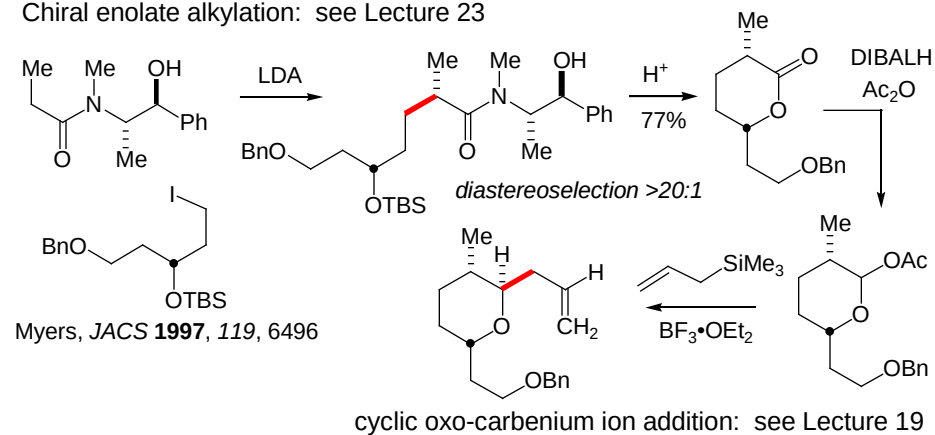
Control of hydroxyl center: see Lecture 20



Evans et al., JACS 1996, 116, 4322

Aldehyde Synthesis

Chiral enolate alkylation: see Lecture 23



<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**

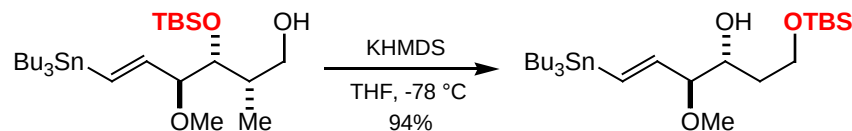
Bois, et al. "Silicon Tethered Reactions" *Chem. Rev.* **1995**, 95, 1253-1277. (**Handout**)

Matthew D. Shair

Wednesday,
December 11, 2002

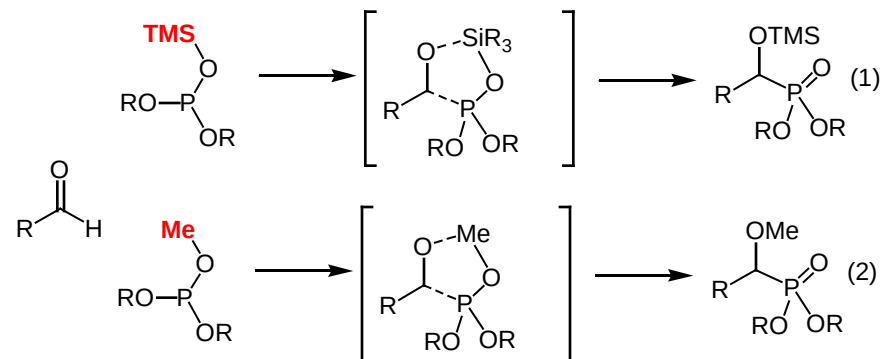
Problems to Contemplate

Explain what drives this rearrangement. TBS =

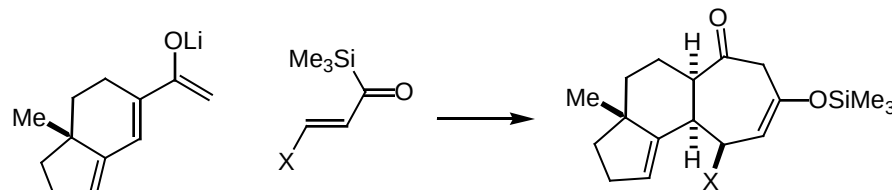


Calter, M. A. Ph. D. Thesis, Harvard University, 1993.

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

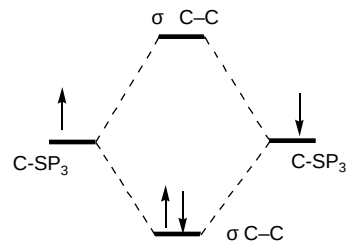
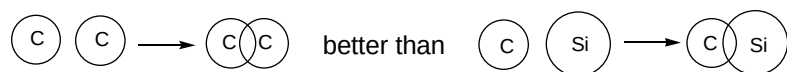
Bonding Considerations: Carbon vs Silicon

Average Bond dissociation energies (Kcal/mol)

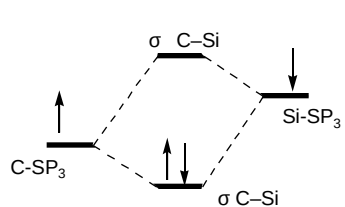
C-C	C-Si	Si-Si	C-F	Si-F	C-O	Si-O
83	76	53	116	135	86	108

Average Bond Lengths (Å)

C-C	C-Si	C-O	Si-O	C-H	Si-H
1.54	1.87	1.43	1.66	83	76



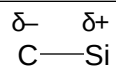
$\text{H}_3\text{C}-\text{CH}_3$ BDE = 83 kcal/mol
Bond length = 1.534 Å



$\text{H}_3\text{C}-\text{SiH}_3$ 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



Group IV Electronegativities (Pauling)

Carbon	Silicon	Germanium	Tin	Lead
2.55	1.90	2.01	1.96	2.33

+2 Oxidation state becomes increasingly more stable $\longrightarrow$

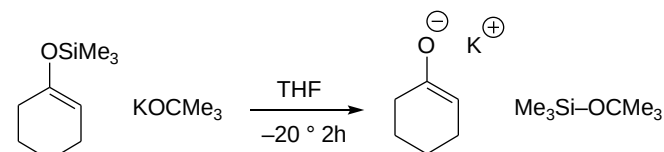
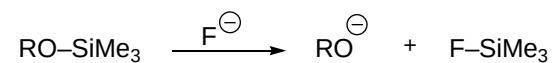
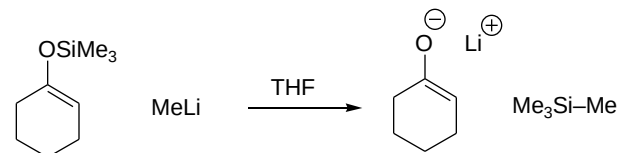
Hypervalent 5-Coordinate Silicon Compounds

Akiba, "Chemistry of hypervalent Compounds" Wiley-VCH, Chapters 4-5, 1999

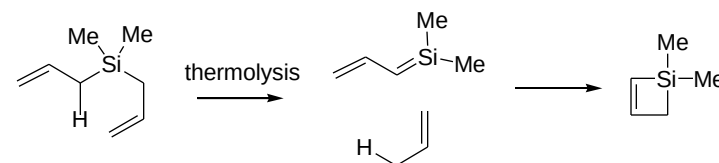
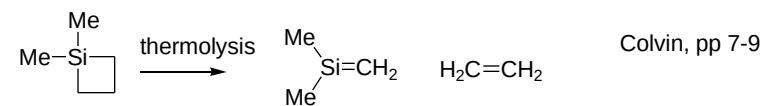
Penta-coordinate silicates are commonly observed

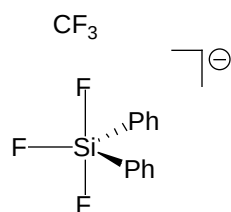
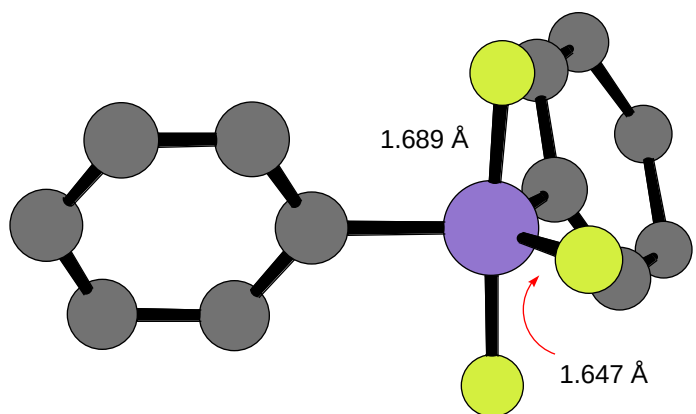


Nucleophilic substitution at Silicon

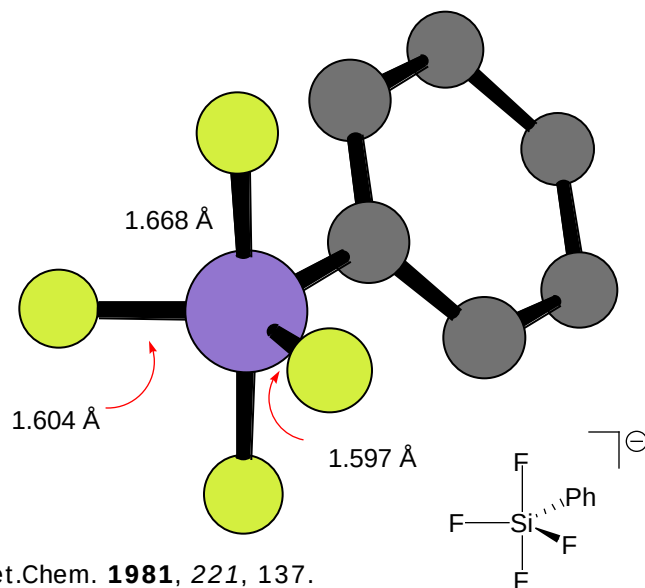
Duhamel et al. *J. Org. Chem.* **1996**, 61, 2232Stork et al. *JACS.* **1968**, 90, 4462, 4464

Thermal Rearrangements One may readily access divalent intermediates

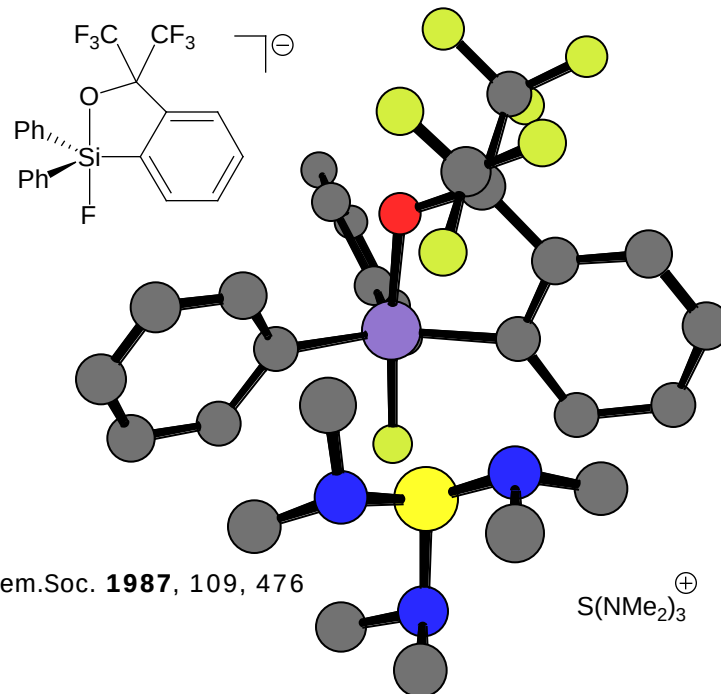
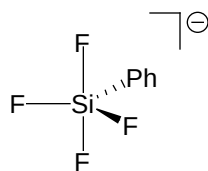




Inorg. Chem. **1984**, 23, 1378

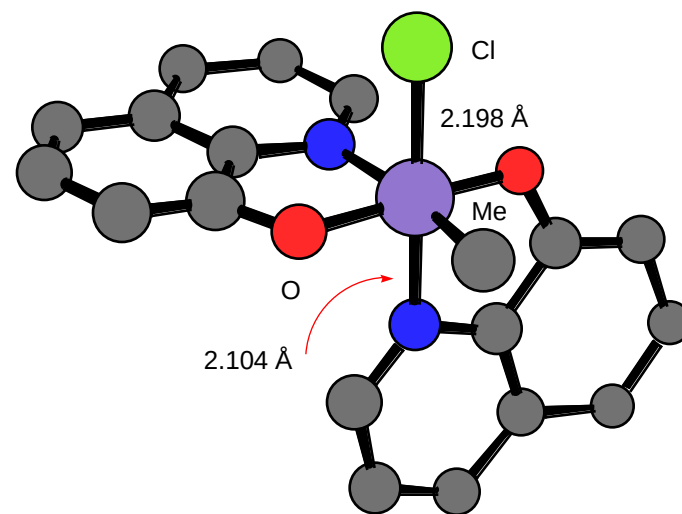


J. Organomet.Chem. **1981**, 221, 137.



J. Am. Chem.Soc. **1987**, 109, 476

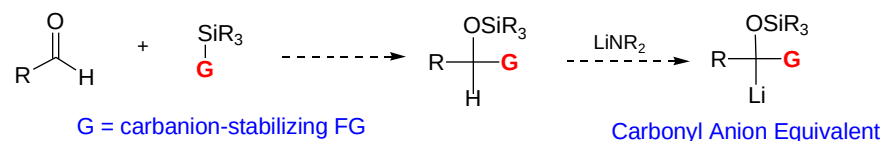
$\text{S}(\text{NMe}_2)_3^+$



Acta Crystallogr. Sect. C **1984**, 40, 476

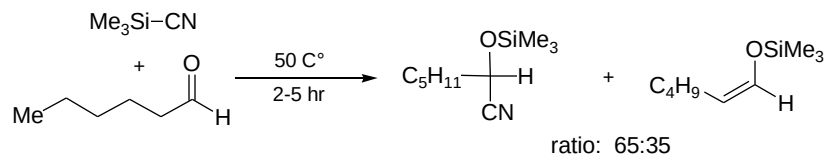
Carbonyl addition Reactions

1970 DAE Objective: Develop a reagent that will transform aldehydes into protected cyanohydrins in one step

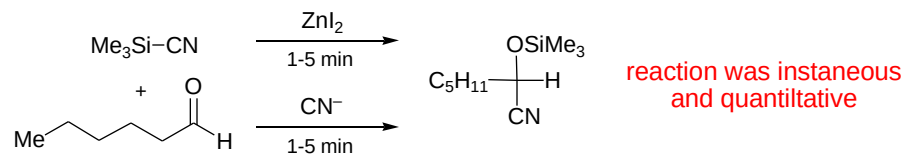


$\text{R}_3\text{Si}-\text{G}$ Candidates	Carbonyl Adducts
$\text{R}_3\text{Si}-\text{CN}$	$ \begin{array}{c} \text{OSiR}_3 \\ \\ \text{R}-\text{C}-\text{CN} \\ \\ \text{H} \end{array} $
$\text{R}_3\text{Si}-\text{OSO}_2\text{Ar}$	$ \begin{array}{c} \text{OSiR}_3 \\ \\ \text{R}-\text{C}-\text{SO}_2\text{Ar} \\ \\ \text{H} \end{array} $
$\text{R}_3\text{Si}-\text{OPR}_2$	$ \begin{array}{c} \text{OSiR}_3 \\ \\ \text{R}-\text{C}-\text{POR}_2 \\ \\ \text{H} \end{array} $

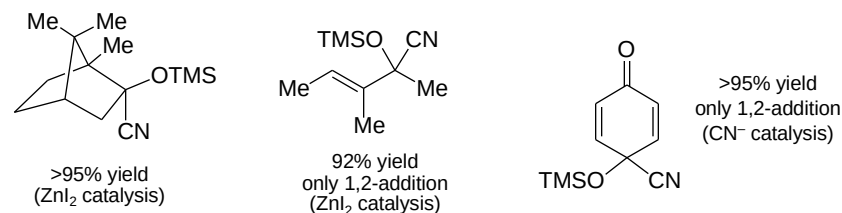
Thermal C=O addition of TMS-CN is not a clean reaction



The prospect of catalysis was investigated



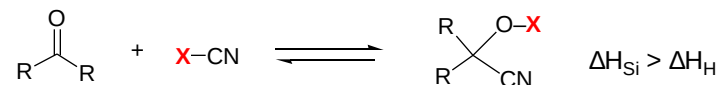
Principle established that normally inaccessible cyanohydrin derivatives may now be accessed



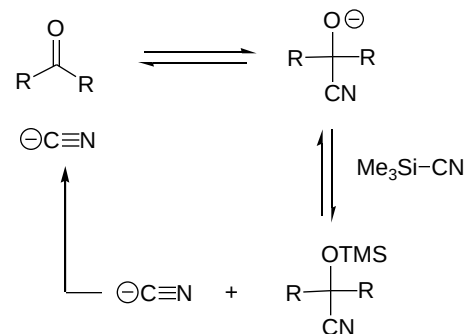
with Truesdale, Carroll, *Chem Commun.* **1973**, 55; *J. Org. Chem.* **1974**, 39, 914
Tetrahedron Lett **1973**, 4929 (first discussion of Nu catalysis)

"The Silicon Advantage"

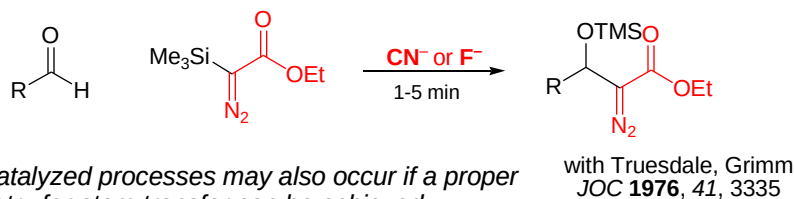
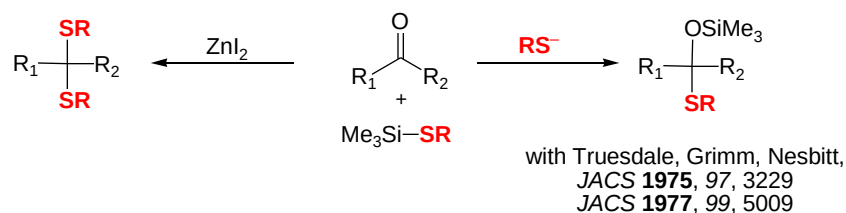
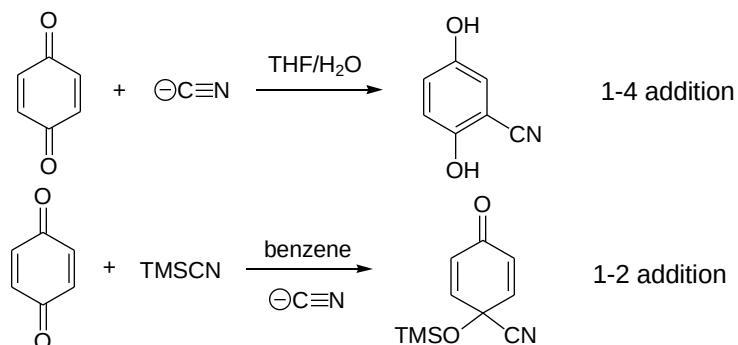
From the preceding case, it is clear that ΔH_{Si} is more exothermic than ΔH_{H}



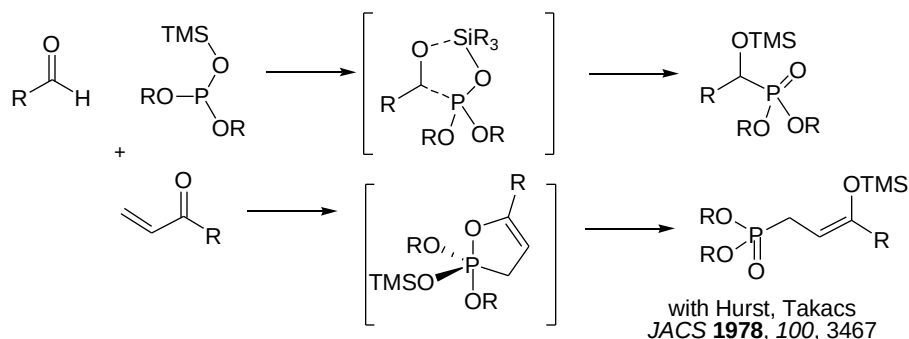
Nucleophilic Catalysis



Explain the following observations

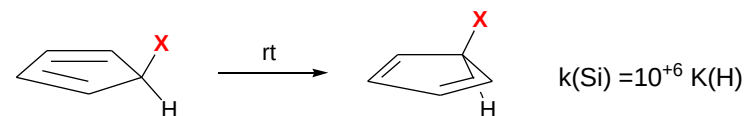


Non-catalyzed processes may also occur if a proper geometry for atom transfer can be achieved

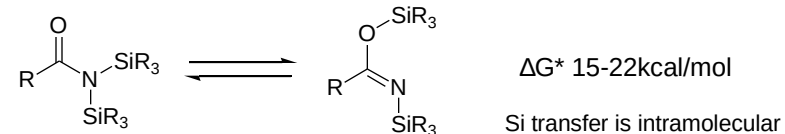
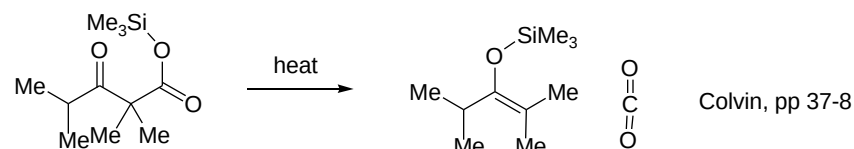


"The Proton-Silicon Correlation"

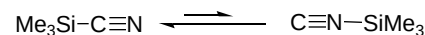
- Organosilanes undergo carbonyl addition processes in direct analogy with their proton counterparts but with an attendant greater exothermicity.
- Organosilanes undergo a range of thermal rearrangements processes in direct analogy with their proton counterparts.



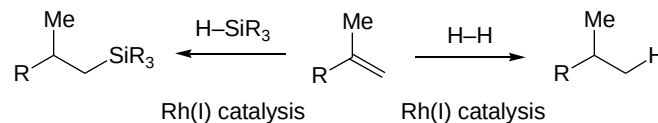
A. J. Ashe III, JACS **1970**, 92, 1233



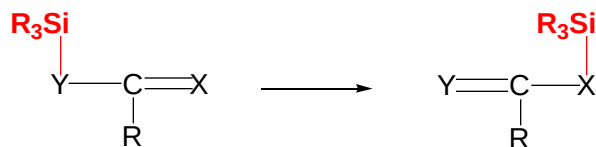
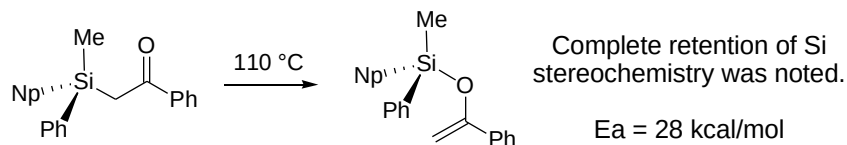
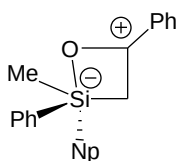
Yoder et al., JACS **1974**, 96, 4283



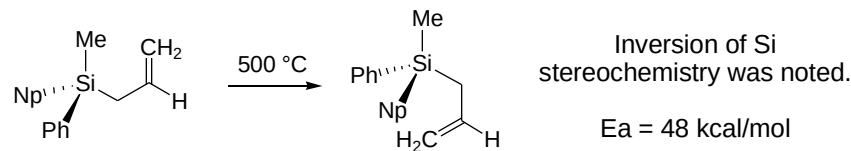
- Organosilicon hydrides undergo transition metal catalyzed hydrosilylation processes in direct analogy with normal hydrogenation reactions



"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**A. G. Brook Accts. Chem. Research **1974**, 7, 77-84

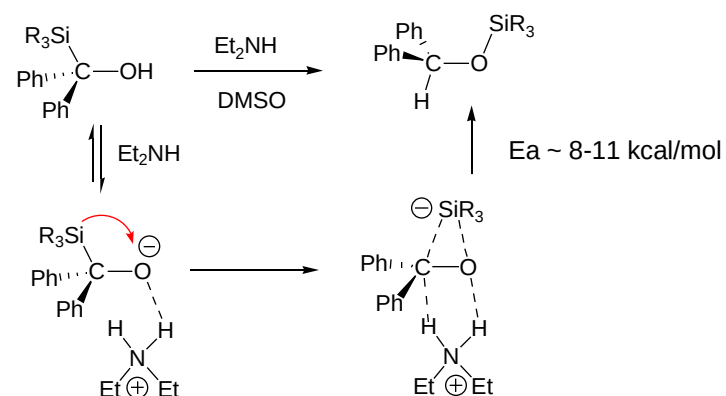
Brook speculates that a hypervalent Si intermediate might be involved in the rearrangement.

Y = C; X = CH. 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

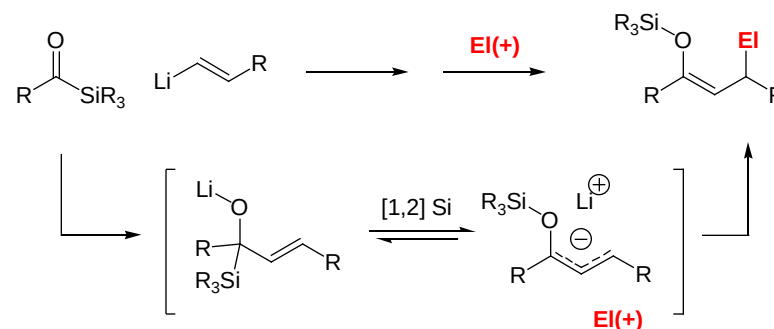
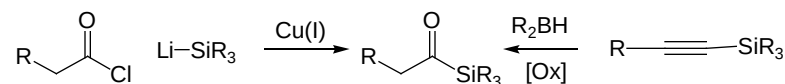
At the present time these rearrangements are not well studied,

"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.

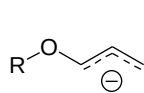
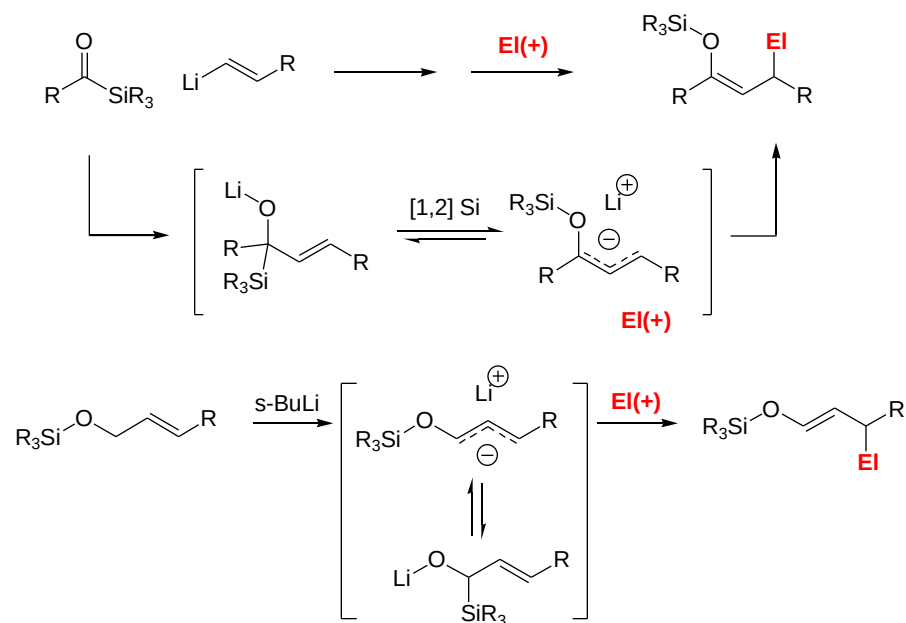
Transformations Involving the Brook Rearrangement

Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, 57, 2065-2084

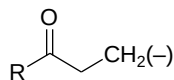
Acylsilanes

Transformations Involving the Brook Rearrangement

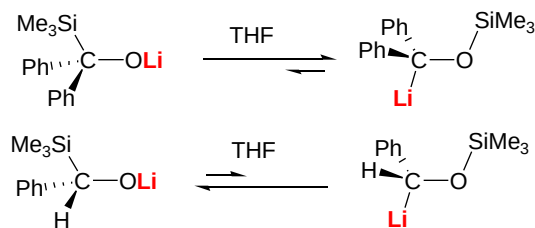
Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, 57, 2065-2084



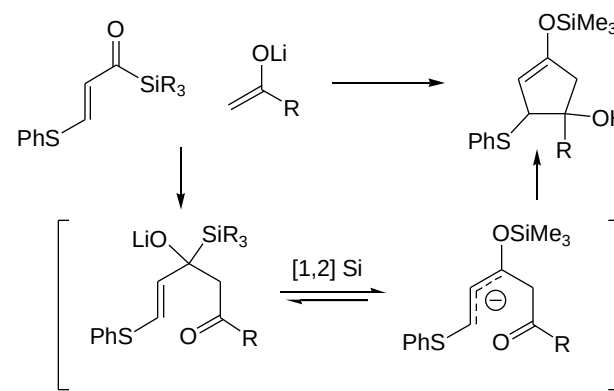
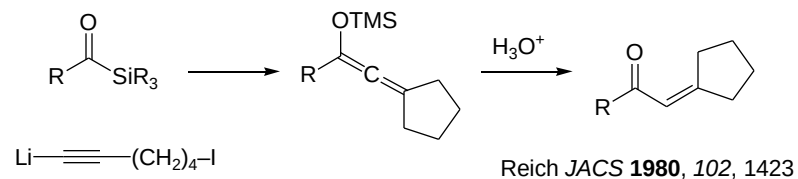
These reagents are useful
homoenolate anion equivalents



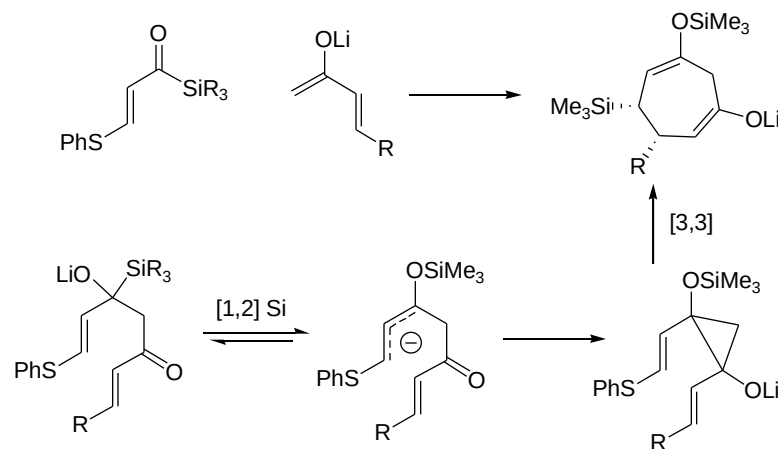
"Metalated Allylic Ethers as Homoenolate Anion Equivalents".
Evans, D. A.; Andrews, G. C.; Buckwalter, B. *JACS* **1974**, 96, 5560.
Si-Variant: Still & MacDonald *JACS* **1974**, 96, 5561

Brook Equilibrium Reich *JACS* **1980**, 102, 1423 (see footnote 8)

