

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

<http://evans.harvard.edu/problems/>

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:

Kirby, Stereoelectronic Effects

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

Fleming, Chapter 1 & 2

Fukui, *Acc. Chem. Res.* **1971**, 4, 57. (pdf)

Curnow, *J. Chem. Ed.* **1998**, 75, 910 (pdf)

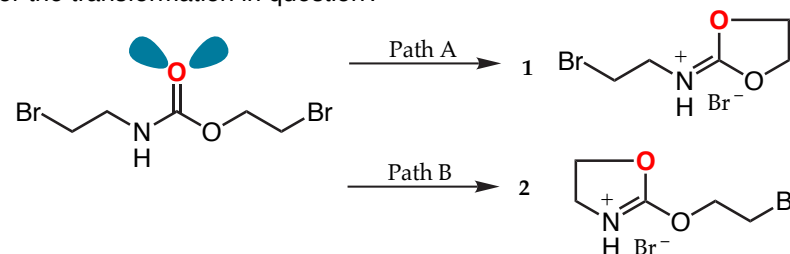
Alabugin & Zeidan, *JACS* **2002**, 124, 3175 (pdf)

D. A. Evans

Monday,
September 15, 2003

■ Problems of the Day

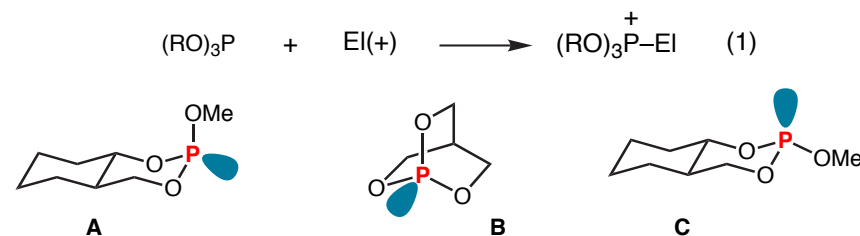
The molecule illustrated below can react through either Path A or Path B to form salt **1** or salt **2**. In both instances the carbonyl oxygen functions as the nucleophile in an intramolecular alkylation. What is the preferred reaction path for the transformation in question?



This is a "thought" question posed to me by Prof. Duilo Arigoni at the ETH in Zuerich some years ago

(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).

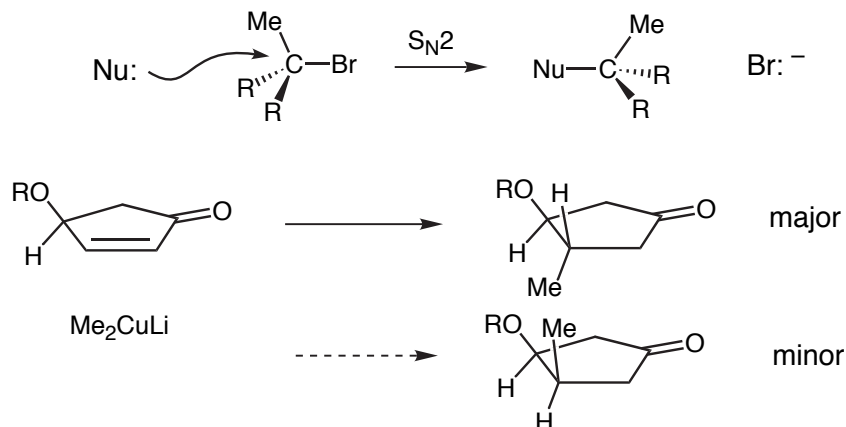


Rank the phosphites from the least to the most nucleophilic and provide a concise explanation for your predicted reactivity order.

Universal Effects Governing Chemical Reactions There are three:

■ Steric Effects

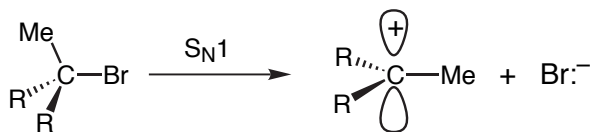
Nonbonding interactions (Van der Waals repulsion) between substituents within a molecule or between reacting molecules



■ Electronic Effects (Inductive Effects):

The effect of bond and through-space polarization by heteroatom substituents on reaction rates and selectivities

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



rate decreases as R becomes more electronegative

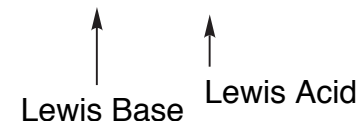
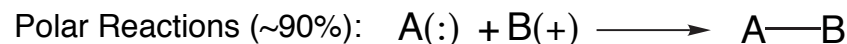
■ Stereoelectronic Effects

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

Fukui Postulate for reactions:

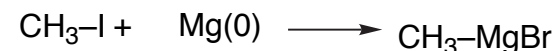
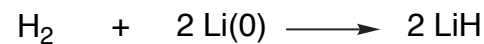
"During the course of chemical reactions, the interaction of the highest filled (HOMO) and lowest unfilled (antibonding) molecular orbital (LUMO) in reacting species is very important to the stabilization of the transition structure."

■ General Reaction Types



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

■ Examples to consider



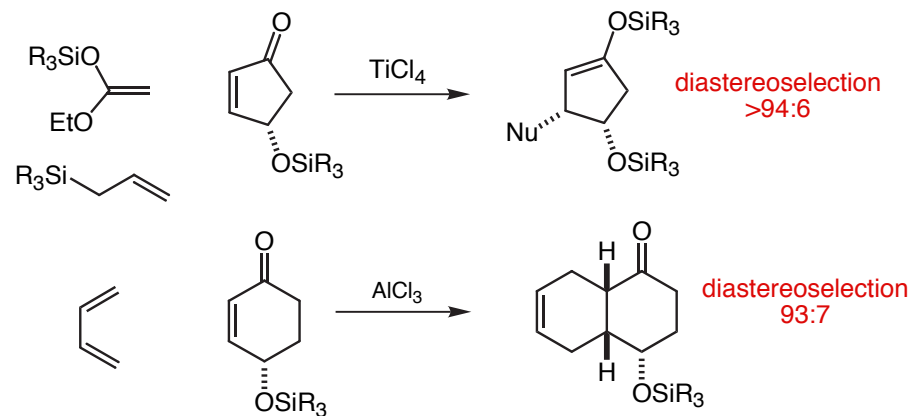
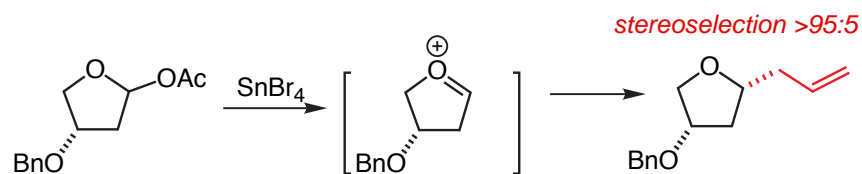
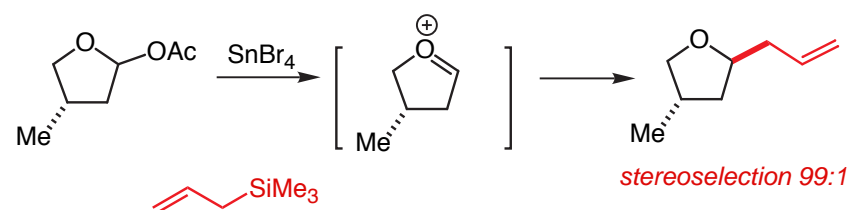
"Organic chemists are generally unaware of the impact of electronic effects on the stereochemical outcome of reactions."

"The distinction between electronic and stereoelectronic effects is not clear-cut."

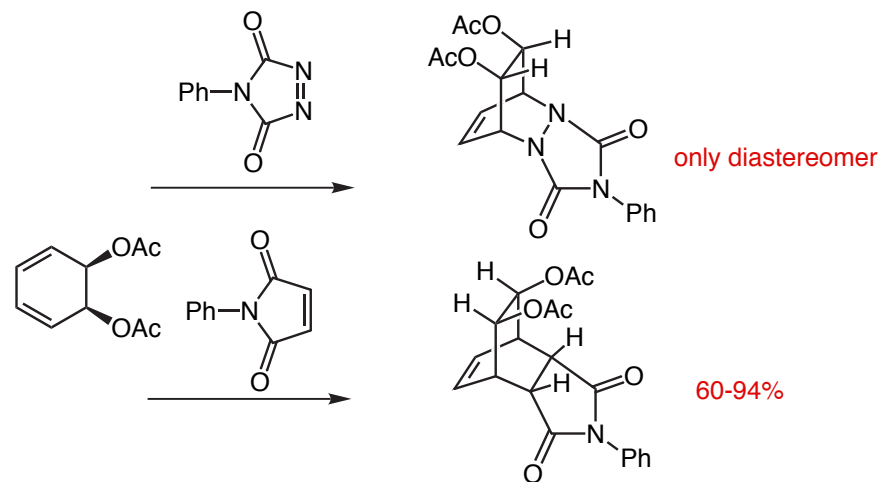
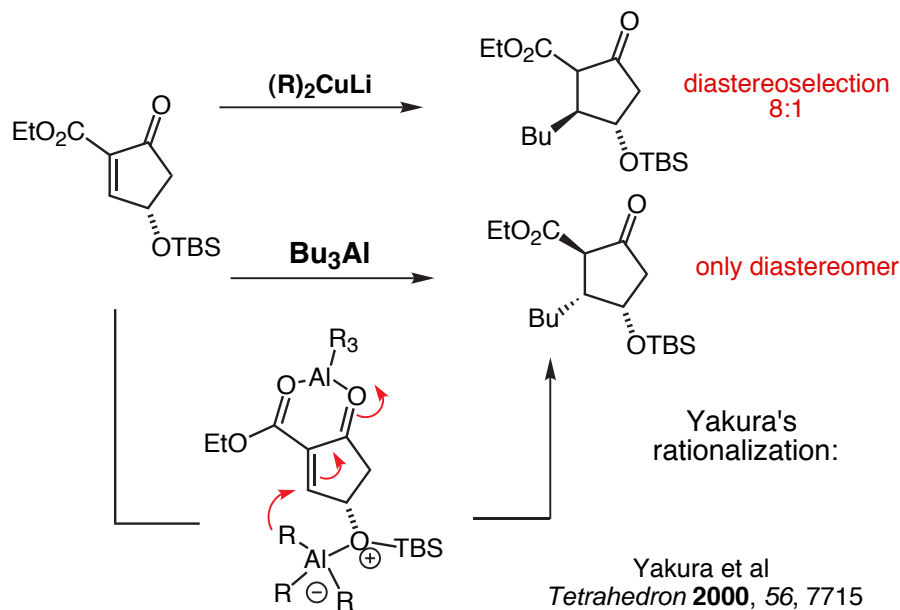
■ Steric Versus electronic Effects: Some Case Studies

When steric and electronic (stereoelectronic) effects lead to differing stereochemical consequences

Woerpel et al. *JACS* **1999**, 121, 12208.



Danishefsky et al *JOC* **1991**, 56, 387

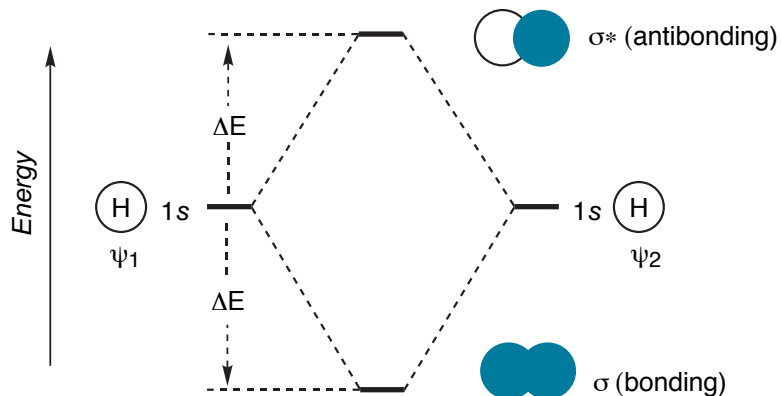


Mehta et al, *Acc Chem. Res.* **2000**, 33, 278-286

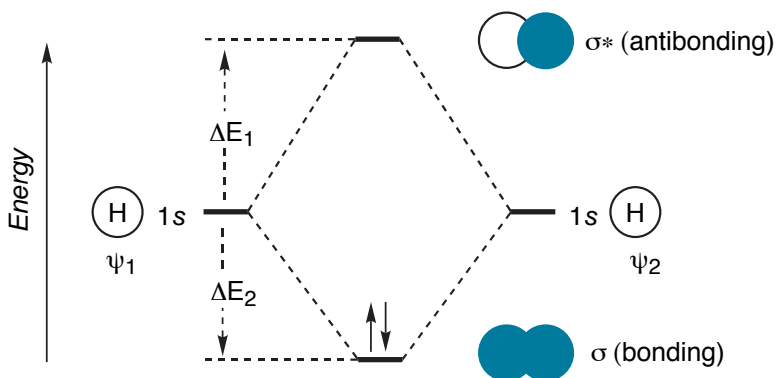
The H₂ Molecule (again!!)

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 ΔE_1 is greater than ΔE_2 . Why?

Linear Combination of Atomic Orbitals (LCAO): Orbital Coefficients

■ Rule Two:

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

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

$$\text{Antibonding MO} \quad \sigma^* = C^*_1\psi_1 - C^*_2\psi_2$$

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

■ Rule Three:

$$(C_1)^2 + (C_2)^2 = 1$$

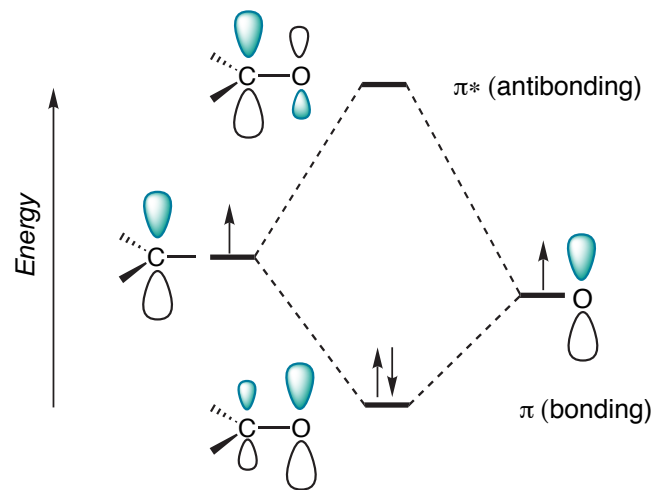
The squares of the C-values are a measure of the electron population in neighborhood of atoms in question

■ 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 ($\delta E_{\text{covalent}}$) and an ionic contribution (δE_{ionic}).**

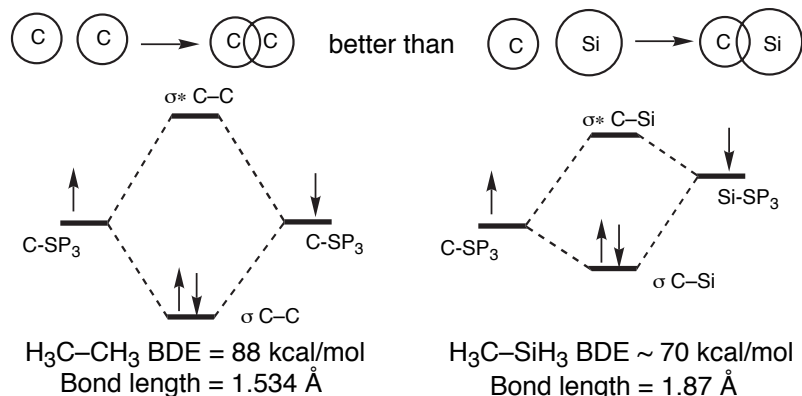
$$\text{Bond Energy (BDE)} = \delta E_{\text{covalent}} + \delta E_{\text{ionic}} \quad (\text{Fleming, page 27})$$

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:

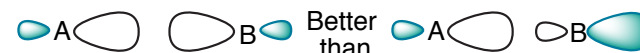
$$\pi \text{ C}-\text{C} = 65 \text{ kcal/mol} \quad \pi \text{ C}-\text{Si} = 36 \text{ kcal/mol} \quad \pi \text{ Si}-\text{Si} = 23 \text{ kcal/mol}$$

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

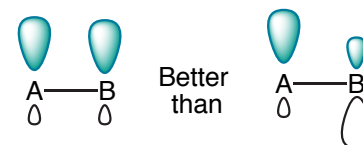
Formation of a weak bond will lead to a corresponding low-lying antibonding orbital. Such structures are reactive as both nucleophiles & electrophiles

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

For σ Bonds:



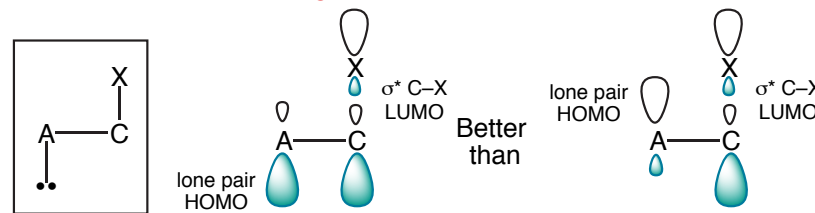
For π Bonds:



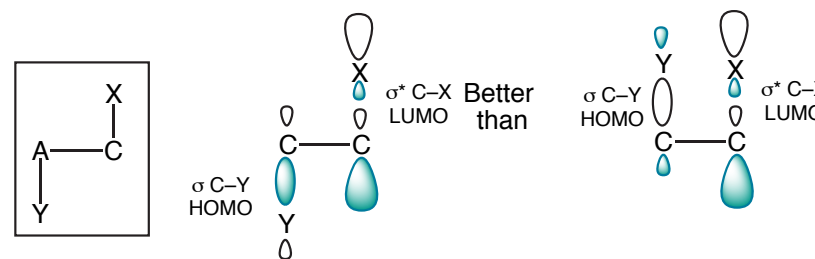
This is a simple notion with very important consequences. It surfaces in the delocalized bonding which occurs in the competing anti (favored) syn (disfavored) E2 elimination reactions. Review this situation.

■ **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

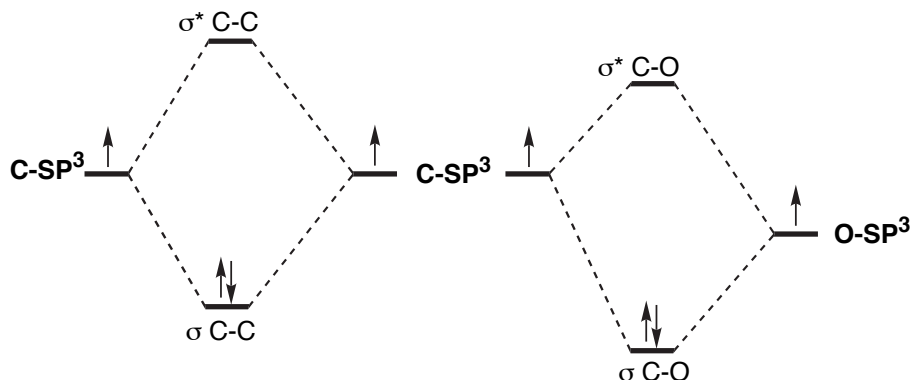


Case-2: Two anti sigma bonds



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

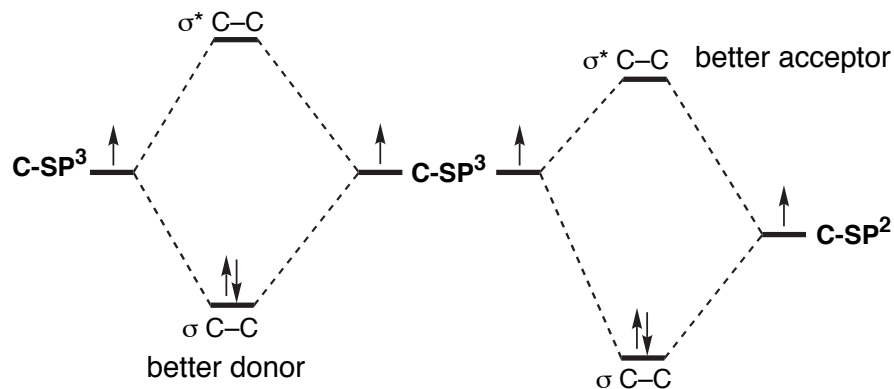
Consider the energy level diagrams for both bonding & antibonding orbitals for C-C and C-O bonds.



■ 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

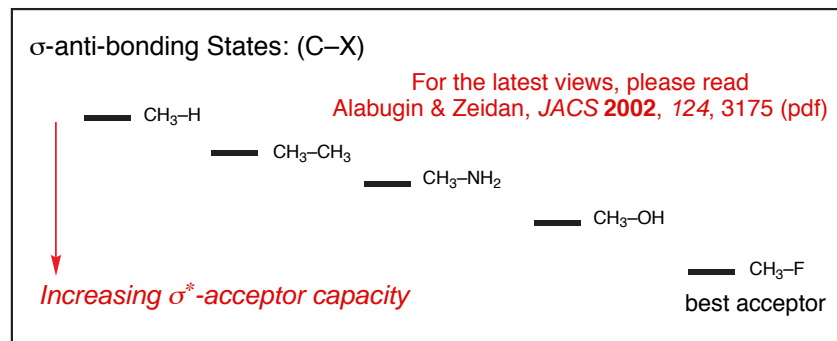
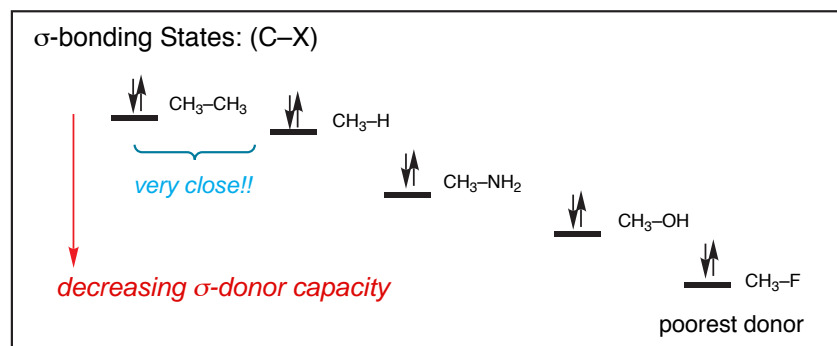


■ The greater electronegativity of C_{SP^2} lowers both the bonding & antibonding C-C states. Hence:

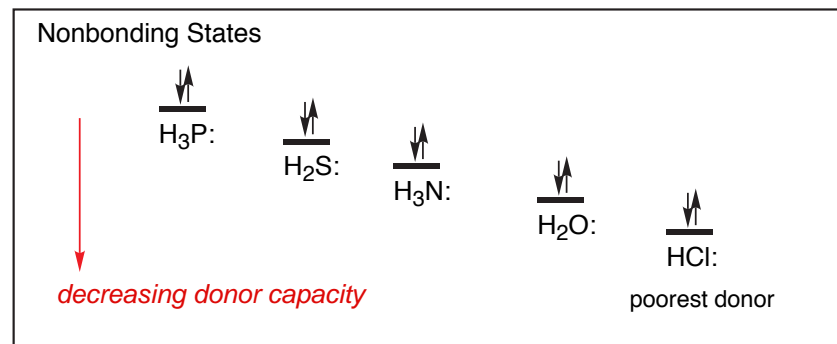
- σ C_{SP^3} - C_{SP^3} is a better donor orbital than σ C_{SP^3} - C_{SP^2}
- σ^* C_{SP^3} - C_{SP^2} is a better acceptor orbital than σ^* C_{SP^3} - C_{SP^3}

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

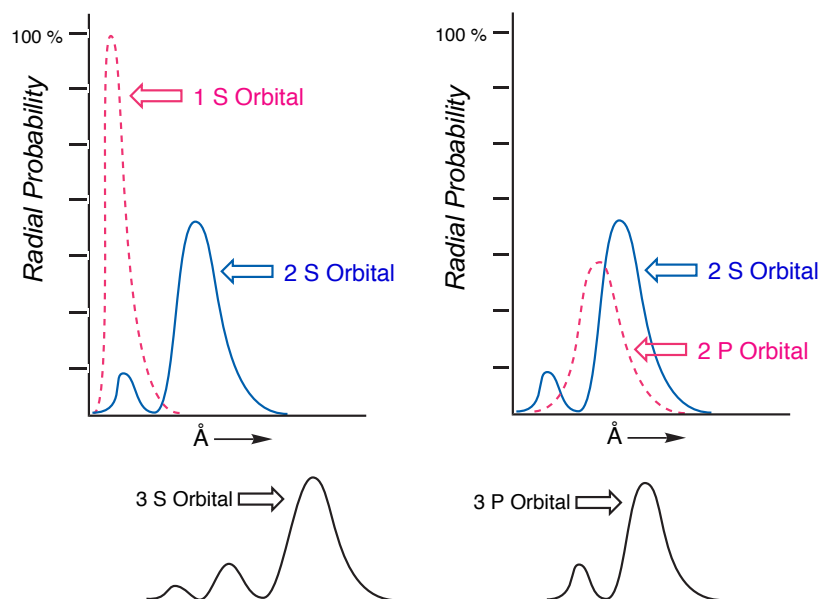


The following are trends for the energy levels of *nonbonding states* of several common molecules. Trend was established by photoelectron spectroscopy.



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.



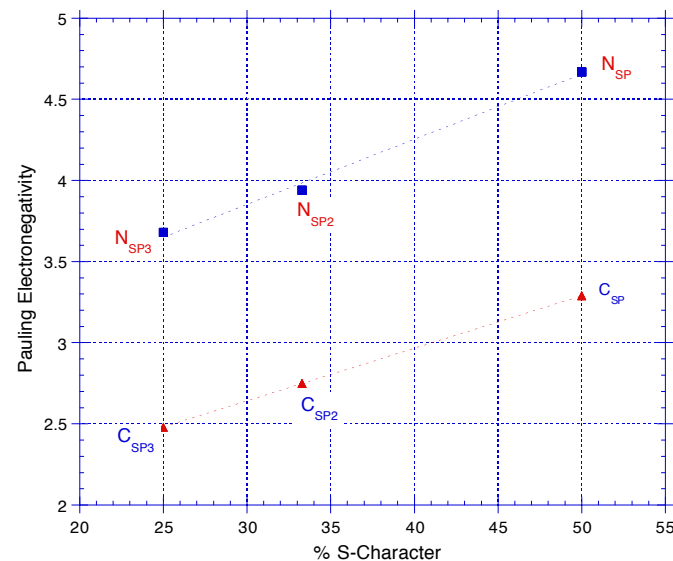
S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in S-states "see" a higher nuclear charge.

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

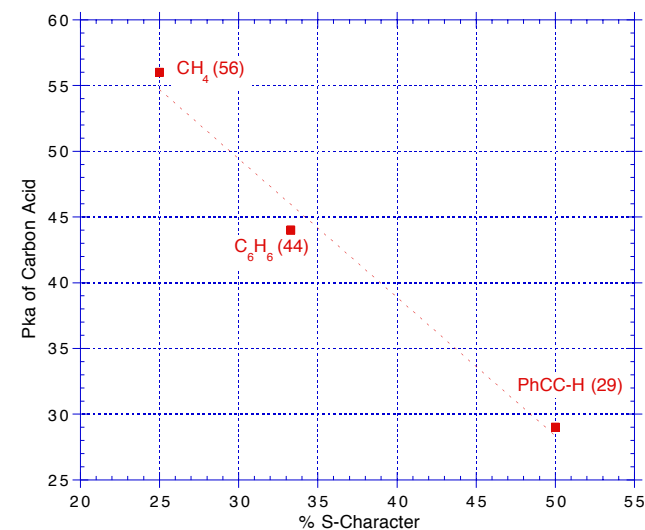


The above trend indicates that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

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

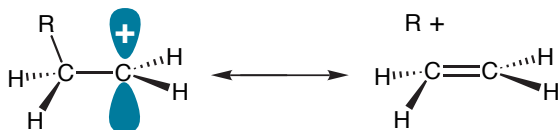


There is a direct relationship between %S character & hydrocarbon acidity



- 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.

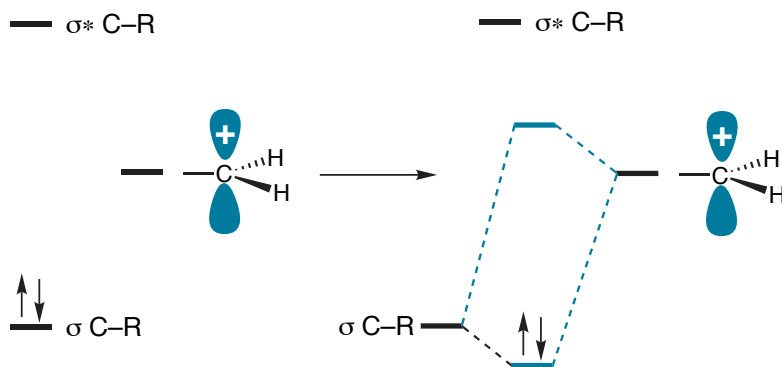


The graphic illustrates the fact that the C-R bonding electrons can "delocalize" to stabilize the electron deficient carbocationic center.

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



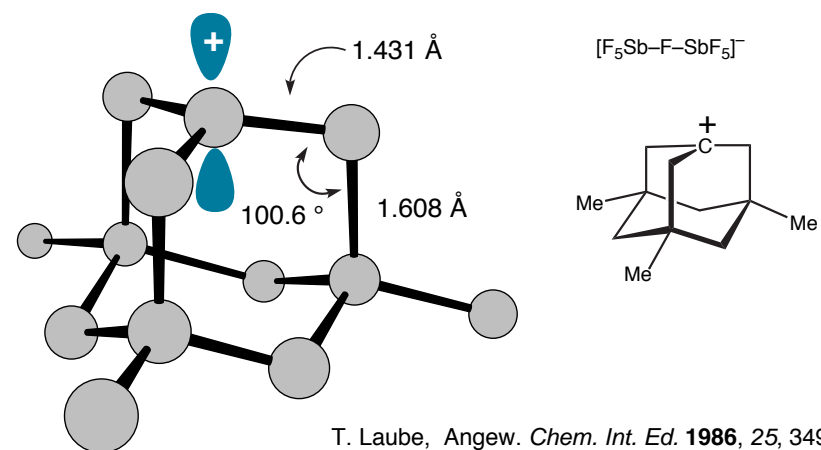
- Take a linear combination of σ C-R and CSP_2 p-orbital:

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

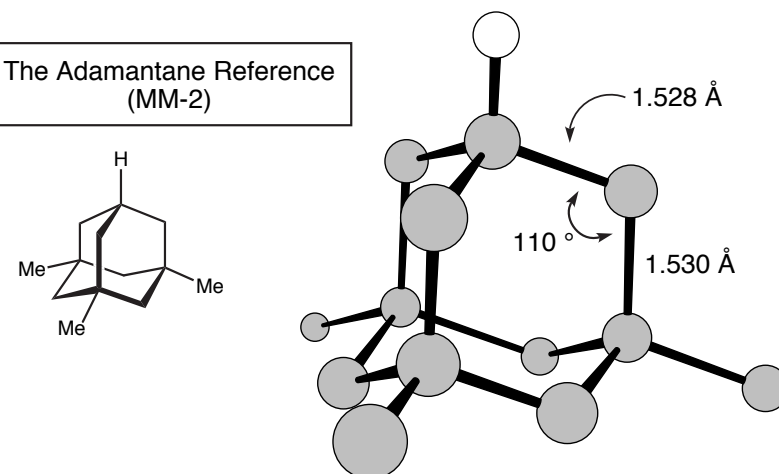
Physical Evidence for Hyperconjugation

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

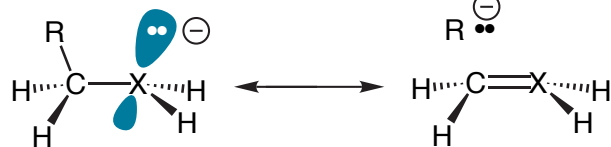
First X-ray Structure of an Aliphatic Carbocation



The Adamantane Reference (MM-2)



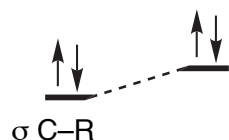
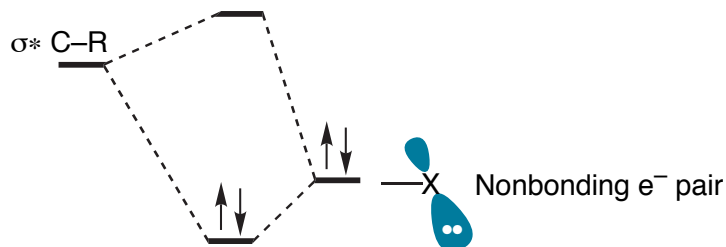
- Delocalization of nonbonding electron pairs into vicinal antibonding orbitals is also possible



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.

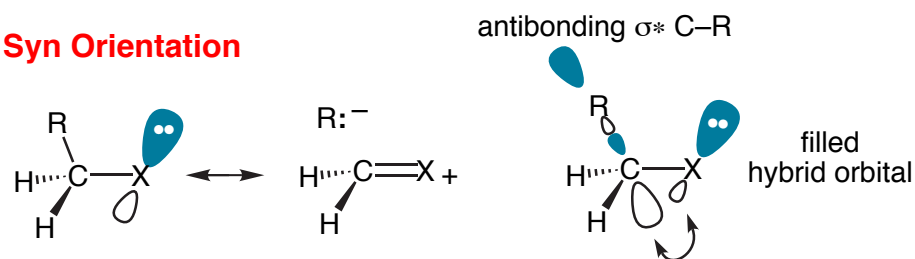
The Molecular Orbital Description



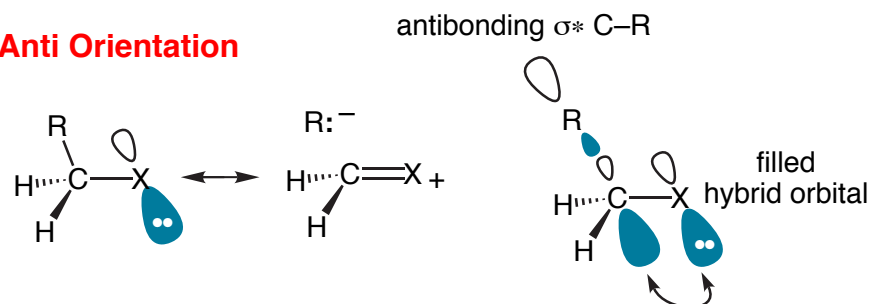
As the antibonding C-R orbital decreases in energy, the magnitude of this interaction will increase

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.

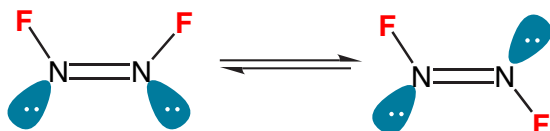
The Expected Structural Perturbations

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



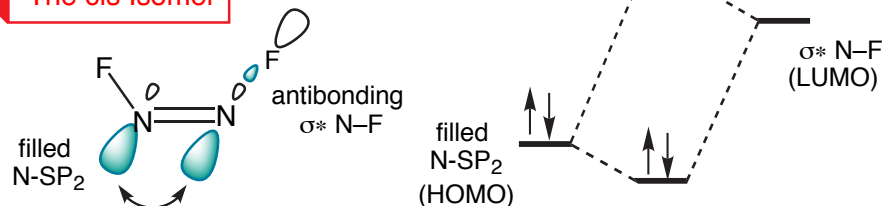
There are two logical reasons why the trans isomer should be more stable than the cis isomer.

- 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.

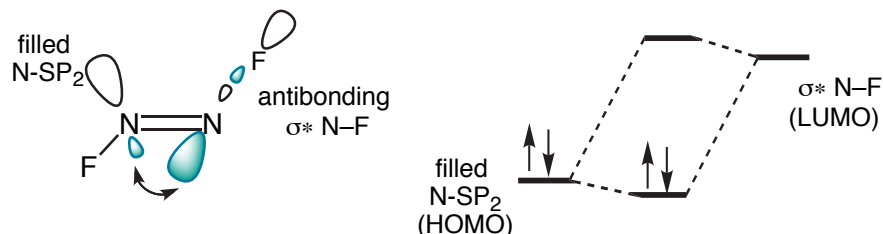
The cis Isomer



- 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.



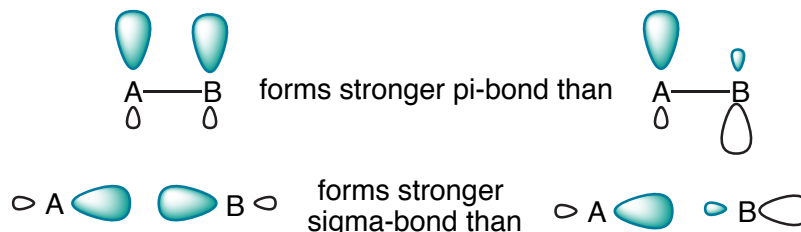
- In this geometry the "small lobe" of the filled $N-SP_2$ is required to overlap with the large lobe of the antibonding C–F orbital. Hence, when the new MO's are generated the new bonding orbital is not as stabilizing as for the cis isomer.

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.



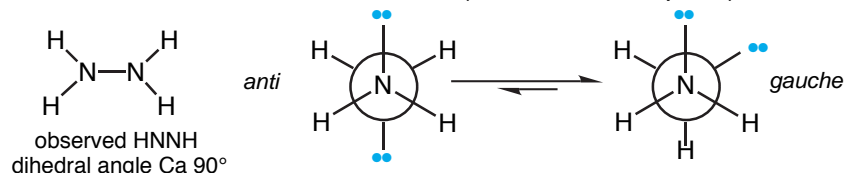
This is a simple notion with very important consequences. It surfaces in the delocalized bonding which occurs in the competing anti (favored) syn (disfavored) E2 elimination reactions. Review this situation.

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).

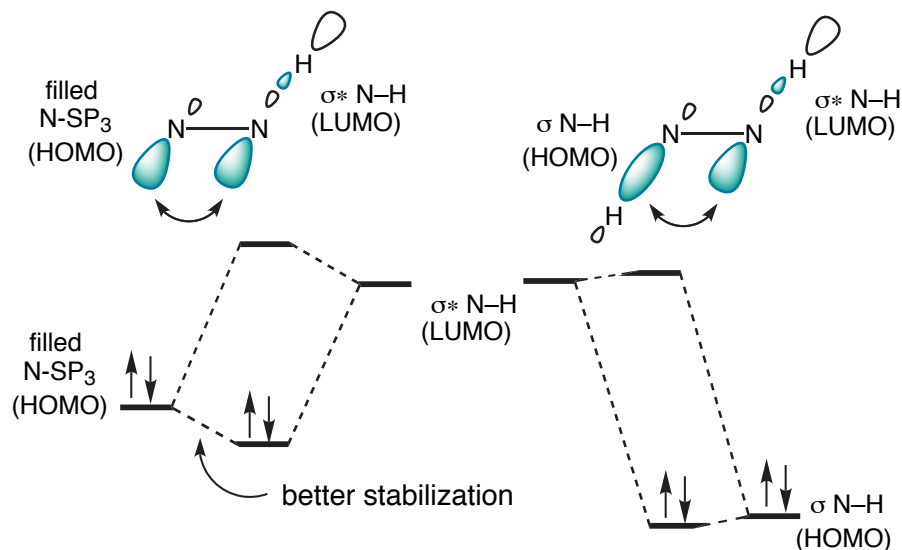


There is a logical reason why the anti isomer should be more stable than the gauche isomer. The nonbonding lone pair orbitals in the gauche isomer should be destabilizing due to electron-electron repulsion.

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.

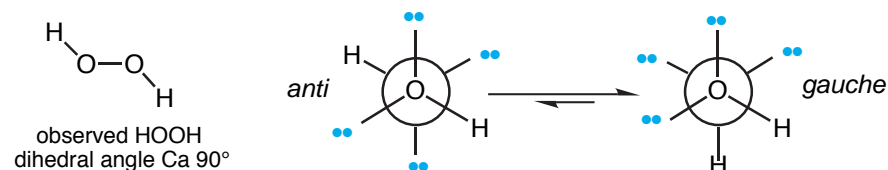
■ Hence, N-lone pair \leftrightarrow σ^* N-H delocalization better than σ N-H \leftrightarrow σ^* N-H delocalization.

■ Hence, hydrazine will adopt the gauche conformation where both N-lone pairs will be anti to an antibonding acceptor orbital.

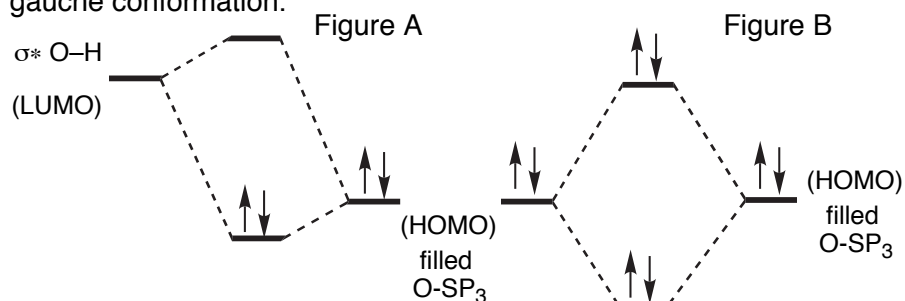
The trend observed for hydrazine holds for oxygen derivatives as well

Hydrogen peroxide

H_2O_2 can exist in either gauche or anti conformations (relative to hydrogens). The gauche conformer is 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-2

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

Reading Assignment: Kirby, Chapters 1-3

D. A. Evans

Wednesday,
September 17, 2003

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.

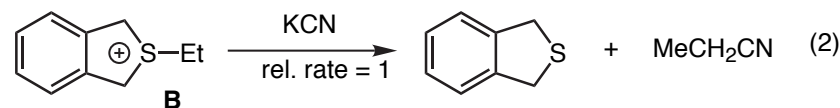
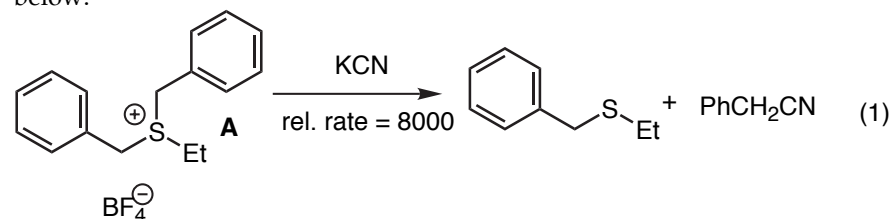
Plavec, J., C. Thibaudeau, et al. (1996). "How do the Energetics of the Stereoelectronic Gauche and Anomeric Effects Modulate the Conformation of Nucleos(t)ides?" *Pure Appl. Chem.* **68**: 2137-44.

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

Problem 121

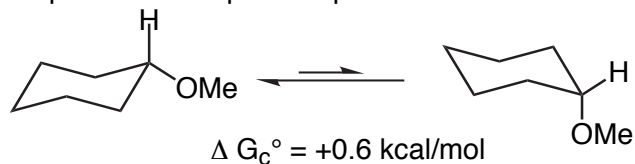
<http://evans.harvard.edu/problems/>

Sulfonium ions **A** and **B** exhibit remarkable differences in both reactivity and product distribution when treated with nucleophiles such as cyanide ion (eq 1, 2). Please answer the questions posed in the spaces provided below.

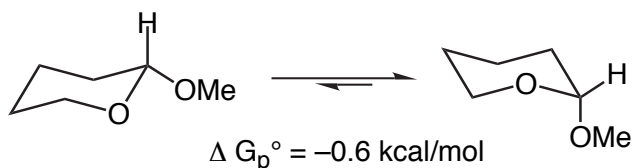


The Anomeric Effect

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.

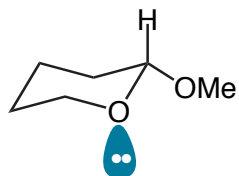
Let anomeric effect = A

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

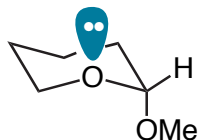
$$A = \Delta G_p^\circ - \Delta G_c^\circ$$

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

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



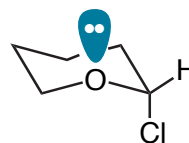
axial O lone pair \leftrightarrow σ^* C-H



axial O lone pair \leftrightarrow σ^* C-O

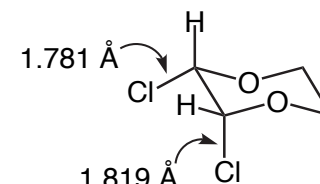
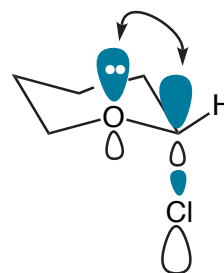
■ Since the antibonding C-O orbital is a better acceptor orbital than the antibonding C-H bond, the axial OMe conformer is better stabilized by this interaction which is worth ca. 1.2 kcal/mol.

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

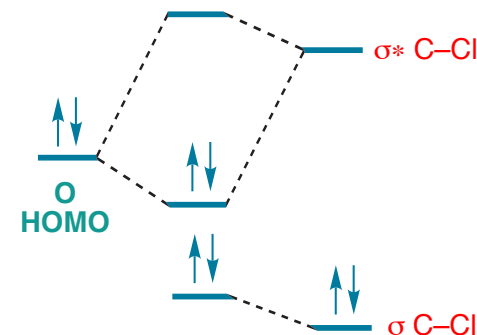


This conformer preferred by 1.8 kcal/mol

axial O lone pair \leftrightarrow σ^* C-Cl

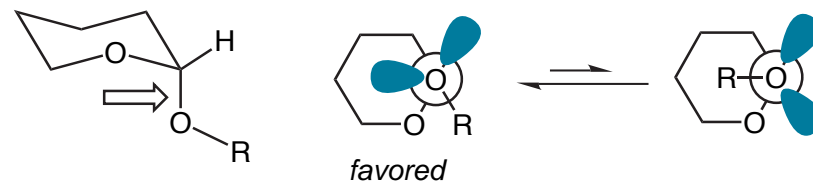


Why is axial C-Cl bond longer ?



The Exo-Anomeric Effect

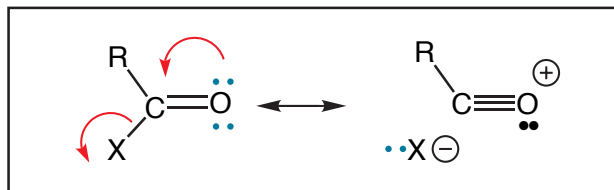
■ There is also a rotational bias that is imposed on the exocyclic C-OR bond where one of the oxygen lone pairs prefers to be anti to the ring sigma C-O bond



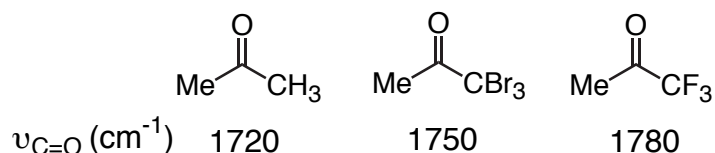
A. J. Kirby, *The Anomeric and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, 1983

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

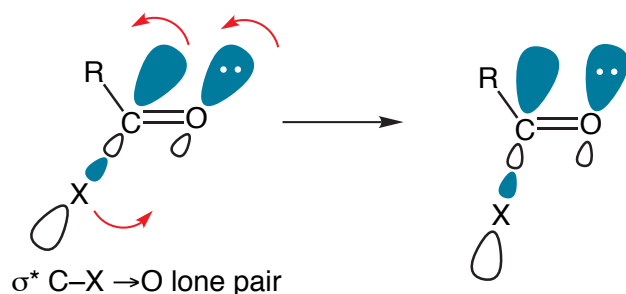
Do the following valence bond resonance structures have meaning?



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.

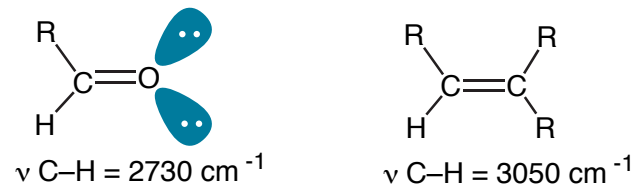


Evidence for this distortion has been obtained by X-ray crystallography

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

Aldehyde C-H Infrared Stretching Frequencies

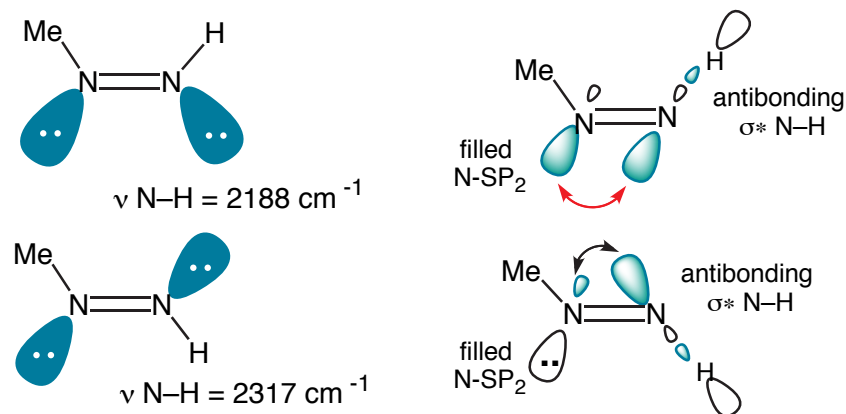
Prediction: The IR C-H stretching frequency for aldehydes is lower than the closely related olefin C-H stretching frequency. For years this observation has gone unexplained.



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.

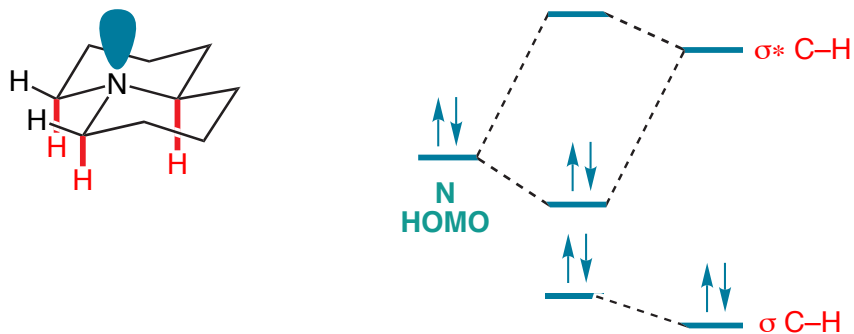
The N-H stretching frequency of cis-methyl diazene is 200 cm^{-1} lower than the trans isomer.



■ 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

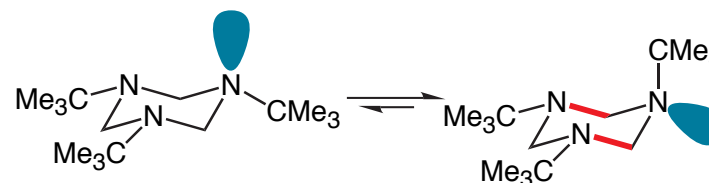
H₁₀ (axial): shifted furthest upfield

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

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

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

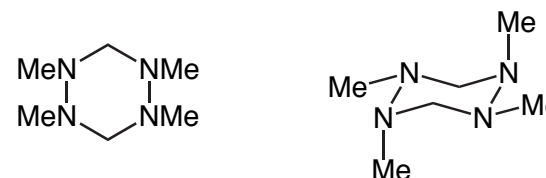
J. B. Lambert et. al., *JACS* **1967** 89 3761



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

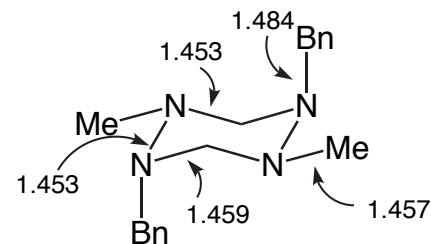
A. R. Katritzky et. al., *J. Chemm. Soc. B* **1970** 135

Favored Solution Structure (NMR)



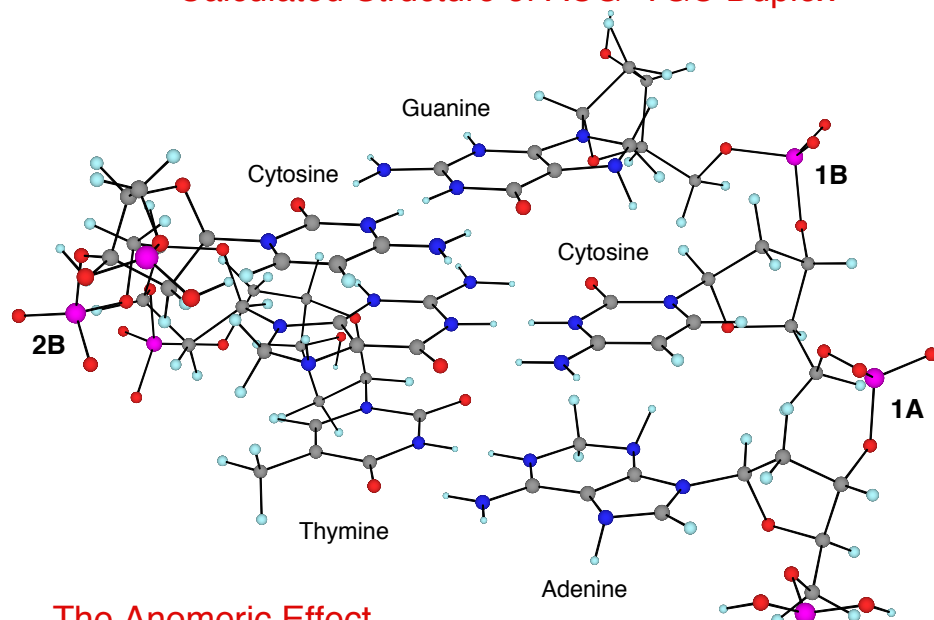
J. E. Anderson, J. D. Roberts, *JACS* **1967** 96 4186

Favored Solid State Structure (X-ray crystallography)

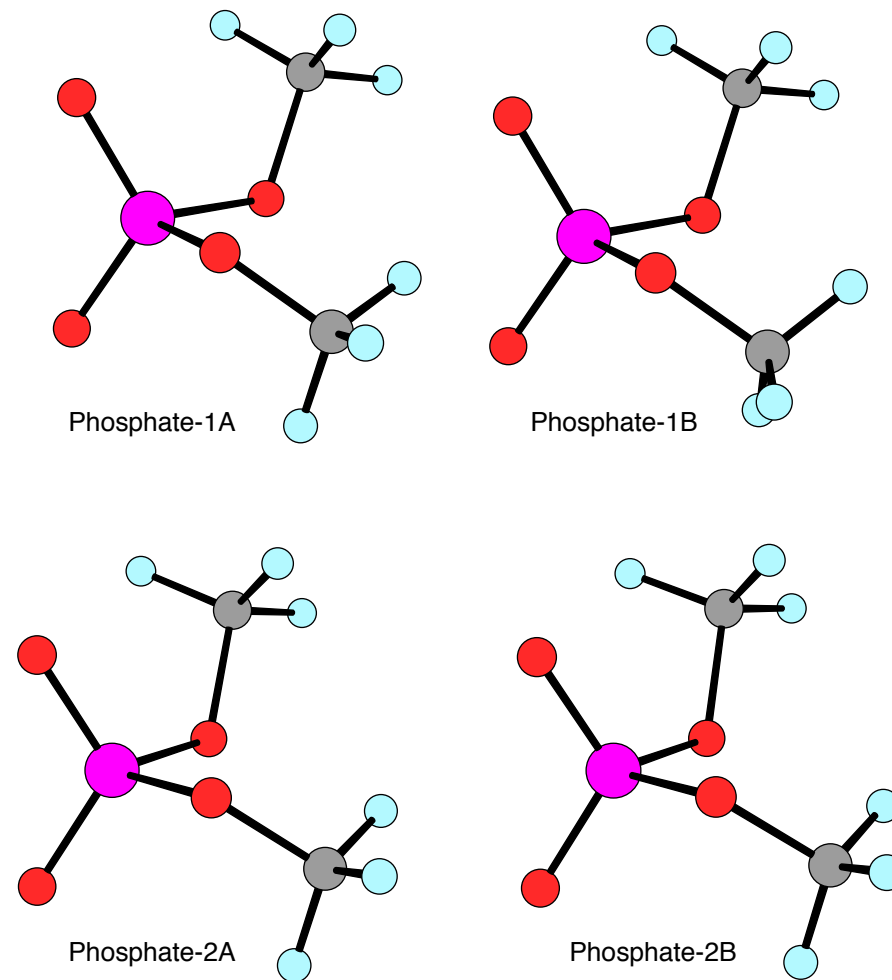


A. R. Katritzky et. al., *J. C. S. Perkin II* **1980** 1733

Calculated Structure of ACG-TGC Duplex

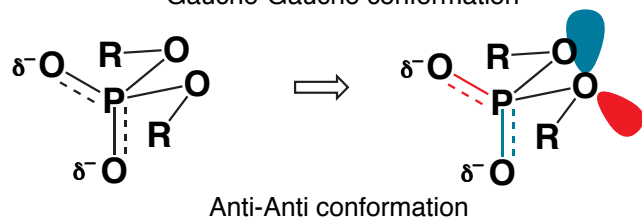
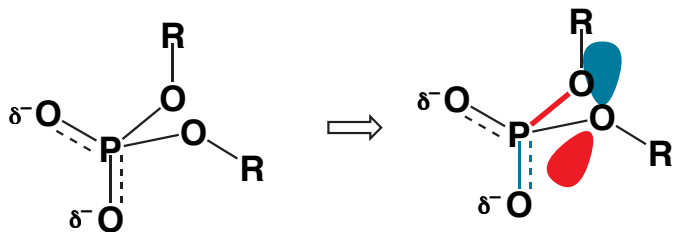


The Phospho-Diesters Excised from Crystal Structure



The Anomeric Effect

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

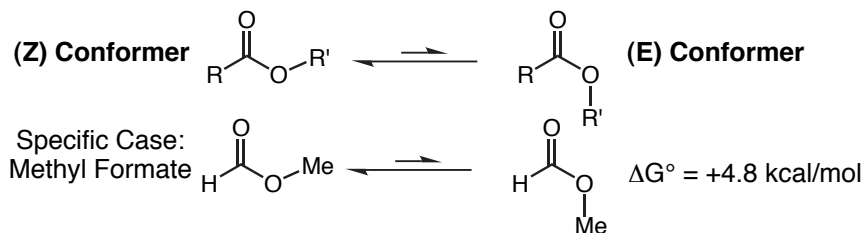


Gauche-Gauche conformation affords a better donor-acceptor relationship

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.

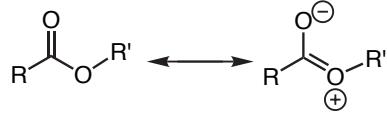
■ **Conformations:** There are 2 planar conformations.



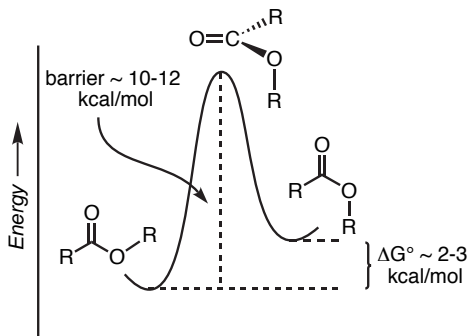
The (E) conformation of both acids and esters is less stable by 3-5 kcal/mol. If this equilibrium were governed only by steric effects one would predict that the (E) conformation of formic acid would be more stable (H smaller than =O). Since this is not the case, there are electronic effects which must also be considered. These effects will be introduced shortly.

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

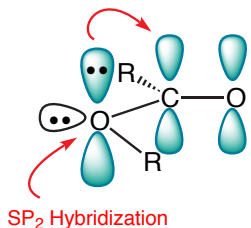
These resonance structures suggest hindered rotation about =C-OR bond. This is indeed observed:



Rotational barriers are ~ 10-12 kcal/mol. This is a measure of the strength of the pi bond.



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

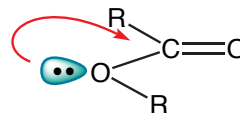


The filled oxygen p-orbital interacts with pi (and pi*) C=O to form a 3-centered 4-electron bonding system.

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

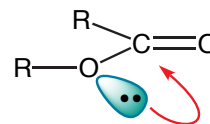
■ **Hyperconjugation:** Let us now focus on the oxygen lone pair in the hybrid orbital lying in the sigma framework of the C=O plane.

(Z) Conformer

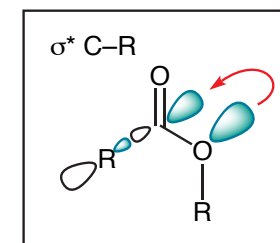
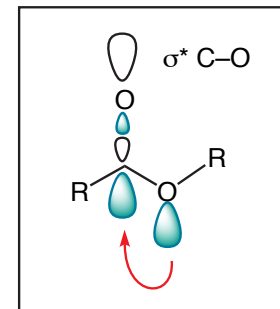


In the (Z) conformation this lone pair is aligned to overlap with $\sigma^* \text{ C-O}$.

(E) Conformer



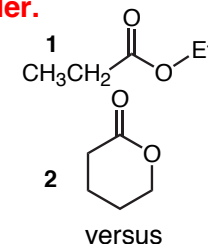
In the (E) conformation this lone pair is aligned to overlap with $\sigma^* \text{ C-R}$.



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.

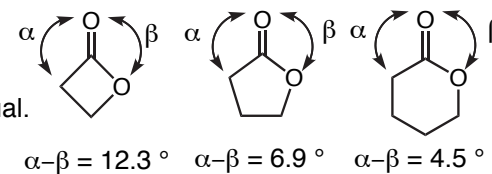
Esters versus Lactones: Questions to Ponder.

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:



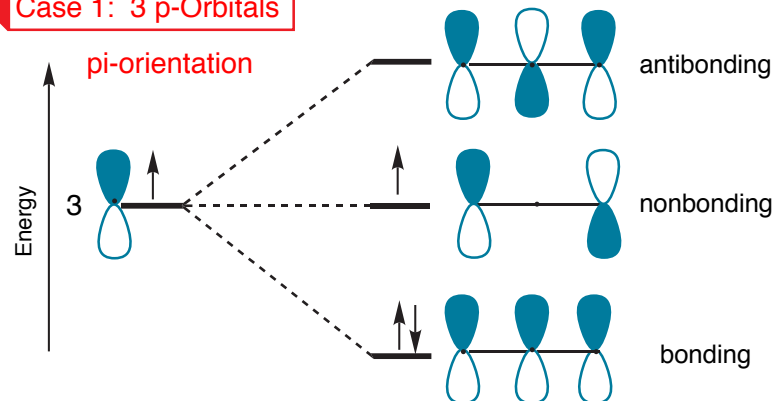
- 1) Lactone **2** is significantly more susceptible to nucleophilic attack at the carbonyl carbon than **1**? Explain.
- 2) Lactone **2** is significantly more prone to enolization than **1**? In fact the pK_a of **2** is ~25 while ester **1** is ~30 (DMSO). Explain.

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

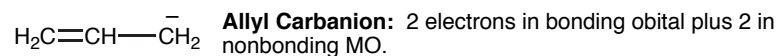
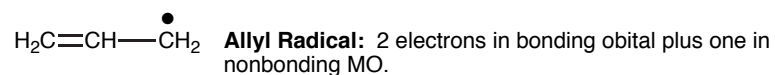


Consider the linear combination of three atomic orbitals. The resulting molecular orbitals (MOs) usually consist of one bonding, one nonbonding and one antibonding MO.

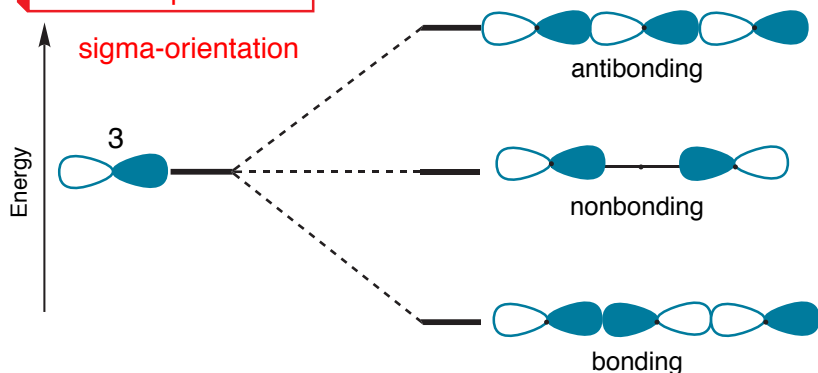
Case 1: 3 p-Orbitals



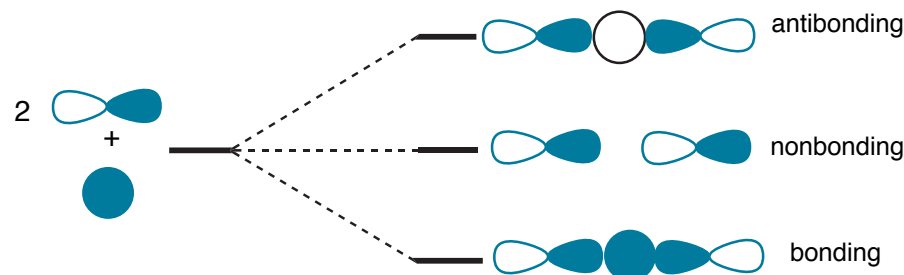
Note that the more nodes there are in the wave function, the higher its energy.



Case 2: 3 p-Orbitals



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

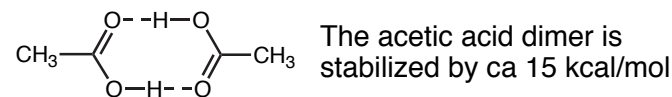


Case 4: 2 s-Orbitals; 1 p-orbital

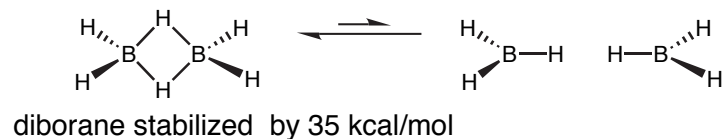
Do this as an exercise

Examples of three-center bonds in organic chemistry

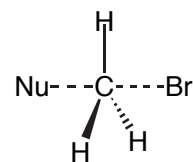
A. H-bonds: (3-center, 4-electron)



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



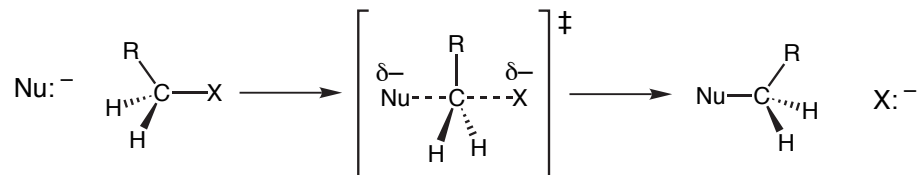
C. The $\text{S}_{\text{N}}2$ Transition state: (3-center, 4-electron)



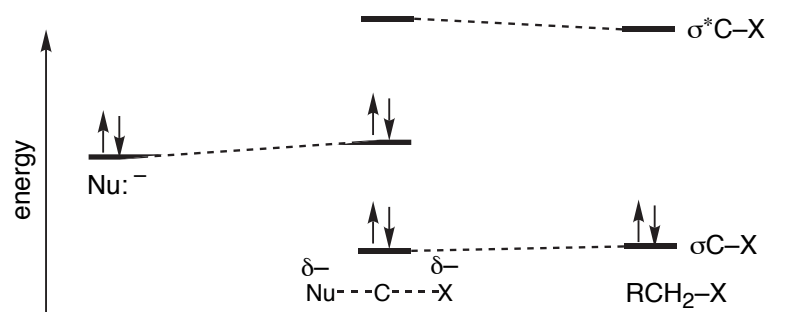
The $\text{S}_{\text{N}}2$ transition state approximates a case 2 situation with a central carbon p-orbital

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

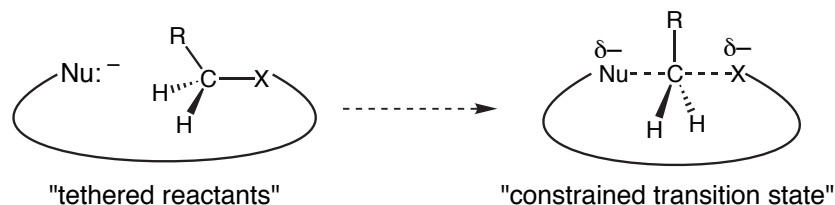
The reaction under discussion:



■ 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:

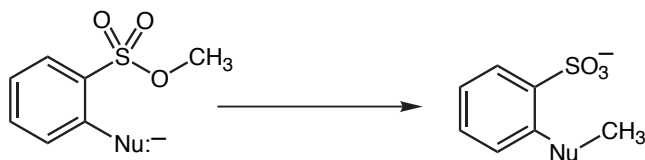


■ Experiments have been designed to probe inherent requirement for achieving a 180° Nu–C–X bond angle: Here both Nu and leaving group are constrained to be part of the same ring.



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

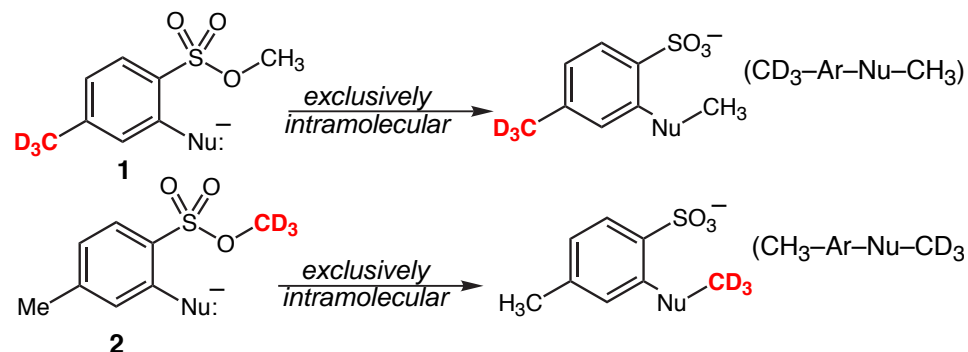
■ The reaction illustrated below proceeds exclusively through bimolecular pathway in contrast to the apparent availability of the intramolecular path.



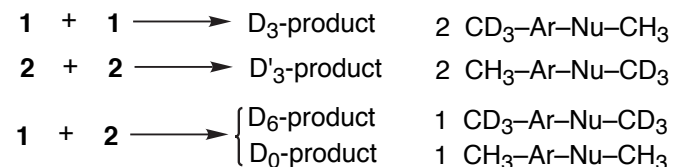
The use of isotope labels to probe mechanism.

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:



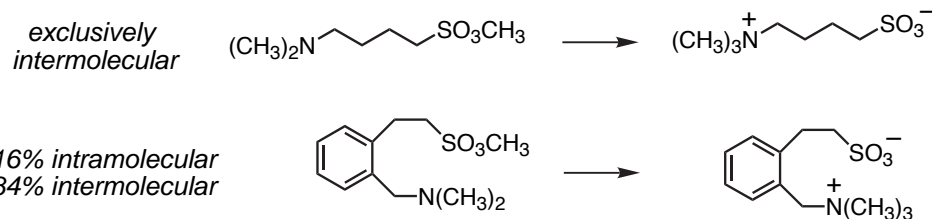
■ If the reaction was **exclusively intermolecular**, products would only contain differing amounts of D-label depending on which two partners underwent reaction. The deuterium content might be analyzed by mass spectrometry. Here are the possibilities:



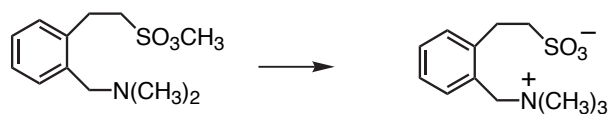
Hence, for the strictly intermolecular situation one should see the following ratios
D₀ : D₃ : D'₃ : D₆ = 1 : 2 : 2 : 1.

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

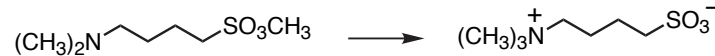
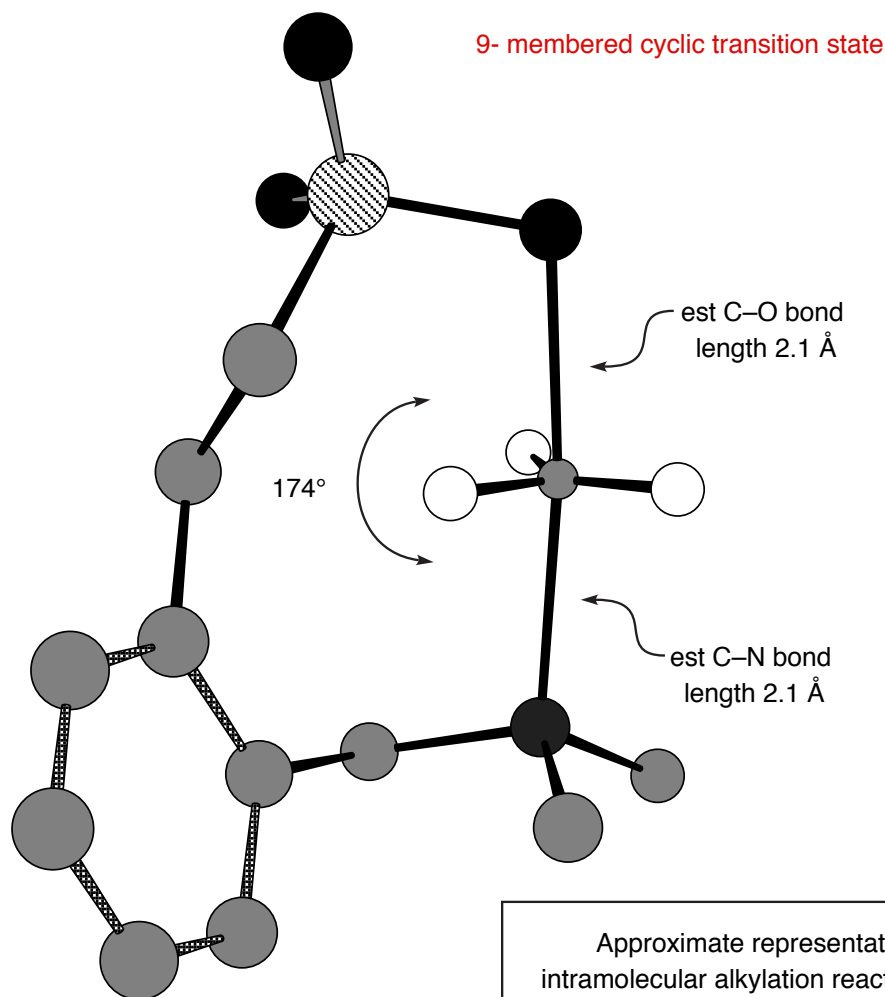
Other Cases:



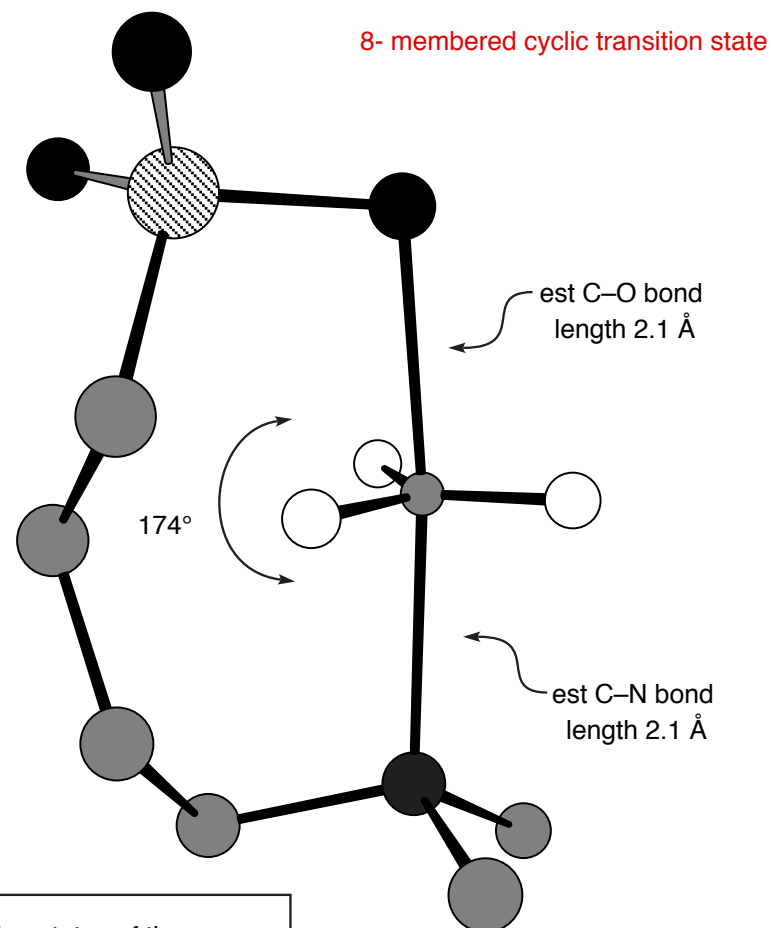
Hence, the Nu–C–X 180° transition state bond angle must be rigidly maintained for the reaction to take place.



16% intramolecular; 84% intermolecular

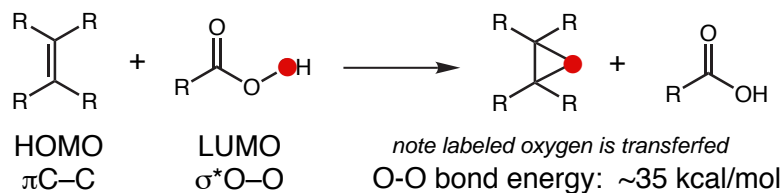


exclusively intermolecular

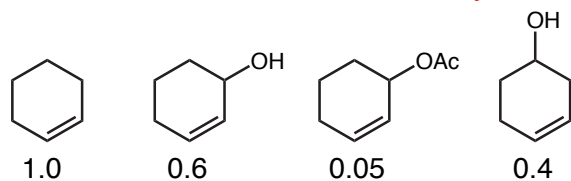


Approximate representation of the transition states of the intramolecular alkylation reactions. Transition state C-O and C-N bond lengths were estimated to be 1.5x(C-X) bond length of 1.4 Å

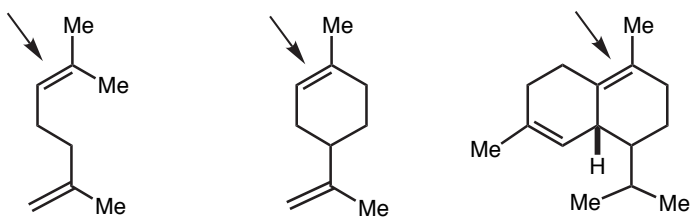
■ **The General Reaction:**



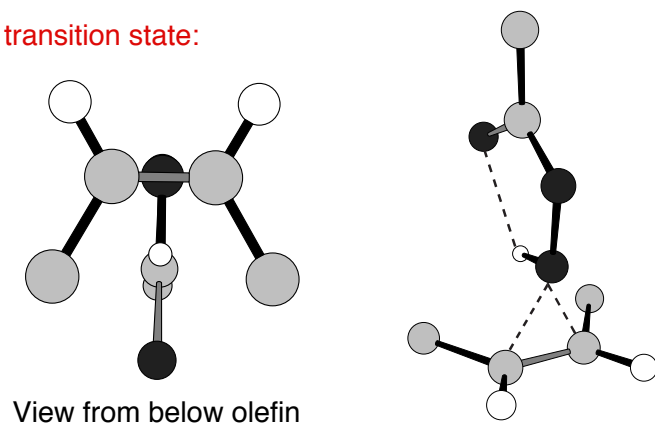
■ Reaction rates are governed by olefin nucleophilicity. The rates of epoxidation of the indicated olefin relative to cyclohexene are provided below:



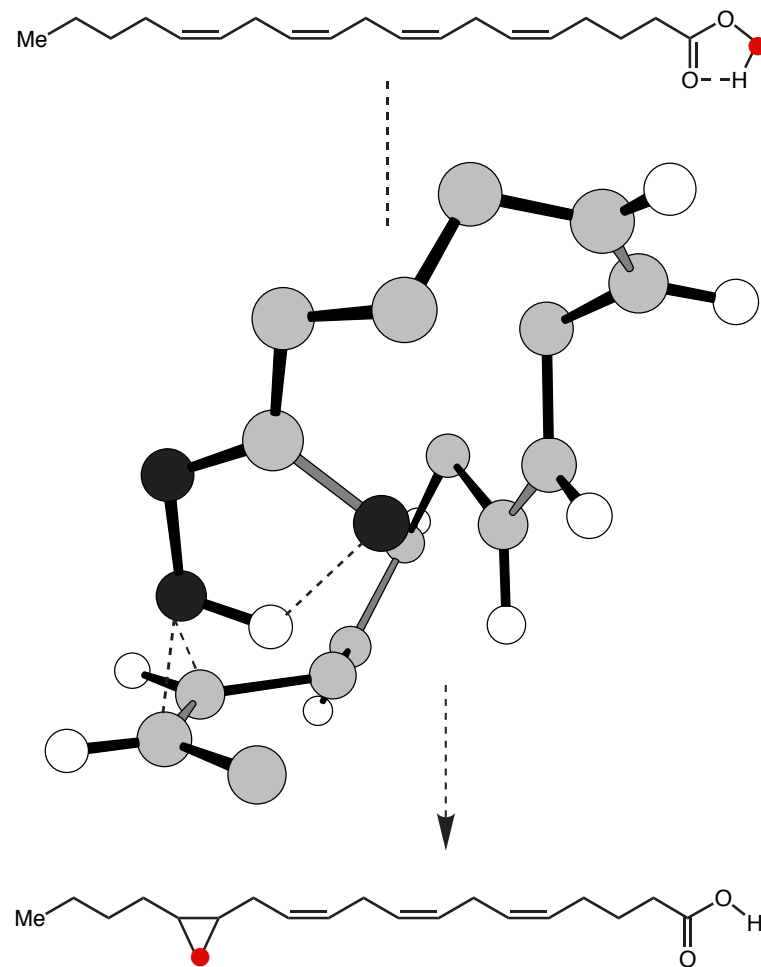
■ The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



■ **The transition state:**



Per-arachidonic acid Epoxidation

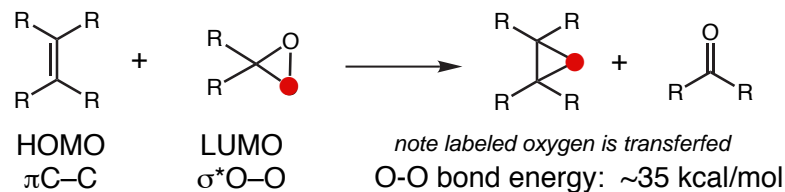


E. J. Corey, *JACS* **101**, 1586 (1979)

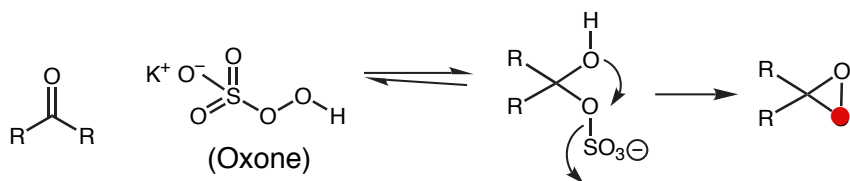
For a more detailed study see P. Beak, *JACS* **113**, 6281 (1991)

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

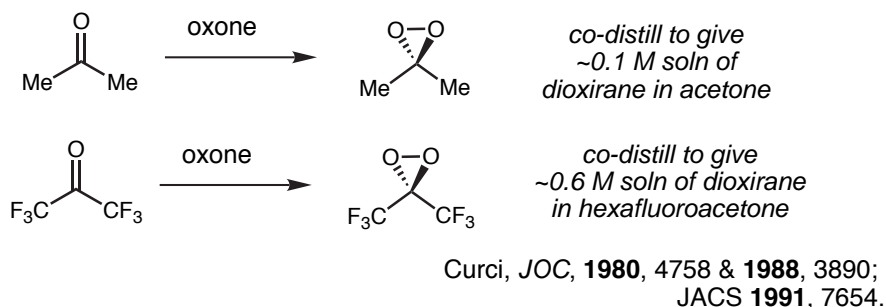
The General Reaction:



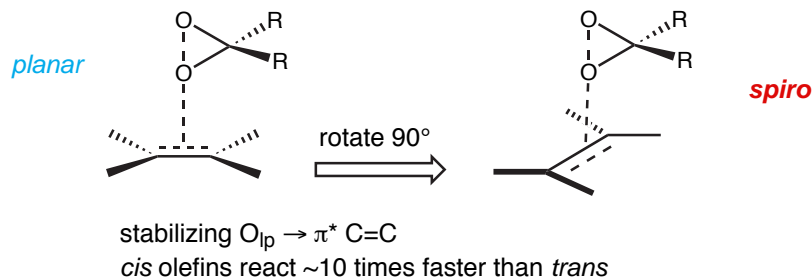
Synthesis of the Dioxirane Oxidant



Synthetically Useful Dioxirane Synthesis



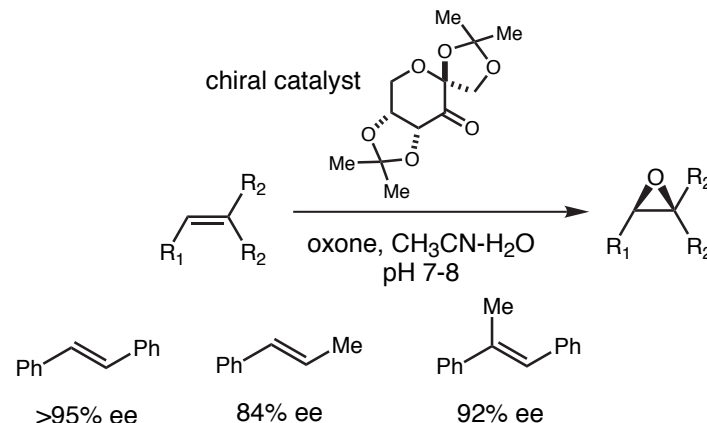
Transition State for the Dioxirane Mediated Olefin Epoxidation



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

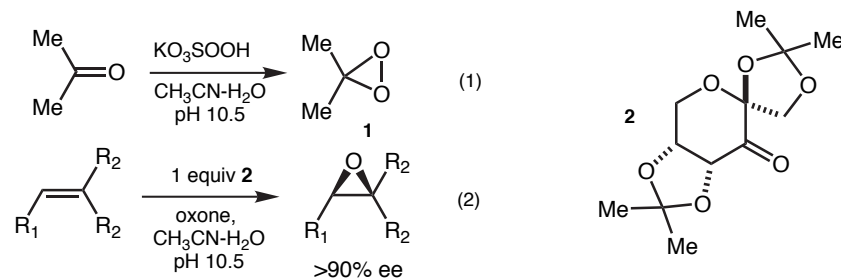
Asymmetric Epoxidation with Chiral Ketones

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



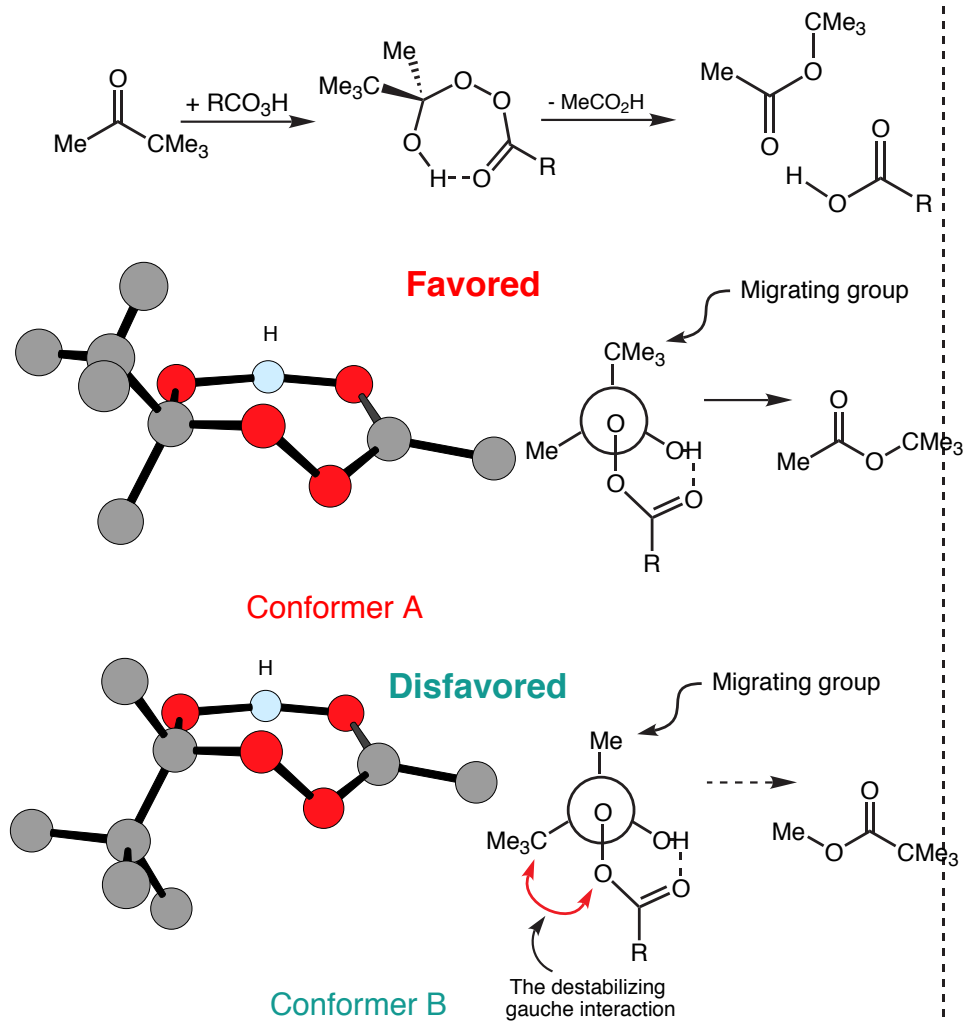
Question: First hour Exam 2000 (Database Problem 34)

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

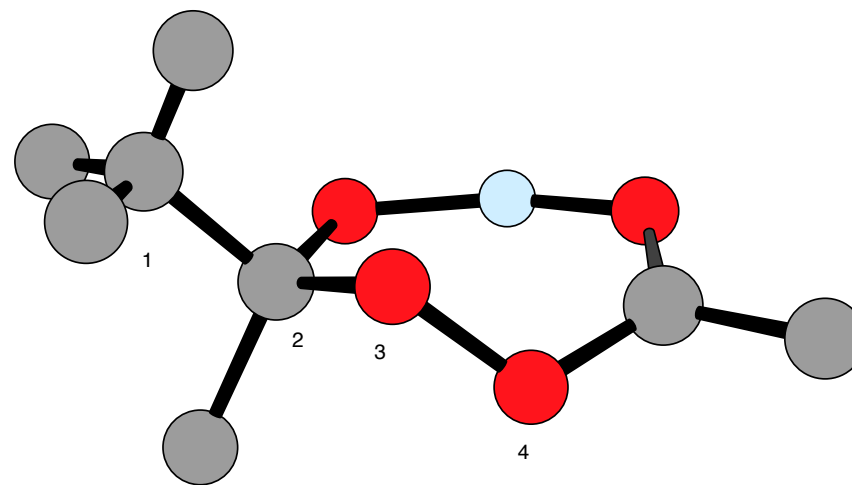
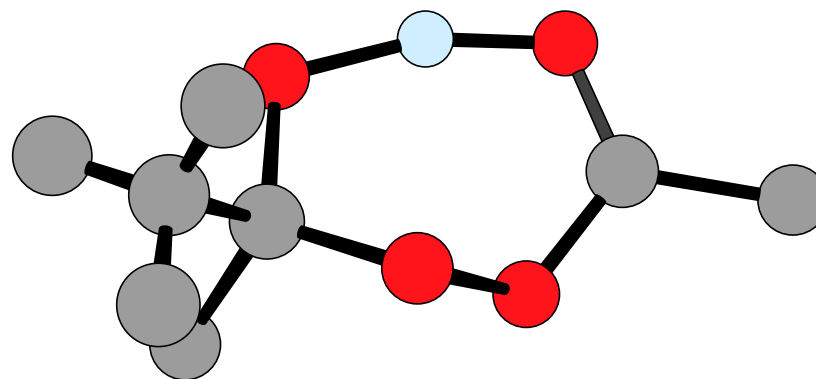


Part A (8 points). Provide a mechanism for the epoxidation of ethylene with dimethyldioxirane (**1**). Use three-dimensional representations, where relevant, to illustrate the *relative* stereochemical aspects of the oxygen transfer step. Clearly identify the frontier orbitals involved in the epoxidation.

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.



Conformer A in three dimensions



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.

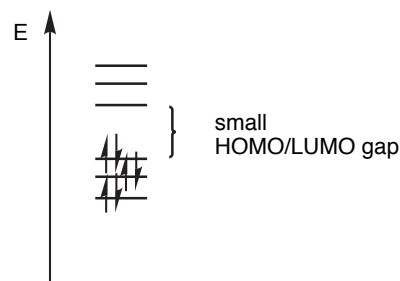
Soft Acids are usually uncharged and large (low charge density), they have an energy poor (low lying) LUMO (usually with large MO coefficient).

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

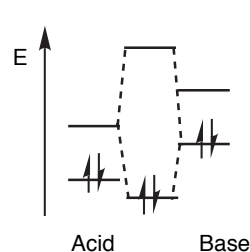


idealized Hard Species



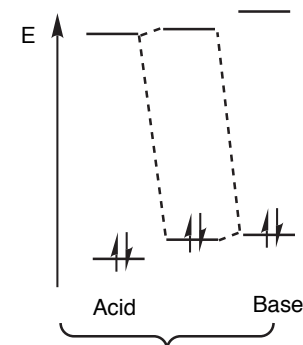
FMO-Theory for interaction:

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

Hard-Hard Interactions: Frontier orbital term small because of large $\Delta E(E_{\text{HOMO}}/E_{\text{LUMO}})$. Dominant interaction is described by the Coulomb term (Q is large for hard species), i.e. electrostatic interaction.
 \Rightarrow 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	Al ³⁺	6.01
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
		Ag ⁺	-2.82
		Tl ³⁺	-3.37
		Au ⁺	-4.35
		Hg ²⁺	-4.64

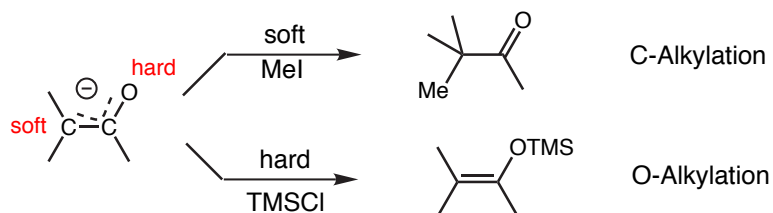
Hard Soft

Hard

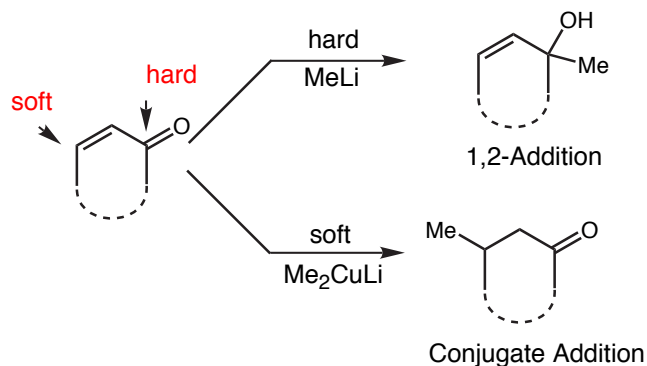
Soft

HSAB principle - Application to Chemoselectivity Issues

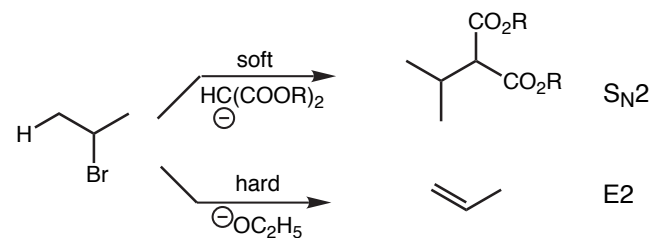
(a) Enolate Alkylation



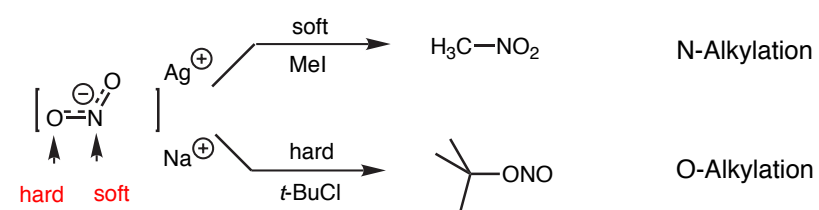
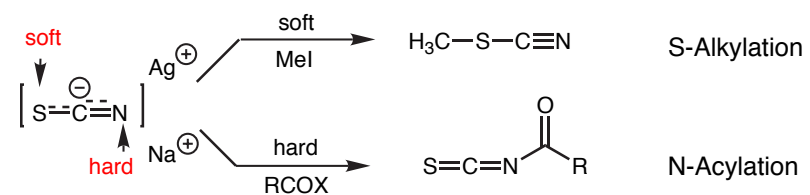
(b) 1,2- vs. 1,4-addition to α,β -unsaturated carbonyl compounds



(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-3

"Rules for Ring Closure: Baldwin's Rules"

Kirby, "Stereoelectronic Effects" Chapters 4, 5

Useful Literature Reviews

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

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

D. A. Evans

Friday,
September 19, 2003

The Primary Literature

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

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

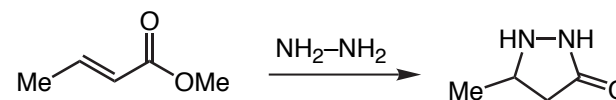
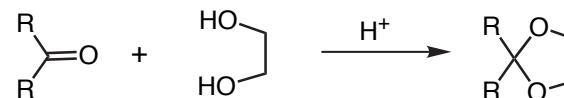
Baldwin, *J. Org. Chem.* **1977**, *42*, 3846.

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



Problems of the Day

Propose mechanisms for the following reactions



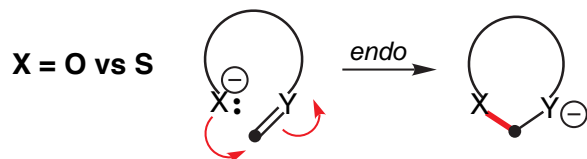
Ring Closure and Stereoelectronic Considerations An Examination of Baldwin's Rules

"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.

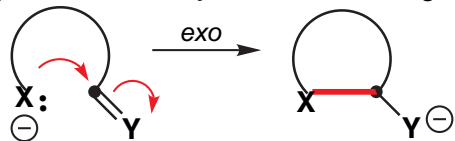


■ The "rules" do not apply to electrocyclic processes.

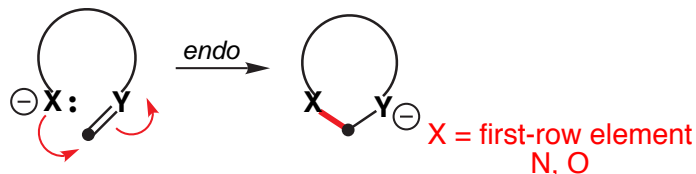
Nomenclature

Classes of Ring Closing Processes

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

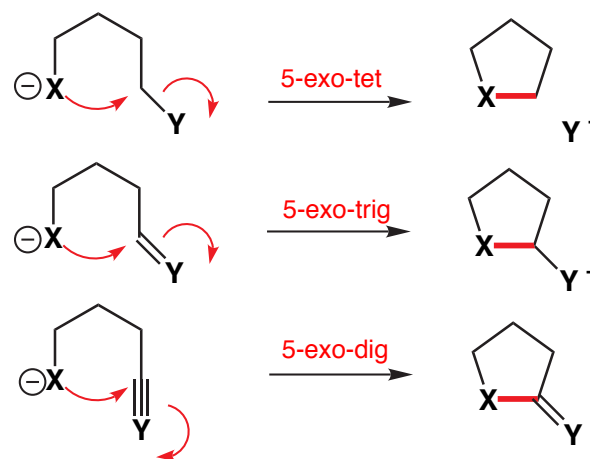


B. Endo-cyclization modes identified by the breaking bond being positioned endocyclic to the forming cycle.

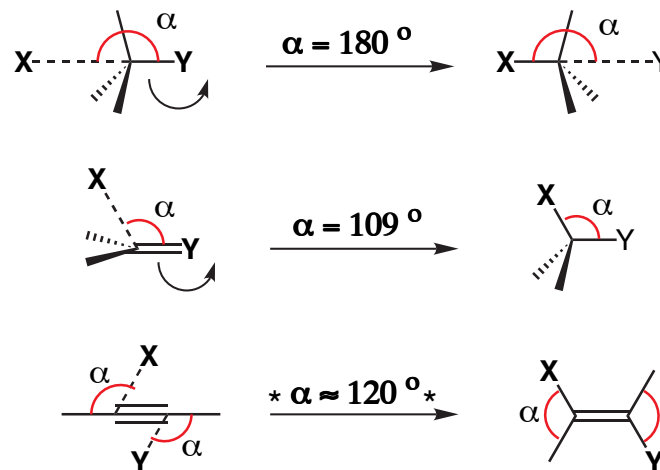


C. Nucleophilic ring closures sub-classified according to hybridization state of electrophilic component:
(tetrahedral = tet; trigonal = trig; digonal = dig)

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



Required trajectories (Baldwin):

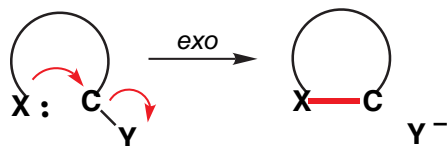


Will come back to this case later

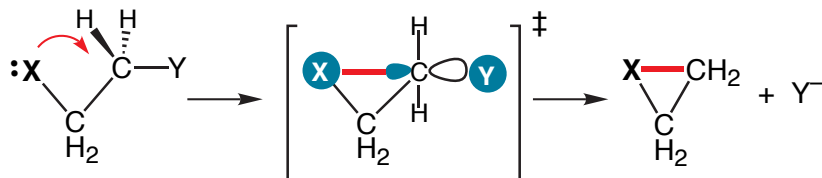
Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

Tetrahedral Carbon

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

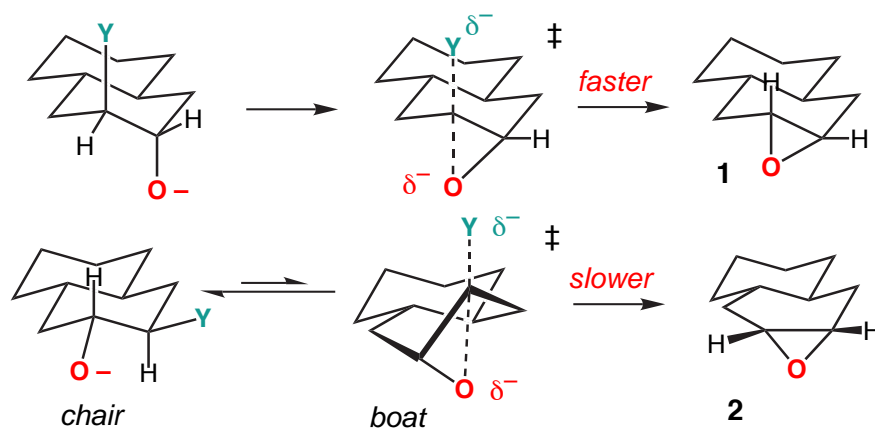


There are stereoelectronic issues to consider for *n*-*exo*-tet cyclizations

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

Conformational Effects in Epoxide Ring Formation/cleavage

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



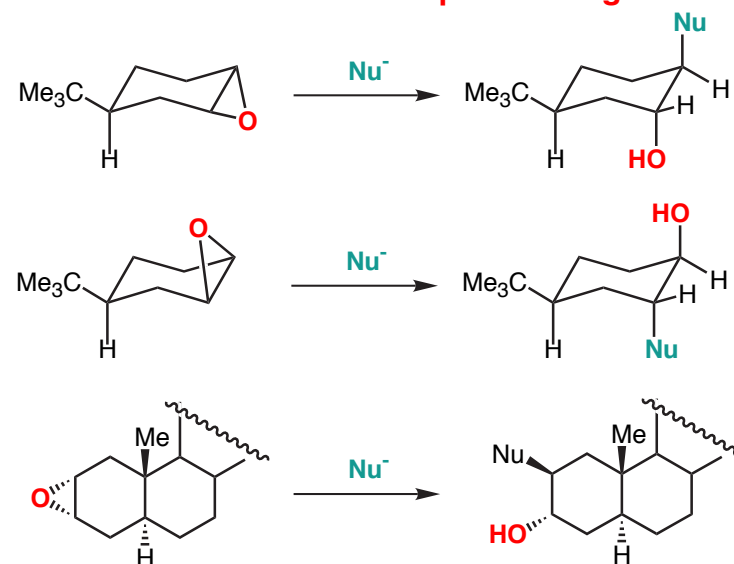
FÜRST-PLATTNER RULE

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

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

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

Stereoelectronic Effects in Epoxide Ring Cleavage

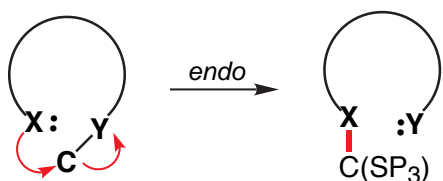


"The diaxial nucleophilic ring cleavage of epoxides"

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

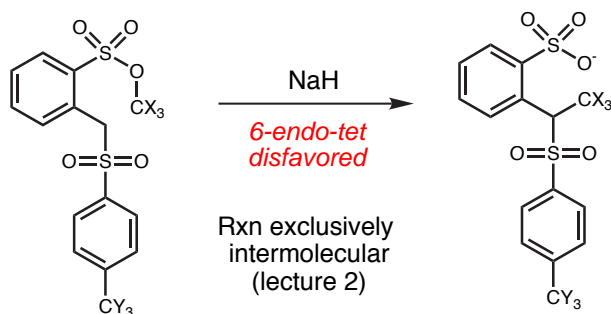
Tetrahedral Carbon

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

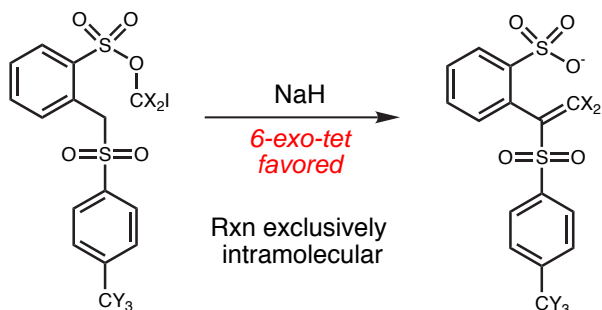


The stereoelectronic requirement for a 180° X-C-Y bond angle is only met when the endo cyclization ring size reaches 9 or 10 members.

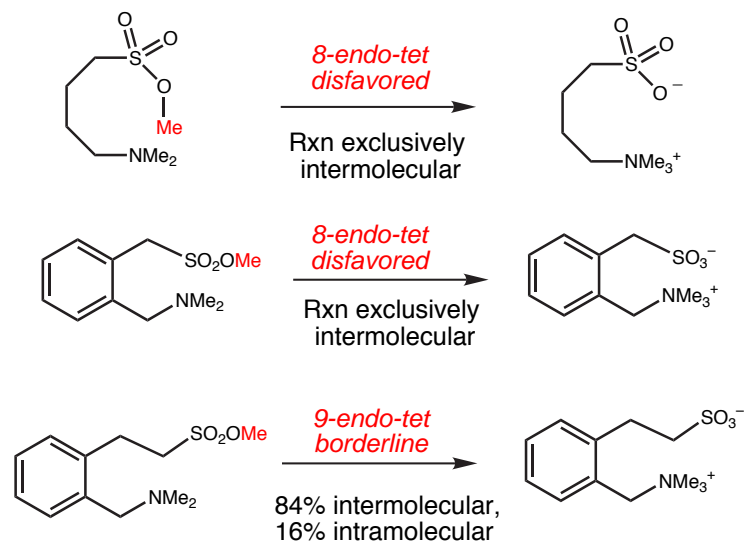
Case 1: Eschenmoser, *Helvetica Chim. Acta* **1970**, 53, 2059.



Cyclization exclusively intermolecular. However the exocyclic analog is exclusively intramolecular



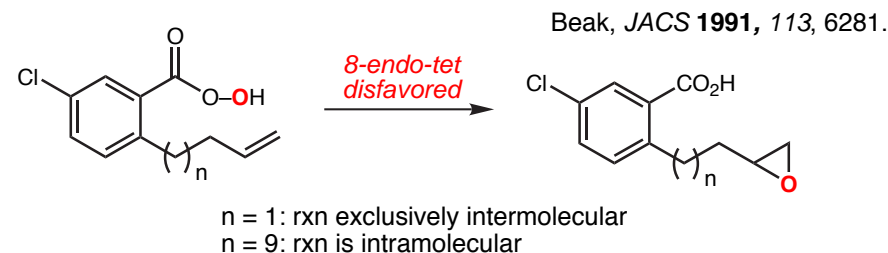
Case 2: King, *J.C.S. Chem. Comm.*, **1979**, 1140.



Conclusions

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

Intramolecular epoxidation has also been evaluated

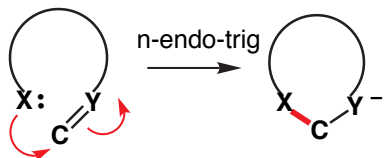


Beak states that the conclusions made with carbon substitution also hold for oxygen atom transfer.

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

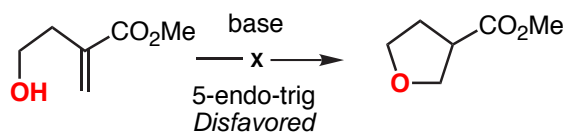
Endo cyclization modes that are disallowed
(3 to 5-endo-trig)



X = first-row element

The 5-endo-trig cyclization is a watershed case

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

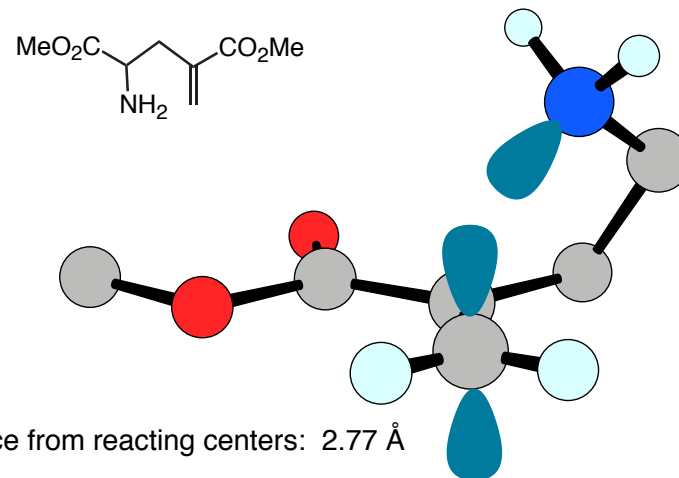
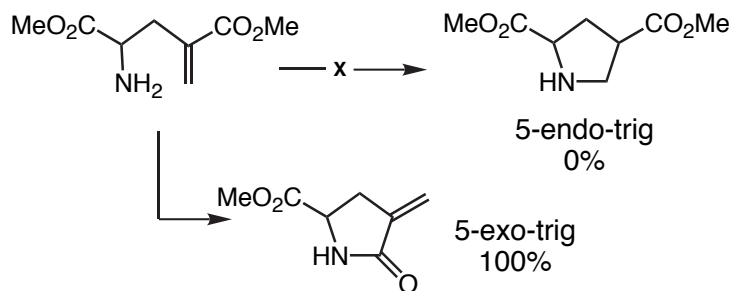


however



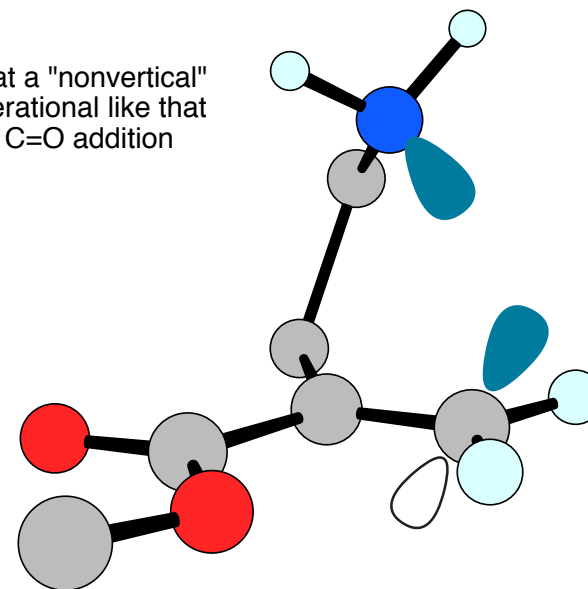
Second row atom relaxes the cyclization geometrical requirement

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

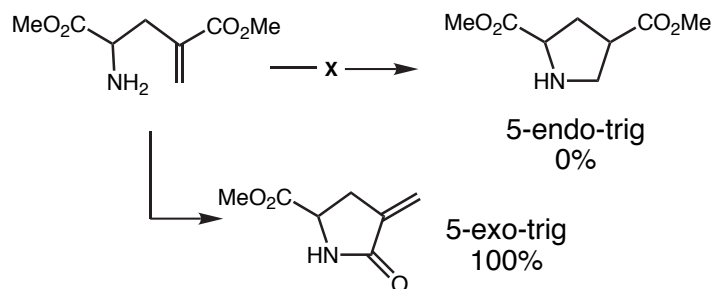


distance from reacting centers: 2.77 Å

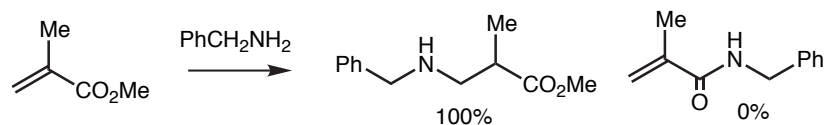
It is possible that a "nonvertical" trajectory is operational like that suspected in C=O addition



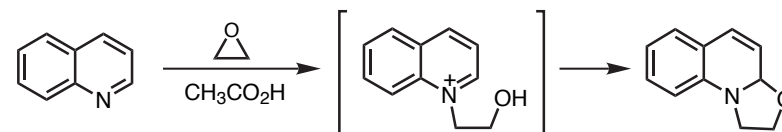
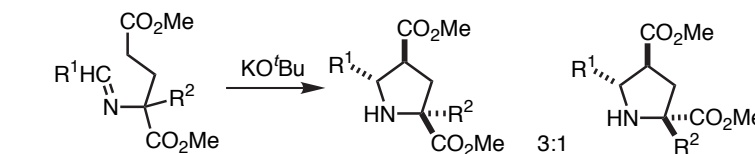
Case 2: continued...



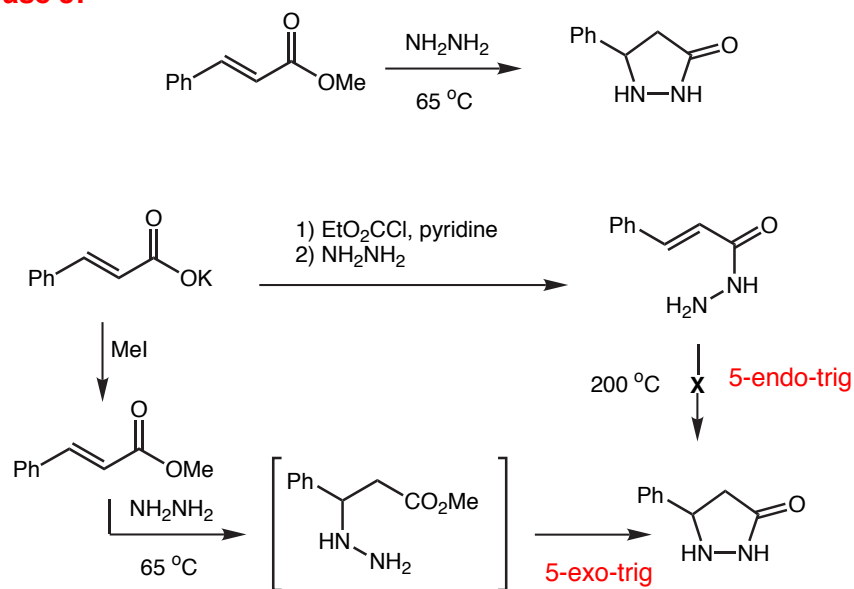
Control experiment: Intermolecular reaction favors conjugate addition.



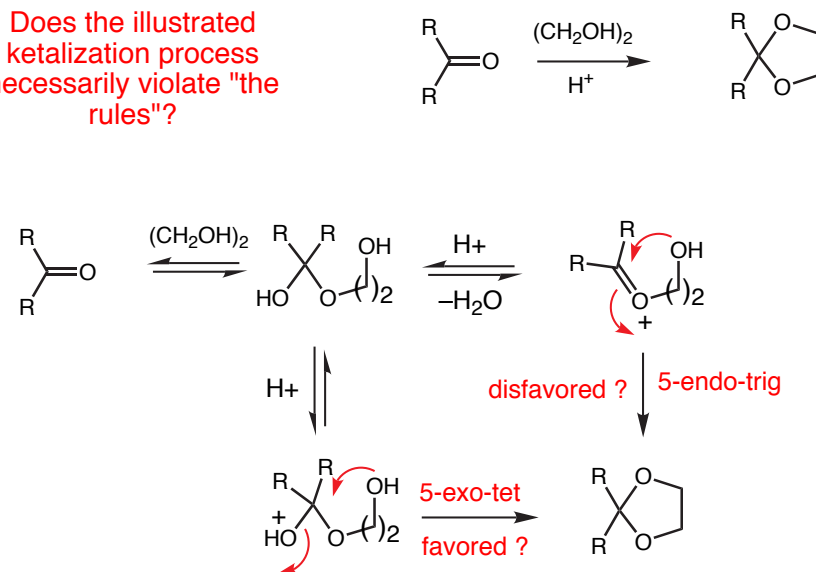
Apparent exceptions to disallowed 5-endo-trig cyclization process

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

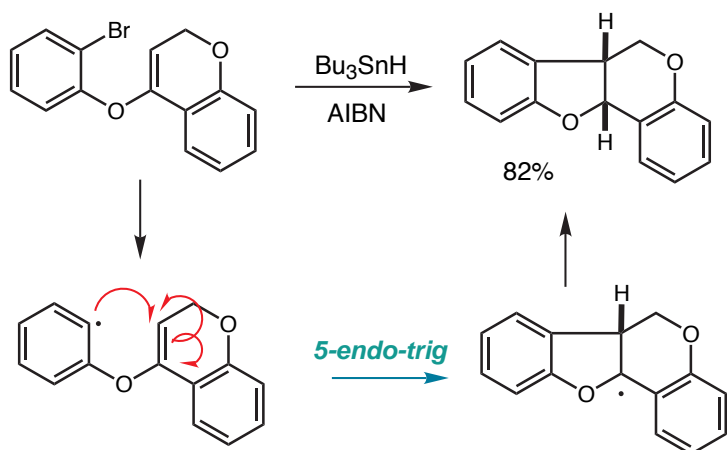
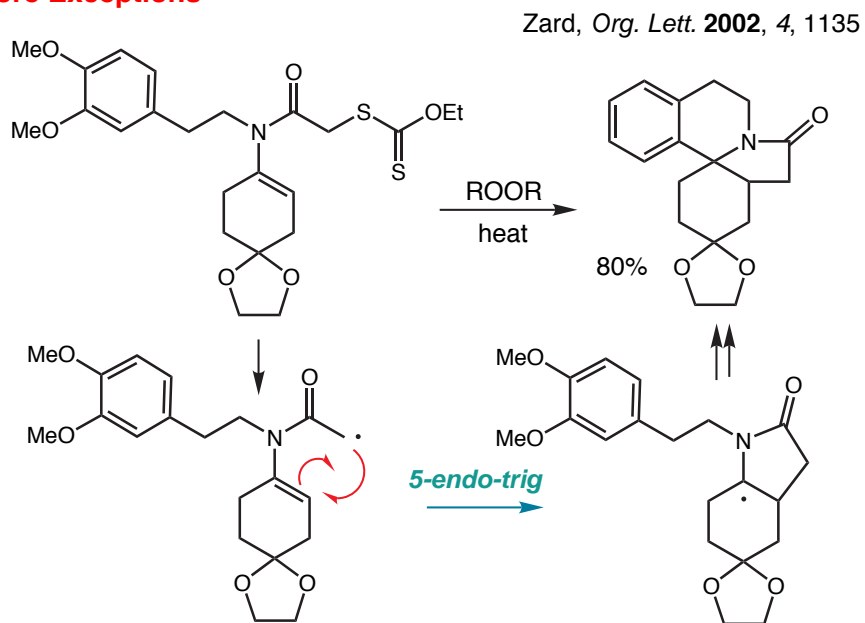
Case 3:



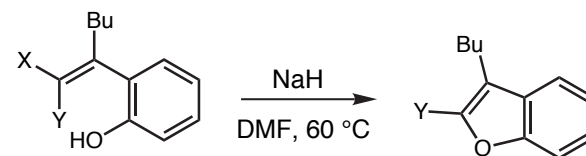
Does the illustrated ketalization process necessarily violate "the rules"?

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.

More Exceptions

Chem. Comm **2088**, 28

Review: "5-Endo-Trig Radical Cyclizations" Ishibashi, et al *Synthesis* **2002**, 695-713, [PDF on Course Website](#)

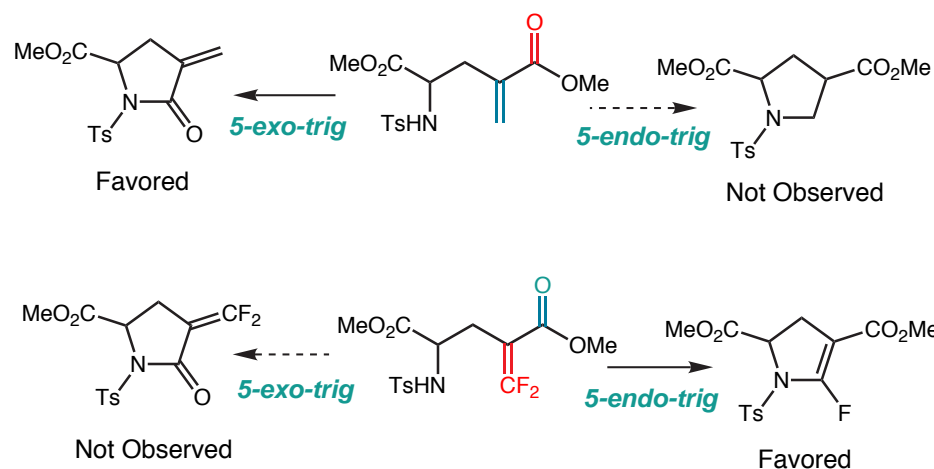


X	Y	Cond	Yield
F	F	DMF, 60 °C, 2 h	80
F	H	DMF, 80 °C, 43 h	17
Cl	Cl	DMF, 60 °C, 8 h	—
Br	Br	DMF, 60 °C, 5 h	15

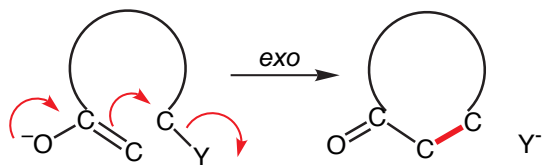
Ichikawa, et al *Synthesis* **2002**, 1917-1936, [PDF on Course Website](#)

Numerous other cases are provided in this review.

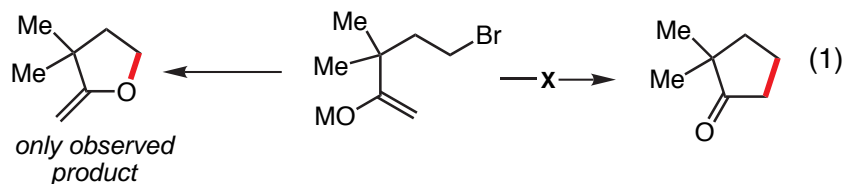
Revisiting Case 2 with Fluorines



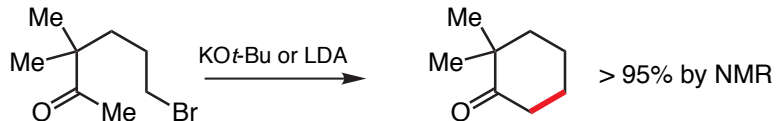
Trigonal Carbon: Exocyclic Enolate Alkylation



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

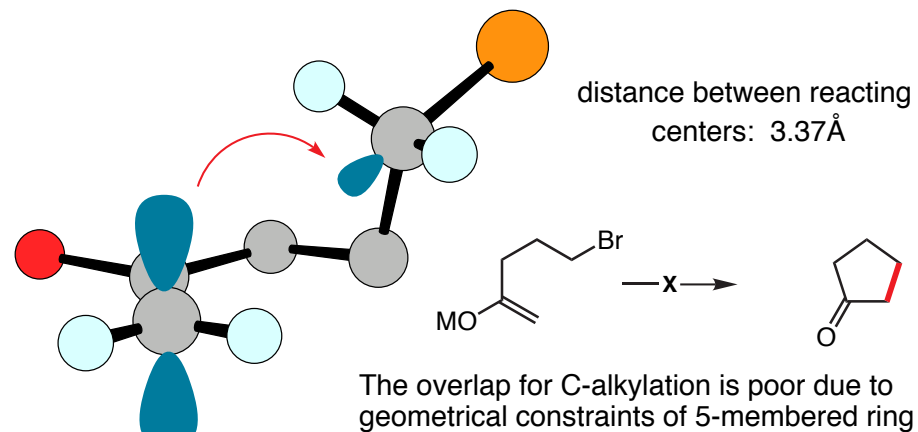
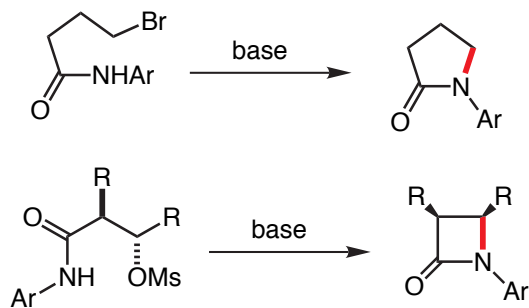


However:

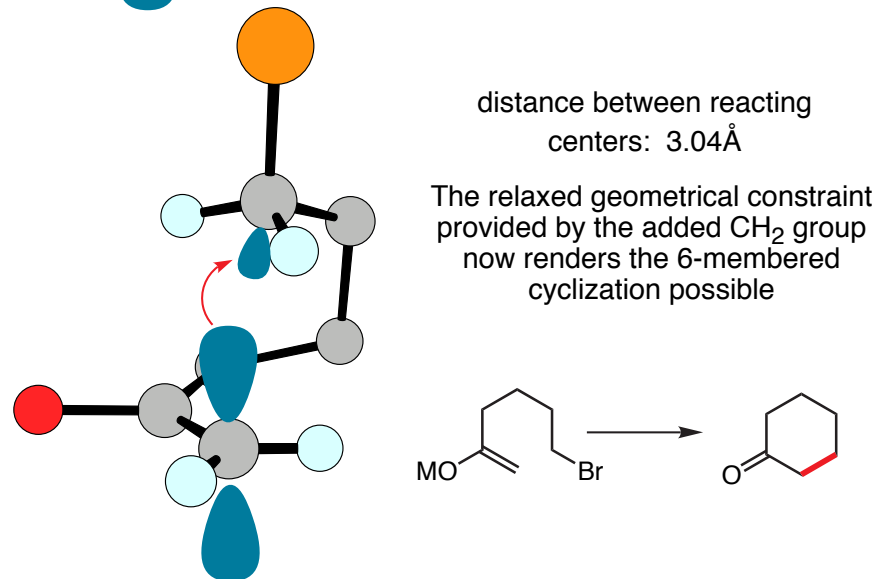


Baldwin, *J. Chem. Soc., Chem. Commun.* **1977**, 233.

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

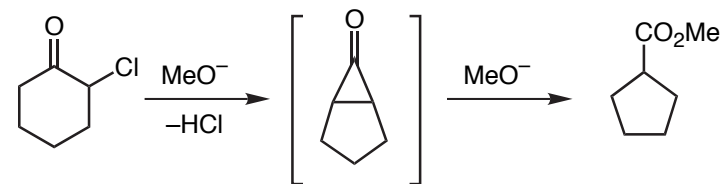


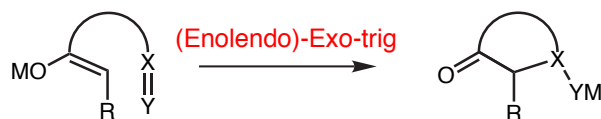
The overlap for C-alkylation is poor due to geometrical constraints of 5-membered ring



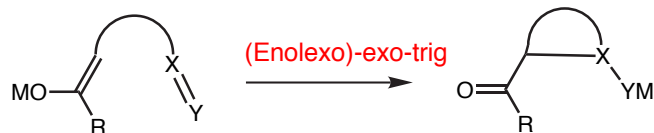
The relaxed geometrical constraint provided by the added CH₂ group now renders the 6-membered cyclization possible

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

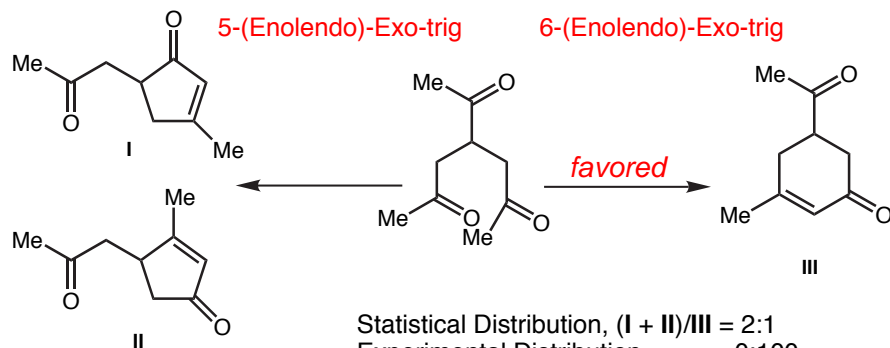


Trigonal Carbon: *Intramolecular Aldol Condensations*Baldwin, *Tetrahedron* **1982**, 38, 2939

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



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

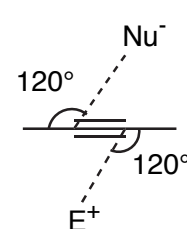


(KOH, MeOH, r.t., 5 min, 77% y.)

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

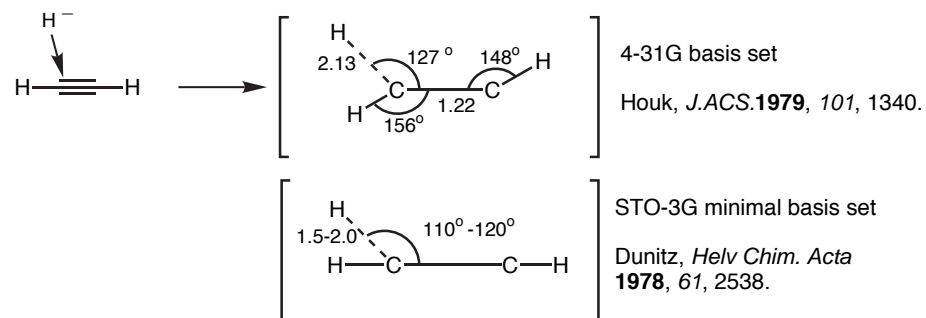
DIGONAL: Angle of approach for attack on triple bonds



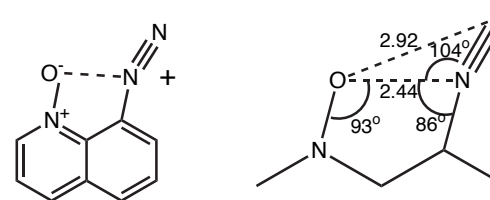
Baldwin:

- 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:



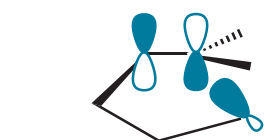
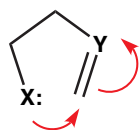
Crystal Structures do not support Baldwin



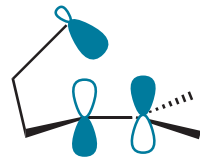
J. Dunitz and J. Wallis *J. C. S. Chem. Comm.* **1984**, 671.

Endo Digonal versus Endo Trigonal Cyclizations

5-endo-trig

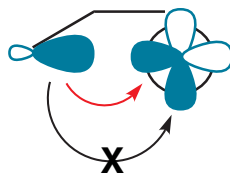
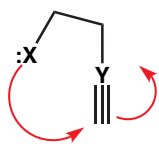


In-plane approach;
nucleophile lone pair is
orthogonal to π^*



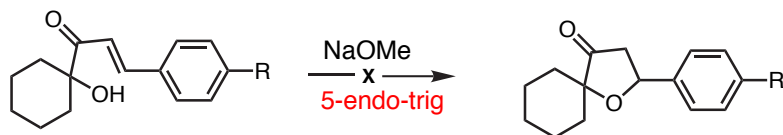
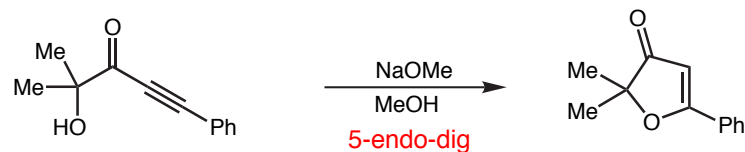
Out-of-plane approach;
nucleophile lone pair can't
achieve Bürgi-Dunitz angle

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

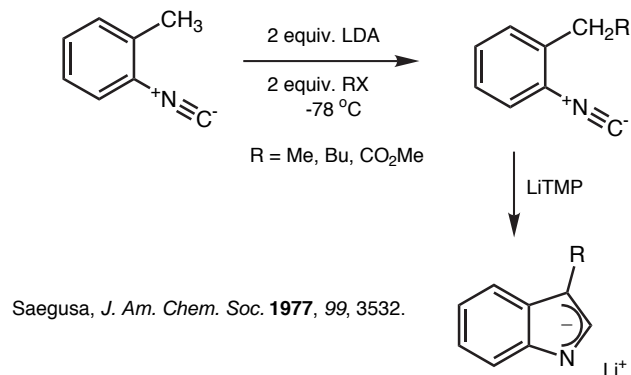
Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 736.

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

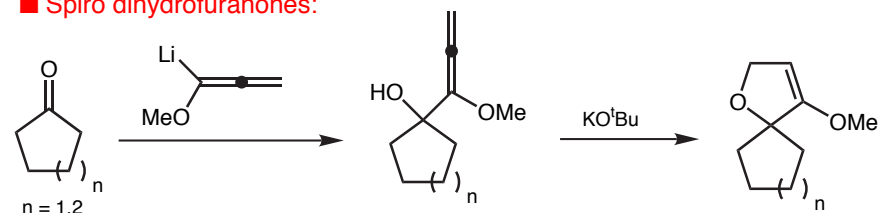
J. Am. Chem. Soc. **1983**, 105, 5090

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

■ Indole synthesis:

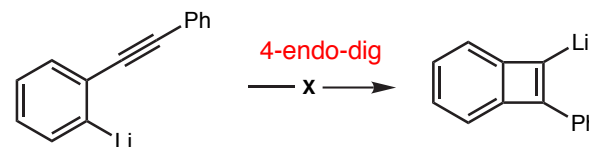
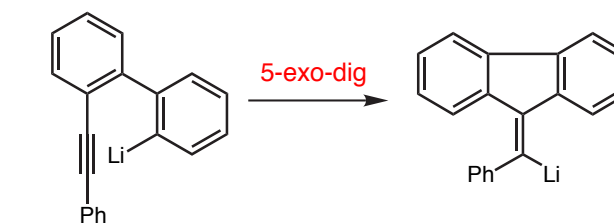


■ Spiro dihydrofuranones:

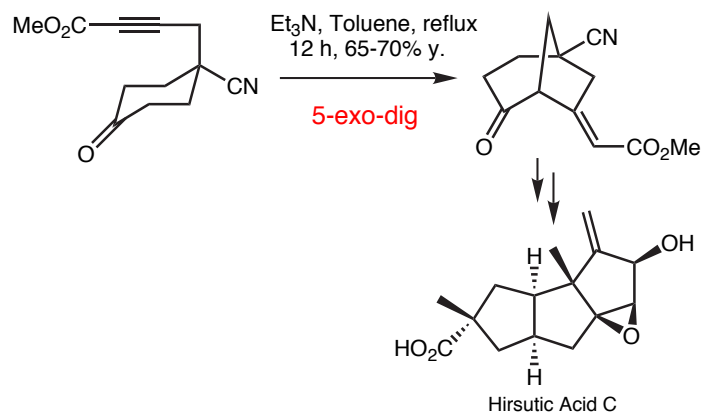


Developing negative charge on the central allenic carbon is
in the same plane as the OMe group

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

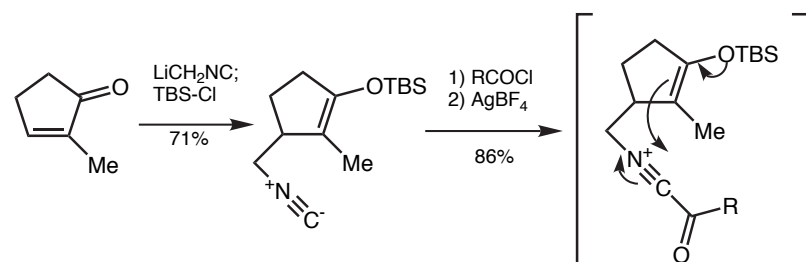
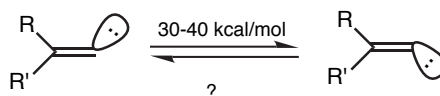


Digonal Cyclizations: Interesting Examples



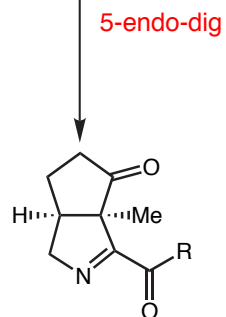
■ Trost, *J. Am. Chem. Soc.*, **1979**, *101*, 1284.

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	✓	✓	X		X	✓
4	✓	✓	X		X	✓
5	✓	✓	✓	X	X	✓
6	✓	✓	✓	X	✓	✓
7	✓	✓	✓	X	✓	✓

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 4

Acyclic Conformational Analysis-1

- Ethane, Propane, Butane & Pentane Conformations
- Simple Alkene Conformations

■ Reading Assignment for week

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

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

The Ethane Barrier Problem

F. Weinhold, *Nature* **2001**, 411, 539-541
"A New Twist on Molecular Shape" (**handout**)

F. M. Bickelhaupt & E. J. Baerends, *Angew. Chem. Int. Ed.* **2003**, 42, 4183-4188, "The Case for Steric Repulsion Causing the Staggered Conformation in Ethane" (**handout**)

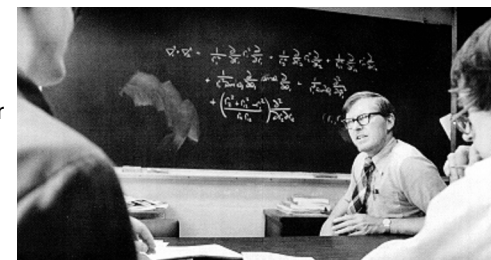
F. Weinhold, *Angew. Chem. Int. Ed.* **2003**, 42, 4188-4194, "Rebuttal of the Bickelhaupt-Baerends Case for Steric Repulsion Causing the staggered Conformation of Ethane" (**handout**)

D. A. Evans

Monday,
September 22, 2003

Professor Frank Weinhold

Univ. of Wisconsin, Dept of Chemistry
B.A. 1962, University of Colorado, Boulder
A.M. 1964, Harvard University
Ph.D. 1967, Harvard University
Physical and Theoretical Chemistry.



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.

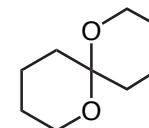
Kleinpeter, E. (1997). "Conformational Analysis of Saturated Six-Membered Oxygen-Containing Heterocyclic Rings." *Adv. Heterocycl. Chem.* **69**: 217-69.

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

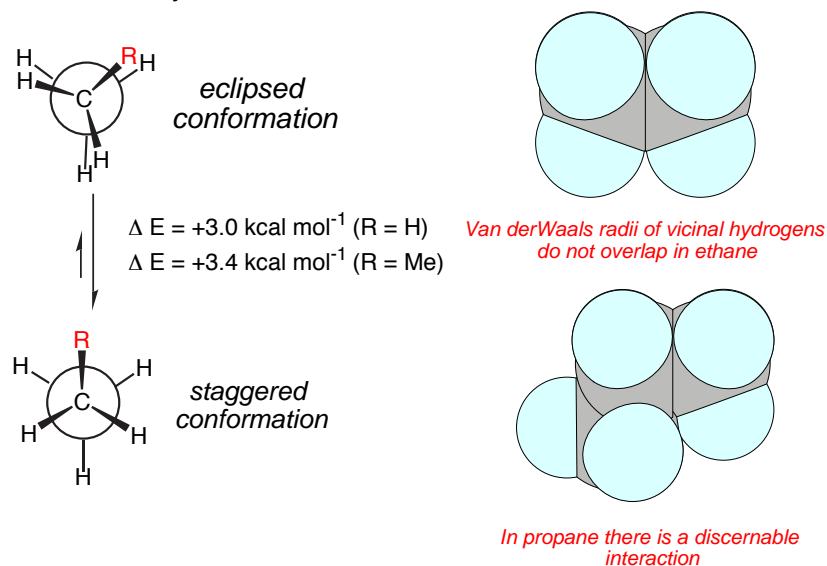
Predict the most stable conformation of the indicated dioxospiran?



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	δE (kcal mol ⁻¹)
ethane	3 (H↔H)	+1.0 kcal mol ⁻¹
propane	2 (H↔H)	+1.0 kcal mol ⁻¹
	1 (H↔Me)	+1.4 kcal mol ⁻¹

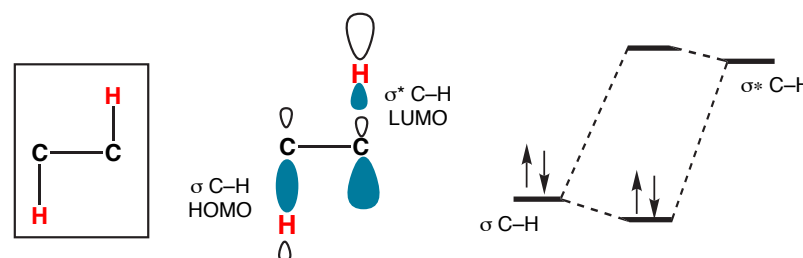
Ethane Rotational Barrier: The FMO View

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

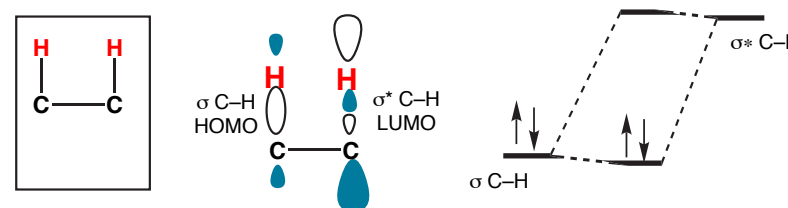
One can see from the space-filling models that the Van der Waals radii of the hydrogens do not overlap in the eclipsed ethane conformation. This makes the steric argument for the barrier untenable.

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

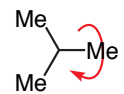


Following this argument one might conclude that:

■ The staggered conformer has a better orbital match between bonding and antibonding states.

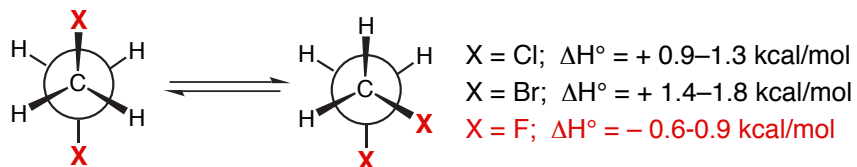
■ The staggered conformer can form more delocalized molecular orbitals.
 J. P. Lowe was the first to propose this explanation

"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 stabilization of the difluoro analog.

Recent Article: *Chem. Commun* **2002**, 1226-1227 (**handout**)

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: $2.3RT = 1.4$ (ΔG in kcal Mol^{-1})

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

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

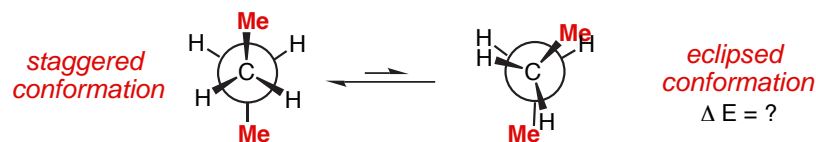
$$\Delta G^\circ_{298} = 1.4 pK_{\text{eq}}$$

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

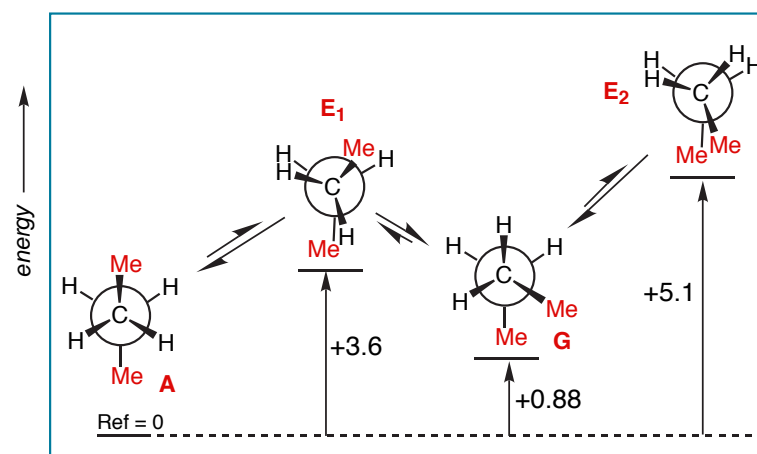
Butane

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



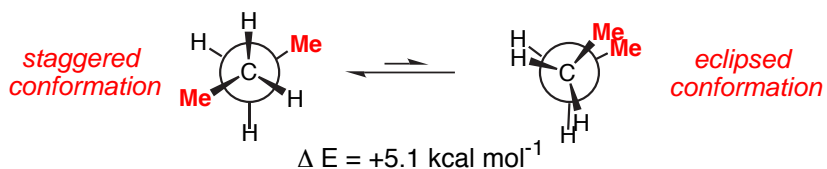
Eclipsed atoms	δE (kcal mol^{-1})
1 (H \leftrightarrow H)	+1.0 kcal mol^{-1}
2 (H \leftrightarrow Me)	+2.8 kcal mol^{-1}
ΔE est = 3.8 kcal mol^{-1}	

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

n-Butane Torsional Energy Profile

Butane continued

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



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

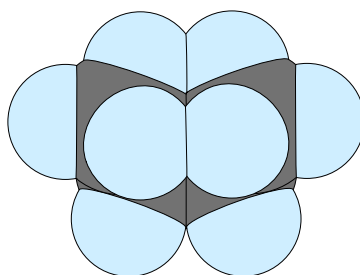
$$2 (\text{H} \leftrightarrow \text{H}) + 1 (\text{Me} \leftrightarrow \text{Me}) = +5.1$$

$$1 (\text{Me} \leftrightarrow \text{Me}) = +5.1 - 2 (\text{H} \leftrightarrow \text{H})$$

$$1 (\text{Me} \leftrightarrow \text{Me}) = +3.1$$

Incremental Contributions to the Barrier.

Eclipsed atoms	δE (kcal mol ⁻¹)
2 (H↔H)	+2.0
1 (Me↔Me)	+3.1



Eclipsed Butane conformation

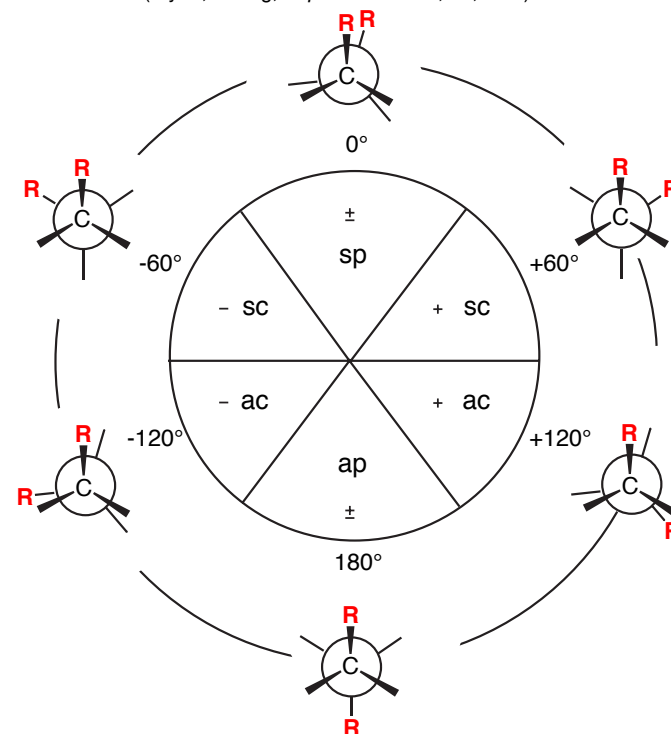
From the energy profiles of ethane, propane, and n-butane, one may extract the useful eclipsing interactions summarized below:

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

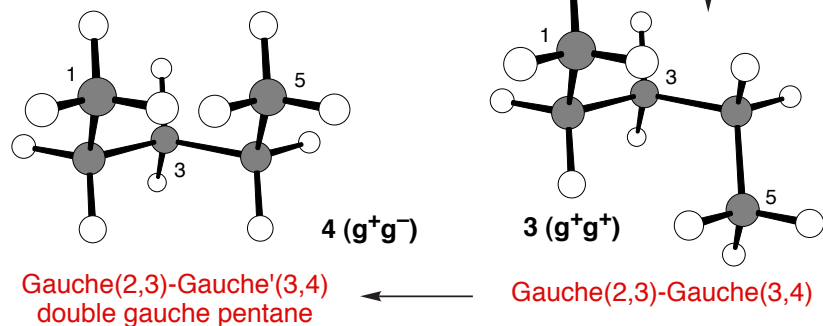
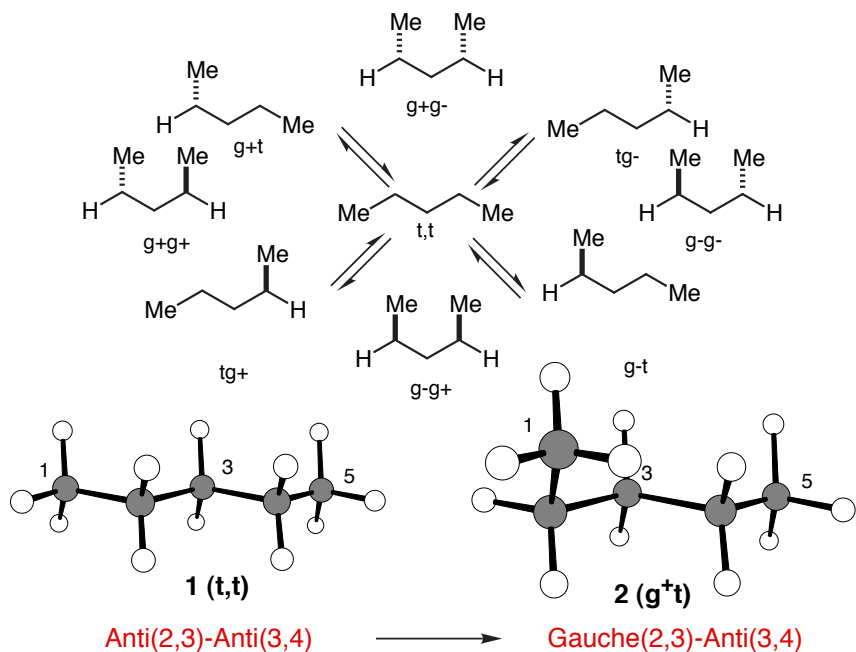
(Klyne, Prelog, *Experientia* 1960, 16, 521.)



	Torsion angle	Designation	Symbol	n-Butane Conformer
Energy Maxima	0 ± 30°	± syn periplanar	± sp	E ₂
Energy Minima	+60 ± 30°	+ syn-clinal	+ sc (g ⁺)	G
	+120 ± 30°	+ anti-clinal	+ ac	E ₁
	180 ± 30°	antiperiplanar	ap (anti or t)	A
	-120 ± 30°	- anti-clinal	- ac	E ₁
	-60 ± 30°	- syn-clinal	- sc (g ⁻)	G

n-Pentane

Rotation about both the C₂-C₃ and C₃-C₄ bonds in either direction (+ or -):

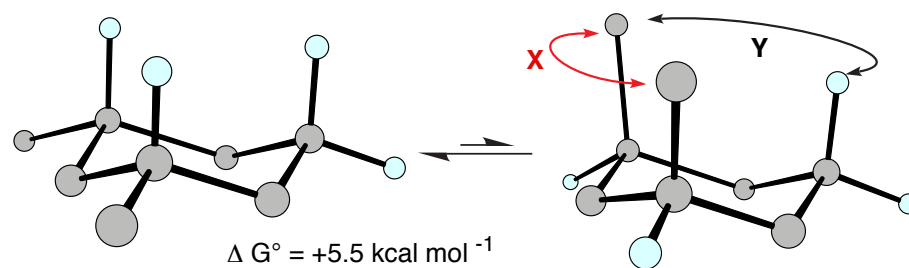


From prior discussion, you should be able to estimate energies of 2 & 3 (relative to 1). On the other hand, the least stable conformer 4 requires additional data before its relative energy can be evaluated.

The double-gauche pentane conformation

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

Estimate of 1,3-Dimethyl Eclipsing Interaction



$$\Delta G^\circ = +5.5 \text{ kcal mol}^{-1}$$

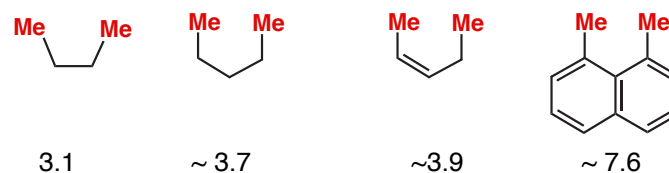
$$\Delta G^\circ = X + 2Y \text{ where:}$$

$$X = 1,3(\text{Me} \leftrightarrow \text{Me}) \text{ \& Y = } 1,3(\text{Me} \leftrightarrow \text{H})$$

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

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

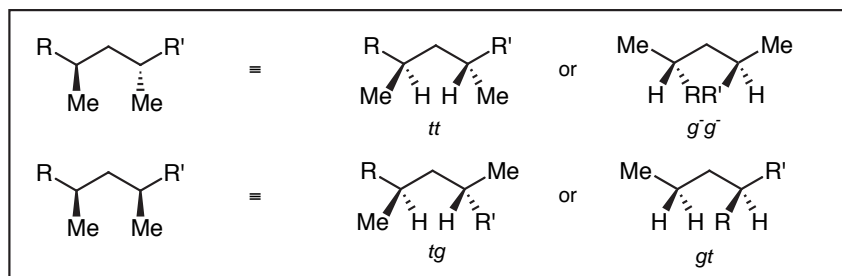
$$1,3(\text{Me} \leftrightarrow \text{Me}) = +3.7 \text{ kcal mol}^{-1}$$

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.

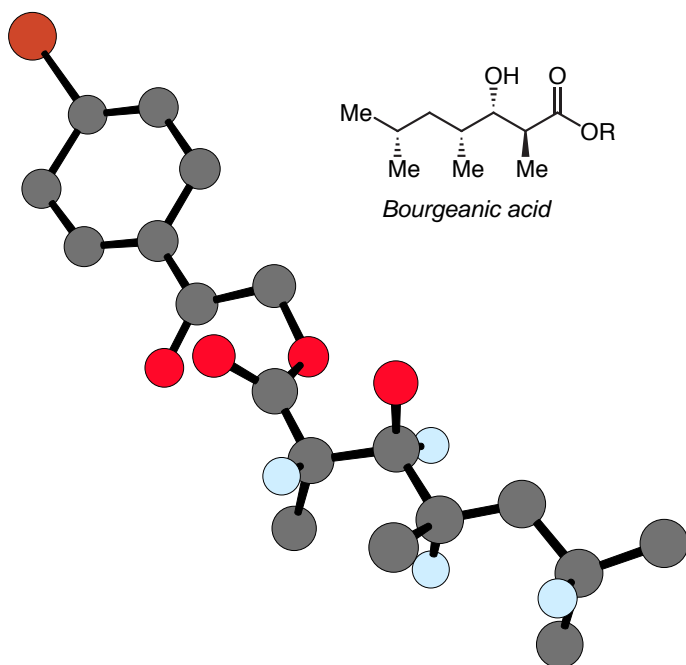
The *syn*-Pentane Interaction - Consequences

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



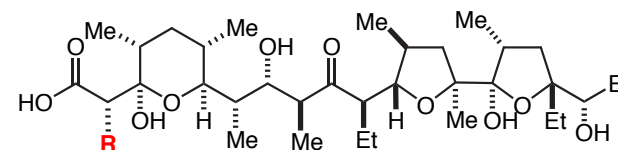
Consequences for the preferred conformation of polyketide natural products

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



Lactol & Ketol Polyether Antibiotics

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

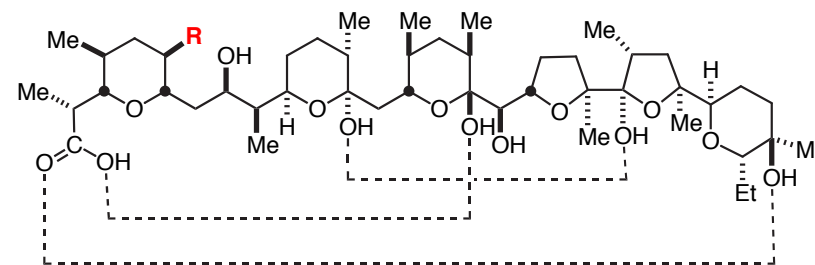


Ferensimycin B, R = Me
 Lysocellin, R = H

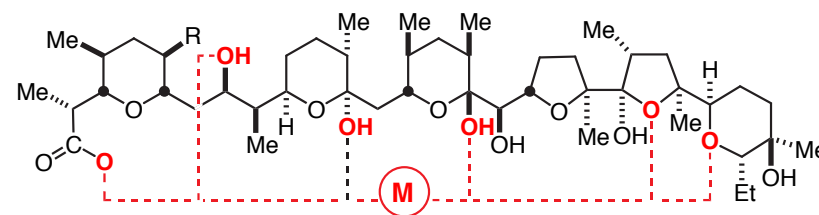
The conformation of these structures are strongly influenced by the acyclic stereocenters and internal H-bonding

Alborixin R = Me; X-206 R = H

Internal H-Bonding

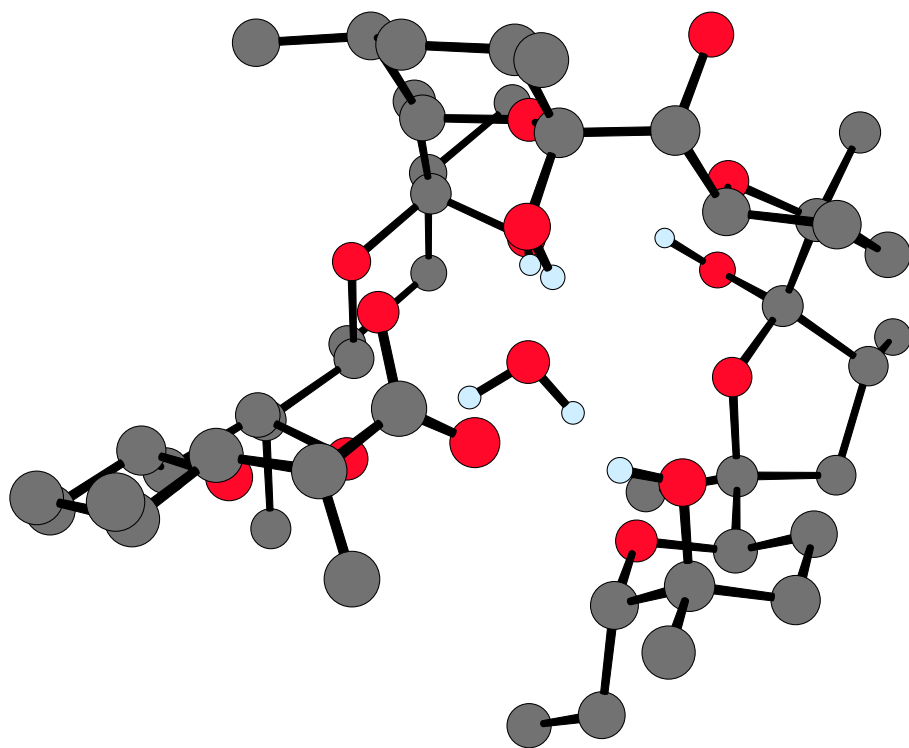
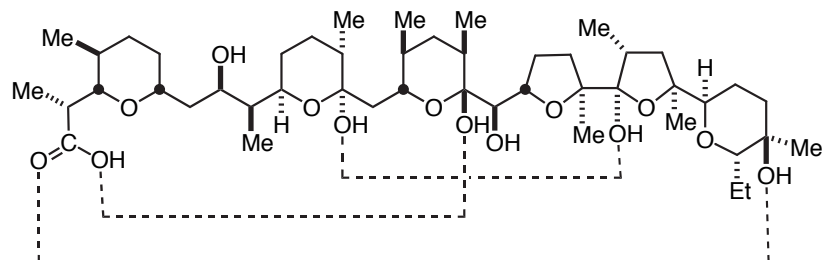


Metal ion ligation sites (M = Ag, K)



X-ray of Ionophore X-206 · H₂O

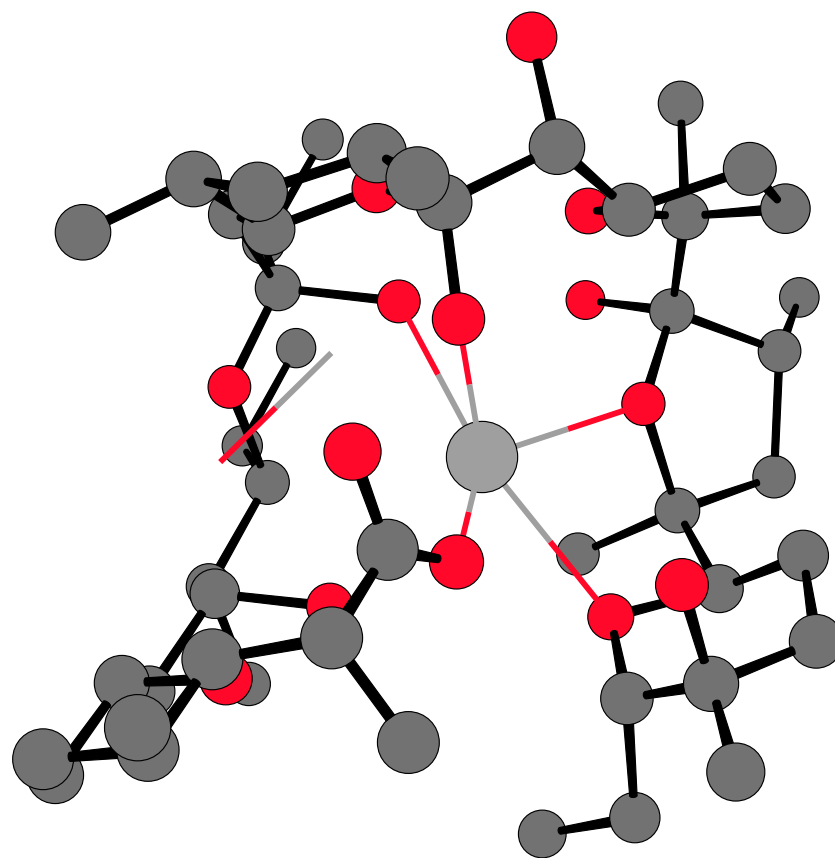
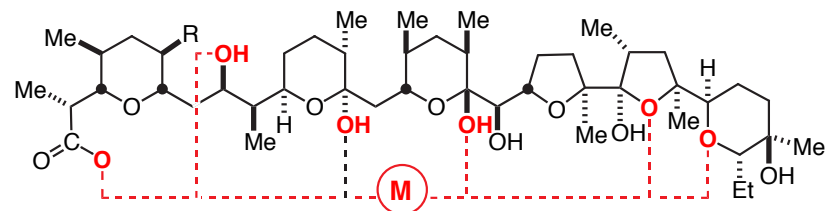
Internal H-Bonding

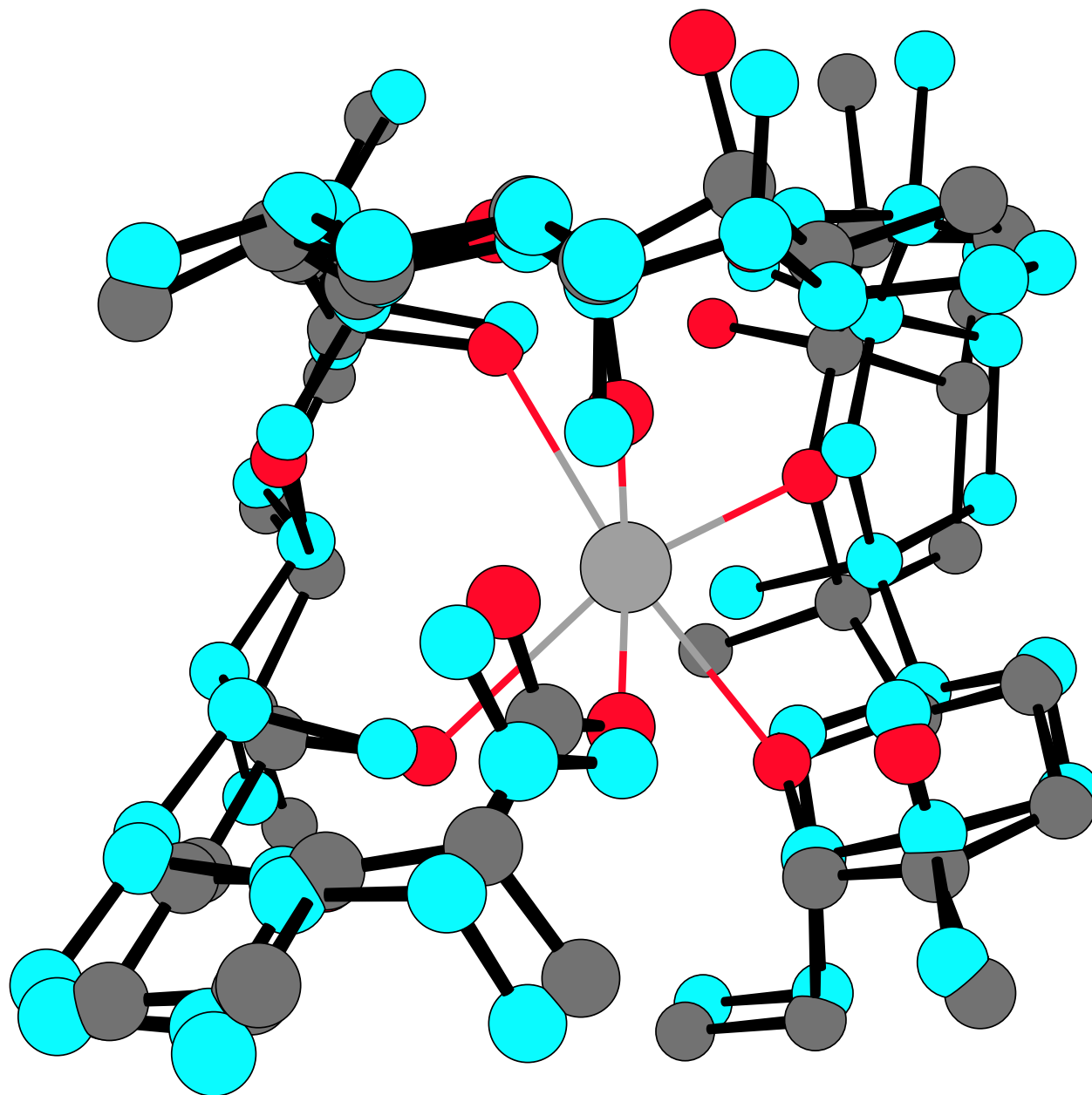


"The Total Synthesis of the Polyether Antibiotic X-206". Evans, D. A.; Bender, S. L.; Morris, J. J. *Am. Chem. Soc.* **1988**, *110*, 2506-2526.

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

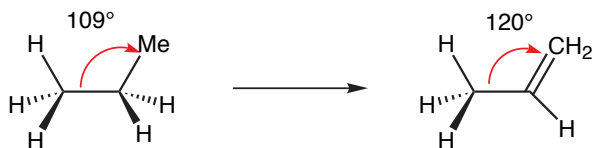
Metal ion ligation sites (M = Ag, K)





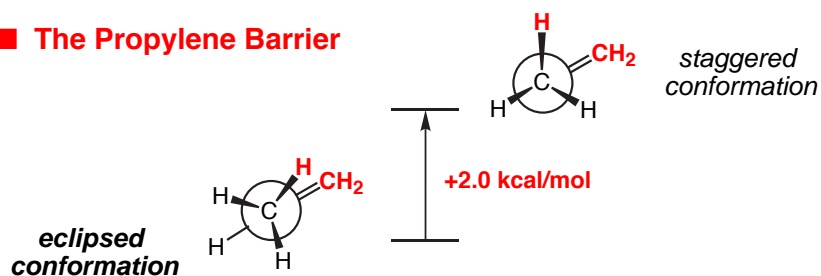
Simple olefins exhibit unusual conformational properties relative to their saturated counterparts

Propane versus Propene

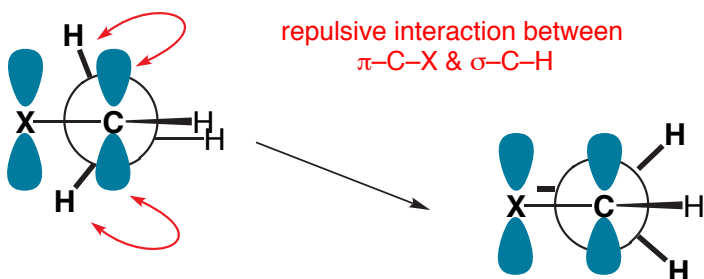


Hybridization change opens up the C-C-C bond angle

■ The Propylene Barrier



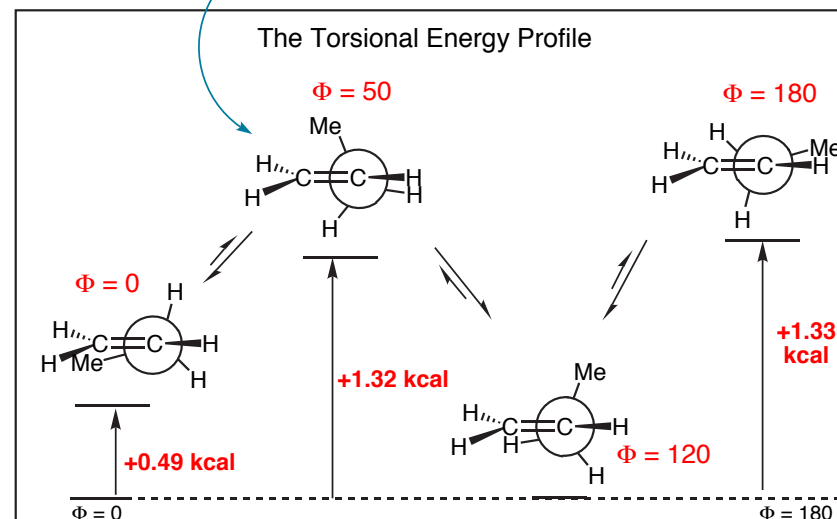
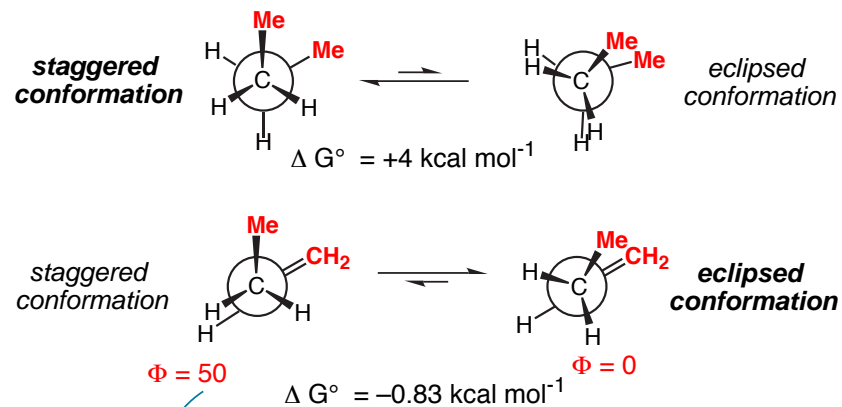
New destabilizing effect



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

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

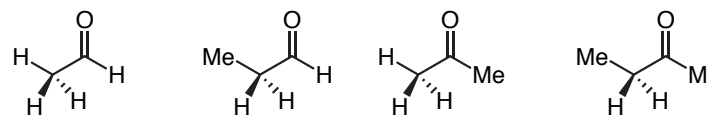
Butane versus 1-Butene



Conforms to *ab initio* (3-21G) values:

Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035.

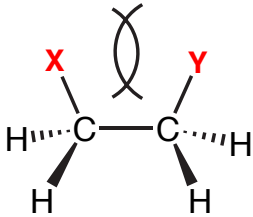
■ Acetaldehyde exhibits a similar conformational bias



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

Useful Destabilizing Interactions to Remember

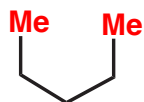
Hierarchy of Vicinal Eclipsing Interactions

	X—Y	$\delta E \text{ kcal mol}^{-1}$
	H—H	+1.0
	H—Me	+1.4
	Me—Me	+3.1

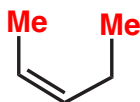
Estimates of In-Plane 1,2 & 1,3-Dimethyl Eclipsing Interactions



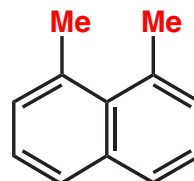
~ 3.1



~ 3.7

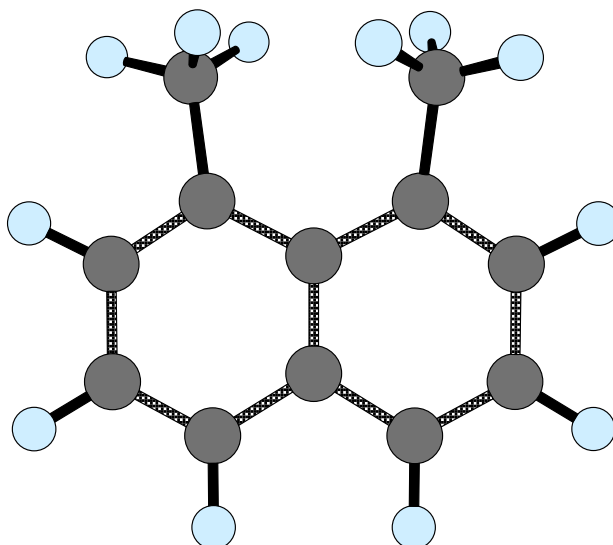


~3.9



~ 7.6

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



minimized structure

<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, *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 2054-2070
Conformation Design of Open-Chain Compounds (handout)

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

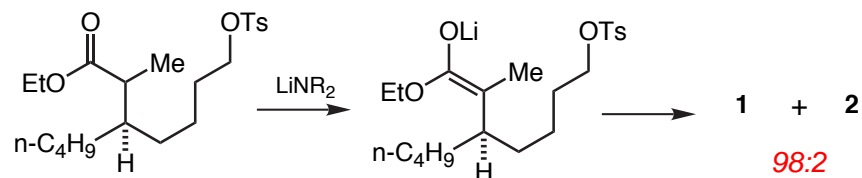
F. Weinhold, *Nature* **2001**, 411, 539-541
"A New Twist on Molecular Shape" (handout)

D. A. Evans

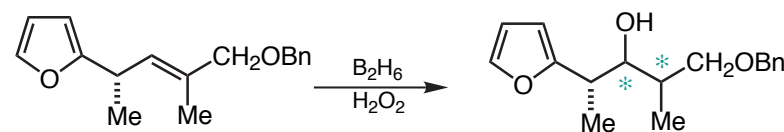
Wednesday,
September 24, 2001

■ Problems of the Day:

Can you predict the stereochemical outcome of this reaction?

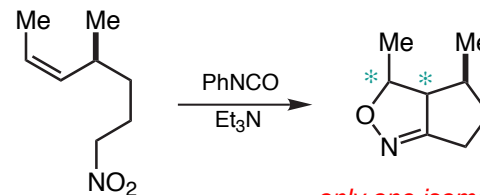


D. Kim & Co-workers, *Tetrahedron Lett.* **1986**, 27, 943.



diastereoselection 8:1

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

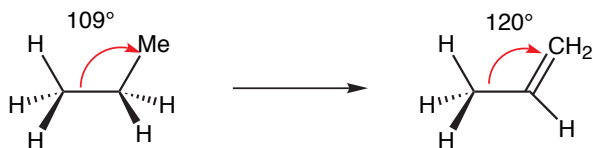


only one isomer

A. Kozikowski & Co-workers, *Tetrahedron Lett.* **1982**, 23, 2081.

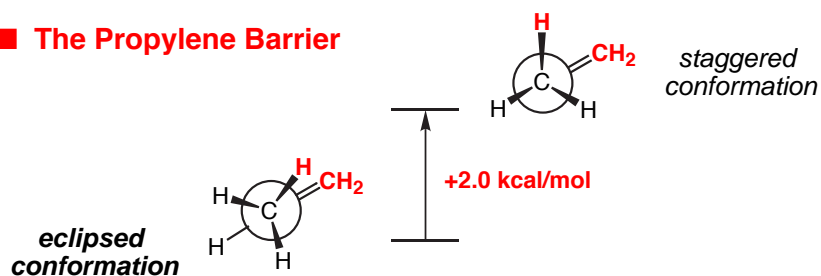
Simple olefins exhibit unusual conformational properties relative to their saturated counterparts

Propane versus Propene

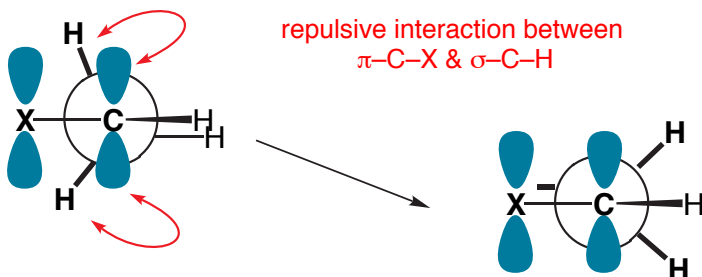


Hybridization change opens up the C-C-C bond angle

■ The Propylene Barrier



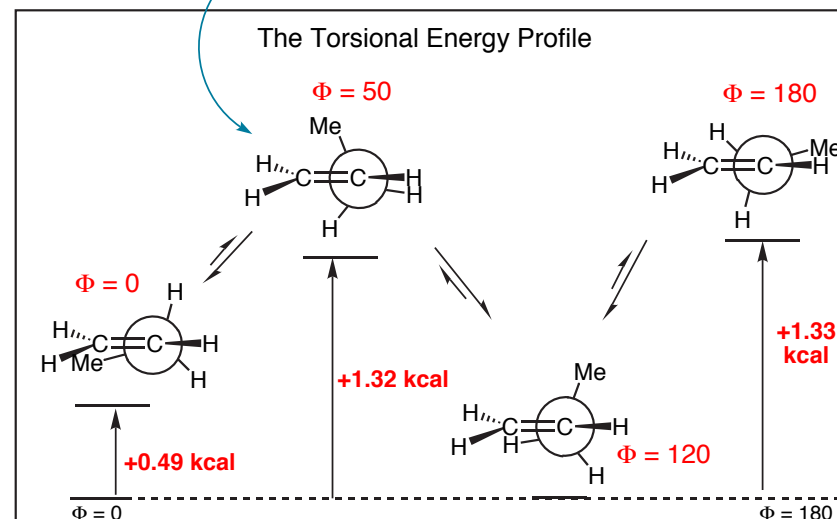
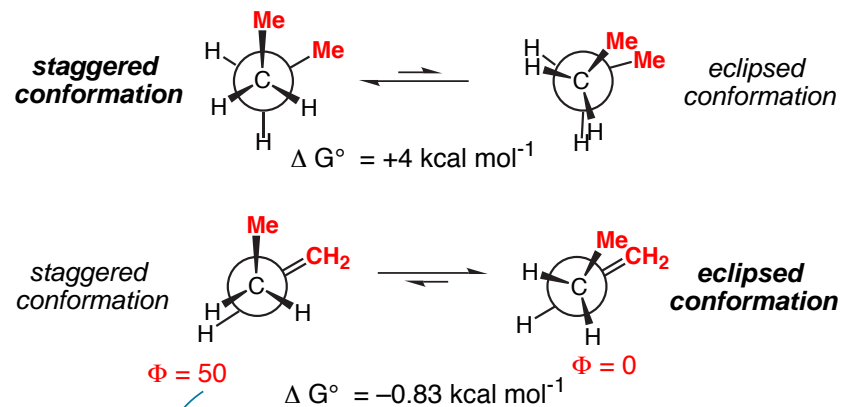
New destabilizing effect



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

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

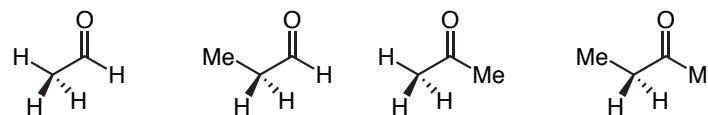
Butane versus 1-Butene



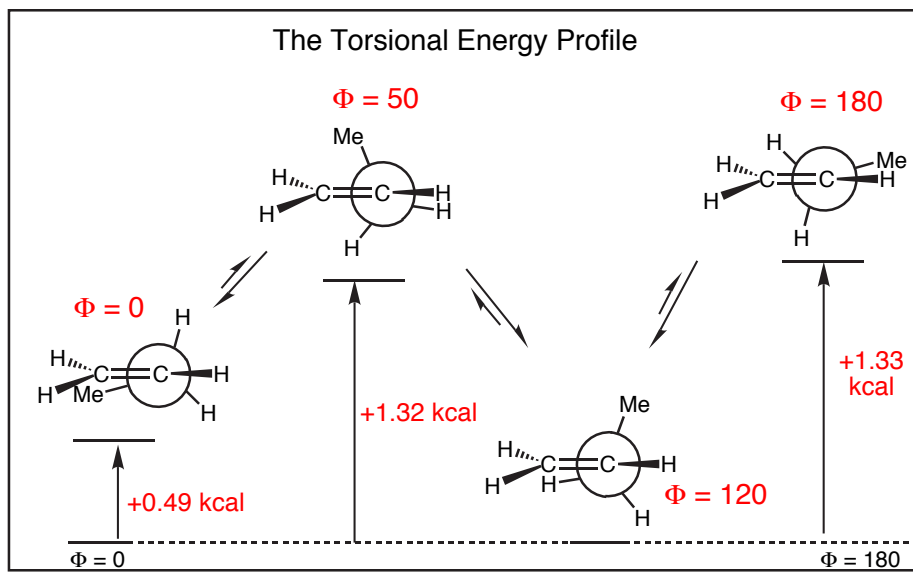
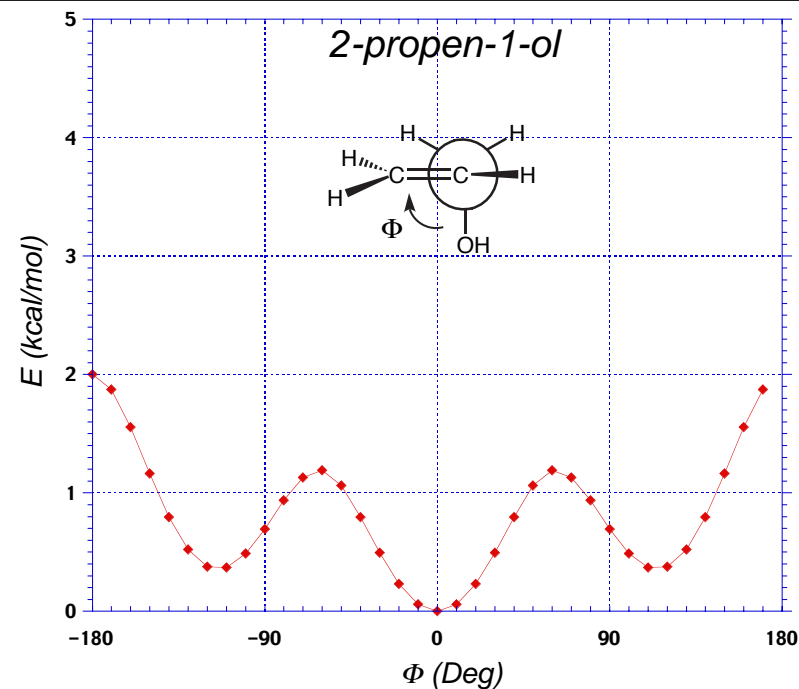
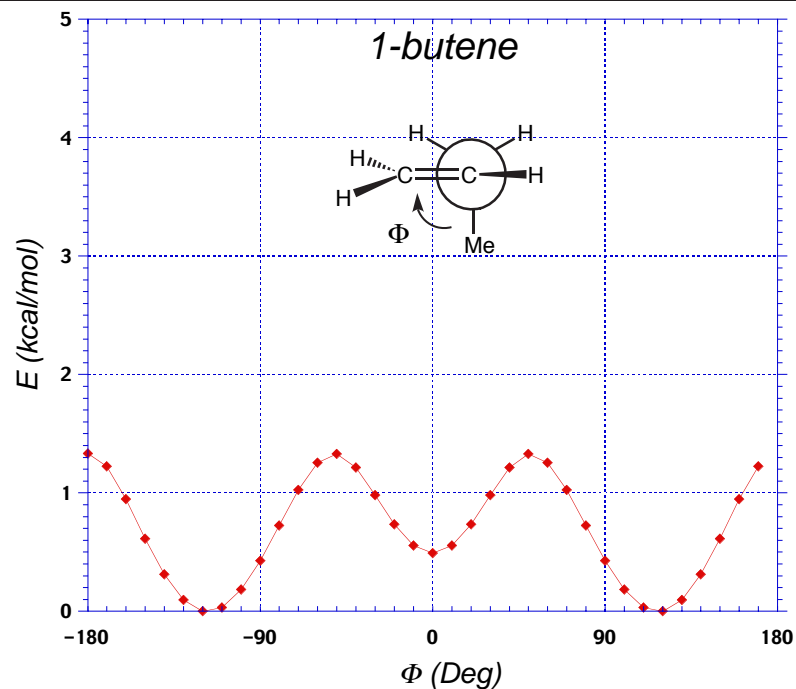
Conforms to *ab initio* (3-21G) values:

Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035.

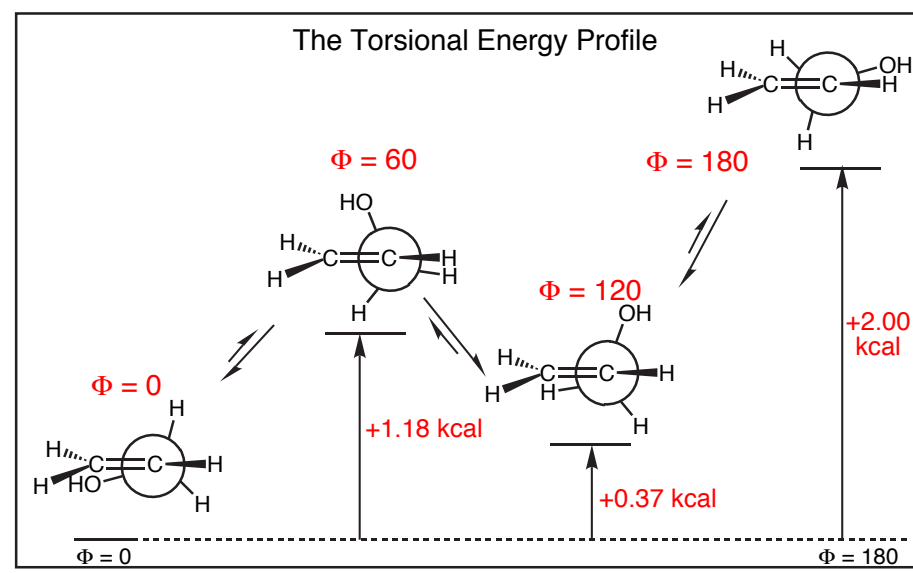
■ Acetaldehyde exhibits a similar conformational bias

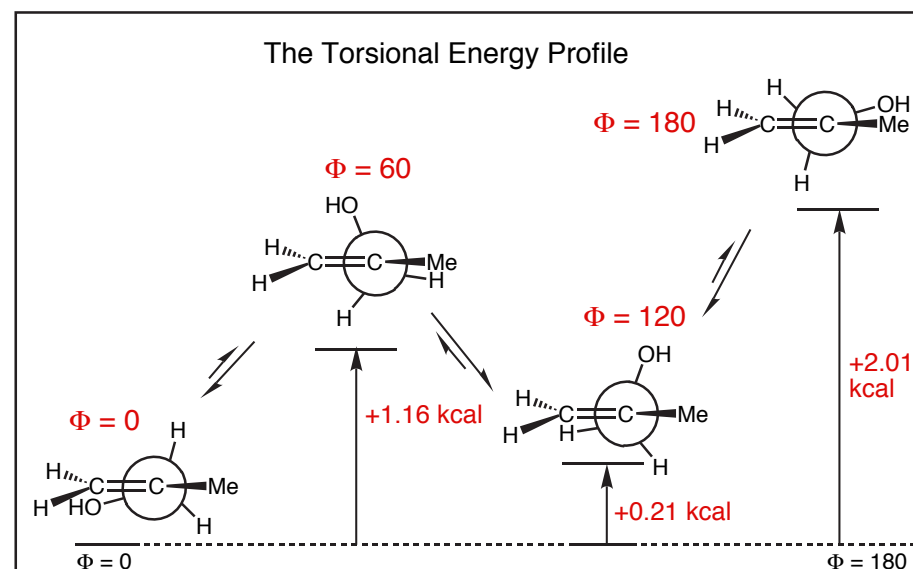
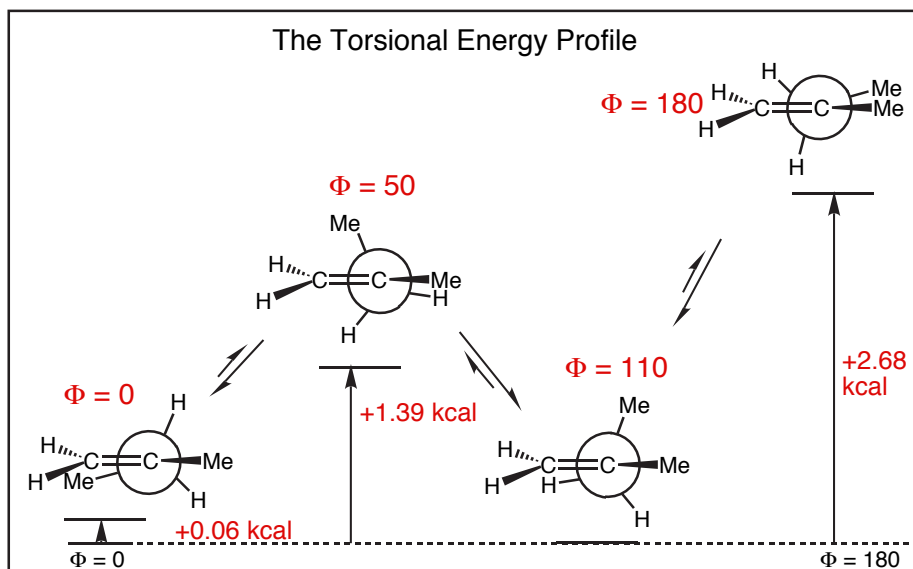
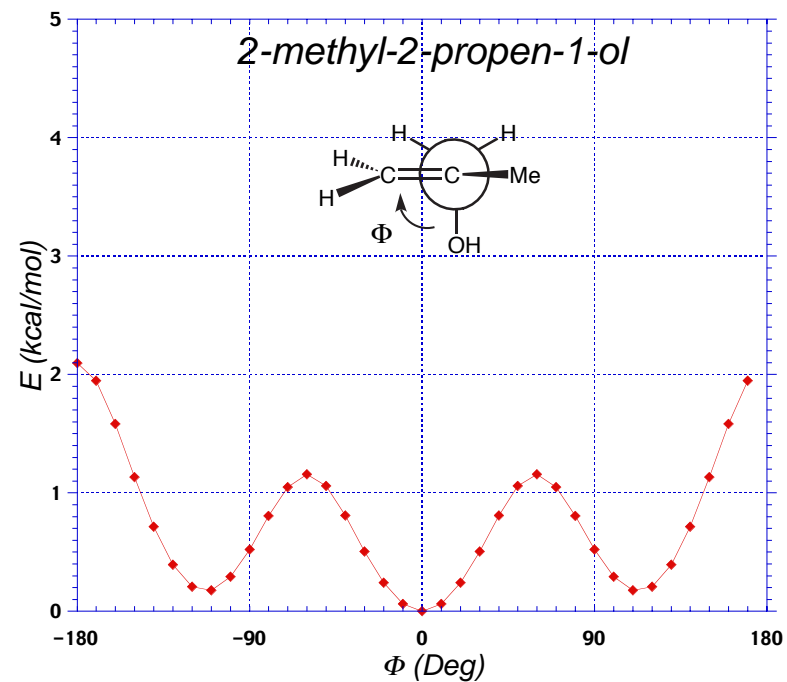
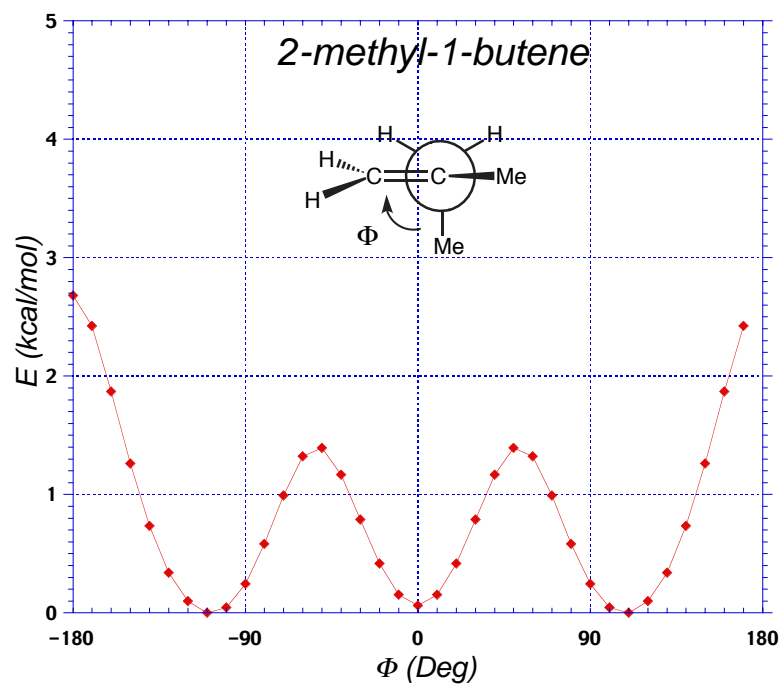


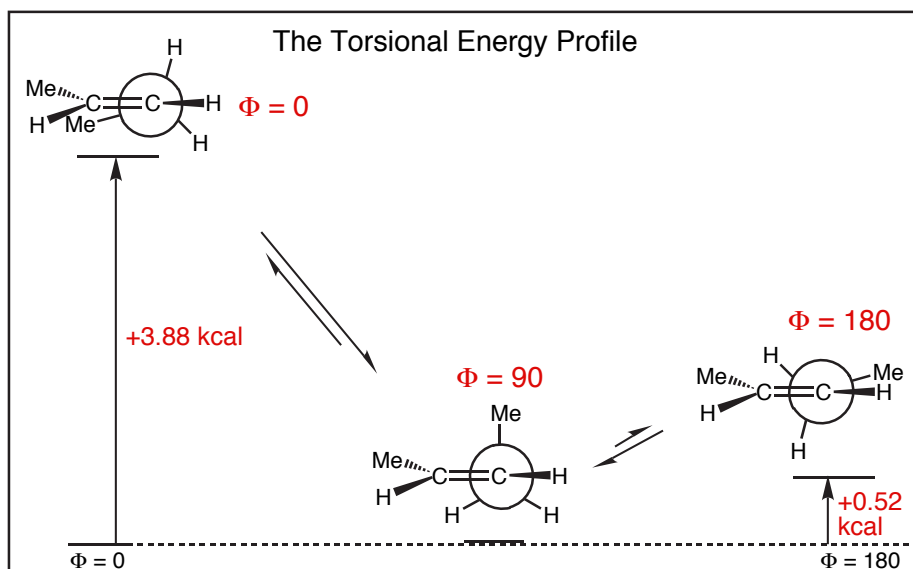
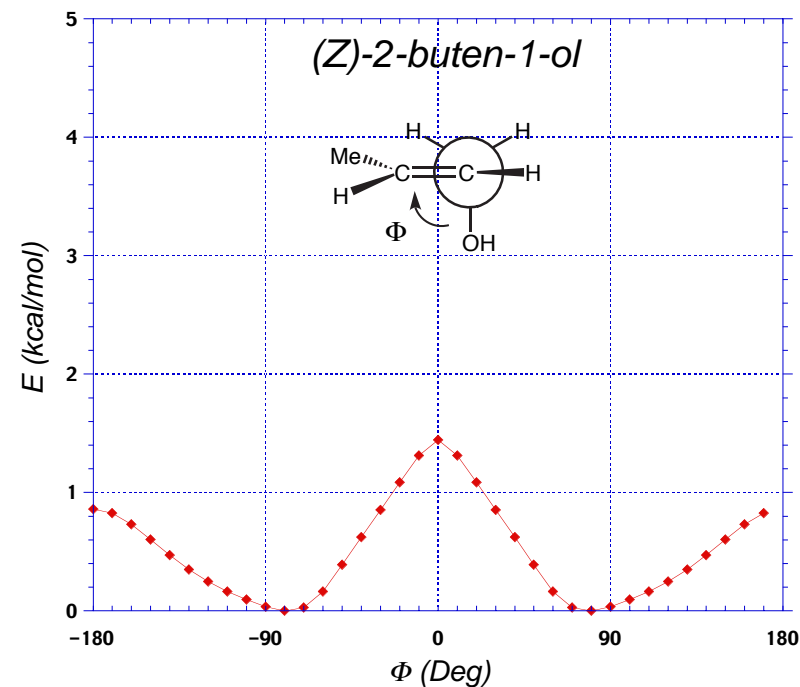
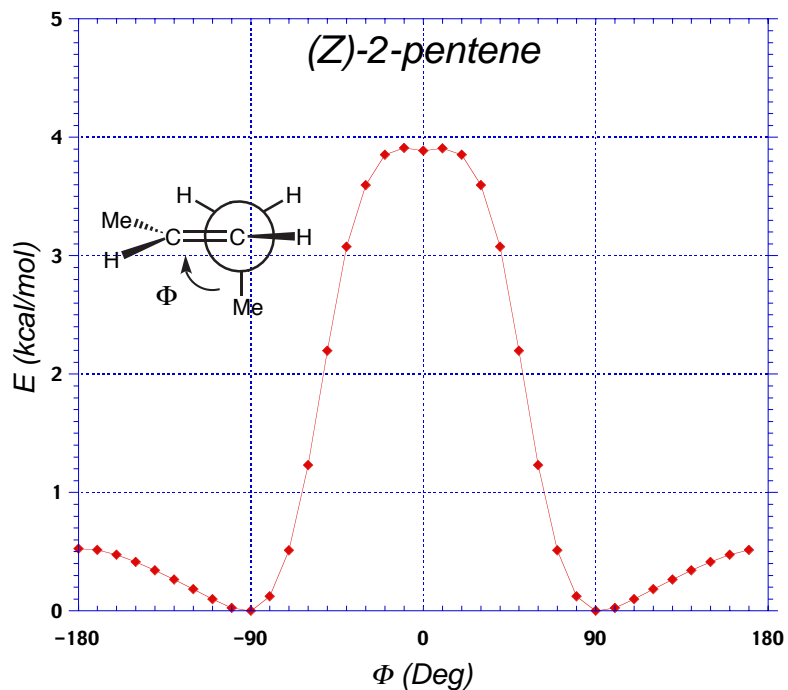
The low-energy conformation in each of above cases is eclipsed



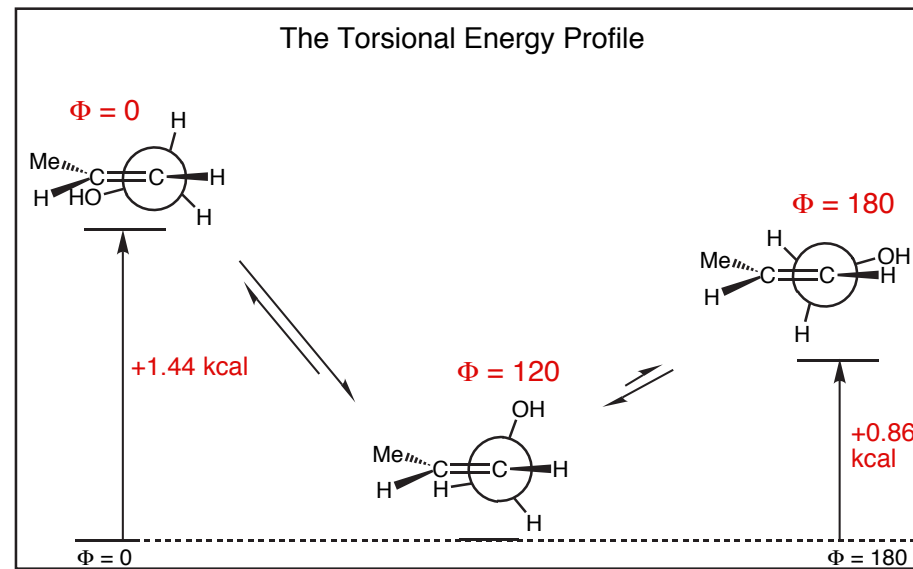
Conforms to *ab initio* (3-21G) values:
Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035.



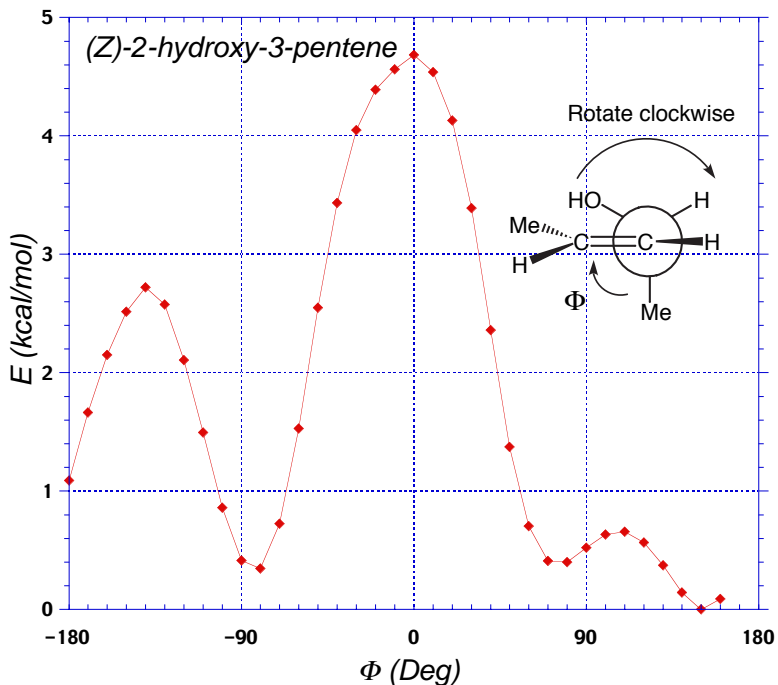




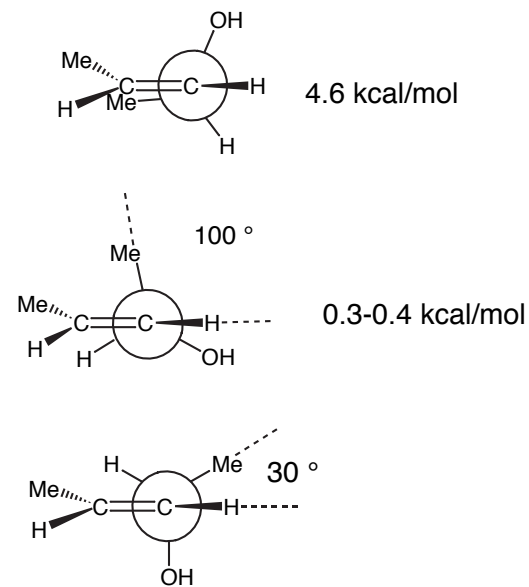
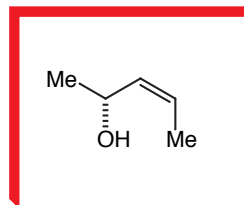
Values calculated using MM2 (molecular mechanics) force fields via the Macromodel multiconformation search.



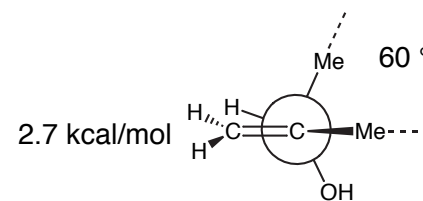
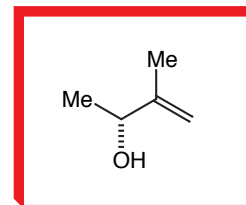
Review: Hoffman, R. W. *Chem. Rev.* **1989**, 89, 1841.



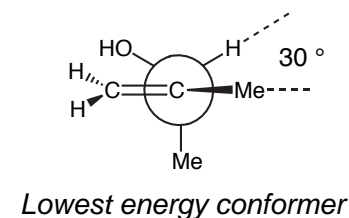
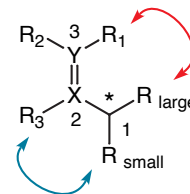
The Torsional Energy Profile



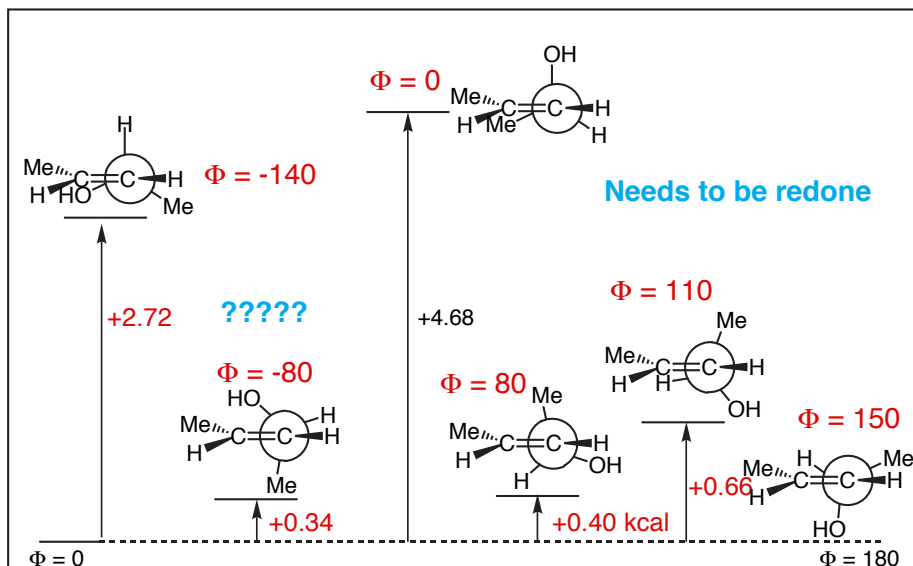
Lowest energy conformer



A(1,3) interaction 4.0 kcal/mol



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



The Definition of Allylic Strain

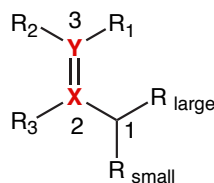
F. Johnson, *Chem. Rev.* **1968**, 68, 375; *Allylic Strain in Six-Membered Rings*

R. W. Hoffmann, *Chem. Rev.* **1989**, 89, 1841-1860 (**handout**)

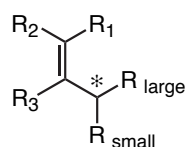
Allylic 1-3-Strain as a Controlling Element in Stereoselective Transformations

Houk, Hoffmann *JACS* **1991**, 113, 5006

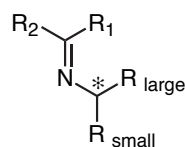
Consider the illustrated general structure where X & Y are permutations of C, N, and O:



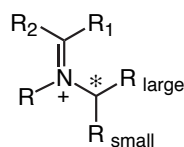
Typical examples:



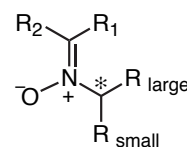
Olefin



Imine



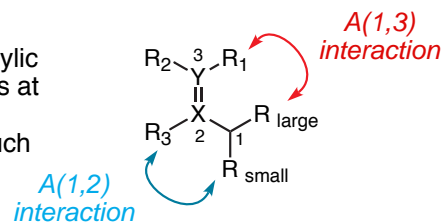
Iminium ion



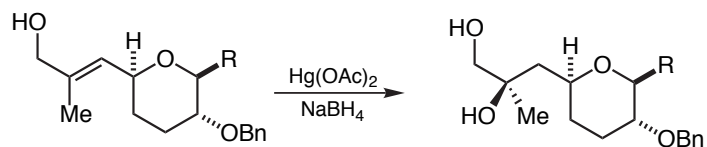
Nitron

In the above examples, the resident allylic stereocenter (*) and its associated substituents frequently impart a pronounced bias towards reactions occurring at the pi-bond.

Nonbonding interactions between the allylic substituents (R_{large} , R_{small}) & substituents at the 2- & 3-positions play a critical role in defining the stereochemical course of such reactions



Representative Reactions controlled by Allylic Strain Interactions

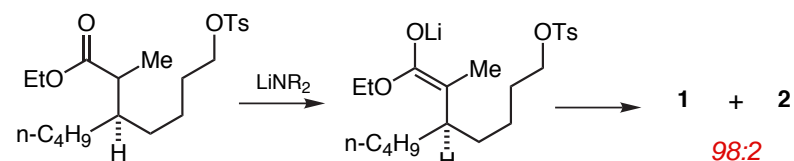


diastereoselection 10:1

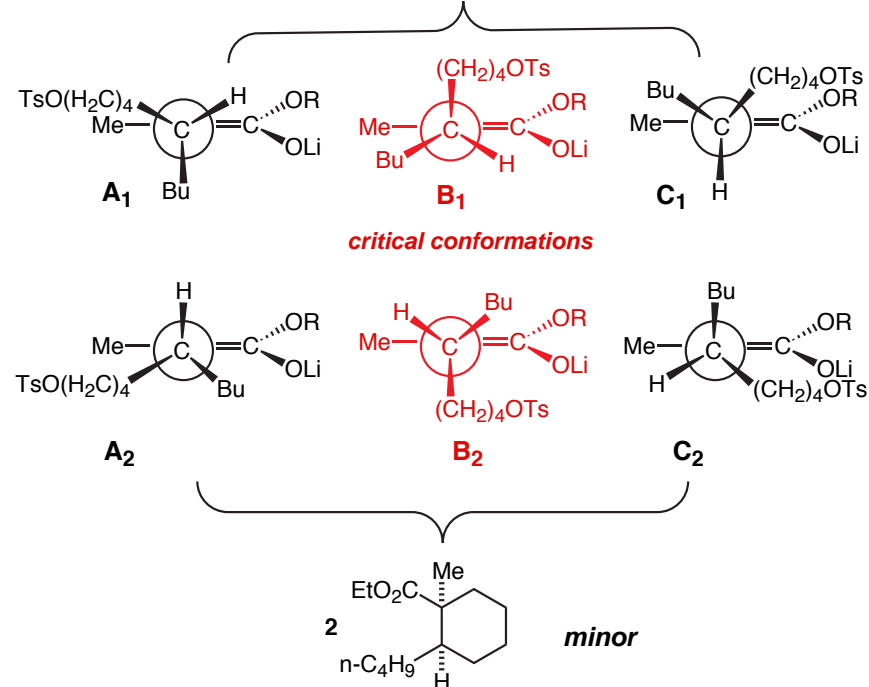
M. Isobe & Co-workers, *Tetrahedron Lett.* **1985**, 26, 5199.

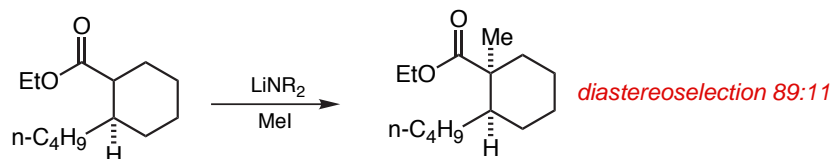
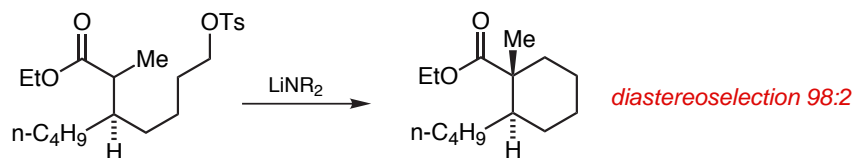
Can you predict the stereochemical outcome of this reaction?

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

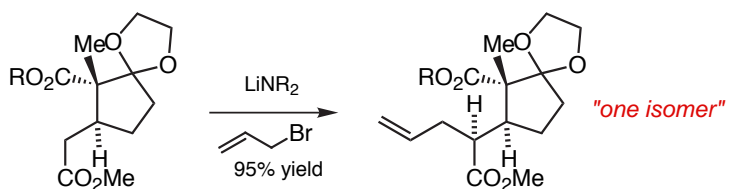


■ Relevant enolate conformations

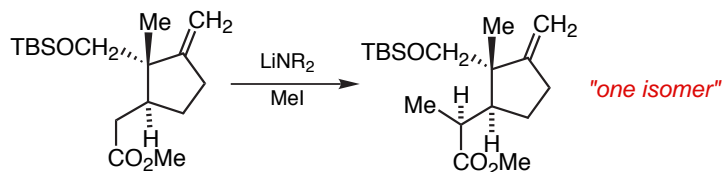




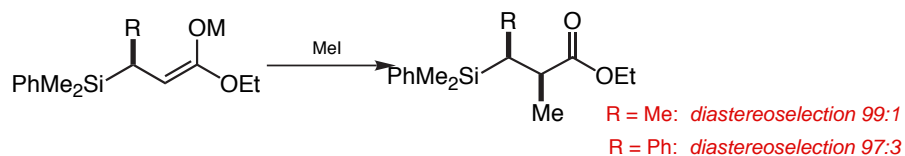
D. Kim & Co-workers, *Tetrahedron Lett.* **1986**, 27, 943.



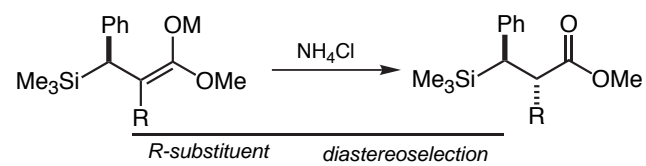
G. Stork & Co-workers, *Tetrahedron Lett.* **1987**, 28, 2088.



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



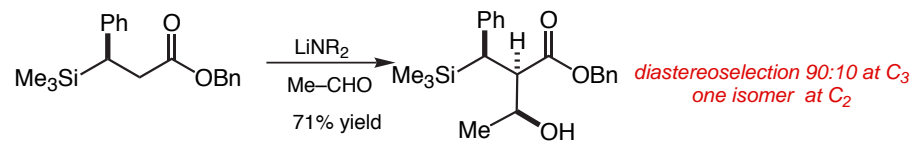
I. Fleming & Co-workers, *Chem. Commun.* **1984**, 28.



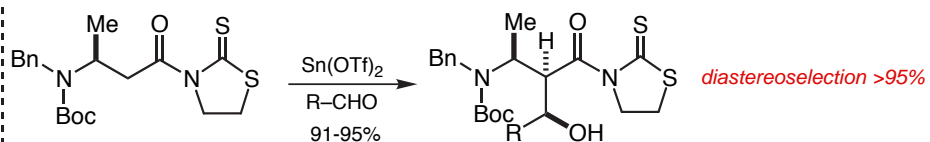
R-substituent	diastereoselection
R = Me	87:13
R = Et	80:20
R = CHMe ₂	40:60

major diastereomer opposite to that shown

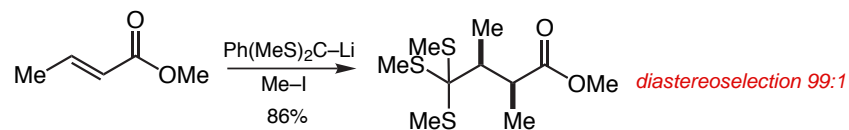
I. Fleming & Co-workers, *Chem. Commun.* **1985**, 318.
Y. Yamamoto & Co-workers, *Chem. Commun.* **1984**, 904.



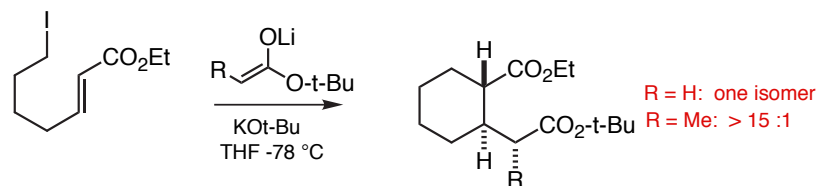
I. Fleming & Co-workers, *Chem. Commun.* **1986**, 1198.



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

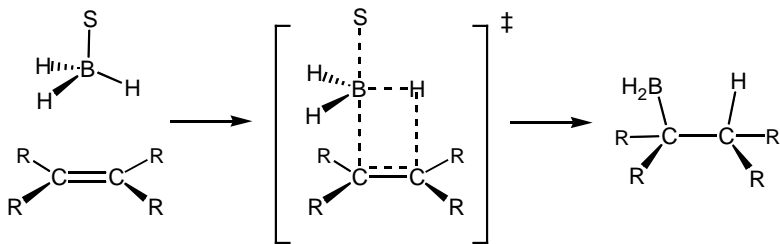


K. Koga & Co-workers, *Tetrahedron Letters* **1985**, 26, 3031.

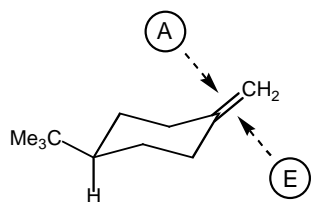


Y. Yamaguchi & Co-workers, *Tetrahedron Letters* **1985**, 26, 1723.

■ The basic process

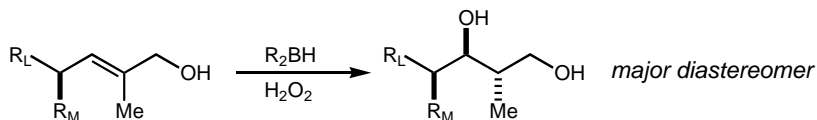


■ Response to steric effects: Here is a good calibration system:



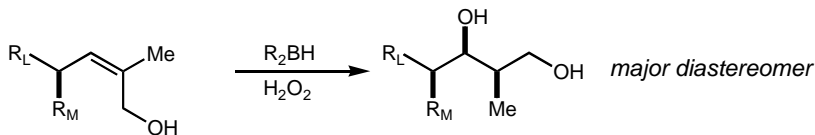
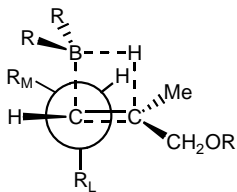
Oxidant	Ratio, A:E	Reference
MCPBA	69:31	JOC, 1967 , 32, 1363
BH ₃ , H ₂ O ₂	34:66	JOC, 1970 , 35, 2654

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

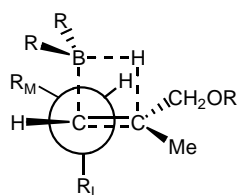


control elements

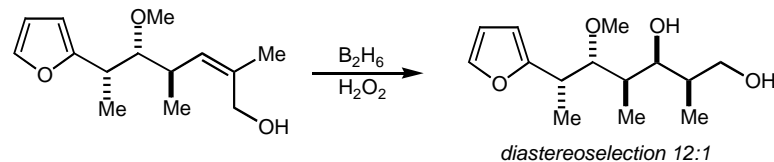
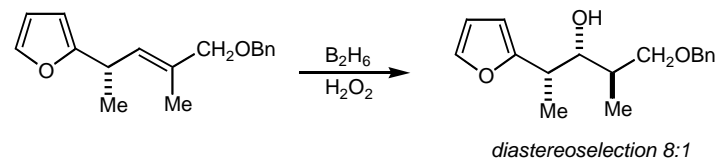
A(1,3) allylic strain
Steric effects; R_L vs R_M
Staggered transition states



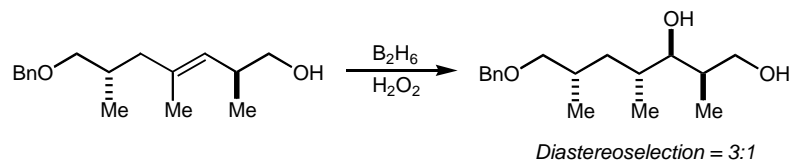
See Houk, *Tetrahedron* **1984**, 40, 2257



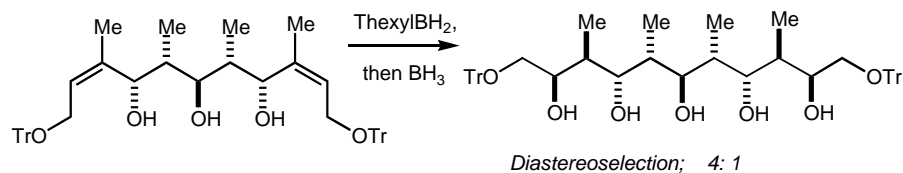
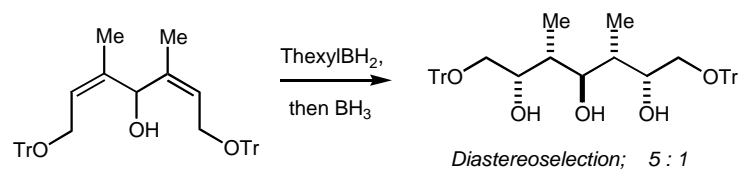
Hydroborations dominated by A(1,3) Strain



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

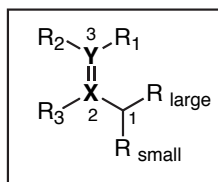
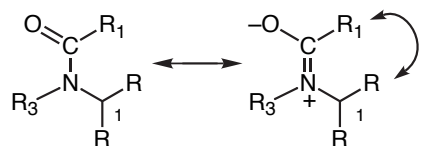


C. H. Heathcock et. al. *Tetrahedron Lett* **1984** 25 243.

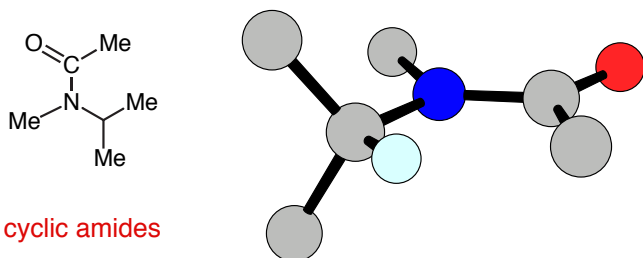


Still, W.C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, 105, 2487.

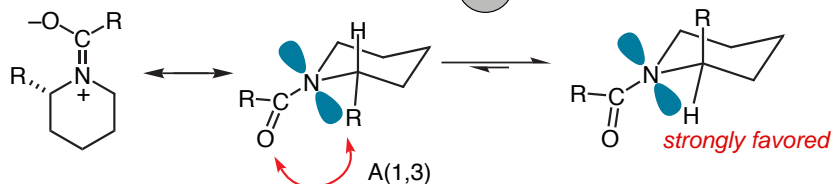
Consider the resonance structures of an amide:



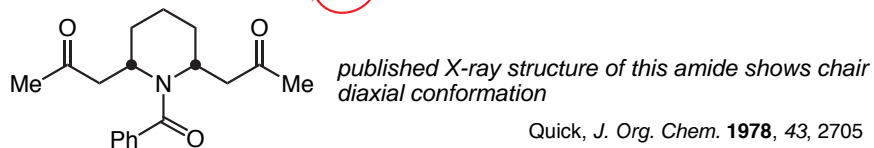
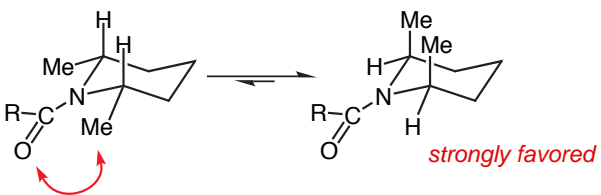
A(1,3) interactions between the "allylic substituent" and the R1 moiety will strongly influence the torsion angle between N & C1.



conformations of cyclic amides

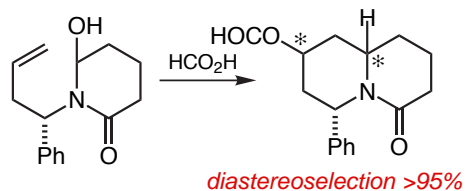


Chow
Can. J. Chem. **1968**, 46, 2821

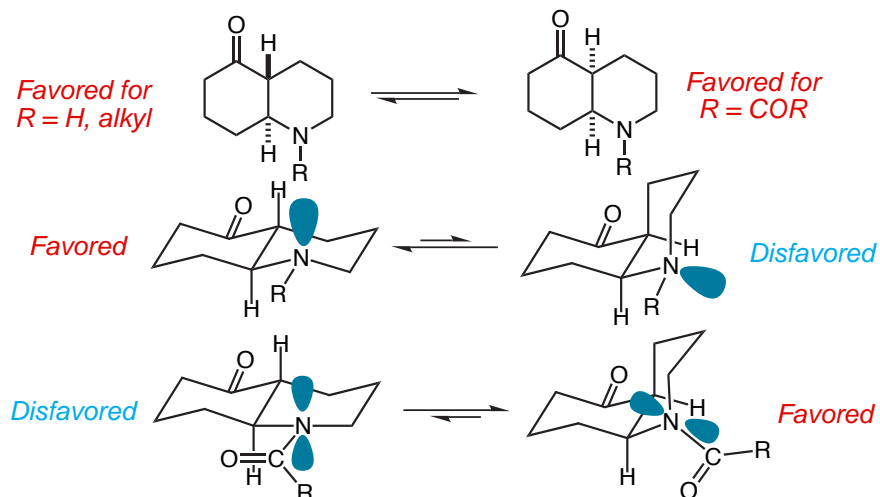


Problem: Predict the stereochemical outcome of this cyclization.

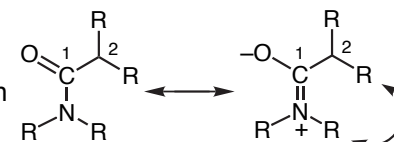
D. Hart, JACS **1980**, 102, 397



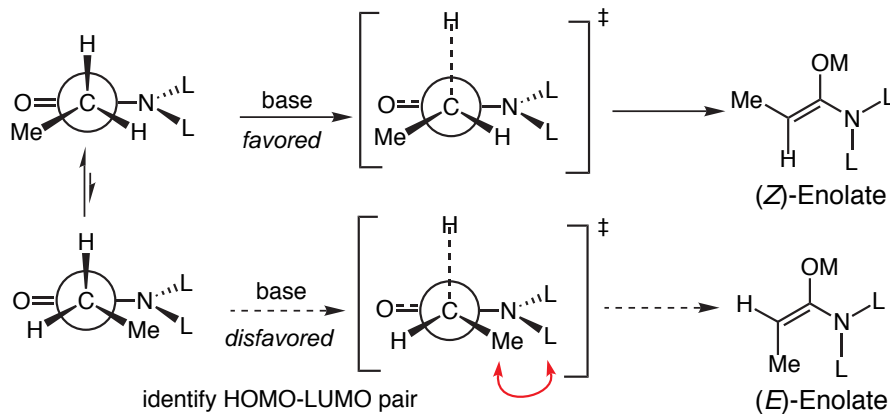
The selection of amide protecting group may be done with the knowledge that altered conformational preferences may result:



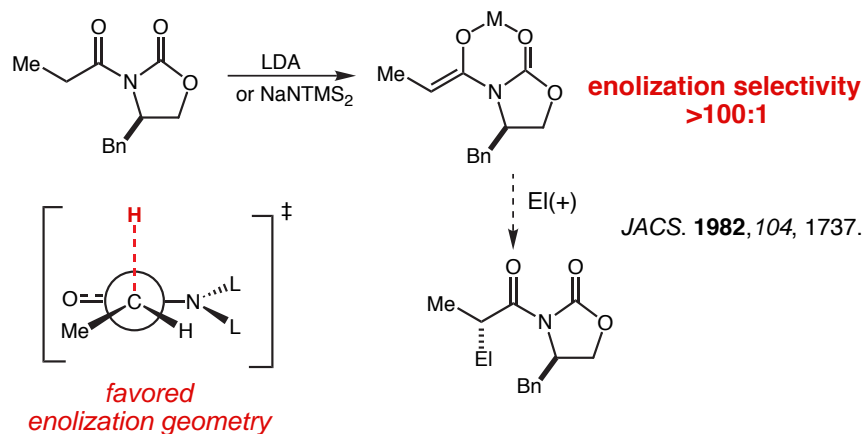
A(1,3) interaction between the C2 & amide substituents will strongly influence the torsion angle between C1 & C2.



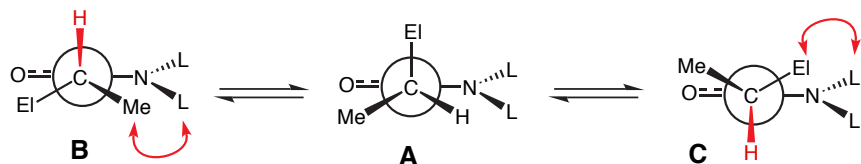
As a result, amides afford (Z) enolates under all conditions



A(1,3) Strain and Chiral Enolate Design

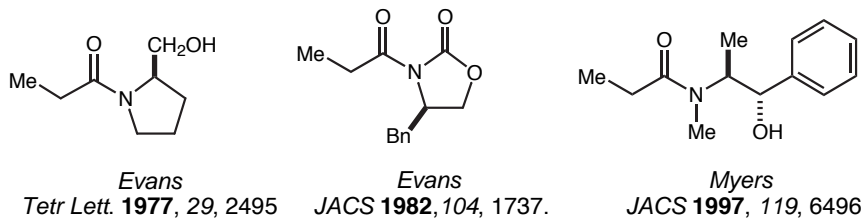


■ In the enolate alkylation process product epimerization is a serious problem. Allylic strain suppresses product enolization through the intervention of allylic strain

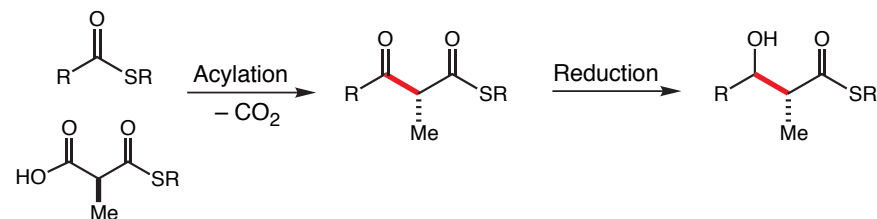


While conformers **B** and **C** meet the stereoelectronic requirement for enolization, they are much higher in energy than conformer **A**. Further, as deprotonation is initiated, A(1,3) destabilization contributes significantly to reducing the kinetic acidity of the system

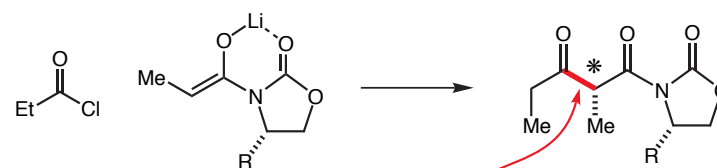
These allylic strain attributes are an integral part of the design criteria of chiral amide and imide-based enolate systems



Polypropionate Biosynthesis: The Acylation Event



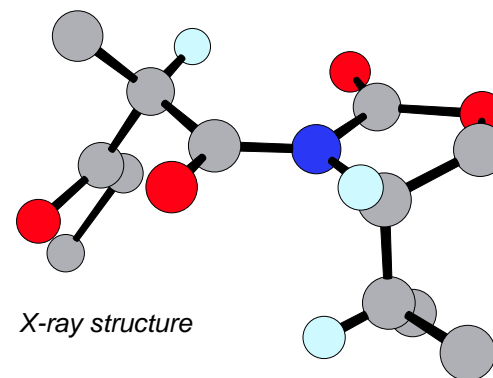
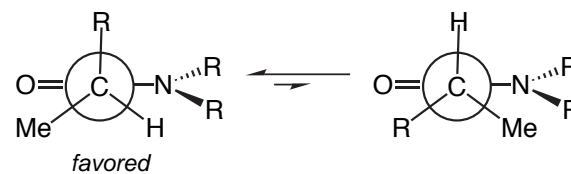
First laboratory analogue of the acylation event

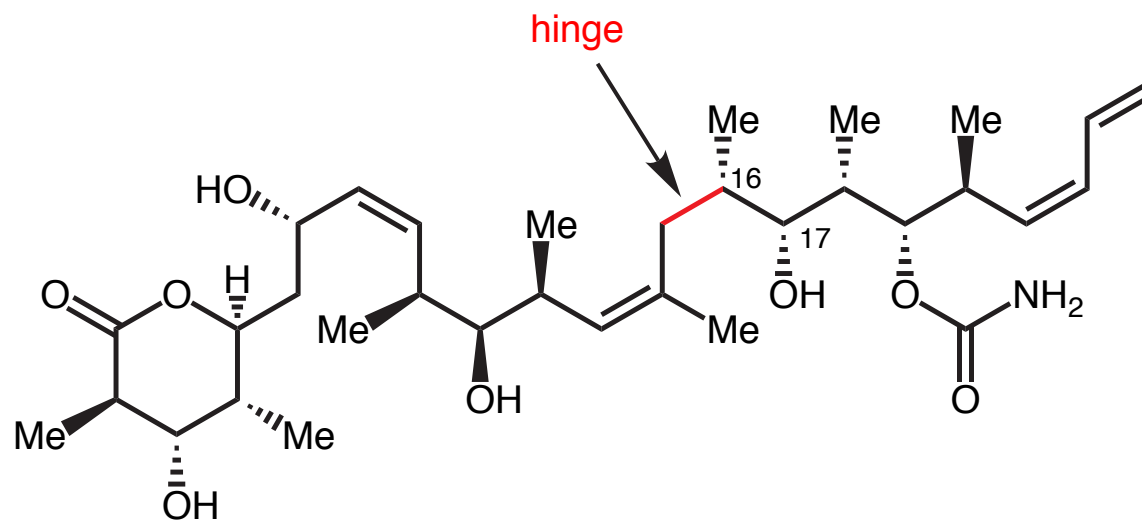


with M. Ennis *JACS* 1984, 106, 1154.

Diastereoselection ~ 97 : 3

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



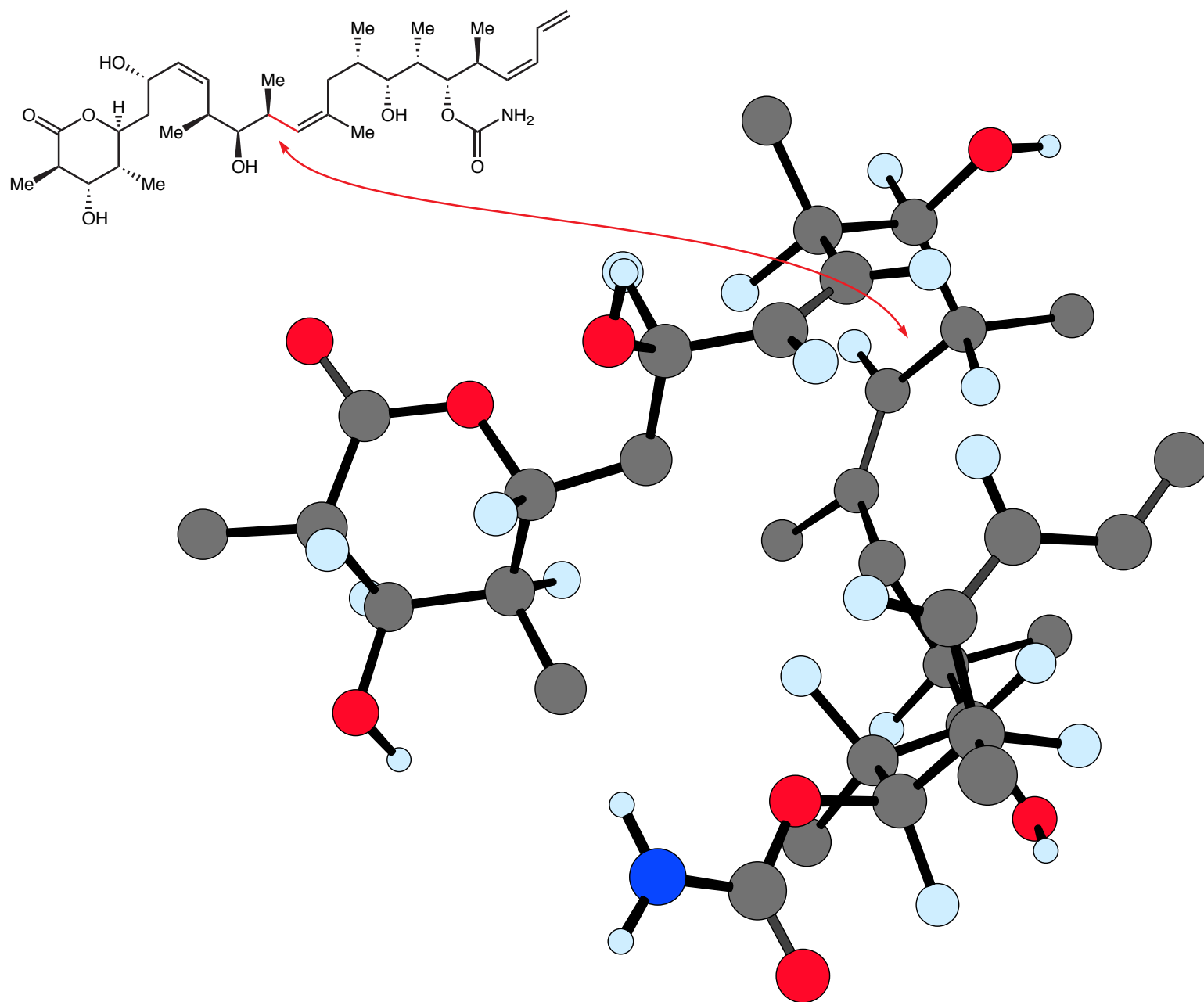


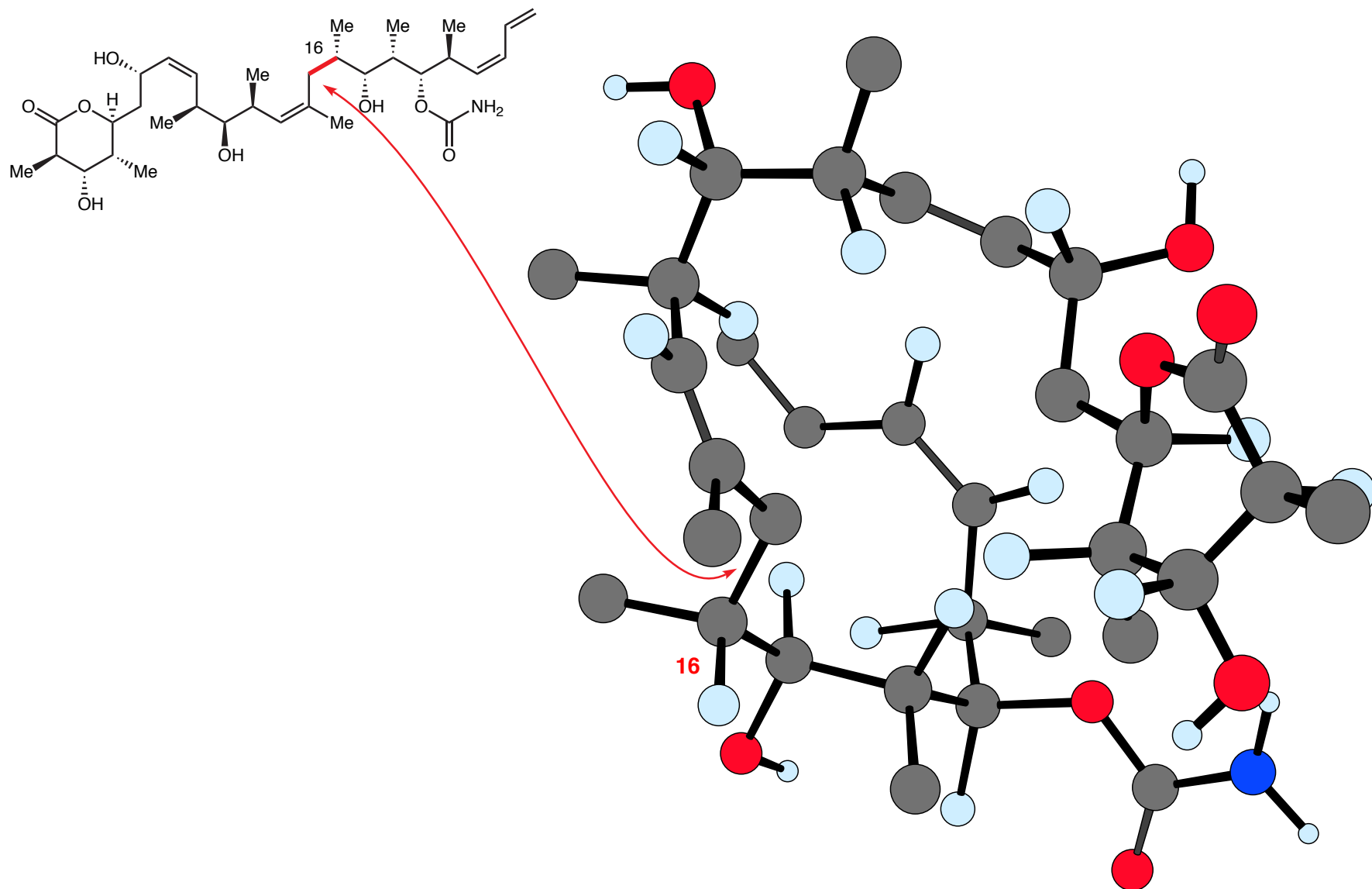
- immunosuppressive activity
- potent microtubule-stabilizing agent
(antitumor activity similar to that of taxol)

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

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

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





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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 6

Conformational Analysis-3

■ Conformational Analysis of $C_4 \rightarrow C_6$ Rings

■ Reading Assignment for week

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

Eliel & Wilen, "Stereochemistry of Organic Compounds," Chapter 11, Configuration and Conformation of Cyclic Molecules, Wiley, 1994

Ribeiro & Rittner, "The Role of Hyperconjugation in the Conformational Analysis of Methylcyclohexane and Methylheterocyclohexanes" *J. Org. Chem.*, **2003**, 68, 6780-6787 (**handout**)

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

D. A. Evans

Friday,
September 26, 2003

6-00-Cover Page 9/26/03 8:44 AM

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	

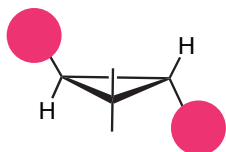
Eliel, E. L., Wilen, S. H. *Stereochemistry of Organic Compounds* Chapter 11, John Wiley & Sons, 1994.

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

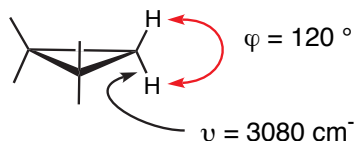
■ Discrepancies between calculated strain/ CH_2 and the "angle strain" results from puckering to minimize van der Waals or eclipsing torsional strain between vicinal hydrogens.

■ 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



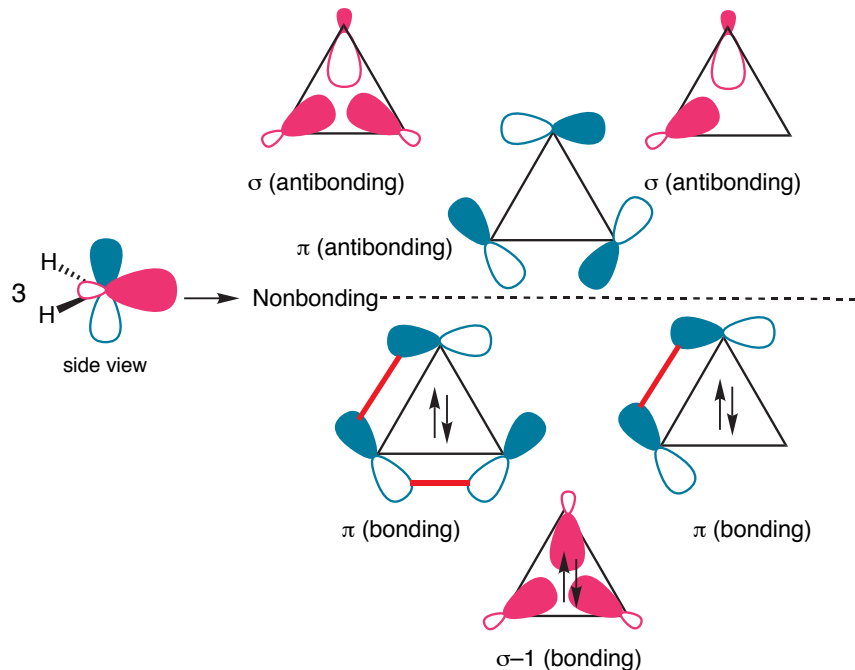
- Necessarily *planar*.
- Substituents are therefore eclipsed.
- Disubstitution prefers to be *trans*.



- Almost sp^2 , not sp^3

Walsh Model for Strained Rings:

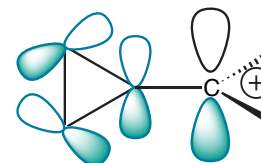
- Rather than σ and σ^* c-c bonds, cyclopropane has sp^2 and p-type orbitals instead.



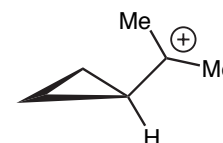
de Meijere, "Bonding Properties of Cyclopropane & their Chemical Characteristics" *Angew Chem. Int. Ed.* **1979**, 18, 809-826 (handout)

de Meijere, A.; Wessjohann, L. "Tailoring the Reactivity of Small Ring Building Blocks for Organic Synthesis." *Synlett* **1990**, 20.

Carbocation Stabilization via Cyclopropylgroups

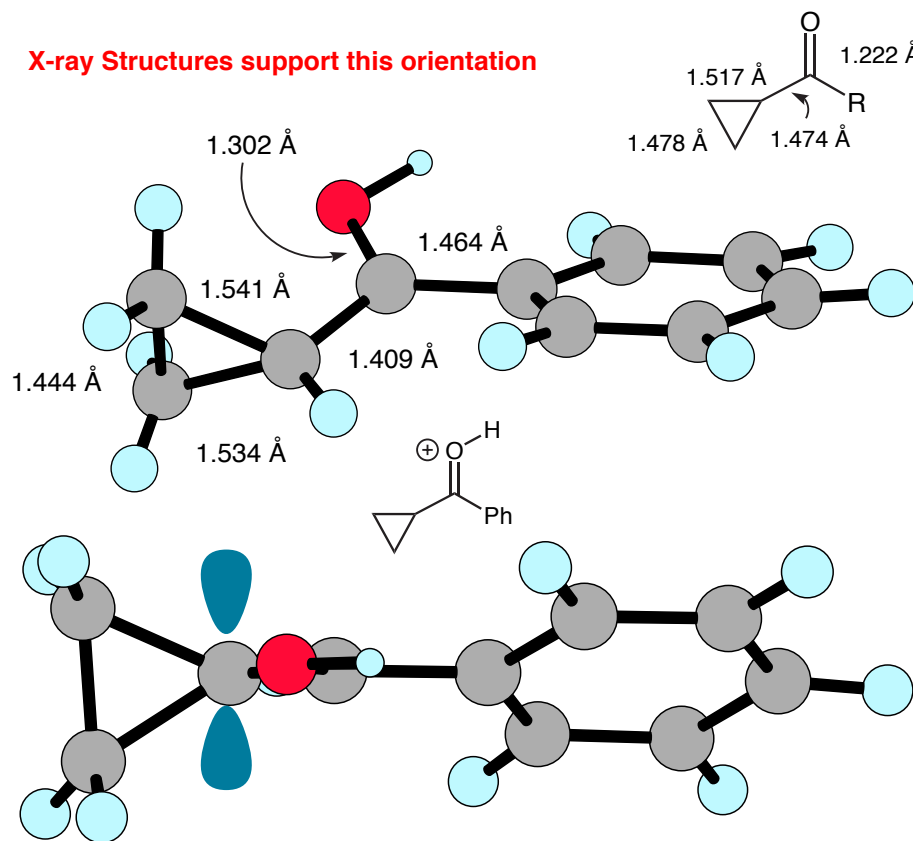


A rotational barrier of about 13.7 kcal/mol is observed in following example:



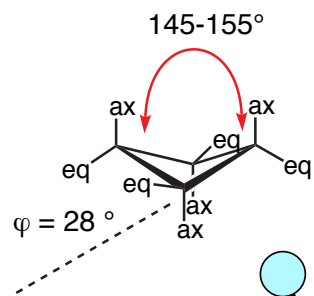
NMR in super acids
 $\delta(\text{CH}_3) = 2.6$ and 3.2 ppm

X-ray Structures support this orientation

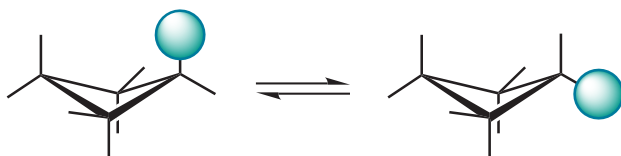
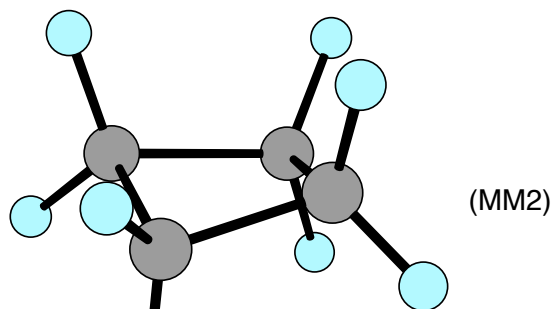


R. F. Childs, *JACS* **1986**, 108, 1692

Cyclobutane



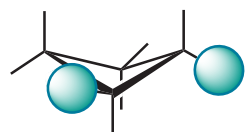
- Eclipsing torsional strain overrides increased bond angle strain by puckering.
- Ring barrier to inversion is 1.45 kcal/mol.



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

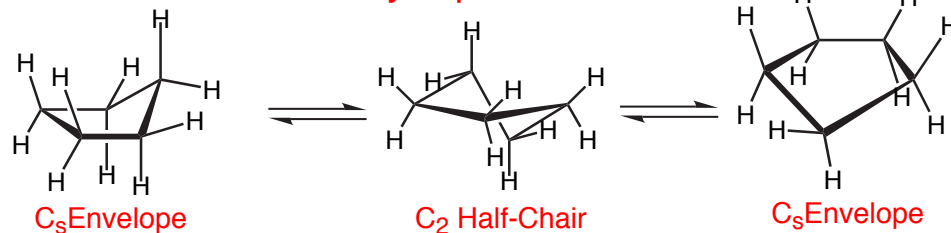


- 1,3 Disubstitution prefers *cis* diequatorial to *trans* by 0.58 kcal/mol for di-bromo compd.



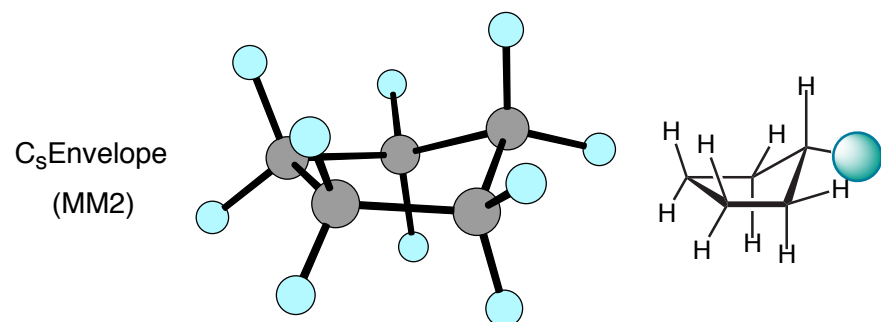
- 1,2 Disubstitution prefers *trans* diequatorial to *cis* by 1.3 kcal/mol for diacid (roughly equivalent to the cyclohexyl analogue.)

Cyclopentane



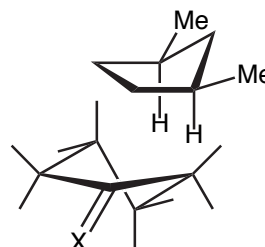
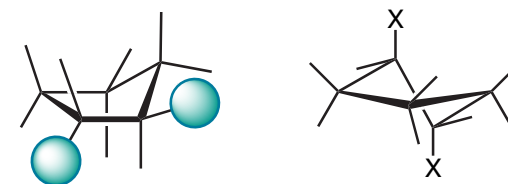
- Two lowest energy conformations (10 envelope and 10 half chair conformations C_5 favored by only 0.5 kcal/mol) in rapid conformational flux (pseudorotation) which causes the molecule to appear to have a single out-of-plane atom "bulge" which rotates about the ring.

- 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).

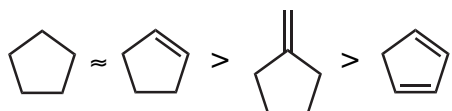


- 1,3 Disubstitution: **Cis**-1,3-dimethyl cyclopentane 0.5 kcal/mol **more stable** than *trans*.

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

Methylenecyclopentane and Cyclopentene

Strain trends:

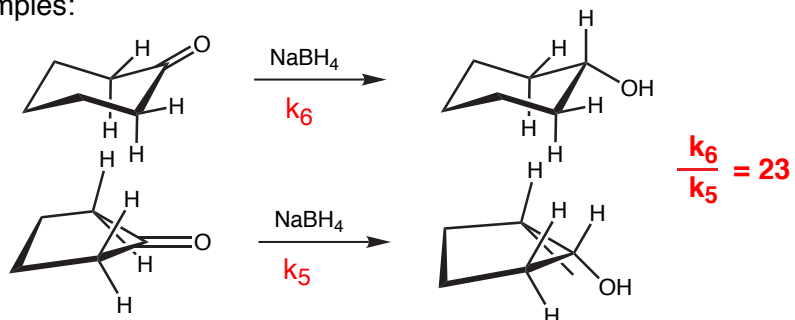


■ Decrease in eclipsing strain more than compensates for the increase in angle strain.

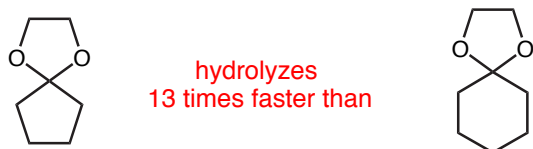
Relative to cyclohexane derivatives, those of cyclopentane prefer an sp^2 center in the ring to minimize eclipsing interactions.

"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.

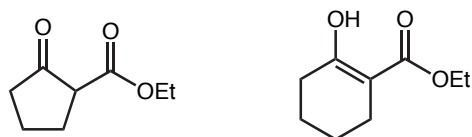
Examples:



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



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

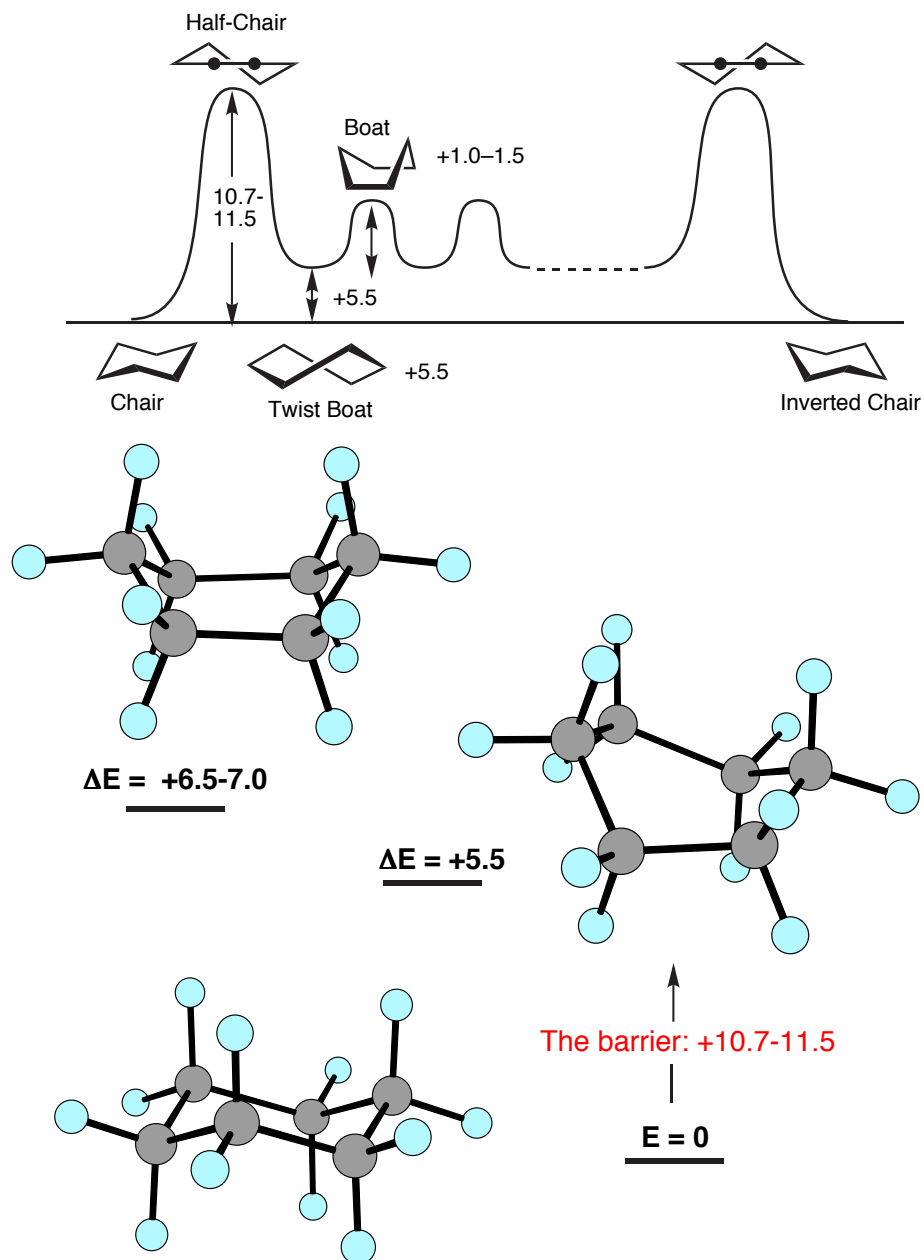


95.5:4.5 keto:enol

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: $\approx 2(0.88)$ kcal/mol $\approx \sim 1.8$ kcal/mol;
Observed: 1.74 kcal/mol



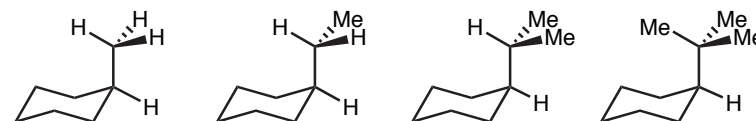
- The A-Value, or $-\Delta G^\circ$, is the preference of the substituent for the equatorial position.

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

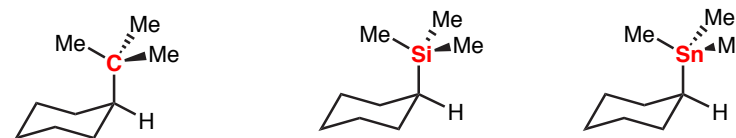
- a. F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.* **3**, 140 (1971).
 b. N. L. Allinger and L. A. Freiberg, *J. Org. Chem.* **31**, 804 (1966).
 c. J. A. Hirsch, *Top Stereochem.* **1**, 199 (1967).
 d. E. L. Eliel and M. Manoharan, *J. Org. Chem.* **46**, 1959 (1981).
 e. H. J. Schneider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

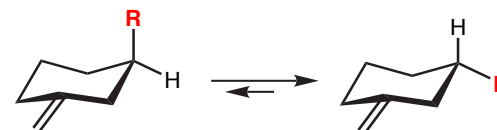


A-Value 4.5-5.0 2.5 1.1

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.

Rigberio & Rittner, "The Role of Hyperconjugation in the Conformational Analysis of Methylcyclohexane and Methylheterocyclohexanes"
JOC **2003**, 68, 6780

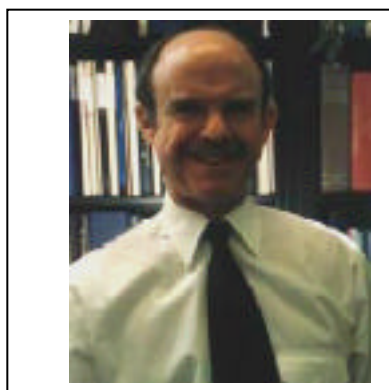
Commentary by Ken Houk University of California, Los Angeles

Department of Chemistry

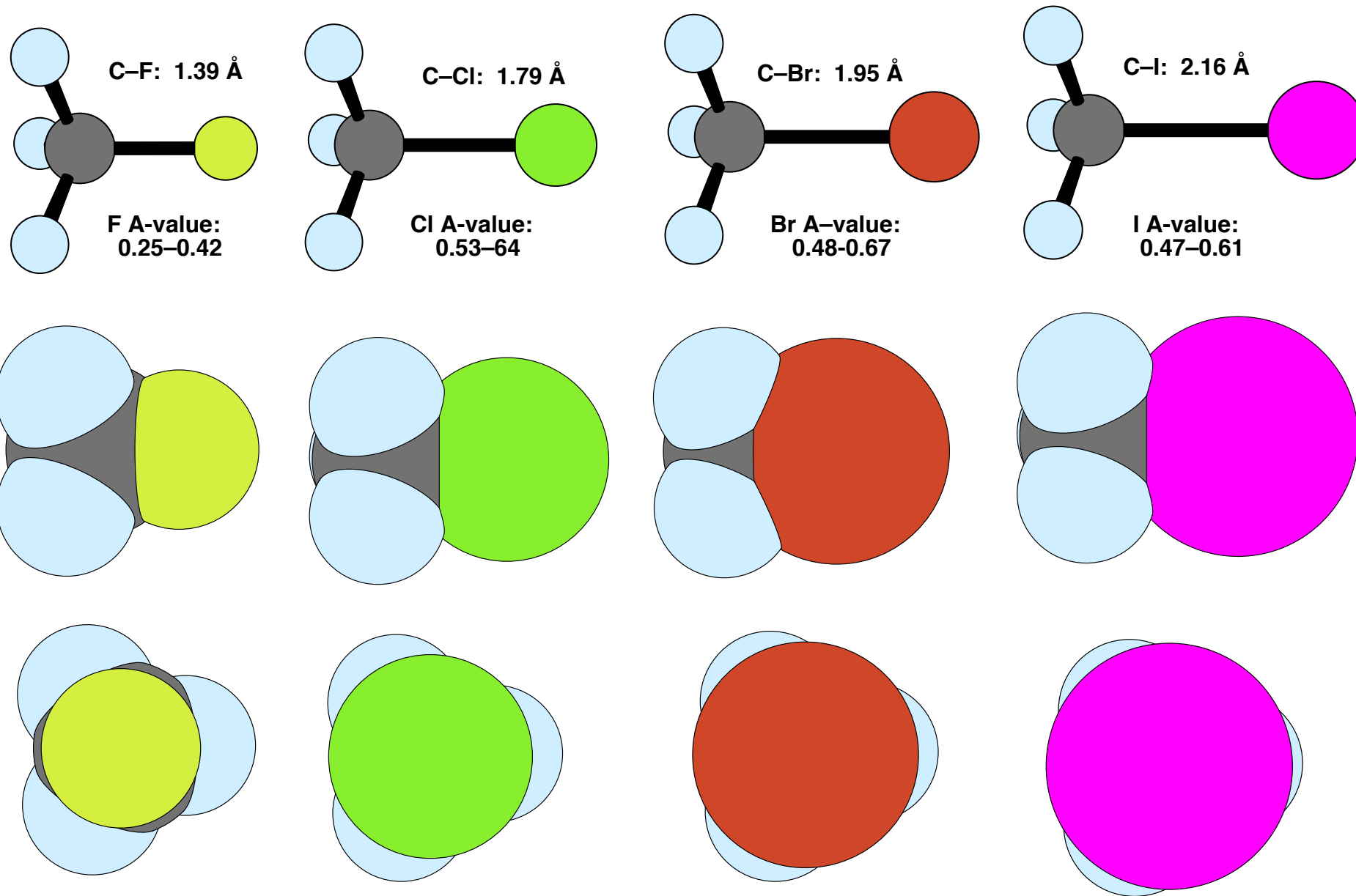
Dear David,

"The calculations in the Ribeiro article look fine, but I am not convinced by the interpretation. It does seem to work pretty well for many systems, but not obviously for the isomeric 1,3-dioxane cases they note early on. There seems no explanation of why C–H hyperconjugates better than C–C. Further, the results with alkyls larger than methyl still require traditional steric arguments. I would say that the equatorial methyl preference has been attributed in part to hyperconjugative effects that occur when the CH bonds are anti-periplanar. But I would not yet go much beyond that!

Best regards,



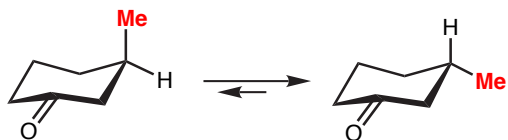
(b. 1943) **A.B. 1964, Ph.D. 1968, Harvard University**; Assistant-Full Professor, Louisiana State University, 1968-1980; Alfred P. Sloan Fellow, 1975-1977; Camille and Henry Dreyfus Teacher-Scholar, 1972-1977; LSU Distinguished Research Master, 1978; Professor, University of Pittsburgh, 1980-1985; Alexander von Humboldt Senior U.S. Scientist Award, 1982; Akron Section, American Chemical Society Award, 1983; Arthur C. Cope Scholar Award, 1988; Director, Chemistry Division, National Science Foundation, 1988-1990; James Flack Norris Award in Physical Organic Chemistry, 1991; Schrödinger Medal, World Association of Theoretically Oriented Chemists, 1998; Tolman Medal, Southern California Section, American Chemical Society, 1999; Fellow of the American Academy of Arts and Sciences, 2002; American Chemical Society Award for Computers in Chemical and Pharmaceutical Research, 2003; International Academy of Quantum Molecular Science, 2003.



Chem 3D Pro (Version 5.0)

The impact of trigonal Carbon

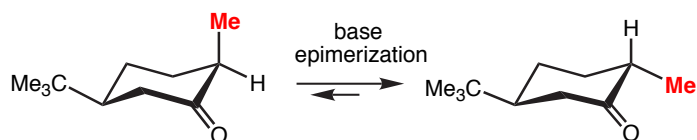
- Let's now compare look at the carbonyl analog in the 3-position



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

versus -1.74 for cyclohexane

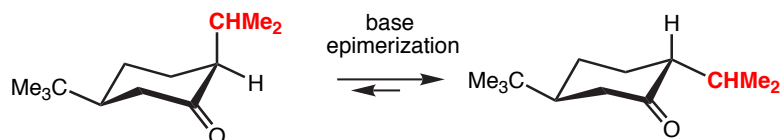
- Let's now compare look at the carbonyl analog in the 2-position



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

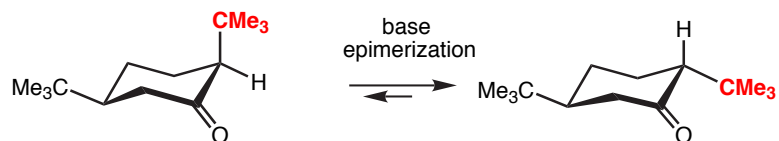
versus -1.74 for cyclohexane

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

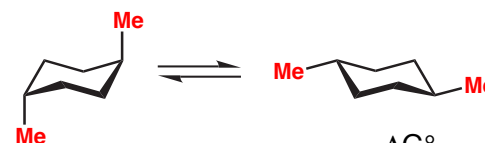
Polysubstituted Cyclohexane A Values

- 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.

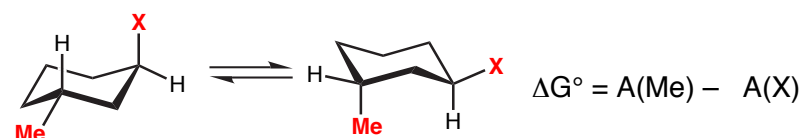


$$\Delta G^\circ = 0 \text{ kcal/mol}$$

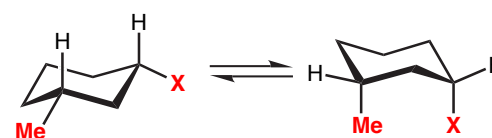


$$\Delta G^\circ = -2(1.74) = -3.48 \text{ kcal/mol}$$

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

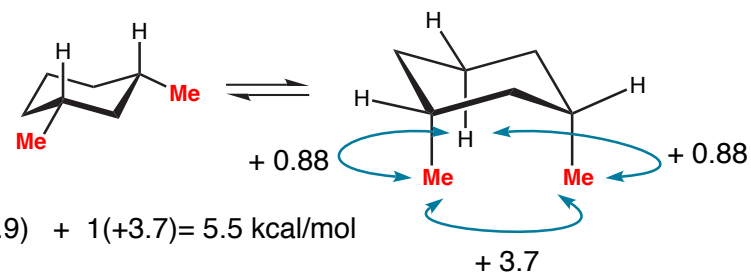


$$\Delta G^\circ = A(\text{Me}) - A(\text{X})$$



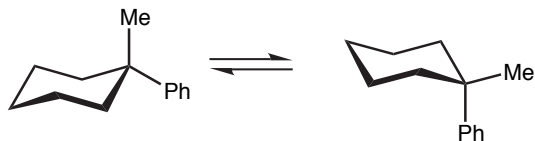
The new interaction!

For X = Me



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

Let's now consider geminal substitution

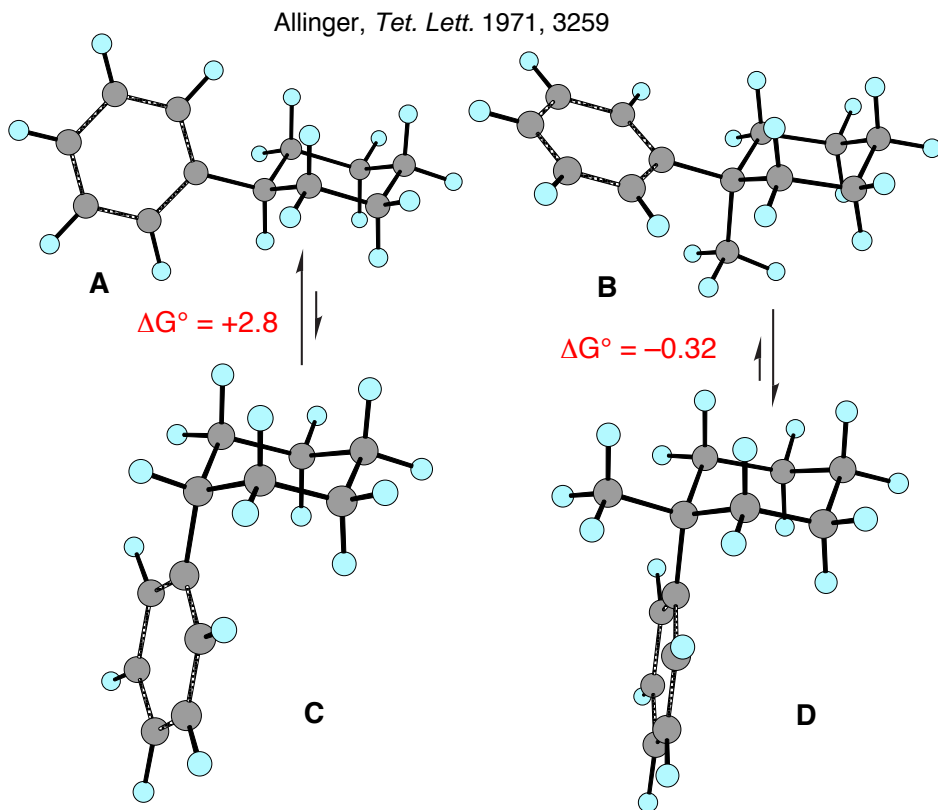


The prediction: $\Delta G^\circ = A(\text{Ph}) - A(\text{Me})$

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

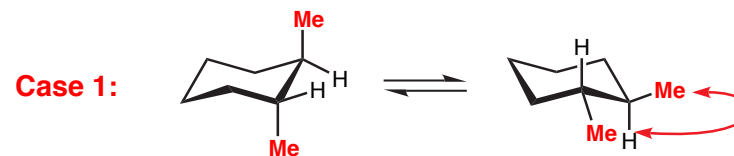
Observed: $\Delta G^\circ = -0.32 \text{ kcal/mol}$

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

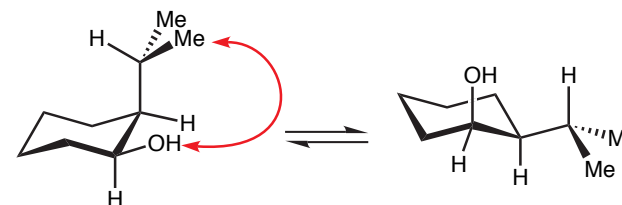


The prediction: $\Delta G^\circ = 1 \text{ gauche butane} - 2A(\text{Me})$

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

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

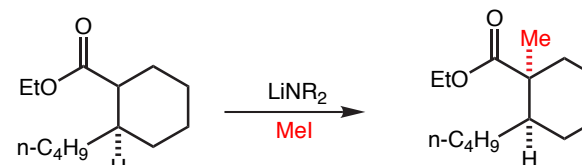
If the added gauche butane destabilization in the di-equatorial conformer had not been added, the estimate would have been off.

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?

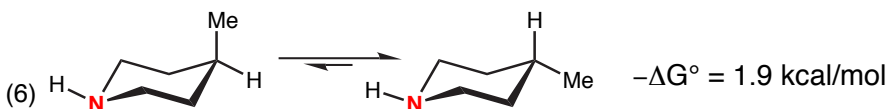
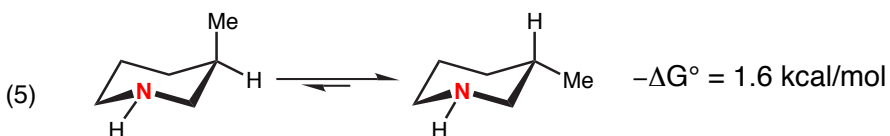
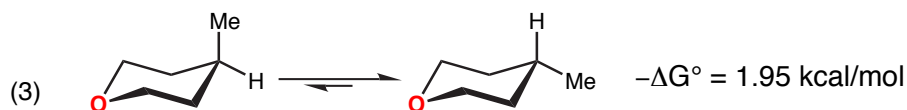
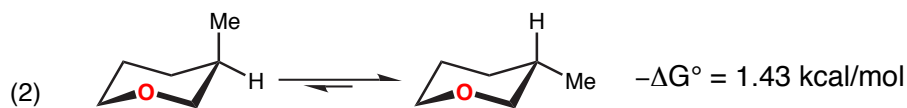
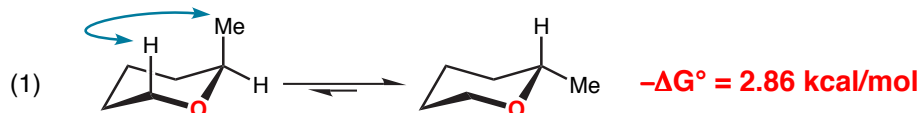
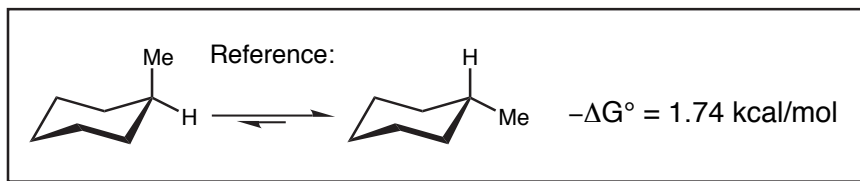


diastereoselection 89:11

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

Heteroatom-Substituted 6-Membered Rings

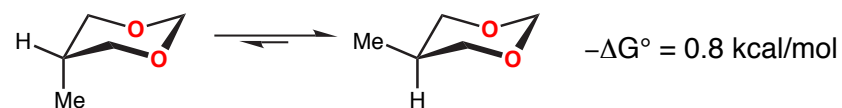
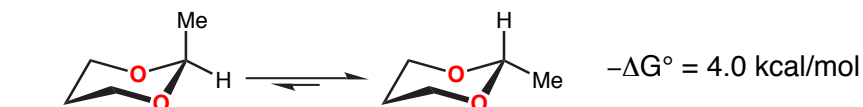
■ A-values at the 2-position in both the O & N heterocycles are larger than expected. This is due to the shorter C–O (1.43 Å), and C–N (1.47 Å) bond lengths relative to carbon (C–C; 1.53 Å). The combination of bond length and bond angle change increases the indicated 1,3-diaxial interaction (see eq 1,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



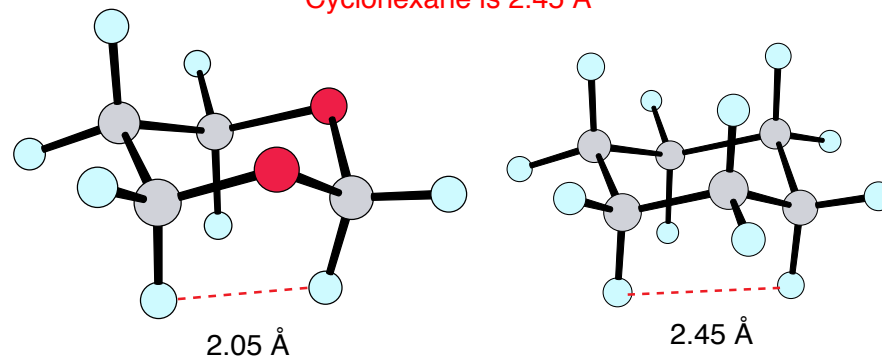
A-Values for N-Substituents in Piperidine



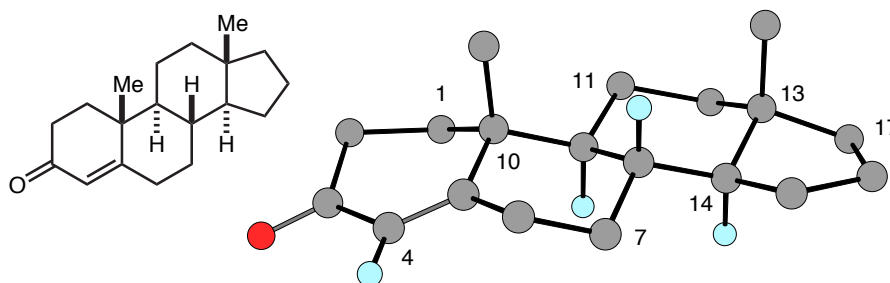
- Hydrogen is "bigger" than the N–lone pair.
- The A-value of N–substituents is slightly larger than the corresponding cyclohexane value. Rationalize



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

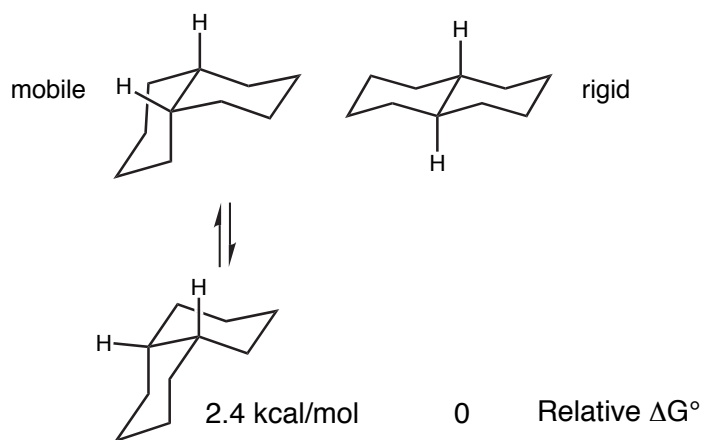


Conformations of Bicyclic Ring Systems

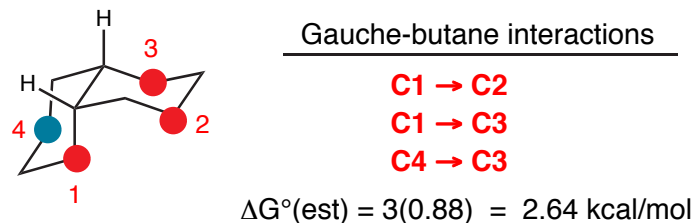


The steroid nucleus provided the stimulation for the development of conformational analysis, particularly of polycyclic ring systems. D. H. R. Barton was awarded a Nobel prize in 1969 for his contributions in this area.

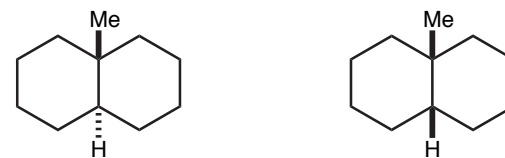
Decalin Ring System (6/6)



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

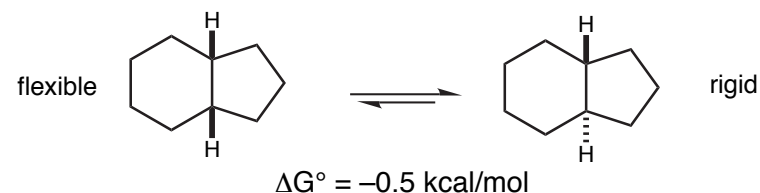


Estimate the energy difference between the two methyl-decalins shown below.



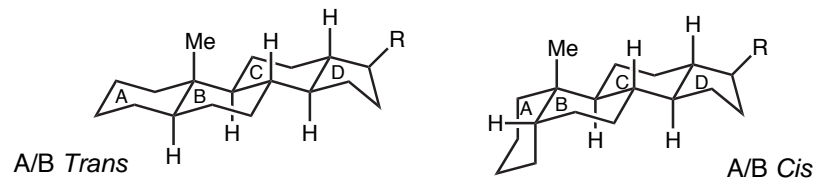
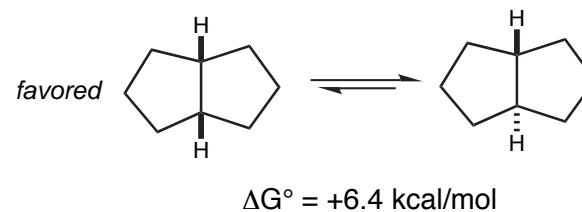
see Elier, p 780

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

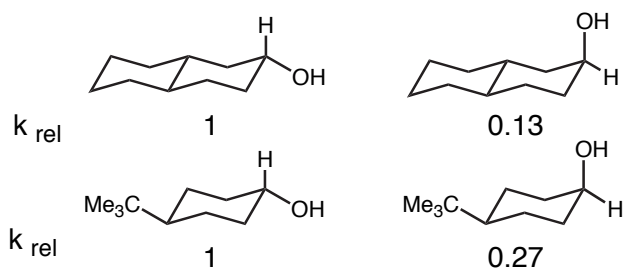


Rationalize the conformational flexibility of a *A/B Trans* vs. *A/B Cis* Steroid!

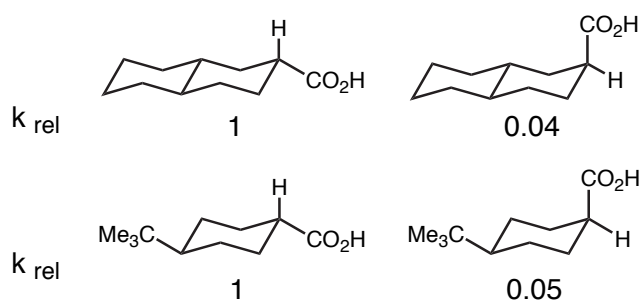
Different reactivity for axial and equatorial substituents

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

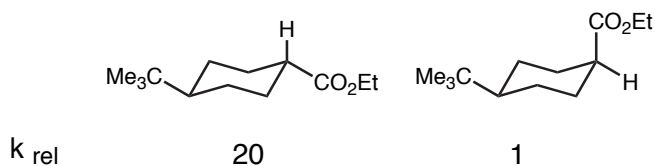
Acetylation with $\text{Ac}_2\text{O}/\text{Py}$



Acid-catalyzed esterification

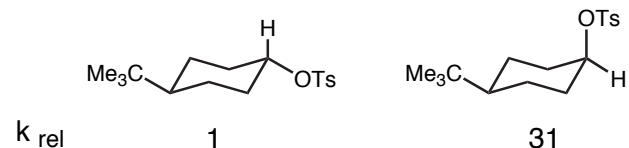


Ester Saponification



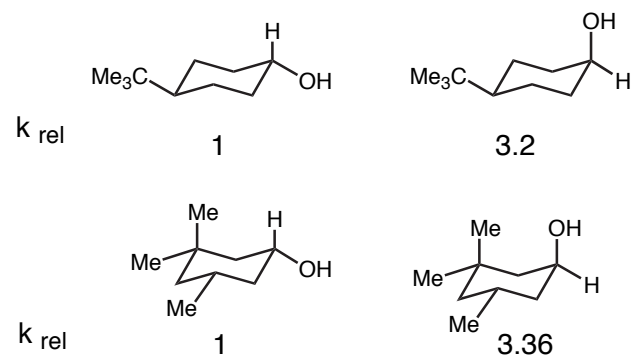
For a more detailed discussion of this topic see:
 Eliel, E. L., S. H. Wilen, et al. (1994). *Stereochemistry of Organic Compounds* pp 720-726

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



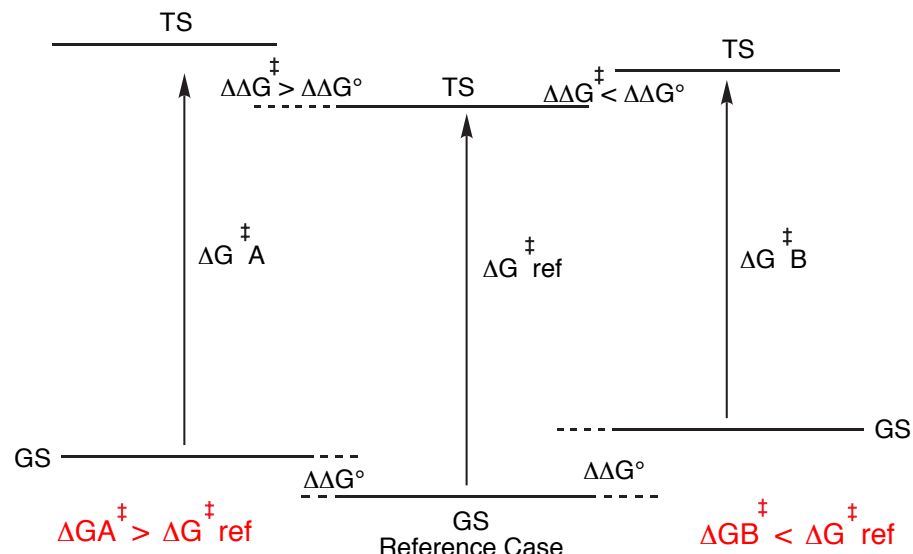
The axial diastereomer is not always slower reacting:

Alcohol Oxidation with $\text{Cr}(6+)$



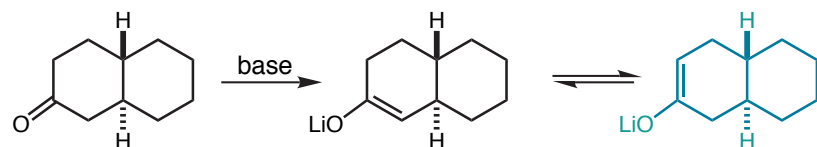
The rate-determining step is breakdown of the chromate ester. This is an apparent case of strain acceleration

Steric Hindrance and Steric Assistance

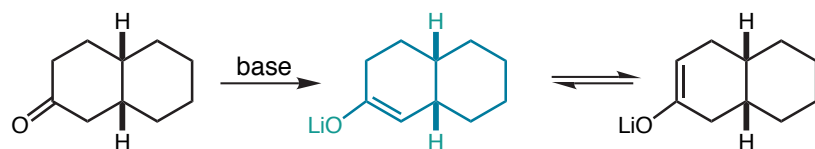


Observation:

Relative enolate stability correlates to ring junction stereochemistry



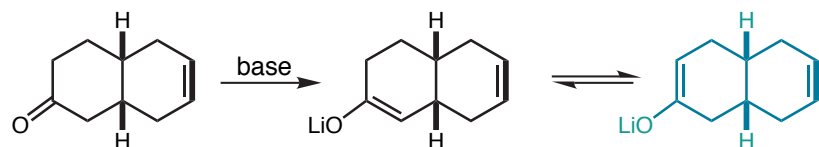
ratio: 13 : 87



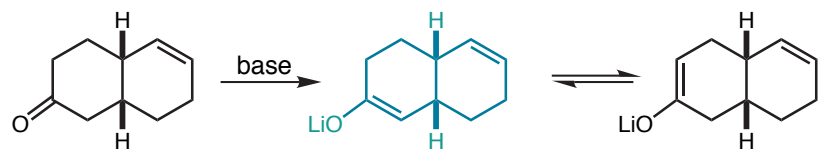
ratio: 70 : 30

House, *JOC* **1965**, 30, 1341**Observation:**

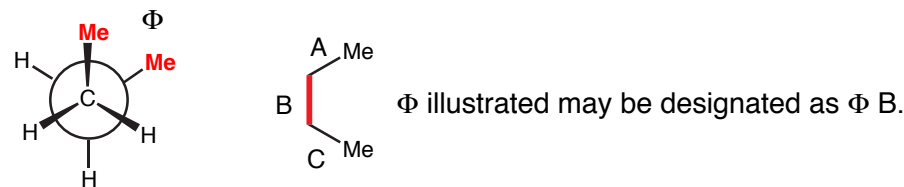
Relative enolate stability seems to be correlated to position of C=C



ratio: 10 : 90



ratio: 92 : 8

How do we explain the experimental observations shown above?Readings: Velluz et al, *Angew. Chemie, Int Ed.* **1965**, 4, 181-270Let Φ be defined as the torsion or dihedral angle for butane Φ illustrated may be designated as Φ_B .

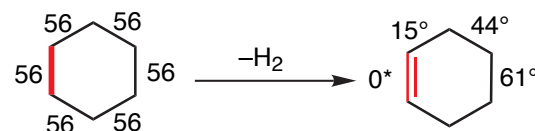
Let's now consider cyclohexane

	Perfect chair	real chair
Φ	60°	56°
CCC \angle	$109^\circ 28'$	111°

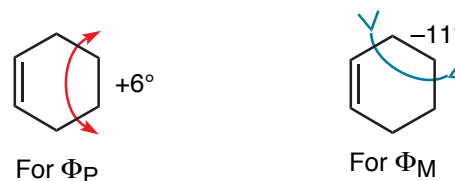
Given cyclohexane with an identified torsion angle Φ_R , if Φ_R either increases or decreases what effects in angle change are transmitted to Φ_O , Φ_M , and Φ_P ?

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

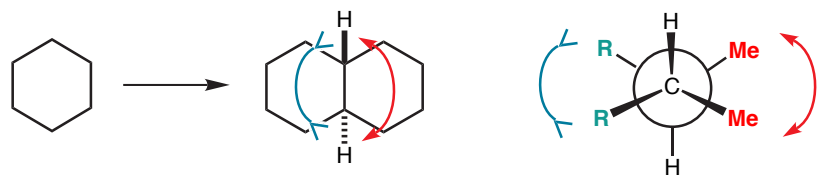
$[\Delta] = \Phi_R(0^\circ) - \Phi_R(56^\circ)$

Operation:

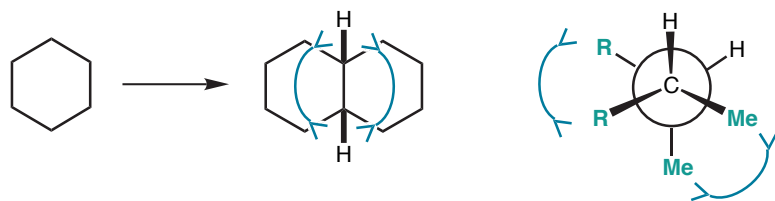
Hence, relative to cyclohexane, the following notation for torsion angle change may be denoted:



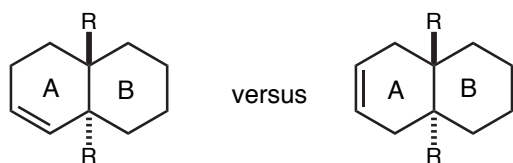
Operation:



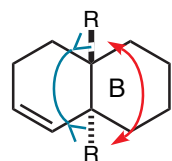
Operation:



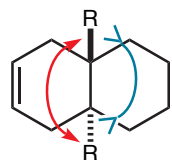
Simple Application: Reinforcing Torsional Effects



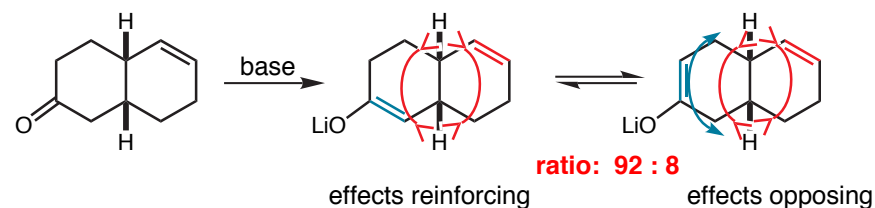
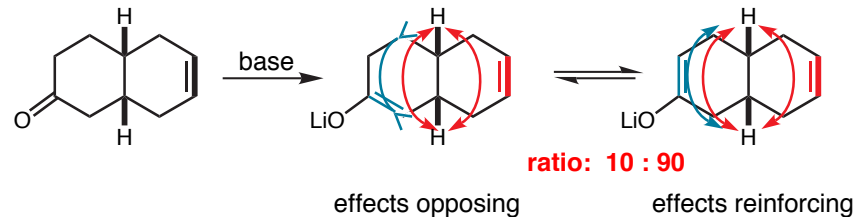
Which C=C bond isomer is more stable?



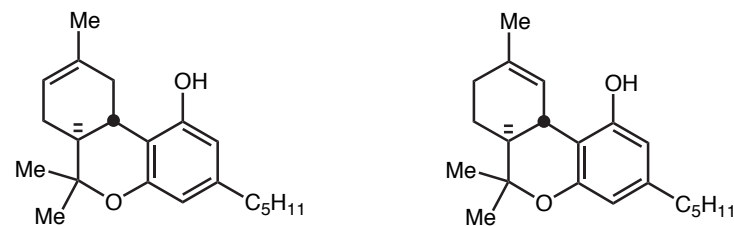
- 1) C=C will open up ring=B torsion angle
- 2) Ring B will resist increase in its ring fusion torsion angle
- 3) Therefore torsion effects are opposed



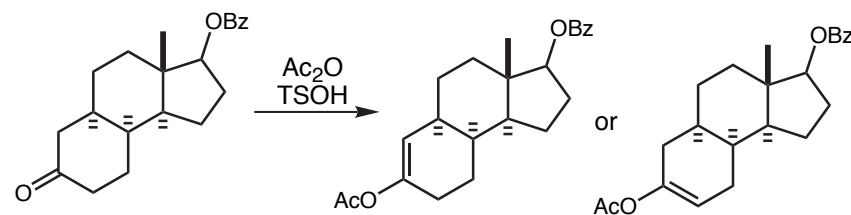
- 1) C=C will close down ring=B torsion angle
- 2) Ring B will accommodate decrease in its ring fusion torsion angle
- 3) Therefore torsion effects are reinforcing

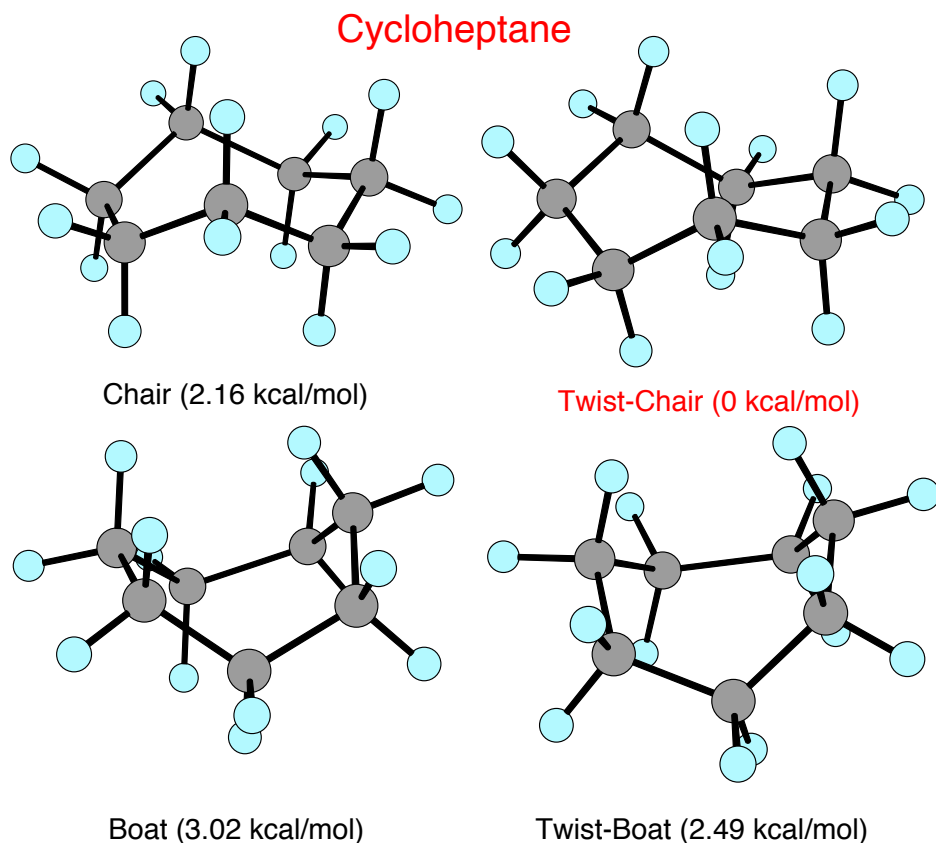


Question: Which is the more stable C=C isomer in the two THC structures?

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

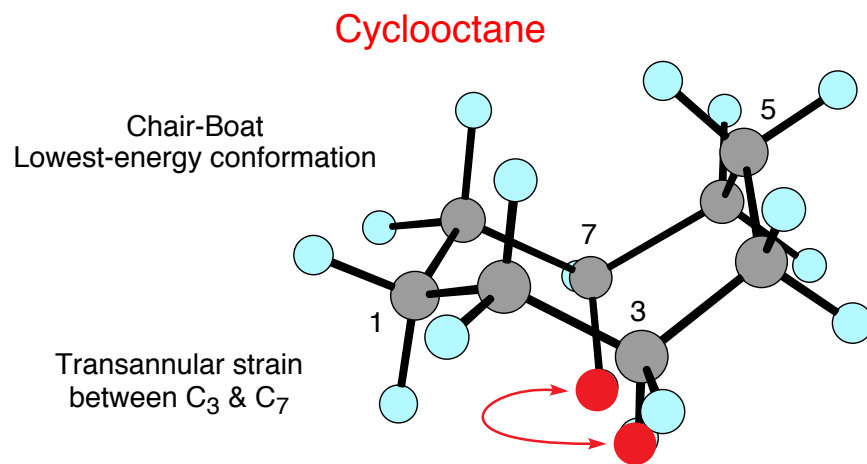
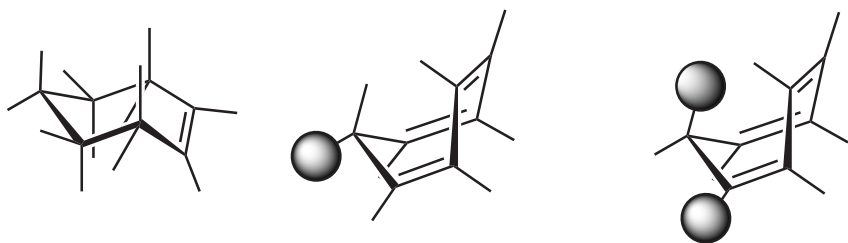
Question: Which enol acetate is more stable?





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

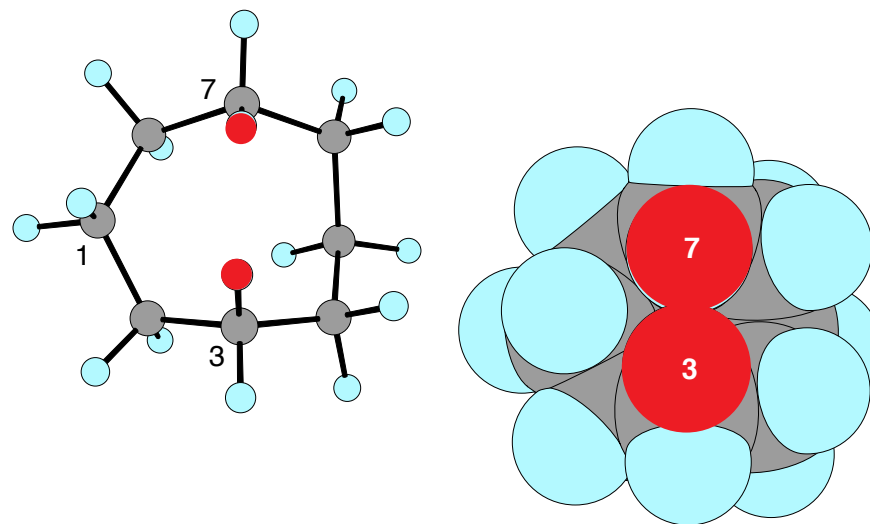
Olefins are preferentially orientated to eliminate eclipsing interactions.



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

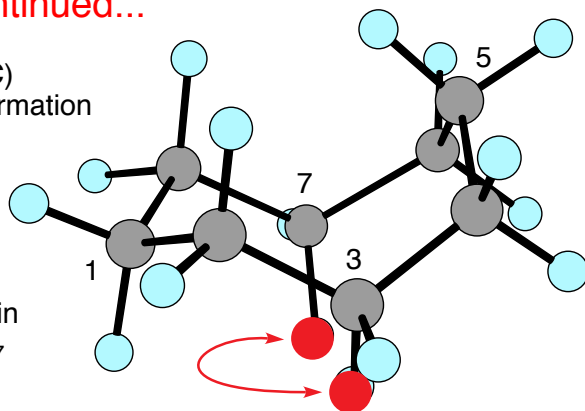
Methyl position	1	2	3	4	5
ΔG (pseudoeqatorial)	1.8	2.8	>4.5	-0.3	6.1
(pseudoaxial) (kcal/mol)					

Underside view of boat-chair C₃ & C₇ eclipsing interactions



Cyclooctane continued...

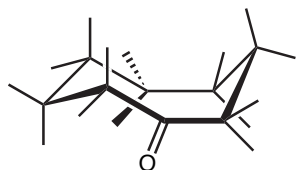
Chair-Boat (**BC**)
Lowest-energy conformation



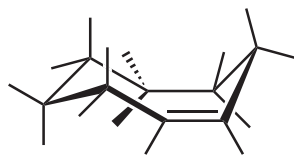
Transannular strain
between C₃ & C₇

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

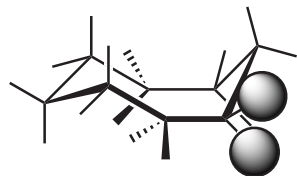
Cyclooctane derivatives



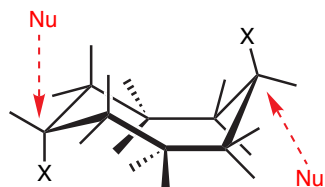
Carbonyl is positioned at C₃ or C₇



Olefin is positioned at C₃-C₄ or C₆-C₇

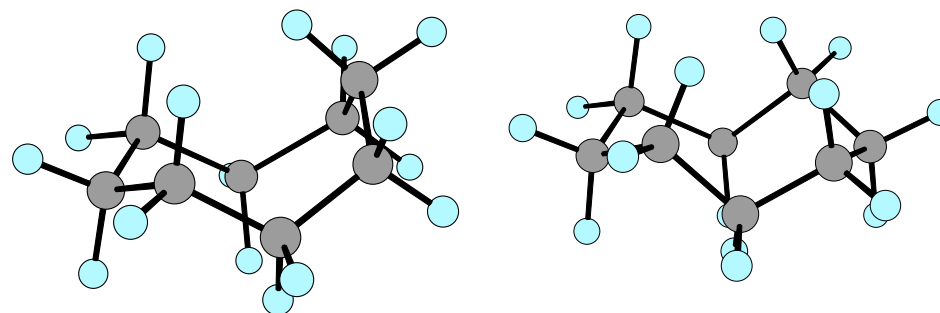


Disubstitution occurs at C₄ or C₆



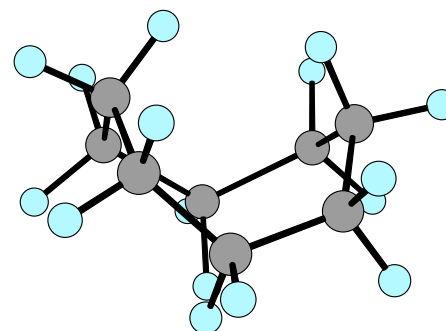
S_N2 occurs at C₁ and C₅

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

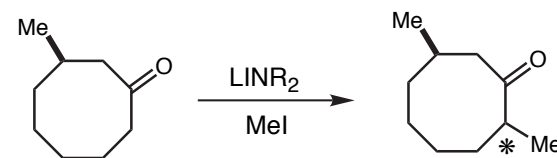


Chair-Boat (**CB**) conformation
reference structure

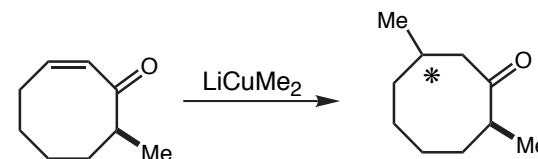
Chair-Chair (**CC**) conformation
(+1-1.6 kcal/mol)



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



Predict
stereochemistry



Predict
stereochemistry

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 7

Conformational Analysis-4

- Ground State Torsional Effects (Conformational Transmission)
- Conformational Analysis of C₆ C₈ Rings continued
- Transition State Torsional Effects
- Curtin-Hammett Principle (**Will not cover in lecture**)

■ Reading Assignment for week

Eliel & Wilen, *Stereochemistry of Carbon Compounds*
Chapter 11

Configuration and Conformation of Cyclic Molecules (handout)

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)

D. A. Evans

Monday,
September 29, 2003

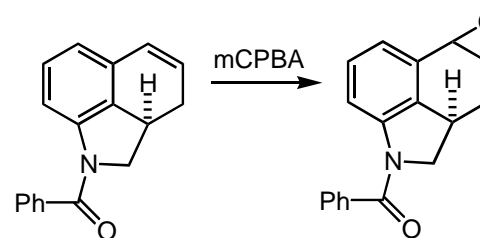
■ Other Reading Material

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

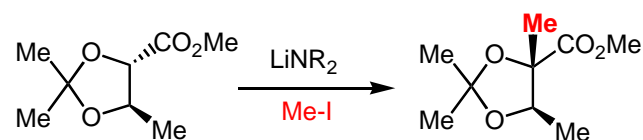
■ Problems of the Day: (To be discussed)

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.

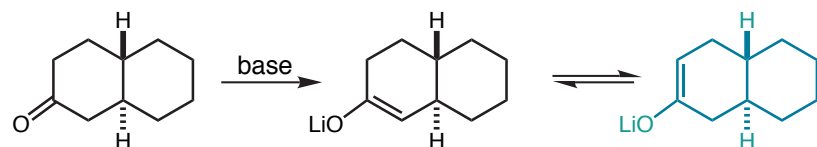


diastereoselection is 8:1.

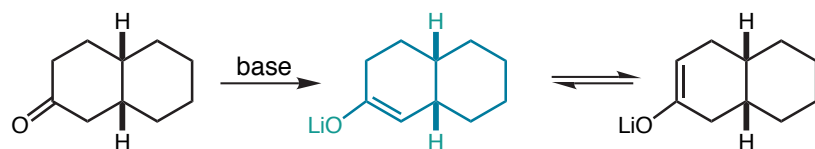
Ladner, et.al. *Angew. Chemie, Int. Ed* **1982**, *21*, 449-450

Observation:

Relative enolate stability correlates to ring junction stereochemistry



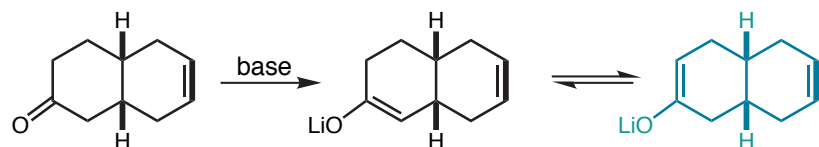
ratio: 13 : 87



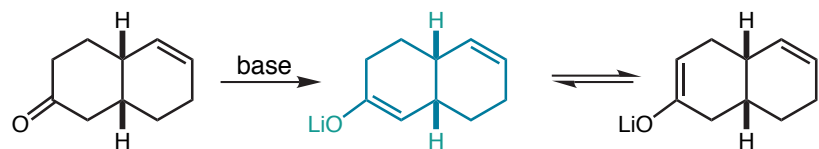
ratio: 70 : 30

House, *JOC* **1965**, 30, 1341**Observation:**

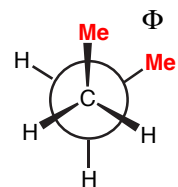
Relative enolate stability seems to be correlated to position of C=C



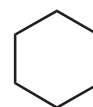
ratio: 10 : 90



ratio: 92 : 8

How do we explain the experimental observations shown above?Readings: Velluz et al, *Angew. Chemie, Int Ed.* **1965**, 4, 181-270Let Φ be defined as the torsion or dihedral angle for butane Φ illustrated may be designated as Φ_B .

Let's now consider cyclohexane

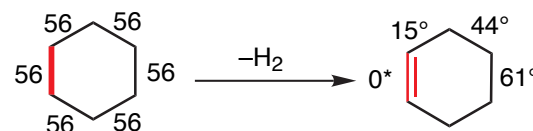


	Perfect chair	real chair
Φ	60°	56°
CCC \angle	$109^\circ 28'$	111°

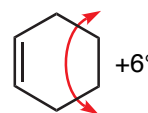
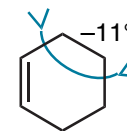
Given cyclohexane with an identified torsion angle Φ_R , if Φ_R either increases or decreases what effects in angle change are transmitted to Φ_O , Φ_M , and Φ_P ?

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

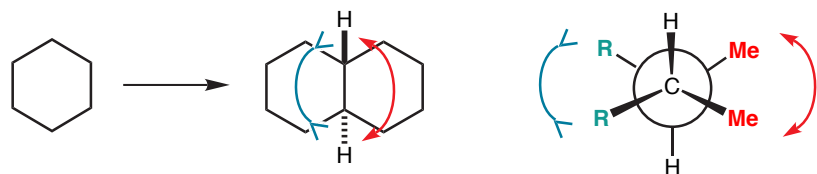
$$[\Delta] = \Phi_R(0^\circ) - \Phi_R(56^\circ)$$

Operation:

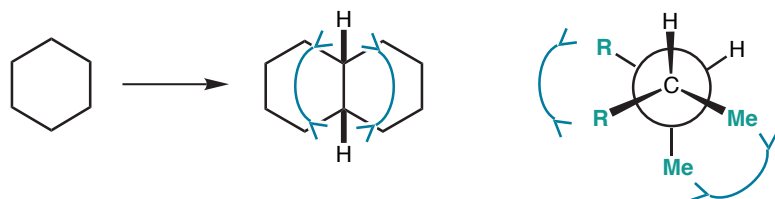
Hence, relative to cyclohexane, the following notation for torsion angle change may be denoted:

For Φ_P For Φ_M

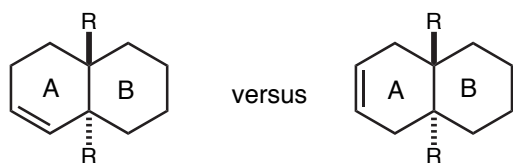
Operation:



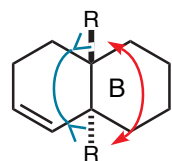
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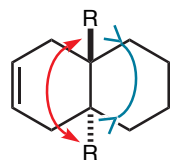
Simple Application: Reinforcing Torsional Effects



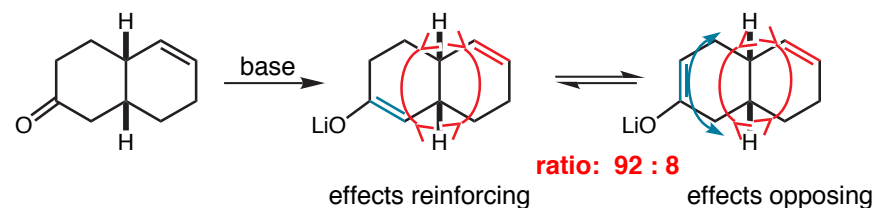
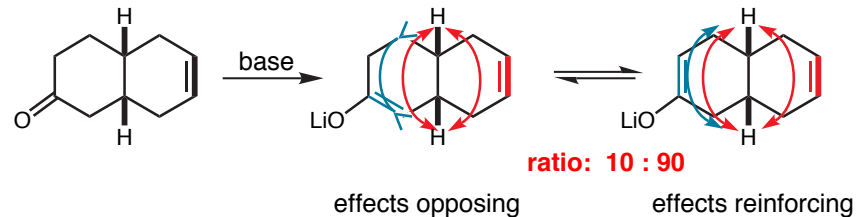
Which C=C bond isomer is more stable?



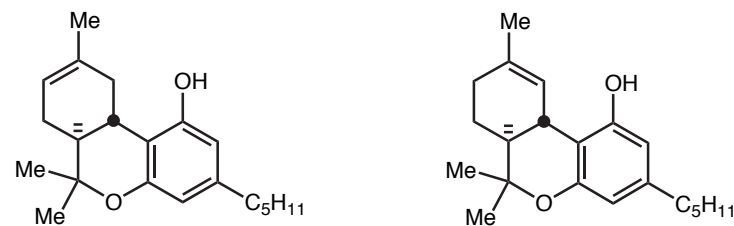
- 1) C=C will open up ring=B torsion angle
- 2) Ring B will resist increase in its ring fusion torsion angle
- 3) Therefore torsion effects are opposed



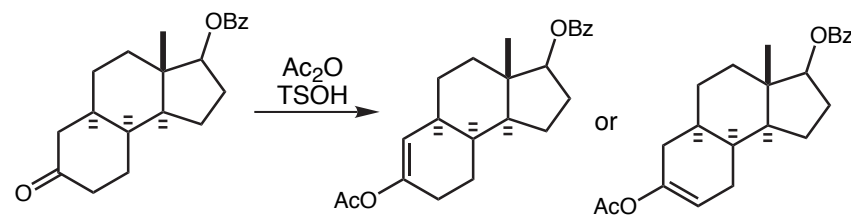
- 1) C=C will close down ring=B torsion angle
- 2) Ring B will accommodate decrease in its ring fusion torsion angle
- 3) Therefore torsion effects are reinforcing

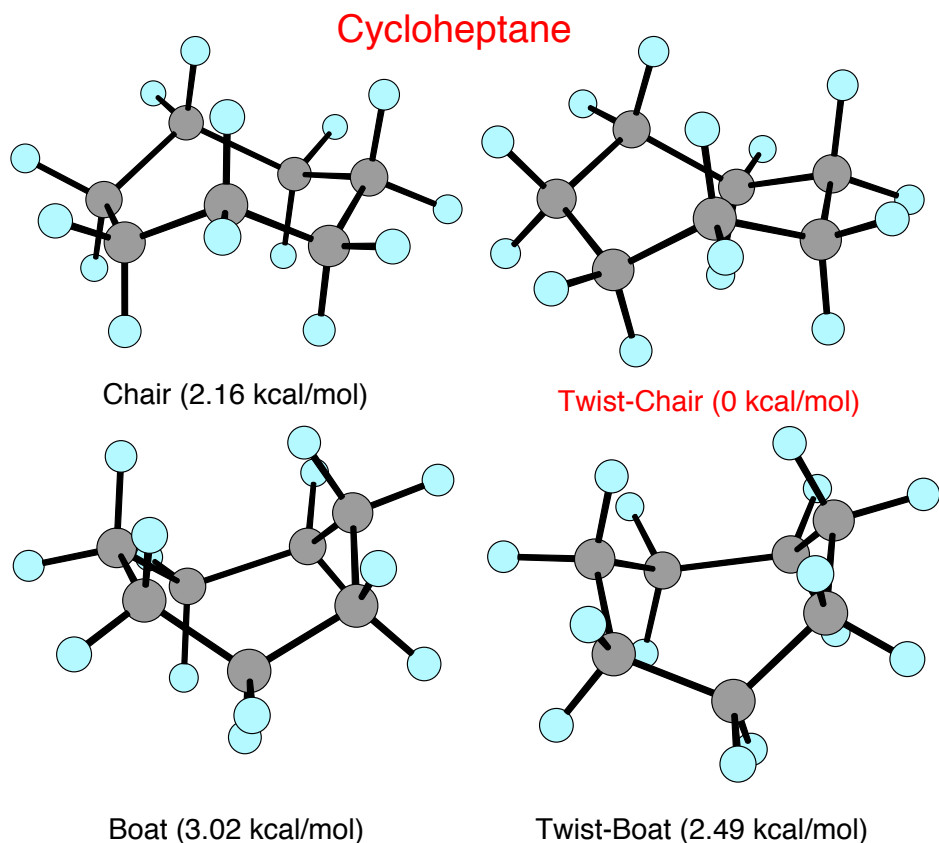


Question: Which is the more stable C=C isomer in the two THC structures?

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

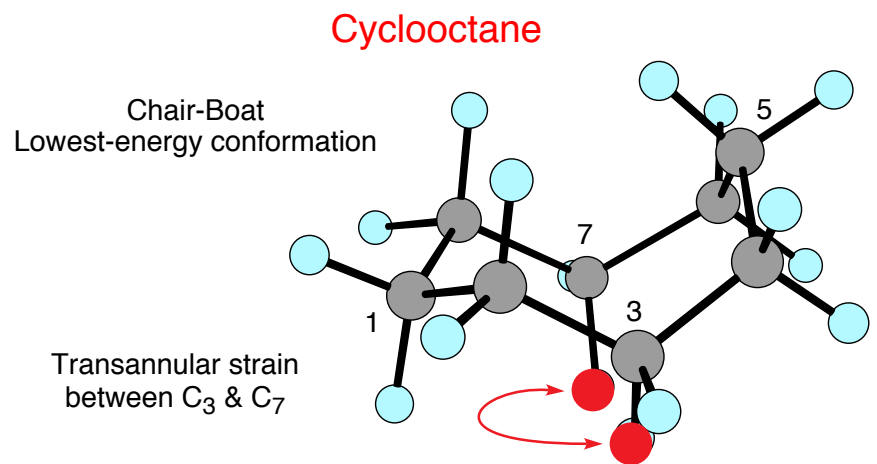
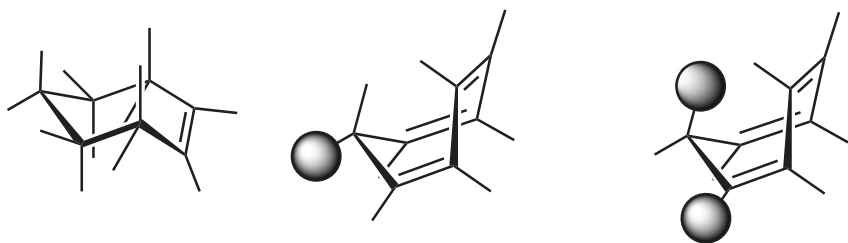
Question: Which enol acetate is more stable?





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

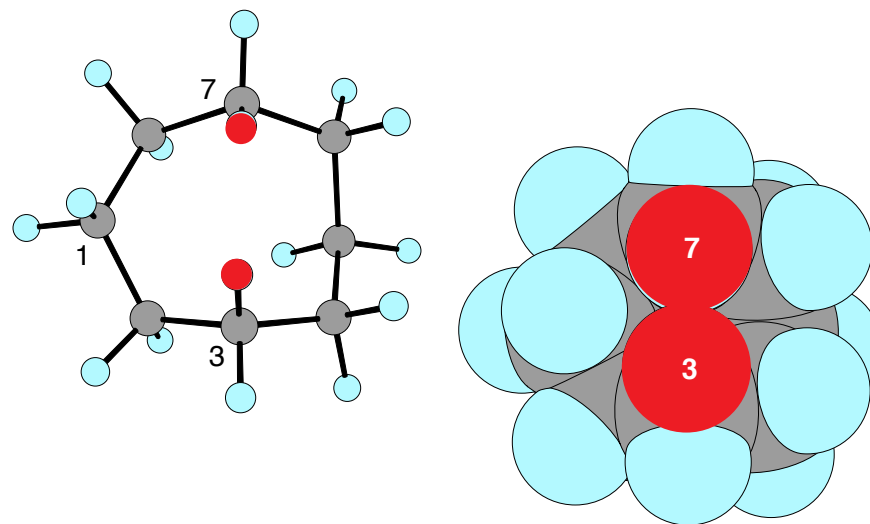
Olefins are preferentially orientated to eliminate eclipsing interactions.



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

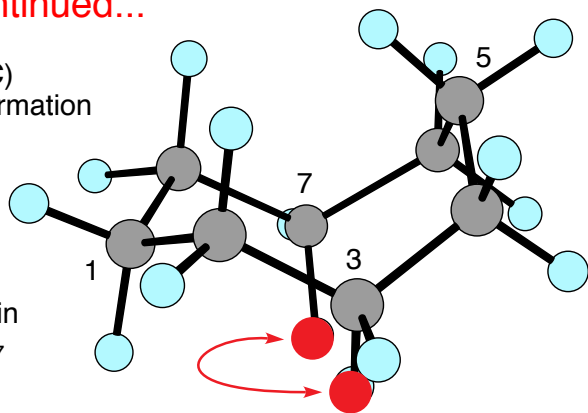
Methyl position	1	2	3	4	5
ΔG (pseudoeqatorial) (pseudoaxial) (kcal/mol)	1.8	2.8	>4.5	-0.3	6.1

Underside view of boat-chair C₃ & C₇ eclipsing interactions



Cyclooctane continued...

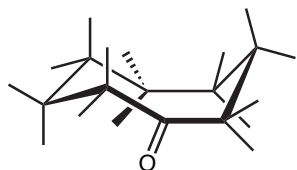
Chair-Boat (**BC**)
Lowest-energy conformation



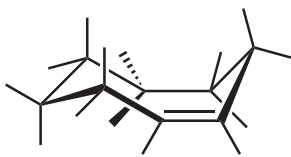
Transannular strain
between C₃ & C₇

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

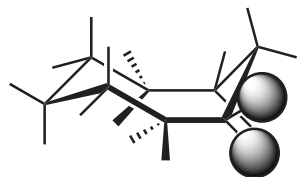
Cyclooctane derivatives



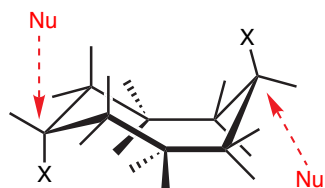
Carbonyl is positioned at C₃ or C₇



Olefin is positioned at C₃-C₄ or C₆-C₇

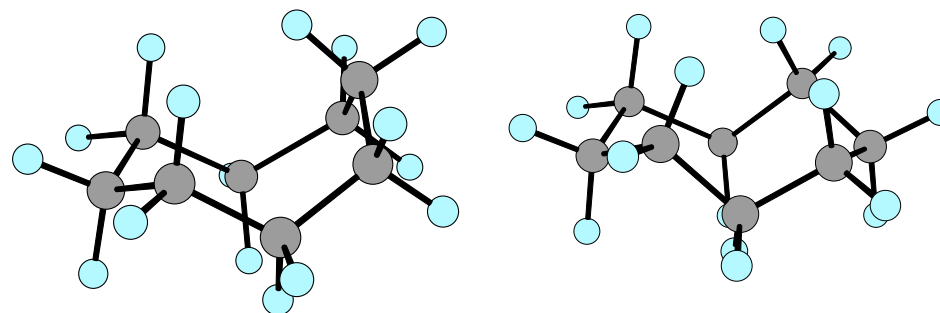


Disubstitution occurs at C₄ or C₆



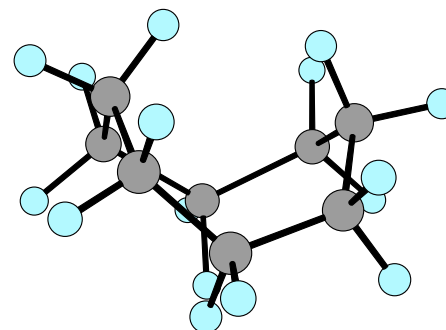
S_N2 occurs at C₁ and C₅

Still, W. C.; Galynker, I. *Tetrahedron* **1981**, 37, 3981.

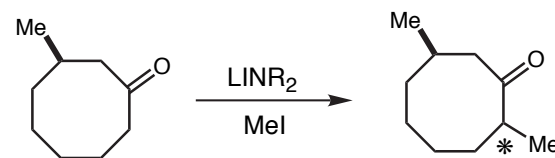


Chair-Boat (**CB**) conformation
reference structure

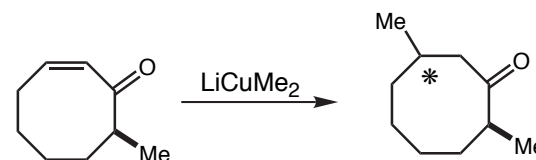
Chair-Chair (**CC**) conformation
(+1-1.6 kcal/mol)



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



Predict
stereochemistry



Predict
stereochemistry

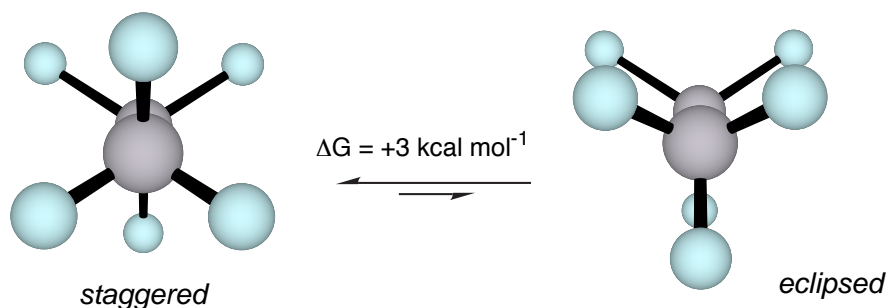
Torsional Effects

Torsional Strain: the resistance to rotation about a bond

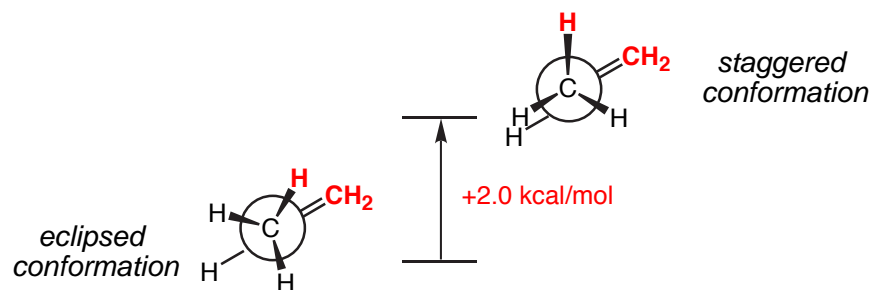
Torsional energy: the energy required to obtain rotation about a bond

Torsional Angle: also known as dihedral angle

Torsional steering: Stereoselectivity originating from transition state torsional energy considerations



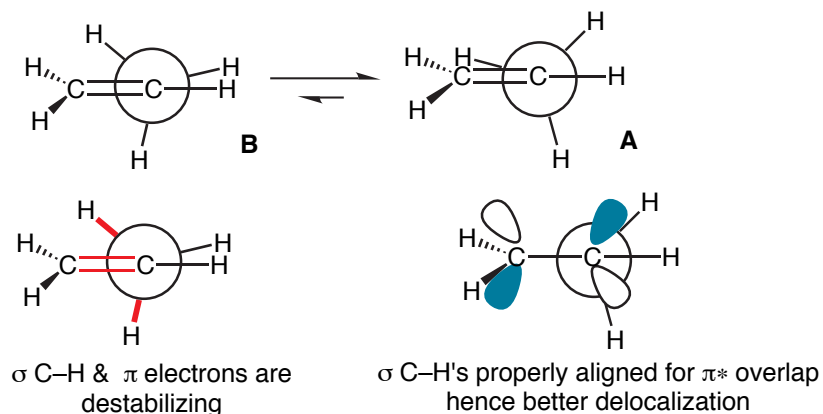
Torsional Strain (Pitzer Strain): Ethane



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

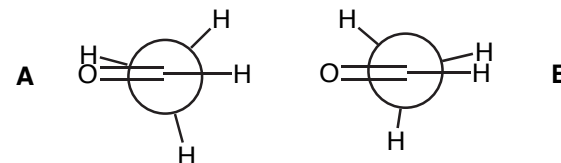
See Lecture 4 for previous discussion

Relevant Orbital Interactions:



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

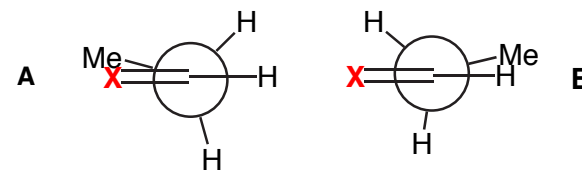
Conformational Preferences: Acetaldehyde



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

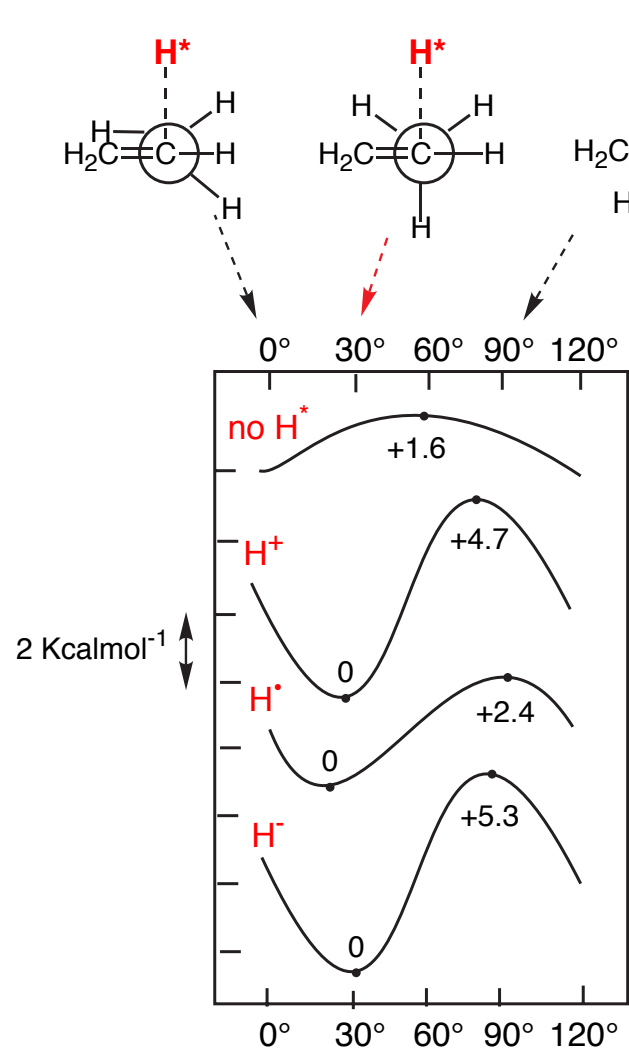
Houk, *JACS* **1983**, *105*, 5980-5988.

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



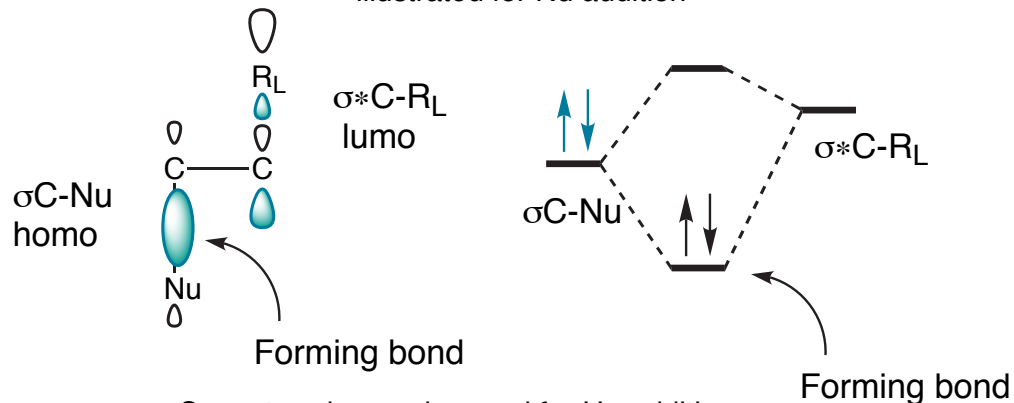
Conformation **A** is preferred. There is little steric repulsion between the methyl and the X-group in conformation **A**.

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

Houk, *JACS* **1981**, *103*, 2438Houk, *JACS* **1982**, *104*, 7162

Transition states

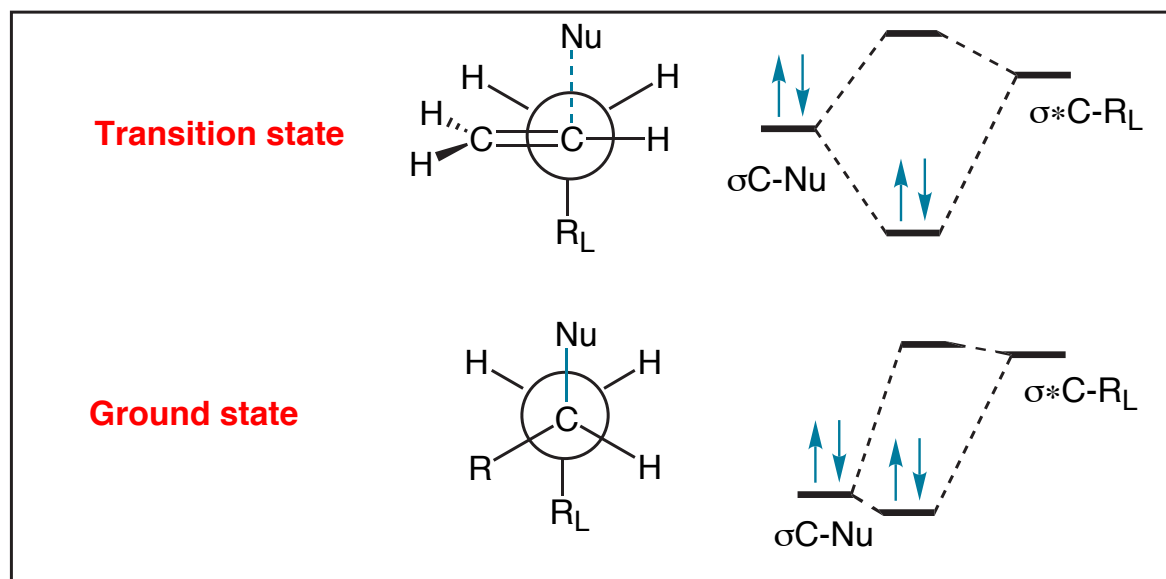
H-radical and H-anion: antiperiplanar σ^*C-R orbital stabilized the TS illustrated for Nu addition



Same trends are observed for H⁺ addition

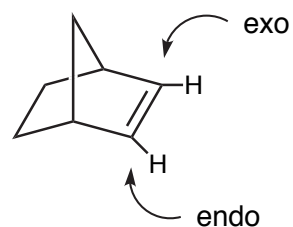
Houk, *Science* **1981**, *231*, 1108-1117

"The Theory and Modeling of Stereoselective Organic Reactions"



■ 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

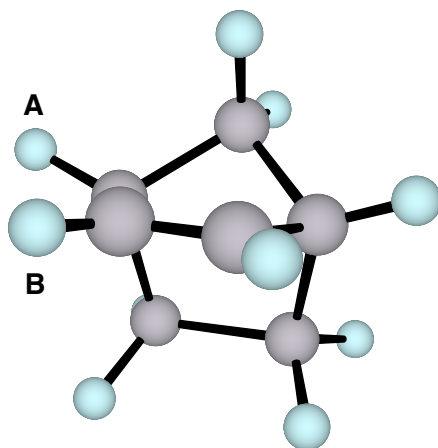
The Controversy over origin of high exoselectivities

Steric effects

Least nuclear motion

Orbital distortion

Schleyer: torsional steering

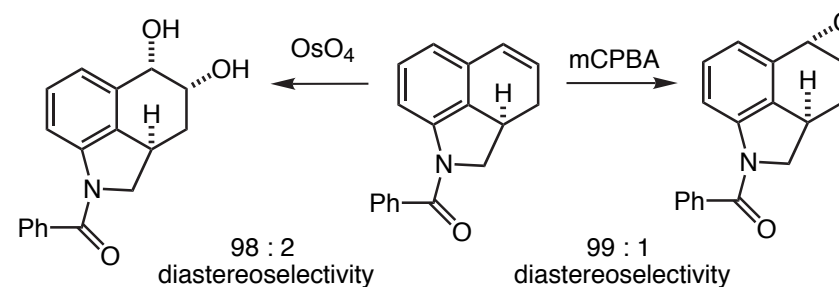


Schleyer, P. R. *J. Amer. Chem. Soc.* **1967**, *89*, 701.

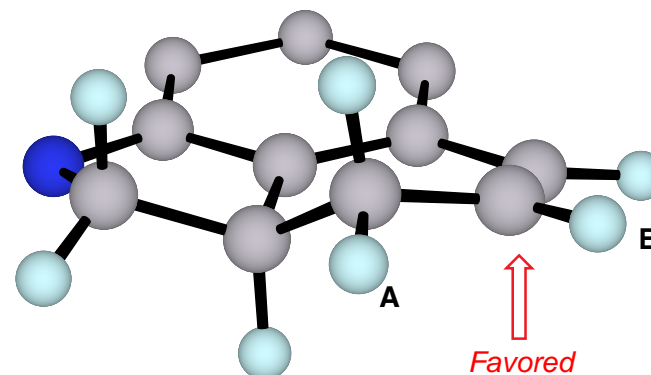
Addition from exo face avoids eclipsing A & B hydrogens
(better hyperconjugative stabilization of transition state)

■ 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

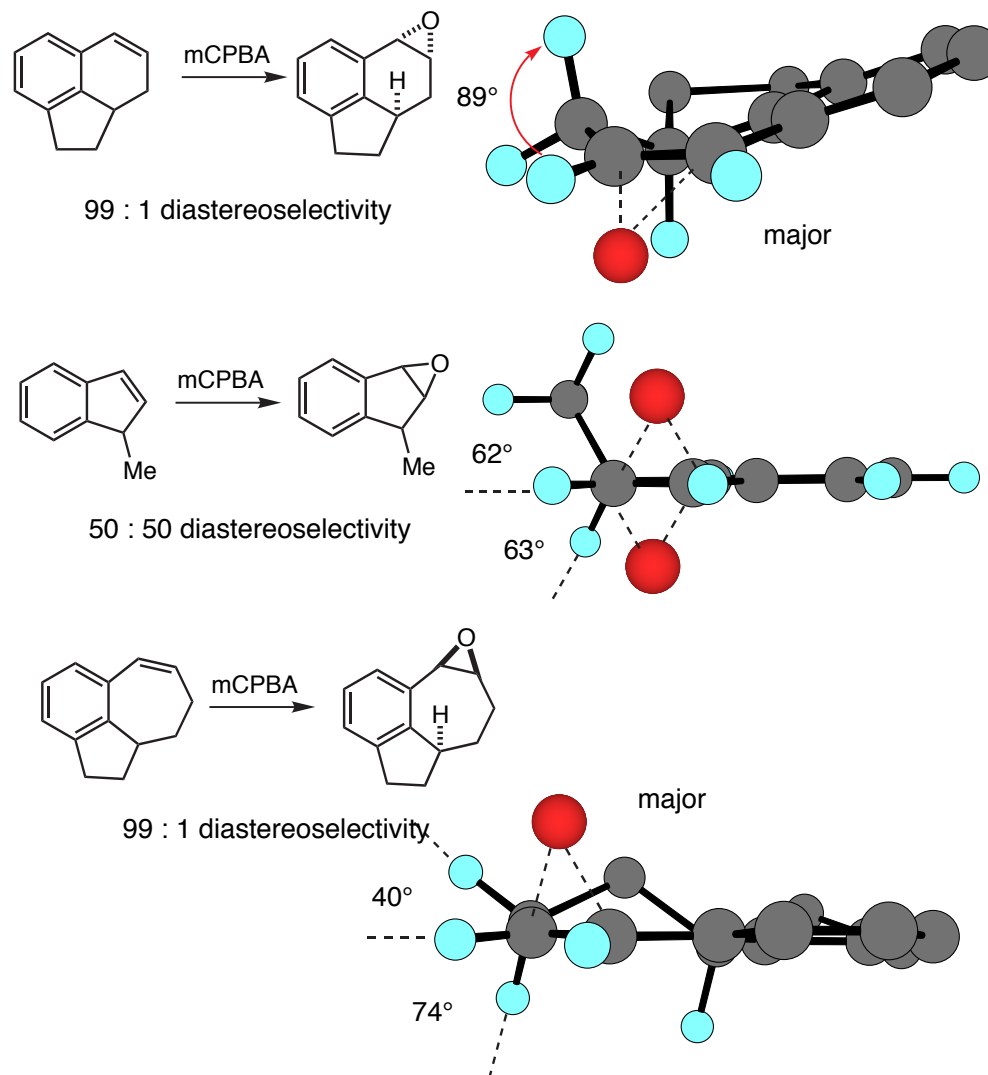


Martinelli, et.al. *Tett. Lett.* **1989**, *30*, 3935

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.....

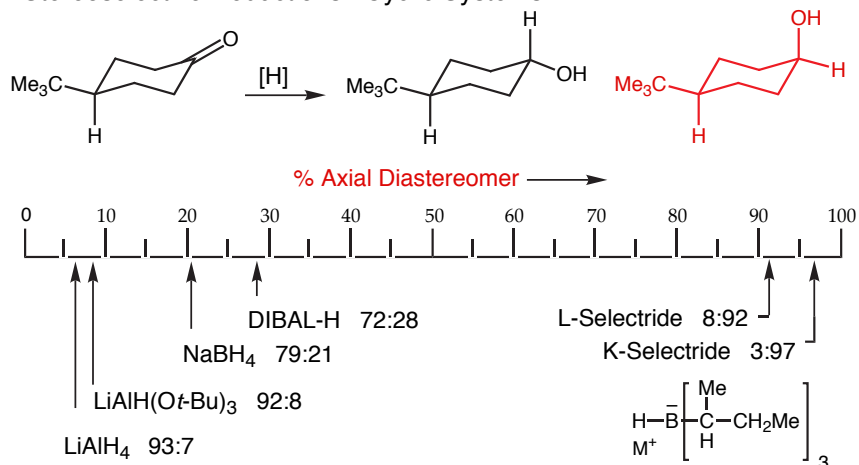
Martinelli: Torsional steering important in selectivity



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

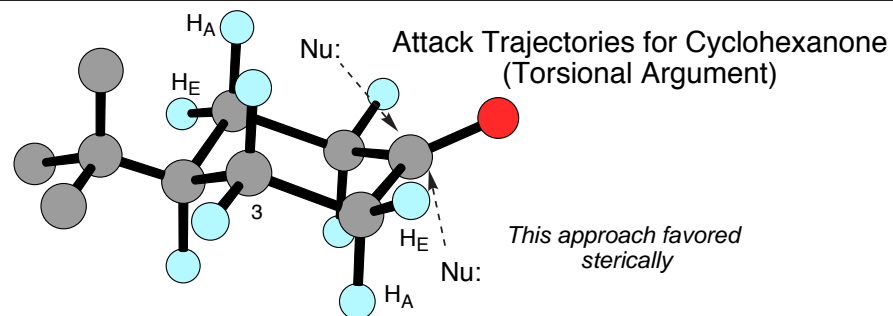
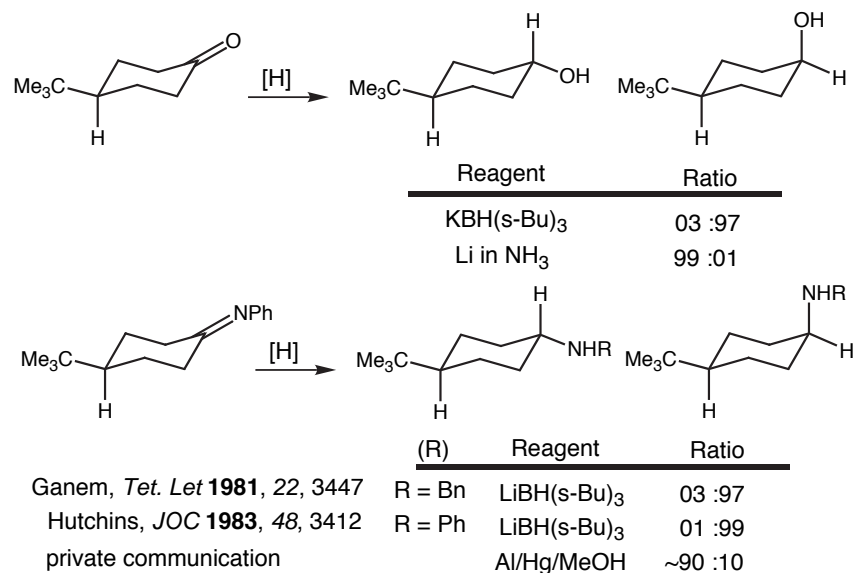
Martinelli & Houk, *J. Org. Chem.* **1994**, *59*, 2204.

Steroselective Reductions: Cyclic Systems

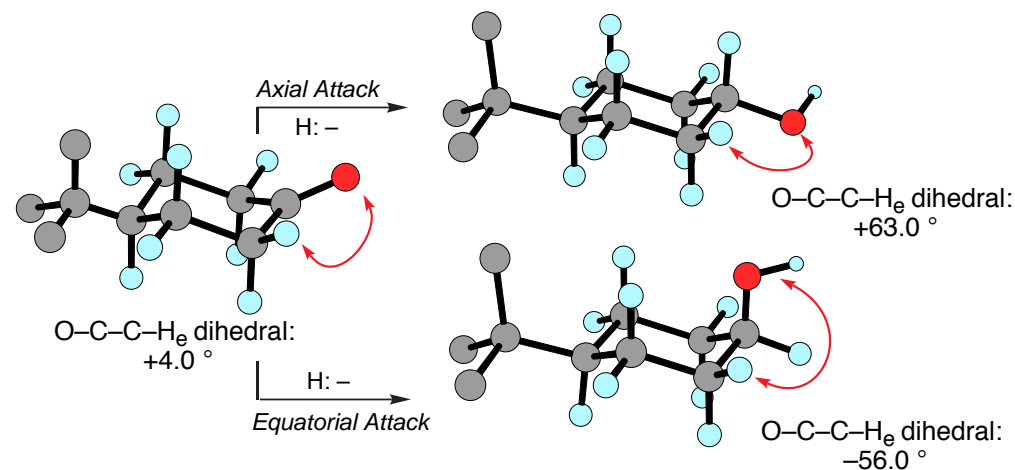


Observation: Increasingly bulky hydride reagents prefer to attack from the equatorial C=O face.

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.

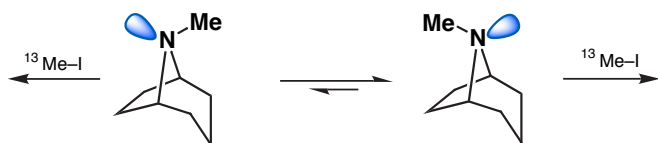
Prediction

For "large" hydride reagents such as H-BR₄, steric effects now are dominant and this explains the predisposition for equatorial attack.

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?

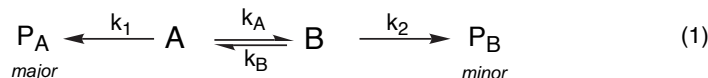
Consider the following example:



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.



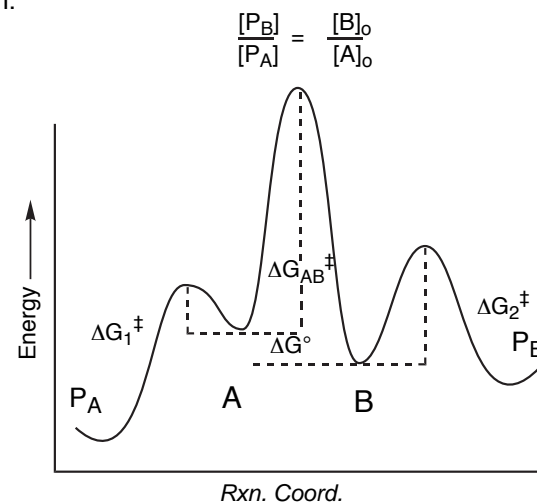
We'll consider two limiting cases:

- (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

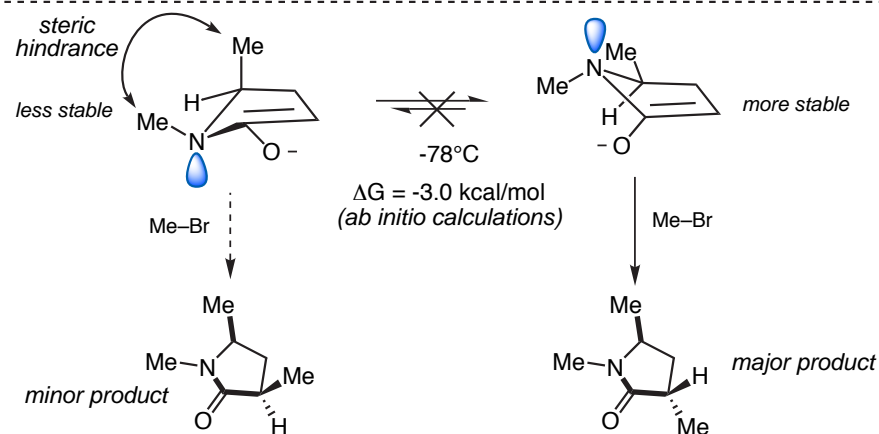
If the rates of conformational interconversion and reaction are comparable, the reactants are not in equilibrium during the course of the reaction and complex mathematical solutions are necessary. See Seeman, *Chem. Rev.* **1983**, 83 - 144 for analytical solutions.

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.

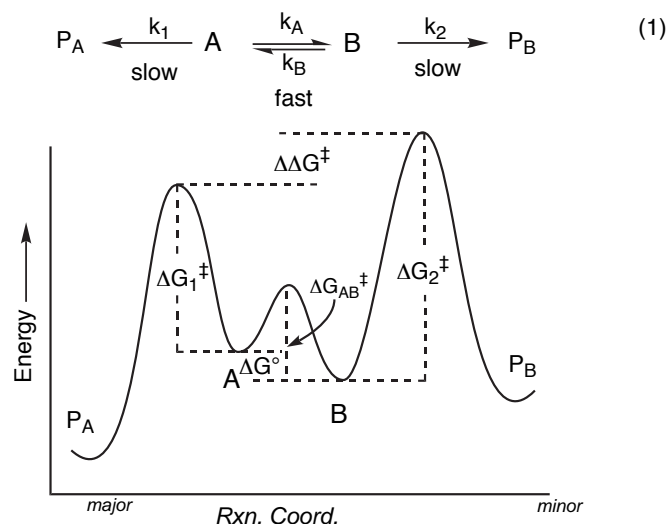


While enolate conformers can be equilibrated at higher temperatures, the products of alkylation at -78° C always reflect the initial ratio of enolate isomers.

Padwa, *JACS* **1997** 4565

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, (ΔG_{AB}^\ddagger is small relative to ΔG_1^\ddagger and ΔG_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:

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

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

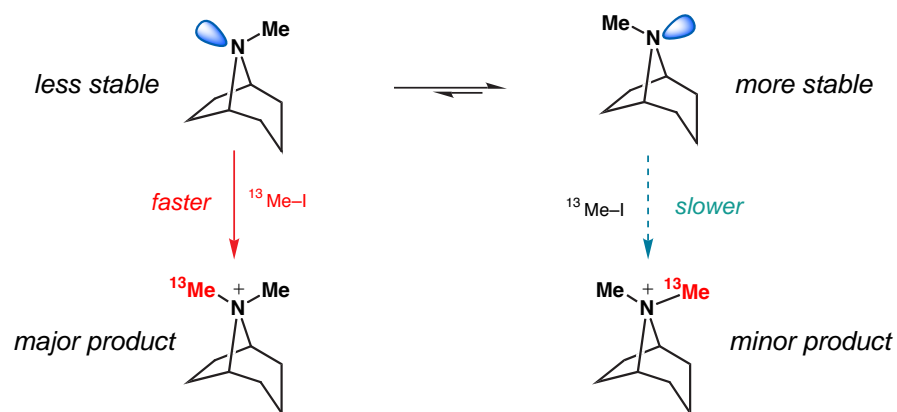
Curtin - Hammett Principle: The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.

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!

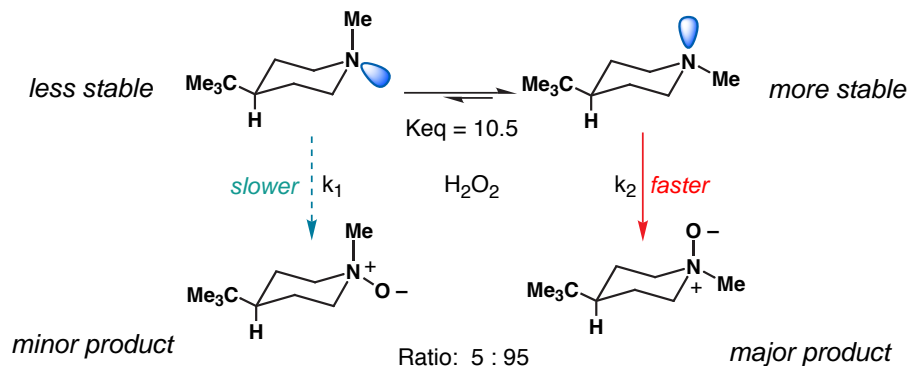
Tropane alkylation is a well-known example.



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

JOC 1974 319

Oxidation of piperidines:

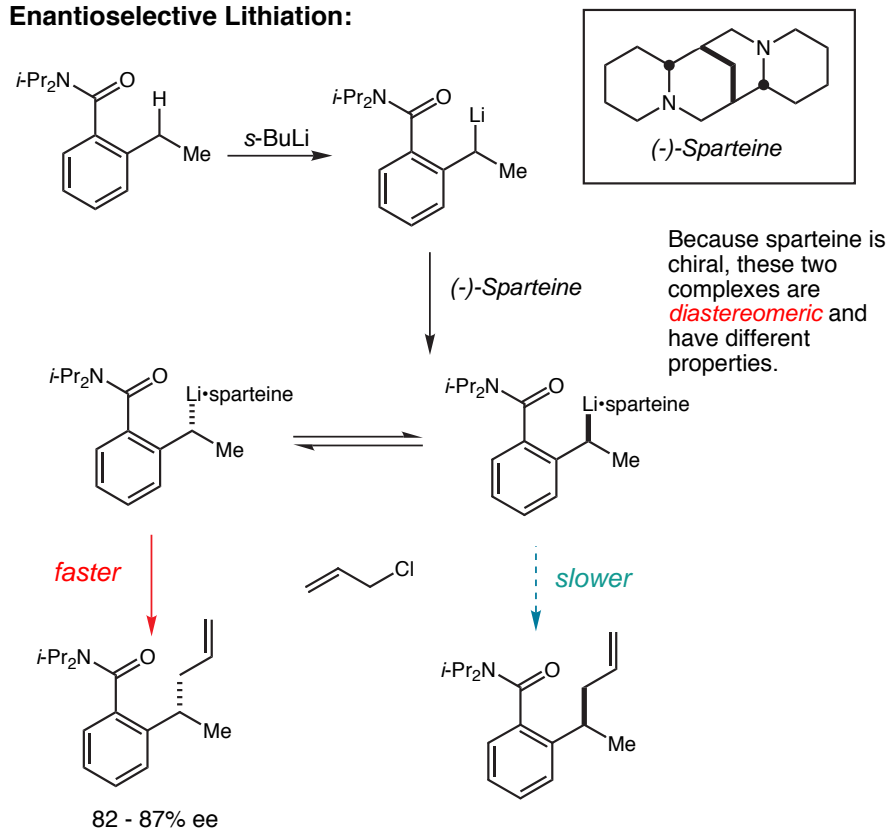


When the equilibrium constant is known, the Curtin-Hammett derivation can be used to calculate the relative rates of reaction of the two conformers. Substituting the above data into $[P_B]/[P_A] = k_2K/k_1$, the ratio $k_2/k_1 \sim 2$.

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

Tet. 1972 573
Tet. 1977 915

Enantioselective Lithiation:



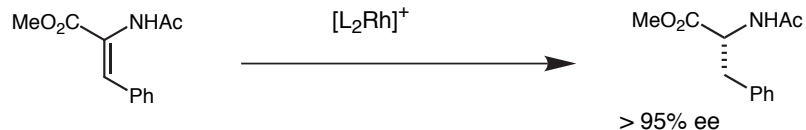
Enantioselectivities are the same, regardless of whether or not the starting material is chiral, even at low temperatures. Further, reaction in the absence of $(-)\text{-sparteine}$ results in racemic product.

Note that the two alkyl lithium 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.

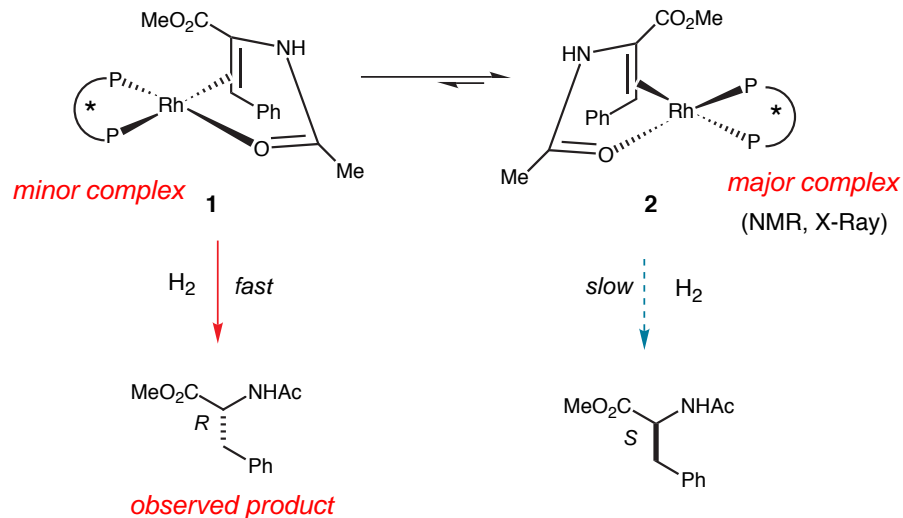
Beak, Acc. Chem. Res, 1996, 552

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)

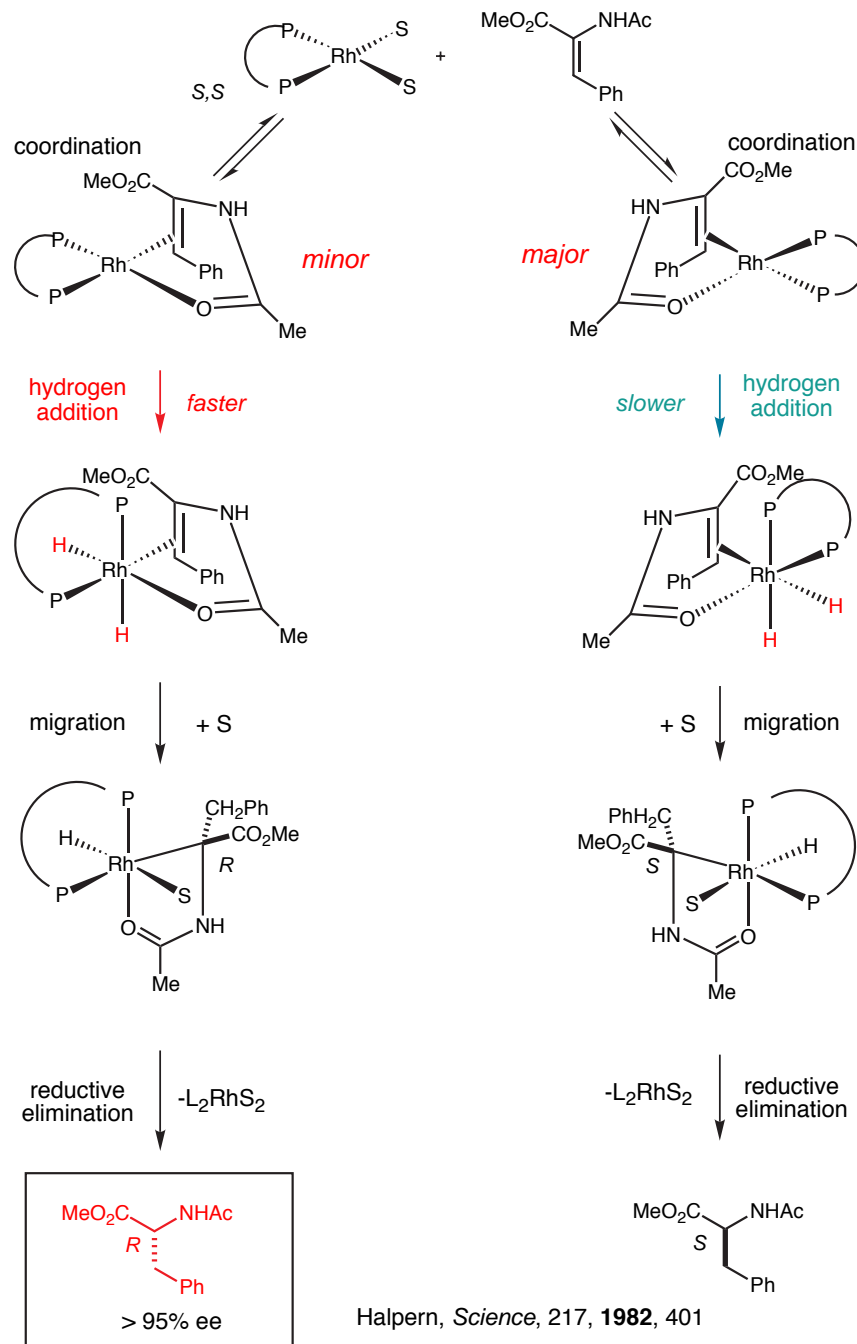
When a chiral ligand is used, there are two diastereomeric complexes which may be formed:



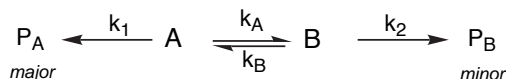
Observations:

- 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 dependent on the pressure of H_2 , and degrades rapidly at higher hydrogen pressures
- The observed enantiomer is exclusively derived from the minor complex 2

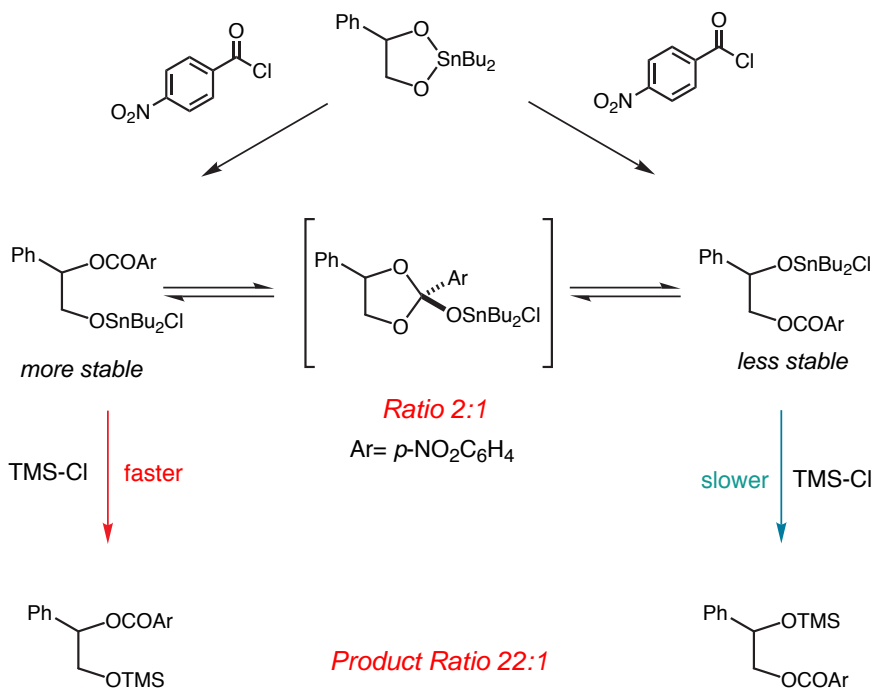
These observations may be explained using the Curtin - Hammett Principle



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 alkoxy-stannane.

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, *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, *Chem Rev.* **1993**, 93, 1307-1370
Substrate-Directable Chemical Reactions
(Electronic Handout)

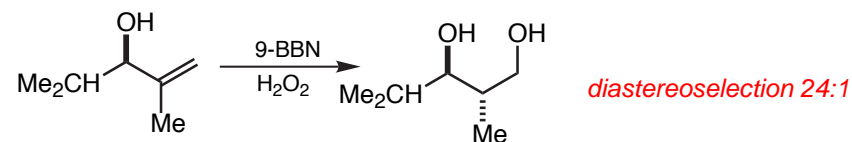
E. Vedejs, *JACS* **2003**, 125, 10502-3
A Mechanistic Alternative for the Intramolecular Hydroboration of Homoallylic Amine and Phosphine Borane Complexes
(Electronic Handout)

D. A. Evans

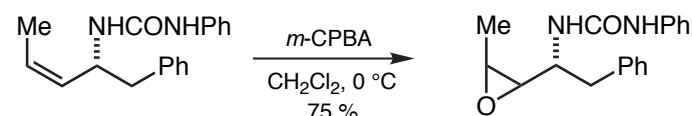
Wednesday,
October 1, 2003

■ Problems of the Day: (To be discussed)

Rationalize the stereochemical outcome of these reactions.

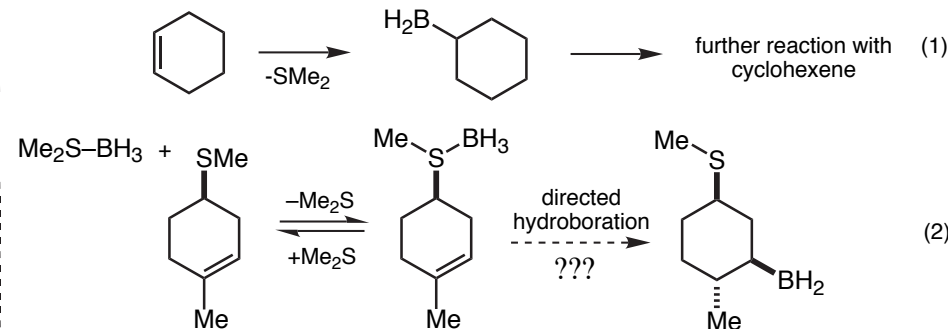


W. C. Still & J. C. Barrish, *J. Am. Chem. Soc.* **1983**, 105, 2487.



Roush, *J. Org. Chem.* **1987**, 52, 5127. *Diastereoselection = 95 : 5*

Web Problem 163: The following is an idea that has been proposed to you by a fellow student. The proposal is based on the fact that borane-methyl sulfide complex is an effective hydroboration reagent (eq 1). It is proposed that homoallylic sulfides such as that illustrated below should be capable of "directing" the hydroboration process from this substituent through the borane-substrate complex.

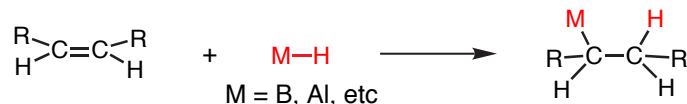


Part A. In order to begin your critique, you must possess a good working knowledge of the details of the hydroboration of olefins with borane-methyl sulfide. Provide a clear depiction of the transition state for the hydroboration process using ethylene as the olefinic substrate and borane-methyl sulfide as the hydroborating agent.

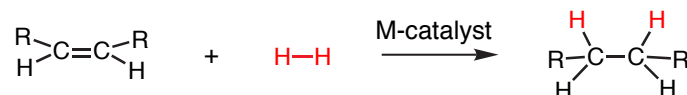
Part B. Now, based on your knowledge of the hydroboration reaction and the principles learned thus far in Chem 206, critique the idea proposed in Eq 2. You must concisely state the logic upon which you base your assessment. *Pictures speak a thousand words.*

Representative Cis-Addition Processes

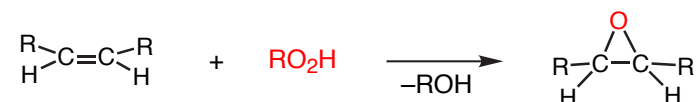
■ Hydrometallation



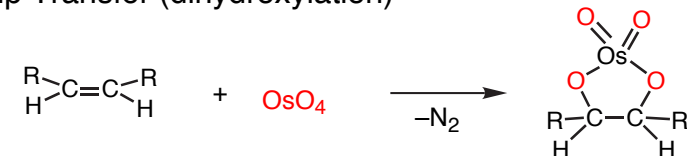
■ Hydrogenation



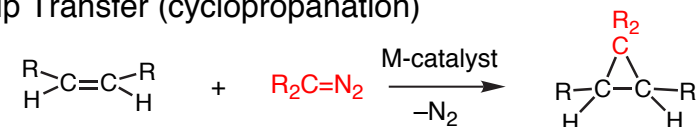
■ Group Transfer (epoxidation)



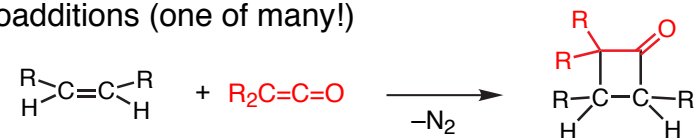
■ Group Transfer (dihydroxylation)



■ Group Transfer (cyclopropanation)



■ Cycloadditions (one of many!)



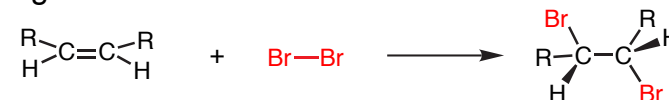
Attributes:

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

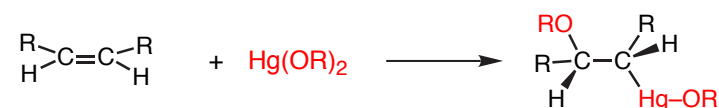
Intermediates *may* be involved in some of the indicated reactions

Representative Trans-Addition Processes

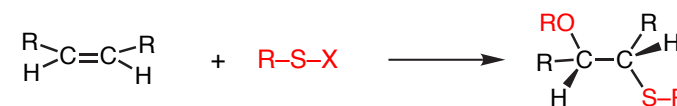
■ Halogenation



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



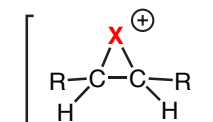
■ Oxy-sulfenation (M = S(II), Se(II))



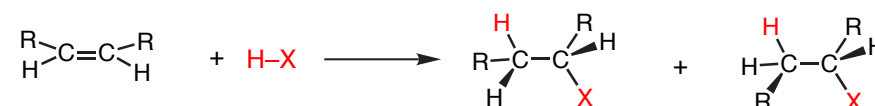
Attributes:

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

Olefin substitution may disrupt bridging



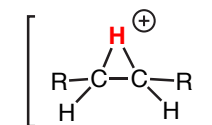
■ Addition of hydrogen halides



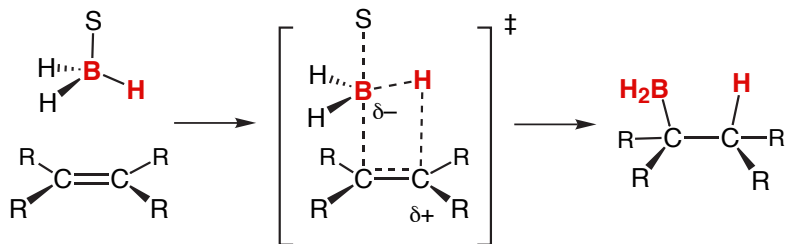
Attributes:

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

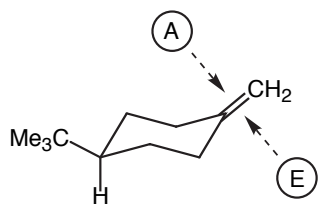
Olefin substitution, reaction conditions as well as halide type may disrupt bridging



The basic process

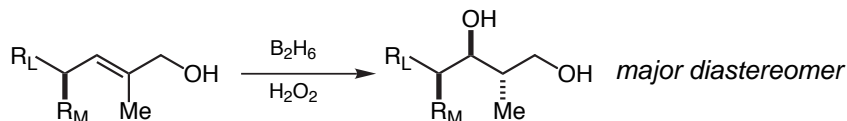


Response to steric effects: Here is a good calibration system:



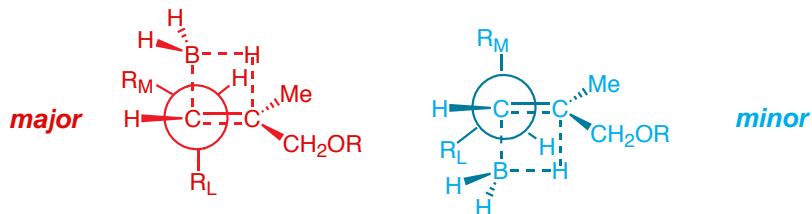
Oxidant	Ratio, A:E	Reference
MCPBA	69:31	JOC, 1967, 32, 1363
BH ₃ , H ₂ O ₂	34:66	JOC, 1970, 35, 2654

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



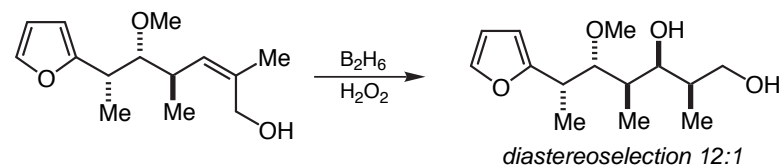
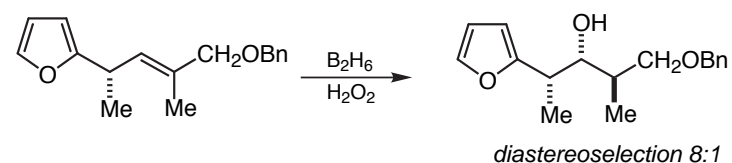
control elements

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

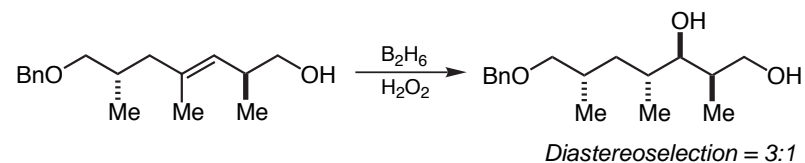


Houk, "Theoretical Studies of Stereoselective Hydroboration Reactions" *Tetrahedron* 1984, 40, 2257 (Handout)

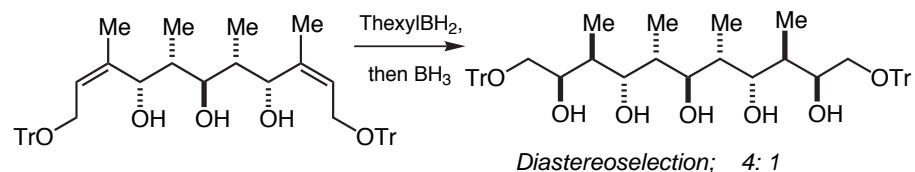
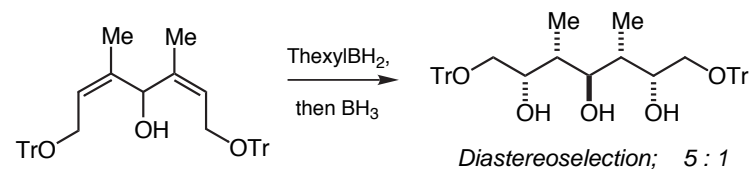
Hydroborations dominated by A(1,3) Strain



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

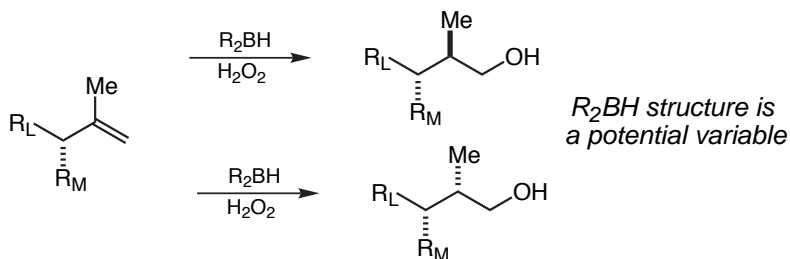


C. H. Heathcock et. al. *Tetrahedron Lett* 1984 25 243.



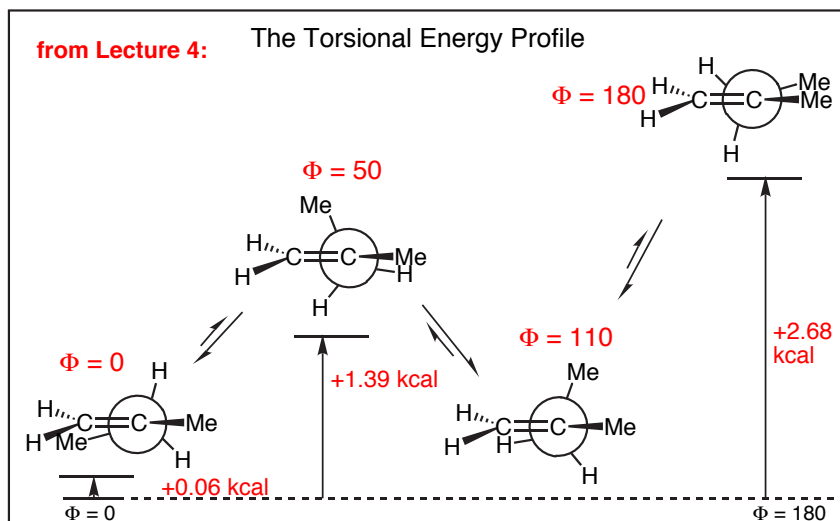
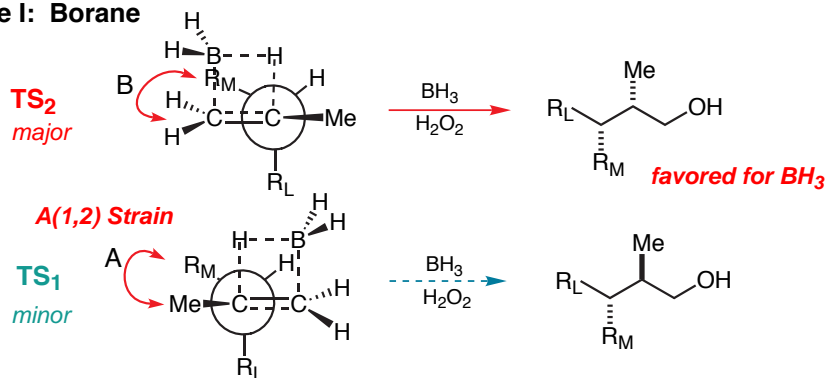
Still, W.C.; Barrish, J. C. *J. Am. Chem. Soc.* 1983, 105, 2487.

Hydroborations dominated by A(1,2) Strain

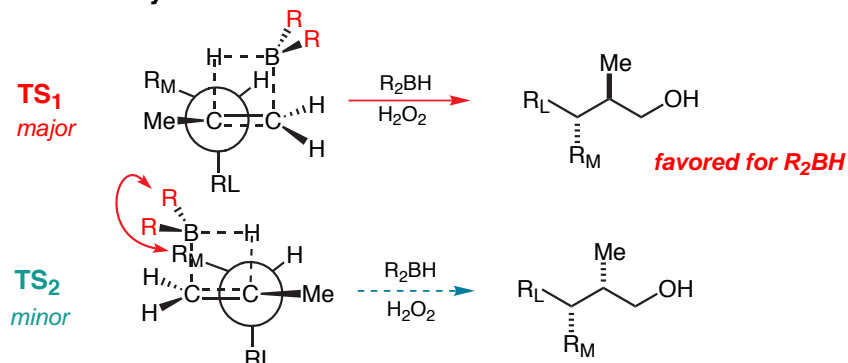


Houk's rules: Orient R_L anti-periplanar to incoming reagents to avoid TS eclipsing:

■ Case I: Borane



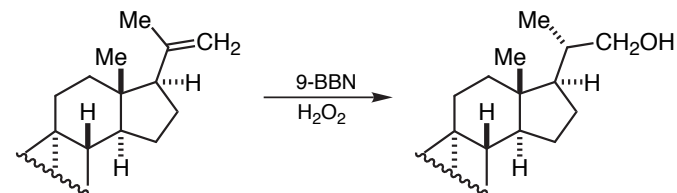
■ Case II: Dialkylboranes



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

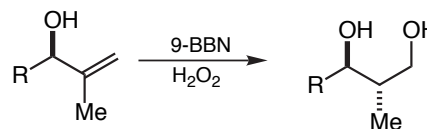
Others have found that TS_1 favored over TS_2 for BH_3

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

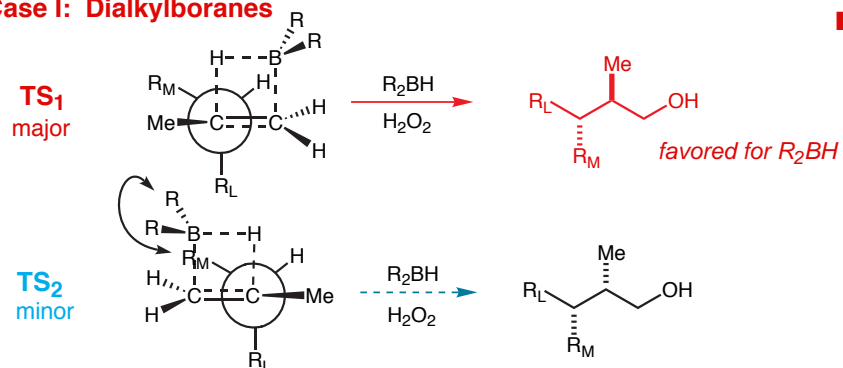


R = n-Bu: diastereoselection 11:1
R = CHMe₂: diastereoselection 24:1

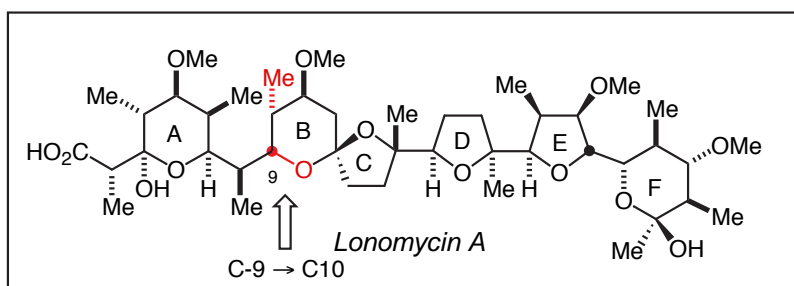
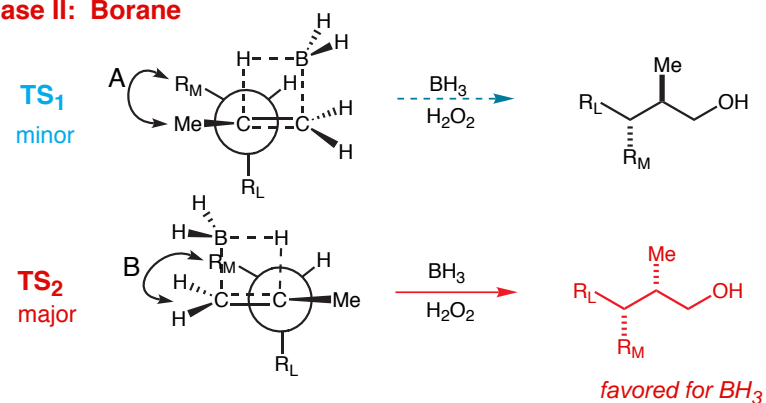
Model is consistent if you presume $HO = R_M$: $R = R_L$

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

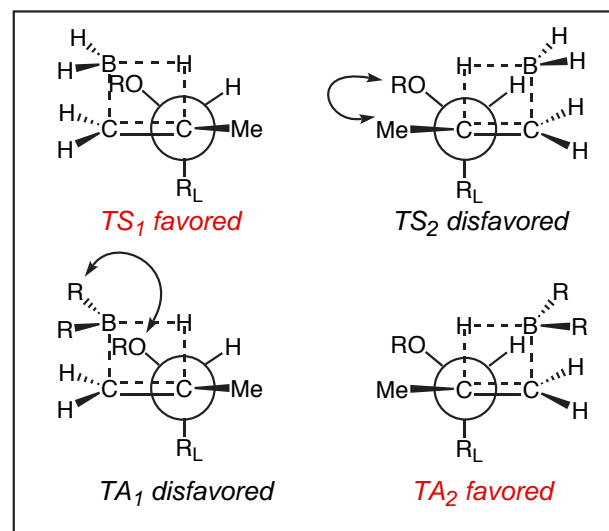
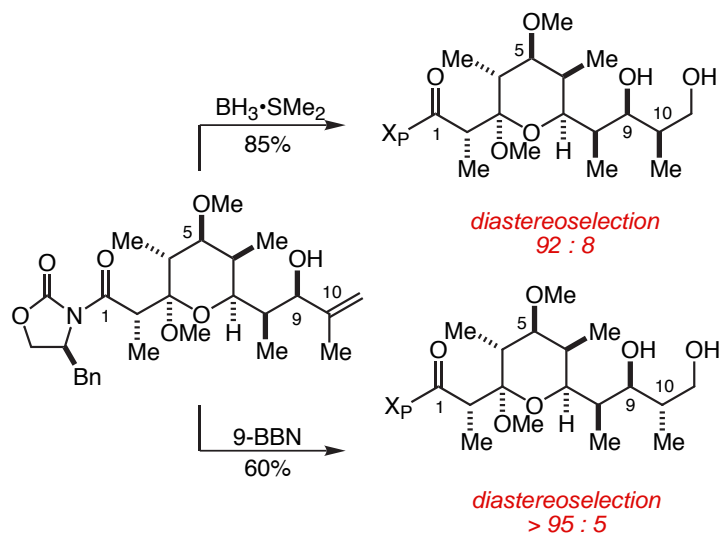
■ **Case I: Dialkylboranes**



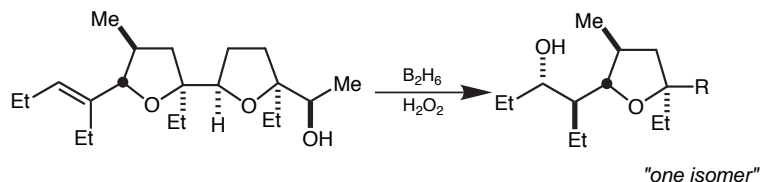
■ **Case II: Borane**



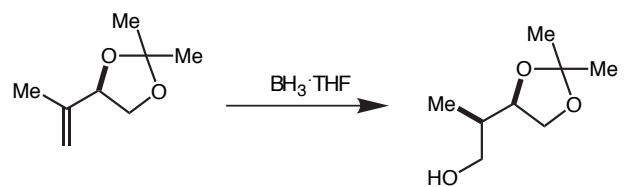
Evans, Ratz, Huff, Sheppard, *JACS* **1995**, *117*, 3448-3467.



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.

