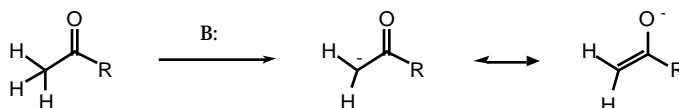


Carbon- Carbon Bond Formation

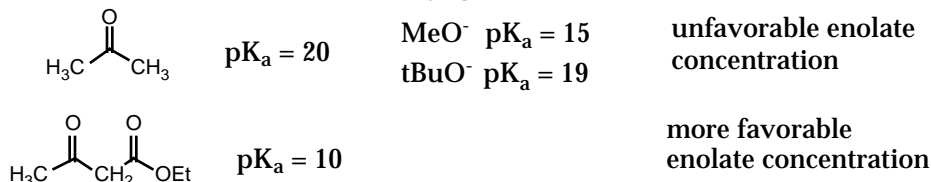
- Alkylation of enolates, enamines and hydrazones
C&S: Chapt. 1, 2.1, 2.2 problems Ch 1: 1; 2; 3, 7; 8a-d; 9; 14 Ch. 2: 1; 2; 4)
Smith: Chapt. 9
- Alkylation of heteroatom stabilized anions C&S :Chapt. 2.4 - 2.6)
- Umpolung Smith: Chapt. 8.6
- Organometallic Reagents
C&S: Chapt. 7, 8, 9 problems ch 7: 1; 2; 3, 6; 13 Ch. 8: 1; 2
Smith: Chapt. 8
- Sigmatropic Rearrangements . C&S Chapt. 6.5, 6.6, 6.7 # 1e,f,h,op
Smith Chapt. 11.12, 11.13

Enolates *Comprehensive Organic Synthesis* **1991**, vol. 2, 99.

- deprotonation of a ketone, aldehyde or ester by treatment with a strong non-nucleophilic base.
- carbonyl group stabilizes the resulting negative charge.



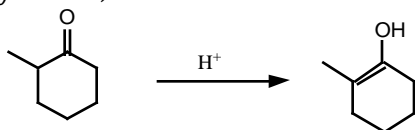
- Base is chosen so as to favor enolate formation. Acidity of C-H bond must be greater (lower pK_a value) than that of the conjugate acid of the base (C&S table 1.1, pg 3)



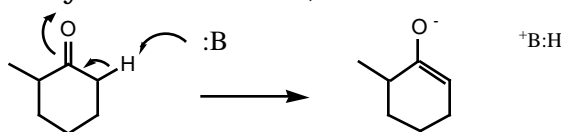
- Common bases: NaH, EtONa, tBuOK, NaNH₂, LiNiPr₂, M N(SiMe₃)₂, Na CH₂S(O)CH₃

Enolate Formation:

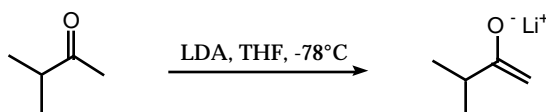
- H⁺ Catalyzed (thermodynamic)



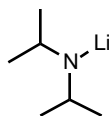
- Base induced (thermodynamic or kinetic)

**Regioselective Enolate Formation** *Tetrahedron* **1976**, 32, 2979.

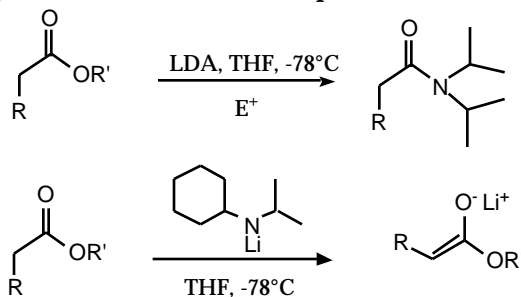
- Kinetic enolate- deprotonation of the most accessible proton (relative rates of deprotonation). Reaction done under essentially irreversible conditions.



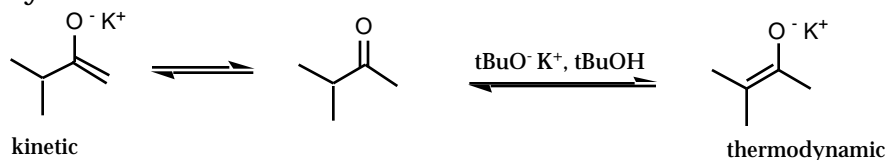
typical conditions: strong hindered (non-nucleophilic) base such as LDA
 R_2NH $pK_a = \sim 30$



Ester Enolates- Esters are susceptible to substitution by the base, even LDA can be problematic. Use very hindered non-nucleophilic base (Li isopropylcyclohexyl amide)

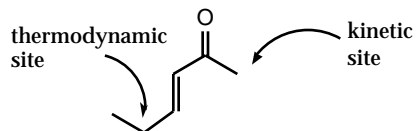


- Thermodynamic Enolate- Reversible deprotonation to give the most stable enolate: more highly substituted C=C of the enol form



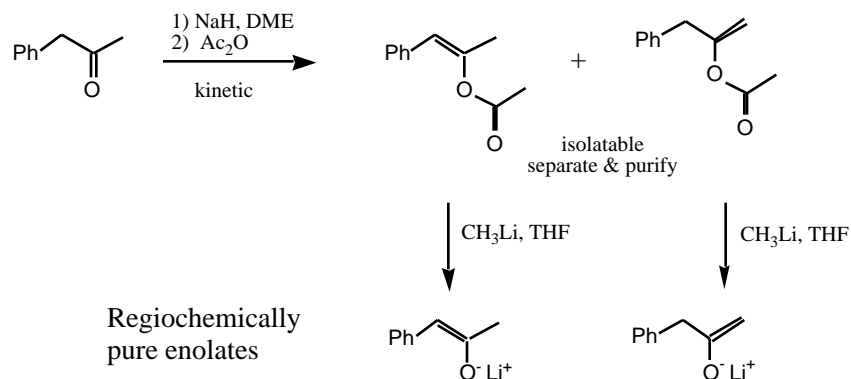
typical conditions: $RO^- M^+$ in ROH, protic solvent allows reversible enolate formation. Enolate in small concentration (pK_a of ROH = 15-18 range)

- note: the kinetic and thermodynamic enolate in some cases may be the same
- for α,β -unsaturated ketones

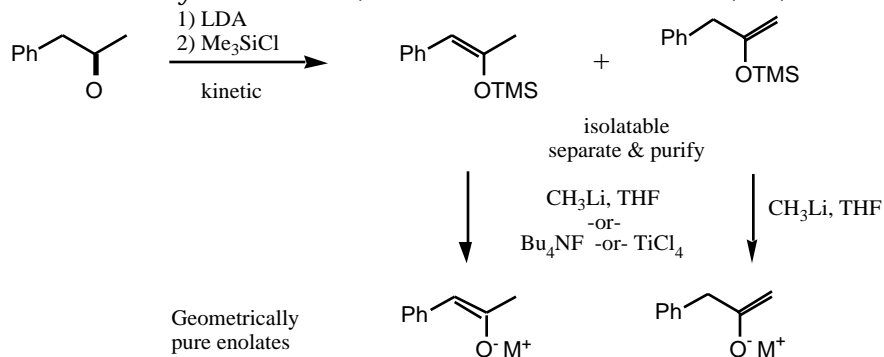


Trapping of Kinetic Enolates

- enol acetates

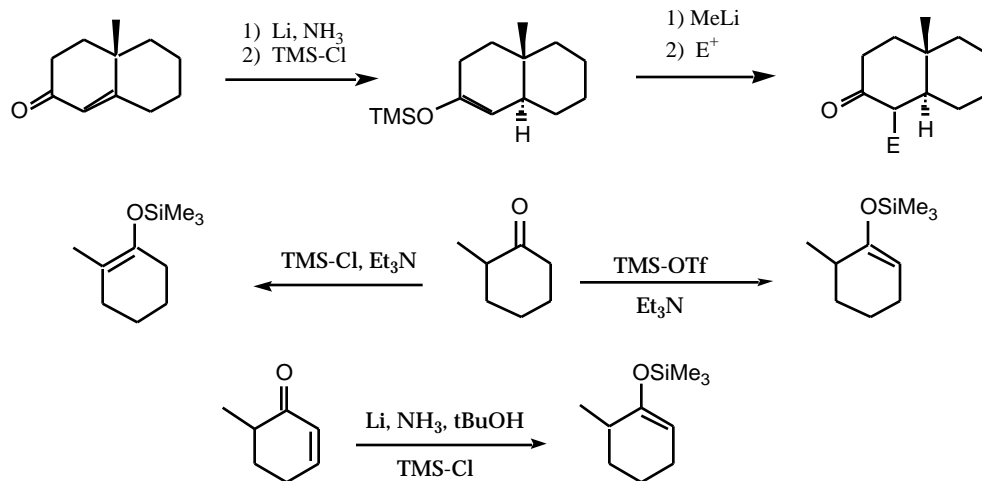


- silyl enolethers *Synthesis* **1977**, **91**. *Acc. Chem. Res.* **1985**, **18**, **181**.

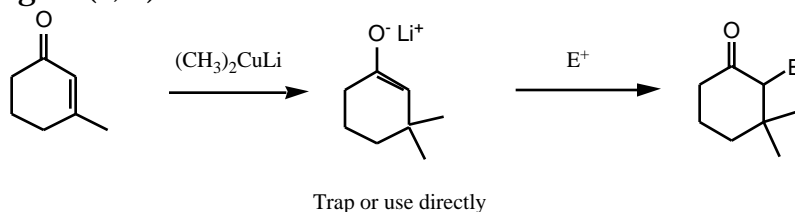


- tetraalkylammonium enolates- "naked" enolates
- TMS silyl enol ethers are labile: can also use Et_3Si -, iPr_3Si - etc.
- Silyl enol ether formation with $\text{R}_3\text{SiCl} + \text{Et}_3\text{N}$ gives thermodynamic silyl enol ether

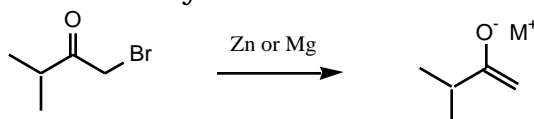
- From Enones



- From conjugate (1,4-) additions



- From reduction of -halo carbonyls



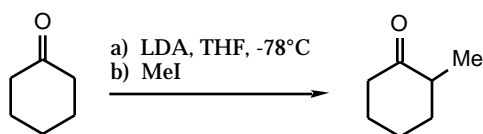
Alkylation of Enolates (condensation of enolates with alkyl halides and epoxides)

Comprehensive Organic Synthesis **1991**, vol. **3**, **1**.

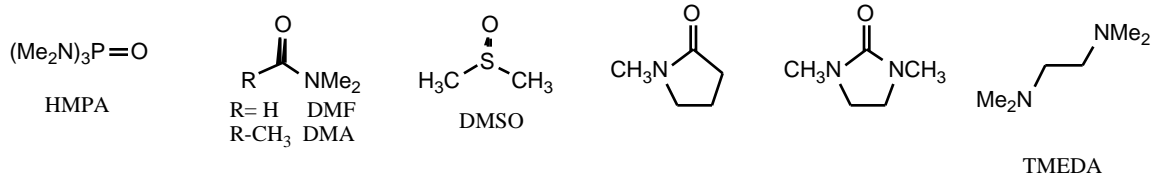
1° alkyl halides, allylic and benzylic halides work well

2° alkyl halides can be troublesome

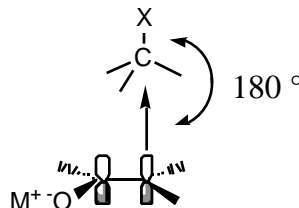
3° alkyl halides don't work



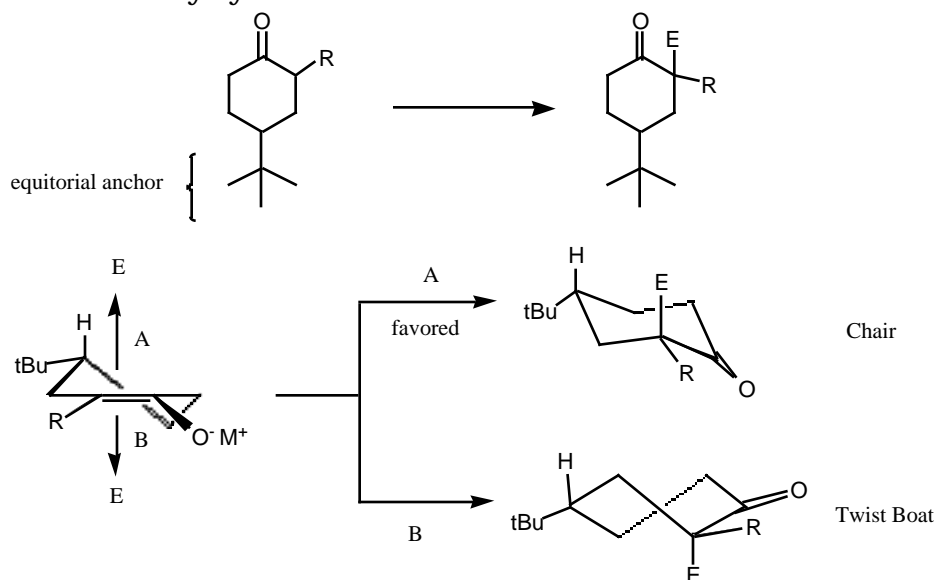
- Rate of alkylation is increased in more polar solvents (or addition of additive)



Mechanism of Enolate Alkylation: $\text{S}_{\text{N}}2$ reaction, inversion of electrophile stereochemistry

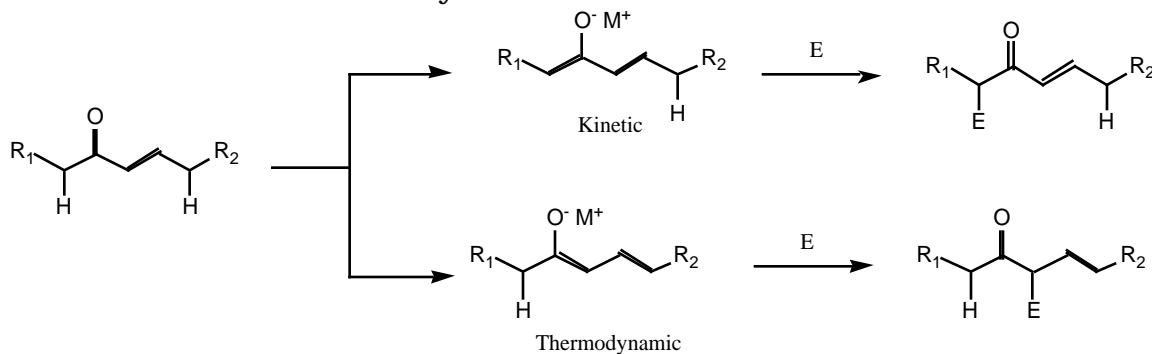


Alkylation of 4-t-butylcyclohexanone:

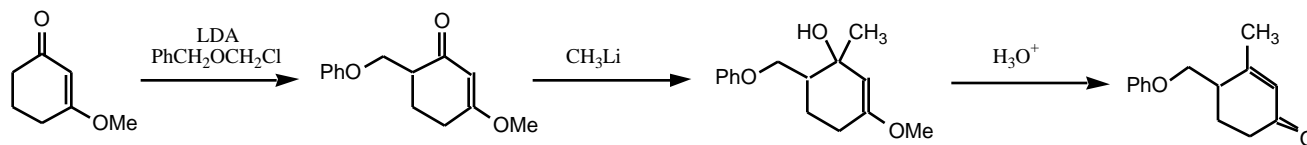


on cyclohexanone enolates, the electrophile approaches from an "axial" trajectory. This approach leads directly into a chair-like product. "Equitorial approach leads to a higher energy twist-boat conformation.