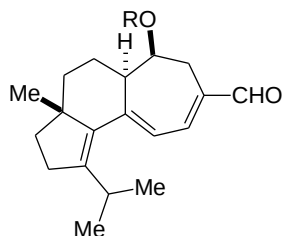
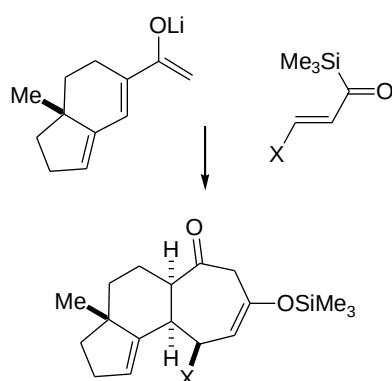
Intramolecular alkylations may be carried out:



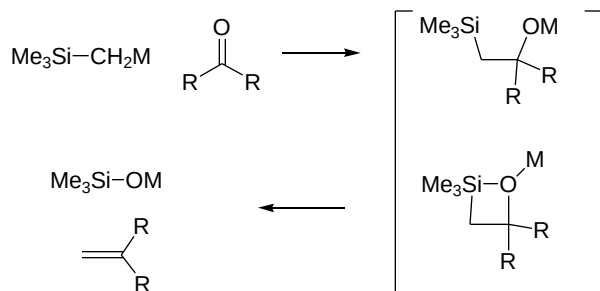
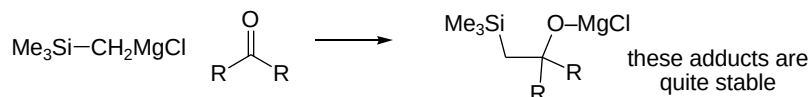
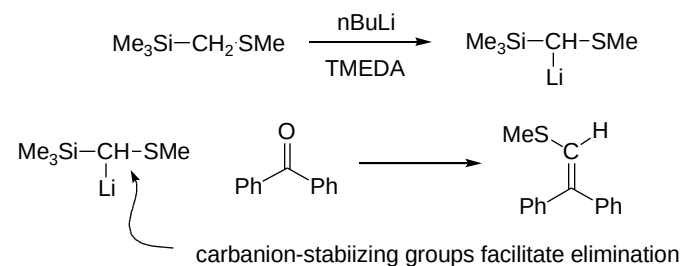
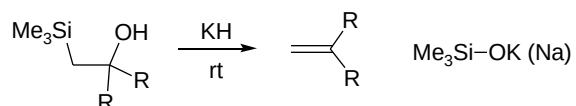
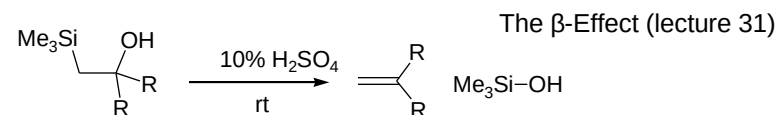
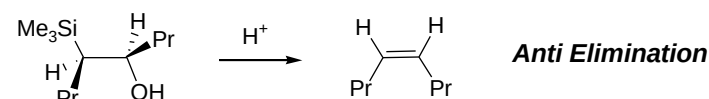
Takeda *JACS* **1993**, 115, 9351; *Synlett* **1994**, 178; *SynLett* **1997**, 255



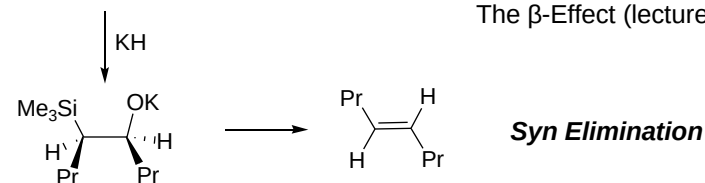
Tetrahedron **2001**, 57, 2065-2084, footnote 16

The natural product target:Takeda, *Org. Lett.*, **2000**, 2, 903-1905**The key reaction****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, 780-784It was Peterson's intent to find a silicon analog to the Wittig rxn.
The reaction concept is outlined below:

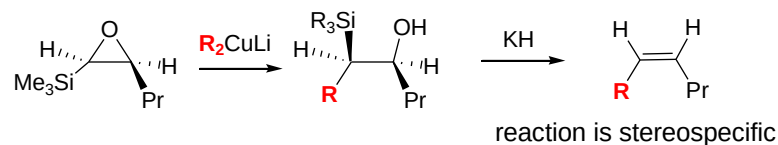
C	N
Si	P

**Magnesium alkoxides: Stable****Na & K alkoxides: Eliminate****Elimination could also be effected with dilute acid**analogy provided by Whitmore et al. *JACS* **1947**, 69, 1551**Mechanistic aspects of Beta-OH Elimination**

The β-Effect (lecture 31)

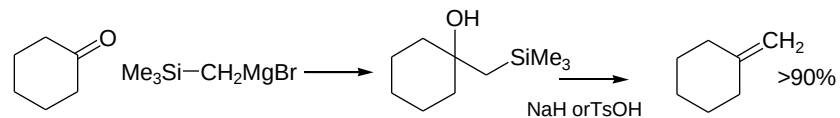
Hudrlik et al. *JACS* **1975**, 97, 1464

Colvin chapter 12, pp 141

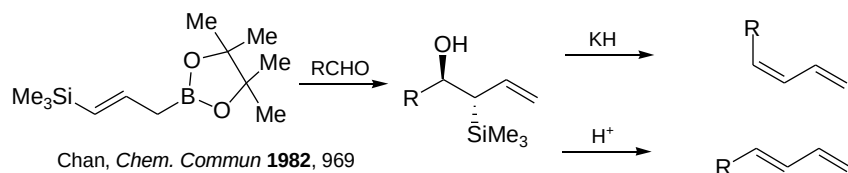
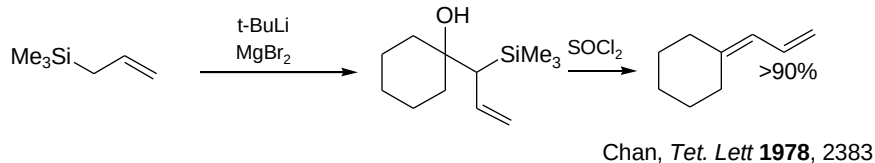
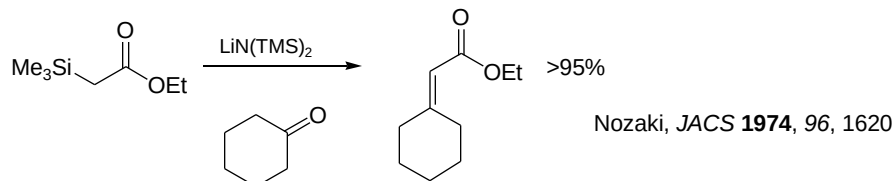
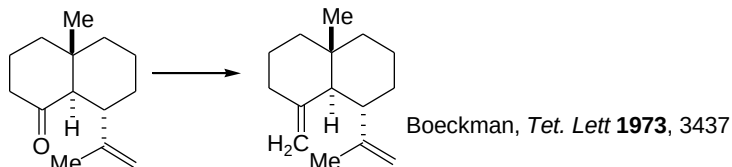


note site of nu attack. Why?

■ Simple Examples: Taken from Organic Rxns review

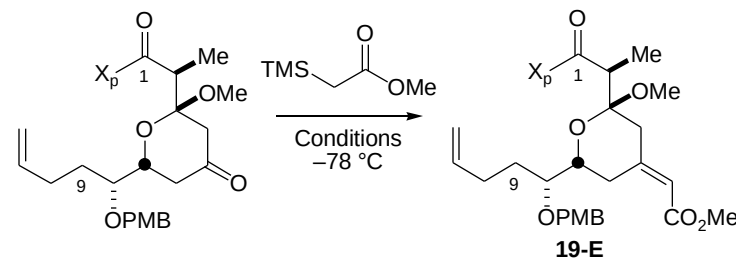
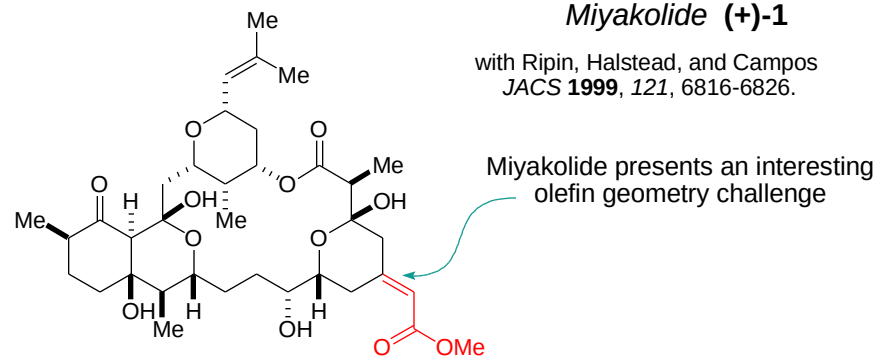


This reagent is better than $\text{H}_2\text{C}=\text{PPh}_3$ for hindered ketones

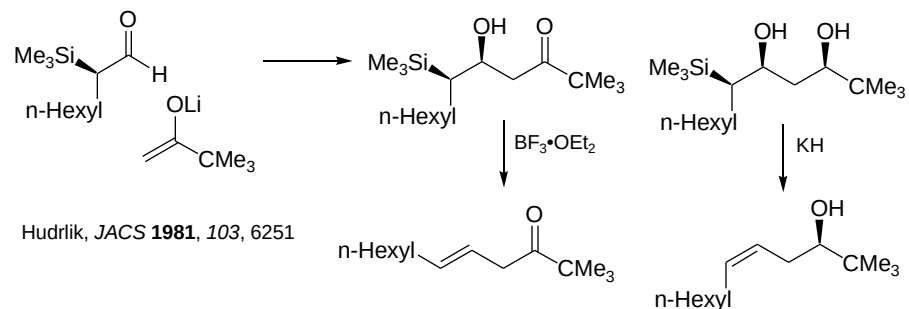


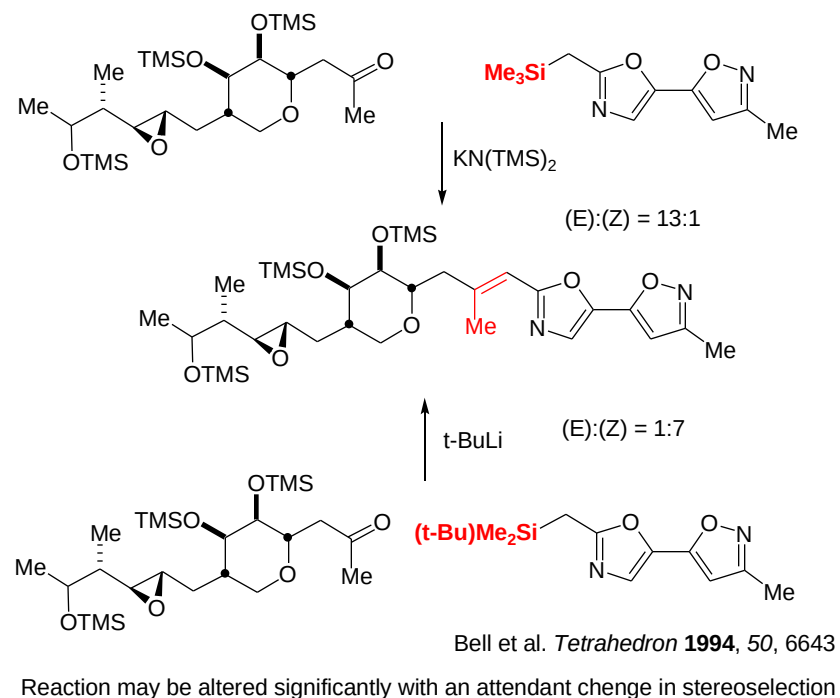
Miyakolide (+)-1

with Ripin, Halstead, and Campos
JACS **1999**, 121, 6816-6826.

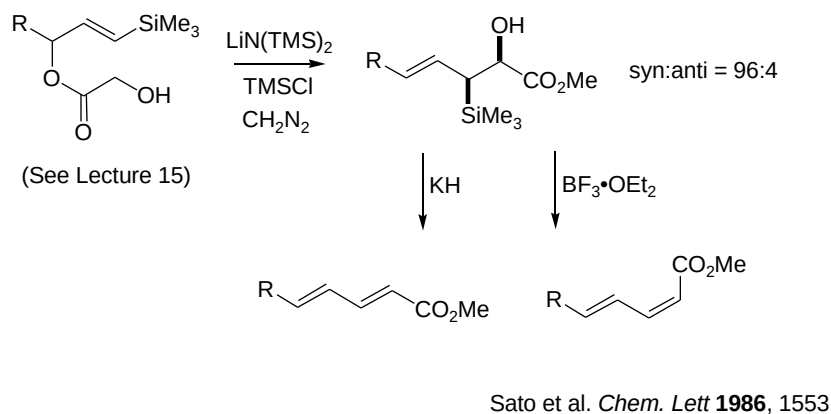


entry	base	solvent	E : Z
1	LDA	THF	73 : 27
2	NaHMDS	THF	18 : 82
3	LDA	Et ₂ O	66 : 33
4	LDA	PhMe	66 : 33

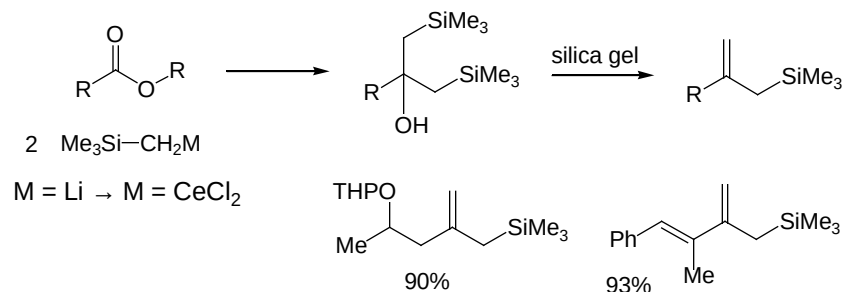
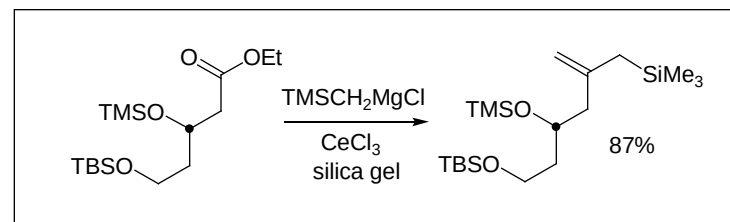
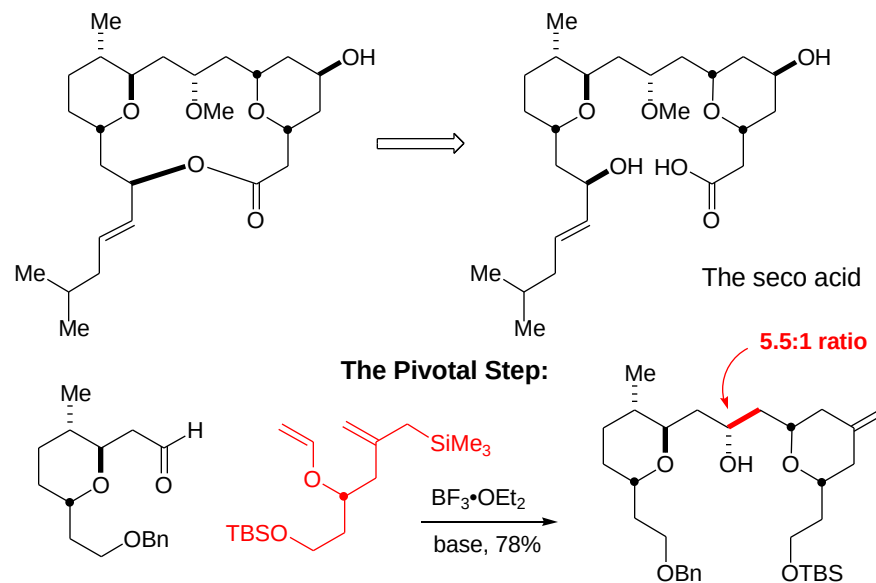




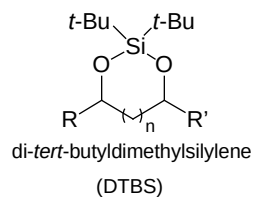
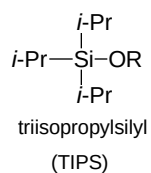
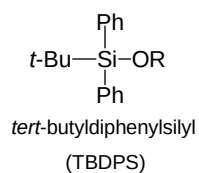
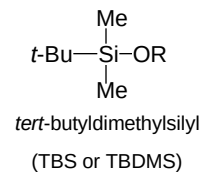
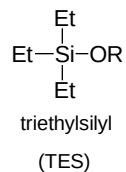
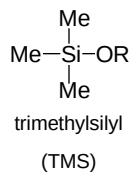
Ireland Enolate Claisen Coupled to Peterson Olefination



Bunnelle-Peterson Allylsilane Synthesis

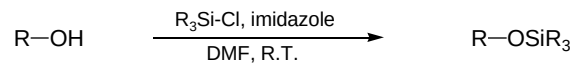
Application to Leucasandrolide: Rychnovsky JACS, **2001**, 123, 8420

Silyl Ethers:



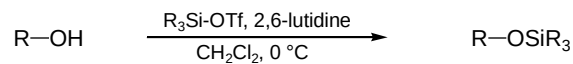
Formation:

By far the two most common methods:



2 equiv of imidazole are required relative to R_3SiCl .

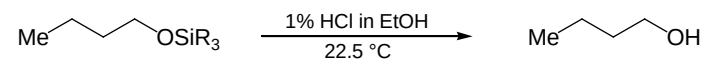
Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, 94, 6190.



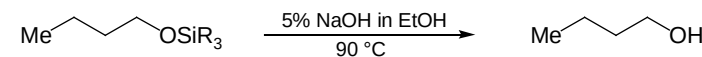
Corey, E. J. et al., *Tetrahedron Lett.* **1981**, 22, 3455.

Relative stabilities:

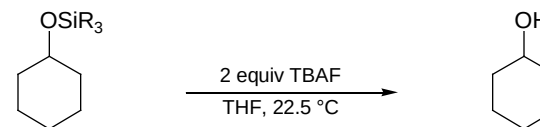
TES $\sim 10^2$ times more stable to acidic hydrolysis than TMS
TBS $\sim 10^4$ times more stable to acidic hydrolysis than TMS



SiR ₃	Half-life
TBS	< 1 min
TIPS	18 min
TBDPS	244 min



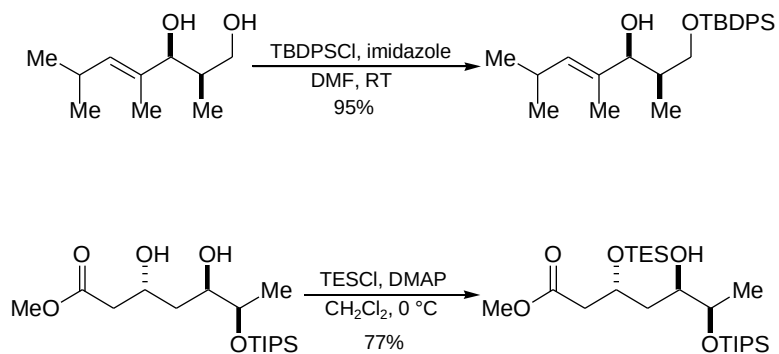
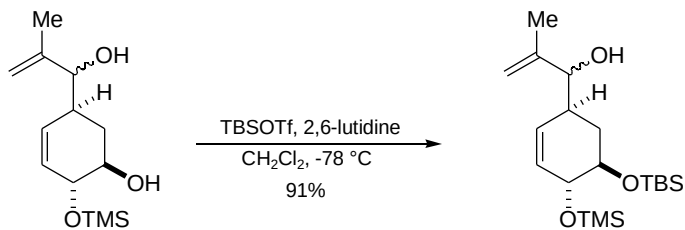
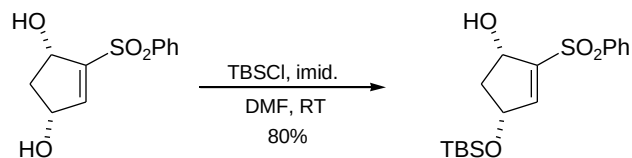
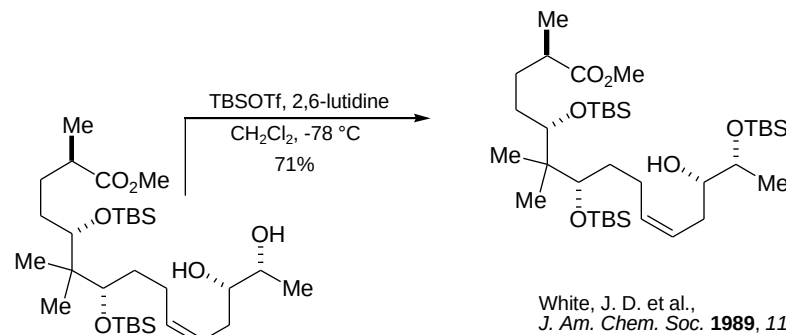
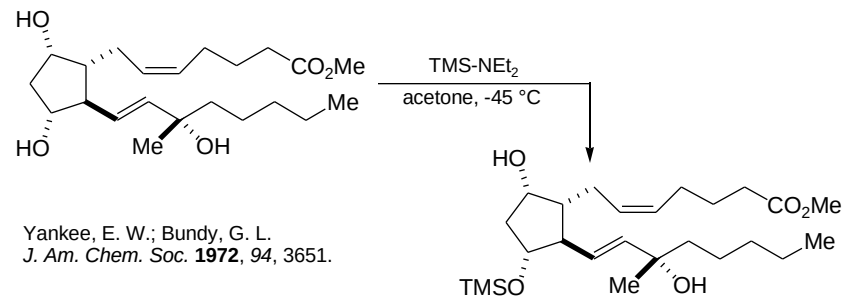
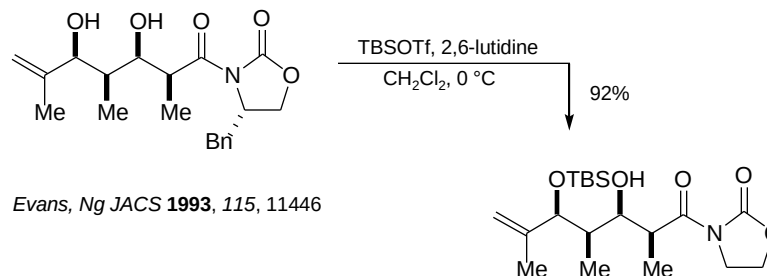
SiR ₃	Half-life
TBS	1 h
TIPS	14 h
TBDPS	< 4 h



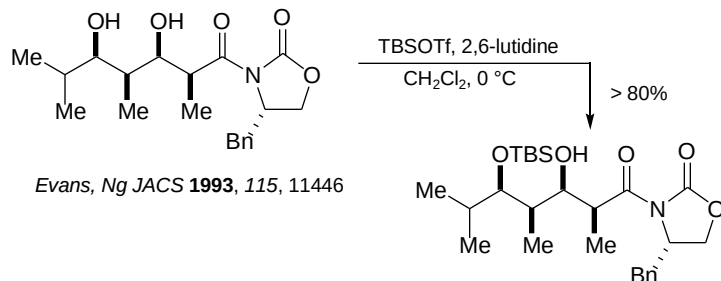
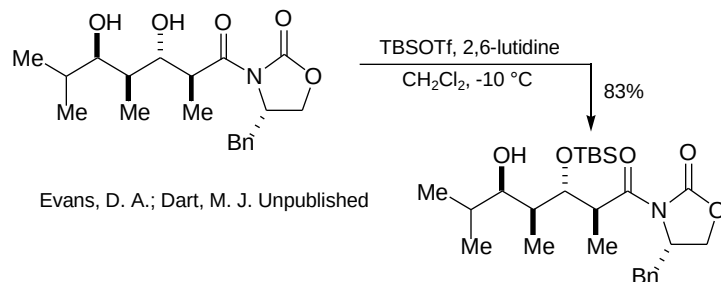
SiR ₃	Half-life
TBS	76 min
TIPS	137 min

Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, 45, 4797-4798.

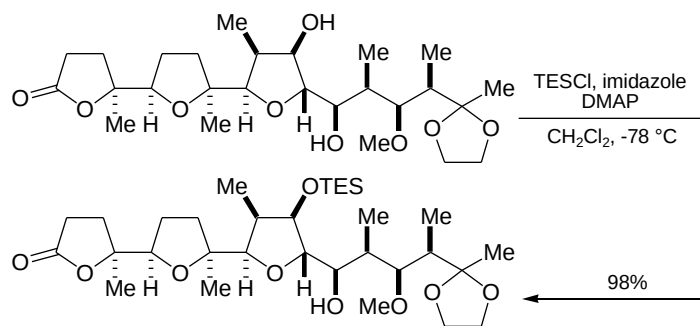
Selective Protection:

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-NEt₂ 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

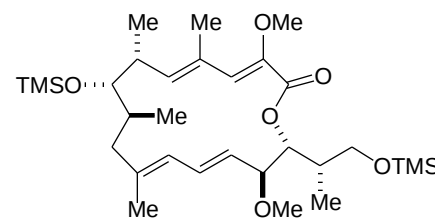
Selective Protection:

Evans, Ng JACS **1993**, 115, 11446

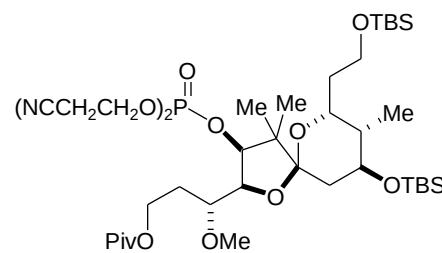
Evans, D. A.; Dart, M. J. Unpublished

Evans, Ratz JACS **1995**, 117, 3448

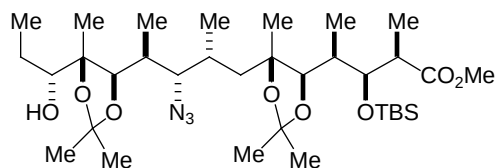
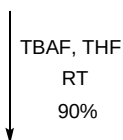
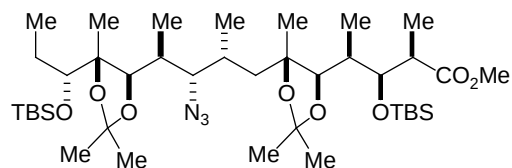
Selective Deprotection:



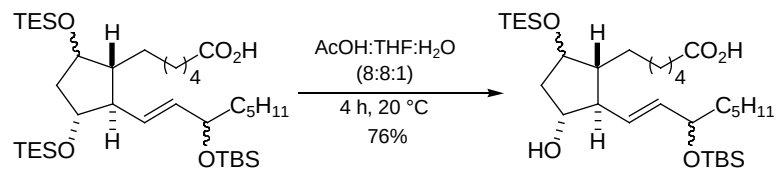
Calter, M. A. Ph. D. Thesis, Harvard University, 1993

Evans, Gage, Leighton JACS **1992**, 114, 9434

Selective Deprotection:

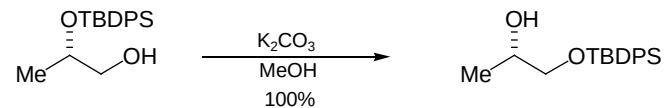


Nakaba, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, 29, 2219, 2223.



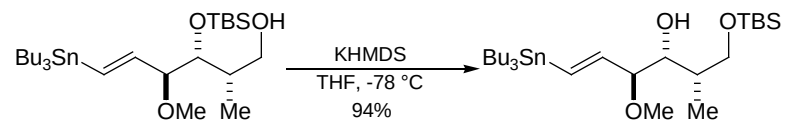
Hart, T. W.; Metcalfe, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156.

1,2-Migration:

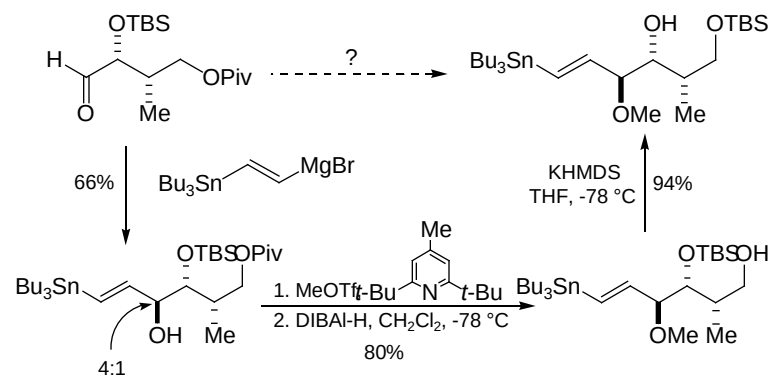


Mulzer, J.; Schollhorn, B. *Angew. Chem., Int. Ed. Eng.* **1990**, 29, 431-432.

1,3-Migration:



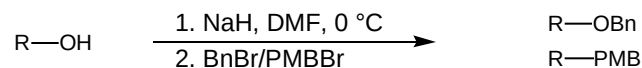
Calter, M. A. Ph. D. Thesis, Harvard University, 1993.



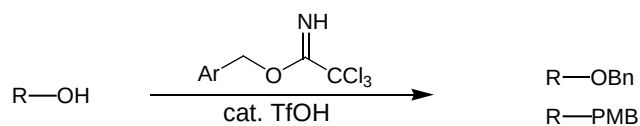
Calter, M. A. Ph. D. Thesis, Harvard University, 1993.

Principle Methods for Benzylation of Alcohols:

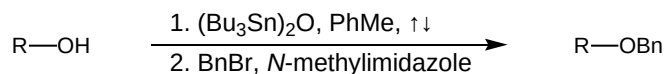
1.



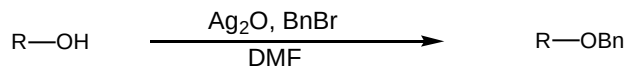
2.

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.

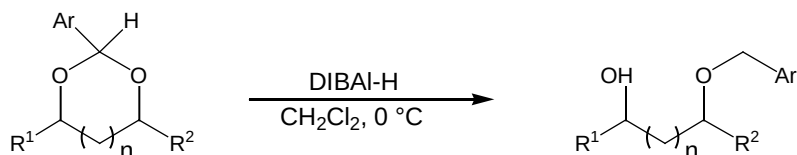
3.

Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *J. Org. Chem.* **1989**, 54, 465.Review: David, S.; Hanessian, S. *Tetrahedron*, **1985**, 41, 643-663.

4.

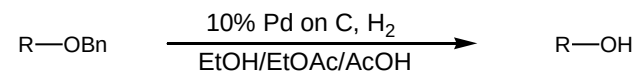
Van Hijfte, L.; Little, R. D. *J. Org. Chem.* **1985**, 50, 3940.

Via Benzyldene Acetal:

Takano, S. et al., *Synthesis* **1986**, 811-817.

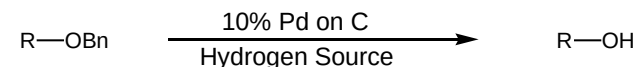
Principle Methods for Deprotection:

1. Hydrogenation



See Greene, p. 49.

2. Transfer Hydrogenation

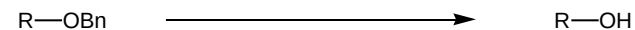


Hydrogen Source

Ref.