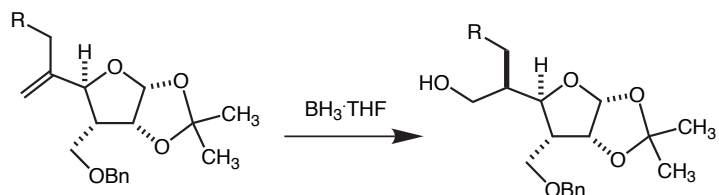


Y. Kishi & Co-workers, *J. Am. Chem. Soc.* **1978**, *100*, 2933.



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

diastereoselection 12:1



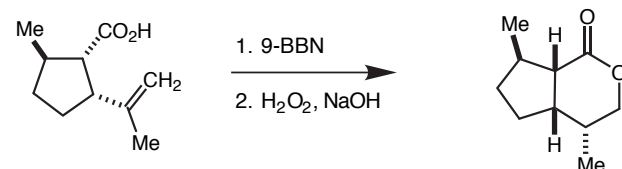
Oikawa et al.
Tetrahedron Lett. **1983**, *19*, 1987.

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



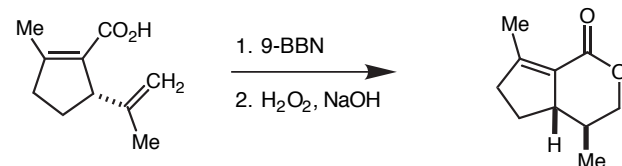
Birtwistle et al.
Tetrahedron Lett. **1986**, *25*, 243.

R = CH₃; Diastereoselection = 6.7:1
R = isopropyl "One Compound"



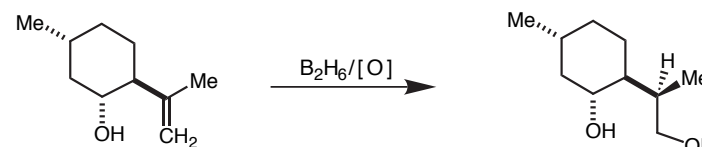
Wolinsky, J.; Eustace, E. J.
J. Org. Chem. **1972**, *37*, 3376.

Diastereoselection = 7:1

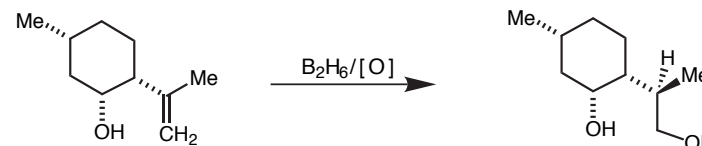


Wolinsky, J.; Nelson, D.
Tetrahedron. **1968**, *25*, 3767.

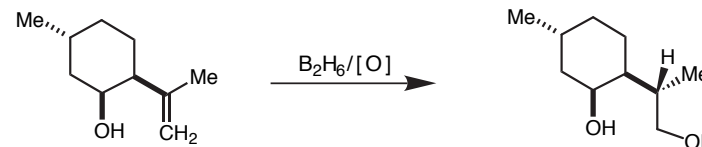
Diastereoselection = 10:1



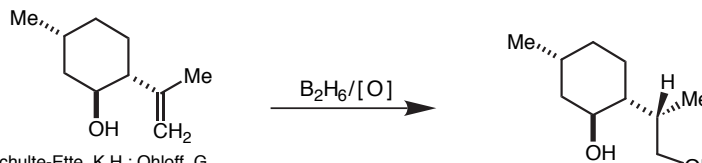
Diastereoselection = 19:1



Diastereoselection = 32:1

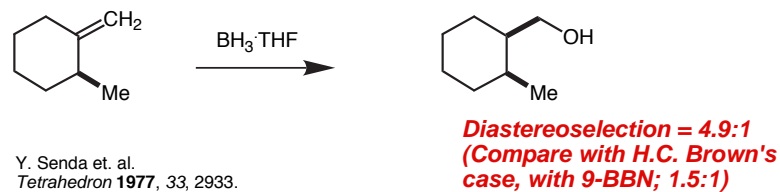
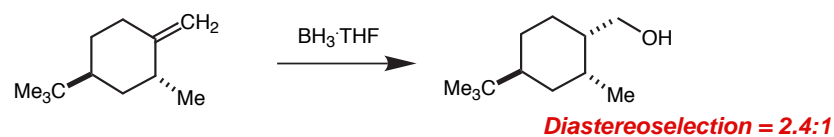
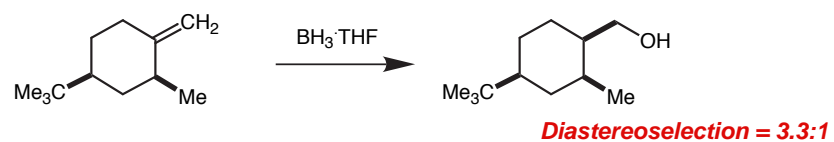
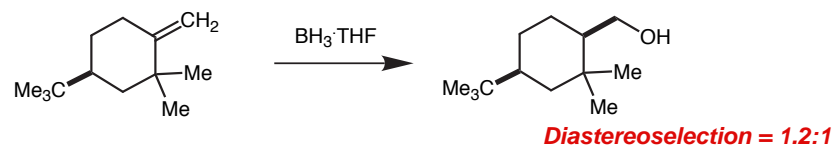
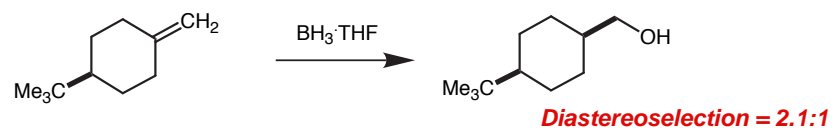


Diastereoselection = 10:1

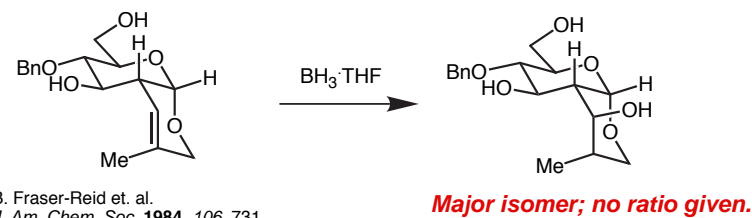


Schulte-Ette, K.H.; Ohloff, G.
Helv. Chim. Acta **1967**, *50*, 153.

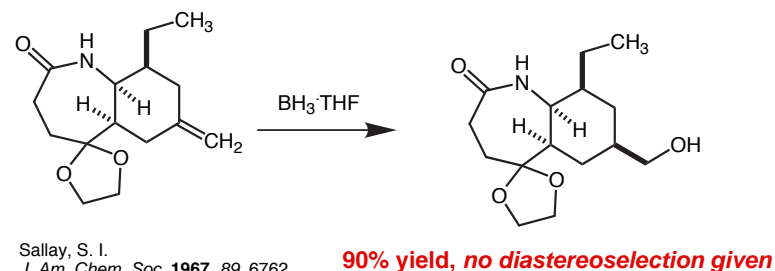
Diastereoselection = 4.6:1



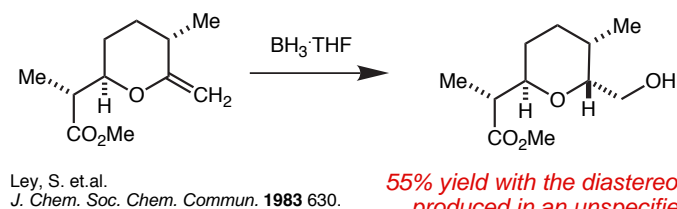
Y. Senda et. al.
Tetrahedron **1977**, 33, 2933.



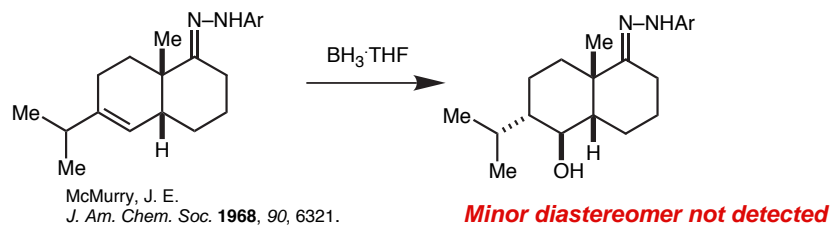
B. Fraser-Reid et. al.
J. Am. Chem. Soc. **1984**, 106, 731.



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



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

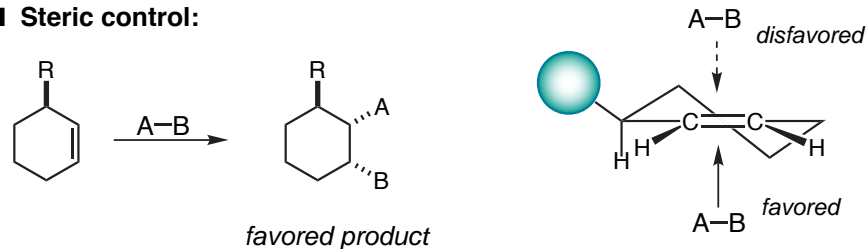


McMurry, J. E.
J. Am. Chem. Soc. **1968**, 90, 6321.

Stereochemical Control Elements for all reactions

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

■ Steric control:

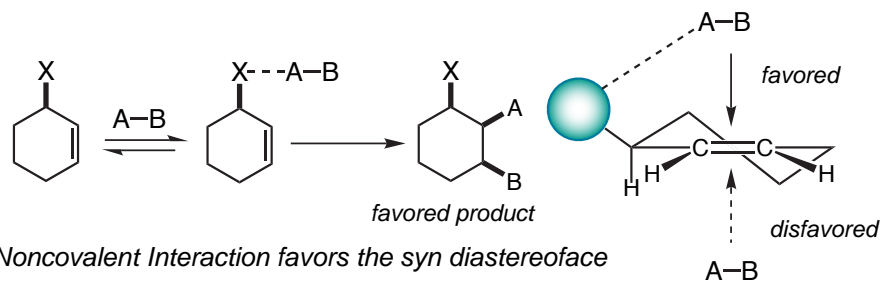


Nonbonding Interactions disfavor the syn diastereoface

Directed Reactions

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

■ Associative Substrate-Reagent Interactions



Agenda

Directed Oxidations

Epoxidation
Hydroboration

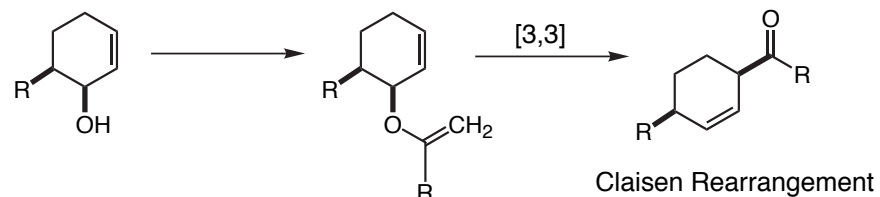
Directed Reductions

Hydrogenation
Hydride reduction

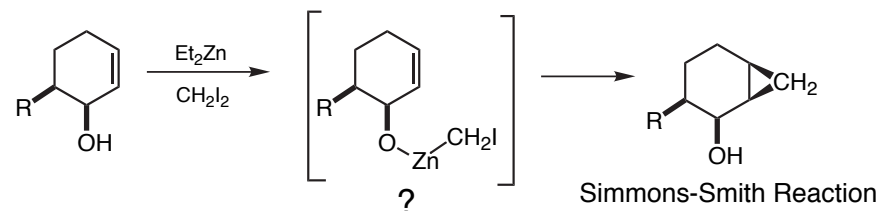
Directed C-C Bond Constructions

Heteroatom-directed Reactions

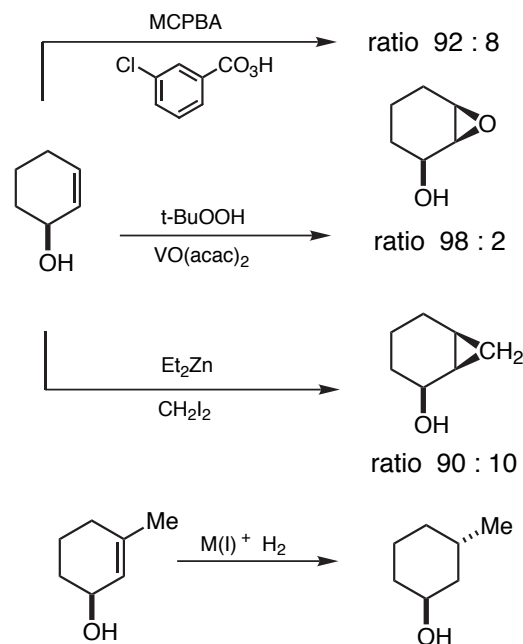
Mechanism-based: (HO & C=C must be allylic)



via Reagent Ligation



Hydroxyl-directed Reactions



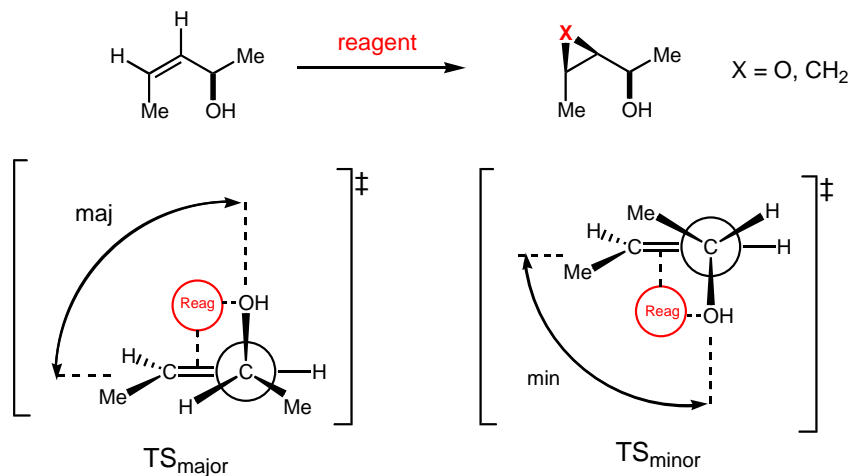
Henbest
J. Chem. Soc. 1958, (1957)

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 reactions

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

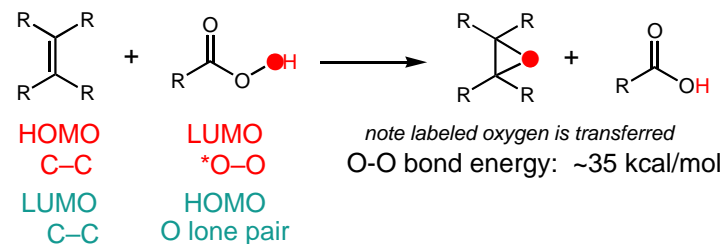
The transition state bite angles for the above reactions are either not known or have been only crudely estimated.

The "best guesses" are provided.

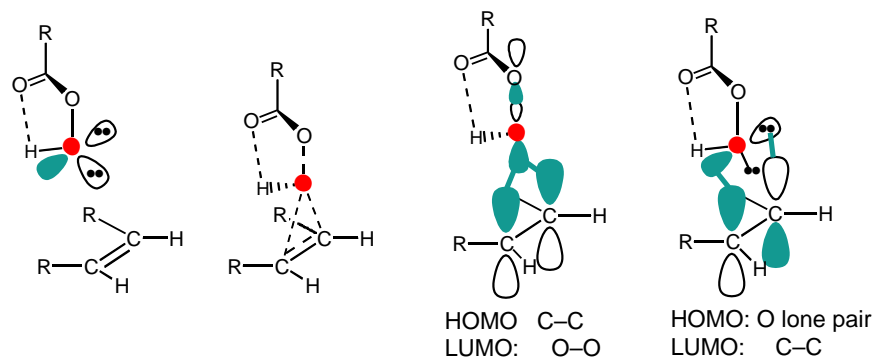
Peracid Epoxidation

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

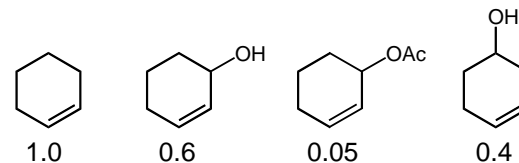
■ General Reaction:



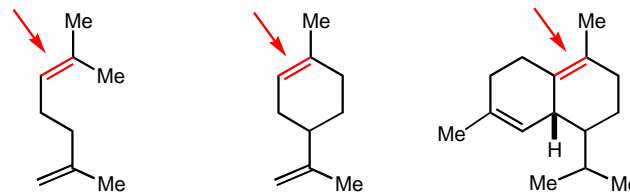
■ Transition state: What about lone pairs. [Consider ● to be Sp² hybridized].



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

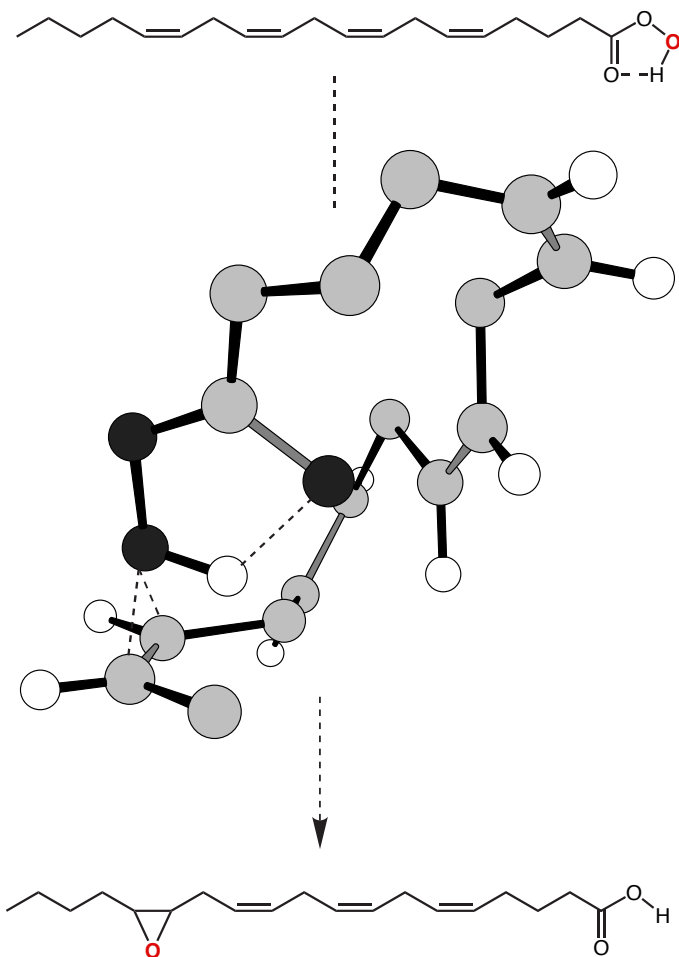


■ The indicated olefin in each of the diolefinic substrates may be oxidized selectively.



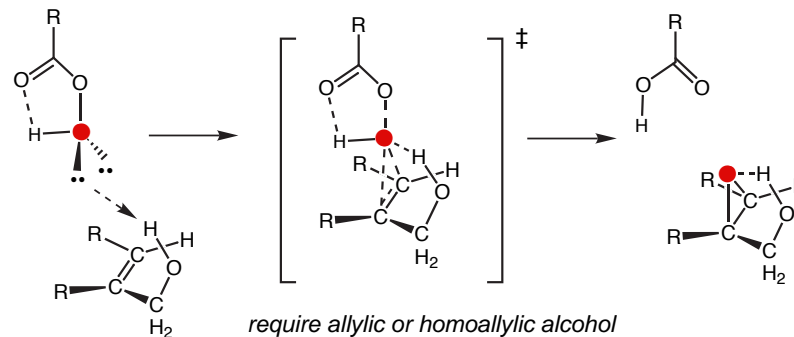
Stereoelectronic Implications of intramolecular Peracid Epoxidation

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

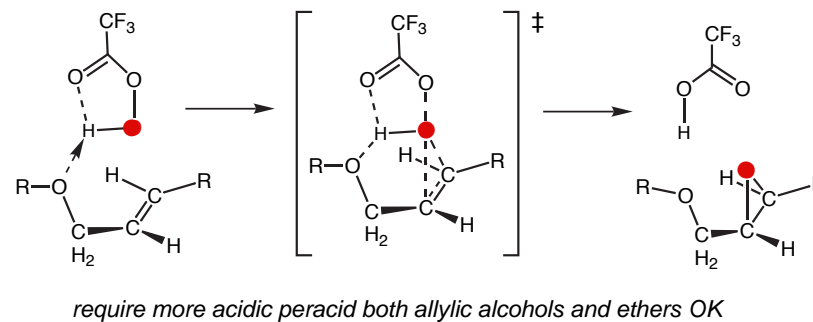


The Directed Peracid Epoxidation

- 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)

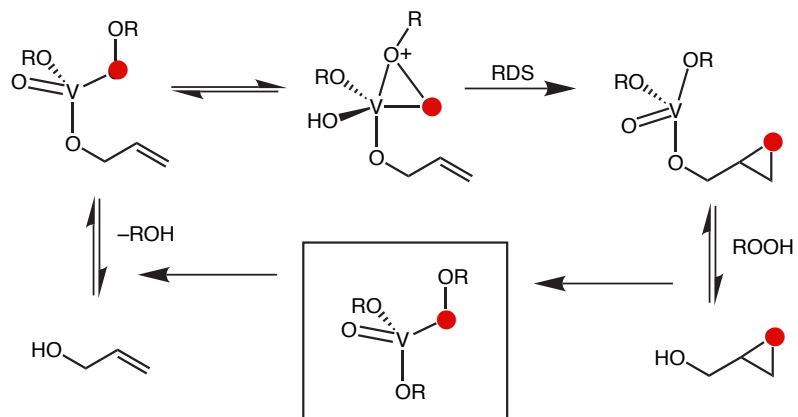
Epoxidation of Cyclic Homoallylic Alcohols

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.

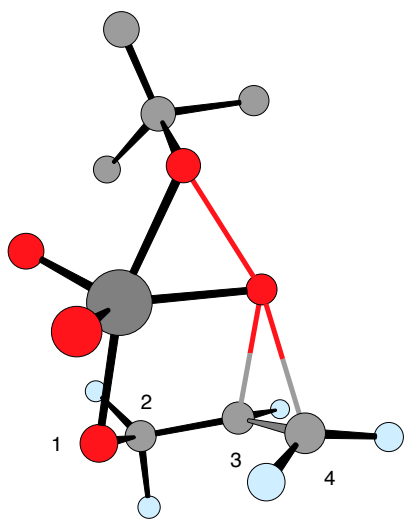
(Table 14, p1318, from the Evans, Hoveyda, Fu review article)

The Sharpless Epoxidation

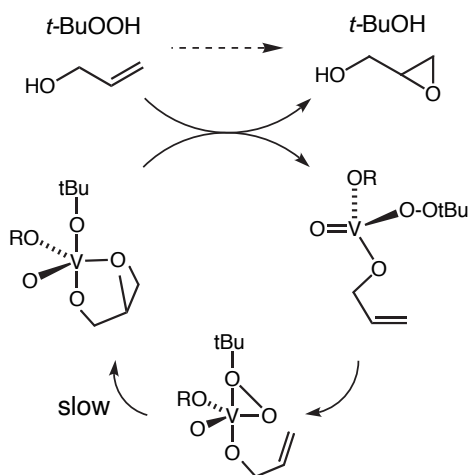


Aldrichimica Acta, 12, 63 (1979)

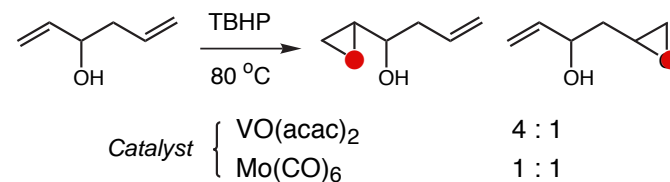
O-C₂-C₃-C₄ = 41°
The Sharpless estimate: ~50°



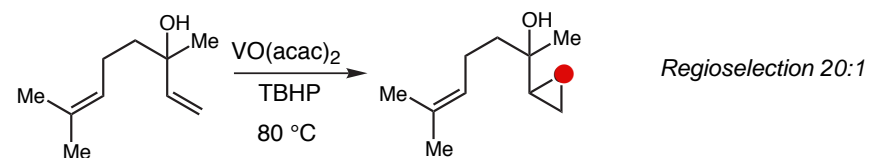
Chem 3D Transition State



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



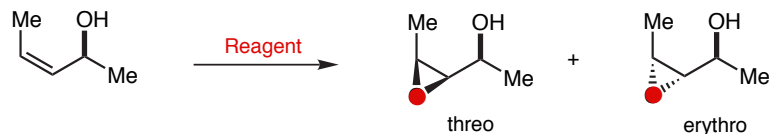
■ Next step: Sharpless, Michaelson *JACS* **1973**, 95, 6136

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

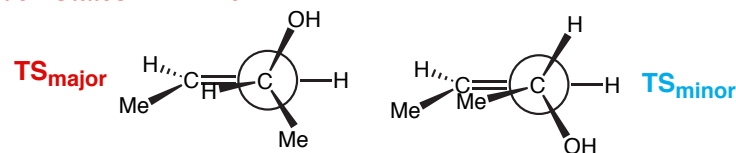
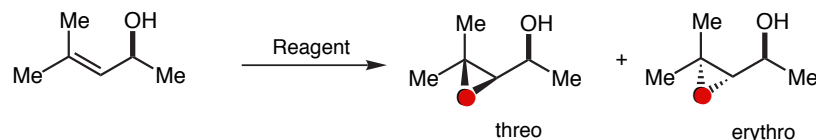
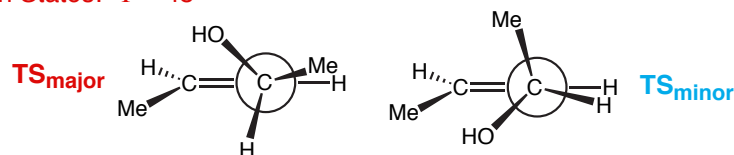
Substrate	$k_{\text{rel}}^{a,b}$ (diastereoselectivity ^c)		
	peracid	Mo(CO) ₆	VO(acac) ₂
	1.00	1.00	1.00
	0.55 (92 : 8)	4.5 (98 : 2)	>200 (98 : 2)
	0.046 (37 : 63)	0.07 (40 : 60)	--
	0.42 (60 : 40)	11.0 (98 : 2)	10.0 (98 : 2)

^{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: $\Phi \sim 45^\circ$ 

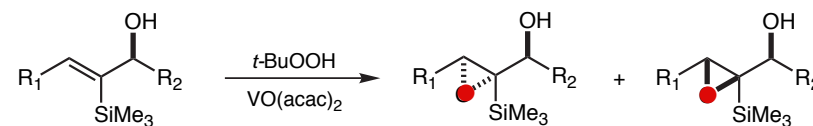
K. Oshima & Coworkers
Tetrahedron Lett. **1980**, 21, 1657, 4843.

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.

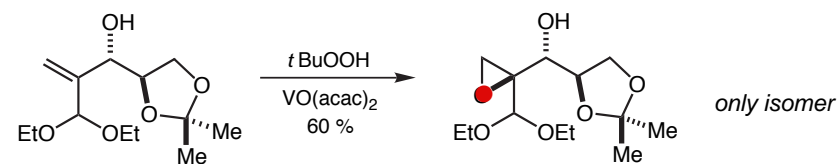


Reagent	Ratio
<i>m</i> -CPBA	64 : 36
<i>t</i> -BuOOH / VO(acac) ₂	29 : 71
<i>t</i> -BuOOH / Mo(CO) ₆	62 : 38
<i>t</i> -BuOOH / (<i>t</i> -BuO) ₃ Al	64 : 36

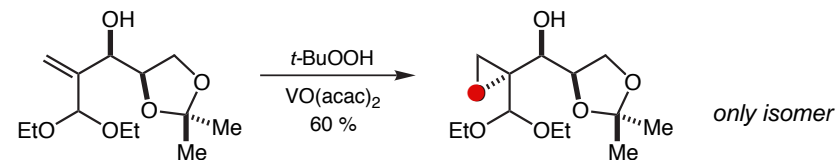


Oshima, *Tetrahedron Lett.* **1982**, 23, 3387.

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

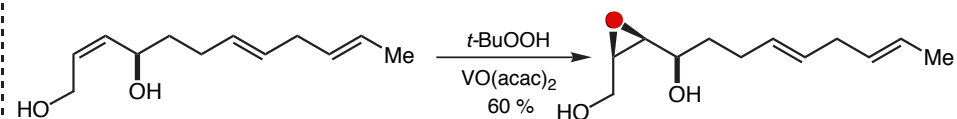


only isomer



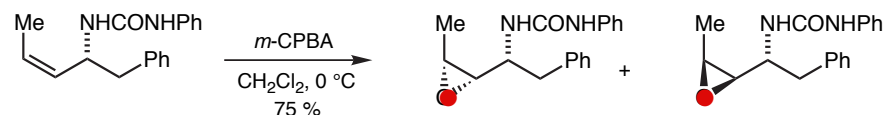
only isomer

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



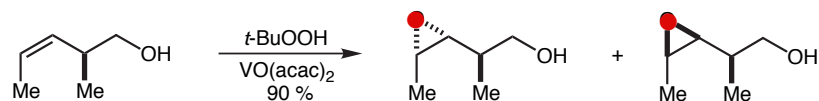
Boeckman, *JACS* **1977**, 99, 2805.

Diastereoselection = 7 : 1



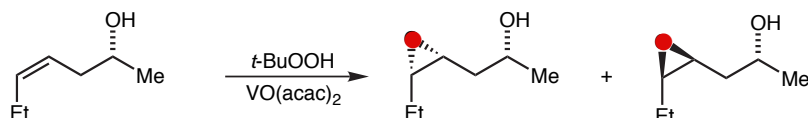
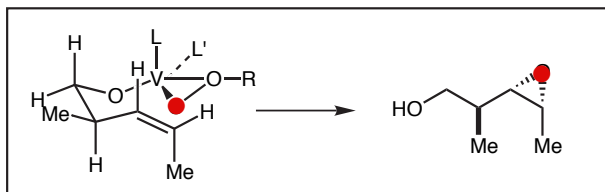
Roush, *J. Org. Chem.* **1987**, 52, 5127.

Diastereoselection = 95 : 5

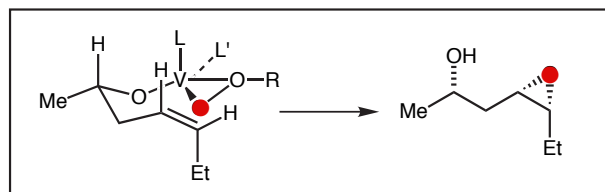
Homoallylic Alcohols (Mihelich, *JACS* **1981**, 103, 7690)

Control Elements

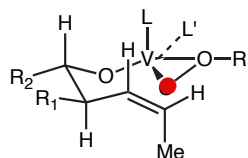
A(1,3) Strain
Directed Rxn



Control Elements
Directed Rxn

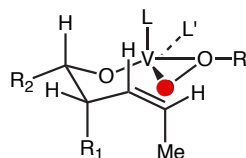


Prediction



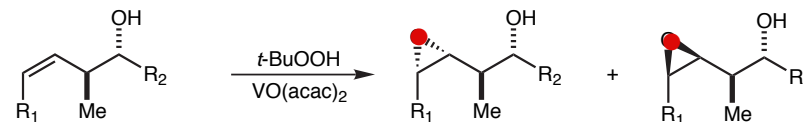
Anti diastereomer

Anti should be more
diastereoselective
than syn



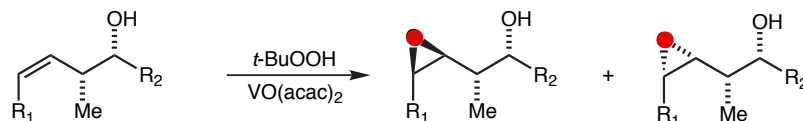
Syn diastereomer

Anti diastereomer

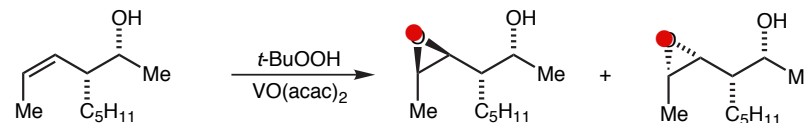


R ₁	R ₂	Yield	Ratio
C ₆ H ₁₃	Me	92 %	104 : 1
Me	<i>i</i> -Pr	97 %	> 400 : 1

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



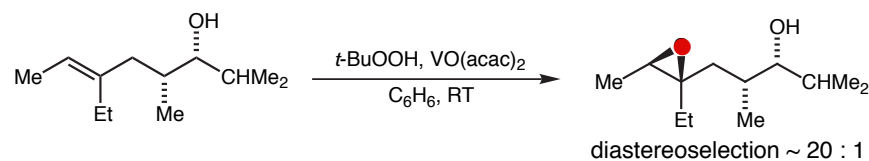
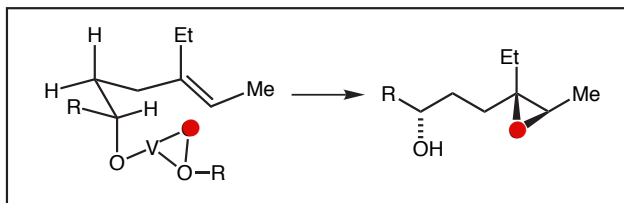
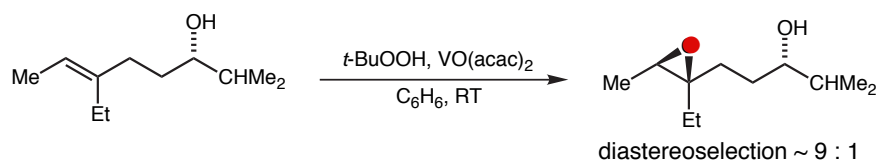
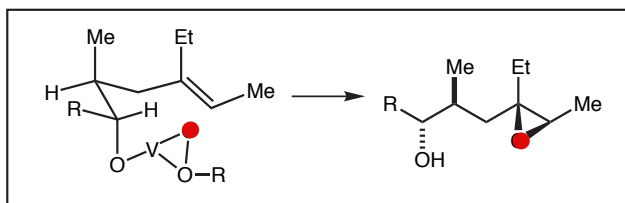
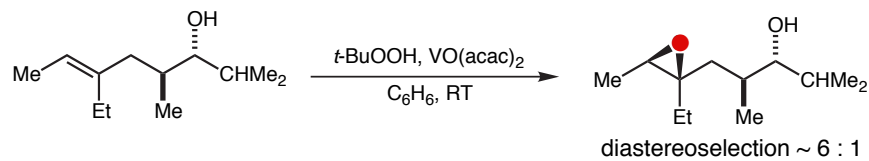
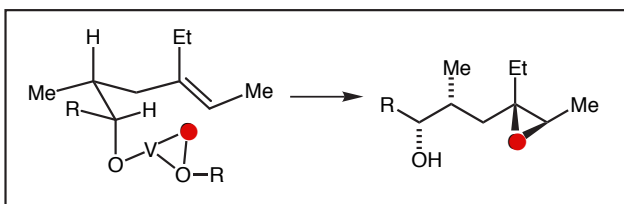
E. D. Mihelich & Coworkers
J. Am. Chem. Soc. **1981**, 103, 7690.

Diastereoselection = 211 : 1

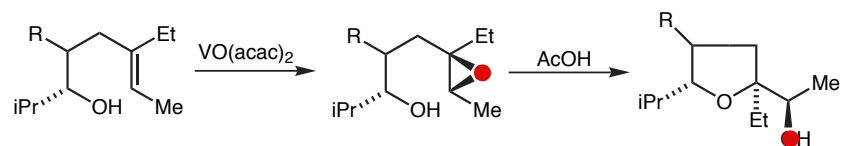
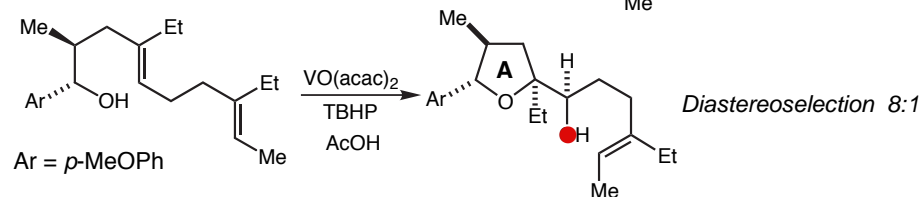
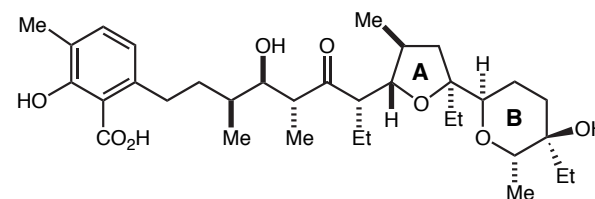
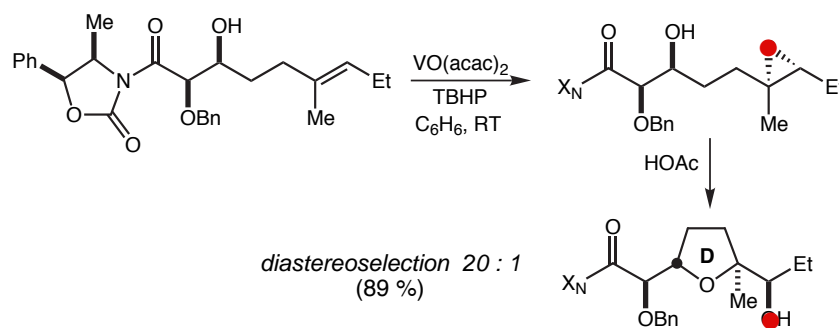
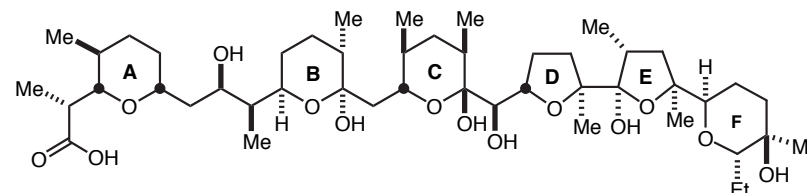
Epoxidation of Homoallylic Alcohols with TBHP, $\text{VO}(\text{acac})_2$

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
- Olefin Bromination

■ 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**)

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

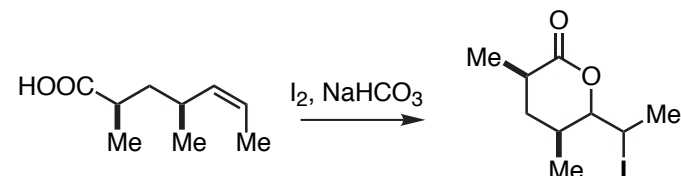
Bromonium Ions or β -Bromocarocations in Olefin Bromination. A Kinetic Approach to Product Selectivities
M-F. Ruasse, *Accts. Chem. Res.* **1990**, 23, 87 (**handout**)

D. A. Evans

Friday,
October 3, 2003

■ Problems of the Day: (To be discussed)

Predict the stereochemical outcome of the indicated reaction.

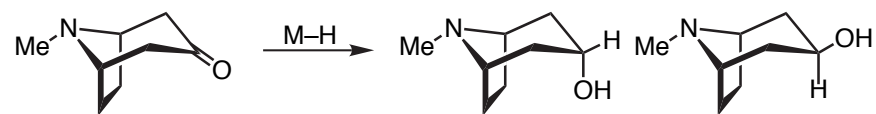


Kinetic Control: 3 eq. I₂, MeCN, NaHCO₃, 0°C

diastereoselection: 20:1

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

Rationalize the stereochemical outcome of the indicated reaction.



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

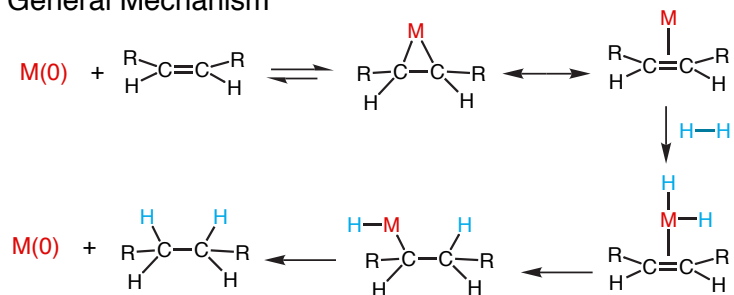
R₂AlH 97 : 3

LiAlH₄ 28 : 72

The Hydrogenation Reaction

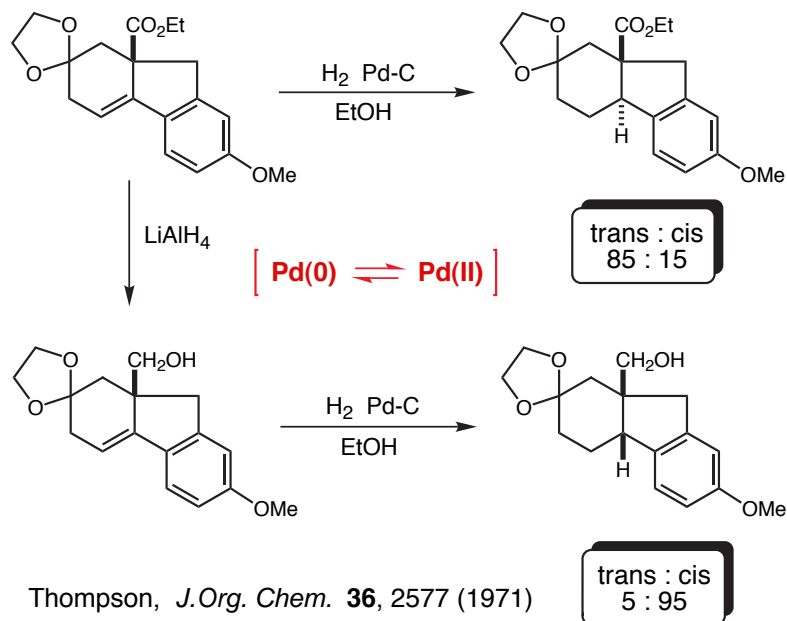
Relevant Review articles: J. M. Brown, *Angew. Chem. Int. Edit.* **26**, 190-203 (1987).

General Mechanism

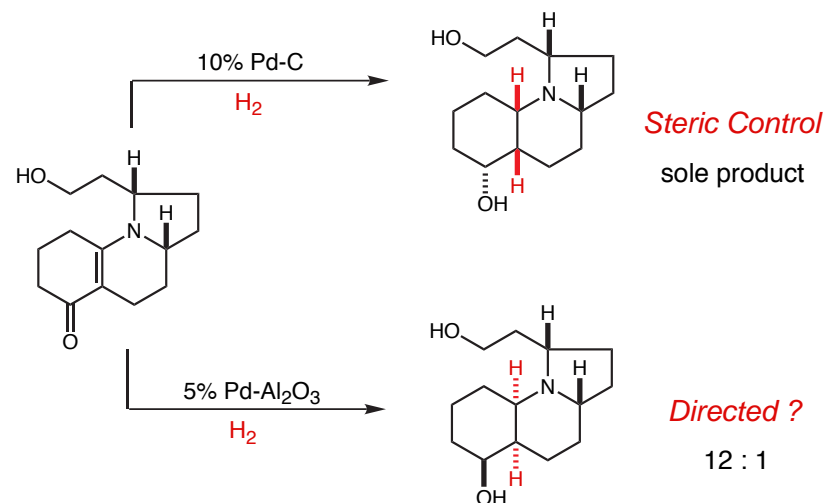
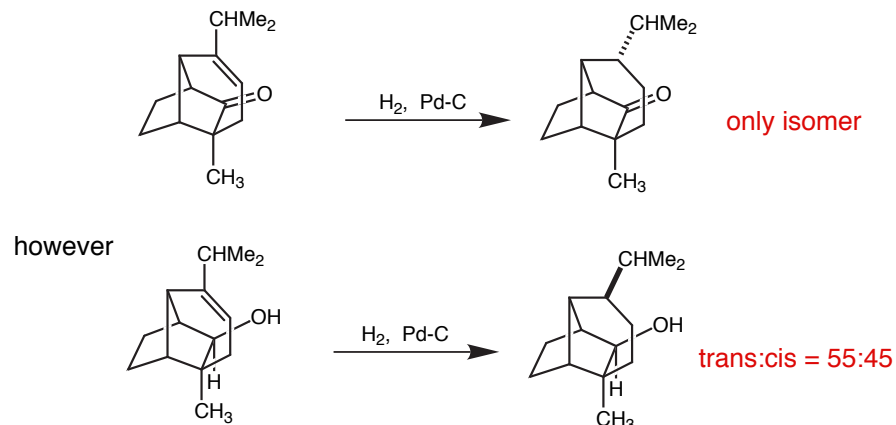


Historically, primary stereochemical control designed around analysis of steric environment in vicinity of $C=C$.

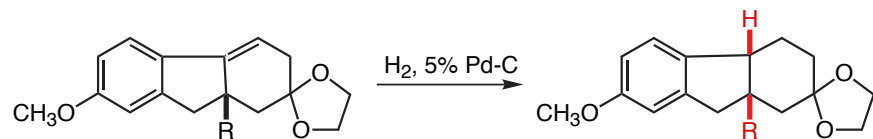
However, the influence of polar effects was documented



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



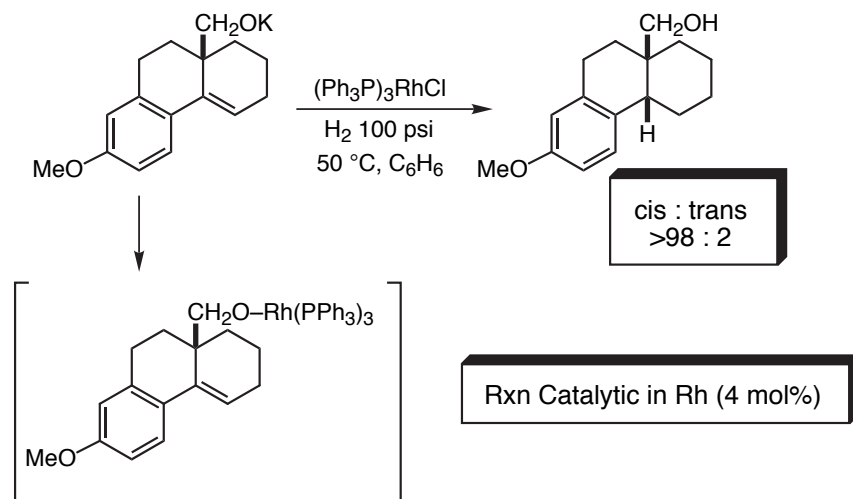
The first rational attempt to identify those FGs which will direct the reaction



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

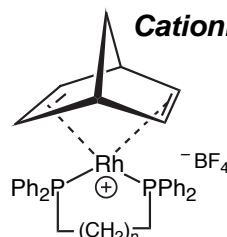
H. Thompson & Co-workers, *J. Am. Chem. Soc.* **95**, 838 (1973)

The first rational attempt to associate catalyst with substrate:

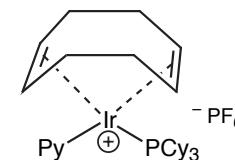


Thompson & Coworkers, *J. Am. Chem. Soc.* **97**, 6232 (1974)

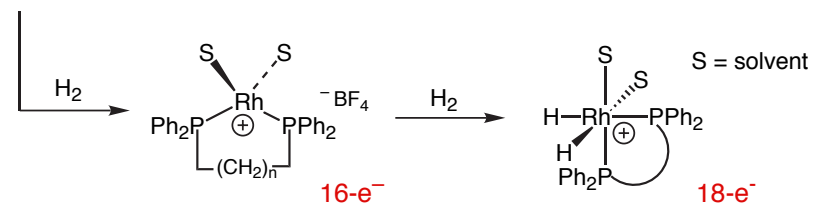
Cationic Hydrogenation Catalysts



Schrock & Osborne,
J. Am. Chem. Soc. **91**, 2816 (1969)

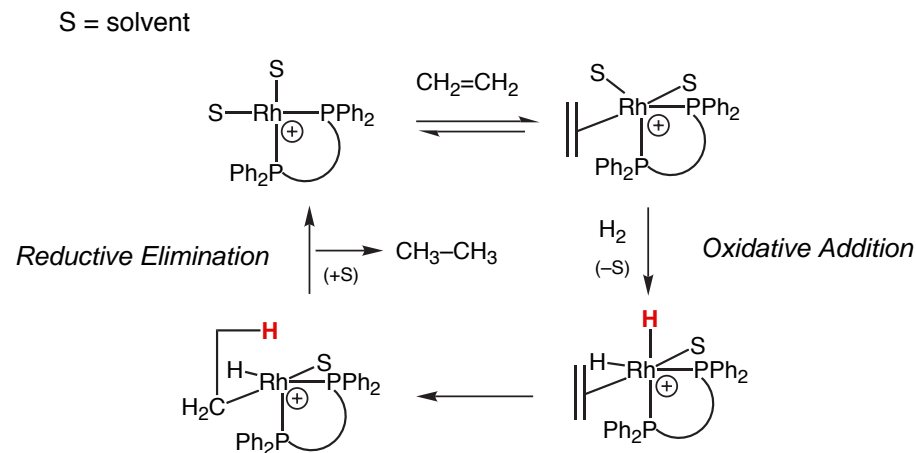


R. Crabtree
J. Organomet. Chem. **168**, 183 (1979)

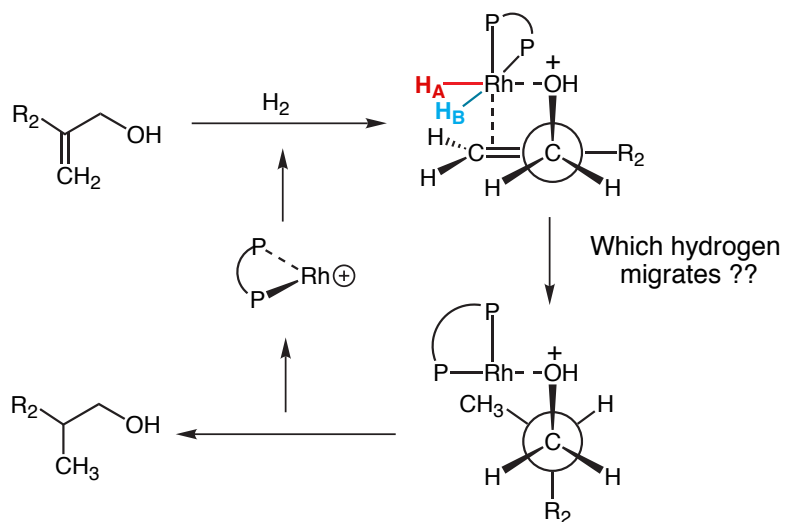
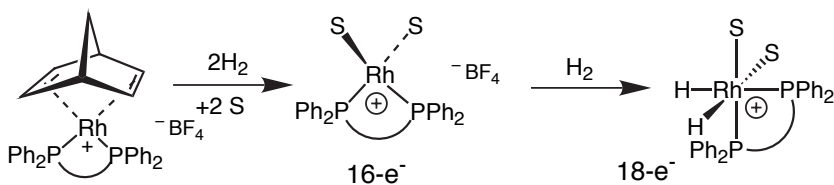


Rh(+I): d8

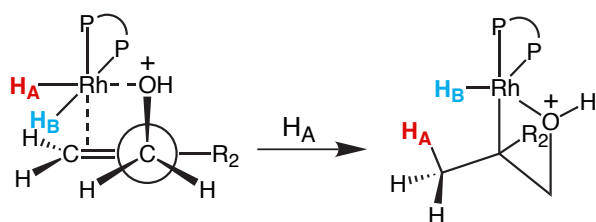
Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.



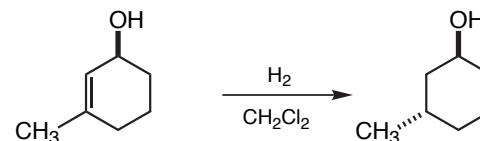
Mechanism of Hydrogenation Cationic Rhodium-(I) Catalysts.



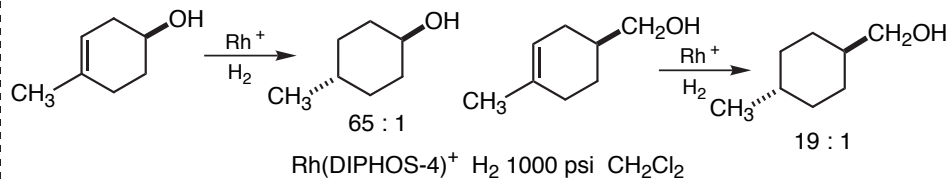
A potential stereoelectronic effect



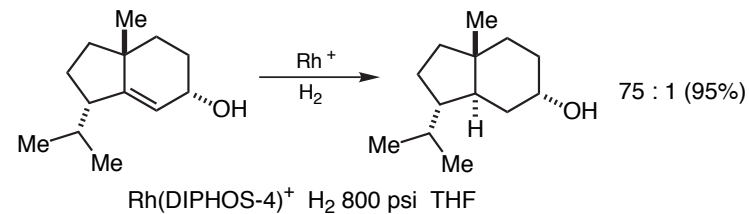
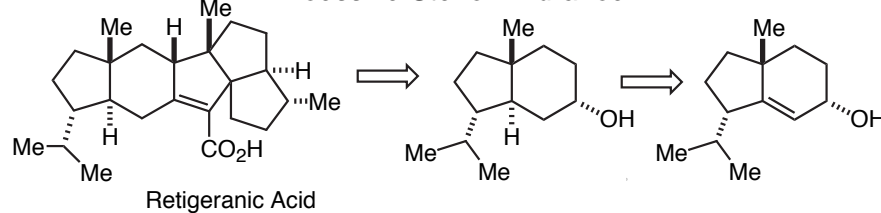
That H atom lying parallel to the π -system (H_A) should migrate preferentially if the dihydride is an intermediate.

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%)

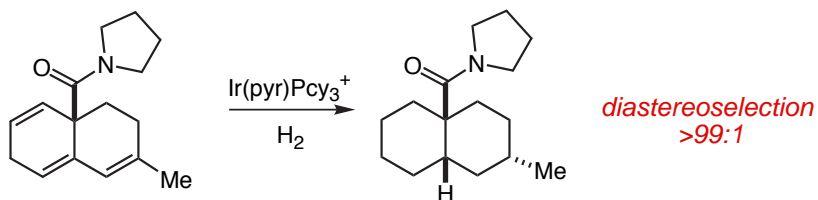
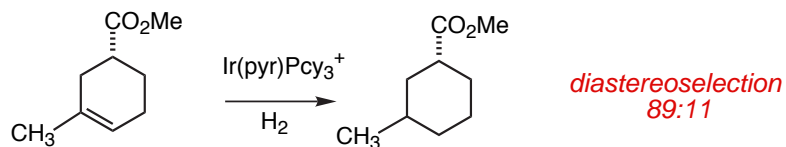
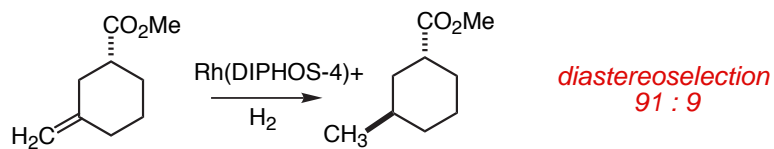


Excessive Steric Hindrance

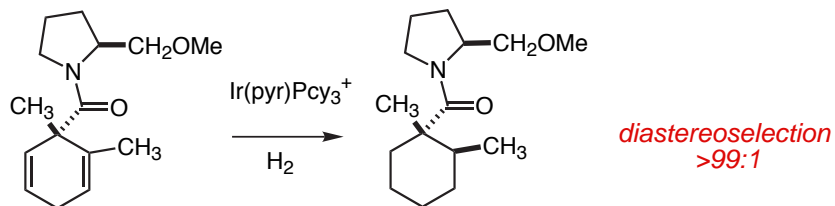
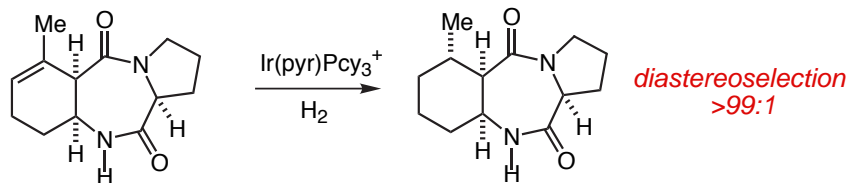


THF is important to success of rxn to buffer the Lewis acidity of the catalyst which causes elimination of ROH under normal conditions

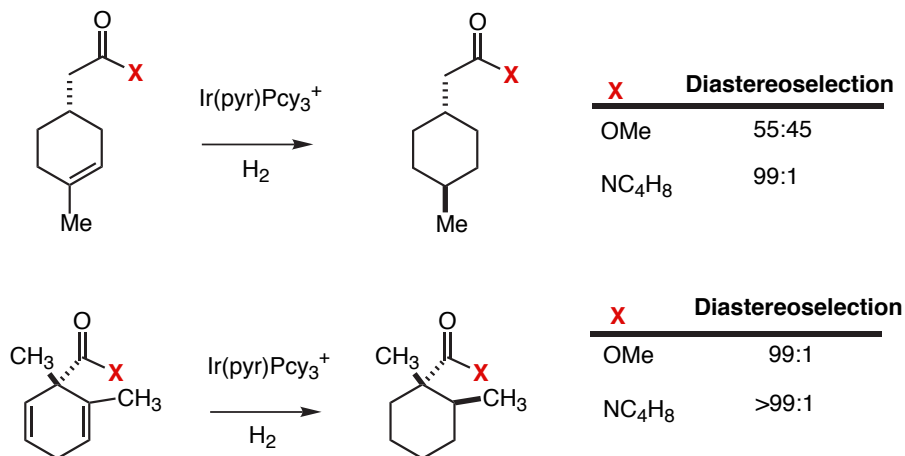
Polar functional groups other than OH may also direct the process



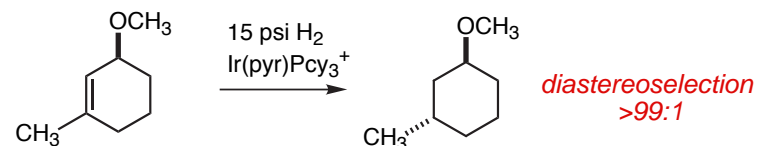
J.M. Brown and S.A. Hall, *J. Organomet. Chem.*, **1985**, 285, 333.



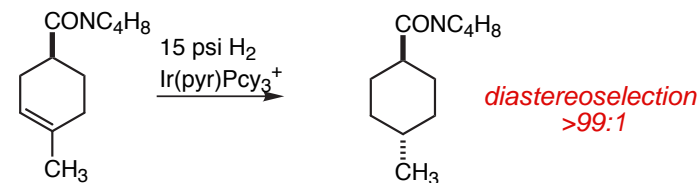
A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, 50, 5907.



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

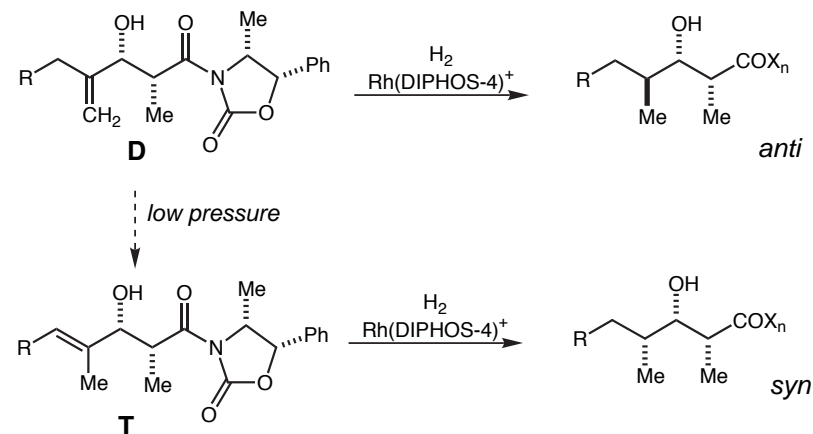
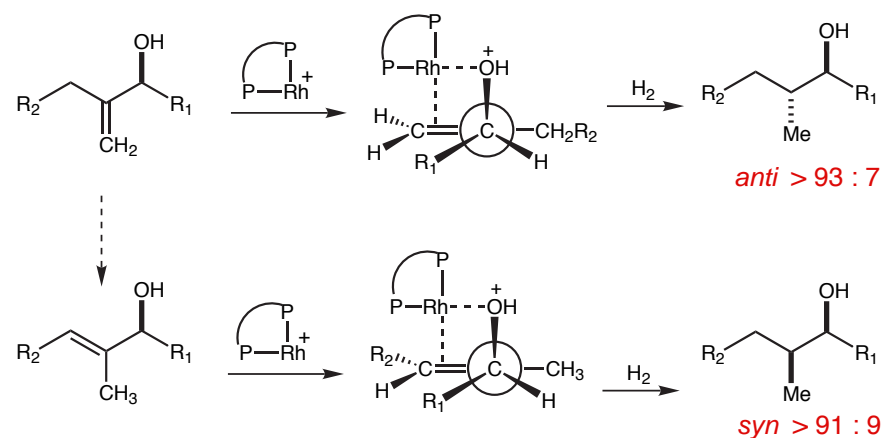
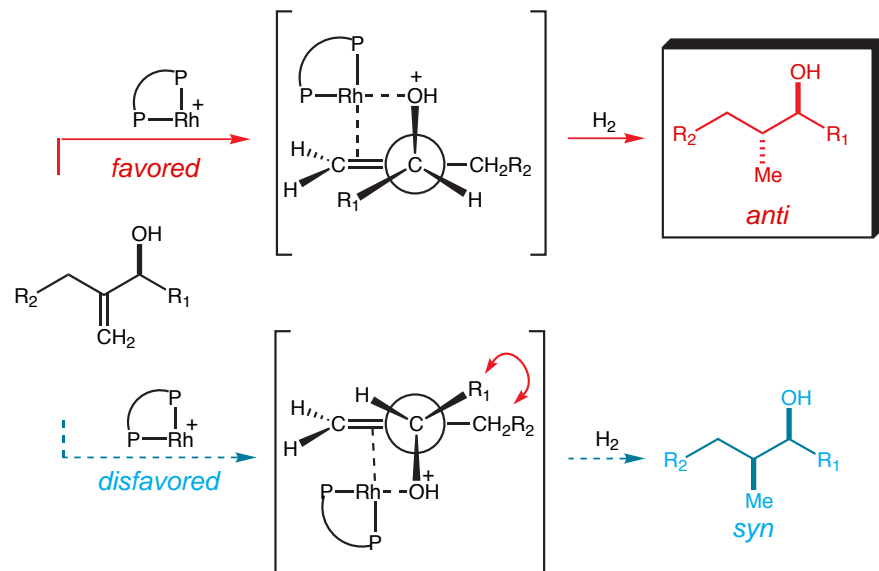


R.H. Crabtree and M.W. Davis, *J. Org. Chem.*, **1986**, 51, 2655.



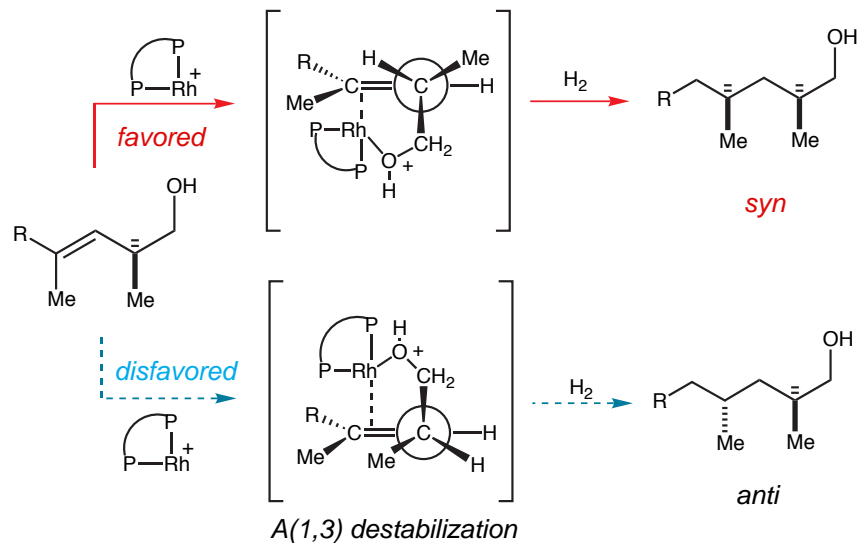
A.G. Schultz and P.J. McCloskey, *J. Org. Chem.*, **1985**, 50, 5907.

Acyclic Allylic Alcohols

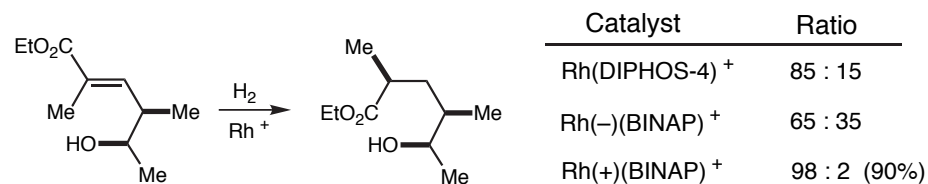
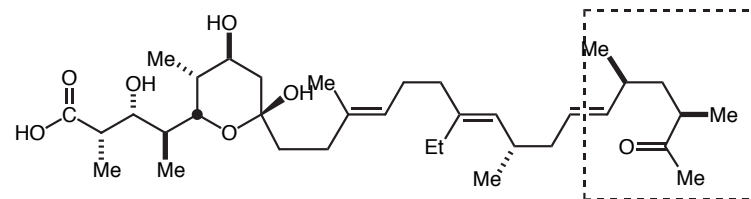
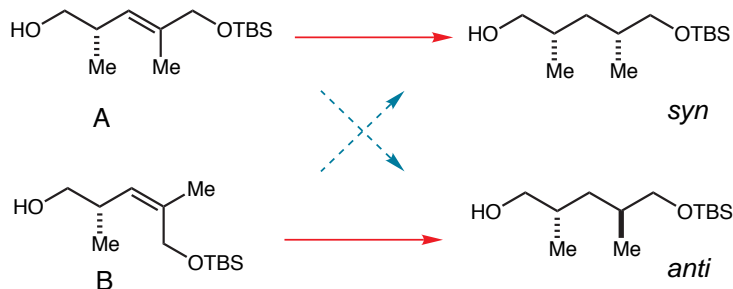


Hydroxy-Olefin	Anti : Syn Ratio		
	15 psi H ₂	640 psi H ₂	
D	R = CH ₃	25 : 75 (23%)	93 : 7
	R = (CH ₃) ₂ CH	52 : 48 (35%)	94 : 6
	R = Ph	71 : 29 (-)	93 : 7
T	R = CH ₃	13 : 87 (6%)	9 : 91
	R = (CH ₃) ₂ CH	12 : 88 (8%)	8 : 92
	R = Ph	21 : 79 (-)	6 : 94

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

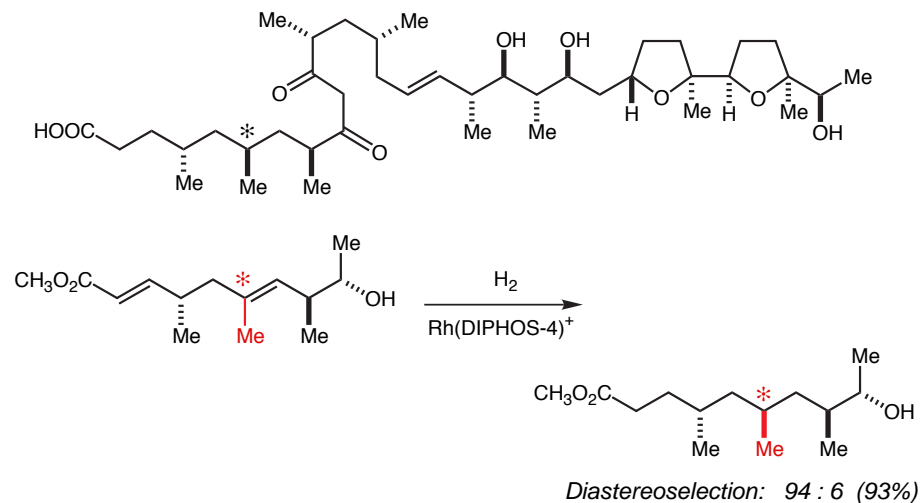
Homoallylic Alcohols Evans, Morrissey *Tetrahedron Lett.* **26** 6005 (1985)

The Premonensin Synthesis

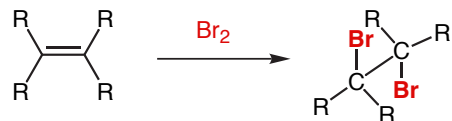
Evans, DiMare, *JACS*, **1986**, *108*, 2476)

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

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** .

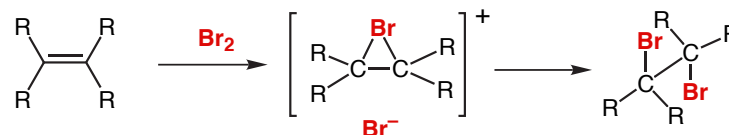
- Substituent Effects on Bromination Rates

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
cis- $\text{CH}_3\text{CH}=\text{CHCH}_3$	2620
trans- $\text{CH}_3\text{CH}=\text{CHCH}_3$	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

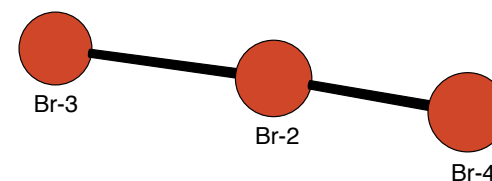
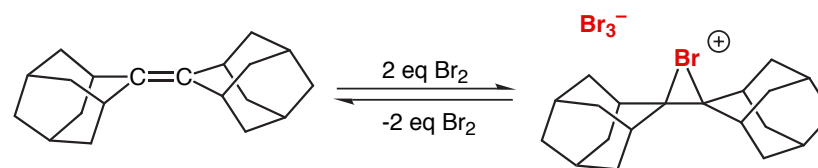
- Stereochemical outcome versus structure (Br_2 in HOAc @ 25°)

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

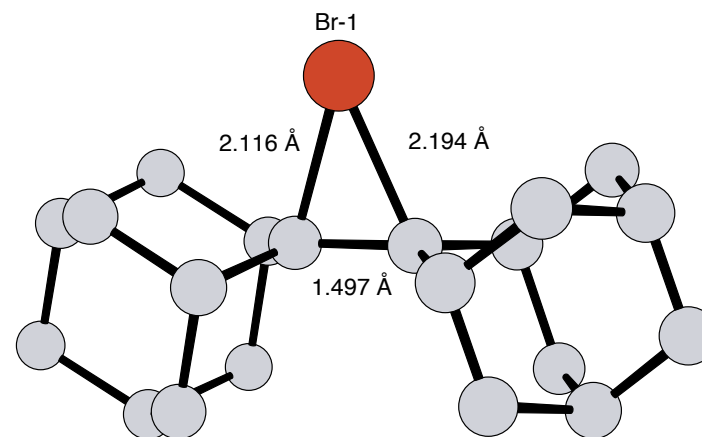
- Bromonium ion origin of the anti (trans) selectivity first suggested by Roberts, *JACS* **1937**, 59, 947



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

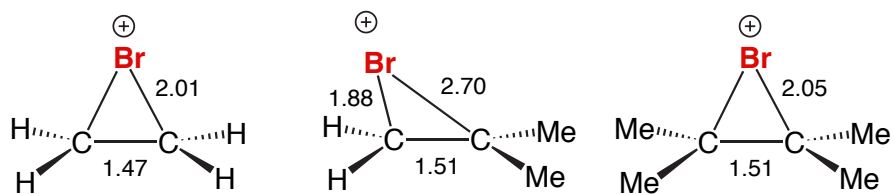


X-ray structure



- Calculated Geometries of Substituted Bromonium Ions
Ruisse, *Chem Commun.* **1990**, 898

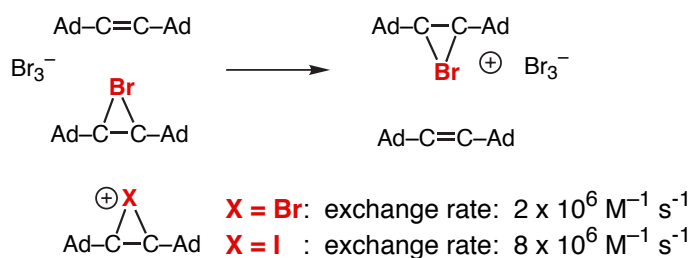
More recent calculations: Sigalas, *Tetrahedron* **2003**, 59, 4749



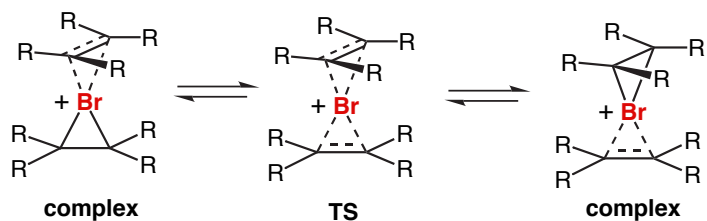
Note; the C-Br bond lengths in previous X-ray structure are 2.116 Å.

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

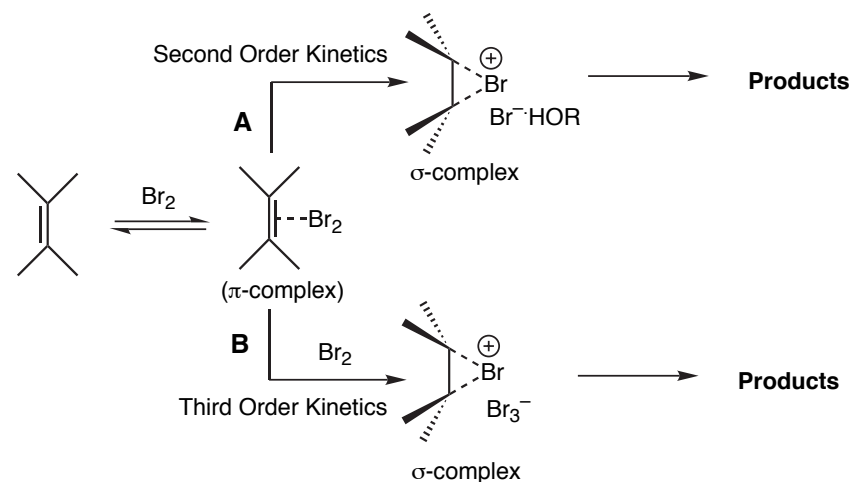
Unprecedented until 1991 (Bennet, *JACS* **1991**, 113, 8532)



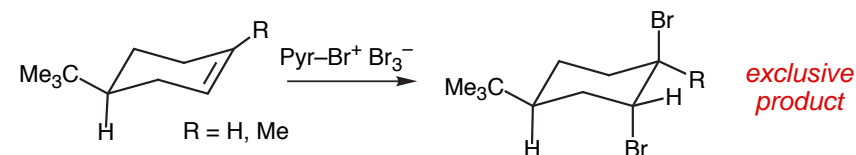
There is an intermediate in the halogen transfer (ab initio calcs):



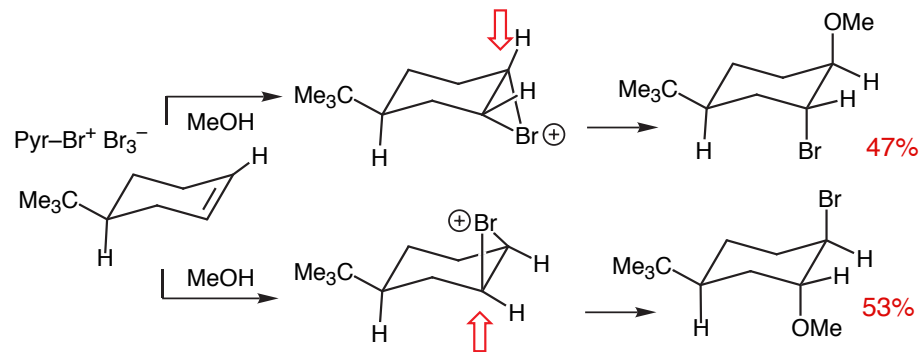
Overall Reaction Mechanism



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



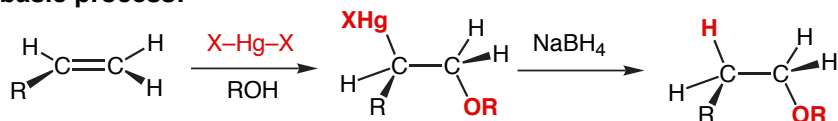
Di axial opening of bromonium ions may be viewed as an extension of the **Furst-Plattner Rule** for epoxide ring opening (**Lecture-3**).



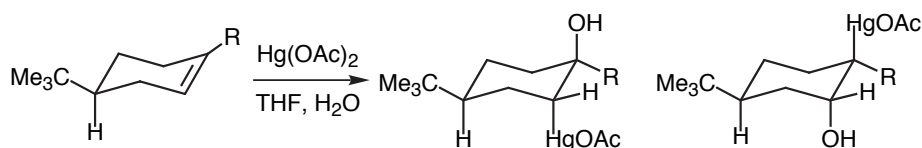
It appears that bromine attack from both olefin faces occurs with near equal probability.

Oxymercuration Pasto, JACS 1970, 92, 7480

The basic process:

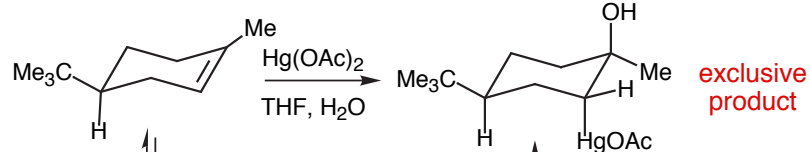


Kinetics: Halpern, JACS 1967, 89, 6427 Reduction: Pasto, JACS 199, 91, 719
 Overview: Brown, JOC 1981, 46, 3810.

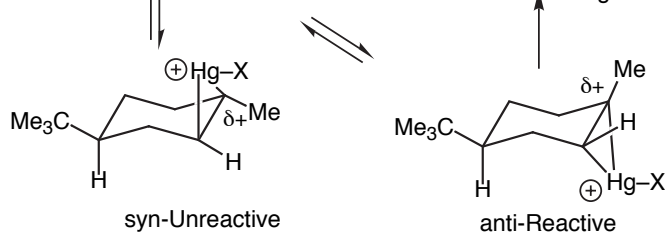
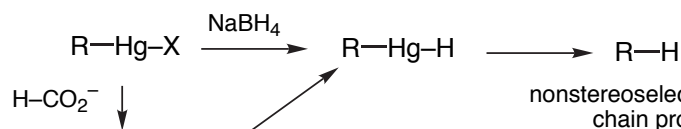
Oxy-Mercuration & bromination follow identical pathways (Pasto)

R = H 41% 48%

R = Me 100%



exclusive product

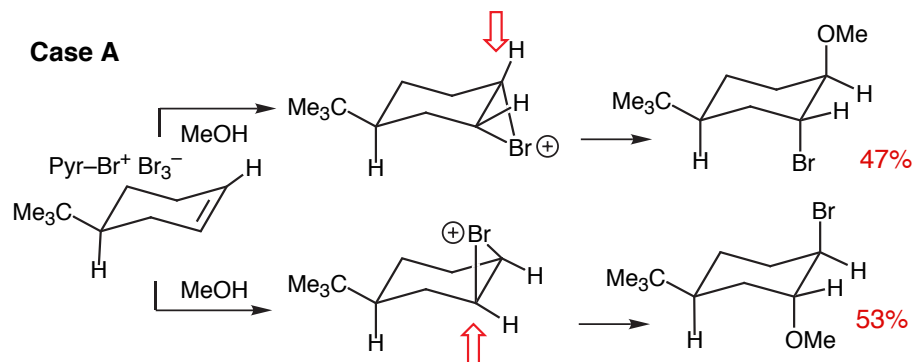
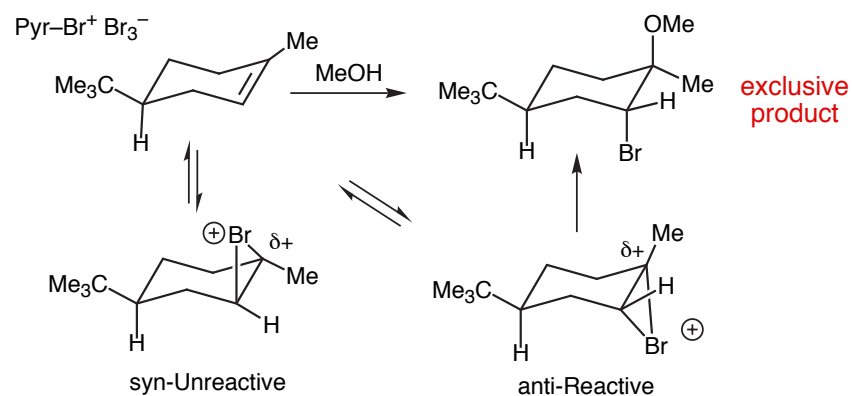
**Reduction of the Hg-C bond**

Formate is an excellent source of hydride ion for late transition and heavy main-group metals

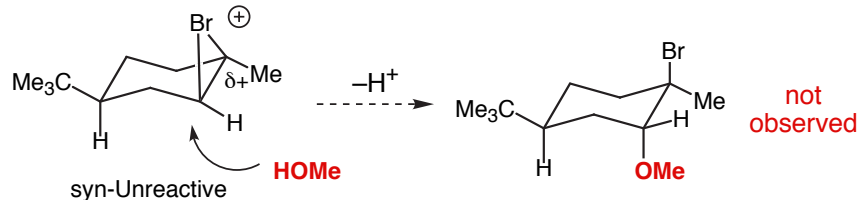
9-10-oxymercuration-1 10/3/03 8:21 AM

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

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

Case A**Case B**

exclusive product



not observed

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

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 10

Olefin Addition Reactions-3

- 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**)

D. A. Evans

Monday,
October 3, 2003

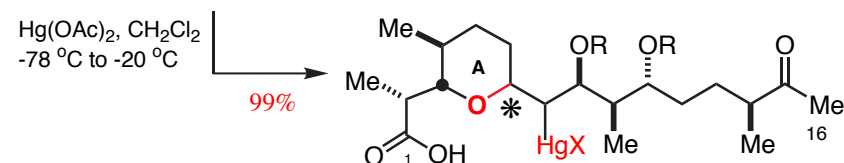
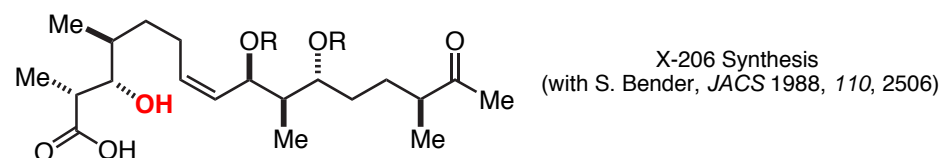
Bromonium Ions or β -Bromocarboxocations in Olefin Bromination. A Kinetic Approach to Product Selectivities

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

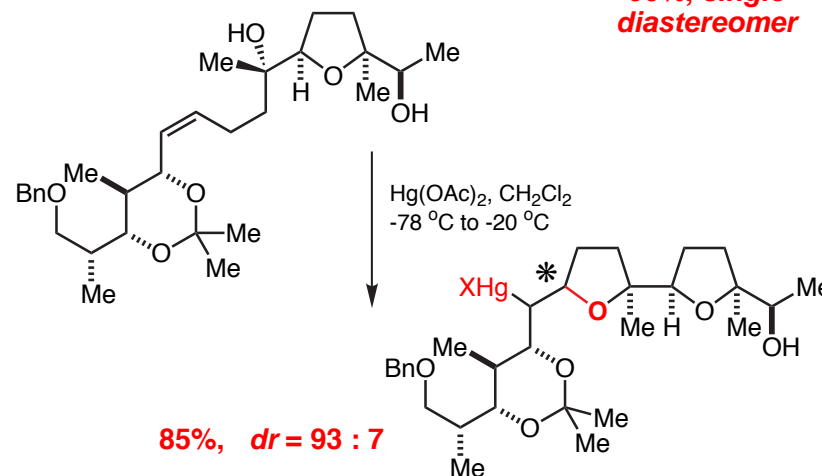
Investigation of the early Steps in Electrophilic Bromination through the Study of the Reaction of Sterically Encumbered Olefins

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

■ Predict stereochemical outcome



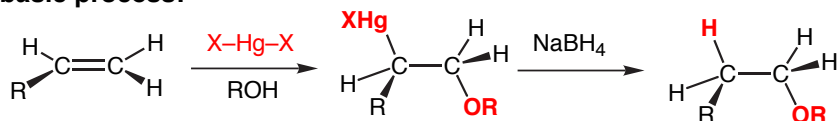
99%, single diastereomer



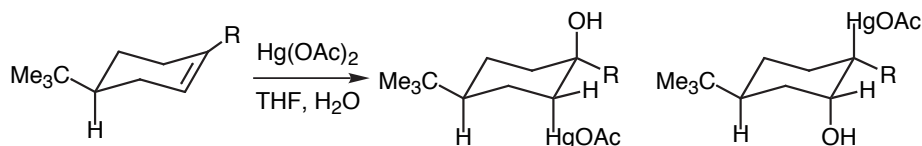
Ionomycin Synthesis
(with Dow & Shih, *JACS* 1990, 112, 5290)

Oxymercuration Pasto, JACS 1970, 92, 7480

The basic process:

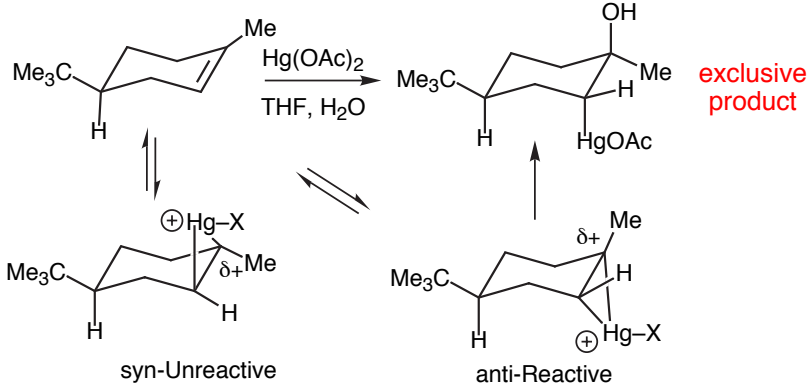
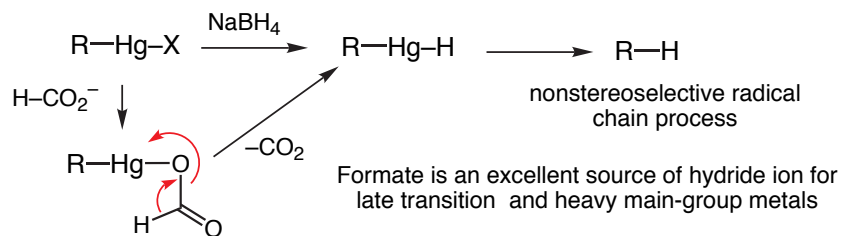


Kinetics: Halpern, JACS 1967, 89, 6427 Reduction: Pasto, JACS 199, 91, 719
 Overview: Brown, JOC 1981, 46, 3810.

Oxy-Mercuration & bromination follow identical pathways (Pasto)

R = H 41% 48%

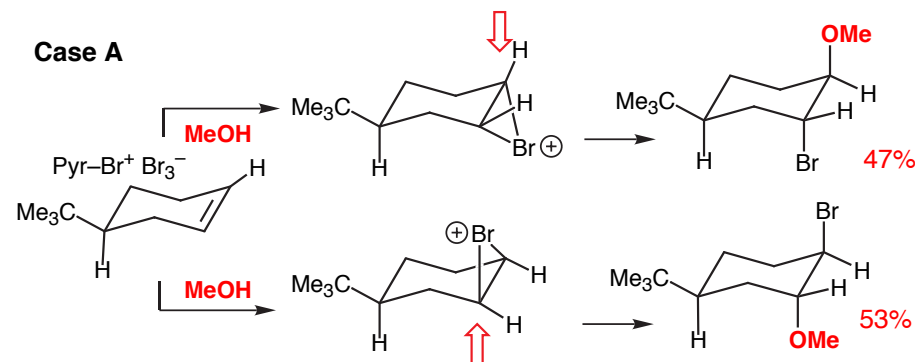
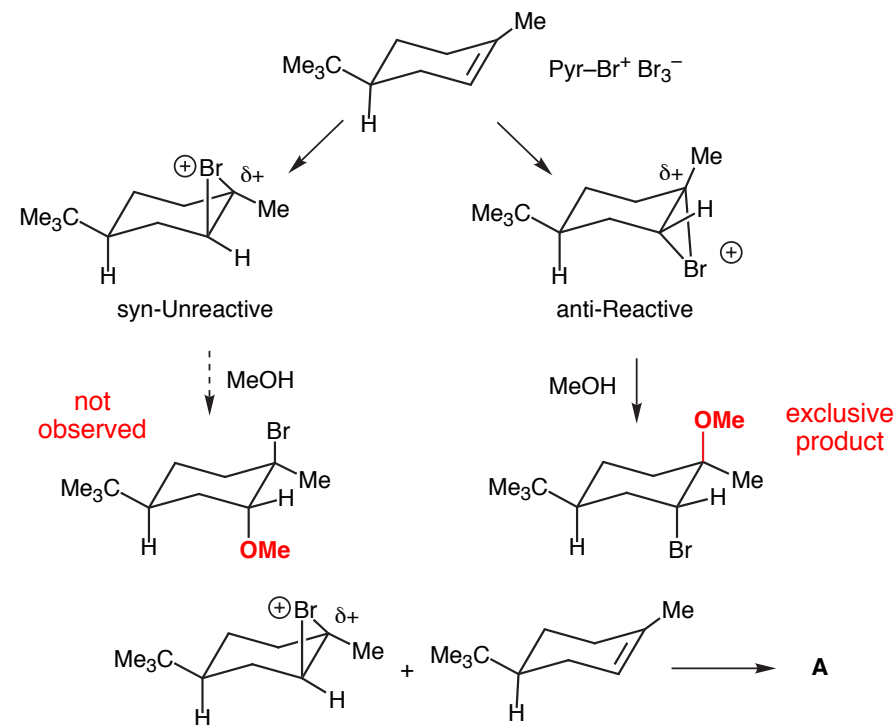
R = Me 100%

**Reduction of the Hg-C bond**

10-01-oxymercuration-1 10/5/03 11:20 AM

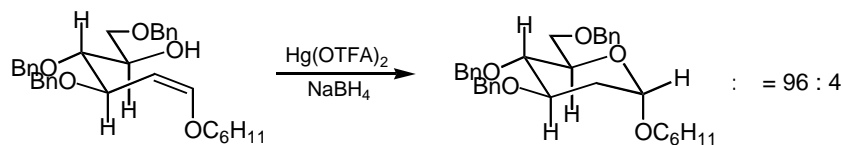
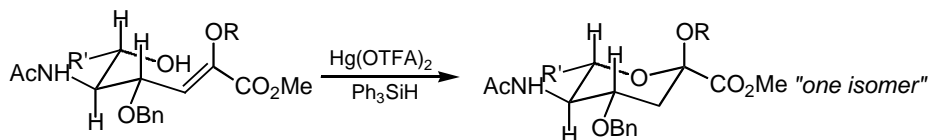
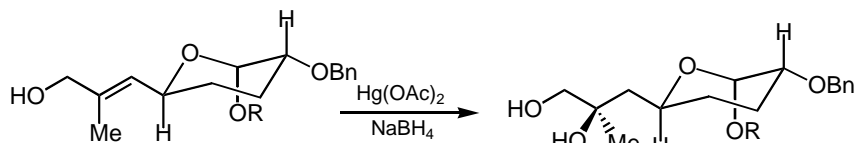
Bromination of Cyclohexene Derivatives Pasto, JACS 1970, 92, 7480

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

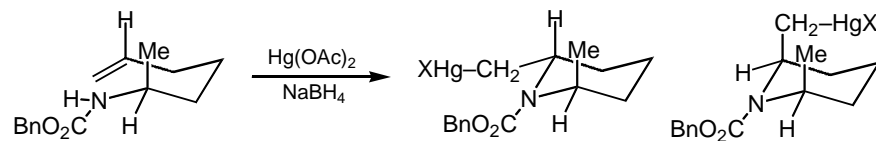
**Case B**

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

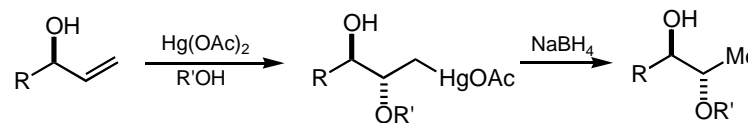
Mukaiyama, *Chem. Lett.* **1981**, 683Sinay, *Tet. Lett.* **1984**, 25, 3071Isobe, *Tet. Lett.* **1985**, 26, 5199

Kinetic vs Thermodynamic control:

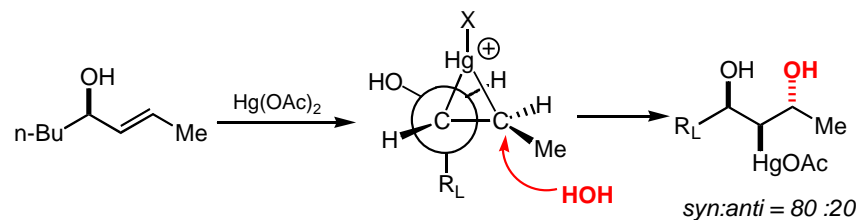
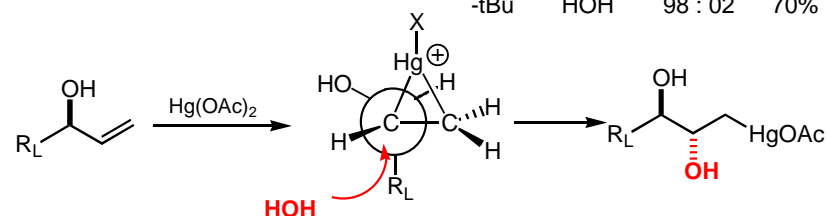
Harding, *JOC* **1984**, 49, 2838Hg(OAc)₂: short rxn times : 40 : 60Hg(OTFA)₂: longer rxn times : 2 : 98

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

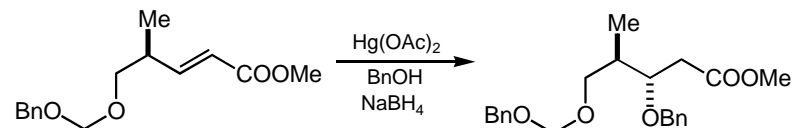
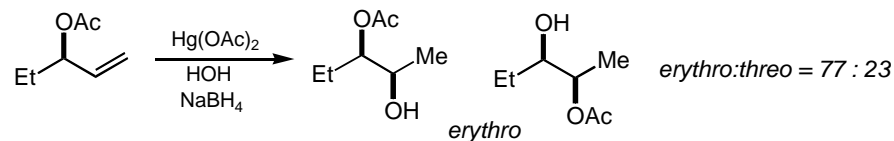
Acyclic allylic alcohols:



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%

Giese, *Tet. Lett.* **1985**, 26, 1197Chamberlin, *Tetrahedron* **1984**, 40, 2297

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

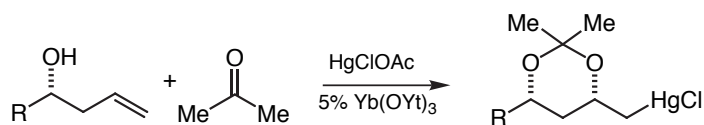
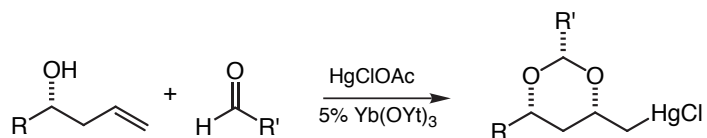
Seebach, *JACS* **1983**, 105, 7407

diastereoselection = 83 : 17 (79%)

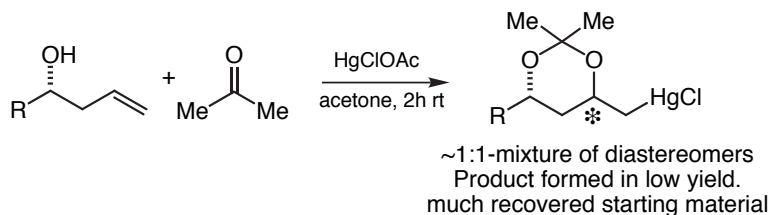
Oxymercuration via Hemiketals & Hemiacetals

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

■ General Reaction: diastereoselection >10:1

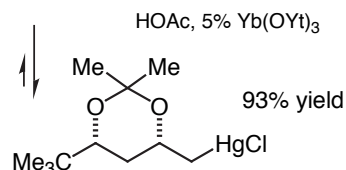
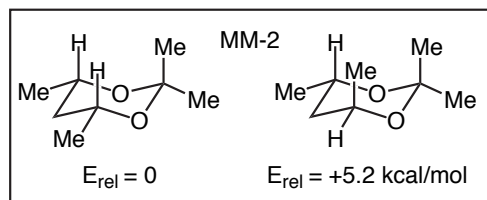
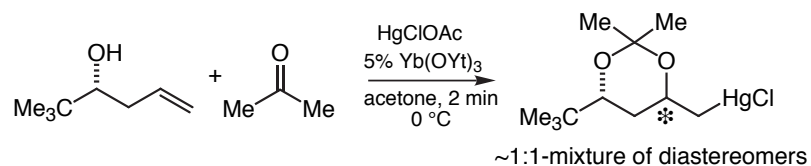


■ Mechanistic Observations:



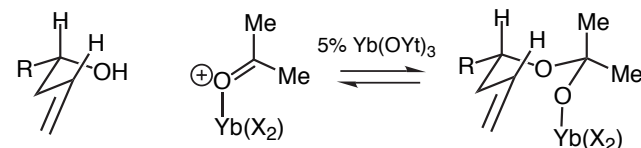
Lewis acid addends were surveyed. the logic for this step was two-fold:

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

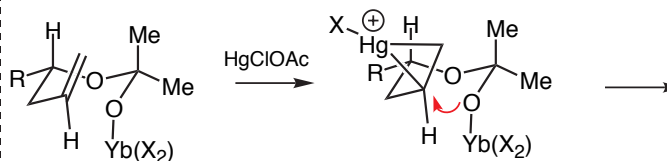
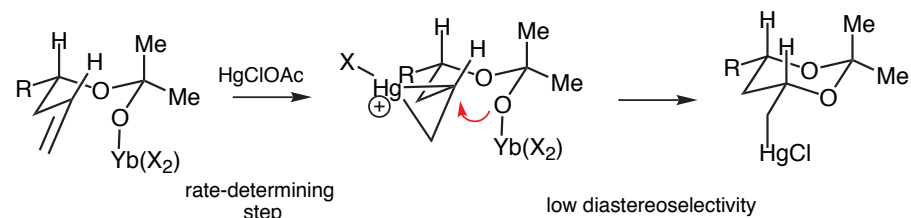


Proposed Mechanism

■ Lewis acid catalyzes formation of hemiketal

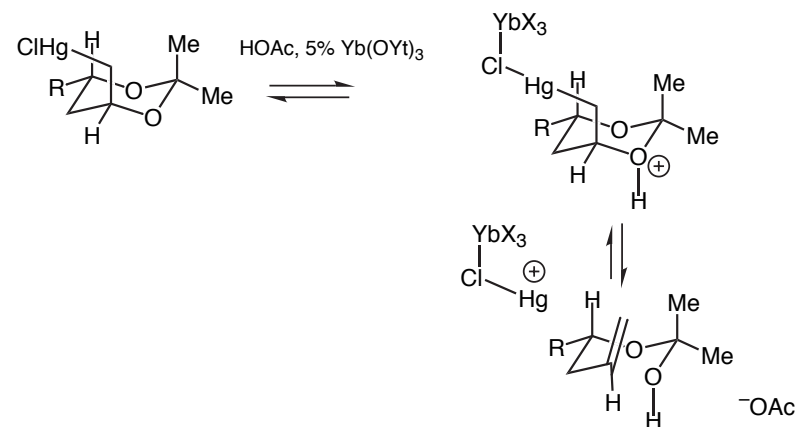


■ The Oxymercuration Step (Kinetic Phase)

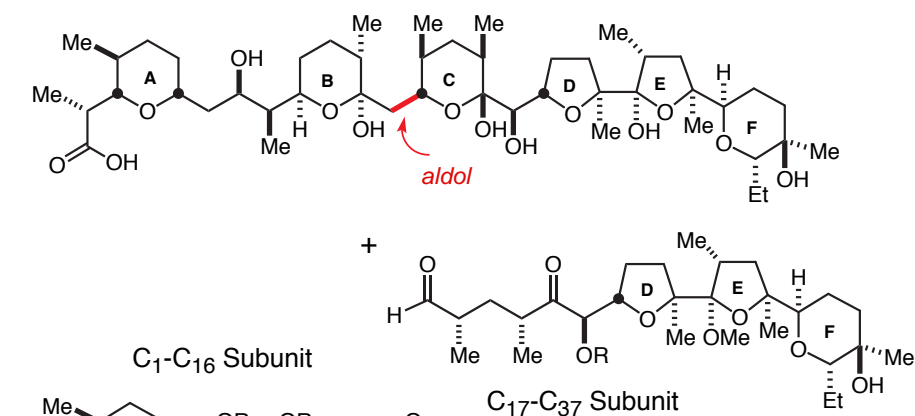


Leighton presumes that mercurium ion formation is rate-determining under kinetic conditions.

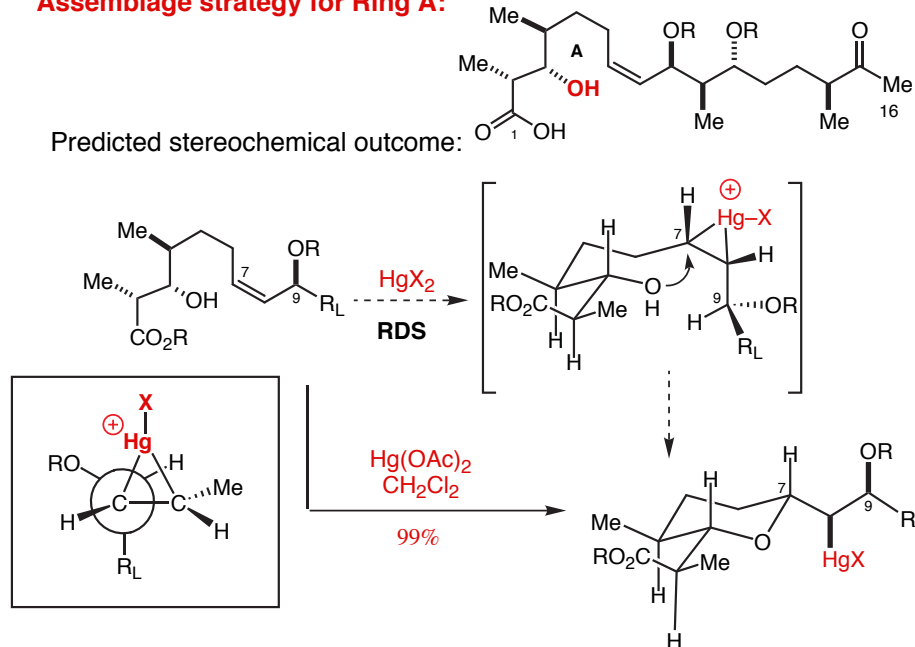
At higher temperatures and longer reaction times the products are shown to interconvert.



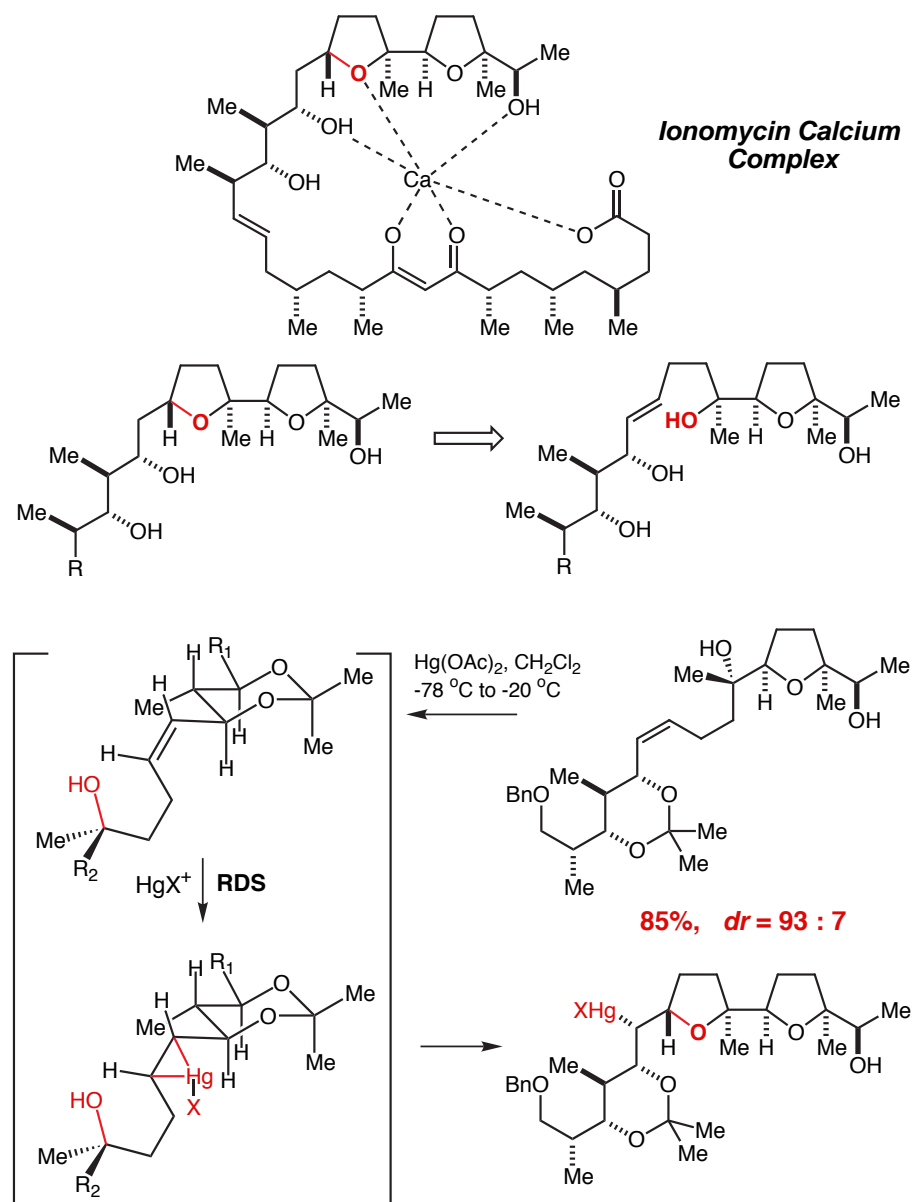
X-206 Synthesis (with S. Bender, JACS 1988, 110, 2506)



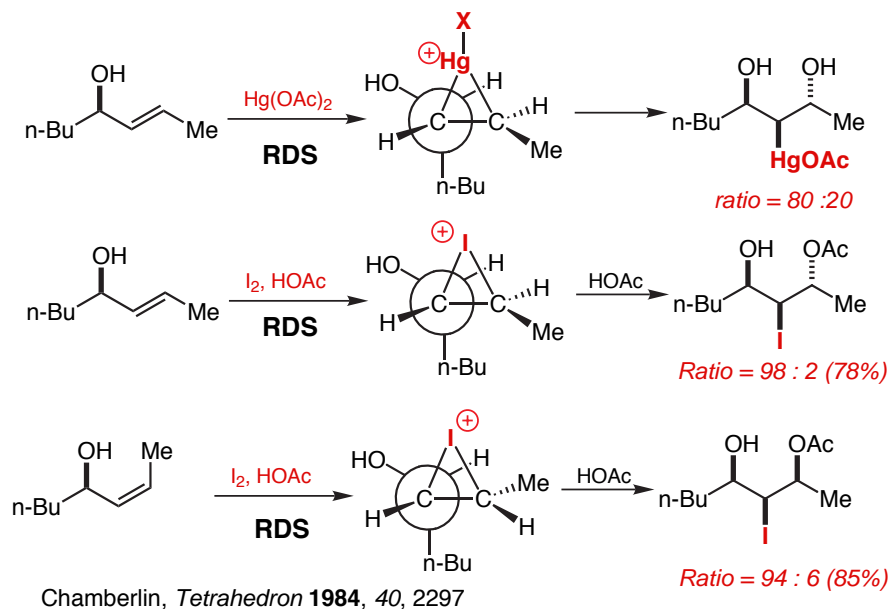
Assemblage strategy for Ring A:



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

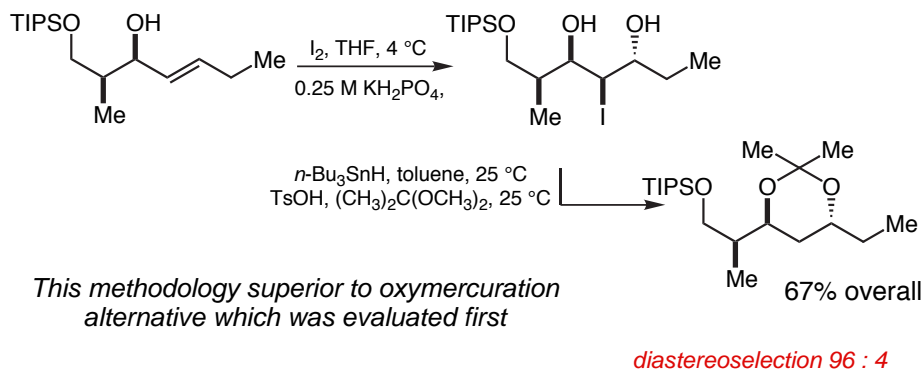


Other electrophilic olefin addition reactions afford the same stereochemical outcome



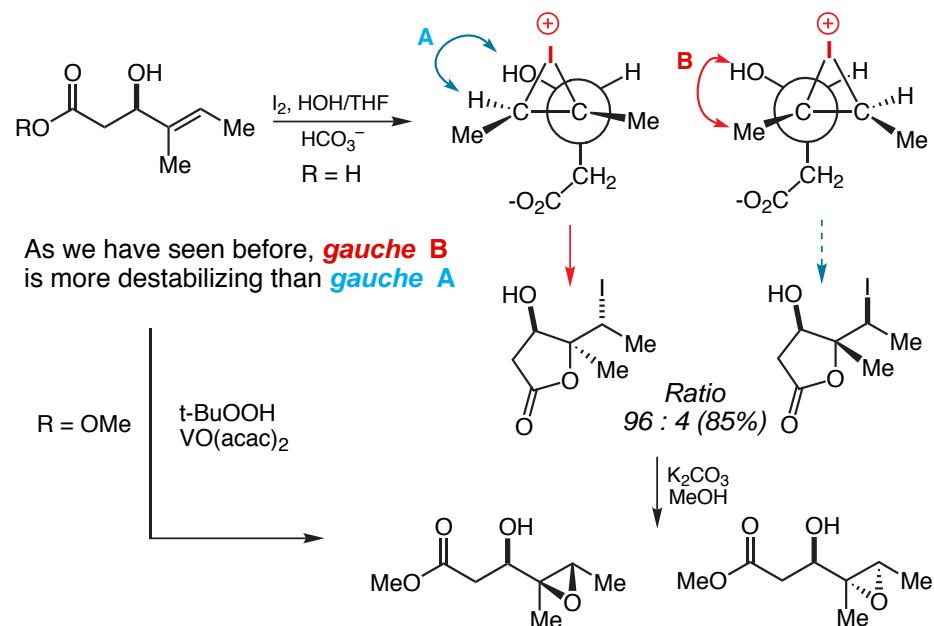
This is an exceptional approach to the creation of either syn or anti 1,3-dioxygen relationships

Evans, Kaldor, Jones, *J. Am. Chem. Soc.* **1990**, *112*, 7001.

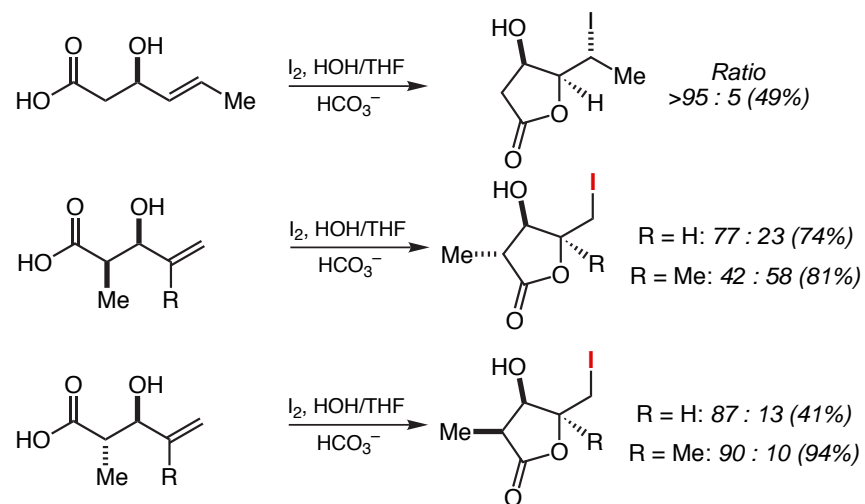


Iodine-induced lactonization is also highly stereoselective

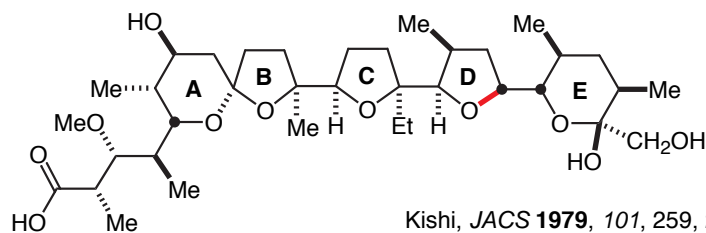
■ Chamberlin (*JACS* **1983**, *105*, 5819)



■ Other cases:

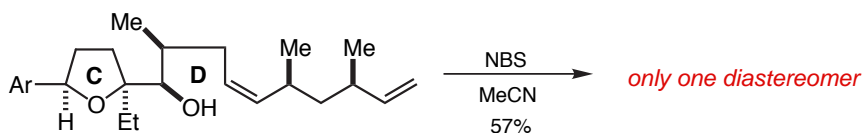


Halogen-induced heterocyclization in the synthesis of monensin

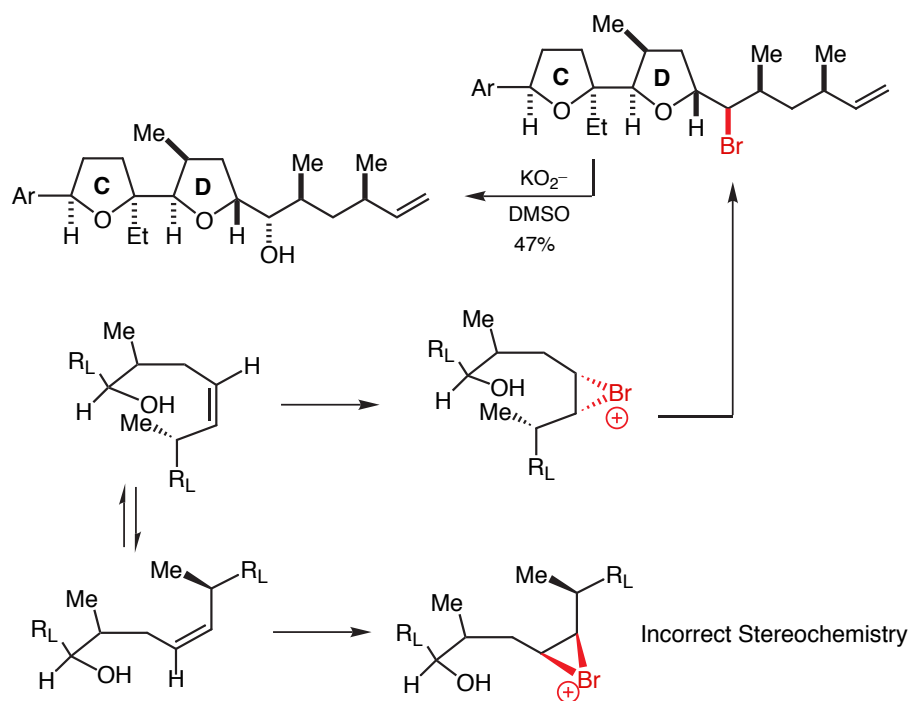


Kishi, *JACS* **1979**, *101*, 259, 260, 262
 Still, *JACS* **1980**, *103*, 2117-2121

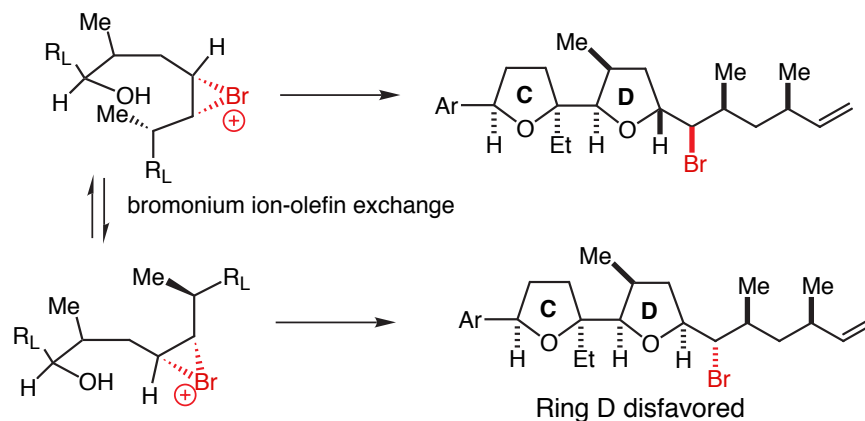
■ The Kishi Ring D Construction:



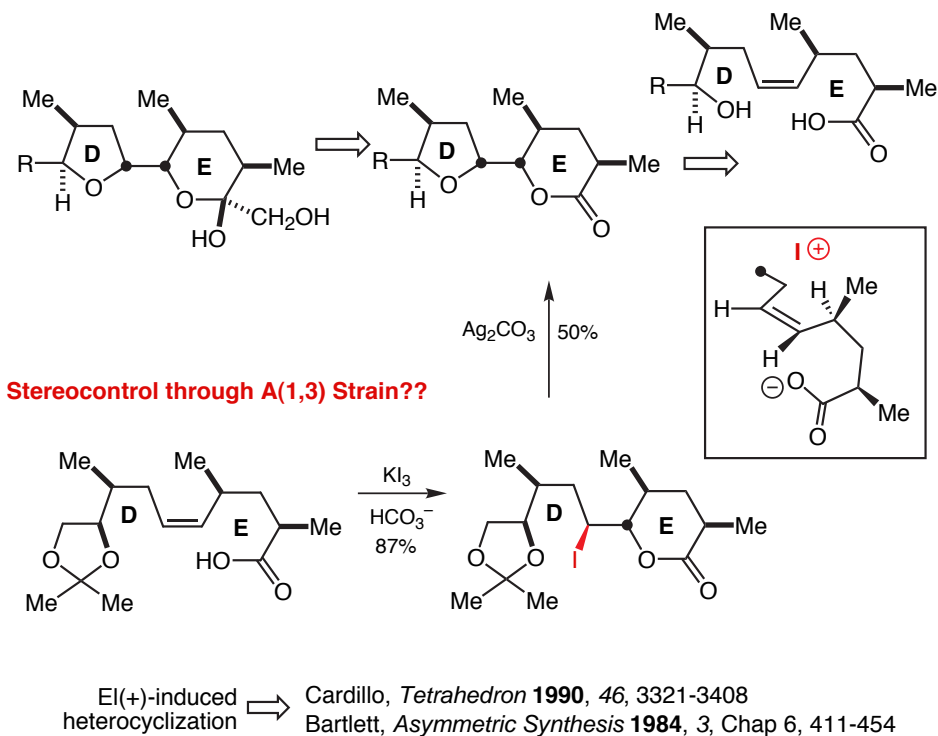
Hypothesis-A: Stereocontrol through A(1,3) Strain??



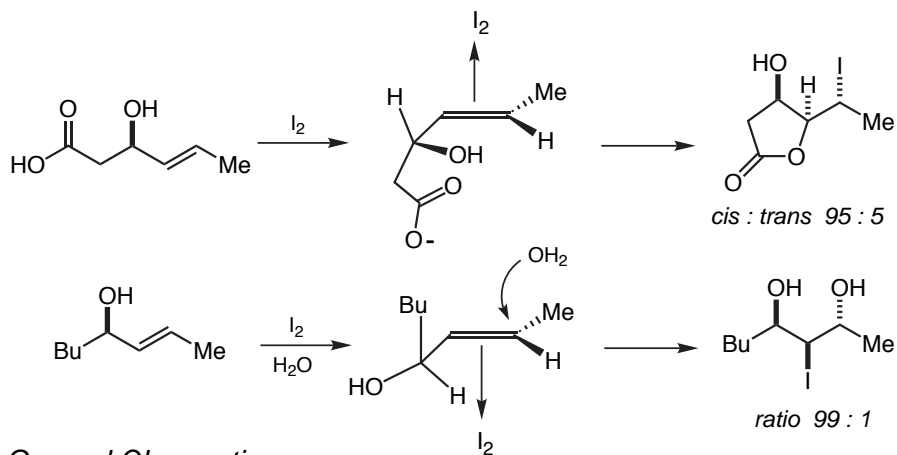
Hypothesis-B: Stereocontrol through Reversal of Bromonium Ion Intermediate



■ The Still Ring E Construction:



- A complete turnover in olefin diastereofacial selectivity is observed when adding *internal* and *external* nucleophiles



General Observation:

For electrophiles that react via onium intermediates (I_2 , Br_2 , $Hg(OAc)_2$, $PhSeCl$), the major diastereomer from electrophile-induced cyclization is opposite to that observed in the analogous intermolecular electrophilic addition.

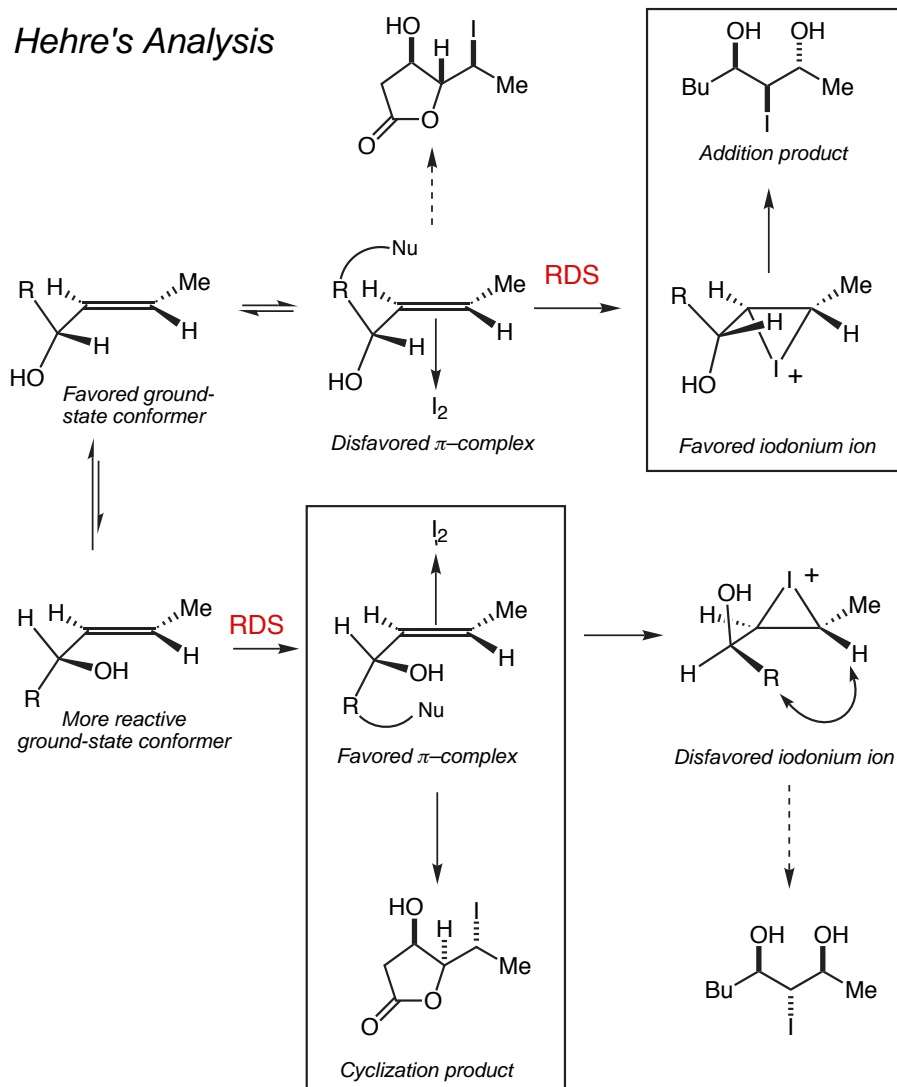
For a review of electrophilic induced olefin cyclization reactions see:
G. Cardillo & M. Orena, *Tetrahedron* **1990**, 46, 3321.

Chamberlin & Hehre's Rationalization

- "Facial preferences in electrophilic addition reactions are *not* invariant with respect to the location of the transition state along the reaction coordinate."
- *Change in diastereoselectivity is a consequence of a change in the rate-limiting step*
 - Addition reactions: Formation of an **onium ion intermediate** (subsequently trapped by a Nu from the medium)
 - Cyclization reactions: Intramolecular attack on a **π -complex** (not an onium ion)
- Analysis of the stereoselectivity of electrophilic addition to chiral olefins:
 1. Relative abundances of conformational minima
 2. *Relative reactivities of the available forms*
 3. Stereoselectivities of the individual conformers

Chamberlin & Hehre, *J. Am. Chem. Soc.* **1987**, 109, 672-677.

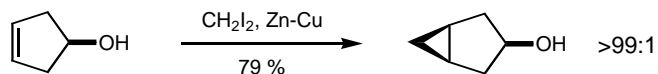
Hehre's Analysis



Houk: Argument for the "inside alkoxy effect" in π -complex formation

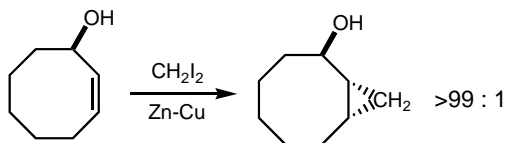
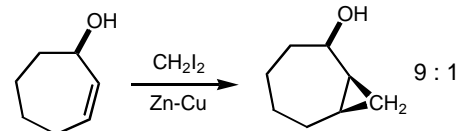
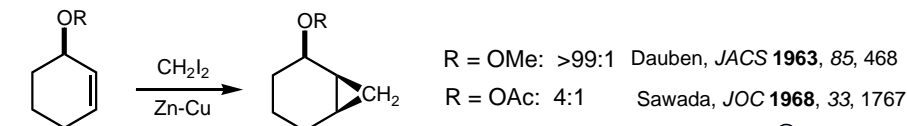
- π -complex cyclizes if R contains a Nu and its formation is rate determining
- Onium ion formation is rate determining in the addition reactions
- "The presence or absence of an internal nucleophile acts to determine the stereochemical outcome of the reaction by modifying the nature (timing) of transition state."

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

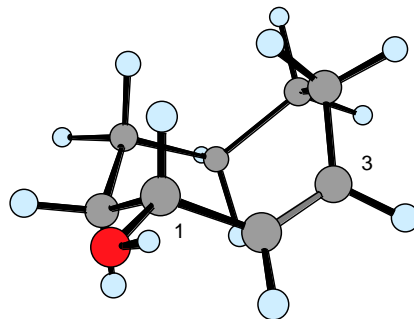


S. Winstein, *JACS* **1959**, *81*, 6523; **1961**, *83*, 3235; **1969**, *91*, 6892

A large rate acceleration relative to simple olefins was observed.



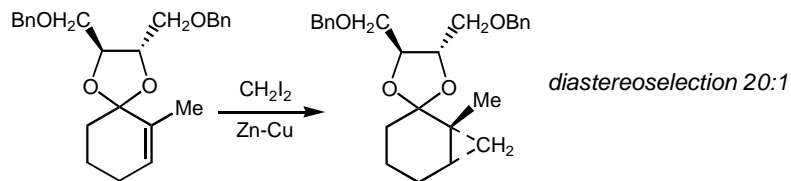
epoxidation also gives anti adduct



O-C₁-C₂-C₃ dihedral = 165°

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

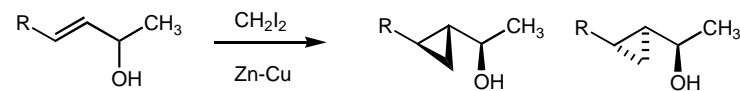
Absolute control of stereochemistry is possible through chiral ketal auxiliaries



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

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

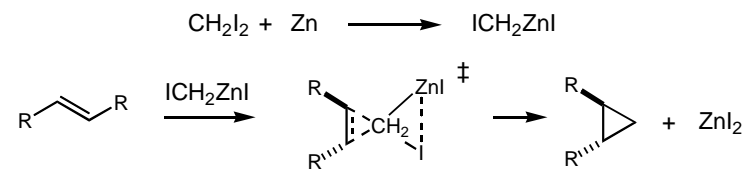
Yamamoto, *Tetrahedron*, **1986**, *42*, 6458



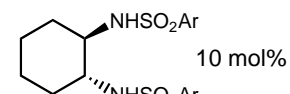
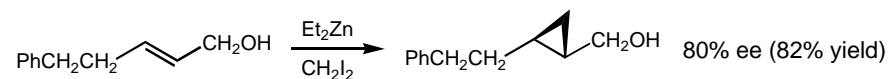
M. Pereyre and Co-workers
J. Chem. Res. (S) **1979**, 179

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

The classical mechanism

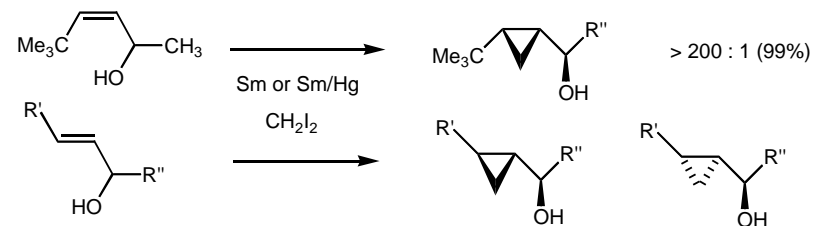


Enantioselective Simmons-Smith Variants: Kobayashi, *Tet. Let.* **1992**, *33*, 2575



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

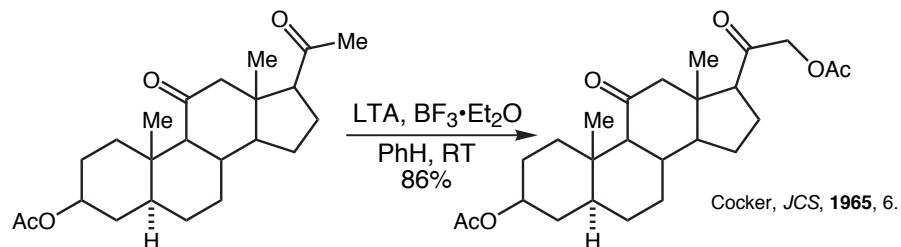
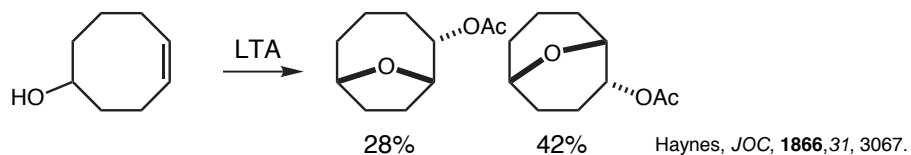
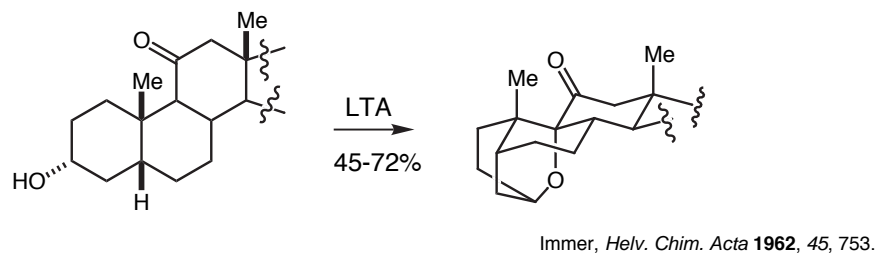
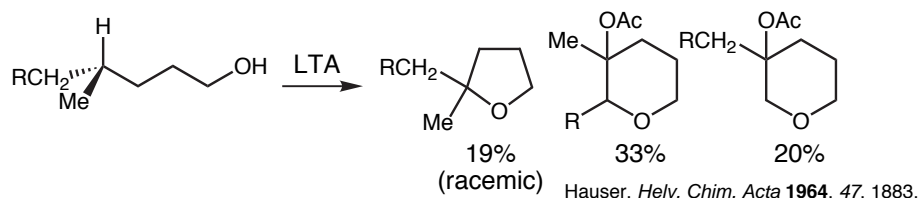
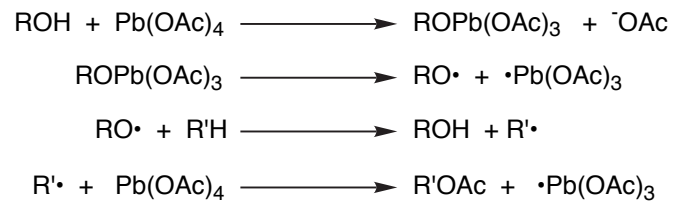


Isolated alkenes and homoallylic alcohols are inert to these reaction conditions.

G. A. Molander and J. B. Etter
J. Org. Chem. **1987**, *52*, 3942

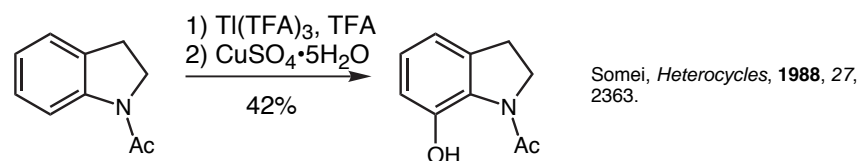
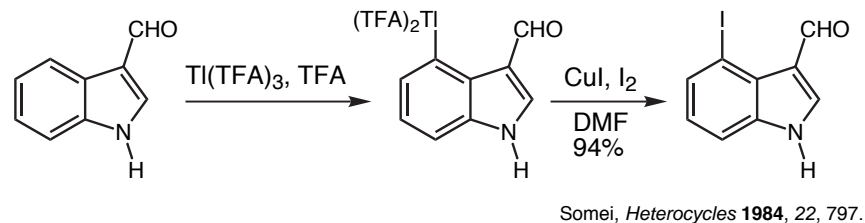
R'	R''	Ratio	
Ph	nBu	1	: 1.4
Ph	iPr	> 200	: 1
Ph	tBu	> 200	: 1
tBu	CH ₃	1	: 5.1
tBu	iPr	> 200	: 1

Radical Lead Tetraacetate Mechanism



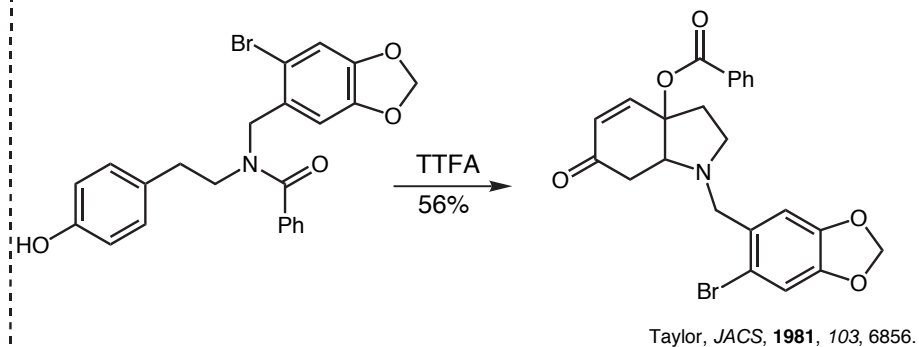
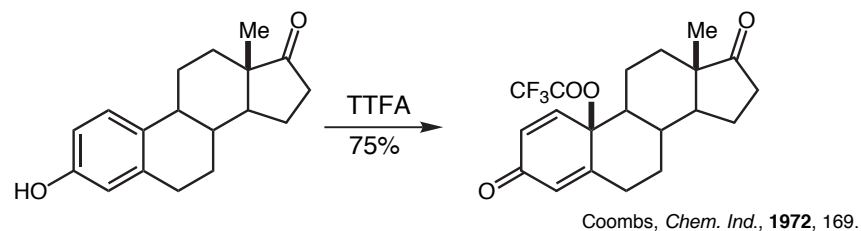
Vinyl and Aryl C-H Oxidations

Thallium

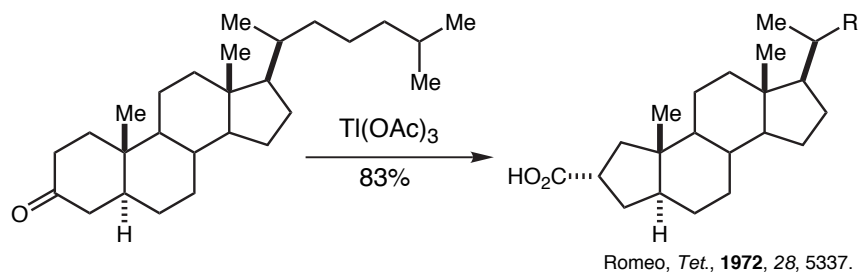
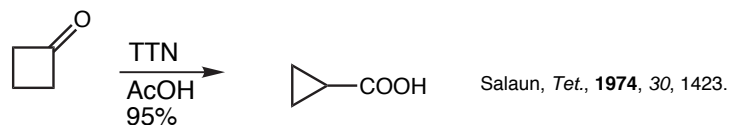
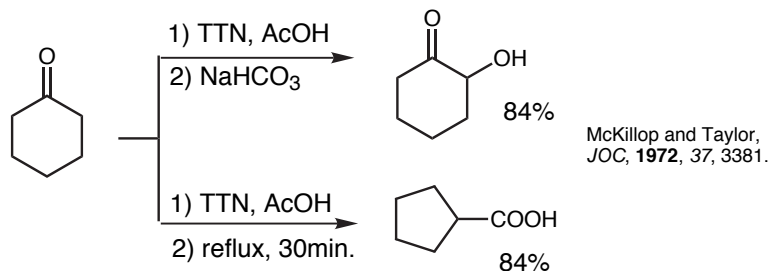
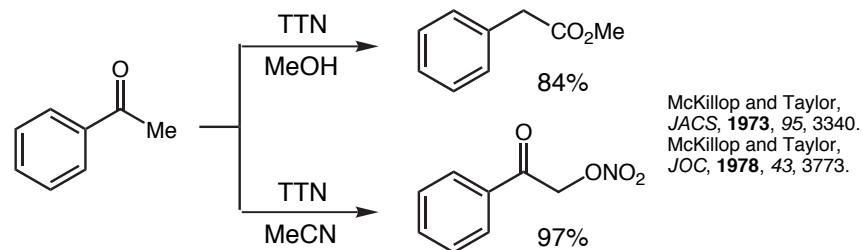


Phenolic Oxidations:

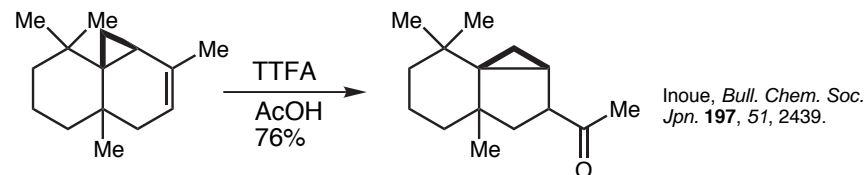
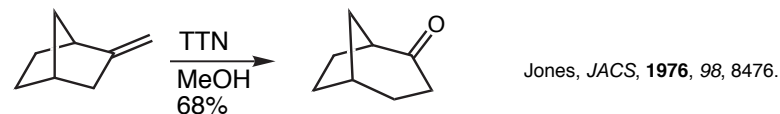
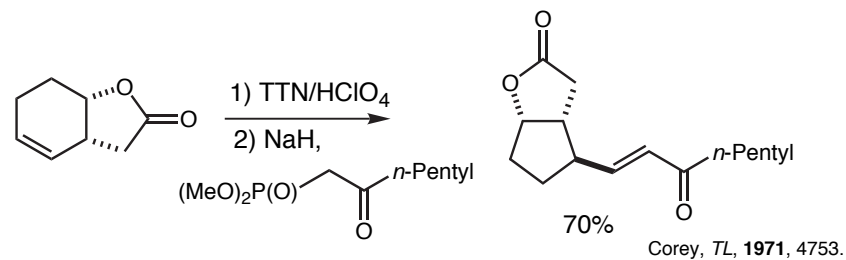
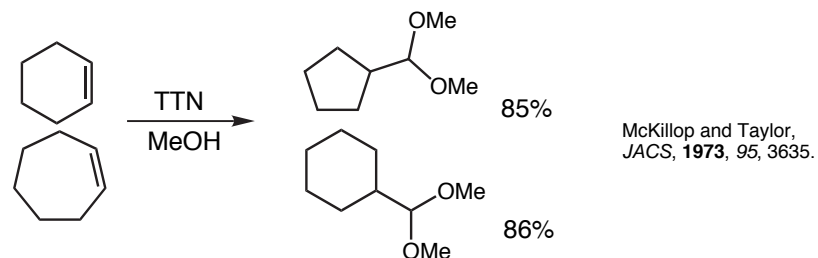
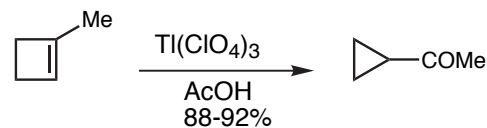
For a review of oxidative aryl couplings, see: Dinsmore, C. Evening Seminar, February 1993.



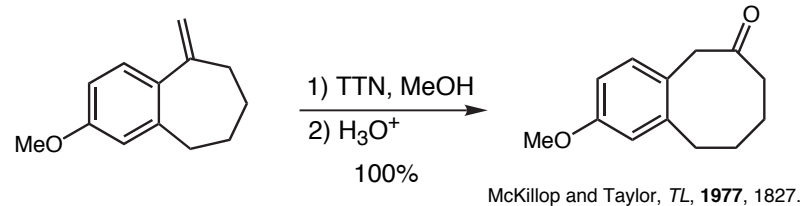
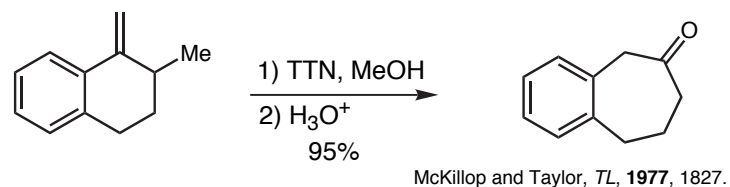
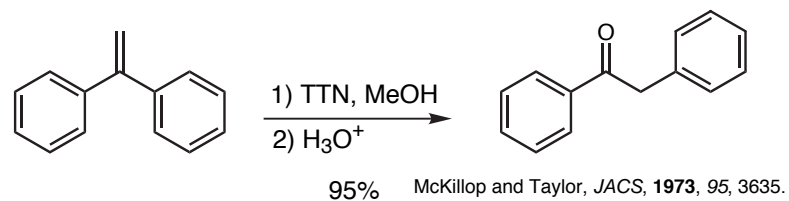
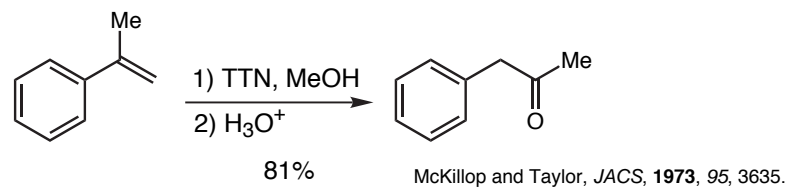
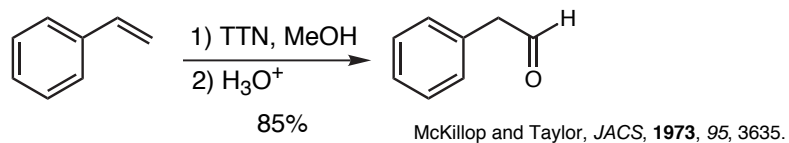
Oxythallation of Ketones (Enols) with Ring Contraction

TTN = $Tl(NO_3)_3$ 

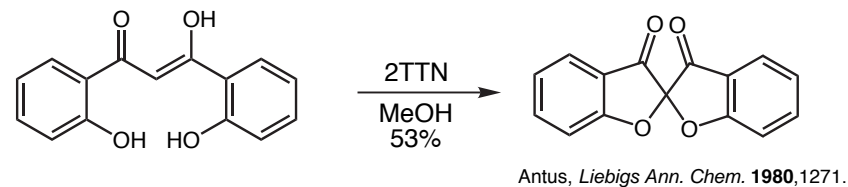
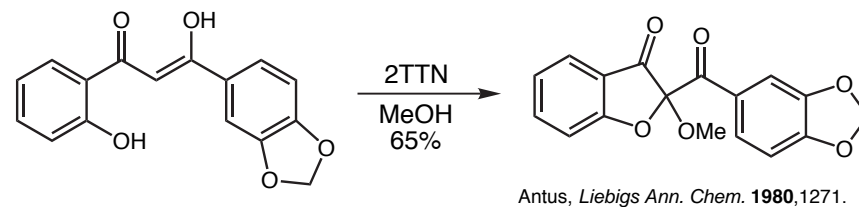
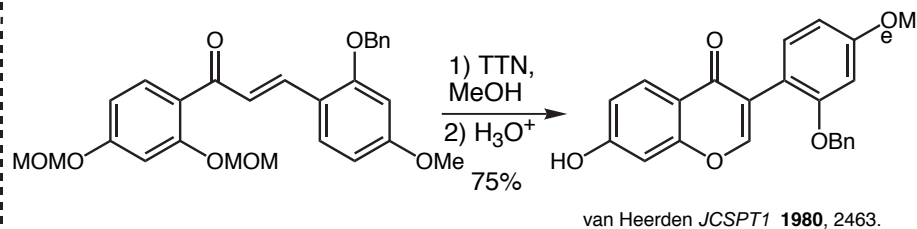
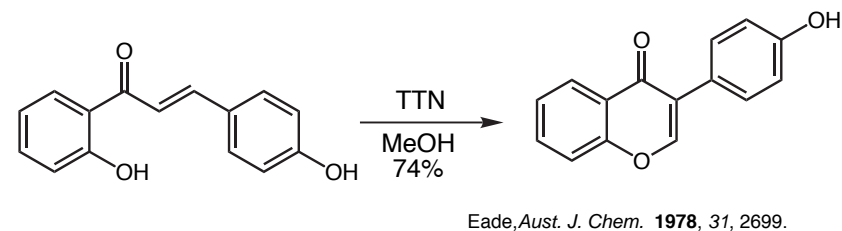
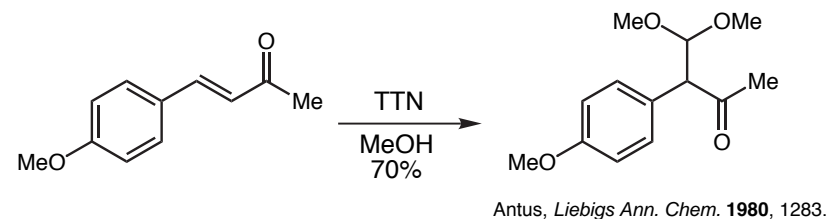
Oxythallation of Double and Triple Bonds



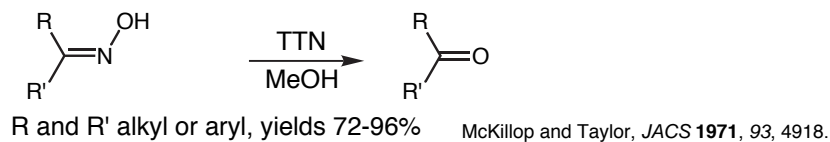
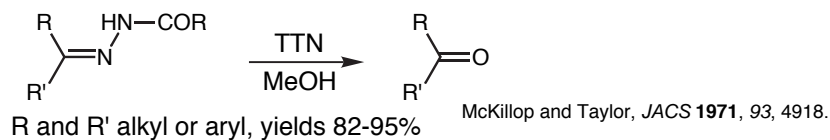
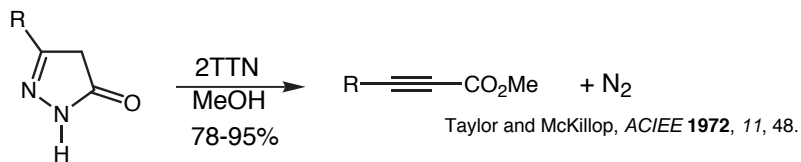
Oxidative Rearrangements of Styrenes

TTN = $Tl(NO_3)_3$ 

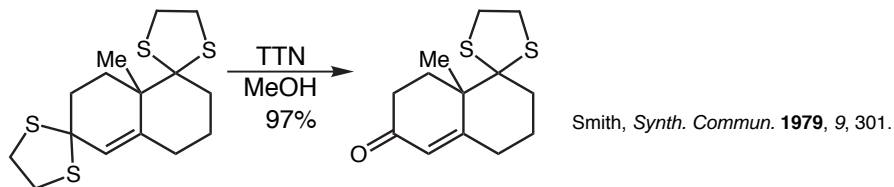
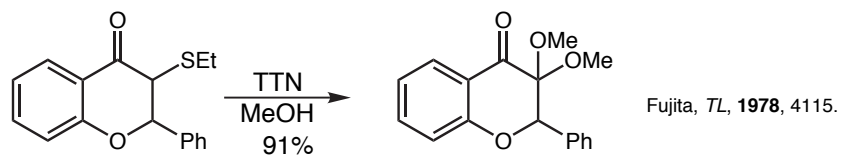
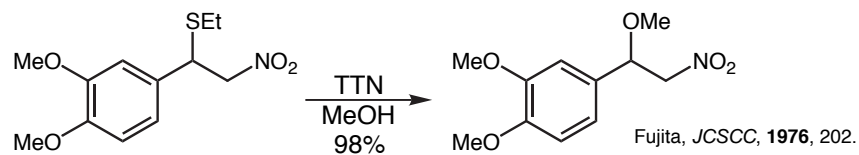
Oxidative Rearrangements of Chalcones



Oxidation of Nitrogen Compounds



Oxidation of Sulfur Compounds



<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

Travis Dunn

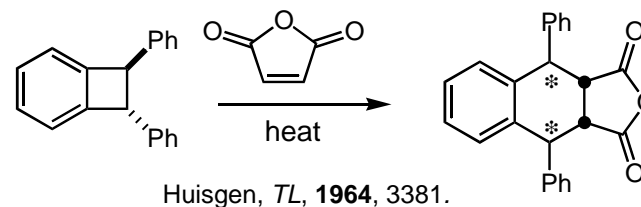
Wednesday,
October 7, 2003

■ Other Reading Material:

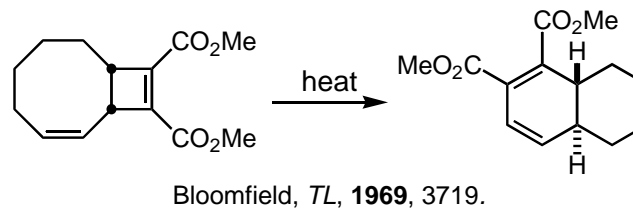
- Woodward-Hoffmann Theory
R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1970.
- Frontier Molecular Orbital Theory
I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John-Wiley and Sons, New York, 1976.
- Dewar-Zimmerman Theory
T. H. Lowry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

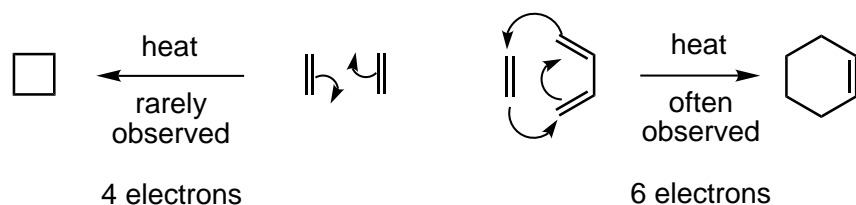
A pericyclic reaction is characterized as a change in bonding relationships that takes place as a **continuous, concerted reorganization of electrons**.

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**.

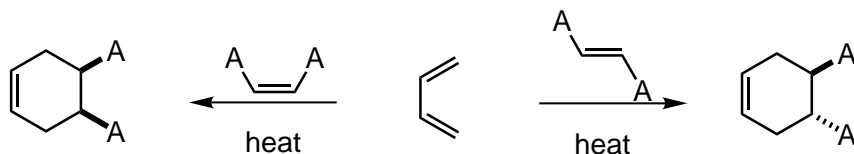
More precisely: The cyclic transition state must correspond to an arrangement of the **participating orbitals** which has to **maintain a bonding interaction** between the reaction components throughout the course of the reaction.

Some factors to consider in our analysis:

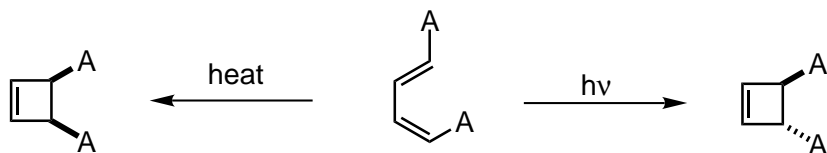
The number of electrons involved has a profound influence on reactivity:



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"

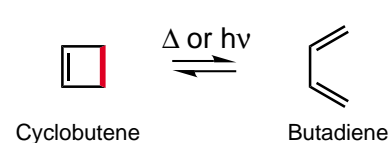
The Five Major Categories of Pericyclic Reactions

(1) ELECTROCYCLIC RING CLOSURE/RING OPENING:

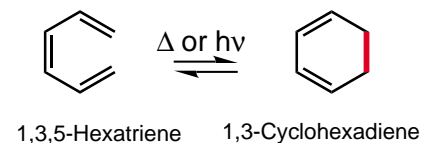
An electrocyclic ring closure is the creation of a new sigma bond at the expense of the terminal p orbitals of a conjugated pi system. There is a corresponding reorganization of the conjugated pi system. We usually classify the reaction according to the number of electrons involved.

Examples:

A 4 e⁻ electrocyclic reaction



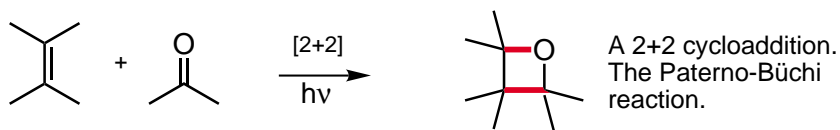
A 6 e⁻ electrocyclic reaction



(2) CYCLOADDITION REACTIONS/CYCLOREVERSION REACTIONS:

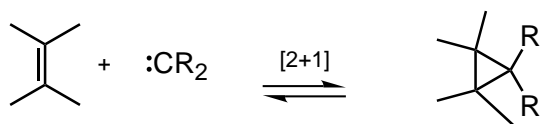
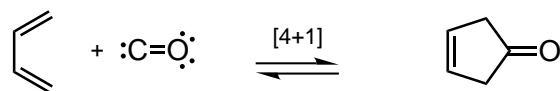
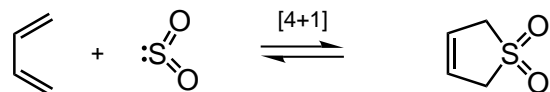
A cycloaddition reaction is the union of two smaller, independent pi systems. Sigma bonds are created at the expense of pi bonds. A cycloaddition can occur in an intramolecular sense, but it must be between two **independent** pi systems. Cycloaddition reactions are referred to as **[m + n]** additions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

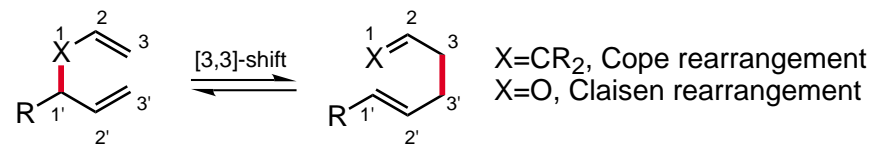
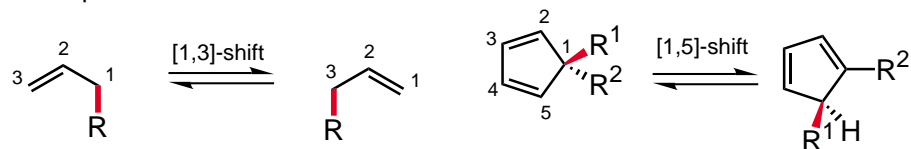
Cheletropic reactions are a special group of cycloaddition/cycloreversion reactions. Two bonds are formed or broken at a single atom. The nomenclature for cheletropic reactions is the same as for cycloadditions.

Examples:

**(4) SIGMATROPIC REARRANGEMENTS:**

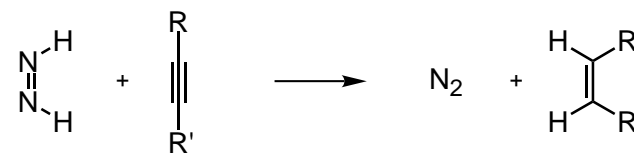
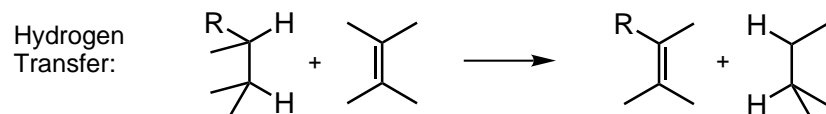
A sigmatropic rearrangement is the migration of a sigma bond from one position in a conjugated system to another position in the system, accompanied by reorganization of the connecting pi bonds. The number of pi and sigma bonds remains constant. The rearrangement is an **[m,n]** shift when the sigma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

Examples:

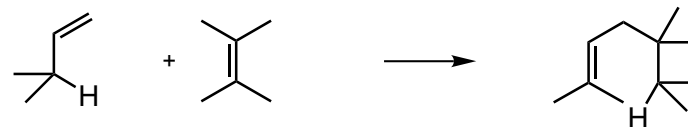
**(5) GROUP TRANSFER REACTIONS:**

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

Examples:



Ene Reaction:



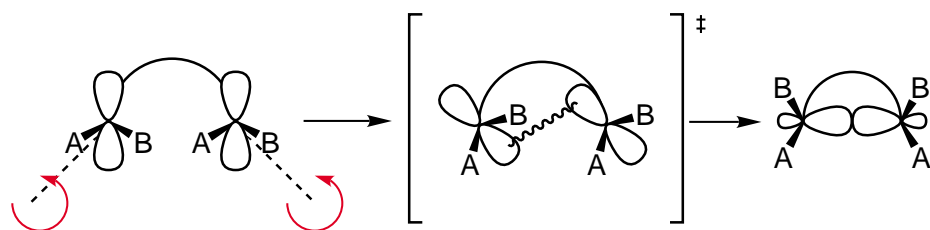
ELECTROCYCLIC RING CLOSURE/RING OPENING:

The Stereochemical issues:

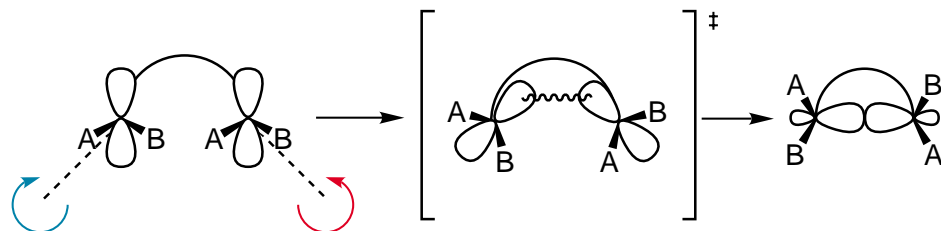
Ring closure can occur in two distinct ways. This has consequences with regard to:

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

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

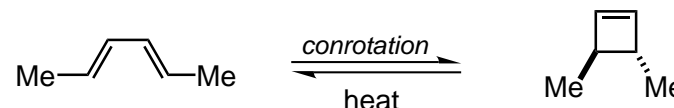
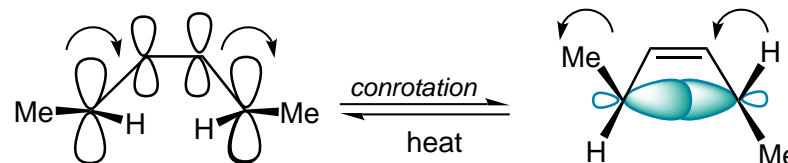


Disrotatory Closure: The termini rotate in **opposite directions**

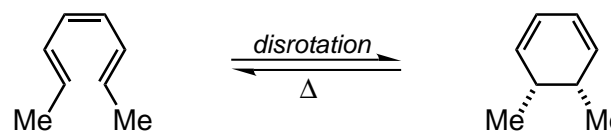
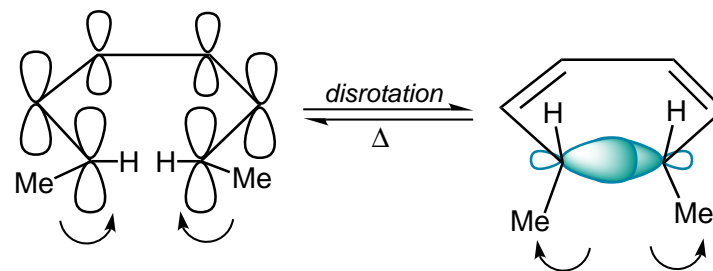
**Empirical Observations:**

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.)

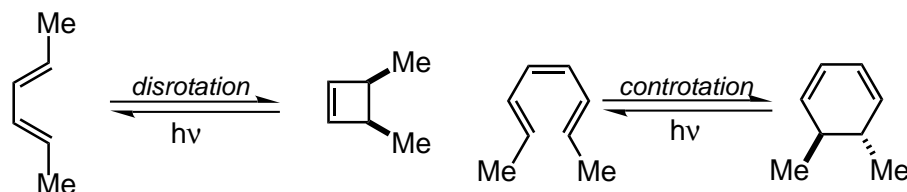
Butadiene to cyclobutene: A 4-electron ($4q$) system

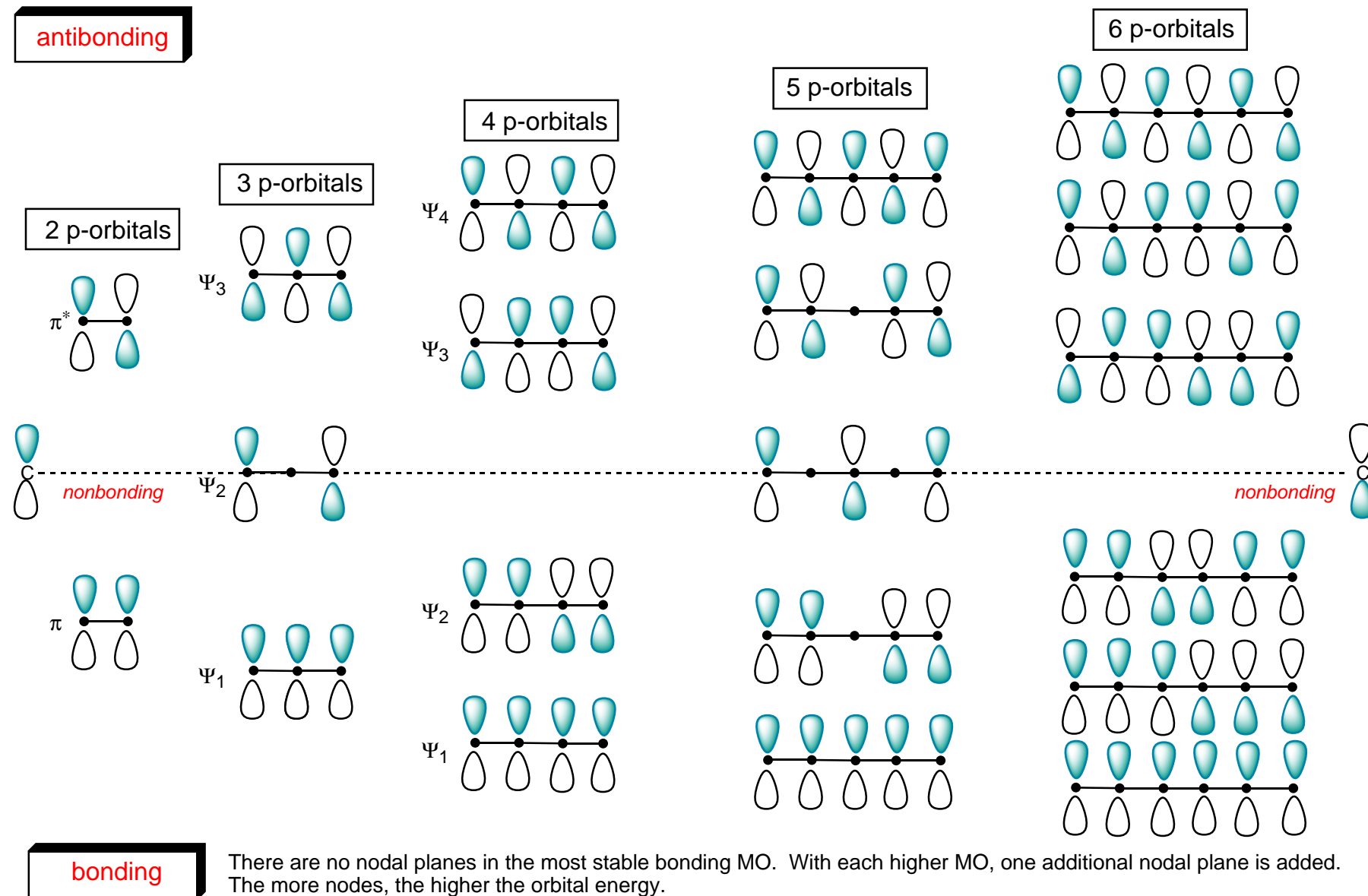


Hexatriene to cyclohexadiene: A 6-electron ($4q+2$) system



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.



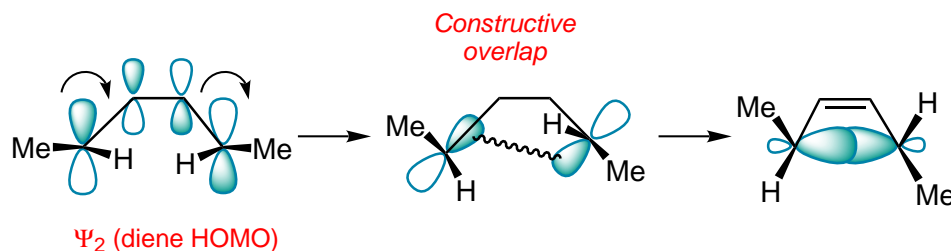


■ FMO Treatment of Electrocyclic reactions.

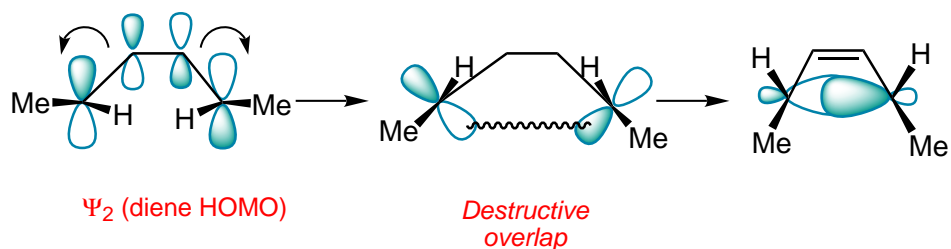
- Examine the interactions that occur in the HOMO as the reaction proceeds.
- If the overlap is constructive (i.e. of the same phase) then the reaction is "allowed."
- If the overlap is destructive (i.e. of different phases) then the reaction is "forbidden."

Thermal Activation:

Conrotatory Closure: (Allowed and observed)



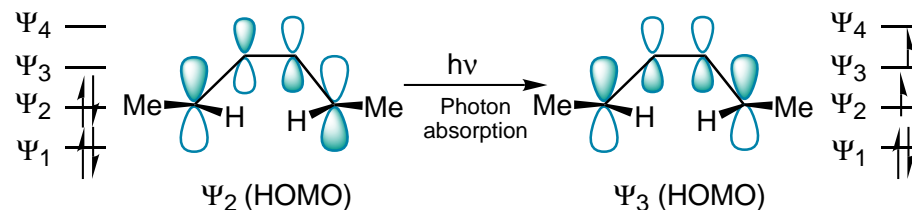
Disrotatory Closure: (Forbidden and not observed)



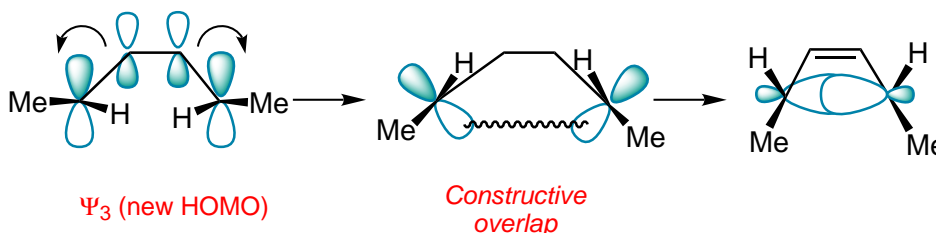
A similar analysis for the hexatriene system proves that under thermal conditions, disrotation is allowed and conrotation is forbidden.

Photochemical Activation:

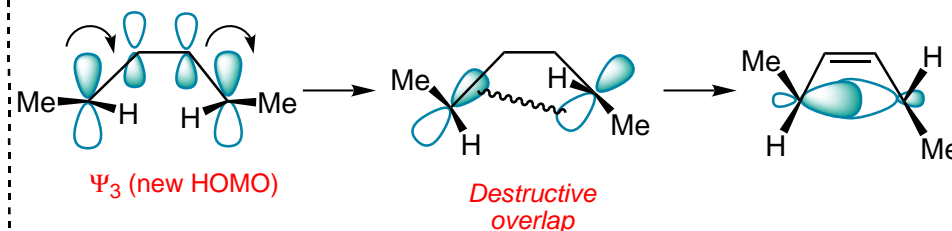
When light is used to initiate an electrocyclic reaction, an electron is excited from Ψ_2 to Ψ_3 . Treating Ψ_3 as the HOMO now shows that disrotatory closure is allowed and conrotatory closure is forbidden.



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**.

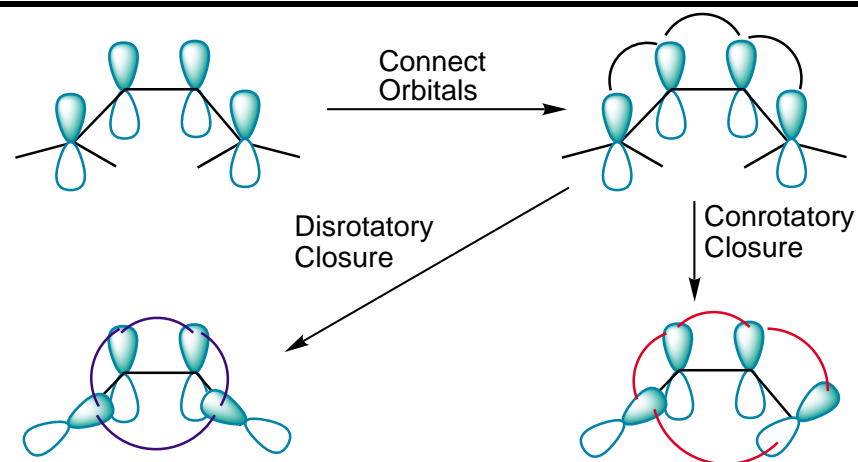
■ Based on the phase inversions, identify the topology of the system.

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	$4q$	$4q + 2$

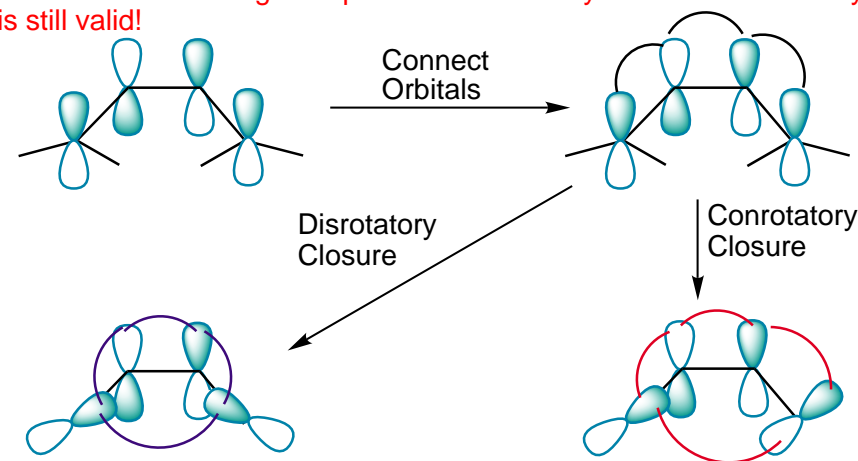
■ If the transition state is **aromatic**, then the reaction will be allowed **thermally**. If the transition state is **antiaromatic**, then the reaction will be allowed **photochemically**.



Zero Phase Inversions
∴ Hückel Topology
4 electrons in system
∴ Antiaromatic and Forbidden

One Phase Inversion
∴ Möbius Topology
4 electrons in system
∴ Aromatic and Allowed

Note that I can change the phase of an arbitrary orbital and the analysis is still valid!



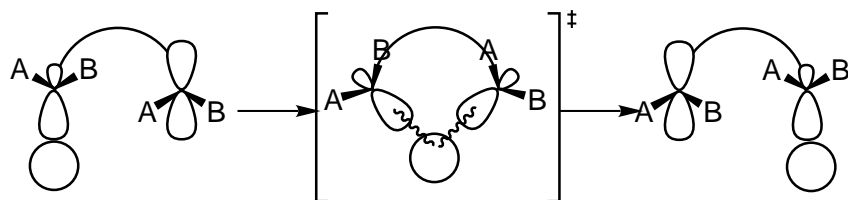
Two Phase Inversions
∴ Hückel Topology
4 electrons in system
∴ Antiaromatic and Forbidden

Three Phase Inversions
∴ Möbius Topology
4 electrons in system
∴ Aromatic and Allowed

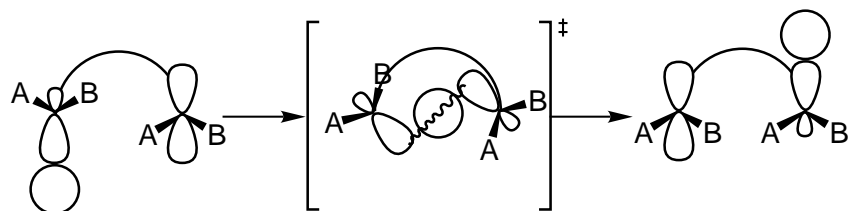
The Stereochemical issues:

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.

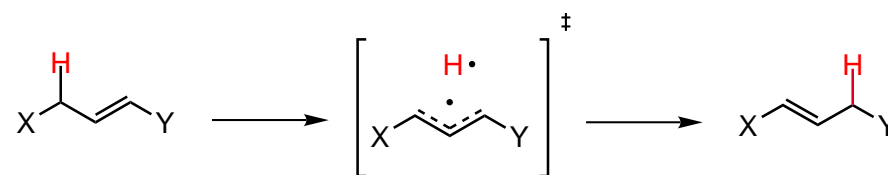
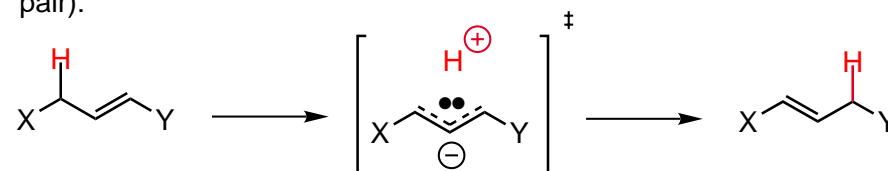
■ If the overlap is constructive at both termini then the reaction is allowed. If the overlap is destructive at either terminus then the reaction is forbidden.

■ 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).

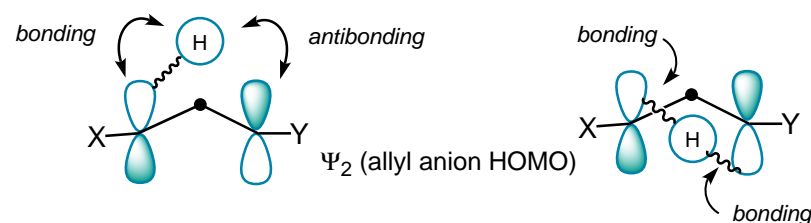
■ If the migrating atom is hydrogen, then it cannot migrate with inversion.

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

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



Proton 1S (LUMO)



Suprafacial Geometry

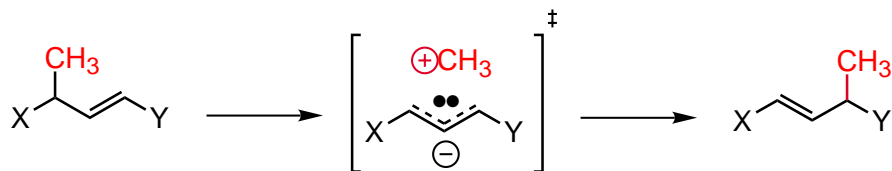
Antarafacial Geometry

■ 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.

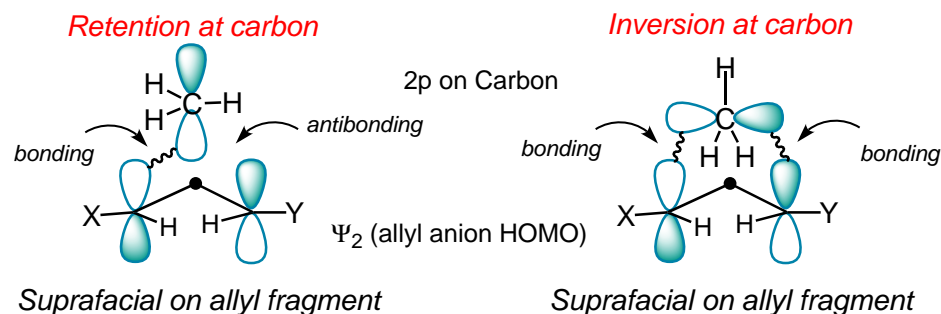
■ The suprafacial migration is forbidden and the bridging distance too great for the antarafacial migration. Hence, [1,3] hydrogen migrations are not observed under thermal conditions.

■ 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.

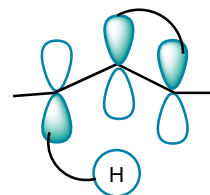
■ The stereochemical constraints on the migration of carbon with inversion of configuration is highly disfavored on the basis of strain. Such rearrangements are rare and usually only occur in highly strained systems.

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.

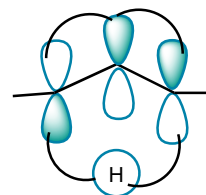
■ Sigmatropic Rearrangements: Dewar-Zimmerman

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

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



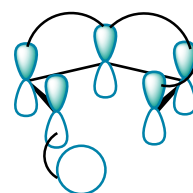
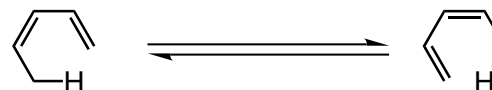
Orbital interactions in the parent system



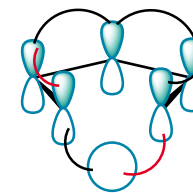
Completing the circuit across the bottom face

Two Phase Inversions
Hückel Topology
Four Electrons
Forbidden thermally

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



Orbital interactions in the parent system

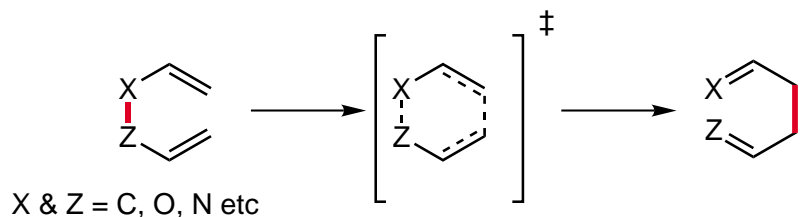


Completing the circuit across the bottom face

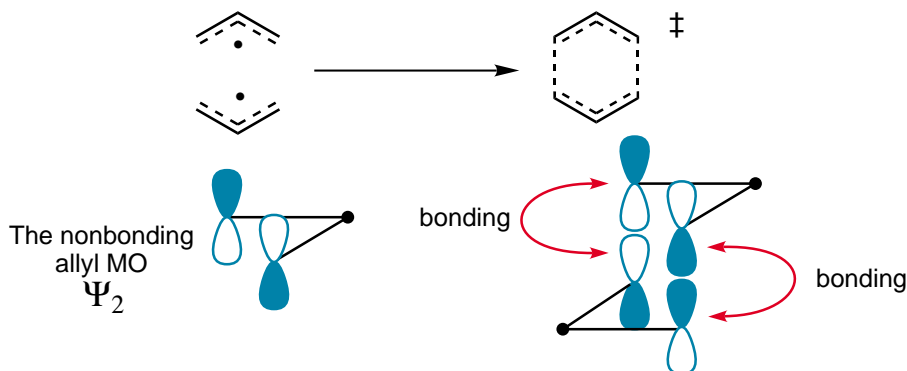
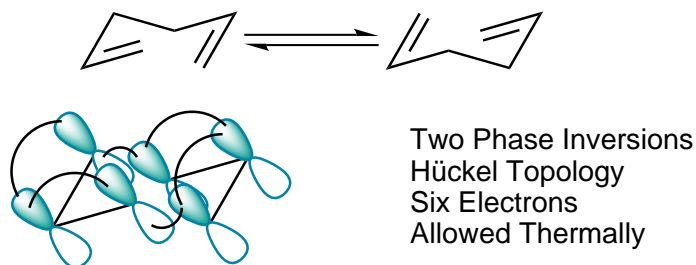
Zero Phase Inversions
Hückel Topology
Six Electrons
Allowed thermally

[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:

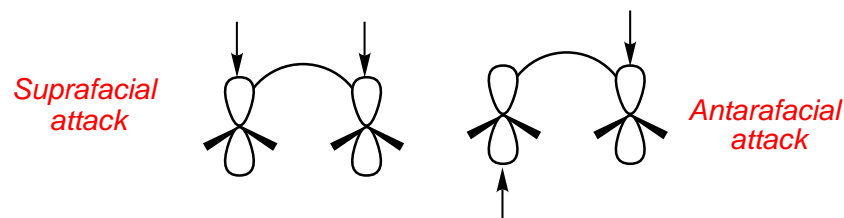
Take the [1,3] sigmatropic rearrangement of an alkyl group. We know this is forbidden under thermal conditions in a supra-supra manner, and so we make it the first entry in the table.

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?

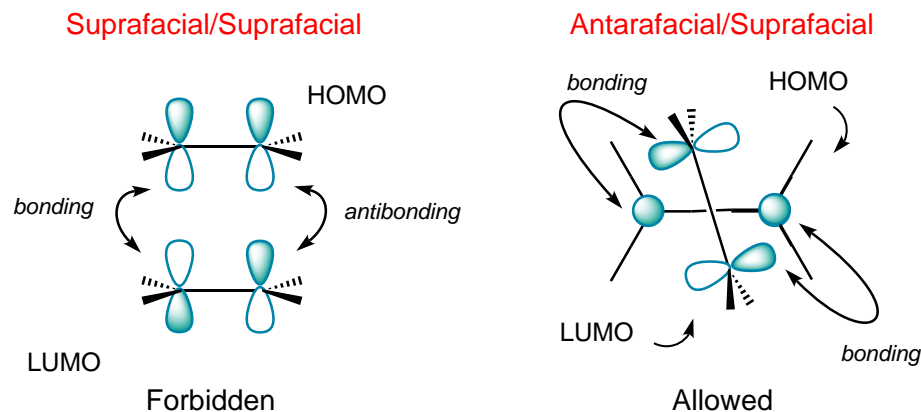
The Stereochemical issues:

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

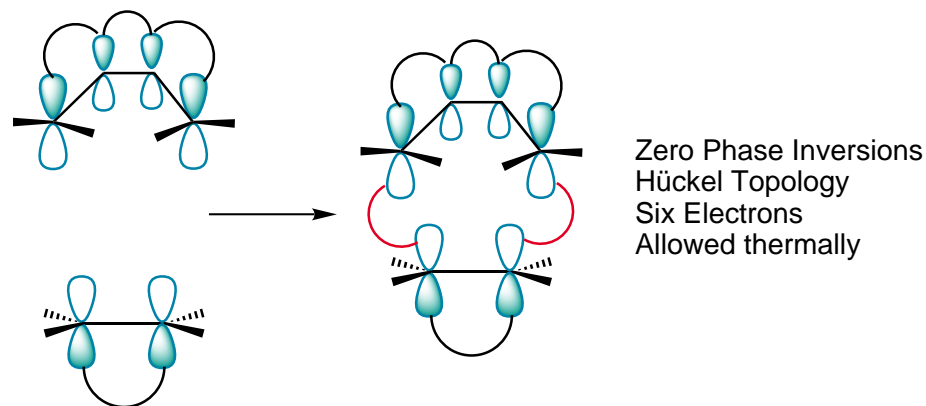
For the [2+2] cycloaddition two different geometries have to be considered.



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

■ Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11
Concerted Pericyclic Reactions

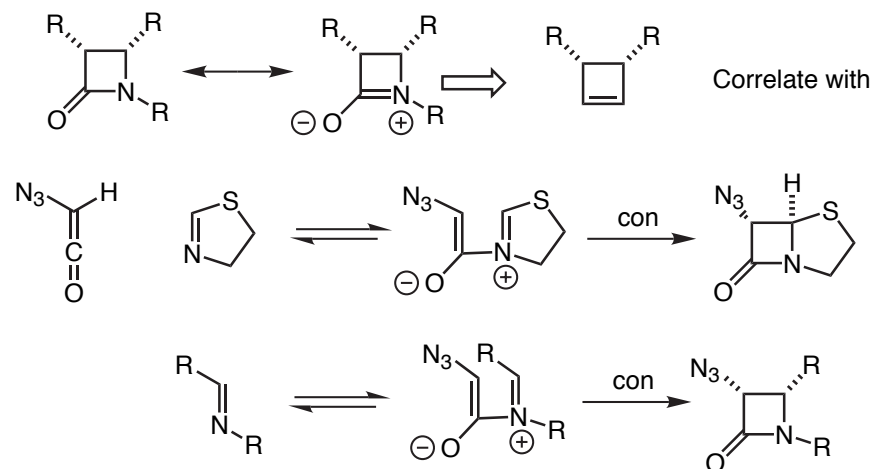
Fleming: Chapter 4
Thermal Pericyclic Reactions

D. A. Evans

Monday,
October 12, 2003

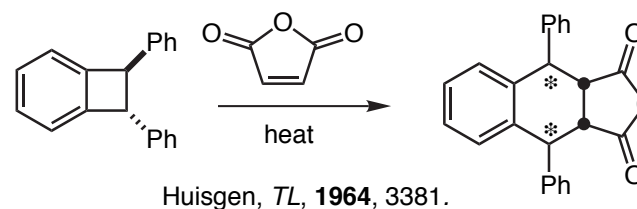
■ Other Reading Material:

C. Palomo, "Asymmetric Synthesis of β -Lactams by Stauginger Ketene-Imine Cycloaddition Reaction, *Eur. J. Org. Chem.* 1999, 3223-3235.

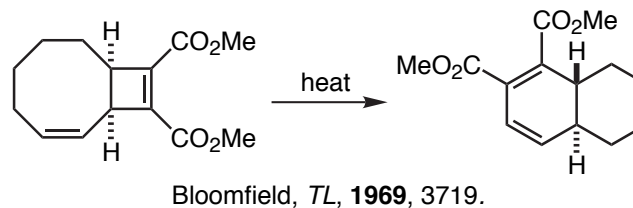


■ Problems of the Day:

Predict the stereochemical outcome of this reaction.



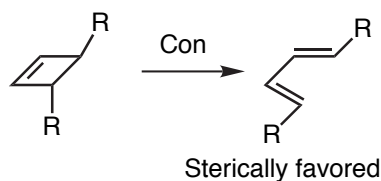
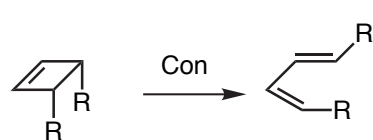
Suggest a mechanism for the following reaction.



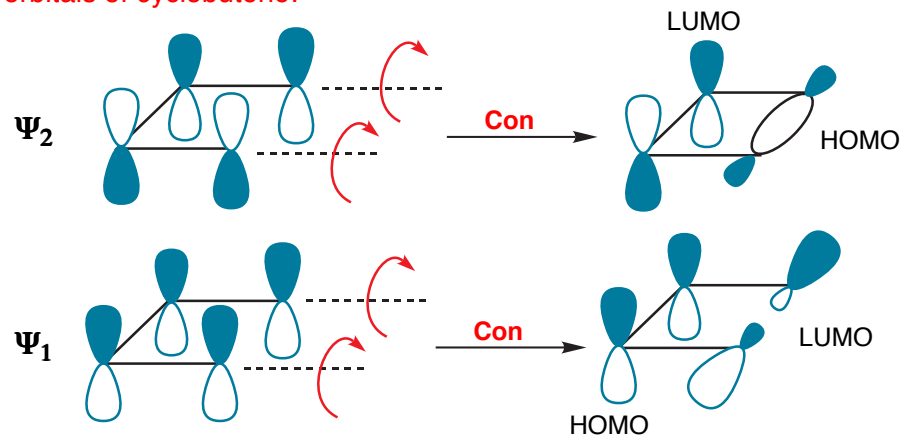
Electrocyclic Reaction - Selection Rules

	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

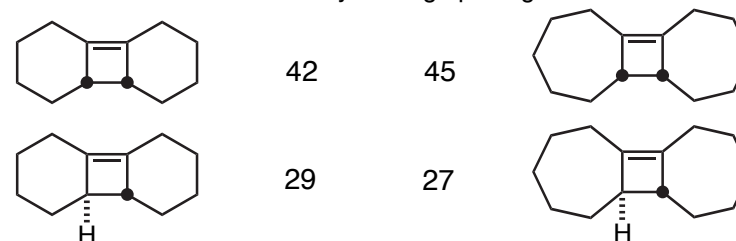
Examples	Ground State	Excited State
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory
	Conrotatory	Disrotatory
	Conrotatory	Disrotatory
	Disrotatory	Conrotatory



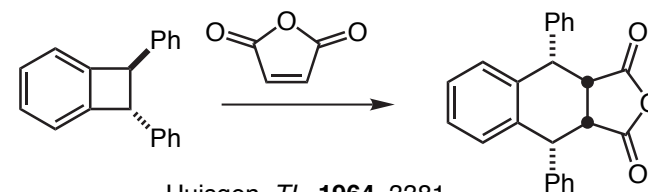
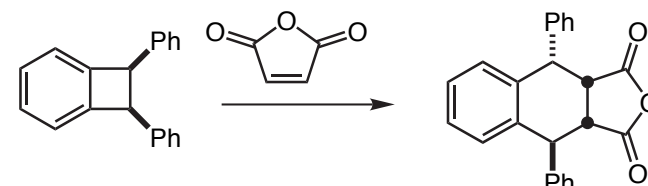
Conrotation Ψ_1 and Ψ_2 on to the indicated bonding and anti-bonding orbitals of cyclobutene:



Activation Energy (kcal/mol)
for electrocyclic ring opening

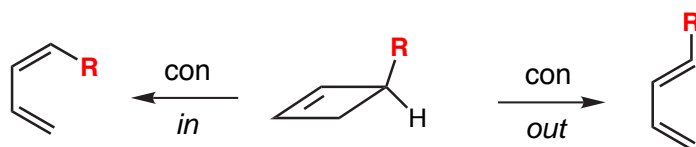


Criegee, *Chem. Ber.* **1968**, 101, 102.

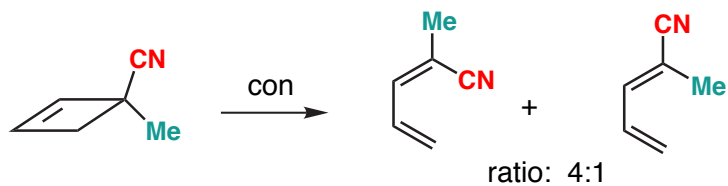
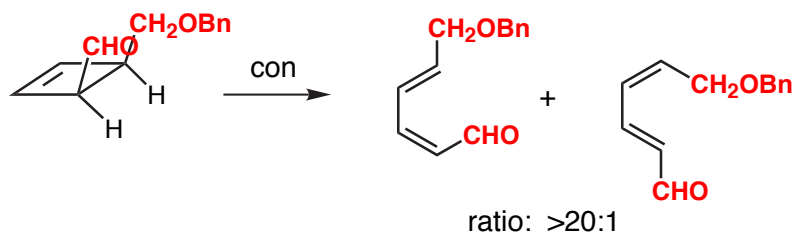
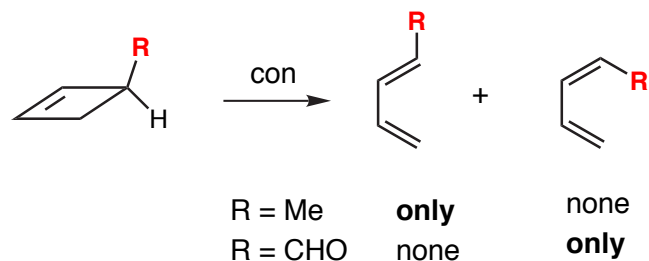


Torquoselectivity is defined as the predisposition of a given R substituent for a given conrotatory motion

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

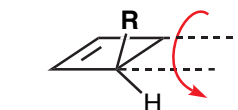
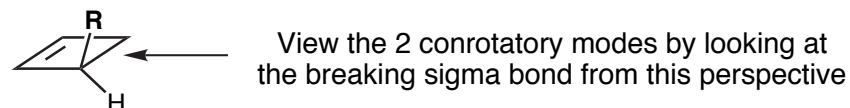


Examples: Donor substituents prefer con-out mode
Pi acceptor substituents prefer con-in mode

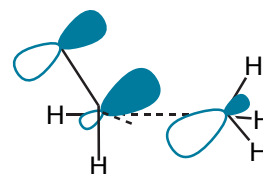


How do we explain?

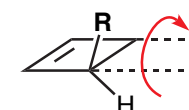
Donor substituents prefer con-out mode
Pi acceptor substituents prefer con-in mode



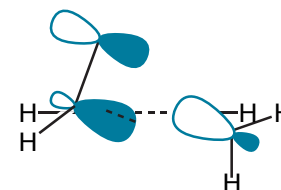
Outward Motion



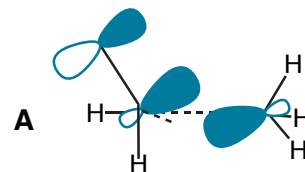
LUMO + p



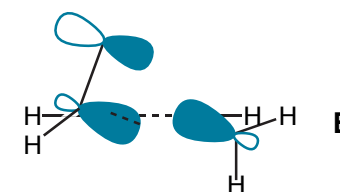
Inward Motion



LUMO + p



HOMO + p



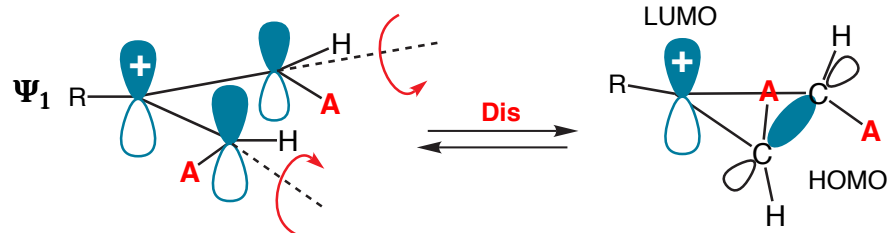
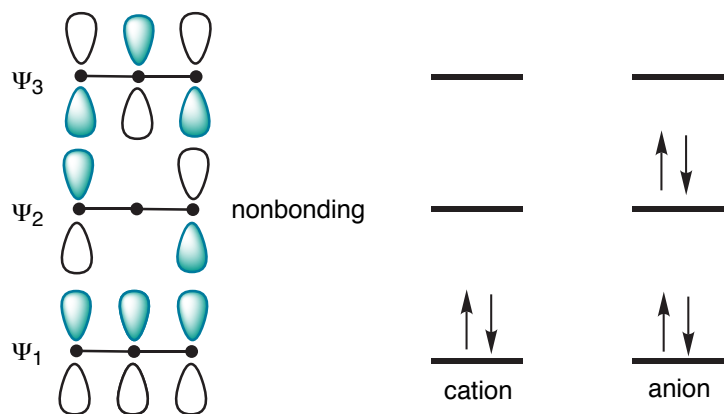
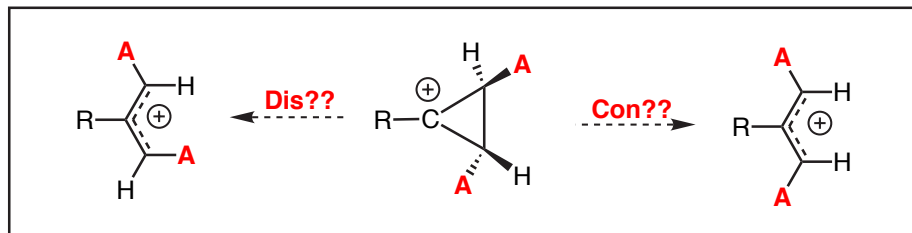
HOMO + p

destabilizing 4 electron
interaction for donor
substituents

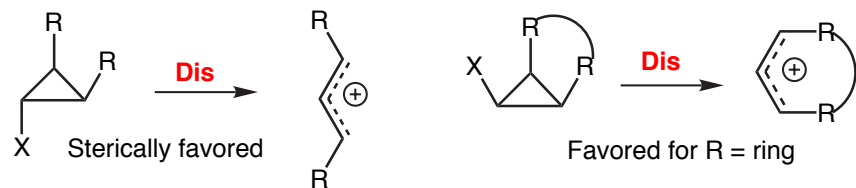
As conrotation begins the energy of the breaking sigma bond rises steeply. Hyperconjugation with a pi* orbital, while possible in both **A** & **B**, is better in **B**. (Houk)

stabilizing 2 electron
interaction for acceptor
substituents

Three-Atom Electrocyclizations (2 electrons)

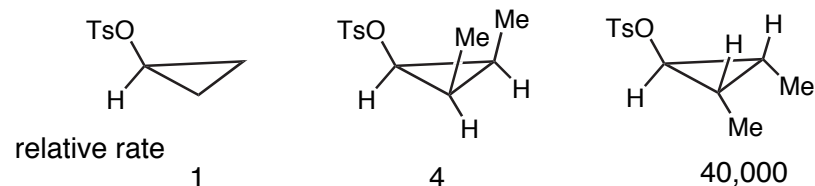
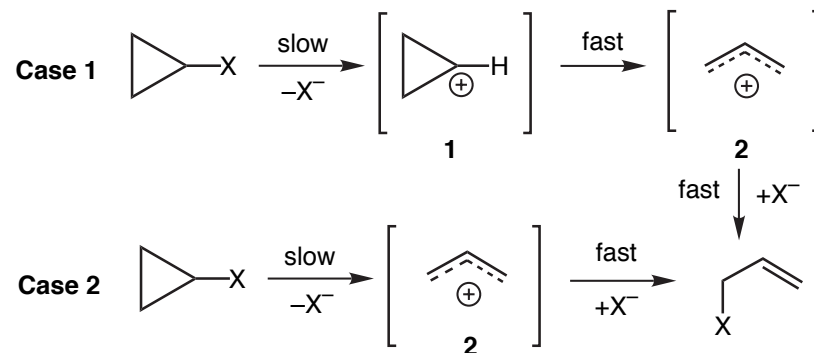


Note that there are two disrotatory modes

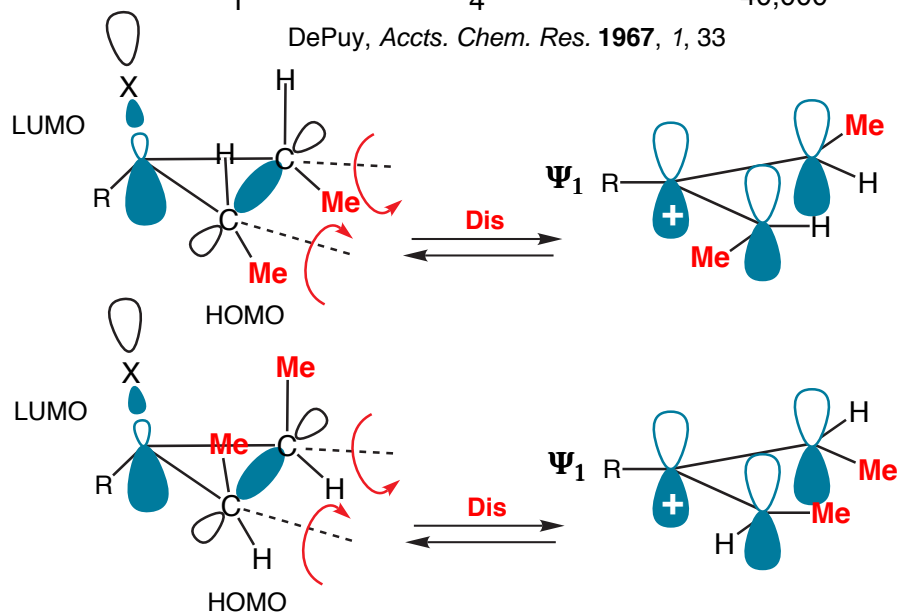


Solvolysis of Cyclopropyl Derivatives

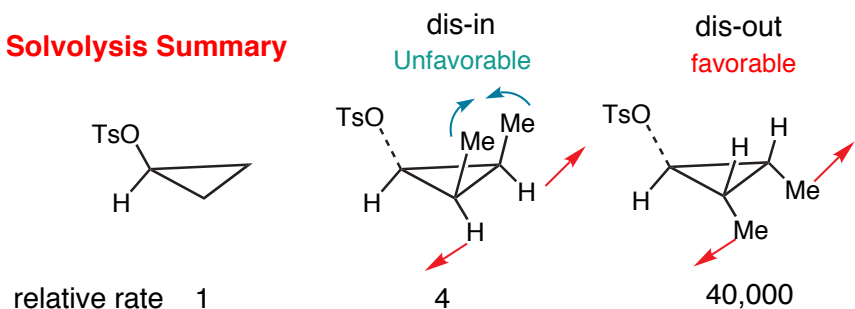
Does solvolysis proceed via cation **1** followed by rearrangement to **2** (Case 1), or does it proceed directly to **2** (Case 2)?



DePuy, *Accts. Chem. Res.* **1967**, 1, 33

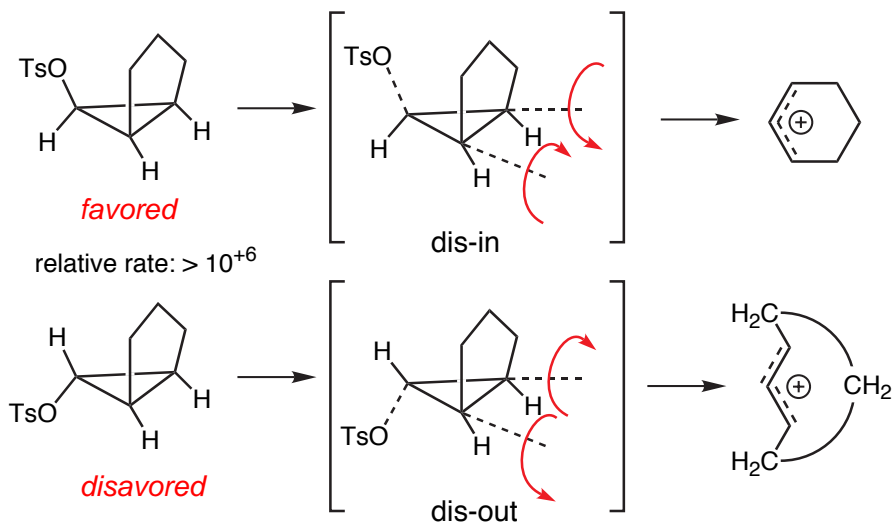


Solvolysis Summary

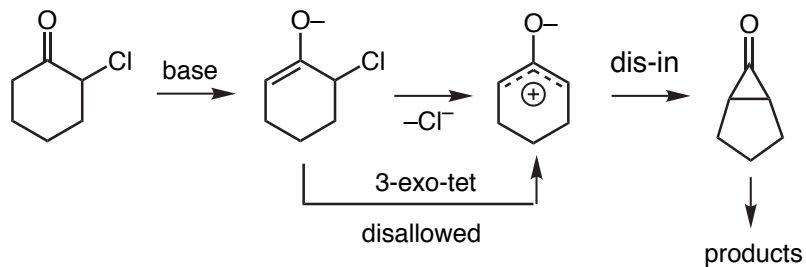


Ring-fused Cyclopropyl Systems

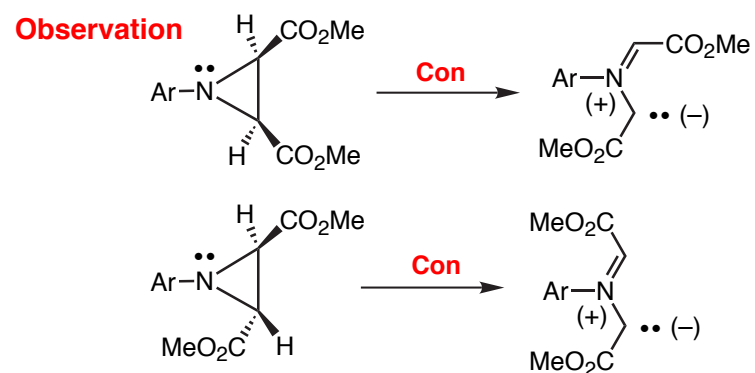
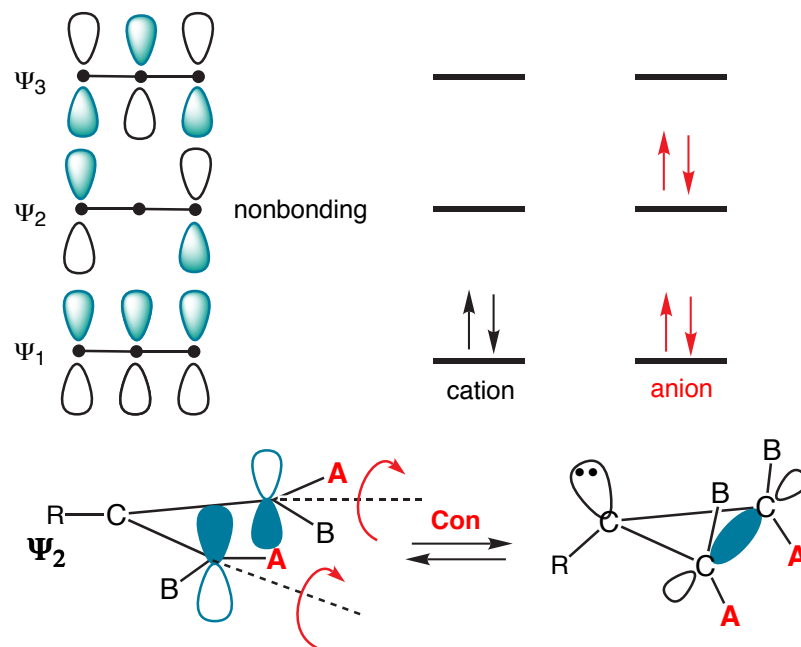
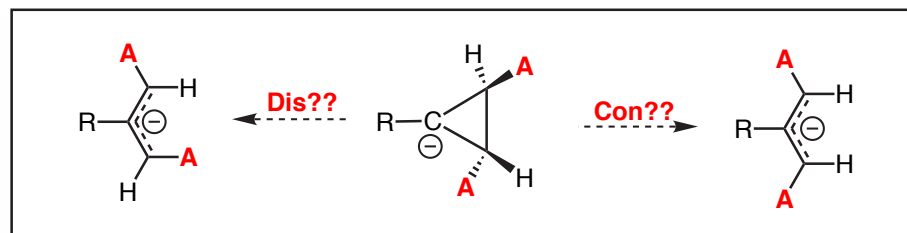
When the cis substituents on the cyclopropyl ring are tied together in a ring the following observations have been made



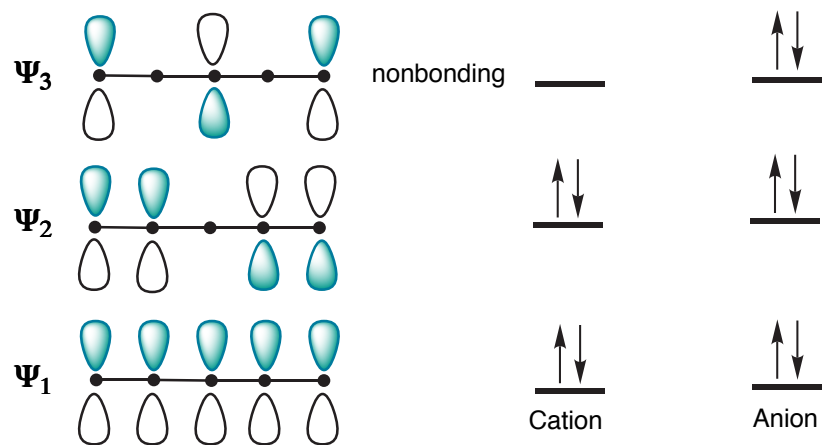
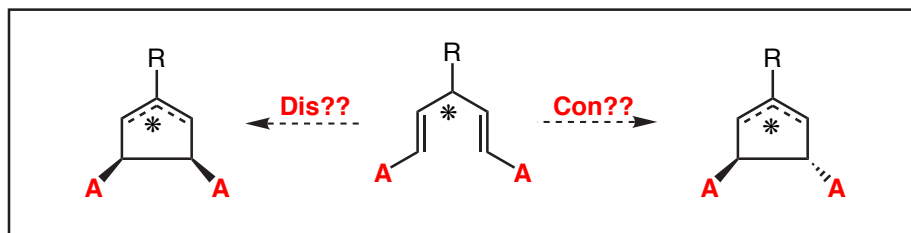
Revisiting the Favorski rearrangement: (Carey, Part A, pp 506-8)



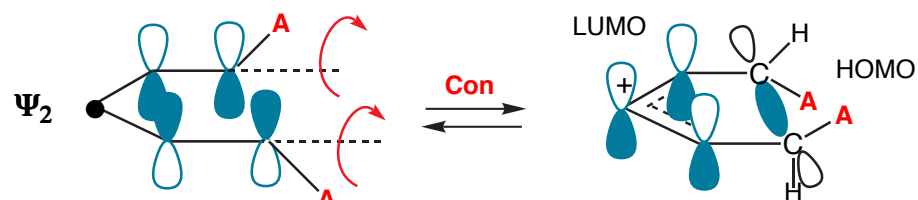
Three-Atom Electrocyclizations (4 electrons)



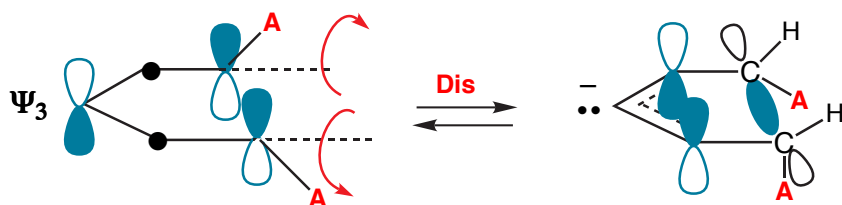
Five-Atom Electrocyclizations (4 electrons)



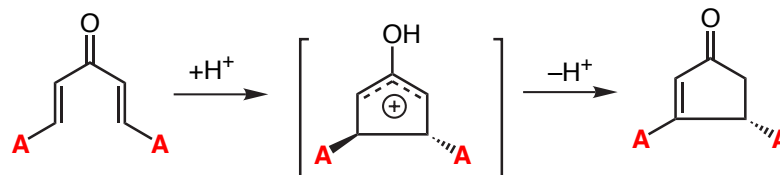
Pentadienyl Cation



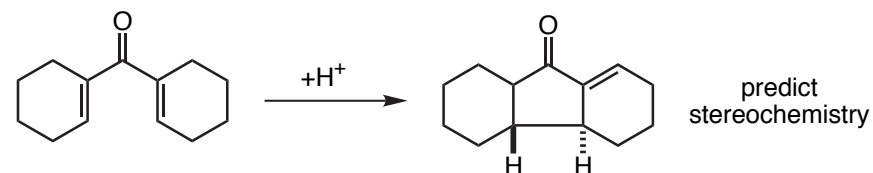
Pentadienyl Anion



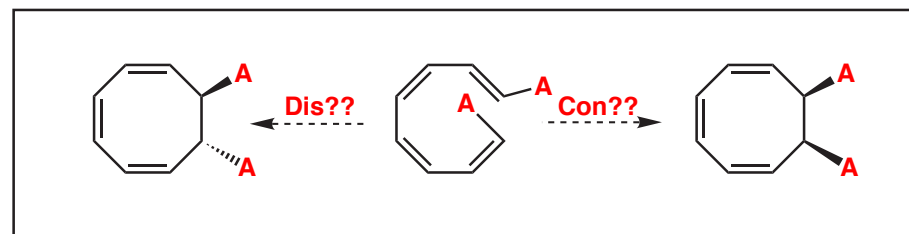
The Nazarov Reaction



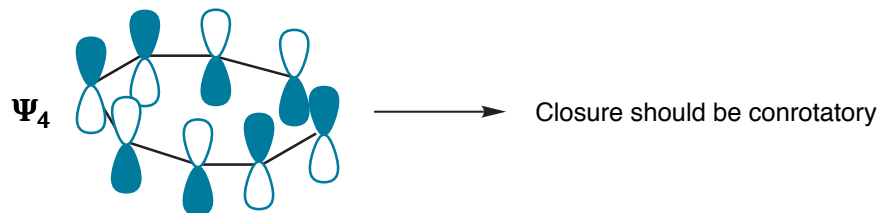
Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5; pp 751.



Eight-Atom Electrocyclizations (8 electrons)

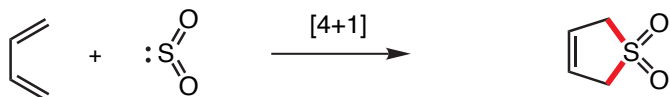
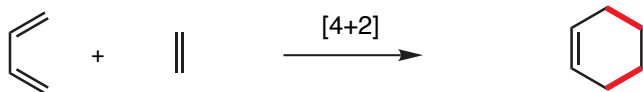


Let's use the "Ready" shortcut to find the homo: Nodes will appear at single bonds

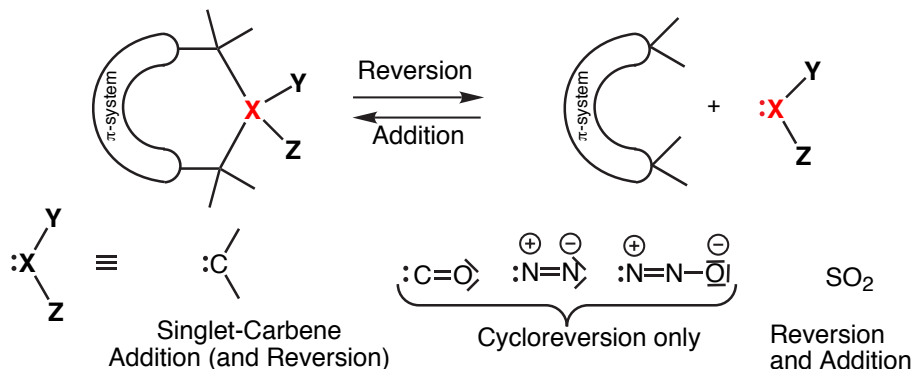


CHELETROPIC REACTIONS: $[n+1]$ Cycloadditions (or Cycloreversions)

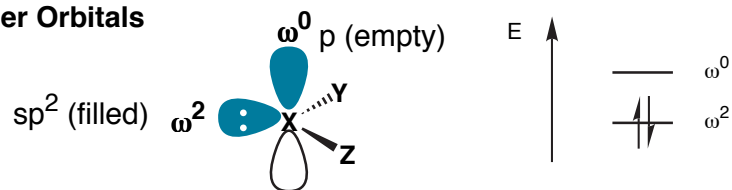
Concerted processes in which 2 σ -bonds are made (or broken) which terminate at a single atom.



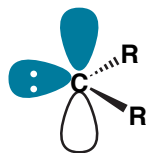
General



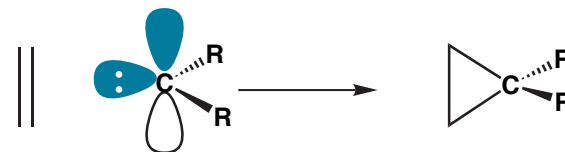
Frontier Orbitals



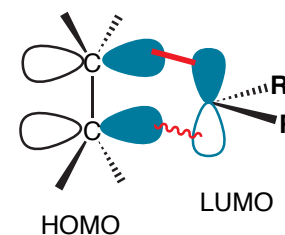
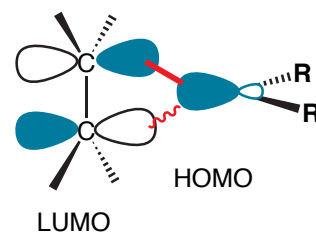
Question: what is orientation of carbene relative to attacking olefin??



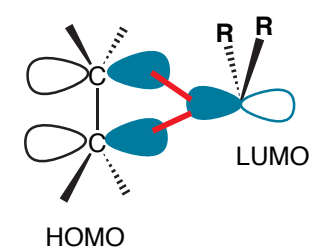
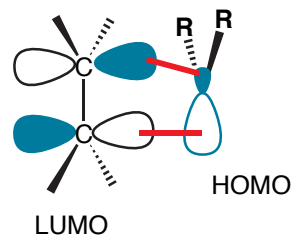
2 + 1 Cheletropic Reaction: Olefins + Singlet Carbene



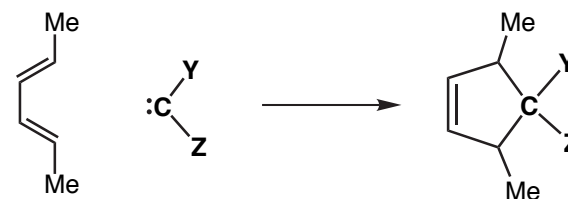
Linear Approach: 2 HOMO-LUMO Interactions



Nonlinear Approach: 2 HOMO-LUMO Interactions

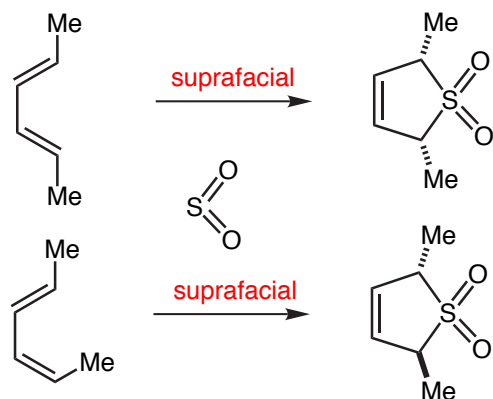
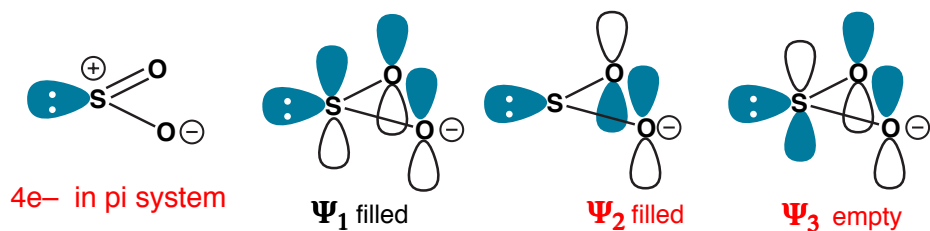


Carry out the analysis of the indicated hypothetical transformation

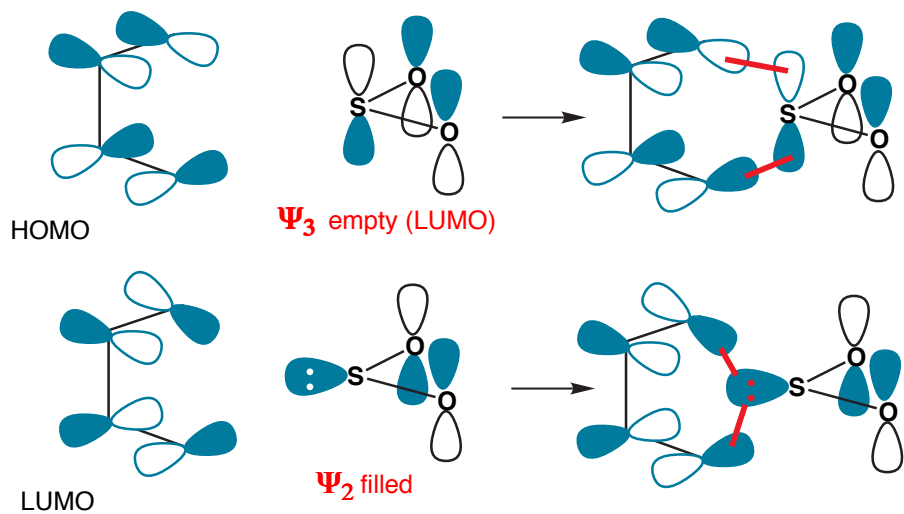


predict approach geometry of carbene

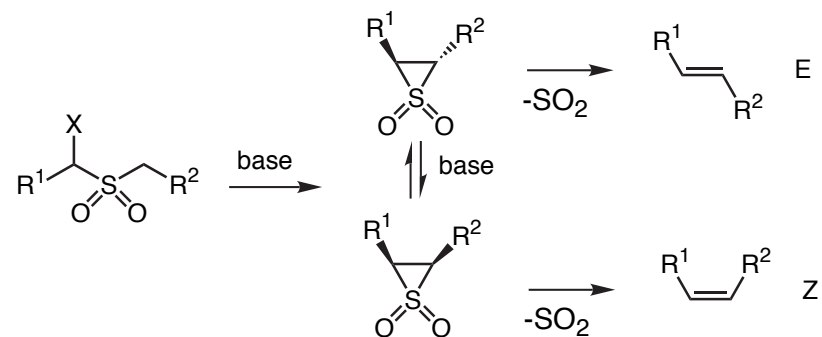
Let's now consider SO_2 as the one-atom component



reactions are:
stereospecific & reversible

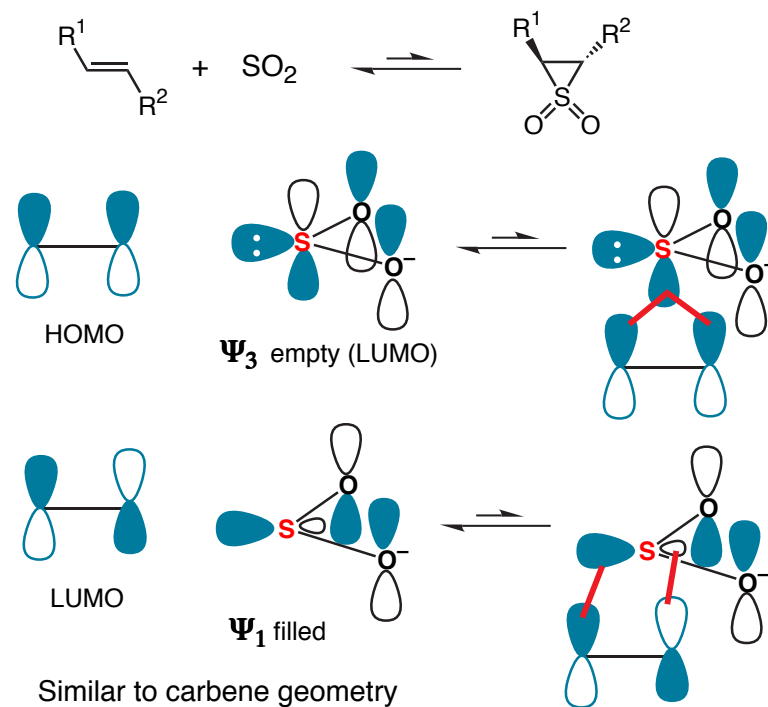


Key step in the *Ramberg Bäcklund Rearrangement*



Clough, J. M. *The Ramberg-Backlund Rearrangement*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 861.
"The Ramberg-Backlund Rearrangement.", Paquette, L. A. *Org. React. (N.Y.)* **1977**, 25, 1.

Analysis of the Suprafacial SO_2 Extrusion (nonlinear)



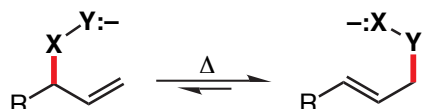
Sigmatropic rearrangements are those reactions in which a sigma bond (& associated substituent) interchanges termini on a conjugated pi system

■ **Examples:**

[1,3] Sigmatropic rearrangement



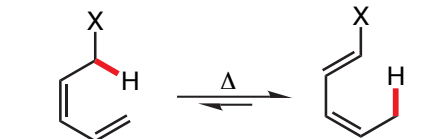
[2,3] Sigmatropic rearrangement



[3,3] Sigmatropic rearrangement

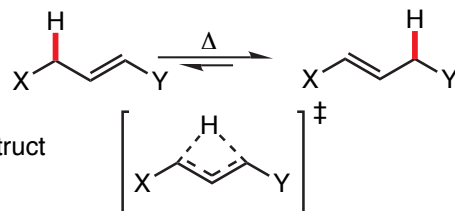


[1,5] Sigmatropic rearrangement



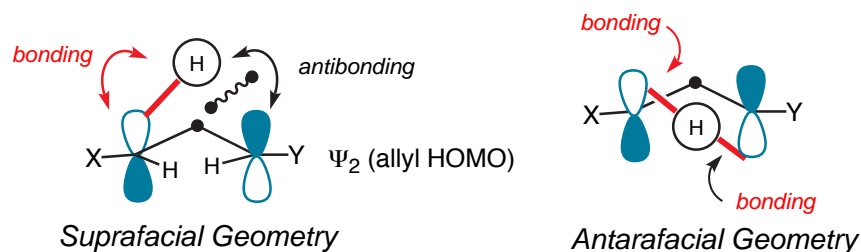
■ **[1,3] Sigmatropic Rearrangements (H migration)**

consider the 1,3-migration of H



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

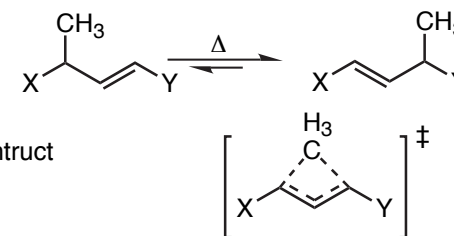
■ **Construct TS by uniting an allyl and H radical:**



Bridging distance too great for antarafacial migration.

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

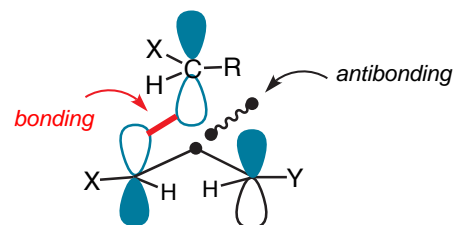
consider the 1,3-migration of Carbon



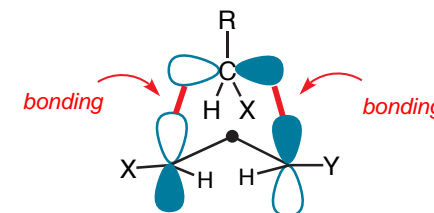
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□ Construct TS by uniting an allyl and Me radicals:

Retention at carbon



Inversion at carbon



Suprafacial on allyl fragment

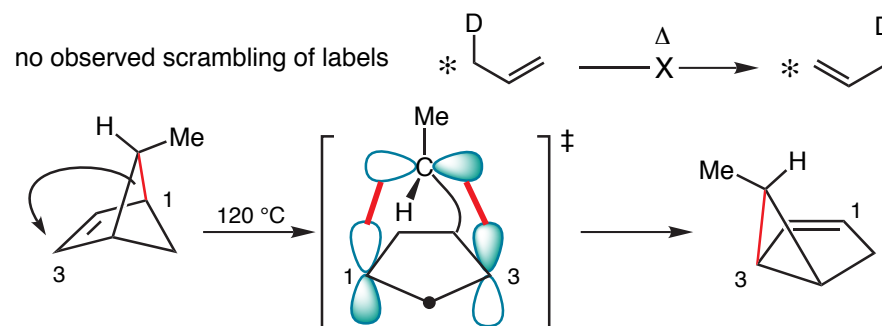
Suprafacial on allyl fragment

Synchronous bonding to both termini cannot be achieved from this geometry

Synchronous bonding to both termini is possible from this geometry

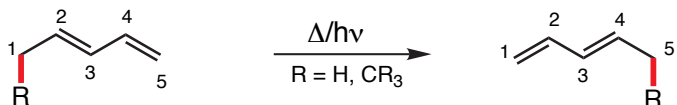
□ The stereochemical constraints on the suprafacial migration of carbon with inversion of configuration is highly disfavored on the basis of strain.

[1,3]-Sigmatropic rearrangements are not common

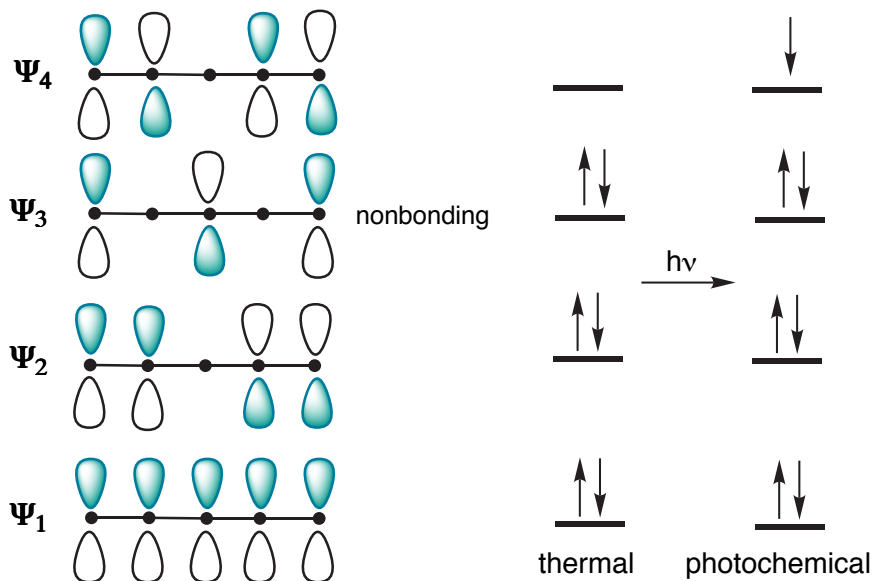


These rearrangements are only seen in systems that are highly strained, an attribute that lowers the activation for rearrangement.

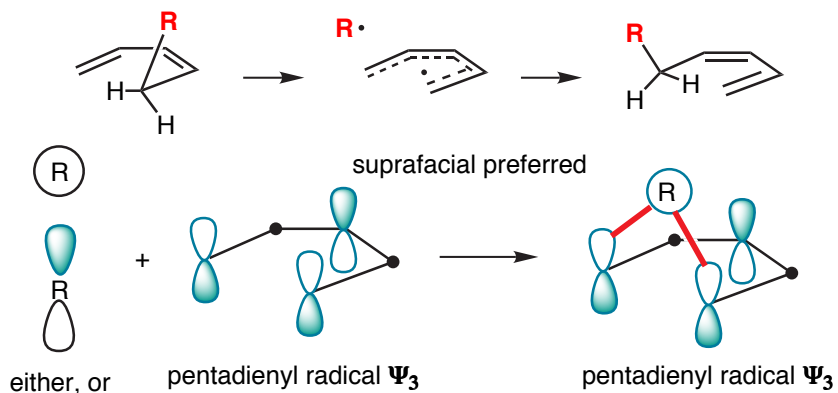
SIGMATROPIC REACTIONS - FMO-Analysis



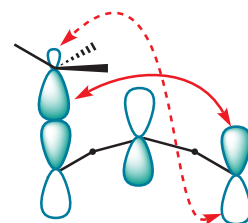
■ [1,5] Sigmatropic Rearrangements (H migration)



View as cycloaddition between following species:

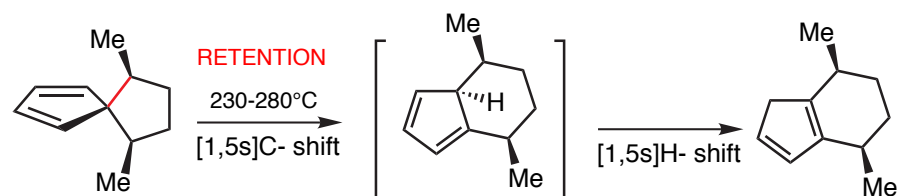


■ [1,5] Sigmatropic Rearrangements (C migration)

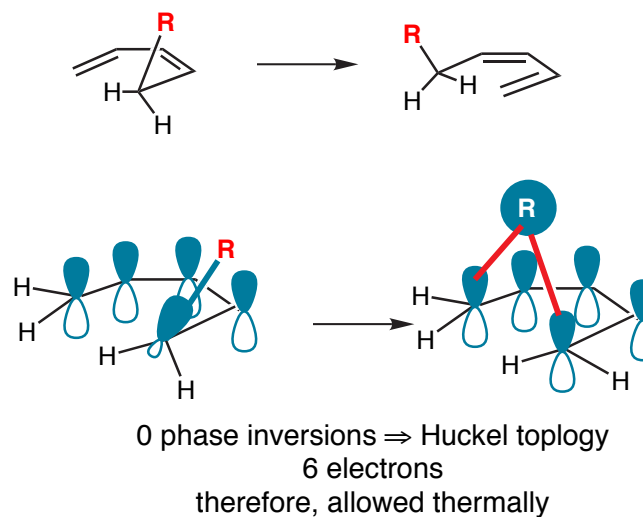


— [1s,5s] alkyl shift ⇒ RETENTION
 - - - [1a,5a] alkyl shift ⇒ INVERSION
 disfavored

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

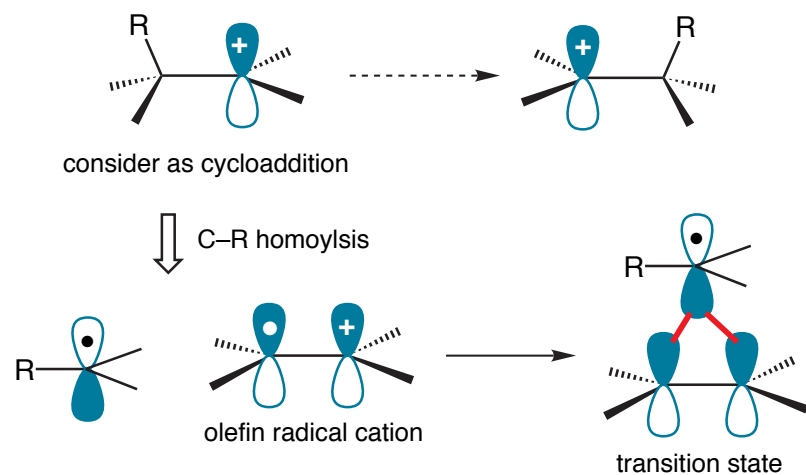


Dewar-Zimmerman Analysis: Retention

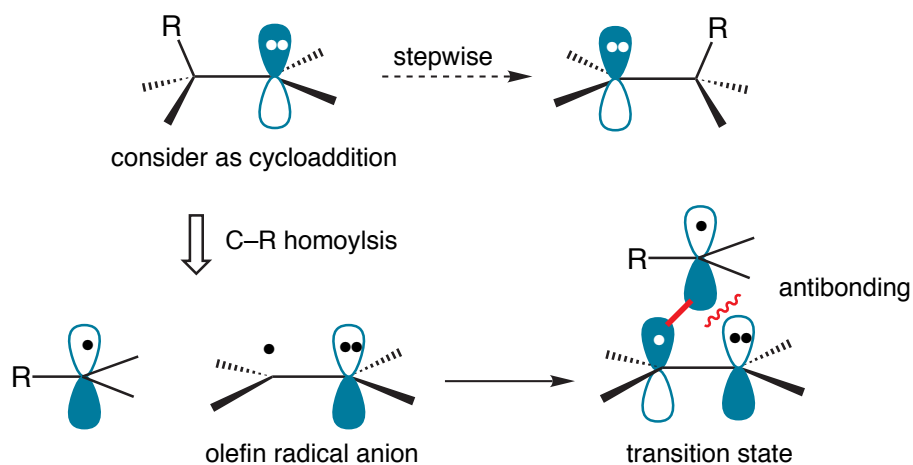


■ [1,2] Sigmatropic Rearrangements: Carbon

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

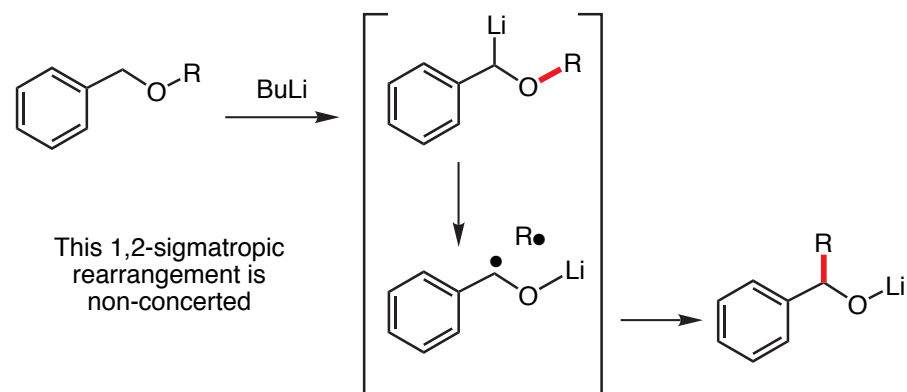


[1,2] Concerted sigmatropic rearrangements to carbanionic centers not observed

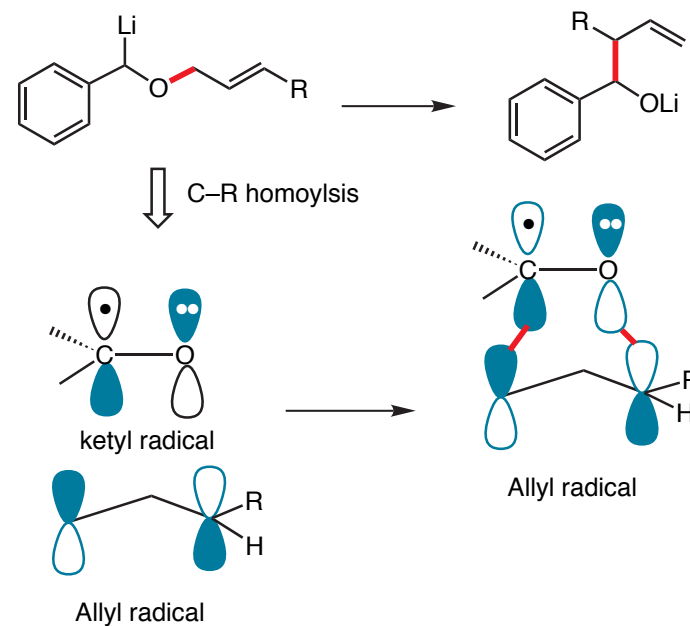


The Wittig Rearrangement [1,2]

"[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

D. A. Evans

Wednesday,
October 14, 2003

■ Other Reading Material:

[2,3] Sigmatropic Rearrangements

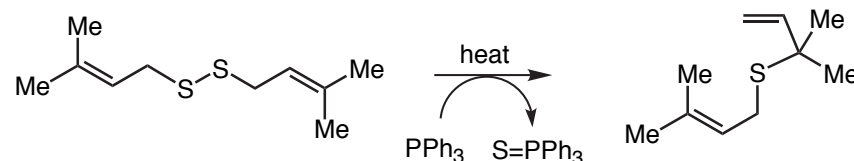
- Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 6, Chapter 4.6:
Nakai, T.; Mikami, K. *Org. React. (N.Y.)* **1994**, 46, 105-209.
Hoffmann, *Angew. Chem. Int. Ed.* **1979**, 18, 563-572 (Stereochemistry of)
Nakai, *Chem. Rev.* **1986**, 86, 885-902 (Wittig Rearrangement)
Evans, *Accts. 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.

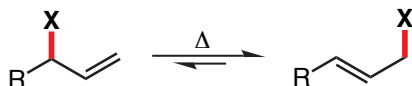


For study on this [2,3] rxn See Baldwin *JACS* **1971**, 93, 6307

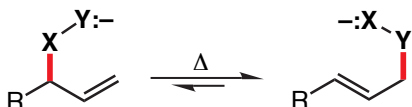
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■ **Examples:**

[1,3] Sigmatropic rearrangement



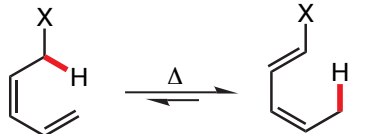
[2,3] Sigmatropic rearrangement



[3,3] Sigmatropic rearrangement

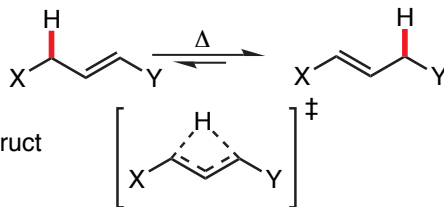


[1,5] Sigmatropic rearrangement



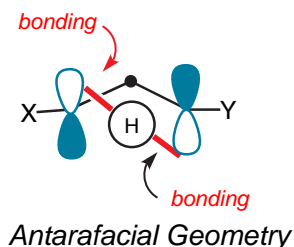
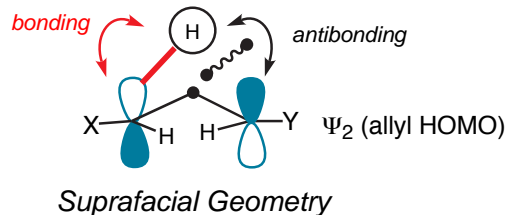
■ **[1,3] Sigmatropic Rearrangements (H migration)**

consider the 1,3-migration of H



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

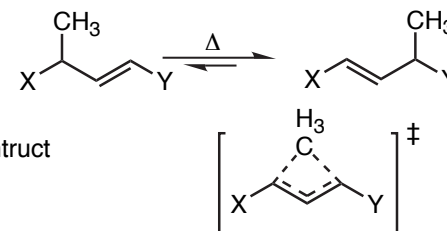
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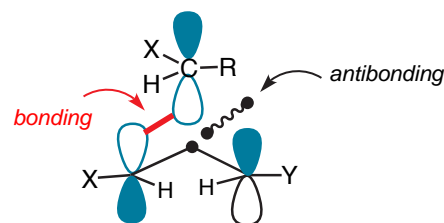
consider the 1,3-migration of Carbon



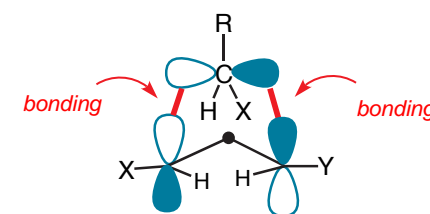
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Retention at carbon



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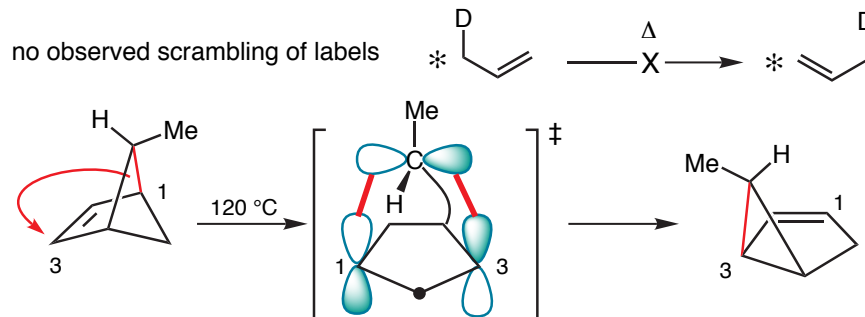
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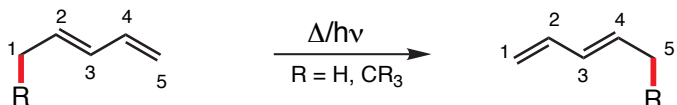
□ The stereochemical constraints on the suprafacial migration of carbon with inversion of configuration is highly disfavored on the basis of strain.

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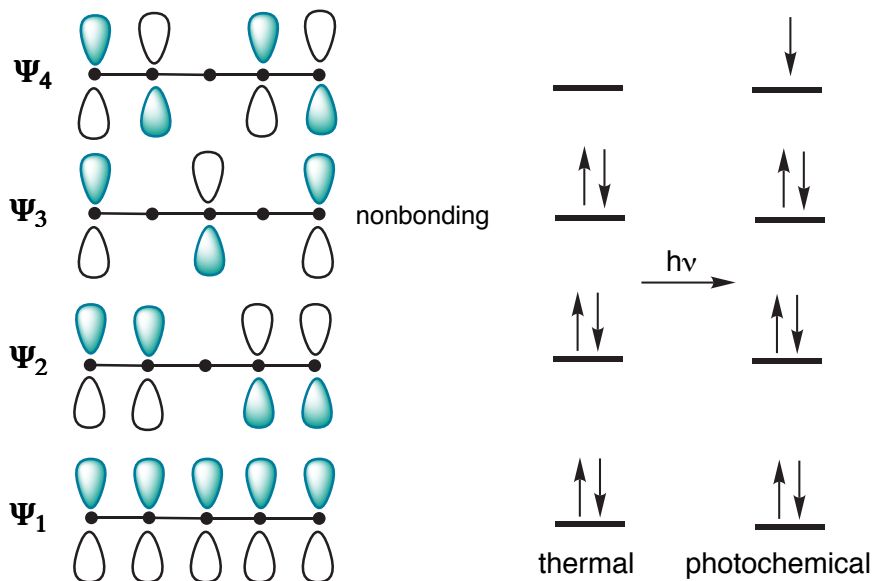


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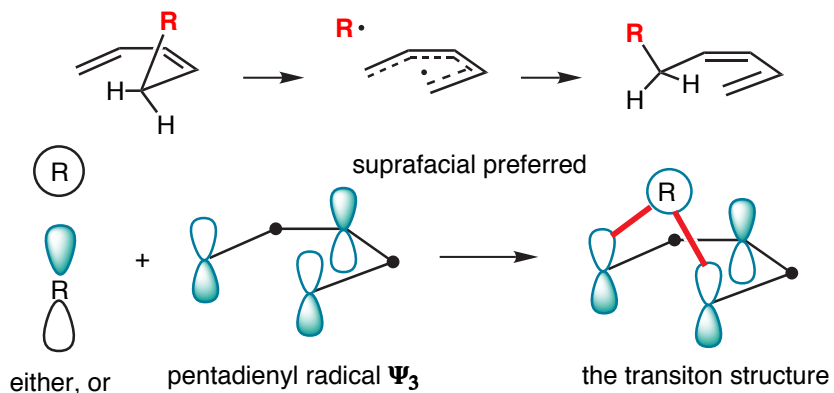
SIGMATROPIC REACTIONS - FMO-Analysis



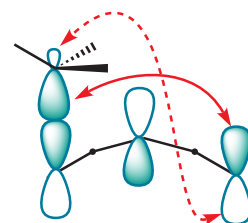
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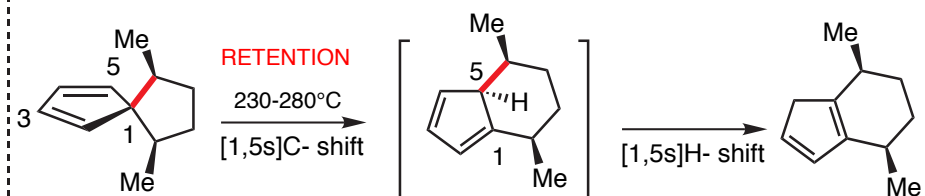
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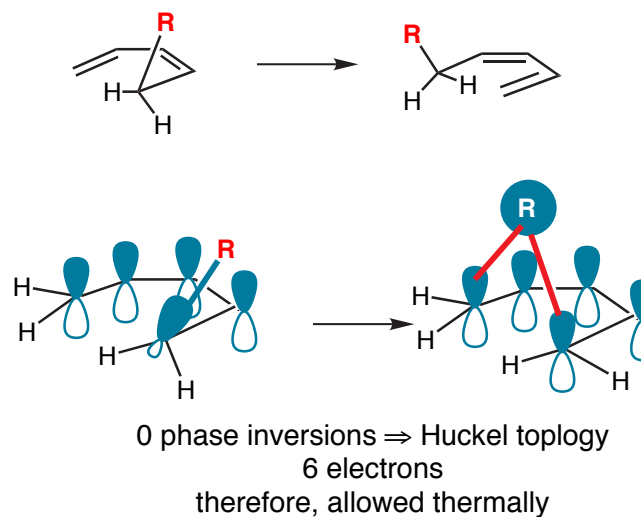
— [1s,5s] alkyl shift ⇒ RETENTION

- - - [1a,5a] alkyl shift ⇒ INVERSION
disfavored

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

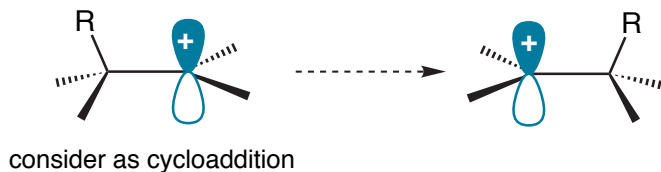
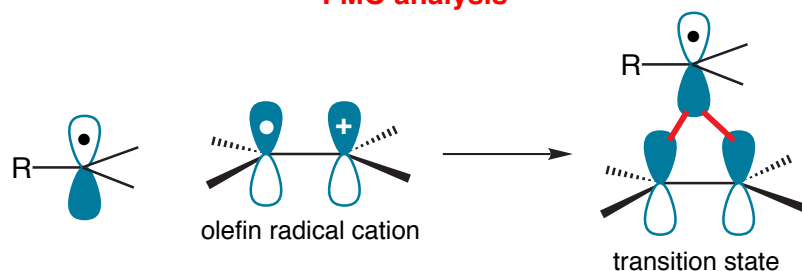


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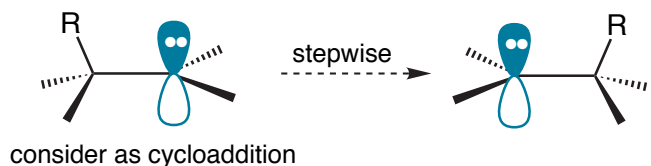
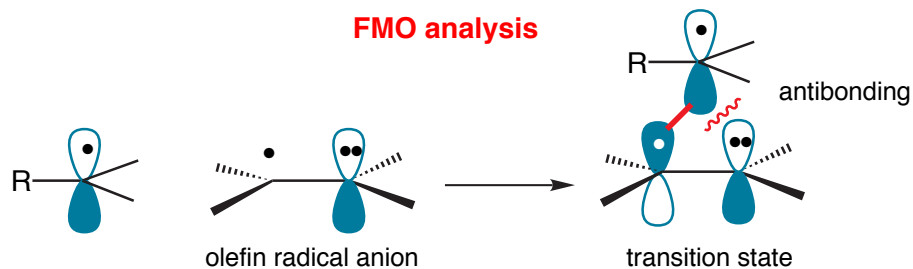


[1,2] Sigmatropic Rearrangements: Carbon

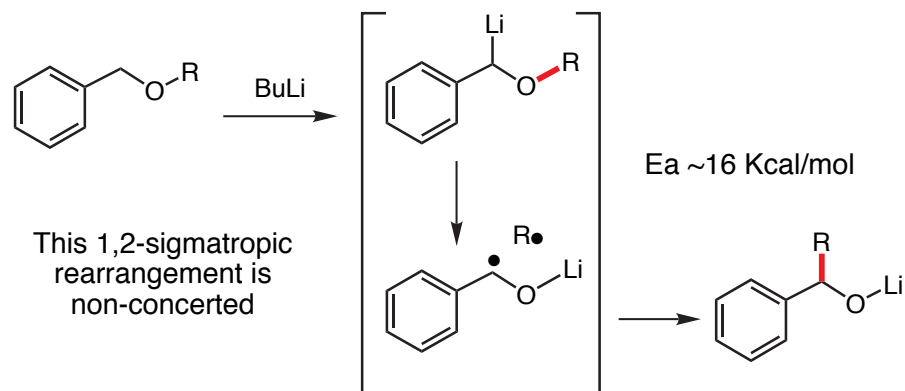
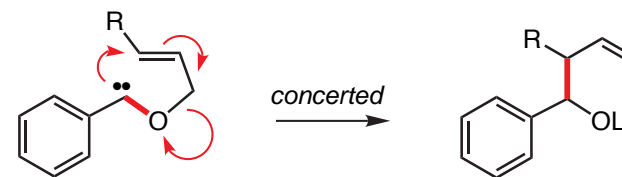
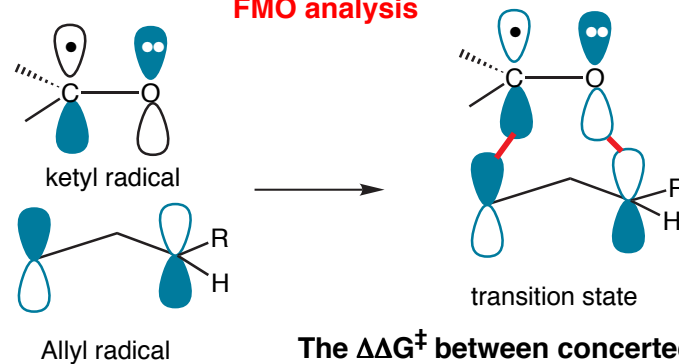
[1,2]-Sigmatropic rearrangements to cationic centers allowed.
Wagner-Meerwein Rearrangement

**FMO analysis**

[1,2]-Sigmatropic rearr to carbanionic centers not observed

**FMO analysis****The Wittig Rearrangement [1,2]**

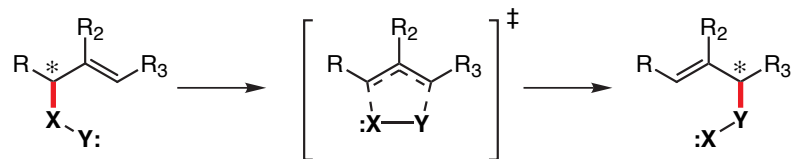
"[2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis.", Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, 86, 885.
 Marshall, J. A. *The Wittig Rearrangement.*; Trost, B. M. and Fleming, I., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 975.

**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:

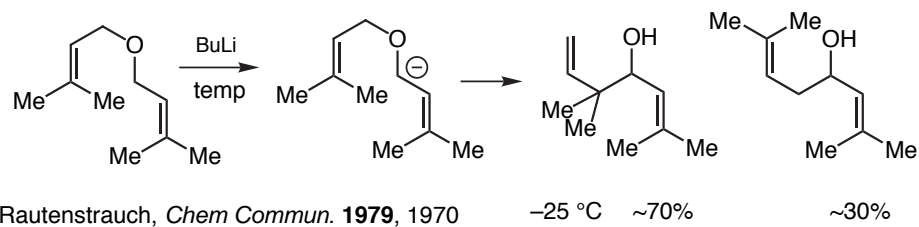
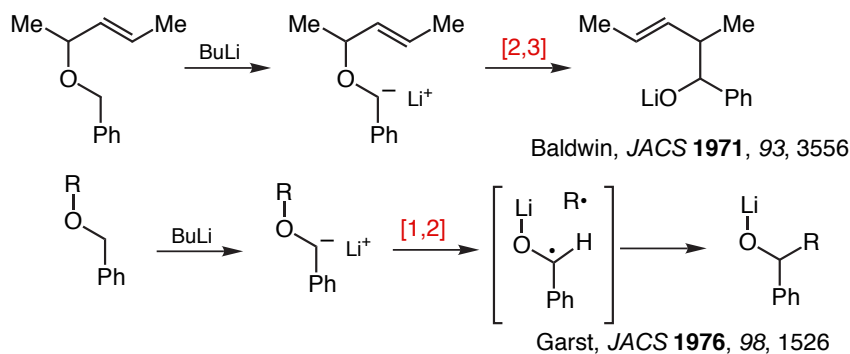
N-O (amine oxides)	S-P, S-N, S-O (sulfoxides)
S-C (sulfur ylids)	O-P (phosphites)
O-C (Wittig rearrangement)	N-N, Cl ⁺ -C (haloium ylids)
N-C (nitrogen ylids)	P-C, C-C (homoallylic anions).
S-S (disulfides)	

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

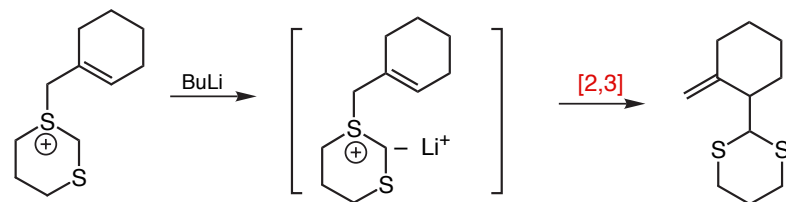
■ General Reviews:

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:



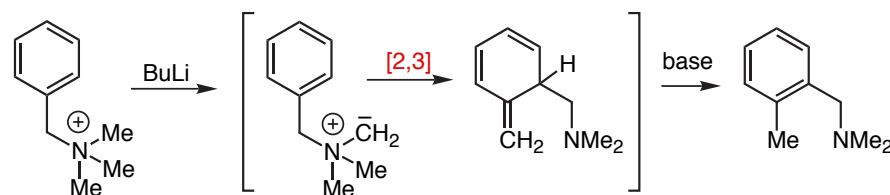
■ X - S, Y = C; Sulfonium Ylide Rearrangement:



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

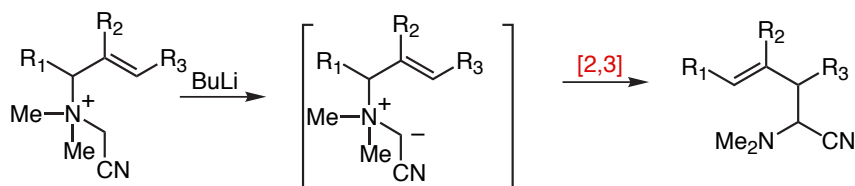
■ X - N, Y = C; Ammonium Ylide Rearrangement:

Sommelet-Hauser:



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

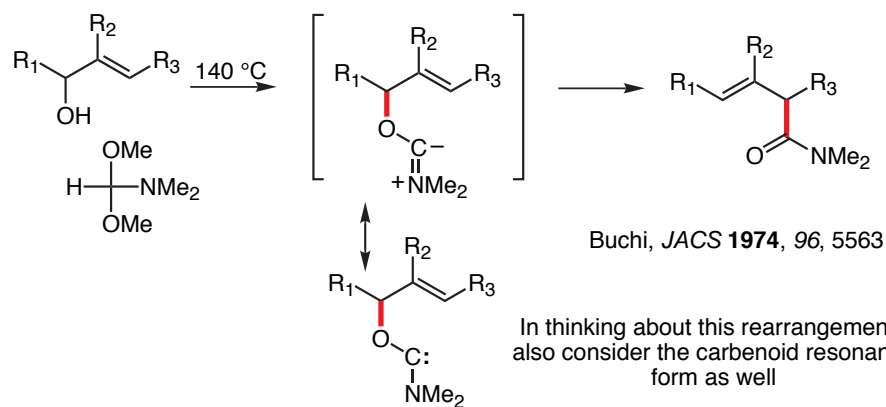
Modern versions of Stevens:



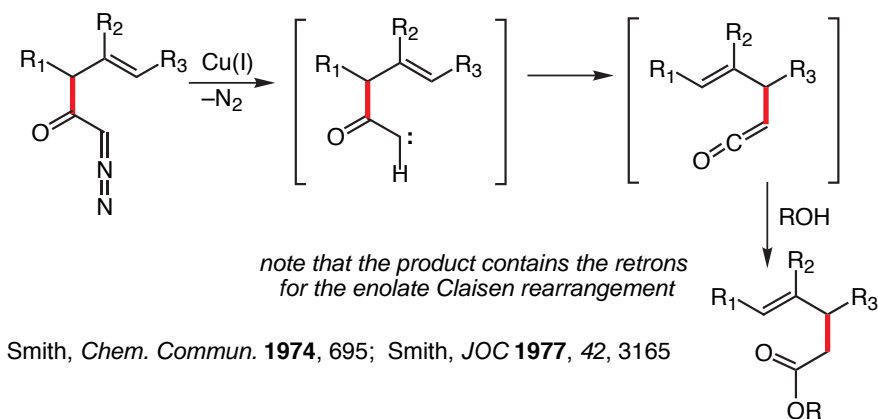
Buchi, *JACS* **1974**, 96, 7573
 Mander, *JOC* **1973**, 38, 2915

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

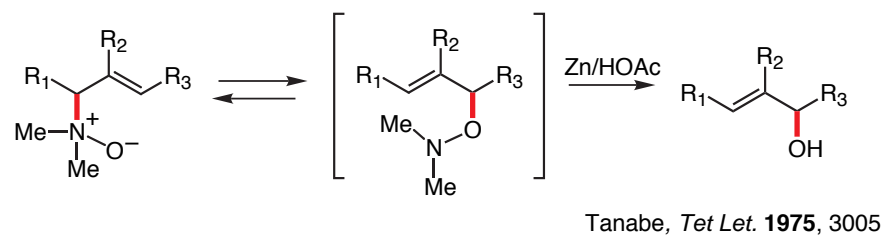
■ X - O, Y = C; Wittig-like Rearrangements



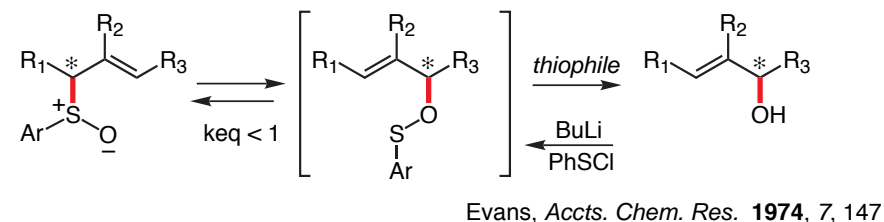
■ X - O, Y = C; An all-carbon Rearrangement



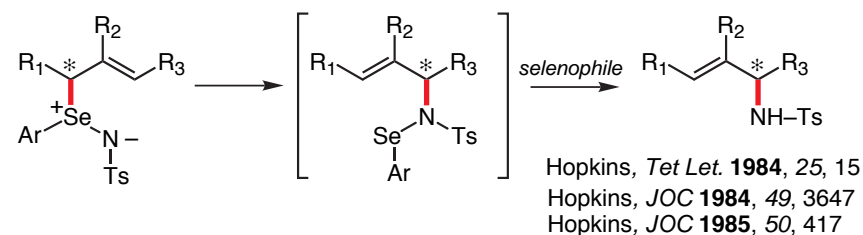
■ X - N, Y = O; Meisenheimer Rearrangement



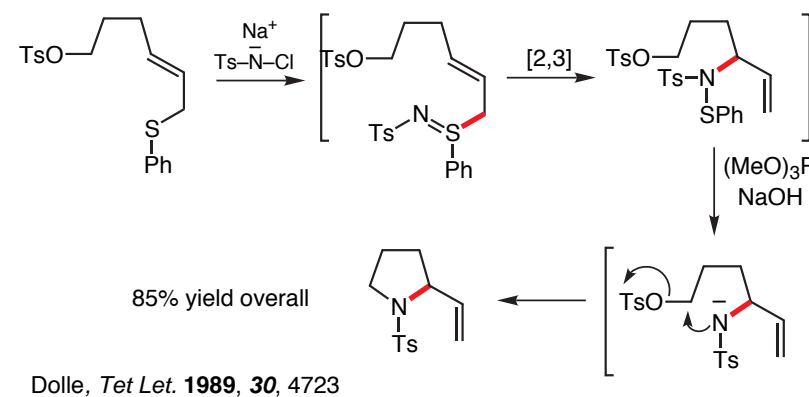
■ X - S, Y = O; Sulfoxide Rearrangement



■ X - Se, Y = N; Related Rearrangement

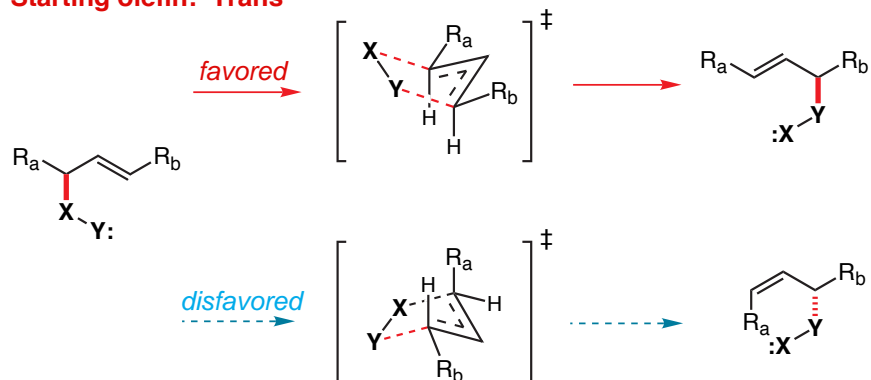


■ X - S, Y = N; Related Rearrangement



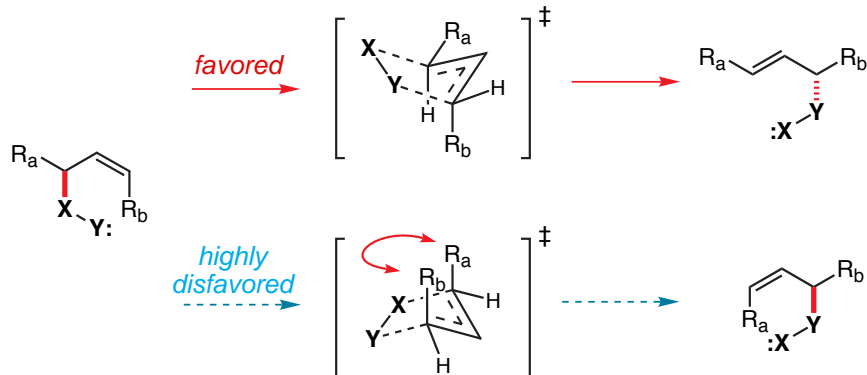
1,2-Disubstitution: Good Trans Olefin Selectivity

Starting olefin: Trans



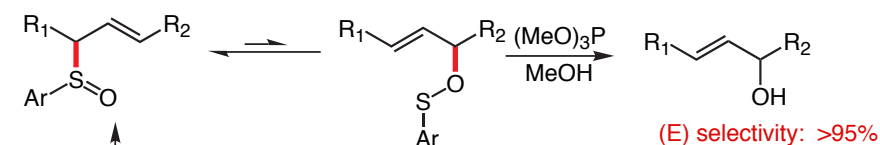
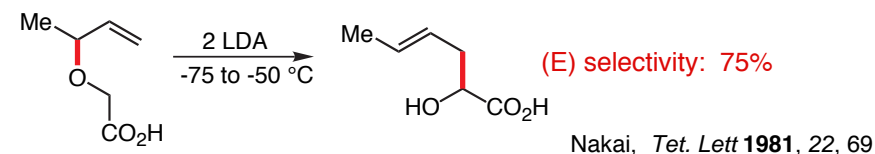
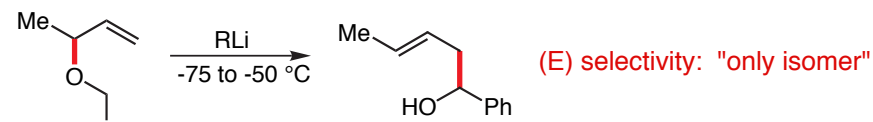
R_a & R_b prefer to orient in pseudo-equatorial positions during rearrangement; nevertheless, this is a delicately balanced situation

Starting olefin: Cis



Conclusions

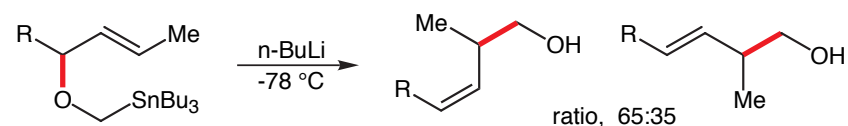
- Olefin geometry dictates sense of asymmetric induction in rearrangement
- (Z) Olefin rearrangements might exhibit higher levels of 1,3 induction
- Product olefin geometry can be either (E) or (Z) from (E) starting material
- Product olefin geometry will be (E) from (Z) starting material



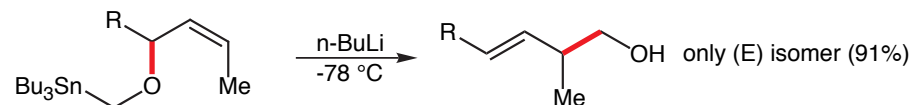
Evans, *Accts. Chem. Res.* **1974**, 7, 147-55

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

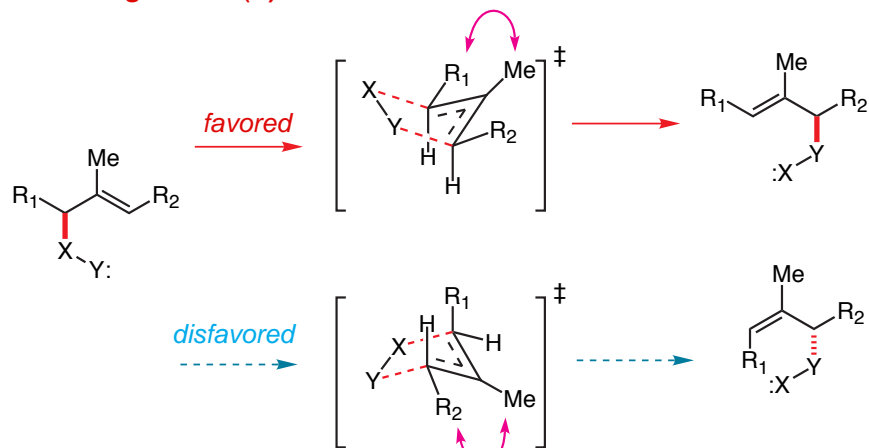


Several theoretical studies have been published: Good reading

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

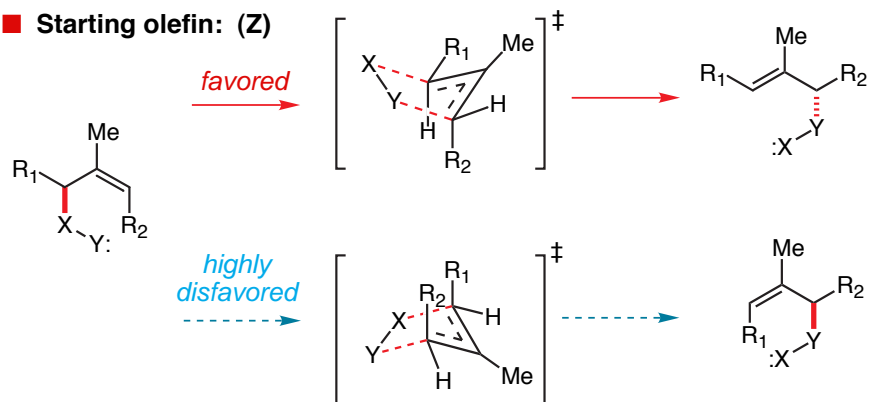
Houk *JOC* **1990**, 55, 1421 (Wittig transition states)

■ 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.

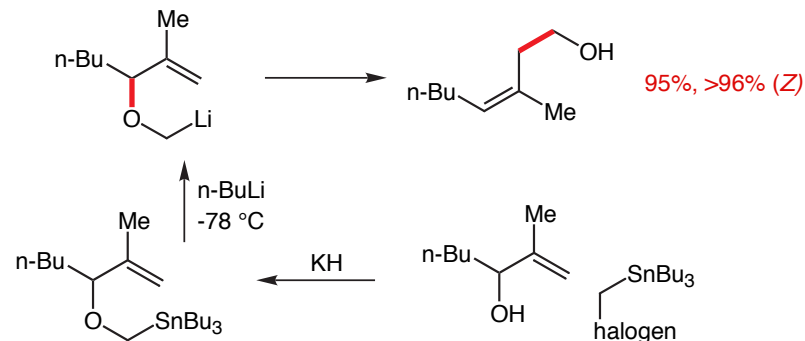
■ Starting olefin: (Z)



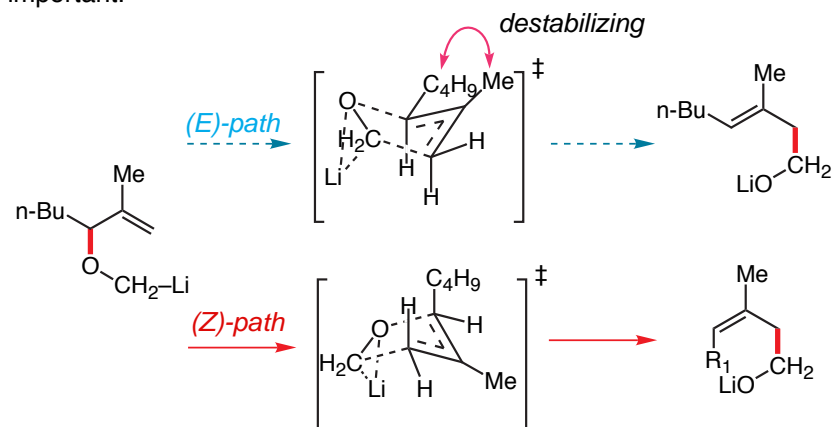
Conclusions

- 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

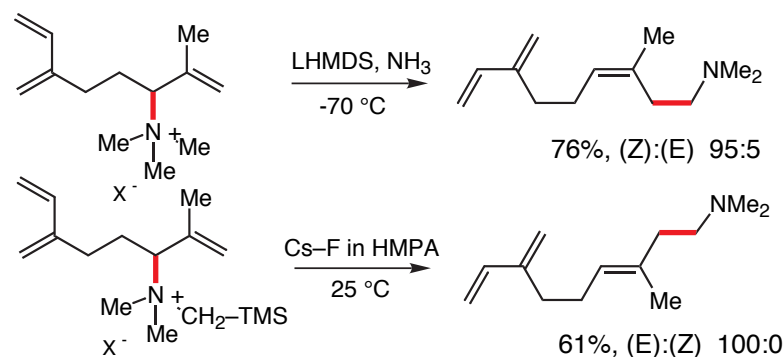
■ (Z) selectivity has been observed: Still JACS 1978, 100, 1927.



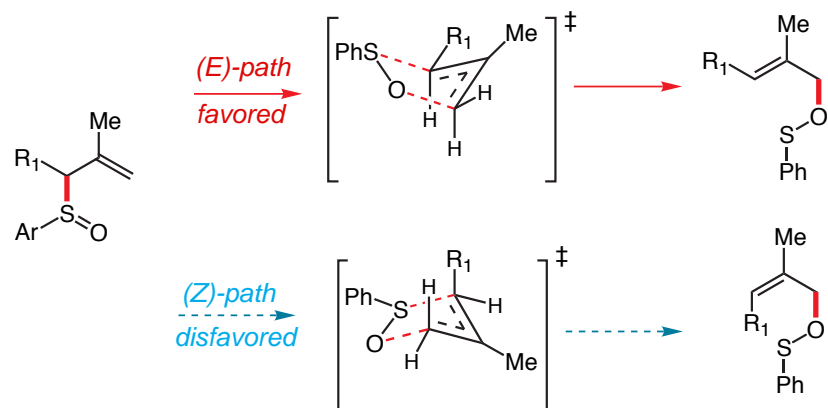
Still says that the TS is early, so that the 1,2 interactions in the TS are most important.



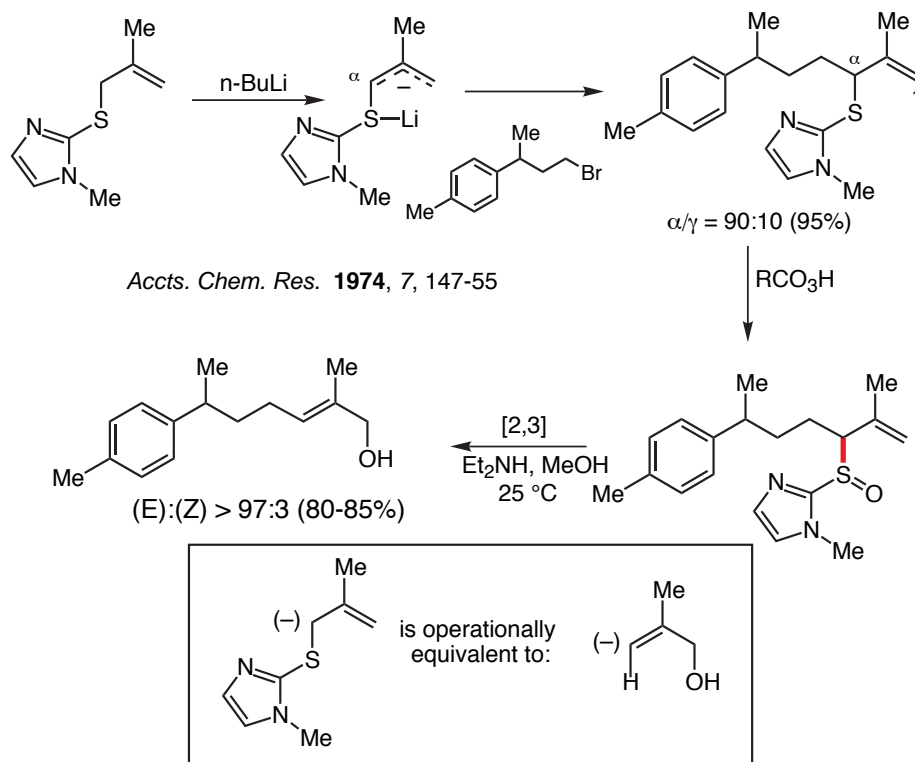
■ (Z) selectivity has also been observed by others: Sato JACS 1990, 112, 1999.



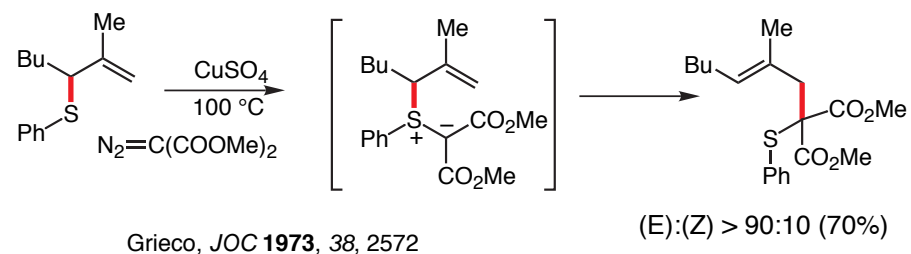
Trisubstituted olefins via [2,3]-rearrangement of sulfoxides:



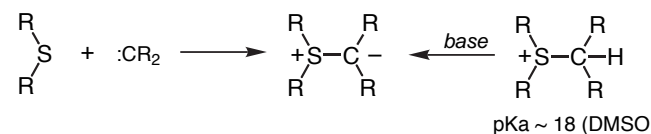
- In contrast to the previous cases exhibiting (Z) selectivity rearrangements (E)-selective rearrangements has been observed:



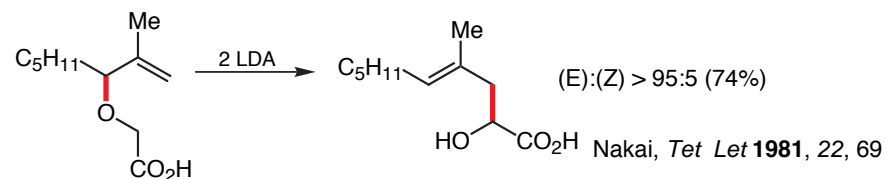
■ Trisubstituted olefins via [2,3]-rearrangement of sulfonium ylides:



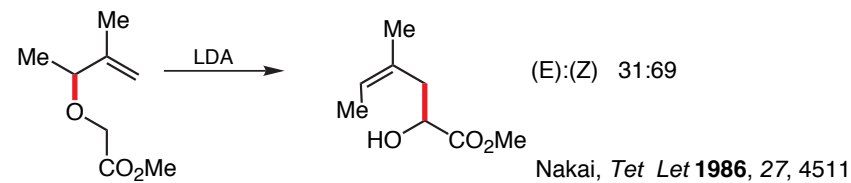
A general procedure for the direct synthesis of sulfur ylides:



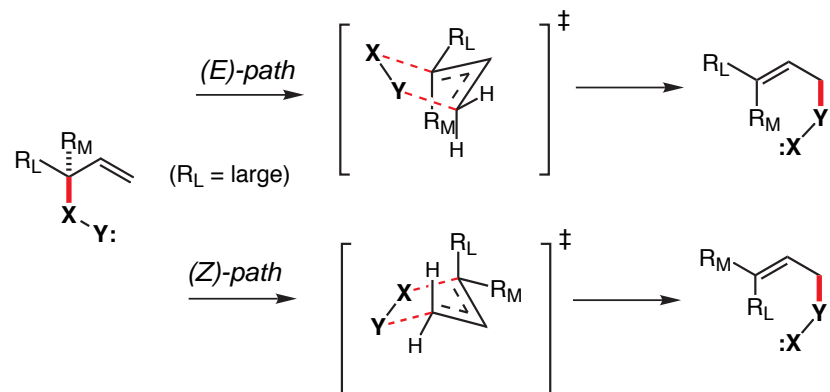
■ Trisubstituted olefins via Wittig [2,3]-rearrangement:



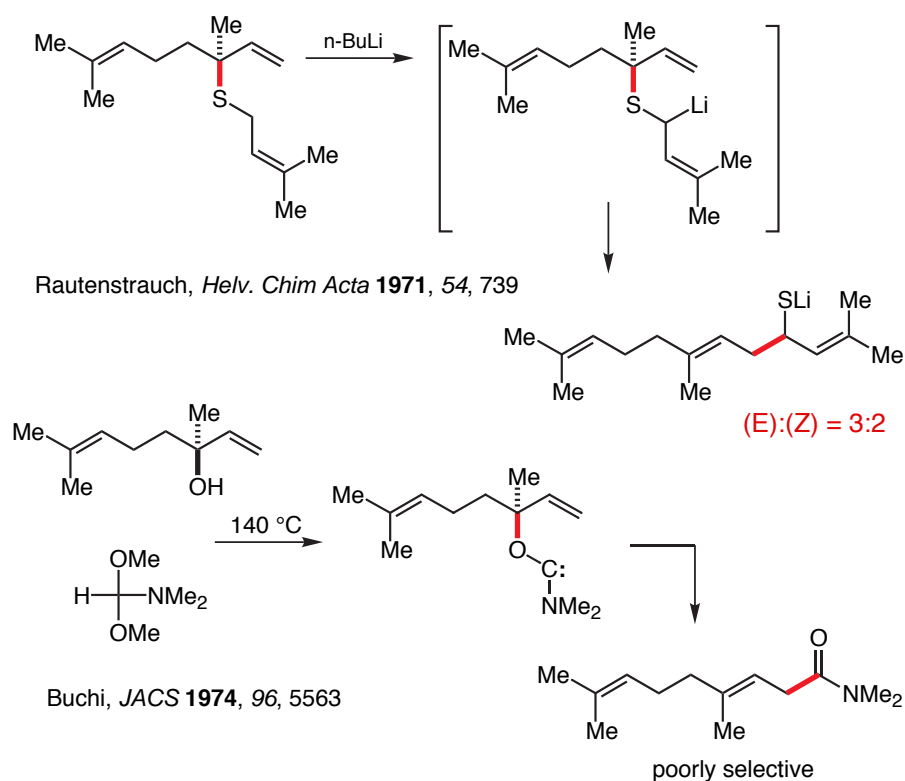
However, this reaction is not general:



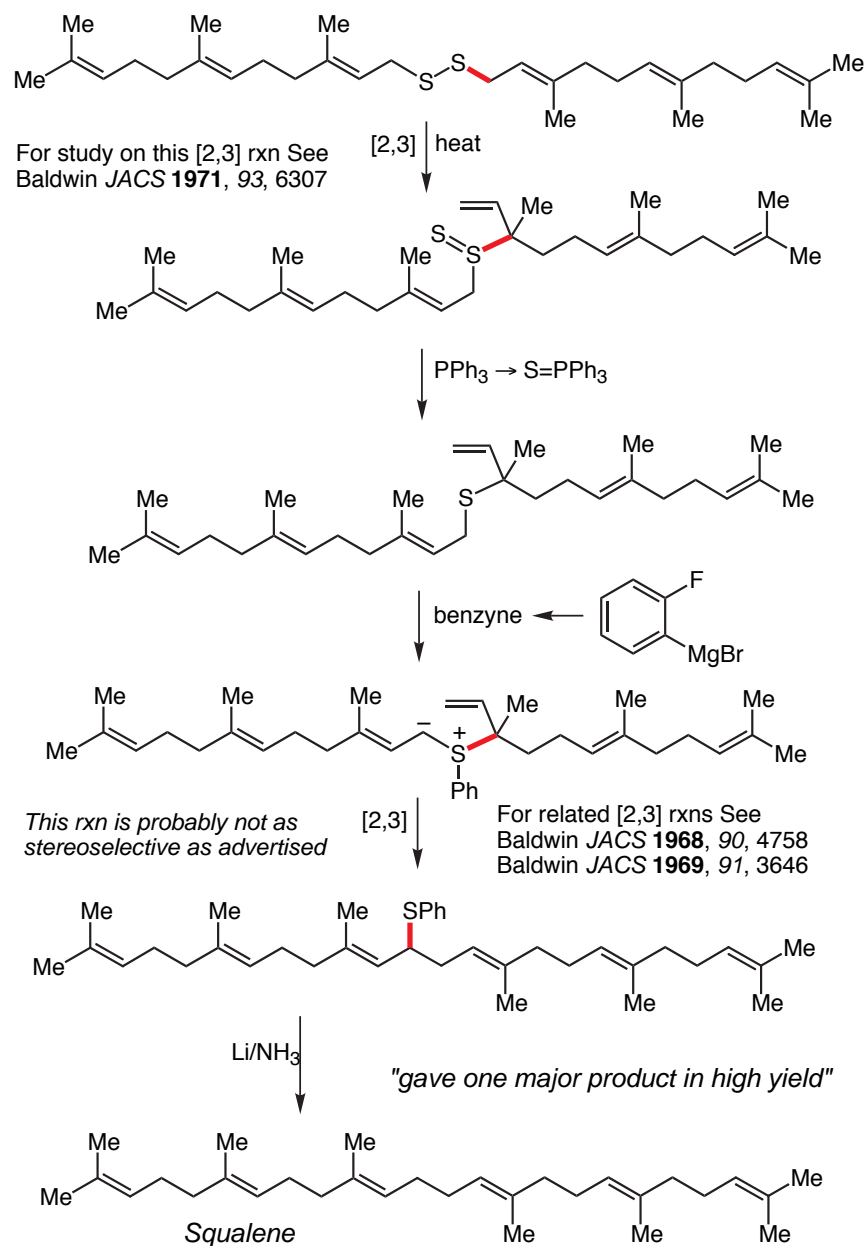
■ Trisubstituted olefins via [2,3]-rearrangement:

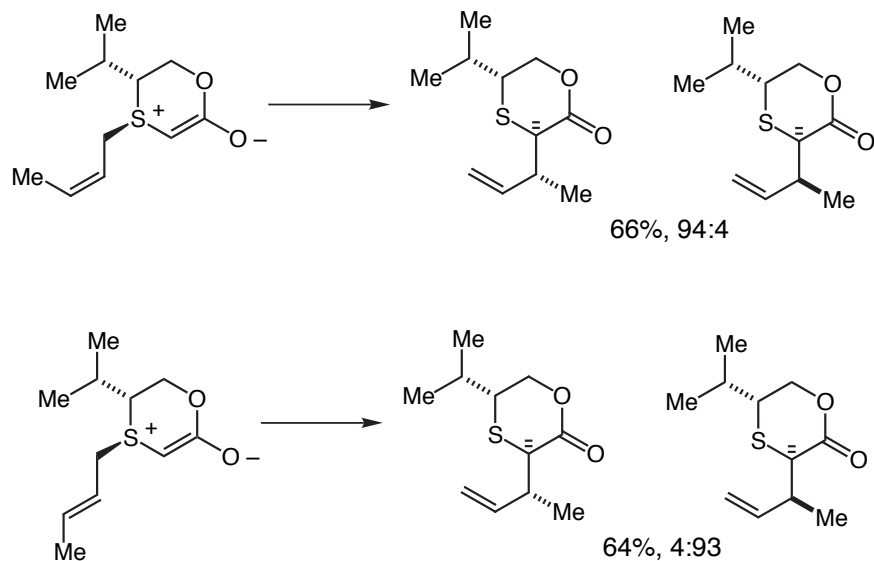
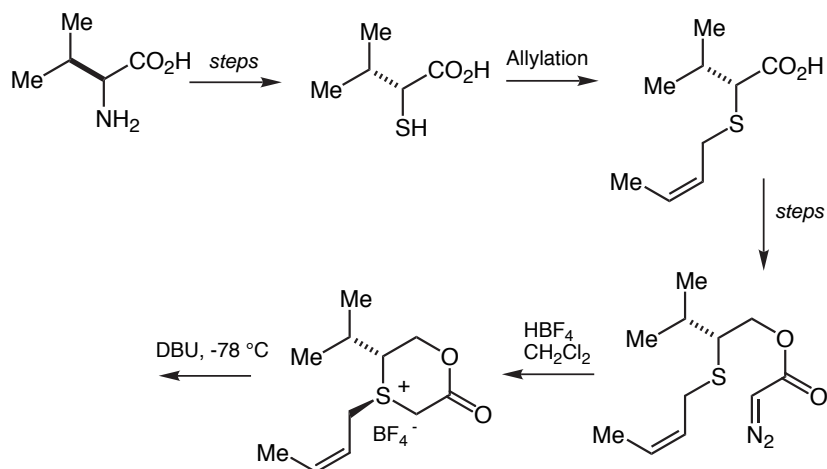
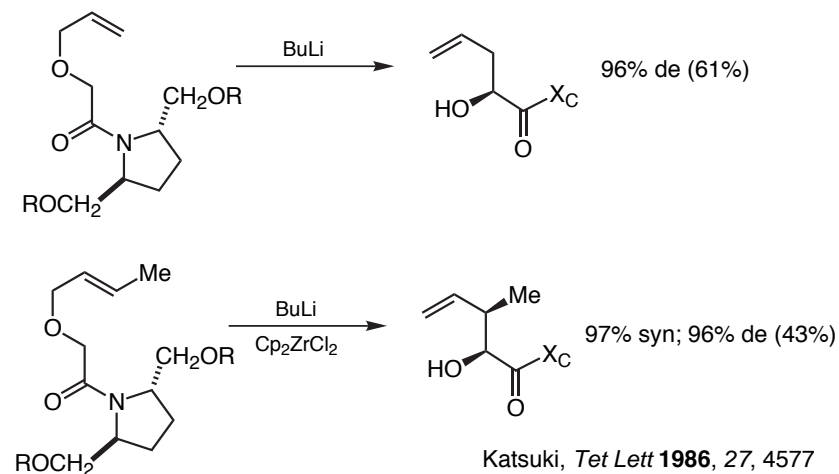
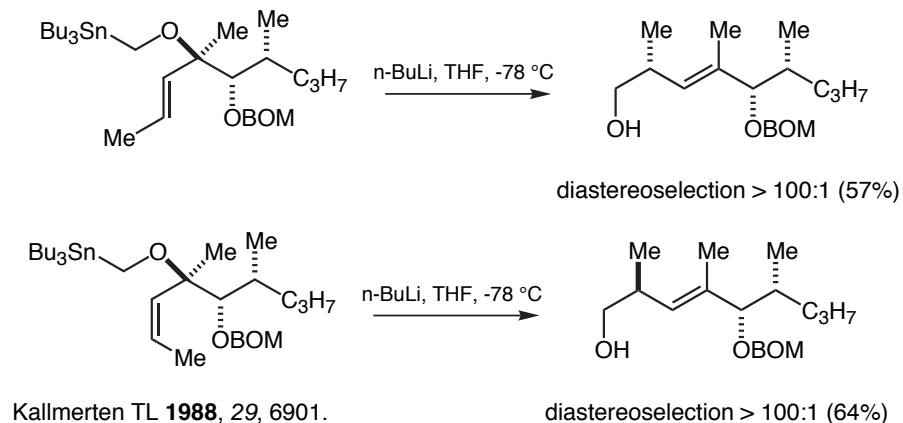


One might project that the (E) path will be moderately favored with selectivity depending on size difference between R_L & R_M



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

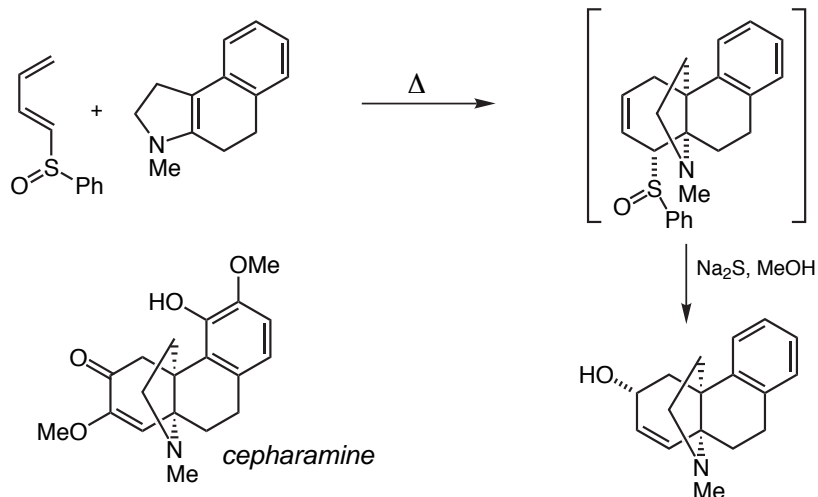


[2,3] Sulfur Ylide Rearrangement Using a Chiral AuxiliaryKurth JOC **1990**, 55, 2286 and TL **1991**, 32, 335**Chiral Auxiliaries can also be used in the Wittig Rearrangement****Internal Relay of Stereochemistry in C-C Constructions**

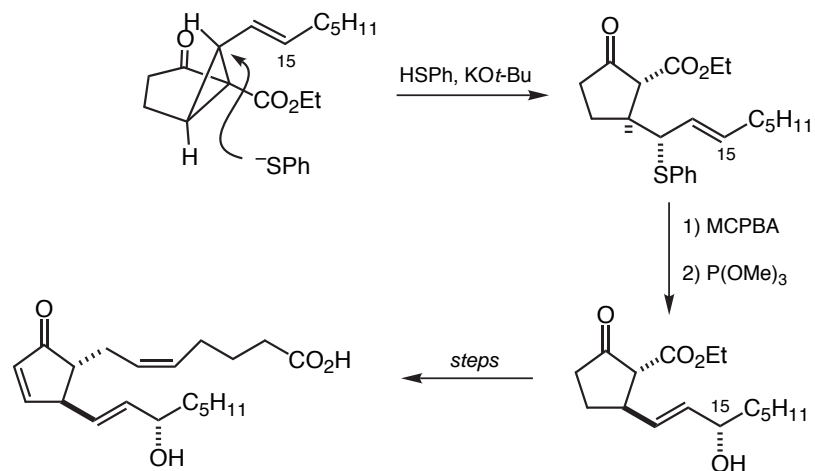
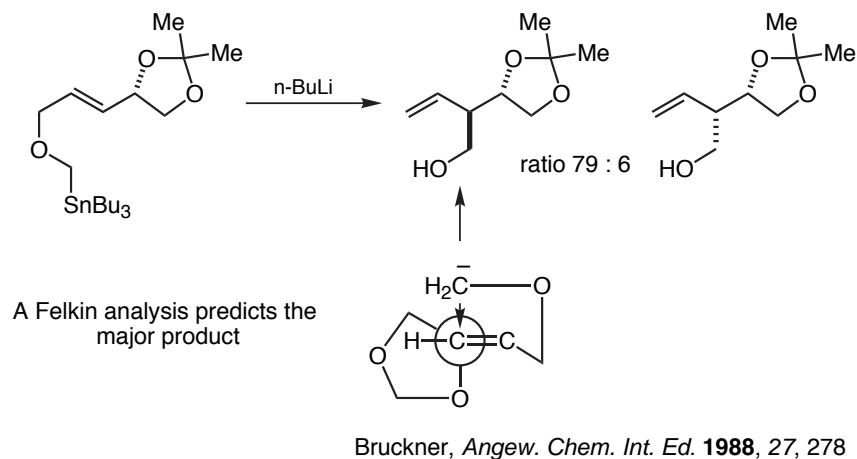
See these papers for other applications

- Kallmerten TL **1993**, 34, 753.
- Kallmerten TL **1993**, 34, 749.
- Kallmerten SynLet **1992**, 845.

Internal Relay of Stereochemistry in C–O Constructions

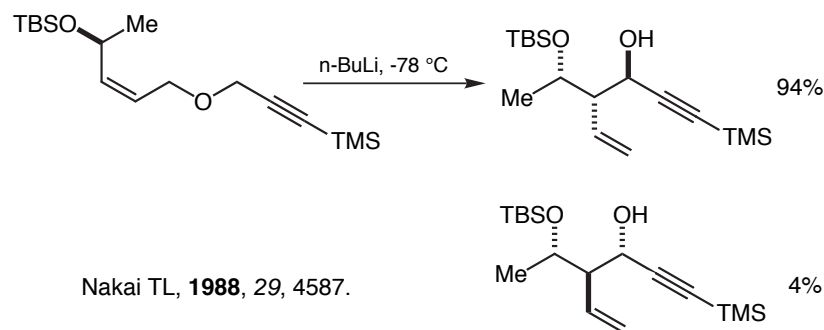
Tandem [4+2] & [2,3] Process: Evans, Bryan, Sims *J. Am. Chem. Soc.* **1972**, 2891.

Cases where the chirality is exocyclic to the rearrangement



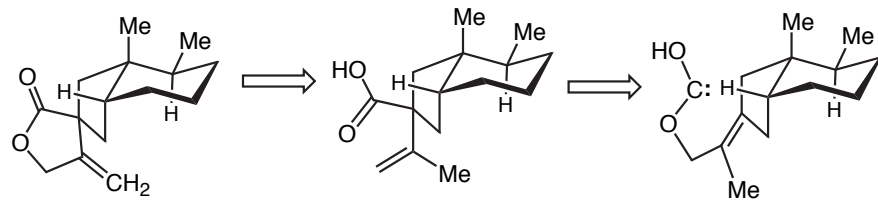
Taber *J. Am. Chem. Soc.* **1977**, 99, 3513.
Kondo *Tet. Lett.* **1978**, 3927.

Allylic Ethers to Make Three Contiguous Stereocenters

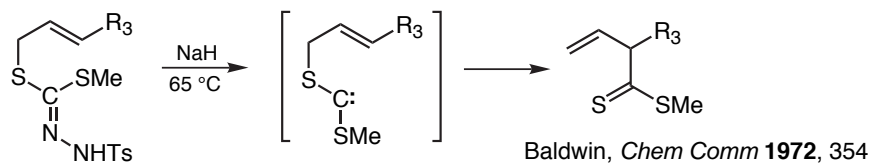
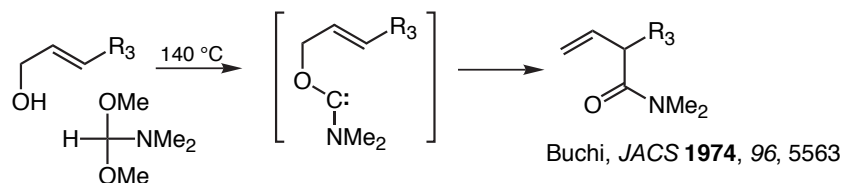


Can you rationalize the stereochemical outcome of this reaction?

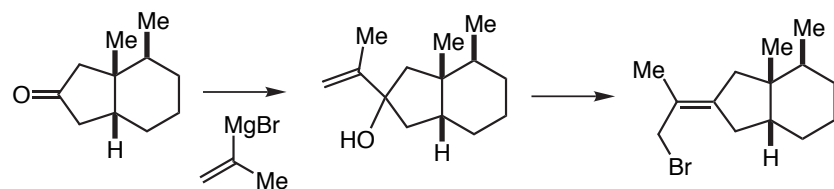
The Synthesis of Bakkenolide-A (Evans JACS 1977, 99, 5453)



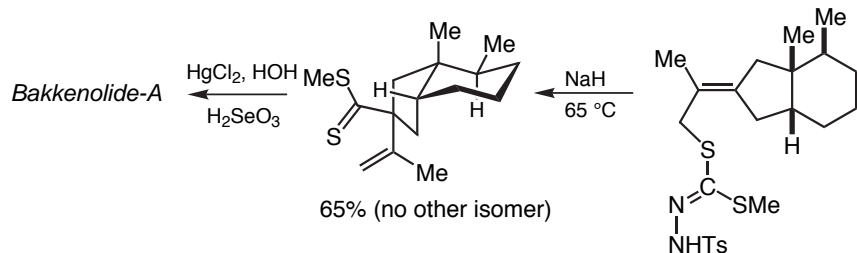
Candidate processes:



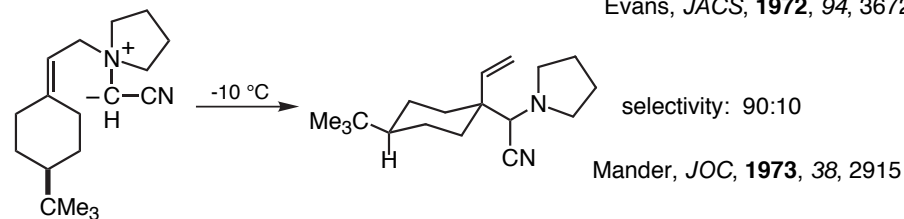
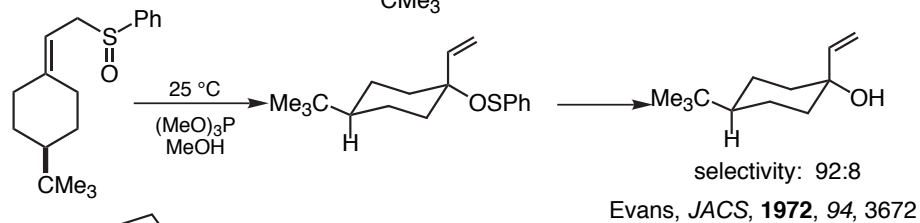
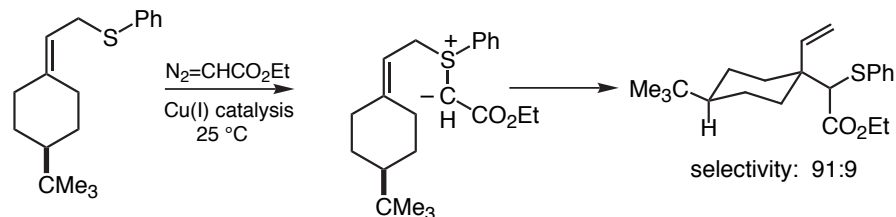
The synthesis:



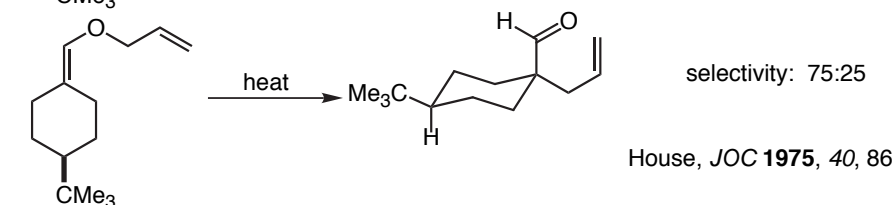
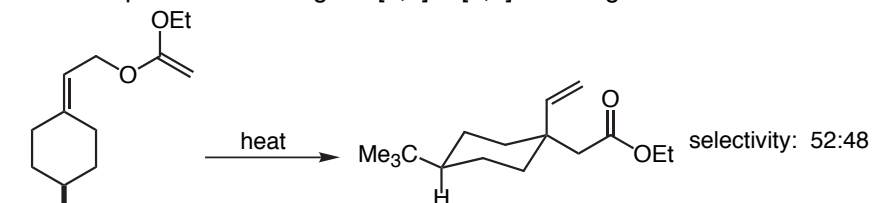
Note that rearrangement is not required to proceed via the carbenoid. propose alternate mechanism



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

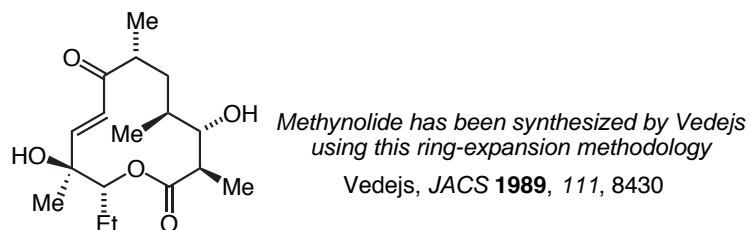
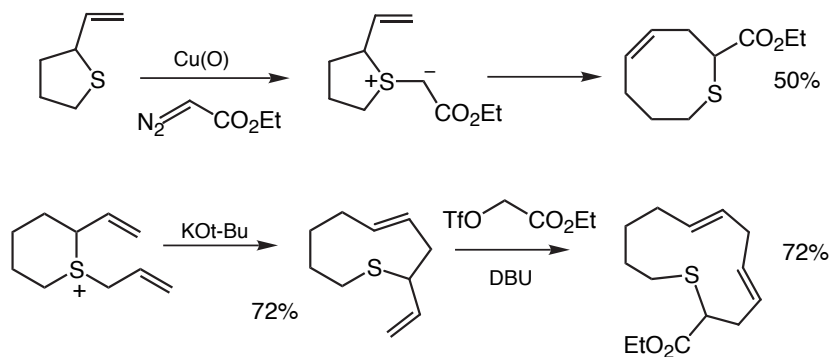


The comparison of analogous [2,3] & [3,3] rearrangements:

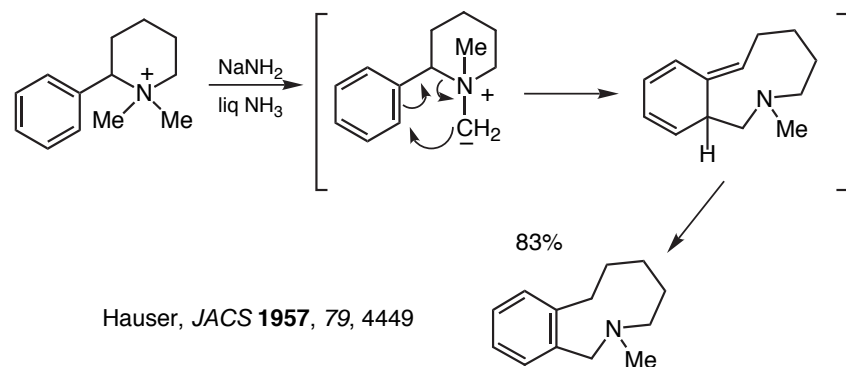


Ring expansion reactions have been investigated

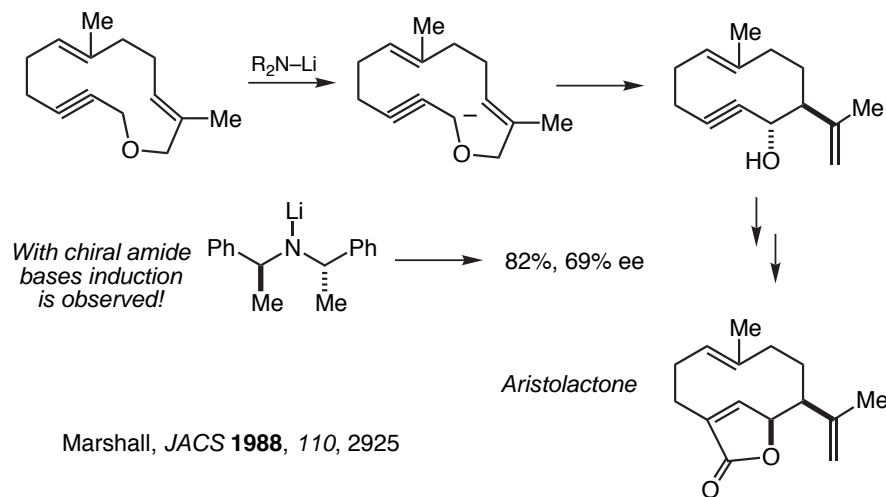
Methods based on sulfur ylides: (review) Vedejs, *Accts. Chem. Res.* **1984**, 17, 358



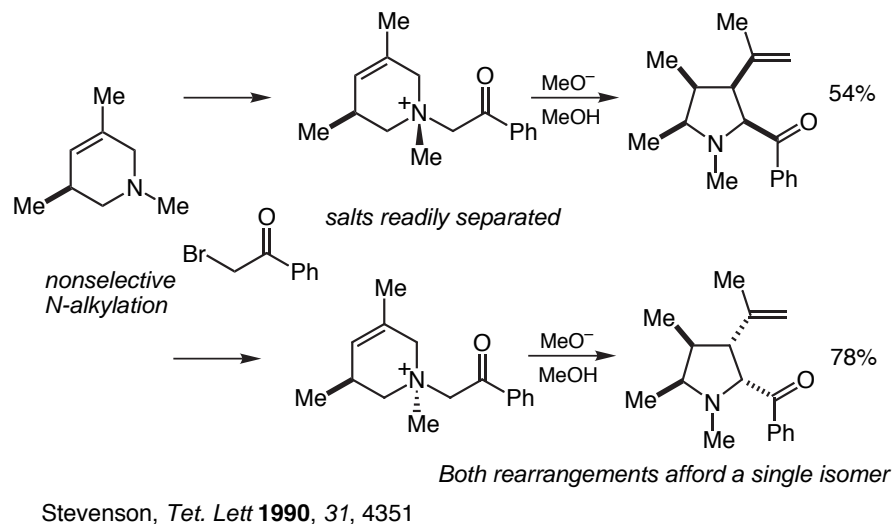
An early ring expansion using the Sommelet-Hauser Rearrangement



A ring contraction using the Wittig Rearrangement



A ring contraction using the Stevens Rearrangement



<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*

K. Houk, *Transition Structures of Hydrocarbon Pericyclic Rxns*
Angew Chem. Int. Ed. Engl. **1992**, 31, 682-708

K. Houk, *Pericyclic Reaction Transition States: Passions & Punctilios, Accts.*
Chem. Res. **1995**, 28, 81-90
Angew Chem. Int. Ed. Engl. **1992**, 31, 682-708

D. A. Evans

Friday,
October 16, 2003

■ 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)

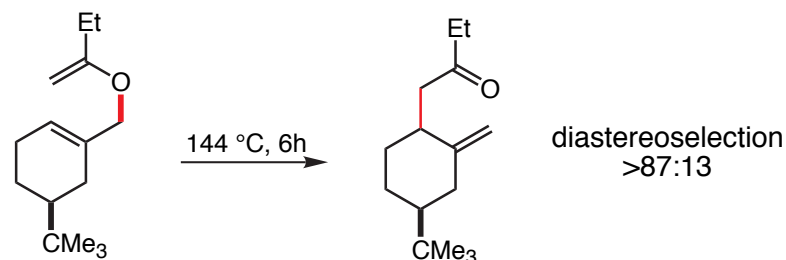
S. R. Wilson, *Organic Reactions* **1993**, 43, 93 (oxy-Cope)

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.

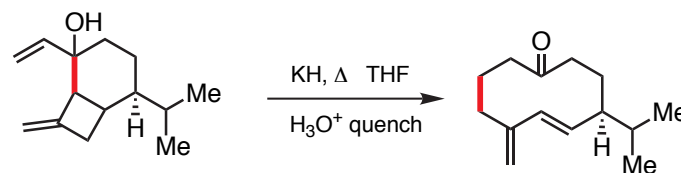
■ Problems of the Day:

Predict the stereochemical outcome of this Claisen rearrangement



Ireland, *JOC* 1983, 48, 1829

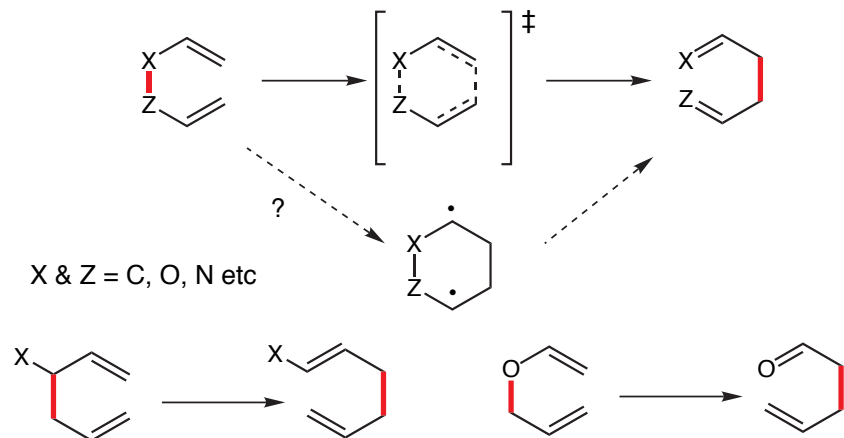
Provide a mechanism for the indicated transformation



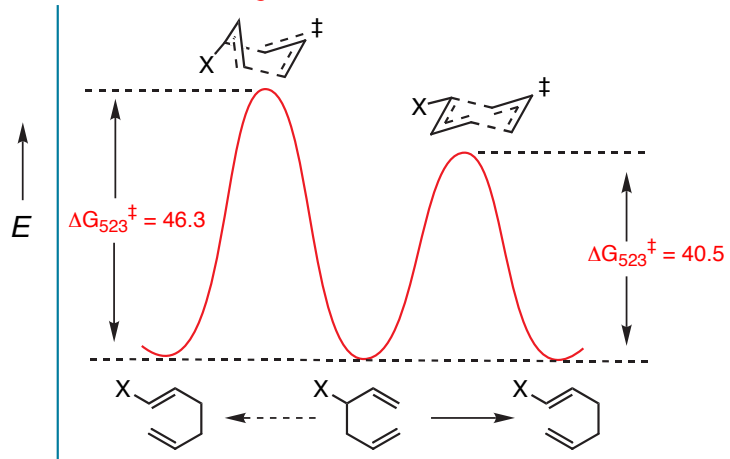
Schreiber, *JACS* **1984**, 106, 4038

General Reviews:

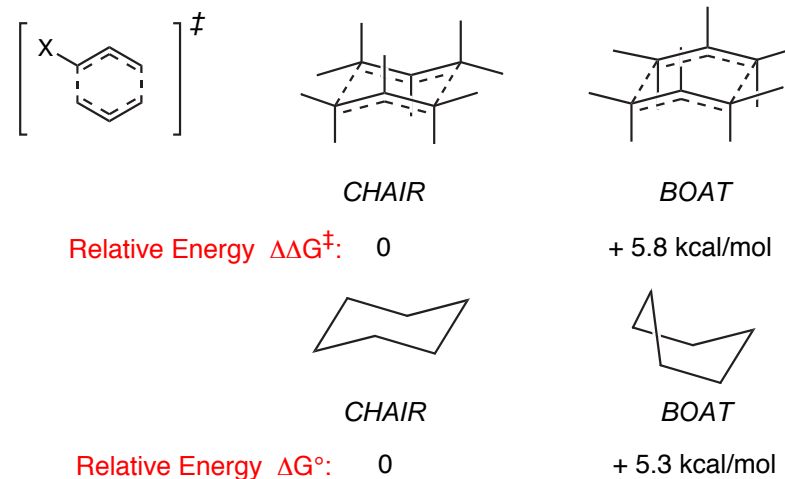
S. J. Rhoades, *Organic Reactions* **1974**, 22, 1 (Cope, Claisen)
 S. R. Wilson, *Organic Reactions* **1993**, 43, 93 (oxy-Cope)
 T. S. Ho, *Tandem Organic Reactions* **1992**, Chapter 12 (Cope, Claisen)
 Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5,
 Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
 Chapter 7.2, Claisen



Cope Rearrangement, $E_a = 33.5$ kcal/mol Claisen Rearrangement $E_a = 30.6$ kcal/mol

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

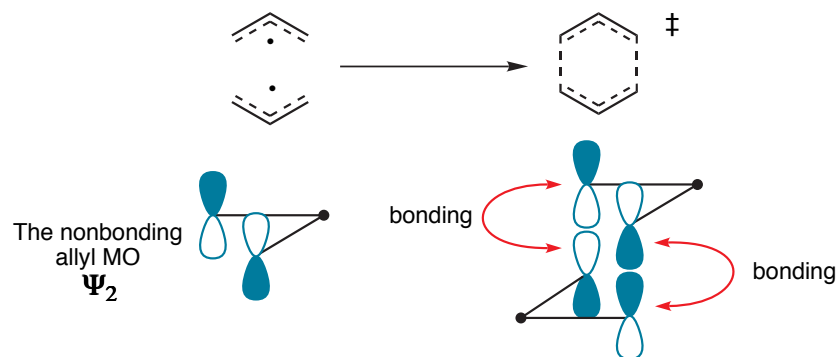
The Cope Transition States



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

The FMO Analysis (Fleming page 101)

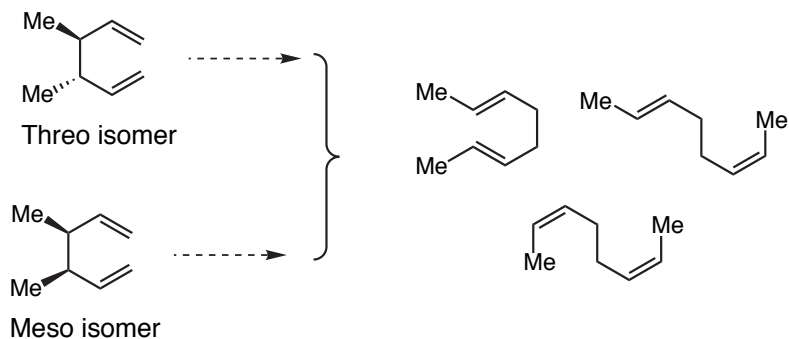
Bring two allyl radicals together to access for a possible bonding interaction between termini.



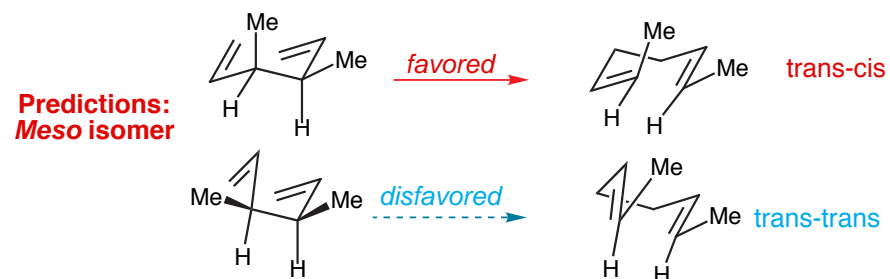
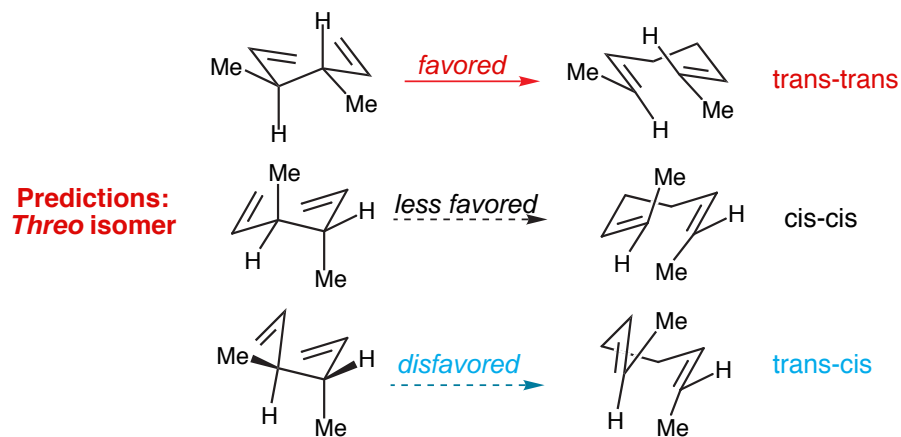
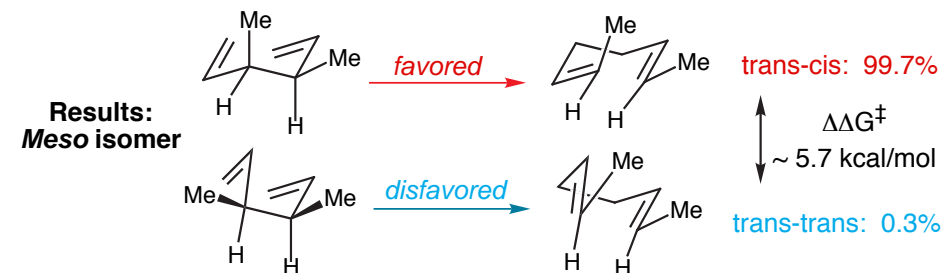
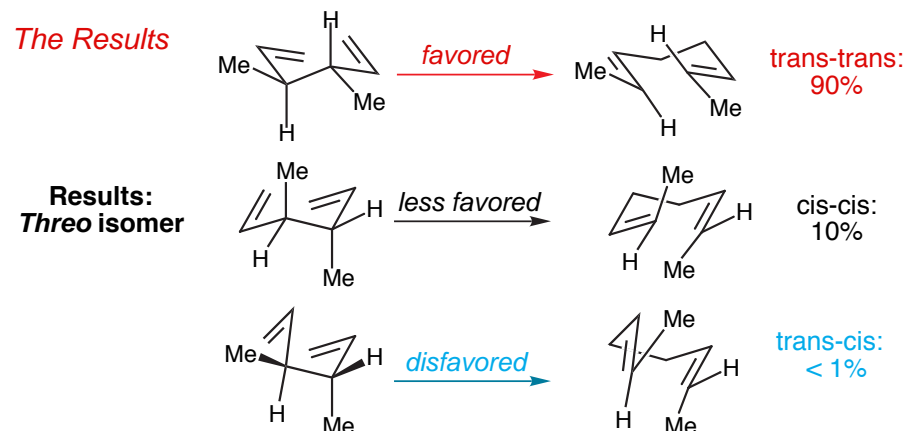
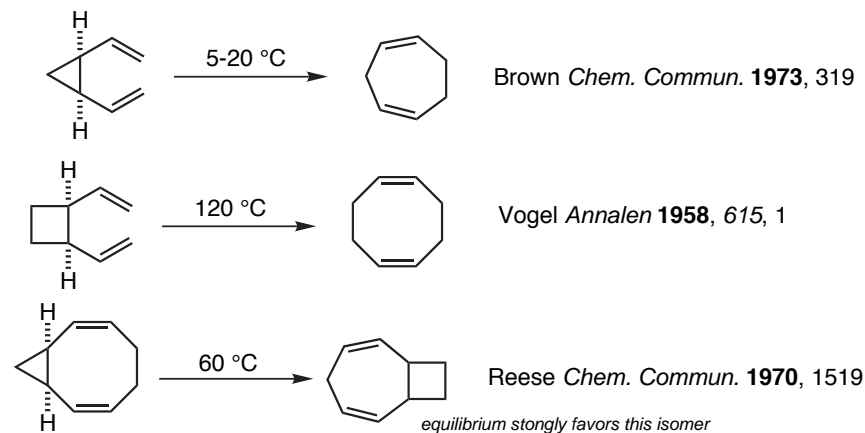
It is evident that synchronous bonding is possible in this rearrangement

Doering/Roth Experiments: Tetrahedron 18, 67, (1962):

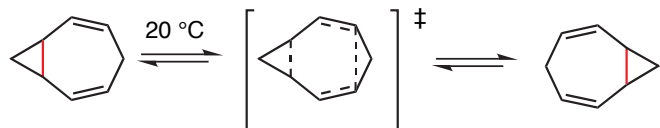
The Geometry of the transition state (boat vs chair) can be analyzed via the rearrangement of substituted 1,5-dienes:



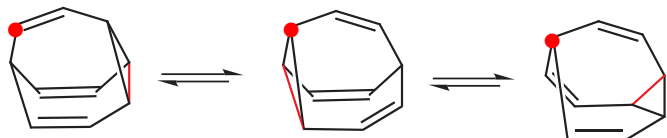
■ Measure product composition from rearrangement of each diene isomer

**The Results****Ring Strain can be employed to drive the Cope process:**

Ring Strain can be employed to drive the Cope process:



W. von E. Doering's Bullvalene

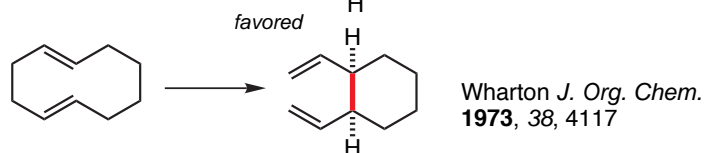
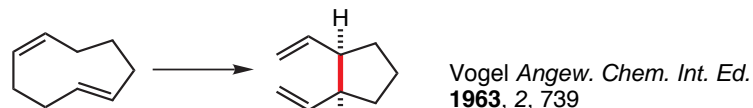


Bullvalene: $E_a = 13.9$ kcal/mol

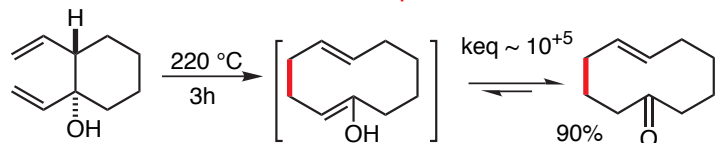
At 100 °C one carbon is observed in nmr spectrum

Carey, Vol 1, page 630-630

Position of Equilibrium dictated by ring strain issues:



However, tautomerism can shift the equilibrium:



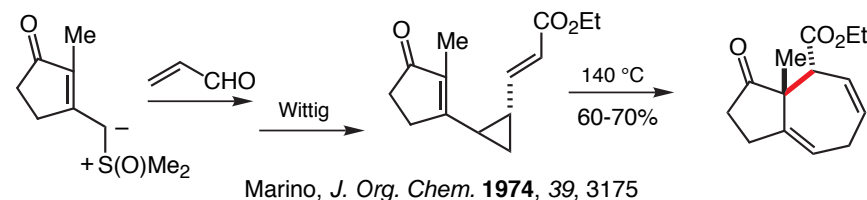
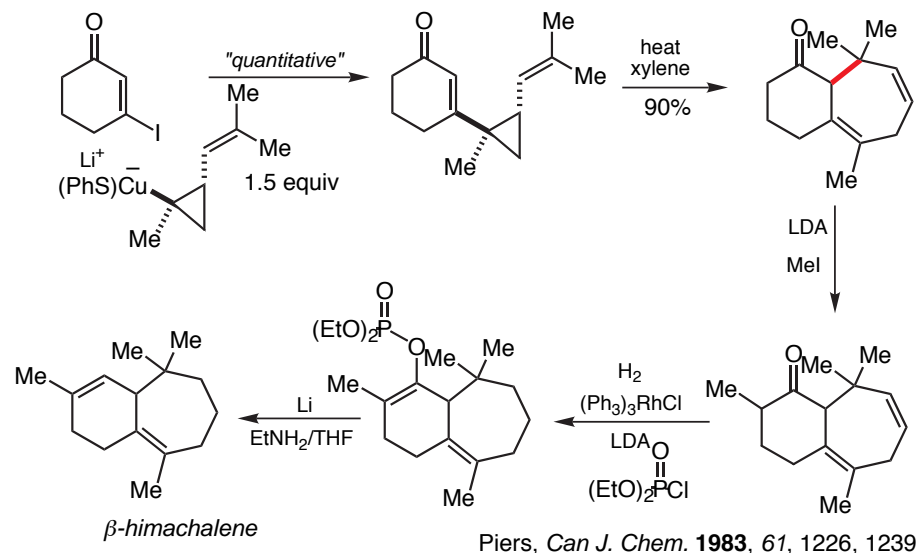
Energetically, how much does tautomerization give you?

$k_{eq} \sim 10^{+5}$

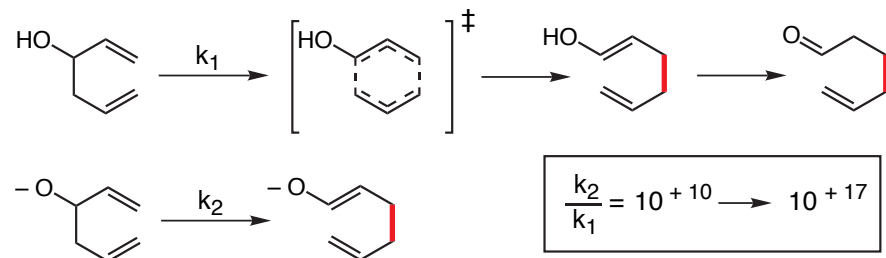
$k_{eq} \sim 10^{+5}$

$\Delta G = 1.4(pK_{eq}) = 1.4 \times (-5) = -7$ kcal/mmol

Ring extension via divinylcyclopropane rearrangement



Accelerated Cope Rearrangements

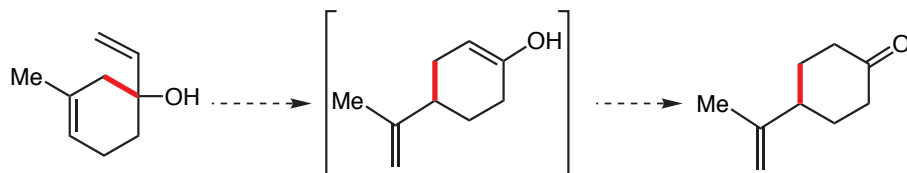


Evans, Golob, *JACS* **1975**, 97, 4765.

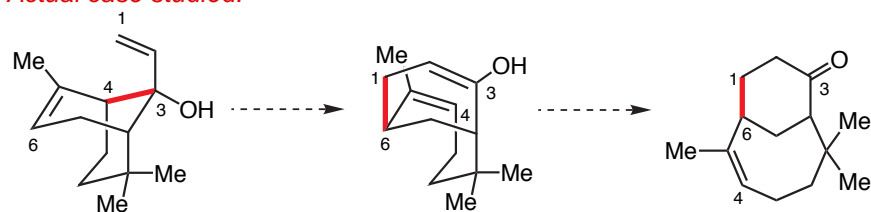
Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5, Chapter 7.1: (Cope, oxy-Cope, Anionic oxy-Cope)
"Recent applications of anionic oxy-Cope rearrangements."
Paquette, L. A. *Tetrahedron* **1997**, 53, 13971-14020

The Aborted Oxy-Cope Reaction (circa 1969)

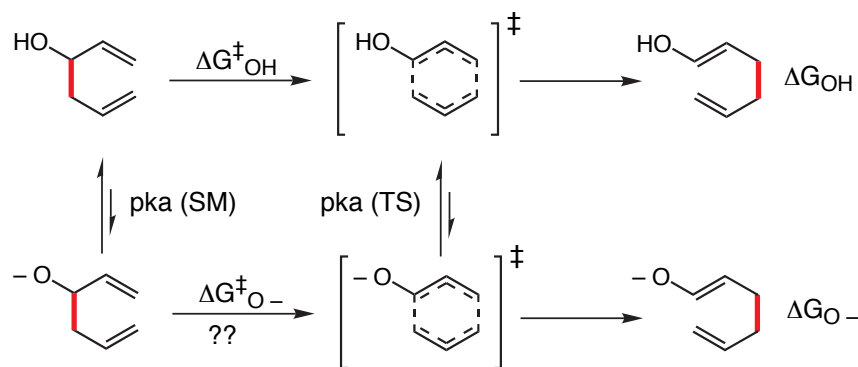
■ The basic reaction



■ Actual case studied:



Prediction of Substituent Effect (circa 1969)



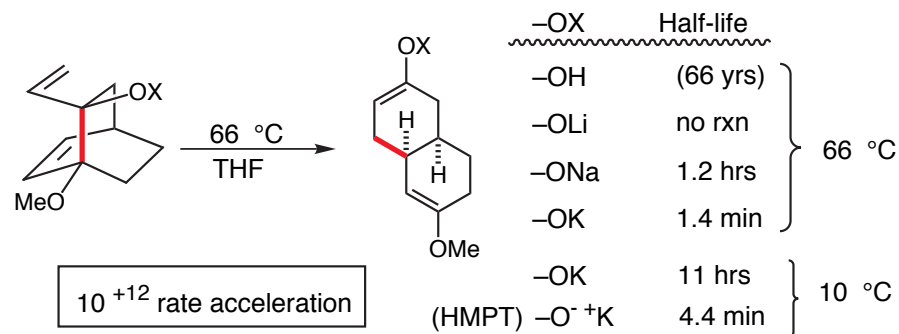
$$\Delta G_{O-}^{\ddagger} = \Delta G_{OH}^{\ddagger} + 2.3RT [pka_{TS} - pka_{SM}]$$

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

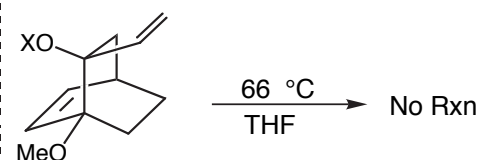
$$\Delta G_{O-}^{\ddagger} = \Delta G_{OH}^{\ddagger} + 1.4 [-11]$$

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

Documentation of Alkoxy Substituent Effect



-OX	Half-life	66 °C
-OH	(66 yrs)	
-OLi	no rxn	66 °C
-ONa	1.2 hrs	
-OK	1.4 min	10 °C
(HMPT) -OK	11 hrs	
(HMPT) -O ⁻ K	4.4 min	

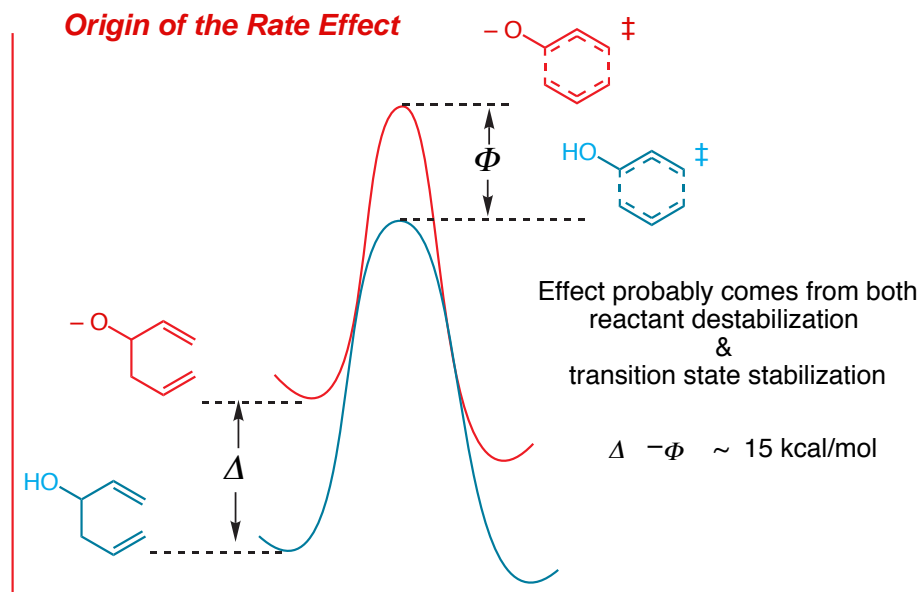


$$\Delta \Delta G_{\text{estimate}}^{\ddagger} = 15 \text{ kca mol}^{-1}$$

$$\Delta \Delta G_{\text{experiment}}^{\ddagger} = 13 \text{ kca mol}^{-1}$$

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

Origin of the Rate Effect

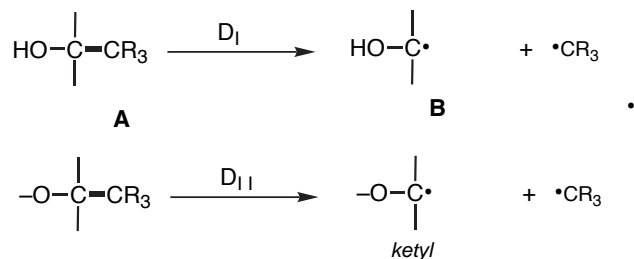


Effect probably comes from both reactant destabilization & transition state stabilization

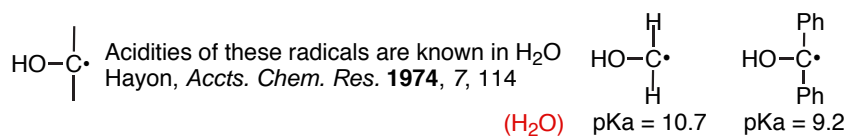
$$\Delta -\phi \sim 15 \text{ kcal/mol}$$

Maximal rates are observed under conditions where reactant is maximally destabilized

Substituent Effects in Bond Homolysis



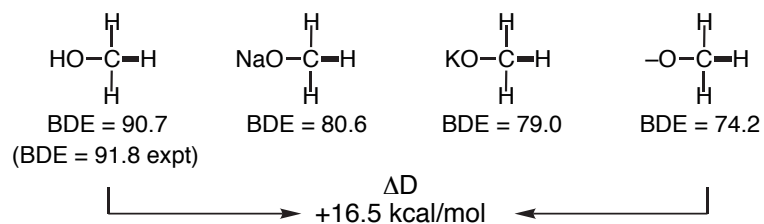
$$D_1 - D_{11} = 2.3 RT[\text{pKa}(\text{A}) - \text{pKa}(\text{B})]$$



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

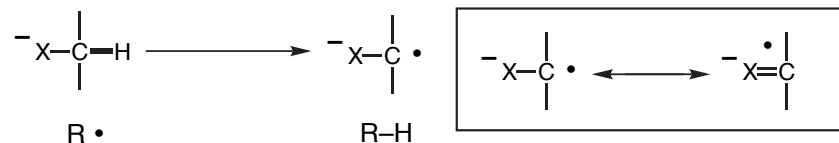
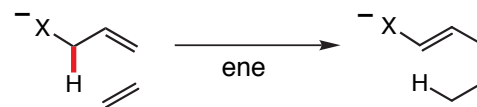
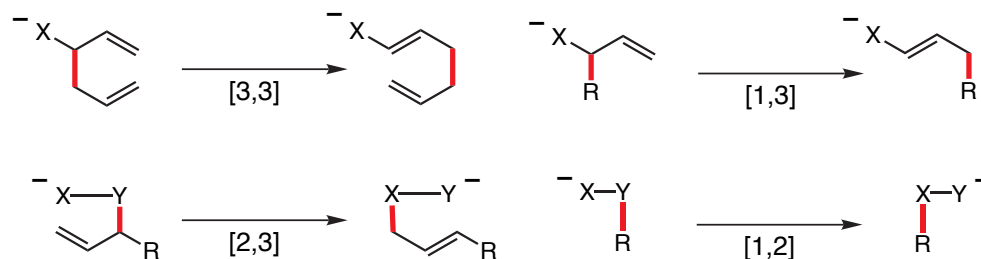
Substituent Effect based on ab initio calculations

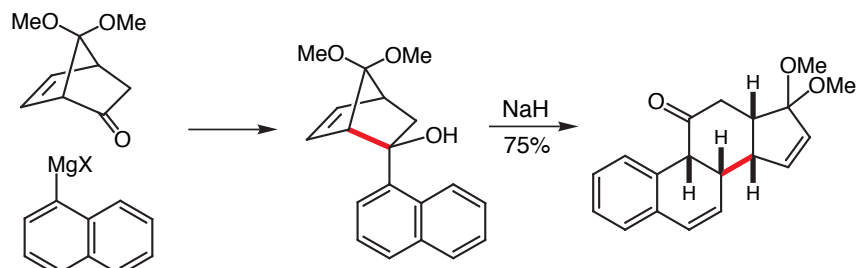
(Evans, Goddard, *JACS* **1979**, 101, 1994)



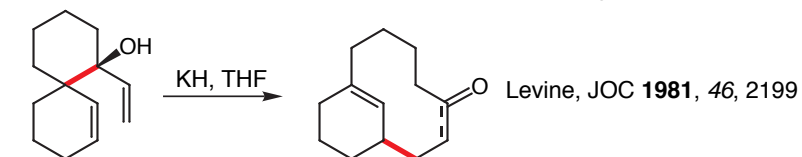
Related papers: Evans, Baillargeon, *Tet Lett.* **1978**, 36, 3315, 3319

Substituent Effects in Molecular Rearrangements

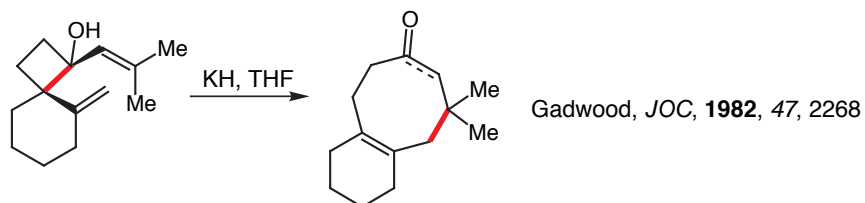




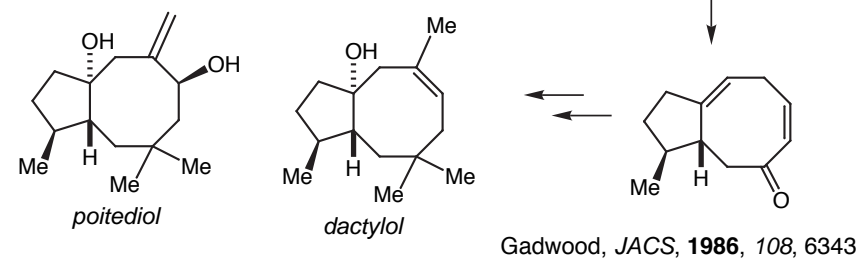
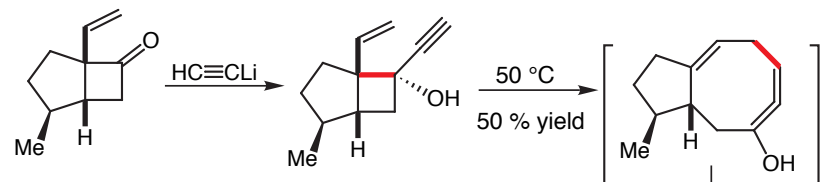
Jung, JACS **1978**, *100*, 4309
Jung, JACS **1980**, *102*, 2463



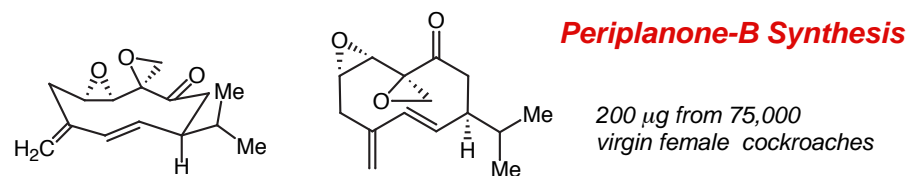
Levine, JOC **1981**, *46*, 2199



Gadwood, JOC, **1982**, *47*, 2268

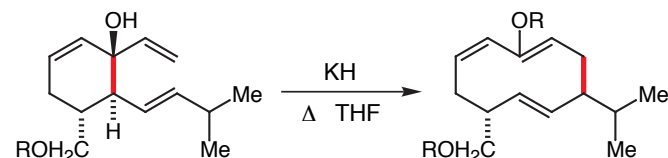


Gadwood, JACS, **1986**, *108*, 6343

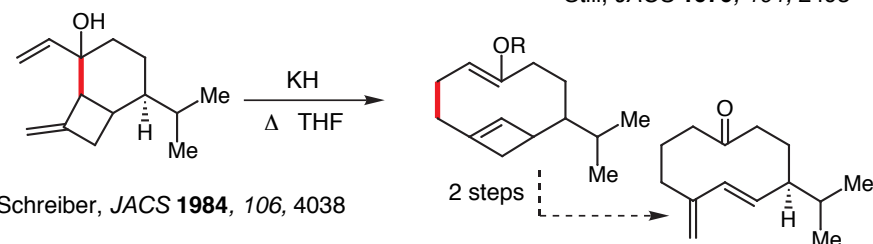


Periplanone-B Synthesis

200 μg from 75,000 virgin female cockroaches

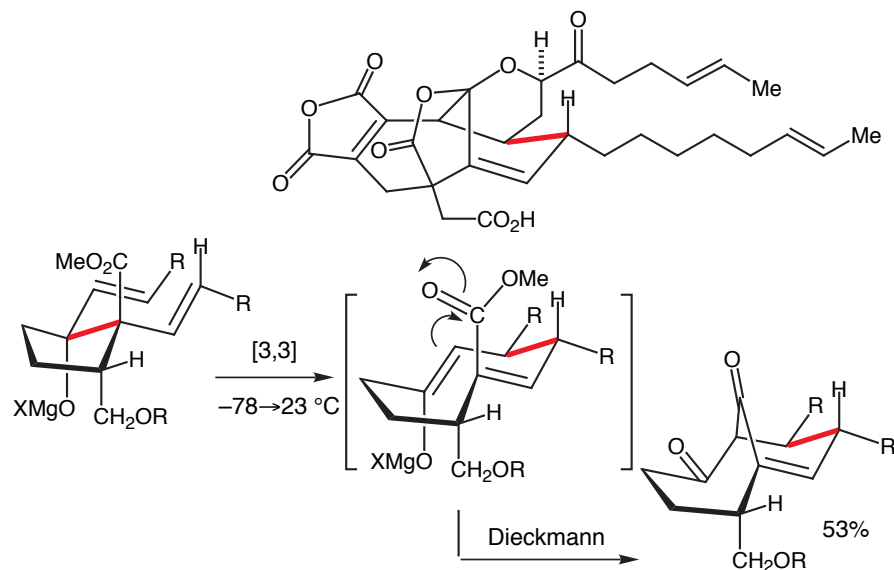


Still, JACS **1979**, *101*, 2493

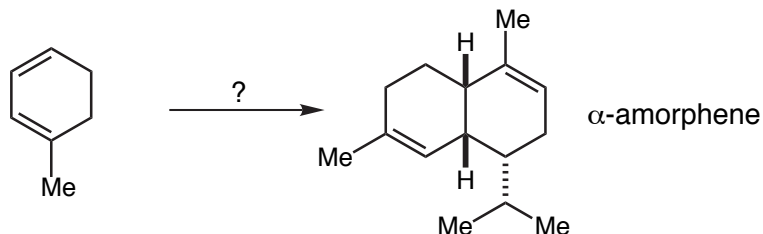


Schreiber, JACS **1984**, *106*, 4038

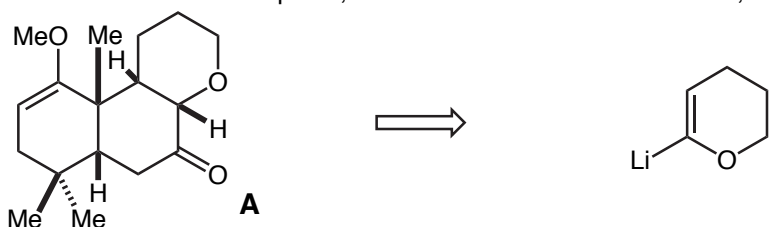
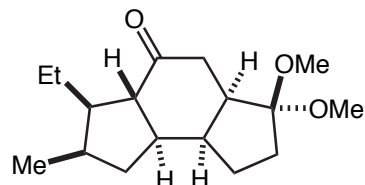
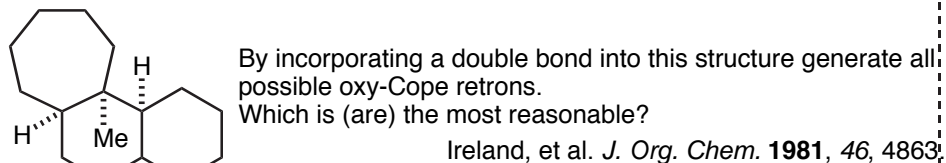
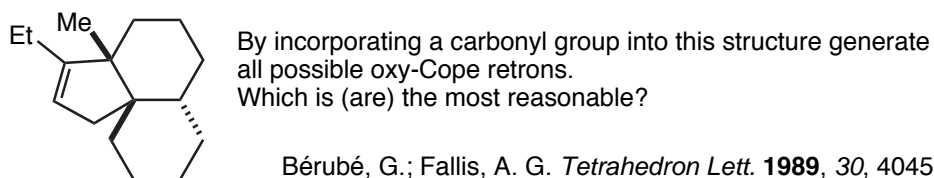
Synthesis of (+)-CP-263,114: Shair, JACS **2000**, *122*, 7424-7425.



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

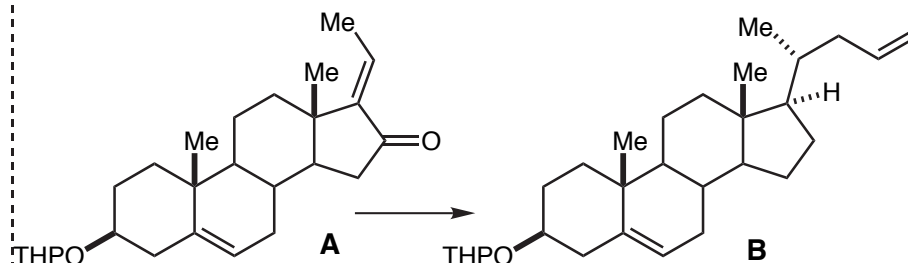


Gregson, R. P.; Mirrington, R. N. *J. Chem. Soc., Chem. Commun.* **1973**, 598.



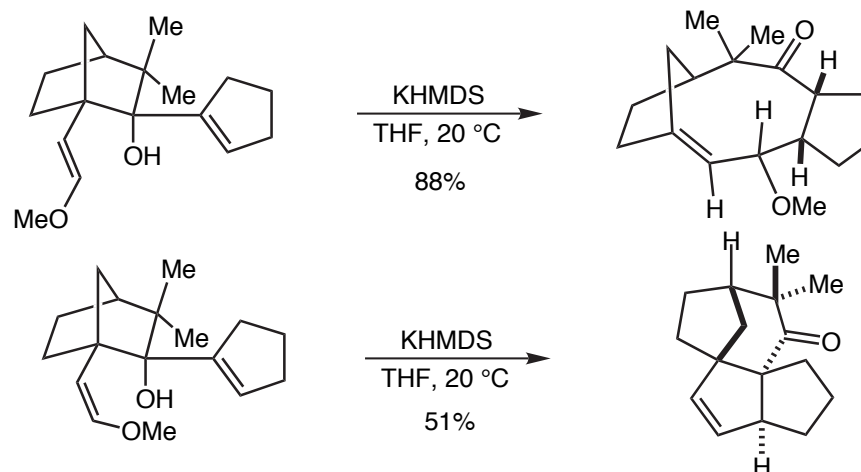
Propose a synthesis of **A** using the illustrated dihydropyran synthon.

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



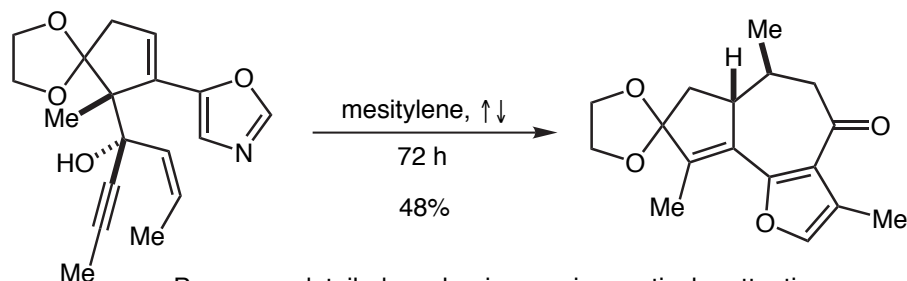
Propose a three step synthesis of **B** from **A**.

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.



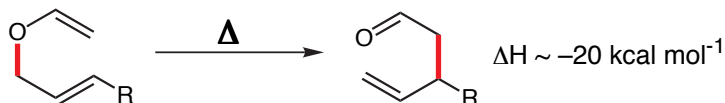
Propose a detailed mechanism paying particular attention to issues of chemo- and stereoselectivity.

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

General Reviews:

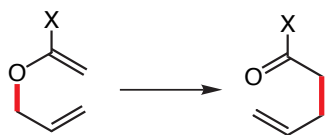
S. J. Rhoades, *Organic Reactions* **1974**, 22, 1 (Cope, Claisen)
 Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5, Ch 7.2
 Ziegler, *Accts. Chem. Res.* **1977**, 10, 227 (Claisen)
 Bennett, *Synthesis* **1977**, 589 (Claisen)
 Blechert, *Synthesis* **1989**, 71 (HeteroCope)
 R. K. Hill, *Asymmetric Synthesis* vol 3, Ch 8, p503 (chirality transfer)
 Ziegler, *Chem Rev.* **1989**, 89, 1423 (Claisen)

The Reaction:



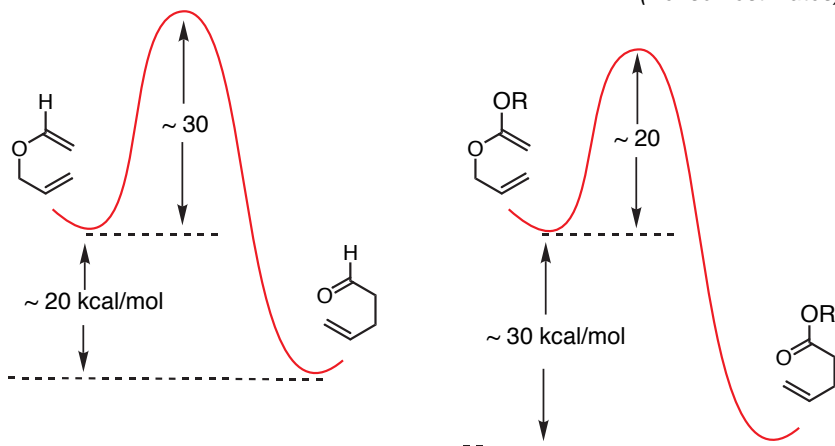
There is good thermodynamic driving force for this reaction.
 Bonds Broken: C-C $_{\pi}$ (65 kcal mol $^{-1}$) & C-O $_{\sigma}$ (85 kcal mol $^{-1}$)
 Bonds Made: C-O $_{\pi}$ (85 kcal mol $^{-1}$) and C-C $_{\sigma}$ (85 kcal mol $^{-1}$)

Thermodynamics of Claisen Variants:



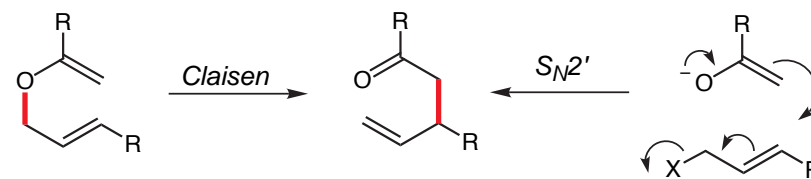
Substituent	ΔH (kcal mol $^{-1}$)
X = H	-16
X = OH	-31
X = NH $_2$	-30

(Benson estimates)

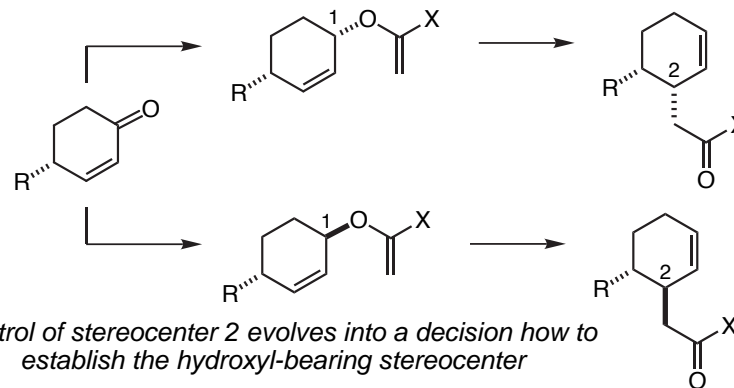


Heteroatom substitution at the indicated position increases exothermicity as well as reaction rate

Recognition Pattern for Organic Synthesis: An Enforced S $_N2'$

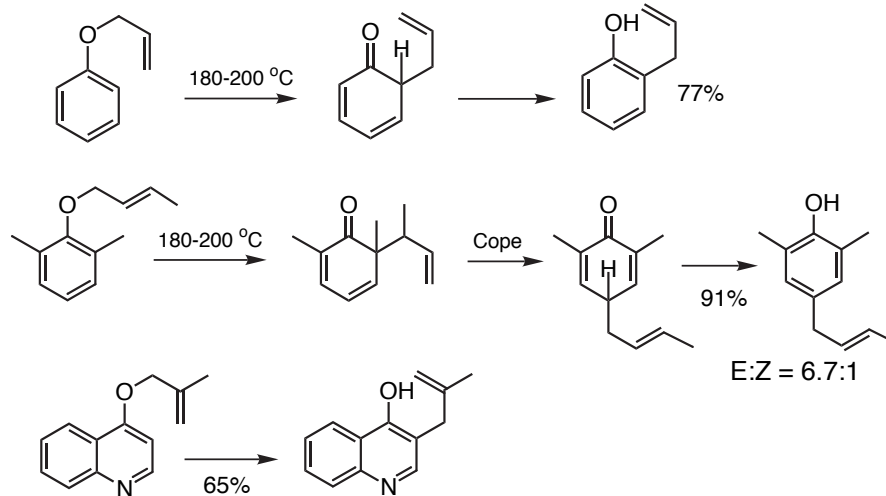


Stereochemical outcome is syn and controlled by hydroxyl stereocenter



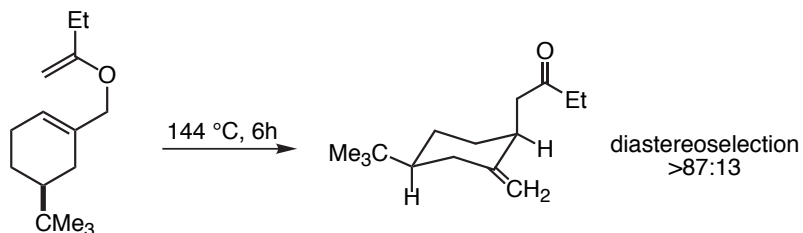
Control of stereocenter 2 evolves into a decision how to establish the hydroxyl-bearing stereocenter

Rearrangements of Aryl Allyl Ethers: Traditional Applications

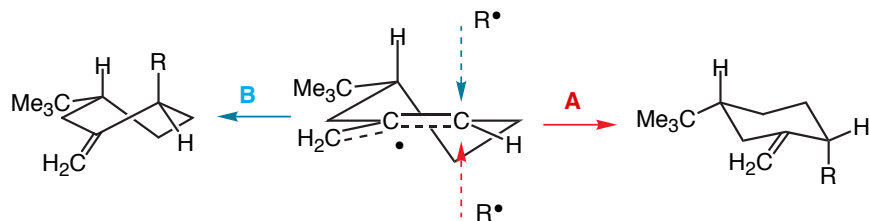


Stereoelectronic & steric constraints

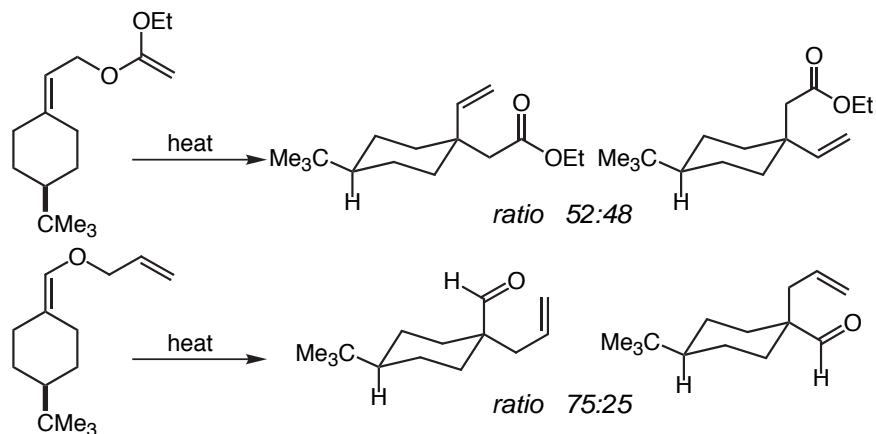
■ Endocyclic Olefins: Ireland, *JOC* 1983, 48, 1829



for endocyclic olefins, overlap between developing sigma and pi bonds required. Best overlap for forming chair geometry. As shown below, bring a radical up to either face of the allylic radical. As the bond is formed, overlap must be maintained. **Path A** evolves into a **chair** conformation while **Path B** evolved into a **boat** conformation.

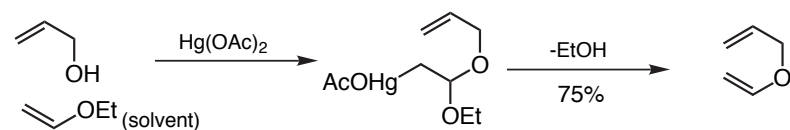


■ Exocyclic Olefins: House, *JOC* 1975, 40, 86

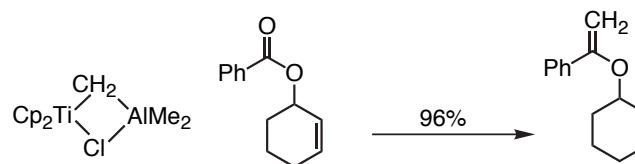


for exocyclic olefins, overlap between developing sigma and pi bonds is equally good from either olefin diastereoface. In this instance, steric effects dominate & this system shows a modest preference for "equatorial attack." A related case is provided below.

Synthesis of Allyl Vinyl Ethers

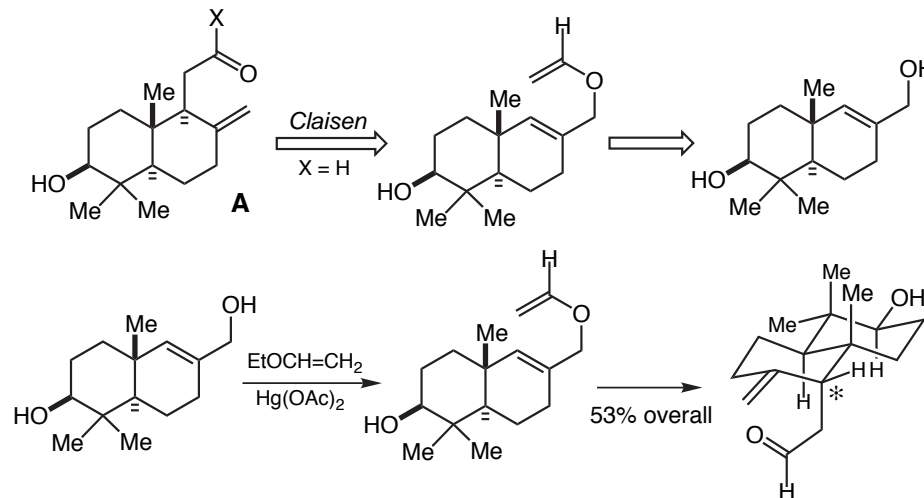


Watanabe, Conlon, *JACS* 1957, 79, 2828
Bronsted acids can also serve as catalysts



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

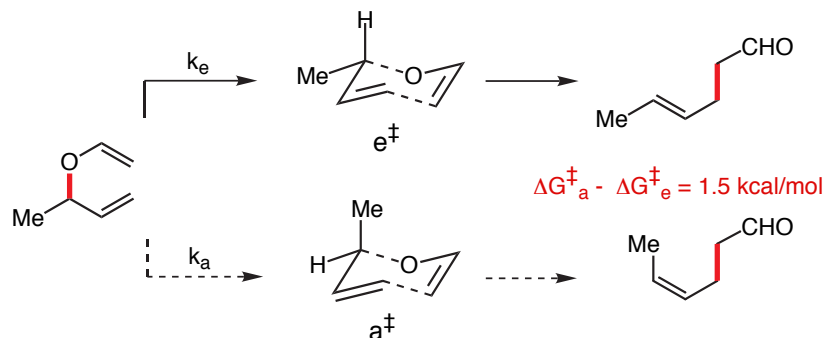
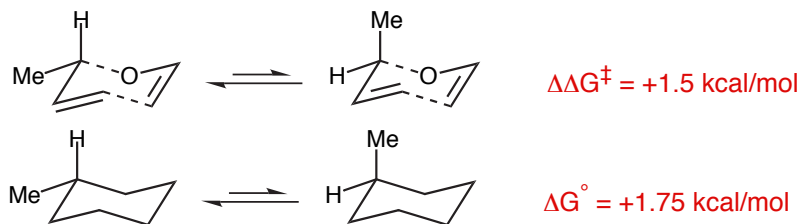
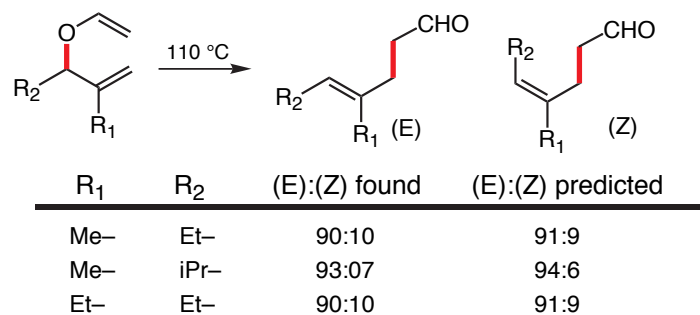
The Ireland approach to the bicyclic acid **A**: *JOC* 1962, 27, 1118



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

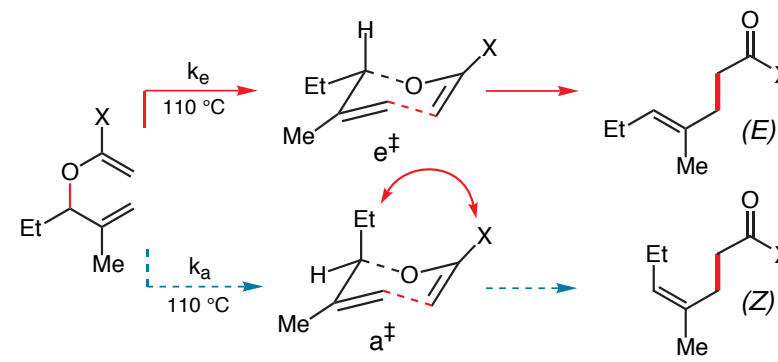
Claisen Rearrangement as vehicle for stereoselective olefin synthesis

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 (LectureNo. 6)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.

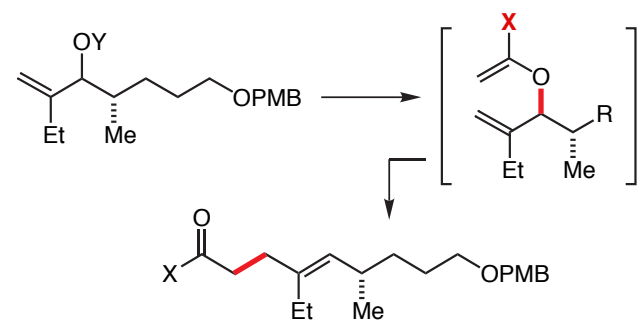
X	(E):(Z) found
H-	90:10
Me-	>99:1
MeO-	>99:1
Me ₂ N-	>98:2

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

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 15

Pericyclic Reactions-5

■ Claisen Rearrangements & Variants

■ 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

Wipf, P. *Claisen Rearrangements*; Trost, B. M. and Fleming, I., Ed.;
Pergamon Press: Oxford, 1991; Vol. 5, pp 827.

New Aspects of the Ireland and Related Rearrangements,
Tetrahedron **2002**, 58, 2905-2928 **(handout)**

D. A. Evans

Wednesday,
October 20, 2003

■ Other Reading Material:

Enders, D.; Knopp, M.; Schiffrs, R. "Asymmetric [3.3]-sigmatropic rearrangements in organic synthesis."

Tetrahedron: Asymmetry **1996**, 7, 1847-1882

Ziegler, F. E. "The Thermal Aliphatic Claisen Rearrangement." *Chem. Rev.* **1988**, 88, 1423.

Gajewski, J. J. "The Claisen rearrangement. Response to solvents and substituents: The case for both hydrophobic and hydrogen bond acceleration in water and for a variable transition state." *Acc. Chem. Res.* **1997**, 30, 219-225.

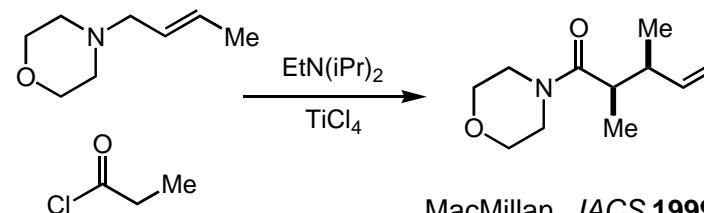
Tietze, L. F. "Domino reactions in organic synthesis." *Chem. Rev.* **1996**, 96, 115-136.

Parsons, P. J.; Penkett, C. S.; Shell, A. J. "Tandem reactions in organic synthesis: Novel strategies for natural product elaboration and the development of new synthetic methodology." *Chem. Rev.* **1996**, 96, 195-206.

Pereira, S.; Srebnik, M. "The Ireland-Claisen rearrangement." *Aldrichimica Acta* **1993**, 26, 17.

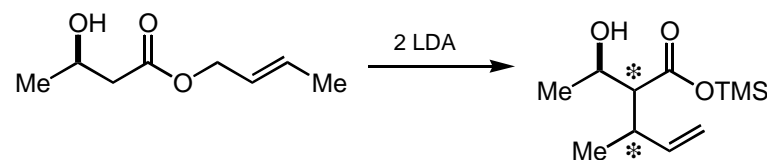
■ Problems of the Day:

Propose a mechanism for this transformation



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

Predict the stereochemical outcome of this reaction

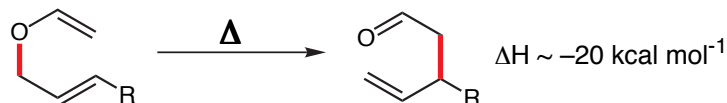


Kurth, *JOC* **1985**, 50, 1840

General Reviews:

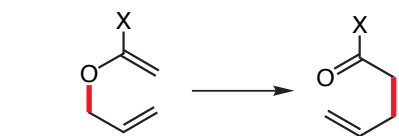
S. J. Rhoades, *Organic Reactions* **1974**, 22, 1 (Cope, Claisen)
 Trost, Ed., *Comprehensive Organic Synthesis* **1992**, Vol 5, Ch 7.2
 Ziegler, *Accts. Chem. Res.* **1977**, 10, 227 (Claisen)
 Bennett, *Synthesis* **1977**, 589 (Claisen)
 Blechert, *Synthesis* **1989**, 71 (HeteroCope)
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 Ziegler, *Chem Rev.* **1989**, 89, 1423 (Claisen)

The Reaction:



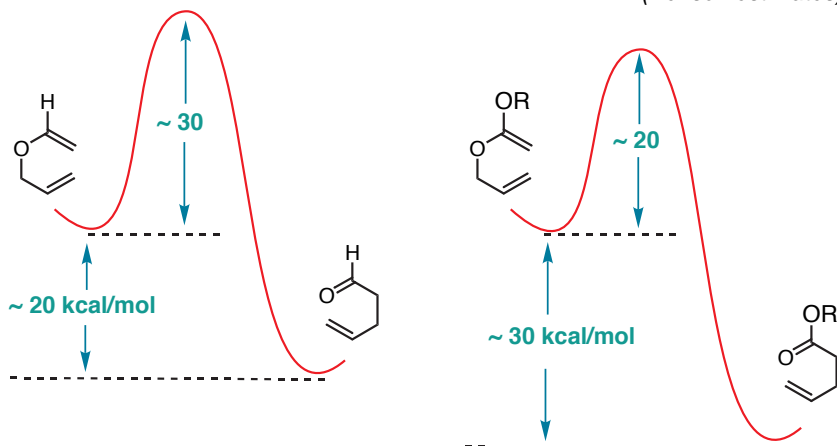
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Thermodynamics of Claisen Variants:



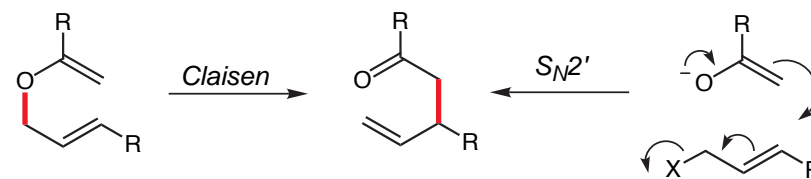
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X = H	-16
X = OH	-31
X = NH $_2$	-30

(Benson estimates)

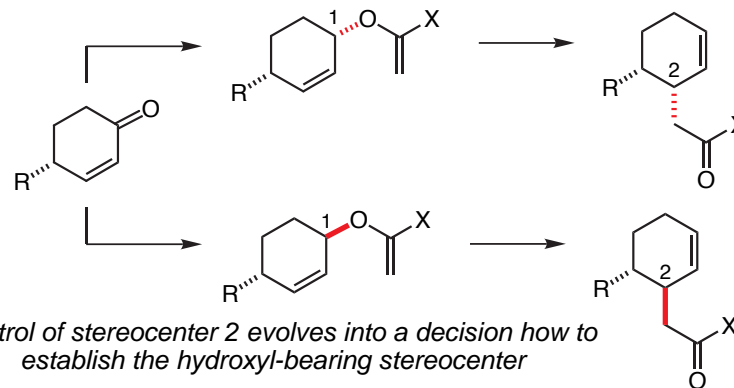


Heteroatom substitution at the indicated position increases exothermicity as well as reaction rate

Recognition Pattern for Organic Synthesis: An Enforced S $_N2'$

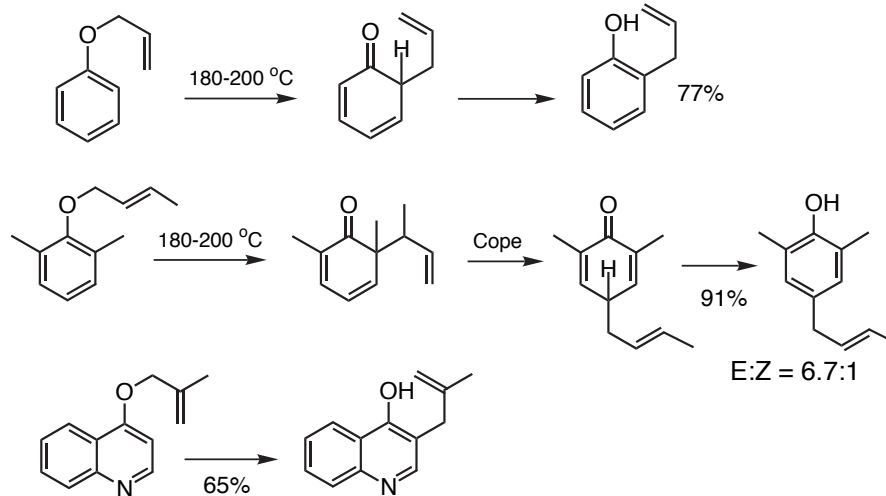


Stereochemical outcome is syn and controlled by hydroxyl stereocenter



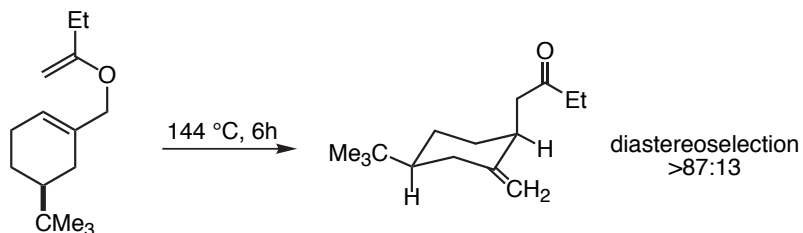
Control of stereocenter 2 evolves into a decision how to establish the hydroxyl-bearing stereocenter

Rearrangements of Aryl Allyl Ethers: Traditional Applications

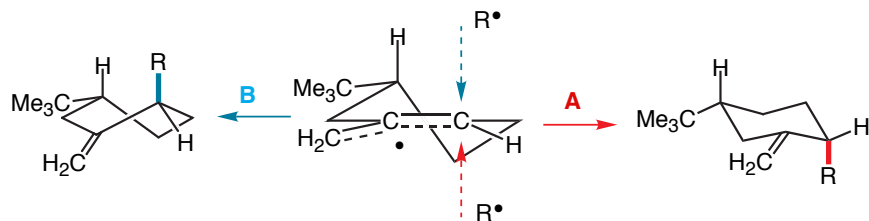


Stereoelectronic & steric constraints

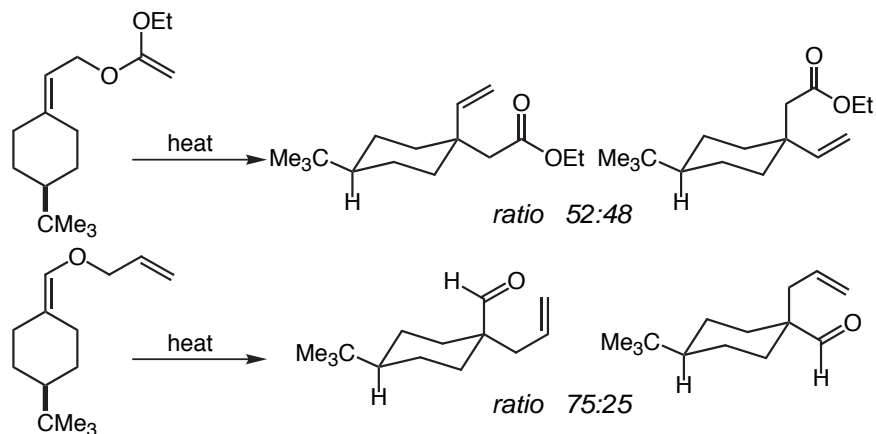
■ Endocyclic Olefins: Ireland, *JOC* 1983, 48, 1829



for endocyclic olefins, overlap between developing sigma and pi bonds required. Best overlap for forming chair geometry. As shown below, bring a radical up to either face of the allylic radical. As the bond is formed, overlap must be maintained. **Path A** evolves into a **chair** conformation while **Path B** evolved into a **boat** conformation.

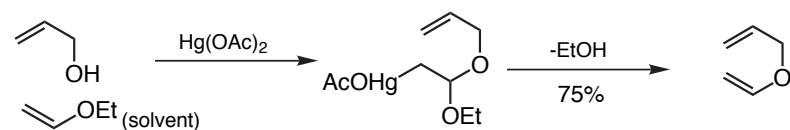


■ Exocyclic Olefins: House, *JOC* 1975, 40, 86

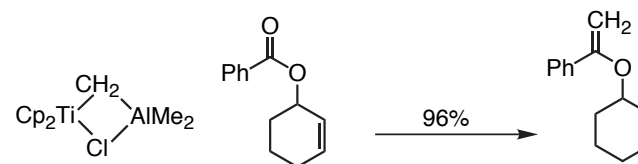


for exocyclic olefins, overlap between developing sigma and pi bonds is equally good from either olefin diastereoface. In this instance, steric effects dominate & this system shows a modest preference for "equatorial attack." A related case is provided below.

Synthesis of Allyl Vinyl Ethers

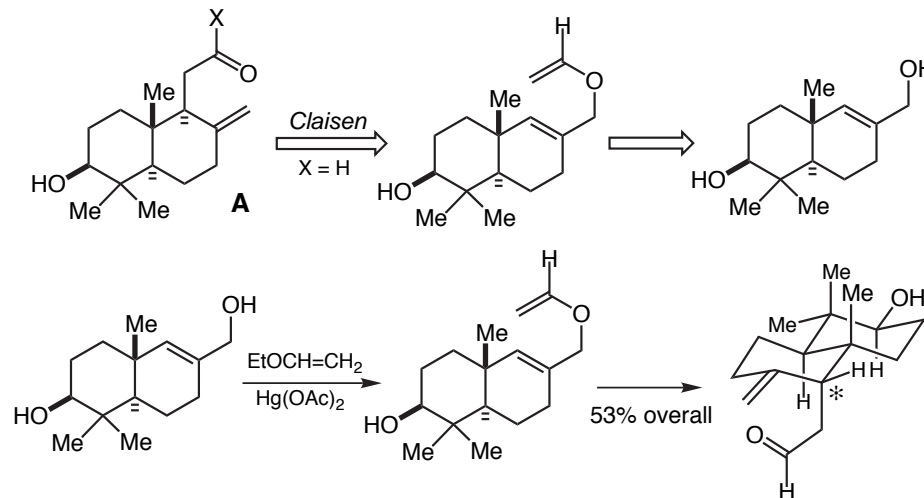


Watanabe, Conlon, *JACS* 1957, 79, 2828
Bronsted acids can also serve as catalysts



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

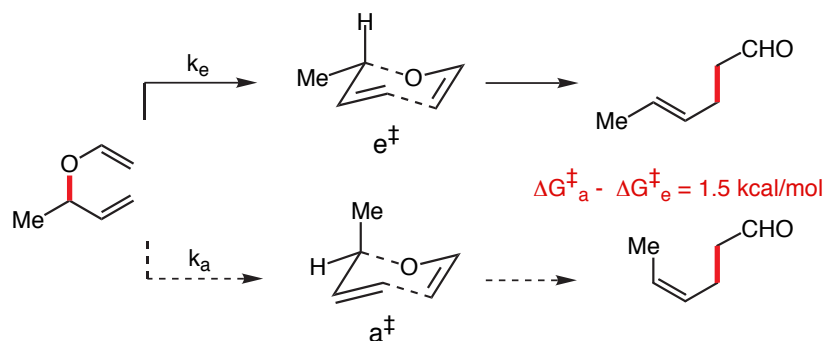
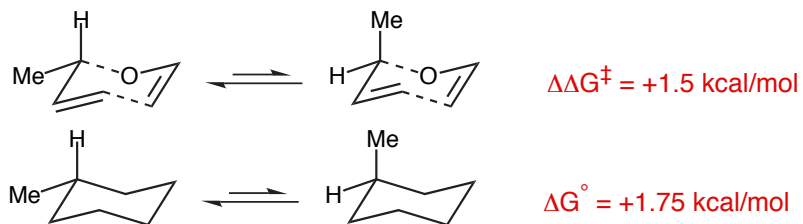
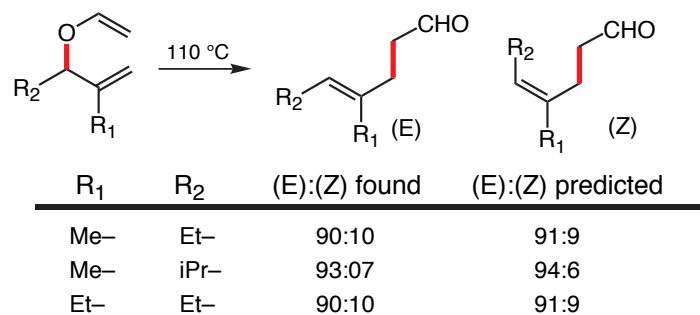
The Ireland approach to the bicyclic acid A: *JOC* 1962, 27, 1118



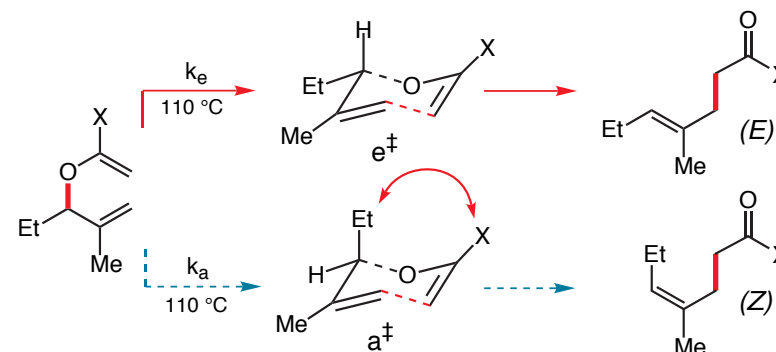
The new stereocenter (*) introduced via the rearrangement had the wrong configuration!

Claisen Rearrangement as vehicle for stereoselective olefin synthesis

Consider the following rearrangement:

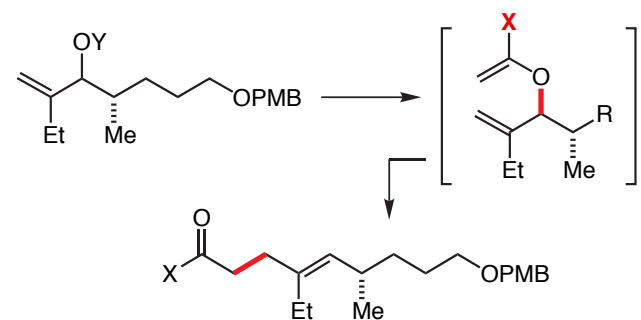
Faulkner & Perrin (*Tet. Lett.* 2783 (1969) have made the correlation between $\Delta\Delta G^\ddagger$ for rearrangement & ΔG° for the corresponding cyclohexane[#] equilibria:[#]Note: The A-value of 2-methyl-tetrahydropyran is +2.86 kcal/mol (Lecture No. 6)They then suggest that there is a good correlation 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	Faulkner, <i>Tet Let</i> 1969, 3243
Me-	>99:1	Faulkner, <i>JACS</i> 1973, 95, 553
MeO-	>99:1	Johnson, <i>JACS</i> 1970, 92, 741
Me ₂ N-	>98:2	

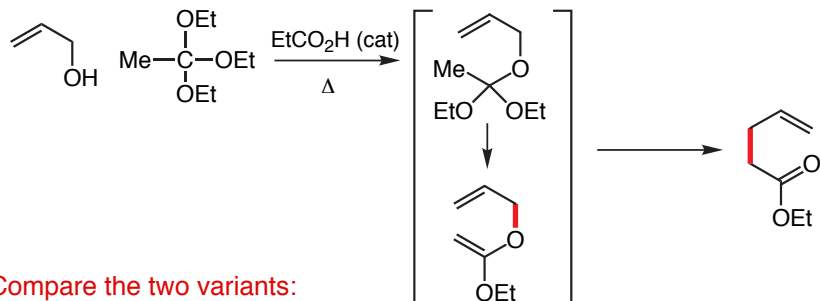
■ Another comparison: (DAE) M. DiMare, Ph. D. Harvard University, 1988



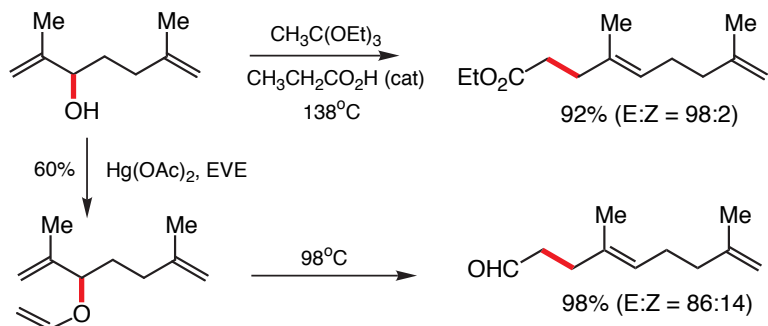
procedure	conditions	X	T, °C	(E):(Z) ratio
Y = Ac, Ireland	LDA, TMSCl	TMSO-	-78→+55	97:3
Y = H, Johnson	HC(OMe) ₃ , H ⁺	MeO-	130	94:6
Y = H, Eschenmoser	MeC(OMe) ₂ NMe ₂	Me ₂ N-	80	97.5:2.5

Johnson Orthoester Claisen

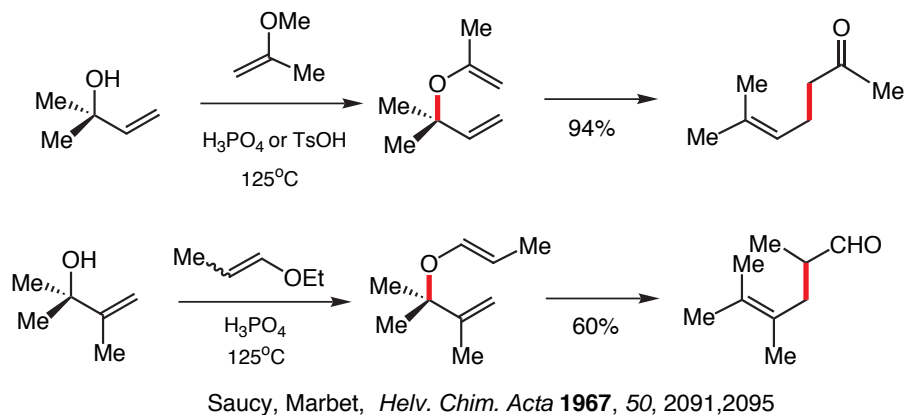
■ Lead paper: Johnson, Faulkner, Peterson, *JACS* **1970**, *92*, 741



■ Compare the two variants:

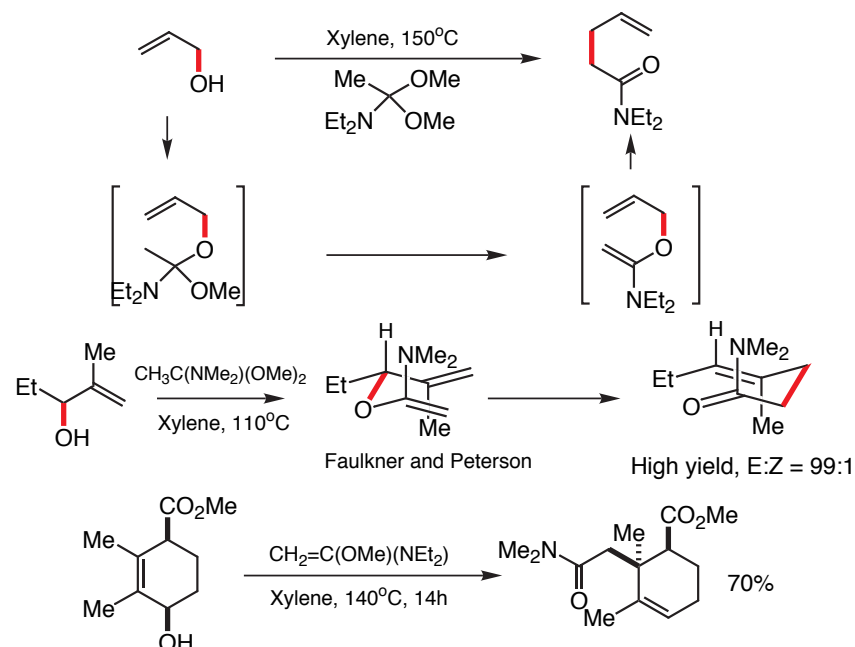


The Saucy Marbet Alternative

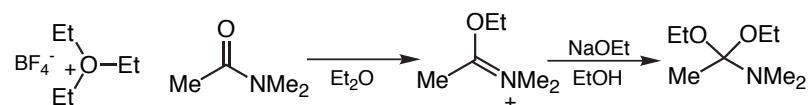


Eschenmoser-Claisen

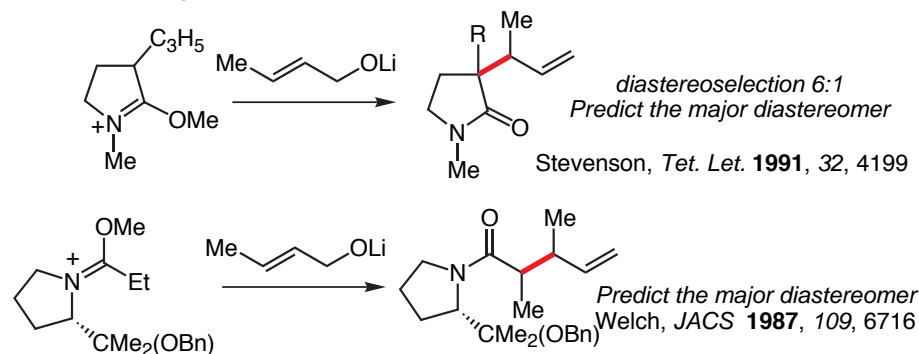
Eschenmoser, A. *Helv. Chem. Acta* **1964**, *47*, 2425; *Helv. Chim. Acta* **1969**, *52*, 1030.



