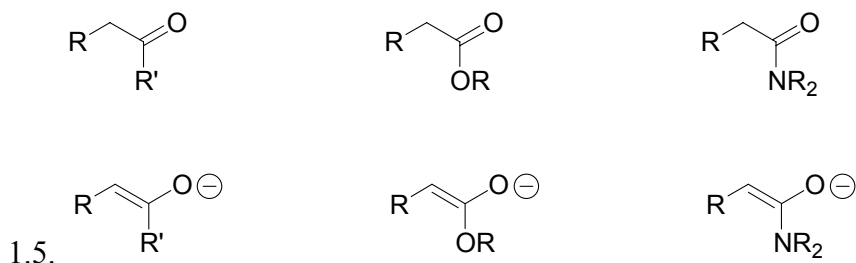
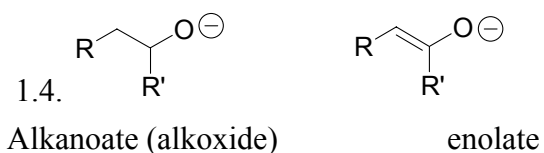
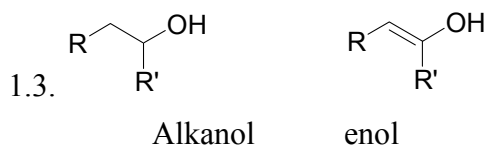


**Enolate Chemistry, alkylation, kinetic protonation, aldol reaction, and asymmetry!**

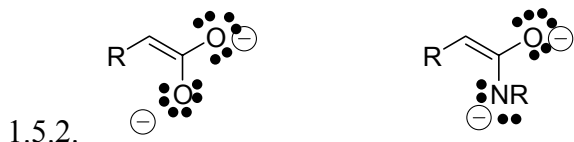
1. If there is a main protagonist in the epic of synthetic organic chemistry it has to be the enolate.

1.1. Enolates are starting points in many constructions of complex molecules.

1.2. As usual we have some terminology and principles with which to wrestle before we can appreciate the argument completely.



1.5.1. One can make enolates of ketones, esters and amides via deprotonation.



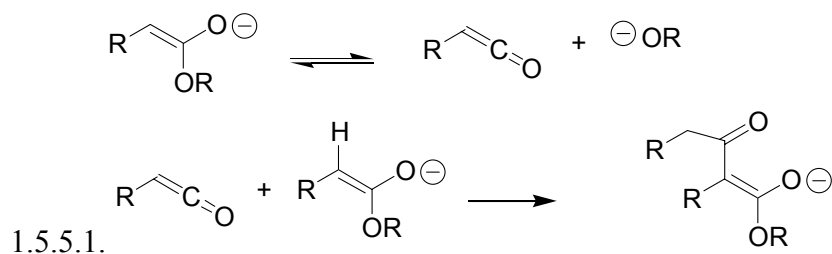
1.5.3. In the case carboxylic acids and secondary or primary amides the protic H always is abstracted first.

1.5.3.1. O and N atoms attached to H *in general* are more kinetically and more thermodynamically labile than H attached to C.