Cyclohexene	<i>Synthesis</i> 1981 , 396.
Cyclohexadiene	<i>J. Org. Chem.</i> 1978 , 43, 4194.
HCO_2H	<i>J. Org. Chem.</i> 1979 , 44, 3442.
<i>i</i> -PrOH	<i>Tetrahedron Lett.</i> 1986 , 27, 2497

3. Lewis Acids

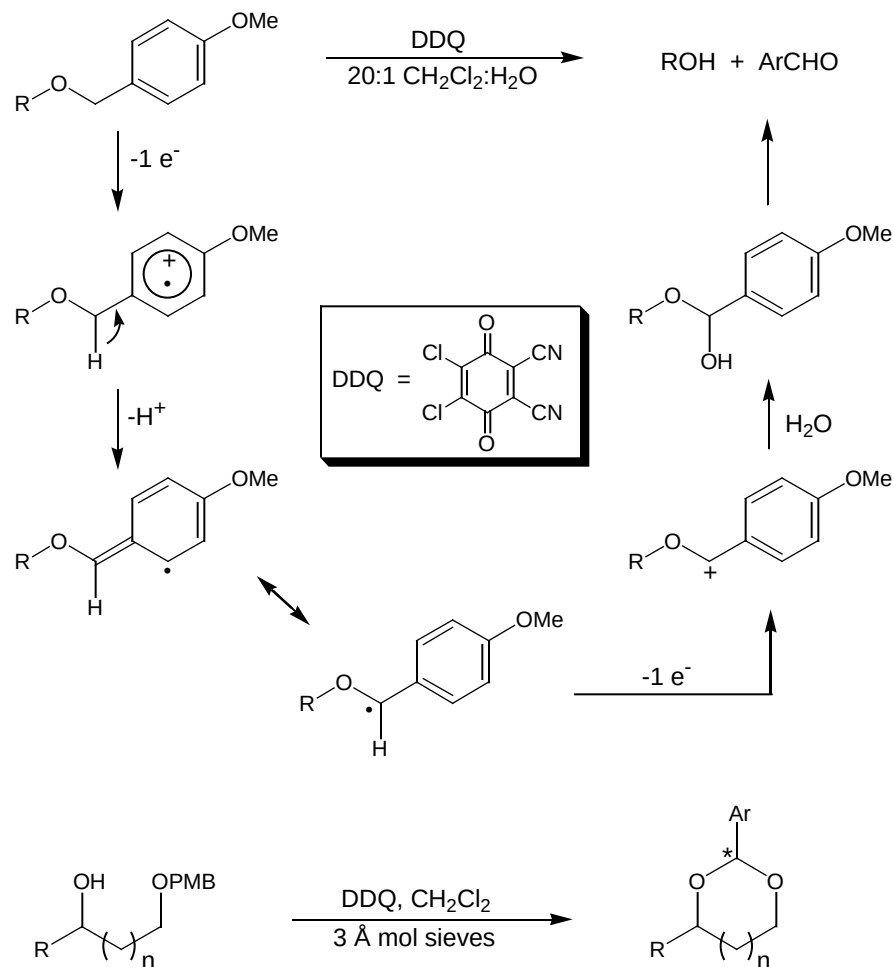


Reagents

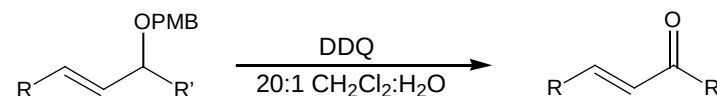
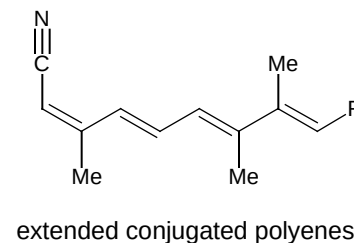
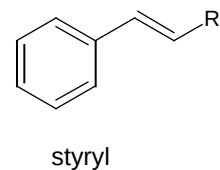
Ref.

$\text{BF}_3 \cdot \text{OEt}_2$, EtSH	<i>Tetrahedron Lett.</i> 1989 , 30, 5713.
1. BCl_3 , -78°C to 0°C . 2. MeOH, -78°C .	<i>J. Am. Chem. Soc.</i> 1989 , 111, 1923.
TMSBr, $\text{C}_6\text{H}_5\text{SMe}$	<i>Chem. Pharm. Bull.</i> 1987 , 35, 3880.

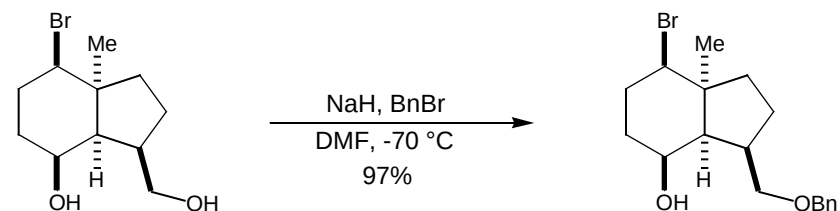
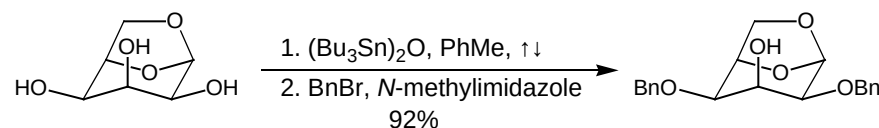
PMB Deprotection:

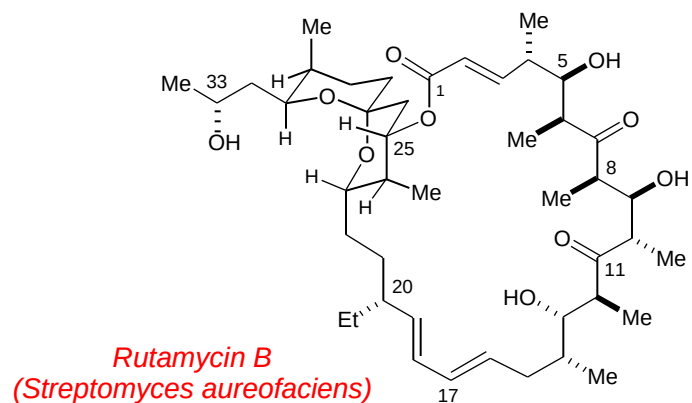
Other Oxidants: NBS, Br₂, CAN ((NH₄)₂Ce(NO₃)₆).*Acta Chem. Scand. Ser. B*, **1984**, B38, 419.*J. Chem. Soc., Perkin Trans. I*, **1984**, 2371.

DDQ is incompatible with:

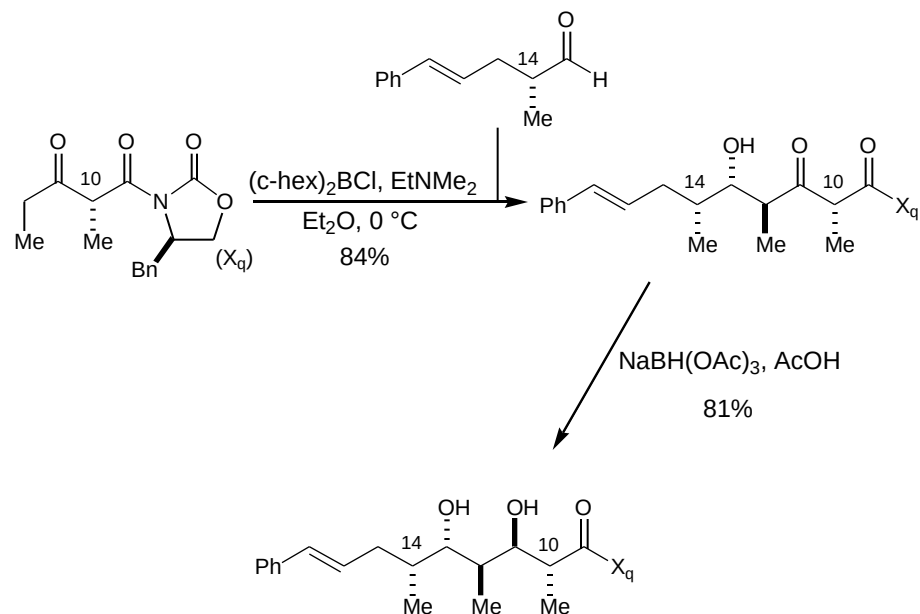
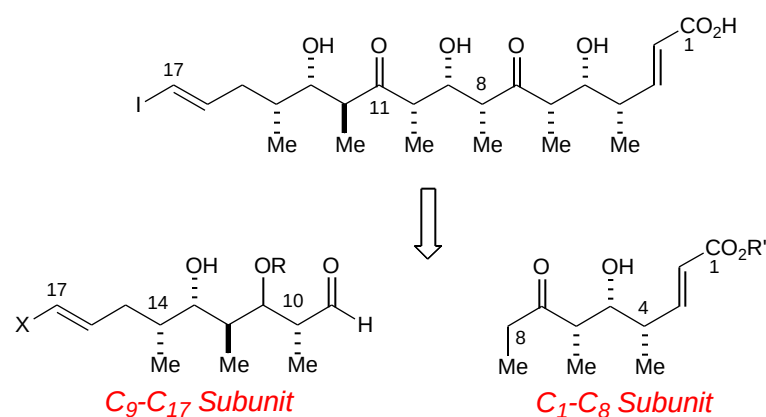
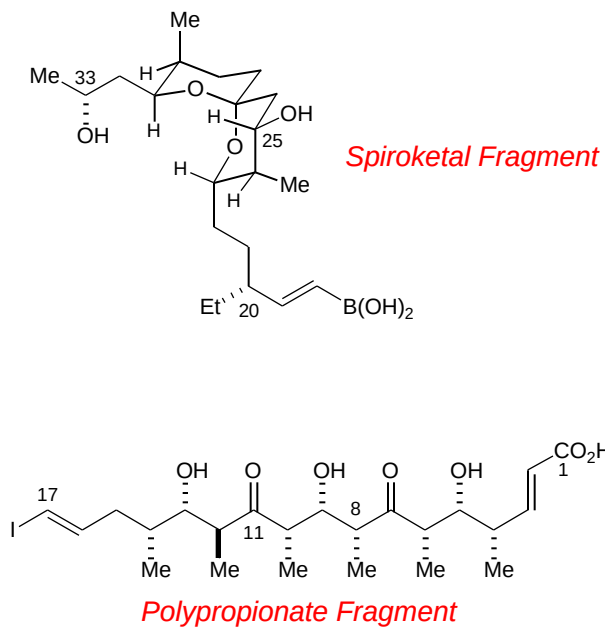


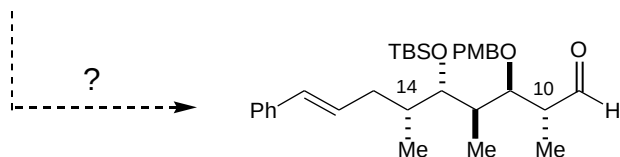
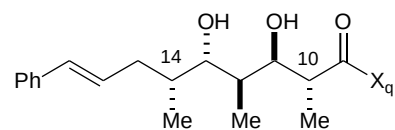
Selective Benzylation:

Fukuzawa, A. et al. *Tetrahedron Lett.* **1987**, 28, 4303.Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *J. Org. Chem.* **1989**, 54, 465.

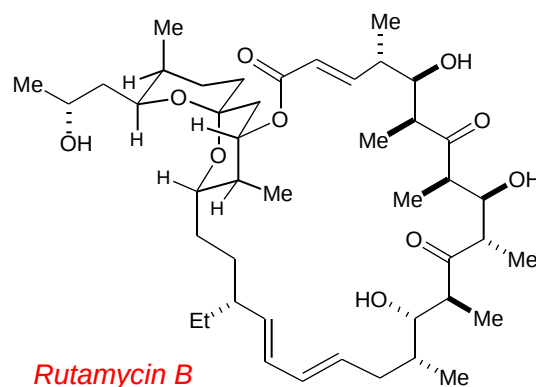
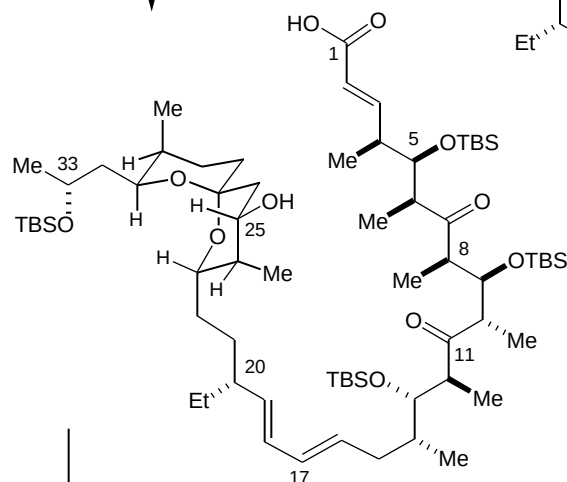
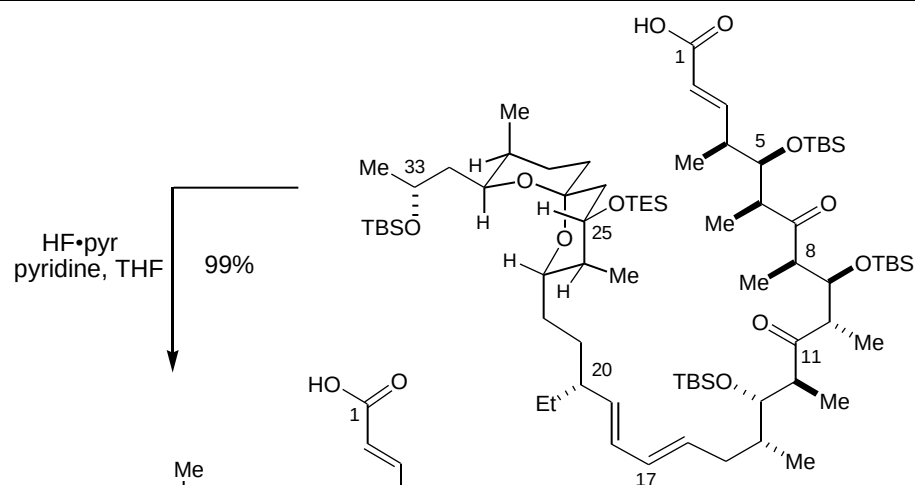
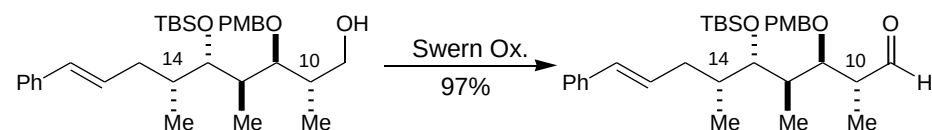
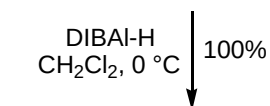
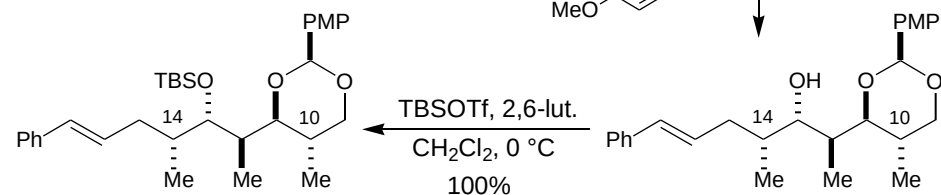
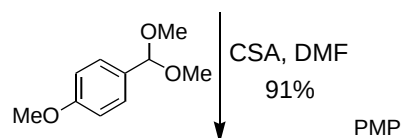
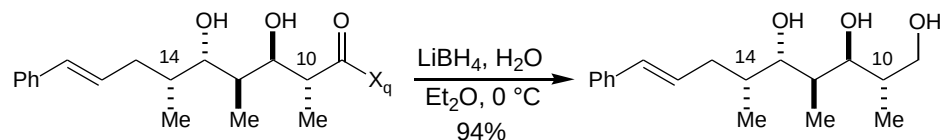


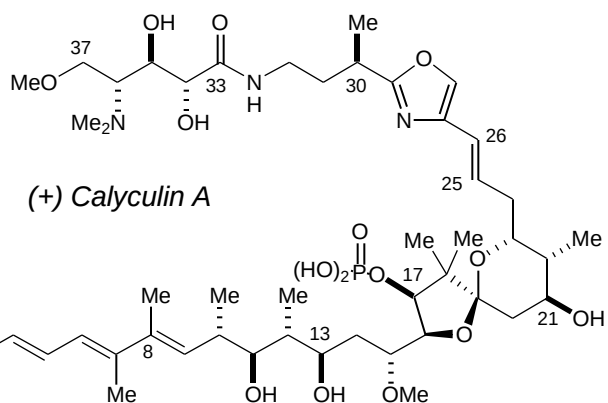
Ng, H. P. Ph. D. Thesis,
Harvard University, 1993





Selective silylation was unsuccessful.

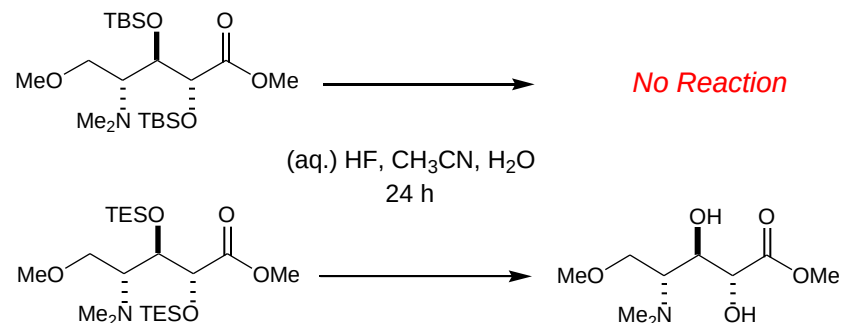
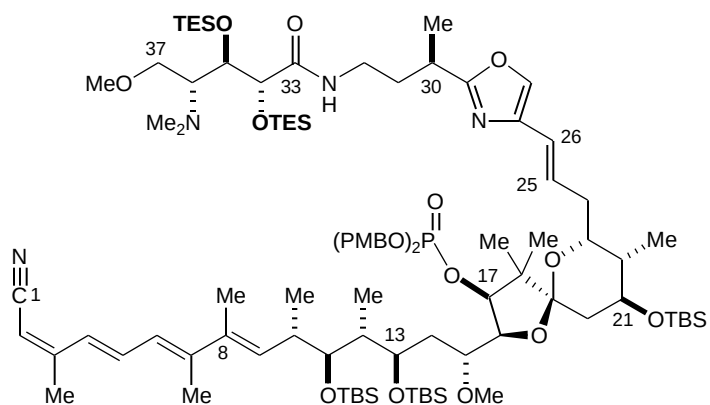




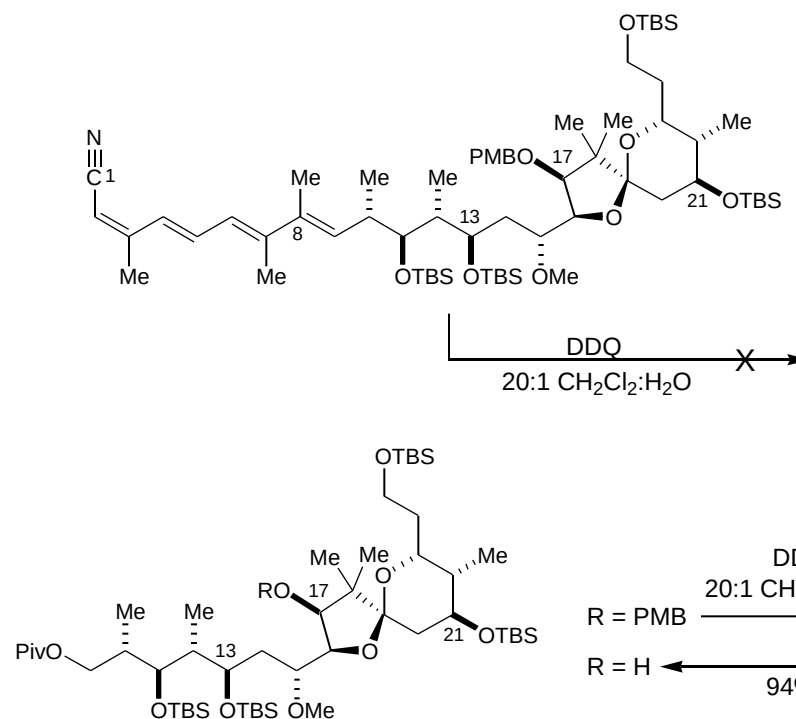
Evans, D. A.; Gage, J. R.; Leighton, J. L.
J. Am. Chem. Soc. **1992**, *114*, 9434-9453.

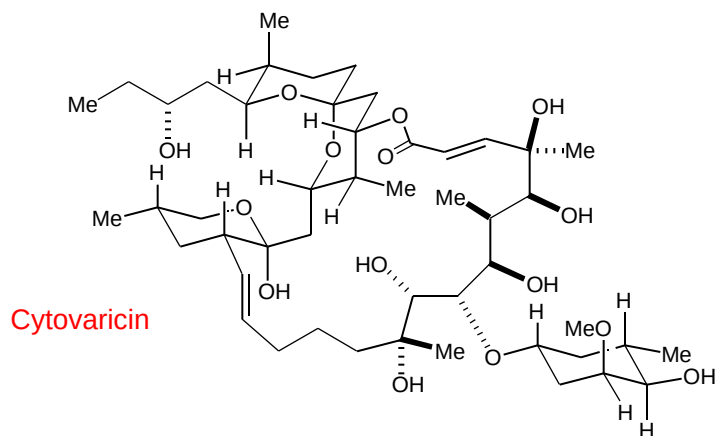
(aq.) HF, CH₃CN, H₂O
 92 h

70%



After protonation of the amine, coulombic repulsion insulates against formation of another cationic site in the vicinity.

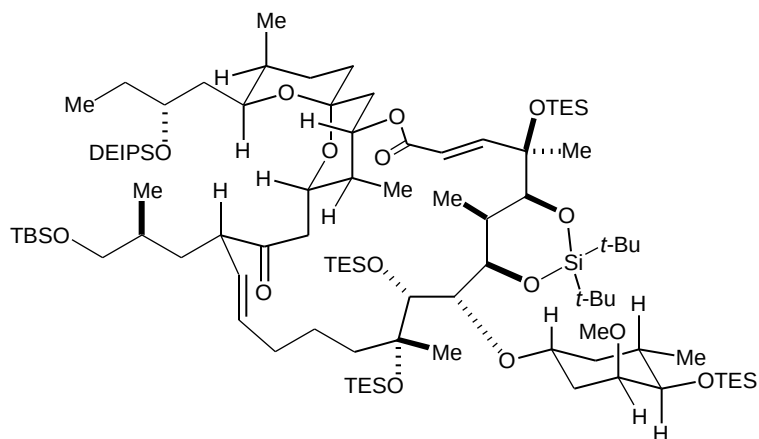
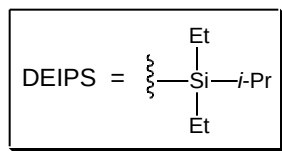




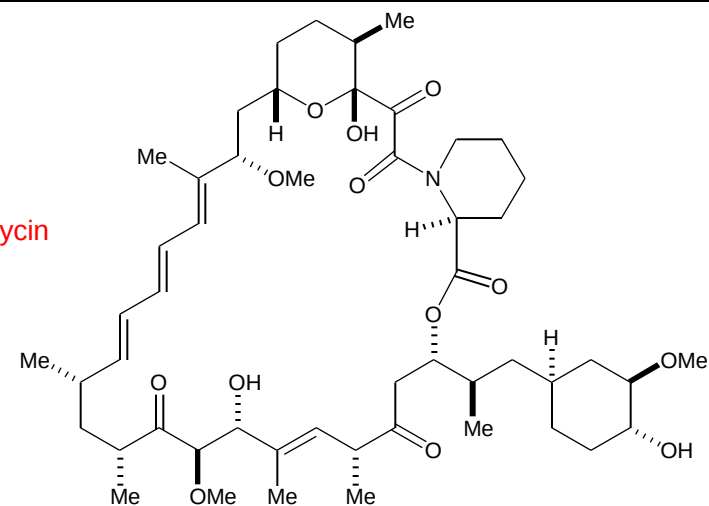
Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J.
J. Am. Chem. Soc. **1990**, *112*, 7001-7031.

HF•pyr, pyridine
 THF, RT

74%



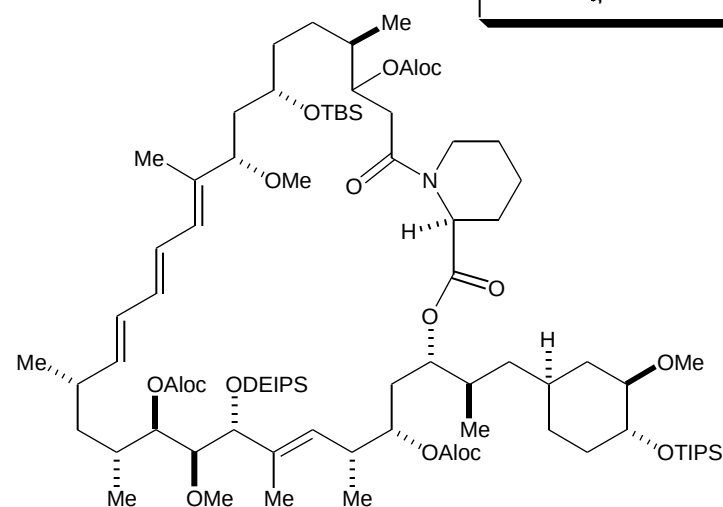
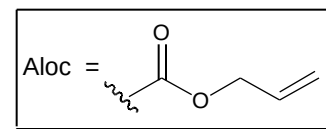
Rapamycin



Romo, D.; Meyer, S. D.;
 Johnson, D. D.; Schreiber, S. L.
J. Am. Chem. Soc. **1993**, *115*, 7906-7907.

1. $\text{Pd}(\text{Ph}_3\text{P})_4$, HCO_2NH_4 , THF
2. Dess-Martin Periodinane
3. HF•pyr, pyridine, THF

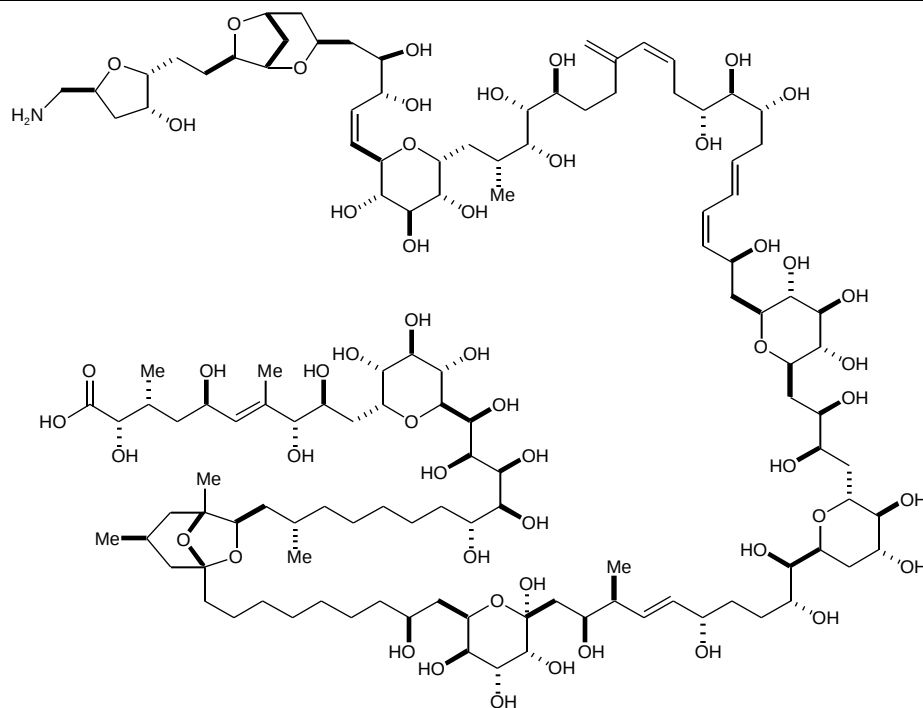
30% overall



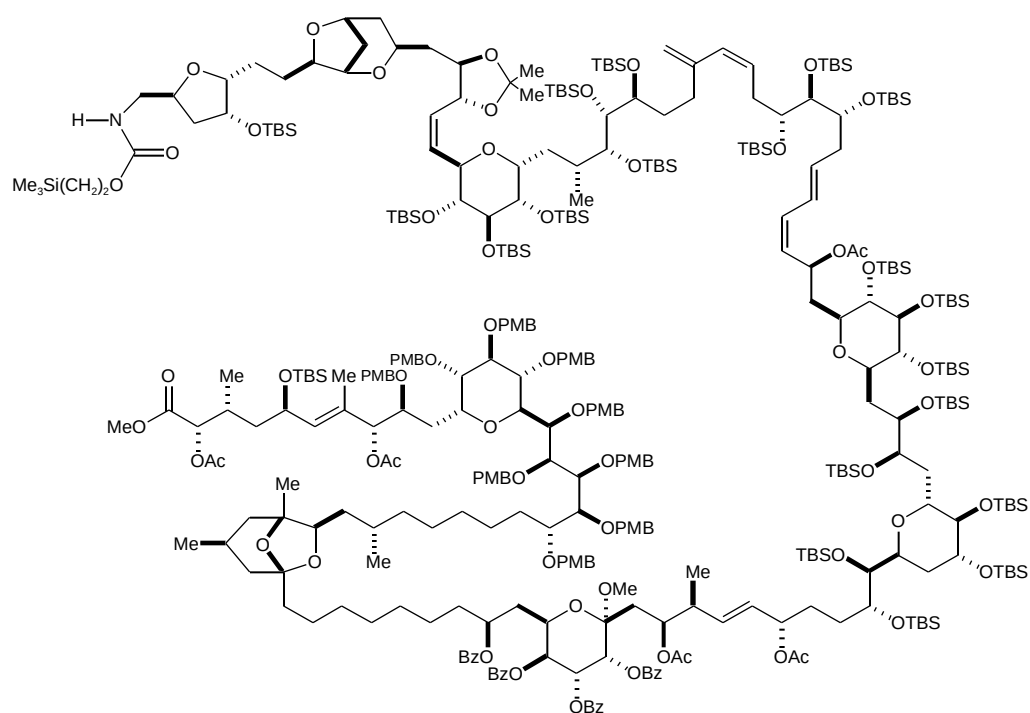
1. DDQ, *t*-BuOH-CH₂Cl₂; Ac₂O, DMAP, pyr.
2. aq. HClO₄, THF, 8 days
3. LiOH, H₂O/MeOH/THF, RT, 20 h
4. TBAF, THF/DMF, RT, 90 h
5. AcOH, H₂O, RT, 36 h

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 Compds" Padwa et al. *Angew Chem Int Ed.* **1994**, 33, 1797

Chiral Dirhodium Carboxamidates: 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

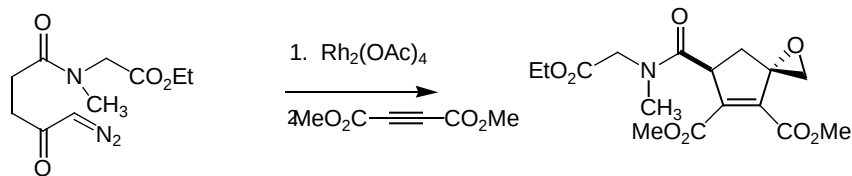
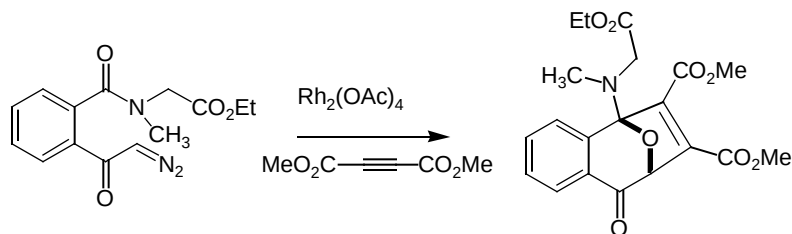
Friday,
December 13, 2002

Useful References to the Carbene Literature**Books:**

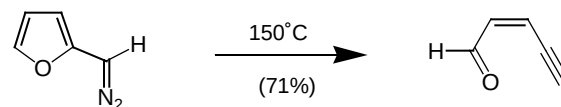
Modern Catalytic methods for Organic Synthesis with Diazo Compounds;
M. P. Doyle, Wiley, 1998.