■ Synthesis of Amide Acetals



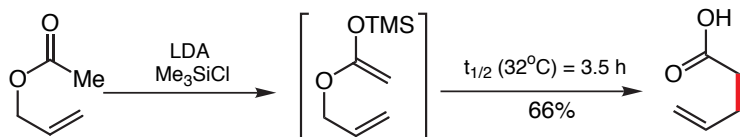
■ Reactions to ponder:



Ireland-Enolate Claisen

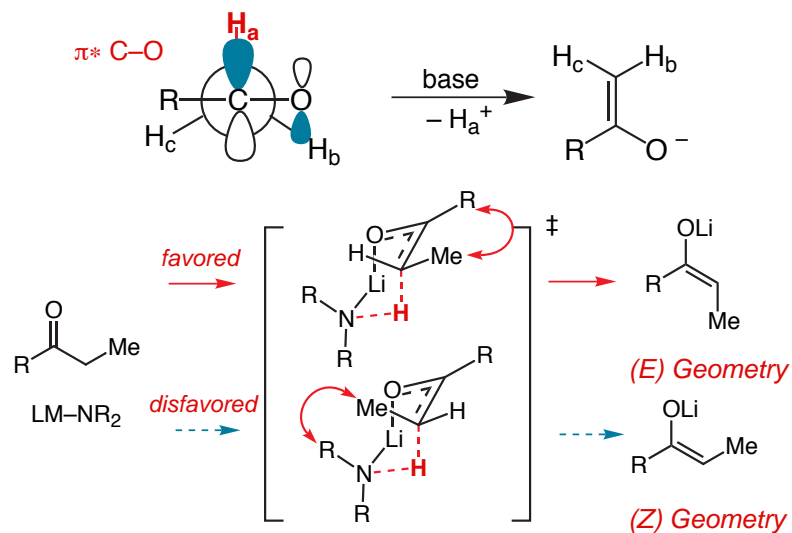
Reviews New Aspects of the Ireland and Related Rearrangements, *Tetrahedron* **2002**, 58, 2905–2928 (**handout**)

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



Enolization: Amide Bases & Ireland Enolization Model

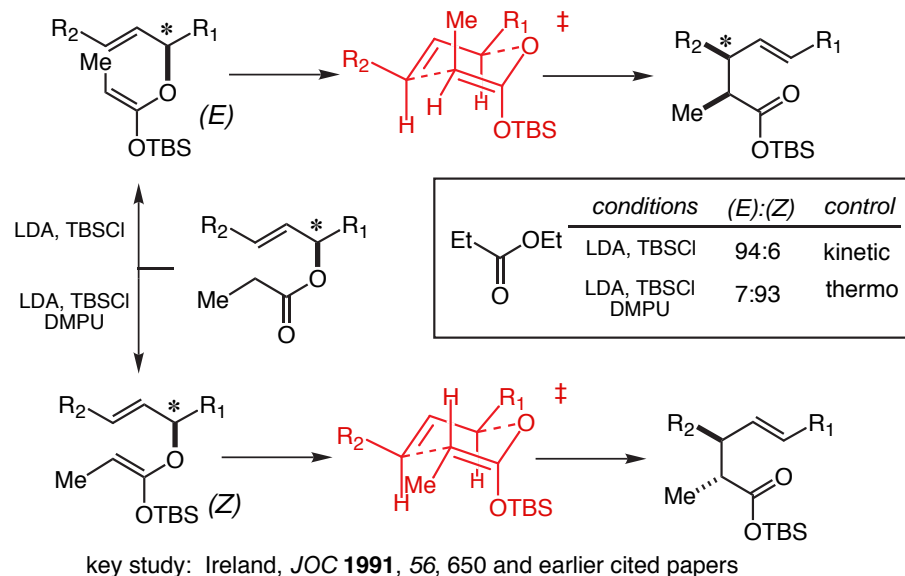
Stereoelectronic Requirements: α -C-H bond must be able to overlap with π^* C=O



The Ireland Model (*JACS* **1976**, 98, 2868); *Narula, Tetrahedron Lett.* **1981**, 22, 4119; more recent study: Ireland, *JOC* **1991**, 56, 650

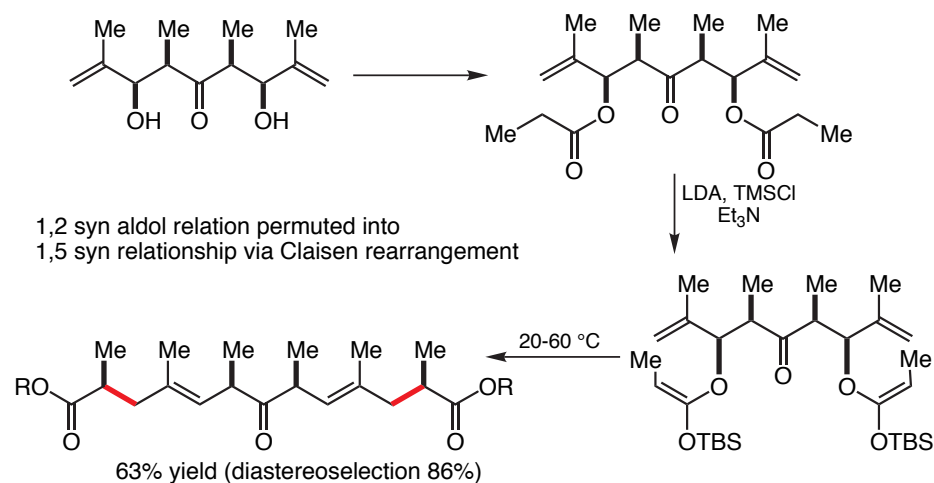
For a recent study on the effect of amide base structure on (E)/(Z) selectivity in the context of the Ireland enolization model see: *JOC* **1997**, 62, 7516.

Substituted enolates afford an additional stereocenter

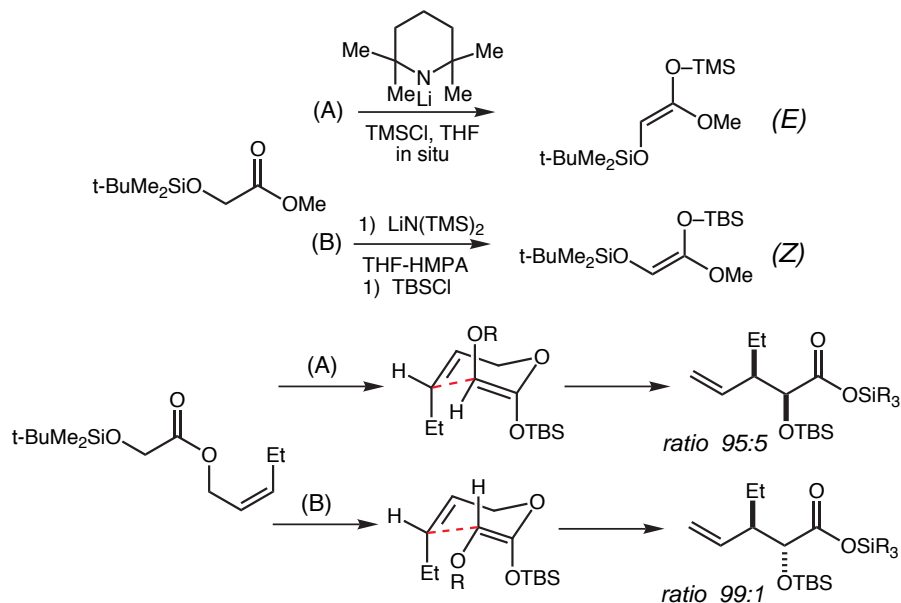


Double Claisen Rearrangements are also possible

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

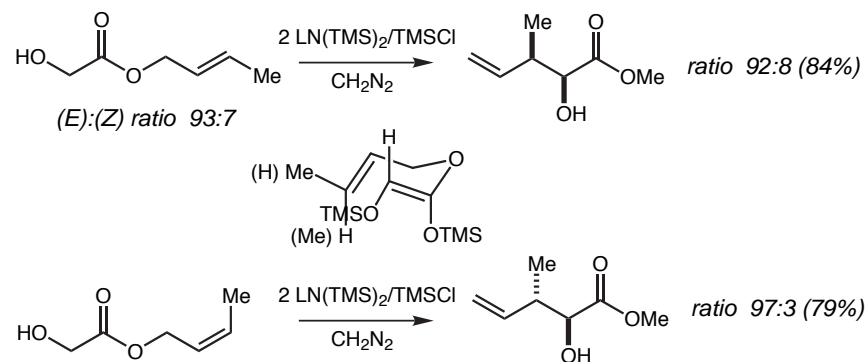


Recent studies on controlling enolization conditions have appeared
Yamamoto, *JOC* **1993**, 58, 5301



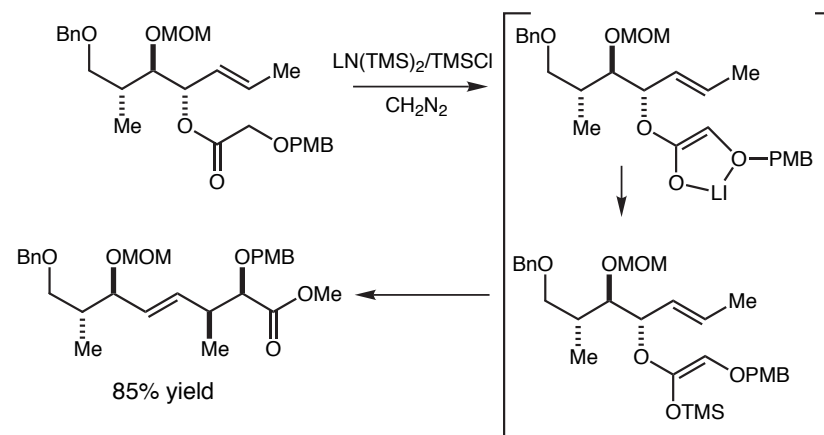
Chelating substituents on α -carbon afford (Z)-enolates

Fujisawa, *Tet Lett* **1983**, 24, 729



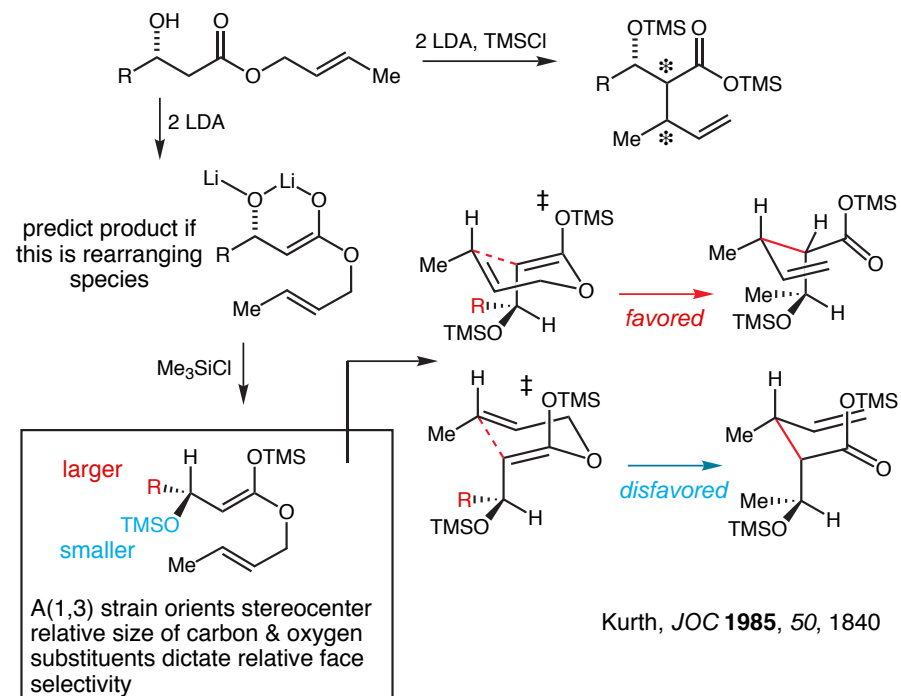
These Chelating substituents can be benzyl ethers as well

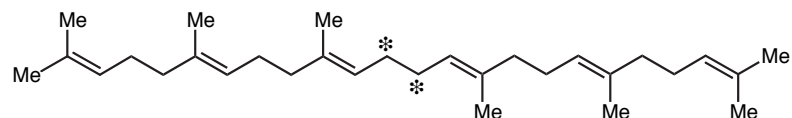
Kalmerton, *Tet Lett* **1993**, 34, 1103



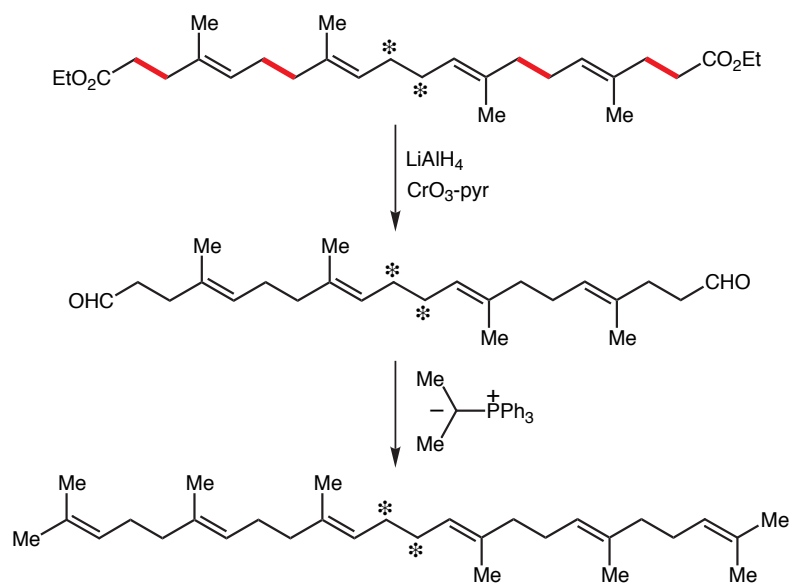
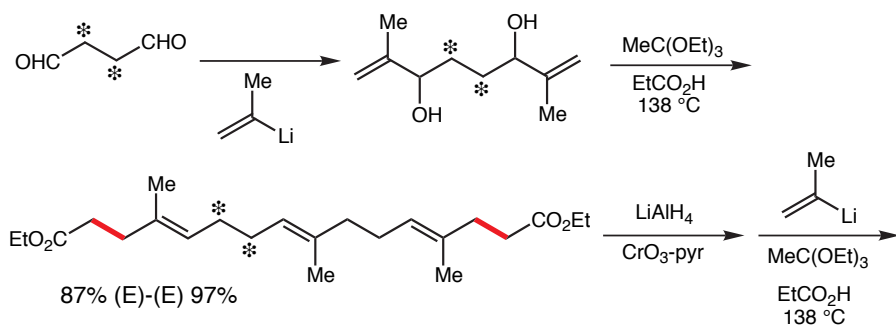
A Problem to consider

Predict the stereochemical outcome of this reaction

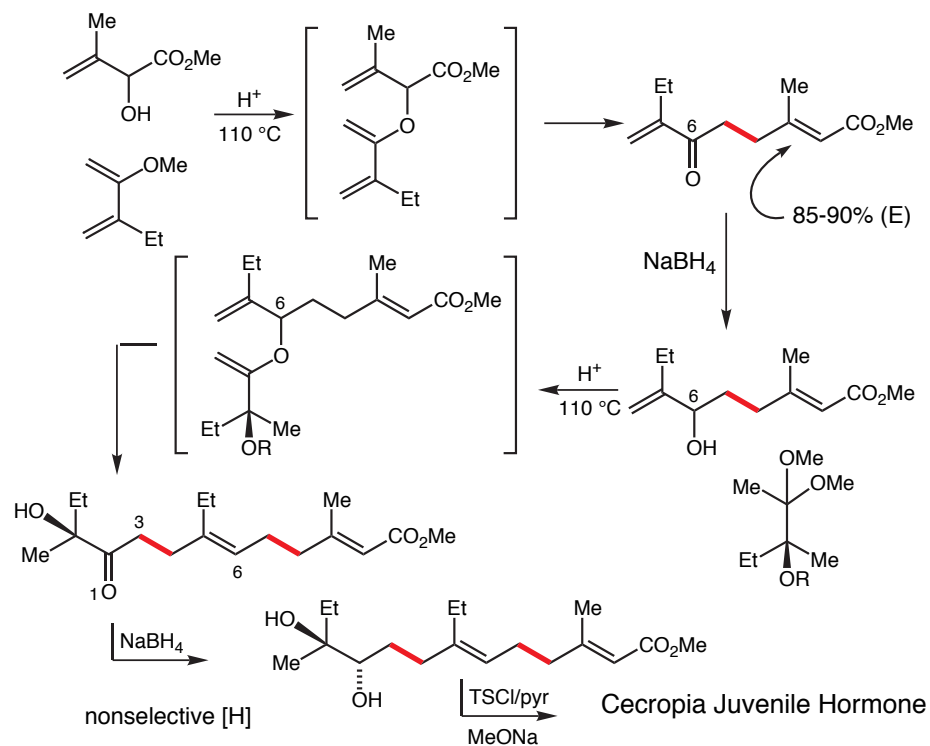
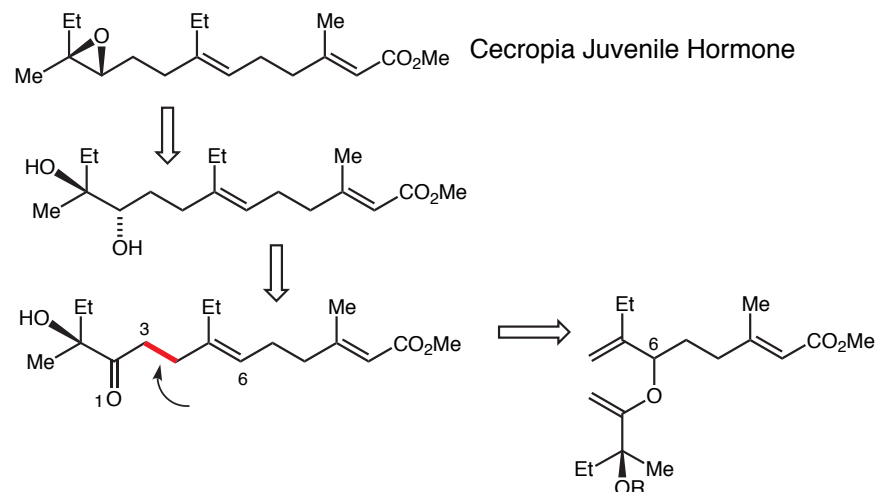


Johnson Squalene Synthesis: JACS 1970, 92, 741

Observations: Molecule contains an obvious symmetry plane
The trisubstituted C=C's are the issue

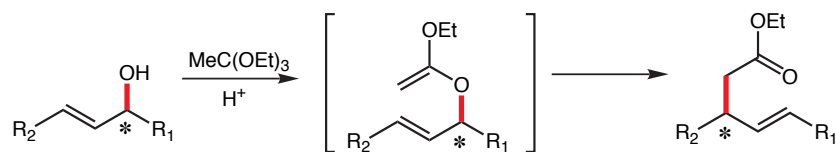


Isomeric purity is Ca 95%

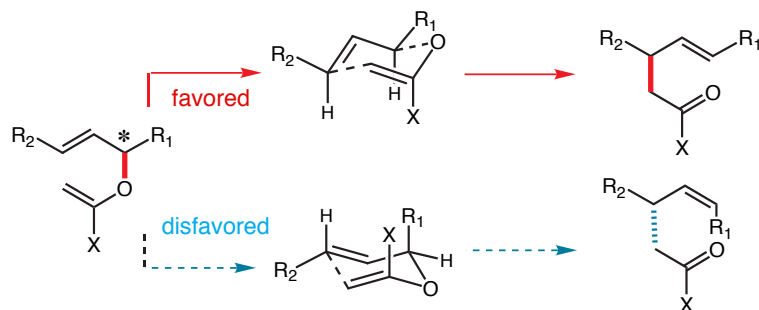
Faulkner Juvenile Hormone Synthesis: JACS 1973, 95, 553

Chirality transfer via the Claisen rxn is an integral aspect of the general utility of process

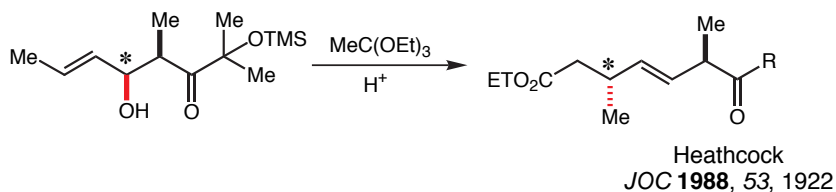
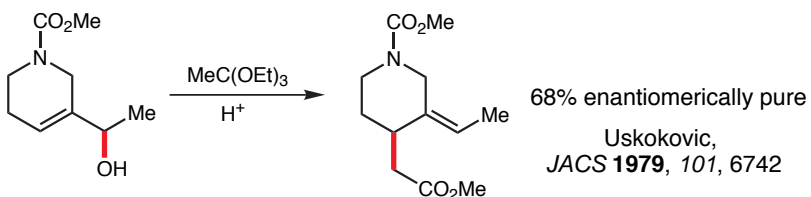
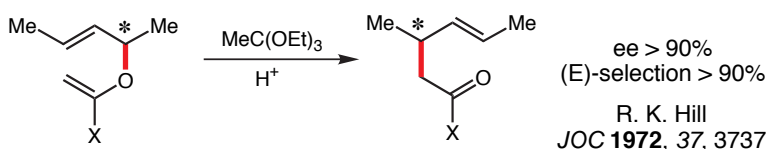
R. K. Hill, *Asymmetric Synthesis* vol 3, Ch 8, p503 (chirality transfer)



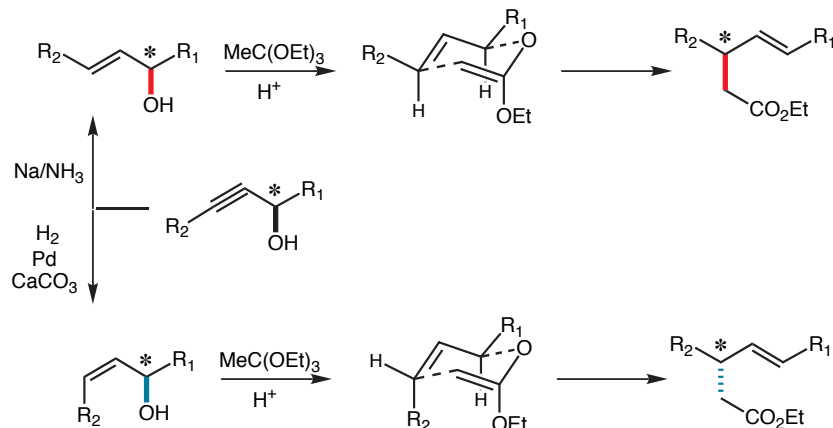
Such chirality permutation processes are only as stereoselective as the energy difference between diastereomeric chair transition states:



Note that chirality transfer is coupled to olefin geometry in product. Prior arguments (Faulkner) imply that the X substituent will play significant role in promoting selectivity.



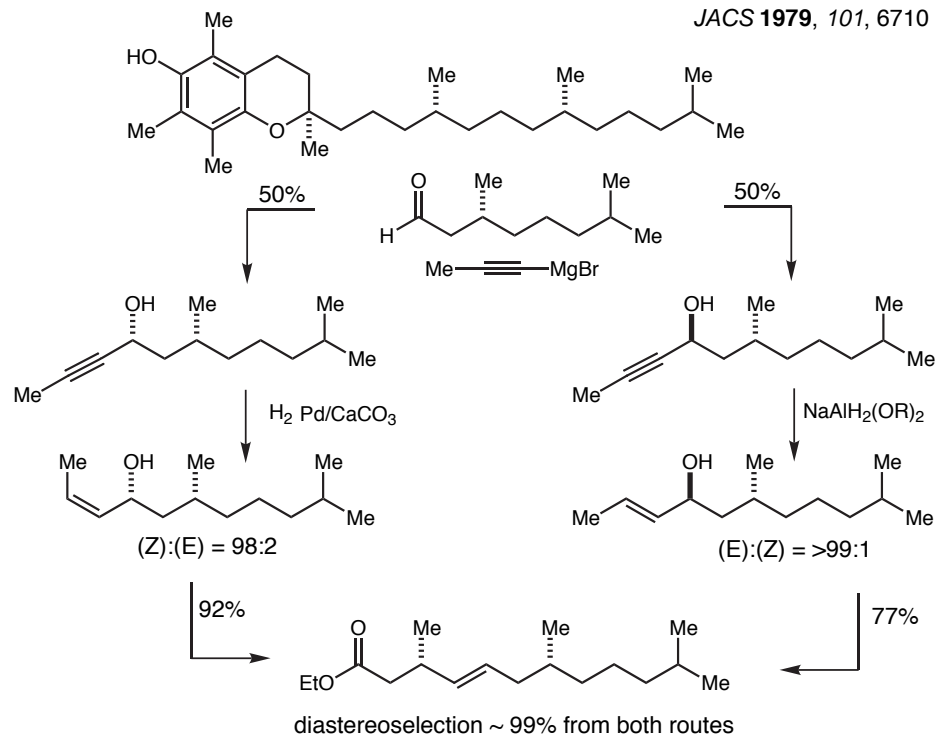
Sense of Asymmetric induction may be controlled by olefin geometry



Since stereoselection in reduction of acetylenes is >98%, either product accessible

tocopherol (Vitamin E) Cohen JOC **1976**, 41, 3497

JACS **1979**, 101, 6710

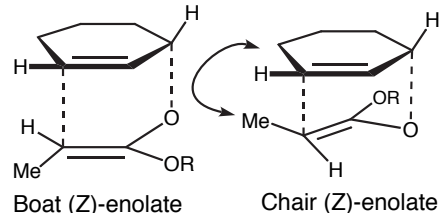


Boat transition states more accessible in Claisen than in Cope rearrangements

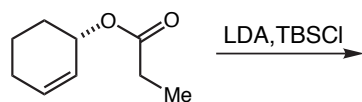
■ A case where the chair-boat preference depends on enol geometry

Factors controlling diastereoselection
Enolate geometry
Chair vs Boat transition states

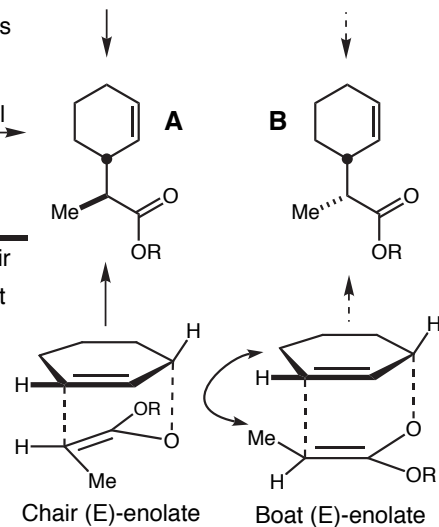
Bartlett, *JOC* **1981**, *46*, 3896
Ireland, *JACS* **1991**, *56*, 3572



Ireland study supports Bartlett's conclusions

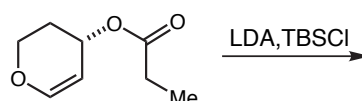


conditions	(E):(Z)	A:B	TS
LDA, THF	83:17	84:16	(E)-chair
LDA, THF DMPU	04:96	72:28	(Z)-boat



Boat geometries can be favored in these and related systems

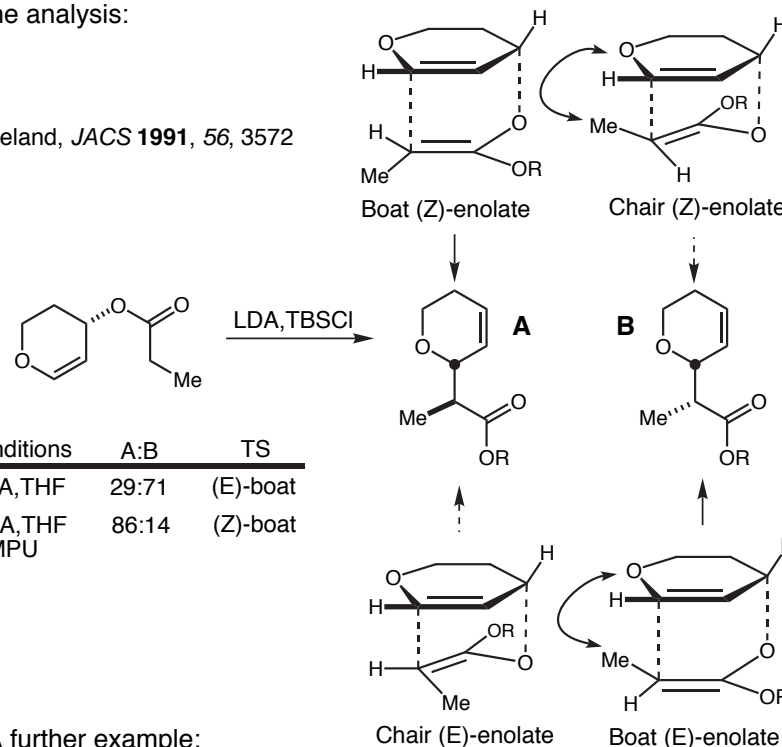
■ In this case the boat geometry is preferred from either enol geometry



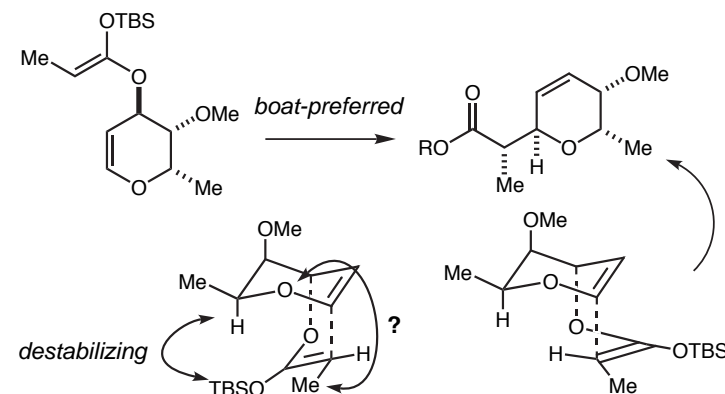
conditions	A:B	TS
LDA, THF	29:71	(E)-boat
LDA, THF DMPU	86:14	(Z)-boat

■ The analysis:

Ireland, *JACS* **1991**, *56*, 3572

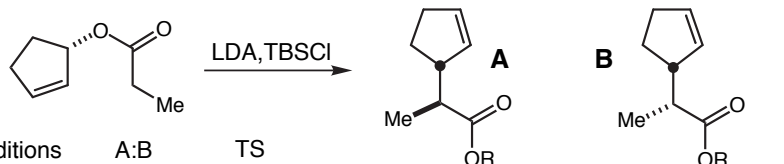


■ A further example:



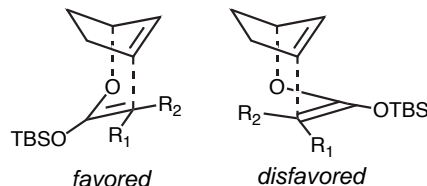
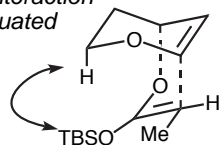
It appears that both of the indicated interactions contribute to the destabilization of chair geometry

■ In this case the chair geometry is preferred from either enol geometry

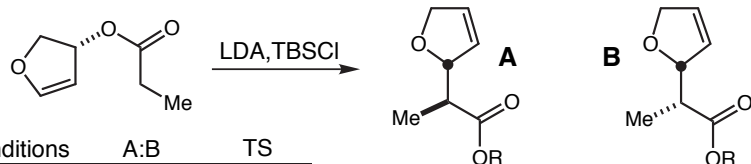


conditions	A:B	TS
LDA, THF	75:25	(E)-chair
LDA, THF DMPU	40:60	(Z)-chair

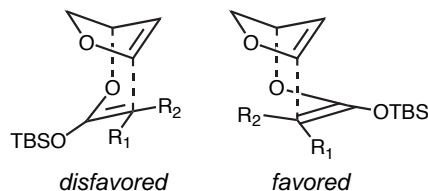
This destabilizing interaction has been attenuated



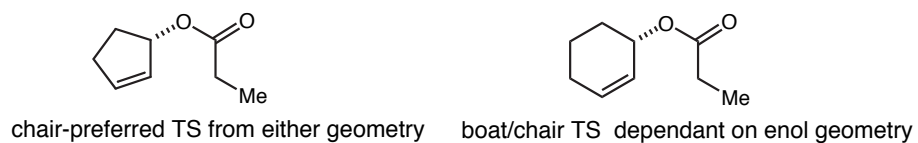
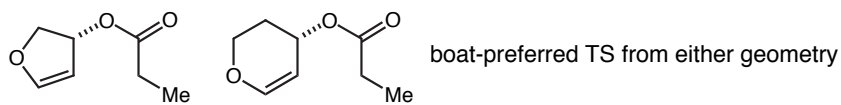
■ In this case the boat geometry is preferred from either enol geometry



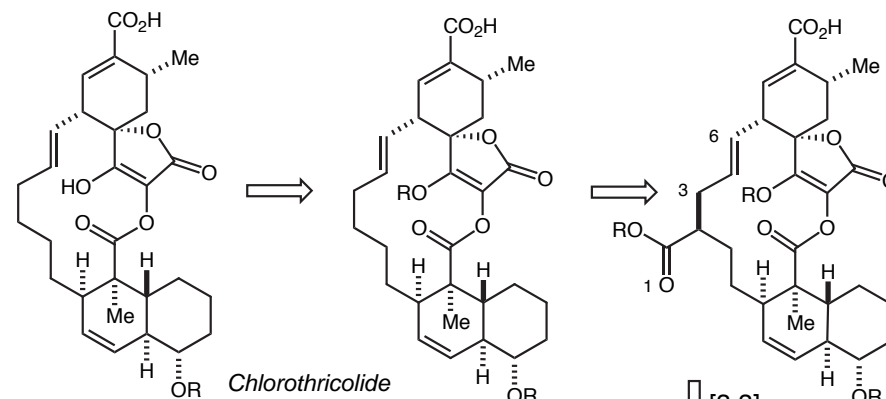
conditions	A:B	TS
LDA, THF	43:57	(E)-boat
LDA, THF DMPU	80:20	(Z)-boat



■ Summary:

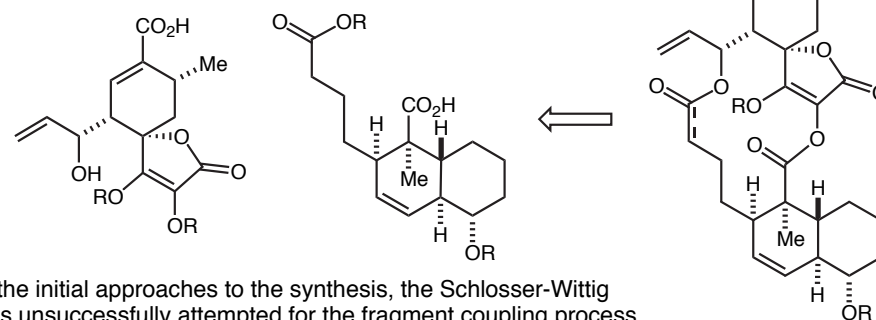


The Claisen Rearrangement has been used in fragment coupling

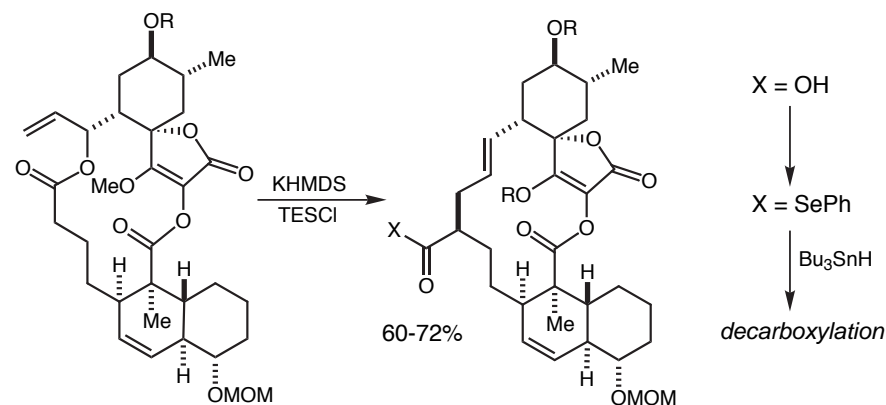


Ireland, *J. Org. Chem.* **1986**, *51*, 635

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

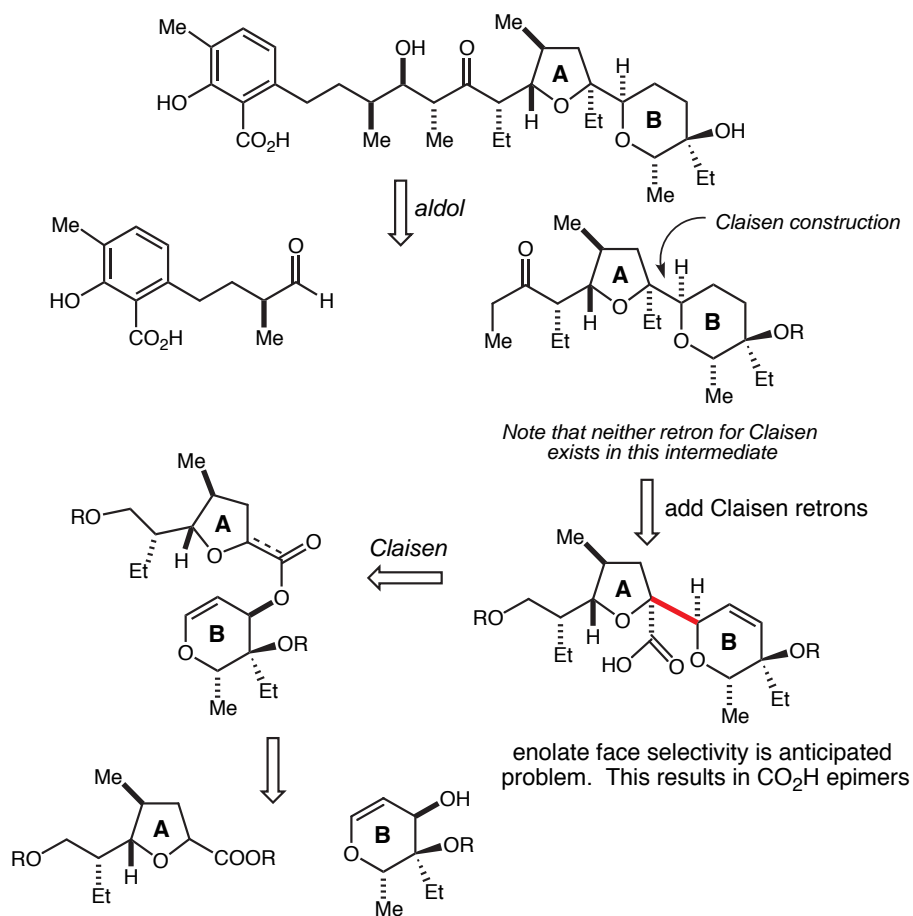


In the initial approaches to the synthesis, the Schlosser-Wittig was unsuccessfully attempted for the fragment coupling process.

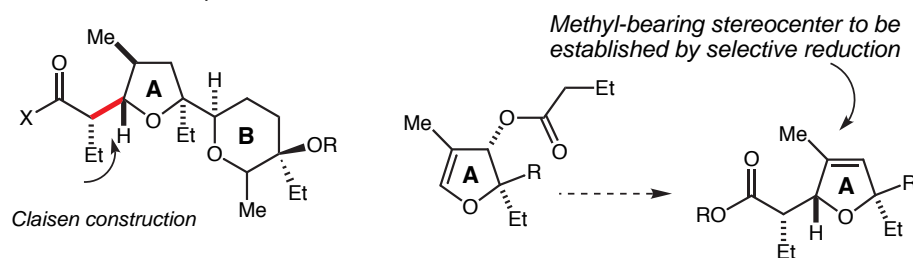


key paper for decarboxylation: Ireland, *JACS* **1985**, *107*, 3285

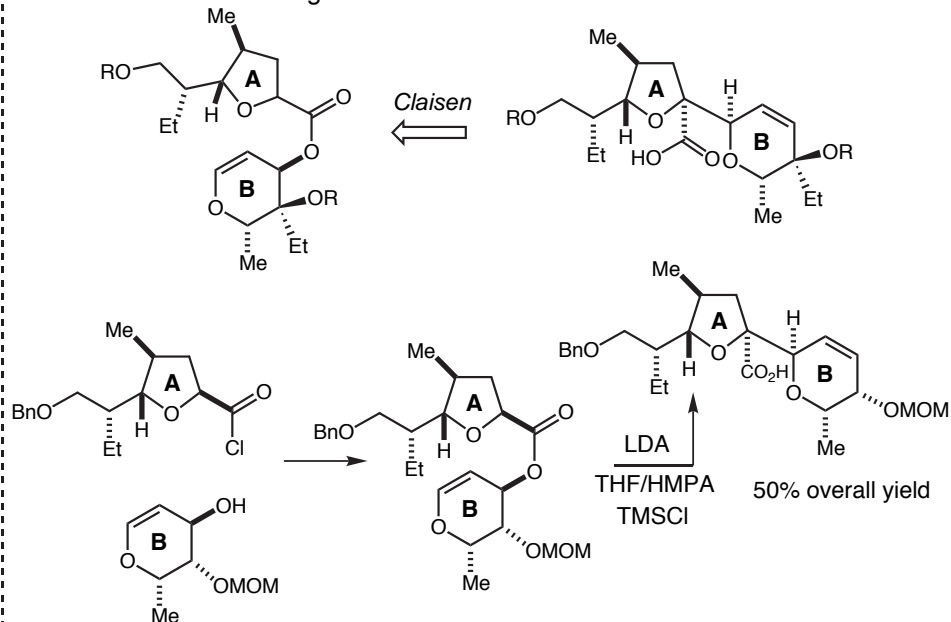
The Ireland lasalocid synthesis: *JACS* **1983**, 105, 1988



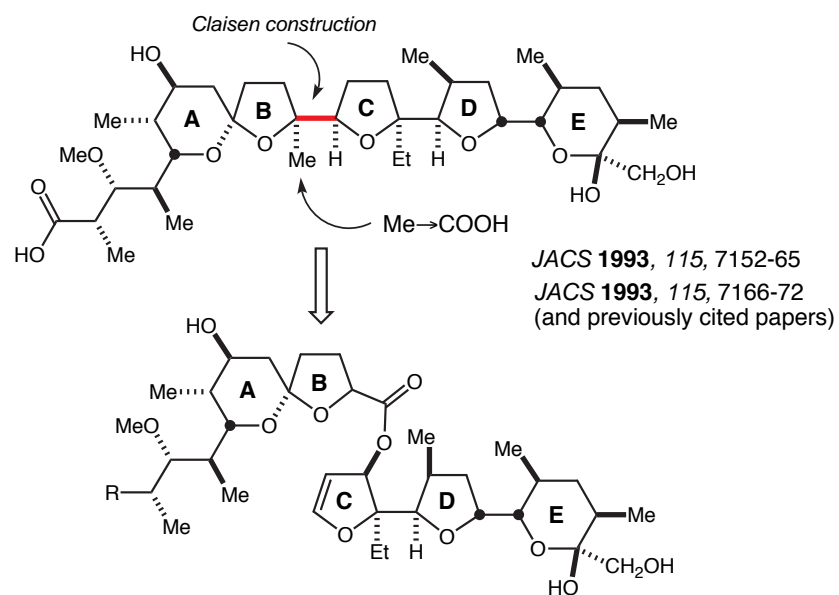
■ Here is another potential Claisen construction



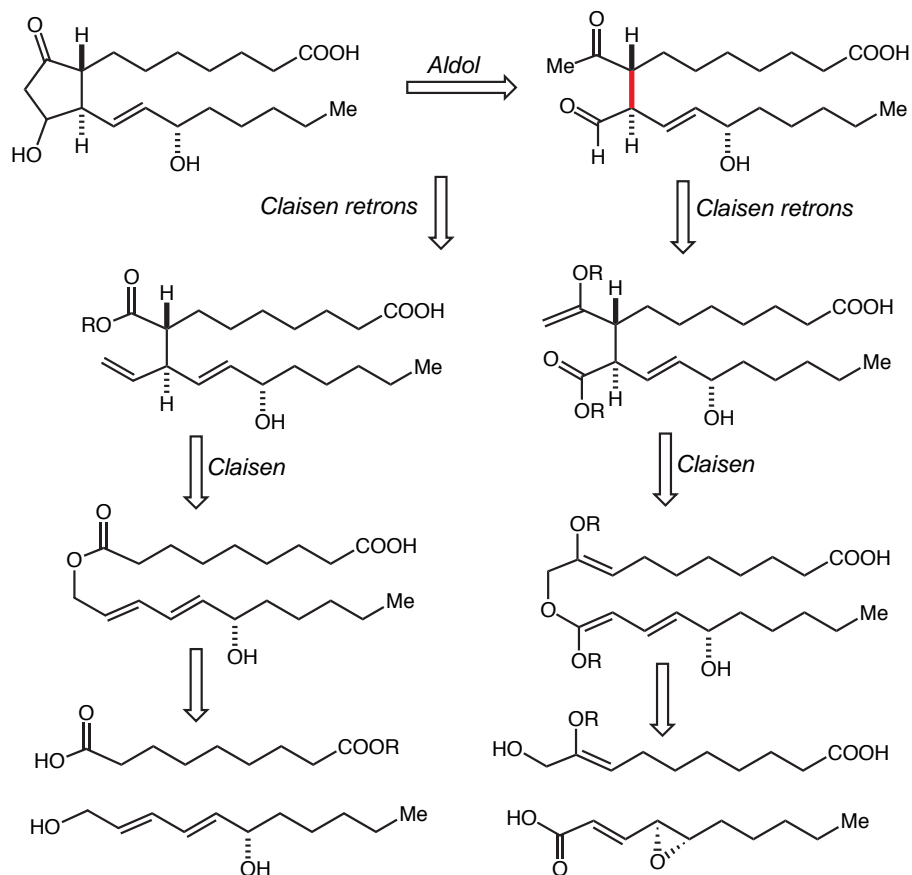
■ The relevant rearrangements:



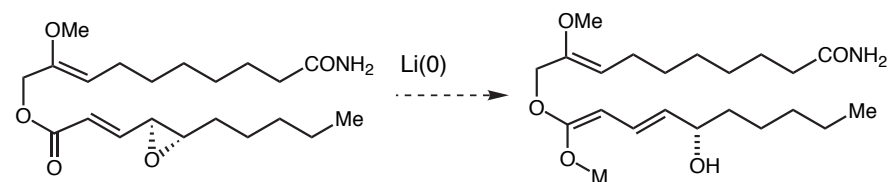
The Ireland monensin synthesis:



Consider the prostaglandin nucleus

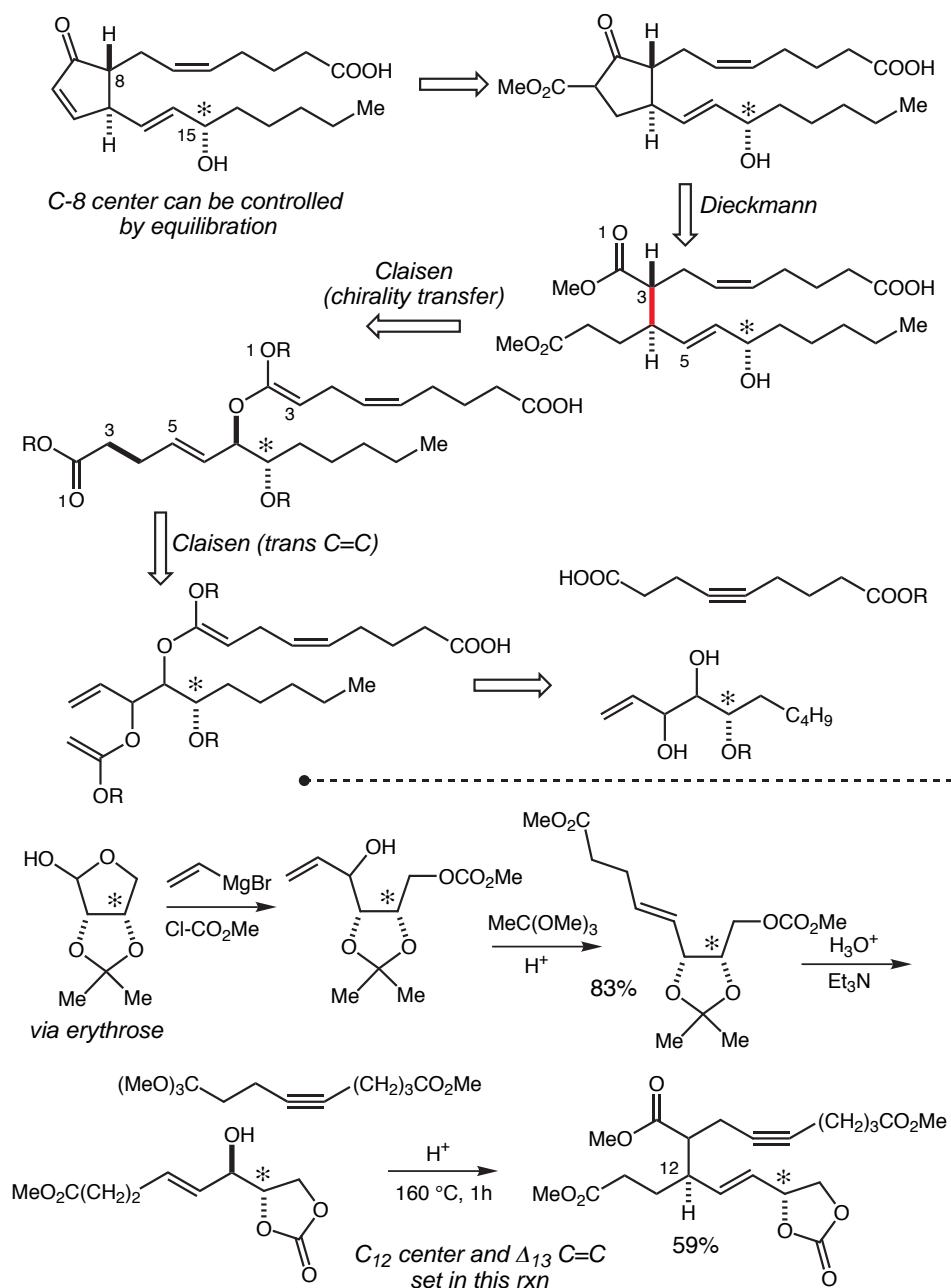


■ Unrealized plan to generate the required enolate

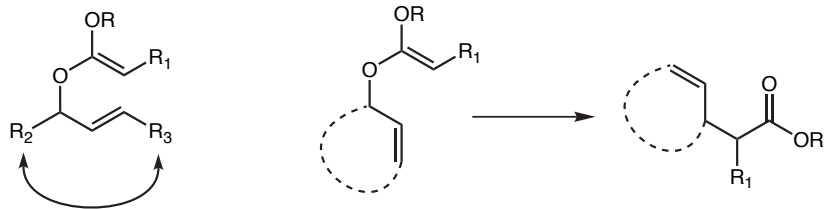


An Application PGA_1 : Ireland *JOC* **1976**, 41, 986; *Aldrichimica Acta* **1988**, 21, 59

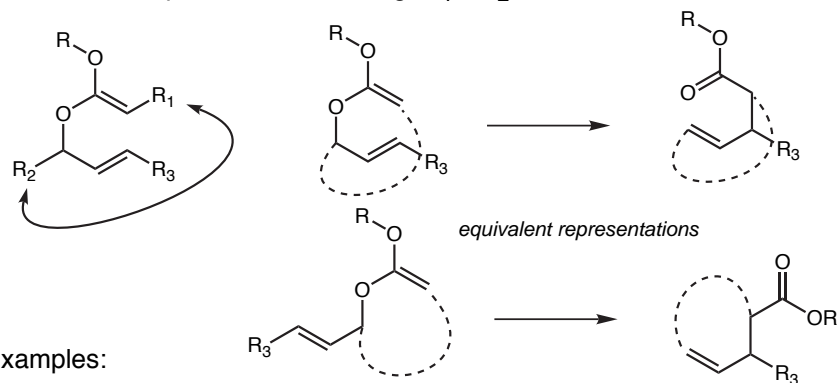
Prostaglandin A_2 Synthesis, G. Stork, *JACS* **1976**, 98, 1583



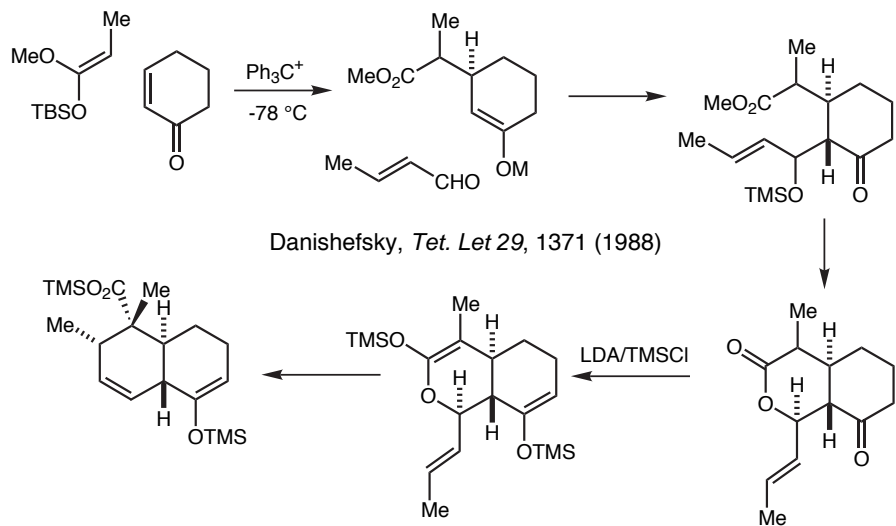
- The previous cases were derived from a connection between R₂ & R₃



- Consider consequence of connecting R₁ & R₂

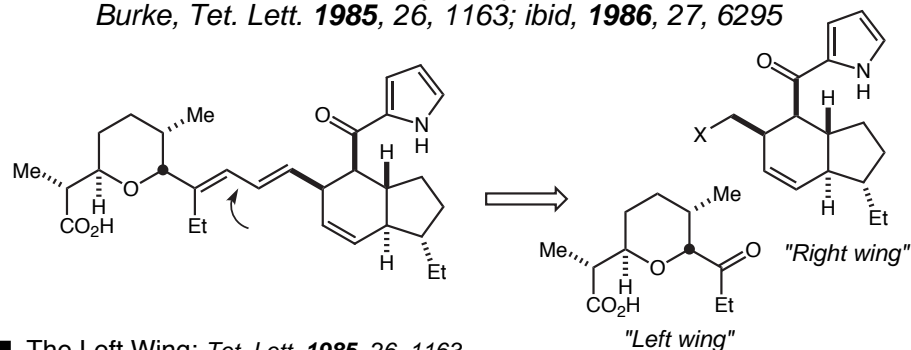


- Examples:

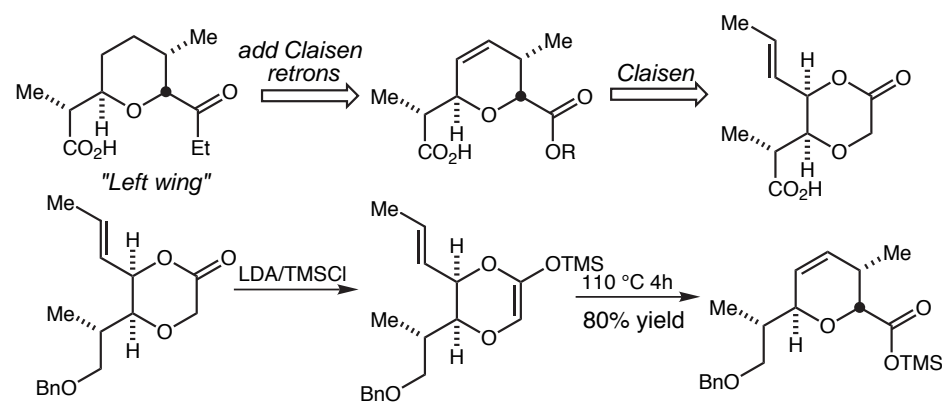


see also Danishefsky, *JACS* 1980, 102, 6889, 6891

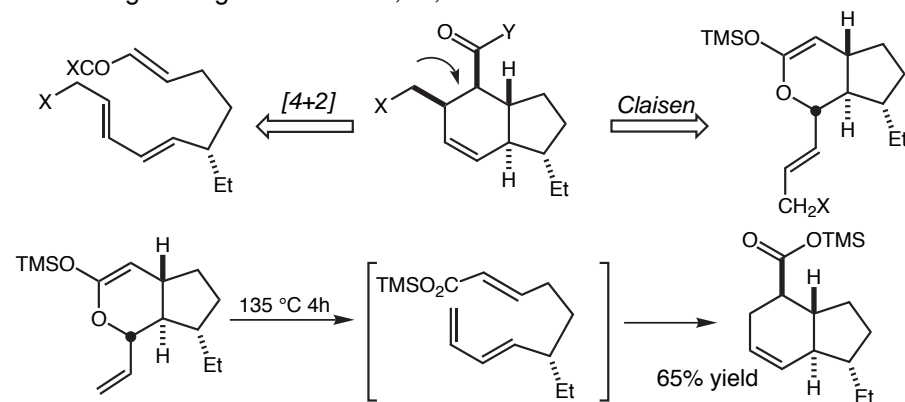
The Indanomycin Synthesis,
Burke, *Tet. Lett.* 1985, 26, 1163; *ibid.* 1986, 27, 6295



- The Left Wing: *Tet. Lett.* 1985, 26, 1163



- The Right Wing: *Tet. Lett.* 1986, 27, 6295

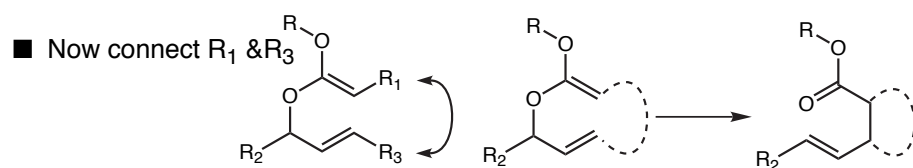
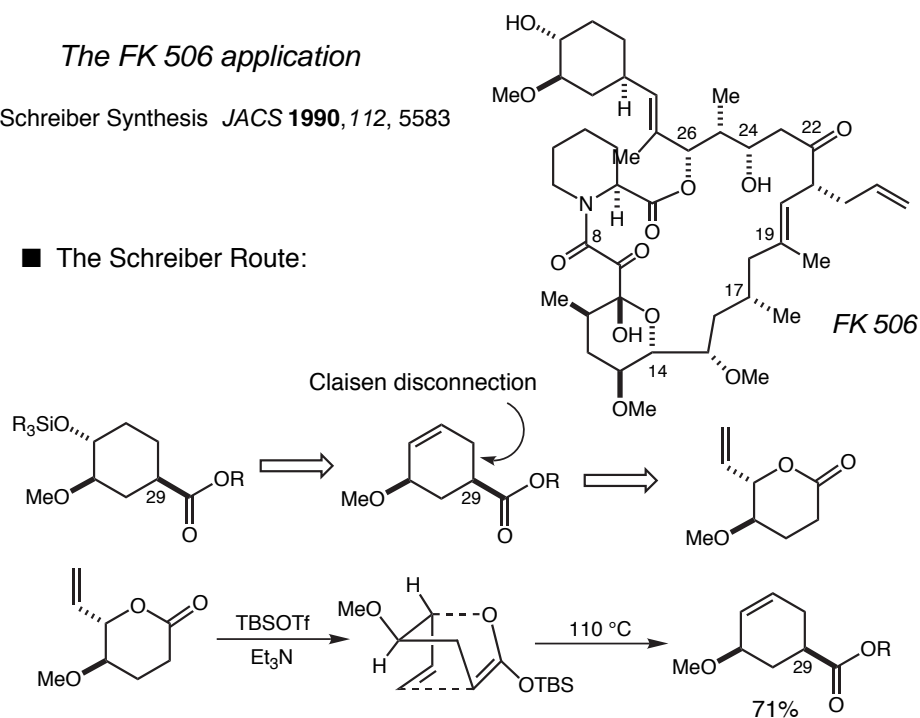


The "apparent" Claisen process is more complicated than anticipated.

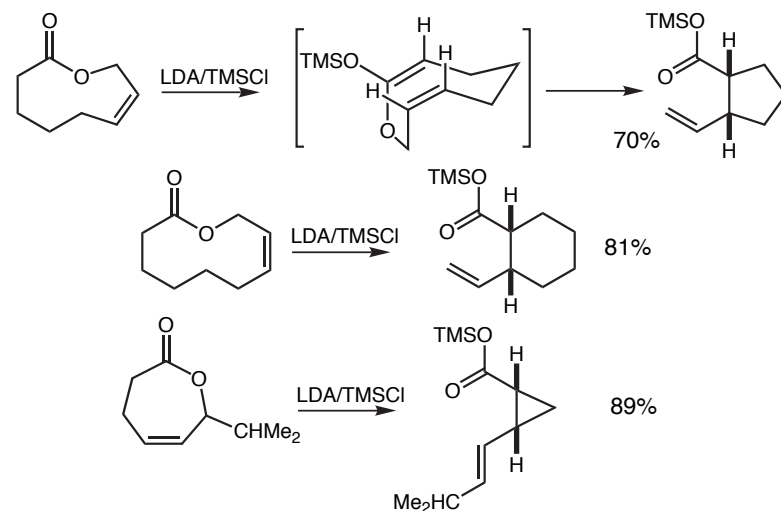
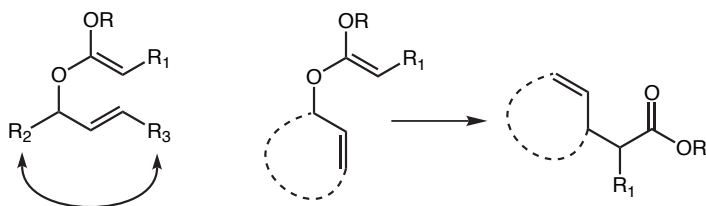
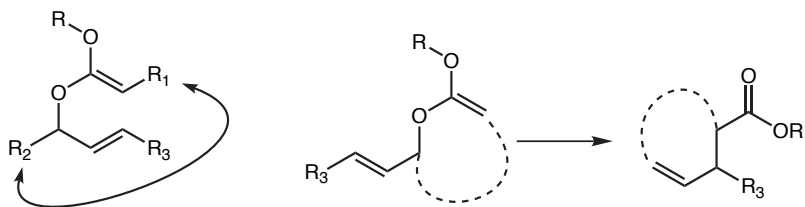
The FK 506 application

Schreiber Synthesis JACS 1990, 112, 5583

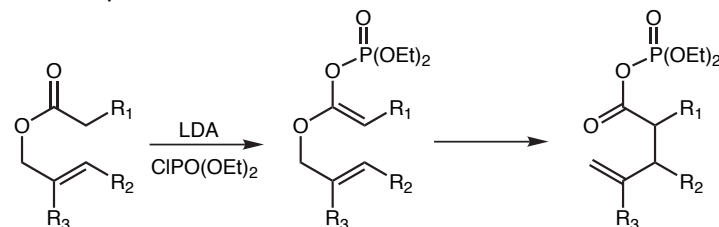
The Schreiber Route:



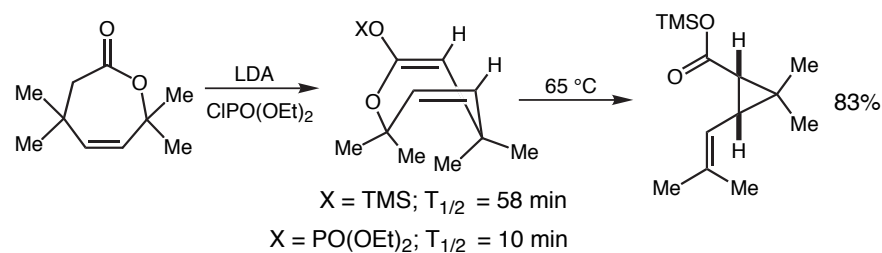
Examples: Funk, JACS 1982, 104, 4030

The previous cases were derived from a connection between R₂ & R₃and R₁ & R₂

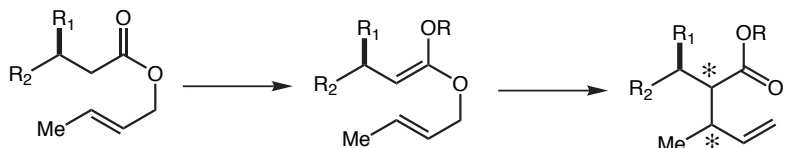
Recent improvements: Funk, JACS 1993, 115, 8847



chrysanthemic acid application

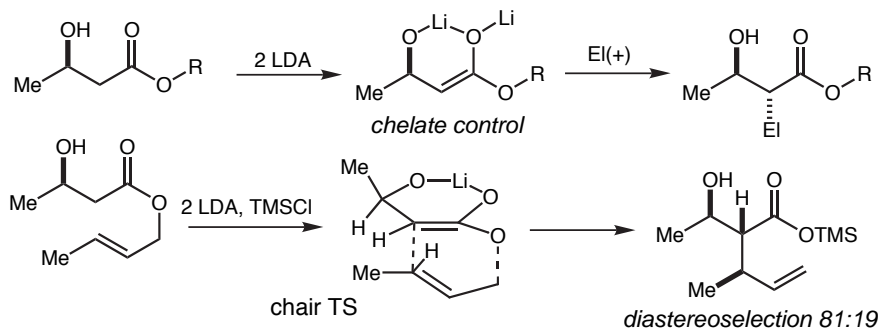


Exocyclic Stereochemical Issues



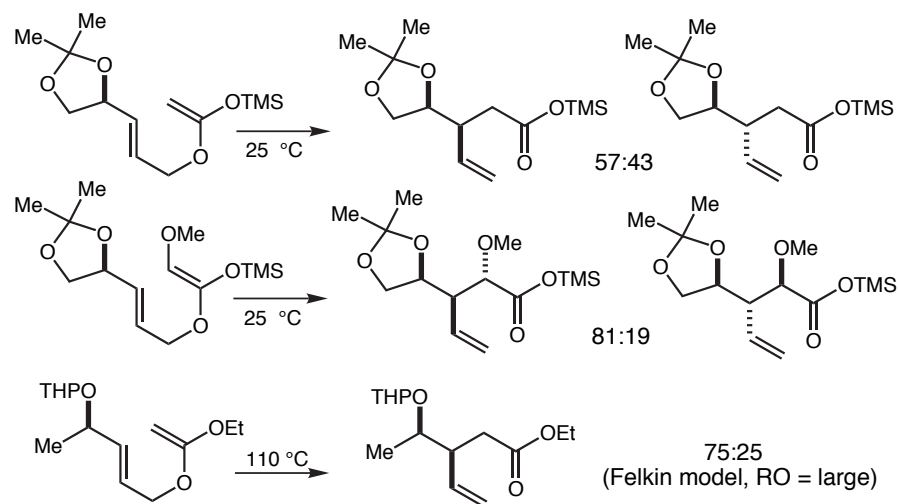
These rearrangements present many of the same issues which were encountered during our discussion of carbonyl addition with regard to asymmetric induction.

■ Chelate Control: β -Hydroxy ester enolates: Kurth, *JOC* **1985**, 50, 1840



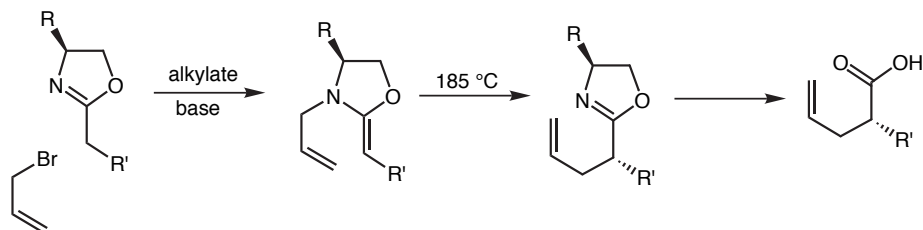
We again see the consequence of chelate-organized asymmetric induction

■ Felkin Control?: Cha, *Tet. Lett.* **1984**, 25, 5263

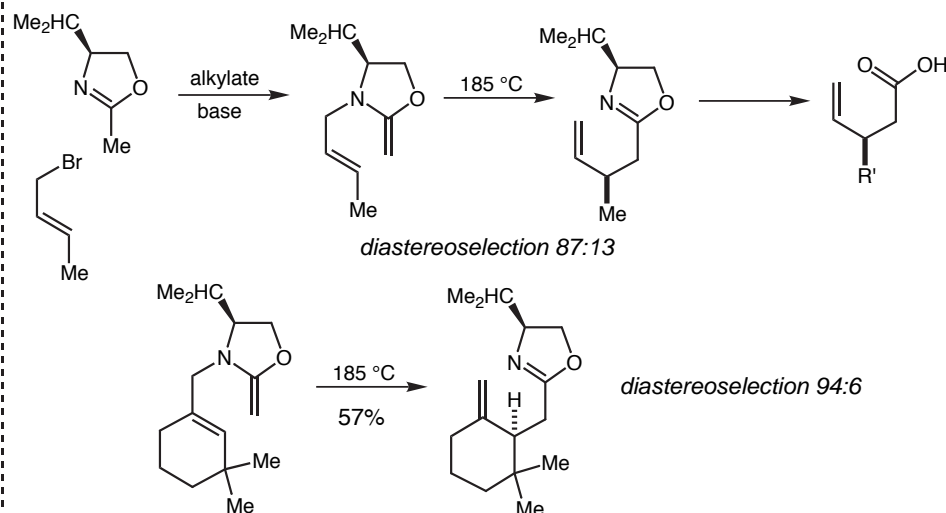


Takano, *Tet. Lett.* **1985**, 26, 865

N-Allylketene-*N*-O-Acetals: Kurth, *JACS* **1985**, 107, 443



β -Hydroxy ester enolates: Kurth, *JOC* **1985**, 50, 5769



The Claisen Rearrangement is subject to acid catalysis



$\text{BF}_3\text{-HOAc}$: Bryusova, *J. Gen. Chem. (USSR)* **1941**, 11, 722

BCl_3 : Gerrard, *Proc. Chem. Soc.* **1957**, 19;
Schmid, *Helv. Chem. Acta* **1973**, 56, 14

Et_2AlCl : Sonnenberg, *J. Org. Chem.* **1970**, 35, 3166

TiCl_4 : Mukaiyama, *Chem. Lett.* **1975**, 35, 1041

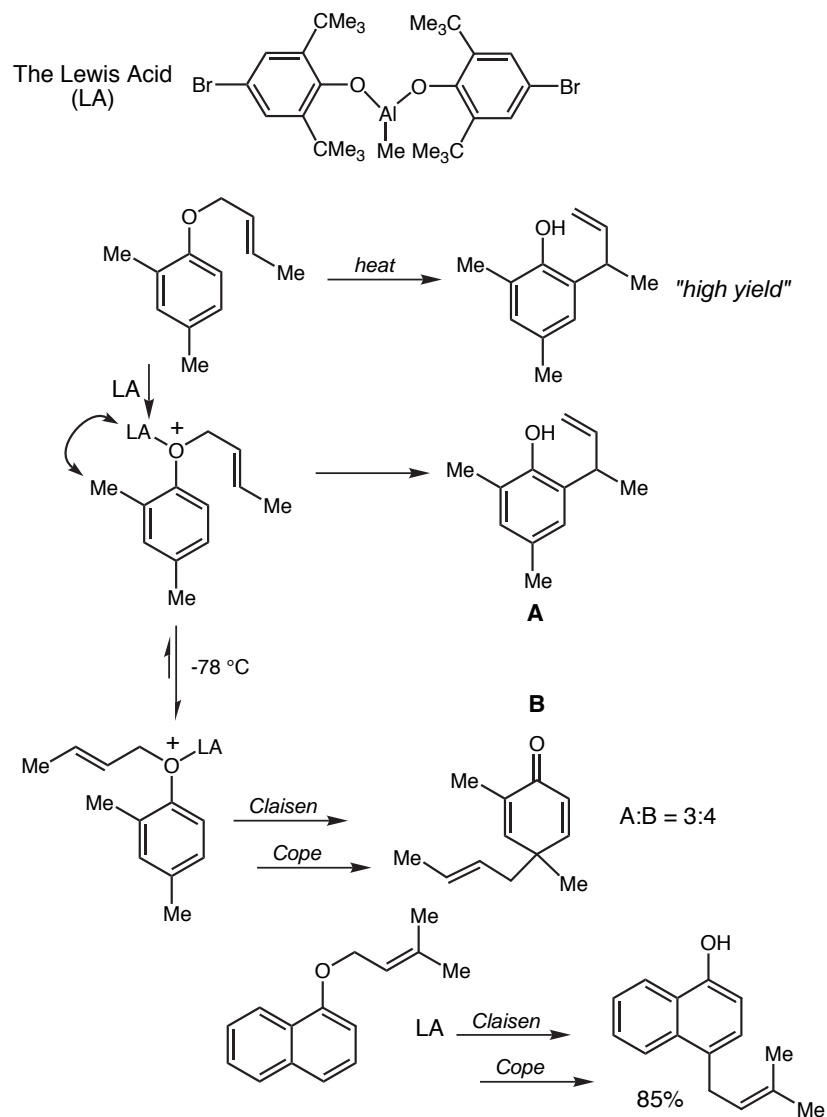
$(\text{RO})_2\text{AlMe}$: Yamamoto, *JACS.* **1988**, 110, 7922

$(\text{RO})_2\text{AlMe}$: Yamamoto, *Tet. Lett.* **1989**, 30, 1265

$(\text{RO})_2\text{AlMe}$: Yamamoto, *JACS.* **1990**, 112, 316

LiClO_4 : Reetz, *Tetrahedron.* **1993**, 49, 6025

Catalyzed Claisen Rearrangement of Allyl-phenyl Ethers

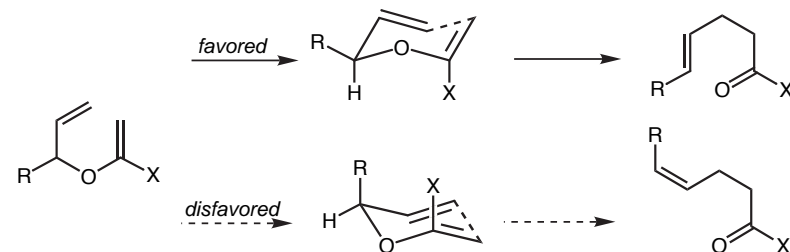
(RO)₂AlMe: Yamamoto, *Tet. Lett.* **1990**, 31, 377

The hindered Lewis acid will alter the partitioning of the Claisen process to the two ortho positions

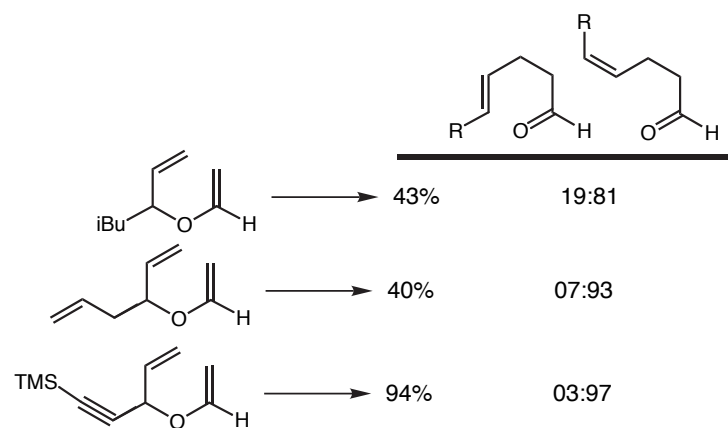
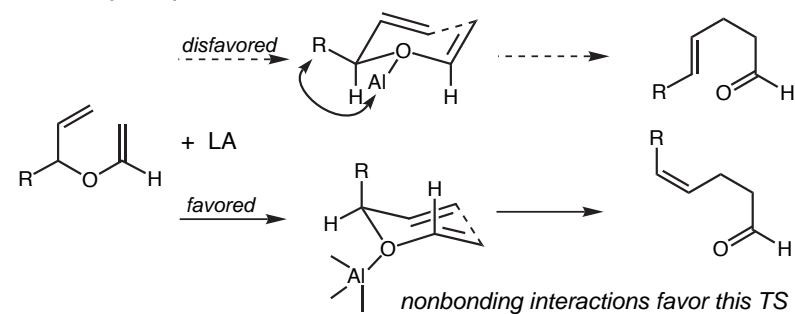
Catalyzed Claisen Rearrangement of Allyl-vinyl Ethers

(RO)₂AlMe: Yamamoto, *JACS.* **1990**, 112, 316

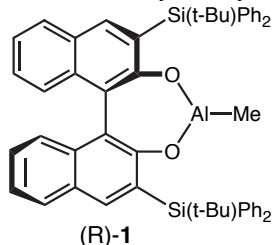
■ The thermal process



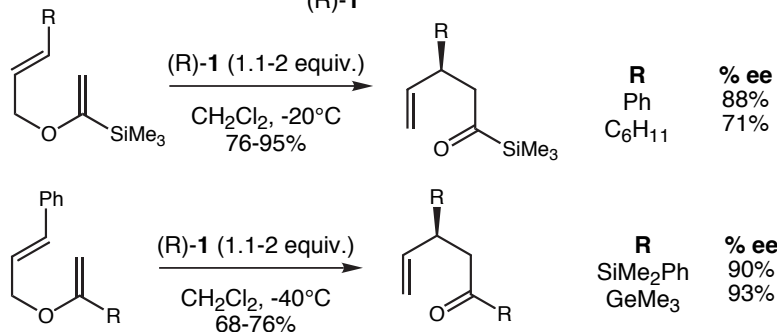
■ The catalyzed process



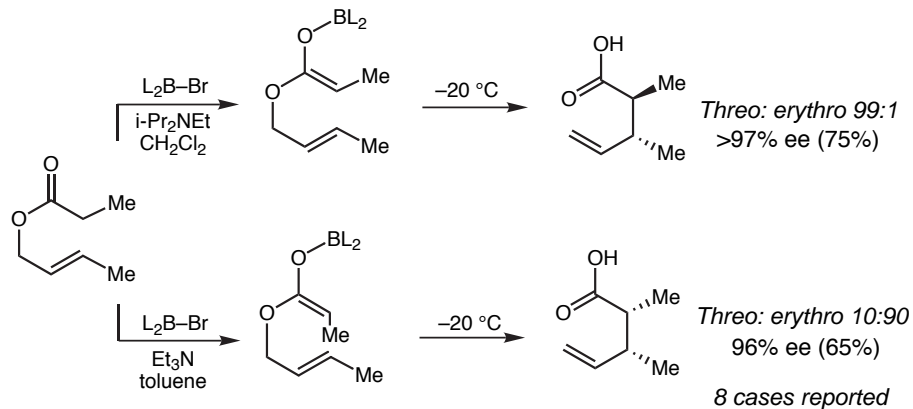
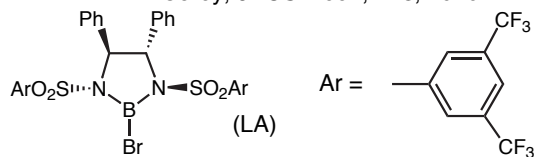
Chiral Lewis Acid Promoted Claisen Rearrangements

Yamamoto, *JACS* **1990**, 112, 7791Yamamoto, *Tet. Asymmetry* **1991**, 2, 647-662

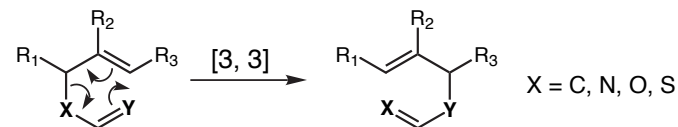
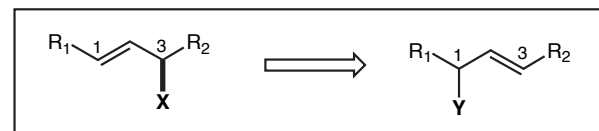
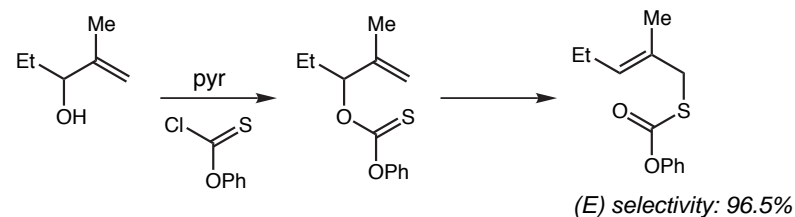
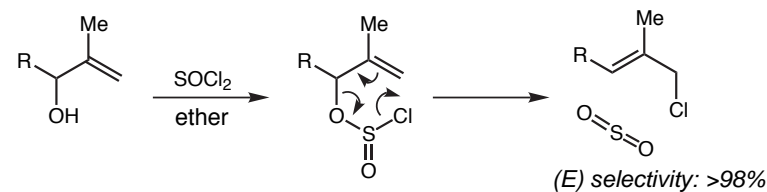
Note that these reactions are not catalytic



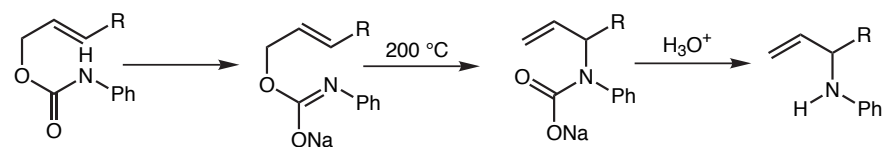
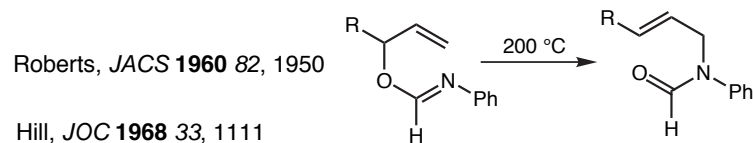
Enantioselective Claisen Rearrangements: Metal-Centered Chirality

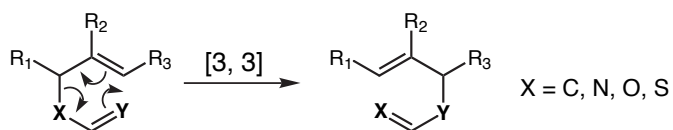
Corey, *JACS* **1991**, 113, 4026

Allylic rearrangements may be included as a subset of other sigmatropic processes:

■ X = O; Y = S Faulkner, *Synthesis* **1971** 175 (see pg 183)■ A stereochemically related case Johnson, *JACS* **1970** 92, 735

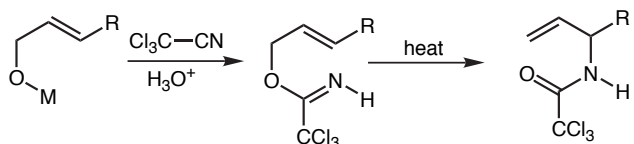
■ X = O; Y = N



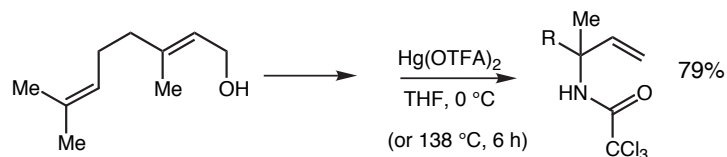
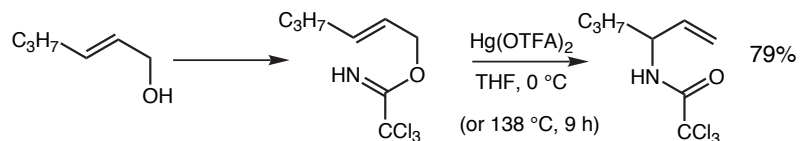


■ X = O; Y = N:

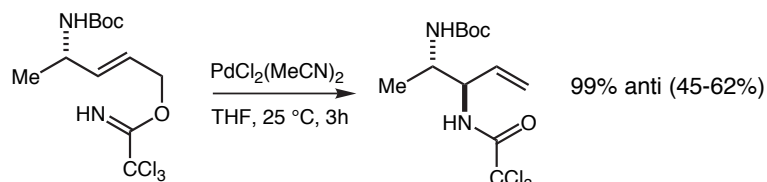
The Trichloroacetimidate Rearrangement, Overman, *JACS* **1974**, 96, 597



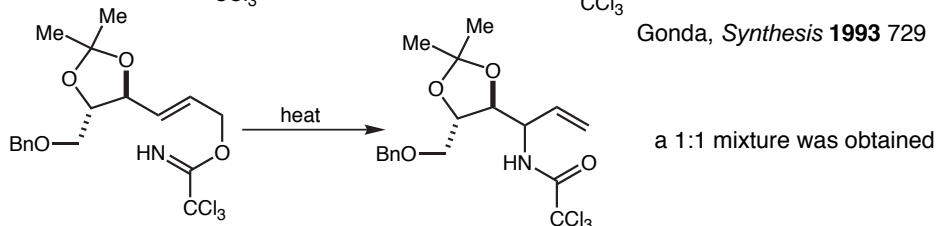
This reaction is also catalyzed by Hg(II) ion



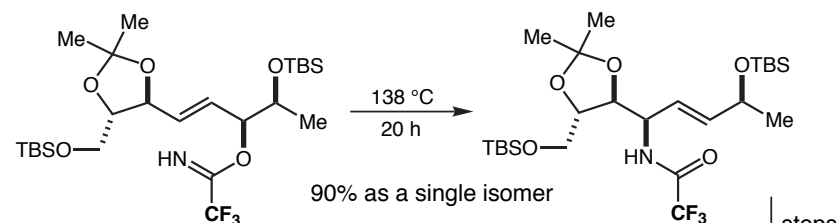
For an excellent review see: Overman, *Angew. Chem. Int. Ed.* **1984**, 23, 579



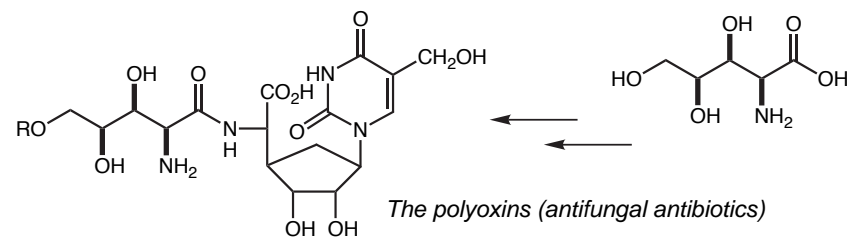
Gonda, *Synthesis* **1993** 729



Saksena, *JOC* **1986** 51, 5024

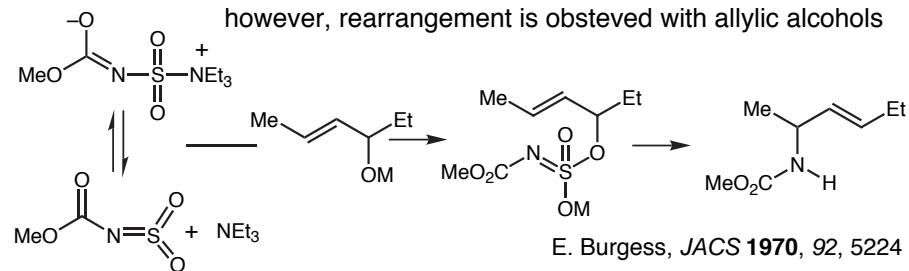


Thomas, *Chem. Commun* **1989** 717

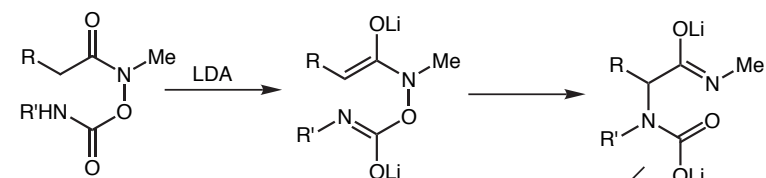


■ The "Burgess Reagent" is normally used for alcohol dehydration

however, rearrangement is observed with allylic alcohols

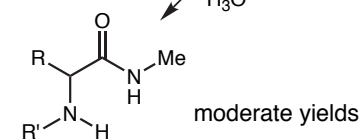


■ A new approach to the synthesis of α -amino acids



Endo, *SynLett* **1991** 649

This may not be a concerted process



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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 16

Cycloaddition Reactions-1

- Cycloadditions: Introduction
- Ketene Cycloadditions
- 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

D. A. Evans

Wednesday,
October 22, 2003

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
(electronic handout)

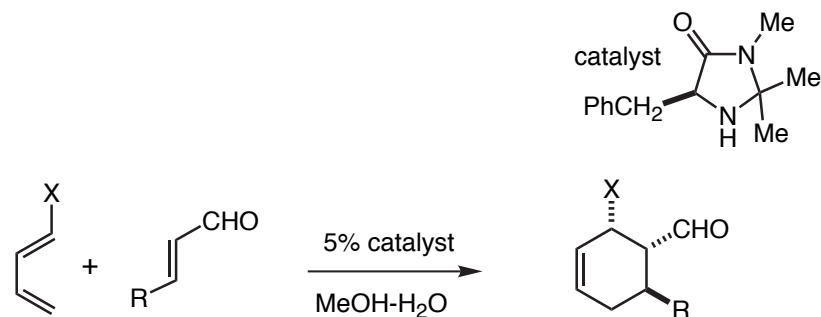
The Diels-Alder Reaction in Total Synthesis, K. C. Nicolaou, *Angew Chem. Int. Ed.* **2002**, 41, 1668-1698 **(electronic handout)**

Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications, E. J. Corey, *Angew Chem. Int. Ed.* **2002**, 41, 1650-1667 **(electronic handout)**

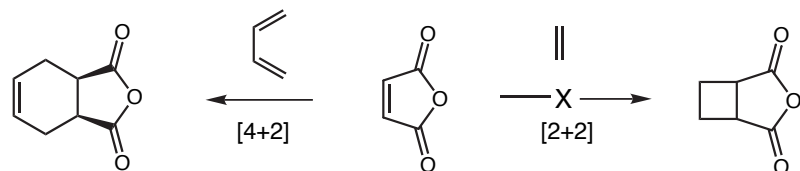
Chemistry and Biology of Biosynthetic Diels–Alder Reactions Emily M. Stocking and Robert M. Williams, *Angew Chem. Int. Ed.* **2003**, 42, 3078-3115 **(electronic handout)**

Problem of the Day:

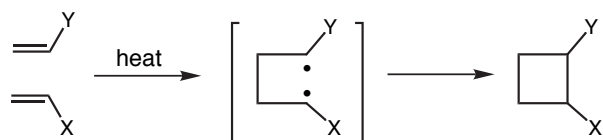
Rationalize the sense of asymmetric induction for this Diels-Alder Reaction reported by MacMillan, *JACS*, **2000**, 122, 4243. **(pdf)**



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



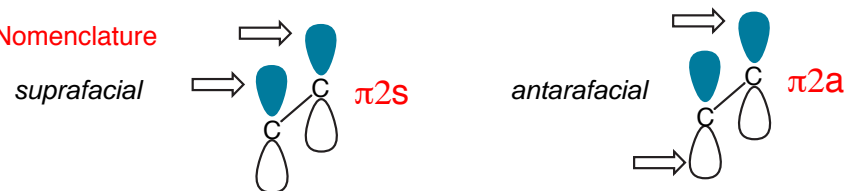
■ The related reaction of 2 ethylenes is nonconcerted: [2 + 2] cycloaddition



■ We also know that the photochemical variant is concerted

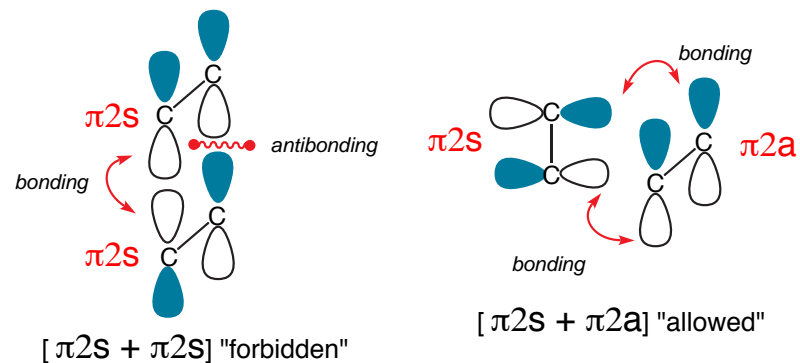
The frontier orbitals of the reacting species must have the proper symmetries

■ Nomenclature

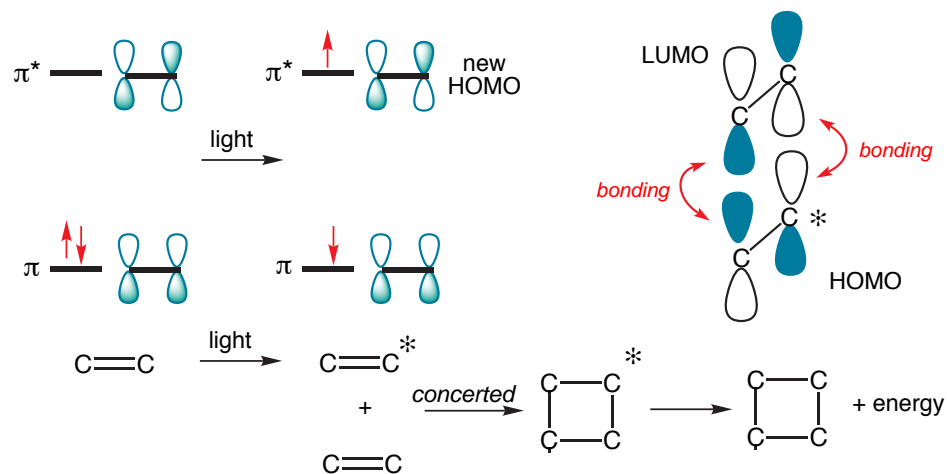


Using this nomenclature, the Diels-Alder reaction is a $\pi^4_s + \pi^2_s$ cycloaddition

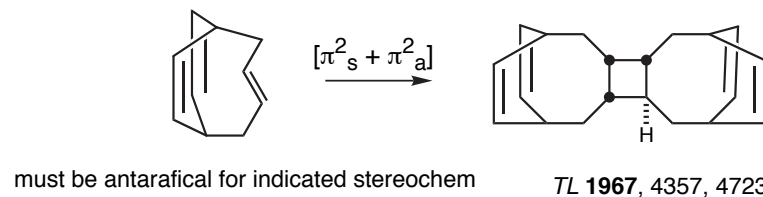
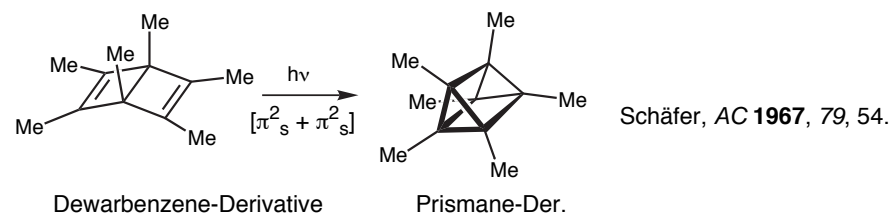
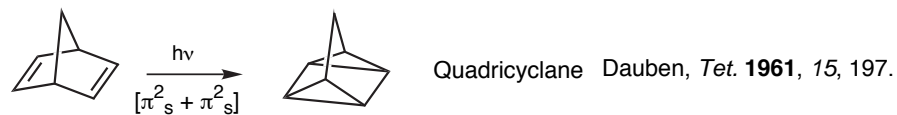
■ Consider [2 + 2] cycloaddition: Thermal activation [$\pi^2_s + \pi^2_s$]



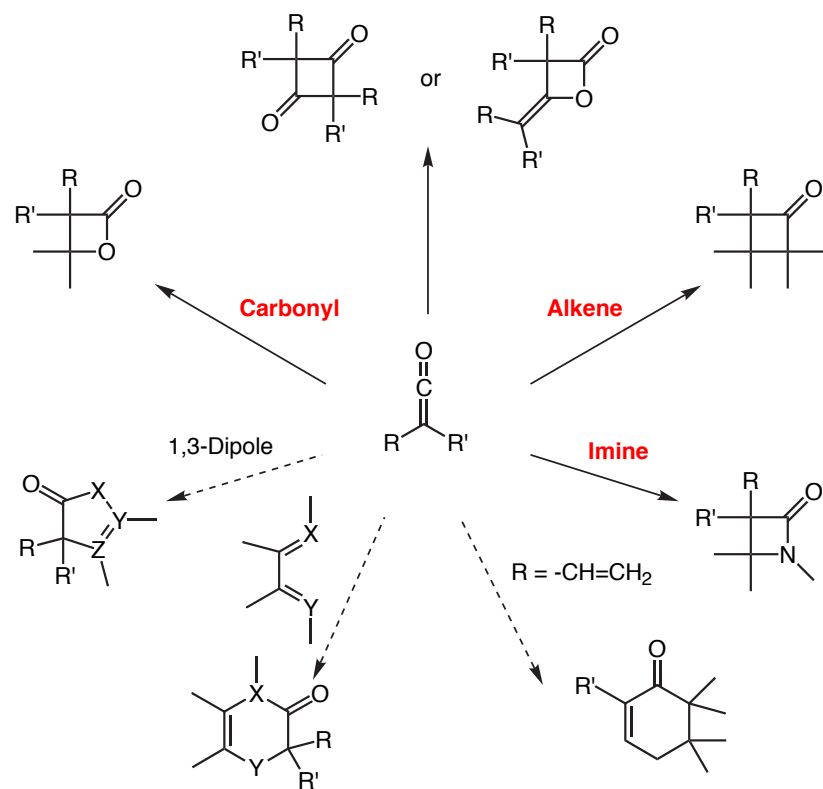
■ Consider [2 + 2] cycloaddition: Photochemical activation [$\pi^2_s + \pi^2_s$]



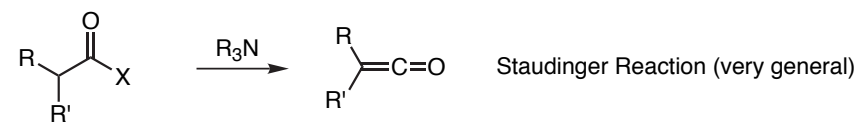
[2+2] Cycloaddition - Examples



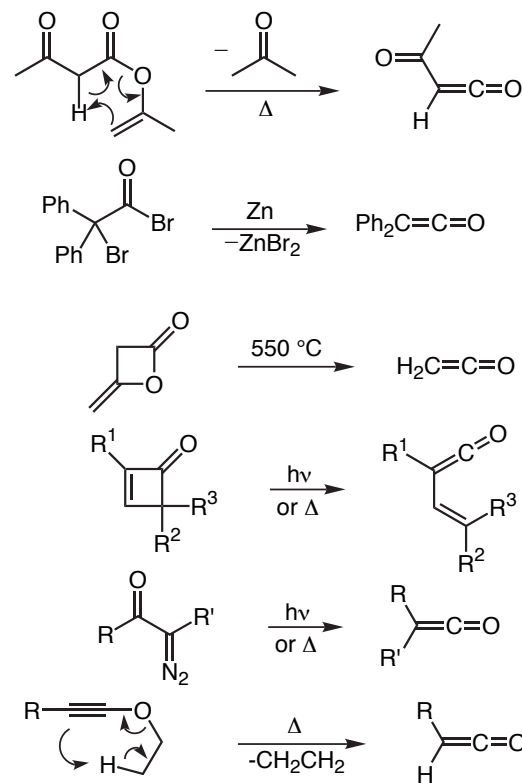
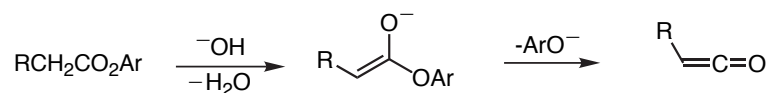
Summary of Ketene Cycloadditions



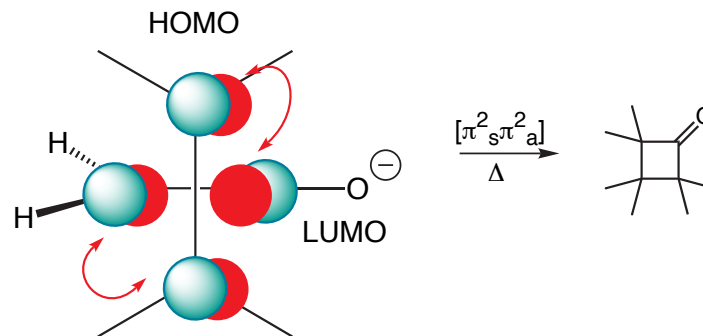
Ketene Preparation

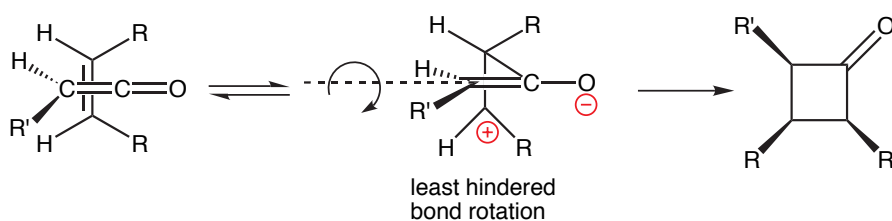


X = Cl, Ts, AcO, DCC, etc...



FMO Analysis

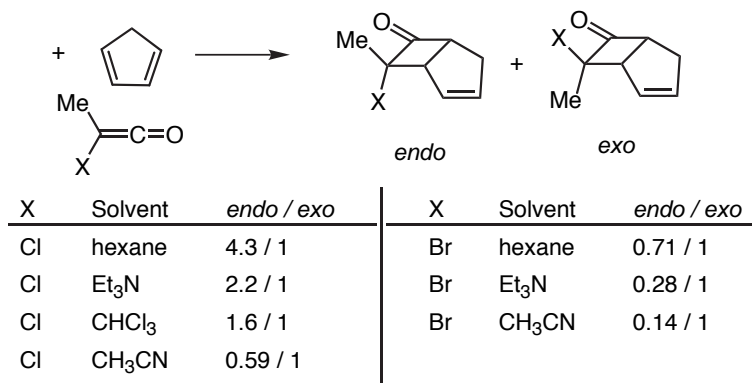


[2+2]: Stepwise Versus Concerted**Stepwise**

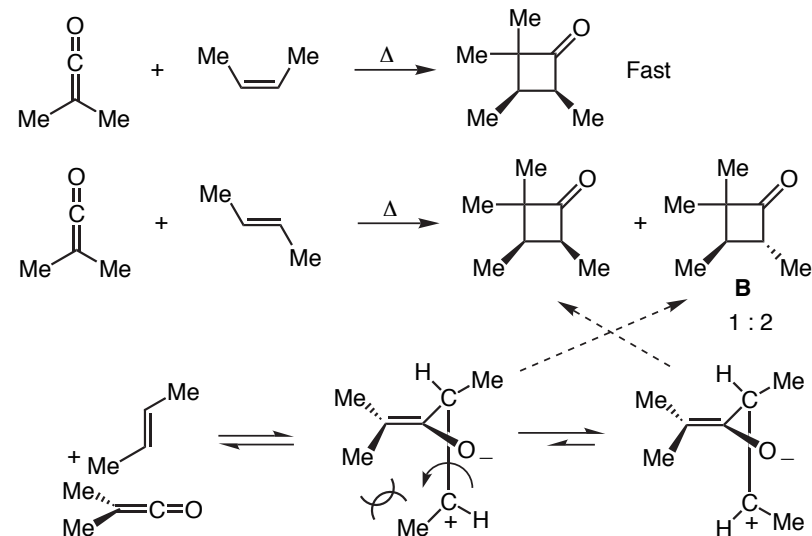
- Very large polar effects
- E olefins yield a mixture of *cis* and *trans* products
- Solvent effects observed, but it could merely be a ground state effect
- KIE seen for many reactions support stepwise mechanism
- Calculations (Wang and Houk) show a highly asynchronous transition state in the gas phase reaction
- All stereochemical outcomes can be rationalized assuming a stepwise mechanism

Concerted

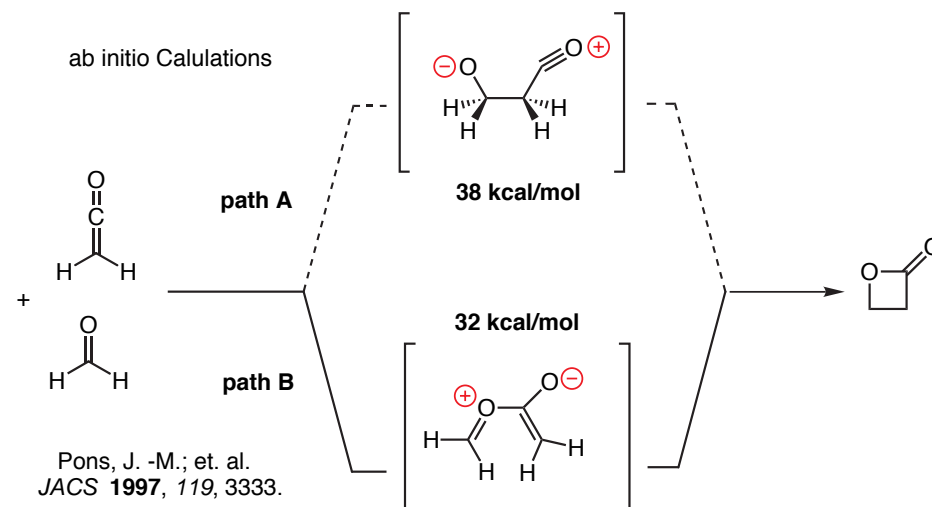
- Ketenes add stereoselectively to Z alkenes
- Z olefins are much more reactive than E

Solvent Effects

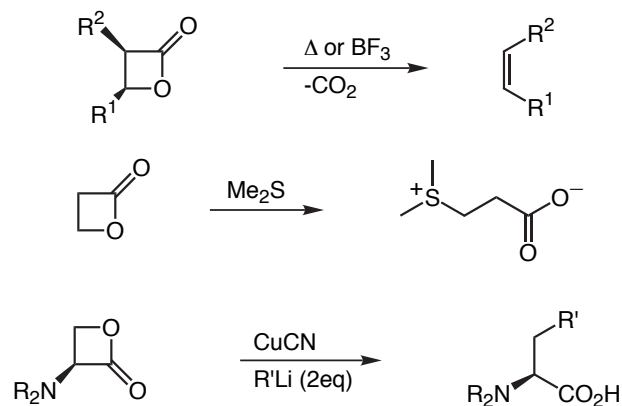
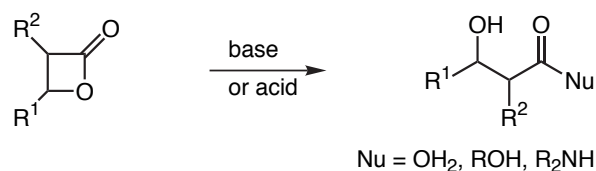
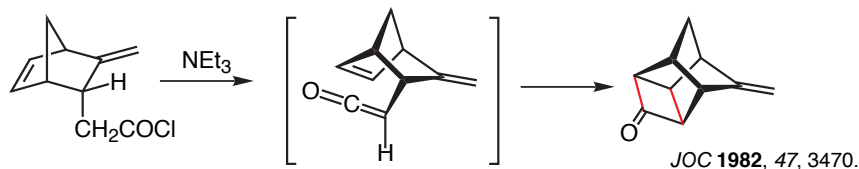
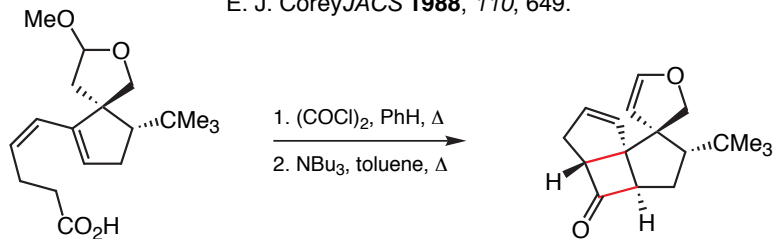
- Solvent effects implicate a zwitterionic intermediate
Brady, et. al, *JACS* **1970**, 92, 146-148.

Ketene-Alkene [2+2]

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

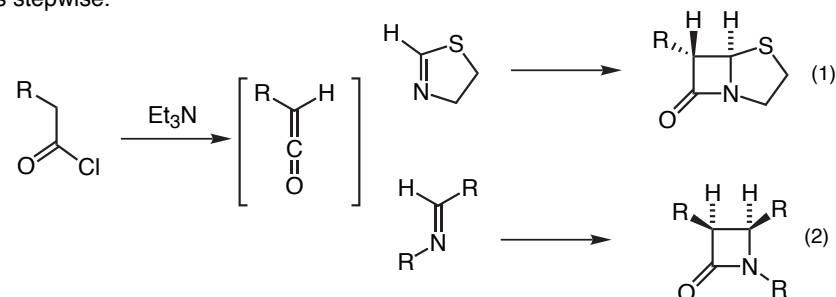
Ketenes + Aldehydes Afford β -Lactones

Mechanism and Origin of Stereoselectivity in Lewis Acid Catalyzed [2+2] Cycloadditions of Ketenes with Aldehydes, Singleton, *Angew. Chem. Int. Ed.* **2002**, 41, 1572

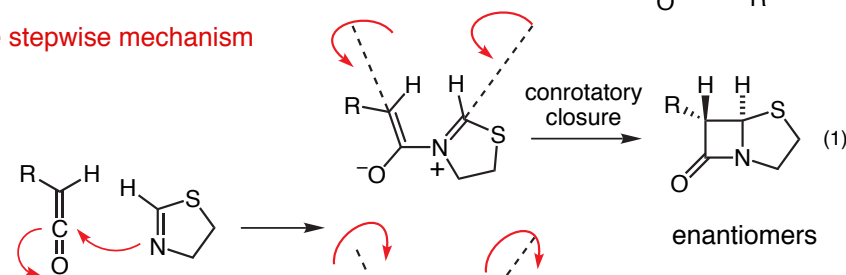
Transformations of β -LactonesVederas et al *JACS* **1987**, *107*, 4649.Application in Natural Product Synthesis: Ginkgolide B,
E. J. Corey *JACS* **1988**, *110*, 649.

The Staudinger Reaction

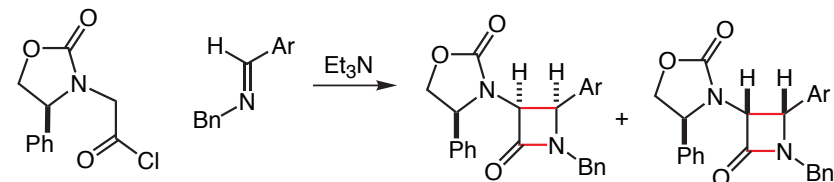
In this process, the illustrated ketene, generated *in situ* from an acid chloride, undergoes reaction with the indicated substrates to form β -lactams in a stereoselective process. When the azo-methine (RN=CHR) geometry in the reactant is (Z) the product stereochemistry is trans (eq 1). In a complementary fashion, the (E) imine affords the cis-substituted product (eq 2). While this 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:



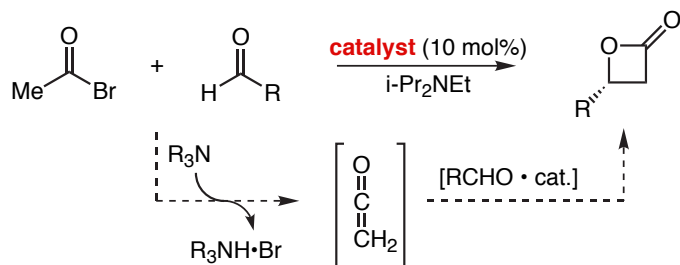
Evans, Sjogren *Tet. Lett.* **1985**, *26*, 3783, 3787.
See also Evans, Williams, *Tet. Lett.* **1988**, *29*, 5065.

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.

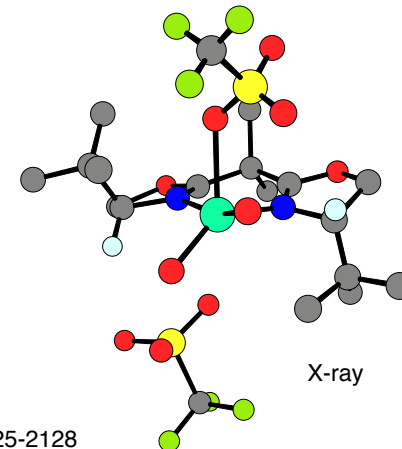
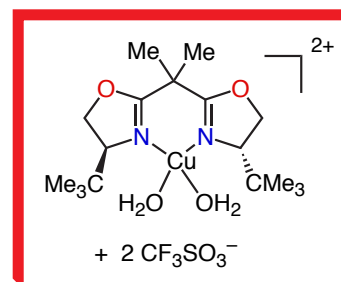
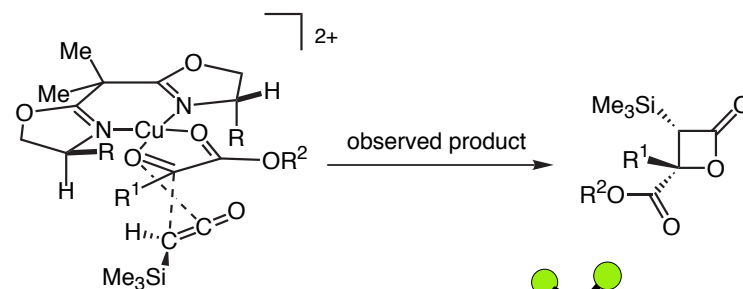
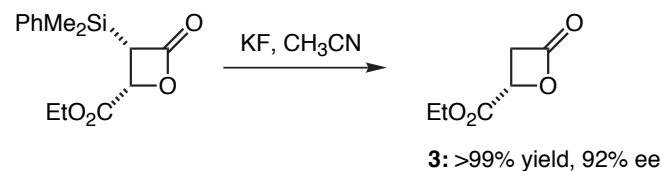
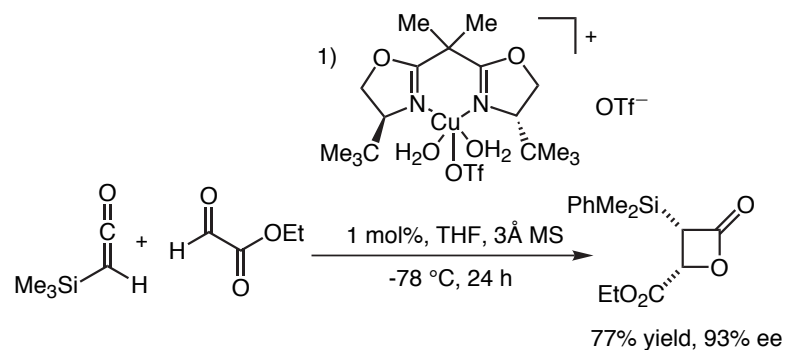
Enantioselective Ketene-Aldehyde Cycloadditions



cat. = **5a**: R = Me
5b: R = Cl

entry	Aldehyde 2 (R)	catalyst [time (h), temp (°C)]	% yield	% ee 3 (configuration)
a	BnOCH ₂ —	5b (8, -40)	91	92 (<i>R</i>)
b	PhCH ₂ CH ₂ —	5a (16, -50)	93	92 (<i>S</i>)
	PhCH ₂ CH ₂ —	5a (72, -78)	89	95 (<i>S</i>)
c	CH ₂ CH(CH ₂) ₈ —	5b (16, -50)	91	91 (<i>S</i>)
d	Me ₂ CHCH ₂ —	5a (24, -50)	80	93 (<i>S</i>)
e	BnOCH ₂ CH ₂ —	5b (16, -40)	90	91 (<i>S</i>)
f	TBDPSOCH ₂ —	5b (16, -40)	74	89 (<i>R</i>)
g	BnOCH ₂ —C≡C—	5a (16, -50)	86	93 (<i>R</i>)
h	Me ₃ C—C≡C—	5a (16, -50)	91	85 (<i>R</i>)
i	C ₆ H ₁₁ —	5b (24, -40)	56	54 (<i>R</i>)

Nelson, S. G.; Peelen, T. J.; Wan, Z. *JACS*, **1999**, 121, 9742-9743



with J. Janey, *Org. Lett.* **2001**, 3, 2125-2128

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

The Diels-Alder Reaction in Total Synthesis, K. C. Nicolaou,
Angew Chem. Int. Ed. **2002**, 41, 1668-1698 (**handout**)

Catalytic Enantioselective Diels-Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications, E. J. Corey, *Angew Chem. Int. Ed.* **2002**, 41, 1650-1667 (**handout**)

Hetero Diels-Alder Methodology in Organic Synthesis
Boger, D.L. and Weinreb, S.N., Academic Press, 1987

Natural Products Synthesis Through Pericyclic Reactions
Desimoni, Tacconi, Barco, Polini, ACS Monograph 180, 1983, Chapter 5,

Asymmetric Diels-Alder Reactions with Chiral Enoates as Dienophiles
Modern Synthetic Methods **1986**, Scheffold, Ed. Springer-Verlag,

Intramolecular Diels-Alder and Alder Ene Rxns, D. F. Taber, Springer-Verlag, **1984**

Synthetic Aspects of D-A Cycloadditions with Heterodienophiles
Weinreb, *Tetrahedron*, **1982**, 38, 3087-3128

The Intramolecular DA Rxn: recent advances and synthetic applications
Fallis, *Can. J. Chem.*, **1984**, 62, 183-234

Intramolecular [4 +2] & [3 + 2] Cycloadditions in Organic Synthesis
Oppolzer, *Angew. Chem. Int. Ed.*, **1977**, 16, 10-23

Preparation & DA Reactions of Heterosubstituted 1, 3-Dienes
Petrzilka, *Synthesis*, **1981**, 753-786

DA Reactions of Azadienes
Boger, *Tetrahedron*, **1983**, 39, 2869-2939

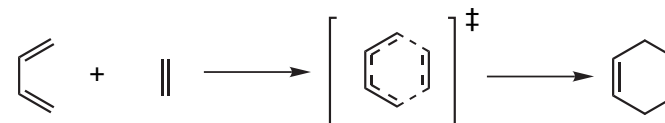
Silyloxydienes in Organic Synthesis
Danishefsky, *Acct. Chem. Res.*, **1981**, 14, 400-406

DA Reactions Part I: New Preparative Aspects
Sauer, *Angew. Chem. Int. Ed.*, **1966**, 5, 211-230

DA Reactions Part II: The Reaction Mechanism
Sauer, *Angew. Chem. Int. Ed.*, **1967**, 6, 16-33

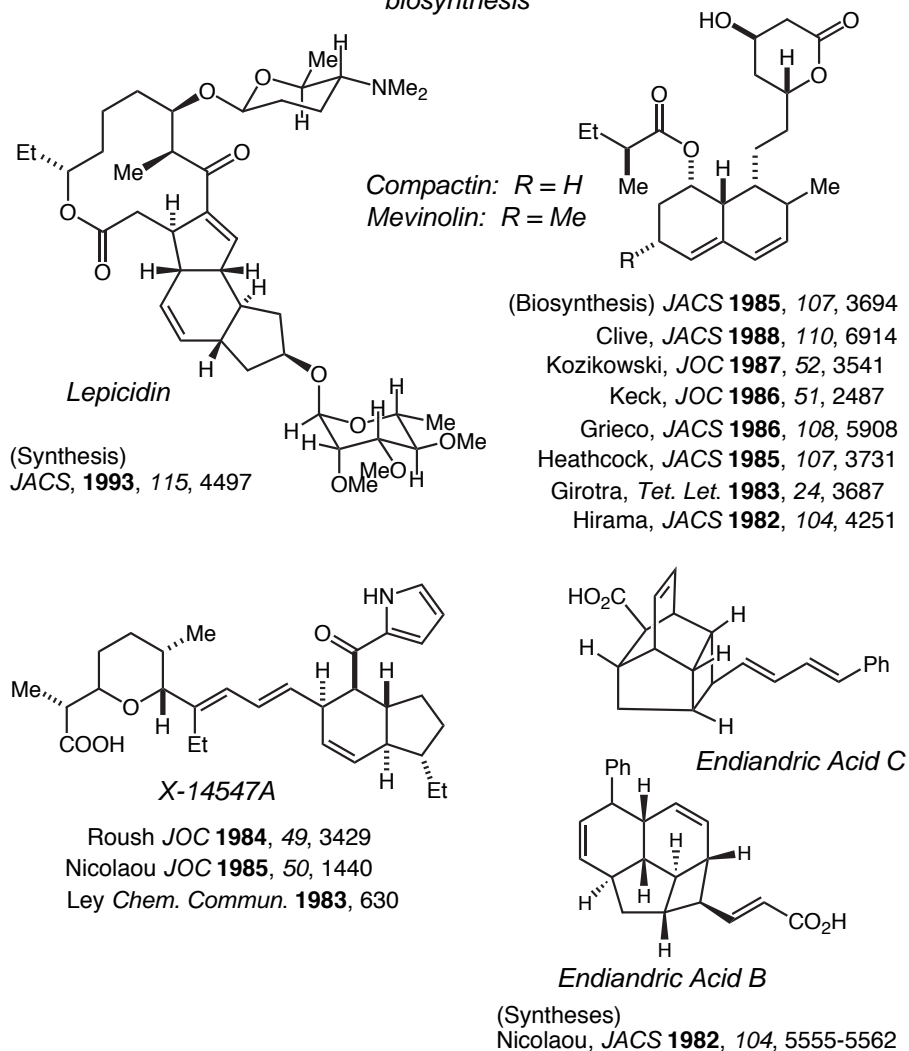
Mechanistic Aspects of Diels-Alder Reactions: A Critical Survey
Sauer, *Angew. Chem. Int. Ed.*, **1980**, 19, 779-807

■ The Reaction:



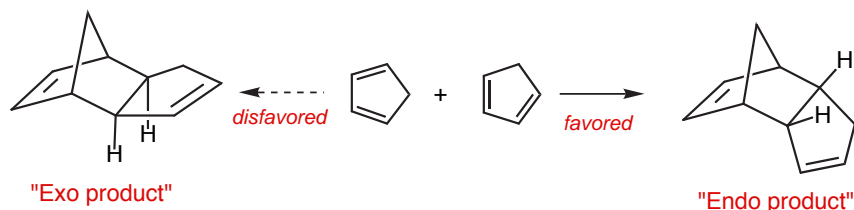
■ Representative natural products displaying the Diels-Alder retron:

These natural products could well have incorporated the DA rxn into the biosynthesis

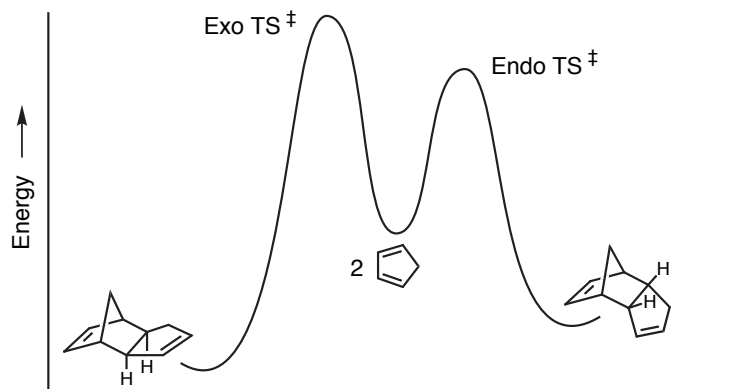


The Alder Endo Rule

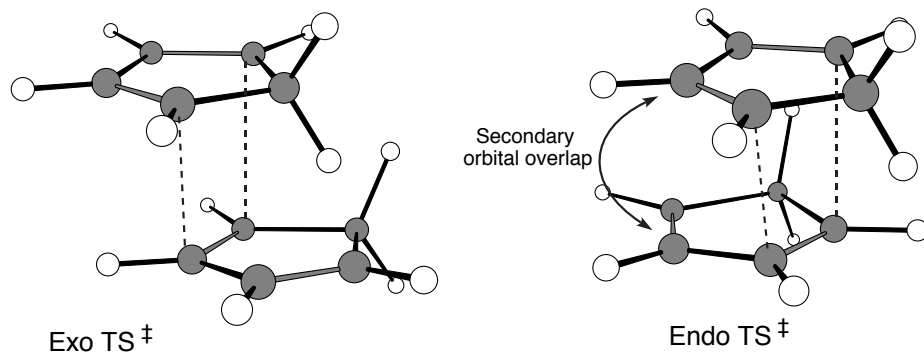
The following observation illustrates an example of the Alder Rule which will be defined below.



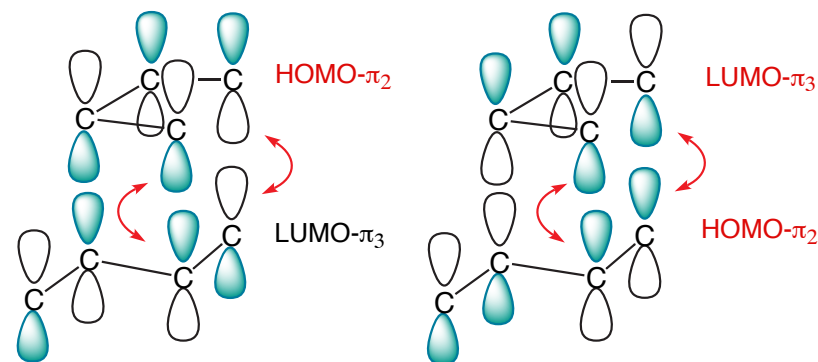
Observation: The endo Diels-Alder adduct is formed faster even though the exo product is more stable. There is thus some special stabilization in the transition state leading to the endo product which is lacking the exo transition state.



■ 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**

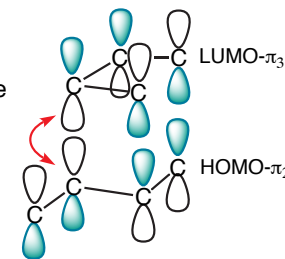
If the symmetries of the frontier MO's of reacting partners are "properly matched" the reaction is referred to as "symmetry-allowed". The Diels-Alder reaction is such a case. As illustrated, the HOMO and LUMO of both the diene and dienophile, which in this case are the same, will constructively overlap as indicated in formation of both sigma bonds.



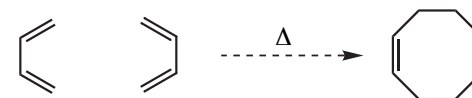
■ Primary orbital overlap leads directly to the formation of new chemical bonds.

Frontier MO Explanation for the Endo Rule

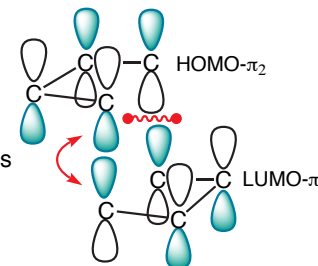
■ Secondary (transient) orbital overlap can also occur in the stabilization of certain transition state geometries. Such a transient stabilizing interaction can occur in the endo, but not exo, transition state:

**The Other Dimerization Possibility for Butadiene**

Does the possibility for the following concerted dimerization exist?

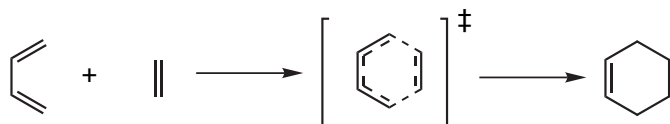


■ Note that the termini only match at one end for the HOMO-LUMO pairing. Hence we say that the symmetry requirements for the reaction in question are not met. This does not mean that the reaction will not occur, only that the reaction will not be concerted. Such reactions are called "symmetry-forbidden".



Additional Reading: Lowry & Richardson, Chapter 10, theory of Pericyclic Rxns pp 839-900

Transition State Modelling is Coming of Age

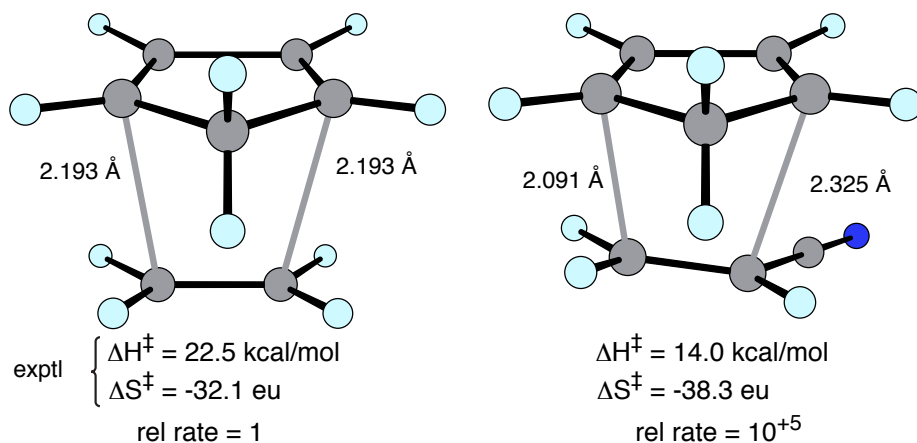


- The lengths of the forming C–C bonds are Ca. 1.5 times the normal bond distance. This factor comes out of the *ab initio* work of Jorgensen & Houk

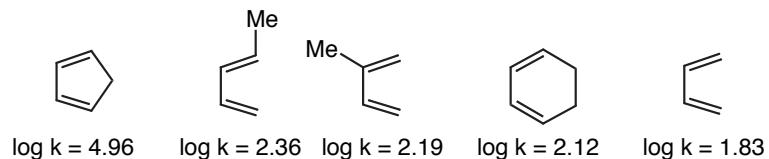
leading references: Jorgensen, *JACS* **1993**, *115*, 2936-2942
 Houk, Jorgensen, *JACS* **1989**, *111*, 9172

Transition Structures of Hydrocarbon Pericyclic Reactions
 Houk *Angew. chem. Int. Ed.* **1992**, *31*, 682-708

- Bond formation is not synchronous with substituted dienophiles (Jorgensen)



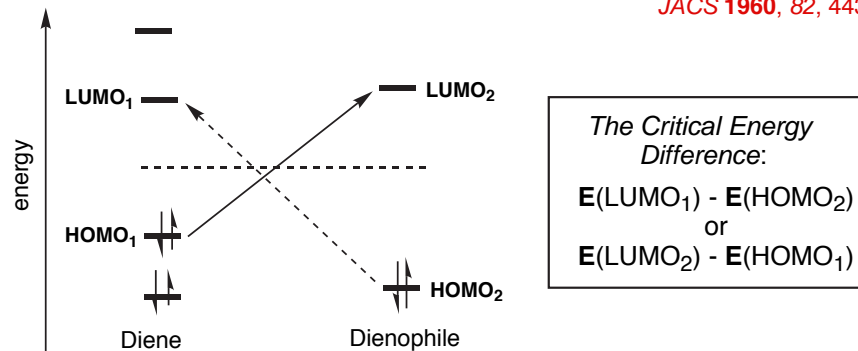
- Diene Reactivity as measured against Maleic anhydride



Sauer, *Angew. Chem. Int. Ed.*, **1980**, *19*, 779-807

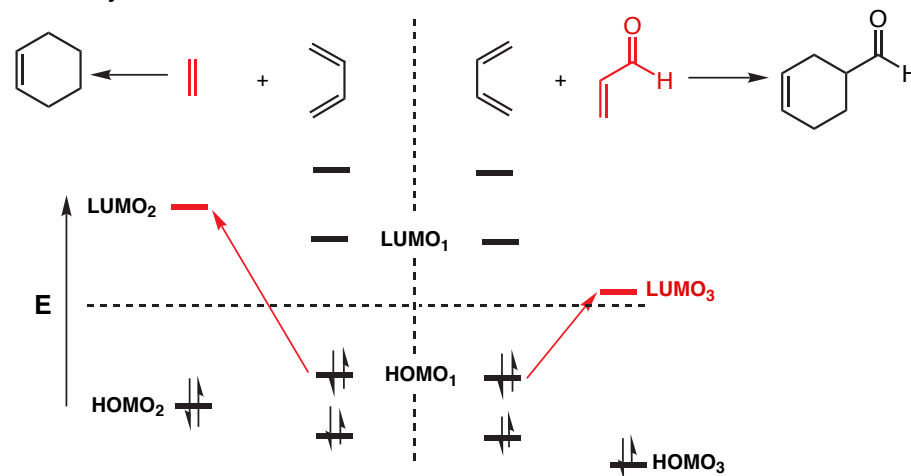
- Lewis Acid Catalysis of the reaction is possible:

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

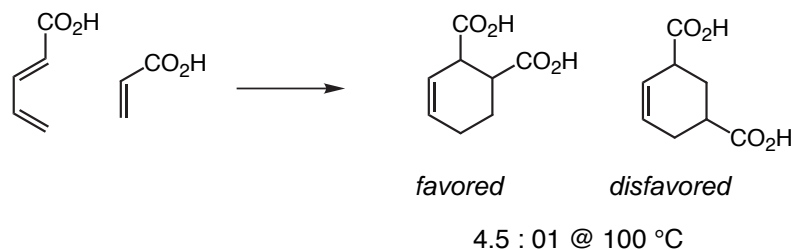
Ethylene & Butadiene Vs Butadiene & Acrolein



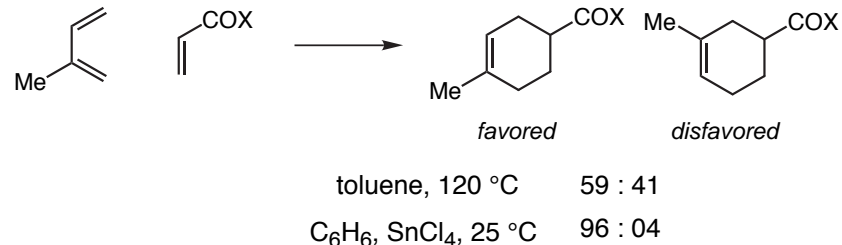
$\Delta E (\text{LUMO}_3\text{-HOMO}_1) < \Delta E (\text{LUMO}_2\text{-HOMO}_1) \implies \text{Rate Acceleration}$

Lewis acid catalysis not only dramatically increases rates by ca 10^{+6} it also improves reaction regiochemistry & endo diastereoselectivity

Orientation of Reacting Partners

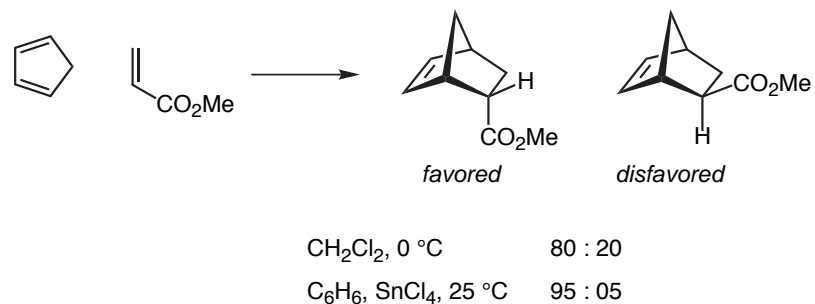


Lewis acid catalysis improves orientation



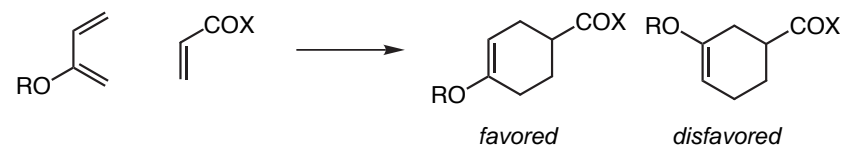
In general, 1-substituted dienes are more regioselective than their 2-substituted counterparts: Sauer, *Angew. Chem. Int. Ed.*, **1967**, 6, 16-33

Lewis acid catalysis improves endo diastereoselection

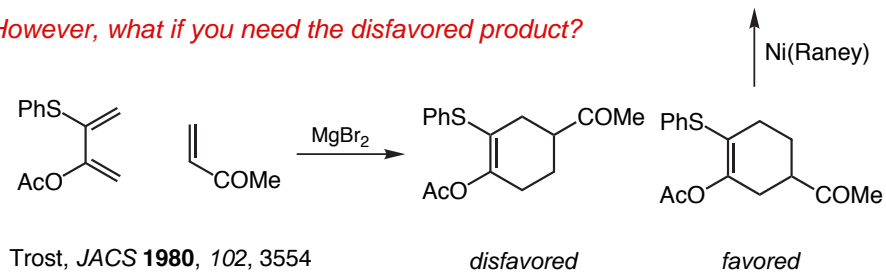


DA Reactions Part II: The Reaction Mechanism, Sauer, *Angew. Chem. Int. Ed.*, **1967**, 6, 16-33

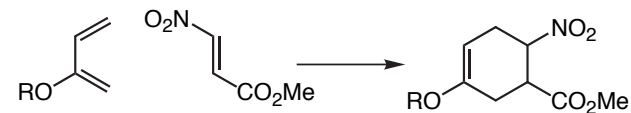
Here is an interesting problem in reaction design



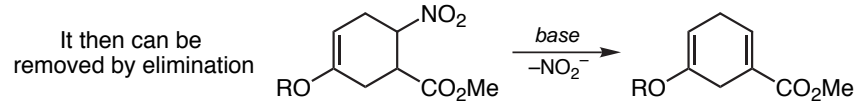
However, what if you need the disfavored product?



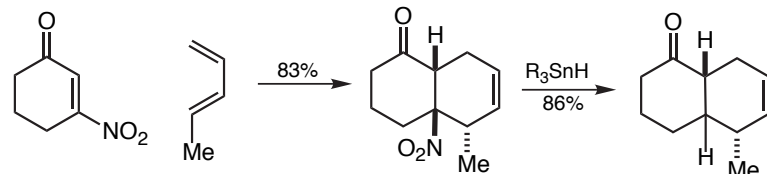
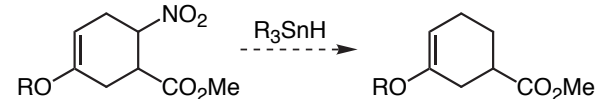
By employing a removable substituent, it is possible to access the normally disfavored product diastereomer



Danishesky, *JACS* **1978**, 100, 2918: The NO₂ FG completely dominates directivity

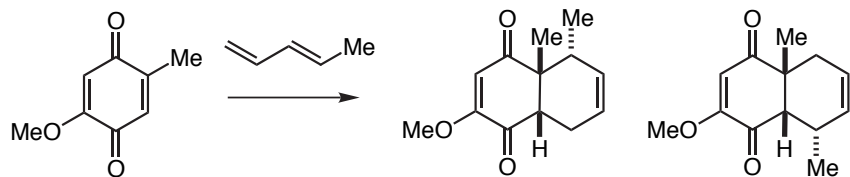


or by reduction
Ono, *Tet.* **1985**, 4013



Ono, *Chem. Commun.* **1982**, 33-34

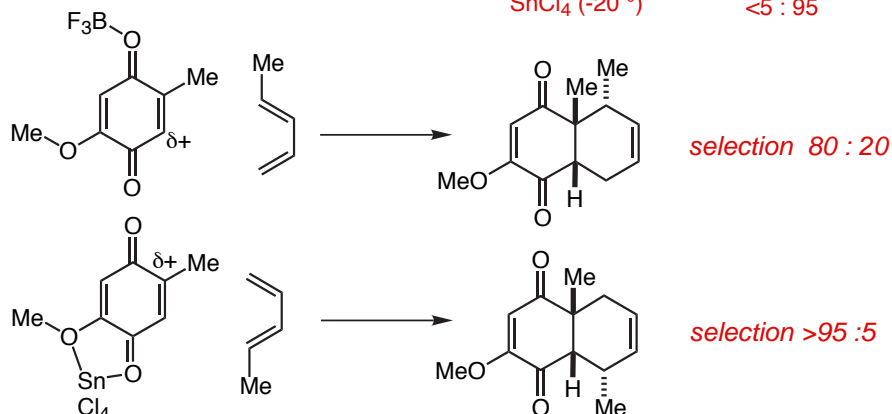
mixture of ring-fusion isomers

Instructive Issues of Regiocontrol with Quinone Dienophiles

Orientation of Reacting Partners
controlled by Lewis acid structure

Reusch *JOC* **1980**, 45, 5013

Conditions	Ratio
thermal (100 °)	50 : 50
$\text{BF}_3 \cdot \text{OEt}_2$ (-20 °)	80 : 20
SnCl_4 (-20 °)	<5 : 95

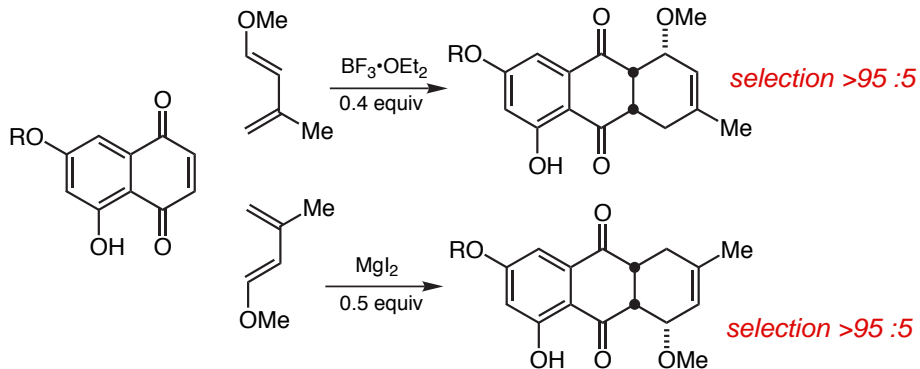


selection 80 : 20

selection >95 : 5

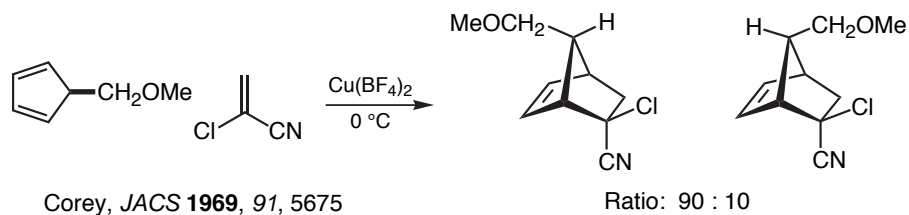
Similar results provided by Stoodley *Chem. Comm.* **1982**, 929

Kelly *Tet. Let.* **1978**, 4311



selection >95 : 5

selection >95 : 5



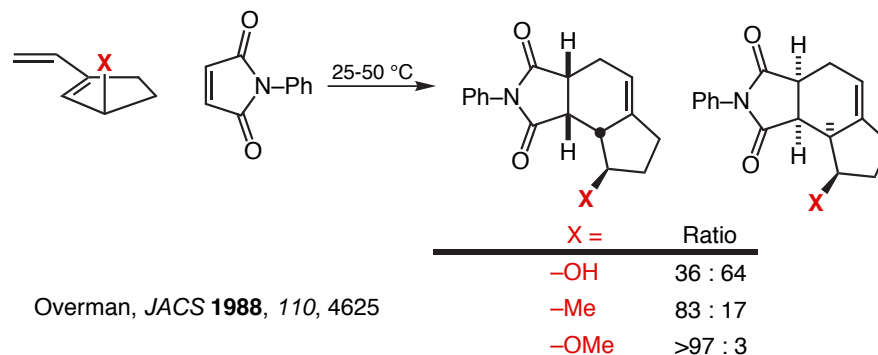
Corey, *JACS* **1969**, 91, 5675

Ratio: 90 : 10

Diels-Alder Reactions with Chiral Dienes

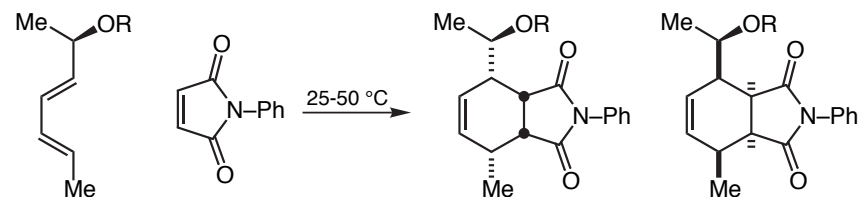
Comprehensive Organic Synthesis, Vol. 5, Trost, Ed. **1991**

4.1 Intermolecular Diels-Alder Reactions, W. Oppolzer, See page 347



Overman, *JACS* **1988**, 110, 4625

X =	Ratio
-OH	36 : 64
-Me	83 : 17
-OMe	>97 : 3



Franck, *Tet. Lett.* **1985**, 26, 3187

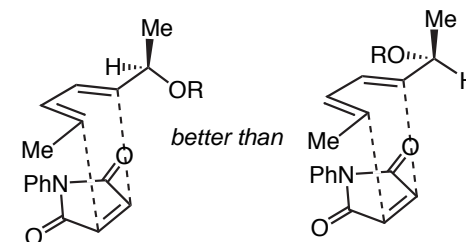
Franck, *JACS* **1988**, 110, 3257

R = Me: Ratio; 83 : 17

R = 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 17

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

D. A. Evans

Friday,
October 24, 2003

The Diels-Alder Cycloaddition Reactions

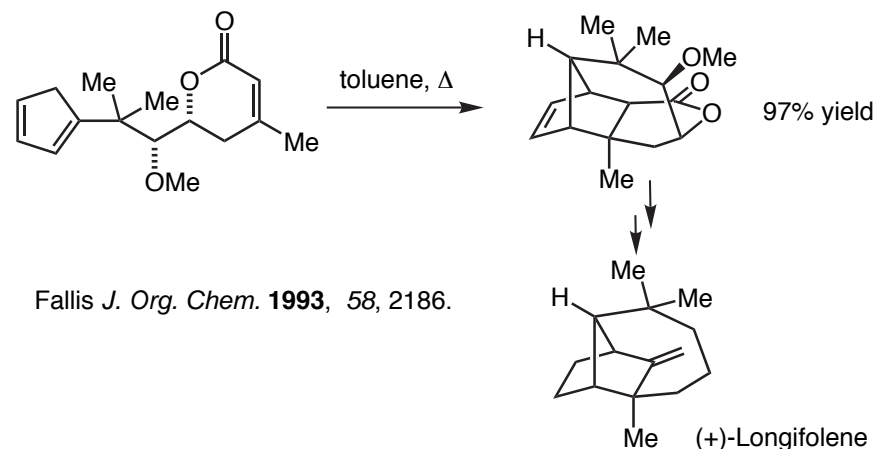
"Diels-Alder Reactions". Evans, D. A.; Johnson J. S. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 1178-1235 ([pdf](#))

"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](#))

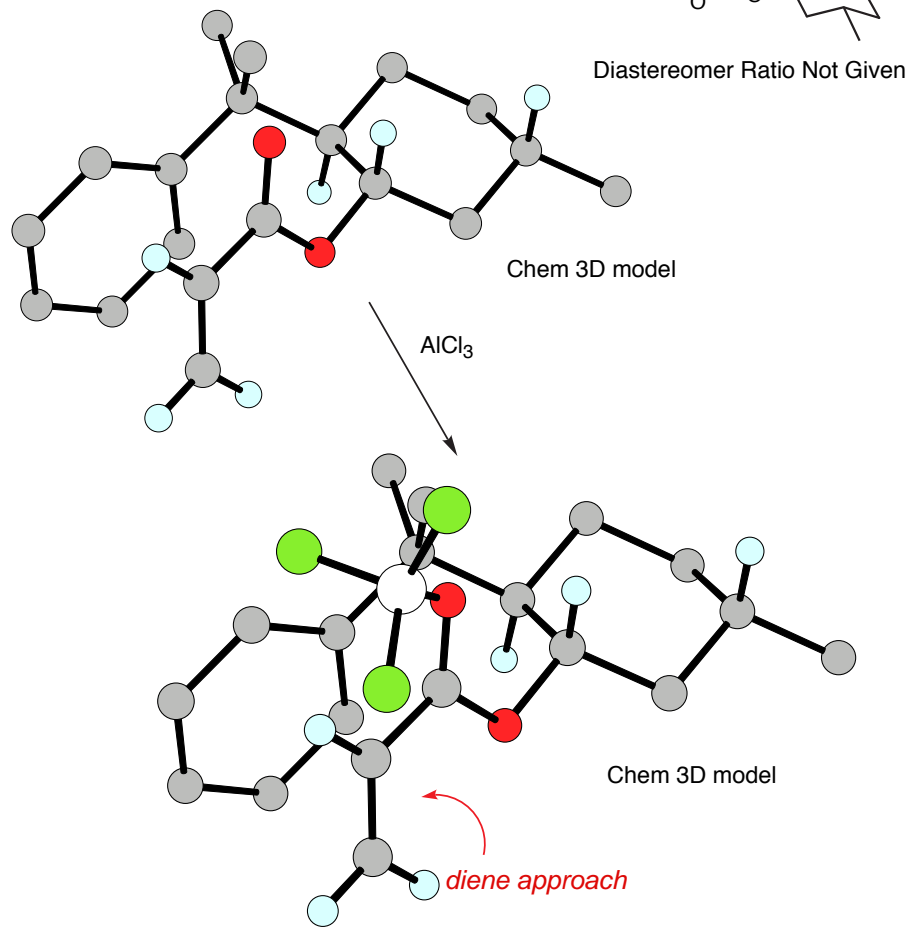
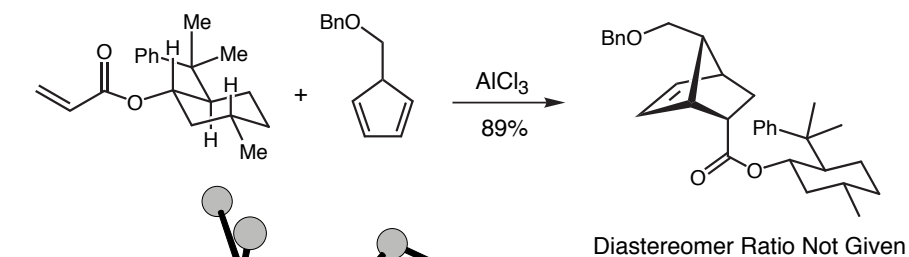
"New Strategies for Organic Catalysis: The first Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition", MacMillan, *JACS*, **2000**, 122, 9874. ([pdf](#))

■ Problem of the Day:

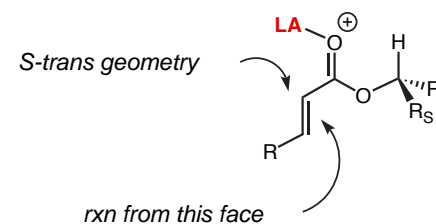


Review: Oppolzer in *Comprehensive Organic Synthesis* 1992, Vol. 4, 315-399.

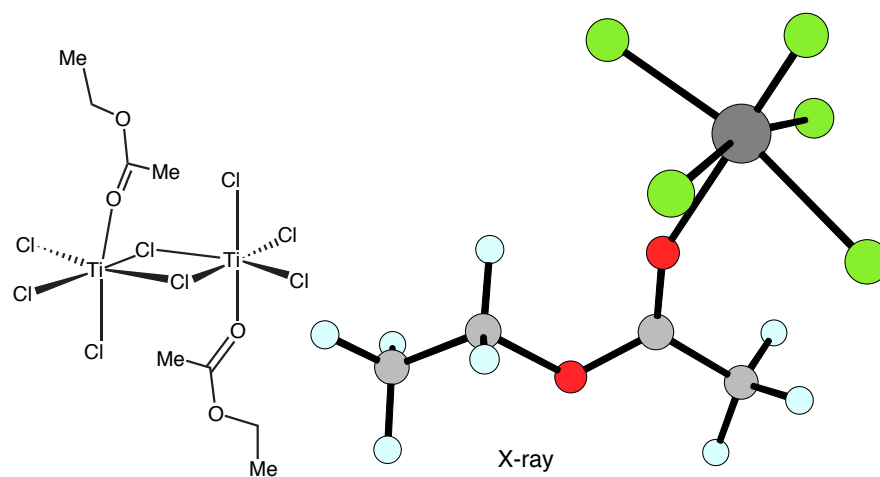
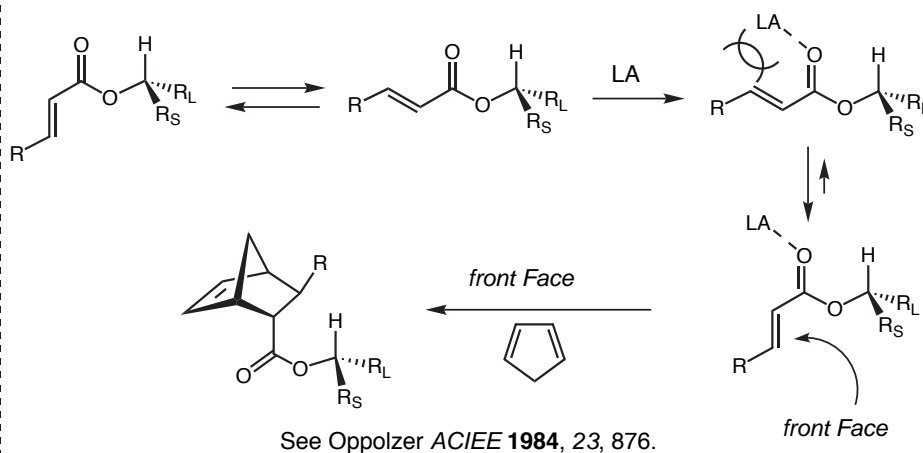
■ Ester-Type Chiral Auxiliaries Corey *JACS* 1975, 97, 6908.

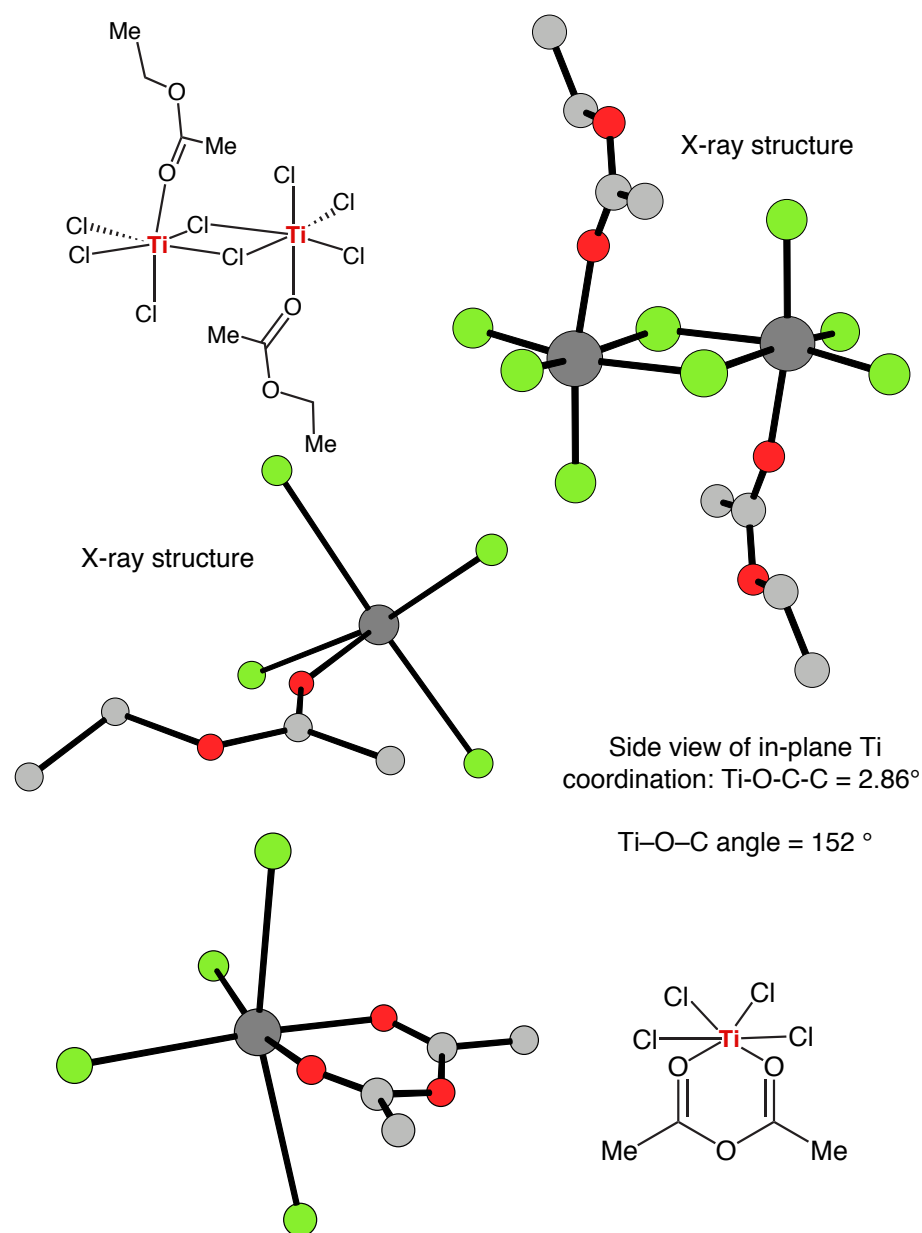
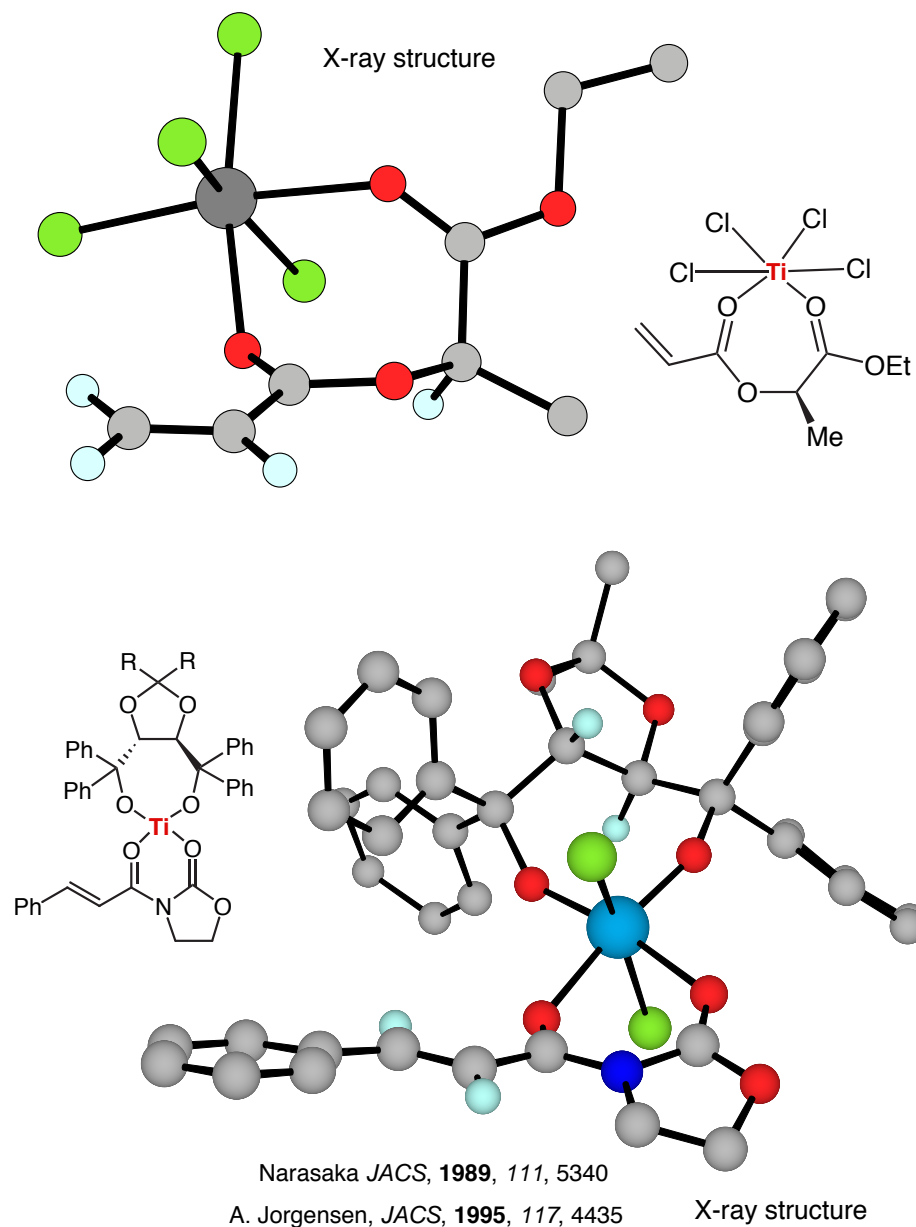


■ Non-Chelate Ester-Type Chiral Auxiliaries

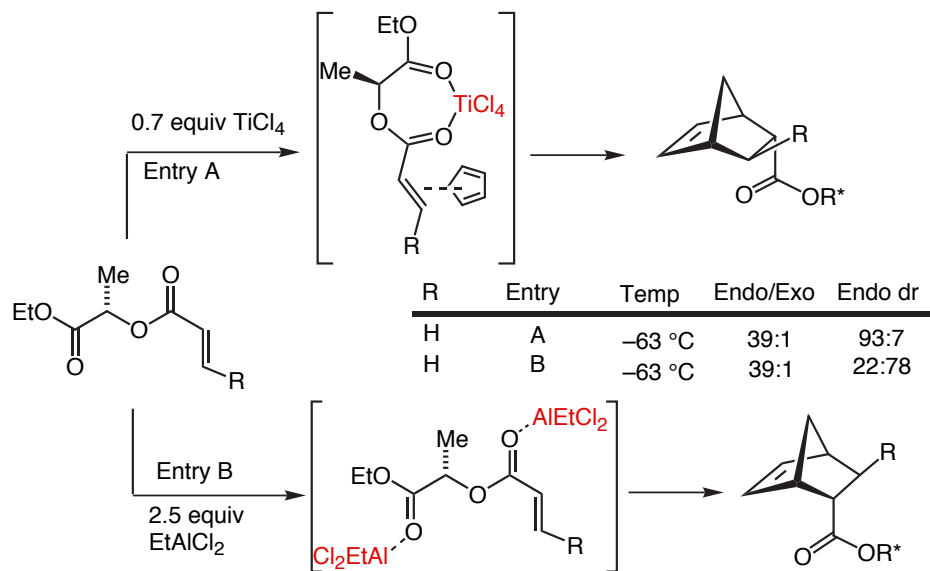


Lewis Acid-Ester Complex Conformation Dictates Diastereoselection

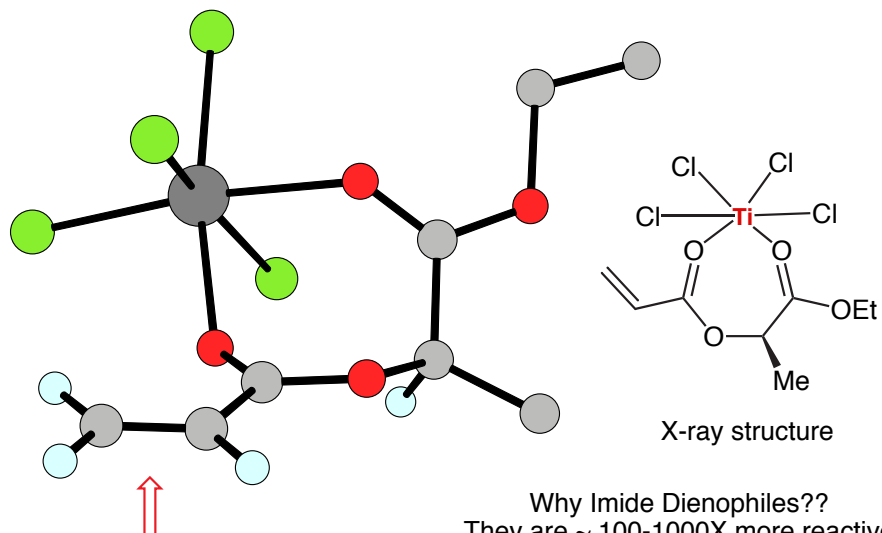


Representative η_1 -titanium complexes with organic compoundsRepresentative η_1 -titanium complexes with organic compounds

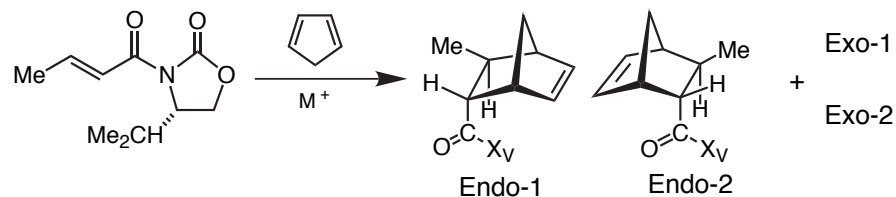
Ester-Type Chiral Auxiliaries: Chelating Dienophiles



Helmchen *Tetrahedron Lett.* **1984**, 25, 2191.
ACIEE **1985**, 24, 112.
Tetrahedron Lett. **1985**, 26, 3095.

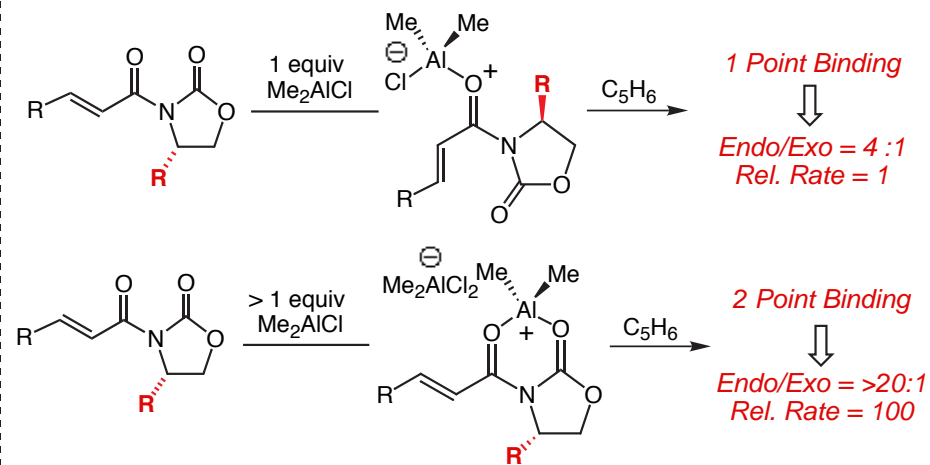


Why Imide Dienophiles??
 They are ~ 100-1000X more reactive

Chelating Imide-type Chiral Auxiliaries
Metal ion Dependent DiastereoselectionEvans *JACS*, **1984**, 106, 4261.Evans *JACS*, **1988**, 110, 1238.

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
(2.0 equiv) Et₂AlCl	-78	15.7	>99 : 1
(0.7 equiv) Et₂AlCl	-78	4.4	92 : 8

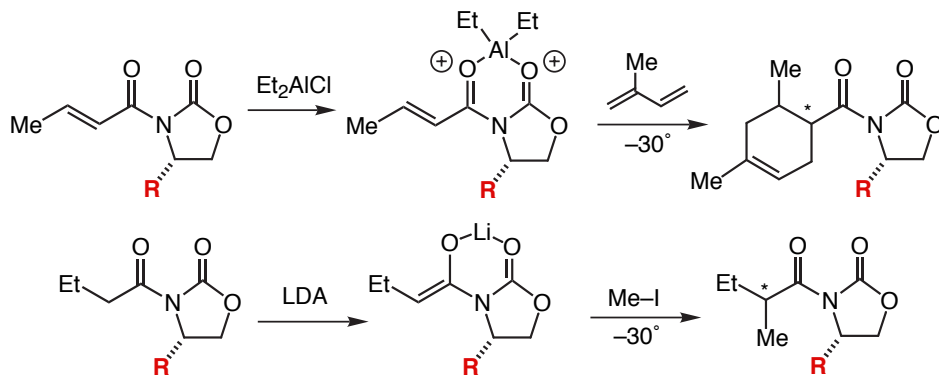
Binding Mode Dictates Diastereoselectivity



R = CH₂Ph much more stereoselective than R = CHMe₂

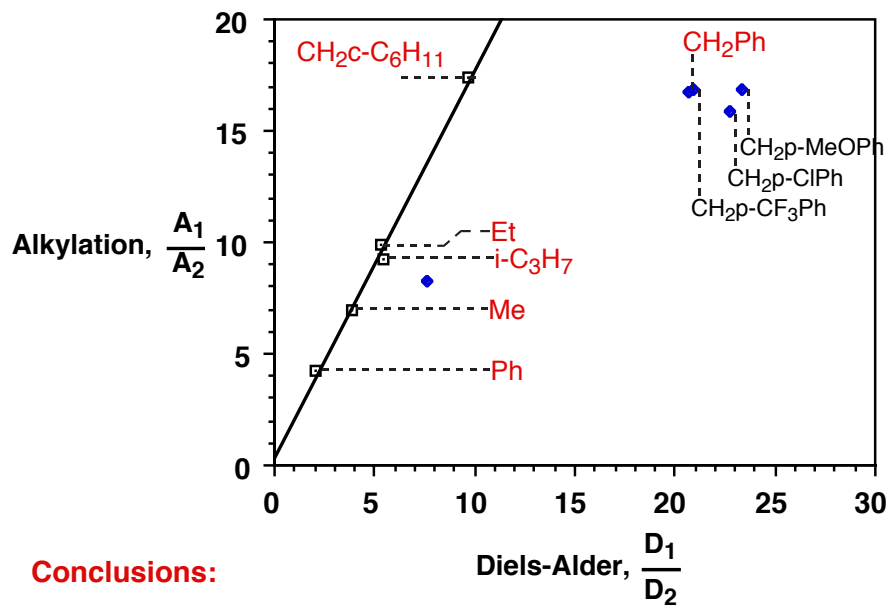
A Case for π -Stacking: *Angew Chem, Int Ed.* 1987, 26, 1184

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.

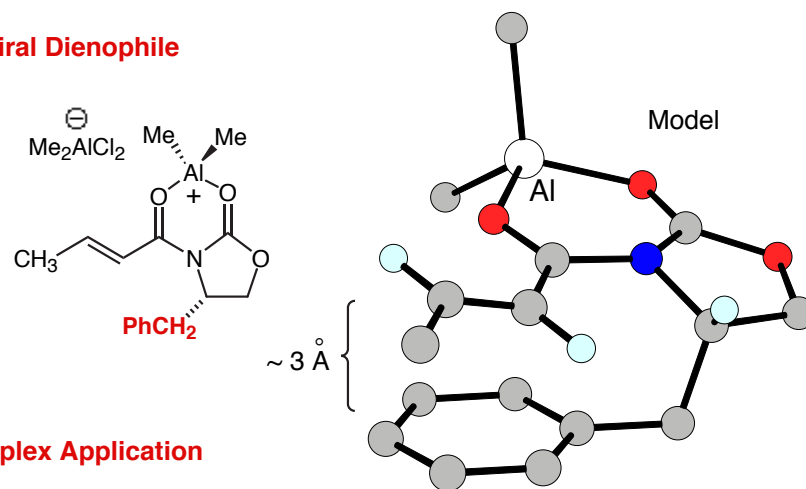


Conclusions:

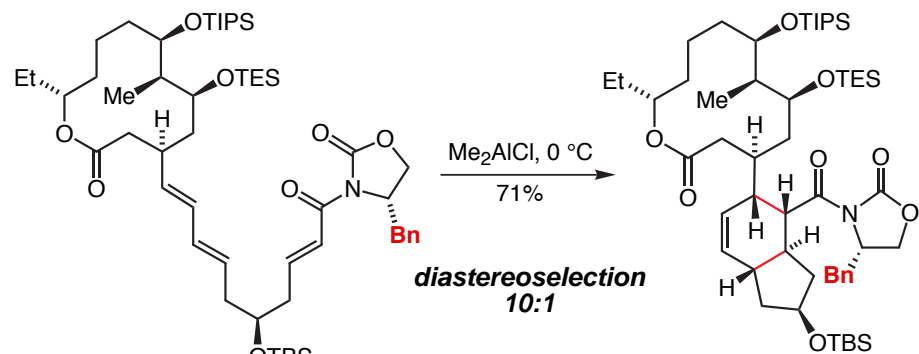
Steric effects correlate well for the two reactions

Added electronic effects from Bn group enhance facial bias

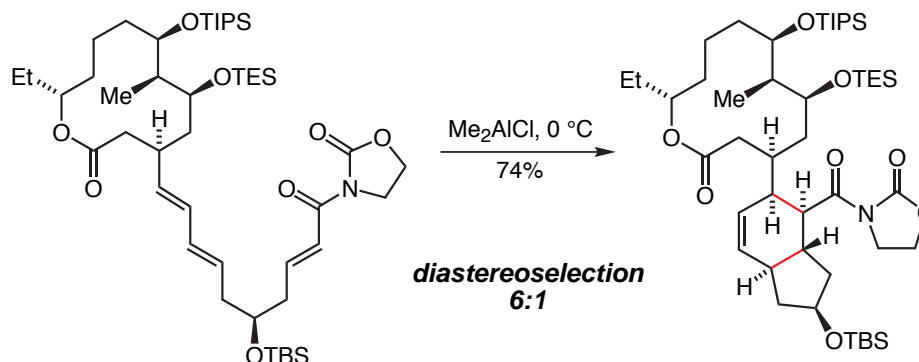
The Chiral Dienophile



A Complex Application

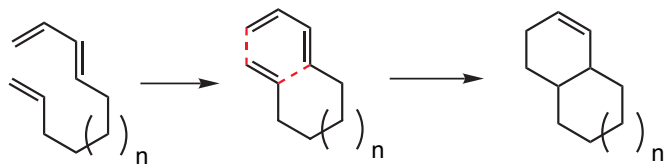


The control experiment with no chiral auxiliary:

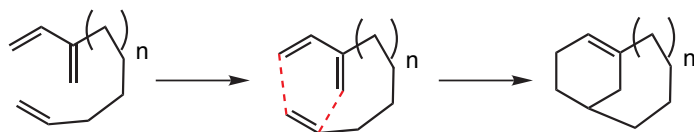


Evans, BlackLepicidin Synthesis, *JACS*, 1993, 115, 4497

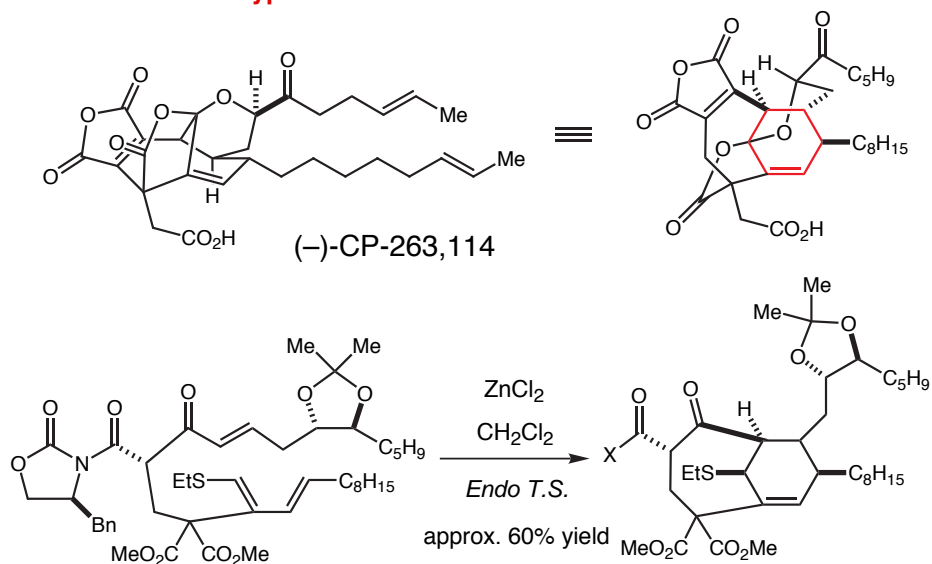
Type I intramolecular Diels-Alder Reaction:



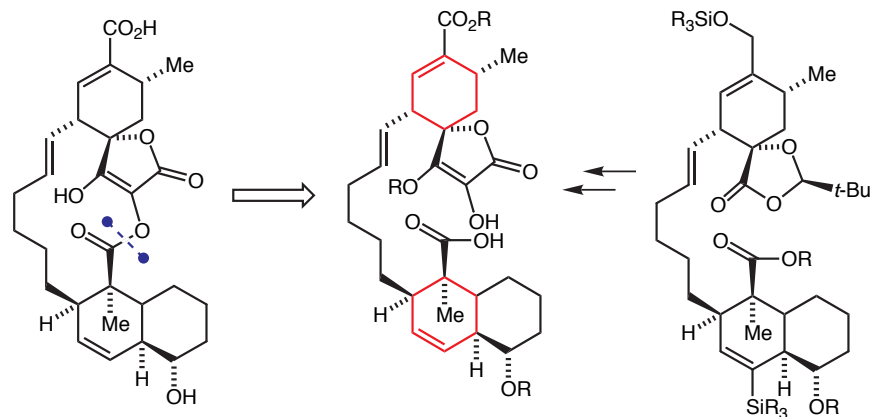
Type II intramolecular Diels-Alder Reaction:



A Type II Intramolecular Diels-Alder:

Fukuyama et al *JACS* **2000**, 122, 7825-7826.The concept: Evans, et al *Angew. Chem. Int. Engl.* **1997**, 36, 2119-2121.

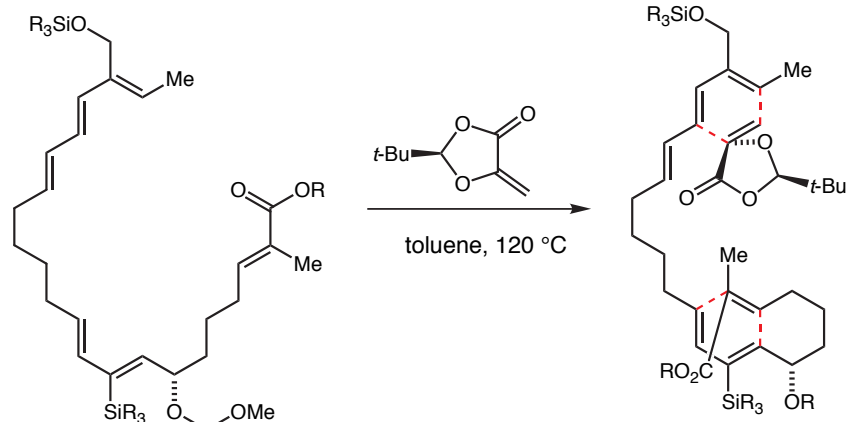
A Type I Intramolecular Diels-Alder:



(-)- Chlorothricolide

2 Diels-Alder Retrons

45% yield

Roush, Sciotti *J. Am. Chem. Soc.* **1998**, 120, 7411-7419.

Some Intramolecular Diels-Alder Reviews:

Shea *Angew. Chem. Int. Ed.* **2001**, 40, 820.Fallis *Acc. Chem. Res.* **1999**, 32, 464-474.

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

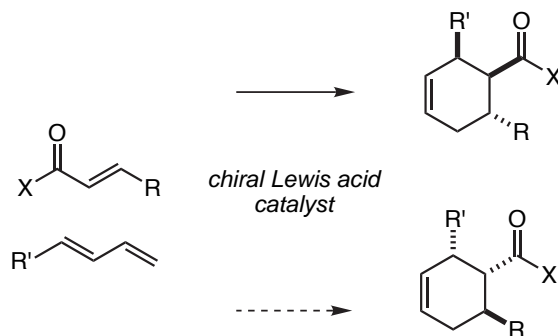
(Carbonyl-Lewis Acid Complexes)
Schreiber, *Angew. Chem. Int. Ed.*, **1990**, 29, 256-272

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

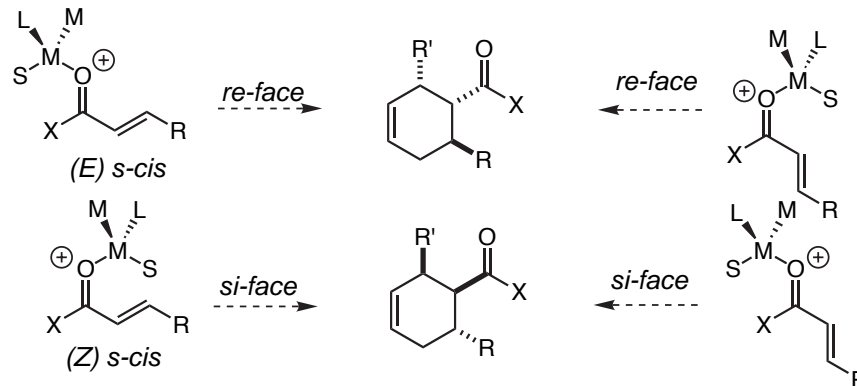
C₂ Symmetry and Asymmetric Induction, Whitesell, *Chem. Rev.*, **1989**, 89, 1581-1590

The Design of Enantioselective Diels-Alder Catalysts



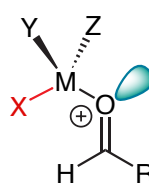
The conformation of the dienophile is also an issue

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

Stereoelectronic Effects (?) in Lewis acid-C=O Complexes

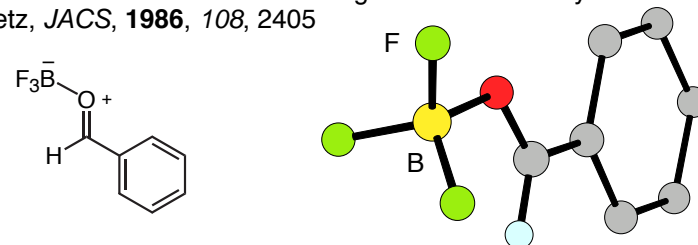


Let X be the most electronegative ligand in the Lewis acid

The stabilizing hyperconjugative interaction between the O-lone pair and σ^* M-X will provide a stabilizing interaction for the illustrated conformation.

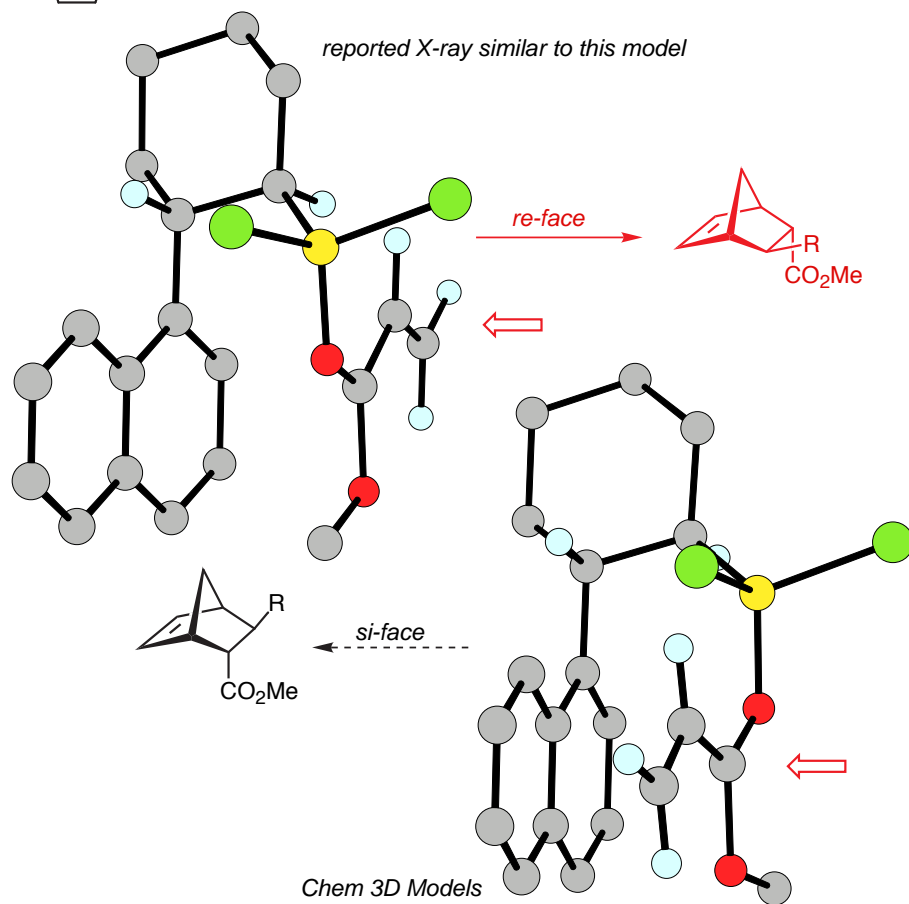
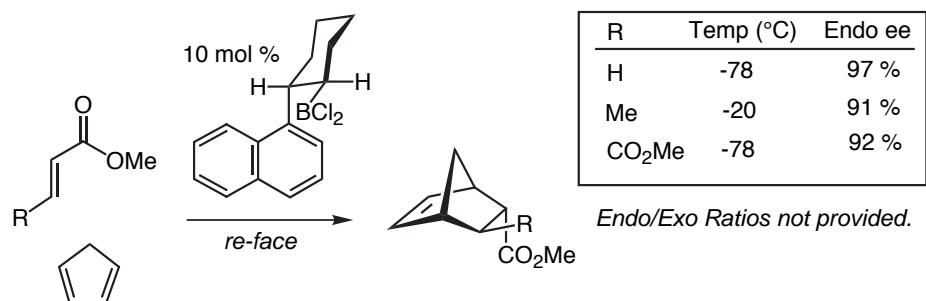
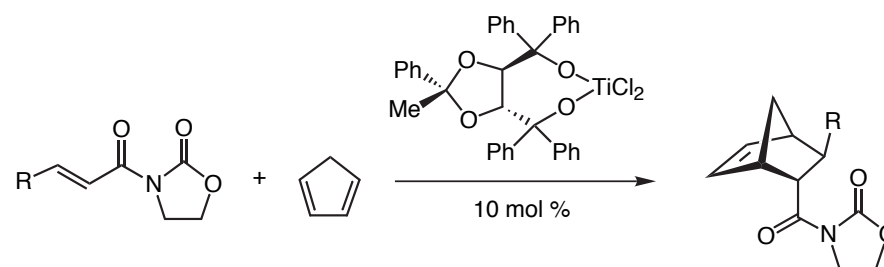
J. M. Goodman, *Tet. Lett.* **1992**, 33, 7219

However, there is no evidence for this orienting effect in this X-ray structure reported by Rietz, *JACS*, **1986**, 108, 2405

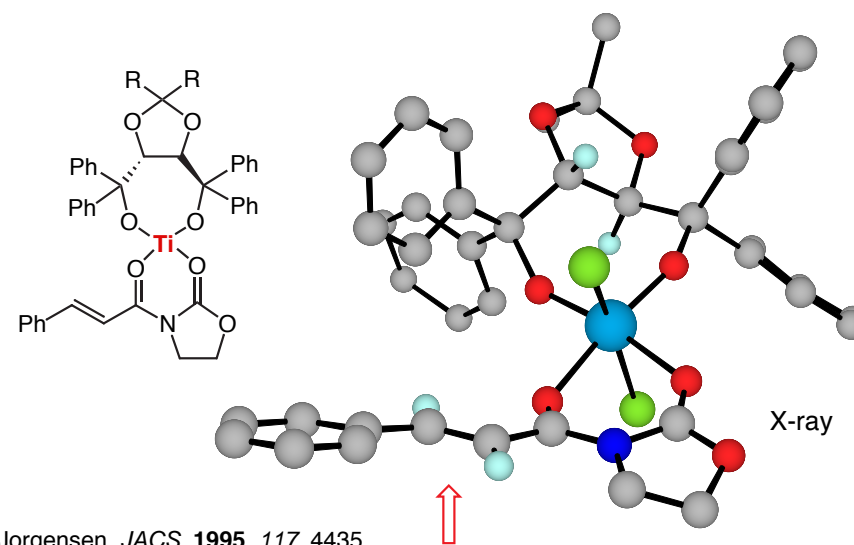
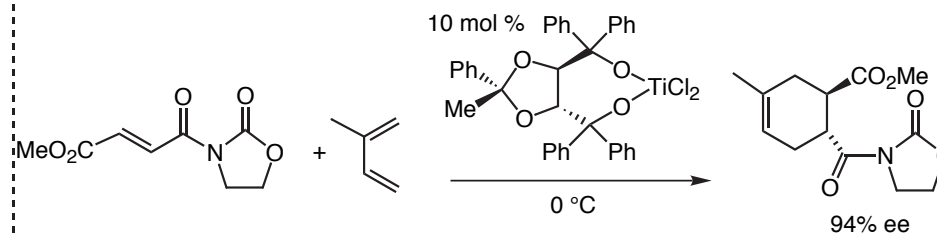


However pi-bonding to coordinated C=O-Al complexes has been reported Barron, *JACS*, **1990**, 112, 3446, *JACS*, **1990**, 112, 2950

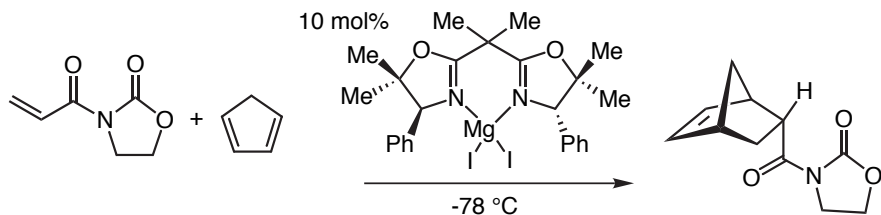
Theory predicts a small rotational barrier about B-O bond: Wiberg *JACS*, **1988**, 110, 6642

Boron-Based Catalysts: Hawkins JACS 1991, 113, 7794**Titanium-Based Catalysts: Narasaka JACS 1989, 111, 5340.**

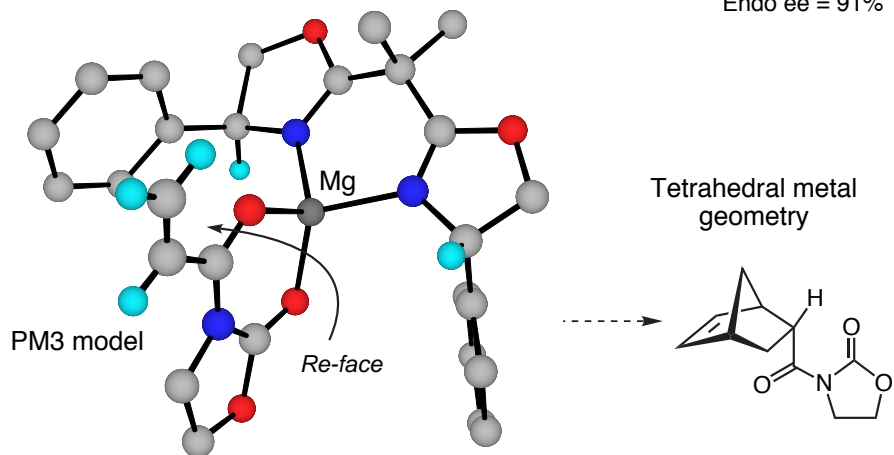
R	Temp (°C)	Endo/Exo	Endo ee
H	-40	96:4	64 %
Me	0	92:8	91 %
Ph	25	88:12	64 %



A. Jorgensen, JACS, 1995, 117, 4435

Mg(2+)-Based Catalysts: Corey *Tetrahedron Lett.* 1992, 33, 6807.

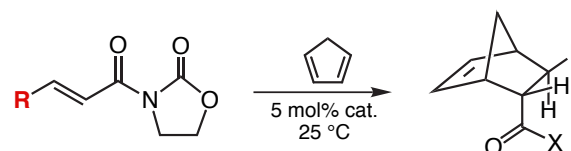
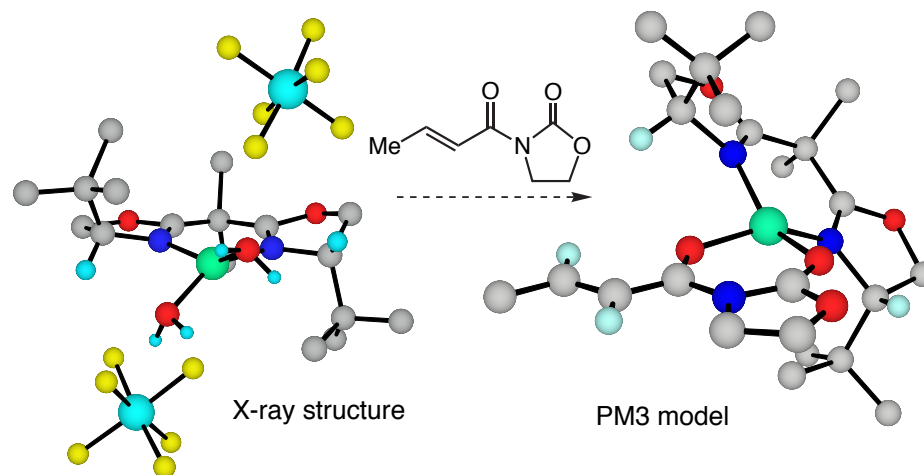
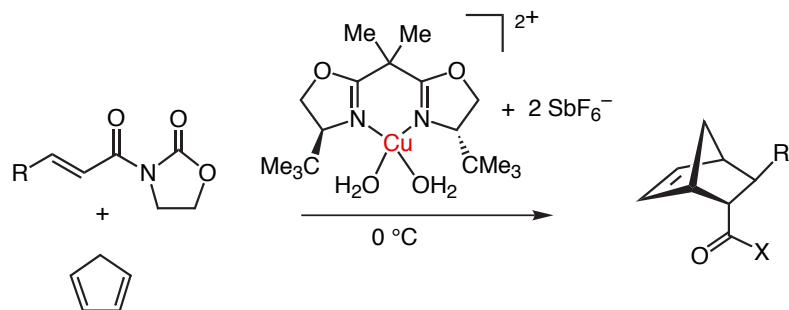
Stereochemical Model:



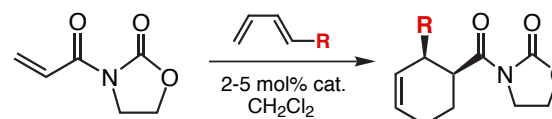
Limitations: Scope limited to illustrated reaction

Cu(2+)-Based Catalysts:

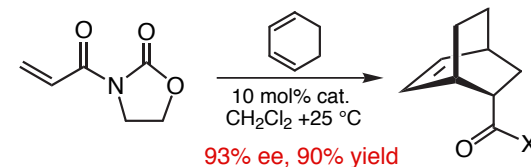
Evans, Miller, Lectka *JACS* 1993, 115, 6460.
Angew. Chem. Int. Engl. 1995, 34, 798-800.
JACS 1999, 121, 7559-7573.
JACS 1999, 121, 7582-7594



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%

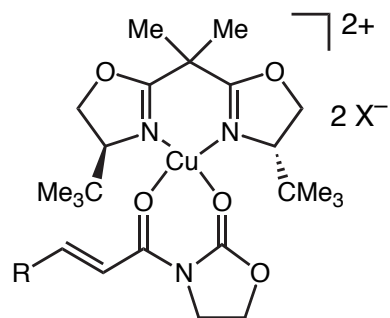


R	temp	endo ee	yield
R = Me	25 °C	94% ee	89%
R = Ph	-20 °C	97% ee	95%
R = OAc	0 °C	97% ee	100%

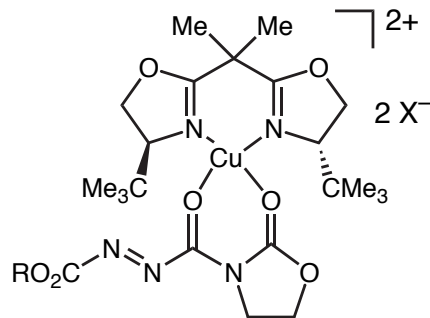


Cu(box) and Cu(pybox) catalyst-substrate complexes implicated in enantioselective reactions.

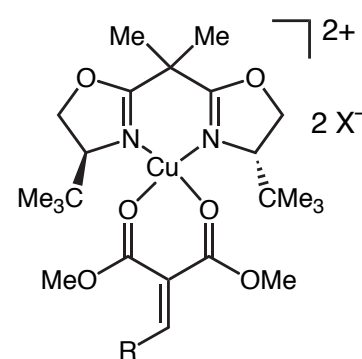
"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Aldol, Michael and Carbonyl Ene Reactions". Johnson, Evans, *Acc. Chem. Res.* **2000**, 33, 325-335. (pdf)



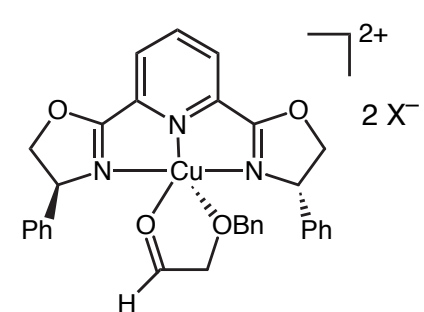
Cycloaddition Reactions
Michael Reactions



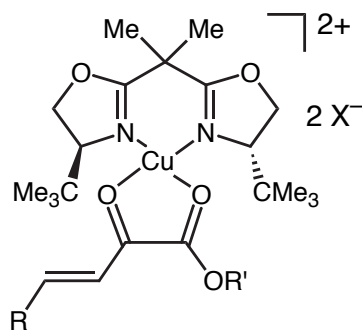
Enol Amination Reactions



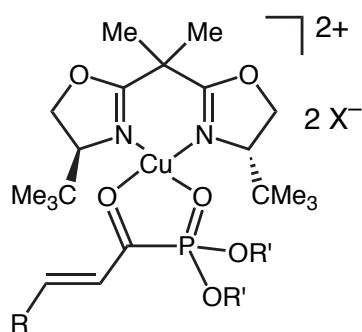
Michael Reactions



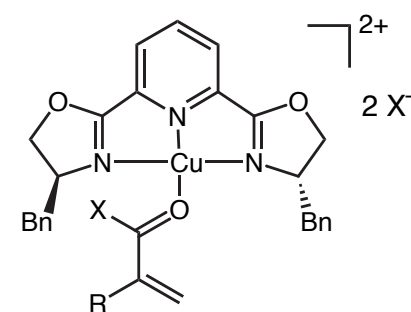
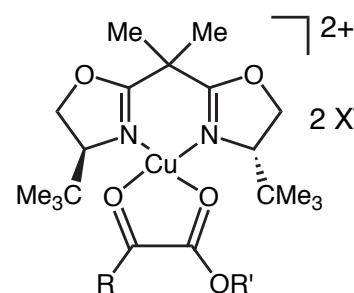
Aldol Reactions



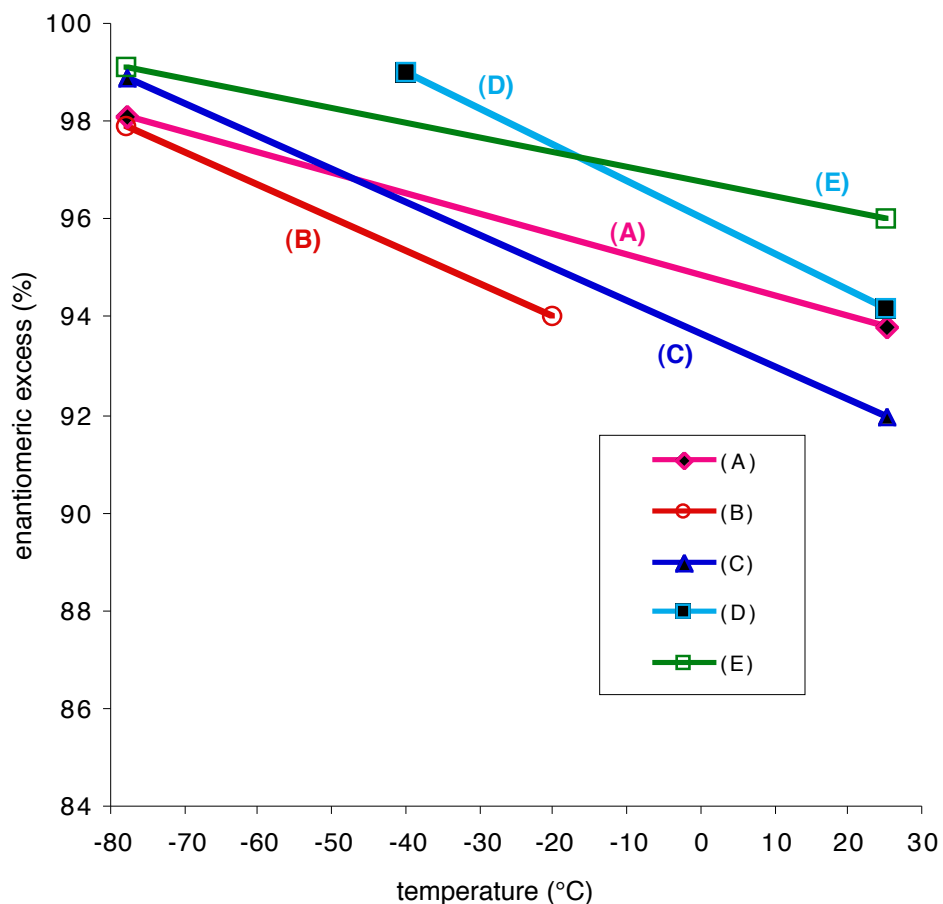
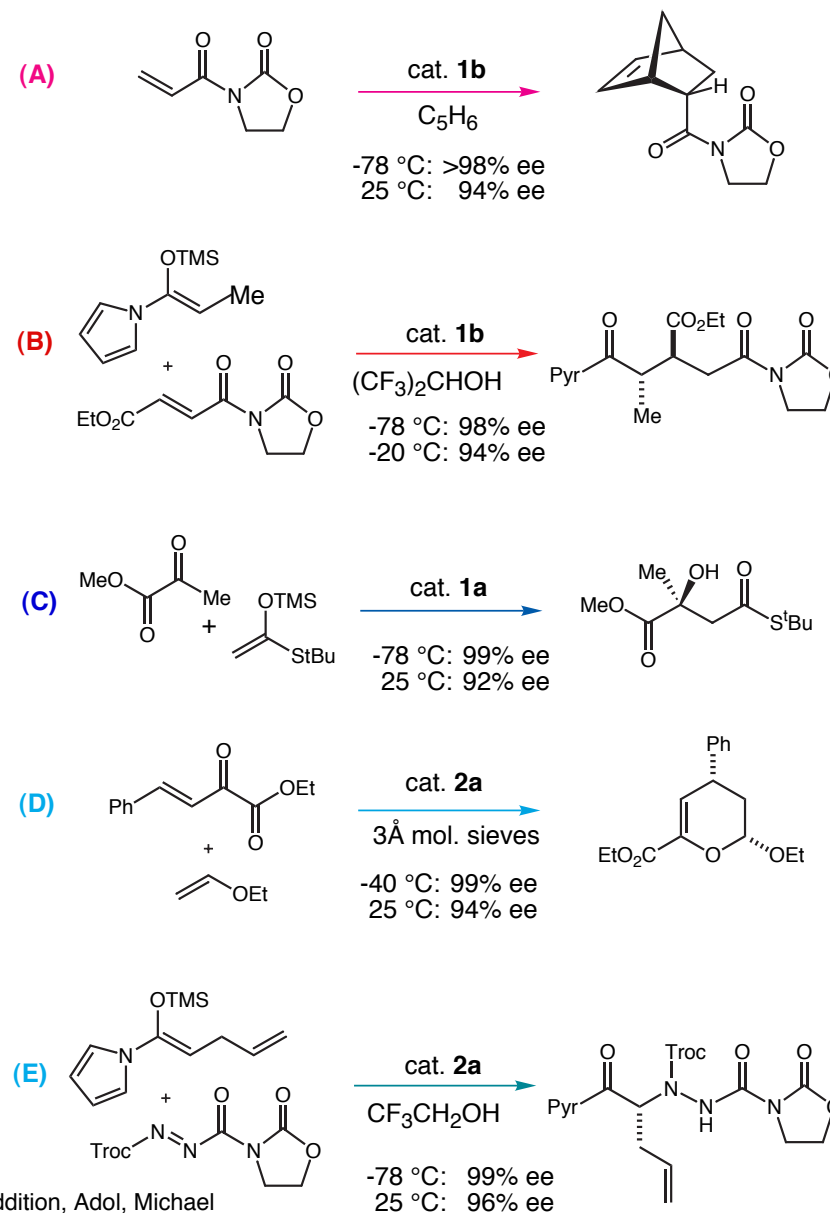
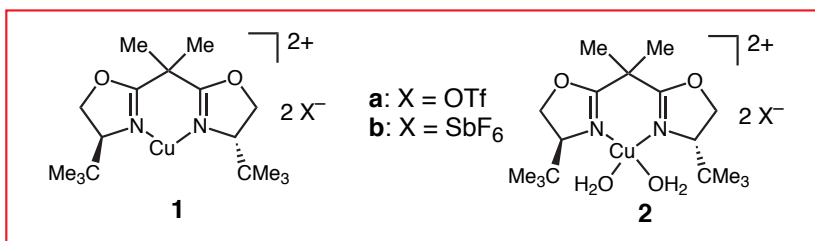
Hetero Diels-Alder Reactions



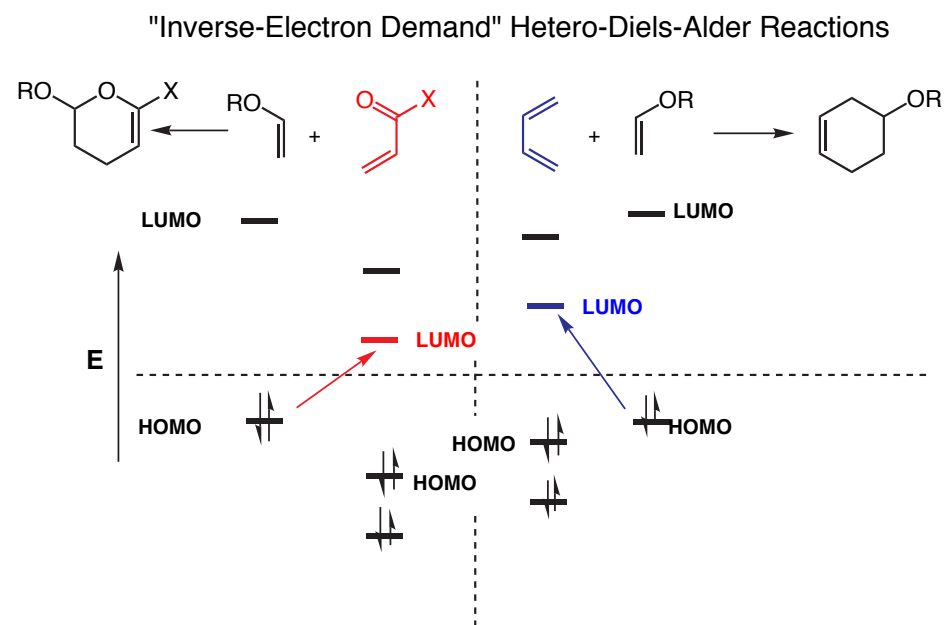
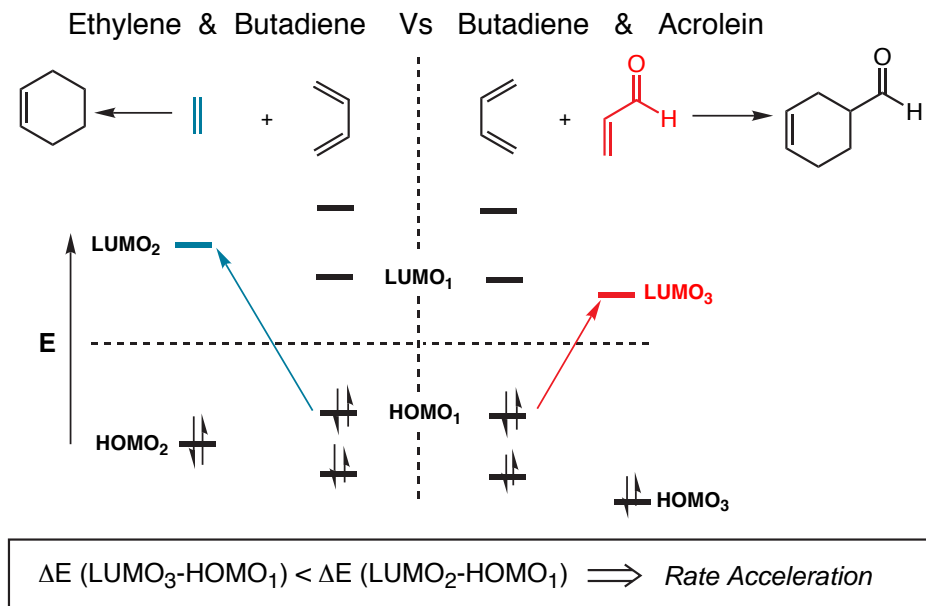
$R = H$, Cycloaddition Reactions
Ene Reactions
 $R = Alkyl$, Cycloaddition Reactions
Aldol Reactions



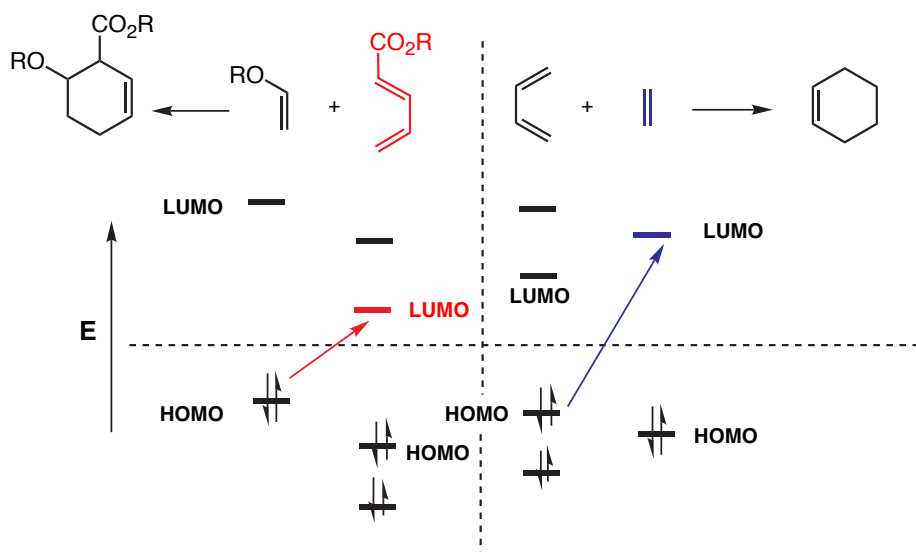
Diels-Alder Reactions



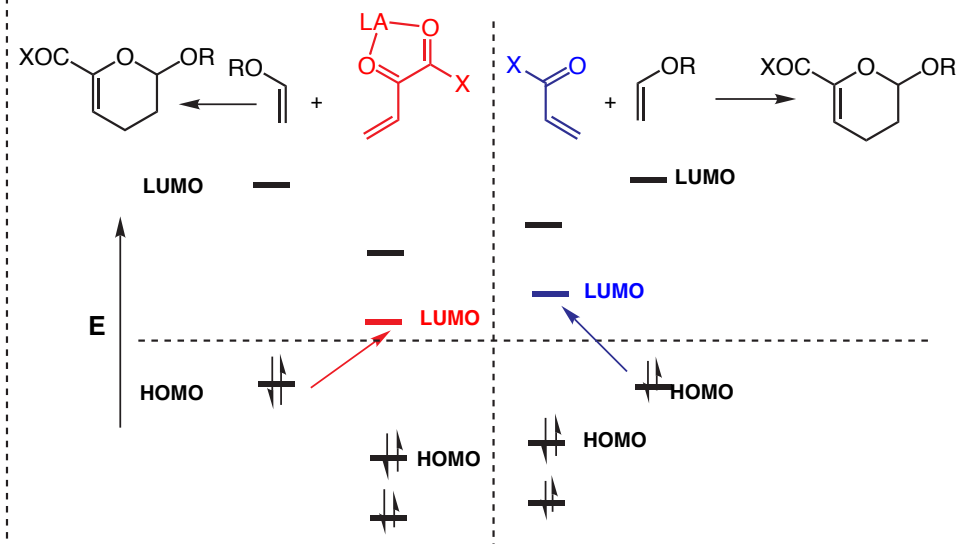
"Chiral Bis(oxazoline) Copper (II) Complexes: Versatile Catalysts for Enantioselective Cycloaddition, Adol, Michael and Carbonyl Ene Reactions". Johnson, Evans, *Acc. Chem. Res.* **2000**, 33, 325-335. ([electronic pdf](#))



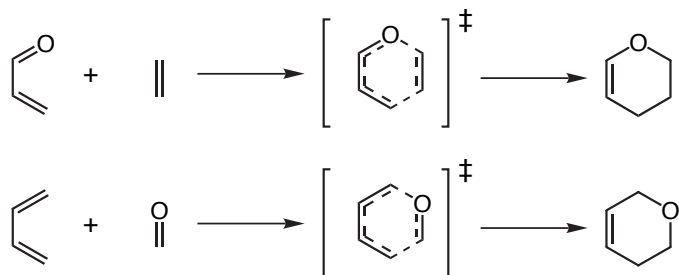
"Inverse-Electron Demand" Diels-Alder Reactions



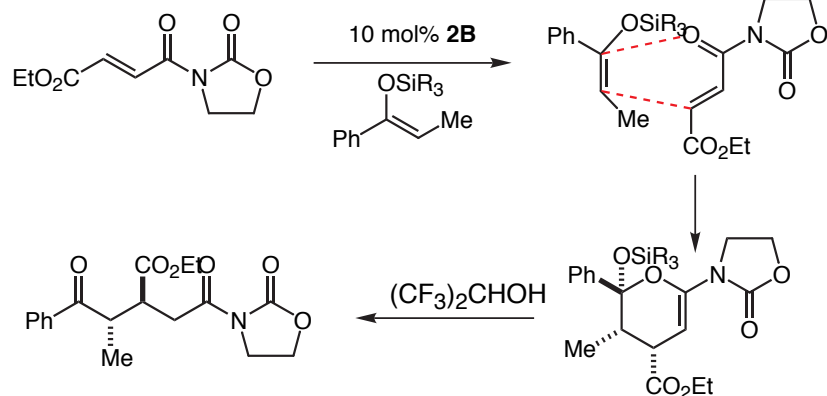
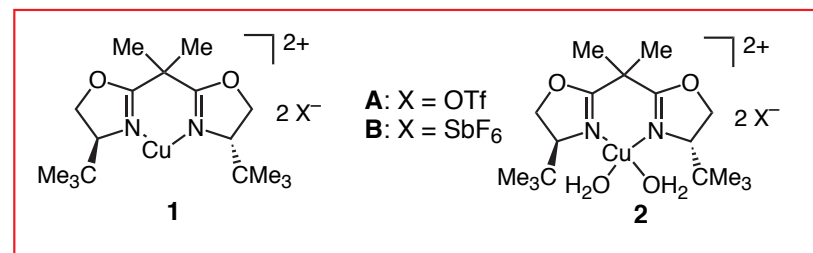
■ Lewis Acid Catalysis of the reaction is possible:



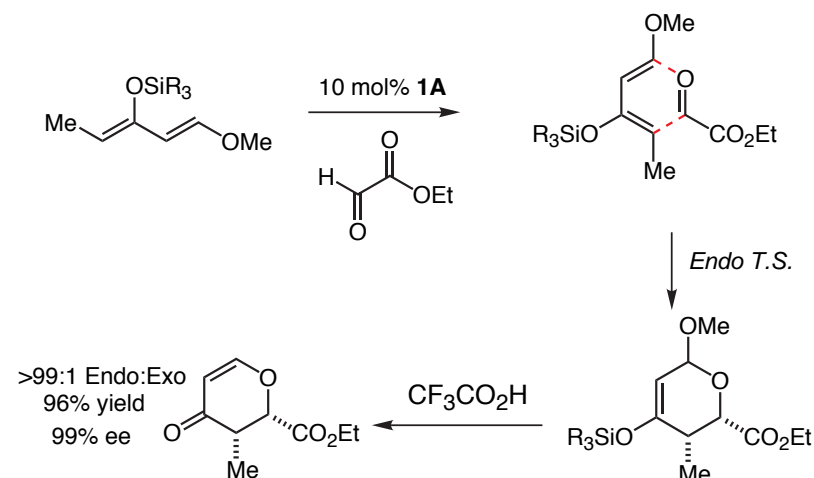
•Heteroatom-substituted reactions are also possible:



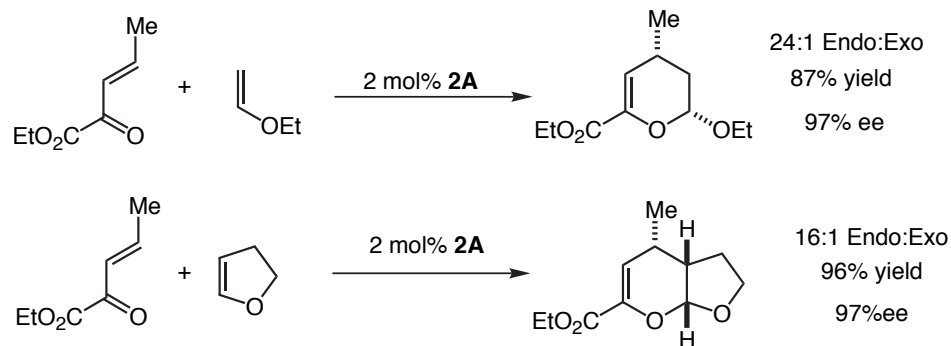
Chiral Copper Lewis Acids:



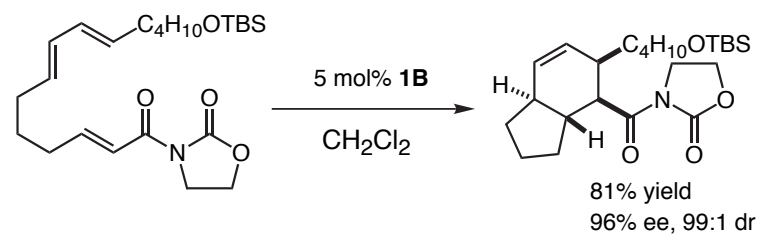
Evans, Scheidt, Johnston, Willis *J. Am. Chem. Soc.* **2001**, 123, 4480.



Jorgensen *J. Am. Chem. Soc.* **1998**, 120, 8599.

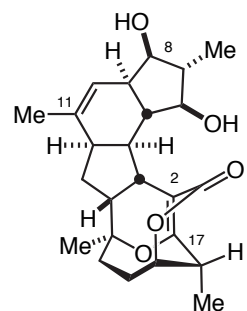


Evans, Johnson, Olhava *J. Am. Chem. Soc.* **2000**, 122, 1635.



Evans, Johnson *J. Org. Chem.* **1997**, 62, 786-787.

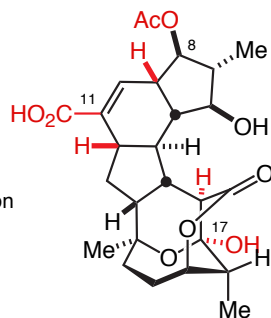
Structures of FR182877 & Hexacyclinic acid



(-)-FR182877

Sato, B. *J. Antibiot.* **2000**, 123, 204, 615.
Corrected Structure: *J. Antibiot.* **2002**, C-1.

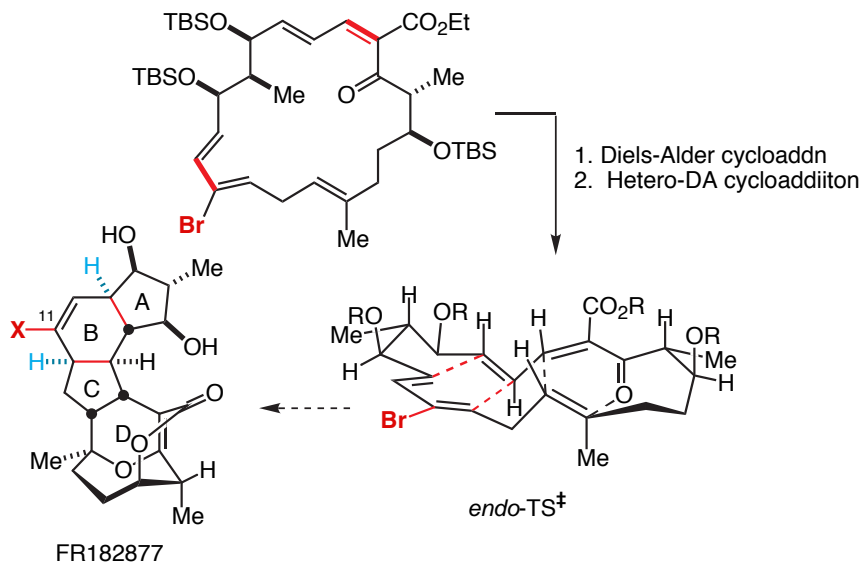
Structural Differences:

Acylation at C₈ hydroxylOxidation at C₁₁*endo* vs. *exo* Diels-Alder retronHydration across
C₂-C₁₇ double bond

Hexacyclinic Acid

Hofs, R., et al. *Angew. Chem. Int. Ed.* **2000**, 39, 3258.

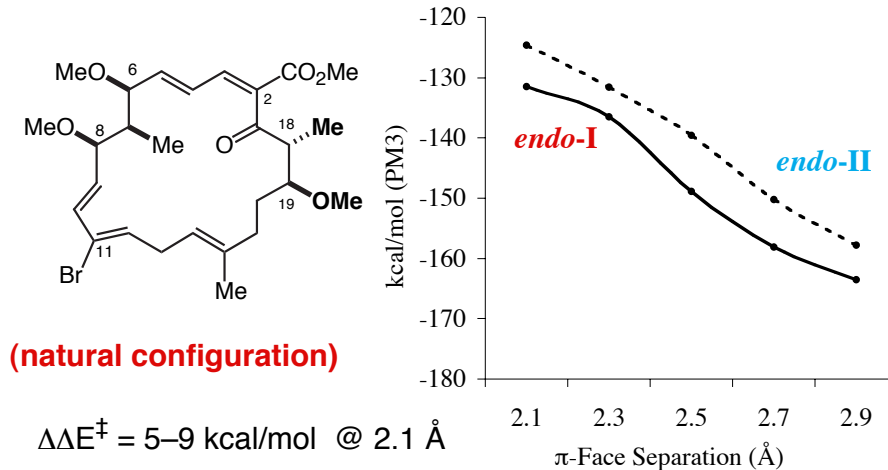
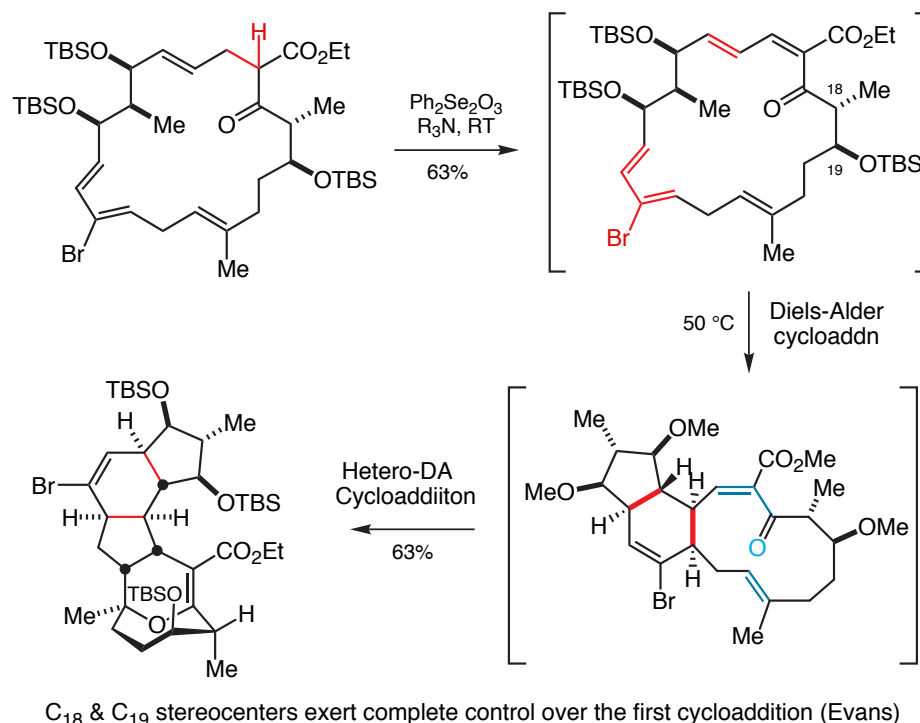
Hypothesis: A Transannular Diels-Alder Cycloaddition Cascade



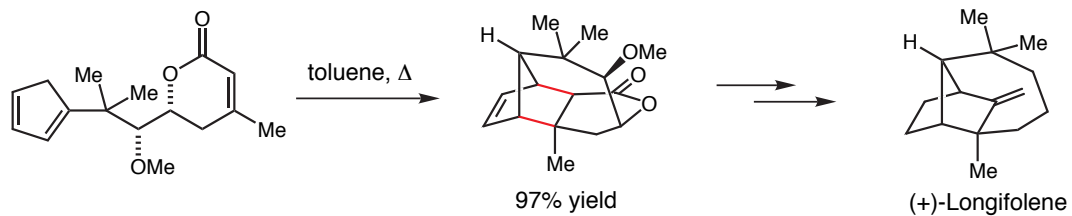
Evans & Starr, *JACS*, **2003**, 125, ASAP

Sorensen et al, *JACS*, **2003**, 125, 5393

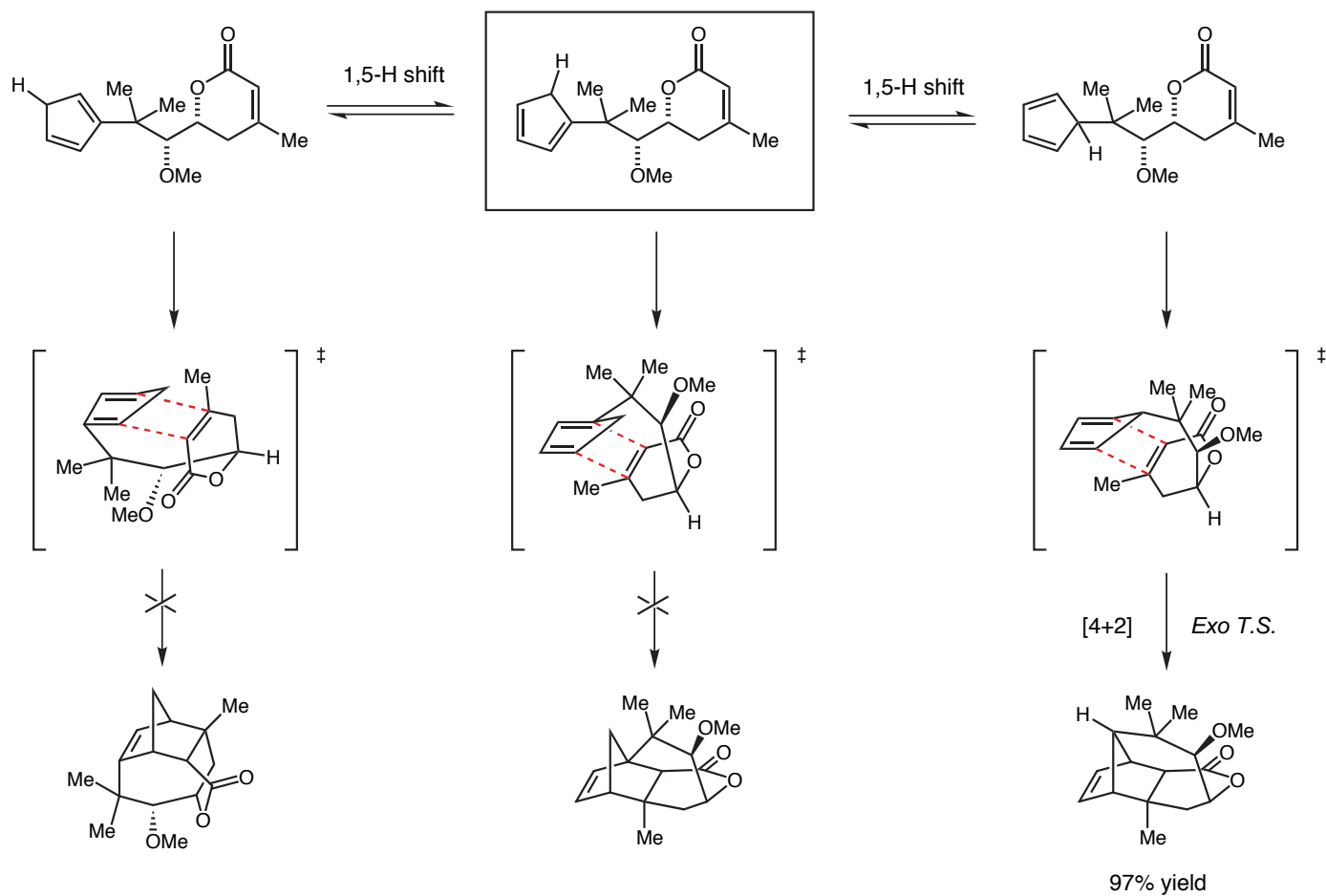
The Transannular Diels-Alder Step



■ Problem of the Day:



Fallis *J. Org. Chem.* **1993**, *58*, 2186.



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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 17

Dipolar cycloaddition Reactions

■ Reading Assignment for week:

Carey & Sundberg: **Part A**; Chapter 11, p 647-648
Concerted Pericyclic Reactions

Carruthers, W. *Cycloaddition Reactions in Organic Synthesis.*; Pergamon: Elmsford, NY, **1990**.pp 294-331 (**Handout**)

D. Ripin, W. *Use of Isoxazoles as 1,3-Dicarbonyl equivalents in Organic synthesis*; Evans Group Seminar **1997** (**ElectronicHandout**)

D. A. Evans

Monday,
October 27, 2003

Dipolar Cycloaddition Reactions

General References

Carruthers, W. *Cycloaddition Reactions in Organic Synthesis.*; Pergamon: Elmsford, NY, **1990**.

Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, John Wiley, **1984**, Volumes 1 & 2,

Jorgensen, *Asymmetric 1,3-Dipolar cycloadditions*, *Chem Rev.* **1998**, 98, 863-909

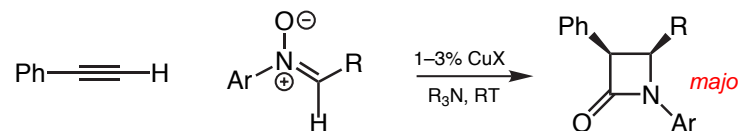
Padwa, A. Generation and utilization of carbonyl ylides via the tandem cyclization-cycloaddition method." *Acc. Chem. Res.* **1991**, 24, 22. (**handout**)

Confalone, P. N.; Huie, E. M. *The [3+2] Nitron-Olefin Cycloaddition Reaction Org. React. (N.Y.)* **1988**, 36, 1.

S. Kanemasa, *Metal Assisted 1,3-Dipolar Cycloaddition Reactions*, *SynLett* **2002**, 1371-1387 (**handout**)

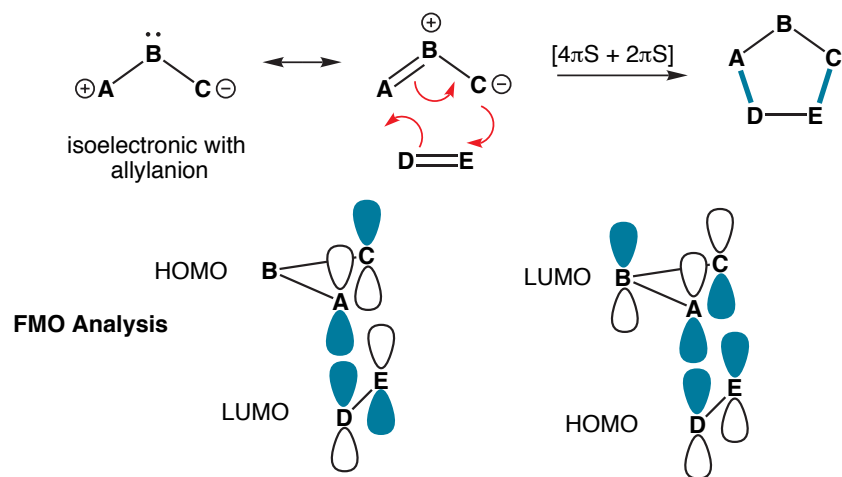
Problem of the Day

Provide a plausible mechanism for this transformation in the space below. *In attacking this question, it is important that you are aware of the transformation that transpires when terminal acetylenes are treated with Cu(I) or Ag(I) in the presence of an amine base.*



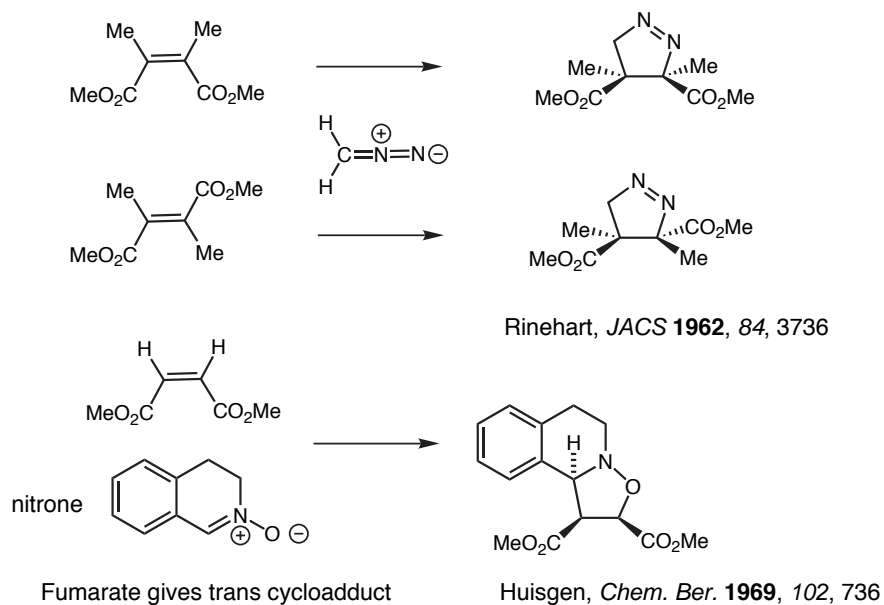
In 1995 Miura and co-workers reported the remarkable reaction illustrated below (*J. Org. Chem.* **1995**, 60, 4999). Recently, Fu has reported an enantioselective variant of this transformation (*J. Am. Chem. Soc.* **2002**, 124, 4572). In most instances, the cis adduct is formed in large excess (>90%). There is really no thoughtful mechanism in the literature for this transformation. You will be graded on "reasonability"

The General Reaction Family

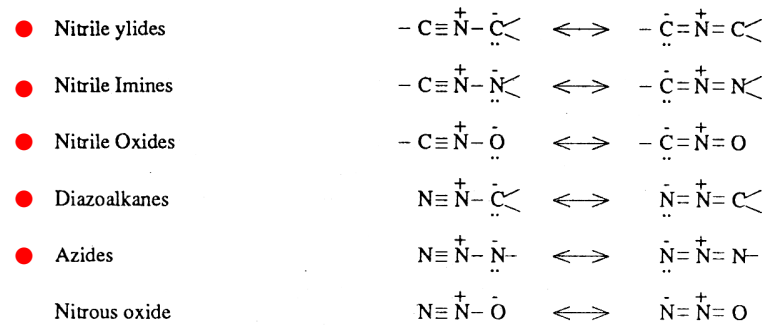


The specific set of reaction partners, will define the dominant frontier orbitals

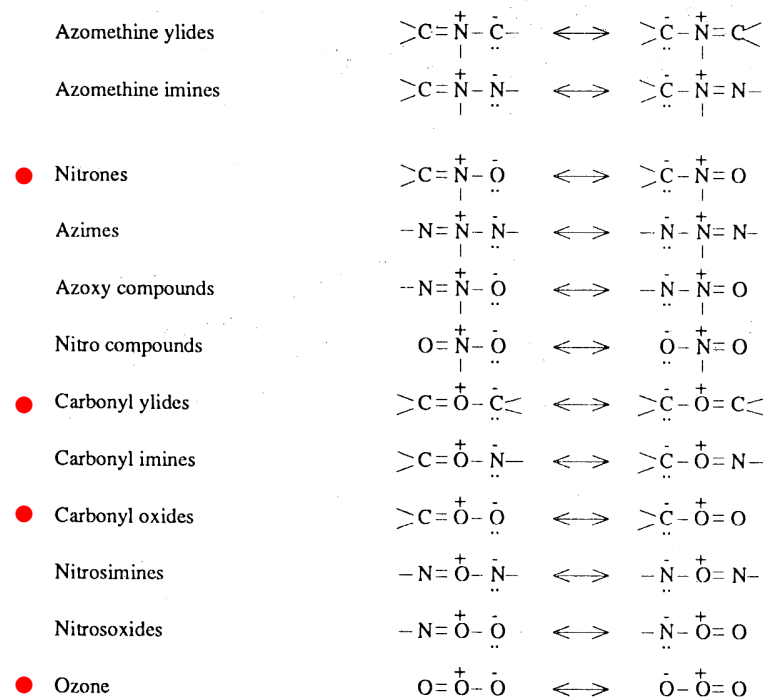
Reaction Stereospecificity: The Dipolarophile (Padwa, Vol 1, pp 61-90)



Classification of 1,3-Dipoles Containing C, N, & O Atoms

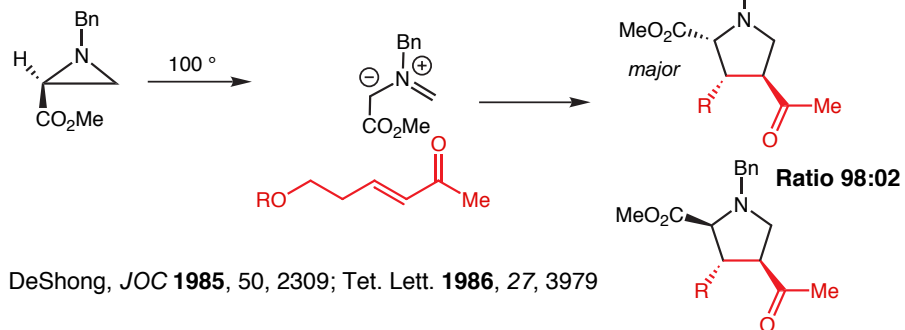


Allyl Type



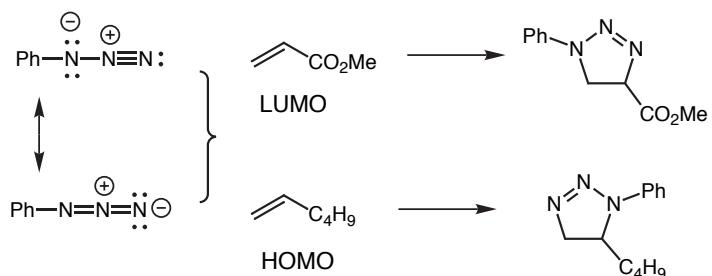
(After R.Huisgen, *J.Org.Chem.*, 1976, *41*, 403.)

Reaction Stereospecificity: Dipolarophile continued



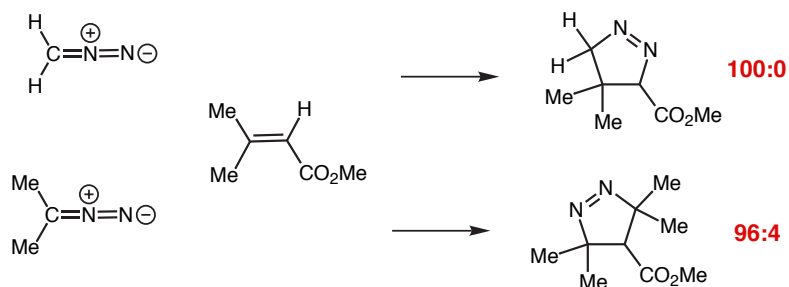
We will return to the other stereochemical element of this reaction shortly

Reaction Regiochemistry (Padwa, Vol 1, pp 135)



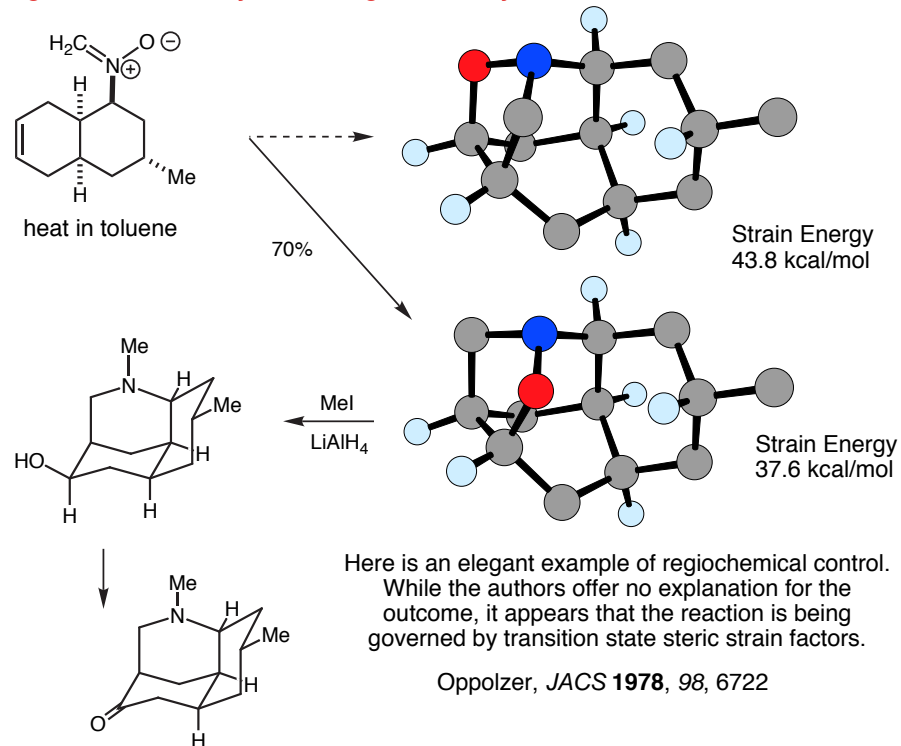
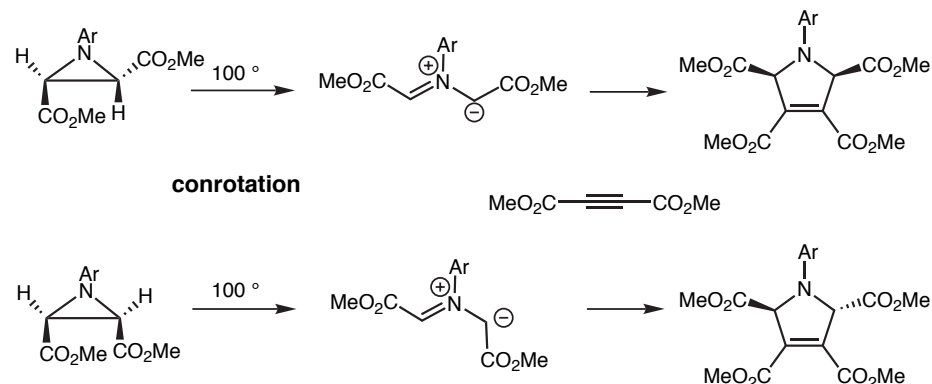
The specific set of reaction partners, will define the dominant frontier orbitals

Steric Effects will frequently alter regioselectivity (Padwa, Vol 1, pp 144)

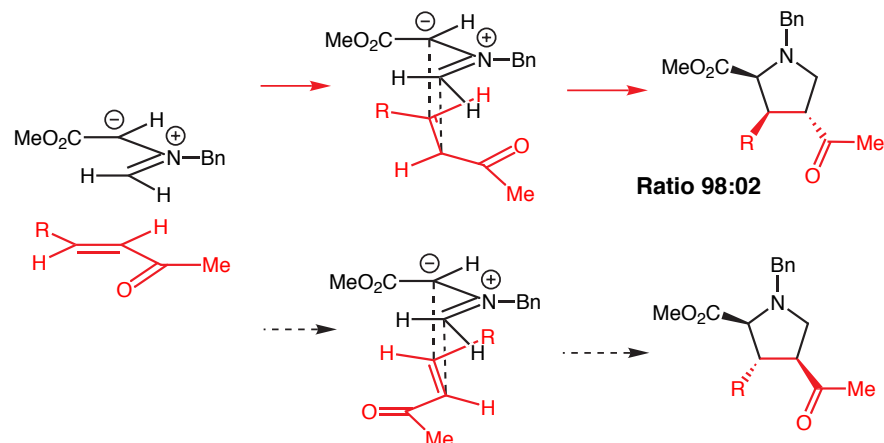


Steric effects are also important considerations in reaction regiochemistry

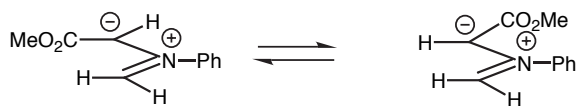
Ring strain factors may control regioselectivity

Reaction Diastereoselectivity Huisgen et al, *Angew.Chem. Int. Ed.* **1969**, 8, 604

Relative Orientation of Reaction Partners

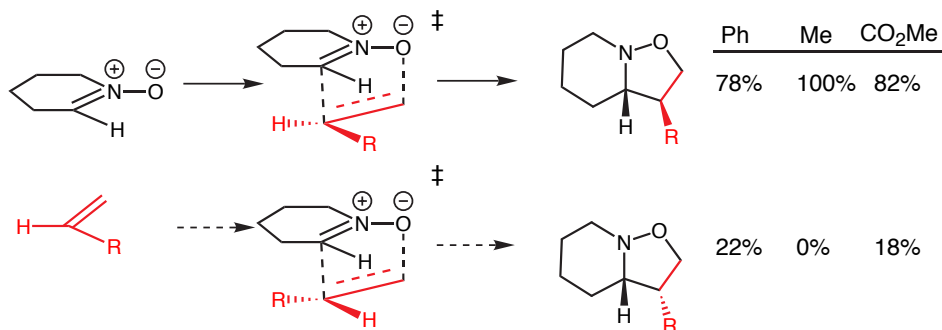
DeShong, *JOC* **1985**, 50, 2309; *Tet. Lett.* **1986**, 27, 3979

The above analysis is clouded by the fact that the geometry of the 1,3-dipole is not fixed.



Monosubstituted Olefins.

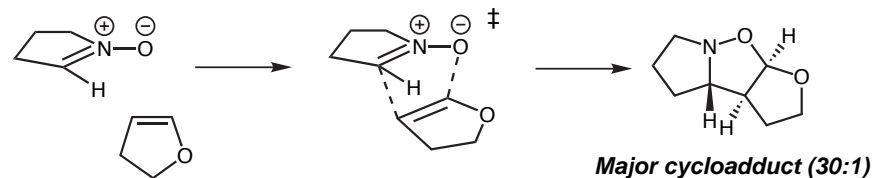
In the following study, 1,3-dipole isomerism is not an issue



Diastereoselection appears to be dictated by steric effects

Tufariello, *Accounts. Chem. Res.* **1979**, 12, 396-1403

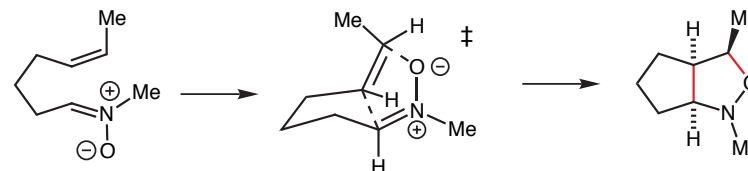
Cis Disubstituted Olefins.



The preceding trend appears to be reinforced by cis disubstitution

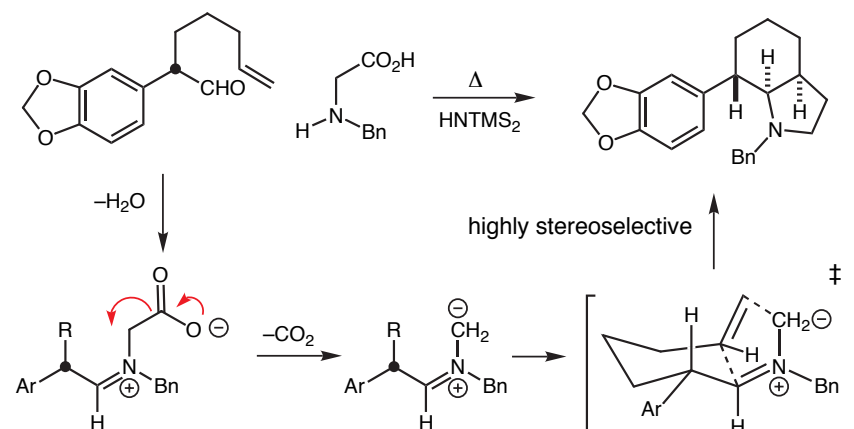
I. Washita et al, *Chem Lett* **1979**, 1337

Intramolecular Reaction Variants

N. LeBel et al, *JACS* **1964**, 86, 3759

Orientation probably driven by ring strain as in Oppolzer case (previous page)

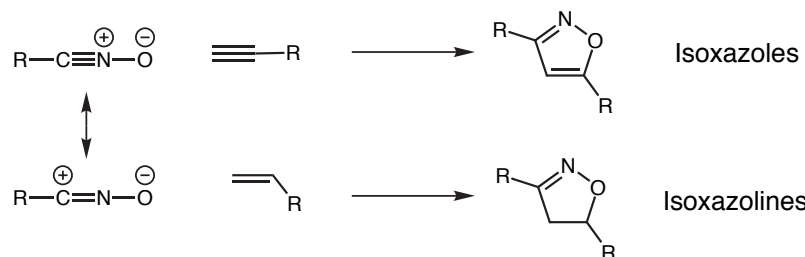
Intramolecular Reaction Variants

P. Confalone et al, *Tet. Lett.* **1984**, 25, 4613

Conclusions on Reaction Diastereoselection

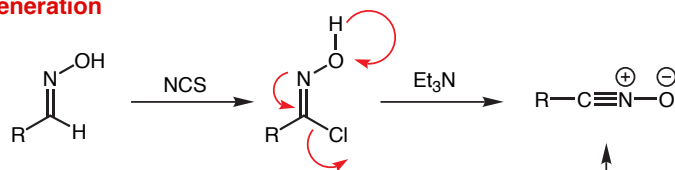
In general reaction diastereoselection appears to be dictated by steric and torsional rather than electronic factors

The Basic Reactions

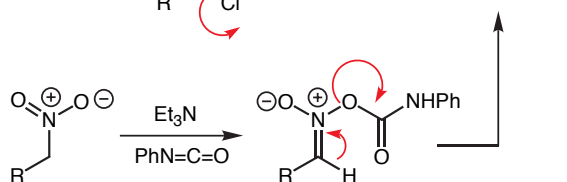
Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, John Wiley, **1984**, Vol 1, Chapter 3

Methods of Generation

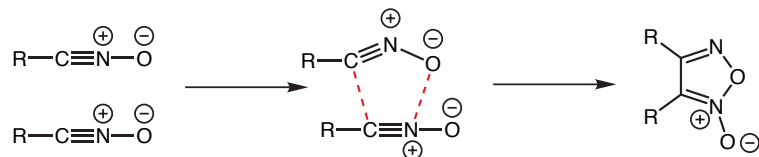
Method A



Method B



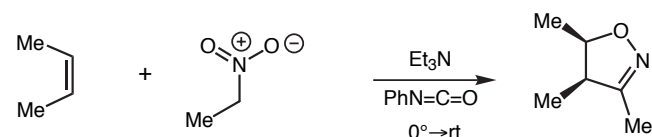
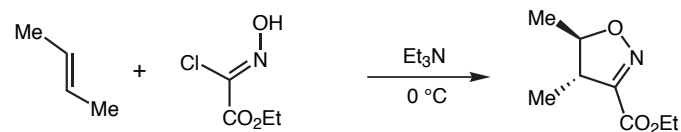
Stability Nitrile oxides are usually prepared in the presence of the olefin or acetylene acceptor. These intermediates are generally unstable and will dimerize if not given an alternative reaction course



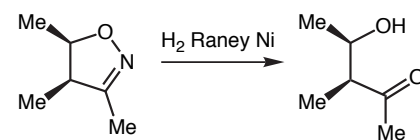
Regioselectivity Nitrile oxide cycloadditions with olefins and acetylenes are usually quite regioselective and in the direction as illustrated above.

DeShong, *JOC* **1985**, 50, 2309; *Tet. Lett.* **1986**, 27, 3979

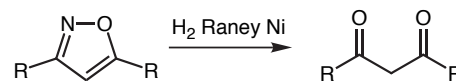
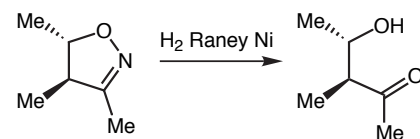
Reactions with olefins are stereospecific

Carruthers, W. *Cycloaddition Reactions in Organic Synthesis.*; Pergamon: Elmsford, NY, **1990**. Chapter 6, pp2 69–298

Oxazoline Cleavage



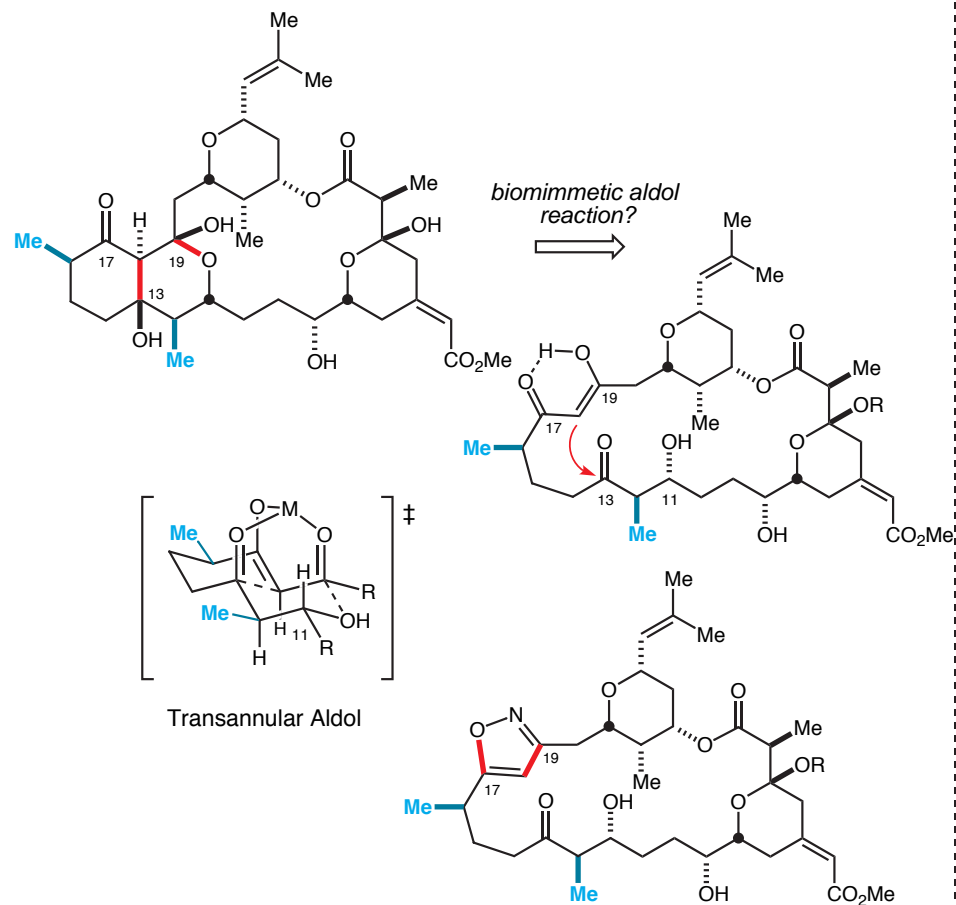
Non-aldol approach to aldol adducts



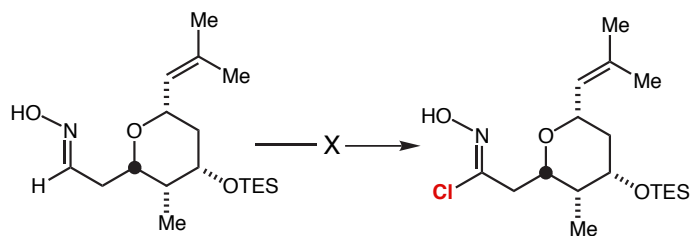
Non-aldol approach to 1,3-dicarbonyls

Preferred method for reducing oxazoles and oxazolines:
Nitta et al, *Chem. Comm.* **1982**, 877-878: $\text{Mo}(\text{CO})_6 \text{MeCN}$

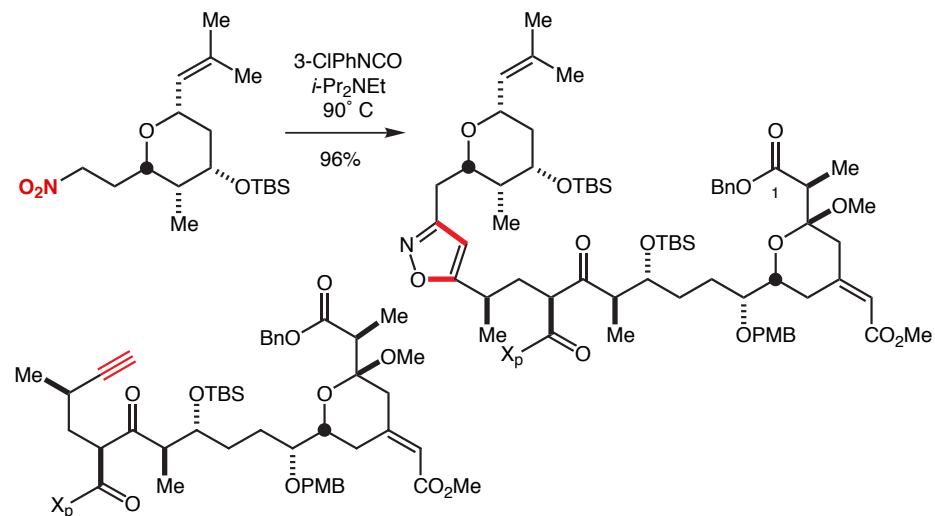
Miyakolide Synthesis: with David Ripin & David Halstead, *JACS* **1999**, 121, 6816-6826



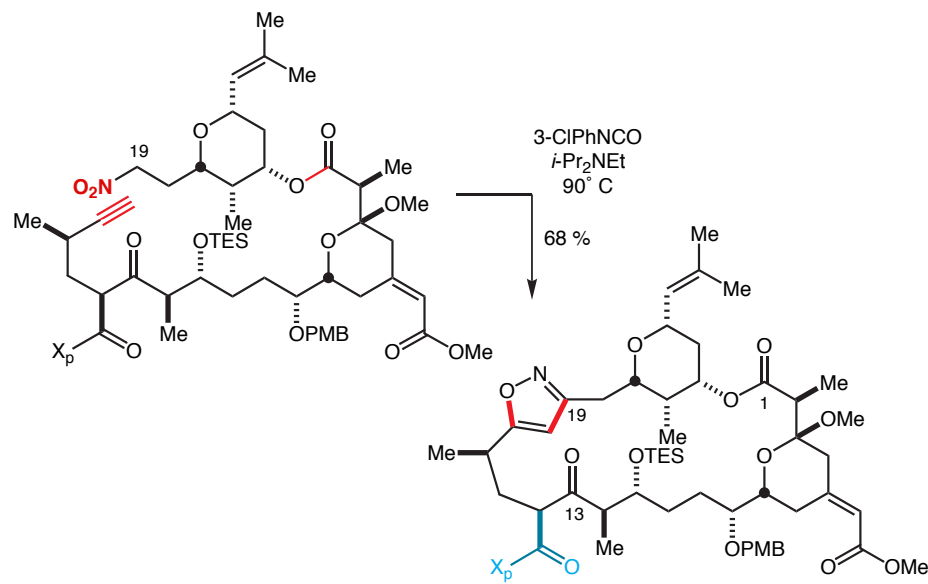
Competing olefin chlorination eliminated this approach to the nitrile oxide precursor



The Intermolecular Case

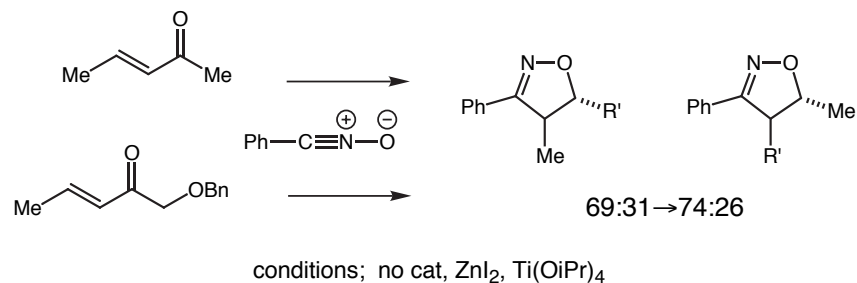


The Intramolecular Case



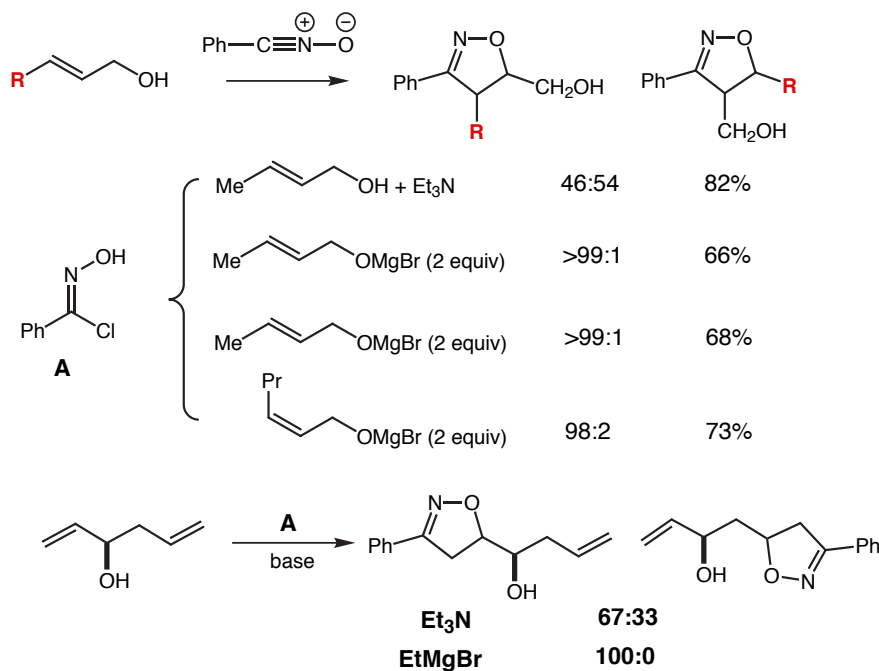
Development of Directed Cycloadditions

Kanemasa et al, *JACS* **1994**, *116*, 2324-2339 (**electronic handout**)
 Kanemasa et al, *Metal-Assisted Stereocontrol of 1,3-Dipolar Cycloaddition Reactions*
SynLett 2002, 1371-1387 (**electronic handout**)

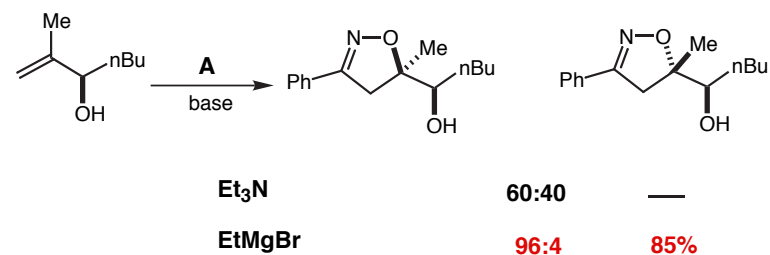
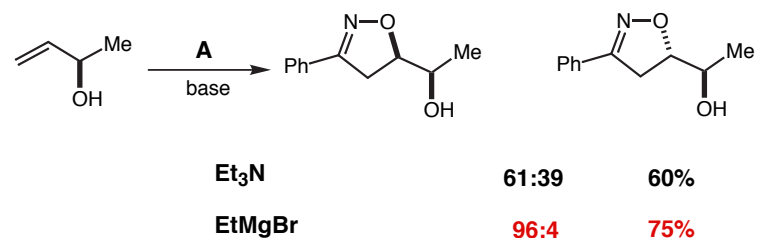
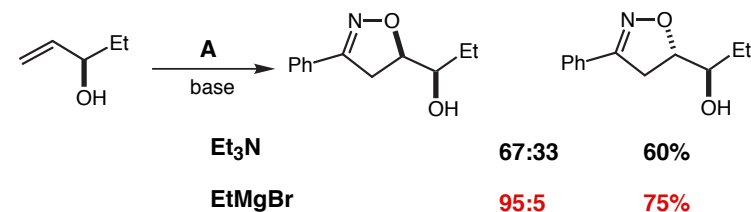


While Lewis acid activation is known, no change in regiochemistry was noted under above conditions

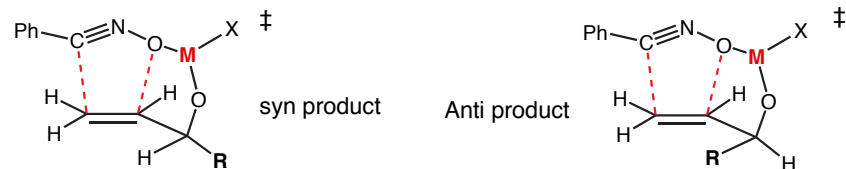
Magnesium alkoxides found to effect regiochemical control



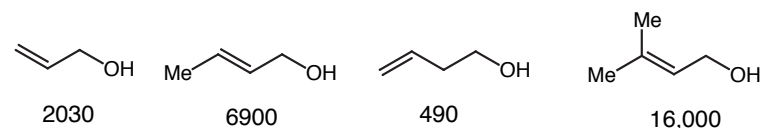
Reaction Diastereoselectivities



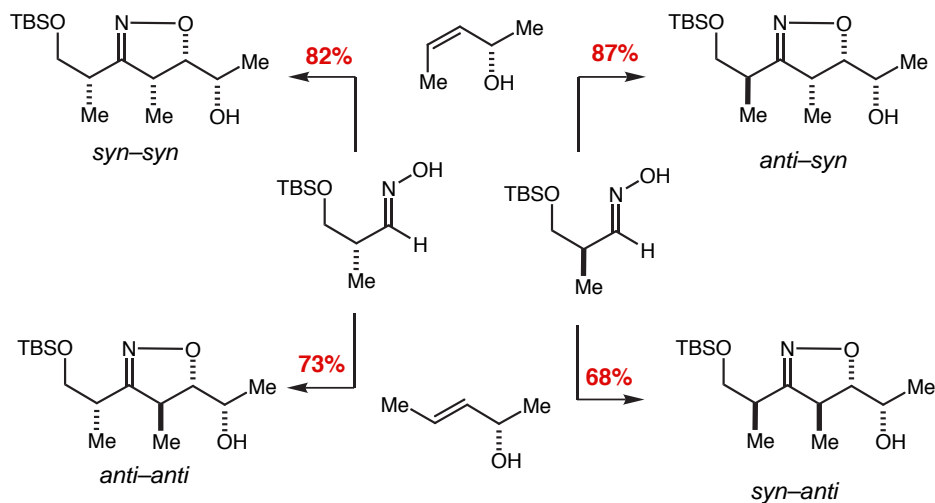
Stereochemical Rationale



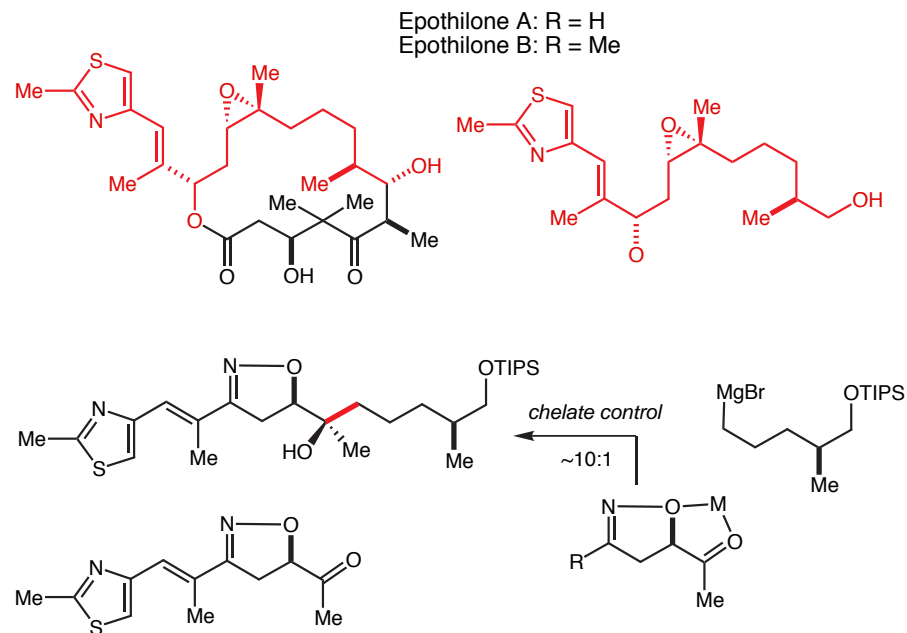
Rate accelerators



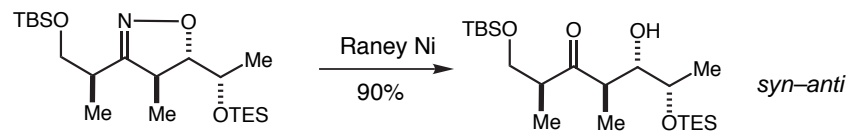
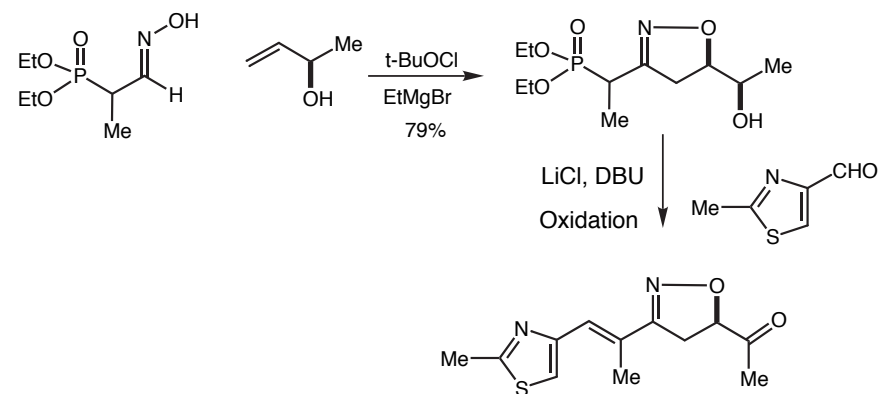
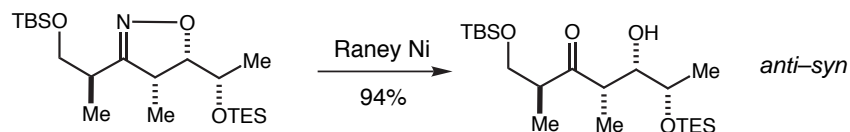
Applications in Polypropionate Synthesis

Carreira et al, *Angew. Chem. Int. Ed.* **2001**, 40, 2082–2085a, Oxime Chlorination: $t\text{-BuOCl}$; b, 3 Equiv EtMgBr , room temp, 12 h

Applications to the Synthesis of Epothilones A, B

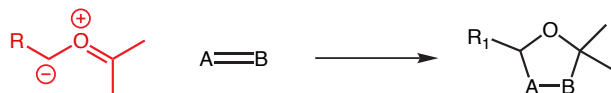
Carreira & Bode *JACS* **2001**, 123, 2082–2085

Oxazoline Reduction

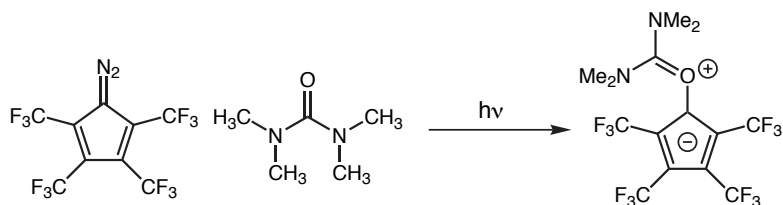
Lit Conditions: Curran, *JACS* **1983**, 105, 5826; *JOC* **1984**, 49, 3474

The Basic Reactions

Reviews - Ylides Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263-309.
 Padwa, A.; Krumpke, K. E. *Tetrahedron.* **1992**, *48*, 5385-5483.
 Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22-28.

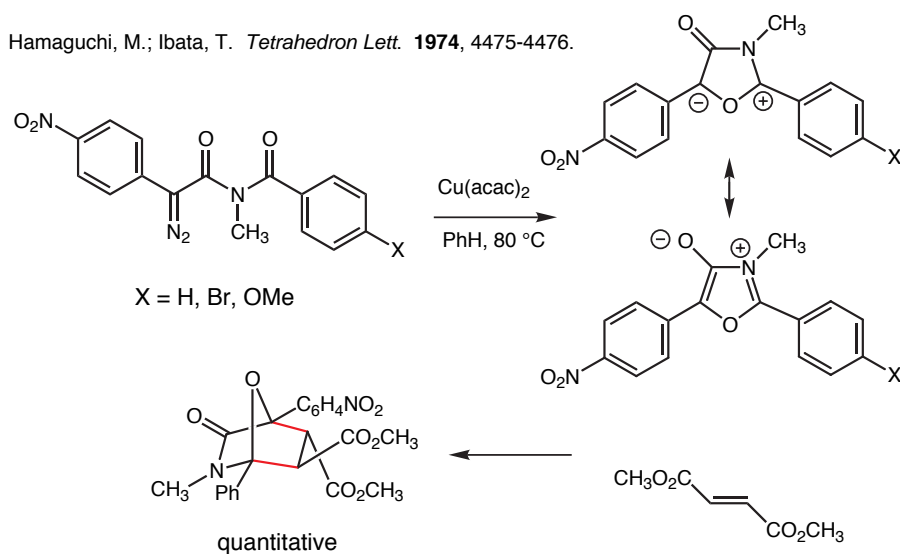


Stabilized (Isolable) Carbonyl Ylides



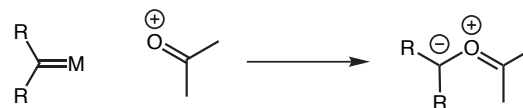
Arduengo, A. J., III; Janulis, E. P., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 5929-5930

Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974**, 4475-4476.

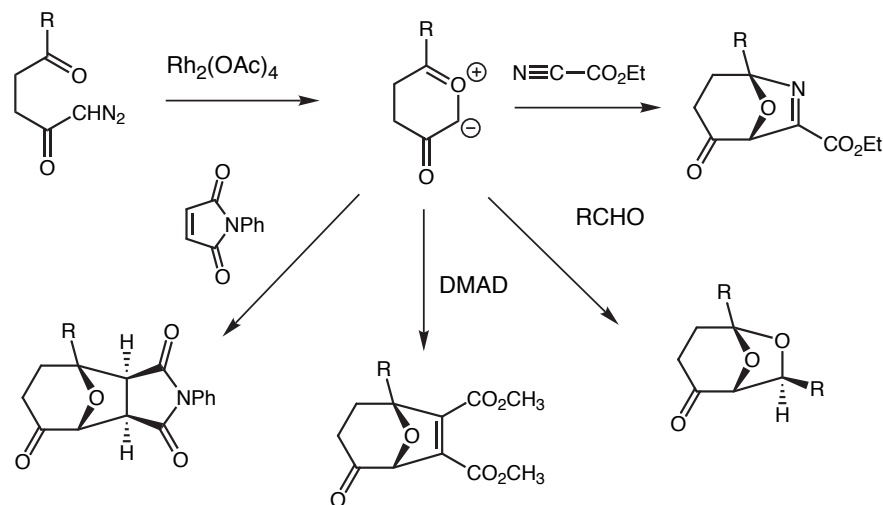


Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1975**, 499-502.

Carbenes Plus Carbonyl Groups

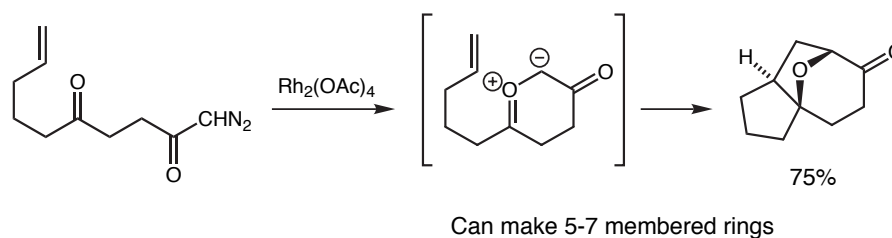


Tandem Intramolecular Cyclization-Intermolecular Cycloaddition

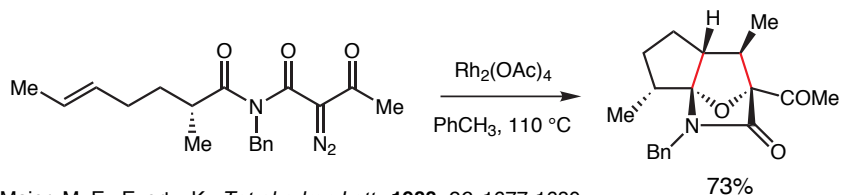
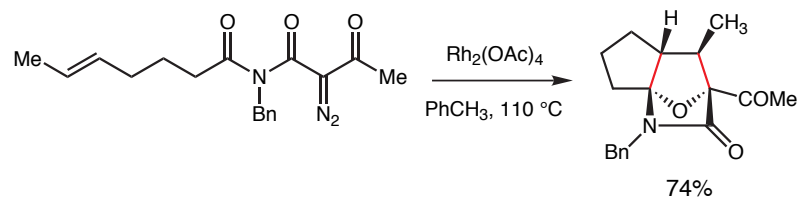


Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817-824.

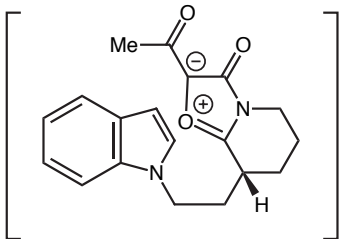
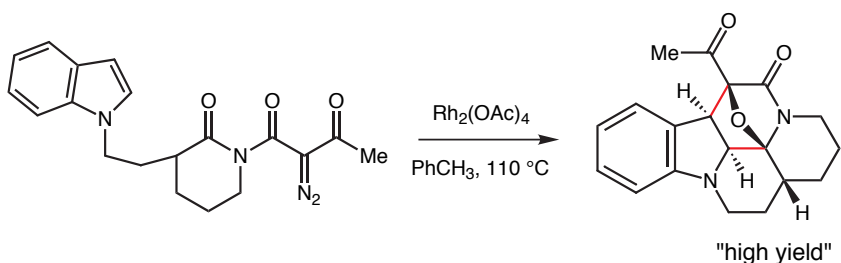
Intramolecular Variants



Carbonyl Ylide Cycloadditions of Diazoimides

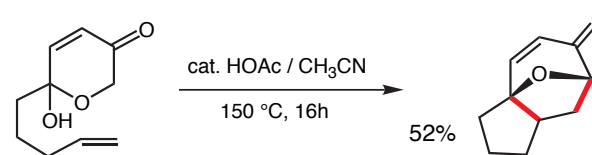
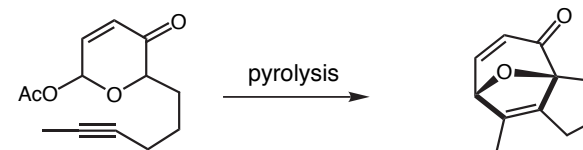
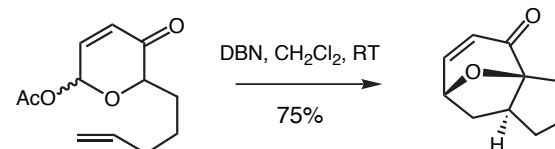
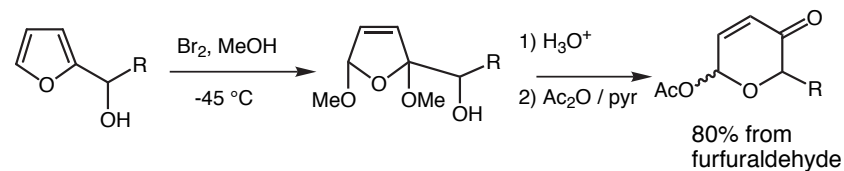
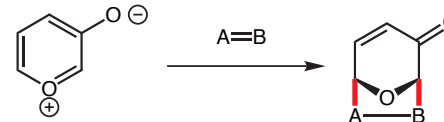


Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, 29, 1677-1680.



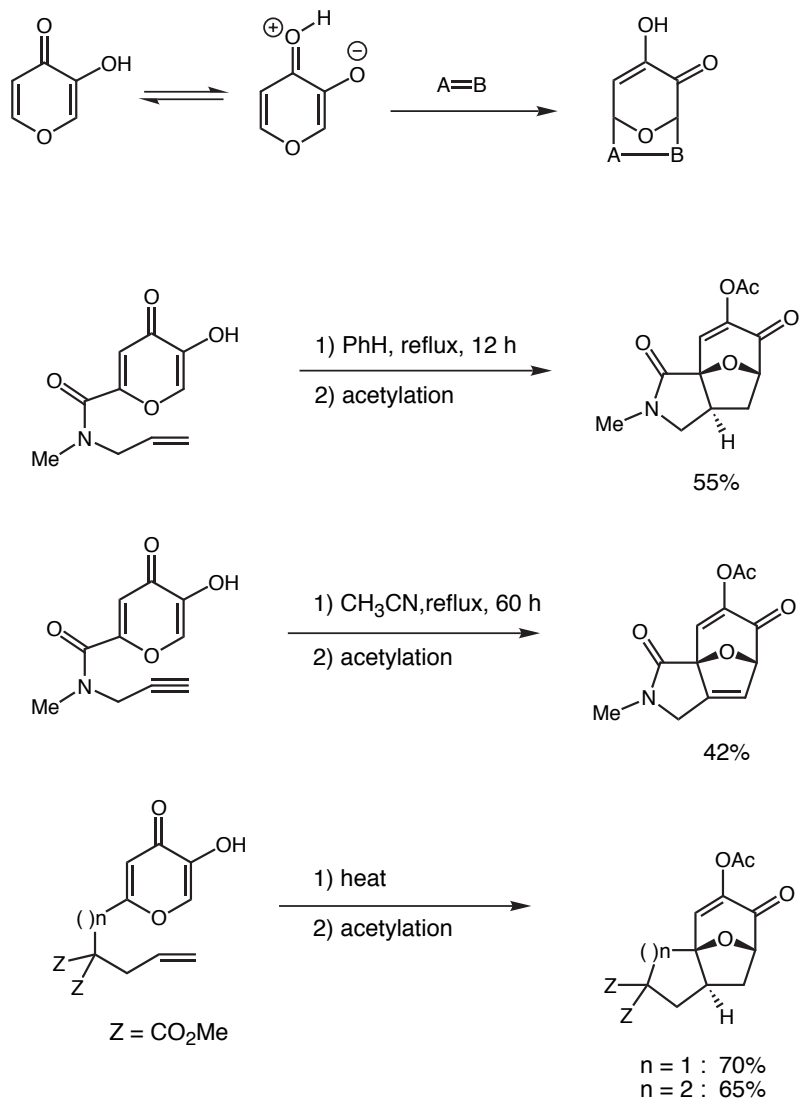
Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett.* **1992**, 33, 4731-4734.

Cycloadditions with Oxidopyrylium Ylides



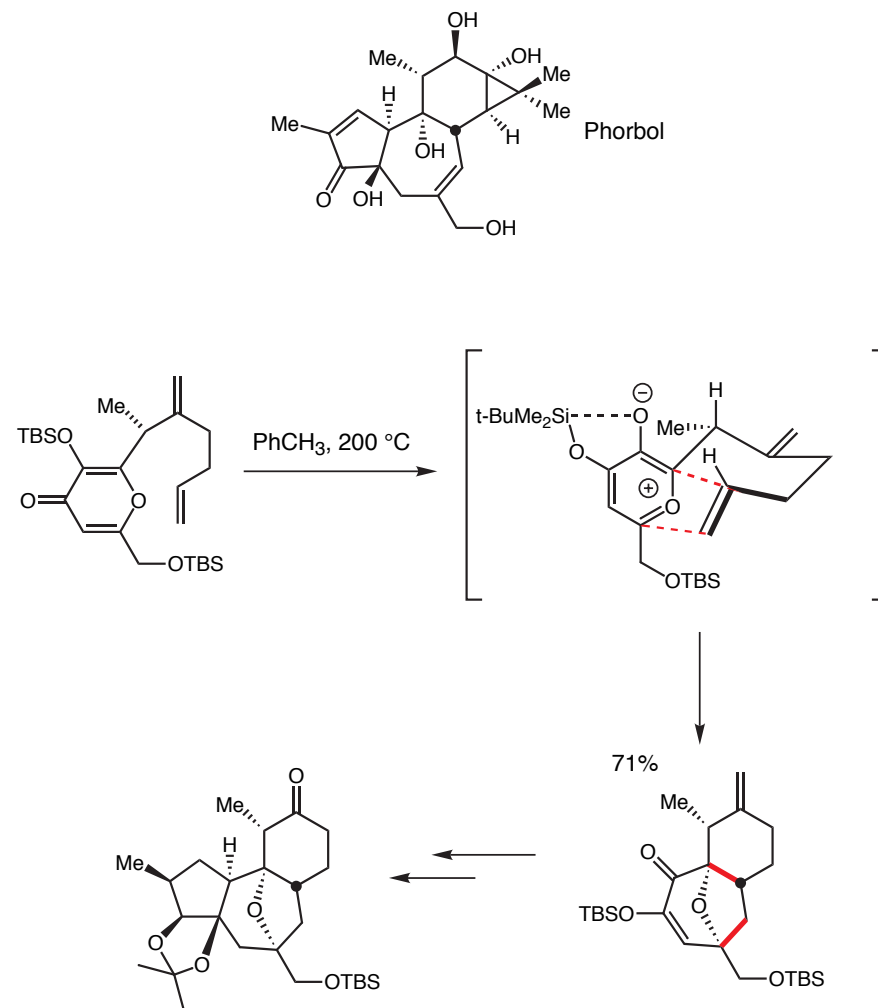
Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1056-1057

Cyclizations with 5-Hydroxy-4-Pyrones



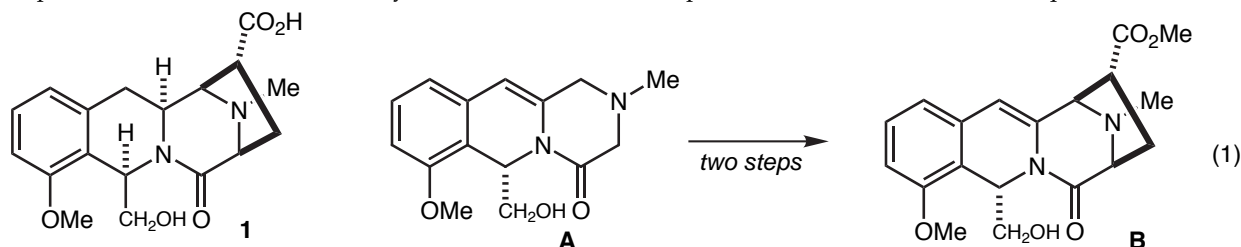
Garst, M. E.; McBride, B. J.; Douglass, J. G. III. *Tetrahedron Lett.* **1983**, 24, 1675-1678.

Phorbol: The Hydroxypyrrone Approach



Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, 112, 4956-4958

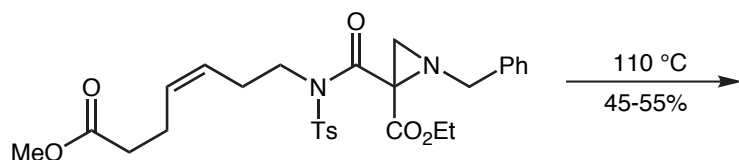
Problem 53. Williams recently reported an approach to the synthesis of quinocarcinamide (**1**) (*J. Org. Chem.* **1995**, *60*, 6791). The pivotal process that establishes the tetracyclic nucleus is the two-step transformation shown below (eq 1).



Devise a strategy for transforming A into B and clearly illustrate your answer in the space below. Full credit will be awarded to concise answers.

Problem 55. The following transformation was recently reported by Heathcock during studies directed toward the synthesis of sarain A

(*Tetrahedron Lett.* **1995**, *6*, 2381). From your knowledge of the functionality present in the starting material, deduce the structure (including stereochemistry) of the reaction product which has the same molecular weight as the starting material. Hint. the ¹H NMR spectrum of the product reveals that the olefinic resonances have disappeared.

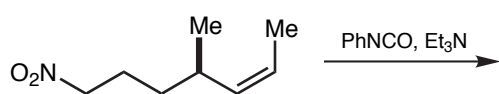


Your mechanism for the transformation

●—————●
product structure

Problem 65. The following stereoselective nitrile oxide cycloaddition has been reported by Kozikowski (*Tetrahedron Lett.* **1982**, *23*, 2081;

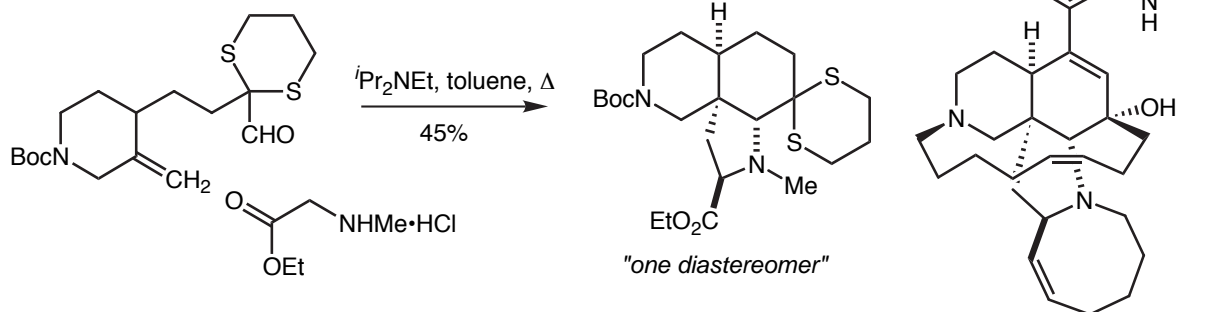
J. Org. Chem. **1984**, *49*, 2762). Provide the stereostructure of the major product and rationalize the stereochemical outcome as indicated in the directions.



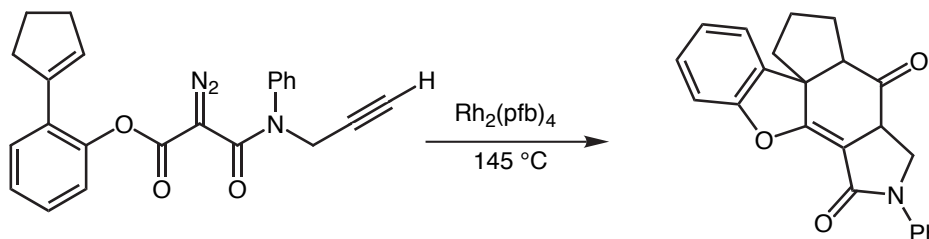
The product ?
Stereoselection: 16/1

●—————●
product structure

Problem 87. The illustrated transformation has been utilized by Coldham (*Chem. Commun.* **1999**, 1757) to construct the core ring system of the manzamines.

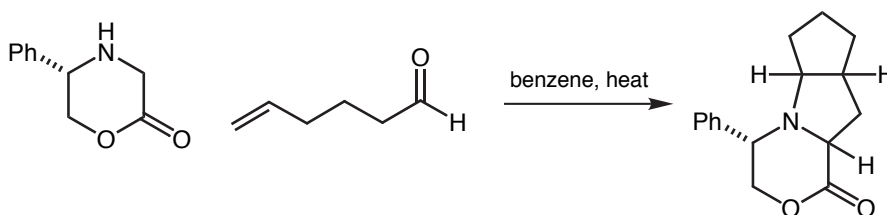


Problem 90. Padwa and co-workers recently disclosed the illustrated multistep polycyclisation as a possible route to the strychnine core (*Org. Lett.* **2001**, ASAP)



In the space below, provide a mechanism for the indicated transformation. *Hint: The management suggests that a careful bidirectional analysis might help you to arrive at a solution of this question.*

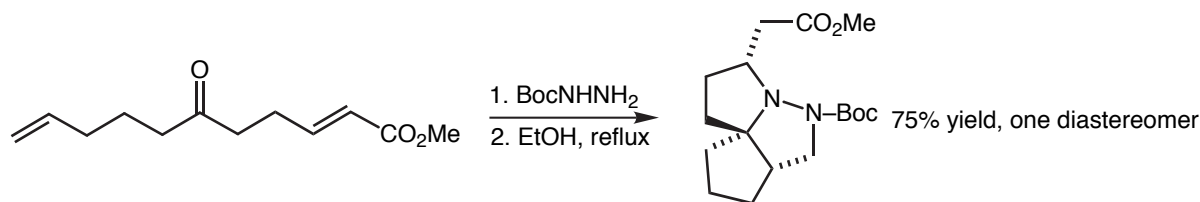
Problem 136. A recent paper by Harwood and Park highlights the rapidity with which one may assemble complex architecture in a single chemical operation (*Tetrahedron Lett.* **1999**, 40, 2907 and earlier cited references). The transformation in question is illustrated below. You are asked to address two aspects of this transformation.



Part A. Provide a concise mechanism for the indicated transformation. For now, ignore the stereochemical aspects of the reaction.

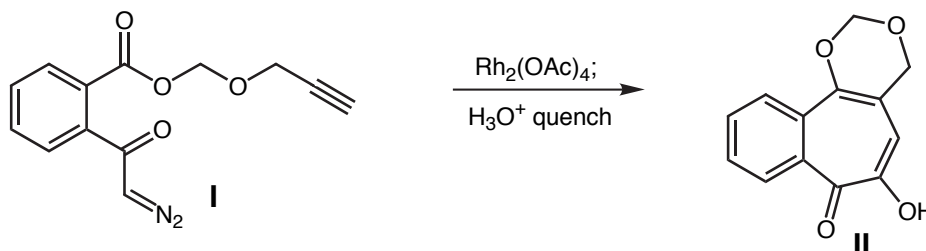
Part B. Predict the stereochemical outcome of the reaction at the three new stereocenters, and provide a three-dimensional drawing of the transition state wherein these centers are produced.

Problem 171. A recent paper by Dolle (*Tetrahedron Lett.* **1999**, 40, 2907) highlights the rapidity with which one may assemble complex architecture in a single chemical operation. The transformation in question is illustrated below.



Provide a concise mechanism for the indicated transformation. In that step where the complex stereochemical relationships are established, a carefully rendered three dimensional illustration is requested.

Problem 189. This question is taken from recent work reported by Jack Baldwin (*Org. Lett.*, **1999**, 1933 and 1937). Provide a mechanism for the conversion of I to II.



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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 19

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. (**handout**)

D. A. Evans

Wednesday,
October 29, 2003

Articles on the Acidities of Organic Molecules

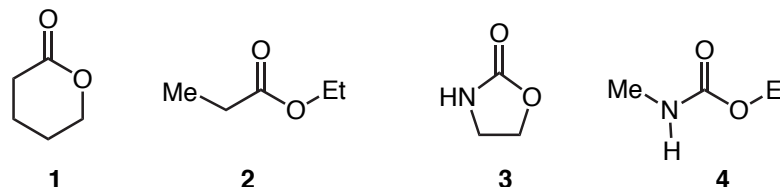
Lowry & Richardson: 3rd Edition, Chapter 3
Acids and Bases

Here is a web site containing Bordwell pKa data

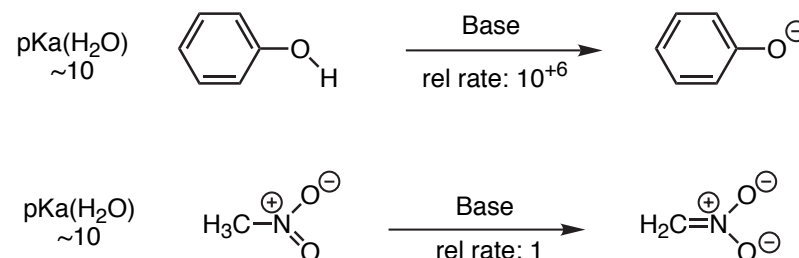
<http://www.chem.wisc.edu/areas/reich/pkatable/index.htm>

■ 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)

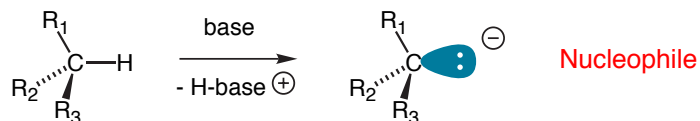


The thermodynamic acidities of phenol and nitromethane are both ~10; however, using a common base, phenol is deprotonated 10^{+6} times as fast. Rationalize



Activation of Organic Molecules

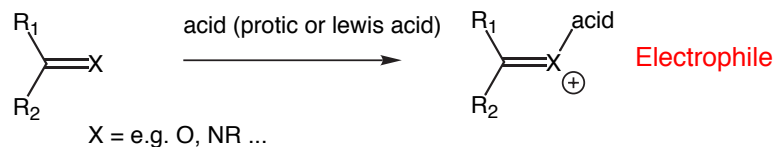
■ Base Activation



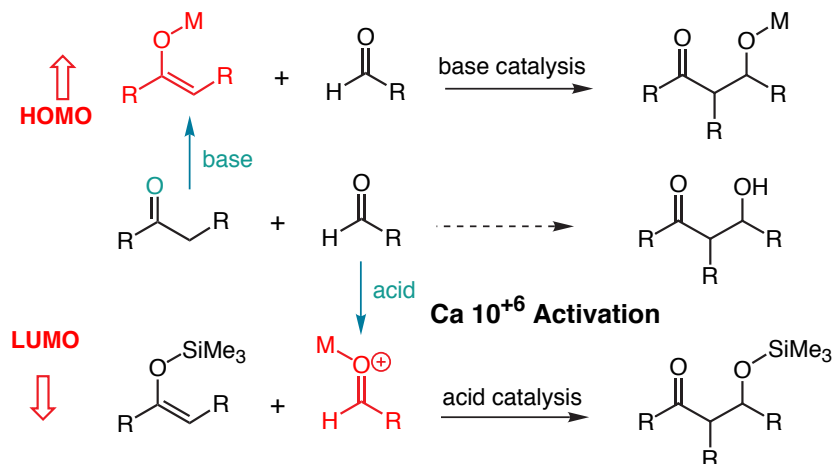
pK_a describes quantitatively a molecule's propensity to act as an acid, i.e. to release a proton.

- Medium effects
- Structural effects (influence of substituents R_1)

■ Acid Activation



■ The Aldol Example



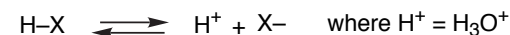
■ Definition of K_a

Let H-X be any Bronsted acid. In water ionization takes place:



where
$$K_{\text{eq}} = \frac{[\text{H}_3\text{O}^+][\text{X}^-]}{[\text{H-X}][\text{HOH}]}$$
 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.

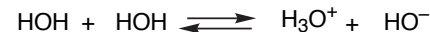


Hence
$$K_a = \frac{[\text{H}^+][\text{X}^-]}{[\text{H-X}]} \quad \text{(B)}$$

From the above definitions, K_a is related to K_{eq} by the relation:

$$K_a(\text{H-X}) = 55.5 K_{\text{eq}}(\text{H-X}) \quad \text{(C)}$$

■ Autoionization of water



$$K_{\text{eq}} = 3.3 \times 10^{-18}$$

From Eq C: $K_a = 55.5 K_{\text{eq}} = 55.5(3.3 \times 10^{-18})$

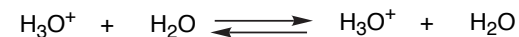
Hence $K_a = 1.8 \times 10^{-16}$

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: $K_{\text{eq}} = 1$

$$K_a = [\text{HOH}] \times K_{\text{eq}} \quad \text{hence } K_a = 55.5$$

$$\text{pK}_a = -\log_{10} K_a = -1.7$$

The strongest acid that can exist in water is H_3O^+ .

■ The Gibbs Relationship

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

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

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

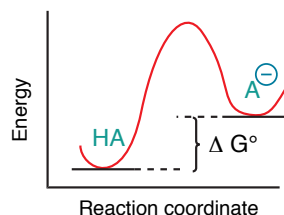
$$2.3 RT = 1.4$$

$$\text{at } T = 298 \text{ K} \\ \text{in kcal} \cdot \text{mol}^{-1}$$

$$\Delta G^\circ_{298} = 1.4 \text{ p}K_{\text{eq}} \approx 1.4 \text{ p}K_{\text{a}} \quad \text{with } \text{p}K = -\log_{10} K$$

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



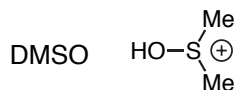
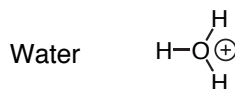
■ Medium Effects

Consider the ionization process:

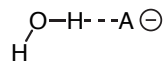


In the ionization of an acid in solution, the acid donates a proton to the medium. The more basic the medium, the larger the dissociation equilibrium. The ability of the medium to stabilize the conjugate base also plays an important role in the promotion of ionization. Let us consider two solvents, HOH 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

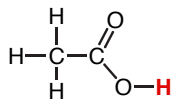
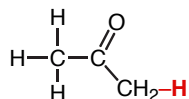
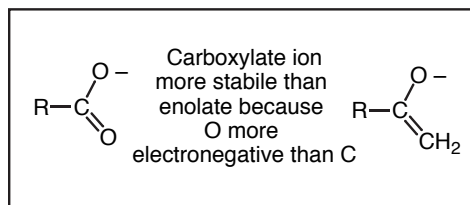
■ Representative pKa Data

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
	11.1	11.2	0

Substituent Effects

Electronegativity e.g. Compare Carboxylic Acids vs. Ketones(H₂O) pK_A = 4.8pK_A ≈ 19(DMSO) pK_A = 12.3pK_A ≈ 26.5**Hybridization**

- S-character of carbon hybridization

Remember:

sp³-orbitals 25% s-charactersp²-orbitals 33% s-character

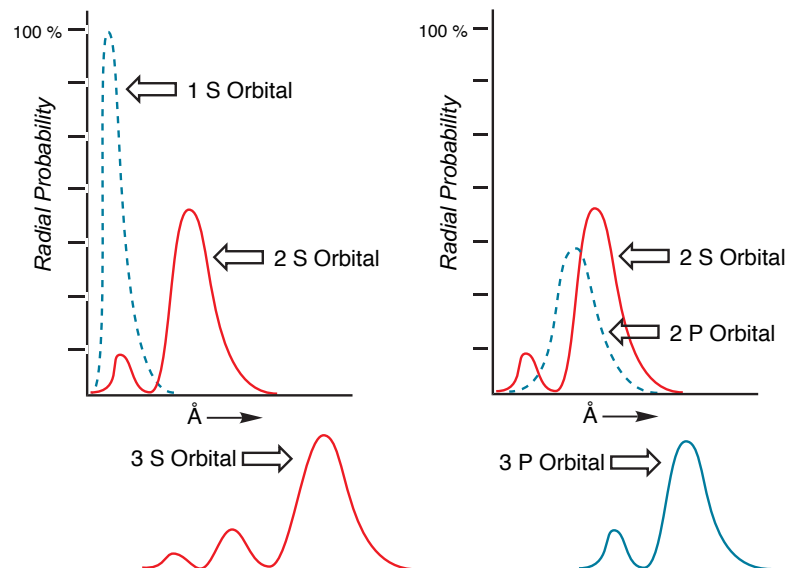
sp-orbitals 50% s-character

Carbon Acids

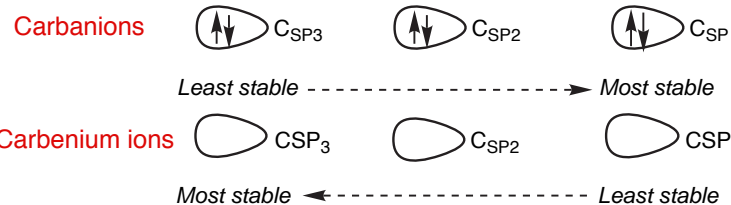
	$\text{R}-\text{C}\equiv\text{H}$	$\begin{array}{c} \text{R} \quad \text{R} \\ \diagdown \quad / \\ \text{C}=\text{C} \\ / \quad \diagdown \\ \text{R} \quad \text{H} \end{array}$	$\begin{array}{c} \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{H} \end{array}$	$\begin{array}{c} \text{R} \quad \text{R} \\ \quad \\ \text{C}-\text{C} \\ \quad \\ \text{R} \quad \text{H} \end{array}$
Hybridization	sp	sp ²	≈ sp ²	sp ³
Bond Angle	180°	120°	≈ 120	109°
pK _a (DMSO)	23	≈ 44	≈ 39	≈ 60

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.



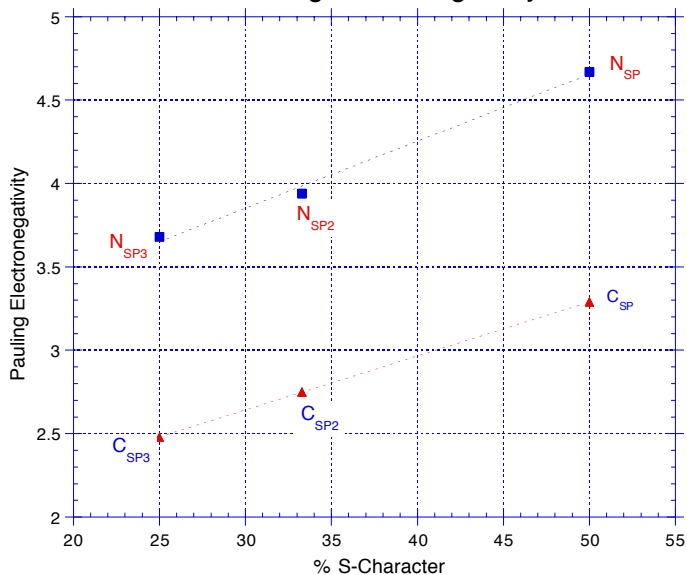
S-states have greater radial penetration due to the nodal properties of the wave function. Electrons in s states see a higher nuclear charge. The above observation correctly implies that the stability of nonbonding electron pairs is directly proportional to the % of S-character in the doubly occupied orbital.



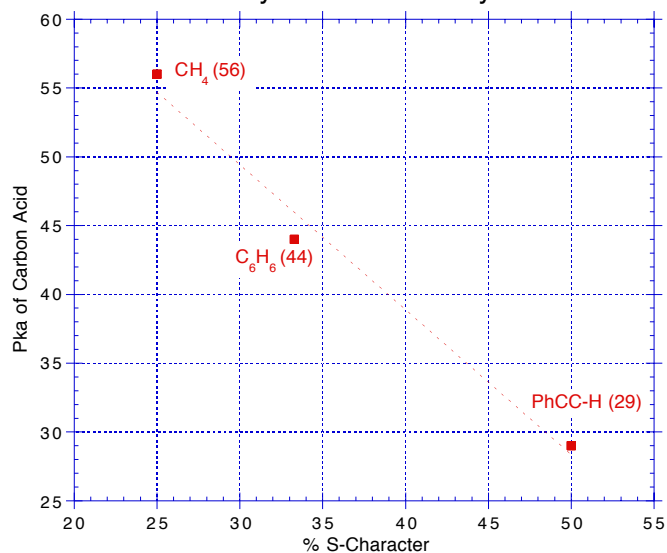
The above trends indicate that the greater the % of S-character at a given atom, the greater the electronegativity of that atom.

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)

Structure	pK _A (DMSO)	Structure	pK _A (DMSO)
<chem>PhSO2-CH2-H</chem>	29	<chem>C1S1C1</chem>	31.1
<chem>PhSO2-CH2-Me</chem>	31	<chem>C1S1C1C</chem>	38.3

Heteroatom-Substituents: - 1st row elements of periodic table

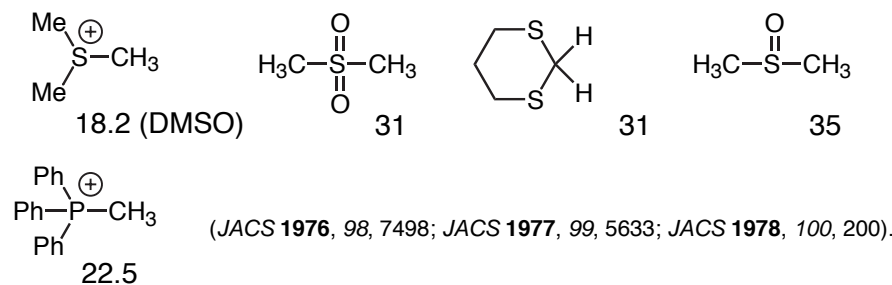
Structure	pK _A (DMSO)	Effect
<chem>PhSO2-CH2-OCH3</chem>	30.7	Inductive Stabilization versus Lone Pair Repulsion (-I vs +M -Effect)
<chem>PhSO2-CH2-OPh</chem>	27.9	
<chem>PhSO2-CH2-NMe3+</chem>	19.4	Inductive Stabilization

Heteroatom-Substituents: - 2nd row elements of periodic table

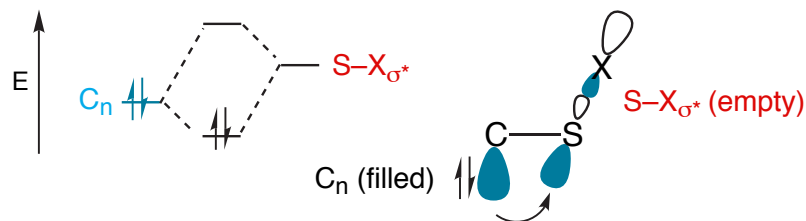
Strong carbanion stabilizing effect

Structure	pK _A (DMSO)	Structure	pK _A (DMSO)
<chem>PhSO2-CH2-H</chem>	29	<chem>PhSO2-CH2-SO2Ph</chem>	12.2
<chem>PhSO2-CH2-SPh</chem>	20.5	<chem>PhSO2-CH2-PPh2</chem>	20.5

Carbanion Stabilization by 2nd-Row Atoms: SR, SO₂R, PR₃ etc

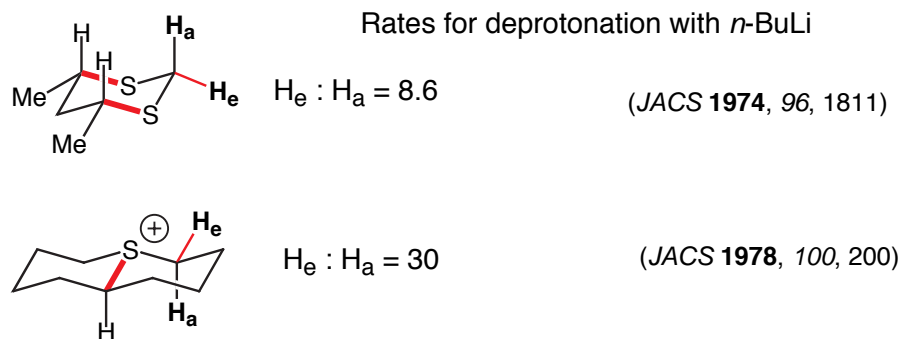


The accepted explanation for carbanion stabilization in 3rd row elements is delocalization into vicinal antibonding orbitals

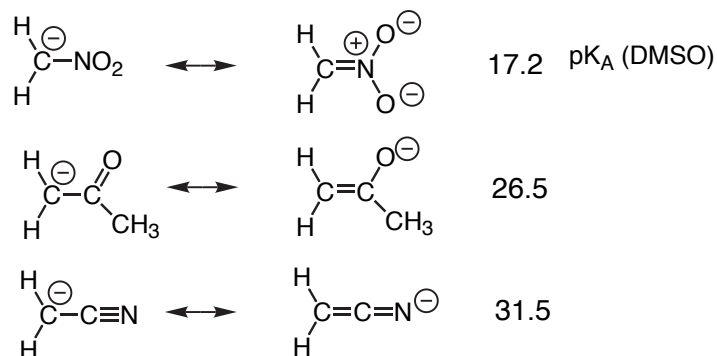


This argument suggests a specific orientation requirement. This has been noted:

Anti (or syn) periplanar orientation of Carbanion-orbital and σ^* orbital mandatory for efficient orbital overlap.



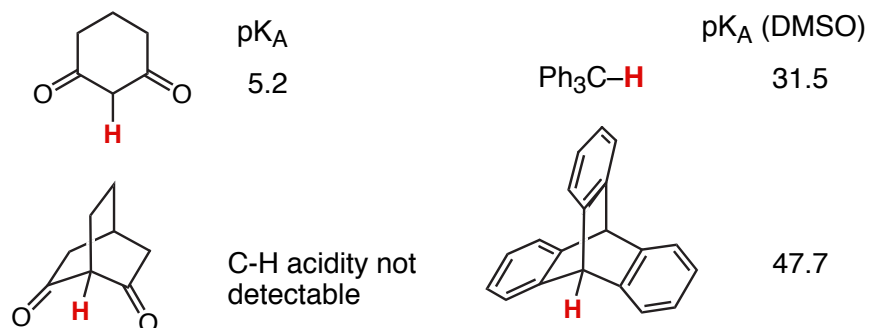
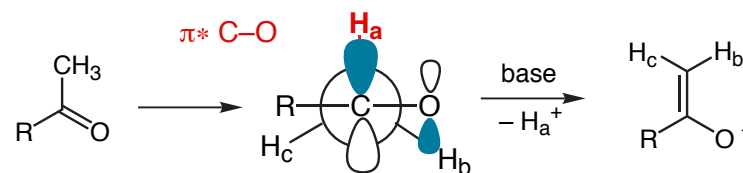
Conjugative Stabilization of Conjugate Base



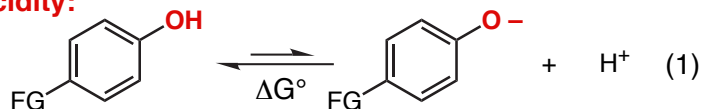
For efficient conjugative stabilization, rehybridization of carbanion orbital from n_{sp^3} to n_p is required for efficient overlap with low-lying π^* -orbital of stabilizing group. However, the cost of rehybridization must be considered.

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:

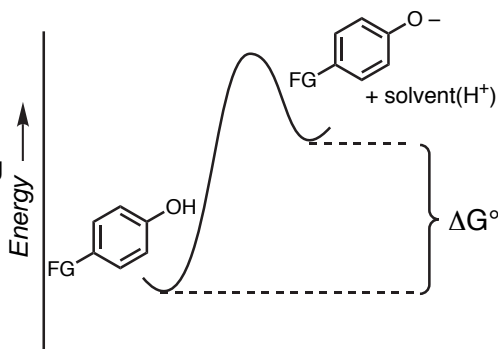


This topic has a number of take-home lessons. Most importantly, is is a useful construct on which to discuss the role of FG's in influencing the acidity of this oxygen acid.

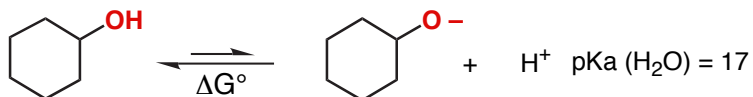
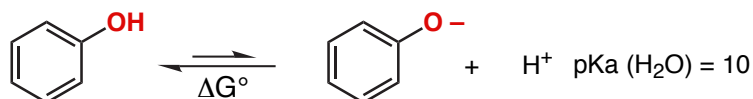
How does one analyze the impact of structure on pKa of a weak acid (pKa > 0) ?

The Approach:

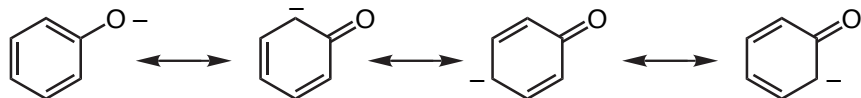
For equilibria such as that presented above, analyze the effect of stabilizing (or destabilizing) interactions on the more energetic constituent which in this case is the conjugate base.



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."

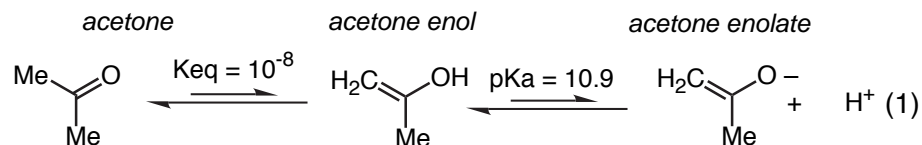


from previous discussion, $\Delta G^\circ_{298} = -1.4 \log_{10} K_{\text{eq}} = 1.4 \text{ pK}_{\text{eq}}$

$\Delta G^\circ (\text{stab}) = 1.4(\text{pK}_{\text{a phenol}} - \text{pK}_{\text{a cyclohexanol}}) = 1.4(-7) = 9.8 \text{ kcal/mol}$

Is the benzene ring somehow special. i.e "larger resonance space."

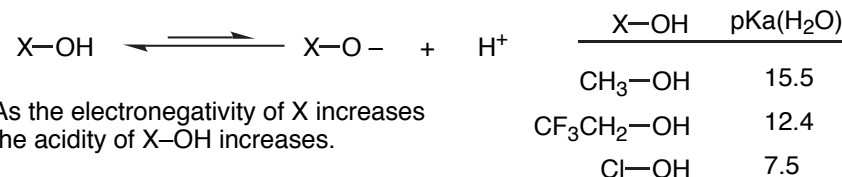
Acetone enol:



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 $\text{C}_6\text{H}_5\text{O}^-$?

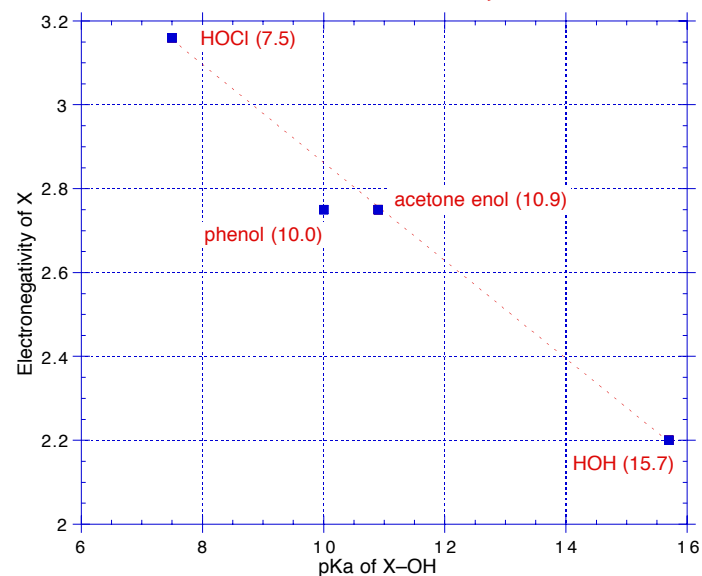
Consider the following general oxygen acid X-OH where X can only stabilize the conjugate base through induction:



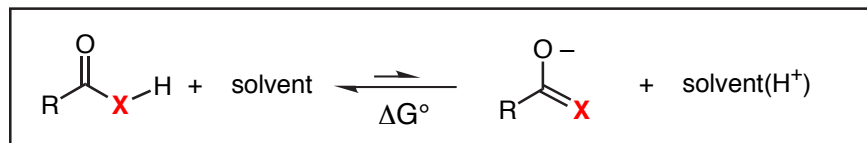
As the electronegativity of X increases the acidity of X-OH increases.

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 ($pK_a > 0$)



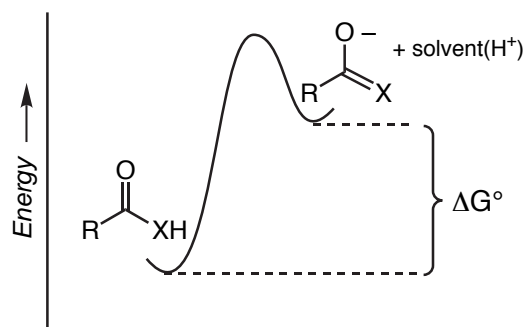
Variables:

X = O (carboxylic acid)

X = NH (amide)

X = CH₂ (Ketone/ester)R = CR₃

R = OR

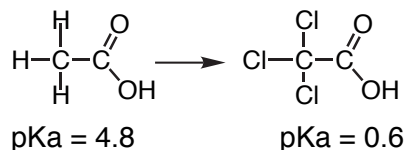
R = NR₂

■ The Question: How does one analyze the impact of structure on pK_a ?

■ The Approach:

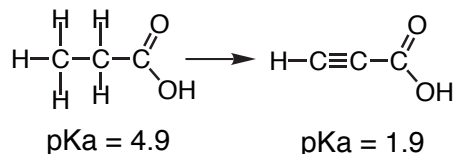
For equilibria such as that presented above, analyze the effect of stabilizing (or destabilizing) interactions on the more energetic constituent which in this case is the conjugate base.

Case I: Carboxylic Acids: Inductive Effects



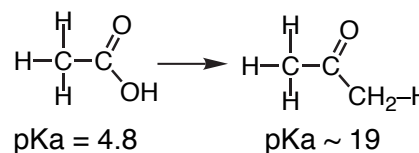
Carboxylate ion stabilized by increased electron-withdrawing CCl₃ group.

Case II: Carboxylic Acids: Inductive Effects & Carbon Hybridization



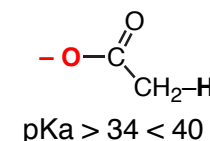
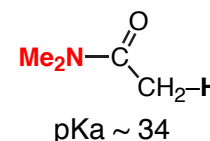
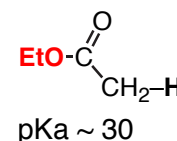
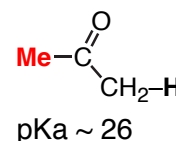
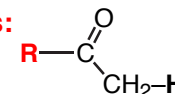
Carboxylate ion stabilized by increased electron-withdrawing SP-hybridized carbon

Case III: Carboxylic Acids vs Ketones:



Carboxylate ion more stable than enolate because O more electronegative than C

Case IV: Carboxylic Acids, Esters, Amides & Ketones:



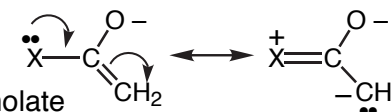
The Analysis:

In this series of compounds, there are two variables to consider:

■ Inductive Effect: OEt > Me₂N > H₃C but (O-?)

■ Resonance Effect:

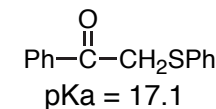
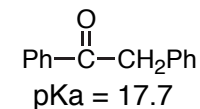
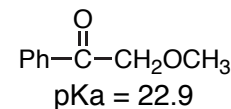
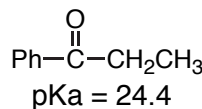
The degree to which substituent X: "contributes" electron density into enolate represents a destabilizing interaction:



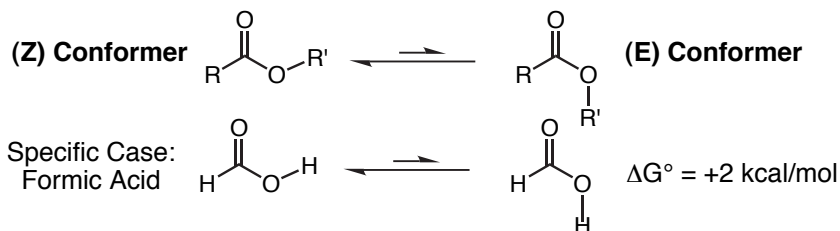
Trend: O- > Me₂N > OEt

■ Resonance donation dominates inductive electron withdrawal as indicated by the data.

Substituents on the α -carbon: Stabilization by either resonance, induction, or both is observed:



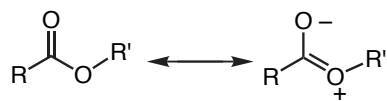
■ **Conformations:** There are 2 planar conformations.



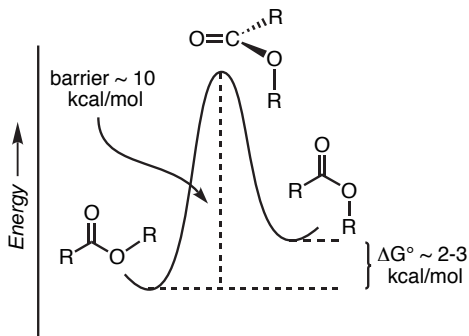
The (E) conformation of both acids and esters is less stable by 2-3 kcal/mol. If this equilibrium were governed only by steric effects one would predict that the (E) conformation of formic acid would be more stable (H smaller than =O). Since this is not the case, there are electronic effects which must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

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

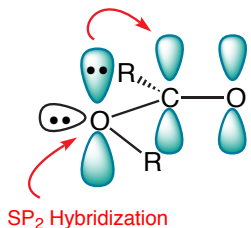
These resonance structures suggest hindered rotation about =C-OR bond. This is indeed observed:



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.

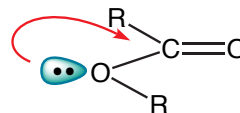


The filled oxygen p-orbital interacts with pi (and pi*) C=O to form a 3-centered 4-electron bonding system.

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

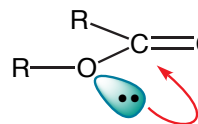
■ **Hyperconjugation:** Let us now focus on the oxygen lone pair in the hybrid orbital lying in the sigma framework of the C=O plane.

(Z) Conformer

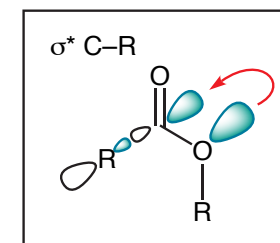
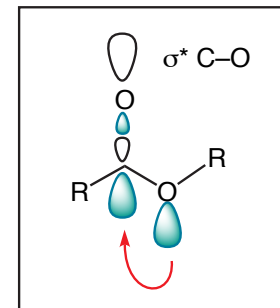


In the (Z) conformation this lone pair is aligned to overlap with $\sigma^* \text{ C-O}$.

(E) Conformer



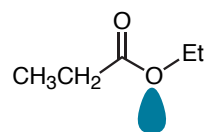
In the (E) conformation this lone pair is aligned to overlap with $\sigma^* \text{ C-R}$.



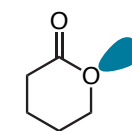
Since $\sigma^* \text{ C-O}$ is a better acceptor than $\sigma^* \text{ C-R}$ (where R is a carbon substituent) it follows that the (Z) conformation is stabilized by this interaction.

Lone pair orientation & Impact on pKa (DMSO)

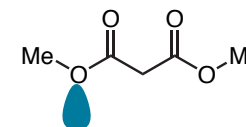
See Bordwell, *J. Org. Chem.* **1994**, *59*, 6456-6458



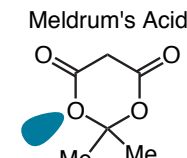
pKa ~ 30



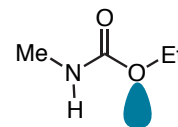
pKa = 25.2



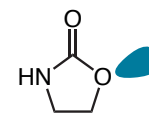
pKa = 15.9



pKa = 7.3

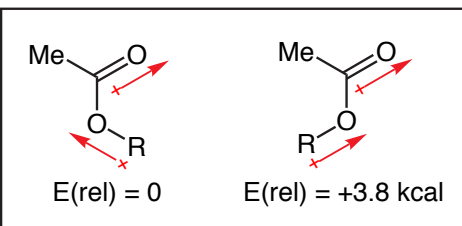


pKa = 24.5



pKa = 20.6

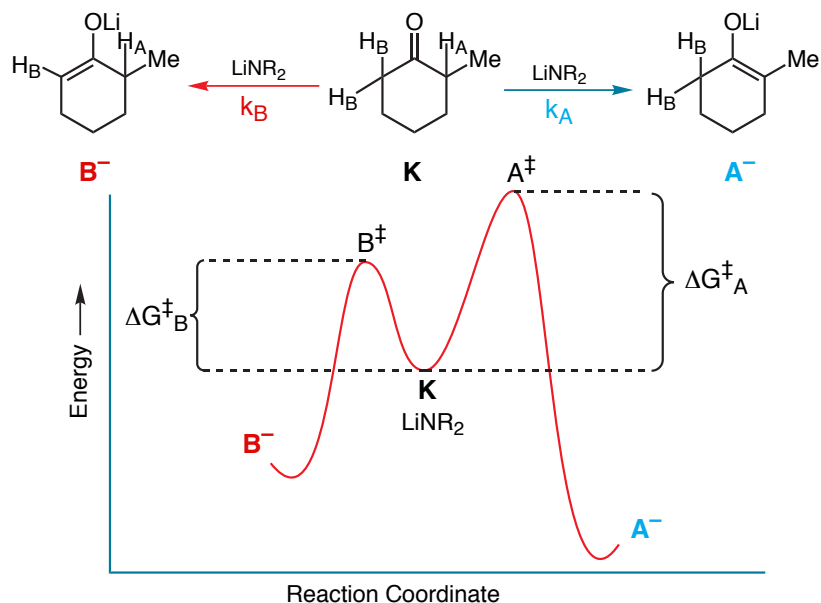
Is this a dipole effect? See Bordwell



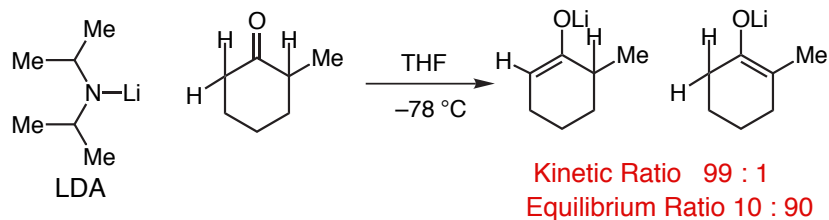
Houk, *JACS* **1988**, *110*, 1870 supports the dipole argument

■ Kinetic Acidity: Rates of proton removal

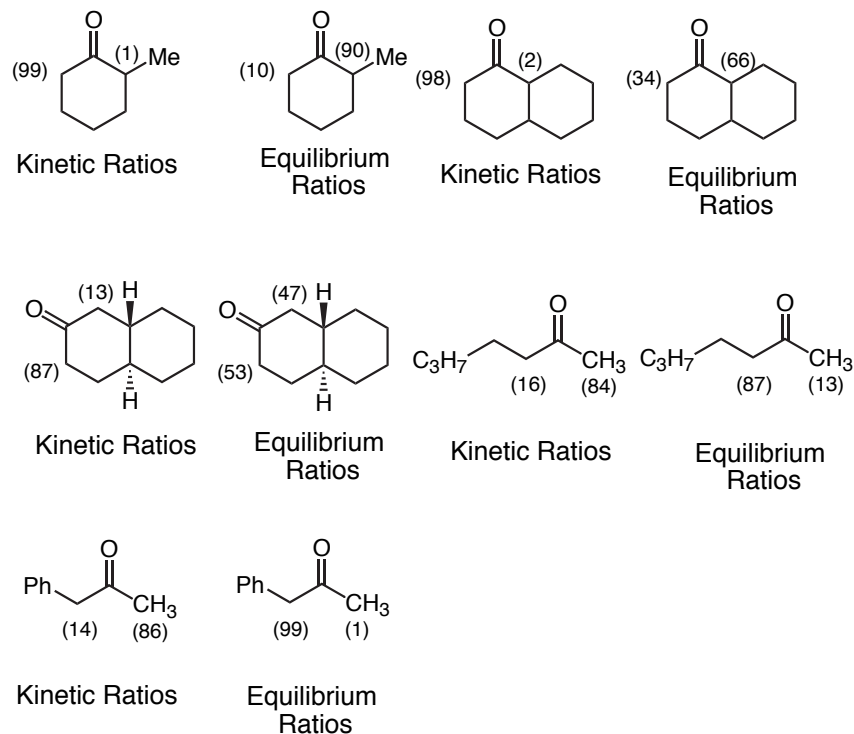
Consider enolization of the illustrated ketone under non-equilibrating conditions:



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, ΔG^\ddagger_A will increase more than ΔG^\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

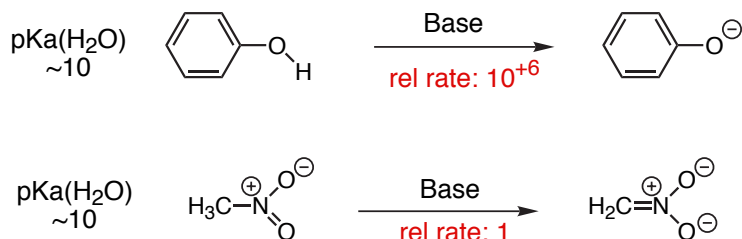


■ Note that alkyl substitution stabilizes the enolate (Why??). This effect shows up in the equilibrium ratios shown above.

■ 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

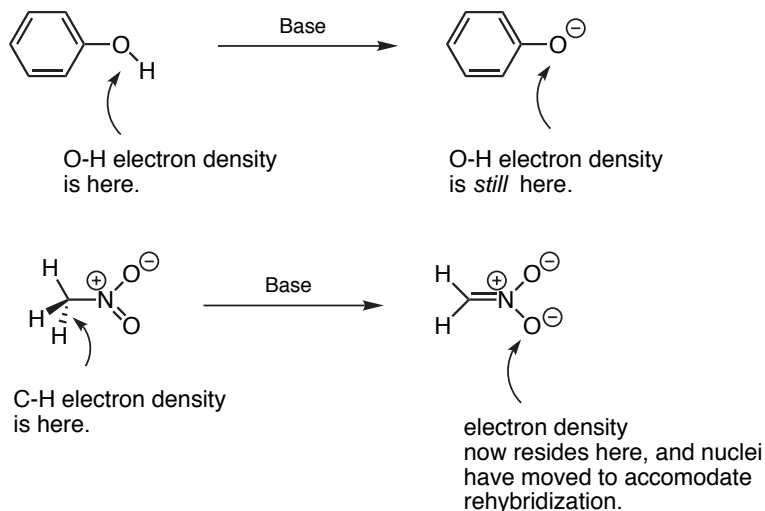
Observation: The thermodynamic acidities of phenol and nitromethane are both approximately 10; however, using a common base, phenol is deprotonated 10^{+6} times as fast.



Proton transfers from C-H Bonds are slow.

Why???

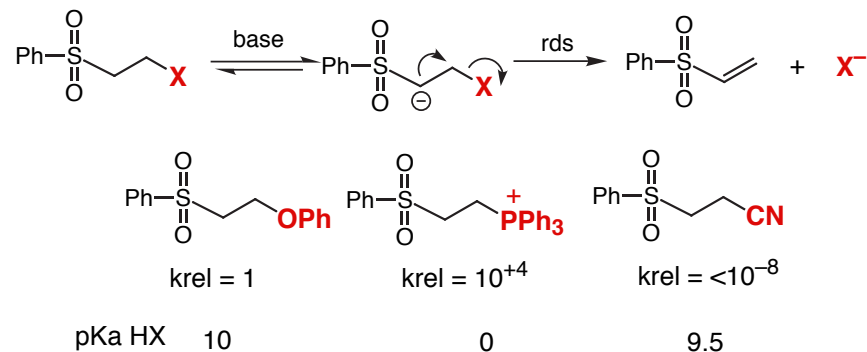
Most carbon acids are stabilized by resonance. Hence significant structural reorganization must accompany deprotonation.



The greater the structural reorganization during deprotonation, the lower the kinetic acidity

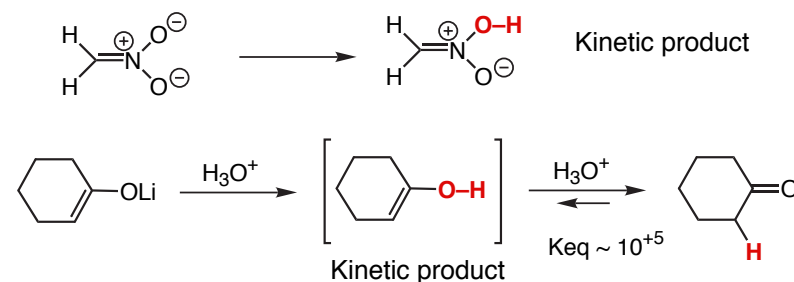
Kinetic Acidity vs. Leaving Group Ability: E1cb Elimination Reactions

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

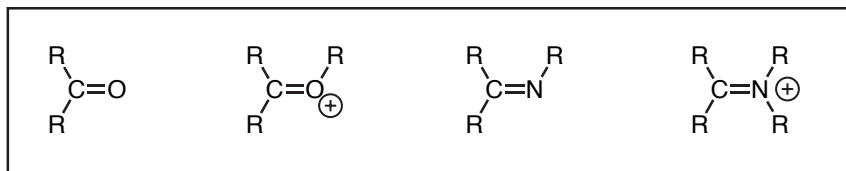
<http://www.courses.fas.harvard.edu/~chem206/>

Chemistry 206

Advanced Organic Chemistry

Lecture Number 20

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

D. A. Evans

Friday,
October 31, 2003

Additional Reading Material Provided

Additions to 5- & 6-Membered oxocarbenium Ions:

Woerpel et al. *JACS* **1999**, 121, 12208 (**Handout**)

Woerpel et al. *JACS* **2000**, 122, 168 (**Handout**)

Woerpel et al. *JACS* **2003**, 125, ASAP (**Handout**)

"From Crystal Statics to Chemical Dynamics", *Accounts Chem. Research* **1983**, 16, 153. (**Electronic Handout**)

"Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein *Nouv. J. Chem.* **1977**, 1, 61-70. (**Handout**)

"Around and Beyond Cram's Rule" A. Mengel & O. Reiser, *Chem Rev.* 1999, 99, 1191-1223 (**Electronic Handout**)

■ 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. (**Electronic Handout**)

"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.

Chemistry Reviews Issue on Diastereoselection in C=O Addition

Chem Rev. **1999**, *99*, (5), 1069-1480

Mengel, A. and O. Reiser, "Around and beyond Cram's rule." *Chem. Rev.* **1999**, 1191-1223.

Reetz, M. T., "Synthesis and diastereoselective reactions of N,N-dibenzylamino aldehydes and related compounds." *Chem. Rev.* **1999**, 1121-1162.

Dannenberg, J. J., "Using perturbation and frontier molecular orbital theory to predict diastereofacial selectivity." *Chem. Rev.* **1999**, 1225-1241.

Tomoda, S., "The exterior frontier orbital extension model." *Chem. Rev.* **1999**, 1243-1263.

Cieplak, A. S., "Inductive and resonance effects of substituents on pi-face selection." *Chem. Rev.* **1999**, 1265-1336.

Ohwada, T., "Orbital-controlled stereoselections in sterically unbiased cyclic systems." *Chem. Rev.* **1999**, 1337-1375.

Gung, B. W., "Structure distortions in heteroatom-substituted cyclohexanones, adamantanones, and adamantanes: Origin of diastereofacial selectivity." *Chem. Rev.* **1999**, 1377-1386.

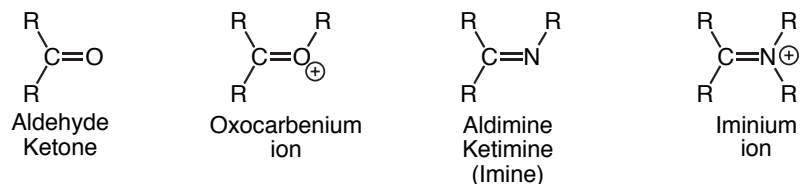
Kaselj, M., W. S. Chung, et al., "Face selection in addition and elimination in sterically unbiased systems." *Chem. Rev.* **1999**, 1387-1413.

Adcock, W. and N. A. Trout, "Nature of the electronic factor governing diastereofacial selectivity in some reactions of rigid saturated model substrates." *Chem. Rev.* **1999**, 1415-1435.

Mehta, G. and J. Chandrasekhar, "Electronic control of facial selection in additions to sterically unbiased ketones and olefins." *Chem. Rev.* **1999**, 1437-1467.

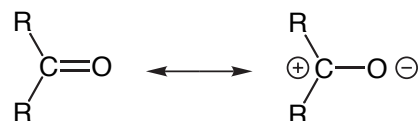
Wipf, P. and J. K. Jung, "Nucleophilic additions to 4,4-disubstituted 2,5-cyclohexadienones: Can dipole effects control facial selectivity?." *Chem. Rev.* **1999**, 1469-1480.

■ The Set of Functional Groups:

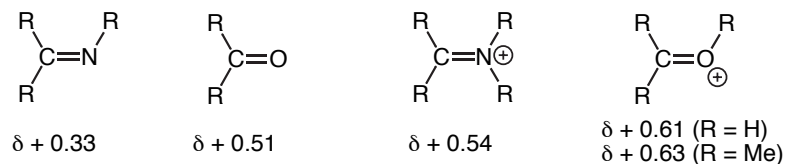


These functional groups are among the most versatile sources of electrophilic carbon in both synthesis and biosynthesis. The ensuing discussion is aimed at providing a more advanced discussion of this topic.

■ C=X Polarization

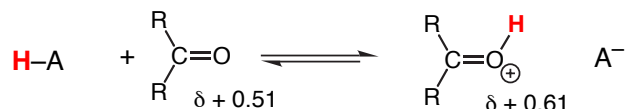


Partial Charge: As the familiar polar resonance structure above indicates, the carbonyl carbon supports a partial positive charge due to the polarization of the sigma and pi system by the more electronegative heteroatom. The partial charges for this family of functional groups derived from molecular orbital calculations (ab initio, 3-21(G)*, HF) are illustrated below:

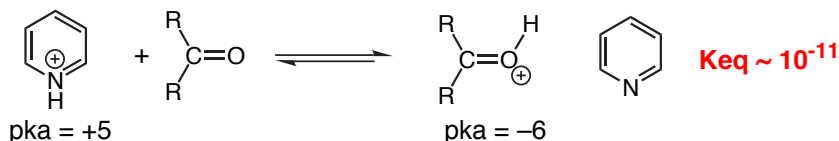


electrophilic reactivity →

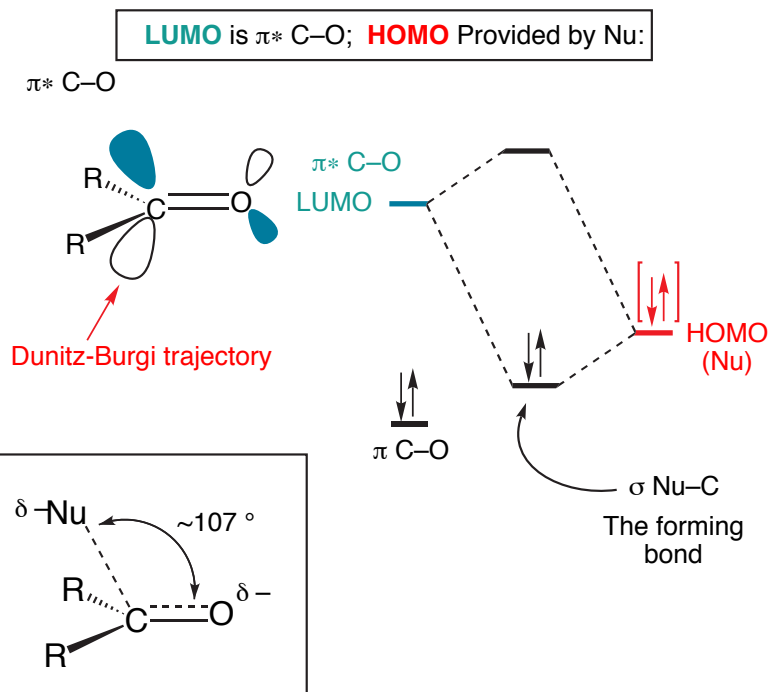
■ Proton Activation of C=X Functional groups



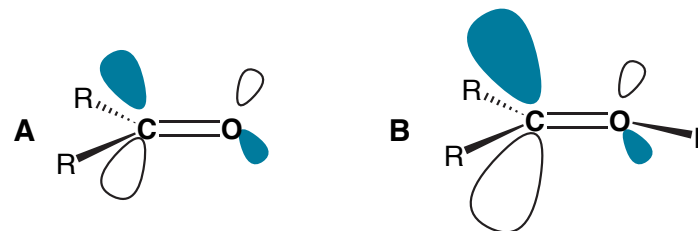
The electrophilic potential of the C=O FG may be greatly increased by either Lewis acid coordination or by protonation. The magnitude of this increase in reactivity is $\sim 10^{+6}$. Among the weakest Bronsted acids that may be used for C=O activation (ketalization) is pyridinium ion (pKa = 5). Hence, the Keq below, while quite low, is still functional.



Stereoelectronic Considerations for C=O Addition



■ What about C=O vs C=O-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

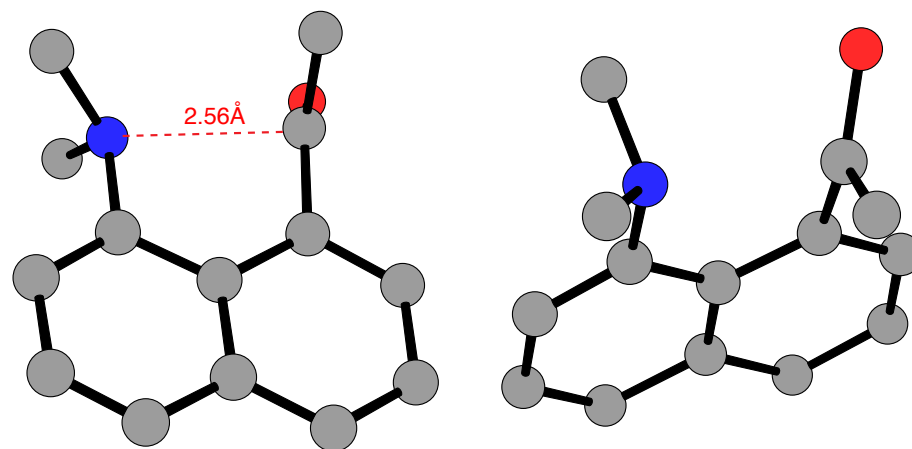
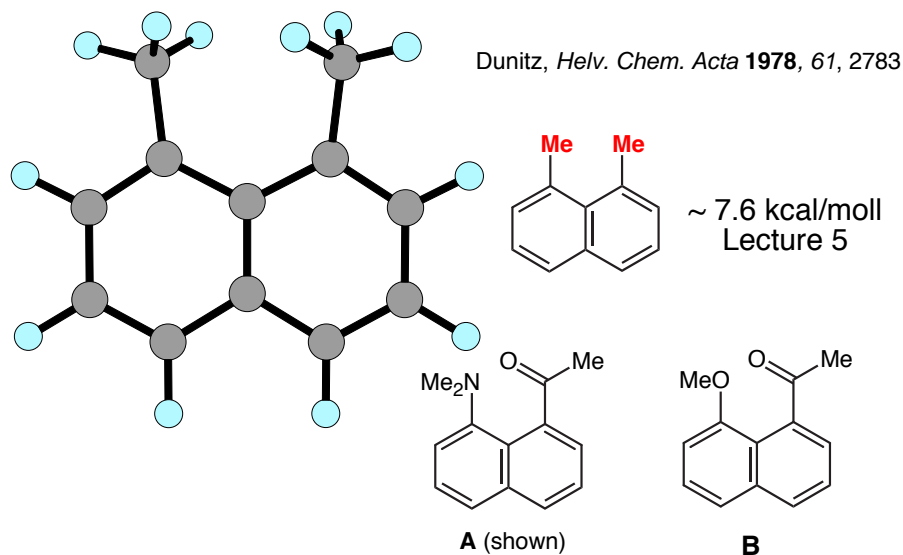
"From Crystal Statics to Chemical Dynamics", *Accounts Chem. Research* **1983**, *16*, 153.

"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

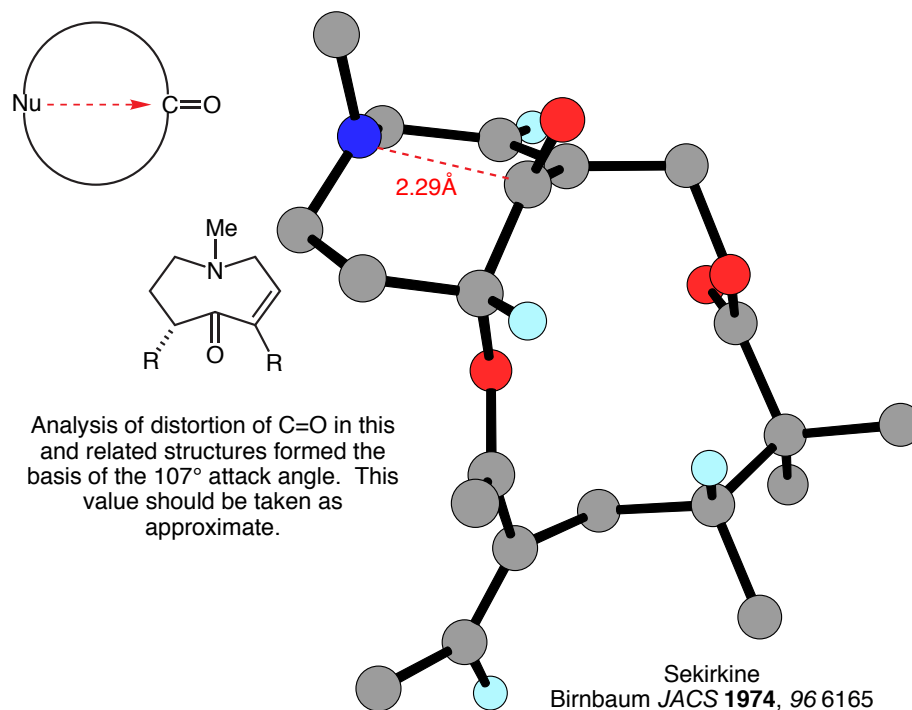
A series of organic structures containing both C=O and Nu FG's disposed in a geometry for mutual interaction were designed. These structures positioned the interacting FGs an increasingly closer distances. The X-ray structures of these structures were determined to ascertain the direction of C=O distortion. 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.



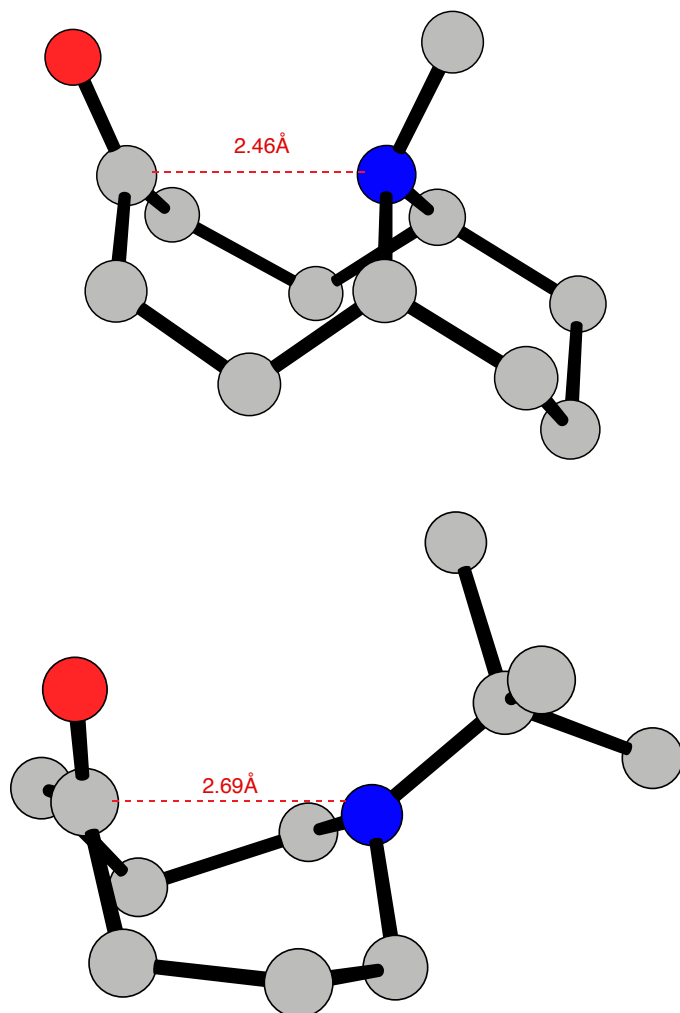
In this structure (A), at 2.56Å the C=O is starting to pyramidalize

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.

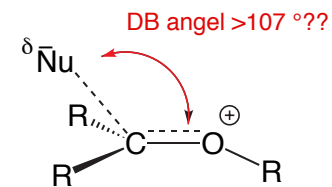
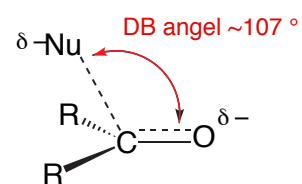
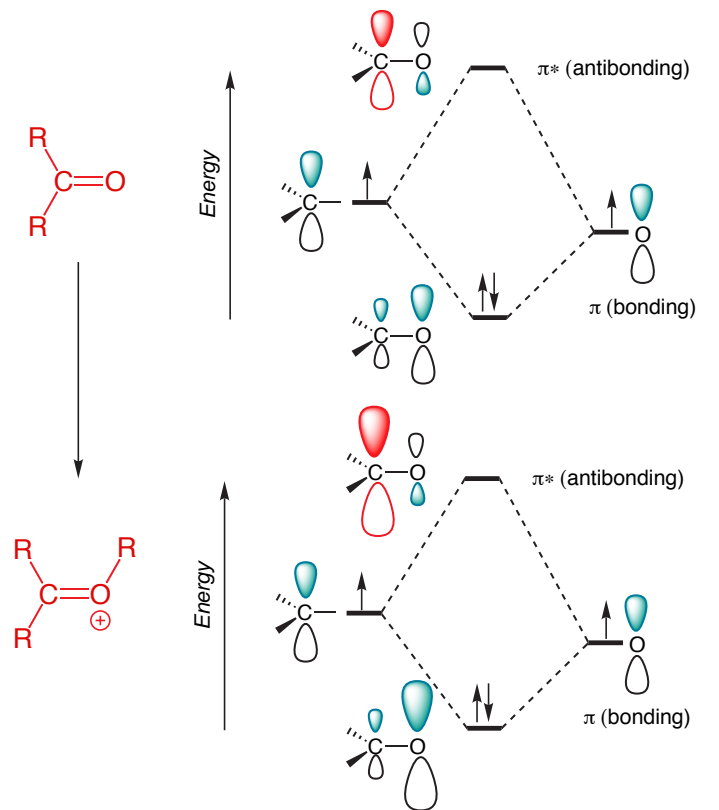
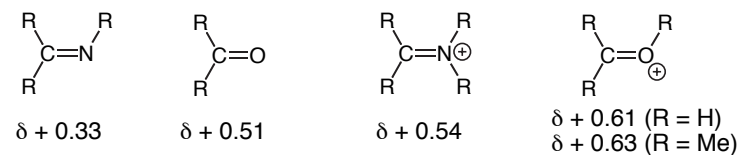


Cyclic aminoketones. Medium-ring ketones of various ring sizes were analyzed for the interaction of amine an C=O FGs. Two examples are shown below.

Sekirine
Birbaum JACS 1974, 96 6165



Should these crystallographic data be relevant to the addition to complexed C=O & Iminium ions?

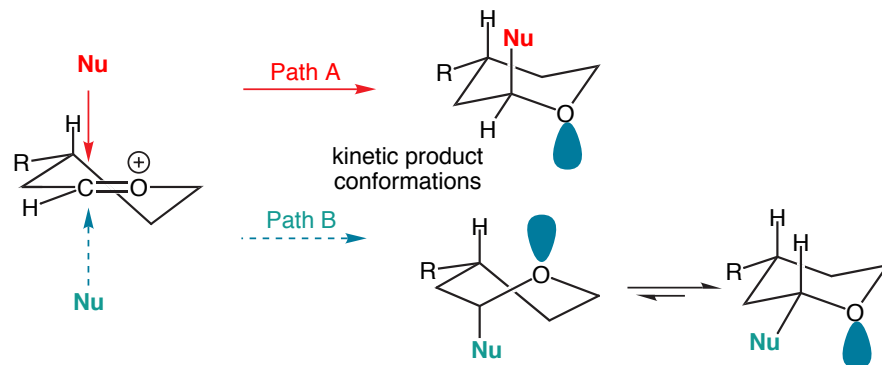


■ Pivotal Articles

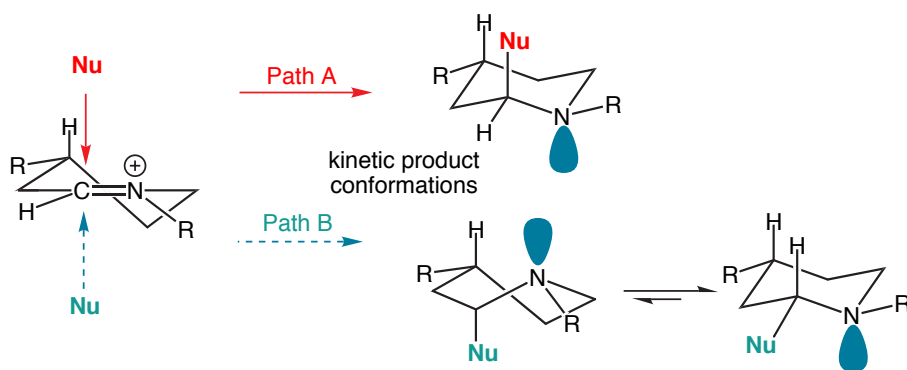
R. V. Stevens in
 "Strategies and Tactics in Organic Synthesis", Vol. 1.
On the Stereochemistry of Nucleophilic Additions to Tetrahydropyridinium Salts: a Powerful Heuristic Principle for the Stereorationale Design of Alkaloid Synthesis.;
 Lindberg, T., Ed.; Academic Press, 1984;

Eliel et al. , *JACS* **1969**, *91*, 536
 Kishi et al. , *JACS* **1982**, *104*, 4976-8

■ The Proposal for Oxo-carbenium Ions (Eliel, Kishi)

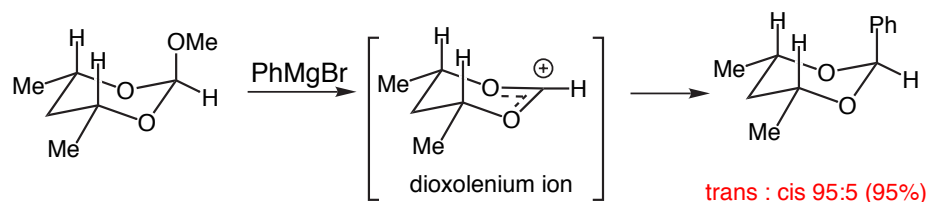


■ The Proposal for Iminium Ions (Stevens)



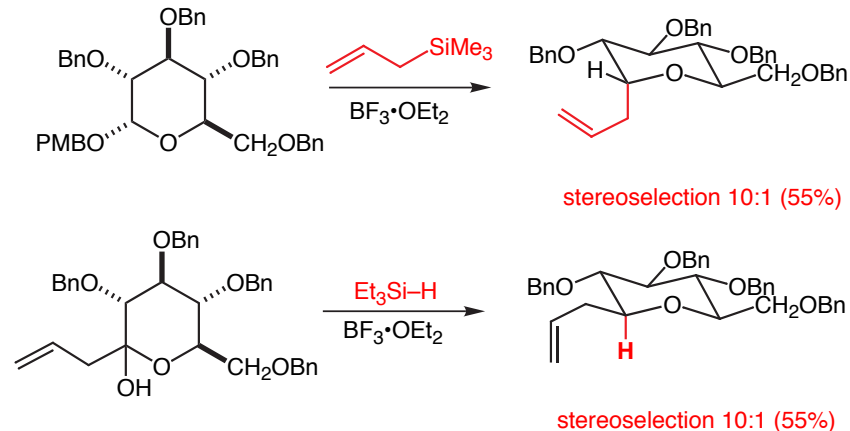
It was proposed that chair-axial addition would be preferred as a consequence of the intervention of a transition state anomeric effect (Path A). Attack through Path B would necessitate the generation of the twist-boat kinetic product conformation thus destabilizing attack from the equatorial diastereoface. 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



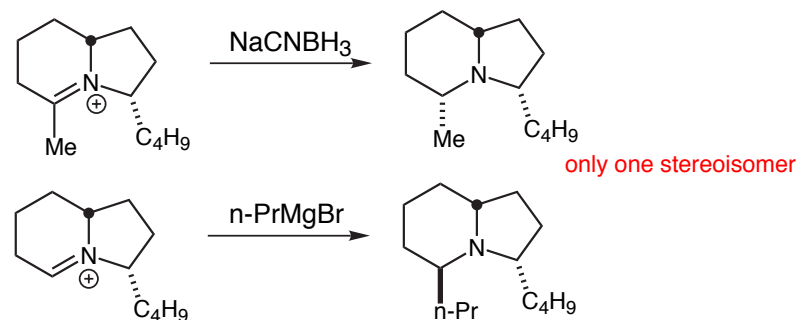
Eliel was the first to attribute stereoelectronic factors to the addition of nucleophiles to cyclic oxo-carbenium ions.

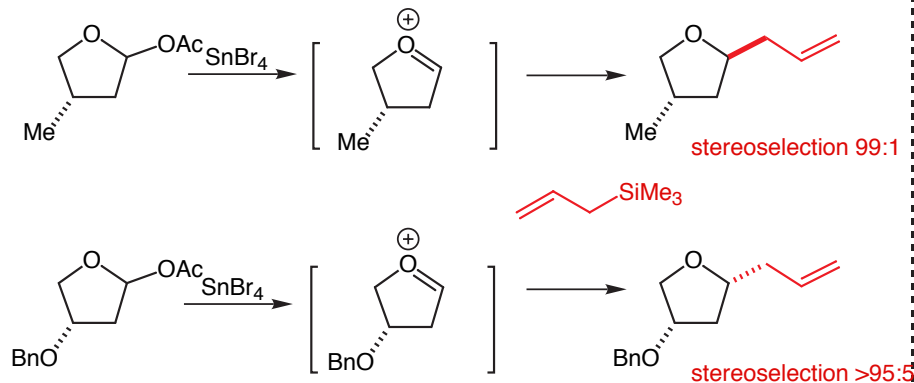
■ Kishi Examples; *JACS* 1982, 104, 4976-8



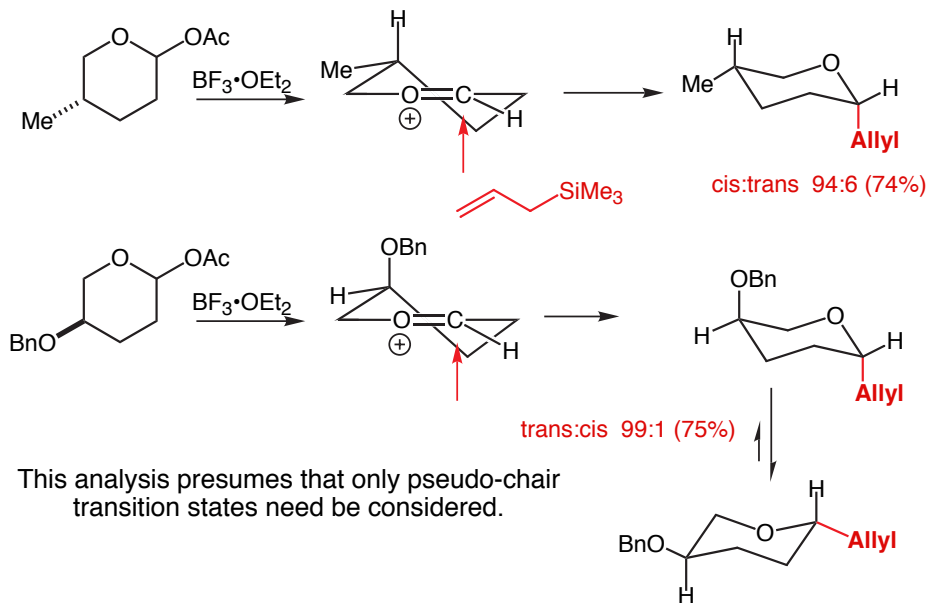
Chair-axial attack on oxo-carbenium ion occurs for both carbon and hydride nucleophiles

■ Iminium Ions (Stevens) cited reference



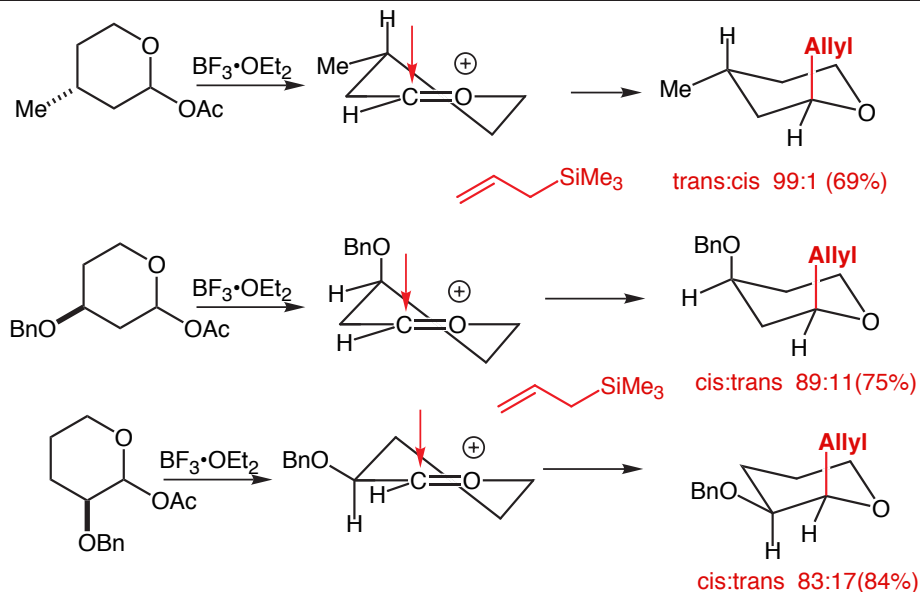
5-Membered oxocarbenium ions: Woerpel et al. *JACS* 1999, 121, 12208.

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.

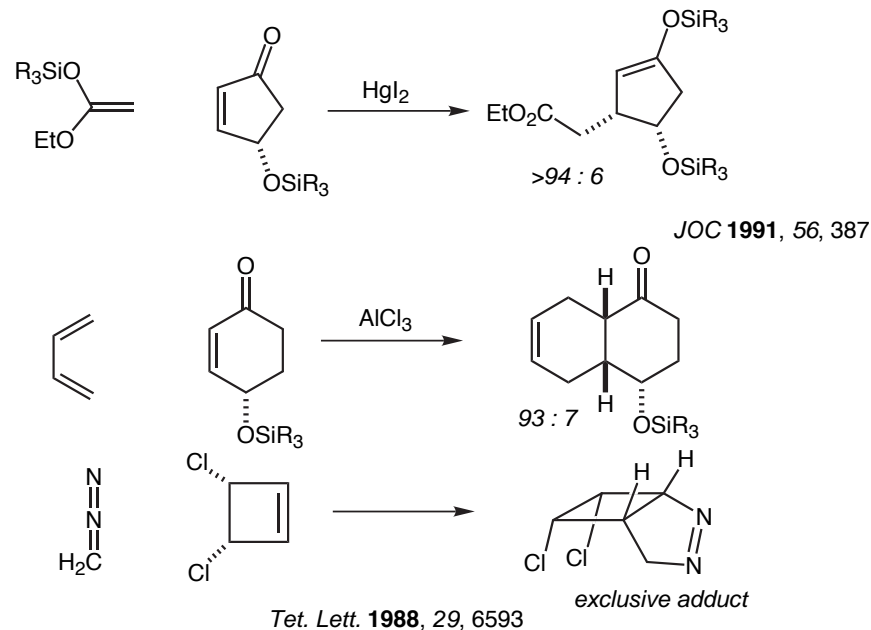
This analysis presumes that only pseudo-chair transition states need be considered.

Woerpel's model states that axial attack from the most stable chair conformer predicts the major product.

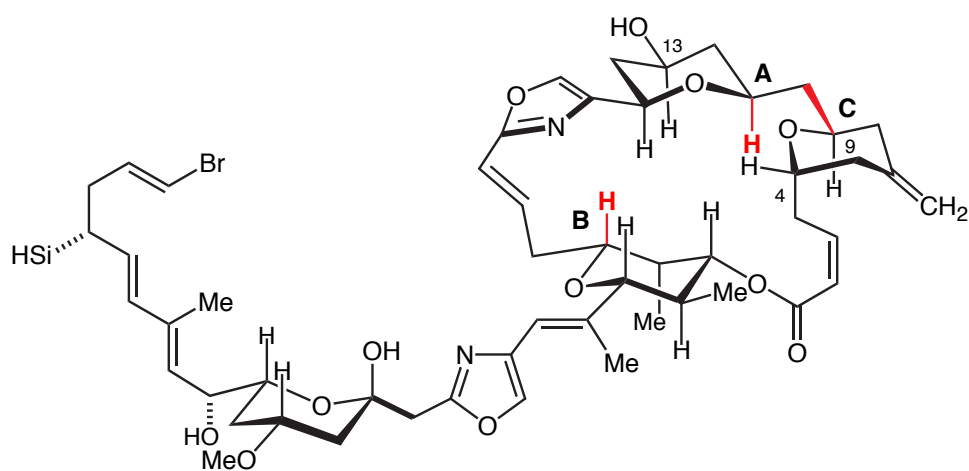


These cases provide dramatic evidence for the importance of electrostatic effects in controlling face selectivity.

Are the preceding addition reactions somehow related to the apparently contrasteric reactions shown below??

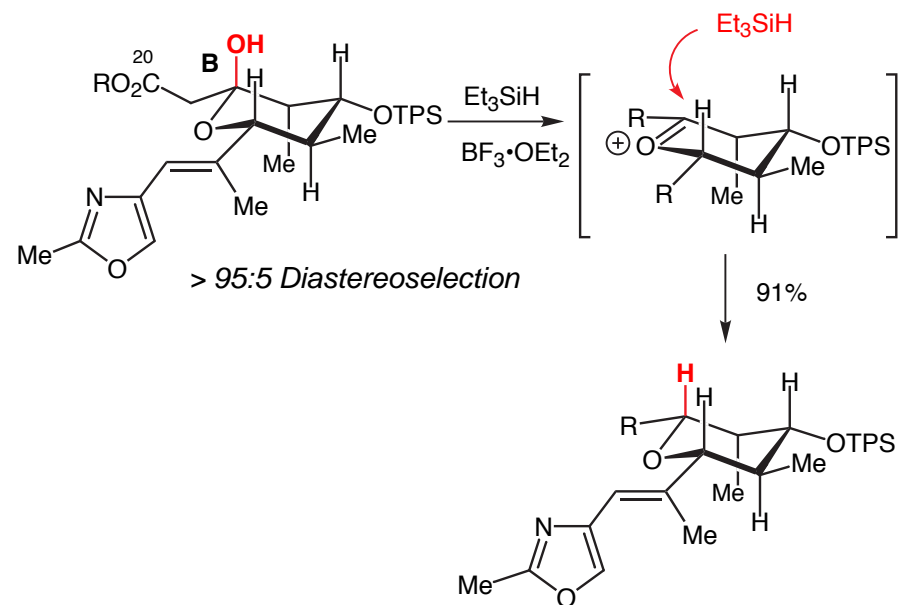


Phorboxazole B

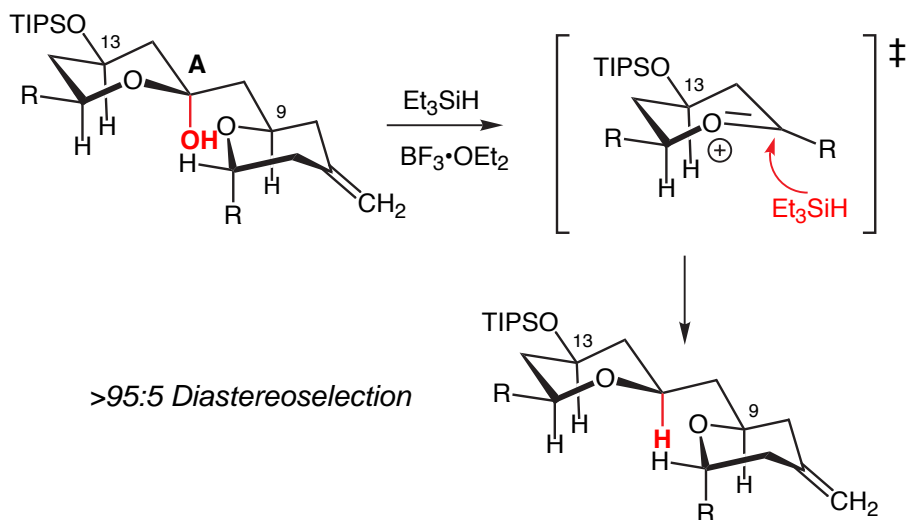
Evans, Fitch, Smith, Cee, *JACS* **2000**, *122*, 10033

Stereochemical analogies:
Kishi et. al.: *JACS* **1982**, *104*, 4976-8

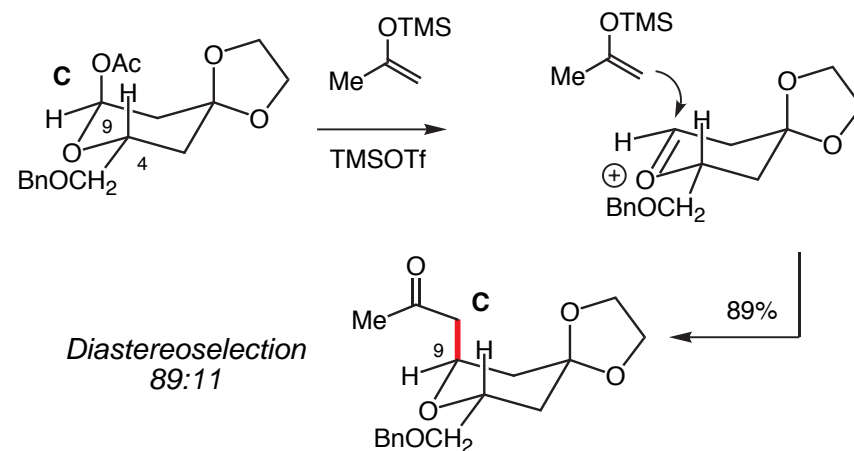
B: The C-22 Reduction



A: The C-11 Reduction

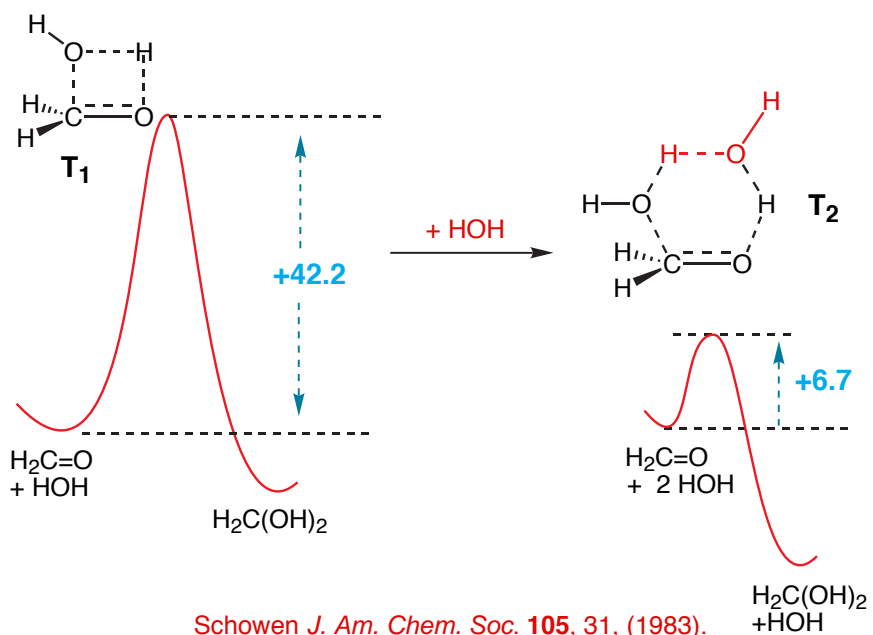


C: The C-9 C-C Bond Construction

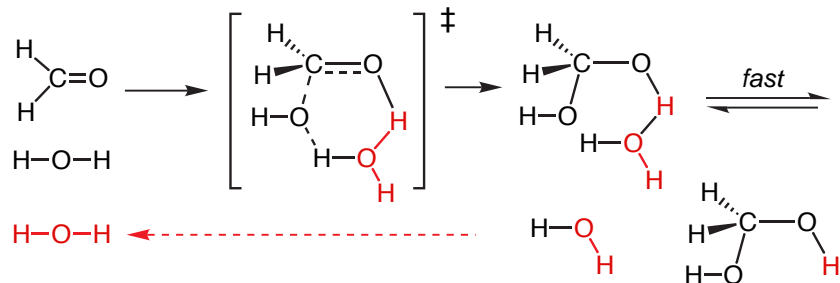


4- vs 6-Membered Transition Structures for C=O Addition

Consider carbonyl hydration:

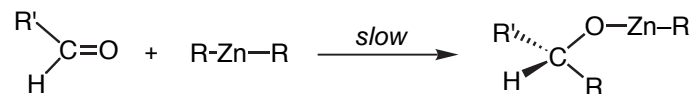


Overall Process: The value of the proton shuttle



Transition structure $T_2 \sim 40$ kcal/mol more stable than transition structure T_1 .

Do these results relate to "real" reactions? Yes!

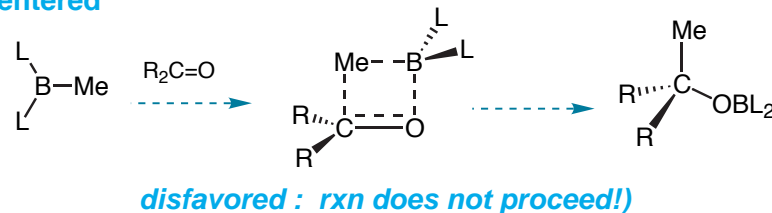


Observation: catalytic amounts of ZnI_2 dramatically catalyze addition process.

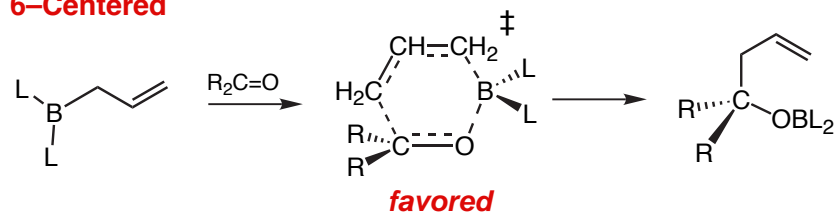


4- Versus 6-Center Transition States for Boron

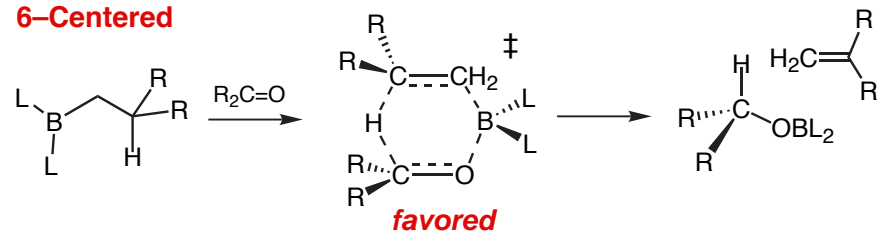
4-Centered



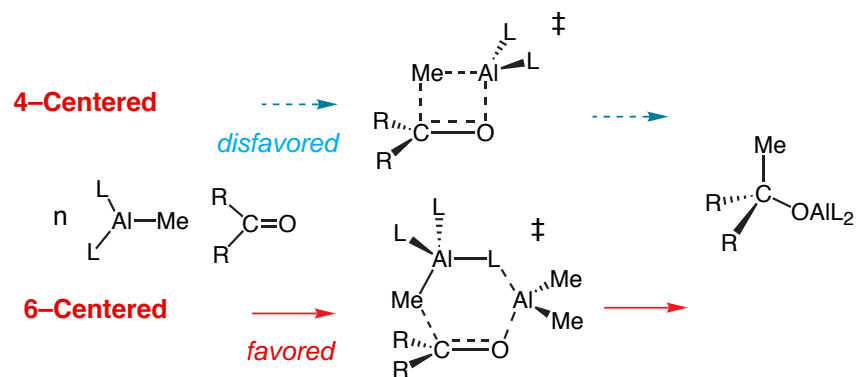
6-Centered



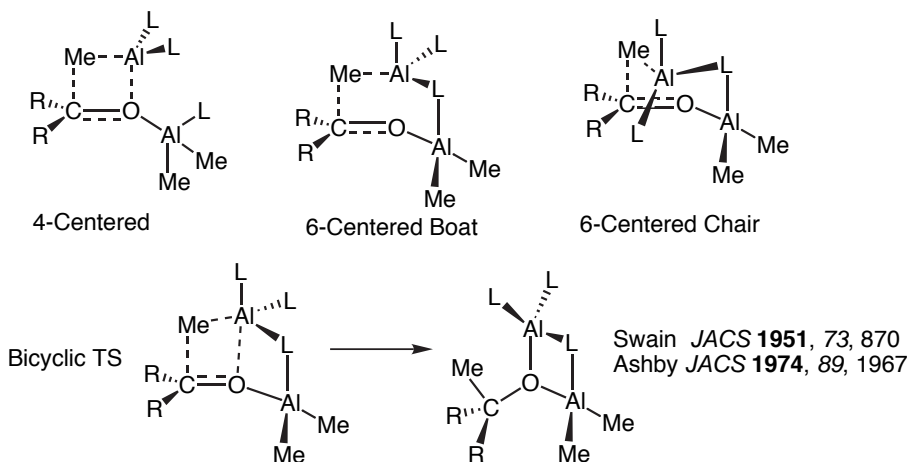
6-Centered



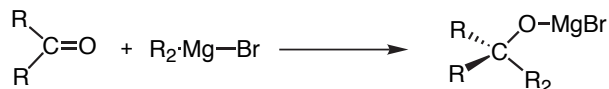
Carbonyl Addition: 4- Versus 6-Center Transition States for Aluminum



The Bimetallic Transition States are preferred

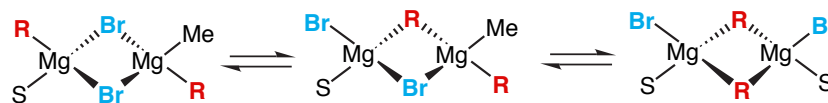


Grignard Reagents:



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.

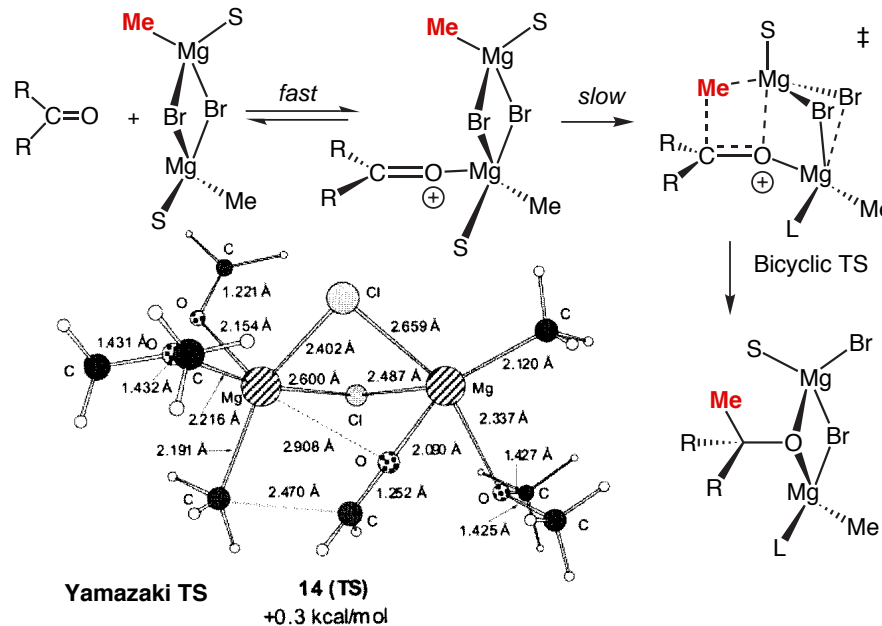
The Schlenk Equilibrium



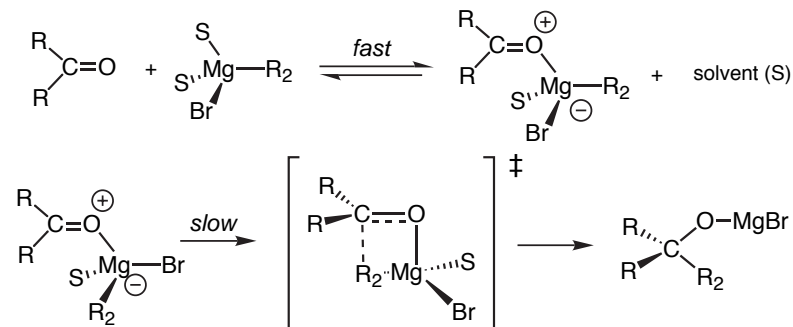
Solution structure of R-MgBr is in dynamic equilibrium through Schlenk equilibrium

The Bimetallic (Binuclear) Mechanism for C=O Addition

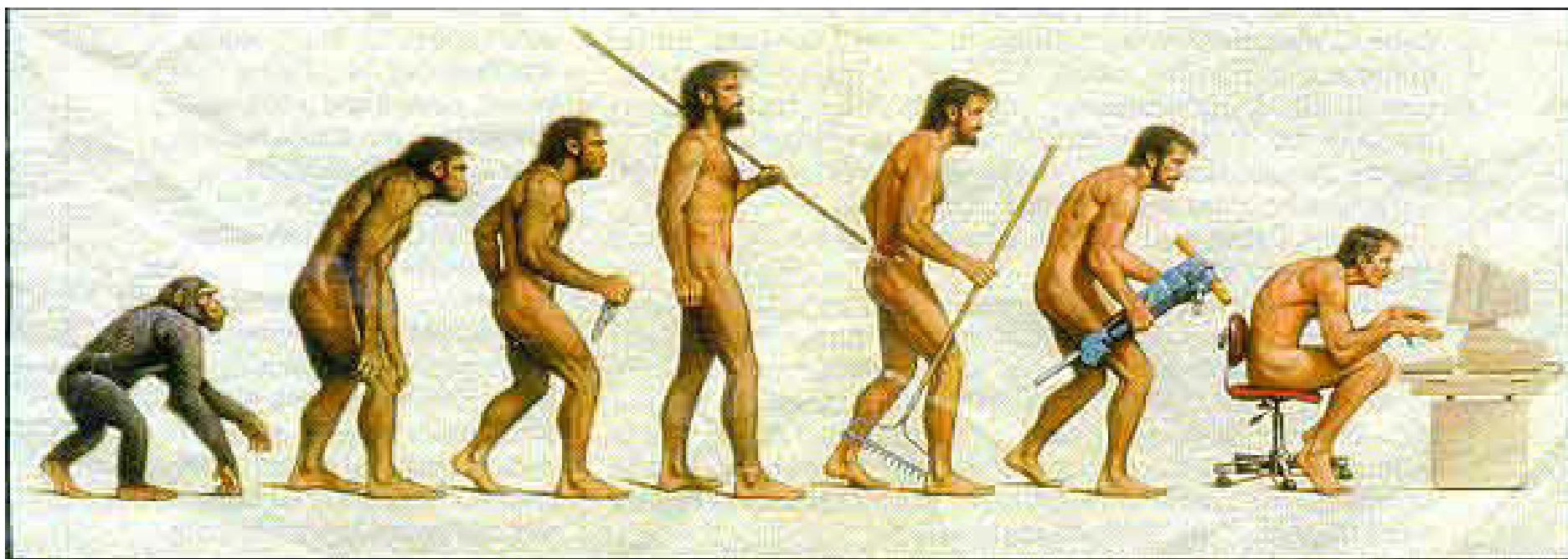
Recent theoretical study: Yamazaki & Yambe, *J. Org. Chem.* **2002**, 67, 9346



The Mononuclear Mechanism is now in disfavor



Mengel, A. and O. Reiser, "Around and Beyond Cram's Rule."
Chem. Rev. **1999**, 1191-1223



Fischer

Cram

Cornforth

Felkin

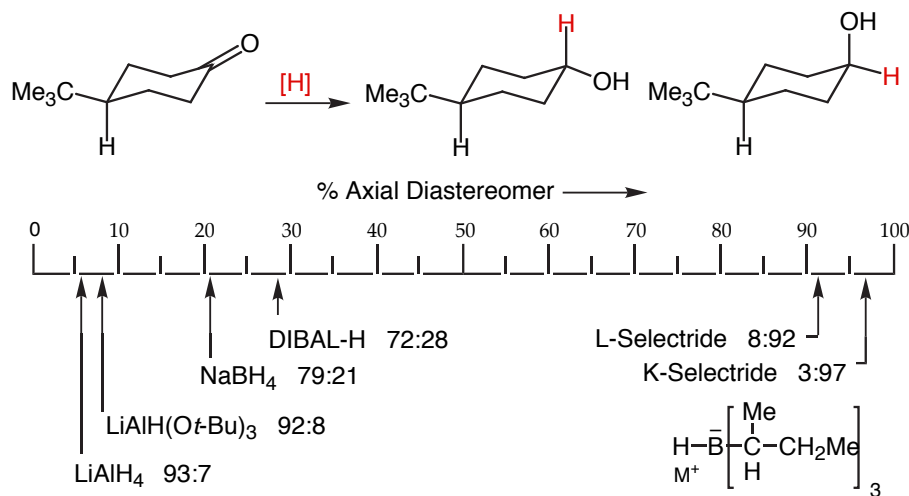
Anh/Eisenstein

Cieplak

Tomoda

Humor provided by Sarah Siska

Product Development & Steric Approach Control:

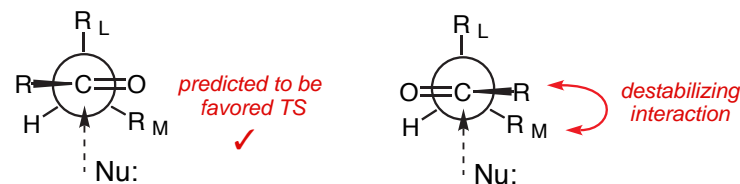
Dauben, *JACS* **1956**, 78, 2579

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

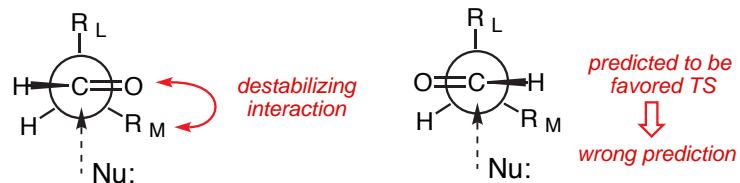
Assumption: Hindered reagents react through more highly developed transition states than unhindered reagents

Assumptions in Felkin Model:

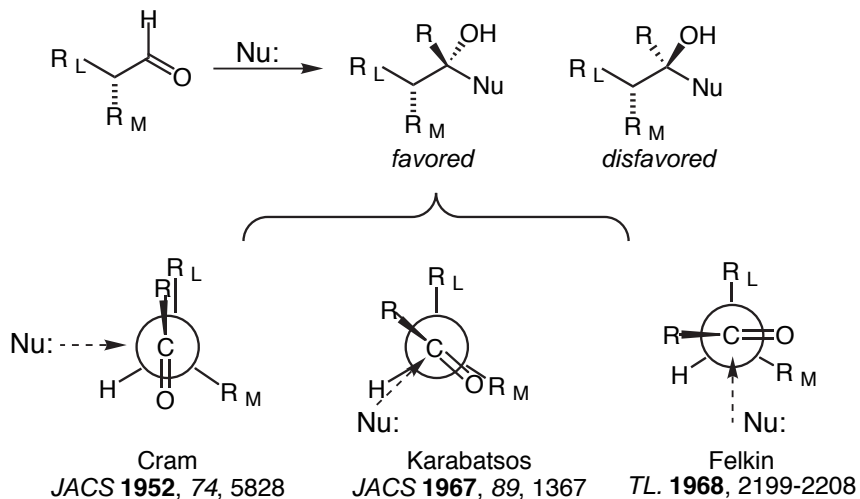
- Transition states are all reactant-like rather than product-like.
- Torsional strain considerations are dominant. Staggered TS conformations preferred
- The principal steric interactions are between Nu & R.