**1.5.4. Enolates of aldehydes tend to be unstable. They tend to self condense.**

1.5.4.1. Don't propose using the enolate of an aldehyde without sound literature precedent.

1.5.5. Ester enolates are also unstable above room temperature.

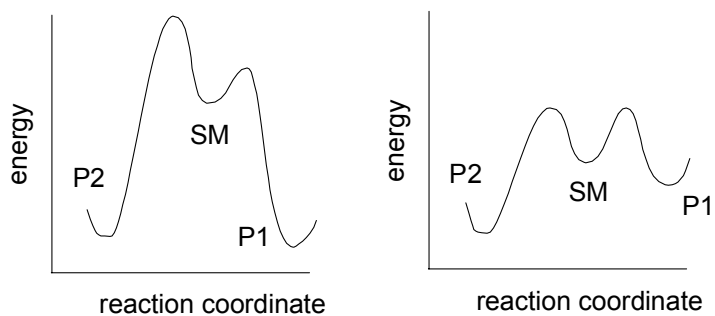


1.5.5.2. Appropriate care should be taken when using them.

2. Enolates can be alkylated at the alpha carbon atom in a kinetic fashion.

2.1. Caine, D. "Alkylations of Enols and Enolates." In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3; pp 1.

### 3. KINETIC VERSUS THERMODYNAMIC CONTROL OF ENOLIZATION



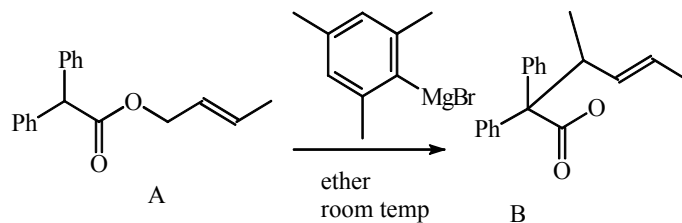
3.2. The products in the reaction diagram on the left can only be a result of kinetic control that is if mostly P1 dominates the product distribution.

3.2.1. The rate of the formation of P1 is faster than that of P2.

3.2.2. The rates of the formation of P2 and P1 are identical in the reaction diagram on the right.

3.2.2.1. However if material is exchanging the ratio of P1:P2 is going to be a function of their stabilities.

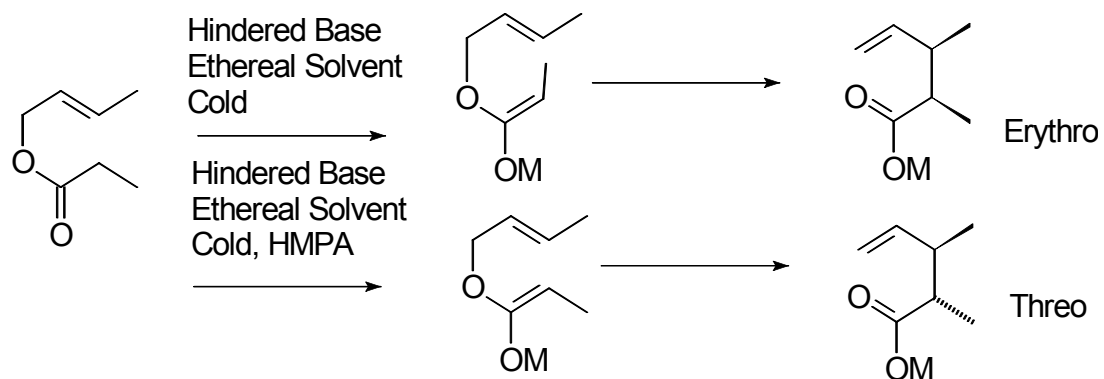
3.2.2.2.  $\Delta G = -RT \ln(P1/P2)$



4. Here an enolizable ester was used to first elaborate (homologate) the allylic alcohol in the Ireland Ester Enolate Claisen. We have discussed this.

4.1. Claisen rearrangements involving enolates take place easier than their uncharged counterparts

4.1.1. If the above enolate were not stabilized by extended conjugation with the phenyl ring and if a quaternary and a tertiary carbon centers were not being formed adjacent to one another the above rearrangement would probably occur at about  $-30\text{ }^{\circ}\text{C}$ .



4.2. Now let's add stereochemistry to the argument.

4.2.1. In the scheme above what would happen if the *Z* allylic alcohol were used instead of the *E* allylic?

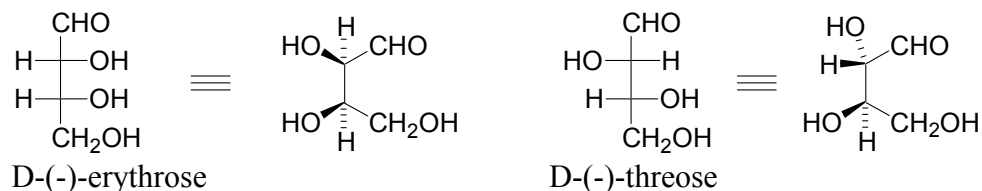
4.2.2.  $\text{M}=\text{Li}$ , or  $\text{Mg}$  work best for the kinetic enolization, top scheme to make Erythro diastereomer.

