Carbonyl Chemistry V: Problem Solving with α-Carbonyl Chemistry

After two problem sets, you should have a strong sense of the fundamentals of α-carbonyl chemistry. You know that ketones and aldehydes are electrophilic. You know that their α-hydrogens are acidic. You know how to make enols and enolates. You know that enols and enolates are nucleophilic. You know that these reactions have acid and base catalyzed versions.

There are certainly more subtle things to worry about, but these are the basics that you MUST know. If you are not 100% solid on all of these concepts, you should crack open Loudon and brush up. It is pointless to worry about specific details if you haven't mastered the fundamentals. For the exam, you need both the fundamentals *and* the details, but don't put the cart before the horse. Don't lose sight of the forest for the trees. Keep your eyes on the big picture. Insert more clichés here.

As far as problem solving goes, there are really only two general classes of problems. The first class comprises synthetic problems. You must know reactions in the forward direction (for filling in reagents, etc.) and backward direction (transforms for retrosynthetic analysis). The second type comprises mechanistic problems. These are most often arrow-pushing mechanisms, but they can also be in the form of A + B → C questions where you must derive the major product from first principles. Stereochemical considerations based on conformational analysis of the transition state are often of prime importance. For this reason, let's begin with a brief review of conformational analysis.

Conformational Analysis

- Conformational analysis is the study of the equilibrium between isomers obtained by rotating σ bonds in a molecule.

- The most stable conformation is the isomer with the least strain. There are four important types of conformational strain interactions that we've learned. Remember, the cause of the strain is usually electron-electron repulsion between the electron clouds of atoms forced in close proximity to each other. Strain can also result from loss of favorable stereoelectronic interactions.
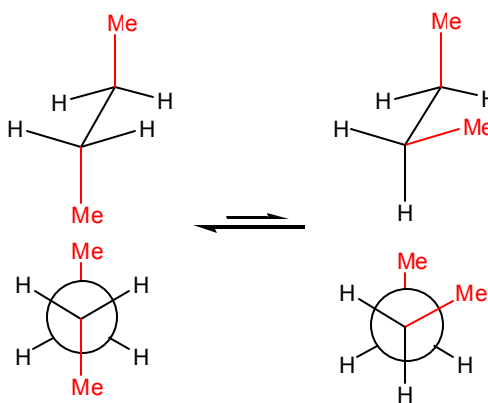
Torsional Strain
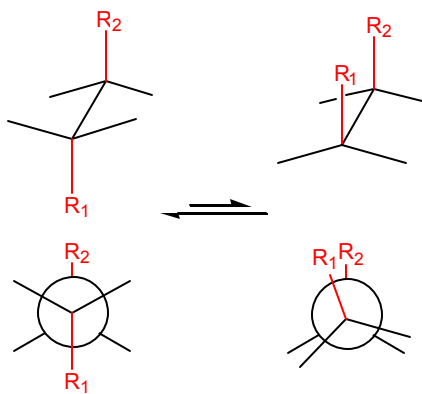
staggered　　　　**eclipsed**

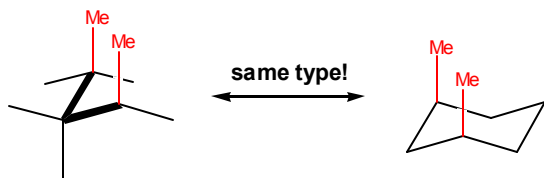| R_1 = H,	R_2 = H	1.0 kcal/mol
R_1 = H,	R_2 = Me	1.3 kcal/mol
R_1 = Me,	R_2 = Me	~ 3.0 kcal/mol

Gauche Interactions

anti conformation　　　**gauche interaction**
set as reference　　　　+0.8 kcal/mol

- The dihedral bond angle is 60° for gauche interactions.

Syn-Pentane Interactions

same type!

syn-pentane interaction　　　**1,3-diaxial interaction**
+ 3.7 kcal/mol

Allylic Strain ($A^{1,3}$ Interactions)
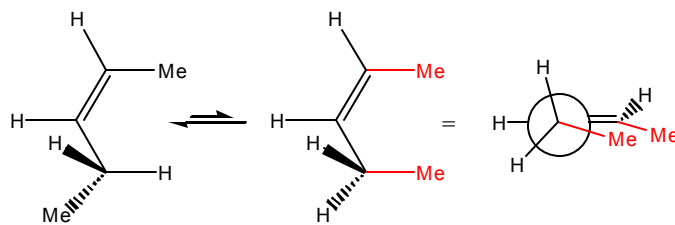
$A^{1,3}$ **strain**
+3.9 kcal/mol

- It is generally better to place large substituents in equatorial positions of cyclohexane rings
- Be on the lookout for $A^{1,3}$ interactions, especially on something, like, say, a problem set 8.

