

Organic Division June Cumulative Examination

C^d-Disconnections: Nucleophilic Species that form C-C Bonds: Enolate Anions

1. C-H Bond Acidity:

A.(5 pts.) Rank the following common functional groups based on their ability to enhance the acidity of a C-H bond.

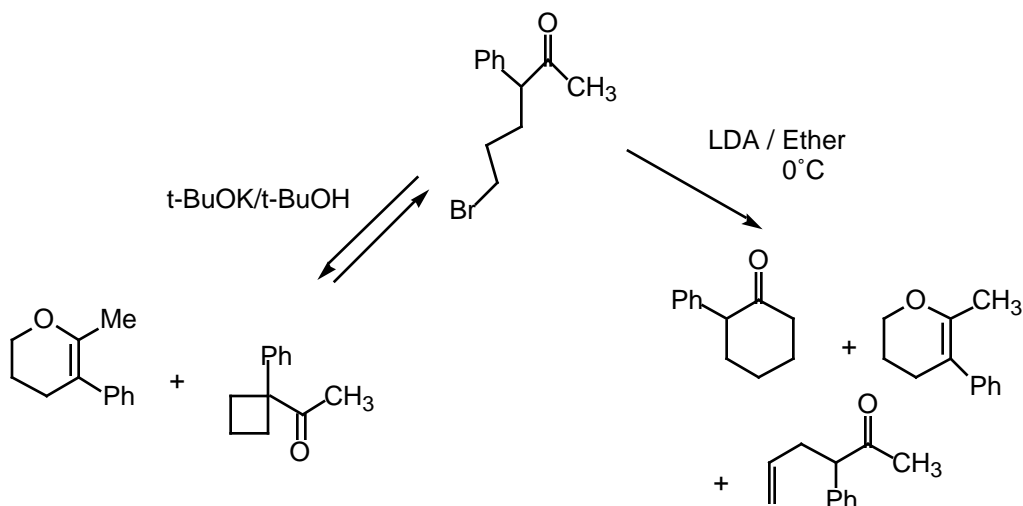
alkyl, CO, SO₂, H, halide, NO₂, CO₂R

B.(5 pts.) Rank the following according to increasing acidity and provide **approximate** pK_a values for each:

Acetone, Ethylene, Cyclopentadiene, Cyclohexane,
Dinitromethane, Ethanol, Acetylene, Diethyl Malonate

2. General Enolate Reactivity:

Consider the following reaction scheme:

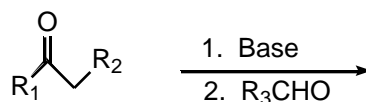


(30 pts.) Provide a mechanism for the formation of each product and predict which is the major product under each set of conditions, explain your reasoning.

Specific application of a Common C^d disconnection: Aldol Reaction

The Aldol reaction is one of the most important C-C bond forming reactions available to the synthetic chemist. The structure and geometry of the enolate ion significantly influences the stereochemical outcome of the Aldol reaction. With this in mind regarding the stereochemical outcome of Aldol reactions answer the following questions.

3. Let us first consider simple diastereoselection between an achiral aldehyde and achiral enolate. In this case you may assume that **R₁** and **R₃** do not contain α -hydrogens.

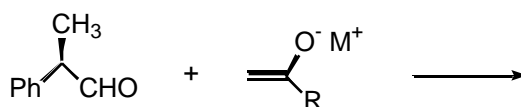


A.(15 pts.) Predict all the possible products of this reaction and use transition state models to explain the relative diastereoselectivities.

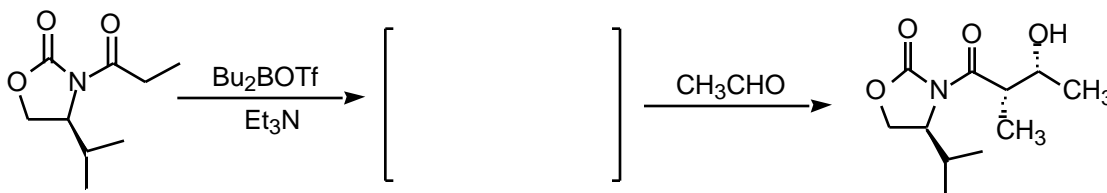
B.(5 pts.) Based on your transition state models what is the expected major product for each enolate geometry ?

4. In the problem above we were concerned with simple diastereoselection between achiral substrates. If either the enolate or carbonyl partner has an asymmetric center, this will influence facial selectivity (Diastereofacial Selectivity).

A.(15 pts.) Predict the major product of the following reaction and explain the stereochemistry.



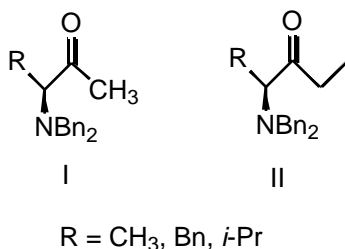
B.(20 pts.) Another common method of controlling selectivity is to use a chiral auxiliary on the enolate, for example:



Provide a mechanism and explanation for the formation of the observed product.

Based on the stereochemistry of the product provide a likely structure for the intermediate boron enolate.

5. Recently in our **Organic Day Seminar Professor Dennis C. Liotta** presented some highly diastereoselective Aldol reactions of α -(*N,N*-Dibenzylamino) ethyl and methyl ketones, **I** and **II** respectively.



The sodium enolates of **I** and **II**, prepared by treating **I** and **II** with sodium hexamethyldisilazide (NaHMDS), were very selective for the all *syn*-Aldol products when reacted with various aldehydes. The following observations were made:

1. Sodium enolates were more selective than lithium enolates.
2. Two and three point chelation metals such as ZnCl₂ and ClTi(O-*i*Pr)₃ did not enhance the diastereoselectivities relative to the lithium enolates.
3. Additives such as HMPA and TMEDA did not diminish the diastereoselectivity.

Based on these observations answer the following:

- A.(5 pts.) Show the all *syn*-Aldol products resulting from the enolates of **I** and **II** reacting with benzaldehyde.
- B.(15 pts.) Explain the observed selectivity using a transition state that is consistent with the observations.
- C.(5 pts.) How can ¹H-NMR be used to determine the geometry of the enolate derived from **II** ?
- D.(5 pts.) For the all *syn* product derived from **II**, how can ¹H-NMR and ¹³C-NMR confirm the relative and absolute stereochemistry ?