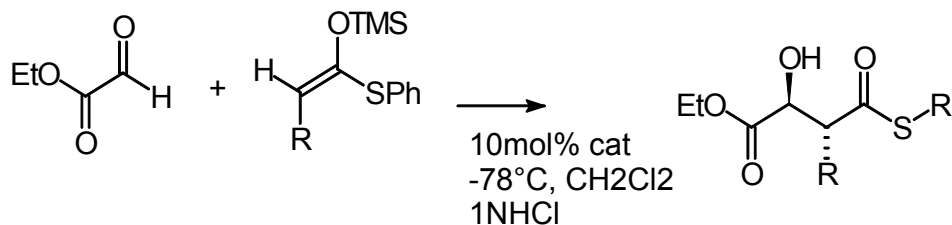


## Chem 535-Synthetic Organic Chemistry

**Enolate Chemistry II, aldol reaction, double diastereoselection (general concept)****Related chemistry of enamines.**

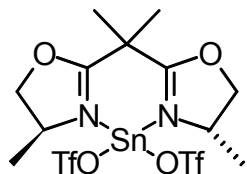
In recent years the Aldol Reaction chemistry has gotten very competitive

1.1. *J. Am. Chem. Soc.* **1997**, *119*, 10859-60.



1.3. Ethyl glyoxalate + Z-thiophenyl trimethylsilylketene acetal

1.3.1. Catalyst is below

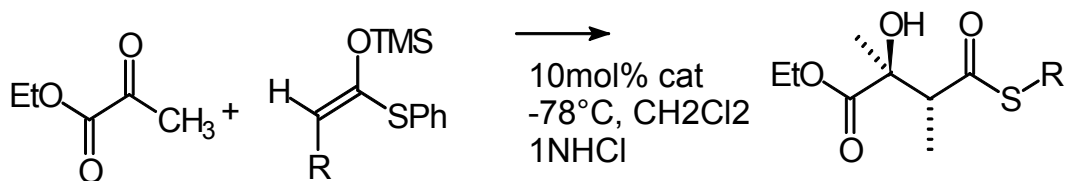


1.3.2.

1.3.3. Anti:syn ~9:1, %ee >95, %yield ~75-85

1.3.4. The reaction is much improved when the materials involved are methyl pyruvate and thioalkyl trimethylsilylketene acetals.

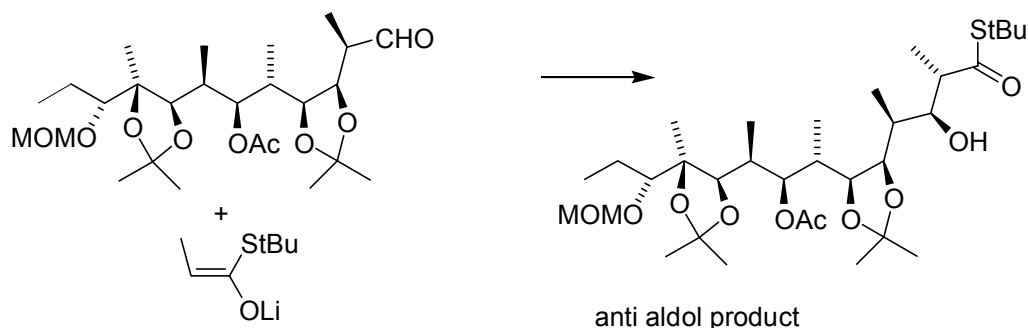
1.3.5. anti:syn →99:1 %ee is as high as 99, and the yields are above 80%!



## 2. Complex chiral induction

2.1. Think about the Aldol chemistry in the following reaction.

2.2. I would like you to be able to predict the stereochemistry of the reaction below and reactions like the reaction below.



2.3. Woodward, R.B. et. al. *J. Am. Chem. Soc.* **1981**, *103*, 3210.

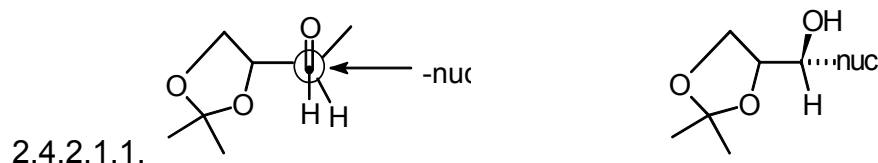
2.3.1. Kinetic Li enolate

2.4. The anti aldol is obtained above.

2.4.1. Why and how does it come about and could you have predicted the result of such a complex reaction?

2.4.2. Break the problem down into two parts.

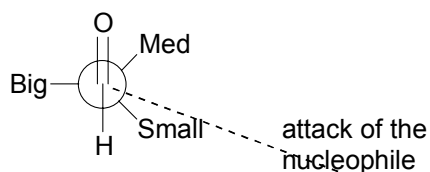
2.4.2.1. **A nucleophile reacting with an aldehyde that has facial selectivity.**