Why is this important? The lowest energy conformation of the substrate often controls reactivity and stereoselectivity:

lowest-energy conformation

"top" face of double bond is less hindered

2
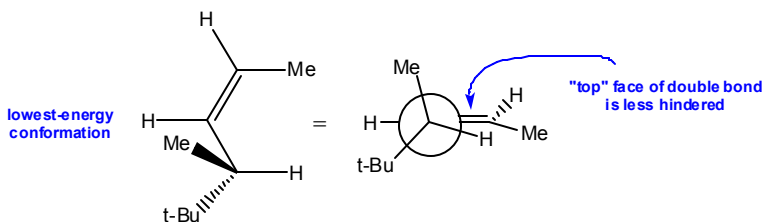
The Basics of the Aldol Reaction

The General Case (assuming basic conditions)

β-keto alcohol   α,β-unsaturated ketone
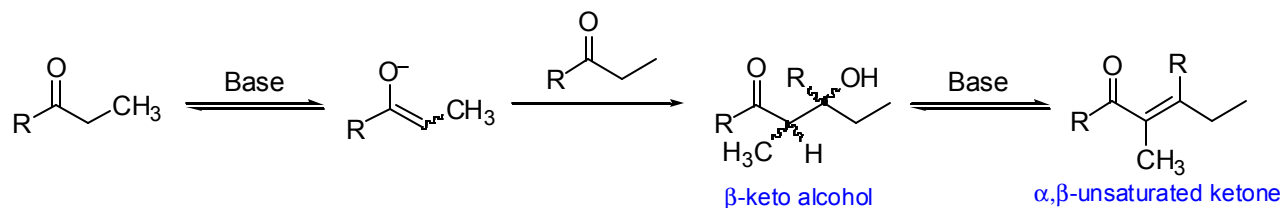
- To keep these reactions simple, it is generally best for only one of the reactants to have acidic α-hydrogens.

- Dehydration: In the second step above, the loss of water leads to the formation of the α,β-unsaturated product. If you are heating this reaction in acid or reversible bases (e.g. NaOH, NaOEt), then you can expect to generate the α,β-unsaturated compound. If you are using soft enolization conditions or one equivalent of very strong bases (e.g., LDA), you can expect the β-keto alcohol.

Thermodynamic vs. Kinetic Enolates

- When a ketone has α-hydrogens on both sides of the carbonyl group, you must decide which enolate the reaction conditions favor. The hydrogens on the less substituted side of the double bond will be deprotonated faster, but the more substituted enolate is more stable (Zaitsev's rule).

- Thermodynamic conditions are those in which the deprotonation is reversible, so the enolates are in equilibrium and the more substituted enolate will predominate. Common conditions: HCl, NaOH, or NaOR (alkoxides).

favored
(more substituted)

disfavored
(less substituted)
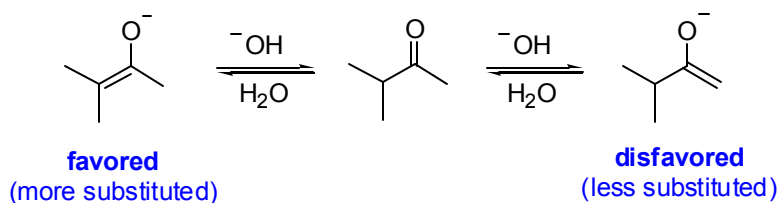
- Kinetic conditions are those in which the deprotonation is irreversible. Thus, since the protons from the less hindered side are abstracted faster, the less substituted enolate will predominate. Common conditions: LDA, temperature-controlled soft enolizations.

- A frequent clue that a problem is asking for the kinetic enolate is the use of low temperature, often -78 °C (dry ice-acetone bath). Kinetic enolates will equilibrate to the thermodynamic enolates when heated.

Soft Enolization

- "Soft" enolization refers to the fact that a harsh base need not be used to make the enolate. The most typical example is the use of dialkylboranes (e.g., $Bu_2B^{+-}OTf$) with a mild base. The bases most often employed are trialkylamines (e.g. Hunig's base: iPr_2NEt). The borane, a Lewis acid, binds to the carbonyl group, lowering the LUMO. This acidifies the α-hydrogens to the point where they can be deprotonated with a mild base.
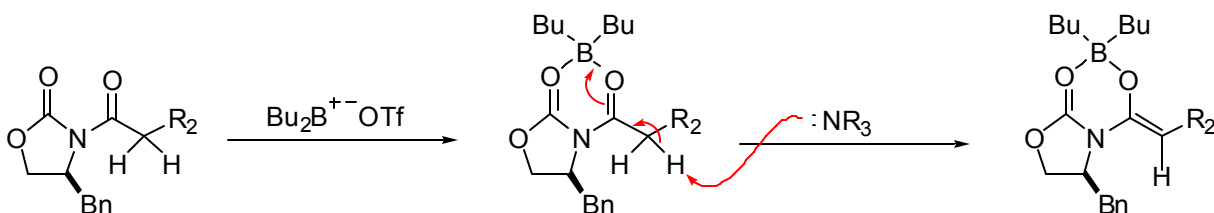
_E_ vs. _Z_ enolates

- The most stable resonance forms of enolates are those with a C=C double bond. This means that enolates can come in two stereoisomers (_E_ and _Z_). The _E_ and _Z_ notation is not based on size—it is based on the Cahn-Ingold-Prelog convention. When the highest priority groups are on the same side of the double bond, you have the _Z_ isomer. When they are on opposite sides, you have the _E_ isomer.

Z-enolate
(typically favored)

E-enolate
(typically disfavored)
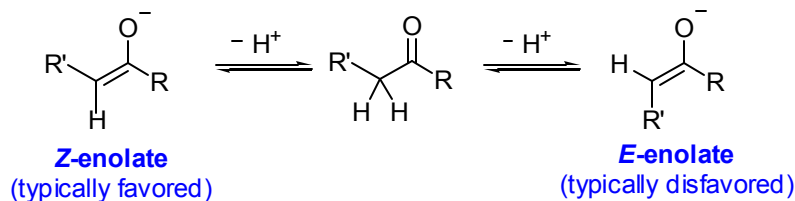
- In general, most deprotonations lead to the formation of the _Z_-enolate.