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.

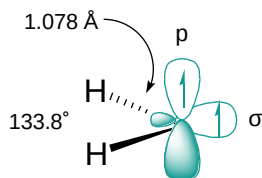
Books:

Modern Catalytic methods for Organic Synthesis with Diazo Compounds;
M. P. Doyle, Wiley, 1998.

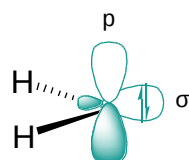
Carbenes and Nitrenes in "Reactive Molecules: The Neutral Reactive Intermediates in Organic Chemistry", Wentrup, C. W. 1984, Wiley, p. 162.

Rearrangements of Carbenes and Nitrenes in Rearrangements in Ground & Excited States, Academic Press, DeMayo ed., Jones, W. M. 1980, p. 95.

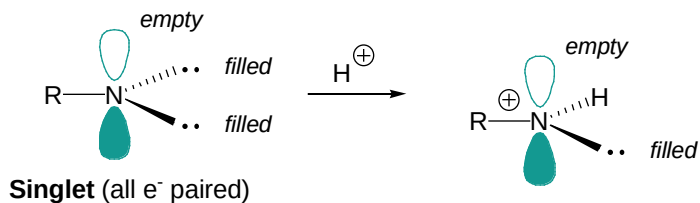
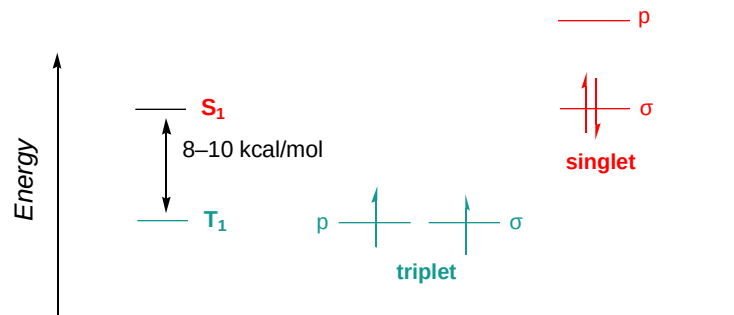
Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

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**).

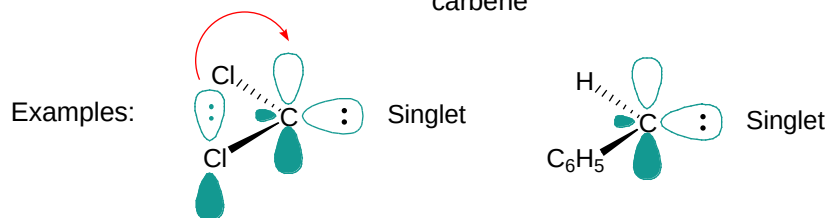
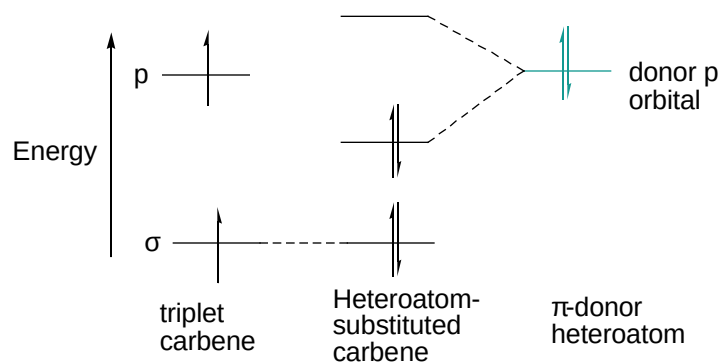
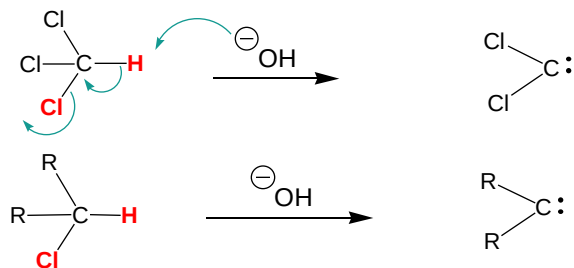
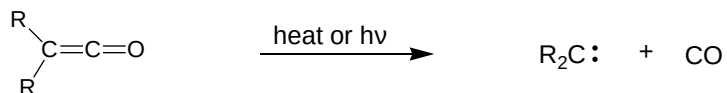
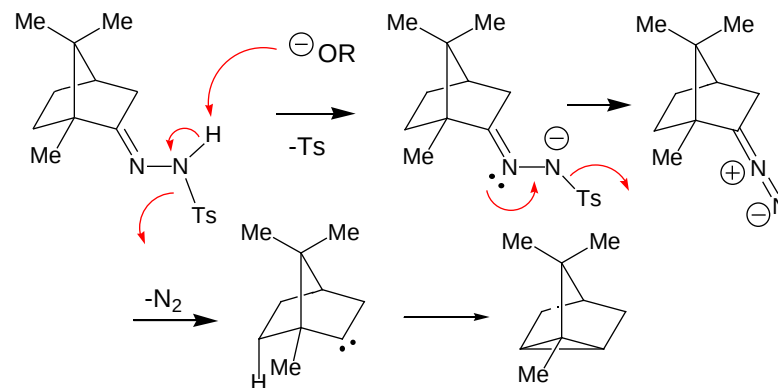
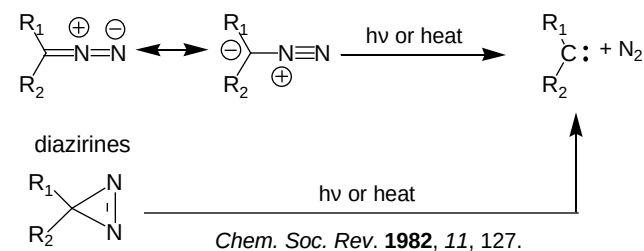
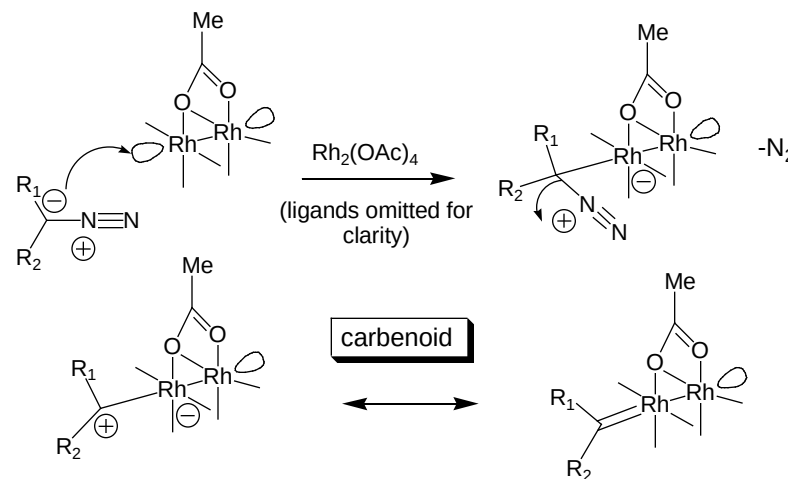
■ the History of the Singlet-Triplet Gap

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

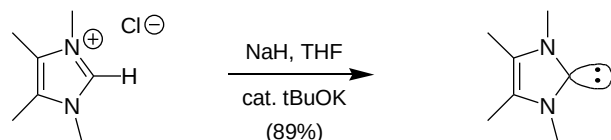
The p orbital of carbenes substituted with **p-donor atoms** (N, O, halogen) is raised high enough in energy to make the pairing of the electrons in the σ orbital energetically favorable. As a result, these carbenes are often in the **singlet** state.

**Methods of Synthesis****Alkyl Halides:****ketenes****Bamford-Stevens Reaction:** See Lecture 28 on Hydrazones
Shapiro *Org. Rxns.* **1976**, 23, 405.**diazo compounds****metal-catalyzed decomposition** Doyle *Chem Rev.* **1988**, 86, 919.

■ "Stable Carbenes"

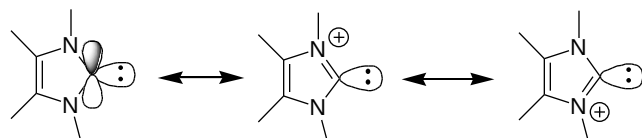
"Stable Carbenes—Illusion or reality"?

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:



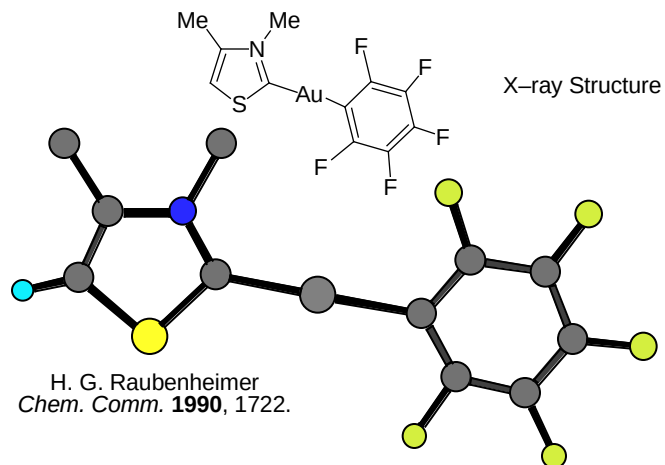
Arduengo argues that these resonance structures are not players based on electron distribution from neutron diffraction.

These are nucleophilic carbenes which display high stability.

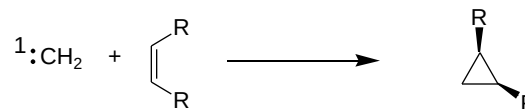
For reviews on the subject, see:

Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 725.

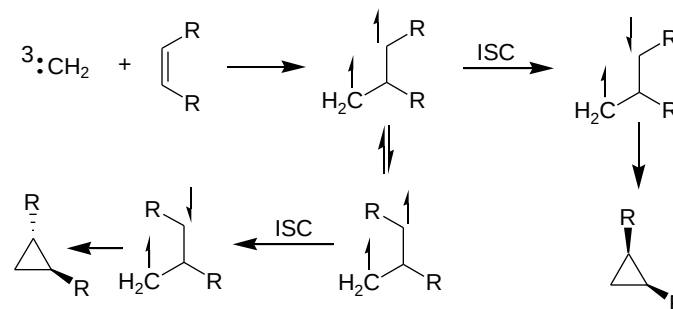
Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 674.



■ Cyclopropanation The Skell Rule:



Singlet carbenes add to olefins stereospecifically;

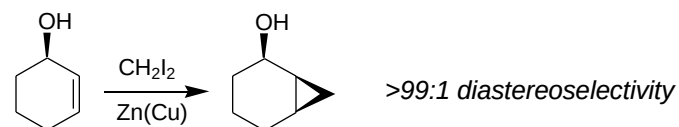


Triplet carbenes add non-stereospecifically

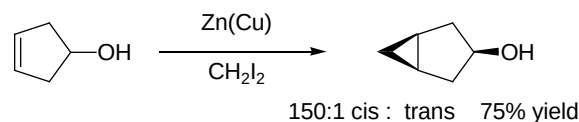
Skell and Woodward *JACS*, **1956**, 78, 4496.

■ Simmons-Smith Cyclopropanation (See Tedrow handout 09B)

Simmons, H.; Smith, R. *J. Am. Chem. Soc.*, **1958**, 80, 5323.



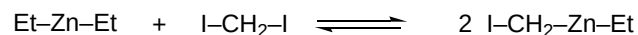
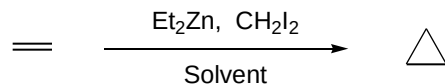
The intermediate organometallic reagent: $I-CH_2-Zn-I$



Winstein & Sonnenberg, *JACS* **1961**, 91, 3235

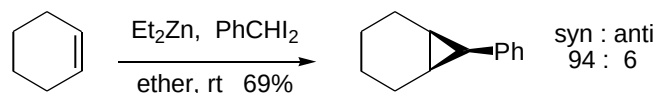
■ The Furukawa Simmons-Smith Variant

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

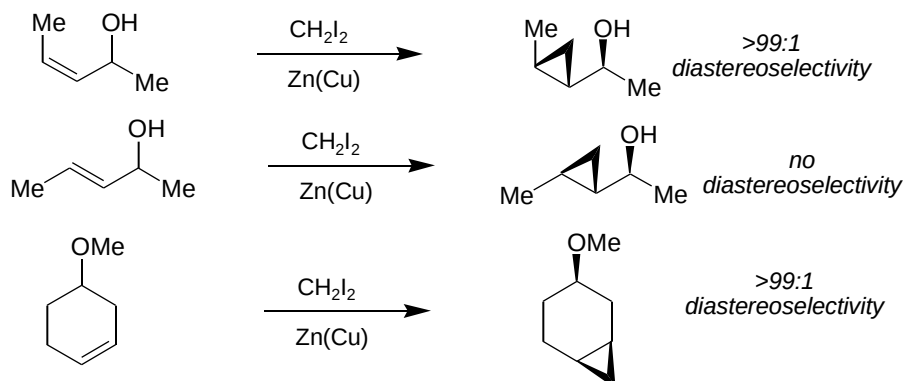


Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron*, **1968**, *24*, 53

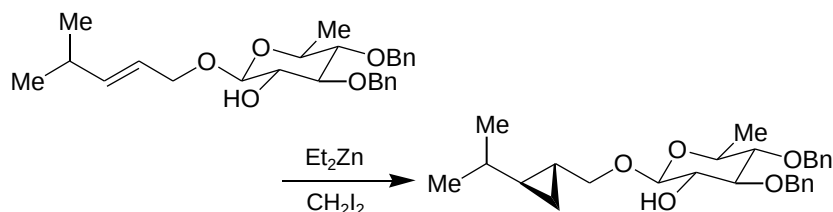
Furukawa, J.; Kawabata, N.; Fujita, T. *Tetrahedron*, **1970**, *26*, 243



■ Hydroxyl directivity is a powerful attribute of the S-S Rxn

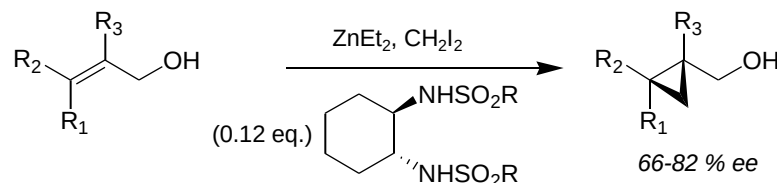


For an review of the directed Simmons-Smith, see: with A. Hoveyda and G. Fu *Chem. Rev.* **1993**, *93*, 1307.



Charette, A. B. *JACS* **1991**, *113*, 8166.

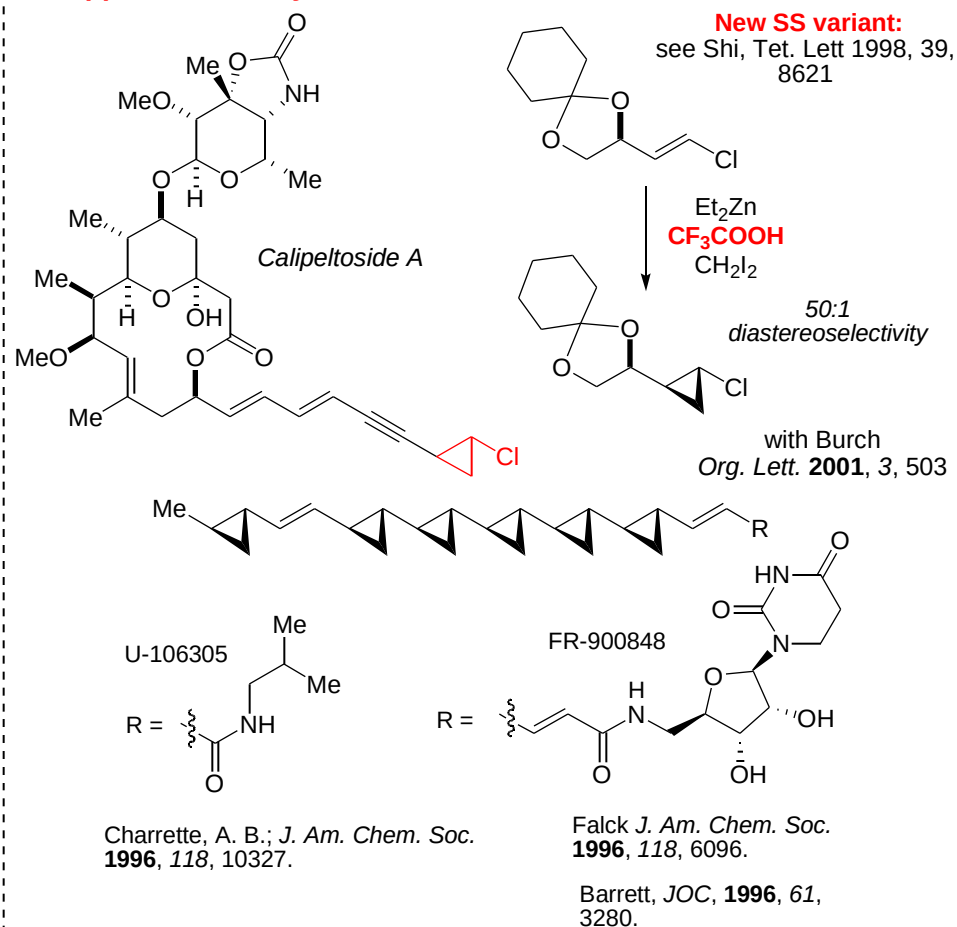
■ Catalytic Asymmetric Cyclopropanation:



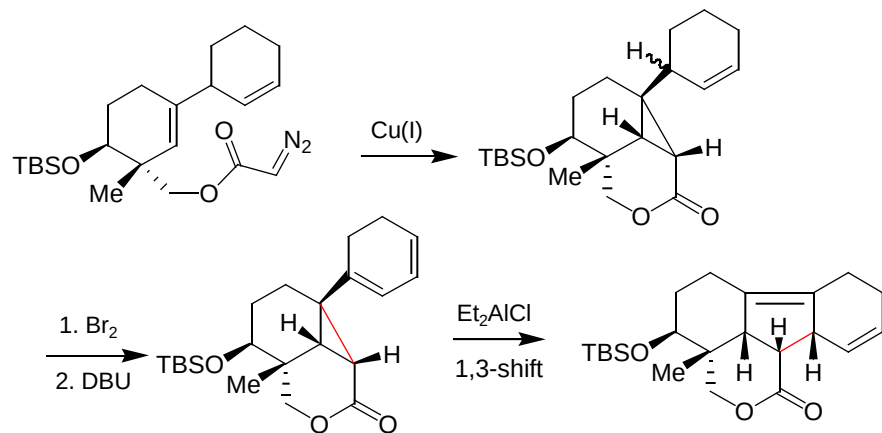
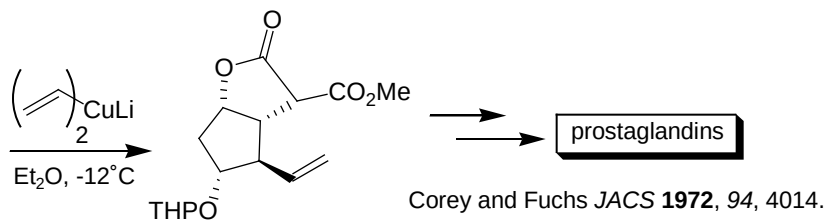
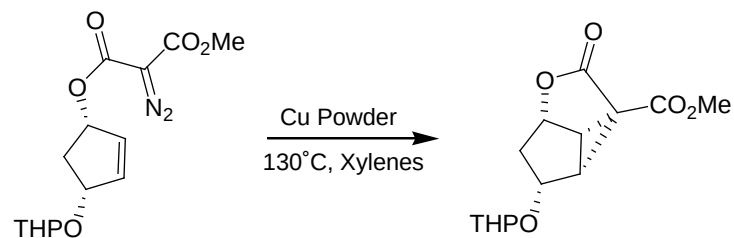
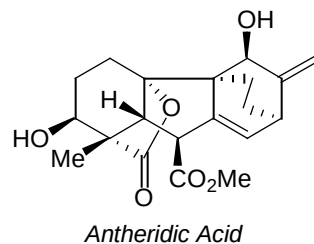
Kobayashi, et al. *Tetrahedron Lett.* **1994**, *35*, 7045.

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.

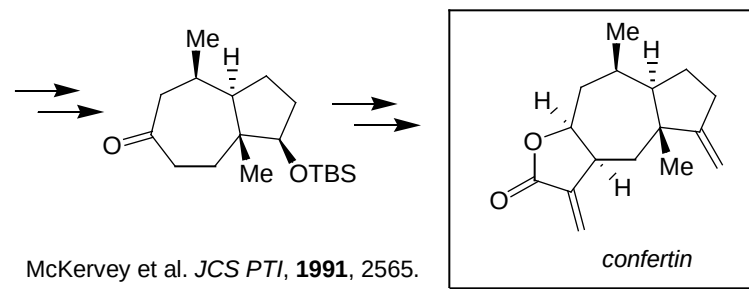
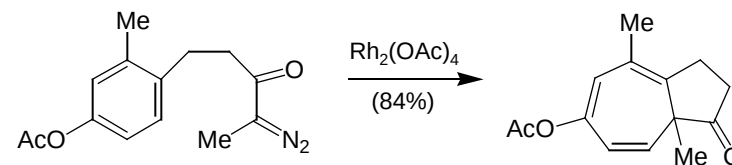
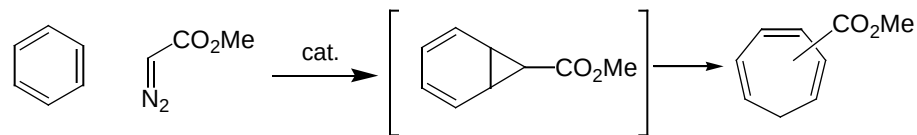
■ Applications in Synthesis



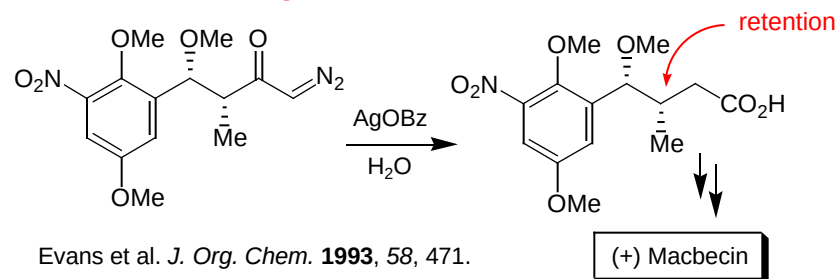
Synthetic Applications

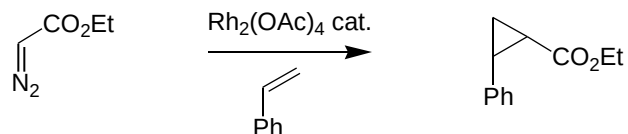
Corey & Myers JACS **1985**, 107, 5574.

Buchner Reaction



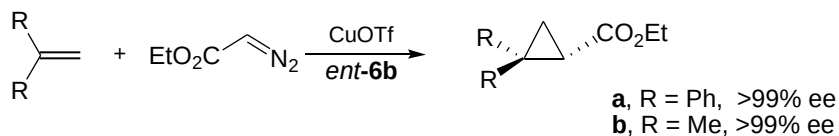
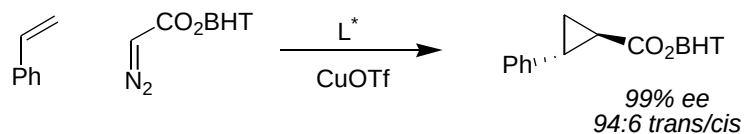
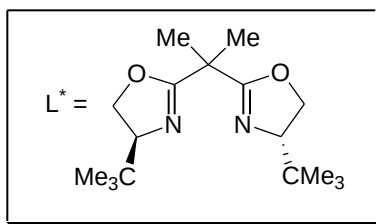
Wolff Rearrangement





** For a detailed mechanistic study which provides supporting evidence for the intermediacy of a Rh carbene, see: Kodacek, *Science*, **1992**, 256, 1544.

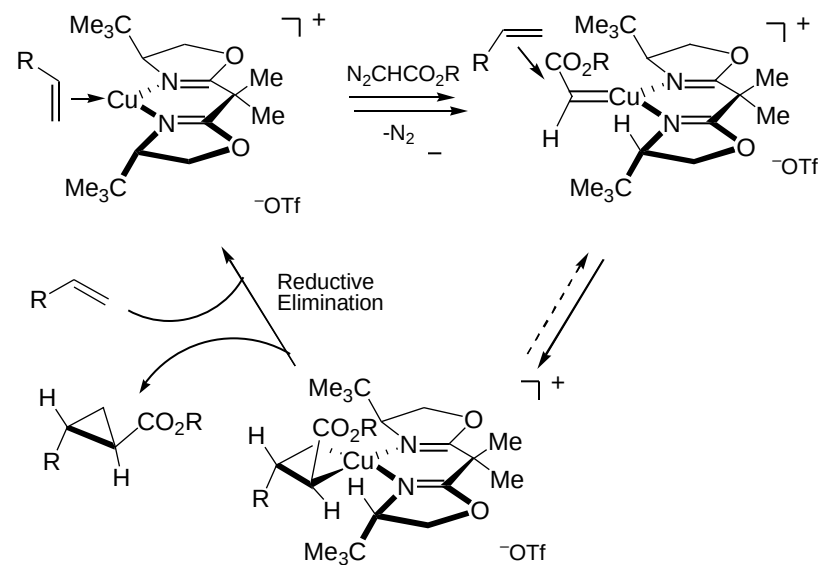
■ Catalytic Asymmetric Variants: Chiral Cu(I) Complexes



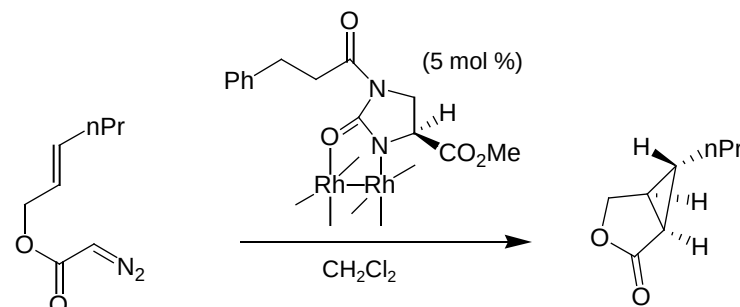
Evans, et al. *J. Am. Chem. Soc.* **1991**, 113, 726.

■ 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

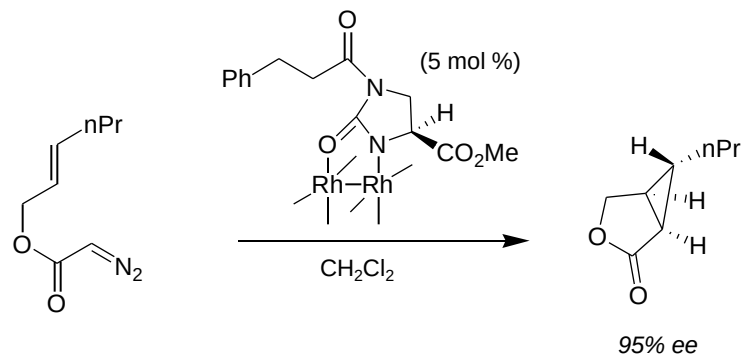
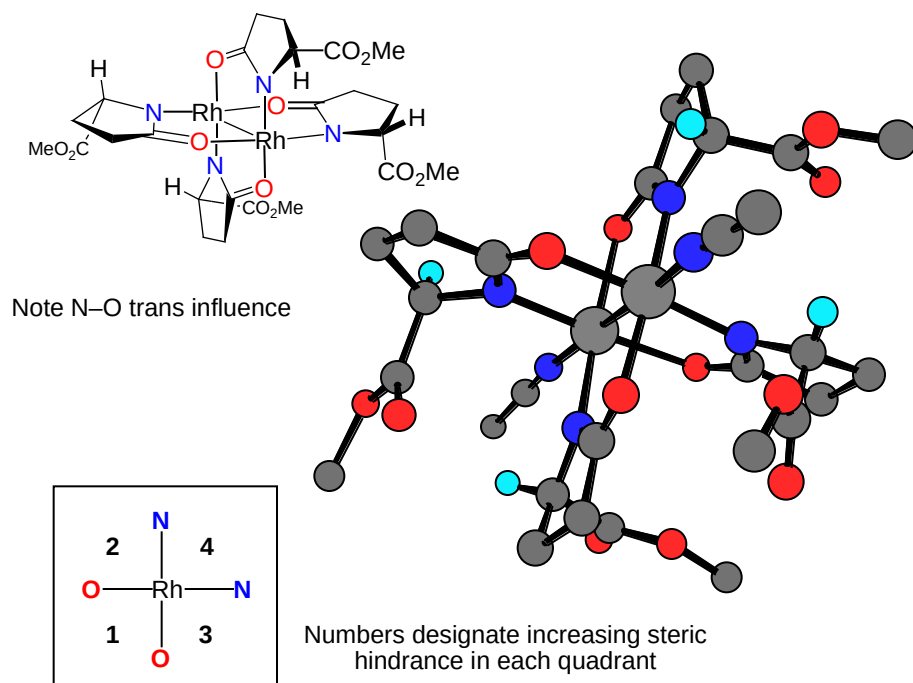


Doyle et al. *Tetrahedron Lett.* **1995**, 36, 7579.