Alkylation of α,β -unsaturated carbonyls



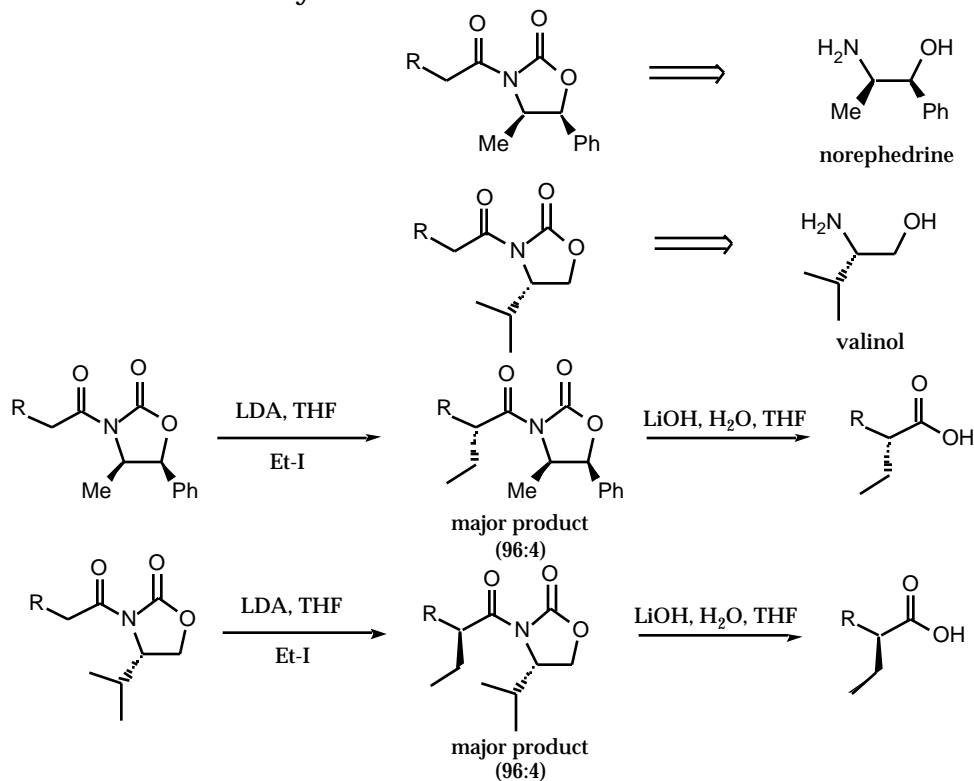
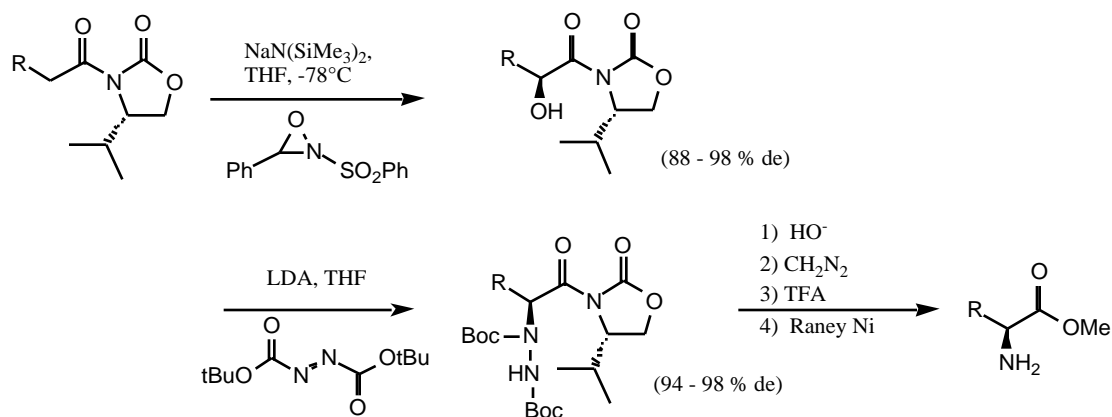
Stork-Danheiser Enone Transposition:

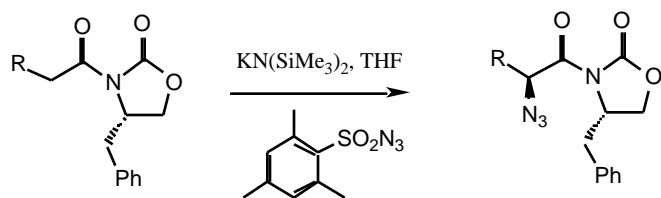
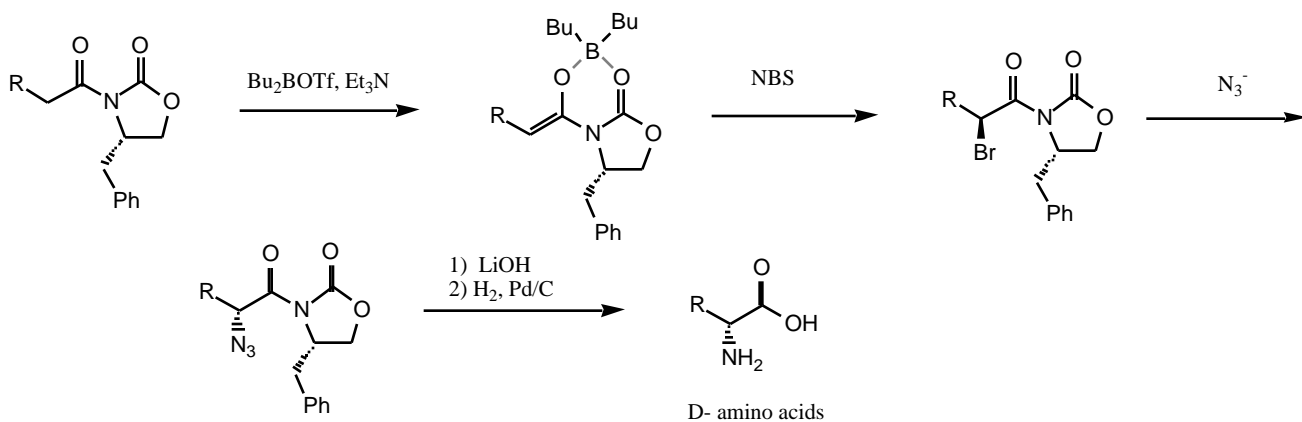
- overall α -alkylation of an α,β -unsaturated ketone*J. Org. Chem.* **1995**, *60*, 7837.

Chiral enolates- Chiral auxiliaries.

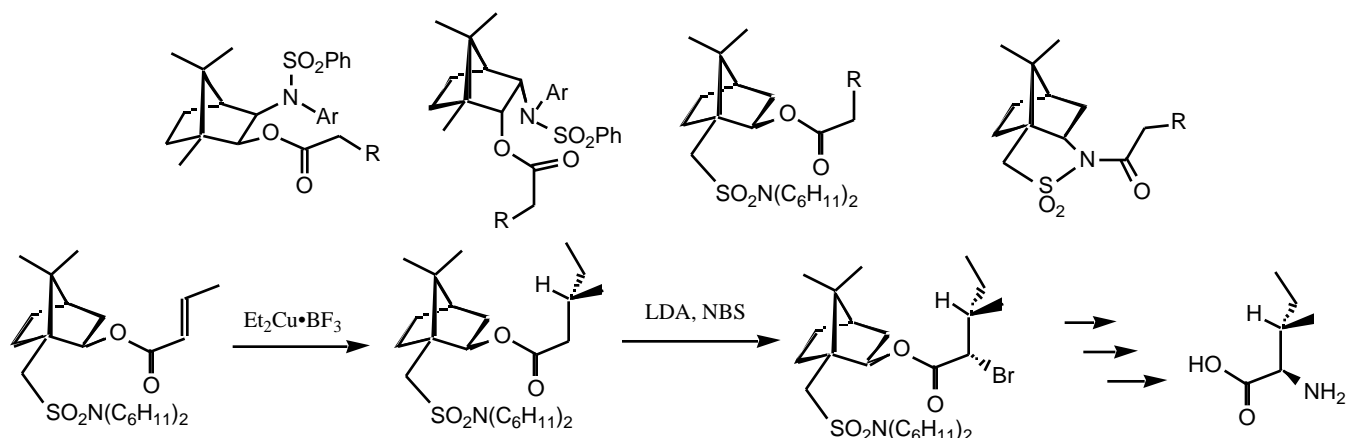
D.A. Evans *JACS* **1982**, *104*, 1737; *Aldrichimica Acta* **1982**, *15*, 23.Asymmetric Synthesis **1984**, *3*, 1.

- N-Acyl oxazolidinones

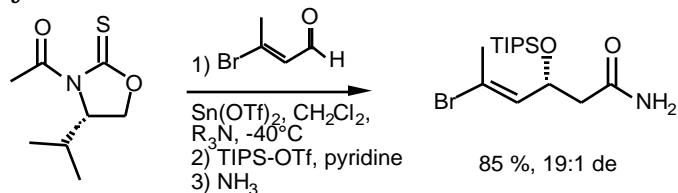
Complimentary Methods
for enantiospecific alkylationsDiastereoselectivity: 92 - 98 %
for most alkyl halidesEnolate Oxidation *Chem. Rev.* **1992**, *92*, 919.



Oppolzer Camphor based auxiliaries *Tetrahedron*, **1987**, 43, 1969.
 diastereoselectivities on the order of 50 : 1

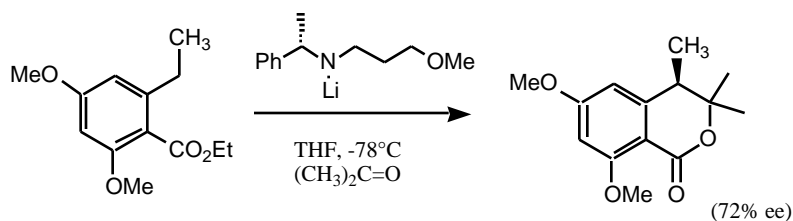


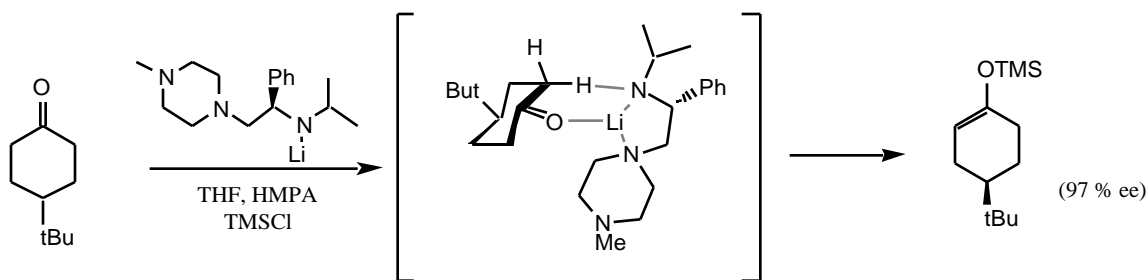
Asymmetric Acetate Aldol



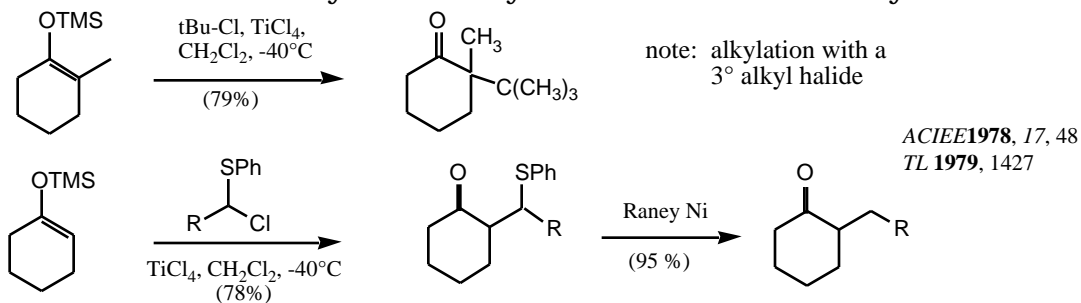
J. Am. Chem. Soc. **1998**, 120, 591
J. Org. Chem. **1986**, 51, 2391

Chiral lithium amide bases





Lewis Acid Mediated Alkylation of Silyl Enolethers- SN1 like alkylations

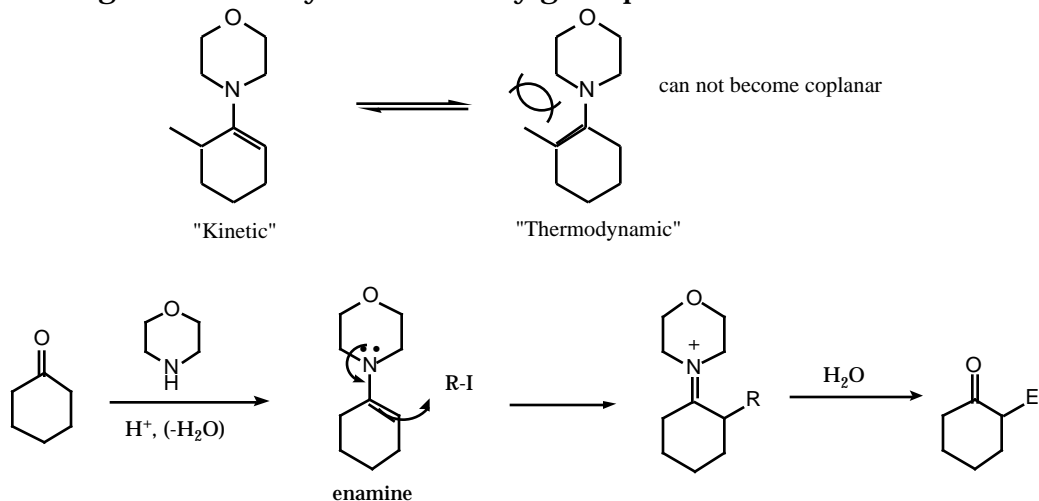


Enamines

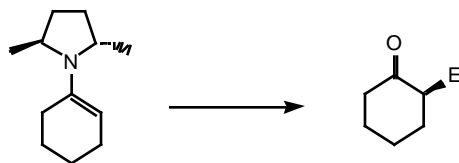
Gilbert Stork

Tetrahedron **1982**, 38, 1975, 3363.

