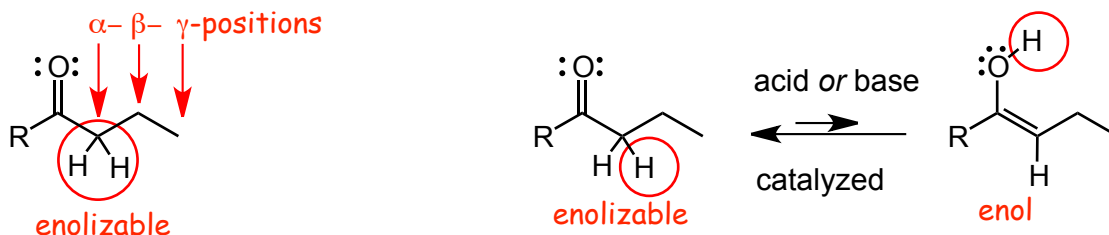


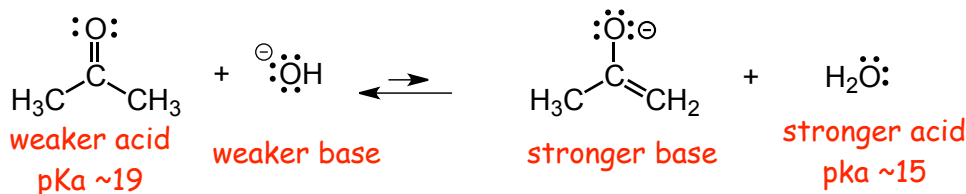
- The hydrogen atoms on the carbon that is alpha- to (α -, i.e. adjacent to) the carbon of a C=O bond are the ones involved in keto/enol tautomerization and they are unusually acidic for an sp^3 hybridized carbon.
- These hydrogens are **enolizable** (although we didn't call them that when we first discussed enols).



- Alpha (α -), beta (β -), gamma (γ -) terminology refers to relative position, alpha means next to, beta means one position further away etc., in **this context**, alpha (α -) means the carbon next to the C=O bond.

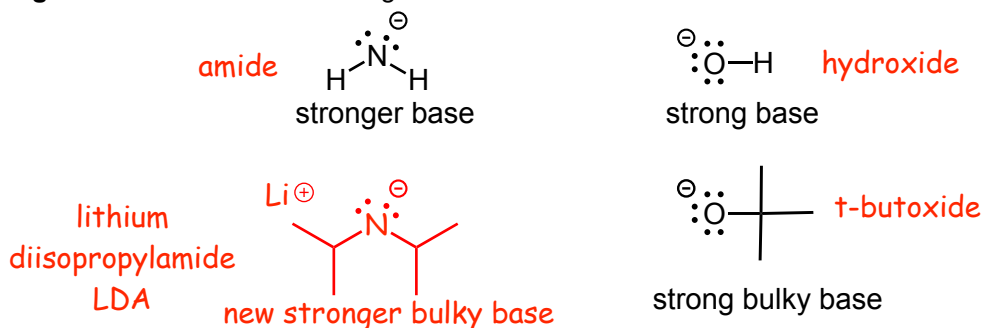
1 Bronsted Acidity of Enolizable Hydrogens

Which bases can be used to make an enolate anion?

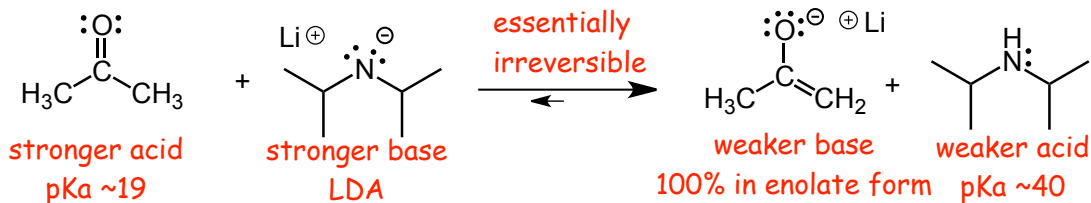


- In the equilibrium above, water is stronger acid, therefore the equilibrium lies mostly on ketone side, which means that the hydroxide anion can not be used to irreversibly make an enolate.
- However, hydroxide could be used to produce a **small amount** of enolate that is in equilibrium with the neutral aldehyde/ketone.