The flaw in the Felkin model: A problem with aldehydes!!

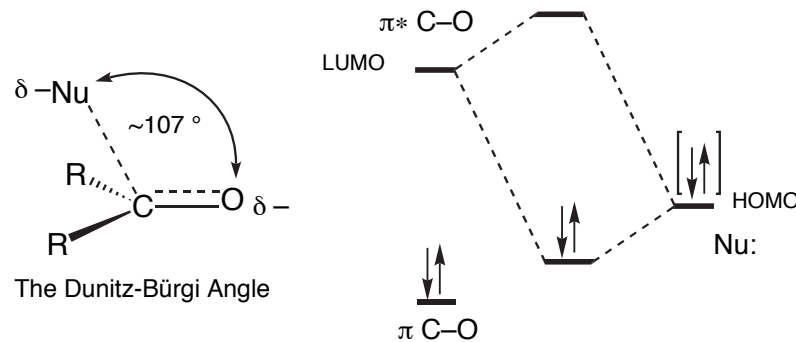


Carbonyl Addition: Evolution of Acyclic Models



Stereoelectronic Effect:

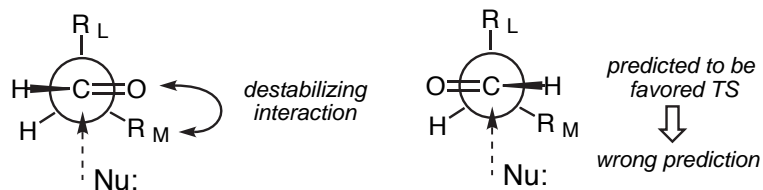
The HOMO-LUMO interaction dictates the following reaction geometry:



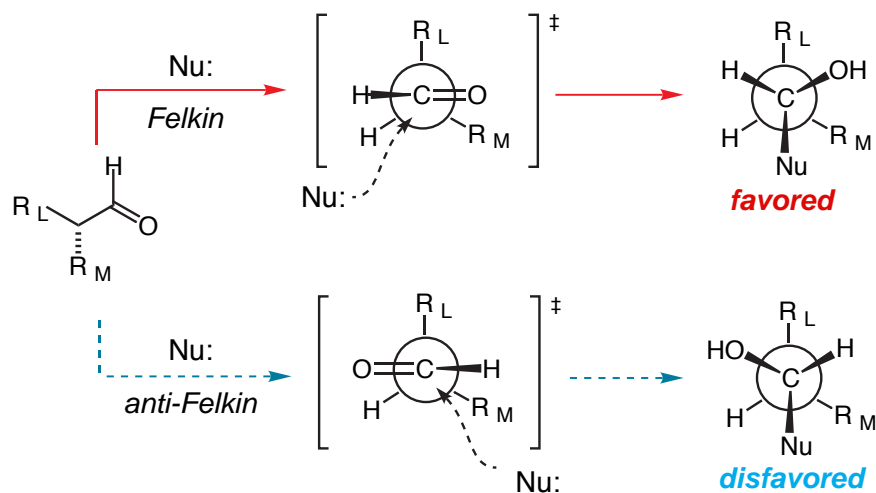
attack angle greater than 90 °; estimates place it in the 100–110 ° range

Burgi, Dunitz, *Acc. Chem. Res.* **1983**, 16, 153-161

The flaw in the Felkin model: A problem with aldehydes!!



Anh & Eisenstein *Nouvea J. Chim.* **1977**, 1, 61-70
 Anh *Topics in Current Chemistry.* **1980**, No 88, 146-162



New Additions to Felkin Model:

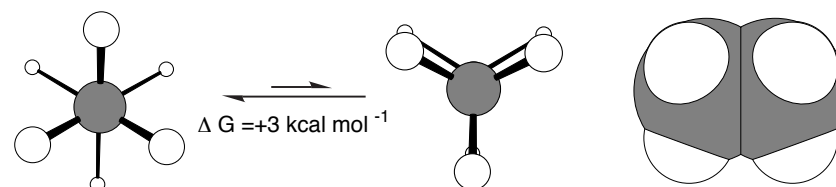
- Dunitz-Bürgi C=O–Nu orientation applied to Felkin model.
- The antiperiplanar effect: Hyperconjugative interactions between C-R_L which will lower π* C=O will stabilize the transition state.

Theoretical Support for Staggered Transition states (Lecture 7)

(Read this) Houk, *JACS* **1982**, 104, 7162-6
 (Read this) Houk, *Science* **1986**, 231, 1108-17

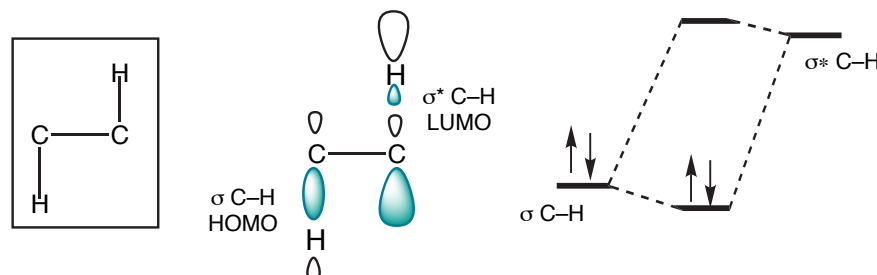
Houk: "The tendency for the staggering of partially formed vicinal bonds is greater than for fully formed bonds"
Lecture-7

Lets begin with ground state effects: Ethane Rotational Barrier

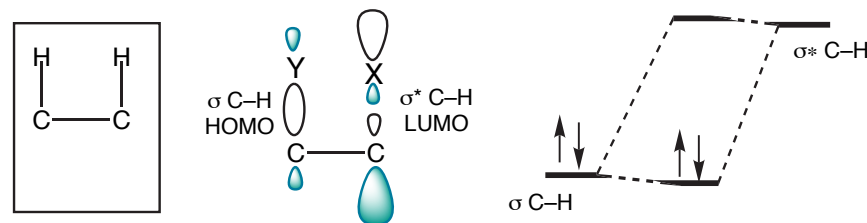


One explanation for the rotational barrier in ethane is that better overlap is achieved in the staggered conformation than in the eclipsed conformation.

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



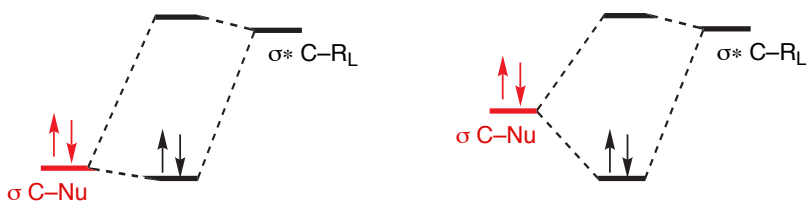
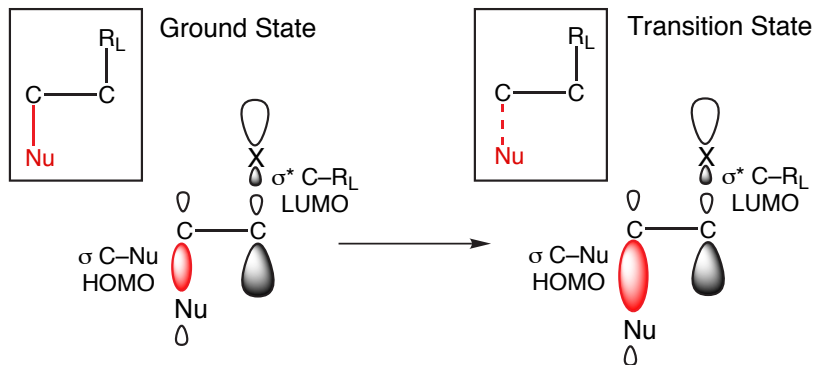
In the eclipsed conformation there are 3 syn-periplanar C–H Bonds



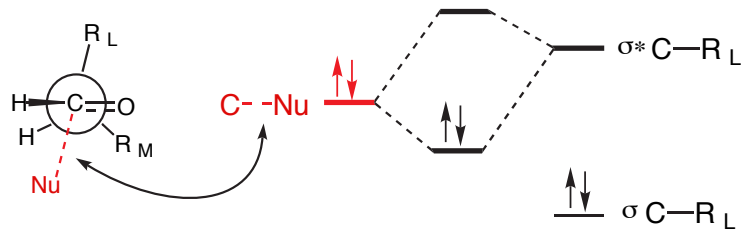
Following this argument one might conclude that:

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

The tendency for the staggering of partially formed vicinal bonds is greater than for fully formed bonds



Best acceptor σ^* orbital is oriented anti periplanar to forming bond



Theoretical support:

Padden-Row, *Chem. Commun.* **1990**, 456; *ibid* **1991**, 327

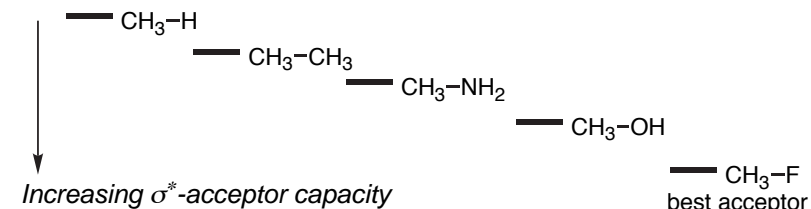
Houk, *J. Am. Chem. Soc.* **1991**, 113, 5018

Frenking & Reetz, *Tetrahedron* **1991**, 47, 8091

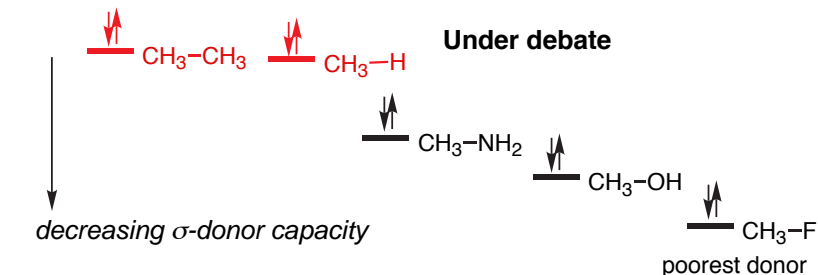
Hierarchy of Donor & Acceptor States

The following trends are made on the basis of comparing the bonding and antibonding states for the molecule CH₃-X where X = C, N, O, F, and H.

σ -anti-bonding States: (C-X)

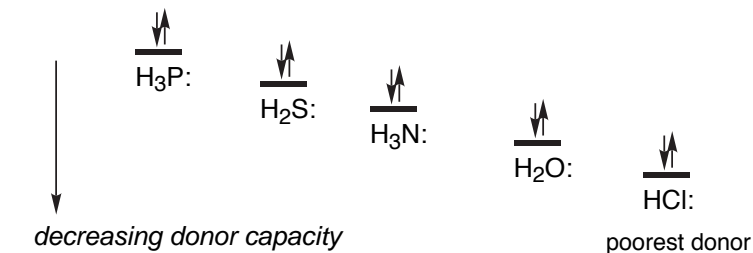


σ -bonding States: (C-X)

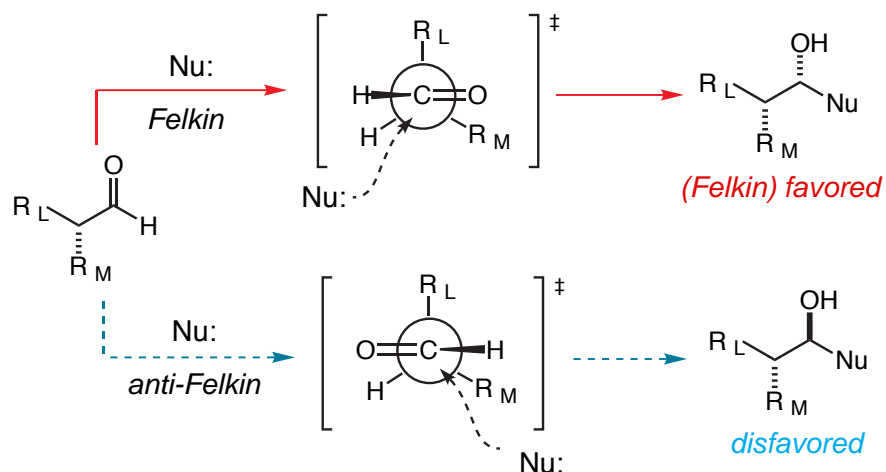


The following are trends for the energy levels of *nonbonding states* of several common molecules. The trend was established by photoelectron spectroscopy.

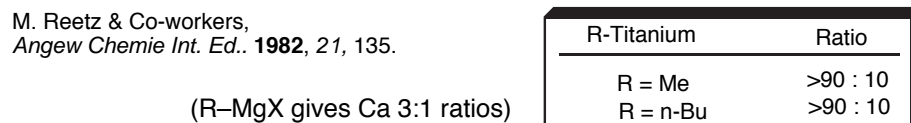
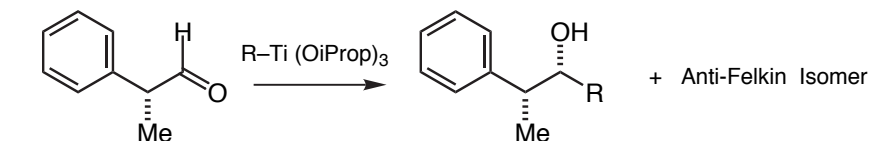
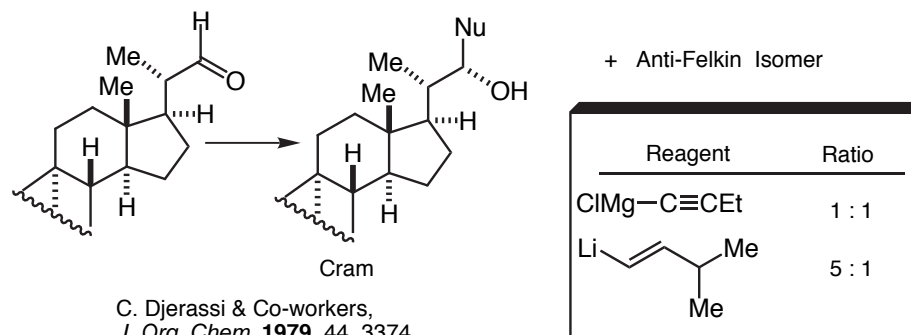
Nonbonding States



Addition of Enolate & Enol Nucleophiles

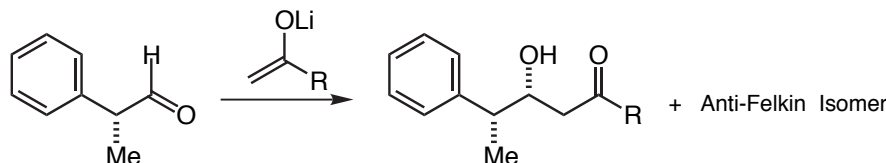


■ This trend carries over to organometallic reagents as well



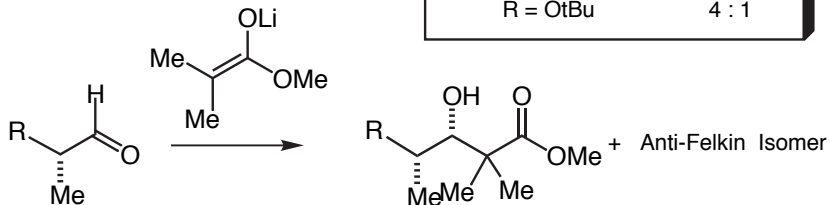
Trend-1:

For Li enolates, increased steric hindrance at enolate carbon results in enhanced selectivity



L. Flippin & Co-workers,
Tetrahedron Lett. **1985**, 26, 973.

Enolate (R)	Ratio
R = Me	3 : 1
R = OtBu	4 : 1

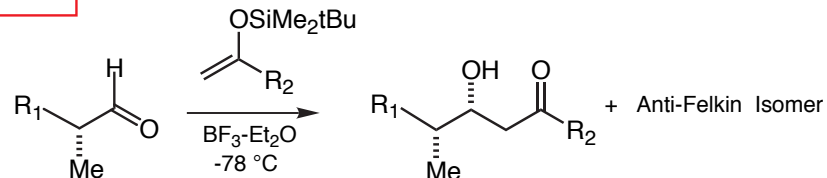


L. Flippin & Co-workers,
Tetrahedron Lett. **1985**, 26, 973.

Ketone (R)	Ratio
R = Ph	>200 : 1
R = c-C ₆ H ₁₁	9 : 1

Trend-2:

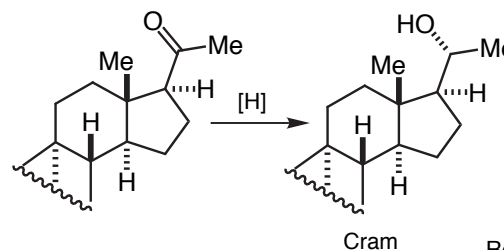
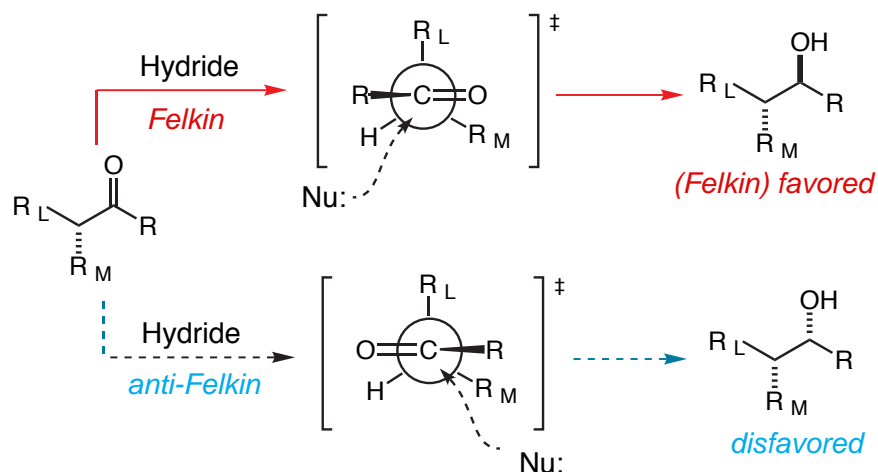
Lewis acid catalyzed reactions are more diastereoselective



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

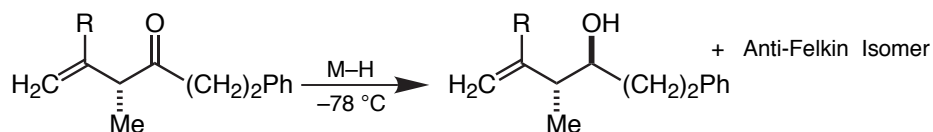


+ Anti-Felkin Isomer

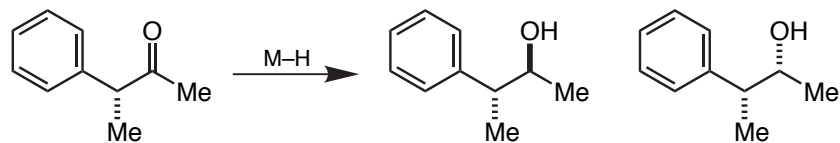
M. M. Midland & Co-workers,
J. Am. Chem. Soc. **1983**, 105, 3725.

Reagent	Ratio	TS [‡]
Li ⁺ H-B ⁻ (sec-Bu) ₃	54 : 1	Felkin
NaBH ₄	5 : 1	Felkin
LiAlH ₄	3 : 1	Felkin
H-B(Sia) ₂	1 : 10	Anti-Felkin

Note: Borane reducing agents do not follow the normal trend

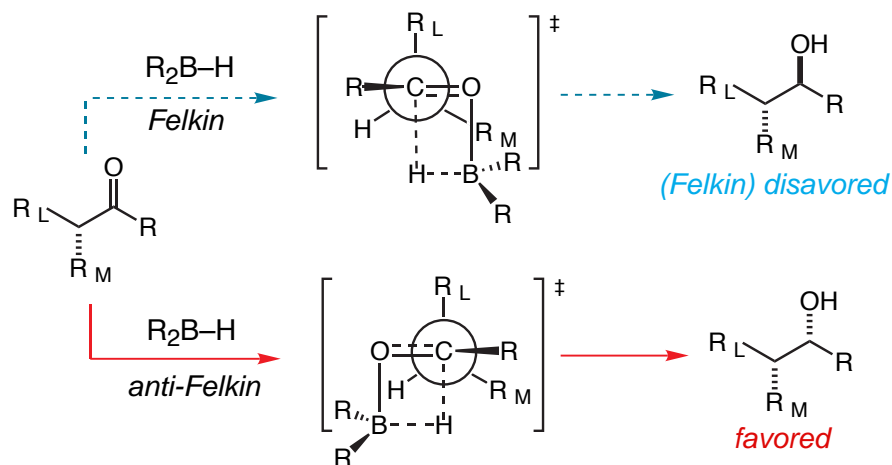
G. Tsuchihashi & Co-workers,
Tetrahedron Lett. **1984**, 25, 2479.

Ketone (R)	Reagent	Ratio
R = H	Li ⁺ H-B ⁻ (sec-Bu) ₃	96 : 4
R = H	DIBAL	47 : 53
R = Me	Li ⁺ H-B ⁻ (sec-Bu) ₃	>99 : 1
R = Me	DIBAL	88 : 12

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

Reagent	Ratio	TS [‡]
Li ⁺ H-B ⁻ (sec-Bu) ₃	22 : 1	Felkin
H-B(Sia) ₂	1 : 4	Anti-Felkin

Transition States for C=O-Borane Reductions

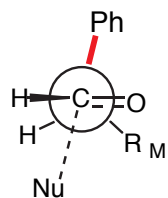
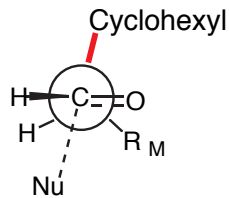
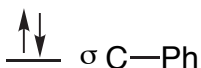
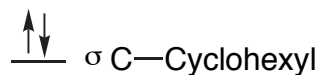
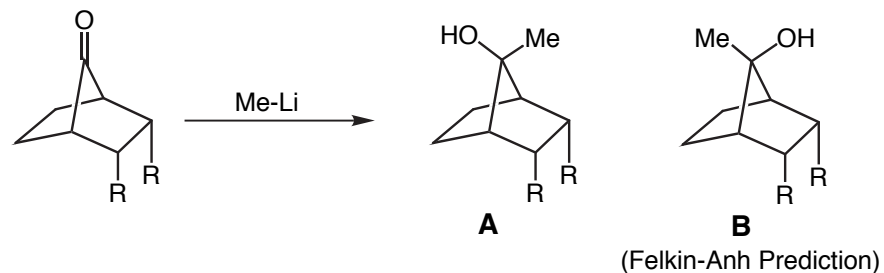


Nonspherical nucleophiles are unreliable in the Felkin Analysis

Exercise: Draw the analogous bis(R₂BH)₂ transition structures

Are there cases not handled by the Anh-Eisenstein Model?

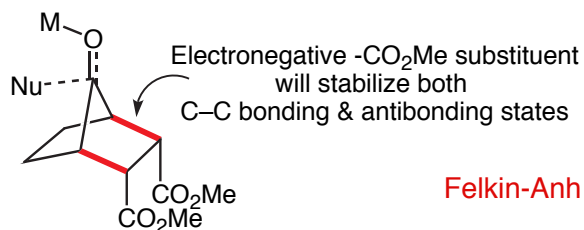
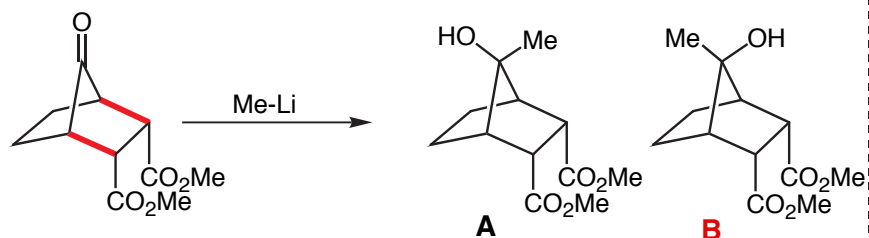
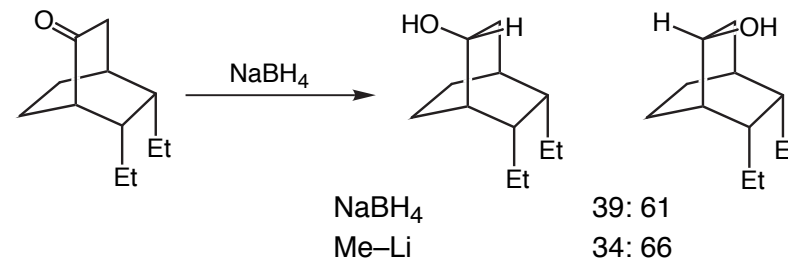
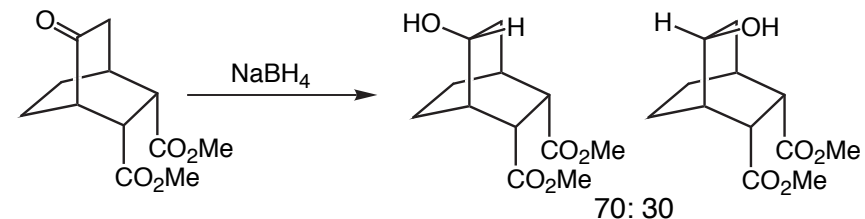
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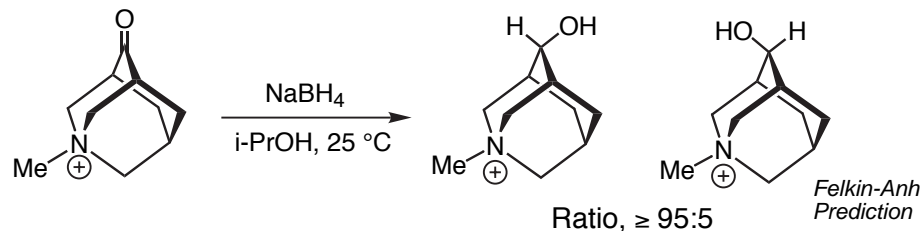
(R) Substituent	A/B Ratio
	>90:10
	34:66
	27:73
	17:83

Felkin-Anh analysis predicts the wrong product!

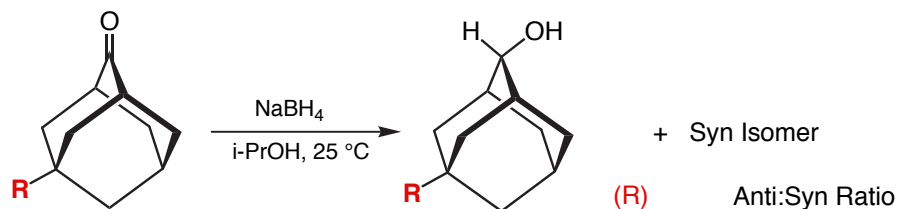
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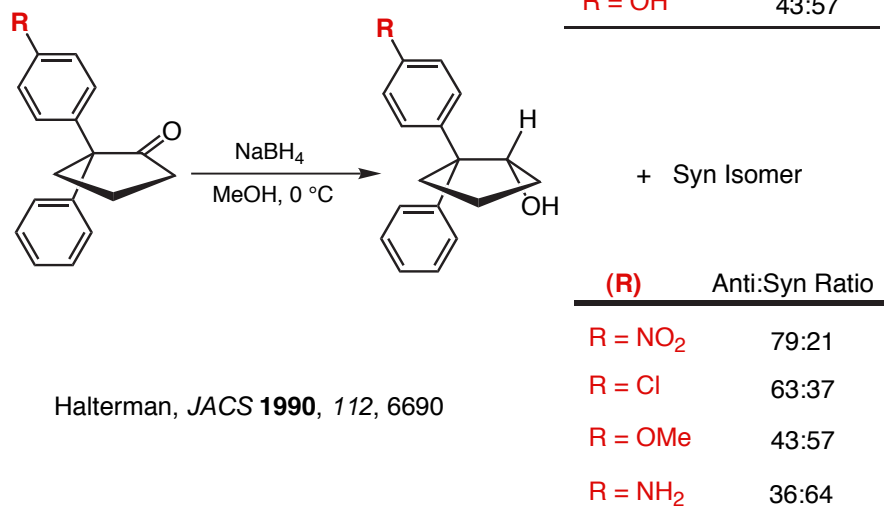
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Case II: The Le Noble Examples Le Noble, *JACS* 1992, 114, 1916

Pyramidally distorted C=O ruled out from inspection of X-ray structures.



Le Noble, *J. Org. Chem.* 1989, 54, 3836



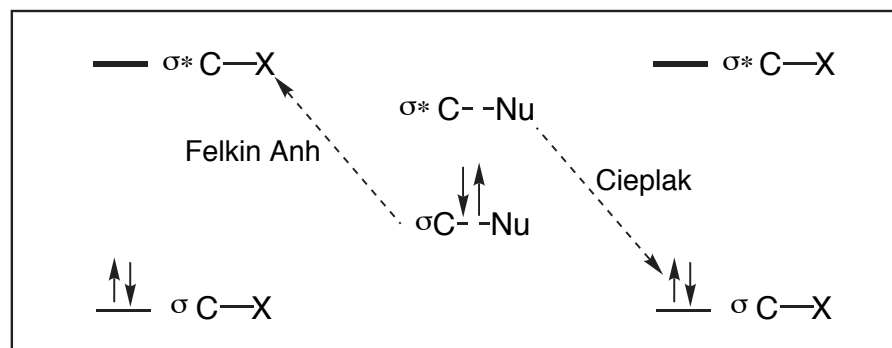
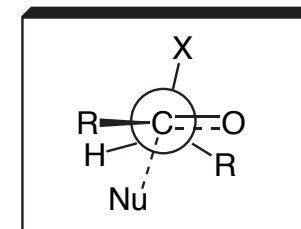
Halterman, *JACS* 1990, 112, 6690

Cieplak Model for C=O Addition

Cieplak, *JACS* 1981, 103, 4540; Cieplak/Johnson, *JACS* 1989, 111, 8447

Point A: TS is stabilized by antiperiplanar allylic bond, but....

Point B: Nature of the stabilizing secondary orbital interactions differ:



Point C: C-X Electron donating ability follows the order:
C-H > C-C > C-N > C-O

(Houk disputes the ordering of C-H, C-C)

Point D: Importance of torsional effects
(Felkin, Anh, Houk, Padden-Row) disputed.

"Structures are stabilized by stabilizing their highest energy filled states. This is one of the 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."

The management

Quotes for the Day

"Every generation of scientists starts where the previous generation left off, and the most advanced discoveries of one age constitute elementary axioms of the next."

Aldous Huxley

"It is a capital mistake to theorise before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts."

(Sherlock Holmes, A Scandal in Bohemia)

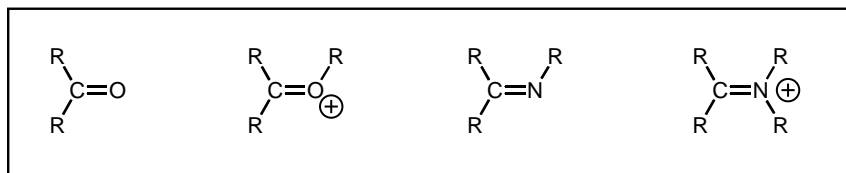
<http://www.courses.fas.harvard.edu/~chem206/>

Chemistry 206

Advanced Organic Chemistry

Lecture Number 21

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

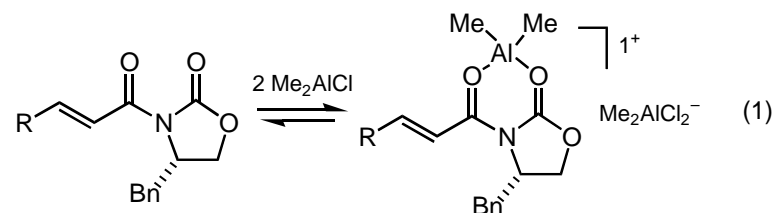
Carey & Sundberg: **Part B**; Chapter 5
Reduction of Carbonyl & Other Functional Groups

D. A. Evans

Monday,
November 3, 2003

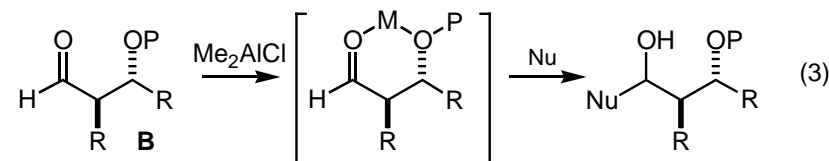
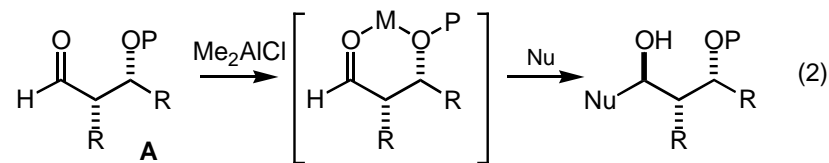
1. "Theoretical Interpretation of 1,2-Asymmetric Induction. The Importance of Antiperiplanarity", N. T. Anh, O. Eisenstein *Nouv. J. Chem.* **1977**, 1, 61-70. (pdf)
2. "Structural, mechanistic, and theoretical aspects of chelation controlled carbonyl addition reactions." Reetz, *Acc. Chem. Res.* **1993** 26: 462. (pdf)
3. "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)
4. "The Exceptional Chelating Ability of Dimethylaluminum Chloride and Methylaluminum Dichloride. The Merged Stereochemical Impact of - and - Stereocenters in Chelate-Controlled Carbonyl Addition Reactions with Enolsilane and Hydride Nucleophiles". Evans, Allison, Yang, Masse, **2001**, 123, 10840-10852. (pdf)

Me₂AlCl is the most powerful chelating Lewis acid yet documented



"Asymmetric Diels-Alder Cycloaddition Reactions with Chiral, -Unsaturated-*N*-Acyloxazolidinones". Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, 110, 1238-1256.

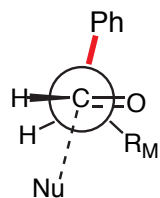
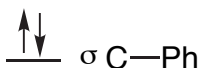
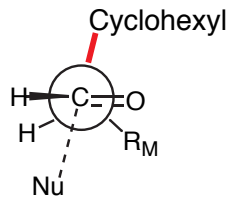
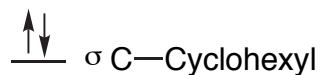
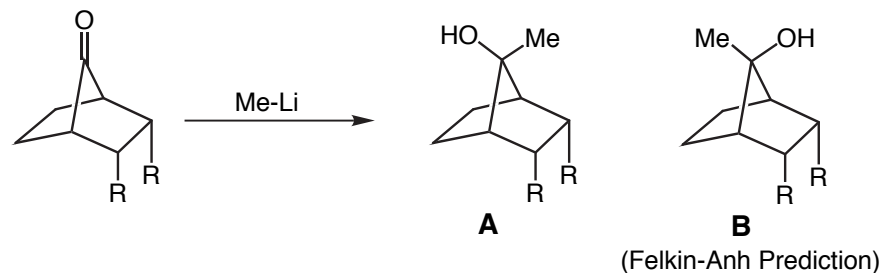
Syn Diastereomer: α & β Centers Reinforcing



Anti Diastereomer: α & β Centers Opposing

Are there cases not handled by the Anh-Eisenstein Model?

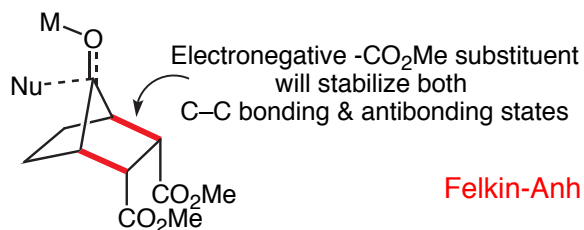
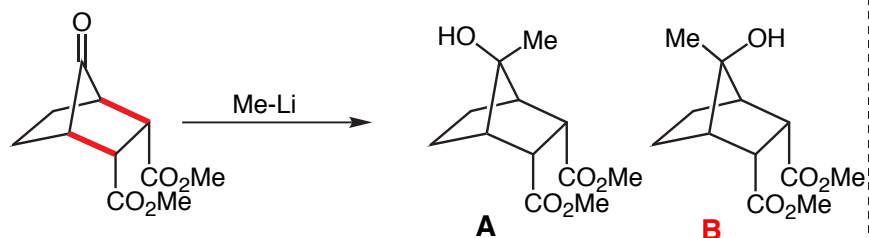
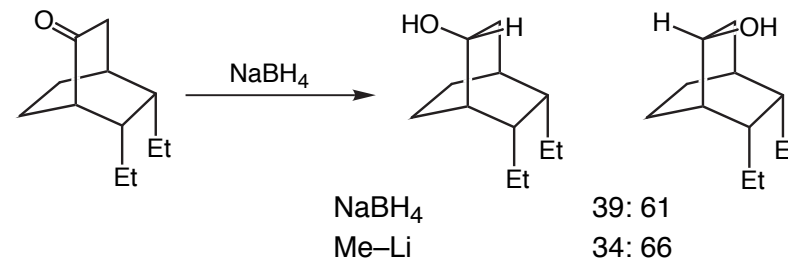
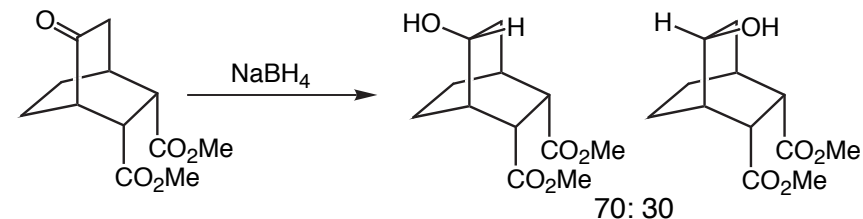
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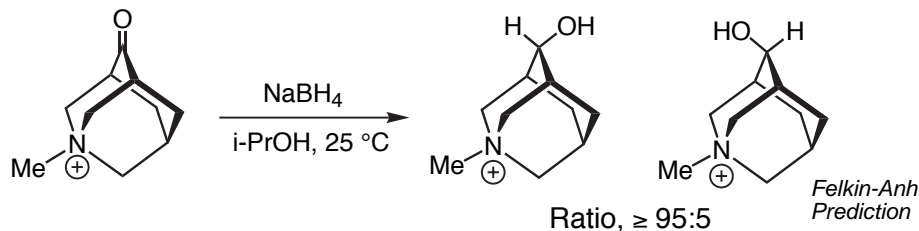
(R) Substituent	A/B Ratio
$-\overset{\text{O}}{\parallel}{C}-\text{OMe}$	>90:10
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$-\text{CH}_2-\text{CH}_3$	17:83

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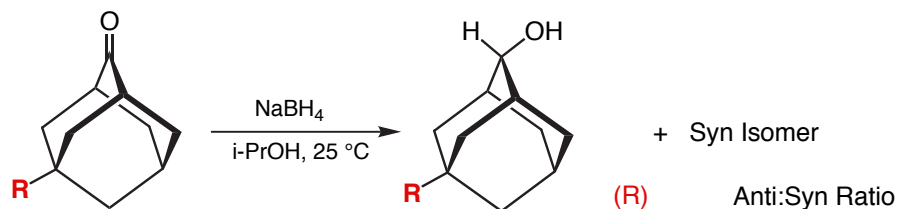
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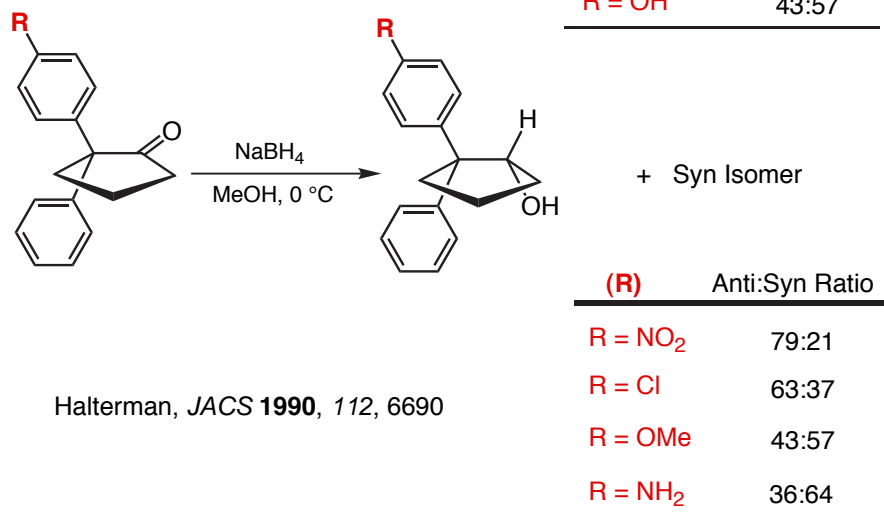
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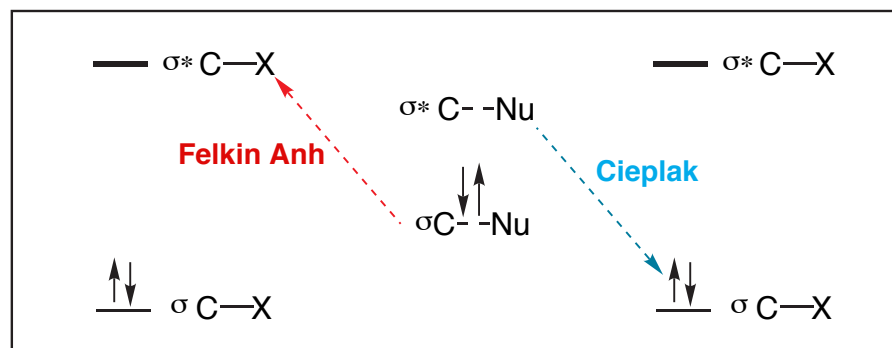
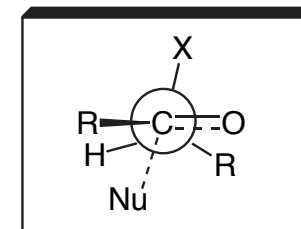
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Cieplak Model for C=O Addition

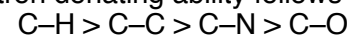
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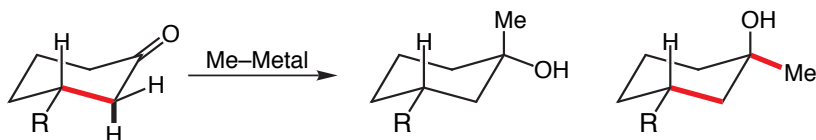
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"Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct." The management

"It is a capital mistake to theorise before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts."
(Sherlock Holmes, *A Scandal in Bohemia*)

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:

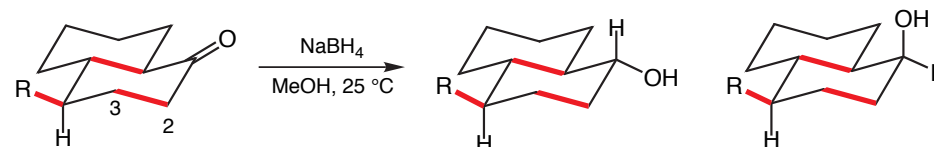
- Cieplak stabilizing interaction is "dubious." Why not stabilize the forming sigma bond?
- Enhanced rate of axial Nu attack on cyclohexanone is caused by better electrostatic interactions of the ketone with the attacking reagent and not by torsional considerations.
- Nonequivalence of the $\pi^*C=O$ LUMO with a greater extension on the axial face dictates stereoselection (Klein, 1973).

"Since interactions between the $\pi C=O$ & $\pi^* C=O$ and the bonding & anti-bonding (β) C-H & (β) C-C orbitals are all **symmetry** allowed, it is difficult to predict a priori which interactions are dominant without carrying out quantum mechanical calculations."

Frenking & Reetz, *Angew. Chem. Int. Ed.* **1991**, 30, 1146

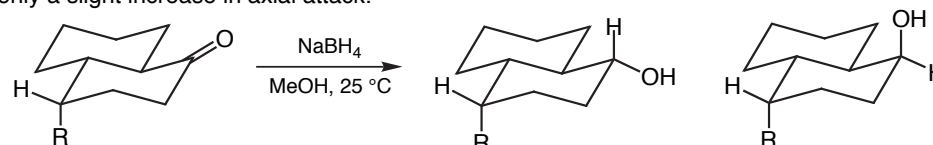
Houk: Electrostatic rather than covalent considerations may be dominant.

"Equatorial electronegative substituents should interact more strongly with the C(2-3) and C(9-10) bonds than axial substituents."



(R) Substituent	Product Ratio
R = H	60:40
R = OAc	71:29
R = Cl	71:29

"If nucleophilic addition occurs anti to the better donor bond (Cieplak), the equatorial isomers should have considerably more axial attack than the parent while the axial isomers should have only a slight increase in axial attack."

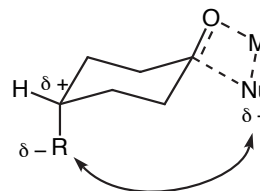


(R) Substituent	Product Ratio
R = OAc	83:17
R = Cl	88:12

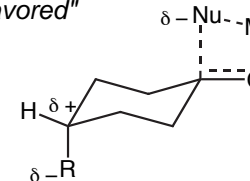
"Exactly the opposite is observed."

Axial 4-substituents favor axial attack for electrostatic reasons:

"Disfavored"



"Favored"



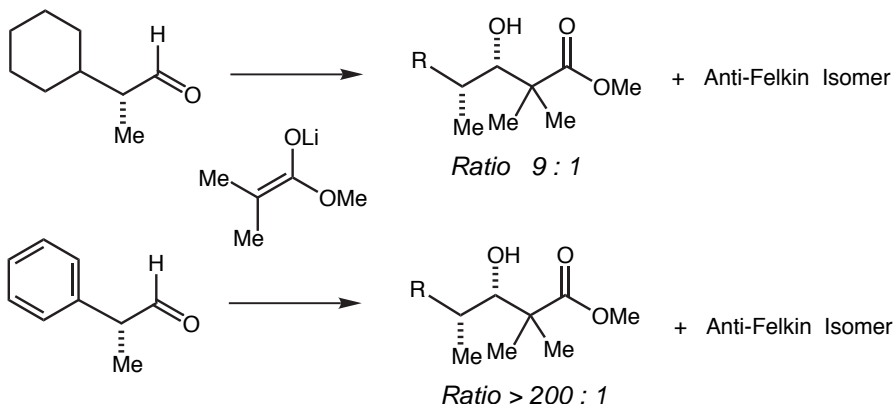
(DAE: Bimetallic transition states were not considered)

K. Houk & Co-workers, *J. Am. Chem. Soc.* **1991**, 113, 5018

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.

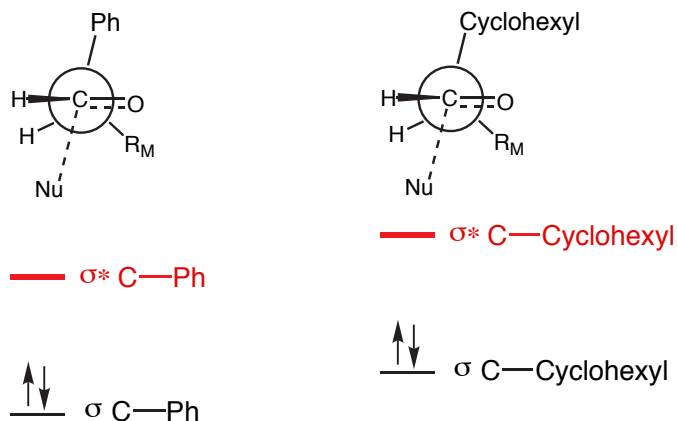


The molecular volume occupied by cyclohexyl acknowledged to be larger than that for phenyl. Because of shape phenyl "can get out of the way."

■ Anh-Eisenstein Explanation based on HOMO-LUMO Analysis:

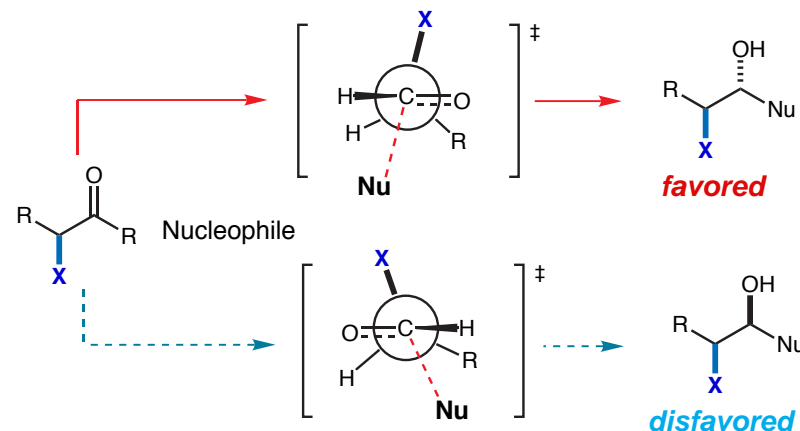
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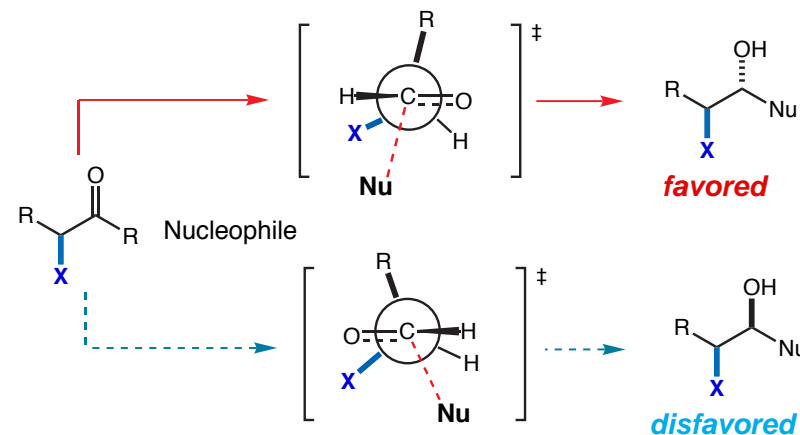
The Polar Felkin-Anh Model

Premise: Transition state **hyperconjugation** between forming bond (HOMO) and best antiperiplanar acceptor ($\sigma^* C-X$, LUMO). Steric effects are also considered; X = Halogen, OR, SR etc



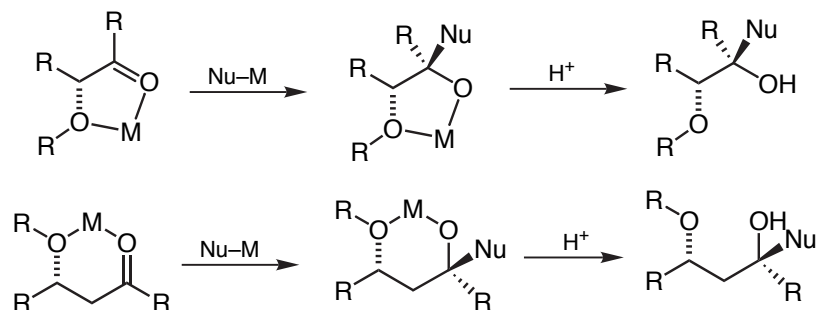
Modified Cornforth Model

Premise: Transition State **dipole minimization** between polar C-X substituent and the transforming carbonyl function dictate preferred TS geometrics. Steric effects are also considered; X = Halogen, OR, SR etc



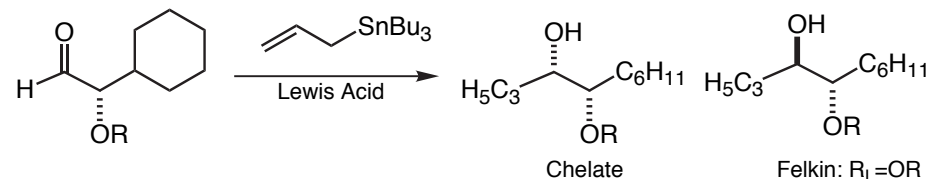
Both models lead to the same stereochemical prediction.

Chelate organization also provides a powerful control element in carbonyl addition reactions



Reviews

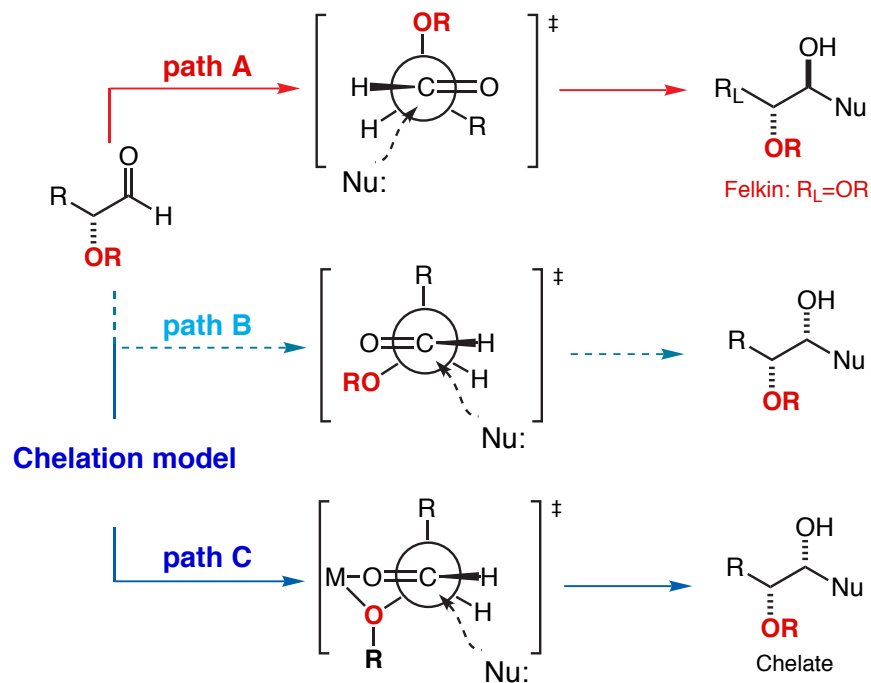
Reetz, *Accs. Chem. Res.* **1993**, 26, 462-468 (pdf)
 Reetz, *Angew. Chem. Int. Ed.* **1984**, 23, 556-569



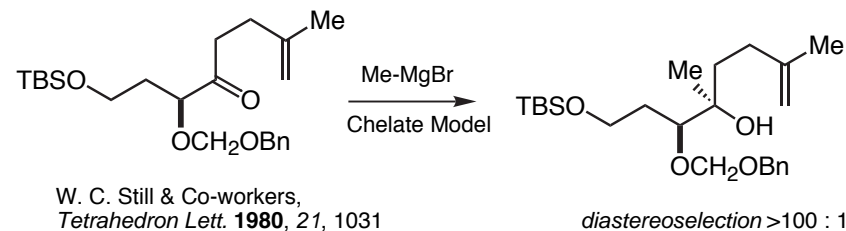
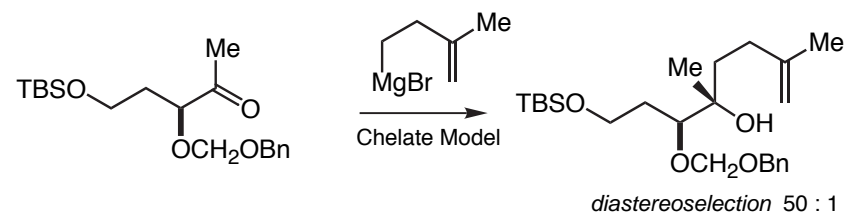
(OR)	Acid	Solv.	Ratio
R = CH ₂ OBn	MgBr ₂	THF (0°)	20 : 80
R = CH ₂ OBn	MgBr ₂	CH ₂ Cl ₂ (-20°)	>99 : 1
R = CH ₂ OBn	TiCl ₄	CH ₂ Cl ₂ (-78°)	>99 : 1
R = SiMe ₂ (t)Bu	BF ₃ -Et ₂ O	CH ₂ Cl ₂ (-78°)	5 : 95

G. Keck & Co-workers, *Tetrahedron Lett.* **1984**, 25, 265

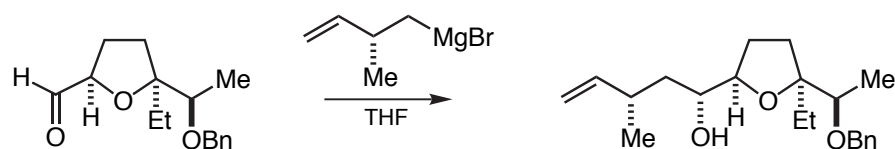
Addition of Carbon Nucleopiles



Chelation model



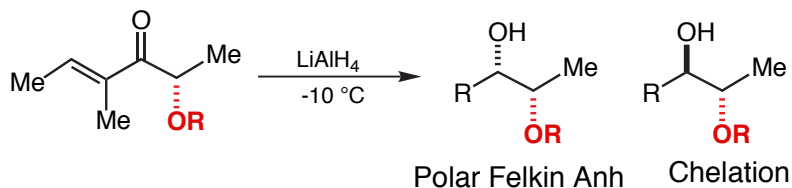
W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, 21, 1031



Y. Kishi & Co-workers,
Tetrahedron Lett. **1978**, 19, 2745

"only one isomer"
 Chelate Model

Chelate organization provides a powerful control element in carbonyl addition reactions

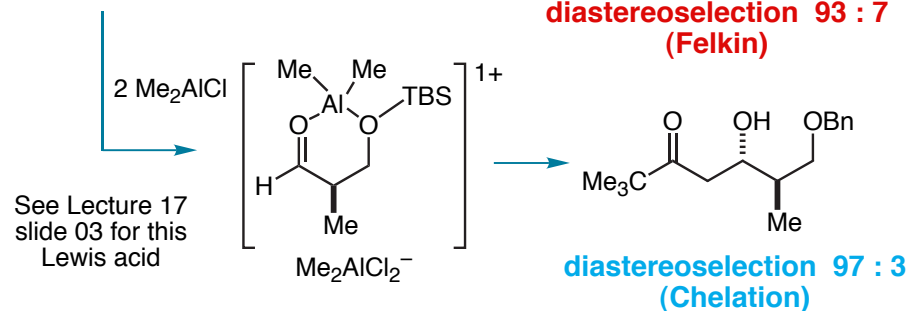
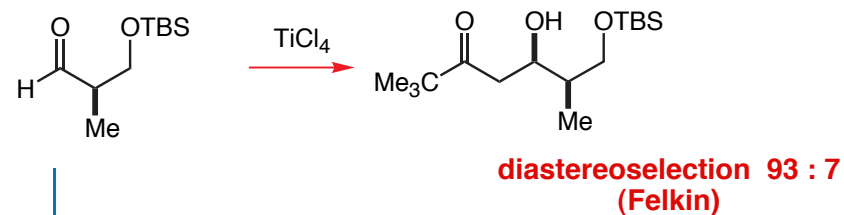
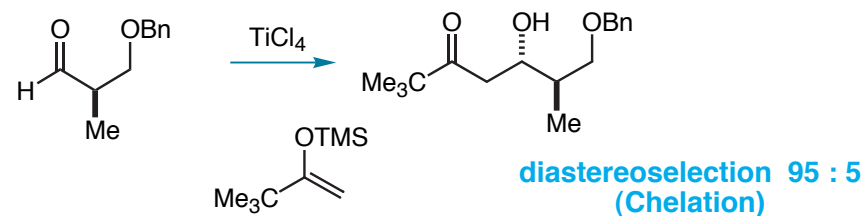
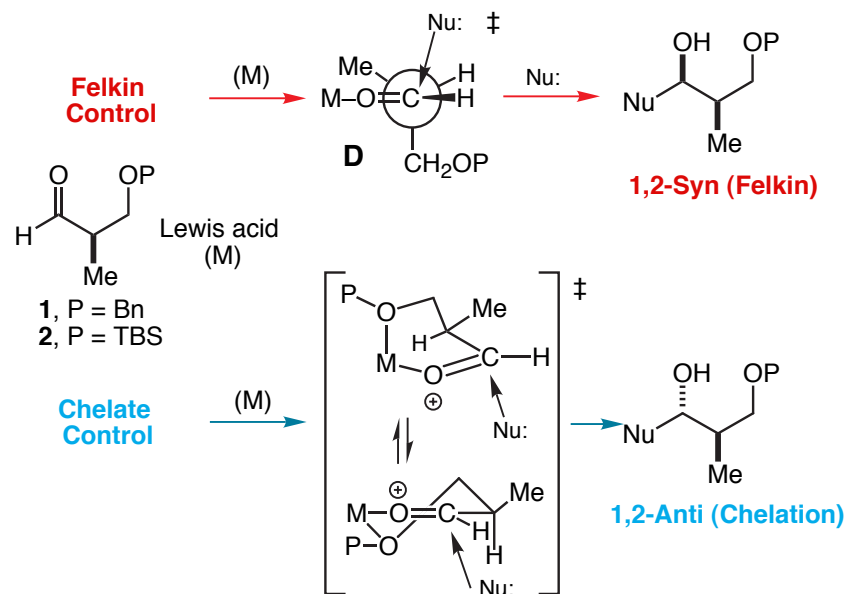


Overman
Tet Lett. **1982**, 23, 2355

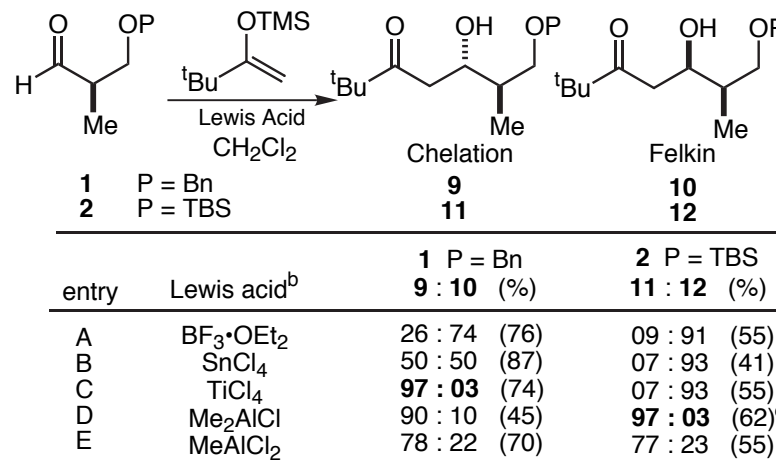
(OR)	Solv.	Ratio	Model
R = CH ₂ OBn	THF	30 : 70	Chelate
R = CH ₂ OBn	Et ₂ O	2 : 98	Chelate
R = SiPh₂(t)Bu	THF	95 : 5	F-A: R_L=OR

Degree of chelate organization may be regulated by choice of solvent and protecting group. Note that SiPh₂(t)Bu group prevents chelation.

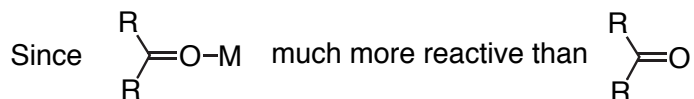
Case Study



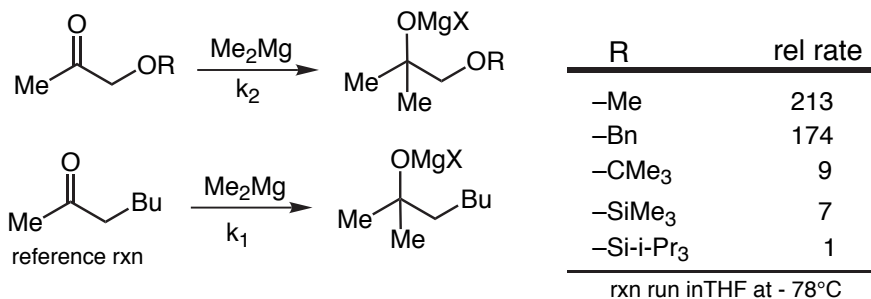
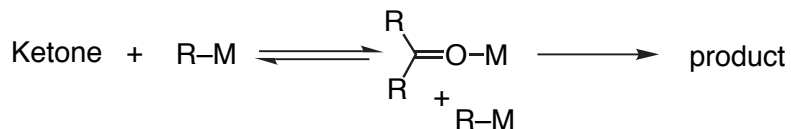
Me₂AlCl & MeAlCl₂ only Lewis acids that will chelate strongly to OSiR₃ Groups.
Evans, Allison, Yang, Masse, *JACS* **2001**, 123, 10840–10852



Kinetic Evidence for Chelate-Controlled C=O Addition

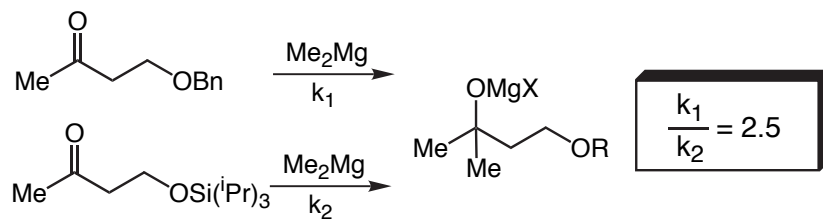


Substrates which can participate in C=O chelation will be more reactive since the effective concentration of chelated intermediate will be higher.

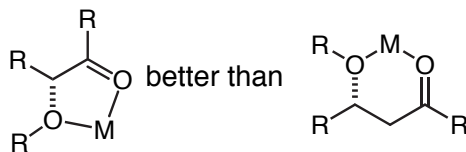


Eliel, Frye, *JACS* **1992**, 114, 1778-84 (read)

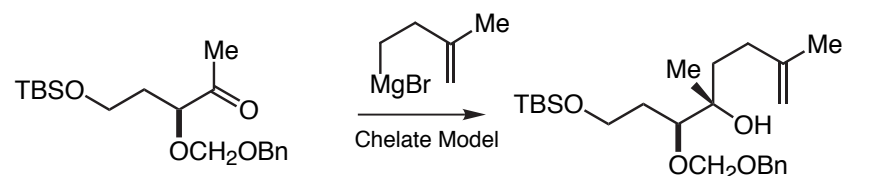
However, these trends are not transmitted strongly to β -chelation



Hence, organization through

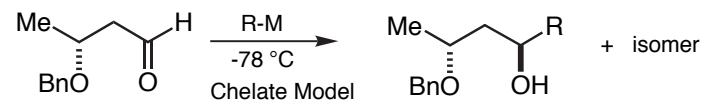


Alpha-Versus Beta-Chelation



W. C. Still & Co-workers,
Tetrahedron Lett. **1980**, 21, 1031

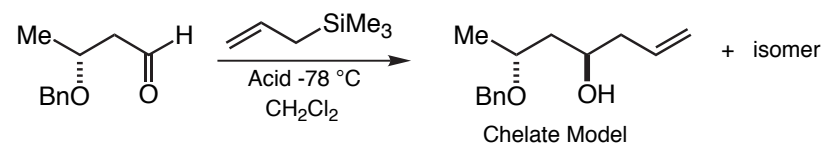
diastereoselection 50 : 1



M. T. Reetz & Co-workers
J. Am. Chem. Soc. **1983**, 105, 4833.

Other nucleophiles reported

R-M	Solv.	Ratio
Me-MgCl	THF	40 : 60
Me-TiCl ₃	CH 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

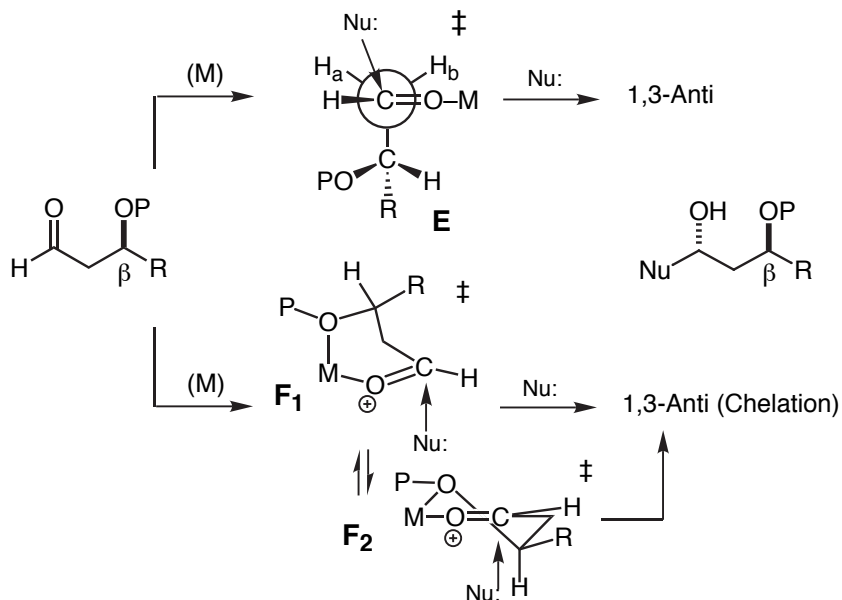
- Note that beta chelation can be developed as a control element by varying solvent & Nu.
- Note BF₃ gives "apparent" chelate control

1,3-Stereinduction Models for Chelate & non-Chelate Rxns

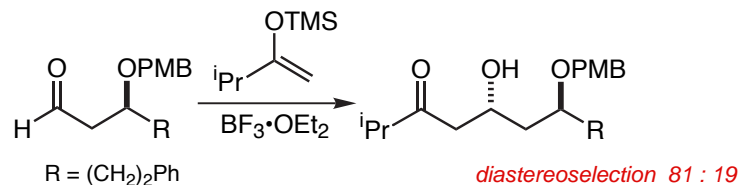
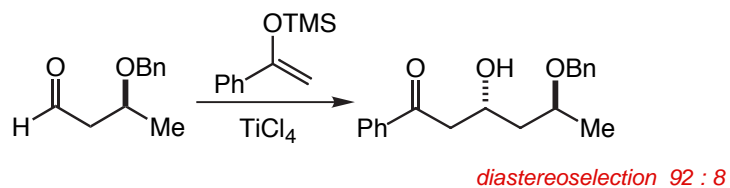
1,3-Stereinduction Polar Model:

Evans, Dart, Duffy, Yang, *JACS* **1996**, 118, 4322–4343

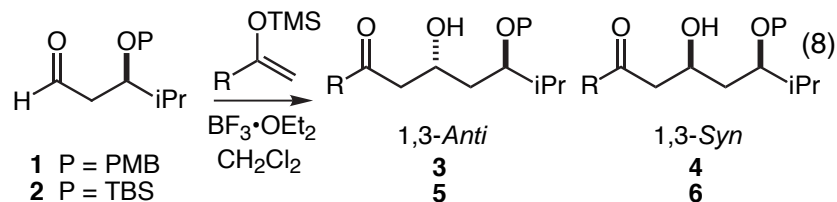
1,3-Stereinduction Chelate Model:

Evans, Allison, Yang, Masse, *JACS* **2001**, 123, 10840–10852

1,3-Anti Relationship is favored by either polar or chelate models

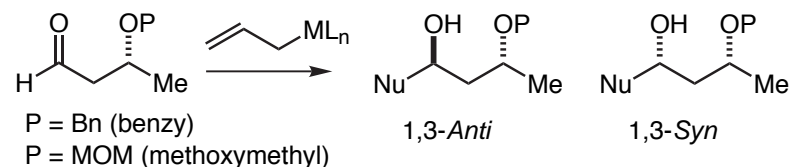
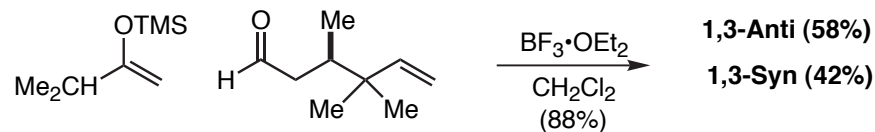


1,3-Stereinduction Polar Model:



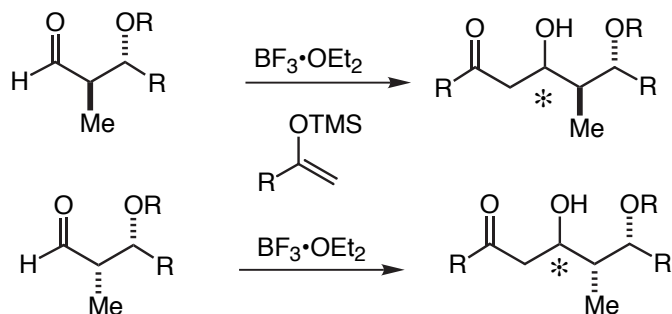
entry	R	3 : 4 (P = PMB)	(%)	5 : 6 (P = TBS)	(%)
A	t-Bu	89 : 11	(82)	84 : 16	(79)
B	i-Pr	92 : 08	(91)	80 : 20	(84)
C	Me	91 : 09	(89)	93 : 07	(87)

Steric effects appear to play a minor role in stereinduction:



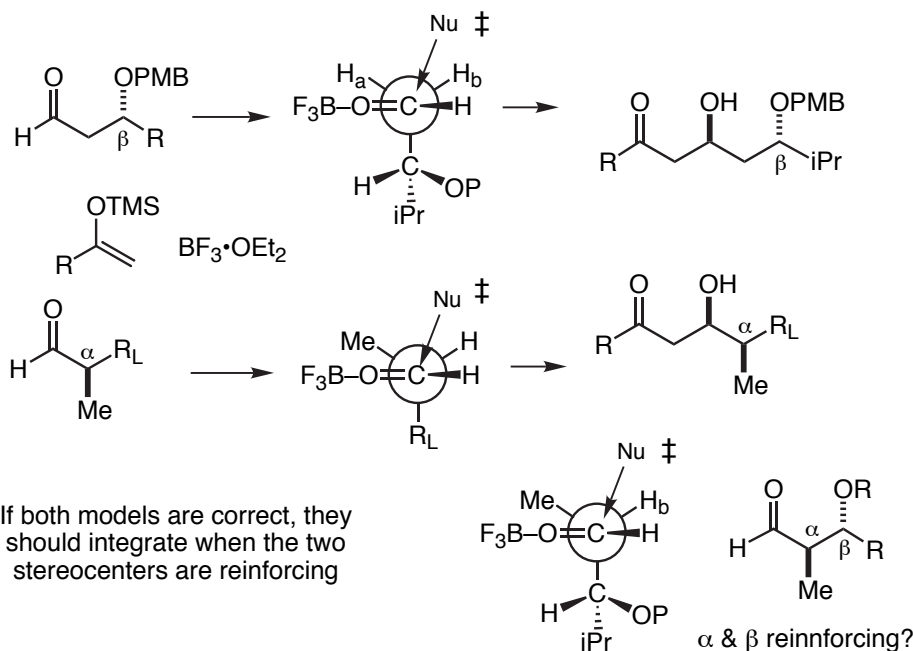
entry	conditions	(P = Bn) <i>anti</i> : <i>syn</i>	(P = MOM) <i>anti</i> : <i>syn</i>
A	BF ₃ ·OEt ₂	85 : 15	—
B	BF ₃ ·OEt ₂	79 : 29	—
C	BF ₃ ·OEt ₂	—	70 : 30

1,3-Stereinduction Polar Model

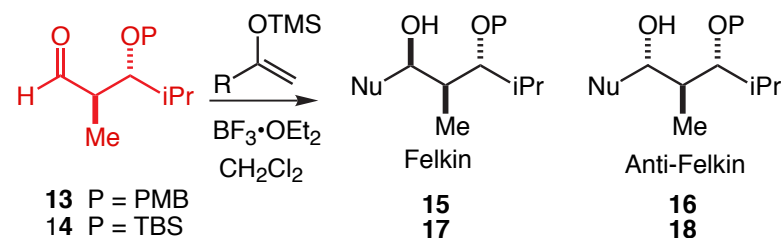
Evans, Dart, Duffy, Yang, *JACS* **1996**, *118*, 4322–4343Can one develop a Rational model for α & β Stereocenters?

Which of the two stereochemical representations is reinforcing? Non-reinforcing?

Integration of 1,3- Polar Model & Felkin-Anh Model

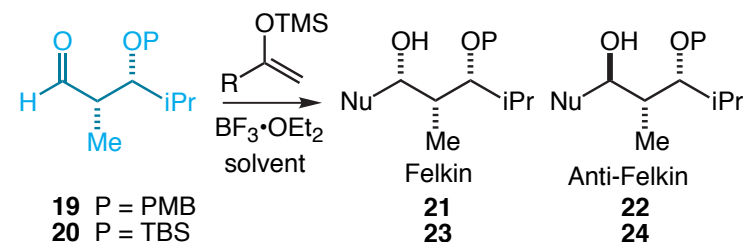


The Anti Diastereomer



entry	R	15 : 16 (P = PMB)	17 : 18 (P = TBS)
A	t-Bu	99 : 01	99 : 01
B	i-Pr	98 : 02	95 : 05
C	Me	97 : 03	71 : 29

The Syn Diastereomer

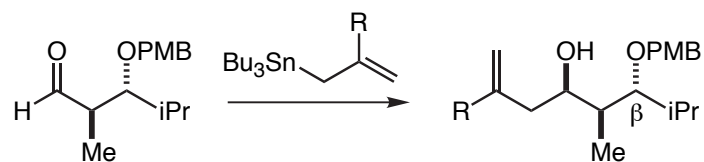


entry	R	Solvent	21 : 22 (P = PMB)	23 : 24 (P = TBS)
A	t-Bu	CH ₂ Cl ₂	96 : 04	96 : 04
B	t-Bu	toluene	88 : 12	94 : 06
C	i-Pr	CH ₂ Cl ₂	56 : 44	87 : 13
D	i-Pr	toluene	32 : 68	75 : 25
E	Me	CH ₂ Cl ₂	17 : 83	58 : 42
F	Me	toluene	06 : 94	40 : 60

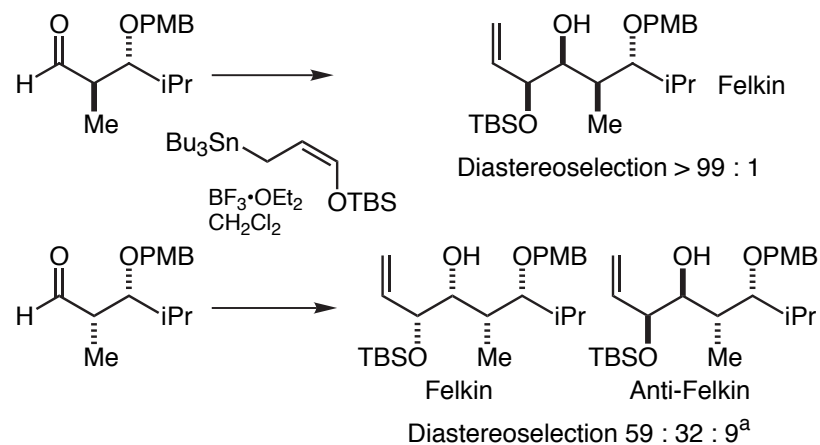
Conclusions

- A:** Anti diastereomer is reinforcing. Both models integrate.
B: Syn diastereomer transitions from Felkin control (Large Nu) to 1,3-control (Small Nu).

The Anti Diastereomer: Both Centers Reinforcing

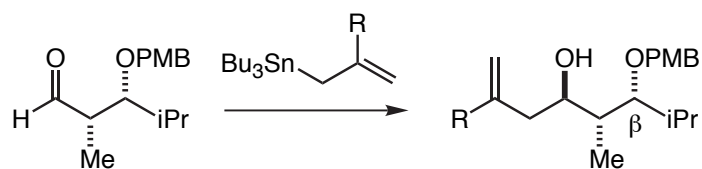


entry	Conditions	R	Felkin : anti-Felkin
A	BF ₃ ·OEt ₂ , toluene	Me	>99 : 1
B	BF ₃ ·OEt ₂ , toluene	H	>99 : 1
C	Ph ₃ CClO ₄ , CH ₂ Cl ₂	H	>99 : 1



^aThe third unpictured product is the Felkin-3,4-*anti* diastereomer.

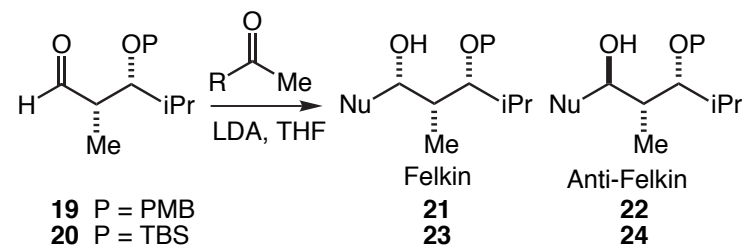
The Syn Diastereomer: Stereocenters are Non-reinforcing



entry	Conditions	R	Felkin : anti-Felkin
A	BF ₃ ·OEt ₂ , toluene	Me	20 : 80
B	BF ₃ ·OEt ₂ , toluene	H	13 : 87
C	Ph ₃ CClO ₄ , CH ₂ Cl ₂	H	62 : 38

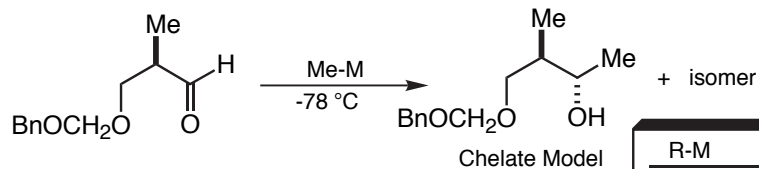
In this example, the OR substituent is the dominant stereo-control element

The Syn Diastereomer: Stereocenters are Non-reinforcing

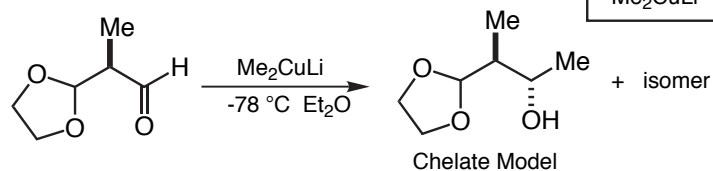


entry	R	21 : 22 (P = PMB) (%)	23 : 24 (P = TBS) (%)
A	t-Bu	11 : 89 (71)	08 : 92 (91)
B	i-Pr	14 : 86 (95)	13 : 87 (64)
C	Me	22 : 78 (73)	14 : 86 (88)

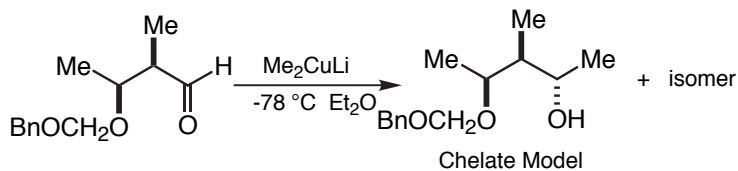
Beta Chelation with Organometals



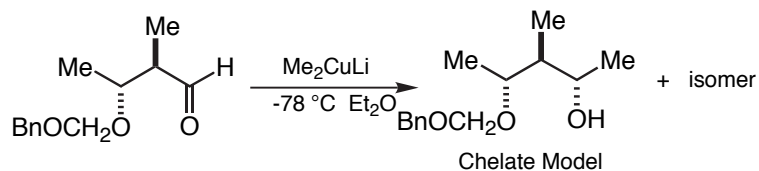
R-M	Ratio
MeMgBr	50 : 50
Me ₂ CuLi	97 : 3



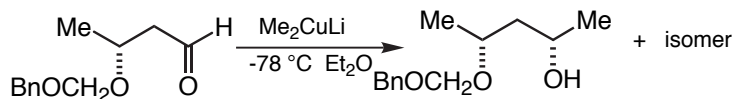
diastereoselection > 95 : 5



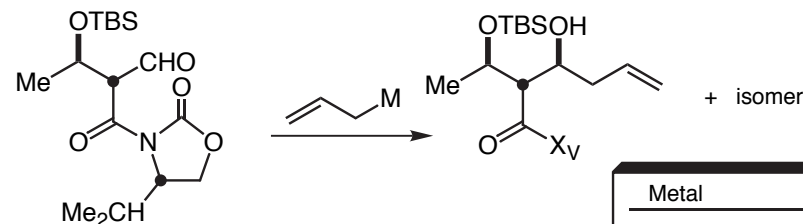
diastereoselection > 95 : 5



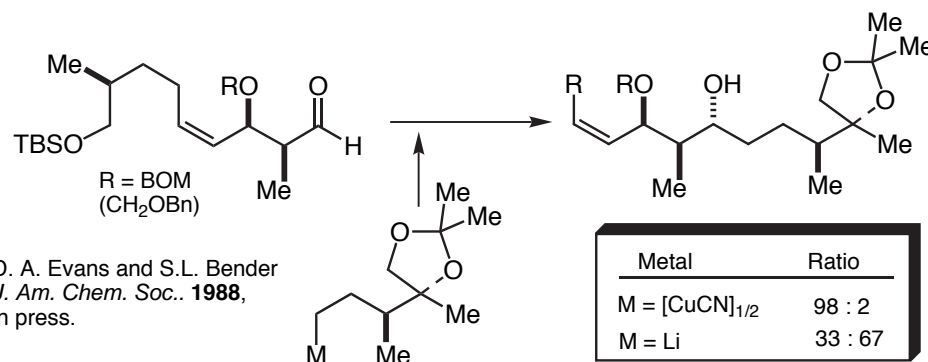
diastereoselection 70 : 30



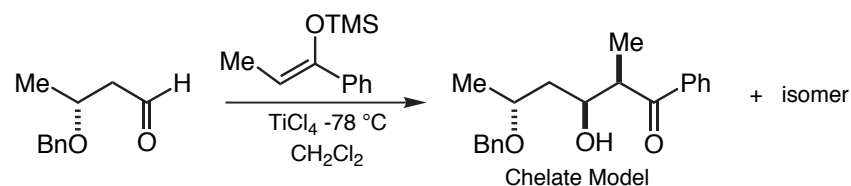
diastereoselection 50 : 50

W.C. Still & Co-workers,
Tetrahedron Lett. **1980**, 21, 1035.D. A. Evans & E. Sjogren
Tetrahedron Lett. **1986**, 27, 4961.

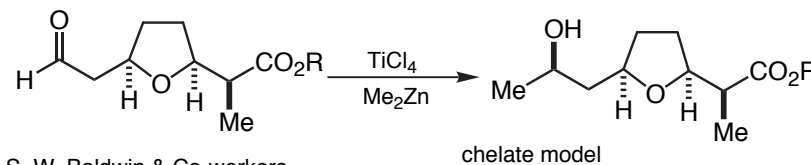
Metal	Ratio
M = MgCl	70 : 30
M = ZnCl	97 : 3

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



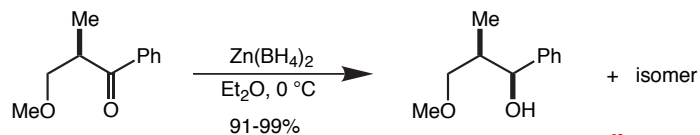
diastereoselection >92 %

M. T. Reetz & Co-workers
Tetrahedron Lett. **1984**, 25, 729.

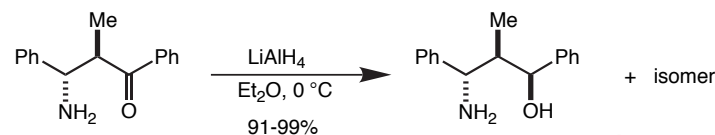
diastereoselection 96 : 4

S. W. Baldwin & Co-workers
J. Org. Chem. **1987**, 52, 320.

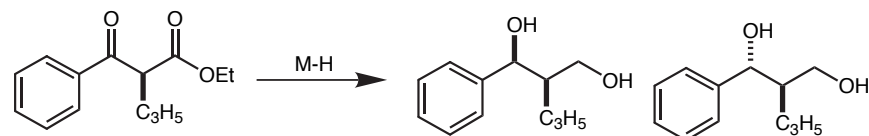
Beta Chelate-Controlled Reduction



T. Oishi & Co-workers
Chem. Pharm. Bull. **1984**, 32, 1411.

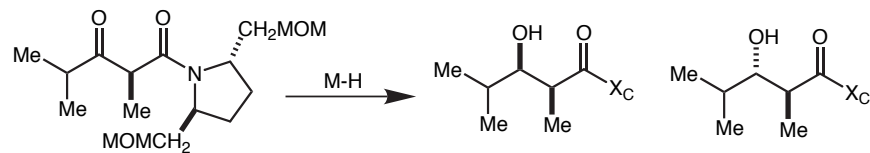


J. Barluenga & Co-workers
J. Org. Chem. **1985**, 50, 4052.



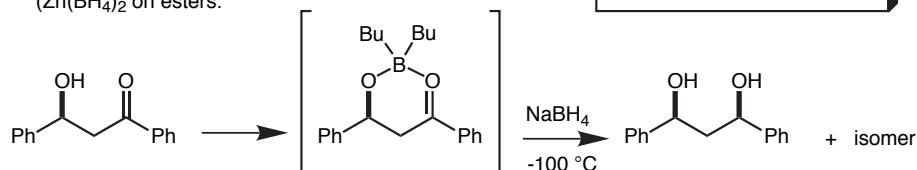
G. R. Brown & Co-workers
Chem. Commun. **1985**, 455.

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.

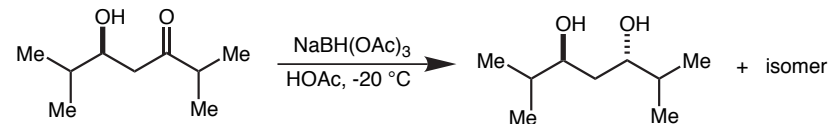
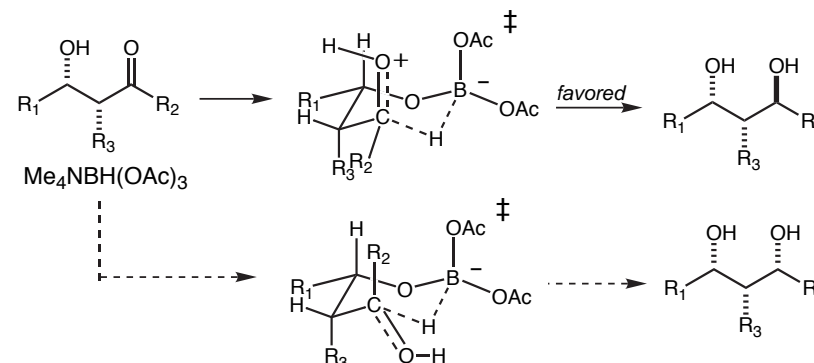
T. Oishi & Co-workers
Tetrahedron Lett. **1980**, 21, 1641
(Zn(BH₄)₂ on esters.)



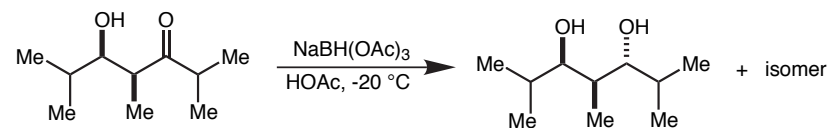
K. Narasaka & Co-workers
Chem. Lett. **1980**, 1415.

Directed reductions of β-hydroxyketones

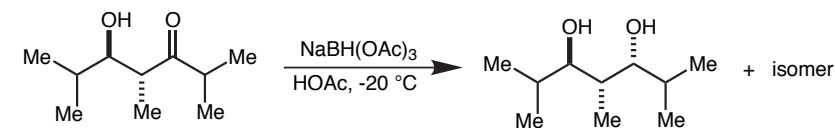
Evans, Chapman, Carreira, *JACS* **110**, 3560 (1988)



diastereoselection 96 : 4

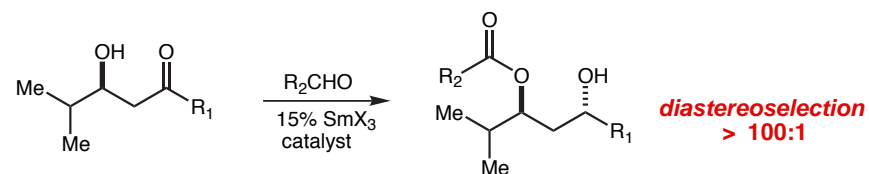


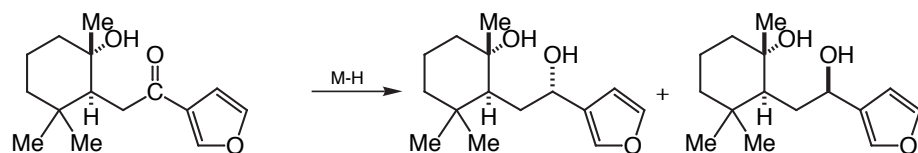
diastereoselection 98 : 2



diastereoselection 98 : 2

Propose a mechanism for this highly diastereoselective transformation,
Evans, Hoveyda *JACS* **112**, 6447 (1990)

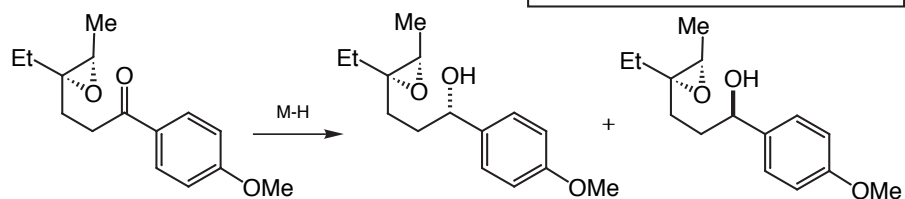




Temp. & Solvent not specified in this study
in first three cases

R. Baker & Co-workers
Chem. Commun. **1984**, 74

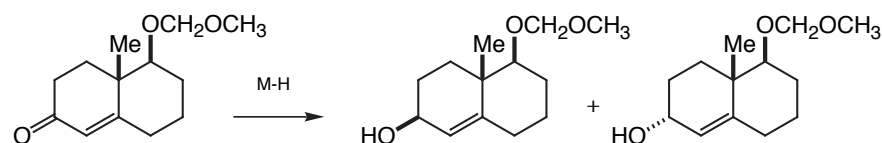
Reagent	Ratio
Li-AlH ₄	40 : 60
Na-BH ₄	50 : 50
Zn-BH ₄	60 : 40
Li-BHEt ₃ , (THF, -78 °C)	100 : 0



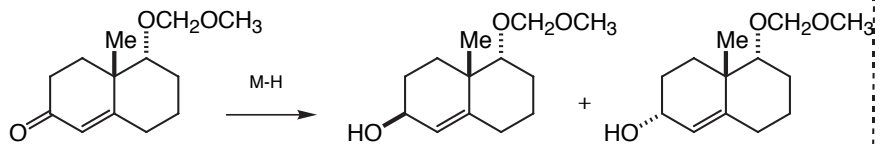
Y. Kishi & Co-workers
Tetrahedron Lett. **1978**, 2741.

* 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

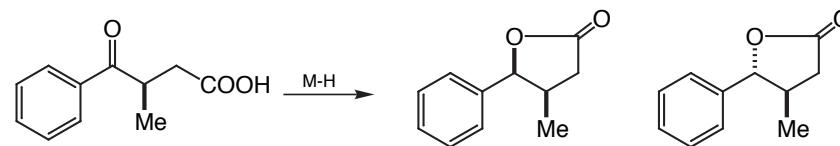


Li-BH(R) ₃ ,	73 : 27
LiAlH ₄	76 : 24



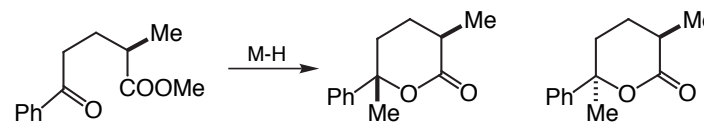
Li-BH(R) ₃ ,	28 : 72
LiAlH ₄	72 : 28

W. G. Dauben & Co-workers
Tetrahedron Lett. **1978**, 2741.



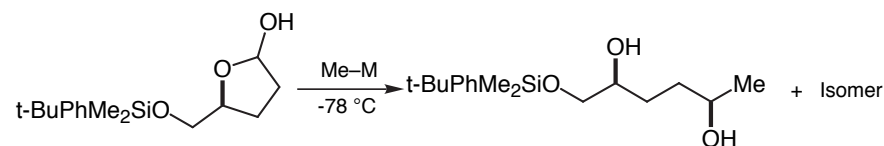
R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

Reagent	Ratio
NaBH ₂ (OR) ₂	50 : 50
NaBH ₄	70 : 30
DIBAL (2.4 equiv)	95 : 5
DIBAL (2.4 equiv) with ZnCl ₂	99 : 1



R. Frenette & Co-workers
J. Org. Chem. **52**, 304 (1987)

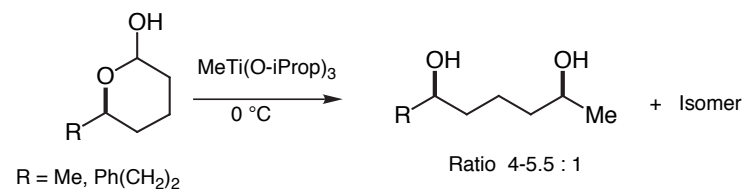
Solvent	Ratio
THF	50 : 50
C ₆ H ₆	70 : 30



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



Quote for the Day

Richard P. Feynman (as an undergraduate) in Surely you're Joking Mr. Feynman

"When I was an undergraduate student at MIT I loved it. I thought it was a great place, and I wanted to go to graduate school there too of course. But when I went to Professor Slater and told him of my intentions, he said,

'We won't let you in here.'

I said, "what"?

Slater asked, 'Why do you think that you should go to graduate school at MIT'?

"Because it is the best school for science in the country."

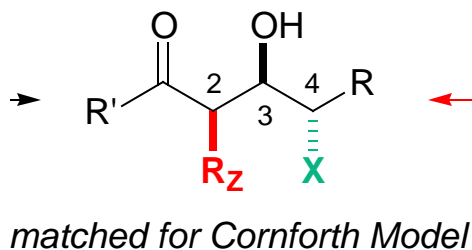
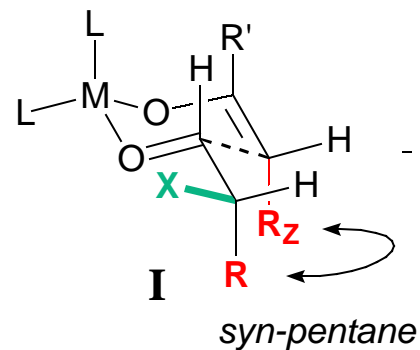
'You think *that*'?

"Yeah."

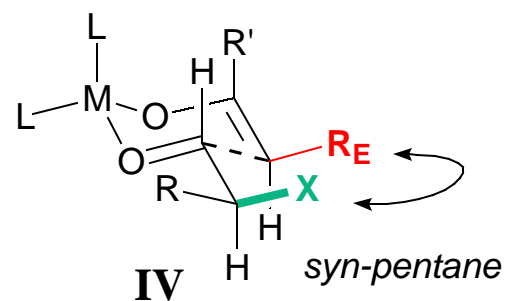
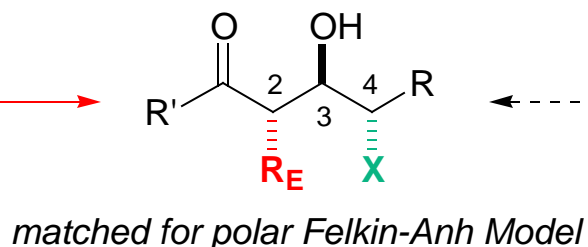
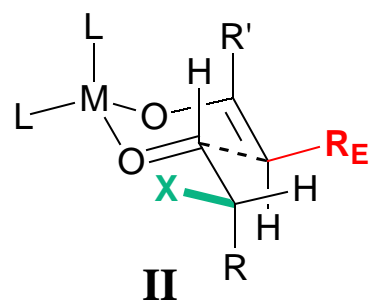
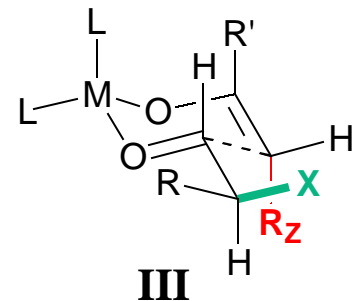
'That's why you should go to some other school. You should find out how the rest of the world is.'

Experimental Support for Cornforth or Felkin–Anh Models

Polar Felkin-Anh Model



Cornforth Model



PFA Model Prediction: The (*Z*) enolate substituent causes a destabilizing syn-pentane interaction (**I**), while the (*E*) enolate substituent experiences no such interaction (**II**). Therefore, (*E*) enolates are predicted to give superior 3,4-anti selectivity relative to (*Z*) enolates.

Cornforth Model Prediction: The (*E*) enolate substituent causes a destabilizing syn-pentane interaction (**IV**) while the (*Z*) enolate substituent experiences no such interaction (**III**). Therefore, (*Z*) enolates are predicted to give superior 3,4-anti selectivity relative to (*E*) enolates. Due to this dichotomy, the experimentally determined relationship between enolate geometry and aldehyde diastereofacial selectivity should validate a single model for asymmetric induction.

Angew. Chem. Int. Ed., **2003**, 42, 1761-1765.

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 22

Enantioselective Carbonyl Addition

- Enantioselective addition of R_2Zn to aldehydes
- Enantioselective Reduction of Ketones & Imines
- Introduction to Enolate-based Nucleophiles

■ 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

Enantioselective Carbonyl Reduction: Corey *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012 (**handout**)

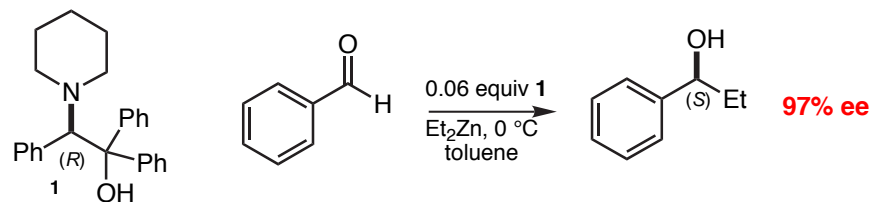
Enantioselective Carbonyl Addition (R_2Zn): Noyori *Angew. Chem. Int. Ed.* **1991**, *30*, 49-69 (**handout**)

D. A. Evans

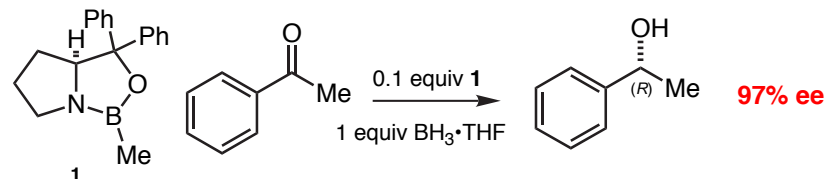
Wednesday,
November 5, 2003

■ Relevant Problems:

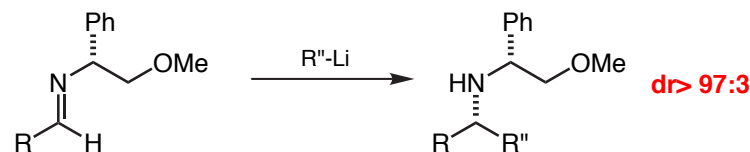
Database Problem 27: Chiral amino alcohol **1** efficiently mediates the addition of diethylzinc to aromatic aldehydes. While a number of other amino alcohols are also effective in controlling the absolute course of the addition process, this amino alcohol has been the focus of a recent computational 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.



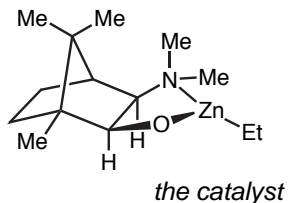
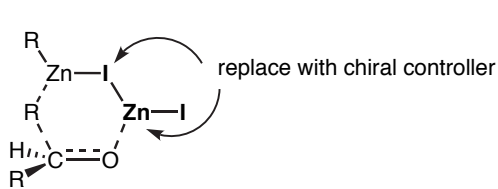
Cume Question, 2000: Corey's introduction of chiral oxazaborolidine catalysts **1** in the borane-mediated enantioselective reduction of ketones represents an important advance in asymmetric synthesis (Corey & Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012). Provide a detailed mechanism for the overall transformation. Use 3-dimensional representations to illustrate the absolute stereochemical aspects of the indicated transformation.



Database Problem 151: The following stereoselective transformation has been reported by Fujisawa (*Chem. Lett.* **1991**, 1555). Given the structure of the product, rationalize the stereochemical outcome of the process.



Catalytic Asymmetric Carbonyl Addition

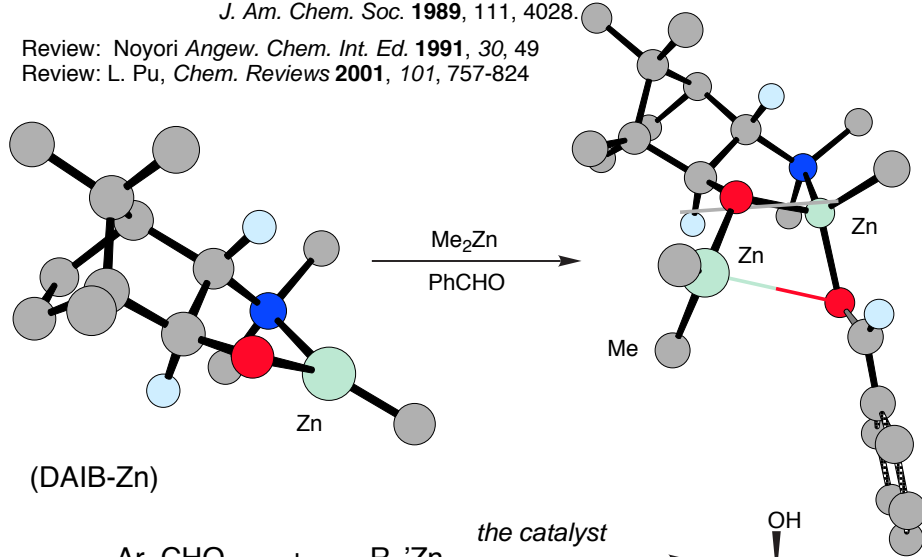


Noyori & co-workers, *J. Am. Chem. Soc.* **1986**, 108, 6072.

J. Am. Chem. Soc. **1989**, 111, 4028.

Review: Noyori *Angew. Chem. Int. Ed.* **1991**, 30, 49

Review: L. Pu, *Chem. Reviews* **2001**, 101, 757-824

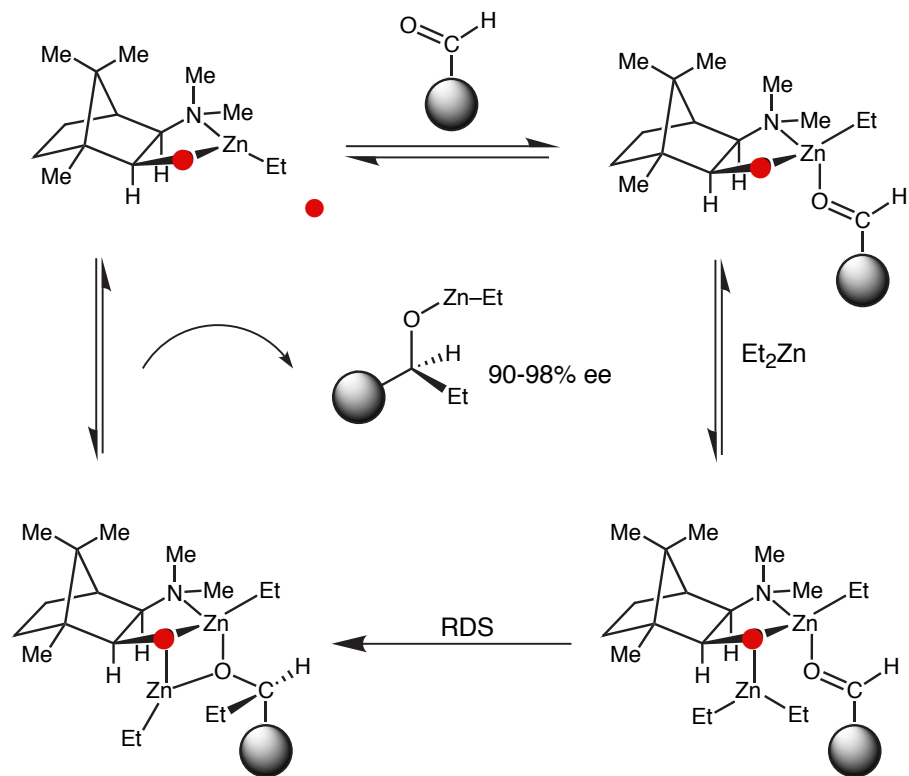


C ₆ H ₅ CHO	Et ₂ Zn	98% e.e.
"	Me ₂ Zn	91% e.e.
p-ClC ₆ H ₄ CHO	Et ₂ Zn	93% e.e.
p-MeOC ₆ H ₄ CHO	Et ₂ Zn	93% e.e.
Cinnamyl	Et ₂ Zn	96% e.e.
PhCH ₂ CH ₂ CHO	Et ₂ Zn	90% e.e.
n-C ₆ H ₁₃ CHO	Et ₂ Zn	61% e.e.

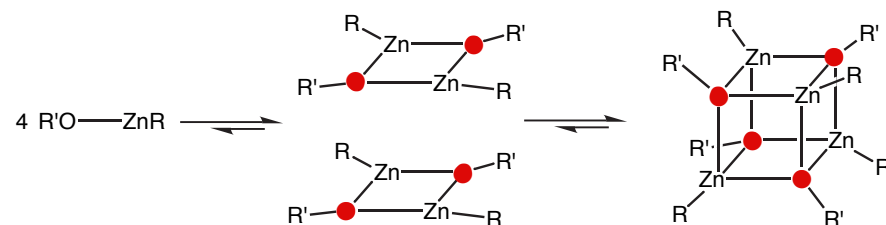
■ The method is catalytic in aminoalcohol.

■ Two zinc species per aldehyde are involved in the alkylation step.

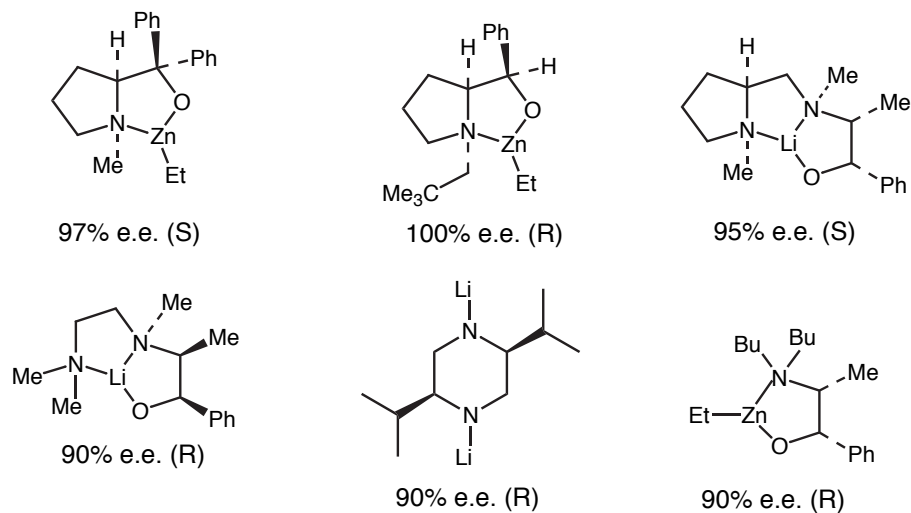
The Catalytic Cycle



■ Catalyst must be sterically hindered so that association is precluded



■ Product is taken out of the picture by aggregation

Other Catalysts for the R_2Zn Addition Process

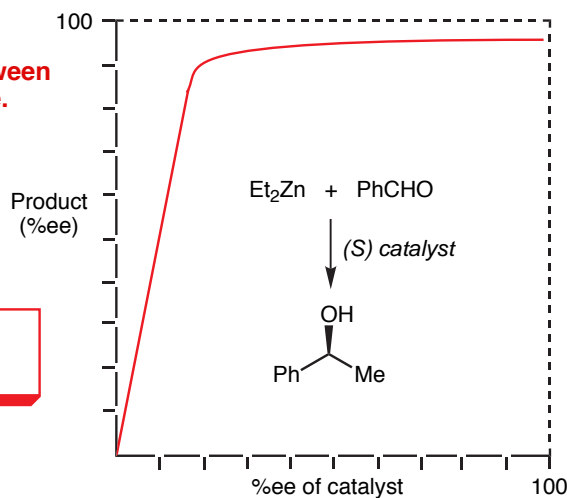
(Results are cited for the reaction of benzaldehyde and Et_2Zn)

Problem: Rationalize the stereochemical course of each of the catalysts

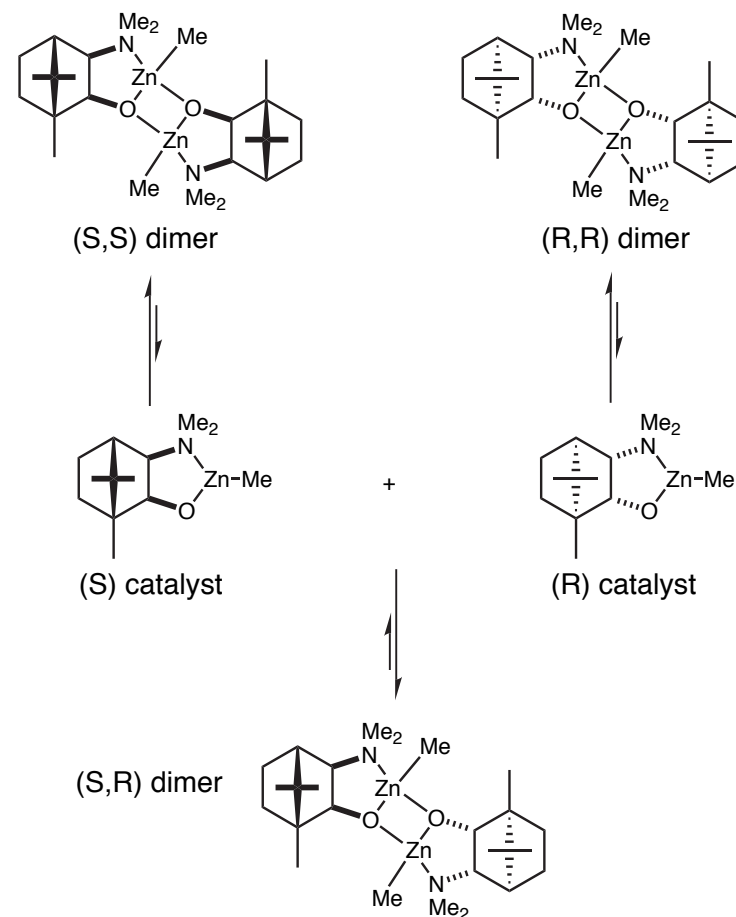
- Non-linear effects observed with the Noyori Catalyst (DAIB-Zn)

There is no correlation between catalyst and product ee.

25% ee Catalyst affords product in 95% ee.



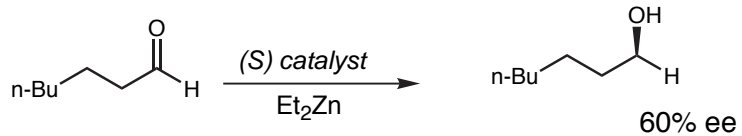
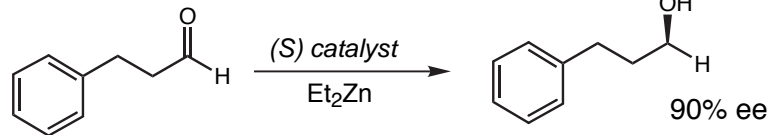
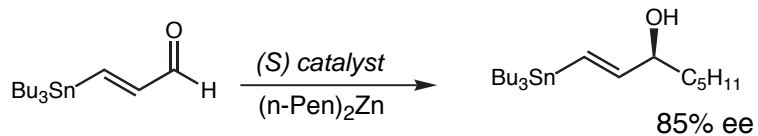
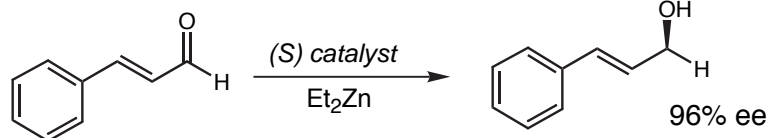
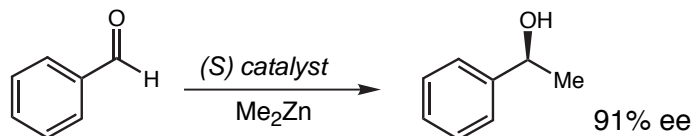
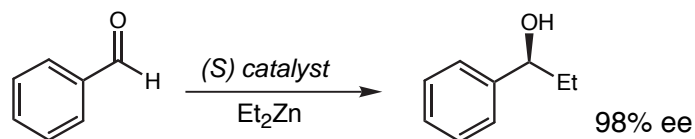
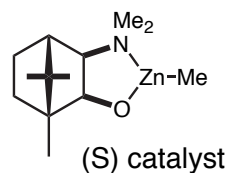
Explanation for Nonlinearity of DAIB Catalyst



Observations

- (S,S) dimer dissociates upon addition of RCHO & effects catalysis
- (S,R) dimer is overwhelmingly more stable than (S,S) homodimer
- (S,R) dimer is ineffective as a catalyst

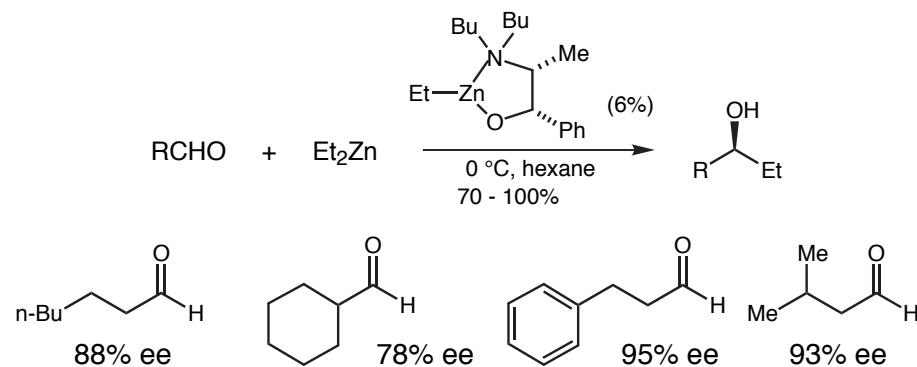
Scope of the DAIB Catalyst



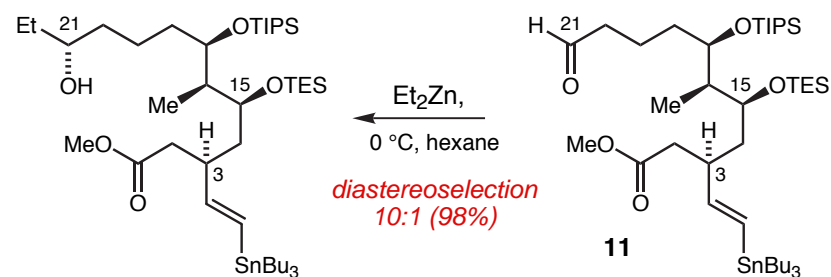
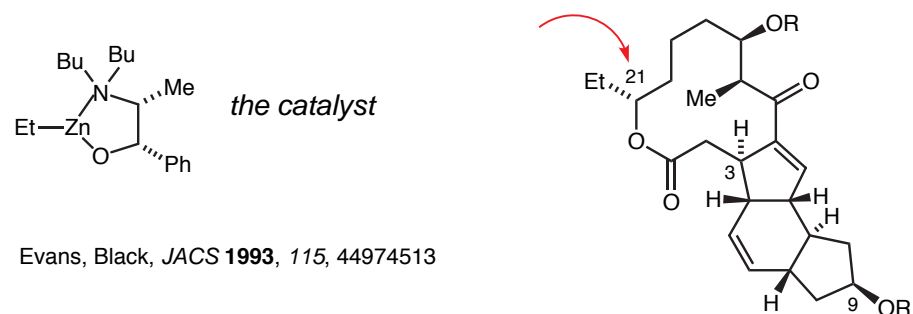
Review: Noyori *Angew. Chem. Int. Ed.* **1991**, 30, 49

Improved Selectivity with Aliphatic Aldehydes

Soai, *J. Org. Chem.* **1991**, 56, 4264



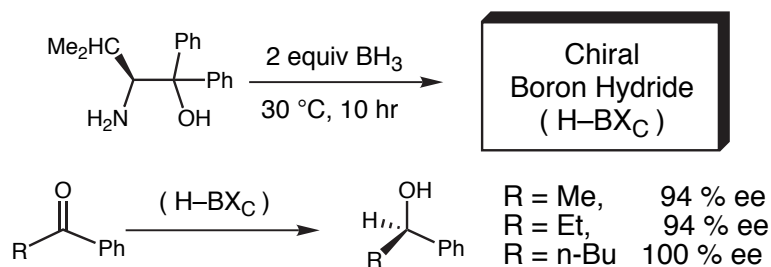
Lepicidin Application: The reaction functions in complex systems



Discovery of a Catalytic Process

Enantioselective Carbonyl Reduction: Corey *Angew. Chem. Int Ed.* **1998**, 37, 1986-2012 (**handout**)

■ The Stoichiometric Process: Itsuno, 1983-1985

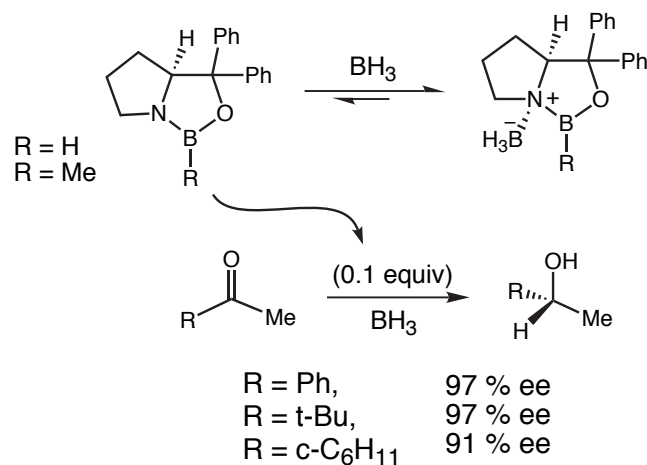


Itsuno, *Chem. Commun.* **1983**, 469

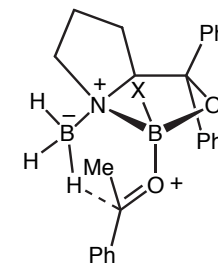
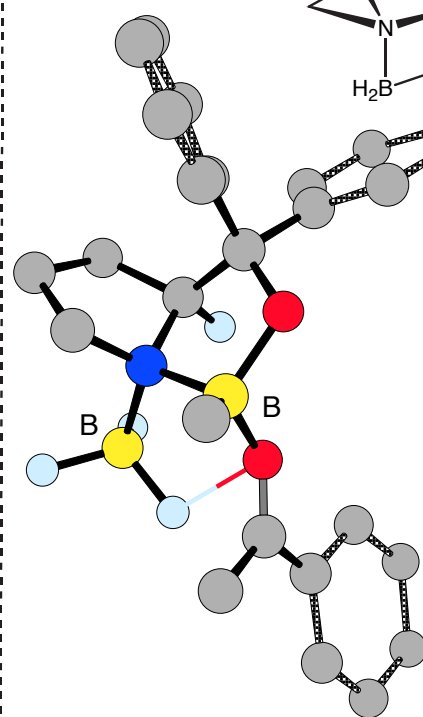
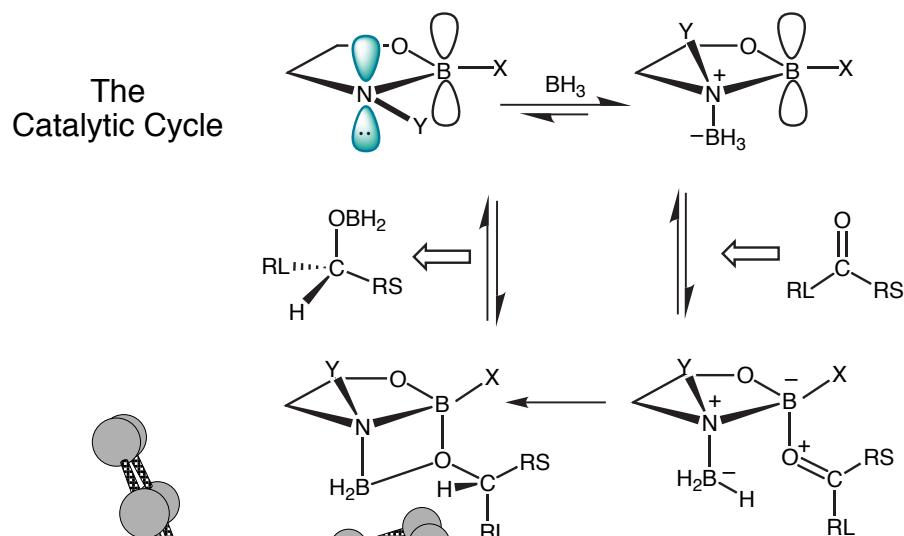
Itsuno, *J. Org. Chem.* **1984**, 49, 555

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

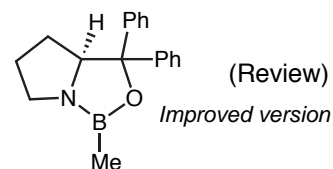
Catalyst X-ray, Corey, *Tet. Let* **1992**, 33, 3429

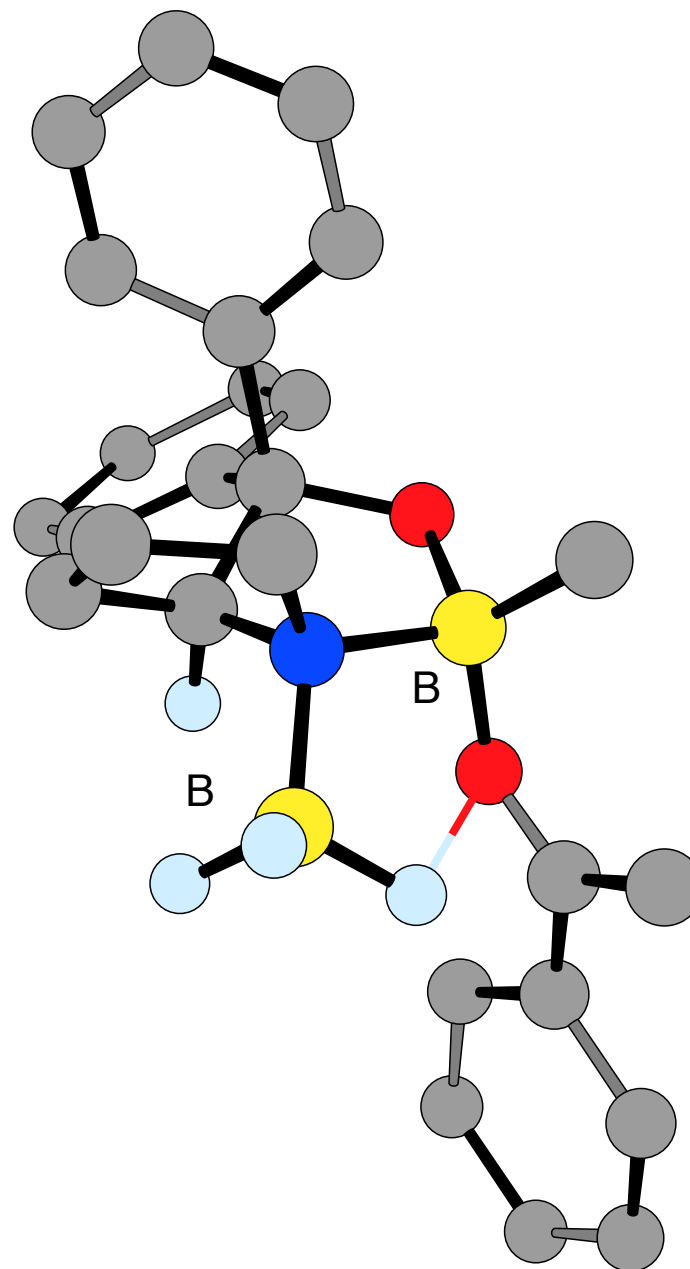
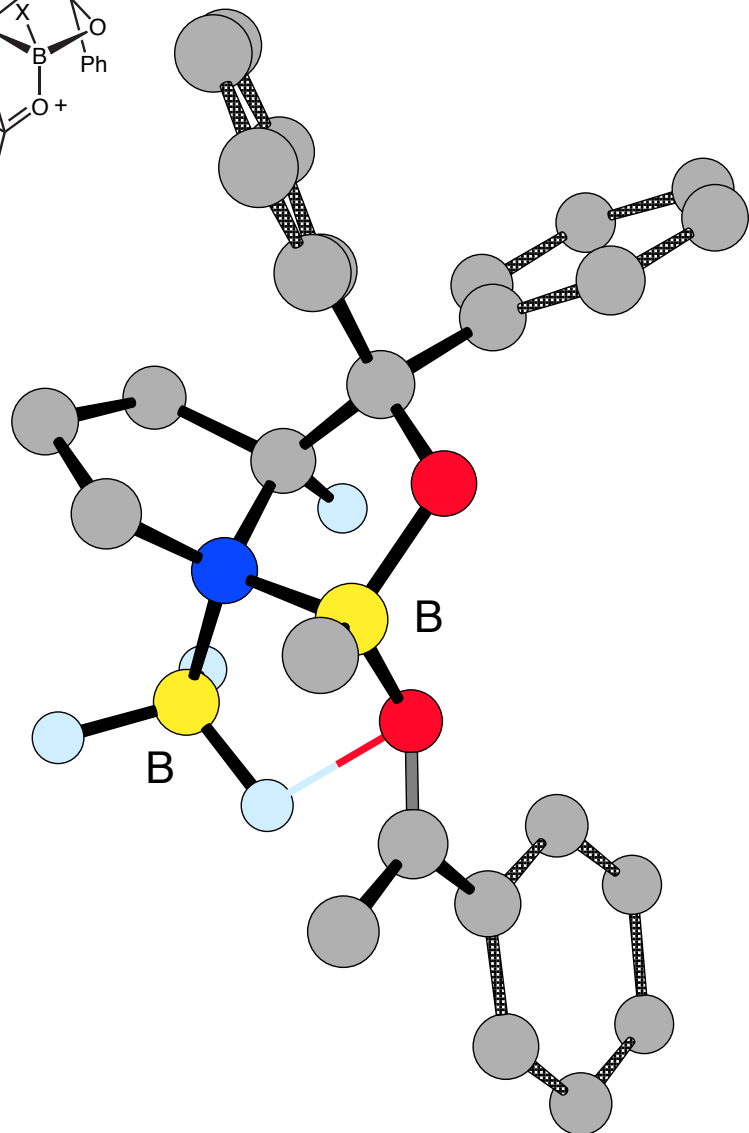
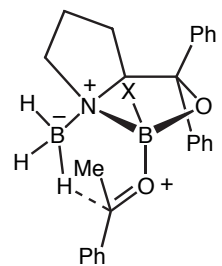
Mathre, *JOC* **1993**, 58, 2880

catalyst prep: Mathre, *JOC* **1993**, 58, 799

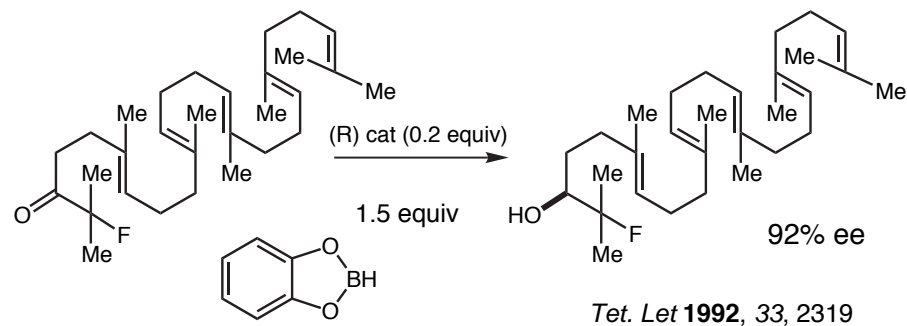
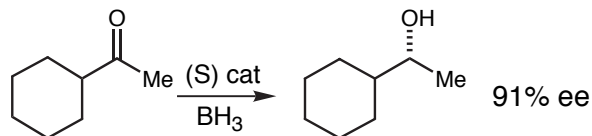
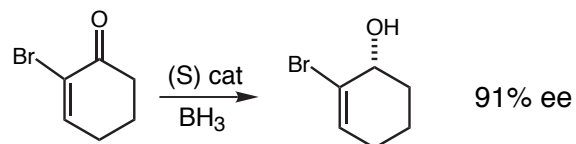
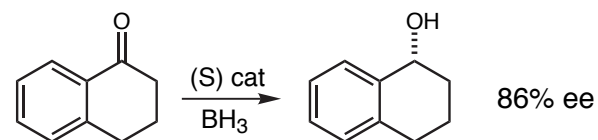
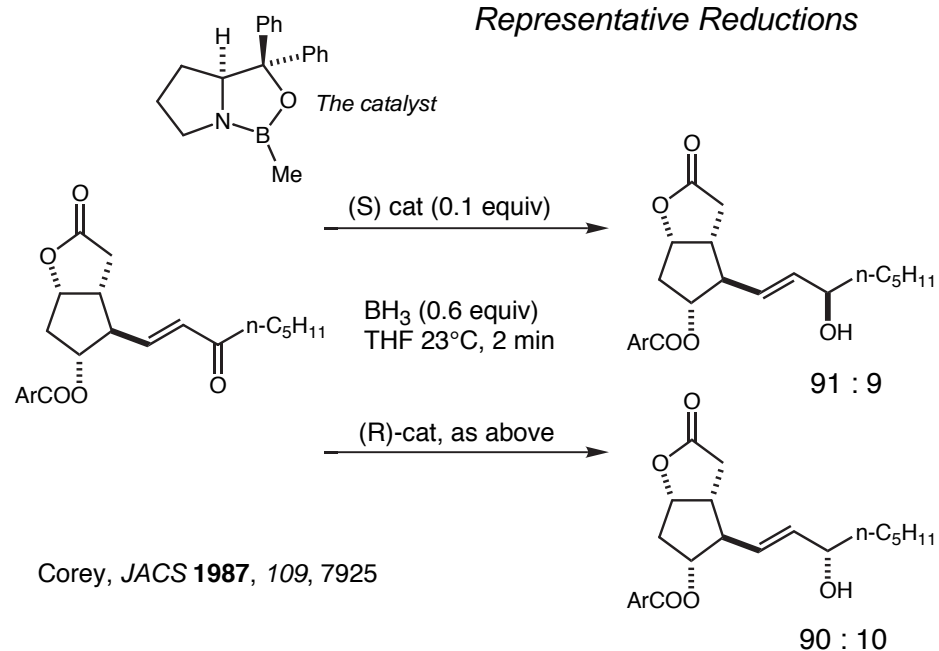
Mathre, *JOC* **1991**, 56, 751

(Review) Martens, *Tetrahedron Asymmetry* **1992**, 3, 1475

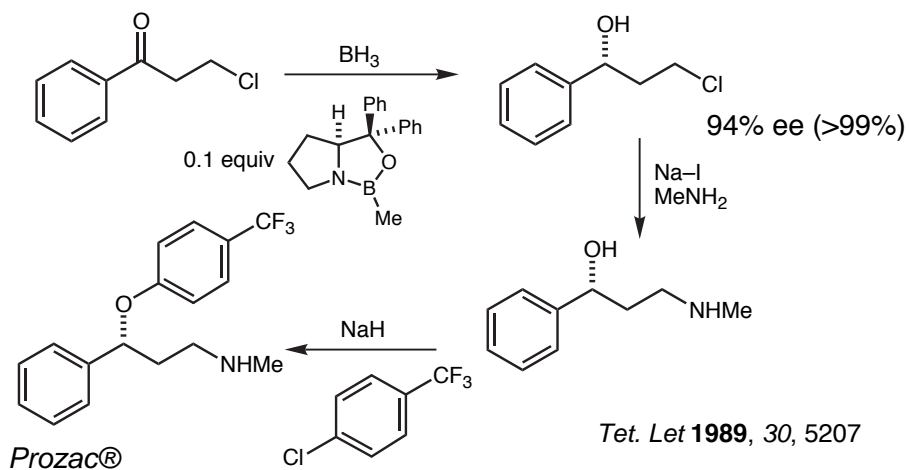
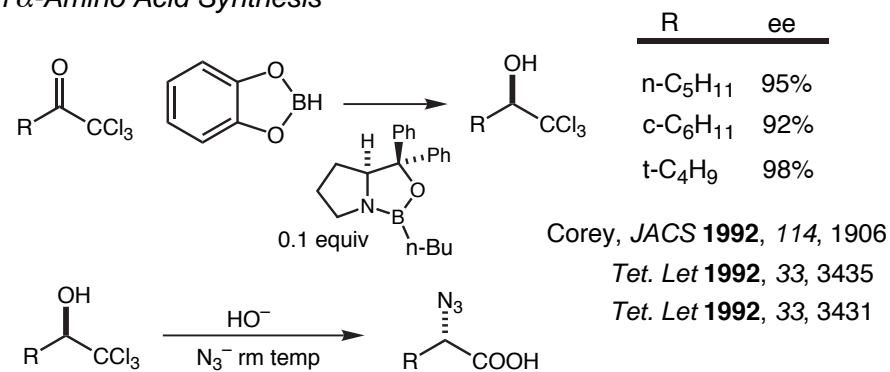




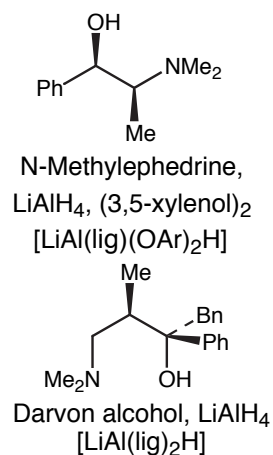
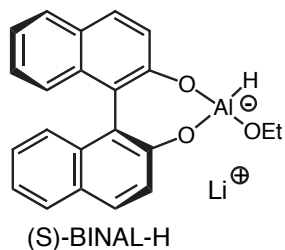
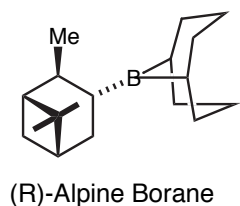
Representative Reductions



Fluoxetine (Prozac®) Synthesis

An α -Amino Acid Synthesis

Enantioselective Reducing Agents

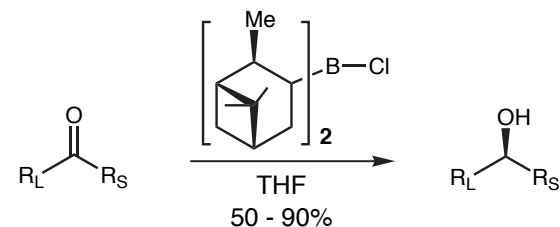


Reviews: Midland, *Asymmetric Synthesis*, Vol 2, p 45-
Granbois, *Asymmetric Synthesis*, Vol 2, p 71-
Brown, *Accts. Chem. Res.* **1992**, 25, 16-24
Singh, *Synthesis* **1992**, 605-617

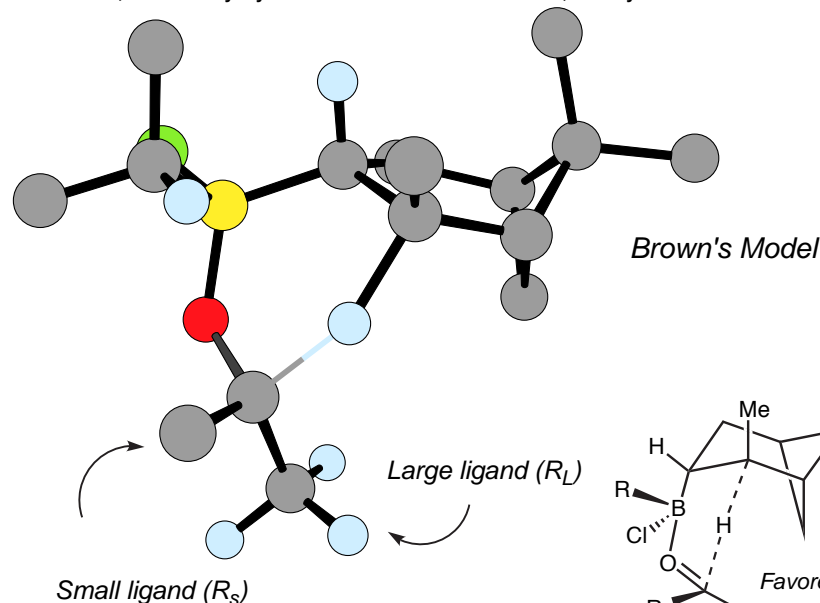
Reductions of Representative Carbonyl Compounds

Reagent			
Alpine-Borane	72 - 92% e.e.	59 - 89% e.e.	78% e.e. R=Me 90% e.e. R=CO $_2$ Me
BINAL-H	84 - 96% e.e. (57% ee, R=i-Pr)	>95% e.e.	95 - 100% e.e. (71% ee, R=i-Pr)
Darvon-LiAlH $_4$	34 - 90% e.e.	25% e.e.	15 - 75% e.e.
N-Methylephedrine-LiAlH $_4$	75 - 90% e.e.	78 - 98% e.e. (cyclic ketones)	----

Stoichiometric Chloroborane Reducing Agents



Ketone	Reaction Conditions	% ee
acetophenone	-25 °C	98%
butyrophenone	-25 °C	98%
2,2-dimethylpropiophenone	-25 °C	79%
3,3-dimethyl-2-butanone	25°C, 12 days	95%
2,2-dimethylcyclohexanone	25°C, 2 days	91%



Less hindered aliphatic ketones are not reduced with useful levels of enantioselectivity

Brown, *J. Org. Chem.* **1985**, 50, 5446
Brown, *J. Org. Chem.* **1986**, 51, 3394
Brown, *J. Org. Chem.* **1988**, 53, 2916

Important References

"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures".

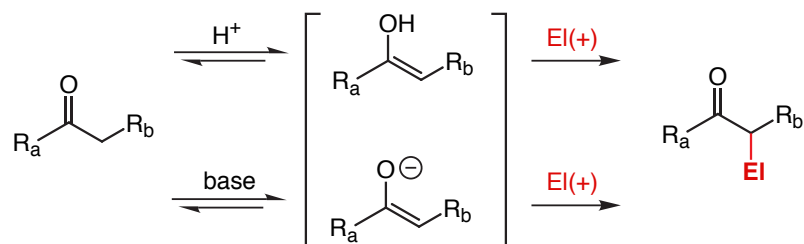
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983).

"Stereoselective Alkylation Reactions of Chiral Metal Enolates". D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984).

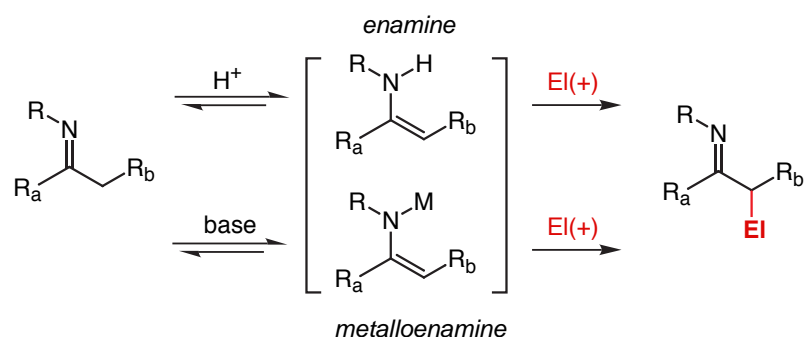
"Generation of Simple Enols in Solution". B. Capon, B.-Z. Guo, F. C. Kwok, A. K. Siddhanta, and C. Zucco *Acc. Chem. Res.* **21**, 121 (1988).

"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.



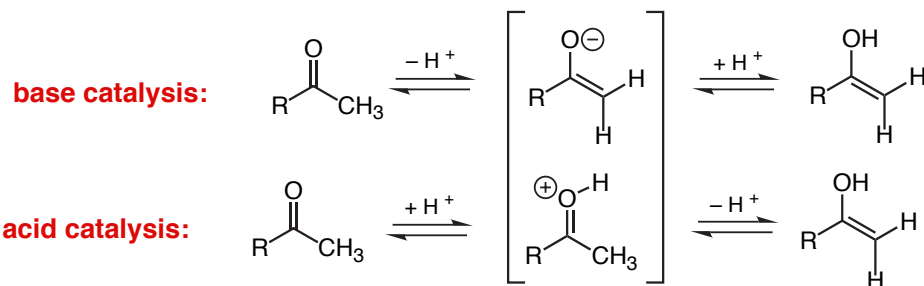
Enamines & metalloenamines, their nitrogen counterparts, are equally important.



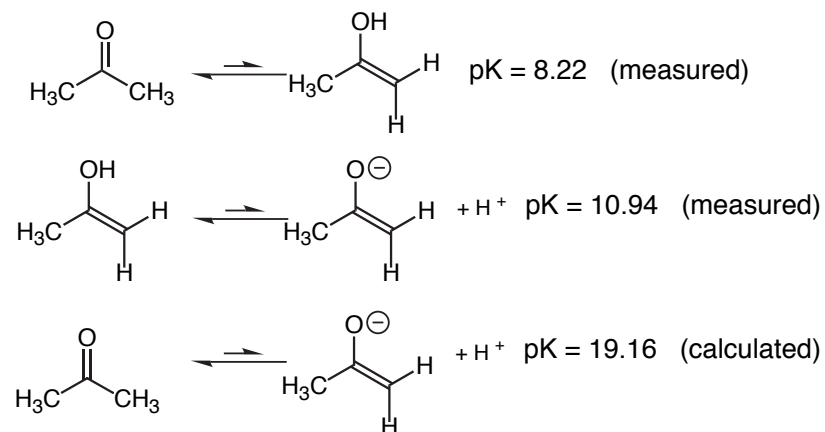
Tautomers: Structural isomers generated as a consequence of the 1,3-shift of a proton adjacent to a X=Y bond. for example:



Keto-Enol Tautomers: Tautomerism may be catalyzed by either acids or bases:



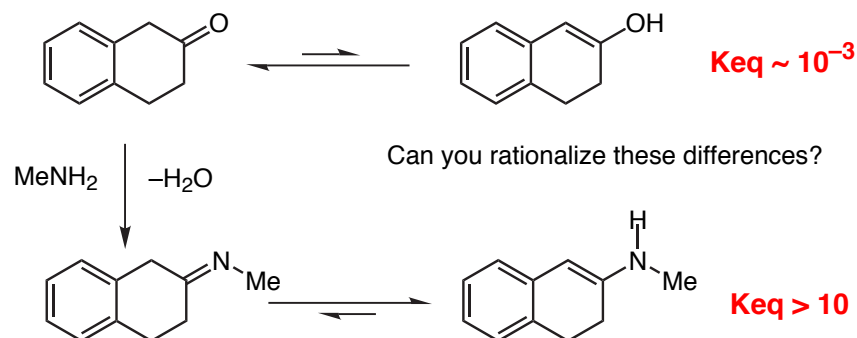
Acidity of Keto and Enol Tautomers: Consider Acetone:



Kresge, *JACS* **1984**, *106*, 460

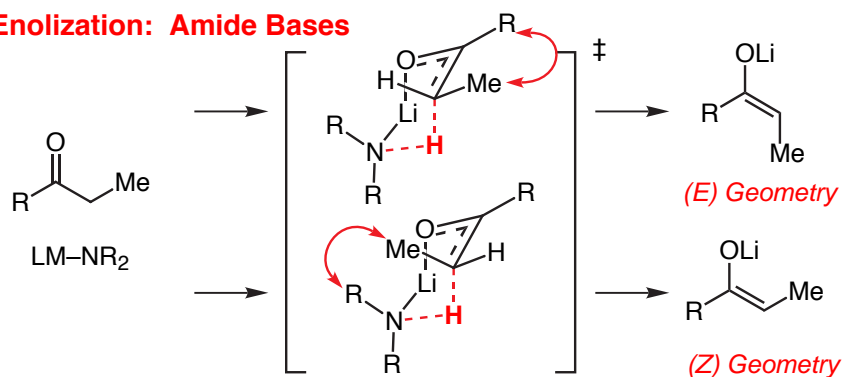
On the origin of the acidity of enols: Wiberg, *JACS* **1996**, *118*, 8291-8299

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.

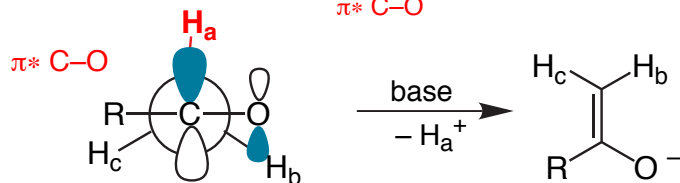
Enolization: Amide Bases



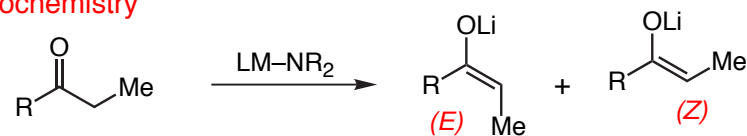
The Ireland Model (*J. Am. Chem. Soc.* **1976**, 98, 2868)
 Narula, *Tetrahedron Lett.* **1981**, 22, 4119
 more recent study: Ireland, *JOC* **1991**, 56, 650

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



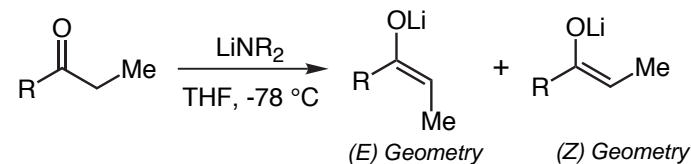
Stereochemistry



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

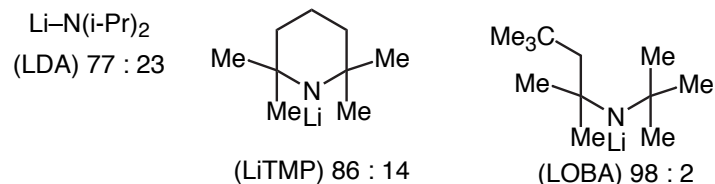
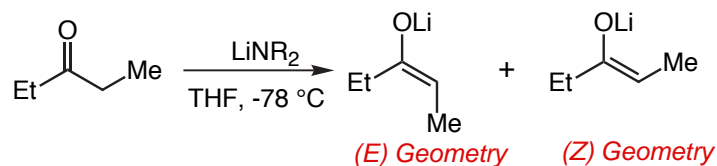
Solvent

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)

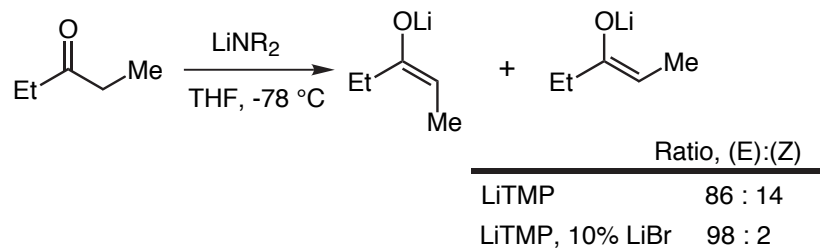
Base	R = Et, (E):(Z)	R = Cy, (E):(Z)
Li-N(i-Pr) ₂	70 : 30	39 : 61
Li-N(SiMe ₃) ₂	30 : 70	15 : 85
Li-N(SiEt ₃) ₂	1 : 99	4 : 96
Li-N(SiMe ₂ Ph) ₂	0 : 100	0 : 100
at equilibrium	16 : 84	—

Base Structure Corey & Co-workers, *Tetrahedron Lett.* **1984**, 25, 491, 495

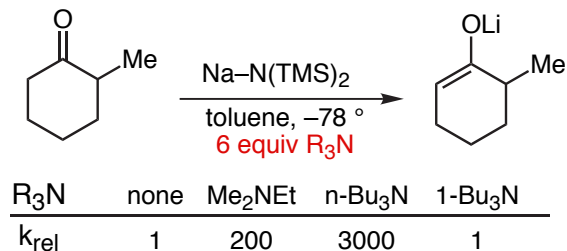


Lithium Halide Effects Collum (*J. Am. Chem. Soc.* **1991**, 113, 9572)
 Collum (*J. Am. Chem. Soc.* **1991**, 113, 9575)
 Collum (*J. Am. Chem. Soc.* **1991**, 113, 5053)

For the latest in the series of Column papers see: *JACS* **2000**, 122, 2452-2458

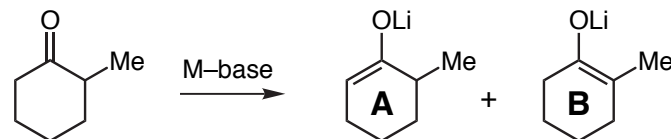


Enolization in Non-Ethereal Solvents Collum (*JACS* **2003**, 125, ASAP)



Reaction kinetics suggest (TMS₂NLi)₂(R₃N)(Ketone)[‡]

Regioselective Enolization

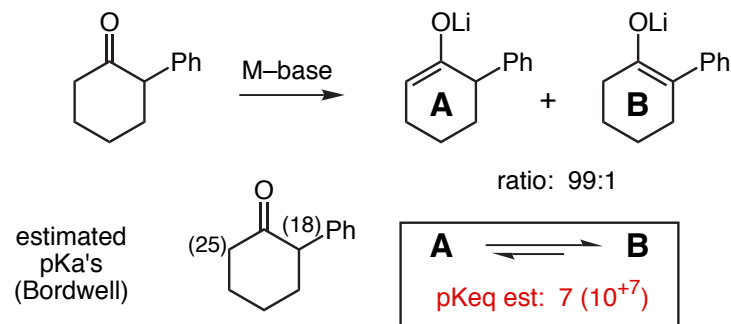


Base	temp	control	Ratio (A:B)
LiN(i-Pr) ₂	-78 °	kinetic	99:1
LiN(SiMe ₃) ₂	-78 °	kinetic	95:5
Ph ₃ C-Li	-78 °	kinetic	90:10
Ph ₃ C-Li	heat	thermo	10:90
Na-H	heat	thermo	26:74
K-H	heat	thermo	38:62

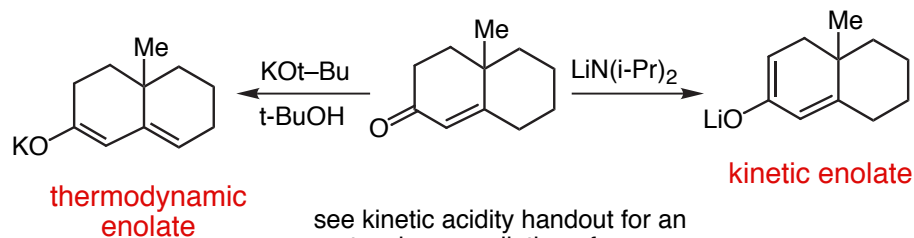
A: Alkyl groups stabilize metal enolate

A: As M-O bond becomes more ionic A is attenuated

Kinetic Selection sensitive to structure

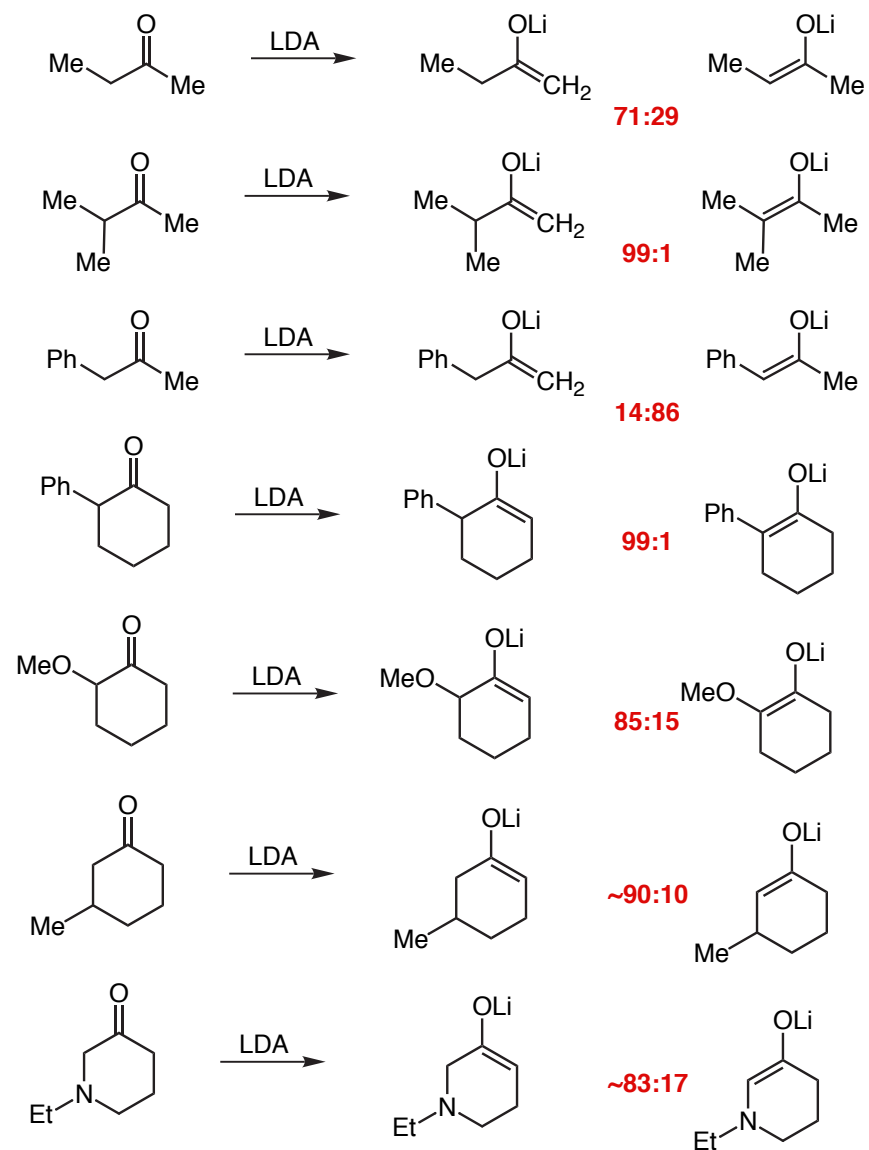


Unsaturated Ketones

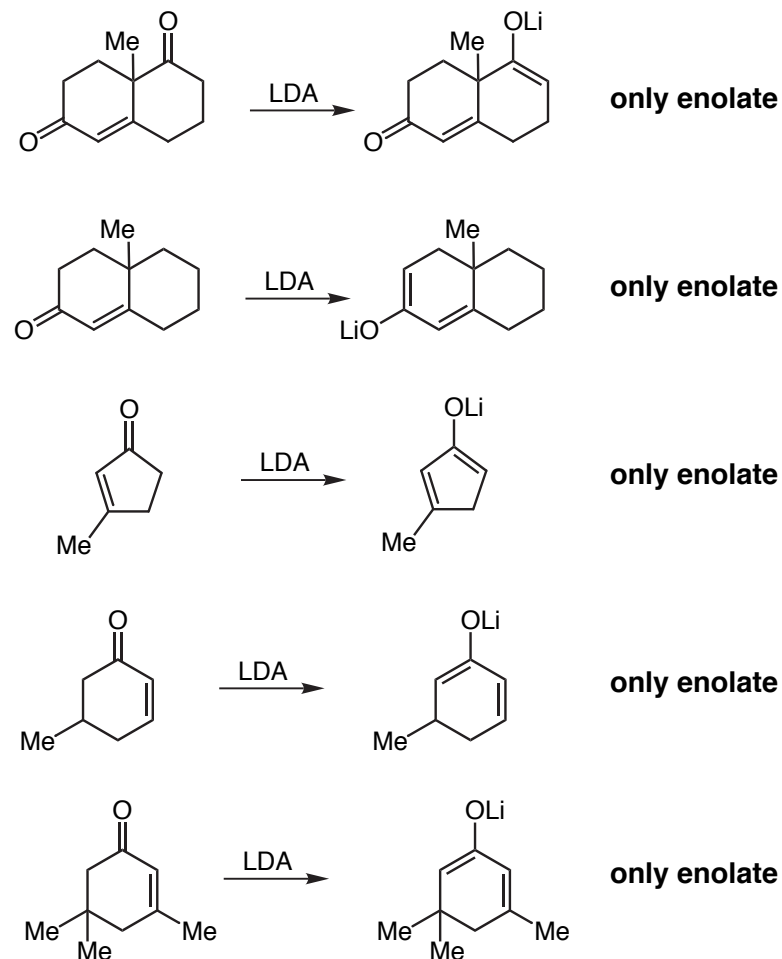


see kinetic acidity handout for an extensive compilation of cases.

Kinetic Selection sensitive to structure



Kinetic Selection in Enolization of Unsaturated Ketones



Quote for the Day

Professor Robert Milikan (1928), Nobel Laureate in Chemistry

"There is no likelihood man can ever tap the power of the atom. The glib supposition of utilizing atomic energy when our coal has run out is a completely unscientific Utopian dream, a childish bug-a-boo. Nature has introduced a few foolproof devices into the great majority of elements that constitute the bulk of the world, and they have no energy to give up in the process of disintegration."

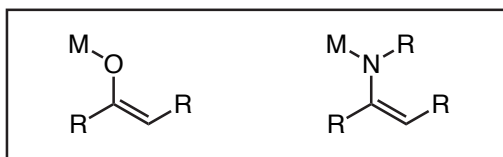
<http://www.courses.fas.harvard.edu/~chem206/>

Chemistry 206

Advanced Organic Chemistry

Lecture Number 23

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

D. A. Evans

Friday,
November 7, 2003

■ 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. Petragrani and M. Yonashiro *Synthesis*, 521 (1982).

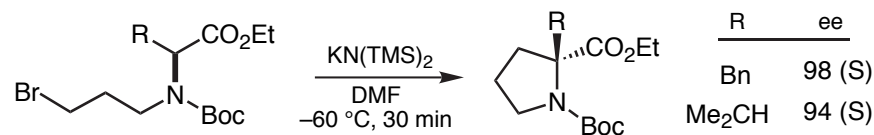
"Generation of Simple Enols in Solution". Capon, Guo, Kwok, Siddhanta, and Zucco *Acc. Chem. Res.* **21**, 121 (1988).

"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).

■ Database Problem 314

Kawabata and co-workers recently reported the remarkable enolate alkylation illustrated below (*JACS* **2003**, *125*, 13012). When the indicated α -amino acid ester is treated with KHMDS in DMF at $-60\text{ }^\circ\text{C}$, the derived cyclic amino acid ester is formed in high yield and enantioselectivity. The stereochemical outcome represents a formal retention of configuration. This reaction exhibits some generality as the 4-, 5-, 6-, and 7-membered lactams may be obtained in high ee.



Provide a rationalization of these results. Three-dimensional drawings are recommended.

Important References

"Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective C-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures".

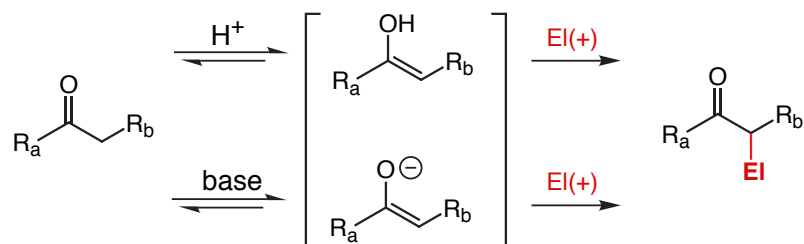
D. Seebach *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1983).

"Stereoselective Alkylation Reactions of Chiral Metal Enolates". D. A. Evans *Asymmetric Synthesis*, **3**, 1 (1984).

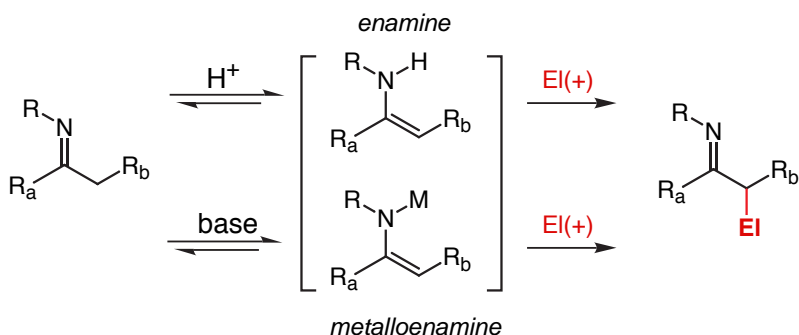
"Generation of Simple Enols in Solution". B. Capon, B.-Z. Guo, F. C. Kwok, A. K. Siddhanta, and C. Zucco *Acc. Chem. Res.* **21**, 121 (1988).

"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.



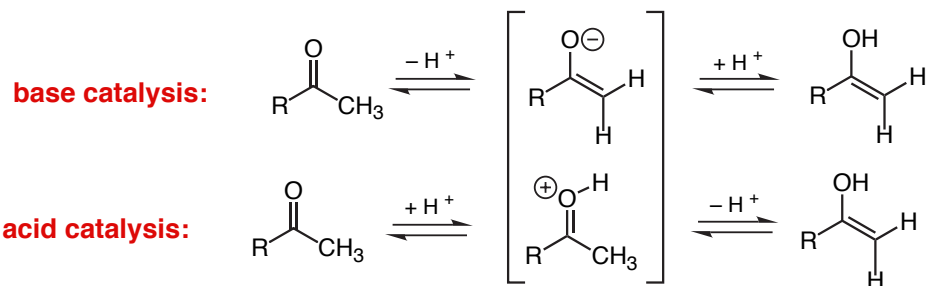
Enamines & metalloenamines, their nitrogen counterparts, are equally important.



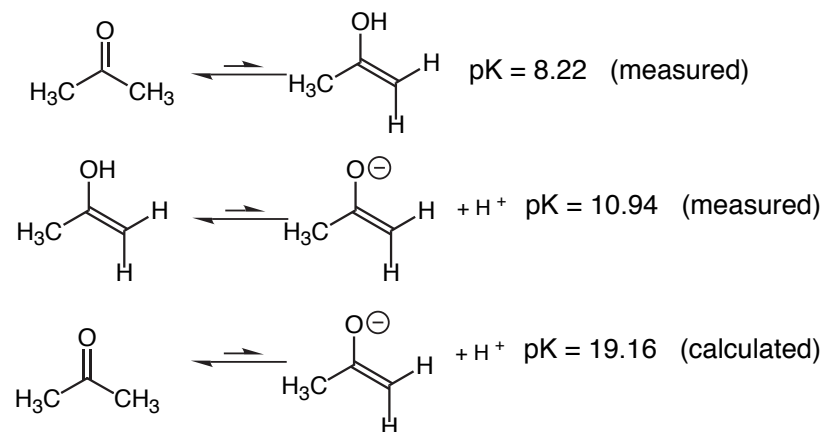
Tautomers: Structural isomers generated as a consequence of the 1,3-shift of a proton adjacent to a X=Y bond. for example:



Keto-Enol Tautomers: Tautomerism may be catalyzed by either acids or bases:



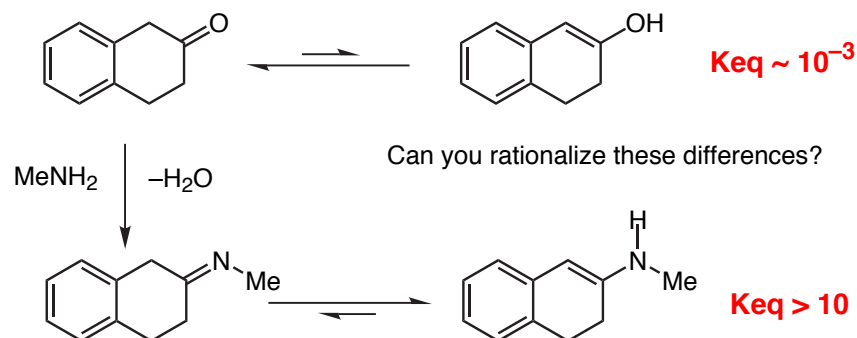
Acidity of Keto and Enol Tautomers: Consider Acetone:



Kresge, *JACS* **1984**, *106*, 460

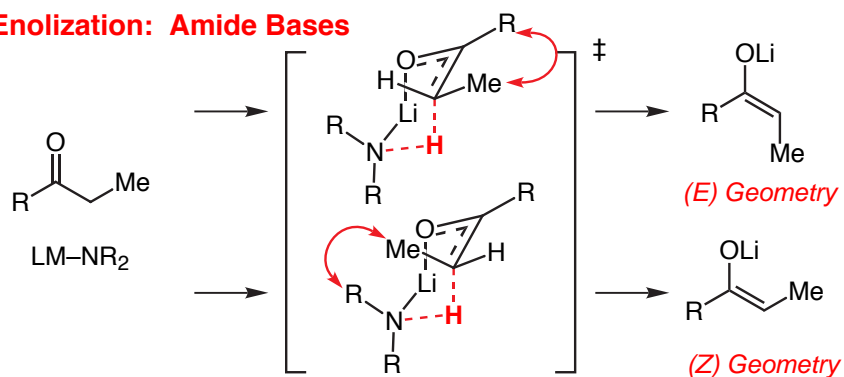
On the origin of the acidity of enols: Wiberg, *JACS* **1996**, *118*, 8291-8299

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.

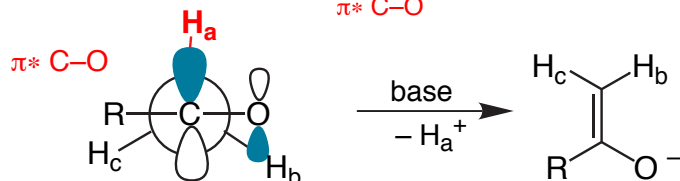
Enolization: Amide Bases



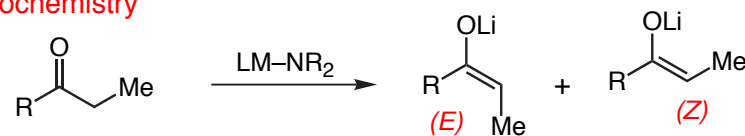
The Ireland Model (*J. Am. Chem. Soc.* **1976**, 98, 2868)
 Narula, *Tetrahedron Lett.* **1981**, 22, 4119
 more recent study: Ireland, *JOC* **1991**, 56, 650

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



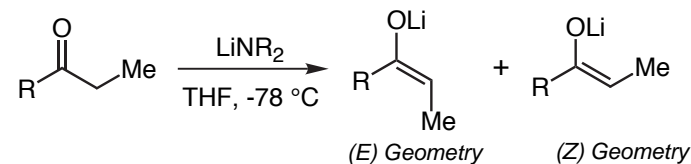
Stereochemistry



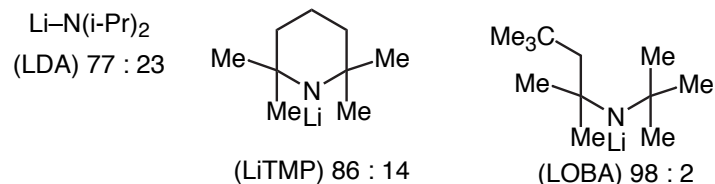
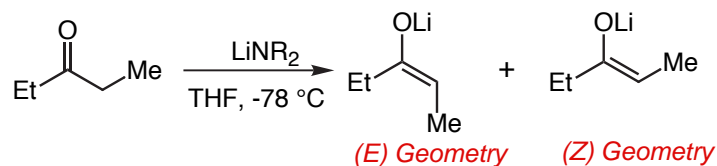
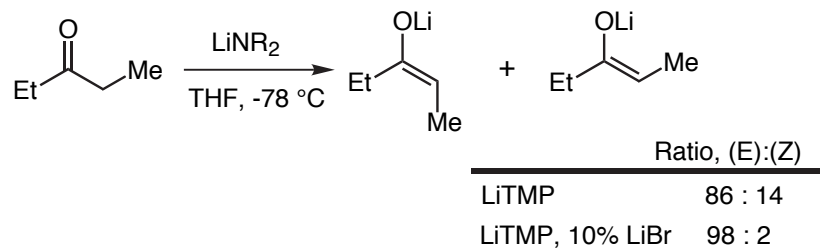
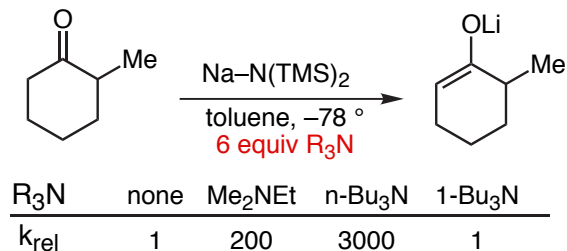
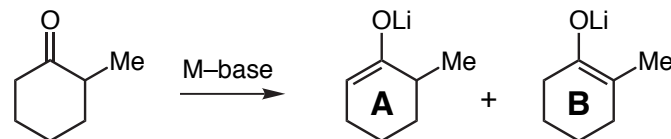
Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe, O-t-Bu	95 : 5
LDA (THF)	-S-t-Bu	95 : 5
LDA (THF)	-Et	77 : 23
LDA (THF)	-CHMe ₂	40 : 60
LDA (THF)	-CMe ₃	0 : 100
LDA (THF)	-C ₆ H ₅	0 : 100
LDA (THF)	-NEt ₂	0 : 100
s-BuLi (THF)	-NEt ₂	25 : 75

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)

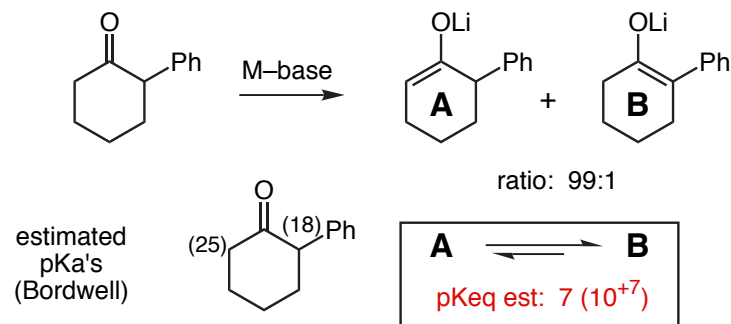
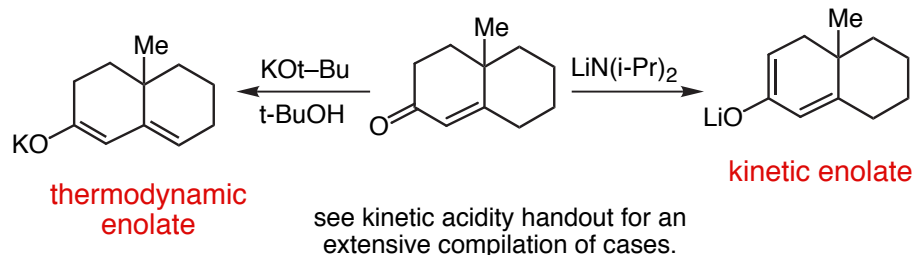
Base	R = Et, (E):(Z)	R = Cy, (E):(Z)
Li-N(i-Pr) ₂	70 : 30	39 : 61
Li-N(SiMe ₃) ₂	30 : 70	15 : 85
Li-N(SiEt ₃) ₂	1 : 99	4 : 96
Li-N(SiMe ₂ Ph) ₂	0 : 100	0 : 100
at equilibrium	16 : 84	—

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 Column papers see: *JACS* **2000**, 122, 2452-2458**Enolization in Non-Ethereal Solvents** Collum (*JACS* **2003**, 125, ASAP)Reaction kinetics suggest (TMS₂NLi)₂(R₃N)(Ketone)[‡]**Regioselective Enolization**

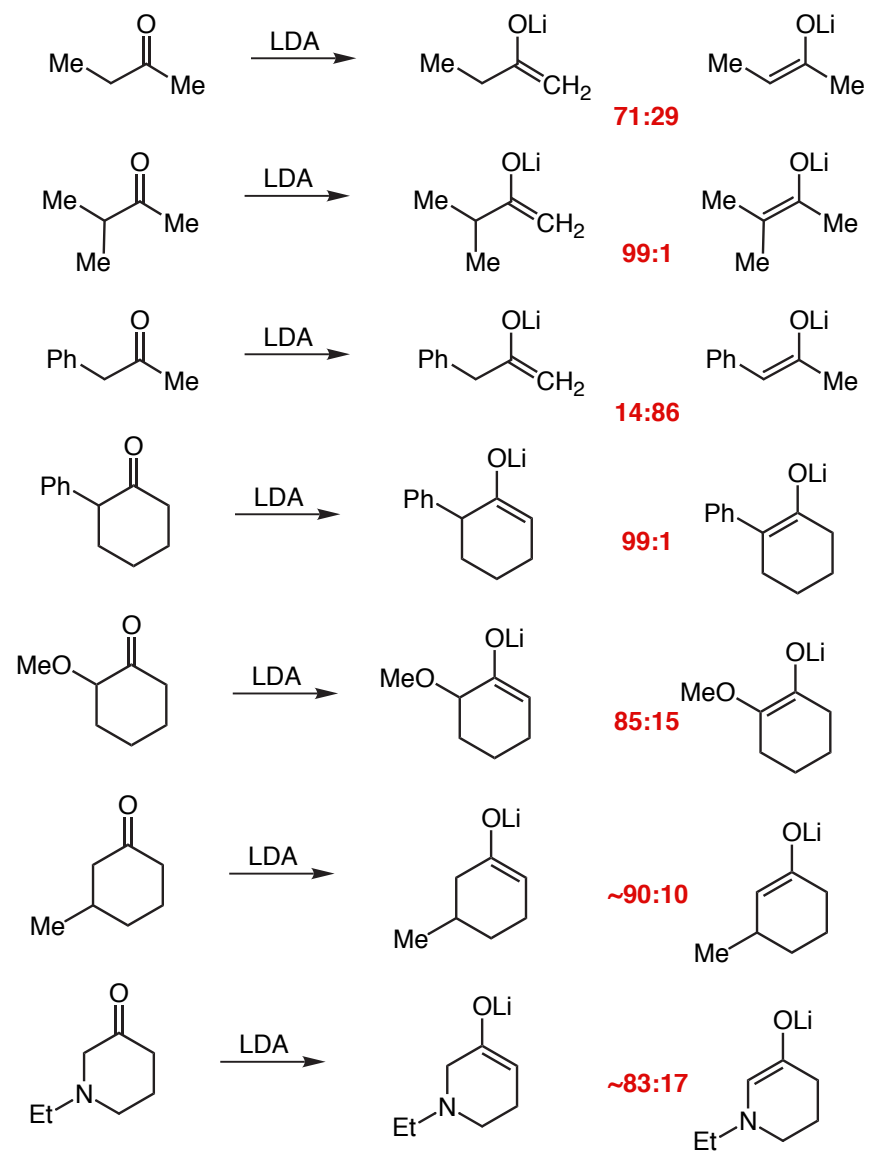
Base	temp	control	Ratio (A:B)
LiN(i-Pr) ₂	-78 °	kinetic	99:1
LiN(SiMe ₃) ₂	-78 °	kinetic	95:5
Ph ₃ C-Li	-78 °	kinetic	90:10
Ph ₃ C-Li	heat	thermo	10:90
Na-H	heat	thermo	26:74
K-H	heat	thermo	38:62

A: Alkyl groups stabilize metal enolate

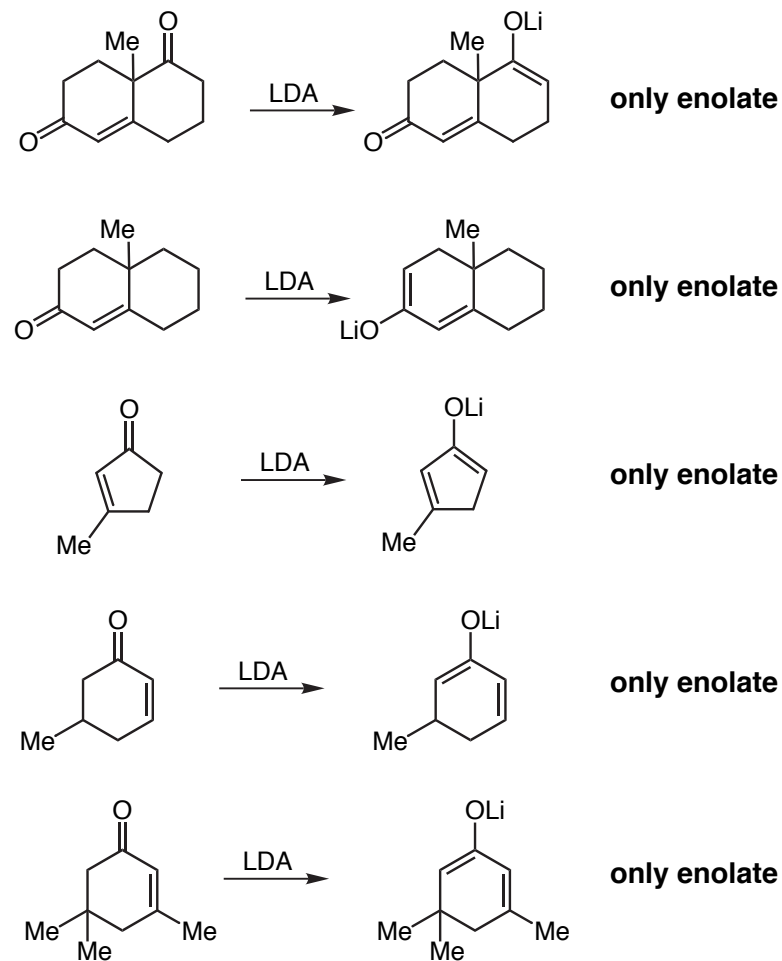
A: As M-O bond becomes more ionic A is attenuated

Kinetic Selection sensitive to structure**Unsaturated Ketones**

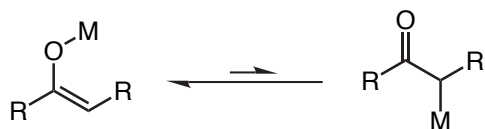
Kinetic Selection sensitive to structure



Kinetic Selection in Enolization of Unsaturated Ketones



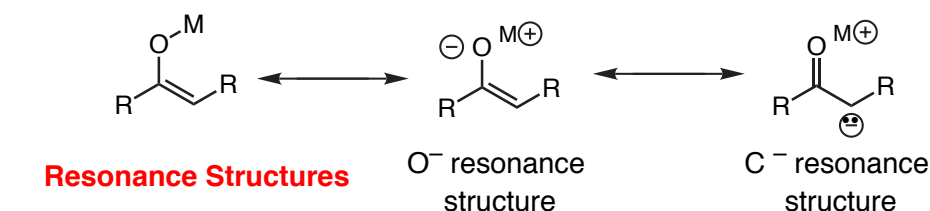
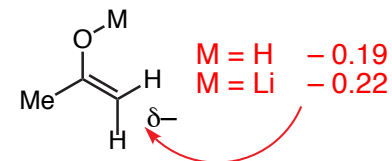
Metal Tautomerism



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.

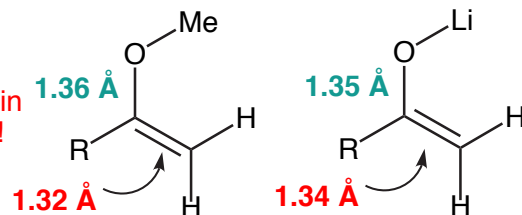
Ab initio calculations (Spartan) indicate that the partial negative charge on the alpha carbon is ~ -0.22 for the Li enolate



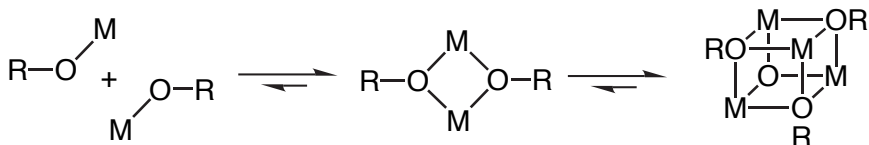
Since enolates usually function as carbon nucleophiles, it is therefore of some interest to assess the relative importance of the illustrated contributing polar resonance structures. Within the last decade good X-ray crystal structures of a number of metal enolates have been obtained.

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.

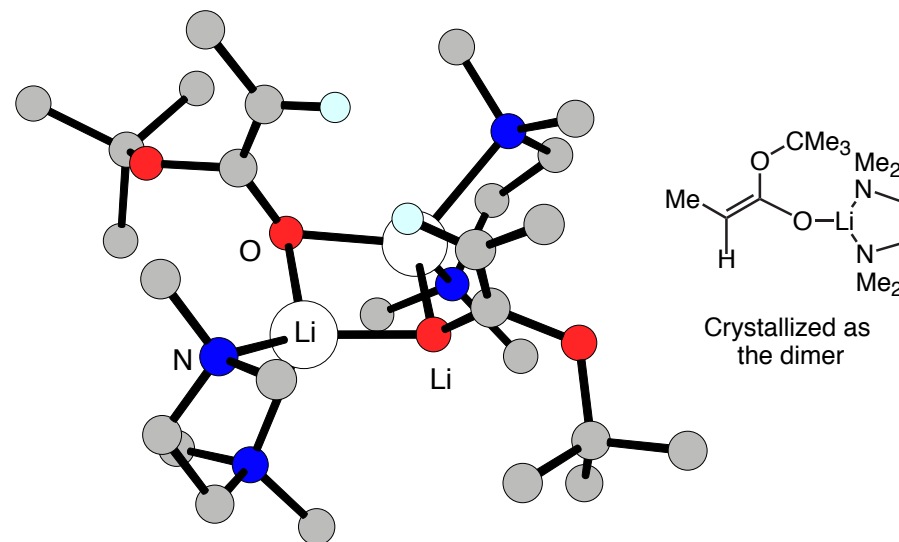
The prediction stated above does hold, but the net change in the C-C bond length is < 2 % !



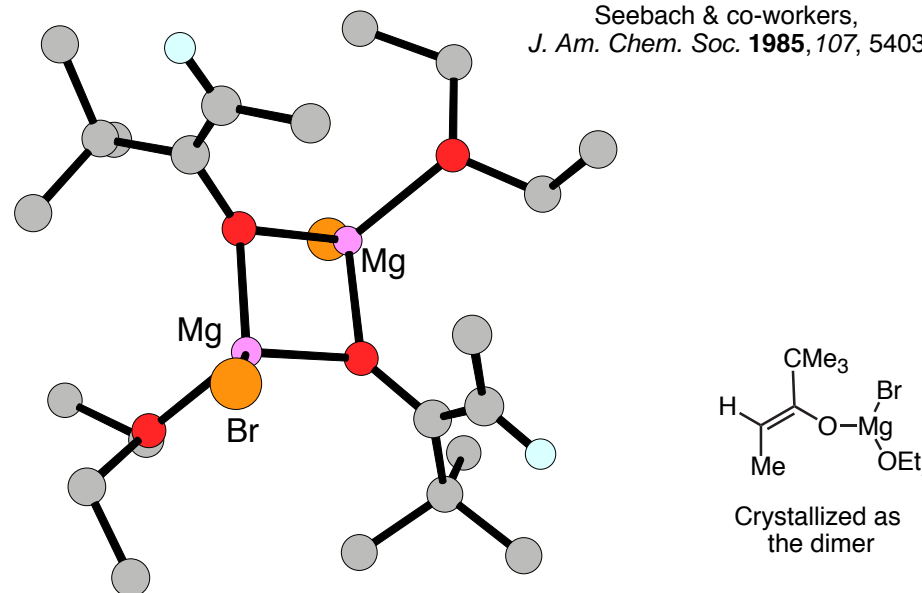
In solution and in the solid state metal enolates have a strong tendency to aggregate into dimers and tetramers to satisfy metal solvation requirements.



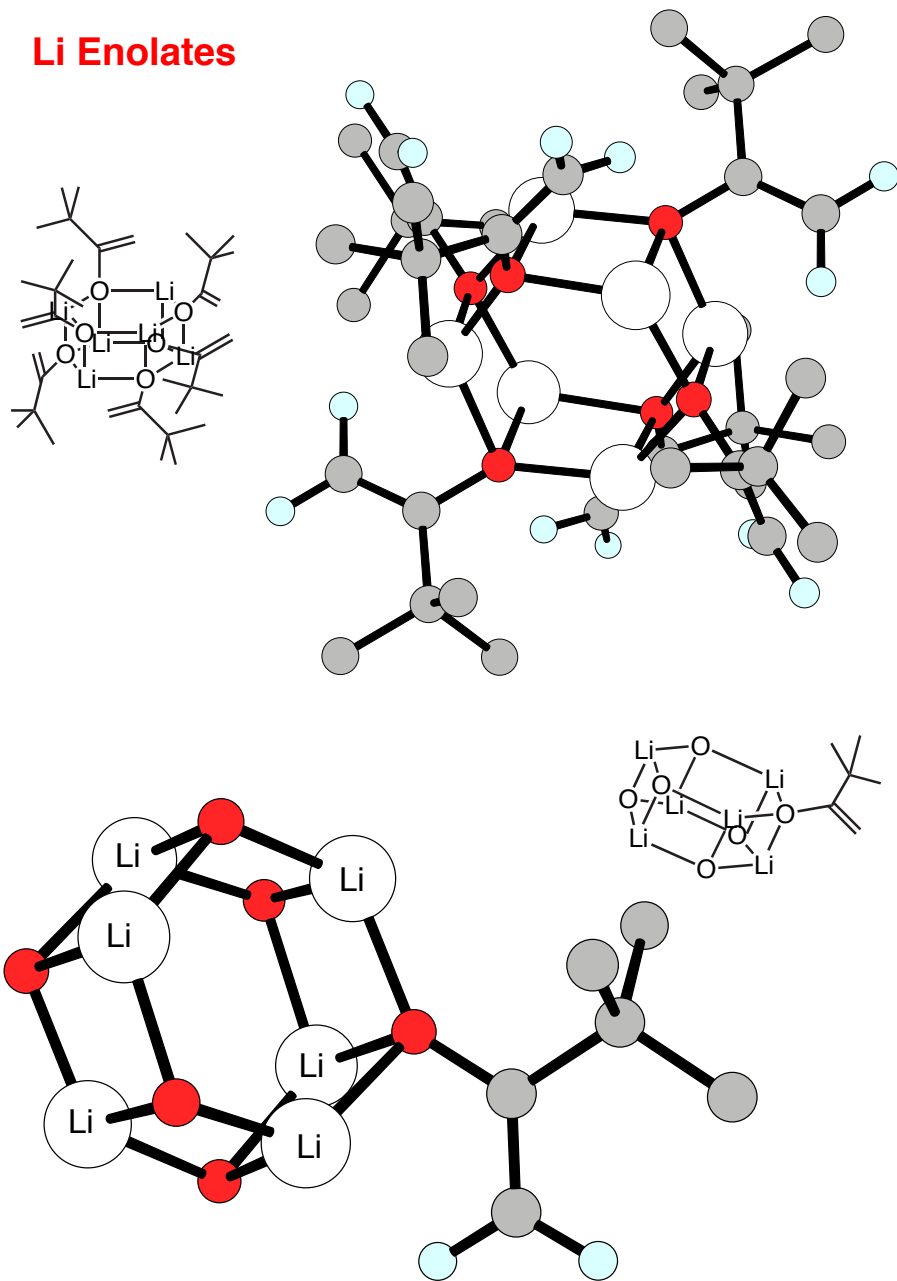
23-05 enolate structure-1 11/7/03 8:15 AM



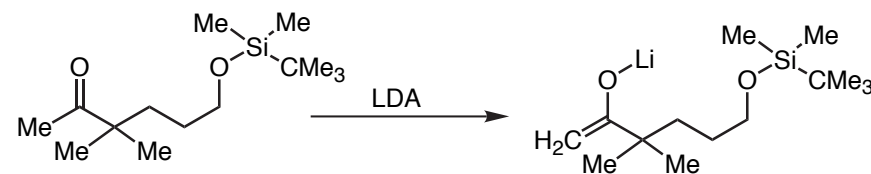
Seebach & co-workers,
J. Am. Chem. Soc. 1985, 107, 5403.



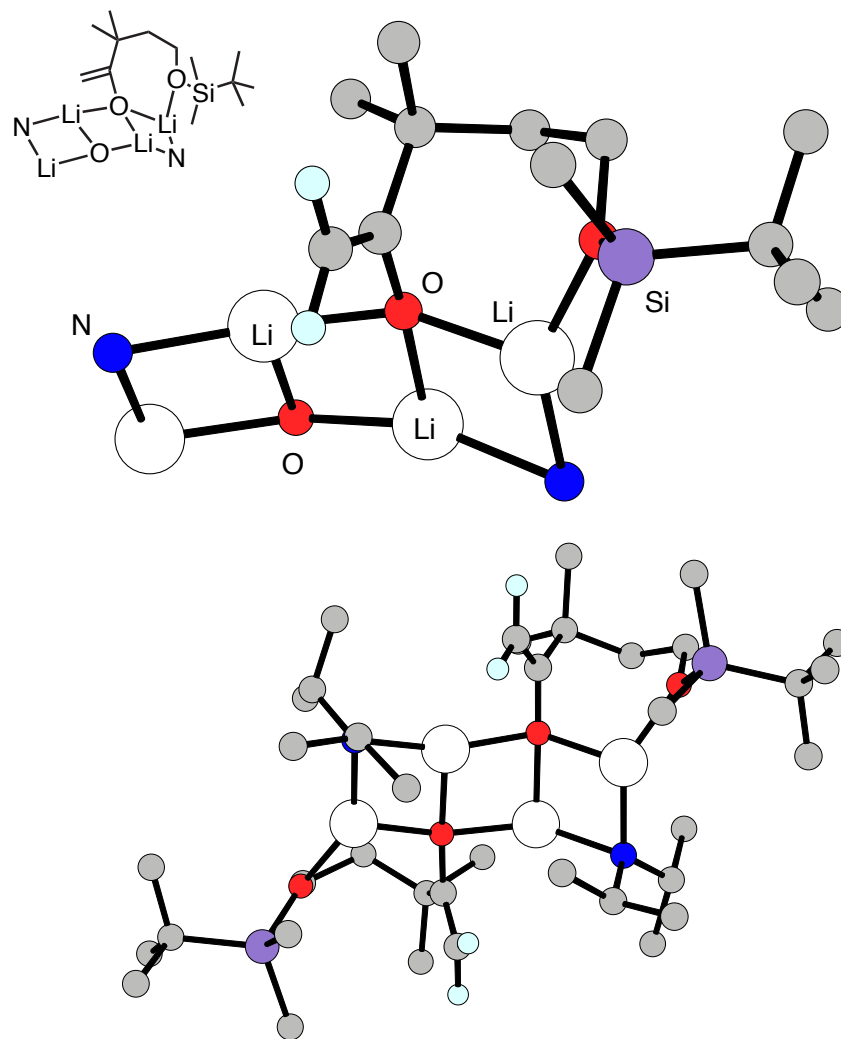
Li Enolates



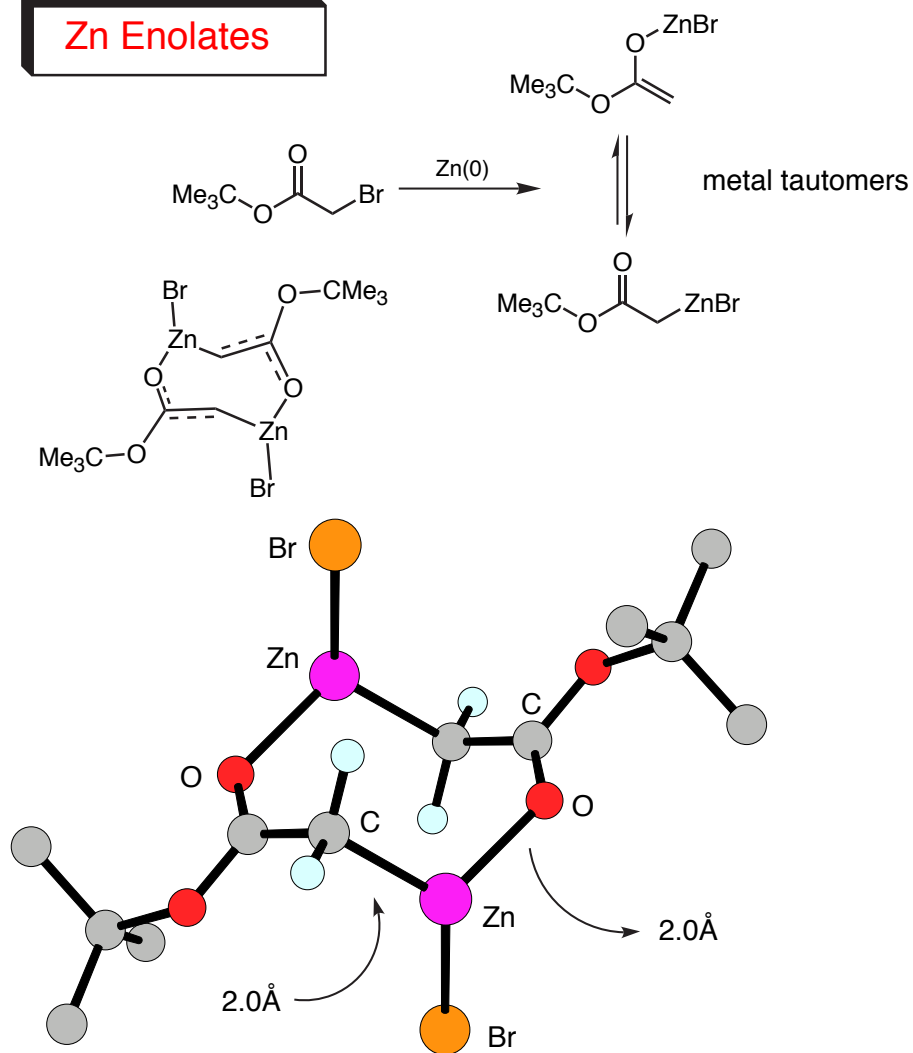
Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462-468.



Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539-5541.

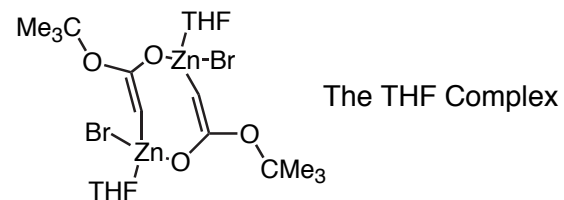


Zn Enolates

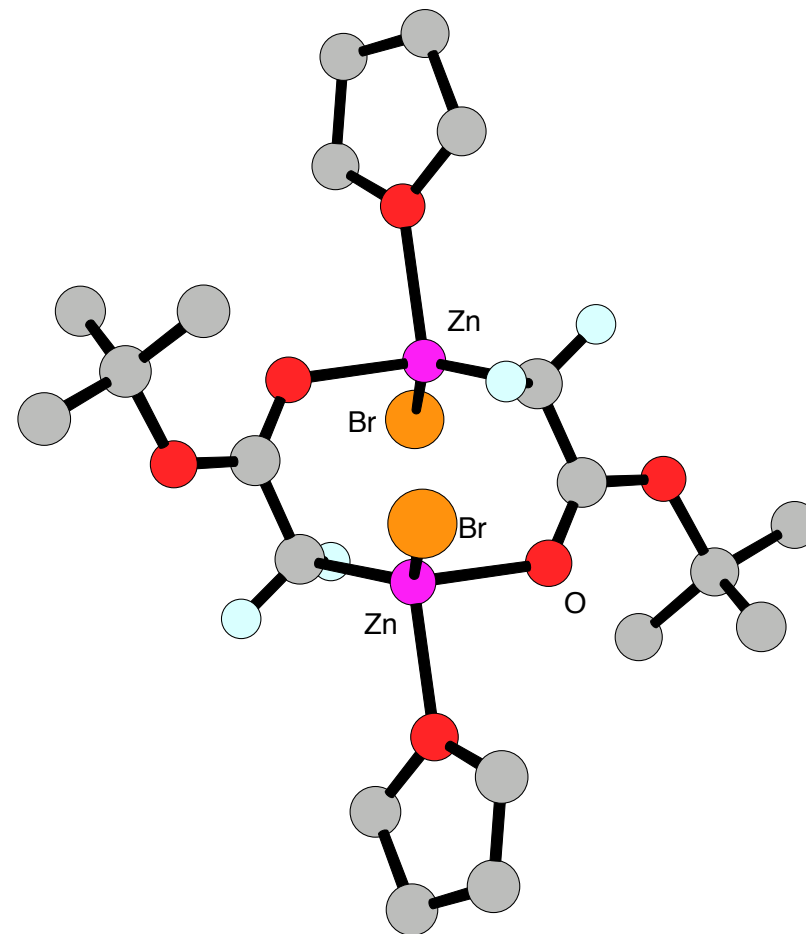


Dekker, J.; Boersma, J.; van der Kerk, G. J. M. *J. Chem. Soc. Chem. Commun.* **1983**, 553.

Dekker, J.; Budzelaar, J.; Boersma, J.; van der Kerk, G. J. M. *Organometallics* **1984**, 3, 1403.

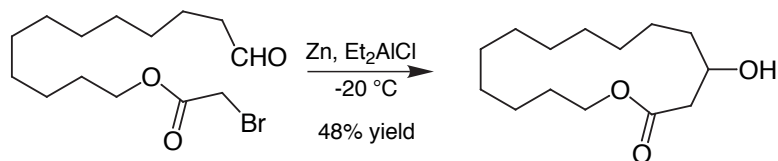


The THF Complex

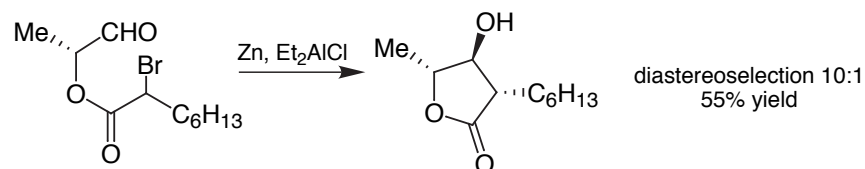


The "Classical" Reformatsky Process

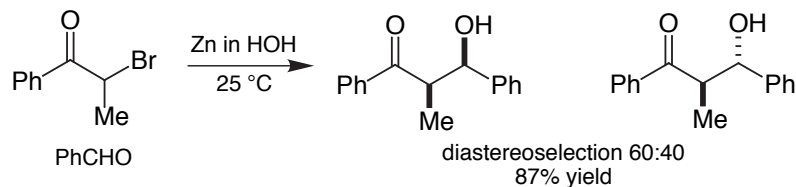
Review: *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.8, pp 277-299
 Fürstner, A. "Recent Advances in the Reformatsky Reaction." *Synthesis* **1989**, 571.



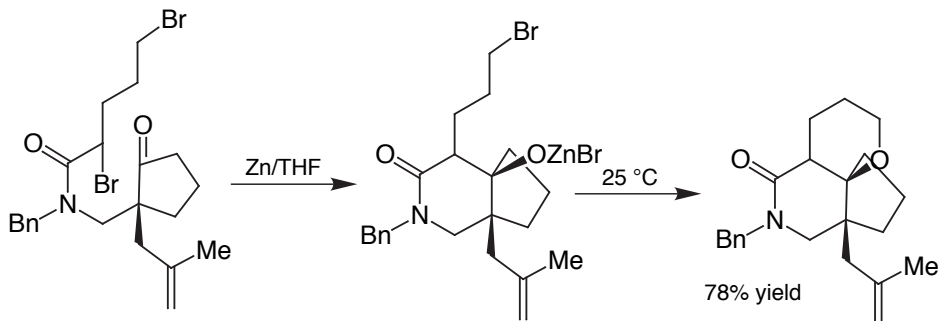
H. Nozaki & Co-workers,
J. Am. Chem. Soc. **197**, 99, 7705 Both cyclic and acyclic cases studied (11 cases).



T. Nishida & Co-workers,
Tetrahedron **1991**, 47, 6623. Based on the Nozaki recipe *JACS* **1977**, 99, 7705



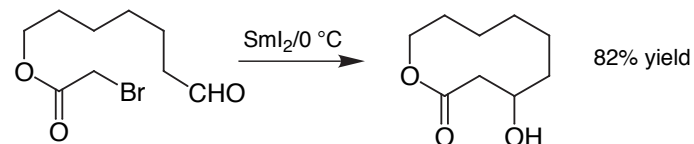
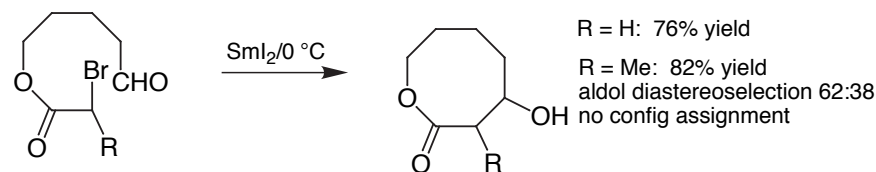
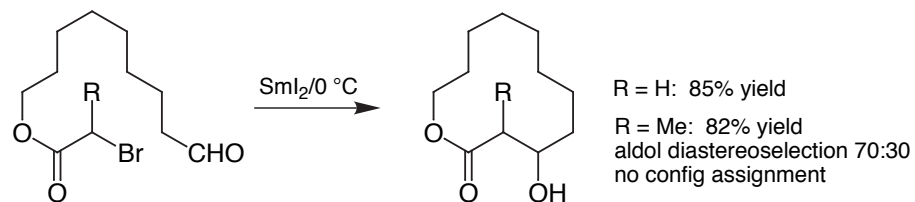
T. H. Chan & Co-workers,
Chem. Commun. **1990**, 505. Rxns carried out in water with either activated Zn or Sn. 19 cases reported.



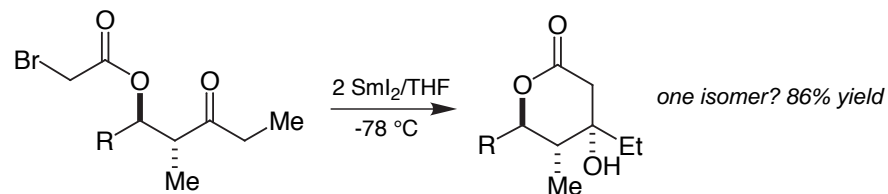
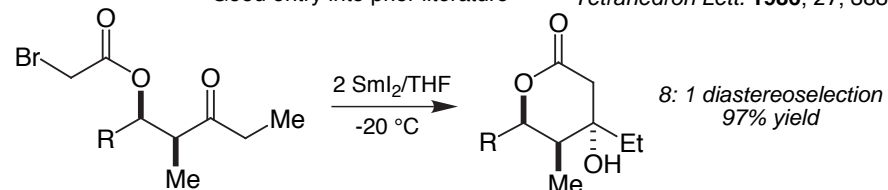
C. H. Heathcock & Co-workers,
J. Org. Chem. **1987**, 52, 5745.

The Samarium(II) Variant

Molander, "Reductions with Samarium (II) Iodide." *Org. Reactions* **1994**, 46, 211-367.

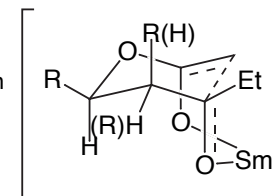


Good entry into prior literature
 T. Tabushi & Co-workers,
Tetrahedron Lett. **1986**, 27, 3889.



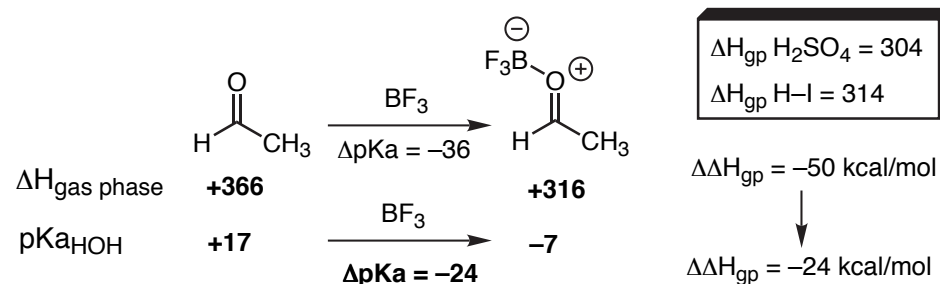
G. A. Molander & Co-workers,
J. Am. Chem. Soc. **1987**, 109, 6556.

Proposed Transition structure



Mild Methods for Forming Enolates

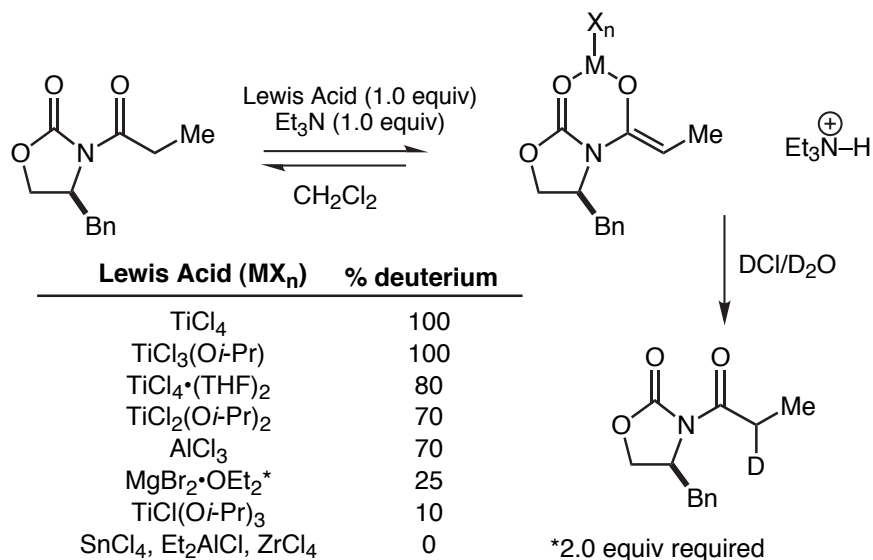
Lewis Acid C=O Complexation Enhances C-H Acidity (Computation)



BF₃ complexation generates a "superacid" comparable to the acidity of H₂SO₄

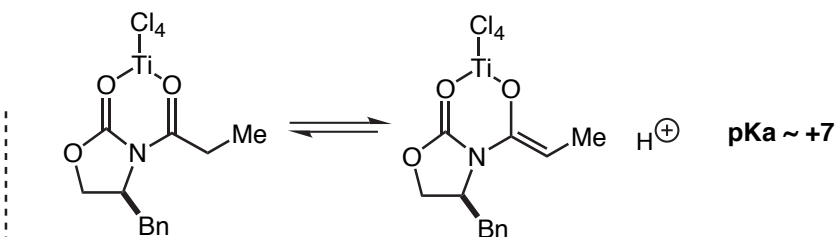
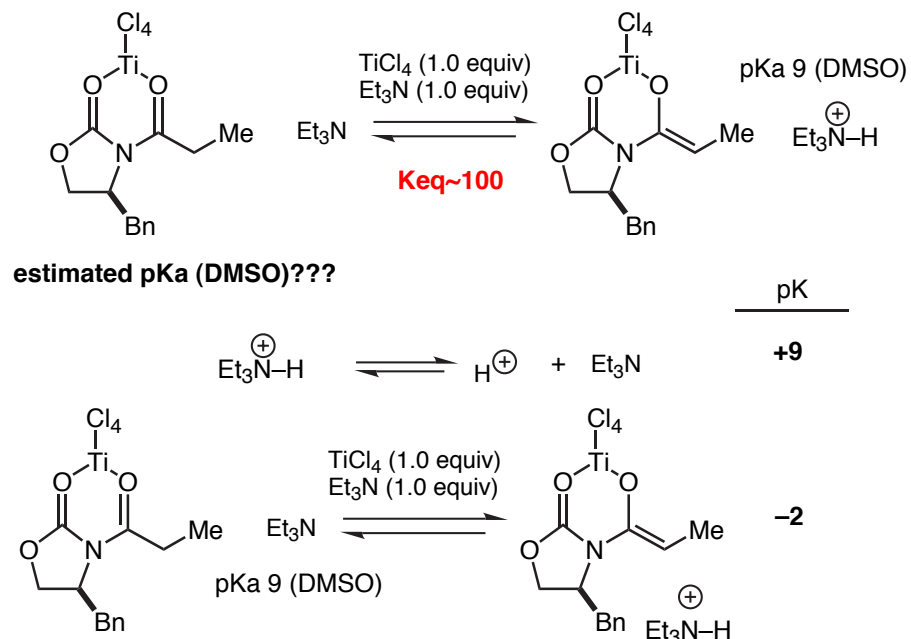
Ren et al, JACS 1999, 121, 2633-2634 (pdf)

Some qualitative observations (Evans Group, Unpublished)

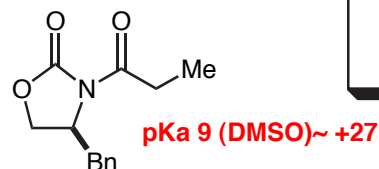


In these experiments, the Lewis acid was added first followed by the amine.

Some qualitative observations (Evans Group, Unpublished)



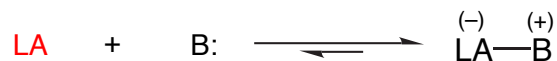
estimated pKa (DMSO) ~ +7



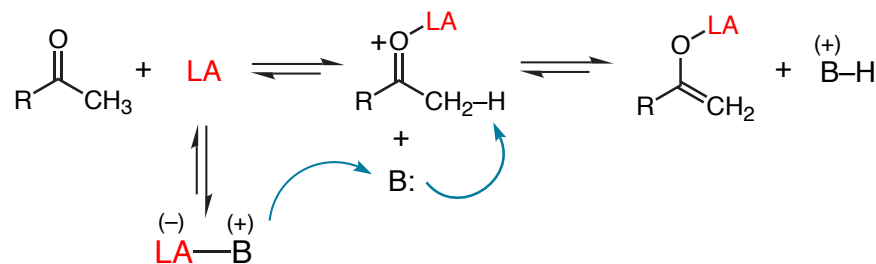
Hence TiCl₄ complexation lowers acidity by ~20 pKa units. this number is the same magnitude as the BF₃-acetaldehyde case just discussed

Strategy

Choose Lewis Acid (LA) which can reversibly associate with amine base (B):



This system has the potential to enolize carbonyl functional groups:

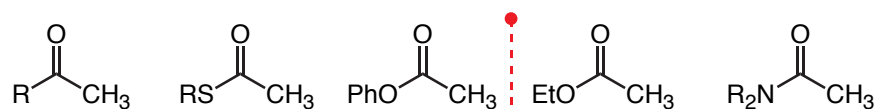


Useful Lewis Acid Pairs

Lewis Acid	Base	Complexation
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 (Et₃N, EtNi-Pr₂)
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)

⁻OTf = ⁻OSO₂CF₃

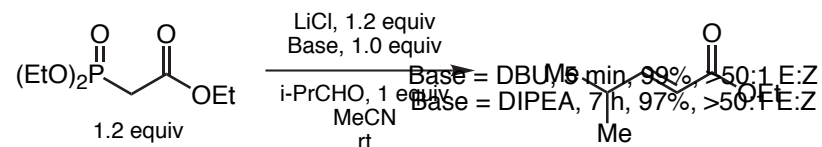
All of the above systems will enolize simple ketones to some extent.



100% enolization for B, Sn, Ti
partial enolization for Li, Mg

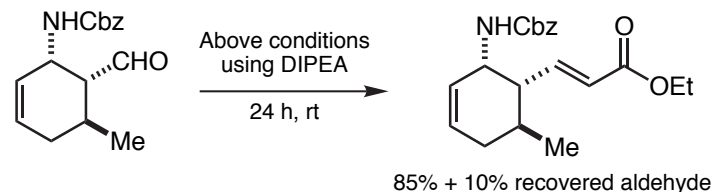
Lithium Enolates

Horner-Wadsworth-Emmons Reaction.



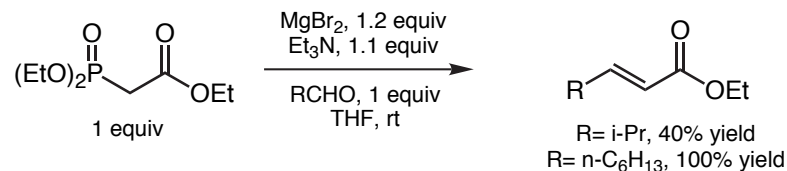
pKa 19.2 (DMSO), K⁺ counterion
pKa 12.2 (Diglyme), Li⁺ counterion

Roush & Masamune, Tet. Lett. 1984, 25, 2183-2186



Conventional methods of deprotonation (NaH) resulted in epimerization (Overman JACS **1978**, 5179).

Magnesium Enolates

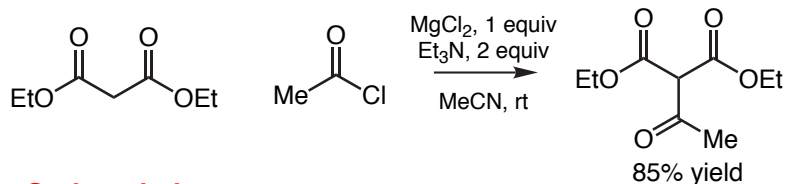


Rathke, Nowak *J. Org. Chem.* **1985**, 50, 2624-2626.

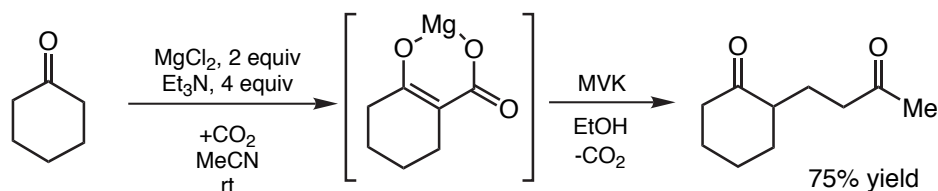
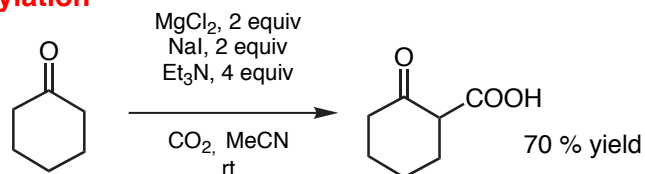
Magnesium Enolates

Rathke *J. Org. Chem.* **1985**, *50*, 2622-2624.
J. Org. Chem. **1985**, *50*, 4877-4879.
Syn. Comm. **1986**, *16*, 1133-1139.

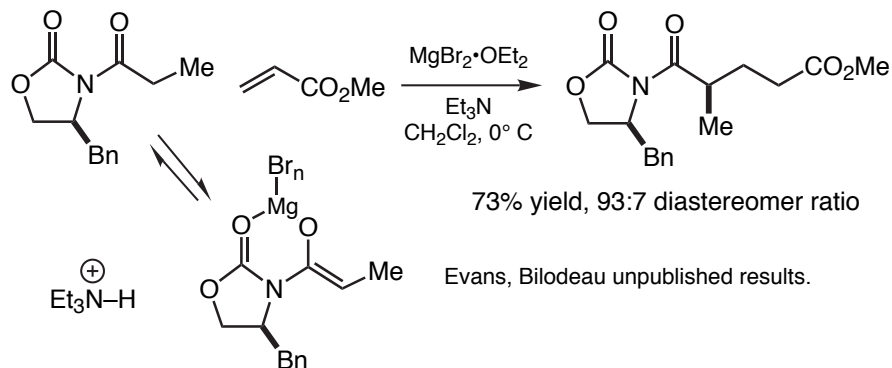
Diethylmalonate acylations



Ketone Carboxylation



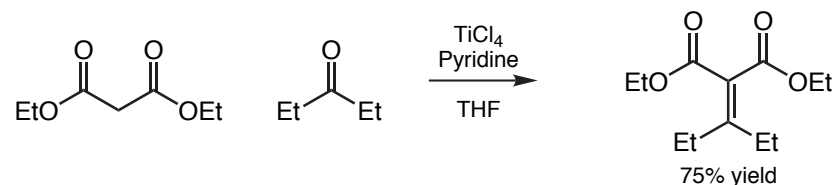
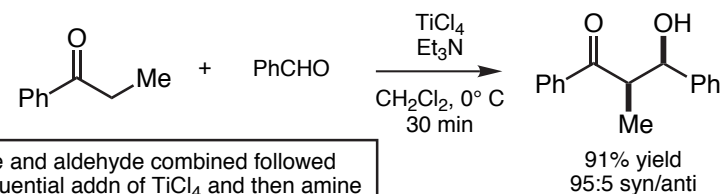
Michael reaction



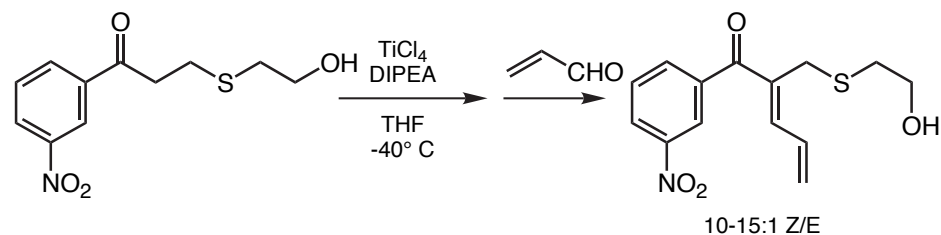
Deuterium quench indicates 25% enolization of *N*-propionyloxazolidinone

Titanium Enolates

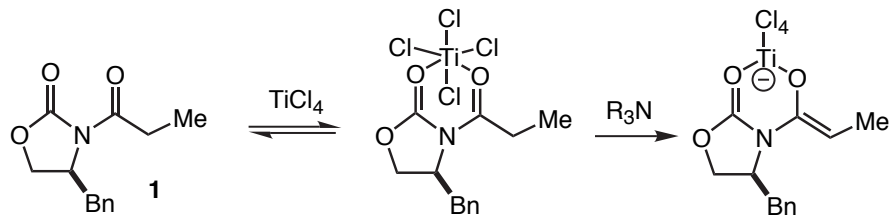
The Early Literature

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



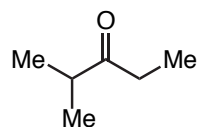
- Enolization process not responsive to tertiary amine structure
- DIPEA, Et_3N , N-Ethylpiperidine all suitable bases.
- DBU and tetramethylguanidine do not provide enolate.
- CH_2Cl_2 is the only suitable solvent for these enolizations.

N-Propionyloxazolidone (1)

Lewis Acid	% Enolization
TiCl_4	100
<i>i</i> -PrOTiCl ₃	100
$\text{TiCl}_4 \cdot 2\text{THF}$	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



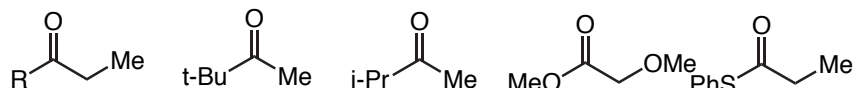
- Order of addition of reagents is important for TiCl_4 .



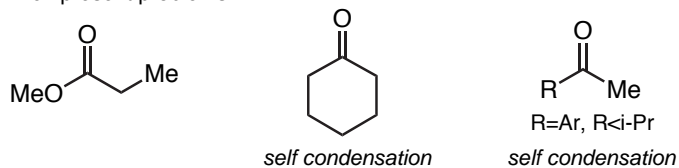
- Order of addition of reagents is not important for *i*-PrOTiCl₃ or (*i*-PrO)₂TiCl₂.



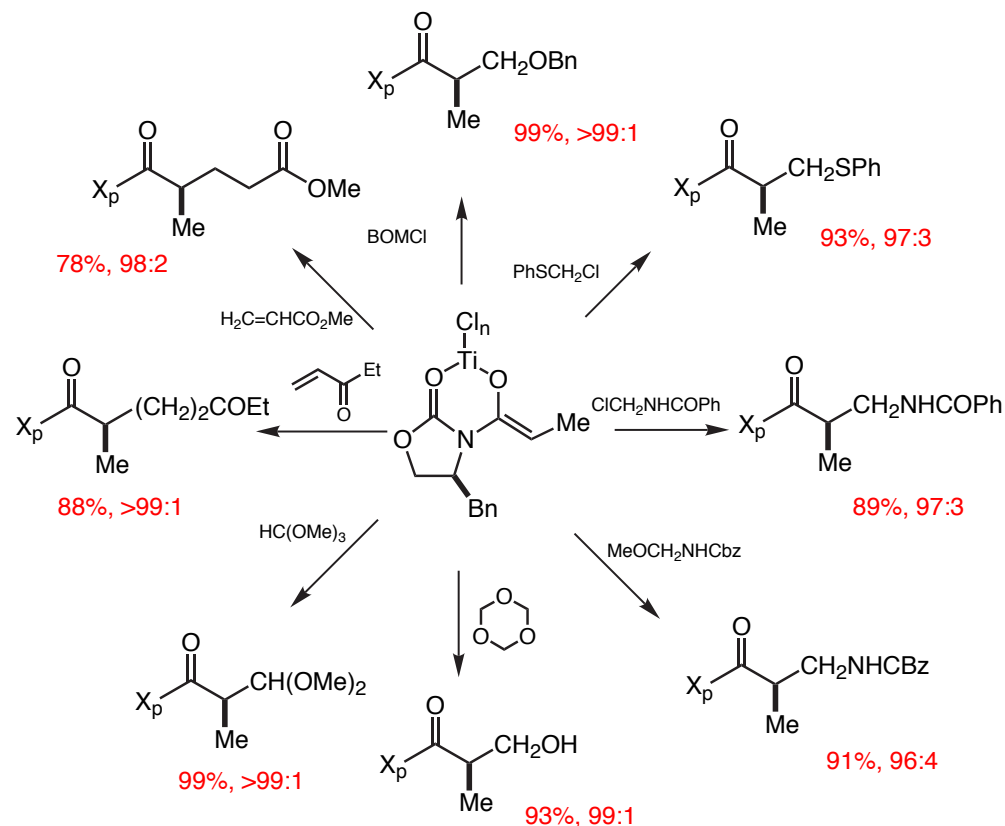
- Enolizable substrates:



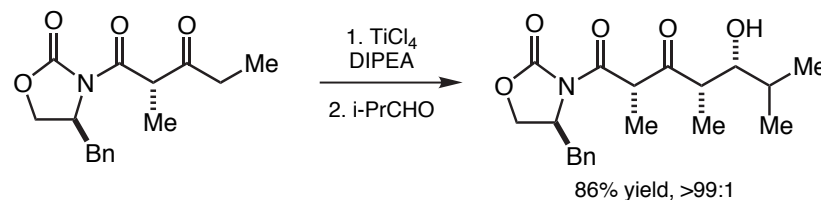
- Substrates Which present problems:



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.

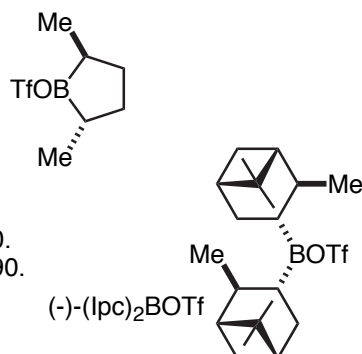
Evans, Vogel, Nelson *J. Am. Chem. Soc.* **1979**, 101, 6120.
 Evans, Nelson, Vogel, Taber *J. Am. Chem. Soc.* **1981**, 103, 3099-3111.
 Evans, Bartroli, Shih *J. Am. Chem. Soc.* **1981**, 103, 2127.
 Masamune, S. et. al. *Tetrahedron Lett.* **1979**, 2225, 2229, 3937.
 Masamune, S. et. al. *J. Am. 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.

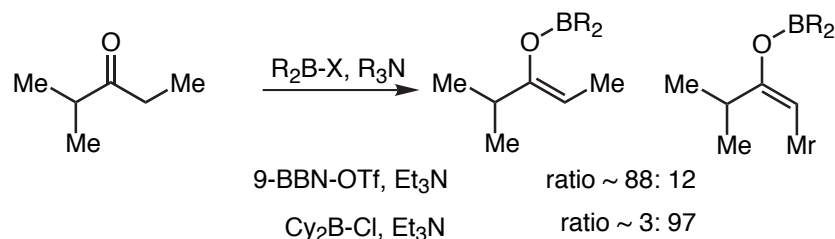
Tetrahedron **1990**, 46, 4663-4684.
Tetrahedron Lett. **1989**, 30, 997-1000.
Tetrahedron Lett. **1986**, 27, 4787-4790.



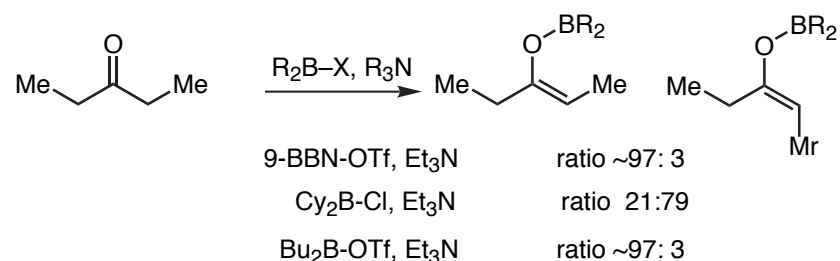
Enolate Stereochemistry

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.

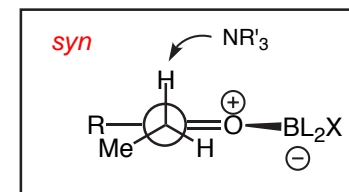
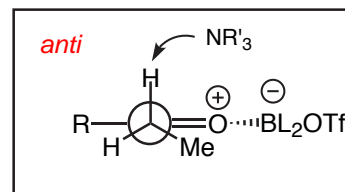
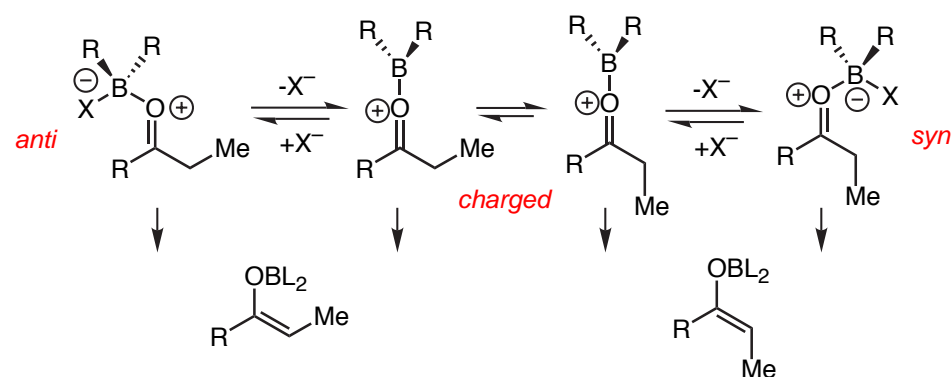


Brown, *J. Org. Chem.* **1993**, 58, 147-153



Borane and lutidine or DIPEA form 1:1 complex with L₂B-OTf. Complexation reversible as enolization will occur upon addition of ketone. Less hindered nitrogen bases - pyridine, Dabco, DBU, irreversibly complex with L₂B-OTf.

The Ketone-Boron Complexes as enolate precursors:

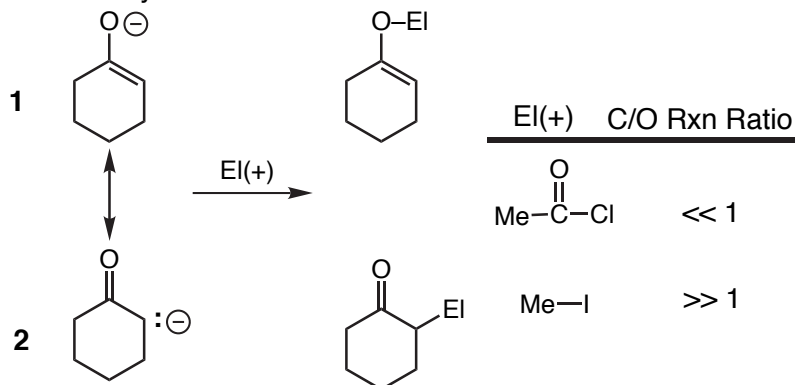


Cy₂B-Cl-ketone complex may deprotonate through syn complex

R₂BOTf-ketone complex may deprotonate through charged complex with (Z) preference

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."

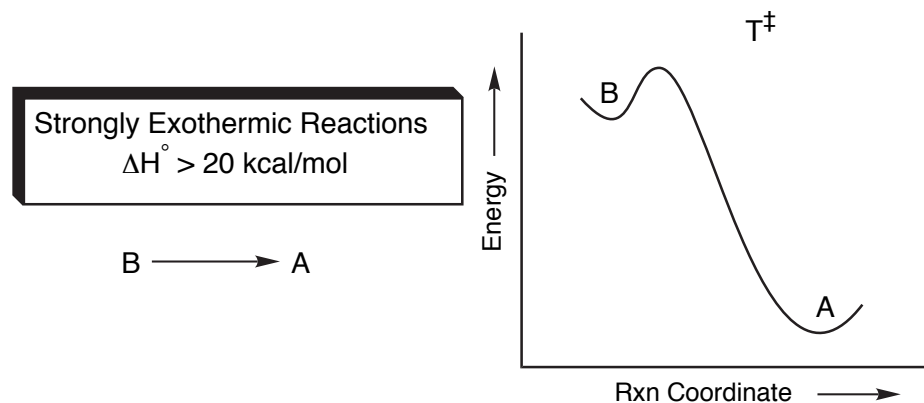
See Hine in *Advances in Phys. Org. Chem.* 1977, 15, 1-61

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 (handout)

■ In attempting to grasp the Hammond Postulate, let's consider two extreme reactions, one which is strongly endothermic and one which is strongly exothermic.



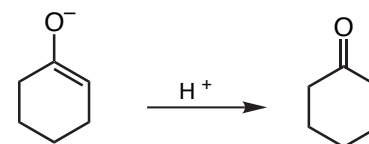
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"For strongly exothermic reactions, the transition state T^\ddagger looks like reactant(s) e.g. B."

■ 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

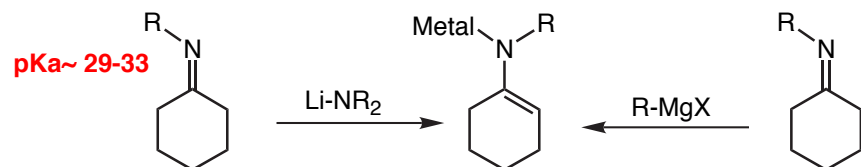
Carey & Sundberg: **Part A**; Chapter 4, pp217-220 for discussion of Hammond's Postulate

Based upon the above discussion draw a detailed mechanism for the protonation of cyclohexanone enolate.



■ Metalloenamines:

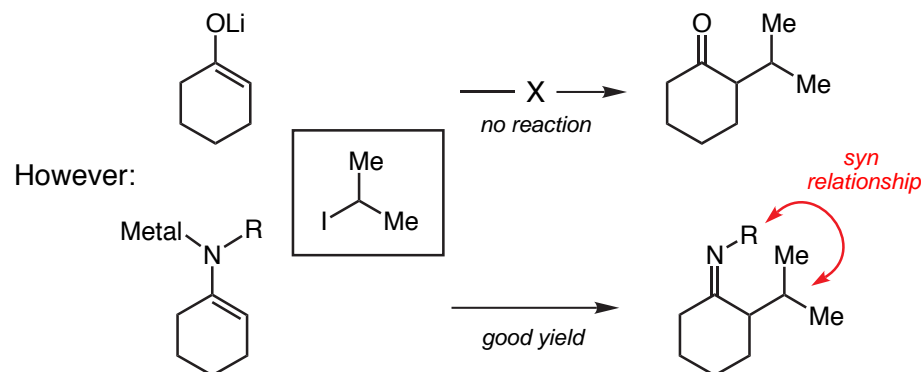
Imines may be transformed into their conjugate bases (enolate counterparts) with strong bases:



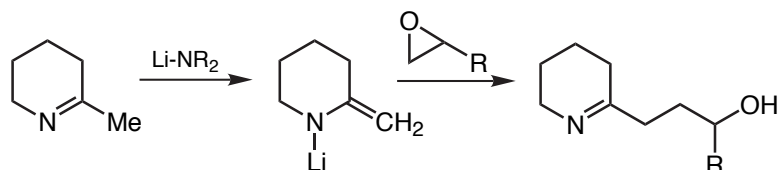
The usual bases employed are either lithium amides (LDA) or Grignard reagents. Note that Grignard reagents do not add to the C=N pi-bond due to the reduced dipole. With this functional group, deprotonation is observed to be the preferred reaction.

■ 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				
Br ₂ , O ₃	+	+	+	+
H ₃ O ⁺	+	+	+	+
	+	+	+	
	+	+	+	
	+	+		
Me-I	+	+		
	+	+		
	+			
Me ₂ CH-I	+			

Decreasing Electrophilicity----->

■ Nature uses enamines, "stabilized" enolates, and enol derivatives in C-C bond constructions extensively.

Quote for the Day

"640K ought to be enough for anybody." Bill Gates, 1981

Today's astrological forecast, Boston Globe, Monday, November 10, 2003

Capricorn (Dec 22–Jan 19th)

"Be prepared for someone to try to steal your ideas or take credit for your work. You're on to something tangible and you need to act fast."

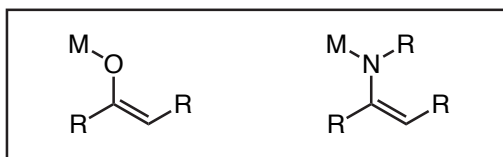
<http://www.courses.fas.harvard.edu/~chem206/>

Chemistry 206

Advanced Organic Chemistry

Lecture Number 24

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

D. A. Evans

Monday,
November 10, 2003

■ 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).

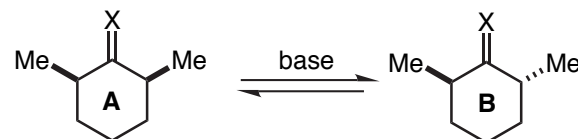
The Reactions of Dianions of Carboxylic Acids and Ester Enolates". N. Petragnani and M. Yonashiro *Synthesis*, 521 (1982).

"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).

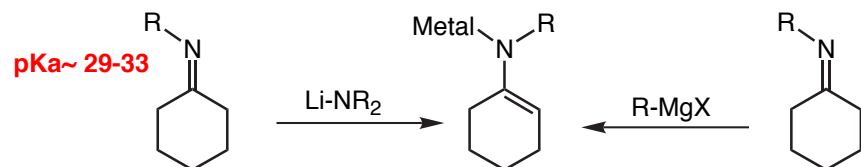
"pKa and Keto-Enol Equilibrium Constant of Acetone in Aqueous Solution". Chiang, Kresge, and Tang *JACS* **106**, 460 (1984).

Explain why **A** is favored for X = O while **B** is favored for X = NNHR



■ Metalloenamines:

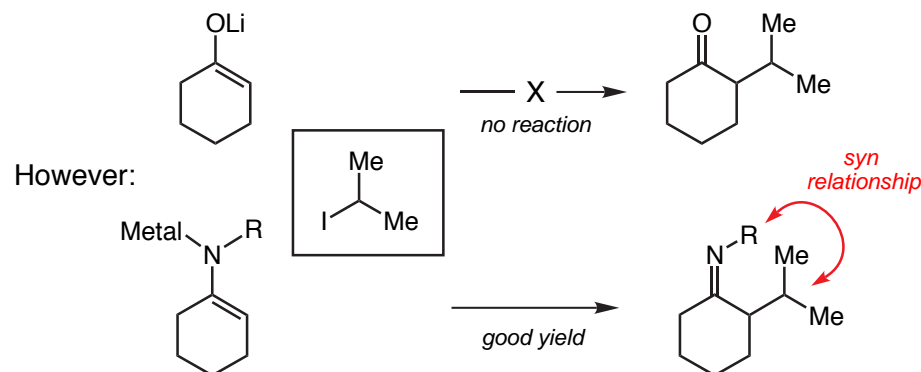
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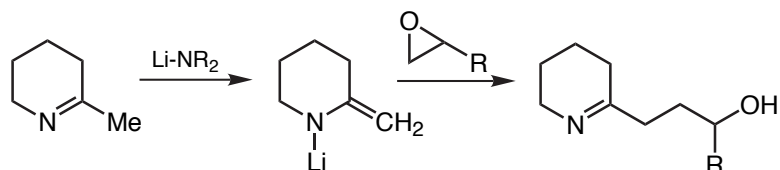
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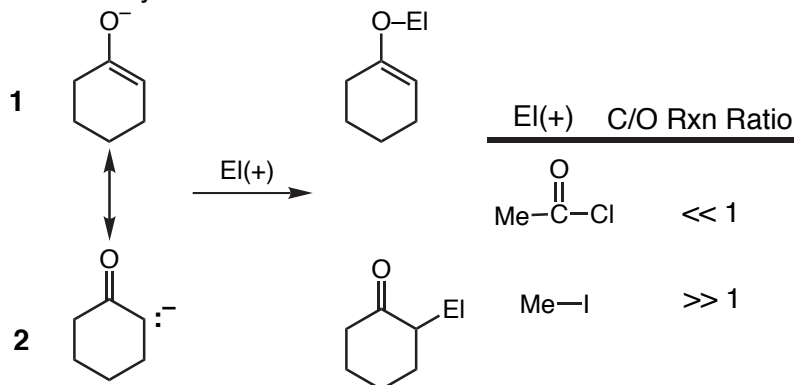
Nucleophile \ Electrophile				
Br ₂ , O ₃	+	+	+	+
H ₃ O ⁺	+	+	+	+
	+	+	+	
	+	+	+	
	+	+		
Me-I	+	+		
	+	+		
	+			
Me ₂ CH-I	+			

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:

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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 Nuclear Motion:

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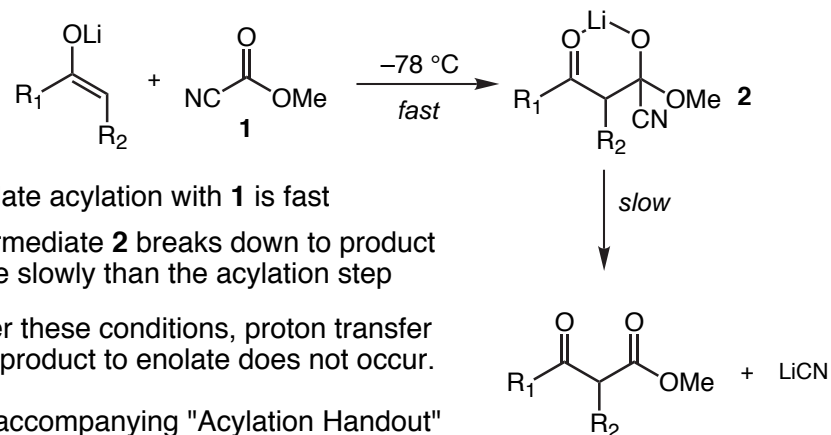
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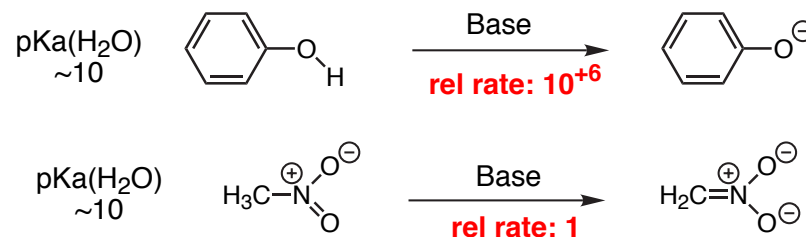
See reinforcing examples on the accompanying page.

C versus O Enolate Reactivity: Enolate Acylation

■ Kinetic C-Acylation of ketone enolates can be carried out:

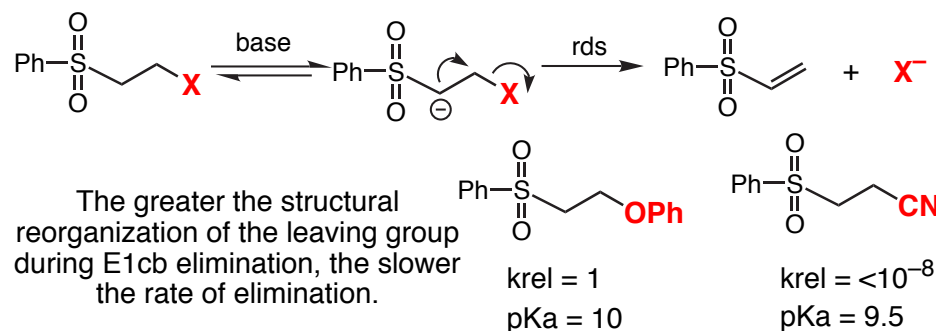


■ Kinetic Acidities nicely illustrate LNM Principle: *Lecture 18"



Proton kinetically controlled transfers from C-H Bonds are slow due to the extensive reorganization required in conjugate base.

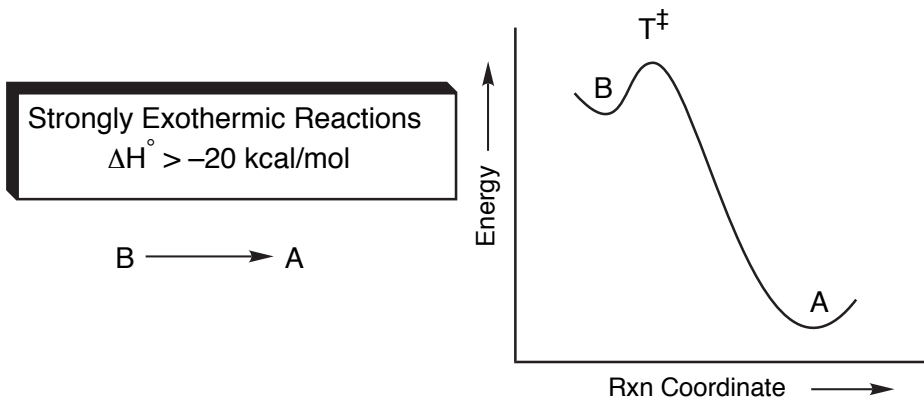
■ Leaving Group Ability: Stirling, *Chem. Commun.* 1975, 940



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.



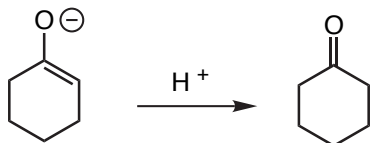
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Carey & Sundberg: **Part A**; Chapter 4, pp217-220 for discussion of Hammond's Postulate

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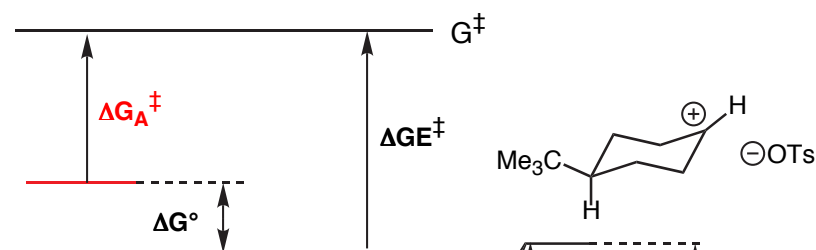
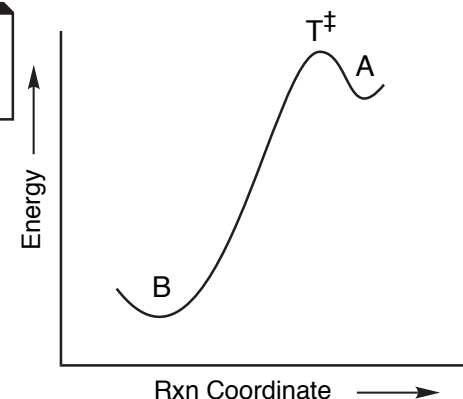
Strongly Endothermic Reactions

$\Delta H^\circ > +20$ kcal/mol

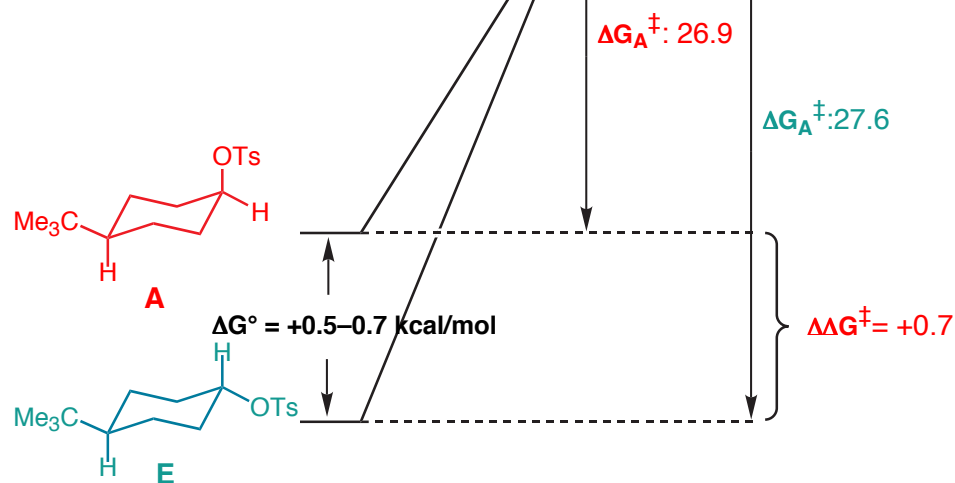


S_N1 reactions are typical examples of strongly endothermic processes

Hammond: "The transition state will look like products."



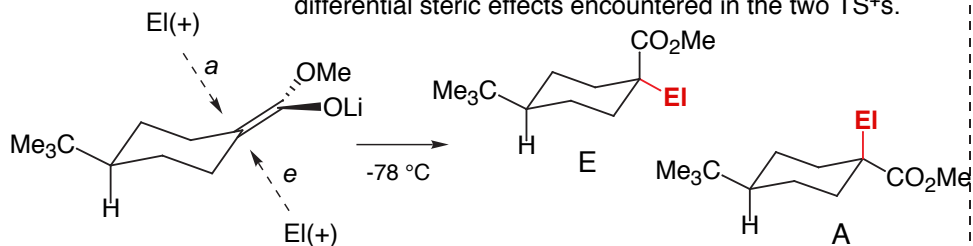
Does $\Delta G_{E^\ddagger} - \Delta G_{A^\ddagger} = \Delta G^\circ (E - A)$??



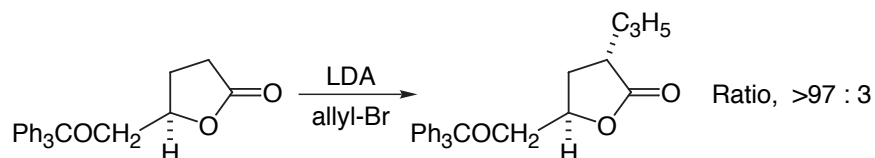
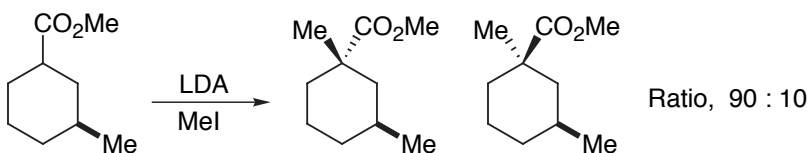
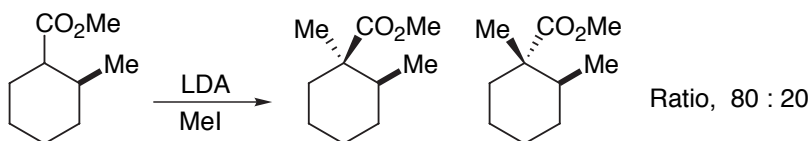
Wnstein & Holness, *JACS* **1955**, *55*, 5562

Steric Effects

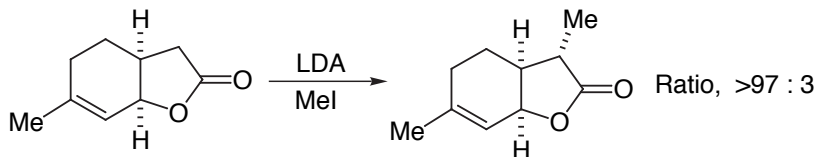
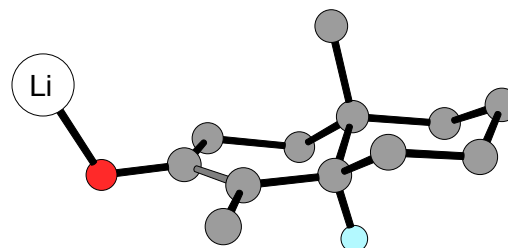
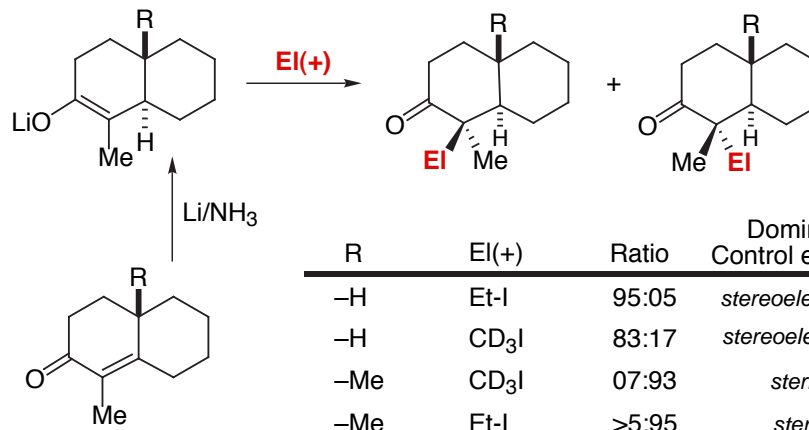
In this case, both *e* and *a* paths are stereoelectronically equivalent. Diastereoselectivity is now determined by the differential steric effects encountered in the two TS[‡]s.



Electrophile	Ratio, E:A
Me-I	84:16
n-Bu-Br	87:13

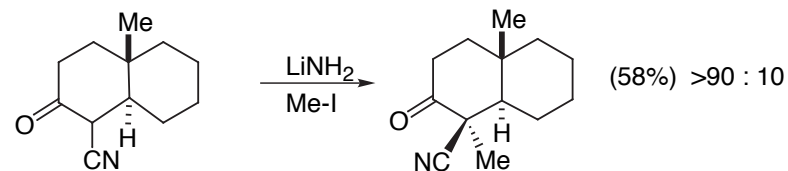
Representative cases

diastereoselectivity depends strongly on O-protecting group

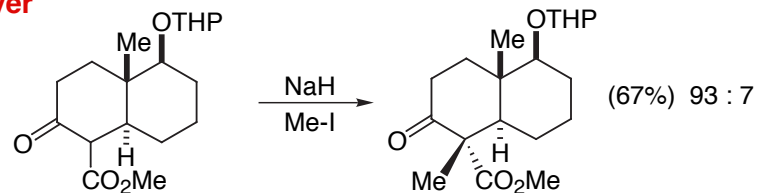
**Cases with Opposed steric & electronic effects**

The enolate R = Me
(Chem 3D)

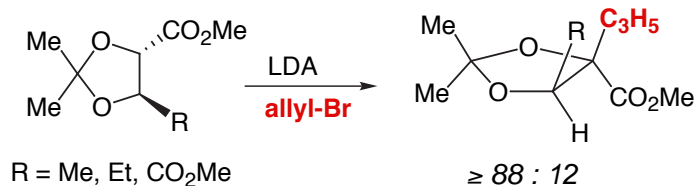
Based on above data, this case is reasonable:



However



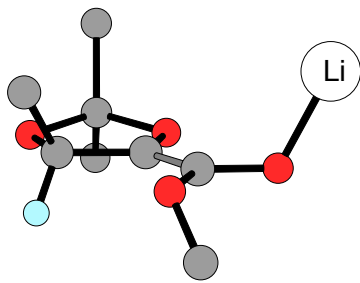
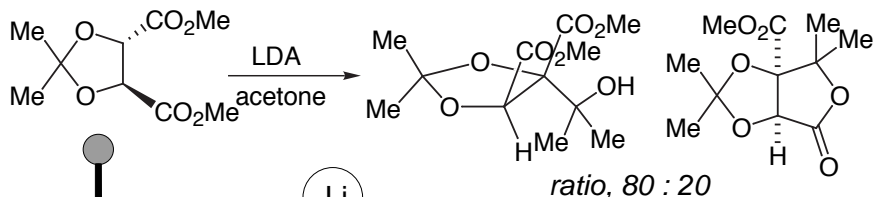
Cases which do not appear to give the expected product based on the analysis of steric effects



Seebach, *Angew. Chem. Int. Ed* **1981**, 20, 1030

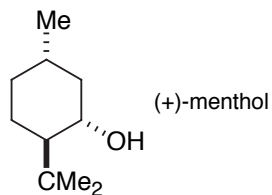
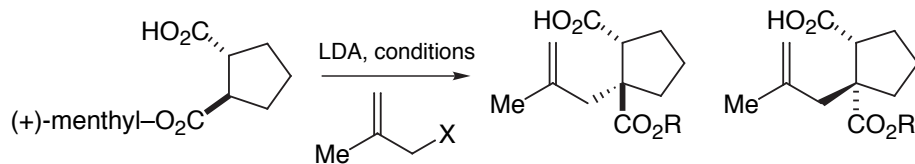
Ladner, *Angew. Chem. Int. Ed* **1982**, 21, 449

■ However:



The enolate (MM-2)

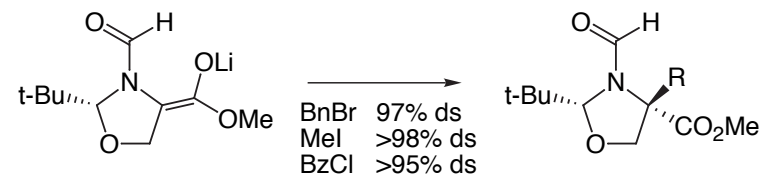
Here is another example of a contrastric alkylation



K. Yamada, *Organic Synthesis Past Present, and Future*, p 255

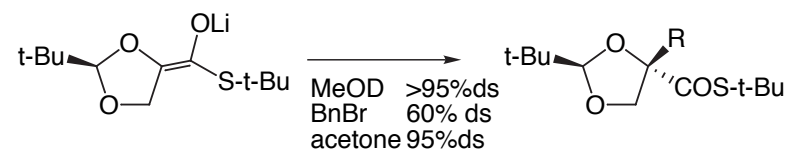
X	conditions	Ratio
R-Cl	THF, 23 °C	80:20
R-Br	THF-HMPA -78 → -20 °C	02:98

Sterically Expected Results:

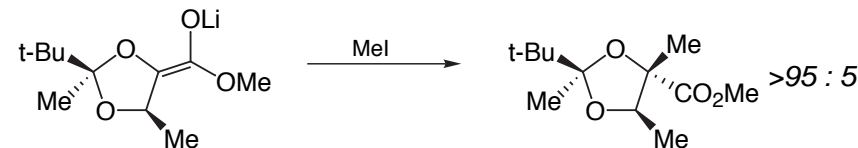


Seebach, *Helv. Chim. Acta* **1987**, 70, 1194.

Contrastric relatives:

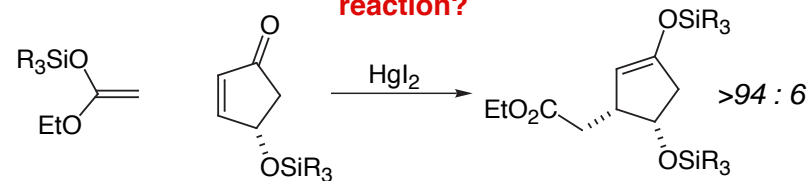


Seebach, *Helv. Chim. Acta* **1987**, 70, 1194.



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?

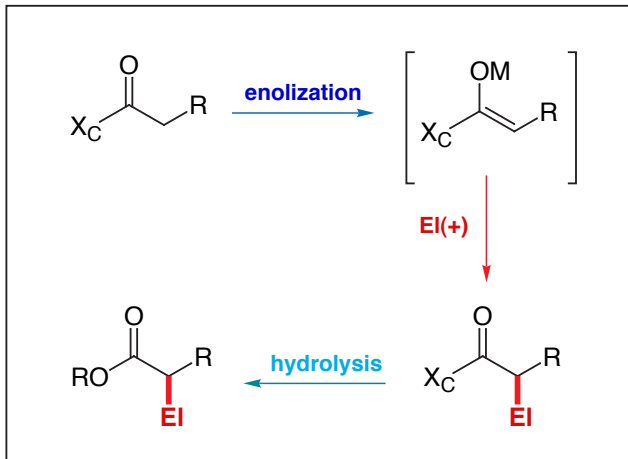


Danishefsky *J. Org. Chem.* **1991**, 56, 387

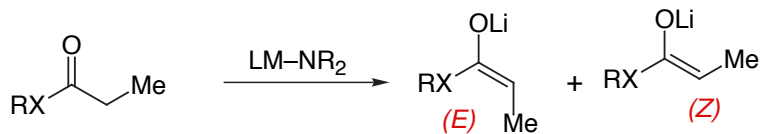
Chiral Enolate Design Requirements Circa 1978

Overall enantioselection will be the sum total of the defects introduced through:

- Enolization selectivity
- Enolate-electrophile face selectivity
- Racemization attendant with X_C removal

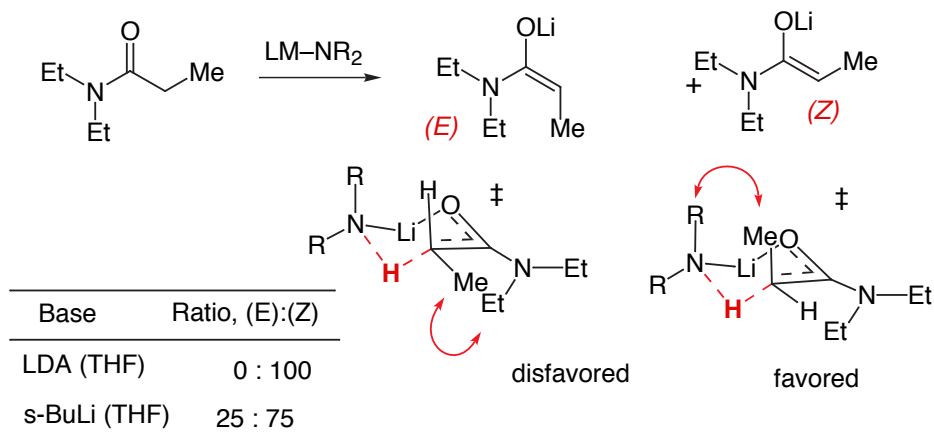


■ **Enolization selectivity:** Ester-based chiral controllers X_C limited by enolization selectivity (Lecture 23)

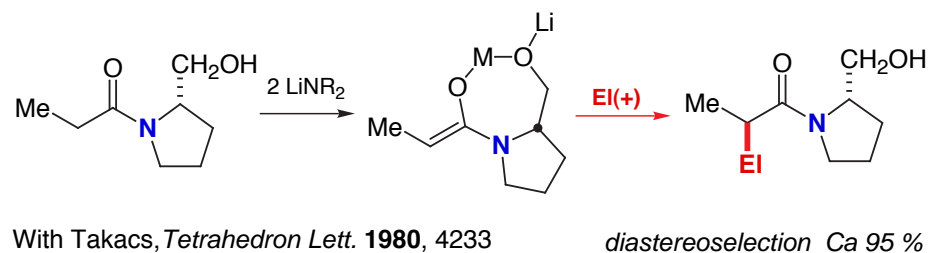


Base	R-Substituent	Ratio, (E):(Z)
LDA (THF)	-OMe, O-t-Bu	95 : 5
LDA (THF)	-S-t-Bu	95 : 5

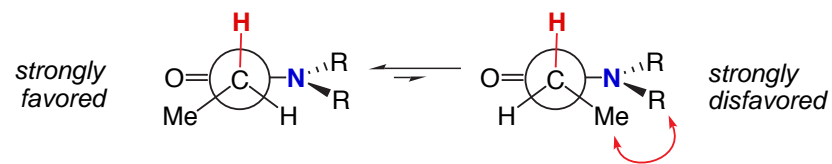
■ **Enolization selectivity:** Amide-based controllers X_C limited by enolization selectivity (Lecture 22)



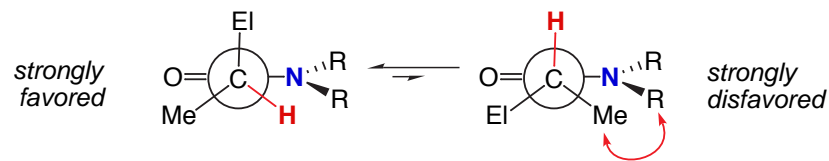
■ **Amide Based Chiral Auxiliaries**



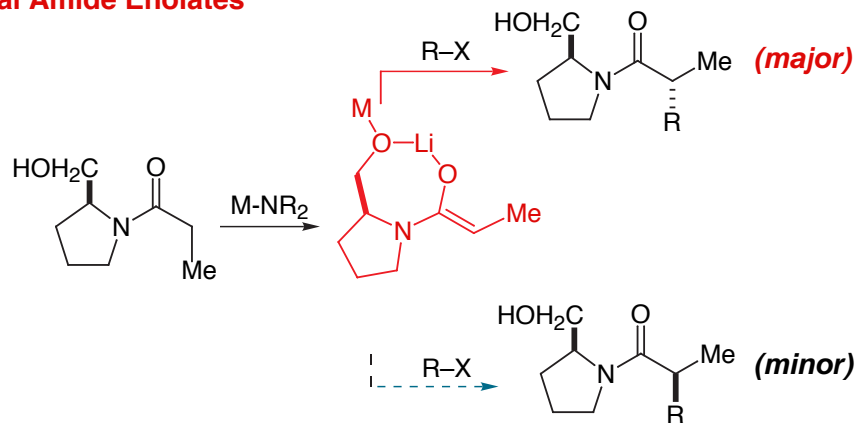
Allylic Strain controls Enolate Geometry:



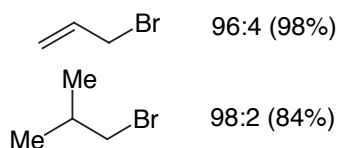
Allylic Strain Prevents Product Enolization:



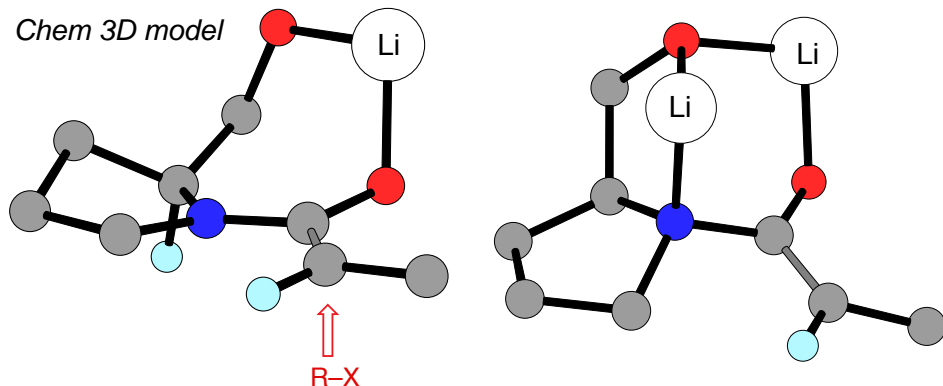
Chiral Amide Enolates



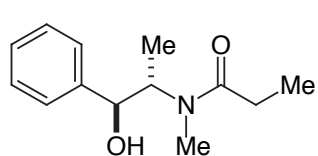
Evans, Takacs,
Tet. Lett. **1980**, 21, 4233-4236



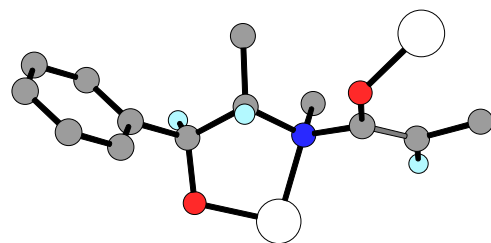
Chem 3D model



The nature of enolate chelation is ambiguous. Nitrogen chelation is a real possibility.

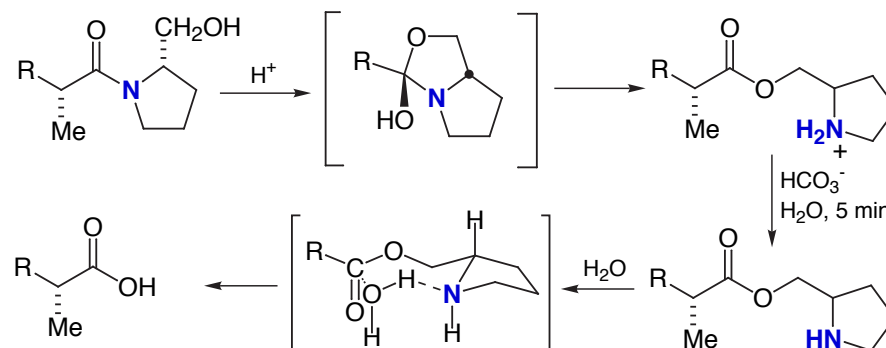


Myers, *JACS* **1997**, 119, 6496



24-07-Enolate alk-5 11/9/03 9:05 PM

Amide Hydrolysis

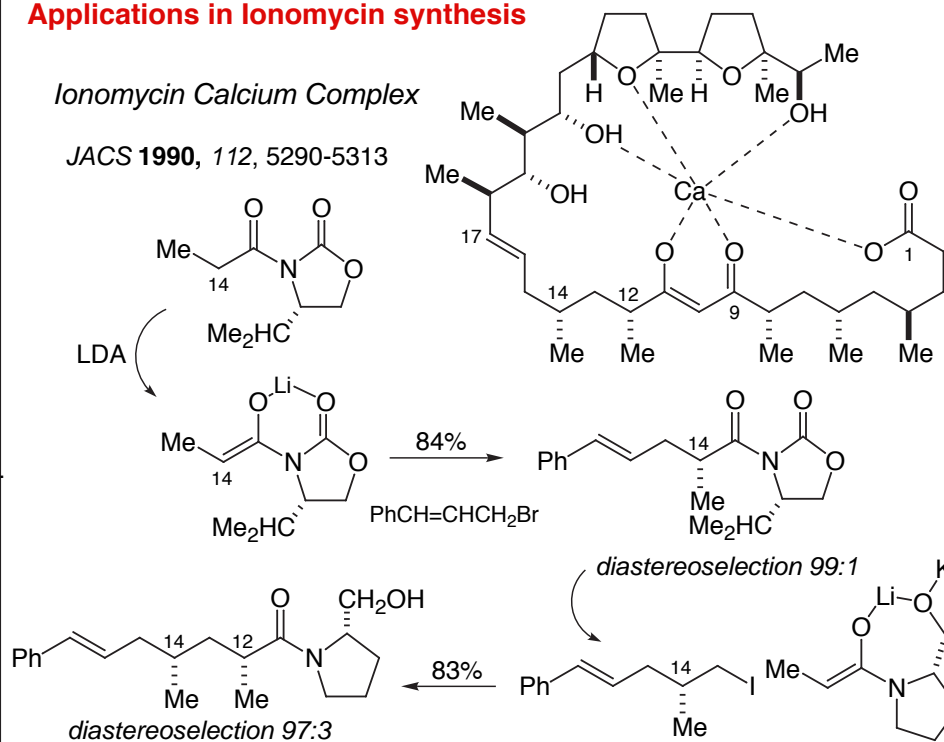


intramolecular general base catalysis

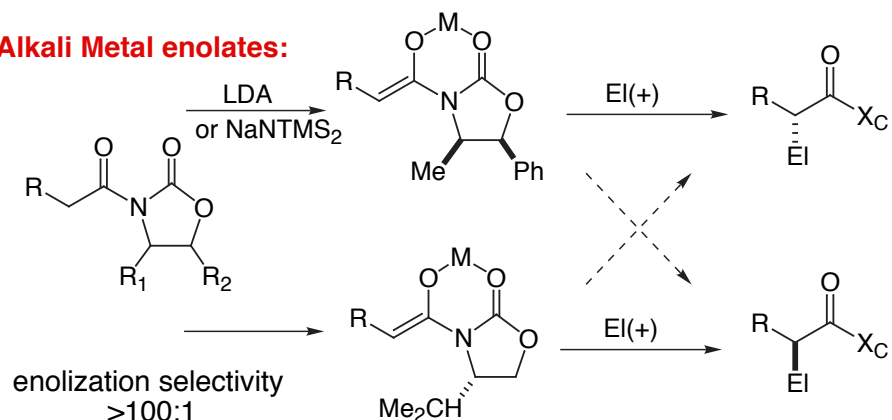
Applications in Ionomycin synthesis

Ionomycin Calcium Complex

JACS **1990**, 112, 5290-5313



Alkali Metal enolates:



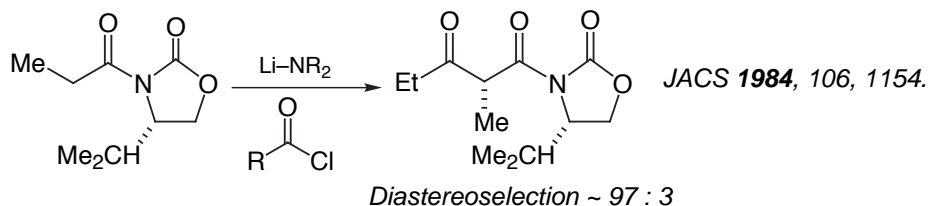
M = Li, THF < 0 °C

M = Na, THF -78 to 0 °C

Alkyl Halide	Ratio
ArCH ₂ Br	50-120 : 1
CH ₂ C=CHCH ₂ Br	50 : 1
ArCH ₂ OCH ₂ Br	50 : 1
<i>marginal reaction</i> CH ₃ CH ₂ I	25 : 1
CH ₃ I	13 : 1

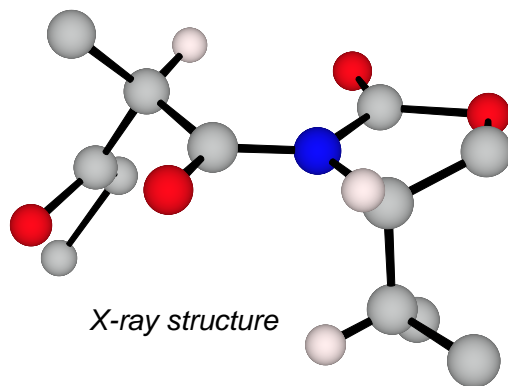
JACS. 1982, 104, 1737.

Enolate Acylation

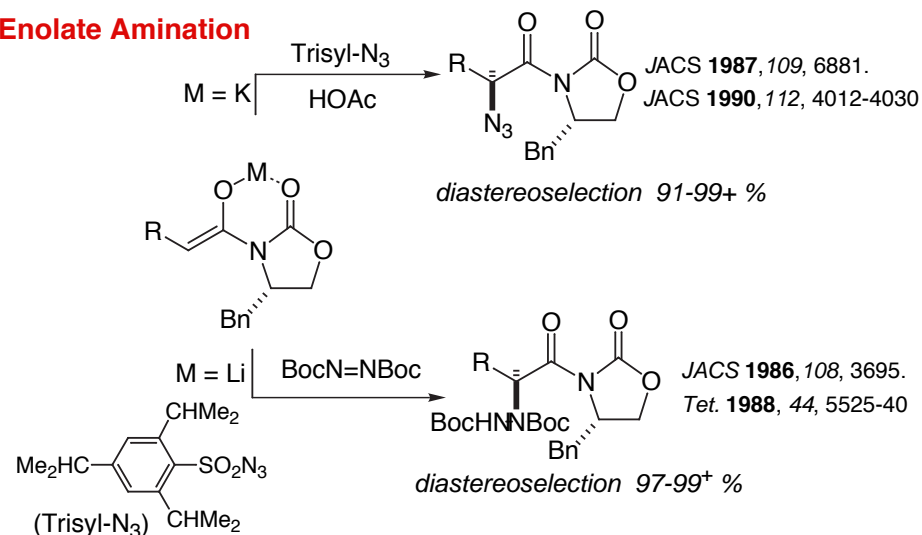


JACS 1984, 106, 1154.

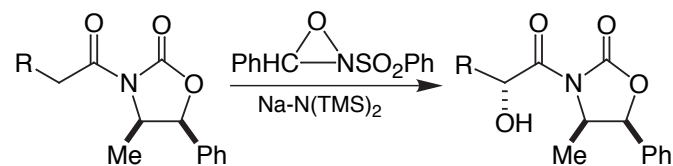
New stereocenter not lost through enolization



Enolate Amination



Enolate Hydroxylation

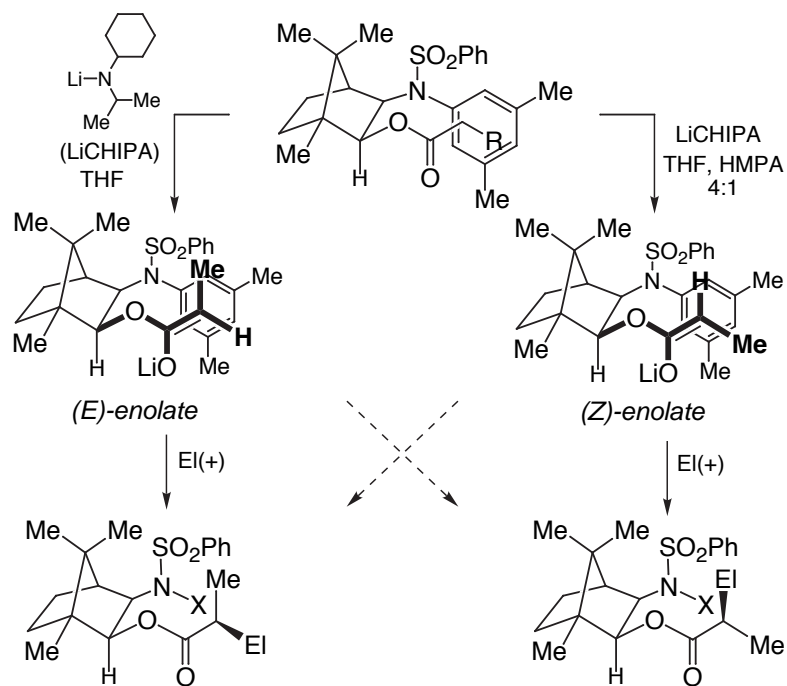
Na enolate is required.
Why?

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 %

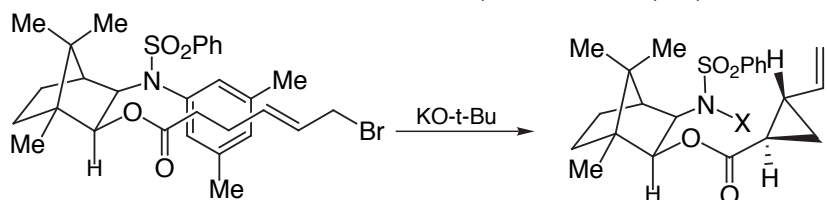
JACS. 1985, 107, 4346.

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, 207-208

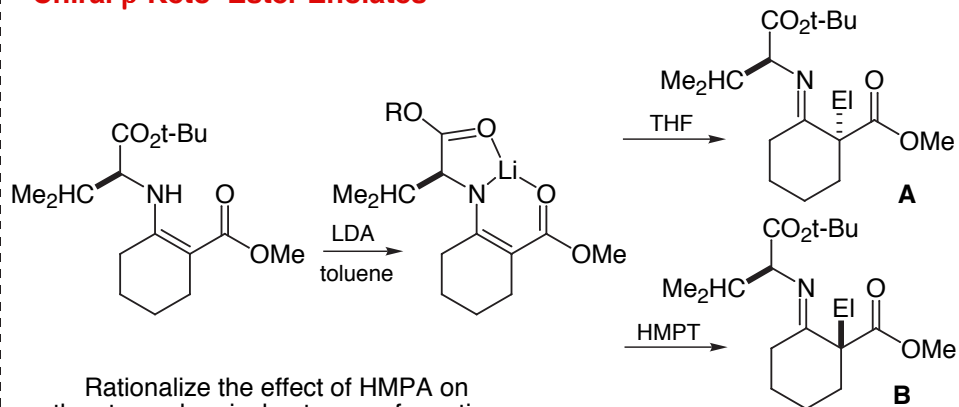
enolate	El(+)	Ratio
(E)	n-C ₁₄ H ₂₉ -I	98.5:1.5
(Z)	n-C ₁₄ H ₂₉ -I	06:94 <i>enolate contamination</i>

Helmchen, *Angew. Chem. Int. Ed.* **1984**, 23, 60-61Helmchen, *Tet. Lett.* **1983**, 24, 1235-1238Helmchen, *Tet. Lett.* **1983**, 24, 3213-3216

Ratio, 93:7 (74%)

Helmchen, *Tet. Lett.* **1985**, 26, 3319-3322

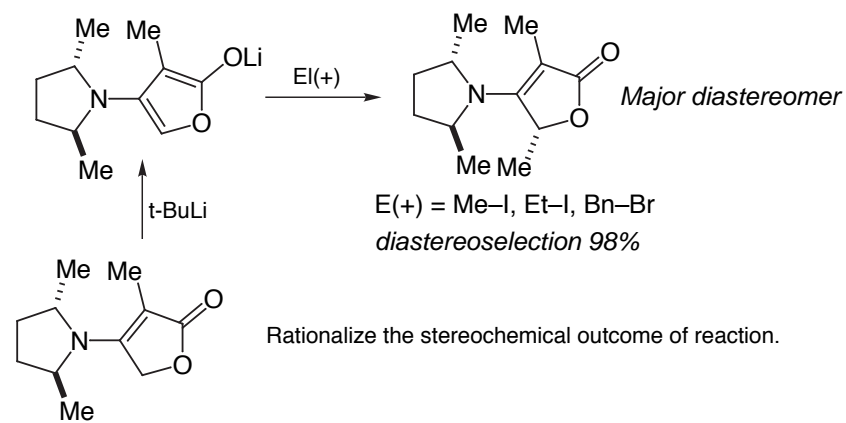
Chiral β-Keto Ester Enolates

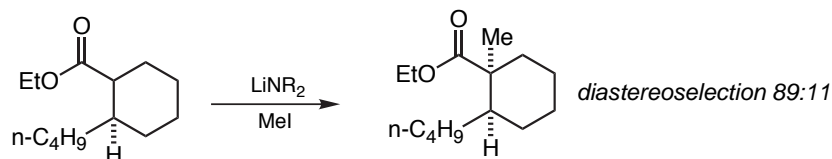
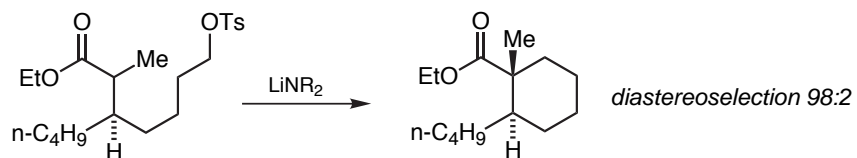
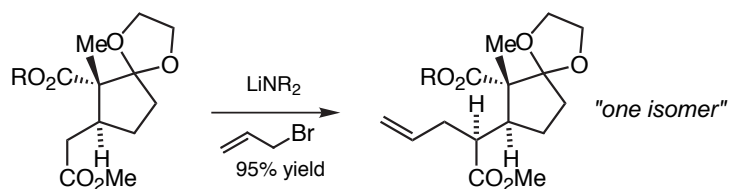
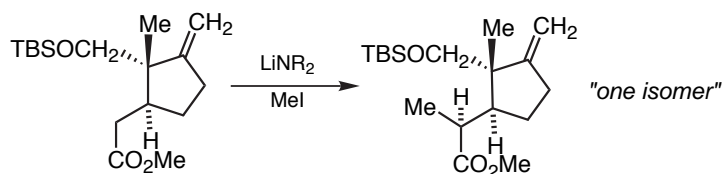
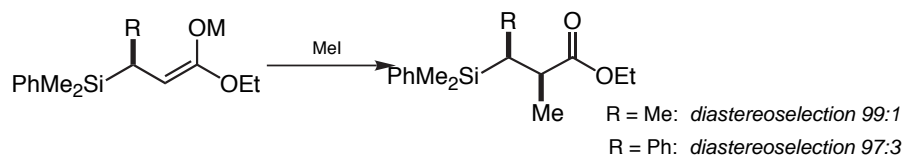
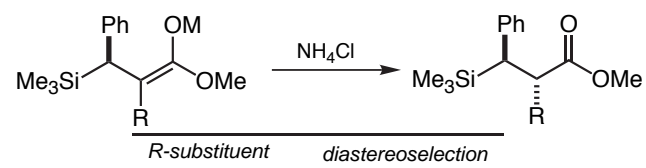


El(+)	addend	Yield	Ratio (A:B)
Me-I	THF	63%	96:04
Me-I	HMPT	57%	01:99
Bn-Br	THF	48%	99:01
Bn-Br	HMPT	77%	15:85

Koga, *JACS* **1984**, 106, 2718-2719

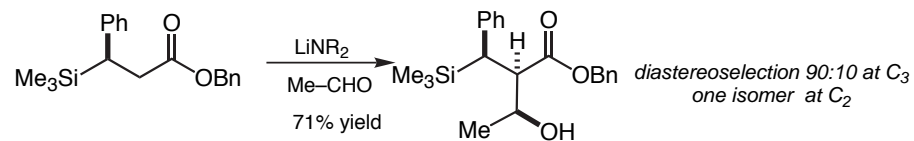
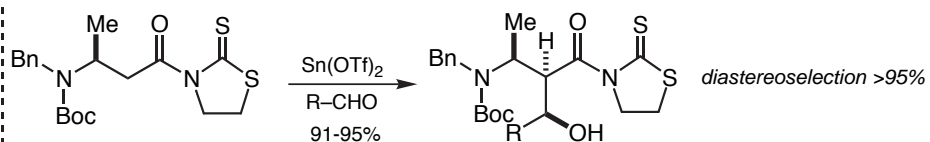
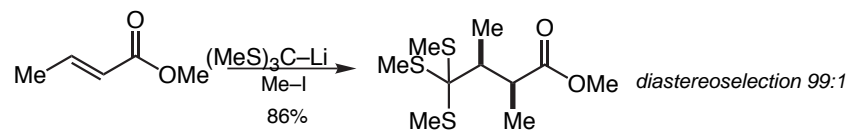
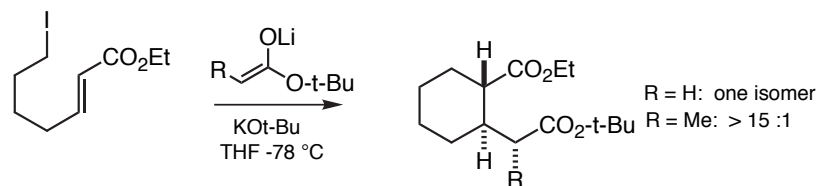
Chiral β-Keto Ester Dienolates

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 = 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:**

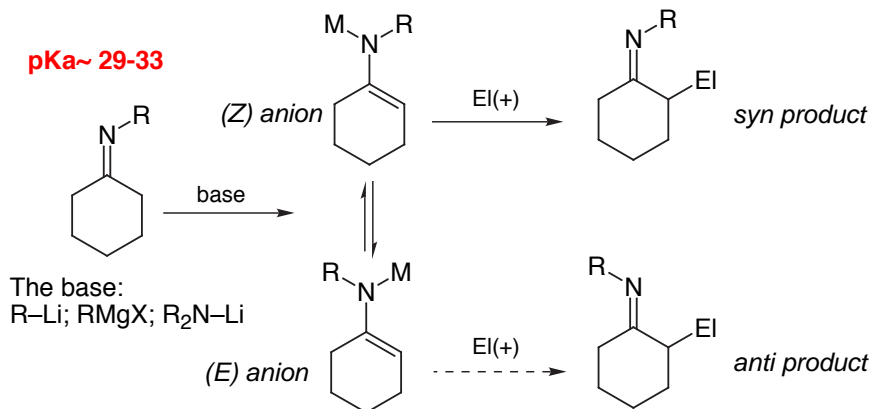
Martin in *Comprehensive Organic Synthesis*, **1991**; Vol 2, Chapter 1.16, pp 475-502

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

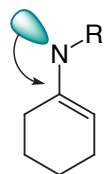
Collum, *JACS* **1984**, *106*, 4865-4869

Collum, *JACS* **1985**, *107*, 2078-2082

Collum, *JACS* **1986**, *108*, 3415-3422

Collum, *JACS* **1993**, *115*, 789-790

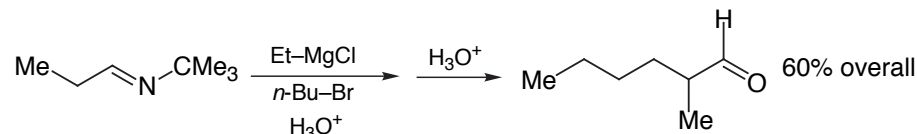
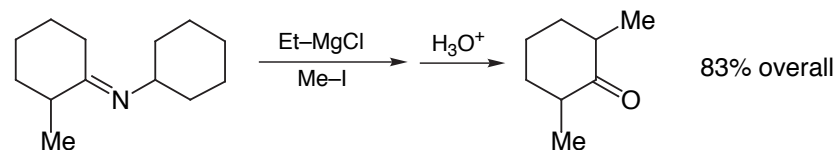
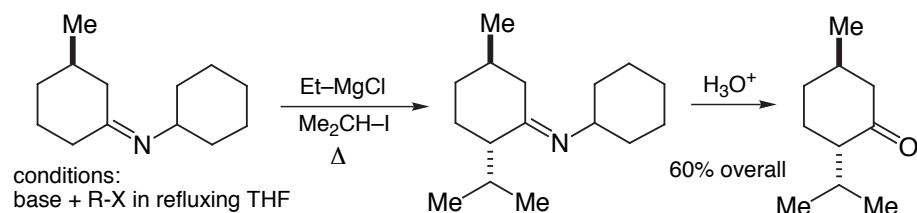
■ **Geometry Rationalization:**



nonbonding N-lone pair may be stabilized by delocalization into antibonding orbital of C=C.

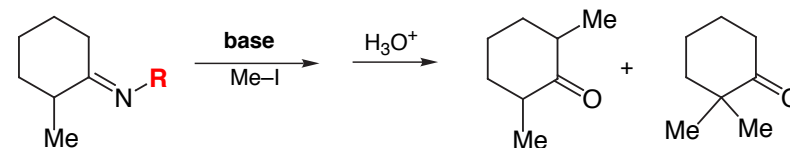
Remember, (Z) geometry also favored for enol ethers

■ **Representative Reactions:**

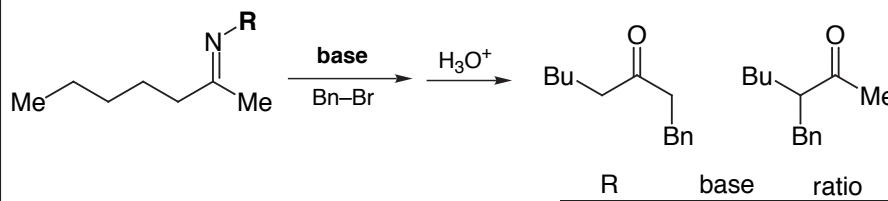


Stork & Dowd, *JACS*, **1963**, *85*, 2178-2180

■ **Nature of N-substituent, base, and solvent additive can play a role in deprotonation regioselectivity:** Hosomi, *JACS*, **1982**, *104*, 2081-2082

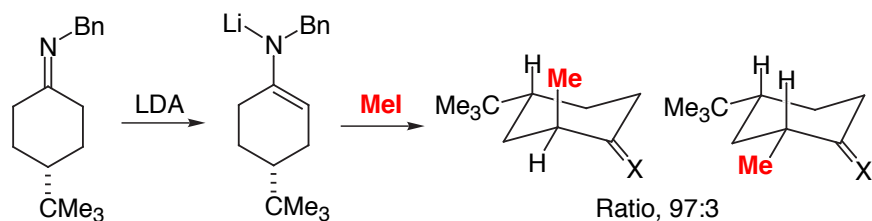


R	base	ratio
-cyclohexyl	s-BuLi	10:90
-NMe ₂	s-BuLi	100:0

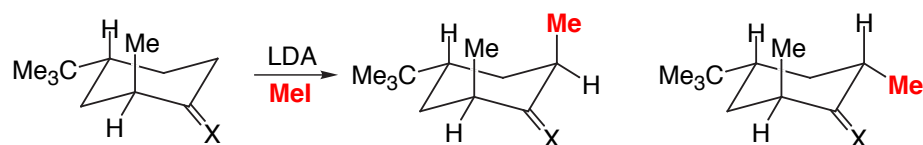


R	base	ratio
-cyclohexyl	s-BuLi	74:26
-cyclohexyl	s-BuLi + 1 equiv HMPA	100:0

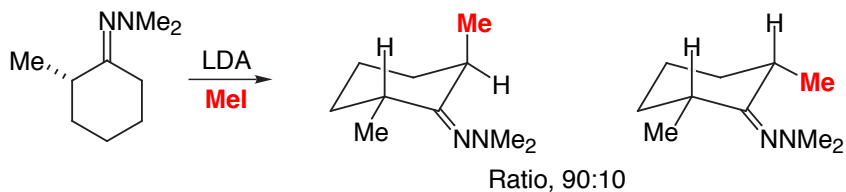
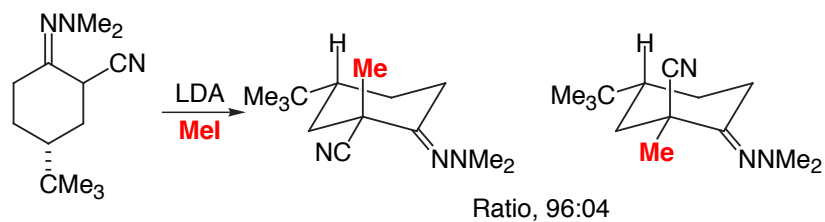
Stereochemical Issues:

Fraser, *JACS* **1978**, *100*, 7999 (handout)

Tendency for axial-chair alkylation is significantly greater than for ketones



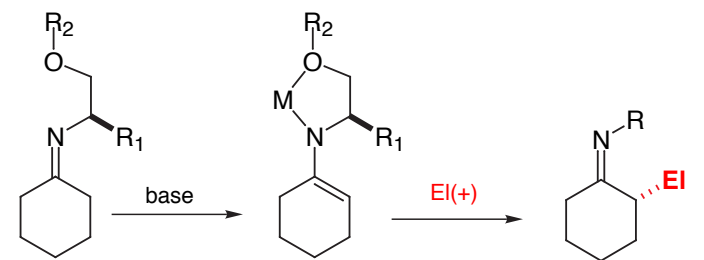
X	Ratio
X = N-Bn	94:06
X = O	60:40

Fraser, *JACS* **1978**, *100*, 7999 (handout)Collum, *JACS* **1984**, *106*, 4865-4869 (handout)

Chiral Metalloenamines:

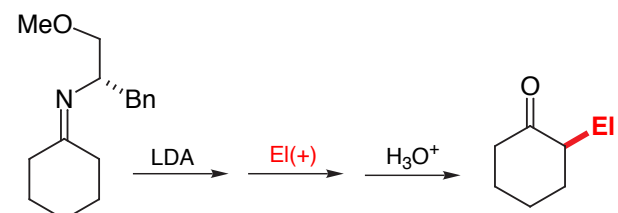
early papers: { Meyers, *J. Am. Chem. Soc.* **1976**, *98*, 3032
Whitesell, *J. Org. Chem.* **1978**, *42*, 377-378

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

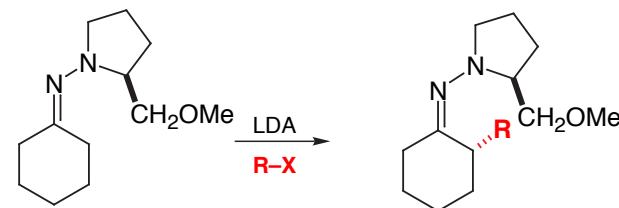
Major Product

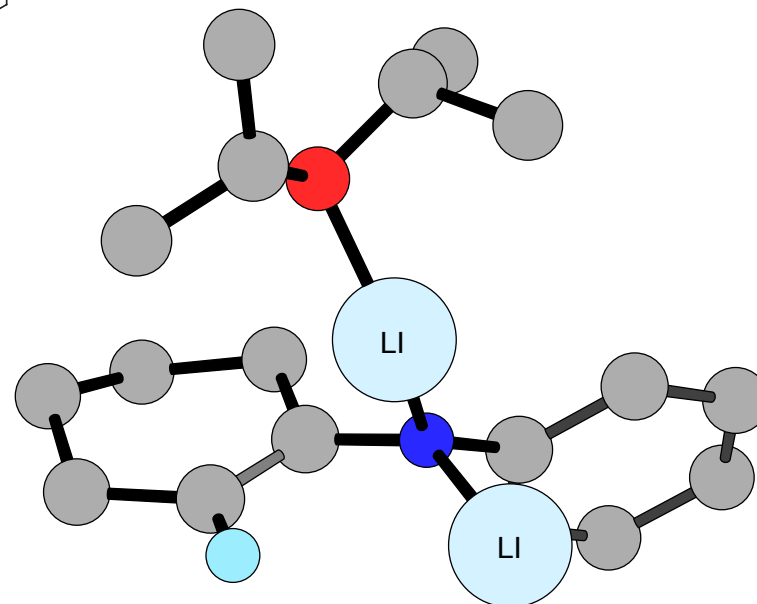
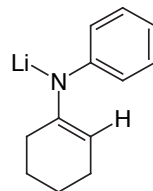
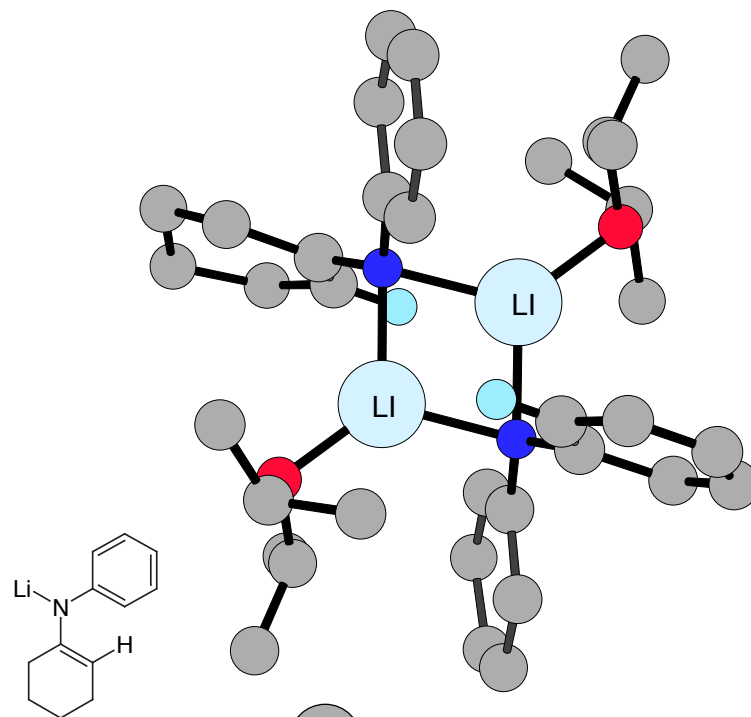
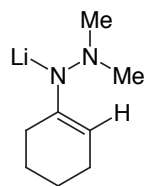
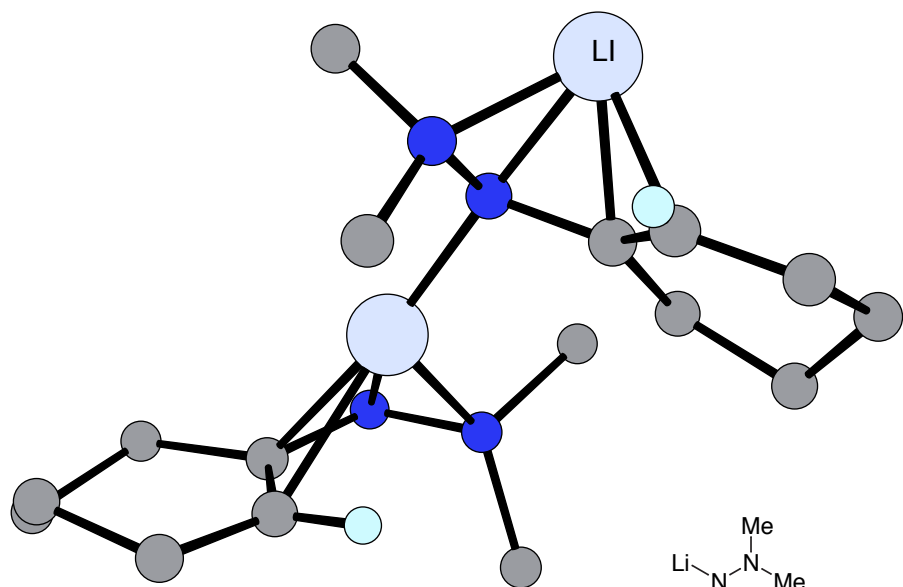


R-X	ee
Me-I	87
Et-I	94
n-Pr-I	99

Meyers, *J. Am. Chem. Soc.* **1981**, *103*, 3081

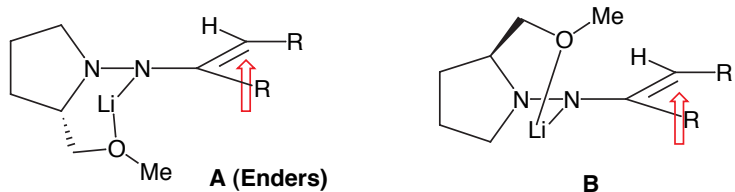
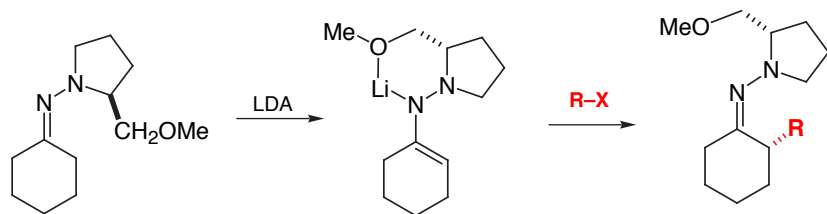
Chiral Metallated Hydrazones

Enders in *Asymmetric Synthesis*, **1984**; Vol 3, Chapter 4, pp 275-339

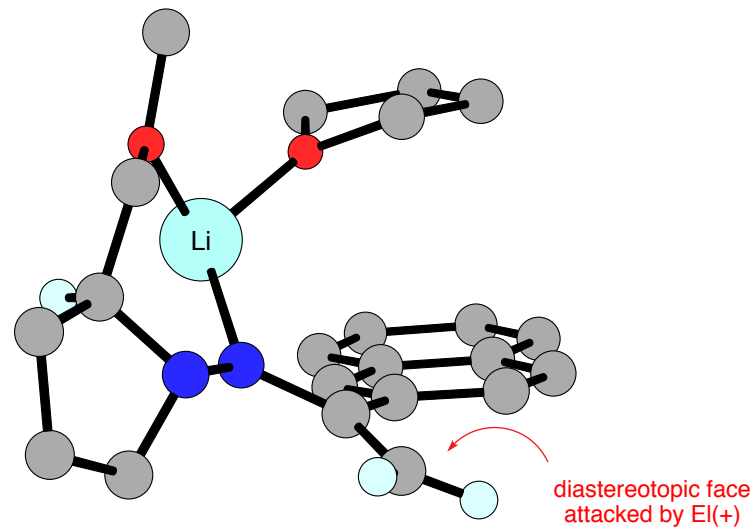
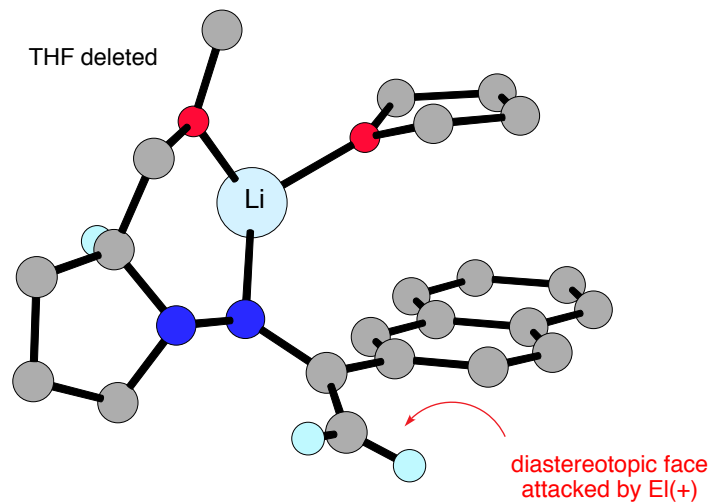


Collum & Clardy, *JACS* **1984**, *106*, 4865

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.

Chemistry 206

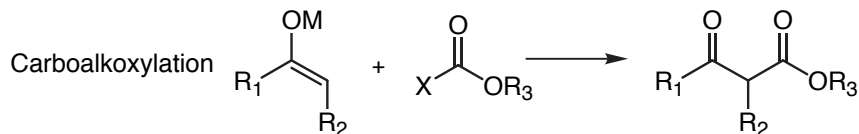
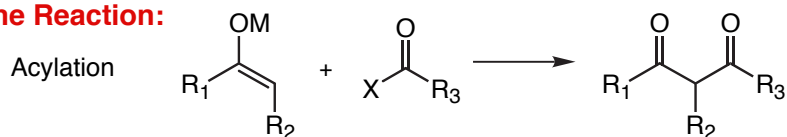
Advanced Organic Chemistry

Handout-24A

Enolate Acylation

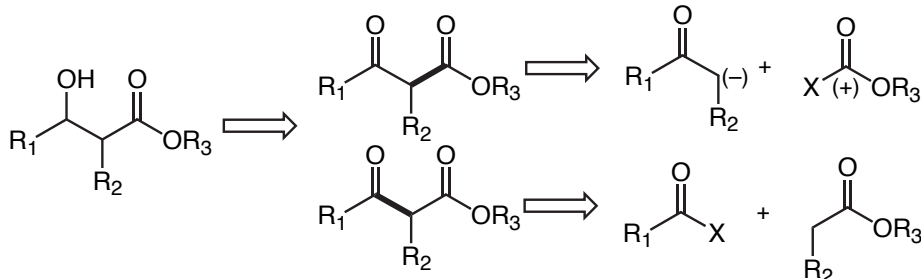
D. A. Evans

Monday ,
November 10, 2003

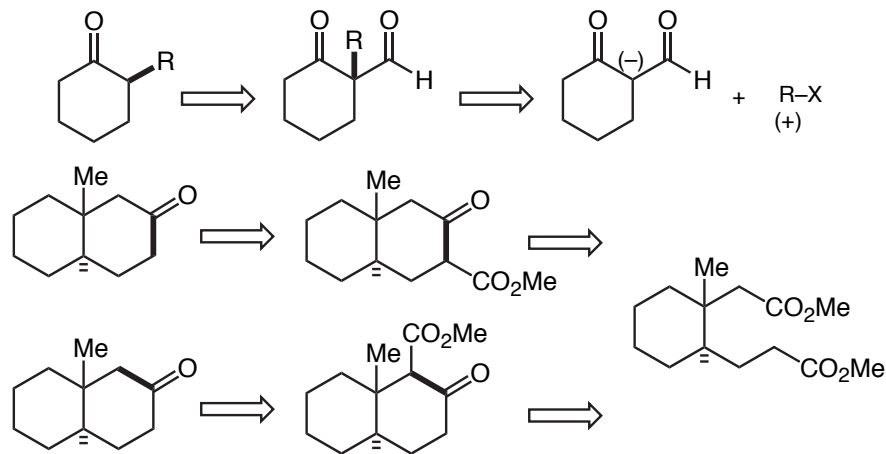
The Reaction:

Situations where the reaction is employed:

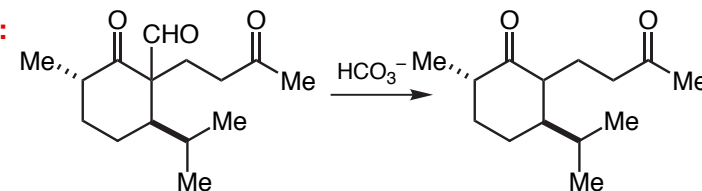
■ Acyl moiety is a constituent of the target structure:



■ Acyl moiety employed in assisting bond construction but not part of the target structure:



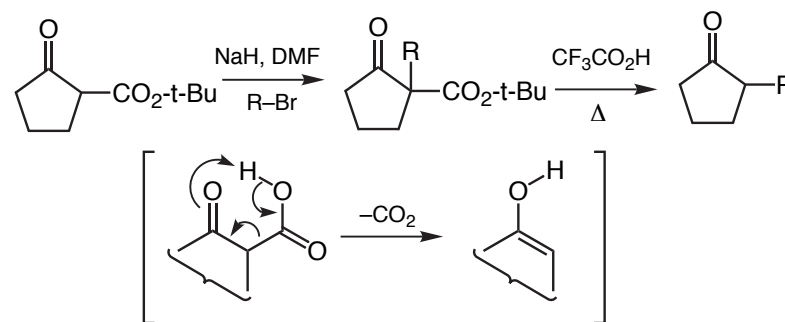
Deacylation: When an acyl residue is employed in the one of the illustrated bond constructions, it may then be removed by nucleophilic deacylation: Several examples are provided.

Deformylation:

competitive ring cleavage not a problem due to more electrophilic formyl C=O

Decarboxylation:

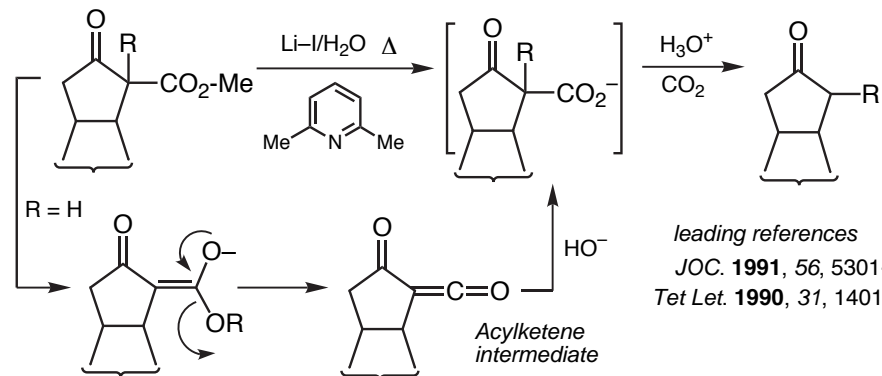
■ Alkyl-Oxygen Cleavage: *tert*-butyl esters



Decarboxylation in this system is a sigmatropic rearrangement involving C=O participation

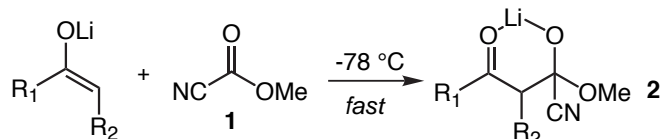
representative procedure: Henderson, *Synthesis* **1983**, 996

■ Alkyl-Oxygen Cleavage: Methyl esters



leading references
JOC. **1991**, 56, 5301-7
Tet Let. **1990**, 31, 1401-4

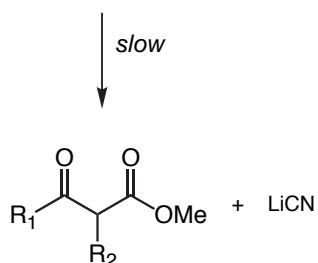
■ Kinetic Acylation: Methyl Cyanoformate (1):



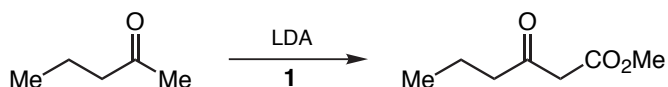
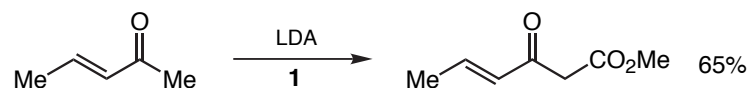
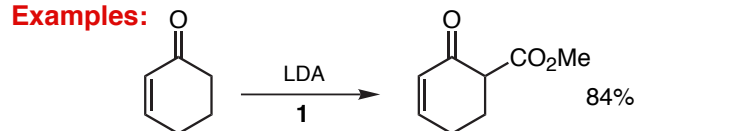
Enolate acylation with 1 is fast

Intermediate 2 breaks down to product more slowly than the acylation step

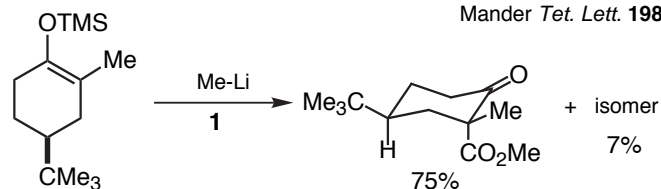
Under these conditions, proton transfer from product to enolate does not occur.



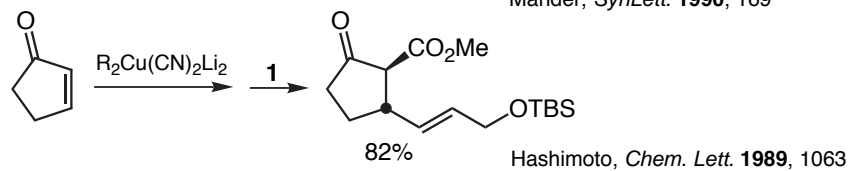
■ Examples:



Mander *Tet. Lett.* **1983**, 24, 5425

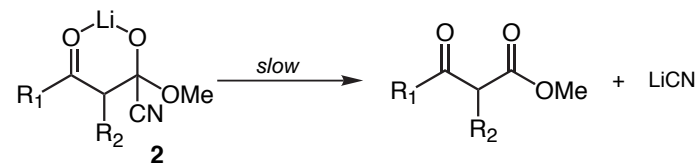


Mander, *SynLett.* **1990**, 169



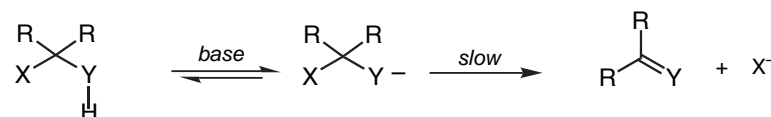
Hashimoto, *Chem. Lett.* **1989**, 1063

■ The Tetrahedral Intermediate 2; Why is it so stable?



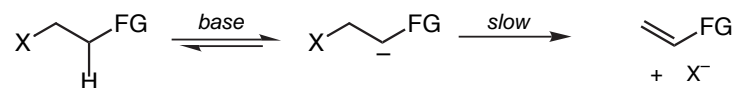
Consider this process in the broader context of elimination reactions of the E1cb classification where:

Y might be either C or some heteroatom
X might be various leaving groups such as CN, OR etc.



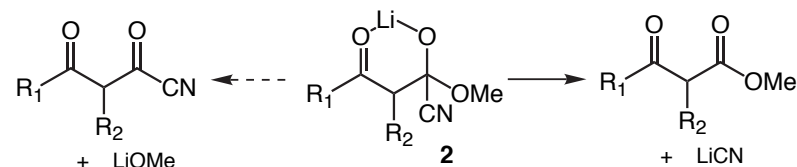
Data is available for the case where X = CN, OR & Y = carbanion:

Stirling, *Chem. Commun.* **1975**, 940-941

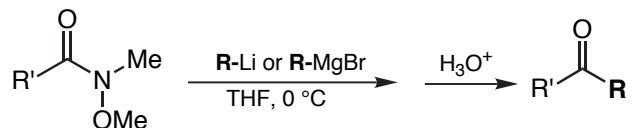
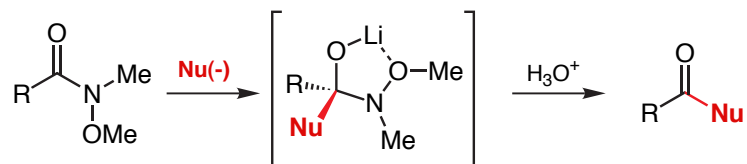


leaving grp (X)	pKa H-X	$\log \left[\frac{k_X}{k_{OPh}} \right]$
-OPh	10	1
-CN	9.5	<-7
-C(Me) ₂ -NO ₂	~10	<-9
-OMe	16	-3.9

Above data makes the point that CN is a poor LG but it also leads one to the faulty conclusion that 2 should partition to acyl cyanide rather than methyl ester!



Acyating agents can be designed where the tetrahedral intermediate exhibits exceptional stability:



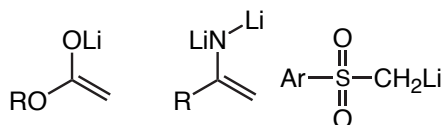
R = Me, n-Bu, or Ph; yields > 90%

Weinreb *Tet. Lett.* **1981**, 22, 3815.

Nucleophiles:

Acceptable

R-Li, R-MgX



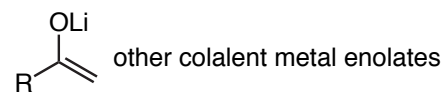
DIBAL

LiAlH₄

LiB(R)₃H

Unacceptable

R-ZnX & other colalent metal alkyls

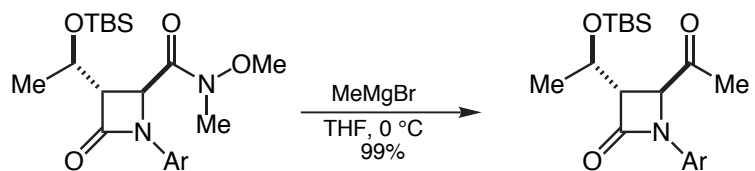


Weak hydride reagents: NaBH₄

An excellent review on all aspects of Weinreb amide chemistry:

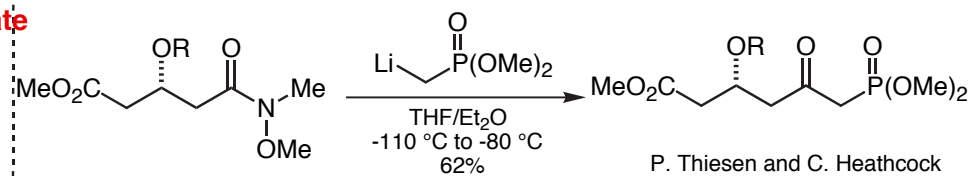
M. Sibi, *Organic Preparations and Procedures Int.*, **1993**, 25 (1), 15-40.

Representative Organometals:

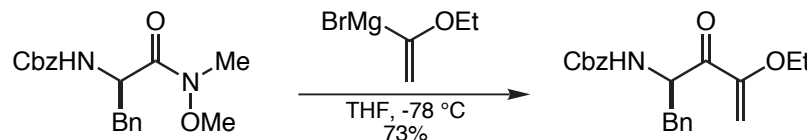


Several other examples reported.

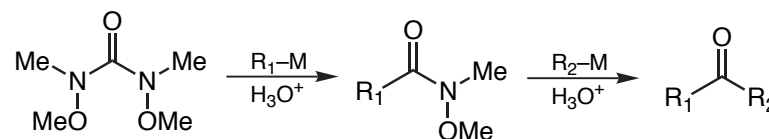
J. Prasad and L. Liebeskind
Tetrahedron Lett. **1987**, 28, 1857.



P. Thiesen and C. Heathcock
J. Org. Chem. **1988**, 53, 2374.

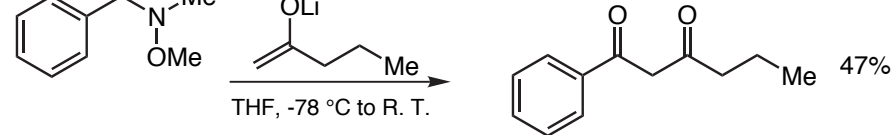
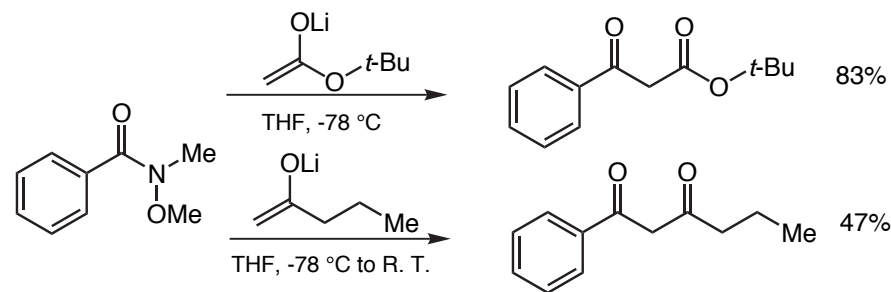


M. Angelastro, N. Peet and P. Bey
J. Org. Chem. **1989**, 54, 3913.



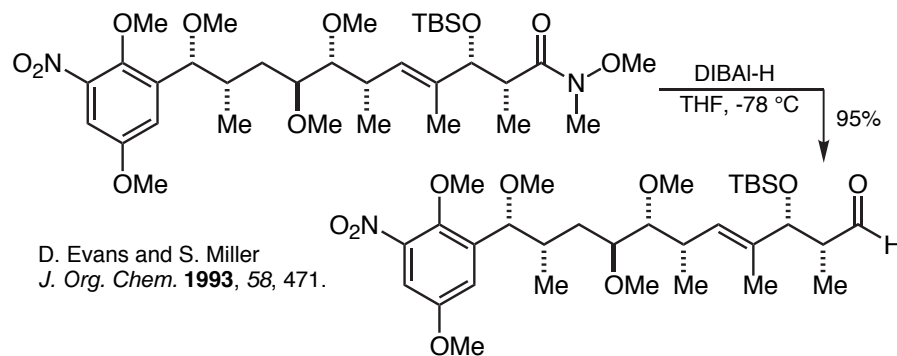
W. Wipple, H. Reich
J. Org. Chem. **1991**, 56, 2911-2.

Enolates and Metalloenamines:



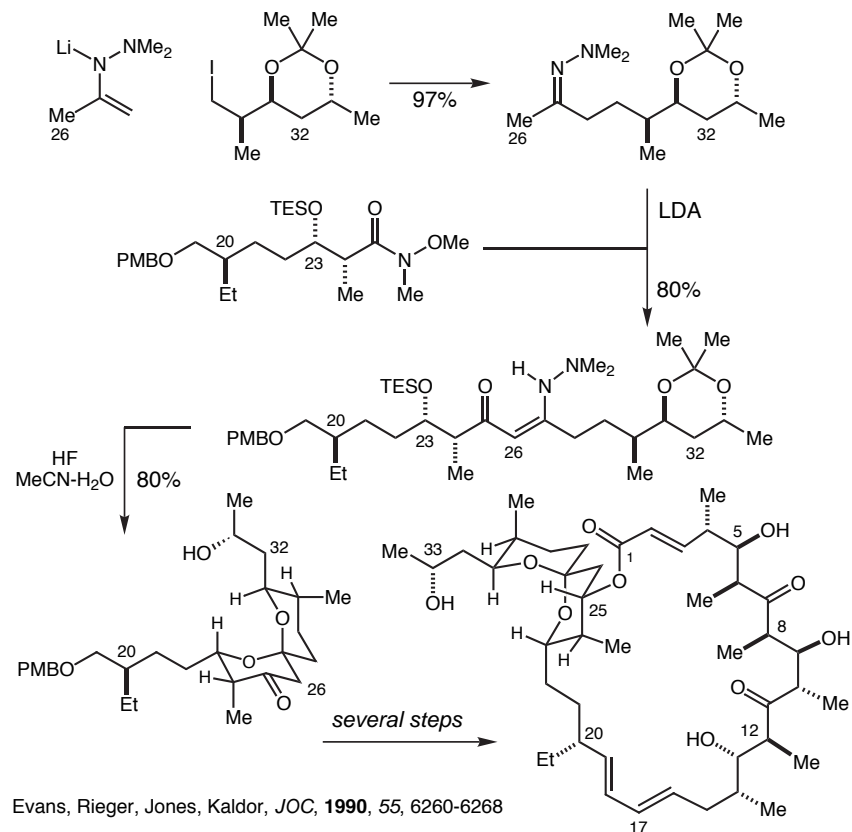
J. Org. Chem. **1989**, 54, 4229.

Hydride Reductions:

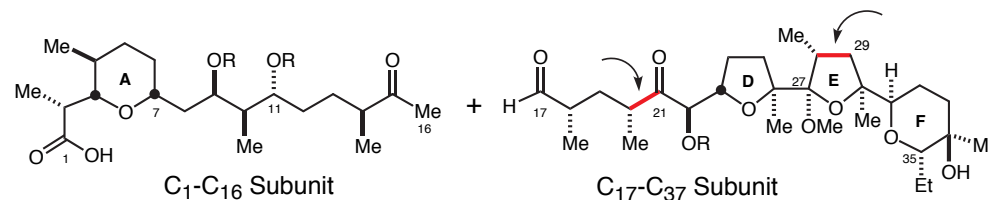
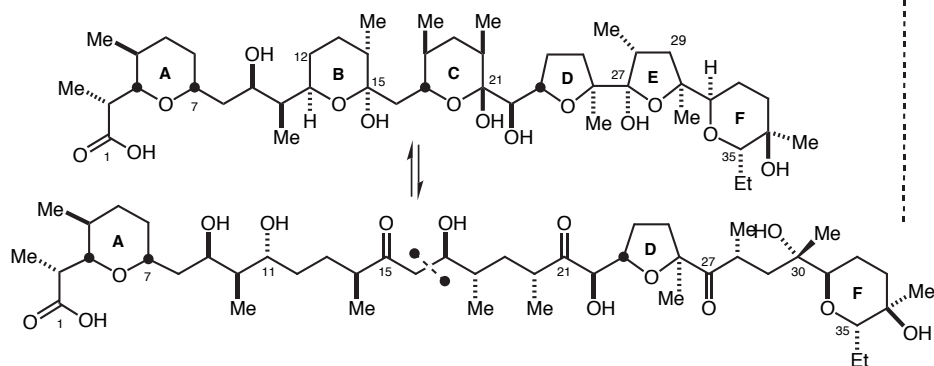


D. Evans and S. Miller
J. Org. Chem. **1993**, 58, 471.

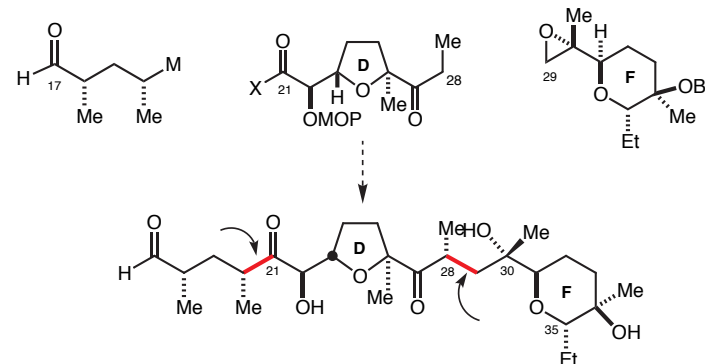
The Rutamycin B Synthesis, H. Ng, Ph. D. Thesis, Harvard University, 1993



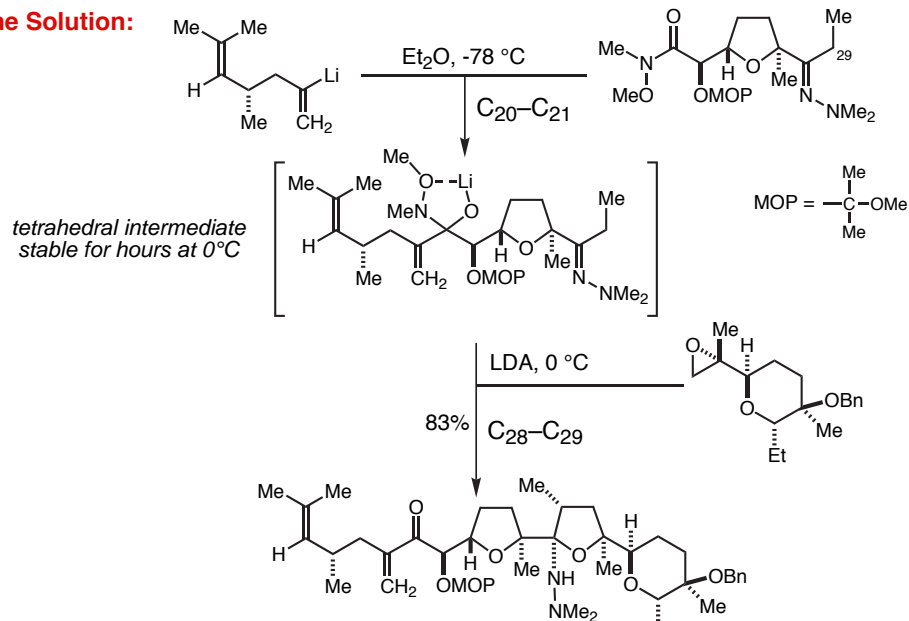
The X-206 Synthesis, S. L. Bender, Ph. D. Thesis, Harvard University, 1986



Problem is to control C=O reactivity on central D-fragment

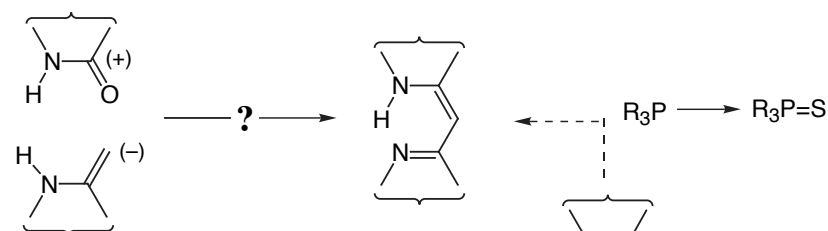
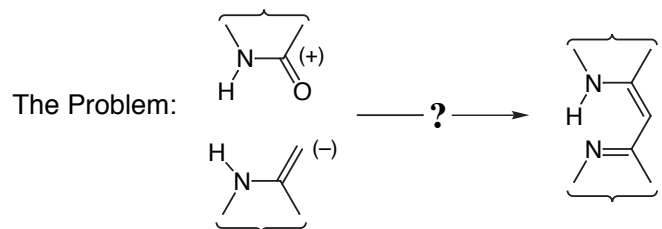


The Solution:

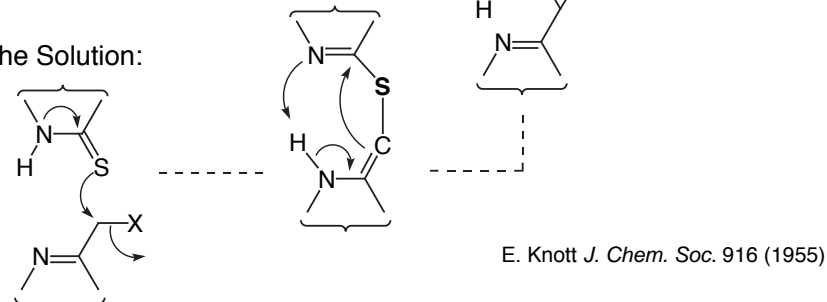


Evans, Bender, Morris *J. Am. Chem. Soc.* **1988**, 110, 2506.

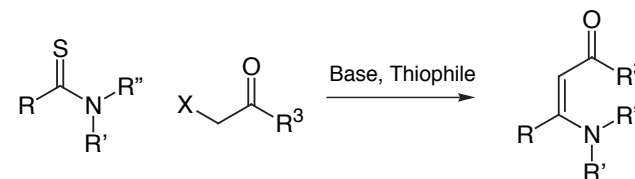
Key Bond Construction Needed for the B12 Synthesis:



The Solution:



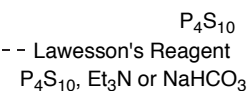
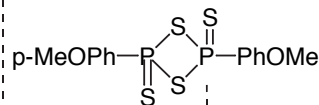
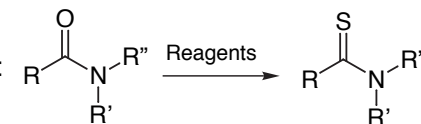
The General Reaction: Acylation of an Amide C=O



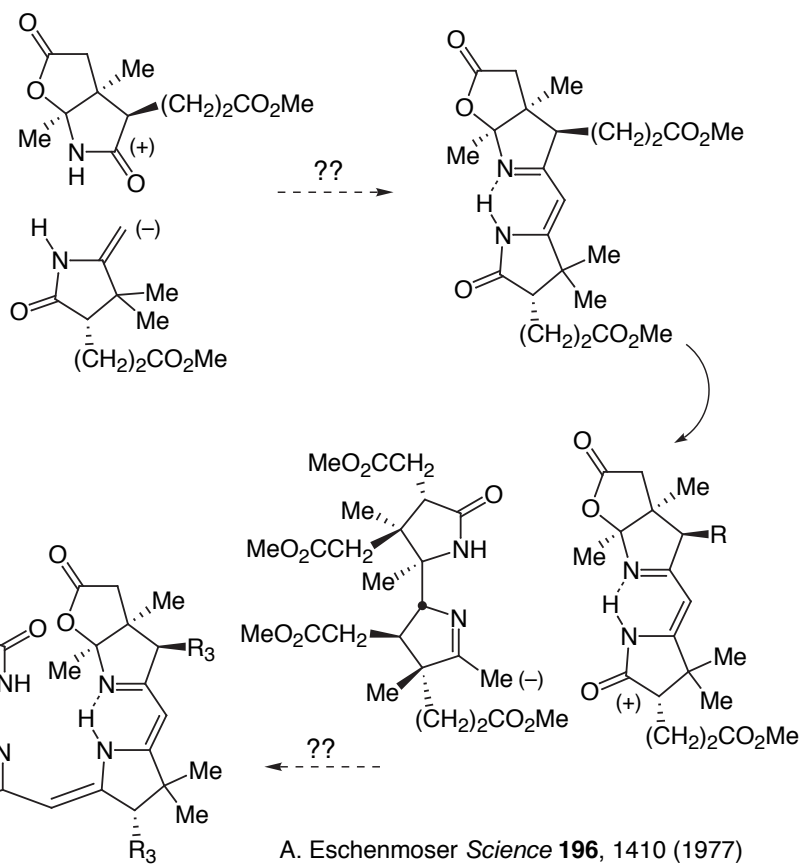
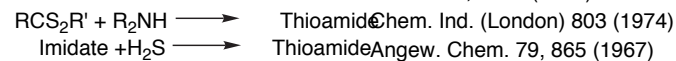
Key papers:

- A. Eschenmoser *Helv. Chim. Acta.* **54**, 710 (1971)
 A. Eschenmoser *Angew. Chem., Int. Ed. Engl.* **6**, 866 (1967)
 A. Eschenmoser *Angew. Chem., Int. Ed. Engl.* **8**, 343 (1969)
 Review: Trost *Comp. Org. Synth.* Vol. 2, Ch. 3.7 (1991)

The Thioamide component:

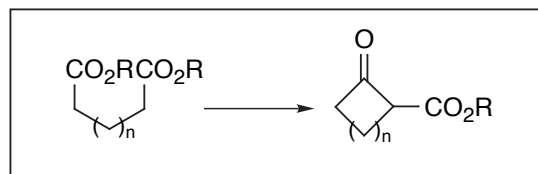


- P_4S_{10} *JOC* 46, 3558 (1981), *Synthesis* 149 (1973)
 Bull. Chim. Soc. Belg. 87, 229 & 293 (1978)
 Indian J. Chem., Sect. B 14, 999, (1976)
 JACS 102, 2392 (1980)

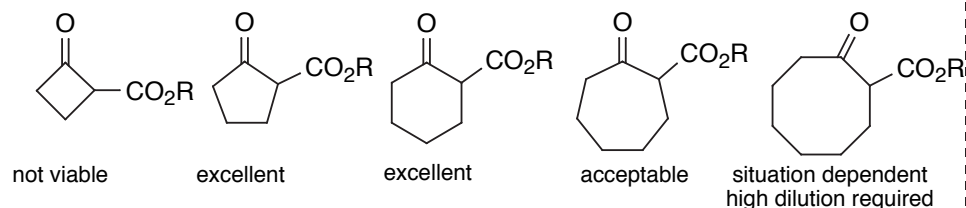


The Dieckmann Condensation

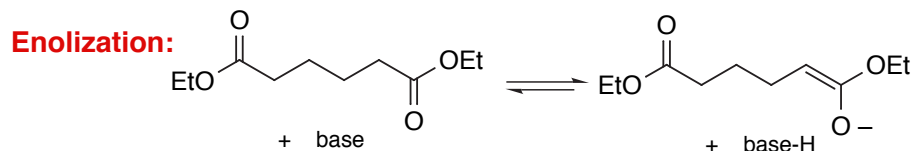
Reviews: Schaefer, Bloomfield, *Organic Reactions* **1967**, 15, 1.
Davis & Garratt, *Comprehensive Organic Synthesis* **1991**, 2, 806-829



Accessible Ring Sizes

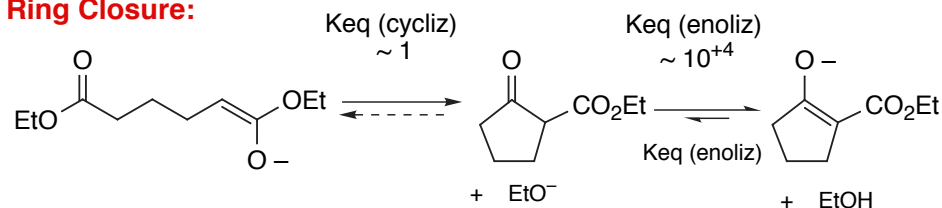


The individual steps:



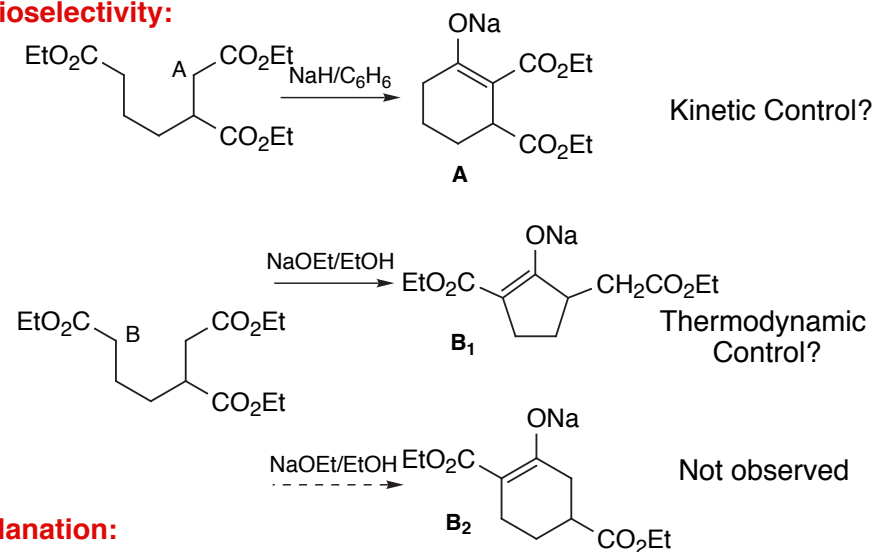
A variety of bases may be considered for the enolization step. Either alkoxide or a non-nucleophilic base such as NaH are commonly used. Choice of base can be important (Vide infra).

Ring Closure:



Statements claiming that the final enolization step renders the process irreversible are simply incorrect.

Regioselectivity:



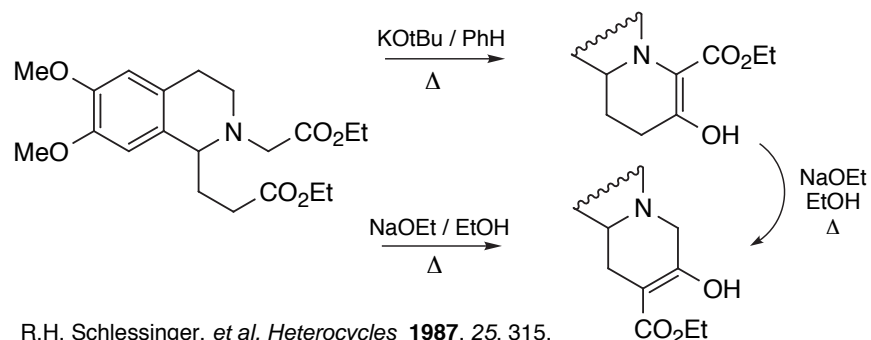
Explanation:

Enolization at (A) preferred on basis of inductive effects. Hence, Path A preferred in kinetically controlled situation

Enolates (B1) and (B2) both more stable than enolate (A)

Under equilibrating conditions (B1) appears to be preferred over (B2)

The effect of beta heteroatoms: classical kinetic vs. thermodynamic control

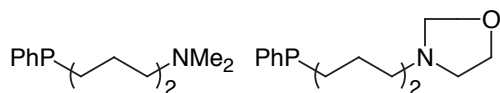
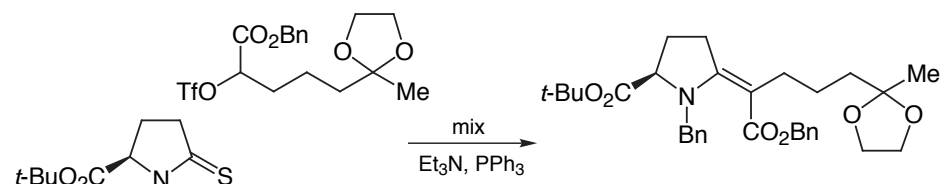
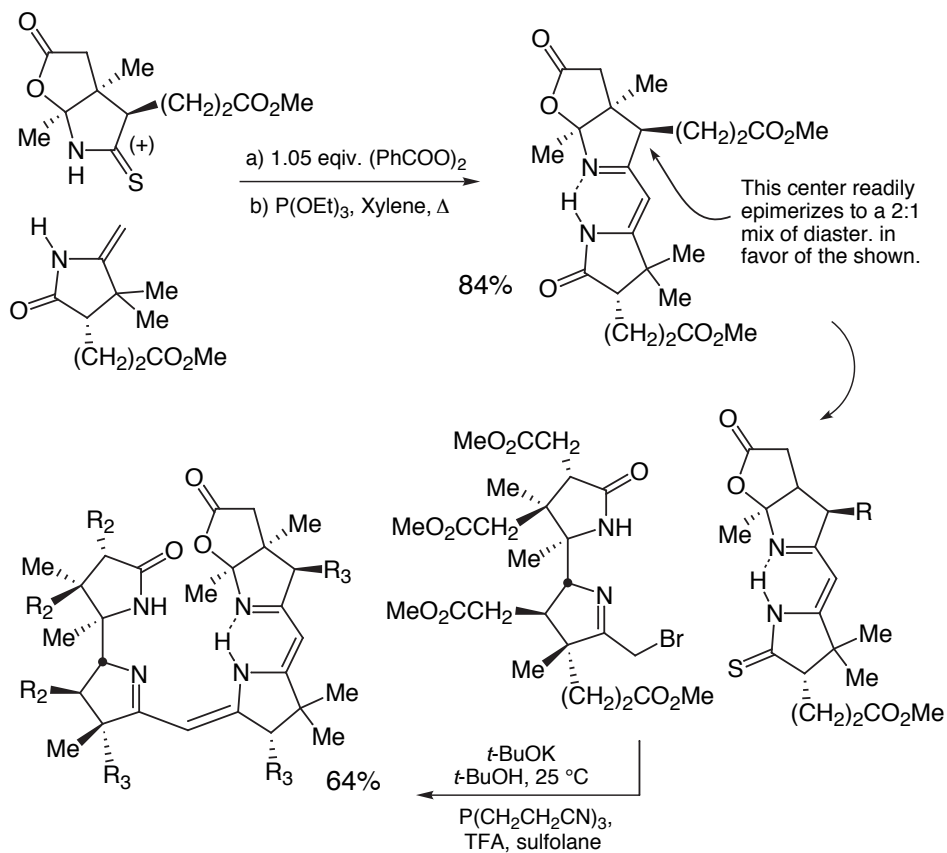
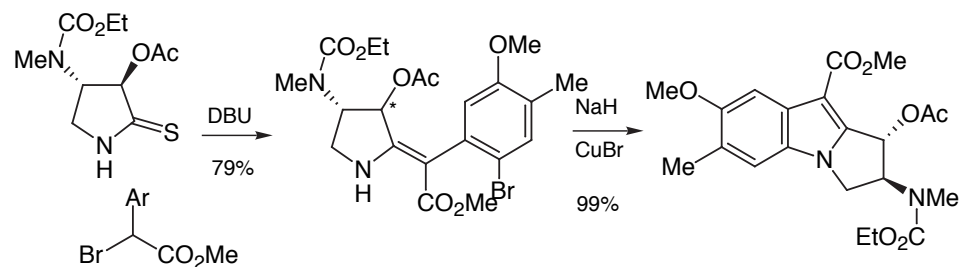
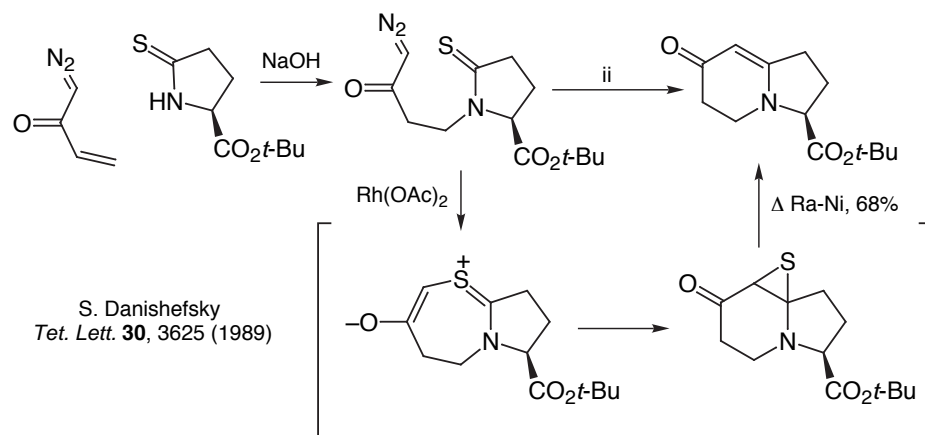
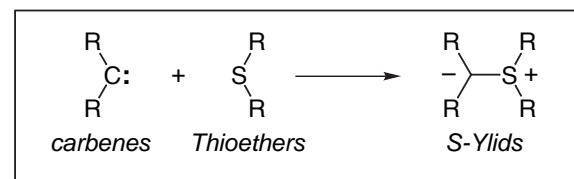


Reagents for the Reaction:

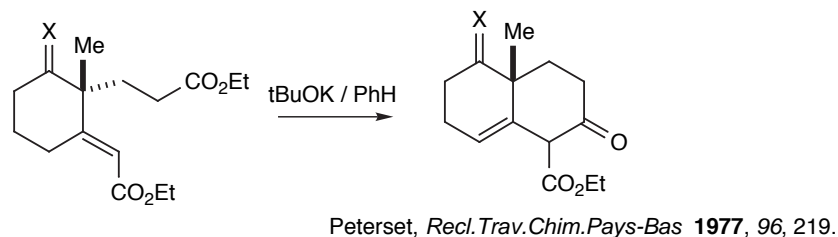
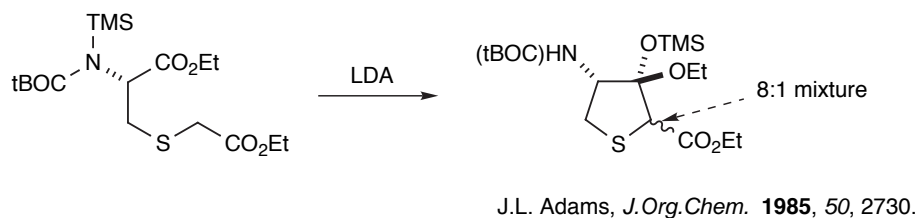
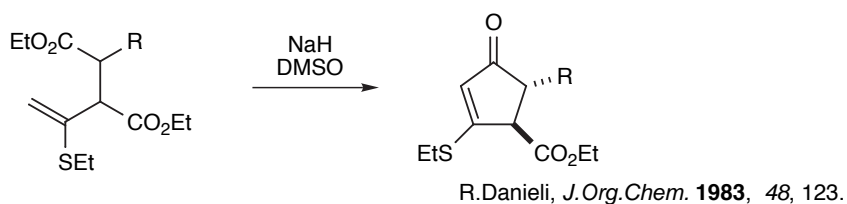
Bases:

Inorganic: MHCO_3 , MOH , MH , MOR Organic: R_3N , N -methylmorpholine, buffered solutionsThiophiles: Ar_3P , R_3P , $(\text{RO})_3\text{P}$

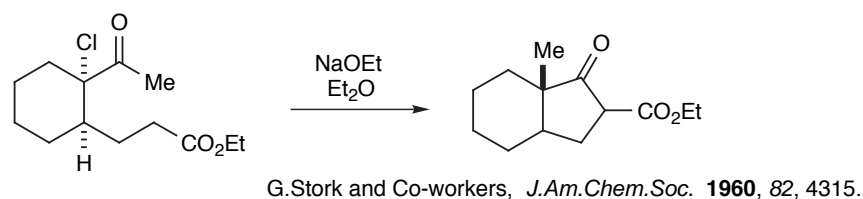
Combination:

H. Rapoport *J. Org. Chem.* **46**, 3230 (1981)A. Eschenmoser *Helv. Chim. Acta.* **54**, 710 (1971)A. Eschenmoser *Science* **196**, 1410 (1977)H. Rapoport *J. Org. Chem.* **46**, 3230 (1981)T. Kametani *J. Chem. Soc., Perkin Trans. I* 1607 (1980)S. Danishefsky
Tet. Lett. **30**, 3625 (1989)

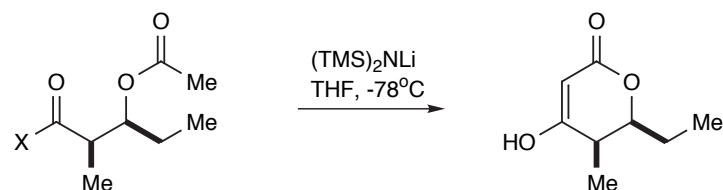
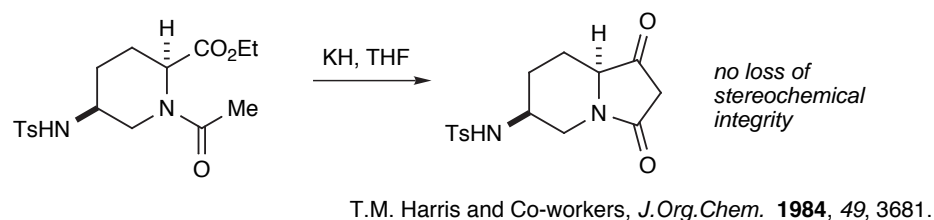
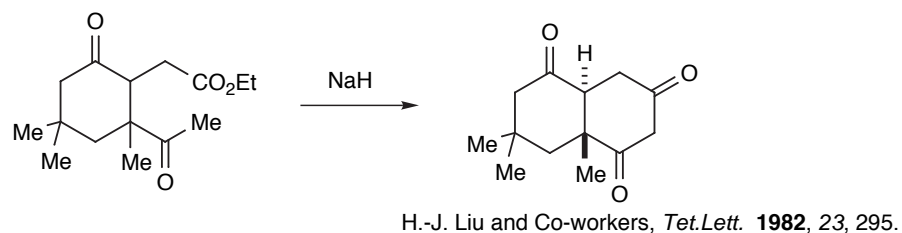
Miscellaneous Dieckmann Reactions of Potential Interest



Deduce the mechanism of this multistep process.

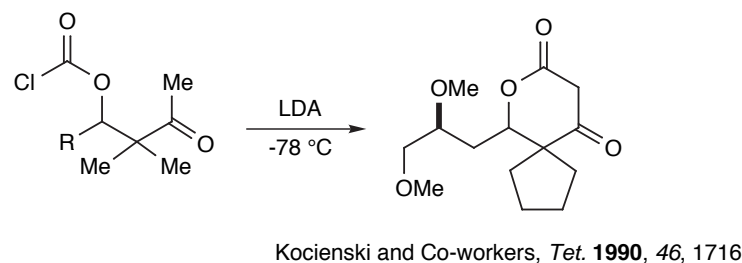


Intramolecular Ketone Acylation

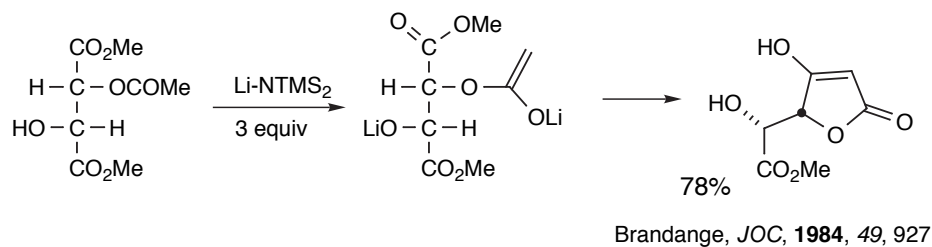
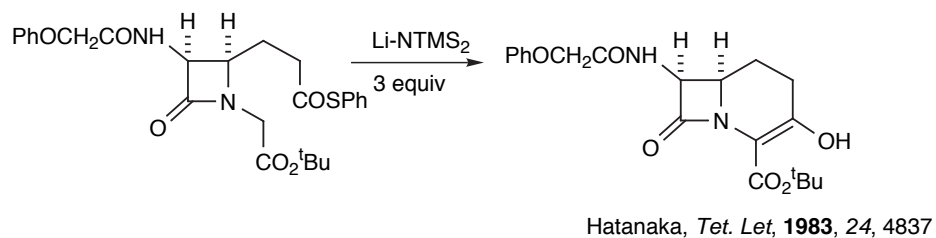
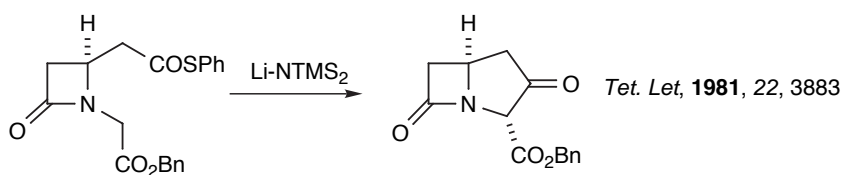
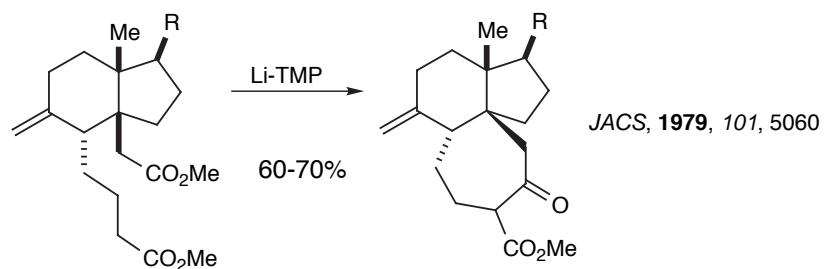
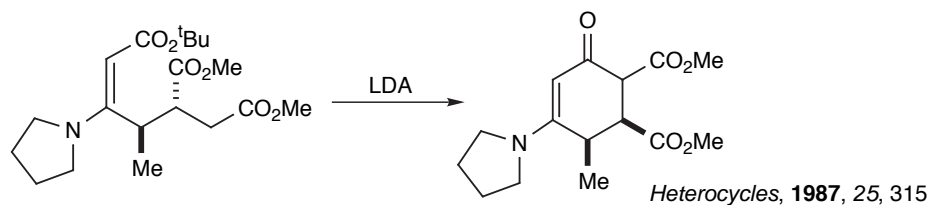


When X = NR₂, this is a good reaction, but when X = OR, it is a poor reaction.

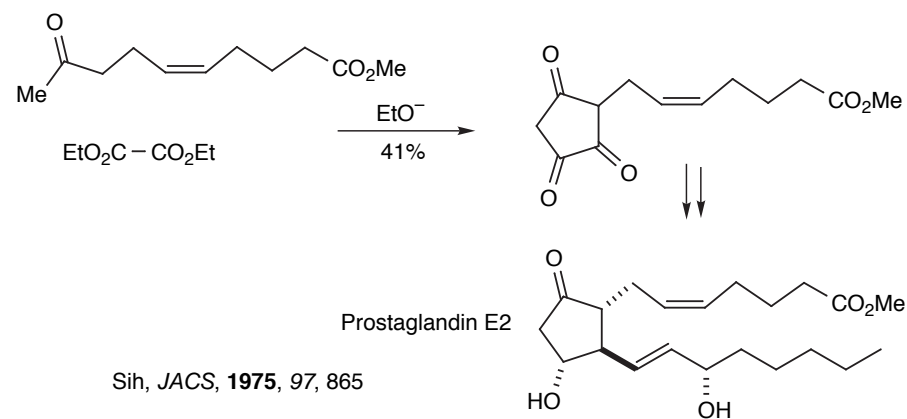
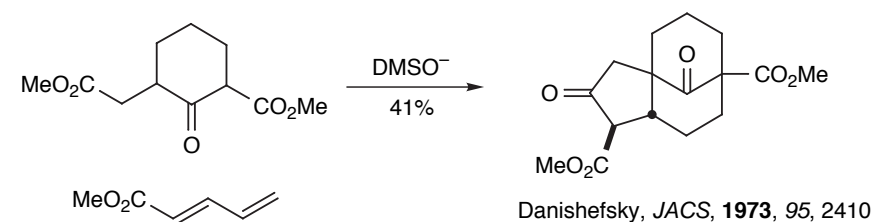
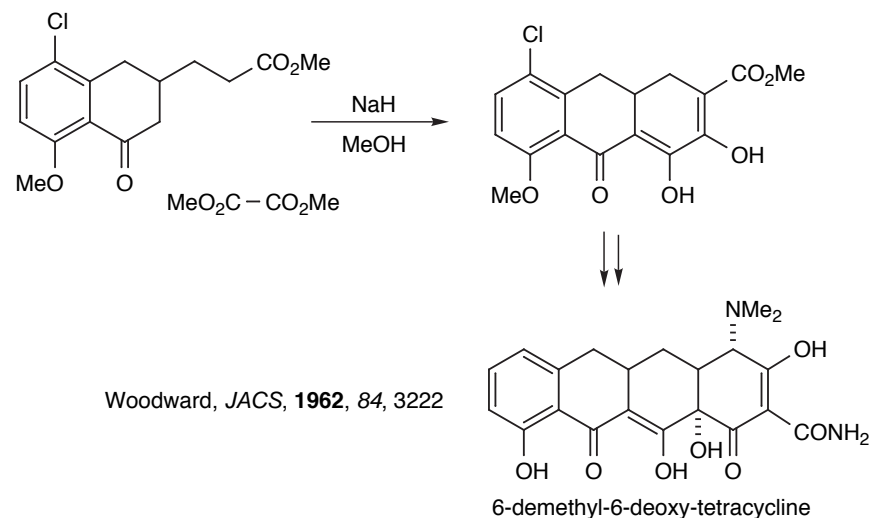
S. Brandawge and Co-workers, *Tet. Lett.* **1992**, *33*, 3025.



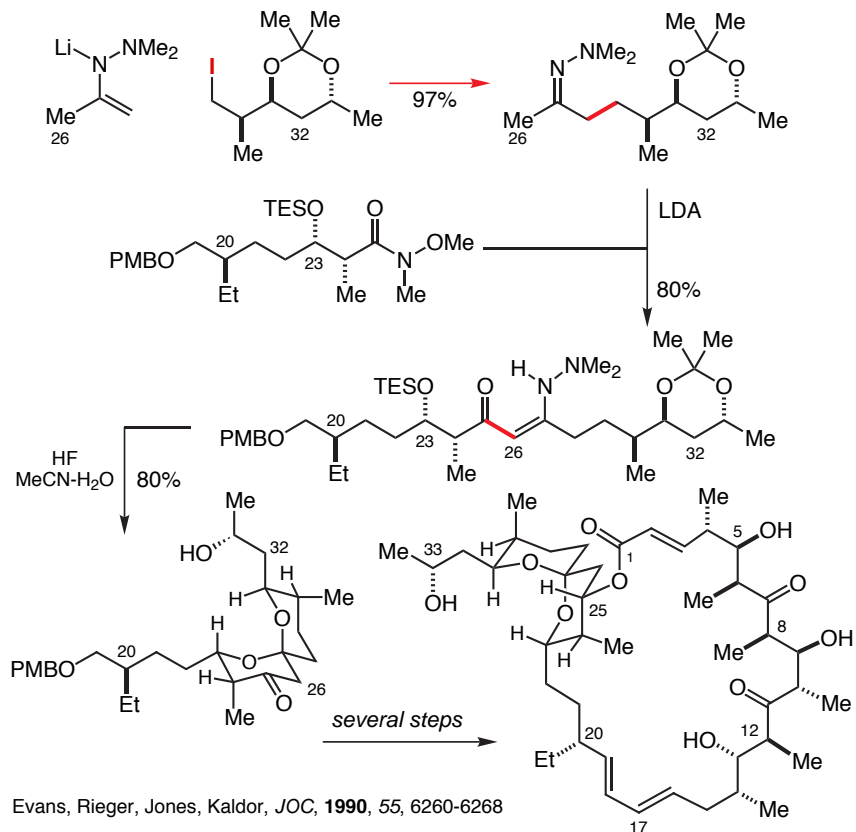
Kinetically controlled Cyclizations



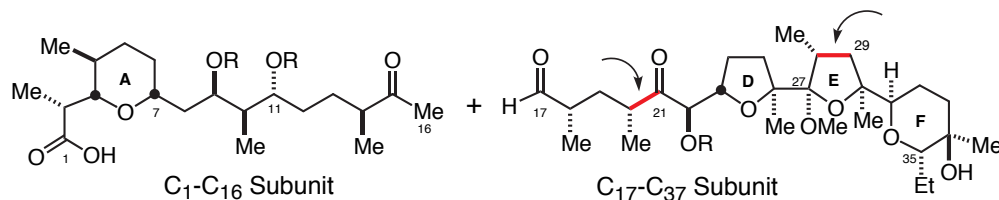
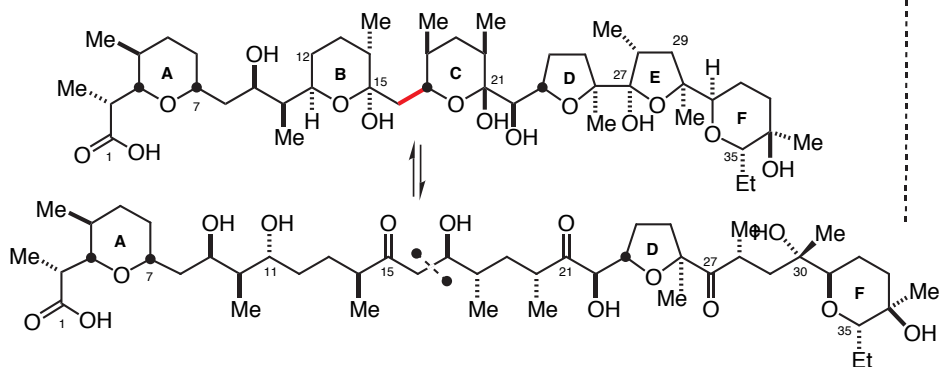
Multistep Condensations



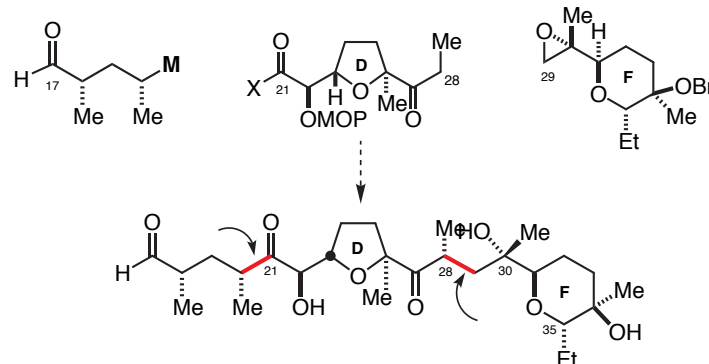
The Rutamycin B Synthesis, H. Ng, Ph. D. Thesis, Harvard University, 1993
JACS 1993, 115, 11446-11459.



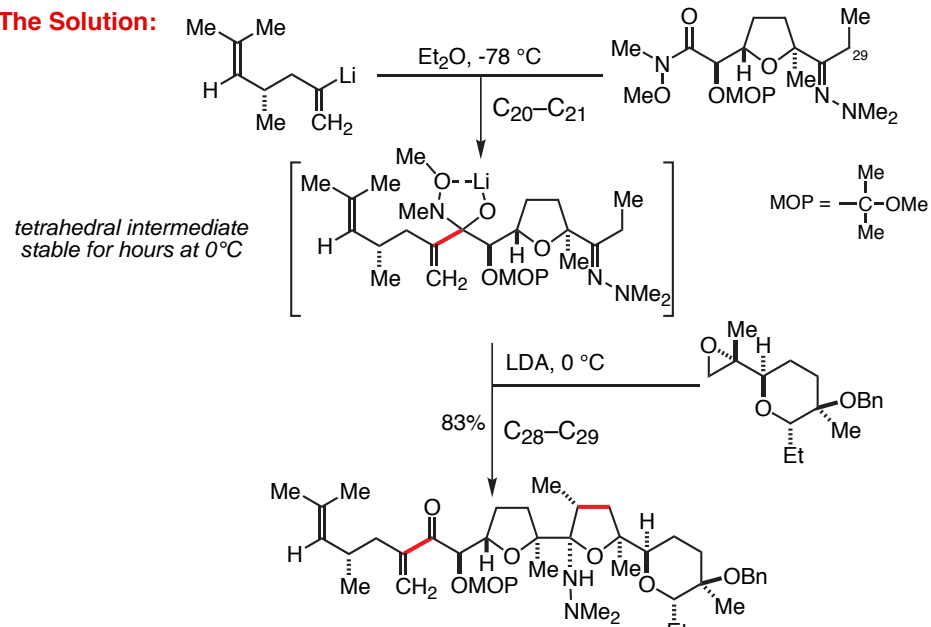
The X-206 Synthesis, S. L. Bender, Ph. D. Thesis, Harvard University, 1986



Problem is to control C=O reactivity on central D-fragment

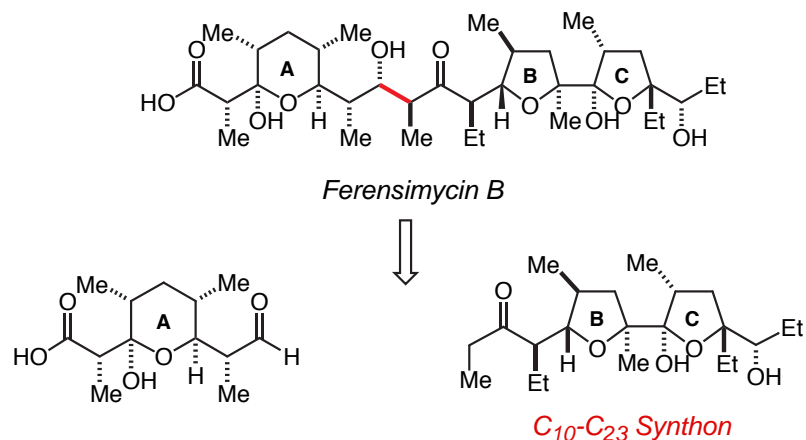


The Solution:

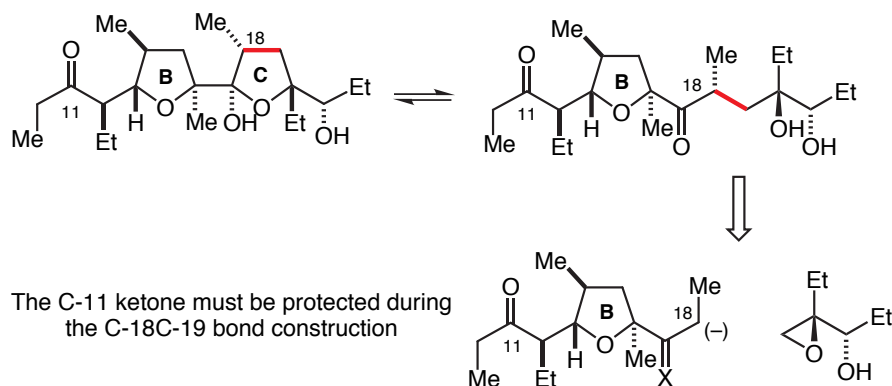


Evans, Bender, Morris *J. Am. Chem. Soc.* **1988**, 110, 2506.

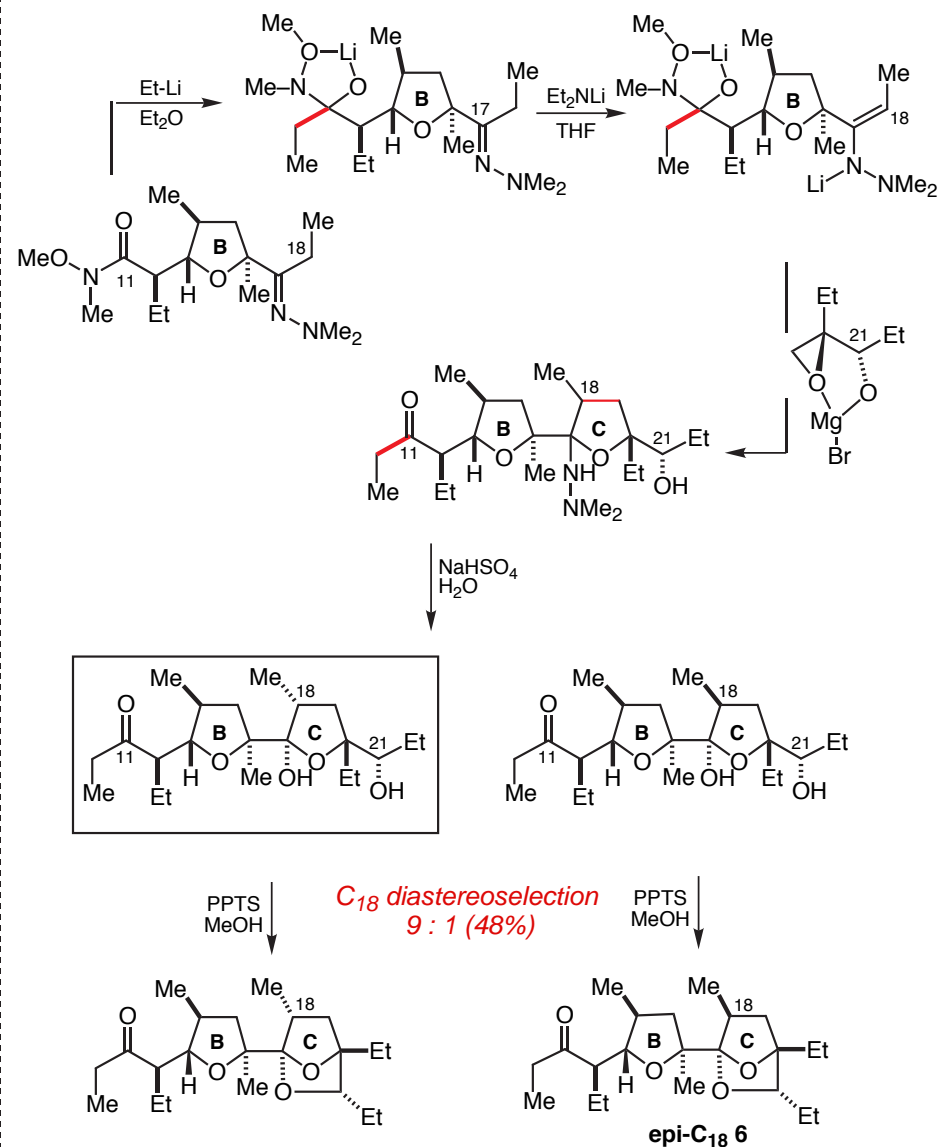
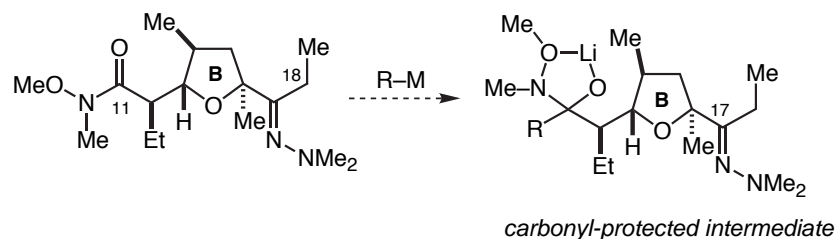
■ The Ferensimycin B Synthesis, *JACS* 1991, 113, 7613-7630



■ The B-C Fragment (*C*₁₀-*C*₂₃ Synthon)



■ The In situ protection of the C-11 Carbonyl



Quote for the Day

Quote and limrick by J. W. Cornforth

*"Nature, it seems, is an organic chemist having some predilection
for the aldol and related condensations."*

*"That Outpost of Empire, Australia
Produces some Curious Mammalia
The Kangaroo Rat
The Blood-sucking Bat
and Aurthur J. Birch, inter alia."*

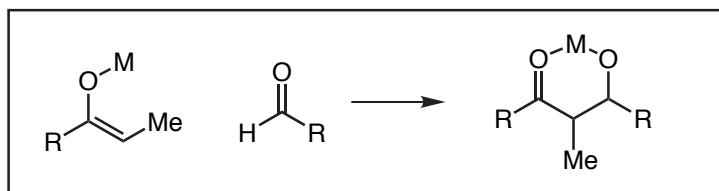
<http://www.courses.fas.harvard.edu/~chem206/>

Chemistry 206

Advanced Organic Chemistry

Lecture Number 25

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

D. A. Evans

Wednesday,
November 12, 2003

■ Suggested 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)**

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.

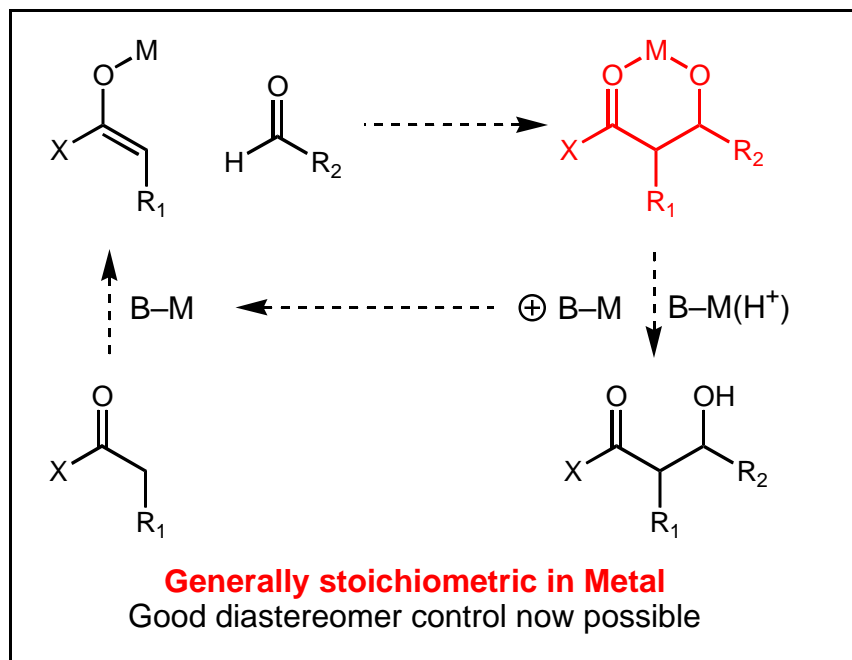
Cowden, C. J. and I. Paterson (**1997**). "Asymmetric aldol reactions using boron enolates." *Org. React. (N.Y.)* 51: 1-200.

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.

Aldol Reaction Variants: Each has its Merits & Liabilities

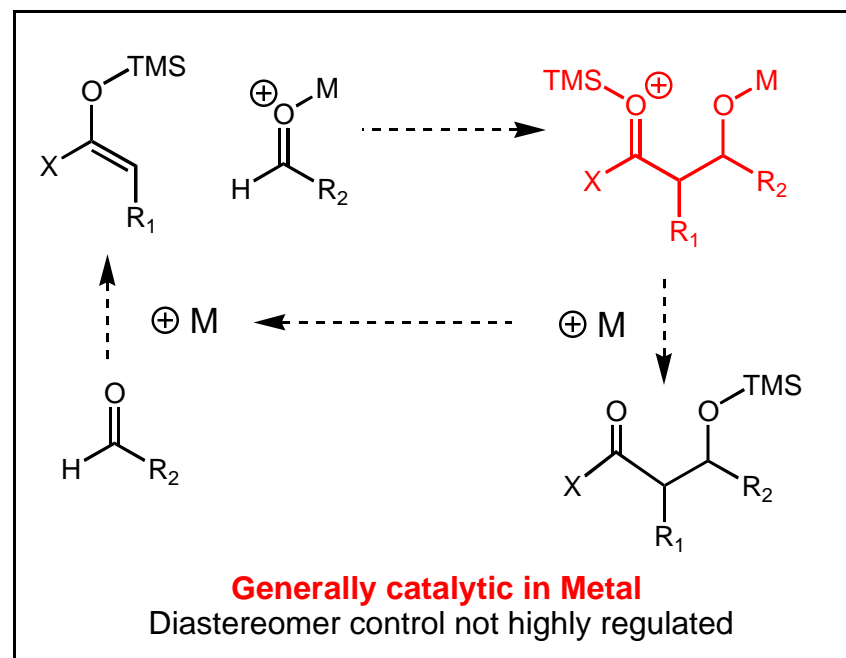
Metal Aldol Process



Teruaki Mukaiyama

Chem Lett. **1973**, 1011

Mukaiyama Aldol Process



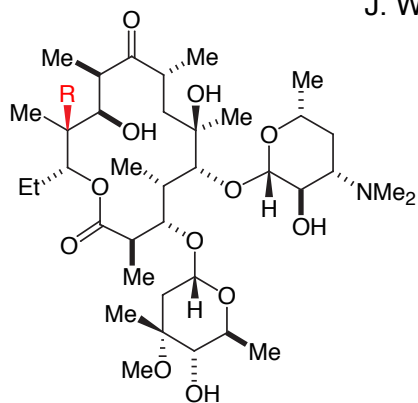
Clayton Heathcock



Satoru Masamune

"Nature, it seems, is an organic chemist having some predilection for the aldol and related condensations."

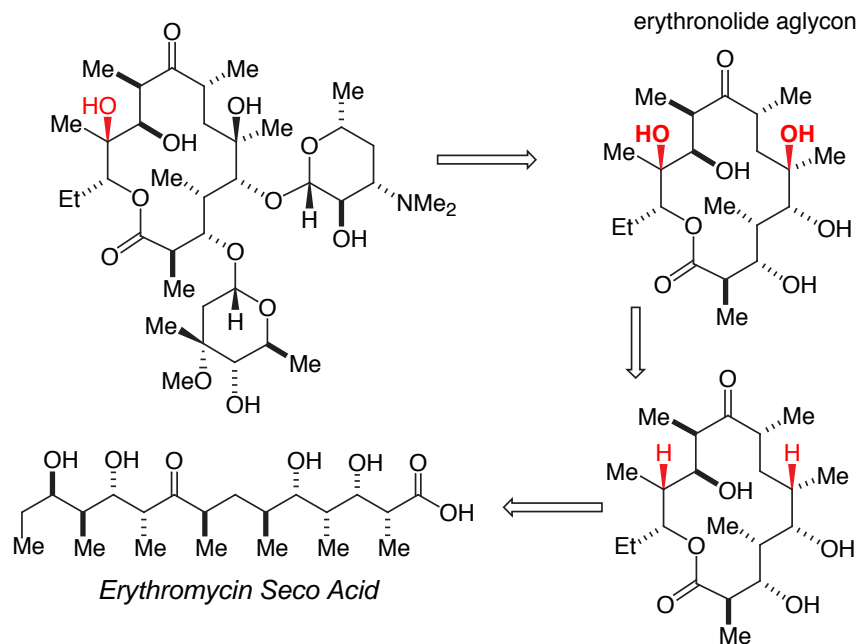
J. W. Cornforth



Erythromycin A, R = OH
Erythromycin B, R = H

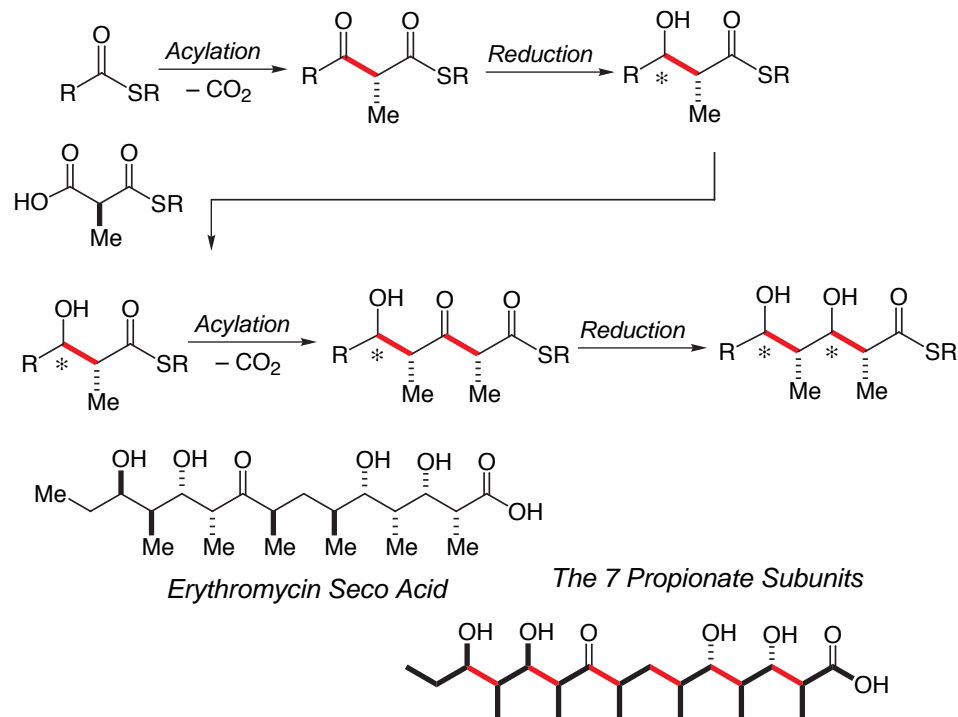
J. W. Cornforth
Nobel Prize, 1975

Retro-biosynthesis: Erythromycin A



Recent overview: Staunton, "Polyketide biosynthesis: a millennium review." *Nat. Prod. Rep.* **2001**, 18, 380-416.

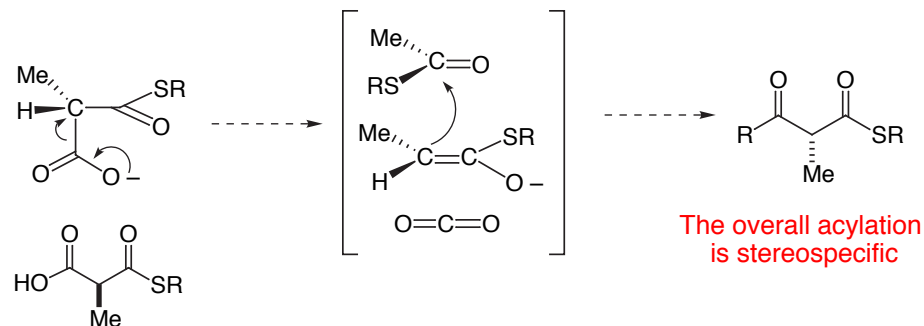
Polypropionate Biosynthesis: The Elementary Steps



The Acylation Event

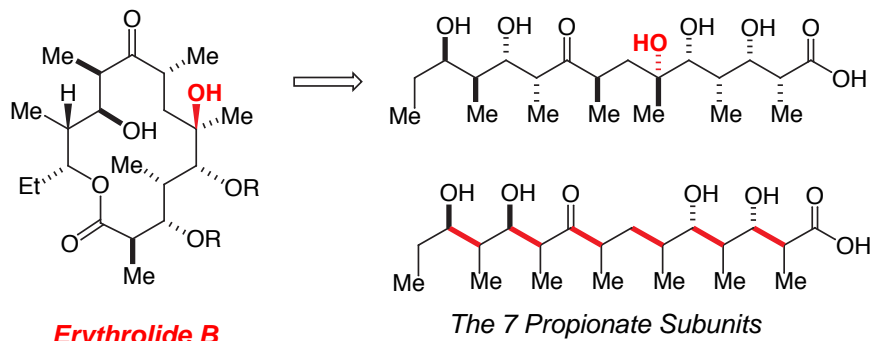
Decarboxylation-Acylation could either be stepwise (Option A) or concerted (Option B).