- For synthetic purposes, it is important that you know conditions for the selective generation of _both E and Z_ enolates. In the case of the use of dialkylborane reagents to acidify carbonyl compounds, the most common reagent for the generation of _Z_-enolates is Bu$_2$BOTf. The use of Cy$_2$BCl or Cp$_2$BCl yields _E_-enolates preferentially (Cy = cyclohexyl, Cp = cyclopentyl). The exact reason for the preference of _E_- enolates under these conditions is still the subject of scientific debate.
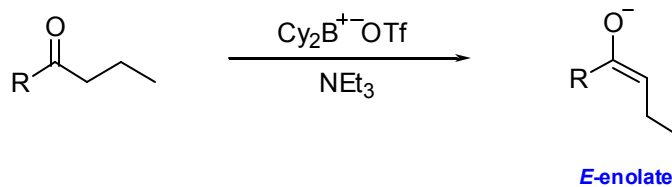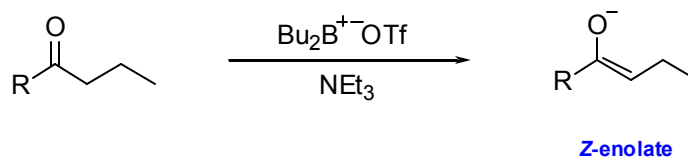

Z-enolate

E-enolate

- No matter what reagent is selected, you cannot generate _E_-enolates of chiral oxazolidiones—they are too strained.

Z-enolate

E-enolate
is too strained
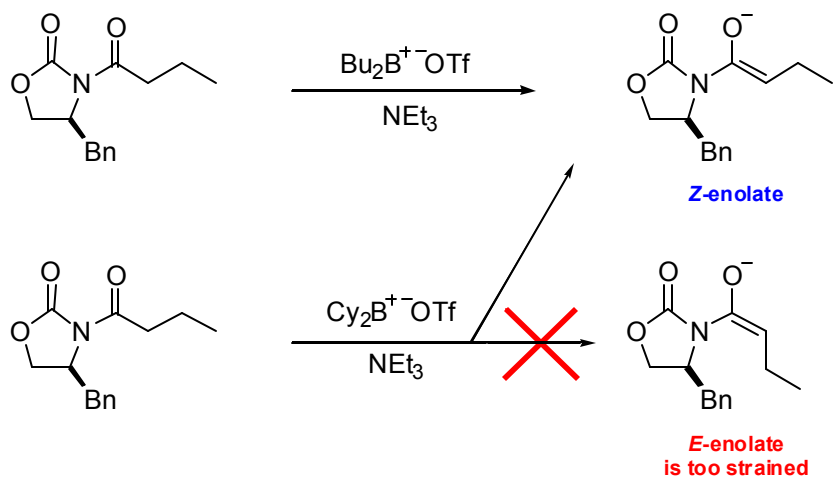
Chelation vs. Dipole Minimization

- Unless prevented by chelation, molecules prefer the conformation that has the lowest net dipole moment. This preference is exaggerated in organic solvent.

chelated   **dipole minimized**

versus

opposite faces of enolate are hindered!
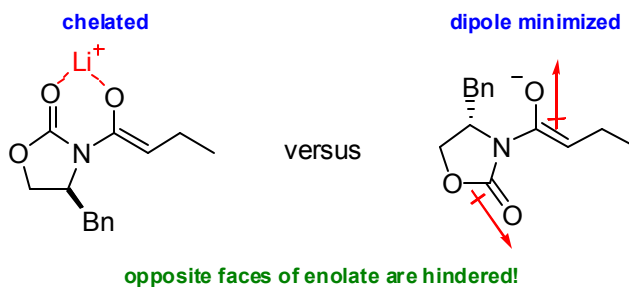
- Zn^{2+}, Mg^{2+}, BR_2L (R = bad leaving group, L = good leaving group) are good at chelating bidentate ligands
- Li^+ and BR_3 (R = bad leaving group) are good for activating carbonyl groups, but not chelating bidentate ligands.   But, for alkylations with oxazolidinones, these will chelate the two carbonyl groups.
- Na^+, K^+ are generally neither good at activating carbonyl groups nor chelating. But, for alkylations with oxazolidinones, these will chelate the two carbonyl groups.

A Step-by-Step Solution to an Evans' Asymmetric Aldol Problem

Let's take the following run-of-the-mill problem:

1) $Bu_2B^+ {}^-OTf$
   NEt_3

2) PhCHO
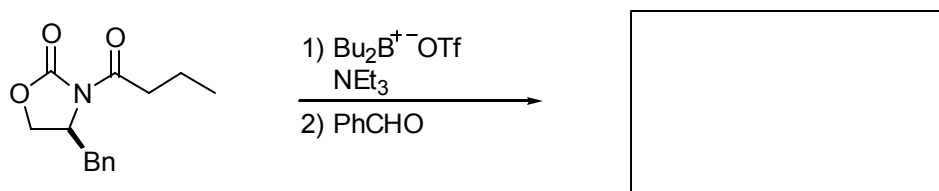
1. The first thing to do is to work out the mechanism by arrow pushing in 2D. This should be straightforward for you.