4.2.3.  $\text{M}=\text{Na}$ , or  $\text{K}$  or ( $\text{M}=\text{Li}$ , or  $\text{Mg}$  in the presence of HMPA) for the thermodynamic enolate, bottom scheme to make Threo diastereomer.

4.2.4. Elaborating the allylic alcohol as esters and amides before the Claisen rearrangement adds control to the stereoselectivity of the reaction by choosing the conditions under which we enolize.

4.2.5. Erythro vs. Threo nomenclature

## 4.2.5.1.



## 5. Enolate nomenclature.

5.1. When M=Li and methyl is on the same side of the double bond we call this the E-enolate.

5.2. When M=Si and methyl are on the same side of the double bond we call this the Z-enolate.

5.2.1. Same is true for M=Mg.

## 6. I did not define the base in this case because many hindered bases behave similarly

6.1. The solvent and co-solvents are most important factors.

6.2. The solvent conditions with HMPA allow equilibration of the initial high-energy enolate with the lower-energy enolate.

## 7. kinetic enolate vs. thermodynamic enolate.

7.1. Why does the higher-energy enolate form first and why is the high-energy enolate stable enough to participate in the Ireland Claisen rearrangement (Ireland Ester Claisen).

7.2. The thermodynamic enolate is more stable because steric interaction is minimized.

7.2.1. The high-energy enolate is kinetically stable enough to participate in the Ireland Claisen rearrangement because the Ireland ester enolate Claisen occurs at  $-40$  to  $-15$  °C.

7.2.2. The kinetic enolate forms first due to steric interactions in the transition state of deprotonation.

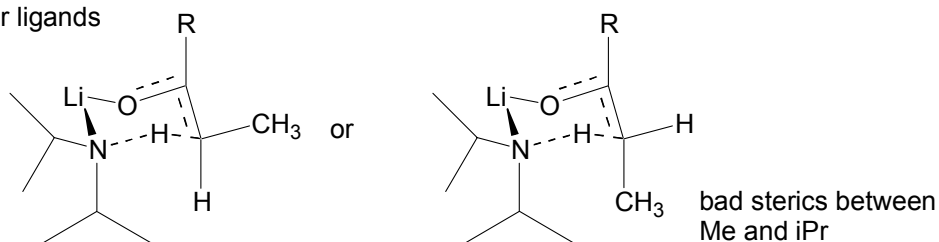
7.2.2.1. *Back to the reaction diagram.*

7.2.2.1.1. The mechanistic pathway to the E-enolate (energy of the transition state of deprotonation) must be lower energy than the path leading to the Z-enolate.

7.2.3. The following argument is routinely offered for the stereoselectivity of the kinetic enolate.

7.2.3.1. Selectivity is better with strong, hindered bases.

Li has four ligands



7.2.3.2. The N-H-C connection in the transition is short. This exacerbates the steric interaction between iPr and CH<sub>3</sub> in the example above.

7.2.3.3. Often the stereoselectivity can be as high as 99:1

7.2.3.4. The kinetic selectivity is usually better than the thermodynamic selectivity in enolization.

7.2.4. When Na and K are used in place of Li the kinetic stereoselectivity often is eroded.

7.2.5. One can make enolates from silylenol ethers.

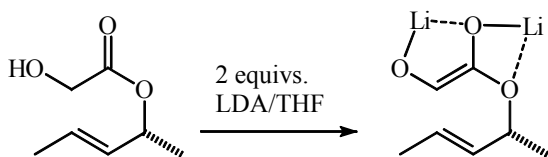


7.2.6. HMPA makes Li behave more like Na and K in enolization.

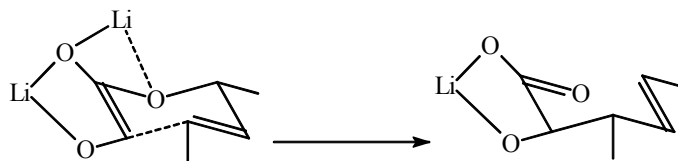
7.2.6.1. It promotes interconversion of the kinetic and the thermodynamic enolate.