- Advantages: mono-alkylation, usually gives product from kinetic enolization

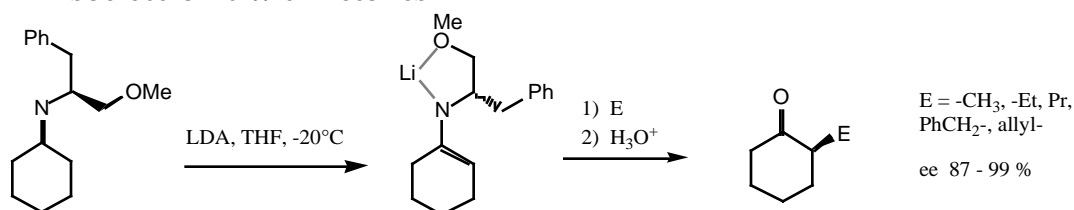


-Chiral enamines

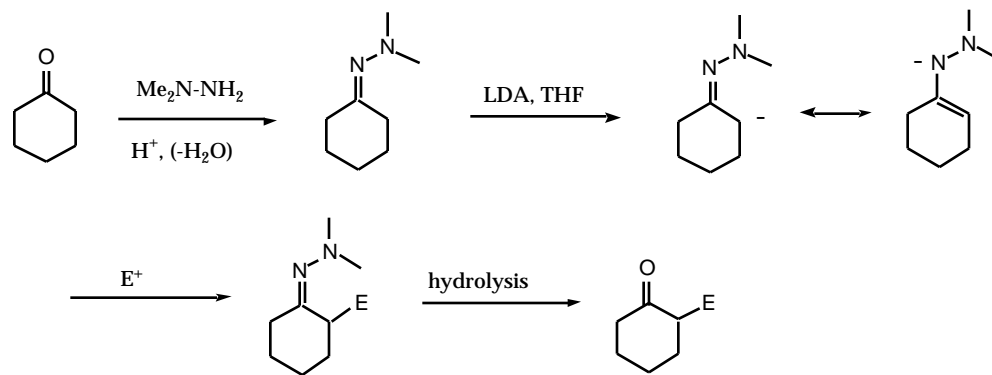


Imines

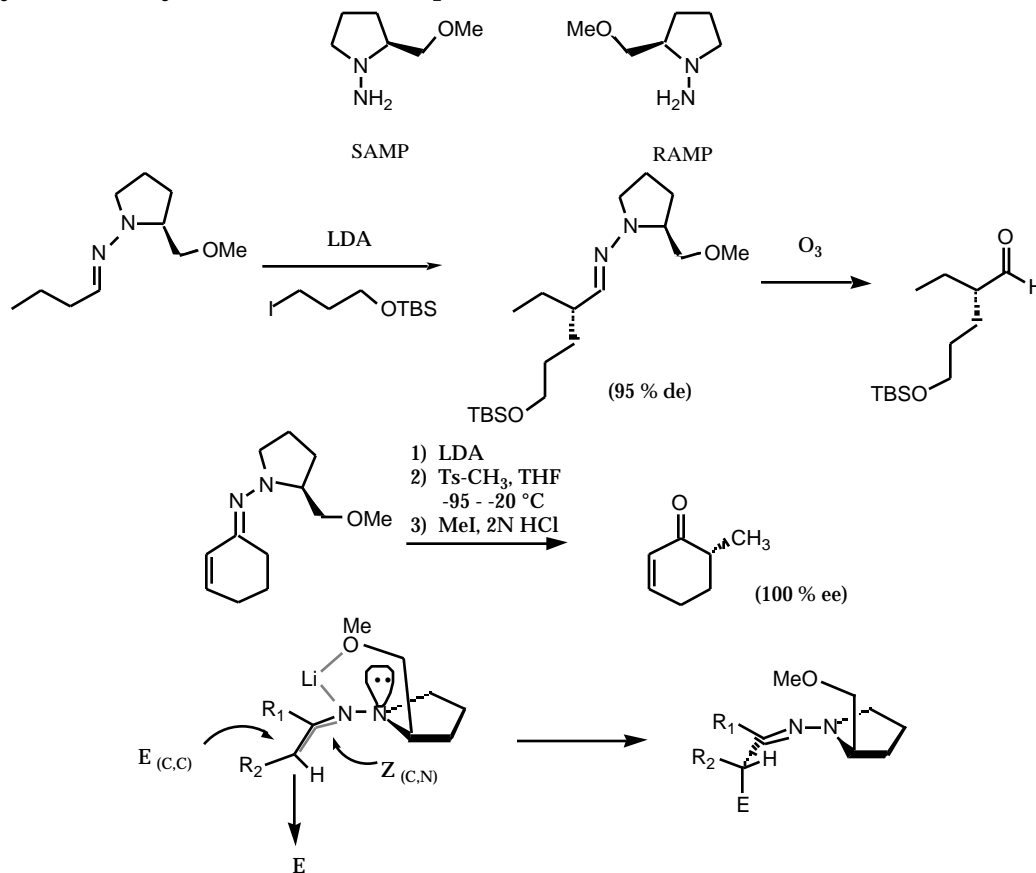
Isoelectronic with ketones



Hydrazones isoelectronic with ketones *Comprehensive Organic Synthesis* **1991**, 2, 503

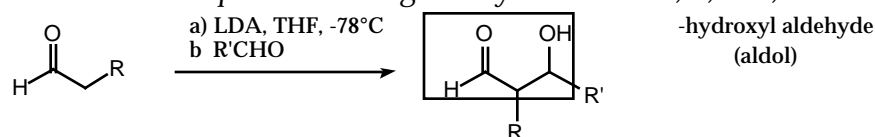


- Hydrazone anions are more reactive than the corresponding ketone or aldehyde enolate.
- Drawback: can be difficult to hydrolyze.
- Chiral hydrazones for asymmetric alkylations (RAMP/SAMP hydrazones- D. Enders "Asymmetric Synthesis" vol 3, chapt 4, Academic Press; **1983**)



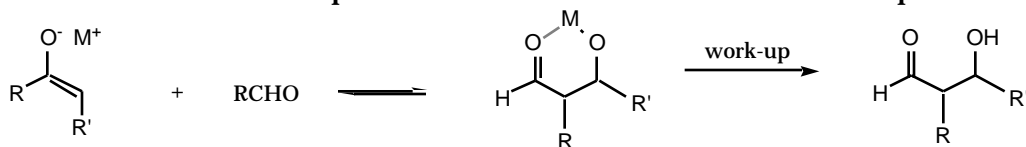
Aldol Condensation

Comprehensive Organic Synthesis **1991**, 2, 133, 181.

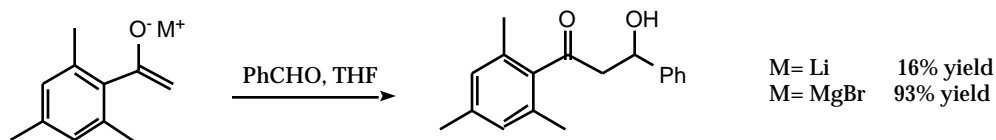


- The effects of the counterion on the reactivity of the enolates can be important
 Reactivity $\text{Li}^+ < \text{Na}^+ < \text{K}^+ < \text{R}_4\text{N}^+$ addition of crown ethers

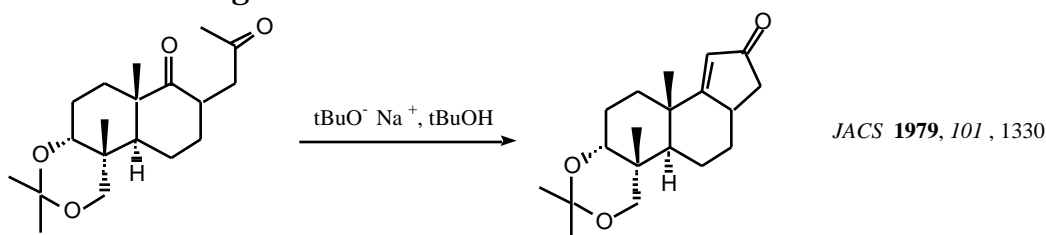
- The aldol reaction is an equilibrium which can be "driven" to completion.



In the case of hindered enolates, the equilibrium favors reactants. Mg^{2+} and Zn^{2+} counterions will stabilize the intermediate α -alkoxycarbonyl and push the equilibrium towards products. (*JACS* **1973**, 95, 3310)

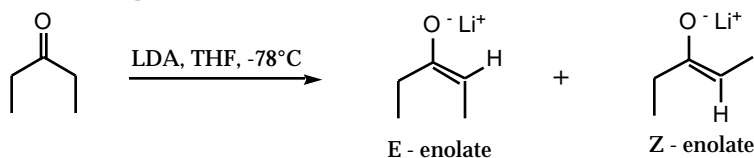


- Dehydration of the intermediate α -alkoxy- or α -hydroxy ketone can also serve to drive the reaction to the right.

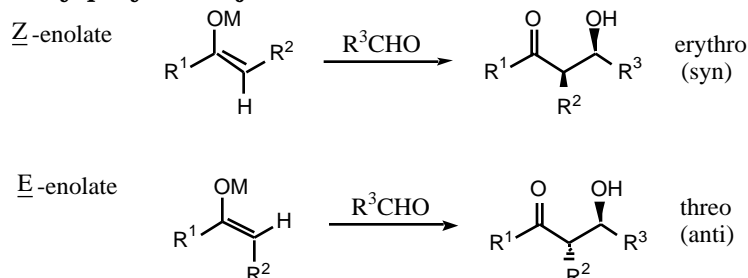


Enolate Geometry

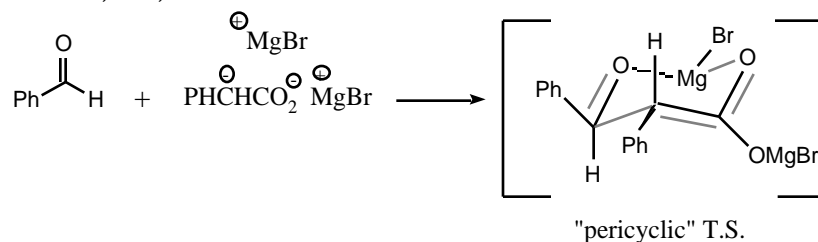
- two possible enolate geometries



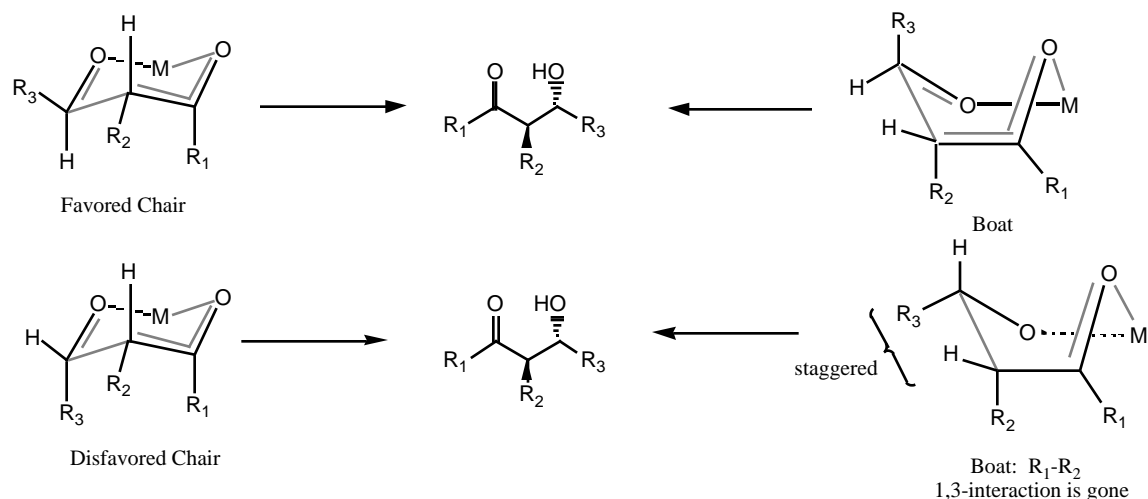
- enolate geometry plays a major role in stereoselection.



- Zimmerman-Traxler Transition State : Ivanov condensation
JACS **1957**, 79, 1920.

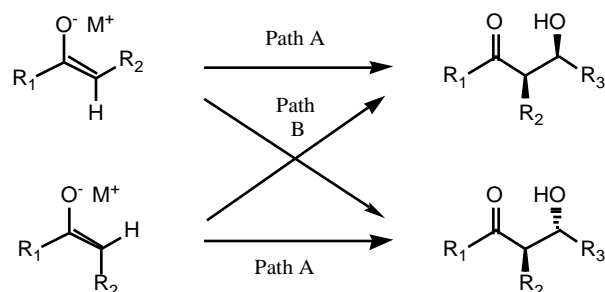


Analysis of Boat Transition State for E-Enolates



Summary of Aldol Transition State Analysis:

1. Enolate geometry (E- or Z-) is an important stereochemical aspect. Z-Enolates usually give a higher degree of stereoselection than E-enolates.
2. Li^+ , Mg^{2+} , Al^{3+} enolates give comparable levels of diastereoselection for kinetic aldol reactions.
3. Steric influences of enolate substituents (R_1 & R_2) play a dominant role in kinetic diastereoselection.



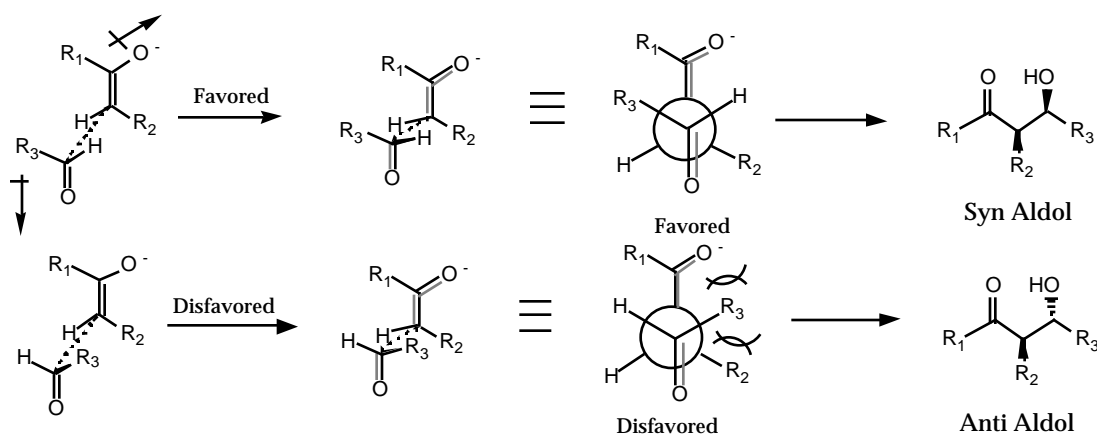
When R_1 is the dominant steric influence, then path A proceeds. If R_2 is the dominant steric influence then path B proceeds.