2.4.2.1.2. Decide from which side the nucleophile will attack the carbonyl.

2.4.2.1.3. Above is the Felkin-Ahn conformation for attack.

2.4.2.1.3.1. Lowest torsional interactions.

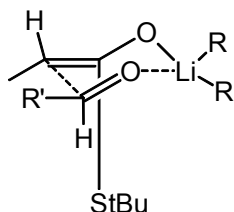


2.4.2.1.3.2. Stereochemistry at this carbon center is determined by the facial selectivity of the aldehyde.

2.4.2.2. **An aldol reaction in an asymmetric environment.**

2.4.2.2.1. The both the carbinol carbon atom and the carbon atom alpha

to the carbonyl are stereogenic in the product; they preferentially transforms to one absolute configuration.



2.4.2.2.2.

2.4.2.2.3. The geometry of the enolate determines the stereochemistry of the carbon  $\alpha$ -to the carbonyl.

2.4.2.2.4. The big group on the aldehyde in an equatorial position in the six-membered ring transition state.

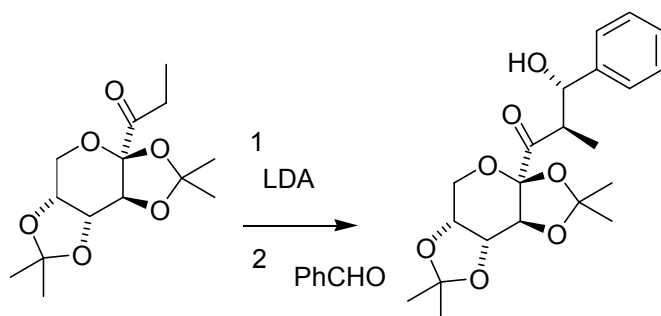
2.4.2.2.4.1. This is reminiscent of the 3,3-sigmatropic rearrangement isn't it? Go back in your notes and make the analogy.

3. In the example of asymmetric synthesis above we put together two pieces, one chiral aldehyde and an achiral enolate.

3.1. What if we had put together two chiral pieces in a similar fashion?

3.1.1. What option, advantages and/or problems does this cause/ offer us?

3.1.2. Let's look at some more examples!

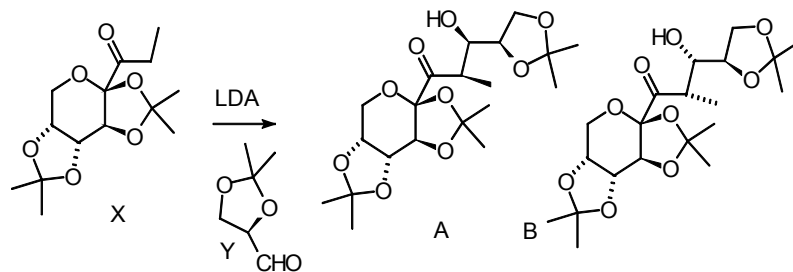


3.1.3.

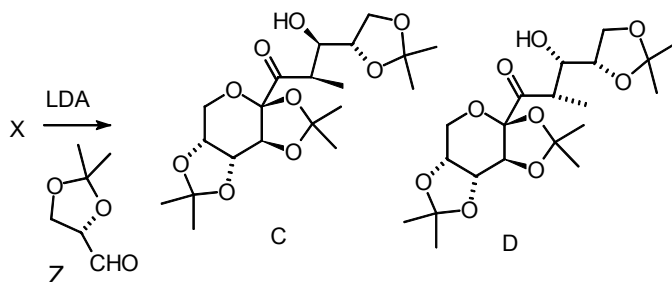
3.1.4. The product ratio above depends on the facial selectivity of the ketone starting material.

3.1.5. Which enolate reacted to produce the products shown (the syn aldols)?

4. Double Stereodifferentiation / kinetic resolution. **EXAMPLE**



4.1.1.