must memorize that Bu$_2$BOTf gives the Z-enolate

$Bu_2B^+ {}^-OTf$

$: NR_3$
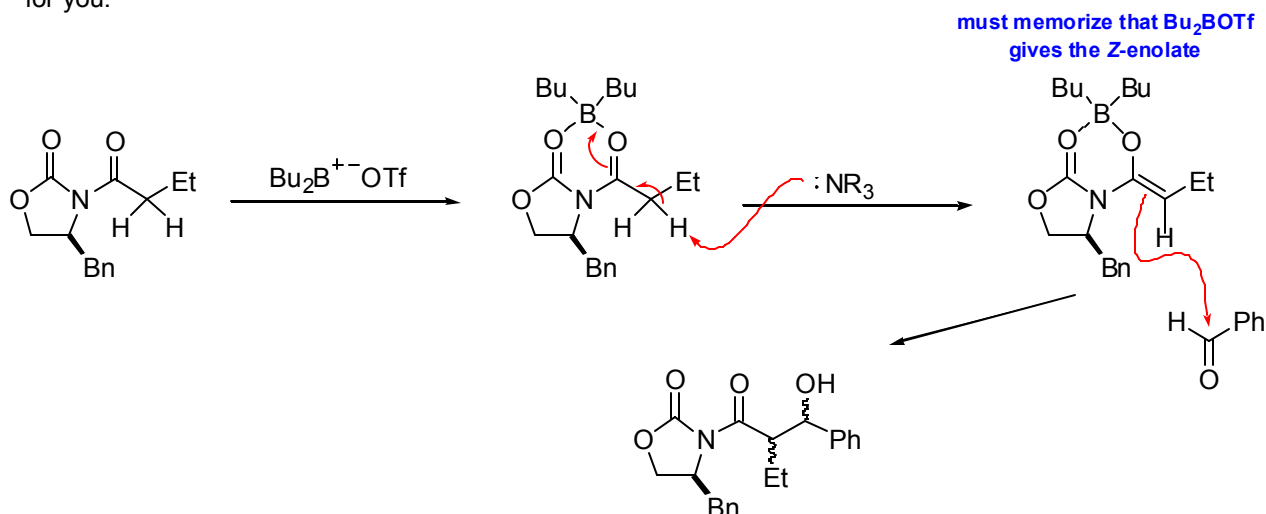
- Now that we know the connectivity in the product, we must figure out the stereochemistry.

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2. For aldol reactions with a chelating agent, we know from experience that the transition state will most likely be of the six-membered "Zimmerman-Traxler" variety. As a result, we begin our analysis by drawing a cyclohexane ring with dotted lines. The stereochemistry of the product will be determined by how we fill out the substituents on the ring.
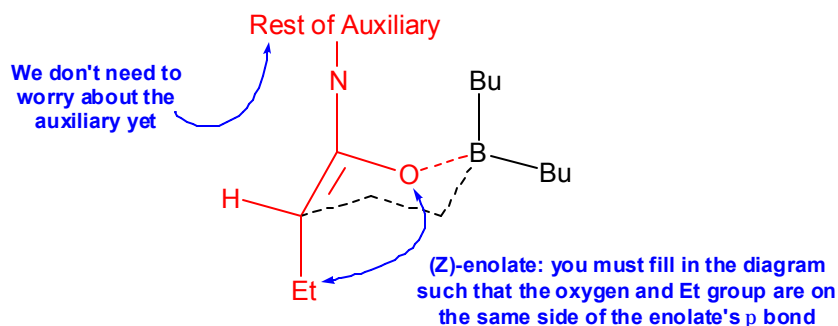
or
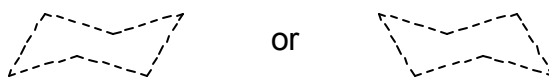
We are going to fill in this outline according to three general guidelines:

   i)   Whatever is E/Z in the 2D case *must* be *E/Z* in the 3D structure

   ii) Whatever is R/S in the 2D case *must* be *R/S* in the 3D structure

   iii) We want to minimize the potential energy of the transition state structure. This includes avoiding unfavorable steric interactions and minimizing the structure's net dipole moment