4. The Zimmerman-Traxler like transition state model can involve either a chair or boat geometry.

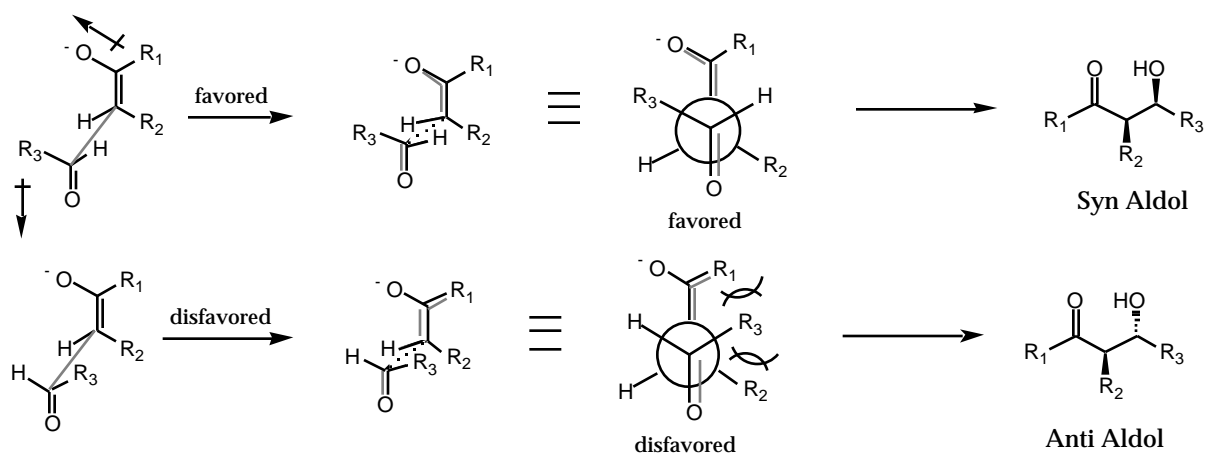
Noyori "Open" Transition State for non-Chelation Control Aldols

Absence of a binding counterion. Typical counter ions: R_4N^+ , K^+ /18-C-6, Cp_2Zr^{2+}
 - Non-chelation aldol reactions proceed via an "open" transition state to give syn aldols regardless of enolate geometry.

Z- Enolates:

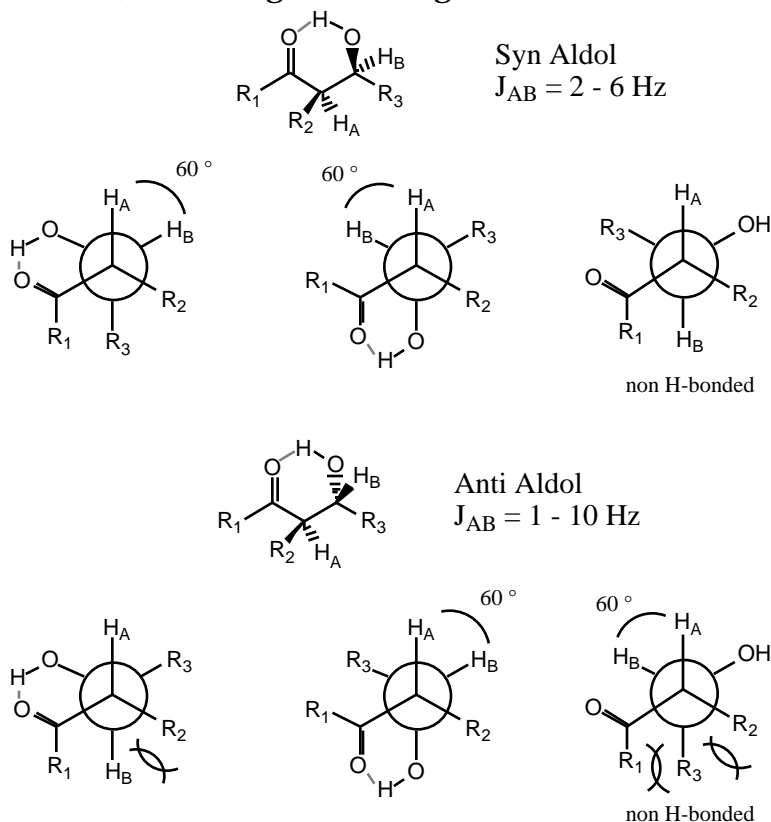


E- Enolate:



NMR Stereochemical Assignment.

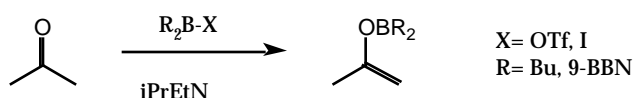
Coupling constants (*J*) are a weighted average of various conformations.

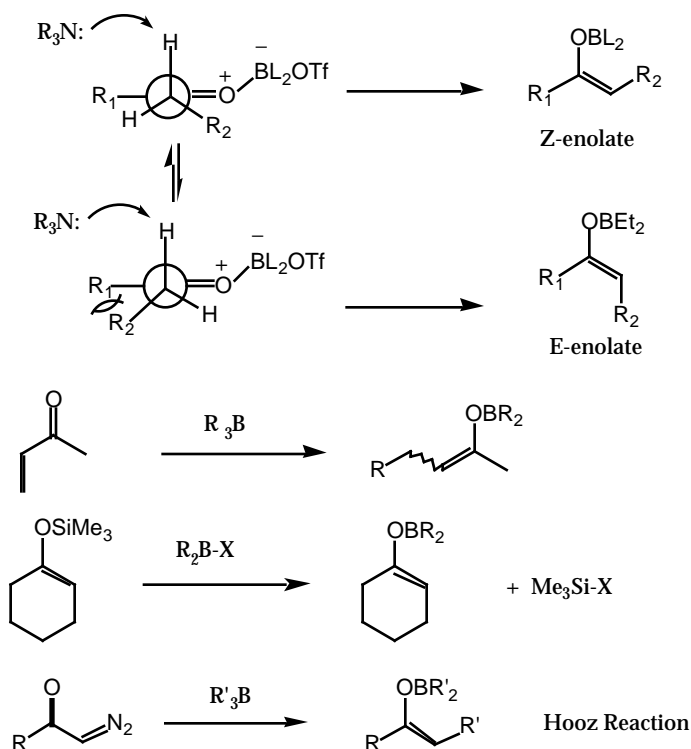


Boron Enolates: *Comprehensive Organic Synthesis* **1991**, 2, 239. *Organic Reactions* **1995**, 46, 1; *Organic Reactions* **1997**, 51, 1. *OPPI* **1994**, 26, 3.

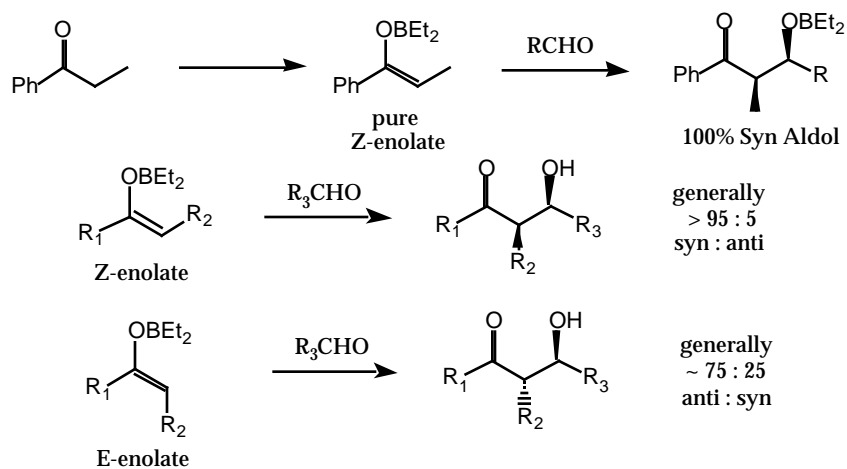
- Alkali & alkaline earth metal enolates tend to be aggregates- complicates stereoselection models.
- Boron enolates are monomeric and homogeneous
- B-O and B-C bonds are shorter and stronger than the corresponding Li-O and Li-C bonds (more covalent character)- therefore tighter more organized transition state.

Generation of Boron Enolates:





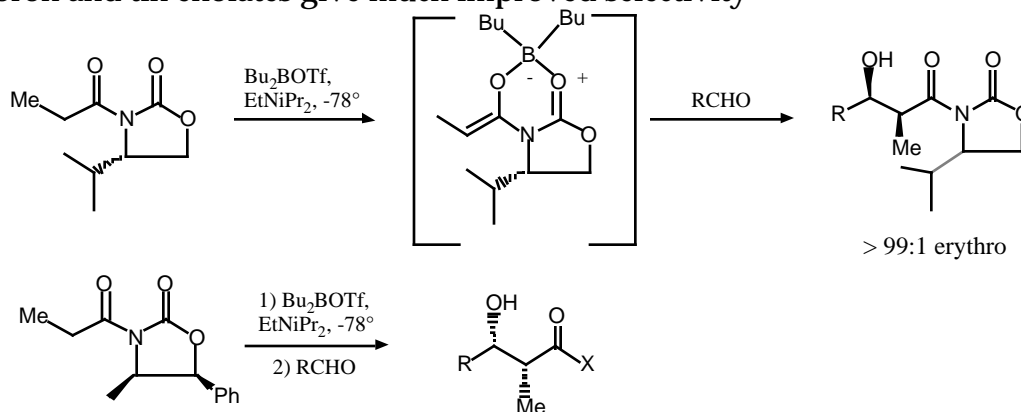
Diastereoselective Aldol Condensation with Boron Enolates

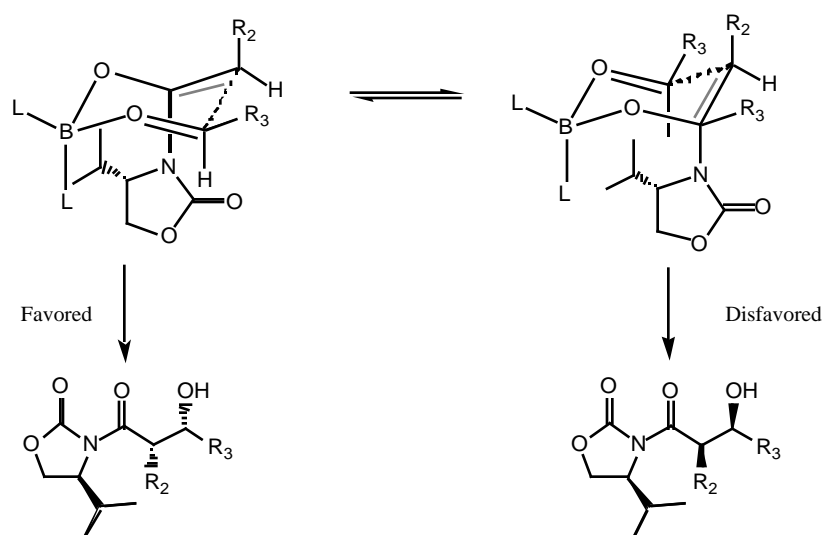
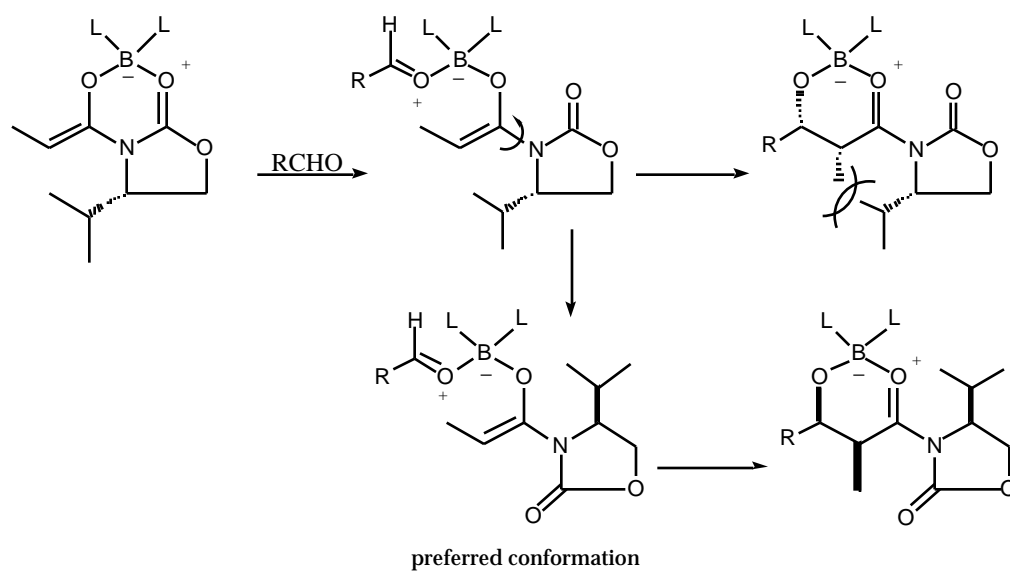


Asymmetric Aldol Condansations with Chiral Auxiliaries-

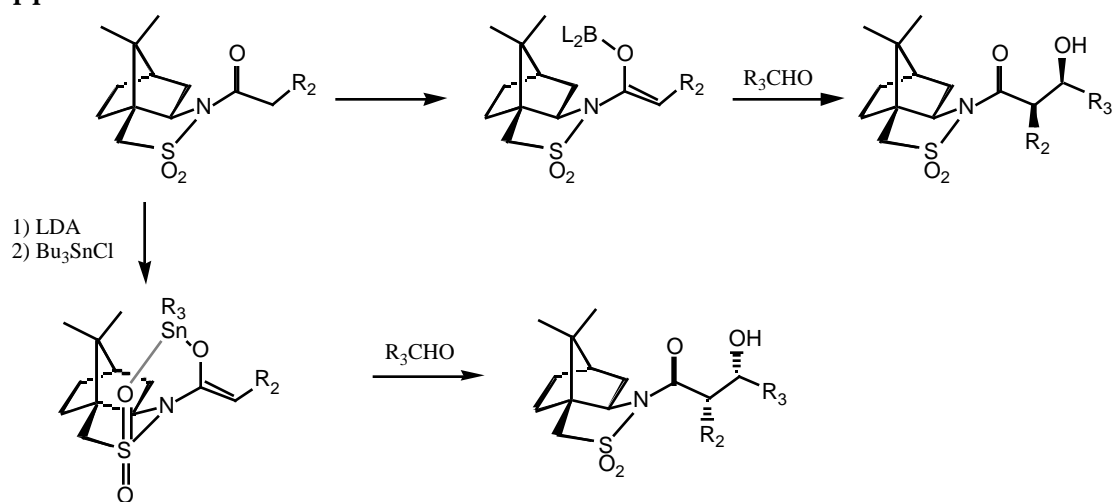
D.A. Evans et al. *Topics in Stereochemistry*, **1982**, 13, 1-115.