The stepwise Option

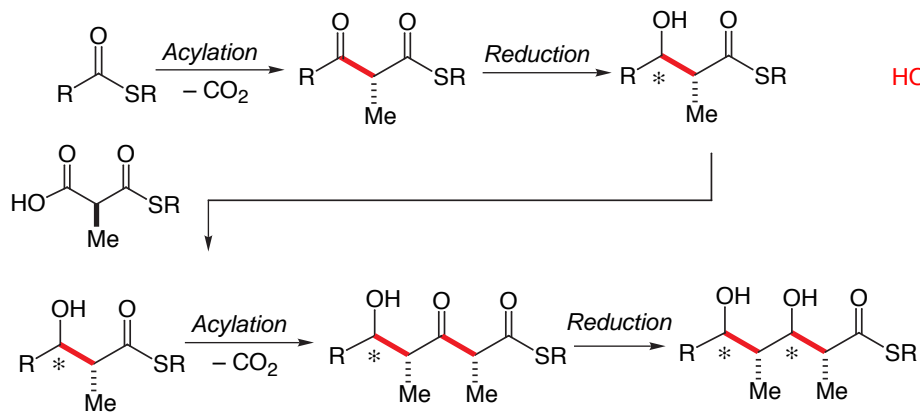


See Lecture 24; page 24-08 for first laboratory example

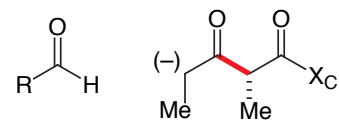
Polypropionate & Polyacetate Biosynthesis: Develop a Laboratory Simulation



Polypropionate Biosynthesis: The Elementary Steps

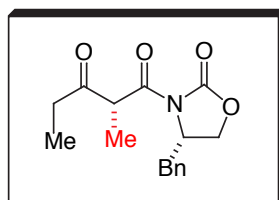


The Laboratory Mimic:

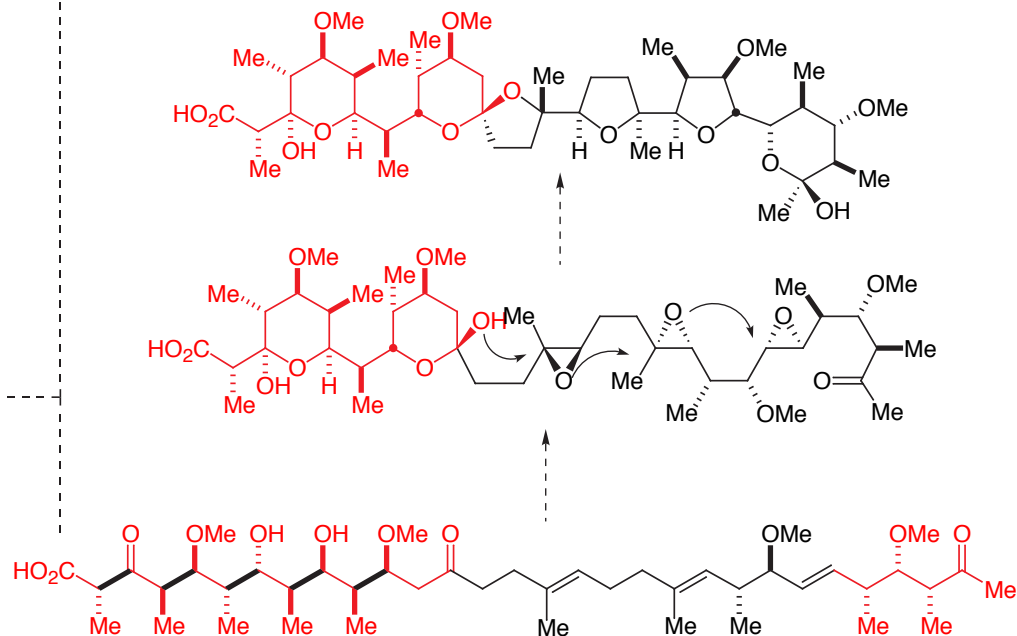


See Lecture 23; page 23-08:
with M. Ennis JACS **1984**, 106, 1154.

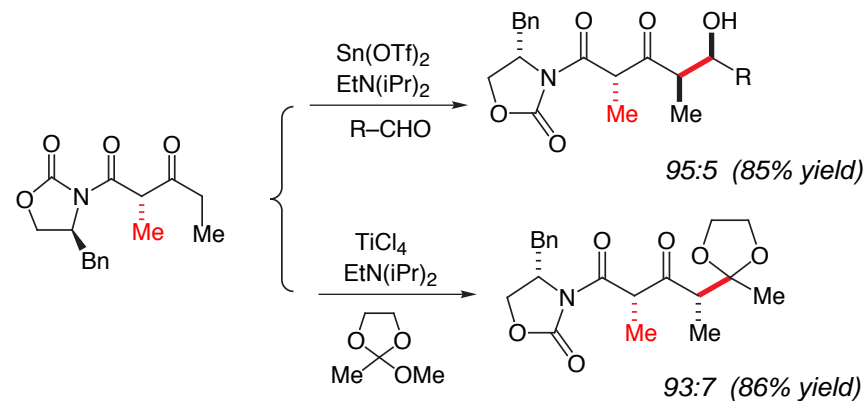
Dipropionyl Synthone



Latter Stages of Lonomycin Biosynthesis



Cane, Celmer, Westley JACS **1983**, 105, 3594



with Ratz, Huff, & Sheppard, JACS **1995**, 117, 3448

General Reviews of the Aldol Literature:Mukaiyama in *Organic Reactions*, **1982**; Vol 28, pp 203-331Evans in *Topics in Stereochemistry*, **1982**; Vol 13, pp 1-115Heathcock 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

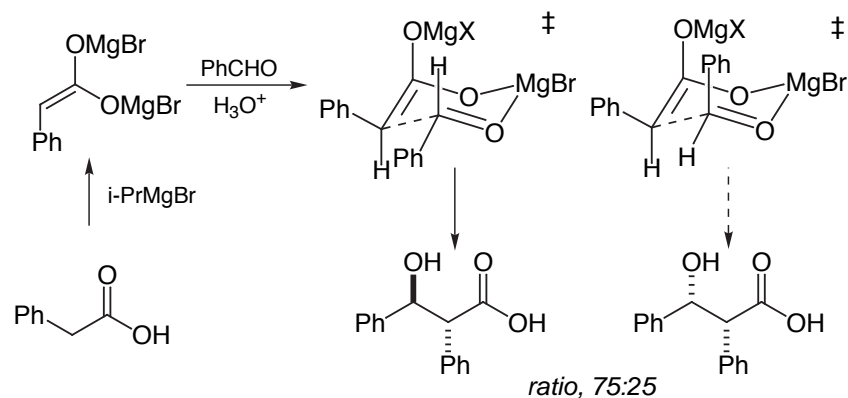
Group III metal enolates: Masamune; Chapter 1.7, pp 239

Transition metal enolates: Paterson; Chapter 1.9, pp 301

Control relative stereochemical relationships

Zimmerman 1957:

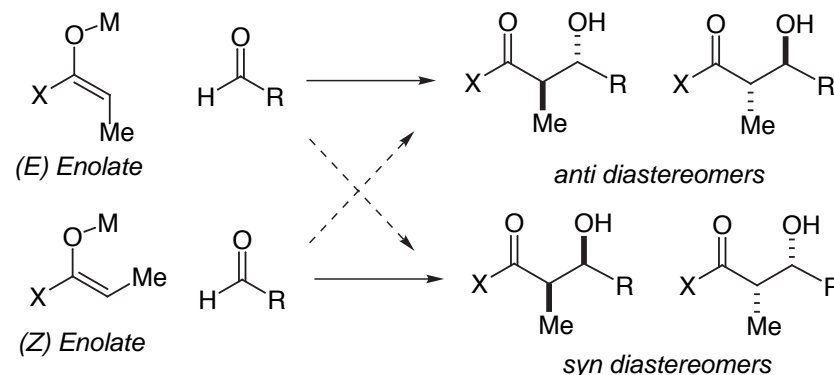
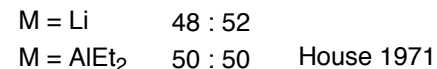
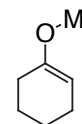
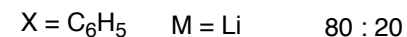
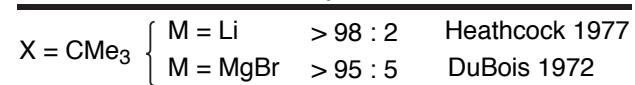
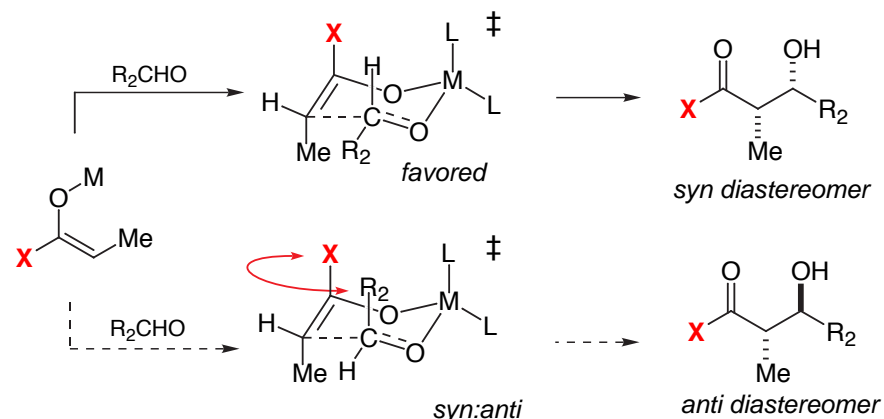
Proposed chair-like geometry for the Ivanov Reaction



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.

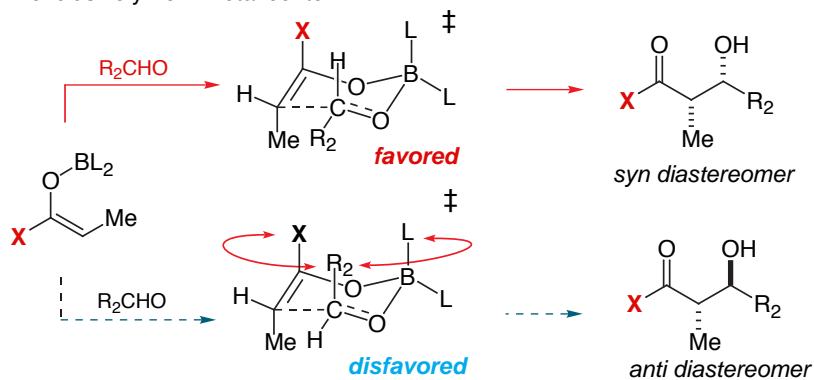
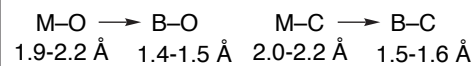
The only flaw in the study was that he failed to determine whether the aldol adducts were stable to the reaction conditions.

Zimmerman, *J. Am. Chem. Soc.* **1956**, 79, 1920 (handout)**DuBois 1965-67:** Rough correlation between enolate structure & product stereochemistry for alkali and alkaline earth enolates**Zimmerman-Traxler Model for (Z) Enolates**

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



		<i>syn:anti</i>		
X = CMe₃	M = Li	> 98 : 2	Heathcock 1977	
	M = MgBr	> 95 : 5	DuBois 1972	
	M = BBu ₂	> 97 : 3	DuBois 1972	
X = C₆H₅	M = Li	80 : 20	Evans, Masamune 1979-81	
	M = BBu ₂	> 97 : 3		
X = Et	M = Li	80 : 20		
	M = BBu ₂	> 97 : 3		
	M = Li	48 : 52	House 1971	
	M = AlEt ₂	50 : 50	Yamamoto 1977	
	M = BBu ₂	33 : 67 (ether)	Evans, Masamune 1979-81	
	M = BBu ₂	17 : 83 (pentane)		
M = BCy(thex)	6 : 94 (CH ₂ Cl ₂)			
M = B(Cyp) ₂	<5 : 95 (pentane)			
	M = B(Cyp) ₂	<5 : 95 (pentane)		

Evans et al. *JACS* **1979**, *101*, 6120-6123; *JACS* **1981**, *103*, 3099-3111

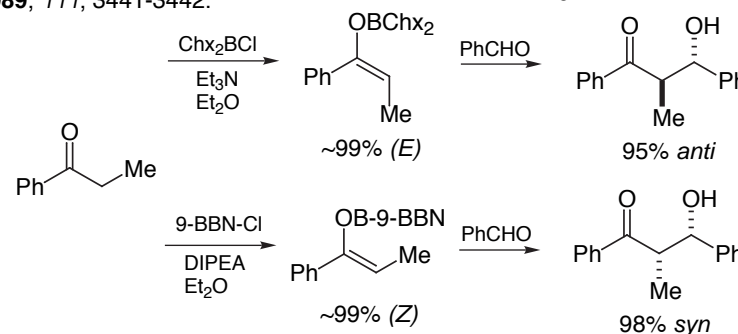
Masamune, *Tet. Lett* **1979**, 1665, 2225, 2229, 3937

Are (E) enolates intrinsically less diastereoselective?

Now that there are good methods for preparing (E) enolates, it appears that both enolate geometries are nearly equivalent.

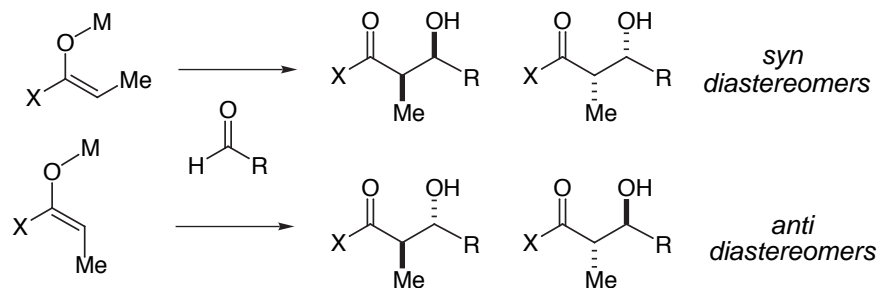
Dialkylboron chlorides (Brown)
JACS. **1989**, *111*, 3441-3442.
J. Org. Chem. **1992**, *57*, 499-504.
J. Org. Chem. **1992**, *57*, 2716-2721.
J. Org. Chem. **1992**, *57*, 3767-3772.
J. Org. Chem. **1993**, *58*, 147-153.

JACS. **1989**, *111*, 3441-3442.

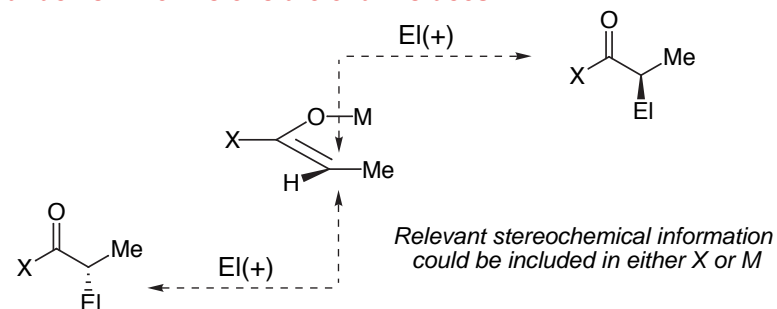


It appears that there is not a great difference in aldol diastereoselectivity

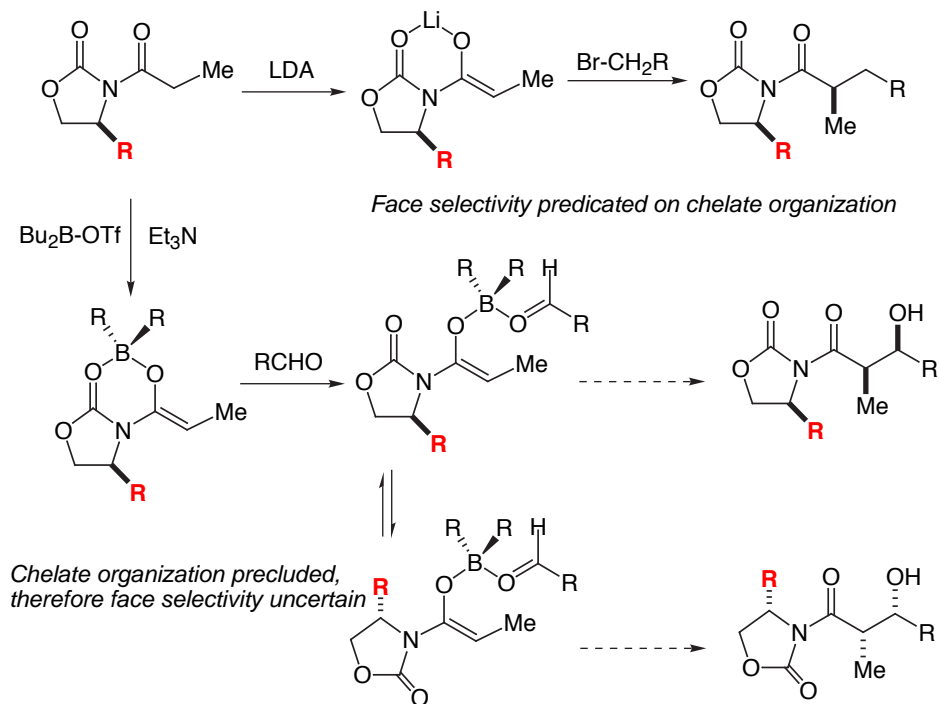
Dissection of the Aldol Problem: Select for one product diastereomer



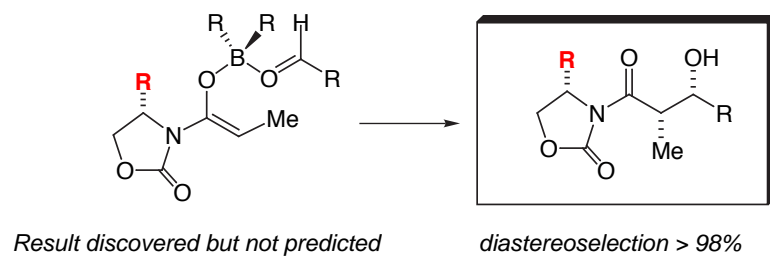
Control attack on the two enolate enantiofaces



Imide Enolates: The problem of enolate face selectivity

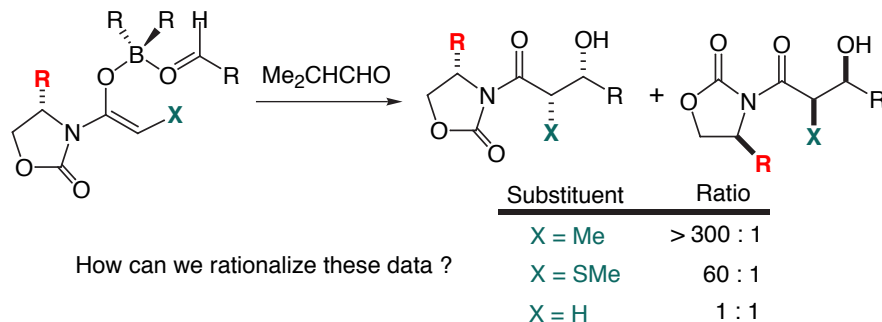


The aldol reaction selects for the opposite enolate diastereoface

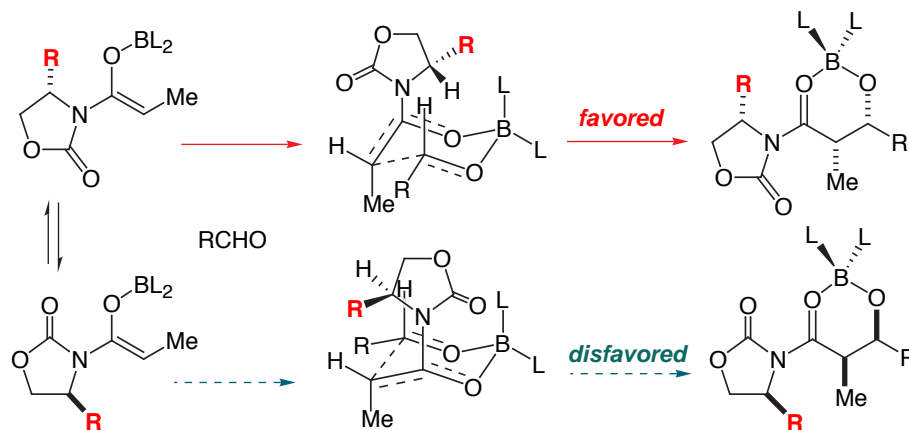


J. Am. Chem. Soc. **1981**, 103, 2127-2129 (Handout)

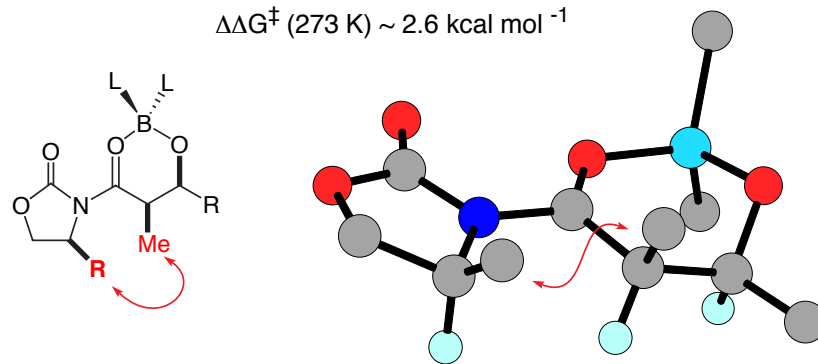
The Alpha substituent, X, plays pivotal role in aldol diastereoselection



Model for Asymmetric Induction (unpublished)



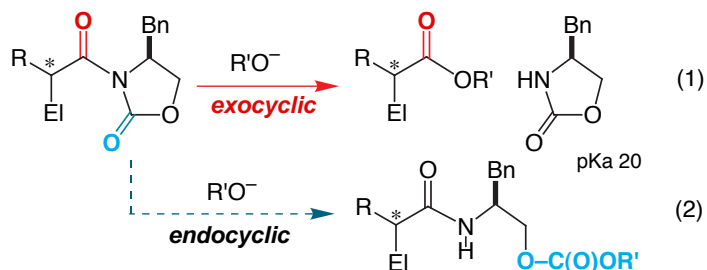
$$\Delta\Delta G^\ddagger (273 \text{ K}) \sim 2.6 \text{ kcal mol}^{-1}$$



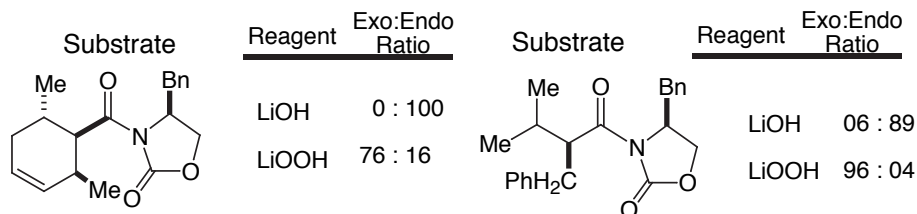
disfavored product diastereomer: The destabilizing interaction?

Imide Hydrolysis

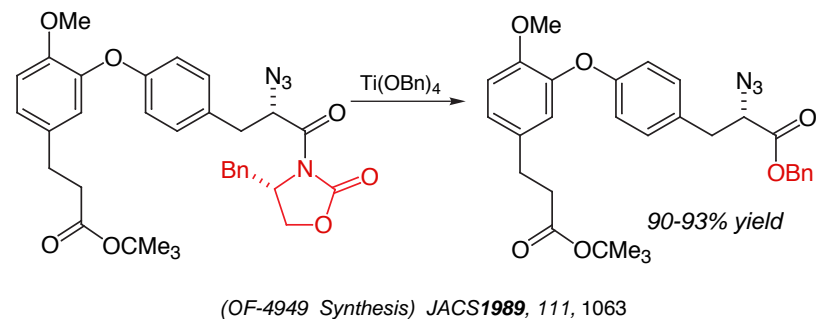
Imides may suffer attack at either of the two C=O functions (eq 1, eq 2)



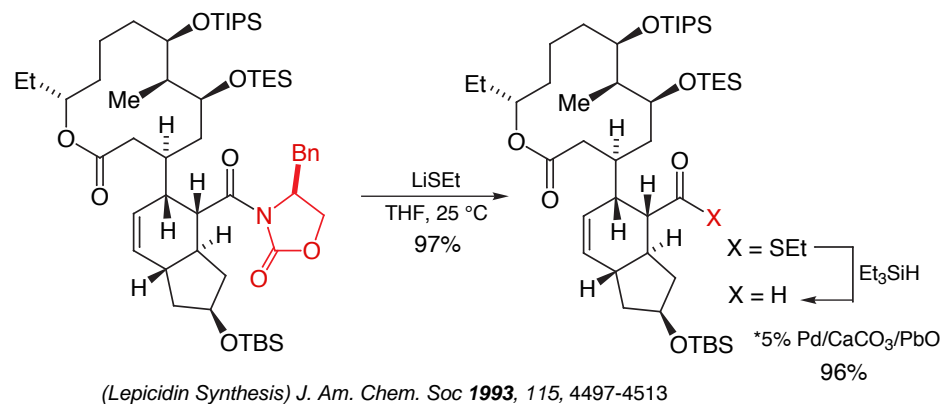
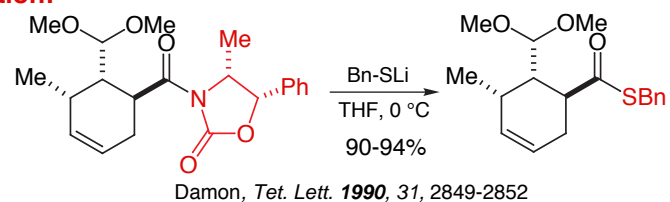
Product distribution a function of attacking nucleophile (*Tet. Lett.* **1987**, 28, 6141)



Trans-esterification

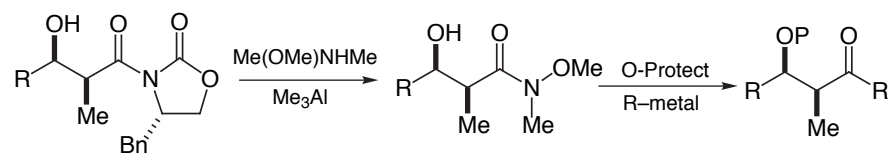


Trans-thioesterification:

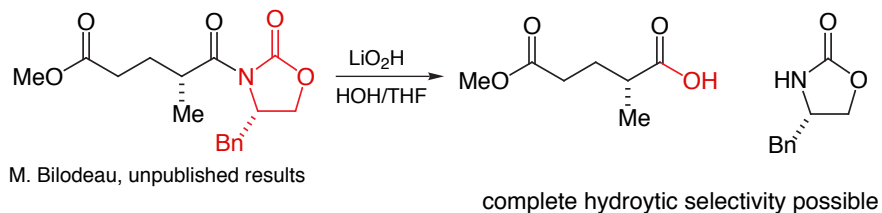
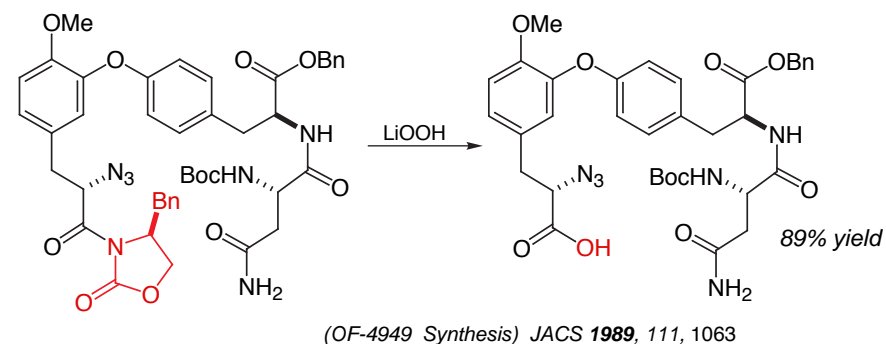


RCOSR \longrightarrow RCHO Fukuyama, *J. Am. Chem. Soc.* **1990**, 112, 7050-7051

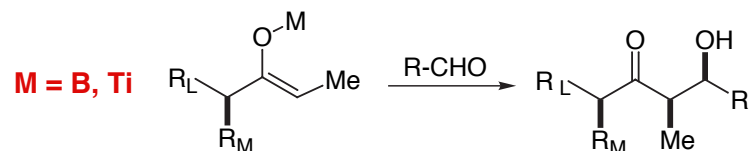
Transamination to Weinreb Amides (see Handout 24A)



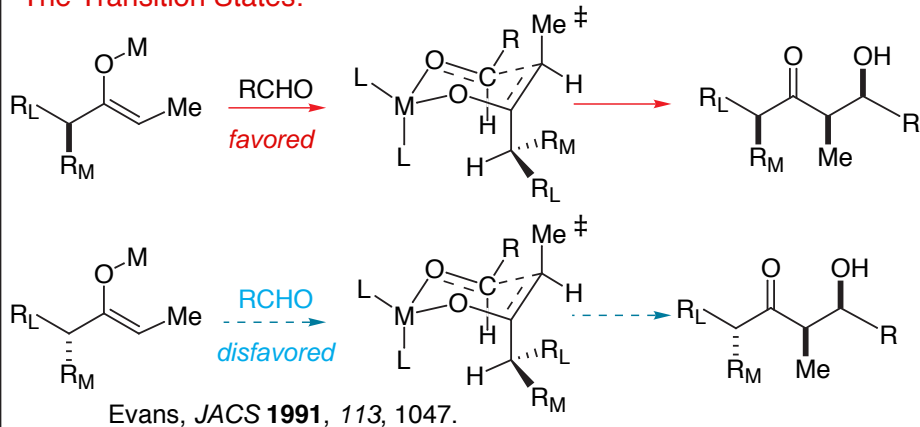
for recent examples see, *J. Am. Chem. Soc.* **1992**, 114, 9434-9453



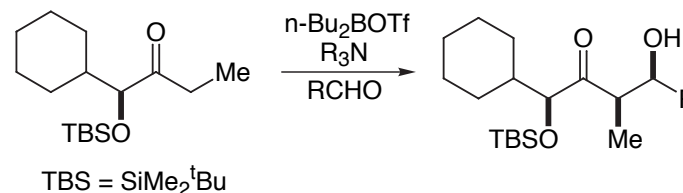
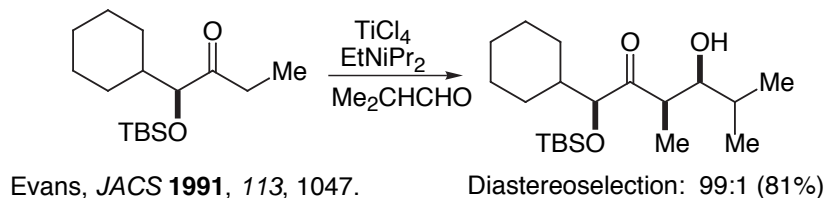
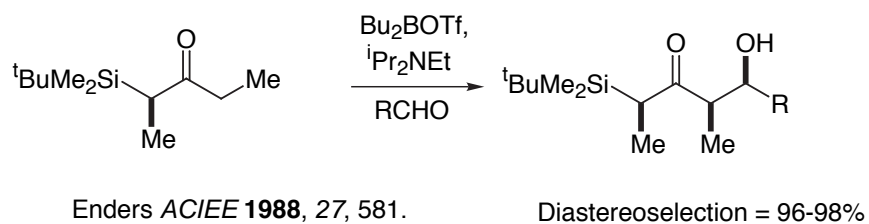
General Reaction for Syn Aldols: M = B, Ti



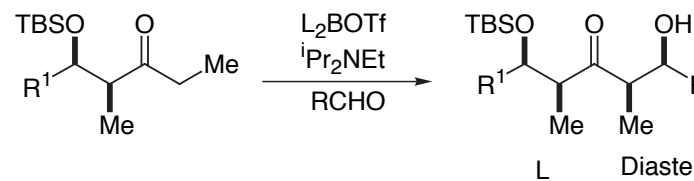
The Transition States:



Examples:

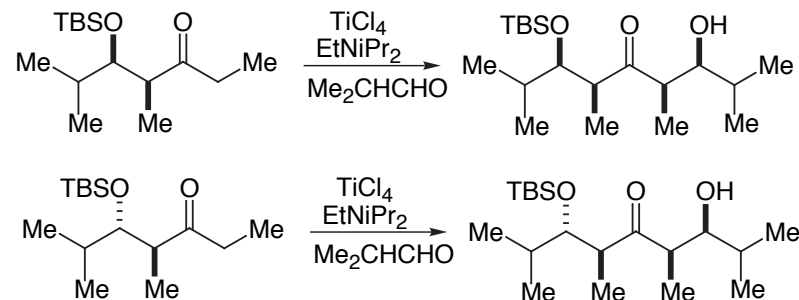


R	Diastereoselection
Ph	97:3
Et	98:2
BnOCH ₂ CH ₂	96:4
Me ₂ CH	>99:<1

Masamune, *JACS* **1981**, 103, 1566.

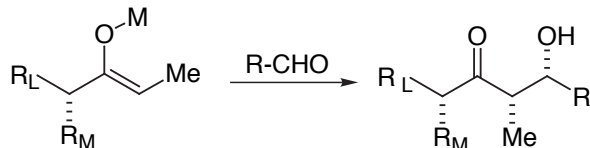
This system does not give a completely clean (Z) enolate

L	Diastereoselection
Bu	63:37 - 84:16
9-BBN	83:17 - 85:15
(-)-Ipc	72:28
(+)-Ipc	91:9 - 94:6

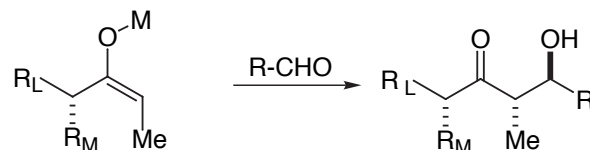
Paterson, McClure, *Tet.Lett.* **1987**, 28, 1229.Evans, *JACS* **1991**, 113, 1047.

Diastereoselection: 95:5 (80-90%)

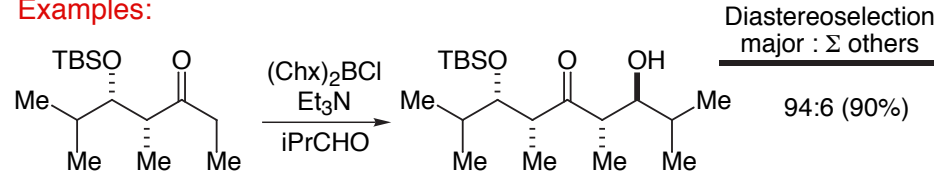
General Reaction
for
Syn Aldols:



General Reaction
for
Anti Aldols:



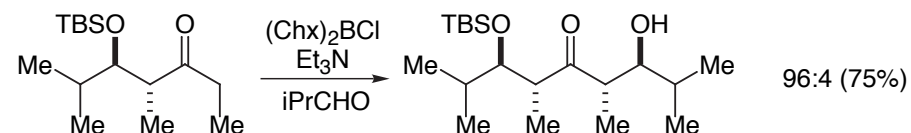
Examples:



Diastereoselection
major : Σ others

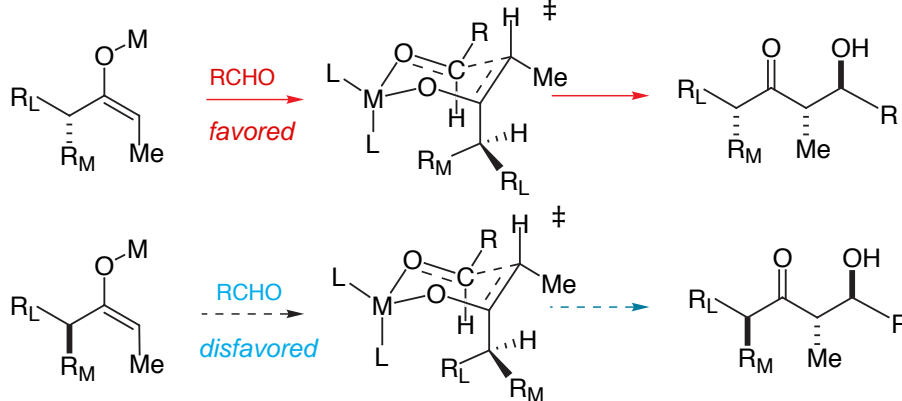
94:6 (90%)

syn-anti diastereomer



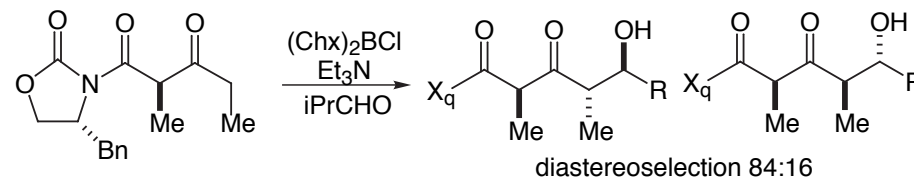
96:4 (75%)

The Transition States:



Evans, JACS **1991**, 113, 1047.

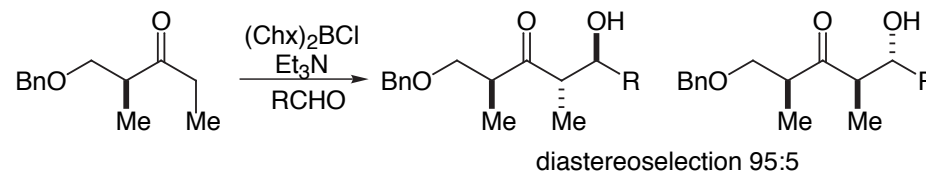
However, the preceding precedent does not extend to these systems:



diastereoselection 84:16

D. A. Evans, H. P. Ng, J. S. Clark, D. L. Rieger *Tetrahedron*, **1992**, 48, 2127-2

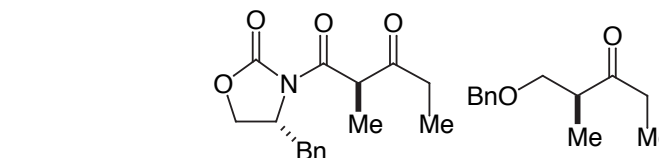
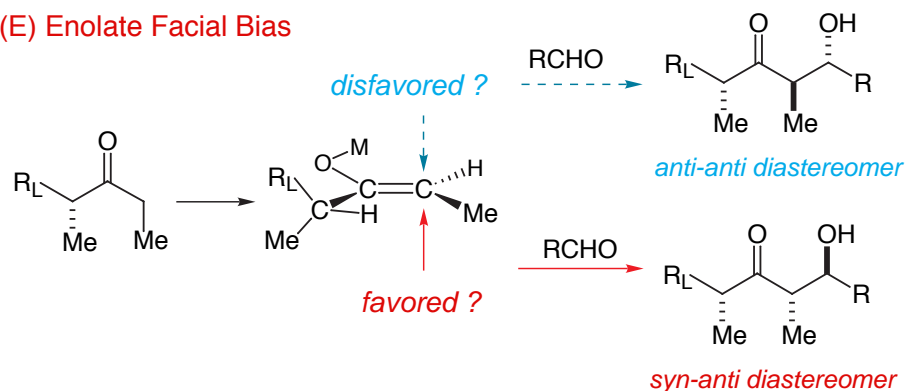
An analogous case:



diastereoselection 95:5

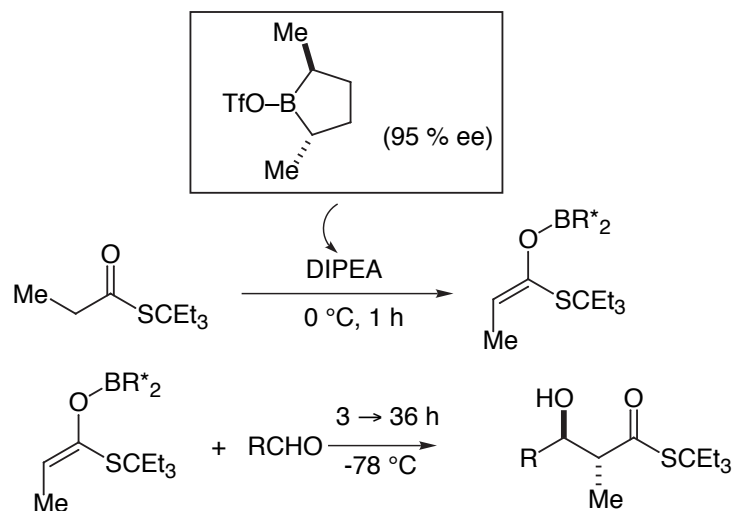
I. Patterson, J. M. Goodman, M. Isaka *Tetrahedron Lett.* **1989**, 30, 7121-7

(E) Enolate Facial Bias

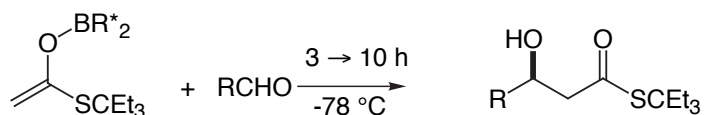


These enolates do not comply with steric analysis: \rightarrow electronic effects?

Tetrahedron, **1992**, 48, 2127-2142.

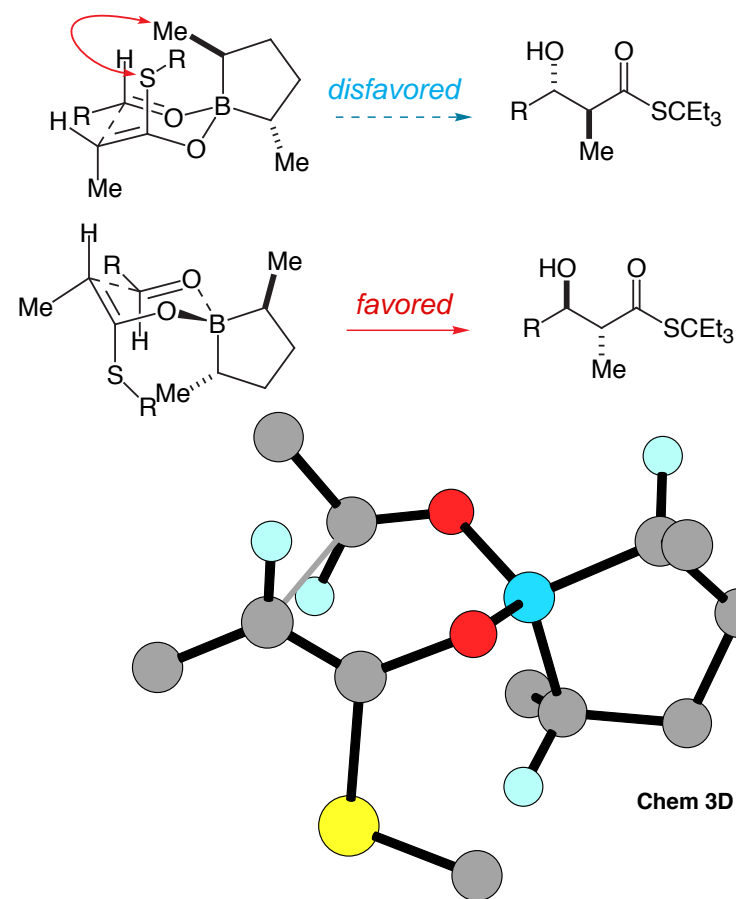
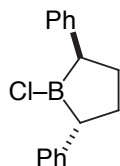
Masamune, Sato, Kim, Wollmann *J. Am. Chem. Soc.* **1986**, *108*, 8279-8281.

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	82	32:1	93 (98)
PhCHO	(71)	33:1	96 (99.8)

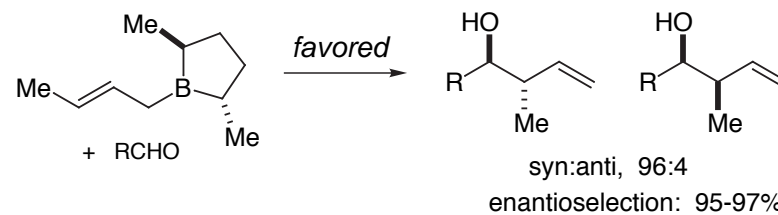


RCHO	Yield, %	ee % (corrected)
n-PrCHO	82	87 (91)
i-PrCHO	81	87 (92)
t-BuCHO	71	94 (98)
c-C ₆ H ₁₁ CHO	95	86 (90)
PhCHO	78	88 (92)

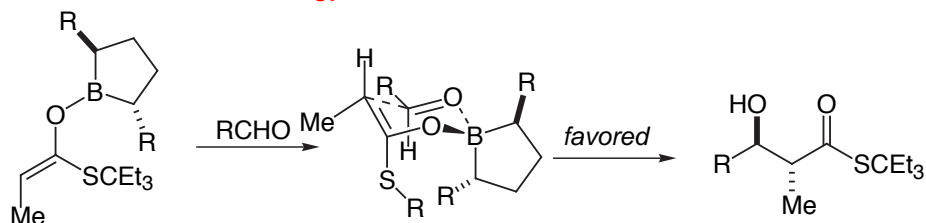
See analogous study by Reetz

Reetz *Tetrahedron Lett.* **1986**, 4721

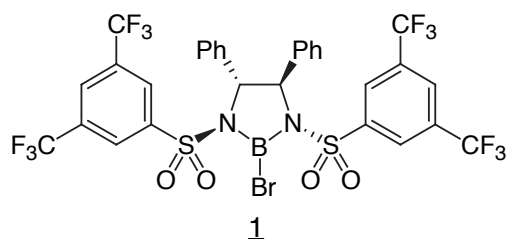
Analogous Carbonyl Allylation

Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, *52*, 4831

Masamune-Reetz Analogy:



■ Metal-Based Chiral Auxilliary:



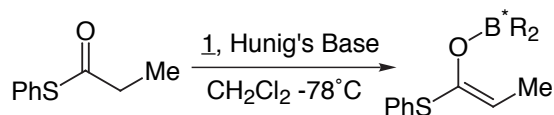
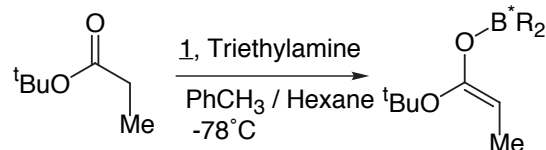
References:

(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

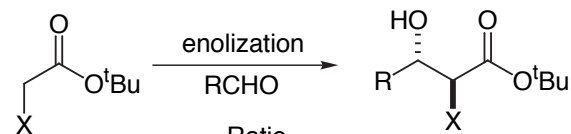
■ Enolization:

Either enolate geometry possible with proper choice of base, solvent, and substrate.



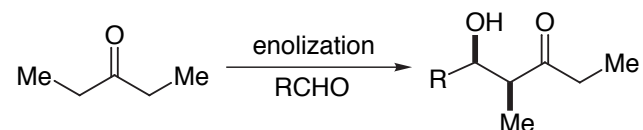
A mechanistic proposal for enolization control is presented in paper

(Corey) *JACS*. **1989**, *111*, 5494

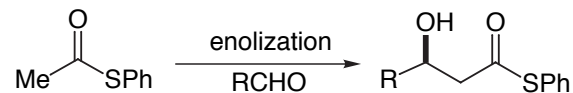
■ Chiral Anti Aldol Reaction: *JACS* **1990**, *112*, 4977; *TL* **1991**, *32*, 2857.

(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 %

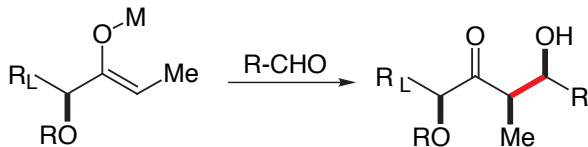
■ Chiral Syn Aldol Reaction *JACS* **1989**, *111*, 5494.

(R)	Ratio syn:anti	% ee	Yield
Ph-	94 : 6	97	86 %
Me ₂ CH-	98 : 2	95	91 %
MeCH ₂ -	>98 : 2	>98	68 %

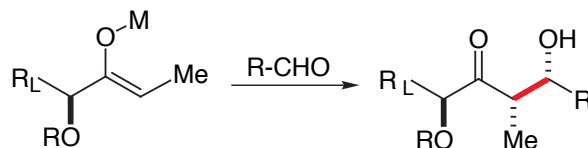
■ Chiral Acetate Aldol Reaction *JACS* **1989**, *111*, 5494.

(R)	% ee	Yield
Ph-	91	84 %
Me ₂ CH-	83	82 %

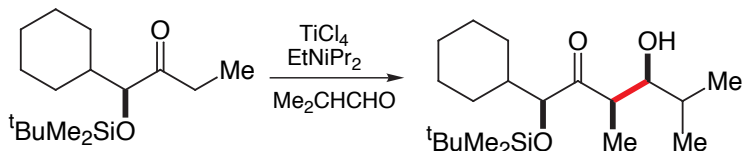
Reference Rxn



Chelate-Organized Variant

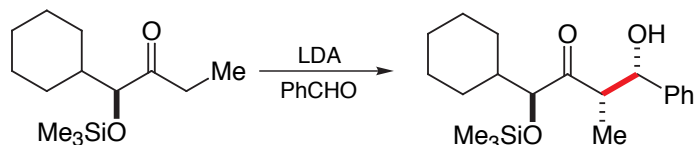


Nonchelate Reaction

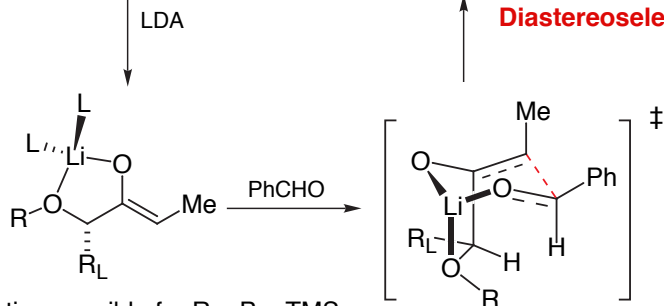


Masamune, *JACS* **1981**, *103*, 1566 (boron enolate)
 Evans, *JACS* **1991**, *113*, 1047 (titanium enolate)

Diastereoselection: 99:1



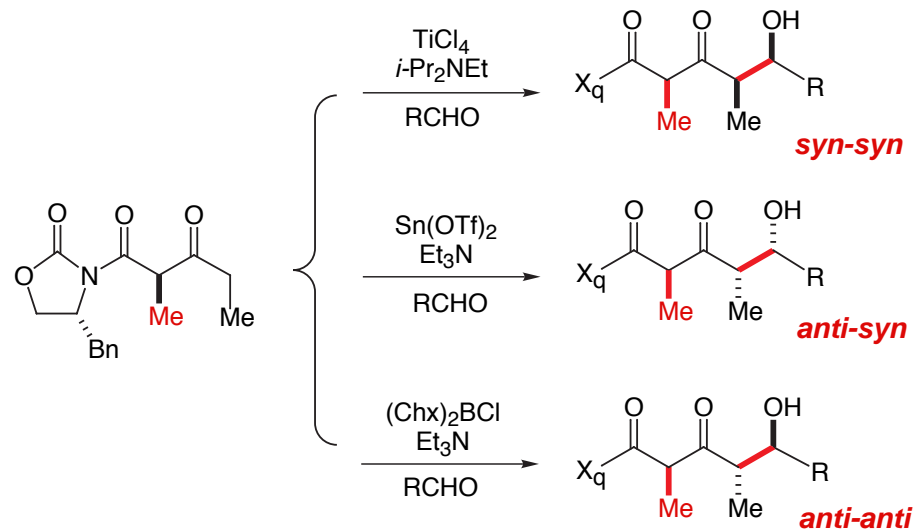
Diastereoselection: 90:10



Chelation possible for R = Bn, TMS
 but marginal for TBS

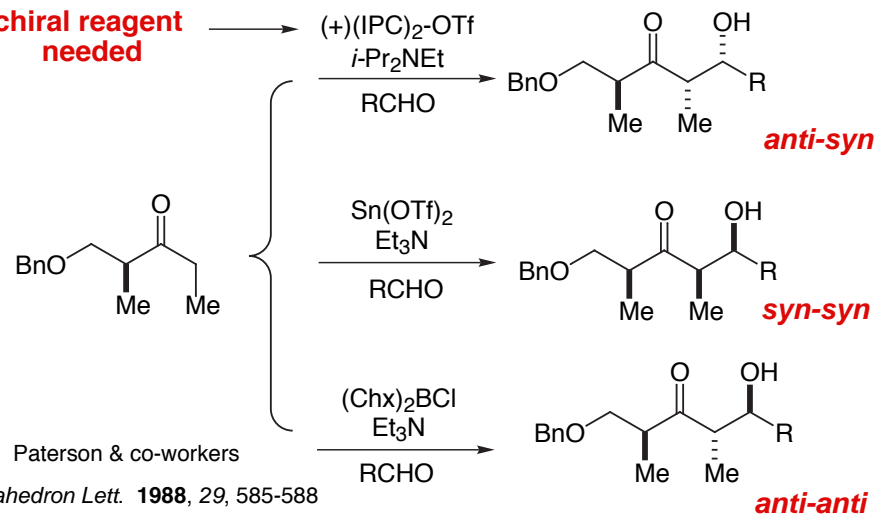
Thorton, *Tet. Let.* **1990**, *31*, 6001

Complimentary aldol reactions may be obtained by changing metal as well as enolate geometry



JACS, **1990**, *112*, 866; *Tetrahedron*, **1992**, *48*, 2127-2142.

chiral reagent needed



Paterson & co-workers

Tetrahedron Lett. **1988**, *29*, 585-588

Tetrahedron Lett. **1989**, *30*, 7121-7124

Tetrahedron Lett. **1992**, *33*, 4233-4236

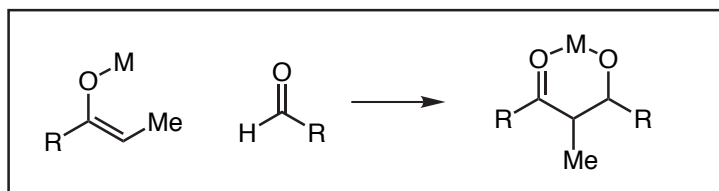
<http://www.courses.fas.harvard.edu/~chem206/>

Chemistry 206

Advanced Organic Chemistry

Lecture Number 26

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

D. A. Evans

Monday,
November 17, 2002

■ Assigned Reading

Lithium Diisopropylamide-Mediated Lithiations of Imines: Insights into highly Structure -Dependent Rates and Selectivities. D. Colum, *JACS* **2003**, *125*, ASAP (**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.

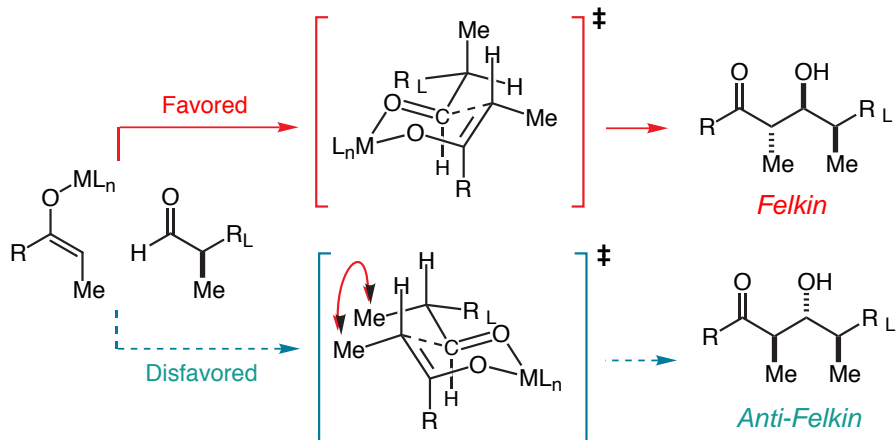
Kim, B. M., S. F. Williams, et al. (**1991**). The Aldol Reaction: Group III Enolates. *Comprehensive Organic Synthesis.* B. M. Trost and I. Fleming. Oxford, Pergamon Press. **2**: 239.

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.

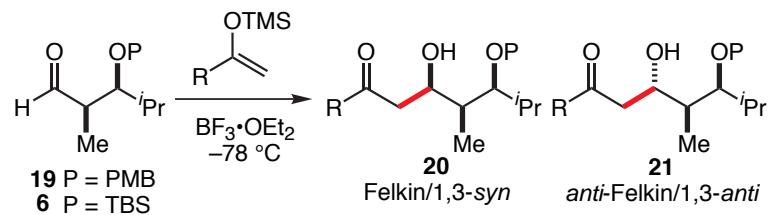
Mahrwald, R. (**1999**). "Diastereoselection in Lewis-acid-mediated aldol additions." *Chem. Rev.* **99**(5): 1095-1120.

(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.

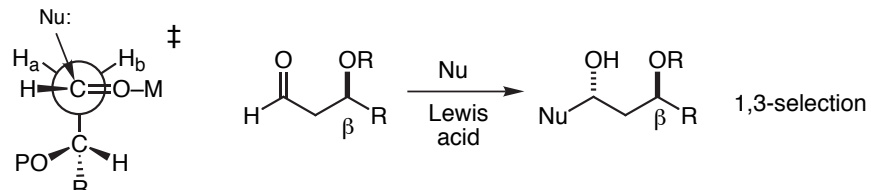
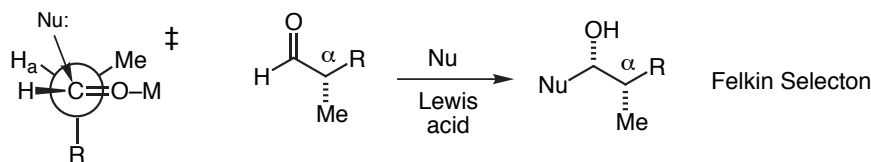
W. R. Roush, *J. Org. Chem.* **1991**, 56, 4151-4157.

**The Non-Reinforcing syn-RCHO is the most Interesting
Dependence of the Selectivity of Felkin-controlled Reactions on Nu Size**

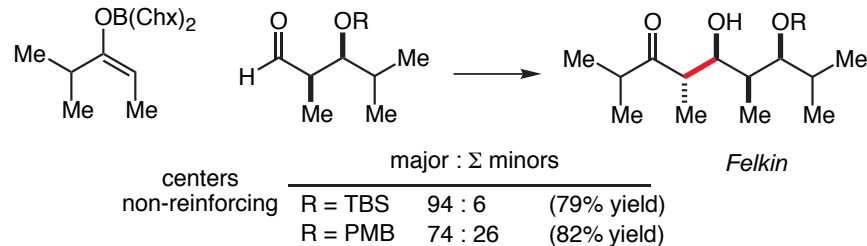
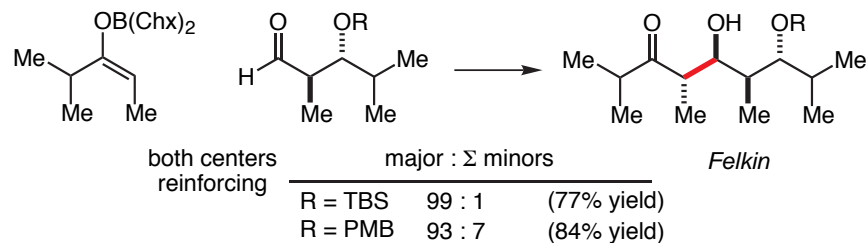
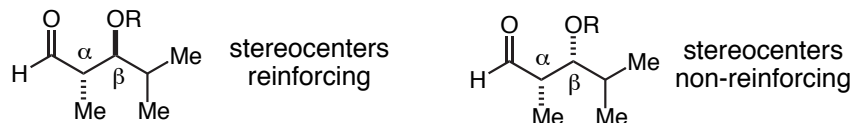
	P = PMB	P = TBS
R	20 : 21	20 : 21
α-substituent dominates for Large Nu		
t-Bu	96 : 04	94 : 06
i-Pr	56 : 44	75 : 25
β-substituent dominates for small Nu		
Me	17 : 83	40 : 60

Background Information: The influence of β -OR substituents on RCHO

Evans, *JACS* **1996**, 118, 4322-4343

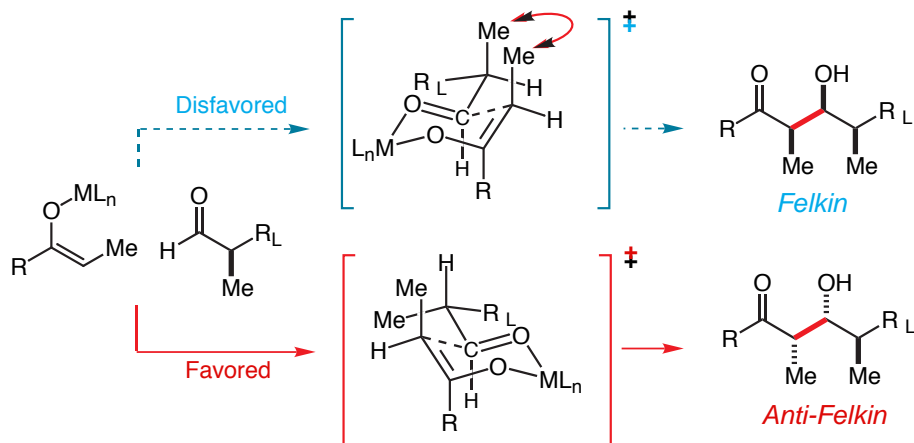


Therefore, one might conclude that:



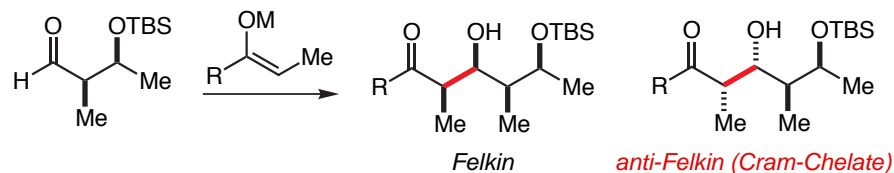
Achiral (E) enolates preferentially add to the Felkin diastereoface
High *anti:syn* diastereoselectivity ($\geq 97 : 3$) is observed in all cases

Evans et al. *JACS* **1995**, 117, 9073

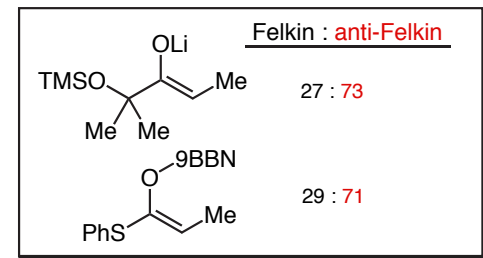
(Z) Enolates Exhibit Anti-Felkin Aldehyde Diastereoface Selection

The illustrated syn-pentane interaction disfavors the Felkin pathway.

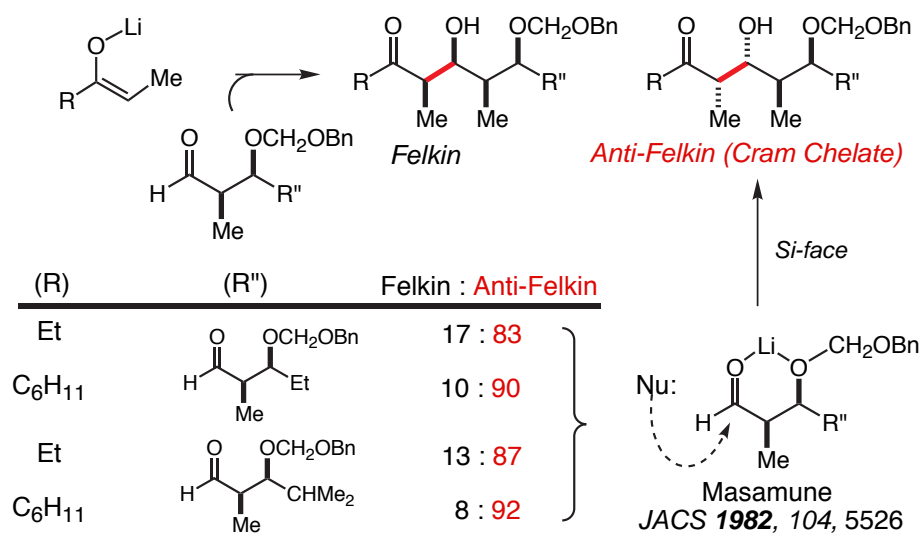
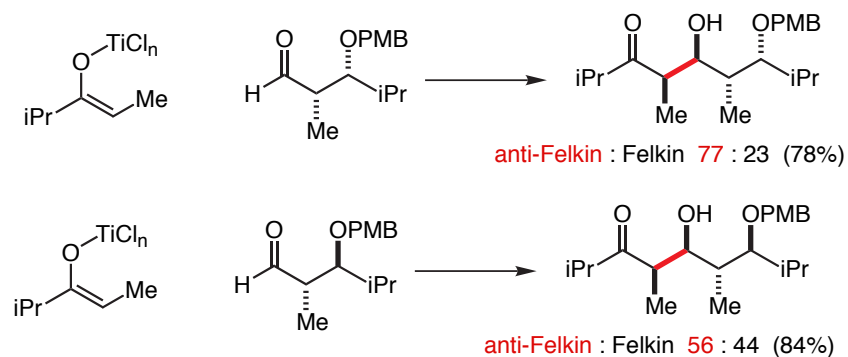
Evans, Nelson, Taber, *Topics in Stereochemistry* **1982**, 13, 1-115.
W. R. Roush, *J. Org. Chem.* **1991**, 56, 4151-4157.



D. W. Brooks & Co-workers
Tetrahedron Lett. **1982**, 23, 4991-4994.

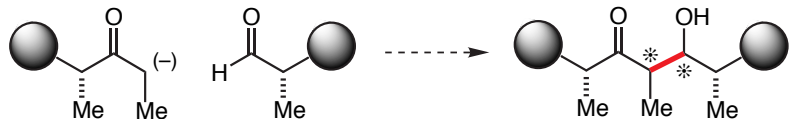


- The bulky OTBS group disfavors chelation. (see Keck, *JACS* **1986**, 108, 3847.)
- The boron and lithium enolates display nearly equal levels of anti-Felkin selectivity.

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

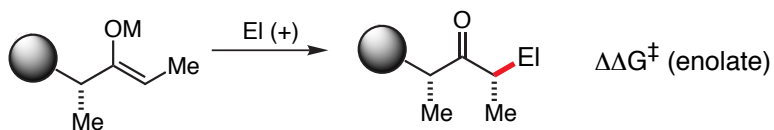
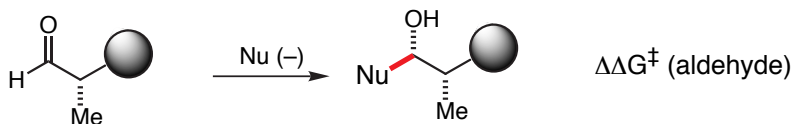


Product

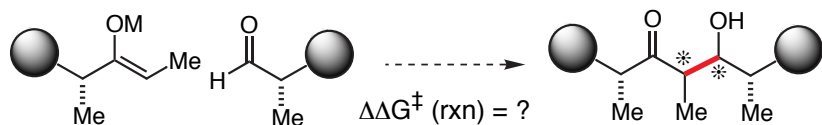
Enolate facial bias \rightleftharpoons Stereochemistry \leftleftharpoons Aldehyde facial bias

The Issue: Can one reliably take the diastereoselectivities of the individual reaction partners and use this information in the illustrated extrapolation:

The model reactions:



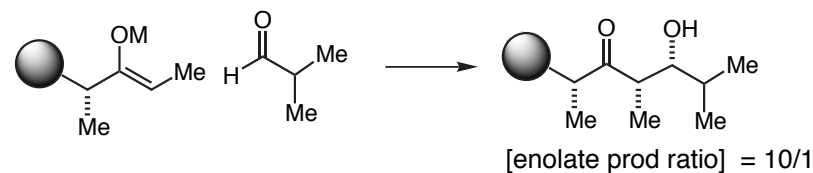
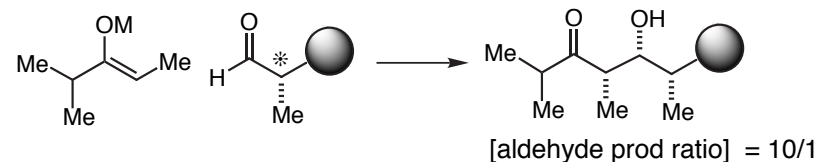
The extrapolation:



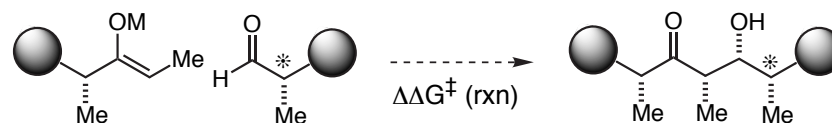
Masamune, *Angew. Chem. Int. Ed.* **1985**, *24*, 1-76

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:

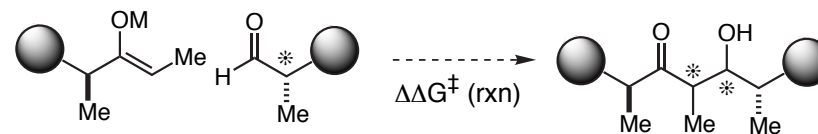
$$\Delta\Delta G^\ddagger (\text{Rxn}) \sim \Delta\Delta G^\ddagger (\text{enolate}) + \Delta\Delta G^\ddagger (\text{RCHO})$$

$$\log [\text{Product ratio}] \sim \log [\text{enolate ratio}] + \log [\text{aldehyde ratio}]$$

$$[\text{Product ratio}] \sim [\text{enolate prod ratio}] \times [\text{aldehyde prod ratio}]$$

■ Hence, for the case at hand: [Product ratio] \sim [10] \times [10] \sim 100

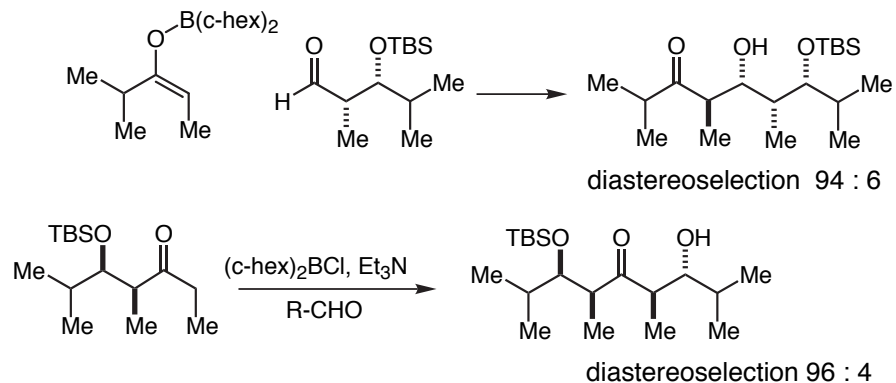
Mismatched reactant pair: Stereo-induction from partners nonreinforcing



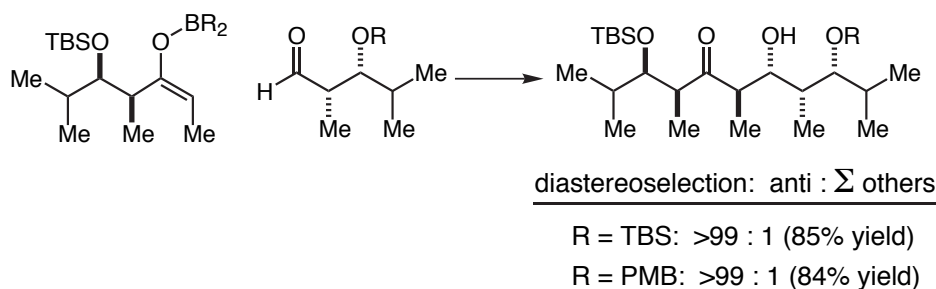
$$\Delta\Delta G^\ddagger (\text{Rxn}) \sim \Delta\Delta G^\ddagger (\text{enolate}) - \Delta\Delta G^\ddagger (\text{RCHO})$$

The Masamune-Heathcock generalizations hold to a point:

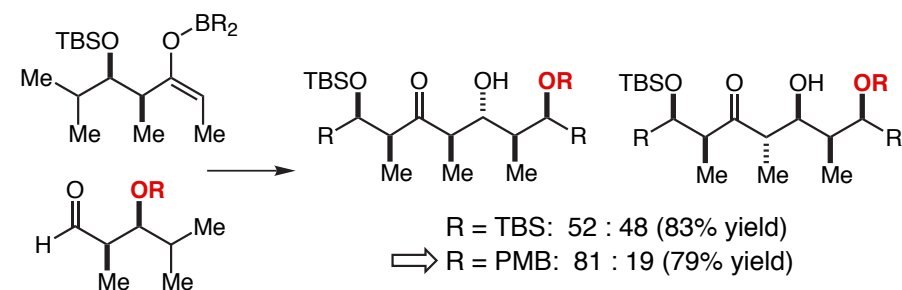
(E)-Boron Enolates: The reference reactions



(E)-Boron Enolates: The matched cases

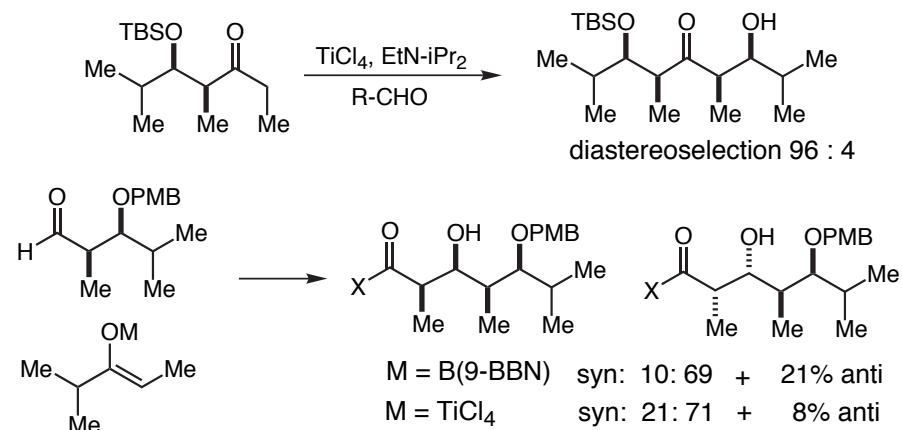


(E)-Boron Enolates: The mismatched cases

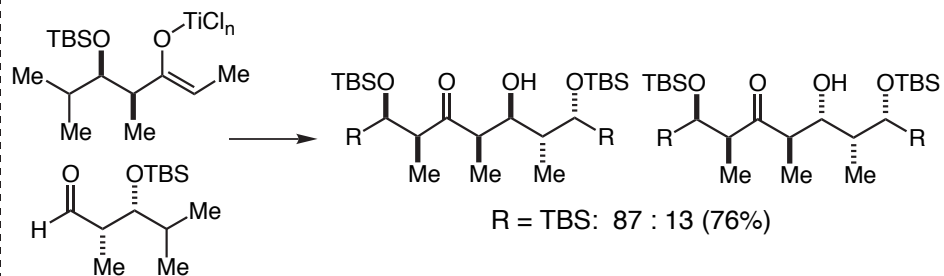


β -center on RCHO can play a significant role in this marginal situation

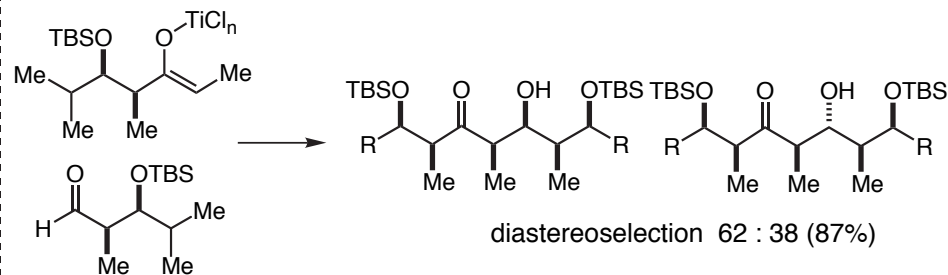
(Z)-Titanium Enolates: The reference reactions



(Z)-Titanium Enolates: The matched cases



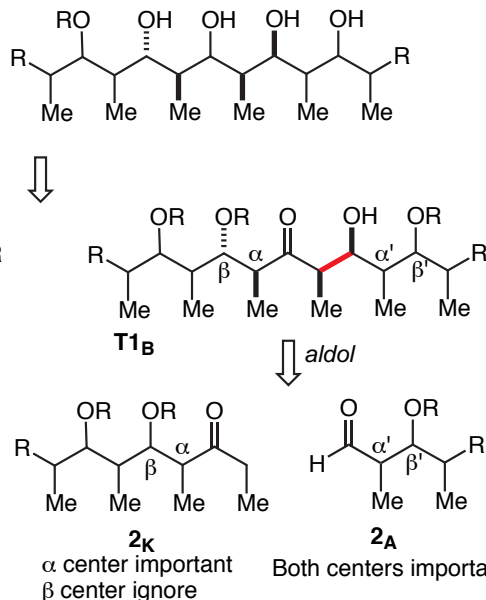
(Z)-Titanium Enolates: The mismatched cases



"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.

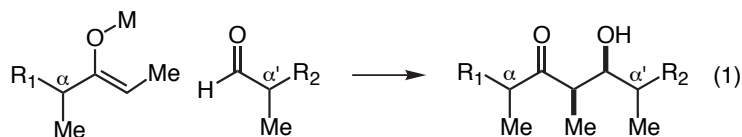
Synthesis of Polyketide chains

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 **T1B**. Carry out the disconnection to subunits **2K** and **2A**.

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.

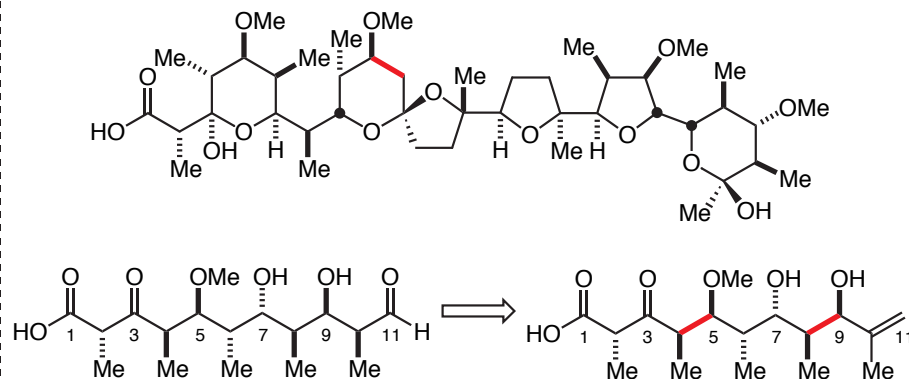


Stereochemical Determinants

	M = BR ₂	M = SiR ₃
enolate facial bias	✓	✓
aldehyde facial bias	✓	✓
pericyclic transition state	✓	✗

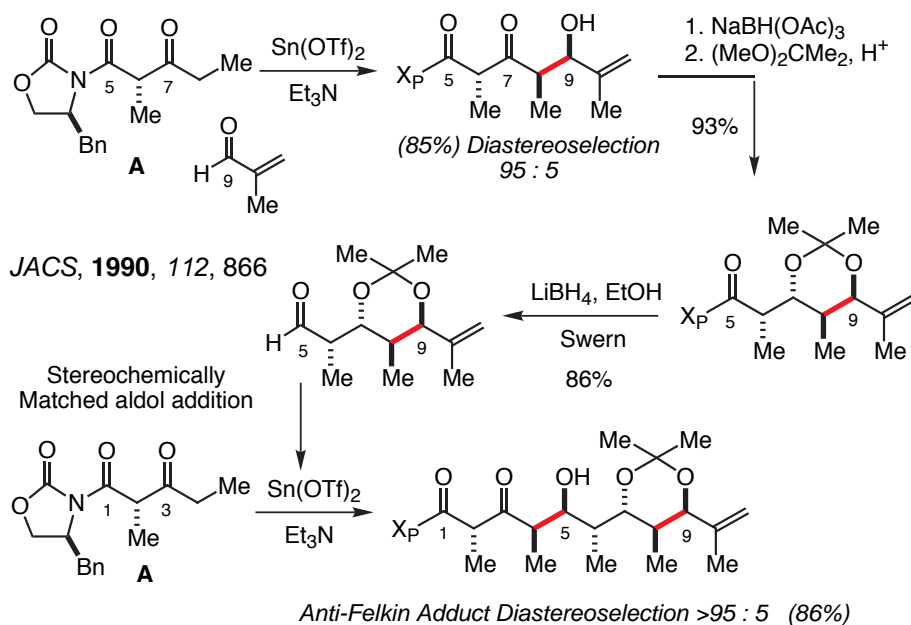
The Lonomycin Synthesis: An example of polypropionate assemblage

Evans, Ratz, Huff, Sheppard JACS **1995**, 117, 3448

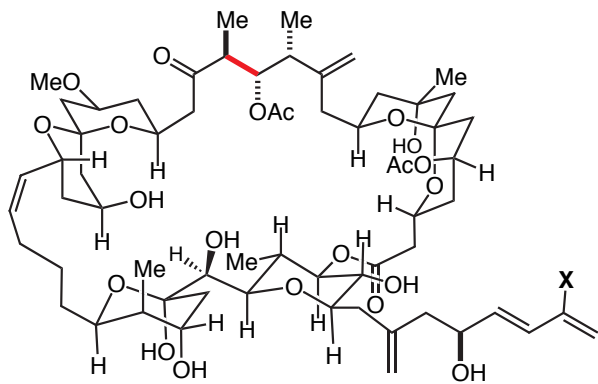
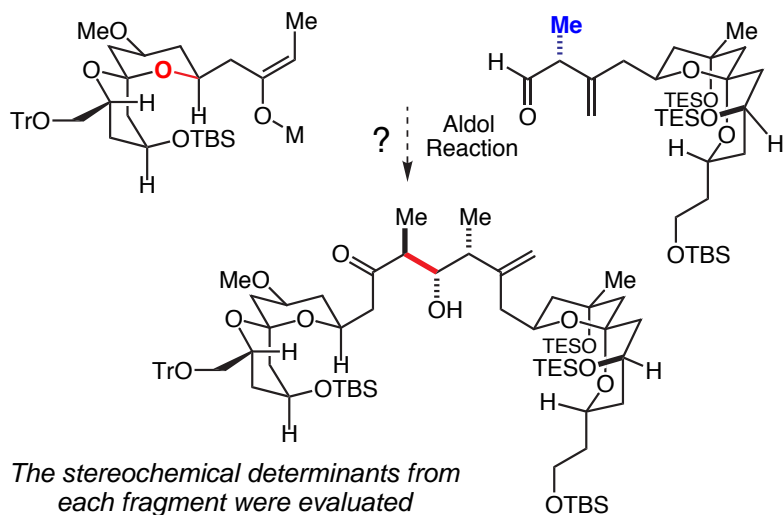


BH₃ Transform: See Lecture No. 8

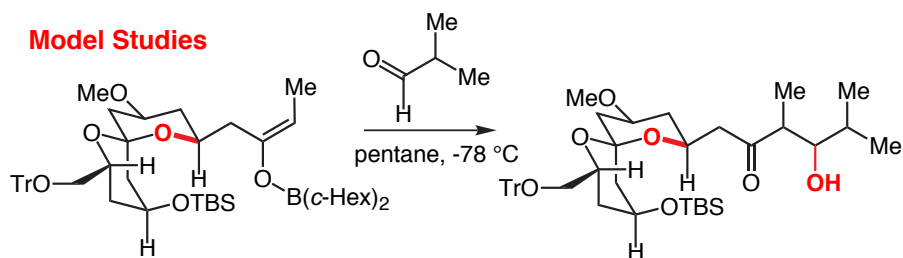
C₁-C₁₁ Assemblage



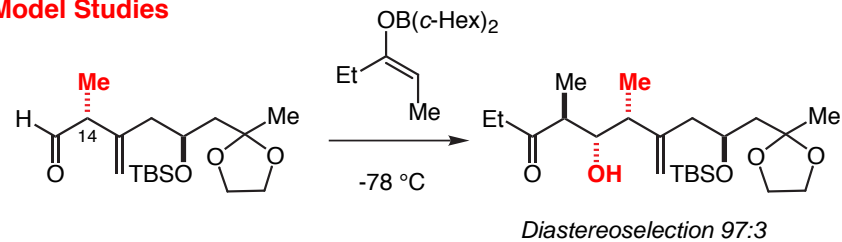
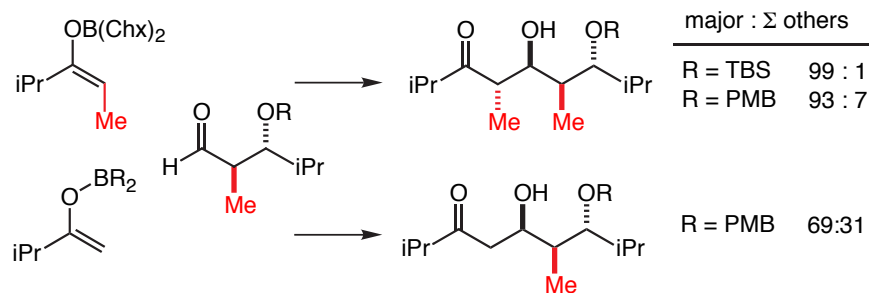
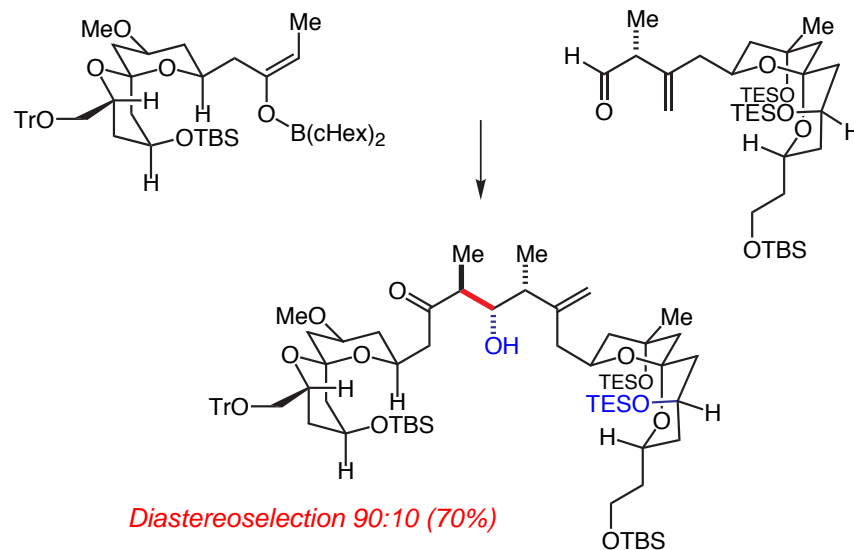
The Sn(OTf)₂ aldol reaction of A: see this lecture + JACS, **1990**, 112, 866

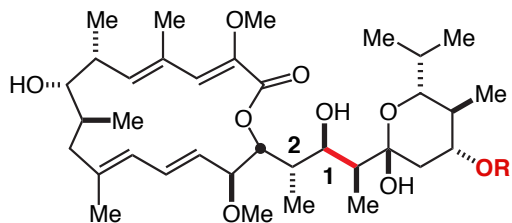
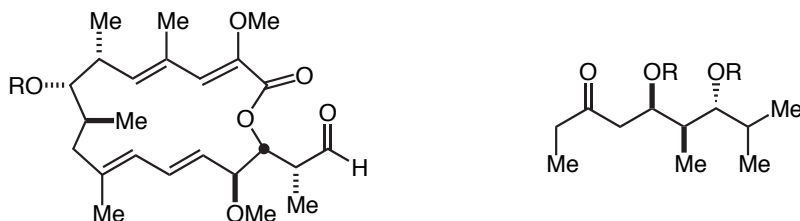
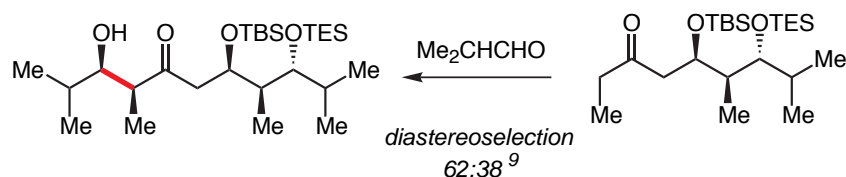
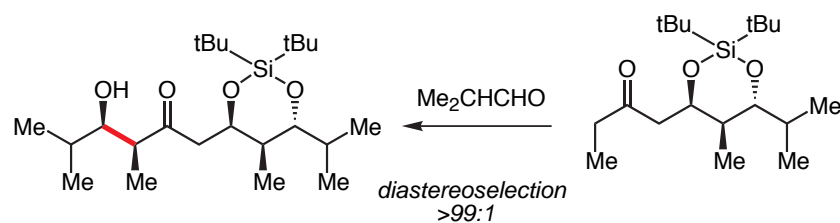
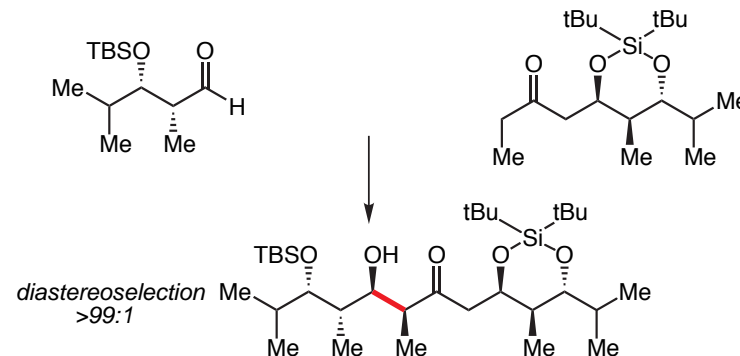
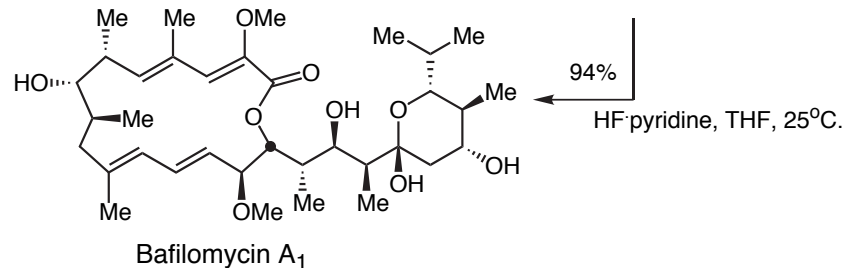
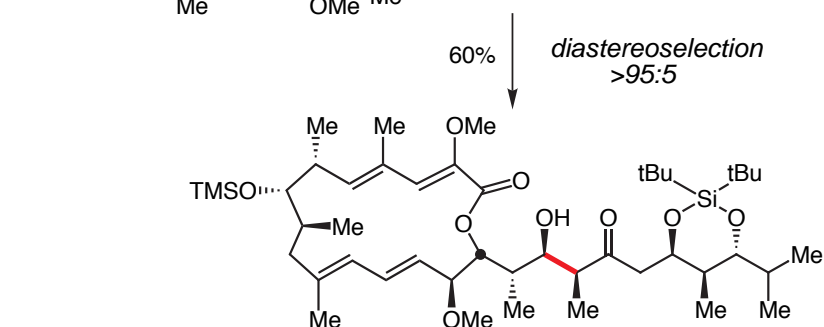
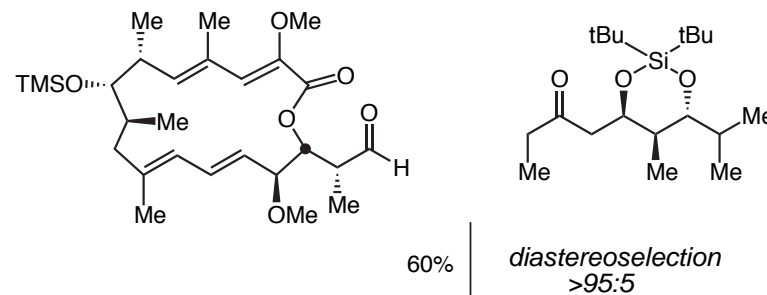
The Althoirtin Synthesis: An example of polypropionate assemblageEvans, Trotter, Coleman, Côté, Dias, Rajapakse, *Tetrahedron* **1999**, *55*, 8671-8726.

The stereochemical determinants from each fragment were evaluated

Model Studies

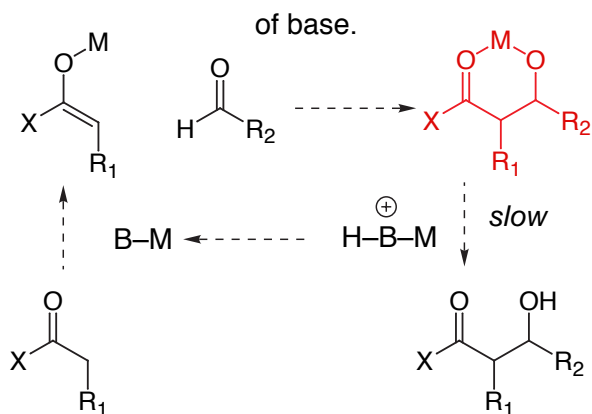
2:1 mixture of diastereomers

Model Studies**Background****The Aldol Fragment Coupling**

Bafilomycin A₁ Synthesis: An example of polypropionate assemblageEvans, Calter, *Tetrahedron Lett.* **1993**, 34, 6871Bafilomycin A₁**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

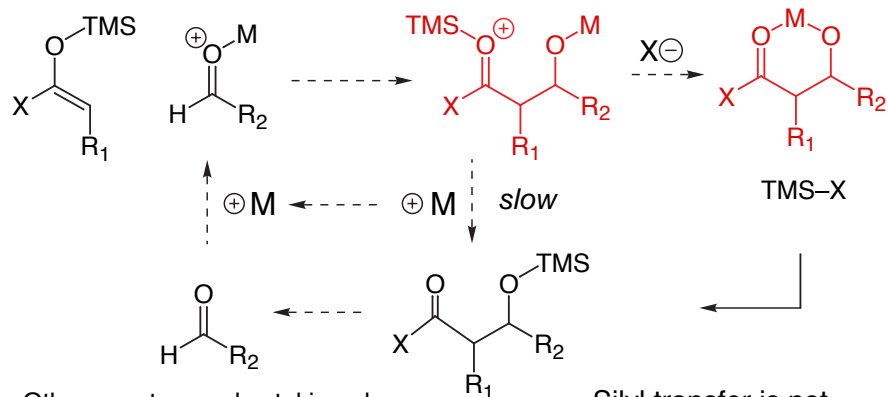


Catalytic Version: Slow step in the catalytic variant is protonation of the intermediate metal aldolate

Type II Aldol Reaction: Mukaiyama Aldol Process

This reaction may be run with either a stoichiometric or catalytic amount of Lewis acid.

The minimalist mechanism: $MX = \text{Lewis acid}$



Other events are also taking place:
Carreira *Tet. Lett* **1994**, 35, 4323

Silyl transfer is not necessarily intramolecular

Recent Reviews

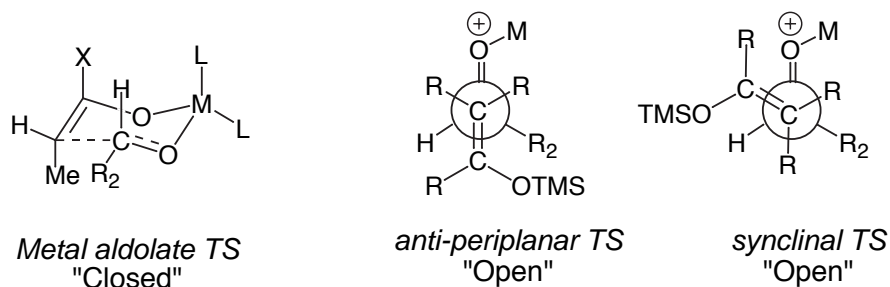
R. Mahrwald, *Diatereoselection in Lewis Acid Mediated Aldol Additions*, *Chem. Rev.* **1999**, 99, 1095-1120

S. G. Nelson, *Catalyzed enantioselective aldol additions of latent enolate equivalents* *Tetrahedron: Asymmetry* **1998**, 9, 357-389.

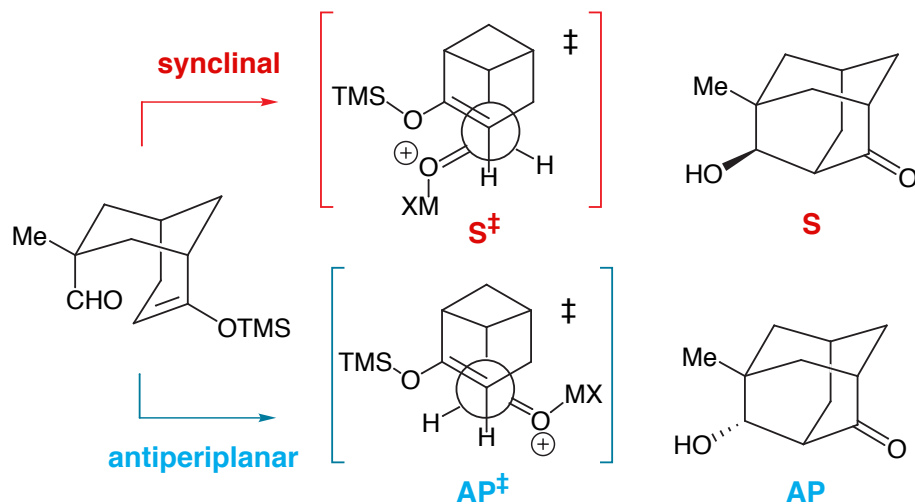
Mukaiyama Aldol Reaction, E. Carreira In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol III, 998-1059.

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.



Denmark has designed a nice substrate to distinguish between synclinal and antiperiplanar transition states:
Denmark, *J. Org. Chem.* **1994**, *59*, 707-709

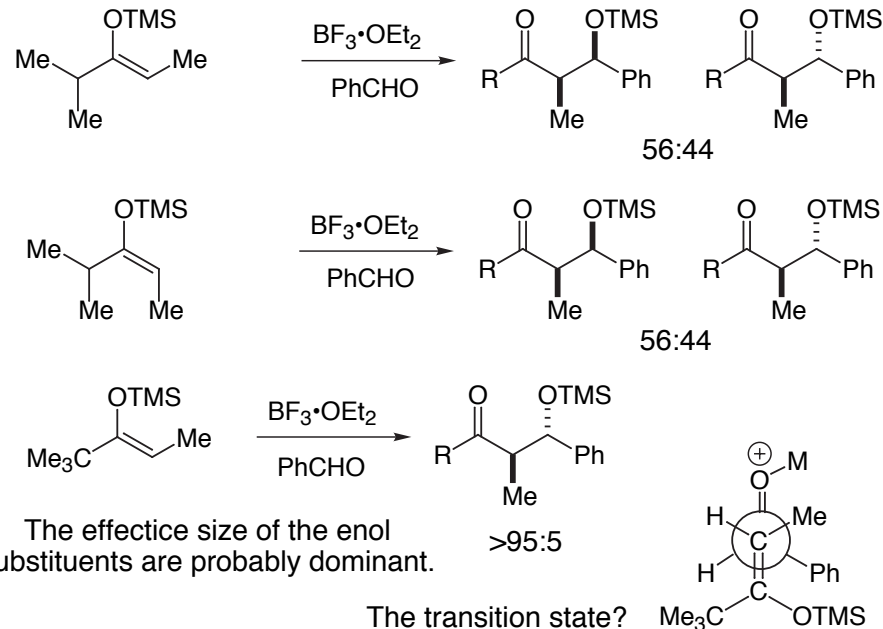


Lewis Acid	syn:anti
TiCl ₄	21:79
SnCl ₄	18:82
BF ₃ ·OEt ₂	29:71
TrClO ₄	27:73
SnCl ₂	78:22

conclusion: there is a modest preference for the antiperiplanar TS

Syn-Anti Aldol Diastereoselection

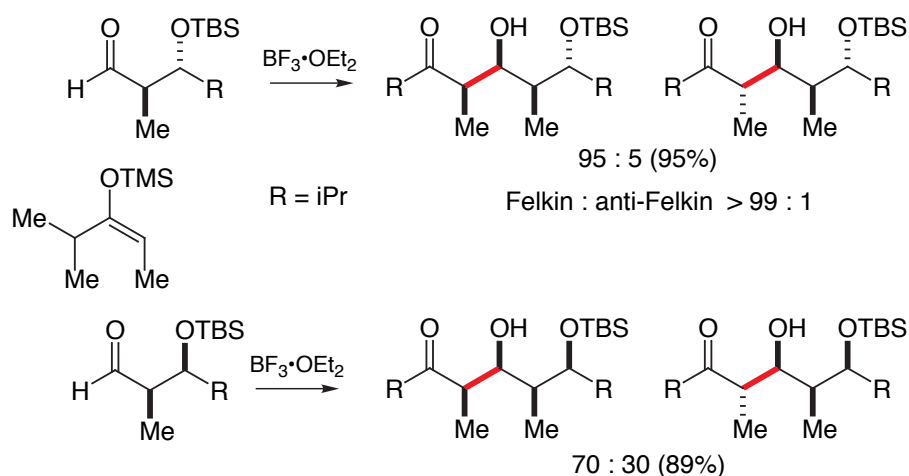
Heathcock: *J. Org. Chem.* **1986**, *51*, 3027



These reactions "exhibit little simple diastereoselection except in special cases."....Heathcock

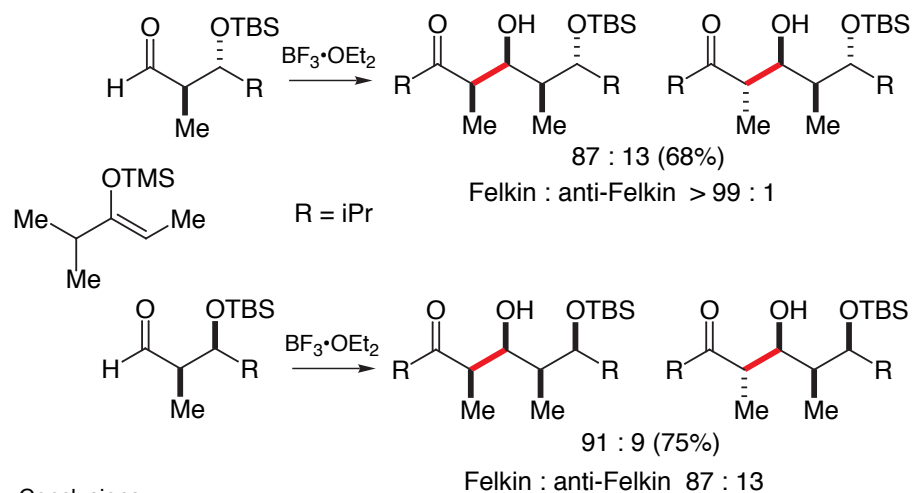
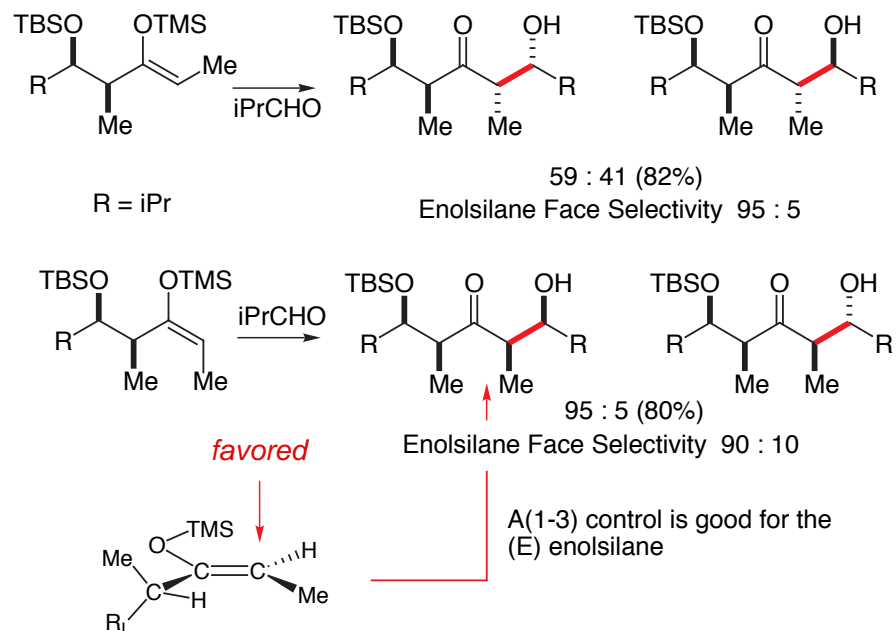
Merged Syn-Anti & Felkin Diastereoselection

Evans: JACS 1995, 117, 9598



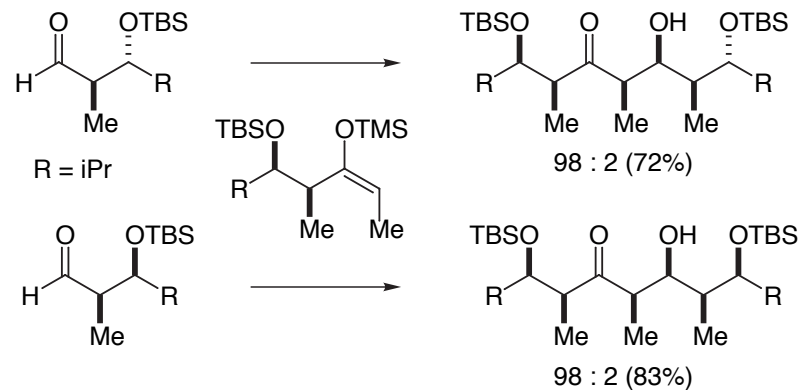
Conclusions:
 Moderate to Good syn diastereoselection
 Excellent Felkin diastereoselection

Enolsilane Face Selection



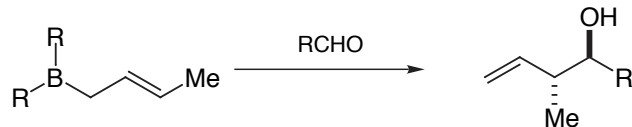
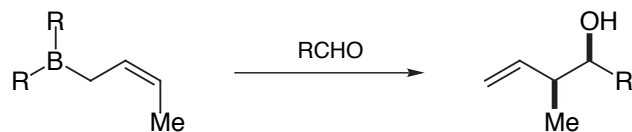
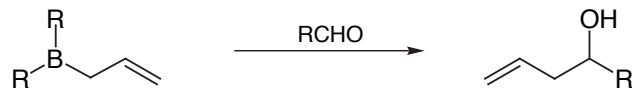
Conclusions:
 Moderate to Good syn diastereoselection
 Excellent Felkin diastereoselection

Double Stereodifferentiating Syn Aldol Rxns with Enolsilanes

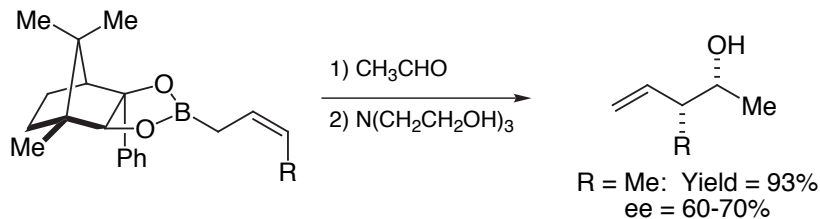


■ General Reviews of Allyl Metal Reagents:
Comprehensive Organic Synthesis, **1991**; Vol. 2.

■ The General Reactions

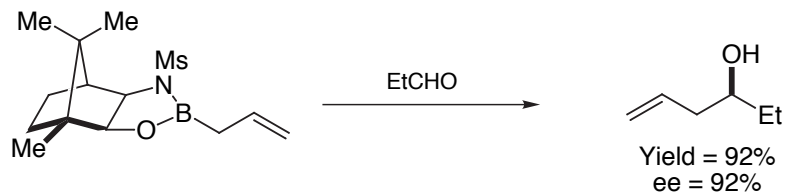


■ The Hoffman Chiral Allylboronic Esters



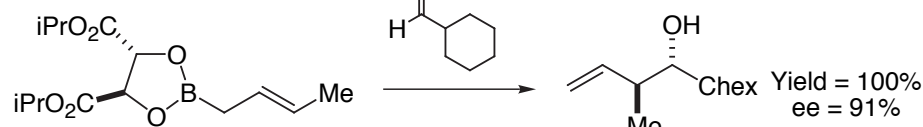
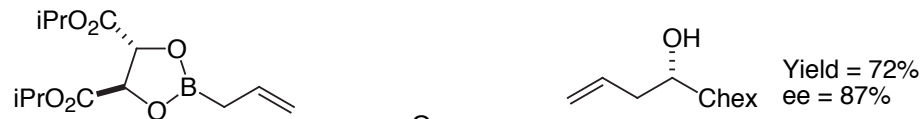
R. Hoffman *Tetrahedron Lett.* **1979**, 4653-4656.
ACIEE, **1978**, 17, 768-769.

R = H: Yield = 92%
ee = 65%

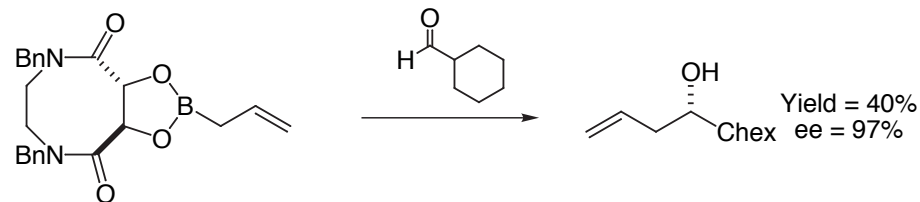


M. Reetz *Chem. Ind. (London)* **1988**, 663-664.

■ The Tartrate-derived Allylboronic Esters

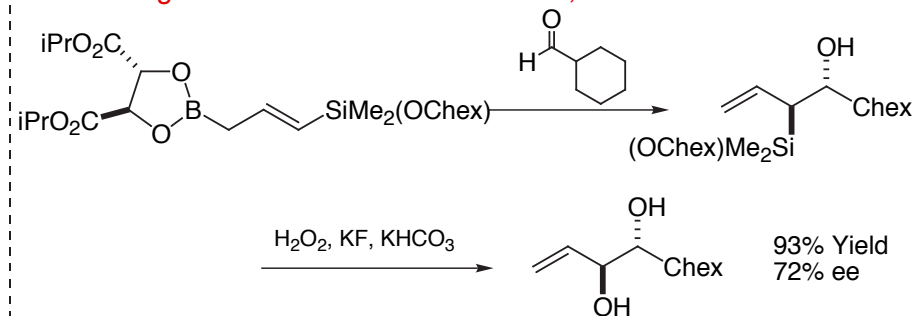


W. Roush, *J. Am. Chem. Soc.* **1985**, 107, 8186-8190.
Tetrahedron Lett. **1988**, 29, 5579-5582.



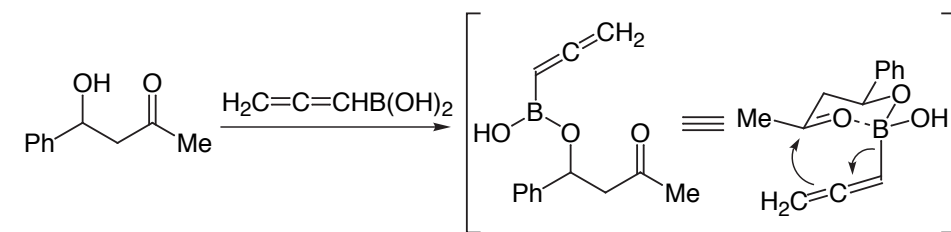
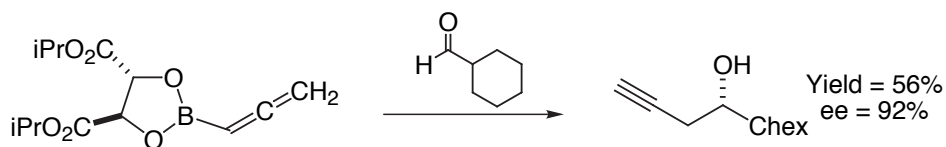
W. Roush, *J. Am. Chem. Soc.* **1988**, 110, 3979-3982.

■ A Reagent for the Generation of Anti-1,2-Diols



W. Roush, *Tetrahedron Lett.* **1990**, 31, 7563-7566.

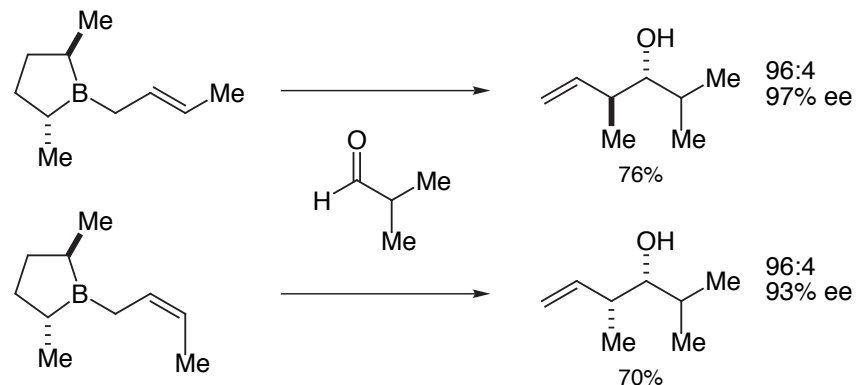
■ Allenylboronic Esters: Tartrate-derived Controllers and Internal Delivery



H. Yamamoto, *J. Am. Chem. Soc.* **1982**, *104*, 7667-7669
Tetrahedron Lett. **1986**, *27*, 1175-1178.

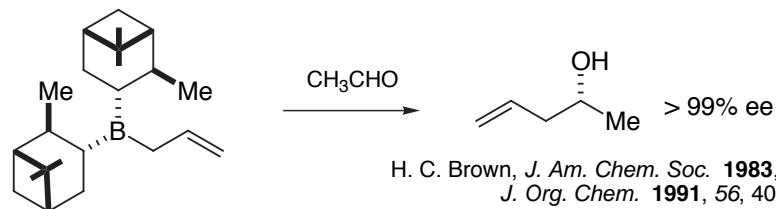
95% Yield
 >99:1

■ The Masamune Borolane

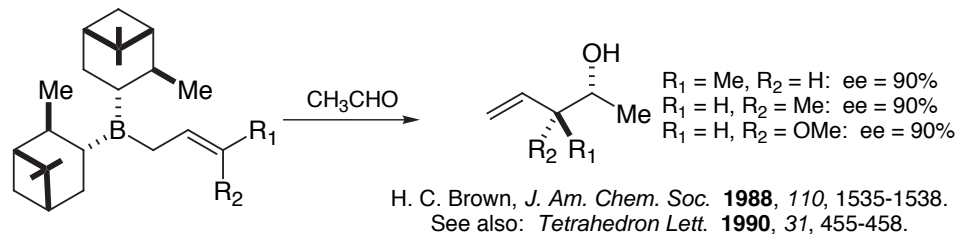


S. Masamune, *J. Org. Chem.* **1987**, *52*, 4831-4832.

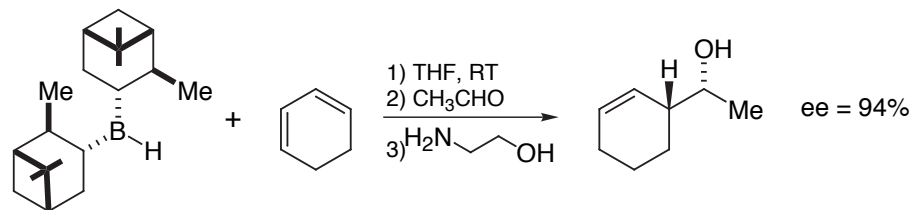
■ The Brown IPC Controller



H. C. Brown, *J. Am. Chem. Soc.* **1983**, *105*, 2092-2093.
J. Org. Chem. **1991**, *56*, 401-404.
J. Org. Chem. **1992**, *57*, 6614.

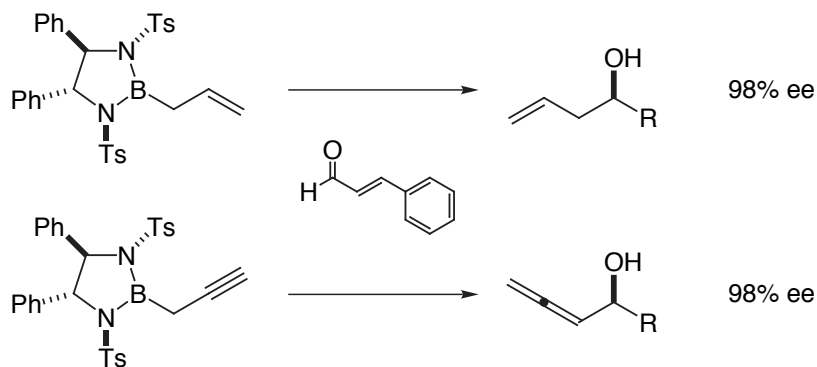


H. C. Brown, *J. Am. Chem. Soc.* **1988**, *110*, 1535-1538.
 See also: *Tetrahedron Lett.* **1990**, *31*, 455-458.



H. C. Brown, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2633.

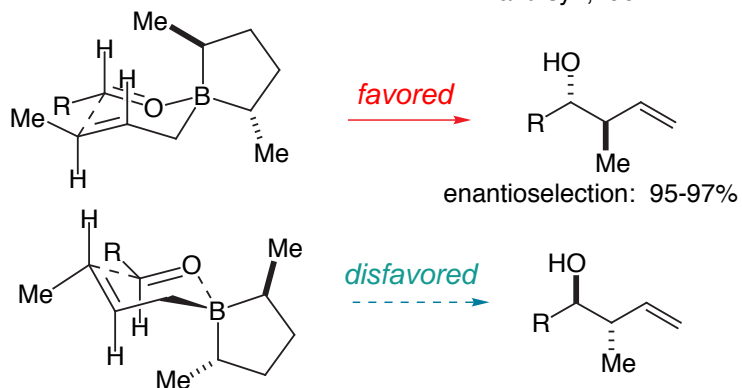
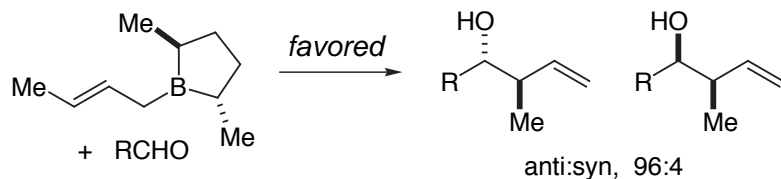
■ The Corey Stein Controller



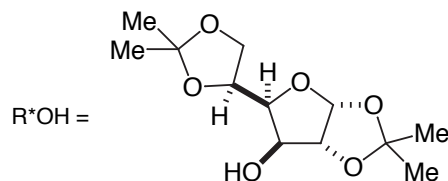
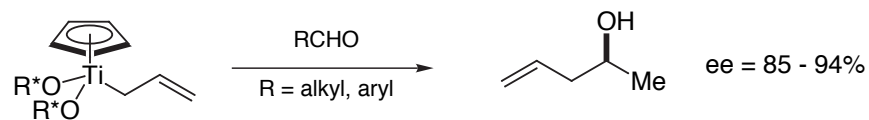
E. J. Corey, *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.
J. Am. Chem. Soc. **1990**, *112*, 878-879.

The Allylboron Reagents Add to Carbonyl Compounds via a Zimmerman-Traxler Transition State

Masamune, Sato, Kim, Wollmann *J. Org. Chem.* **1987**, 52, 4831

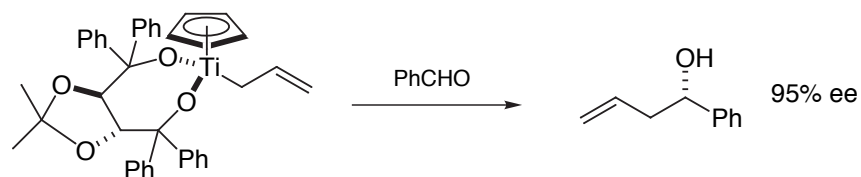


An Enantioselective Allyltitanium Reagent



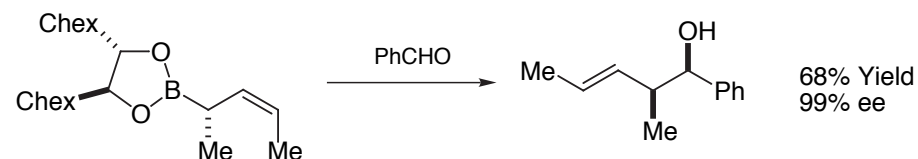
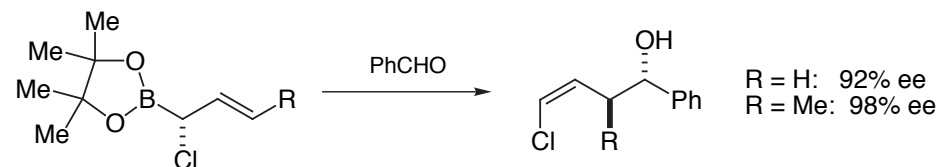
M. Riediker, R. Duthaler, *ACIEE*, **1989**, 28, 494-495.
In *Organic Synthesis via Organometallics*, **1991**, 285-309.
J. Am. Chem. Soc. **1992**, 114, 2321-2336.
Duthaler *Chem. Rev.* **1992**, 92, 807

Another Enantioselective Allyltitanium Reagent

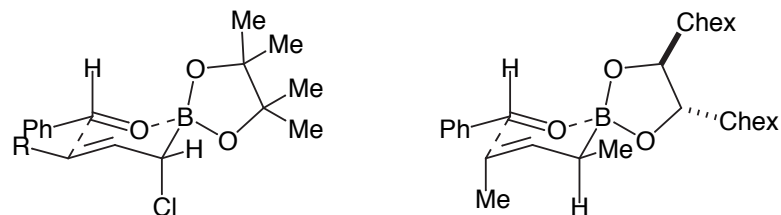


R. Duthaler, *J. Am. Chem. Soc.* **1992**, 114, 2321-2336.

Chiral α -Substituted Allyl Metal Reagents: Boron

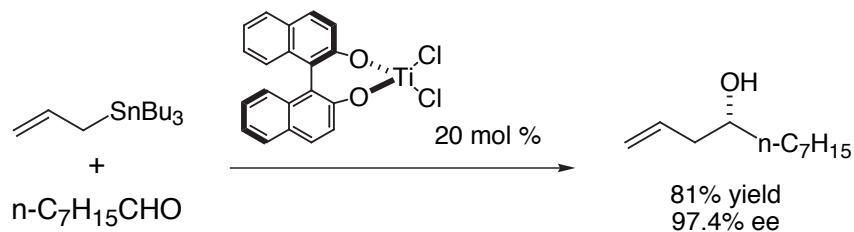
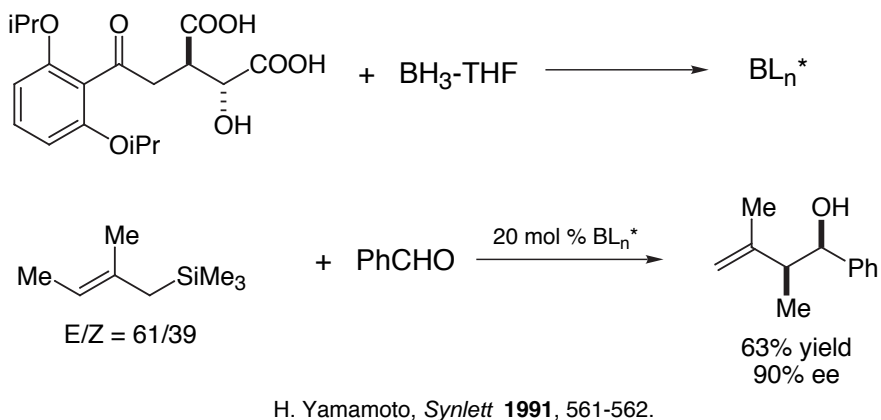


R. Hoffman, *Chem. Ber.* **1986**, 119, 2013-2024.
Chem. Ber. **1988**, 121, 1501-1507.
ACIEE, **1986**, 25, 1028-1030.

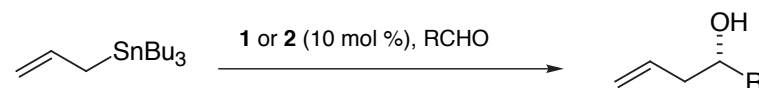
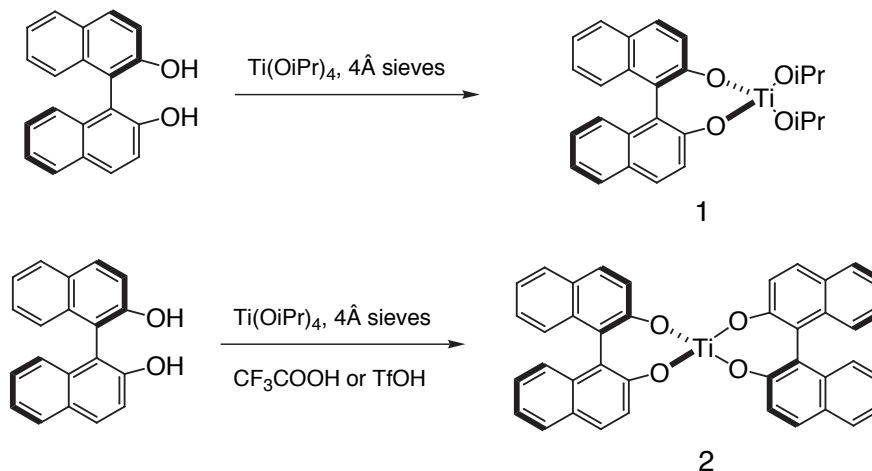


The favored transition states

■ 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.

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Advanced Organic Chemistry

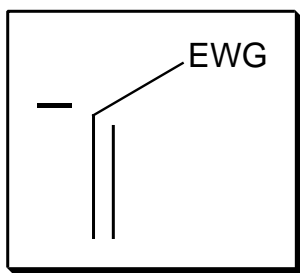
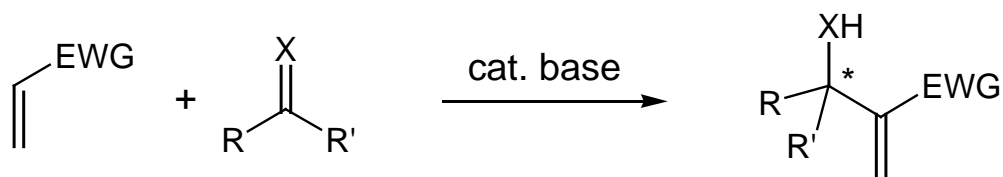
Handout 26A

The Asymmetric Baylis-Hillman Reaction

An Evans Group Afternoon Seminar

Jake Janey

March 29th, 2001



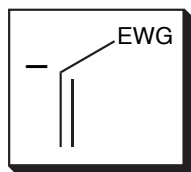
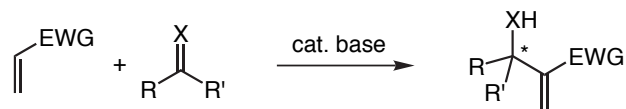
J. Janey

Monday,
November 17, 2003

An Evans Group Afternoon Seminar

Jake Janey

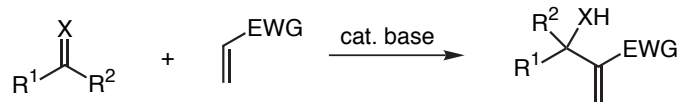
March 29th, 2001



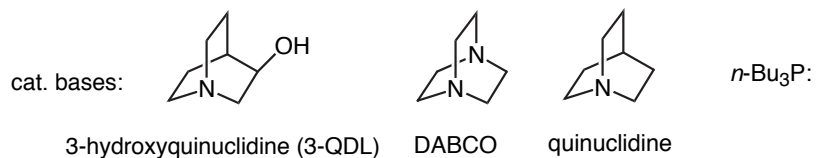
Leading References:

Langer, P. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 3049-3052.Ciganek, E. *Org. React.* **1997**, 51, 201-350.Basavaiah, D.; et al. *Tetrahedron*, **1996**, 52, 8001-8062.Drewes, S. E.; Roos, G. H. P. *Tetrahedron*, **1988**, 44, 4653-4670.

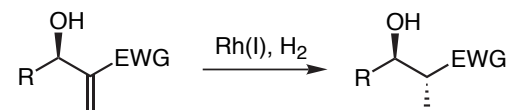
Baylis-Hillman Reaction Scope



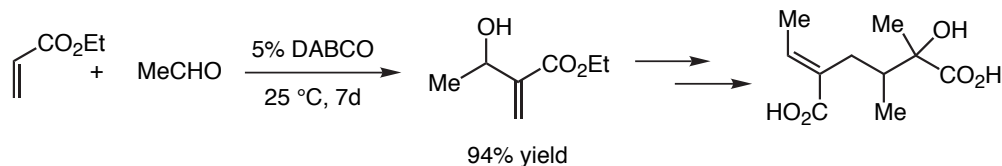
X = O, NTs, NCO₂R, NPPPh₂, NSO₂Ph EWG = CO₂R, CN, POEt₂,
 R¹ = alkyl, aryl CHO, COR, SO₂Ph, SO₃Ph
 R² = H, alkyl, EWG



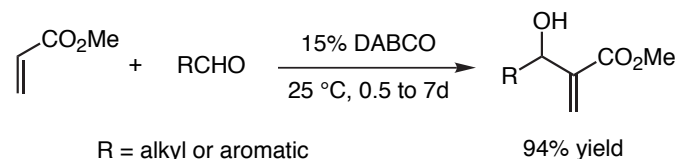
An anti propionate aldol equivalent...



Early Synthetic Examples

10 years after the Baylis-Hillman German patent...used in a C₁₀ integerrineic acid synthesis:Drewes, S. E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079-2083.

Shortly thereafter, a more extensive, published study:

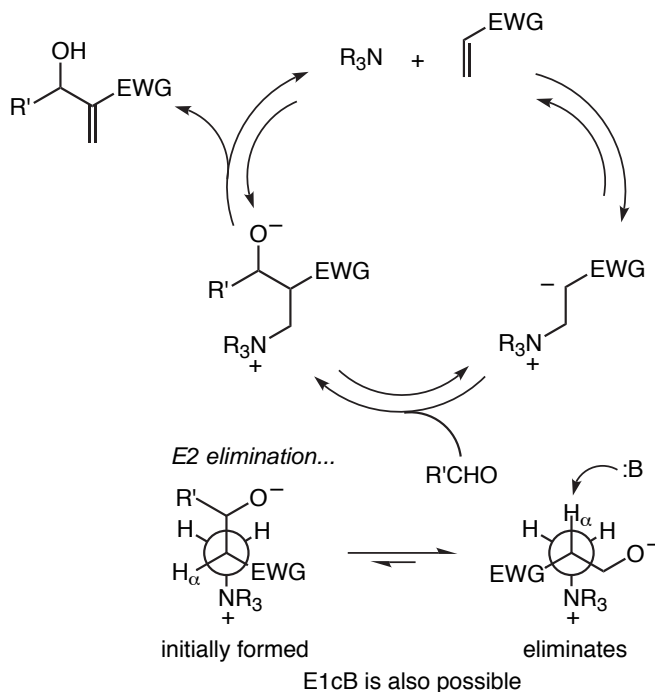


R = alkyl or aromatic

• All reactions run neat in a sealed tube with 1.5-2 equivalents of acrylate.

Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 795-797.

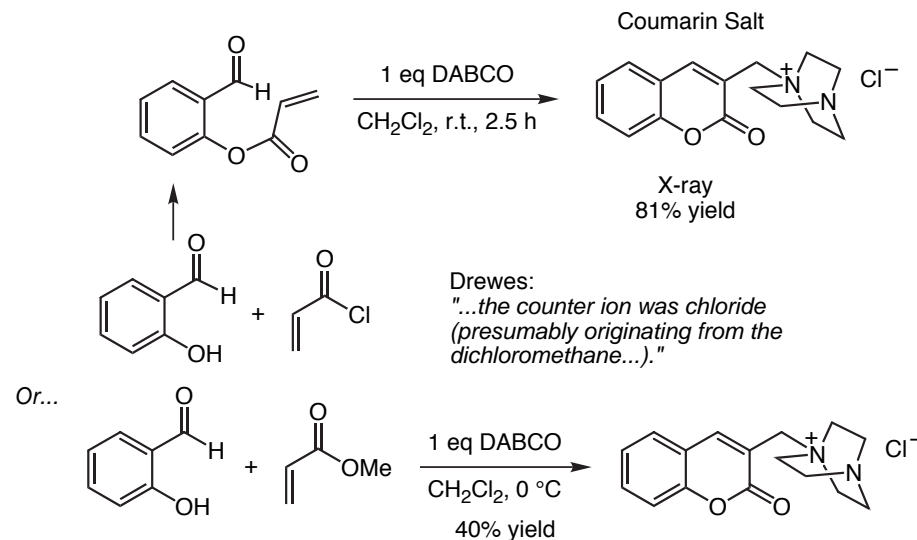
Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.* **1990**, 3, 285-288.
 Kaye, P. T.; Bode, M. L. *Tetrahedron Lett.* **1991**, 32, 5611-5614.



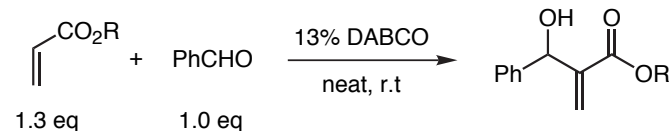
- rate = $K_{obs}[\text{aldehyde}][\text{alkene}][\text{amine}]$
- pseudo-second order if [amine] ≈ constant
- addition to aldehyde is r.d.s. because the dipole is increased by further charge separation
- acrylonitrile and methyl acrylate studied
- enolate geometry not considered
- ethereal solvent inhibits reaction whereas alcohols (especially diols) accelerate reaction
- huge volume of activation: ΔV^\ddagger of $-79 \text{ cm}^3 \text{ mol}^{-1}$ (the Diels-Alder is $-35 \text{ cm}^3 \text{ mol}^{-1}$) found by plotting $\ln k_{obs}$ vs. P. 5000 bar increases rate by 1.1×10^6
- Reaction is reversible (i.e. a Grob type fragmentation), thus mechanism could be ternary, with no discrete enolate intermediate (supported by ΔV^\ddagger and temperature effects).

Evidence for an Intermediate

Drewes, S. E.; *et. al. Syn. Comm.* **1993**, 23, 2807-2815.



Effects of Acrylate Ester Substituent



R	time (days)	yield (%)
Me	6	89
Et	7	79
Bn	2	88
<i>n</i> -C ₁₀ H ₂₁	14	75
<i>t</i> -Bu	65	65
2-adamantyl	62	40
CH ₂ CH ₂ F	3	81
CH ₂ CH ₂ Br	2	NR
CH₂CF₃	15 h	58
CH ₂ CH ₂ OMe	4	89
CH ₂ CH ₂ NMe ₂	8	82
(CH ₂) ₆ Cl	15	NR

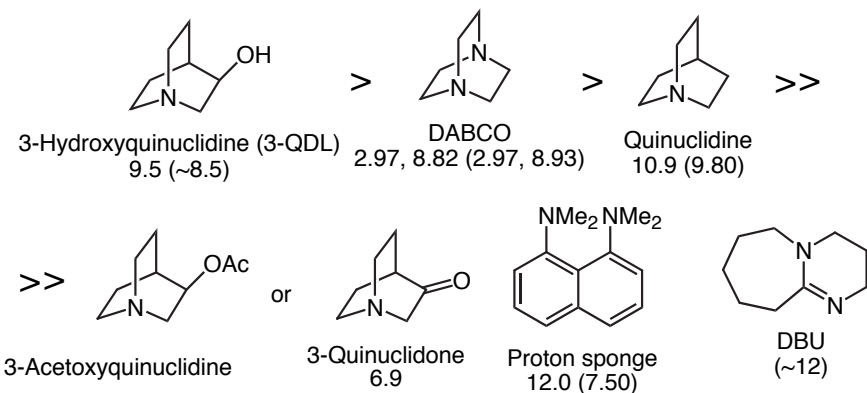
• For aryl substituted benzyl ethers, no clear relation between σ values and reactivity was observed.

• Trends hold for furfural.

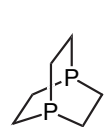
• The products undergo retro Baylis-Hillman, i.e. the reaction is reversible.

Caubere, P.; *et. al. Tetrahedron* **1992**, 48, 6371-6384.

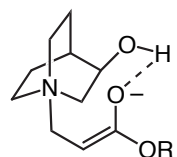
Bases for Catalysis

 pK_a H_2O (DMSO)

Sterics also important:

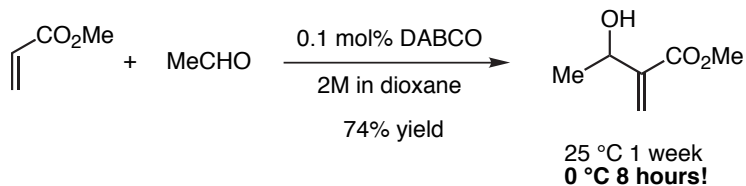
 $Me_2NH > Me_2NEt > MeNEt_2 > NEt_3$ 10.75 (9.00)Many, many phosphines screened...the winner: $n-Bu_3P$ ~9• $n-Bu_3P$ is only a slightly better catalyst than DABCO.

unreactive

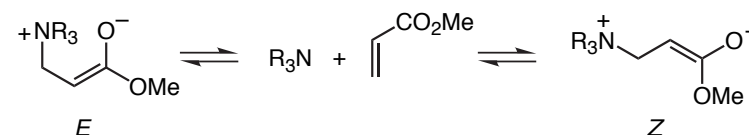


...or could accelerate protonation of intermediate, as any alcohol additive will accelerate reaction

Temperature Effects



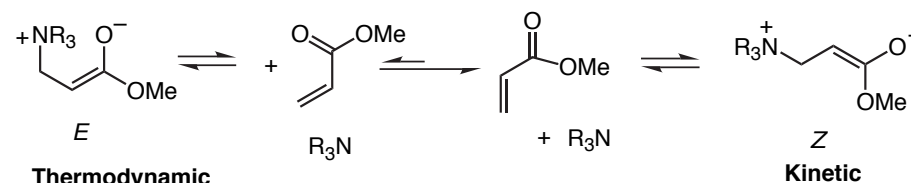
- Reaction is accelerated for a wide variety of aldehydes when conducted at 0 °C
- Temperature effect not seen with acrylonitrile (cannot form enolate)
- Author concludes that one enolate must react faster than another (i.e. a kinetic versus a thermodynamic enolate).



Which enolate is more stable and which is more reactive?

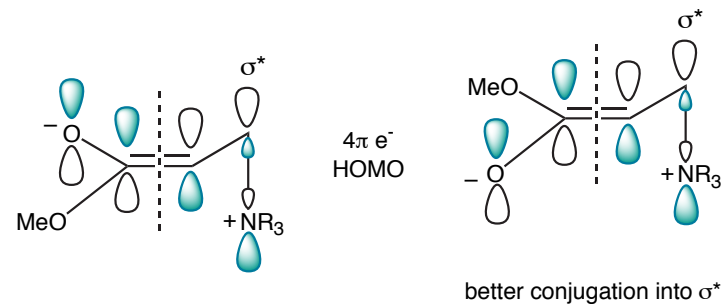
Leahy, J. W.; Rafel, S. *J. Org. Chem.* **1997**, *62*, 1521-1522.

Enolate Geometry

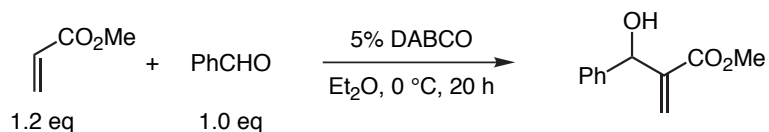


- less charge separation
- less reactive

- more charge separation
- less stable
- enolate twists out of plane by PM3

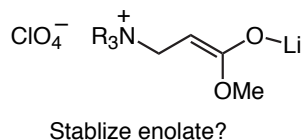


Salt Additive

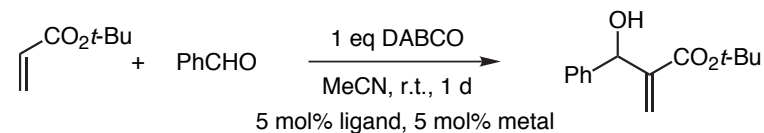


LiClO ₄ (mol%)	yield (%)
0	trace
5	12
10	40
50	63
70	72 (81) ^a
100	25
200	12
500	trace

^a 15 mol% DABCO was used.



Lewis Acid Catalysis



Relative Reaction Rates

ligand	Sc(OTf) ₃	Yb(OTf) ₃	Eu(OTf) ₃	La(OTf) ₃
none	3.3	3.6	3.5	4.7
(+)-BINOL	9.4	14.4	12.8	14.6
(+)-diethyl tartrate	5.2	9.7	5.5	7.3
(+)-diisopropyl tartrate	3.5	9.5	4.6	8.1
(+)-TMTDA	4.1	8.0	3.6	4.0
(+)-hydrobenzoin	3.5	16.2	5.8	5.3
(+)-triphenylethanediol	3.2	5.2	2.2	5.9
(+)-TADDOL	2.9	4.5	3.8	4.7
ethylene glycol	3.3			
triethanolamine	4.65			10.8
salen	2.31	6.3	5.2	4.0
box	3.6			
<i>N</i> -methylephedrine	2.87	5.8	3.2	4.4

- no enantioselectivity observed
- DABCO loading dropped to <10 mol% with (+)-BINOL
- *rac*-BINOL showed no rate acceleration

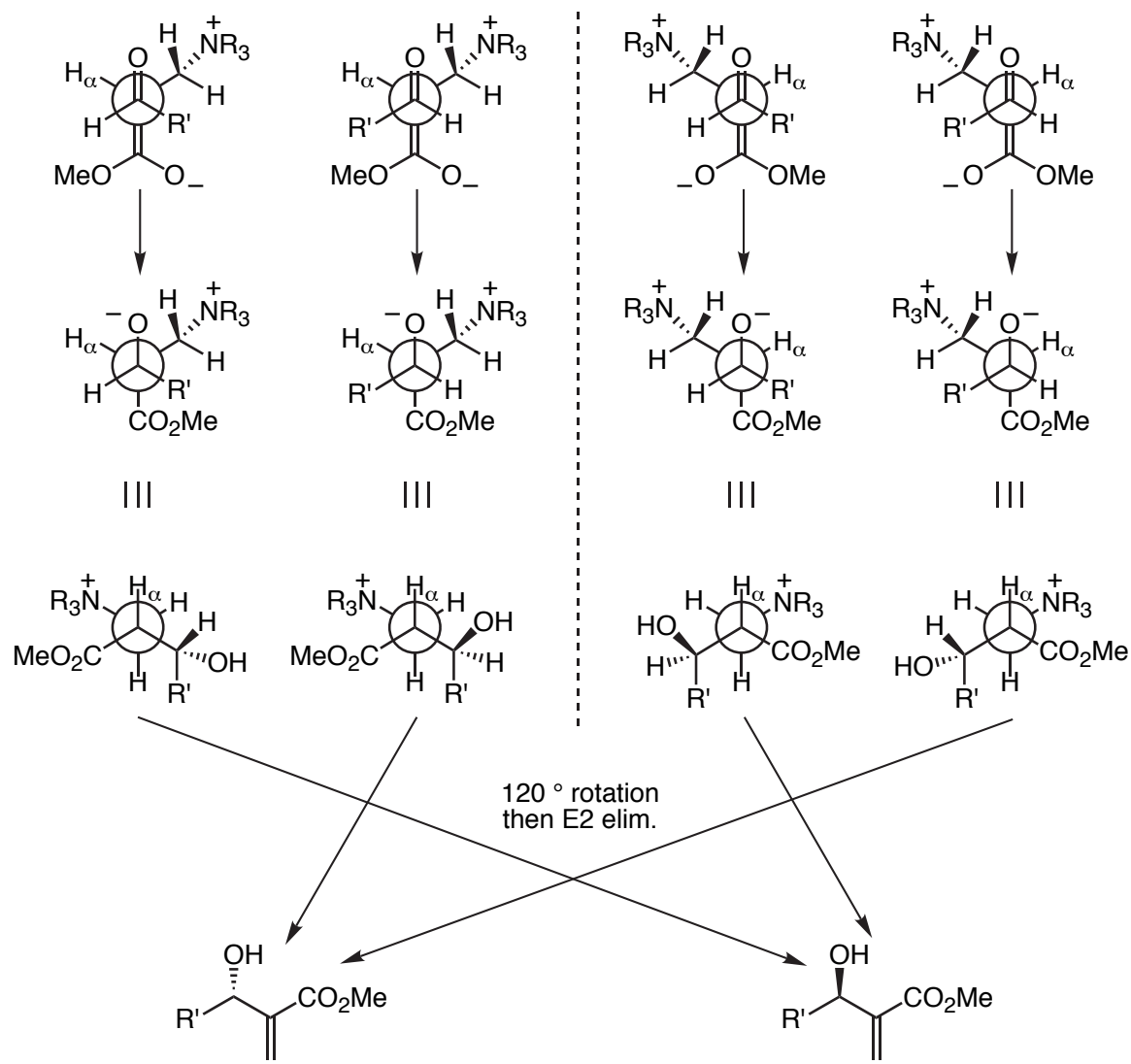
Aggarwal, V. K.; *et. al. Chem. Commun.* **1996**, 2713-2714.

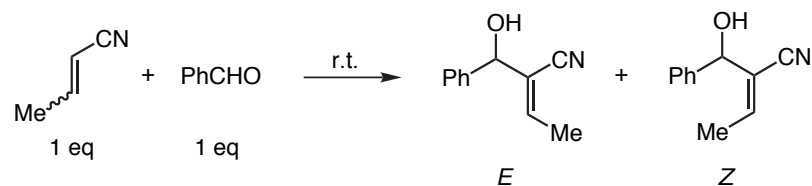
Aggarwal, V. K.; *et. al. J. Org. Chem.* **1998**, 63, 7183-7189.

- Ether was found to be optimal from solvent screening.
- General for a variety of alkenes and aldehydes.

Kobayashi, S.; Kawamura, M. *Tetrahedron Lett.* **1999**, 40, 1539-1542.

Possible Stereoisomers



E/Z Selectivity with Crotononitrile

Solvent	<i>E/Z</i> ratio
neat	1.2 : 1
THF	1.4 : 1
CHCl ₃	1.5 : 1
CH ₃ CN	3.1 : 1
MeOH	4 : 1

5 mol% DABCO, 8 kbar, 17 h, solvent 50 vol%

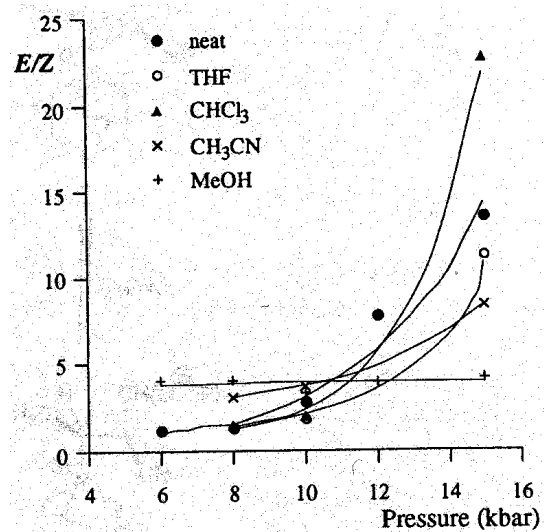
Base	<i>E/Z</i> ratio
DABCO	1 : 1
3-QDL	2 : 1
NEt ₃	4 : 1

10 mol% base, 8 kbar, 17 h, CHCl₃ 50 vol%

- *E* and *Z* crotononitrile is easily isomerized under the reaction conditions.

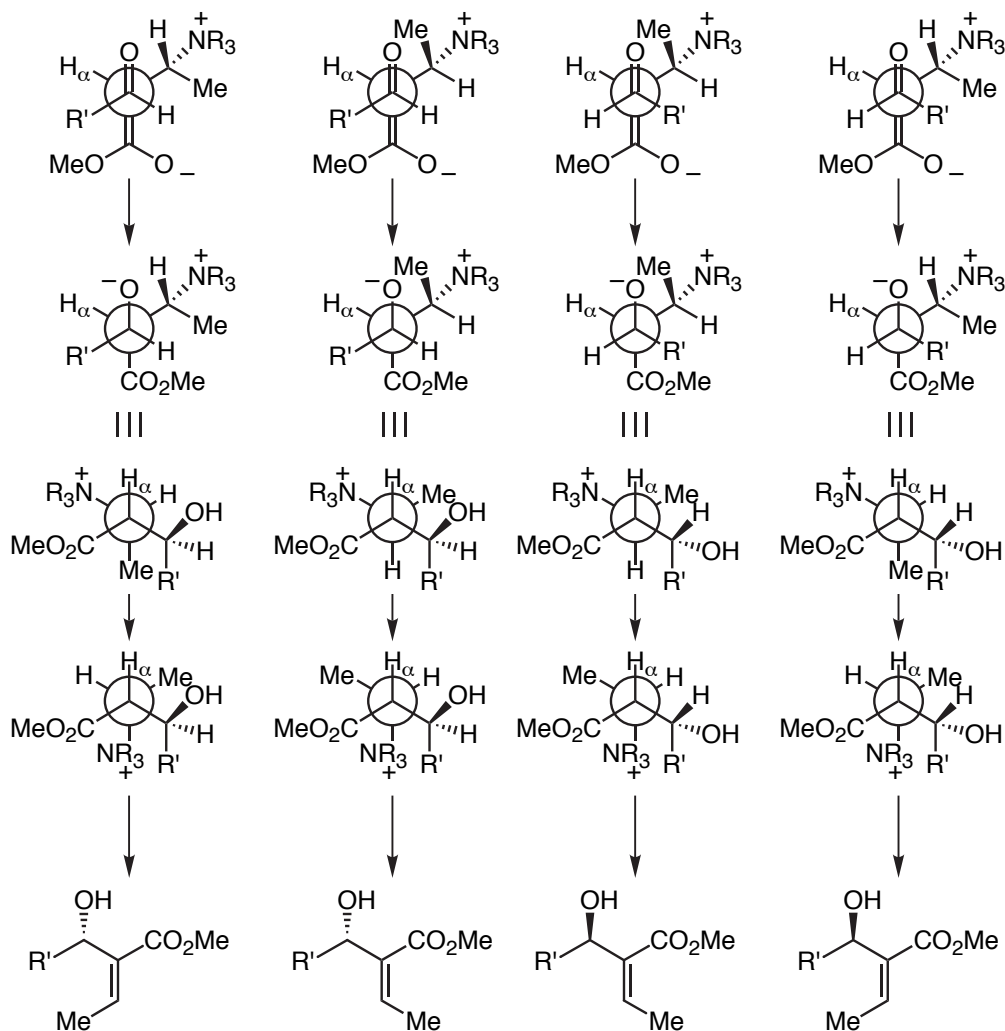
- Products did not undergo retro-Baylis-Hillman.

Rozendaal, E. L. M.; Voss, B. M. W.; Scheeren, H. W. *Tetrahedron* **1993**, 49, 6931-6936.



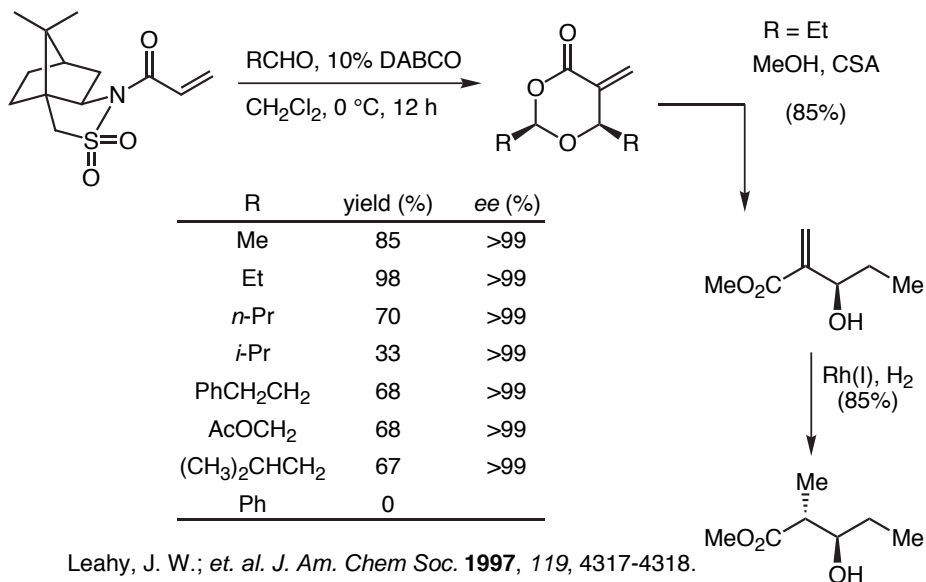
5 mol% DABCO, 17 h, solvent 50 vol%

Possible Stereoisomers for Methylcrotonate

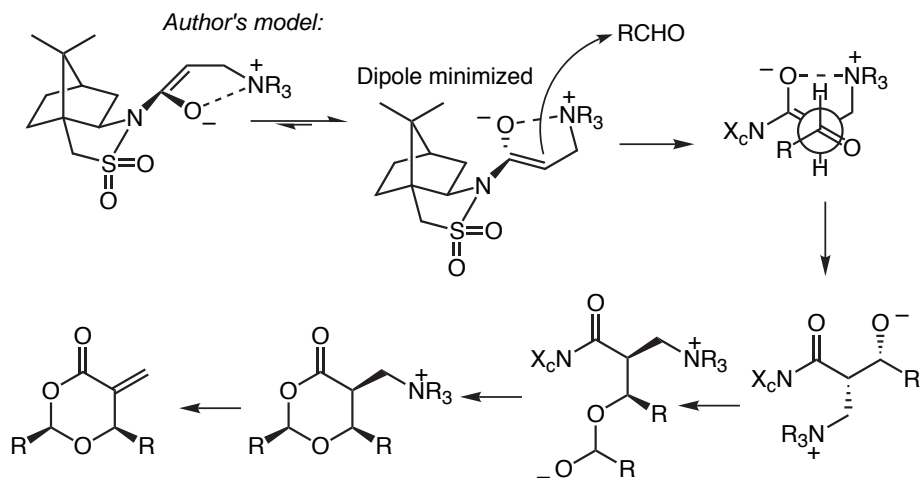
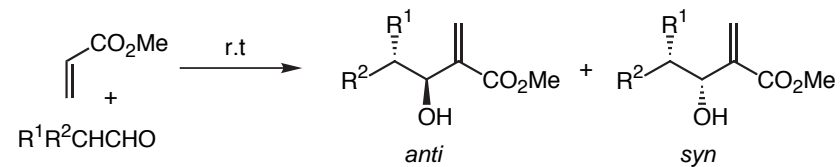
Assumptions:

- *E* enolate formed
- *E2* favored over *E1* pathway, only after rotation of ammonium to *anti* conformation
- $-\text{NR}_3^+$ is orthogonal to π face (stereoelectronics)
- only **one** π face of enolate considered, thus there are an **additional 4 stereoisomers** possible
- starting geometry of methylcrotonate and *in situ* isomerization not considered
- retro-Baylis-Hillman not considered

Camphorsultam Acrylate Baylis-Hillman



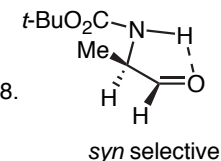
Camphorsultam Acrylate Mechanism

 α -Branched Aldehydes: Modest Felkin-Anh Selection

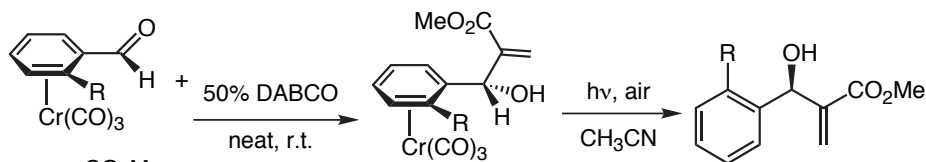
R ¹	R ²	Conditions	yield (%)	<i>anti</i> : <i>syn</i>
MeOCH ₂ O	Me	DABCO, 4 d	55	70:30
MeOCH ₂ O	Me	3-QDL, 1.5 d	60	72:28
BnOCH ₂ O	Me	DABCO, 6 d	42	70:30
MeOCH ₂ O	Ph	DABCO, 10 d	42	37:63
Me	<i>n</i> -Pr	3-QDL, 60 d	30	35:65
	-OC(Me) ₂ OCH ₂ -	DABCO, 55 d	62	69:31
NHCO ₂ <i>t</i> -Bu	Me	DABCO, 7 d	80	26:74
<i>N</i> -Phthalimidyl	Me	DABCO, 3.5 d	28	46:54
	-N(CO ₂ <i>t</i> -Bu)C(Me) ₂ OCH ₂ -	DABCO, 11 d	43	89:11

- Varying the amount of catalyst only affects the rate, not selectivity.
- *Anti* and *syn* drawn incorrectly in review, should be reversed.

Ciganeck, E. *Org. React.* **1997**, *51*, 217-218.



Chiral Aldehydes: Chromium Auxiliary

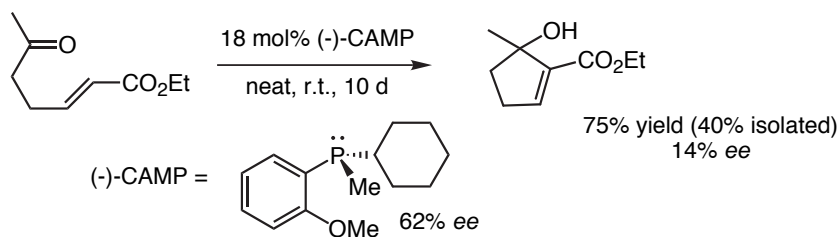


excess	aldehyde	R	time (h)	yield (%)	dr
	rac	OMe	93	87	>98:2
	rac	Cl	6	89	>98:2
	rac	F	7	92	92:8
	rac	Me	58	90	84:16
	S-(+)	OMe	93	85	>98:2
	S-(+)	Cl	8	97	>98:2

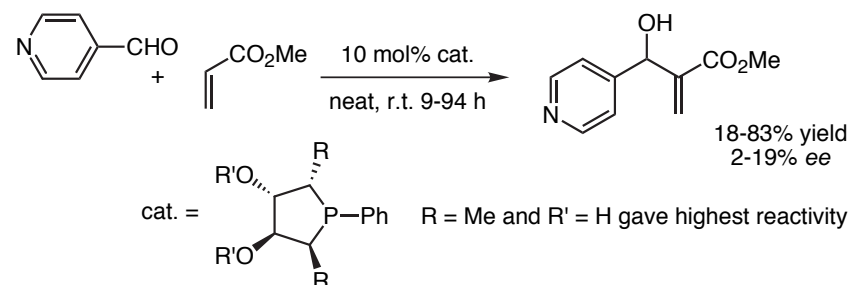
- dr determined by 200 MHz ^1H NMR
- *N*-Tosyl arylimine chromium complex also reacts

Kundig, P. E.; *et. al. Tetrahedron Lett.* **1993**, 34, 7049-7052.

Chiral Phosphine Catalysts

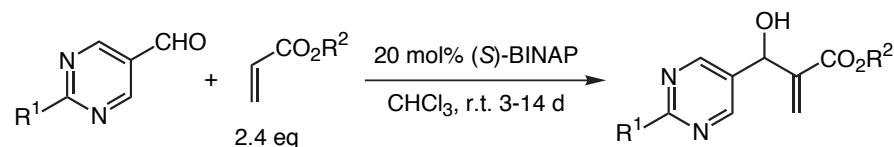


Frater, G.; *et. al. Tetrahedron Lett.* **1992**, 33, 1045-1048.



Zhang, X.; *et. al. J. Org. Chem.* **2000**, 65, 3489-3496.

The High Point of Chiral Phosphine Catalysts



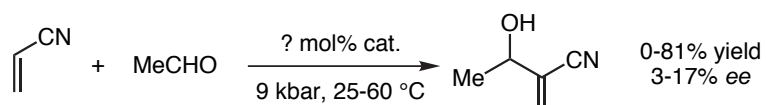
R ¹	R ²	time (d)	yield (%)	ee (%)
H	<i>i</i> -Pr	4	8	9
H	Et	3	12	25
H	Me	4	24	44
Me	Me	14	18	37
Me	Me	3	26	30 ^a

^a Tol-BINAP was used

- other phosphines screened gave ~racemic products: DIOP, NORPHOS, BPPFOH, and MOP

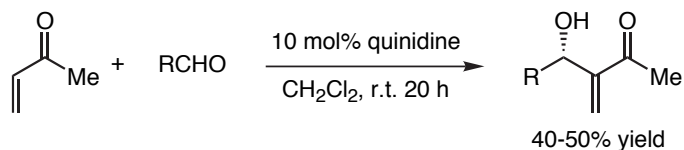
Soai, K.; *et. al. Chem. Commun.* **1998**, 1271-1272.

Naturally Occurring Alkaloids as Chiral Catalysts



- (-)-quinine, (1*R*,2*S*) *N*-methylephedrine, *S*-(-)-nicotine, *S*-(-)-*N*-methylprolinol screened
- (-)-menthyl acrylate ester gave 100% *de* with aromatic aldehydes and DABCO under high P

Isaacs, N. S.; *et. al. Tetrahedron: Asymm.* **1991**, 2, 969-972.



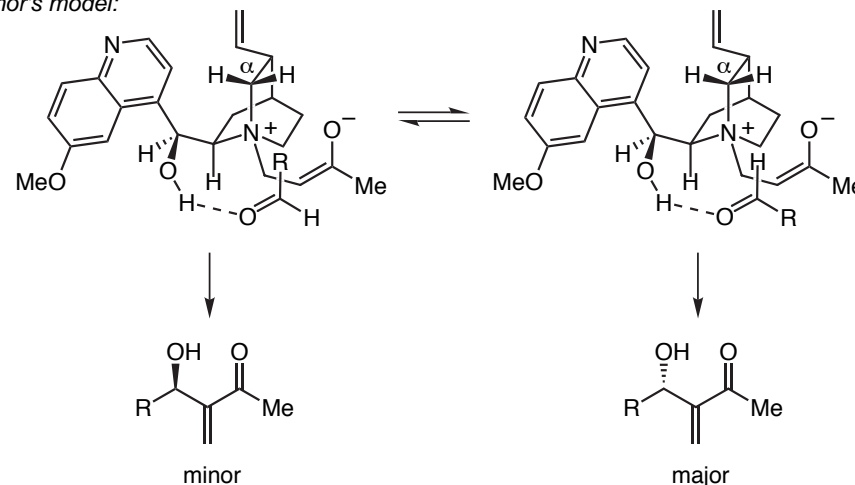
R	Pressure	ee (%)
<i>n</i> -Pr	3 kbar	18
<i>n</i> -C ₉ H ₁₉	10 kbar	31
<i>i</i> -Pr	3 kbar	37
<i>c</i> -hex	3 kbar	45

- 3-QDL, quinine, cinchonine, cinchonidine, *O*-acetyl quinidine, *N*-methylprolinol, *N*-methylephedrine also screened
- ee is highly pressure dependent, optimized pressure is shown in table

Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, 53, 1015-1024.

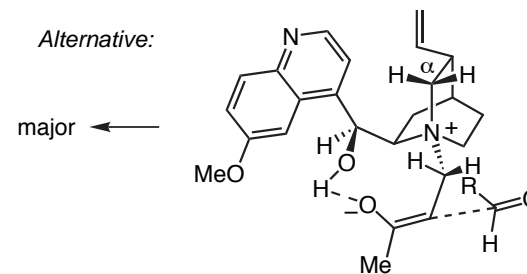
Model For Quinidine Catalyst

Author's model:

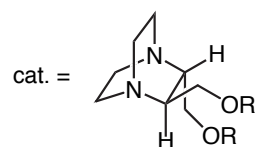
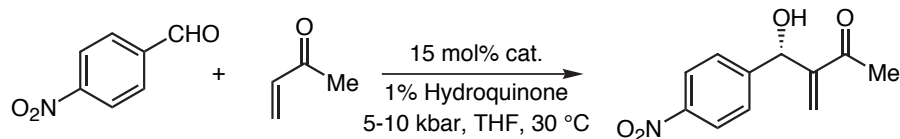


- C_α hydrogens control π face of the aldehyde
- bulky R should enhance selectivity, a trend that they say is "...clearly visible."
- H-bonding plays a "clear role" as *O*-acyl quinidine gives no enantioselectivity

Alternative:

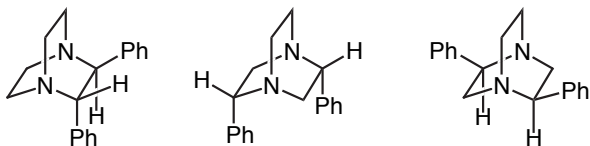


Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, 53, 1015-1024.

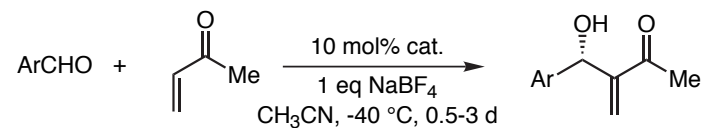
C₂ Symmetric DABCO Catalyst

R	time (h)	yield (%)	ee (%)
Bn	12	45	47
TBDPS	12	23	34
TIPS	28	33	19
Ph	16	60	35
Mesityl	28	67	16
1-naphthyl	16	66	42
1-anthranyl	24	9	11
1-naphthoyl	17	68	15
N-Cbz-Gly	24	63	21

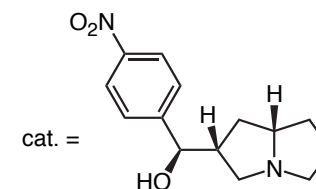
- racemic alcohol product can be easily resolved by kinetic resolution with Sharpless asymmetric epoxidation
- other chiral DABCO's made, but not tested...



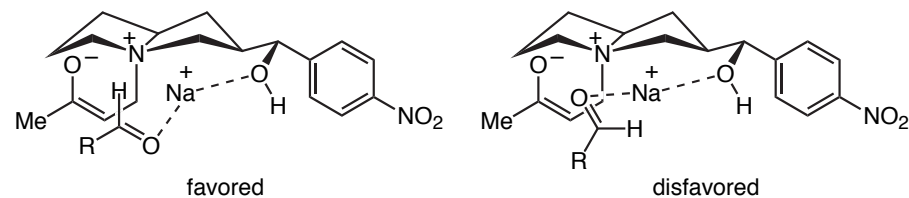
Hirama, M.; *et. al. Tetrahedron: Asymm.* **1995**, 6, 1241-1244.

Chiral Pyrrolizidine Catalyst

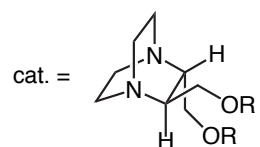
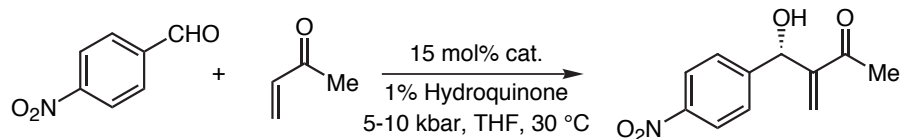
Ar	yield (%)	ee (%)
2-NO ₂	71	67
2-F	31	63
2-Cl	58	72
2-Br	63	71
3-NO ₂	51	37
2-pyridyl	83	21
3-pyridyl	93	49
4-quinoliny	63	70
4-NO ₂	17	39



Author's model:



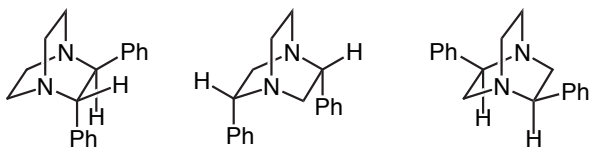
Barrett, A. G. M.; *et. al. Chem. Commun.* **1998**, 2533-2534.

C₂ Symmetric DABCO Catalyst

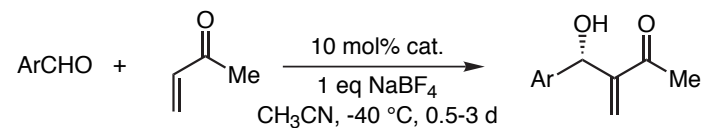
R	time (h)	yield (%)	ee (%)
Bn	12	45	47
TBDPS	12	23	34
TIPS	28	33	19
Ph	16	60	35
Mesityl	28	67	16
1-naphthyl	16	66	42
1-anthranyl	24	9	11
1-naphthoyl	17	68	15
N-Cbz-Gly	24	63	21

- racemic alcohol product can be easily resolved by kinetic resolution with Sharpless asymmetric epoxidation

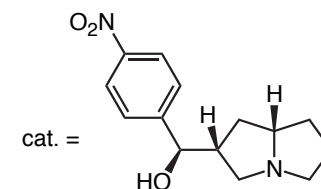
- other chiral DABCO's made, but not tested...



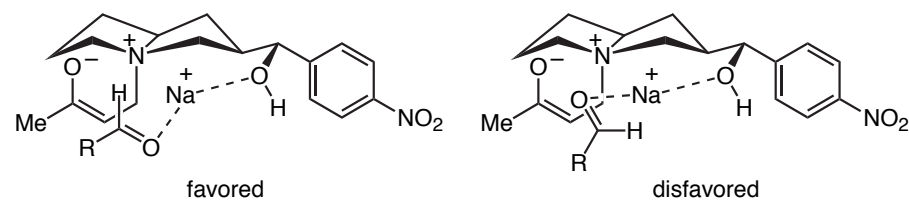
Hirama, M.; *et. al. Tetrahedron: Asymm.* **1995**, 6, 1241-1244.

Chiral Pyrrolizidine Catalyst

Ar	yield (%)	ee (%)
2-NO ₂	71	67
2-F	31	63
2-Cl	58	72
2-Br	63	71
3-NO ₂	51	37
2-pyridyl	83	21
3-pyridyl	93	49
4-quinoliny	63	70
4-NO ₂	17	39

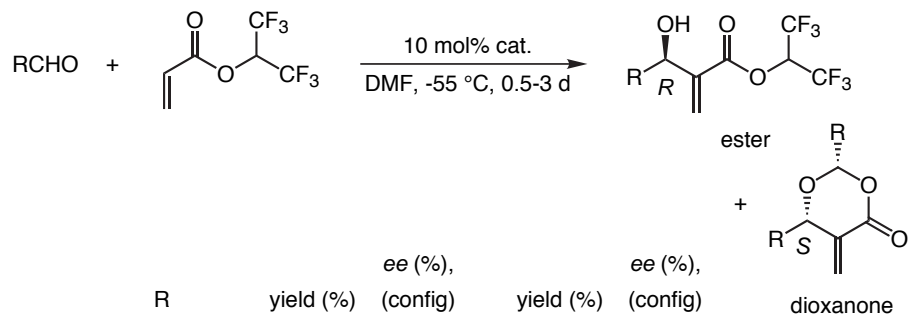


Author's model:



Barrett, A. G. M.; *et. al. Chem. Commun.* **1998**, 2533-2534.

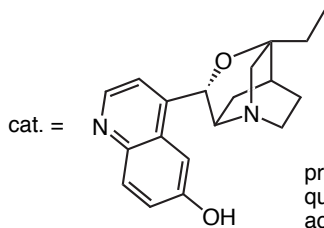
Quinidine Ether Catalyst



R	yield (%)	ee (%), (config)	yield (%)	ee (%), (config)
<i>p</i> -NO ₂	58	91 (<i>R</i>)	11	4 (<i>R</i>)
Ph	57	95 (<i>R</i>)	--	--
(<i>E</i>)-PhCH=CH	50	92 (<i>R</i>)	--	--
Et	40	97 (<i>R</i>)	22	27 (<i>S</i>)
<i>t</i> -Bu	51	99 (<i>R</i>)	18	18 (<i>S</i>)
<i>i</i> -Pr	36	99 (<i>R</i>)	25	25 (<i>S</i>)
<i>c</i> -Hex	31	99 (<i>R</i>)	23	23 (<i>S</i>)
<i>t</i> -Bu	--	--	--	--

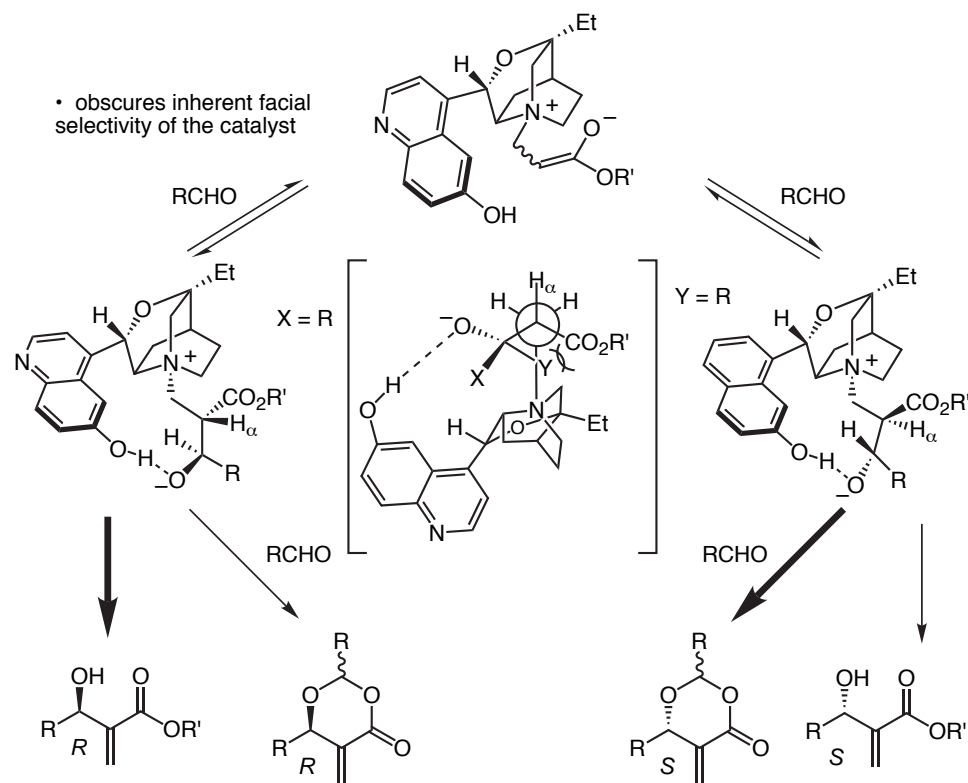
- Quinidine and other acyclic derivatives showed no enantioselection and very low reactivity.
- Free hydroxyl on quinoline is essential for enantioselectivity.
- Reactions conducted at room temperature showed lower enantioselection.
- Racemic ester does not react to give dioxanone under the reaction conditions.

Hatakeyama, S.; *et. al J. Am. Chem. Soc.* **1999**, 121, 10219-10220.

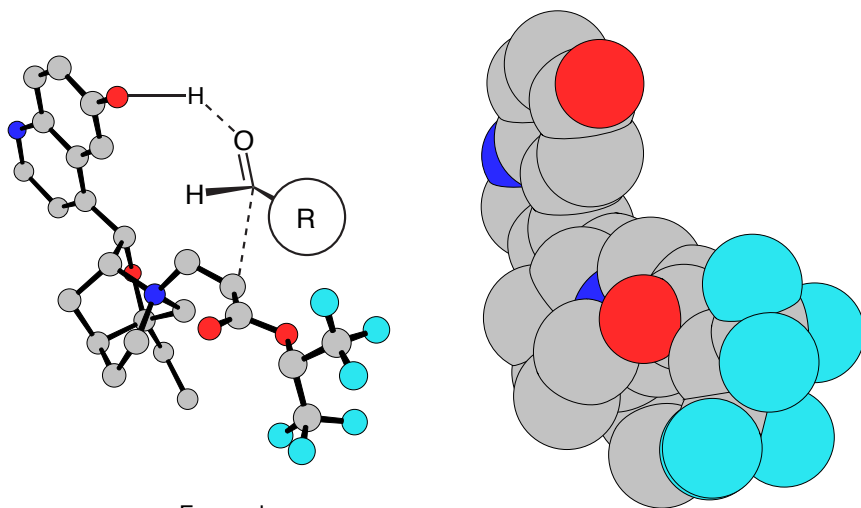


prepared in 65% yield from quinidine in 85% phosphoric acid and KBr (100 °C, 5 d).

Proposed Mechanism: Partial Kinetic Resolution



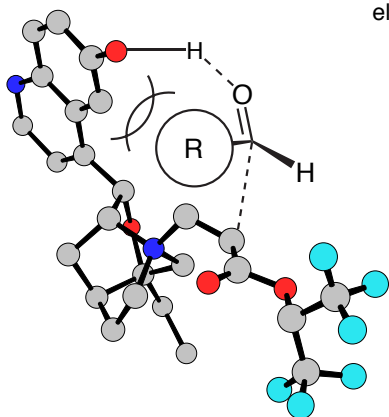
A Model for Facial Selectivity



Favored

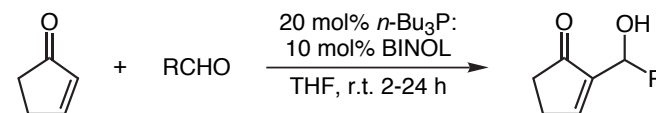
PM3 minimized: C-N bond to enolate constrained to 1.6 Å

- Catalyst orthogonal to opposite π face of the enolate leads to same major enantiomer after elimination.



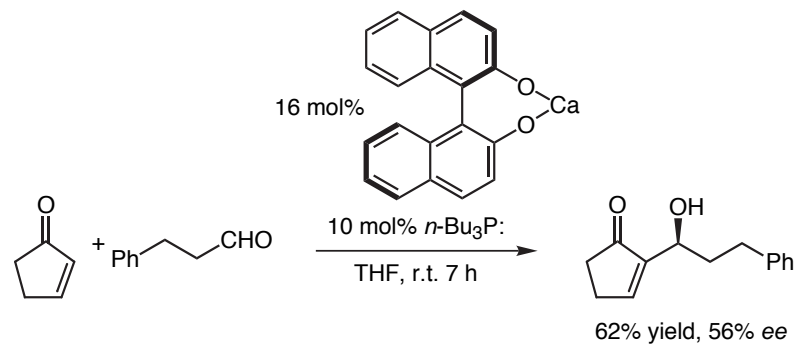
Disfavored

BINOL as an Additive or Ligand

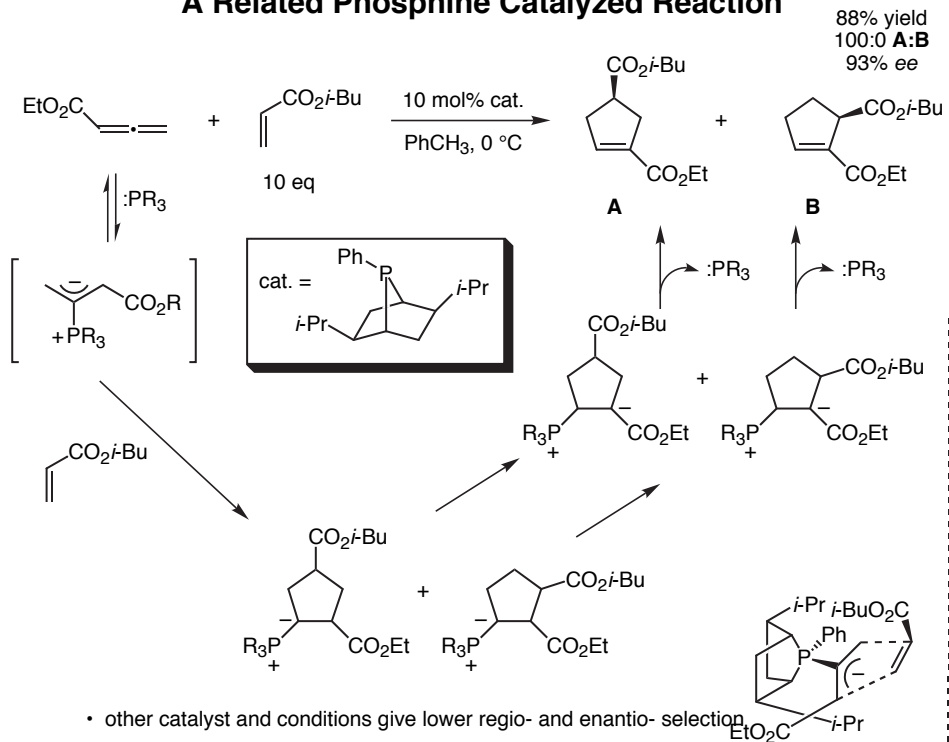


R	yield (%)
<i>n</i> -C ₇ H ₁₅	quant.
Ph	92
MEMO(CH ₂) ₃	98
Et	91
PhCH ₂ CH ₂	quant.

- ee were all <10%
- phenol also accelerates reaction
- other acrylates also tolerated

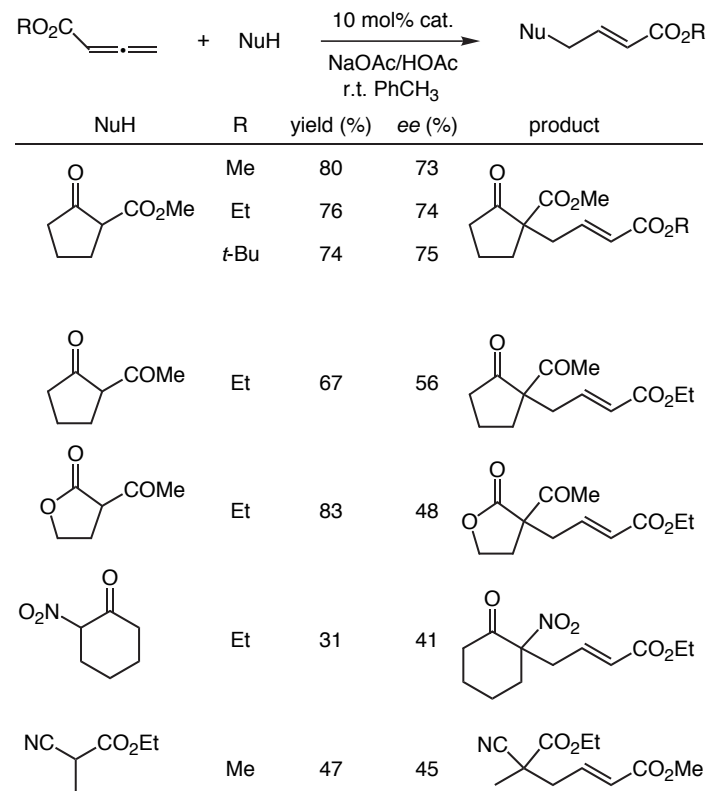
Ikegami, S.; Yamada, Y. M. A. *Tetrahedron Lett.* **2000**, 41, 2165-2169.

A Related Phosphine Catalyzed Reaction

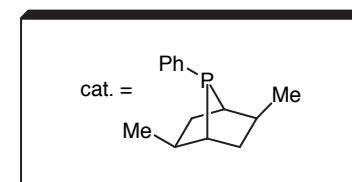


Zhang, X.; *et. al. J. Am. Chem. Soc.* **1997**, *119*, 3836-3837.
 Lu, X.; *et. al. J. Org. Chem.* **1995**, *60*, 2906-2908.

Phosphine Catalyzed Addition

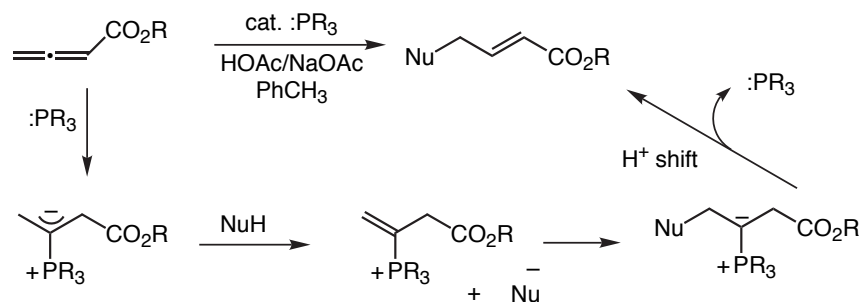


Zhang, X.; *et. al. J. Org. Chem.* **1998**, *63*, 5631-5635.

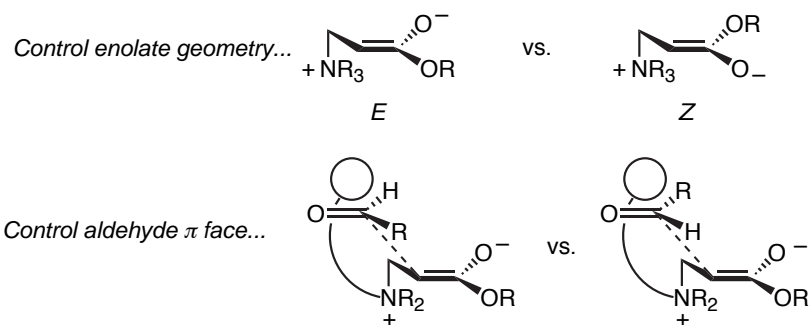


Addition Mechanism

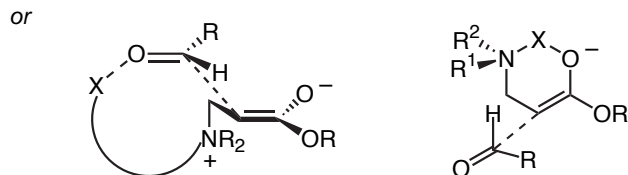
Author's proposal:



Recipe for a Good Catalyst?



- for substituted acrylates, must control enolate π facial selectivity
- chirality on catalyst may also gear ester substituent to influence aldehyde approach



Conclusions

- The Baylis-Hillman reaction provides convenient access to valuable allylic alcohol building blocks which may serve as synthetic equivalents to *anti*-propionate aldol addition products.
- The basics of the reaction mechanism are understood, but the mechanistic details still remain elusive at best.
- Few examples of a general, diastereoselective Baylis-Hillman have been reported and the successful ones are rather limited in scope.
- Only one synthetically useful enantioselective, base catalyzed Baylis-Hillman reaction exists. There is no rational design, nor models for asymmetric catalysis.
- The asymmetric, catalytic Baylis-Hillman reaction is very promising and attractive methodology, but remains an elusive goal of chiral Lewis base catalysis.

Chemistry 206

Advanced Organic Chemistry

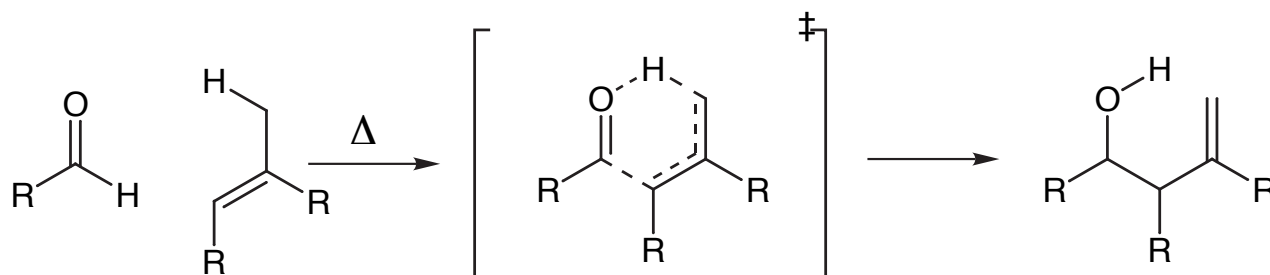
Handout 26B

Asymmetric Carbonyl Ene Reactions

Evans Group Seminar

by

Steven Tregay, December 12, 1997



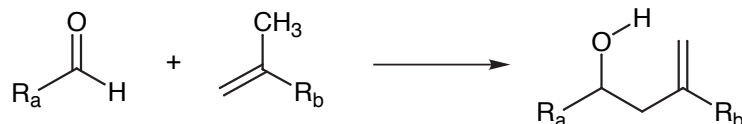
D. A. Evans

Monday,
November 17, 2003

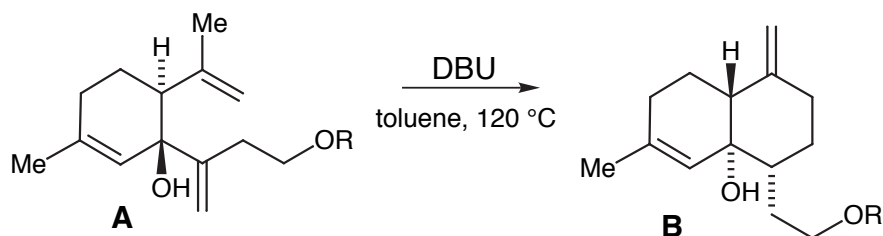
Chem 206 Problems Containing the Ene Reaction

The problems provided on this and the following page deal with the ene reaction either directly or indirectly. In the latter cases, this reaction is imbedded within a multistep rearrangement sequence. Answers to these questions may be obtained by entering the descriptors "Rearrangement" and "Ene" into the problems database: <http://evans.harvard.edu/problems/>

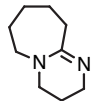
Problem 210. The carbonyl ene reaction is illustrated below. Using FMO analysis, evaluate the transition state of this reaction. Your answer should include: a transition state drawing; clear orbital depictions and HOMO-LUMO assignments; an indication of the number of electrons from each segment; and indication of whether the reaction is thermally allowed.



Problem 19. The following transformation was recently reported by Barriault and Deon in conjunction with their synthesis of arteannium M (*Org. Lett.* **2001**, 3, 1925-1927). Provide a mechanism for the illustrated thermal rearrangement(s) of **A** to **B**. Where stereochemical issues are at stake, provide clear three dimensional drawings to support your answer.

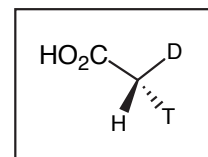
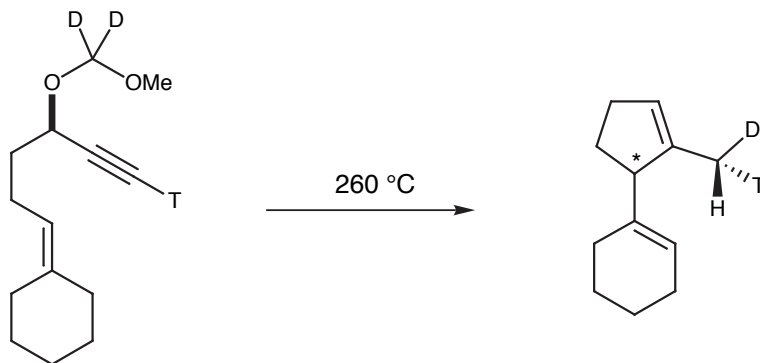


Single product diastereomer



DBU is a useful amidine base; $pK_a \sim 12$

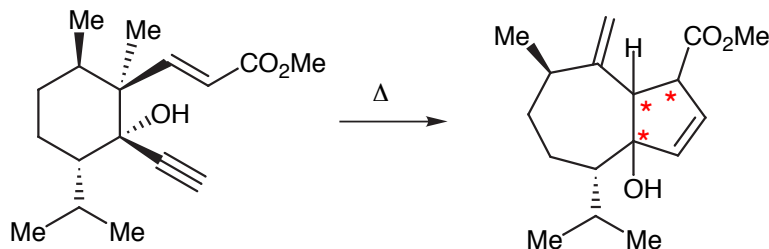
Problem 83. Chiral methyl groups are commonly used to probe the stereochemical outcome of biological reaction mechanisms. Many interesting strategies have been developed to synthesize chiral methyl groups in high enantiomeric excess. The first approach, designed by Arigoni (*Chem. Commun.* **1975**, 921), is illustrated below.



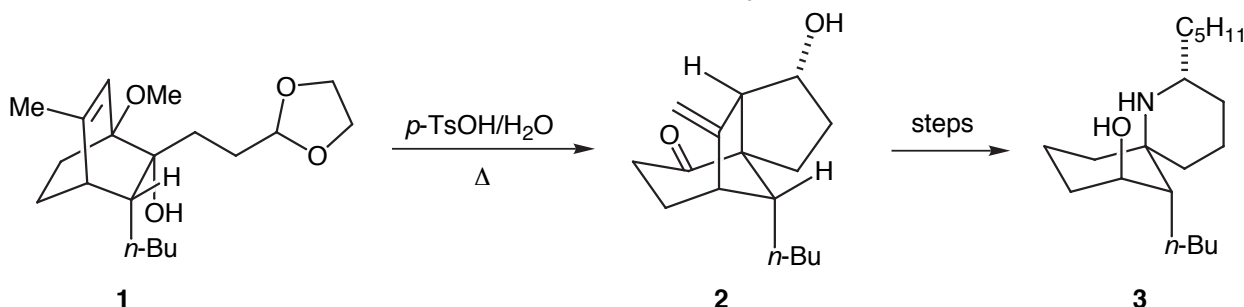
Provide a mechanism for the following transformation that accounts for the (H,D,T) stereochemistry of the chiral methyl group. You do not need to account for the stereochemistry at the starred carbon (it was not determined by the investigators).

Chem 206 Problems Containing the Ene Reaction

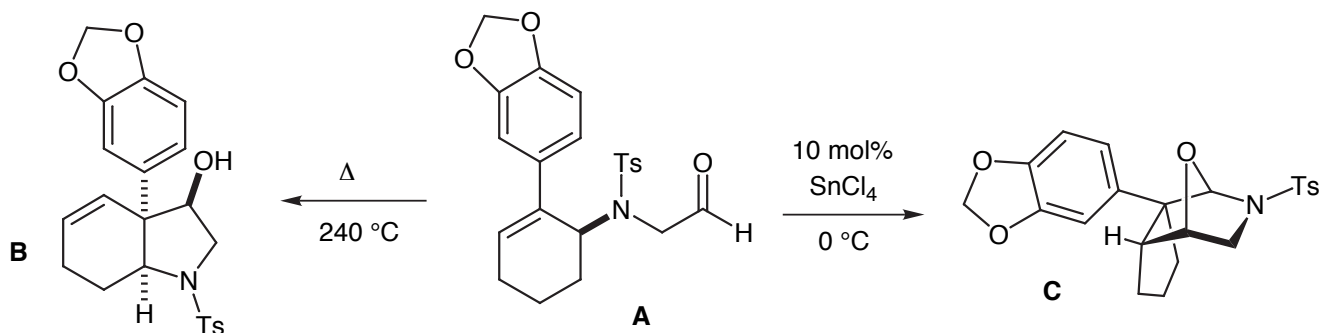
Problem 177. Provide a mechanism that predicts the observed stereochemistry at the starred (*) carbon atoms (Rajagopalan, *Tetrahedron Lett.* **1998**, 39, 4133). Draw the starting material, each intermediate, and the product clearly in 3D.



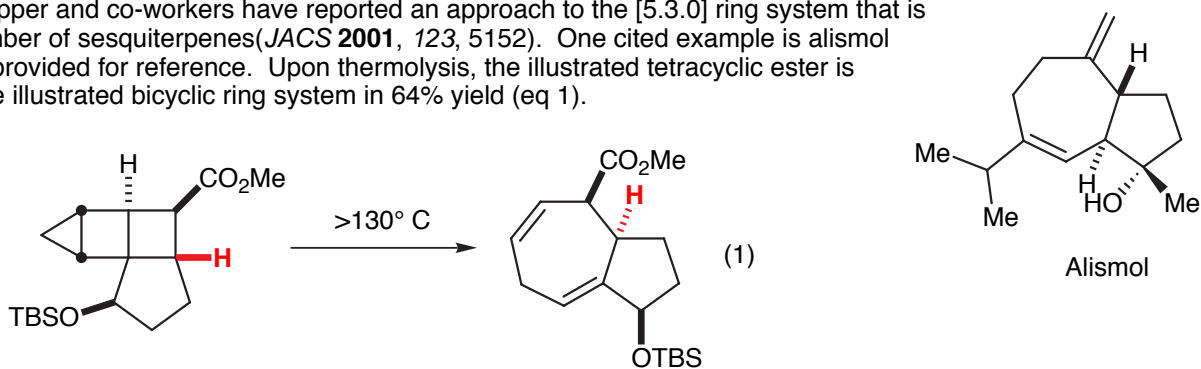
Problem 184. The key step in Kim's synthesis of perhydrohistrionicotoxin, **3**, was the conversion of intermediate **1** to ketone **2** in a single acid-catalyzed transformation (*Chem. Commun.*, **1997**, 2263). Provide a mechanism for the conversion of **1** to **2** that accounts for the observed stereochemistry.



Problem 203. Provide mechanisms that account for the stereoselective formation of the products obtained by treatment of aldehyde **A** to the conditions shown below. Briefly comment on the difference in reactivity under the two sets of conditions (*JOC*, **1998**, 7586).

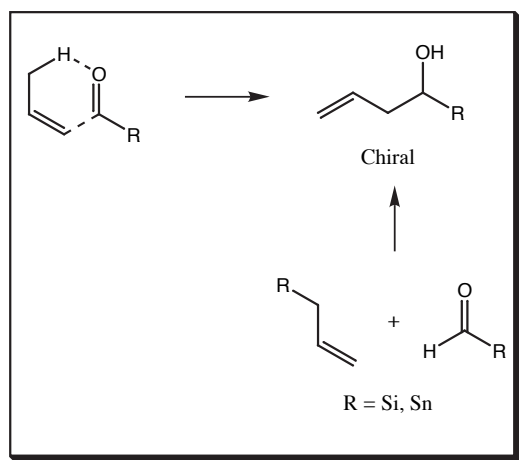


Problem 233. Snapper and co-workers have reported an approach to the [5.3.0] ring system that is common to a number of sesquiterpenes (*JACS* **2001**, 123, 5152). One cited example is alismol whose structure is provided for reference. Upon thermolysis, the illustrated tetracyclic ester is transformed into the illustrated bicyclic ring system in 64% yield (eq 1).



Provide a plausible mechanism for this transformation. Your answer should include an explanation of the somewhat unusual stereochemical inversion of the center carrying the flagged "red" hydrogen.

Seminar Topics



History:

Alder, *Ber.*, **1943**, 76, 27.
Alder, *Ann.*, **1962**, 651, 141.

Covered in this Seminar:

Asymmetric Ene
(Metallo-Ene not covered)

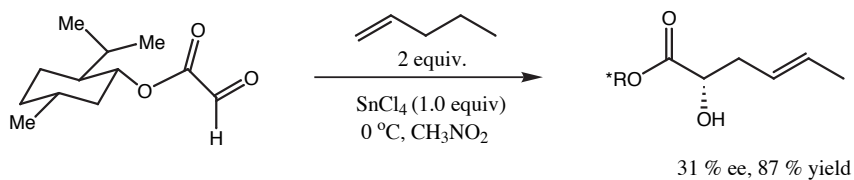
Chiral Auxiliaries

Catalytic/Promoted

Reviews:

Snider in *Comprehensive Organic Chemistry*, **1991**, vol 2, 527.
Mikami, *Chem. Rev.* **1992**, 92, 1021.
Mikami, *Advances in Asymmetric Synthesis*, **1995**, 1.
Bolm, *ACIEE*, **1995**, 34, 1717.
Mikami, *Advances in Catalytic Processes*, **1995**, 1, 123.
Mikami, *Pure & Applied Chem.*, **1996**, 68, 639.

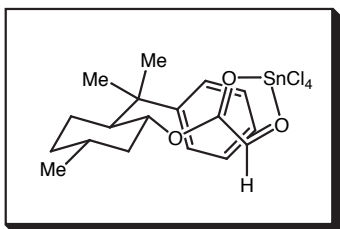
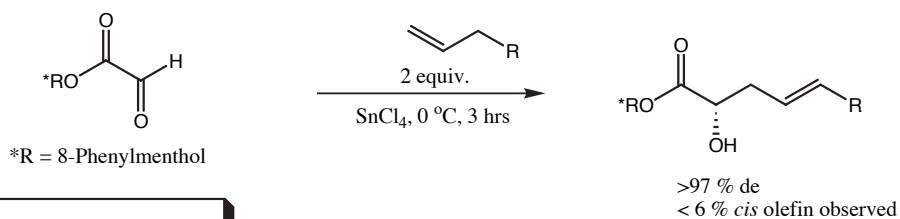
Early Work on Chiral Glyoxylates



Thermal reaction (160 °C) gave no induction

Achmatzowicz, *JOC*, **1972**, 37, 964.

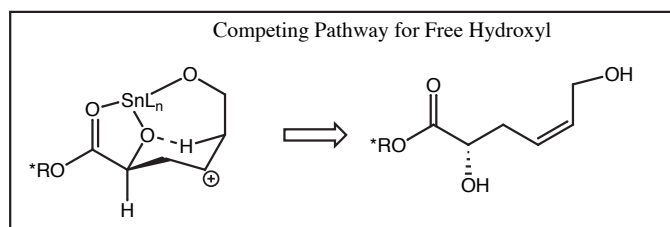
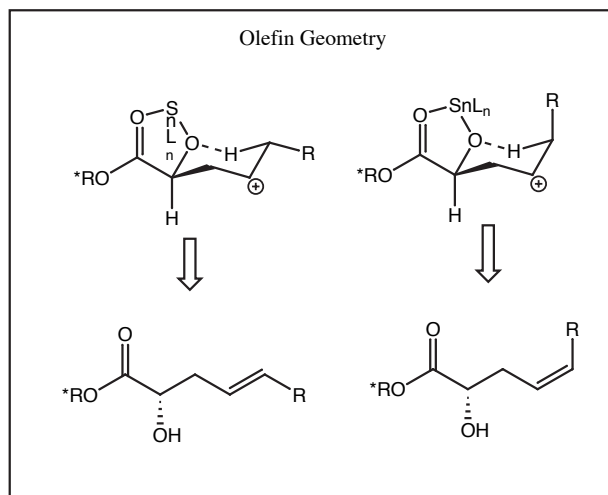
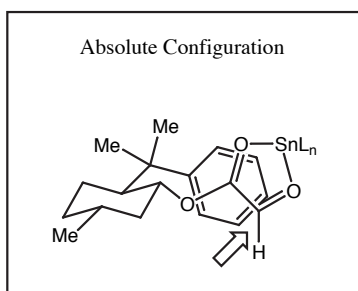
Ene reactions of 8-Phenylmenthol Glyoxylate Ester



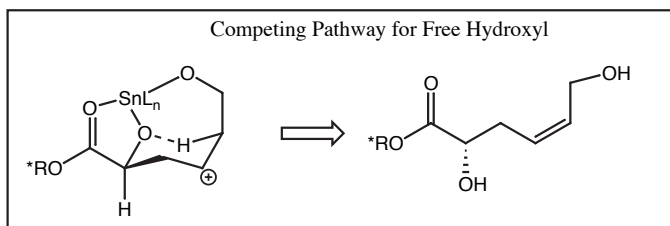
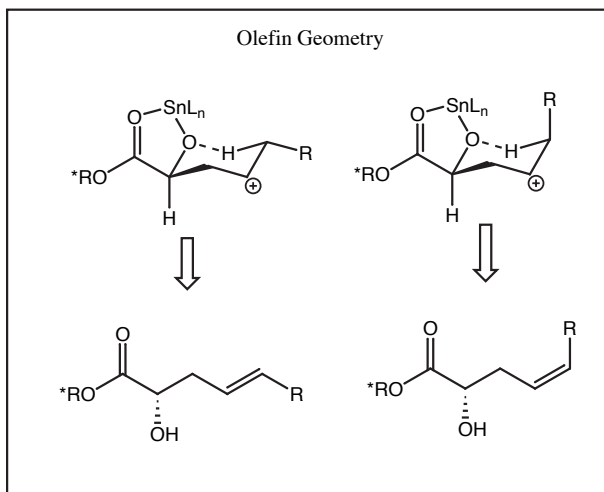
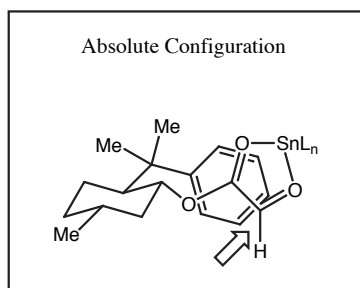
Alkene	Product	Yield
		99 %
		92 %
		R=H 100 % (2:1 <i>cis</i> : <i>trans</i>) R=OAc 59 % R=Bn 99 % R=TBS 89 %

Whitesell, JCS CC, **1982**, 989.
Whitesell, Tetrahedron, **1986**, 42, 2993.

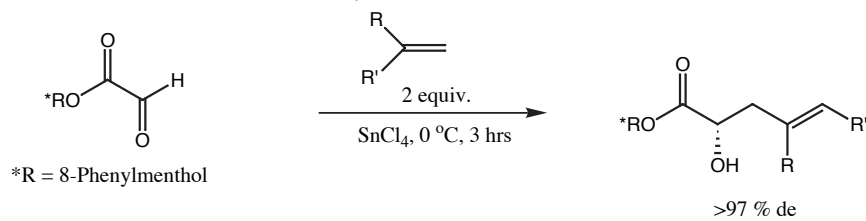
Mechanism for 1-Substituted Olefins



Mechanism for 1-Substituted Olefins



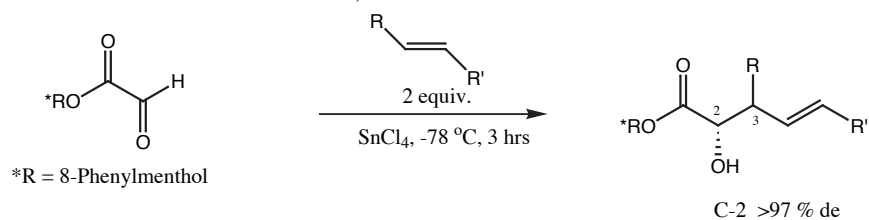
1,1 Disubstituted Olefins



Alkene	Product	Yield
		94 %
		84%
		R=H "Dominant product" R=OAc 42 % 24 % trans olefin 20 % cis olefin

Whitesell, JCS CC, **1982**, 989.
 Whitesell, Tetrahedron, **1986**, 42, 2993.

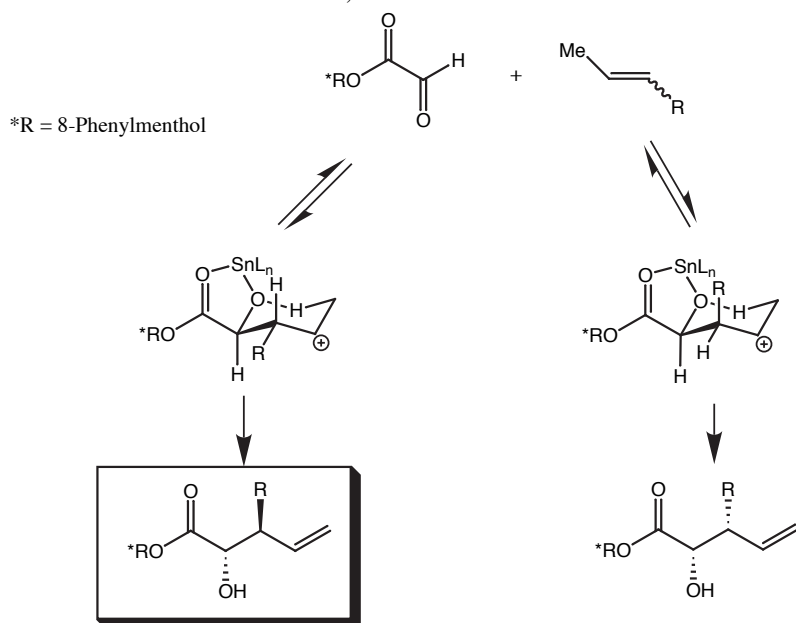
1,2 Disubstituted Olefins



Alkene	Product	Yield
		C-3 92 % de "Exo TS" 90 % yield
		C-3 15 : 1
		85 % yield
		C-3 8 : 1 one compound 86 % yield

Whitesell, JCS CC, **1982**, 989.
Whitesell, Tetrahedron, **1986**, 42, 2993.

1,2 Disubstituted Olefin Mechanism

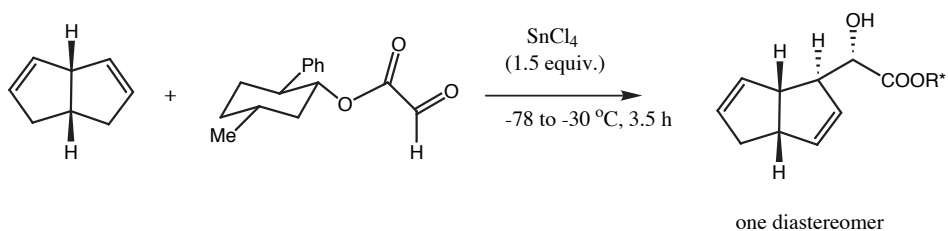
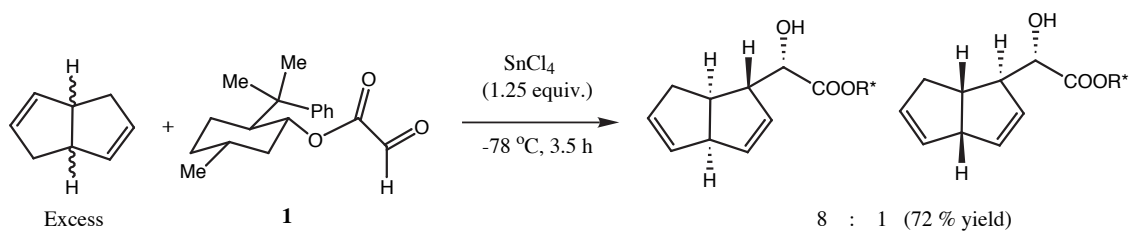


R = Me
trans-butene 15 : 1
cis-butene 8 : 1

R = i-Pr
 4-methyl-*cis*-2-pentene one compound

Note: *cis*-butene does not isomerize in presence of SnCl₄ or SnCl₄/isopropyl alcohol at -78 °C
 Isomerization does occur in the presence of glyoxylate

Asymmetric Desymmetrization using 8-Phenylmenthol Glyoxylate Ester



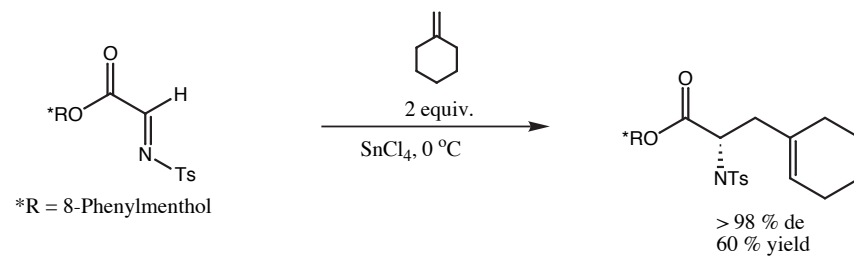
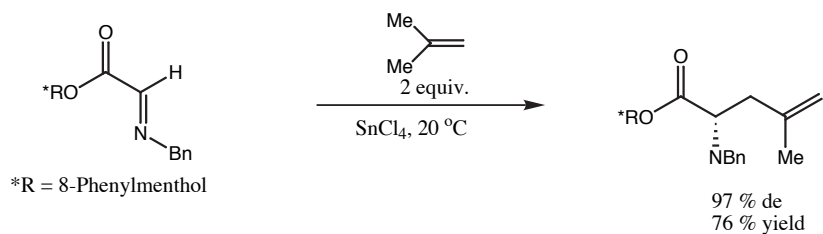
Whitesell, JACS, **1988**, *110*, 3585.

Whitesell, JACS, **1986**, *108*, 6802.

Whitesell, JOC, **1985**, *50*, 3025.

Note: 1 gives opposite bridgehead selectivity

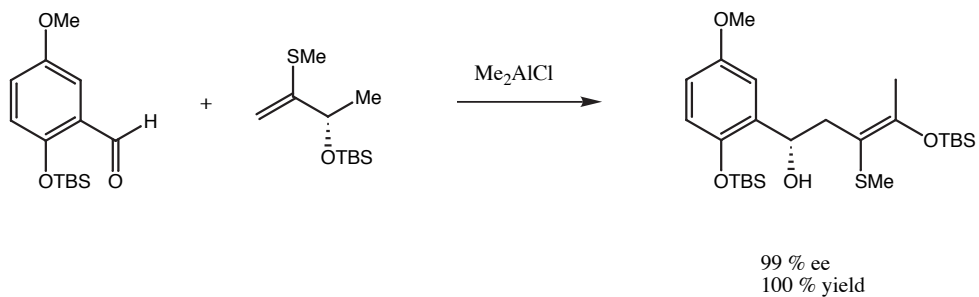
Phenylmenthol Imine-Ene Reaction



Use of Ts rather than Bn was not discussed

Mikami, TL, **1993**, *34*, 4841.

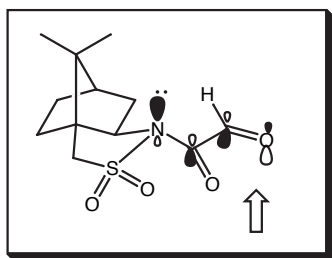
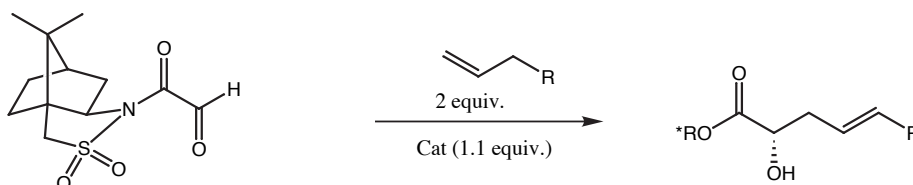
Ene reaction of (S)-2-(Ethylthio)-3-siloxy-1-butene



Referenced in Mikami, *Chem. Rev.*, **1992**, 92, 1021

Kuwajima, Annual Meeting of the Chemical Society of Japan, 1991.

Ene Reactions of N-Glyoxyloyl -(2R)-bornane-10,2-Sultam

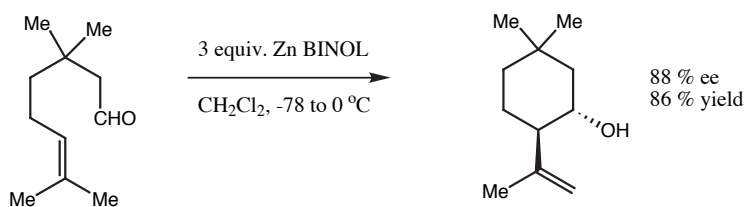


Most Reactive Conformation according to PM3 and *Ab initio* calculations
Chapuis, *Helv. Chim. Acta*, in preparation

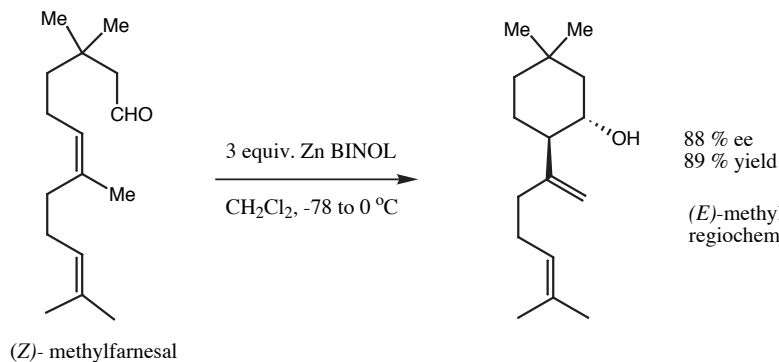
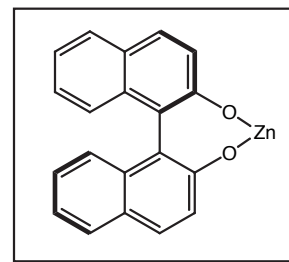
R =	Catalyst	Temp (°C)	% de	% Yield
Et	SnCl ₄	-78	84 : 16	78
	ZnBr ₂	5	90 : 10	50
<i>n</i> -Pr	SnCl ₄	-78	75 : 25	93
	ZnBr ₂	5	89 : 11	43

Jurczak, *Tet.: Asymm.*, **1997**, 8, 1741.

Zn BINOL Promoted Intramolecular Ene Cyclizations



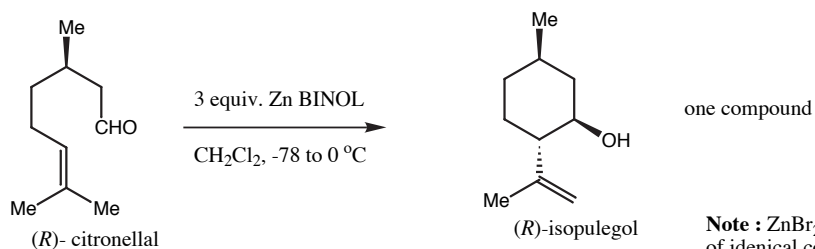
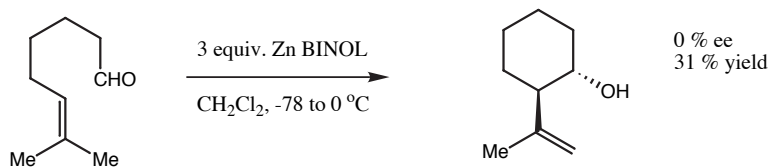
Note: using 1.5 equiv. reagent lowers % ee



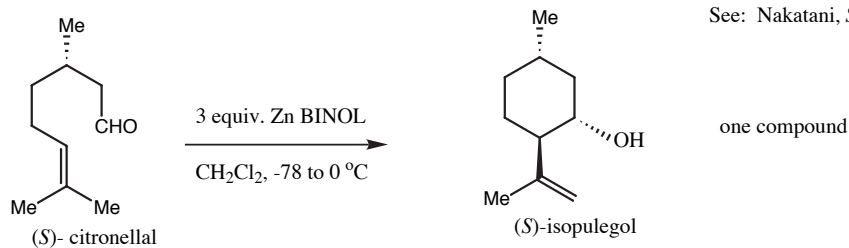
(E)-methylfarnesal afforded other regiochemistry in 20 % ee

Yamamoto, *Tetrahedron*, **1986**, 42, 2203.

Zn BINOL Promoted Intramolecular Ene Cyclizations

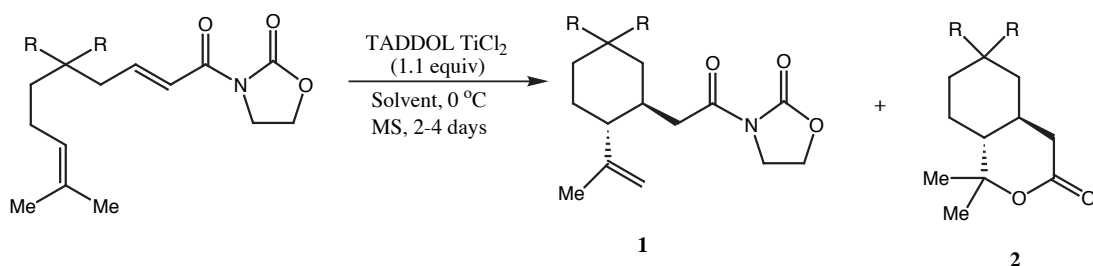


Note : ZnBr₂ gives 95:5 ratio of products of identical configuration
See: Nakatani, *Syn. Comm.*, **1978**, 147.

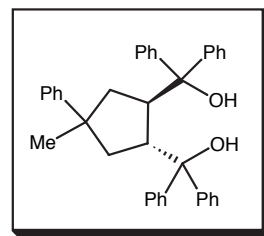


Yamamoto, *Tetrahedron*, **1986**, 42, 2203.

TADDOL Promoted Intramolecular Ene

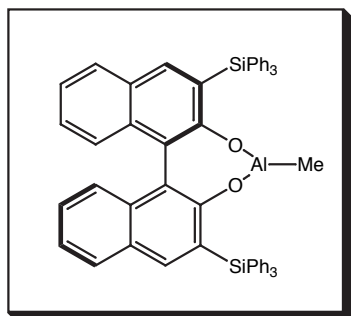
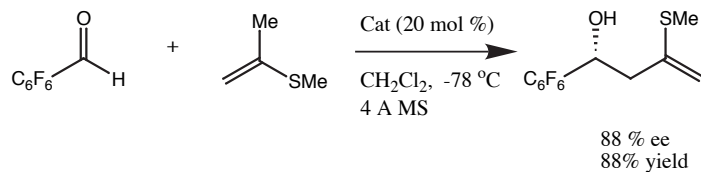


R =	Solvent	1 % ee (% yield)		2 % ee (% yield)	
H	Toluene (20 days)	ND	(17)	ND	(37)
	Toluene	82	(39)	92	(36)
Me	1,3,5 Trimethylbenzene	86	(32)	>98	(37)
	CFCl ₂ CF ₂ Cl/ CH ₂ Cl ₂	97	(47)	ND	(16)
-SCH ₂ CH ₂ S-	CFCl ₂ CF ₂ Cl/ CH ₂ Cl ₂	84	(ND)	>98	(ND)



Narasaka, *Chem. Lett.*, **1988**, 1609.

3-3'-bis(triphenylsilyl)BINOL Aluminium Catalyst



Note: Use of less reactive aldehydes (ie Chloral) afforded lower % ee and stoic. LA were required

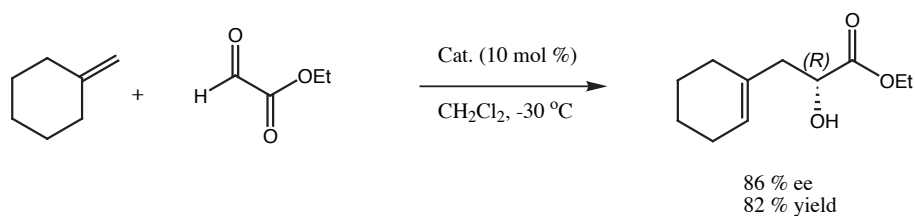
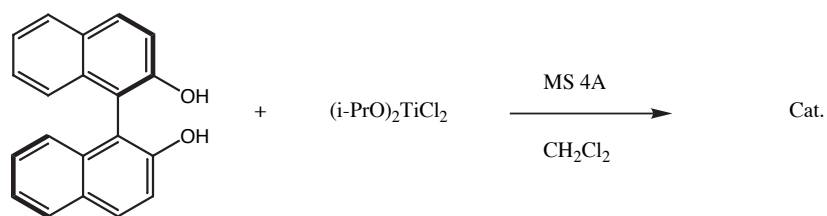
Use of MS is required for catalytic reaction

Use of 3-3'-diphenylbinaphthol complex gave 0 % ee

Yamamoto, *TL*, **1988**, 29, 3967.

(i-PrO)₂TiCl₂ (R)-BINOL Catalyzed Ene Reaction

Preliminary Result:



Nakai, JACS, **1989**, *111*, 1940.
Nakai; Mikami, JACS, **1990**, *112*, 3949.

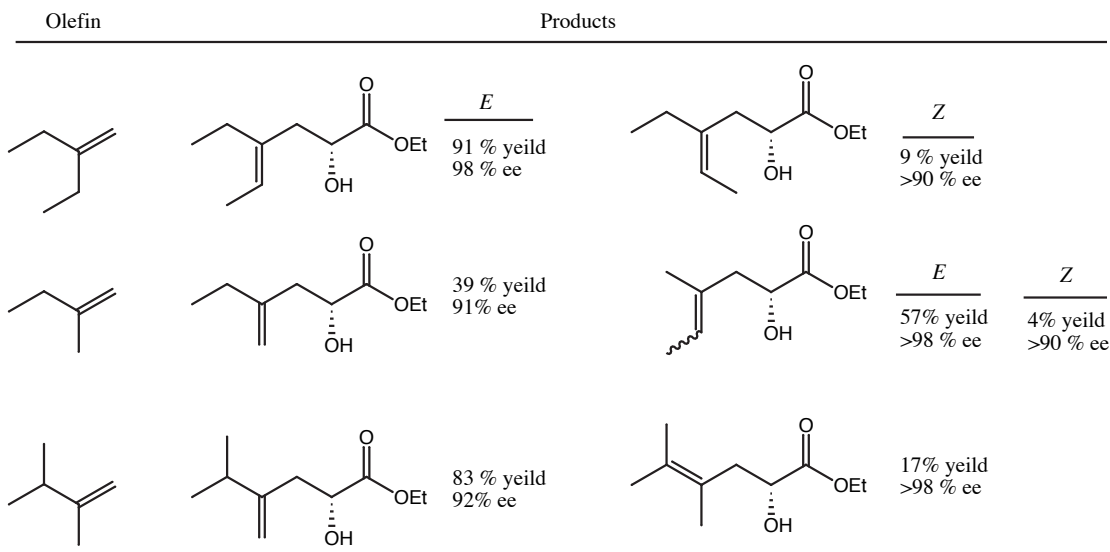
(i-PrO)₂TiBr₂ (R)-BINOL Catalyzed Ene Reaction : 1,1 Disubstituted

Olefin	Product	Cat. Mol %	% yield	% ee
		5	73	98
		10	87	94
		1.0	98	94
		5	92	89

Reaction conditions: Ethyl glyoxylate, -30 °C, 3 hr, MS, CH₂Cl₂

Nakai, JACS, **1989**, *111*, 1940.
Nakai; Mikami, JACS, **1990**, *112*, 3949.
Nakai, *Org. Syn.*, **1993**, 14.

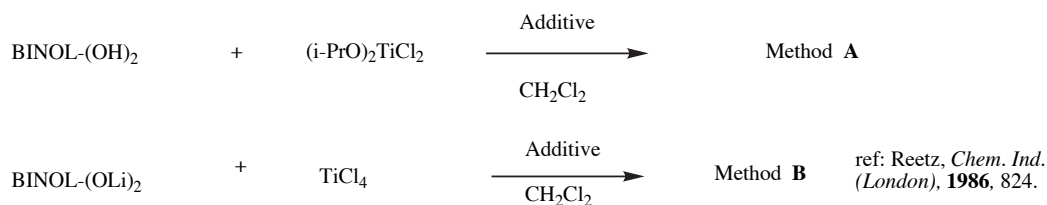
(i-PrO)₂TiBr₂ (R)-BINOL Catalyzed Ene Reaction : More 1,1 Disubstituted



Reaction conditions: Ethyl glyoxylate, 5 -10 mol % cat., -30 °C, 3 hr, MS, CH₂Cl₂

Nakai, JACS, **1989**, *111*, 1940.
Nakai; Mikami, JACS, **1990**, *112*, 3949.

Importance of Molecular Sieves



For reaction of α -methyl Styrene and ethyl gloxylate (CH₂Cl₂, -30 °C)

	Method A				Method B			
	Additive 4 A MS (g/mmol)	Yield	% ee		Additive i-PrOH	Additive 4 A MS (g/mmol)	Yield	% ee
Method A	5	100	97	Method B	0	0	95	93
	0	81	10		10 mol %	0	90	95
	5 then filter	96	97		0	5	100	95
					10 mol %	5	98	96

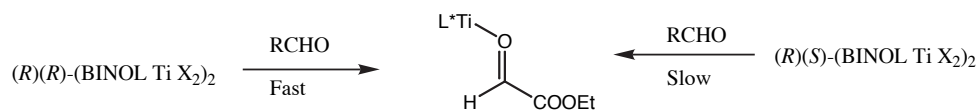
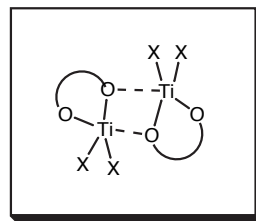
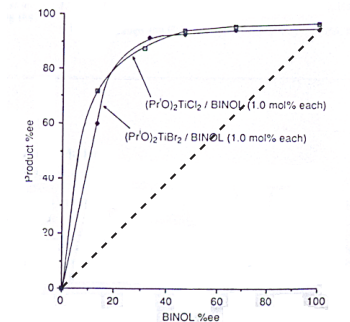
Note : By ¹³C NMR no Ti BINOL complexation occurs until MS are added.

(i-PrO)₂TiCl₂ is a viable catalyst for the reaction.

Note : MeOH, t-BuOH give similar results

Nakai; Mikami, JACS, **1990**, *112*, 3949.

NonLinear Effect in the (i-PrO)₂TiX₂ BINOL Catalyzed Ene Reaction



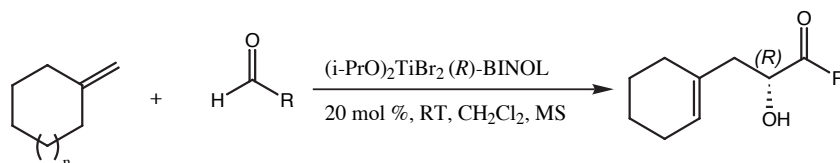
For chiral poisoning of racemic BINOL Complexes see:

Faller, *TL*, **1996**, 37, 3449.
Mikami, *Nature*, **1997**, 385, 613.

Note : For X-ray crystal structure of dimeric ((PhO)₂TiCl₂)₂ See: Watenpaugh, *Inorg. Chem.* **1966**, 5, 1782.

Mikami, *Tetrahedron*, **1992**, 48, 5671.
Mikami, *JACS*, **1994**, 116, 2812.

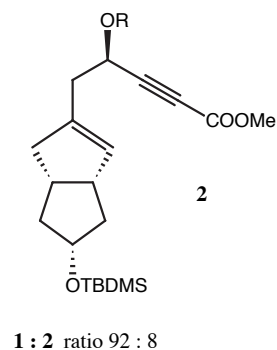
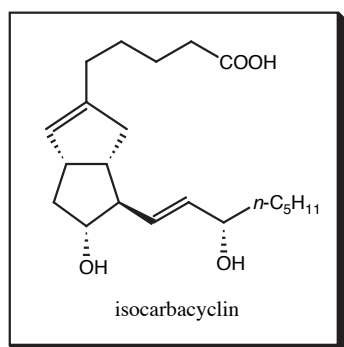
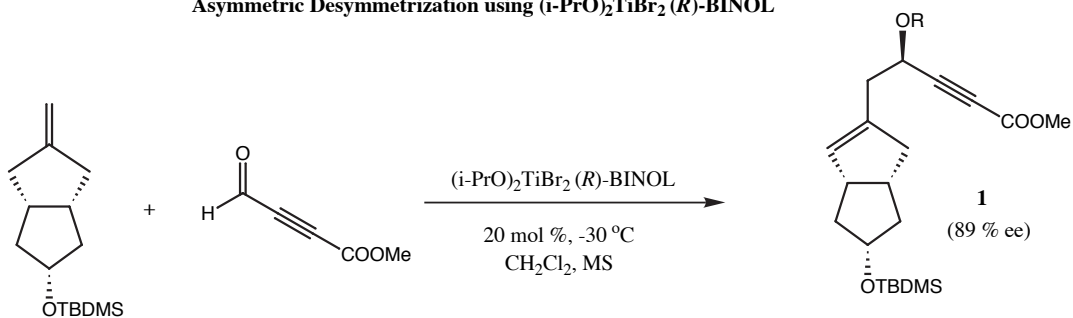
(i-PrO)₂TiBr₂ (R)-BINOL Catalyzed Ene Reaction : Other Enophiles



Enophile	n=	% Yield	% ee
	0	85	87
	1	70	94
	0	80	72
	1	60	86

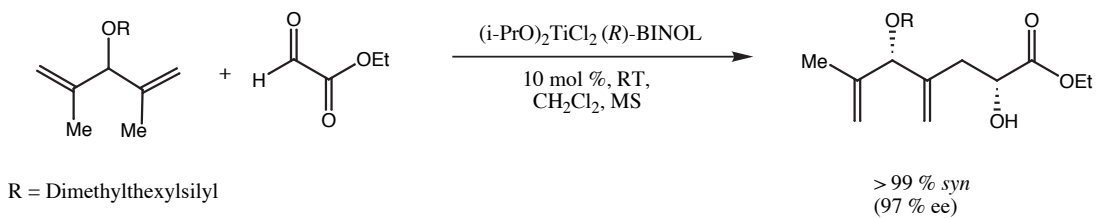
Mikami, *TL*, **1996**, 47, 8515.

Asymmetric Desymmetrization using (i-PrO)₂TiBr₂ (R)-BINOL

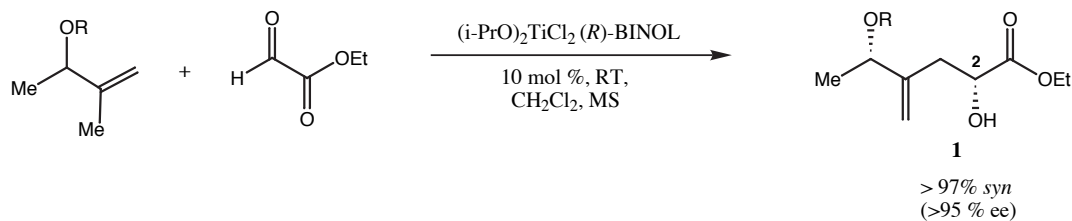


Mikami, TL, **1996**, 47, 8515.
Mikami, Synlett, **1995**, 29.

Asymmetric Desymmetrization / Resolution using (i-PrO)₂TiCl₂ (R)-BINOL



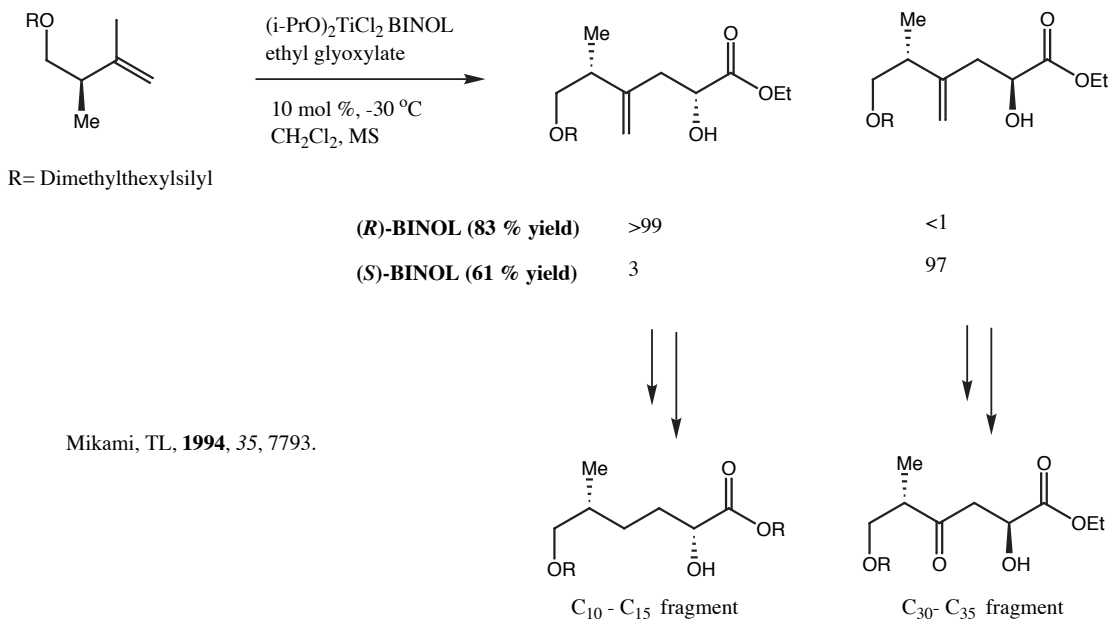
R = Dimethylhexylsilyl



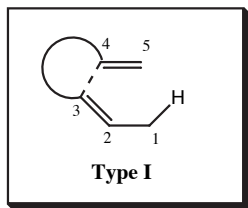
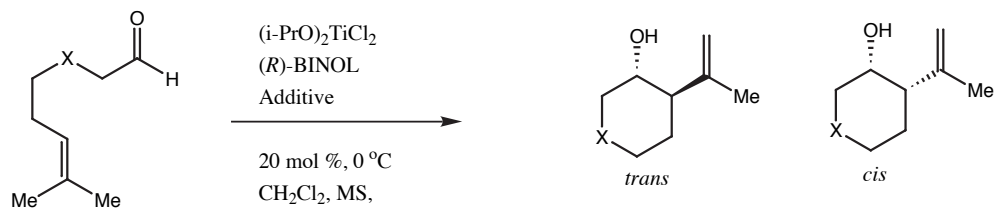
	Catalyst	Product
	(i-PrO) ₂ TiCl ₂ (S)-BINOL	<i>ent</i> -1 (>99 % <i>syn</i> , 71 % yield)
	(i-PrO) ₂ TiCl ₂ (R)-BINOL	<i>ent</i> -1 (50 : 50 at C-2, 31 % yield)

Mikami, Annual Meeting of the Chemical
Society of Japan, **1990** and **1991**.
See : Mikami, Synlett, **1992**, 255.

Synthesis of C₁₀ - C₁₅ and C₃₀- C₃₅ fragments of Rapamycin



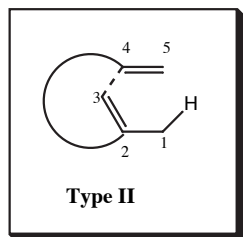
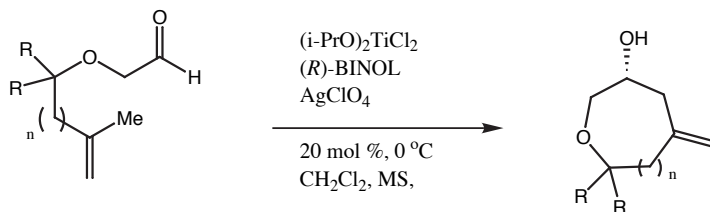
(*i*-PrO)₂Ti(ClO₄)₂ (*R*)-BINOL Catalyzed
{3, 4} *exo, exo* Intramolecular Ene Reaction



X =	Additive	time	% Yield	Ratio <i>trans</i> : <i>cis</i>	<i>trans</i> % ee
O	none	24 h	73	47 : 53	70
O	AgClO ₄	24 h	50	80 : 20	84
-CH ₂ -	AgClO ₄	48 h	66	69 : 31	55

Mikami, TL, **1991**, 32, 6571.
Mikami, *Tet. :Asymm.*, **1991**, 2, 1403.

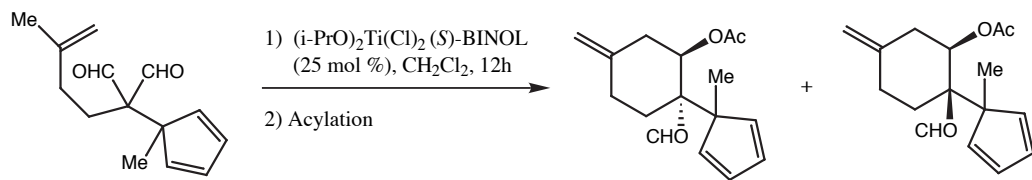
**(i-PrO)₂Ti(ClO₄)₂ (*R*)-BINOL Catalyzed
{2, 4} *exo, exo* Intramolecular Ene Reaction**



n=	R=	% yield	% ee
0	H or Me	NR	--
1	H	43	91
1	Me	40	82

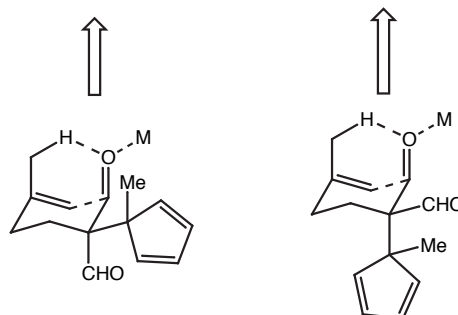
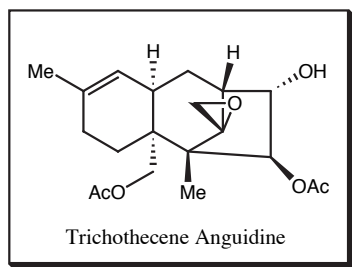
Mikami, TL, **1991**, 32, 6571.
Mikami, Tet. :Asymm., **1991**, 2, 1403.

**(i-PrO)₂Ti(Cl)₂ (*S*)-BINOL Catalyzed
{2, 4} *exo, exo* Intramolecular Ene Reaction**



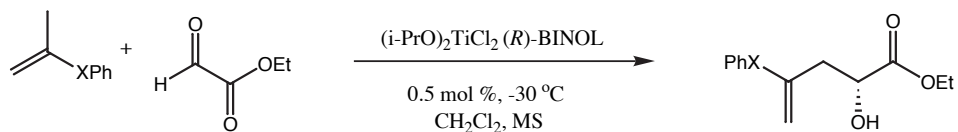
4.5 (38 % ee) :

1

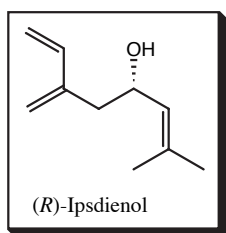
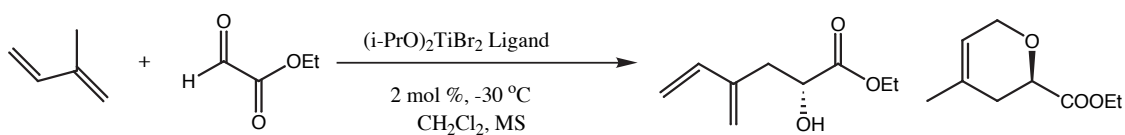


Ziegler, JACS, **1990**, 112, 2749.

Approaches toward Ipsdienol



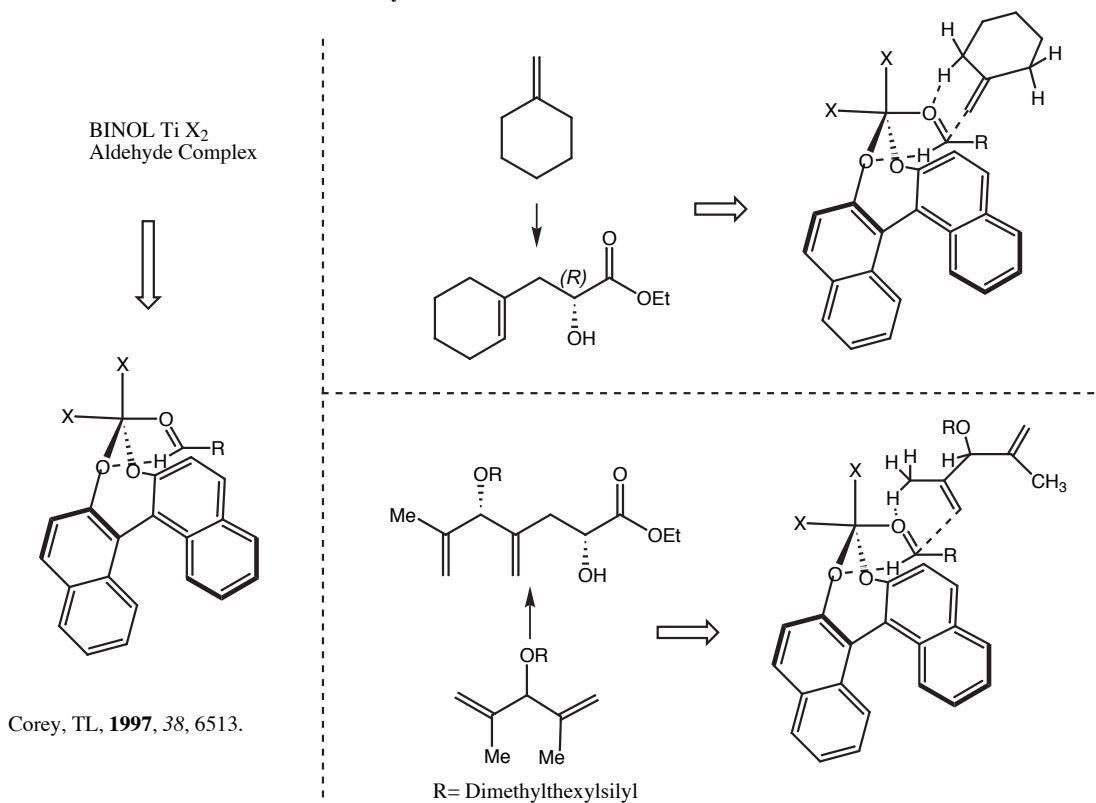
X = S	X = Se
94 % yield	95 % yield
>99 % ee	>99 % ee



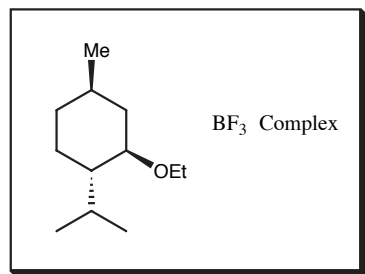
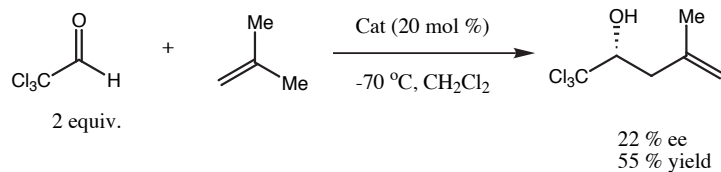
Ligand	Yield	Product Ratio	
		Ene	Hetero D. A.
BINOL	94	79 (97 % ee)	21
	84	92 (>99 % ee)	8

Mikami, JCS CC, **1995**, 2391.
Mikami, JCS CC, **1993**, 327.

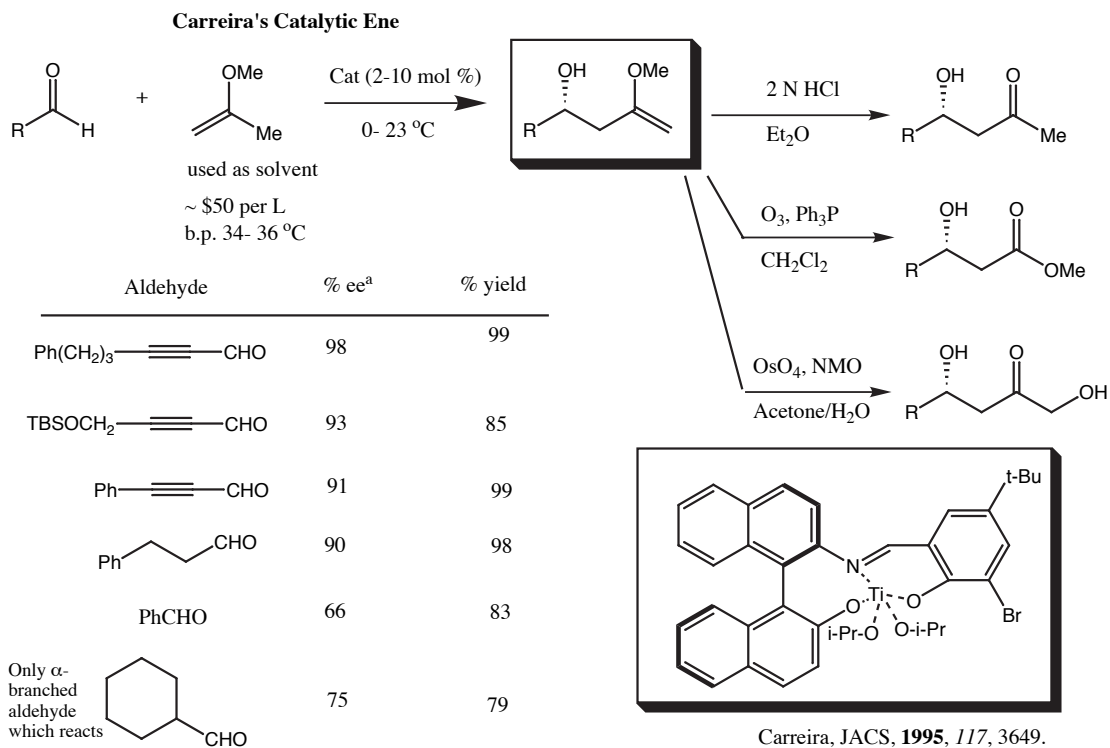
Corey's Model for Ti BINOL Ene Reactions



BF₃ Menthylethyl Etherate catalyzed Ene reaction

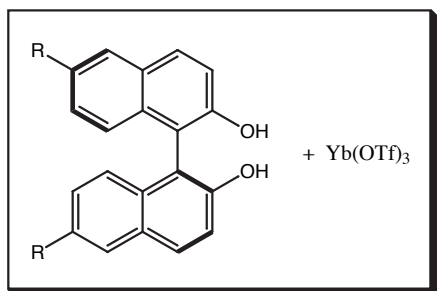
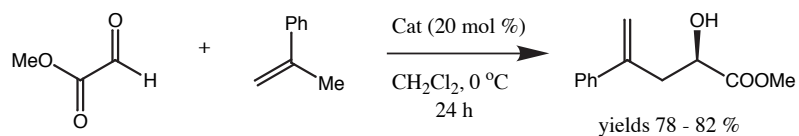


Demir, *Syn. Comm.* **1994**, 24, 137.



^a % ee detrmind by NMR analysis of (S)-MPTA ester of methyl ketone

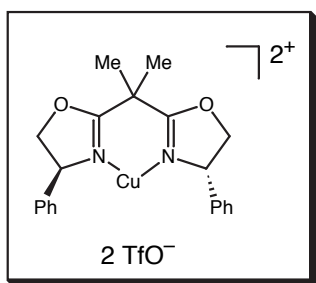
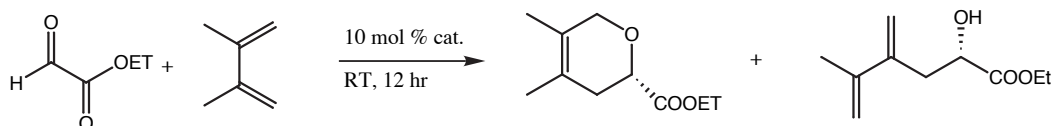
Yb(OTf)₃ BINOL Catalyzed Ene Reaction



Ligand R=	% ee
H	12
Br	38
Ph	25
$\text{-}\overset{\text{R}}{\text{C}}\equiv\text{C-TMS}$	29

Qain, TL, **1997**, 38, 6721.

Jorgensen's Ene byproducts



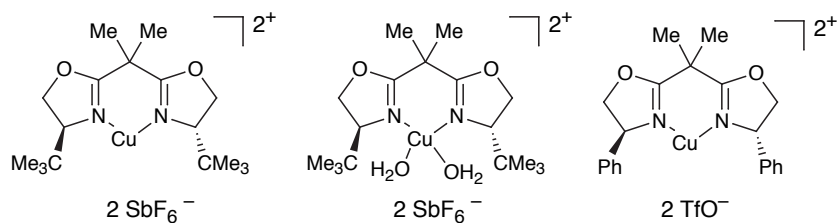
Solvent	Diels-Alder % ee	Ene Product % ee	DA :Ene Ratio
CH ₂ Cl ₂	85	83	1 : 1.8
CH ₃ NO ₂	90	78	1 : 0.8

Jorgensen, *Tetrahedron*, **1996**, 52, 7321.

For optimization of hetero Diels-Alder reaction products
See: Jorgensen, JCS PT 2, **1997**, 1183.

Work from the Evans Groups

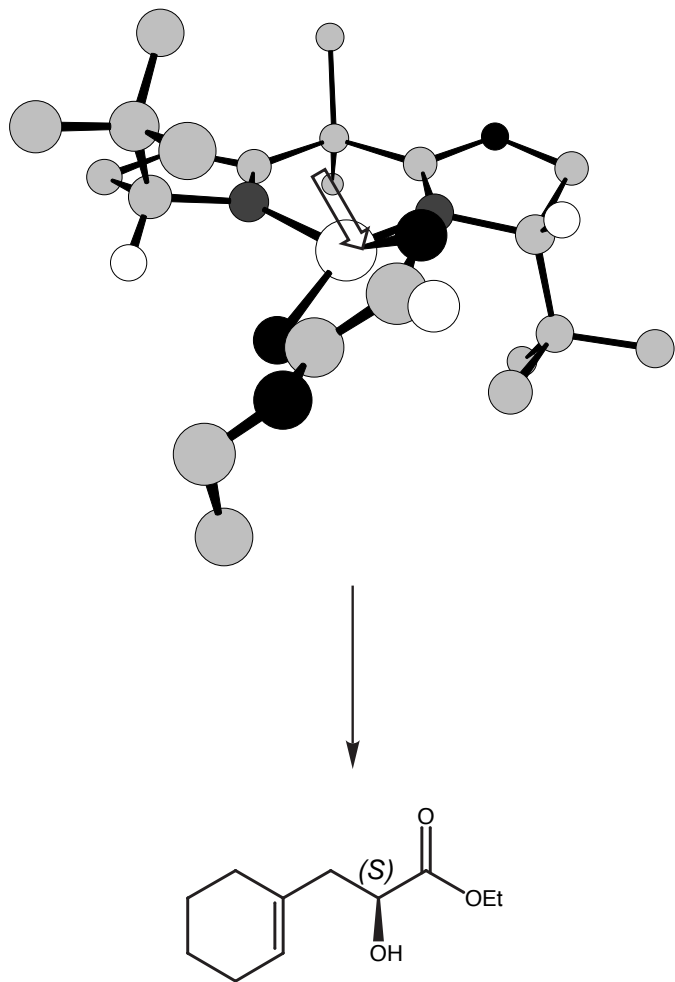
"C₂-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Carbonyl-Ene Reactions with Glyoxylate and Pyruvate Esters". Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojtkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936-7943.



olefin	product ^a	catalyst	mol%	% yield	% ee	
		2	1	90	97 (<i>S</i>)	
		3	10	99	87 (<i>R</i>)	
		2	1	83	96 (<i>S</i>)	
		3	10	92	92 (<i>R</i>)	
		2	1	97	93 (<i>S</i>)	
		3	10	99	89 (<i>R</i>)	
		2	1	95	96 (<i>S</i>)	
		3	10	97	76 (<i>R</i>)	
		2	1	89	96 (<i>S</i>)	Regiochemistry 75 : 25 90 : 10
		3	10	81	92 (<i>R</i>)	
		2	1	72	96 (<i>S</i>)	one regioisomer
		3	10	85	91 (<i>R</i>)	
		2	10	62	98 (<i>S</i>)	one regioisomer
		3	2	88	92 (<i>R</i>)	
		1	10	95	98 (<i>S</i>)	<i>exo:endo</i> 86:14 95:5
		3	10	70	94 (<i>R</i>)	
		1	10	96	98 (<i>S</i>)	<i>E:Z</i> 96 : 4

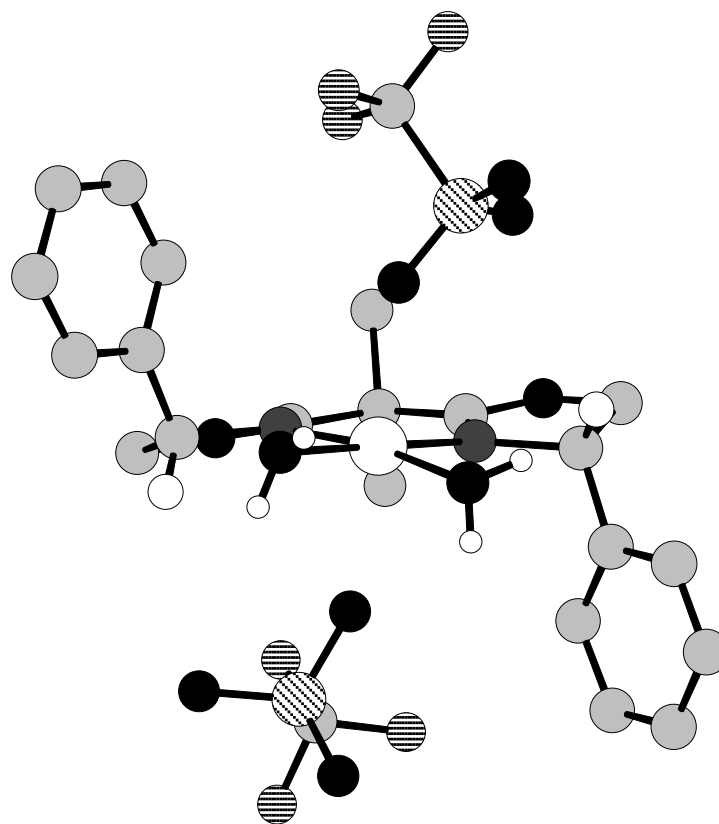
Origins of Enantioselectivity in Cu Box Ene Reactions

(*S,S*)-*t*-Bu Box Cu Glyoxylate (PM3tm)



However, (*S,S*)-Ph-Box Cu (OTf)₂ gives (*R*) configured alcohols:

Tetrahedral Cu center??
Jorgensen, JOC, 1995, 60, 5757.



(*S,S*)-Ph Box Cu (OTf)₂(H₂O)₂ X-ray

Quotes for the Day

"In the last third of his life, there came over Laslo Jamf-so it seemed to those who from out of the wood lecture halls watched his eyelids slowly granulate, spots and wrinkles grow across his image, disintegrating it towards old-age hostility, a strangely personal hatred, for the covalent bond."

Thomas Pynchon, "Gravity's Rainbow"

"Faced with the choice between changing one's mind and proving that there is no need to do so, almost everyone gets busy with the proof. "

John Kenneth Galbraith

Chemistry 206

Advanced Organic Chemistry

Handout-27A

**An Organizational Format for the Classification of
Functional Groups. Applications to the
Construction of Difunctional Relationships**

D. A. Evans

**Wednesday ,
November 19, 2003**

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 27

Functional Group Classification Scheme for Polar Bond Constructions

- 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. (Handout)*

"Methods of Reactivity Umpolung."
D. Seebach *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 239. *(Handout)*

"Nitroaliphatic Compounds—Ideal Intermediates in Organic Synthesis" Seebach,
D. et. al, *Chimia*, **1979**, 33, 1-18. *(Handout)*

D. A. Evans

Wednesday,
November 19, 2003

Papers of Historical Interest:

"Arthur Lapworth: The Genesis of Reaction Mechanism."
M. Saltzman *J. Chem. Ed.* **1972**, 49, 750. *(Handout)*

"A Theoretical Derivation of the Principle of Induced Alternate Polarities."
A. Lapworth *J. Chem. Soc.* **1922**, 121, 416.

"The Electron Theory of Valence as Applied to Organic Compounds."
J. Steiglitz *J. Am. Chem. Soc.* **1922**, 44, 1293.

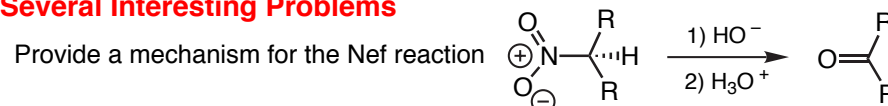
Monographs:

Hase, T. A. "Umpoled Synthons. A Survey of Sources and Uses in Synthesis";
John Wiley & Sons, Inc.: New York, 1987.

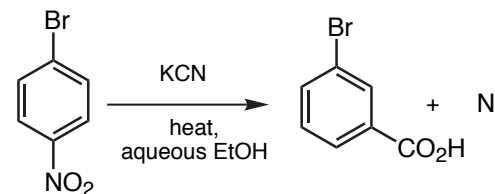
Ho, T.-L. "Polarity Control for Synthesis"; John Wiley & Sons, Inc.: NY, 1991.

Ono, N., "The Nitro Group in Organic Synthesis", Wiley-VCH, 2001

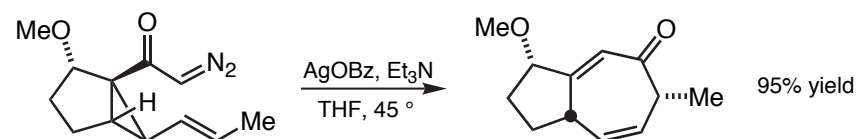
Several Interesting Problems



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.



Stoltz and co-workers recently reported the interesting rearrangement illustrated below (*JACS* **2003**, 125, 13624). Please provide a mechanism for the illustrated transformation. Your answer should include clear 3-D drawings where relevant. the answer may be found in the database.



Required Reading:

"An Organizational Scheme for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships."

D. A. Evans *Unpublished manuscript*.

"Methods of Reactivity Umpolung."

D. Seebach *Angew. Chem. Int. Ed. Engl.* **1979**, 18, 239.

"Nitroaliphatic Compounds—Ideal Intermediates in Organic Synthesis"

Seebach, D. et. al, *Chimia*, **1979**, 33, 1-18.

Papers of Historical Interest:

"Arthur Lapworth: The Genesis of Reaction Mechanism."

M. Saltzman *J. Chem. Ed.* **1972**, 49, 750.

"A Theoretical Derivation of the Principle of Induced Alternate Polarities."

A. Lapworth *J. Chem. Soc.* **1922**, 121, 416.

"The Electron Theory of Valence as Applied to Organic Compounds."

J. Steiglitz *J. Am. Chem. Soc.* **1922**, 44, 1293.

"Displacement of Aliphatic Nitro Groups by Carbon & Heteroatom Nucleophiles." R. Tamura, A. Kamimura, N. Ono *Synthesis* **1991**, 423.

"Functionalized Nitroalkanes as Useful Reagents for Alkyl Anion Synthons." G. Rosini, R. Ballini *Synthesis* **1988**, 833.

"Conjugated Nitroalkenes: Versatile Intermediates in Organic Synthesis."

A. G. M. Barrett, G. G. Graboski *Chem. Rev.* **1986**, 86, 751.

Monographs:

Hase, T. A. "Umpoled Synthons. A Survey of Sources and Uses in Synthesis"; John Wiley & Sons, Inc.: New York, 1987.

Ho, T.-L. "Polarity Control for Synthesis"; John Wiley & Sons, Inc.: New York, 1991.

Arthur Lapworth (1872–1941)

Lapworth was among the first to understand and conceptualize the effect of heteroatomic substituents on the reactivity of individual carbon centers, and how this effect is propagated through the carbon framework of organic molecules.

Lapworth's Theory of Alternating Polarities:

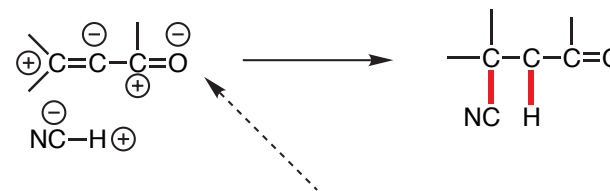
"Latent Polarities of Atoms and Mechanism of Reaction, with Special Reference to Carbonyl Compounds."

A. Lapworth *Mem. Manchester. Lit. Phil. Soc.* **1920**, 64 (3), 1.

"The addition of electrolytes to the carbonyl compound invariably proceeded as if the carbon were more positive than the oxygen atom, and invariably selected the negative ion; for example:"



"The extension of the influence of the directing, or "key atom," over a long range seems to require for its fullest display the presence of double bonds, and usually in conjugated positions...."

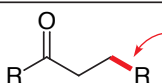


The "key atom" is the one with the most electronegative character, in this case the carbonyl oxygen.

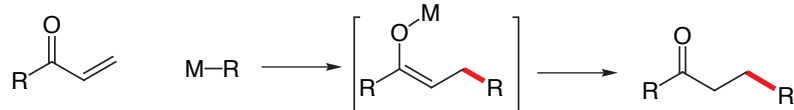
anionoid/cationoid -----> nucleophilic/electrophilic

The Lapworth polarity designations can be used to form the basis of a functional group classification scheme.

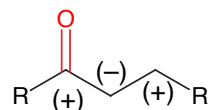
- Polar rxns form the basis set of bond constructions in synthesis
- Generalizations on conferred site reactivity will therefore be important

Given this target  and the desire to form this bond

The functional group =O "dictates" the following bond construction

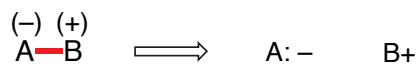


- Conferred site reactivity of =O



Charge Affinity Patterns

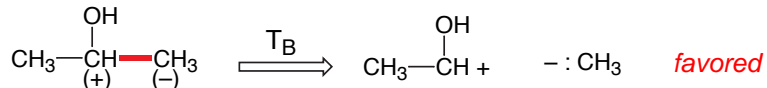
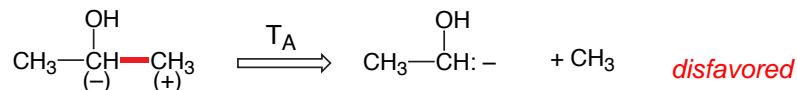
- Use the descriptors (+) and (-) to denote the polar disconnections shown.



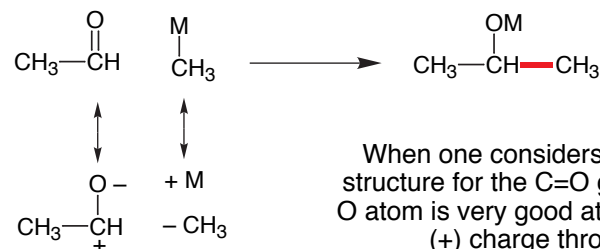
- In the transforms illustrated above, symbols (+) & (-) are used to denote the particular polar transform illustrated.

In the present case there is NO INTRINSIC BIAS in favoring one transform over the other.

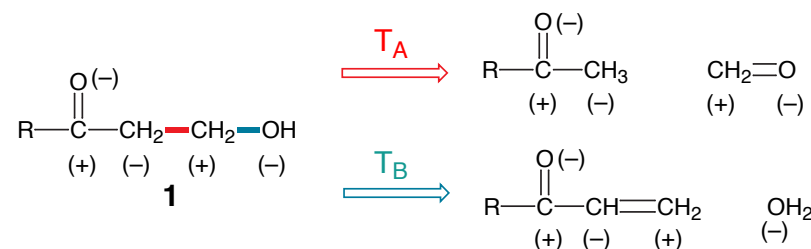
Let's now add an OH functional group (FG) to propane at C-2 and see whether one creates a bias in the favoring of one or the other transforms:



- The actual reaction associated with this transform is the addition of organometals to carbonyl substrates.

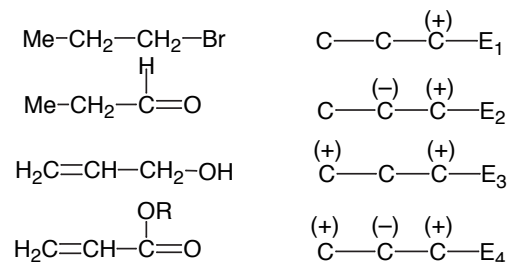


- Consider polar disconnections of the illustrated β -hydroxy ketone **1**:

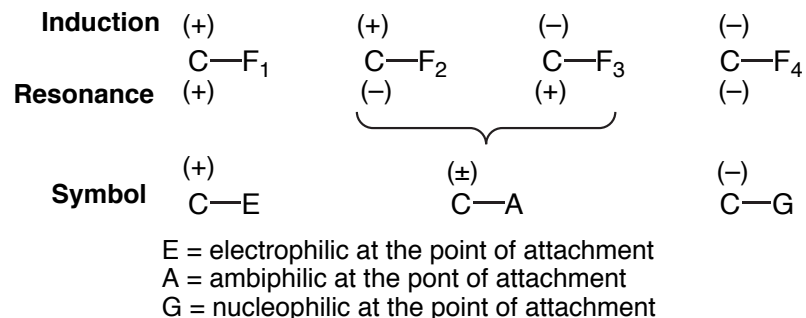


It is evident that the heteroatom functional groups, =O and -OH, strongly bias the indicated polar disconnections.

Charge Affinity Patterns of Common Functional Groups



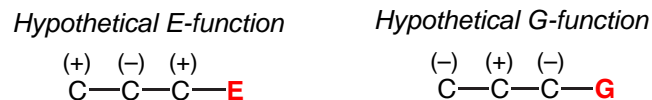
Functional groups activate the carbon skeleton at the point of attachment by either induction & resonance.



For simplicity, we will designate three FG classes according to the designations provided above.

E & G-Functions:

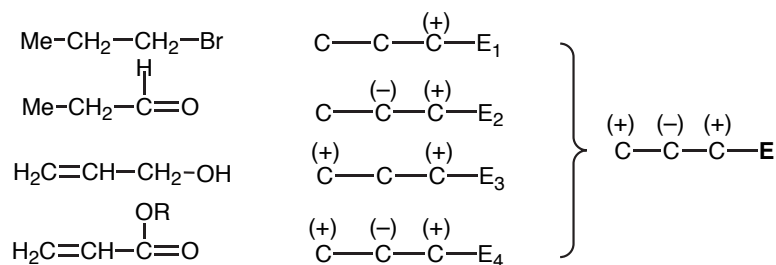
To organize activating functions into common categories it is worthwhile to define "hypothetical" functional groups E, and G, having the charge affinity patterns denoted below.



Given the appropriate oxidation state of the carbon skeleton, such functional groups confer the indicated polar site reactivity patterns toward both electrophiles and nucleophiles.

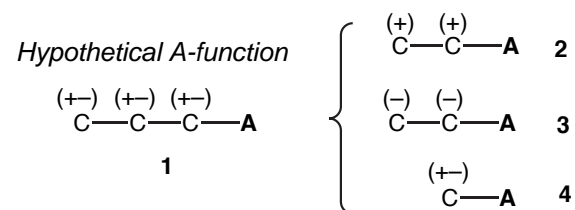
Any FG that conforms either to the ideal charge affinity pattern or a sub-pattern thereof will thus be classified as either an E- or G-function.

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.

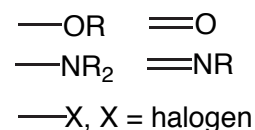


FG-Classification Rules

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: (-)C—G

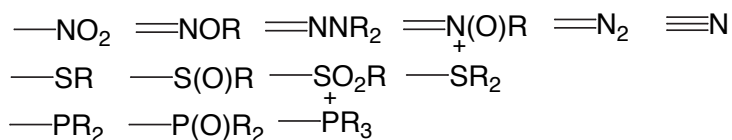
Typical G-class functions are the Group I-IV metals whose reactivity patterns, falls into a subset of the idealized G-FG 5.



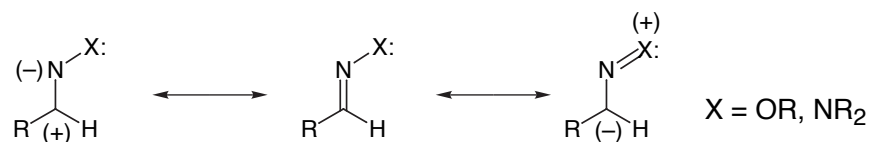
Common A-Functions: Symbol: (±)C—A

A-functions are usually more structurally complex FGs composed of polyatomic assemblages of nitrogen, oxygen and their heavier Group V and VI relatives (P, As, S, Se).

Typical A-functions, classified by inspection, are provided below



■ These FG's are capable of conferring both (+) and (-) at point of attachment.

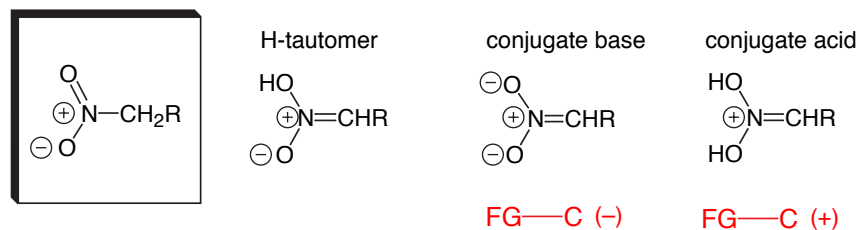


Remarkably, the dual electronic properties of oximes were first discussed by Lapworth in 1924 before the modern concepts of valence bond resonance were developed.

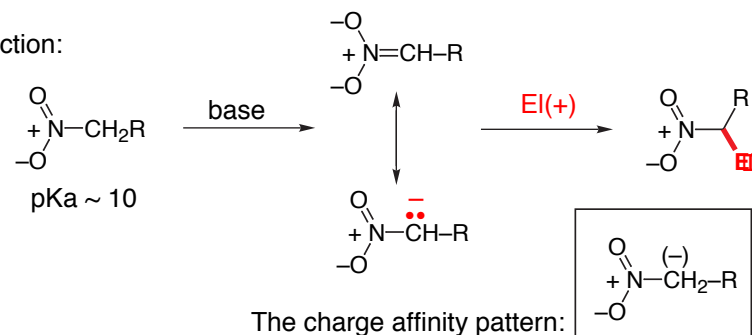
Lapworth, A. *Chemistry and Industry* **1924**, 43, 1294-1295.

The Nitro Functional Group

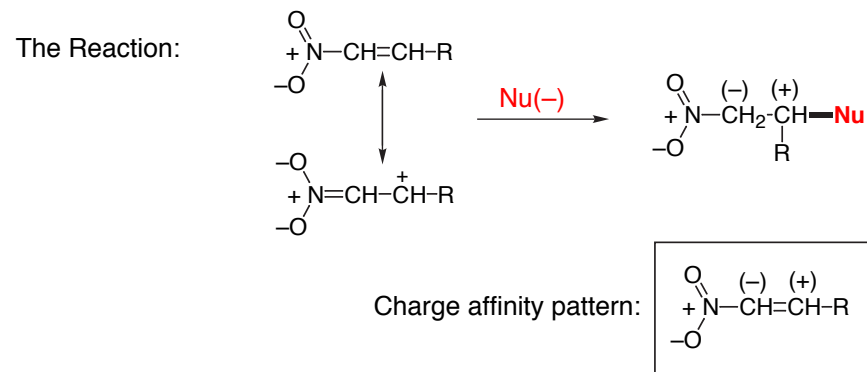
As an example, the class designation of the nitro function is determined by an evaluation of the parent function, its nitronic acid tautomer, as well as conjugate acid and base.



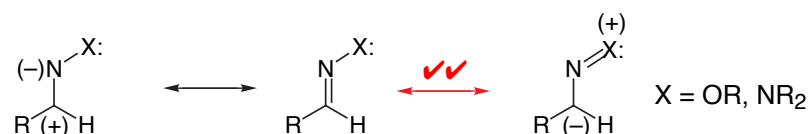
The Reaction:



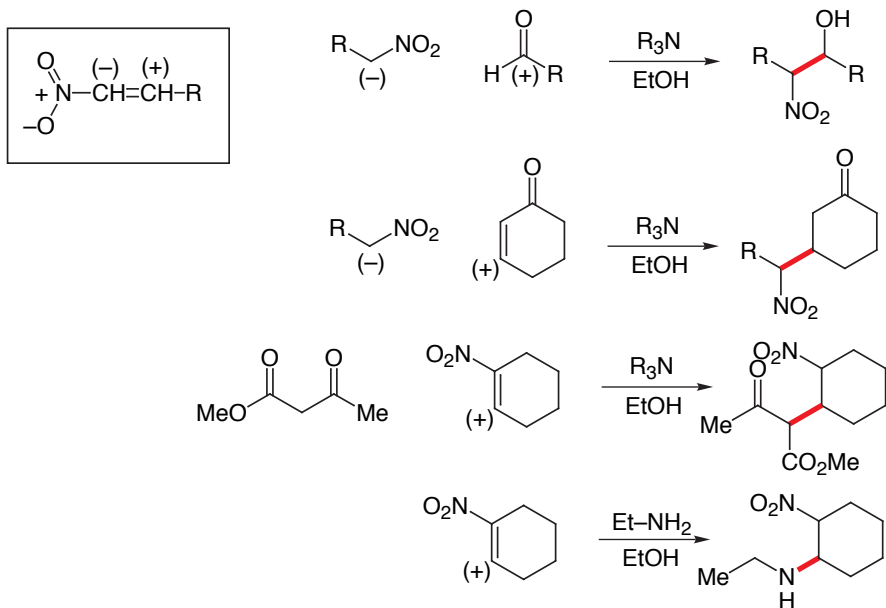
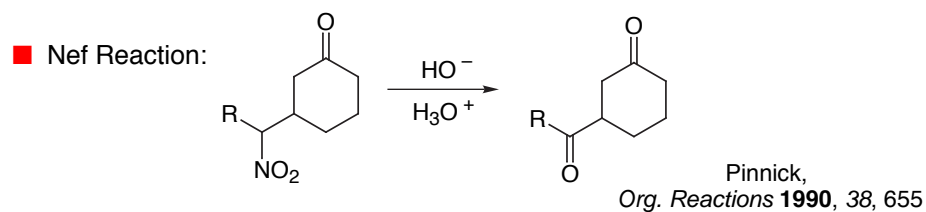
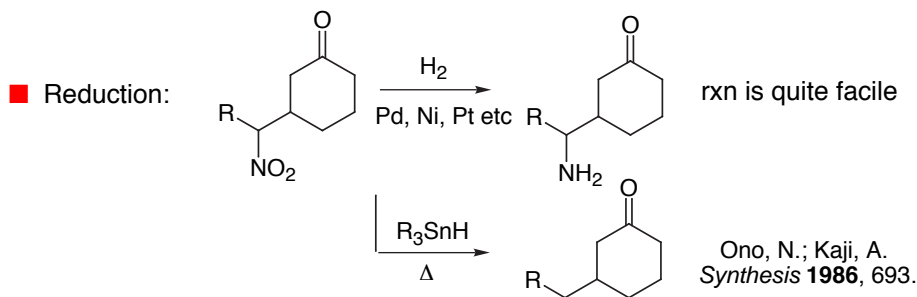
■ This reactivity pattern may be extended via conjugation:



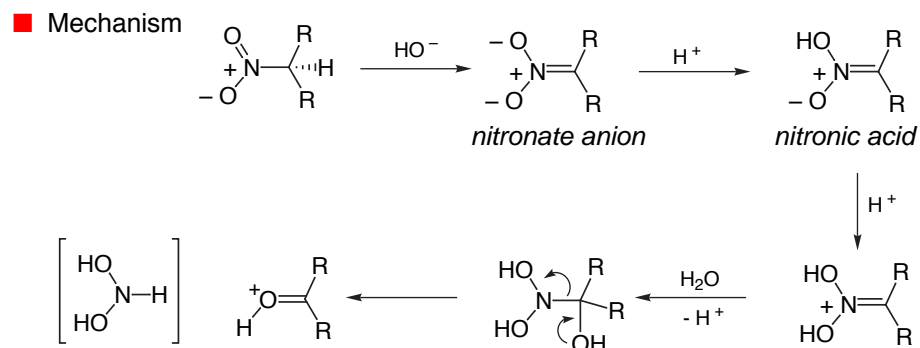
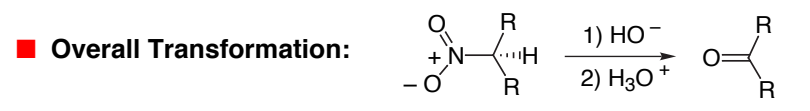
■ The resonance feature which has been exploited:



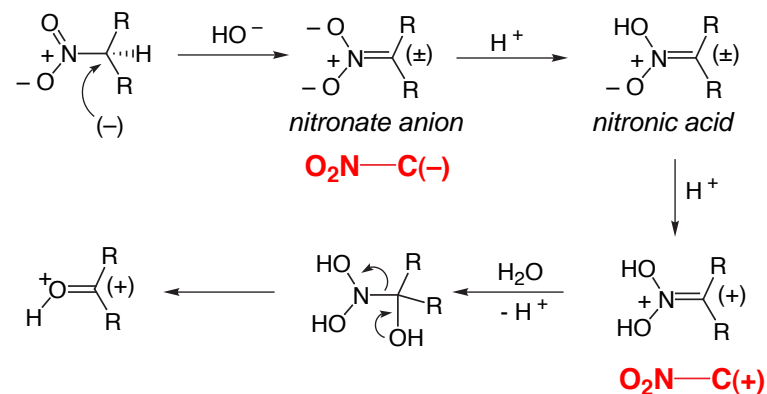
Some Reactions of the Nitro Functional Group

Important Transformations of the $-\text{NO}_2$ Functional Group

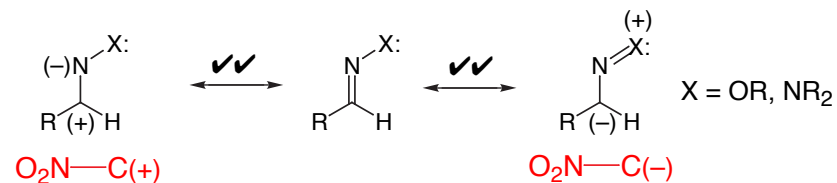
The Nef Reaction

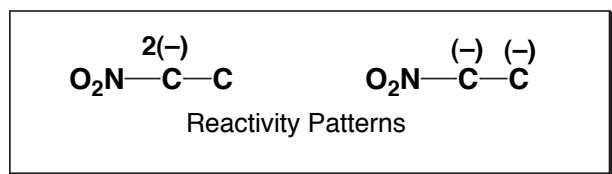
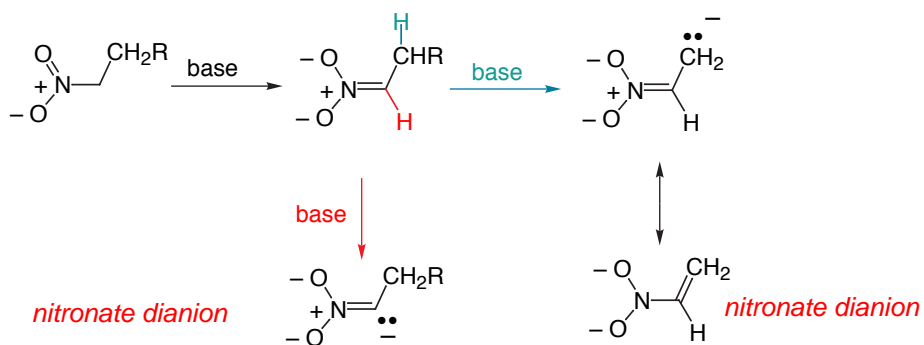
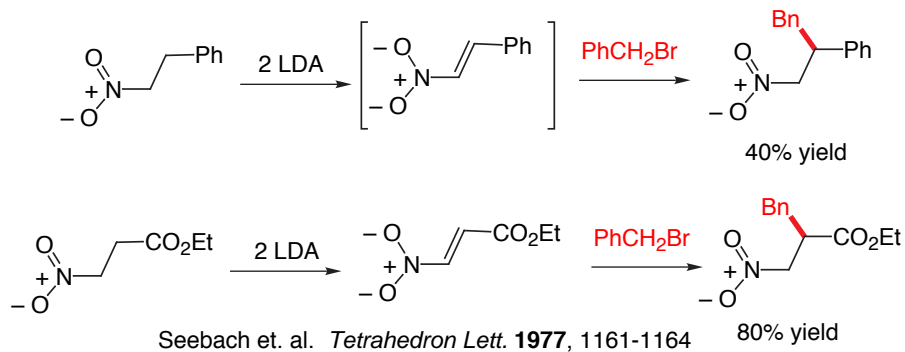
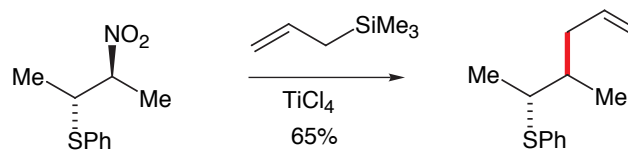
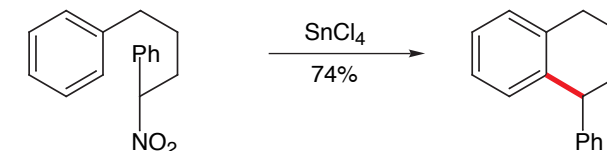
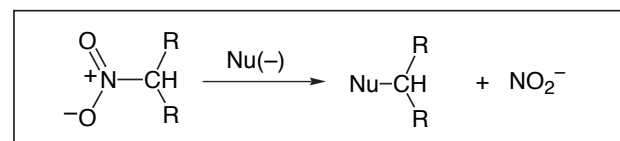
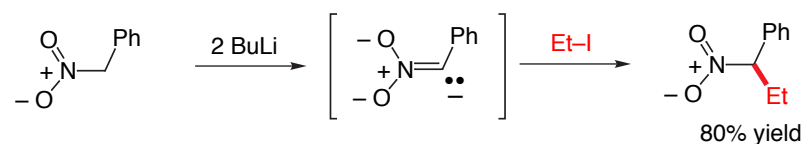
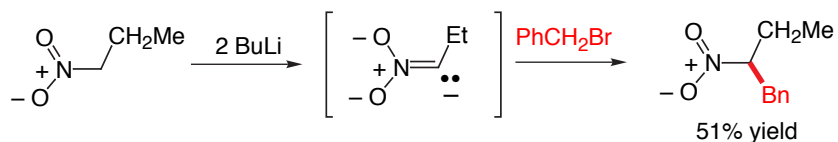


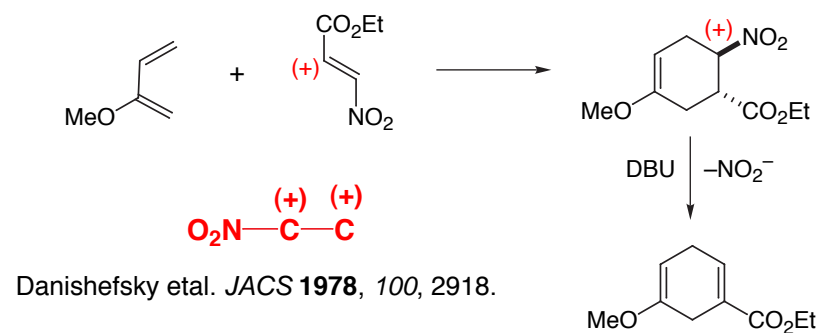
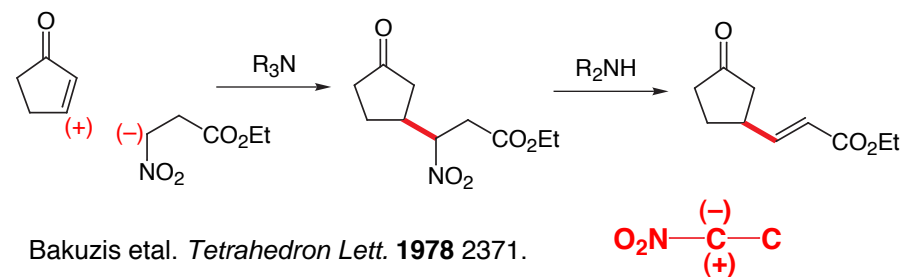
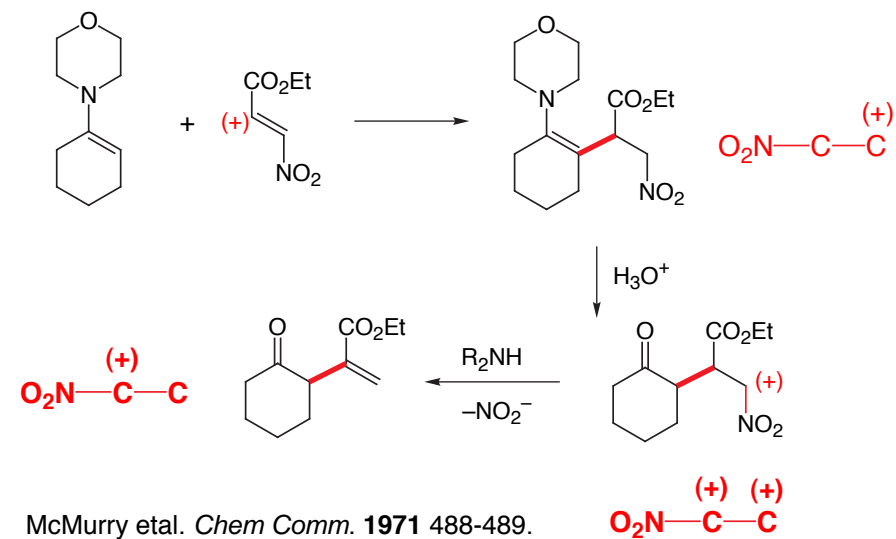
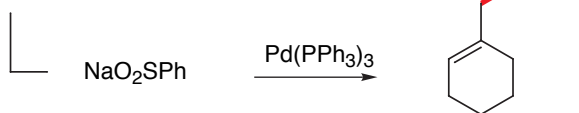
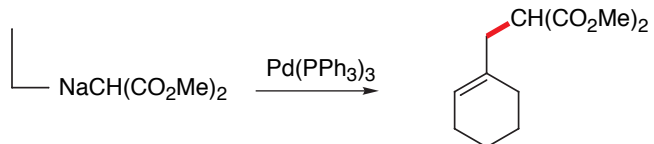
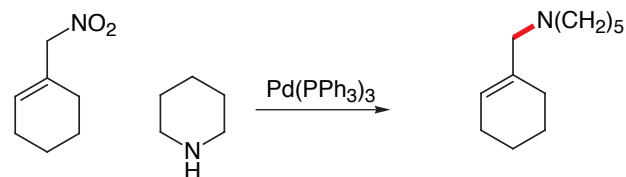
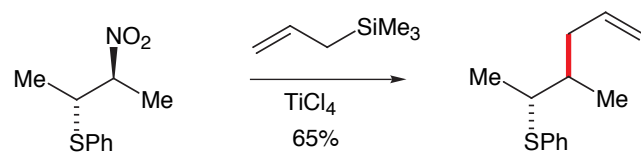
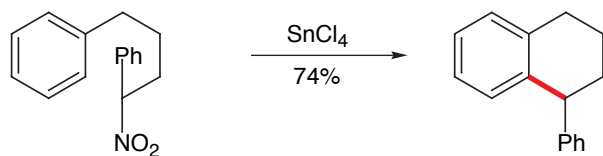
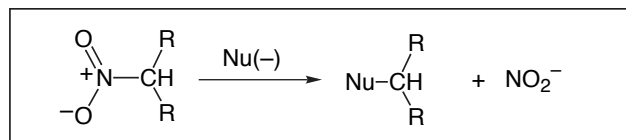
The charge affinity patterns represented



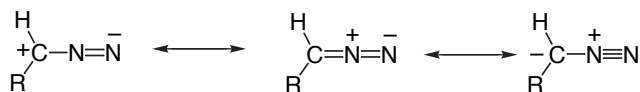
The resonance features which have been exploited:



Other Nonalternate Behavior of $-\text{NO}_2$ FGSeebach et. al. *Tetrahedron Lett.* **1977**, 1161-1164Representative examples: $\text{O}_2\text{N}-\overset{(-)}{\text{C}}-\overset{(-)}{\text{C}}$  $-\text{NO}_2$ 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: $\text{O}_2\text{N}-\text{C}(+)$ Representative examples: $\text{O}_2\text{N}-\overset{2(-)}{\text{C}}$ 

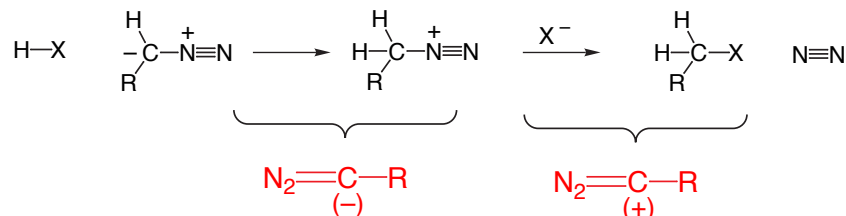
-NO₂ As a Leaving GroupRepresentative examples: **O₂N-C(+)**

The Diazo Functional Group



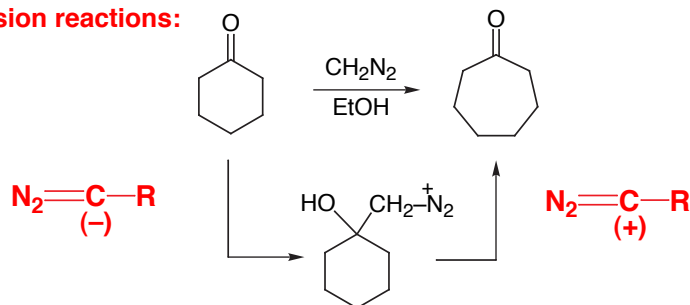
■ Both (+) and (-) reactivity patterns suggested by resonance structures

■ Rxns with acids:



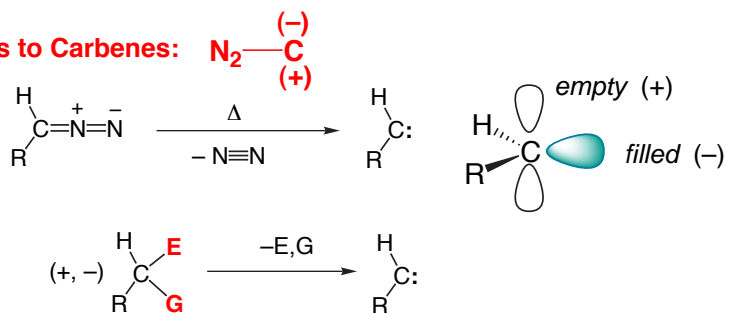
■ Initiating reactivity is (-); subsequent reactivity is (+)

■ Ring expansion reactions:



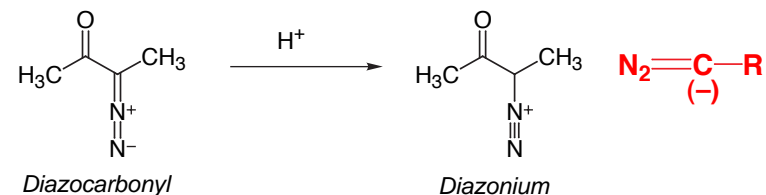
Restriction: Starting ketone must be more reactive than product ketone

■ Precursors to Carbenes: $\text{N}_2=\text{C}^{\ominus}-\text{R}^{\oplus}$



Acid Catalyzed Reactions of Diazo Compounds

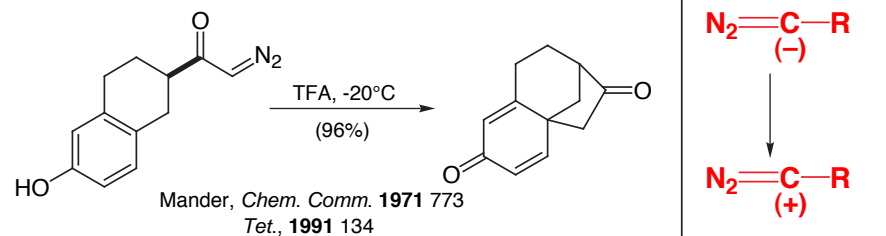
Review: Smith, Tet. 1981 2407



Common acids include $\text{BF}_3 \cdot \text{OEt}_2$, HBF_4 , TFA, etc.

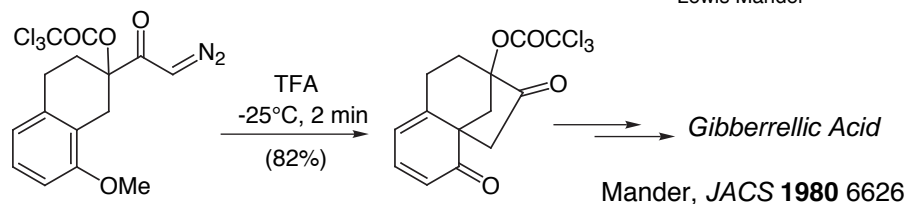
Mechanism of activation is unclear for both Lewis and protic acids; activation may occur by protonation on C or O

Acid-Catalyzed Reactions

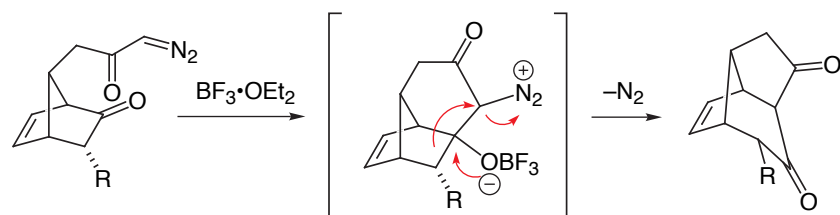


"Having become familiar with the peculiarities of diazoketone chemistry while preparing [other compounds] (and, I might add, inured to handling uncomfortably large quantities of diazomethane), it occurred to us that we might be able to substitute a diazo group for bromine."

Lewis Mander

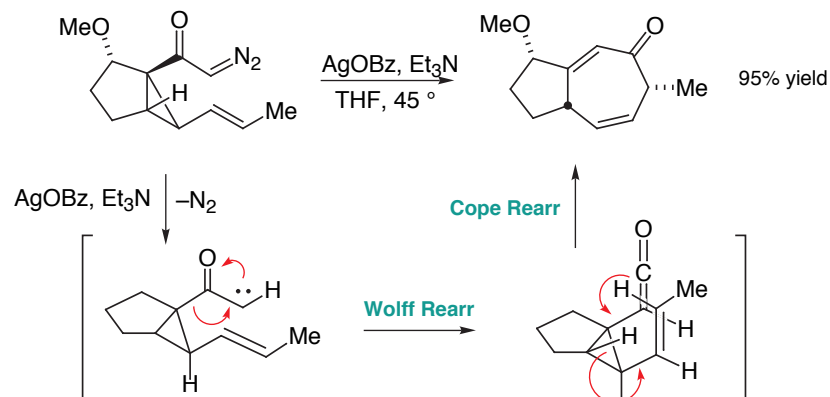


Diazo-Carbonyl Insertions:

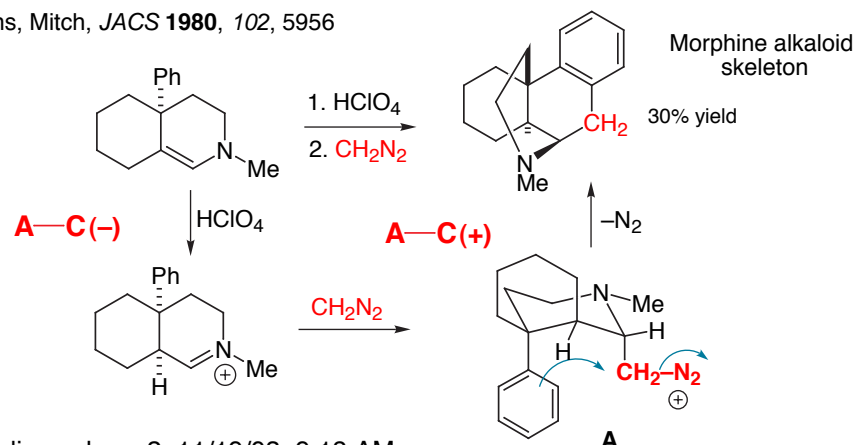
Mander, *Aust. J. Chem.* **1979** 1975

Wolff Rearrangements

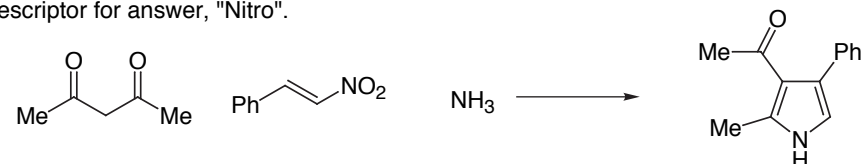
Web Problem 332. Stoltz and co-workers recently reported the interesting rearrangement illustrated below (*JACS* **2003**, 125, 13624).



Diazo-mediated Ring Construction:

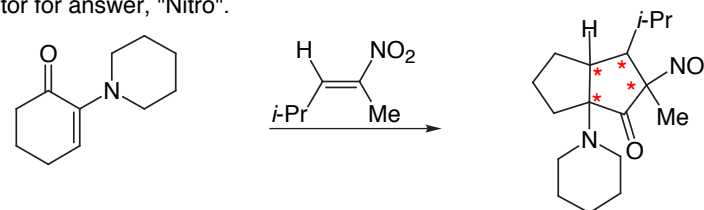
Evans, Mitch, *JACS* **1980**, 102, 5956

Web Problem 109. The following is a general reaction for the formation of pyrroles. In this condensation, any of the three reaction constituents may be widely varied. (Ono, "The Nitro Group in Organic Synthesis" Wiley-VCH, **2001**. Chapter 10, pp 326-328). Since it is not clear what the "inorganic" reaction product is, provide us with anything that is mechanistically sound using the reagents illustrated. Key descriptor for answer, "Nitro".

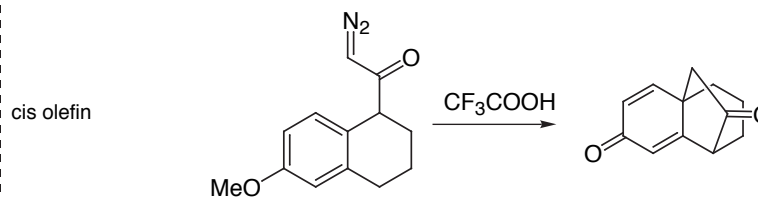


In the space below provide a plausible mechanism for this transformation.

Web Problem 188. Provide a mechanism for the following reaction that predicts the stereochemistry at the starred (*) carbon atoms (Valentin, *TL*, **1983**, 1621). Key descriptor for answer, "Nitro".



Web Problem 150. Provide a concise mechanism for the indicated reaction in the space below. Key descriptor for answer, "Carbene".



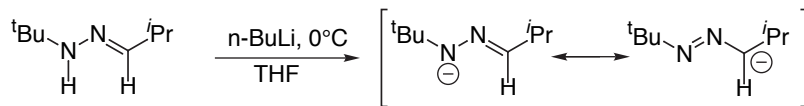
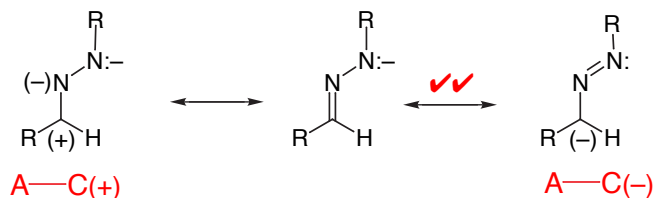
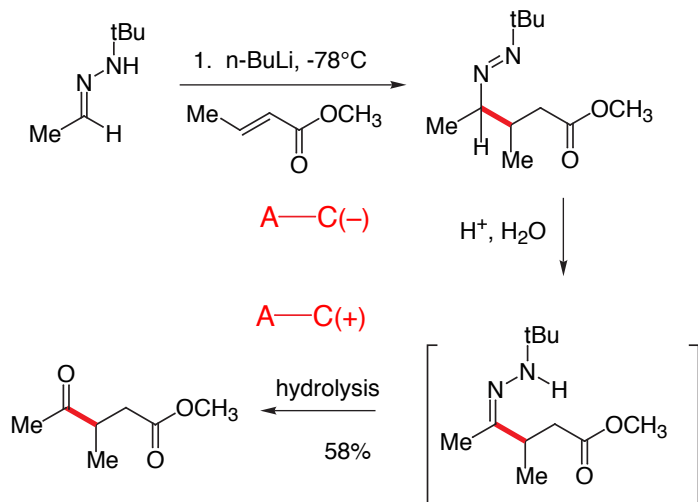
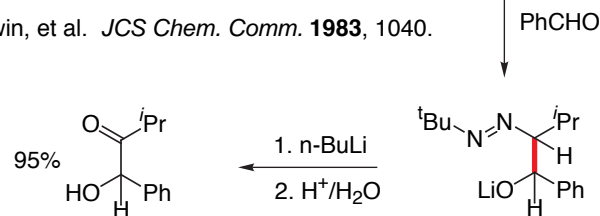
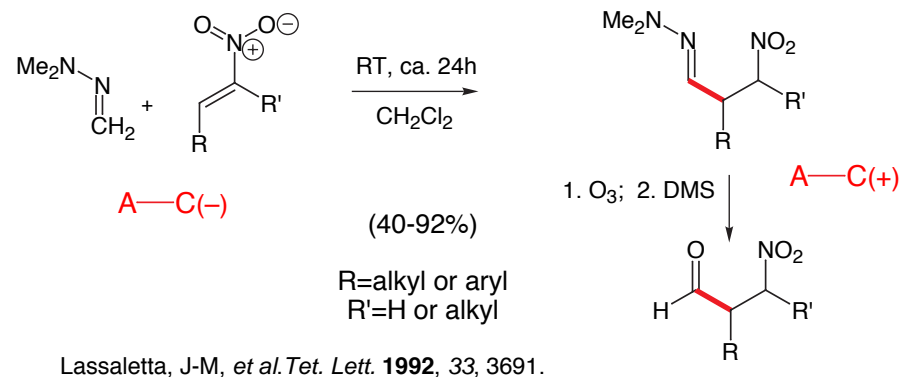
Web Problem 13. The following transformation was recently reported by Stoltz (*J. Am. Chem. Soc.* **2002**, 124, 12426). In addition to the illustrated product, styrene and dinitrogen are produced as by-products in this transformation. Key descriptor for answer, "Carbene".



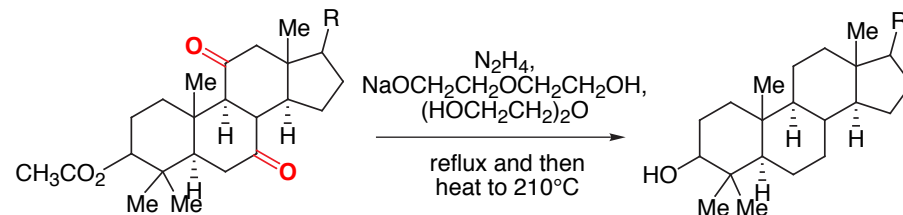
anti diastereoselection > 20:1, 80% yield

Provide a plausible mechanism for this transformation and identify intermediate 1. Your mechanism should provide a rationalization for the product stereochemical relationship.

Hydrazone Anions: A useful Reversed Polarity Equivalent

J. E. Baldwin, et al. *JCS Chem. Comm.* **1983**, 1040.J. E. Baldwin, et al. *JCS Chem. Comm.* **1984**, 1095.

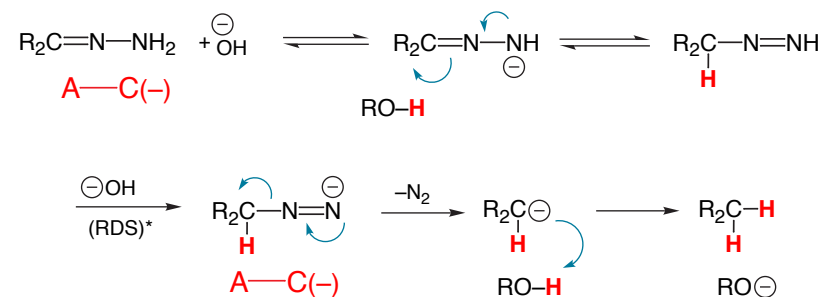
Wolff-Kishner Reduction Procedures

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



Chemistry 206

Advanced Organic Chemistry

Handout-27A

**An Organizational Format for the Classification of
Functional Groups. Applications to the
Construction of Difunctional Relationships**

D. A. Evans

**Wednesday ,
November 19, 2003**

An Organizational Format for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships

D. A. Evans

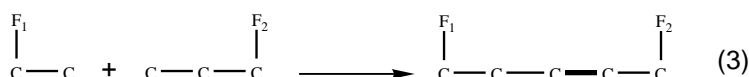
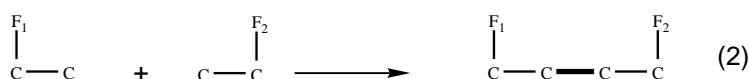
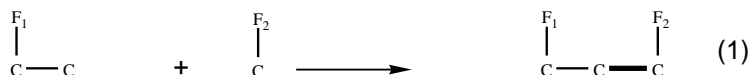
Department of Chemistry & Chemical Biology, Harvard University, Cambridge, MA, 02318

Introduction

Among the subdisciplines of chemistry the area of organic synthesis is probably the least organized in terms of unifying concepts and general methodology. This conclusion has been made quite obvious by the relative scarcity of critical monographs covering this important topic.¹ The wide structural diversity of organic molecules, the vast abundance of organic reactions, and the restrictions imposed upon these reactions when applied to the synthesis of a complex structure all contribute to the magnitude of the problem of making generalizations in this area.

However difficult the overall task of explicitly defining *a priori* a total synthesis of an organic structure may be, there are certain simplifying features which can be developed to generate logical sets of potential synthetic pathways to a given molecular target. Some of the general guidelines which help to define this task have been outlined.² Recently, some of the problems associated with reducing synthetic design to a mathematical basis and the application of machine computation to synthetic analysis have been reported.^{3,4}

Difunctional Relationships. One aspect of the synthesis of any polyfunctional target structure deals with strategies associated with the construction of arrays of relationships between heteroatom functional groups which may be denoted as F₁, F₂, etc. The general reactions illustrated below simply represent the union of two monofunctional organic fragments where the functional groups F₁, F₂ provide the necessary activation for the coupling process. In these reactions, the oxidation states of the associated carbon fragments are purposely left undefined. In relating the generalized notation below to a real situation, if F₁-C-C were an enolate, Equation 1 might be used to represent a generalized aldol or Mannich reaction while equation 3 might represent a Michael reaction.

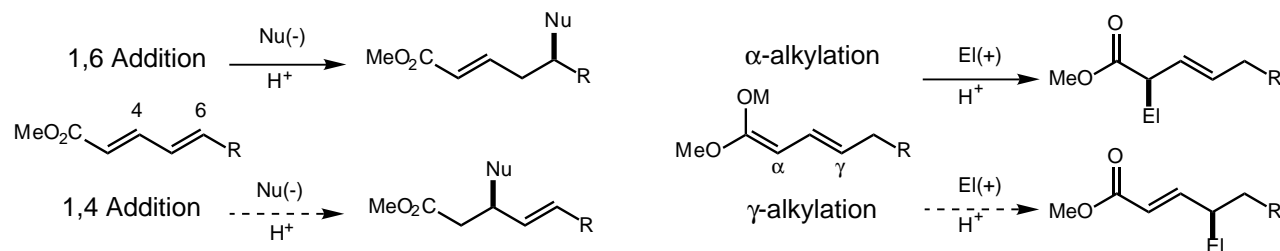


Henrickson has provided some useful generalizations on the construction of difunctional relationships which are worth summarizing. For example, he defines the **construction span** as the number of carbons linking F₁ and F₂. In the cases illustrated above, the product of the reaction illustrated in Equation 1 has a construction span of three. The **construction fragments** are then defined as the monofunctional reactants, such as F₁-C-C and F₁-C. *In general, construction spans are limited to six or less.* This is a consequence of the fact that the operational utility of a given functional group diminishes as it is removed

- 1) (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley, New York, 1979. (b) Fuhrhop, J.; Penzlin, G. *Organic Synthesis: Concepts, Methods, Starting Materials*; Verlag Chemie, Weinheim, 1983. (c) Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge Univ. Press, Cambridge, 1987. (d) *Organic Synthesis, The Disconnection Approach*; Wiley, New York, 1982. (e) Payne, C. A.; Payne, L.B. *How To Do An Organic Synthesis*; Allyn and Bacon., Boston, 1969. (f) Ireland, R. E. *Organic Synthesis*, Prentice-Hall, Inc., Englewood Cliffs, 1969.
- 2) (a) Corey, E. J. *Pure Appl. Chem.* **1967**, *14*, 19. (b) Corey, E. J. *Quart. Rev.* **1971**, *25*, 455.
- 3) (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 6487. (b) Ugi, I; Gillespie, P. *Angew. Chem. Int. Ed.* **1971**, *10*, 914. (c) Corey, E. J.; Wipke, W. T.; Cramer, III, R. D.; Howe, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 421. (d) Corey, E. J.; Cramer, III, R. D.; Howe, W. J. *ibid.* **1972**, *94*, 440, and earlier references cited therein. (e) Corey, E. J.; Howe, W. J.; Pensak, D. A. *ibid.* **1974**, *96*, 7724. (f) Blair, J.; Gasteiger, J.; Gillespie, C.; Gillespie, P. D.; Ugi, I. *Tetrahedron* **1974**, *30*, 1845. (g) Bersohn, M. *J. Chem. Soc., Perkin I* **1973**, 1239.
- 4) (a) Thakkar, A. J. *Fortschritte Chem. Forschung* **1973**, *39*, 3. (b) Dungundji, J.; Ugi, I. *ibid.* **1973**, *39*, 19. (c) Gelernter, H.; Sridharan, N. S.; Hart, A. J.; Yen, S. C.; Fowler, F. W.; Shue, J.-J. *ibid.* **1973**, *41*, 113.

from the C-C bond being formed. The problem of site or ambident reactivity in systems possessing extended conjugation is the principal liability in the extension of the construction span. This point is illustrated below for both conjugate addition and enolate alkylation (Scheme I).

Scheme I The Problem of Ambident Reactivity



The objectives of the present discourse are to present an organizational format which can serve to correlate strategies for the construction simple pairwise functional group relationships. As a result of the overwhelming predisposition of nature to employ **polar** rather than **free radical** processes in the biosynthesis of organic compounds the chosen organizational format reflects this bias in reaction type. The designation of reactions as polar is recognized to be rather arbitrary since known reactions vary widely in their polar character, ranging from essentially nonpolar radical reactions and weakly polar electrocyclic reactions to strongly polar ionic processes. *Of primary concern in this discussion will be those reactions that involve charged species at some point along the reaction coordinate.*

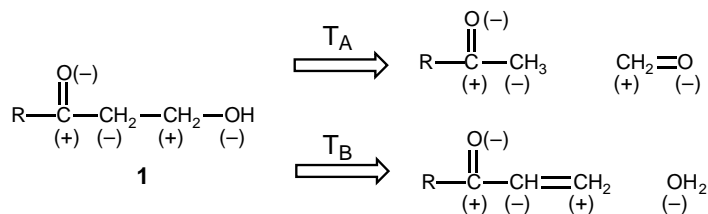
Charge Affinity Patterns.

In order to describe an organizational model for the classification and synthesis of heteroatom-heteroatom $A-B \rightleftharpoons A: - \quad B: +$ (4) (difunctional) relationships in organic molecules, two familiar ideas will be employed. The first is that in a given target molecule $A-B \rightleftharpoons A: + \quad B: -$ (5) the various bonds can be ionically "disconnected" (eq 4, 5). That is, if the A-B bond could be cleaved heterolytically, the indicated set of polar fragments would result.

This antithetic process suggests ionic precursors suitable for the construction of the target molecule via polar coupling processes. *The second well accepted idea is that functional groups determine site reactivities on a carbon skeleton based upon known reactions.* That is, the oxygen atom in both acetone and anisole dictates the site reactivities that are displayed for each molecule with nucleophilic and electrophilic reagents. Thus, if the molecule A-B contained one or more functional groups proximal to the bond to be disconnected, $A-B \rightleftharpoons A: - \quad B: +$ (6) one pair of ionic precursors, eq 6 or 7, would be strongly favored as plausible precursors. In such a case the favored ionic $A-B \rightleftharpoons A: + \quad B: -$ (7) precursors to A-B could be symbolized with either (+) or (-) in the target molecule, e.g.⁵

As an example, two possible polar disconnections for ketone **1** are illustrated below. The parity labels in the target structure suggest plausible monofunctional precursors from which the target structure can be assembled by polar processes. It is also evident that the heteroatom functional groups, =O and -OH, strongly bias the indicated polar disconnections.

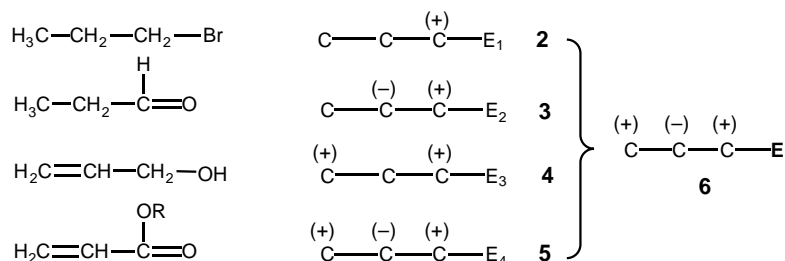
cheme II Polar Disconnections and Charge Affinity Patterns



⁵) The use of the symbols, (+) and (-), in no way represents formal positive or negative charges and will always be bracketed to denote this distinction. Other forms of notation have been considered such as (0) and (1) to denote a potential site of electrophilicity or nucleophilicity; however, the chosen symbols convey more direct information to the organic chemist.

For any given atom or heteroatom assemblage which is defined as a functional group linked to a carbon skeleton, the parity labels, (+) and (-), may be employed to denote the positional polar site reactivity, or **charge affinity pattern** which the functional group confers upon the carbon framework. For the simple molecules shown below (Scheme III) containing a homogeneous set of activating functions, E, there are associated charge affinity patterns **2 - 5** of which each is a sub-pattern of the generalized structure **6**. Note that the carbonyl function is defined as =O rather than C=O in this discussion. You might contemplate why this functional group is defined in this fashion.

Scheme III Charge Affinity Patterns of Common Functional Groups

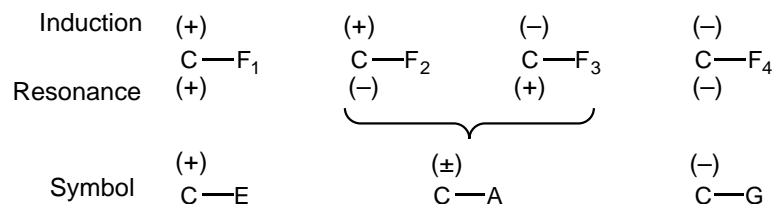


The notion that an organic structure can be viewed as an "ion assemblage" has an interesting history originating with the work of Lapworth and others.^{6,7} Although the ion assemblage viewpoint was developed historically to predict site reactivity in both aliphatic and aromatic systems, this description of an organic structure is equally instructive in defining rational sets of synthetic pathways for a given target structure employing heterolytic processes as the primary set of coupling reactions. Indeed, the thought processes associated with the construction of organic molecules operate intuitively to recognize many sub-units of a given structure in terms of polar fragments. The present use of parity labels to denote viable polar fragments simply formalizes this intuition.

Classification of Functional Groups (FG).

In order to organize general strategies that have been developed to construct heteroatom-heteroatom relationships from monofunctional precursors it is useful to develop a self-consistent classification scheme for single functional groups (FG) based on the concepts of polar disconnection and conferred site reactivity towards nucleophiles and electrophiles. The proposed scheme recognizes the dominate inductive and resonance components of various substituents and establishes⁸ broad categories for activating functions which correlate similar conferred chemical properties to carbon.⁹ Four possible functional group categories (F₁-F₄) are shown below. Those FGs which are *more electronegative than carbon* provide inductive activation defining the electrophilic potential at the point of attachment denoted as (+). In a complementary fashion, FGs which are *less electronegative than carbon* provide inductive activation creating nucleophilic potential at the point of attachment denoted as (-). Since FG activation through induction and resonance are independent variables which contribute to the overall FG reactivity pattern, four possible classes of functional groups can be defined (Scheme IV). This discussion is reminiscent of the classification of FGs according to their impact on electrophilic aromatic substitution.¹⁰

Scheme IV Classification of Functional Groups



⁶⁾ (a) Lapworth, A. *Mem. Proc. Manchester Lit. Phil. Soc.* **1920**, 64, 1. (b) Lapworth, A. *J. Chem. Soc.* **1922**, 121, 416. (c) Lapworth, A. *Chem. Ind.* **1924**, 43, 1294. (d) Lapworth, A. *ibid.* **1925**, 44, 397. For an excellent review of Arthur Lapworth's contributions to chemistry see: Saltzman, M. *J. Chem. Ed.* **1972**, 49, 750-753.

⁷⁾ (a) Vorländer, D. *Chem. Ber.* **1919**, 52B, 263. (b) Stieglitz, J. *J. Am. Chem. Soc.* **1922**, 44, 1293.

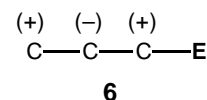
⁸⁾ See reference 3c for an alternate classification scheme for functional groups.

⁹⁾ For an analysis of the relative importance of field and resonance components of substituent effects see: Swain, C. G.; Lupton, Jr., E. C. *J. Am. Chem. Soc.* **1968**, 90, 4328.

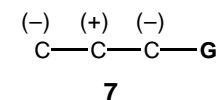
¹⁰⁾ March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; pp 507-512.

E & G-Functions. From the preceding discussion, one might opt for the creation of four classes of functional groups; however, for the sake of simplicity, three FG class designations will be chosen. To organize activating functions into common categories it is worthwhile to define "hypothetical" functional groups E, and G,¹¹ having the charge affinity patterns denoted in **6** and **7** respectively. Given the appropriate oxidation state of the carbon skeleton, such functional groups confer the indicated potential site reactivity patterns towards both electrophilic and nucleophilic reagents. *Any functional groups whose reactivity pattern conforms to the ideal pattern or to a sub-pattern of these hypothetical functions will be thus classified as an E- or G-function respectively.* For example, the halogen and oxygen-based functional groups in four molecules illustrated in Scheme III may be classified as E-functions since their respective charge affinity patterns conform to a subset of the charge affinity pattern of the hypothetical E-function.

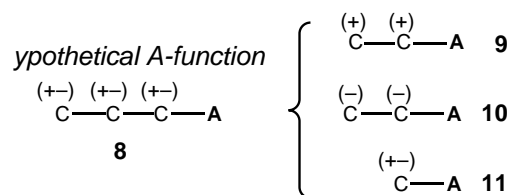
ypothetical E-function



ypothetical G-function

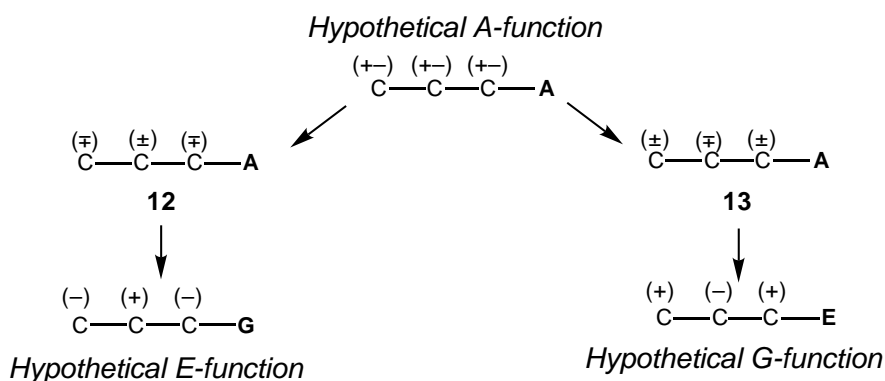


A-Functions. A third hypothetical function, A, (A for amphoteric!) can be defined which has an unbiased charge affinity pattern as in **8**. Such an idealized functional group activates all sites to both nucleophilic and electrophilic reactions and, as such, include those functions classified as either E or G. The importance of introducing this third class designation is that it includes those functional groups having non-alternate charge affinity patterns as in **9**, **10** and **11**.



The differentiation of polar reactivity patterns can be described in an alternative manner. Starting with an ideal A-function, one could imagine a process in which the reactivity pattern is gradually polarized towards E- or G-behavior (Scheme V). Since site reactivity is not an on-off property but varies continuously over a wide range, one could further subdivide A-class functions into those functions with a bias towards E-class or G-class properties. Such a bias could be denoted by the dominant subordinate charge affinity notation in **12** and **13**; however, for the concepts to be presented in this discourse, such A-function subclasses are nonessential. It should be emphasized that the purpose of the E- and G-classification is not to rigidly pigeon-hole functional groups based on site reactivity, but only to separate those which are strongly polarized toward E or G behavior. The decision has been made to avoid the pursuit of an overly detailed FG classification scheme since such attempts will dangerously oversimplify problems since an essentially contiguous function cannot be segmented in to discrete parts.

Scheme V Alternat vs Nonalternat Reactivity Patterns



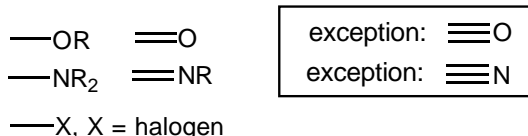
¹¹) The symbol E was selected to denote *electrophilic* at the point of attachment to the carbon skeleton. Unfortunately, the symbol N cannot be used to represent those FGs which are *nucleophilic* at the point of attachment since this is also the symbol for nitrogen. To avoid this conflict, the symbol G was chosen for this FG class designation.

FG Classification Rules. In the proposed classification scheme the following rules are followed in the assignment of class designations to functional groups.

- 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 both proton removals and addition processes are frequently an integral component in functional group activation, the function, its conjugate acid or base, and its possible proton tautomers are considered together in determining its class designation.
- The oxidation state of the FG is de-emphasized since this is a subordinate strategic consideration.

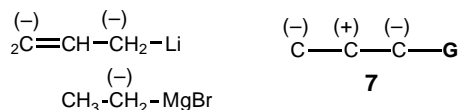
E-Functions. For example, carbonyls and carbonyl derivatives will be represented as =X where X may be either oxygen or substituted nitrogen. Well recognized exceptions to the polar class designations illustrated in Scheme I may be found in the chemistry of CO and HCN. In these instances the carbon bearing the heteroatom exhibits well-defined nucleophilic properties. Accordingly these two functional groups will be classified as A-functions by inspection (*vide infra*).

Table I. Common E-Functions: Symbol(+)-C—E



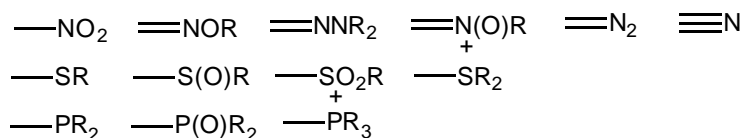
Also consider all combinations of of above FGs; e.g =O + OR

G-Functions. Typical G-class functions are the Group I-IV metals whose reactivity pattern, falls into a subset of 7.



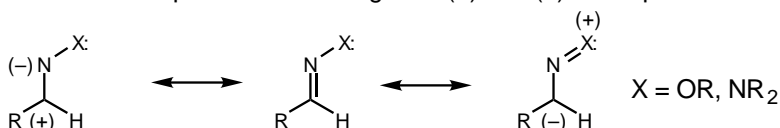
A-Functions. A-functions are usually more structurally complex FGs composed of polyatomic assemblages of nitrogen, oxygen and their heavier Group V and VI relatives (P, As, S, Se). Typical A-functions, classified by inspection, are provided in Table II.

Table II. Common A-Functions: Symbol(±)-C—A



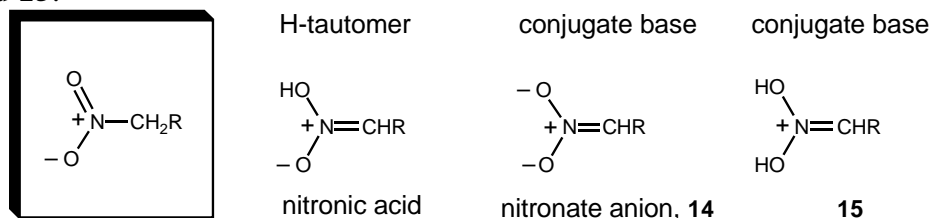
Functional groups possessing the following general structure, =N-X where X is a hetroatom bearing a nonbonding electron pair, have an expanded set of resonance options which create either an electrophilic or nucleophilic potential at the point of attachment. Remarkably, the dual electronic properties of oximes were first discussed by Lapworth¹² in 1924 before the modern concepts of valence bond resonance was developed.

- These FG's are capable of conferring both (+) and (-) at the point of attachment.

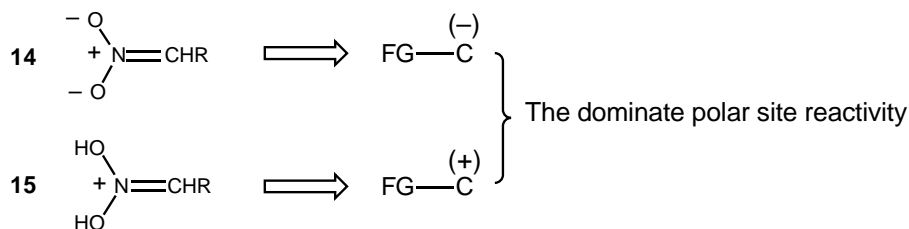


¹²) Lapworth, A. *Chemistry and Industry* **1924**, 43, 1294-1295.

A Case Study: The Nitro 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 **14** and **15**.

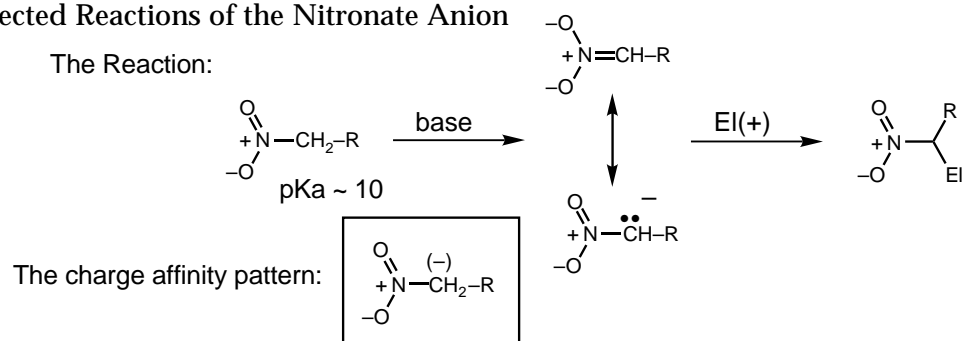


From the collection of transformations of the nitro group one finds that the dominate mode of reactivity of the nitronate anion **14** is that of a G-function while the protonated nitronic acid **15** mirrors the reactivity of an E-function.



The typical behavior of nitronate anions **14** is summarized in the representative transformations provided in Scheme VI. These moderately nucleophilic species, although they are not readily alkylated, readily undergo aldol and conjugate addition reactions.

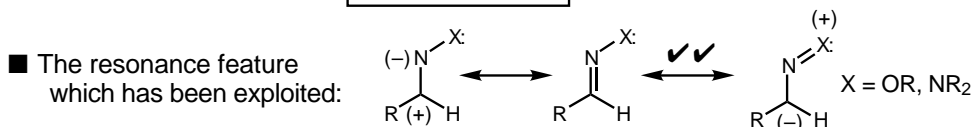
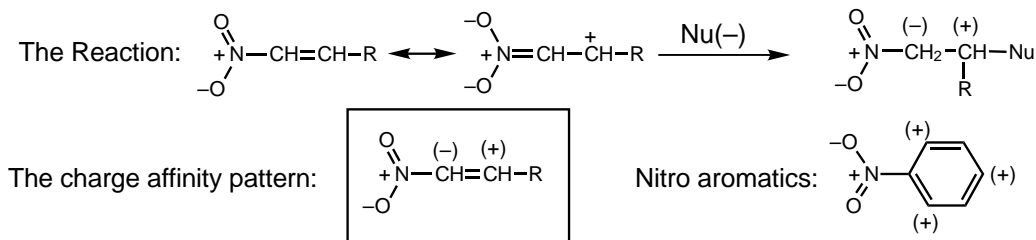
cheme VI Selected Reactions of the Nitronate Anion



■ This reactivity pattern may be extended via conjugation:

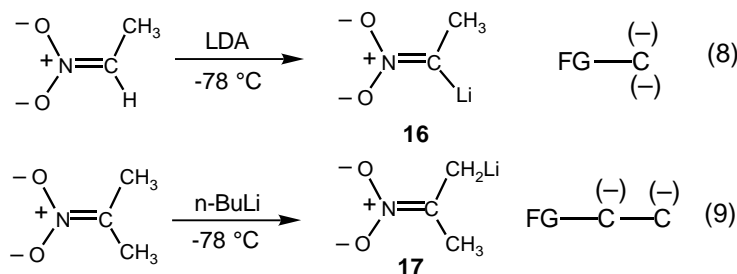
It is no surprise that the charge affinity pattern of this FG may be extended by conjugation, and α,β -unsaturated nitro compounds readily participate in conjugate addition reactions (Scheme VII).

Scheme VII Selected Reactions of the Nitronate Anion



The non-alternate behavior of the nitro functional group is dramatically illustrated in the transformations provided in Scheme VIII. In both instances the derived anions **16** and **17** are highly nucleophilic.¹³ The non-alternate charge affinity patterns of these nucleophiles is provided.

Scheme VIII Deprotonated Nitronate Anions



The nitro group also exhibits the potential of undergoing direct displacement under specific conditions, a general transformation characteristic of E-functions. A recent review by Tamura provides numerous literature precedents for this general class of reactions,¹⁴ while table III provides some of the cited reactions. Although the NO₂ group cannot be considered as a general leaving group, there are a number of conditions under which this moiety can be exploited, particularly when it is either allylic or tertiary.

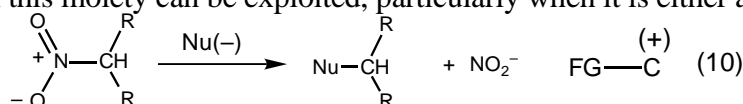
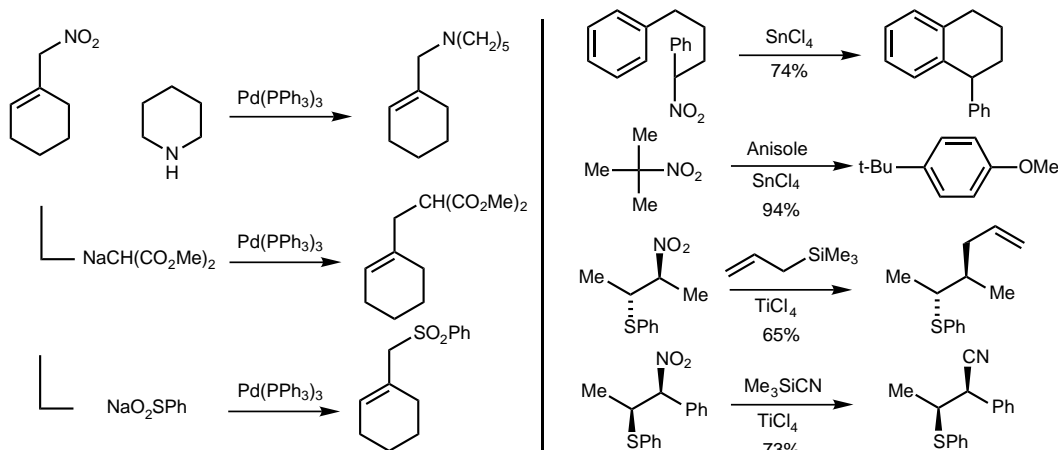


Table III. Representative Substitution Reactions of the Nitro Group (eq 10).



A particularly useful transformation of the nitro group is the Nef Reaction, a process which transforms NO₂ into =O (Scheme IX). A recent comprehensive review of this transformation provides a detailed discussion of this process.¹⁵ In addition to the Pinnick review, Seebach has also written a comprehensive review of the diverse chemistry of the nitro functional group.¹⁶

¹³) (a) Henning, R.; Lehr, F.; Seebach, D. *Helv. Chim. Acta* **1976**, *59*, 2213-2217; (b) Seebach, D.; Henning, R.; Lehr, F.; Gonnermann J. *Tetrahedron Lett.* **1977**, 1161-1164.

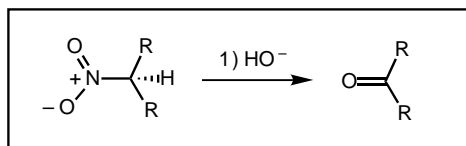
¹⁴) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423-434.

¹⁵) Pinnick, H. W.; *Org. Reactions* **1990**, *38*, 655-792.

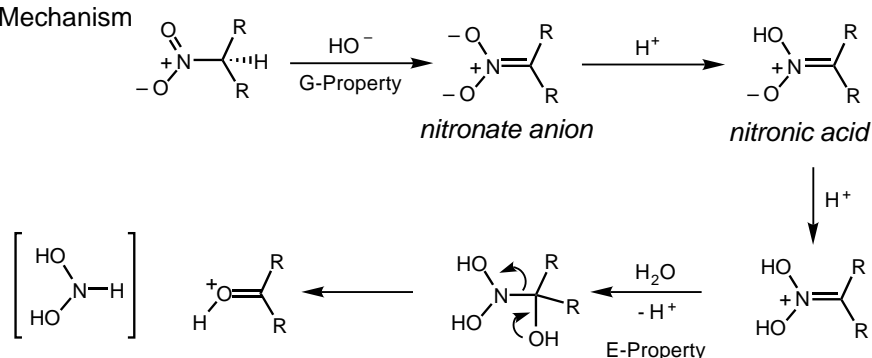
¹⁶) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T.; *Chimia* **1979**, *33*, 1-18.

Scheme IX The Nef Reaction

■ Overall Transformation:



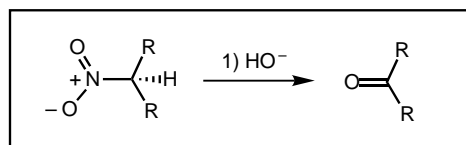
■ Mechanism



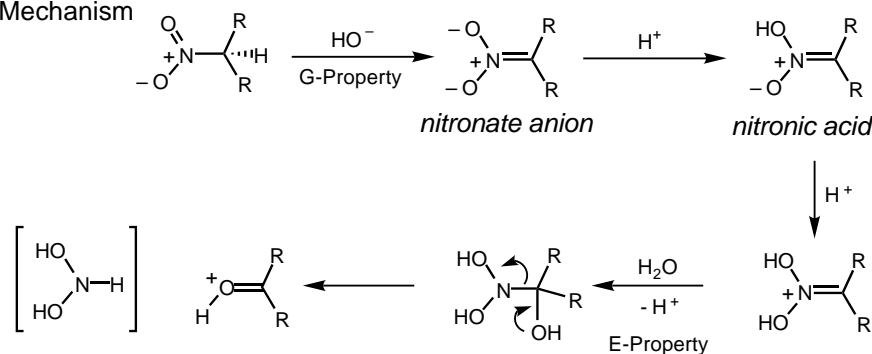
The Diazo Functional Group. This functional group provides one of the best illustrations of an A-function. As illustrated in Scheme X, both (-) and (+) polar site reactivity is observed in its reactions with carboxylic acids.

Scheme IX The Nef Reaction

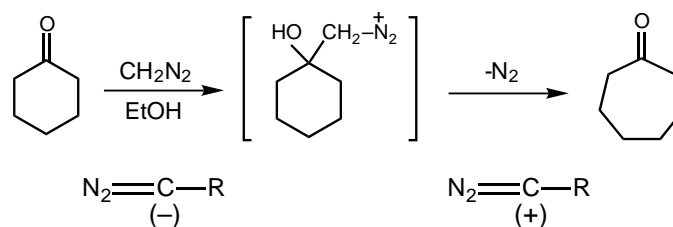
■ Overall Transformation:



■ Mechanism



The same overall reactivity pattern is expressed by the diazo functional group in the Tiffeneau-Demjanov ring expansion reaction¹⁷ wherein diazomethane functions as the nucleophilic agent in the first step and the functional group is lost as a leaving group in the subsequent step (Scheme XI).

Scheme XI The Tiffeneau-Demjanov Ring Expansion

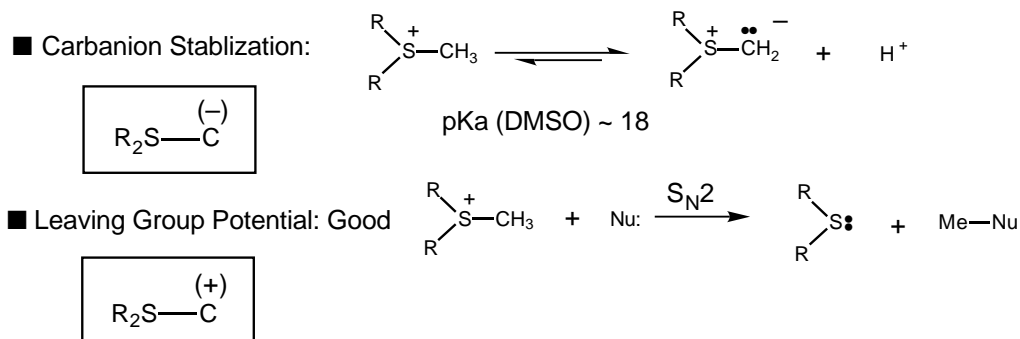
Restriction: Starting ketone must be more reactive than product ketone

¹⁷) For a monograph on ring expansion reactions see: Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: New York, 1991.

Sulfur-Based Functional Groups

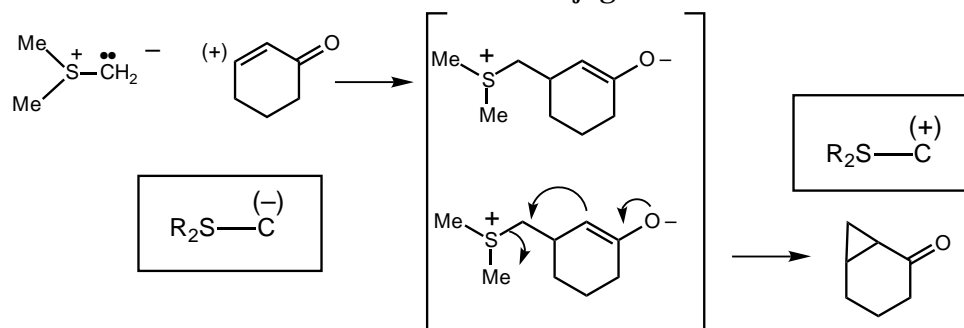
Sulfonium Salts. The dual electronic behavior of sulfur functions may be illustrated in the reactions of sulfur ylids which are excellent examples of A-functions. As illustrated in Scheme XII, sulfonium salts are effective in carbanion stabilization, a characteristic of G-functions, and sulfonium salts are effective leaving groups, a characteristic of E-functions.

Scheme XII. Sulfonium Salts: Modes of Reactivity



The non-alternate reactivity pattern of trimethylsulfonium ylids is revealed in the cyclopropanation of unsaturated ketones as illustrated in the case below (Scheme XIII).¹⁸

Scheme XIII. Reactions of Sulfonium Ylids: Conjugate Addition

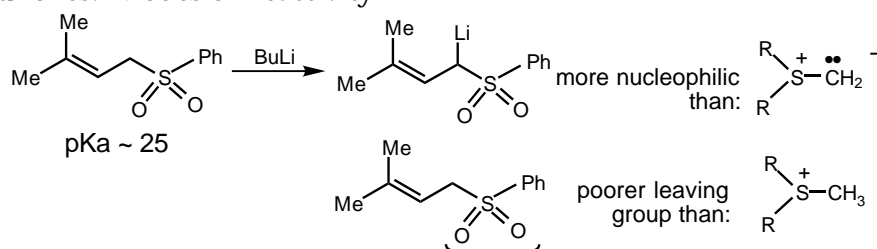


■ Nonalternate reactivity pattern revealed in consecutive reactions

Sulfones. Other types of sulfur-derived functional groups exhibit reactivity profiles similar to that exhibited by sulfonium salts. A number of excellent applications of the arylsulfonyl functional group illustrate this point. Two applications utilizing the sulfone functional groups are presented below.

The phenylsulfonyl moiety strongly stabilizes carbanions and may be equated with the $-\text{CN}$ FG in its potential for hydrocarbon acidification.¹⁹ In addition, this FG is a respectable leaving group in selected situations. In comparisons with sulfonium ions (Scheme XV), arylsulfonyl-stabilized carbanions are more nucleophilic than sulfonium ylids (G-property), while ArSO_2^- is a poorer leaving group than Me_2S^- (E-property).

Scheme XV. Sulfones: Modes of Reactivity

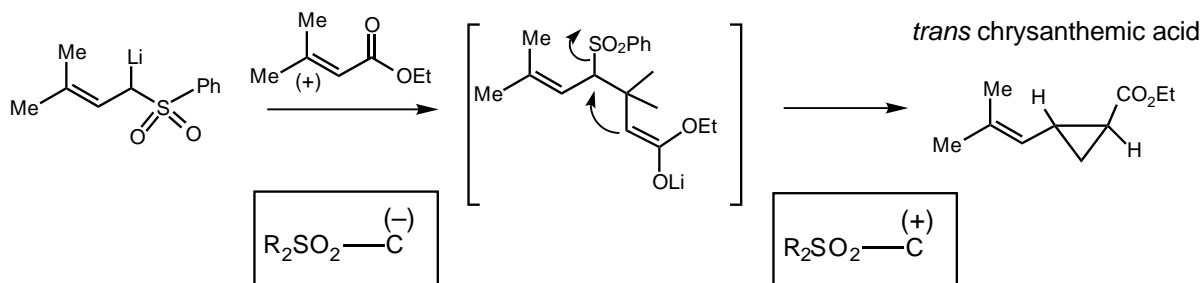


¹⁸) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1352-1364.

¹⁹) For an excellent compilation of pKa data for organic functional groups in DMSO see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456-463.

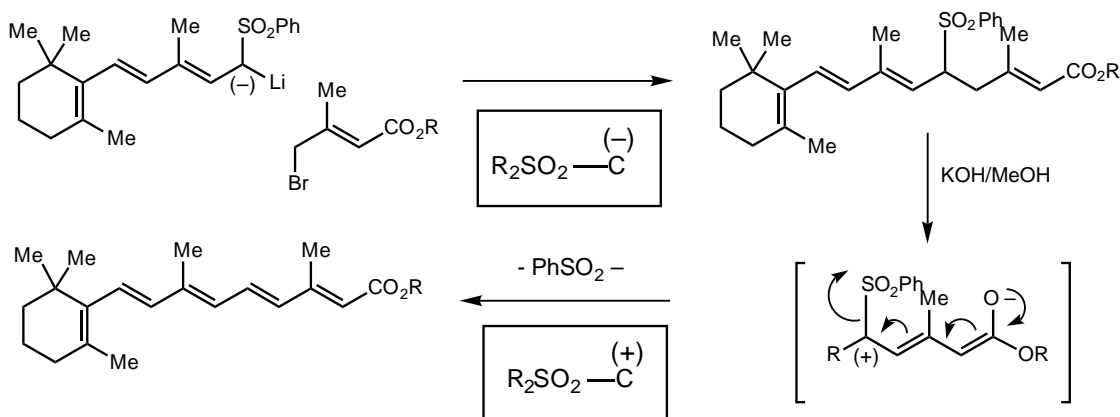
Julia's use of phenylsulfonyl carbanions in the synthesis of *trans*-chrysanthemic acid provides the justification for defining this functional group as an A-function (Scheme XVI).²⁰

Scheme XVI. The Julia Chrysanthemic Acid Synthesis



The dual electronic properties of the sulfone functional group are illustrated in the Julia synthesis of vitamin A (Scheme XVII).²¹ In this application, the E-property of the FG is exploited in the base-induced elimination reaction to generate the fully conjugated polyene.

Scheme XVII. The Julia Vitamin A Synthesis



Julia & Co-workers, *Bull. Soc. Chim. Fr.* **1985**, 130

For additional reading on the utility of the utility of sulfones in organic synthesis a monograph on this subject has recently appeared.²² Several other reviews providing extensive literature coverage are worth reading.²³

Organoboranes. The boron atom exhibits many of the common reactions normally attributed to metals, and when bound to carbon, serves as an excellent source of nucleophilic carbon.²⁴ The transformations provided in (Table IV) represent but a few cases which demonstrate the G-properties of this activating function.^{25,26,27,28,29,30,31}

²⁰) (a) Julia, M.; Guy-Rouault, *Bull. Soc. Chim. Fr.* **1967**, 1141. (b) Campbell, R. V. M.; Crombie, L.; Findley, D. A. R.; King, R. W.; Pattenden, G.; Whiting, J. *J. Chem. Soc., Perkin Trans. I* **1975**, 897.

²¹) Arnould, D.; Chabardes, P. Farge, G.; Julia, M. *Bull. Soc. Chim. Fr.* **1985**, 130.

²²) Simpkins, N. S. *Sulfones in Organic Synthesis*, Pergamon Press, New York 1993.

²³) (a) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107-124. (b) Magnus, P. D. *Tetrahedron*, **1977**, *33*, 2019-2045.

²⁴) (a) Brown, H. C. *Boranes in Organic Chemistry*, Cornell University Press, New York 1973. (b) Cragg, G. M. L. *Organoboranes in Organic Synthesis*, Marcel Dekker, New York, 1973

²⁵) (a) Kow, R.; Rathke, M. *J. Am. Chem. Soc.* **1973**, *95*, 2715. (b) Zweifel, G.; Fisher, R. P.; Horng, A. *Synthesis* **1973**, *37*. (c) Matteson, D. S. *ibid.* **1975**, 147.

²⁶) Negishi, E.; Abramovitch, A.; Merrill, R. E. *J. Chem. Soc., Chem. Commun.* **1975**, 138.

²⁷) For a recent citation on allylboron-based nucleophiles see: Wang, Z.; meng, X. J.; Kablaka, G. W. *Tetrahedron Lett.* **1991**, *32*, 5677-5680 and references cited therein.

²⁸) Marshall, J. A. *Synthesis* **1971**, 229.

²⁹) (a) Brown, H. C.; Rhodes, S. P. *J. Am. Chem. Soc.* **1969**, *2149*, 2149. (b) Hawthorne, M. F.; Dupont, J. A. *J. Am. Chem. Soc.* **1958**, *80*, 5830.

³⁰) (a) Pelter, A.; Subrahmanyam, C.; Laub, R. J.; Gould, K. J.; Harrison, C. R. *Tetrahedron Lett.* **1975**, 1633. (b) Pelter, A.; Harrison, C. R.; Kirkpatrick, D. *ibid.* **1973**, 4491. (c) Pelter, A.; Harrison, C. R. *J. Chem. Soc., Chem. Comm.* **1974**, 828. (d) Naruse, M.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1974**, *30*, 3037.

Table IV. Reactivity Patterns for Organoboranes

Entry	Reaction	Charge Affinity Pattern
A ²⁵		(-) C—A
B ²⁶		(-) C—A
C ²⁷		(-) C—C—(-) C—A
D ²⁸		(-) C—A
E ²⁹		(-) C—A
F ³⁰		(-) (+) C—C—A
EI(+) = <i>n</i> -C ₆ H ₁₃ I, C ₃ H ₅ Br, ethylene oxide, CH ₂ I ₂ , MeSO ₃ H		
G ³¹		(-) (+) C—C—A
<i>stereochemical aspects of this reaction not determined</i>		

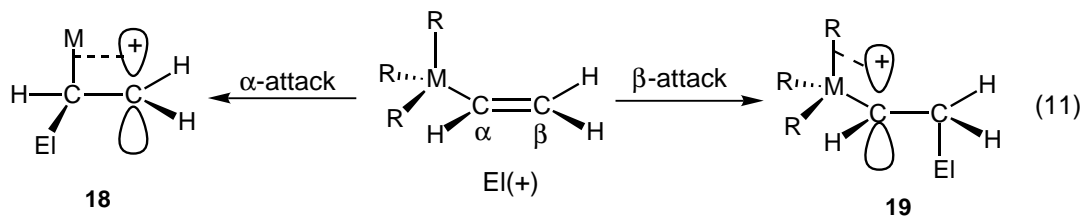
The potential for non-alternate charge affinity patterns for boron have been revealed in the reactions of acetylenic and vinylic boron ate complexes (Table IV, entries F, G).^{30,31} *These compounds exhibit high nucleophilicity towards a variety of electrophiles β to the boron atom.* The origin of such β-nucleophilicity could be a consequence of σ-π conjugation³² (e.g., **19**) not observed with the heavier metallic elements which are attacked by electrophiles α to the metal where the alternate mode of conjugation **18** is possible.³³ In principle, both types of conjugative stabilization are possible with a range of organometaloids; however, in practice this is not the case. It would be expected that the effects of

³¹) (a) Utimoto, K.; Uchida, K.; Nozaki, H. *Tetrahedron* **1973**, *30*, 4527. (b) Utimoto, K.; Uchida, K.; Nozaki, H. *Chem Lett.* **1974**, 1493.

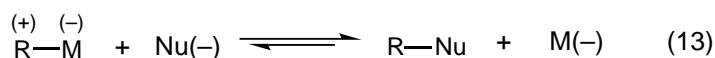
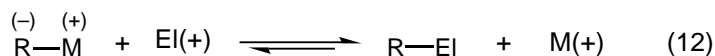
³²) (a) Harmon, G. D.; Traylor, T. G. *Tetrahedron Lett.* **1975**, 939, and reference cited therein. (b) for example of σ-π delocalization of type **25** involving R₃B— see Hanstein W.; Traylor, T. G. *ibid.* **1967**, 4451; (c) for the reaction of vinylsilanes electrophiles see Miller, R. B.; Reichenbach, T. *ibid.* **1974**, 543, and references cited therein.

³³) Kitching, W. in "Organometallic Reactions," Vol. 3, E. I. Becker and M. Tsutsui, Ed., Wiley-Interscience, New York 1972, pp. 319-398.

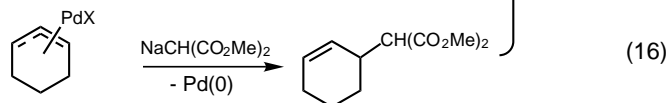
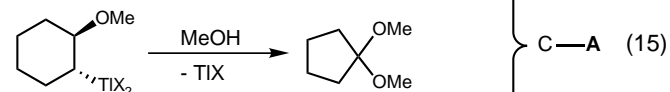
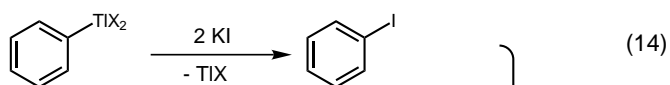
σ - π conjugation, such as that illustrated in **24**, would be more important in those systems having shorter C-M bonds, a situation which may be unique to boron. It is noteworthy that the other group III and IV organometallic compounds, $R_3M-CH=CH_2$ ($M = Al, Si, Ge, Sn$) react with electrophilic reagents α to the metal. These elements all exhibit polar reactivity patterns common to G-class functions.



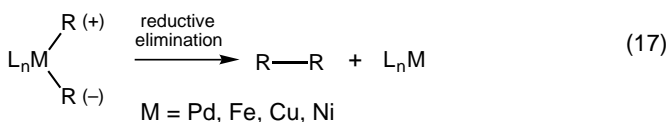
Metals. In deriving a class designation for metals, M, bound to carbon, two reaction types are considered. Metals undergoing *exclusive* substitution at the metal-carbon bond by electrophiles, El^+ , are classified as G-functions (eq 12), while metals which are involved in redox processes (eq 13) are classified as A-functions since such organometallic compounds also exhibit G-type behavior.



The organic chemistry of Tl(III),³⁴ and Pd(II)³⁵ (eq 14-16) illustrate the role of metals as leaving groups (reductive elimination). Oxidative addition reactions of metal carbonyl anions and alkyl halides provide examples of the reverse process.³⁶ In general, transition metal-mediated cross-coupling reactions provide a useful illustration of the A-classification of redox metals (eq 17).³⁷ The assignment of charge affinity labels to R_1 and R_2 in this case is arbitrary.



Employing polar processes as the basis set of synthetic reactions, existing functional groups may be organized according to their known chemical properties. Any number of positions may be taken relative to the classification of atom reactivity. The goal of this section has been to define a general classification scheme which may be used to organize the multitude of different strategies which have been developed to construct pairwise functional group relationships in organic molecules.



³⁴) Taylor, E. C.; McKillop, A. *Acc. Chem. Res.* **1970**, 3, 338.

³⁵) Trost, B. M. *Acc. Chem. Res.* **1980**, 13, 385-393.

³⁶) Ellis, J. E. *J. Organomet. Chem.* **1975**, 86, 1.

³⁷) (a) Neuman, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, 40, 599. (b) Normant, J. F. *Synthesis* **1972**, 63. (c) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, 94, 9268. (d) Tamaki, A.; Magennis, S. A.; Kochi, J. K. *ibid.* **1973**, 95, 6487.

Classification of Difunctional Relationships.

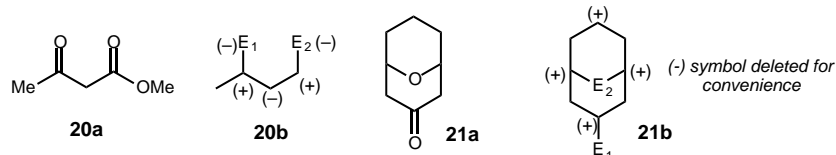
One of the basic assumptions employed in synthetic design involves the *maximum utilization of existing functionality at all intermediate points in the construction of a polyfunctional molecule*. Such guidelines aid in minimizing the number of side reactions and protection-deprotection steps during the assemblage operation. In the synthesis of even simple difunctional organic molecules, the relative positioning of the two activating functions on the carbon framework strongly influences the reaction types that will usually be employed to establish the difunctional relationship. Using the general notation developed in the previous section for activating functions, two distinct classes of difunctional relationships which may be defined between ideal E- and G-functions which may be defined are illustrated in Table V.

Paths. *Difunctional relationships between heteroatoms having "matched" charge affinity patterns will be defined as consonant while unmatched relationships will be labeled dissonant.*

It should be pointed out that the charge affinity notation is unnecessary to define the appropriate relation; other parity labels could serve equally well. For example, the number of bonds between E- and G-functions could be used to define the appropriate relationship. Employing E-functions for the purpose of illustration, the two carbonyl groups in **20a** have a matched charge affinity pattern along the potential construction path. Since they are separated by three atoms they can be defined as 1,3-consonant (1,3-C). The symbol notation **20b** transmits information relative to the E—E' positioning along the construction path and since the E-symbol represents a homogeneous class of electronically equivalent functional groups, a common symbol is employed. In those cases where it is necessary to recognize oxidation states of carbon to derive a symbolic structural notation, one may easily do so.

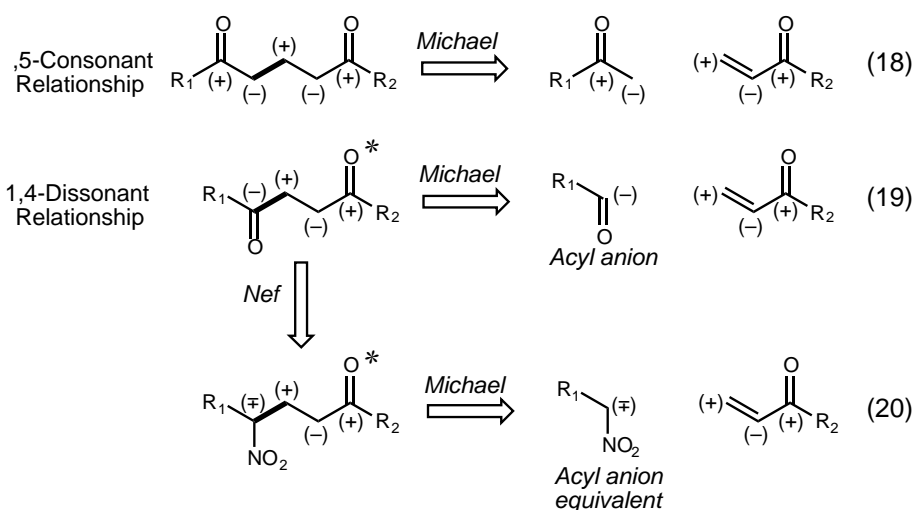
Table V. Consonant & Dissonant Difunctional Pairwise Functional Group Relationships

Consonant Relationships	Symbol	Notation	Dissonant Relationships	Symbol	Notation
		1,3-C			1,1-D
				1,2-D	
				1,4-D	
		1,5-C			D-cycles
		1,4-C			
		C-cycles			
					1,2-D, 1,4-D



Cycles. In cyclic structures, a heteroatom attached to or contained within the cycle creates a relationship with itself. For non-arbitrary mathematical considerations it is convenient to define an even-membered ring with or without a single functional group as consonant and corresponding odd-membered rings as dissonant. For the bicyclic ketone **21a**, both of the oxygen heteroatoms, denoted as E₁ and E₂, establish consonant relationships with each other via all bond paths and individually by virtue of their position either attached to or contained within an even-membered ring.

Consonant and Dissonant Bond Paths. In contrast to the uniformity with which consonant relationships may be established through common classes of polar processes, the synthetic methods and functional groups required for the construction of the bonds define a D-relationship are quite varied and involve either more steps, more functional groups or more reactive intermediates than reactions leading to C-paths. This statement will be reinforced in a series of case studies (*vide infra*); however a single case is presented to reinforce this assertion. Consider the Michael transform executed on the 1,5- and 1,4-diketones shown below (eq 18, 19). In the first instance, the transform may be executed using only the functional groups illustrated; however, this is not possible with the dissonant dicarbonyl relationship since one of the resulting polar fragments will be electronically mismatched with its associated FG. In the illustrated disconnection (eq 19), the electronically mismatched fragment is the carbonyl anion.

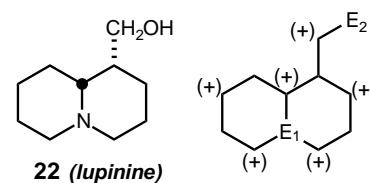


One possible solution to the construction of this dissonant relationship is through FG manipulation. In the present instance the application of the Nef transform (*vide supra*) provides the opportunity to match the charge affinity patterns so that the Michael transform may be properly executed. The use of A-functions in this fashion is just one of a number of strategies which may be employed to construct dissonant difunctional relationships.

In conclusion, dissonant pairwise relationships, either identified in simple acyclic molecules or within complex cyclic structures, generally pose a greater synthetic challenge and represent seams of lower flexibility within the carbon framework. At this point, it may be instructive to the reader to contemplate a synthesis strategy based on how and when D-relationships are incorporated into target structures. This point will be addressed later in the discussion.

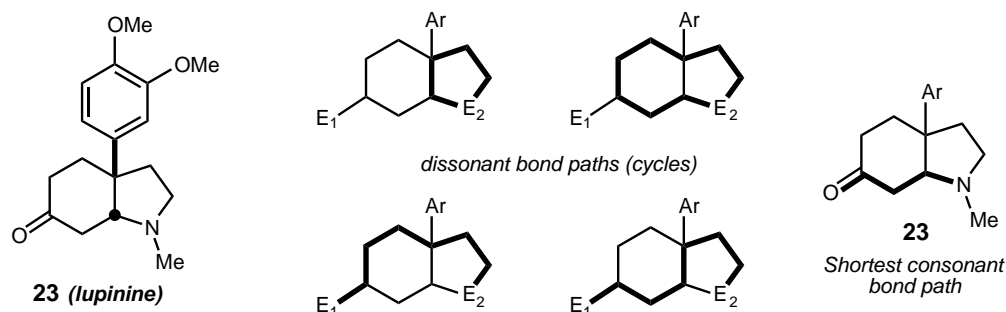
Synthesis of Consonant Difunctional Relationships.

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 (**22**) all possible construction paths interconnecting E₁ and E₂ are consonant. On the other hand, mesembrine (**23**)³⁸ contains the potential dissonant paths and cycles illustrated in heavy lines. Consonant paths within the polyatomic framework define seams in the structure that may be constructed using aldol and related condensation processes.

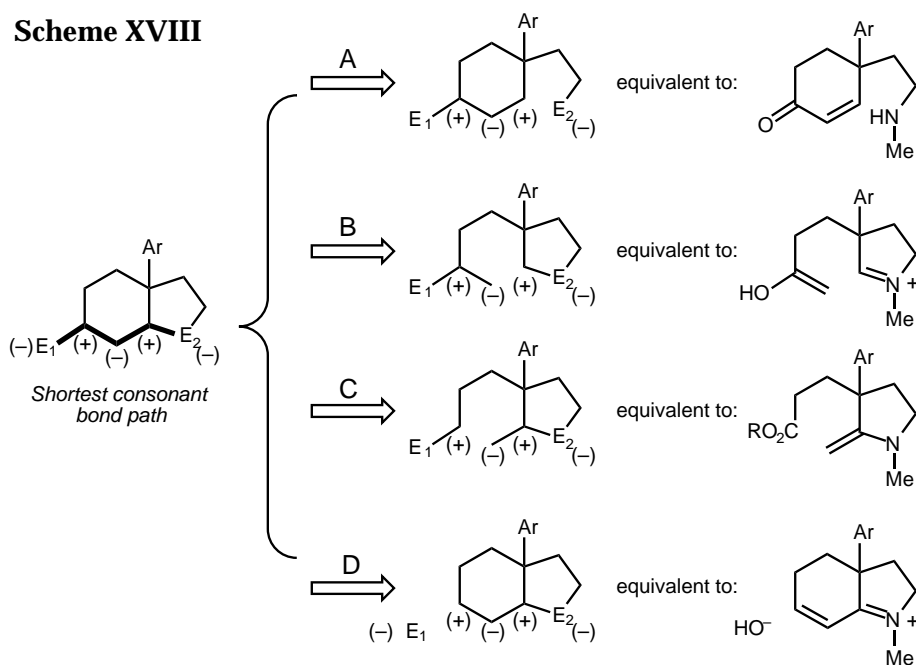


³⁸ (a) Curphey, T. J.; Kim, H. L. *Tetrahedron Lett.* **1968**, 1441. (b) Keely, S. L.; Tahk, F. C. *J. Am. Chem. Soc.* **1968**, 90, 5584. (c) Stevens, R. V.; Wentland, M. P. *ibid.* **1968**, 90, 5580; (d) Shamma, M.; Rodrigues, H. R. *Tetrahedron* **1968**, 24, 6583.

■ Regarding the number of different possibilities available for the synthesis of a consonant di-functional relationship interconnected by n bonds, there exists a set of n different connective operations that may be employed to establish any bond along the construction path from monofunctional or consonant polyfunctional precursors.³⁹



In the analysis of potential routes to structures like lupinine, identify the shortest consonant bond path and then proceed to carry out all polar disconnections along that bond path (Scheme XVIII). Since there four bonds interconnecting =O and N (E_1 and E_2), there will be four associated transforms which one may execute using the illustrated functional groups. In each set of precursors the intrinsic polar reactivity patterns of the heteroatoms are accommodated in the coupling process. The resulting adducts containing the requisite nitrogen-oxygen relationship may then be ranked in order of desirability by considering criteria such as chemical feasibility of the coupling step, ease of subsequent transformation to the target structure, and availability of precursor fragments. In the present example, transforms A and B might be more highly ranked than transform C while transform D might be discarded since it does not lead to structural simplification.

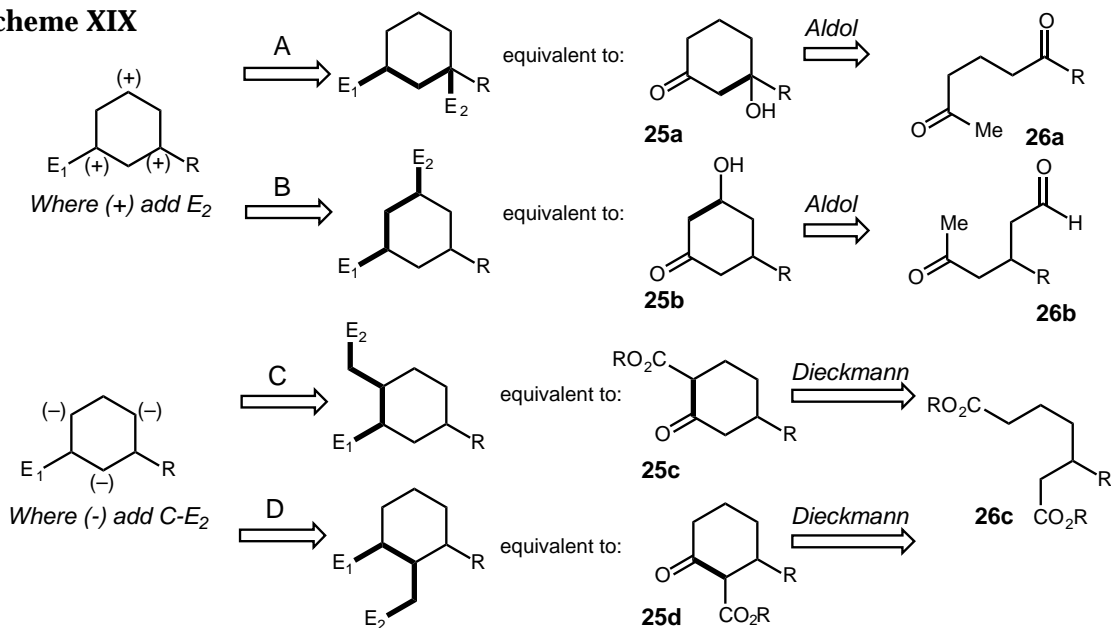


In those cases when a given consonant or dissonant relationship is separated by a significant number of bonds, it is strategically worthwhile to consider the option of incorporating additional functions to aid in the construction of the desired target molecule. The relative placement of such a functional group is of prime importance in dictating the subsequent polar disconnections that are perceived in generating a plausible synthetic tree. This point is illustrated when considering plausible precursors to ketone **24** (Scheme XIX). In this structure, the =O FG establishes a 1,5-relationship with itself on the six-membered ring. Through the addition of an appropriate second

³⁹) The presence of a quaternary or bridgehead center along the construction path limits bond construction to those adjacent to the center.

activating function to the target molecule **24**, an expanded set of potential disconnections is created. In the placement of the second FG, the charge affinity pattern of the resident FG should be used. *For example, consider the installation of a second FG, E₂, at the (+) sites on the ring to set up aldol or Claisen transforms. In a complementary fashion the addition of C-E₂ fragments to the (-) sites will open up the execution of the two possible Dieckmann transforms.*⁴⁰ The preceding analysis leads to the three precursors **26a-26c**. Each of which contains a 1,5-consonant difunctional relationship between the carbonyl functions. These subgoals now become the focus of the next level of analysis wherein the preceding logic is again applied. It should be emphasized that the precursors illustrated in Scheme XIX are not inclusive but represent one set which leads to the generation of a synthetic tree based upon aldol and related reactions. *The point to be emphasized is that in the first stage of the analysis where functionality is being added to the target structure, consonant, rather than dissonant relationships should be created.*

Scheme XIX



⁴⁰) To be completely rigorous with regard to this analysis, the addition of C-E₂ to the 4-position should also be considered; however, the E₁-E₂ construction span from such a precursor is sufficiently large as to render this precursor less attractive than the other precursors **25a-25d**.

Chemistry 206

Advanced Organic Chemistry

Handout 27B

**Synthetic Applications of α -Diazocarbonyl
Compounds**

An Evans Group Afternoon Seminar

Krista B. Goodman

January 15, 1999

D. A. Evans

Monday,
November 17, 2003

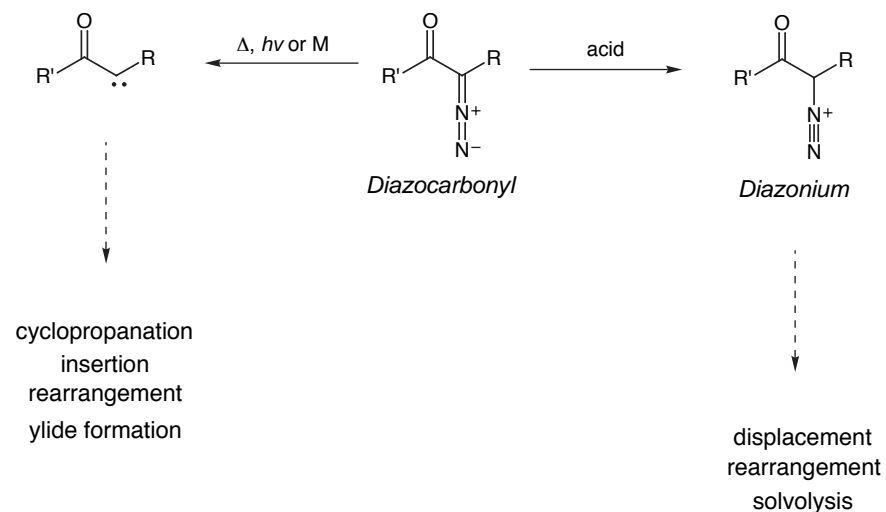
Synthetic Applications of α -Diazocarbonyl Compounds

An Evans Group Afternoon Seminar

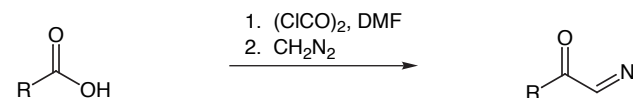
Krista Beaver

January 15, 1999

Leading References:

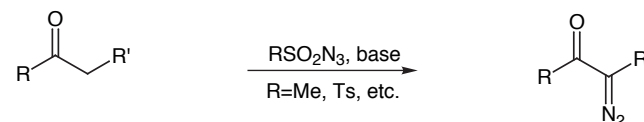
McKervey and Ye, *Chem. Rev.* **1994** 1091Doyle, McKervey and Ye, *Modern Methods for Organic Synthesis with Diazo Compounds*, Wiley, 1998*Diazocarbonyl Compounds: Structure and Nomenclature*Synthesis of α -Diazocarbonyl Compounds

- First synthesized by Curtius in 1883 by diazotization of α -amino acids
- Arndt-Eistert synthesis (1927)



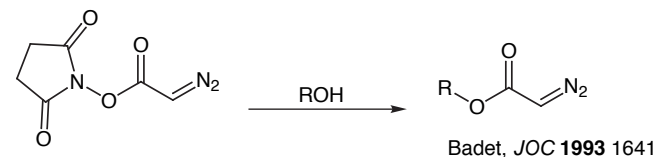
Arndt and Eistert, *Ber. Dtsch. Chem. Ges.* **1927** 60B 1122
 Pettit, *JOC* **1986** 1282

- Diazo Transfer

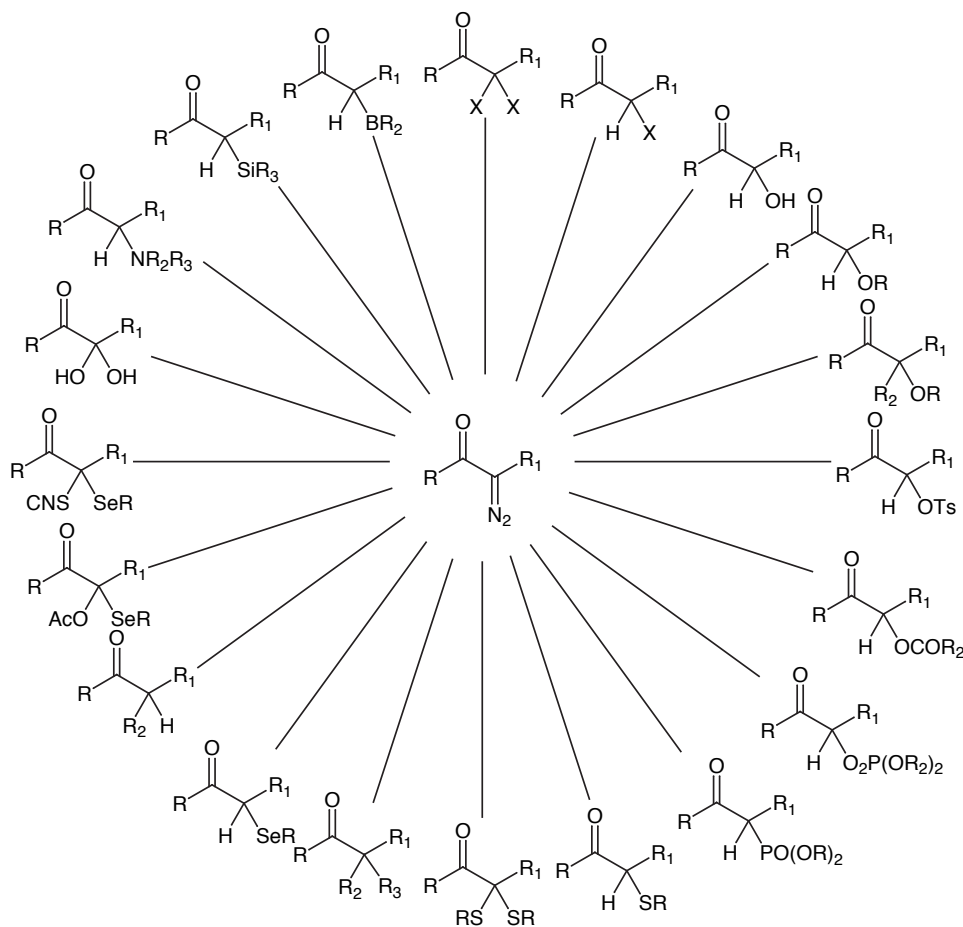
Regitz, *ACIEE* **1967** 733

For temporary activation of carbonyl compounds prior to diazo transfer, see Danheiser, *JOC* **1990** 1960

- Acyl Transfer

Badet, *JOC* **1993** 1641

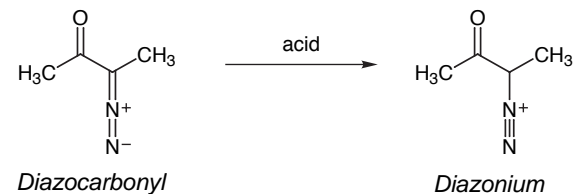
Some Reactions of α -Diazocarbonyl Compounds



Adapted from McKerver, *Chem. Rev.* **1994** 1090

Acid Catalyzed Reactions of Diazo Compounds

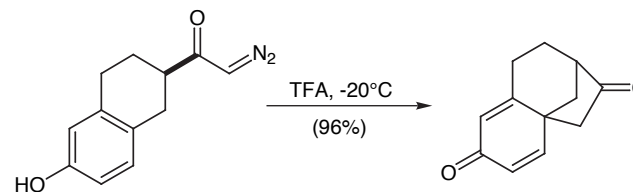
Review: Smith, *Tet.* 1981 2407



Common acids include $BF_3 \cdot OEt_2$, HBF_4 , TFA, etc.

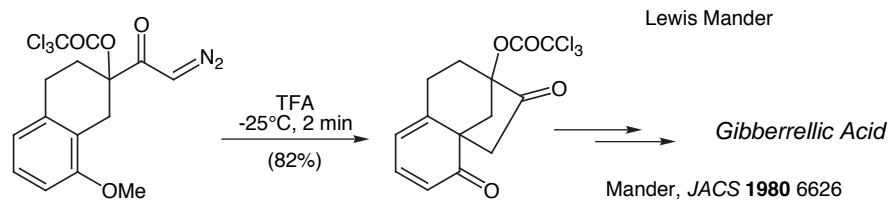
Mechanism of activation is unclear for both Lewis and protic acids; activation may occur by protonation on C or O

Acid-Catalyzed Reactions



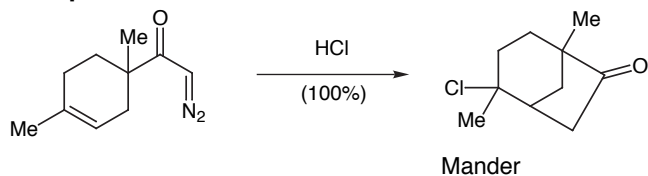
Mander, *Chem. Comm.* **1971** 773
Tet., **1991** 134

"Having become familiar with the peculiarities of diazoketone chemistry while preparing [other compounds] (and, I might add, inured to handling uncomfortably large quantities of diazomethane), it occurred to us that we might be able to substitute a diazo group for bromine."

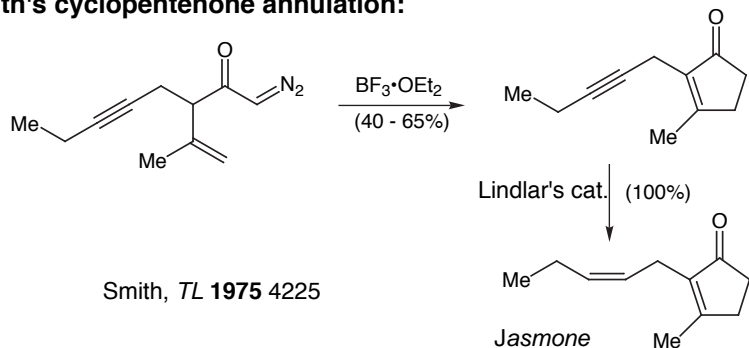


More Acid Catalysis

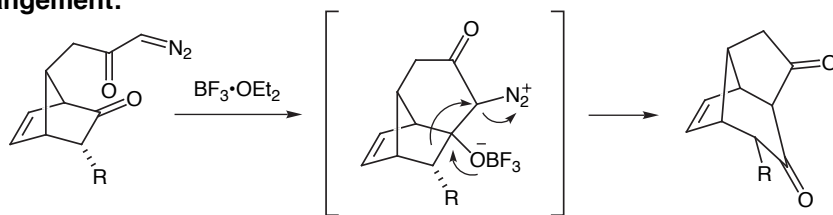
Olefins as nucleophiles:



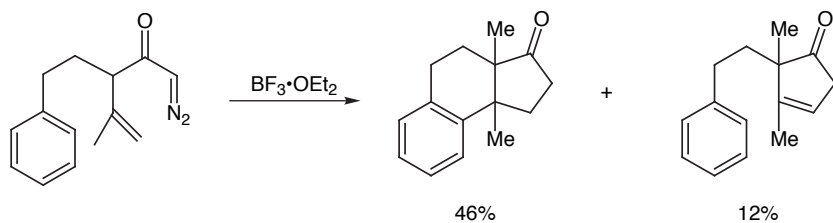
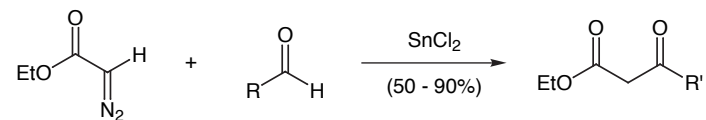
Smith's cyclopentenone annulation:

Smith, *TL* 1975 4225

Rearrangement:

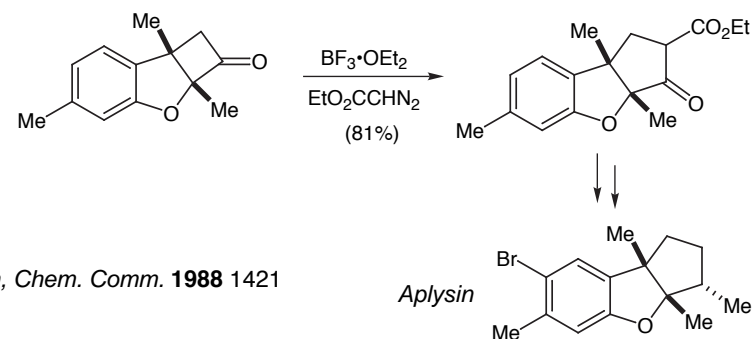
Mander, *Aust. J. Chem.* 1979 1975

Polyene cyclizations:

Smith, *JACS* 1981 2009 β -Ketoester synthesis:Roskamp, *JOC* 1989 3258

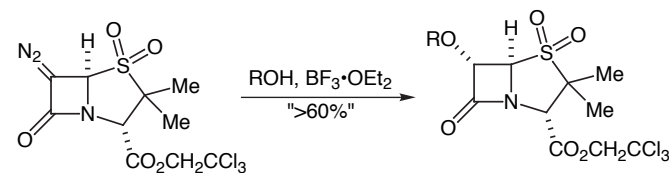
Yields are good when R is aliphatic; moderate when aromatic

Ring expansion:

Ghosh, *Chem. Comm.* 1988 1421

Aplysin

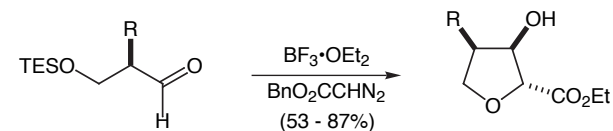
Substitution:



Thiols also work well

John and Thomas *TL* 1978 995

Tetrahydrofuran Synthesis:



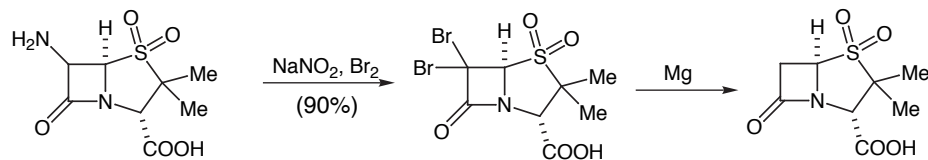
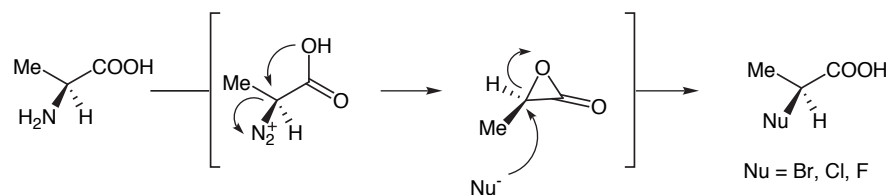
diastereoselection 3:1 - 20:1

Diastereoselectivity increases with size of R; independent of Lewis acid or protecting group

Angle, *TL* 1998 3119
TL 1998 8195

Substitution Reactions

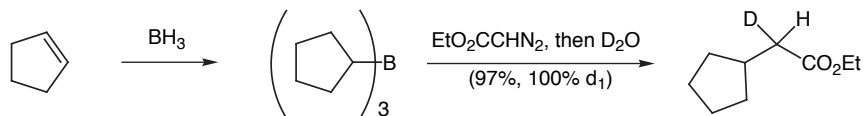
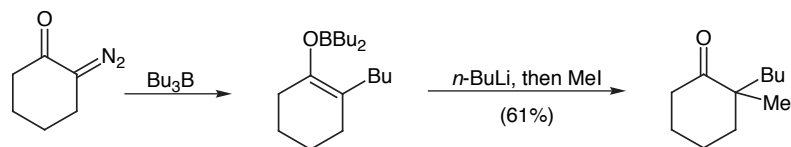
Deamination:

Kapur and Fasel, *TL* **1985** 3875Synthesis of α -substituted chiral acids:

Displacement occurs with retention of stereochemistry

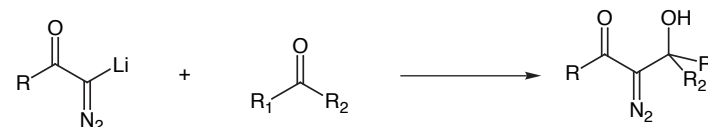
Ingold, *Nature* **1950** 179For other examples, see McKerver, *Chem. Rev.* **1994** 1091

Reaction with Boranes

Hooz, *JACS* **1969** 6195Wojtkowski, *JOC* **1971** 1790

Base-Induced Reactions

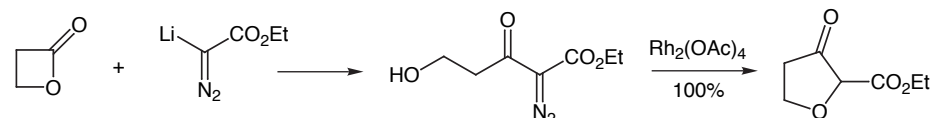
Aldol-type reactions:



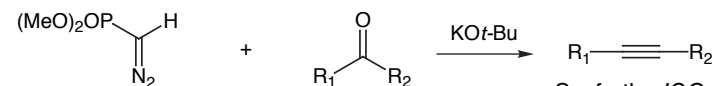
LDA is the optimal base for lithiation

Pellicciari, *JCS Perkins I* **1985** 493

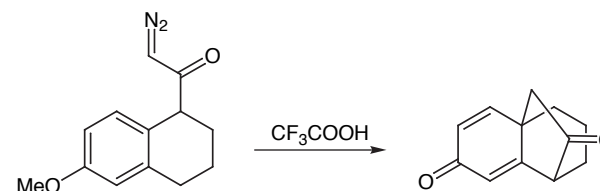
Ester alkylation:

Rapoport, *JOC* **1985** 5223

Gilbert-Seyferth Reagent:

Seyferth, *JOC* **1971** 1379
Gilbert, *JOC* **1982** 1837

Mechanism?