First off, we place the chelating agent at one end of the cyclohexane ring. The fact that the substituent groups are the same means we needn't worry about placing them axial and equatorial—you get one butyl at each position.
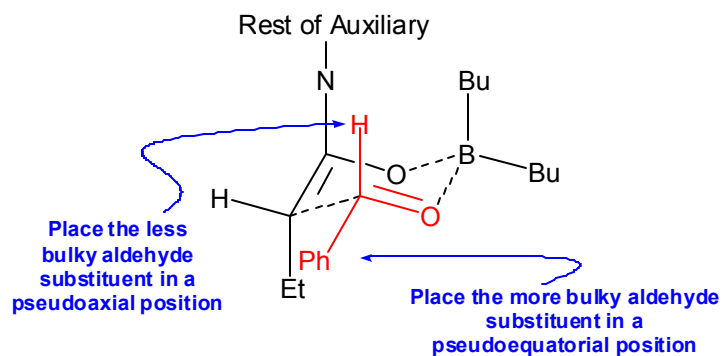
Bu
B
Bu
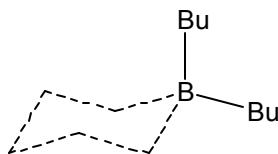
3. Knowing that the boron will chelate the enolate's oxygen, we fill in that bond next. Starting from the chelated oxygen, draw out the rest of the atoms in the enolate molecule. You needn't worry about the atoms in the auxiliary yet—they are not part of the six-membered ring in the transition state.
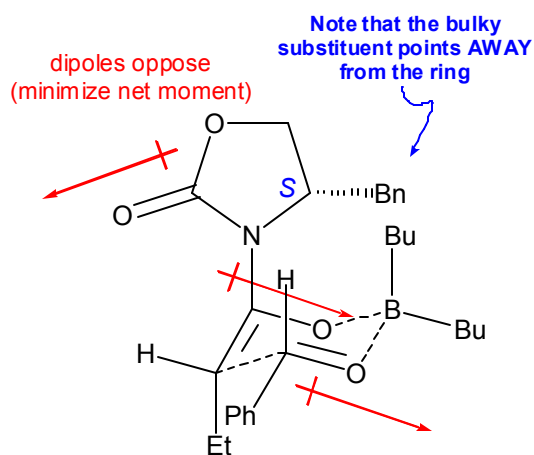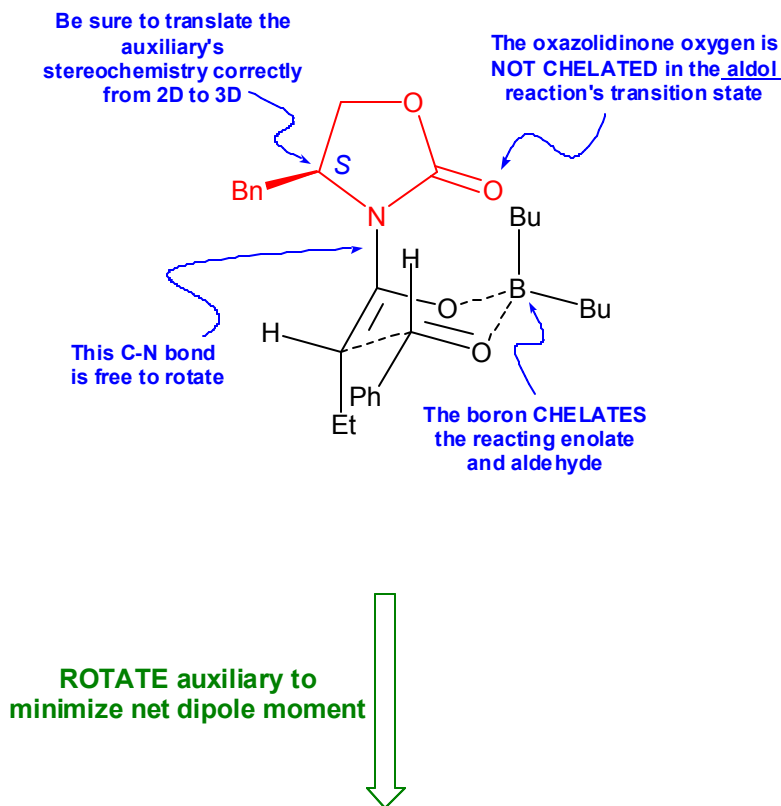
Rest of Auxiliary

We don't need to worry about the auxiliary yet

N

Bu
B
Bu

H

O

Et

(Z)-enolate: you must fill in the diagram such that the oxygen and Et group are on the same side of the enolate's p bond

- IMPORTANT: Looking back at your 2D mechanism, be absolutely sure to translate the *E* or *Z* stereochemistry of the enolate to your 3D structure. In our case, having the *Z*-enolate means that the Et group must be on the same side of the double bond as the oxygen, which results in the ethyl group's occupying a more hindered axial position. We have no choice in the matter. Only the *E*-enolate will place the bulkier group in the equatorial position.

4. Now it is time to fill in the electrophilic aldehyde. This time we do have a choice, and consequently we will choose to put the bulkier phenyl group in a pseudoequatorial position:

Rest of Auxiliary

Place the less bulky aldehyde substituent in a pseudoaxial position

Place the more bulky aldehyde substituent in a pseudoequatorial position

5. Now we must take the auxiliary into account. First, just worry about filling in the atoms correctly, being especially careful to translate the proper *R* or *S* stereochemistry on the oxazolidinone ring. Second, rotate the auxiliary so that the carbonyl group "points in the opposite direction" relative to the others. This favorably minimizes the net dipole moment of the transition state:

Be sure to translate the auxiliary's stereochemistry correctly from 2D to 3D

The oxazolidinone oxygen is NOT CHELATED in the aldol reaction's transition state

This C-N bond is free to rotate

The boron CHELATES the reacting enolate and aldehyde

ROTATE auxiliary to minimize net dipole moment

dipoles oppose (minimize net moment)

**Note that the bulky substituent points AWAY from the ring**

- Unlike for the aldol reaction shown here, in the case of asymmetric alkylations with oxazolidinones, the enolate oxygen and the carbonyl group on the auxiliary are usually chelated by a metal. Even Na^+ chelates them!