4.1.2.

4.1.3. **A** and **B** come out in a 1:1 mixture, but **C** is the only observed product when aldehyde **Z** is used.

4.1.4. **Z** and **X** are matched pairs but **X** and **Y** are mismatched pairs.

4.1.4.1. For more on matched pairs see: *JOC* **1981**, 46, 1296; *J. Am. Chem. Soc.* **1979**, 101, 7076. C. Heathcock et. al.

4.1.4.2. Let's make sense out of this result by considering a simplified chemical kinetic scenario.

4.1.4.3. Let's say that going against the facial preference of either chiral molecule **X** or **Z** will cost us 2 kcal/mol.

4.1.4.4. Whereas the native unimpeded reaction has an energy barrier of 1 kcal/mol.

4.1.4.5.  $X+Y \rightarrow A \quad k_a = ce^{-\Delta G^\ddagger_a/RT} = .0064 \text{ mol}^{-1}\text{Sec}^{-1} \quad : \Delta G^\ddagger_a \sim 3\text{kcal}$

4.1.4.6.  $X+Y \rightarrow B \quad k_b = ce^{-\Delta G^\ddagger_b/RT} = .0064 \text{ mol}^{-1}\text{Sec}^{-1} \quad : \Delta G^\ddagger_b \sim 3\text{kcal}$

4.1.4.7.  $X+Z \rightarrow C \quad k_c = ce^{-\Delta G^\ddagger_c/RT} = .185 \text{ mol}^{-1}\text{Sec}^{-1} : \Delta G^\ddagger_c \sim 1\text{kcal}$

4.1.4.8.  $X+Z \rightarrow D \quad k_d = ce^{-\Delta G^\ddagger_d/RT} = .00023 \text{ mol}^{-1}\text{Sec}^{-1} \quad : \Delta G^\ddagger_d \sim 5\text{kcal}$

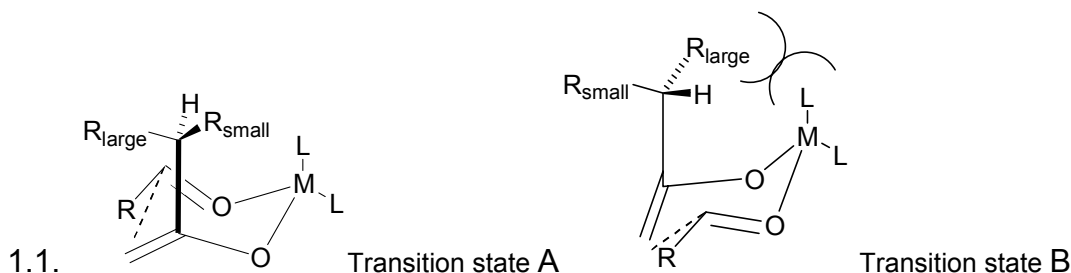
4.1.4.8.1. Assume the preexponential factor, *c* is the same for all rxns.

4.1.5. The amount of product you get out is directly proportional to the rate of the reaction.

- 4.1.5.1. This is always true under conditions that avoid equilibrium (unidirectional chemical change).
- 4.1.6.  $0.185/(0.185 + 0.00023) \times 100 = 99.9$
- 4.1.6.1.  $0.00023/(0.185 + 0.00023) \times 100 = 0.1$
- 4.1.7. So the matched pair results in a 99.9:0.1 mixture (C:D), but the mismatched pair results in a ~1:1 mixture (A:B).

Some of the examples in this next section were taken from the text Organic Synthesis by M. Smith.

1. General stereoselectivity controlled by the chiral enolates.



1.1.1.  $ML_2$  is bulky.

1.1.2.  $R_{large}$  and  $R_{small}$  will hang to the outside of the ring.

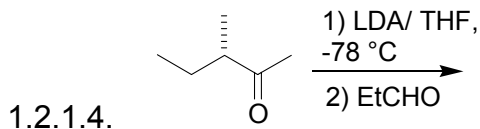
1.2. Consider the other possible transition state that hangs  $R_{large}$  and  $R_{small}$  away from the ring. Transition state B.

1.2.1. Steric interaction between metal ligands and large alkyl group prevent this transition state.

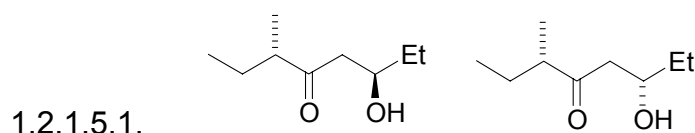
1.2.1.1. What is the nature of the metal ligands? What are they? Why are they usually quite big?