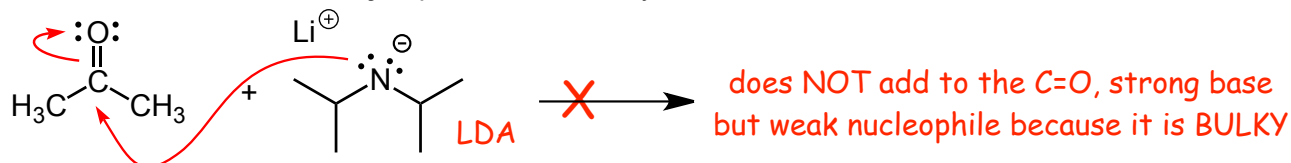
We need a Stronger Base: Recall some strong bases that we know:



- Lithium diisopropylamide is a very strong **bulky** base:



- In the acid/base reaction above, the ketone on the left is a much stronger acid than the amine that is formed on the right, therefore equilibrium lies essentially completely on enolate side.
- LDA can be used to **irreversibly** deprotonate an aldehyde/ketone and form an enolate anion.



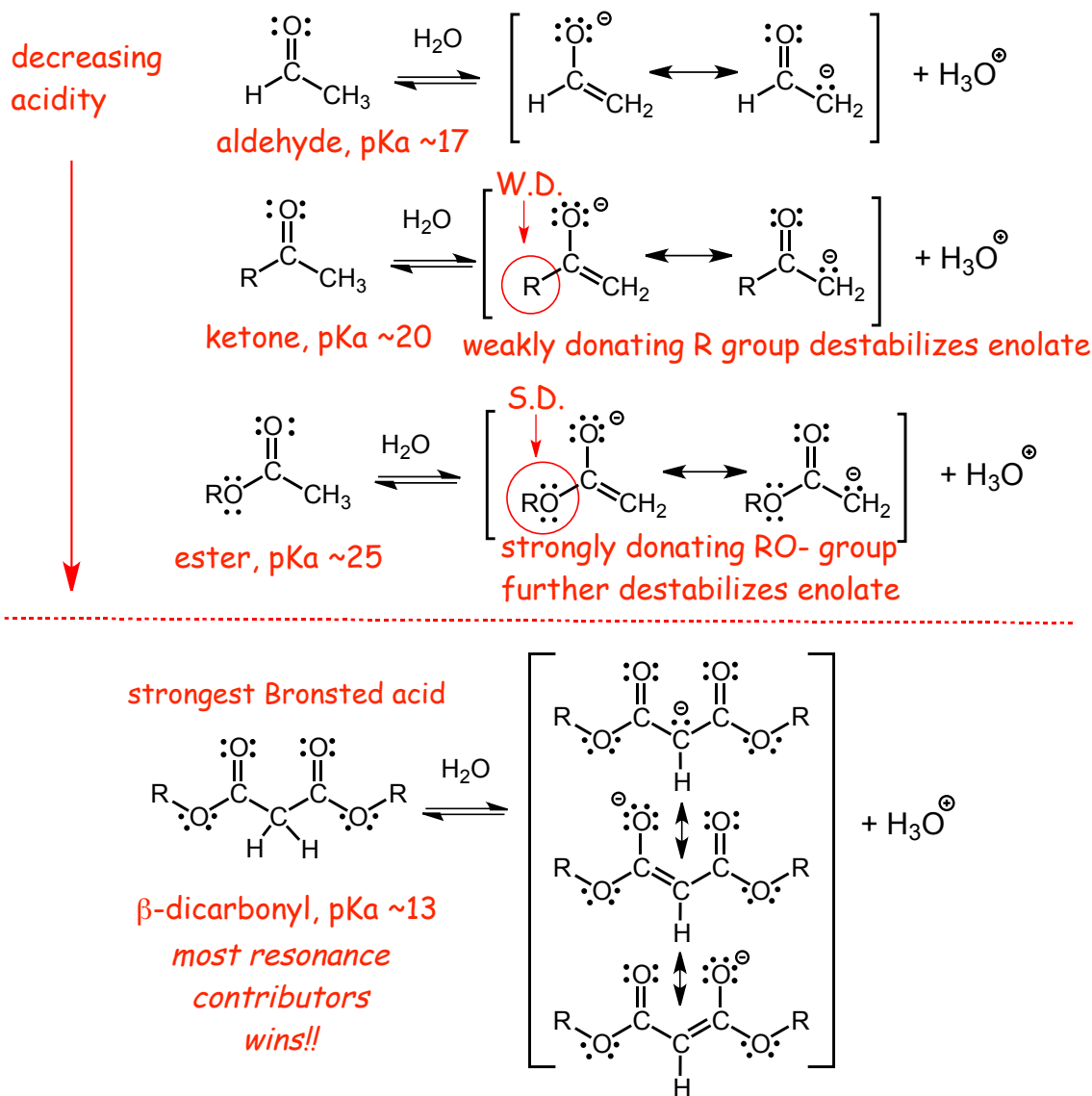
- LDA will **deprotonate** an aldehyde or ketone at a carbon alpha-to the C=O, but it will not **add** to the C=O the same way that other strong nucleophiles do, e.g. the acetylide anion, Grignard reagent etc., because it is **bulky** and therefore **sterically hindered**.