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- After minimizing the dipole moment, hopefully the bulky substituent (here: benzyl) on the auxiliary points AWAY from the cyclohexane ring. This minimizes steric repulsion—the auxiliary hinders access to one face of the enolate ion in this fashion. If you find that the bulky group is pointed TOWARD the ring, you must swap the enolate and aldehyde, like so:
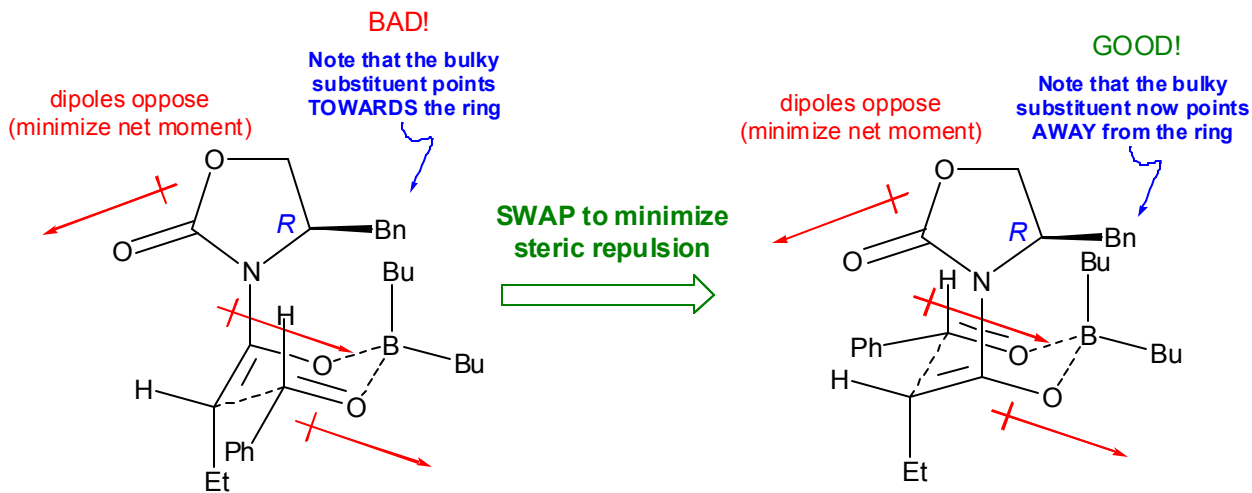
6. The only thing left to do is to assign *R* and *S* designations to the new stereocenters generated in the reaction, then translate these into dashes and wedges in your 2D structure. Be very careful—if you make one simple mistake you blow the whole problem!
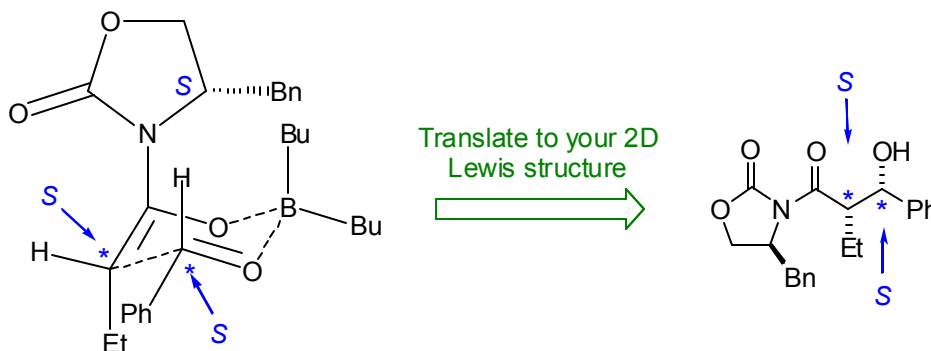

As you become more familiar with the entire process, you will begin to cut out steps. For instance, you can look at the synthetic transform table and memorize which auxiliary stereochemistry gives which product. This will save you from having to draw out the wrong transition state or eliminate the need for drawing out the transition states altogether. It is important to develop mnemonics to save you time on exams.
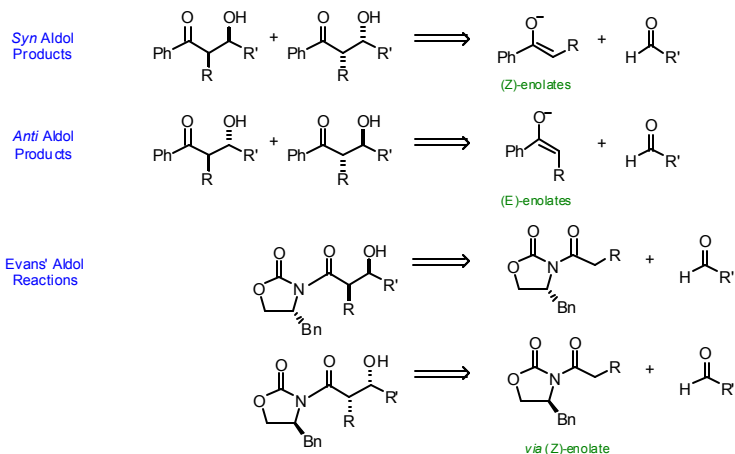
Synthetic Considerations

- You absolutely MUST MEMORIZE the aldol transforms on the previous page. You simply do not have enough time during an exam to draw out Zimmerman-Traxler transition states to figure out stereochemistry.

- Remember that   *E* enolates yield *anti* products
                          Z enolates yield *syn* products

- You can alkylate on either side of a carbonyl group, so long as there are α-hydrogens on both sides. You can select for these reactions using kinetic or thermodynamic conditions (see page 3).