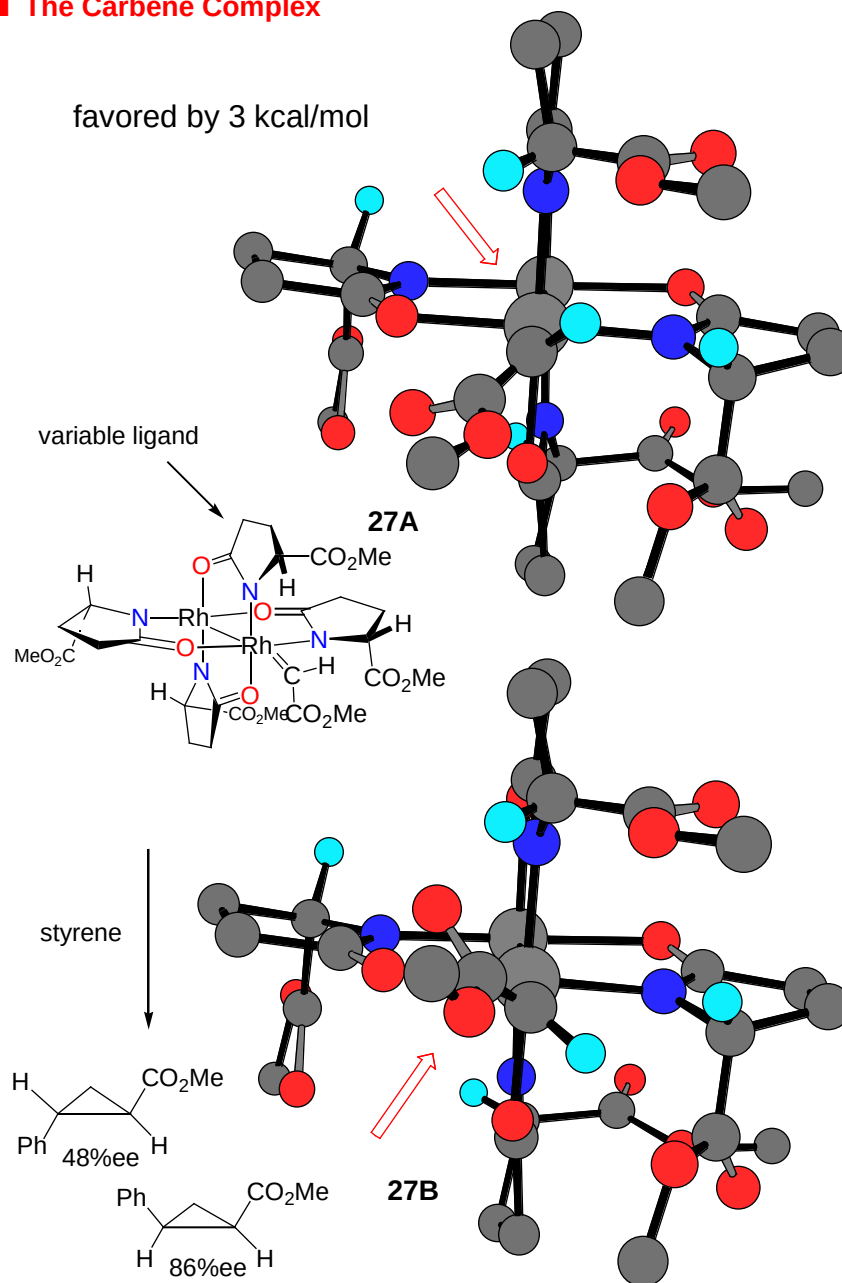
95% ee

How do these complexes really work??

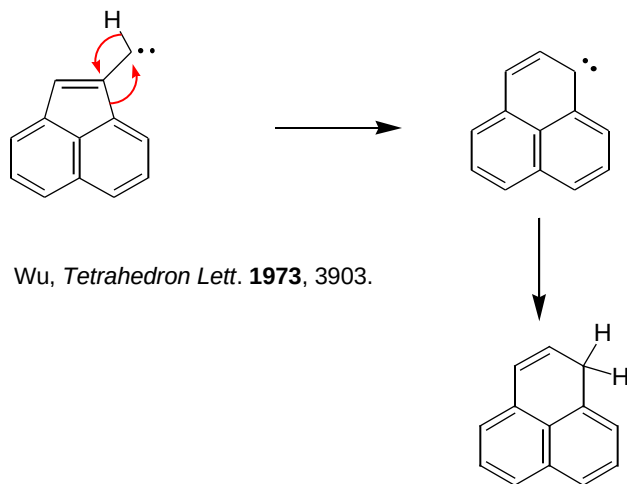
■ Catalytic Asymmetric Variants: Chiral Rh(II) Complexes

Doyle et al. *Tetrahedron Lett.* **1995**, 36, 7579.Doyle, *JACS* **1993**, 115, 9968

■ The Carbene Complex

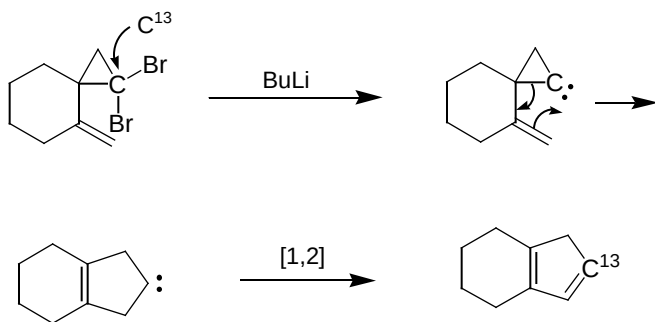


Carbene-Carbene Rearrangements



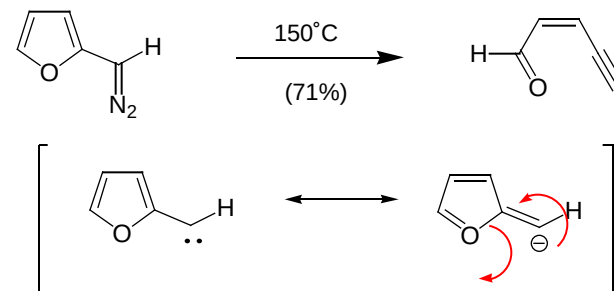
Wu, *Tetrahedron Lett.* **1973**, 3903.

Skattebol Rearrangement

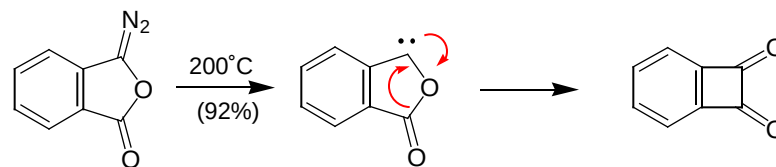


Tetrahedron Lett. **1973**, 2283.

Other Rearrangements



Schechter, *J. Am. Chem. Soc.* **1971**, 93, 5940.

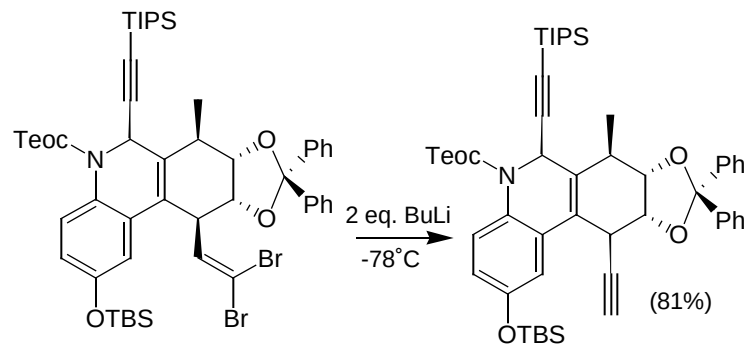


Sammes, *Chem. Comm.* **1975**, 328.

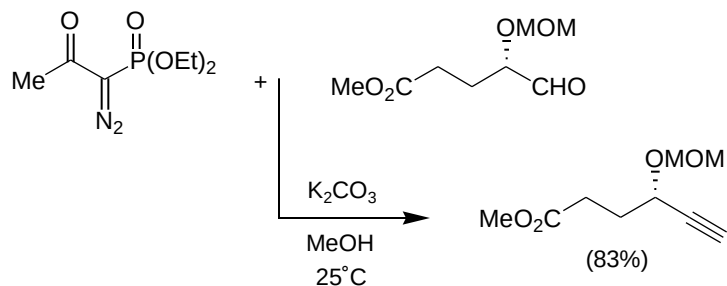
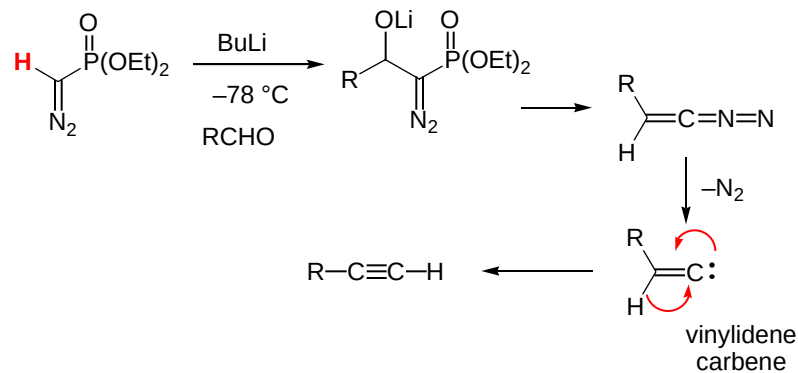
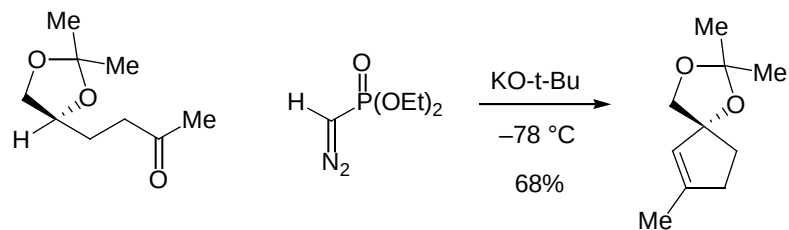
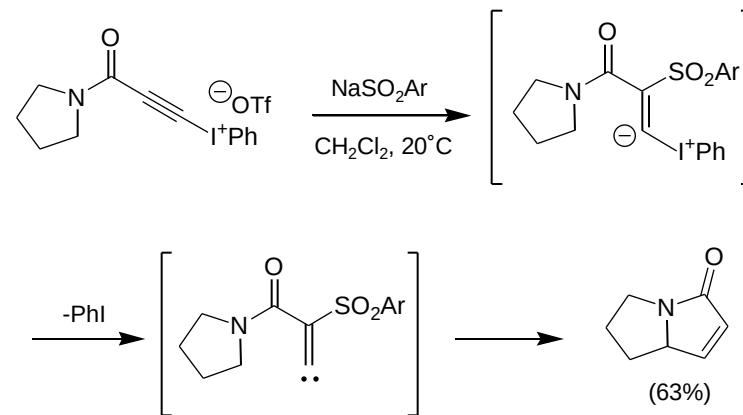
Vinylidenes

Corey-Fuchs:

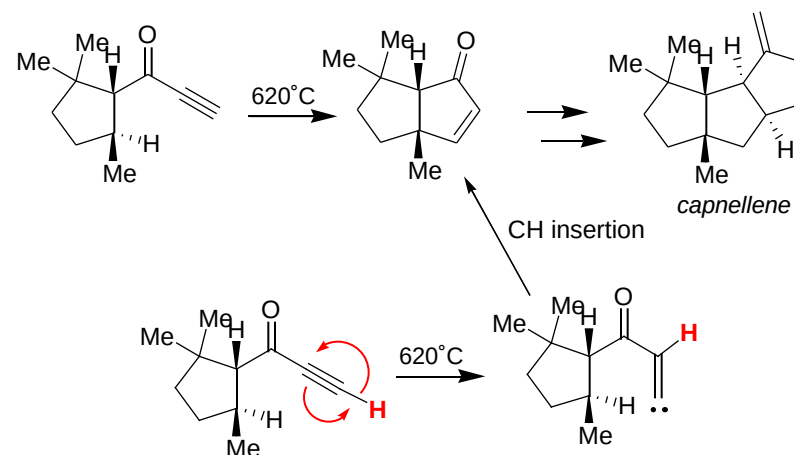
Danishefsky et al.
J. Am. Chem. Soc. **1996**, 118, 9509.



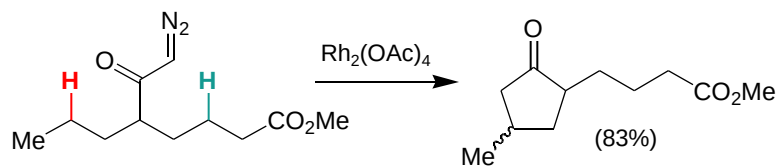
Carbene Rearrangements

Bestmann, et al. *Synlett* **1996**, 521.Gilbert, *JOC* **1983**, 48, 5251Stang et al. *J. Am. Chem. Soc.* **1994**, 116, 93.

carbene intermediates are accessible at high temperatures, more later!

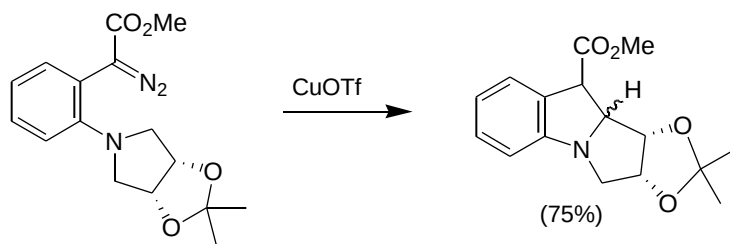


■ C-H Insertions continued...



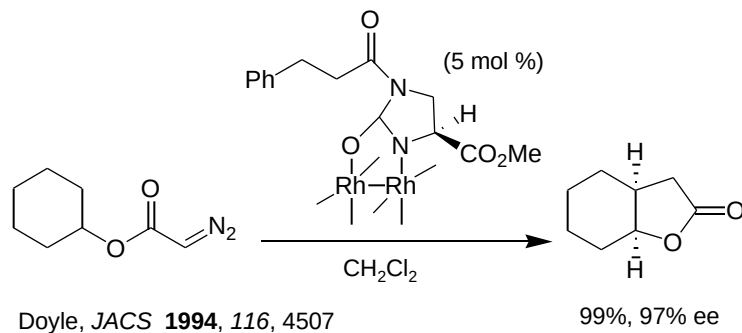
Electrophilic carbenes are very sensitive to electronic effects

Stork *Tetrahedron Lett.* **1988**, 29, 2283.



Sulikowski, *J. Org. Chem.* **1995**, 60, 2326.

Enantioselective C-H Insertion

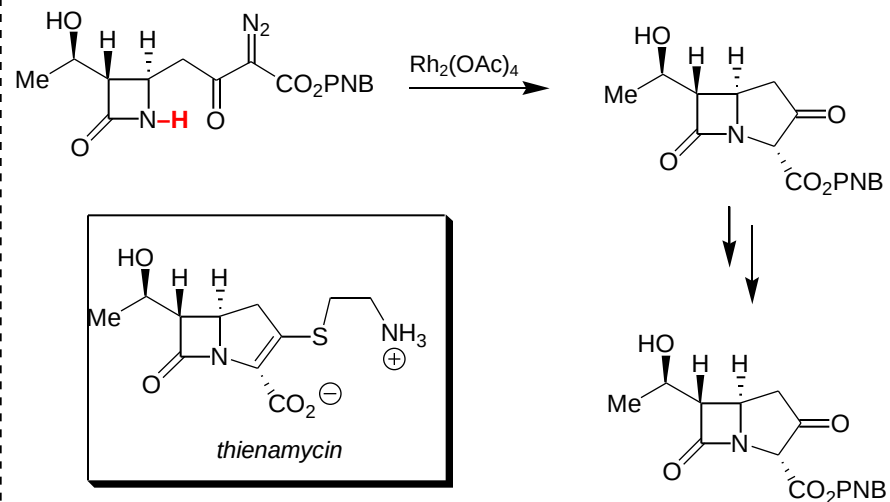


Doyle, *JACS* **1994**, 116, 4507

99%, 97% ee

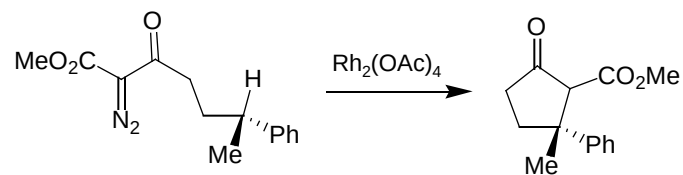
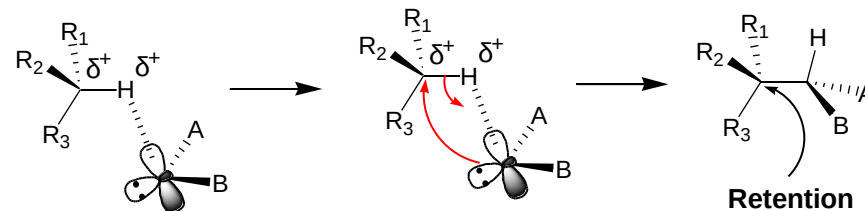
Chiral DirhodiumCarboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta.* **1996**, 29, 3

■ N-H Insertions are also possible...



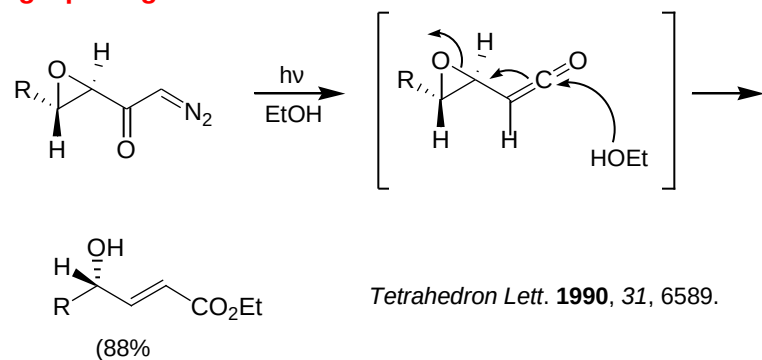
Salzmann, *JACS*, **1980**, 102, 6163.

Insertions (X-H): Stereochemical outcome

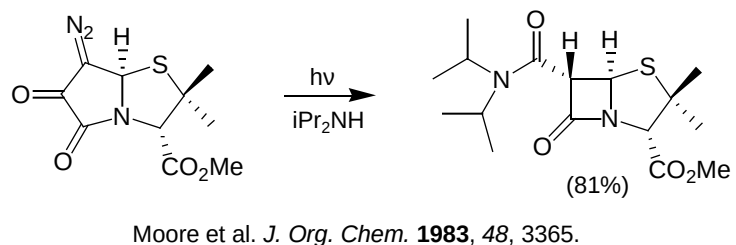


Taber *JACS*, **1996**, 107, 196.

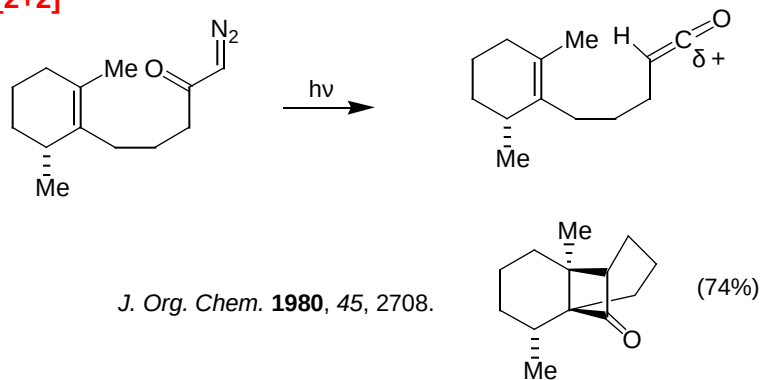
Ring Opening



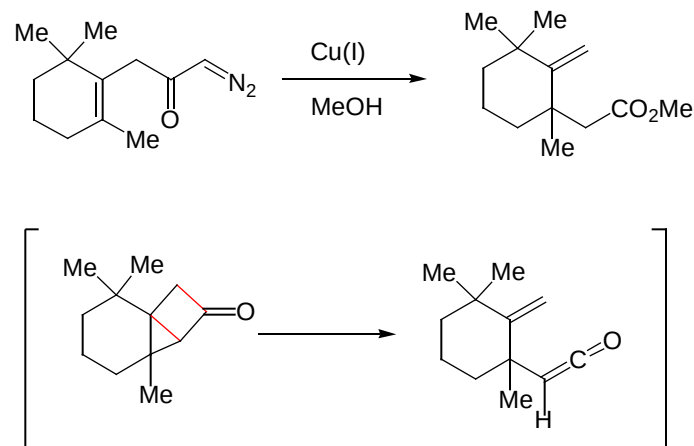
Ring Contraction



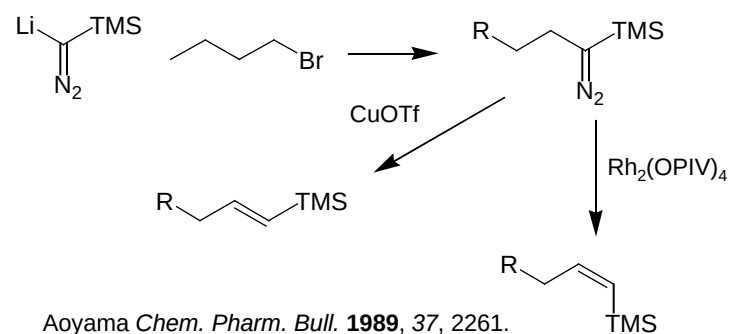
Wolff-[2+2]



Vinyloligous Wolff Rearrangement Doyle pp520-521



[1,2]-Rearrangements



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

Chemistry 206

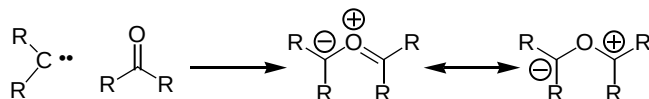
Advanced Organic Chemistry

Lecture Number 35

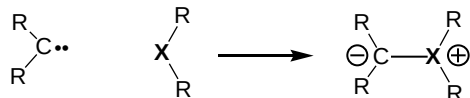
Introduction to Carbenes & Carbenoids-2

■ 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, "Reactions 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:

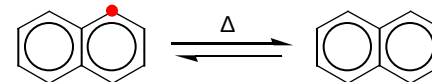
Modern Catalytic methods for Organic Synthesis with Diazo Compounds;
M. P. Doyle, Wiley, 1998.

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.

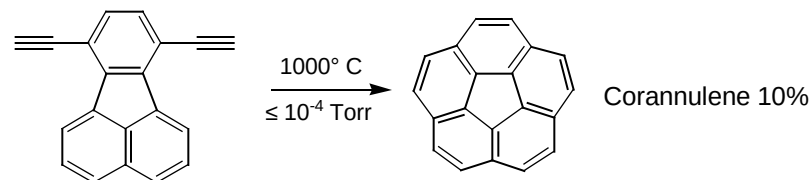
The Automerization of Naphthalene (The Cume Question from Hell!)

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.

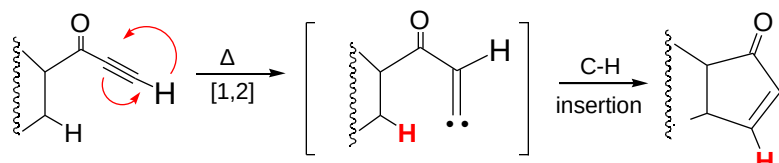
Provide a Mechanism for this Transformation



Scott, L.T., et. al., *JACS* **113** 7082 (1991)

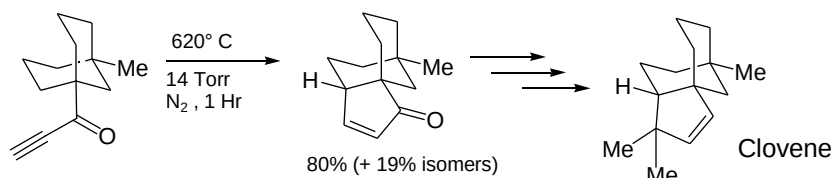
Carbenes are Accessible via Sigmatropic Rearrangement

■ [1,2] Shifts: Alpha-Alkynone Cyclizations

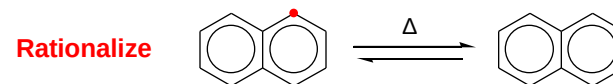
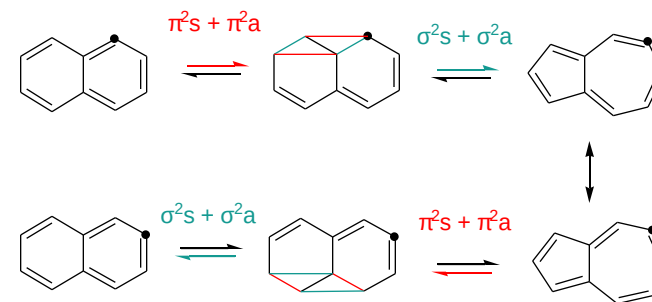
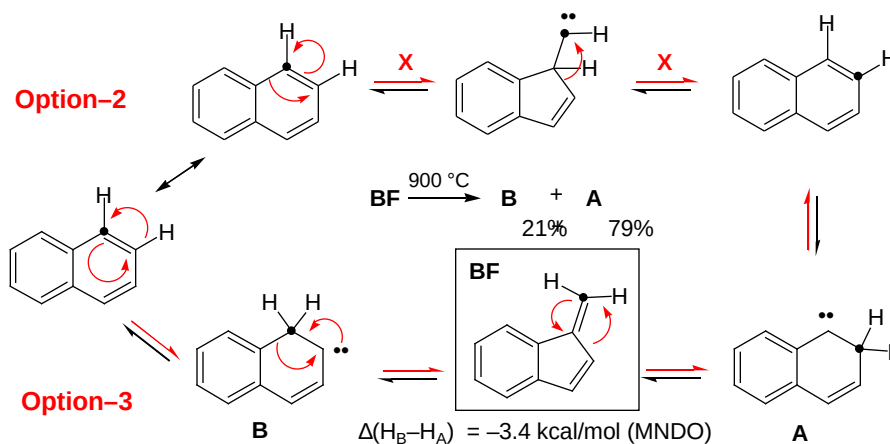


Conditions: 620° C, 12-16 Torr, Quartz filled Quartz Tube

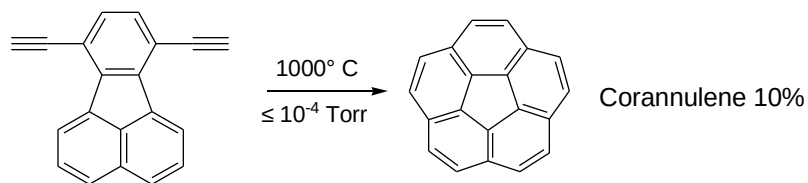
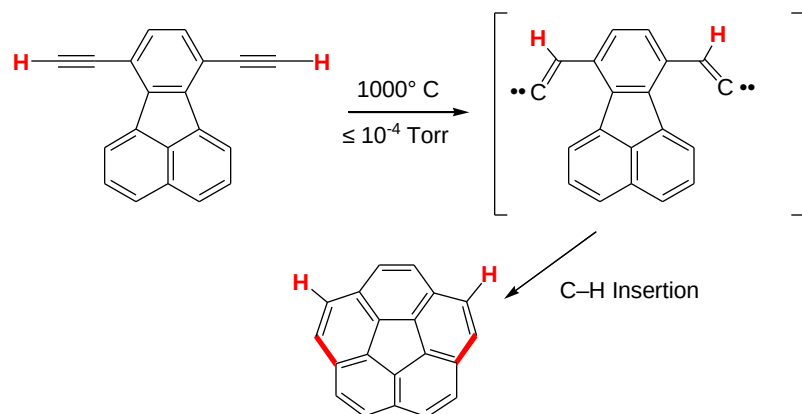
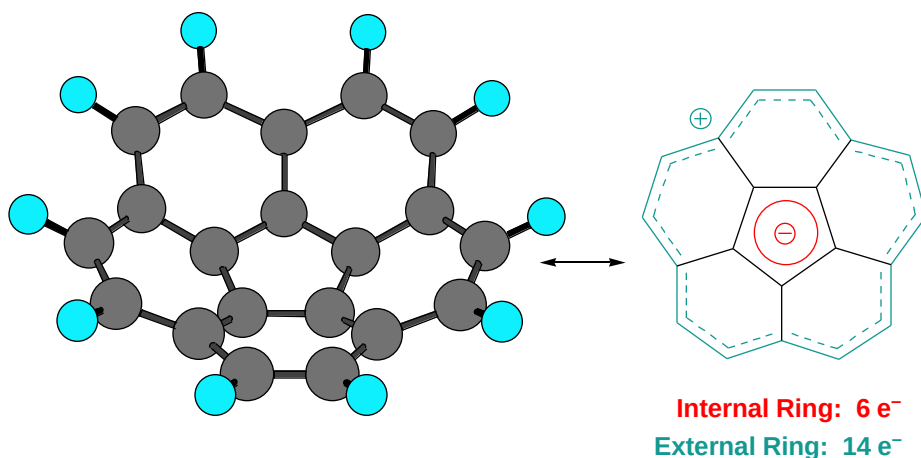
S.M.	3°	2°	1°	Recovery
	—	 60	 22	80%
	 87	—	 13	78%
	 54	 46	—	89%
	—	 92	 8	90%

Karpf, M., Dreiding, A., *Helv. Chim. Acta.* **65** 13 (1982)Karpf, M., Dreiding, A.S., *Helv. Chim. Acta.* **67** 1963 (1984)

The Automerization of Naphthalene (The Cume Question from Hell!!)

 α -¹³C-labeled C₁₀H₈ is isomerized into β -¹³C-labeled C₁₀H₈ at 1035 °C■ Mechanism-1: L. T. Scott, *JACS* **1977**, 99, 4506;■ For the azulene–naphthalene Isomerization: $\Delta G^\circ = -30.7$ kcal/mol (298K)■ The Activation energy for the isomerization: $\Delta G^\ddagger = +86$ kcal/mol■ Mechanism-2,3: L. T. Scott, *JACS* **1991**, 113, 9692.

Provide a Mechanism for this Transformation

Scott, L.T., et. al., JACS **113** 7082 (1991)

Carbenes: Reaction with Heteroatoms

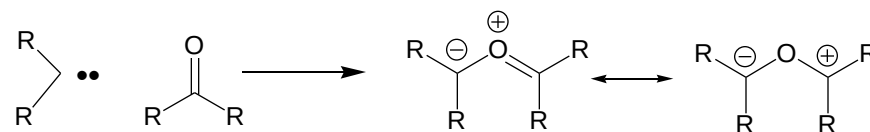
Suggested Reading

Houk and Wu *J. Org. Chem.* **1991**, 56, 5657.Padwa and Hornbuckle *Chem. Rev.* **1991**, 91, 263.

Review Articles

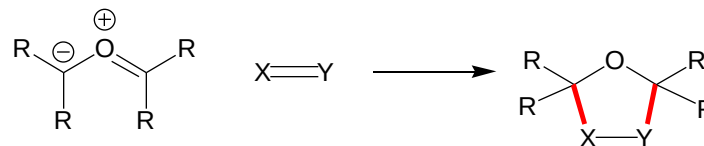
Padwa and Krumpke *Tetrahedron* **1992**, 48, 5385.Hoffman, R. W. *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 563.McKervey et al. *Chem. Rev.* **1994**, 94, 1091.

Ylide Formation by the Interaction of Carbeneoids with Carbonyl Lone Pairs

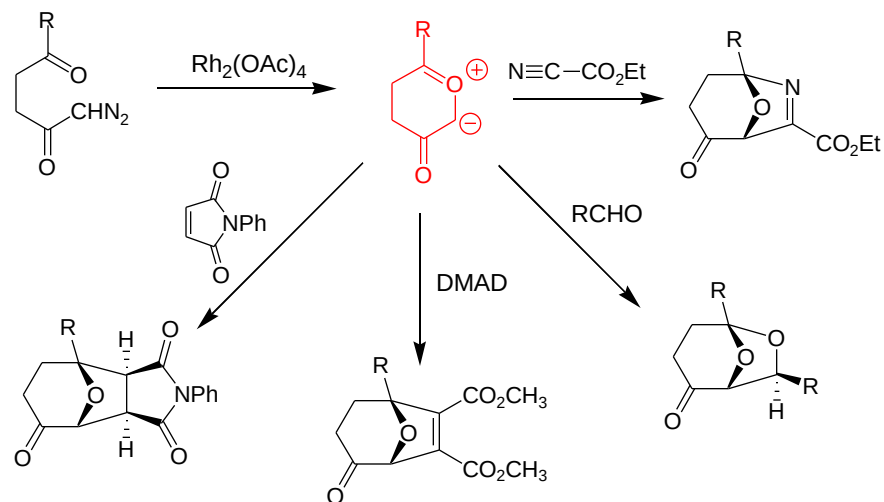


Generally, the carbene precursor of choice is a diazoalkane or, more frequently, an α -diazocarbonyl reagent. These can be decomposed via thermolysis or photolysis. However, the most common method involves catalytic amounts of transition metals, such as copper or rhodium.