- Li^+ enolates give poor selectivity (1:1)
- Boron and tin enolates give much improved selectivity

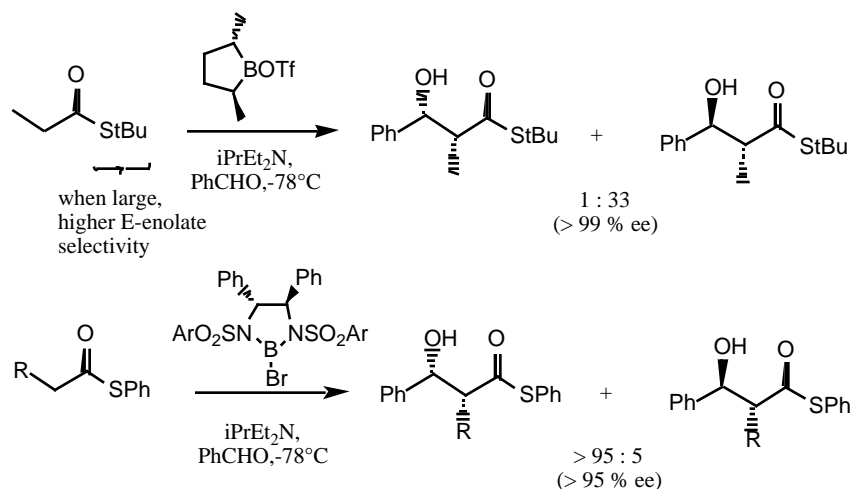




Oppolzer Sultam



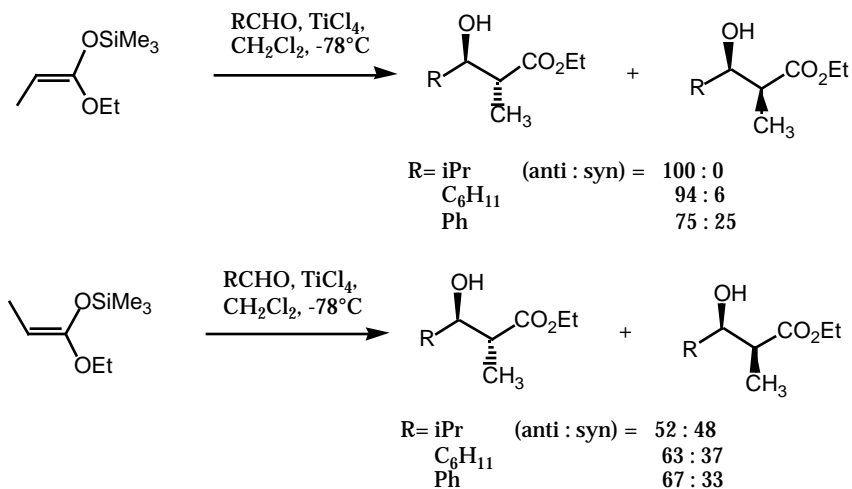
Chiral Boron



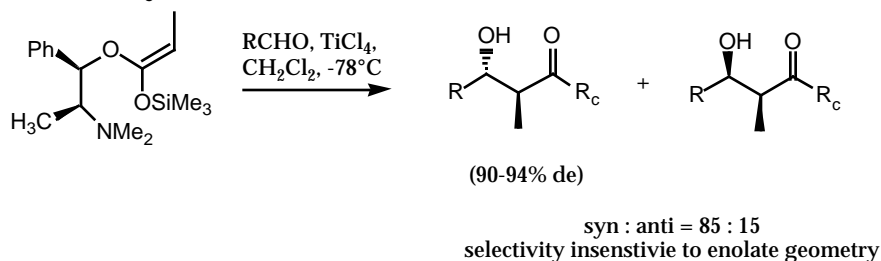
- In general, syn aldol products are achievable with high selectivity, anti aldols are more difficult

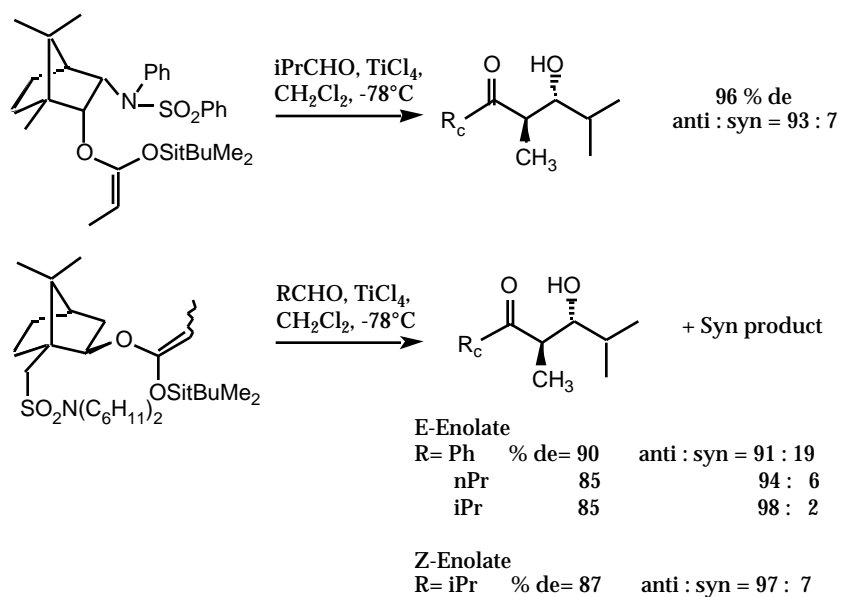
Mukaiyama-Aldol- Silyl Enol Ethers as an enolate precursors.

Lewis acid promoted condensation of silyl ketene acetals (ester enolate equiv.) with aldehydes: proceeds via "open" transition state to give anti aldols starting from either E- or Z- enolates.

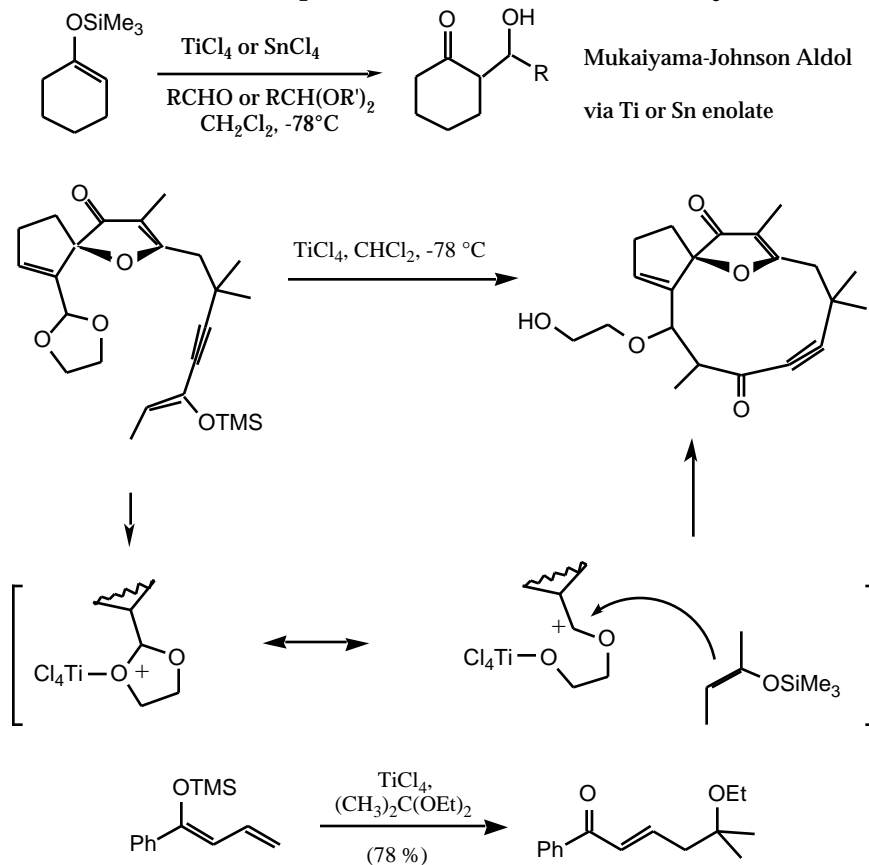


Asymmetric Mukaiyama Aldol:



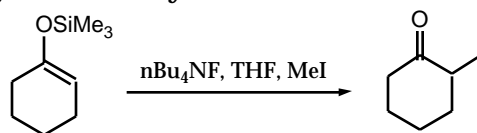


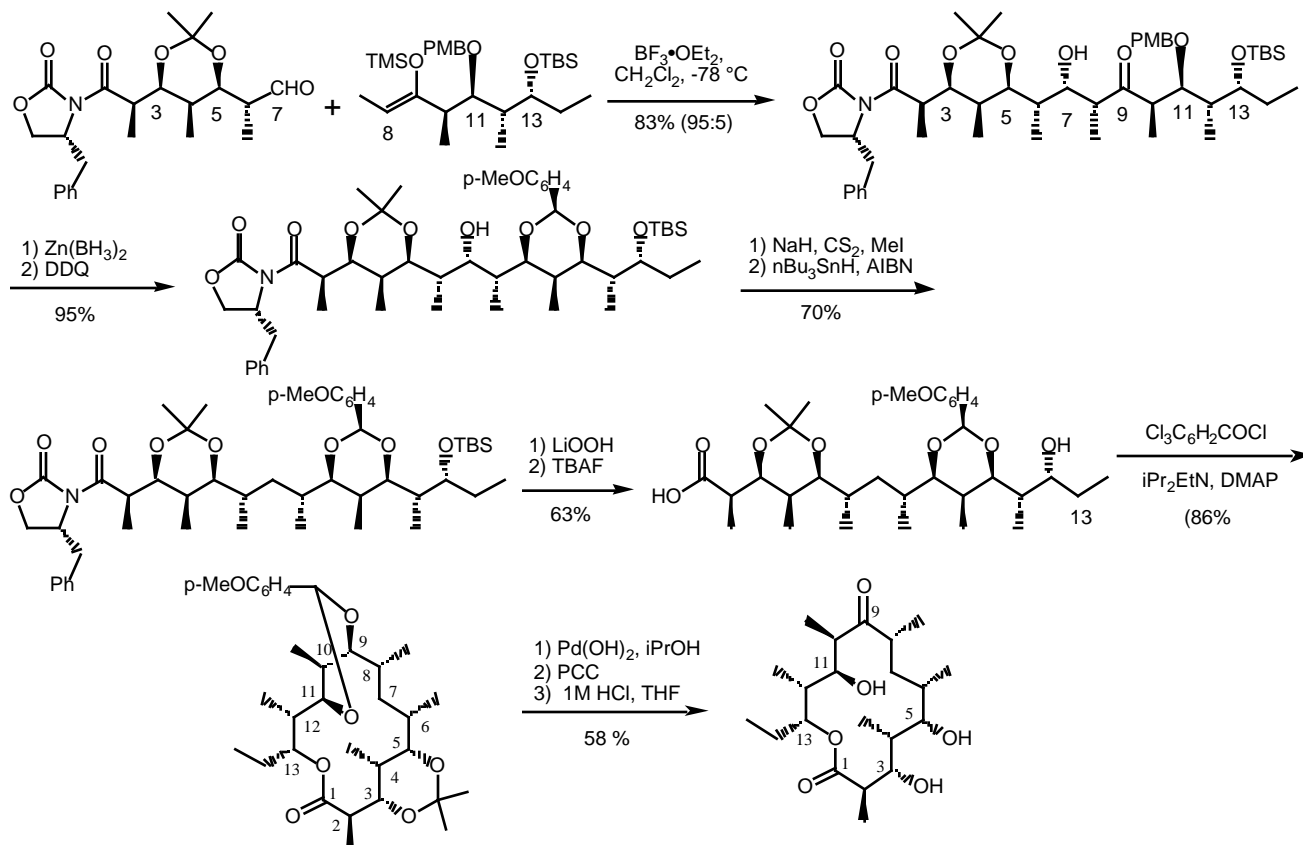
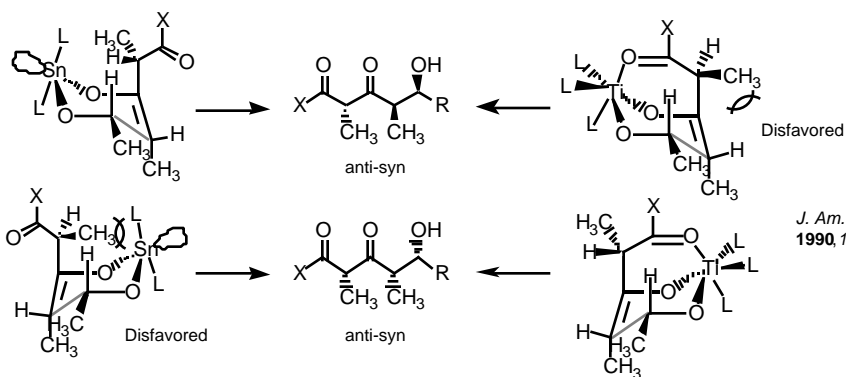
Mukaiyama-Johnson Aldol- Lewis acid promoted condensation of silyl enol ethers with acetals:



Fluoride promoted alkylation of silyl enol ethers

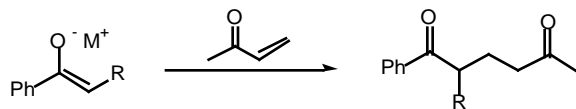
Acc. Chem. Res. **1985**, *18*, 181





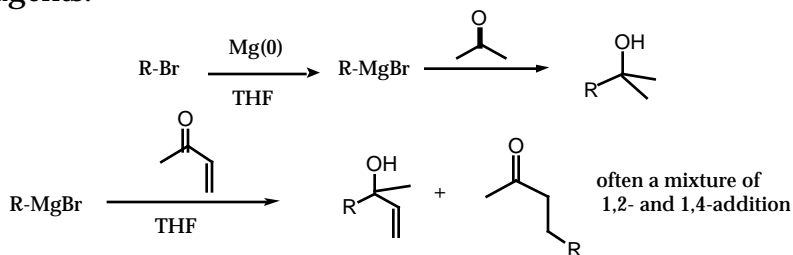
Michael Addition

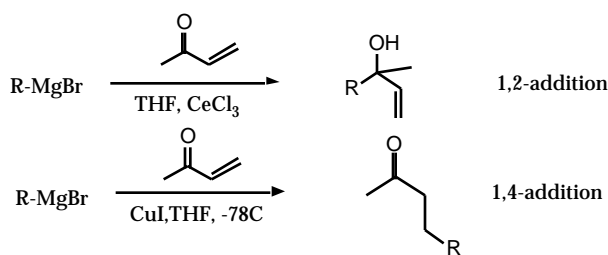
- 1,4-addition of an enolate to an α,β -unsaturated carbonyl to give 1,5-dicarbonyl compounds



Organometallic Reagents

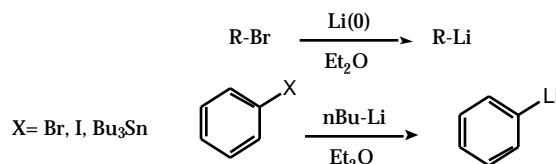
Grignard reagents:





Organolithium reagents

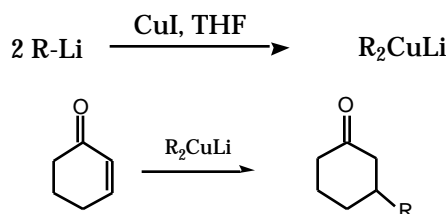
- usually gives 1,2-addition products
- alkyllithium are prepared from lithium metal and the corresponding alkyl halide
- vinyl or aryl- lithium are prepared by metal-halogen exchange from the corresponding vinyl or aryl- halide or trialkyl tin with n-butyl, sec-butyl or t-butyl lithium.