Carbenoid Reactions: The Catalysts

Review: Padwa, *ACIEE* 1994 1797

Decomposition can be catalyzed by:

Heat or light

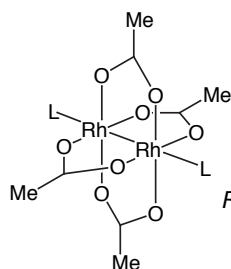
Transition metals, including Cu^{II}, Rh^{II}, Mn^{II}, Fe^{II}, Co^{II}, Ni⁰, Ni^{II}, Zn^{II}, Mo^{II}, Ru^{II}, Ru^{III}, Pd^{III}

Most common catalysts:

Copper (I): CuOTf, Cu(OTf)₂, CuSO₄, CuX, Cu(acac)₂**Rhodium (II):** Much milder catalyst than Cu (introduced in 1973 by Tessié)

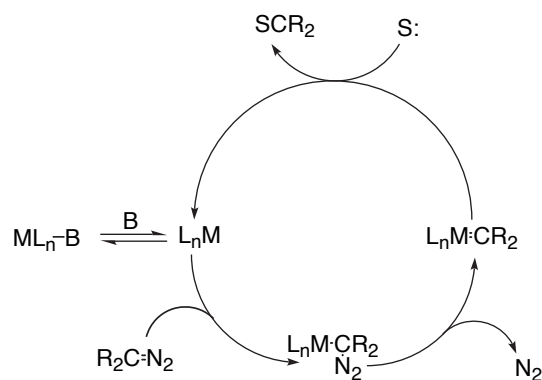
Structures generally contain bridging ligands and contain a Rh-Rh single bond

Reaction pathways are highly sensitive to steric and electronic effects

**Rhodium Carboxylates:** Rh₂(OAc)₄, Rh₂(tfa)₄, Rh₂(oct)₄, Rh₂(tpa)₄, Rh₂(pfb)₄**Rhodium Carboxamidates:** Rh₂(acm)₄, Rh₂(cap)₄, Rh₂(CF₃CF₂CF₂CONH)₄

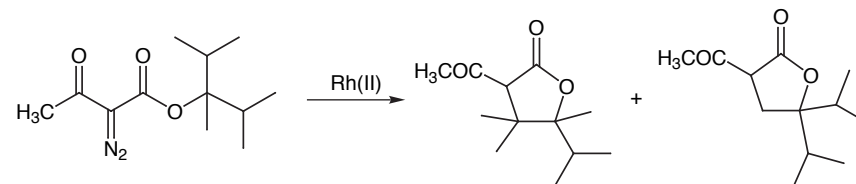
Rhodium Acetate

Transition Metal Catalyzed Diazo Decomposition

Doyle, *Chem. Rev.* 1986 919

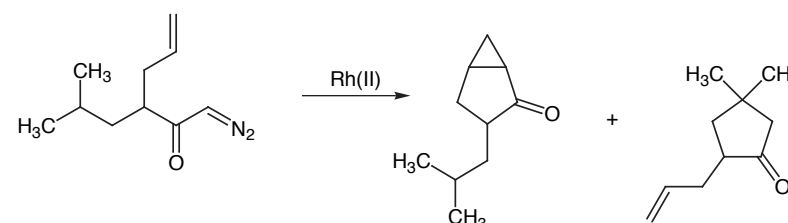
Ligand Effects: Selectivity

Methine versus methyl:

Doyle, *JACS* 1993 958

Rh ₂ (OAc) ₄	90:10
Rh ₂ (pfb) ₄	38:61
Rh ₂ (acam) ₄	100:0

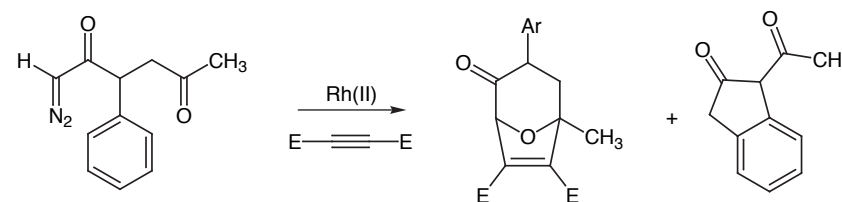
Cyclopropanation versus C-H Insertion:

Padwa and Doyle, *JACS* 1993 8669

Rh ₂ (OAc) ₄	44:56
Rh ₂ (pfb) ₄	0:100
Rh ₂ (cap) ₄	100:0

More Competition Experiments

Dipolar Cycloaddition versus C-H insertion:

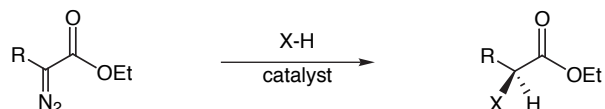
Padwa and Moody, *Tet.* 1993 5109

Rh ₂ (OAc) ₄	75:25
Rh ₂ (pfb) ₄	0:100
Rh ₂ (cap) ₄	100:0

Conclusions:

These results imply that the metal is involved in the transition state
Reaction pathways can be controlled by tuning the ligands on the metal

Generalizations: Sigma Bond Insertion

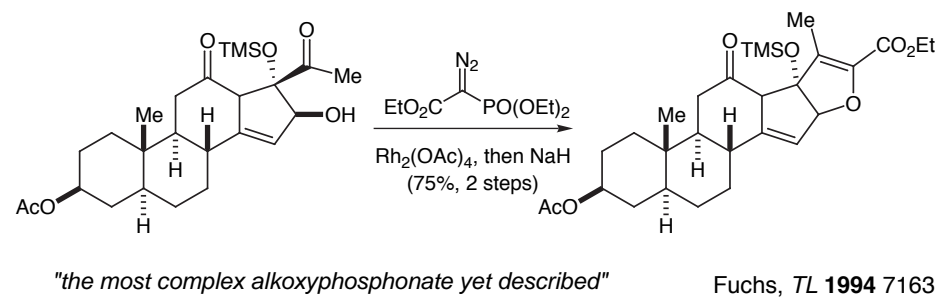
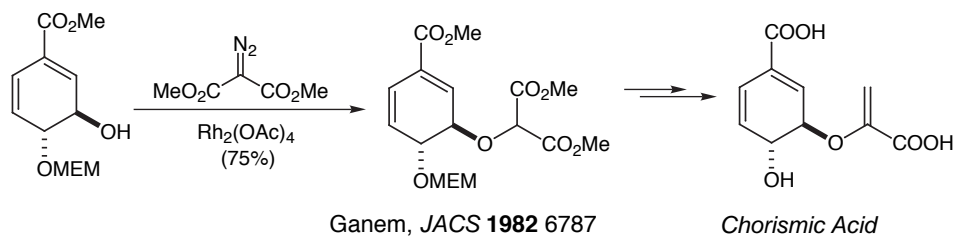


Reviews O-H Insertion: Moody *Tet.* **1995** 10811
 C-H Insertion: Sulikowski *Tet. Asymm.* **1998** 3145

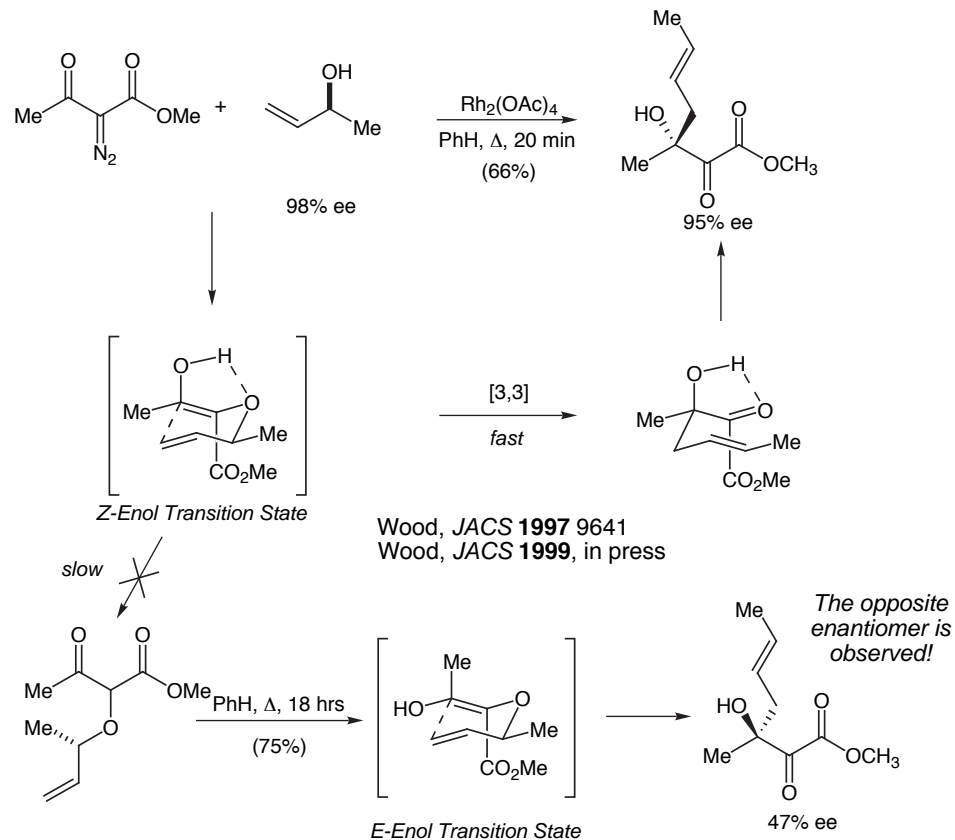
- When X is a heteroatom, insertion is facile
- When X is carbon:

Only intramolecular processes are generally useful
 5 - membered ring formation is favored in general
 Order of selectivity: methine > methylene > methyl

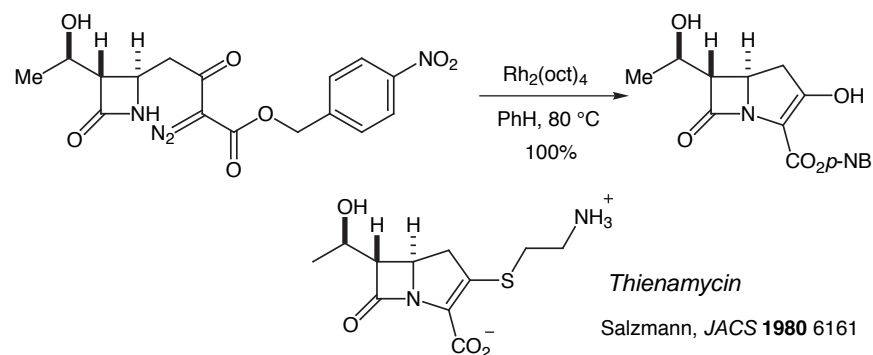
O-H Insertion Reactions



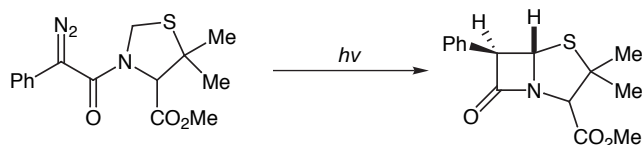
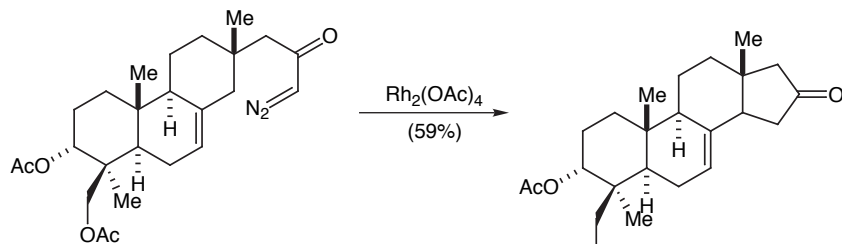
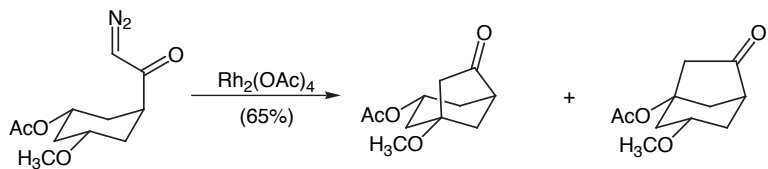
Tandem O-H Insertion/Claisen Rearrangement



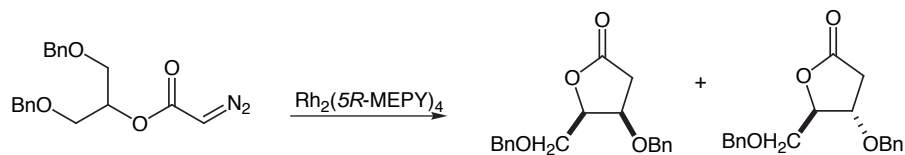
Merck Thienamycin Process



C-H Insertion: Reactions

Corey, *JACS* **1965** 2518Wenkert, *JOC* **1982** 3243Adams, *JACS* **1994** 3296

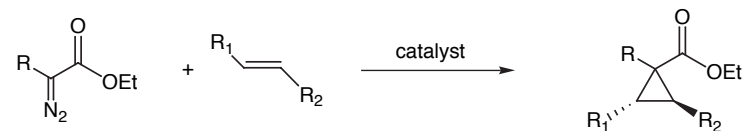
Diastereoselection > 99:1

Doyle, *JACS* **1994** 4507

Diastereoselection 93:7

For a review of catalytic enantioselective carbene reactions, see:
Doyle, *Chem. Rev.* **1998** 911

Generalizations: Cyclopropanation



Reviews: Davies, *Ald. Acta.* **1997** 107
Davies, *Tet.* **1993** 5203

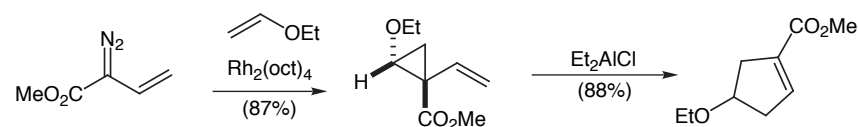
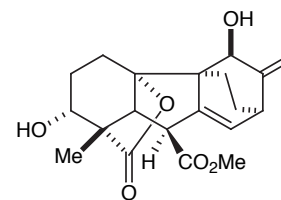
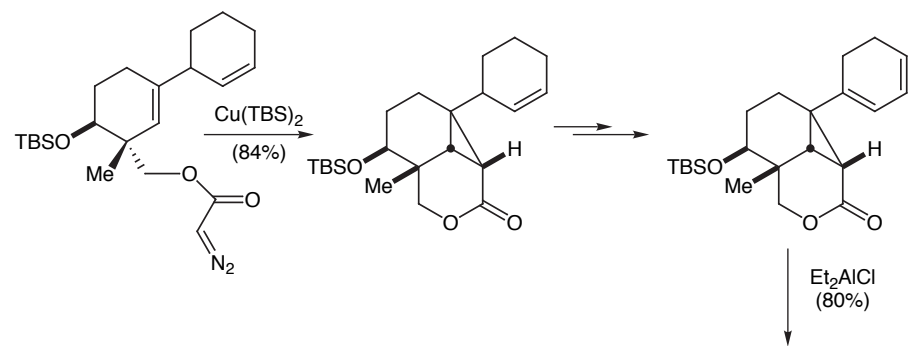
For subsequent reactions: Calter, Evening Seminar 1992

Electron rich olefins work best

Both concerted asynchronous and stepwise mechanisms have been proposed

Cyclopropanes can participate in tandem reactions

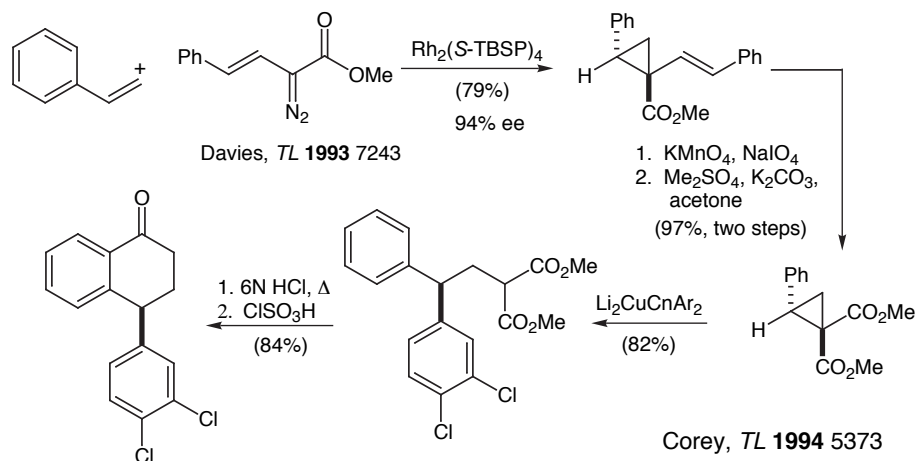
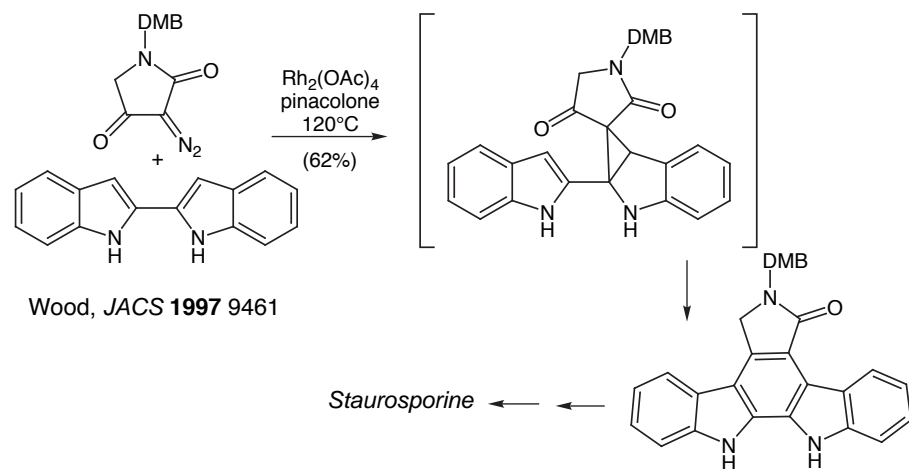
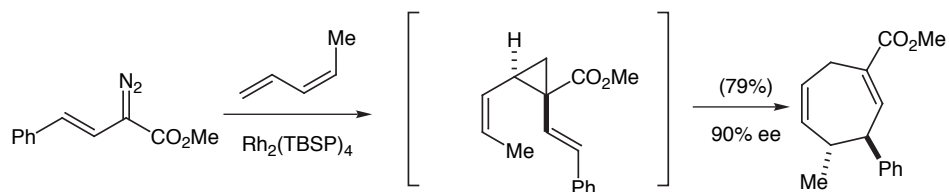
Cyclopropanation Followed by Rearrangement

Davies, *JOC* **1992** 4309; *TL* **1992** 453

Antheridic Acid

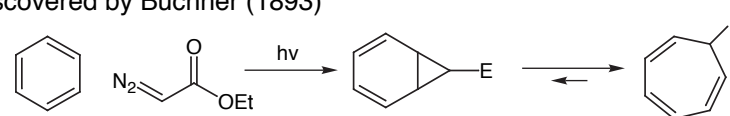
Corey, *JACS* **1985** 5574

More Cyclopropanation

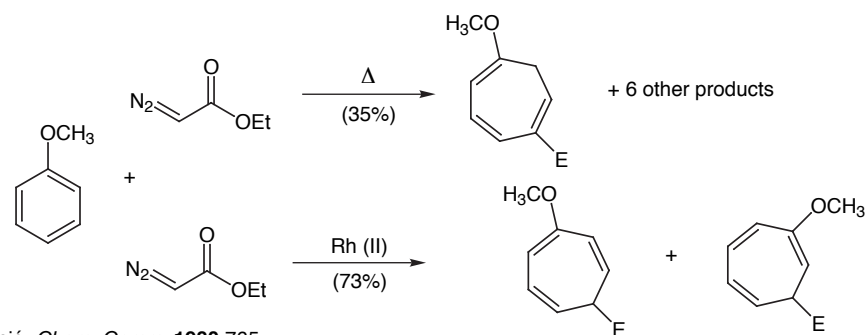


Reaction with Aromatic Rings

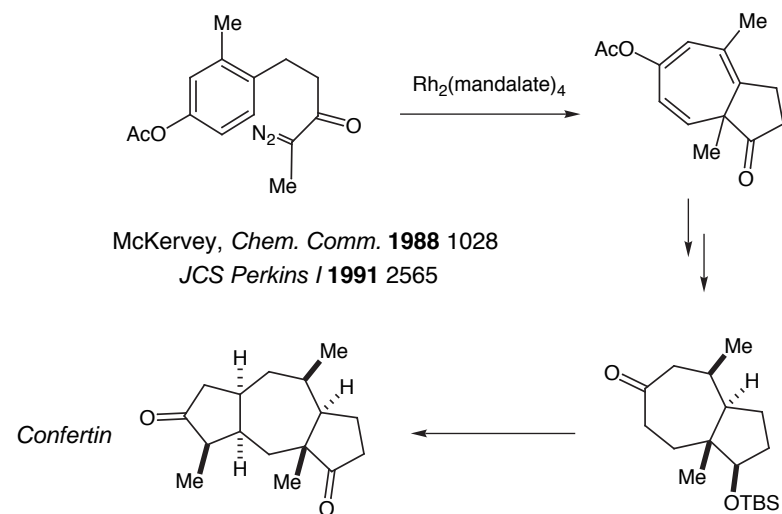
- Discovered by Büchner (1893)



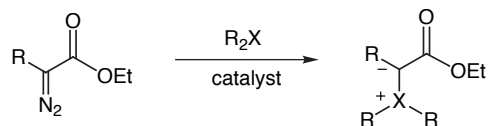
- Initial experiments gave poor selectivity, but transition metals help...



Büchner Reaction: Confertin Synthesis



Ylide Formation

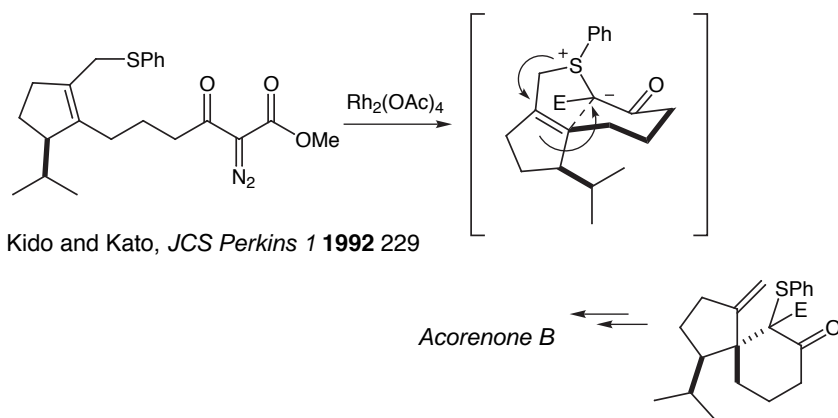
Reviews: Padwa, *Chem. Rev.* **1991** 263Padwa, *Chem. Rev.* **1996** 223

Barnes, Evening Seminar, March 16, 1993

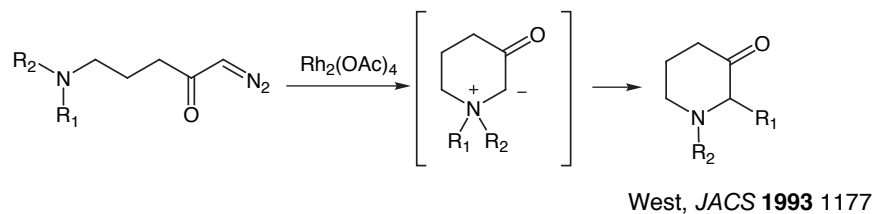
 X is generally S, O or N and can be sp^2 or sp^3 hybridized

Ylides often undergo sigmatropic rearrangements or cycloadditions

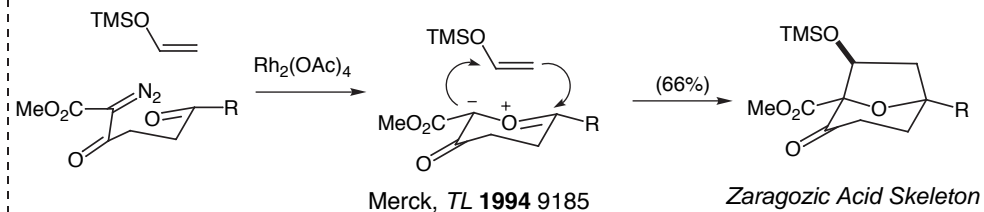
[2,3]-Sigmatropic rearrangement:

Kido and Kato, *JCS Perkins 1* **1992** 229

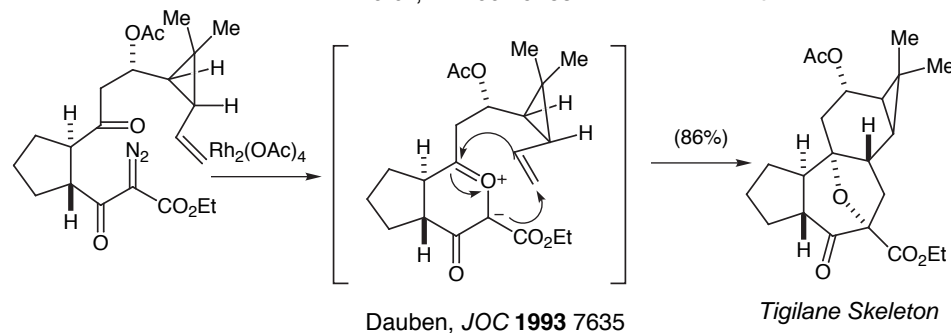
Stevens Rearrangement ([1,2] alkyl shift):

West, *JACS* **1993** 1177

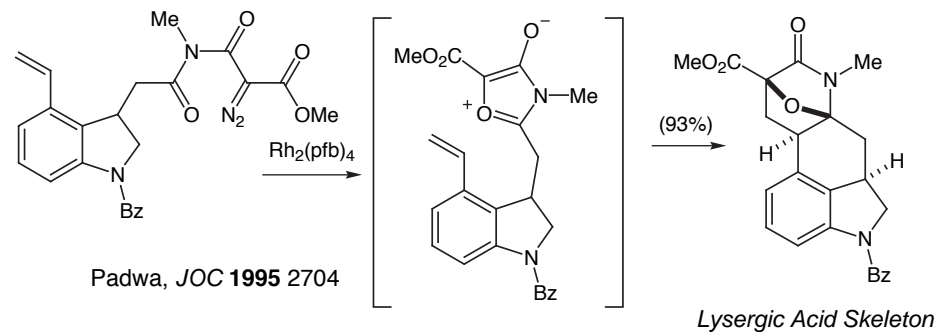
Dipolar Cycloadditions: Carbonyl Ylides

Merck, *TL* **1994** 9185

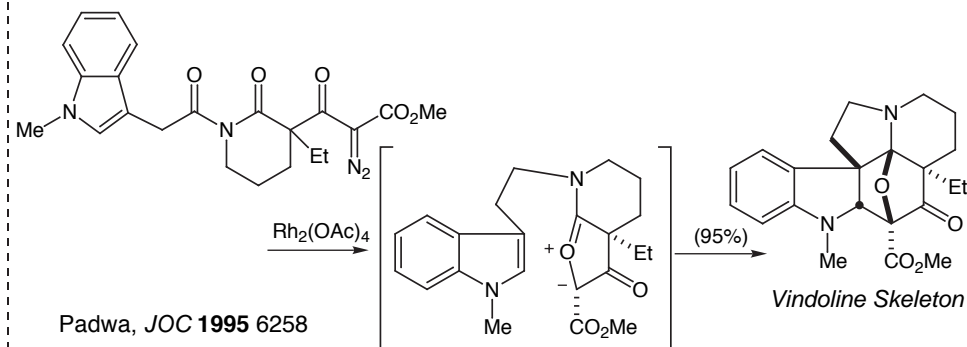
Zarogozic Acid Skeleton

Dauben, *JOC* **1993** 7635

Tigilane Skeleton

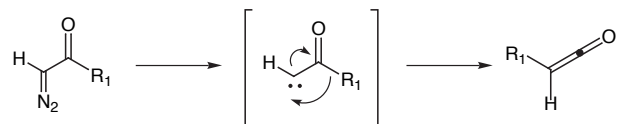
Padwa, *JOC* **1995** 2704

Lysergic Acid Skeleton

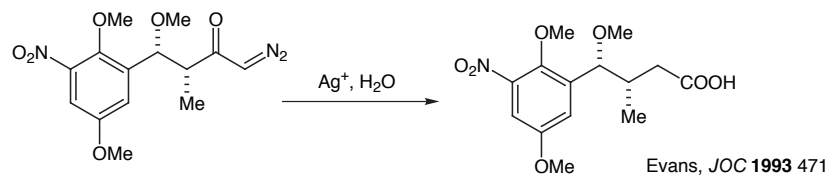
Padwa, *JOC* **1995** 6258

Vindoline Skeleton

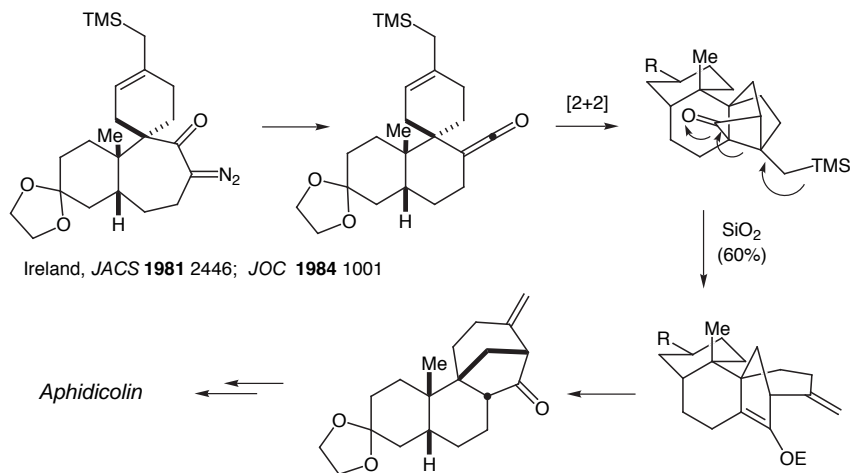
Wolff Rearrangement



Arndt-Eistert Homologation:

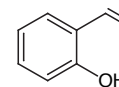


Wolff Rearrangement - [2+2] Cycloaddition

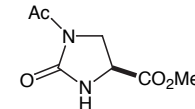


Catalyst Glossary

$\text{Cu}(\text{TBS})_2$ Copper *t*-Butylsalicylaldimine



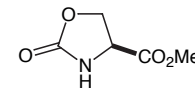
$\text{Rh}_2(\text{MACIM})_4$



$\text{Rh}_2(\text{OAc})_4$ Rhodium Acetate

CH_3CO_2

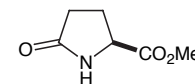
$\text{Rh}_2(\text{MEOX})_4$



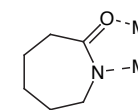
$\text{Rh}_2(\text{acam})_4$ or $\text{Rh}_2(\text{acm})_4$ Rhodium Acetamidate

CH_3CONH

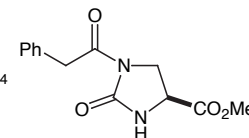
$\text{Rh}_2(\text{MEPY})_4$



$\text{Rh}_2(\text{cap})_4$ Rhodium Caprolactamate



$\text{Rh}_2(\text{MPPIM})_4$



$\text{Rh}_2(\text{oct})_4$ Rhodium Octanoate

$\text{CH}_3(\text{CH}_2)_6\text{CO}_2$

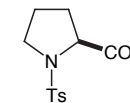
$\text{Rh}_2(\text{pfb})_4$ Rhodium Perfluorobutyrate

$\text{CF}_3\text{CF}_2\text{CF}_2\text{CO}_2$

$\text{Rh}_2(\text{tfa})_4$ Rhodium Trifluoroacetate

CF_3CO_2

$\text{Rh}_2(\text{S-TBSP})_4$



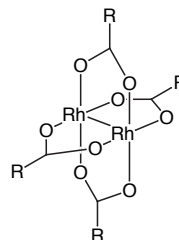
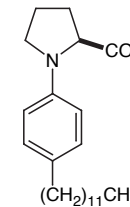
$\text{Rh}_2(\text{tfm})_4$ Rhodium Trifluoroacetamidate

CF_3CONH

$\text{Rh}_2(\text{tpa})_4$ Rhodium Triphenylacetate

Ph_3CCO_2

$\text{Rh}_2(\text{S-DOSP})_4$



All ligands on Rhodium are bridging through the carboxylate or the amide

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 28

Ambiphilic Functional Groups–2 Hydrazone-Based Transformations

- Wolff-Kischner Reduction
- Wharton Rearrangement
- Eschenmoser-Tanabe Fragmentation
- Reduction of Tosyl Hydrazones: "The Alkene Walk"
- Tosyl Hydrazone-Based Fragment Coupling
- The Shapiro Reaction
- Bamford-Stevens Reaction

Reading Assignment for this Week:

Shapiro Reaction: Chamberlin, and Bloom. "Lithioalkenes from arylsulphonyl-hydrazones." *Org. Reactions* **1990**, 39: 1. (**handout**)

Wolff-Kishner & Related Reactions: Hutchins, (1991). "Reduction of C=X to CH₂ by Wolff-Kishner and Other Hydrazone Methods". *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 8: 327. (**in library**)

D. A. Evans

Friday,
November 21, 2003

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.

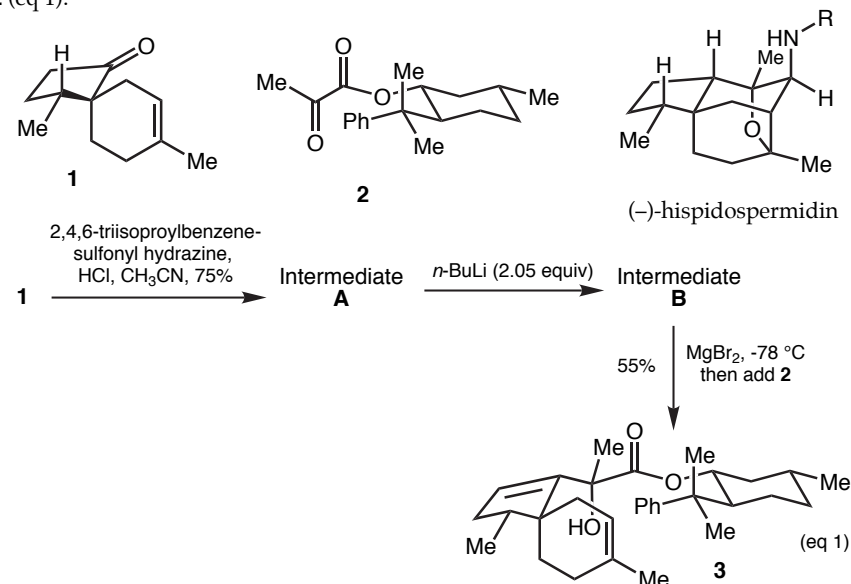
Addington, R. M. and A. G. M. Barrett (1983). "Recent Applications of the Shapiro Reaction." *Acc. Chem. Res.* 16: 55.

Chamberlin, and Bloom (1990). "Lithioalkenes from arylsulphonyl-hydrazones." *Org. React.* (N.Y.) 39: 1.

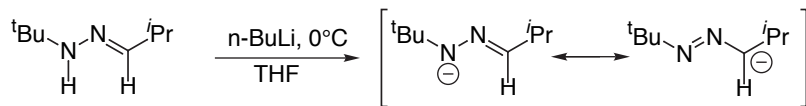
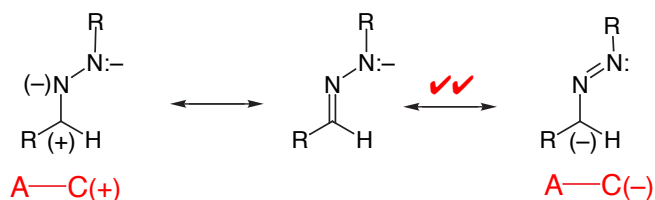
Bergbreiter, and Momongan (1991). "Hydrazone Anions". *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 2: 503.

Cume Question, November, 2000

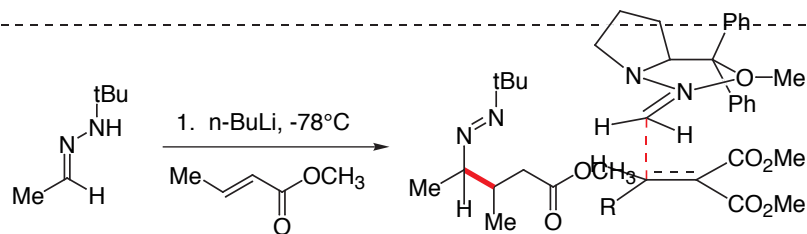
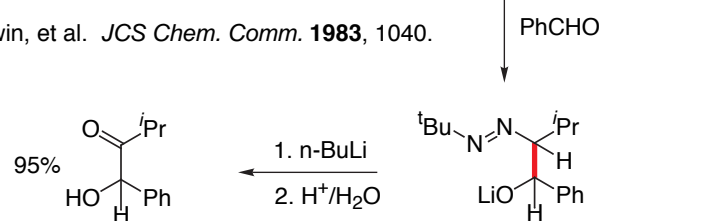
Sorensen and coworkers recently reported the synthesis of (–)-hispidospermidin (Sorensen *JACS*. **2000**, 122, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was used in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



Hydrazone Anions: A useful Reversed Polarity Equivalent

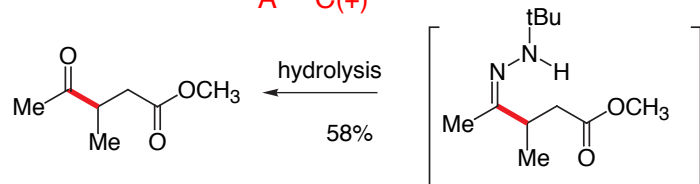


J. E. Baldwin, et al. *JCS Chem. Comm.* **1983**, 1040.

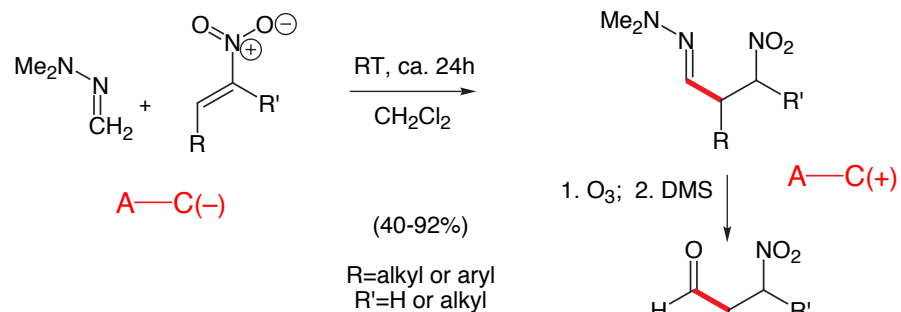


A—C(-)

A—C(+)

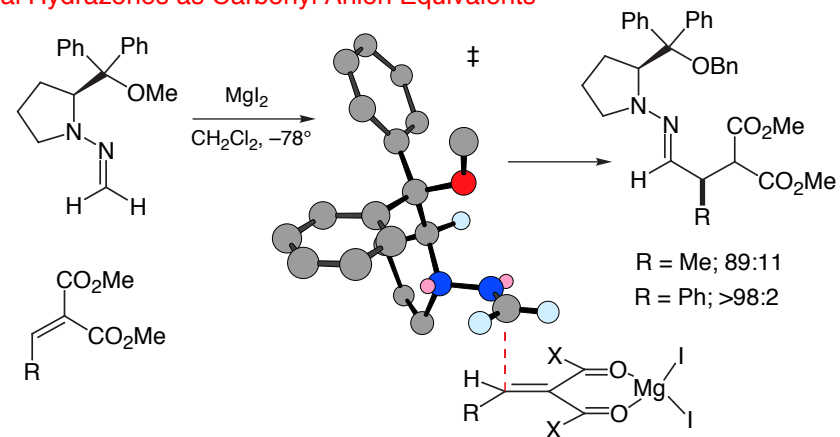


J. E. Baldwin, et al. *JCS Chem. Comm.* **1984**, 1095.

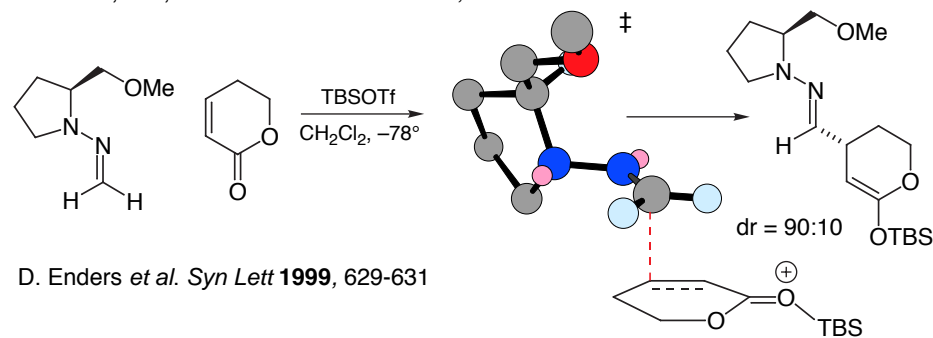


Lassaletta, J-M, et al. *Tet. Lett.* **1992**, 33, 3691.

Chiral Hydrazones as Carbonyl Anion Equivalents

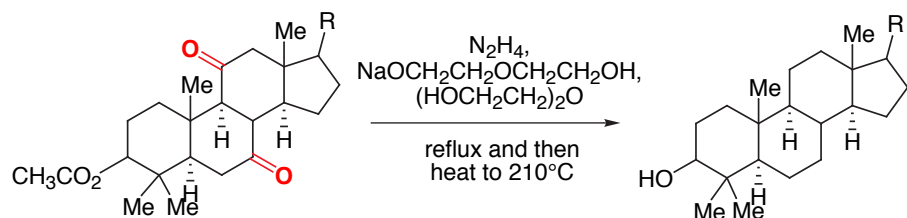


Lassaletta, J-M, et al. *Chem Commun* **2002**, 498-499



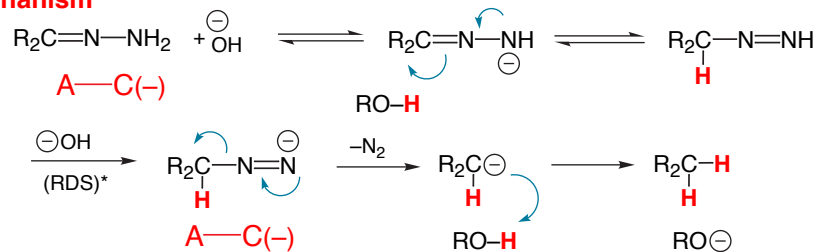
D. Enders et al. *Syn Lett* **1999**, 629-631

Wolff-Kishner Reduction

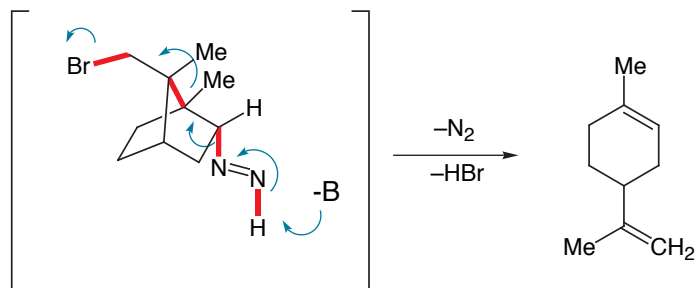
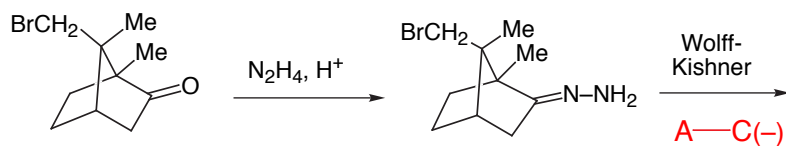


Barton, D. H. R., Ives, D. A. J., and Thomas, B. R. *J. Chem. Soc.* **1955**, 2056.

Mechanism

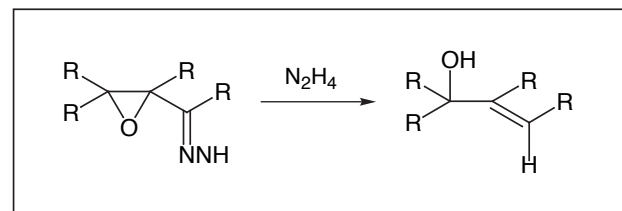


Elimination of α -Leaving Groups

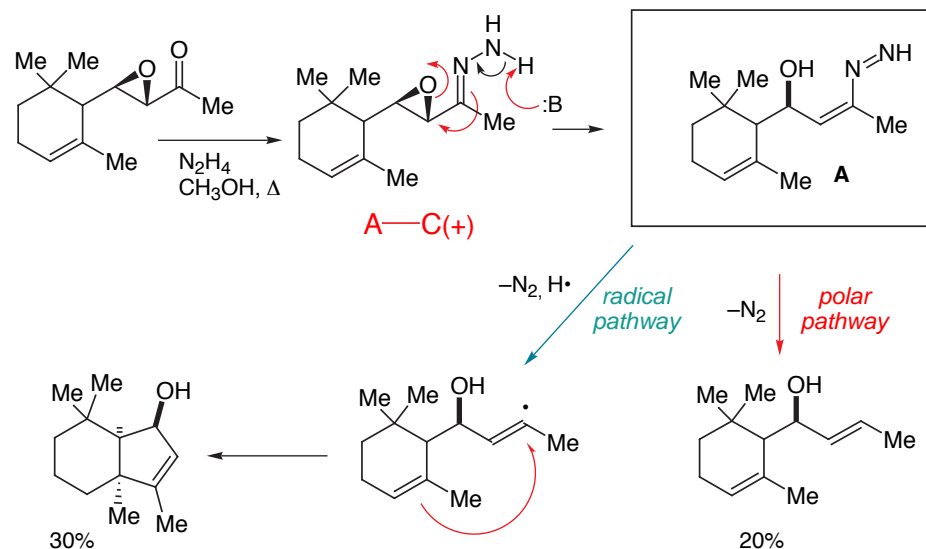


D. H. Gussyafson, W. F. Erman *J. Org. Chem.* **1965**, *30*, 1665.

The Wharton Rearrangement

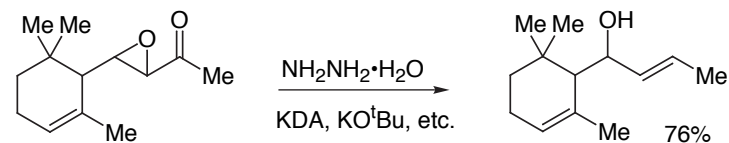


This example illustrates the 2 possible modes for the decomposition of **A**.



G. Stork et al. *JACS* **1977**, *99*, 7067.

Some procedural improvements:



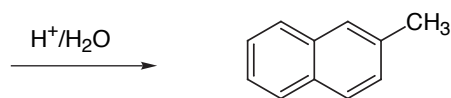
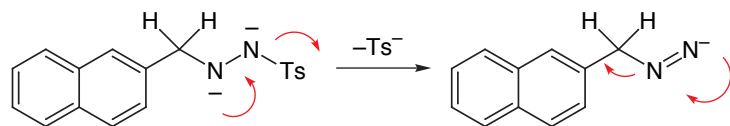
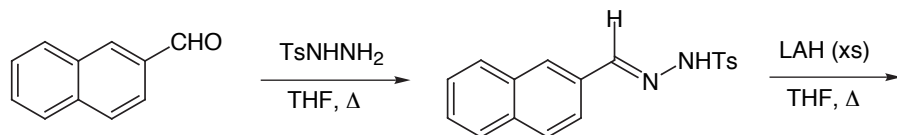
For stable hydrazones, strongly basic conditions favor the ionic pathway.

C. Dupuy, J. L. Luche *Tetrahedron Lett.* **1989**, *44*, 3437.

Tosylhydrazones – Better Than Hydrazones

Tosylhydrazones are isolable, stable, and easily prepared.

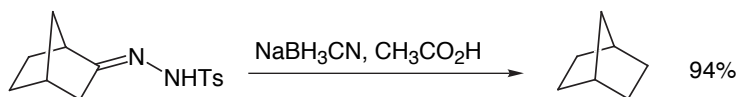
The presence of the tosyl leaving group strongly biases the system towards polar reaction pathways under hydridic reducing conditions.



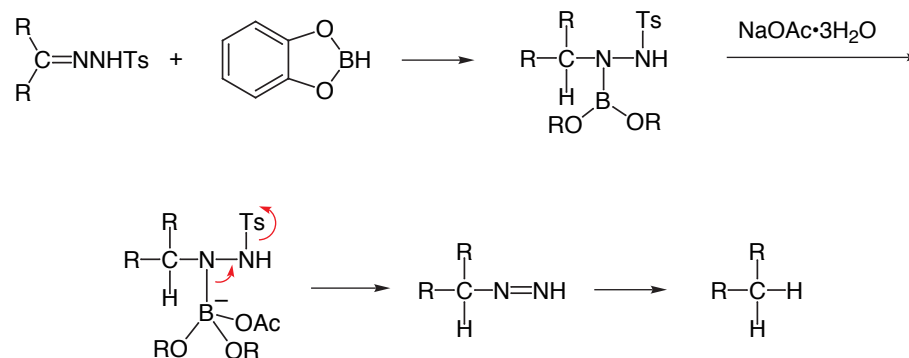
L. Caglioti, M. Magi *Tetrahedron* **1963**, *19*, 1127.

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.

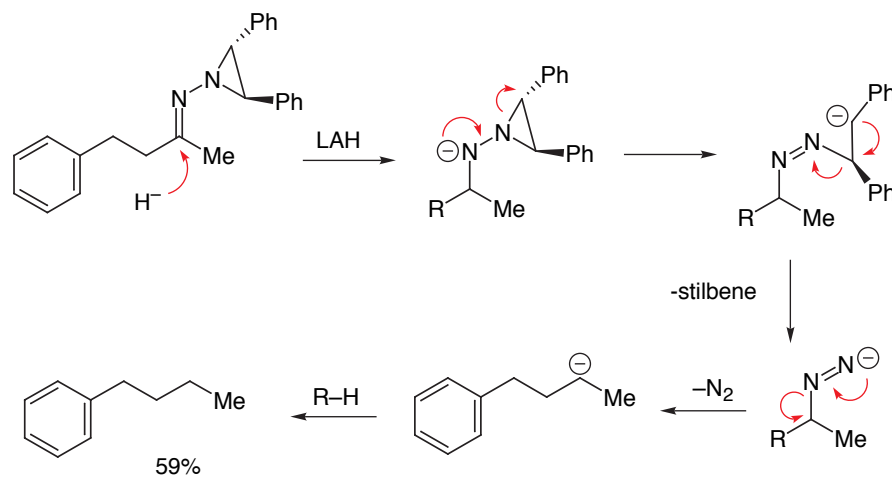


R. O. Hutchins, et al. *JACS* **1973**, *95*, 3662.



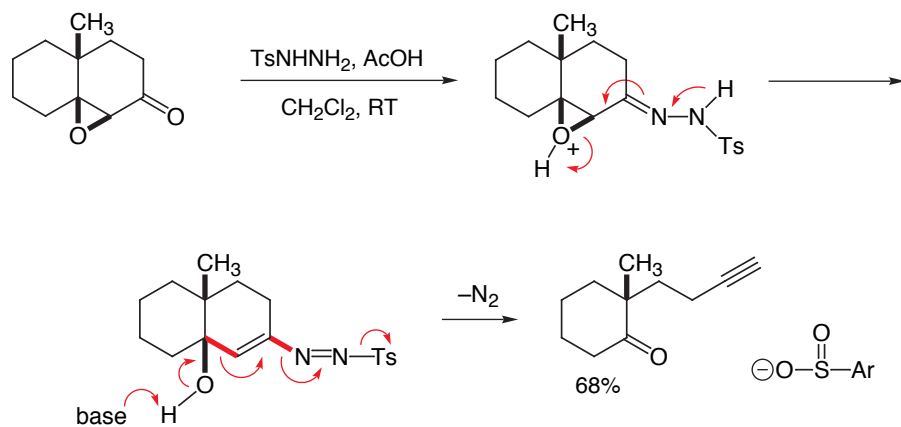
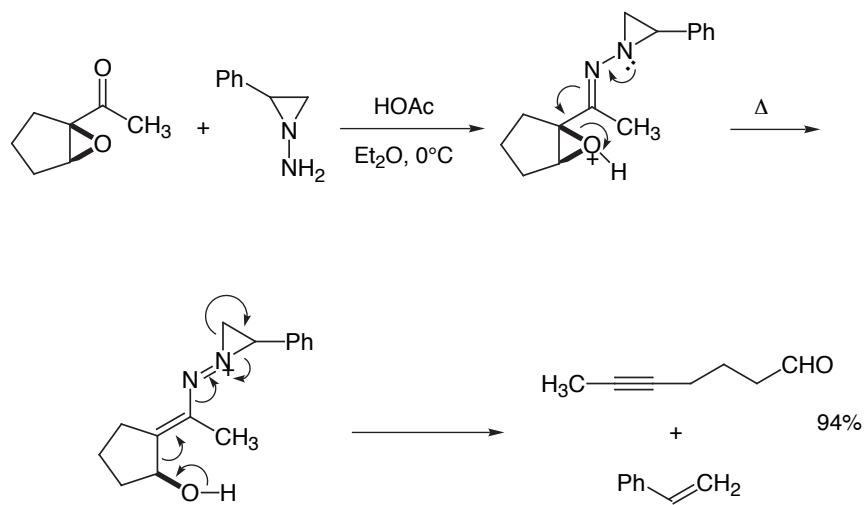
G. W. Kabalka, et al. *J. Org. Chem.* **1975**, *40*, 1834.

Another Interesting Leaving Group

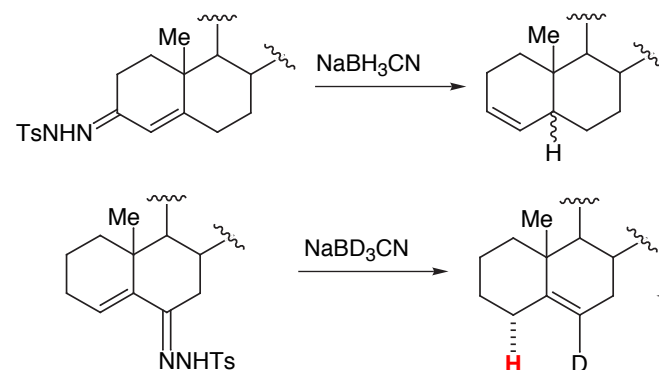
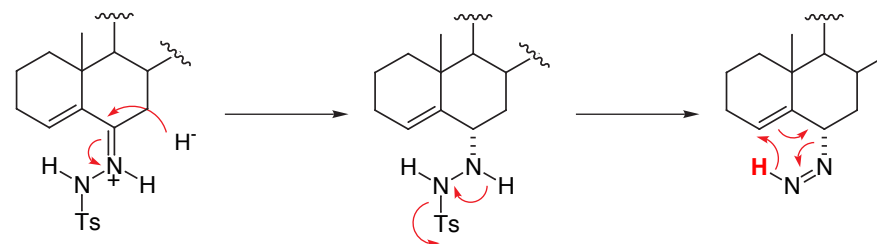


A. R. Chamberlin, et al. *Tetrahedron Lett.* **1991**, *32*, 1691.

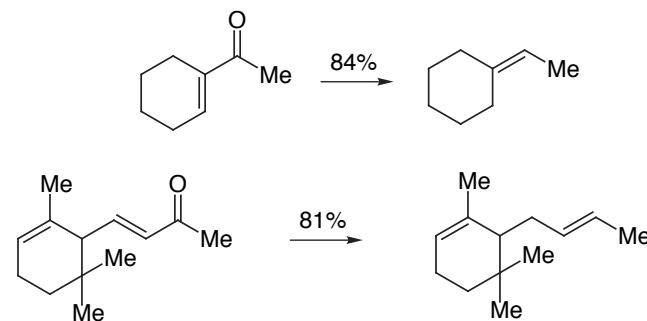
The Eschenmoser–Tanabe Fragmentation

A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, 50, 708.A. Eschenmoser, et al. *Helv. Chem. Acta* **1967**, 50, 2108.

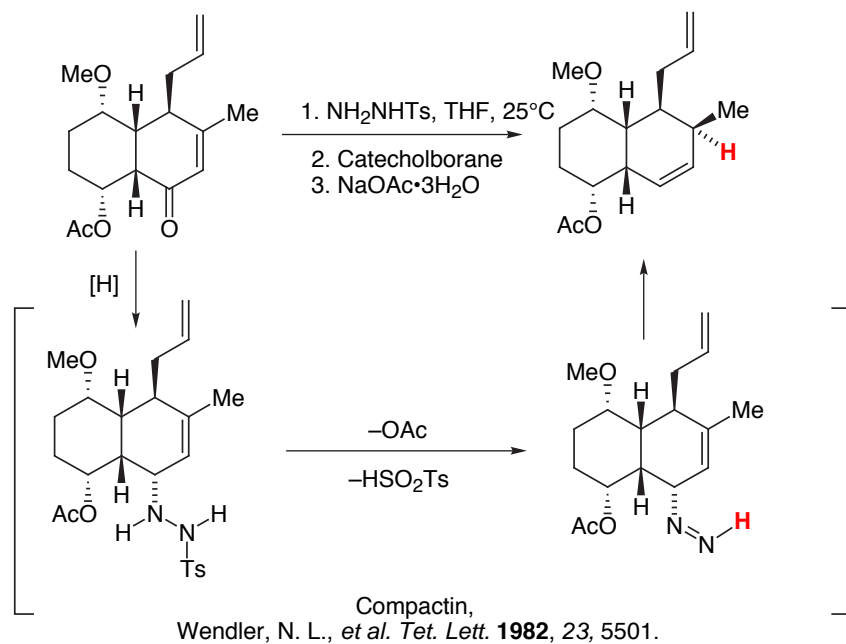
Tosylhydrazone Reductions: The Alkene Walk

C. Djerassi, et al. *JACS* **1976**, 98, 2275.

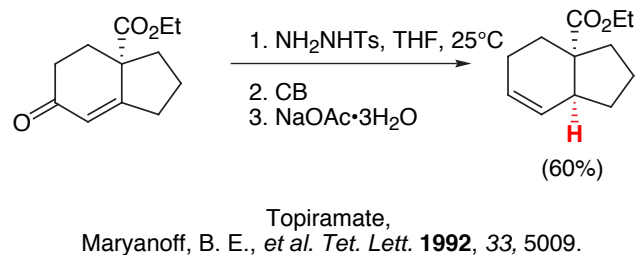
This has been developed into a reliable reduction

16 cases reported: Hutchins, et al. *JOC* **1975**, 40, 923

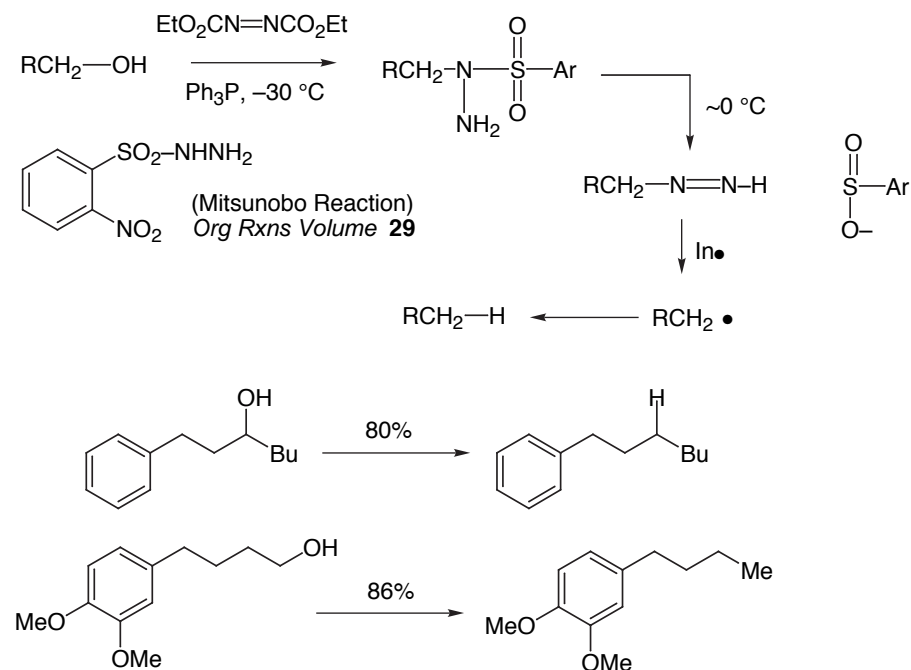
Alkene Walk: Syntheses



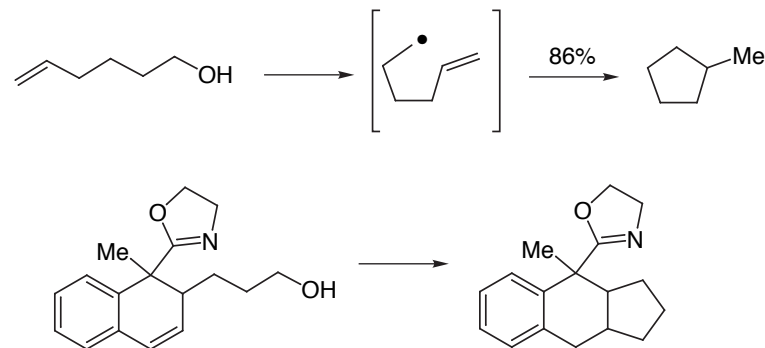
The stereochemical course of the hydrazone reduction may be stereospecifically transferred via the 1, 3-rearrangement



Sulfonylhydrazone Reductions: Alcohol Deoxygenation

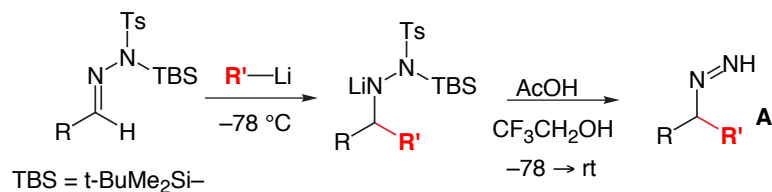
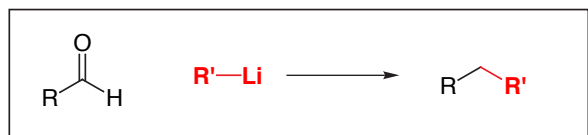


The intervention of radicals has been implicated (again):

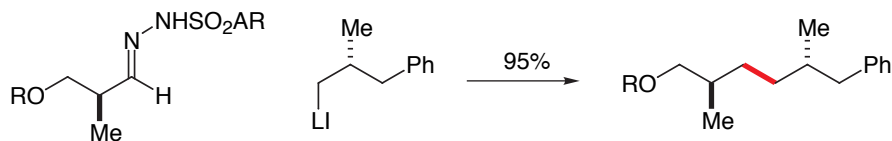


10 cases reported: A. Myers, *et al. JACS* **1997**, 119, 8572.

Tosylhydrazone-Based Fragment Coupling

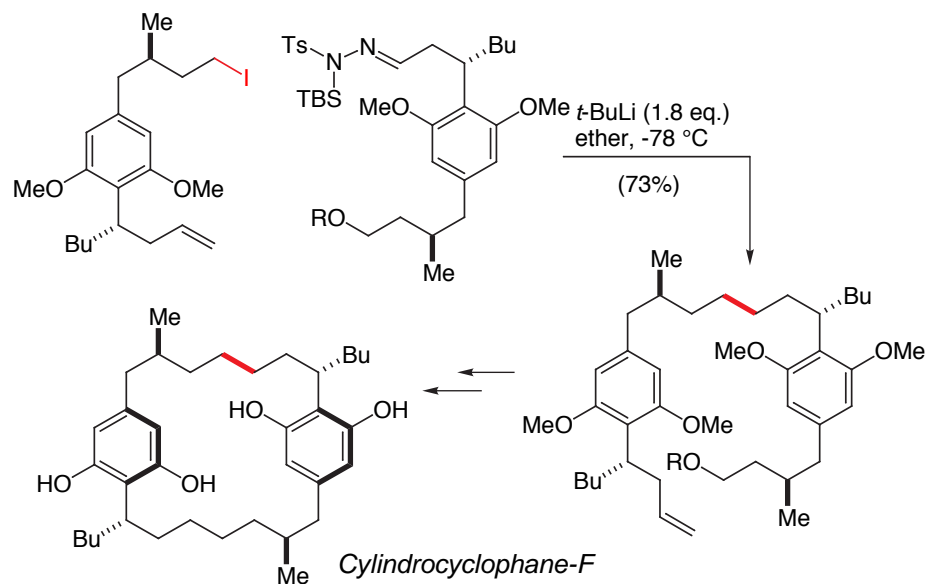


The monoalkyl azene **A** decomposes via a radical pathway



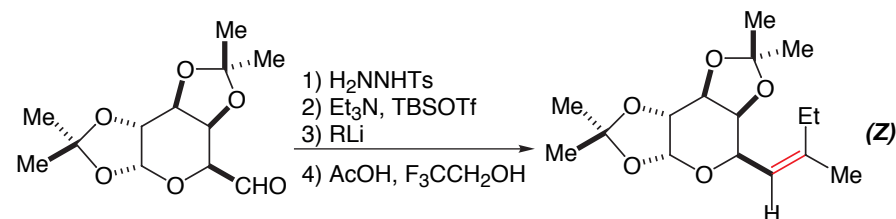
16 cases reported: A. G. Myers et al. *JACS*, **1998**, 120, 8891.

A Complex Application: A. Smith et al. *JACS* **1999**, 121, 7423

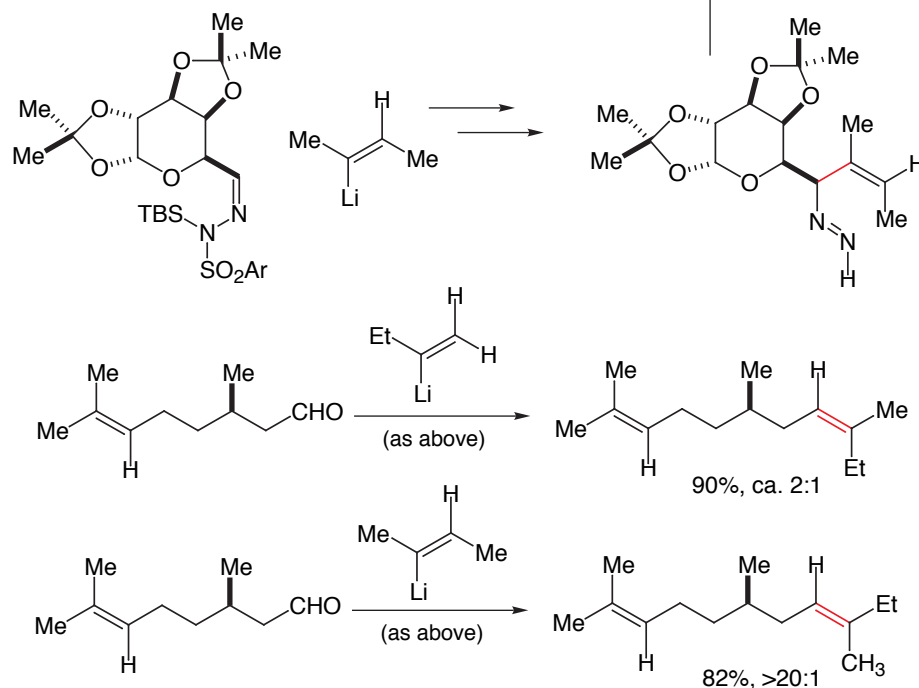


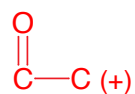
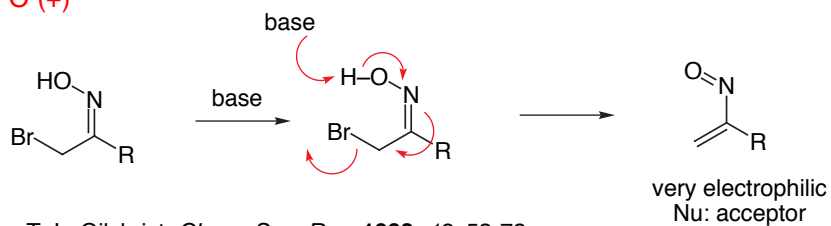
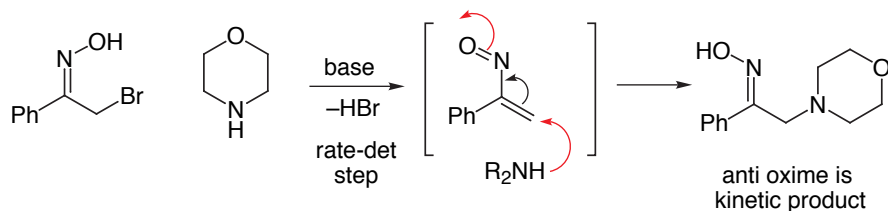
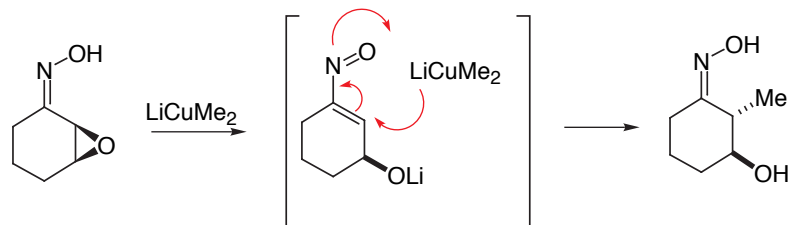
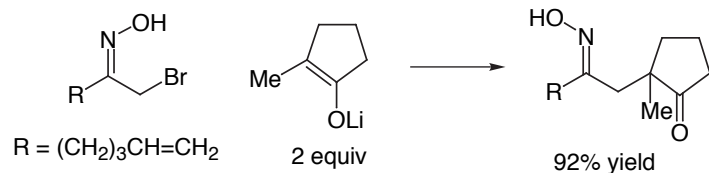
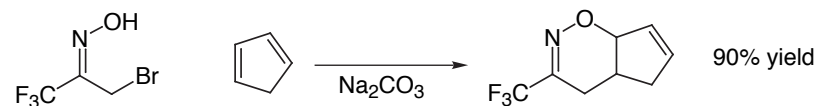
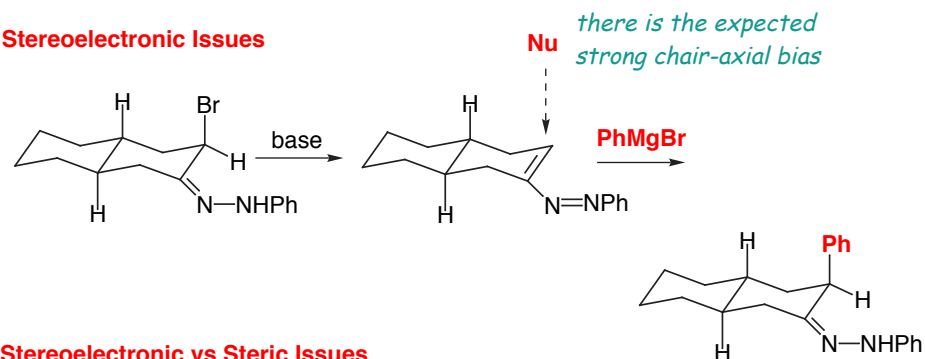
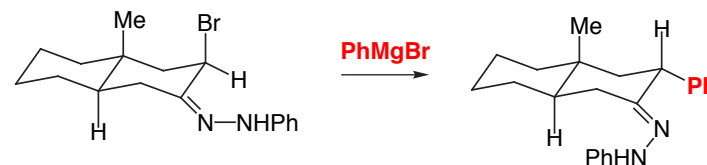
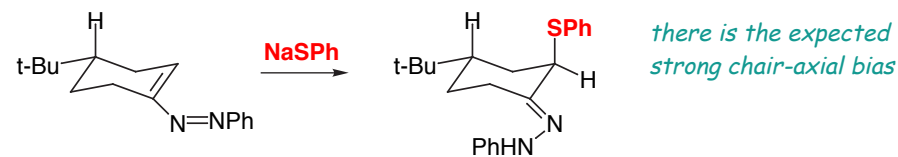
Stereoselective Construction of Trisubstituted Olefins

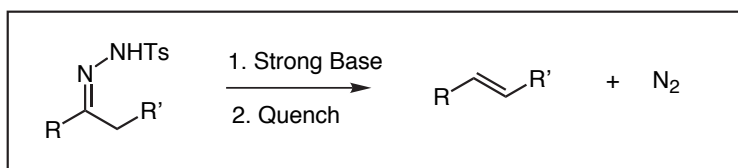
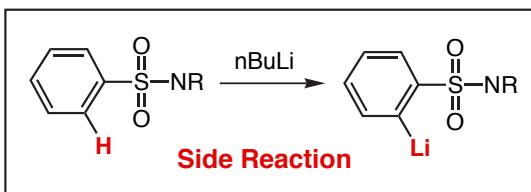
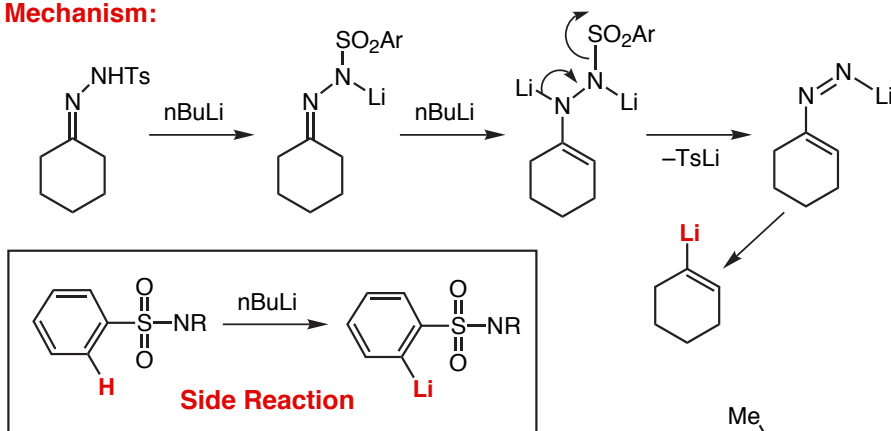
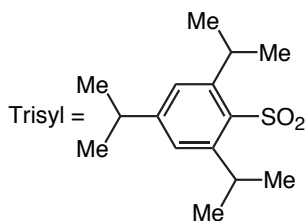
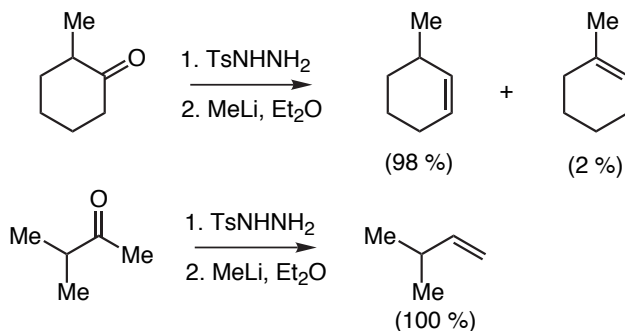
A. G. Myers, P. J. Kukkola *JACS*, **1990**, 112, 8208.



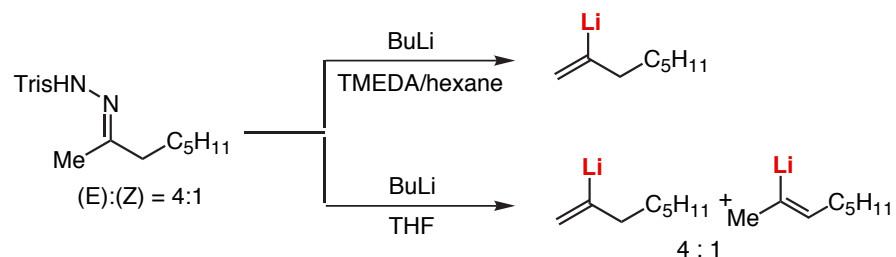
RLi	Ratio Z:E	Yield
	50:50	79%
	<5:95	81%



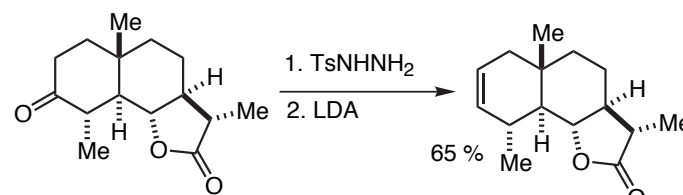
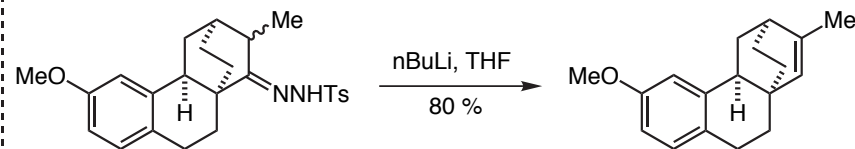
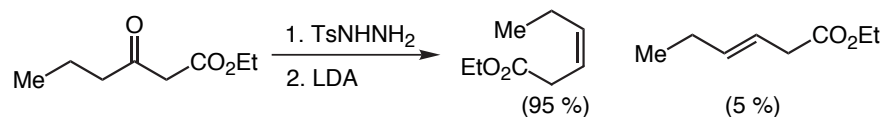
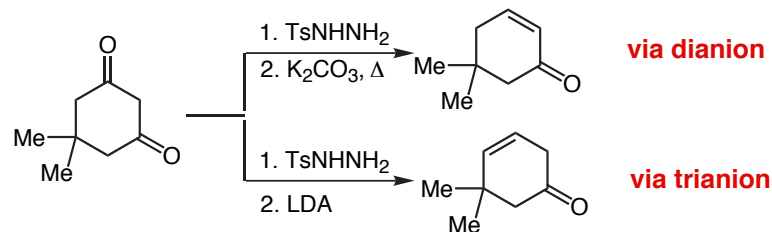
 **α -Keto Carbonium Ion Equivalents**Review: T. L. Gilchrist, *Chem. Soc. Rev.* **1983**, 12, 53-72**Reactions with Nucleophiles**T. Kaiser, *JACS.* **1972**, 94, 9276-9277Corey, *Tetrahedron Lett.* **1975**, 3117Corey, *Helv. Chem. Acta.* **1977**, 60, 2964**Cycloadditions**Ressig, *J. Org. Chem.* **1992**, 57, 339**Stereoelectronic Issues****Stereoelectronic vs Steric Issues**Bozzini, *Tetrahedron* **1982**, 38, 1459Bozzini, *Tetrahedron* **1982**, 39, 3413

**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**

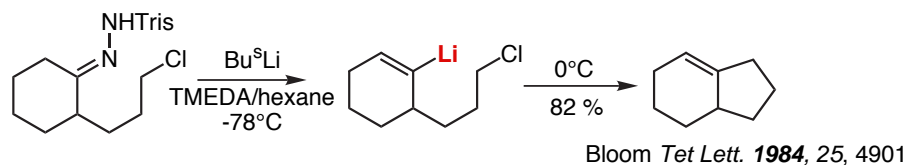
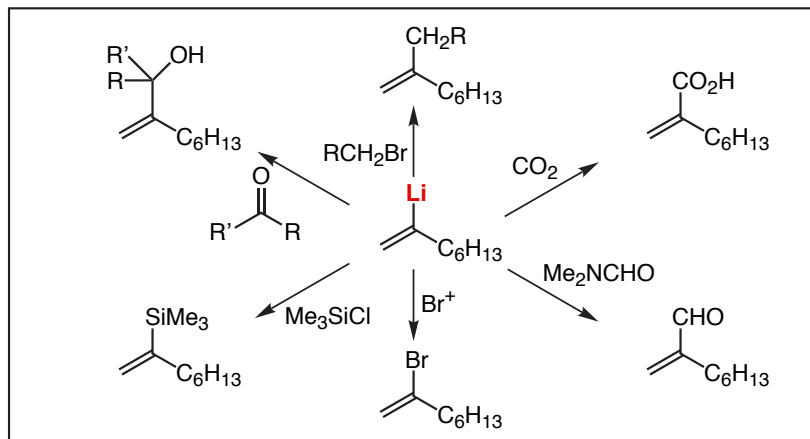
Deprotonation of the monoanion occurs predominantly at the kinetically more acidic site giving after elimination the less substituted alkene product.



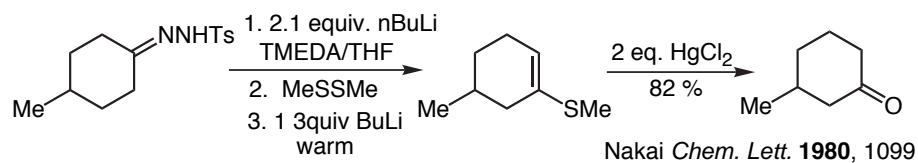
In THF solution regiochemical ratios generally reflect the starting hydrazone geometries

Bond *J. Org. Chem.* **1978**, 43, 154.Grieco *J. Org. Chem.* **1977**, 42, 1717.Nemoto *et. al. JCS, Perkin Trans. 1* **1985**, 927.

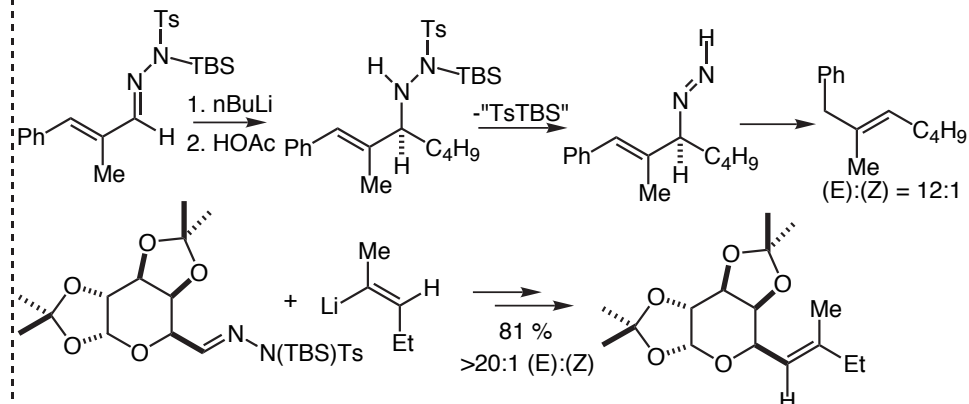
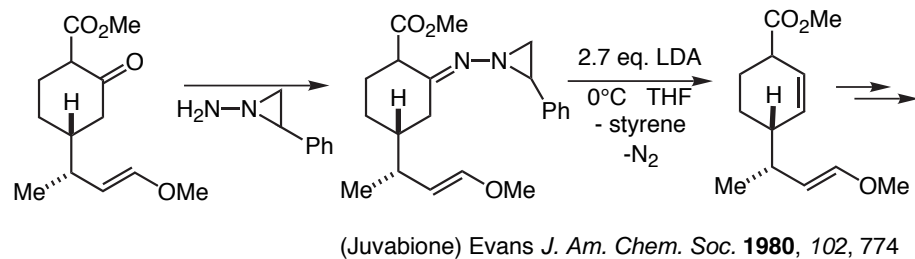
Trapping of the intermediate alkenyllithium



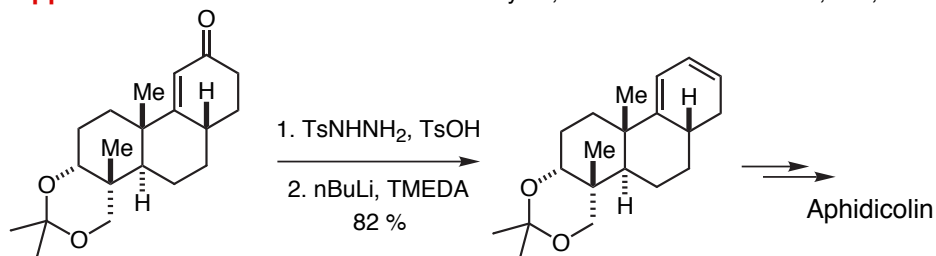
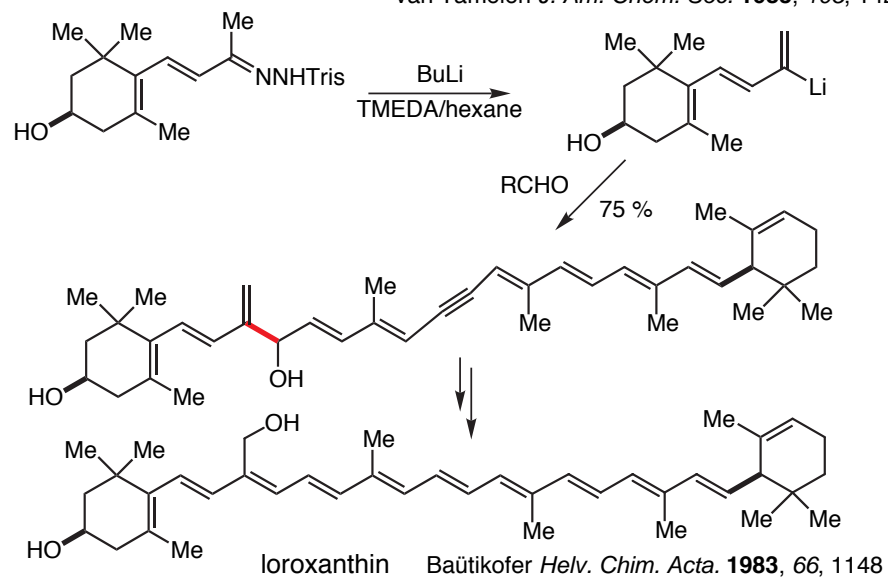
Carbonyl Transposition



Shapiro alternatives

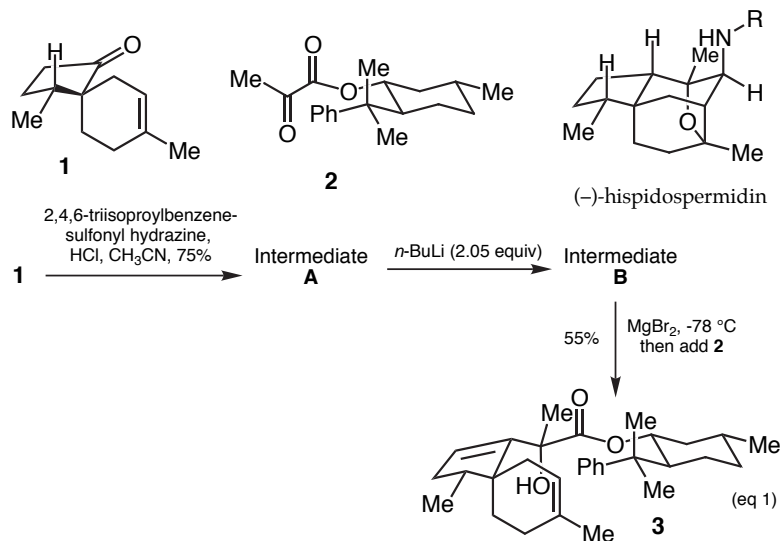


Applications

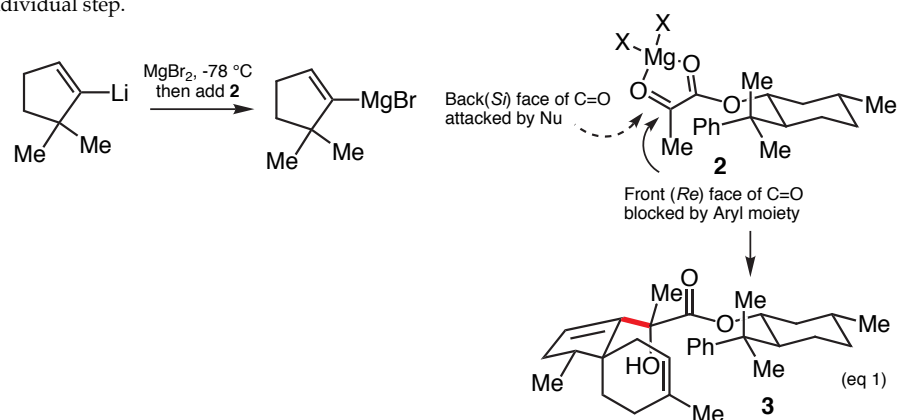
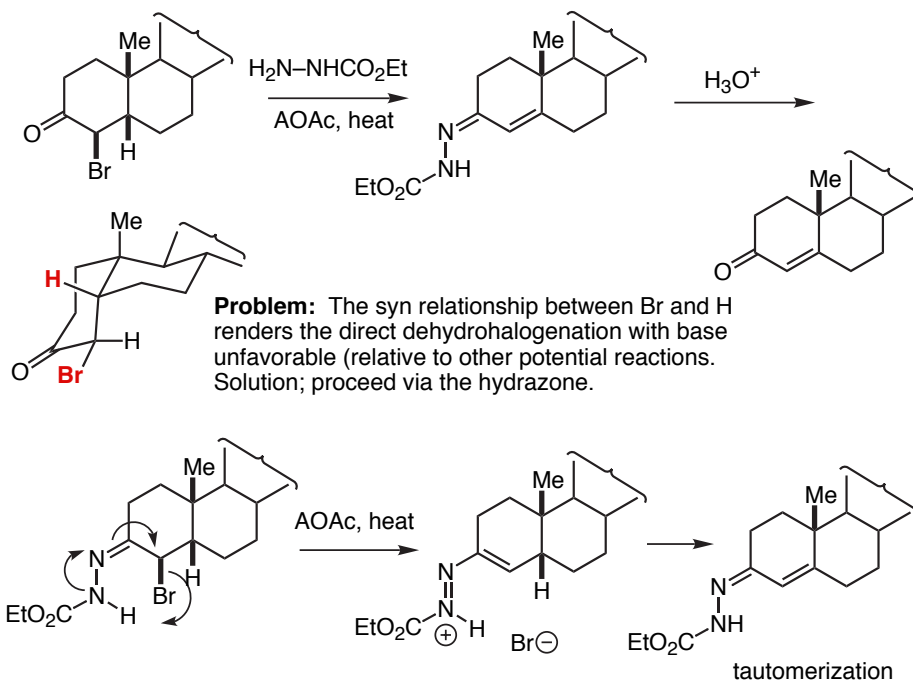
Myers, *J. Am. Chem. Soc.* **1990**, 112, 8208van Tamelen *J. Am. Chem. Soc.* **1983**, 105, 142.

A Recent Application of the Shapiro Reaction

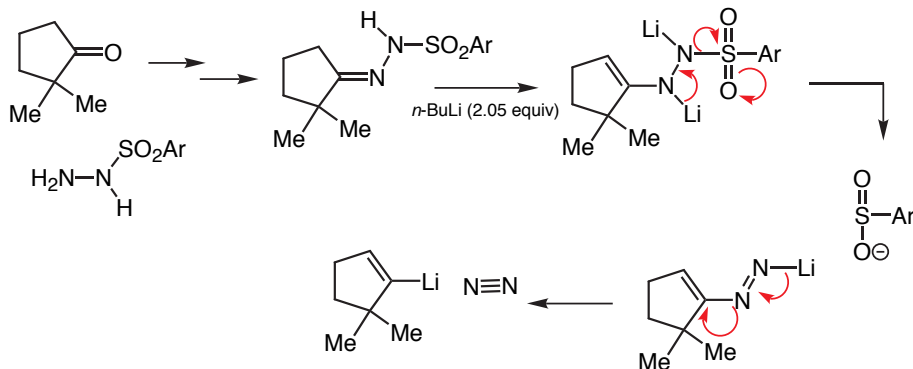
Web Problem 24. Sorensen and coworkers recently reported the synthesis of (-)-hispidospermidin (Sorensen *JACS*, 2000, 122, 9556). The **Shapiro Reaction**, along with methodology developed by Whitesell, was used in the construction of intermediate **3** from the indicated building blocks **1** and **2** (eq 1).



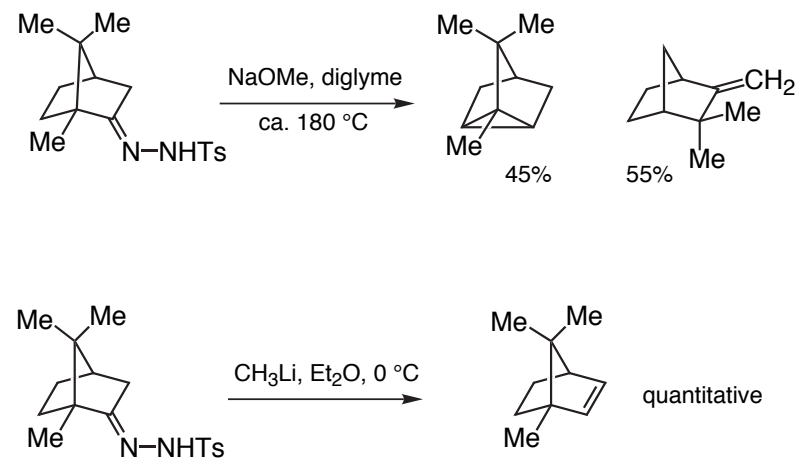
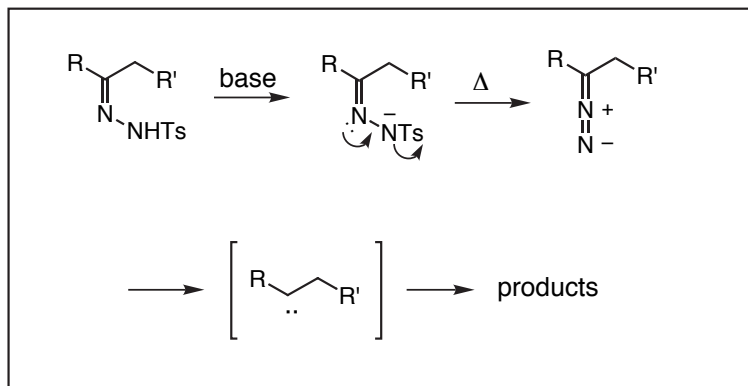
Part B (7 points). Provide a mechanism for the **transformation** of intermediate **B** to the illustrated product **3**. Use 3-dimensional representations to illustrate the stereochemical aspects of this individual step.

Mattox-Kendall Dehydrohalogenation (Paquette, *Reagents*, Vol 5, p 3509)

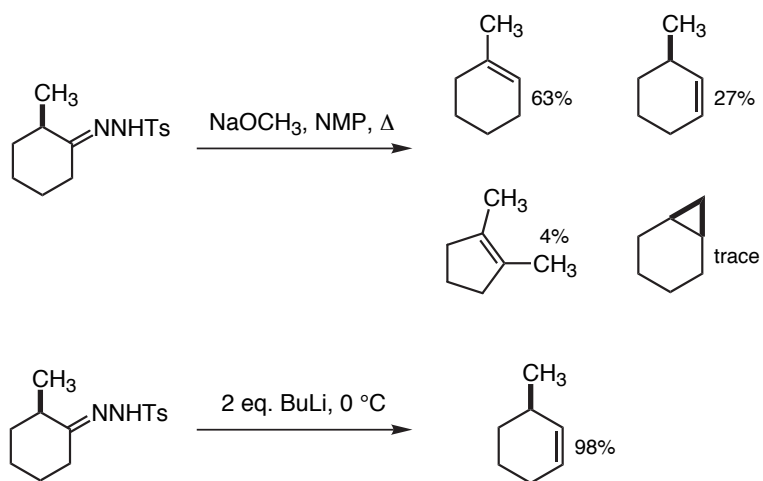
Part A (8 points). Provide a mechanism for the **Shapiro Reaction** of **1** to intermediate **B** in the space below. Feel free to use a simplified analog of **1** such as 2,2-dimethylcyclopentanone to answer this question.



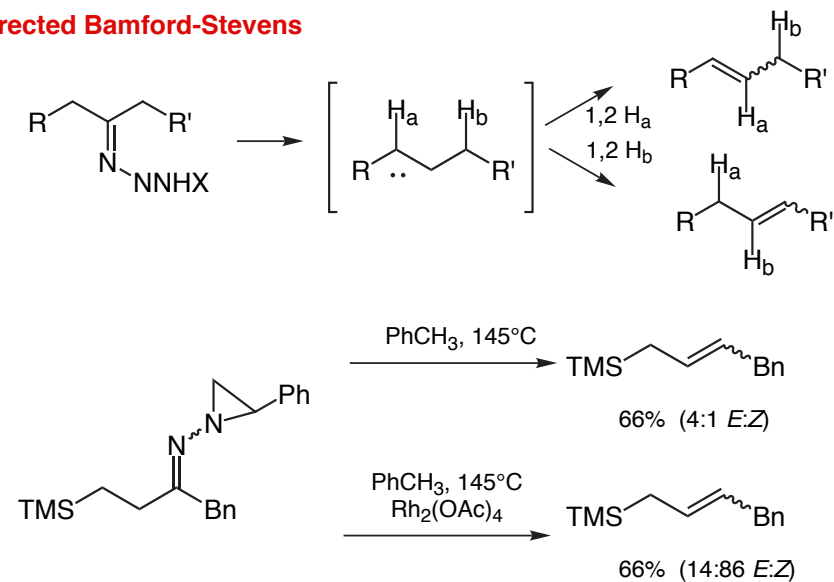
An Alternate Decomposition Pathway for Tosyl Hydrazones



Bamford-Stevens vs. Shapiro

R. H. Shapiro *Org. React.* **1976**, 23, 405.

Directed Bamford-Stevens

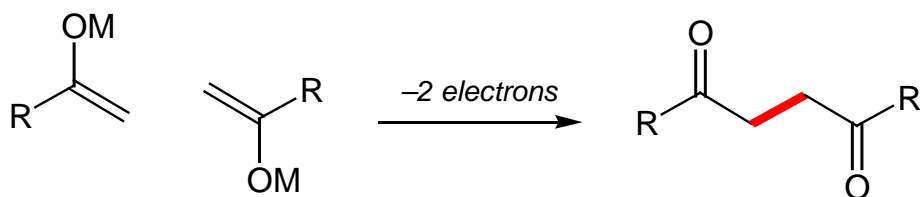
T. K. Sarkar, et al. *JCS Chem. Comm.* **1992**, 1184.

Chemistry 206

Advanced Organic Chemistry

Handout-28A

Oxidative Coupling of Enolates & Enol Derivatives



Chuck Scales

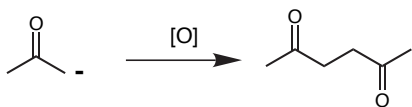
Evans Group Seminar, March, 1995

D. A. Evans

Friday,
November 21, 2003

The Oxidative Coupling of Enolates and Enol Derivatives

Evans Research Seminars
March 14, 1995



An underappreciated umpolung of enolates

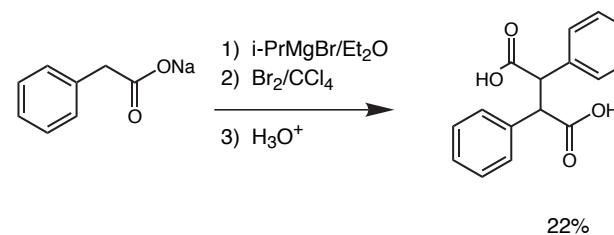
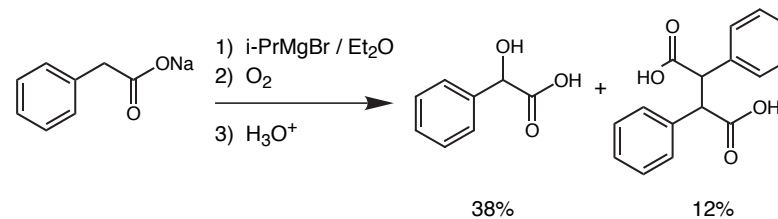
1. Ketone Enolates
2. Ester Enolates
3. Carboxylic Acid Dianions
4. Silyl Enolate Derivates
5. Applications to Organic Synthesis

Leading Papers:
Saegusa, T. *JACS*, **1977**, 99, 1487
Fox, M.A. *JOC*, **1988**, 53, 3745
Narasaka, K. *Chem. Letters*, **1992**, 2099

Chuck Scales

Reaction Background

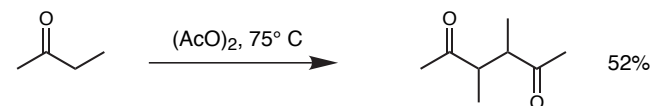
Synthesis of 3,4-diphenyl succinic acid



- Also obtained a "high" yield of α -bromophenylacetic acid
- Proposed radical dimerization as mechanism for production of β -diphenylsuccinic acid.

Ivanoff, *Bull. Soc. Chem. Fr.*, **1935**, 2, 76

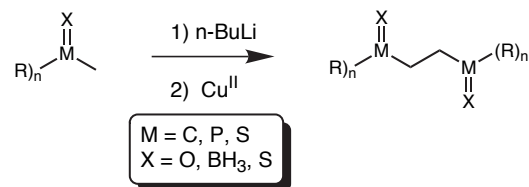
Synthesis of 1,4 Diketones



Kharasch, M.S., McBay, H.C., and Urry, W.H., *JACS*, **1948**, 70, 1269

Reaction Background

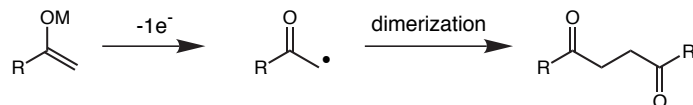
Coupling of Stabilized Anions



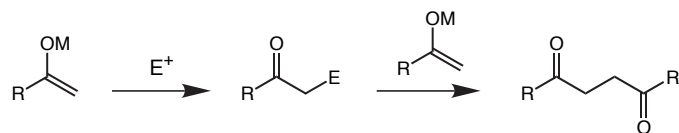
Mislow, K. *JACS*, **1973**, 95, 5839
 Tamaru, Y. *JACS*, **1978**, 100, 1923
 A. Muci and K. Campos, unpublished results

Anion Coupling Models

- Type 1 Oxidants

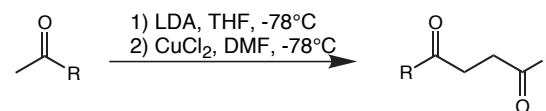



- Type 2 Oxidants



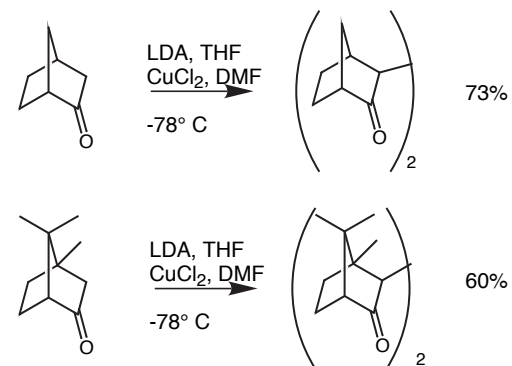
Synthesis of 1,4-Diketones

Methyl Ketone Dimerization



R	Yield
phenyl	95%
ferrocenyl	78%
furanyl	41%
cyclopropyl	46%
-C(CH ₂) ₂ CO ₂ Et	64%
-CH=CH- 	82%

α-Substituted Ketone Dimerization

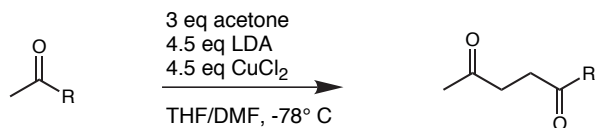


- Product mixture of exo-exo, exo-endo, and endo-endo isomers

Saegusa, *JACS* **1977**, 99, 1487

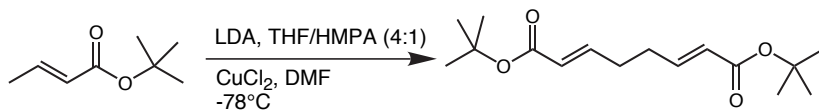
Synthesis of 1,4-Diketones

Cross-Coupling of Methyl Ketones

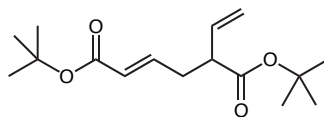


R	Yield	
	Cross-couple	Dimer
	68%	1%
	53%	1%
	59%	4%
	65%	2%

γ Coupling of α,β -unsaturated ketones



33% γ,γ coupling product



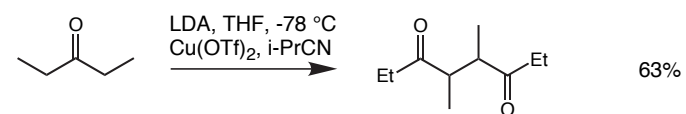
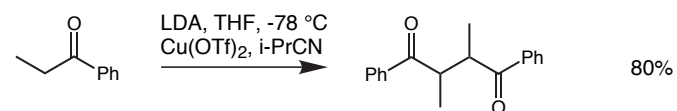
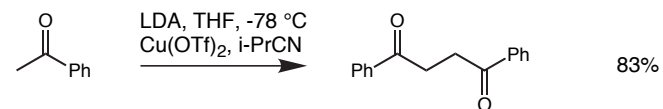
32% α,γ coupling product

- No α,α coupling product seen
- γ,γ couple not produced from thermal rearrangement of α,α product

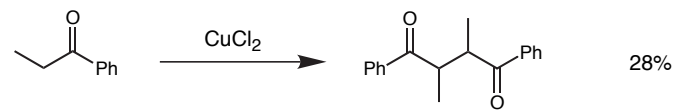
Saegusa, T. et al. *JACS* **1977**, *99*, 1487

1,4-Diketones with Copper (II) Triflate

From enolates



Anions Make a Difference

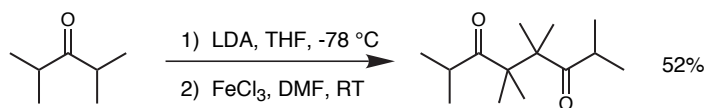


- Yield difference may be due to lability of triflate versus chloride ions

Kobayashi, et al. *TL*, **18**, 3741 (1977)
Kobayashi, et al. *Chem. Pharm. Bull.*, **28**, 262 (1980)

Coupling of Ketone Enolates

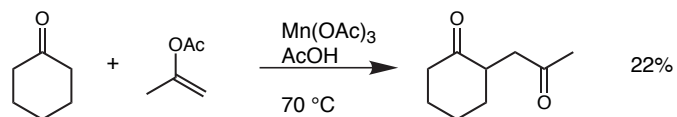
Oxidative Coupling with Ferric Chloride



- Dimers obtained from hindered enolates in moderate yields (40-60%)
- Prepared from kinetic and thermodynamic enolates

Frazier, R.H. et al. *JOC*, **1980**, 45, 5408

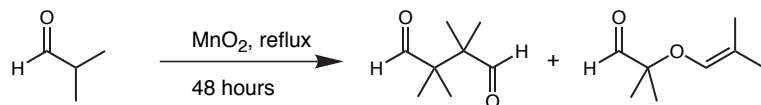
Oxidation with Manganic Acetate



- Proposed radical coupling mechanism for transformation

Dessau, R.M. et al. *JOC*, **1974**, 39, 3457

Oxidative Dimerization of Aldehydes

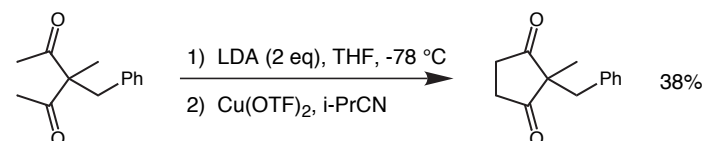


- All examples produced ca 80% yield of dimer in 45:55 ratio (C-C:C-O).

Leffingwell, J.C. *JCS Chem. Comm.*, **1970**, 357

Intramolecular Coupling

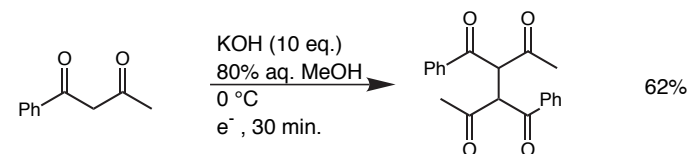
Ketone cyclization



- Generally poor yields; spirocyclic examples included.

Kobayashi, et al. *TL*, **1978**, 19, 3555

Tetraketone Synthesis



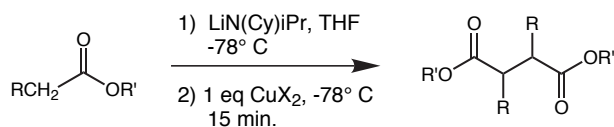
- Synthesized various aryl substituted 3,4-aryol-2,5-hexanediones
- Observed that EDG favor oxidation and EWG disfavor oxidation (correlated to Hammett plot)

Hammett Plot Here

Lacan, M. et al. *Croat. Chem. Acta*, **1973**, 45, 465

Ester Enolate Coupling

Synthesis of Succinate Esters



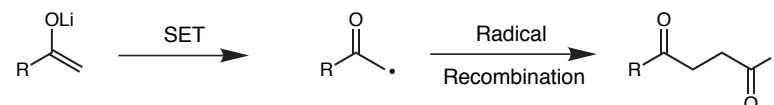
R	R'	Yield	
		CuBr ₂	Cu(O ₂ C ₅ H ₉) ₂
-H	-t-Bu	85	95
-Me	-Et	81	50
-n-Bu	-Et	63	----
-Me ₂	-Et	25	20
-i-Pr	-Et	20	20
-Ph	-Et	75	60
	-Et		

- Increasing alkyl substitution decreases yield of dimer
- Yield of α-bromoester increased with increasing alkyl substitution when copper (II) bromide used as oxidizing agent
- Yield of dimer not increased with copper (II) valerate
- Product obtained as an unspecified mixture of stereoisomers

Rathke, *J. Am. Chem. Soc.* **1971**, 93, 4605

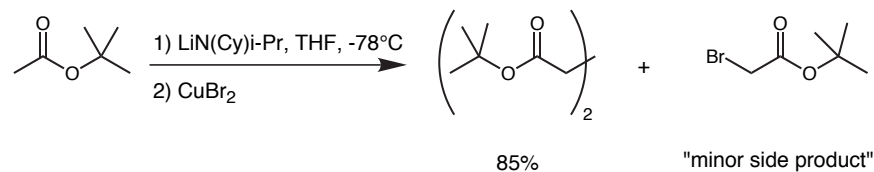
Oxidative Coupling Mechanism

Proposed Mechanism

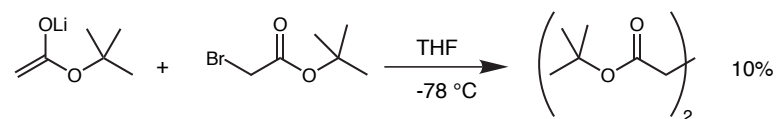


- Radical may be associated with oxidizing agent

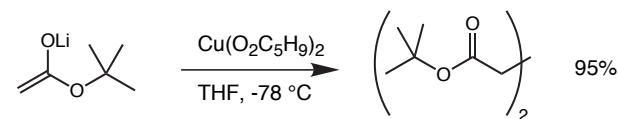
Evidence for Radical Mechanism



- Investigation of possible S_N2 mechanism



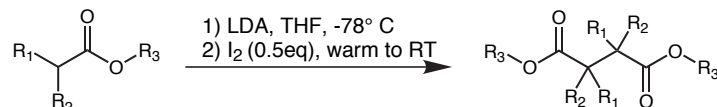
- Exclusion of bromide source also leads to product



Rathke, *J. Am. Chem. Soc.* **1971**, 93, 4605

Succinate Esters with Other Oxidants

Oxidation with Iodine

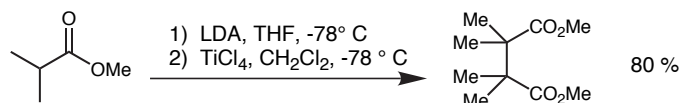


R ₁	R ₂	R ₃	Yield
H	H	t-Bu	97%
Me	H	t-Bu	80%
Me	Me	Me	90%
Me	Me	Et	85%

- Authors propose an S_N2 mechanism for this transformation

Brocksom, T.J., et al. *Synthesis* **1987**, 396

Oxidation with TiCl₄

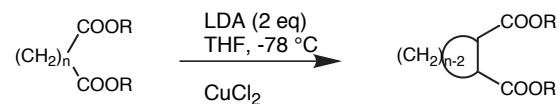


- Excellent yields with α -substituted esters (i-Pr, BnO)
- Other Lewis acids (BF₃·OEt₂, SnCl₄) do not promote oxidation
- ZrCl₄ resulted in Claisen condensation products
- Not applicable for ketones or amides

Ojima, et al. *Chem. Letters* **1992**, 1591

Intramolecular Coupling

Ester cyclization



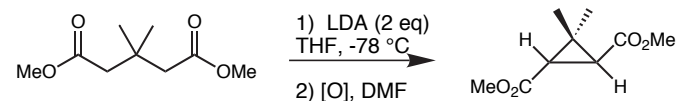
n	R	Yield
3	Me	88% (3:1 cis:trans) ^a
4	t-Bu	20% (undetermined mixture of stereoisomers) ^b
5	t-Bu	>50% (undetermined mixture of stereoisomers) ^b
6	Me	93% (0.6:1 cis:trans) ^a

- Equilibration between cis and trans isomers noted for all reactions.
- Dimethyl adipate and dimethyl pimelate gave exclusively Dieckmann cyclization under the reaction conditions.

^aChung, S.K. et al. *JOC*, **1983**, 48, 1125

^bBabler, J.H. et al. *JOC*, **1987**, 52, 3462

Oxidation of dimethyl β,β -dimethylglutarate



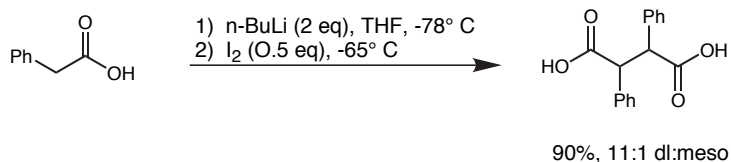
Oxidant	Temp.	Yield	cis:trans
CuCl ₂	-78	71%	57:43
CuCl ₂	0	83%	68:32
I ₂	-78	76%	19:81
AgCl	-78	81%	80:20

- No attempt to rationalize stereochemical outcome of reaction

Babler, J.H. et al. *Synth. Comm.*, **1983**, 13, 905

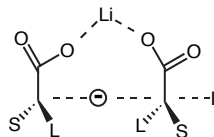
Carboxylic Acid Dianion Coupling

Coupling of Acid Dianions



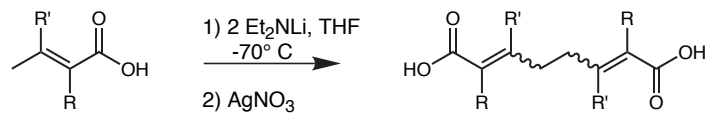
- Yields increased with dianion salt isolation

Stereochemical Model

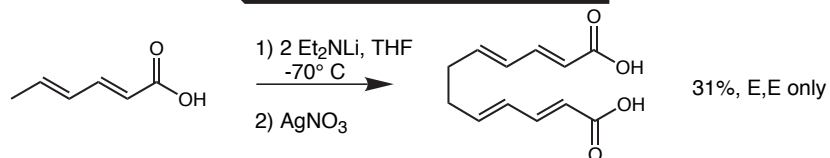


Belletire, J.L. et al. *TL*, **1984**, *25*, 5969

γ Coupling of α,β-Unsaturated Carboxylic Acids



R	R'	Yield	E,E:E,Z:Z,Z
H	H	49	1:0:0
Me	H	63%	1:0:0
H	Me	38%	1:1:1
Me	Me	61%	7:3:0

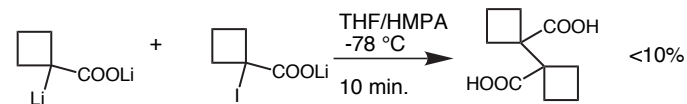
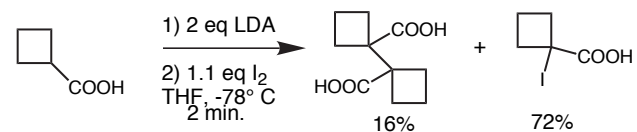


- No rationale for observed stereochemistry
- Also observed unspecified yields of γ,α coupled product

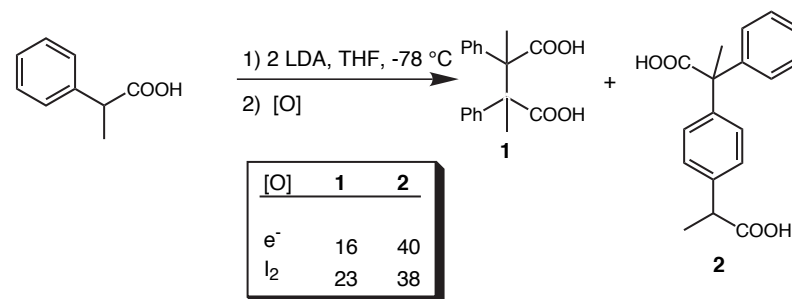
Mestres, R. *TL*, **1988**, *29*, 6181

Iodine Oxidation Mechanism

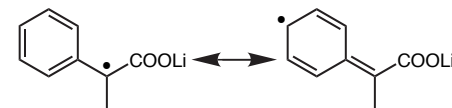
Mechanistic Investigations



- "Dimerization reaction is much faster than nucleophilic substitution under the reaction conditions."



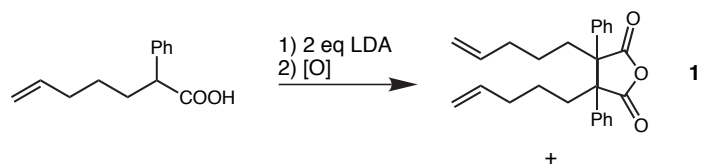
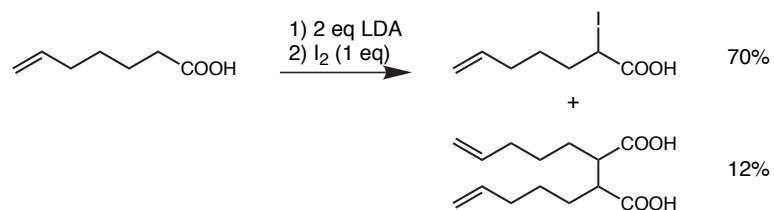
- Formation of α,para coupling product **2** supports radical anion intermediate



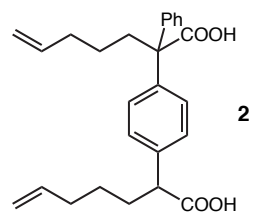
Fox, M.A. et al. *JACS* **1988**, *53*, 3745

Iodine Oxidation Mechanism

5-Hexenyl Radical Trap



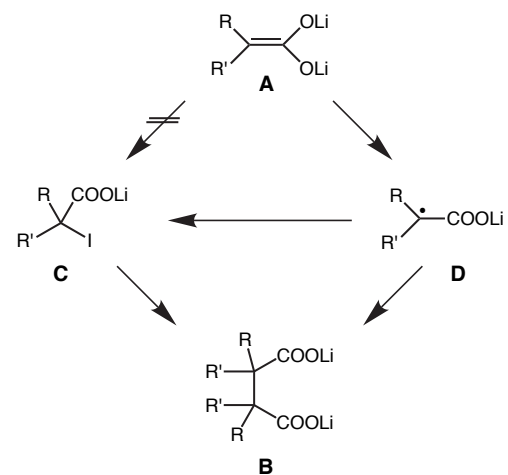
	1	2
[O]		
I ₂	26%	32%
e ⁻	8%	36%



No cyclopentylmethyl products seen!

Fox, M.A. et al. *JACS* **1988**, 53, 3745

Mechanism for Iodine Promoted Coupling

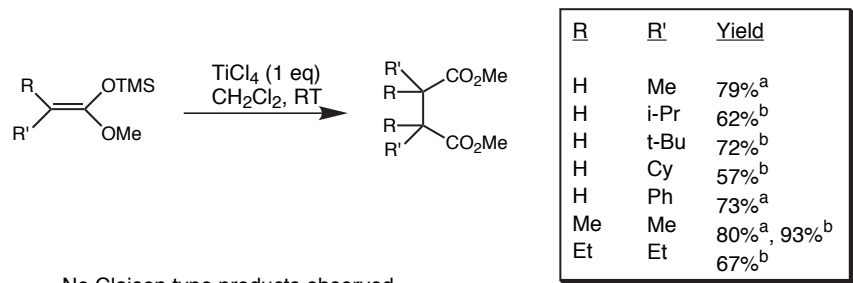


- Proposed initial step is SET to form radical anion (**D**).
- Radical anion (**D**) may iodinate, then form dimer (**B**) via S_N2 reaction
- Radical anion may form dimer directly, especially if R and R' are large (>H)
- Direct iodination of dianion neither supported or excluded by experiments

Fox, M.A. et al. *JACS* **1988**, 53, 3745

Silyl Ketene Acetal Dimerization

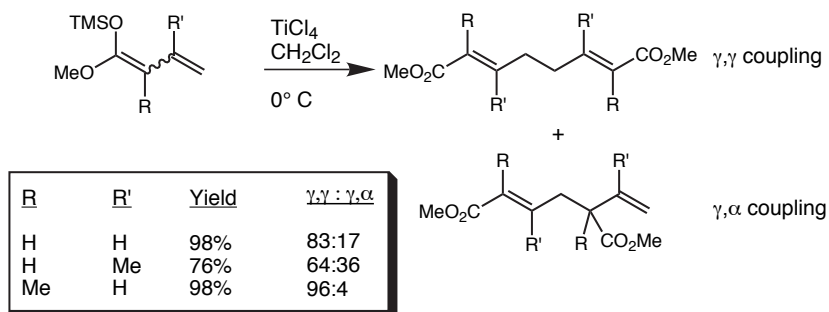
Silyl Ketene Acetals



- No Claisen type products observed
- SET ($Ti^{IV} \rightarrow Ti^{III}$) followed by radical coupling mechanism proposed by both authors
- Other reagents (Cu^{II} salts, $FeCl_3$) ineffective for coupling reaction.

^a Ojima, I. et al. *TL* **1977**, *18*, 2009
^b Rhodes, Y.E. et al. *Synth. Comm.* **1985**, *15*, 301

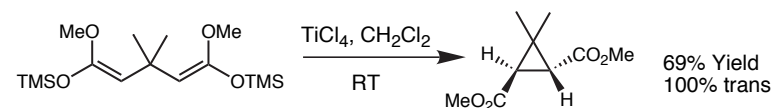
Vinyl Ketene Silyl Acetal Coupling



Ojima, I. et al. *TL* **1983**, *24*, 785

Silyl Ketene Acetal Coupling

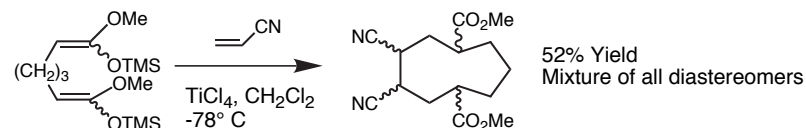
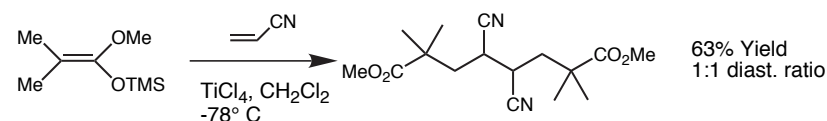
Carbocycle Synthesis



- Stereochemical course under thermodynamic control
- No coupling from ketone-derived enol silyl ethers
- Generally poor yields; exclusively 1,3-trans product.

Chan, T.H. *Tetrahedron*, **1983**, *39*, 847

Acrylonitrile Trapping

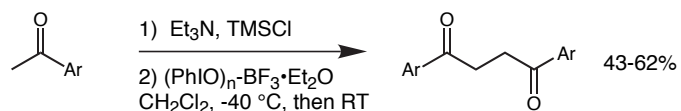


- Authors propose enoxyradical trapping by acrylonitrile, followed by dimerization
- Reactions with methacrylonitrile gave poor yields.
- Attempts to trap putative radical intermediate with $FeCl_3$, CCl_4 , CBr_4 , and tributyltin hydride failed.

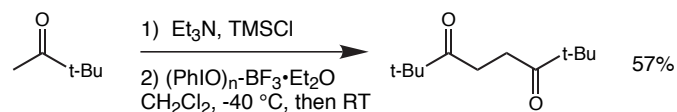
Rousseau, G. *Tetrahedron*, **1990**, *46*, 7011

Silyl Enol Ether Dimerization

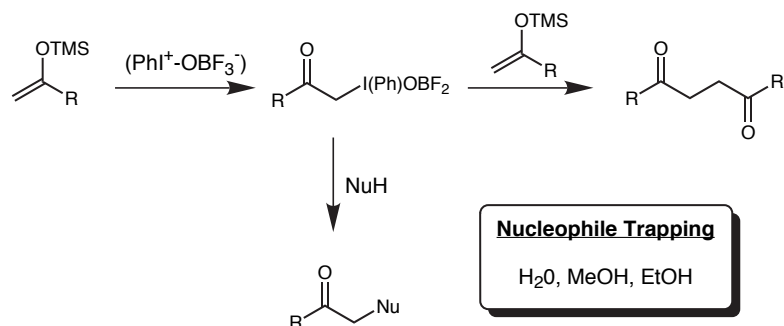
Hypervalent Iodine Oxidants



Ar = Ph, p-HOC₆H₄, p-MeOC₆H₄, p-ClC₆H₄, p-MeC₆H₄



Proposed Mechanism

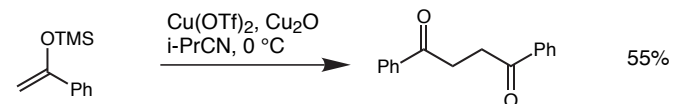


- Nucleophile trapping accomplished in "good yields."

Moriarty, R., et al. *JCS Chem. Comm.*, 420 (1985)
Moriarty, R., et al. *J. Chem. Soc. Perk. Trans. I*, 559 (1987)
Caple, R., et al. *JOC*, 54, 2609 (1989)

Silyl Enol Ether Dimerization

Metal Oxidants



Oxidant	# eq	Solvent	Temp.(°C)	Time (hr)	Yield	Ref.
Cu(OTf) ₂ /Cu ₂ O	1,4	i-PrCN	0	2	55%	a
Ag ₂ O	1	DMSO	65	2	73%	b
Pb(OAc) ₄	0.5	2:1 CH ₂ Cl ₂ :THF	-78, then 23	1.5;1	45%	c
VO(OEt)Cl ₂	2	CH ₂ Cl ₂	-75, then -40	3;4	30%	d

- All authors also reported yields for non-styrenyl silyl enol ethers.
- Yields are extremely substrate dependent.
- Generally, increasing steric hindrance decreases yields.
- All authors propose oxidation to cation radical, followed by loss of trimethylsilyl cation and radical coupling.

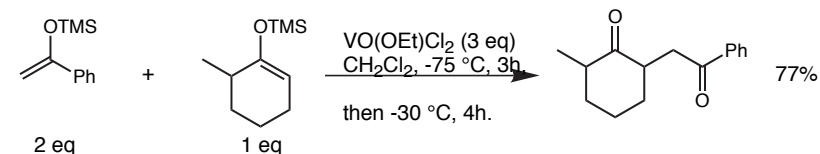
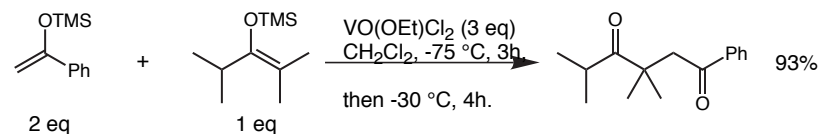
^aKobayashi, Y. et al. *Chem. Pharm. Bull.*, 1980, 28, 262

^bSaegusa, T. et al. *JACS* 1975, 97, 649

^cMoriarty, R.M. et al. *JL* 1987, 28, 873

^dOhshiro, Y. et al. *JL* 1992, 33, 5823

Cross Coupling Experiments

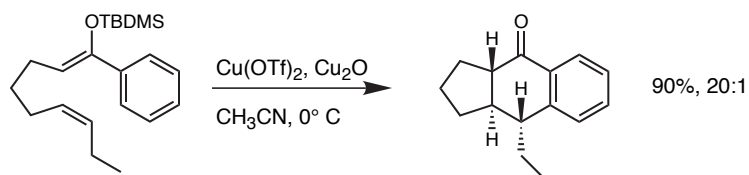


- Less reactive substrate added first, followed by more reactive substrate.
- In all cases, trace amounts of dimers isolated.

Ohshiro, Y. et al. *ibid.*

Silyl Enol Ether Coupling

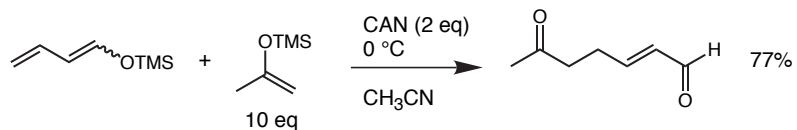
Alkene Trapping



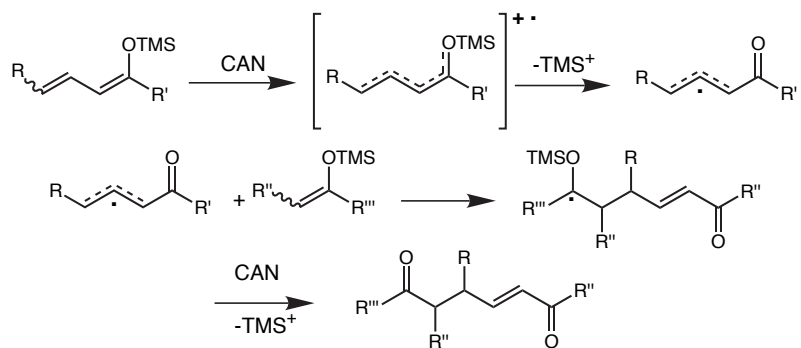
- Also observed for δ,ϵ olefins.
- Kinetic product can be isomerized in KOH/MeOH.

Snider, et al. *JOC*, **1990**, 55, 4786

6-Oxo- α,β -Unsaturated Carbonyl Compounds



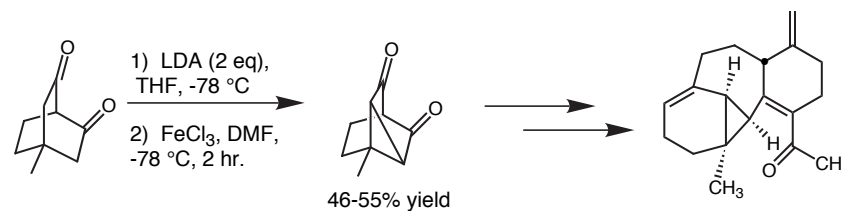
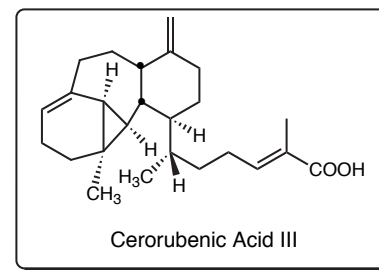
Proposed Mechanism



Ruzziconi, R. et al. *TL* **1993**, 34, 721

Application: Ketone Enolates

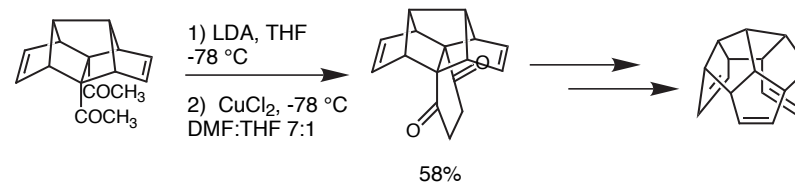
Cerorubenic Acid III: Construction of the Tetracyclic Core



- Other oxidants (CuCl_2 , $\text{Cu}(\text{OTf})_2$) coupled with poor yields

Paquette, L.A. *JOC*, **1993**, 58, 4245

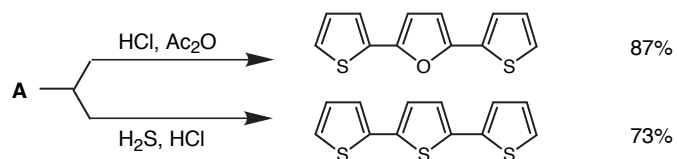
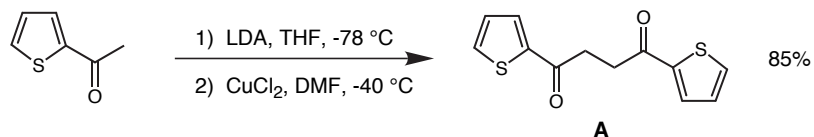
C₁₆ Hexaquinacene



Paquette, L.A. et al. *JACS*, **1978**, 100, 1600

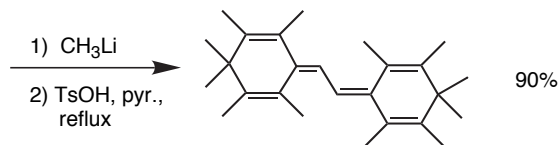
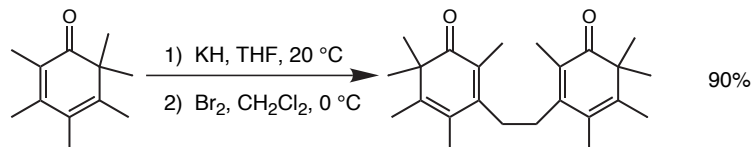
Ketone Enolate Applications II

Coupling of 2-acetylthiophene



Kagan, J. et al *Heterocycles*, **1983**, 20, 1941

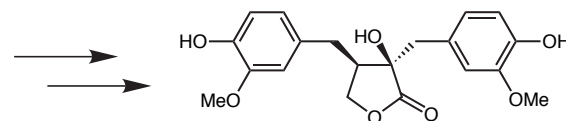
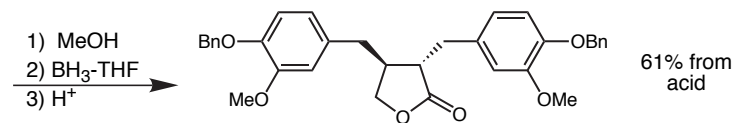
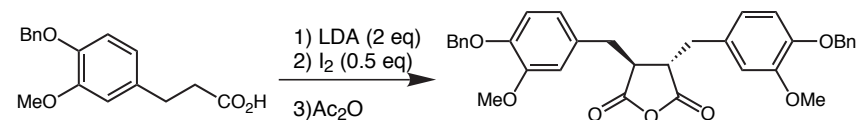
γ-Coupling of Ketone Enolates



Hart, H. et al. *JL*, **1977**, 18, 2307

Application: Carboxylic Acid Dianions

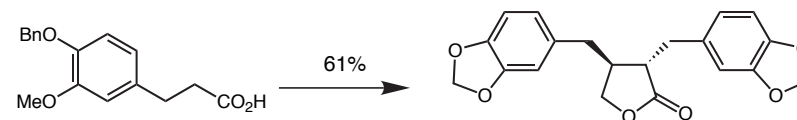
Total Synthesis of Racemic Wikstromol



Belletire, J.L. et al, *JOC*, **1988**, 53, 4724

- Anhydride "obtained as a single diastereomer by NMR analysis."

Total Synthesis of Racemic Hinokinin

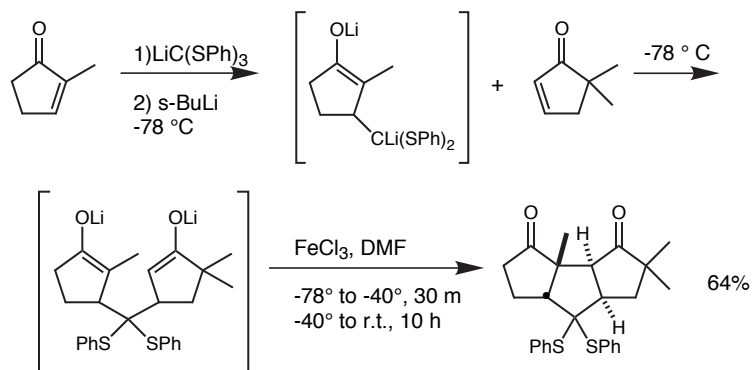


- Mixture of erythro and threo acids; anhydride exclusively threo.

Belletire, J.L. et al, *JOC*, **1987**, 52, 2549

Applications: Ketone Enolates and Silyl Enol Ethers

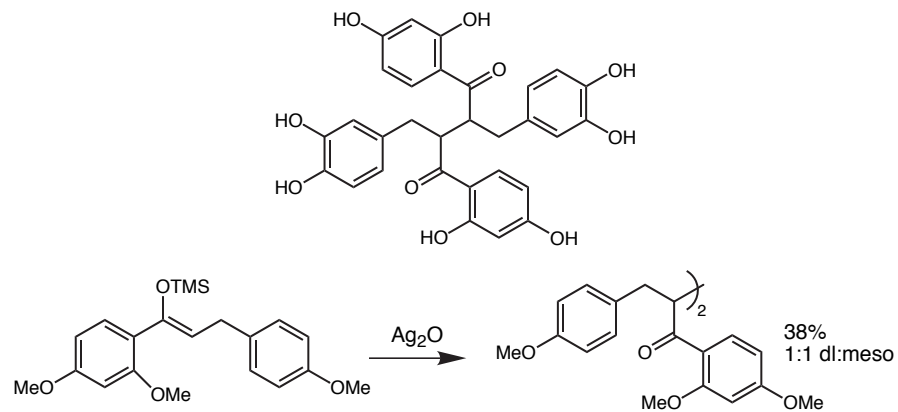
Synthesis of Racemic Hirsutene



- Isolated as a single diastereomer; proof by conversion to hirsutene.

Cohen, T. *JOC*, **1992**, 57, 1968

Studies Toward the Synthesis of Brackenin

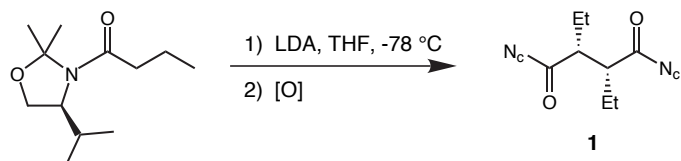


- "Use of Li enolates [for coupling] proved to be unsatisfactory."

Drewes, S.E. *JCS Perkin. Trans 1*, **1989**, 1585

Stereoselective Synthesis of Succinamides

Oxazolidine Auxiliary Experiments

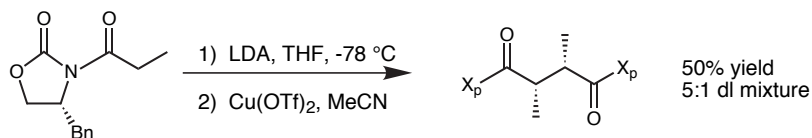


Oxidant	Yield	1:Σ_others
I ₂	40-50%	92:8
CuCl ₂	50-55%	98:2

- No model for induction proposed

Porter, N.A. et al. *JL*, 1993, 34, 4457

Oxazolidinone Auxiliary Experiments

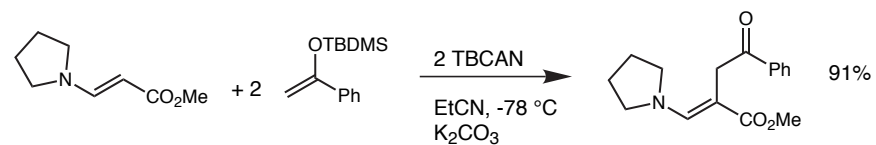
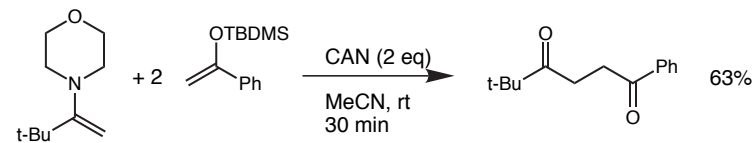


- Also obtained ca. 30% yield of meso dimer

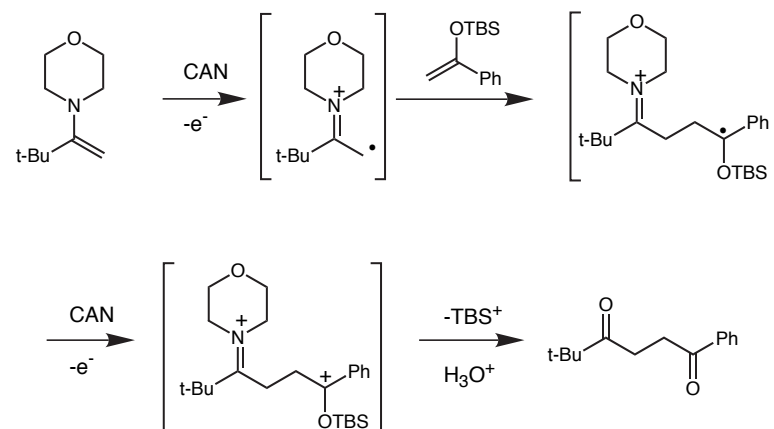
J. Ellman and M. Dart, unpublished results

Oxidative Coupling of Enamines

Silyl Enol Ether Trapping



Proposed Mechanism



Narasaka, K. et al. *Chem. Letters* 1992, 2099

Chemistry 206

Advanced Organic Chemistry

Handout-28A

Oxidative Coupling of Enolates & Enol Derivatives

Chuck Scales

Evans Group Seminar, March, 1995

D. A. Evans

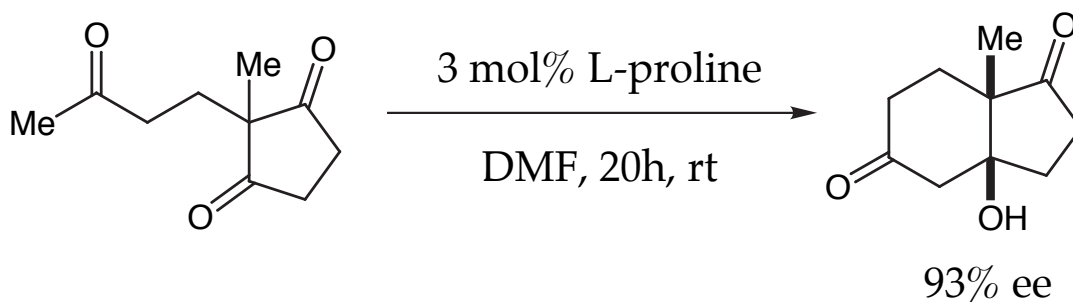
Friday ,
November 21, 2003

Chemistry 206

Advanced Organic Chemistry

Handout-28B

Asymmetric Organocatalysis Using Chiral Amines



An Evans Group Friday Seminar

Jonathan Lawrence

November 14th 2003

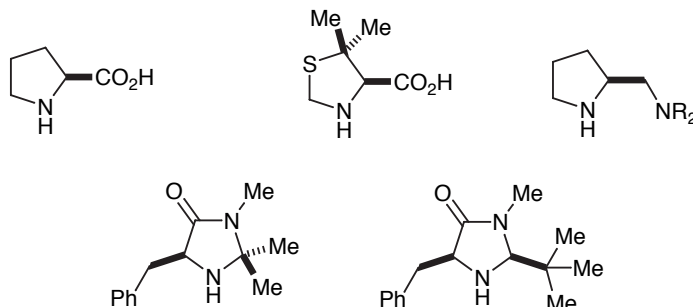
D. A. Evans

Friday,
November 21, 2003

Asymmetric Organocatalysis Using Chiral Amines

Contents:

Background
Aldol reactions
Mannich reactions
Amination/Oxidation reactions
Michael reactions
Cycloaddition reactions
Alkylation reactions



An Evans Group Friday Seminar

Jonathan Lawrence

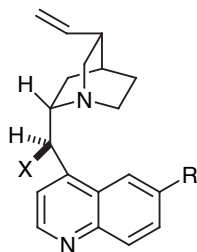
November 14th 2003

Revent Reviews:

List, B. "Proline Catalyzed Asymmetric Reactions", *Tet.* **2002**, *58*, 5573-5590
Miller, S. "Amino Acids and Peptides as Asymmetric Organocatalysts", *Tet.* **2002**, *58*, 2481-2495
List, B. "Asymmetric Aminocatalysis", *Synlett* **2001**, *11*, 1675-1686
Dalko, P. "Enantioselective Organocatalysis", *ACIEE* **2001**, *40*, 3726-3748

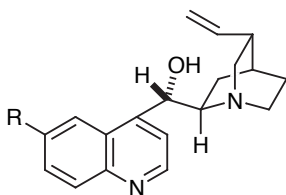
Other Chiral Amines

Cinchona alkaloids:

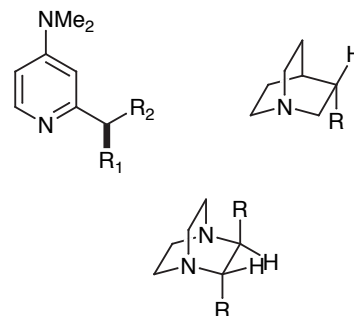


R = OMe, X = OH [(-)-quinine]
R = H, X = OH [(-)-cinchonidine]

The "nucleophilic" catalysts



R = OMe [(+)-quinidine]
R = H [(-)-cinchonine]



Reviews:

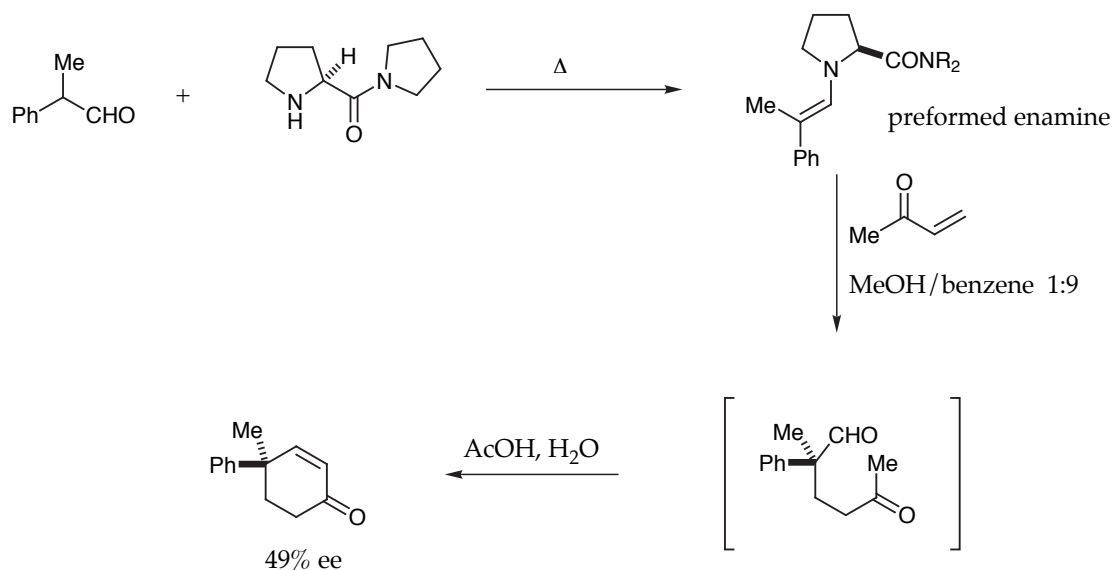
Pracejus, H. *Fortschr. Chem. Forsch.* **1967**, *8*, 493.
Morrison, J., Mosher, H. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, **1971**.
Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.

Relevant Group Seminars:

Karl Scheidt, *Asymmetric Catalysis with Chiral Lewis Bases (Part I)*, March 2001
Hemaka Rajapakse, *Nonmetal-Based Asymmetric Catalysis (Part II)*, March 2001
Essa Hu, *Asymmetric Catalysis with Chiral Lewis Bases (Part III)*, March 2001
Jake Janey, *Asymmetric Catalysis with Chiral Lewis Bases (Part IV)*, March 2001

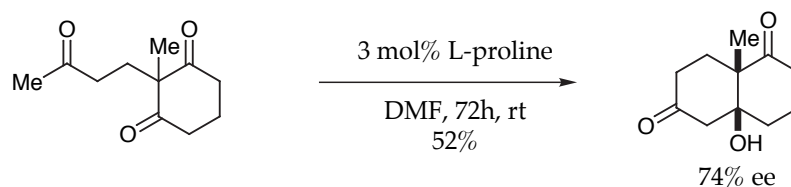
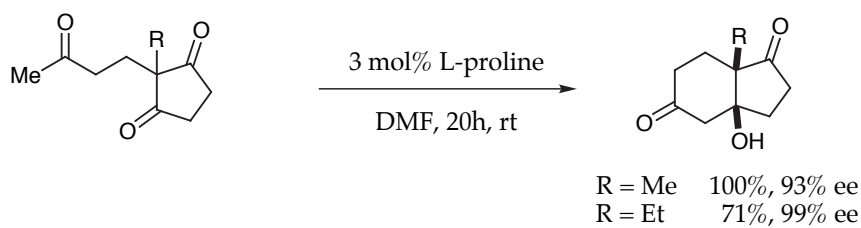
Preliminary Findings

Yamada, 1969:



Yamada, S. *TL* **1969**, *10*, 4237.

The Seminal Experiments

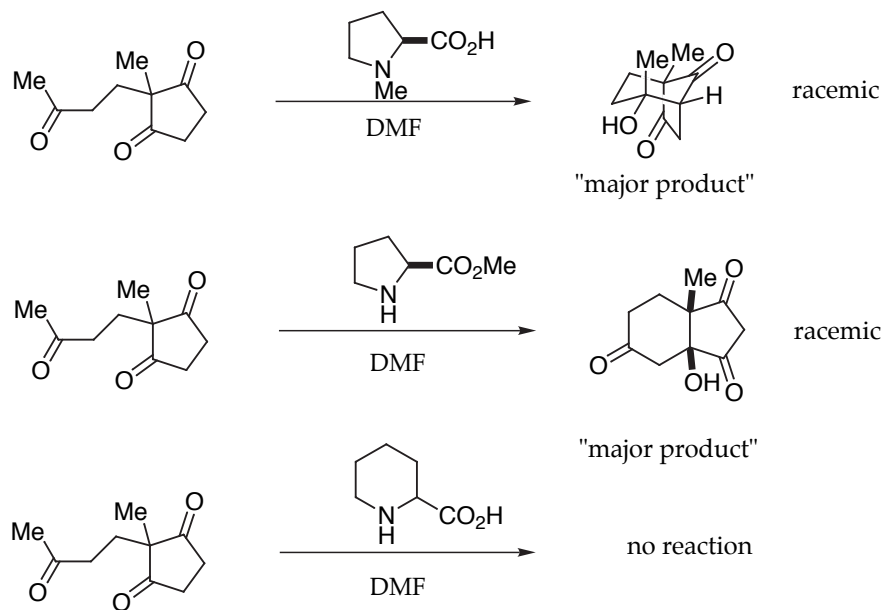


- ♦ the use of protic solvents severely diminishes enantioselectivity
- ♦ other amino acids as catalysts lead to decreased chemical yield and enantioselectivity
- ♦ Eder, Sauer, and Weichert obtained the corresponding aldol condensation products in similar optical purity using 47 mol% L-proline and 1N HClO₄

Hajos, J., Parrish, D. *JOC* **1974**, *39*, 1615.

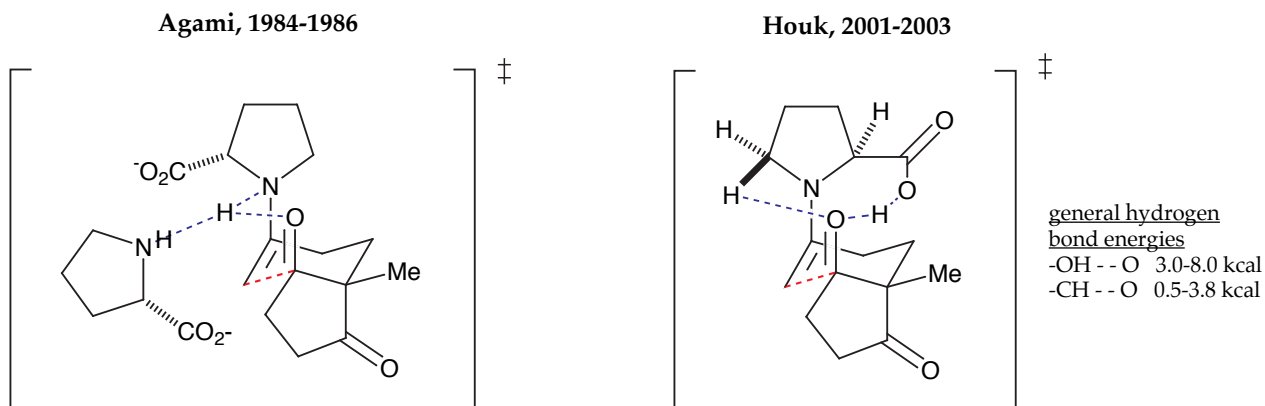
Eder, U., Sauer, G., Weichert, R. *ACIEE* **1971**, *10*, 496.

Effect of the Catalyst



Hajos, J., Parrish, D. *JOC* **1974**, *39*, 1615.

Transition States



- ♦ favorable (enamine) N-H---O hydrogen bond
- ♦ N-H *anti* to carboxylate electrostatically favored
- ♦ reaction is second-order in proline (non-linear effect observed)
- ♦ second proline acts as a proton shuttle, allowing enamine to be nucleophilic

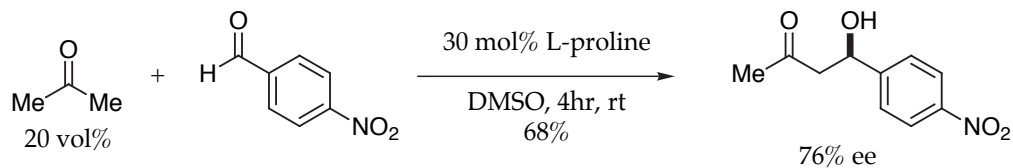
Agami, C. *TL* **1986**, *13*, 1501.
 Houk, K. *JACS* **2001**, *123*, 12911.
 Houk, K., List, B. *JACS* **2003**, *125*, 16.

- ♦ N-H---O hydrogen bond does not lower energy of transition state
- ♦ favorable O-H---O hydrogen bond
- ♦ additional NC-H---O hydrogen bond further stabilizes system
- ♦ reaction is first order in proline (supported by kinetic data) and no non-linear effect observed

for a discussion on $R_3N^+-C-H\cdots O=C$ bonds, see:
 Houk, K. *JACS*, **2002**, *124*, 7163.

Direct Aldol Addition 1

The initial reaction:



Catalyst screen:

(selected examples)

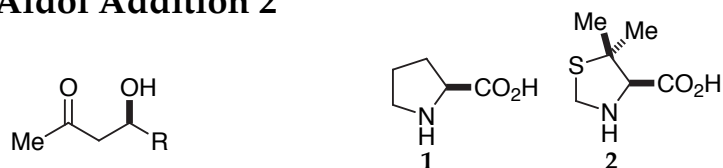
compound	% yield	% ee	compound	% yield	% ee
(L)-His, (L)-Val (L)-Tyr, (L)-Phe	< 10	--		67	73
	55	40		85	78
	< 10	--		> 50	-62
				66	86 *

List, B., Barbas, C. *JACS*, **2000**, *122*, 2395-2396
*Barbas, C. *JACS*, **2001**, *123*, 5260-5267

Direct Aldol Addition 2

Substrate scope:

variation of the aldehyde



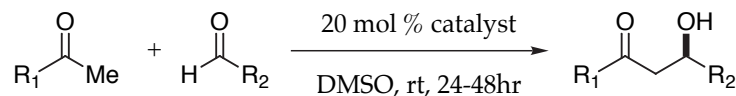
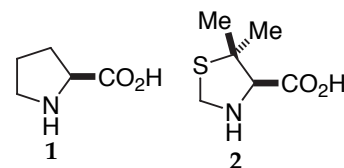
product R =	cat.	% yield	% ee	product R =	cat.	% yield	% ee
	1	68	76		1	94	69
	2	60	86		2	71	74
	1	62	60		1	54	77
	2	60	89		2	60	88
	1	74	65		1	97	96
	2	65	67		2	61	94

- DMTC 2 is catalyst of choice for aromatic aldehydes, although chemical yield decreases due to slower rate of reaction
- α -unbranched aldehydes yield no appreciable amount of product with proline catalyst 1 due to enolization and self-aldolization under reaction conditions (DMSO/acetone = 4:1)

List, B. *JACS*, **2000**, *122*, 2395.
Barbas, C. *JACS*, **2001**, *123*, 5260.

Direct Aldol Addition 3

Substrate scope:
variation of the ketone donor

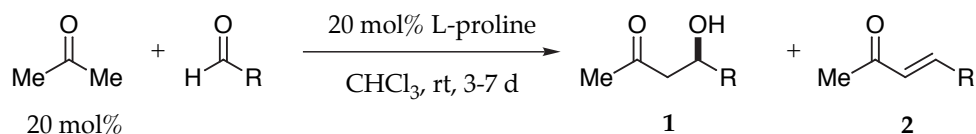


product R =	cat.	% yield	% ee
	1	65	77
	2	57	74
	1	60	80
	2	<5	---
	1	<i>syn</i> 24	67
	1	<i>anti</i> 35	90
	2	<i>syn</i> 21	69
	2	<i>anti</i> 41	89

Barbas, C. *JACS*, 2001, 123, 5260.

Direct Aldol Addition 4

Substrate scope:
use of α -unbranched aldehydes



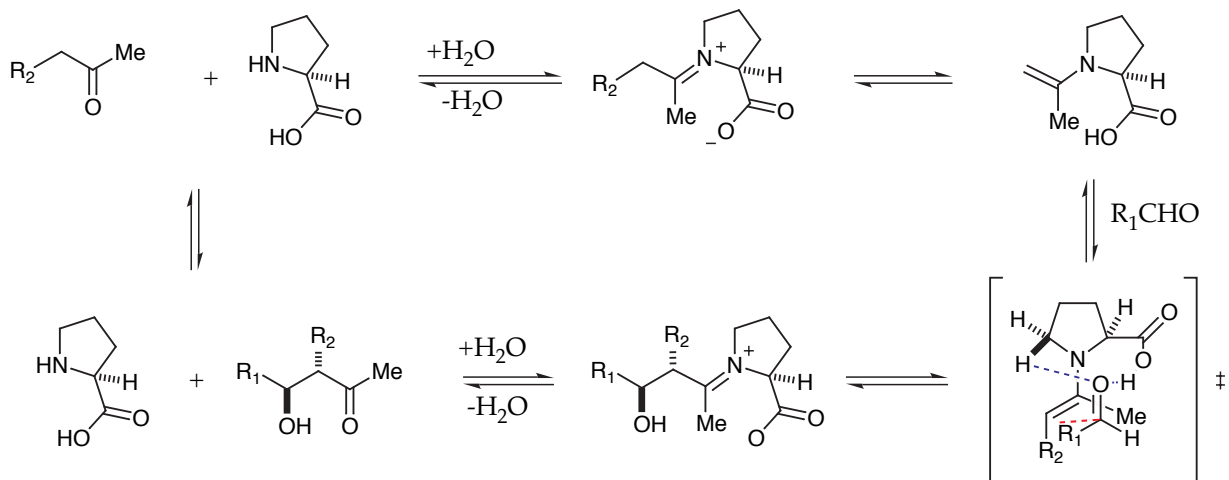
product R =	% yield 1	% yield 2	% ee
	29	0	70
	31	38	67*
	35	40	73*
	34	35	72
	23	46	61
	34	42	73*
	22	50	36

* reaction performed neat in acetone

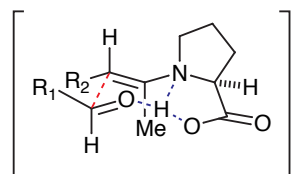
- use of cyclic ketones (cyclopentanone, cyclohexanone) result in moderate yield and diastereoselectivity, and up to 95% ee
- enone products arise from a Mannich addition-elimination sequence

List, B. *OL* 2001, 3, 573.

Direct Aldol Reaction Mechanism



previously proposed T.S.:
metal-free Zimmerman-Traxler model



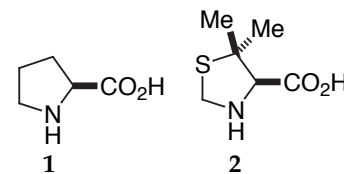
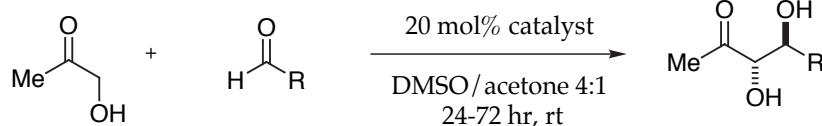
Houk's calculated T.S.

- ♦ synclinal approach of aldehyde
- ♦ R₁ in pseudo-equatorial position
- ♦ C-H -- O distance ~ 2.4 Å
- ♦ DFT calculations in DMSO

List, B. *JACS* **2000**, *122*, 2395.

List, B., Houk, K. *JACS* **2003**, *125*, 2475.

Synthesis of *Anti*-1,2-Diols



product R =	cat.	dr	% yield	% ee
	1	>20:1	60	>99
	2	>20:1	45	95
	1	>20:1	62	>99
	2	---	<5	---
	1	>20:1	51	>99
	2	---	<5	---
	1	3:2	95	67 (32)
	2	3:2	60	92 (78)

product R =	cat.	dr	% yield	% ee
	1	1:1	83	80 (n.d.)
	2	1:1	52	95 (50)
	1	3:1	62	79 (33)
	2	---	<5	---
	1	1.7:1	38	>97 (84)
	2	---	<5	---
	1	2:1	40	>97 (97)
	2	---	<5	---

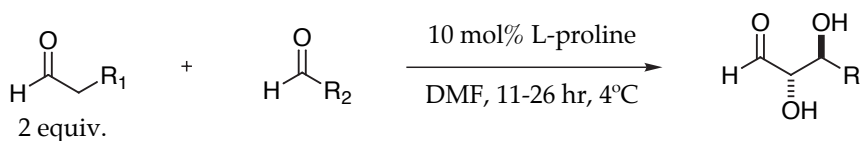
List, B. *JACS*, **2000**, *122*, 2395.

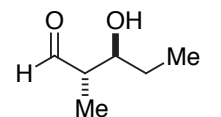
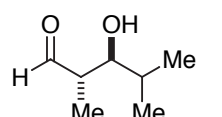
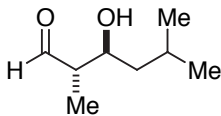
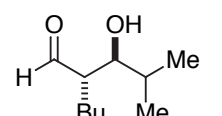
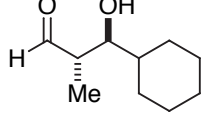
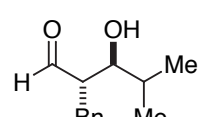
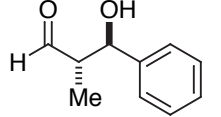
Barbas, C. *JACS*, **2001**, *123*, 5260.

more substituted enamine formed due to:

- ♦ increased acidity of proton removed
- ♦ increased stability of enamine due to O_{n.b.} --> π* C=C

Use of Aldehydes as Donors in Direct Aldol

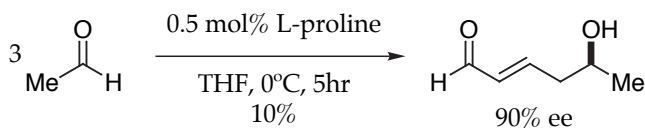


product R =	dr	% yield	% ee	product R =	dr	% yield	% ee
	4:1	80	99		24:1	82	>99
	3:1	88	97		24:1	80	98
	14:1	87	99		19:1	75	91
	3:1	81	99				

♦ reaction requires lower catalyst loading, shorter times, and only 2 equivalents of aldehyde donor

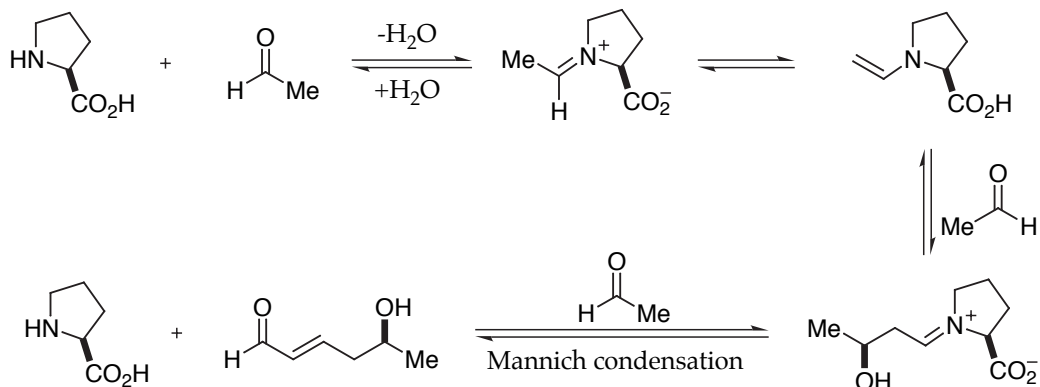
MacMillan, D. *JACS*, 2002, 124, 6798.

Trimerization of Acetaldehyde



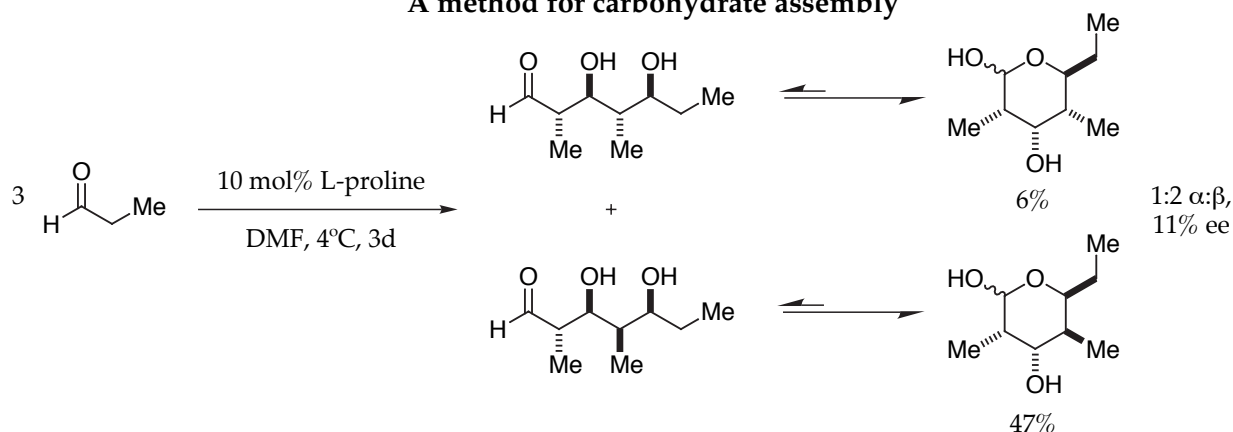
- ♦ THF at 0°C was found to be the optimal conditions for yield and ee (DMSO @ rt = 13% y, 57% ee, CHCl₃ @ rt = 2% y, 68% ee)

Mechanism:



Barbas, C. *JOC*, 2002, 67, 301.

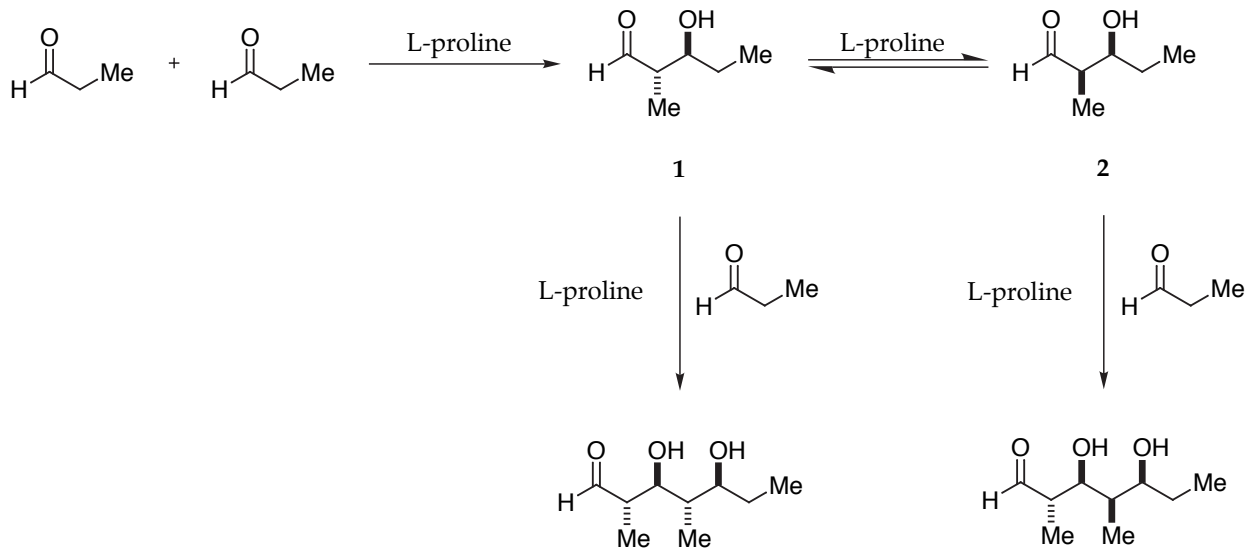
Propionaldehyde Trimerization A method for carbohydrate assembly



- ♦ reaction analogous to an aldolase enzyme that furnishes the minor product shown above
- ♦ propionaldehyde added slowly dropwise in order to obtain trimer over dimer products
- ♦ enantioselectivity erodes with longer reaction times (after 10 hr product ee = 47%)
- ♦ substituent at C-6 variable by using 1 eq. of corresponding aldehyde and 2 eq. of propionaldehyde

Barbas, C. *TL*, 2002, 43, 9591.

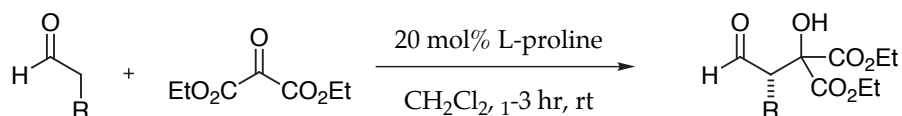
Mechanism of Propionaldehyde Trimerization



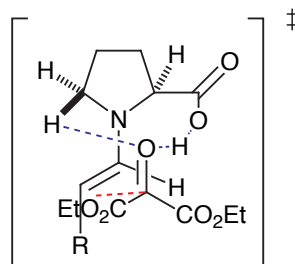
- ♦ incubating isolated 1 with L-proline led to formation of 2 through epimerization (1:1 ratio of 1:2 after 96 hr)

Barbas, C. *TL* 2002, 43, 9591.

Aldehyde Aldol Addition to Activated Carbonyl Compounds



product R =	% yield	% ee
Me	90	90
Et	91	85
<i>i</i> -Pr	88	85
	94	88
<i>n</i> -Hex	91	84
Ph	97	0

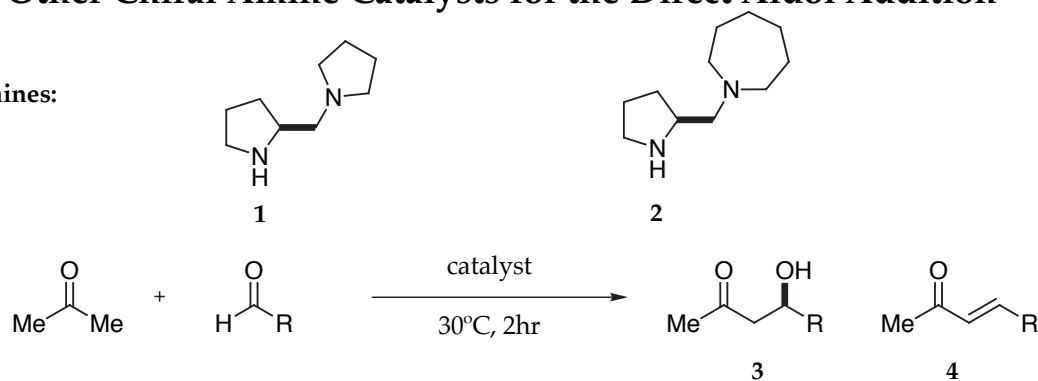


Jorgensen, K. *Chem. Comm.* **2002**, 620.

- ♦ protection of the aldehyde as the dioxolane prevents epimerization of the α center during column chromatography

Other Chiral Amine Catalysts for the Direct Aldol Addition

Chiral diamines:



product R =	cat.	% yield 3	% ee	% yield 4
	1.5 mol% 1 •2TfOH + 1.5 mol% 1	60	88	7
	3 mol% 2	72	93	7
	1.5 mol% 1 •2TfOH + 1.5 mol% 1	37	83	32
	3 mol% 2	13	91	25

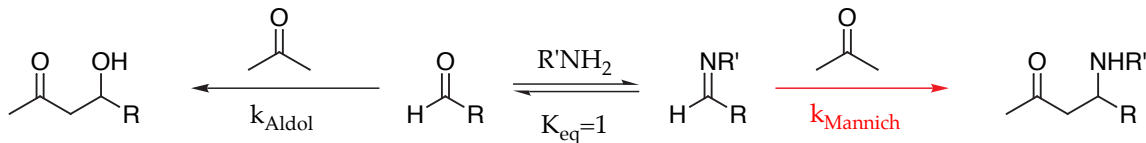
- ♦ proposed mechanism similar to that of proline catalyzed reactions, with proton transfer from protonated tertiary N to O

Yamamoto, *Tet.* **2002**, 58, 8167.

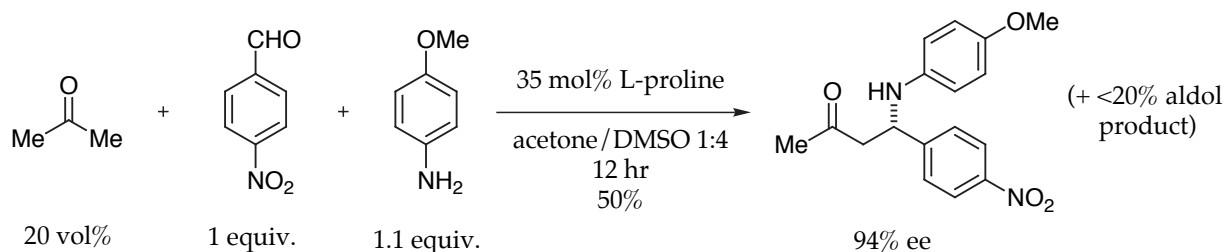
Mannich Reaction: First Report

Required Conditions:

- ♦ enamine addition must be faster to the imine than to the corresponding aldehyde
- ♦ formation of the aldimine from a primary amine must be faster than the aldol addition
 - ♦ NMR studies show that $K_{eq}(\text{aldehyde} \rightleftharpoons \text{imine}) = 1$



3-component reaction verifies hypotheses:

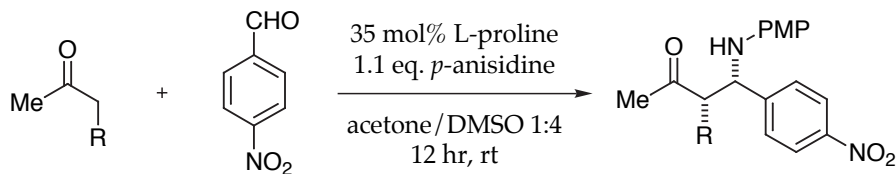


- ♦ 10 mol% proline and 1.3 eq ketone used without loss of efficiency

List, B. *JACS*, 2000, 122, 9336.

Mannich Reaction: Scope

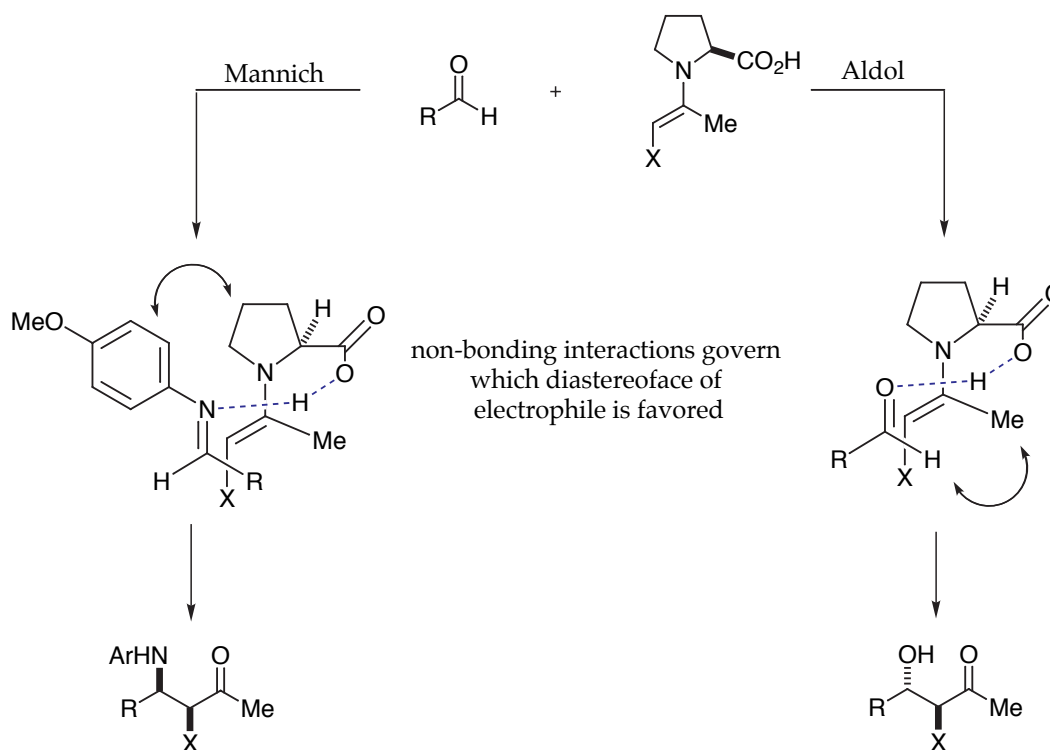
Variation of the ketone donor:



R =	product	% yield	dr	% ee	
Me		2.5	95	>20:1	99
		1	---	>20:1	94
OMe			93	>20:1	98
OH			92	>20:1	>99

List, B. *JACS*, 2000, 122, 9336.

Mannich Reaction: Transition States



List, B. *JACS* **2002**, *124*, 827.

Mannich Reaction: Scope 2

Variation of the aldehyde:

- ♦ aliphatic aldehydes, including α -unbranched are good substrates (60-90% yield, 73-93% ee)
- ♦ aromatic aldehydes are excellent substrates, (79-92% yield, 61-99% ee)

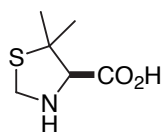
Effect of electron donation from the aldehyde:

R =	% yield	dr	% ee
CN	88	15:1	99
H	83	9:1	93
Me	85	5:1	86
OMe	88	3:1	61

Variation of the catalyst:

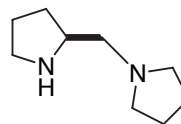
- ♦ proline proves to be the best catalyst, with other catalysts affording reduced yield and optical purity.

Reaction of acetone with isovaleraldehyde:



List, B. *JACS* **2002**, *124*, 827.

60% y., 16% ee

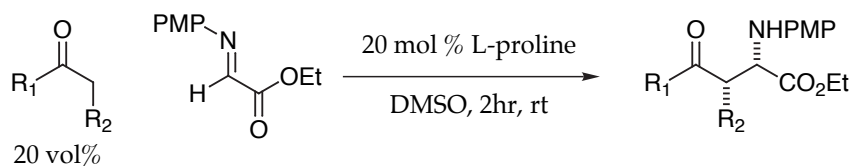


26% y., 0% ee

α -Imino Ethyl Glyoxylate as Mannich Acceptor 1

An entry to α -amino acids

Addition of ketones:



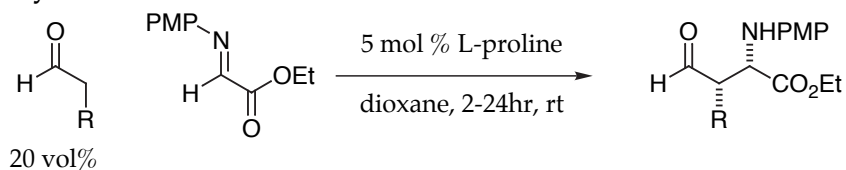
product	% yield	dr	% ee
	86	---	99
	72	>19:1	>99
	79	>19:1	>99
	62	>19:1	99
	47	>19:1	>99
	81	>19:1	>99

Barbas, C. *JACS* 2002, 124, 1842

α -Imino Ethyl Glyoxylate as Mannich Acceptor 1

An entry to α -amino acids

Addition of aldehydes:



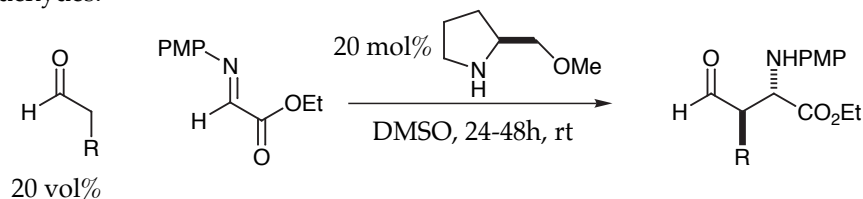
R =	% yield	dr	% ee
Me	72	1.1:1	99
Et	57	1.5:1	99
<i>i</i> -Pr	81	>10:1	93
<i>n</i> -Bu	81	3:1	99
<i>n</i> -Pent	89	>19:1	>99
	71	>19:1	>99

- ♦ aqueous workup or column chromatography may lead to decreased diastereoselectivities
- ♦ reaction has been performed in aqueous media (Barbas, *TL* 2003, 44, 1923)

Barbas, C. *JACS* 2002, 124, 1866.

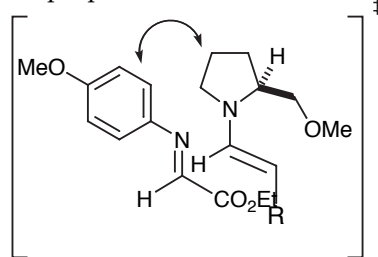
Anti-Selective Mannich Reaction

Addition of aldehydes:

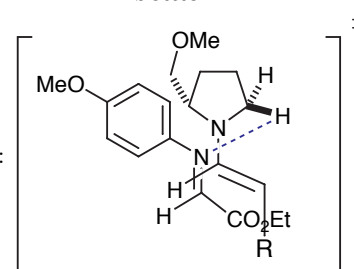


R =	% yield	dr	% ee
Et	44	1:1	75
<i>i</i> -Pr	52	10:1	82
<i>n</i> -Bu	54	10:1	74
<i>t</i> -Bu	57	>10:1	92
<i>n</i> -Pent	78	>10:1	76
<i>n</i> -Hex	68	>19:1	76

proposed transition state



better?

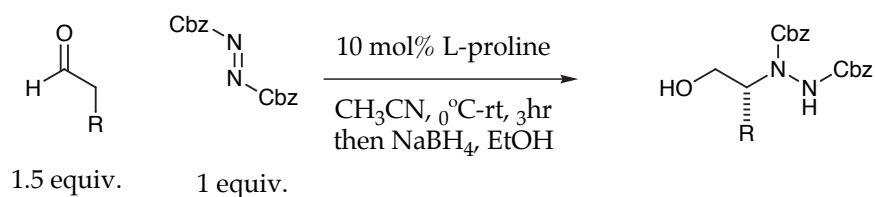


For a review of SMP use in asymmetric synthesis, see:
Enders, D. *Synthesis* **1996**, 1403.

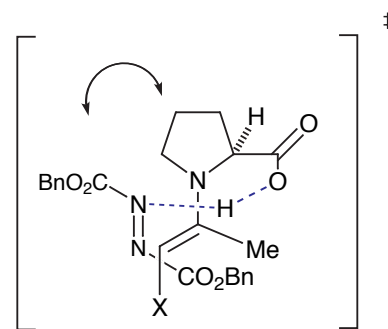
Barbas, C. *TL* **2002**, *43*, 7749.

Direct α -Amination 1

Addition of aldehydes:



R =	% yield	% ee
Me	97	>95
<i>n</i> -Pr	93	>95
<i>n</i> -Bu	94	97
<i>i</i> -Pr	99	96
Bn	95	>95

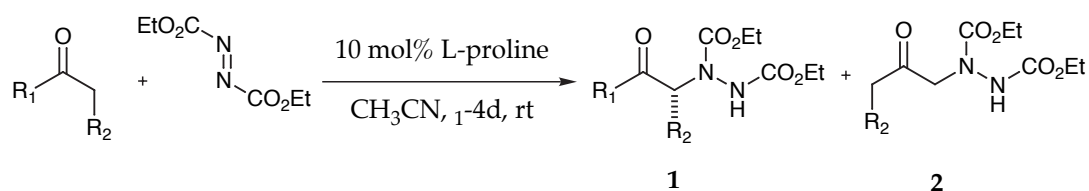


♦ longer reaction time leads to epimerization, so aldehyde is reduced *in situ*

List, B. *JACS* **2002**, *124*, 5656.

Direct α -Amination 2

Addition of ketones:

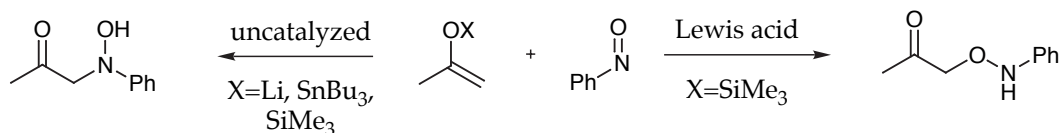


product 1	ratio 1:2	% yield (1+2)	% ee
	10:1	80	95 (93)
	4.5:1	92	98 (94)
	3:1	99	99 (99)
	---	79	94 (93)

Jorgensen, *JACS* **2002**, *124*, 6254.

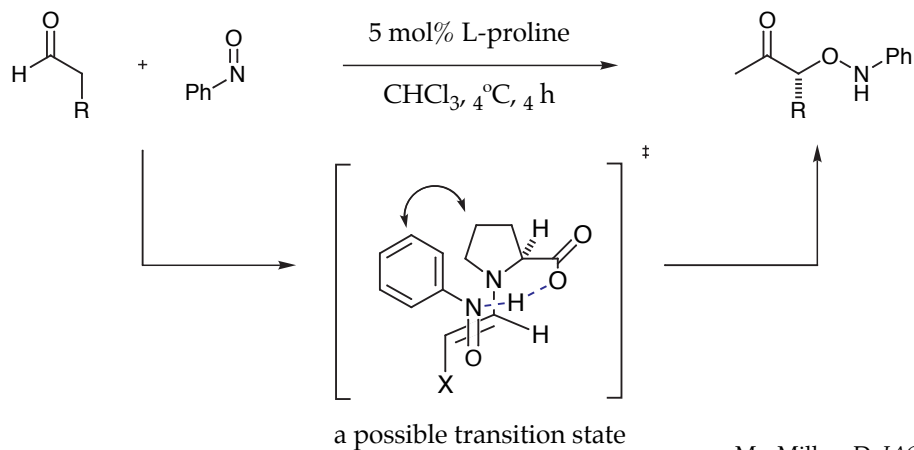
α -Oxidation of Aldehydes with Nitrosobenzene 1

The choice of reaction conditions determine N or O selective addition:



Yamamoto, H. *OL*, **2002**, *4*, 3579.

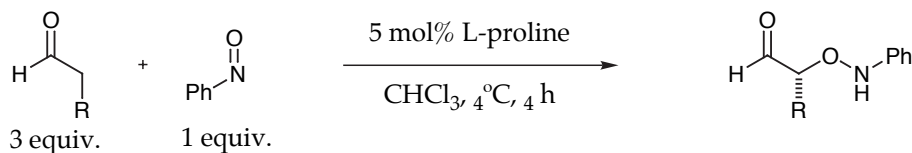
Larger basicity of nitrogen allows proline to catalyze O-nucleophilic addition:



MacMillan, D. *JACS* **2003**, *125*, 10808.

α -Oxidation of Aldehydes with Nitrosobenzene 2

Aldehyde scope:



R =	% yield	% ee	R =	% yield	% ee
Me	88	97	Bn	95	97
<i>n</i> -Bu	79	98	Ph	60	99
<i>i</i> -Pr	85	99	(CH ₂) ₃ OTIPS	76	98
CH ₂ CH=CH ₂	99	96	CH ₂ -(3'-N-methyl indole)	83	98

♦ product most easily isolated as the primary alcohol (NaBH₄ reduction)

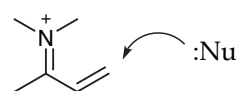
MacMillan, D. *JACS* **2003**, *125*, 10808.

Asymmetric Organocatalysis of the Michael Reaction

Two mechanistic possibilities exist:



or

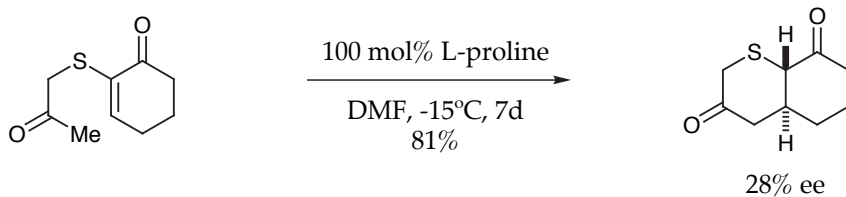


Examples include:

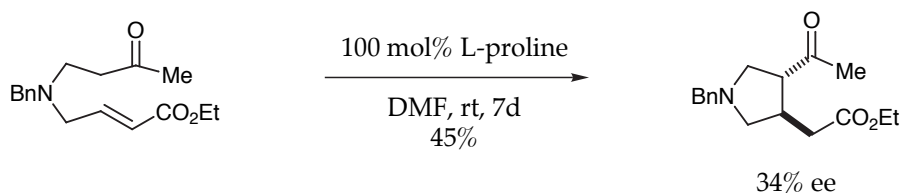
additions to:
alkylidene malonates
 α,β -unsaturated nitroalkenes

additions of:
malonate esters
nitroalkanes
aromatics (Friedel-Crafts reactions)
silyloxy furans
Diels-Alder reaction
Dipolar cycloaddition

Michael Additions using Enamine Catalysis: Moderate Success has been Achieved



Kozikowski, A. *JOC*, **1989**, *54*, 2275.

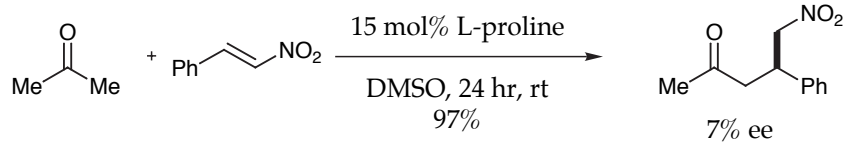


Momose, T. *J.Chem.Soc., Perkin Trans.*, **1992**, 509.

Enamine Catalysis: Examples 2

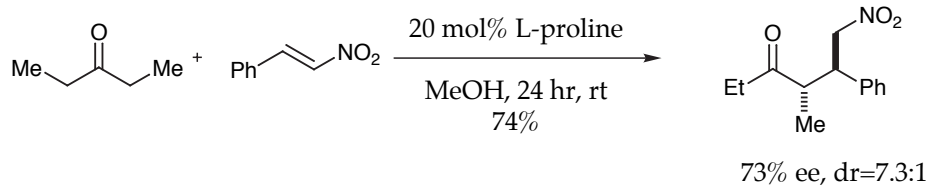
Recent examples:

List:



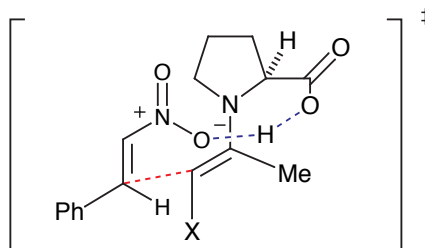
List, B. *OL* **2001**, *3*, 2423.

Enders:



- ♦ use of MeOH as solvent increases ee

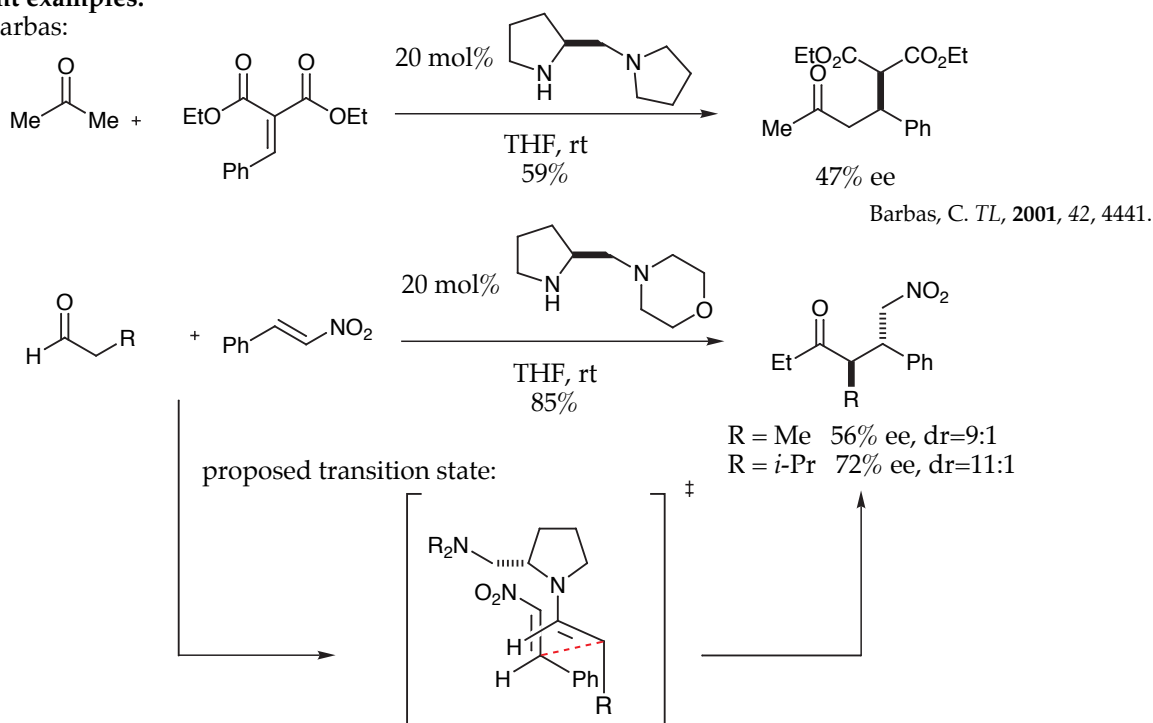
Enders, *Synlett* **2002**, 26.



Enamine Catalysis: Examples 3

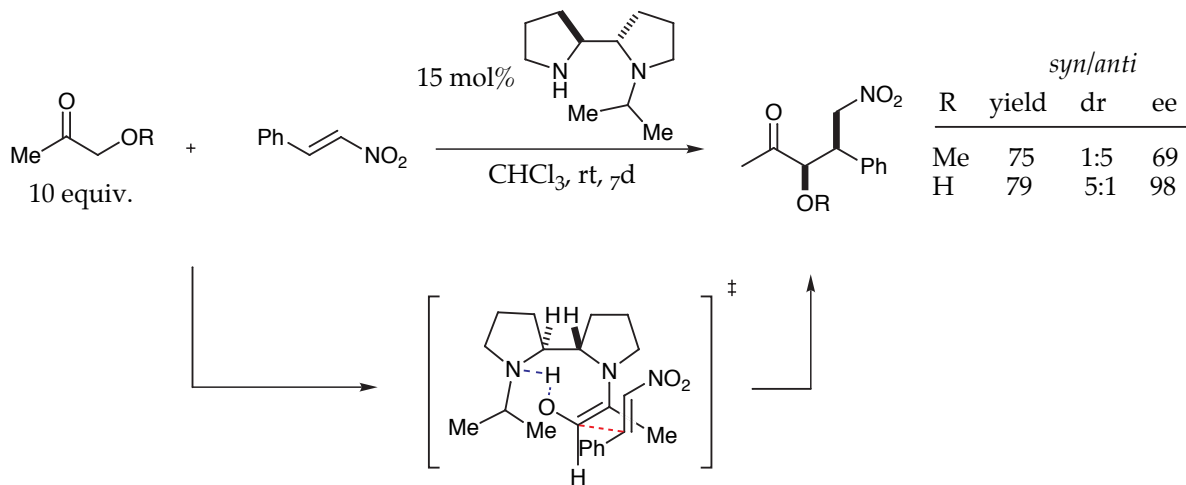
Recent examples:

Barbas:



Barbas, C. *OL* 2001, 3, 3737.

A Highly Enantioselective Michael Addition Using Enamines A New Chiral Diamine Catalyst

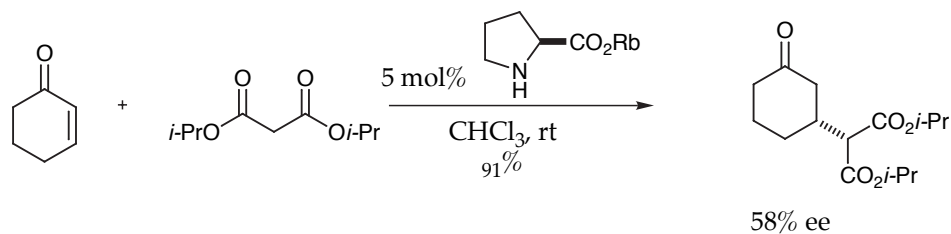


- with variation of aromatic group on nitroolefin:
ee = 96-98%
dr = 3.5:1 - 19:1
- selection of aromatic groups used:
tolyl, *p*-methoxyphenyl, *p*-chlorophenyl, 2-thienyl

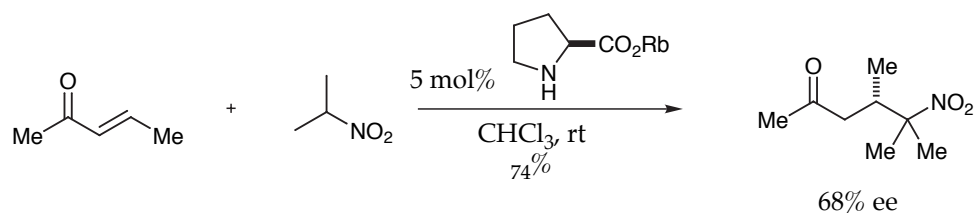
Alexakis, A. *OL*, 2003, 5, 2559.

Imminium Catalysis of Conjugate Additions 1

Proline has been used with only mild success:



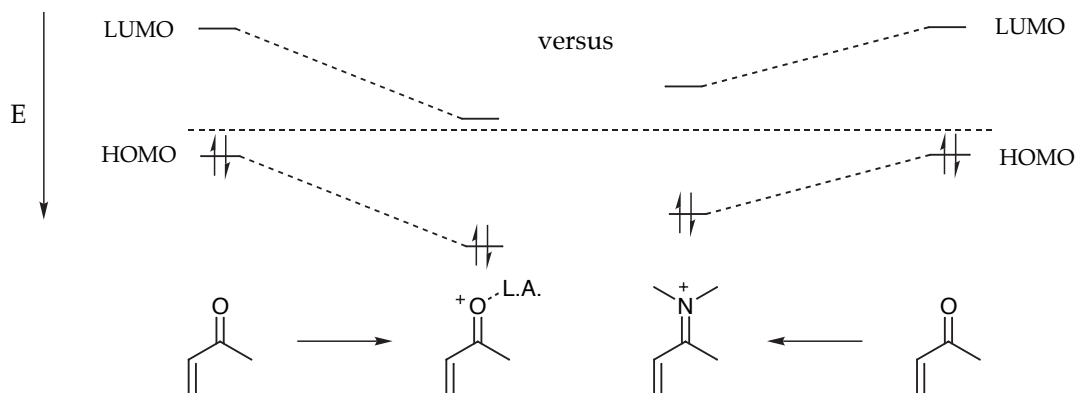
♦ Proline rubidium salt gives lower ee in the Hajos-Parrish-Weichert reaction



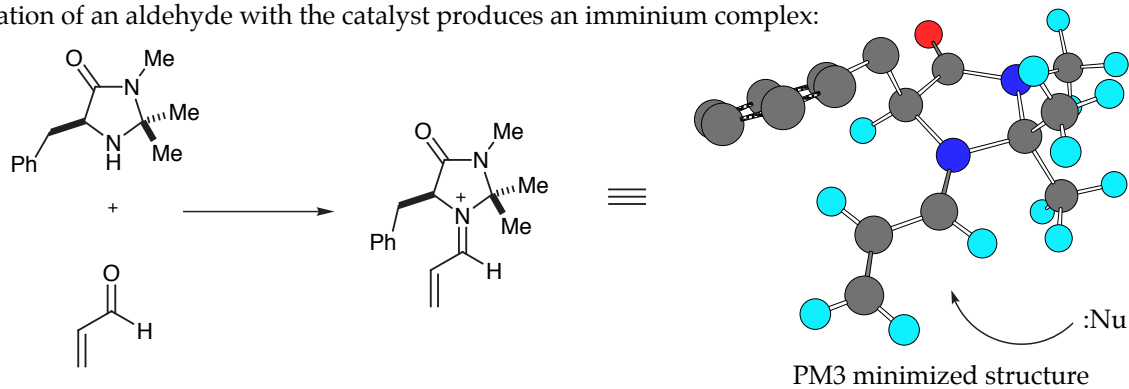
Yamaguchi, *JOC* 1996, 61, 3520.

MacMillan Introduces A New Catalyst

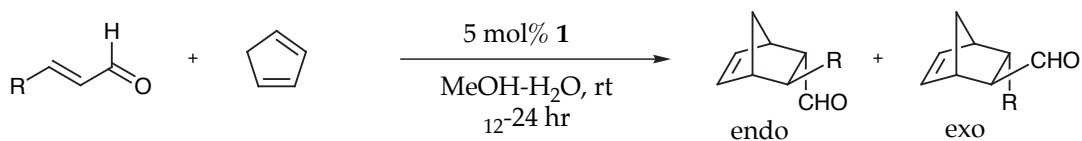
Imminium ion formation lowers the LUMO of the system and allows catalysis to occur:



Consensation of an aldehyde with the catalyst produces an imminium complex:

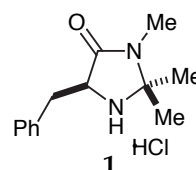


Diels-Alder Cycloaddition 1



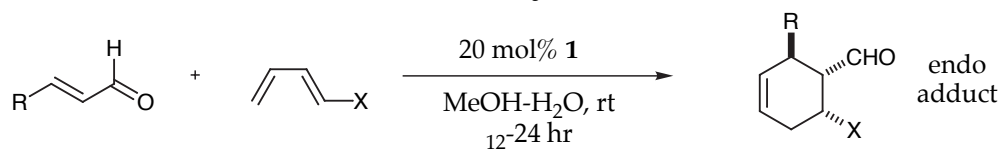
Dienophile scope:

R =	% yield	endo:exo	% ee(endo)	% ee(exo)
Me	75	1:1	86	90
<i>n</i> -Pr	92	1:1	86	90
<i>i</i> -Pr	81	1:1	84	93
Ph	99	1.3:1	93	93
Furyl	89	1:1	91	93



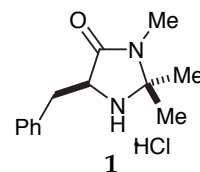
MacMillan, D. *JACS* **2000**, *122*, 4243.

Diels-Alder Cycloaddition 2



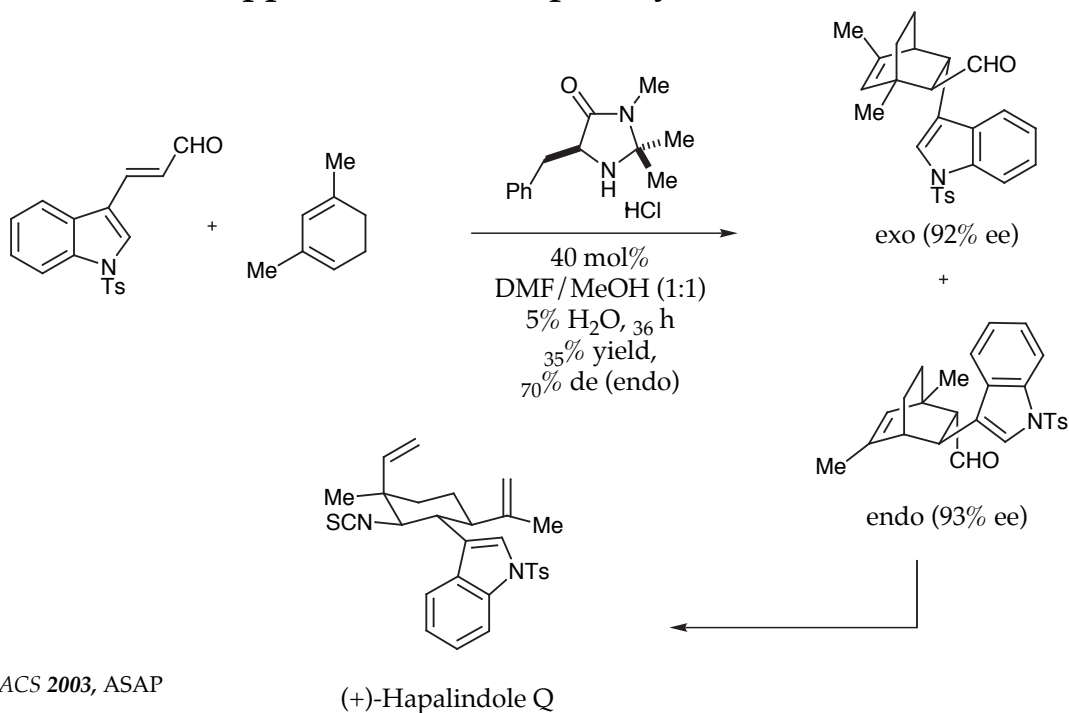
Diene scope:

diene	R	product	% yield	exo:endo	% ee
	Me		75	35:1	96
	H		82	1:14	94
	H		84	---	89
	H		90	---	83
	Me		75	---	90
	H		75	1:5	90
	H		72	1:11	85

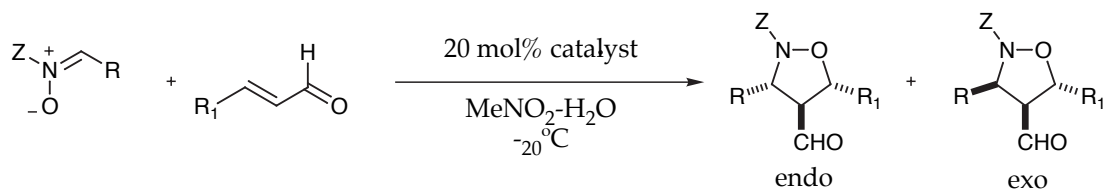


MacMillan, D. *JACS* **2000**, *122*, 4243.

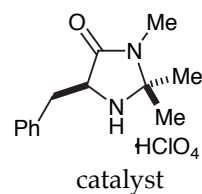
Application to Complex Synthesis



Nitrone Cycloaddition

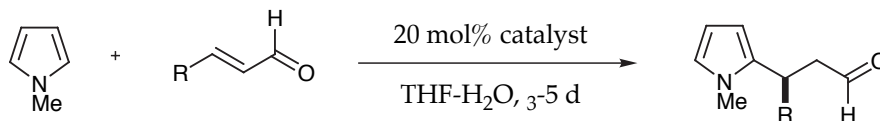


Z	R	R ₁	endo:exo	yield	ee (endo)
Bn	Ph	Me	94:6	98	94
allyl	Ph	Me	93:7	73	98
Me	Ph	Me	95:5	66	99
Bn	C ₆ H ₄ Cl-4	Me	92:8	78	95
Me	C ₆ H ₄ Cl-4	Me	93:7	76	94
Bn	C ₆ H ₄ OMe-4	Me	98:2	93	91
Me	C ₆ H ₄ Me-4	Me	93:7	82	97
Bn	2-naphth	Me	95:5	98	93
Bn	c-Hex	Me	99:1	70	99
Bn	Ph	H	81:19	72	90
Bn	Ph	H	86:14	80	92
Bn	C ₆ H ₄ Cl-4	H	85:15	80	90
Bn	C ₆ H ₄ Cl-4	H	80:20	80	91
Bn	2-naphth	H	81:19	82	90
Bn	C ₆ H ₄ OMe-4	H	91:9	83	90

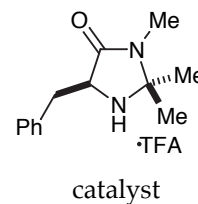


- HClO₄ proved to be the best Bronsted acid cocatalyst to promote only enantioselective catalysis
- high endo selectivity attributed to favorable placement of R group away from geminal dimethyl substituents on catalyst

Friedel-Crafts Alkylation 1: Pyrroles

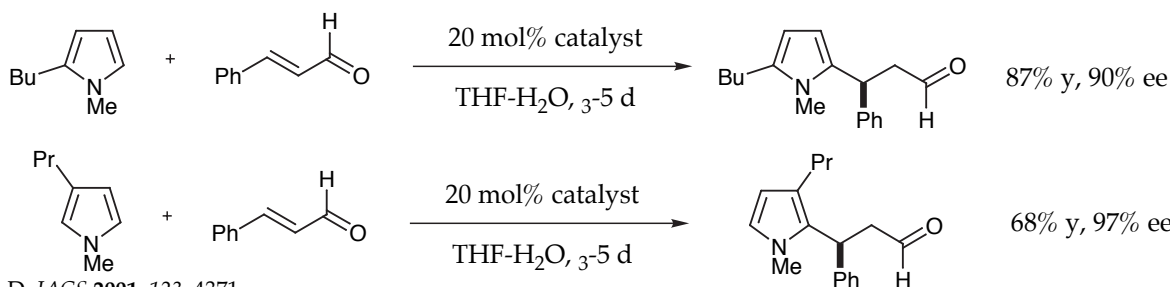


R	temp(°C)	yield	ee
Me	-60	83	91
<i>n</i> -Pr	-50	81	90
<i>i</i> -Pr	-50	80	91
Ph	-30	87	93
PMP	-30	79	91
CH ₂ OBn	-60	90	87
CO ₂ Me	-50	72	90



♦ use of *N*-benzyl pyrrole and *N*-allyl pyrrole give similar results

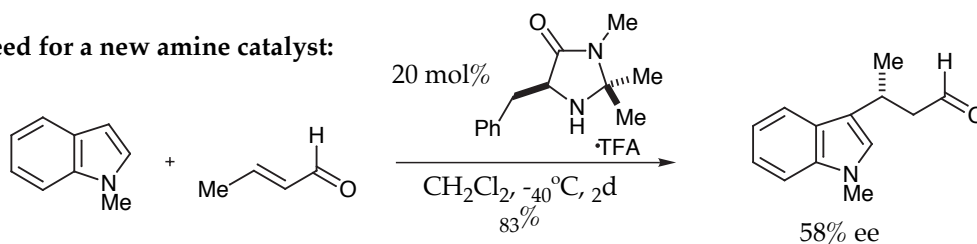
Substitution on the pyrrole is also possible:



MacMillan, D. *JACS* **2001**, *123*, 4371.

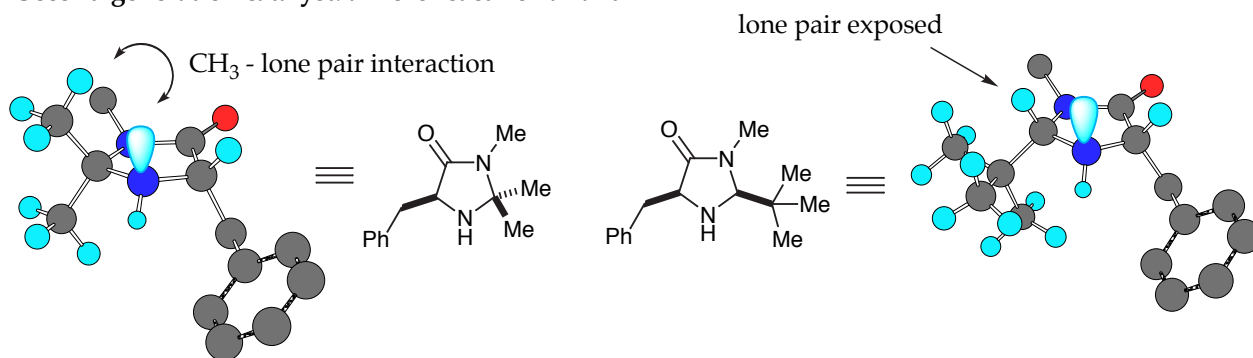
Alkylation of Indoles 1

The need for a new amine catalyst:



♦ Indole is less electron-rich than pyrrole, so is less nucleophilic toward conjugate addition

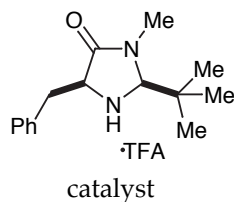
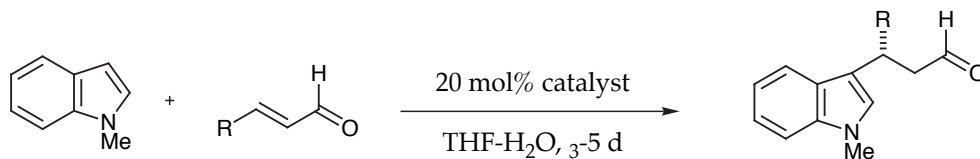
Second generation catalyst: a more reactive variant



♦ Kinetic studies indicate rate of reaction influenced by iminium formation as well as carbon-carbon bond forming event

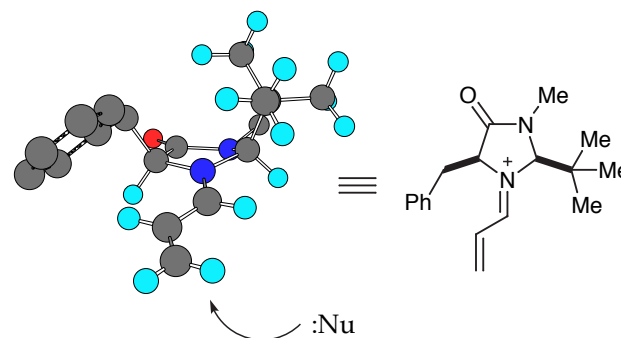
MacMillan, D. *JACS* **2002**, *124*, 1172.

Alkylation of Indoles 2



R	temp(°C)	yield	ee
Me	-83	82	92
<i>n</i> -Pr	-60	80	93
<i>i</i> -Pr	-50	74	93
Ph	-55	84	90
CH ₂ OBz	-83	84	96
CO ₂ Me	-83	89	91

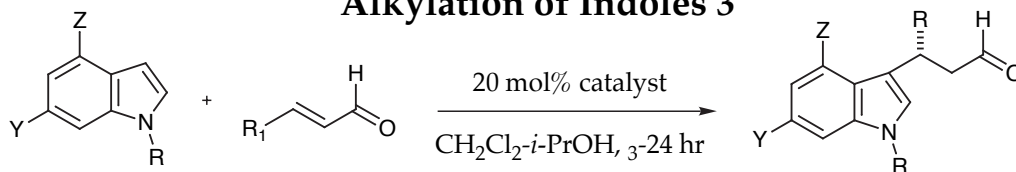
An increase in rate of reaction and enantioselectivity:



- ◆ increased top-face coverage
- ◆ nucleophile-geminal dimethyl interaction removed

MacMillan, D. *JACS* 2002, 124, 1172.

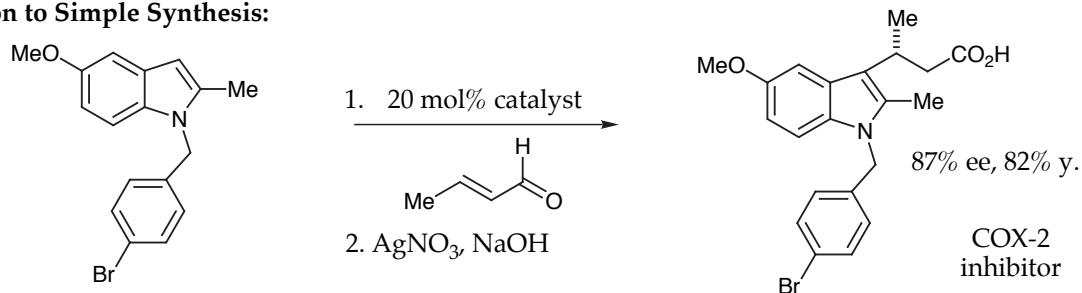
Alkylation of Indoles 3



Indole Scope:

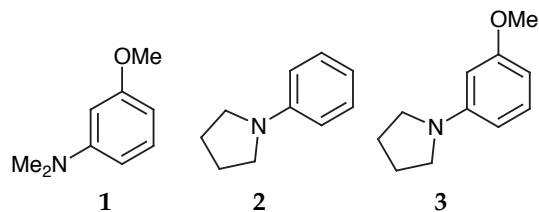
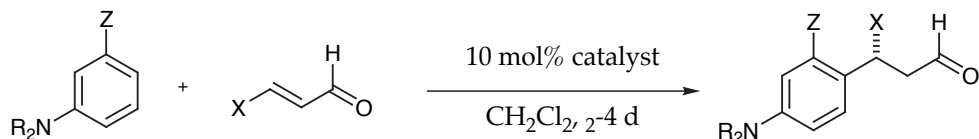
R	Y	Z	R ₁	temp(°C)	% yield	% ee
Me	H	H	Me	-87	82	92
H	H	H	Me	-60	72	91
allyl	H	H	Me	-72	70	92
Bn	H	H	Me	-60	80	89
H	H	Me	-CH ₂ OBz	-60	94	94
Me	H	OMe	-CH ₂ OBz	-87	90	96
H	Cl	H	-CH ₂ OBz	-60	73	97

Application to Simple Synthesis:

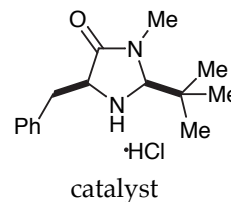


MacMillan, D. *JACS* 2002, 124, 1172.

Alkylation of Benzenes



aniline	X	temp(°C)	% yield	% ee
1	Me	-40	86	89
2	Me	-20	70	87
1	Et	-50	68	88
1	CH ₂ OBz	-20	89	92
2	CH ₂ OBz	+20	73	90
1	CO ₂ Me	-20	90	92
2	CO ₂ Me	-20	97	97
3	Ph	-50	82	84
3	<i>p</i> -ClPh	-10	87	92
1	<i>p</i> -NO ₂ -Ph	-10	87	92
2	<i>p</i> -NO ₂ -Ph	-20	82	90

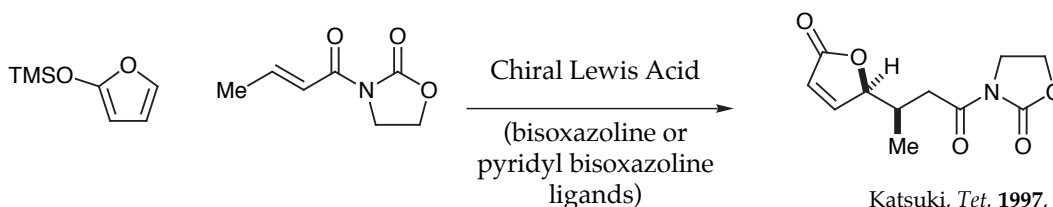


- ♦ other substituted anilines used with similar results
- ♦ catalyst loading can be lowered to 1% without significant loss of yield and enantioselectivity

MacMillan, D. *JACS* **2002**, *124*, 7894.

Mukaiyama-Michael Reaction 1

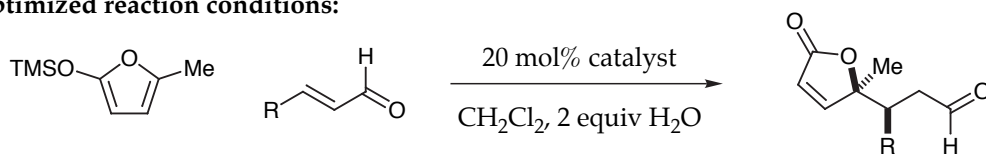
Previous Michael additions with silyloxy furans:



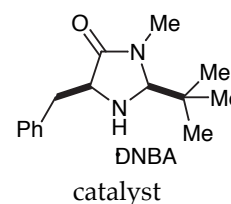
Katsuki, *Tet.* **1997**, *53*, 17015
Desimoni, G. *Tet.* **2001**, *57*, 10203

- ♦ note that Lewis acids promote 1,2-addition products when possible, such as α,β -unsaturated enals

Optimized reaction conditions:

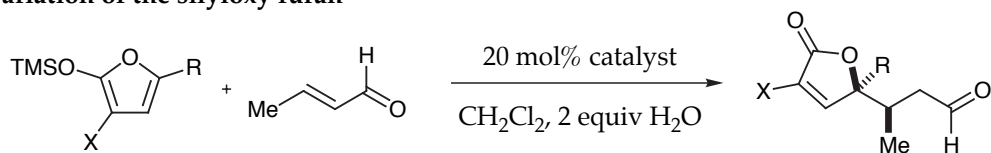


R	temp (°C)	% yield	syn:anti	% ee
Me	-70	81	22:1	92
<i>n</i> -Pr	-50	87	31:1	84
<i>i</i> -Pr	-20	80	7:1	98
Ph	-40	77	1:6	99
CH ₂ OBz	-70	86	20:1	90
CO ₂ Me	-60	84	11:1	99



Mukaiyama-Michael Reaction 2

Variation of the silyloxy furan

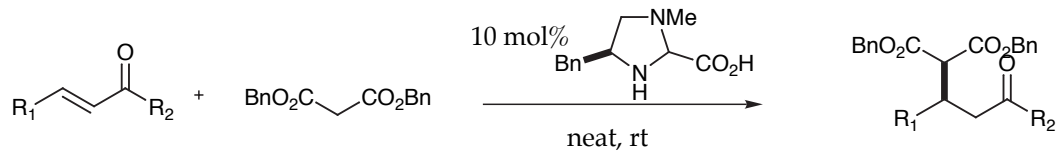


R	X	% yield	<i>syn:anti</i>	% ee	
H	H	87	8:1	90	
Me	H	80	22:1	92	
Et	H	83	16:1	90	
CO ₂ Me	H	86	6:1	98	TFA as cocatalyst
CO ₂ Me	H	83	1:7	98	TfOH as cocatalyst
Me	Me	73	24:1	90	

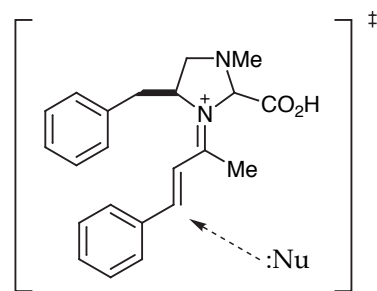
MacMillan, D. *JACS* **2003**, *125*, 1192.

Another Chiral Amine Catalyst

Asymmetric Michael Additions



R ₁	R ₂	% yield	% ee
<i>p</i> -NO ₂ Ph	Me	84	89
<i>p</i> -NMe ₂ Ph	Me	58	77
2-furyl	Me	75	92
2-pyridyl	Me	95	88
<i>n</i> -Bu	Me	61	91
<i>i</i> -Pr	Me	33	84
MeO ₂ C	Me	59	59
Ph	Me	86	99
Ph	Et	66	95
Ph	<i>i</i> -Pr	2	94

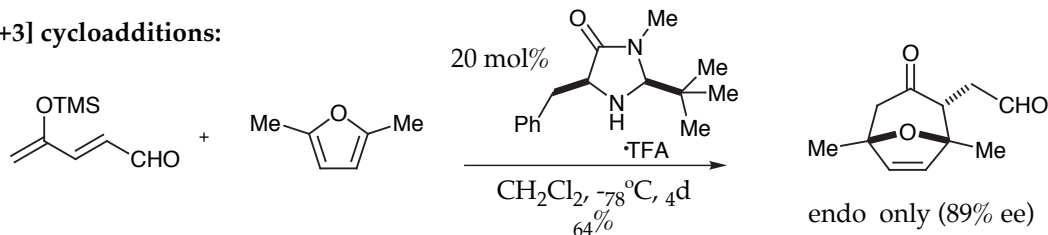


- ♦ Nitroalkane additions to α,β -unsaturated ketones has also been performed in good to excellent selectivity (Jorgensen, K. *JOC* **2002**, *67*, 8331.)

Jorgensen, K. *ACIEE* **2003**, *42*, 661.

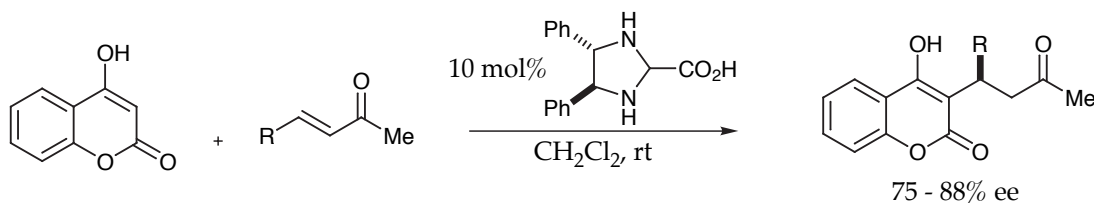
A Listing of Other Asymmetric Organocatalytic Reactions

[4+3] cycloadditions:



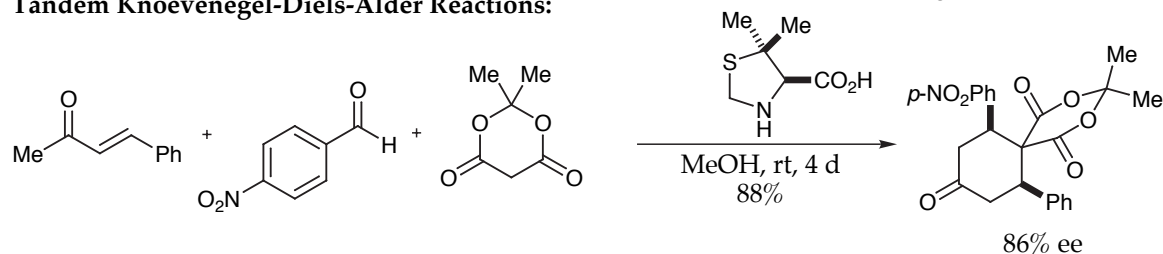
Harmata, M. *JACS*, **2003**, *125*, 2058.

Michael Reactions:



Jorgensen, K. *ACIEE* **2003**, *42*, 4955

Tandem Knoevenegel-Diels-Alder Reactions:



Barbas, C. *ACIEE* **2003**, *42*, 4233

Summary

- ♦ Reactions are direct:
 - Donors can be used without modification -- no need to deprotonate or silylate prior to reaction
 - Electrophiles can be generated *in situ* (Mannich reaction) most of the time
- ♦ Catalysts are:
 - inexpensive
 - commercially available or easily prepared in both enantiomeric forms
 - non-toxic
 - recoverable
- ♦ Many reactions can be run at room temperature, under an aerobic atmosphere, with wet solvents
- ♦ Many types of reactions can be catalyzed; for some reactions, organocatalysis is the only highly efficient way known (Mannich and Mukaiyama-Michael additions)
- ♦ Reaction yield and enantioselectivity is highly dependent on solvent system so require "fine tuning"
- ♦ Only reactions that use ketones or aldehydes as donors (electrophiles for Michael additions) can be catalyzed

Organocatalysis using small molecules is a field that has emerged only within the past decade. It is bound to receive increasing attention in the future; as a result, new catalysts will emerge which will allow for the catalysis of reactions previously unutilized in the realm of organocatalysis.

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 29

Ambiphilic Functional Groups–3 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**)

D. A. Evans

Monday,
November 24, 2003

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: Blakemore, *J. Chem. Soc. Perkin Trans I* **2002**, 2563.

Electrophilic Properties: Trost, B.M. *Bull. Chem. Soc. Jpn.* **1988**, 61, 107.

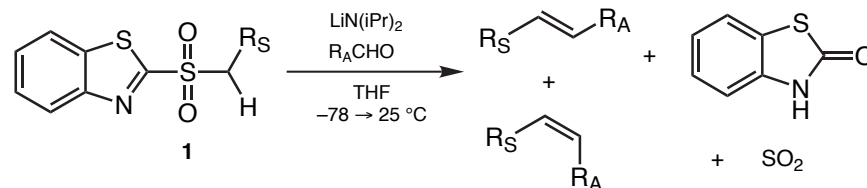
SO₂ Extrusion: Vogtle, F.; Rossa, L. *ACIEE* **1979**, 18, 515.

Ramberg-Bäcklund Rxn: Paquette, L.A. *Org. Reactions* **1977**, 25, 1.

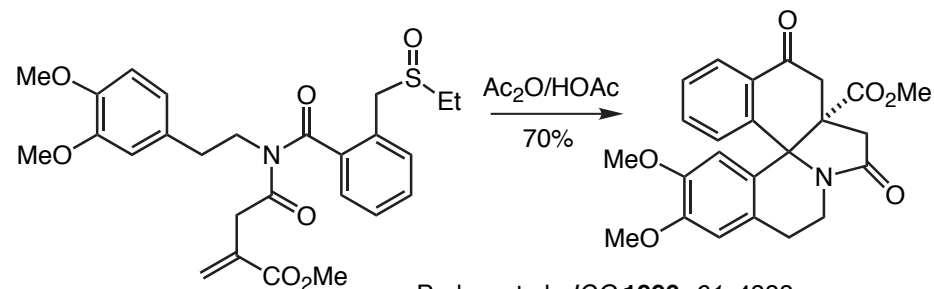
Triflones: Hendrickson, J.B. *Org. Prep. Proc. Int.* **1977**, 175.

Sulfoximides: Johnson, C.R. *Tetrahedron* **1984**, 40, 1225

Cum 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



Padwa et al. *JOC* **1996**, 61, 4888

Relevant Background Reading

General: Simpkins, N.S. *Sulphones in Organic Synthesis*, Pergamon Press, New York, 1993.

General: Magnus, P.D. *Tetrahedron* **1977**, 33, 2019.

Julia: Blakemore, J. *Chem. Soc. Perkin Trans I.* **2002**, 2563.

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

Acidities of Sulfur-based Functional Groups

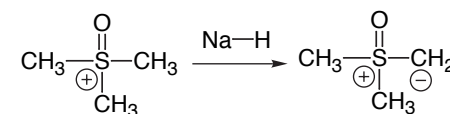
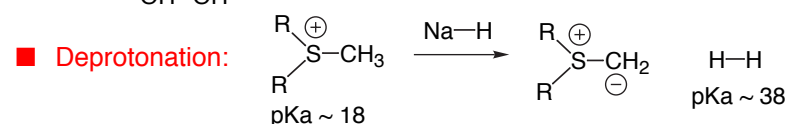
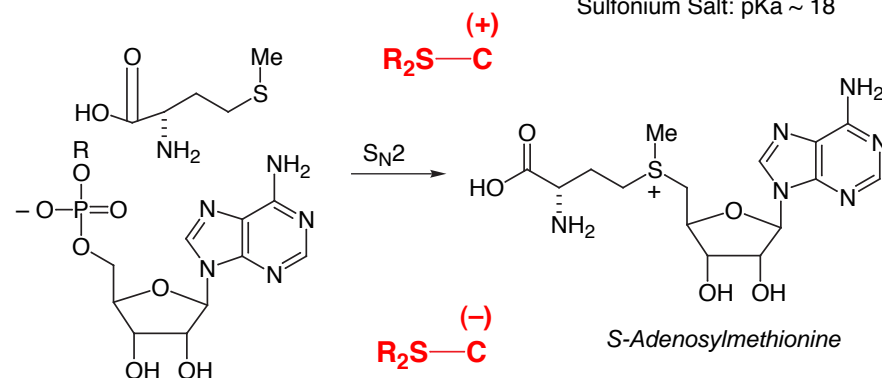
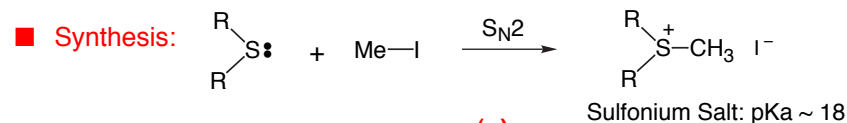
Bordwell, F. G.; Zhang, X.-M. *Acc. Chem. Res.* **1993**, 26, 510-17.

		pKa (DMSO)	
$\text{CH}_3\text{—S—CH}_3$	Sulfide	(45)	← CH ₄ pKa (~56)
$\text{CH}_3\text{—S(=O)—CH}_3$	Sulfoxide	~35	← NH ₃ pKa (~41)
$\text{CH}_3\text{—S(=O)}_2\text{—CH}_3$	Sulfone	~31	← HOH pKa 31
$\text{CH}_3\text{—S}^+\text{(CH}_3)_3$	Sulfonium Salt	18.2	
$\text{CH}_3\text{—S}^+\text{(=O)—CH}_3$	Oxo-Sulfonium Salt		

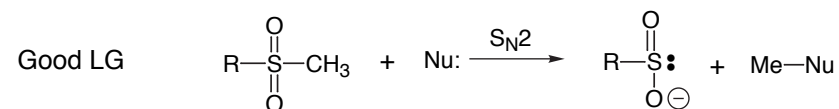
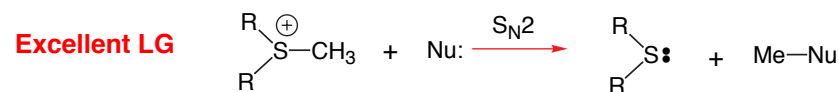
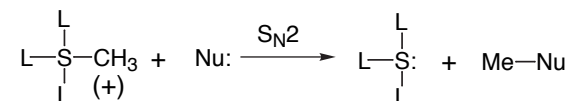
$\text{R}_2\text{S—C}$
 (-)
 (+)

Reactivity Pattern
Nonalternate

Reactions of Sulfonium Ylids

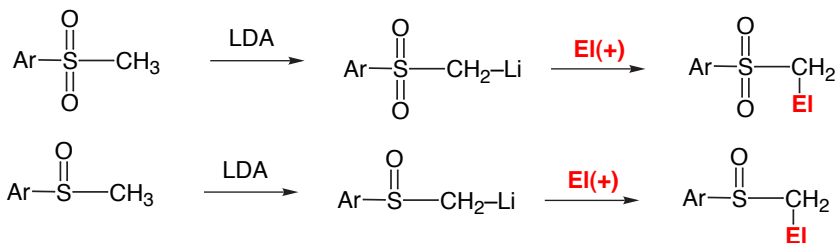


Leaving Group Potential: $\text{R}_2\text{S—C}(+)$



Sulfone- & Sulfoxide Based Carbanions: Structure

- Sulfone- and sulfoxide-stabilized carbanions are extremely useful carbon nucleophiles in organic synthesis.

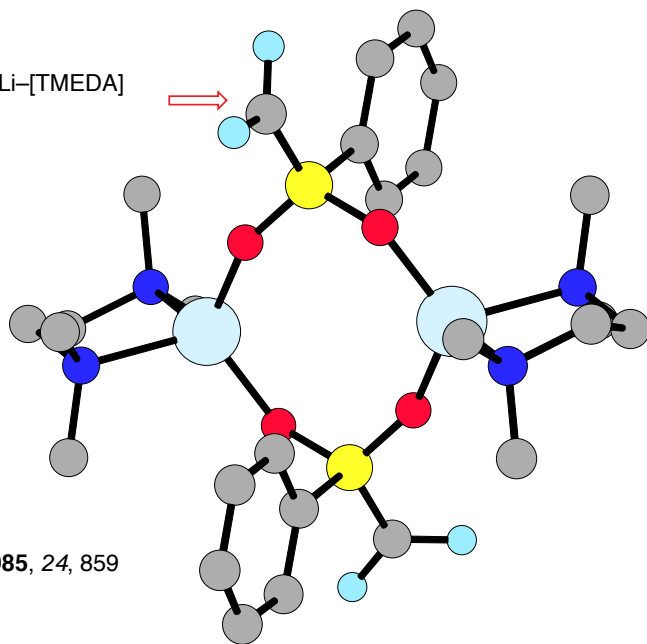
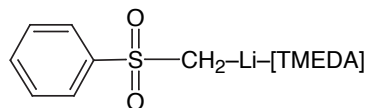


However, until recently little information was available on the solid state structures of these species:

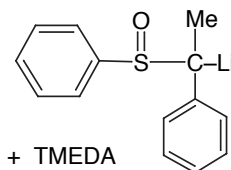
"The Structure of Lithium Compounds of Sulfones, Sulfoximides, Sulfoxides, Thioethers, 1,3 Dithianes, Nitriles, Nitro Compounds, and Hydrazones."

Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

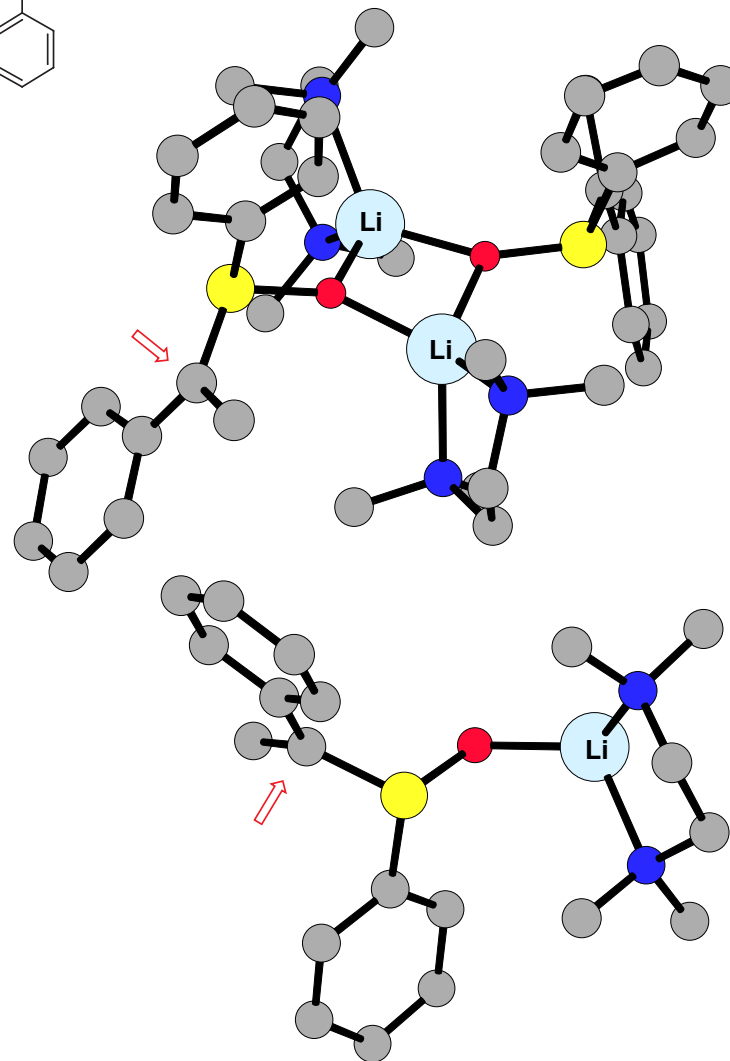
Here are several examples taken from the Boche review:



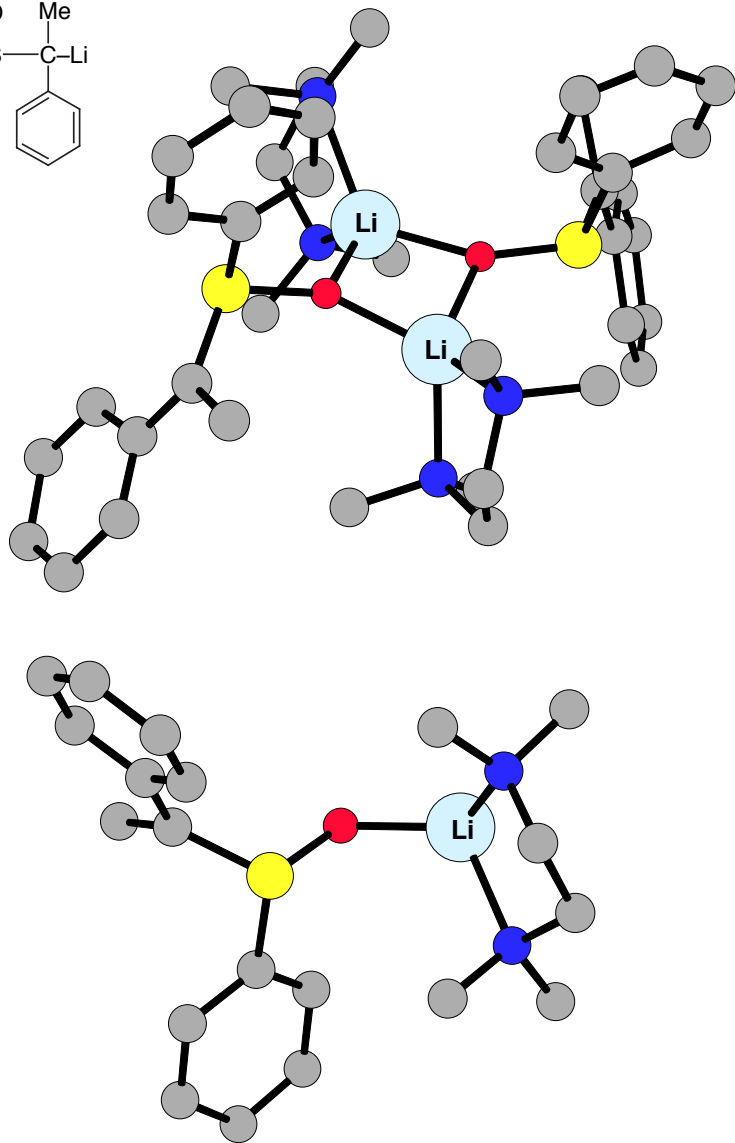
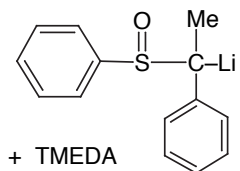
Gais, et al.
Angew. Chem. Int. Ed. **1985**, *24*, 859



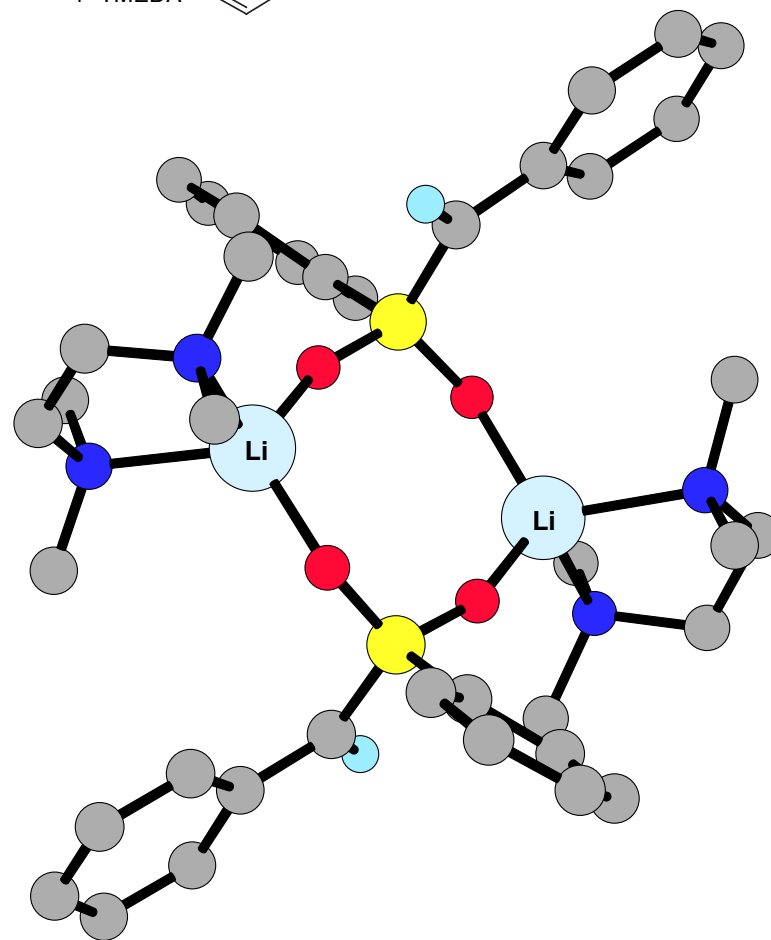
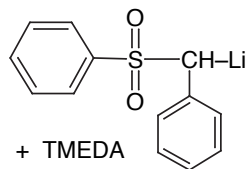
Boche, et al. *Angew. Chem. Int. Ed.* **1986**, *25*, 1101



- The Li counterions are not associated with the charged carbon.
- The carbanions are largely trigonal.

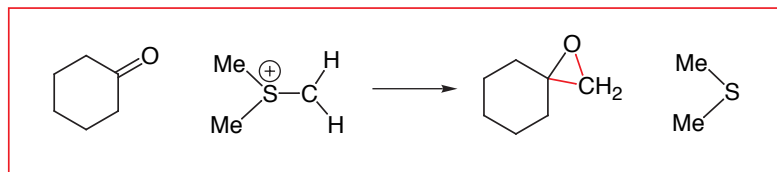


Boche, etal. *Angew. Chem. Int. Ed.* **1986**, 25, 1101

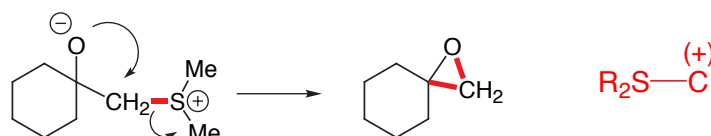
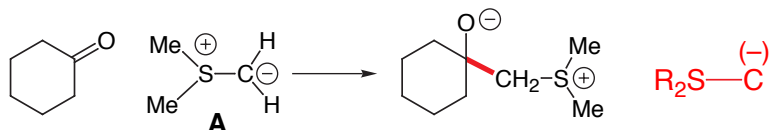


Boche, etal. *Angew. Chem. Int. Ed.* **1985**, 24, 573

■ **Reactions with ketones:** R_2S-C^{\oplus} Reactivity Pattern: Nonalternate

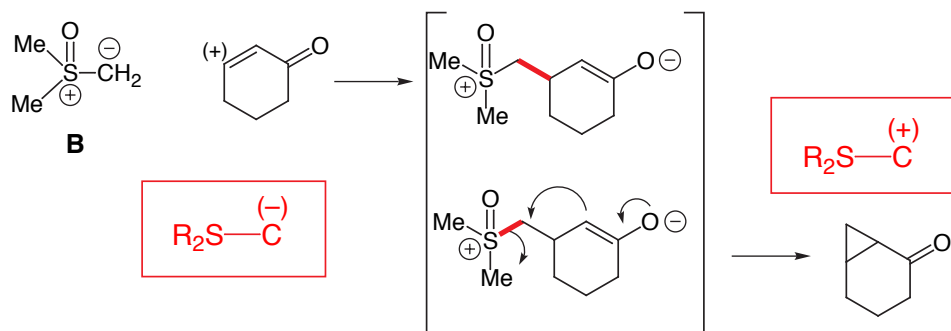


Corey & Chaykovski, *JACS* **1965**, 87, 1353-1364. (Handout)

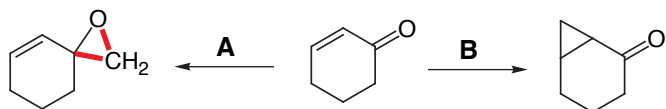


"Twenty-five Years of Dimethylsulfoxonium Methylide (Corey's Reagent).", Gololobov, Y. G.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, 43, 2609. (electronic handout)

Reactions of OxoSulfonium Ylids: Conjugate Addition

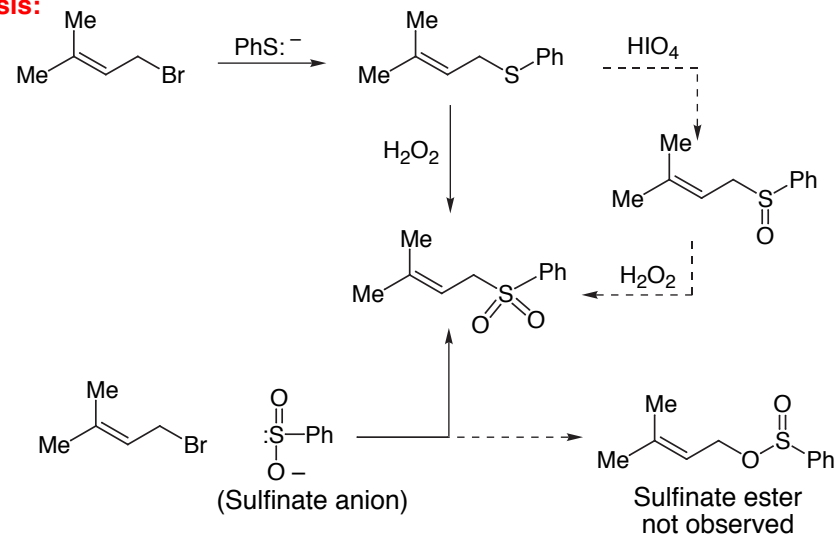


Nonalternate reactivity pattern revealed in consecutive reactions



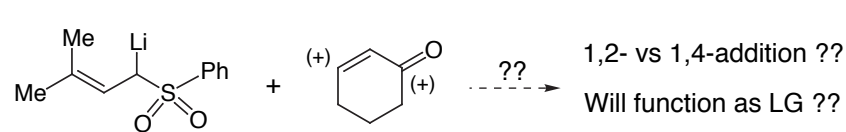
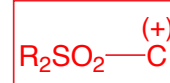
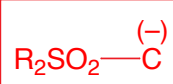
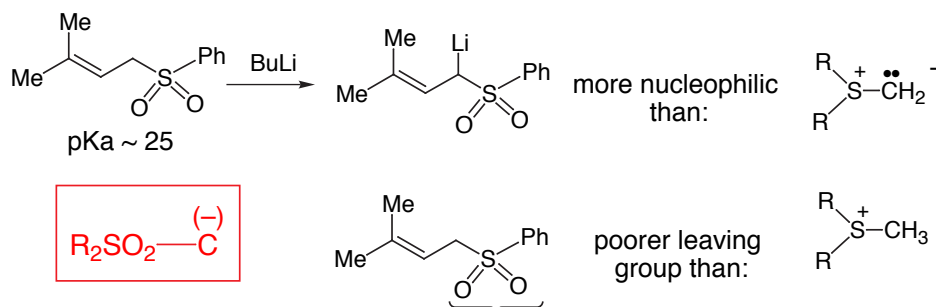
Reactions of Sulfones

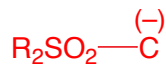
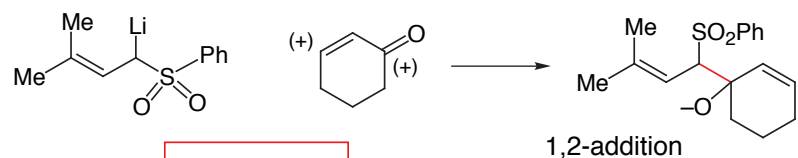
Synthesis:



Good review article: Magnus, *Tetrahedron* **1977**, 33, 2019-2045.

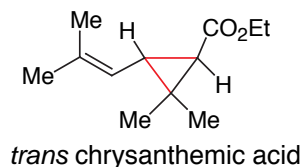
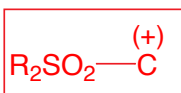
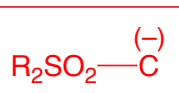
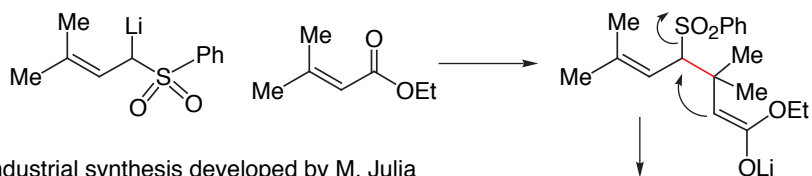
Reactions of Sulfones



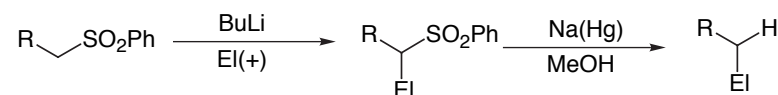


Alkoxide not sufficiently nucleophilic to displace PhSO_2^- anion.

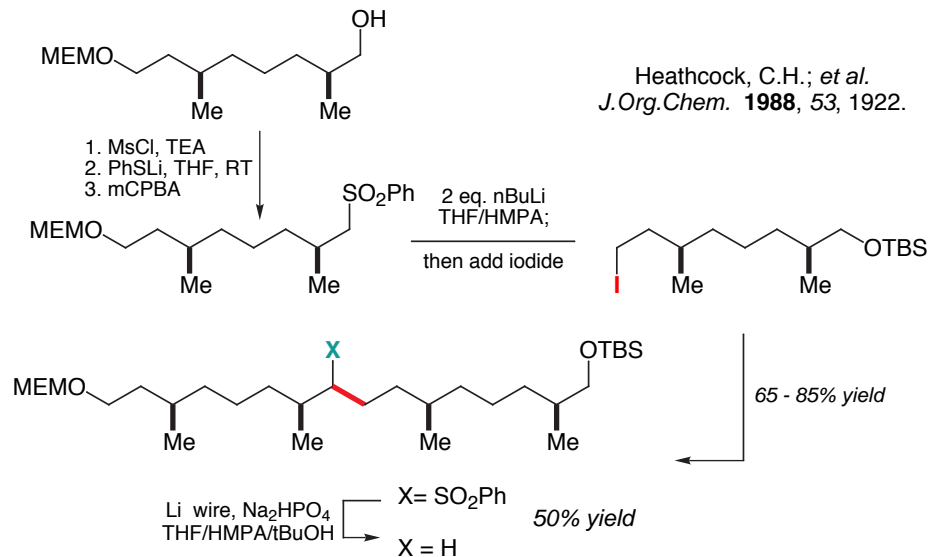
However!!



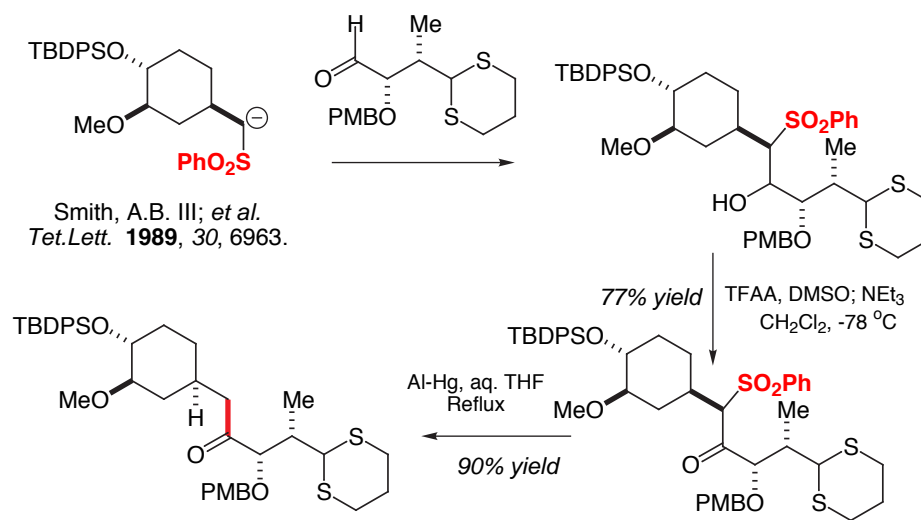
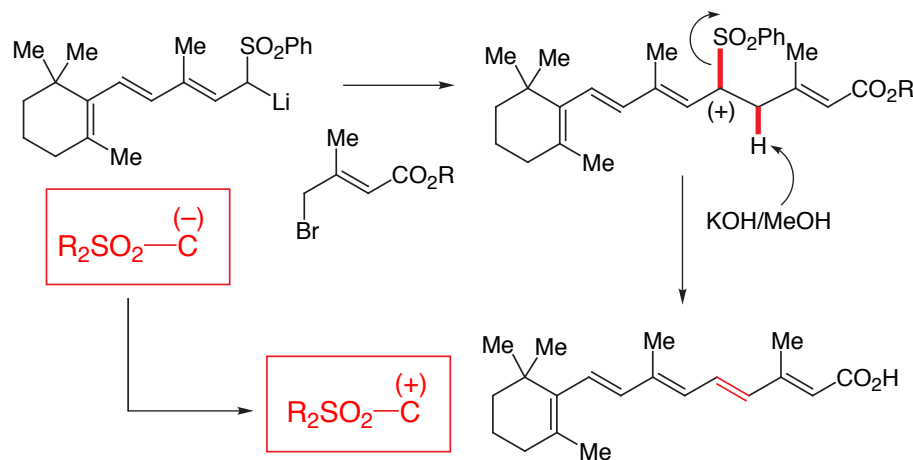
The Sulfone group may also be readily removed reductively:



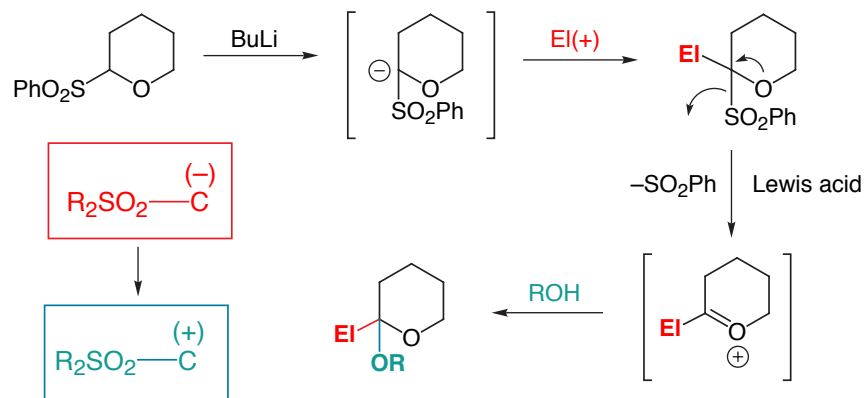
Fragment Coupling with Sulfonyl Carbanions



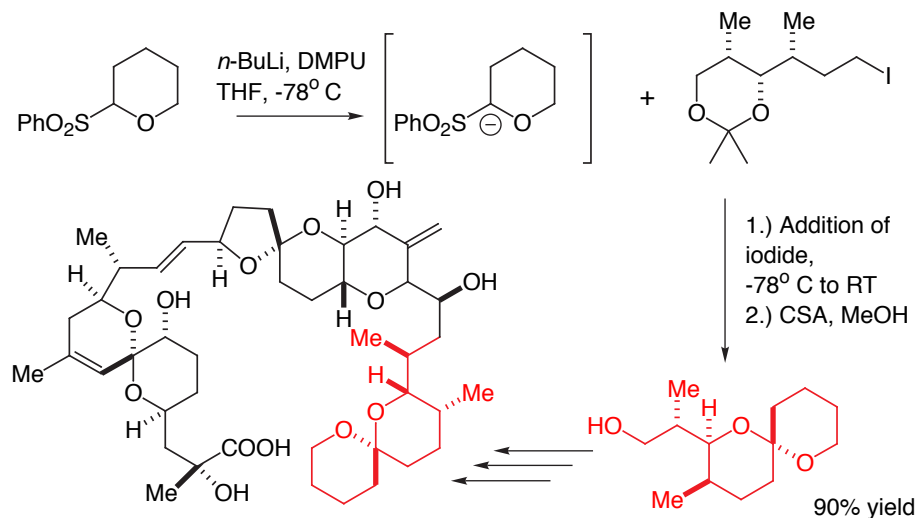
Synthesis of Vitamin A: Julia & Co-workers, *Bull. Soc. Chim. Fr.* **1985**, 130



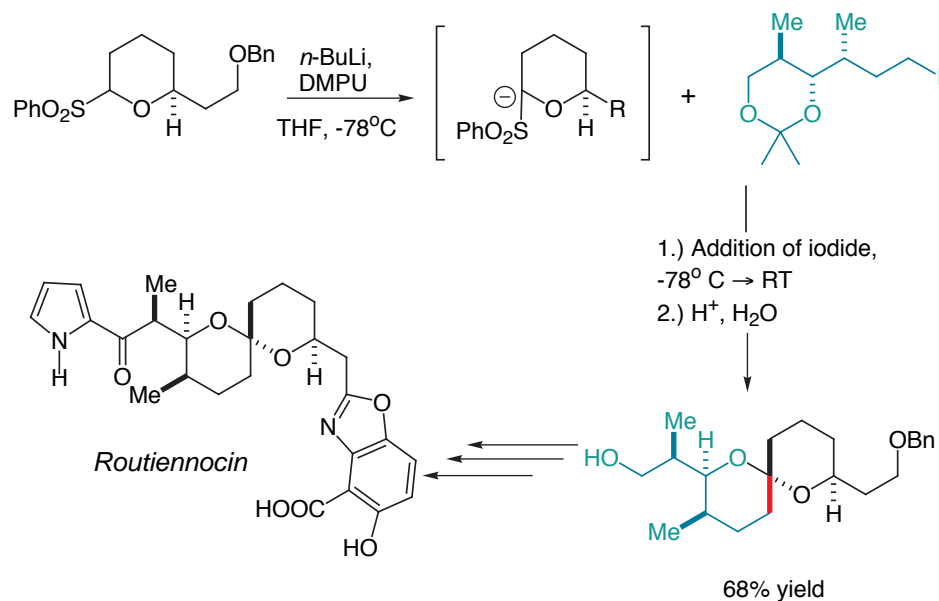
Functionalization of cyclic Ethers

Ley et al, *Synlett*, **1992**, 395; Ley et. al, *Tetrahedron*, **1992**, 48, 7899

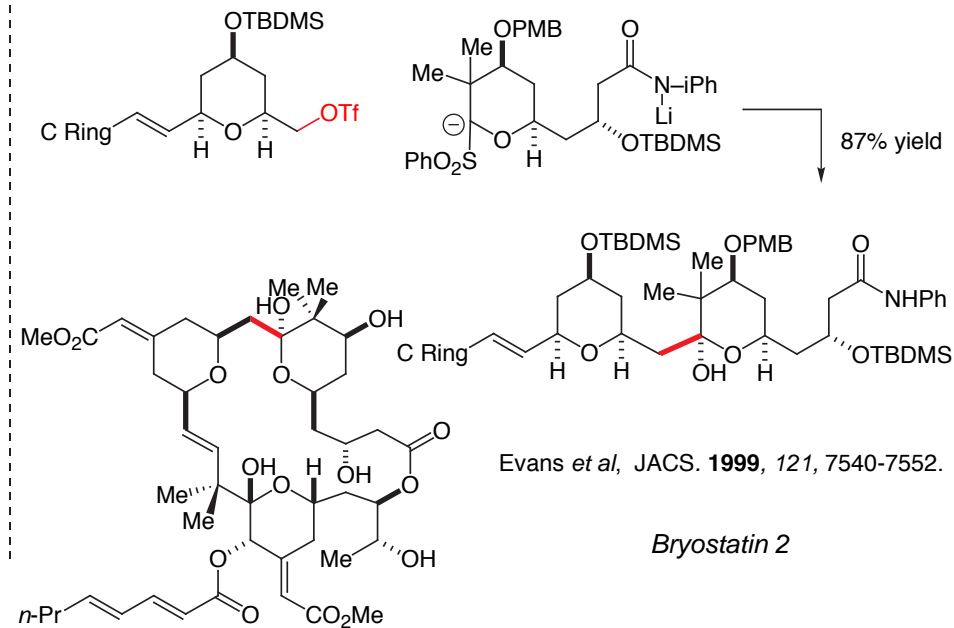
Total synthesis of Okadaic Acid

Ley et al, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3907.

Total Synthesis of Rutiennocin (CP-61,405)

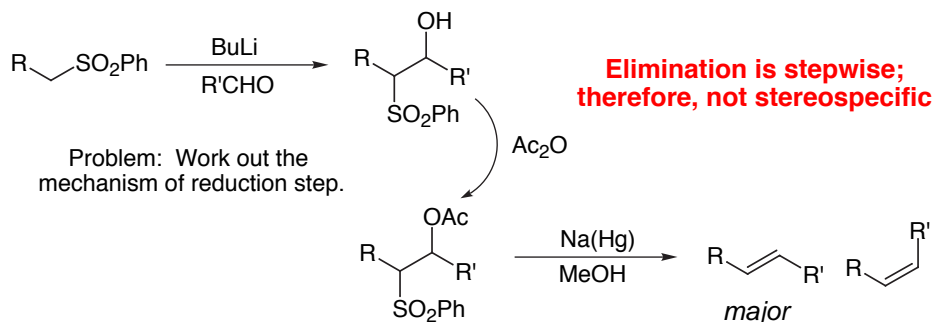


Total synthesis of Bryostatin 2

Evans et al, *JACS*. **1999**, 121, 7540-7552.

Bryostatin 2

First Generation Julia Trans Olefin Synthesis:

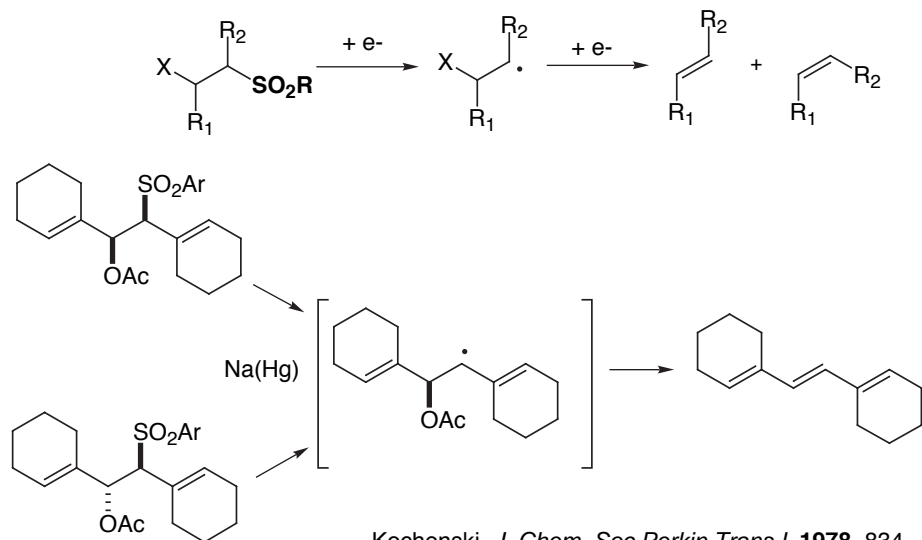


Problem: Work out the mechanism of reduction step.

Good sulfone review: Trost, *Bull Chem. Soc. Japan*, **1988**, 61, 107-124.

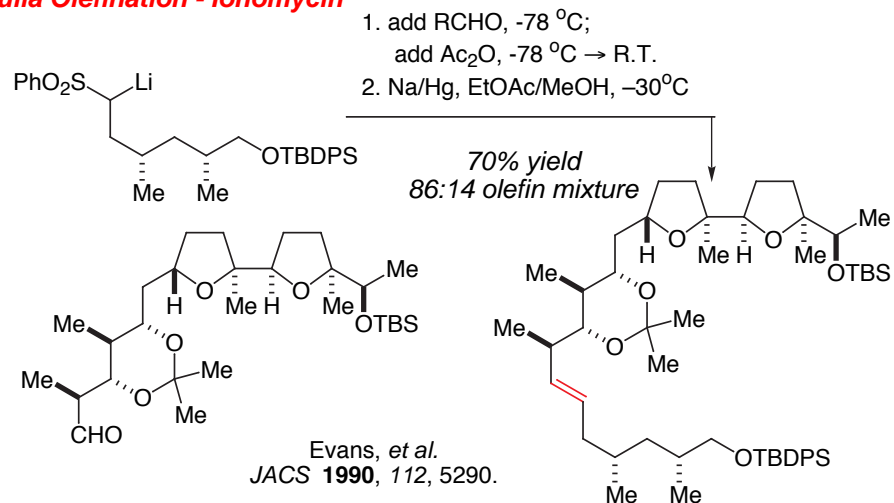
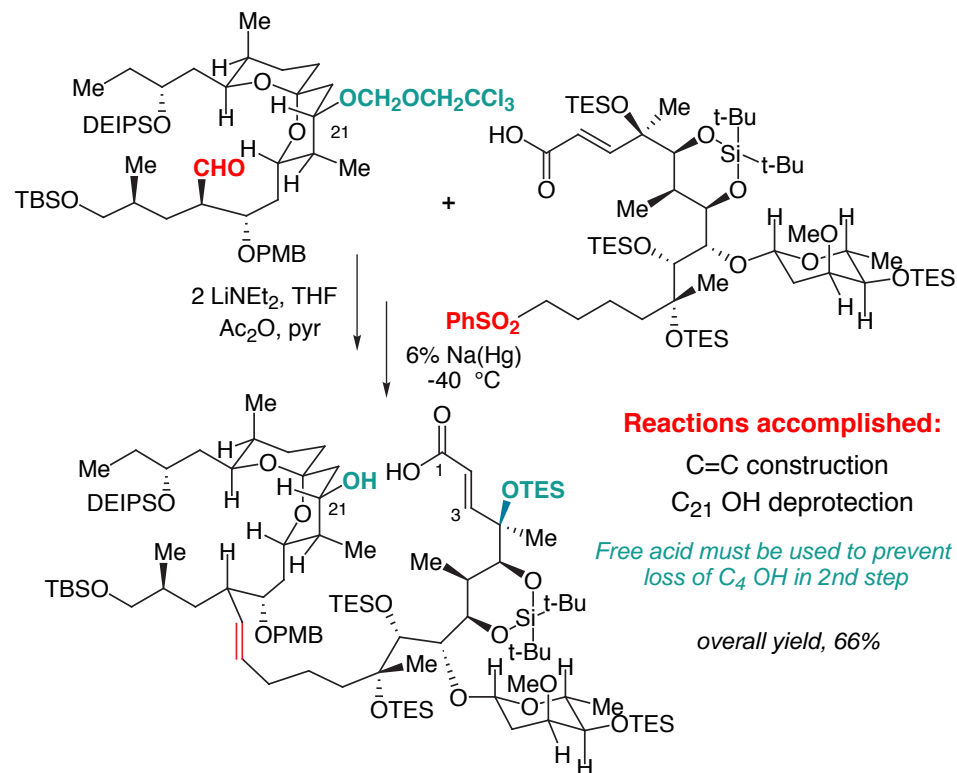
Julia Review,
Blakemore, *J. Chem. Soc. Perkin Trans I*. **2002**, 2563. (electronic handout)

The reduction step is not stereosecific

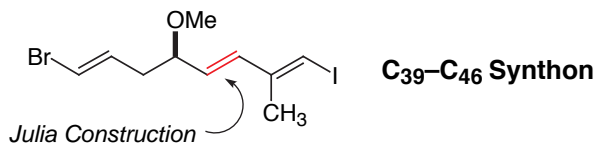
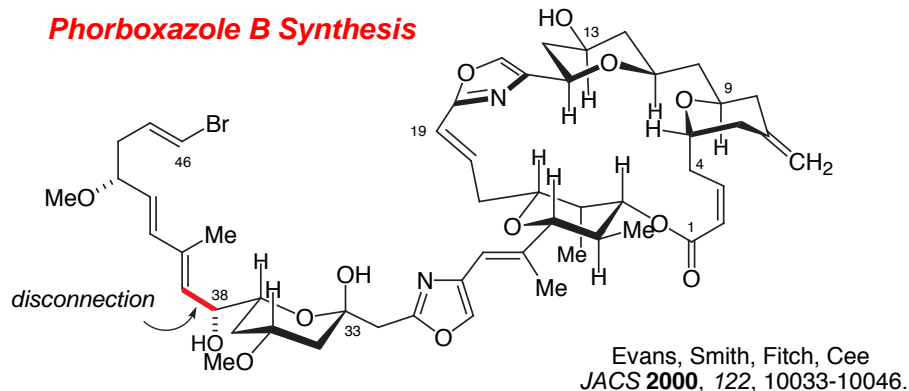


Kochenski, *J. Chem. Soc Perkin Trans I*, **1978**, 834

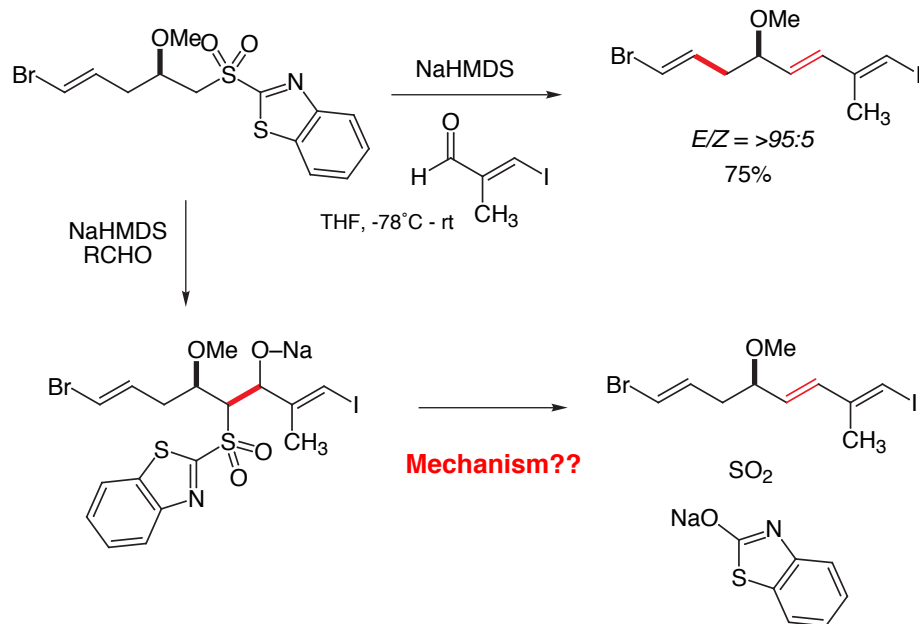
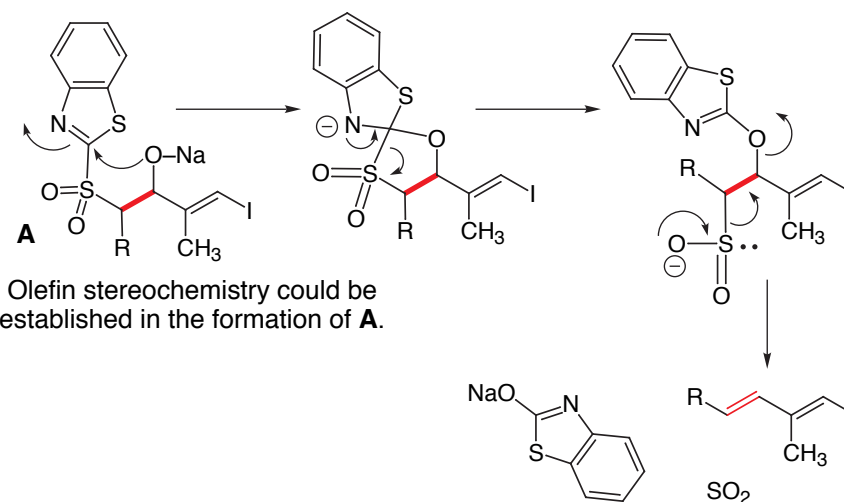
Julia Olefination - Ionomycin

Cytovaricin Synthesis: *JACS* 1990, 112, 7001

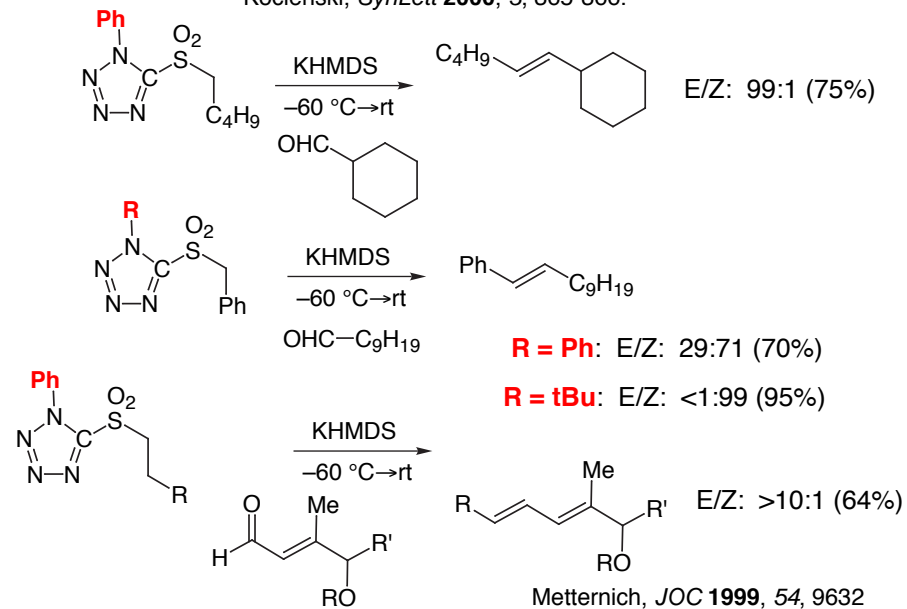
Phorboxazole B Synthesis



The Mechanism:

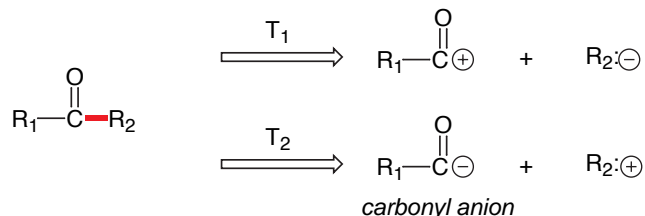


Recent Modifications of the Julia Process:

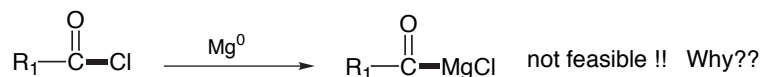
Kocienski, *SynLett* 2000, 3, 365-366.

Carbonyl Anions: A useful Reversed Polarity Equivalent

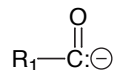
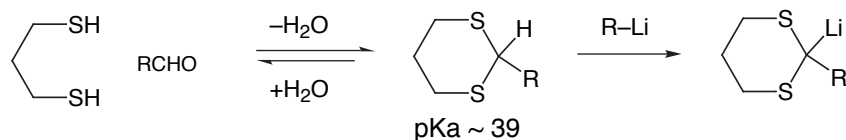
Consider the two possible polar disconnections of the C–R₂ bond of the ketone shown below:



Carbonyl anions are not normally accessible via aldehyde deprotonation

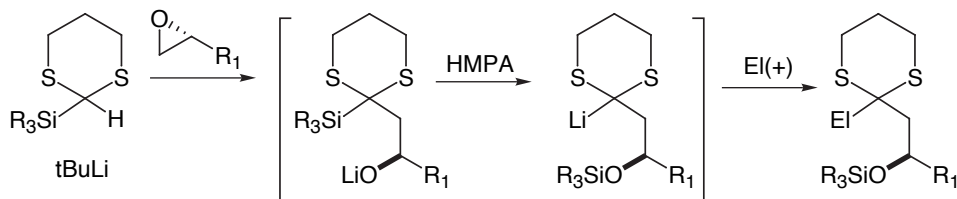


Operational equivalents to the carbonyl anion are useful in synthesis

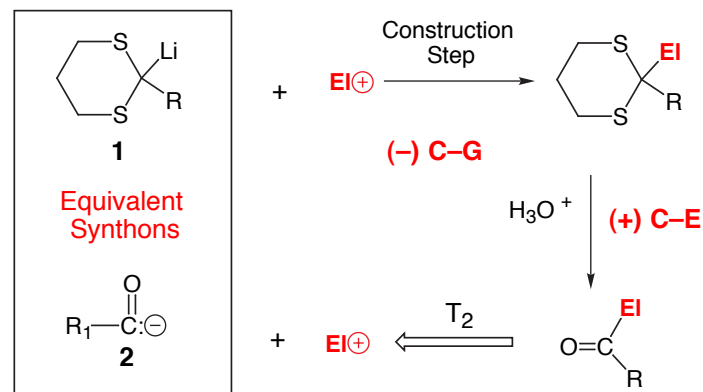
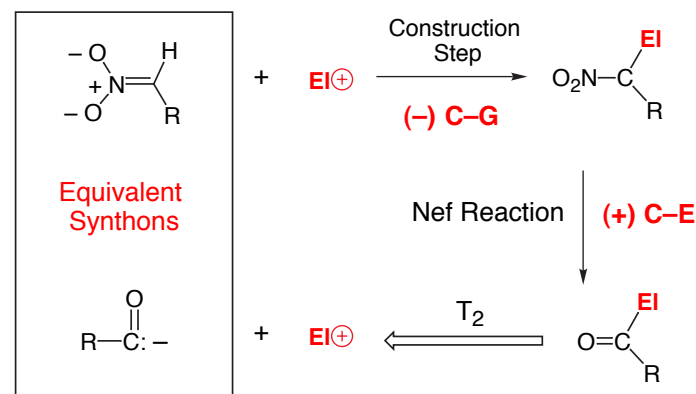
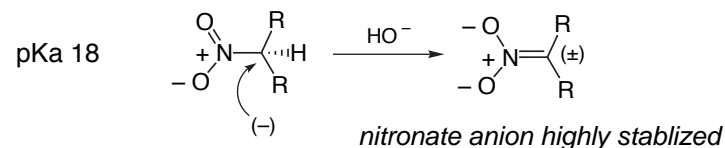
**1,3-Dithianes as Carbonyl Anion Equivalents**

Reactivity Patterns: $(\text{RS})_2\text{-C}(+)$ $(\text{RS})_2\text{-C}(-)$

Latest Innovations: A. B. Smith, *JACS* **2003**, *125*, 14435-14445 (Handout)

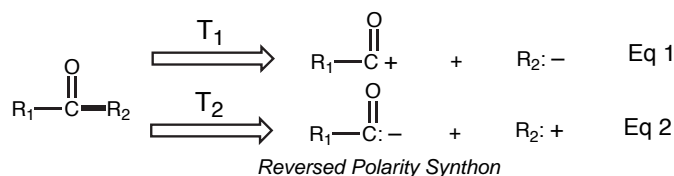


The overall set of reactions which establishes the equivalency of the hypothetical carbonyl anion **1** and its equivalent synthon **2** is shown below:

**Nitronate Anions are also useful Carbonyl Anions**

*Dithianes anions highly nucleophilic (indiscriminate):
Nitronate anions highly discriminating*

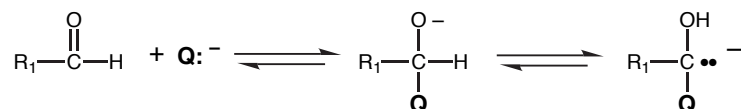
■ **Introduction.** As you know, transform T_1 conforms to the polar bias mapped on to the carbon skeleton by $=O$, while transform T_2 does not. Although T_1 is the more common transform, sometimes, because of the presence other functionality in either R_1 or R_2 , the "reversed-polarity" transform is more suitable for the particular synthesis at hand.



Ideally, one might visualize a catalytic agent (**Q**) which might react reversibly with an aldehyde in conjunction with inverting its charge affinity pattern. Nature has designed such reagents.

General Scheme

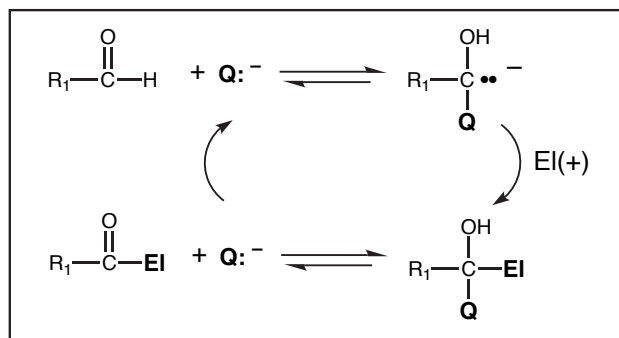
■ **Charge Affinity Inversion Step:** The structural constraints on (**Q**) are that it must be nucleophilic, add reversibly to aldehydes, and stabilize an adjacent carbanionic center.



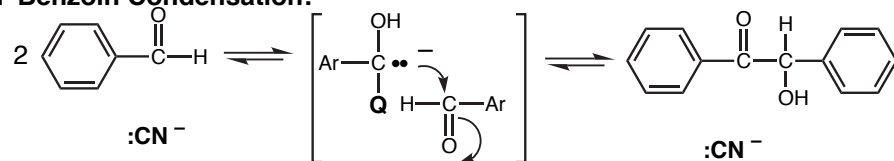
Lets call (**Q**) a charge affinity inversion operator since it operates on RCHO and reverses the intrinsic polar reactivity of the RCHO carbon from (+) to (-).

■ **Overall Process:**

The Inversion Operator



■ **Benzoin Condensation:**



Cyanide ion is the best example of a reagent which functions as an inversion operator. The benzoin reaction is restricted to aromatic aldehydes. Why?

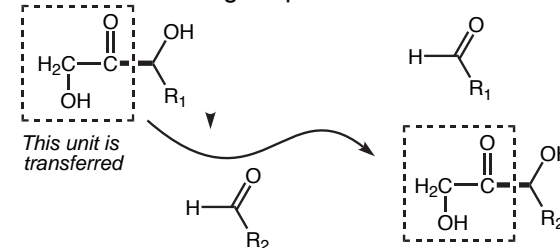
Nature's Inversion Operators

There is a clear need in nature to have both types of polar bond constructions exemplified by Transforms T_1 and T_2 (Eq 1-2). One such reaction is shown below.

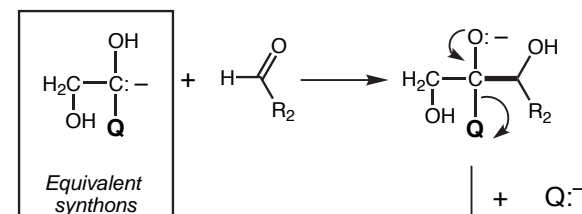
■ This reaction, which is enzyme-catalyzed, requires the cofactor thiamine which functions as the inversion operator in these biological processes.

■ **α -Ketol Transferases:**

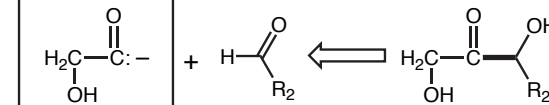
+ thiamine (Q^-)



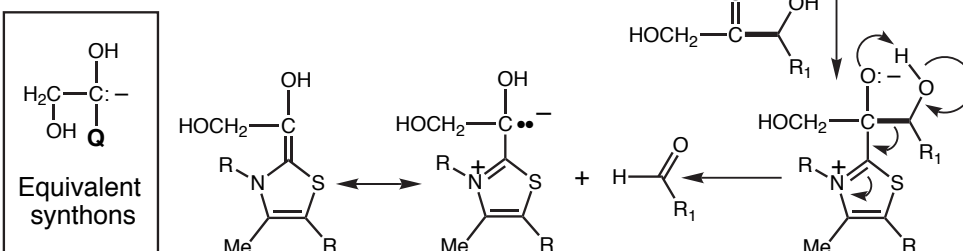
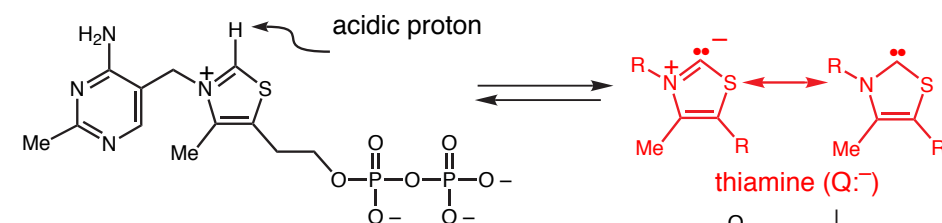
■ **Crucial bond construction:**

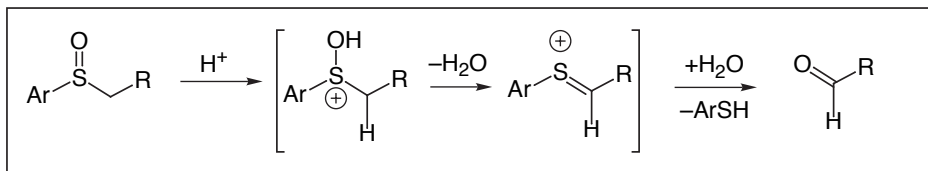


■ **Related transform:**

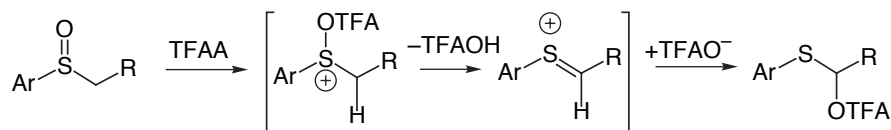


■ **The Thiamine Coenzyme (Vitamin B₁) & how it functions**



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**

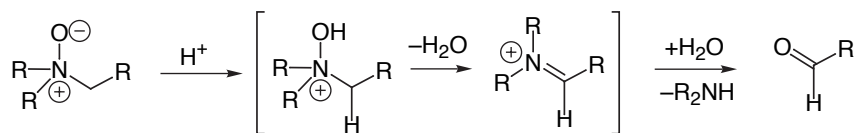
De Lucchi, Miotti, et al. (1991). "The Pummerer reaction of sulfinyl compounds." *Organic Reactions* **1991**, 40: 157.

Grierson, and Husson (1991). Polonovski- and Pummerer-type Reactions and the Nef Reaction. *Comprehensive Organic Synthesis*. Trost and Fleming. Oxford, Pergamon Press. 6: 909.

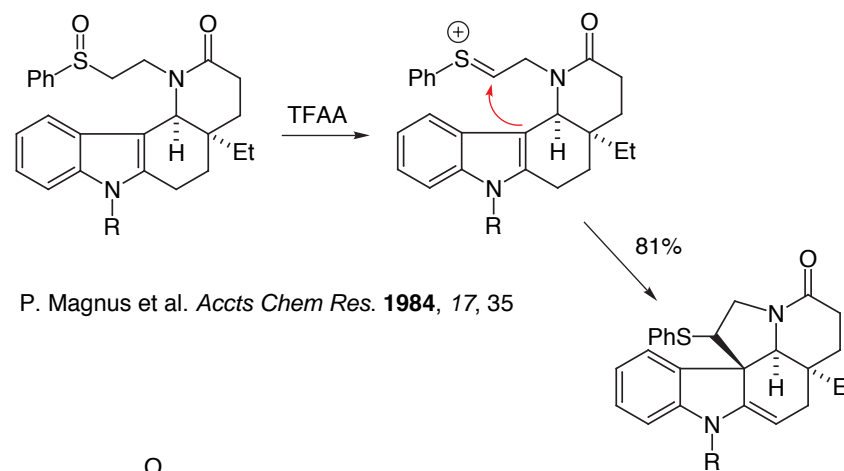
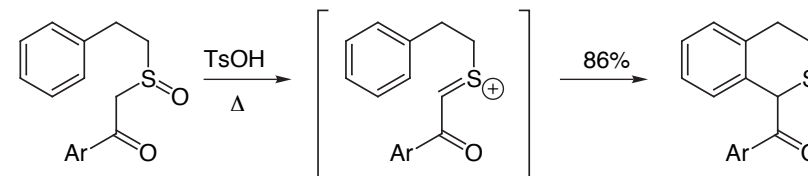
Padwa, A., D. E. Gunn, et al. "Application of the Pummerer reaction toward the synthesis of complex carbocycles and heterocycles." *Synthesis* **1997** 1353-1377.

Carreno, "Applications of sulfoxides to asymmetric synthesis of biologically active compounds." *Chem. Reviews* **1995** 95, 1717-1760.

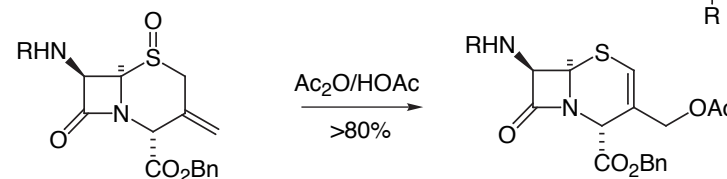
Kita, Y. and N. Shibata (1996). "Asymmetric pummerer-type reactions induced by O-silylated ketene acetals." *Synlett*(4): 289-296.

The Related Polonovski Reaction:

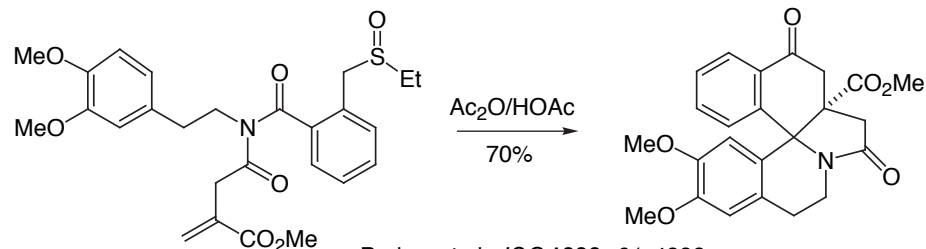
Regioselectivity: Depends on the relative kinetic acidity of the α protons

Transformations Mediated by the Pummerer Rearrangement

P. Magnus et al. *Accts Chem Res.* **1984**, 17, 35

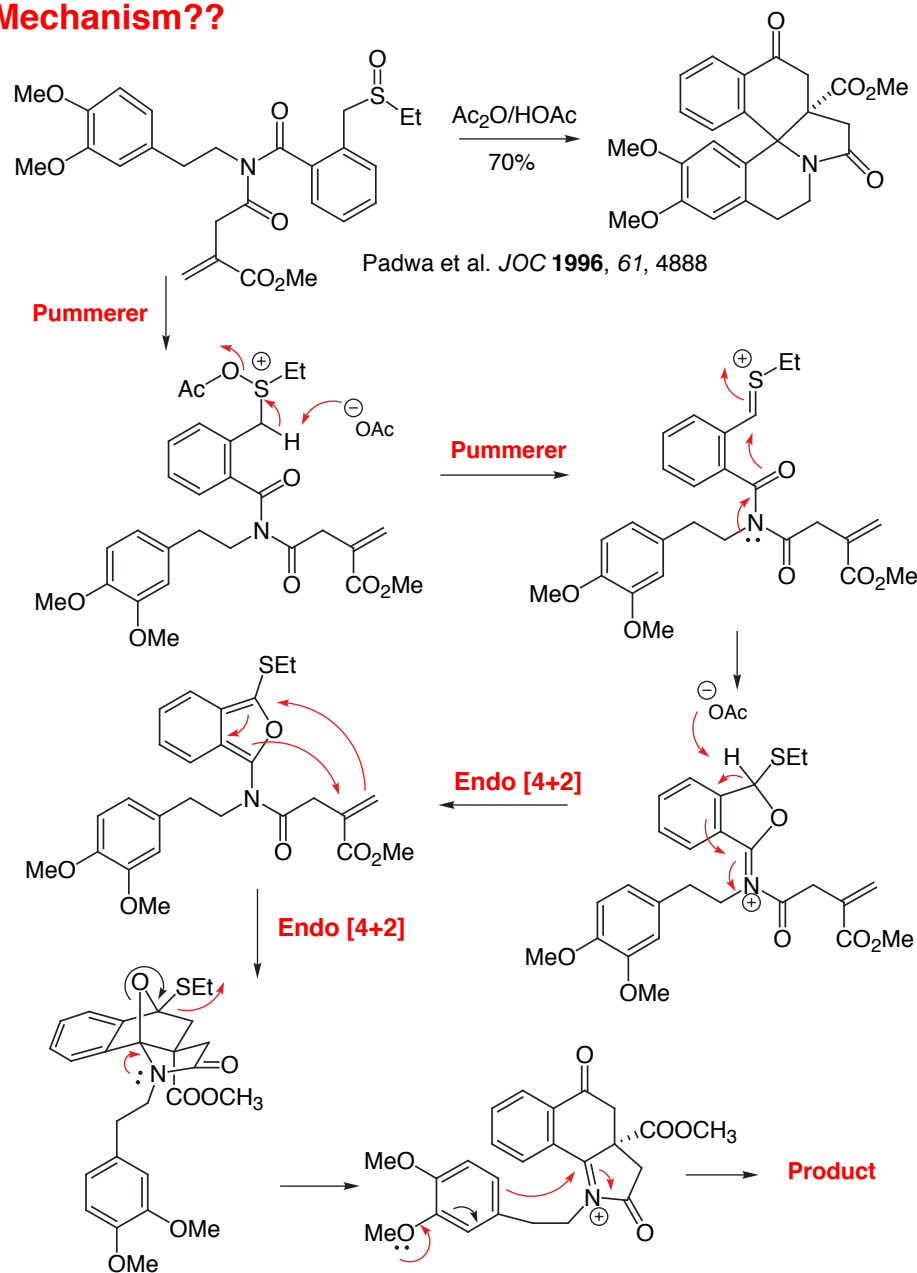


The cruel mechanistic problems that you should be prepared for in Chem 206

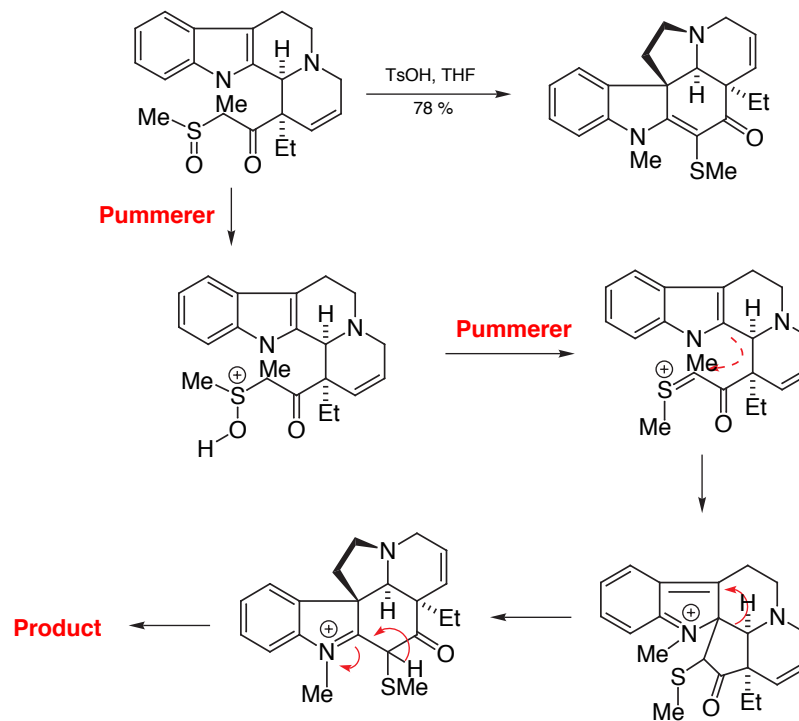


Padwa et al. *JOC* **1996**, 61, 4888

Mechanism??



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.



Chemistry 206

Advanced Organic Chemistry

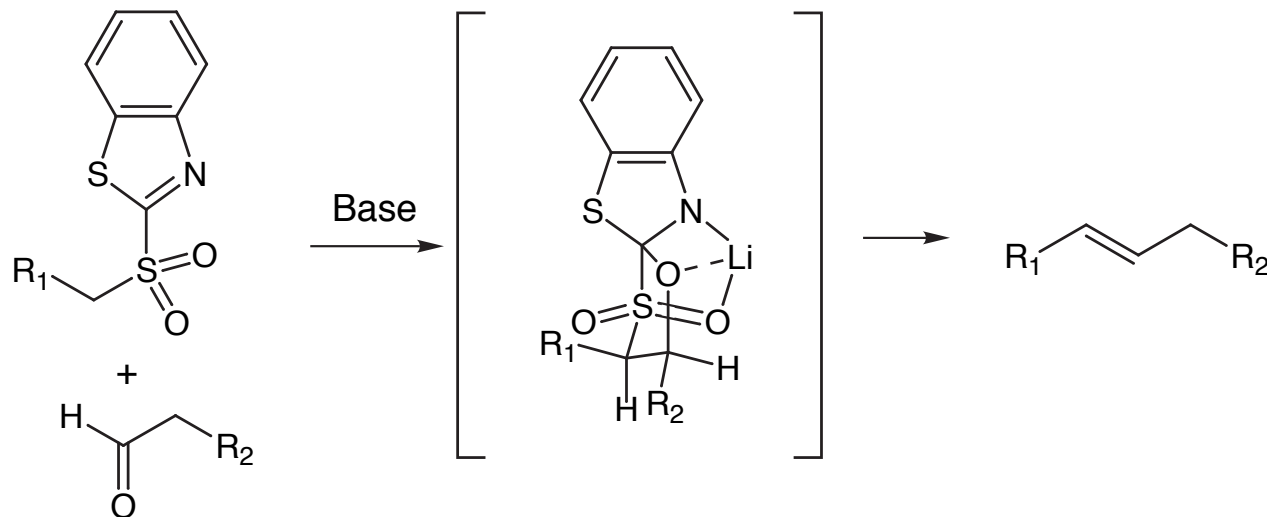
Handout 29A

Overview of the Julia–Kocienski Olefination

Evans Group Seminar

by

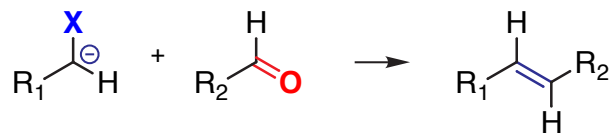
Scott Peterson, September 26, 2003



D. A. Evans

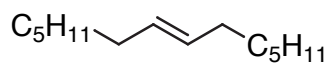
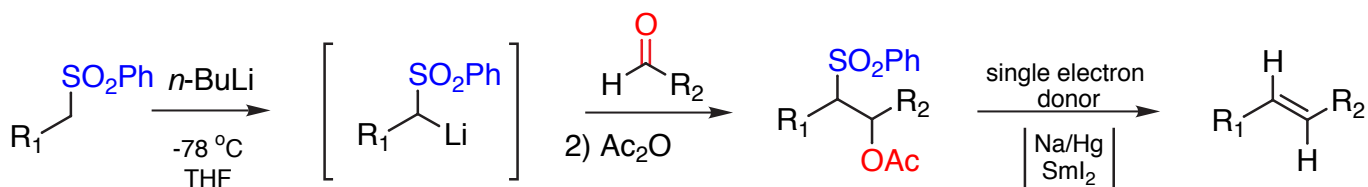
Friday,
November 21, 2003

Examples of Direct Olefination from Carbonyl Compounds

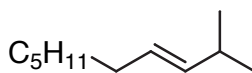


	X	Reaction
B.E Maryanoff, A.B. Reitz, <i>Chem. Rev.</i> , 1989, 89 , 863	R ₃ P ⁺	Wittig
	R ₂ P(=O)	Horner-Wittig
	(RO) ₂ P(=O)	Horner-Wadsworth-Emmons
L.F. van Staden, D Gravstock, D.J. Ager, <i>Chem. Soc. Rev.</i> , 2002, 31 , 195	R ₃ Si	Peterson
	ArS(=O)(=NMe)	Johnson
P.R. Blakemore, <i>J. Chem. Soc.</i> , <i>Perkin Trans. 1</i> , 2002, 2563	ArSO ₂	classical Julia
	HetSO ₂	modified Julia

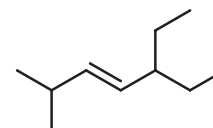
Classical Julia Olefination



E:Z = 80:20

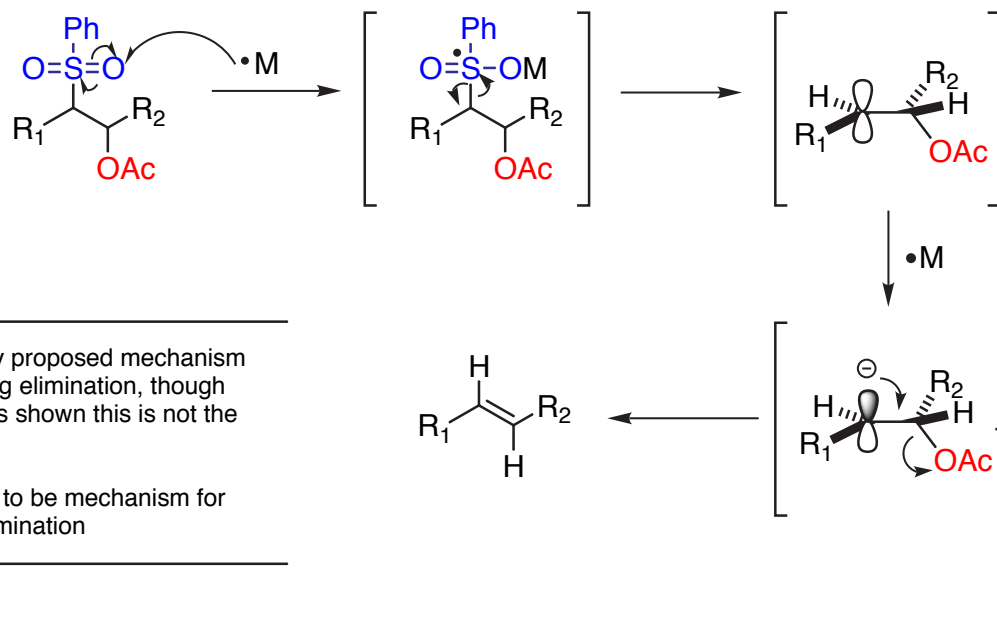


E:Z = 90:10



E:Z = >99:1

Mechanism of Olefin Formation

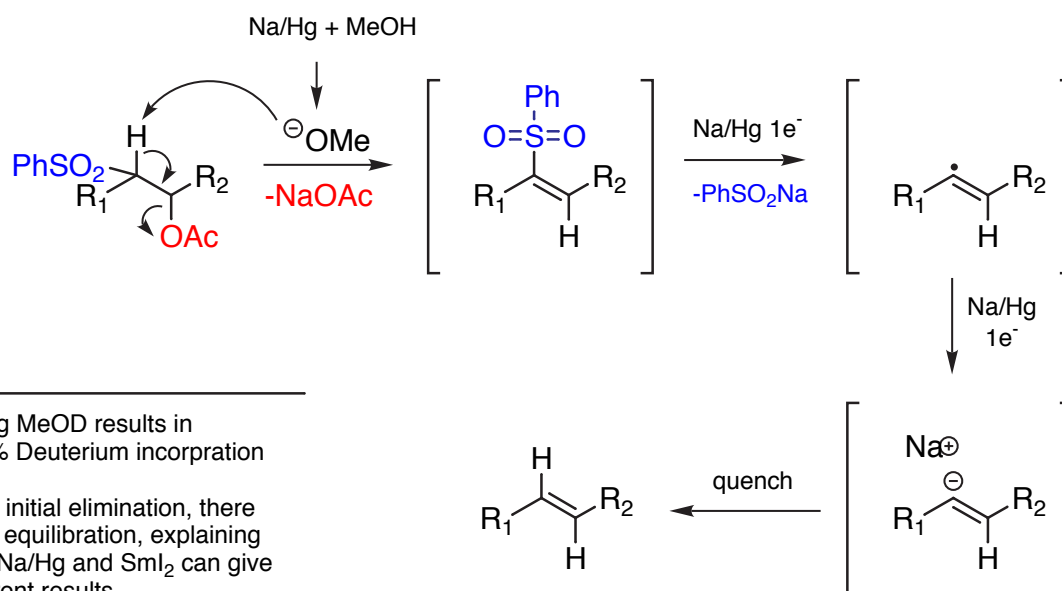


-Originally proposed mechanism for Na/Hg elimination, though Keck has shown this is not the case

-Believed to be mechanism for SmI_2 elimination

G.E. Keck et al., *J. Org. Chem.*, 1995, **60**, 3194

Mechanism of Olefin Formation

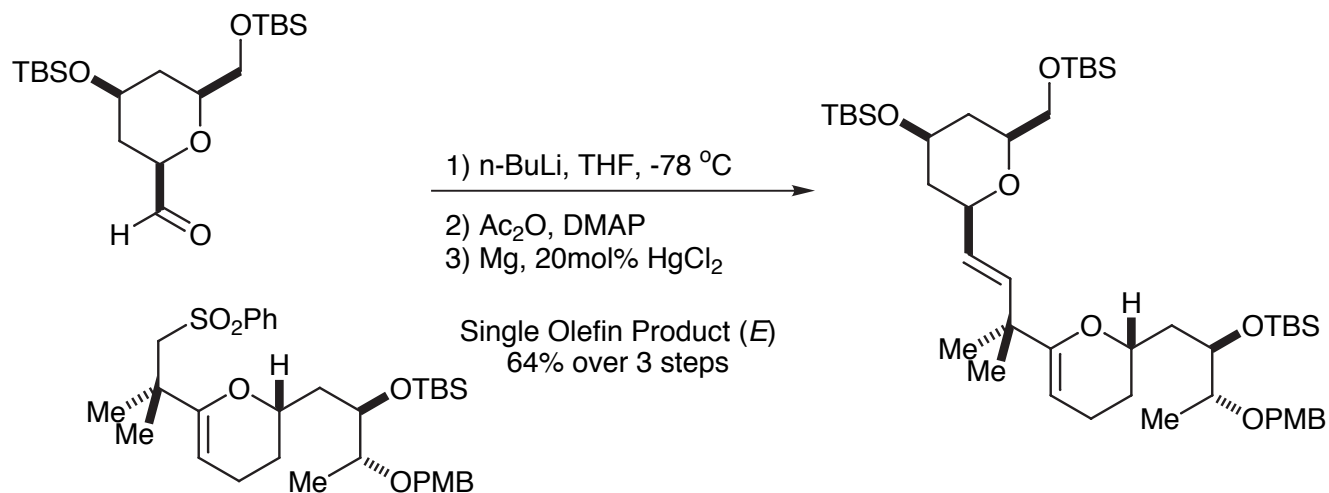


-Using MeOD results in >90% Deuterium incorporation

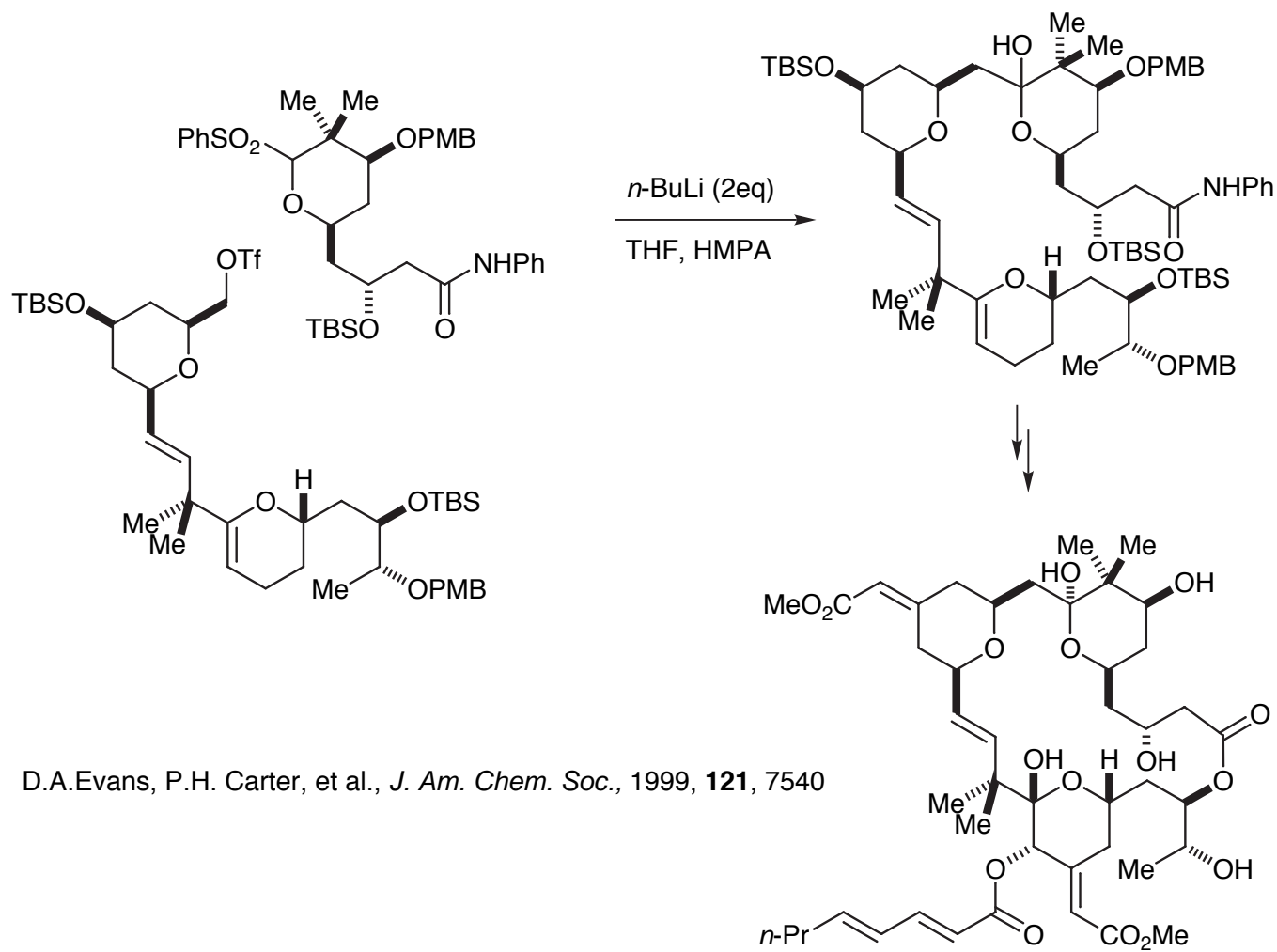
-After initial elimination, there is no equilibration, explaining why Na/Hg and SmI_2 can give different results

G.E. Keck et al., *J. Org. Chem.*, 1995, **60**, 3194

Synthesis of Bryostatin 2

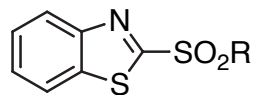


D.A.Evans, P.H. Carter, et al., *J. Am. Chem. Soc.*, 1999, **121**, 7540

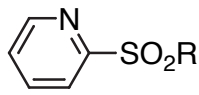


D.A.Evans, P.H. Carter, et al., *J. Am. Chem. Soc.*, 1999, **121**, 7540

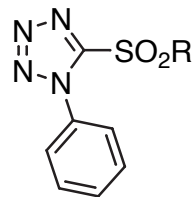
Modified Julia Olefination



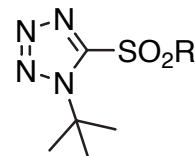
BT



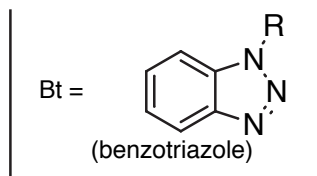
PYR



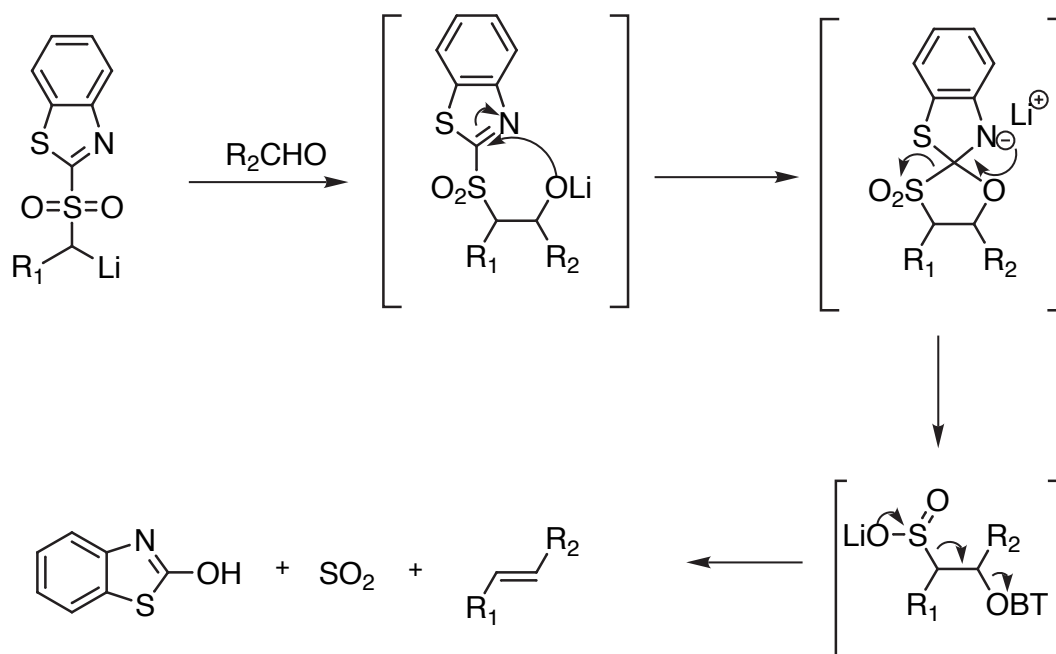
PT



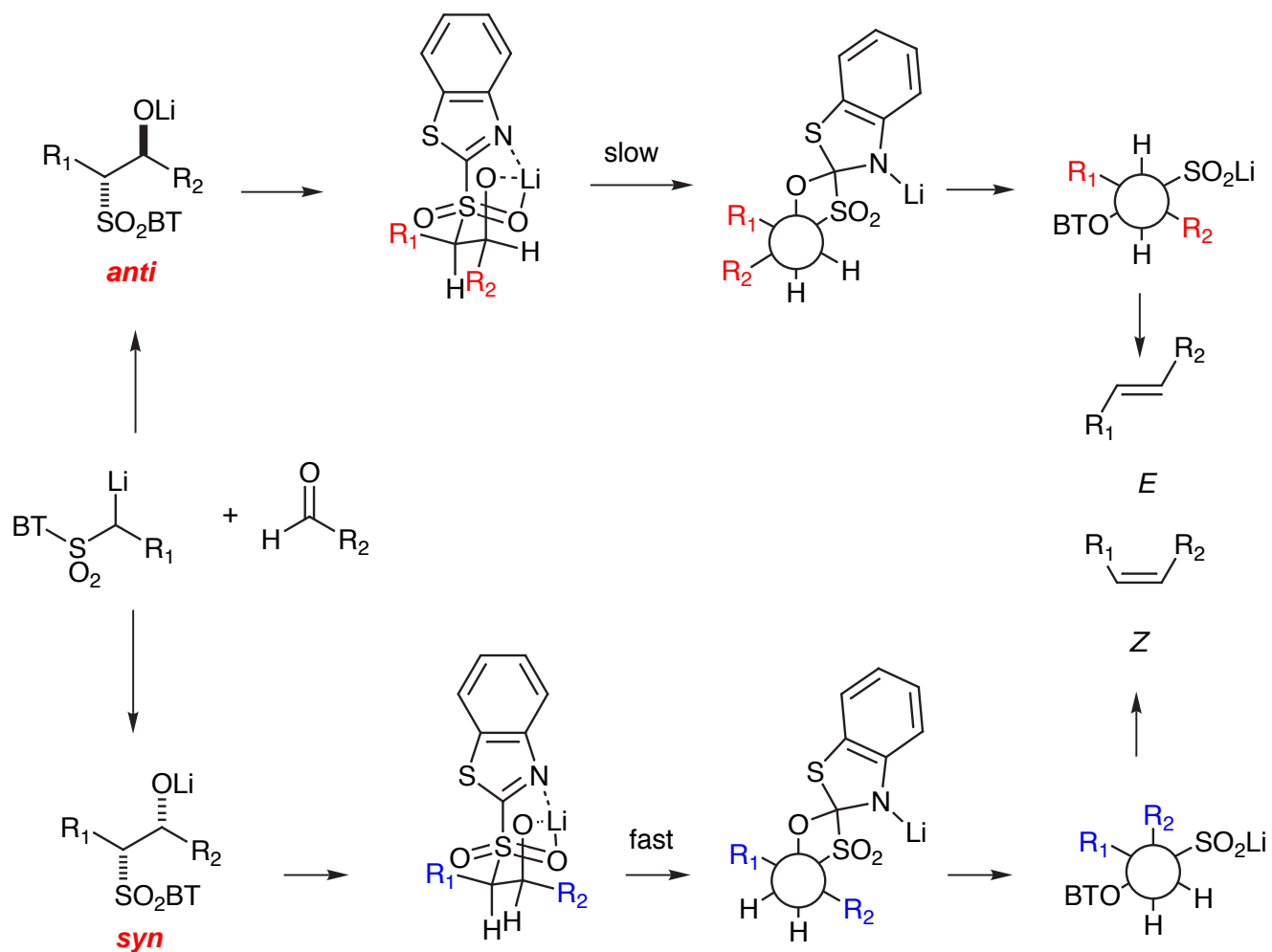
TBT



Modified Julia Olefination - Smiles Rearrangement

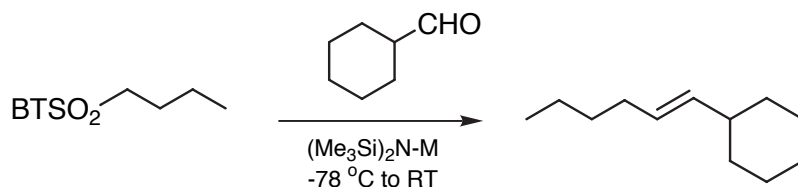


Diastereoselectivity of BT-Sulfones



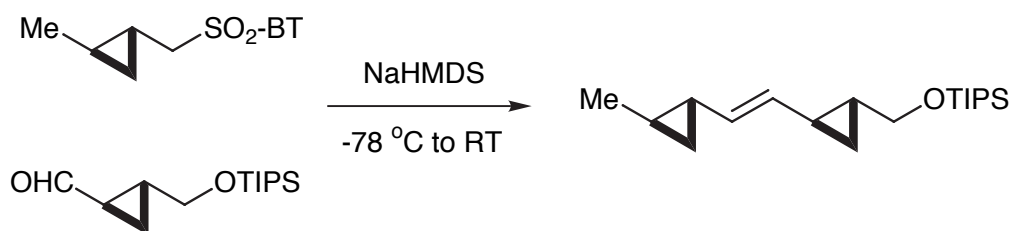
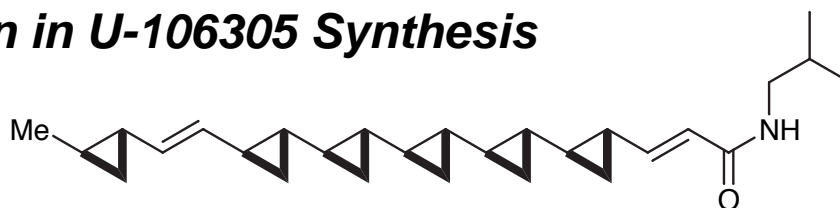
J.B. Baudin, *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

Effects of Solvent and Counterion with BT-Sulfone

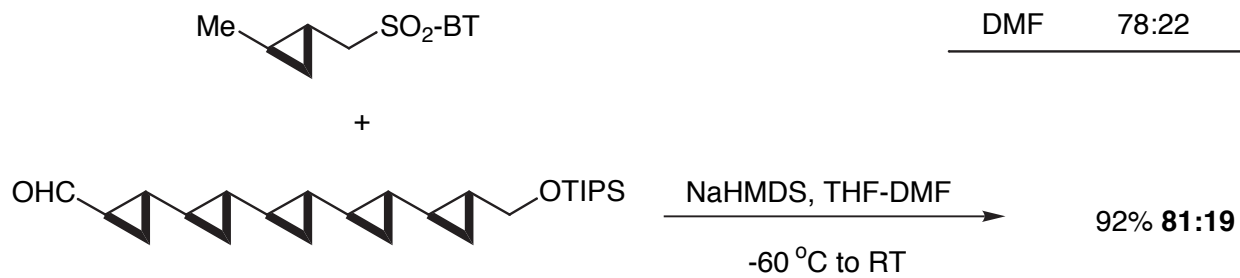


M	Toluene	Et ₂ O	THF	DME
Li	50:50	49:51	66:34	70:30
Na	54:46	50:50	62:38	75:25
K	54:46	51:49	54:46	76:24

Solvent Screen in U-106305 Synthesis

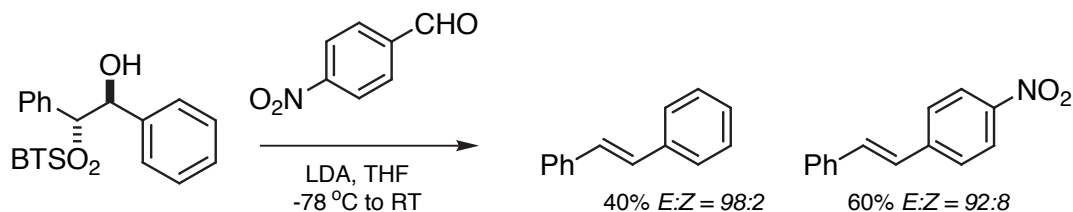
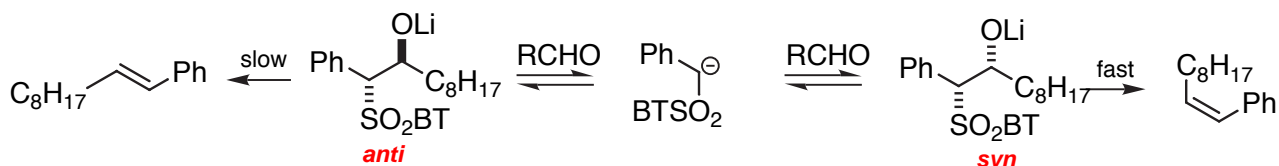
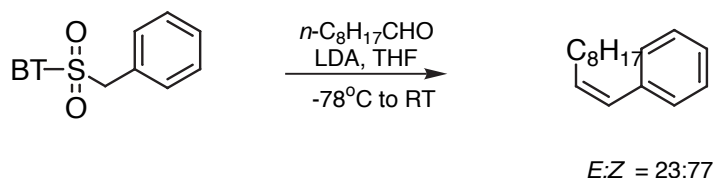


solvent	<i>E:Z</i>
toluene	9:91
CH ₂ Cl ₂	9:91
Et ₂ O	11:89
THF	52:48
DME	71:29
DMF	78:22



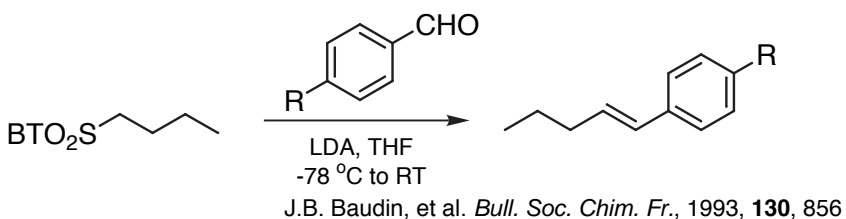
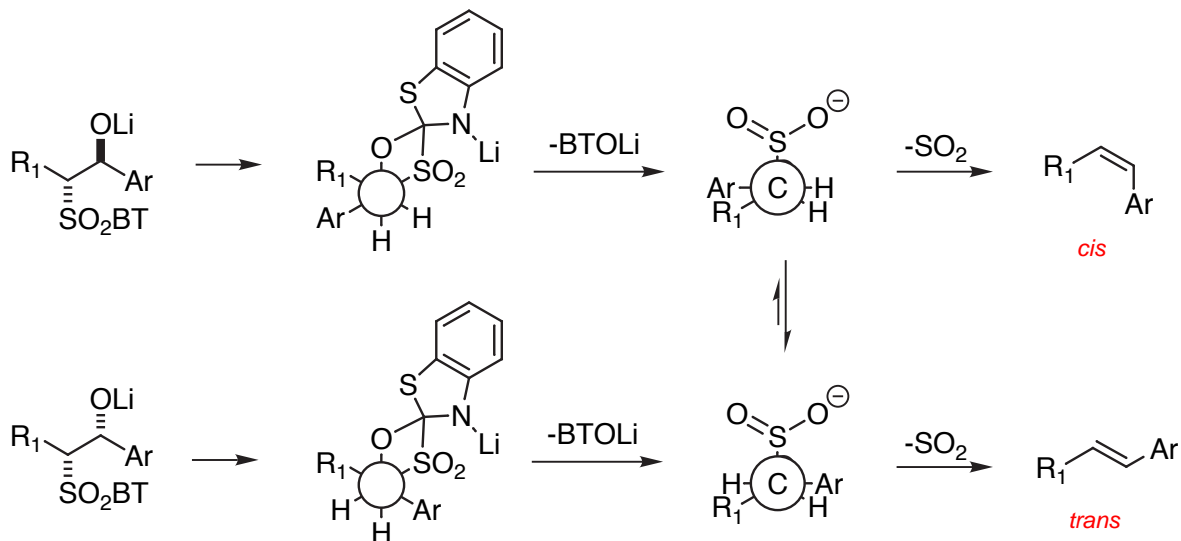
A.B. Charette, et al., *J. Am. Chem. Soc.*, 1996, **118**, 10327

Retroaddition - Addition with BT-Sulfone



P.R. Blakemore, Ph.D. Thesis, University of Glasgow, Glasgow, 1999

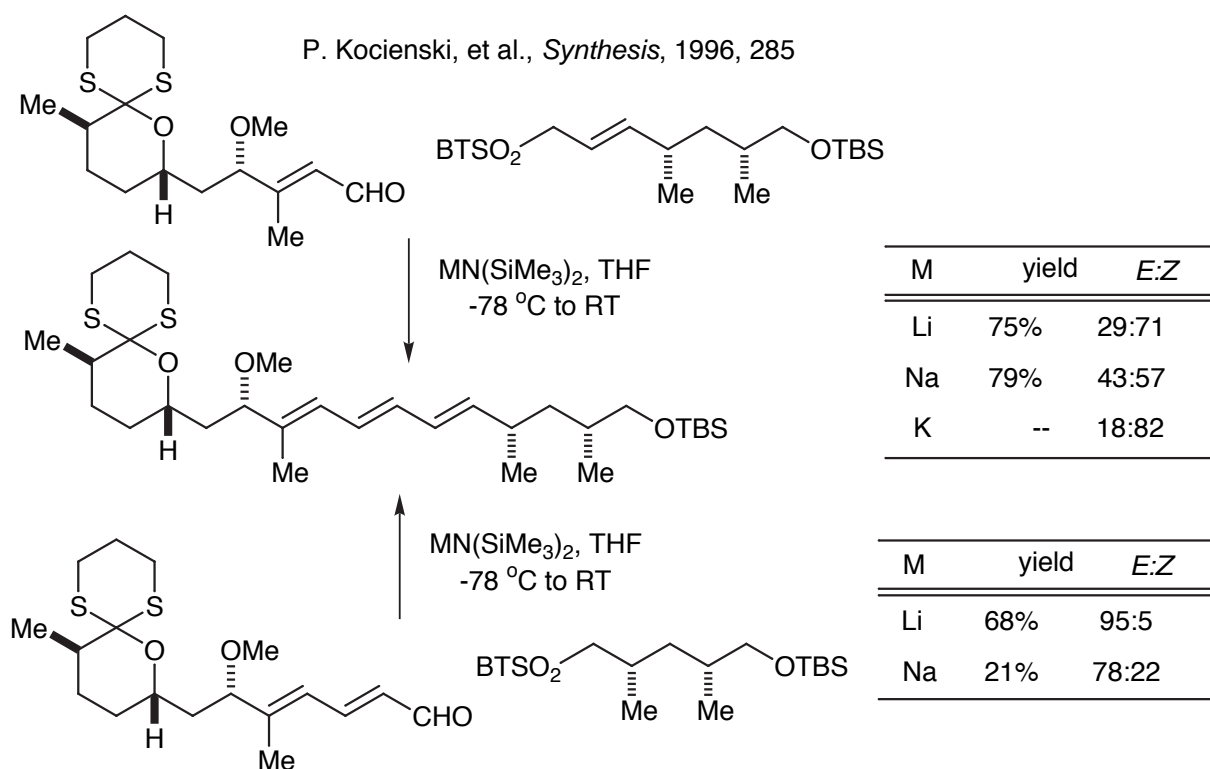
Aromatic Aldehydes with BT-Sulfones



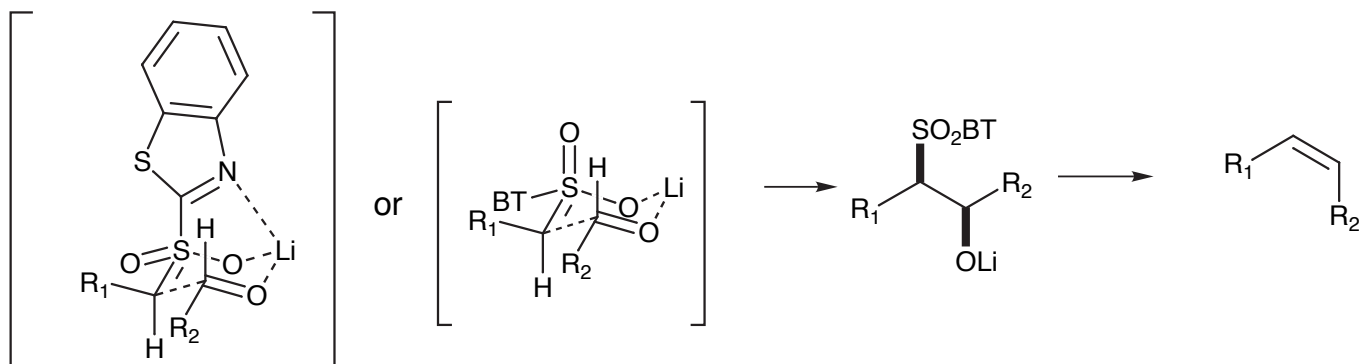
R	yield	E:Z
OMe	95%	99:1
H	68%	94:6
Cl	51%	77:23

Reversibility in Rapamycin Synthesis

P. Kocienski, et al., *Synthesis*, 1996, 285

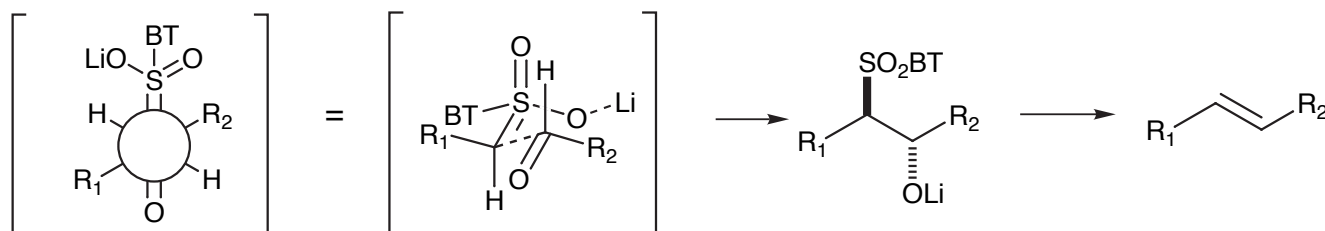


Possible Explanation for Diastereoselectivity



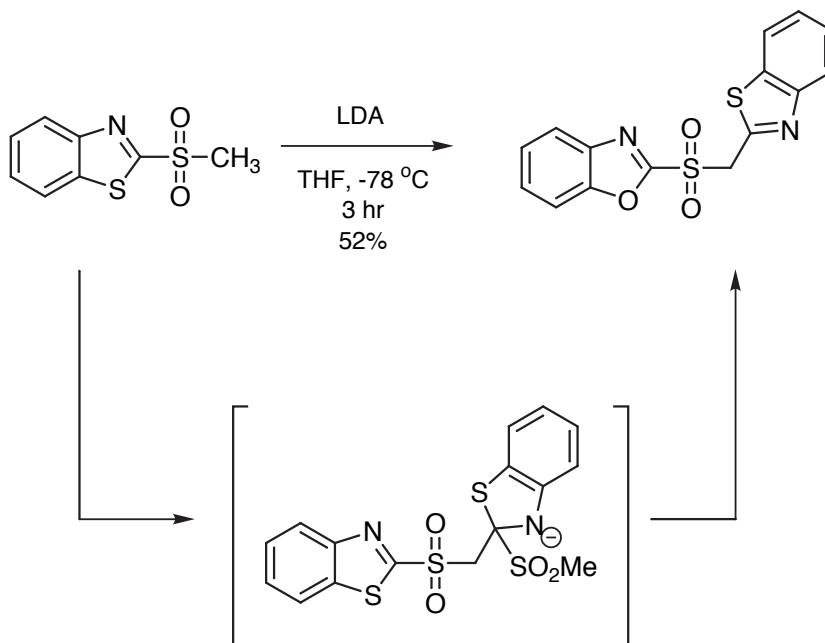
Chelate (closed) Transition State favored for **non-polar solvents**, **small counter-ions** (Li)

Non-chelate (opened) Transition State favored for **polar solvents**, **large counter-ions** (K)



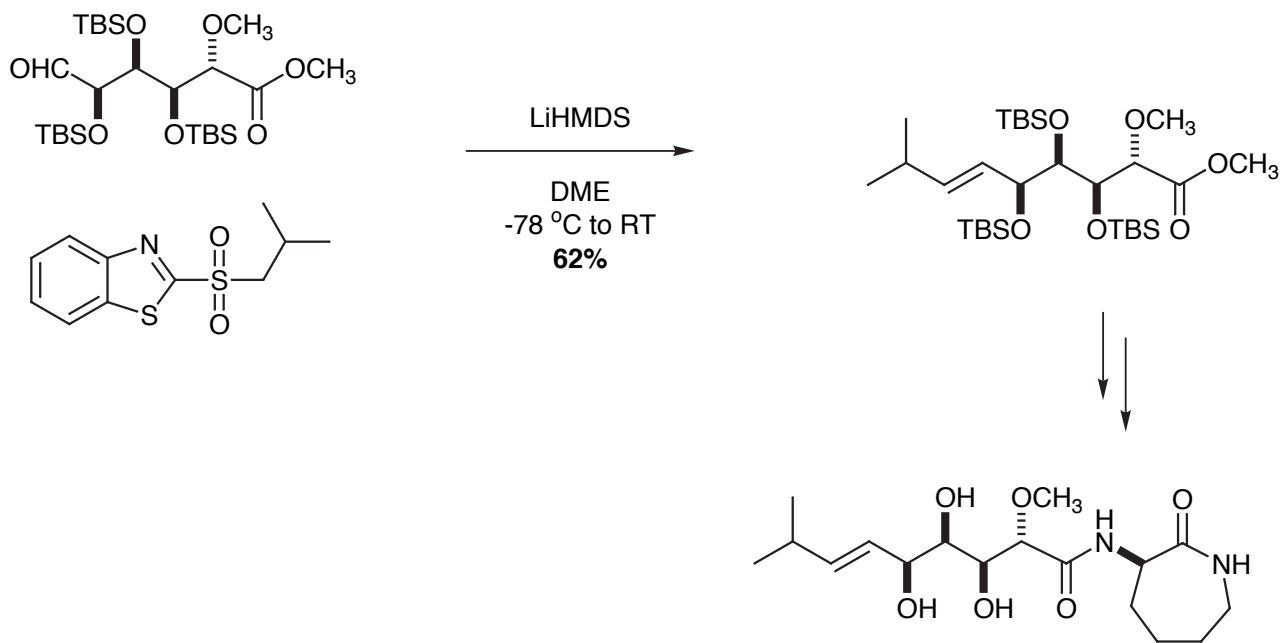
S. Peterson, *Meandering Thoughts*, 2003

Ipsso Substitution with BT-Sulfones



J.B.Baudin, et al., *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

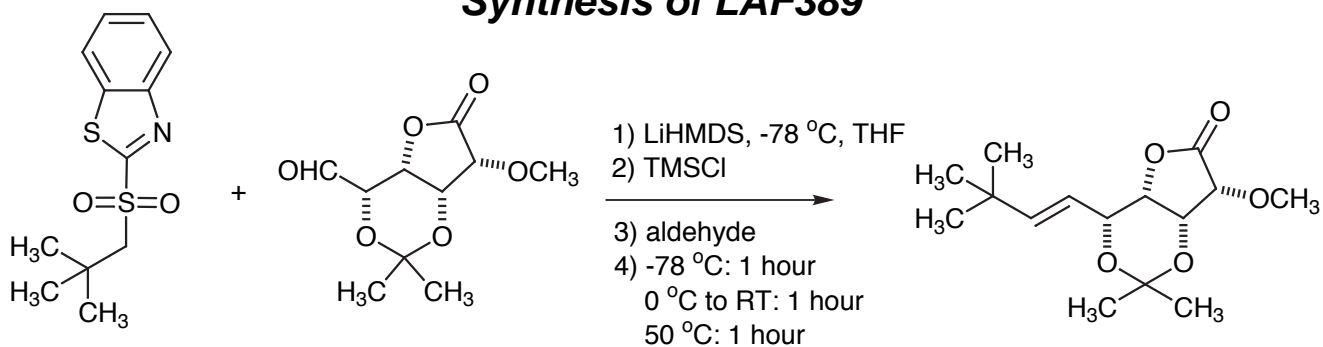
Synthesis of ent-Bengamide E



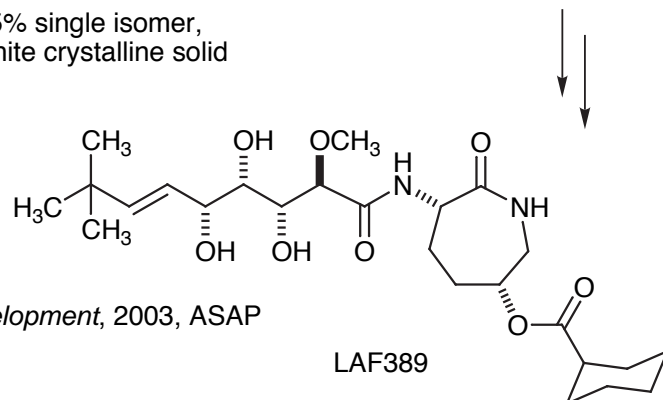
K.J.McRae, PhD Thesis, Research School of Chemistry, Canberra, 2001
J.B.Baudin, et al., *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

ent-Bengamide E

Synthesis of LAF389

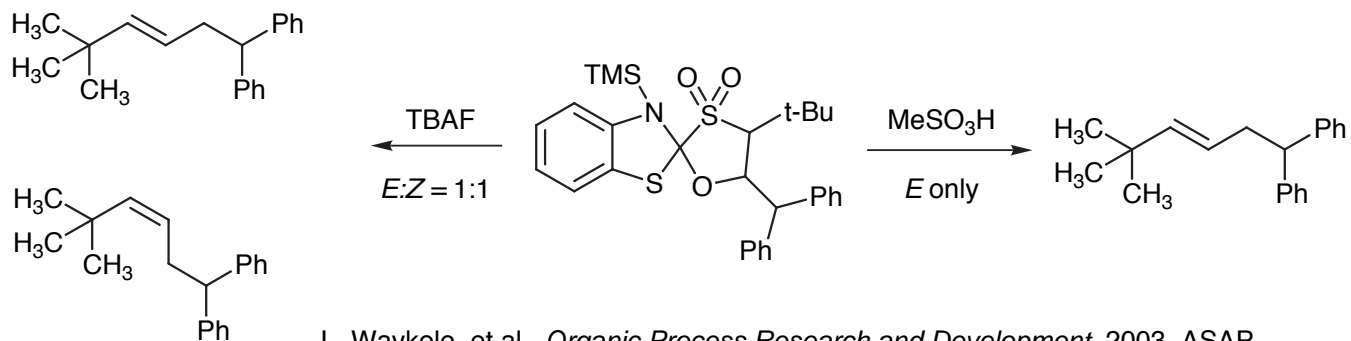
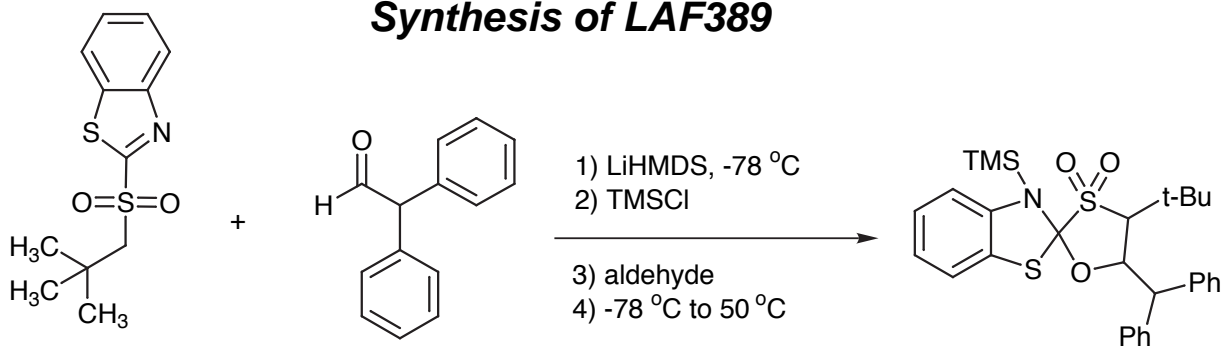


45% single isomer,
white crystalline solid



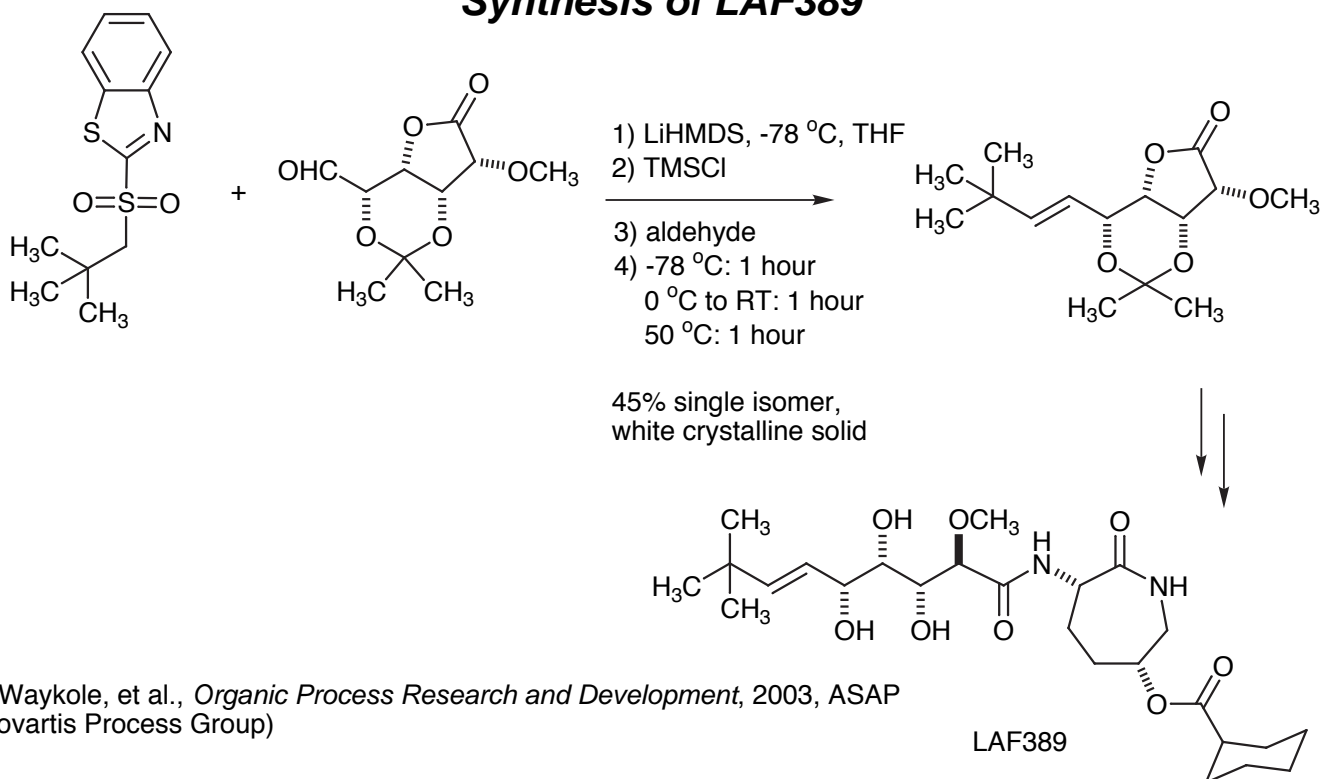
L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

Synthesis of LAF389

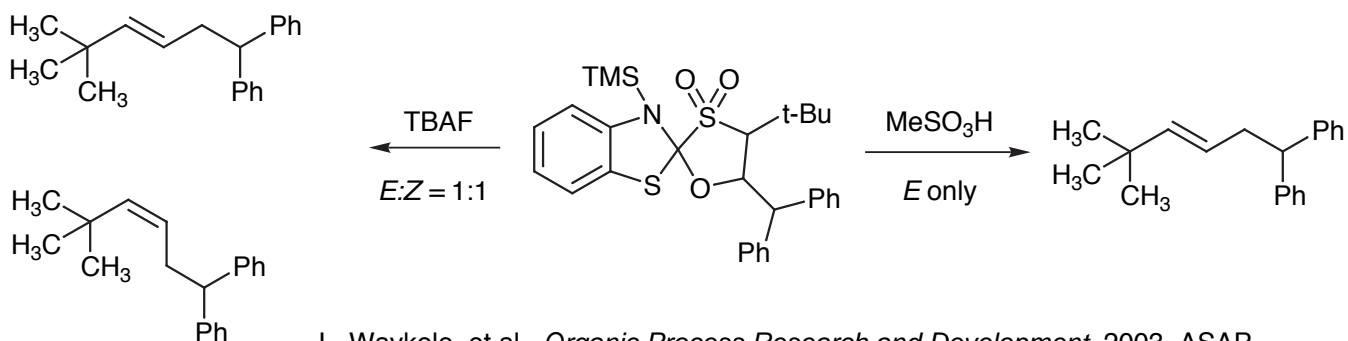
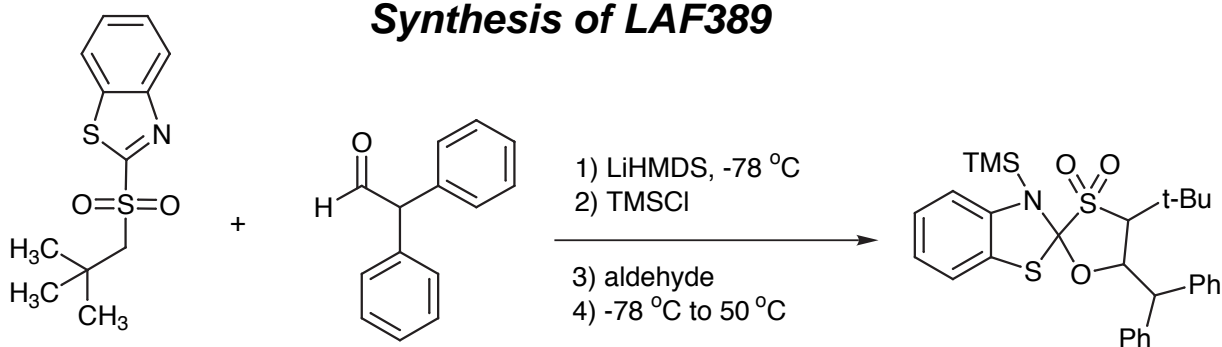


L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

Synthesis of LAF389

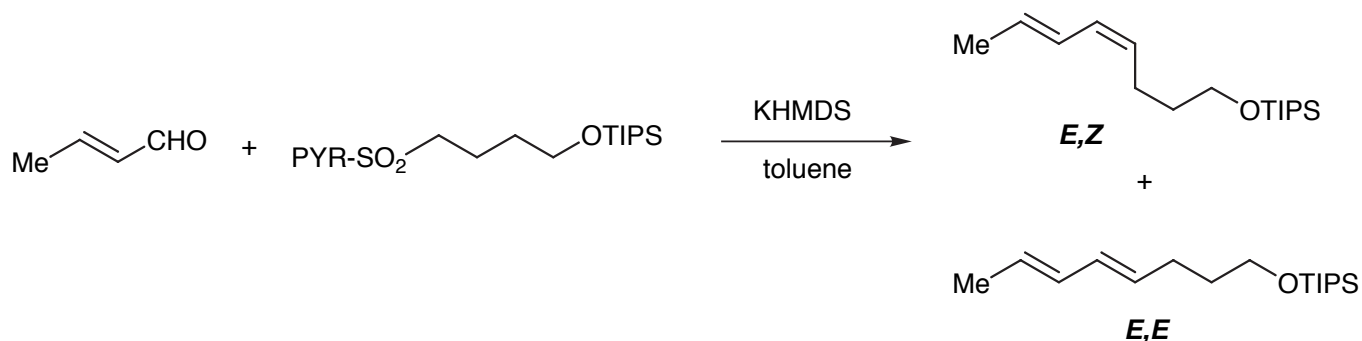


Synthesis of LAF389



L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

Pyridinyl (PYR) Sulfones Examples

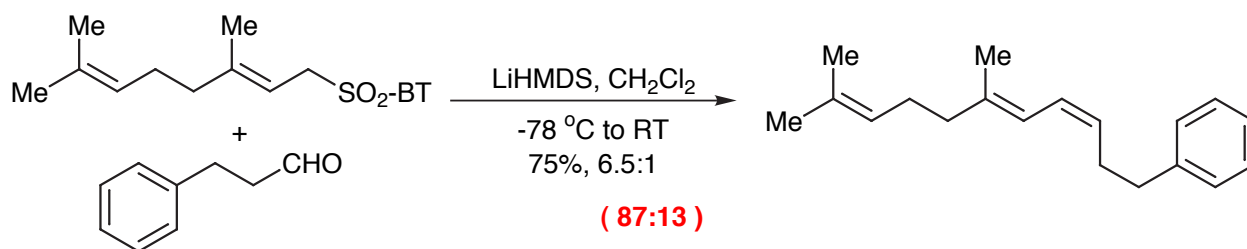
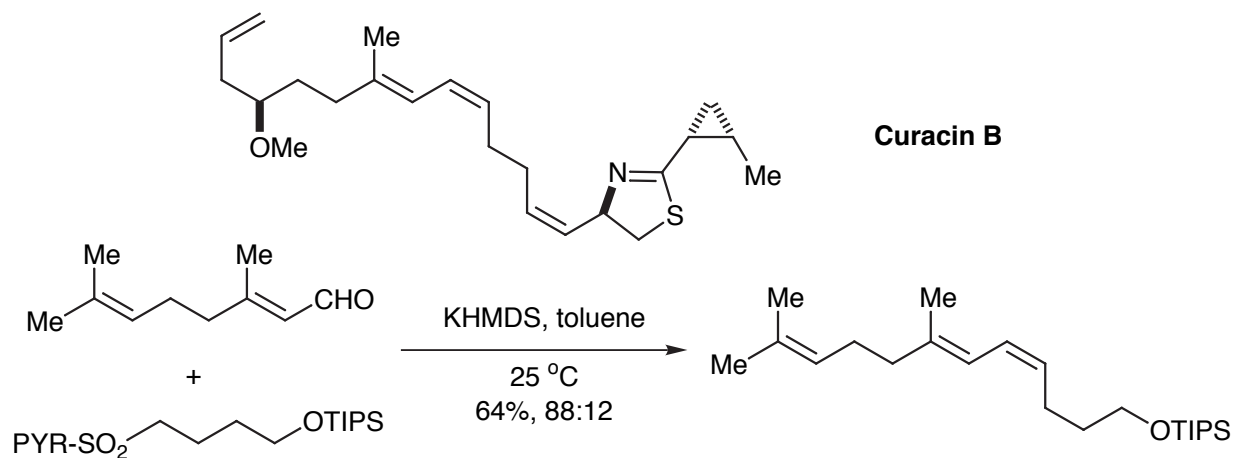


temp	yield	Ratio <i>E,Z</i> : <i>E,E</i>
-78 °C	35%	84:16
0 °C	53%	90:10
25 °C	67%	91:9

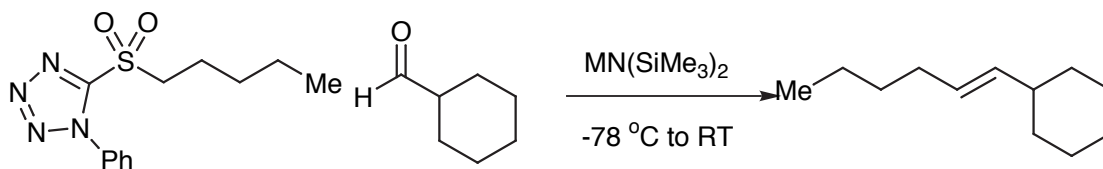
← Potassium metallate is stable at RT for 5 min!

A. B. Charette, et al., *Tet Lett*, 2001, **42**, 5149

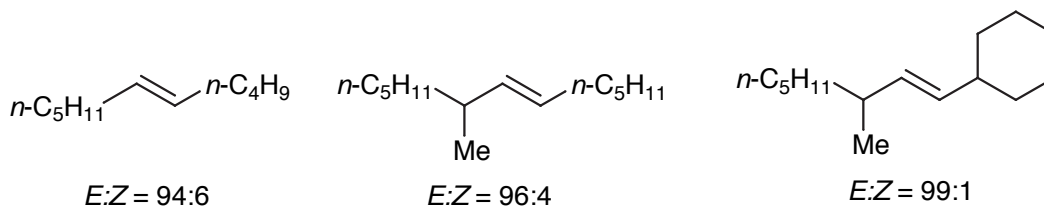
Pyridinyl (PYR) Sulfones Examples



1-Phenyl-1H-tetrazol-5-yl Sulfones



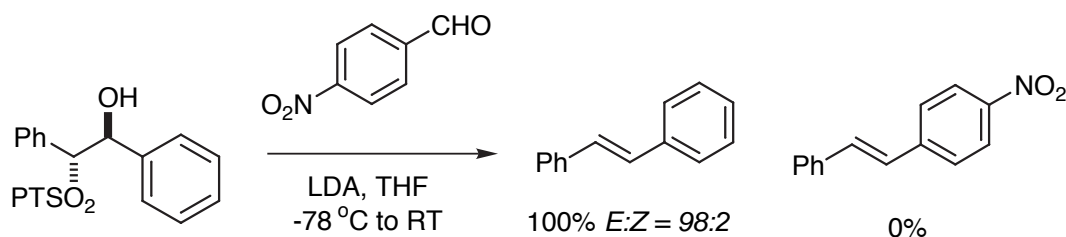
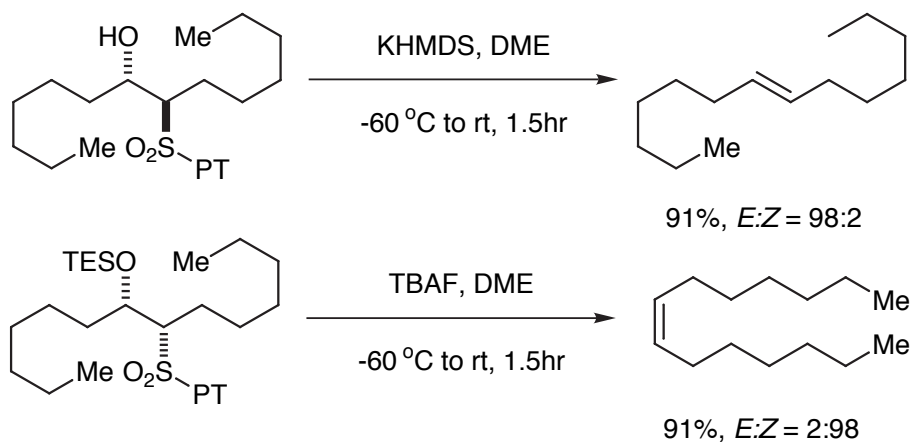
M	toluene	Et ₂ O	THF	DME
Li	51:49	61:39	69:31	72:28
Na	65:35	65:35	73:27	89:11
K	77:23	89:11	97:3	99:1



1.5eq aldehyde, KHMDS, DME -78 °C to RT

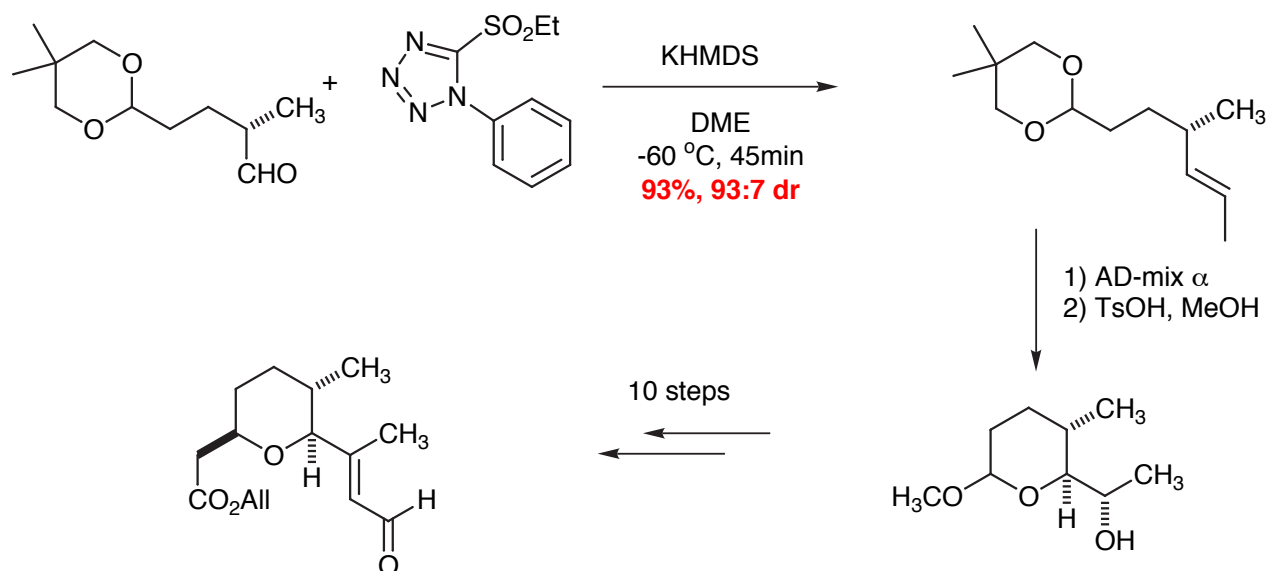
P.J. Kocienski, et al., *Synlett*, 1998, 26

Kinetically Controlled Diastereoselectivity - Irreversible

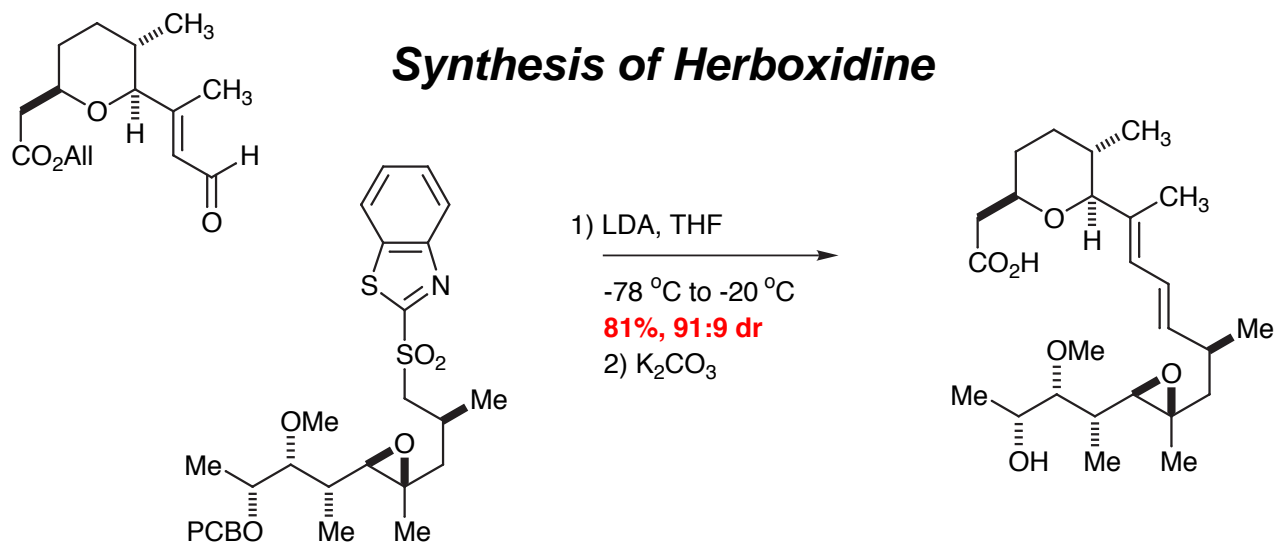


P.R. Blakemore, Ph.D. Thesis, University of Glasgow, Glasgow, 1999

Synthesis of Herboxidine

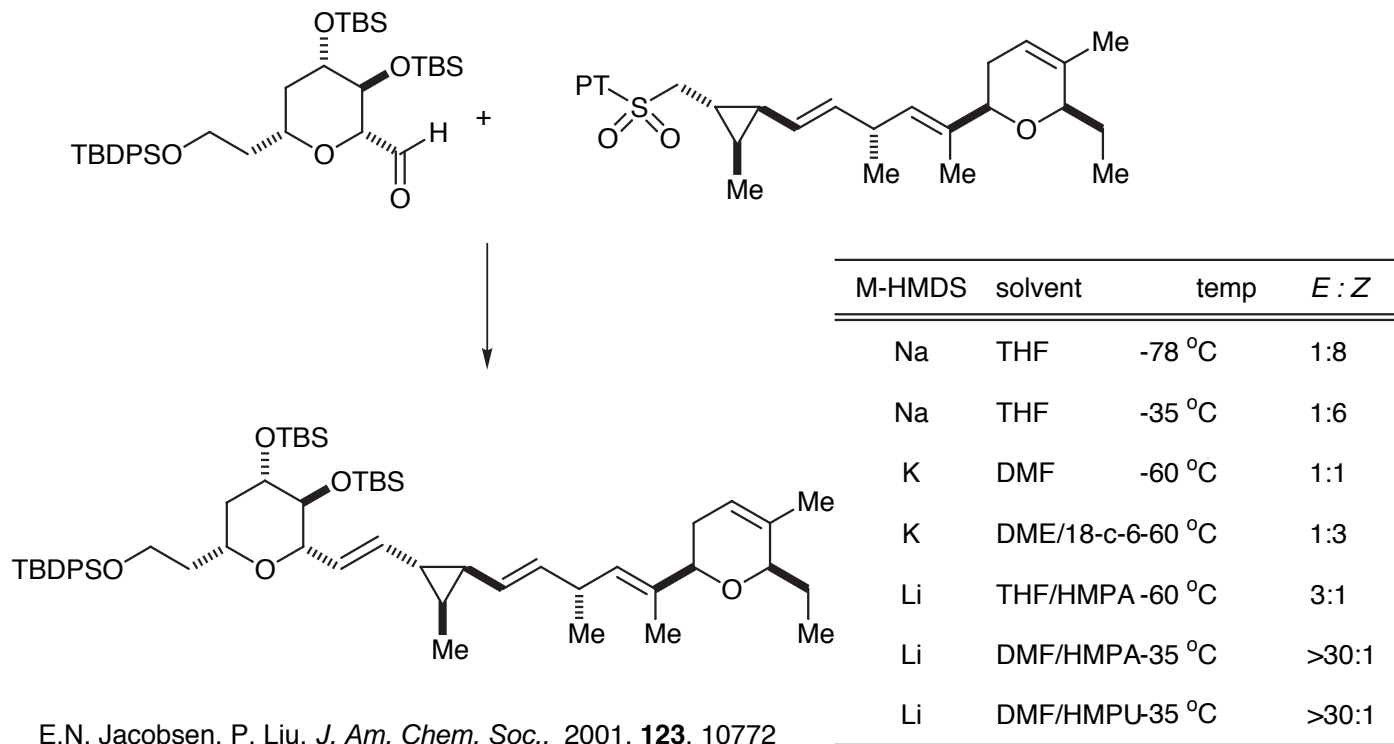


P.J.Kocienski, et al., *J. Chem. Soc., Perkin Trans. 1*, 1999, 955

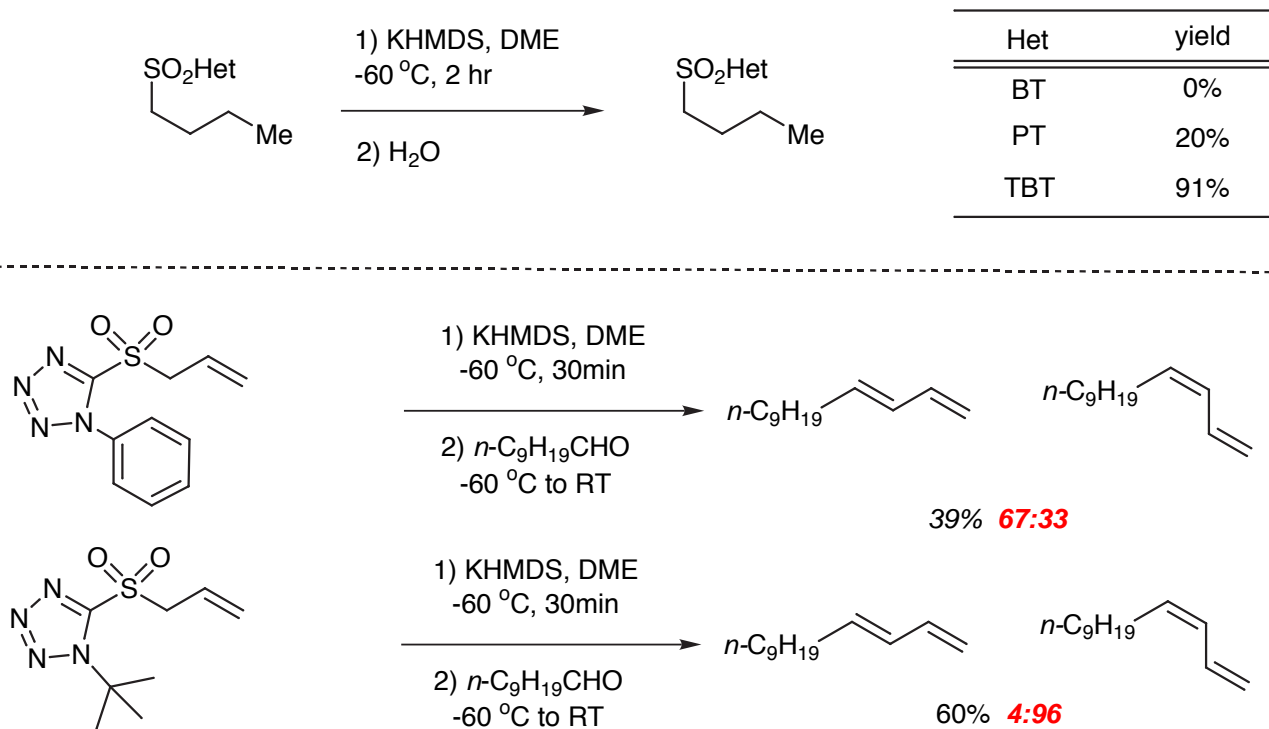


P.J.Kocienski, et al., *J. Chem. Soc., Perkin Trans. 1*, 1999, 955

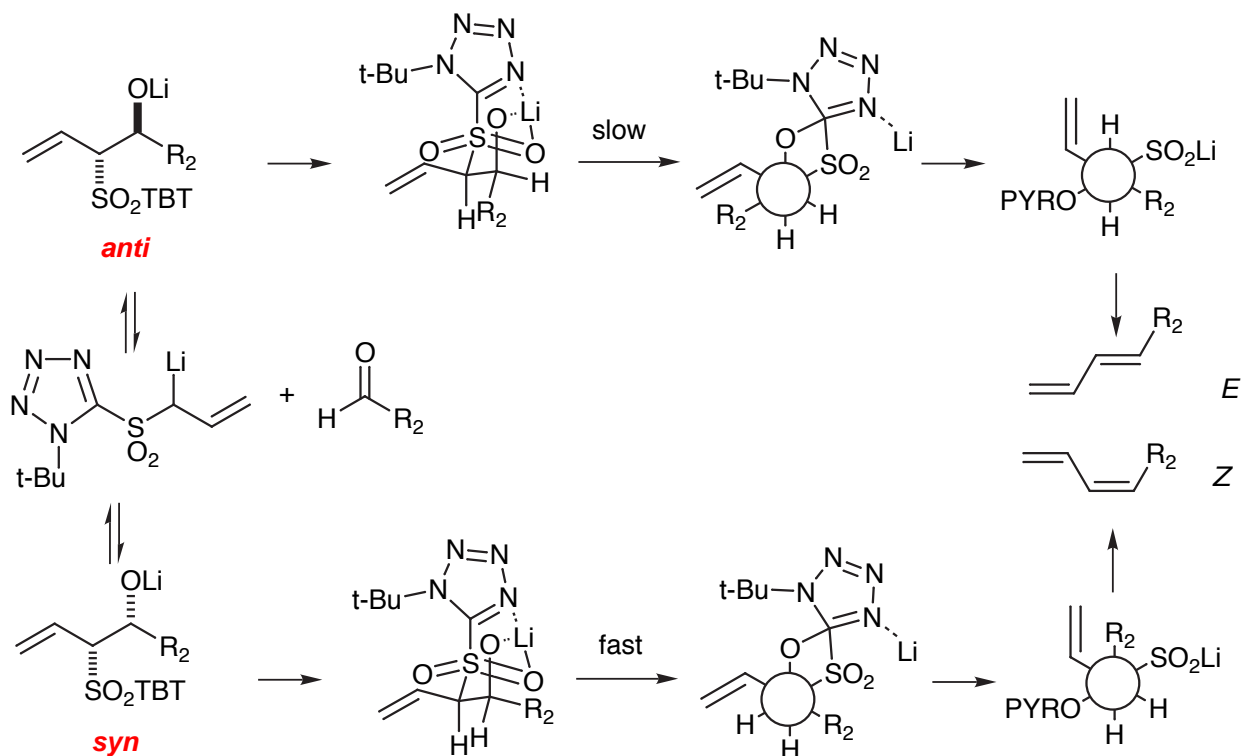
Synthesis of (+)-Ambruticin



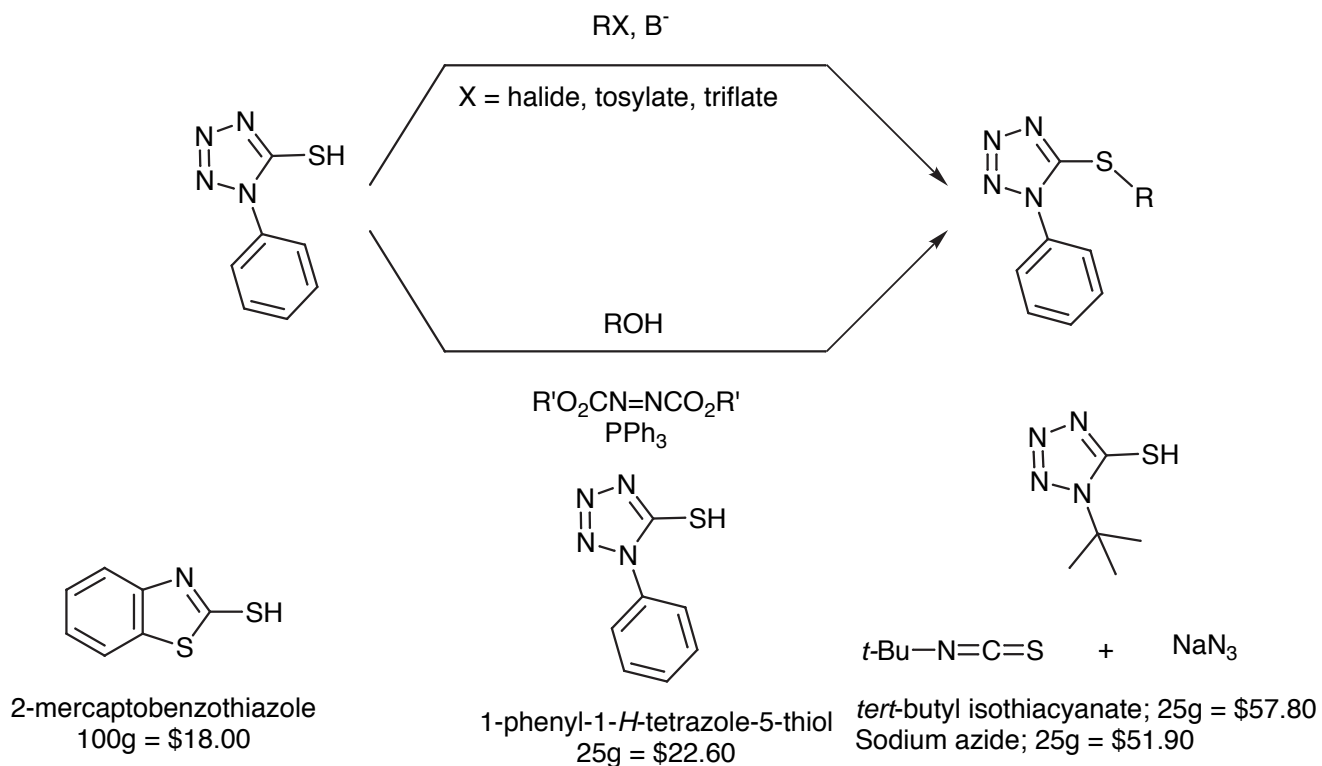
tert-Butyl-1H-tetrazol-5-yl Sulfones



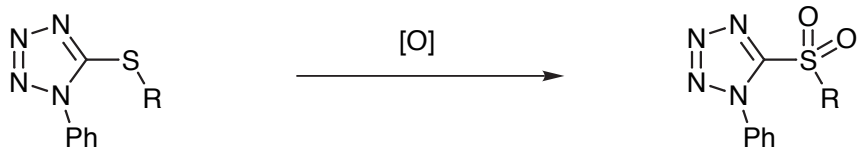
Diastereoselectivity of TBT-Sulfones



Sulfone Synthesis



Sulfone Synthesis



MCPBA

$(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O} / \text{H}_2\text{O}_2$ Mo(VI)

$\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O} / \text{H}_2\text{O}_2$ W(VI)

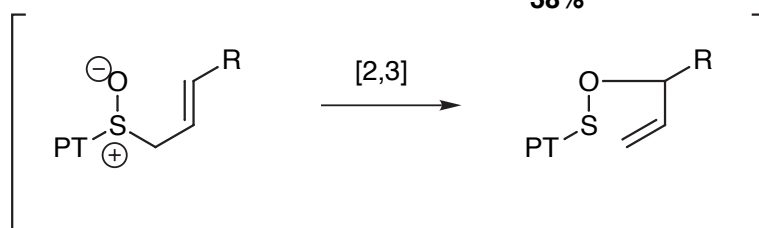
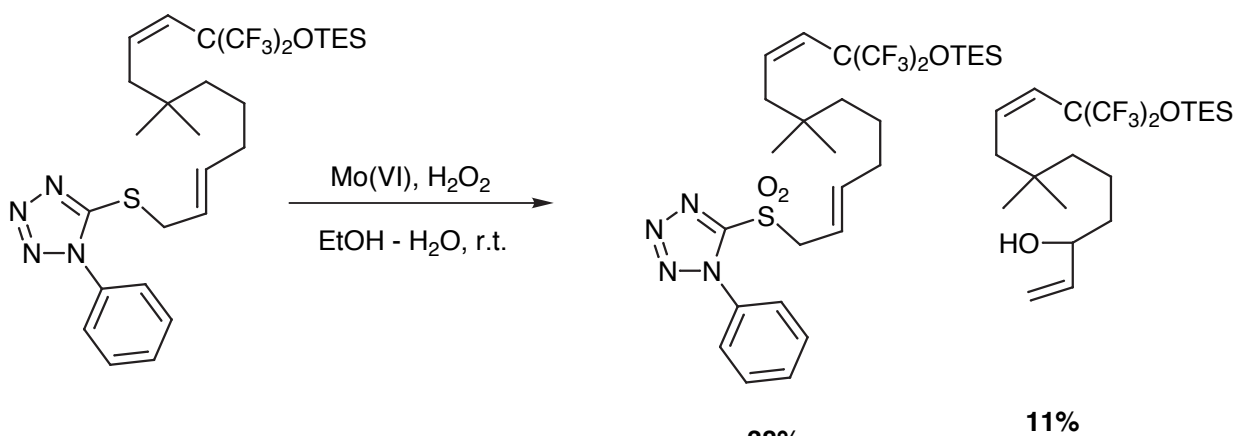
Oxone

$\text{CH}_3\text{CO}_3\text{H}$

KMnO_4

P.R. Blakemore, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2563

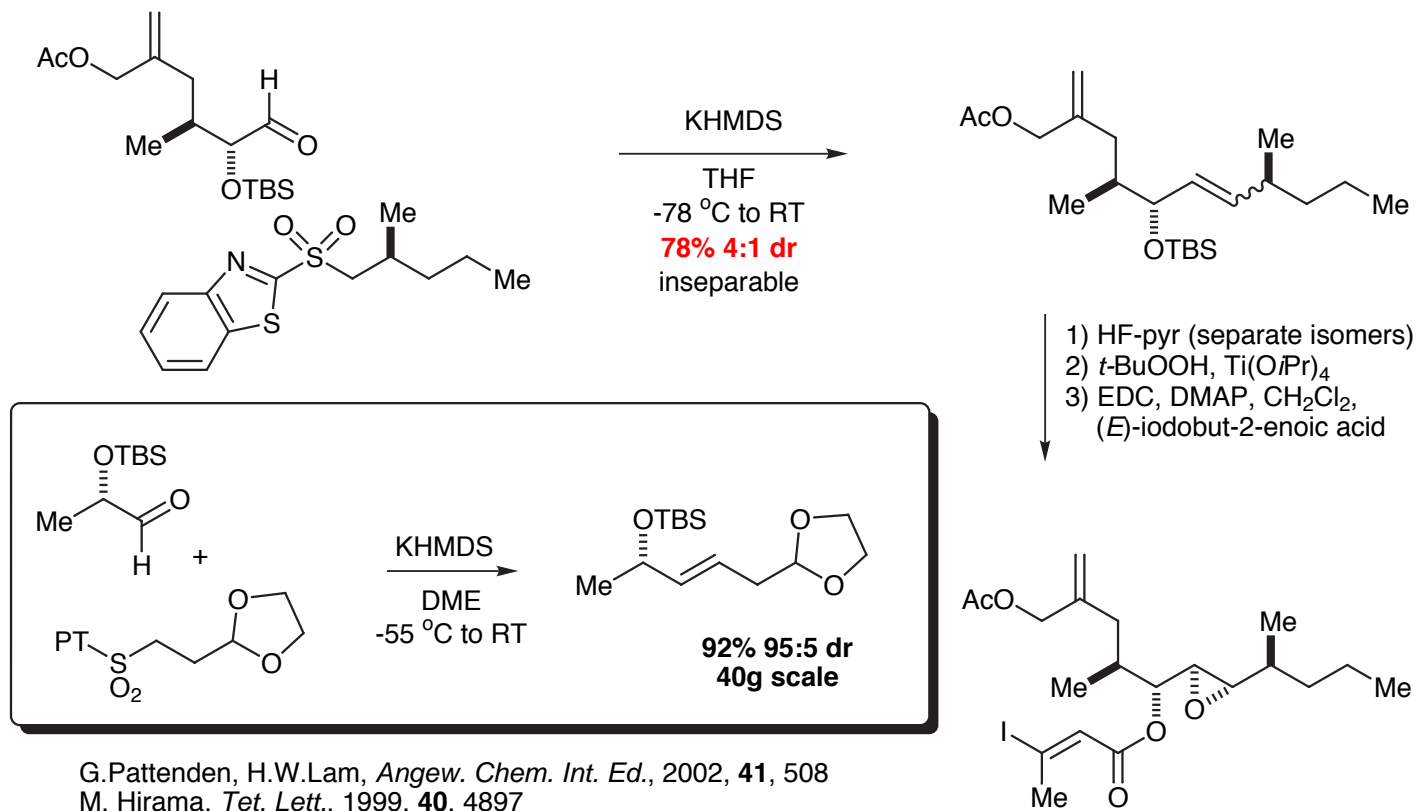
Oxidation Problems - Allylic Sulfones



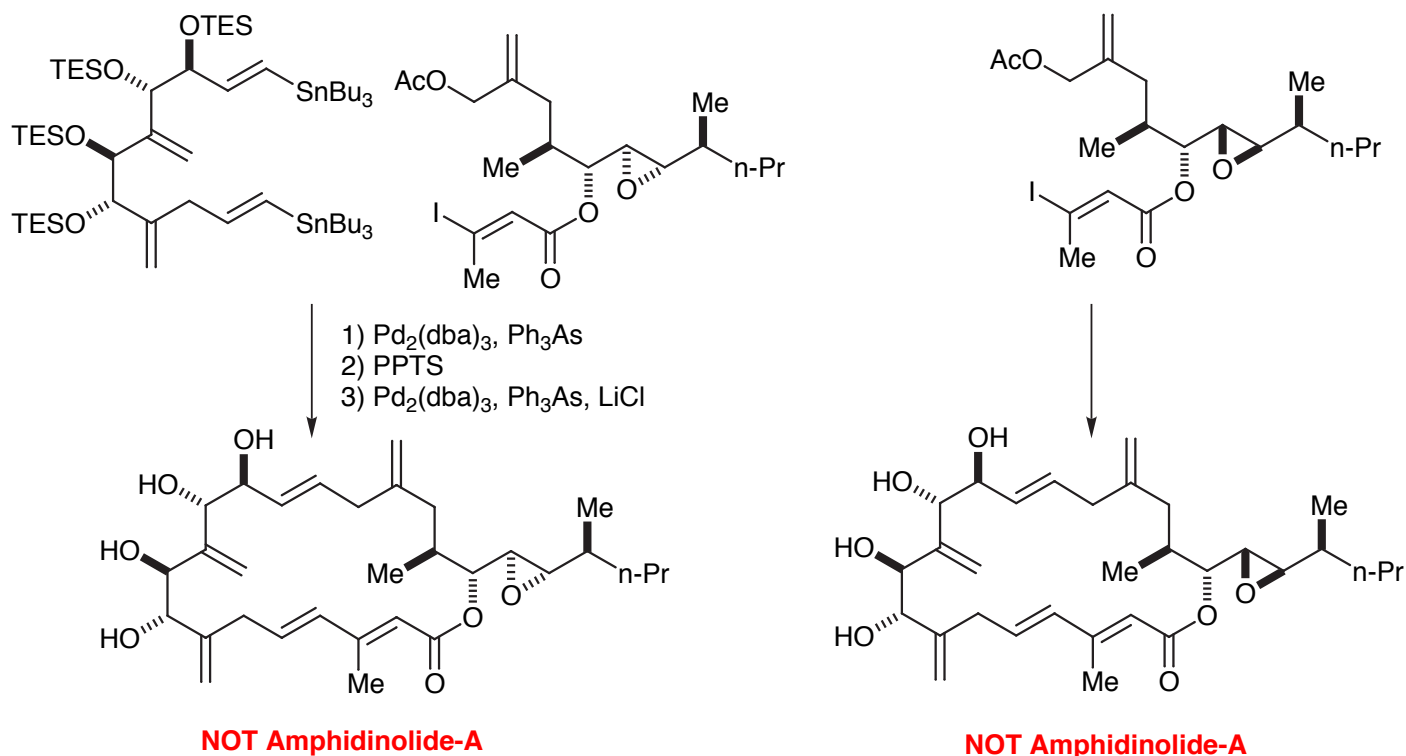
H. Hilpert, B. Wirz, *Tetrahedron*, 2001, **57**, 681

D.A. Evans, G.C. Andrews, *Acc. Chem. Res.*, 1974, **7**, 147

Synthesis of the Proposed Structure of Amphidinolide-A

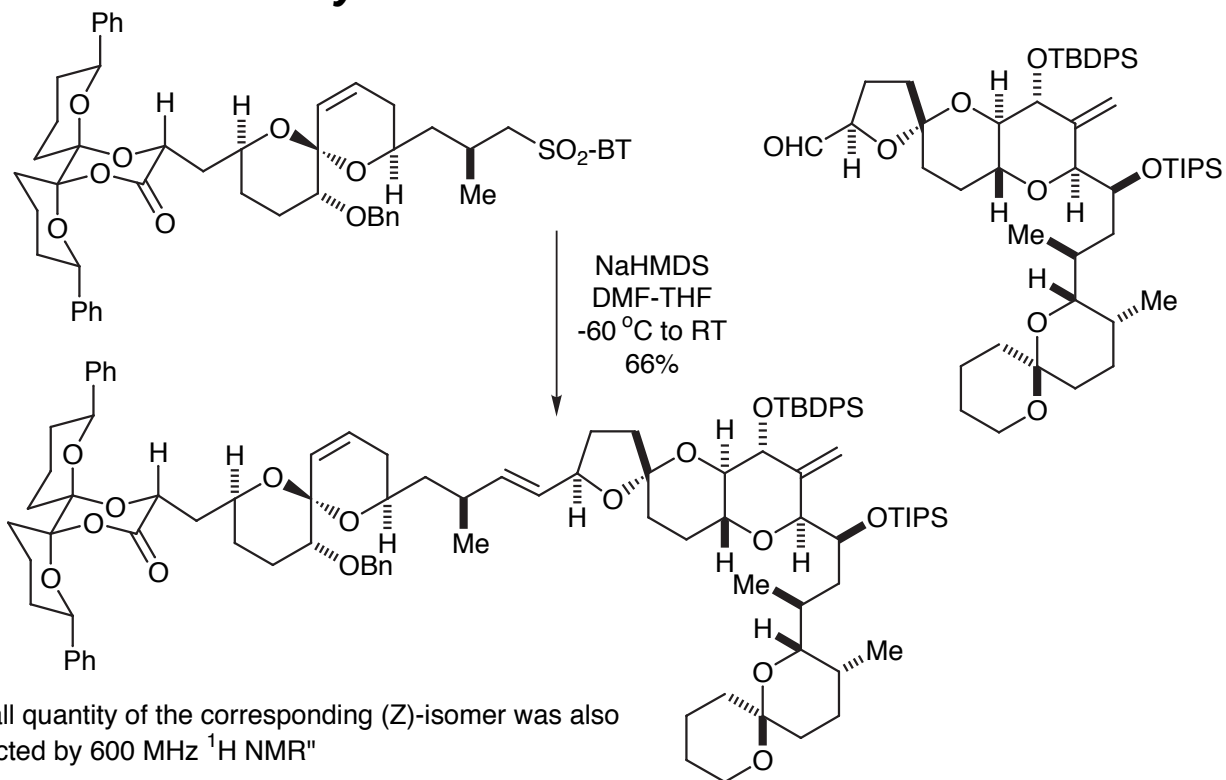


Synthesis of Proposed Structure of Amphidinolide-A



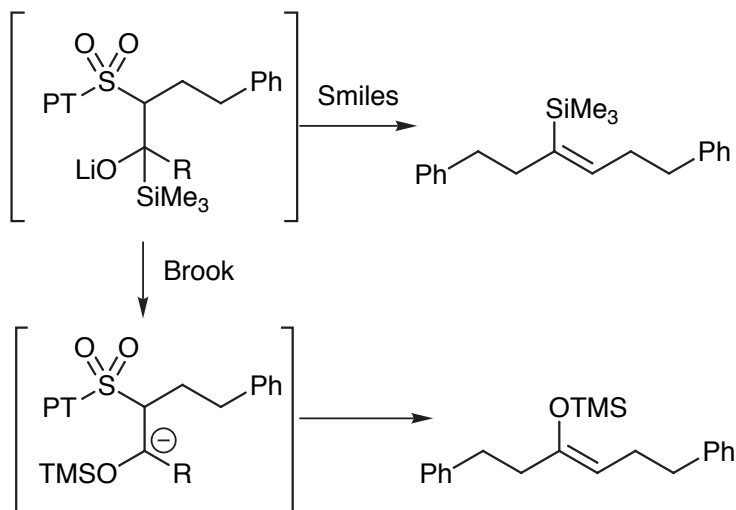
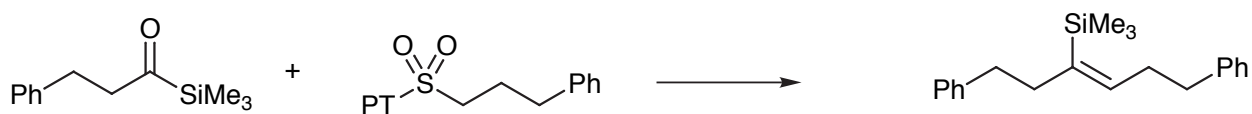
G.Pattenden, H.W.Lam, *Angew. Chem. Int. Ed.*, 2002, **41**, 508

Synthesis of Okadaic Acid



S.V. Ley, et al., *J. Chem. Soc., Perkin Trans. 1*, 1998, 3907

Synthesis of Vinylsilanes



M-HMDS	temp	yield	E : Z
Li	-78 °C	93%	64:36
Li	-85 °C	89%	74:26
Li	-95 °C	84%	75:25
Na	-78 °C	50%	59:41
K	-78 °C	NA	NA

J. Wicha, et al., *Org. Lett.*, 2003, 5, 2789

Conclusions

BT and PT sulfones have become useful functional groups for the synthesis of olefins from aldehydes

inexpensive starting materials

sulfones can be made in high yield from alcohols

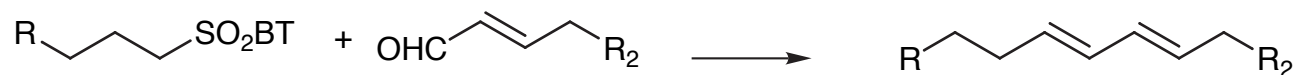
olefination reactions occur under mild conditions, and are typically high yielding and selective

Stereochemical outcome is kinetically controlled in most cases. Though reaction conditions can often influence selectivities

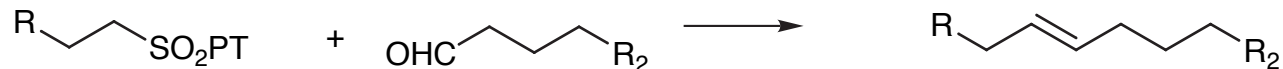
Polar solvents with soft counter ions often favor *E* olefins

Non-polar solvents with hard counter ions often favor *Z* olefins

BT sulfones are most useful for the synthesis of conjugated dienes through reaction with α,β -unsaturated aldehydes



PT sulfones are most useful for the synthesis of non-conjugated (*E*) olefins



PYR and TBT sulfones both produce high levels of *cis* selectivity, though yields are typically lower than BT reactions

Definitely more to come in the future

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

Chemistry 206
Advanced Organic Chemistry

Lecture Number 30

Ambiphilic Functional Groups-4

- Construction of Consonant & Dissonant FG Relationships
- Charge Affinity Inversion Operators

Lecture 27 and handout 27A

Handout 30A: Homo-enolates: Synthesis & Applications

Mesembrine Syntheses: Keely, S. L.; Tahk, F. C. *JACS* **1968**, *90*, 5584.
Stevens, R. V.; Wentland, M. P. *JACS* **1968**, *90*, 5580 (**handouts**)

Stetter, *The catalyzed nucleophilic addition of aldehydes to electrophilic double bonds*. *Org. React. (N.Y.)* **1991**, *40*, 407.

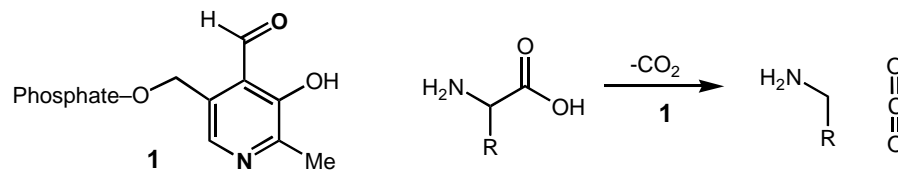
Ahlbrecht, "Stereoselectivity of chiral homo-enolate equivalents." *Synthesis* **1999**, 365-390.