Summary:

- Use OH^- if you don't care about forming enolate reversibly.
- Use LDA if you want to form the enolate irreversibly, using LDA, **all** of the carbonyl is consumed.

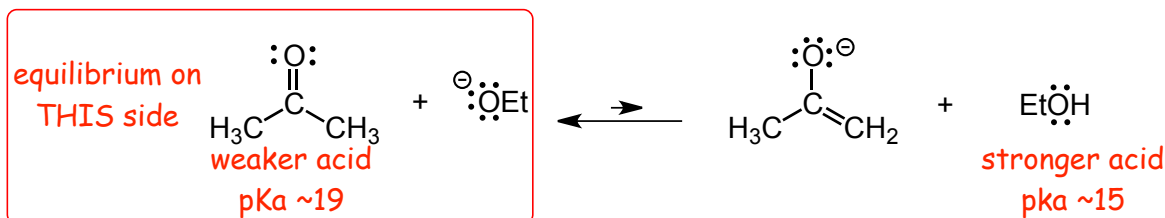
2 Relative Acidities of Carbonyl Compounds

- Compare an aldehyde, a ketone, an ester, and a new structure, a β -dicarbonyl (beta-dicarbonyl):



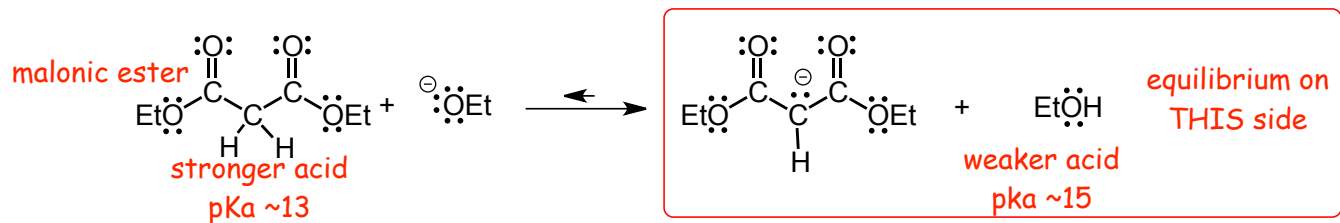
- The acidity order is thus esters (least acidic) < ketones < aldehydes.
- The β -dicarbonyl is by far the strongest acid because the enolate anion is **doubly** resonance stabilized.

And so:



- Adding a base such as an alkoxide (ethoxide is shown above) or hydroxide results in formation of only a very small amount of the enolate of an aldehyde or a ketone, most of the carbonyl is not deprotonated.

But.....

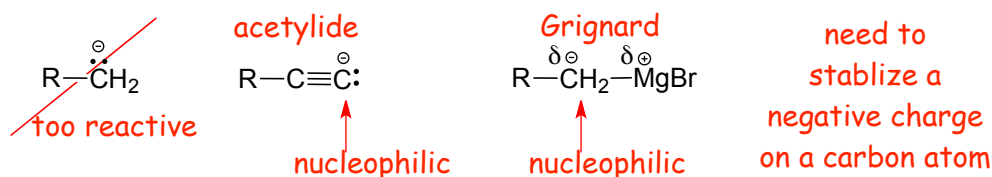


- Adding a base such as an alkoxide to a β -dicarbonyl results in essentially **complete** formation of the enolate anion.

3 Enolizable Hydrogens: What is this all about?

- We understand that the majority of the reactions we encounter can be understood terms of Lewis acid/base and electrophile/nucleophile theory, the Lewis base/nucleophile provides the electrons to make a new bond
- **Carbon** nucleophiles/Lewis bases are difficult to make, however, because carbon is not electronegative, it is not possible to have a simple carbon anion, the non-bonding electrons need to be stabilized somehow.