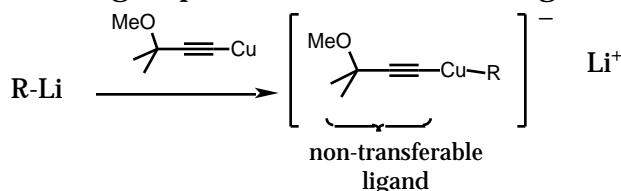
Organocuprates

Reviews: *Synthesis* **1972**, 63; *Tetrahedron* **1984**, 40, 641; *Organic Reactions* **1972**, 19, 1.

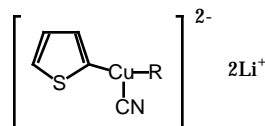
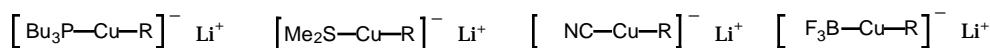
- selective 1,4-addition to α,β -unsaturated carbonyls



- cuprate "wastes" one R group- use non transferable ligand



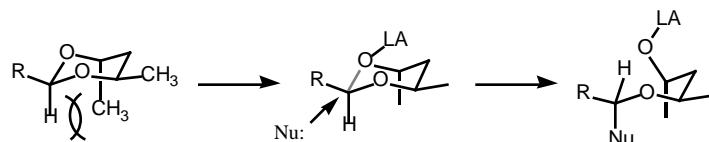
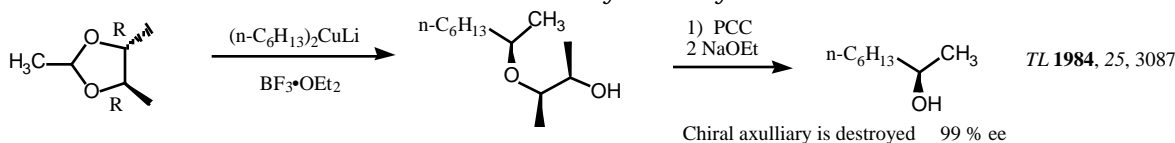
Other non transferable ligands

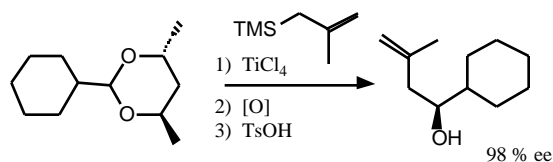


Mixed Higher Order Cuprate
B. Lipshutz *Tetrahedron* **1984**, 40, 5005
Synthesis **1987**, 325.

Addition to Acetals

Tetrahedron Asymmetry **1990**, 1, 477.

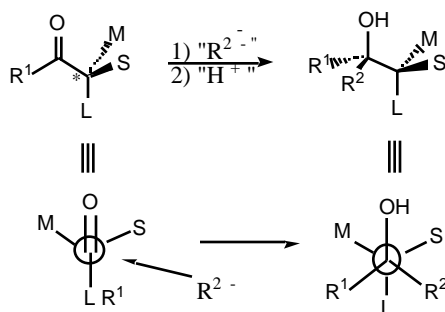




Stereoselective Addition to Aldehydes

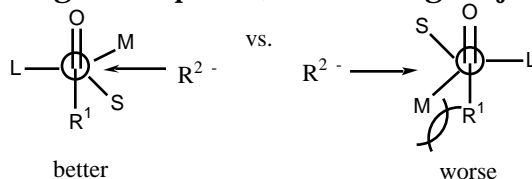
- Aldehydes are "prochiral", thus addition of an organometallic reagent to an aldehydes may be stereoselective.

- Cram's Rule JACS **1952**, *74*, 2748; JACS **1959**, *84*, 5828.
empirical rule



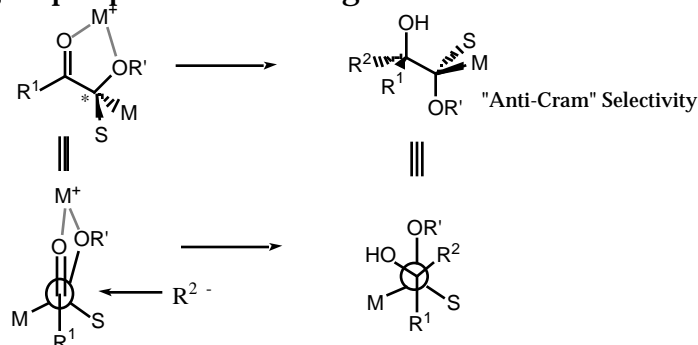
- Felkin-Ahn TL **1968**, 2199; *Nouv. J. Chim.* **1977**, *1*, 61.

based on *ab initio* calculations of preferred geometry of aldehyde which considers the trajectory of the incoming nucleophile (Dunitz-Burgi trajectory).



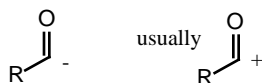
- Chelation Control Model- "Anti-Cram" selectivity

- When L is a group capable of chelating a counterion such as alkoxide groups



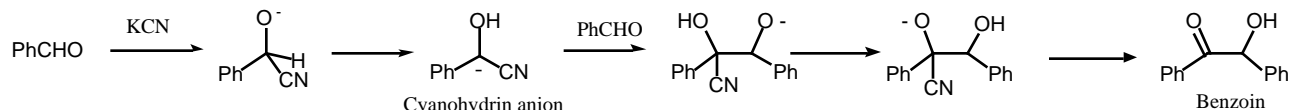
Umpolung - reversal of polarity Aldrichimica Acta **1981**, *14*, 73; ACIE **1979**, *18*, 239.

i.e: acyl anion equivalents are carbonyl nucleophiles (carbonyls are usually electophilic)

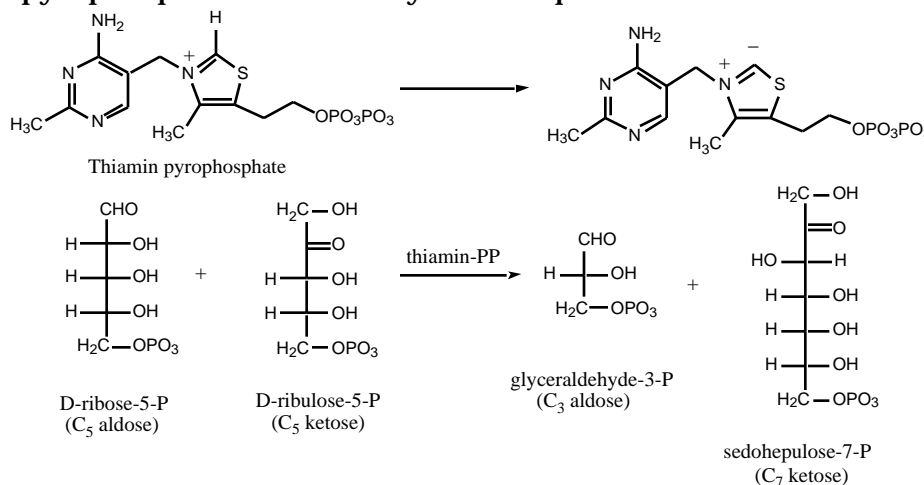


Benzoin Condensation

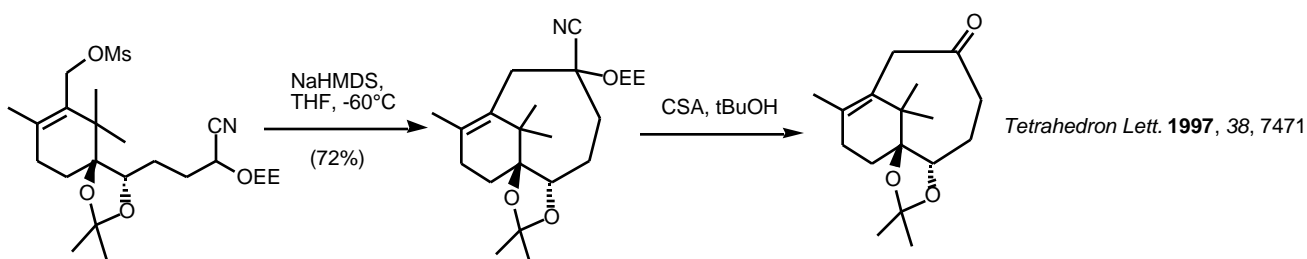
Comprehensive Organic Synthesis **1991**, *1*, 541.



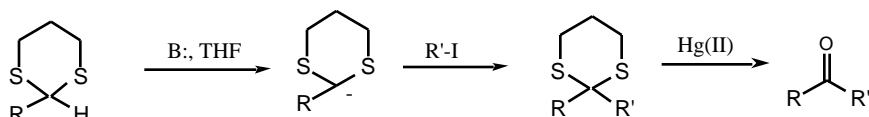
Thiamin pyrophosphate- nature's acyl anion equivalent for trans ketolization reactions



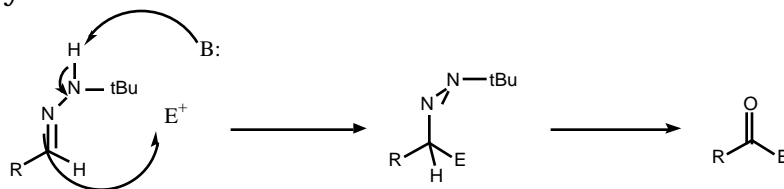
Trimethylsilylcyanohydrins



Dithianes



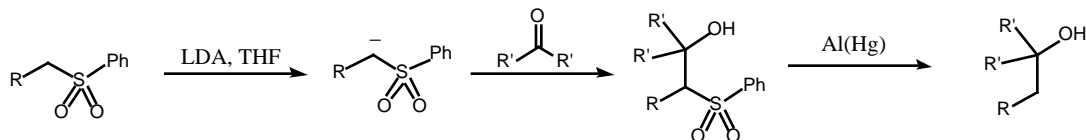
Aldehyde Hydrazones



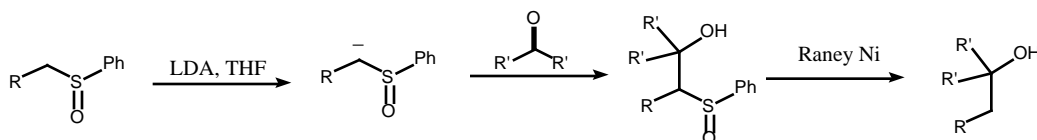
Heteroatom Stabilized Anions

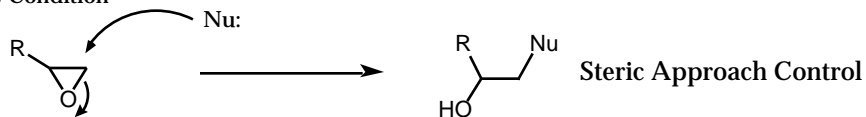
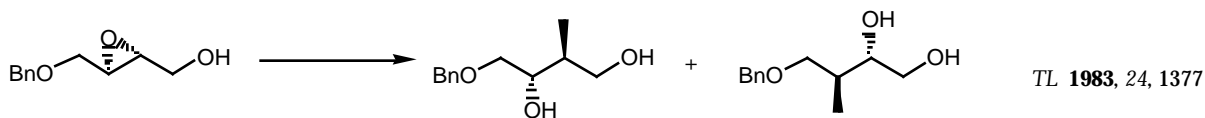
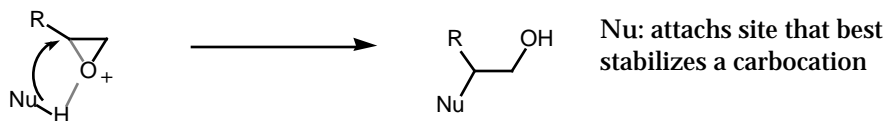
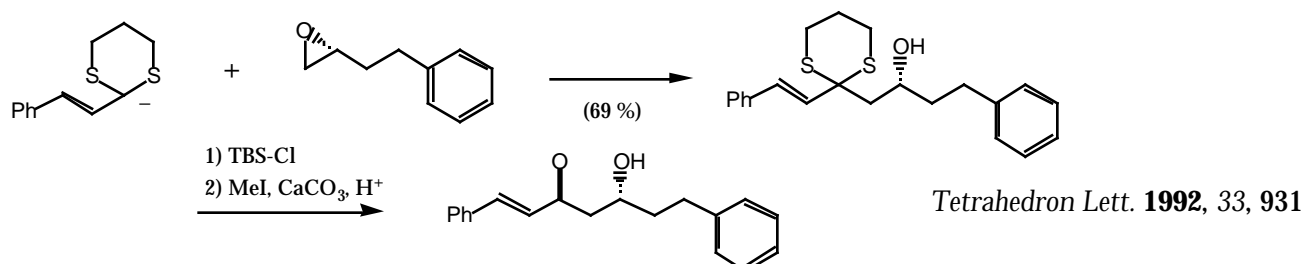
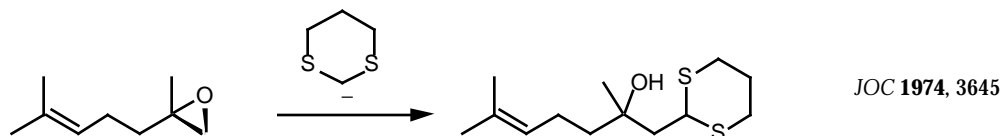
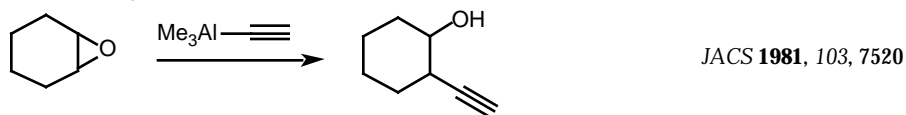
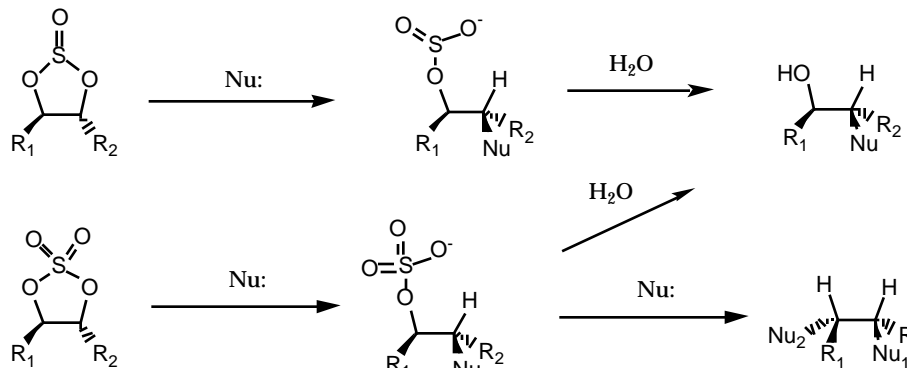
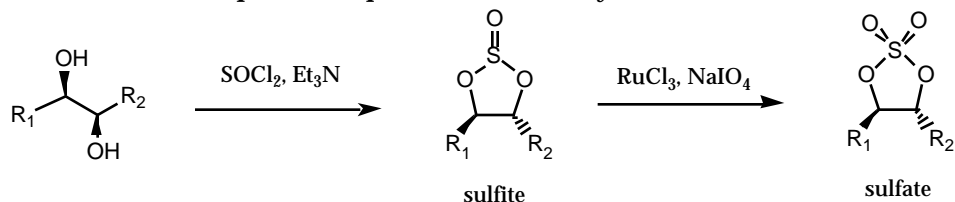
(Dithiane anion is an example)