D. A. Evans

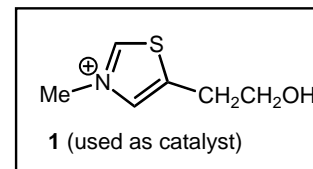
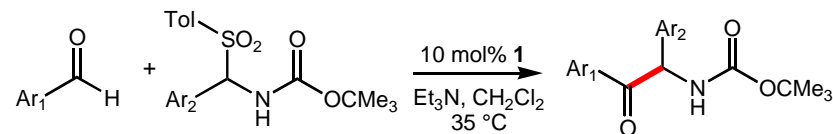
Monday,
December 1, 2003

Relevant Questions

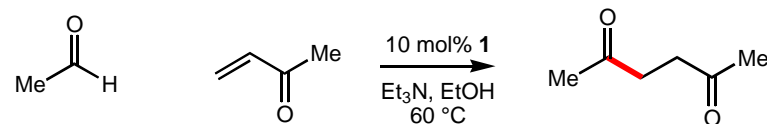
The pyridoxal co-factor (Vitamin B₆) **1**, facilitates the decarboxylation of α -amino acids. Provide a mechanism by which **1** carries out this transformation.



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.

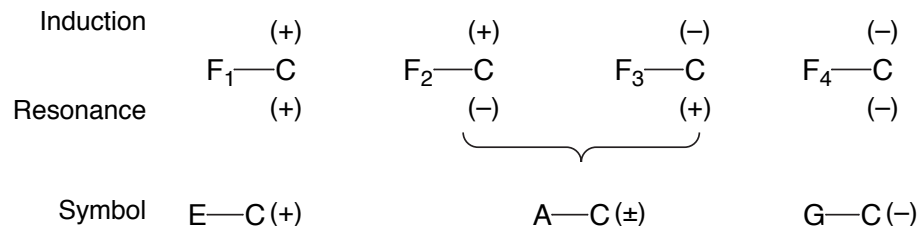


The nucleophilic addition of aldehydes to electrophilic double bonds catalyzed by thiazolium salt **1** is referred to as the Stetter Reaction (Stetter, H.; Kuhlmann, H. *Org. Reactions* **1991**, *40*, 407). Provide a mechanism for this transformation.

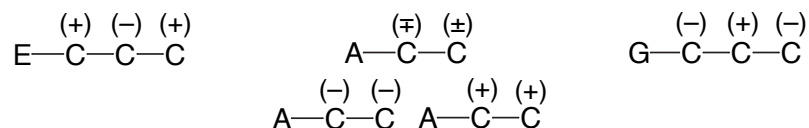


Classification of Functional Groups

Each substituent attached to carbon activates that carbon toward a polar reaction by either resonance or induction or both.



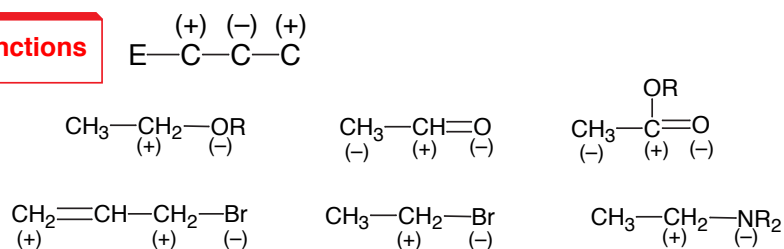
Charge Affinity Patterns



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

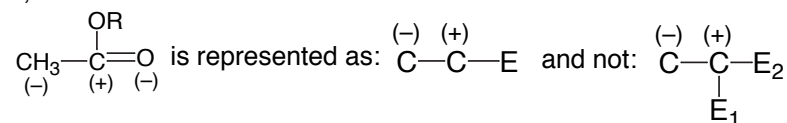
Charge affinities of real functional groups form a subset of the ideal FG classes.

E-Functions

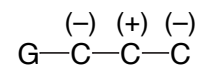


- Note that the issue of oxidation state is not explicitly incorporated. This issue is subordinate to that of defining site reactivity.

For example,

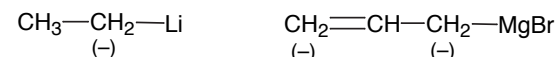


G-Functions

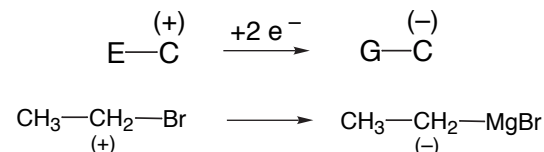


- Those ideal FGs which create nucleophilic carbon at point of attachment.
- Exhibit strictly alternate charge affinity patterns.

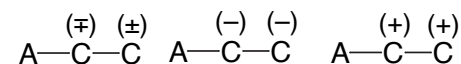
These are your metallic FGs such as Li, Mg, etc.



- Note that a 2-electron reduction (or oxidation) will transform an E-Class FG to a G-Class FG.

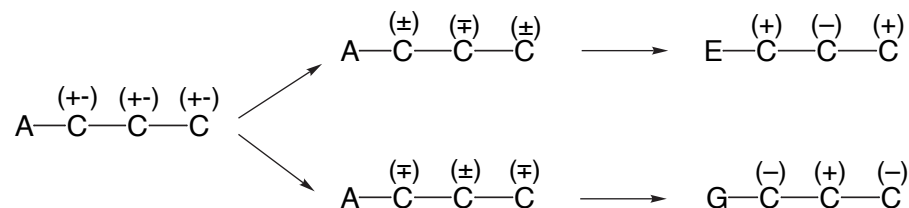


A-Functions



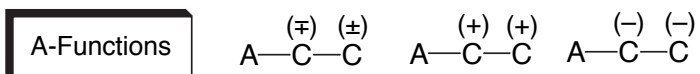
- All sites activated equally for electrophilic & nucleophilic reactivity.
- Those ideal FGs which exhibit nonalternate polar site reactivity are included.

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.

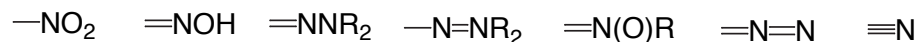


A-functions are some of the most useful FGs in organic synthesis because of the unique reactivity provided.

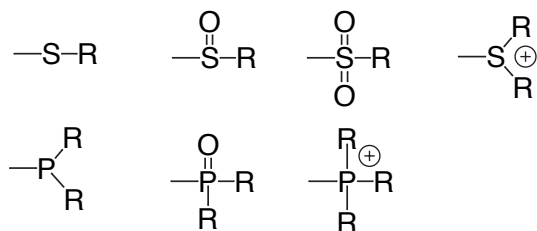
A-Functions: Real Examples



■ A-functions are composed of polyatomic arrangements of N & O.



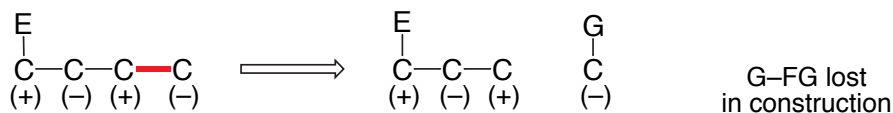
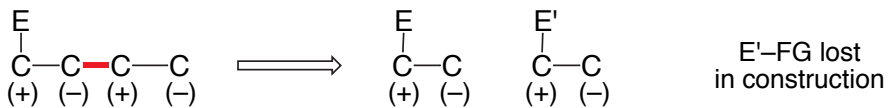
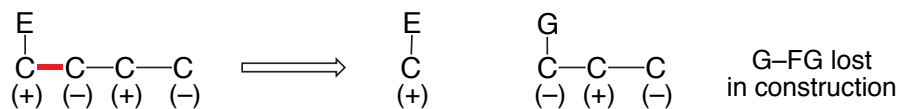
■ A-functions are composed of second-row elements such S and P.



■ Functional groups derived from many of the transition elements

Synthesis of Targets containing E-Functions

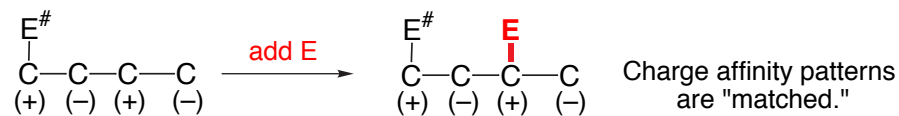
Transforms utilizing target E-function in synthesis plan given highest priority.



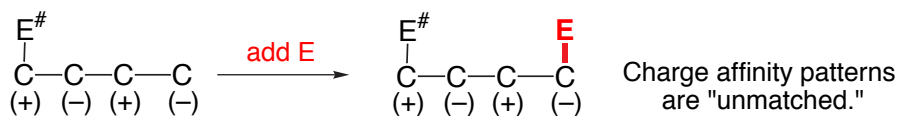
Given the resident E-function, the charge affinity pattern dictates the nature of the polar coupling process and thus functional groups to be employed in synthesis.

Classification of Pairwise Difunctional Relationships

Consider the paired relationships of E-functions. There are two relationships.



Pairwise relationship is
"consonant".

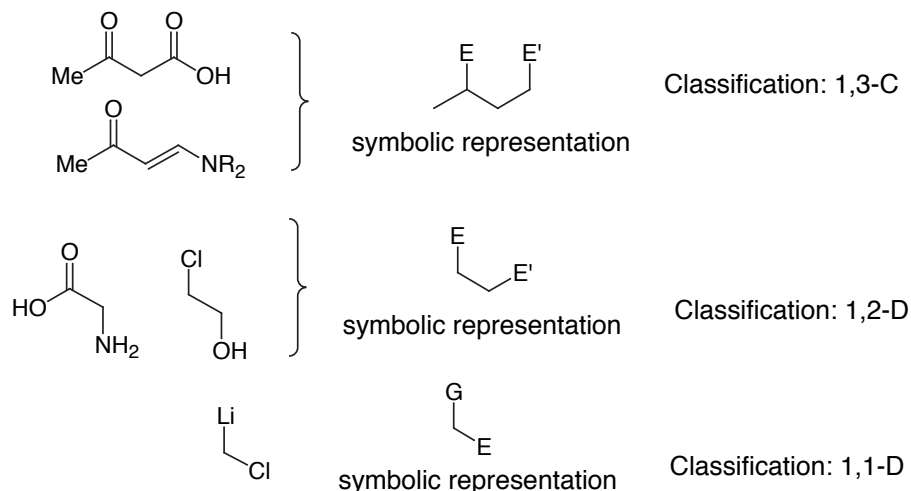


Pairwise relationship is
"dissonant".

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



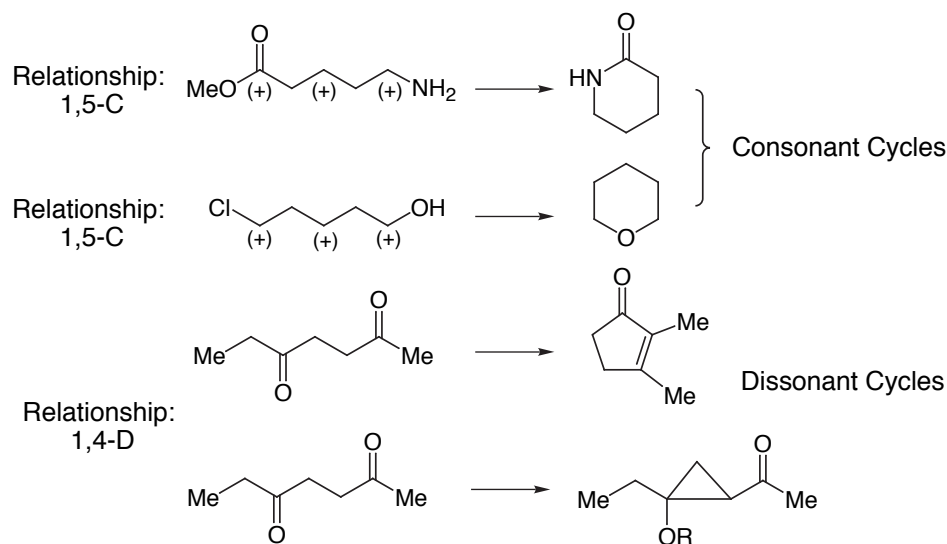
Classification of Pairwise Difunctional Relationships

- A single FG residing either in or appended to a cycle may establish a FG relationship with itself.



Consonant & Dissonant Relationships: Path-Cycle Interconversions

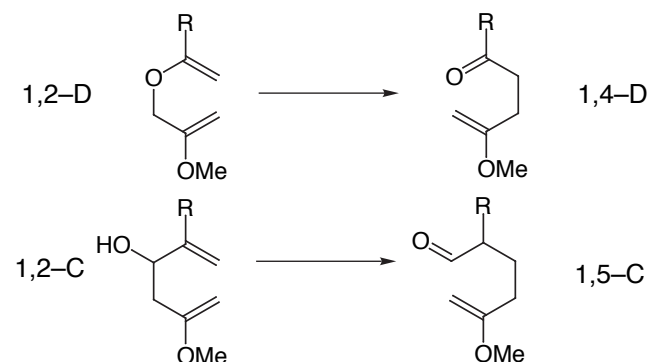
Linear molecules may be transformed into cycles & vice-versa:



Path-cycle interconversions such as those illustrated permute, but do not eliminate the relationship. i.e. D-bond paths are transformed into D-cycles.

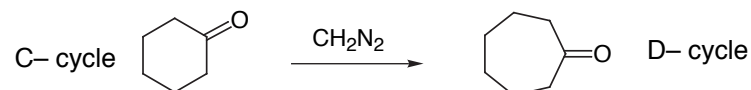
Pairwise Relationships: Path-Path Interconversions via Sigmatropic Rearrangements

[3,3] Sigmatropic Rearrangements:

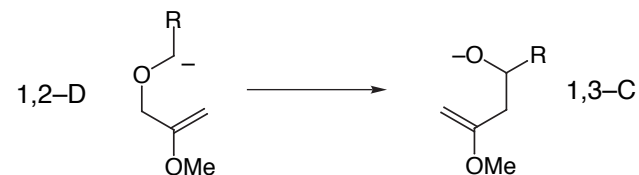


- For these rearrangements, C→C', D→D' but C→D not possible

[1,2] Sigmatropic Rearrangements:



[2,3] Sigmatropic Rearrangements:



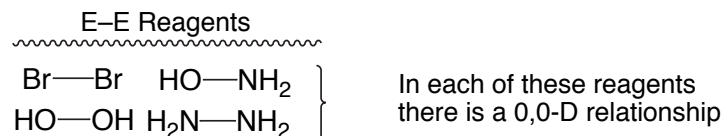
General Rule For [m,n] Sigmatropic Rearrangements:

When the sum of m+n is even, the FG relationship is maintained, e.g. C→C'
 When the sum of integers is odd, the FG relationship is changed, e.g. C→D

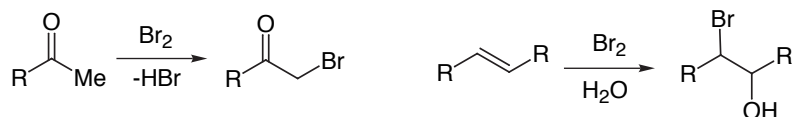
Pairwise Relationships in Inorganic Reagents

- E-functions in their most stable oxidation states (HO^- , NH_3 , Cl^-) are represented as $\text{E}(-)$.

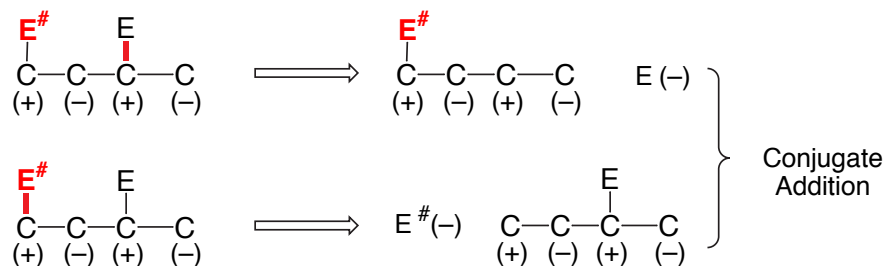
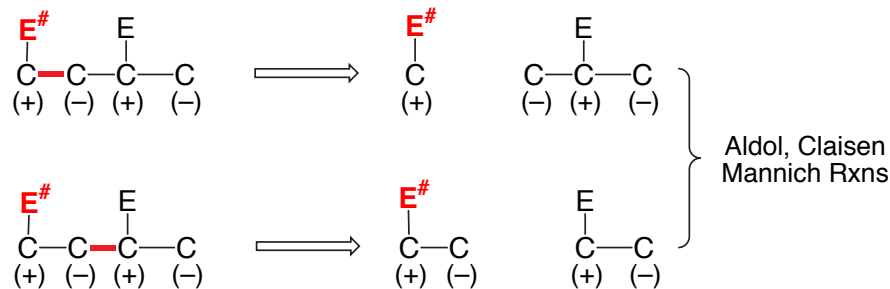
There exist an important family of reagents which have E-FGs directly coupled:



These reagents are used to construct D-Relationships:

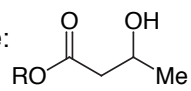


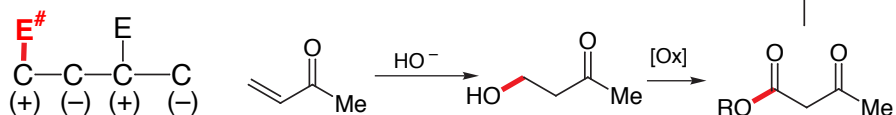
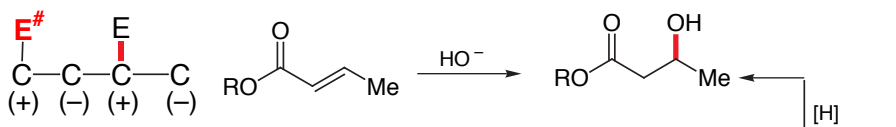
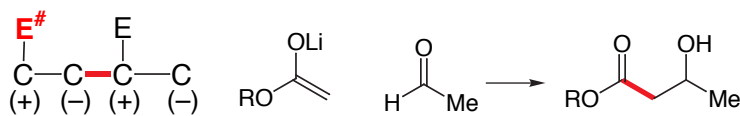
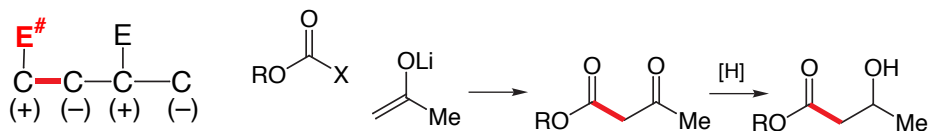
Synthesis of Targets containing Consonant Pairwise Relationships



Consonant difunctional relationships can be constructed from just the functions illustrated & polar bond constructions.

A Specific Case

Target structure:  **Step I:** There are 4 bonds interconnecting E & E'. Hence generate the 4 transforms leading to mono-functional precursors:

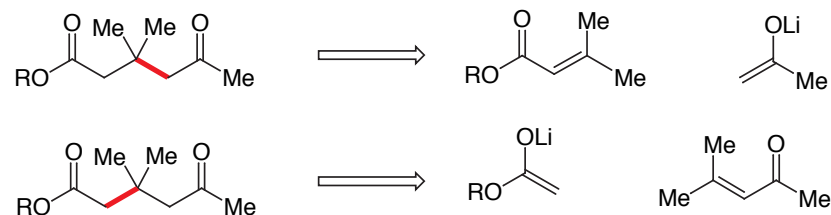


Step II: Evaluate the efficiency of the 4 plausible routes to the target from available precursors.

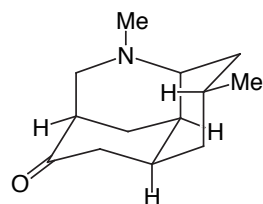
Given the oxidation state in the target, the second synthesis looks the best and the fourth looks the worst.

The Constraint of Quaternary Centers

If a quaternary center occurs along the consonant bond path, one is limited to bond constructions on either side of that restriction

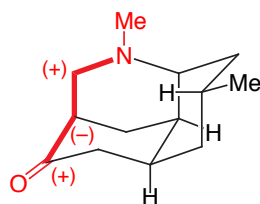


Quaternary Centers & Bridgehead Restrictions

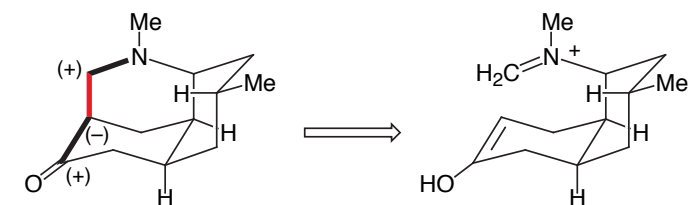


Lucidulene Synthesis: *JACS* **94**, 4779 (1972)

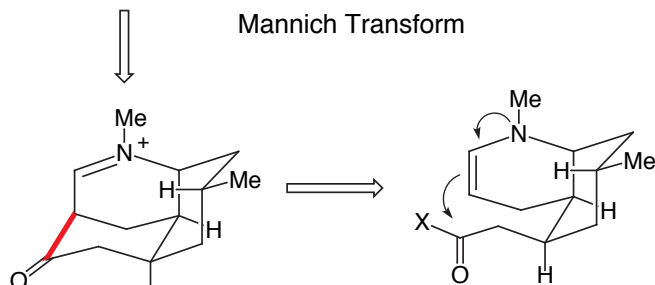
Focus on the shortest consonant bond path:



The two permitted bond constructions along illustrated bond path flank the bridgehead carbon

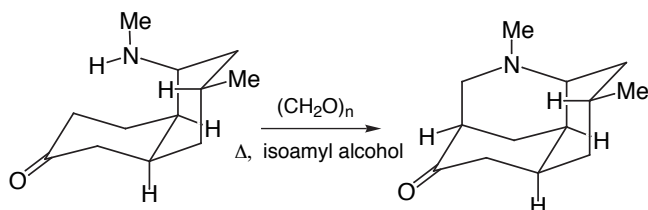


Mannich Transform



Enamine Acylation

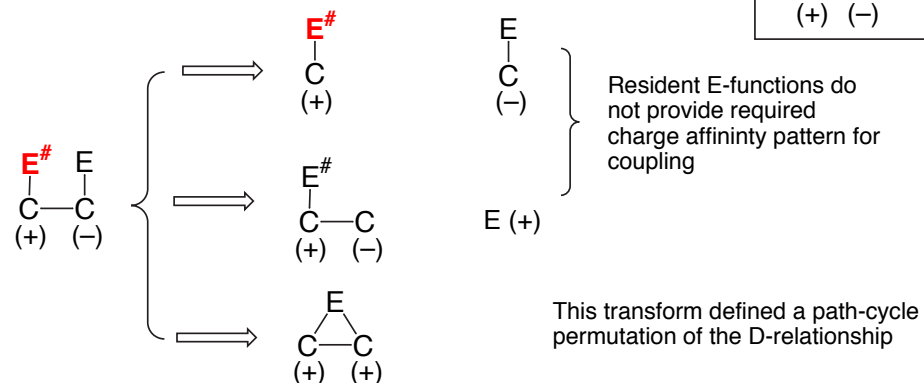
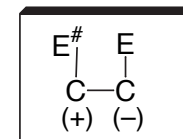
Option Selected:



■ Corollary: π -conjugation cannot be extended through bridgehead or quaternary centers

Synthesis of Dissonant Pairwise Relationships

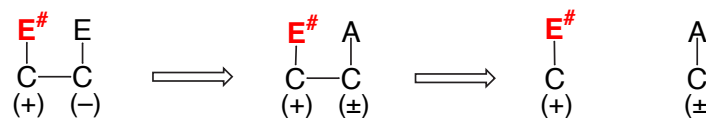
The pairwise relationship is "unmatched"; hence, the illustrated E-functions cannot be used exclusively to construct the bond path. Let's consider the simplest case: a 1,2-D relationship.



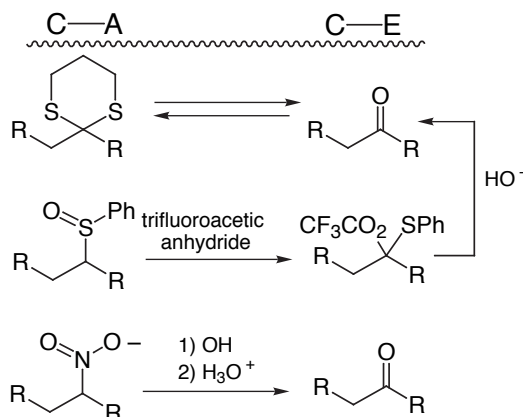
In the illustrated polar disconnections, one of the fragments may exploit the charge affinity pattern of the resident FG while the other may not.

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**



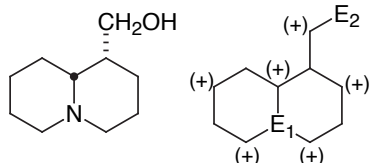
The Pummerer Rearrangement

"The Pummerer reaction of sulfinyl compounds.", De Lucchi, et al. *Org. Reactions* **1991**, 40, 157.

The Nef Reaction

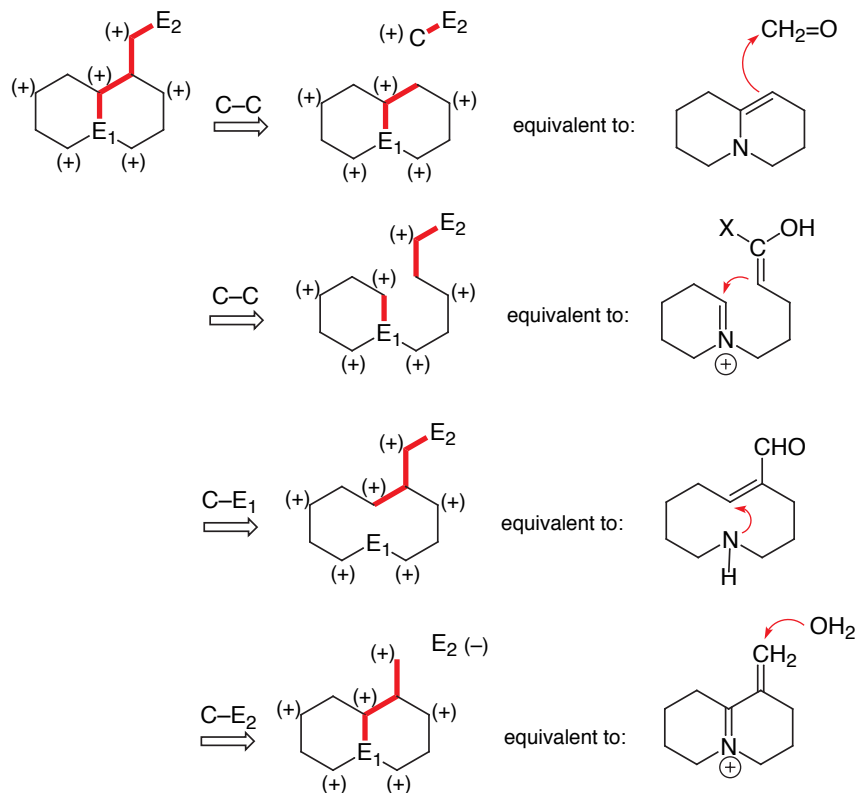
Bond path analysis of simple alkaloids

lupinine



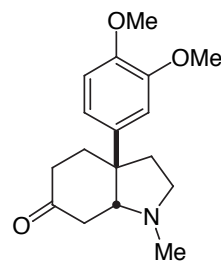
Every complex polyfunctional molecule may be analyzed structurally in terms of its individual consonant or dissonant construction paths or cycles. For example, in the alkaloid lupinine all possible construction paths interconnecting E1 and E2 are consonant. Consonant paths within the polyatomic framework 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



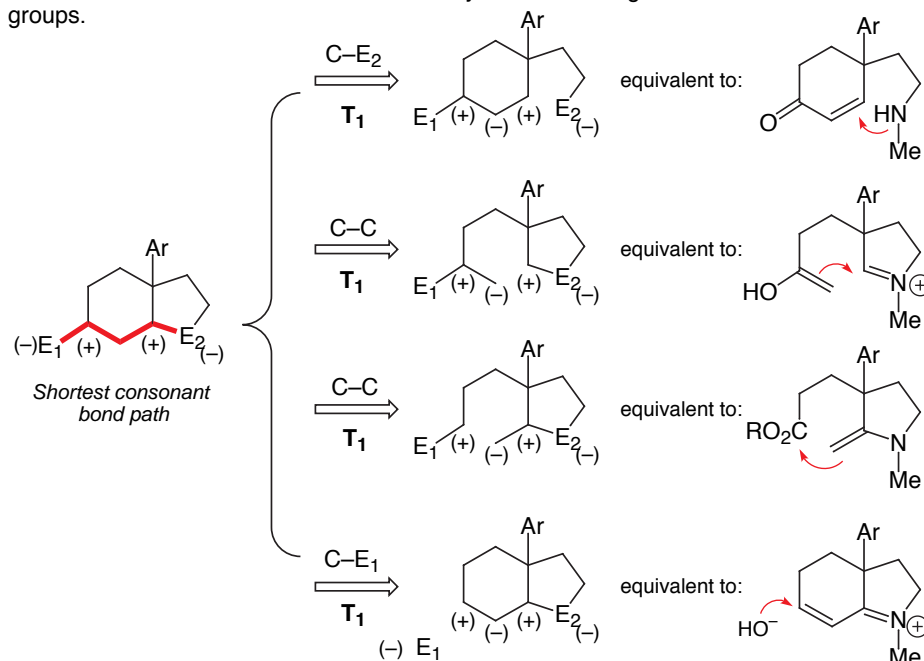
Curphey, T. J.; Kim, H. L. *Tetrahedron Lett.* **1968**, 1441.

Keely, S. L.; Tahk, F. C. *JACS.* **1968**, *90*, 5584.

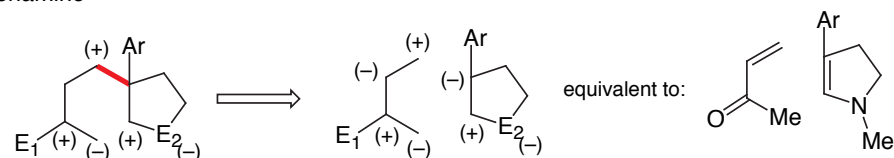
Stevens, R. V.; Wentland, M. P. *JACS* **1968**, *90*, 5580

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

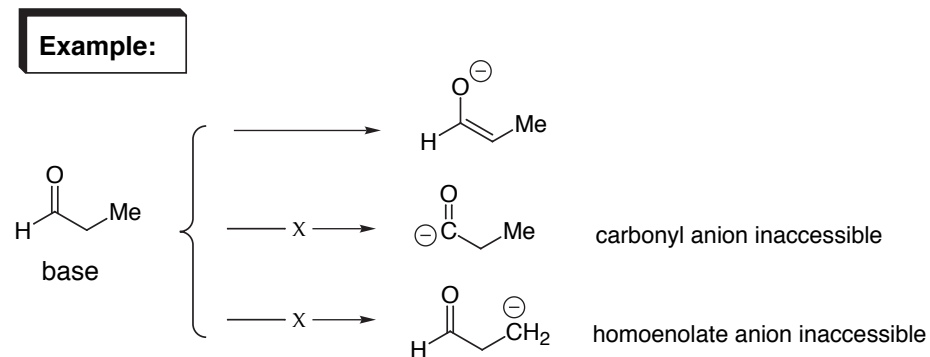


Handouts

Keely, S. L.; Tahk, F. C. *JACS.* **1968**, *90*, 5584.

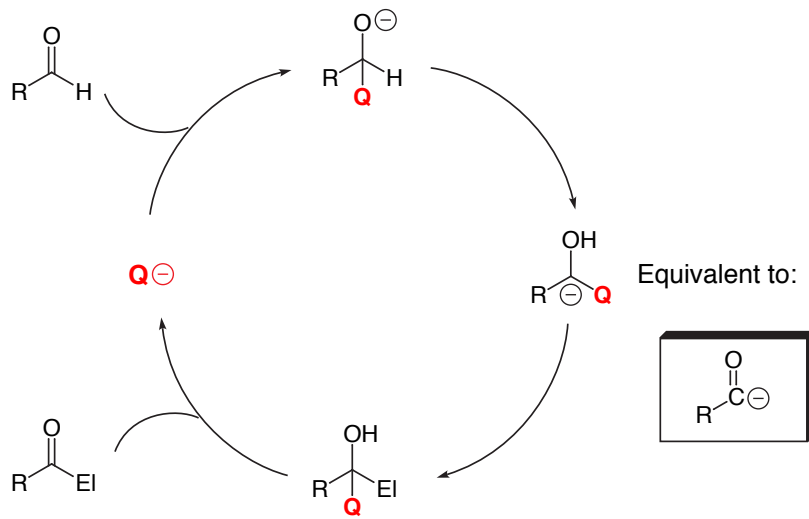
Stevens, R. V.; Wentland, M. P. *JACS* **1968**, *90*, 5580

Inaccessible Reactivity Modes in Carbonyl Deprotonation

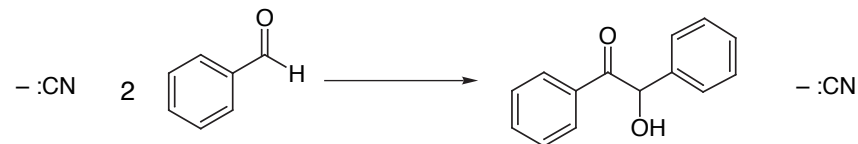


Can one design "catalysts" which will provide access to carbonyl anion equivalents in situ??

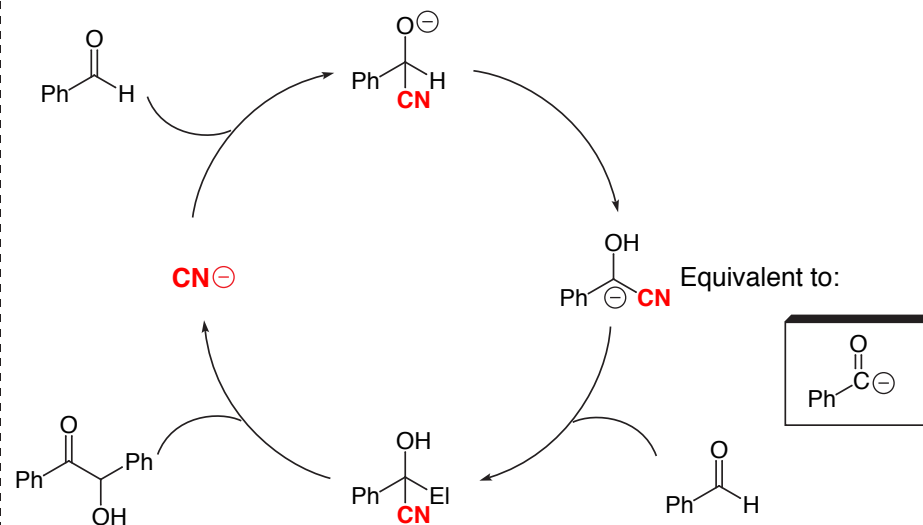
Let Q^- be such a catalyst, we will call it an "inversion operator"



The Benzoin Condensation

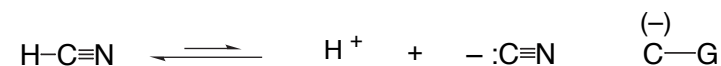


■ Cyanide ion is such a "catalyst"



How do we classify the $\equiv\text{N}$ functional group?

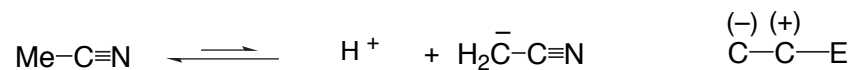
■ Hydrogen cyanide is a fairly good Bronsted acid ($\text{pK}_{\text{a,HOH}} 9.5$)



■ Acetonitrile can be attacked by nucleophiles:

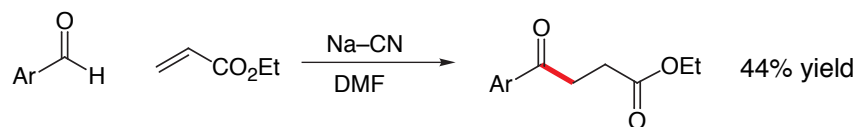


■ Acetonitrile can be deprotonated by strong bases ($\text{pK}_{\text{a,DMSO}} \sim 30$)

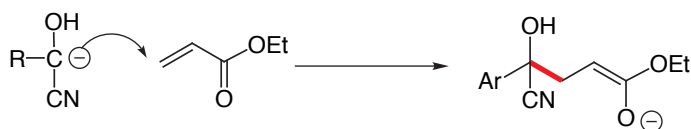


Cyanide-based Carbonyl Anion Equivalents

- Extensions of the Benzoin condensation concept are possible in some instances:

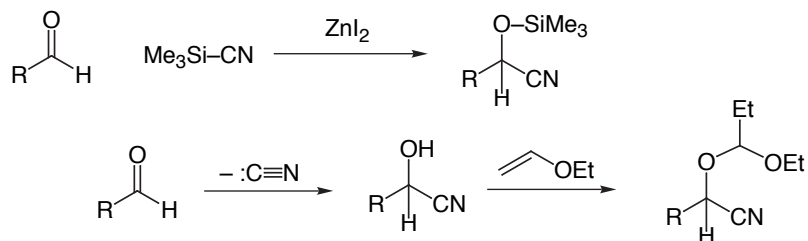


The C-C Bond Construction

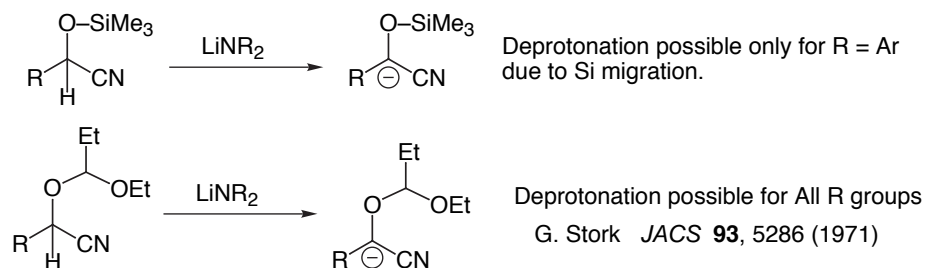
Stetter, *Org. Reactions* **1991**, 40, 407.

- The in situ use of cyanide ion as an inversion operator is limited. Greater generality may be achieved by multistep alternatives:

Aldehyde Derivatization Step

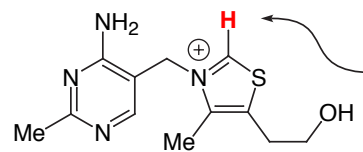


Substrate Deprotonation Step



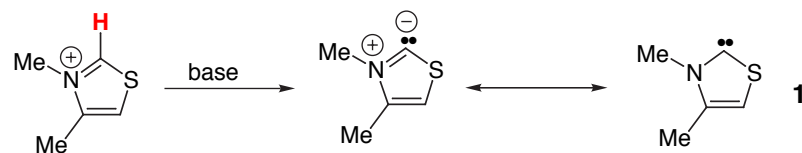
Thiazolium Salts: Nature's Inversion Operators

Reactions equivalent to the benzoin are catalyzed by biological co-factors to make (and break) dissonant difunctional heteroatom-heteroatom relationships



The thiamine cofactor

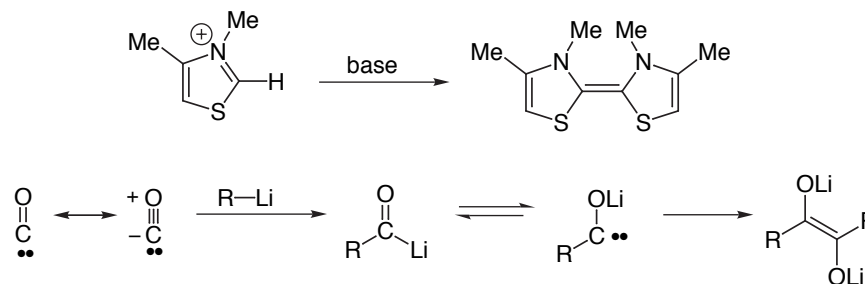
The pKa of this proton has been the subject of considerable study. The current estimates are that the value falls in the range of 16-20 but this number is not firm.

F. G. Bordwell *JACS* **113**, 985, (1991)

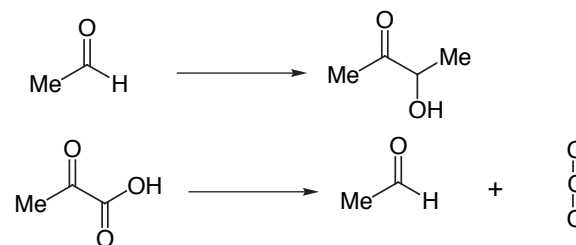
Carbonyl anions might be similarly stabilized



In the absence of electrophiles **1** & **2** dimerize as would be expected for carbene reactivity.

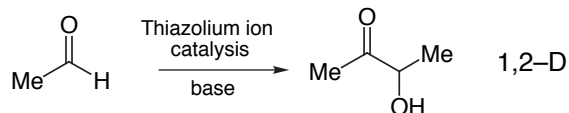


Reactions catalyzed by thiamine

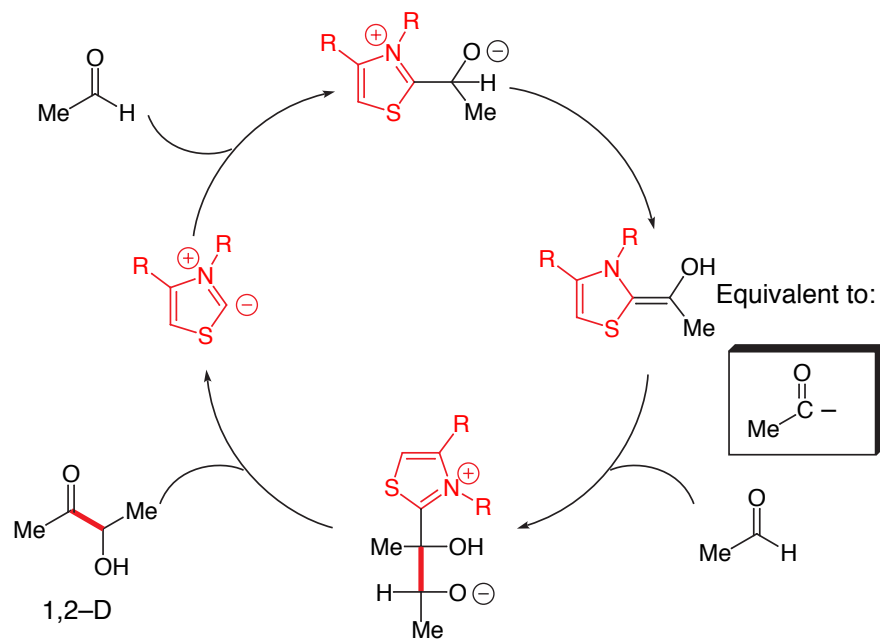


Aldehyde dimerization by Thiazolium Salts

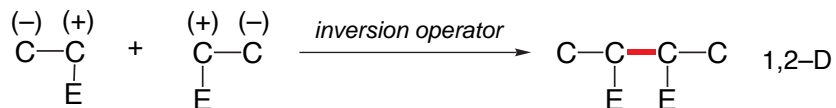
The Reaction



The Catalytic Cycle



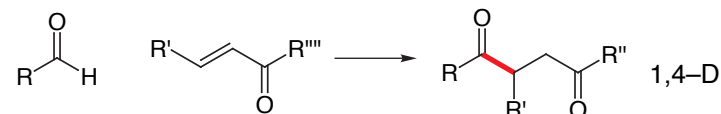
■ Hence dissonant relationships may be made from E-functions if "inversion operator" is employed



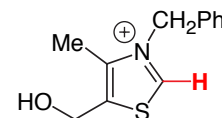
■ This is a fundamental strategy for handling the formation and cleavage of D-relationships in nature.

Catalyzed Michael Reactions by Thiazolium Salts

The Reaction



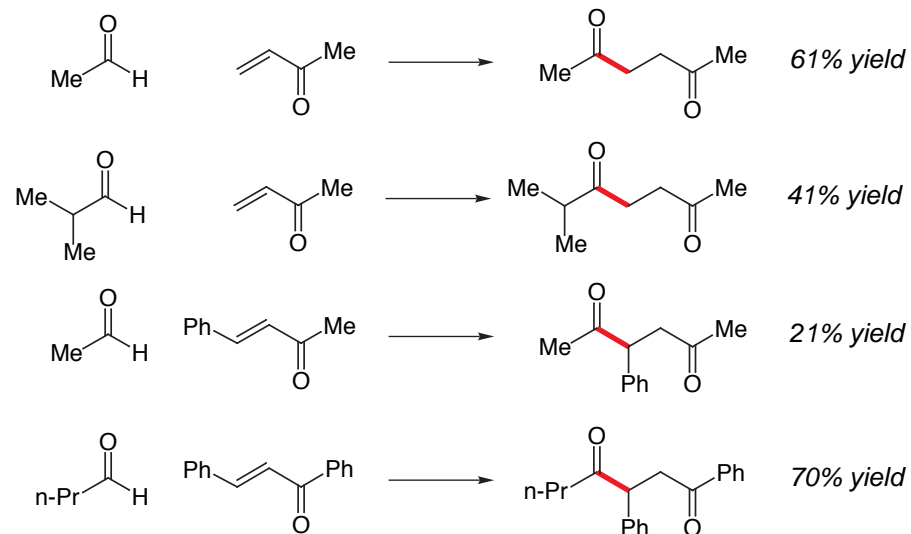
The Catalyst:



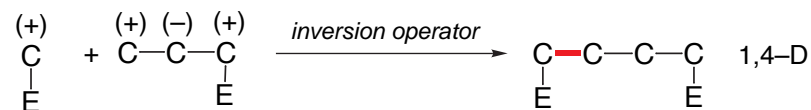
The Conditions:
0.1 equiv catalyst, Et₃N or NaOAc,
EtOH or DMF at 60-80 °C

Examples:

"The catalyzed nucleophilic addition of aldehydes to electrophilic double bonds.", Stetter, H.; Kuhlmann, H. *Org. Reactions* **1991**, *40*, 407.



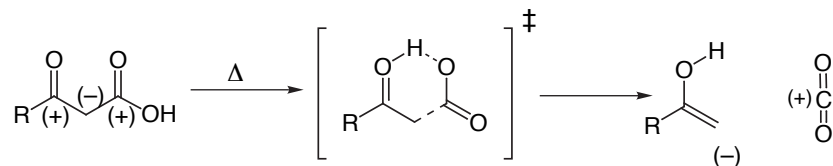
■ 1,4-D relationships may also be made from E-functions if "inversion operator" is employed.



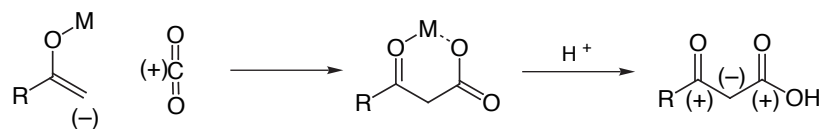
■ There is no analogue to this reaction in nature.

Decarboxylation Catalyzed by Thiazolium Salts

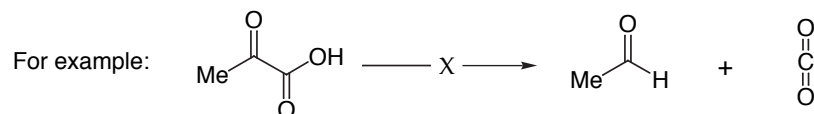
- Background: Decarboxylation from consonant difunctional relationships is facile:



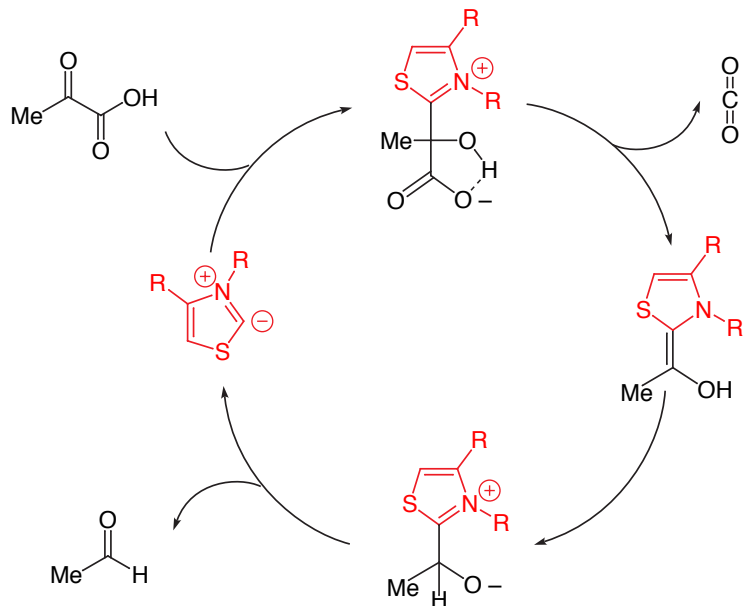
- The reverse process can be achieved under basic conditions:



- Such consonant relationships may be readily made (and broken) via the resident functional groups. The analog reactions for dissonant relationships not possible.



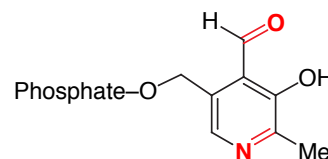
- Nature uses inversion operators to break such 1,2-D relationships



Design Attributes of Inversion Operators

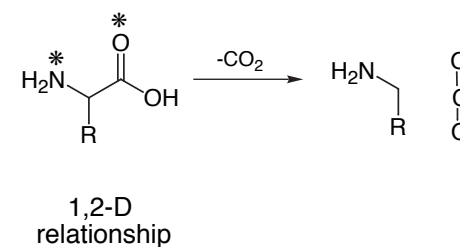
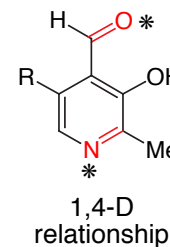
Inversion operators are constructed from A-functions or molecules containing D-relationships.

The pyridoxal Co-factor (Vitamin B₆)

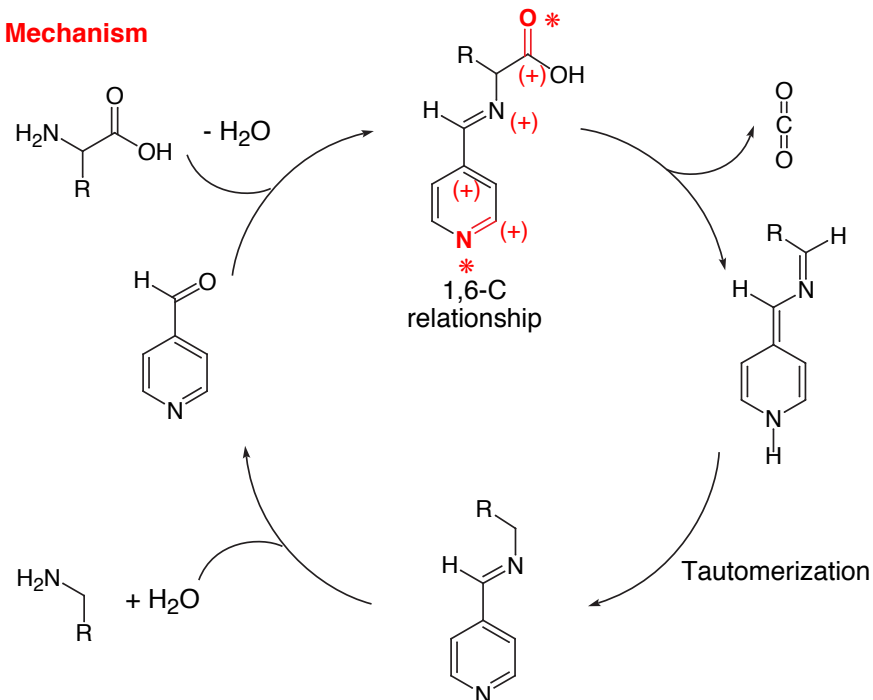


The critical difunctional relationship is that between =O & =N. This is a 1,4-D relationship

The Reaction



The Mechanism



Chemistry 206

Advanced Organic Chemistry

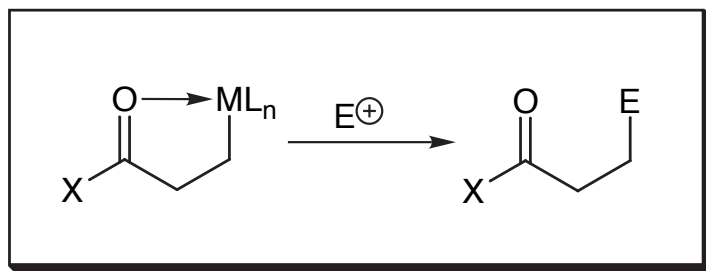
Handout 30A

Homoenolates: Synthesis & Applications

Evans Group Seminar

by

Jason Burch, March 24, 2000



D. A. Evans

Monday,
December 1, 2003

Enolates and Homoenolates

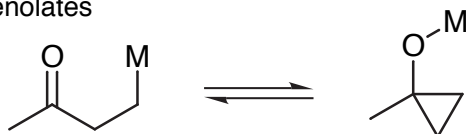
The Tautomerism Problem

- Enolates



- tautomerism is generally not a problem because oxyanionic tautomer still acts as carbon nucleophile

- Homoenolates



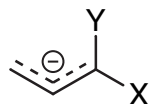
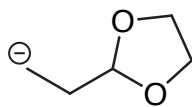
- tautomerism is a much larger problem because it is often irreversible and oxyanionic tautomer rarely acts as a carbon nucleophile

Nakamura in *Comp.Org.Synth.*, **1991**, 2, 441

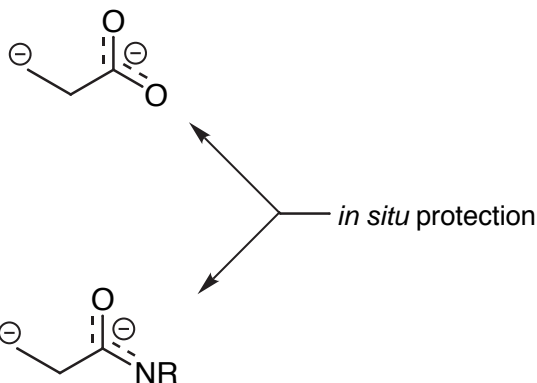
Homoenolate Equivalents

Definition: species containing an ionic carbon β to a moiety which can be converted into a carbonyl group

Examples:

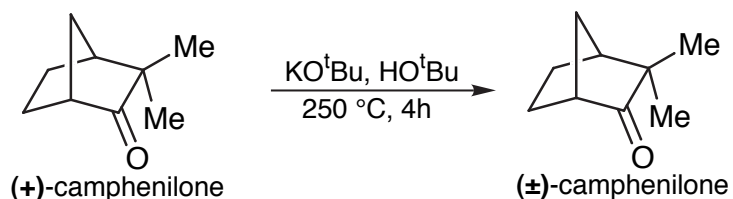


X = OR, NR₂, etc.
Y = H, R, OR, NR₂, etc.

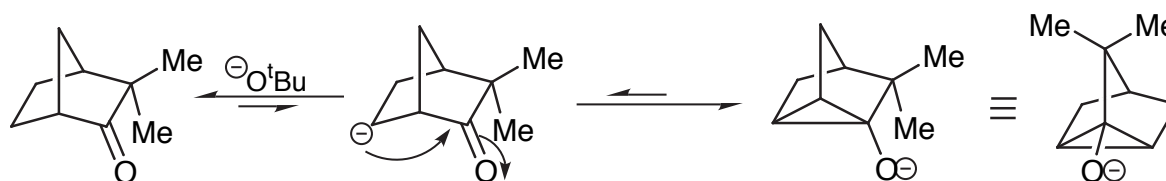


Werstiuk in "Umpeoled Synthons", Hase, Ed.;
Wiley: New York, **1987**, Chap. 6
Ahlbrecht, *Synthesis*, **1999**, 365 (chiral examples)

The First "Homoenolate"



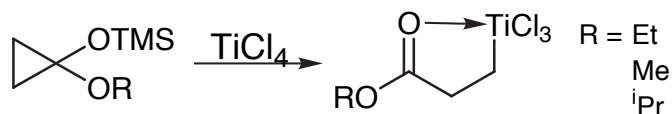
- no racemization occurred in >4 days at 250 °C in the absence of base
- proposed to proceed via a "homoenolate anion"



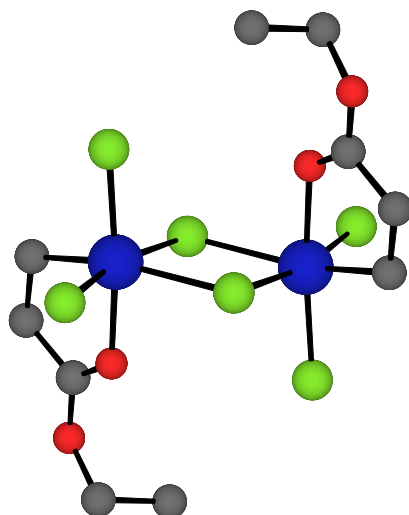
Nickon, *J.Am.Chem.Soc.*, **1962**, 84, 4604

Cyclopropane Ring Opening

Synthesis of Titanium Homo-enolates



- if conducted in CDCl_3 leads to a deep wine-red color; precipitates as purple needles in hexanes
- IR spectrum strongly supports coordinated carbonyl ($\nu_{\text{C=O}} = 1603$ for R = iPr in benzene)
- molecular weight by cryoscopy is 560-620 indicating dimeric structure
→ later verified in solid state by x-ray crystal structure (Floriani)



Relevant bond lengths (Å):

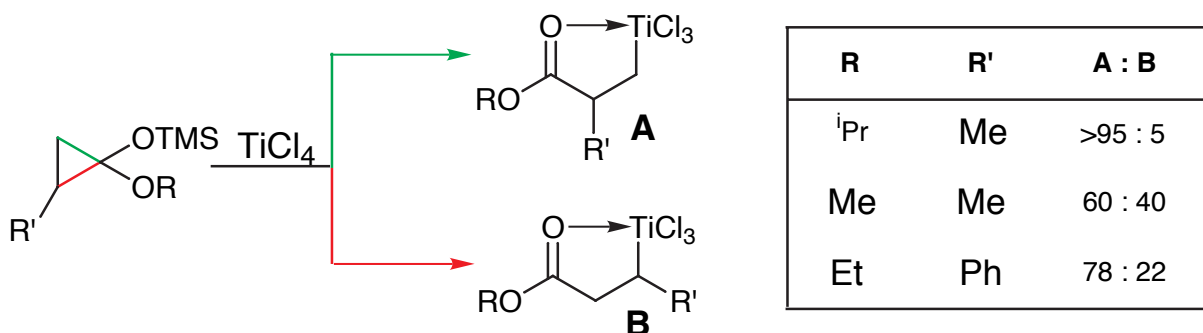
Ti-C	2.081
Ti-O	2.072
C=O	1.235

Nakamura, *J.Am.Chem.Soc.* **1983**, 105, 651
Floriani, *Organometallics*, **1993**, 12, 2845

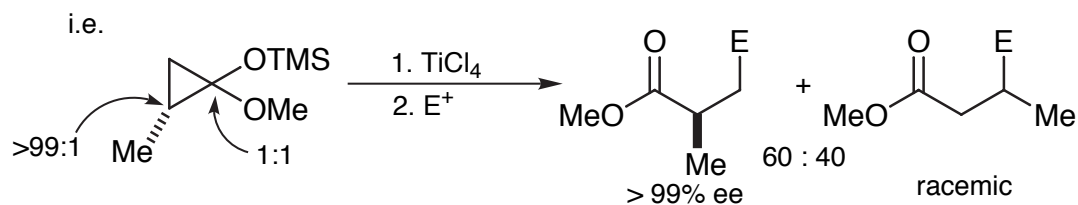
Cyclopropane Ring Opening

Regioselectivity of Ring Cleavage - Titanium

- in general, cleavage occurs selectively at the least substituted cyclopropane bond



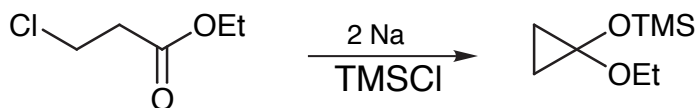
- A** can be isolated, but **B** is too unstable; only detected by *in situ* quench with electrophiles (i.e. Br₂, RCHO)
- if non-racemic starting material is used, quench with electrophiles indicates non-racemized **A** and totally racemic **B**



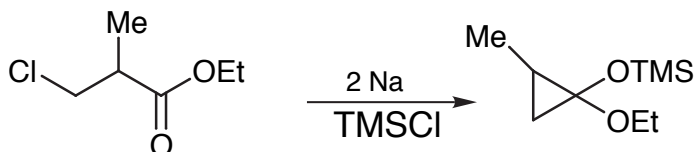
Nakamura, *J. Am. Chem. Soc.*, **1986**, 108, 3749

Cyclopropane Synthesis

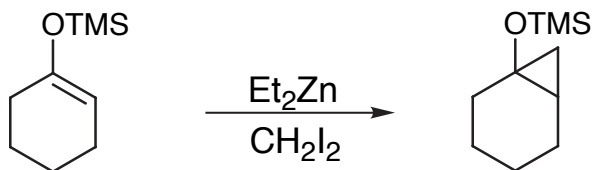
- most common method



- used to prepare substituted cyclopropanes



- use Simmons-Smith for ketone-derived substrates

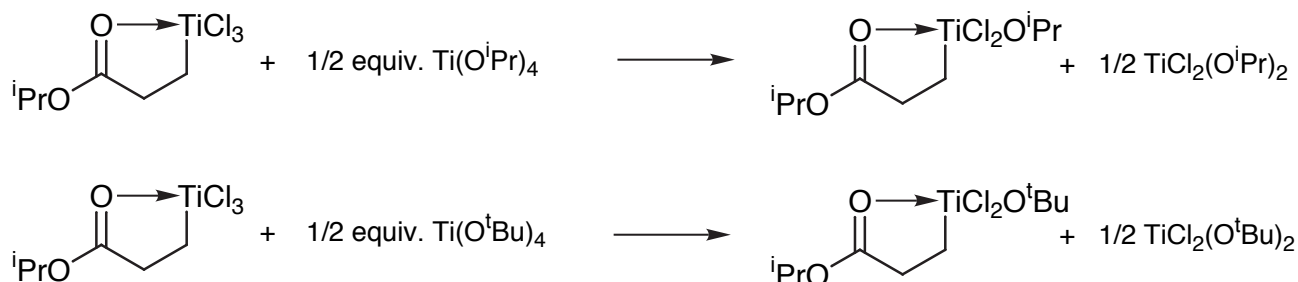


Ruhlmann, *Synthesis*, **1971**, 236.
 Salaun, *Org. Synth.*, **1985**, 63, 147
 Murai, *J. Org. Chem.*, **1973**, 38, 4354

Alkoxide-Modified Homoenoates

Tuning Titanium Homoenoate Reactivity

- Problem: trichlorotitanium homoenoates are not reactive enough for some applications
can also lead to chlorinated byproducts
- Idea: replace 1 or more chlorides with alkoxides to increase nucleophilicity



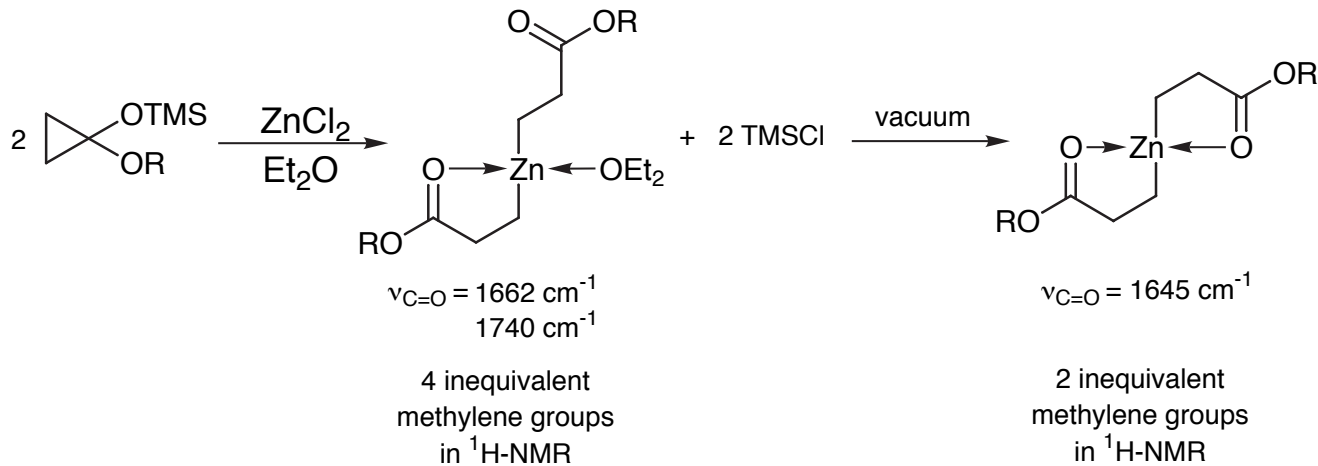
- Have not been characterized to the detail of the trichlorohomoenoates
- Appear to have "significant contribution from monomeric forms" (from molecular weight data)
- Are more reactive than trichloro homoenoates towards homoaldolisation

Nakamura, *J. Am. Chem. Soc.*, **1986**, 108, 3745

Cyclopropane Ring Opening

Zinc Homoenoates

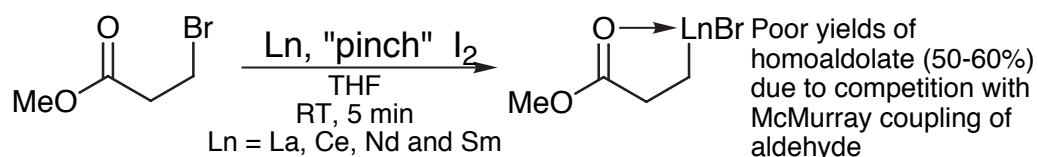
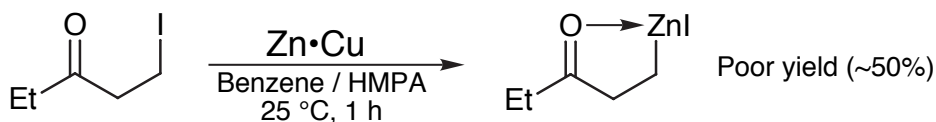
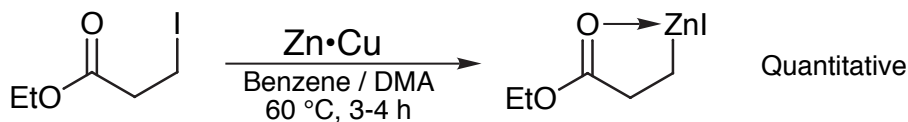
- Zinc homoenoates can be prepared in a similar method to titanium



Nakamura, *Organometallics*, **1985**, 4, 641

Direct Oxidative Addition

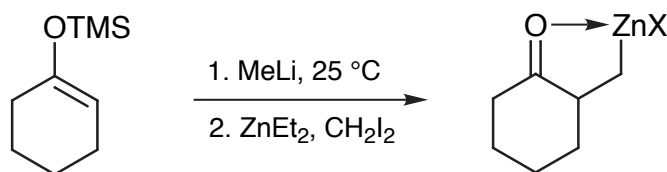
Zinc and Lanthanide Homoenoates



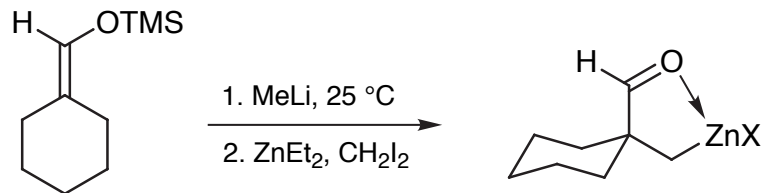
Yoshida, *Tetrahedron Lett.*, **1985**, 26, 5559
Yoshida, *Angew.Chem.,Int.Ed.Engl.*, **1987**, 26, 1157
Fukuzawa, *Chem. Commun.*, **1986**, 475

Enolate Homologation

Synthesis of Zinc Homoenoates



- less reactive than most zinc homoenoates
- can also be used to form aldehyde homoenoates

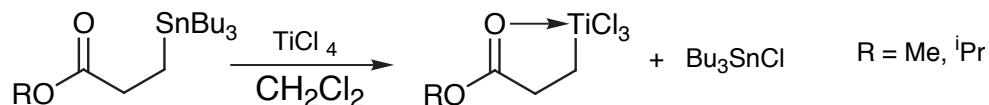


Knochel, *J.Org.Chem.*, **1993**, 58, 2694

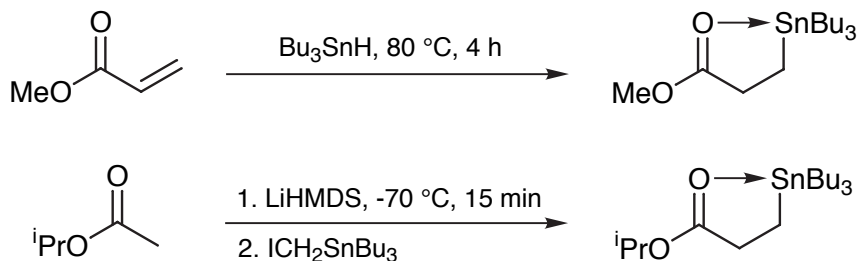
Direct Tin-Titanium Exchange

New Route to Titanium Homoenoates

- Treatment of β -tri-n-butylstannyl esters with TiCl_4 directly forms titanium homoenoate



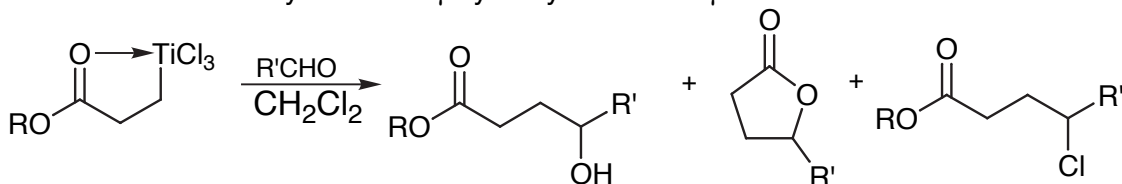
- Isotope labelling studies showed rxn does not proceed via cyclopropane
- Substrates can easily be prepared by two methods:

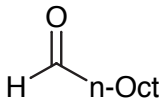
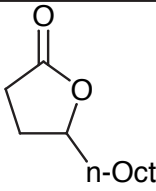
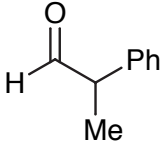
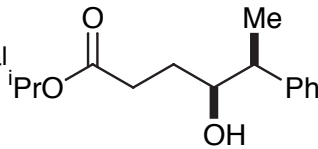
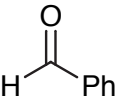
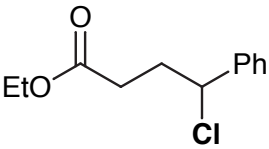


Goswami, *J.Org.Chem.*, **1985**, 50, 5907
 van der Kirk, *J. Appl. Chem.*, **1957**, 7, 356
 Still, *J.Am.Chem.Soc.*, **1978**, 100, 1481

The First Homoaldol Reaction

Synthesis of γ -hydroxyesters and γ -lactones

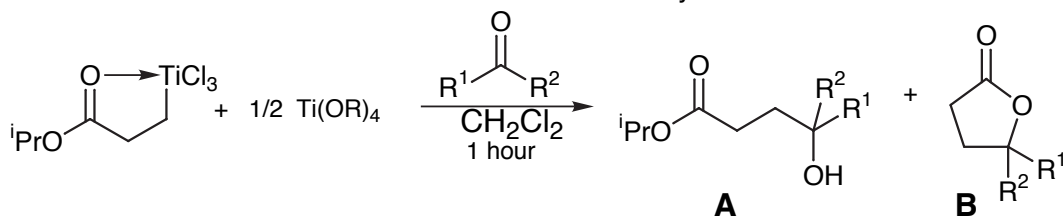


Aldehyde	R	Temp ($^\circ\text{C}$)	Time (h)	Workup	Product	Yield
	Et	0	1	Acidic		81
	<i>i</i> Pr	0	2.5	Neutral		67 (85:15)
	Et	0	1.5	Neutral		90

Nakamura, *J.Am.Chem.Soc.*, **1977**, 99, 7360

Homoaldol Reactions with Alkoxide-modified Homoenoates

Homoaldol Reactions with Aromatic Aldehydes and Ketones

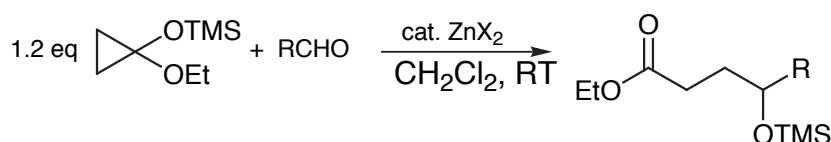


Electrophile	R	Temp(°C)	Yield (A or B)
Benzaldehyde	iPr	0	90(A)
Crotonaldehyde	iPr	0	88(A)
Acetophenone	iPr	20	66(A), 12(B)
	tBu	20	93(B)
Cyclohexanone	iPr	20	62(B)
	tBu	20	91(B)
	tBu	20	91(B)
			dr = 88 : 12 equatorial attack

Nakamura, *J.Am.Chem.Soc.*, **1986**, 108, 3745

Homoaldol Reactions of Zinc Homoenoates

First Catalytic Homoaldol Reactions



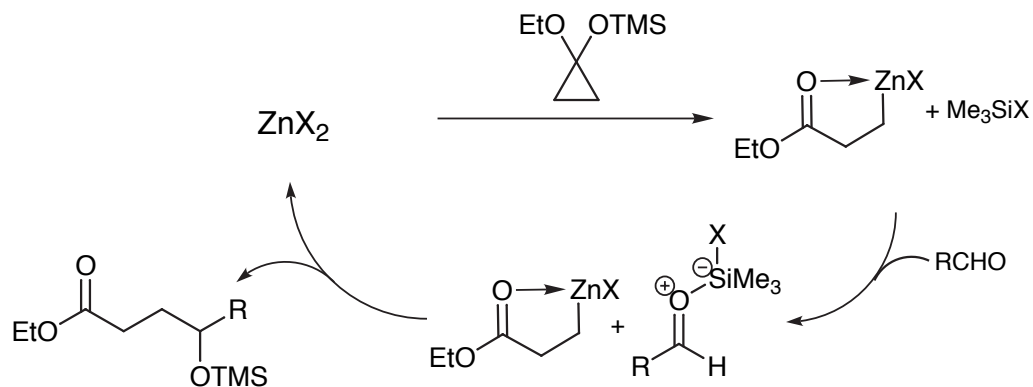
- TMSCl generated is essential (i.e. no reaction if removed *in vacuo* for stoichiometric case)

Aldehyde	Catalyst, yield	
	ZnCl ₂ (30-50 mol%)	ZnI ₂ (0.1-1 mol%)
PhCHO	84	89
	94	84
	91	95
	--	84
	79 93:7 <i>syn</i> : <i>anti</i> chelation product	--

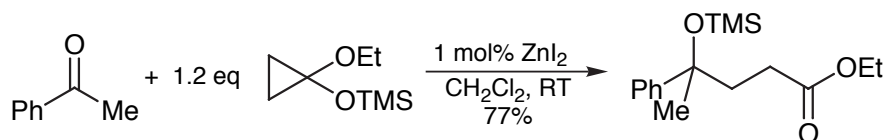
Nakamura, *J.Am.Chem.Soc.*, **1987**, 109, 8056

Homoaldol Reactions of Zinc Homoenoates

Proposed Catalytic Cycle



• with ZnI_2 , the homoenoate is reactive enough to add to ketones:

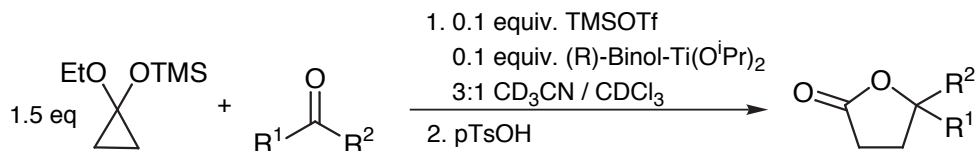


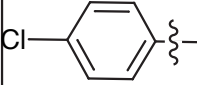
- no reaction even with stoichiometric ZnCl_2

Nakamura, *J. Am. Chem. Soc.*, **1987**, 109, 8056

Gleason's Homoaldol reaction

First Catalytic Titanium Homoaldol Reaction



R ¹	R ²	Conditions	Yield
Ph	H	0 °C, 24 h	99
Ph—≡— ξ	H	0 °C, 36 h	76
TMS—≡— ξ	H	0 °C, 36 h	82
Cl— 	H	0 °C, 80 h	84
^t Bu	H	45-50 °C, 54 h ^a	52
Ph	Me	45-50 °C, 60 h ^a	78

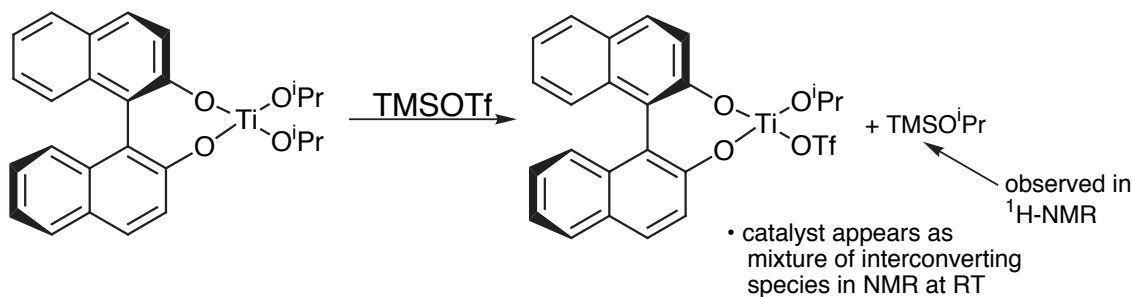
^a2 equiv. of cyclopropane used

Gleason, *Org. Lett.*, **1999**, 1, 1643

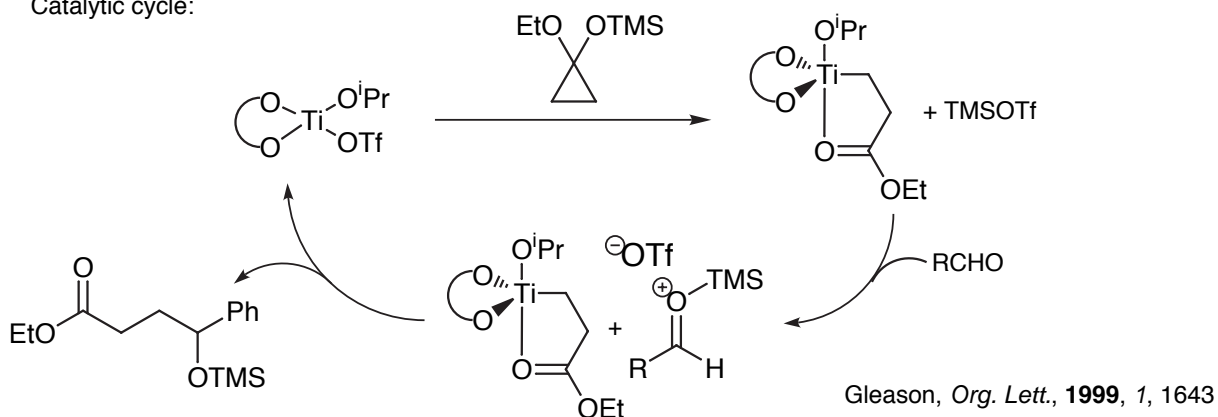
Gleason's Homoaldol reaction

Proposed Catalyst and Catalytic Cycle

Catalyst:

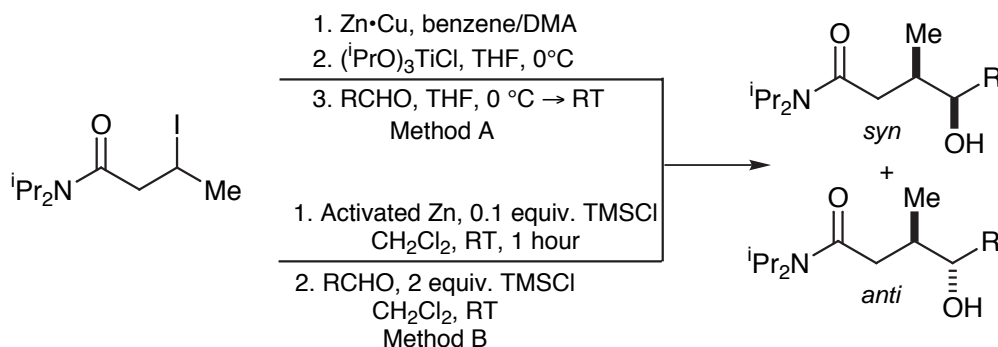


Catalytic cycle:



Diastereoselective Homoaldol Reactions of Amide-homoenolates

Synthesis of *syn*- or *anti*- β -methyl- γ -hydroxyamides

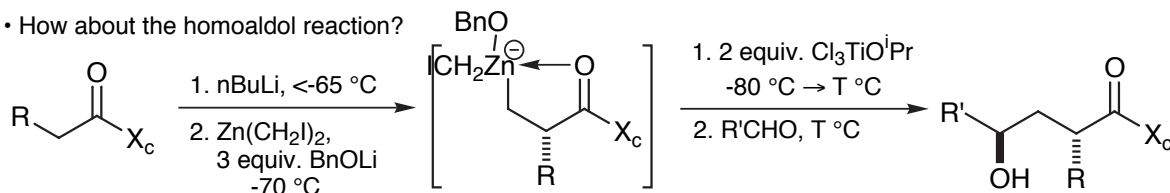


R	Method	Time (h)	Yield	<i>syn:anti</i>
Ph	A	3	79	94 : 6
	B	2.5	82	13 : 87
o-MeOPh	A	3	87	85 : 15
	B	0.6	95	25 : 75
2-furyl	A	0.5	61	96 : 4
	B	0.6	60	38 : 62

Tandem Asymmetric Enolate Homologation - Homoaldol Reaction

Asymmetric Synthesis of α -alkyl, γ -hydroxy Carbonyl Compounds

• How about the homoaldol reaction?

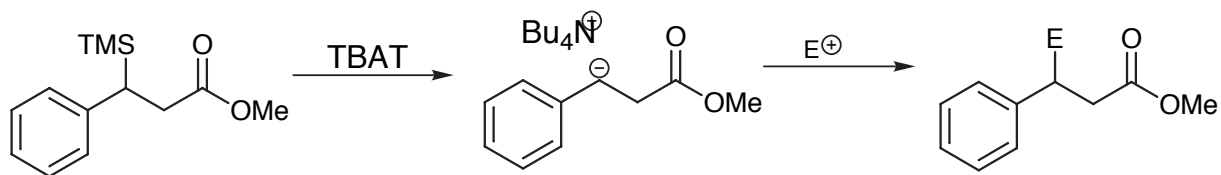


Aldehyde (R')	R	T ($^\circ\text{C}$)	de (%)	Yield
Bn	Bn	-20	≥ 99	59
BocHN	Me	-20	82	58
phenyl	Bn	-40	82	50
phenyl	Me	-40	80	44
iso-propyl	Bn	-50	76	53
n-butyl	Bn	-20	64	53

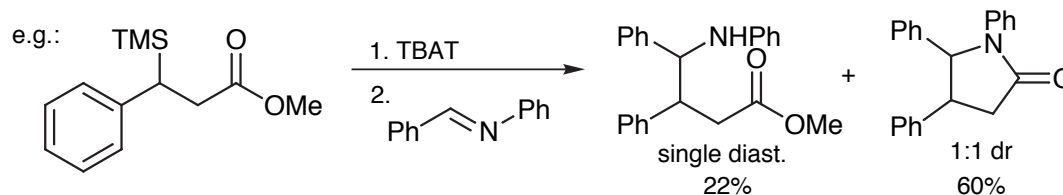
McWilliams, *J. Am. Chem. Soc.*, **1996**, 118, 11970

Reactive Homo-enolates

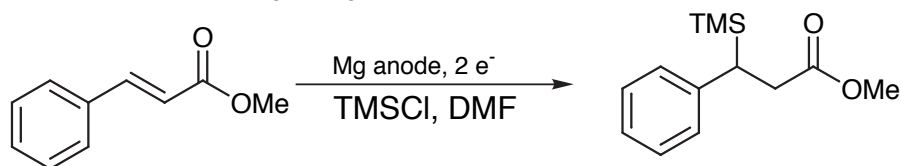
First Synthesis of a Metal-free Homo-enolate



• reactive enough to add to imines, as well as aldehydes and ketones



• substrate made easily using Nishiguchi method

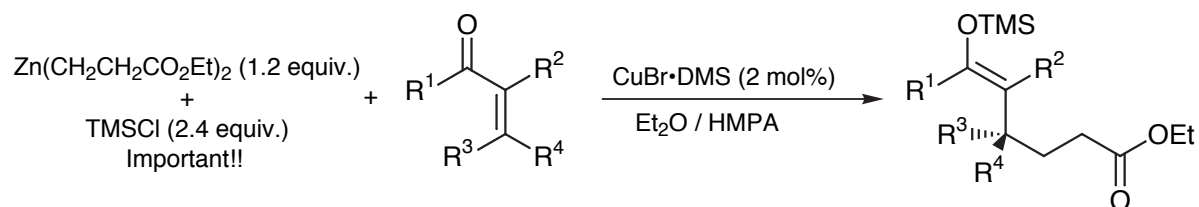


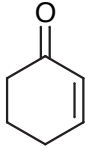
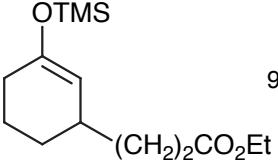
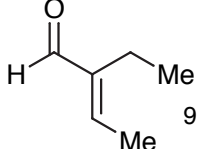
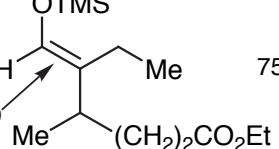
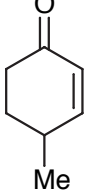
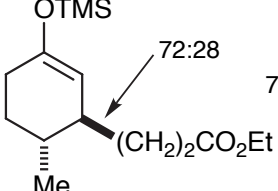
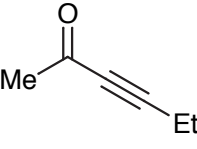
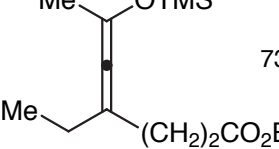
Fry, *Tetrahedron Lett.*, **1999**, 40, 7945

Nishiguchi, *Tetrahedron Lett.*, **1992**, 33, 5515

Conjugate Addition of Zinc Homoenoates

Synthesis of δ,ϵ -(silylenoether)-esters

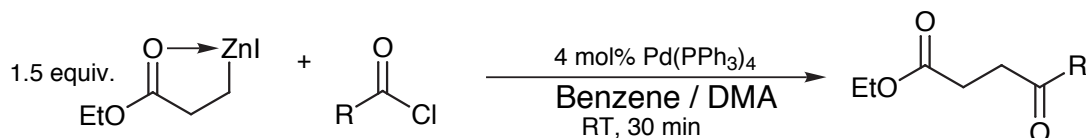


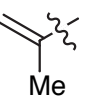
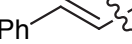
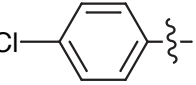
Enone	Product	Yield	Enone	Product	Yield
		93			75
		78			73

Nakamura, *J. Am. Chem. Soc.*, **1987**, 109, 8056
 Nakamura, *Org. Synth.*, **1987**, 66, 43

Acylation of Zinc Homoenoates

Synthesis of γ -ketoesters - Yoshida

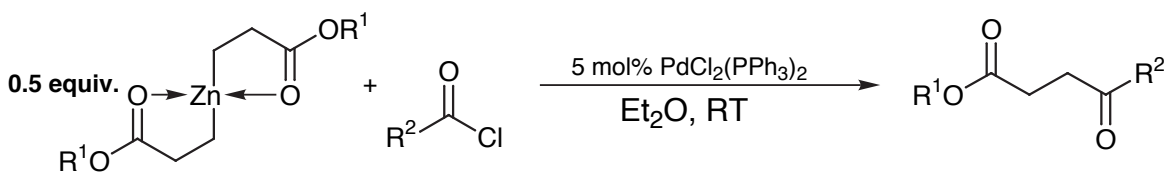


R	Yield
Ph	100
	90
	92
	100

Yoshida, *Tetrahedron Lett.*, **1985**, 26, 5559

Acylation of Zinc Homoenoates

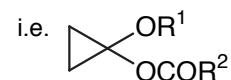
Synthesis of γ -ketoesters - Nakamura



• note: only 0.5 equiv. of Zn species needed so both homoenoates are transferred

R ¹	R ²	Yield
Et	Ph	93
iPr		81
Et		83
iPr	^t Bu	50

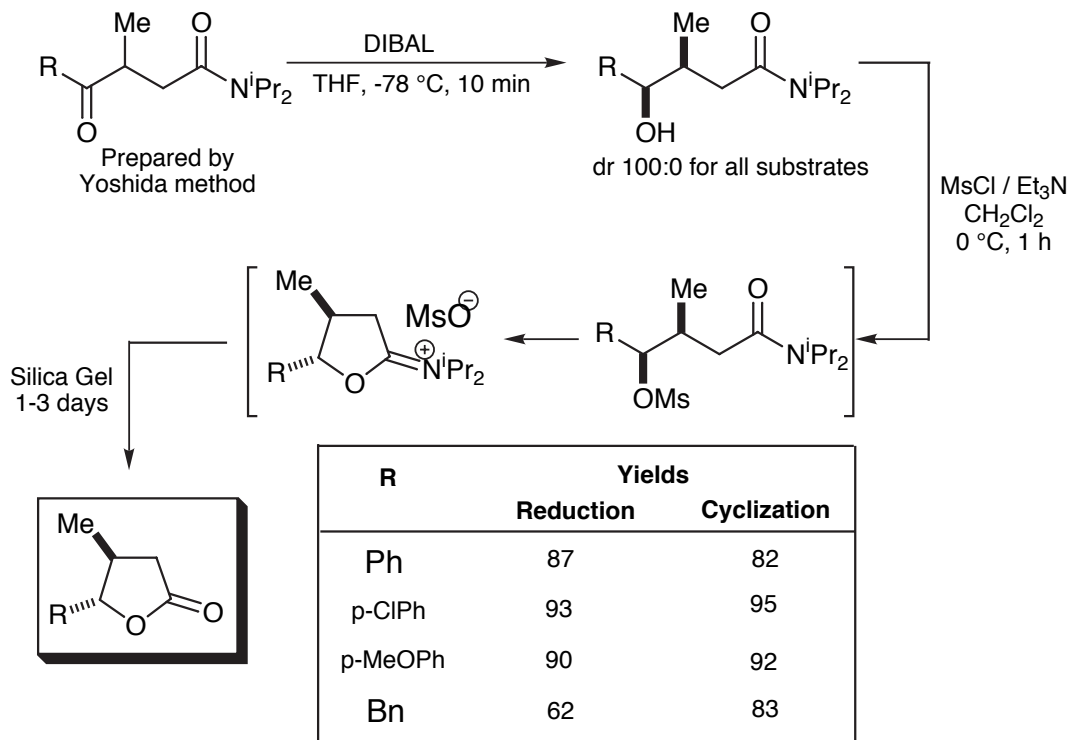
• when carried out in CDCl_3 got quantitative O-acylation (with or without Pd)



Nakamura, *J.Org.Chem.*, **1987**, 26, 8056

Application of Homoenoate Acylation

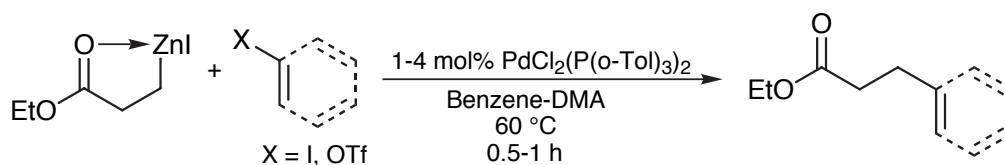
Synthesis of α,β -disubstituted γ -butyrolactones by Diastereoselective Reduction



Asaoka, *Heterocycles*, **2000**, 52, 227

Arylation and Vinylation of Zinc Homoenoates

Synthesis of β -vinyl and β -aryl esters - Yoshida



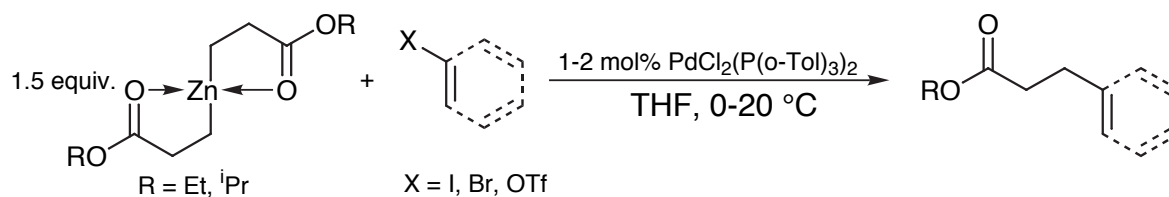
Coupling Partner	Yield
	74
	96
	67
	80

← Only vinylation example given

Yoshida, *Tetrahedron Lett.*, **1986**, 27, 955

Arylation and Vinylation of Zinc Homoenoates

Synthesis of β -vinyl and β -aryl esters - Nakamura

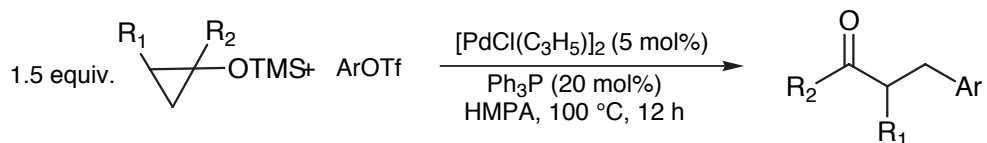


Coupling Partner	Yield
	90
	87
	0
	67
	79
	49

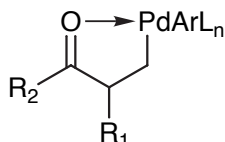
Nakamura, *J. Org. Chem.*, **1987**, 26, 8056

Arylation of Palladium Homoenolates

Catalytic Formation of β -aryl Ketones



• proposed to proceed via

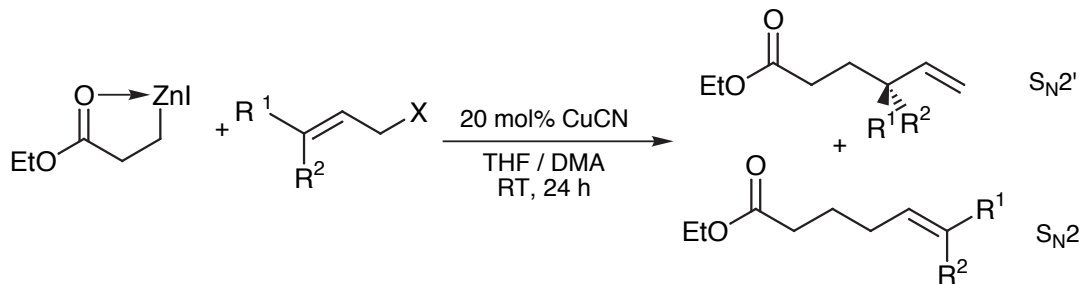


R ₁	R ₂	Ar	Yield
-CH ₂ CH ₂ CH ₂ CH ₂ -		1-naphthyl	84
-CH ₂ CH ₂ CH ₂ CH ₂ -		p-NO ₂ Ph	68
H	p-OMePh	Phenyl	65
n-Heptyl	H	1-naphthyl	58

Nakamura, *J. Am. Chem. Soc.*, **1988**, 110, 3296

Allylation of Zinc Homoenolates

Synthesis of δ,ϵ -unsaturated Esters - Yoshida

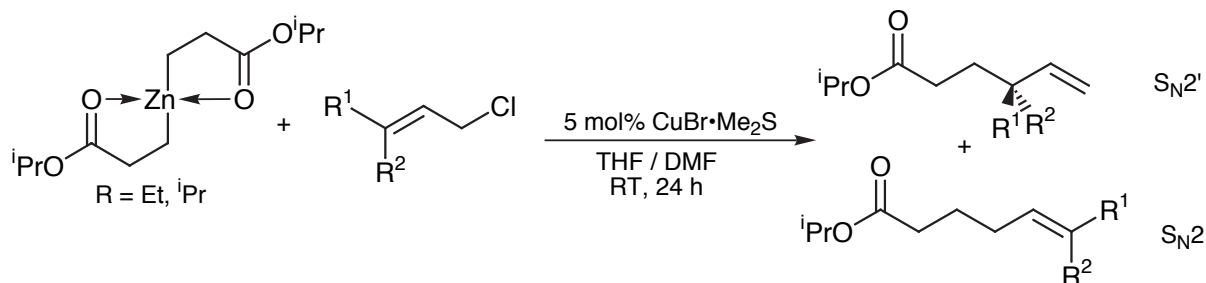


R ¹	R ²	X	Yield	S _N 2' : S _N 2
H	H	OTs	89	--
Ph	H	OTs	80	87 : 13
		Br	93	88 : 12
		Cl	99	87 : 13
CO ₂ Me	H	Br	80	100 : 0

Yoshida, *J. Org. Chem.*, **1987**, 52, 4418

Allylation of Zinc Homoenoates

Synthesis of δ,ϵ -unsaturated Esters - Nakamura



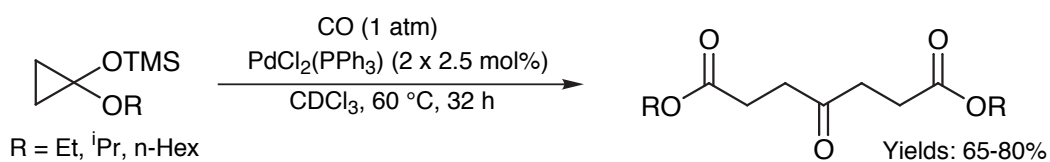
Allyl chloride	Yield	$S_N2' : S_N2$
	97	96 : 4
	65	1 : 99
	81	88 : 12
	72	100 : 0

← Catalyst changed to 5 mol% NiCl₂·dppe

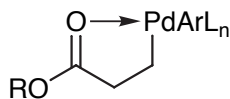
Nakamura, *J. Am. Chem. Soc.*, **1987**, 109, 8056

Carbonylative Symmetrical Coupling of Palladium Homoenoates

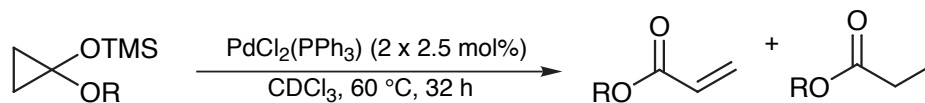
Catalytic Synthesis of 4-keto Pimelates



• proposed to proceed via



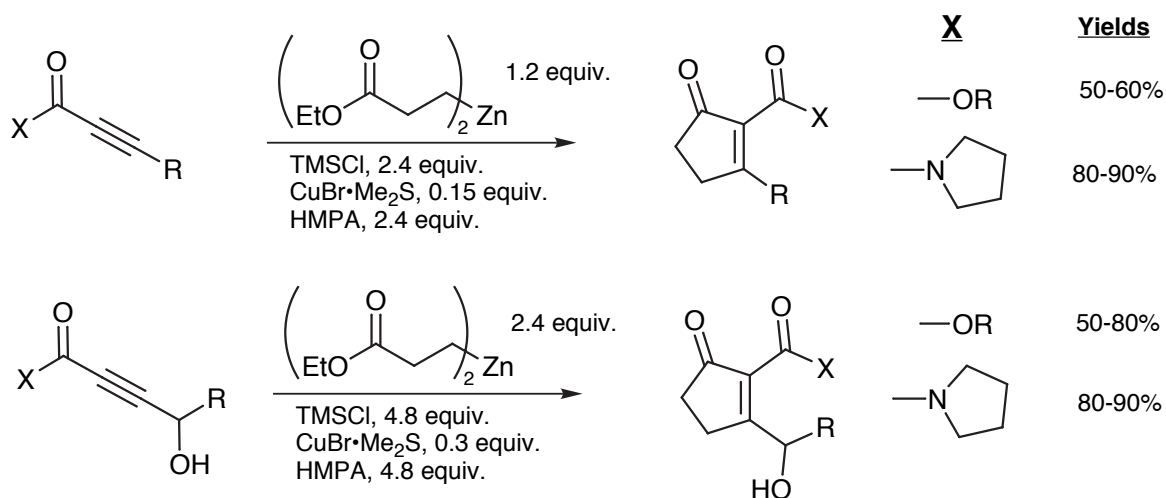
• evidence



Nakamura, *Tetrahedron Lett.*, **1988**, 29, 1541

Crimmins' Cyclopentenone Synthesis

Introduction and Generality

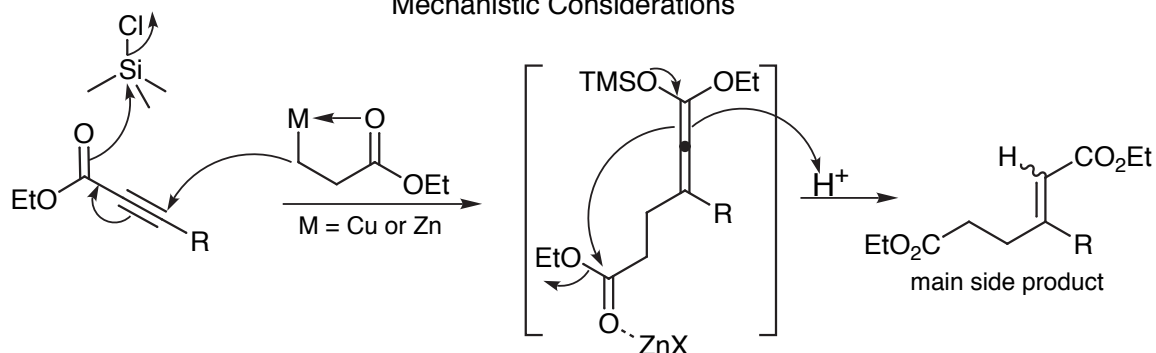


Functionality supported in R: ethers, epoxides, furans, α,β unsaturated esters

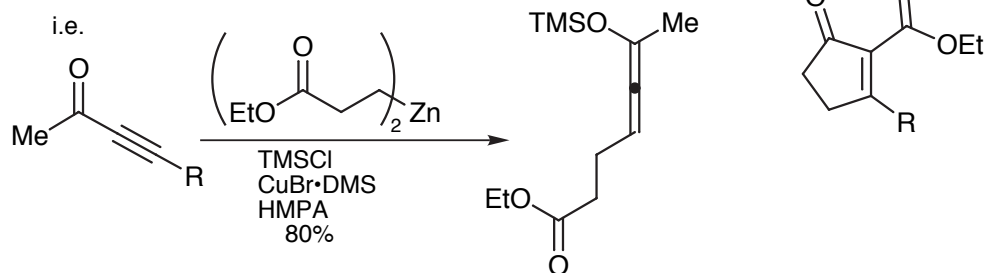
Crimmins, *J.Org.Chem.*, **1993**, *58*, 1038

Crimmins' Cyclopentenone Synthesis

Mechanistic Considerations



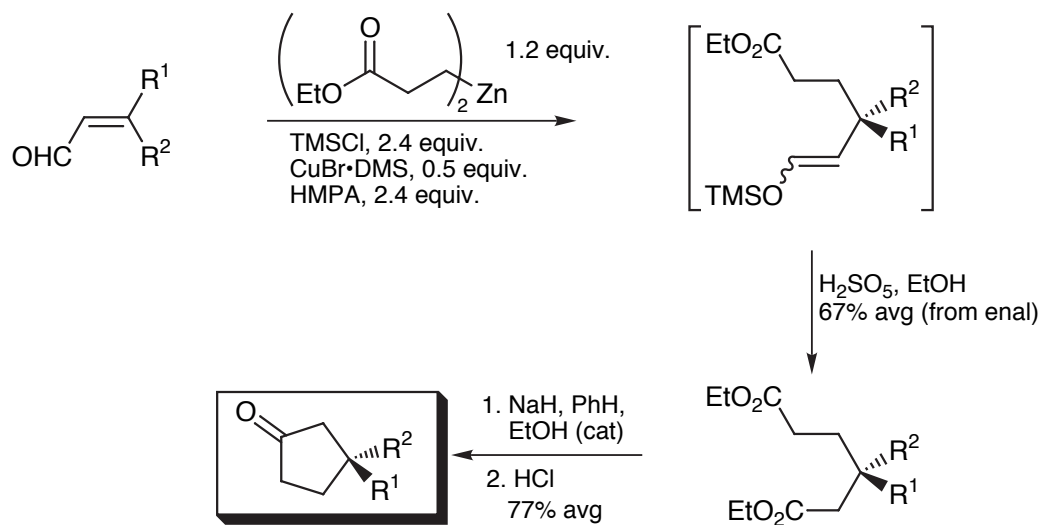
- problem: two steps have opposite electronic requirements
- appears amide and ester have right balance; ketone too electron poor to cyclize



Crimmins, *J.Org.Chem.*, **1993**, *58*, 1038

Leahy Cyclopentannulation

Synthesis of 3,3-disubstituted cyclopentanones



Substrates studied:

$\text{R}^1 = \text{R}^2 = n\text{-Bu}$

$\text{R}^1 = \text{R}^2 = \text{Ph}$

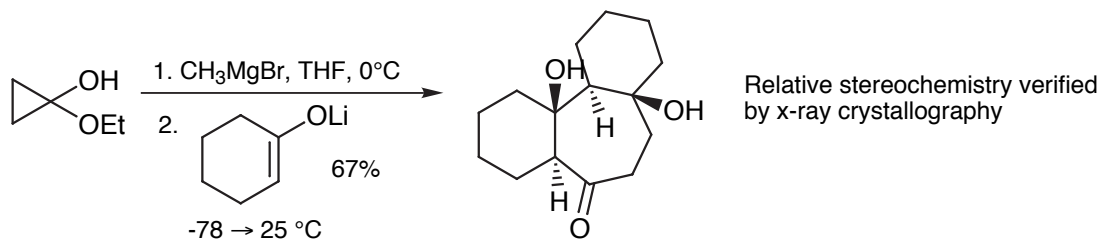
$\text{R}^1 = \text{Ph}, \text{R}^2 = \text{Me}$

$\text{R}^1 = \text{Ph}, \text{R}^2 = \text{H}$

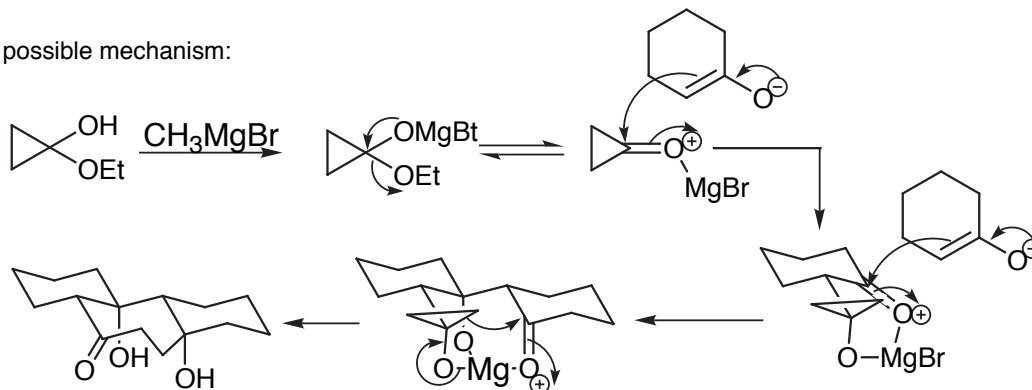
Leahy, *J.Org.Chem.*, **1994**, 59, 5496

Tandem Aldol / Aldol / Homoaldol Reaction

One-pot synthesis of a 6,7,6-tricycle



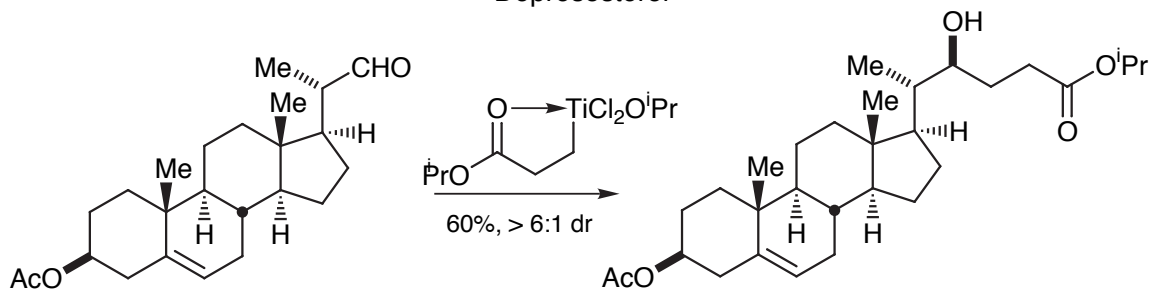
A possible mechanism:



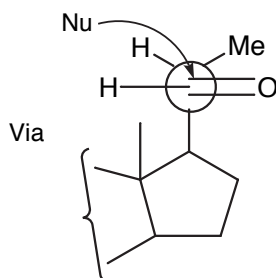
Helquist, *J.Am.Chem.Soc.*, **1986**, 108, 8313

Synthetic Examples

Depresosterol



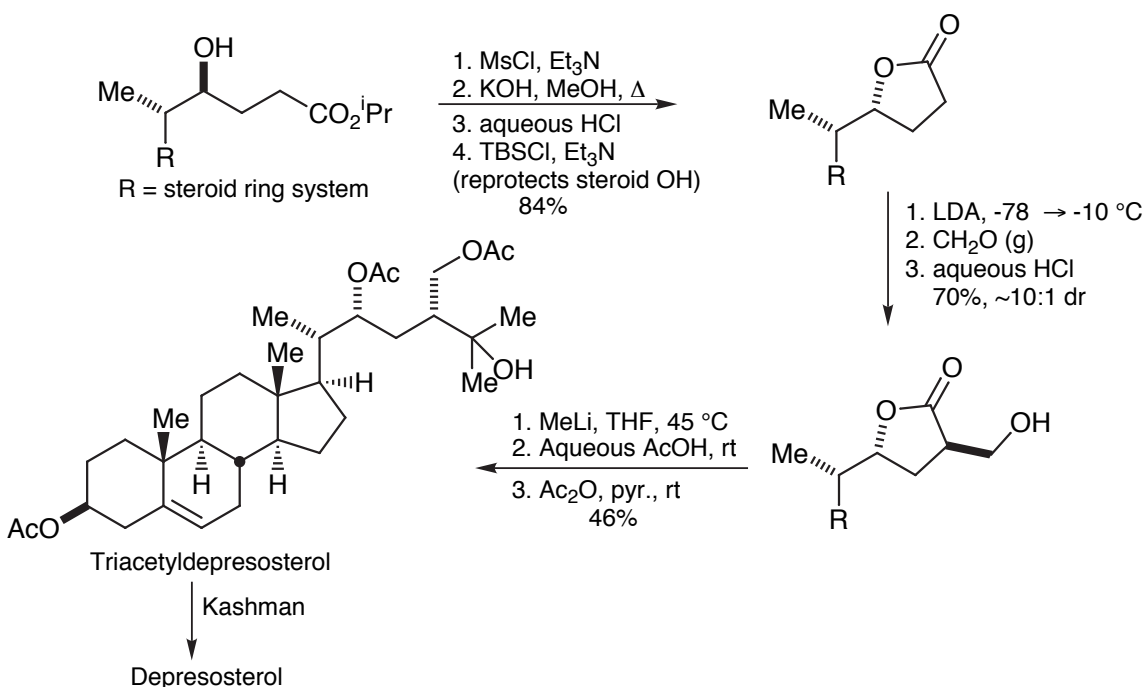
- trichlorotitanium homoenolate is not reactive enough to add to hindered aldehyde



Nakamura, *J.Am.Chem.Soc.*, **1985**, 107, 2138

Synthetic Examples

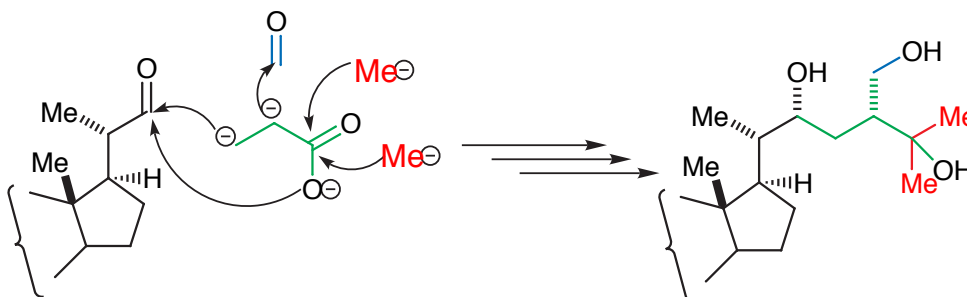
Depresosterol - completion of the formal synthesis



Nakamura, *J.Am.Chem.Soc.*, **1985**, 107, 2138
Kashman, *Tetrahedron*, **1981**, 37, 2397

Synthetic Examples

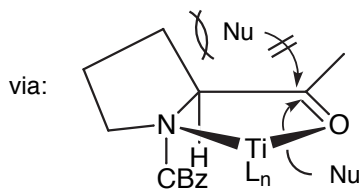
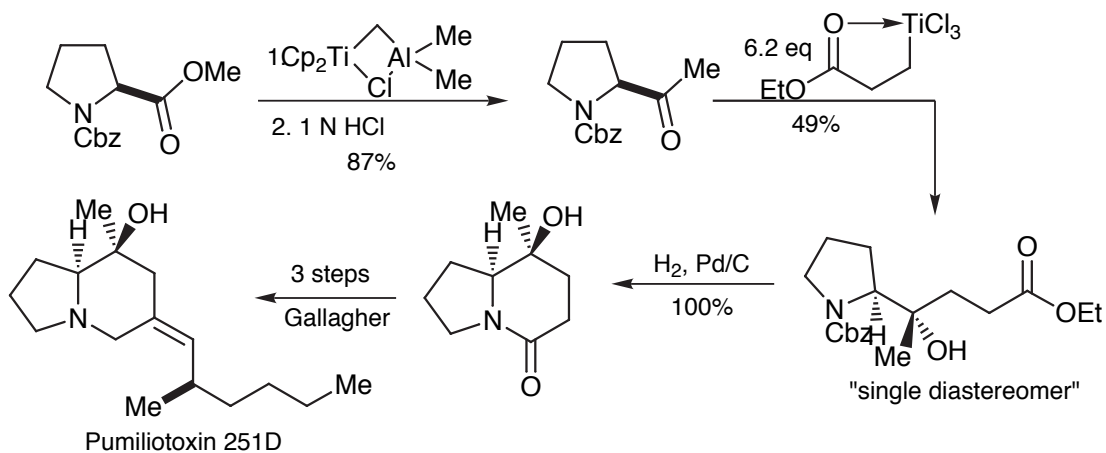
Depresosterol - Maximizing Homoenolate Functionality



Nakamura, *J.Am.Chem.Soc.*, **1985**, 107, 2138

Synthetic Examples

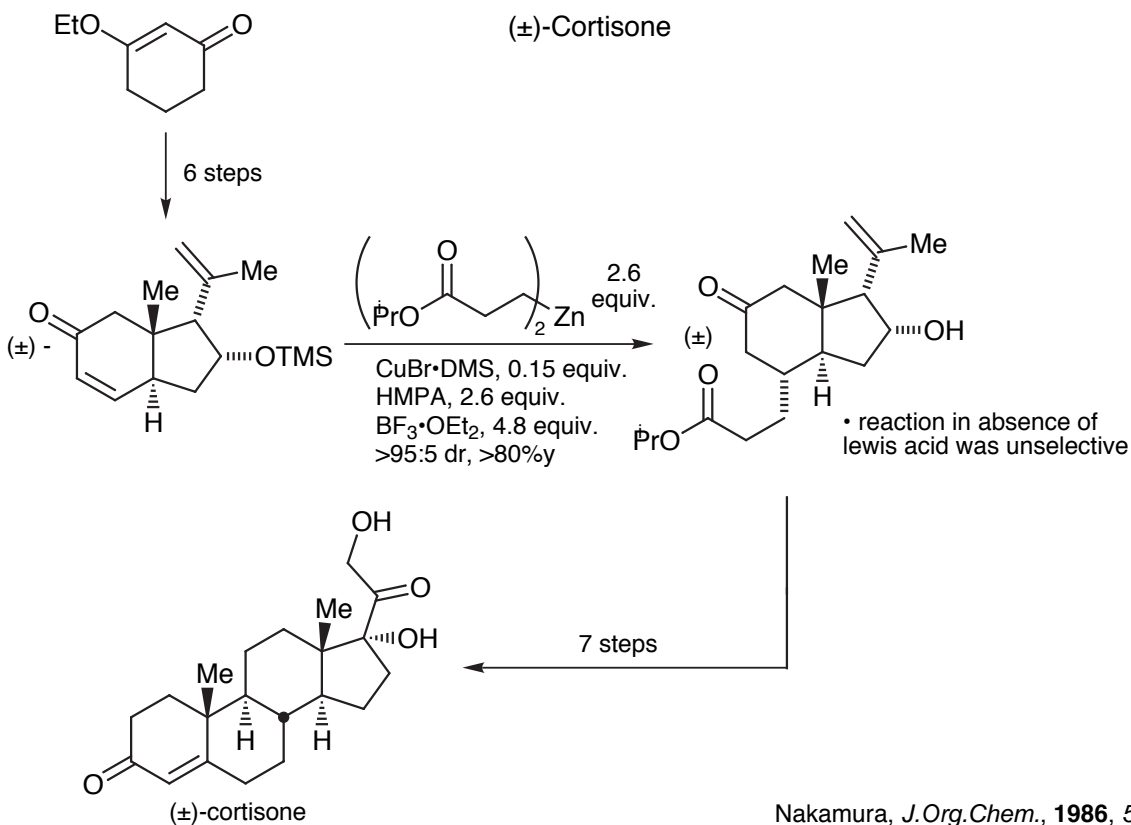
Pumiliotoxin 251D



Barrett, *J.Org.Chem.*, **1999**, 64, 1410
Gallagher, *J.Am.Chem.Soc.*, **1991**, 113, 2652

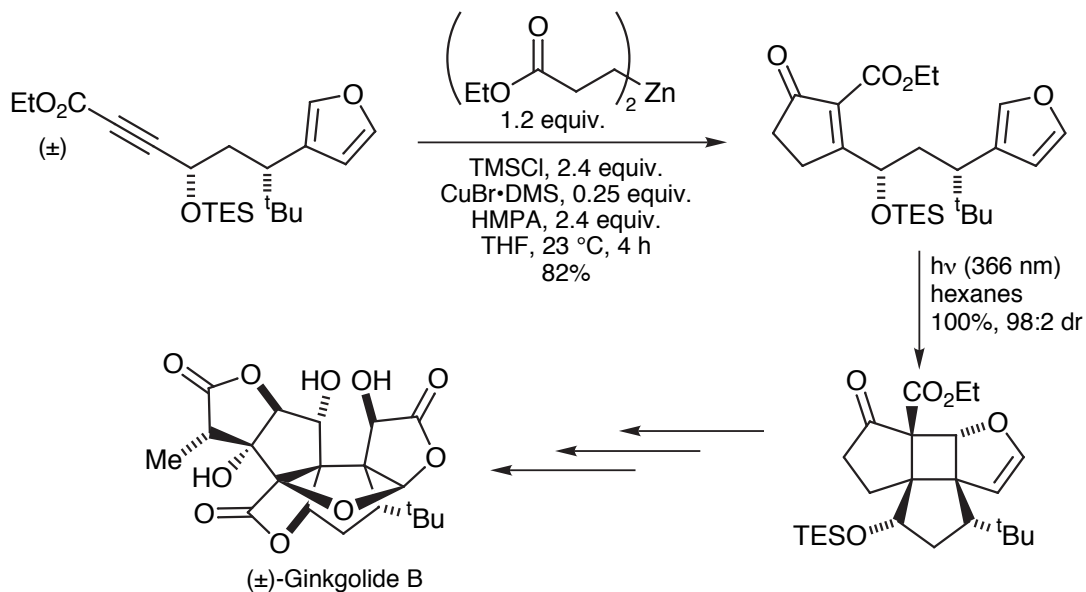
Synthetic Examples

(±)-Cortisone



Synthetic Examples

(±)-Ginkgolide B



Crimmins, *J.Am.Chem.Soc.*, **1999**, *121*, 10249

<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 .

Birladeanu, L. (2000). "The Story of the Wagner-Meerwein Rearrangement." *J. Chem. Ed.* **2000**, 77, 858. (handout)

Olah, G. A. (2001). "100 Years of Carbocations and their Significance in Chemistry." *J. Org. Chem.* **2001**, 66, 5944-5957. (handout)

Walling, C. (1983). "An Innocent Bystander Looks at the 2-Norbornyl Cation." *Acc. Chem. Res.* **1983**, 16, 448. (handout)

Laube (1995). "X-Ray Crystal Structures of Carbocations Stabilized by Bridging or Hyperconjugation." *Acc. Chem. Res.* **1995**, 28, 399 (handout)

D. A. Evans

Wednesday,
December 3, 2003

Other Relevant Background Reading

March, *Advanced Organic Chemistry*, 4th Ed. Chapter 5, pp165-174.

Lowery & Richardson, *Mech. & Theory in Org. Chem.*, 3rd Ed. pp 383-412.

Arnett, Hoeflich, Schriver in *Reactive Intermediates Vol 3*, Wiley, 1985, Chapter 5, p 189.

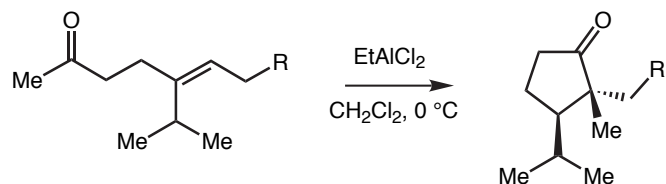
Saunders, M. and H. A. Jimenez-Vazquez (1991). "Recent studies of carbocations." *Chem. Rev.* 91: 375.

Stang, P. J. (1978). "Vinyl Triflate Chemistry: Unsaturated Cations and Carbenes." *Acc. Chem. Res.* 11: 107.

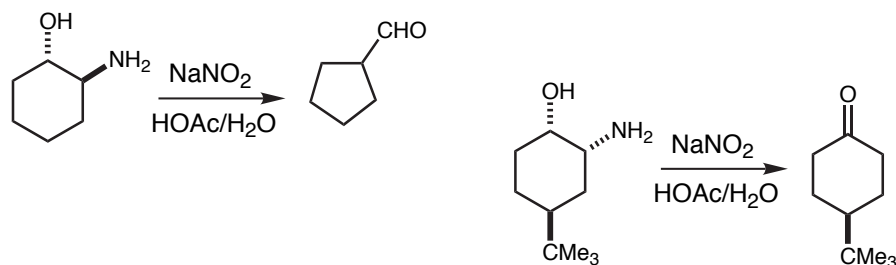
Olah, G. A. and G. Rasul (1997). "Chemistry in superacids .26. From Kekule's tetravalent methane to five-, six- and seven-coordinate protonated methanes." *Acc. Chem. Res.* 30(6): 245-250.

Olah, G. A. (1995). "My search for carbocations and their role in chemistry (Nobel lecture)." *Angew. Chem., Int. Ed. Engl.* **34**, 1393-1405

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.

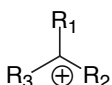


Carey & Sundberg-A, p 337: Provide mechanisms for the following reactions.

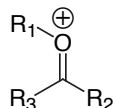
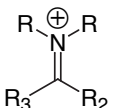


Carbocation Subclasses

Carbon-substituted

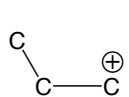
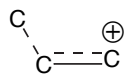
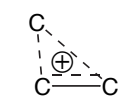
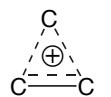
R-R₃ = alkyl or aryl

Heteroatom-stabilized

R-R₃ = alkyl or arylR-R₃ = alkyl or aryl

The following discussion will focus on carbocations unsubstituted with heteroatoms

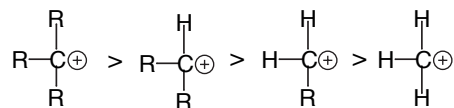
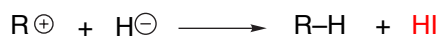
Classical vs nonclassical carbonium ions

open
trivalenthyperconjugation
no bridgingunsymmetrical
bridgingsymmetrical
bridging

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.

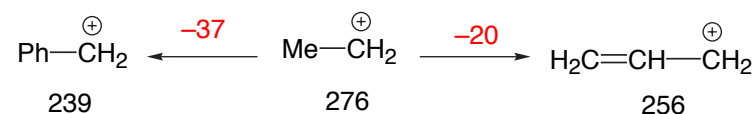
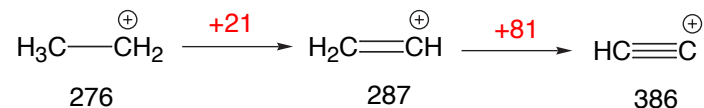
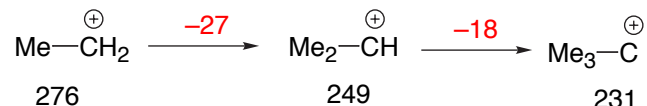
$$\text{Hydride Affinity} = -\Delta G^{\circ}$$

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.

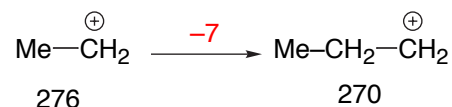
	Hydride ion affinities
CH ₃ ⁺	314
CH ₃ CH ₂ ⁺	276
(CH ₃) ₂ CH ⁺	249
(CH ₃) ₃ C ⁺	231
H ₂ C=CH ⁺	287
H-C≡C ⁺	386
PhCH ₂ ⁺	239

Carey & Sundberg—A, pp 276-

Hydride ion affinities (HI)



The effect of beta substituents: Rationalize



Hydride ion affinities versus Rates of Solvolysis

	PhCH ₂ -Br	CH=CH-CH ₂ -Br	Me ₂ CH-Br
rel rate	100	52	0.7
HI	239	256	249
Δ-HI	0	+17	+10

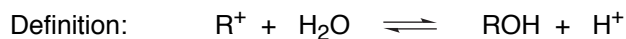
Relative Solvolysis rates in 80% EtOH, 80 °C

A. Streitwieser, *Solvolytic Displacement Reactions*, p75

Conclusion:

Gas phase stabilities do not always correlate with rates of solvolysis

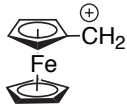
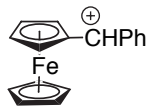
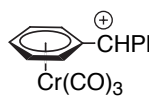
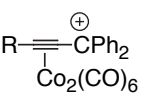
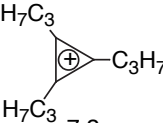

Carbocation Stability: The pK_{R^+} value



$$K_{R^+} = \frac{a_{ROH} \cdot a_{H^+}}{a_{R^+} \cdot a_{H_2O}} \quad a = \text{activity}$$

$$pK_{R^+} = -\log K_{R^+} \quad \text{Carey \& Sundberg, A, p 277}$$

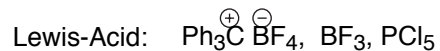
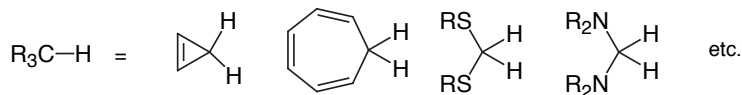
Table: pK_{R^+} values of some selected carbenium salts

$(4\text{-MeO-C}_6\text{H}_4)_3\text{C}^{\oplus}$ 0.82	$\text{Ph}_3\text{C}^{\oplus}$ -6.63	$(3\text{-Cl-C}_6\text{H}_4)_3\text{C}^{\oplus}$ -11.0	$\text{Ph}_2\text{CH}^{\oplus}$ <i>least stable</i> -13.3
 0.40	 0.75	 -10.4	 -7.4
 7.2	 4.77	<i>most stable</i>	

Carey & Sundberg, A, pp 276-

Carbocation Generation

Hydride abstraction from neutral precursors



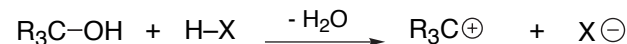
Removal of an energy-poor anion from a neutral precursor via Lewis Acids



LA: Ag, AlCl₃, SnCl₄, SbCl₅, **SbF₅**, BF₃, FeCl₃, ZnCl₂, PCl₃, PCl₅, POCl₃

X: F, Cl, Br, I, OR

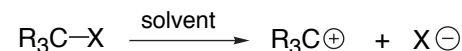
Acidic dehydration of secondary and tertiary alcohols



R: Aryl + other charge stabilizing substituents

X: SO_4^{2-} , ClO_4^- , FSO_3^- , CF_3SO_3^-

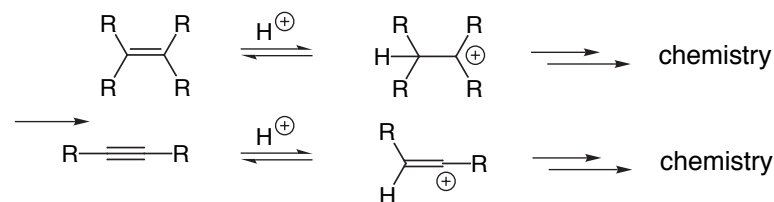
From neutral precursors via heterolytic dissociation (solvolysis) - First step in S_N1 or $E1$ reactions



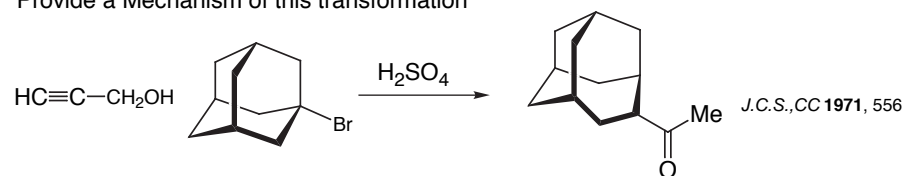
Ability of X to function as a leaving group:

$-\text{N}_2^+ > -\text{OSO}_2\text{R}' > -\text{OPO}(\text{OR}')_2 > -\text{I} \geq -\text{Br} > \text{Cl} > \text{OH}_2^+ \dots$

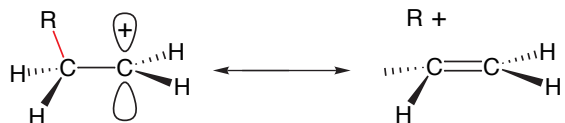
Addition of electrophiles to π -systems



Provide a Mechanism of this transformation

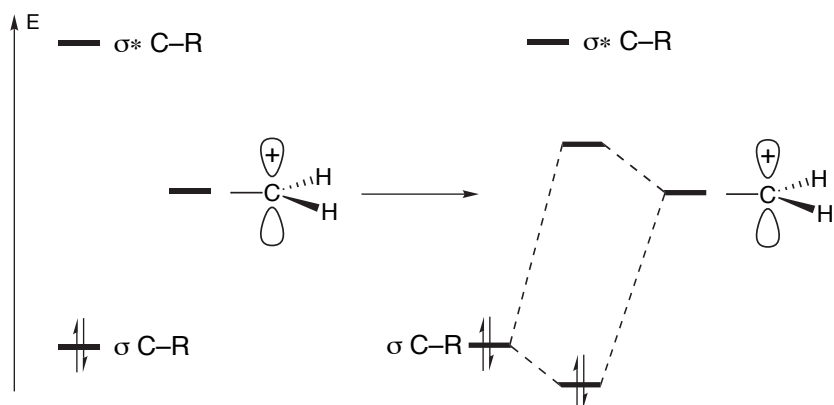


Carbocation Stabilization Through Hyperconjugation



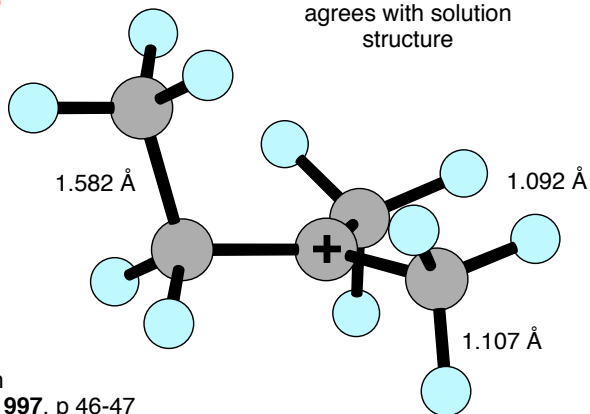
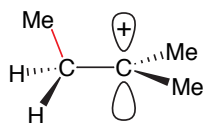
■ FMO Description

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



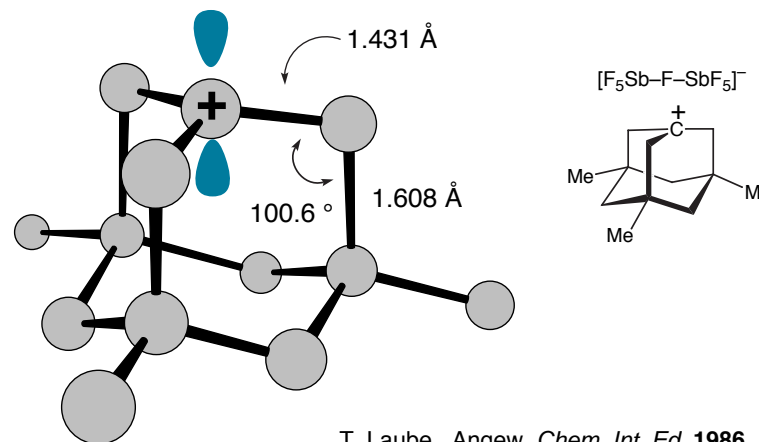
Calculated carbocation agrees with solution structure

R. P von Schleyer in *Stable Carbocation Chemistry*, 1997, p 46-47

Physical Evidence for Hyperconjugation: The Adamantyl Cation

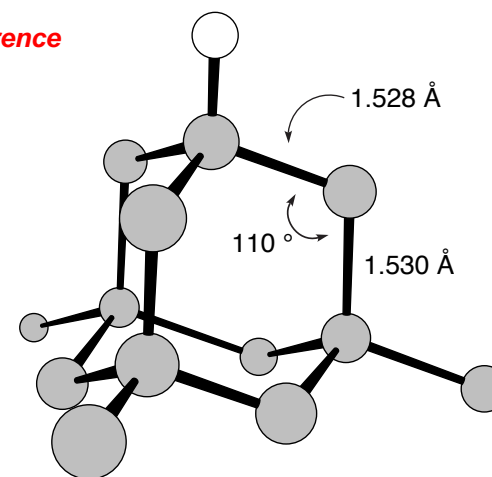
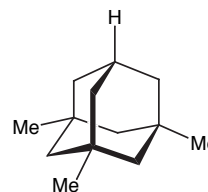
Bonds participating in the hyperconjugative interaction, e.g C-R, will be lengthened while the C(+)-C bond will be shortened.

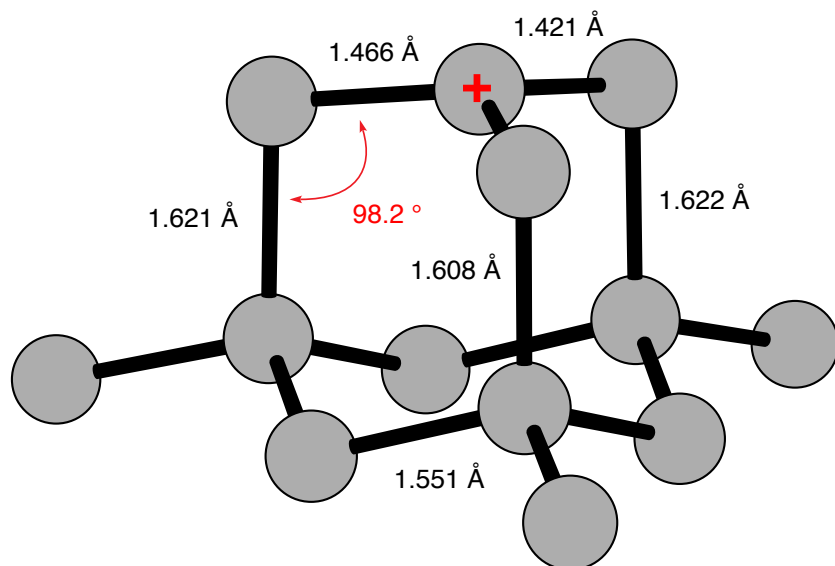
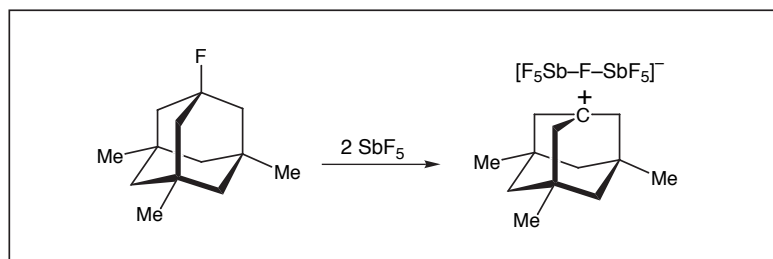
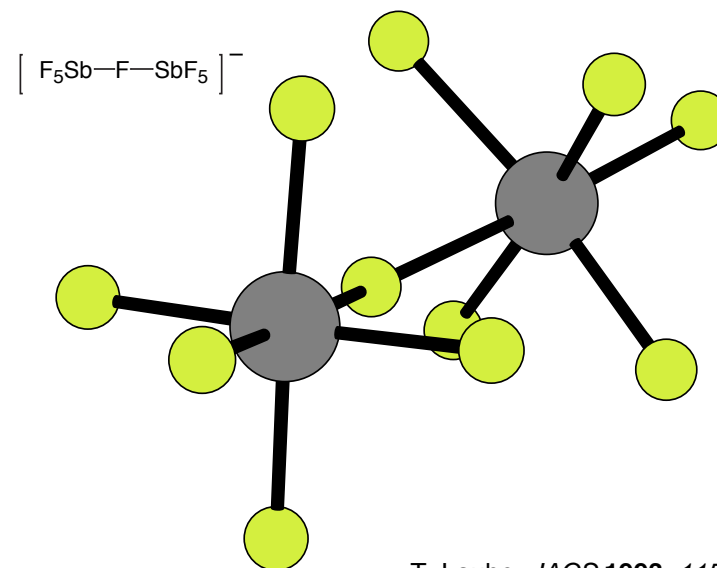
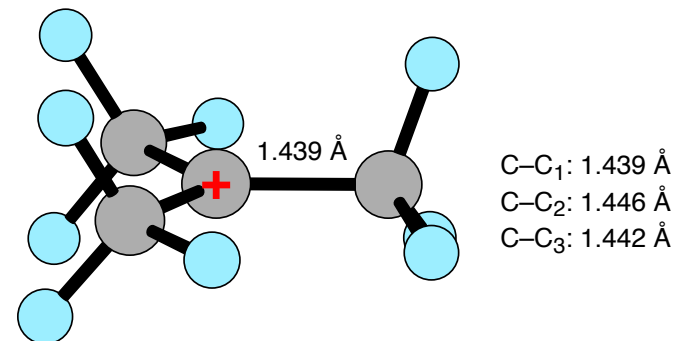
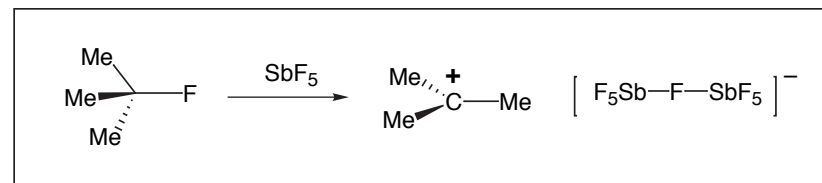
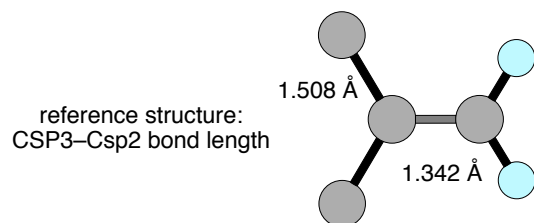
First X-ray Structure of an Aliphatic Carbocation

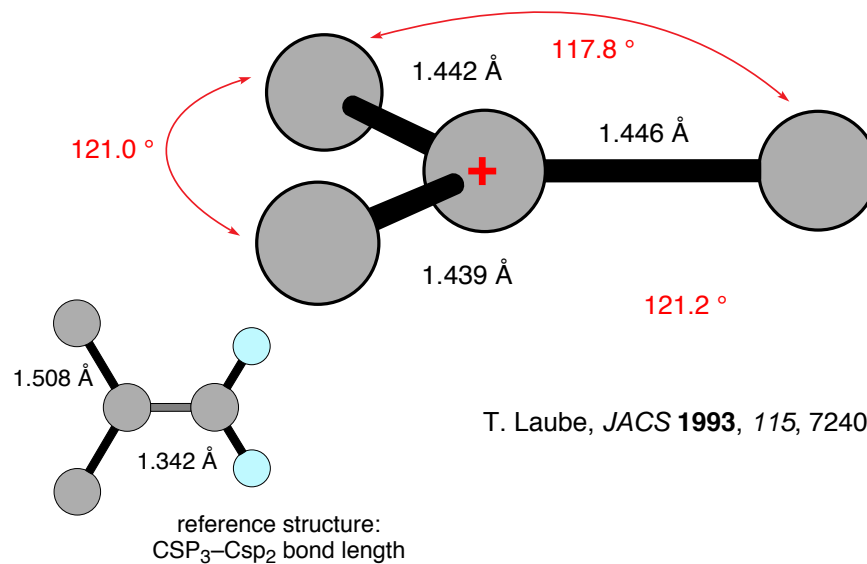
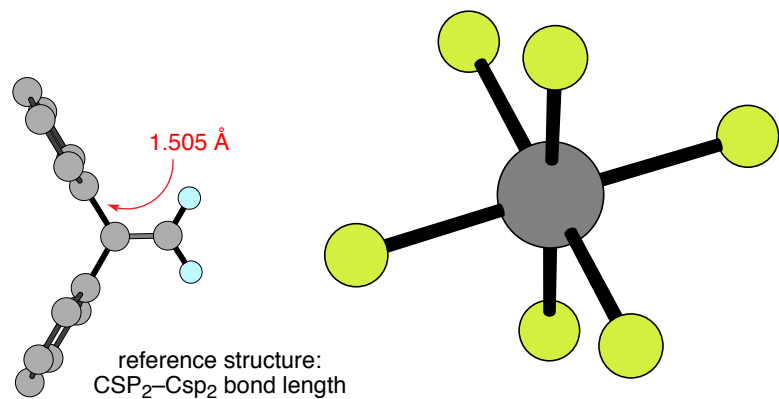
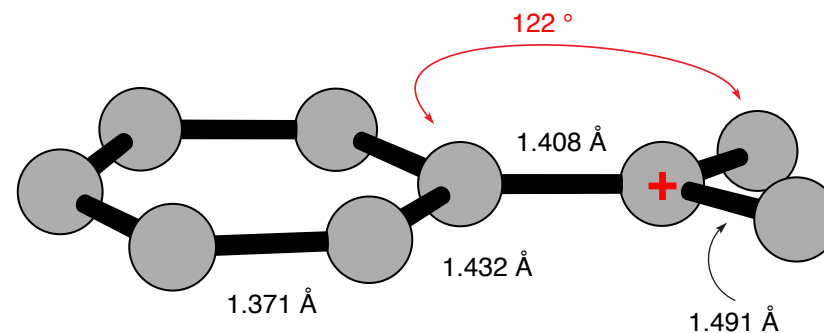
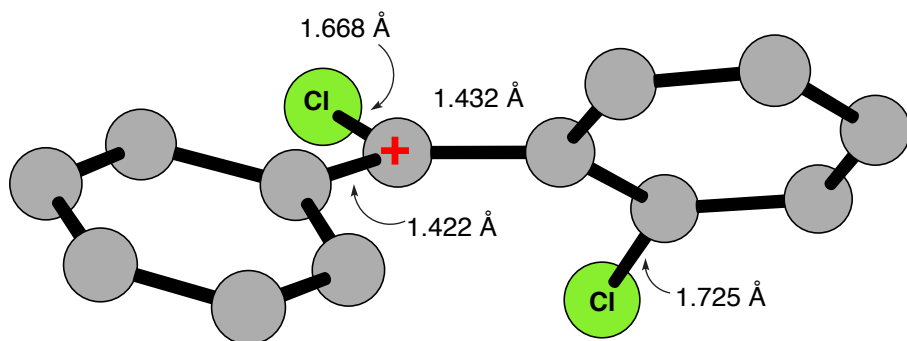
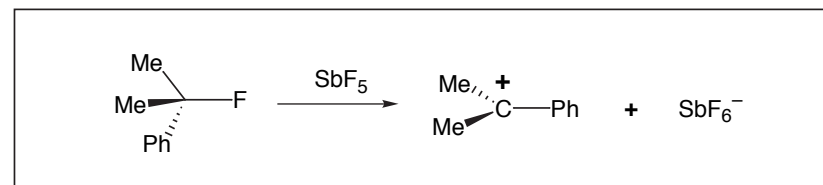
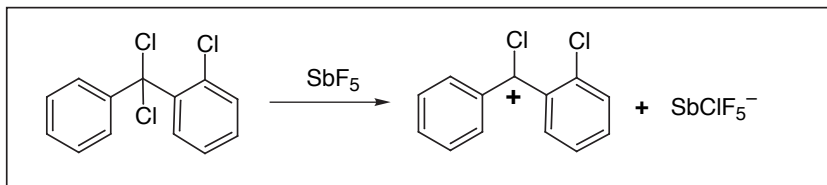


T. Laube, *Angew. Chem. Int. Ed.* **1986**, 25, 349

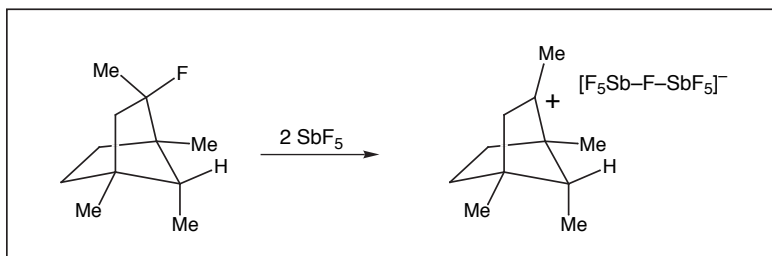
The Adamantane Reference (MM-2)



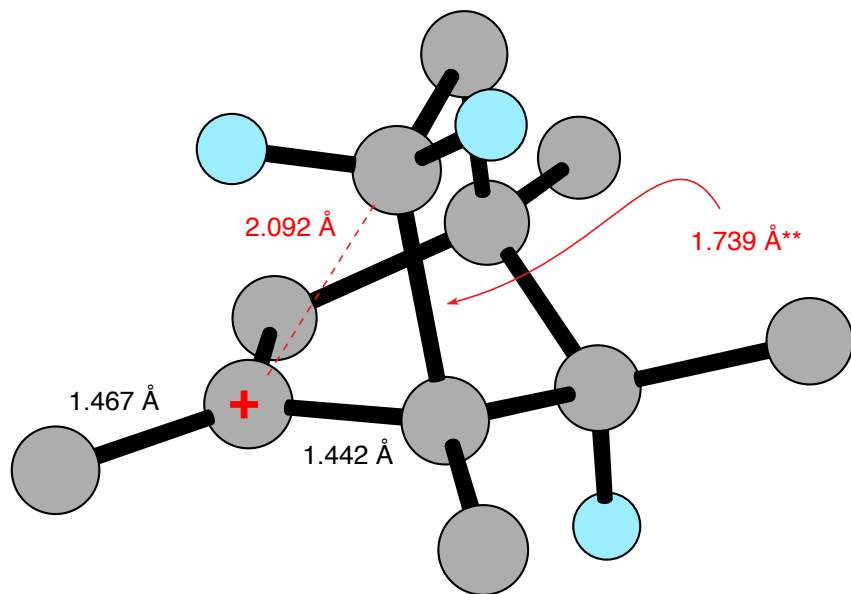
T. Laube, *Angew. Chem. Int. Ed.* **1986**, 25, 349T. Laube, *JACS* **1993**, 115, 7240



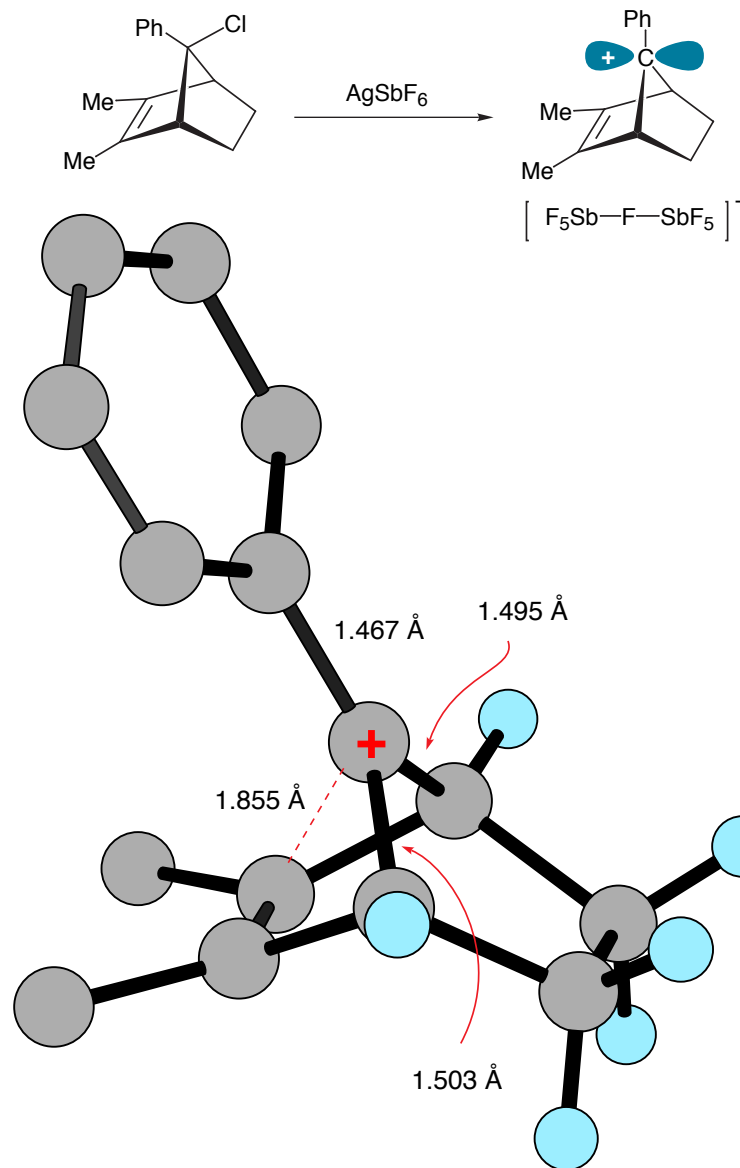
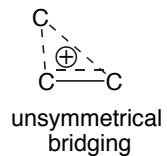
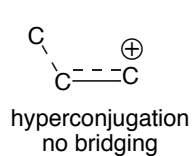
T. Laube, JACS 1993, 115, 7240



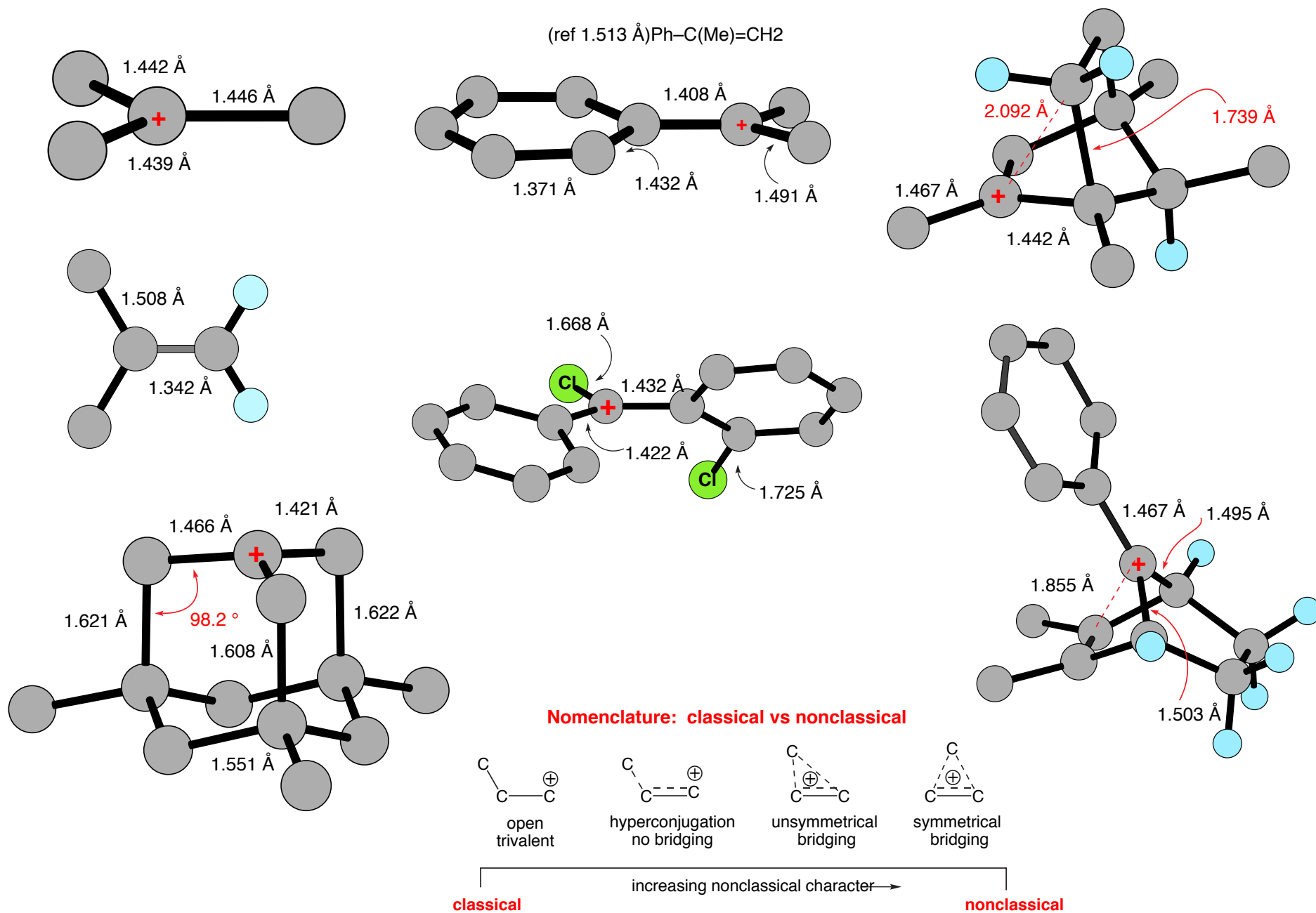
T. Laube, *Angew. Chem. Int. Ed.* **1987**, 26, 560



**One of the longest documented C–C bond lengths.

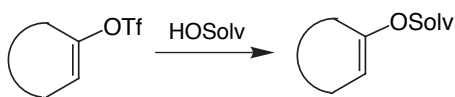


T. Laube, *JACS* **1989**, 111, 9224

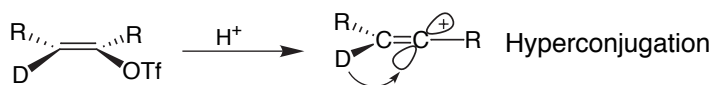


Vinyl & Phenyl Cations: Highly Unstable

Evidence suggests that vinyl cations are linear.



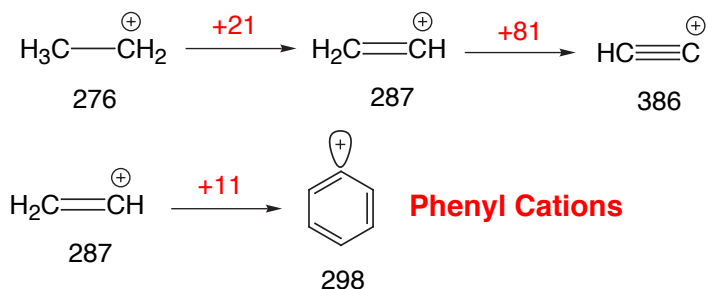
As ring size decreases, the rate of hydrolysis also diminishes. Implying that the formation of the linear vinyl cation is disfavored due to increasing ring strain.



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.

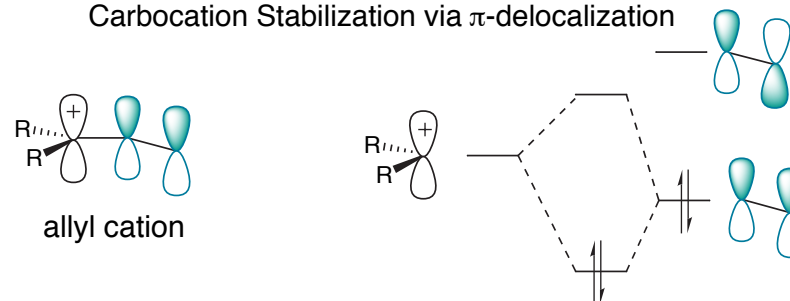
Hydride ion affinities (HI)



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.

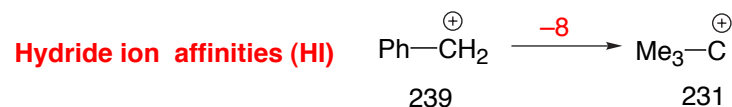
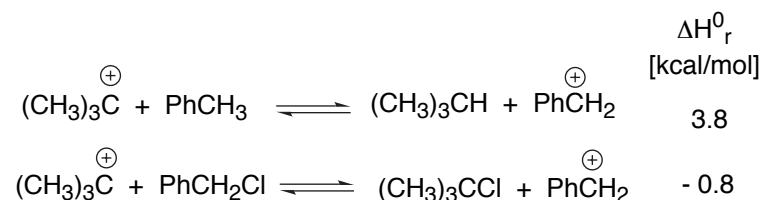
Allyl & Benzyl Carbocations

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:



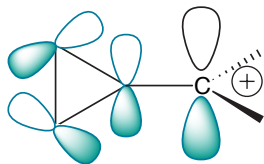
Hydride ion affinities versus Rates of Solvolysis

	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

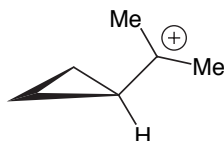
A. Streitwieser, *Solvolytic Displacement Reactions*, p75

Carbocation Stabilization via Cyclopropylgroups



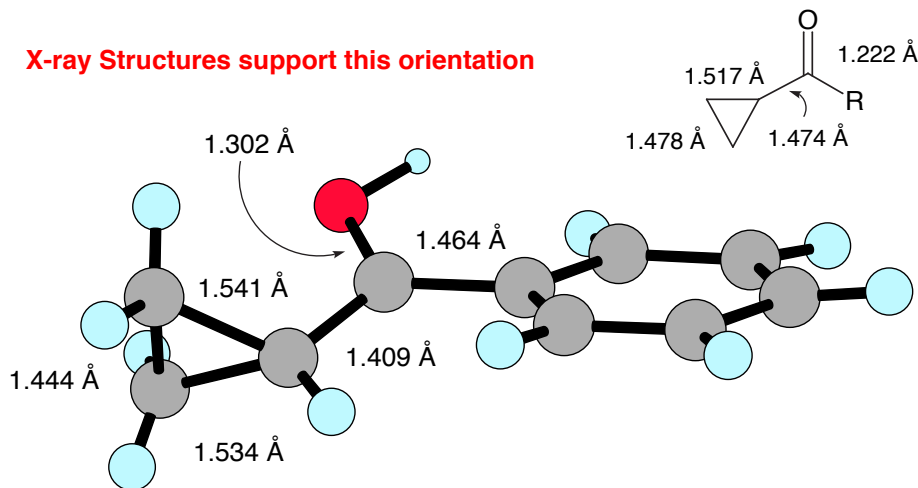
See Lecture 5, slide 5-05 for discussion of Walsh orbitals

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



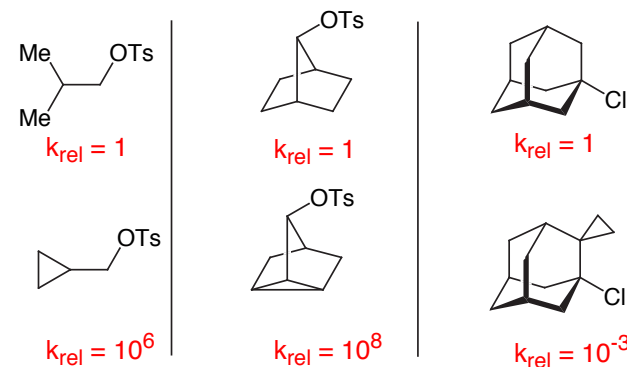
NMR in super acids
 $\delta(\text{CH}_3) = 2.6$ and 3.2 ppm

X-ray Structures support this orientation



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

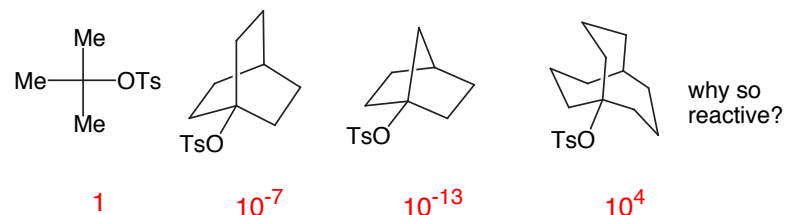
Solvolysis rates represent the extent of that cyclopropyl orbital overlap contributing to the stabilization of the carbenium ion which is involved as a reactive intermediate:



Why??

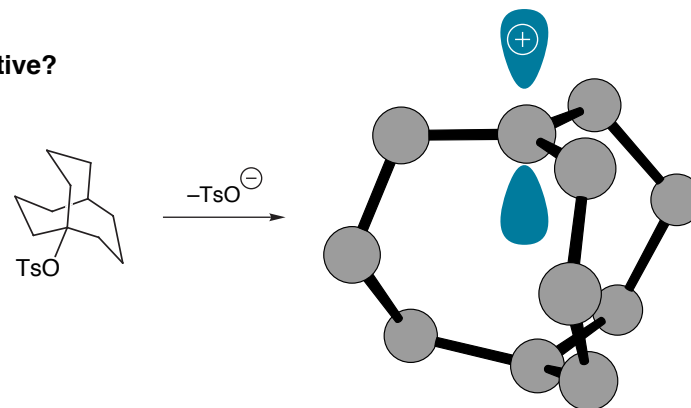
Carey-A, p 286

Bridgehead Carbocations



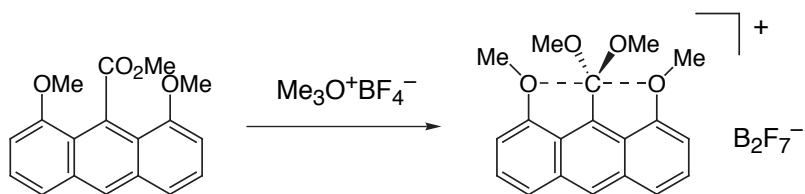
Bridgehead carbocations are highly disfavored due to a strain increase in achieving planarity. Systems with the greatest strain increase upon passing from ground state to transition state react slowest.

why so reactive?

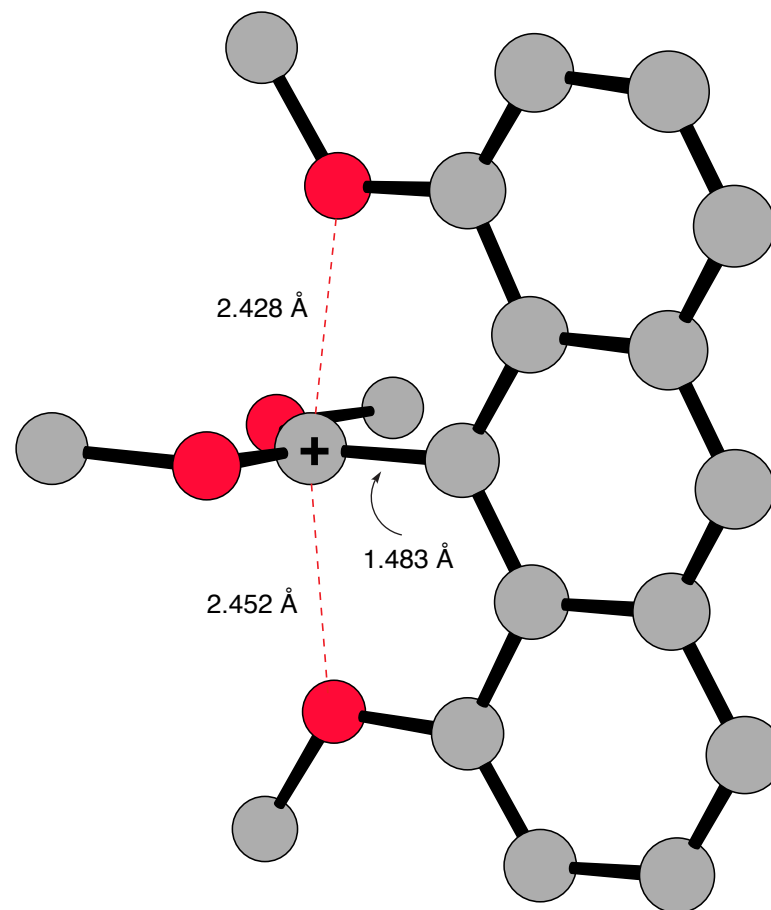
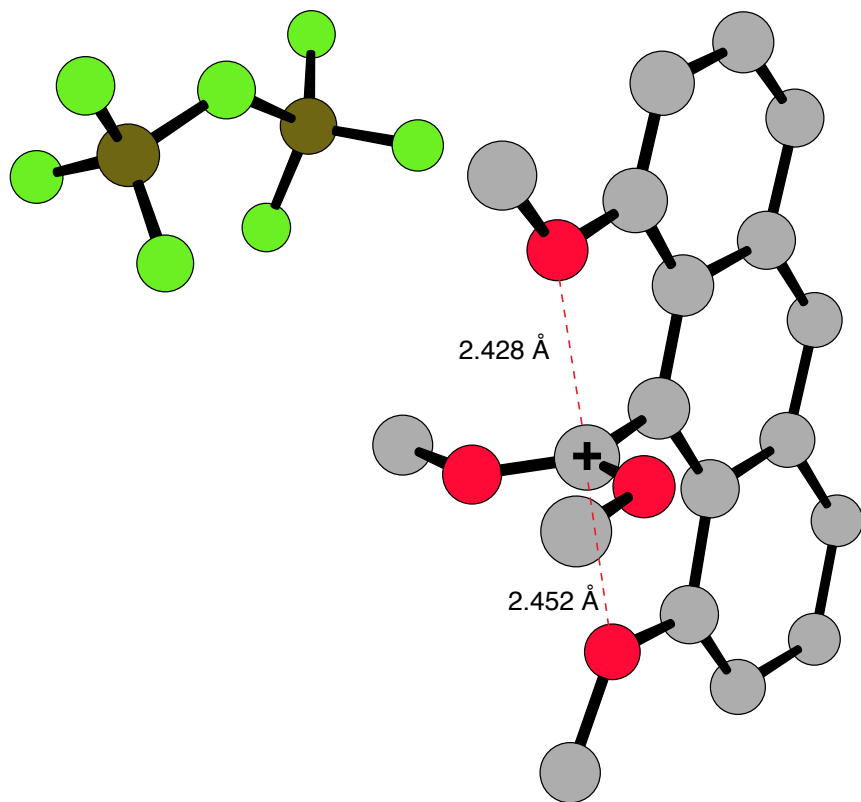


"The Synthesis and Isolation of Stable Hypervalent Carbon Compound (10-C-5) Bearing a 1,8-Dimethoxyanthracene Ligand"

Akibe, et al. *JACS* **1999**, 121, 10644-10645



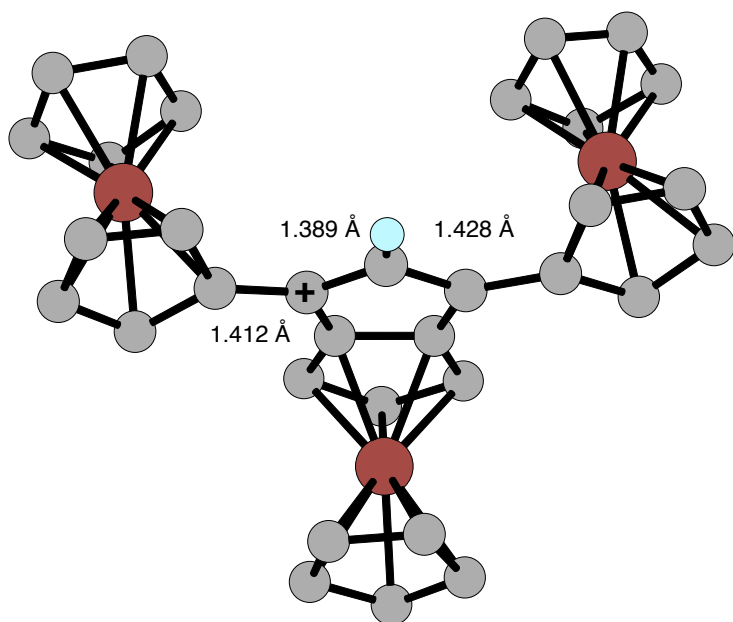
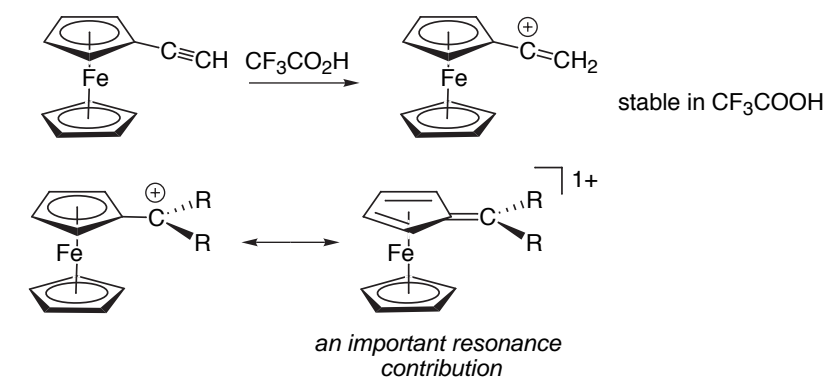
"The relevant C–O distances are longer than a covalent C–O bond (1.43 Å) but shorter than the sum of the van der Waals radii (3.25 Å)."



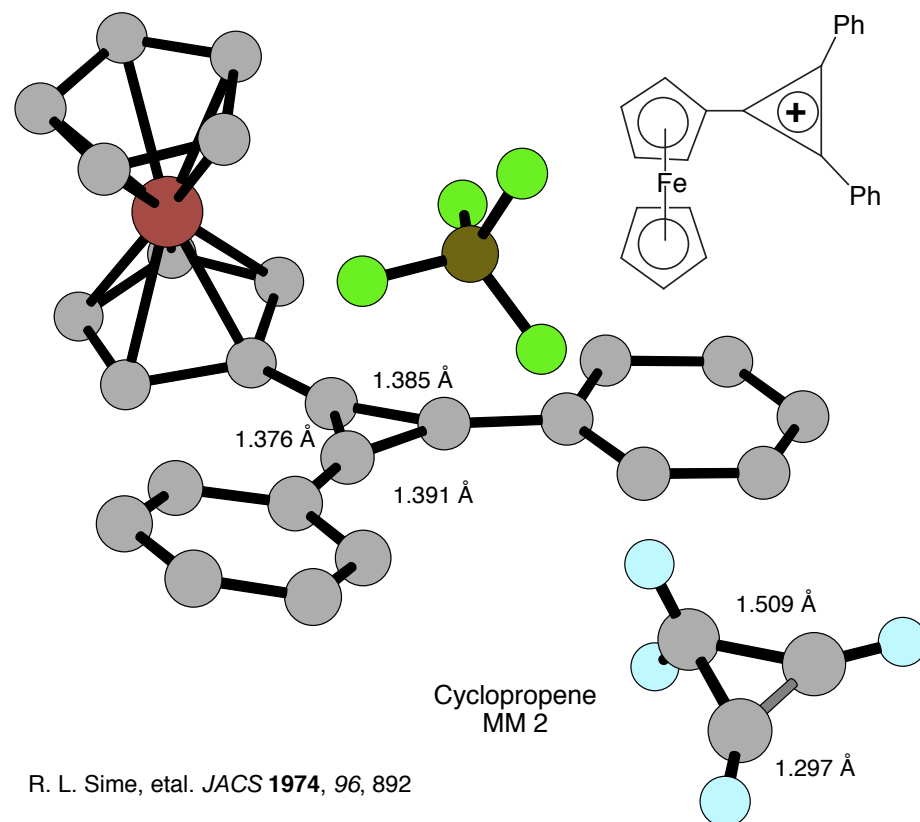
For a recent monograph on hypervalent Compounds see:
"Chemistry of Hypervalent Compounds", K. Akiba, Wiley-VGH, 1999

Carbocation Stabilization - $d(\pi)$ stabilization via Transition metal Fragments

Transition metal not bound directly to carbenium ion: Ferrocenes

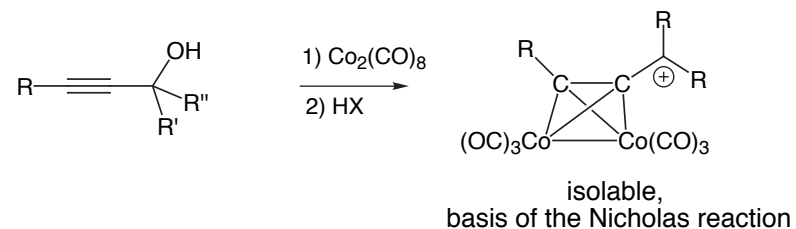


J. Lukasser, et al. *Organometallics* **1995**, *14*, 5566-5578



R. L. Sime, et al. *JACS* **1974**, *96*, 892

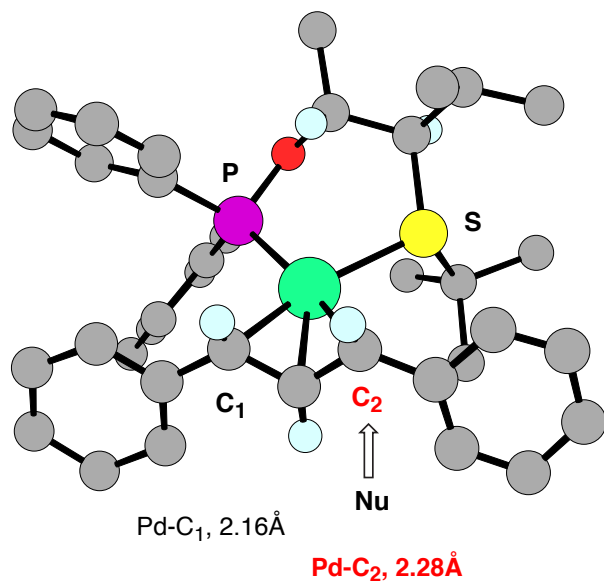
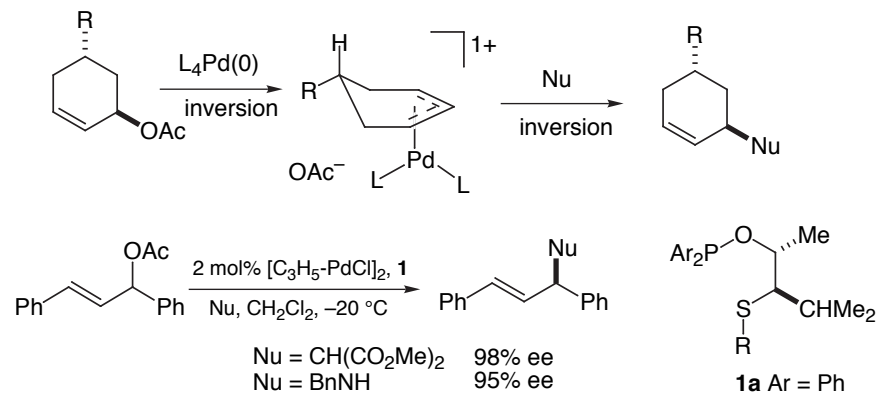
Transition metal not bound directly to carbenium ion: Cobalt-Acetylenes



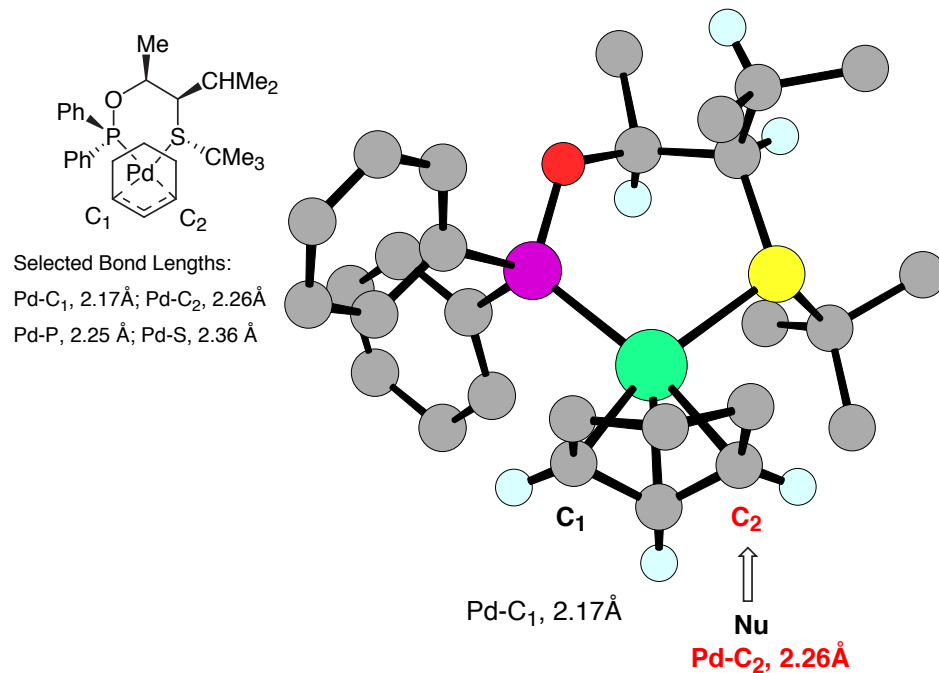
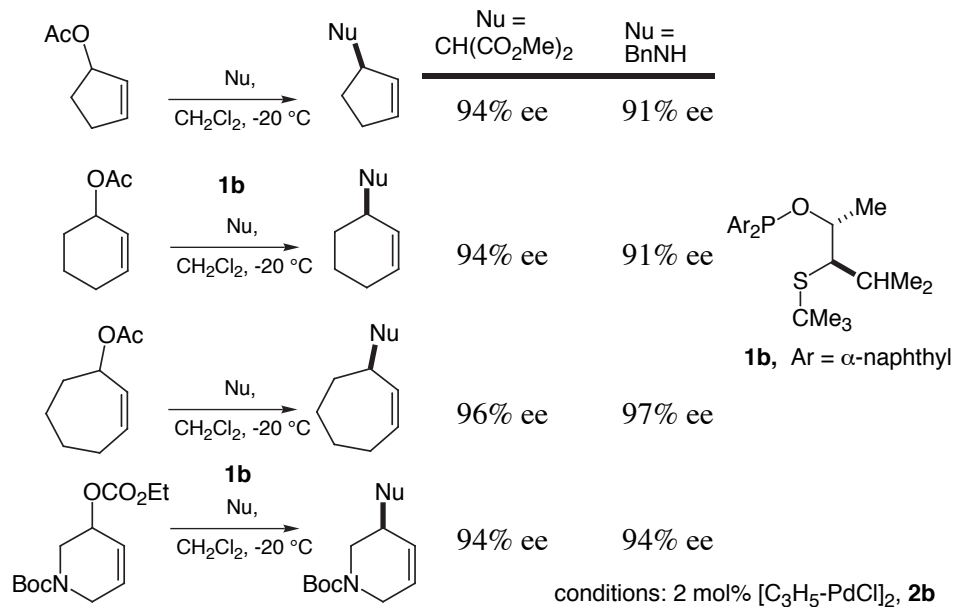
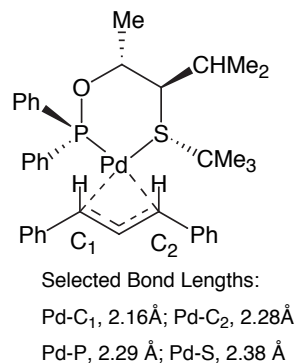
See Houk et al. *JACS* **1999**, *121*, 3596-3606

**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 32

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)

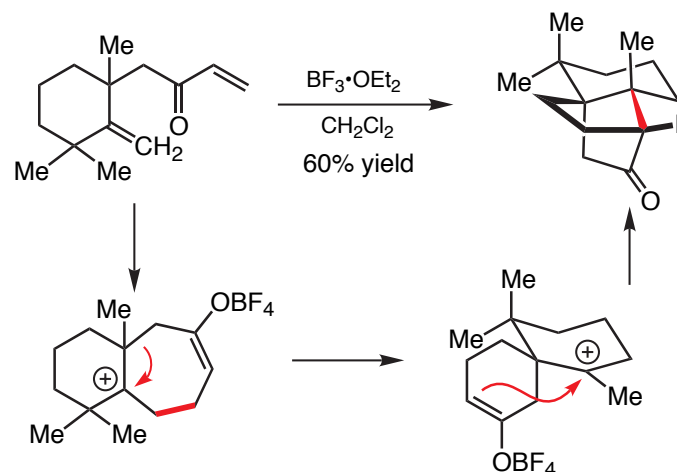
Other Relevant Background Reading

Saunders, M. and H. A. Jimenez-Vazquez (1991). "Recent studies of carbocations." *Chem. Rev.* 91: 375.

D. A. Evans

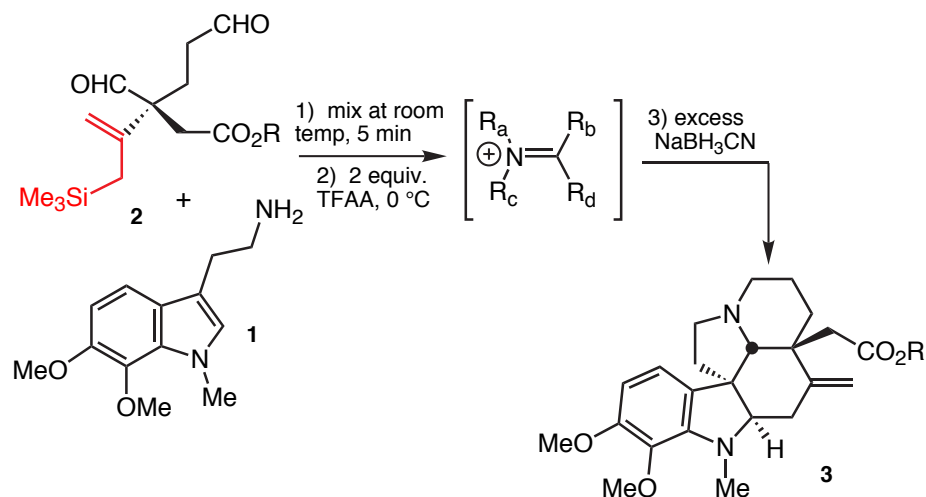
Friday,
December 5, 2003

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.

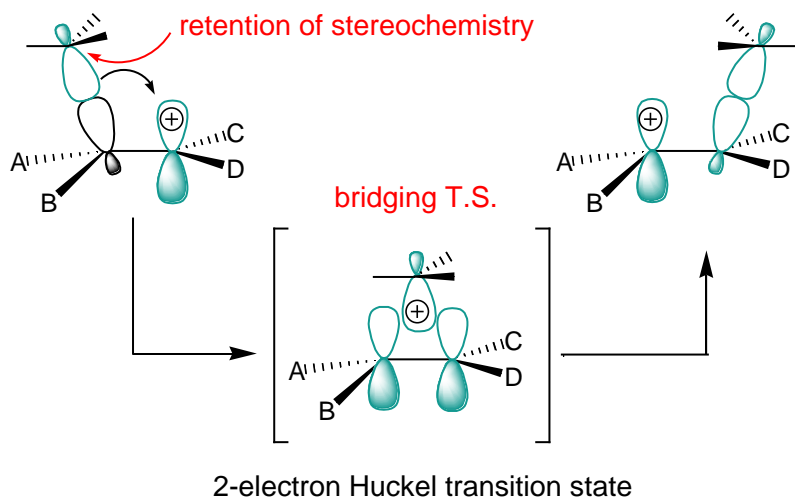


Carbocation [1,2] Sigmatropic Rearrangements

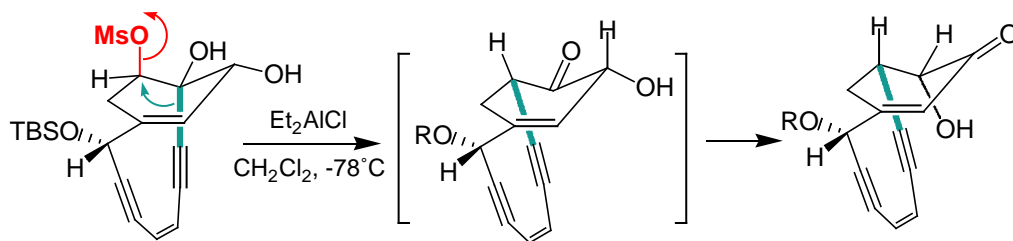
1,2 Sigmatropic shifts are the most commonly encountered cationic rearrangements. When either an **alkyl** substituent or a **hydride** is involved, the term **Wagner-Meerwein shift** is employed to identify this class of rearrangements.

Birladeanu (2000). "The Story of the Wagner-Meerwein Rearrangement." J. Chem. Ed. 77: 858. (**handout**)

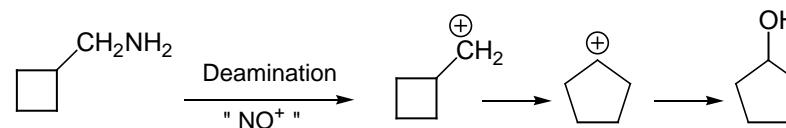
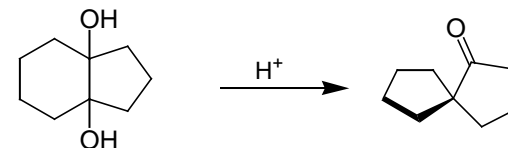
Stereoelectronic requirement for migration....



If **migration accompanies ionization**, the migration terminus will be **inverted**. Overlap between the C-C (migration origin) and the C-X^* (migration terminus) will be maximized in an **antiperiplanar** arrangement.

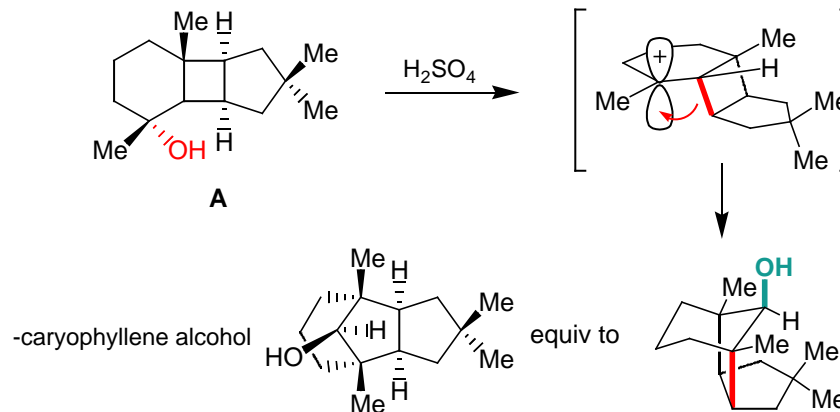


Pinacol rearrangement (vicinal diol): Driving force is the gen. of C=O

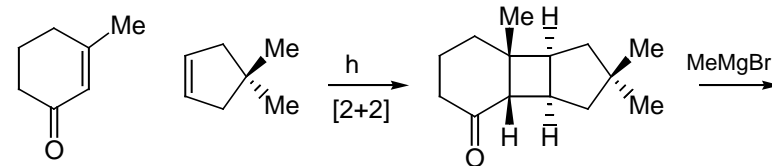


Demjanov-rearrangement (Driving force: relief of ring strain)

Wagner-Meerwein Rearrangements: Application in Total Synthesis



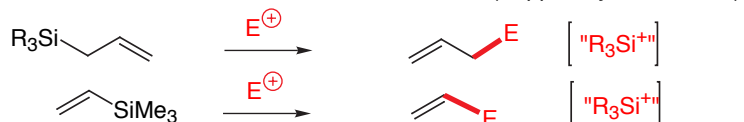
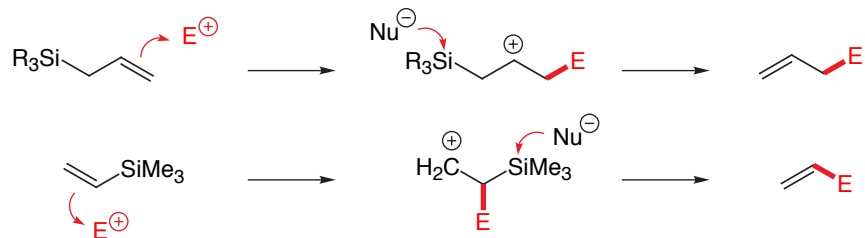
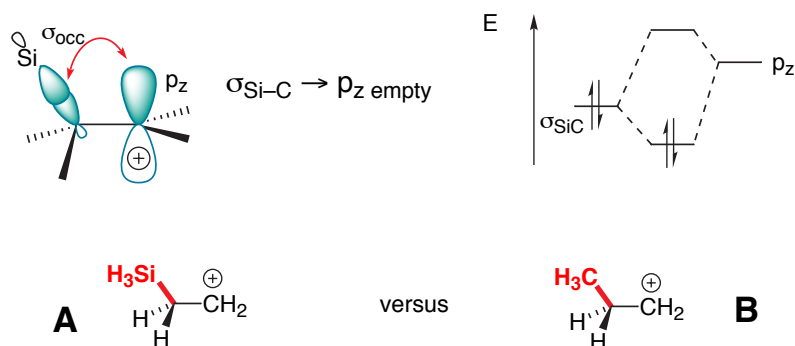
Preparation of A:



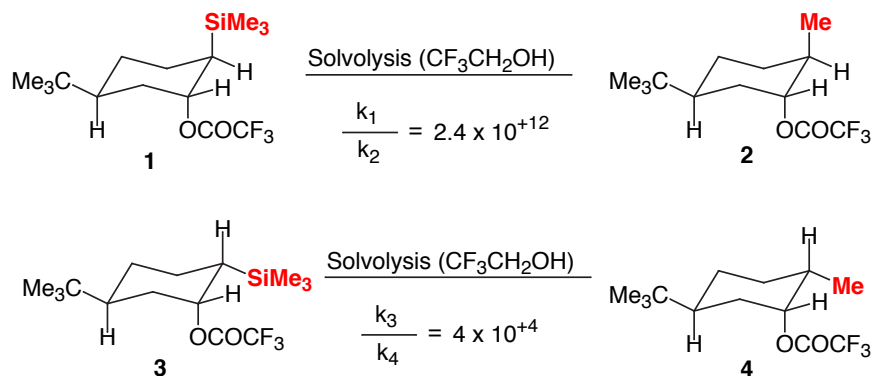
References:

Lambert *Acc. Chem. Res.* **1999**, *32*, 183-190Lambert, *JACS* **1990**, *112*, 8120; **1996**, *118*, 7867.Fleming, *Organic Reactions* **1989**, *37*, 54.Fleming, *Chem. Rev.*, **1997**, 2063.

Allyl- & Vinylsilanes react with electrophiles

Mechanism - the simple picture: β -Silicon stabilizes carbocationFleming, *Organic Reactions* **1989**, *37*, 54. β -Silicon Effect: the origin of regioselectivity

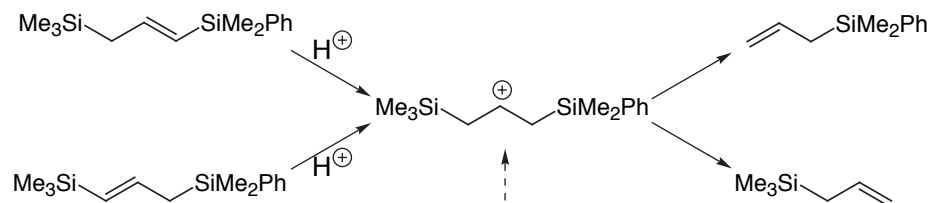
Calculation: A more stable than B by 38 kcal/mol.

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:

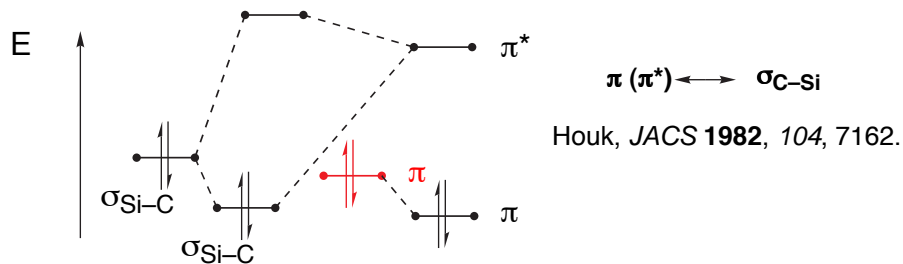
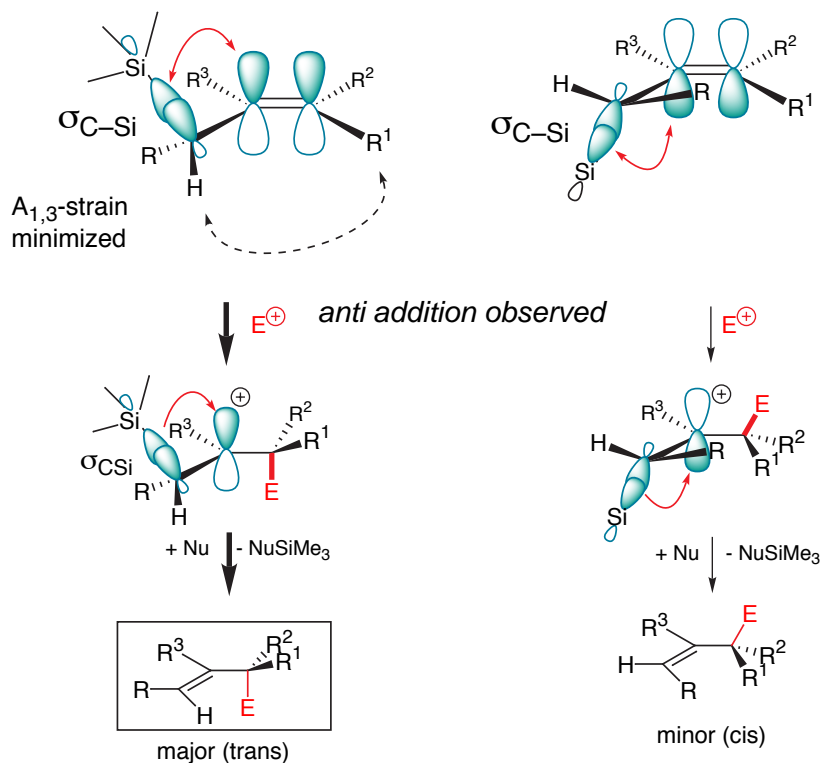


both silanes

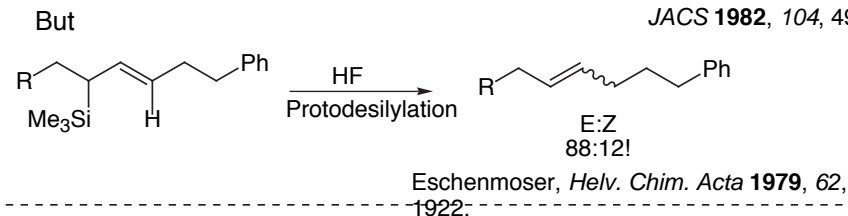
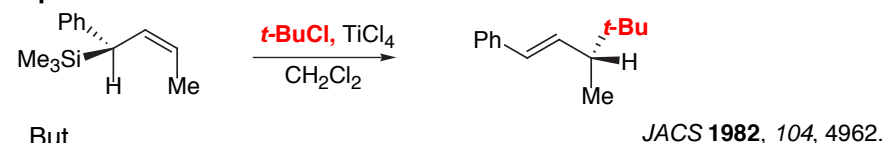
yield the same product mixture. Hence, the reaction proceeds most likely via a common intermediate, a carbenium ion

General: Allylsilanes are more nucleophilic than alkenes

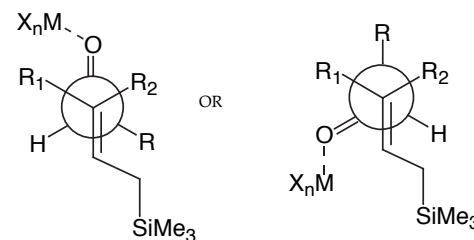
⇒ HOMO is higher in energy due to **negative hyperconjugation**

**Electrophile Addition - Stereoelectronics****The stereochemical consequences for the major product are:**

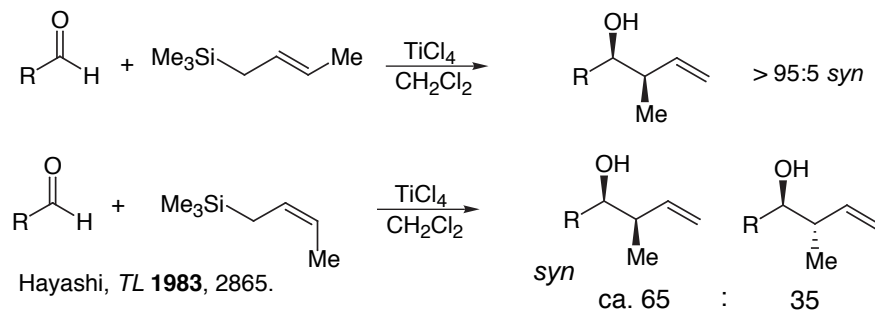
- trans-alkene:
- anti-addition of E^+ with respect to SiR₃

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

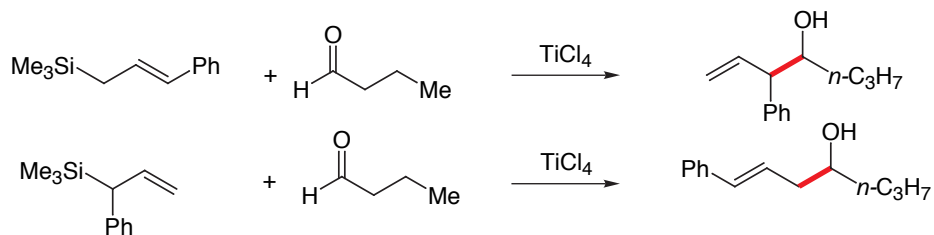
Antiperiplanar TS

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.



Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones, Denmark and Jiping Fu, *Chem. Rev.* 2003, 103, 2763-2793 (**handout**)

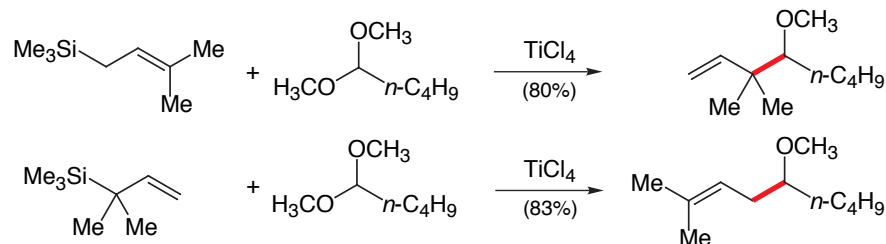
Allylsilanes add to aldehydes and acetals under Lewis acid promotion



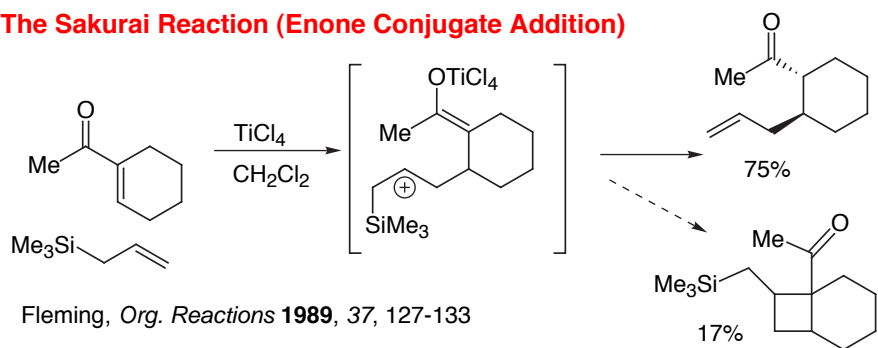
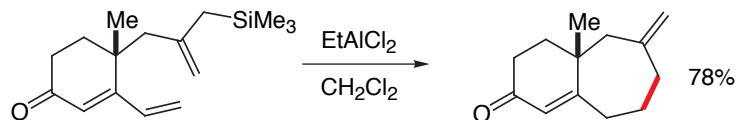
regioselectivity: Allyl inversion

Felkin Selectivity also holds with this class of nucleophiles

Acetals can be used as well

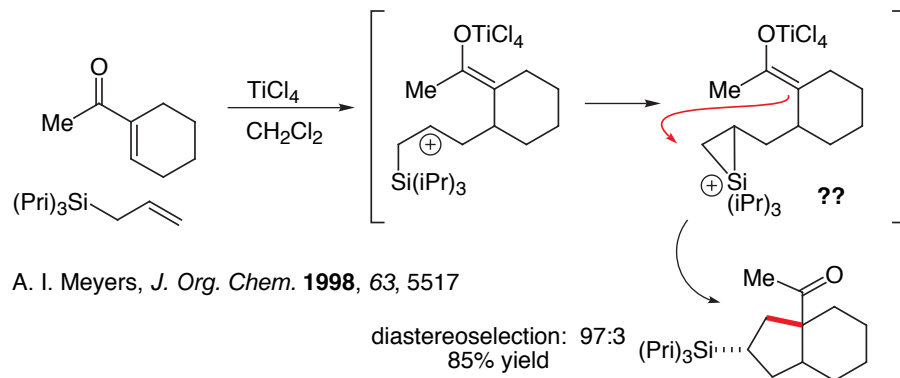
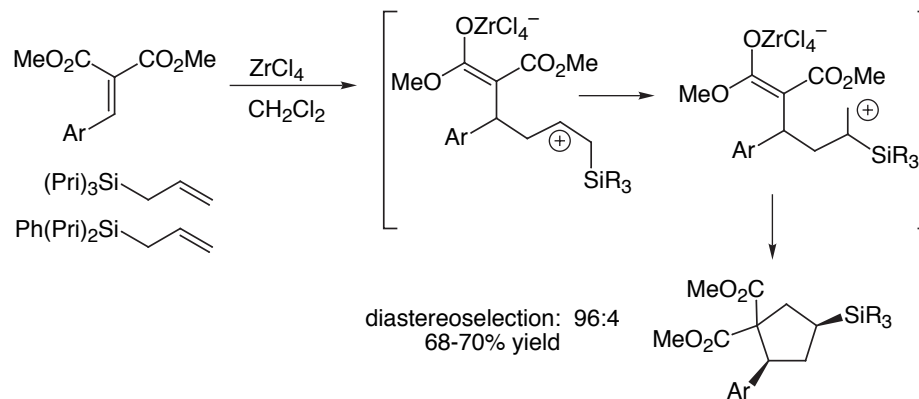


The Sakurai Reaction (Enone Conjugate Addition)

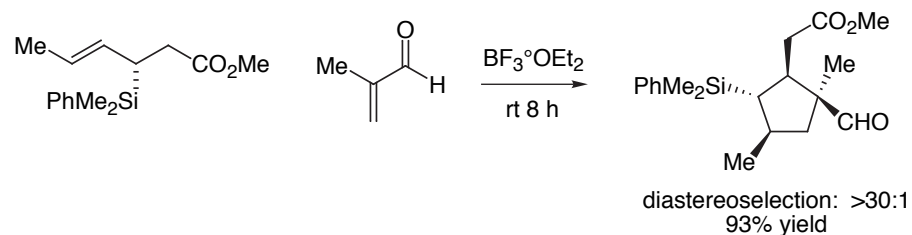
Fleming, *Org. Reactions* **1989**, 37, 127-133Majetich, *Tetrahedron* **1987**, 43, 5621

Reactions Proceeding through Silicon-Migration

Si migration may be promoted by using hindered Si substituents

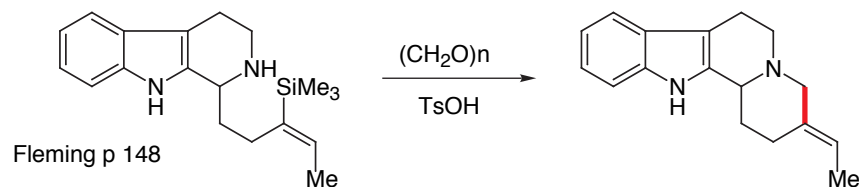
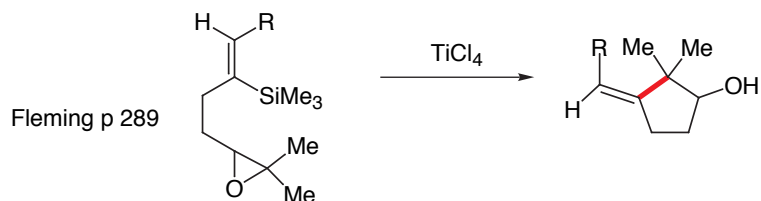
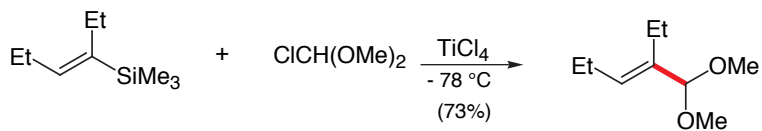
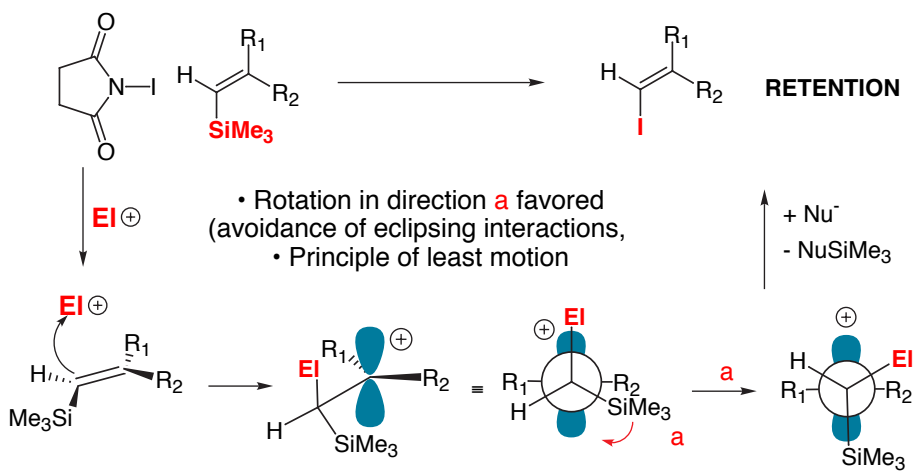
A. I. Meyers, *J. Org. Chem.* **1998**, 63, 5517

Can you work out the mechanism??

Panek, *J. Org. Chem.* **1993**, 58, 2345

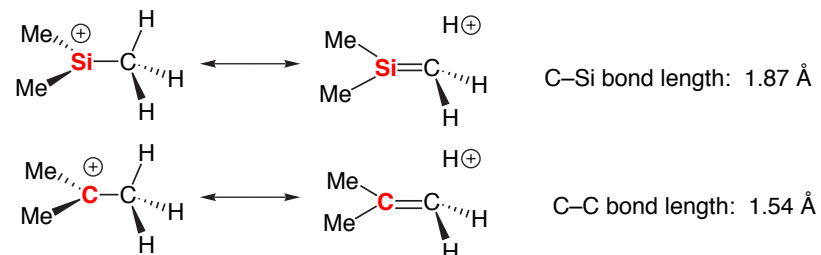
Stereochemistry of Electrophile Addition to Vinylsilanes

Vinyl/Allylsilanes in Organic Synthesis - Selected Examples

Fleming, *Org. Reactions* 1989, 37, 54.

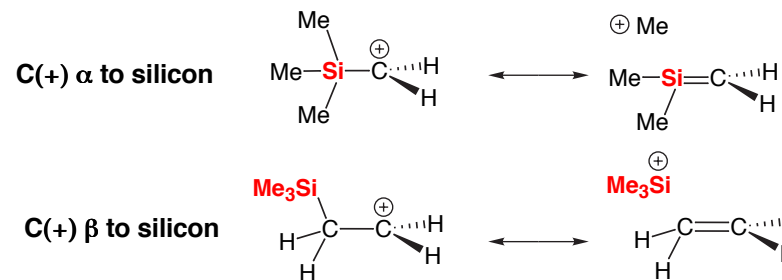
Summary Statements

1. Me₃C⁺ is more stable than Me₃Si⁺ in spite of the fact that Si is less electronegative than C.



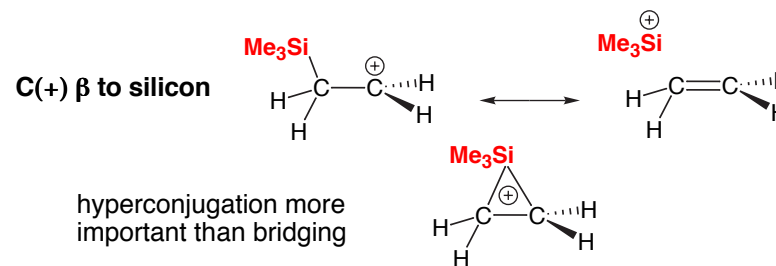
C-Si hyperconjugation is less pronounced than the analogous C-C hyperconjugation due to the impact of the longer C-Si bond lengths.

2. Carbonium ions α to Si are less stabilized than carbonium ions β to Si.



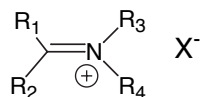
C-Si hyperconjugation is less pronounced than the analogous C-C hyperconjugation due to the impact of the longer C-Si bond lengths.

3. According to Lambert, silicon has a propensity to stabilize β carbonium ion via hyperconjugation (vertical stabilization) rather than bridging (nonvertical stabilization).

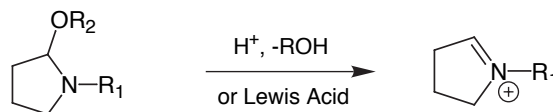
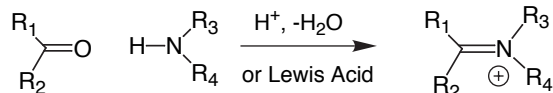


4. Silicon has a lower propensity to undergo Wagner-Meerwein like rearrangements than carbon.

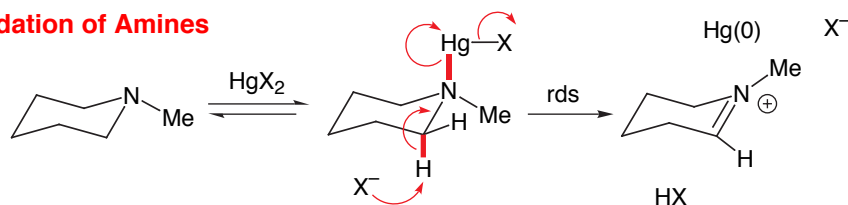
Iminium Ions



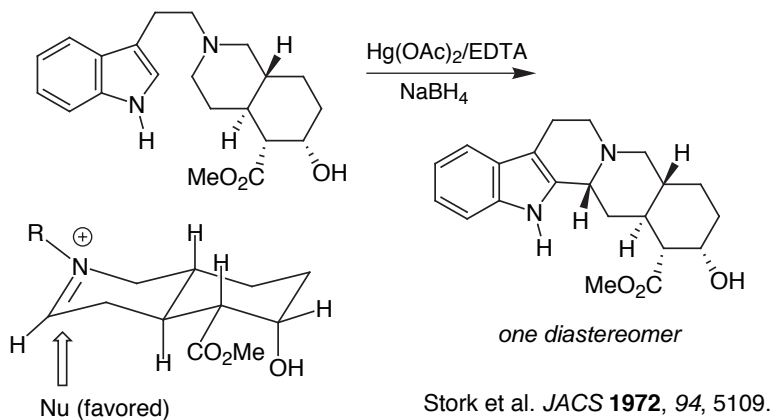
Common Methods of Generation:



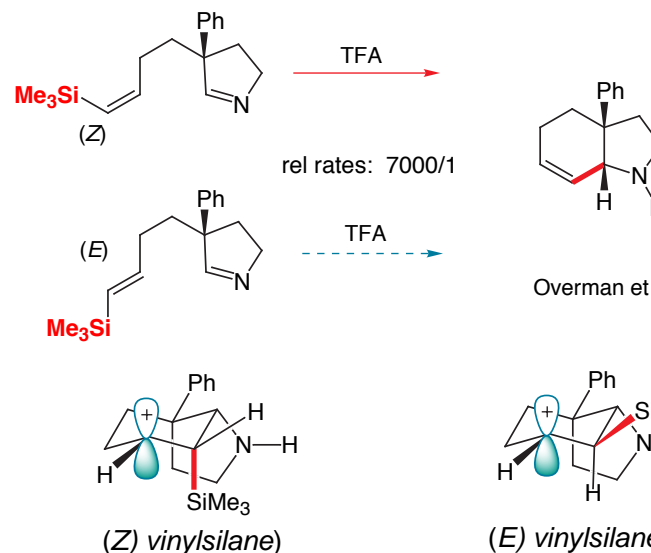
Oxidation of Amines



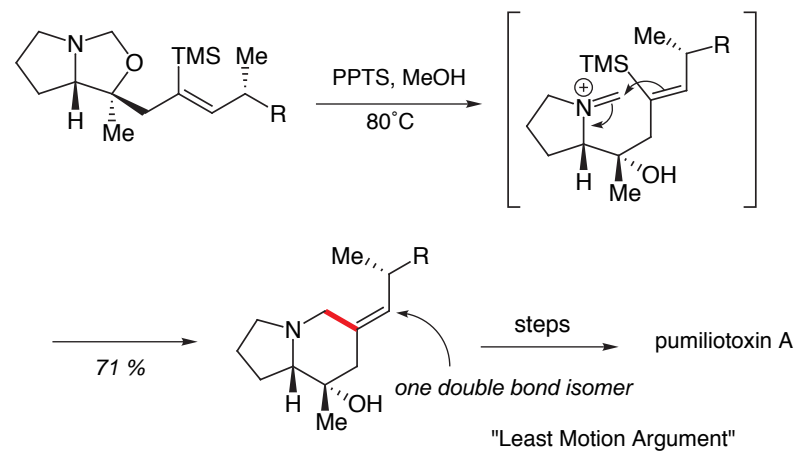
Stereoelectronic Effects on Nu Addition to Iminium Ions



C=N Stereoelectronic Effects: Lecture 20

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.

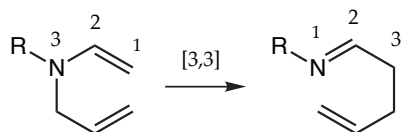
Overman et al. *JOC* **1989**, 54, 2591.

Review:

Heimgartner, H. In "Iminium Salts in Organic Chemistry"; Bohme, H., Viehe, H., Eds.; Wiley: New York, 1979; Part 2, pp 655-732.

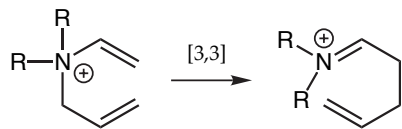
The 3-aza-Cope Rearrangement:

Neutral Variant:



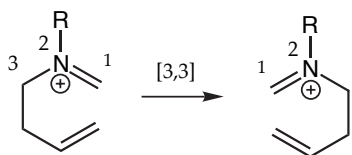
Exothermic as written by $\sim 7\text{-}10\text{kcal/mole}$.

Ammonium Variant:



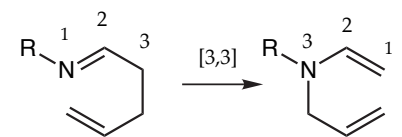
Even more exothermic than the neutral version, since enamine lacks resonance and iminium salt has stronger p-Bond than imine does.

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.

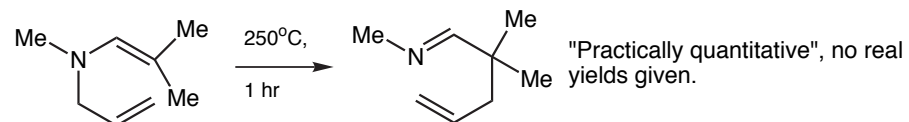
1-aza-Cope Rearrangement:



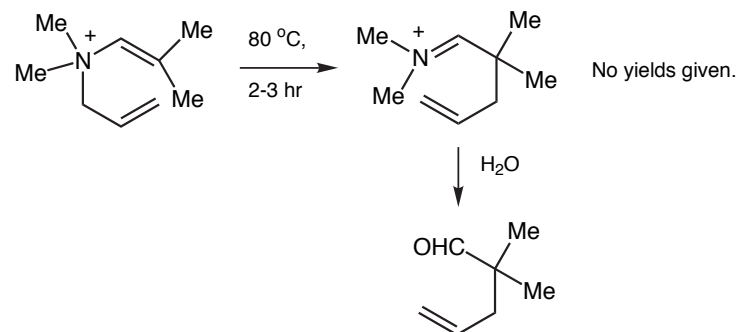
The 3-aza-Cope rearrangement can be driven in reverse by judicious choice of substrates (i.e., incorporating the imine into a strained ring or by making R an acyl group).

The 3-aza-Cope Rearrangement

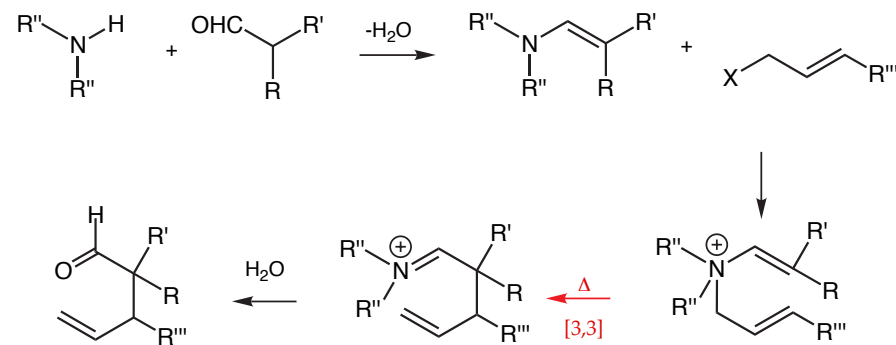
First Neutral Case: Hill TL **1967**, 1421.



First Cationic Case: Elkik *Compt. Rend.* **1968**, 267, 623.

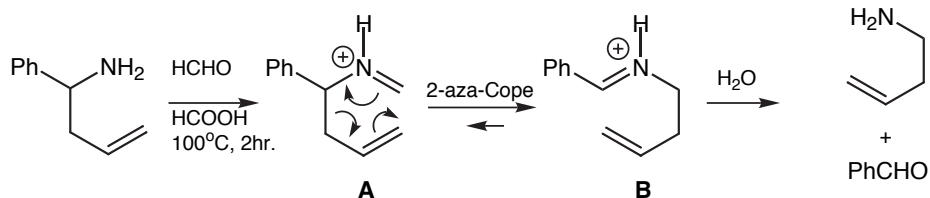


Good way to allylate aldehydes: Opitz *Angew. Chem.* **1960**, 72, 169.

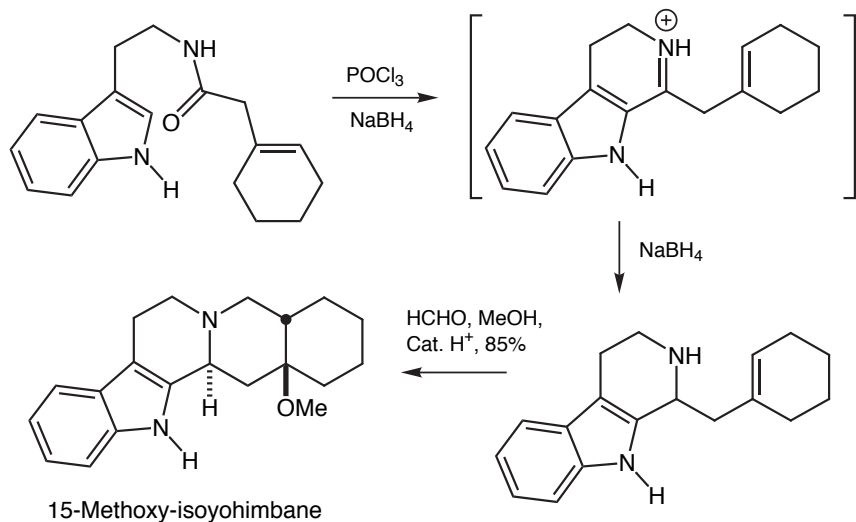
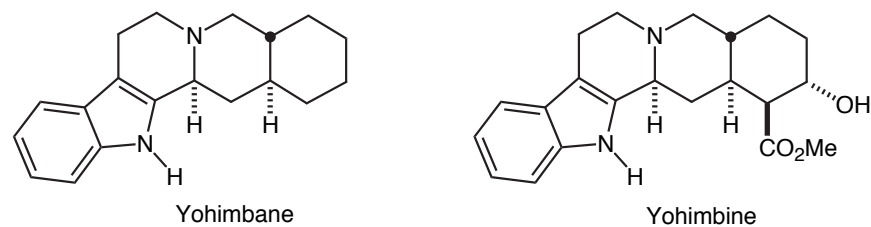


The 2-aza-Cope Rearrangement

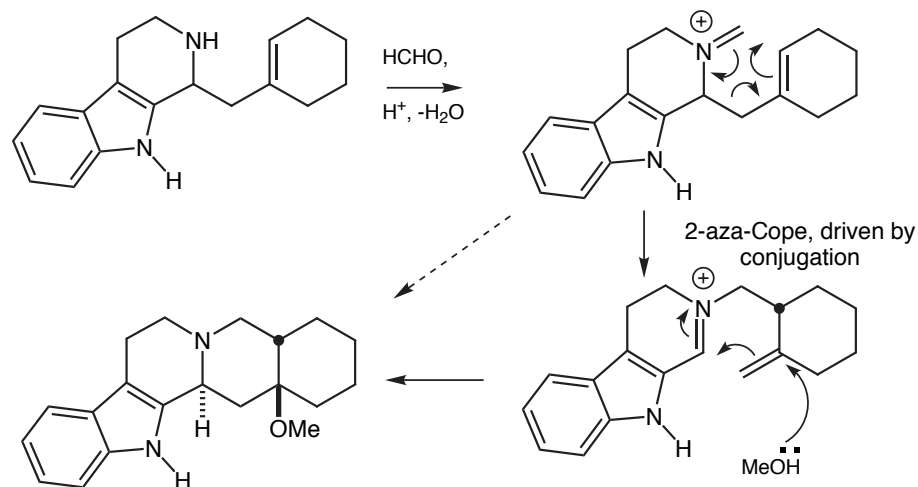
First Reported Case: Horowitz JACS 1950, 72, 1518.



Application to Yohimbine Analog Synthesis: Winterfeldt *Chem. ber.* **1968**, 101, 2938.

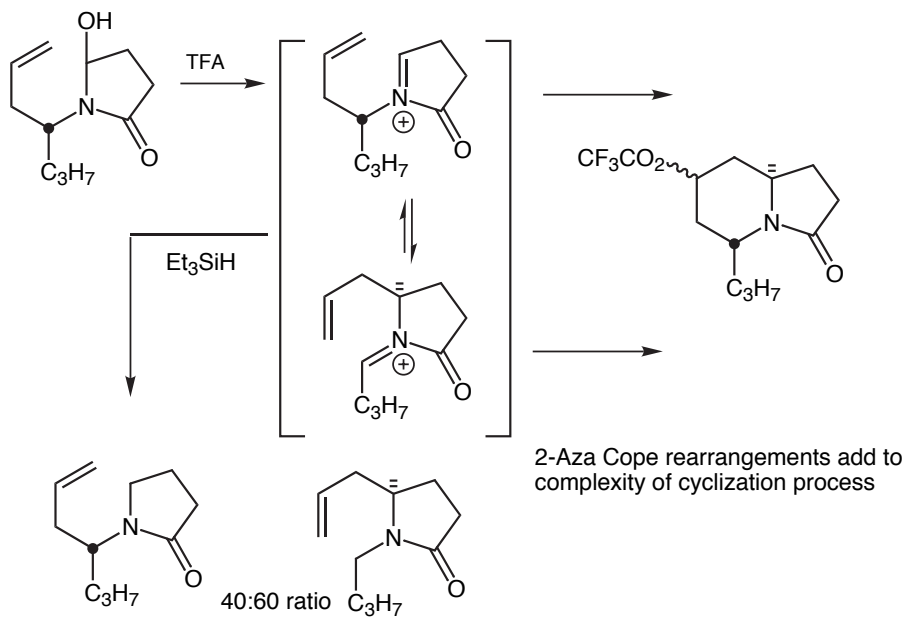


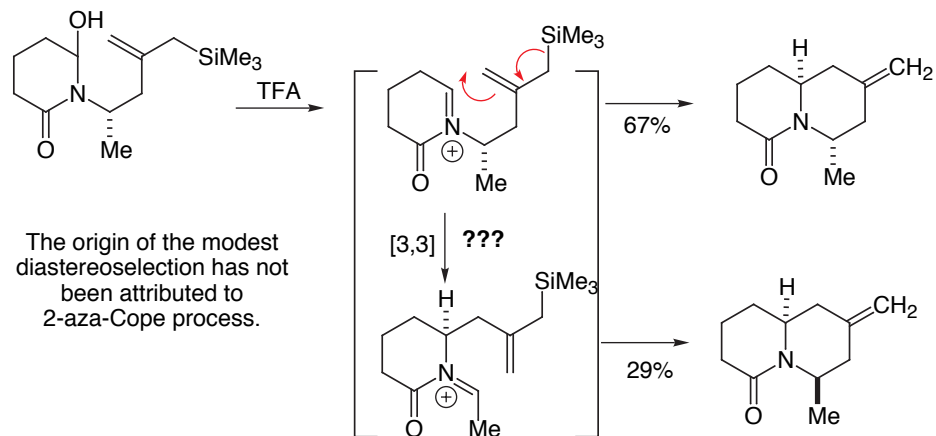
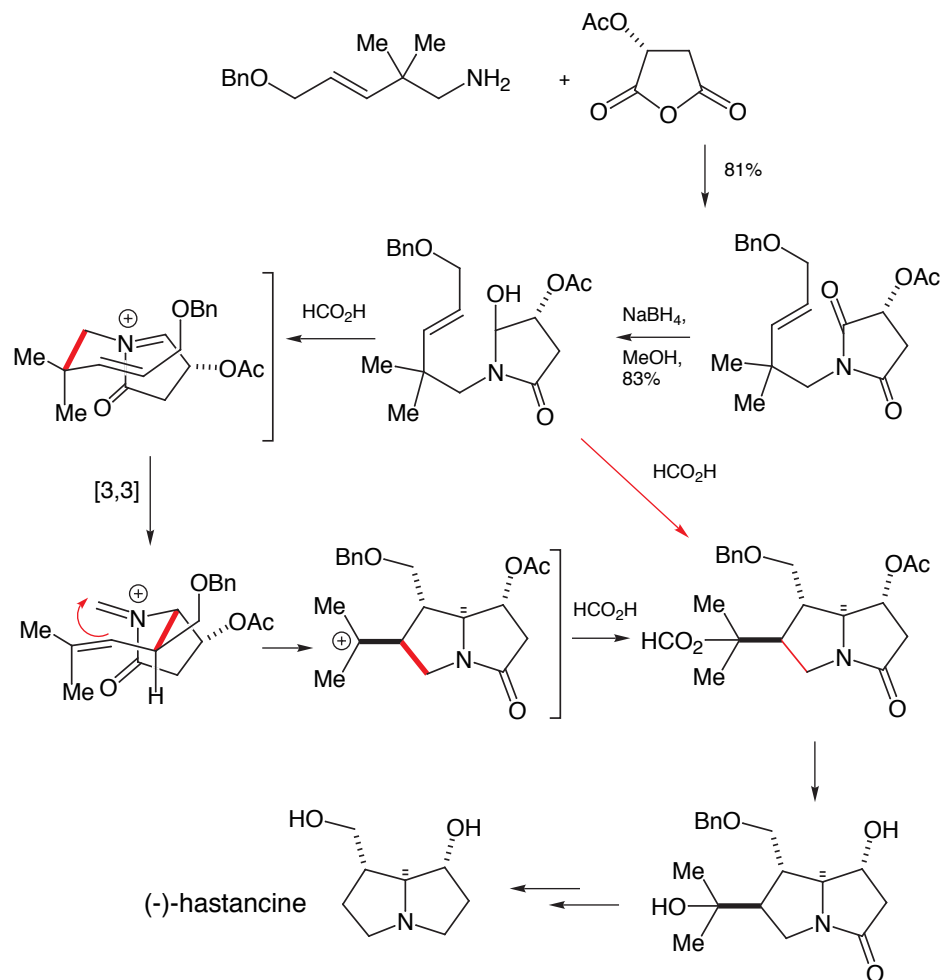
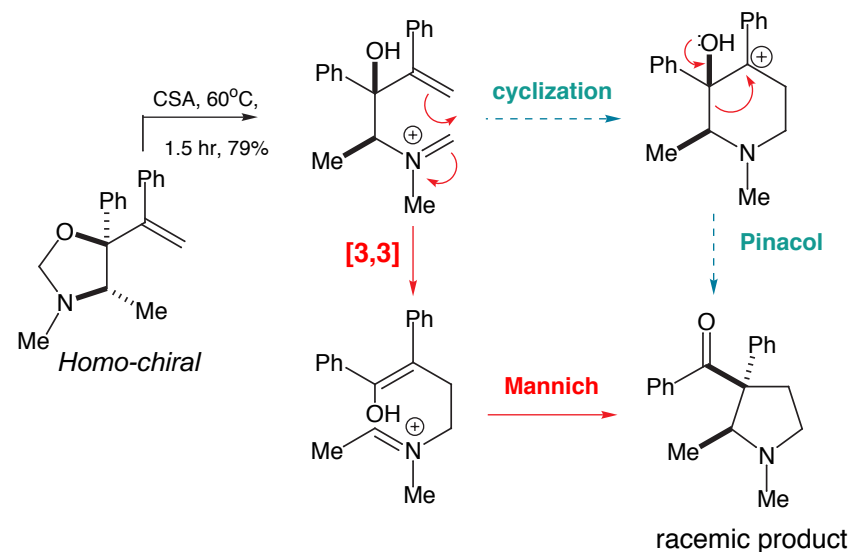
Mechanism for Yohimbane Analog Formation:



N-Acyliminium Ion Rearrangements: Hart JOC **1985**, 50, 235.

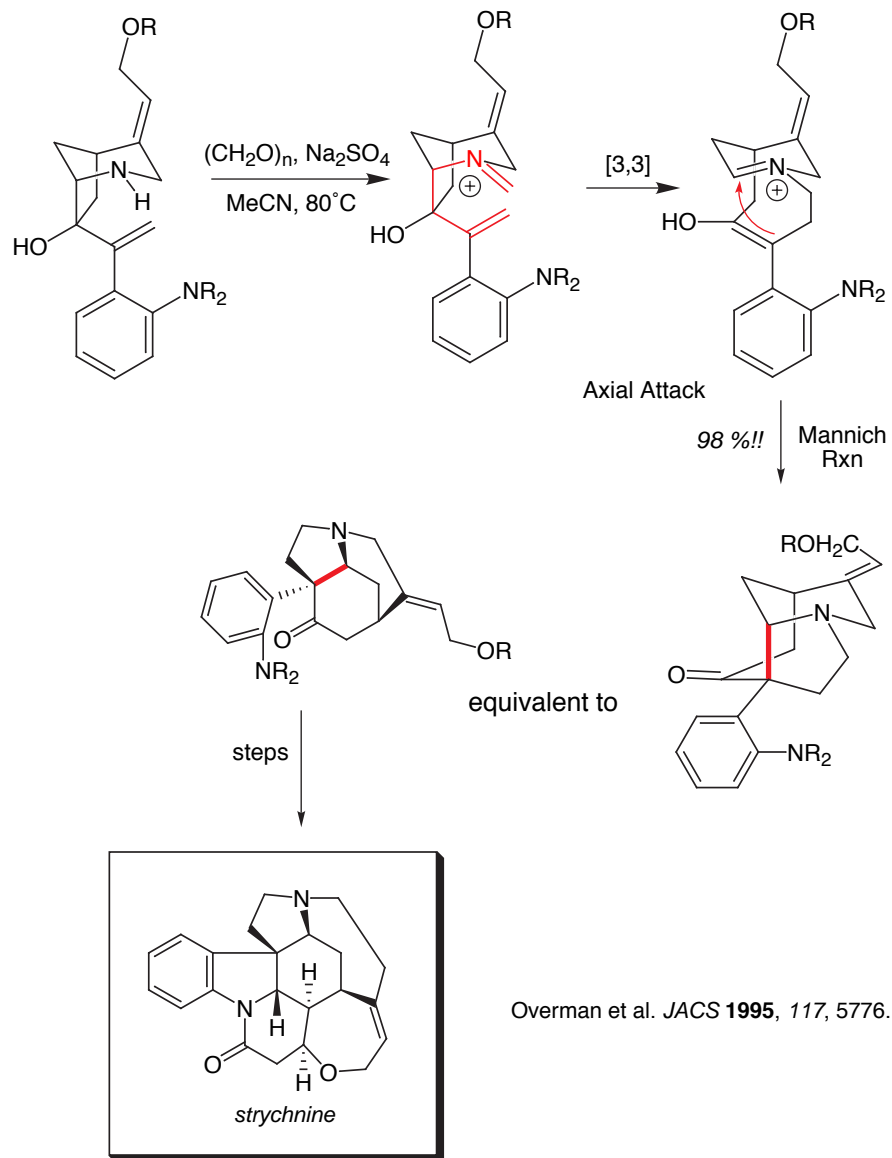
Hart observed an unusual product while trapping the intermediates of *N*-acyliminium olefin cyclizations.



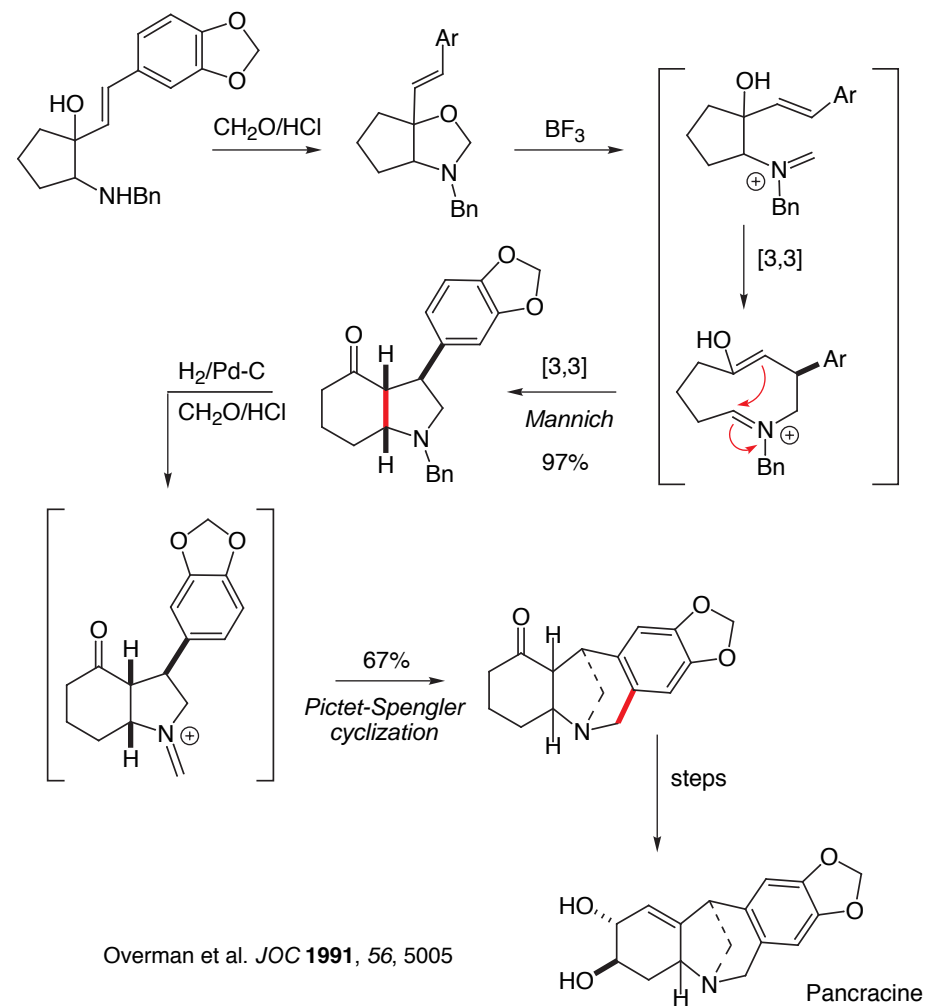
N-Acyliminium Ion RearrangementsSynthesis of (-)-hastanecine: Hart JOC **1985**, 50, 235.Gelas-Mailhe, *Tet. Lett*, **1992**, 33, 73**Competing 2-Aza-Cope and Pinacol Rearrangements: Which Dominates??**

Conclusion: 2-aza-Cope rearrangements afford a low-barrier to competing processes

2-Aza-Cope-Mannich sequence:



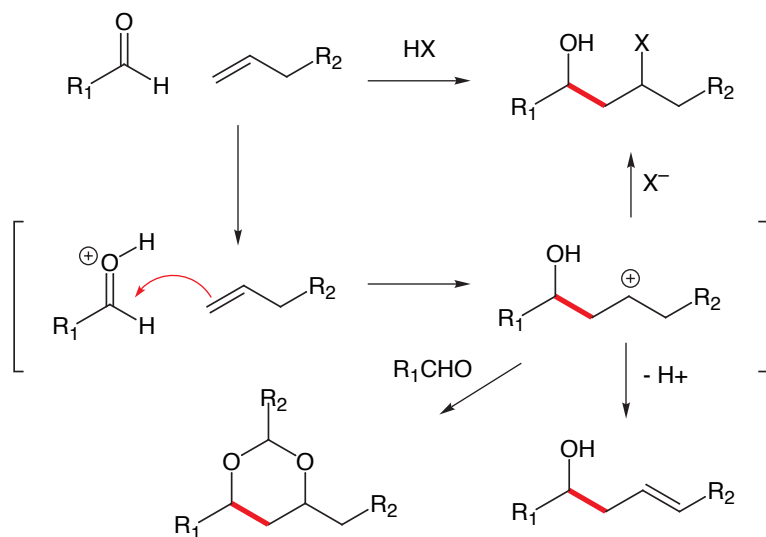
Another aza-Cope-Mannich sequence:



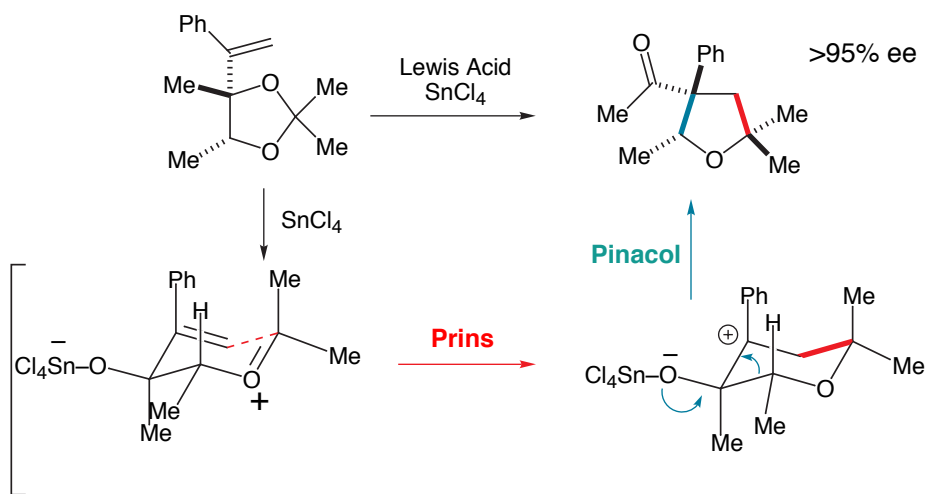
References

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:

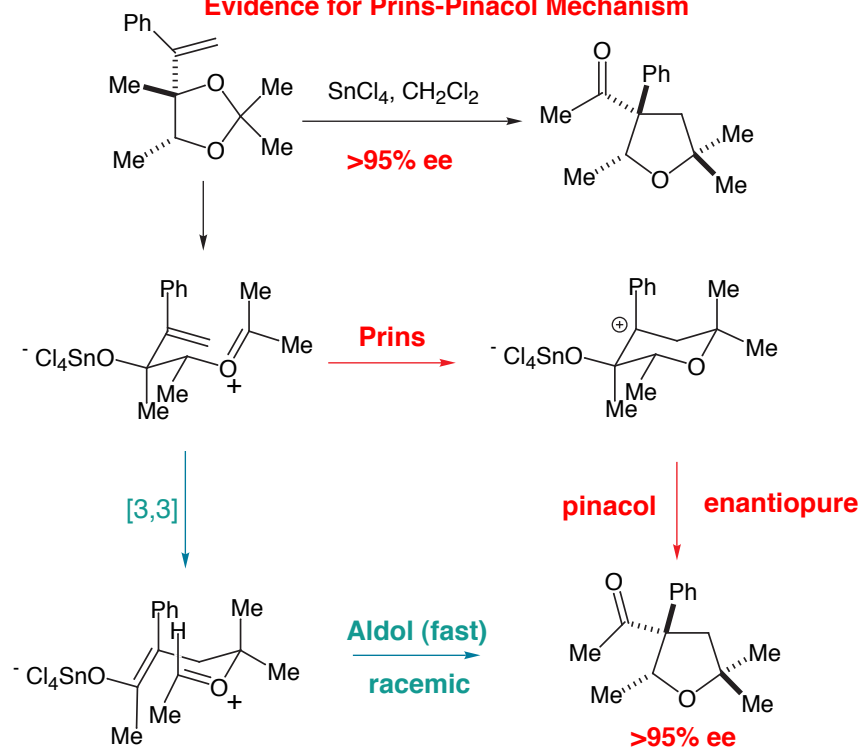


The Prins-Pinacol Variant:



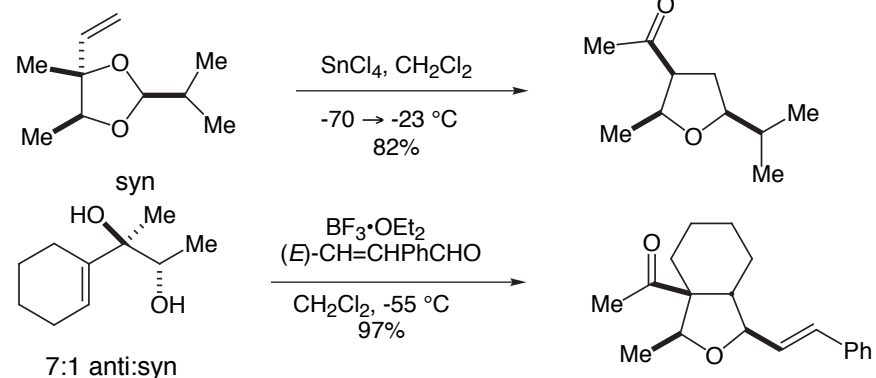
32-12-Prins-1 12/3/03 5:15 PM

Evidence for Prins-Pinacol Mechanism

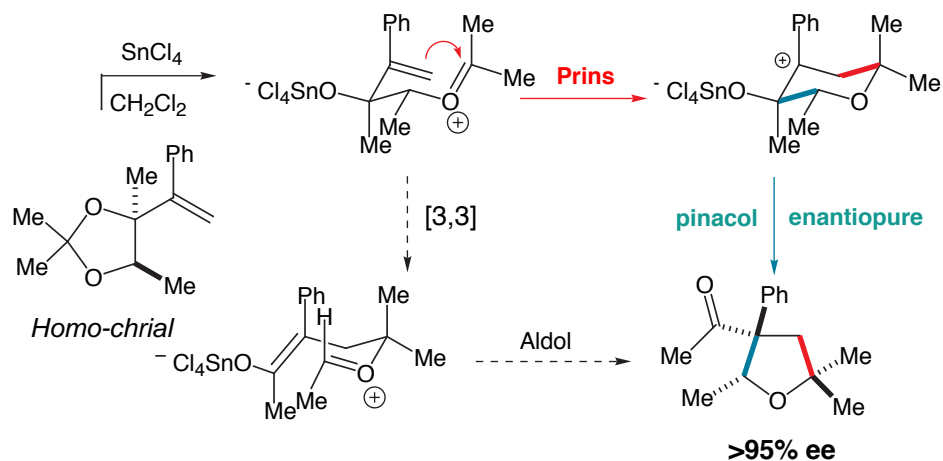


If a [3,3] rearrangement were intervening, the product would be racemic.
 Overman, *JACS* **2000**, 122, 8672
 Overman, *Org Lett* **2001**, 3, 1225

Examples of Stereoselective THF Formation



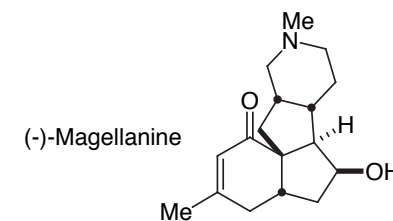
Prins-Pinacol Mechanism



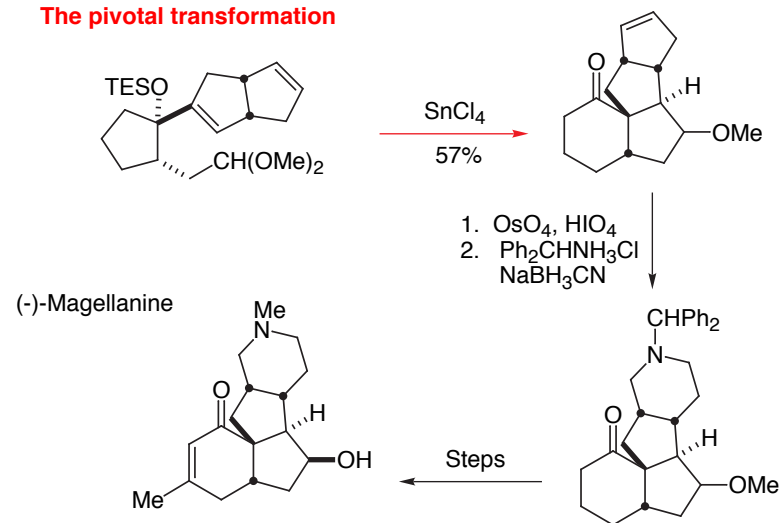
Prins cyclization faster than [3,3] rearrangement

Overman: Magellanine Synthesis

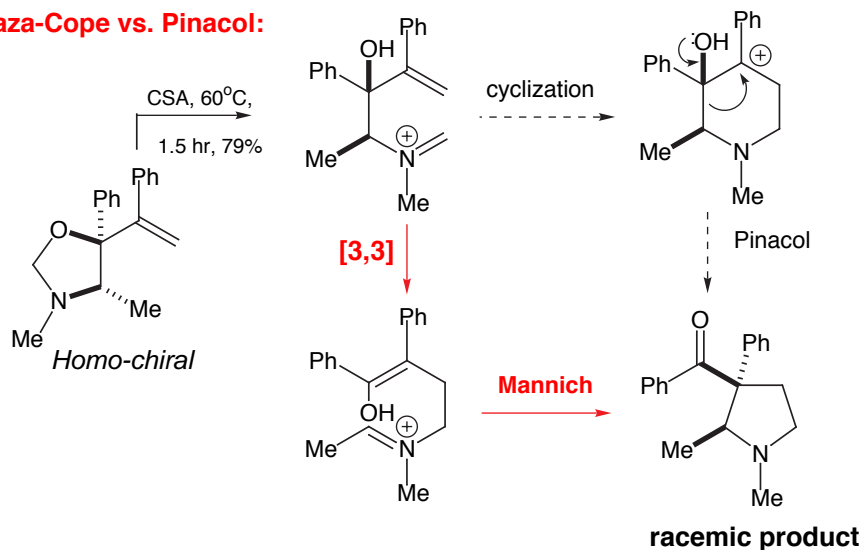
JACS, 1993, 115, 2992



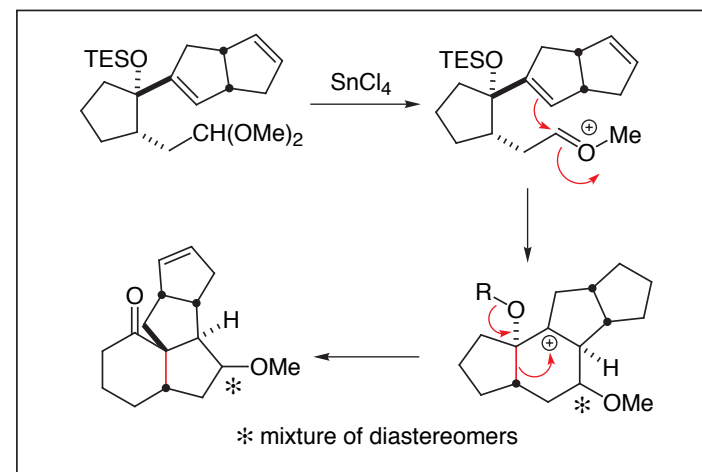
The pivotal transformation



2-aza-Cope vs. Pinacol:



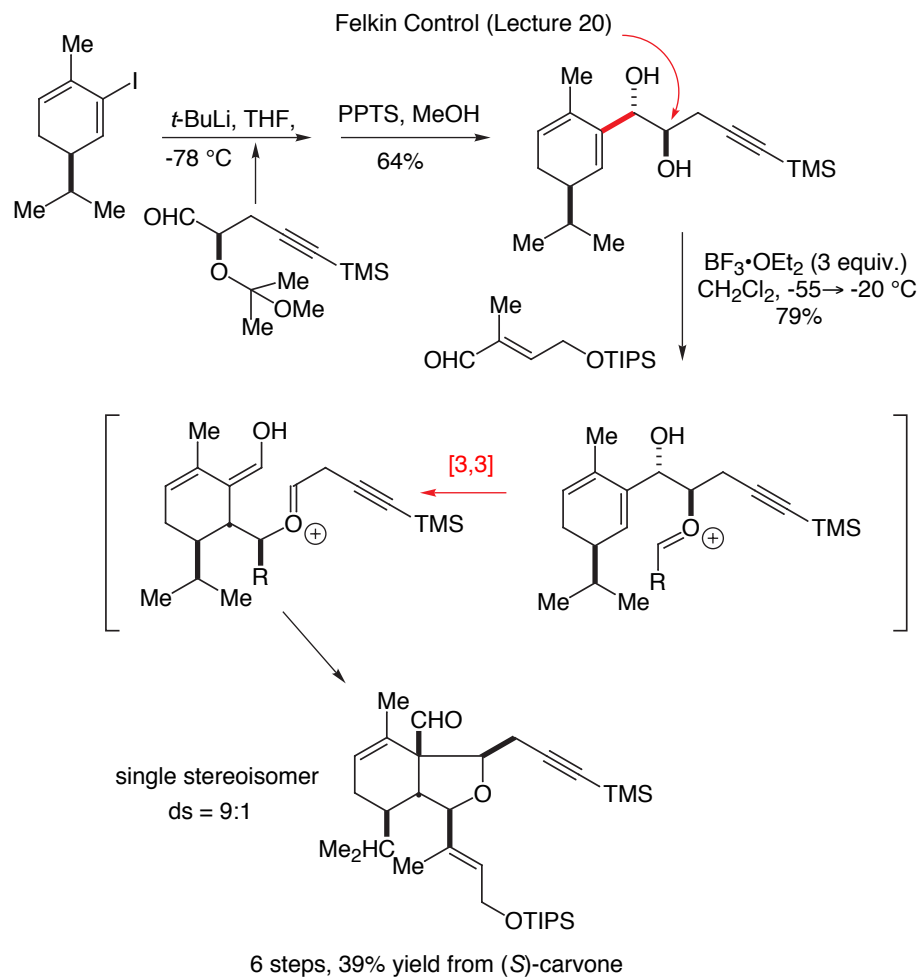
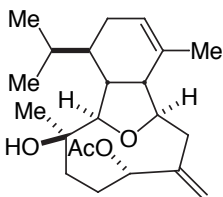
[3,3] rearrangement faster than Mannich cyclization



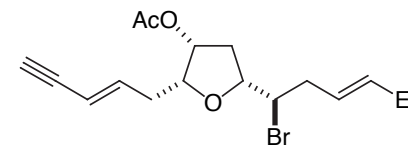
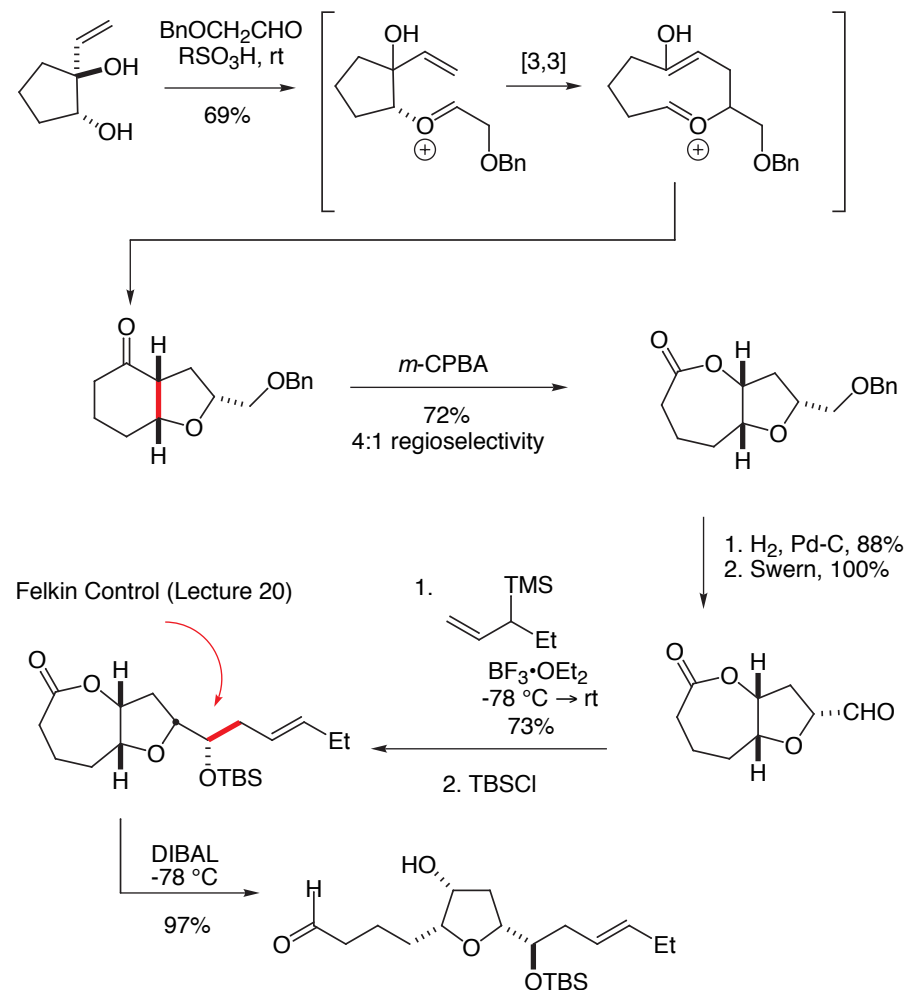
Overman Synthesis of a Eunicellin Diterpene

Overman & MacMillan JACS, 1995, 117, 10391

(-)-7-Deacetoxy-alcyoninacetate

Overman: Synthesis of *trans*-Kumausyne

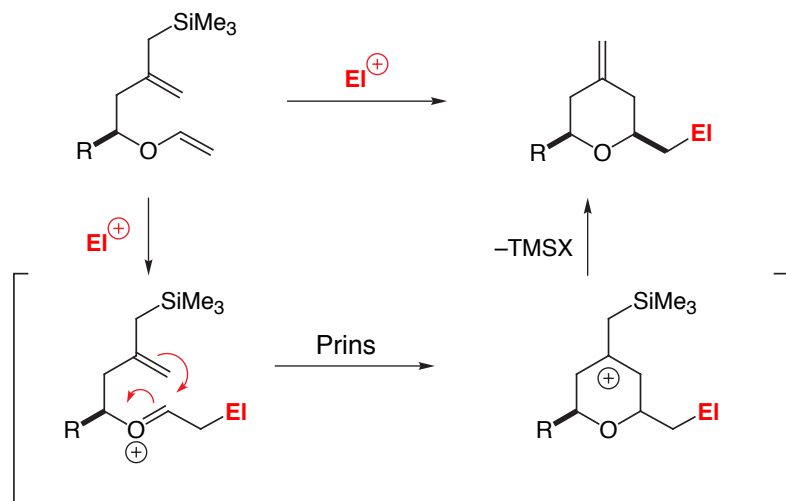
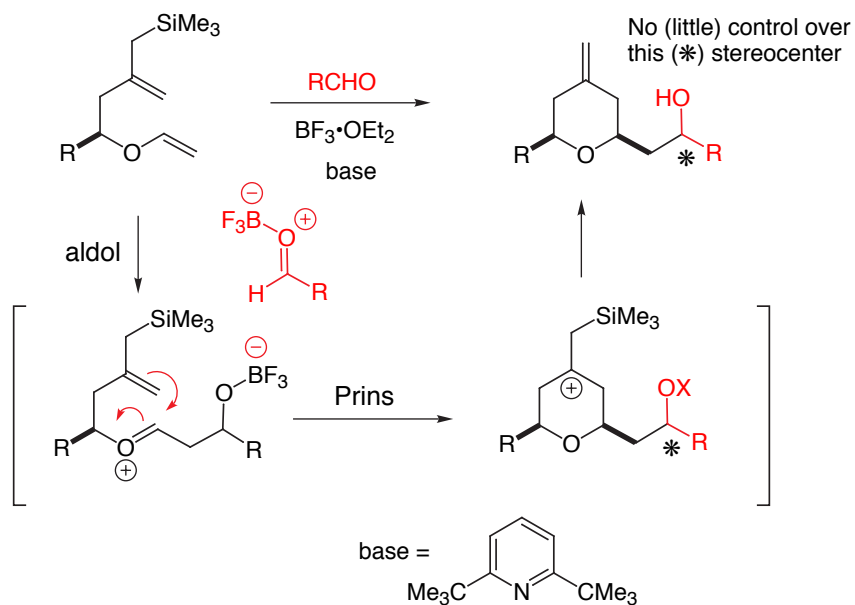
JACS, 1991, 113, 5378

*trans*-Kumausyne

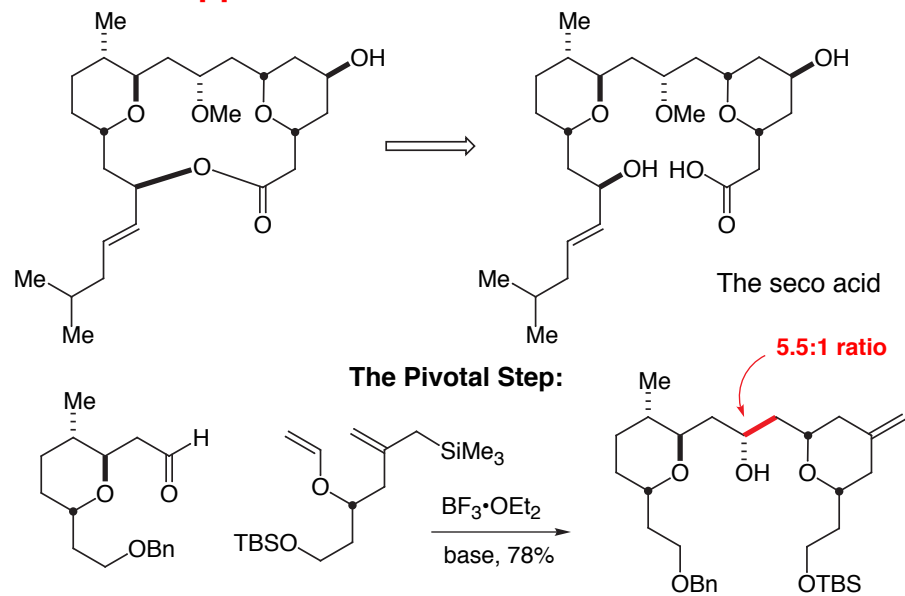
Mukaiyama Aldol-Prins Cascade

Rychnovsky JACS, 2001, 123, 8420

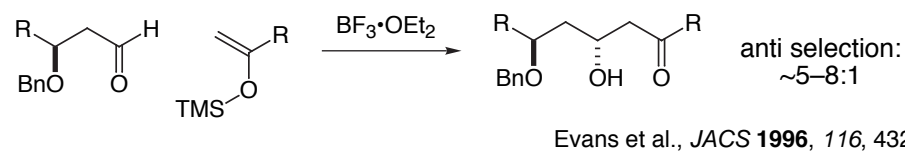
The Basic Process

Let $EI(+)$ = Lewis acid activated RCHO

Application to Leucasandrolide

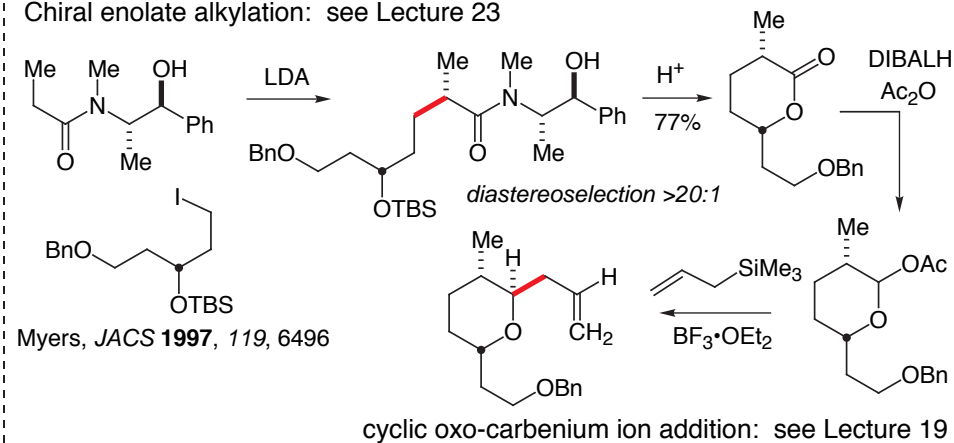


Control of hydroxyl center: see Lecture 20

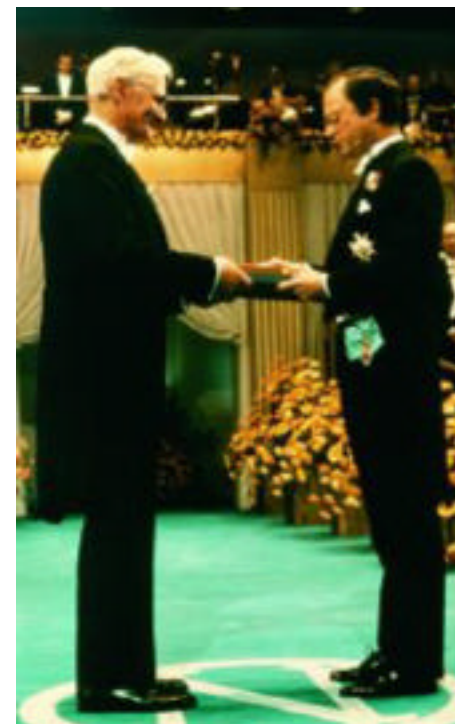
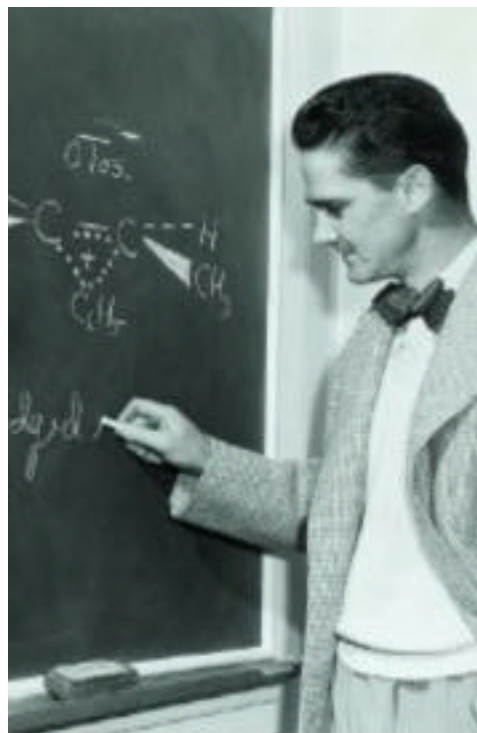
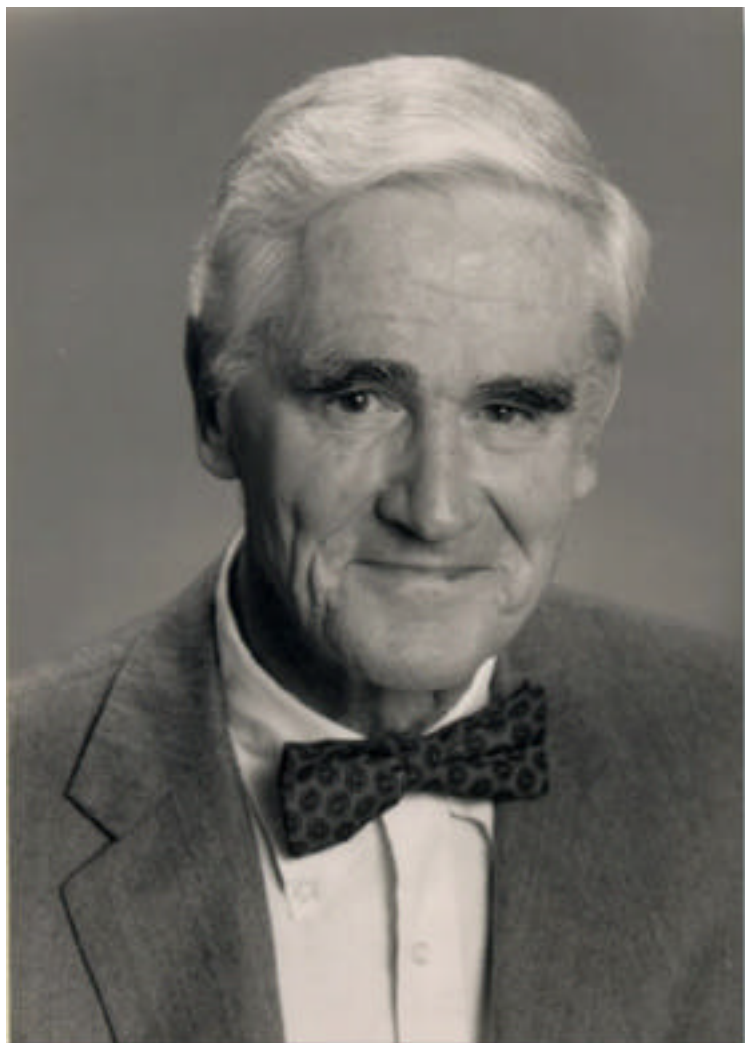


Aldehyde Synthesis

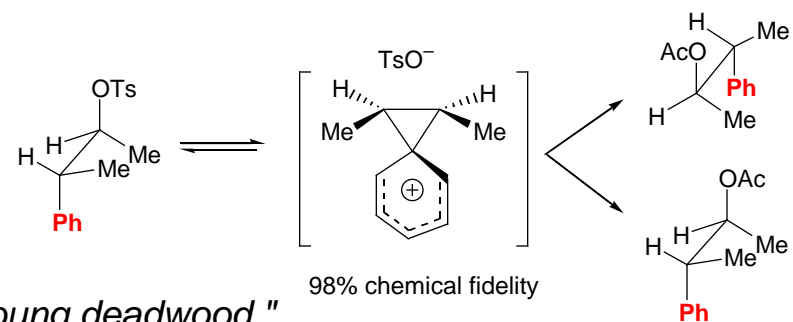
Chiral enolate alkylation: see Lecture 23



Donald J. Cram (1919–2001)



Phenonium Ion Experiments: Cram, *JACS* 1949, 71, 3865



Cram: *"Just remember Dave, old deadwood is better than young deadwood."*

"A View from the Far Side. Memorable Characters and Interesting Places." Evans, D. A. *Tetrahedron* 1999, 55, 8589-8608.

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 33

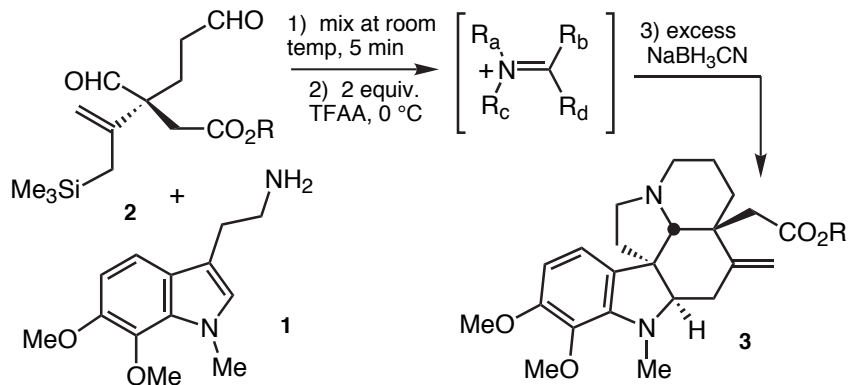
Introduction to Carbonium Ions-3

- Stabilized Carbocations: Iminium Ions ($C=NR_2(+)$)
- Stabilized Carbocations: Oxo-Carbenium Ions ($C=OR(+)$)
- Stabilized Carbocations: Addition & Rearrangements

Reading Assignment for this Lecture:

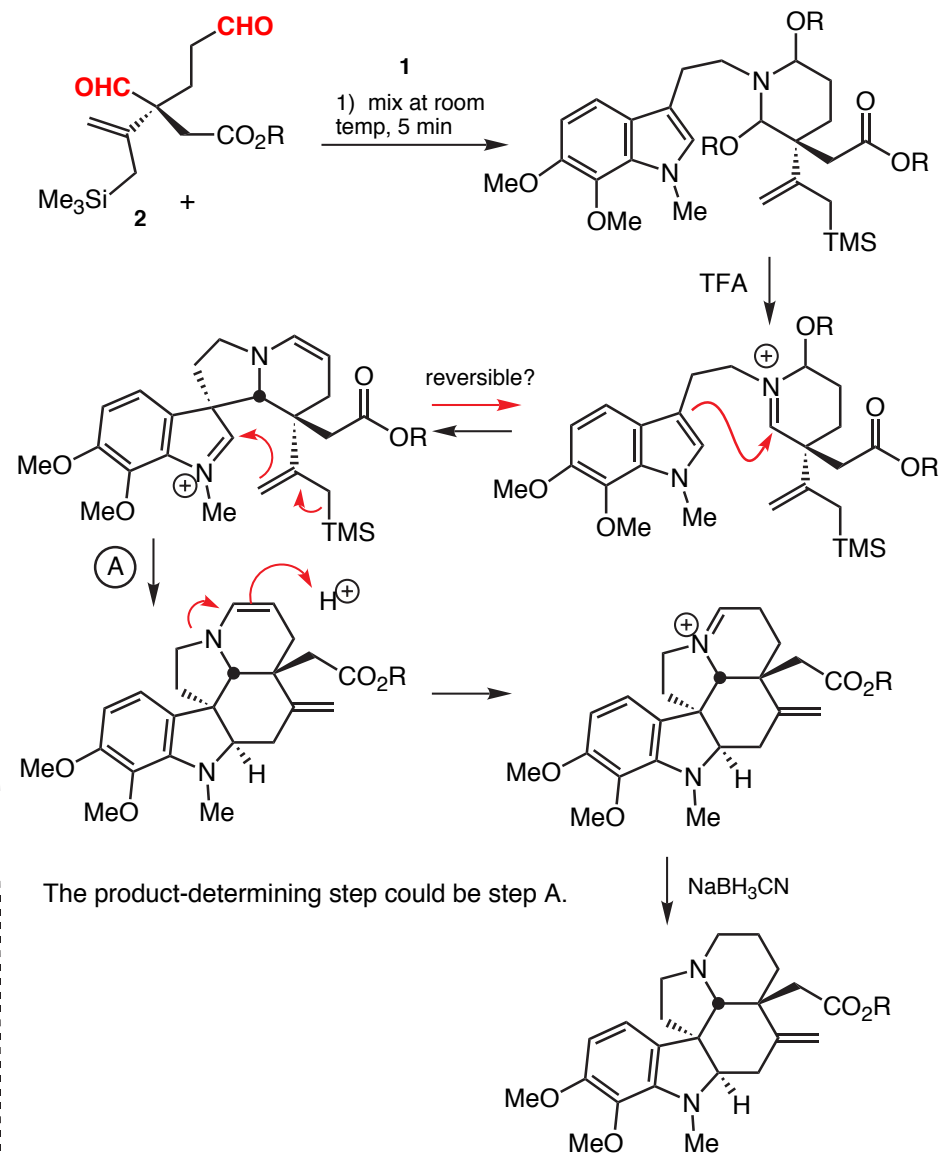
Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed.
Part A Chapter 5, "Nucleophilic Substitution", 263-350.

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.



D. A. Evans

Monday,
December 8, 2003

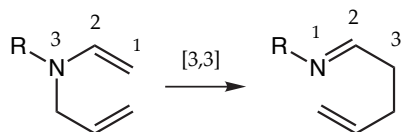


Review:

Heimgartner, H. In "Iminium Salts in Organic Chemistry"; Bohme, H., Viehe, H., Eds.; Wiley: New York, 1979; Part 2, pp 655-732.

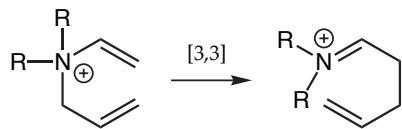
The 3-aza-Cope Rearrangement:

Neutral Variant:



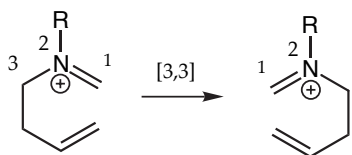
Exothermic as written by ~ 7 -10kcal/mole.

Ammonium Variant:



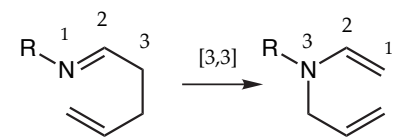
Even more exothermic than the neutral version, since enamine lacks resonance and iminium salt has stronger p-Bond than imine does.

2-aza-Cope Rearrangement:



In the simplest case, degenerate. Steric effects, conjugation, or selective trapping of a particular isomer, will drive equilibrium. As with the 3-aza-Cope, the cationic version proceeds under much milder conditions.

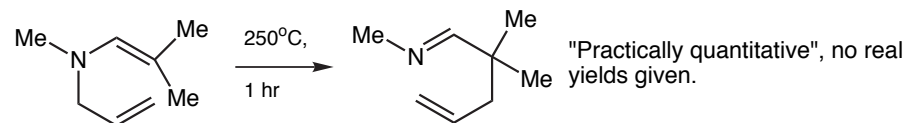
1-aza-Cope Rearrangement:



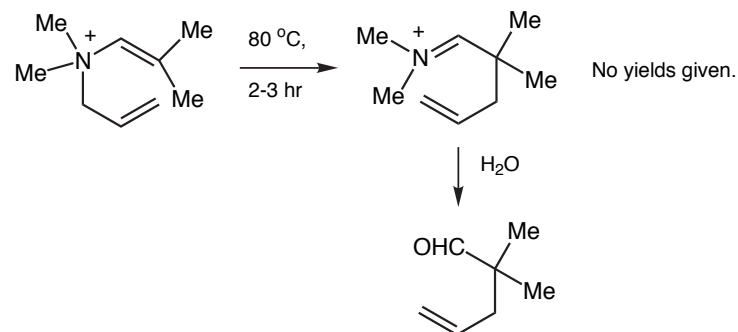
The 3-aza-Cope rearrangement can be driven in reverse by judicious choice of substrates (i.e., incorporating the imine into a strained ring or by making R an acyl group).

The 3-aza-Cope Rearrangement

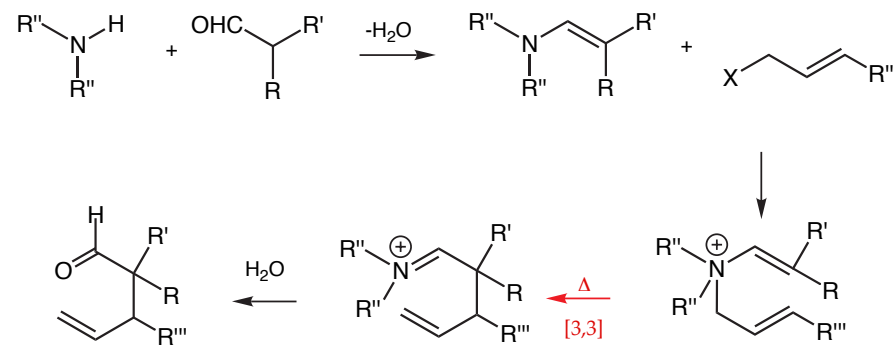
First Neutral Case: Hill TL **1967**, 1421.

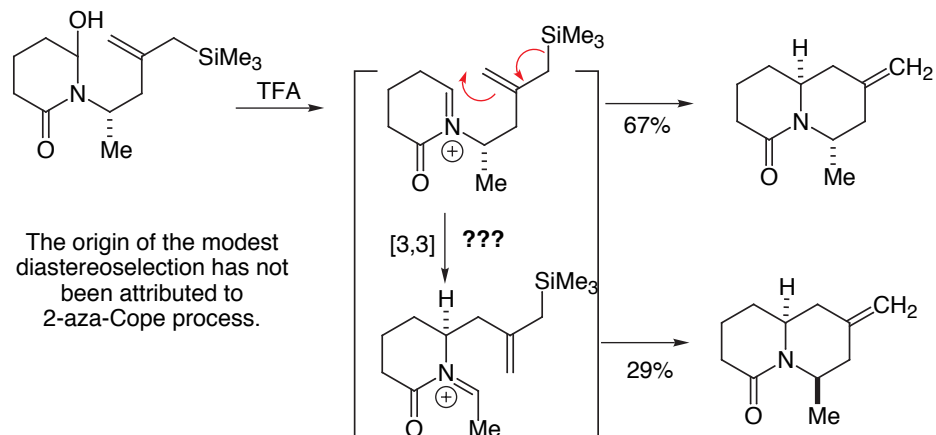
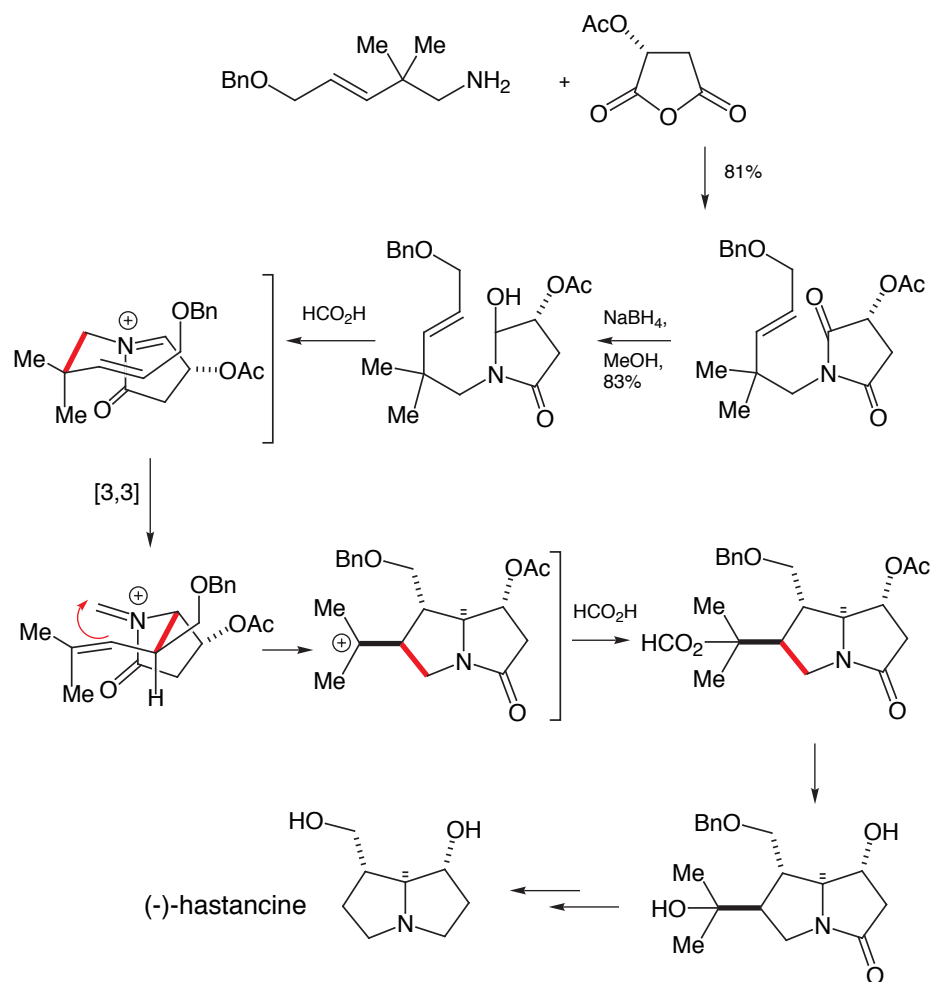
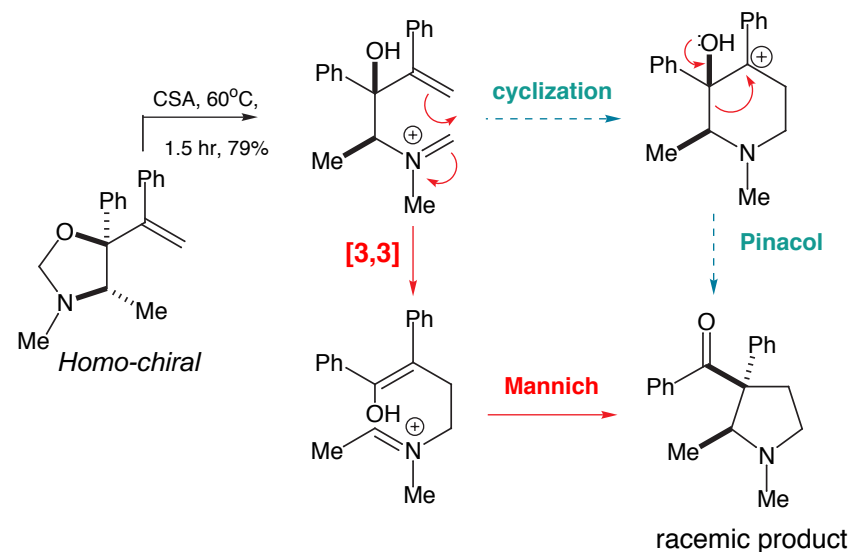


First Cationic Case: Elkik *Compt. Rend.* **1968**, 267, 623.



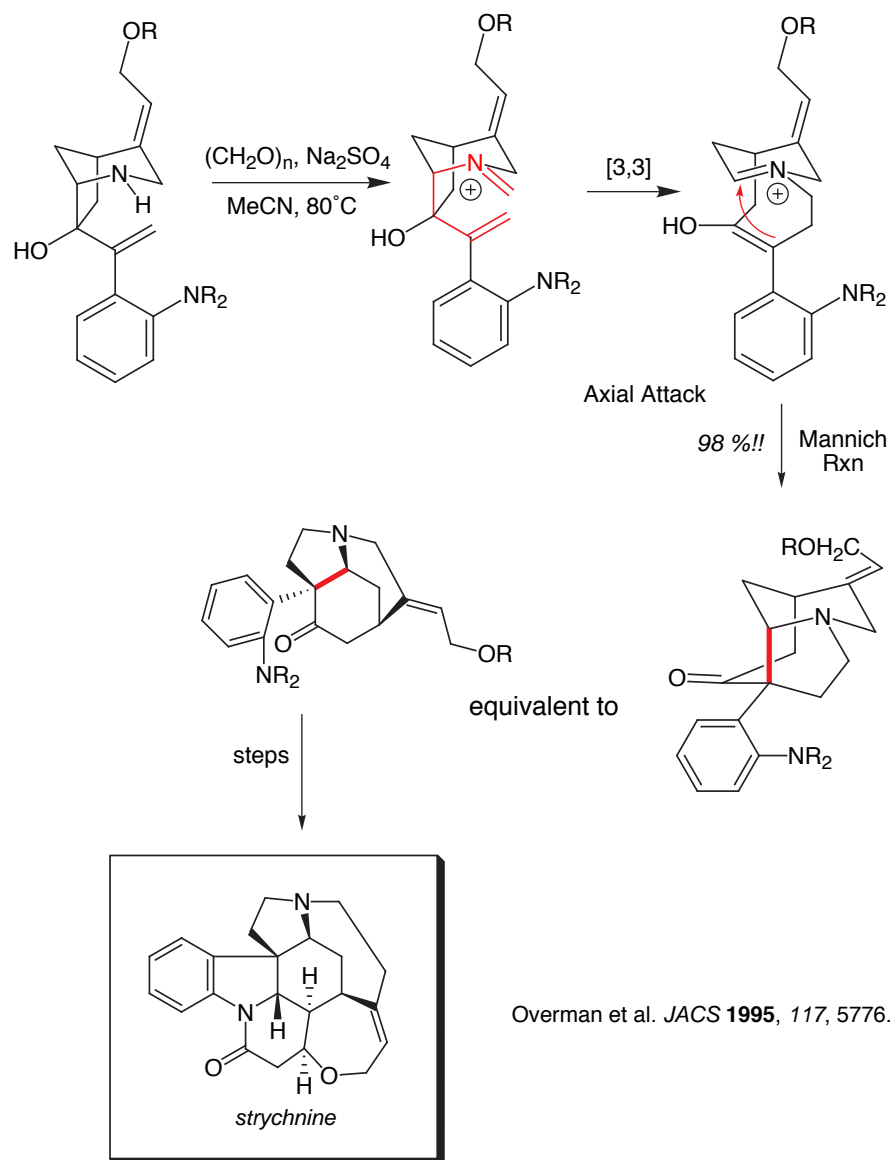
Good way to allylate aldehydes: Opitz *Angew. Chem.* **1960**, 72, 169.



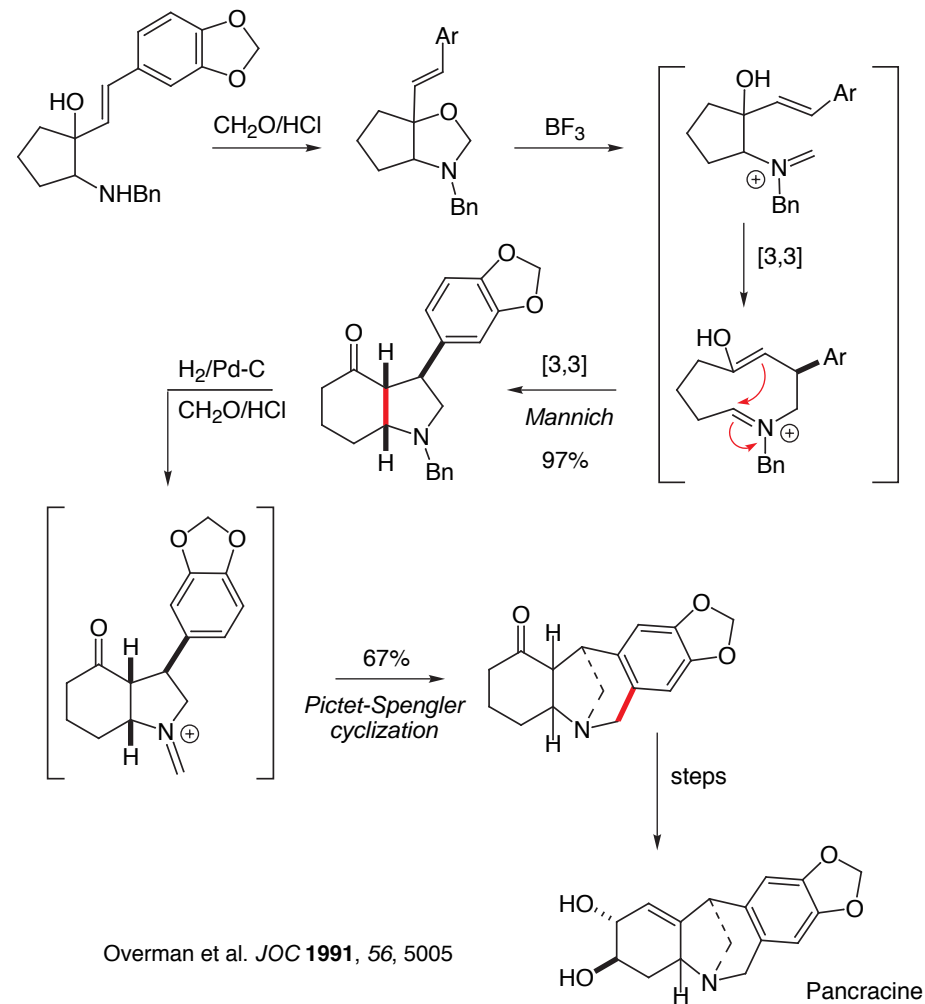
N-Acyliminium Ion RearrangementsSynthesis of (-)-hastanecine: Hart JOC **1985**, 50, 235.Gelas-Mailhe, *Tet. Lett.* **1992**, 33, 73**Competing 2-Aza-Cope and Pinacol Rearrangements: Which Dominates??**

Conclusion: 2-aza-Cope rearrangements afford a low-barrier to competing processes

2-Aza-Cope-Mannich sequence:



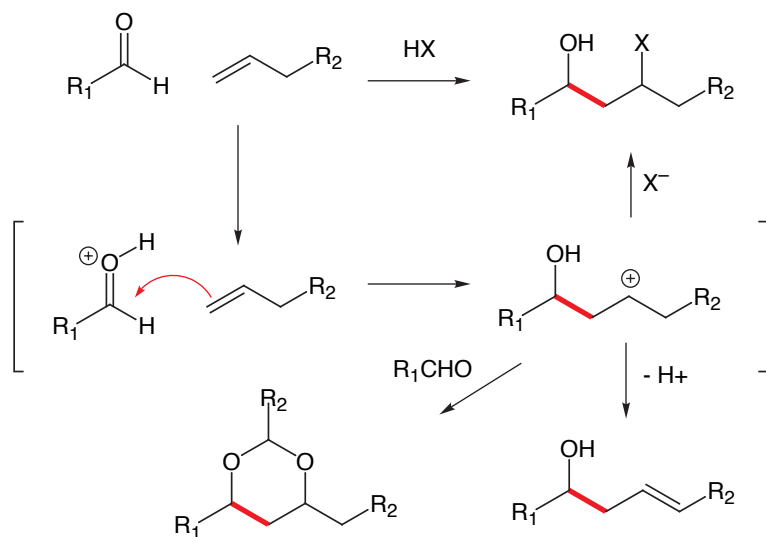
Another aza-Cope-Mannich sequence:



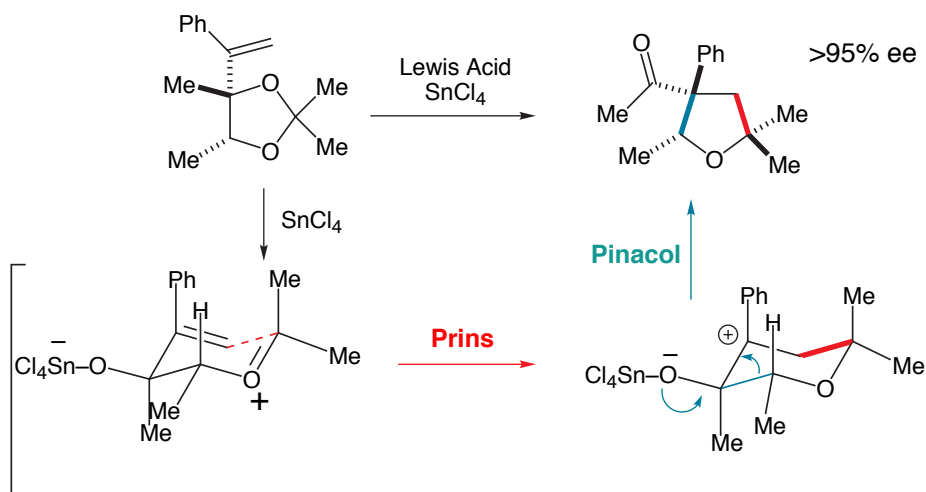
References

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:

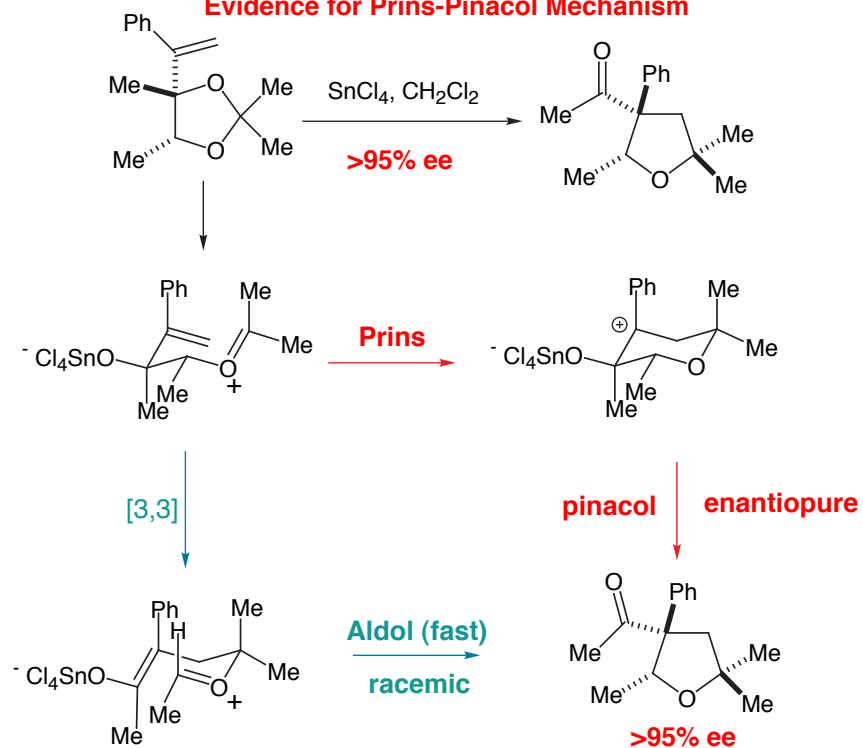


The Prins-Pinacol Variant:



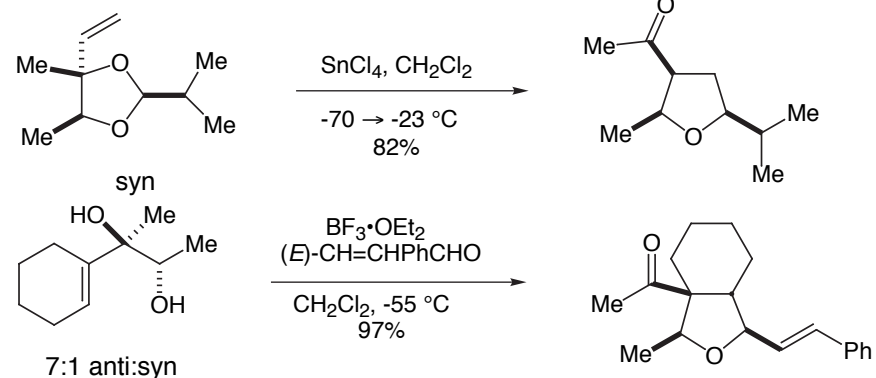
33-04-Prins-1 12/7/03 9:00 PM

Evidence for Prins-Pinacol Mechanism

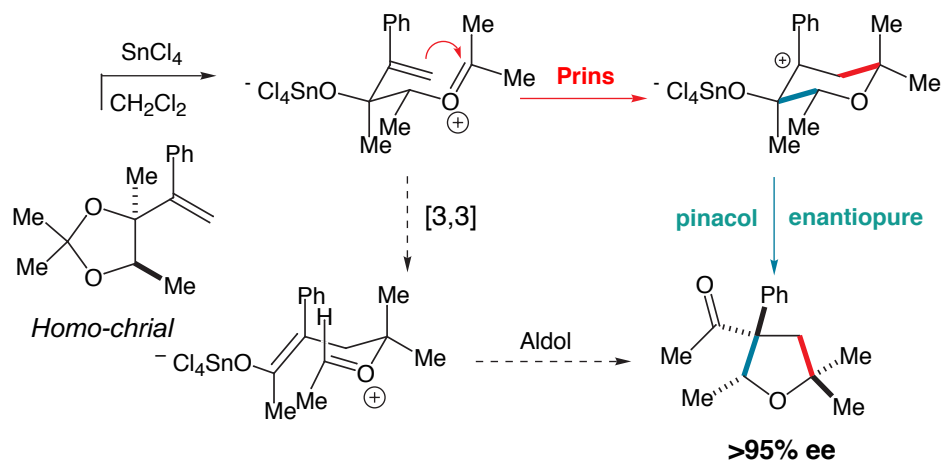


If a [3,3] rearrangement were intervening, the product would be racemic.
 Overman, *JACS* **2000**, 122, 8672
 Overman, *Org Lett* **2001**, 3, 1225

Examples of Stereoselective THF Formation



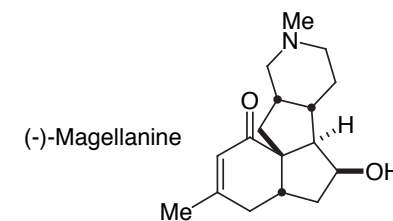
Prins-Pinacol Mechanism



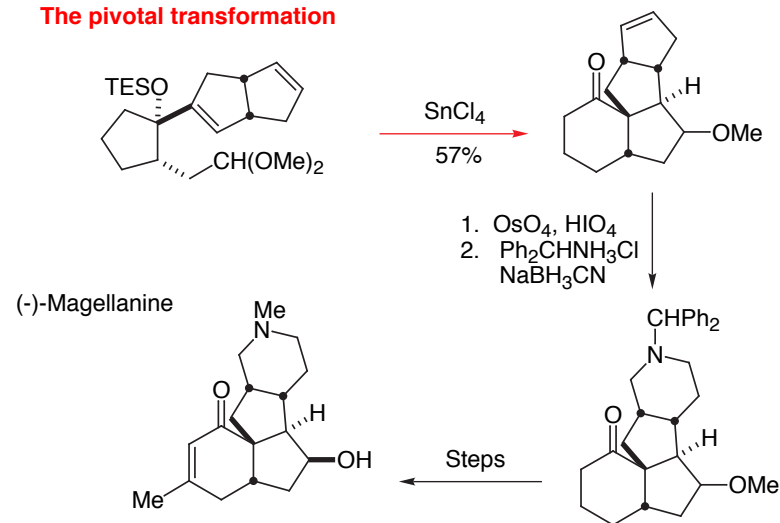
Prins cyclization faster than [3,3] rearrangement

Overman: Magellanine Synthesis

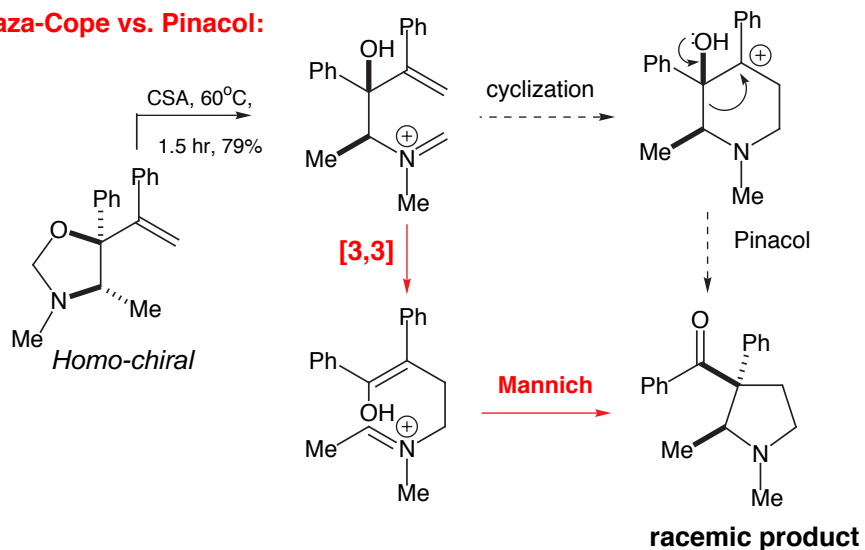
JACS, 1993, 115, 2992



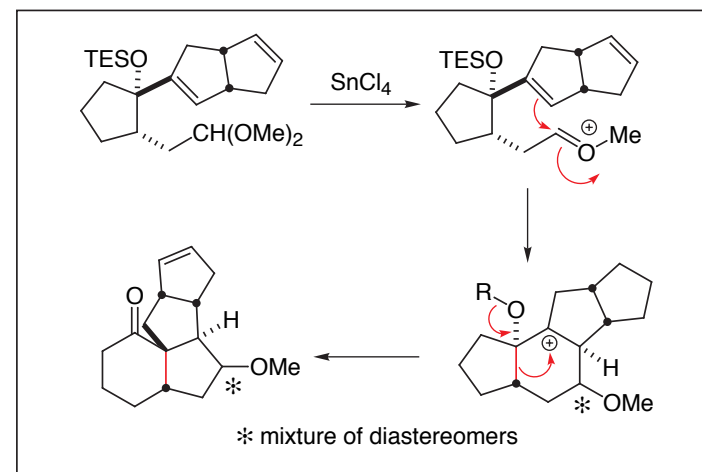
The pivotal transformation



2-aza-Cope vs. Pinacol:



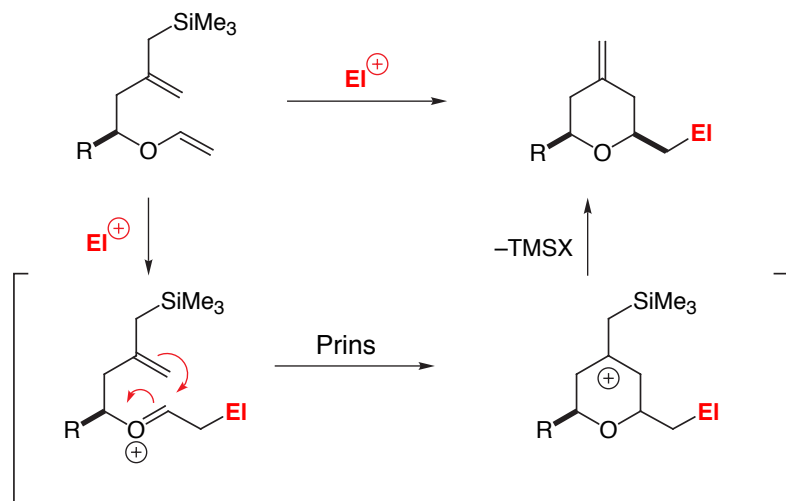
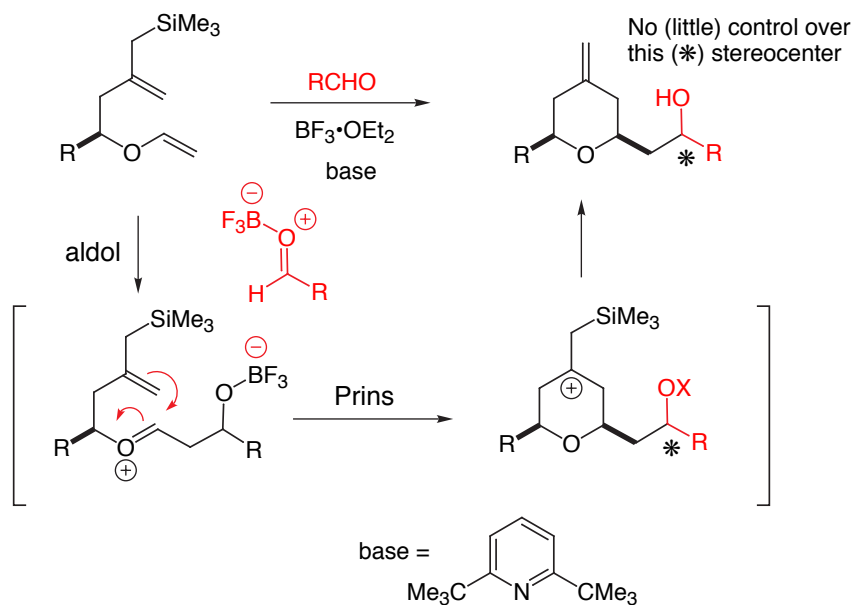
[3,3] rearrangement faster than Mannich cyclization



Mukaiyama Aldol-Prins Cascade

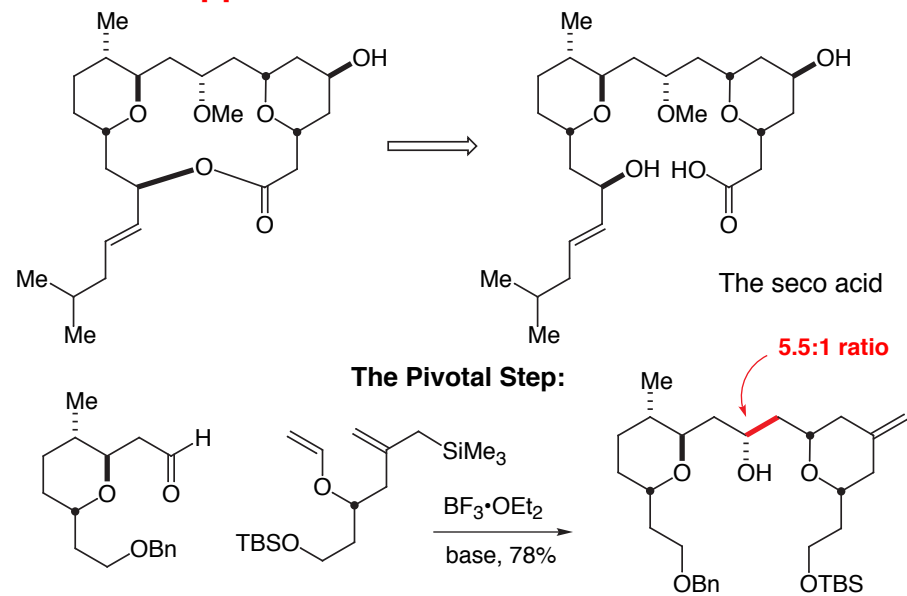
Rychnovsky JACS, 2001, 123, 8420

The Basic Process

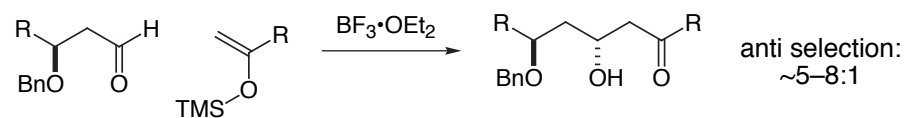
Let $EI(+)$ = Lewis acid activated RCHO

33-07-Prins-4 12/8/03 8:49 AM

Application to Leucasandrolide



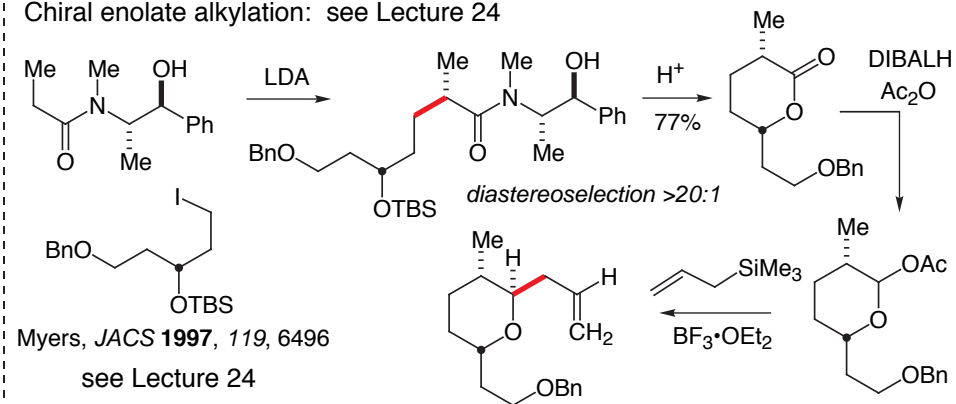
Control of hydroxyl center: see Lecture 20-21



Evans et al., JACS 1996, 116, 4322

Aldehyde Synthesis

Chiral enolate alkylation: see Lecture 24

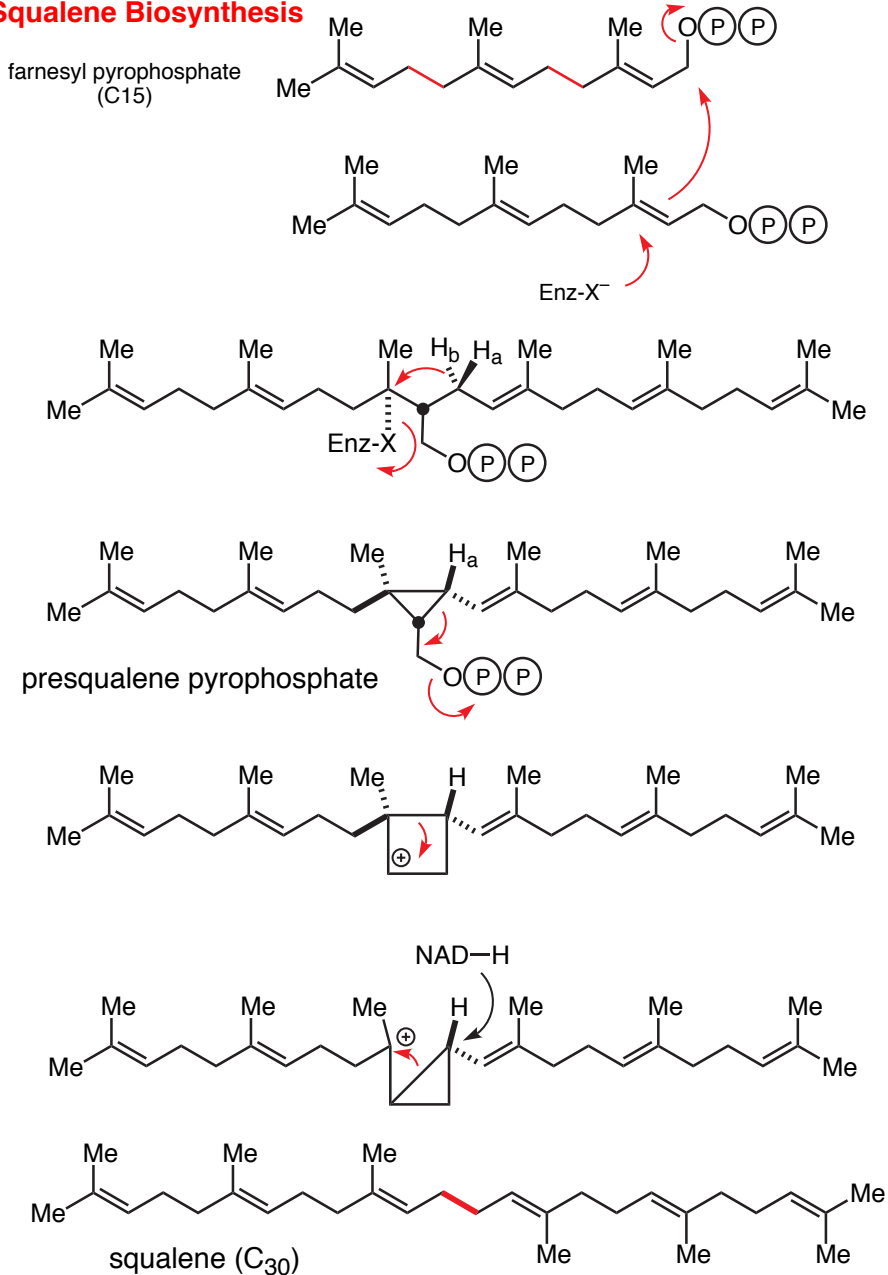


Myers, JACS 1997, 119, 6496

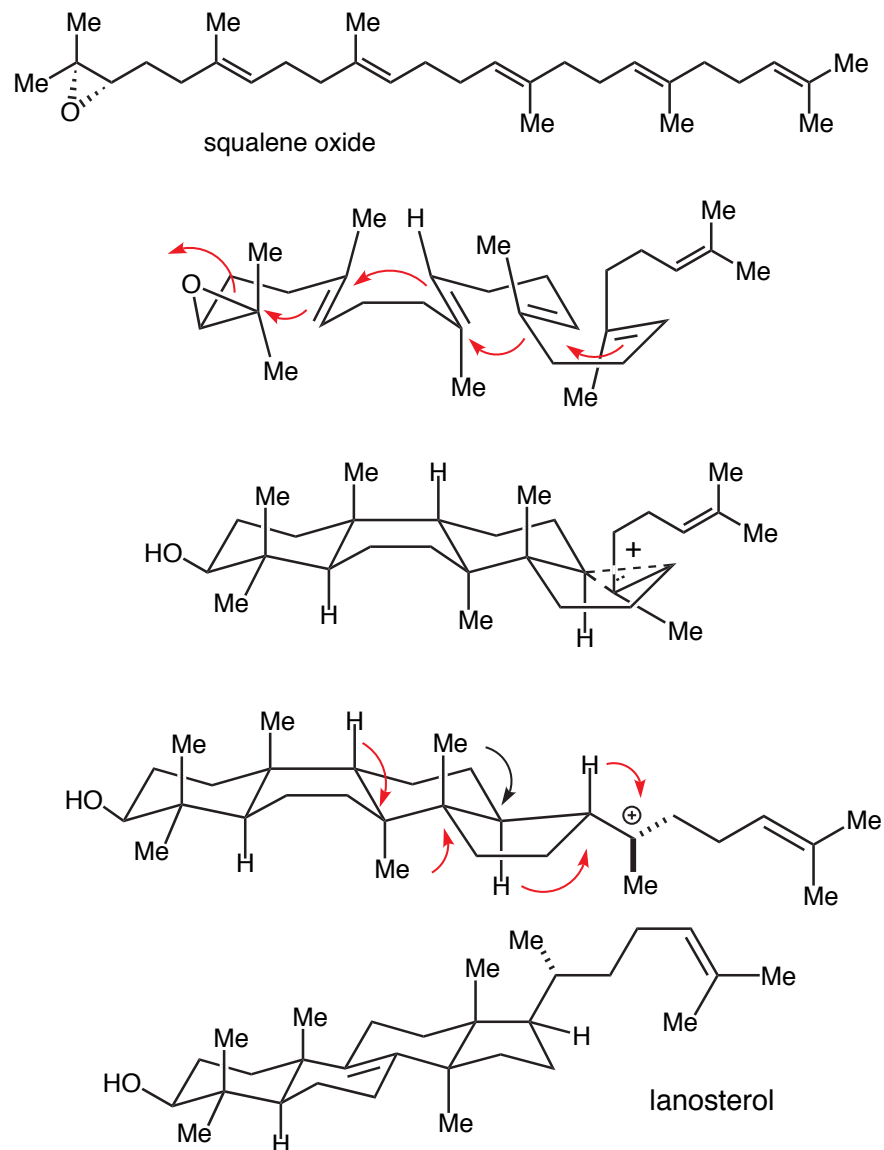
see Lecture 24

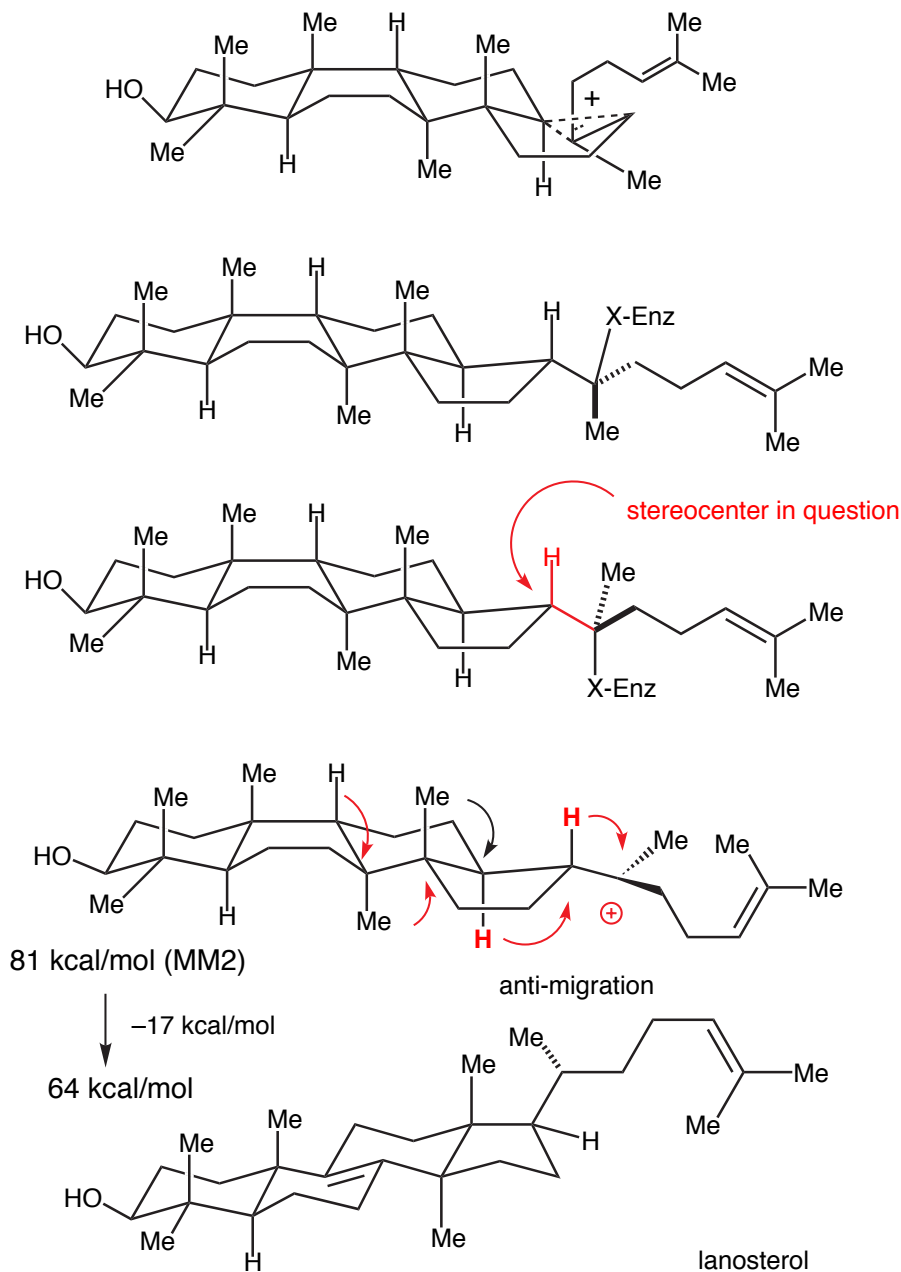
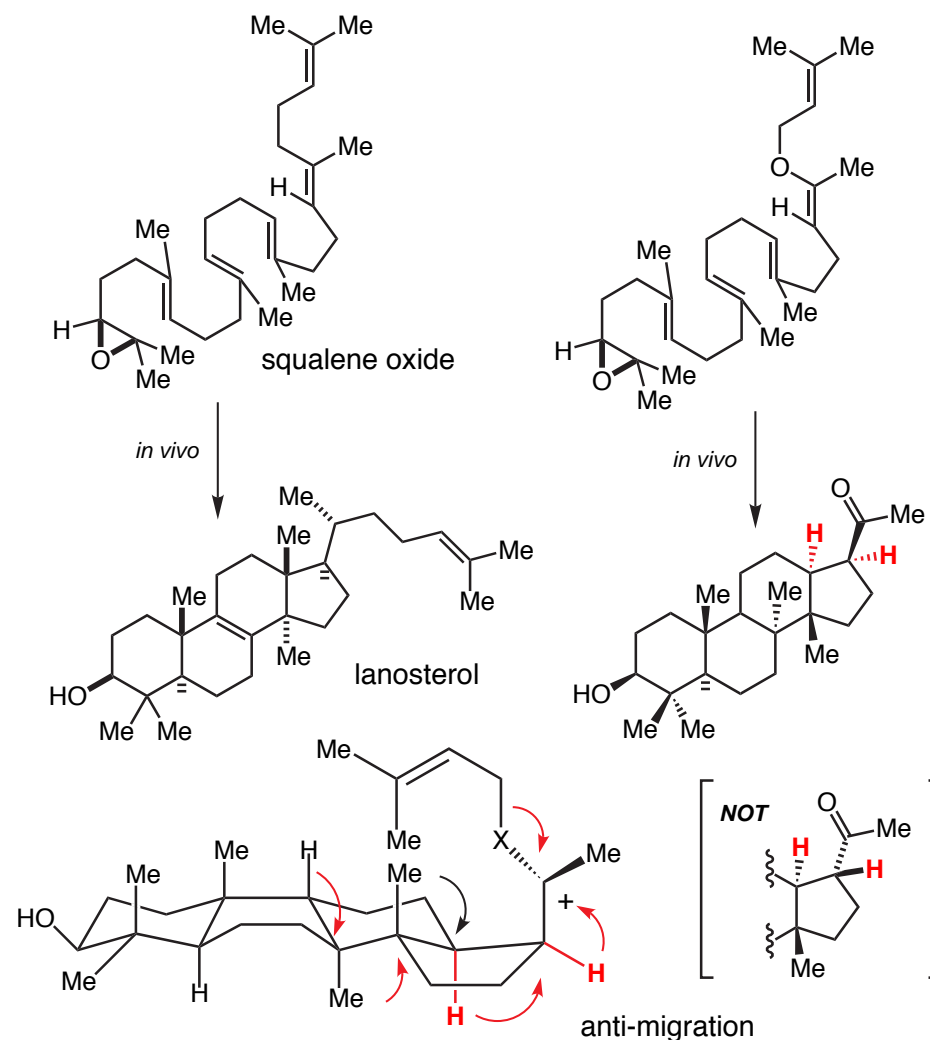
cyclic oxo-carbenium ion addition: see Lecture 20

Squalene Biosynthesis



Squalene Oxide Cyclase

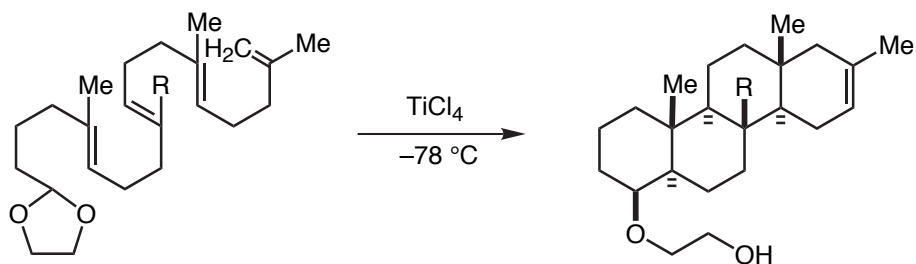
Prestwiltch, et. al. *Chem. Rev.* **1993**, 93, 2189-2206Cornforth Proposal: *ACIEE*, **1968**, 903.

Squalene Oxide Cyclase - Cornforth Proposal: *ACIEE*, 1968, 903.Corey-Virgil Revision: *JACS* 1991, 113, 4025-4026; 8171-8172

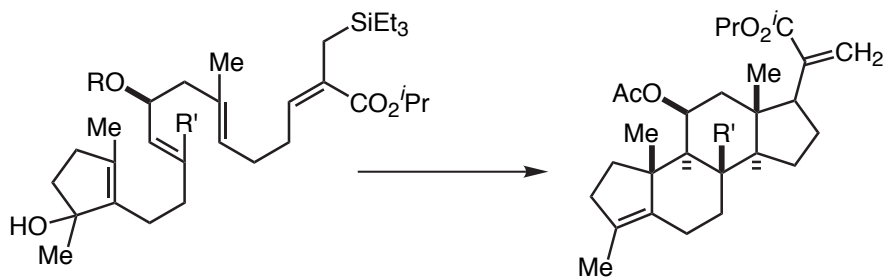
Sir John Cornforth:

*"That outpost of empire Australia,
produces some curious mammalia,
the kangaroo rat,
the blood-sucking bat,
and Arthur J. Birch, inter alia."*

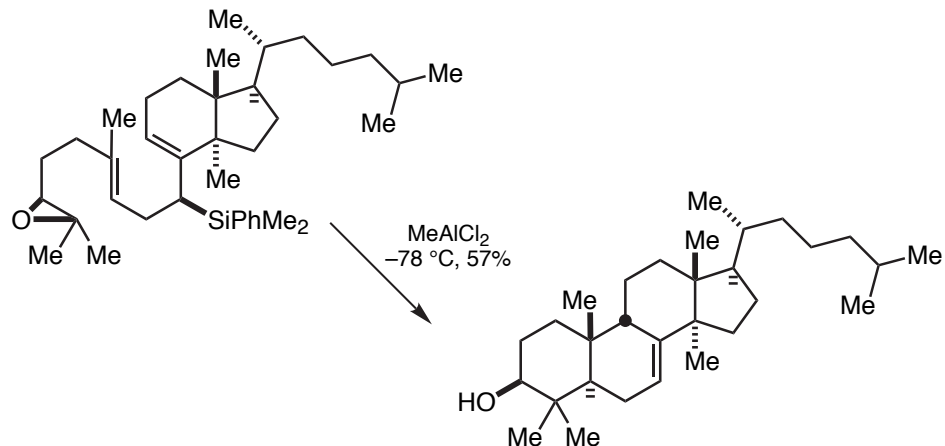
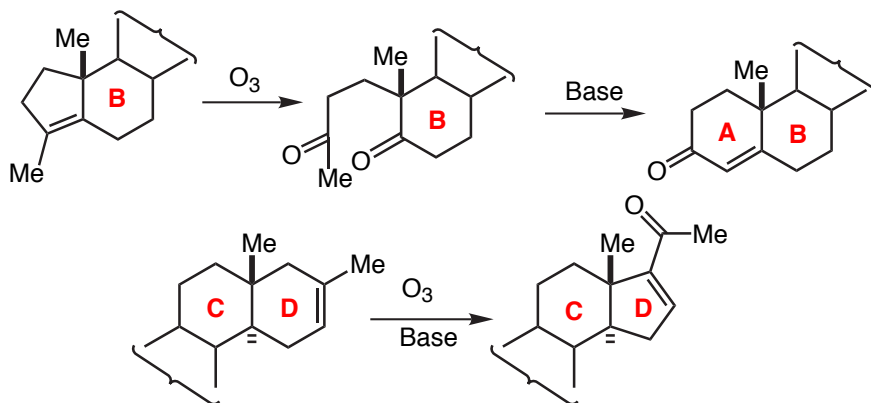
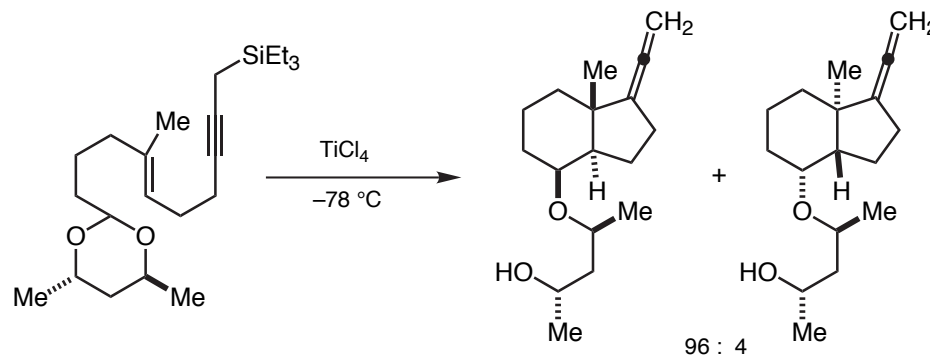
*If you are anxious for over-exposure,
to prepublication disclosure,
to good food and good drink,
without leisure to think,
try IUPAC symposia."*

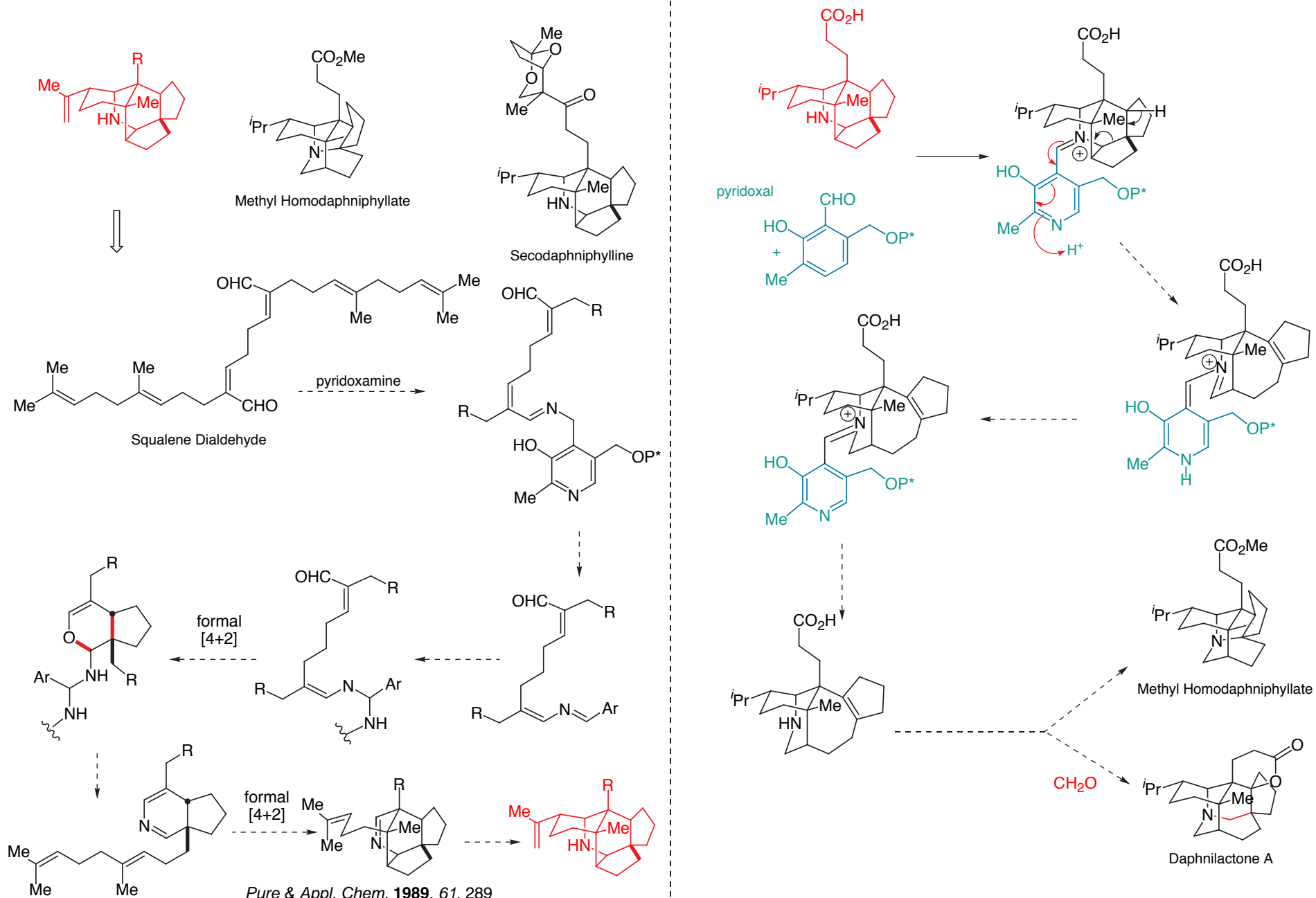
Biomimetic Polyene CyclizationsJohnson, et al. *JACS* **1987**, 109, 2517.

R = H ca. 30%
R = $\text{CH}=\text{CH}_2$ 77%

Johnson, et al. *JACS* **1987**, 109, 5852.

R = OH, R' = H 20%, 24 hr.
R = OAc, R' = $\text{CH}=\text{CH}_2$ 80%, 1 min.

Post cyclization transformation: JohnsonE. J. Corey, et al. *Tetrahedron Lett.* **1994**, 35, 9149.**Cyclization to Form Simpler Bicyclics**Johnson, et al. *JACS* **1984**, 106, 1138.**Introduction of chiral auxiliaries for C=O groups**



Pure & Appl. Chem. **1989**, *61*, 289
J. Am. Chem. Soc. **1986**, *108*, 8274

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

Chemistry 206

Advanced Organic Chemistry

Handout 33A

Introduction to Carbonium Ions—4

- Stabilized Carbocations: Oxo-Carbenium Ions (C=OR(+))
- Introduction to Terpene Biosynthesis
- Squalene, Lanosterol, & Cholesterol Biosynthesis
- Polyene Cyclizations
- Chiral Acetals as C=O Auxiliaries

Reading Assignment for this Lecture:

Carey & Sundberg, *Advanced Organic Chemistry*, 4th Ed. Part A Chapter 5, "Nucleophilic Substitution", 263-350.

Heathcock, C. H. (1992). "The enchanting alkaloids of Yuzuriha." *Angew. Chem., Int. Ed. Engl.* 31: 665. (handout)

Other Excellent References

Bartlett, P. A. (1984). "Olefin Cyclisation Processes That Form Carbon-Carbon Bonds". *Asymmetric Synthesis. Stereodifferentiating Reactions, Part B.* J. D. Morrison. New York, AP. vol 3: 341.

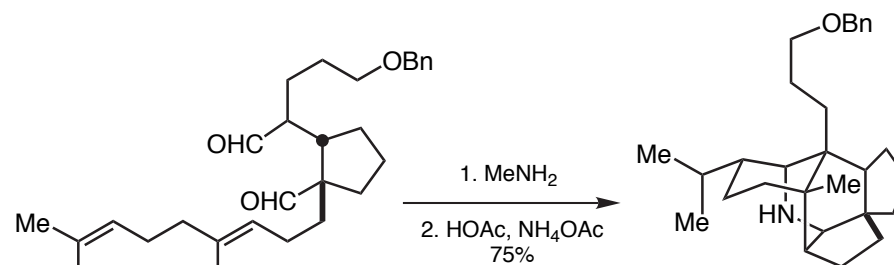
Thebtaranonth, C. and Y. Thebtaranonth (1994). "Cyclization Reactions". Boca Raton, FL, CRC Press.

Corey & Liu, enzyme "Mechanism for Polycyclic Triterpene Formation," *Angew. Chem. Int. Ed.* 2000, 39, 2812-2833

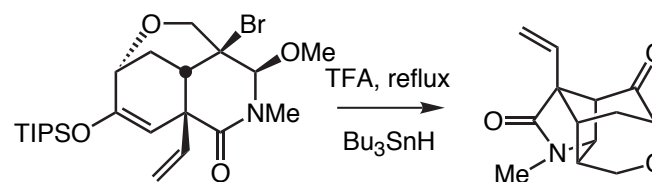
D. A. Evans

Monday,
December 8, 2003

Several Complex Mechanisms



Angew. Chem. Int. Ed. Engl. 1978, 17, 476.
J. Org. Chem. 1990, 57, 2544.



A. P. Johnson et al., *JCS Chem. Commun.* 1994, 6, 765

"That outpost of empire Australia,
produces some curious mammalia,
the kangaroo rat,
the blood-sucking bat,
and Arthur J. Birch, inter alia."

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."

Suggested Reading

"An Experimental Demonstration of the Stereochemistry of Enzymic Cyclization of 2,3-Oxidosqualene...."

E. J. Corey, S. C. Virgil *JACS*, **1991**, 113, 4025.

"New Mechanistic and Stereochemical Insights on the Biosynthesis of Sterols from 2,3-Oxidosqualene Cyclase"

E. J. Corey, et al. *JACS* **1991**, 113, 8171.

"Enzymatic Cyclization of Squalene and Oxidosqualene to Sterols and Terpenoids" Abe, et al. *Chem. Rev.* **1993**, 93, 2189.

"Isoprenoid Biosynthesis. Stereochemistry of the Cyclization of Allylic Pyrophosphates." D. E. Cane *Acc. Chem. Res.* **1985**, 18, 220.

"Biomimetic Polyene Cyclizations"

W. S. Johnson *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 9.

Interesting Reading

Science, **1997**, v277:

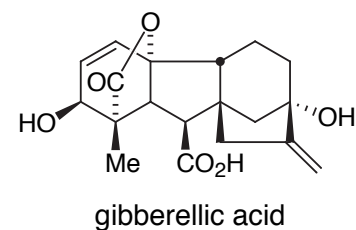
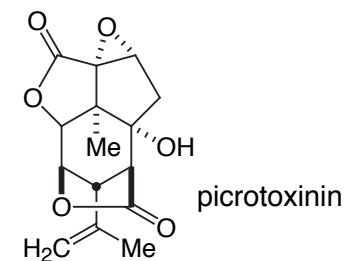
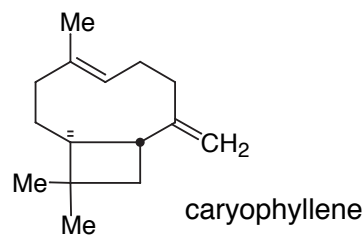
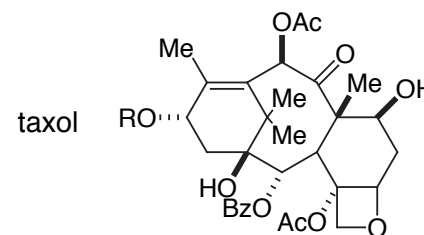
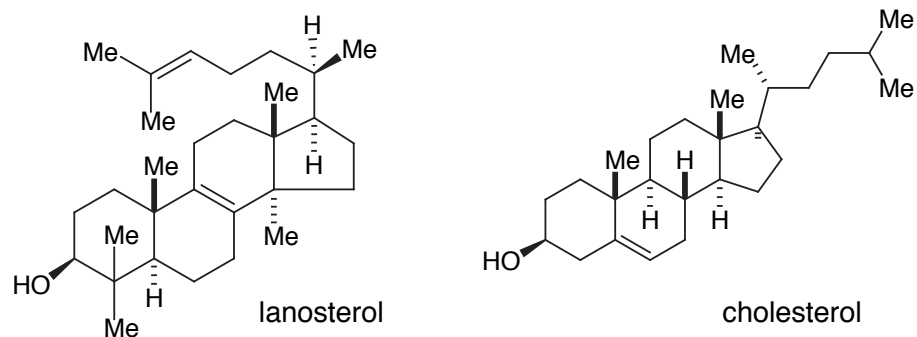
"Structure and Function of the Squalene Cyclase", G. Shultz, p. 1811.

"Structural Basis for Cyclic Terpene Biosynthesis by Tobacco 5-epi-Aristolochene", J. P. Noel, p. 1815.

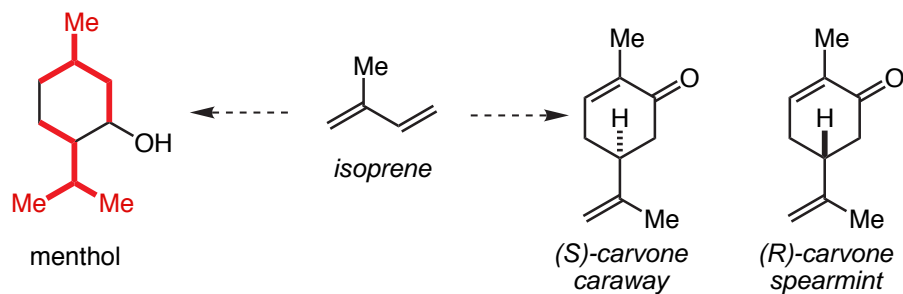
"Crystal Structure of Pentalene Synthase: Mechanistic Insights on Terpenoid Cyclization Reactions in Biology", D. W. Christianson, p. 1821.

"The Stereochemistry of Allylic Pyrophosphate Metabolism." D. E. Cane *Chem. Rev.* **1980**, 36, 1109.

"Biosynthesis of Natural Products" P. Manitto; Wiley&Sons, NY: 1981.

Representative Terpenes

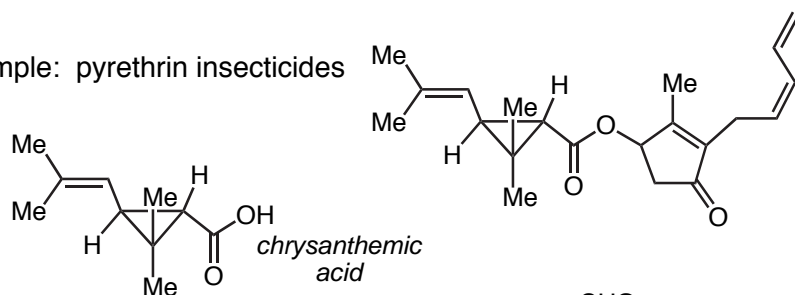
- Definition: Natural products whose carbon skeletons are built up largely from isoprene subunits:



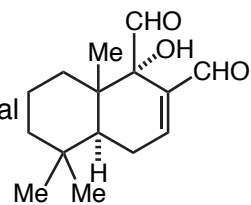
- Occurance: Plants, insects, higher organisms

- Role in plants: hormones, defense etc.

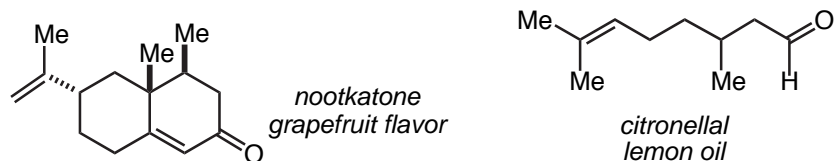
example: pyrethrin insecticides



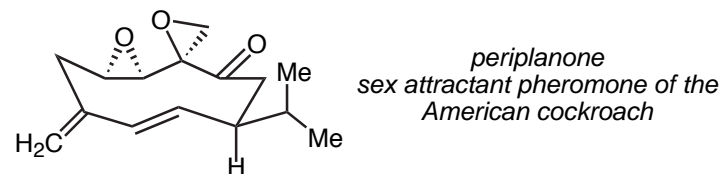
example: antifeedants such as warburganal



example: flavor constituents

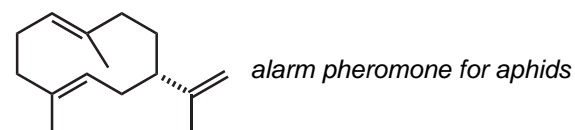
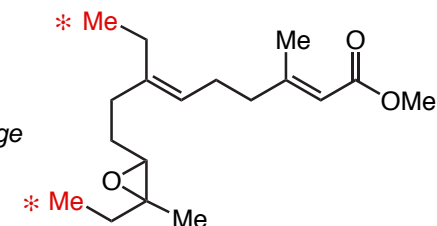


- Role in insects: hormones, pheromones (communication chemicals)

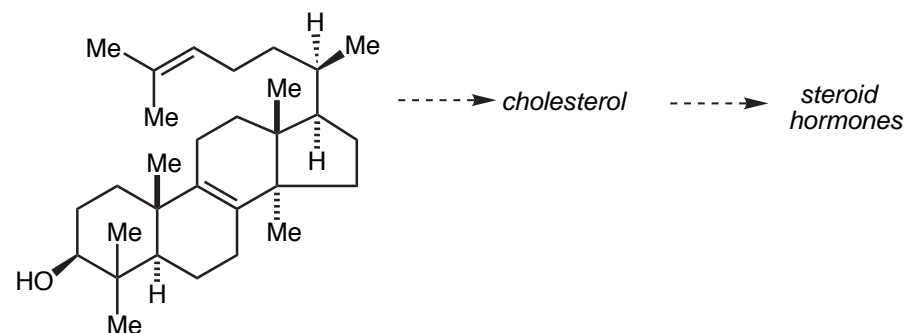


Cecropia juvenile hormone
blocks development at larval growth stage

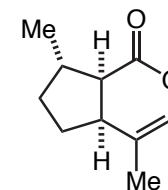
note that the starred methyls are
not derived from isoprene

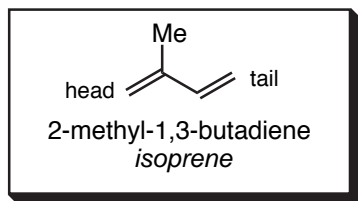


- Role in mammals: hormones, pheromones ??



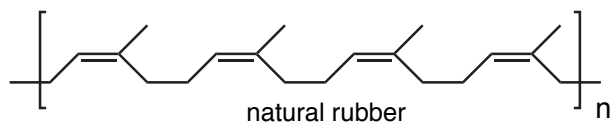
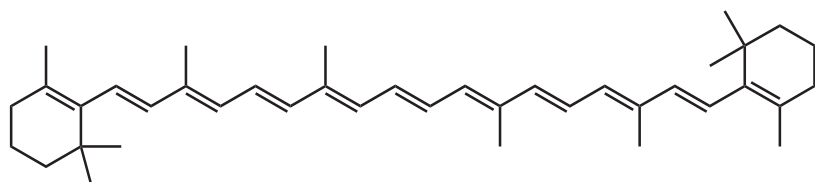
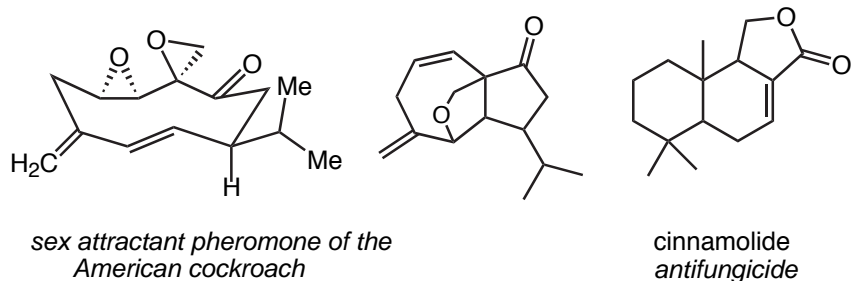
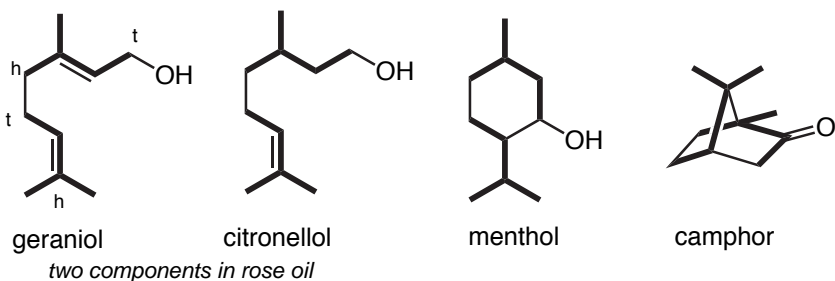
nepetalactone
oil of catnip
active at nanomolar-femtomolar concentrations
is this related to a feline pheromone?





Classification of terpenes

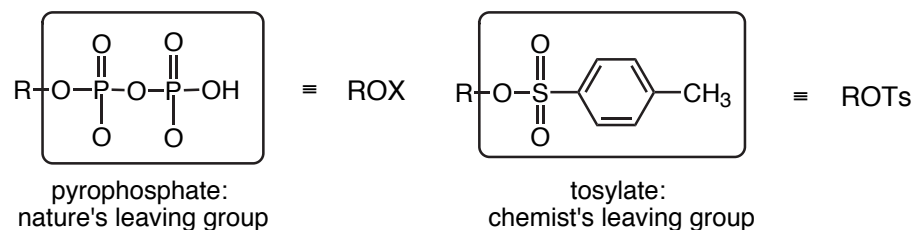
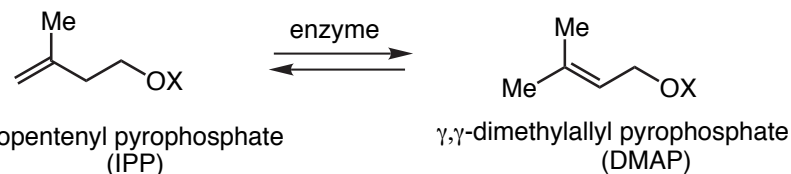
monoterpenes : 10 C-atoms (2 isoprene units)
 sesquiterpenes : 15 C-atoms (3 isoprene units)
 diterpenes : 20 C-atoms (4 isoprene units)
 triterpenes : 30 C-atoms (6 isoprene units)



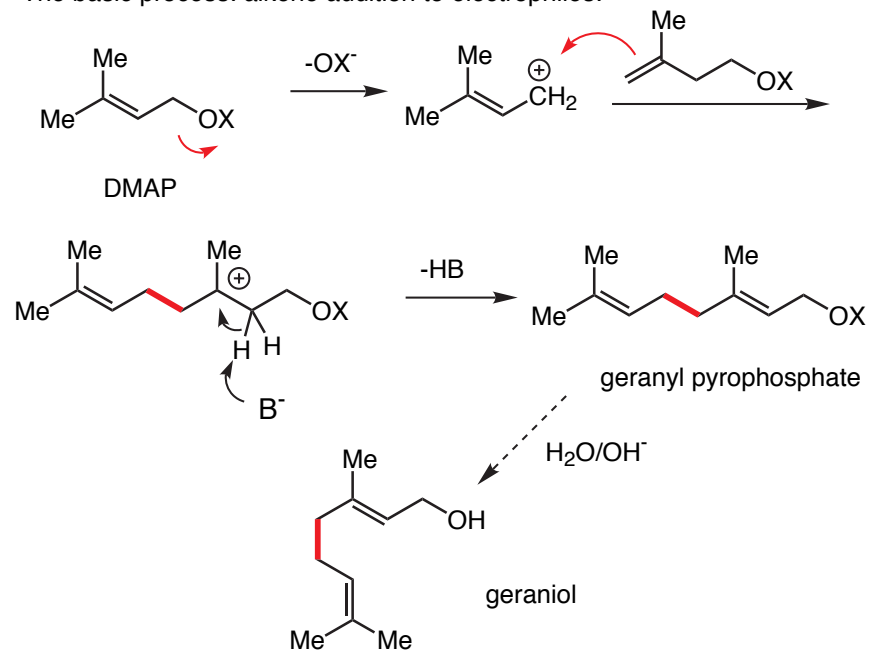
Practice: Recognize the isoprene units in the above structures.

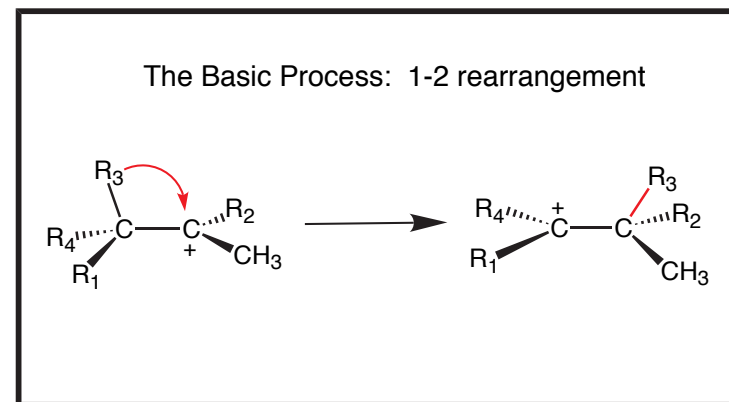
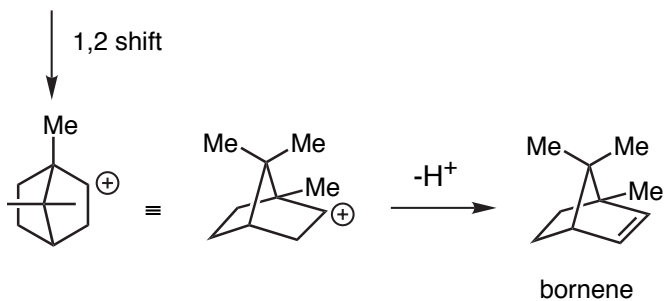
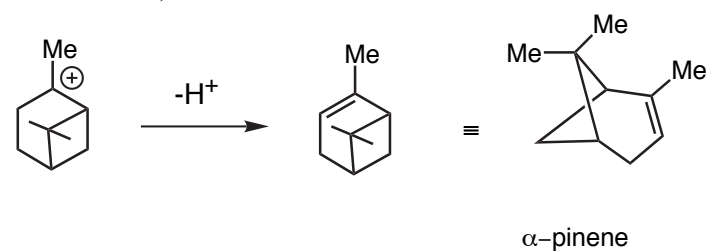
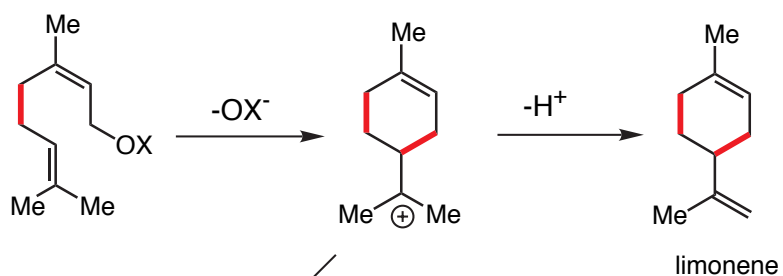
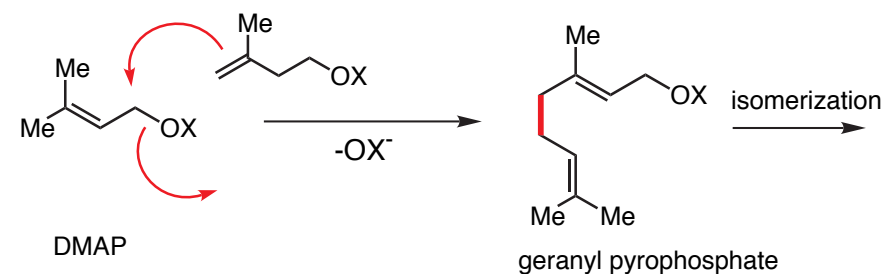
Terpene Biosynthesis

There are two isoprene units which are used to build up terpenes:

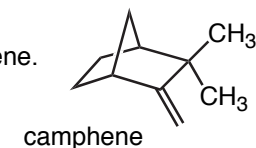


The basic process: alkene addition to electrophiles:

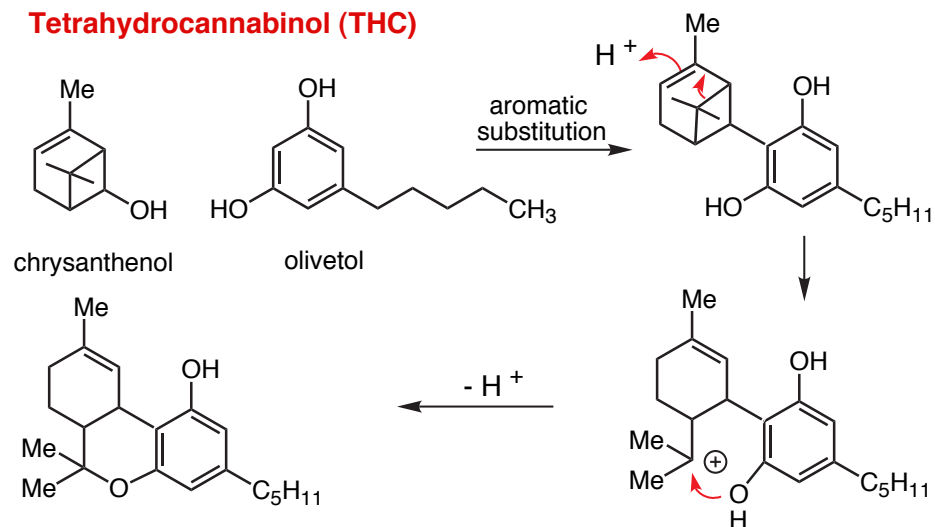


From isoprene to α -pinene and bornene

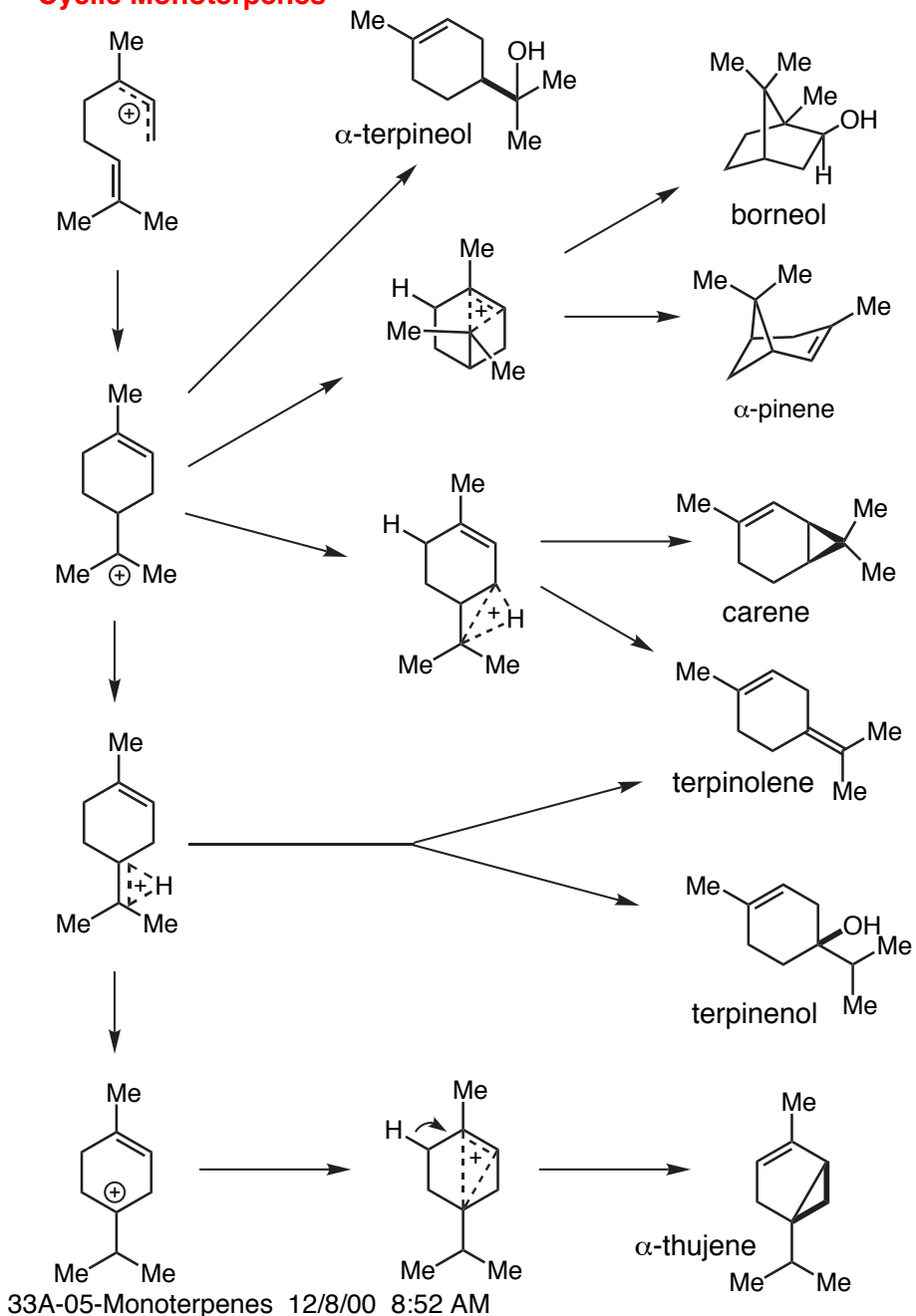
The precursor of bornene could also lead to camphene. Show the mechanism!



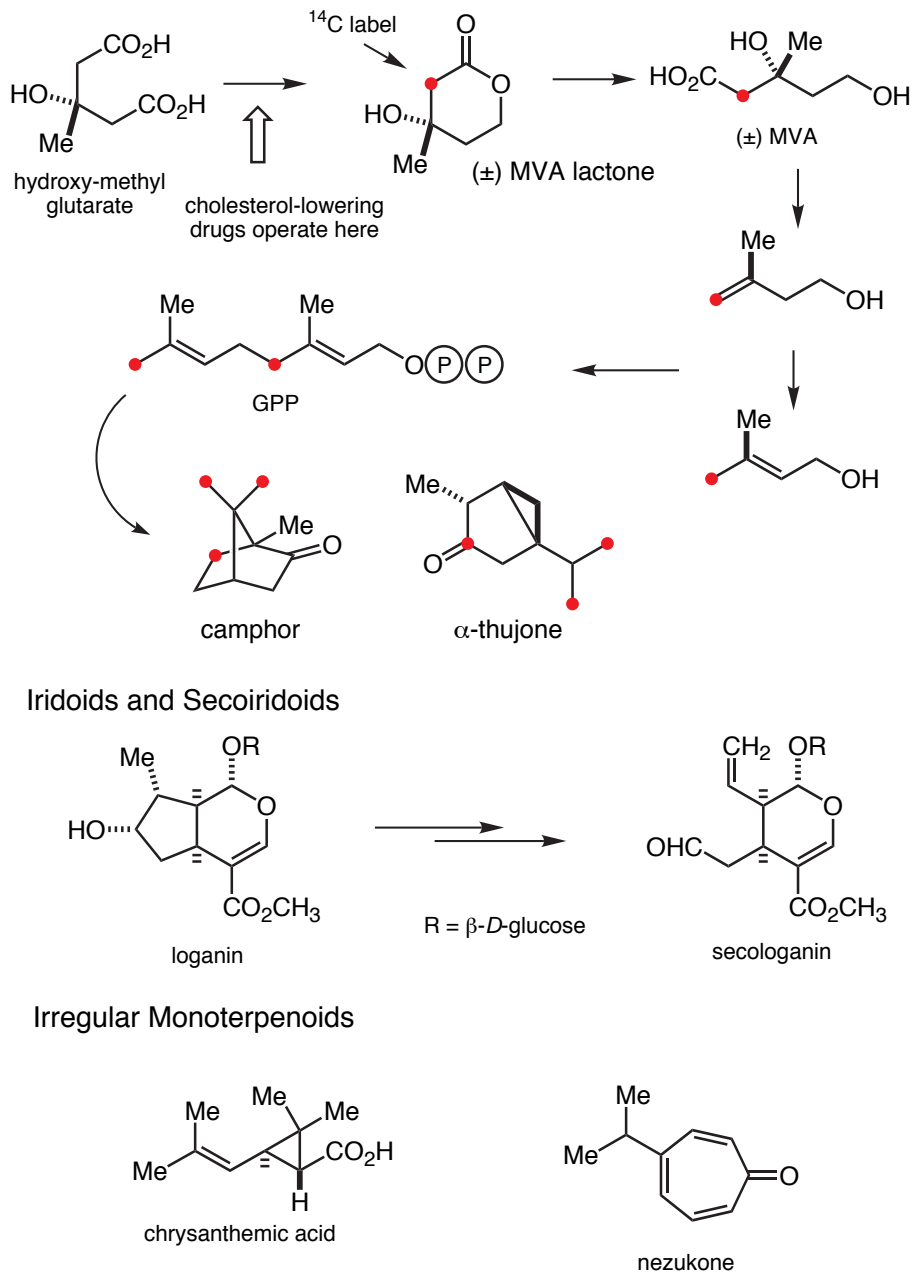
Tetrahydrocannabinol (THC)

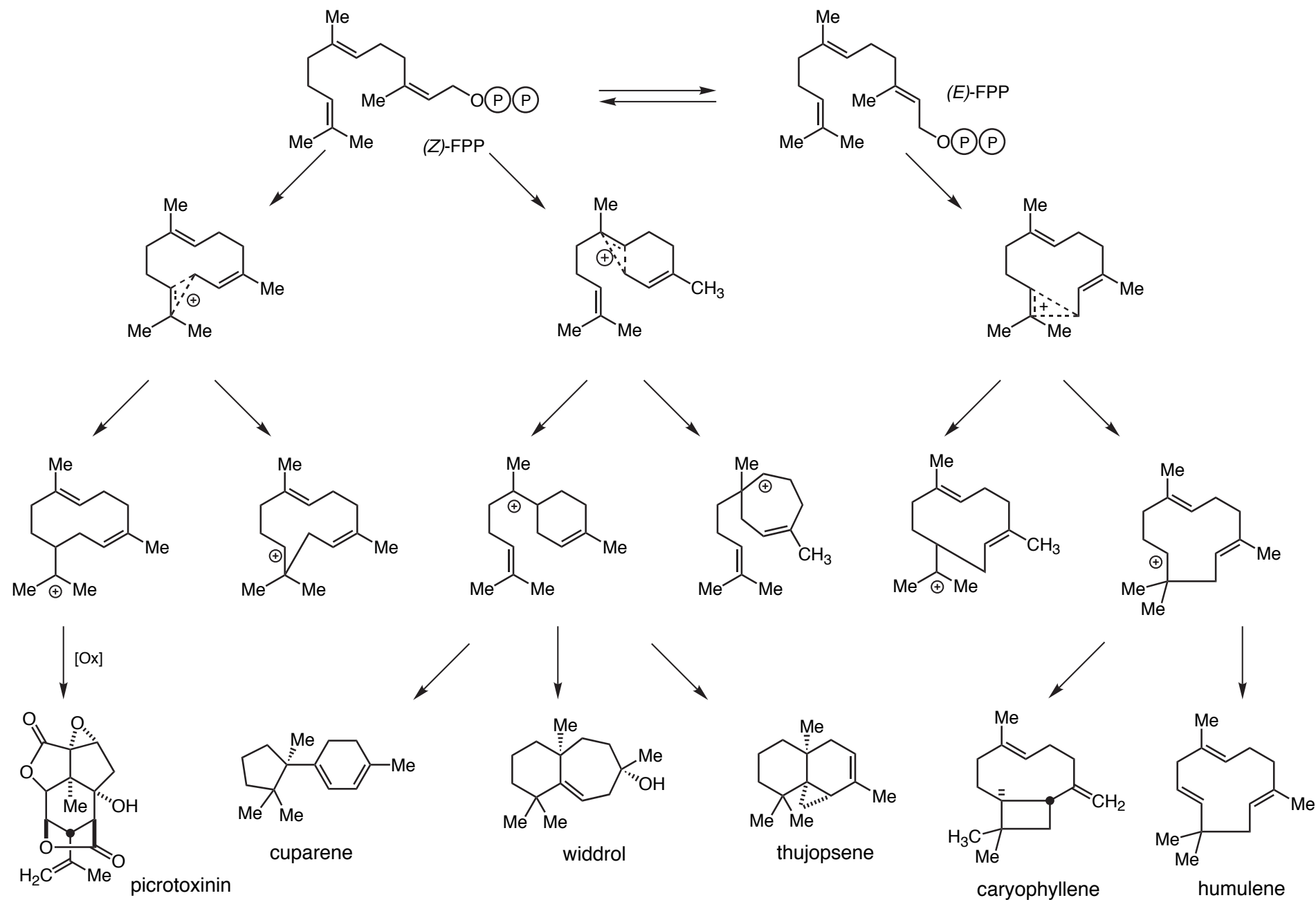


Cyclic Monoterpenes

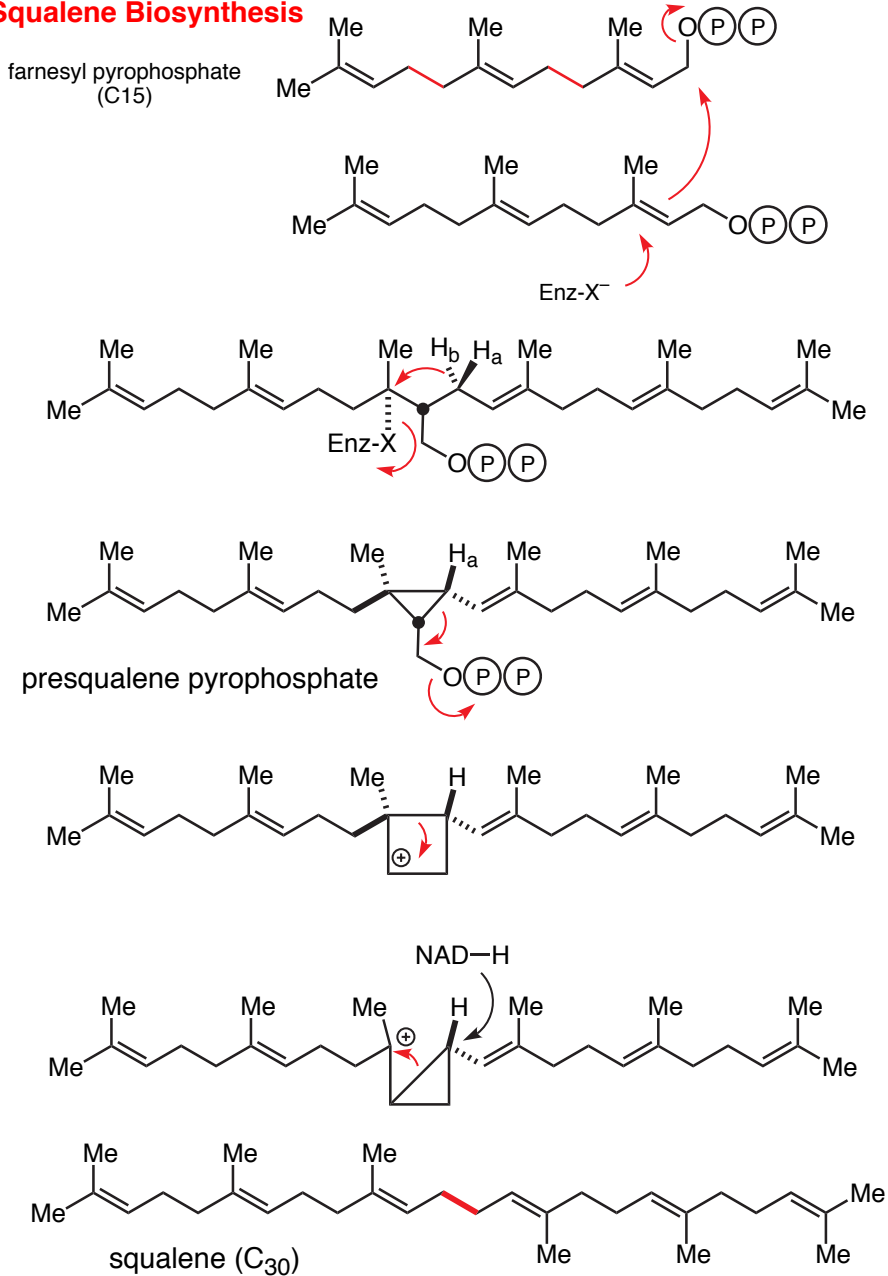


Biosynthetic Study of Monoterpenes

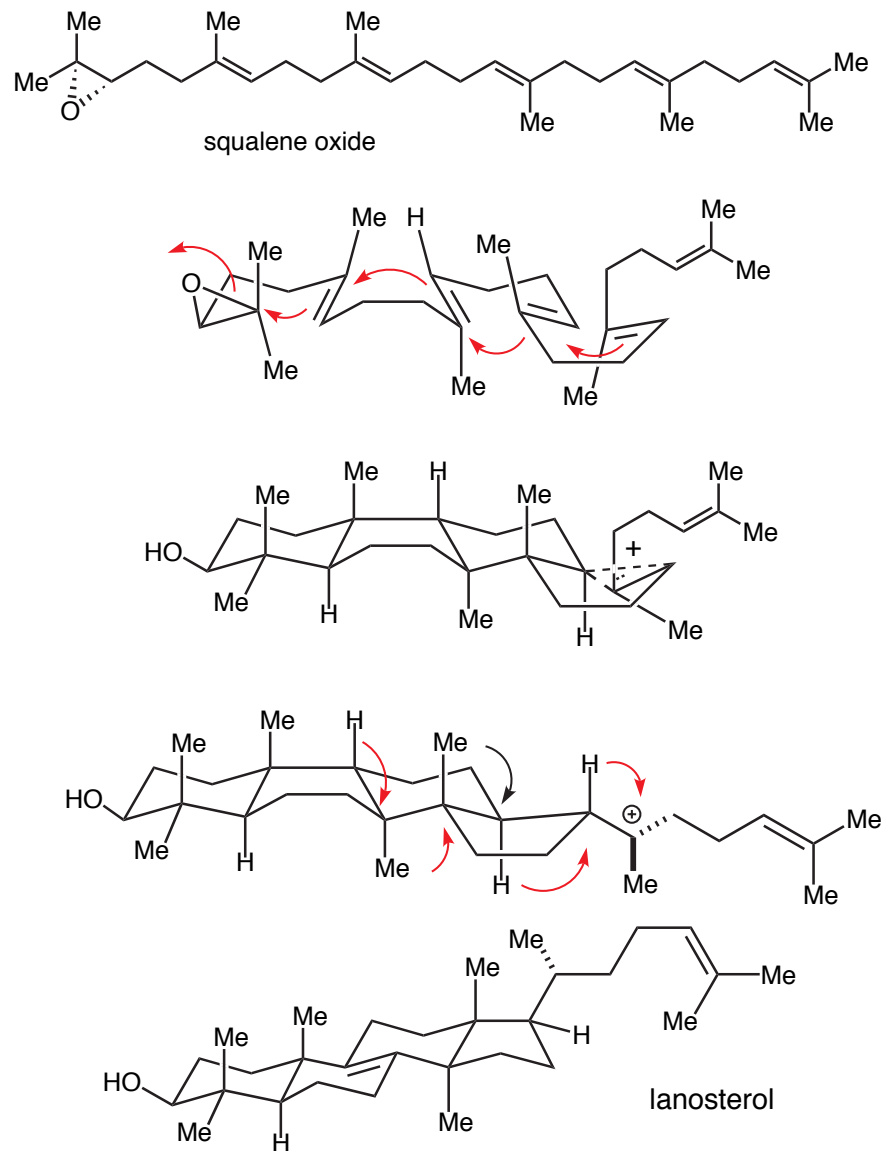




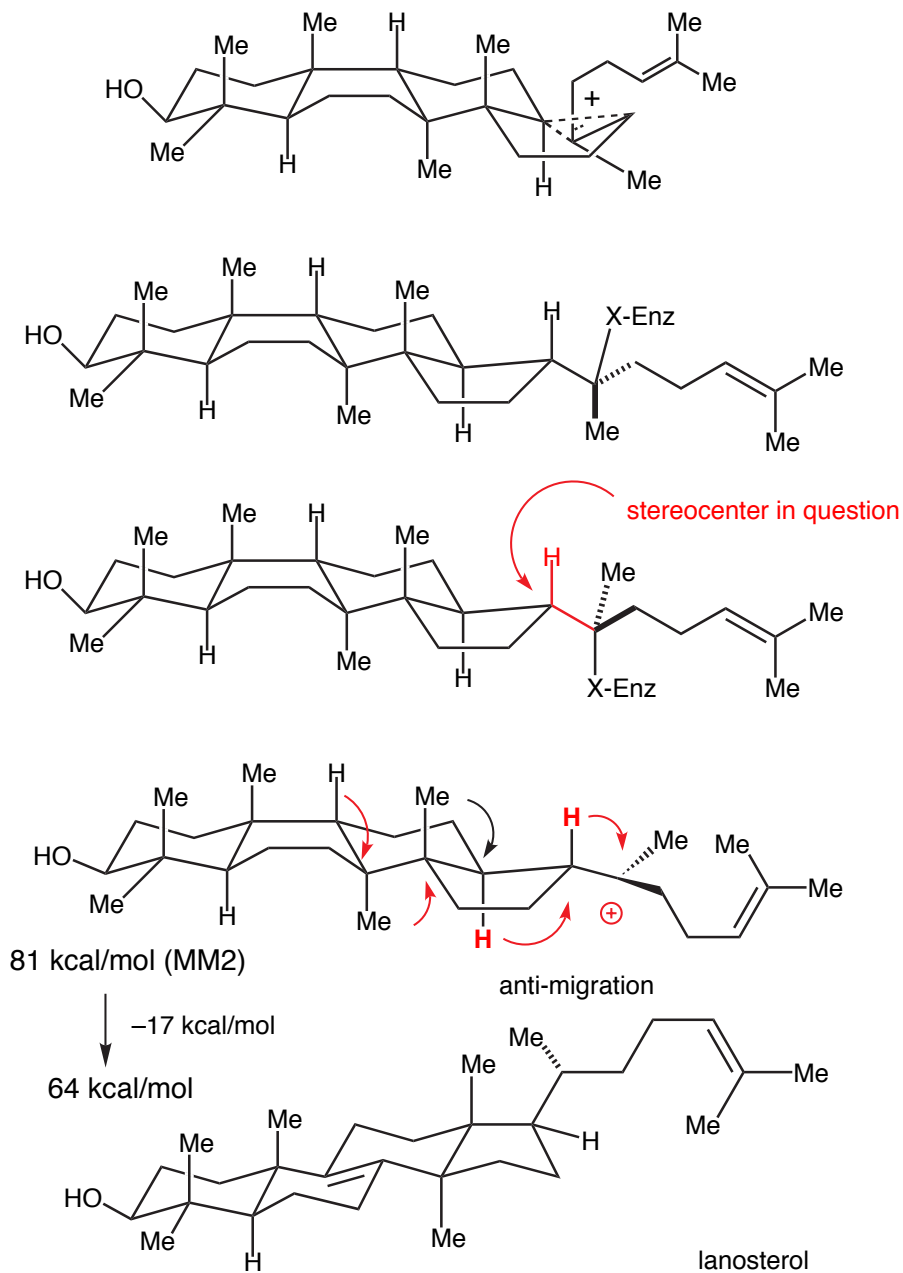
Squalene Biosynthesis



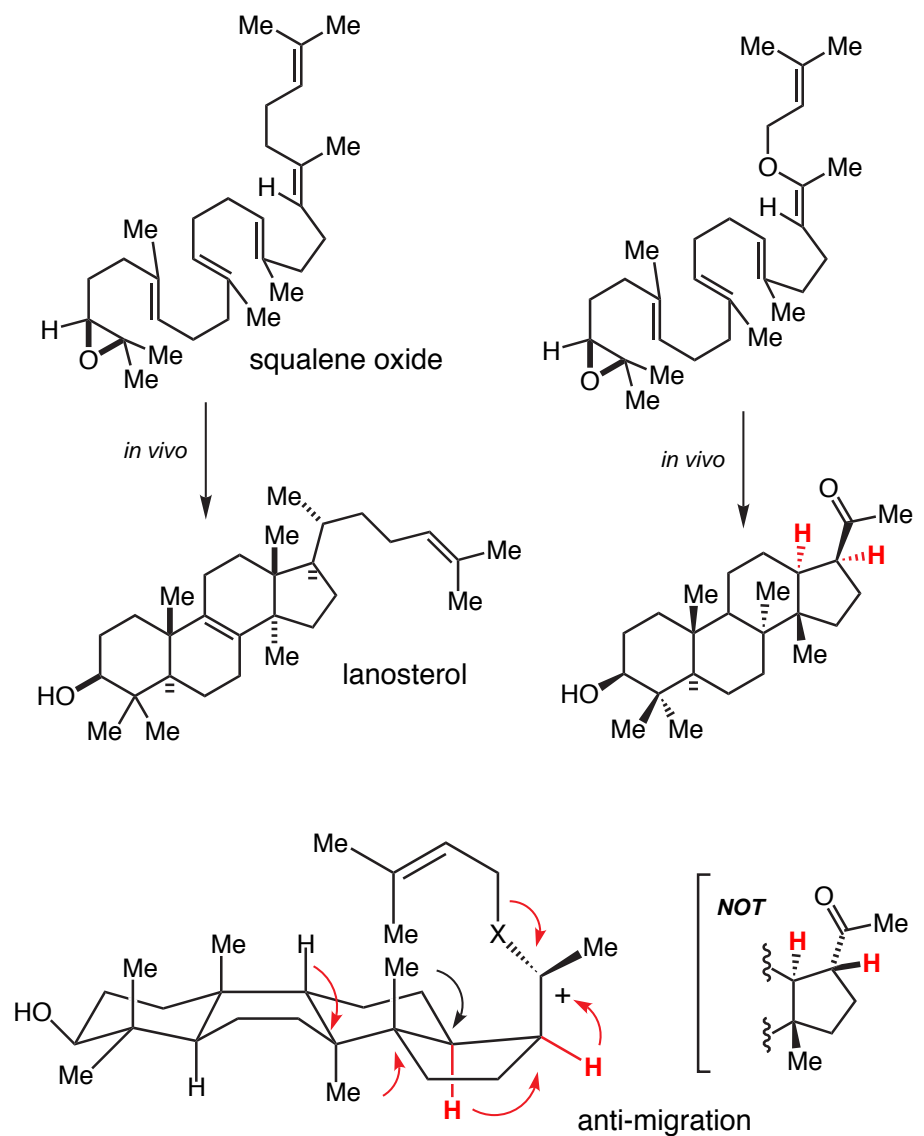
Squalene Oxide Cyclase

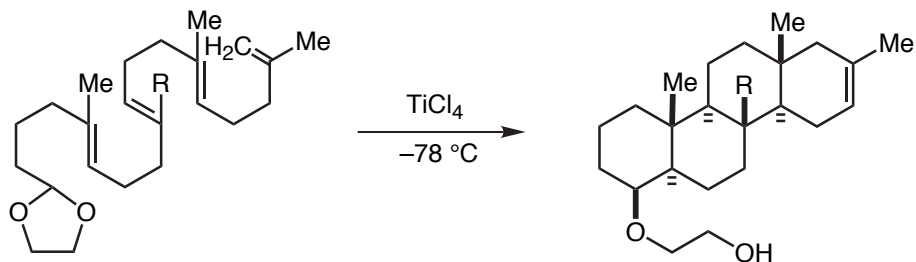
Prestwiltch, et. al. *Chem. Rev.* **1993**, 93, 2189-2206Cornforth Proposal: *ACIEE*, **1968**, 903.

Squalene Oxide Cyclase - Cornforth Proposal: *ACIEE*, 1968, 903.

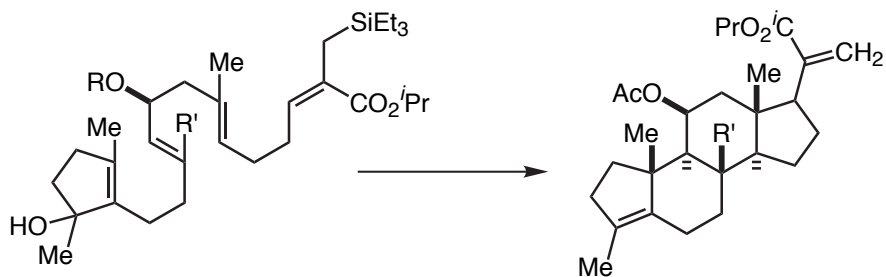


Corey-Virgil Revision: *JACS* 1991, 113, 4025-4026; 8171-8172

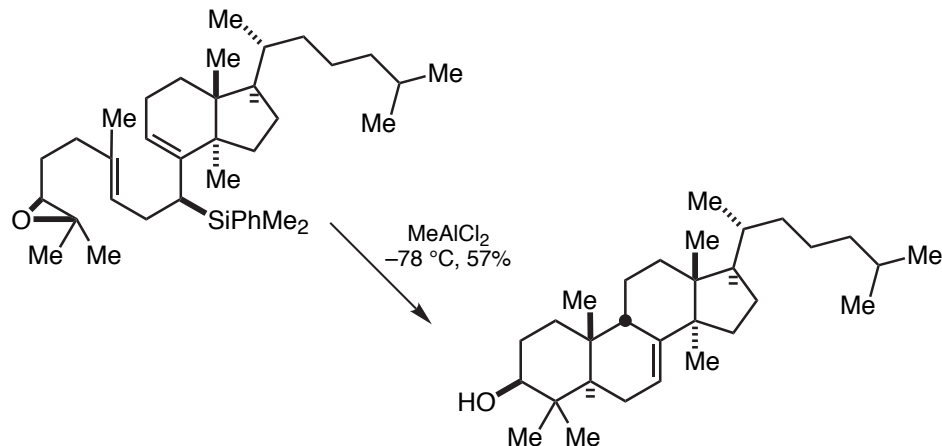
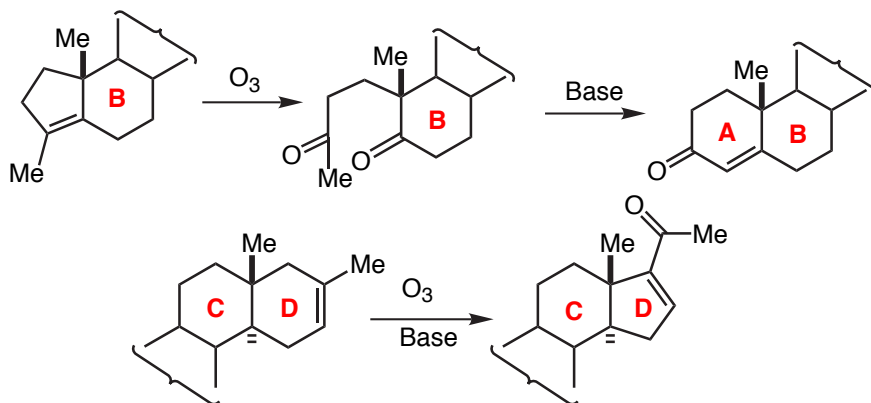
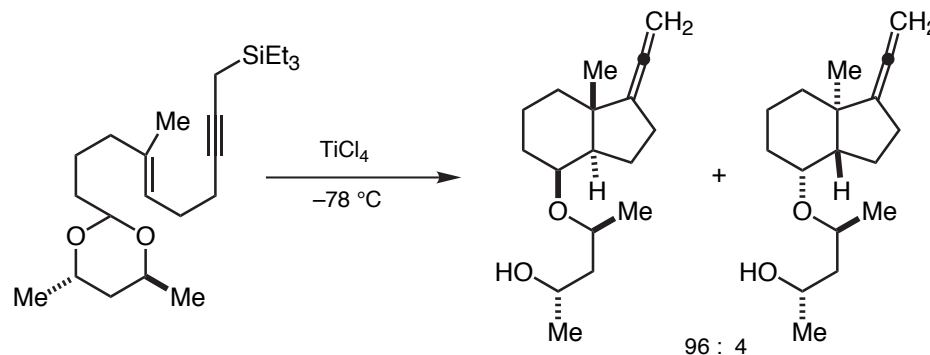


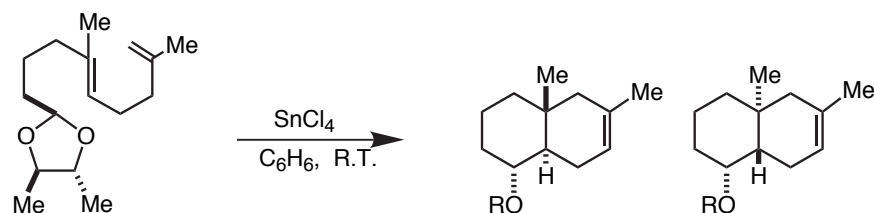
Biomimetic Polyene CyclizationsJohnson, et al. *JACS* **1987**, *109*, 2517.

R = H ca. 30%
R = CH=CH₂ 77%



Johnson, et al. *JACS* **1987**, *109*, 5852.
R = OH, R' = H 20%, 24 hr.
R = OAc, R' = CH=CH₂ 80%, 1 min.

Post cyclization transformation: JohnsonE. J. Corey, et al. *Tetrahedron Lett.* **1994**, *35*, 9149.**Cyclization to Form Simpler Bicyclics**Johnson, et al. *JACS* **1984**, *106*, 1138.**Introduction of chiral auxiliaries for C=O groups**



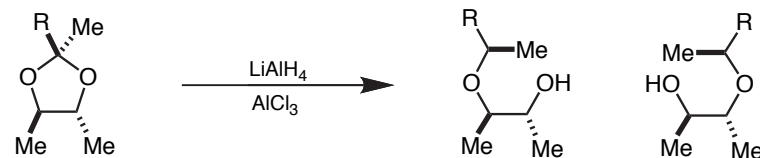
W. S. Johnson & Co-workers,
J. Am. Chem. Soc., **1976**, 98, 6188.

Ratio = 72 : 28 de = 84%



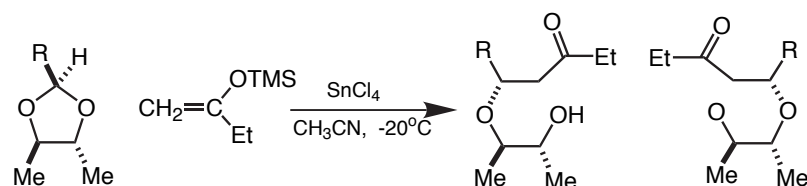
W. J. Richter, *J. Org. Chem.*, **1981**, 46, 5119.

R	ratio
Et	01:99
t-Bu	22:78
Ph	14:86



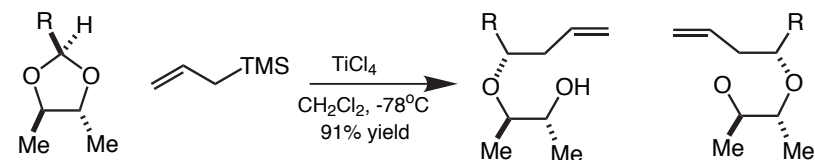
W. J. Richter, *J. Org. Chem.*, **1981**, 46, 5119.