7.2.7.  $\alpha$ -hydroxy ketones are also good Claisen substrates

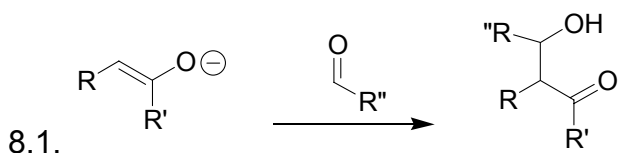
7.2.7.1. Below an excellent example of the aggregation properties of lithium and how important these are to the transformation of organic compounds.



7.2.7.2.



## 8. The aldol reaction



8.2. Heathcock, C. H. "The Aldol Reaction: Group I and Group II Enolates." In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2; pp 181.

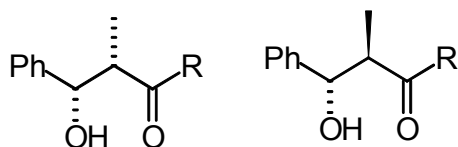
8.3. There are stereochemical issues in the aldol ( $\beta$ -hydroxyketone) product at the carbinol carbon ( $\beta$ -carbon) and the  $\alpha$ -carbon.

8.4. These issues are controllable by kinetic enolization and chiral auxiliaries.

8.5. Chiral Auxiliaries are used in a variety of reactions to make optically pure materials.

## 9. Stereoselective Syn Aldol

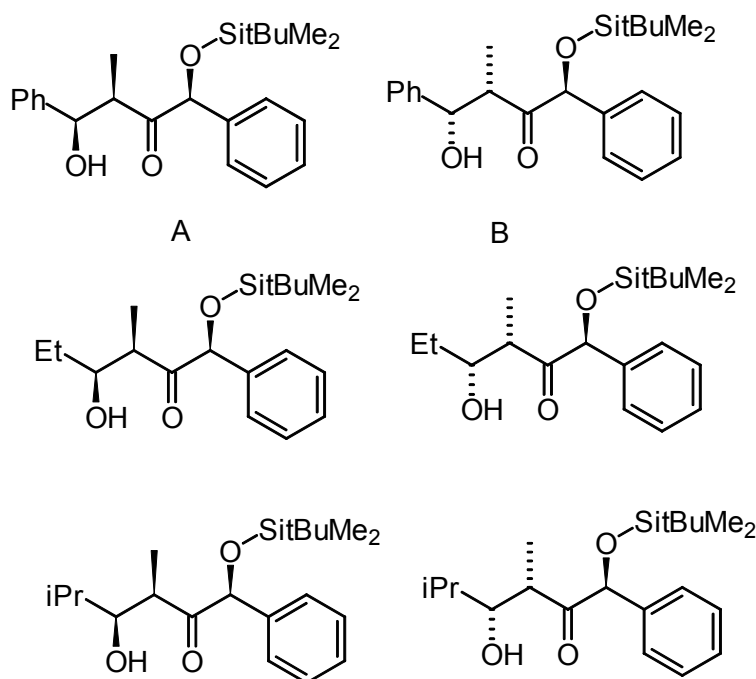
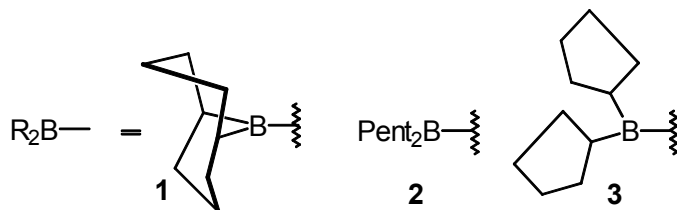
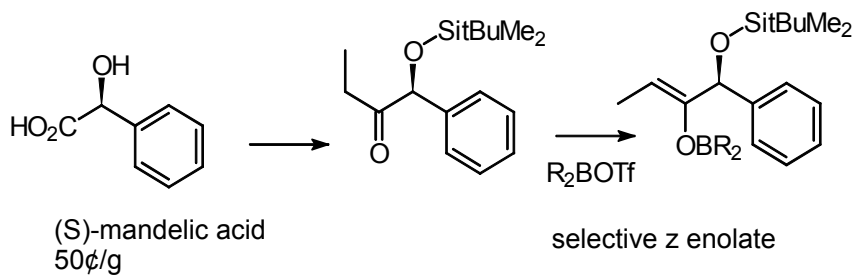
9.1. More common (easier) than the antialdol