Dipolar Cycloaddition

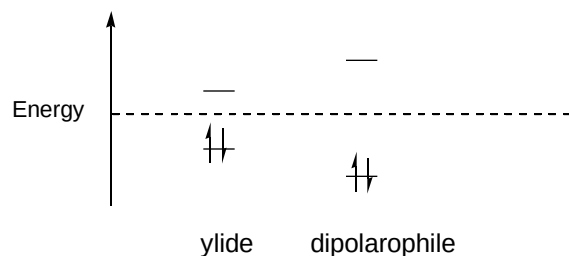


Tandem Intramolecular Cyclization–Intermolecular Cycloaddition

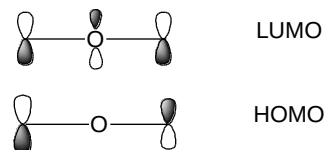


Dipolar-Dipolarophile Cycloadditions: HOMO–LUMO Energies

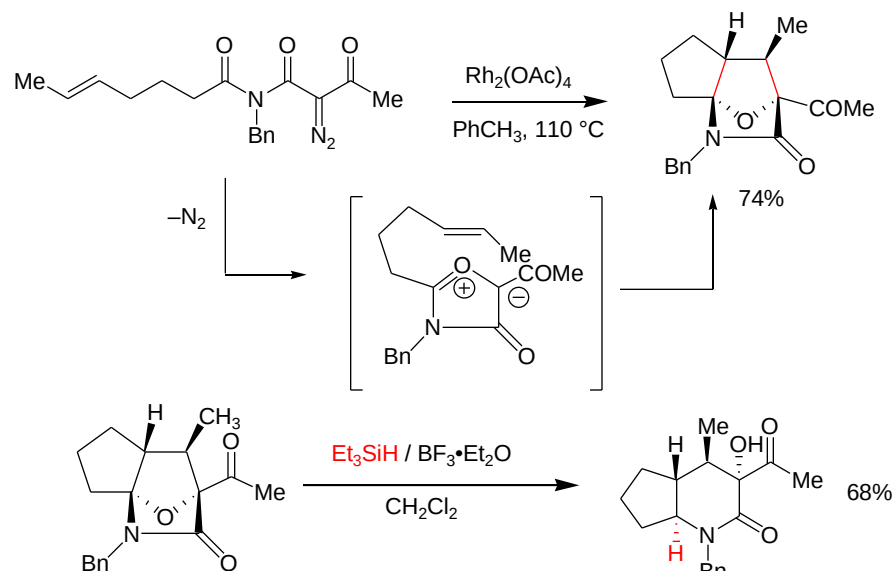
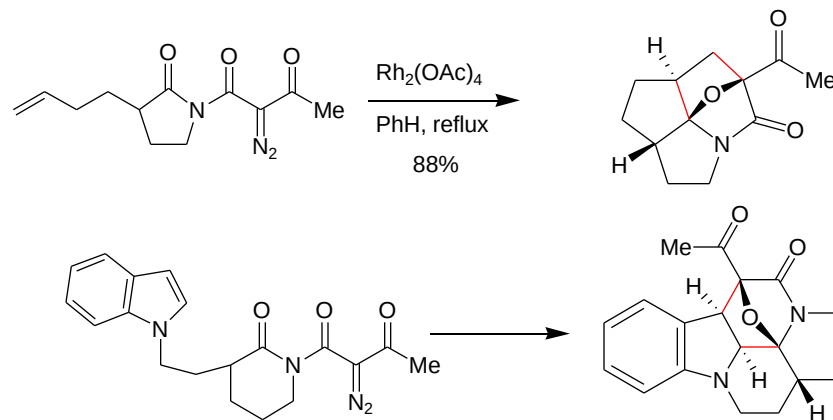
Carbonyl Ylides have very small HOMO-LUMO gaps



Therefore, either raising the dipolarophile HOMO (electron-donating substituents) or lowering the LUMO (electron-withdrawing) will accelerate the reaction.



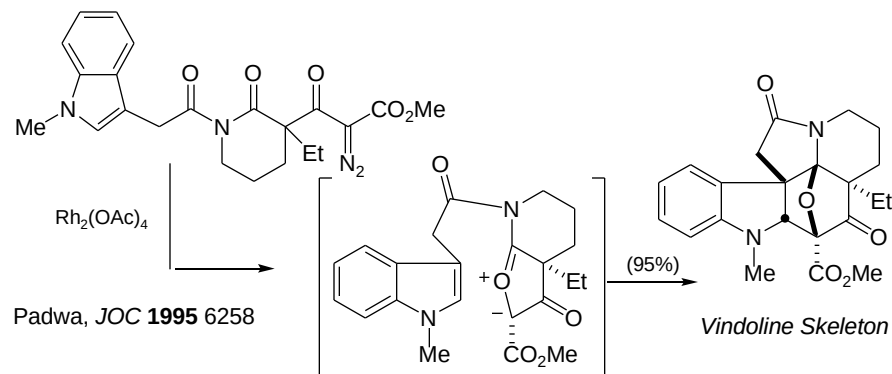
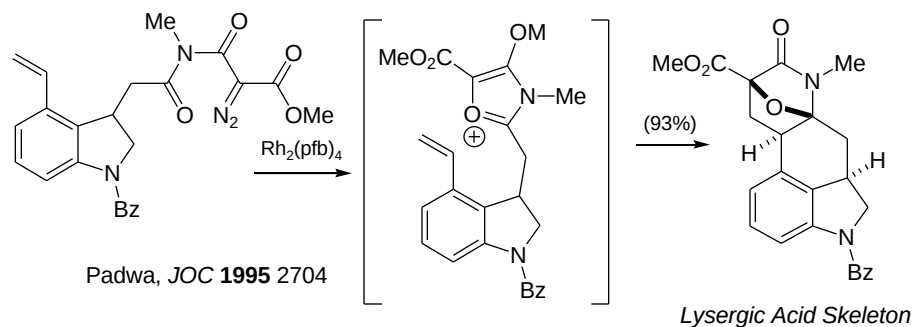
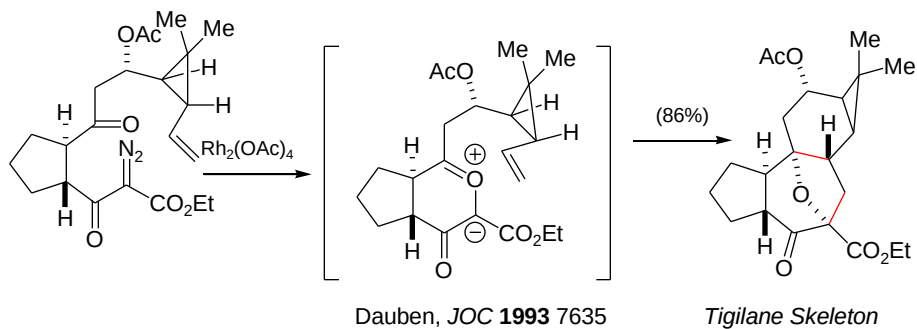
Reactions of Diazoimides: [3+2] addition

Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, 29, 1677-1680.

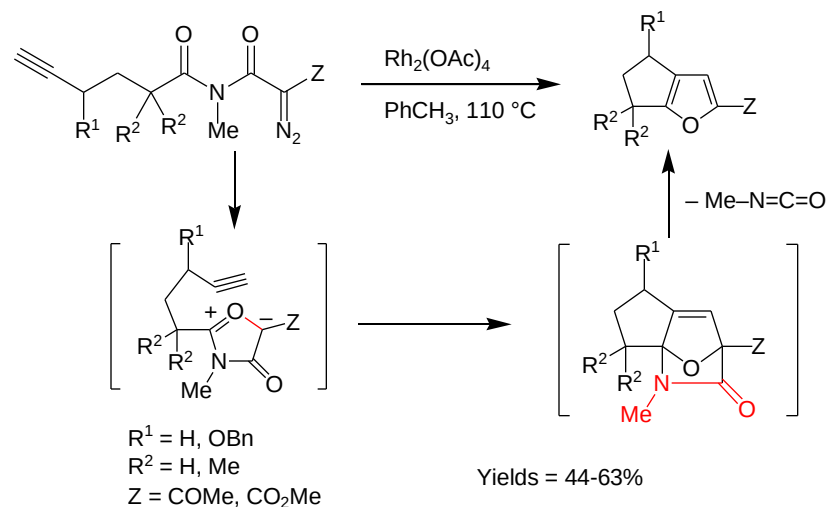
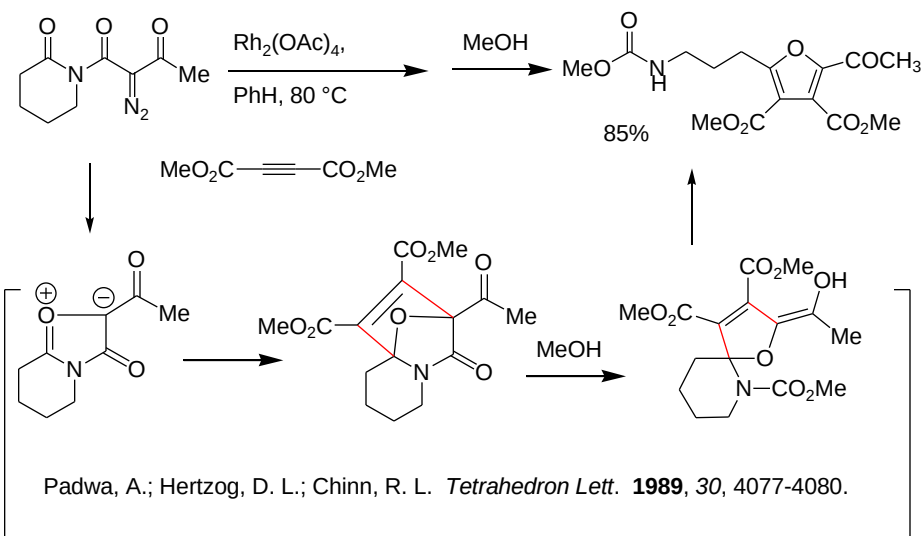
"high yield"

Padwa et. al. *Tetrahedron Lett.* **1992**, 33, 4731-4734.

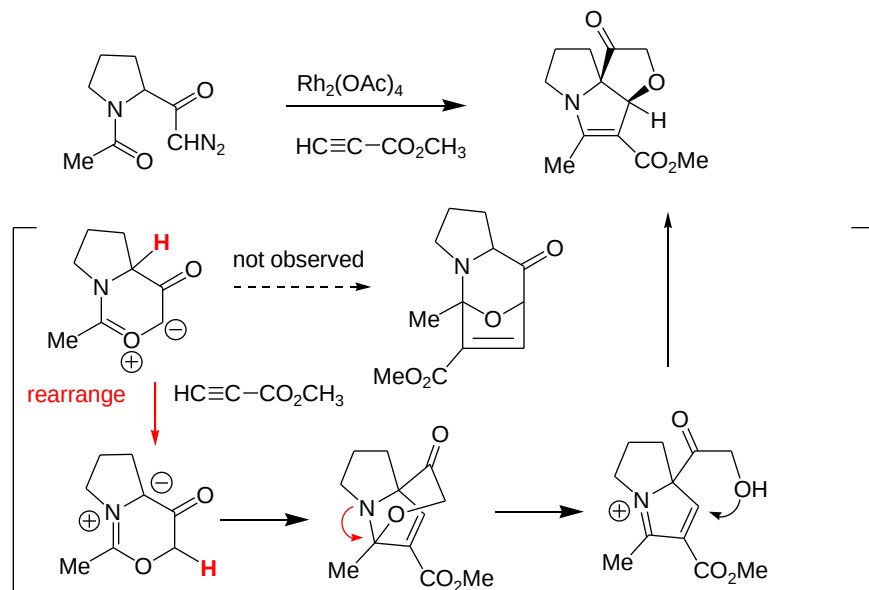
Dipolar Cycloadditions: Carbonyl Ylides



Reactions of Diazoimides: [3+2] addition – [4+2] retroaddition

Maier, M. E.; Schöffling, B. *Chem. Ber.* **1989**, 122, 1081-1087.

The Carbonyl Ylide - Azomethine "Dipole Cascade"



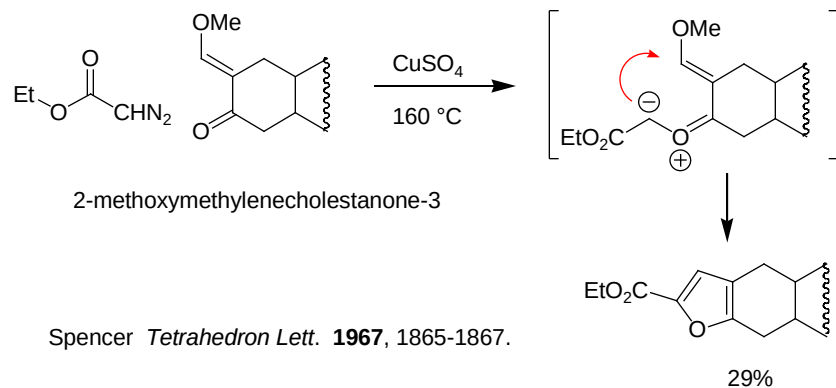
The 1,3-proton shift is catalyzed by trace amounts of water. Azomethine ylide formation requires a proton at the tertiary center.

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.

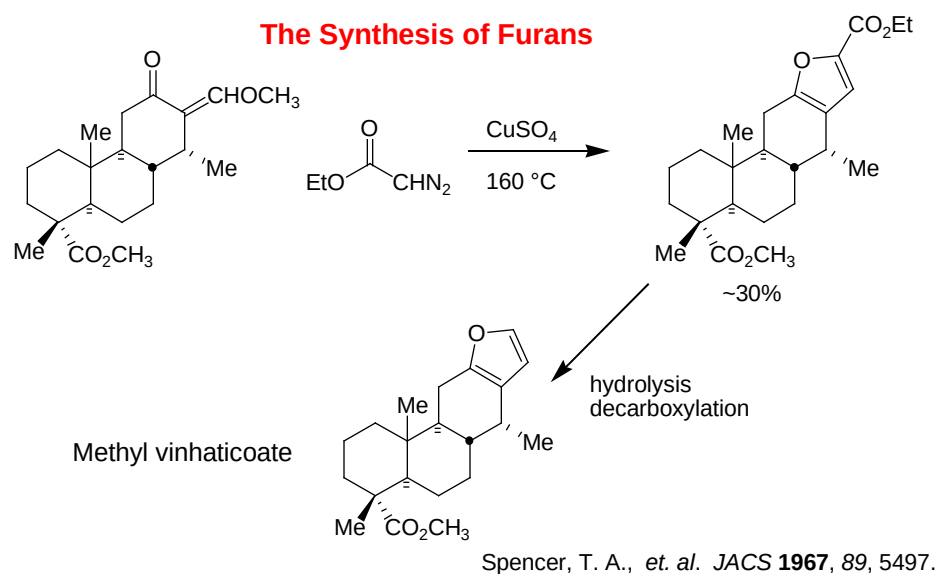
The Synthesis of Furans

Intermolecular addition to α,β -unsaturated carbonyls

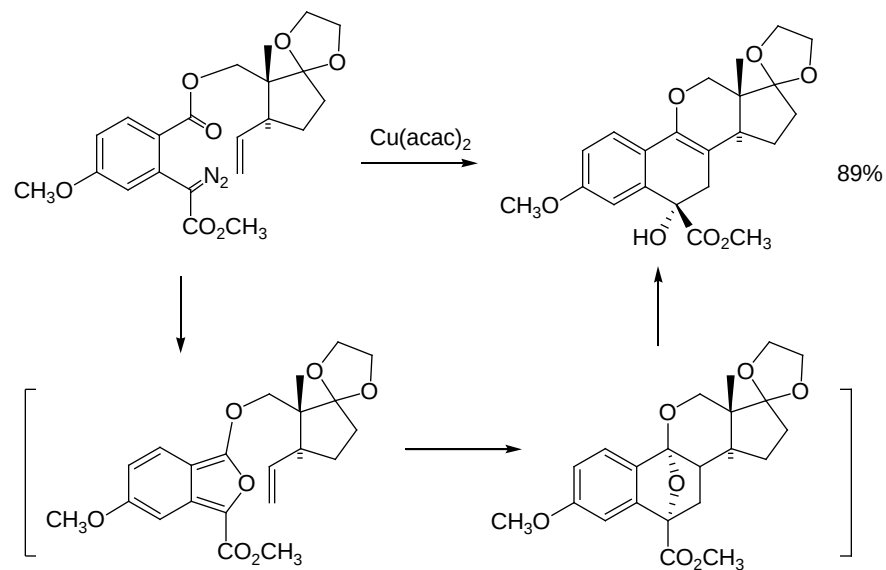


Spencer *Tetrahedron Lett.* **1967**, 1865-1867.

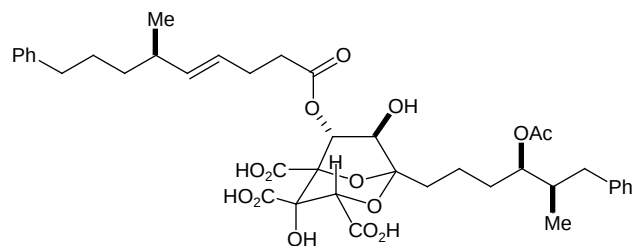
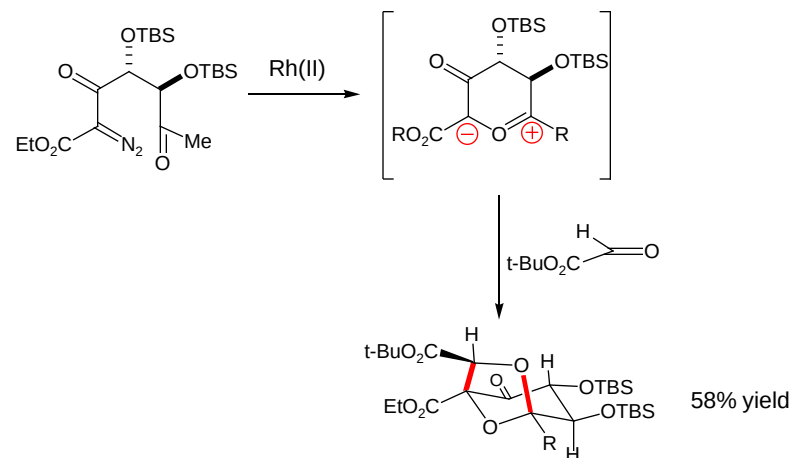
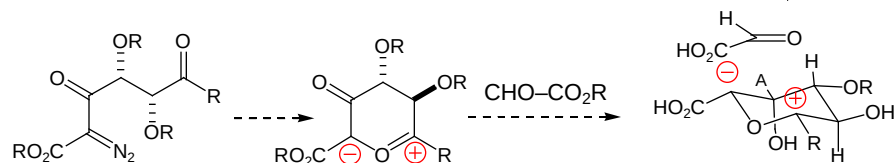
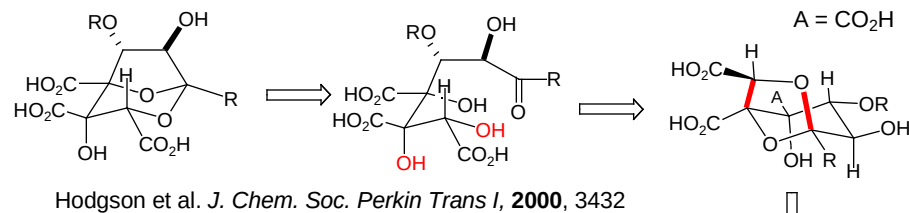
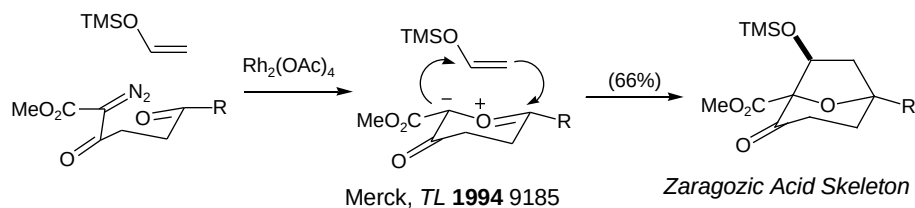
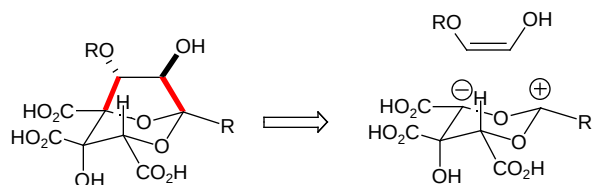
The Synthesis of Furans



Can you propose a rational mechanism for this transformation?



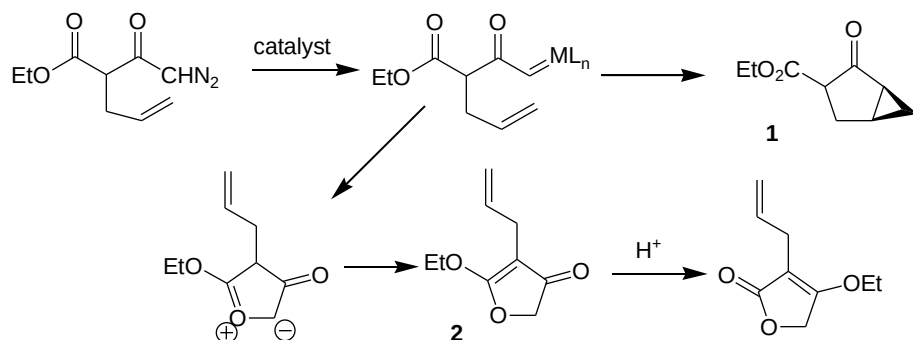
Hildebrandt, *Tetrahedron Lett.* **1988**, *29*, 2045-2046.

Application of Carbonyl Ylids to the Synthesis of Zaragozic acid:**C=O Ylid Transforms**

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."*

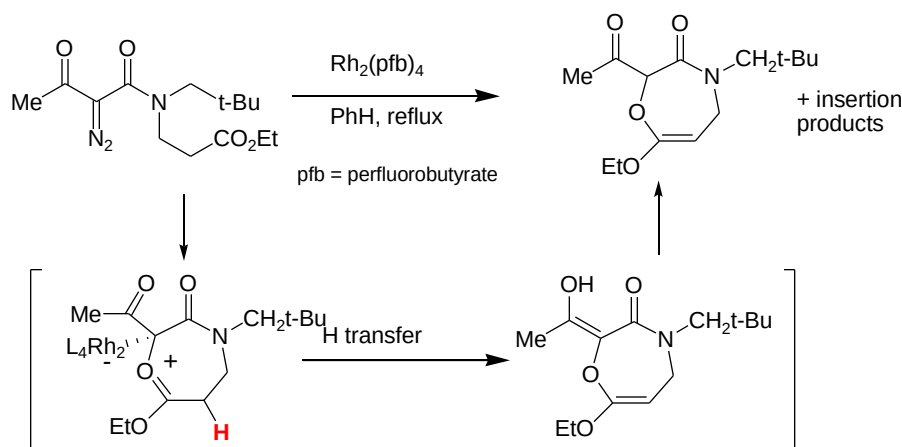
Ylid Formation versus Cyclopropanation



catalyst	Temp (°C)	%1	%2
$\text{Pd}_2\text{Cl}_2(\text{C}_3\text{H}_5)_2$	RT	53	3
$\text{Cu}(\text{PhCOCHCOMe})_2$	80	50	13
$(\text{MeO})_3\text{PCuI}$	RT	3	35
$\text{Rh}_2(\text{OAc})_4$	RT	1	58
None	80	15	54

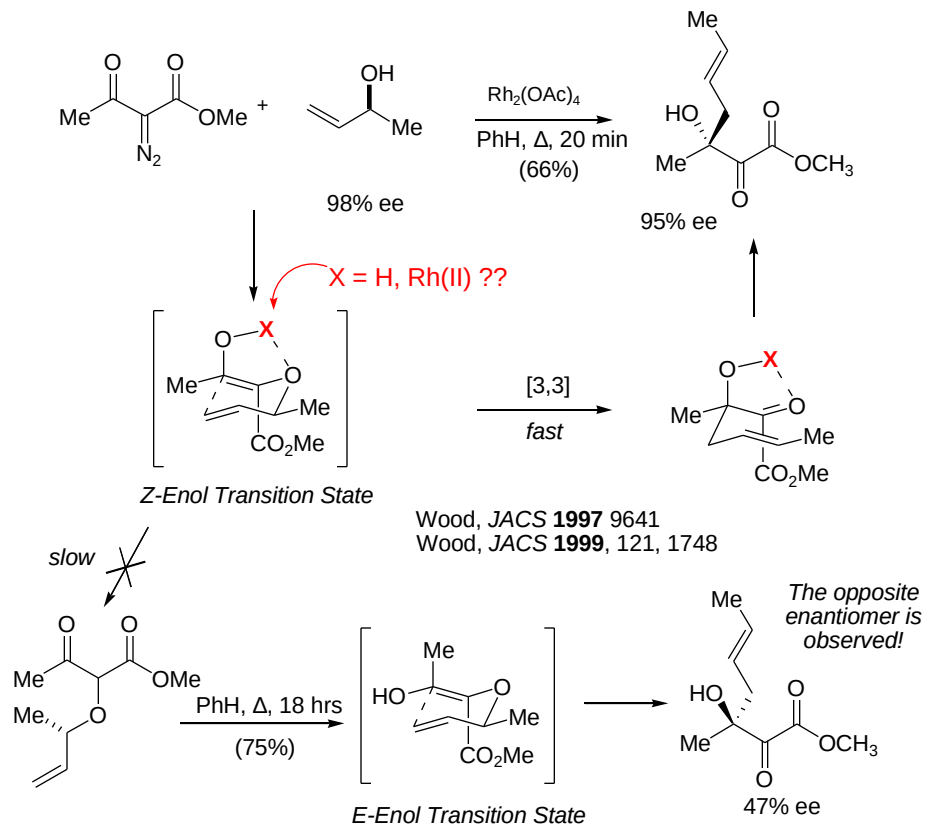
it is evident that these are reactions of metal carbenoids

Bien, S.; Gillon, A.; Kohen, S. *J. Chem. Soc. Perkin Trans. I.* **1976**, 489-492

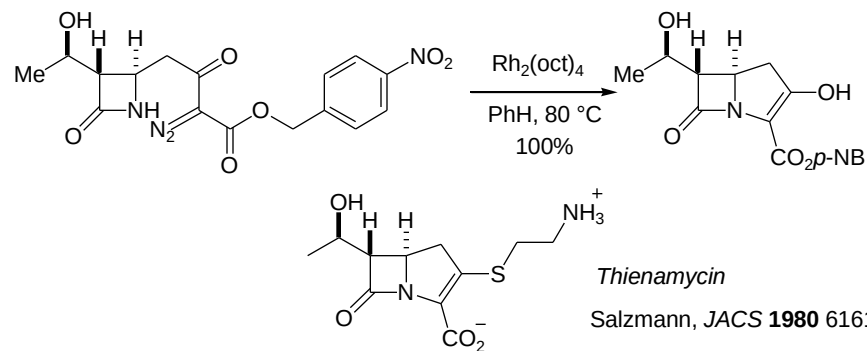


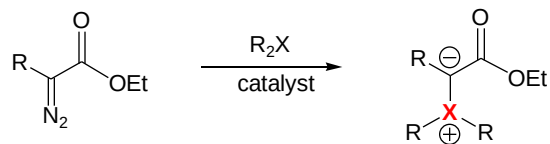
Doyle, M. P., et al. *J. Org. Chem.* **1991**, 56, 820-829.
Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, 30, 5397.

Tandem O-H Insertion/Claisen Rearrangement



Merck Thienamycin Process

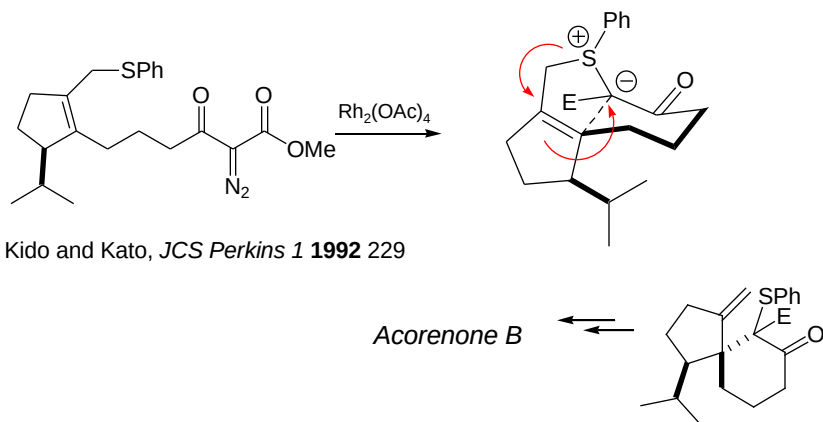
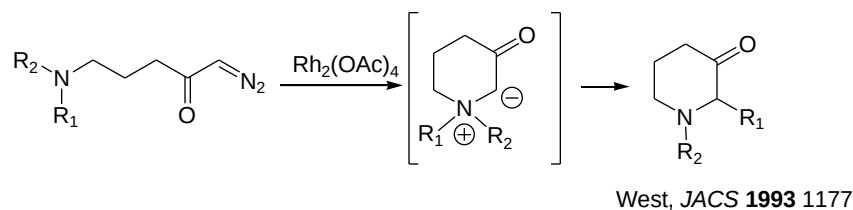


Ylide Formation

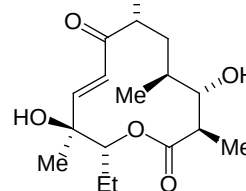
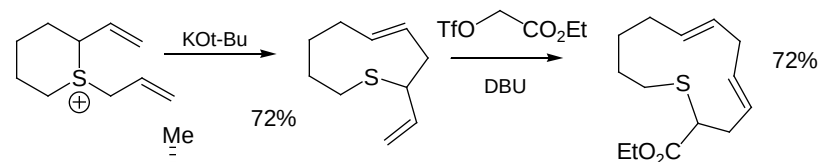
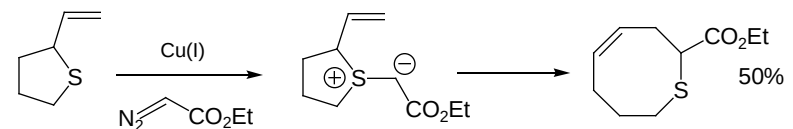
Reviews: Padwa, *Chem. Rev.* **1991** 263
 Padwa, *Chem. Rev.* **1996** 223
 Barnes, Evening Seminar, March 16, 1993

X is generally S, O or N and can be sp^2 or sp^3 hybridized

Ylides often undergo sigmatropic rearrangements or cycloadditions

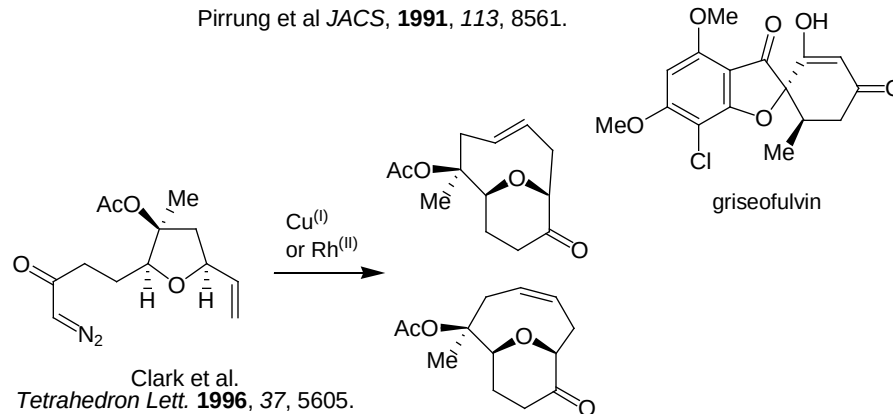
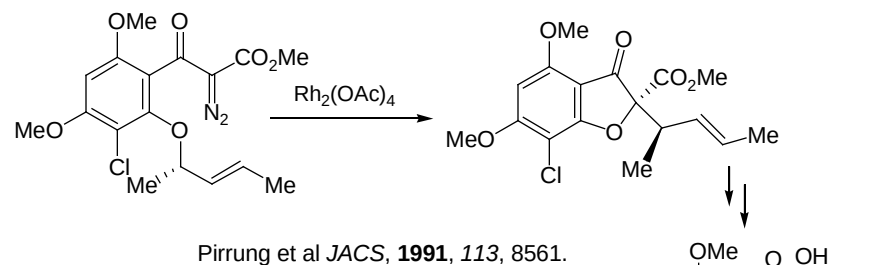
[2,3]-Sigmatropic rearrangement:**Stevens Rearrangement ([1,2] alkyl shift):****Ring expansion reactions have been investigated**

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



<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, Jablonski 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, Chapter 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.