1.2.1.2. Can you predict the product of Transition state A and B above?

1.2.1.3. Can you apply the mechanism to the following reaction?



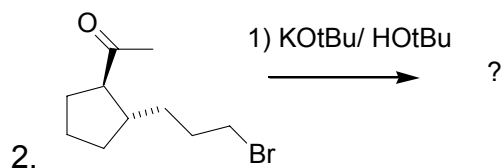
1.2.1.5. Answer: (when  $M=Li$  in ether: ratio is 57:43. when  $M=Bu_2$  in  $CH_2Cl_2$  ratio is 64:36 of the following material.



1.2.1.6. Which kinetic enolate needed to form to access this product?

1.2.1.7. What are the other possible enolates? Which ones of these other possible enolates are more stable? Why does this enolate form versus other possible enolates?

1.2.1.8. Selectivity gets better as the difference in size of the groups attached to the  $\alpha$ -carbon increases.



2.1. House et. al. J. Org. Chem. **1978**, 2153.

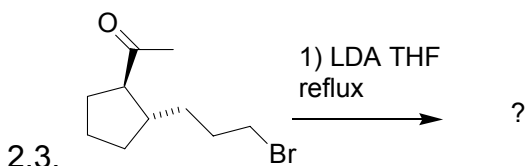
2.2. Predict the product.

2.2.1. Remember that potassium enolates exchange rapidly.

2.2.2. Remember that the more substituted enolate is the most stable. Why? What is the best chemical structural analogy?

2.2.3. Remember that *cis*-fused five membered rings cyclize rapidly versus seven membered rings.

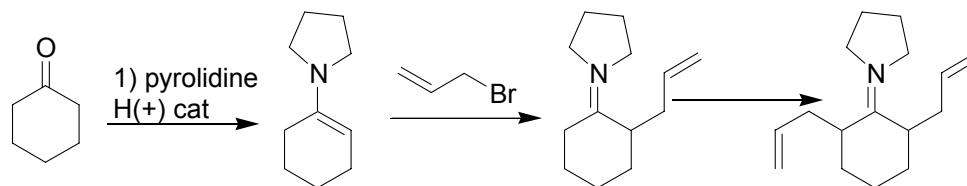
2.2.4. Remember that deprotonation ( $S_N2$  at H) is less sterically demanding than  $S_N2$  at C.



2.3.1. Forms ~80% major product.

2.3.2. Remember that lithium enolates don't readily exchange.

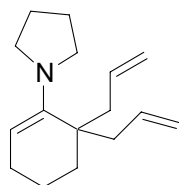
3. **The alkylation of enolates/ The chemistry of enamines.**



3.1.1.

3.1.2. Reaction can be controlled to get monoalkylation.

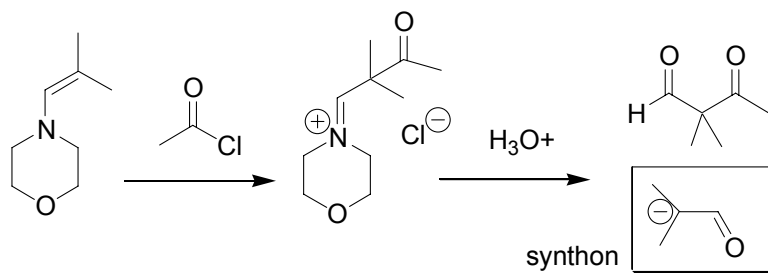
3.1.3. Two equivalents of the electrophile will result in the dialkylation.



3.1.3.1.

This product is not a problem due to 1,2-allylic strain in the enolate needed to get this product.

3.1.3.1.1. Lecturer explains allylic strain.

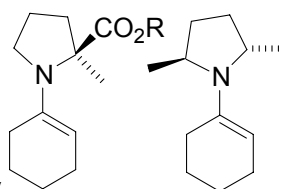


3.2.

3.2.1. Remember enolates of aldehydes are not very useful because they quickly self-condense.

3.2.2. Enamine chemistry offers a method to generate the synthetic equivalent of an aldehyde enolate.

3.2.3. It is not necessary to have two alkyl groups on the  $\alpha$ -carbon. For example



3.3. Asymmetric enamine chemistry