- Putting on the 'done
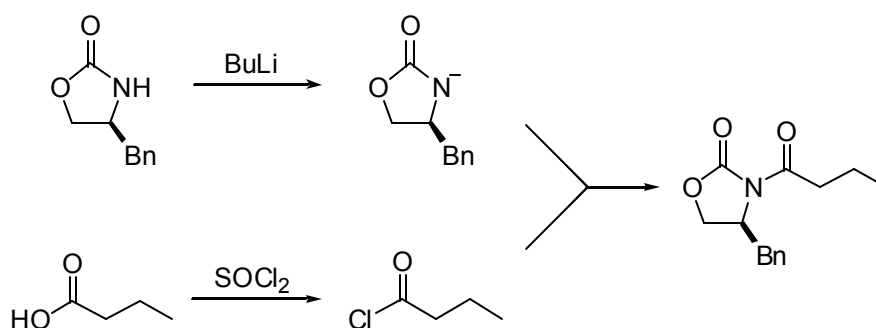
- Cleaving the 'done. There are two methods—one leading to an alcohol and the other to an acid. Use the one that suits your synthetic needs the best.
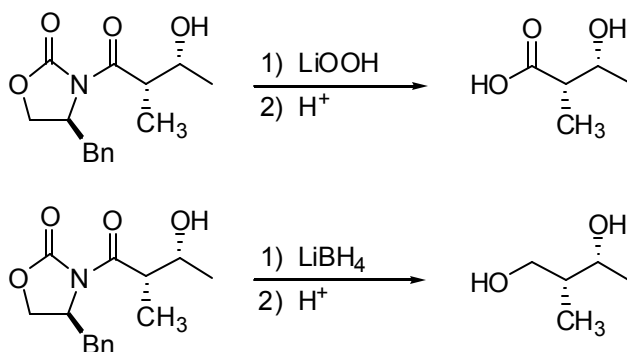
Two Specific Types of Enolate Synthesis Problems

One reason why synthesis problems for the enolate unit can be such @#$%ers is that functional groups have a tendency to "disappear" during the course of the synthesis. As a result, when you look at the product, there are few clues that guide you back to the appropriate intermediates during your retrosynthetic analysis. Here are two specific cases for which you should be on the lookout on this exam.

1) Quaternary Carbons From a,b-Unsaturated Ketones

Basically, you are used to forming carbon–carbon bonds from organometallic reagents reacting with carbonyls. On this exam, you should think about using enolates to attack carbon electrophiles. Conjugate (1,4) additions to unsaturated ketones are especially good routes to quaternary centers (carbons bonded to four other carbons). Thus, on this exam, when you see a quaternary carbon on a synthesis problem, you may wish to start by asking "could I make this from a conjugate addition?"

Example
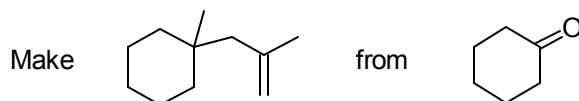
1) Recognize that you have a quaternary carbon in an important location. At this center, break your target into a Michael acceptor. There may be more than one possibility to explore. While this may not be the last bond formed, early in the game you may think "far ahead" just to test if an idea is feasible.
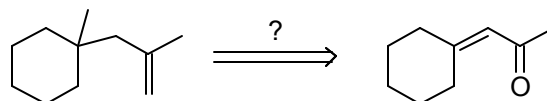
2) If it looks like this initial idea could work. Begin working backwards one step at a time until you get from your target to your "idea intermediate." Then work from your "idea intermediate" back to your starting materials. Don't waste time thinking about or writing down reagents because you may eventually find that the route doesn't work.
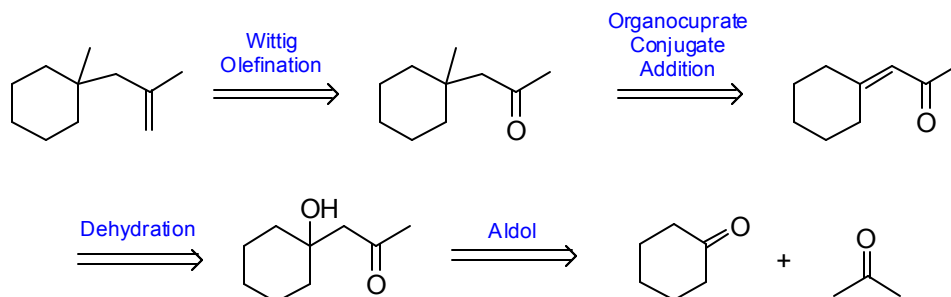
3) As soon as you are convinced that the route is viable, fill in the reagents on your retrosynthesis. When you are done, transfer your answer to your exam being sure to write the steps in the forward direction from starting materials to final product.
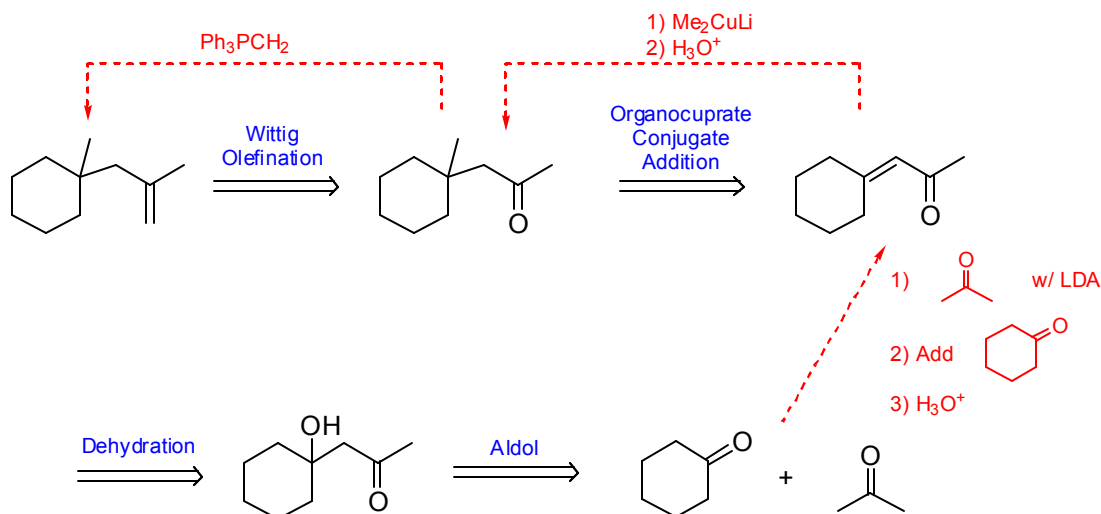