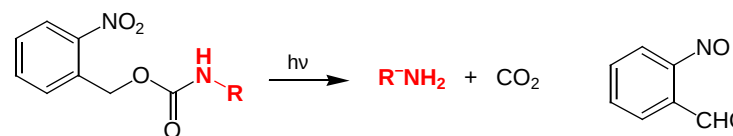
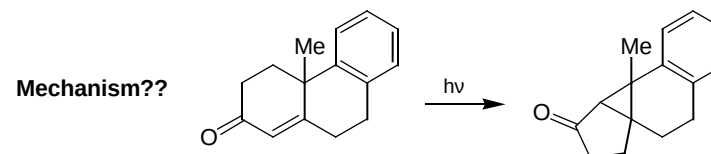
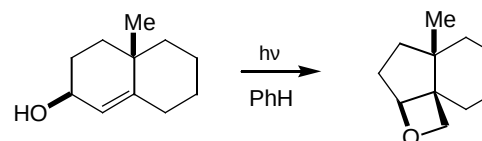
"Stereoselective intermolecular [2+2]-photocycloaddition reactions and their application in synthesis.", Bach, T. *Synthesis* **1998**, 683-703.

"[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).



The above reaction forms the basis of a photo-labile protecting group strategy for amines and alcohols

Background Reading

Carey, and Sundberg, *Advanced Organic Chemistry*, Parts A
Third Edition, Chapter 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.

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"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.

$$E = h\nu = \frac{hc}{\lambda}$$

for $\lambda = 200 \text{ nm}$: $E = 143 \text{ kcal}$

for $\lambda = 700 \text{ nm}$: $E = 40.9 \text{ kcal}$

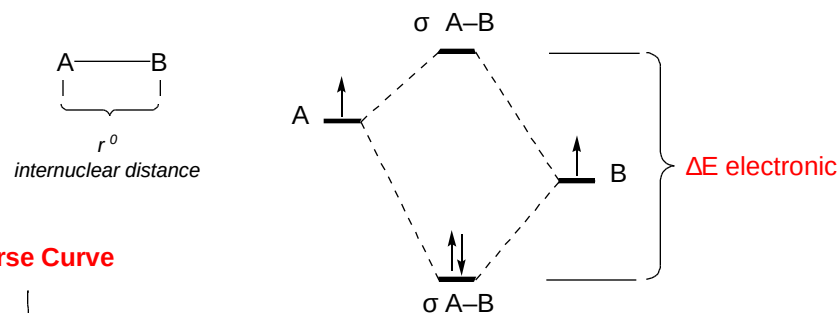
Knowing the absorption wavelength in nm, you can calculate the the energy

$$E \text{ (kcal/mol)} = \frac{2.86 \times 10^4}{\lambda \text{ (in nm)}}$$

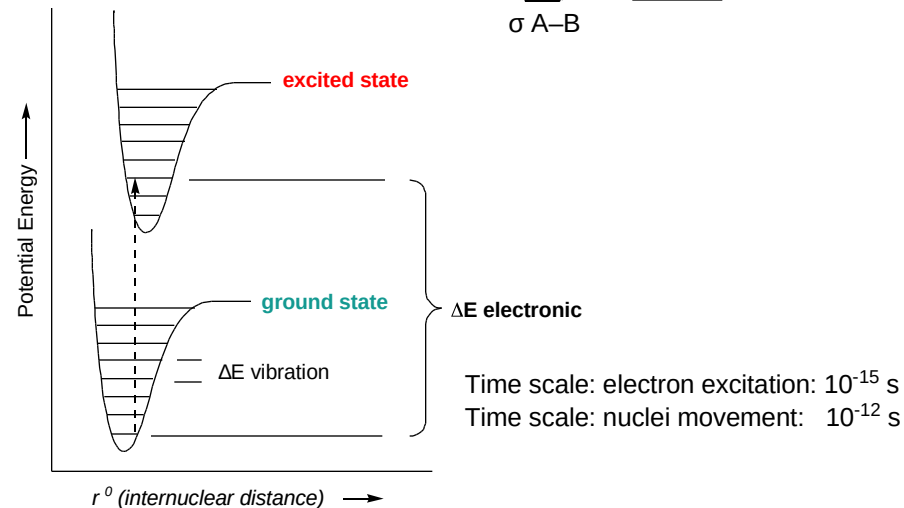
for $\lambda = 200 \text{ nm}$: $E = 143 \text{ kcal}$

for $\lambda = 700 \text{ nm}$: $E = 40.9 \text{ kcal}$

Consider a simple diatomic molecule **A–B**

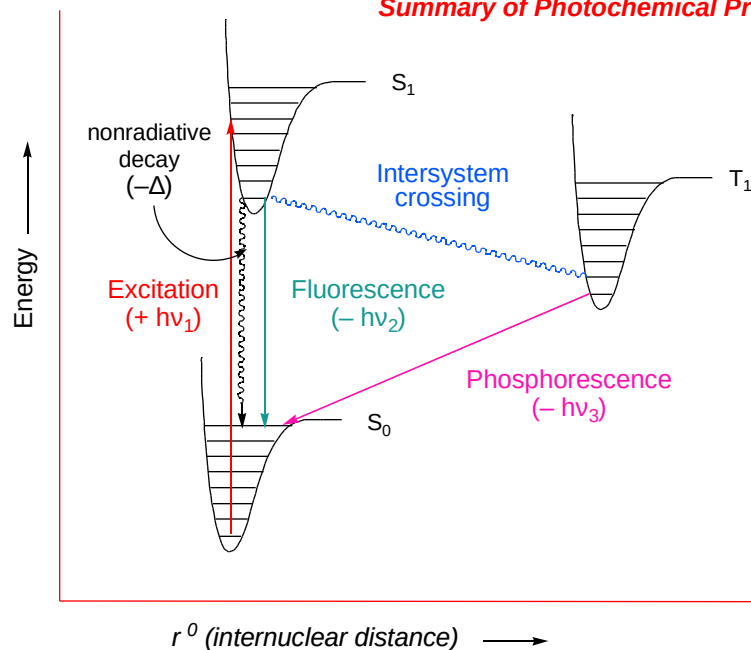


Morse Curve

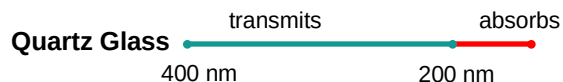
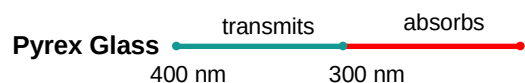


■ **Franck-Condon Principle:** Upon light-induced electronic excitation, only the electrons are reorganized; the heavier nuclei stay in their ground-state geometry. (**Vertical Transitions**)

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

$$M = 2S + 1$$

$$S = \sum s$$

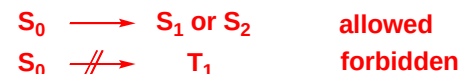
M: multiplicity

S: total spin

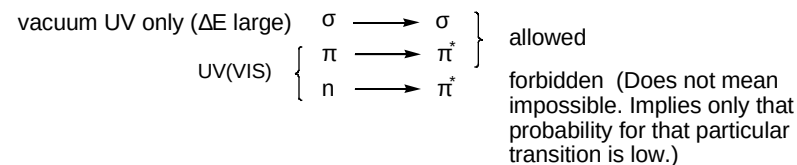
s: spin of a single electron ($\pm 1/2$)

Spins Paired: Singlet State: $S = \sum s = (+1/2 - 1/2) = 0$

Spins Unpaired: Triplet State: $S = \sum s = (+1/2 + 1/2) = 1$

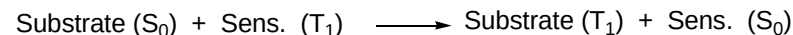


(b) **Space-forbidden:** transitions between orbitals which do not overlap.



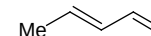
■ **Sensitizer:** e.g. acetophenone, benzophenone

Small ΔE between S_0 & S_1 . Facile excitation into S_1 followed by ISC into T_1 .
Interaction with substrate:

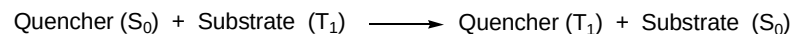


Substrate reacts via T_1 excited state.

■ **Triplet-Quencher:** e.g. O_2 , piperylene



Reacts immediately with molecules in T_1 excited state, depopulate T_1



Substrate reacts via S_1 excited state.

Jablonski Diagram

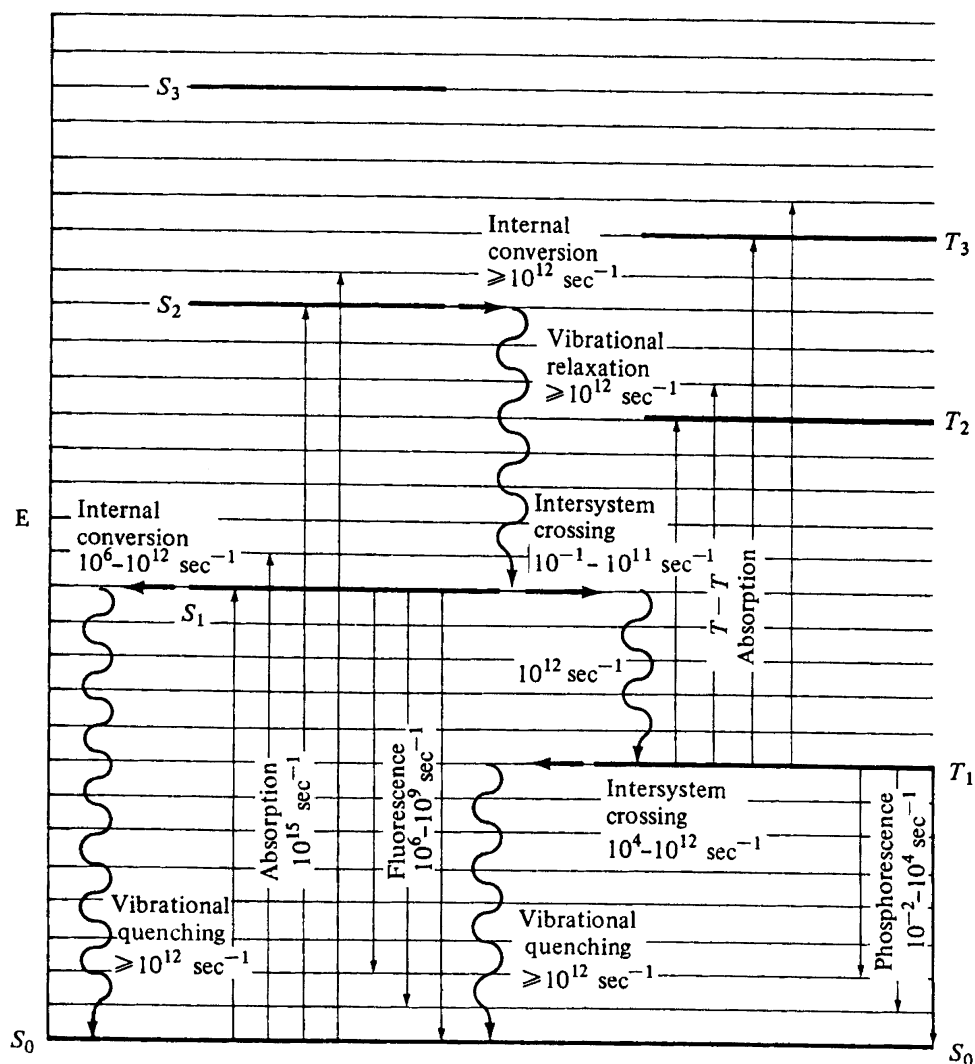


Figure 12.2 Jablonski diagram. Energy levels of excited states of a polyatomic molecule. The lowest vibrational energy levels of a state are indicated by thick horizontal lines; other horizontal lines represent associated vibrational levels. Vertical straight lines represent radiative transitions, wavy 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.

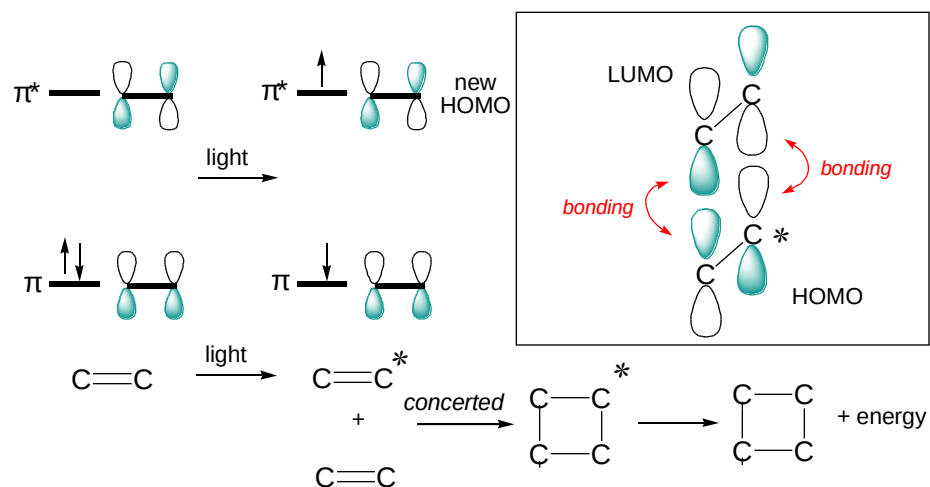
Photochemical Reactions

Frontier MO Description

Fleming, I. "Frontier Orbitals and Organic Chemical Reactions", Chapter 6, "Photochemical Reactions"

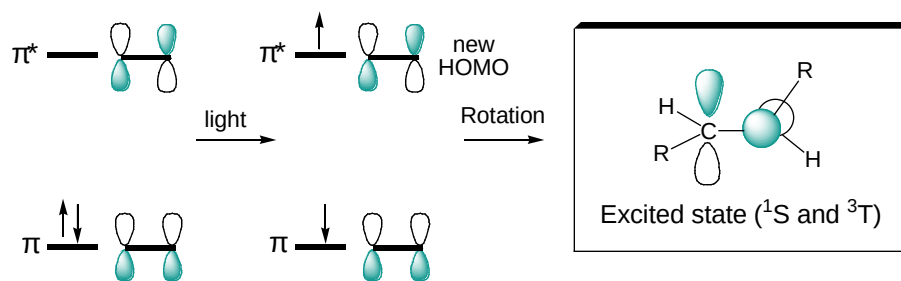
Reactions of Olefins

Consider [2 + 2] cycloaddition: Photochemical activation

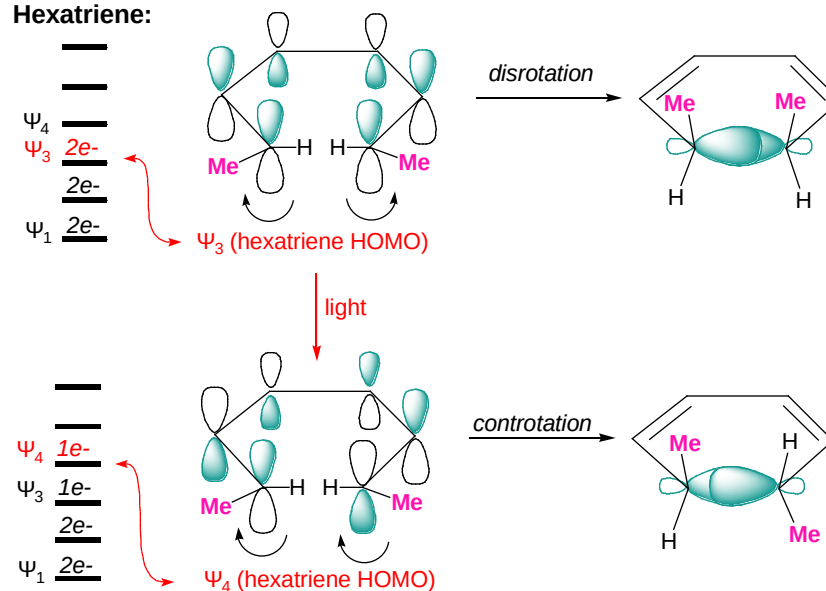


The [2 + 2] cycloaddition of two olefins exhibits the option of being concerted if one of the olefins reacts out of its photochemically excited state.

Excited State Geometry



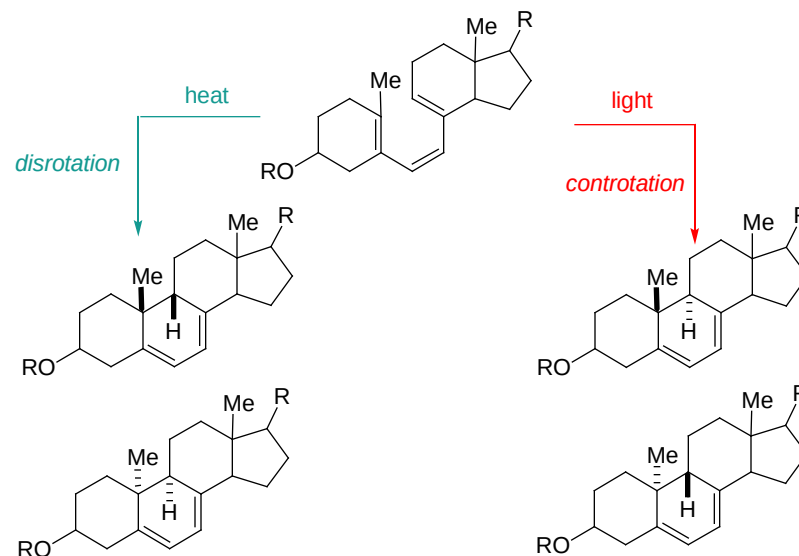
Hexatriene:



The rotatory motion of ring closure may be reversed by photo-activation

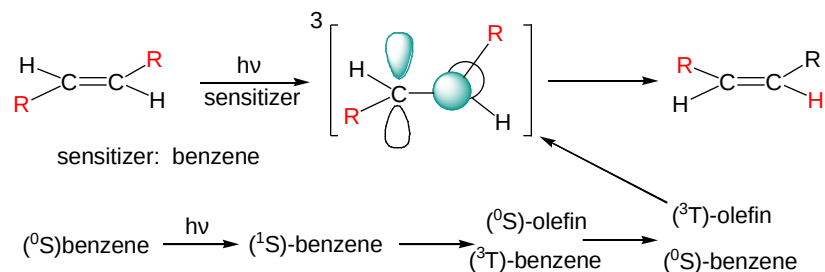
One of the first cases where heat and light induced electrocyclizations followed different pathways.

Havinga, *Tetrahedron*, **1961**, 16, 146.

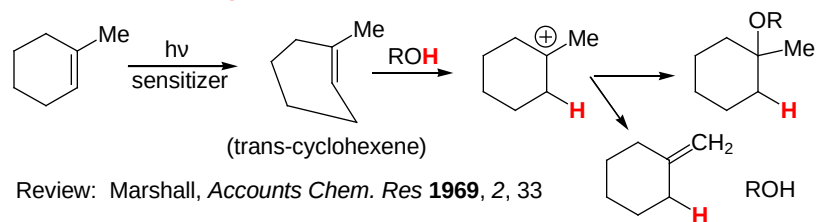


Cis-Trans Isomerization

Cis & trans olefins may be interconverted by either direct or sensitized irradiation

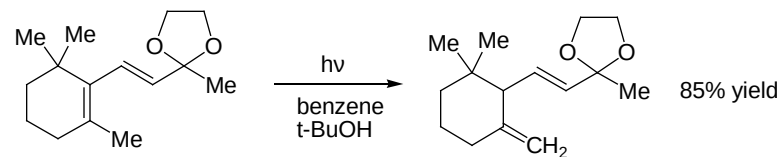
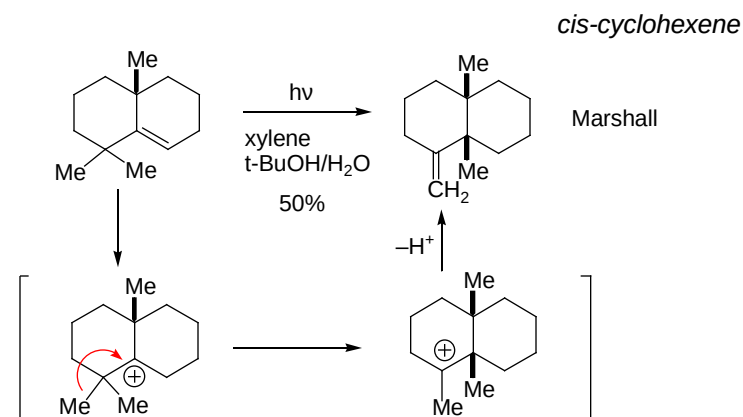
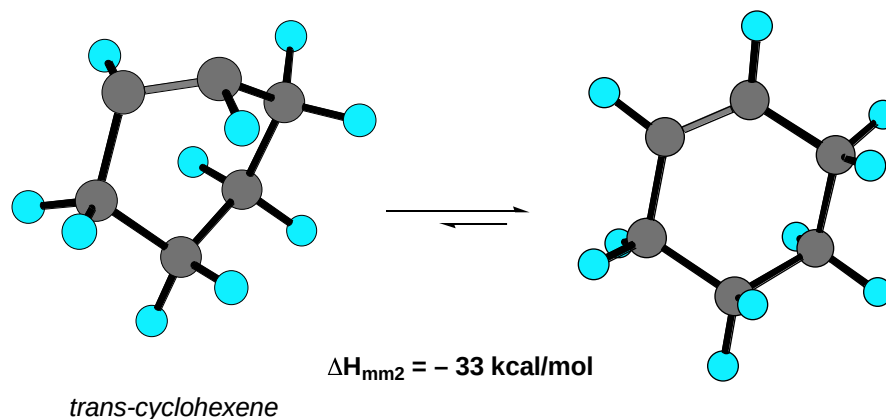
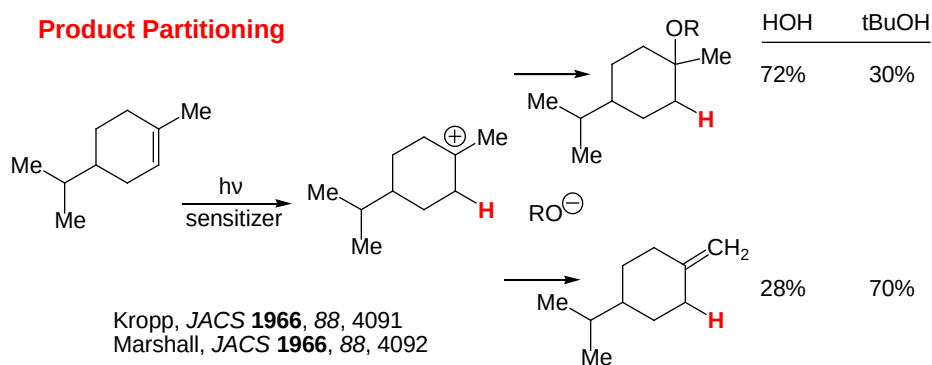


Sensitized Photohydration

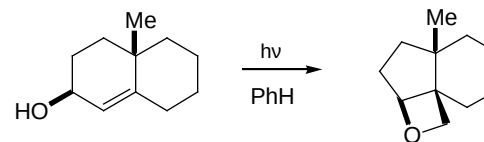


Ground state trans cyclohexene is now sufficiently basic to deprotonate alcohols

Product Partitioning

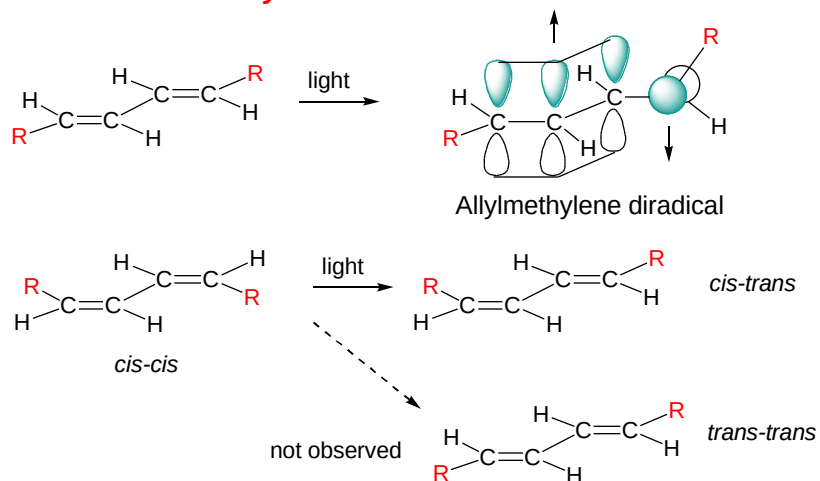


Evans et. al. unpublished results, 1972

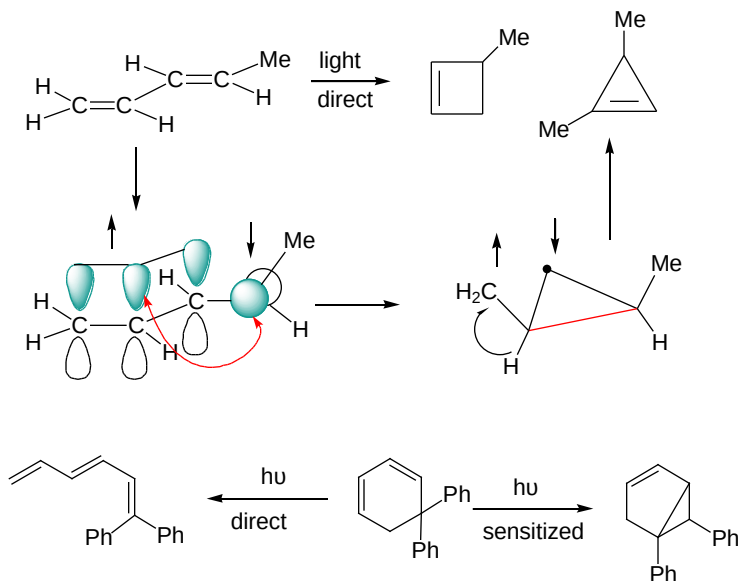


(Marshall, *JOC*, **1971**, 214).

Excited State Geometry of Dienes



Explain why trans-trans isomer is not observed in this photoisomerization

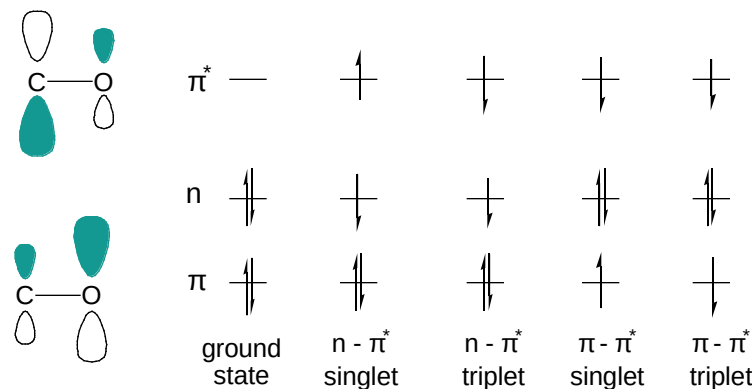
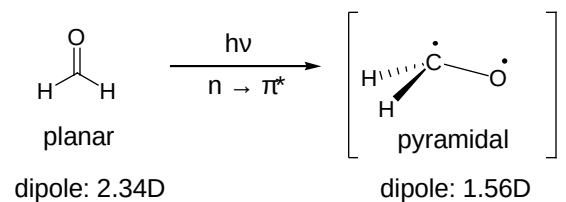


Rationalize the course of the sensitized transformation

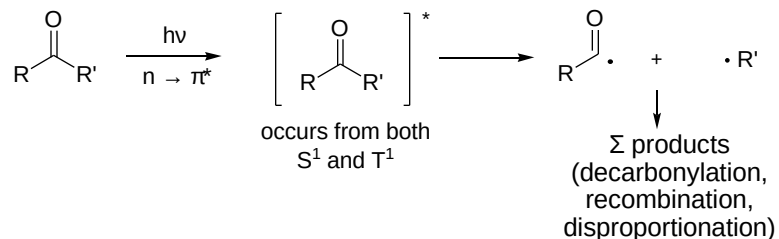
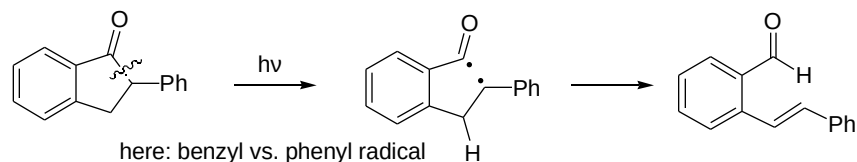
Photochemistry of Carbonyl Compounds

Photochemical excitation of carbonyl group: $n \rightarrow \pi^*$

S^1	80–85 kcal/mol
T^1	75–80 kcal/mol



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.**Regioselectivity of bond cleavage: Depends on relative stability of the two radicals formed.**

Reaction occurs readily if stabilized radicals are formed.