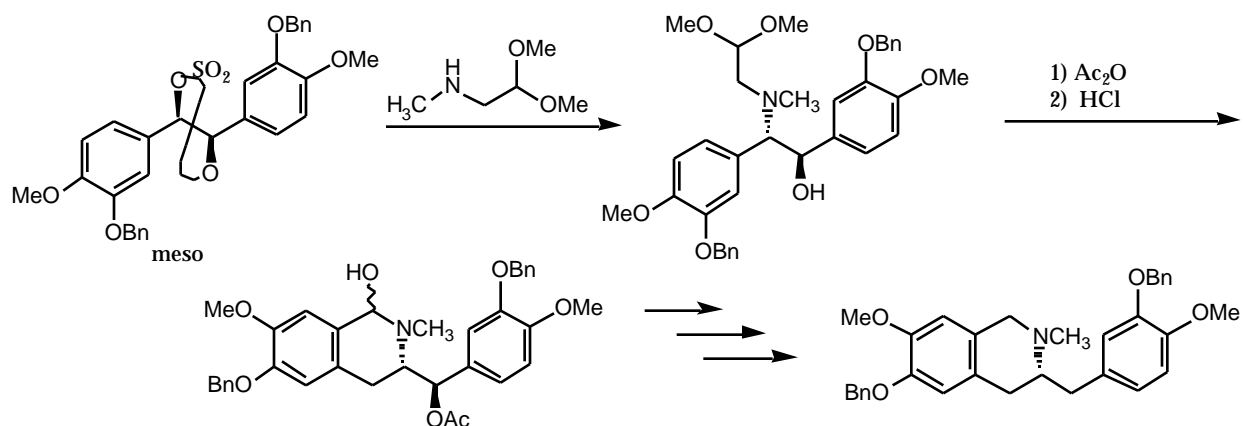
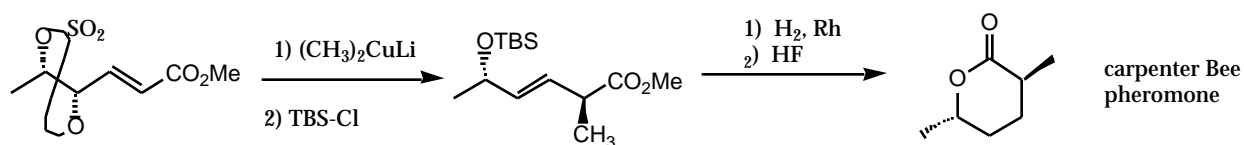
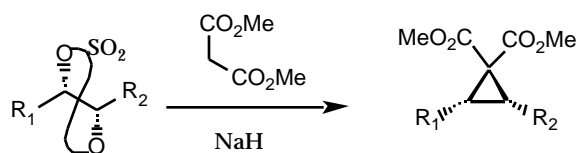
Sulfones



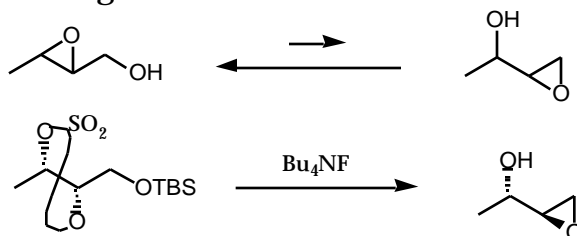
Sulfoxides



Epoxide Opening Asymmetric Synthesis **1984**, 5, 216.Basic (S_N2) ConditionAcid (S_N1-like) ConditionMe₂CuLi
AlMe₃Cyclic Sulfites and Sulfates (epoxide equivalents) Synthesis **1992**, 1035.



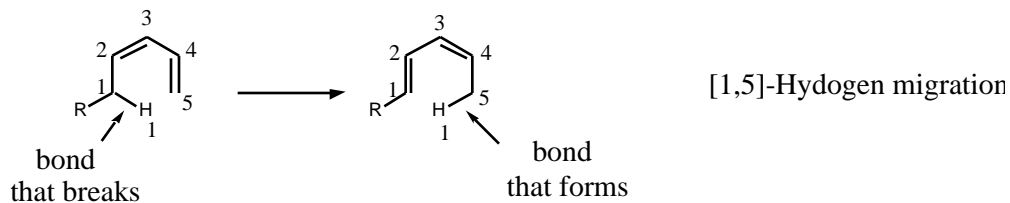
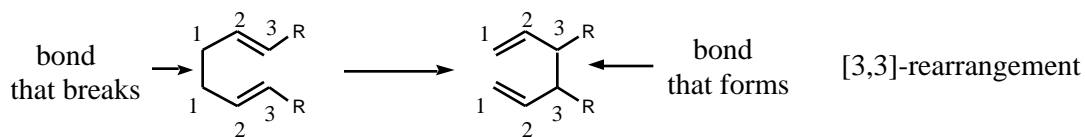
Irreversible Payne Rearrangement



Payne Rearrangement of 2,3-epoxyalcohols *Aldrichimica Acta* **1983**, 16, 60

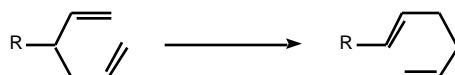
Sigmatropic Rearrangements Nomenclature:

Asymmetric Synthesis **1984**, 3, 503.

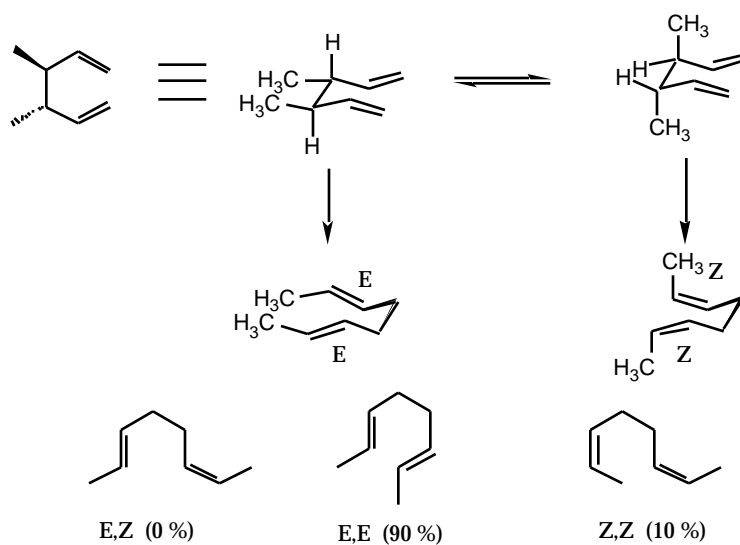
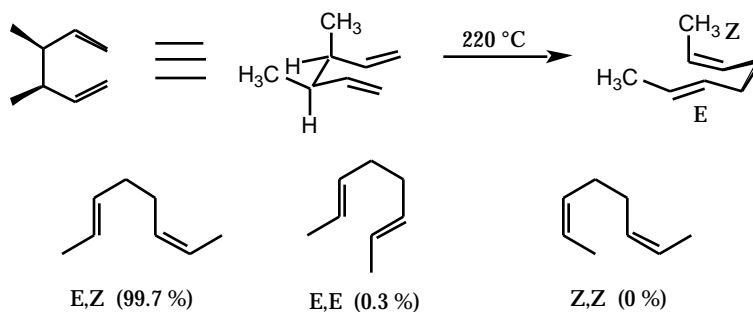


3,3-sigmatropic Rearrangements

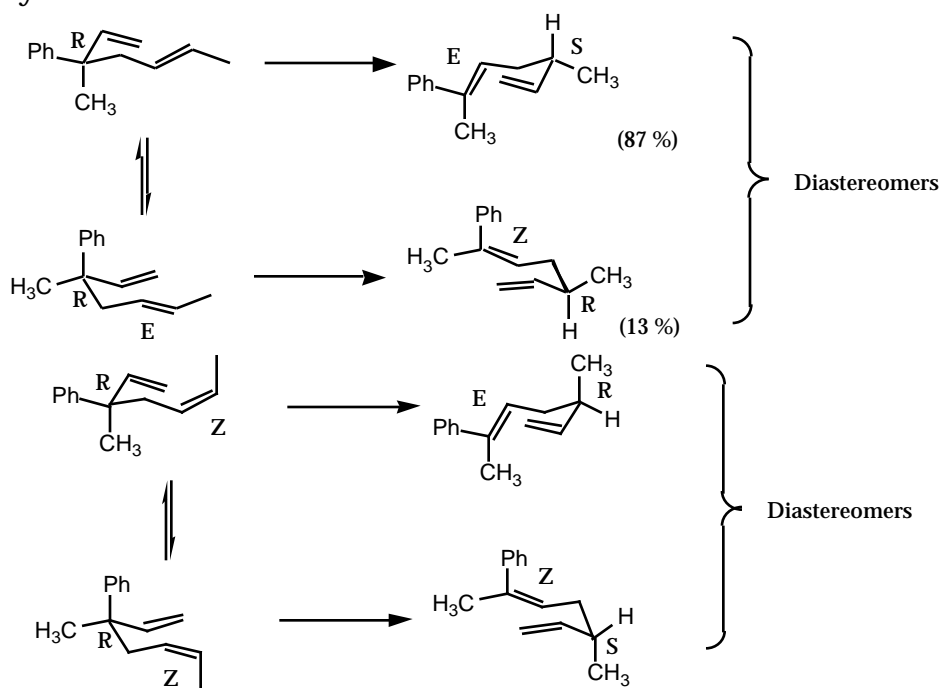
Cope Rearrangements- requires high temperatures *Organic Reaction* **1975**, 22, 1



Chair transition state:

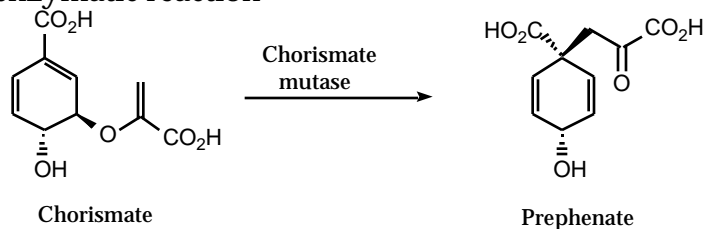


"Chirality Transfer"



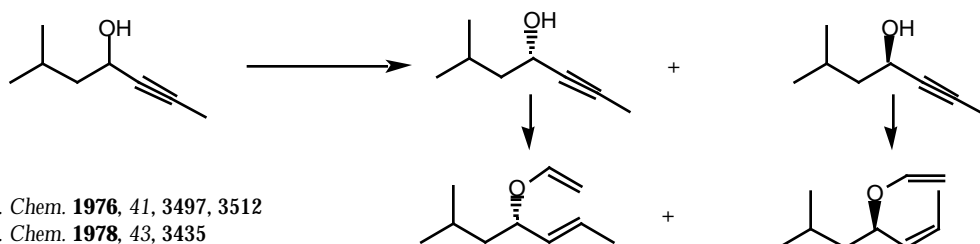
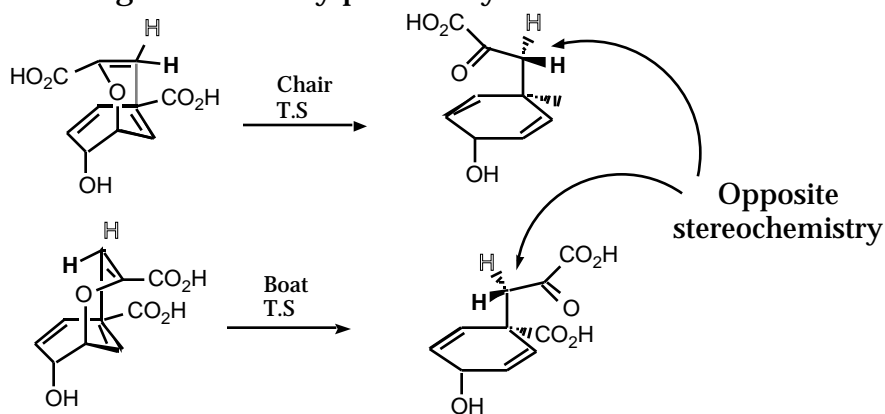
- anion accelerated (oxy-) Cope- proceeds under much milder conditions (lower temperature) *JACS* **1980**, 102, 774; *Tetrahedron* **1978**, 34, 1877; *Organic Reactions* **1993**, 43, 93; *Comprehensive Organic Synthesis* **1991**, 5, 795. *Tetrahedron* **1997**, 53, 13971.

- Chorismate Mutase catalyzed Claisen Rearrangement- 10^5 rate enhancement over non-enzymatic reaction

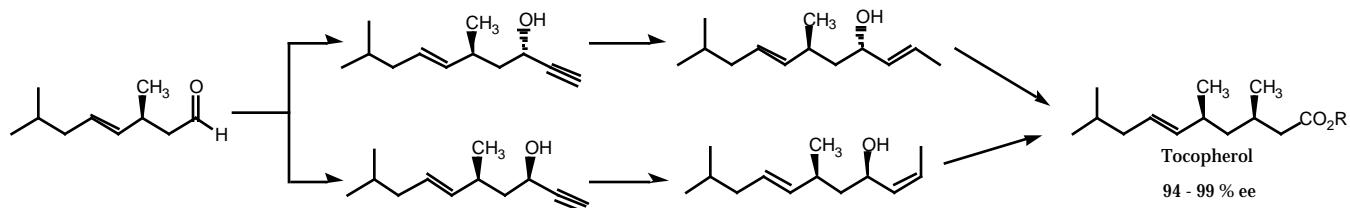
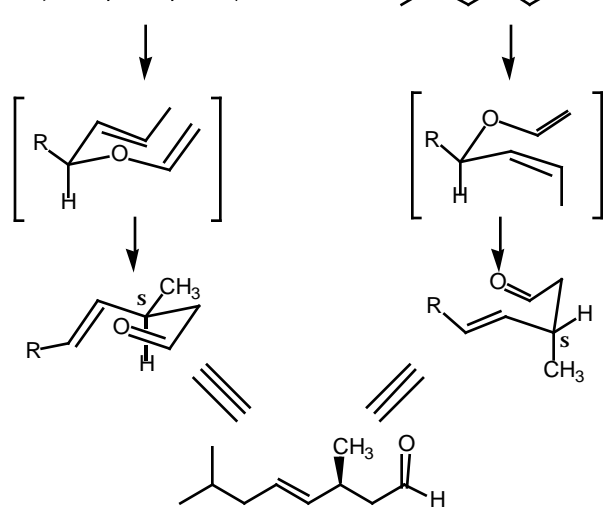


J. Knowles
JACS **1987**, 109, 5008, 5013

- Claisen rearrangement usually proceed by a chair-like T.S.