- The main point here is that you should think about making quaternary centers from conjugate additions, at least for this exam. This is something you learn from experience doing problems—it is not easily "figured out" during an exam because the final product looks nothing like something that would have come from an unsaturated ketone. Note that you can make cyclic quaternary centers by doing intramolecular conjugate additions.

- Also, remember that enolates are likely to play a role in just about every problem on this exam because they're the only things we've focused on this unit (major duh!) Chances are if you are using a whole bunch of reactions from chem 20 and exam 1 that you are barking up the wrong tree.

2) "Seeing" Malonic Ester Syntheses

Malonic ester syntheses are also "hard to see" because at some point you will inevitably have to perform a decarboxylation, losing a carboxylic acid functional group. This goes along the same lines as the previous example, where the final target looks nothing like the starting materials you are given. If you know you need to use a malonic ester (typically it is given as a starting material), it may help you to visualize reactions by just adding a COOEt or COOH group one carbon away from where carbonyls or acids are in the target compound. You can then work backwards by realizing the "middle" carbons act as nucleophiles, as you know by now.

Example
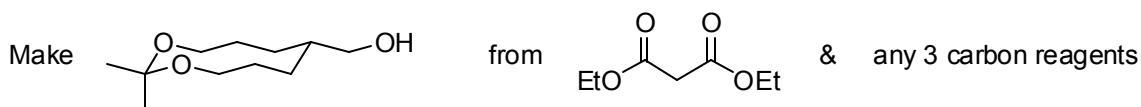
a) The diethyl malonate starting material should scream malonic ester alkylation. Nine times out of ten you will hydrolyze and decarboxylate before the synthesis is done. There are no carboxylic acids in the product, so we must look for what "might have once been" a carboxylic acid. Hmm…that primary alcohol sticks out like a sore thumb. We can make primary alcohols from the reduction of carboxylic acids. After this, we perform the trick (described above) of adding the second acid:
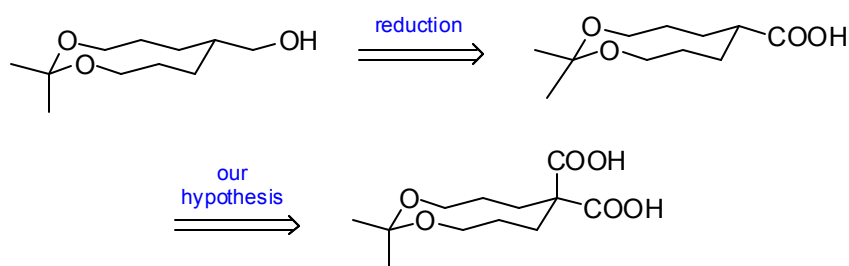
b) Now we're getting somewhere. We have addressed getting back to the required starting material. The next most obvious thing is that we have an acetal present. Let's go another step back and see what we get.
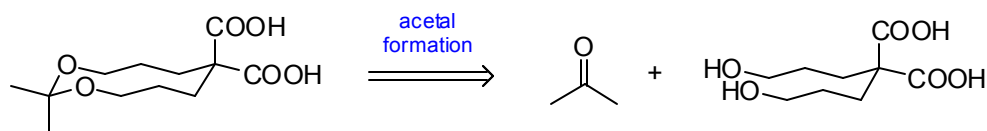
c) OK. We know we are going to alkylate the malonyl (middle) carbon. We are allowed any reagents with three or fewer carbons. Hey…it just so happens that the alkyl chains we have to make are three carbons long. This is not a coincidence—TFs and professors write question prompts to guide you to the product.

(plus some miscellaneous rxns)
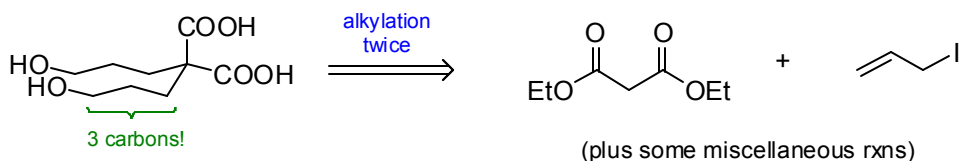
d) Having sketched out the retrosynthetic analysis, we now fill in the proper reagents. The answer should be written in the forward direction when you are done.