R	ratio
Et	73:24
t-Bu	85:15
Ph	51:46



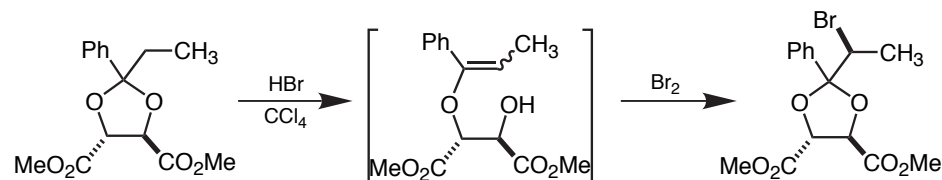
J. M. McNamara, Y. Kishi,
J. Am. Chem. Soc., **1982**, 104, 7371.

R	ratio
Ph	16:1
n-C ₉ H ₁₉	03:1



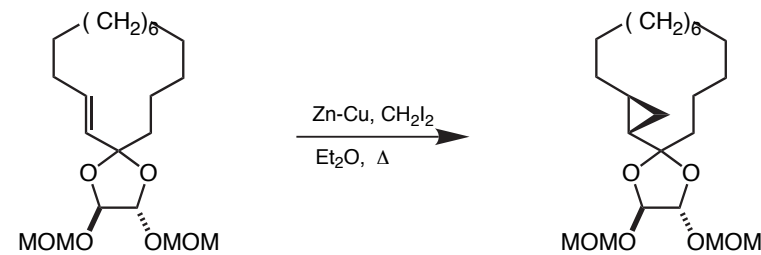
P. A. Bartlett & Co-workers,
J. Am. Chem. Soc., **1983**, 105, 2088

R = C₈H₁₇ Ratio = 88 : 12



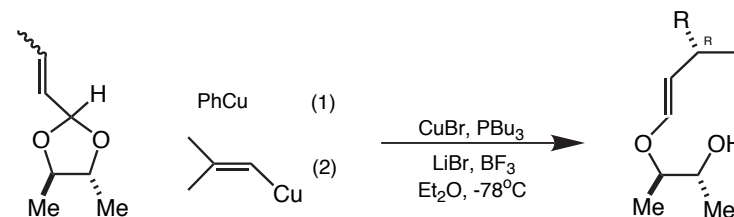
G. Castaldi & Co-workers,
Angew. Chem. I. E., **1986**, 25, 259.

94 % yield de = 86 %



K. A. Nelson & E. A. Mash,
J. Org. Chem., **1986**, 51, 2721.

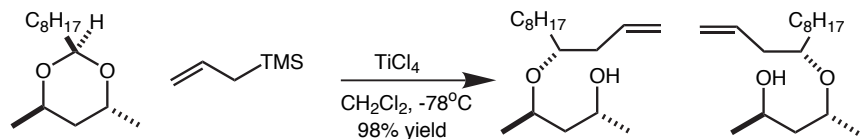
de = >95 %



P. Mangeney & Co-workers,
Tetrahedron Lett., **1987**, 28, 2363.

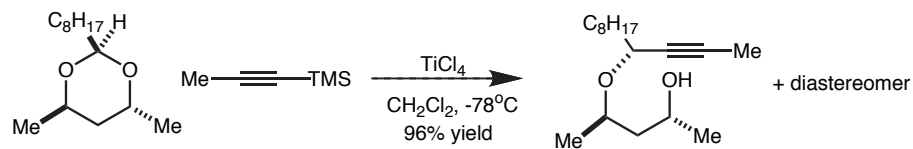
(error in R/S nomenclature in paper)

Acetal Isomer	Alkylating Agent (R)	Product E/Z	% Yield	% de
E	(1)	100/0	75	95 (R)
E	(2)	95/5	70	85 (R)
Z	(1)	100/0	75	69 (S)



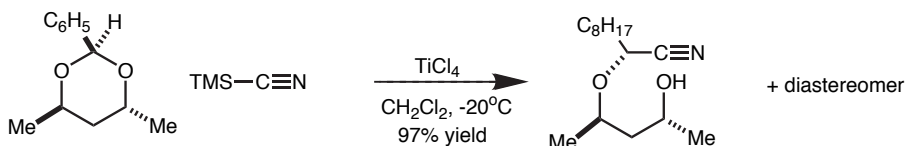
P. A. Bartlett & Co-workers,
J. Am. Chem. Soc., **1983**, *105*, 2088.

Ratio = 87 : 13



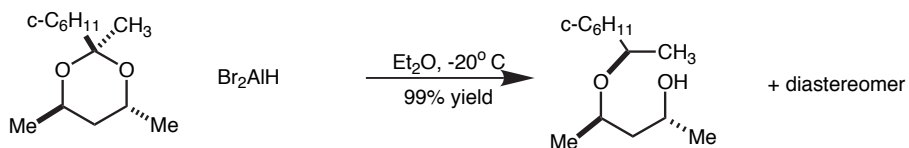
W. S. Johnson & Co-workers,
J. Am. Chem. Soc., **1983**, *105*, 2904.

Ratio = 93 : 7



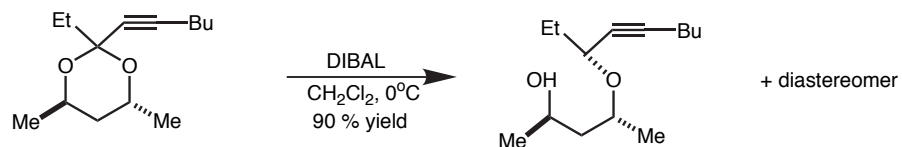
W. S. Johnson & Co-workers,
J. Org. Chem., **1983**, *48*, 2294.

Ratio = 96.5 : 3.5



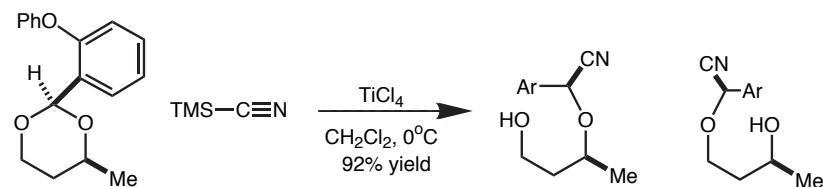
H. Yamamoto & Co-workers,
Tetrahedron Lett., **1983**, *24*, 4581.

Ratio = 23 : 1



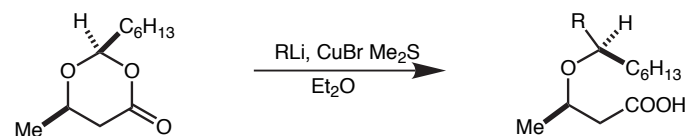
H. Yamamoto & Co-workers,
Tetrahedron Lett., **1986**, *27*, 983.

Ratio = 97 : 3
diastereoselection >99%



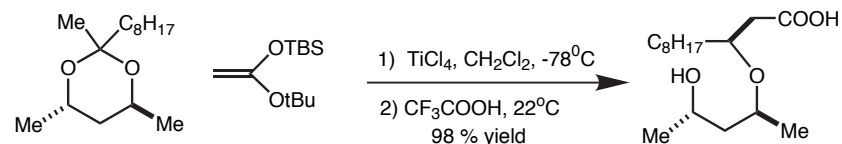
W. S. Johnson & Co-workers,
Tetrahedron Lett., **1984**, *25*, 591.

Ratio = 97 : 3, 88% de



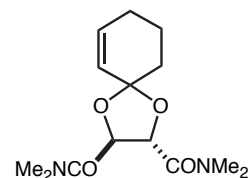
S. L. Schreiber & J. Reagan
Tetrahedron Lett., **1986**, *27*, 2945.

R	Temp.(°C)	% Yield	% de
Me	0	58	94
Ph	-30	90	97



J. D. Elliott & Co-workers,
Tetrahedron Lett., **1985**, *26*, 2535.

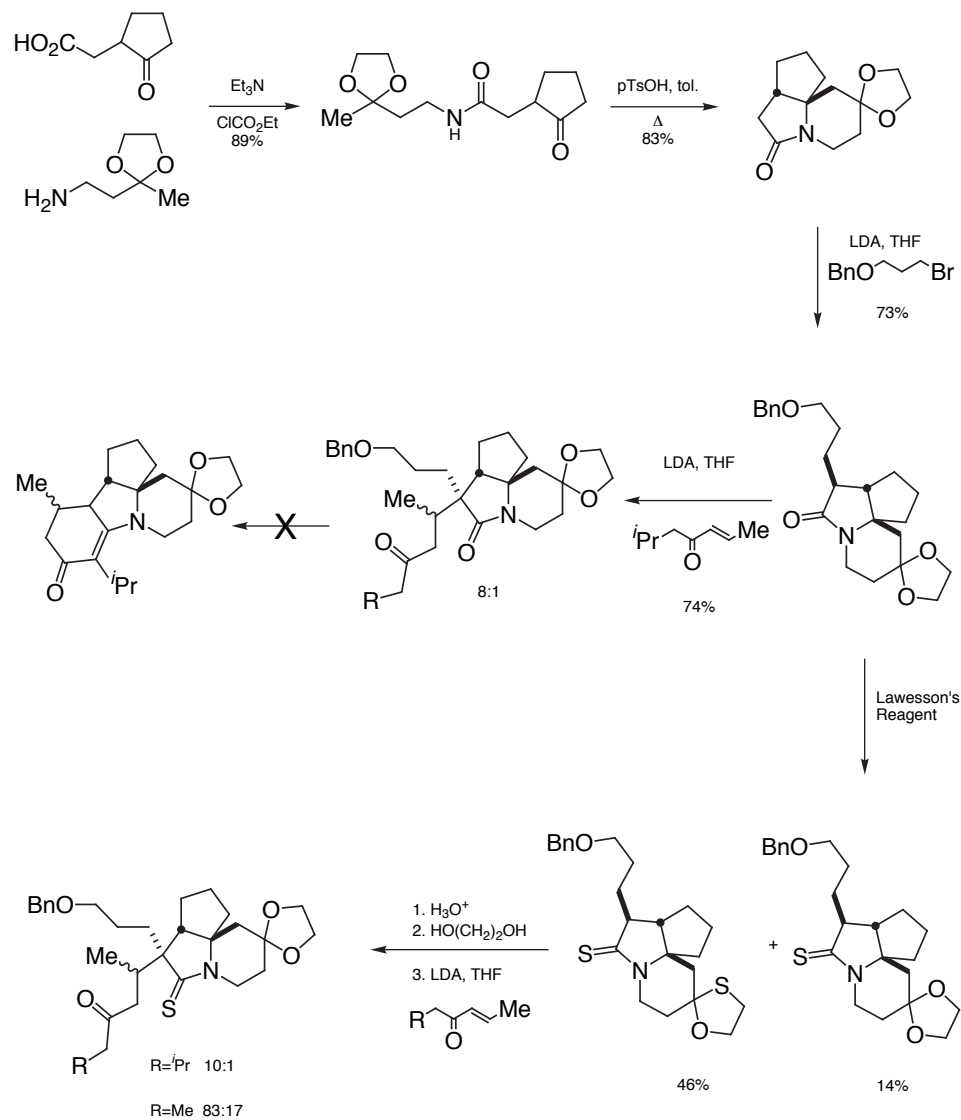
Ratio = 98 : 2



H. Yamamoto & Co-workers,
Tetrahedron Lett., **1984**, *25*, 5911.

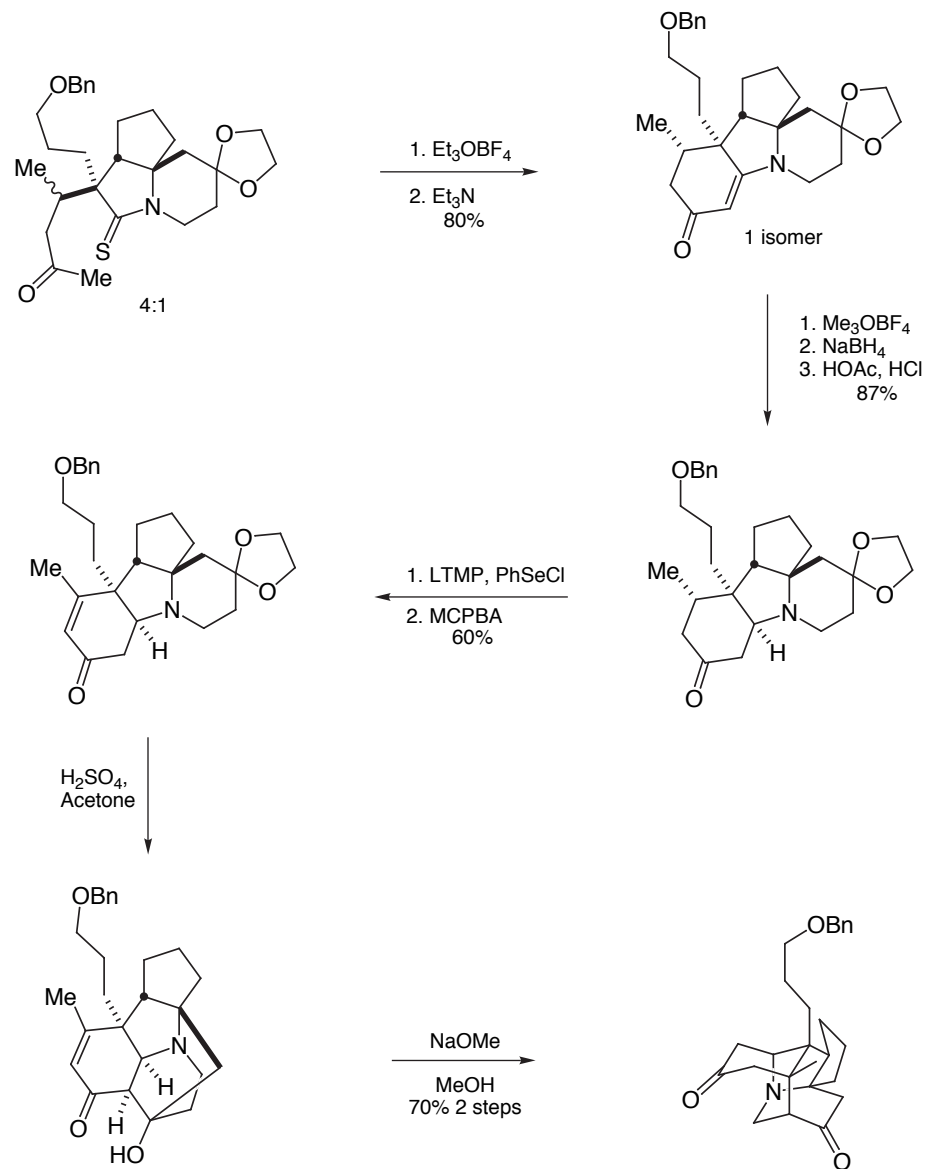
97% yield de = 77%

Synthesis of Methyl Homodaphniphyllate

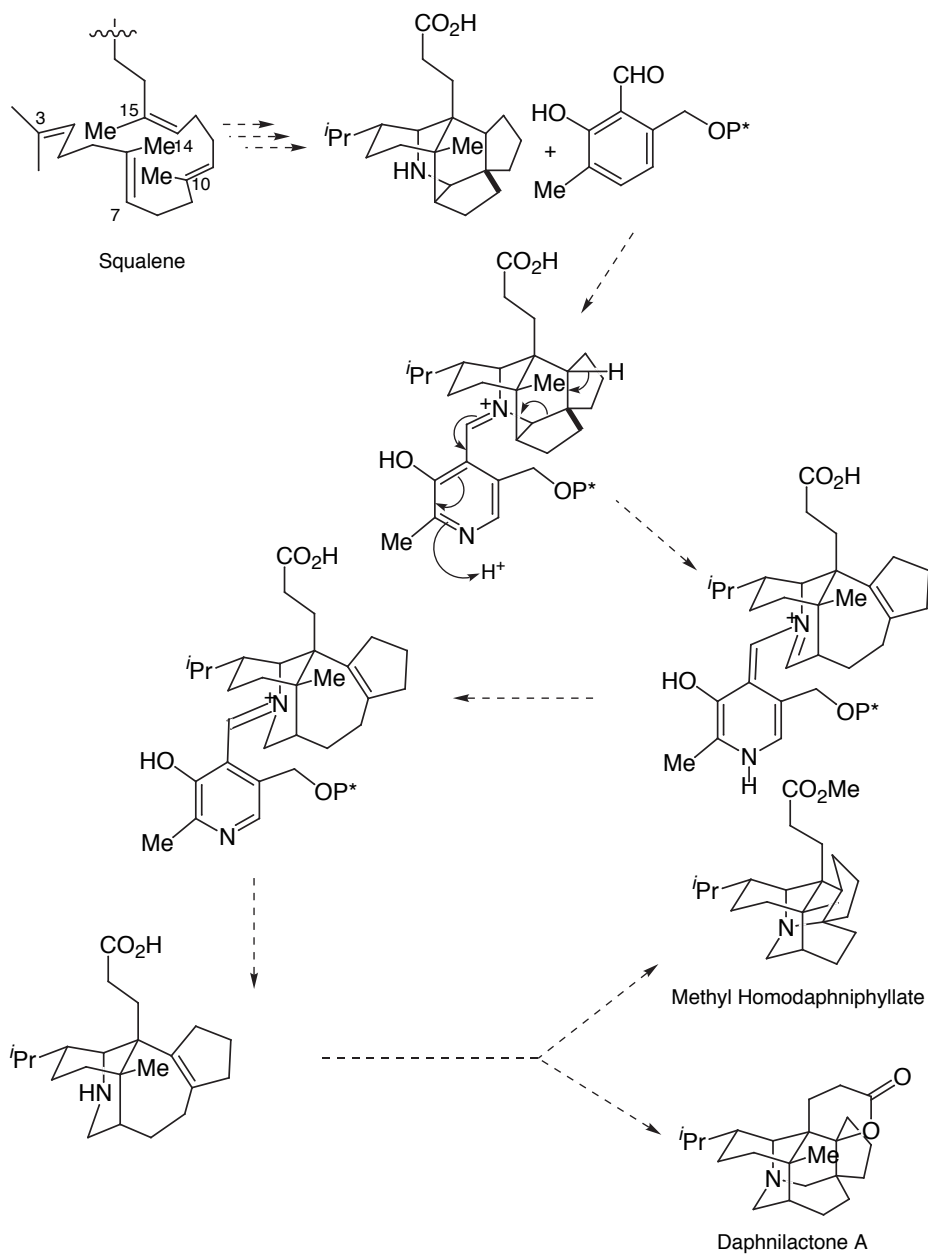


J. Am. Chem. Soc. **1986**, *108*, 5650
J. Org. Chem. **1992**, *57*, 2531
J. Am. Chem. Soc. **1968**, *90*, 6177
Nouv. J. Chem. **1980**, *4*, 47

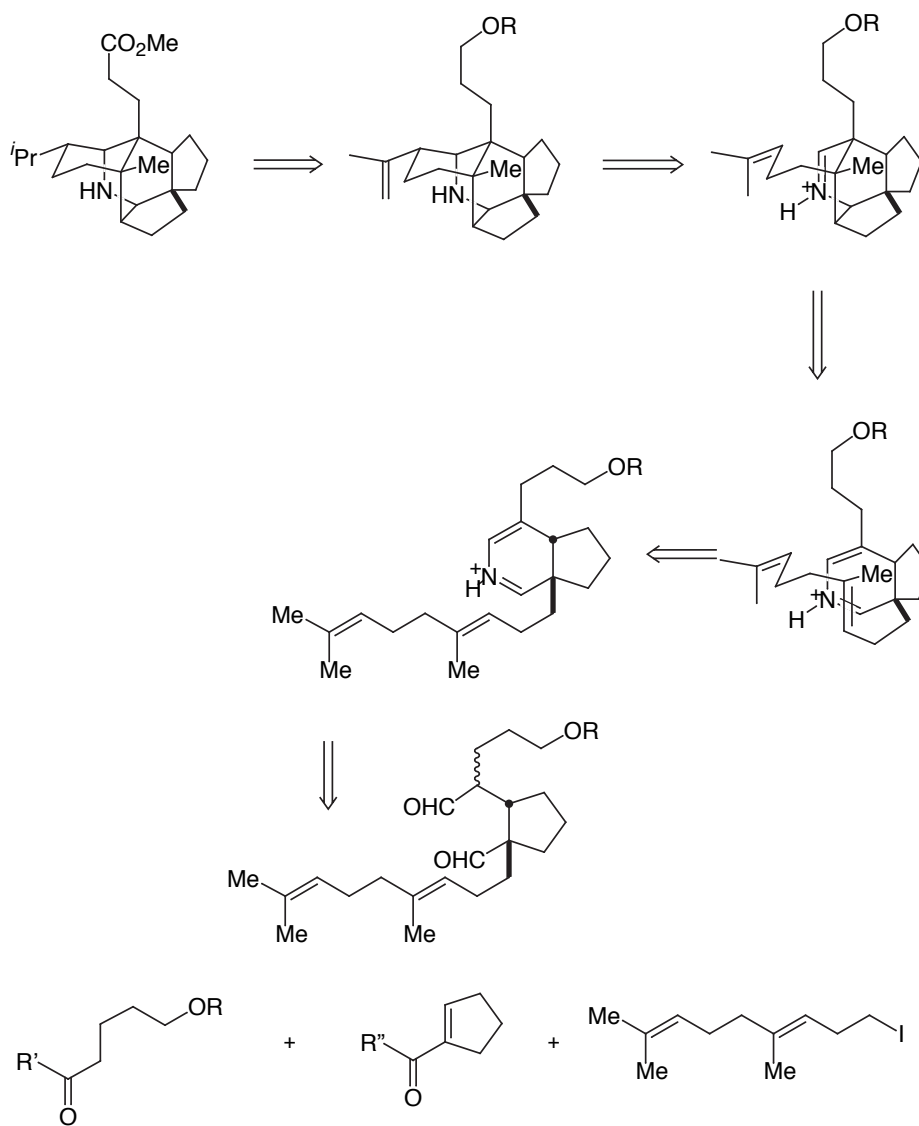
Construction of the Methyl Homodaphniphyllate Skeleton



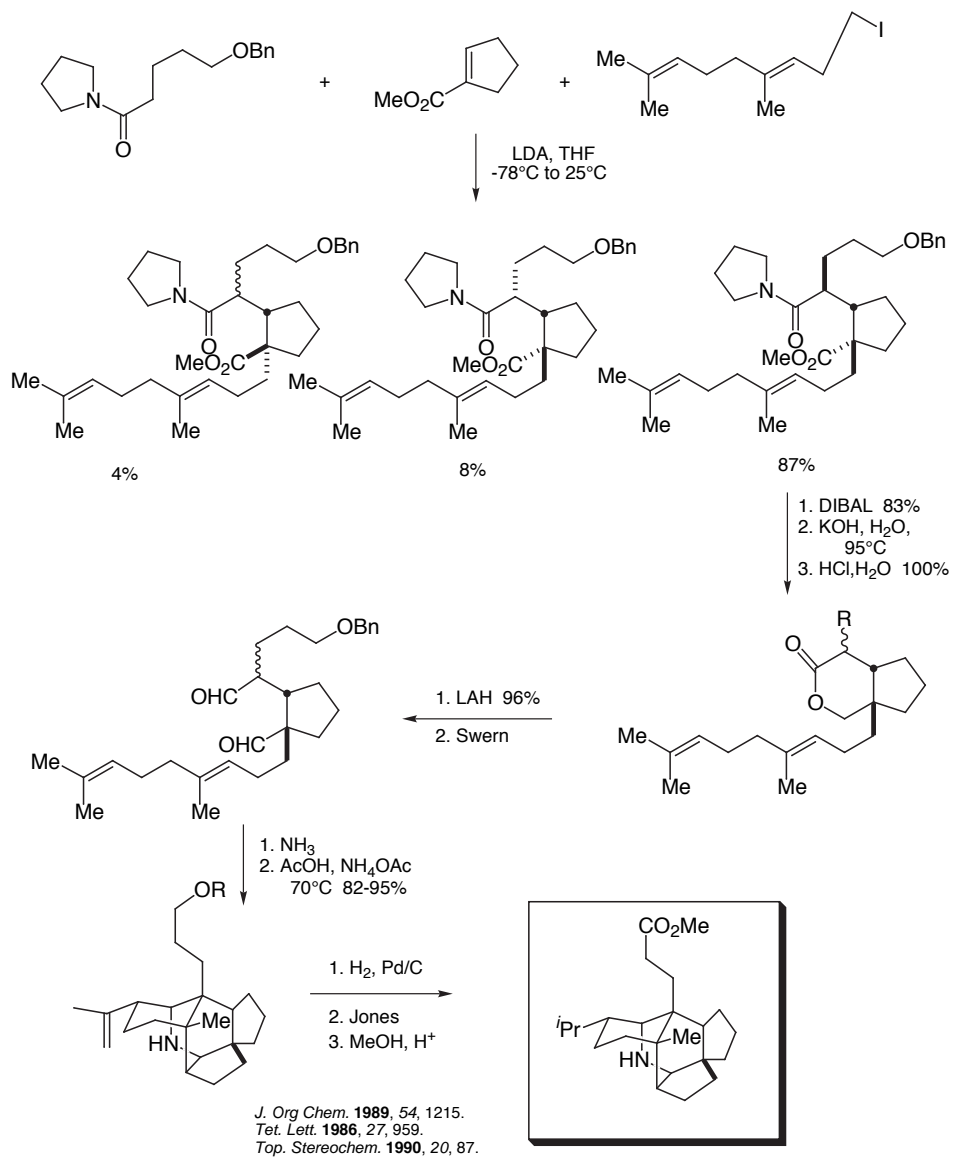
Proposed Biosynthesis cont'd



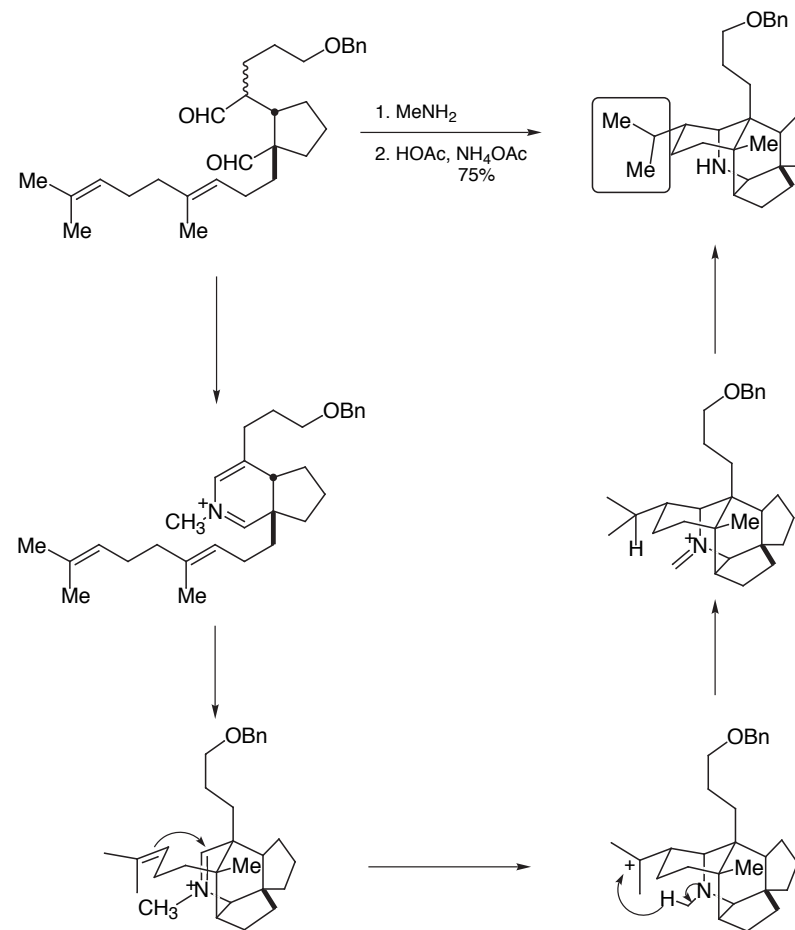
Retrosynthesis of Methyl Homosecodaphniphyllate



Synthesis of Methyl Homosecodaphniphyllate

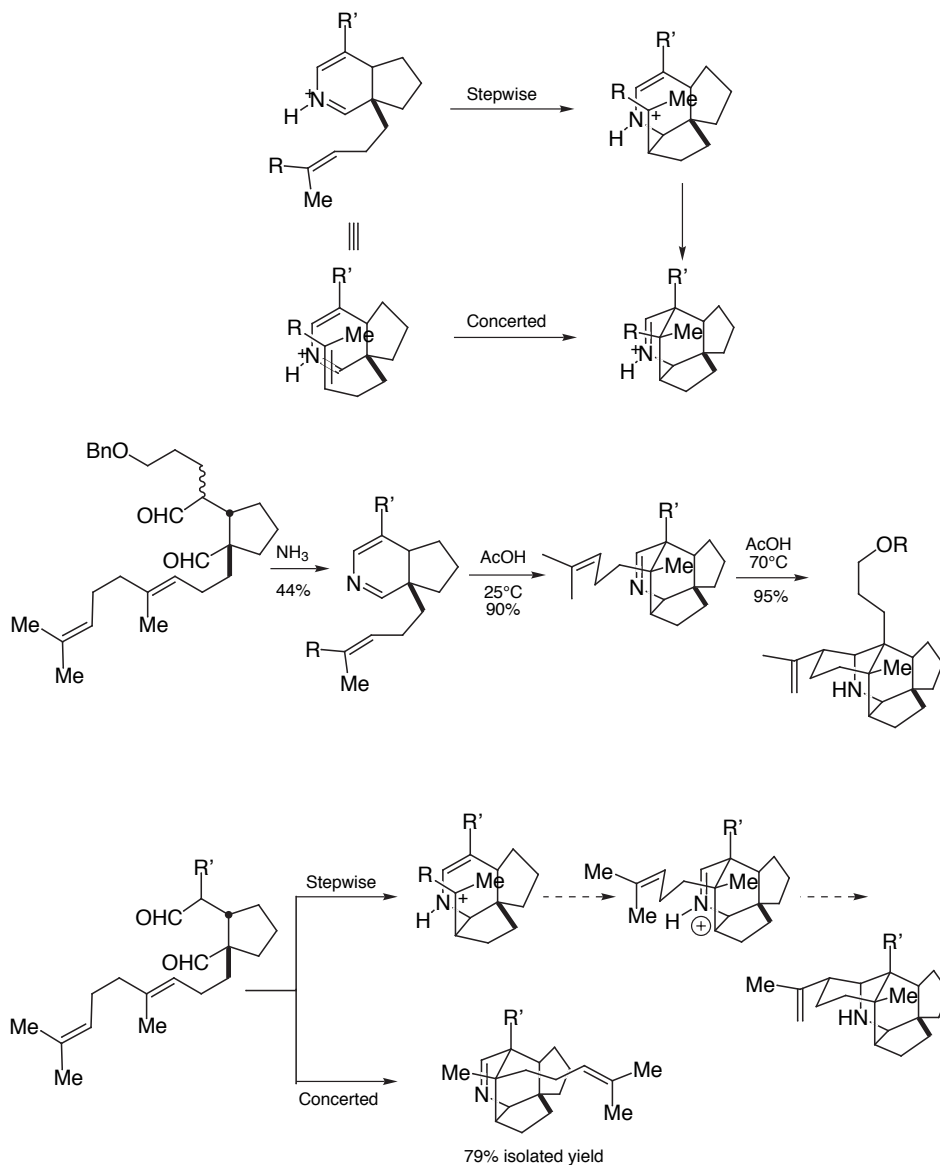


The Vollhardt "Ammonia" Incident

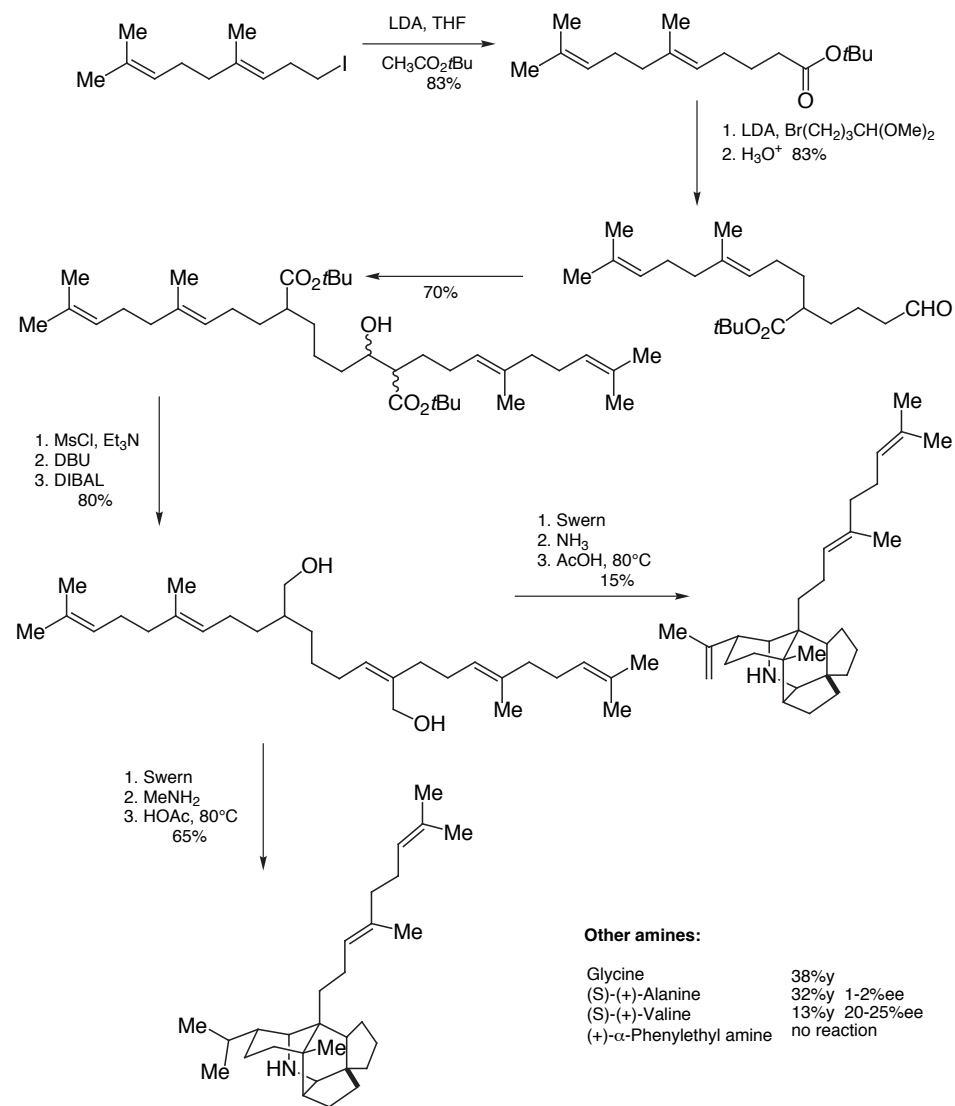


Angew. Chem. Int. Ed. Engl. **1978**, 17, 476.
 J. Org. Chem. **1990**, 57, 2544.

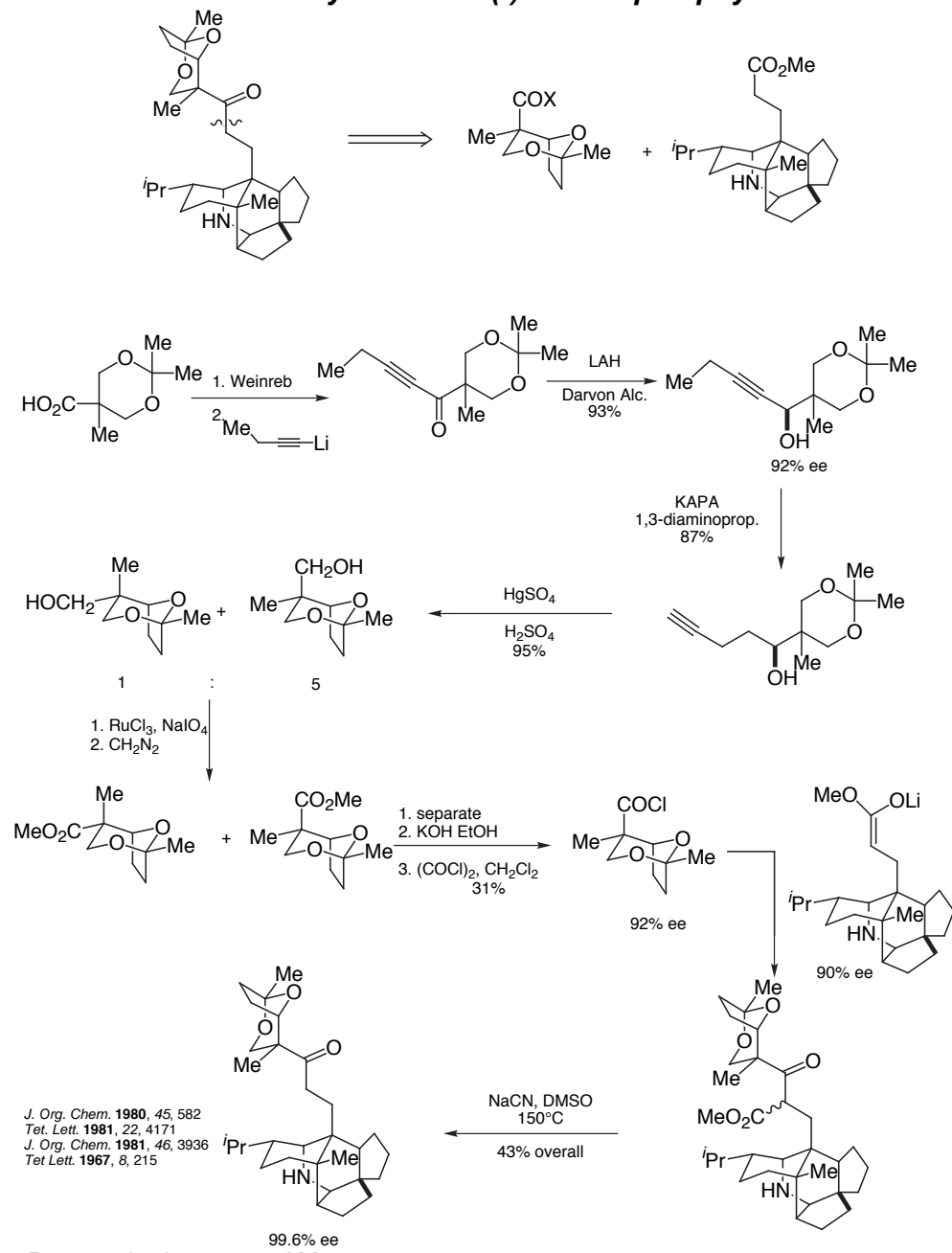
Stepwise vs Concerted Cyclization



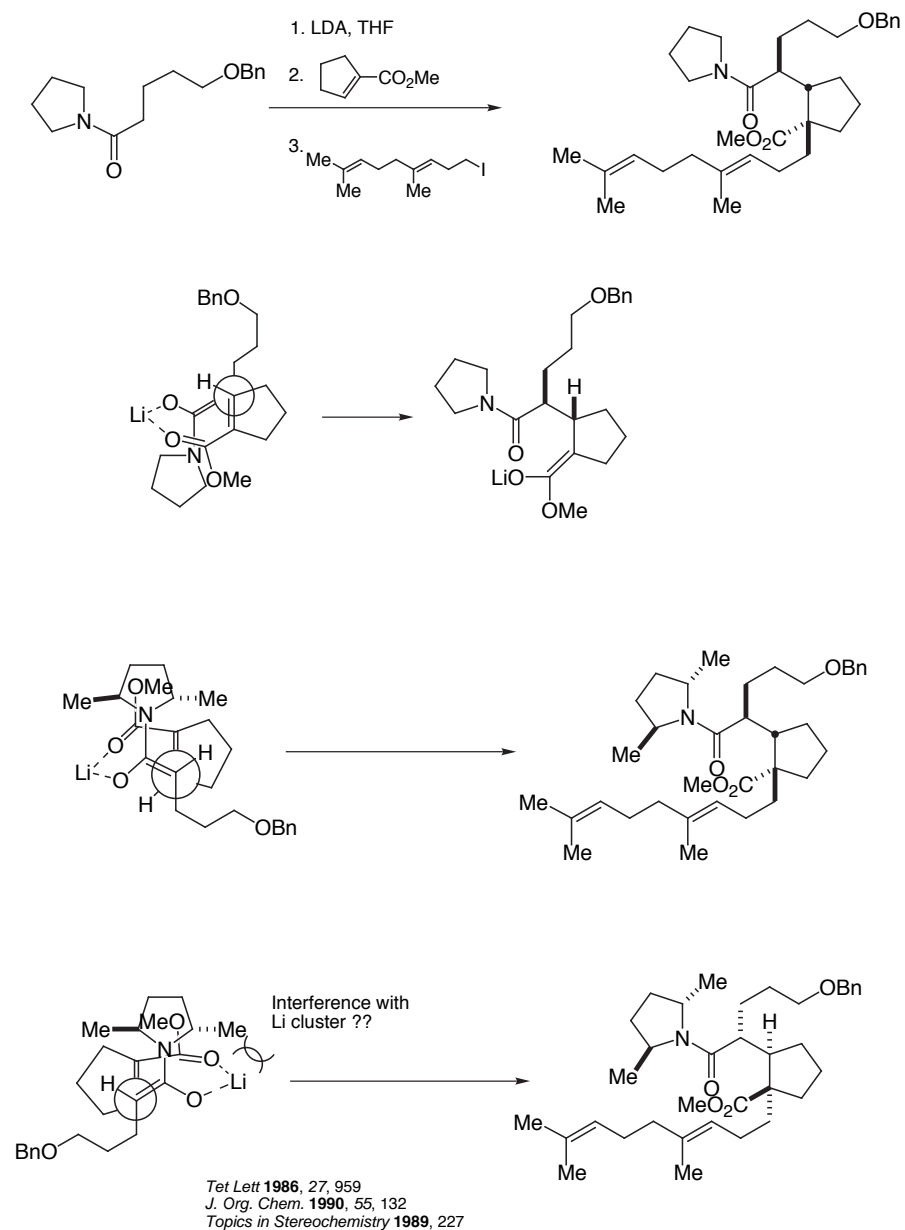
One-Pot Pentacyclization Reaction: Formation of Protodaphniphylline



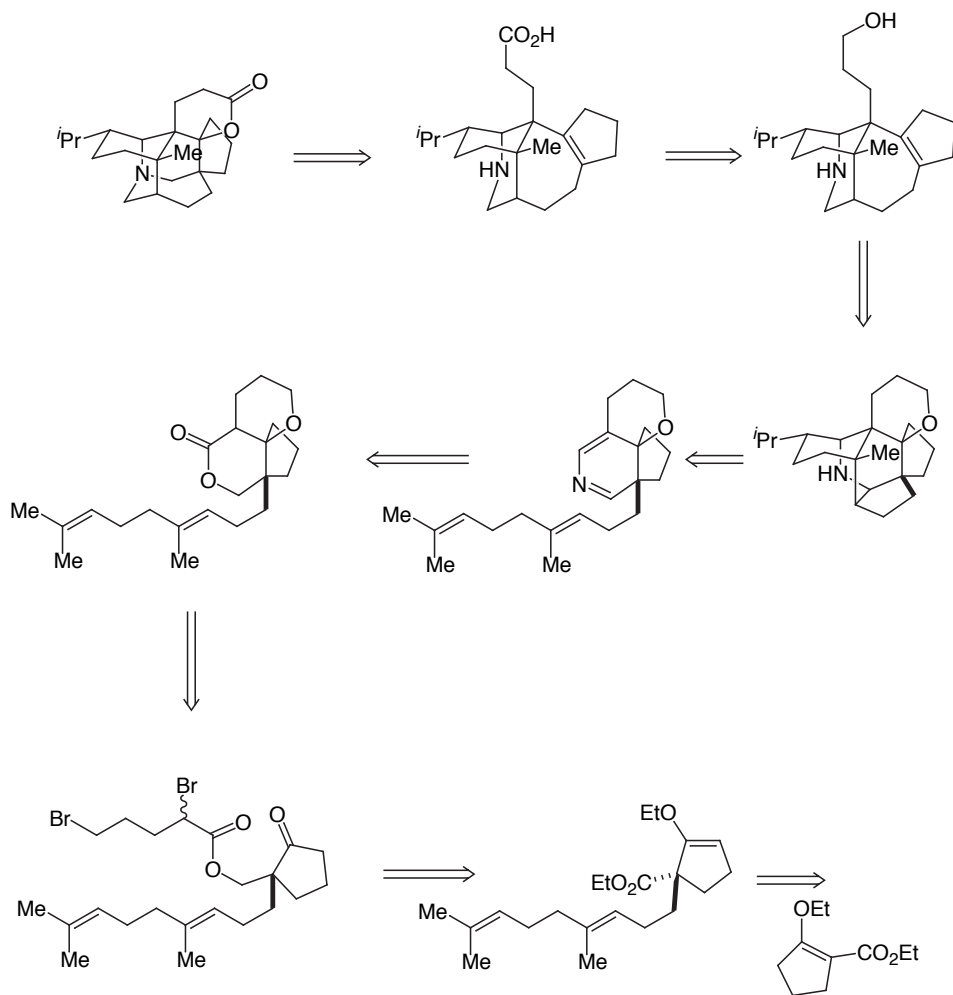
Synthesis of (-)-Secodaphniphylline



Rationale for Stereoselectivity in Michael Additions

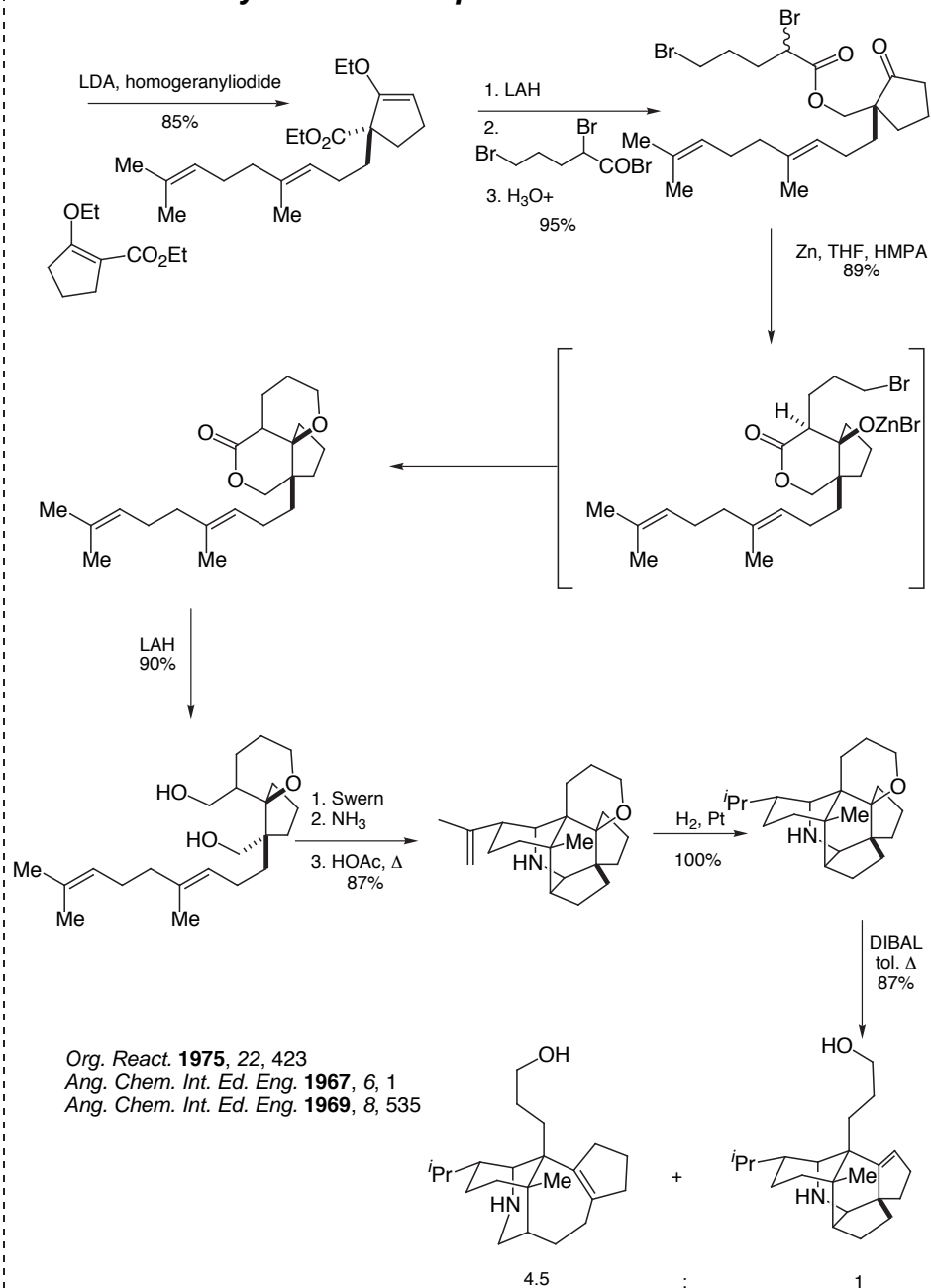


Retrosynthesis of Daphnilactone A

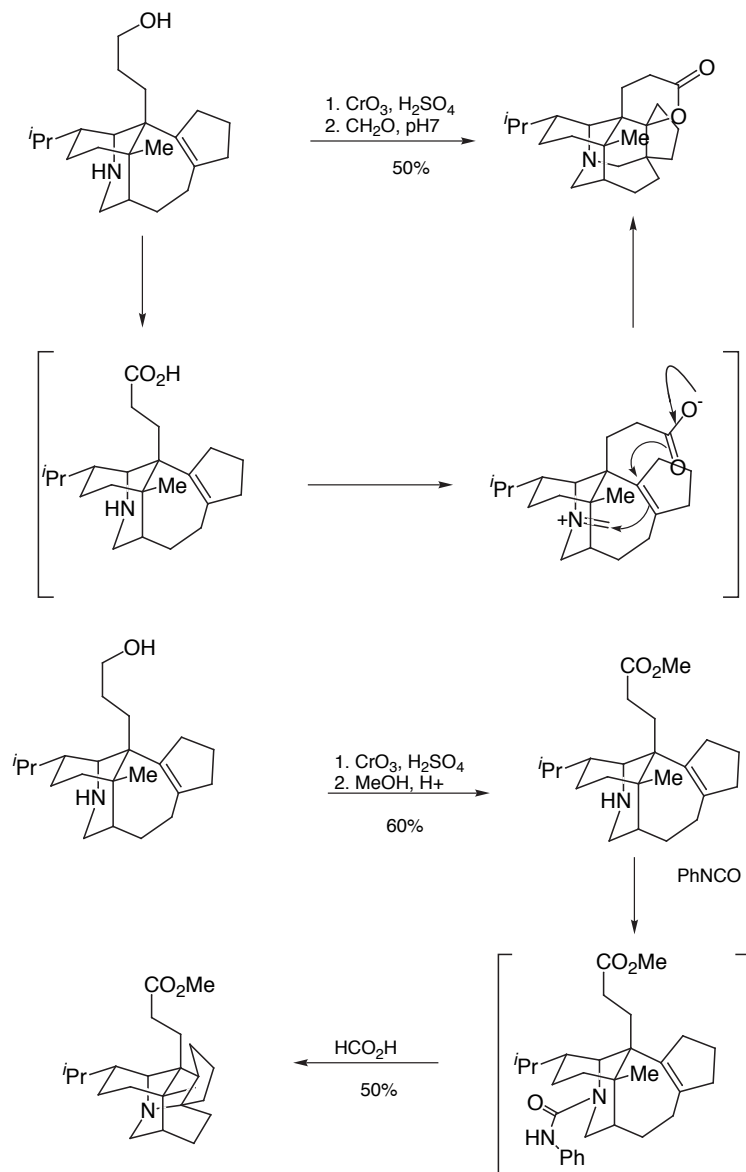


J. Org. Chem. **1992**, *57*, 2585
Angew. Chem. Int. Ed. Engl. **1992**, *31*, 665

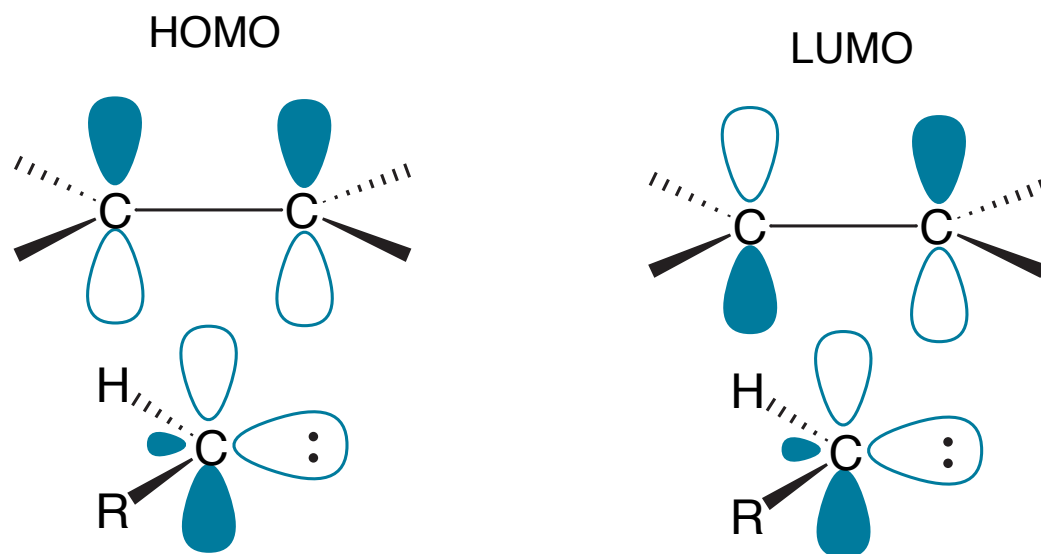
Synthesis of Daphnilactone A



Total Synthesis of Daphnilactone and Conversion to the Daphniphylline Skeleton



Carbene–Olefin Cycloaddition: The FMO Analysis



<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 10, "Reactions Involving Highly Reactive Electron-Deficient Intermediates", 595–680.

Handout 09A Simmons-Smith Reaction: Enantioselective Variants

Handout 26B Synthetic Applications of α -Diazocarbonyl Compounds

Chiral Dirhodium Carboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta*. **1996**, 29, 3 (**handout**)

Doyle, Catalytic Methods for Metal Carbene Transformations, *Chem. Rev.* **1986**, 86, 919-939 (**electronic handout**)

McKervey, Organic Synthesis with α -Diazocarbonyl Compounds, *Chem. Rev.* **1994**, 94, 1091-1160 (**electronic handout**)

Muller, Catalytic Enantioselective Aziridinations & Asymmetric Nitrene Insertions, *Chem. Rev.* **2003**, 103, 2905-2919 (**electronic handout**)

D. A. Evans

Monday,
December 10, 2003

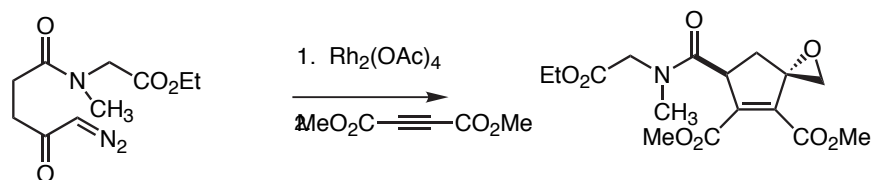
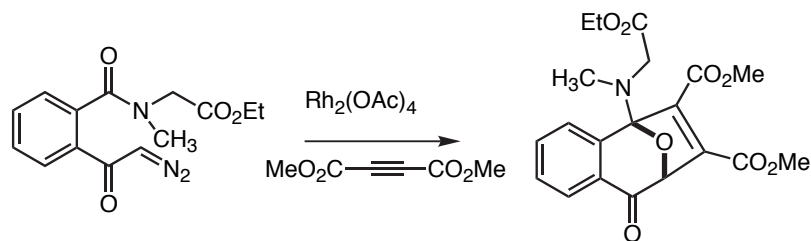
Useful References to the Carbene Literature

Books:

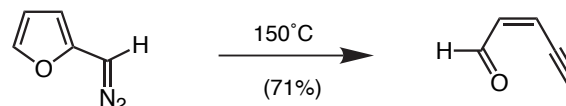
Modern Catalytic methods for Organic Synthesis with Diazo Compounds; M. P. Doyle, Wiley, 1998.

Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

Provide a mechanism for the following transformations.



JACS **1990** 2037



Suggested 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.

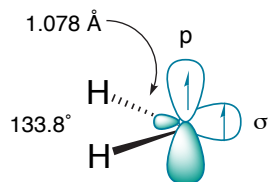
Carbenes and Nitrenes in "Reactive Molecules: The Neutral Reactive Intermediates in Organic Chemistry", Wentrup, C. W. 1984, Wiley, p. 162.

Rearrangements of Carbenes and Nitrenes in Rearrangements in Ground & Excited States, Academic Press, DeMayo ed., Jones, W. M. 1980, p. 95.

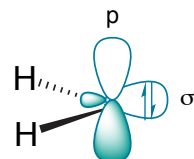
Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

Carbenes: Electronic Structure

Carbene Configuration: Triplet vs. Singlet

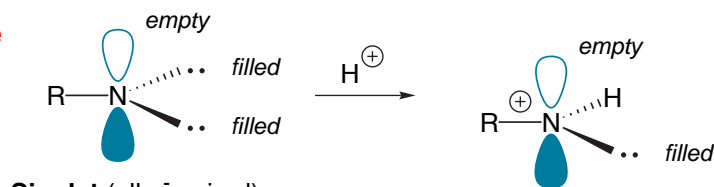
Triplet (two unpaired e⁻)

Often has **radical-like** character

Singlet (all e⁻ paired)

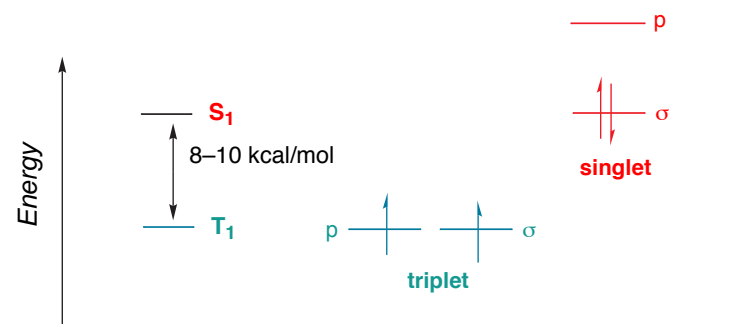
Often has **electrophilic** or **nucleophilic** character: **A-type (Ambiphilic)**

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**).

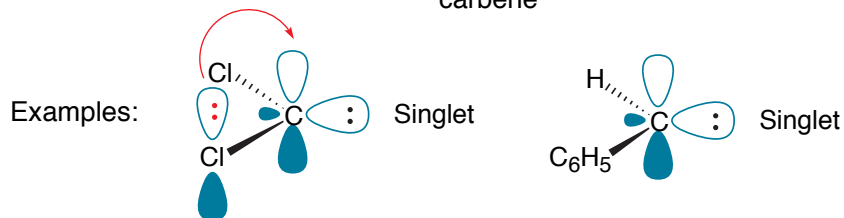
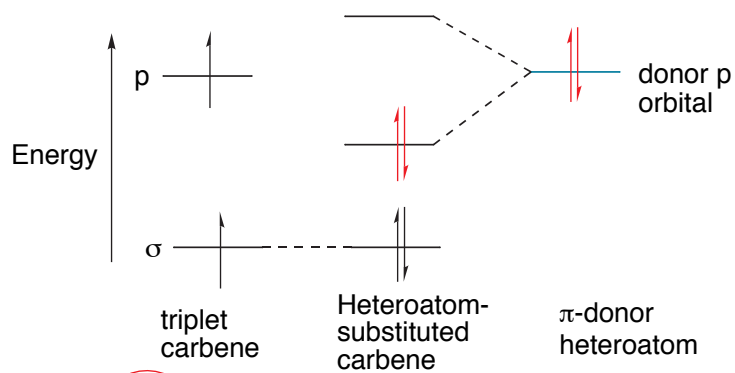
the History of the Singlet-Triplet Gap

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)

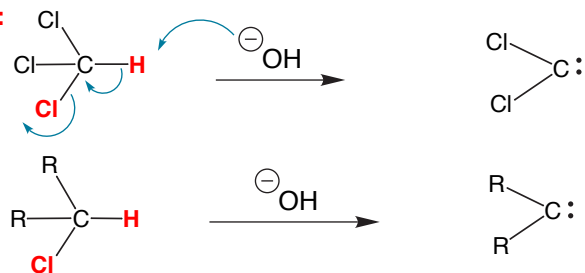
Heteroatom-Substituted Carbenes: Singlets

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.

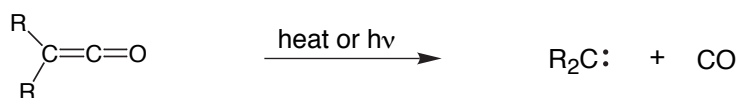


Methods of Synthesis

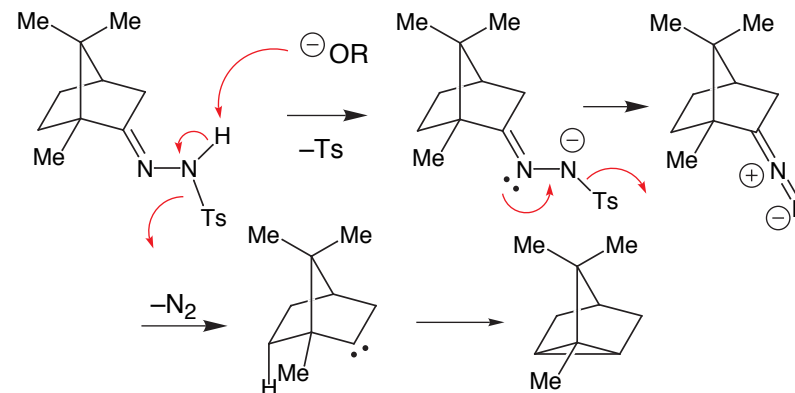
Alkyl Halides:



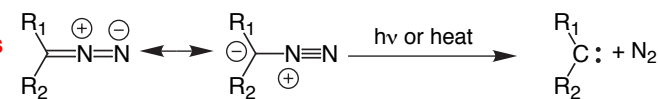
ketenes



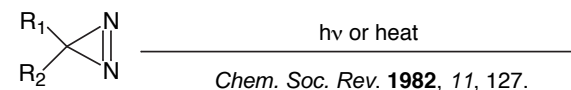
Bamford-Stevens Reaction: See Lecture 28 on Hydrazones Shapiro *Org. Rxns.* **1976**, 23, 405.



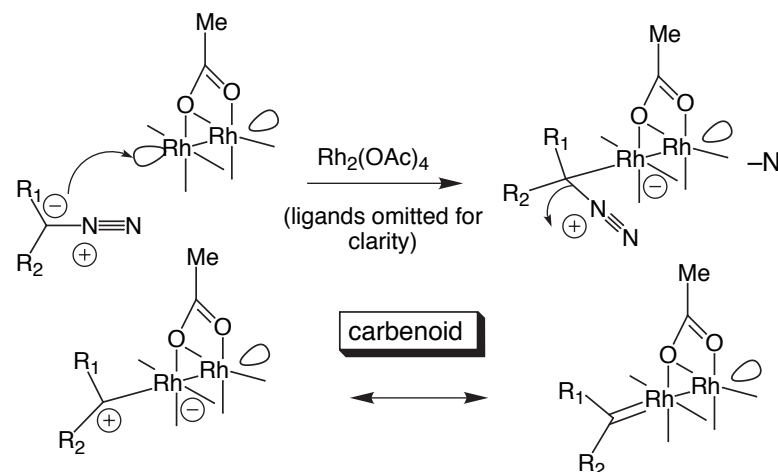
diazo compounds



diazirines



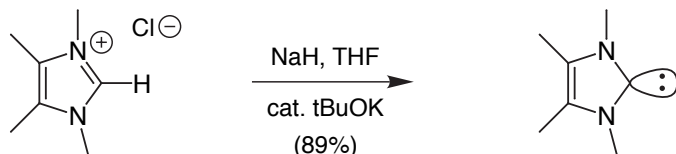
metal-catalyzed decomposition Doyle *Chem Rev.* **1986**, 86, 919 (handout)



■ "Stable Carbenes"

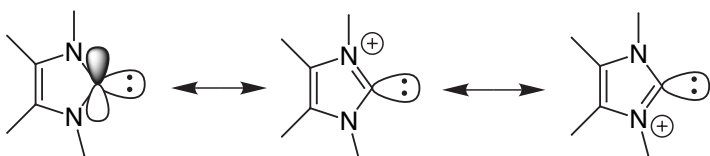
"Stable Carbenes—Illusion or reality"?

Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674 ([handout](#))



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:



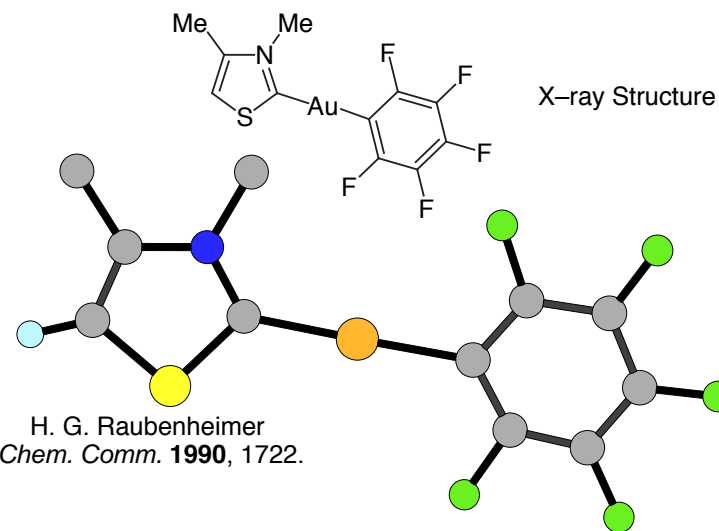
Arduengo argues that these resonance structures are not players based on electron distribution from neutron diffraction.

These are nucleophilic carbenes which display high stability.

For reviews on the subject, see:

Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 725.

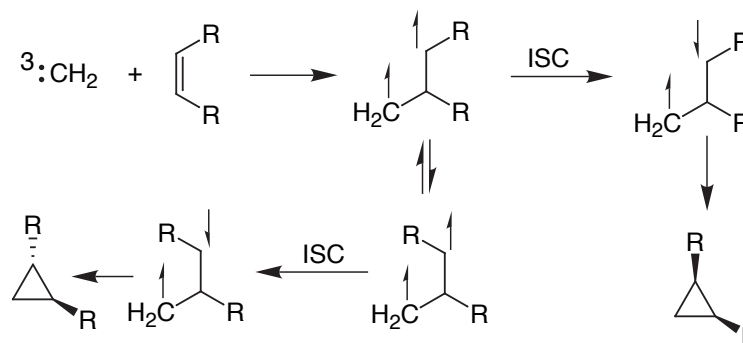
Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 674.



■ Cyclopropanation The Skell Rule:



Singlet carbenes add to olefins stereospecifically;



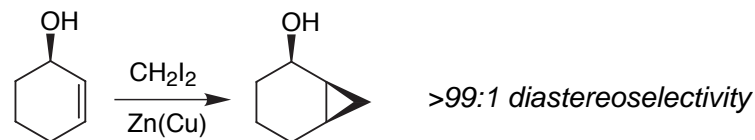
Triplet carbenes add non-stereospecifically

Skell and Woodworth *JACS*, **1956**, *78*, 4496.

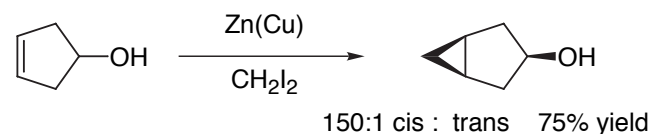
Synthetic Applications

■ Simmons-Smith Cyclopropanation (See Tedrow handout 10B)

Simmons, H.; Smith, R. *J. Am. Chem. Soc.*, **1958**, *80*, 5323.



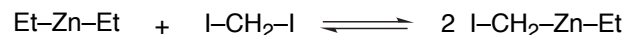
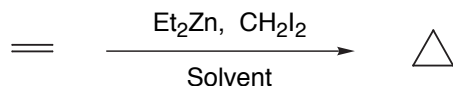
The intermediate organometallic reagent: $I-CH_2-Zn-I$



Winstein & Sonnenberg, *JACS* **1961**, *91*, 3235

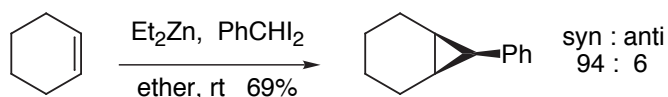
■ The Furukawa Simmons-Smith Variant

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

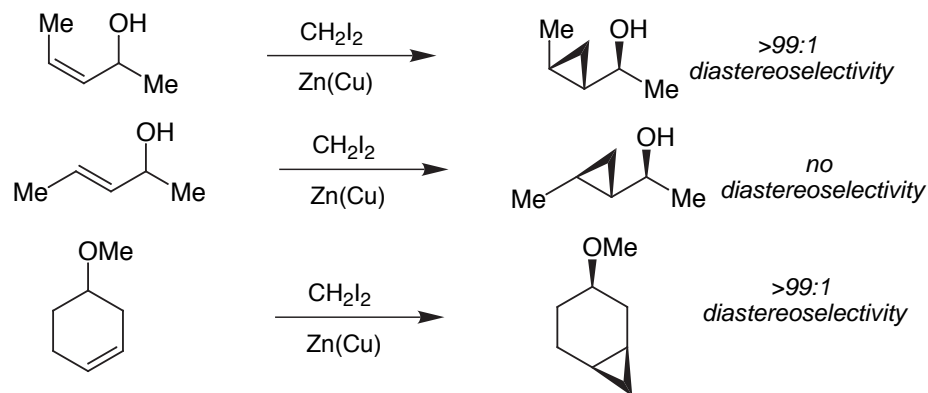


Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron*, **1968**, *24*, 53

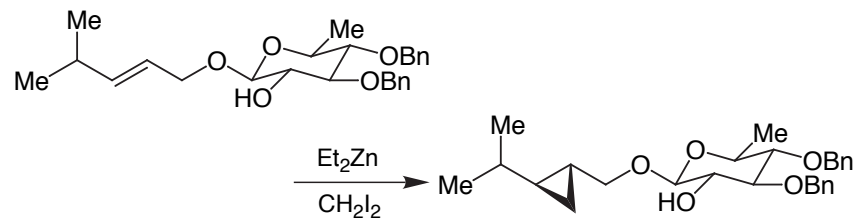
Furukawa, J.; Kawabata, N.; Fujita, T. *Tetrahedron*, **1970**, *26*, 243



■ Hydroxyl directivity is a powerful attribute of the S-S Rxn



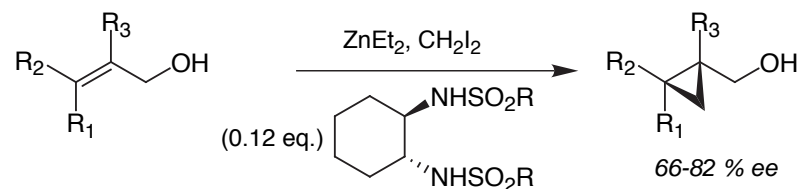
For an review of the directed Simmons-Smith, see:
Evans, D. A.; Hoveyda, A.; Fu, G. *Chem. Rev.* **1993**, *93*, 1307.



Charette, A. B. *JACS* **1991**, *113*, 8166.

>50 : 1 diastereoselection

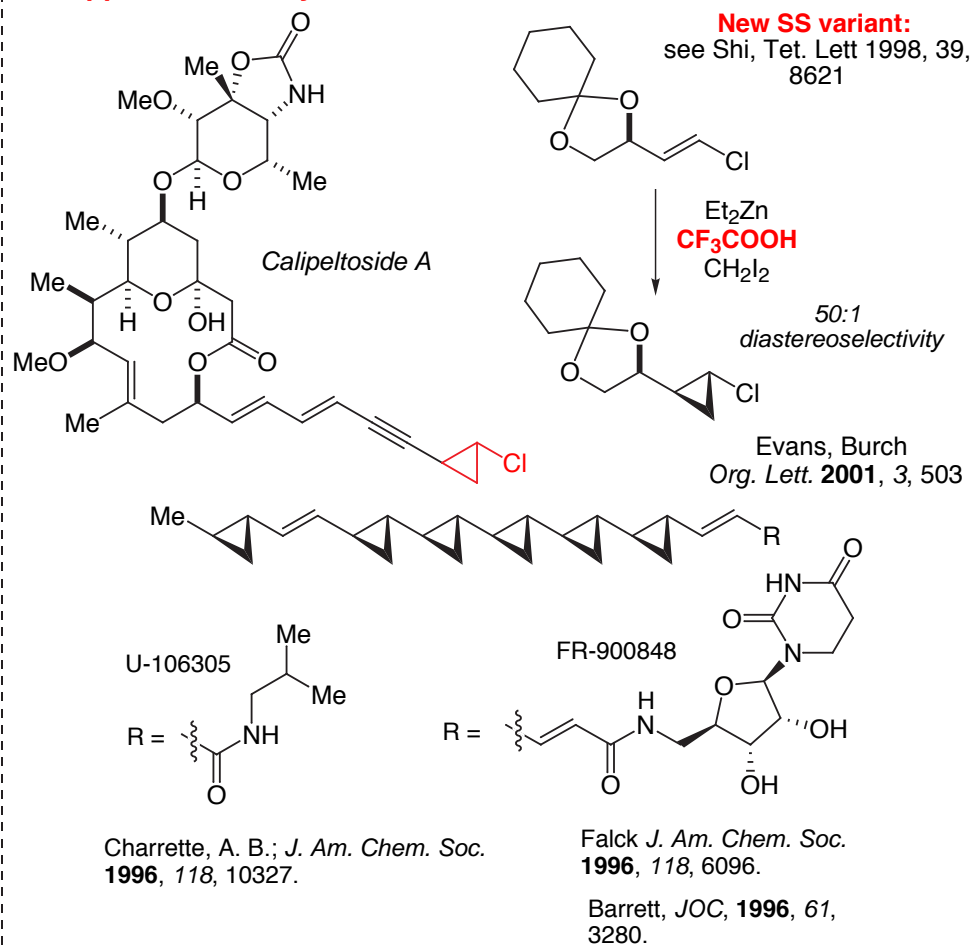
■ Catalytic Asymmetric Cyclopropanation:



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



Tetrahedron Letters 39 (1998) 8621-8624

Exploring New Reactive Species for Cyclopropanation

Zhiqiang Yang, Jon C. Lorenz, and Yian Shi*

Department of Chemistry, Colorado State University,
Fort Collins, CO 80523
Email: yian@lamar.colostate.edu

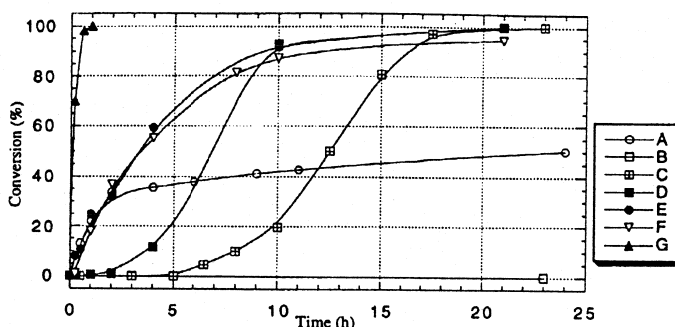
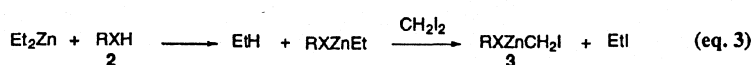
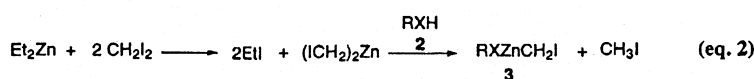
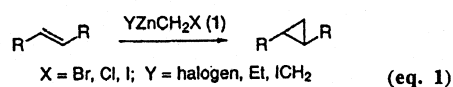
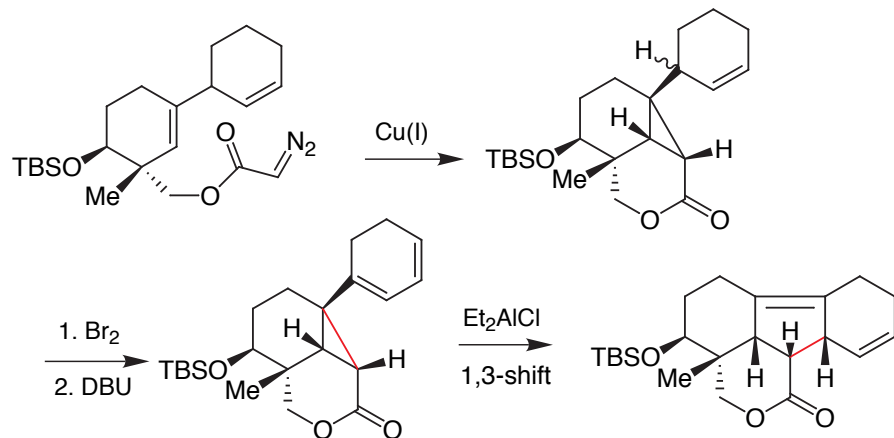
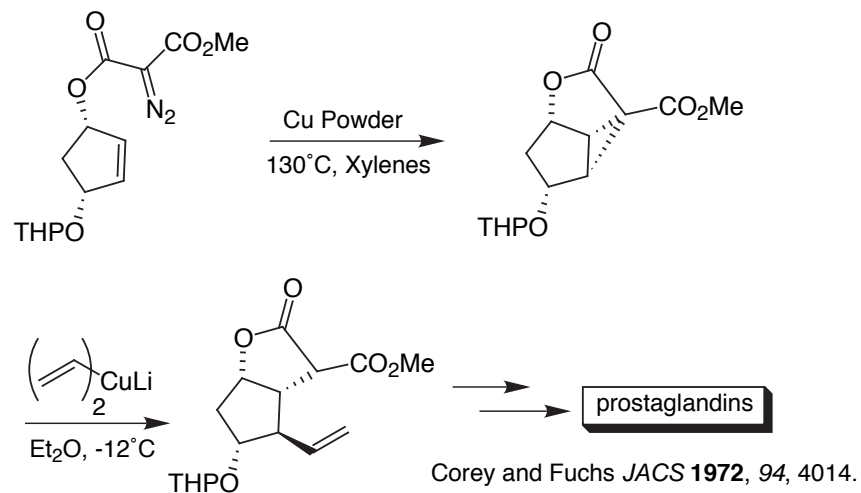
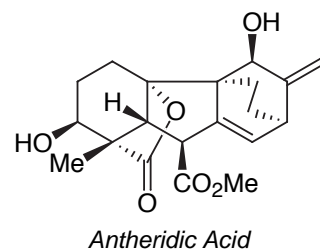


Figure 1. Plot of the conversion of *trans*- β -methylstyrene against time (h). The curves presented are: (A) No RXH, (B) EtOH or ClCH₂CH₂OH, (C) Cl₂CHCH₂OH, (D) CCl₃CH₂OH, (E) CF₃CH₂OH, (F) PhCO₂H, (G) CF₃CO₂H.

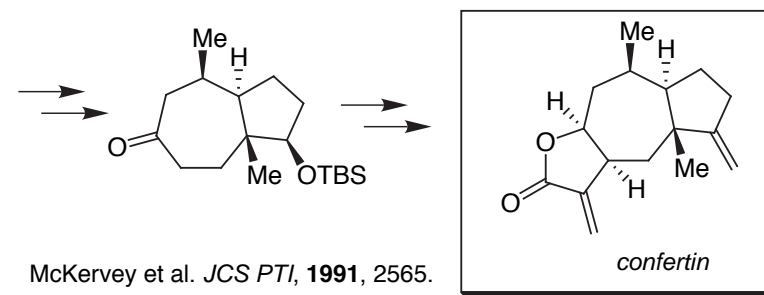
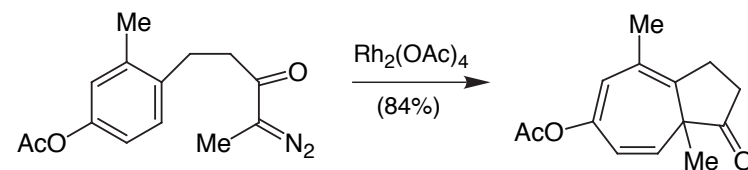
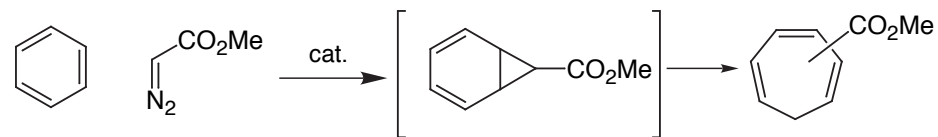
Table 1. Cyclopropanation of Representative Olefins Accelerated by CF₃CO₂H^a

Entry	Substrate	time (min)	Conv. (%) ^b	Yield (%) ^c
1		30	100	77
2		60	>90	70 ^d
3		60	nd	72 ^d
4		30	100	95
5		40	100	80
6		40	100	99
7		20	100	85
8		30	>97	88
9		150	>90	90
10		30	100	78

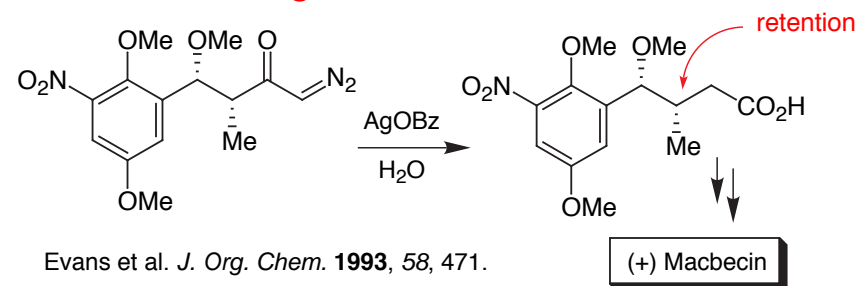
■ Synthetic Applications

Corey & Myers *JACS* **1985**, *107*, 5574.

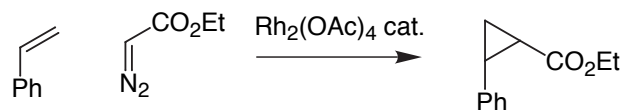
■ Buchner Reaction



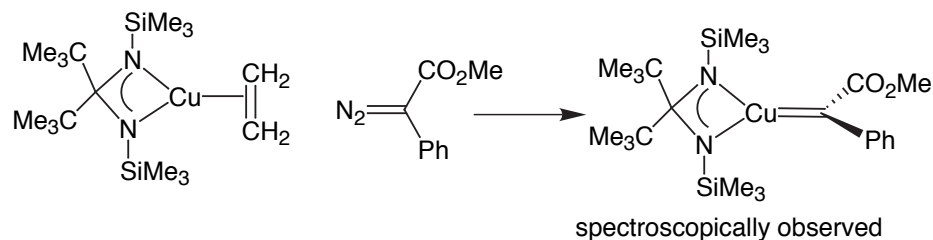
■ Wolff Rearrangement



Characterization of metal carbenoid intermediates: not much data!

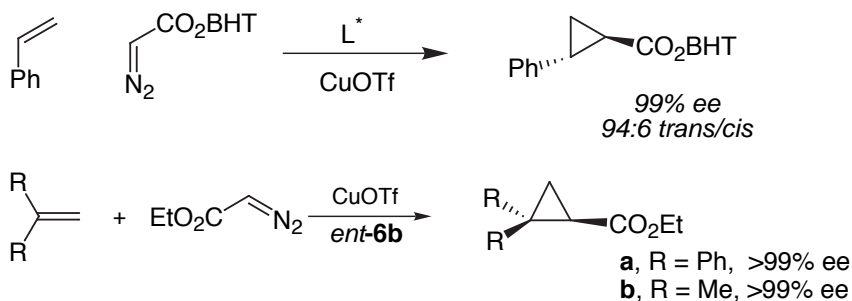
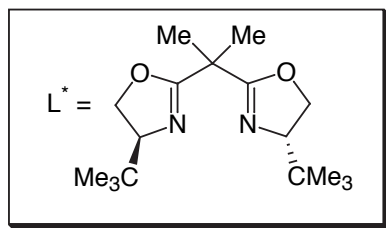


For a detailed mechanistic study which provides supporting evidence for the intermediacy of a Rh carbene, see: Kodacek, *Science*, **1992**, 256, 1544.



"Copper(I) Carbenes: The Synthesis of Active Intermediates in Cu-Catalyzed Cyclopropanation" P. Hoffmann et al, *Angew. Chem. Int. Ed.* **2001**, 40, 1288-1290

■ Catalytic Asymmetric Variants: Chiral Cu(I) Complexes

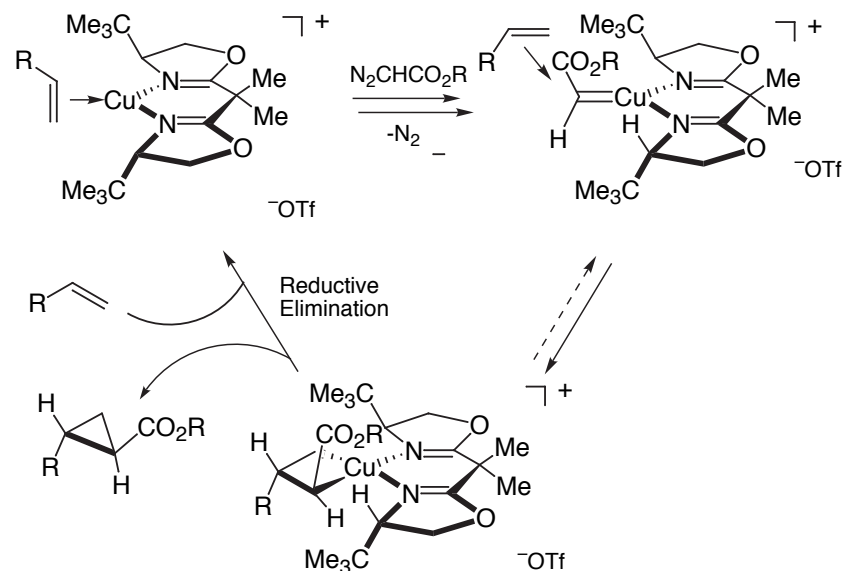


Evans, et al. *J. Am. Chem. Soc.* **1991**, 113, 726.

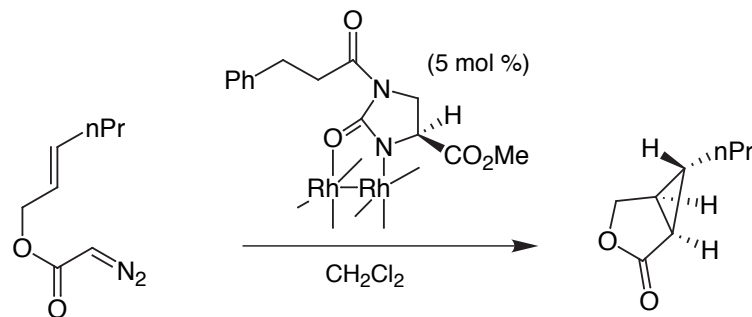
34-06-carbenes 12/10/03 8:38 AM

■ Mechanism

There is no definitive evidence for metal-catalyzed cyclopropanation and the possibility that metallacyclobutane intermediates are involved cannot be ruled out.

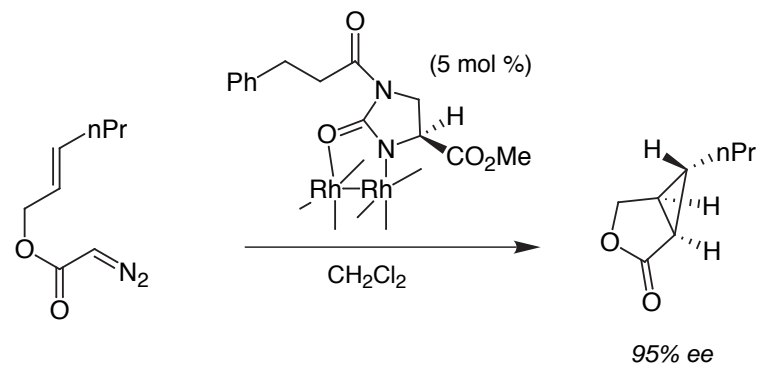


■ Catalytic Asymmetric Variants: Chiral Rh(II) Complexes

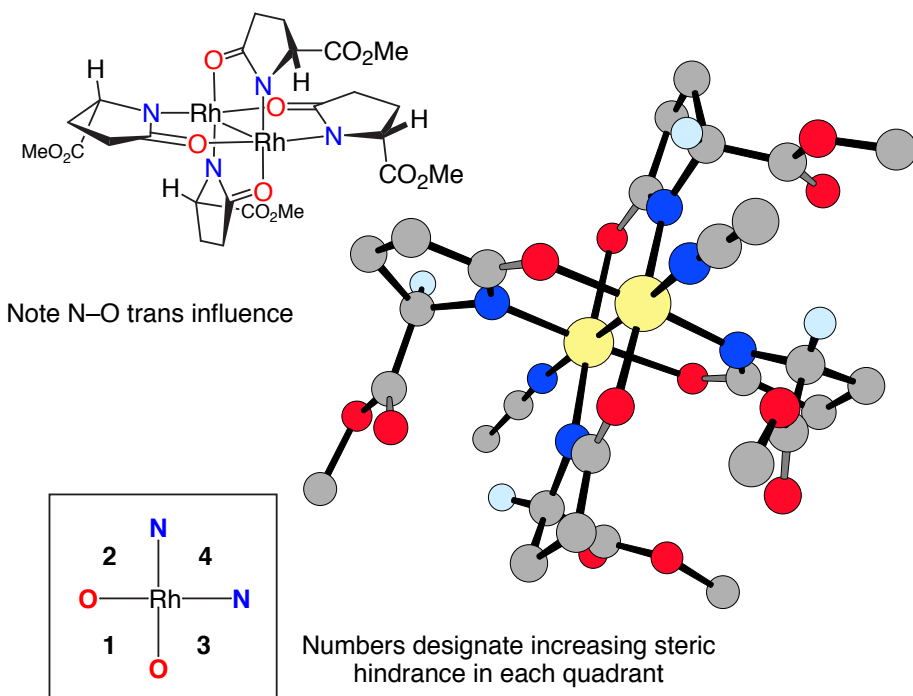


How do these complexes really work??

■ Catalytic Asymmetric Variants: Chiral Rh(II) Complexes



Doyle et al. *Tetrahedron Lett.* **1995**, 36, 7579.

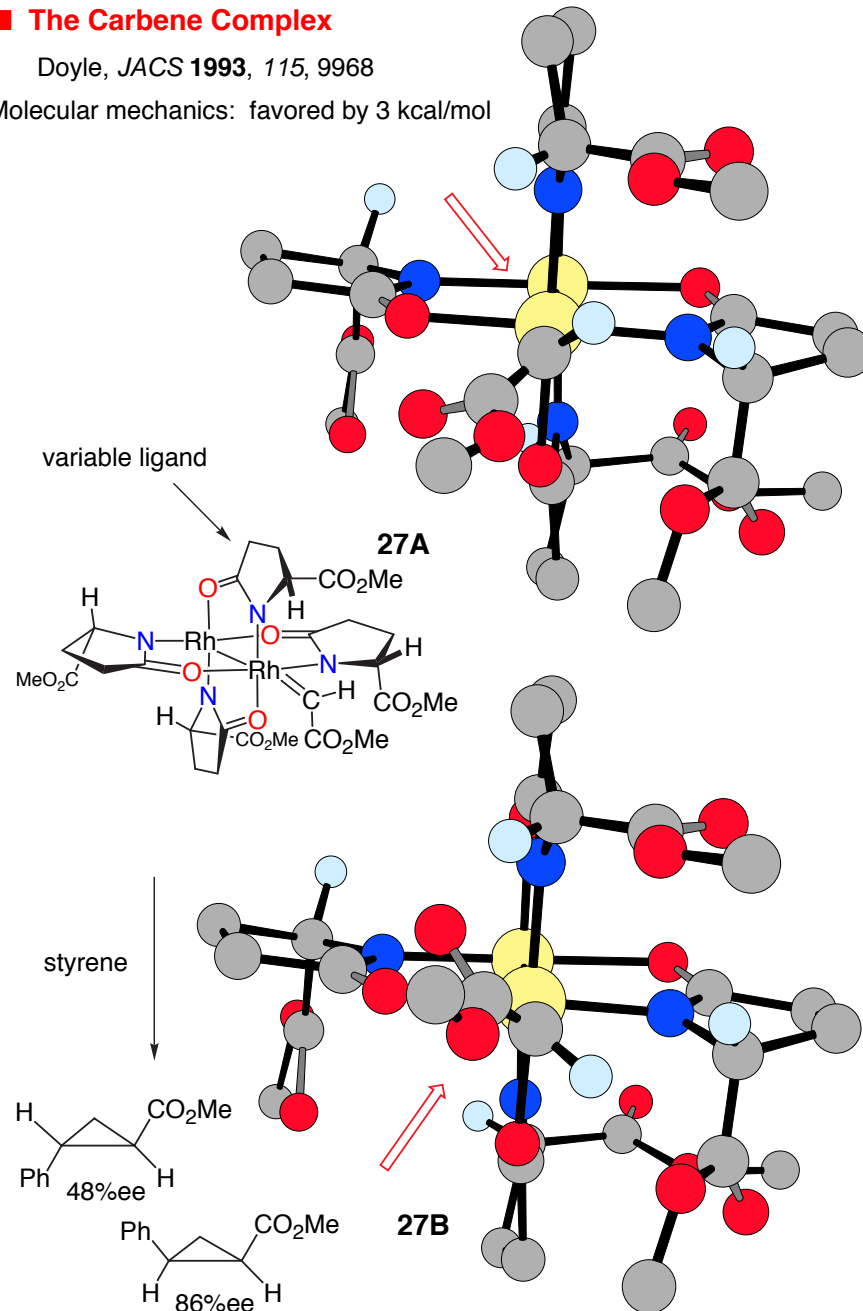


Doyle, *JACS* **1993**, 115, 9968

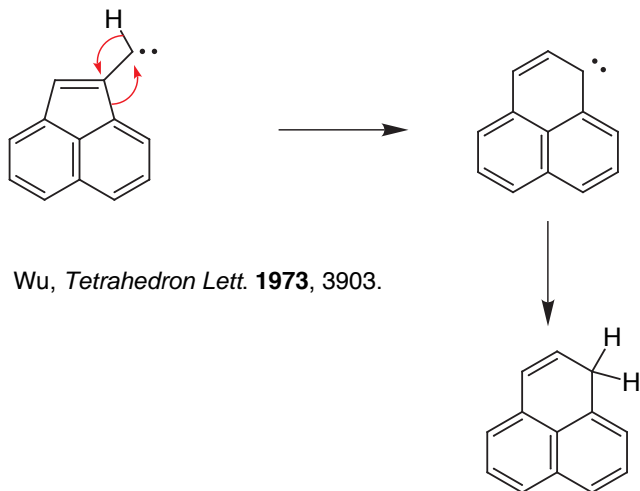
■ The Carbene Complex

Doyle, *JACS* **1993**, 115, 9968

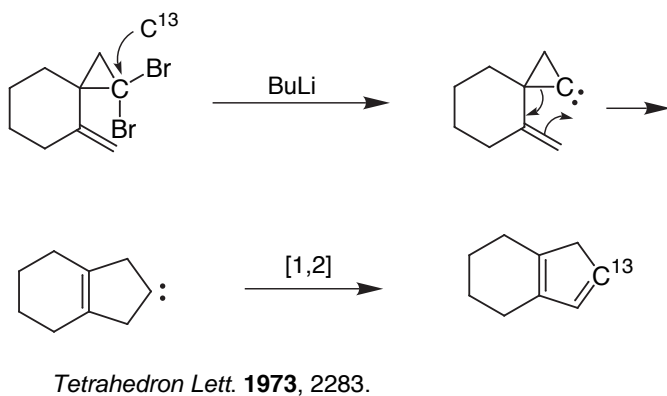
Molecular mechanics: favored by 3 kcal/mol



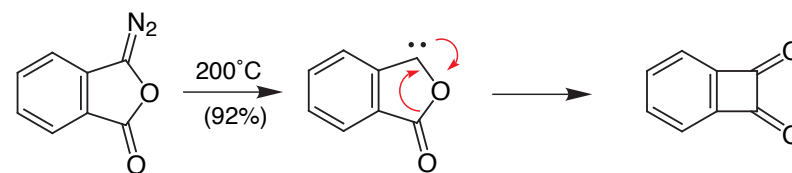
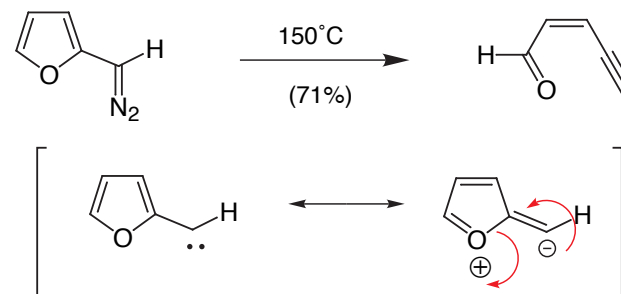
Carbene-Carbene Rearrangements



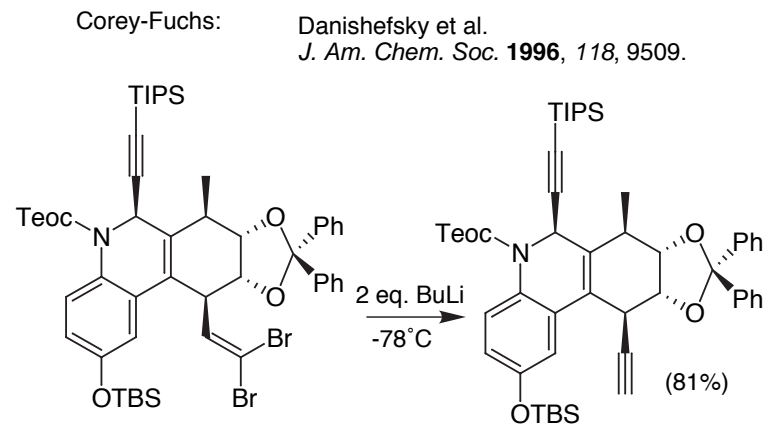
Skattebol Rearrangement



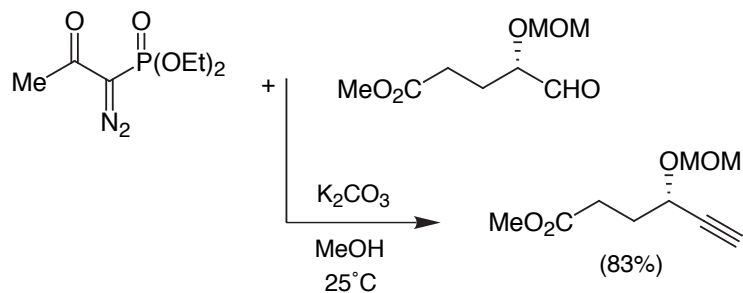
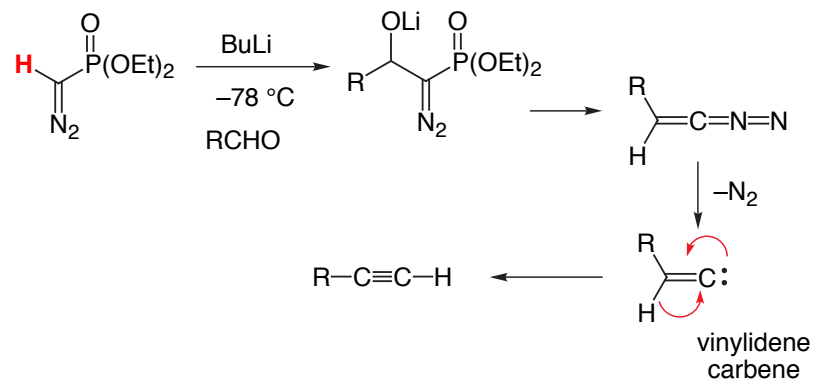
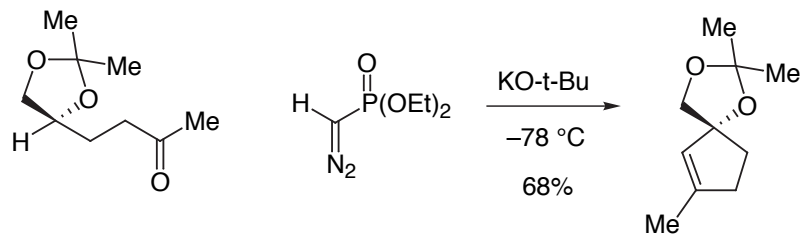
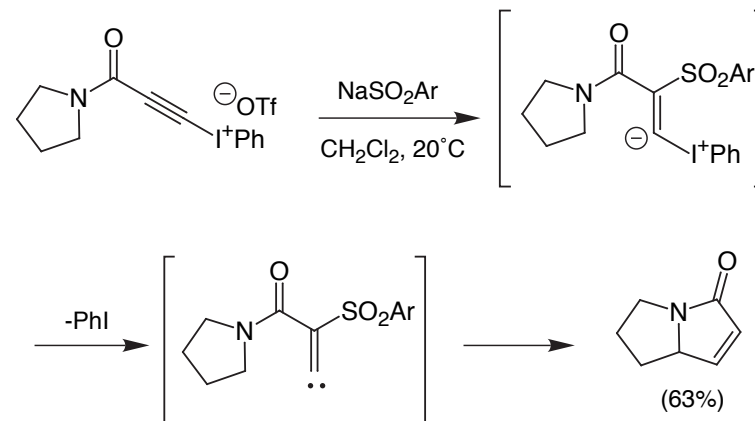
Other Rearrangements



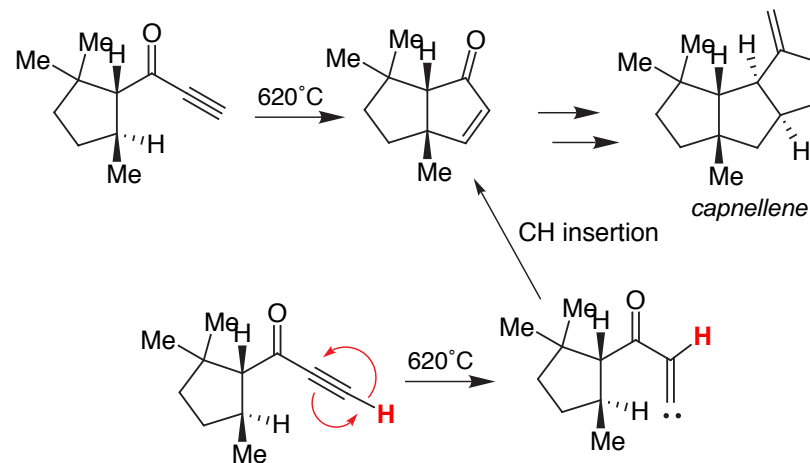
Vinylidenes



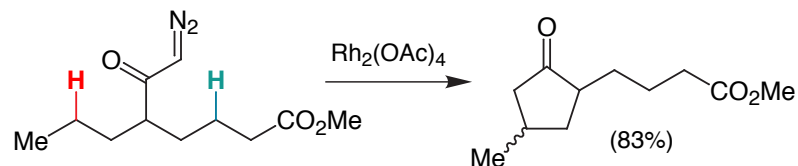
Carbene Rearrangements

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!

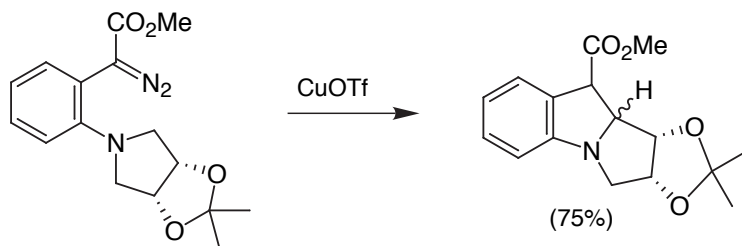


■ C-H Insertions continued...



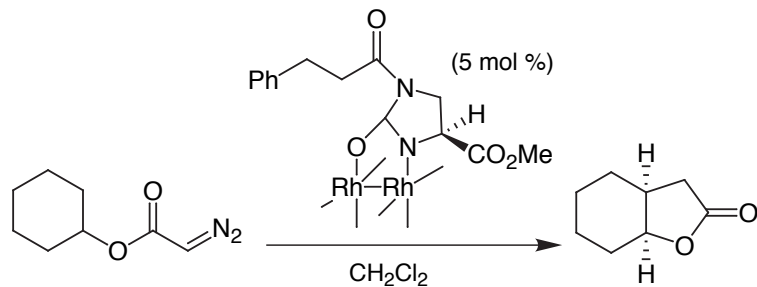
Electrophilic carbenes are very sensitive to electronic effects

Stork *Tetrahedron Lett.* **1988**, 29, 2283.



Sulikowski, *J. Org. Chem.* **1995**, 60, 2326.

Enantioselective C-H Insertion

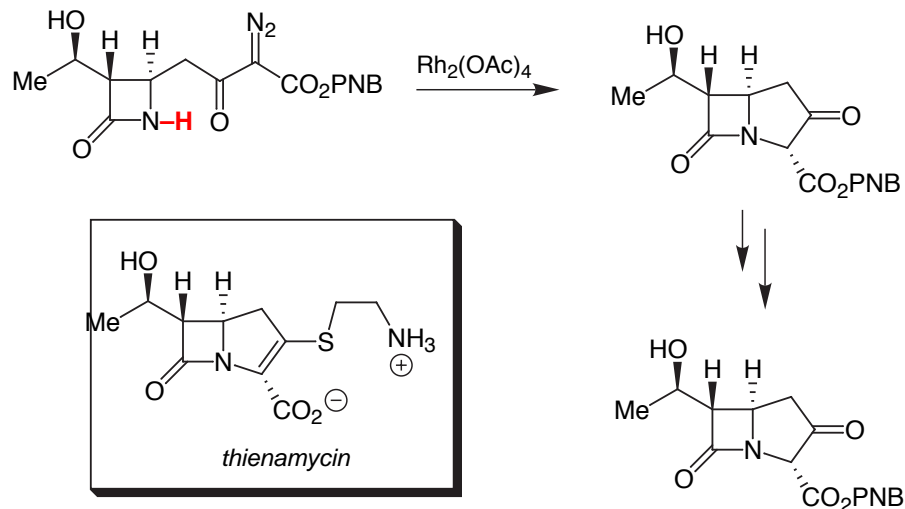


Doyle, *JACS* **1994**, 116, 4507

99%, 97% ee

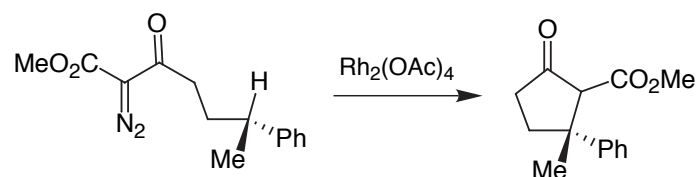
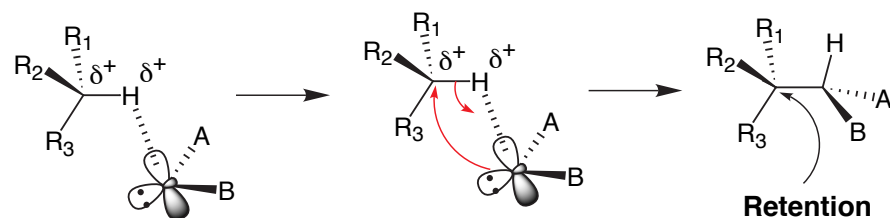
Chiral Dirhodium Carboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta.* **1996**, 29, 3 (**handout**)

■ N-H Insertions are also possible...



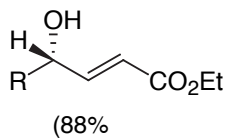
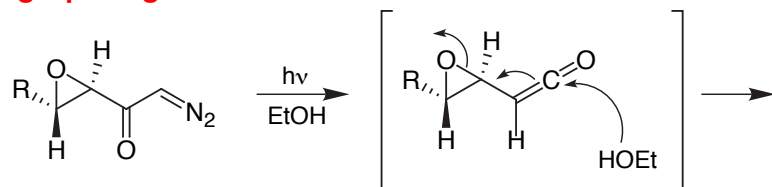
Salzmann, *JACS*, **1980**, 102, 6163.

Insertions (X-H): Stereochemical outcome



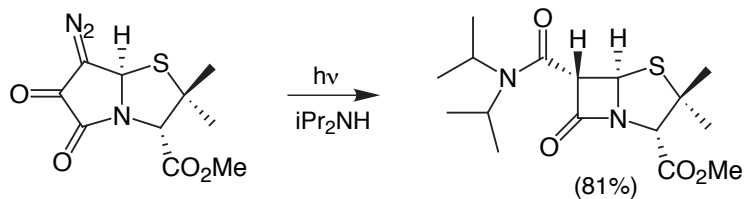
Taber *JACS*, **1996**, 107, 196.

Ring Opening



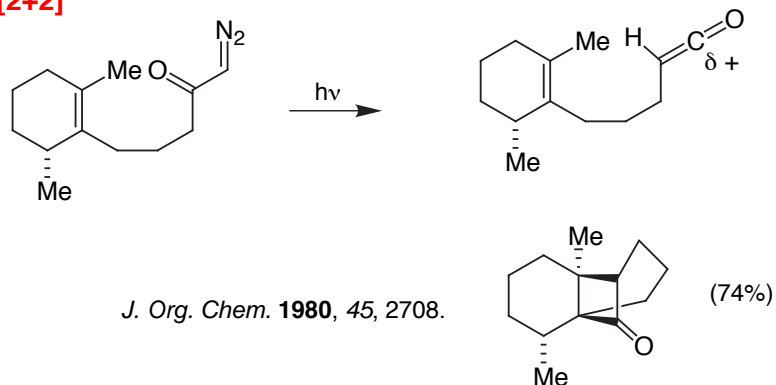
Tetrahedron Lett. **1990**, 31, 6589.

Ring Contraction



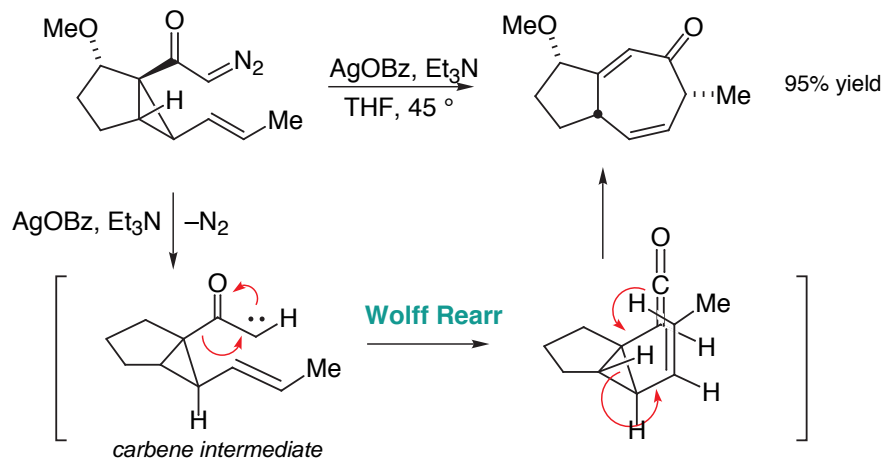
Moore et al. *J. Org. Chem.* **1983**, 48, 3365.

Wolff-[2+2]

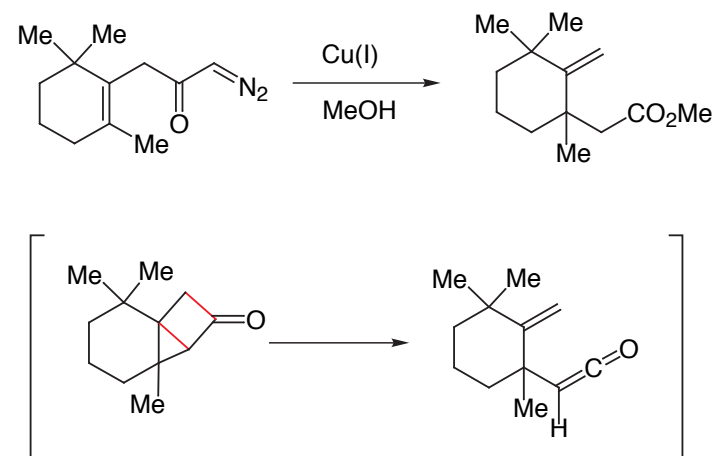


J. Org. Chem. **1980**, 45, 2708.

Problem 332: Wolff Rearrangement Stoltz ACS 2003, 125, 13624



Vinyloligous Wolff Rearrangement Doyle pp520-521



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

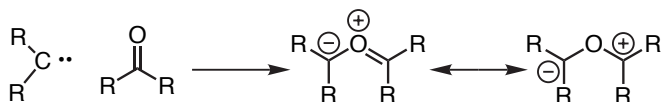
Chemistry 206

Advanced Organic Chemistry

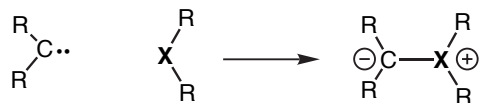
Lecture Number 35

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.

- Handout 10B** Simmons-Smith Reaction: Enantioselective Variants
- Handout 27B** Synthetic Applications of α -Diazocarbonyl Compounds
- Handout 35A** The Use of Fischer Carbenes in Organic Synthesis

D. A. Evans

Friday,
December 12, 2003

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.

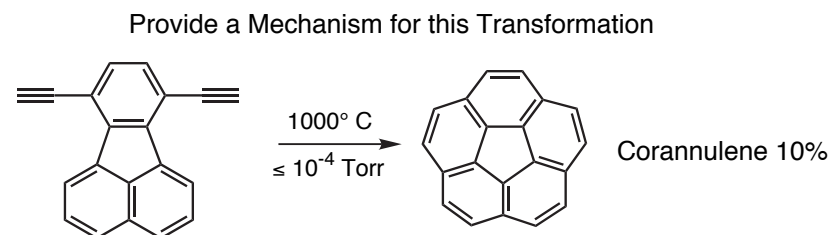
Carbene Chemistry, 2nd ed. Academic Press, Kirmse, W., 1971.

The Automerization of Naphthalene (The Cume Question from Hell!!)



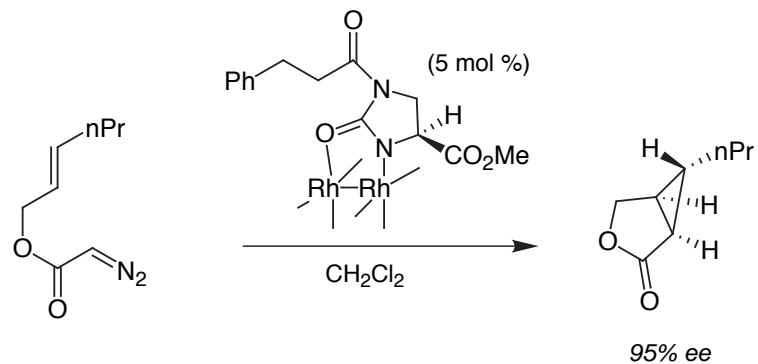
α - ^{13}C -labeled $C_{10}H_8$ is isomerized into β - ^{13}C -labeled $C_{10}H_8$ at 1035 °C

L. T. Scott, *JACS* **1991**, *113*, 9692.

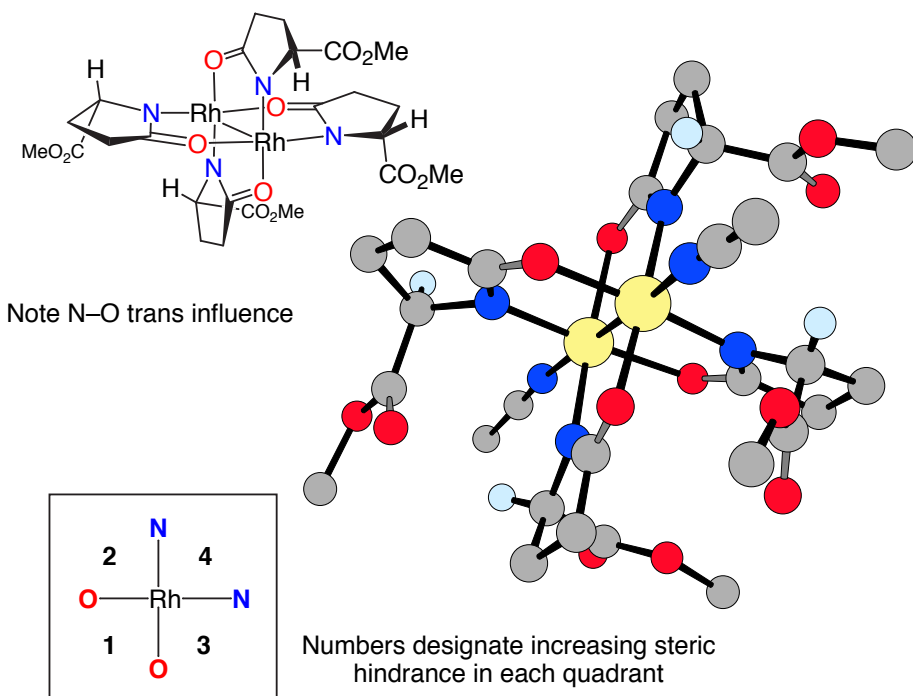


Scott, L.T., et. al., *JACS* **113** 7082 (1991)

■ Catalytic Asymmetric Variants: Chiral Rh(II) Complexes



Doyle et al. *Tetrahedron Lett.* **1995**, 36, 7579.

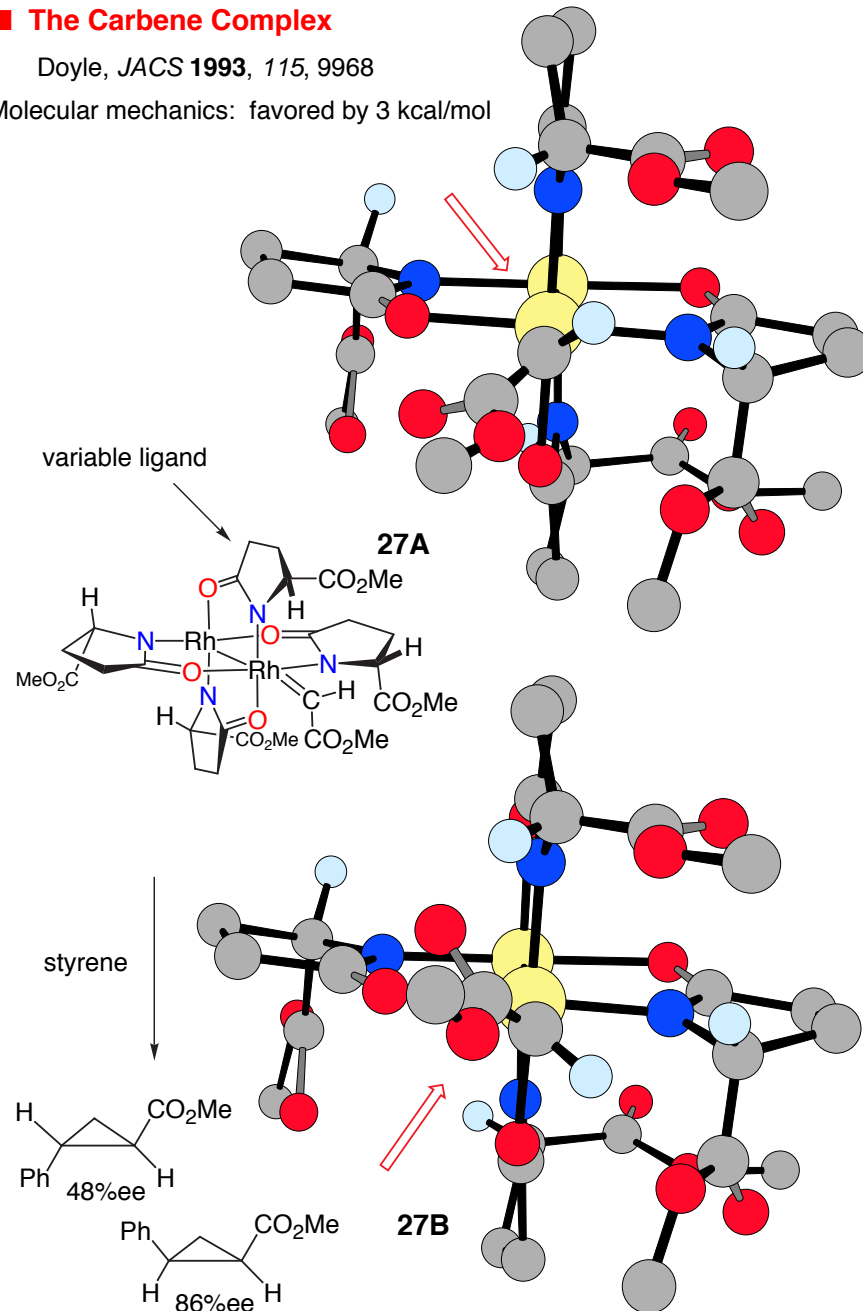


Doyle, *JACS* **1993**, 115, 9968

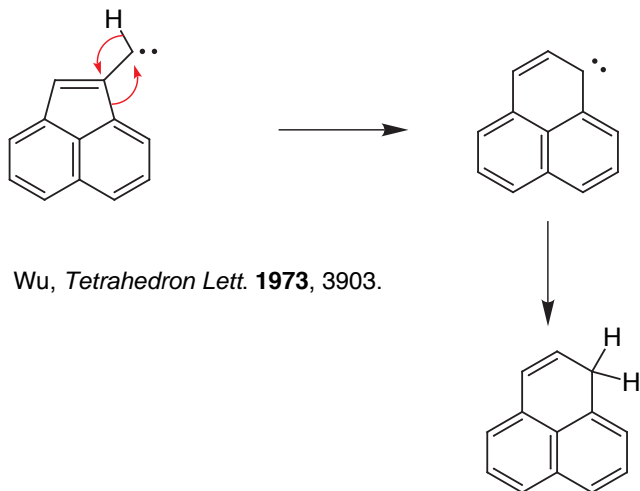
■ The Carbene Complex

Doyle, *JACS* **1993**, 115, 9968

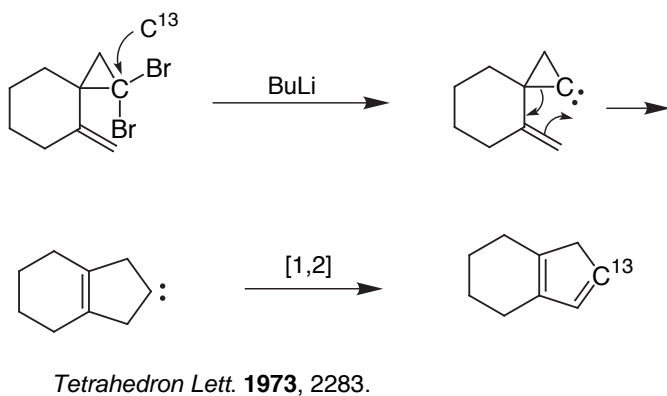
Molecular mechanics: favored by 3 kcal/mol



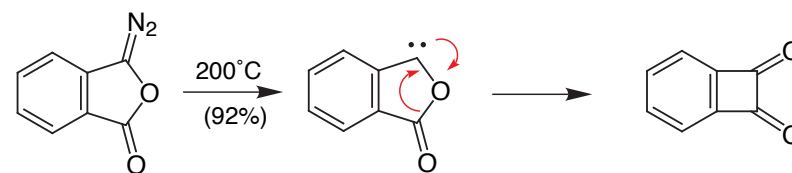
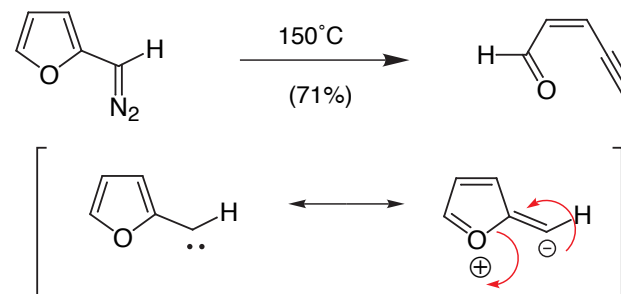
Carbene-Carbene Rearrangements



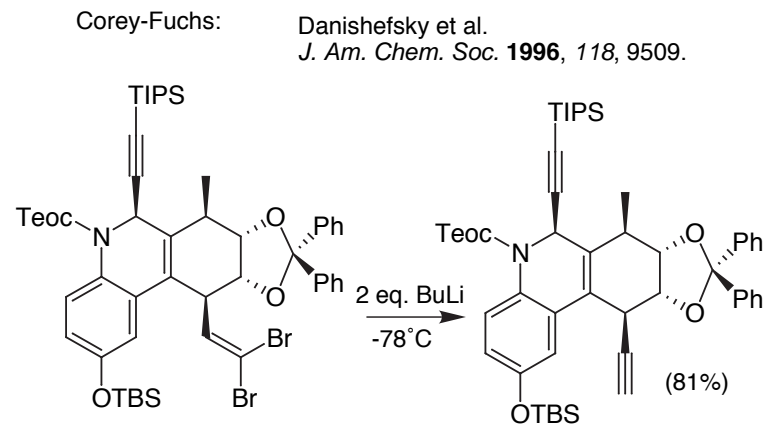
Skattebol Rearrangement



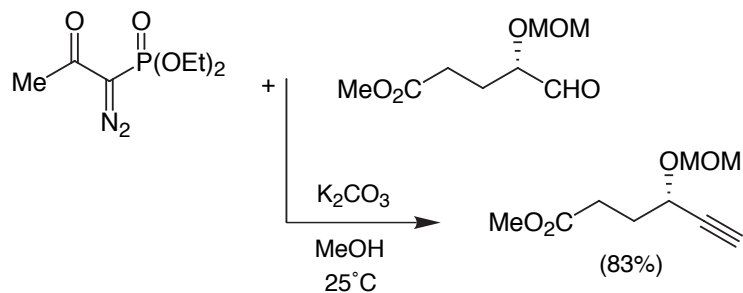
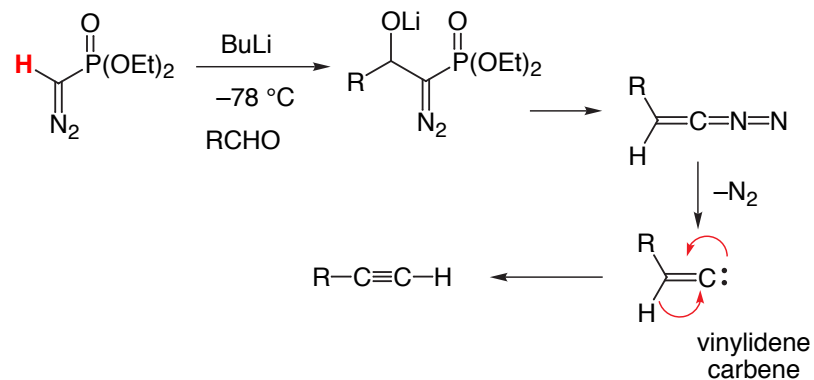
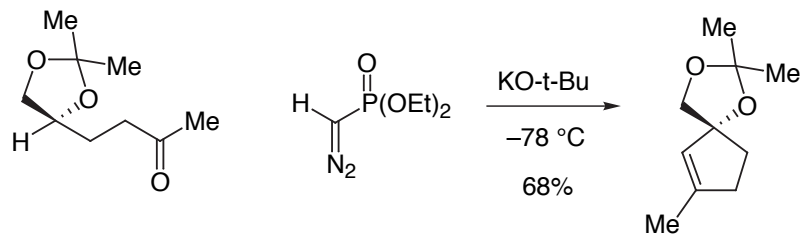
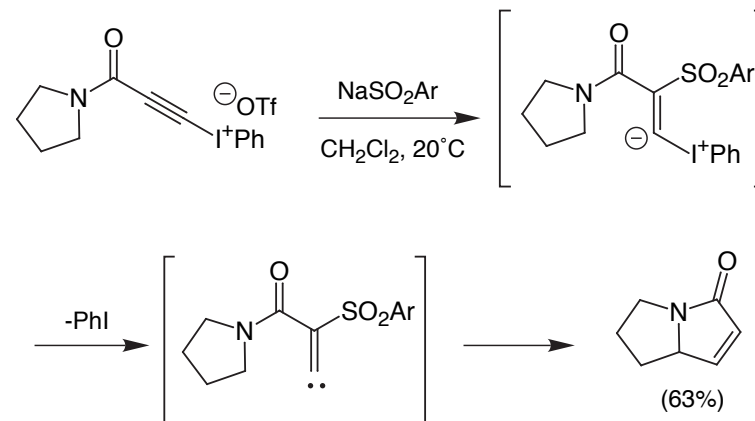
Other Rearrangements



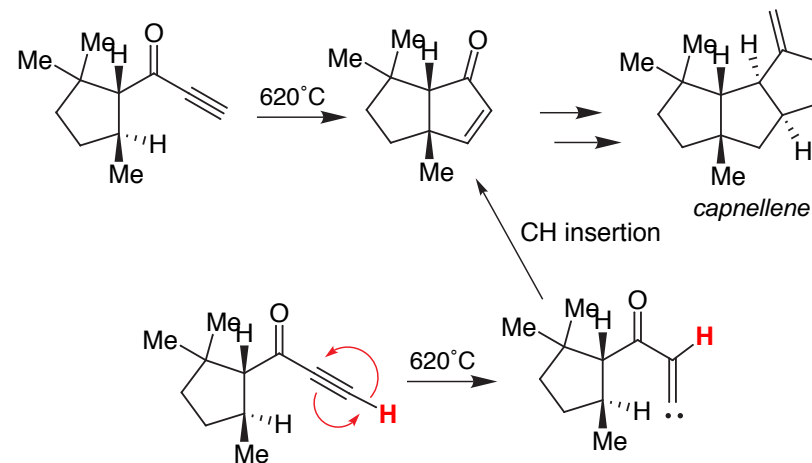
Vinylidenes



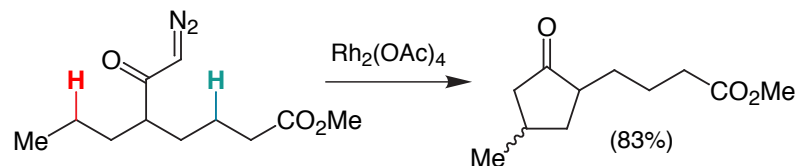
Carbene Rearrangements

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!

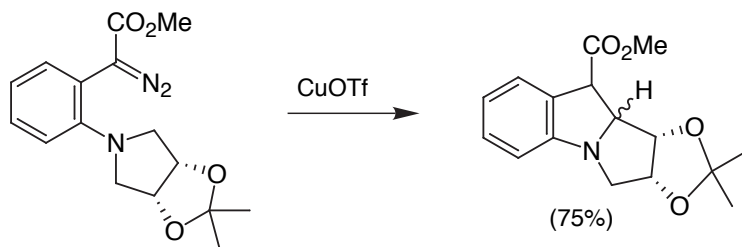


■ C-H Insertions continued...



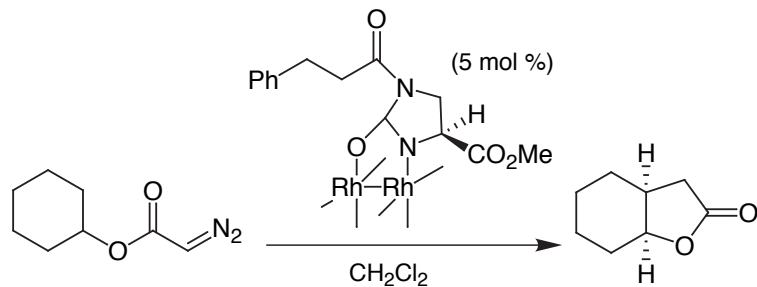
Electrophilic carbenes are very sensitive to electronic effects

Stork *Tetrahedron Lett.* **1988**, 29, 2283.



Sulikowski, *J. Org. Chem.* **1995**, 60, 2326.

Enantioselective C-H Insertion

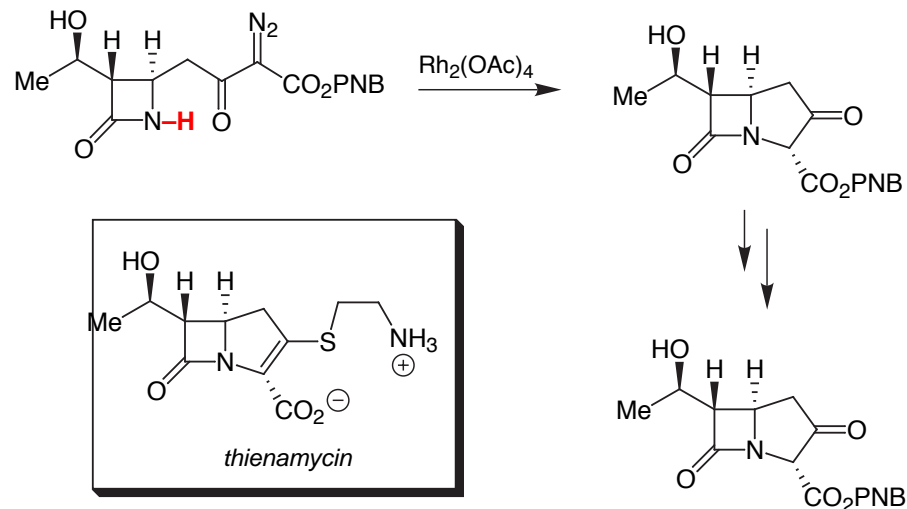


Doyle, *JACS* **1994**, 116, 4507

99%, 97% ee

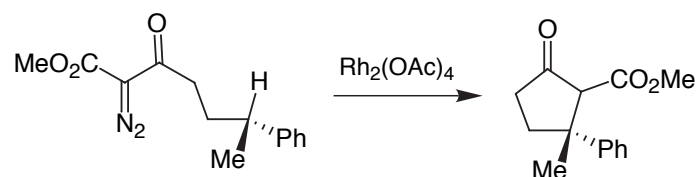
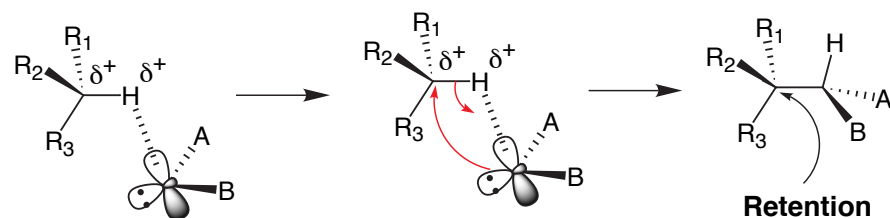
Chiral Dirhodium Carboxamidates: Catalysts for Highly Enantioselective Syntheses of Lactones and Lactams, *Aldrichchimica Acta.* **1996**, 29, 3 (**handout**)

■ N-H Insertions are also possible...



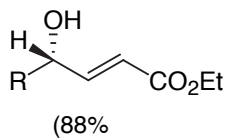
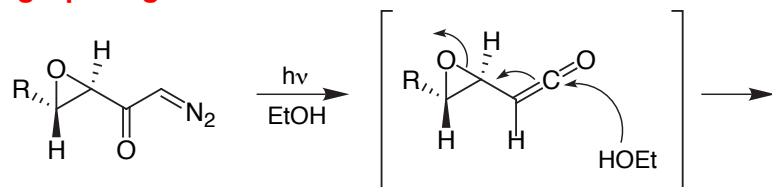
Salzmann, *JACS*, **1980**, 102, 6163.

Insertions (X-H): Stereochemical outcome



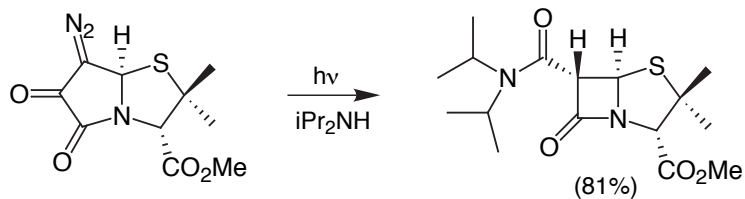
Taber *JACS*, **1996**, 107, 196.

Ring Opening



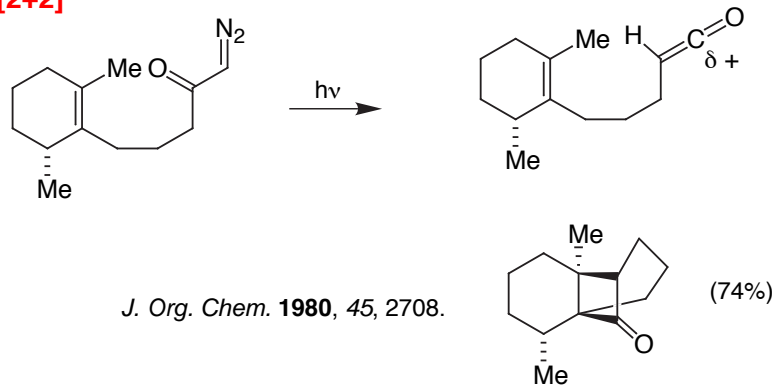
Tetrahedron Lett. **1990**, 31, 6589.

Ring Contraction



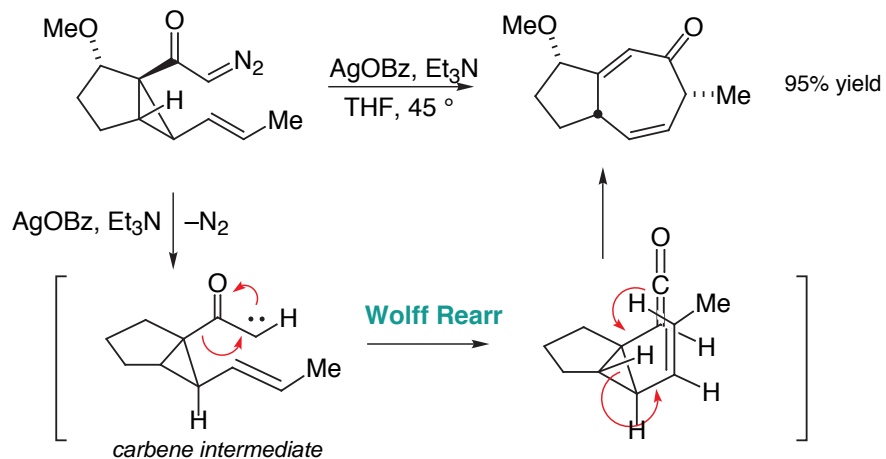
Moore et al. *J. Org. Chem.* **1983**, 48, 3365.

Wolff-[2+2]

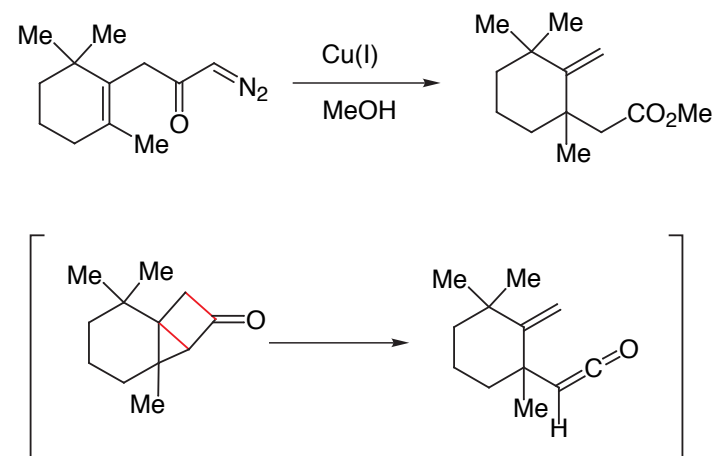


J. Org. Chem. **1980**, 45, 2708.

Problem 332: Wolff Rearrangement Stoltz ACS 2003, 125, 13624

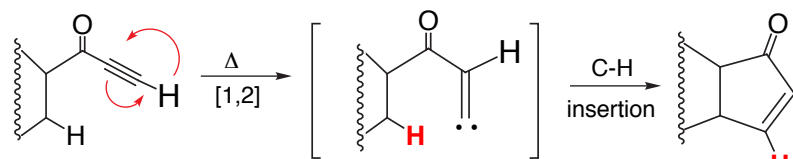


Vinyloligous Wolff Rearrangement Doyle pp520-521



Carbenes are Accessible via Sigmatropic Rearrangement

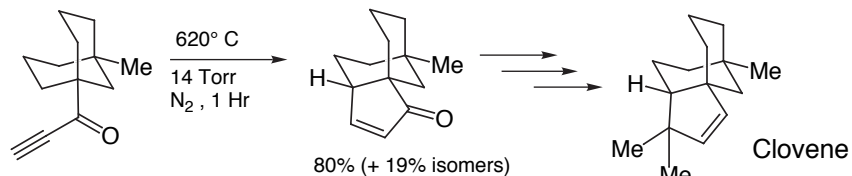
■ [1,2] Shifts: Alpha-Alkynone Cyclizations



Conditions: 620° C, 12-16 Torr, Quartz filled Quartz Tube

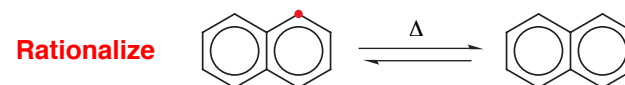
S.M.	3°	2°	1°	Recovery	
	—	 60	 22	 18	80%
	 87	—	 13	78%	
	 54	 46	—	89%	
	—	 92	 8	90%	

Karpf, M., Dreiding, A., *Helv. Chim. Acta.* **65** 13 (1982)

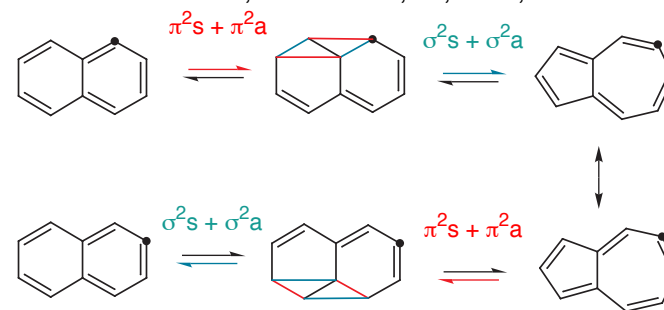


Karpf, M., Dreiding, A.S., *Helv. Chim. Acta.* **67** 1963 (1984)

The Automerization of Naphthalene (The Cume Question from Hell!)

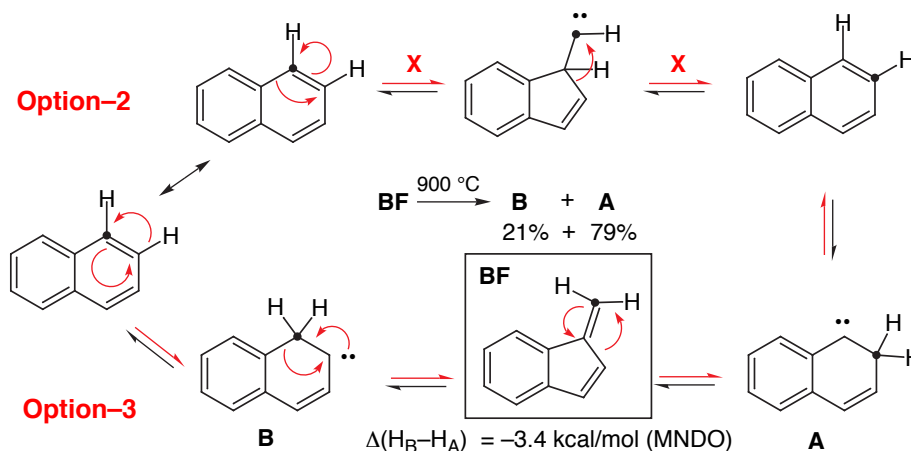


α -¹³C-labeled C₁₀H₈ is isomerized into β -¹³C-labeled C₁₀H₈ at 1035 °C

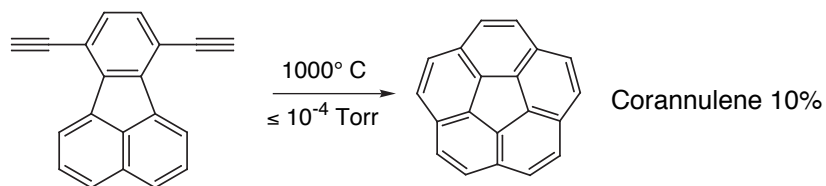
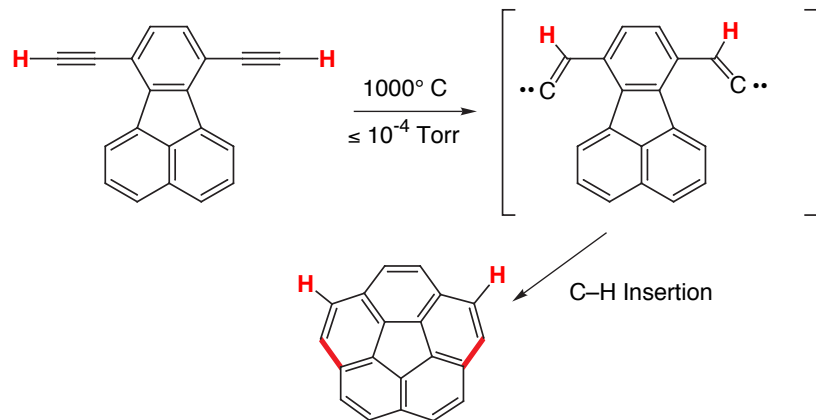
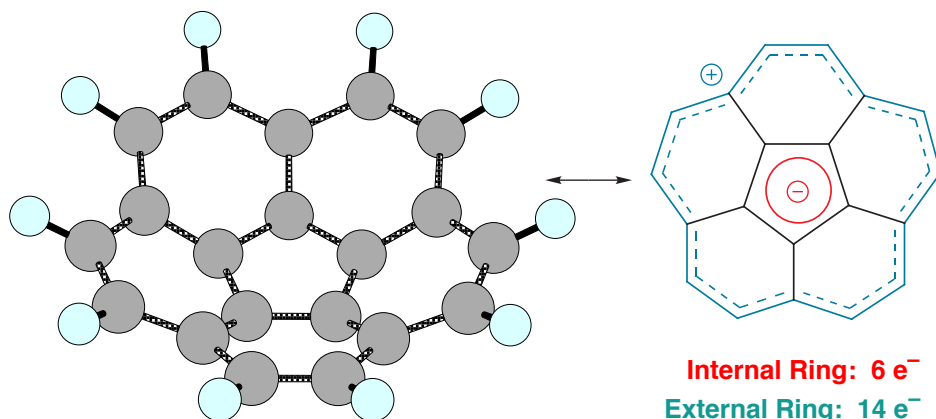
■ Mechanism-1: L. T. Scott, *JACS* **1977**, 99, 4506;

■ 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

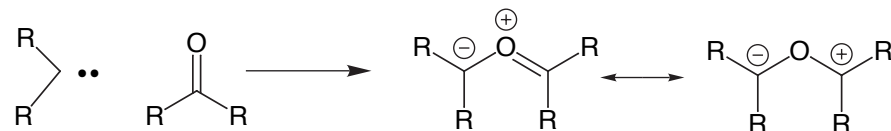
Suggested Reading

Houk and Wu *J. Org. Chem.* **1991**, *56*, 5657.Padwa and Hornbuckle *Chem. Rev.* **1991**, *91*, 263.

Review Articles

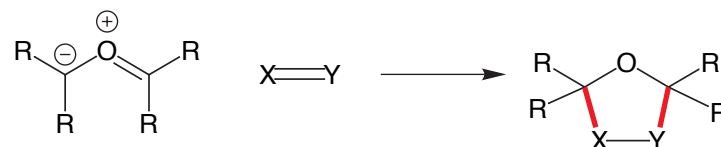
Padwa and Krumpe *Tetrahedron* **1992**, *48*, 5385.Hoffman, R. W. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 563.McKervey et al. *Chem. Rev.* **1994**, *94*, 1091.

Ylide Formation by the Interaction of Carbeneoids with Carbonyl Lone Pairs

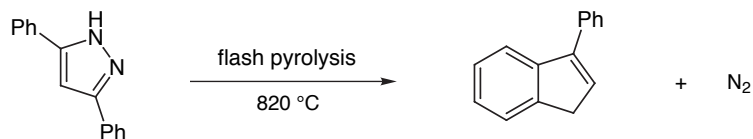


Generally, the carbene precursor of choice is a diazoalkane or, more frequently, an α -diazocarbonyl reagent. These can be decomposed via thermolysis or photolysis. However, the most common method involves catalytic amounts of transition metals, such as copper or rhodium.

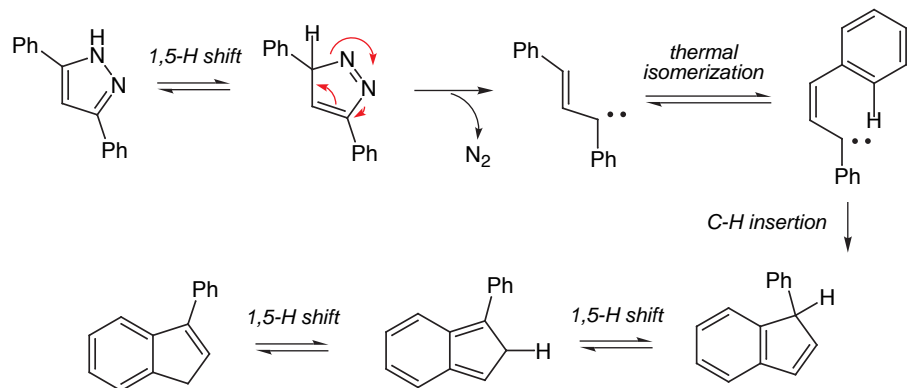
Dipolar Cycloaddition (See Lecture 18)



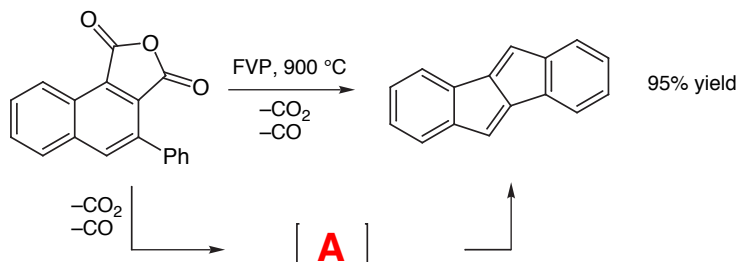
Web Problem 88. Please provide a mechanism for the following high temperature reaction that was reported by Yranzo and co-workers (*J. Org. Chem.* **1998**, 63, 8188).



Draw a plausible mechanism for the transformation to the major product isomer. Do not invoke any radical intermediates in your answer.

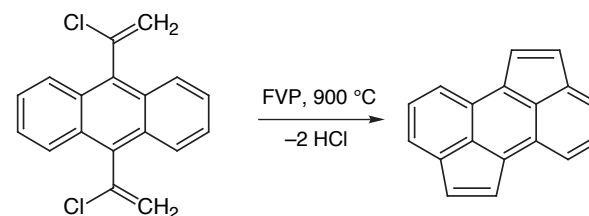


Web Problem 135. Anderson has reported the transformation illustrated below (*Aust J. Chem.* **1990**, 43, 1137) which is implemented by flash vacuum pyrolysis (FVP). As indicated, this reaction proceeds through intermediate **A**.



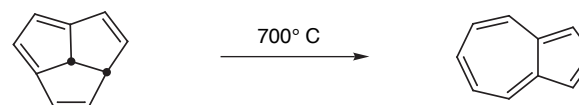
Provide a mechanism for this reaction and identify intermediate **A** in your answer.

Web Problem 172. Scott has recently reported the transformation illustrated below (*Tetrahedron Lett.* **1997**, 38, 1877) which is implemented by flash vacuum pyrolysis (FVP) at the indicated temperature.

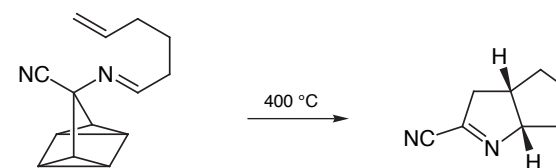


Provide a concise mechanism for this reaction in the space below.

Web Problem 198. Provide a mechanism for the thermal conversion of triquinacene to azulene (*JACS*, **1973**, 2724).

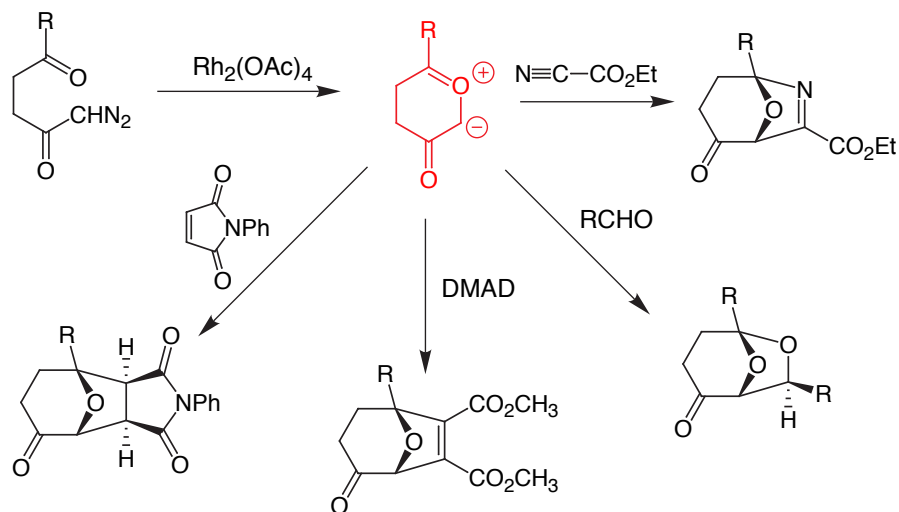


Web Problem 282. Hoffmann has reported the mechanistically interesting thermally induced transformation illustrated below (*Chem. Ber.* **1985**, 634.).



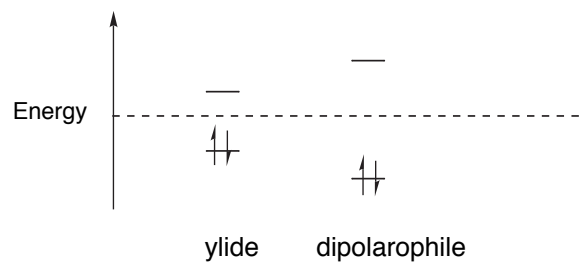
Provide a plausible mechanism for this reaction.

Tandem Intramolecular Cyclization–Intermolecular Cycloaddition

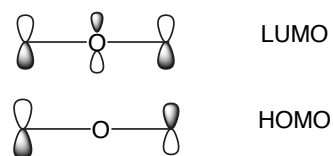


Dipolar-Dipolarophile Cycloadditions: HOMO–LUMO Energies

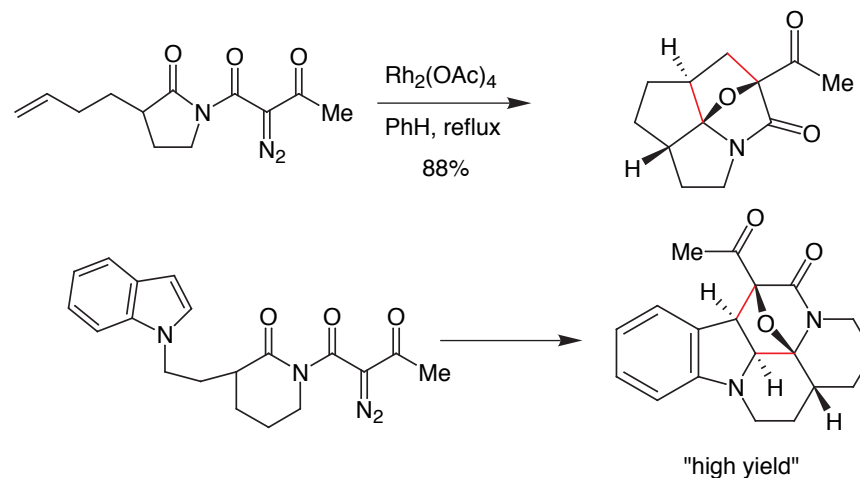
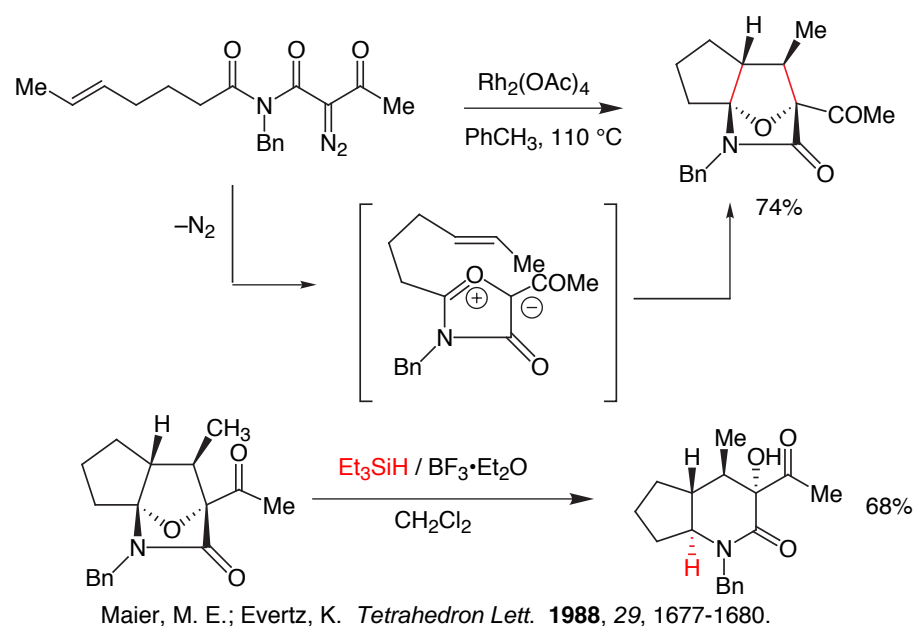
Carbonyl Ylides have very small HOMO-LUMO gaps



Therefore, either raising the dipolarophile HOMO (electron-donating substituents) or lowering the LUMO (electron-withdrawing) will accelerate the reaction.

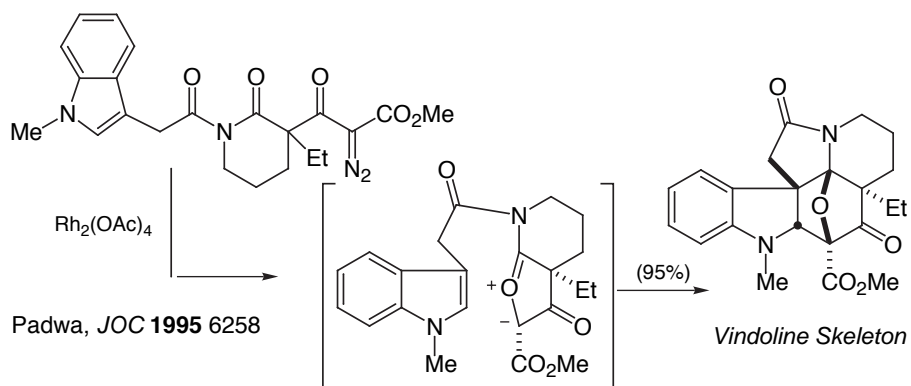
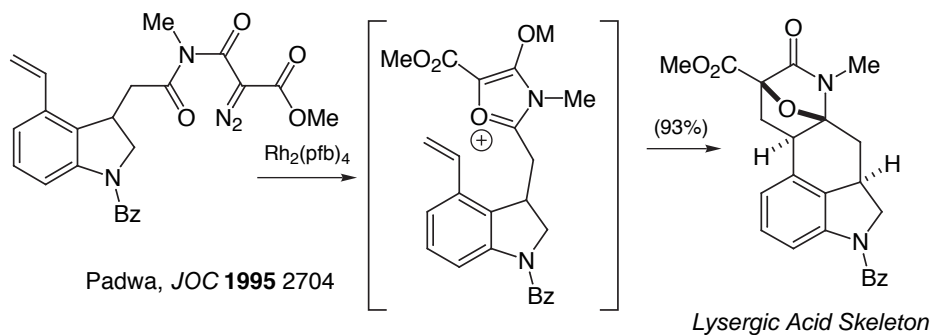
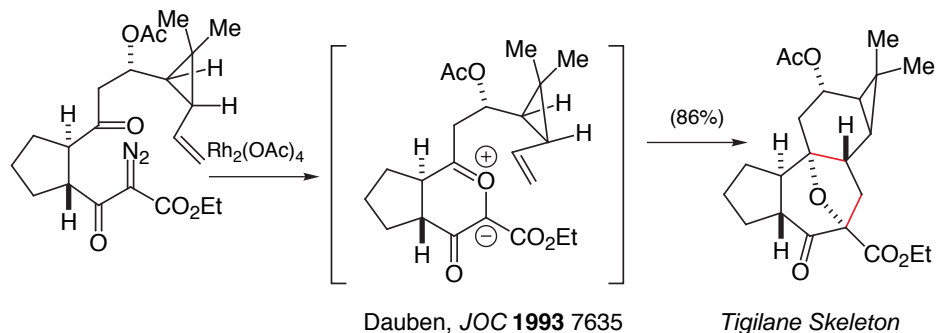


Reactions of Diazoimides: [3+2] addition

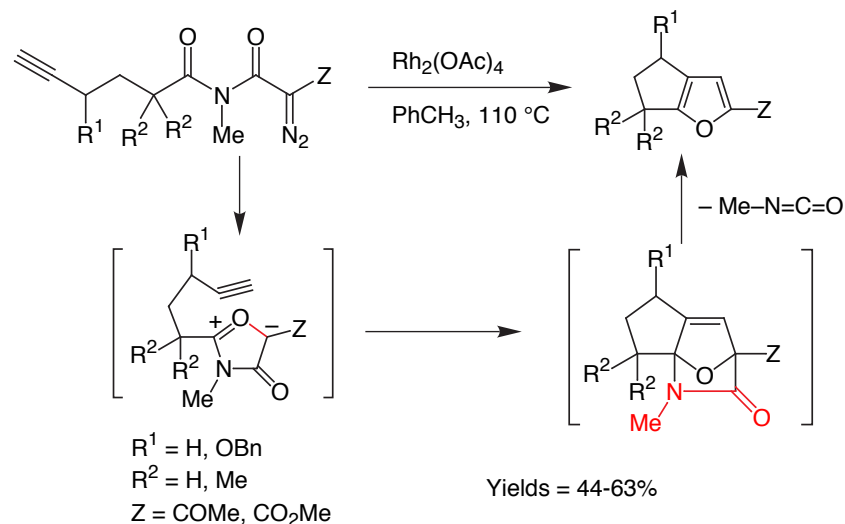
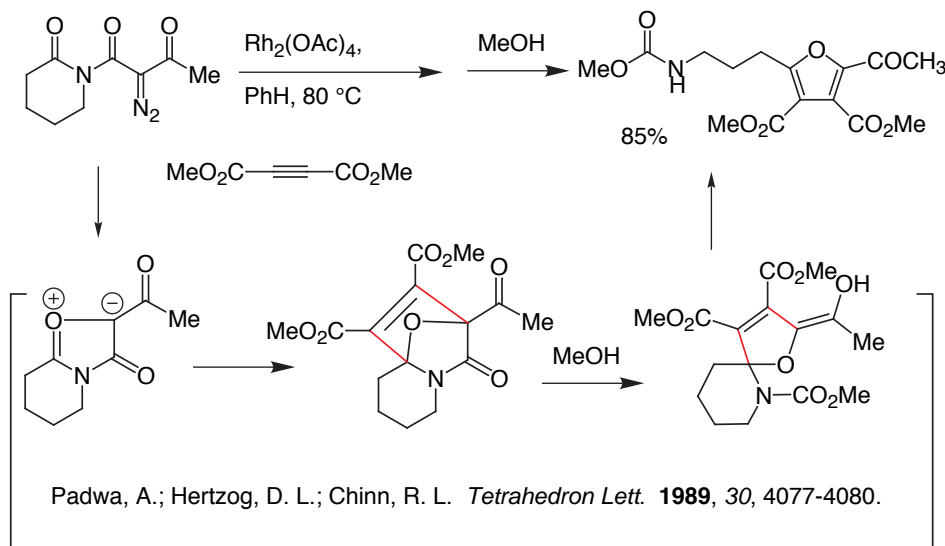


Padwa et. al. *Tetrahedron Lett.* **1992**, 33, 4731-4734.

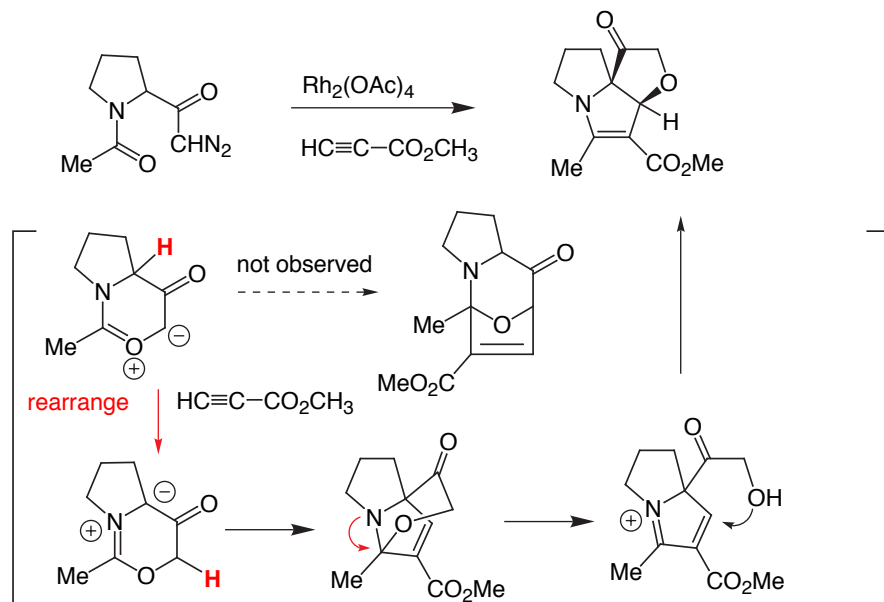
Dipolar Cycloadditions: Carbonyl Ylids



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"



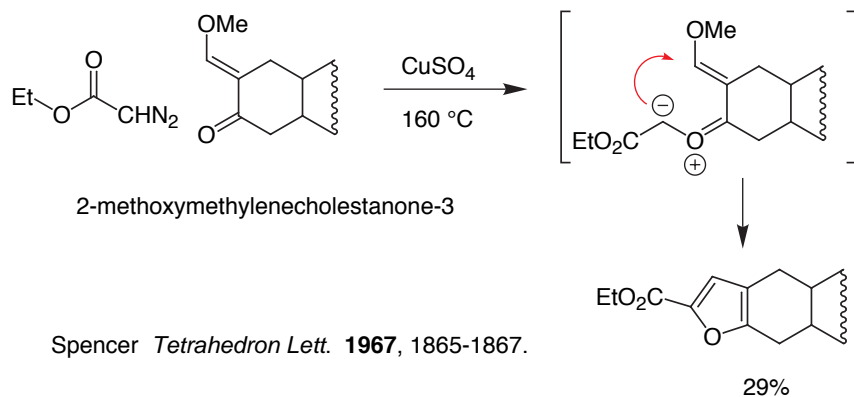
The 1,3-proton shift is catalyzed by trace amounts of water. Azomethine ylide formation requires a proton at the tertiary center.

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.

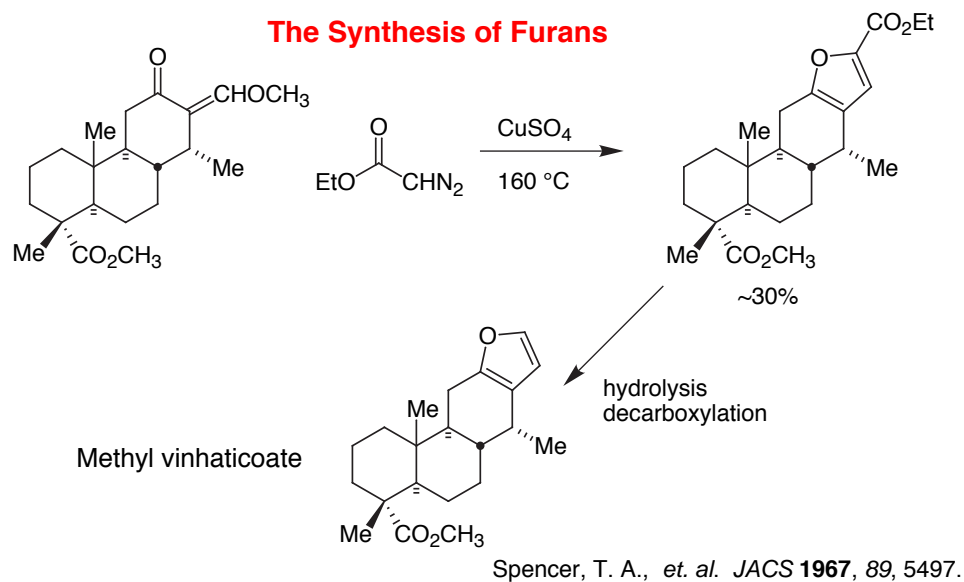
The Synthesis of Furans

Intermolecular addition to α,β -unsaturated carbonyls

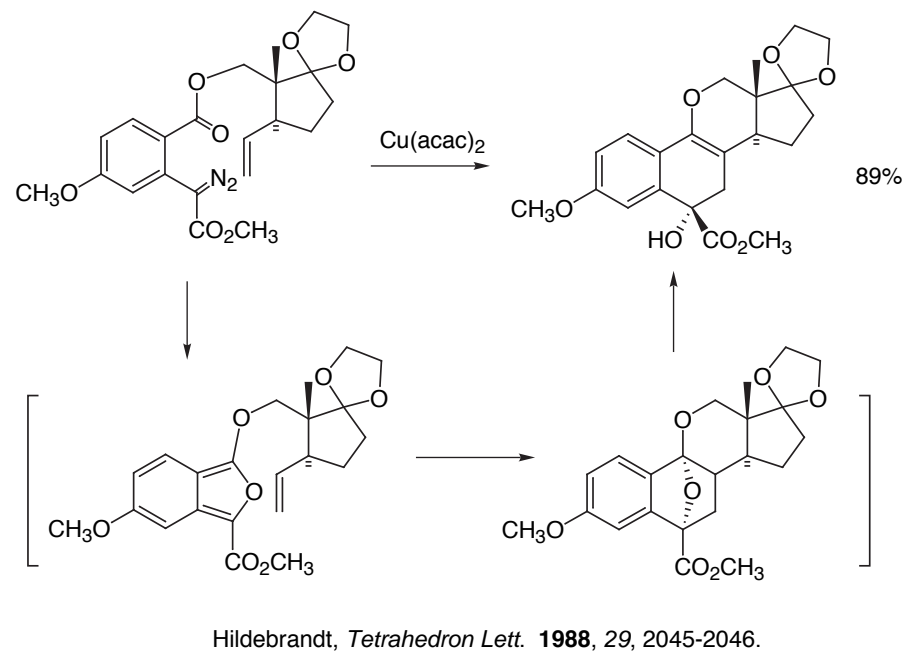


Spencer *Tetrahedron Lett.* **1967**, 1865-1867.

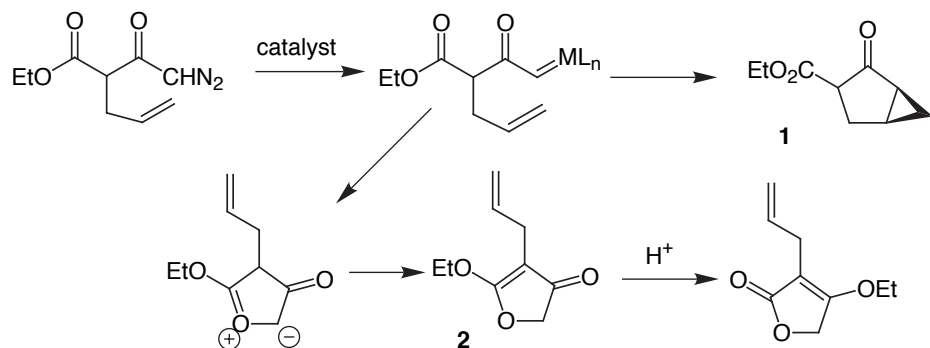
The Synthesis of Furans



Can you propose a rational mechanism for this transformation?



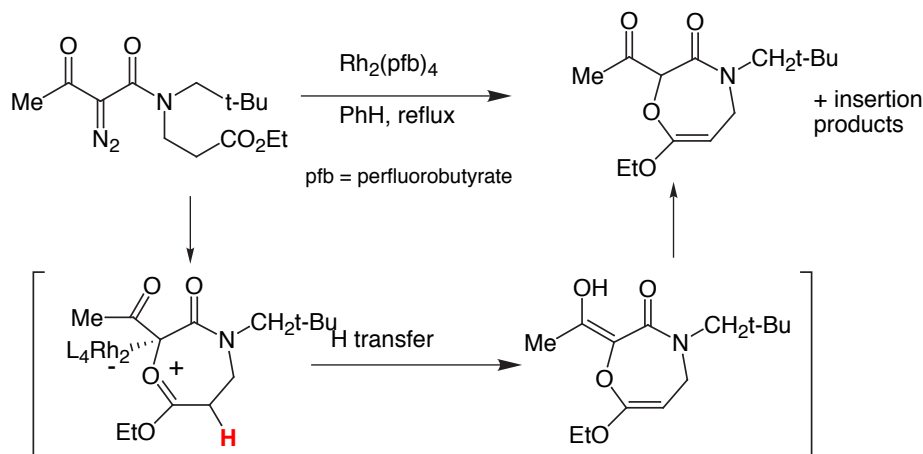
Ylid Formation versus Cyclopropanation



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

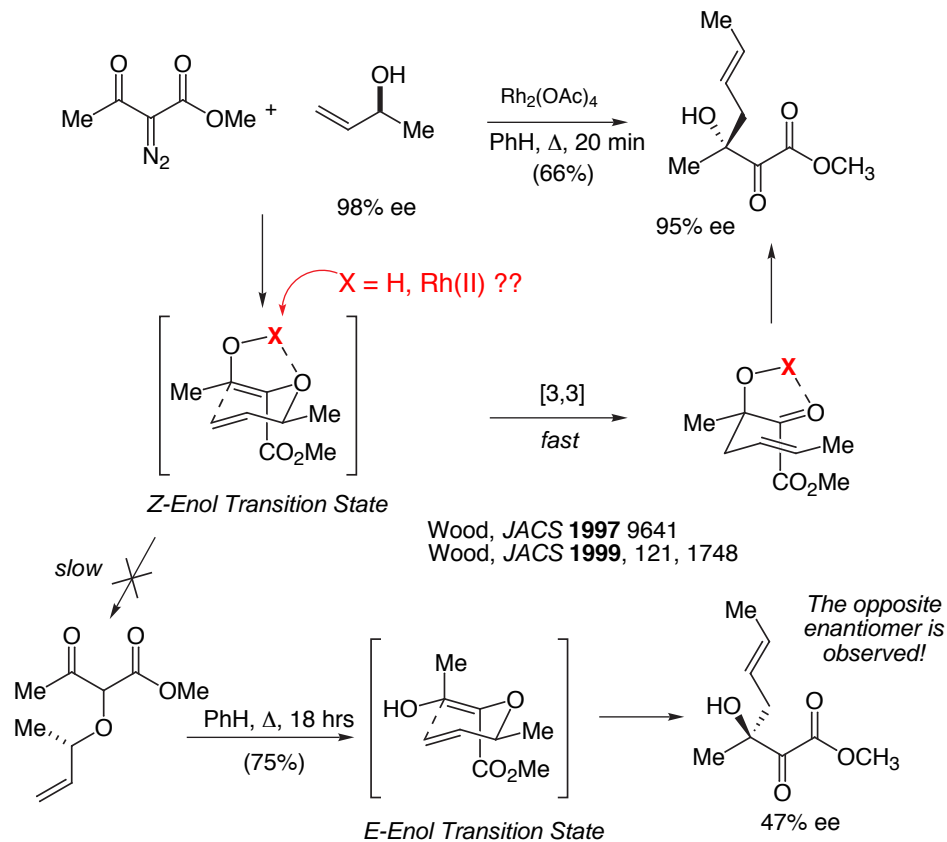
Bien, S.; Gillon, A.; Kohen, S. *J. Chem. Soc. Perkin Trans. I.* **1976**, 489-492



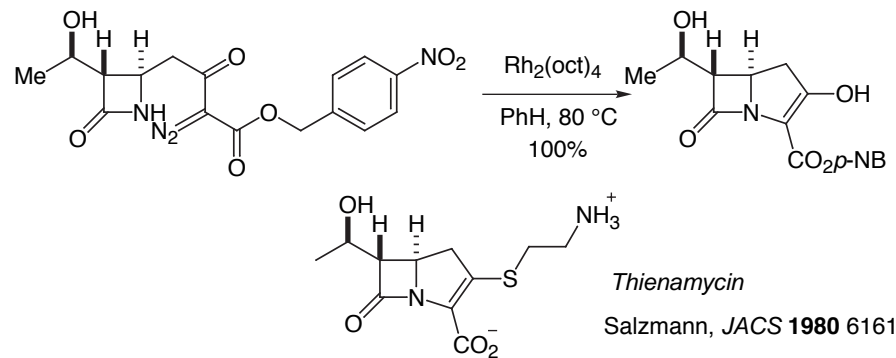
Doyle, M. P., et al. *J. Org. Chem.* **1991**, 56, 820-829.
Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, 30, 5397.

35-07-carbonyl ylids-4 12/11/03 9:09 PM

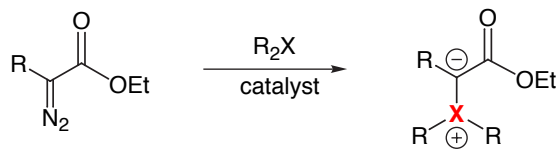
Tandem O-H Insertion/Claisen Rearrangement



Merck Thienamycin Process



Ylide Formation

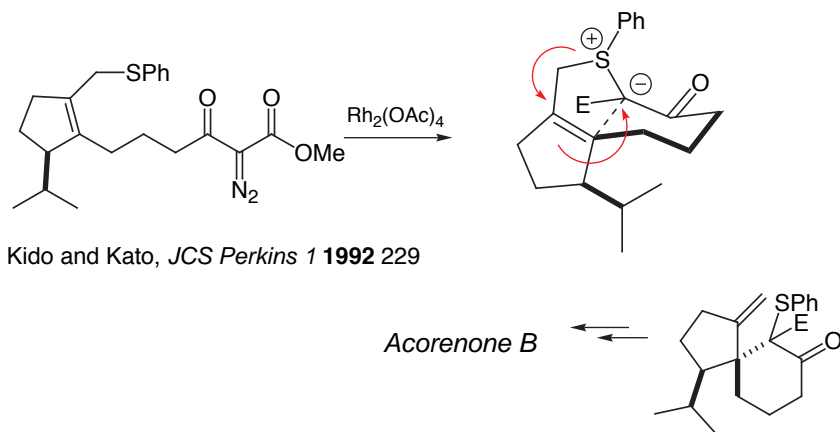


Reviews: Padwa, *Chem. Rev.* **1991** 263
 Padwa, *Chem. Rev.* **1996** 223
 Barnes, Evening Seminar, March 16, 1993

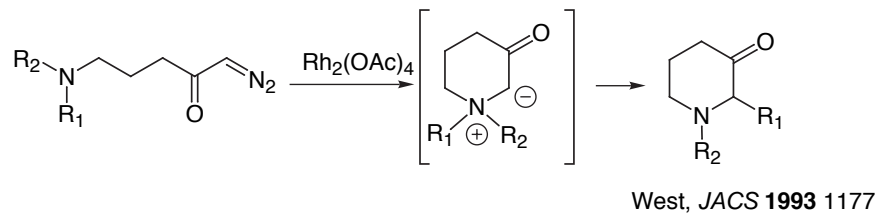
X is generally S, O or N and can be sp^2 or sp^3 hybridized

Ylides often undergo sigmatropic rearrangements or cycloadditions

[2,3]-Sigmatropic rearrangement:

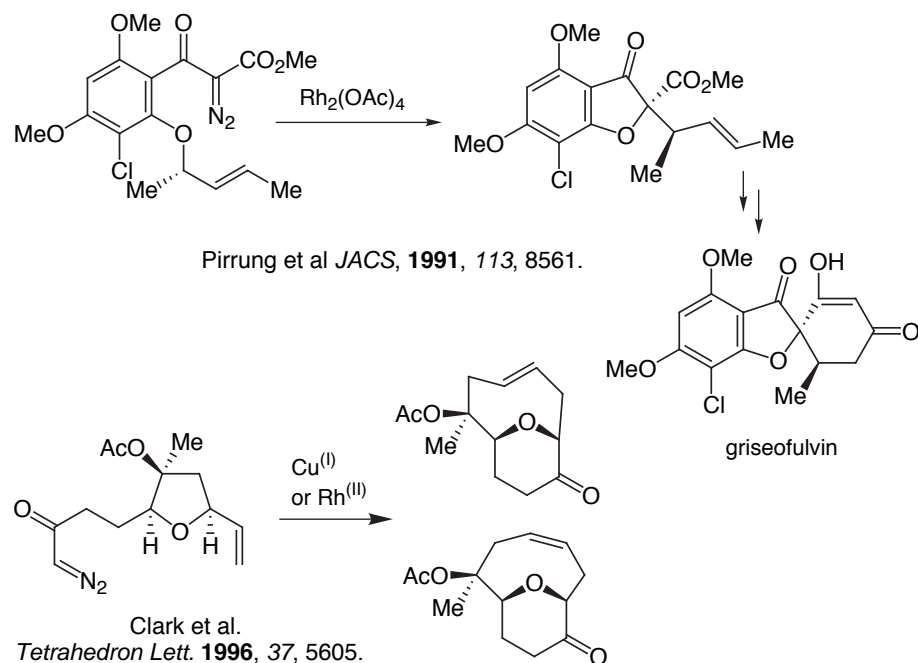
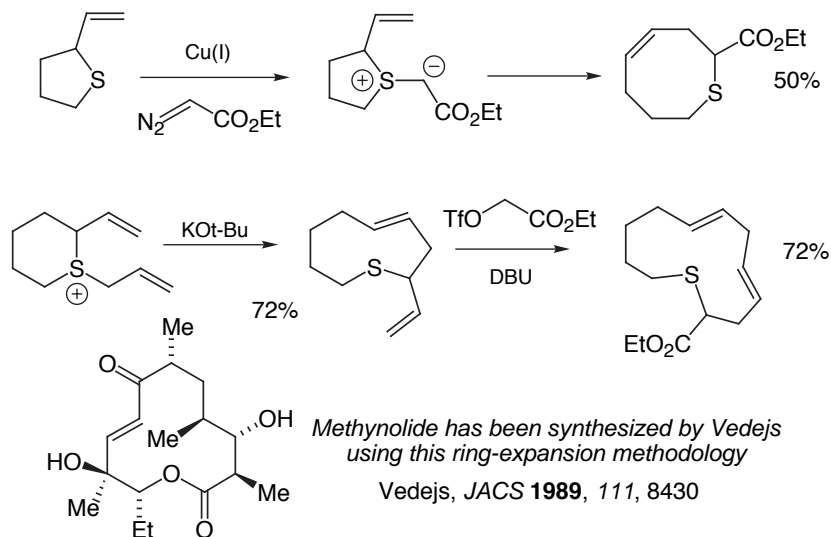


Stevens Rearrangement ([1,2] alkyl shift):



Ring expansion reactions have been investigated

Methods based on sulfur ylides: (review) Vedejs, *Accts. Chem. Res.* **1984**, *17*, 358



Chemistry 206

Advanced Organic Chemistry

Handout-35A

The Use of Fischer Carbenes in Organic Synthesis

"...every synthetic chemist is well advised to follow this fascinating field with appropriate attention."

- Schmalz, H.-G., *ACIEE*, **1994**, 303.

Brian Connell

Evans Group Seminar, February, 1999

D. A. Evans

Friday,
December 12, 2003

The Use of Fischer Carbenes in Organic Synthesis

"...every synthetic chemist is well advised to follow this fascinating field with appropriate attention."

- Schmalz, H.-G., *ACIEE*, **1994**, 303.

Brian Connell
Evans Group Seminar
2/12/99

Outline

- Introduction and Fundamentals
- Reactions
 - Cyclopropanation
 - Diels-Alder Cycloaddition
 - Other Cycloadditions
 - Dotz Reaction and Analogs
 - Photochemistry
 - Conjugate Additions
 - Other Reactions

General References:

Wulff, *Organometallics*, **1998**, 3116.

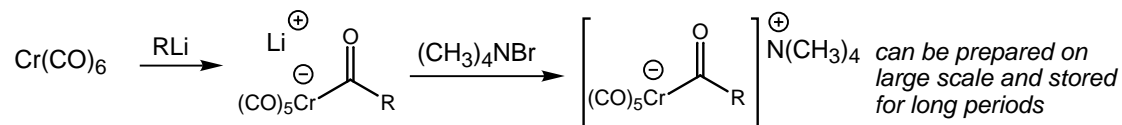
Wulff, *Comprehensive Organic Synthesis*, Vol. 5, Chap 9.2: Metal Carbene Cycloadditions, Pergamon Press, 1991.

Wulff, *Comprehensive Organometallic Chemistry II*, Vol. 12, Chap 5.3: Transition Metal Carbene Complexes: Alkyne and Vinyl Ketene Chemistry, Pergamon Press, 1994.

Hegedus, *Comprehensive Organometallic Chemistry II*, Vol. 12, Chap 5.4: Transition Metal Carbene Complexes: Photochemical Reactions of Carbene Complexes, Pergamon Press, 1994.

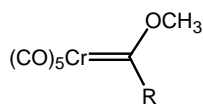
Introduction

- Definition: electrophilic, heteroatom stabilized complexes having formal metal-to-carbon double bonds
- Group 6 metals (Cr, Mo, W) are the most common metals used.
- First prepared by Fischer (*ACIEE*, **1964**, 580):



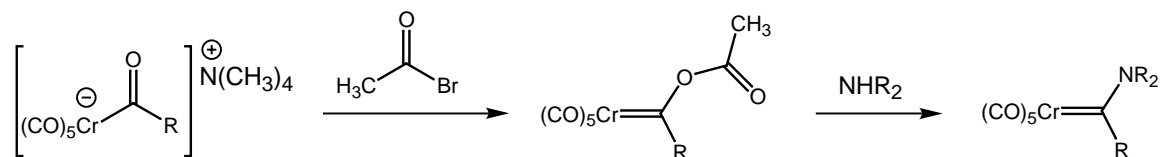
↓ "hard" alkylating reagents
(CH₃)₃OBF₄, CH₃COBr

- excellent yields for all steps
- cheap starting materials (20-50¢/mmol)

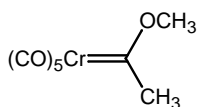


- air, silica stable
- crystalline, easy to handle
- colored (yellow to red)

Nitrogen Analogs

Dotz, *Synlett*, **1991**, 381.

Selected Physical Data

Bond Lengths

$C_{\text{carbene}} - \text{O} = 1.33 \text{ \AA}$
 $C_{\text{carbene}} - \text{Cr} = 2.04 \text{ \AA}$
 $\text{Cr} - \text{CO}_{\text{cis}} = 1.86 - 1.91 \text{ \AA}$
 $\text{Cr} - \text{CO}_{\text{trans}} = 1.87 \text{ \AA}$

IR Frequencies

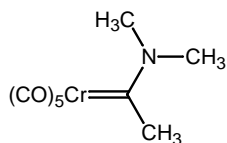
$\nu_{\text{CO}} \sim 2070, 1992, 1953 \text{ cm}^{-1}$

 $^1\text{H NMR}$

$C_{\text{carbene}} - \text{CH}_3 = \sim 5$

 $^{13}\text{C NMR}$

$C_{\text{carbene}} = 320-360 \text{ ppm}$

Bond Lengths

$C_{\text{carbene}} - \text{N} = 1.31 \text{ \AA}$
 $C_{\text{carbene}} - \text{Cr} = 2.16 \text{ \AA}$
 $\text{Cr} - \text{CO}_{\text{cis}} = 1.90 \text{ \AA}$
 $\text{Cr} - \text{CO}_{\text{trans}} = 1.85 \text{ \AA}$

IR Frequencies

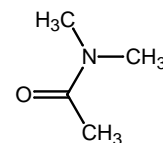
$\nu_{\text{CO}} = \sim 2060, 1970, 1940 \text{ cm}^{-1}$

 $^1\text{H NMR}$

$C_{\text{carbene}} - \text{CH}_3 = \sim 3.2$

 $^{13}\text{C NMR}$

$C_{\text{carbene}} = 250-290 \text{ ppm}$

Bond Lengths

$C_{\text{carbonyl}} - \text{N} = 1.29 \text{ \AA}$
 $C_{\text{carbonyl}} - \text{O} = 1.23 \text{ \AA}$

IR Frequencies

$\nu_{\text{CO}} = \sim 1650 \text{ cm}^{-1}$

 $^1\text{H NMR}$

$C_{\text{carbonyl}} - \text{CH}_3 = \sim 2.1$

 $^{13}\text{C NMR}$

$C_{\text{carbonyl}} = \sim 165 \text{ ppm}$

Major Contributors



Ernst Otto Fischer

I was born in Solln, near Munich, on 10 November 1918 as the third child of the Professor of Physics at the Technical College of Munich, Dr. Karl T. Fischer (died 1953), and his wife, Valentine, née Danzer (died 1935). After completing four years at elementary school I went on to grammar school in 1929, from which I graduated in 1937 with my Abitur. Following a subsequent period of "work service" and shortly before the end of my two years' compulsory military service, the Second World War broke out. I served in Poland, France and Russia. In the winter of 1941/2 I began to study Chemistry at the Technical College in Munich during a period of study leave. I was released by the Americans in the autumn of 1945, and resumed my study of Chemistry in Munich after the reopening of the Technical College in 1946. I graduated in 1949. I took up a position as scientific assistant to Professor Walter Hieber in the Inorganic Chemistry Department, and under his guidance I dedicated myself to working on my doctoral thesis, "The Mechanisms of Carbon Monoxide Reactions of Nickel II Salts in the Presence of Dithionites and Sulfoxylates". After receiving my doctorate in 1952, I was invited by Professor Hieber to continue my activities at the college and consequently chose to specialise in the study of transition metal and organo-metallic chemistry. I wrote my university teaching thesis on "The Metal Complexes of Cyclopentadienes and Indenes". I was appointed a lecturer at the Technical College in 1955 and in 1956 I completed a scientific sojourn of many months in the United States. In 1957 I was appointed Professor at the University of Munich. After turning down an offer of the Chair of Inorganic Chemistry at the University of Jena I was appointed Senior Professor at the University of Munich in 1959. In 1957 I was awarded the Chemistry Prize by the Göttingen Academy of Sciences. The Society of German Chemists awarded me the Alfred Stock Memorial Prize in 1959. In 1960 I refused an appointment as Senior Professor in the Department of Inorganic Chemistry at the University of Marburg. In 1964 I took the Chair of Inorganic Chemistry at the Technical College of Munich, which had been vacated by Professor Hieber. In the same year I was elected a member of the Mathematics/Natural Science section of the Bavarian Academy of Sciences; in 1969 I was appointed a member of the German Academy of Scientists Leopoldina. In 1972 I was given an honorary doctorate by the Faculty of Chemistry and Pharmacy of the University of Munich.

Lectures on my fields, particularly those on metallic complexes of cyclopentadienes and indenenes, metal-pi-complexes of six-membered aromatics, mono-, di- and oligo-olefins and most recently metallocarbonyl carbene and carbyne complexes, led me on lecture tours of the United States, Australia, Venezuela, Brazil, Israel and Lebanon, as well as numerous European countries, including the former Soviet Union. In 1969 I was Firestone Lecturer at the University of Wisconsin, Madison, Wisconsin, USA; in 1971 Visiting Professor at the University of Florida, Gainesville, USA, as well as the first Inorganic Chemistry Pacific West Coast Lecturer. In the spring of 1973 I held lectures as the Arthur D. Little Visiting Professor at the Massachusetts Institute of Technology, Cambridge, Massachusetts, USA; and that was followed by a period when I was Visiting Distinguished Lecturer at the University of Rochester, Rochester, New York, USA.

Nobel lecture: On the way to carbene and carbyne complexes. *Angew. Chem.* (1974), 86(18), 651-63.



Karl Heinz Dotz

Kekule-Institut für Organische Chemie und Biochemie der Universität Bonn

Born 1943

Ph.D. Technical University of Munich (E.O. Fischer) 1971.

Habilitation Technical University of Munich 1980.

Professor of Organometallic Chemistry University of Marburg 1986-1992, Dean of the Faculty 1990-1991.

Professor of Organic Chemistry University of Bonn since 1992.

Karl's research is focused on the following areas:

- Synthetic Organometallic Chemistry (metal carbenes and planar-chiral arene complexes)
- Physical Organic and Organometallic Chemistry (distorted fused arenes and cyclophanes: synthesis and structure-chiroptics correlation, transition metal NMR spectroscopy, Ab initio-calculations on organometallic complexes and intermediates)
- Metal-Mediated Organic Synthesis (stereoselective C-C formation via metal carbenes, diastereoselective benzannulation and cyclopentannulation)
- Organometallic Catalysis (chromium-catalyzed cyclopropanation, axial-chiral and redox-active biaryl ligands)
- Transition Metal Modified Sugars (metal glycosylcarbenes and glycosylidenes: synthesis and application in C-glycosidation, disaccharide mimetics, conformation of acyclic metal modified sugars)

Major Contributors



Claude F. Bernasconi
University of California at Santa Cruz

Claude was born in Zurich, Switzerland. He received his undergraduate and Ph.D. degrees from the Swiss Federal Institute of Technology (ETH) with Heinrich Zollinger. Following a postdoctoral year with Manfred Eigen at the Max Planck Institute for Biophysical Chemistry in Göttingen, he joined the chemistry faculty at the University of California at Santa Cruz in 1967, where he has been a professor of chemistry since 1977. His main research interests are in physical organic chemistry and center on problems of mechanism, structure-reactivity relationships, intrinsic barriers of reactions, and catalysis in organic and organometallic reactions, particularly proton transfer reactions, nucleophilic addition to electrophilic alkenes, nucleophilic vinylic substitution and reactions of Fischer carbene complexes.



Charles P. Casey

University of Wisconsin-Madison
Born 1942, St. Louis, MO
B.S. 1963, St. Louis University
Ph.D. 1968, MIT

Chuck received a Ph.D. in organic chemistry from MIT in 1968, where he studied organocopper chemistry under the direction of Professor George M. Whitesides. After spending 6 months at Harvard as an NSF postdoc with Paul D. Bartlett he joined the faculty at Wisconsin. Chuck is interested in studying the mechanisms of organometallic reactions and in developing an understanding of homogeneous catalysis. In addition, he is trying to design new organometallic reagents for synthesis and new heterobimetallic catalysts.



William D. Wulff

University of Chicago
Born Eau Claire, Wisconsin, 1949
B. S. 1971, University of Wisconsin-Eau Claire
Ph.D. 1979, Iowa State University

Professor Wulff received his Ph.D. degree from Iowa State University in 1979 with Professor Thomas Barton. After NIH postdoctoral work with Martin Semmelhack at Princeton University, he accepted a position at the University of Chicago in 1980. Professor Wulff's research interests are in the applications of organometallics in organic synthesis as both reagents and catalysts.



Jose Barluenga

University of Oviedo

Jose Barluenga obtained his Ph.D. degree (solvomercuration of dienes) at the University of Zaragoza in 1966 under the direction of Professor V. Gomez-Aranda. He spent 3.5 years as a postdoctoral fellow at Max Planck Institut Fur Kohlenforschung, Mulheim, in the group of Professor Hoberg studying aluminum chemistry. In 1970 he took a position as a research associate at the University of Zaragoza, where he was promoted to Associate Professor in 1972. In 1975 he moved to the University of Oviedo as Professor of Organic Chemistry in the Department of Organometallic Chemistry. His major research interest is focused on the development of new synthetic methods in the area of heterocyclic chemistry and functionalized systems.



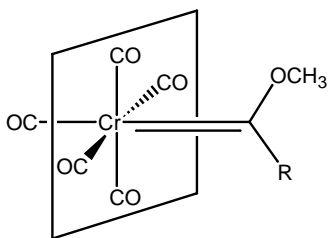
Louis S. Hegedus

Colorado State University
Born Cleveland, Ohio, 1943
B.S. 1965, Penn State University
M.A. 1966, Penn State University
Ph.D., 1970, Harvard

Lou was born in 1943 in Cleveland, Ohio, but grew up in rural Ohio, away from big city temptations. He did his undergraduate studies at Pennsylvania State University, where studied aqueous chromium redox chemistry with Professor Albert Haim. After Ph.D. studies at Harvard on nickel carbonyl chemistry with E. J. Corey (1970), and a NIH postdoctoral year at Stanford with J. P. Collman studying polymer-supported homogeneous catalysis, he moved to Colorado State University, where he remains today as a professor of chemistry. His research interests center on the use of transition metals in organic synthesis.

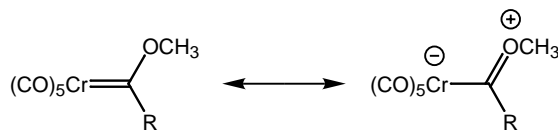
Recurring Themes

The Wall of CO



- $(\text{CO})_5\text{Cr}$ is sterically very large

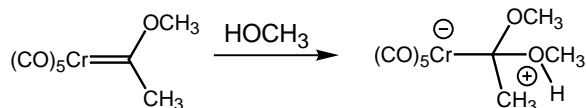
Resonance



- Rotation about heteroatom carbene bond is restricted by 14-25 kcal/mol
- ^{53}Cr NMR is consistent with strong resonance contribution

Hegedus and Dotz *JACS*, **1988**, 8413.

Kinetic Electrophilicity

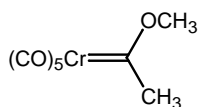


- Formation of tetrahedral intermediate is 10^9 faster than CH_3O^- addition to BnO_2CCH_3 .

Bernasconi
Chem. Soc. Rev., **1997**, 299.
JACS, **1998**, 8632.

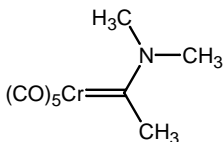
pK_a Data

Thermodynamic Acidity

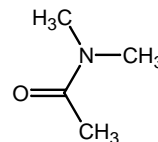


- $\text{pK}_a(\text{THF}) = 8$
- $\text{pK}_a(\text{H}_2\text{O}) = 12.3$

equivalent to *p*-cyanophenol



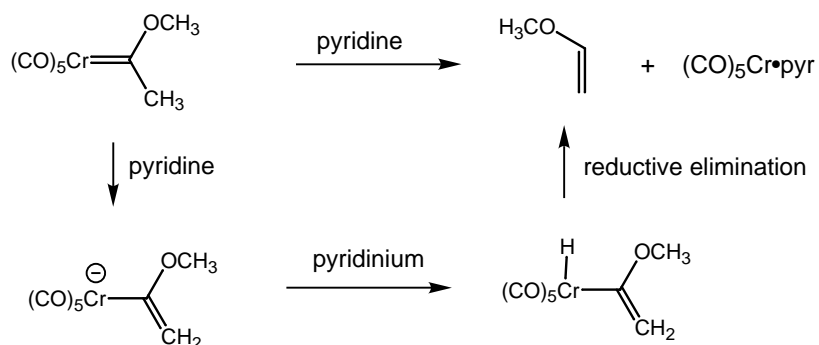
- $\text{pK}_a = 20.4$ (DMSO)



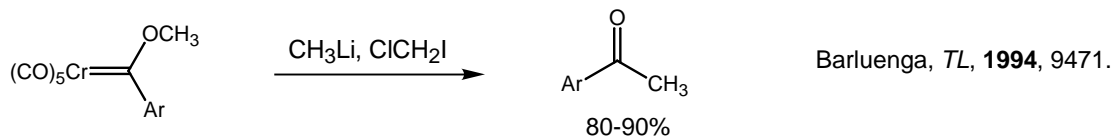
- $\text{pK}_a = 35$ (DMSO)

Casey, *JACS*, **1974**, 1230.

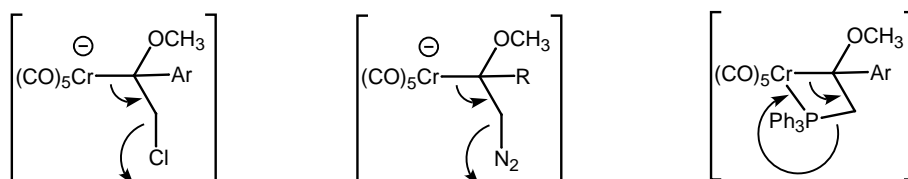
Sensitivity to Acid

See Hegedus, *JACS*, **1990**, 6255.

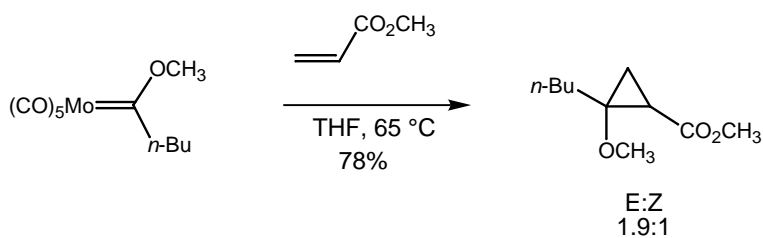
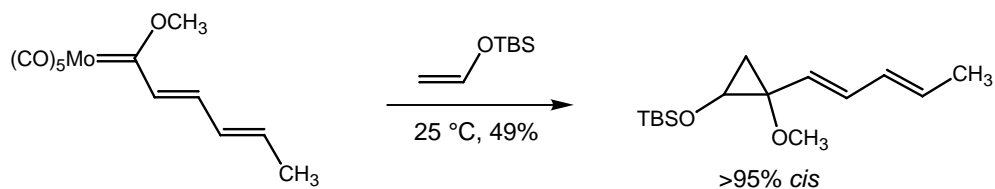
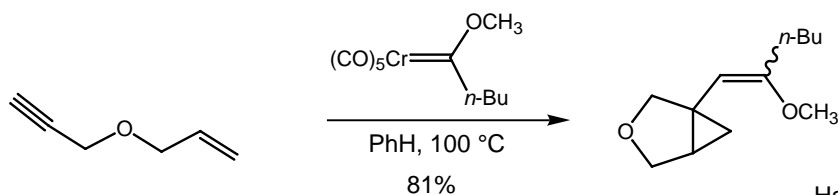
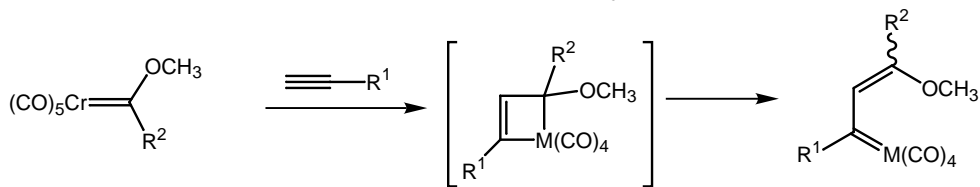
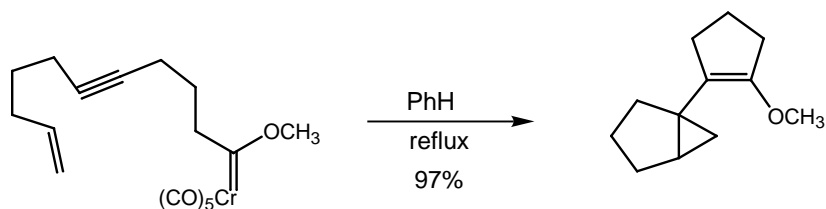
Metal Removal and Functionalization



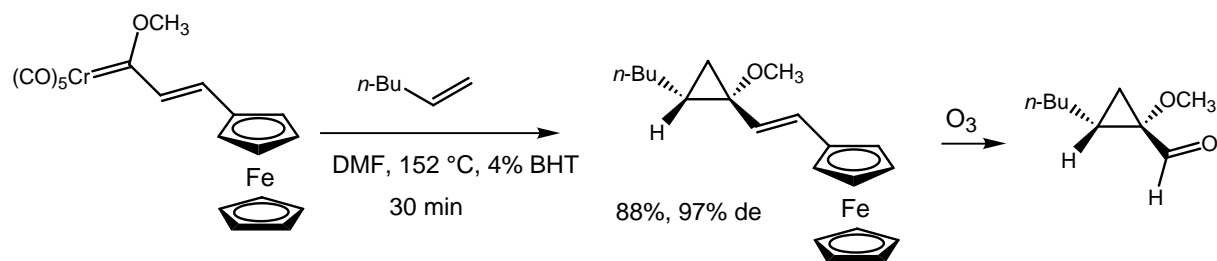
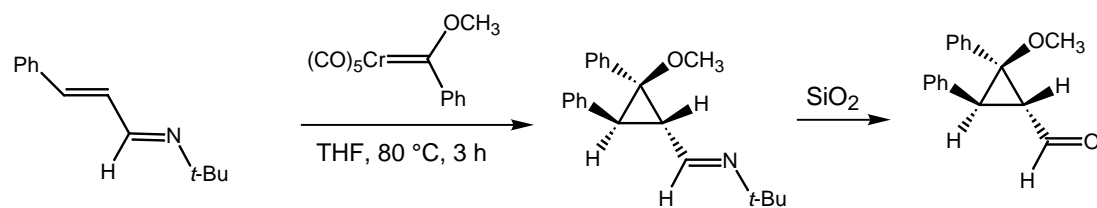
Via similar intermediates:



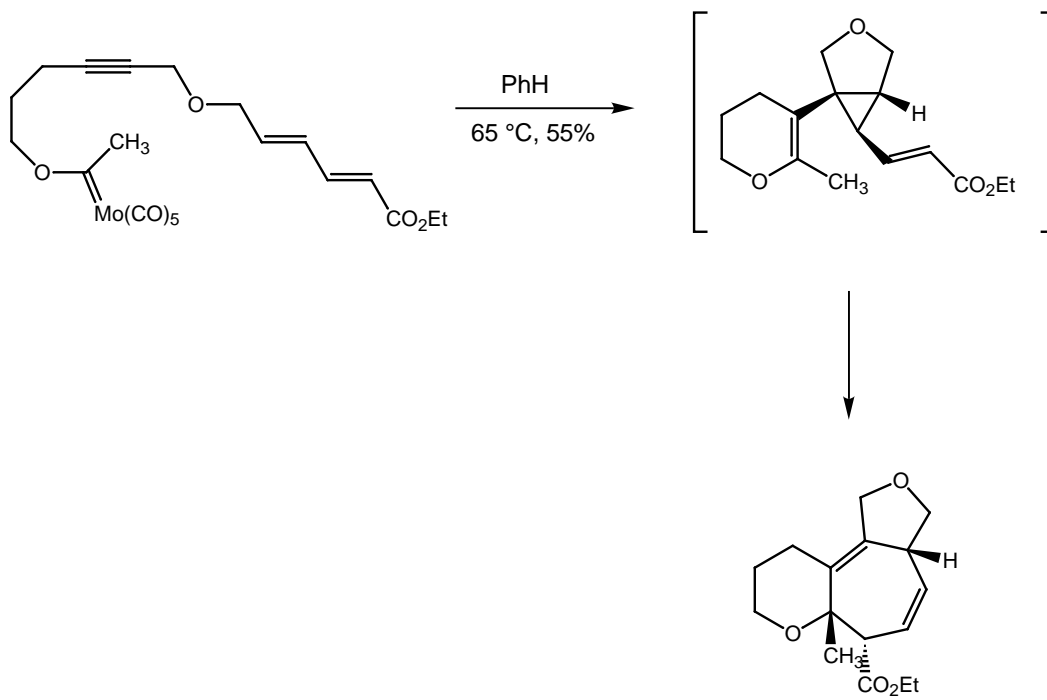
Cyclopropanation

Harvey, *TL*, **1990**, 2529.Wulff
Pure Appl. Chem., **1988**, 137.
JACS, **1988**, 2653.Cyclopropanation
Reaction with AlkynesHarvey, *JACS*, **1992**, 8424.Hoye, *JACS*, **1988**, 2676.

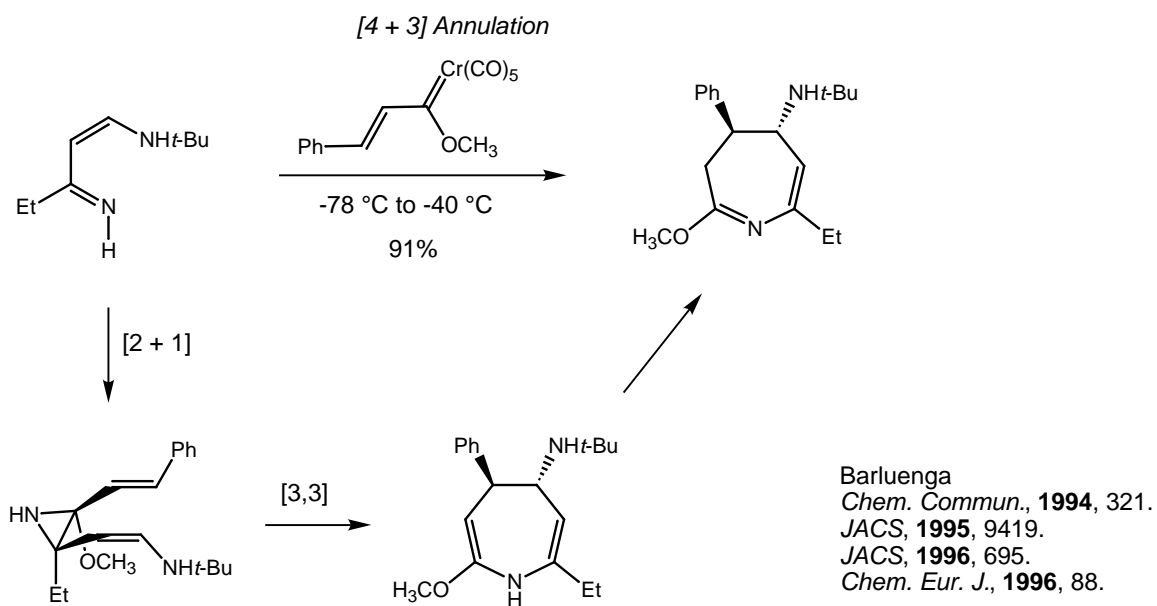
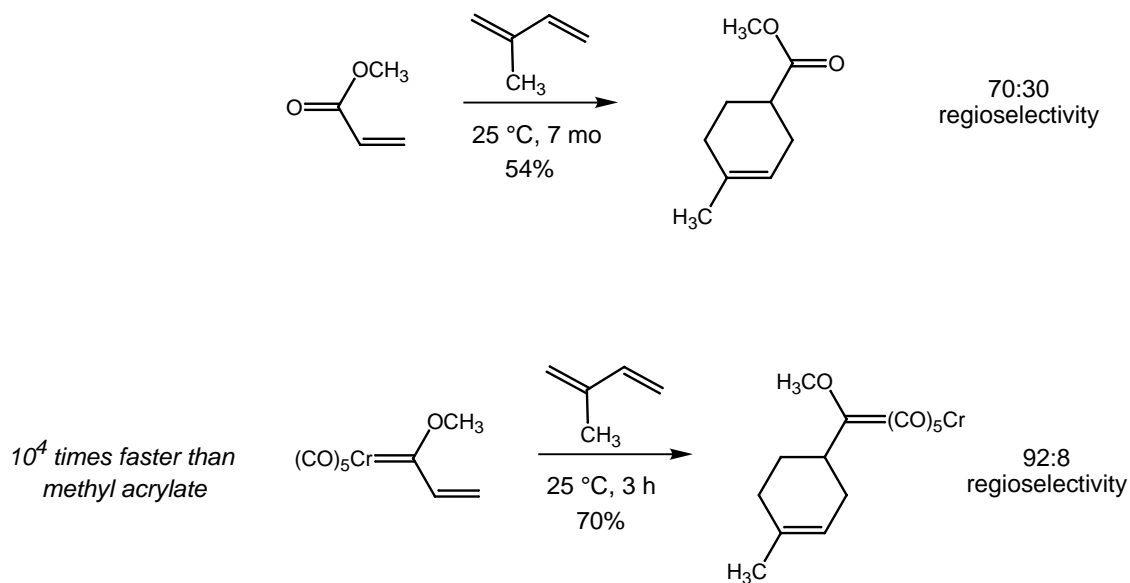
Selective Cyclopropanation



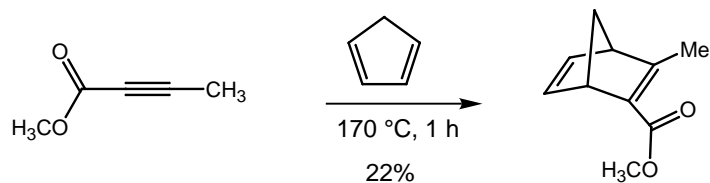
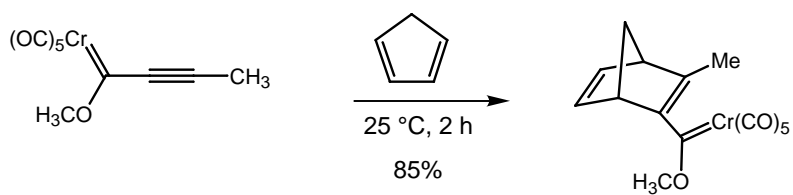
Barluenga
Chem. Commun., **1995**, 665.
JACS, **1997**, 7591.

Cyclopropanation
Reaction with Alkynes

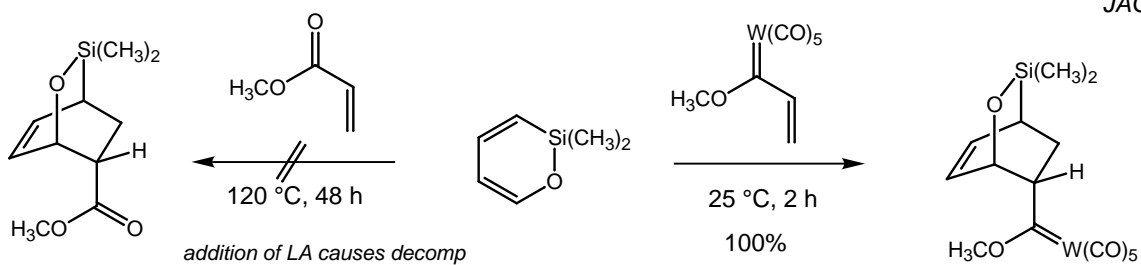
Harvey, *JOC*, **1992**, 5559.

*Diels-Alder Cycloaddition*Wulff, *JACS*, **1990**, 4550.

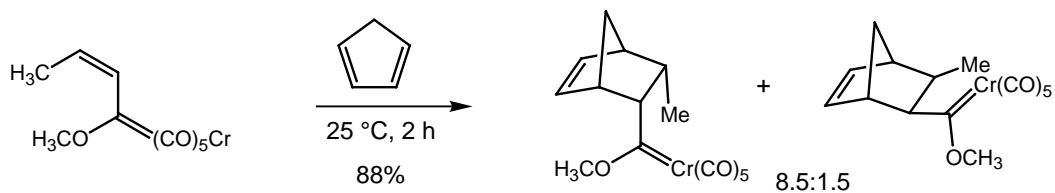
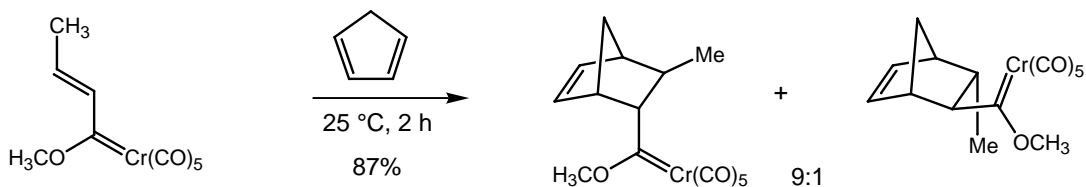
Diels-Alder Cycloadditions



Wulff
 JACS **1983**, 6726.
 JACS **1990**, 3642.

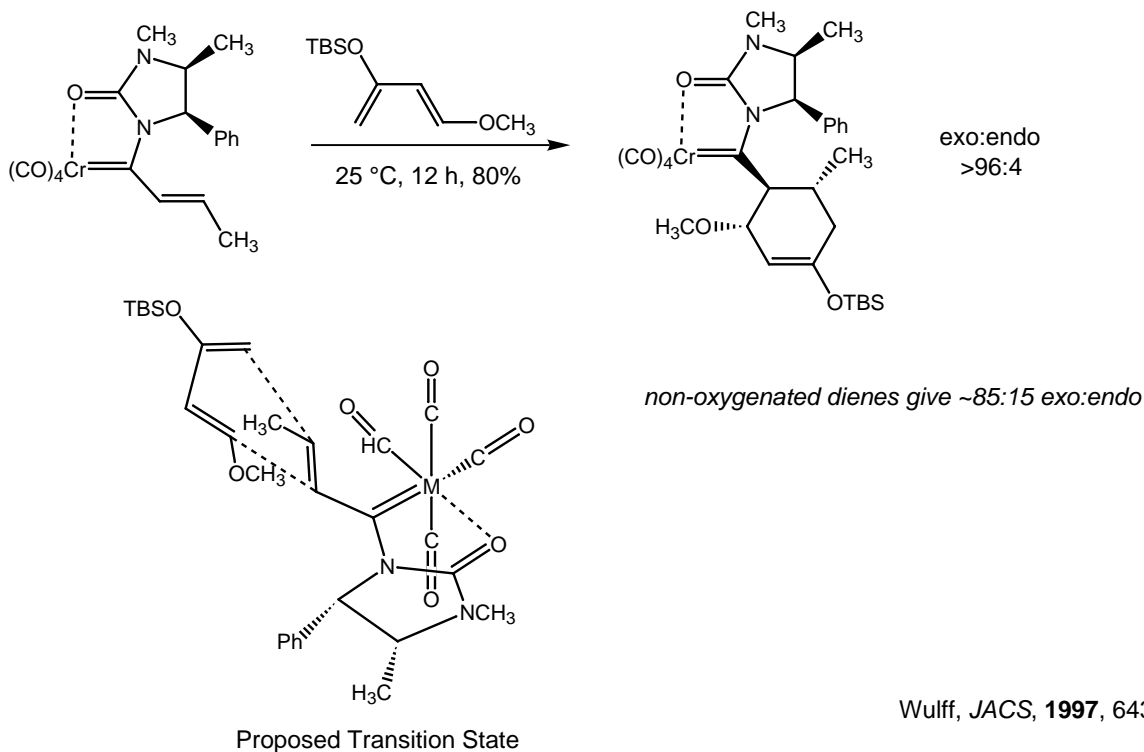


Diels-Alder Cycloadditions

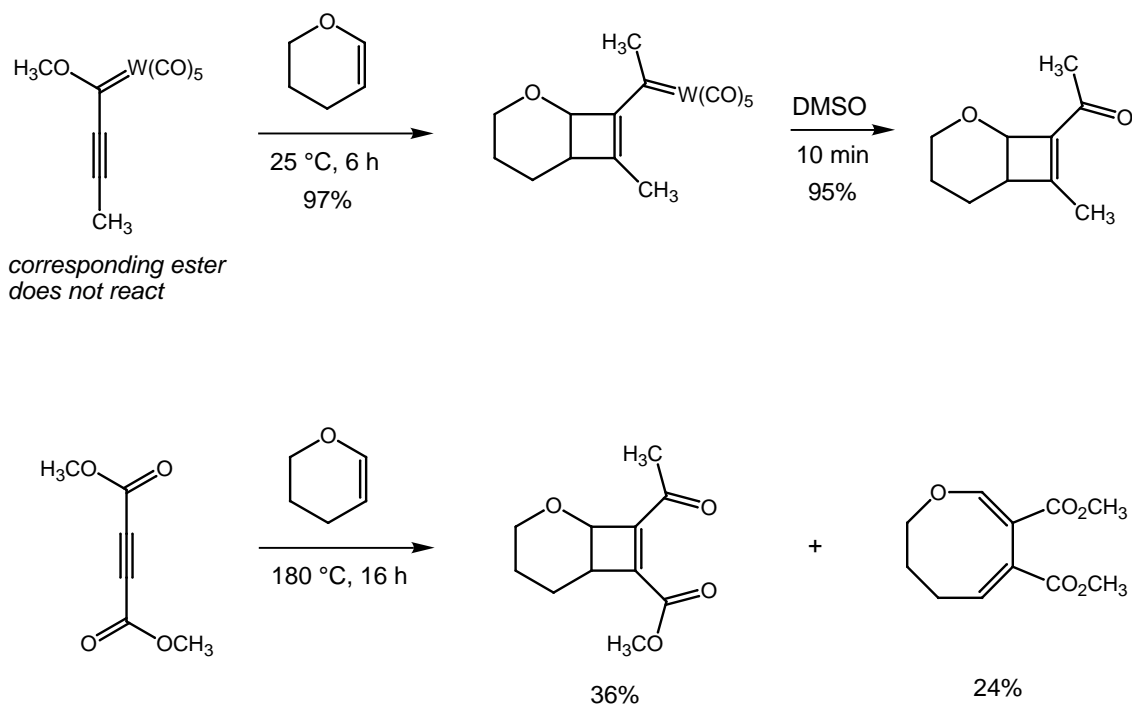


Wulff, JACS, **1990**, 3642.

Asymmetric Exo-Selective Diels-Alder Reaction

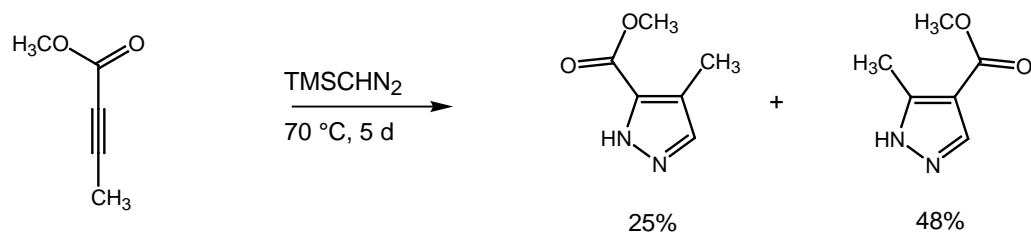
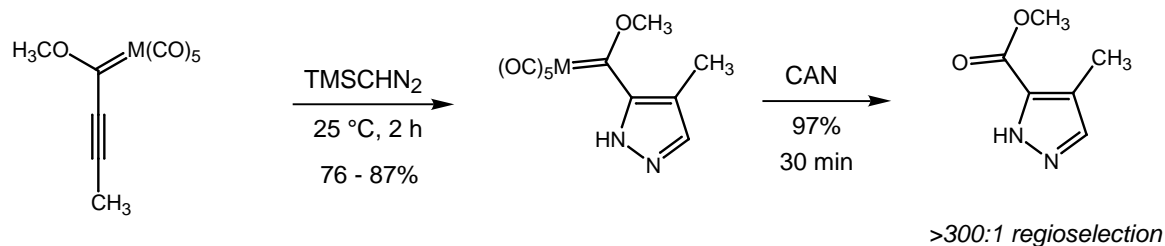


[2 + 2] Cycloaddition



Wulff, JACS, 1988, 8727.

[3 + 2] Cycloaddition

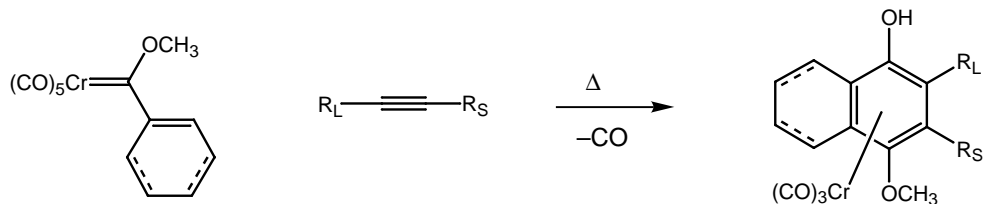


Wulff, *JACS*, **1986**, 6726.
Barluenga *TL*, **1998**, 4887.
Barluenga *JCS Perkin I*, **1997**, 2267.

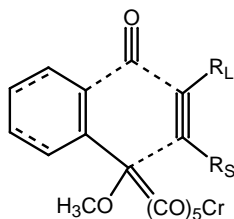
Dotz Reaction

Thermal Reaction of Unsaturated Carbene Complexes

"...one of the most utilized reactions in natural product synthesis involving an organometallic process."

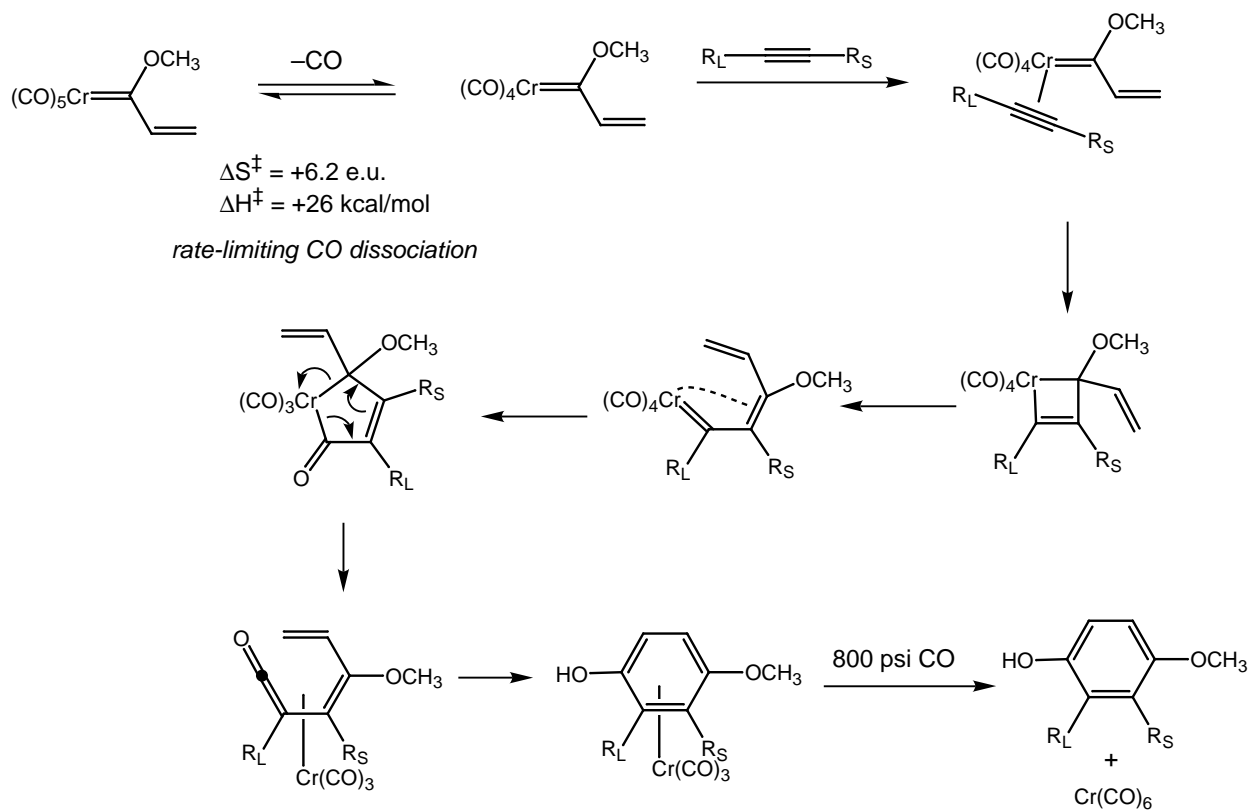


Observed Connectivity:

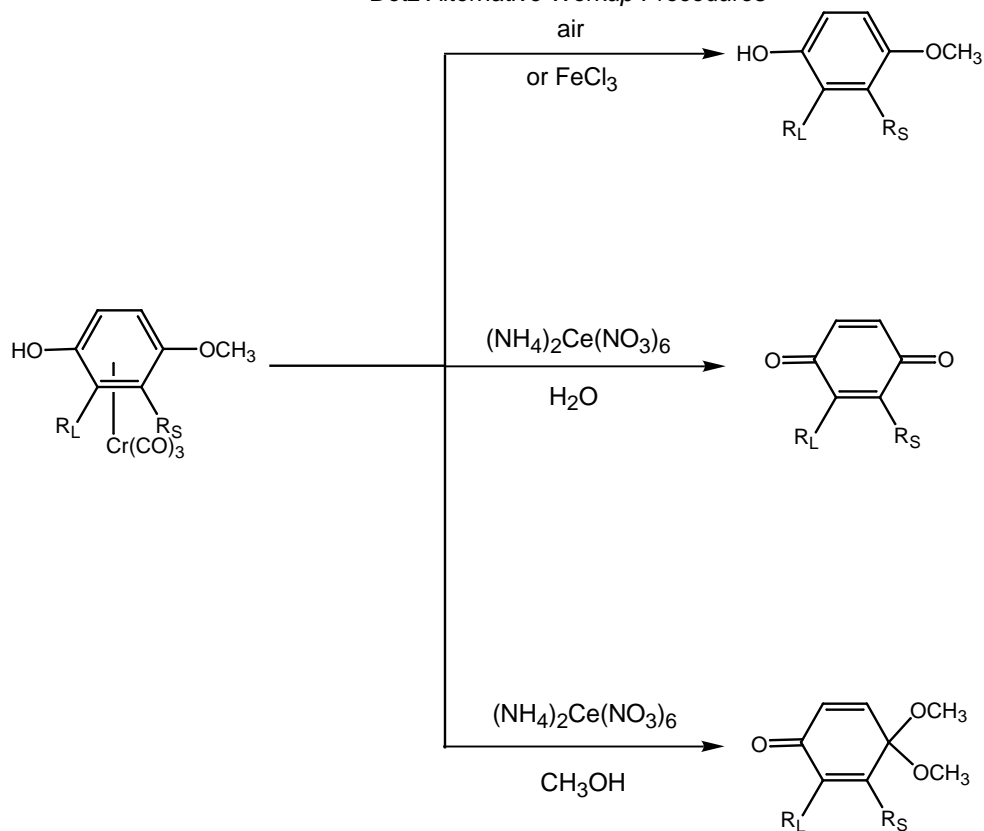


Dotz
ACIEE, **1975**, 644.
New J. Chem., **1990**, 433.
ACIEE, **1984**, 587.

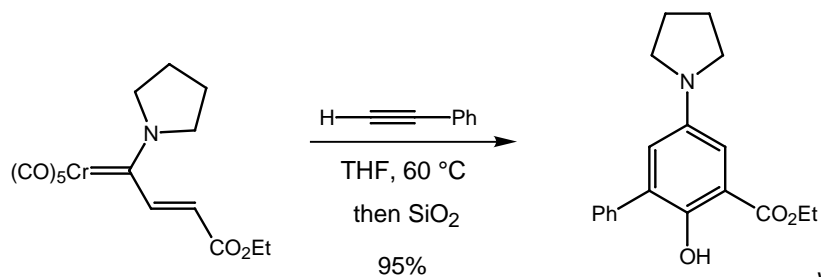
Dotz Proposed Reaction Mechanism

Barluenga, *JACS*, **1994**, 11191.

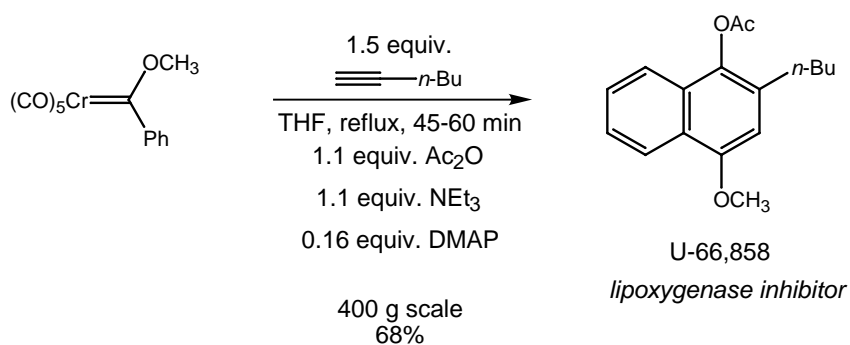
Dotz Alternative Workup Procedures

See Wulff, *JOC*, **1984**, 2293.

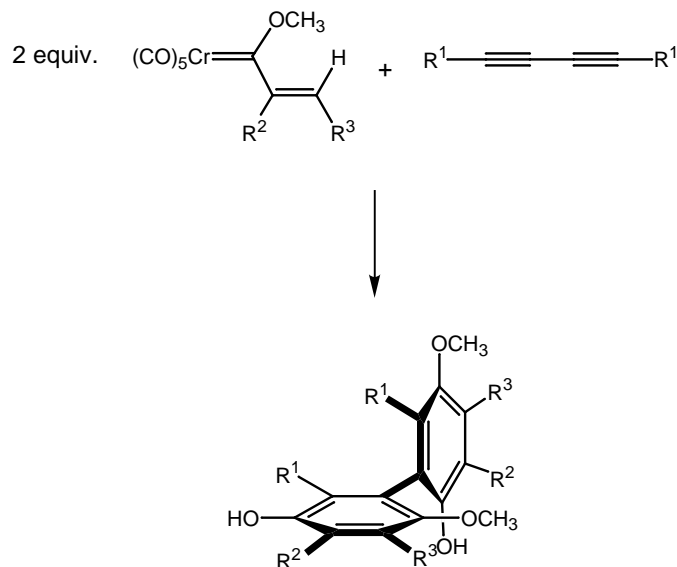
Dotz: Nitrogen Analog

Wulff, *JOC*, **1995**, 4566.Barluenga, *JOC*, **1998**, 7588.

Dotz: Large Scale Applicability

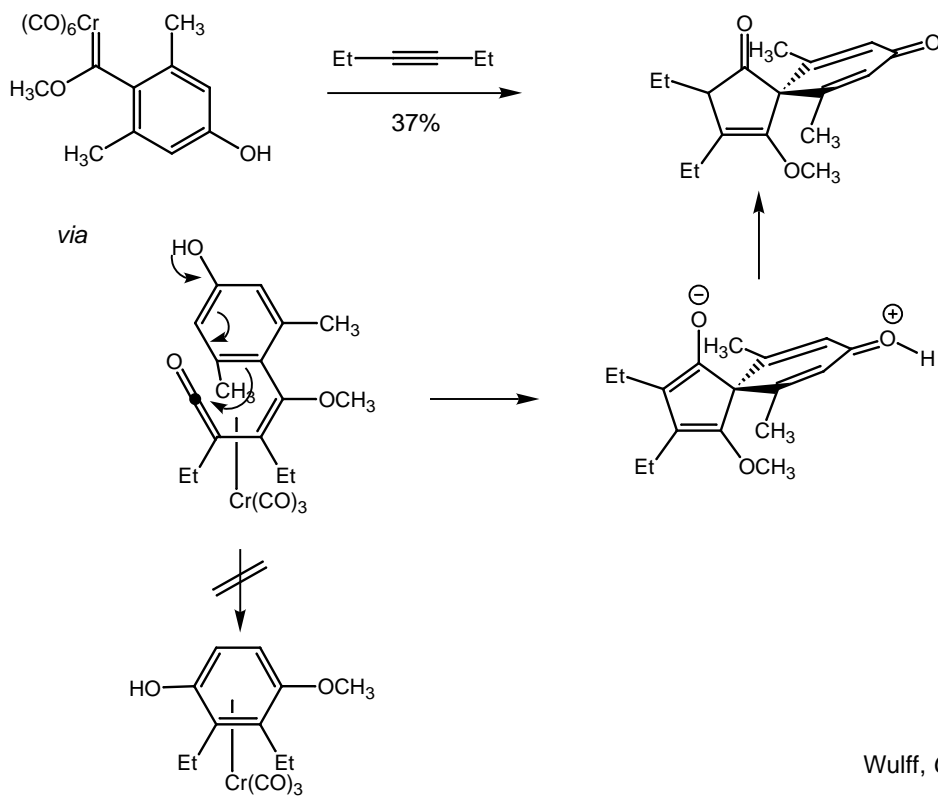
Timko
TL, **1988**, 2513.
Org. Synth., **1992**, 72.

Biaryl Synthesis

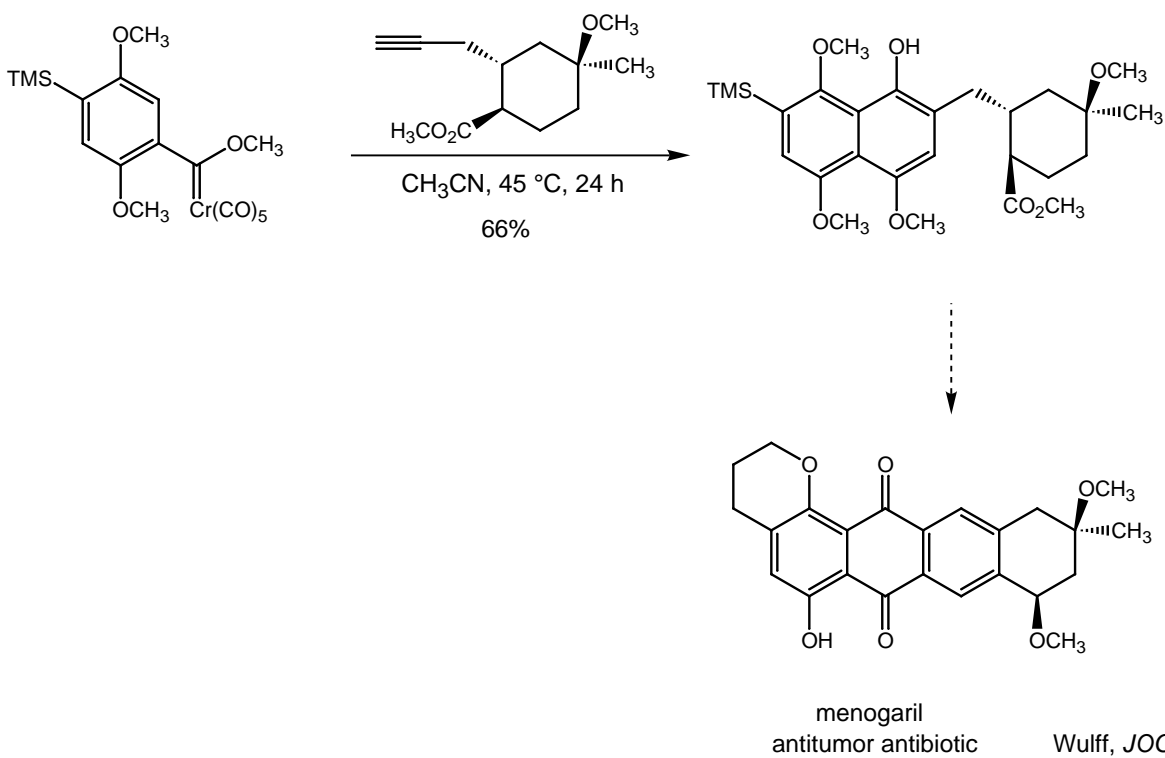


The concept works, in moderate to low yield, but the reactions must be run stepwise. Occasionally CO insertion is suppressed and five-membered rings are formed.

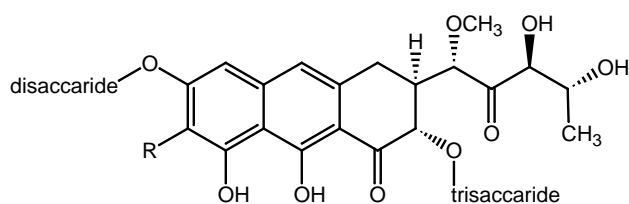
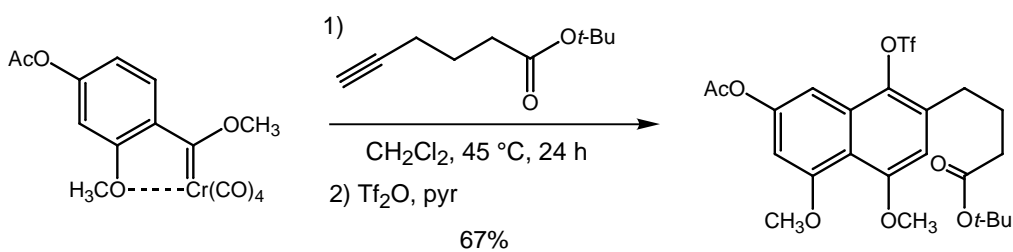
Intercepted Intermediates



Synthetic Uses



Synthetic Uses

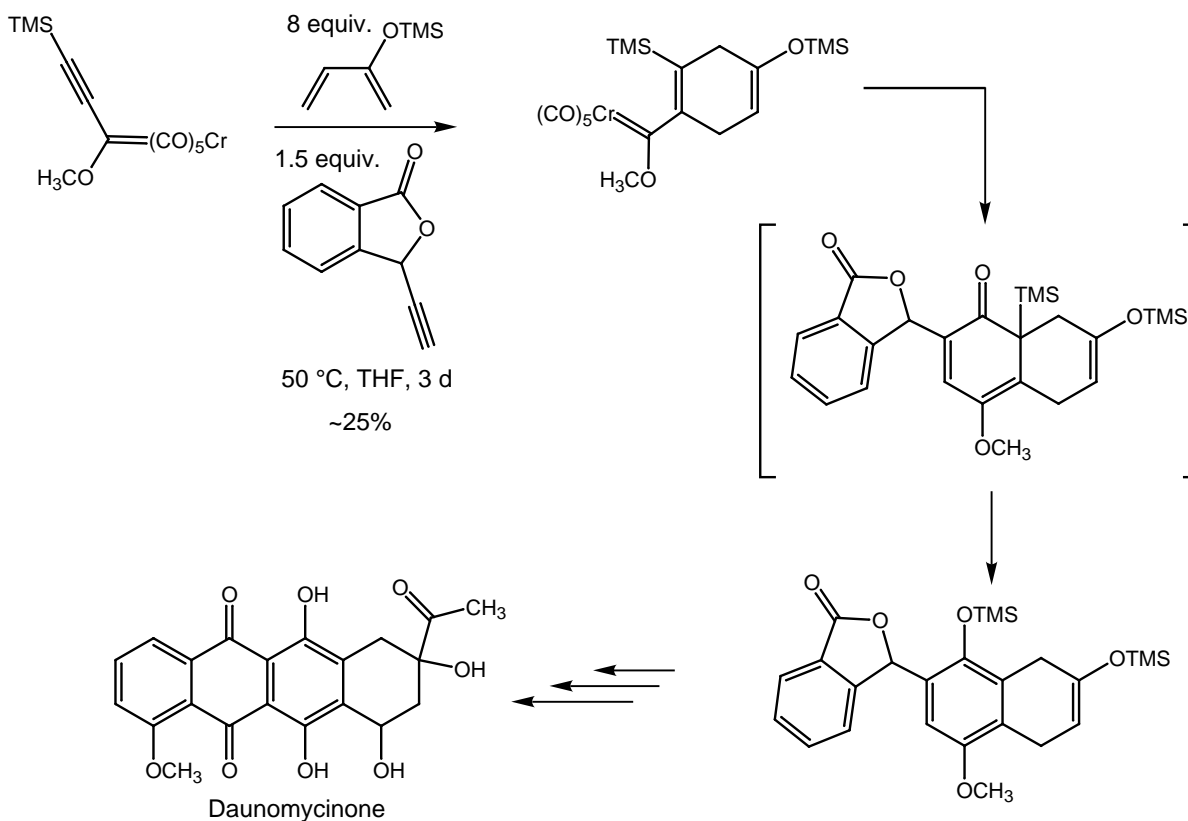


R = CH_3 Chromomycin
R = H, Olivomycin

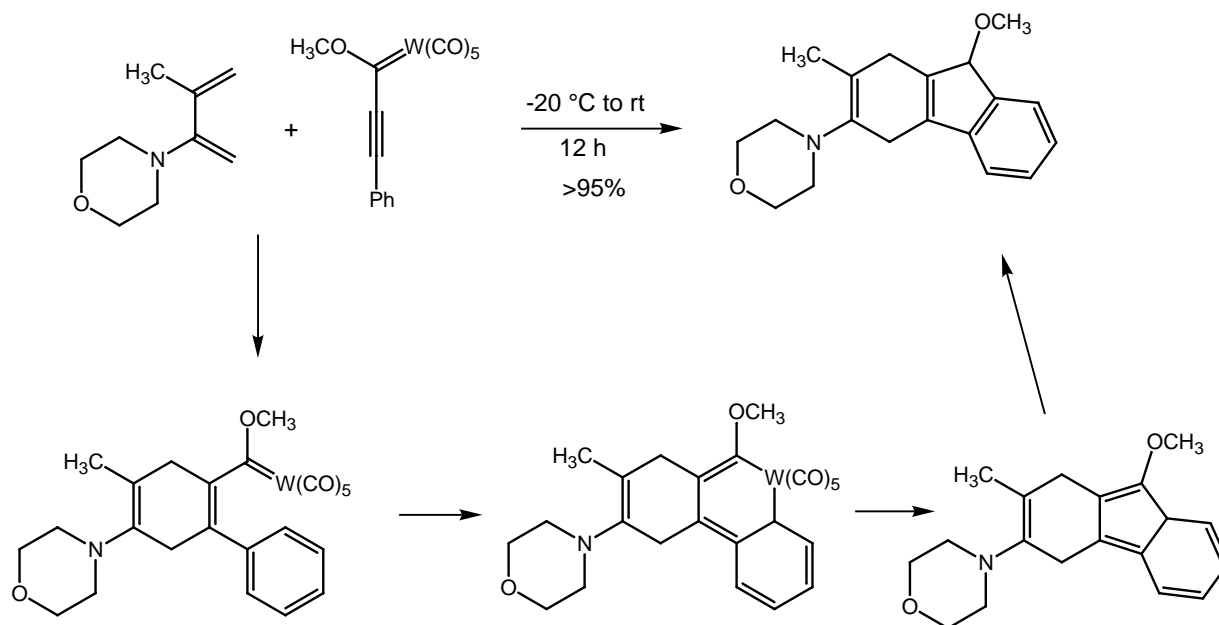
antitumor antibiotics

Wulff, *Synthesis*, **1999**, 80.

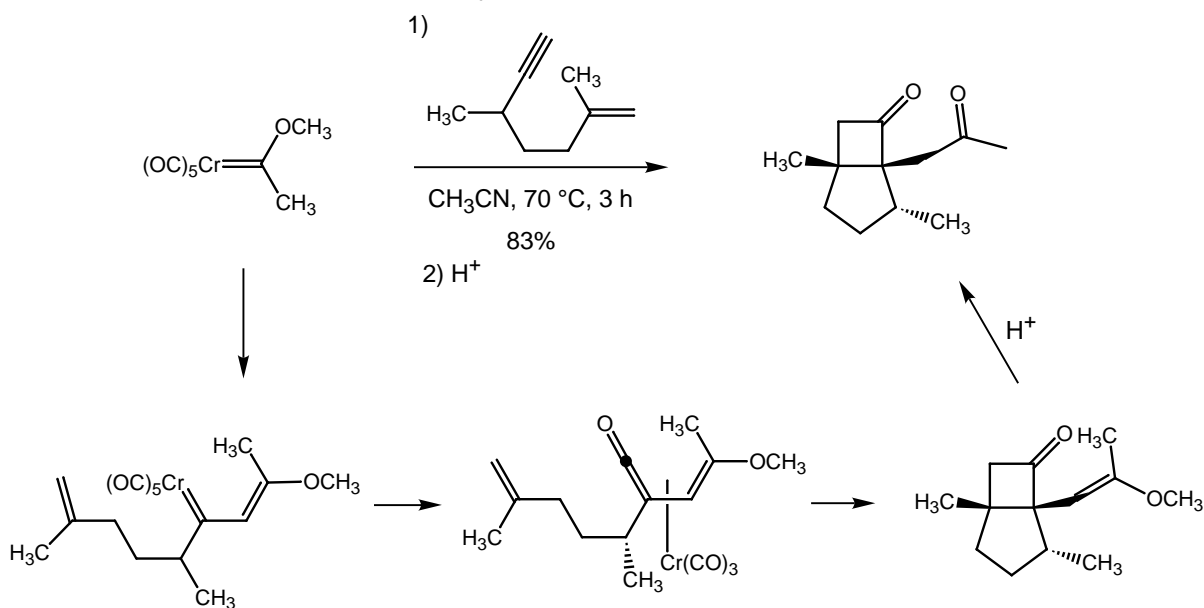
Application to Synthesis

Wulff, *JACS*, **1984**, 434 & 7565.

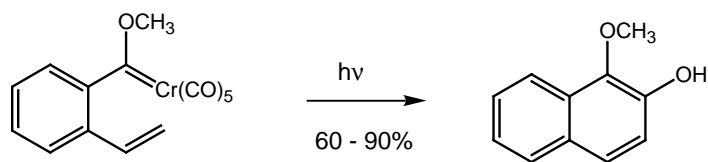
Dihydrofluorene Synthesis

Barluenga, *Chem Commun.*, **1995**, 1973.

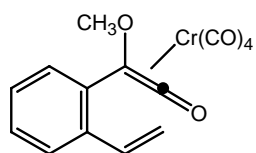
Alkyne-Alkene Reactions

Wulff, *JOC*, **1993**, 5571.

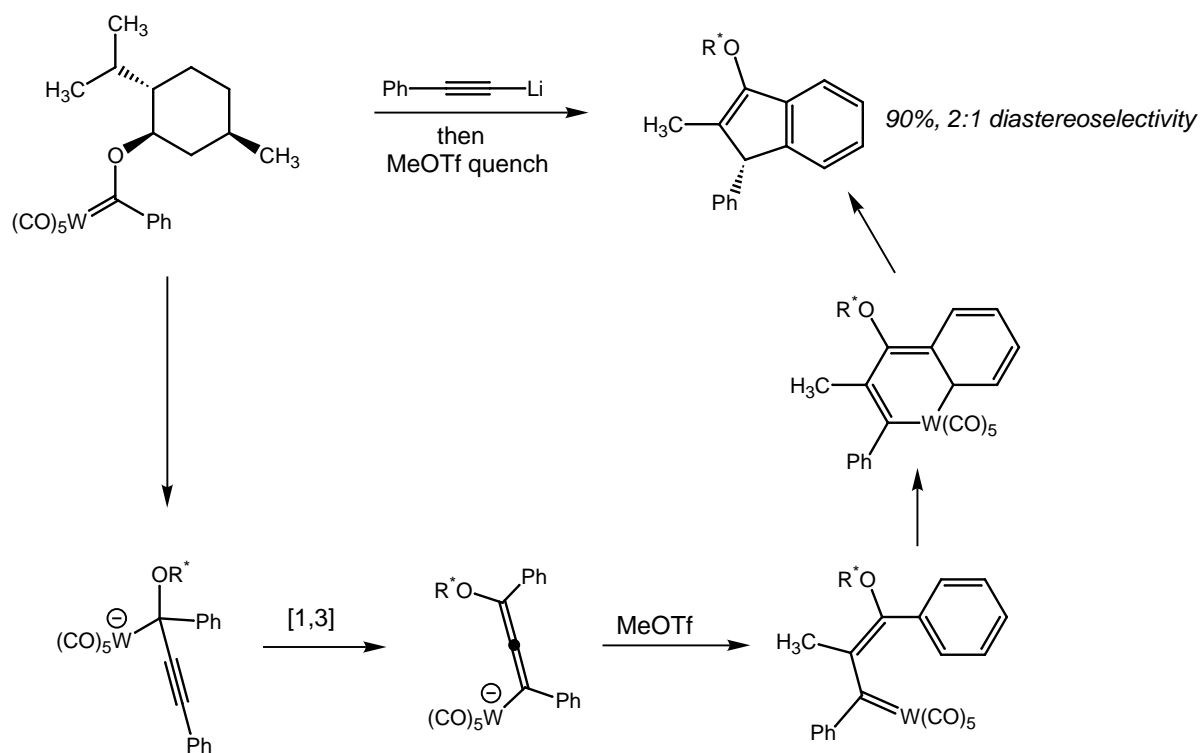
Ketene Cyclizations



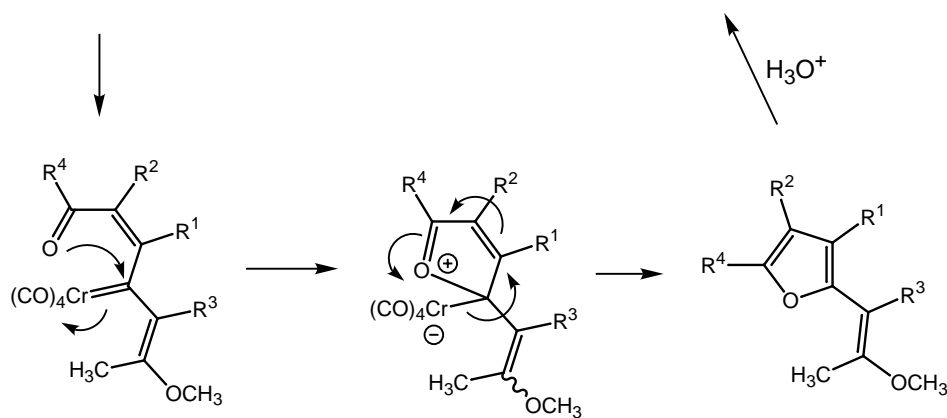
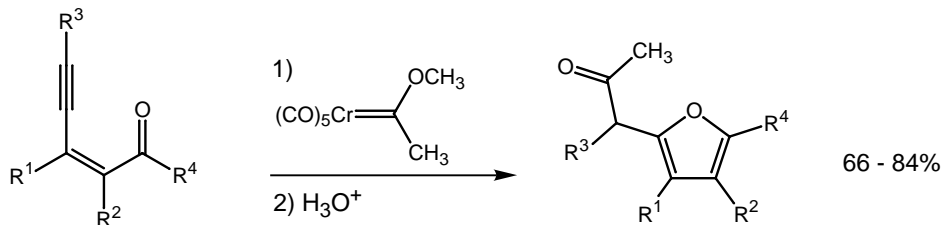
Via:

Merlic, *JACS*, **1992**, 5602.

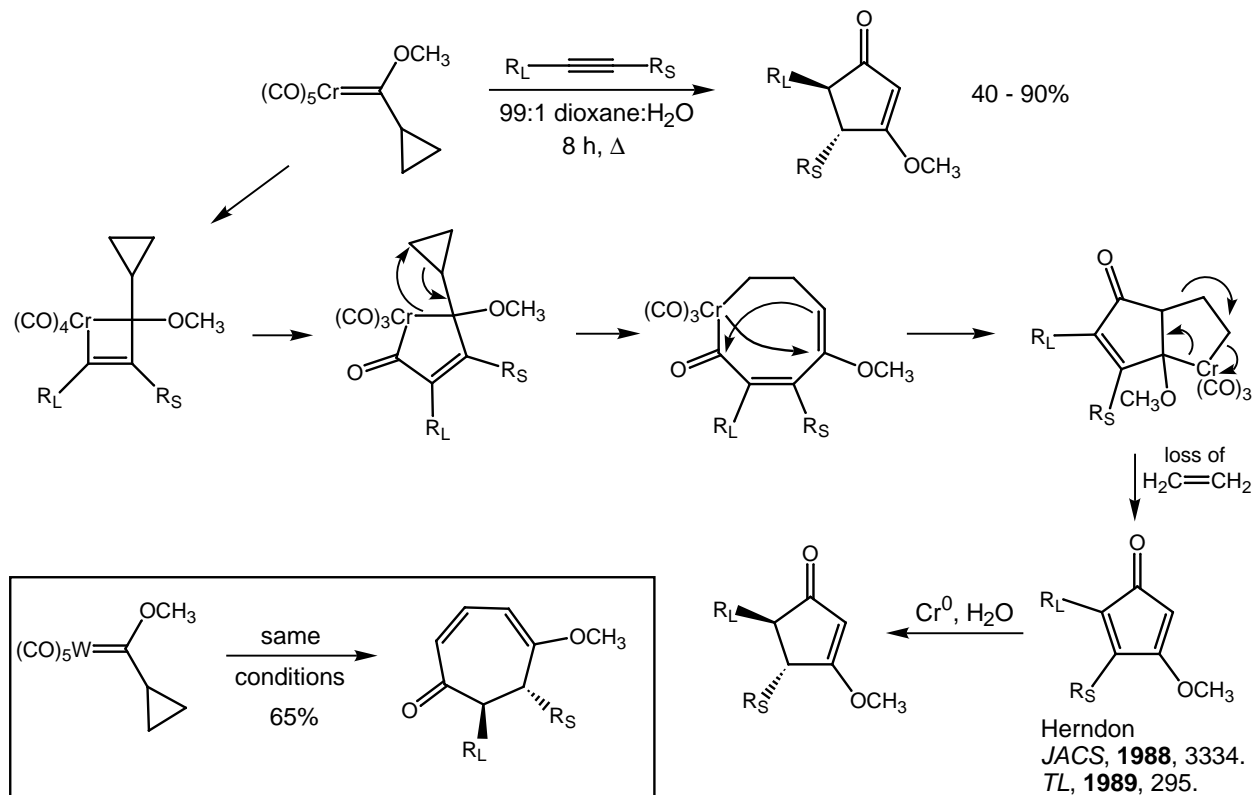
"Asymmetric" Benzopentaannulation

Barluenga, *JACS*, **1998**, 12129.

Furan Synthesis

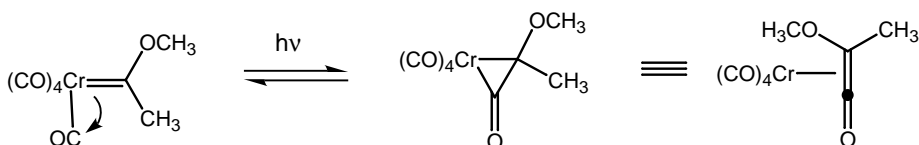
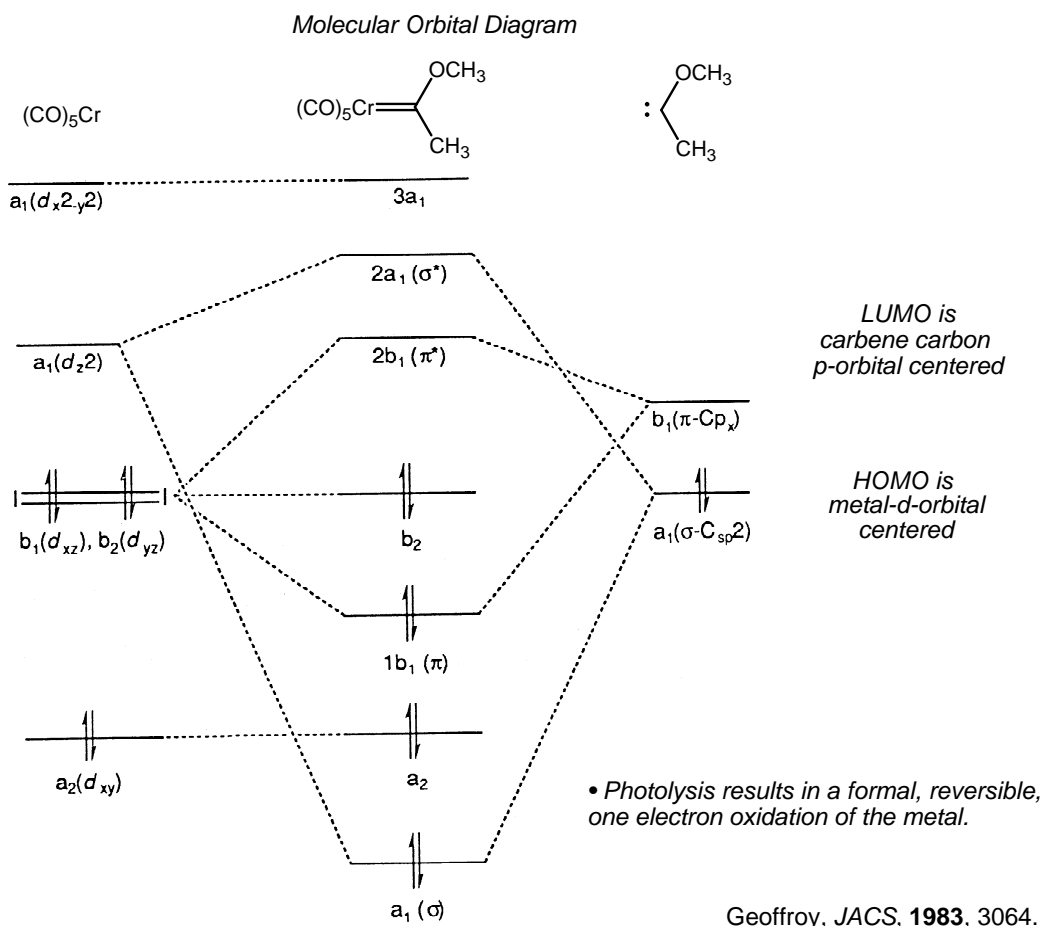
Herndon, *JOC*, **1998**, 4564.

"A Versatile [4 + 2 + 1 - 2] Cycloaddition"

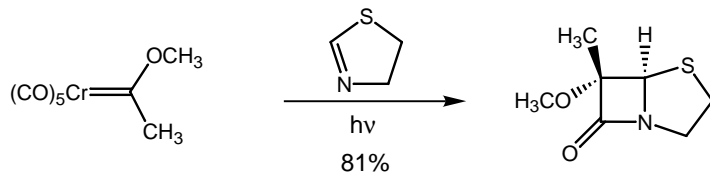
Herndon
JACS, **1988**, 3334.
TL, **1989**, 295.
JOC, **1990**, 786.
JACS, **1991**, 7808.
JACS, **1992**, 8394.

Photochemistry

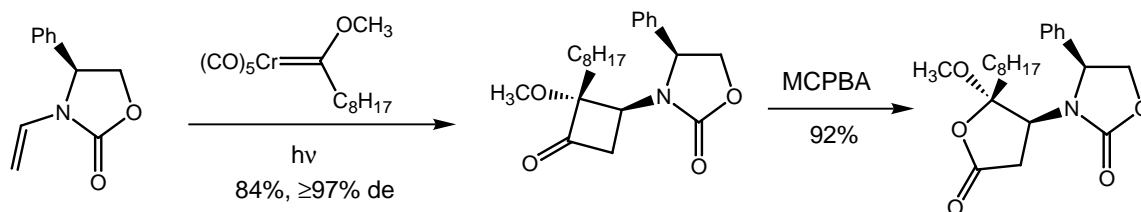
- Electronic absorption consists of three low-lying bands:
 - ~500 nm: spin-forbidden $M \rightarrow$ carbene π^* charge transfer transition
 - 360-450 nm: spin allowed $M \rightarrow$ carbene π^* charge transfer transition (visible)
 - 300-350 nm: ligand field transition
- In addition, all carbene complexes absorb strongly below 300 nm.
- Exposure to light leads to a *reversible* CO insertion:

Geoffroy, JACS, **1983**, 3064.

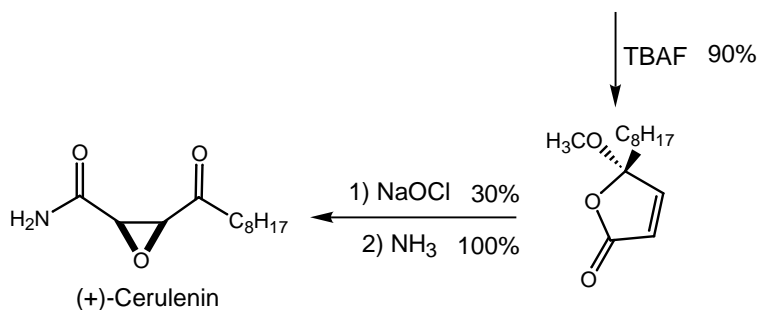
Ketene [2 + 2]



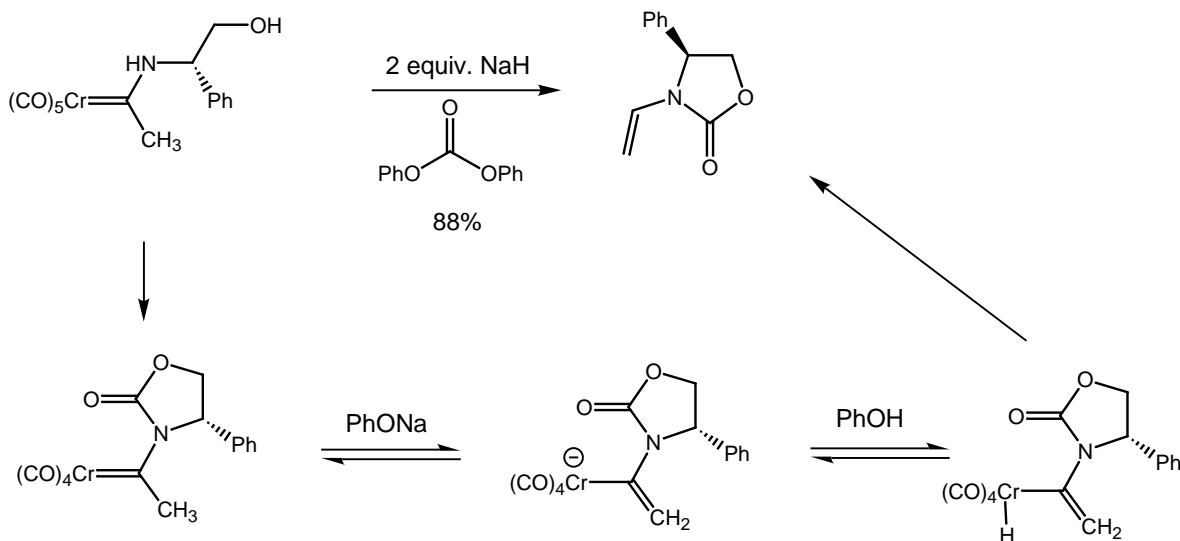
Hegedus
Tetrahedron, **1985**, 5833.
JOC, **1997**, 3586.



Hegedus
JOC, **1995**, 3787.
JOC, **1996**, 6121.
Organometallics, **1997**, 2313.
JOC, **1998**, 4691 & 8012.

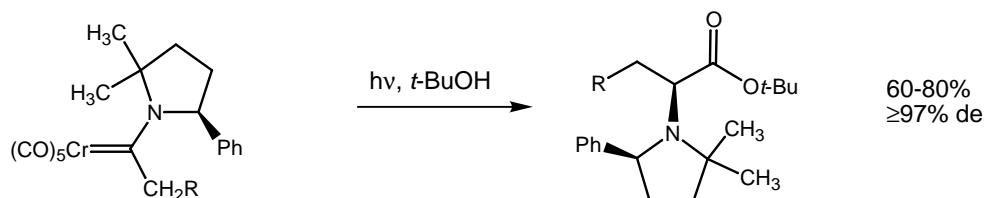


Ene Carbamate Synthesis

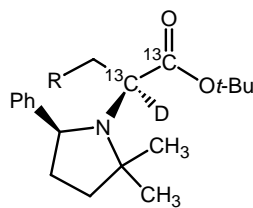


Hegedus, *JACS*, **1990**, 6255.

Amino Acid Synthesis

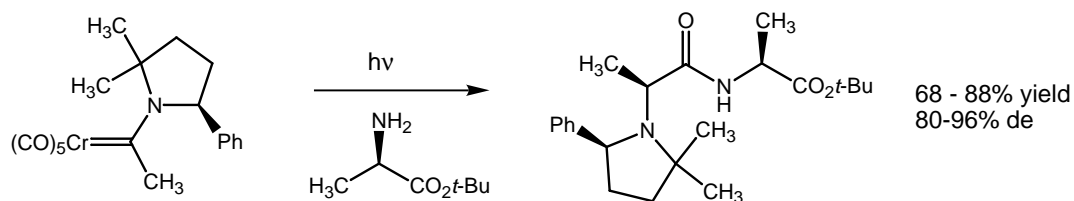


- Multiply-labeled amino acids are readily prepared from $(^{13}\text{C})_6\text{CO}$ and CH_3OD :



Hegedus
JACS, **1990**, 2264.
JACS, **1992**, 5602.
JACS, **1993**, 87.
Acc. Chem. Res., **1995**, 299.
JOC **1995**, 5831.
JACS, **1995**, 3697.
JOC **1997**, 7704.

Peptide Synthesis

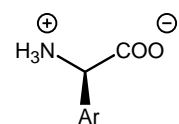
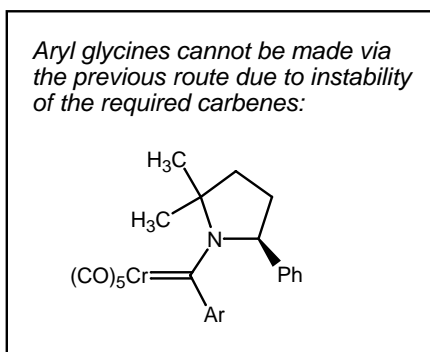
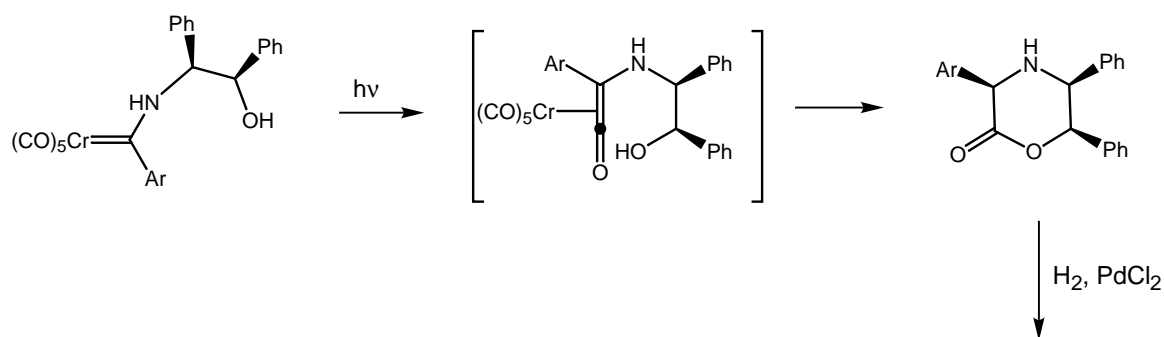


Solid Support

Merrifield Resin: *Acc. Chem. Res.*, **1995**, 299.
 PEG: *JOC* **1995**, 5831; *JOC* **1997**, 7704.

- Reactions have been performed and do work, but are not as practical because the failure to achieve 100% yields and high diastereoselectivity limit this method.
- hard to work with because the polymer "sticks to everything, making quantitative transfer difficult".
Acc. Chem. Res., **1995**, 299.

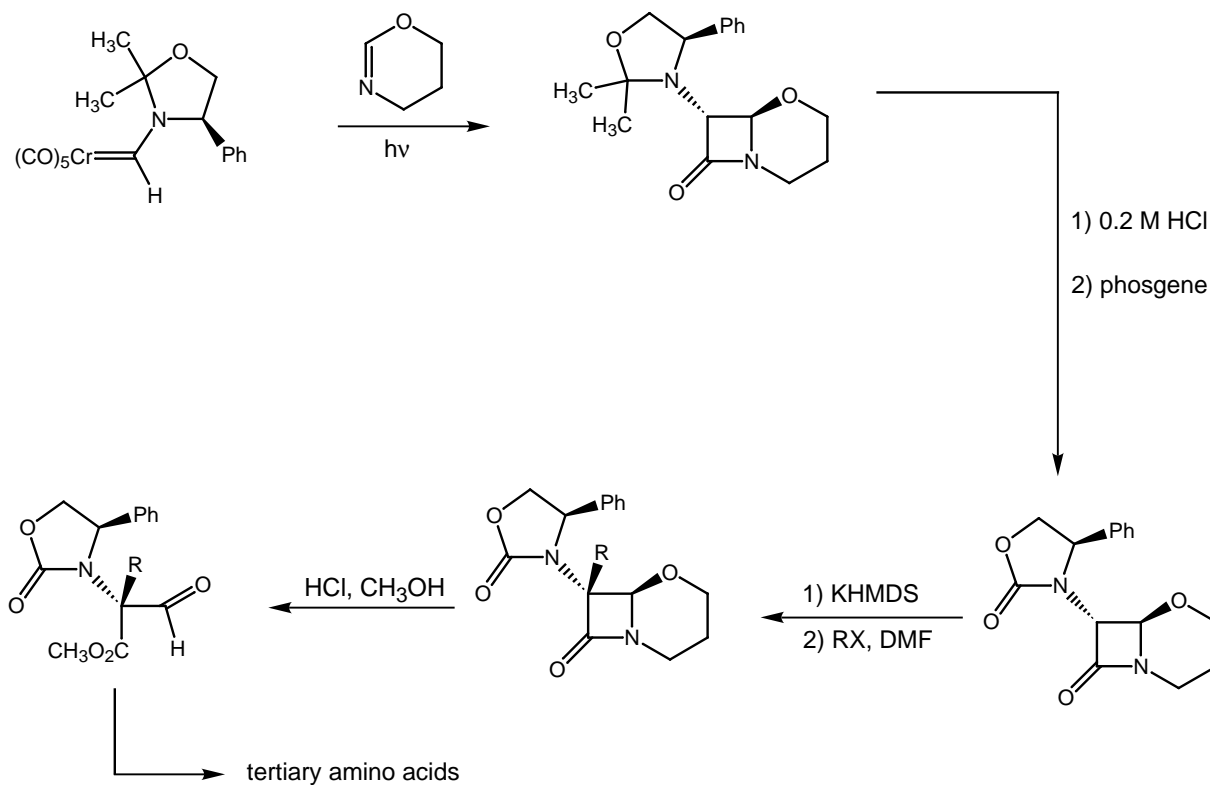
Aryl Glycines



40 - 95% yield
56 - 98% ee

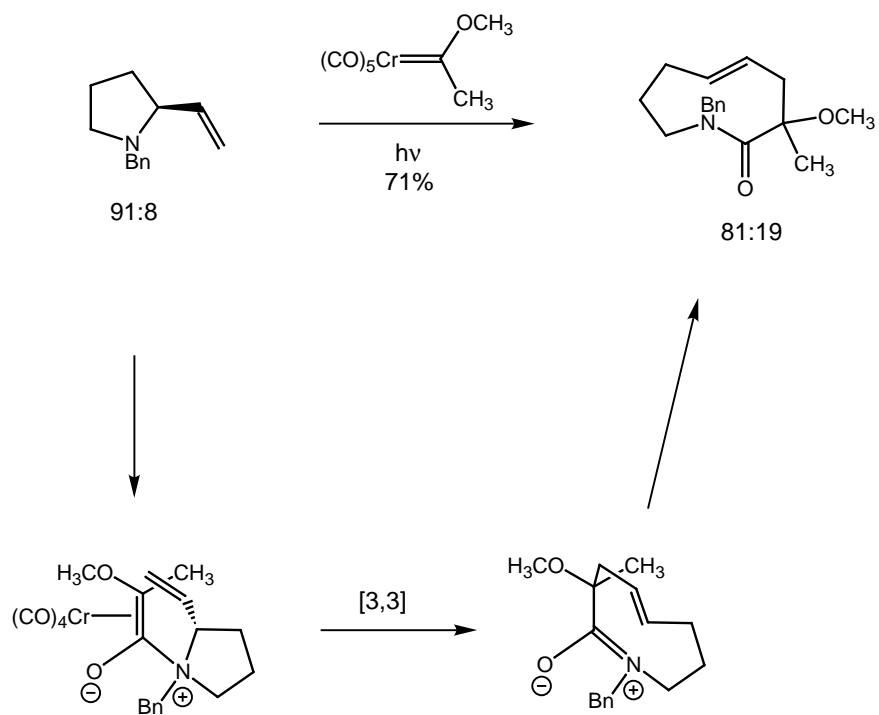
Hegedus, *JOC*, **1992**, 6914.

Tertiary Amino Acids

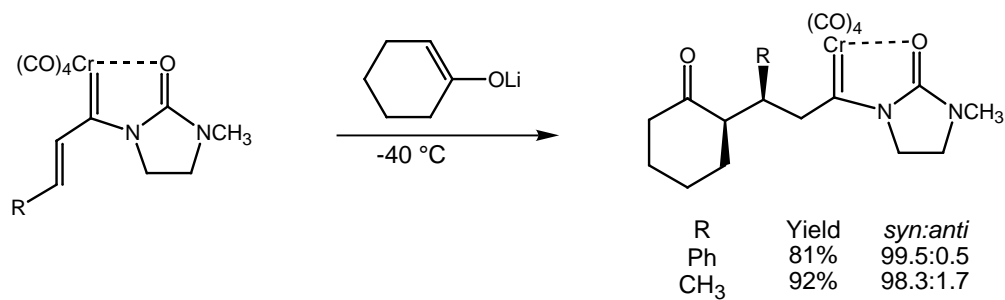
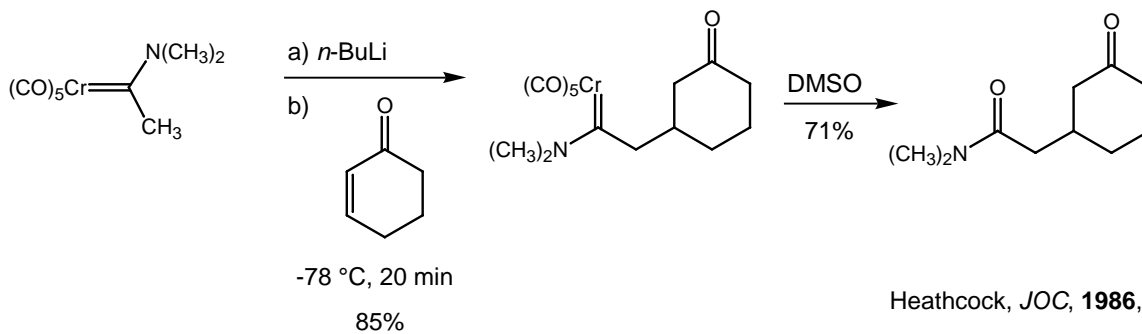


Hegedus, *JOC*, **1993**, 5918.

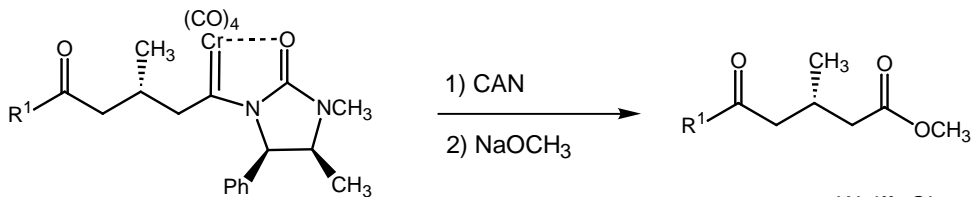
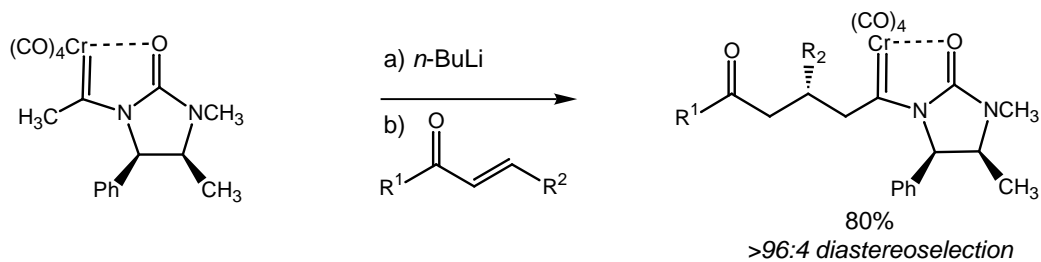
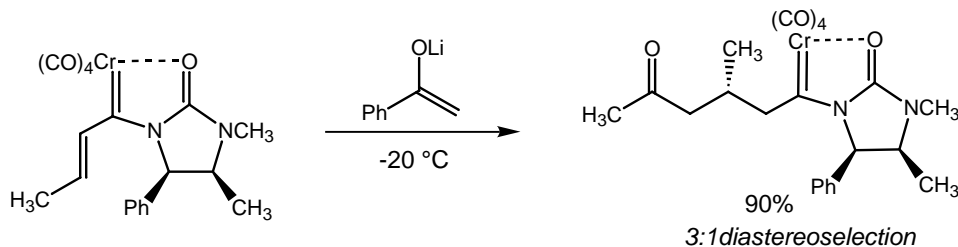
Zwitterionic Aza Cope Rearrangement



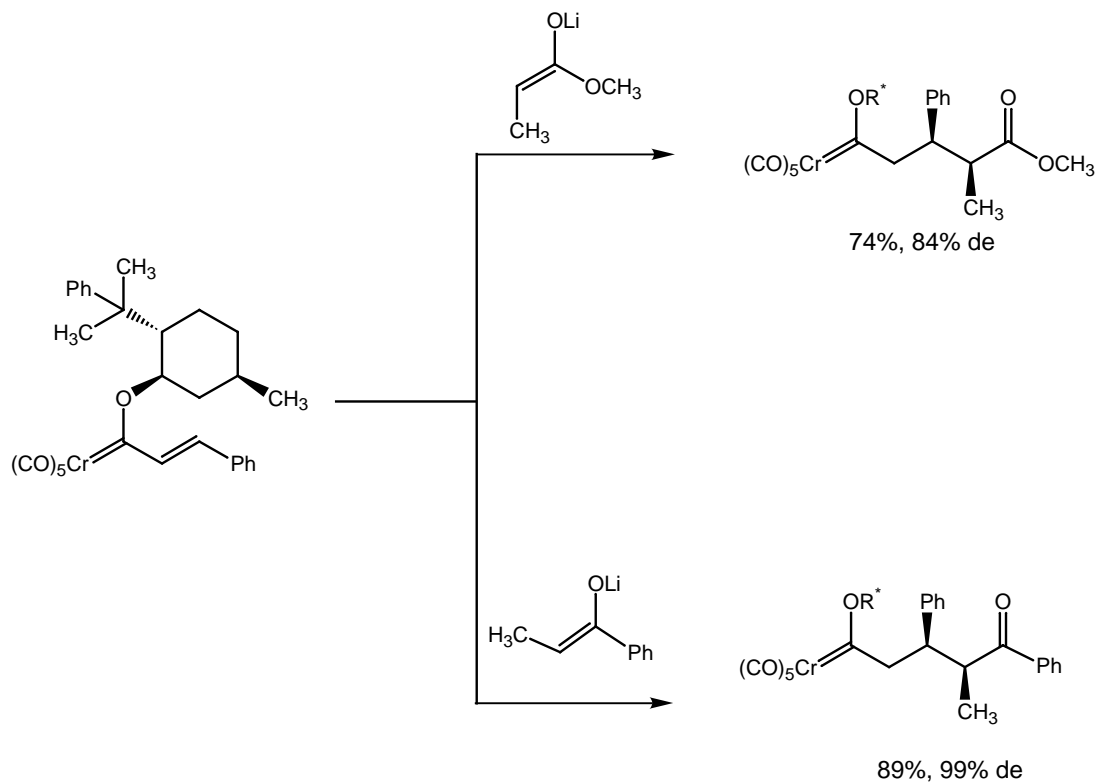
Michael Reaction

Wulff, *JACS*, **1993**, 4602.

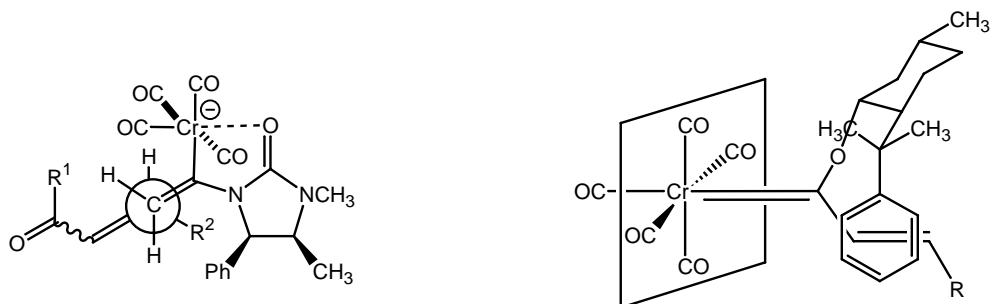
Asymmetric Michael Addition

Wulff, *Chem. Commun.*, **1996**, 2601.

Asymmetric Michael Reaction

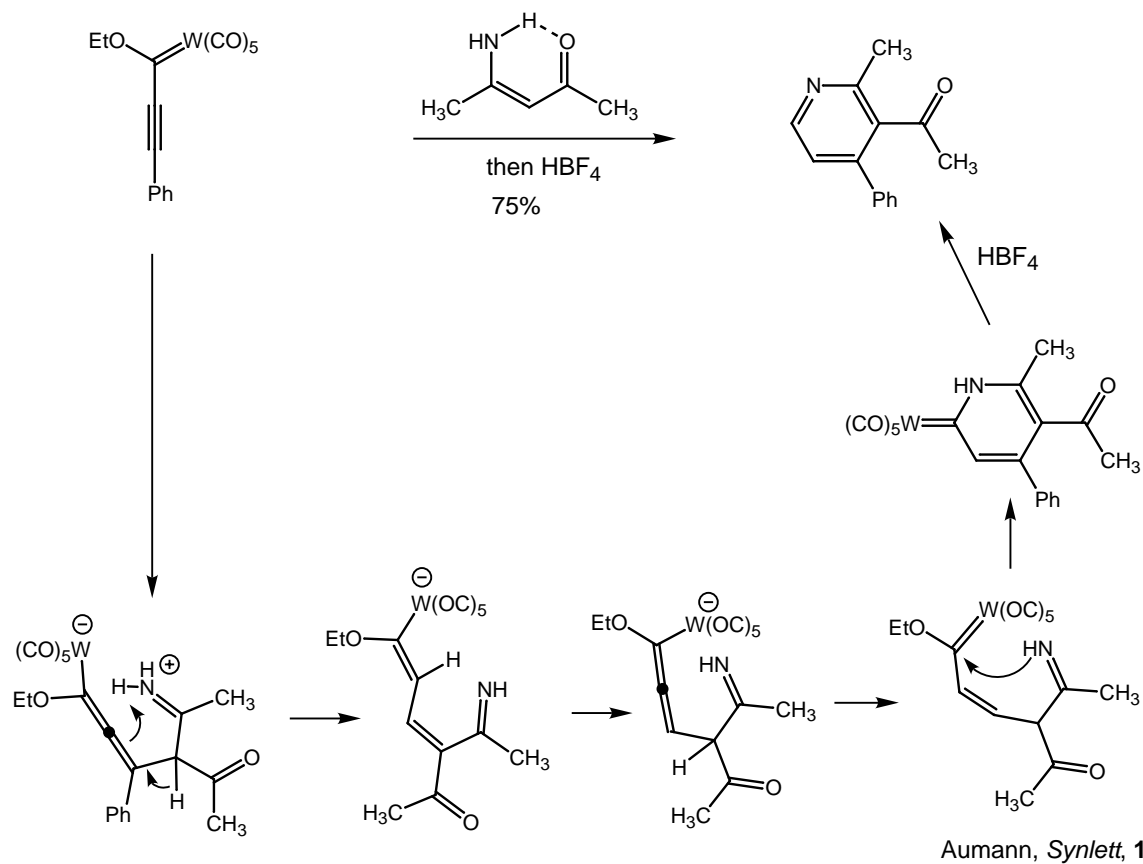
Barluenga, *Chem. Eur. J.*, **1995**, 236.

Michael Reactions: Selectivity

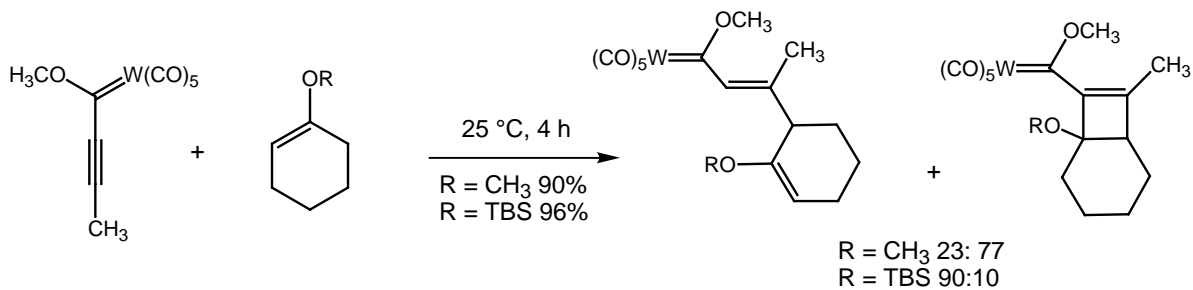


Open Transition States are Postulated

Pyridine Synthesis

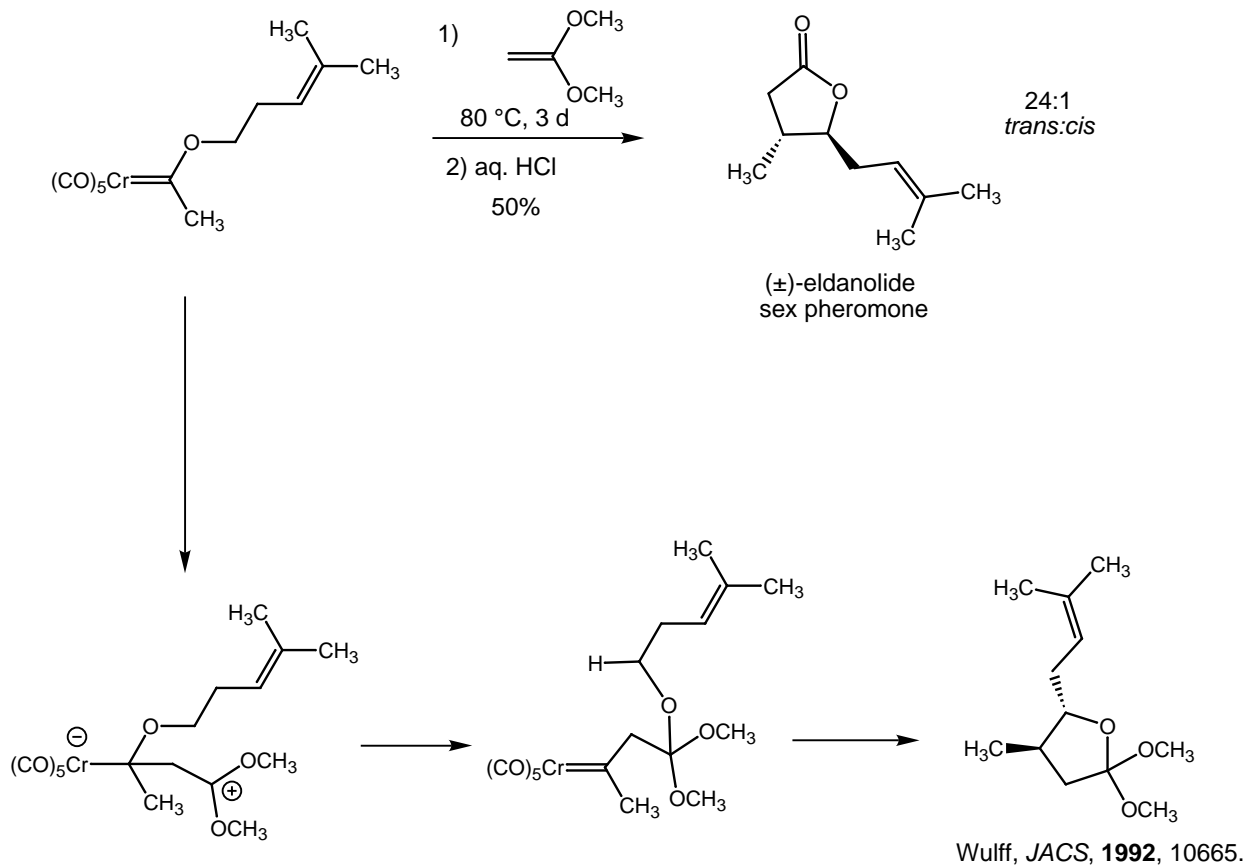


Ene Reaction

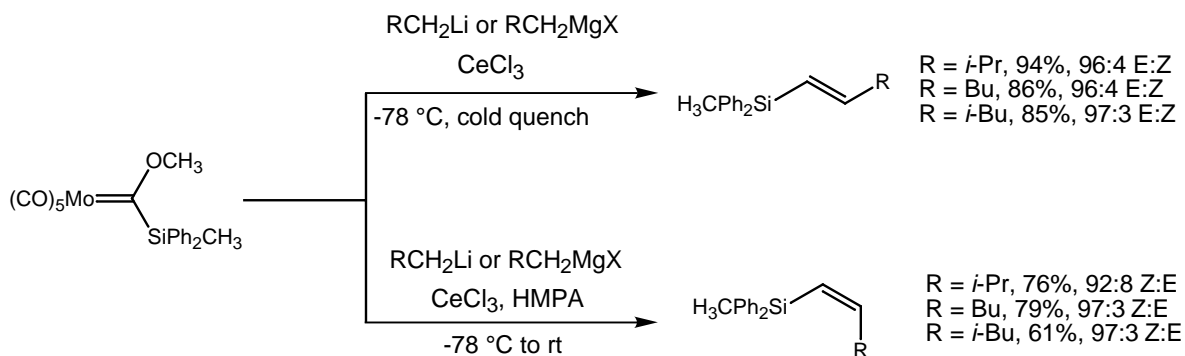
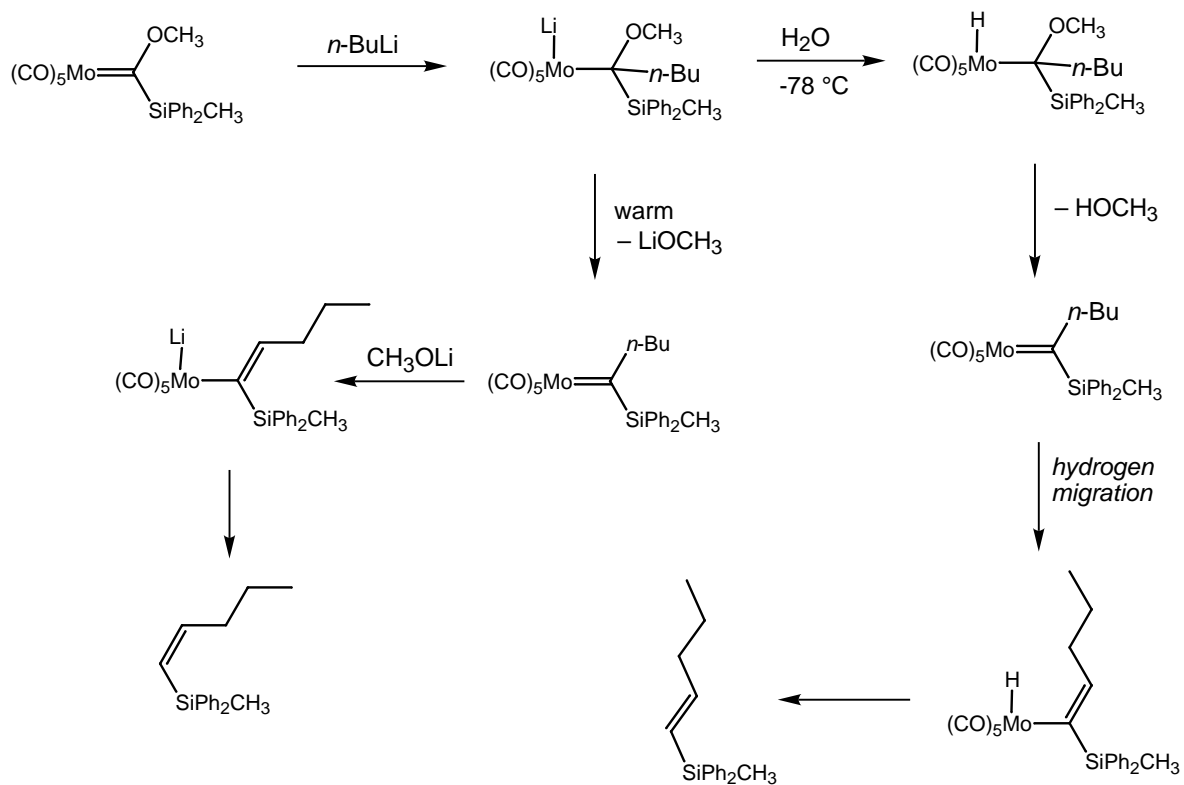


Wulff, JACS, 1990, 6419.

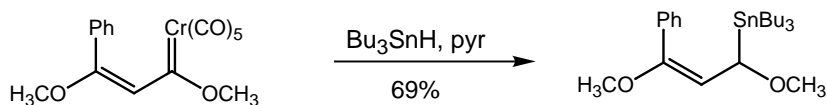
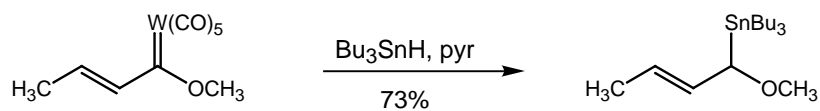
Reaction of Ketene Acetals



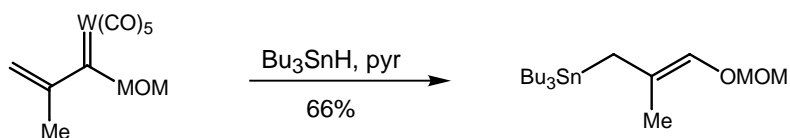
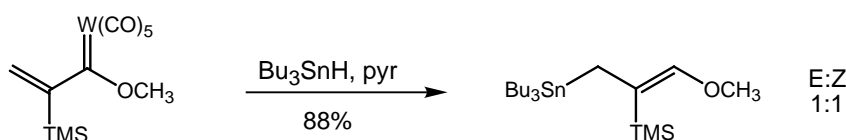
Vinylsilane Synthesis

Iwasawa, *Chem. Lett.*, **1994**, 231.Vinylsilane Synthesis
Proposed Mechanism

Allyl Stannane Synthesis

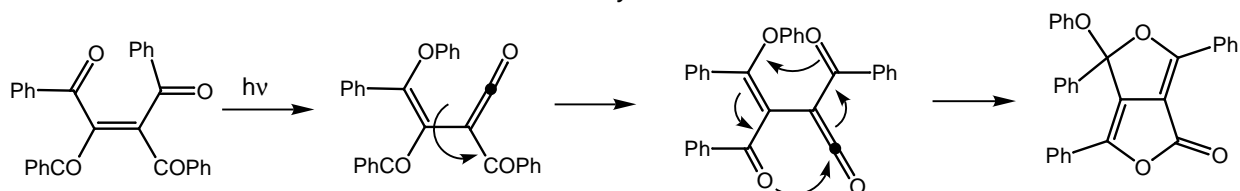


1,1 addition is usually observed, however 1,3 addition is possible:

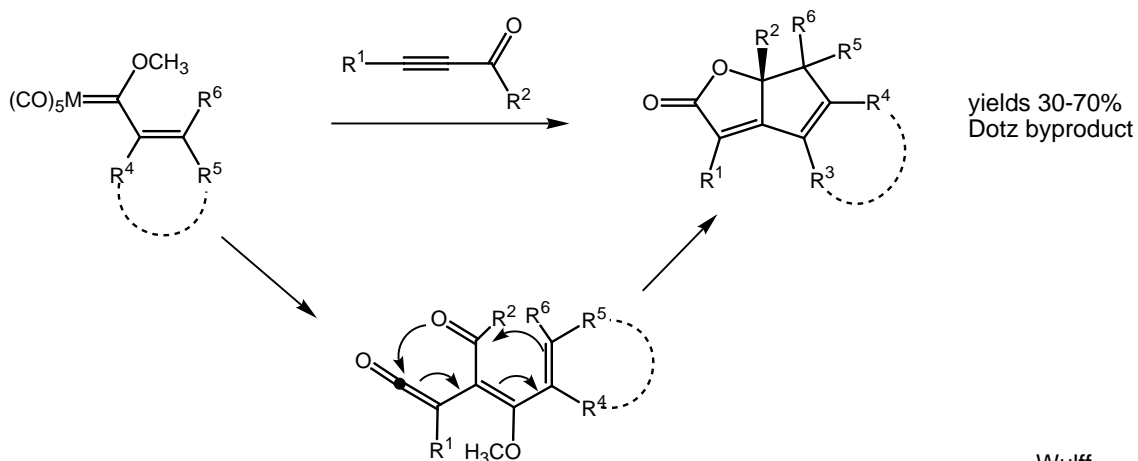


Merlic, *TL*, **1995**, 1007.

Halban-White Cyclizations



Andres, A. Dissertation, Strasbourg, 1911.
van Halban, *Helv. Chim. Acta*, **1948**, 1899.



Wulff
JACS, **1990**, 1645.
JACS, **1991**, 5459.

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

Chemistry 206

Advanced Organic Chemistry

Lecture Number 36

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**

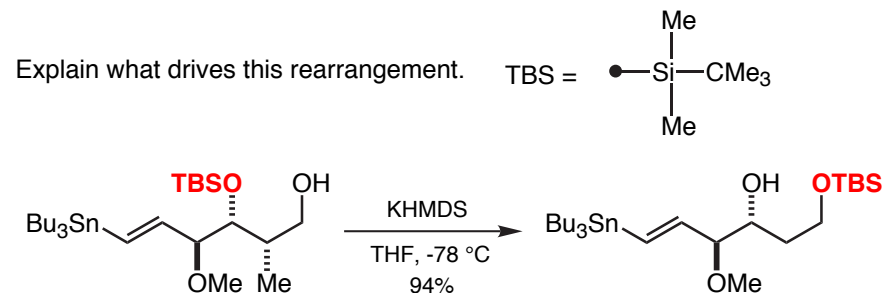
Bois, et al. "Silicon-Tethered Reactions" *Chem. Rev.* **1995**, *95*, 1253-1277. (**Handout**)

Monday,

D. A. Evans December 15, 2003

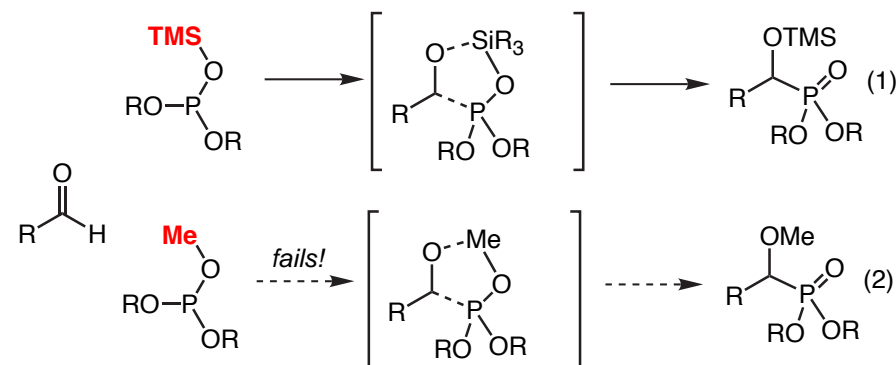
36-00-Cover Page 12/14/03 8:46 PM

Problems to Contemplate

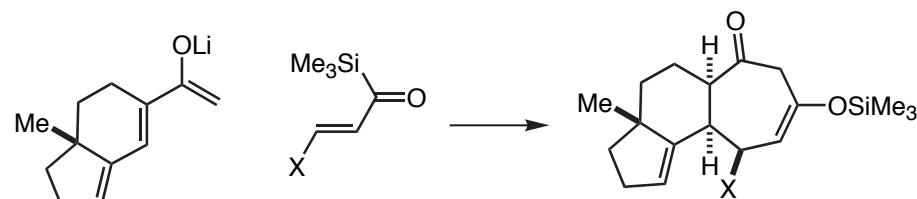


Calter, M. A. Ph. D. Thesis, Harvard University, 1993.

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

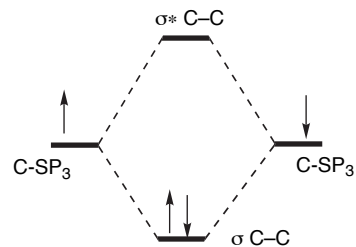
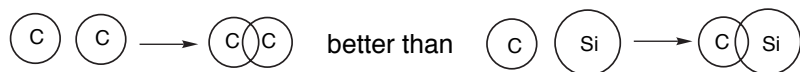
Bonding Considerations: Carbon vs Silicon

Average Bond dissociation energies (Kcal/mol)

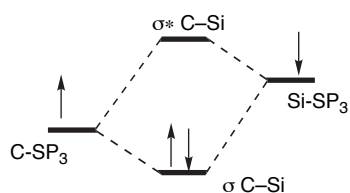
C-C	C-Si	Si-Si	C-F	Si-F	C-O	Si-O
83	76	53	116	135	86	108

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



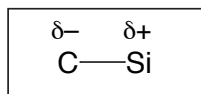
$\text{H}_3\text{C}-\text{CH}_3$ BDE = 83 kcal/mol
Bond length = 1.534 Å



$\text{H}_3\text{C}-\text{SiH}_3$ 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 _____>

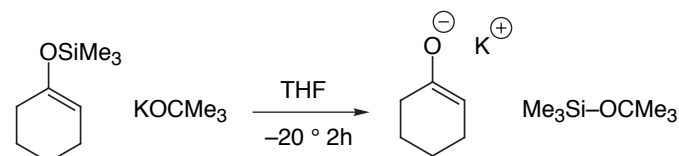
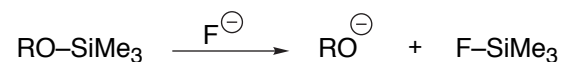
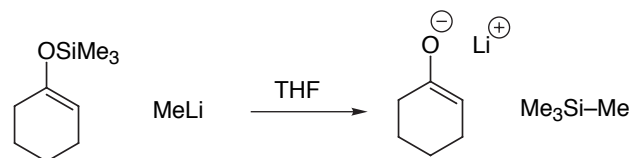
Hypervalent 5-Coordinate Silicon Compounds

Akiba, "Chemistry of hypervalent Compounds" Wiley-VCH, Chapters 4-5, 1999

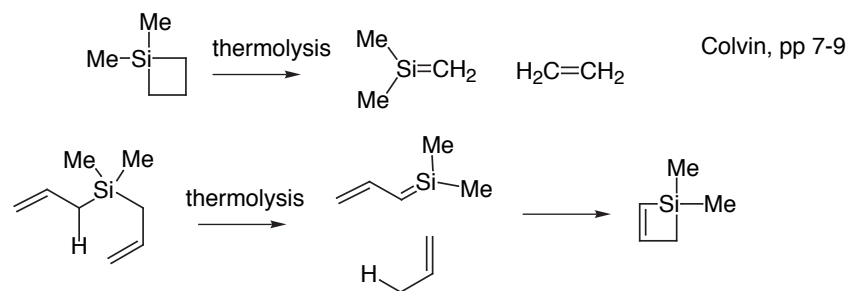
Penta-coordinate silicates are commonly observed



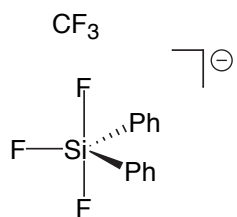
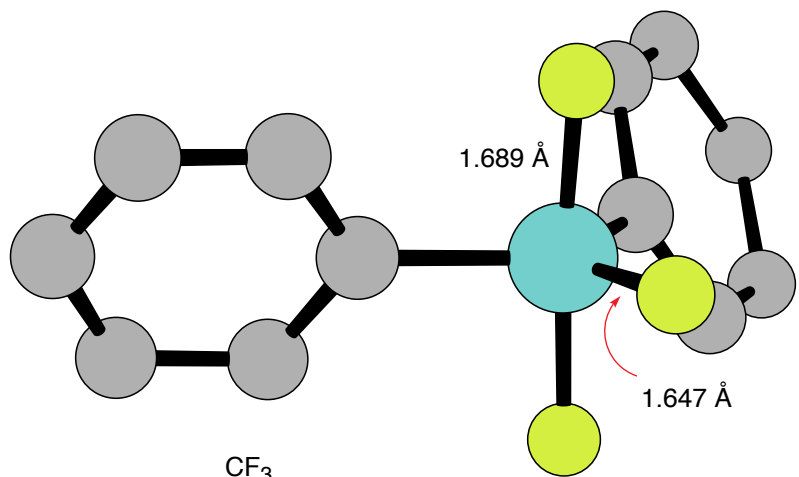
Nucleophilic substitution at Silicon

Duhamel et al. *J. Org. Chem.* **1996**, 61, 2232Stork et al. *JACS.* **1968**, 90, 4462, 4464

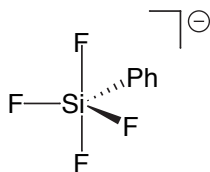
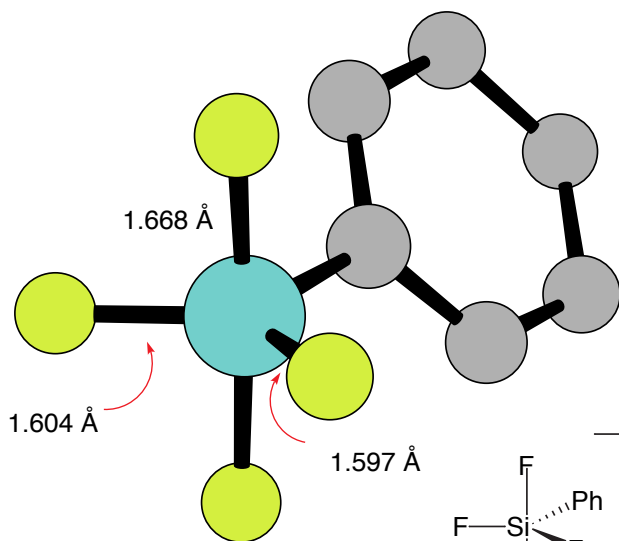
Thermal Rearrangements One may readily access divalent intermediates



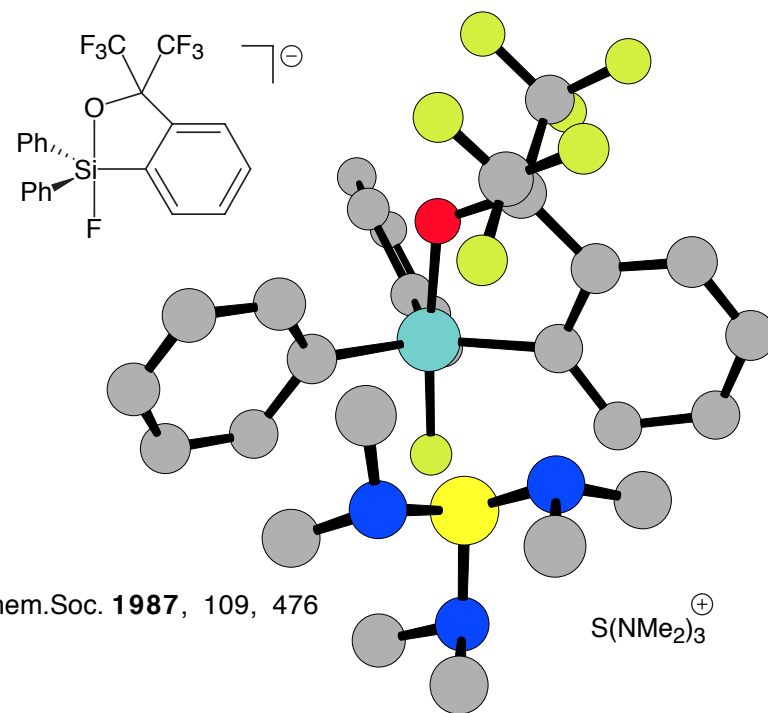
Colvin, pp 7-9



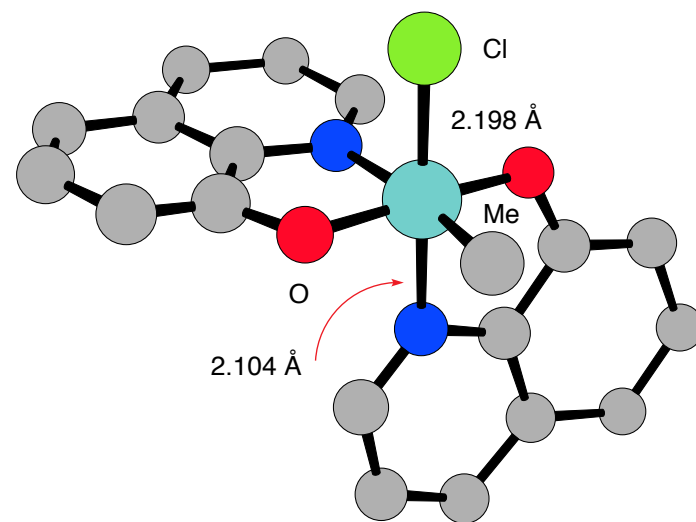
Inorg. Chem. **1984**, 23, 1378



J. Organomet.Chem. **1981**, 221, 137.



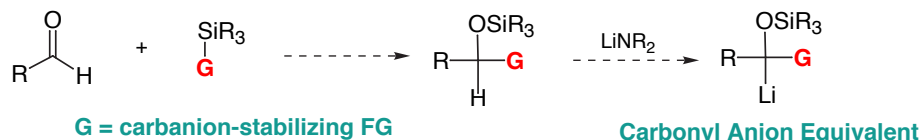
J. Am. Chem.Soc. **1987**, 109, 476



Acta Crystallogr. Sect. C **1984**, 40, 476

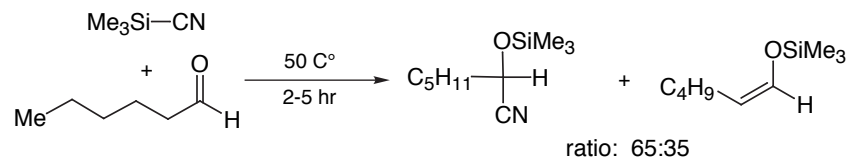
Carbonyl addition Reactions

1970 DAE Objective: Develop a reagent that will transform aldehydes into protected cyanohydrins in one step

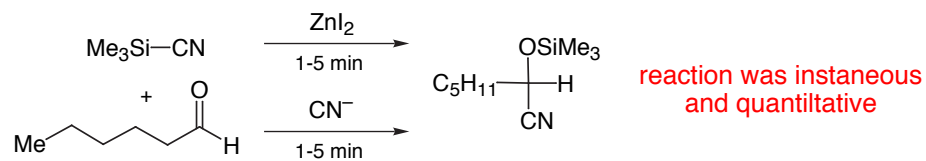


$\text{R}_3\text{Si}-\text{G}$ Candidates	Carbonyl Adducts
$\text{R}_3\text{Si}-\text{CN}$	$\text{R}-\text{CH}(\text{OSiR}_3)-\text{CN}$
$\text{R}_3\text{Si}-\text{OSO}_2\text{Ar}$	$\text{R}-\text{CH}(\text{OSiR}_3)-\text{SO}_2\text{Ar}$
$\text{R}_3\text{Si}-\text{OPR}_2$	$\text{R}-\text{CH}(\text{OSiR}_3)-\text{POR}_2$

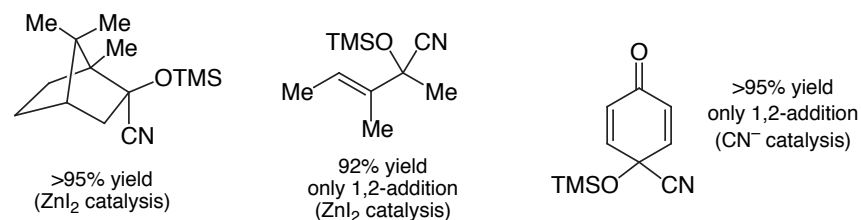
Thermal C=O addition of TMSCN is not a clean reaction



The prospect of catalysis was investigated



Principle established that normally inaccessible cyanohydrin derivatives may now be accessed



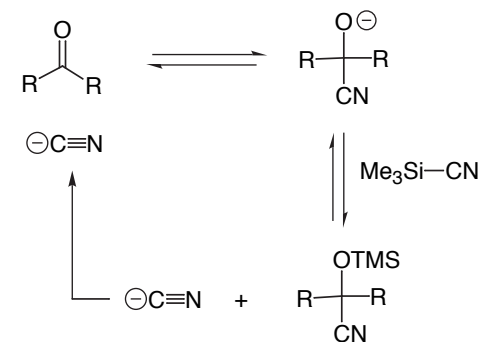
with Truesdale, Carroll, *Chem Commun.* **1973**, 55; *J. Org. Chem.* **1974**, 39, 914
Tetrahedron Lett **1973**, 4929 (first discussion of Nu catalysis)

"The Silicon Advantage"

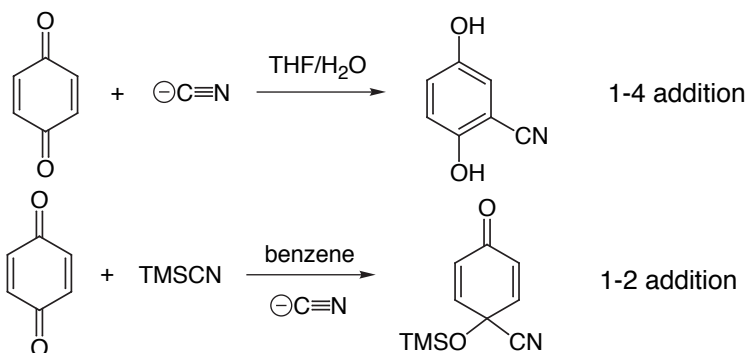
From the preceding case, it is clear that ΔH_{Si} is more exothermic than ΔH_{H}



Nucleophilic Catalysis

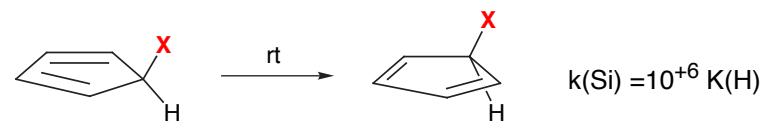
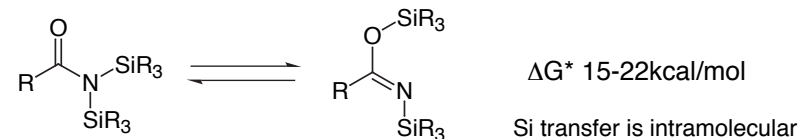
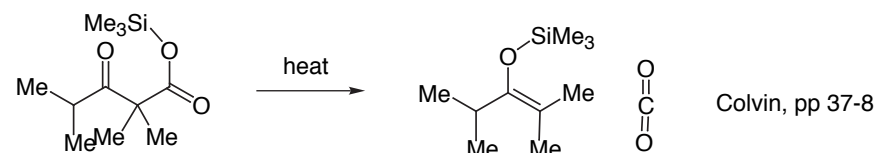
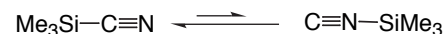


Explain the following observations

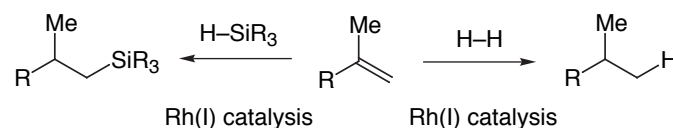


"The Proton-Silicon Correlation"

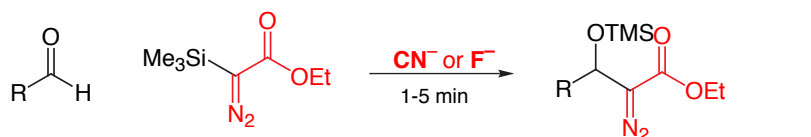
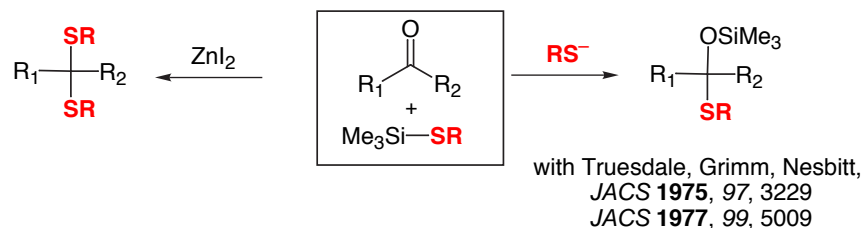
- Organosilanes undergo carbonyl addition processes in direct analogy with their proton counterparts but with an attendant greater exothermicity.
- Organosilanes undergo a range of thermal rearrangement processes in direct analogy with their proton counterparts.

A. J. Ashe III, *JACS* **1970**, 92, 1233Yoder et al., *JACS* **1974**, 96, 4283

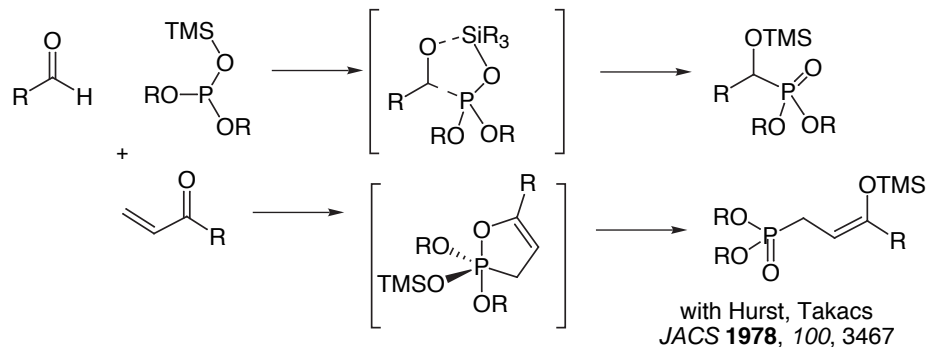
- Organosilicon hydrides undergo transition metal catalyzed hydrosilylation processes in direct analogy with normal hydrogenation reactions

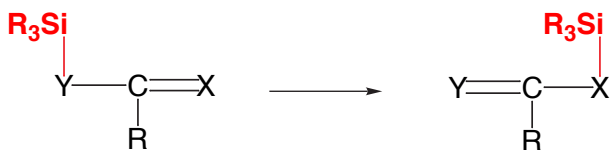
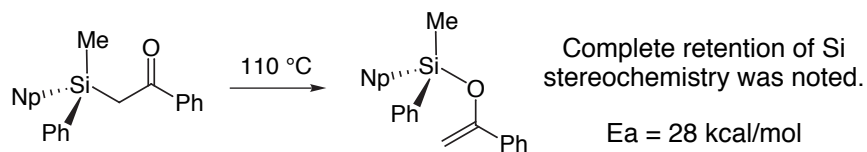
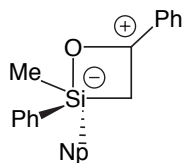


"Hydrosilylation of C-C Bonds". T. Hayashi In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; and Yamamoto, H. Editors; Springer Verlag: Heidelberg, **1999**; Vol 1, 319-332.

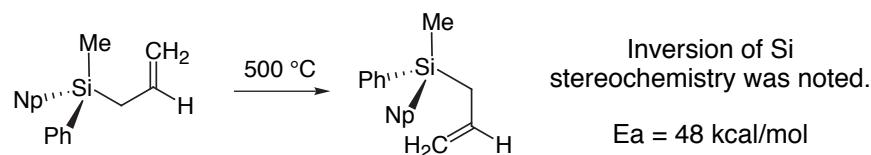


Non-catalyzed processes may also occur if a proper geometry for atom transfer can be achieved



[1,3]-Sigmatropic Rearrangements**Y = C; X = O**A. G. Brook *Accts. Chem. Research* **1974**, 7, 77-84

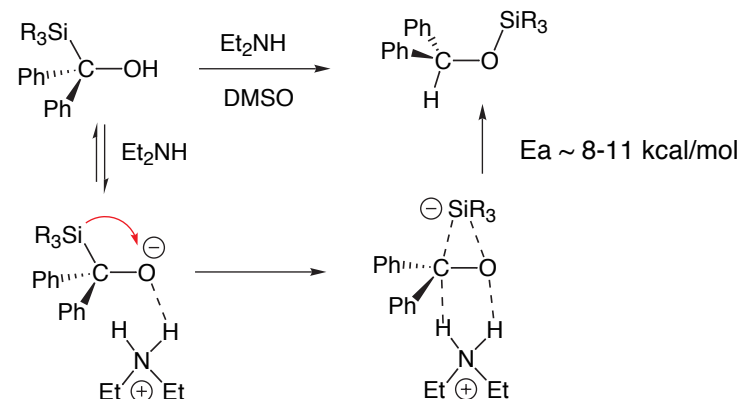
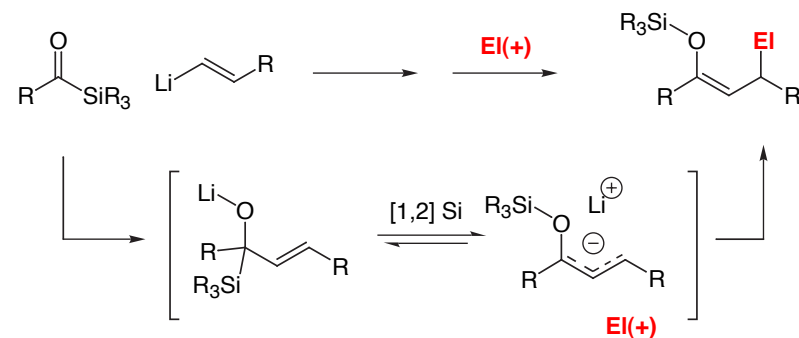
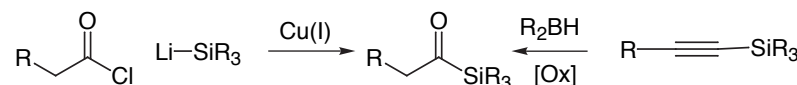
Brook speculates that a hypervalent Si intermediate might be involved in the rearrangement.

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.

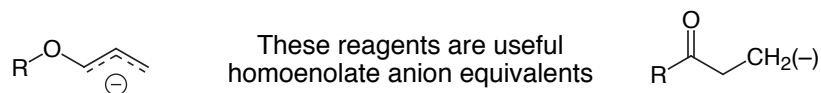
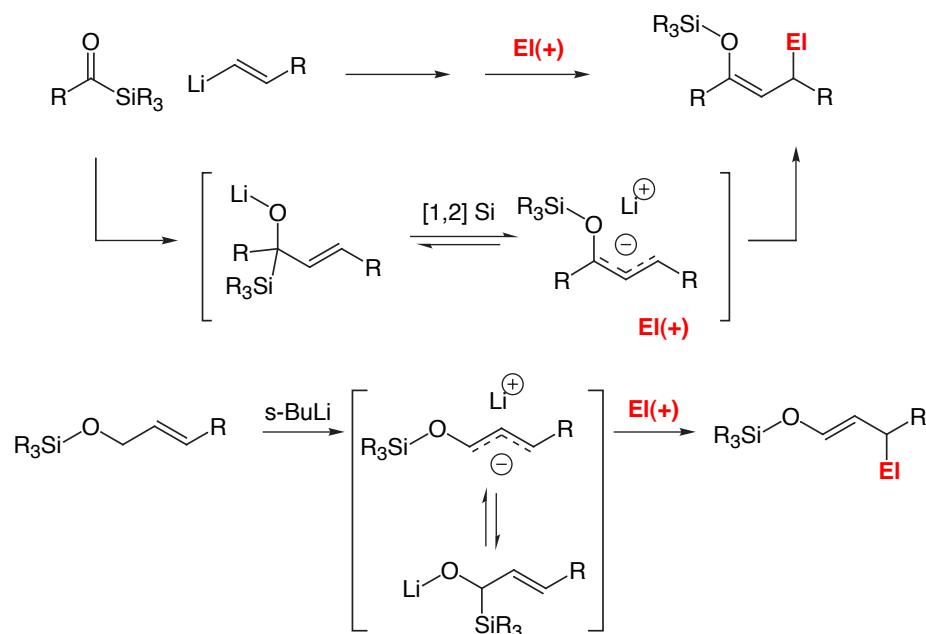
Yamabe, *JACS* **1997**, 119, 808

At the present time these rearrangements are not well studied,

"The Brook Rearrangement(s)"A. G. Brook *Accts. Chem. Research* **1974**, 7, 77-84Brook 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

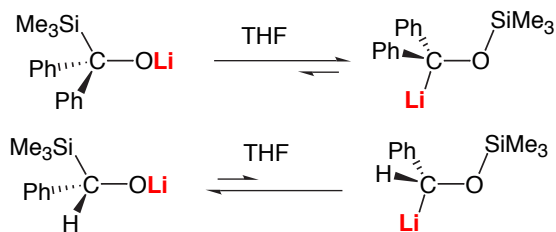
Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," *Tetrahedron* **2001**, 57, 2065-2084



"Metalated Allylic Ethers as Homoenolate Anion Equivalents".
Evans, D. A.; Andrews, G. C.; Buckwalter, B. *JACS* **1974**, 96, 5560.

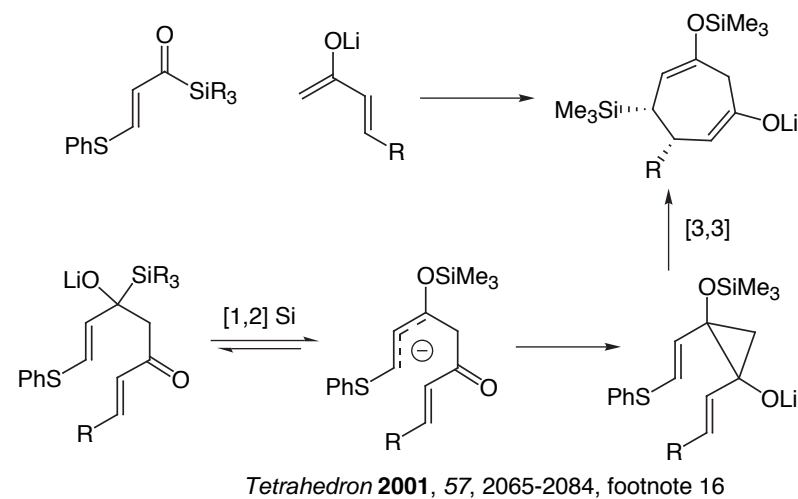
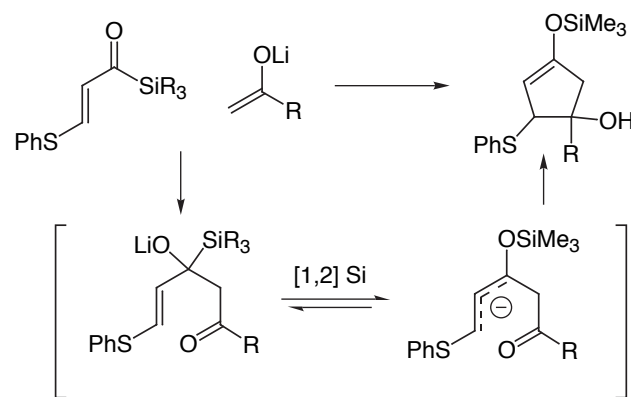
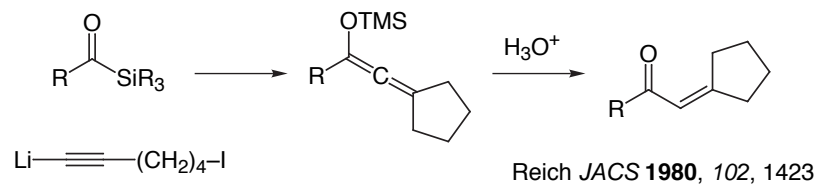
Si-Variant: Still & MacDonald *JACS* **1974**, 96, 5561

Brook Equilibrium Reich *JACS* **1980**, 102, 1423 (see footnote 8)

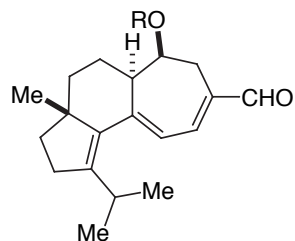


36-05-Brook Rearrangements-2 12/14/03 8:54 PM

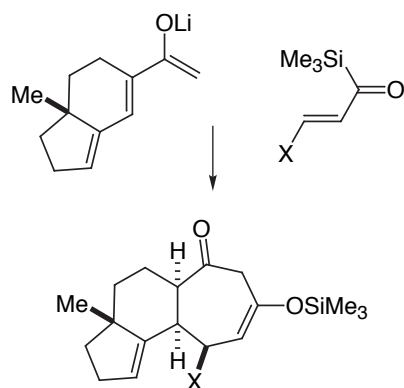
Intramolecular alkylations may be carried out:



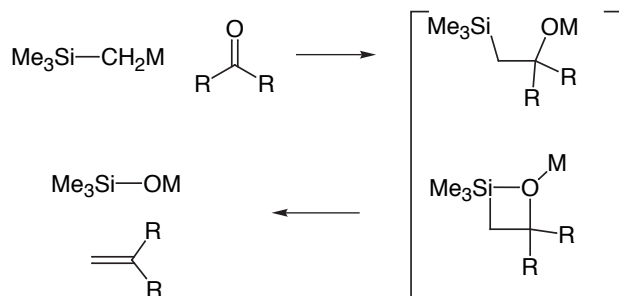
The natural product target:

Takeda, *Org. Lett.* **2000**, 2, 903-1905

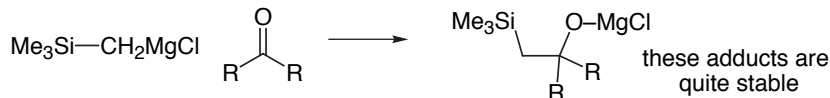
The key reaction



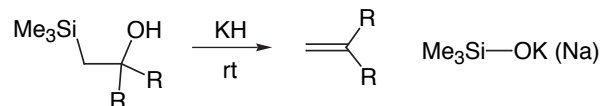
The Peterson Olefination Reaction

Ager, D. J. "The Peterson olefination reaction."
Org. Reactions **1990**, 38, 1-224The 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:

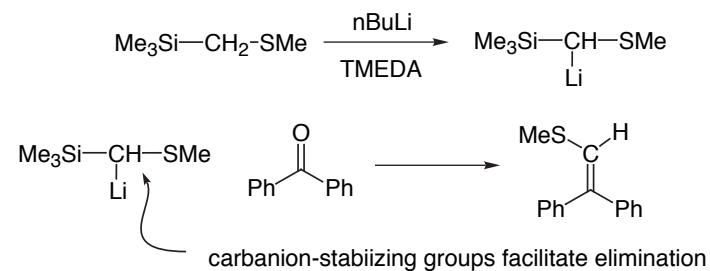
Magnesium alkoxides: Stable



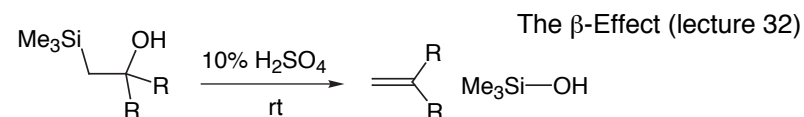
Na & K alkoxides: Eliminate



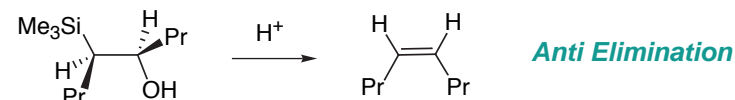
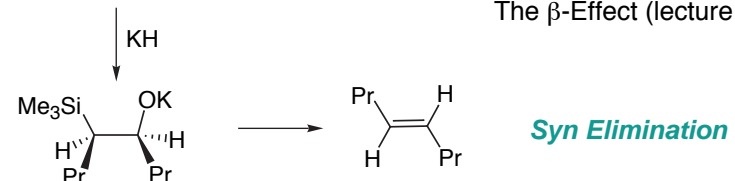
C	N
Si	P



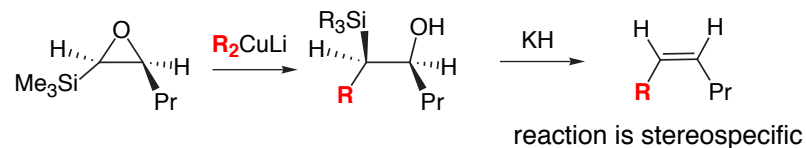
Elimination could also be effected with dilute acid

analogy provided by Whitmore et al. *JACS* **1947**, 69, 1551

Mechanistic aspects of Beta-OH Elimination

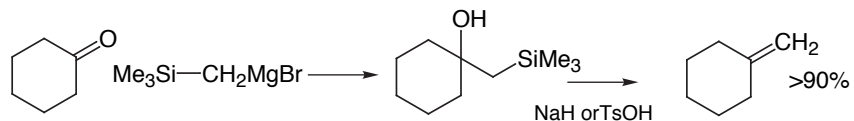
The β -Effect (lecture 32)Hudrlik et al. *JACS* **1975**, 97, 1464

Colvin chapter 12, pp 141

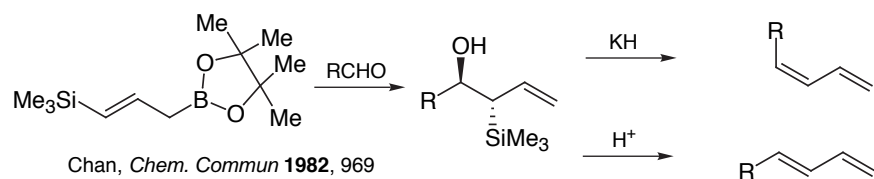
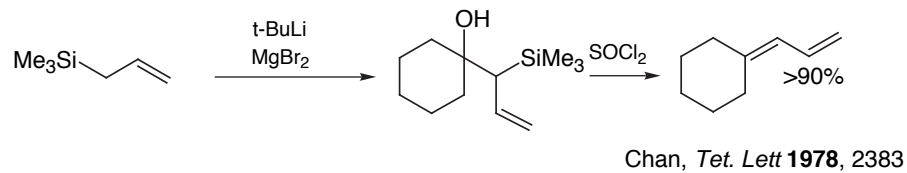
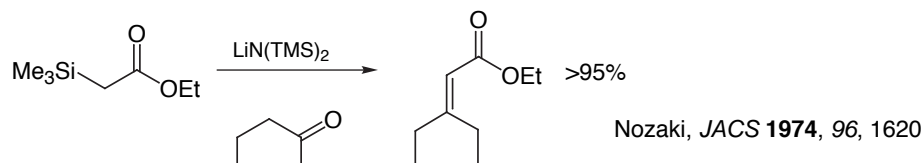
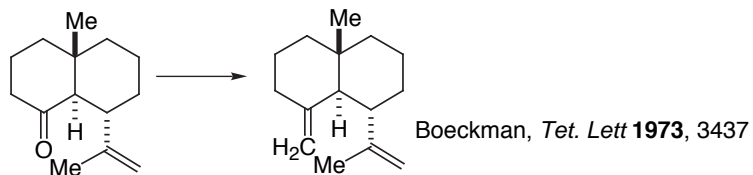


note site of nu attack. Why?

■ Simple Examples: Taken from Organic Rxns review

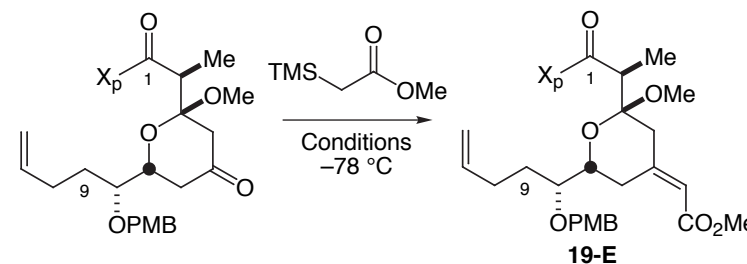
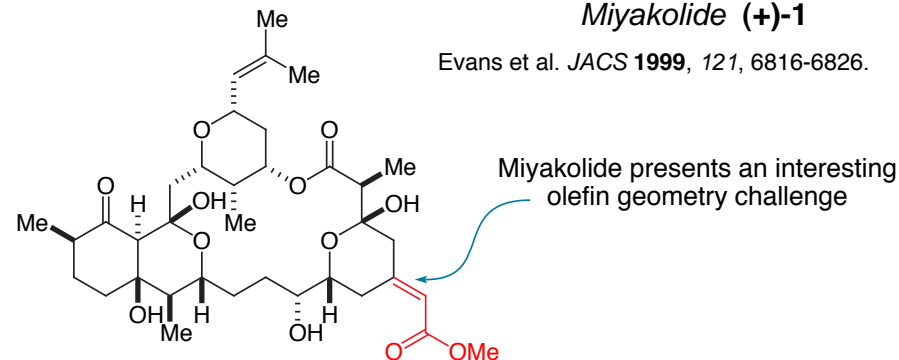


This reagent is better than $\text{H}_2\text{C}=\text{PPh}_3$ for hindered ketones

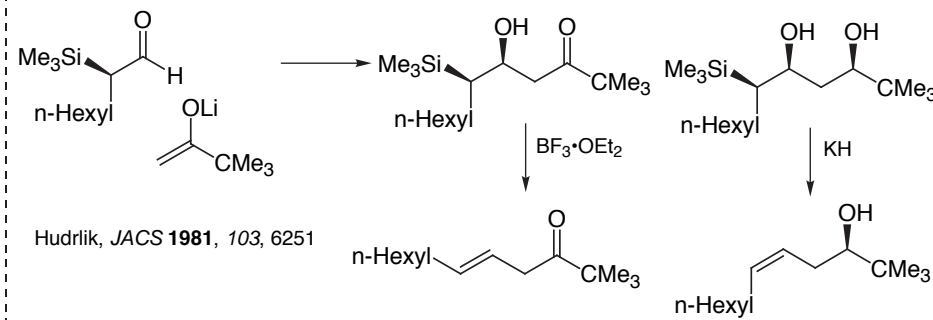


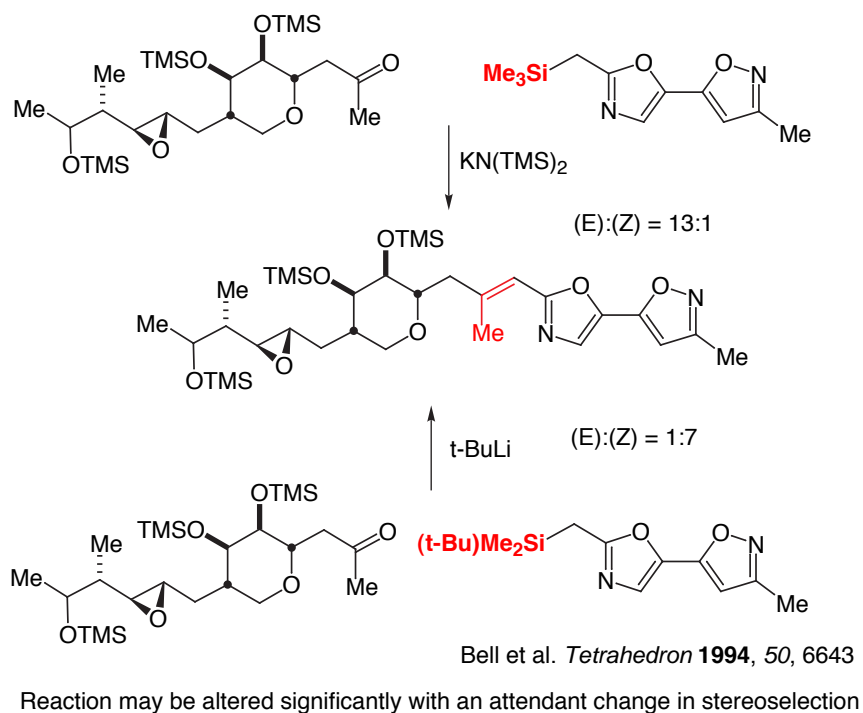
Miyakolide (+)-1

Evans et al. *JACS* **1999**, 121, 6816-6826.

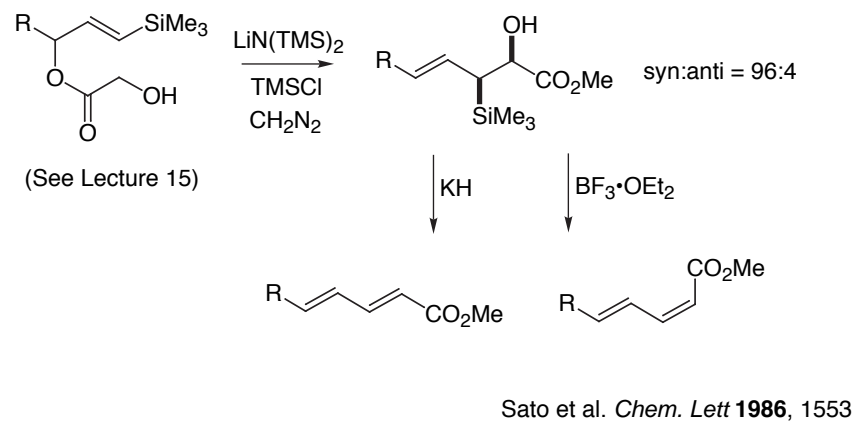


entry	base	solvent	E : Z
1	LDA	THF	73 : 27
2	NaHMDS	THF	18 : 82
3	LDA	Et ₂ O	66 : 33
4	LDA	PhMe	66 : 33

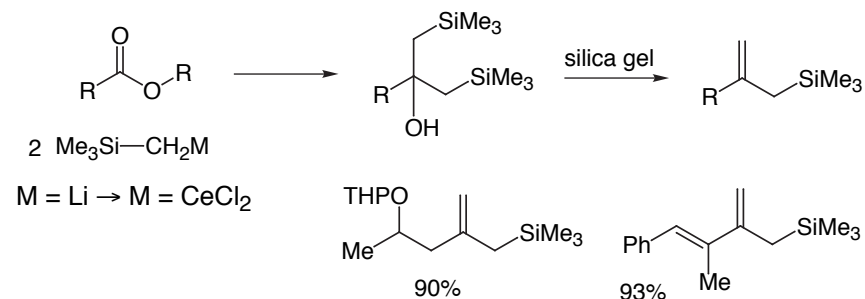
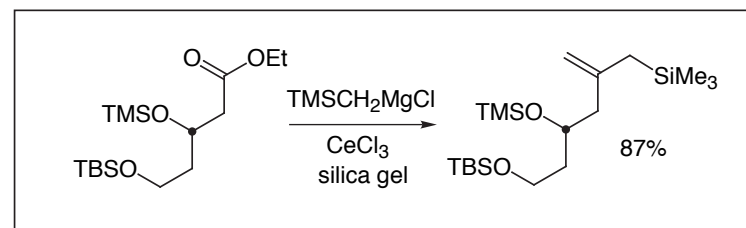
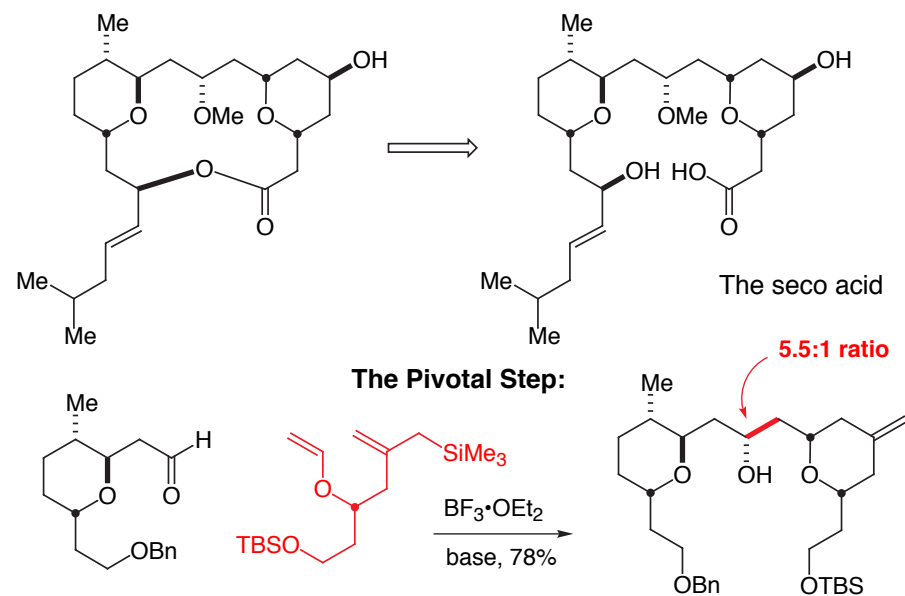




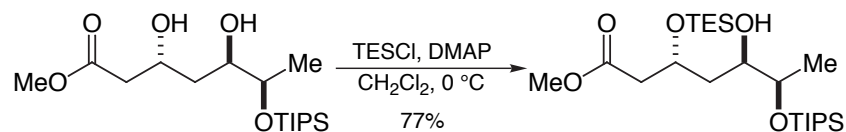
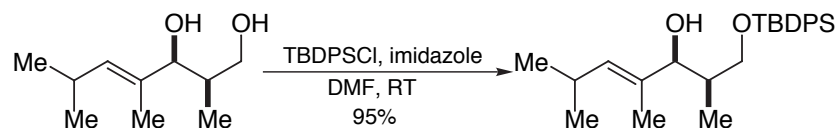
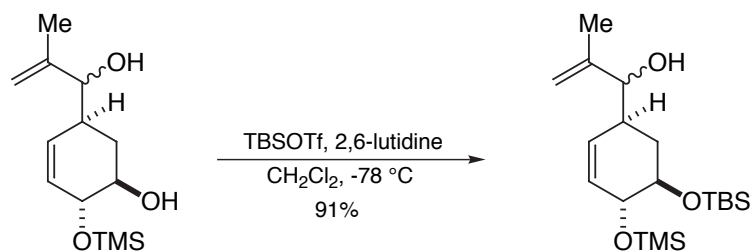
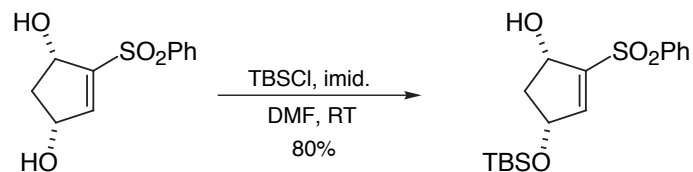
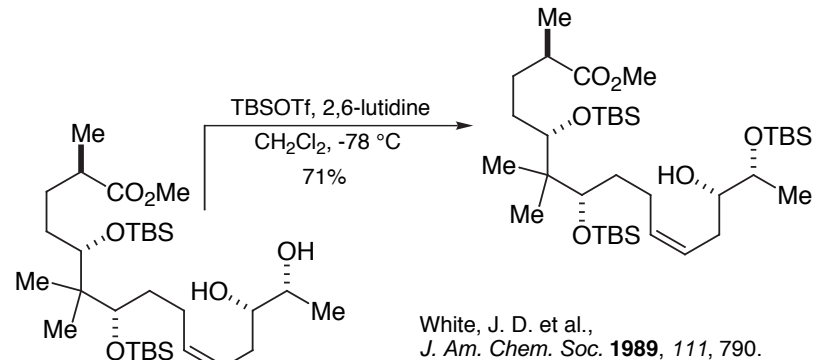
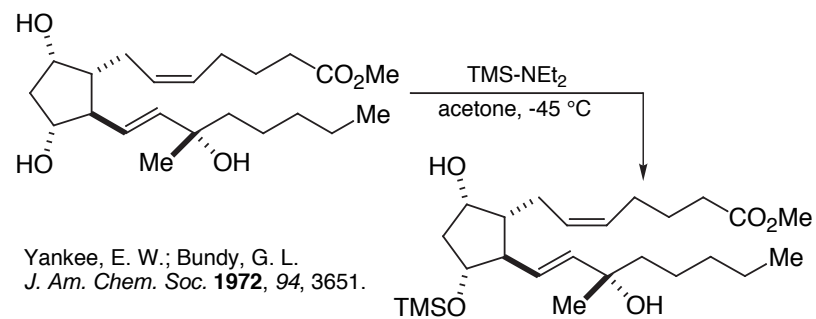
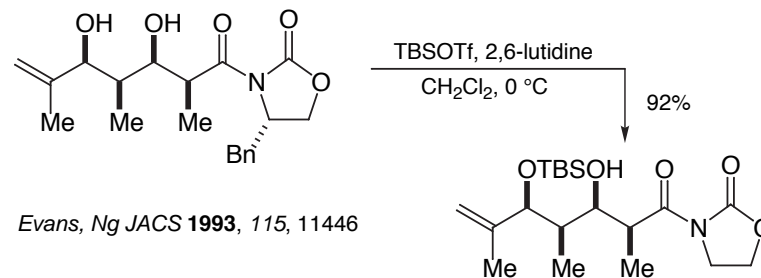
Ireland Enolate Claisen Coupled to Peterson Olefination



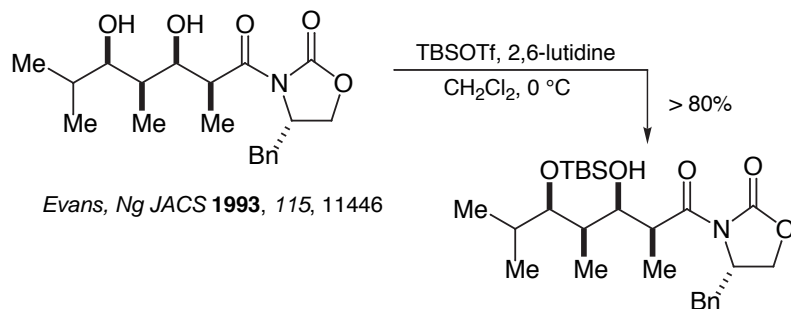
Bunnelle-Peterson Allylsilane Synthesis

Application to Leucasandrolide: Rychnovsky *JACS*, **2001**, *123*, 8420

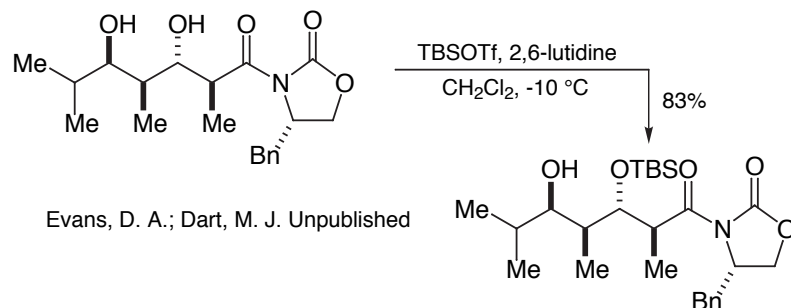
Selective Protection:

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

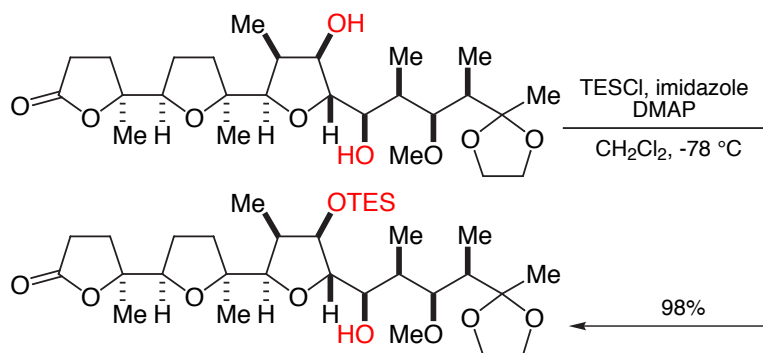
Selective Protection:



Evans, Ng JACS 1993, 115, 11446

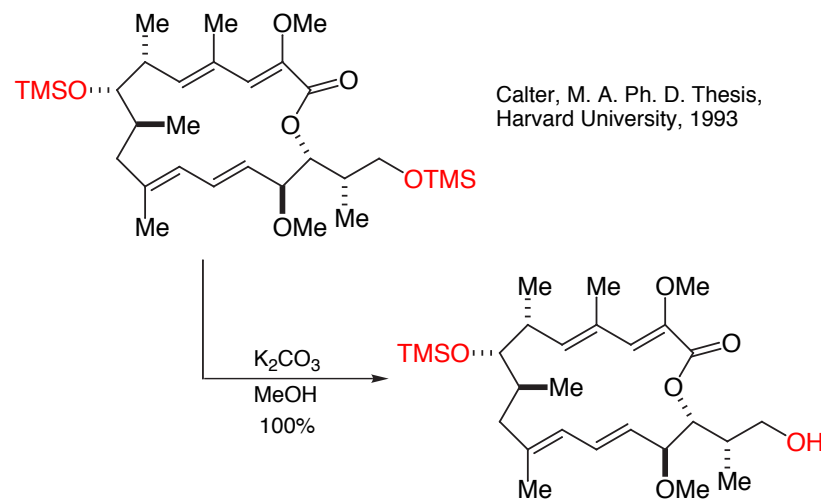


Evans, D. A.; Dart, M. J. Unpublished

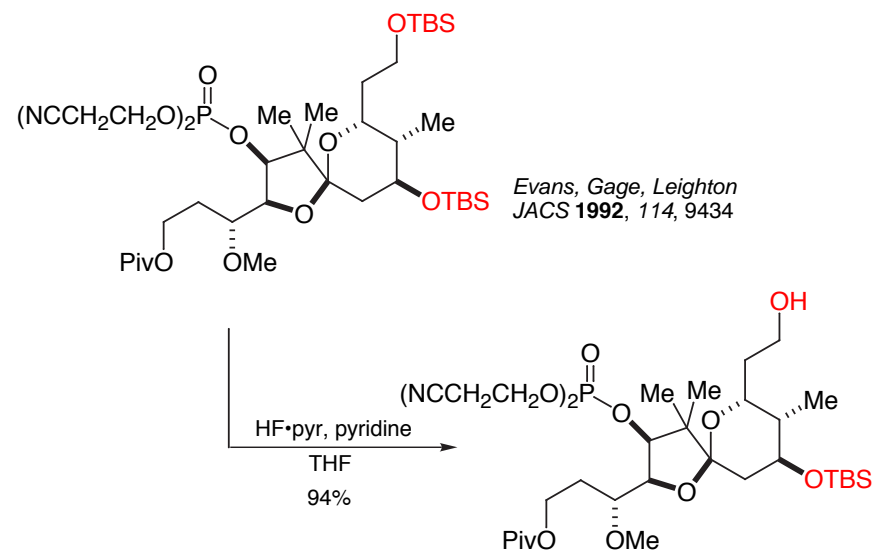


Evans, Ratz JACS 1995, 117, 3448

Selective Deprotection:

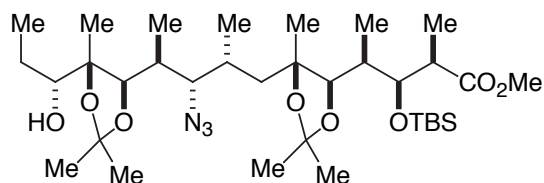
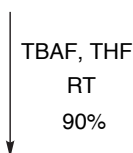
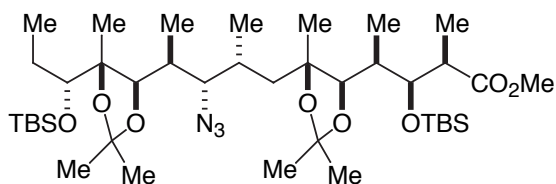


Calter, M. A. Ph. D. Thesis, Harvard University, 1993

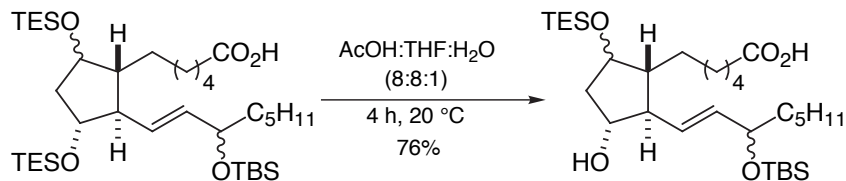


Evans, Gage, Leighton JACS 1992, 114, 9434

Selective Deprotection:

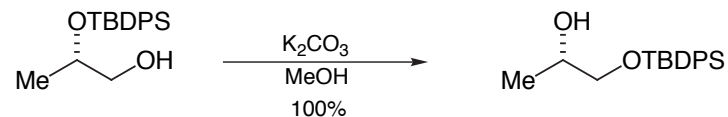


Nakaba, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, 29, 2219, 2223.



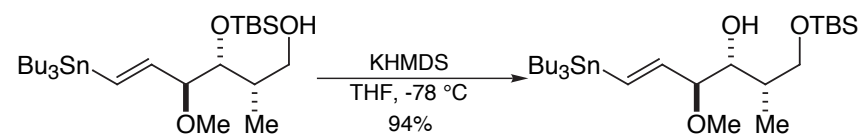
Hart, T. W.; Metcalfe, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156.

1,2-Migration:

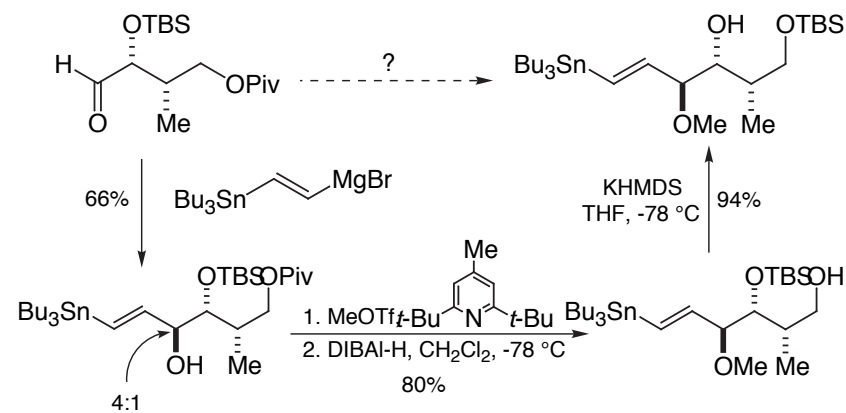


Mulzer, J.; Schollhorn, B. *Angew. Chem., Int. Ed. Eng.* **1990**, 29, 431-432.

1,3-Migration:



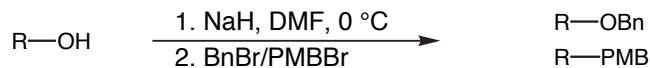
Calter, M. A. Ph. D. Thesis, Harvard University, 1993.



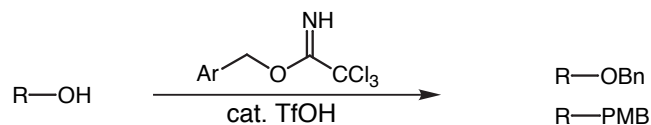
Calter, M. A. Ph. D. Thesis, Harvard University, 1993.

Principle Methods for Benzylation of Alcohols:

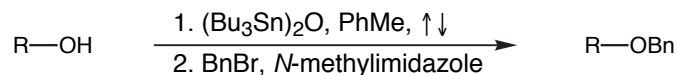
1.



2.

Ar = Ph: CH₂Cl₂Ar = 4-MeO-Ph: Et₂OAr = 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.

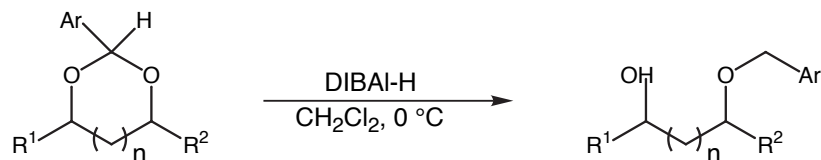
3.

Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *J. Org. Chem.* **1989**, 54, 465.Review: David, S.; Hanessian, S. *Tetrahedron*, **1985**, 41, 643-663.

4.

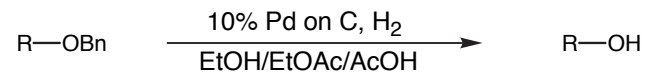
Van Hijfte, L.; Little, R. D. *J. Org. Chem.* **1985**, 50, 3940.

Via Benzylidene Acetal:

Takano, S. et al., *Synthesis* **1986**, 811-817.

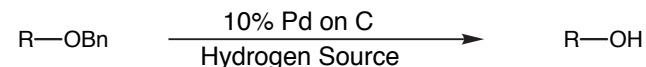
Principle Methods for Deprotection:

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 ₂ H	<i>J. Org. Chem.</i> 1979 , 44, 3442.
<i>i</i> -PrOH	<i>Tetrahedron Lett.</i> 1986 , 27, 2497

3. Lewis Acids

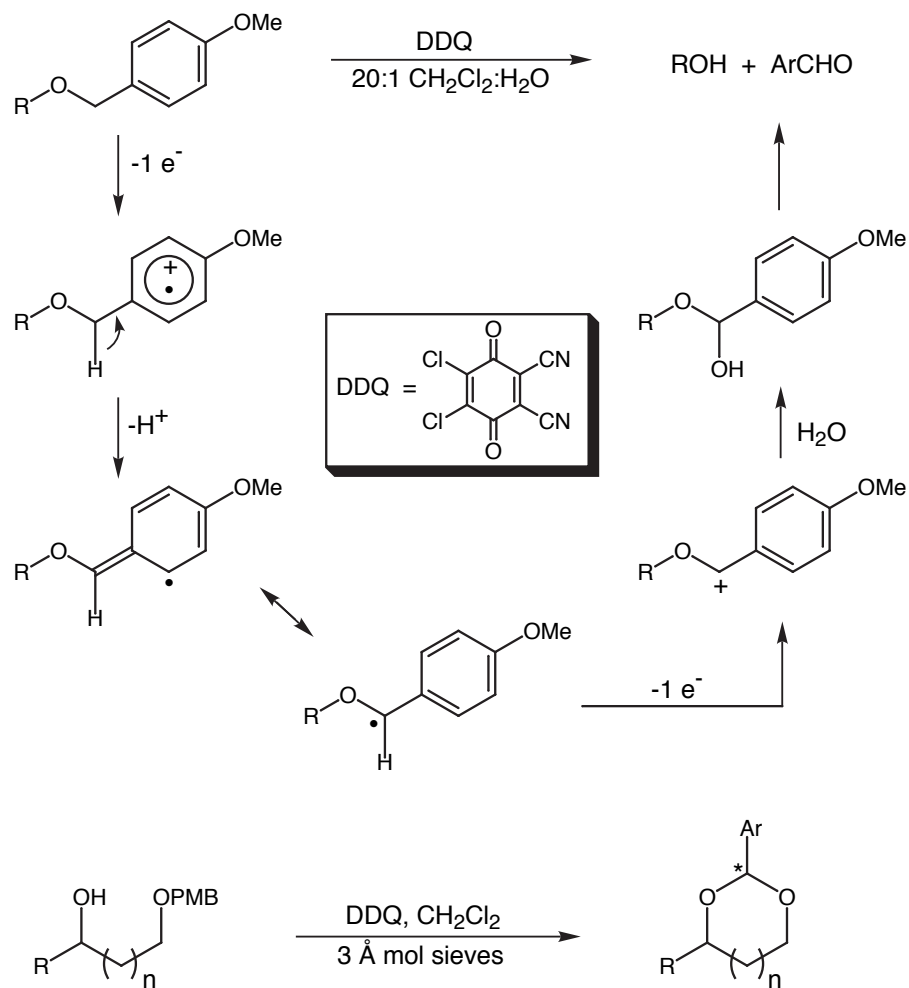


Reagents

Ref.

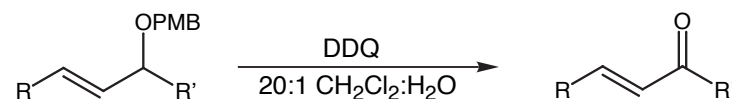
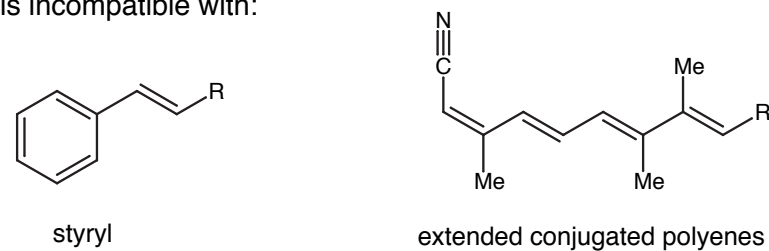
BF ₃ •OEt ₂ , EtSH	<i>Tetrahedron Lett.</i> 1989 , 30, 5713.
1. BCl ₃ , -78 °C to 0 °C. 2. MeOH, -78 °C.	<i>J. Am. Chem. Soc.</i> 1989 , 111, 1923.
TMSBr, C ₆ H ₅ SMe	<i>Chem. Pharm. Bull.</i> 1987 , 35, 3880.

PMB Deprotection:

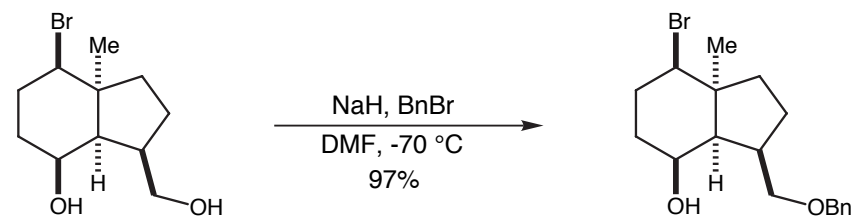
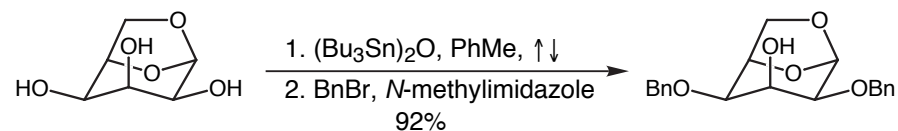
Yonemitsu, O. et al., *Tetrahedron* **1986**, *42*, 3021.Other Oxidants: NBS, Br₂, CAN ((NH₄)₂Ce(NO₃)₆).*Acta Chem. Scand. Ser. B*, **1984**, B38, 419.*J. Chem. Soc., Perkin Trans. I*, **1984**, 2371.

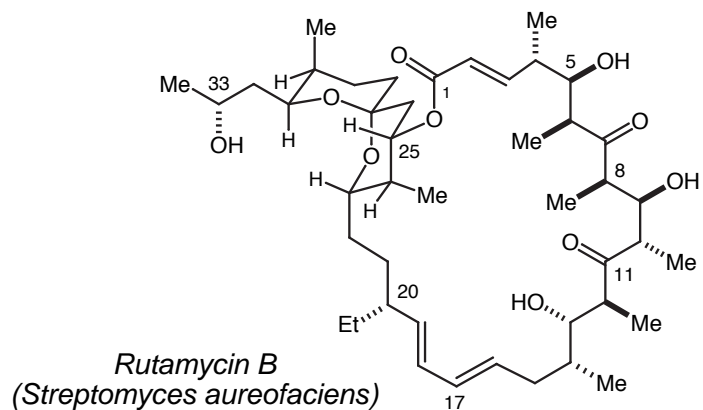
36A-14 Benzyl Protect 12/7/01 8:18 AM

DDQ is incompatible with:

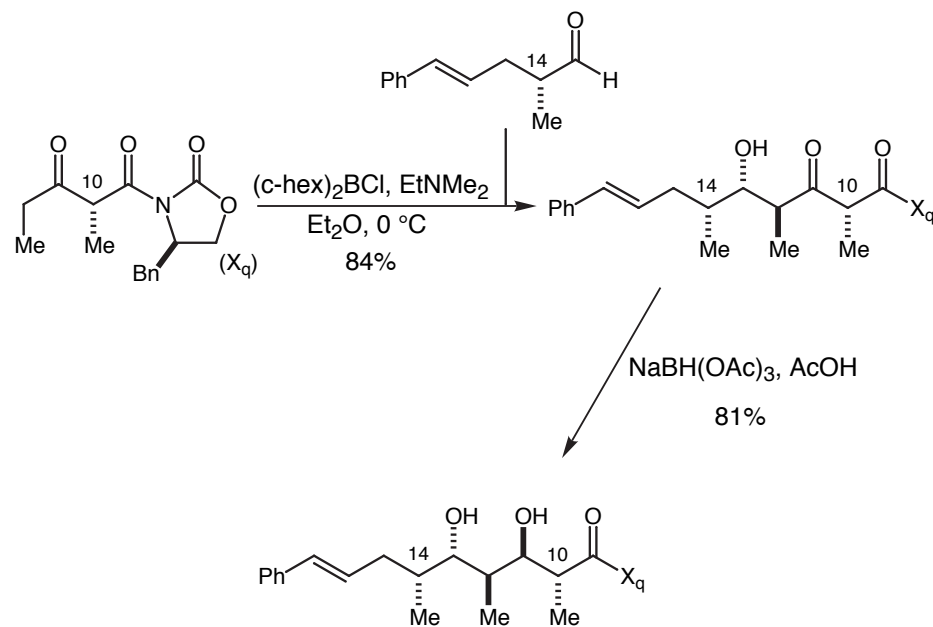
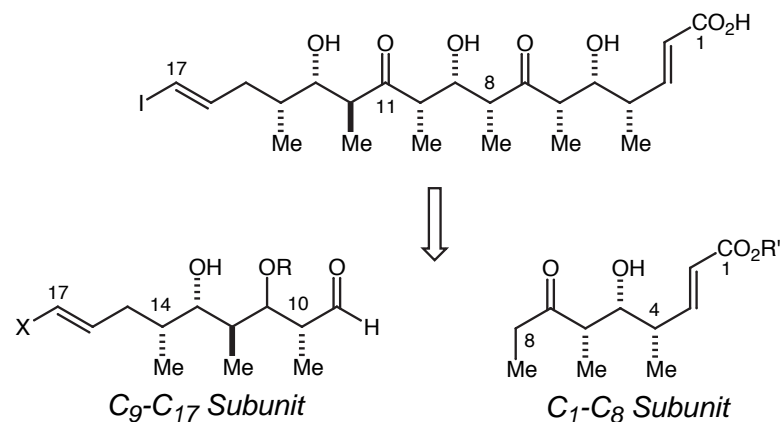
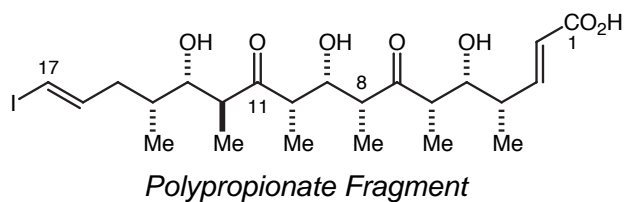
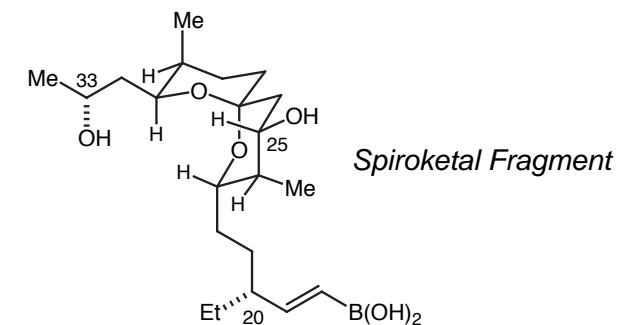


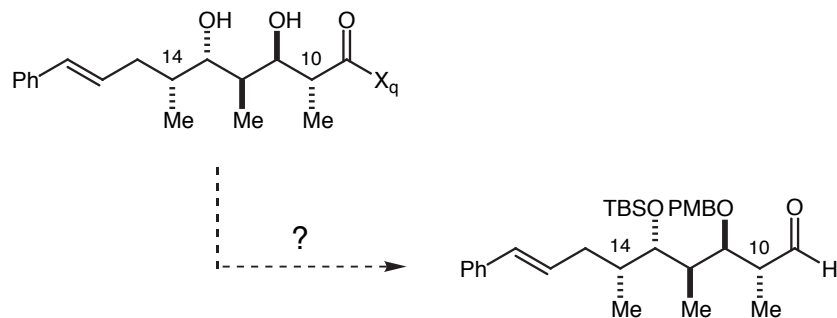
Selective Benzylation:

Fukuzawa, A. et al. *Tetrahedron Lett.* **1987**, *28*, 4303.Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *J. Org. Chem.* **1989**, *54*, 465.

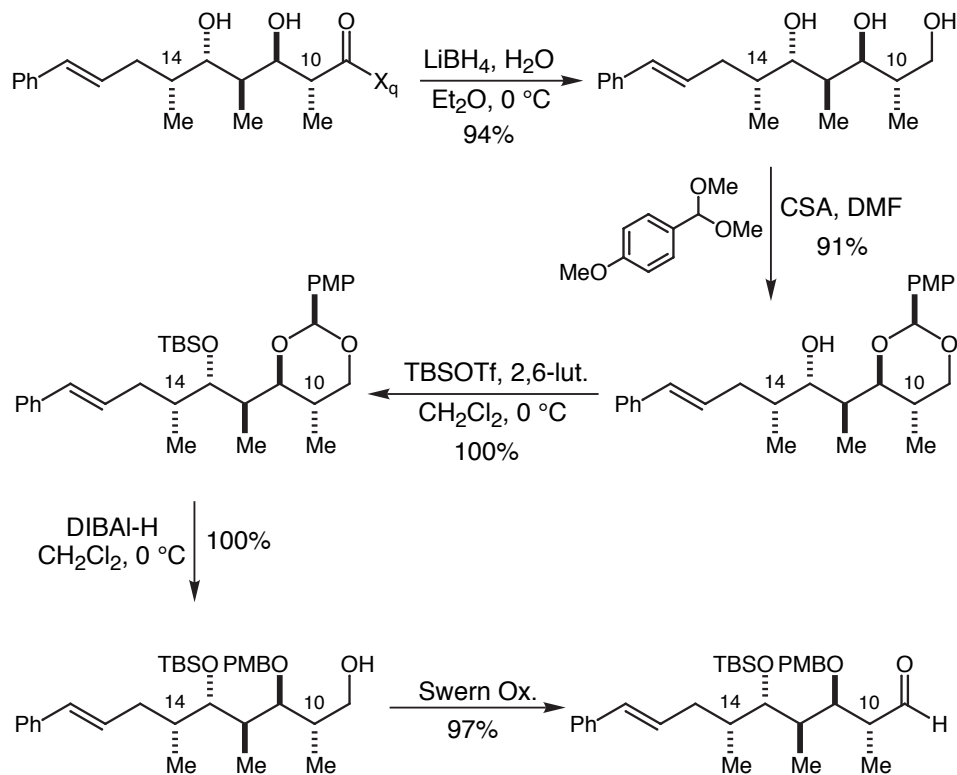


Ng, H. P. Ph. D. Thesis,
Harvard University, 1993

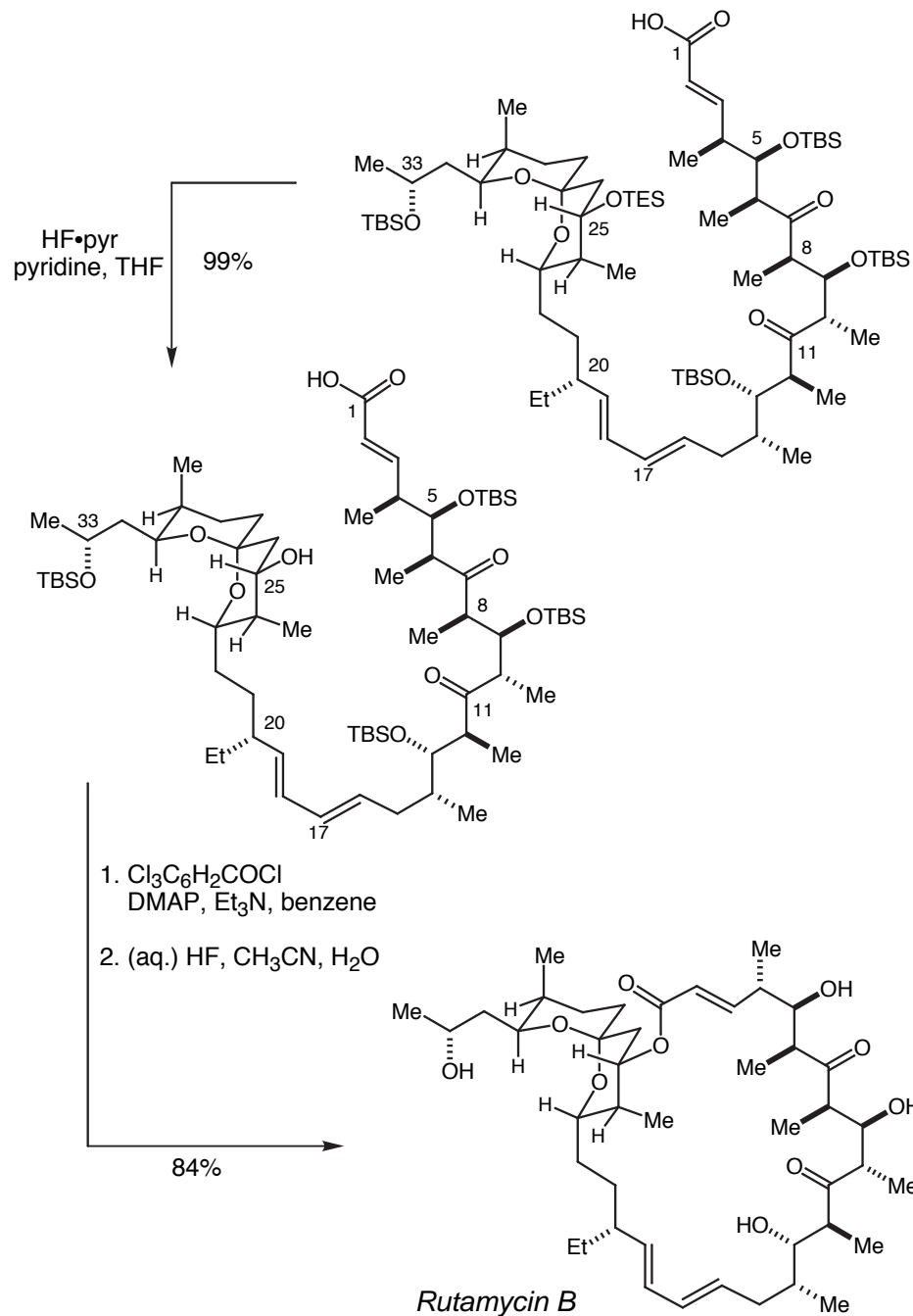


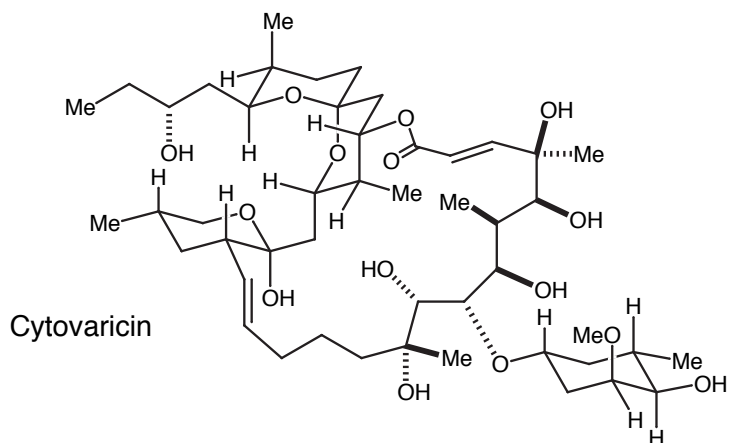


Selective silylation was unsuccessful.



36A-16 Rutamycin 12/7/01 8:18 AM

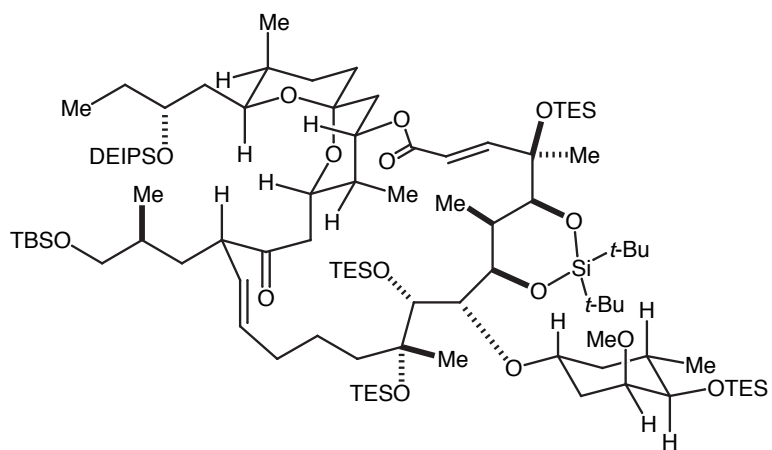
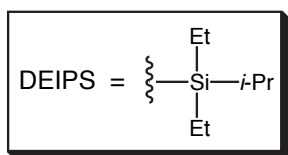




Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J.
J. Am. Chem. Soc. **1990**, *112*, 7001-7031.

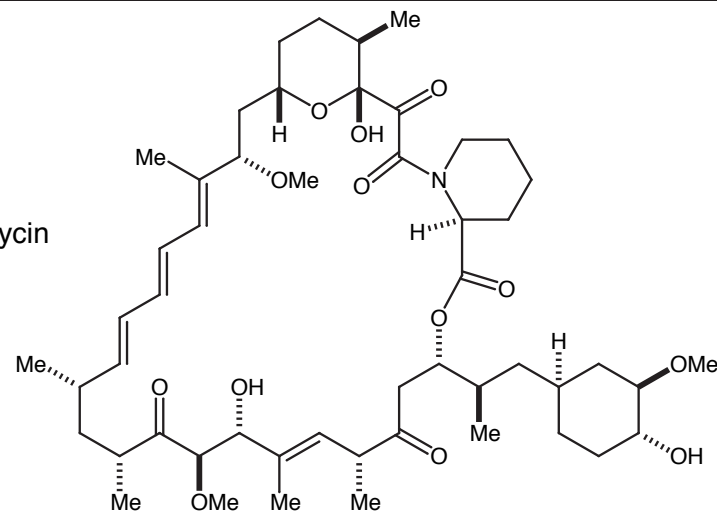
HF•pyr, pyridine
 THF, RT

74%



36A-18 Cytovaricin 12/7/01 8:18 AM

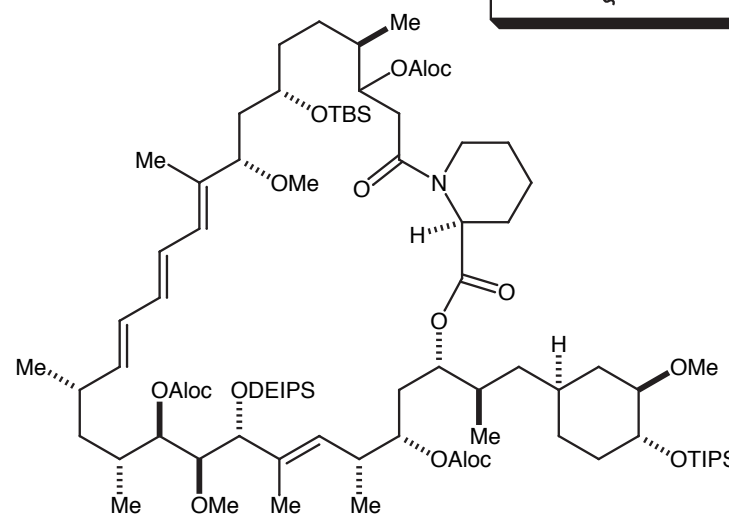
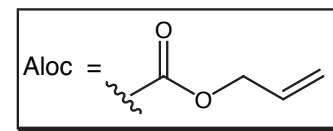
Rapamycin



Romo, D.; Meyer, S. D.;
 Johnson, D. D.; Schreiber, S. L.
J. Am. Chem. Soc. **1993**, *115*, 7906-7907.

1. Pd(Ph₃P)₄, HCO₂NH₄, THF
2. Dess-Martin Periodinane
3. HF•pyr, pyridine, THF

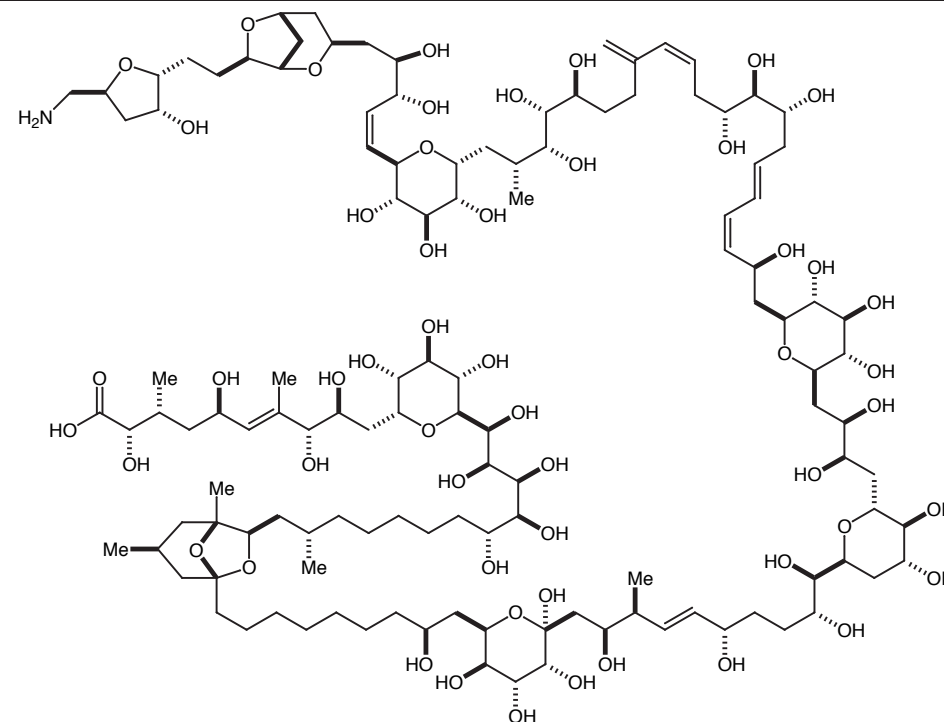
30% overall



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.