9.2.            syn aldol            antialdol

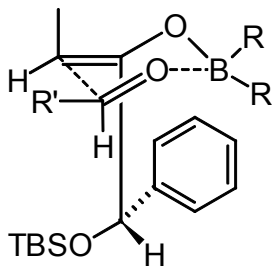
9.2.1. <This reference for the discussion below.> Saratori Masamune et. al. *J.Am.Chem.Soc.* 1981, 103, 1566-68.

9.2.2. *J.Am.Chem.Soc.* 1982, 104, 5521, 5523, 5526, 5528.



BR <sub>2</sub> / R=	Ph	Et	iPr
1	14:1	40:1	75:1
2	17:1	50:1	>100:1
3	100:1	100:1	no rxn

9.2.7. Transition State Leading to Product



9.2.8.

9.2.9. Between TBSO, H, and Ph; Ph is the most sterically demanding group. It hangs to the side of the double bond due to 1,3-allylic strain.

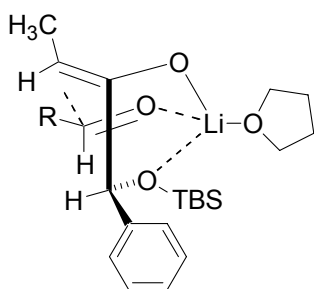
9.2.10. TBSO avoids the bulky ligands around the boron center

9.2.11. aldehyde comes in side opposite phenyl of mandelic acid

9.2.12. R' on aldehyde occupies an equatorial position.

9.2.13. With Li enolate the facial selectivity is reversed

9.2.14. Li is chelate to the TBSO----> Li+



9.2.15.

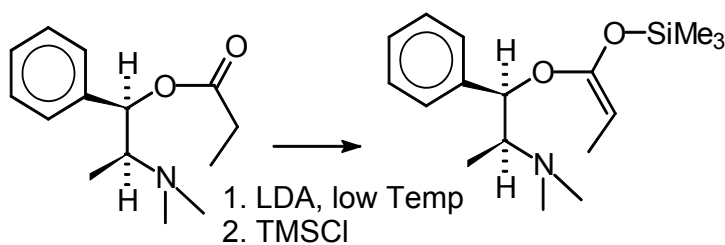
9.2.16. The bigger the interacting ligands get, the more specific the reaction becomes.

9.2.17. Product formation also decelerates.

## 10. Stereoselective antialdol

10.1. The following stereoselective method to the antialdol is inexpensive, recoverable and predictable.

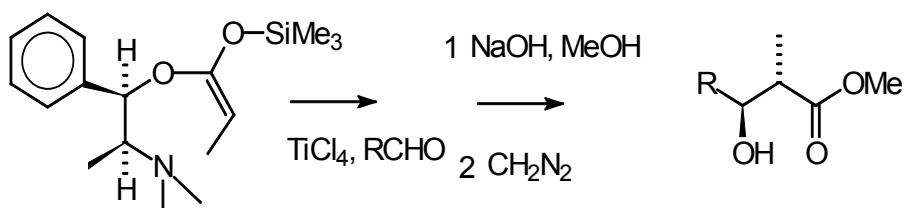
10.1.1. JACS **1985**, *107*, 5813.



10.1.2.

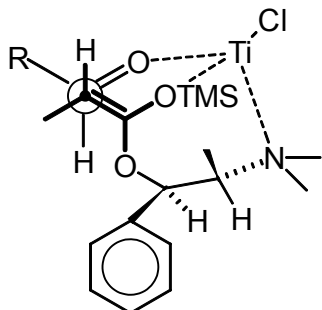
10.1.3. Silylketene acetal

10.1.4. Ester is derived from N-methylephedrine.



10.1.5.

10.1.6. 6:1 syn:anti, 91-94% ee.



10.1.7.

10.1.8. Chiral Camphor carries acetate in asymmetric condensation. *Angew. Chem., Int. Ed. Engl.* 1998, 37, 180.