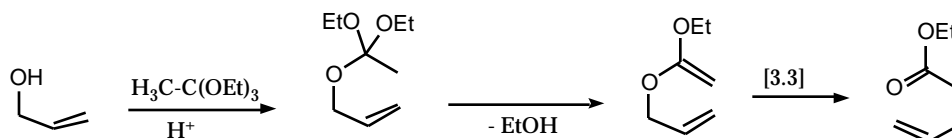


J. Org. Chem. **1976**, 41, 3497, 3512
J. Org. Chem. **1978**, 43, 3435

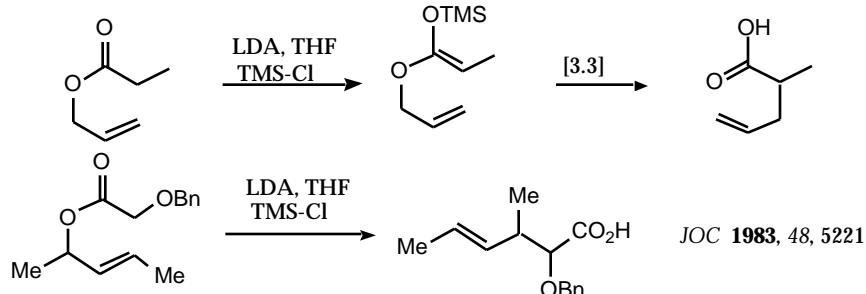


hydrophobically accelerated Claisen - JOC **1989**, 54, 5849

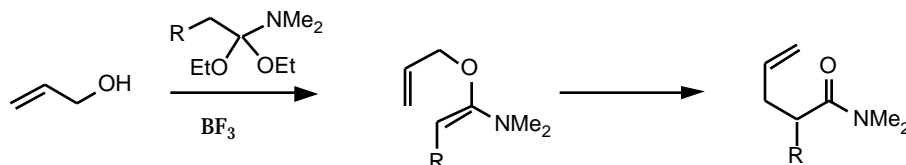
Johnson ortho-ester Claisen:



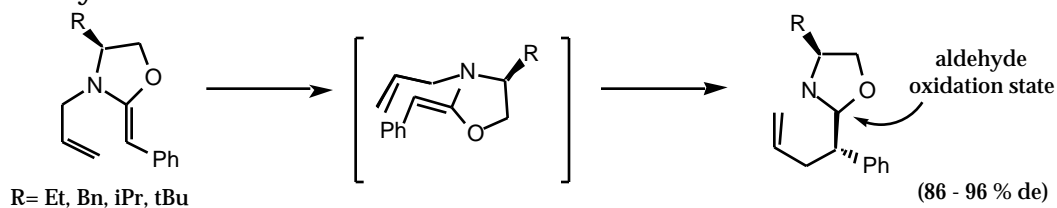
Ireland ester-enolate Claisen.

Aldrichimica Acta **1993**, 26, 17.

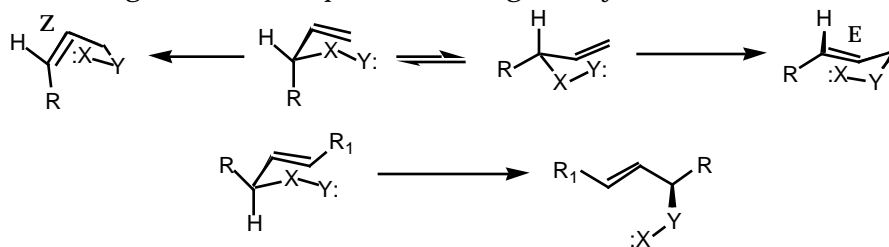
Eschenmoser



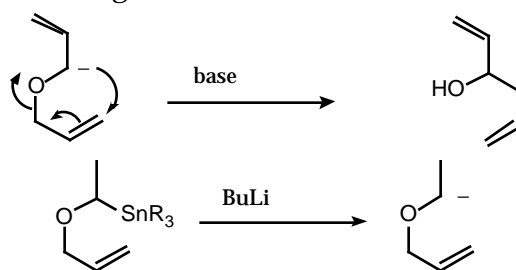
"Chirality Transfer"

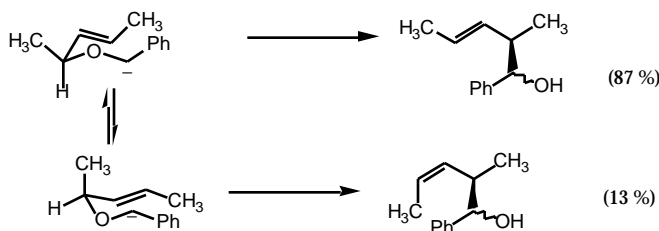
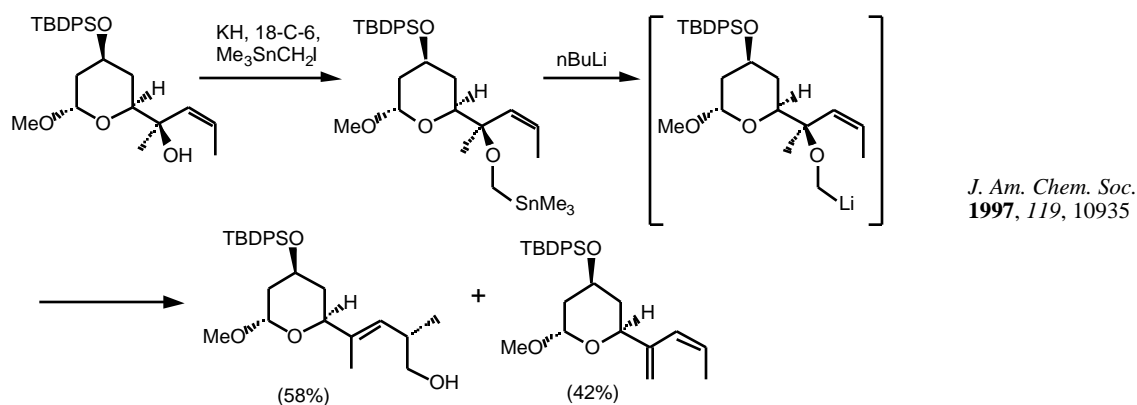


[2,3]-Sigmatropic Rearrangement

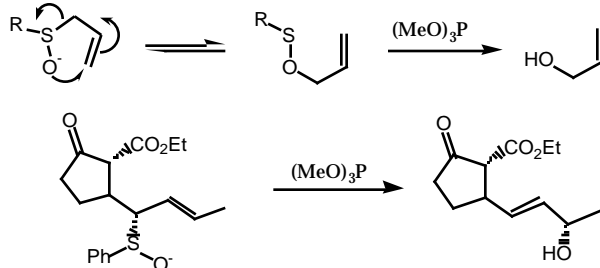
Comprehensive Organic Synthesis **1991**, 6, 873.

-Wittig Rearrangement

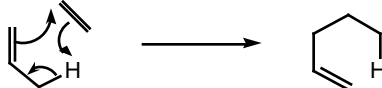
Organic Reactions **1995**, 46, 105Synthesis **1991**, 594.



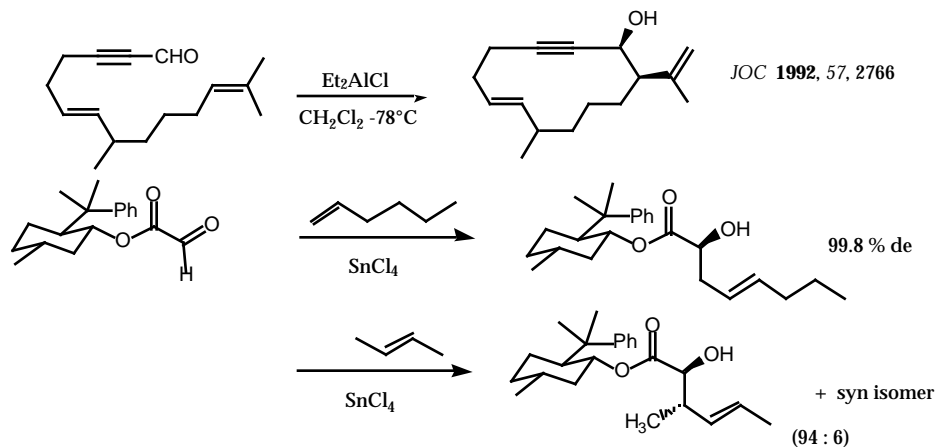
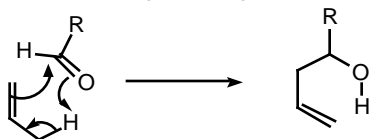
Sulfoxide Rearrangement

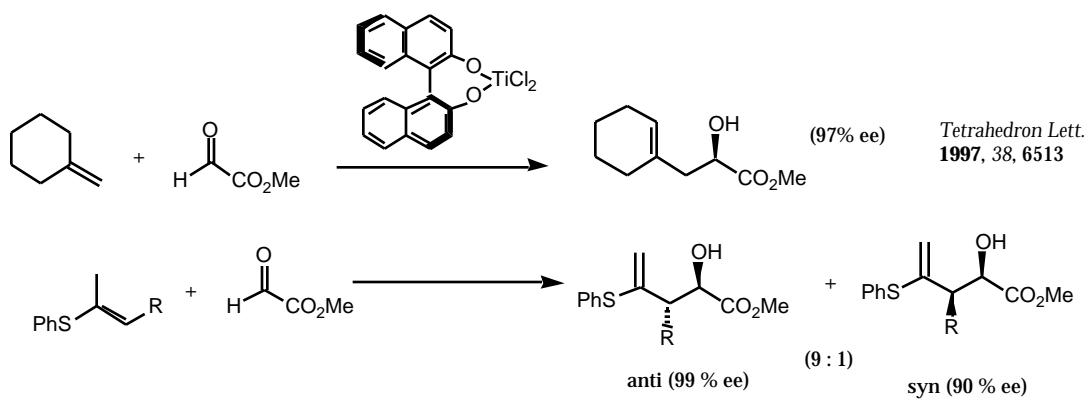


Ene Reaction *Comprehensive Organic Synthesis* **1991**, 5, 1; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 876; ; *Chem. Rev.* **1992**, 28, 1021.

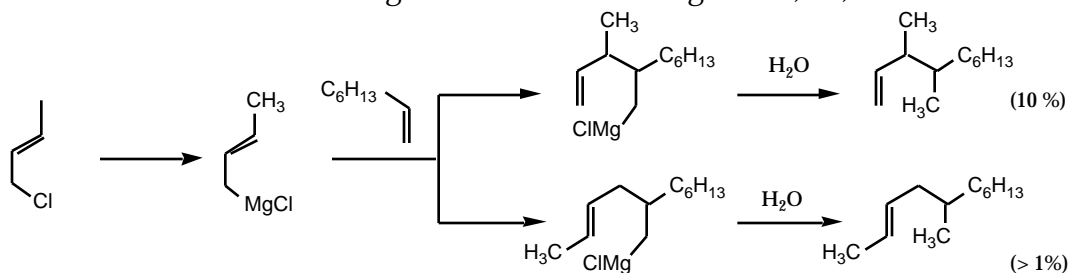


- Ene reaction with aldehydes is catalyzed by Lewis Acids (Et₂AlCl)

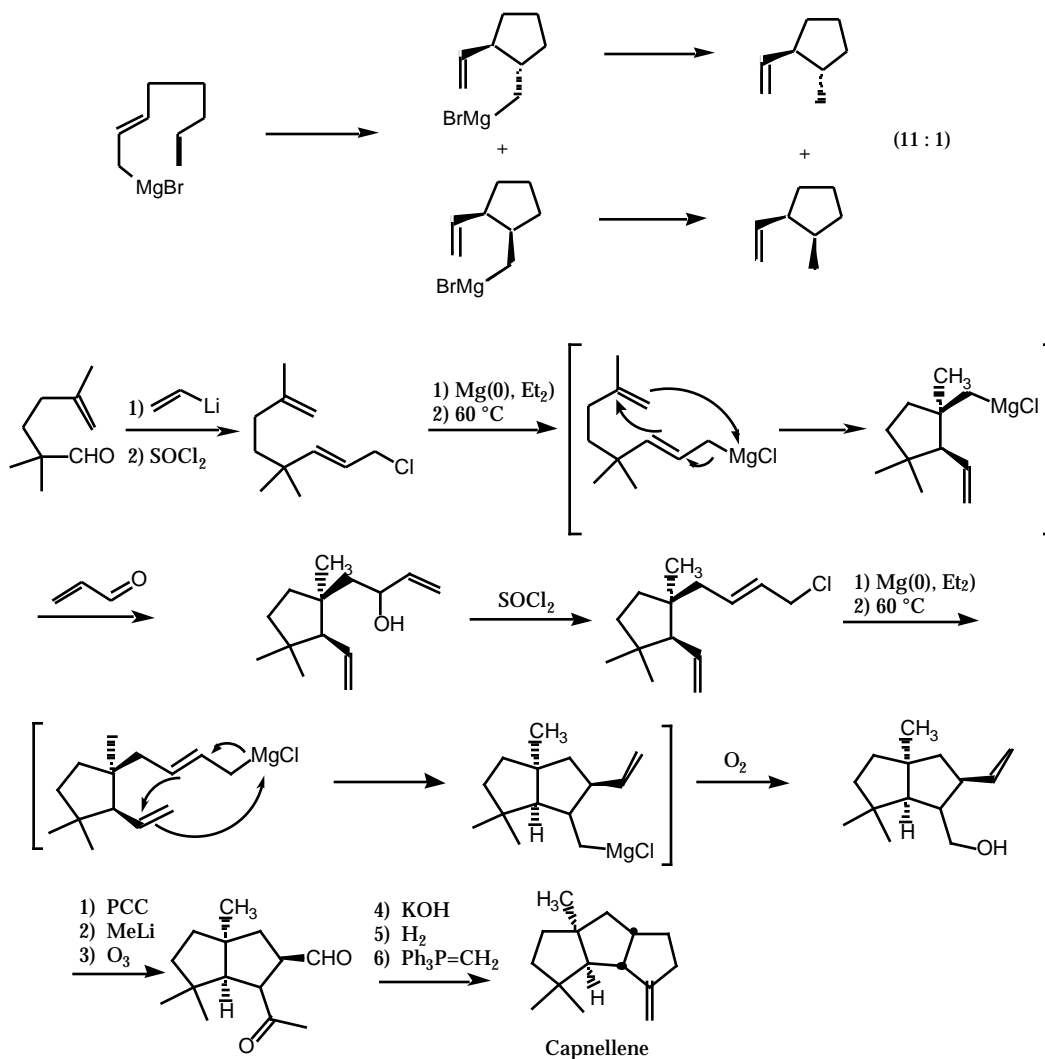




- Metallo-ene Reaction *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 38



intramolecular



Synthesis of Phyllanthocin

A. B. Smith et al. *J. Am. Chem. Soc.* **1987**, *109*, 1269.