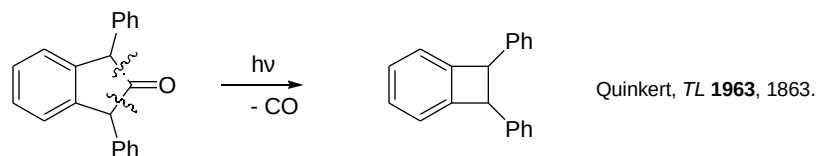
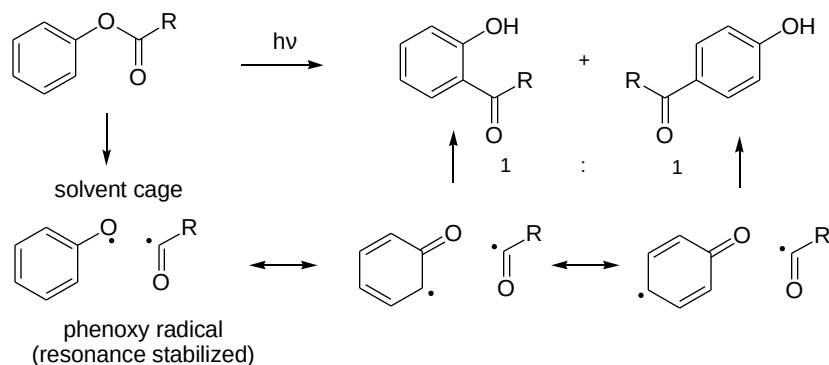
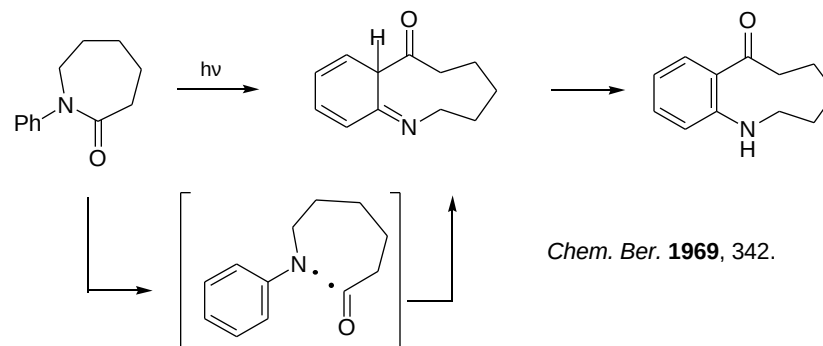
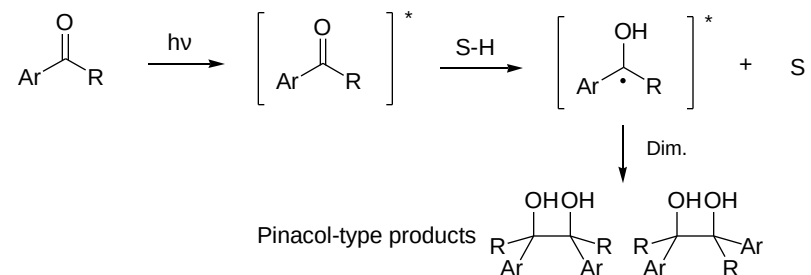
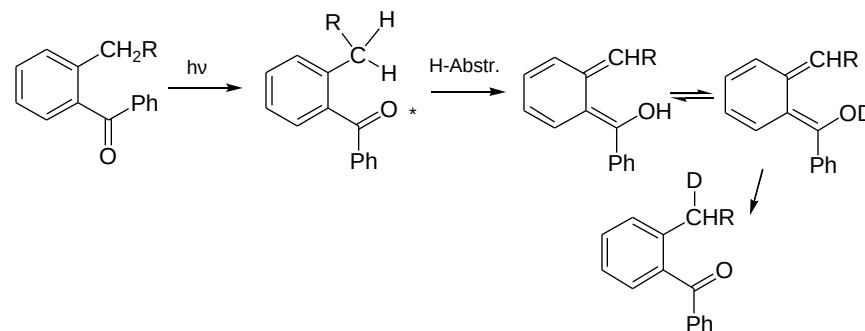
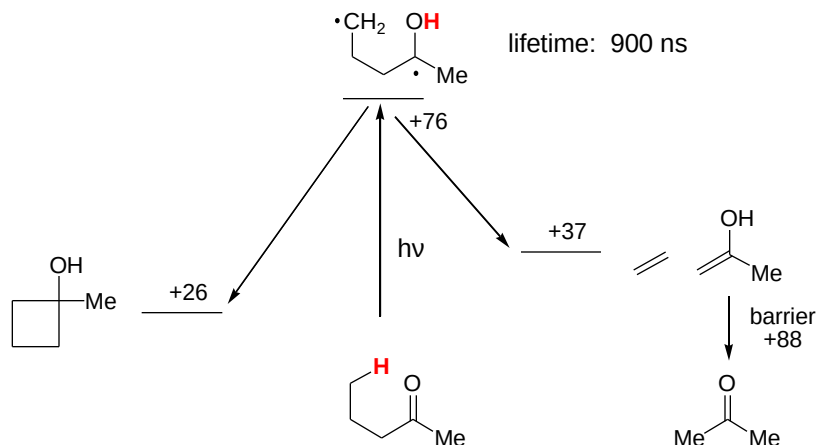
**C/O and C/N bond cleavage: Photo-Fries rearrangement****C/N bond cleavage: Aza-Fries rearrangement****Norrish-type II reactions** Acc. Chem. Res. **1971**, 4, 168.

Photo-excitation of carbonyl is followed by hydrogen atom abstraction.

Intermolecular (Reaction with solvent)**Intramolecular (a) Photoenolization**

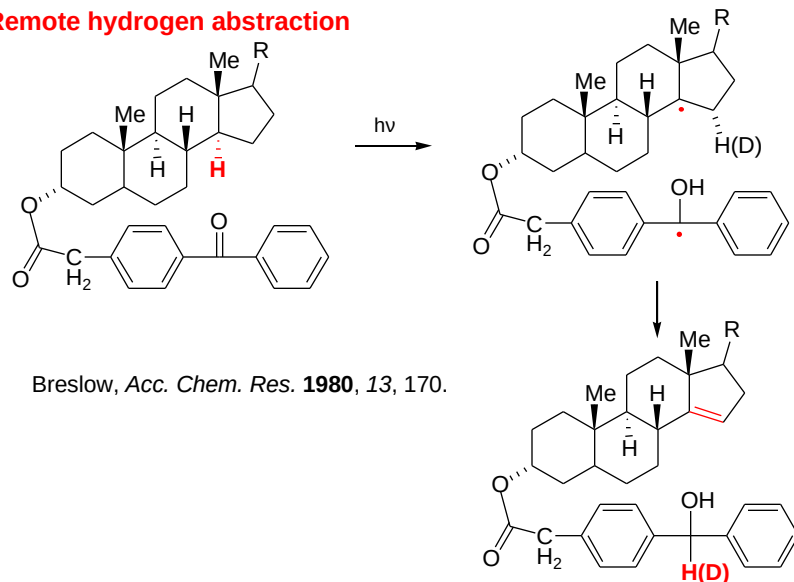
Norrish-type II reactions continued...gamma H Abstraction

"Femtosecond Dynamics of Norrish Type-II Reaction: Nonconcerted Hydrogen Transfer and Diradical Intermediacy", 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
- Fragmentation similar to McLafferty Rearrangement in mass spectroscopy

Remote hydrogen abstraction

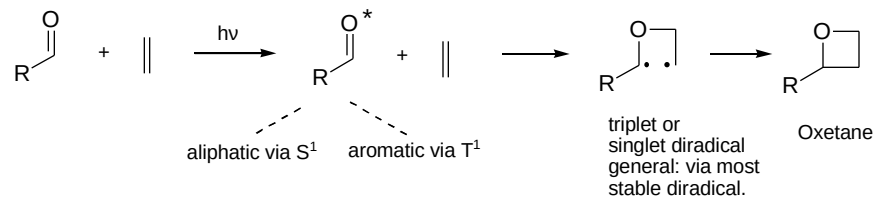


Breslow, *Acc. Chem. Res.* **1980**, *13*, 170.

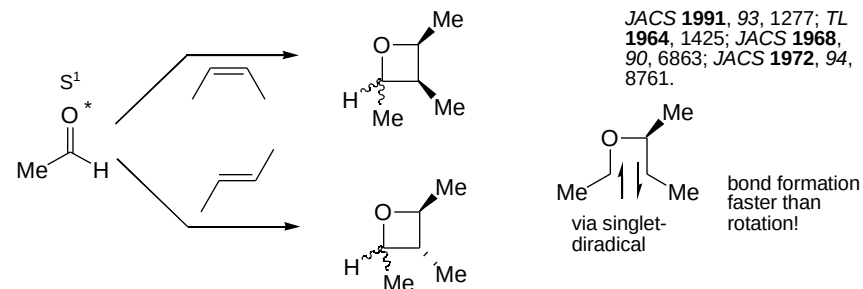
Paterno-Büchi Reaction

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.

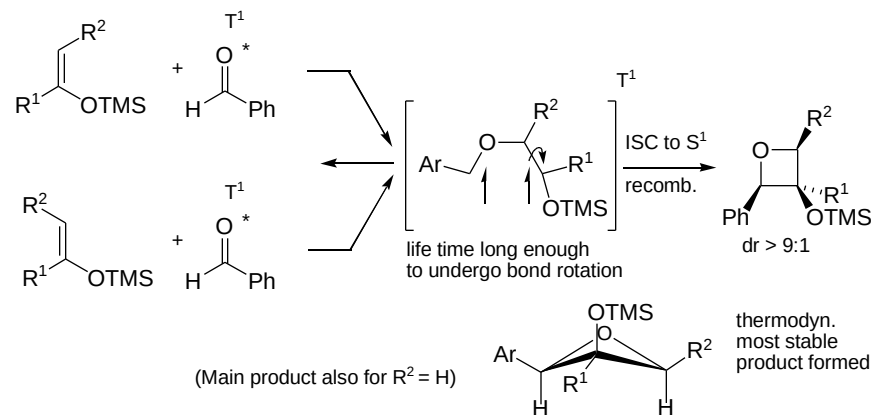
Me  Me
via singlet-diradical

bond formation
faster than
rotation!

Aromatic aldehydes/ketones show stereo-convergent behavior:

(a) simple diastereoselectivity

T. Bach, *Liebigs Ann.*
1997, 1627.

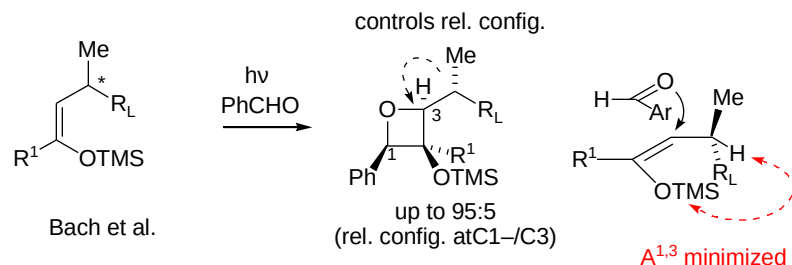


(Main product also for $R^2 = H$)

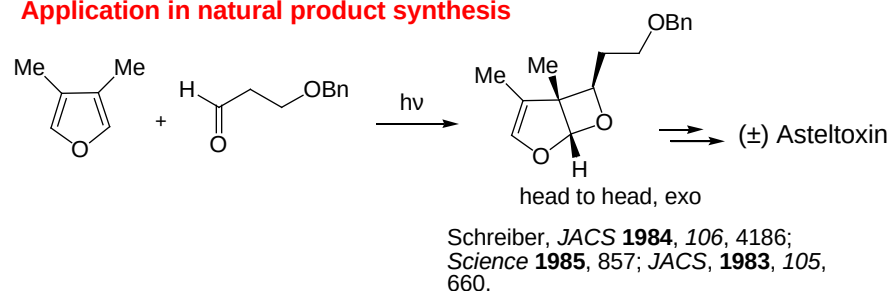
thermodyn.
most stable
product formed

Paterno-Büchi Reaction continued....

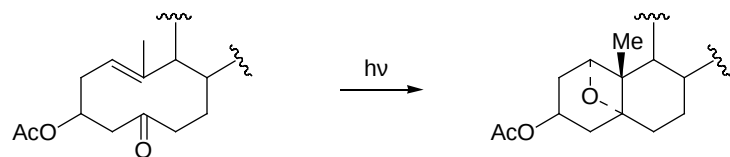
Induced facial diastereoselectivity



Application in natural product synthesis



Transannular reaction



"Stereoselective intermolecular [2+2]-photocycloaddition reactions and their application in synthesis.", Bach, T. *Synthesis* **1998**, 683-703.

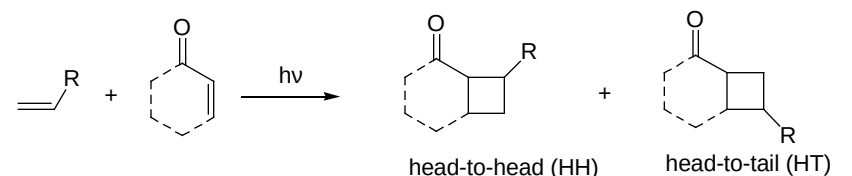
Photocycloaddition of Enones

"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.

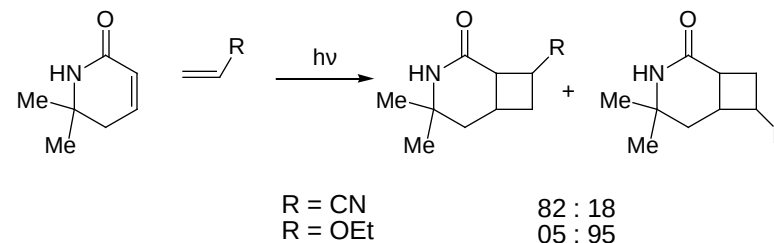
"[2+2] photocycloaddition/fragmentation strategies for the synthesis of natural and unnatural products.", Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, 95, 2003-2020.

"Synthetic Applications of Intramolecular Enone-Olefin Photocycloadditions.", Crimmins, M. T. *Chem. Rev.* **1988**, 88, 1453.

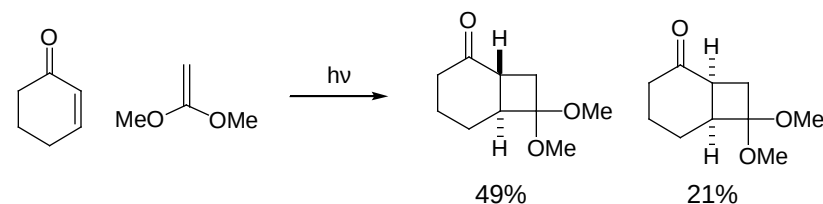
Reaction Regiochemistry



Favored: R = EWG Favored: R = Donor



Ring Fusion Stereochemistry

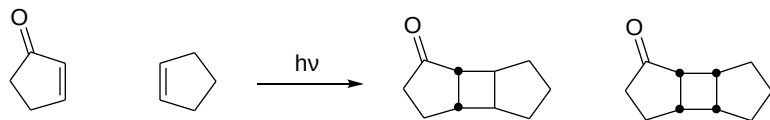


It is hard to rationalize the trans ring fusion stereochemistry through the intervention of a 1,4-diradical

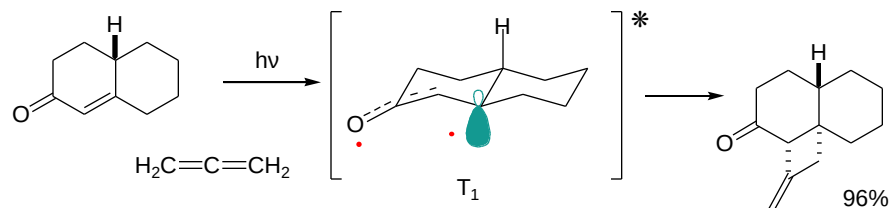
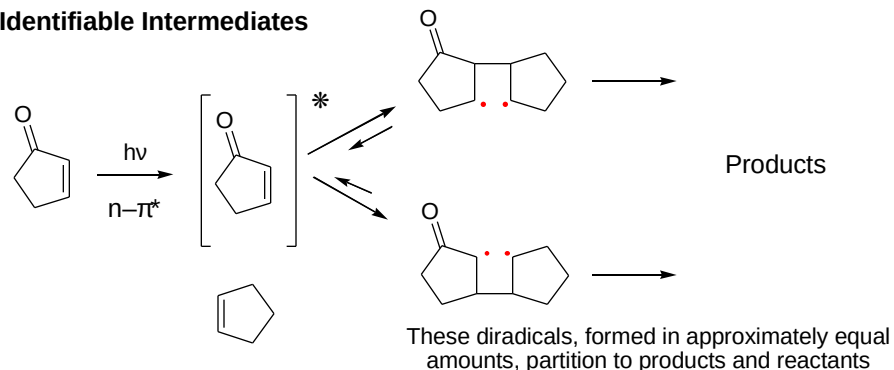
+ 6% other products

Corey *JACS* **1964**, 86, 485

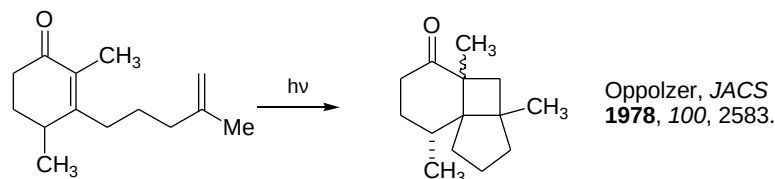
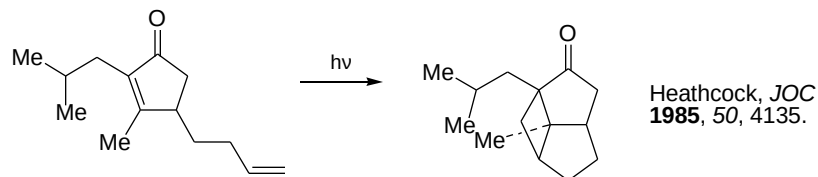
Photocycloaddition of Enones continued.....



Identifiable Intermediates

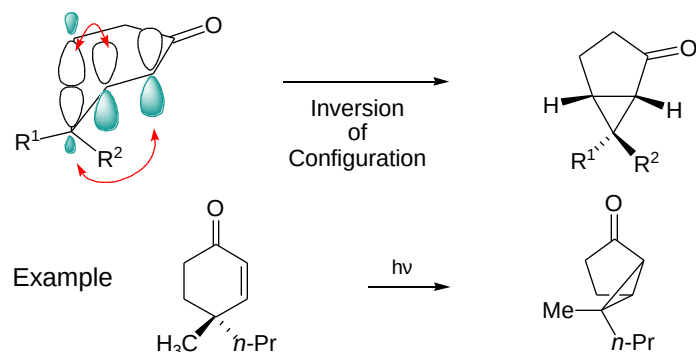
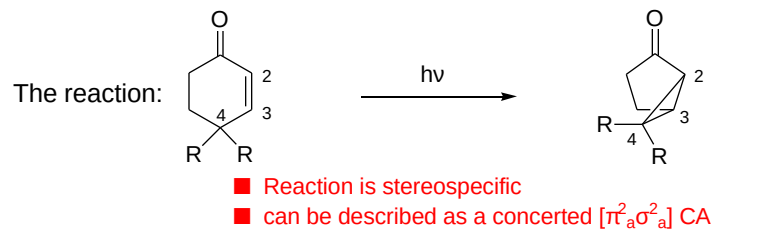


■ Intramolecular reactions work nicely



Photochemical Rearrangement of 4,4-Dialkyl-Substituted Cyclohexenones

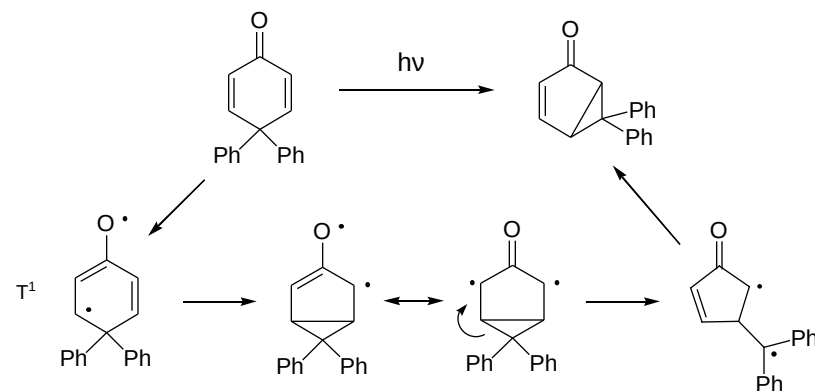
Review: Schuster in "Rearrangements in Ground and Excited States", Vol. 3, de Mayo (Ed.), Academic Press, NY 1980, Chapter 17.



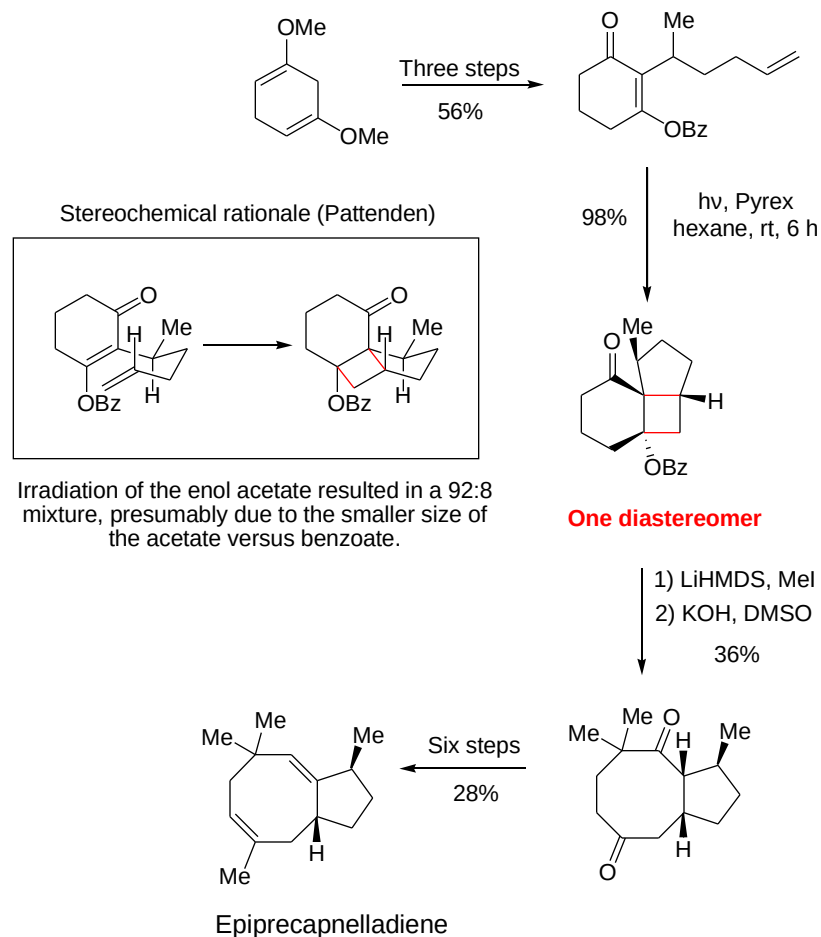
■ for $R^1, R^2 = \text{Aryl}$ non-concerted mechanisms compete

Cyclohexadienone Rearrangement

Zimmerman, ACIEE 1969, 8, 1; Acc. Chem. Res. 1978, 11, 65; de Mayo, Chapter 18.

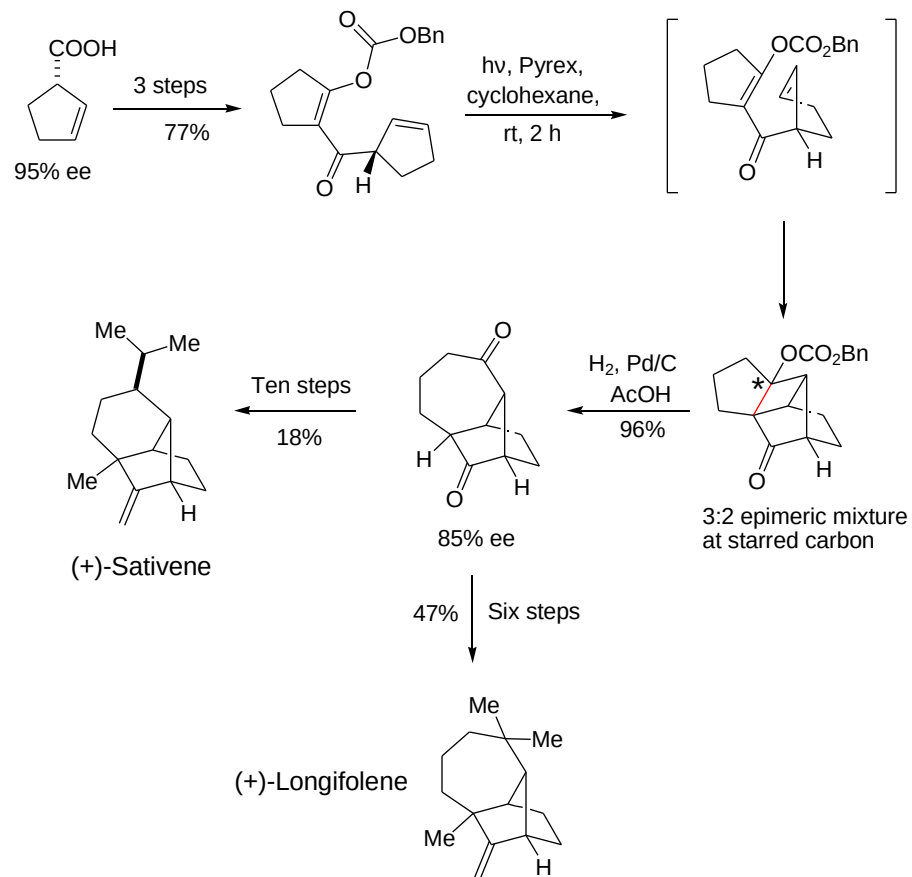


(±)-Epiprecapnelladiene



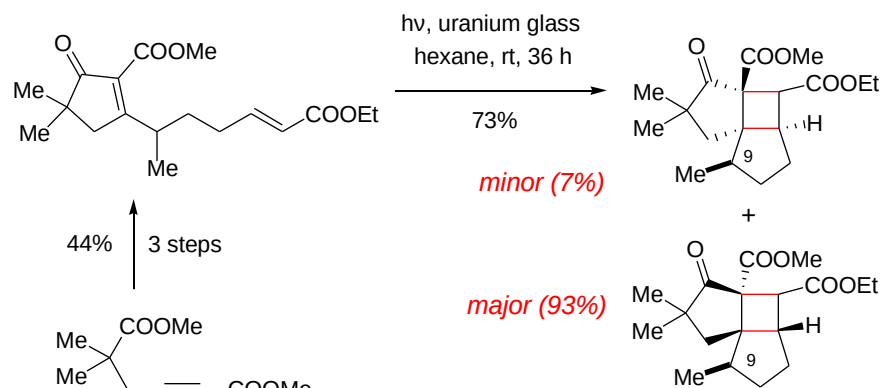
Pattenden, G., et al. *J. Chem. Soc., Chem. Comm.* **1980**, 1195.
Pattenden, G., et al. *J. Chem. Soc., Perkin Trans. I* **1983**, 1913.

(+) -Longifolene and (+) -Sativene



Oppolzer, W., et al. *J. Am. Chem. Soc.* **1978**, 100, 2583.
Oppolzer, W., et al. *Helv. Chim. Acta.* **1984**, 67, 1154.

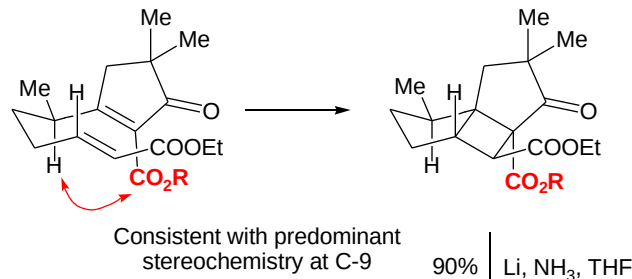
(±)-Pentalenene, (±)-Pentalenic Acid & (±)-Deoxypentalenic Acid from a Common Precursor



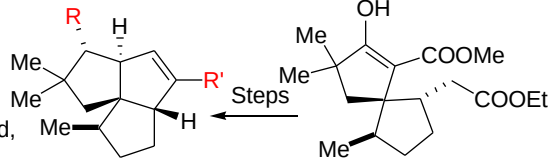
Stereochemical rationale (Crimmins)

R	C-9 dr
Me	13:1
Et	17:1
<i>i</i> -Pr	>20:1

Varying the size of the indicated alkyl group influenced the stereoselectivity

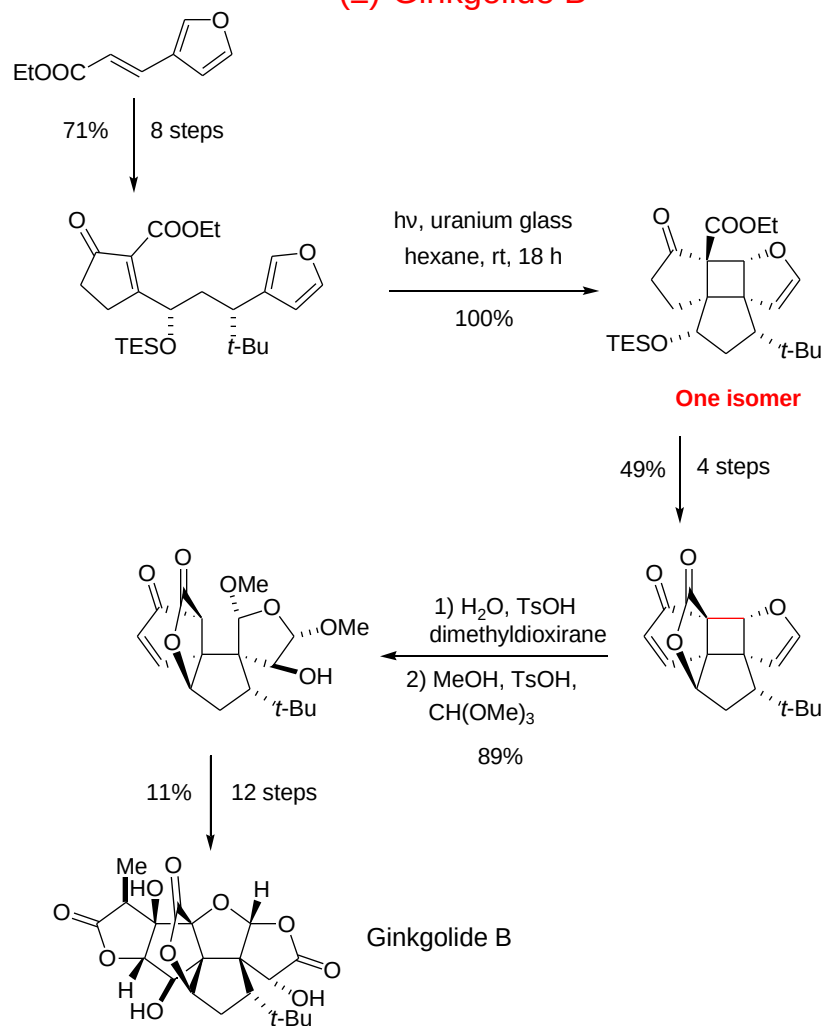


R=H, R'=Me, Pentalenene, nine steps, 27%
 R=OH, R'=COOH, Pentalenic acid, eight steps, 42%
 R=H, R'=COOH, Deoxypentalenic acid, eleven steps, 22%



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.