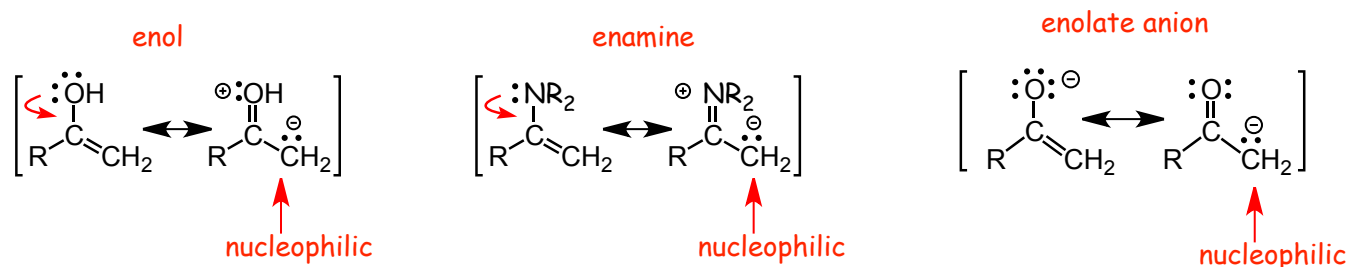
Some stabilized Carbon Nucleophiles/Lewis Bases we have already seen:



- The electrons in the acetylide anion are stabilized by sp hybridization, those in the Grignard reagent are stabilized in a weak bond to magnesium.

New carbon nucleophiles/Lewis bases on carbons based on enolizable Hydrogen atoms:

- Enols and enamines (see previously) and the enolate anion



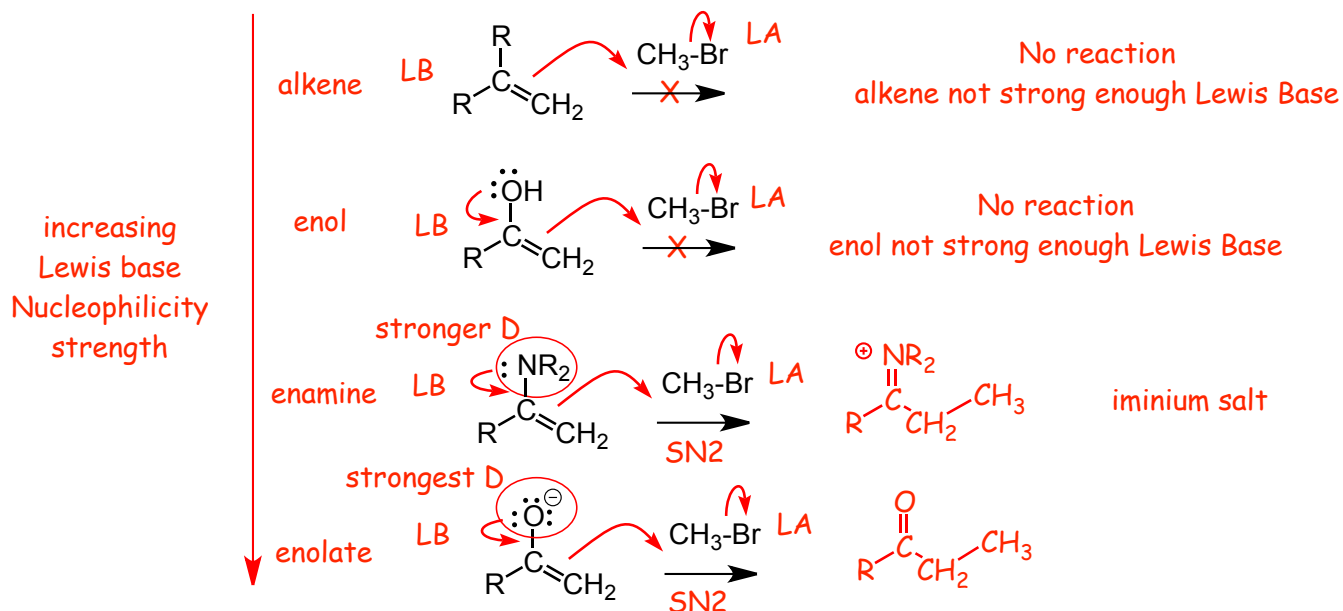
- The electrons on the nucleophilic carbon in the enolate anion are stabilized by **resonance**.
- The nucleophilic carbon in the enamine and enol has a partial negative charge by **resonance**.
- Enolate anions, enamines and enols are Lewis bases with **nucleophile** carbon atoms in the position next to (alpha to) the carbonyl carbon of an aldehyde or ketone.
- Enolates are formed by deprotonation of an enolizable hydrogen using a Bronsted base.
- Enamines are formed in reaction between an aldehyde or ketone with a secondary amine (with acid catalysis) and deprotonation of an enolizable hydrogen (we just didn't call it that previously).
- Enols are structural isomers of aldehydes/ketones where the position of **one enolizable** hydrogen is changed, we just didn't call it that previously.

4 Alkylation Reactions of Enols/Enolates

4.1 Alkylation of Aldehydes/Ketones via the Enolate Anion

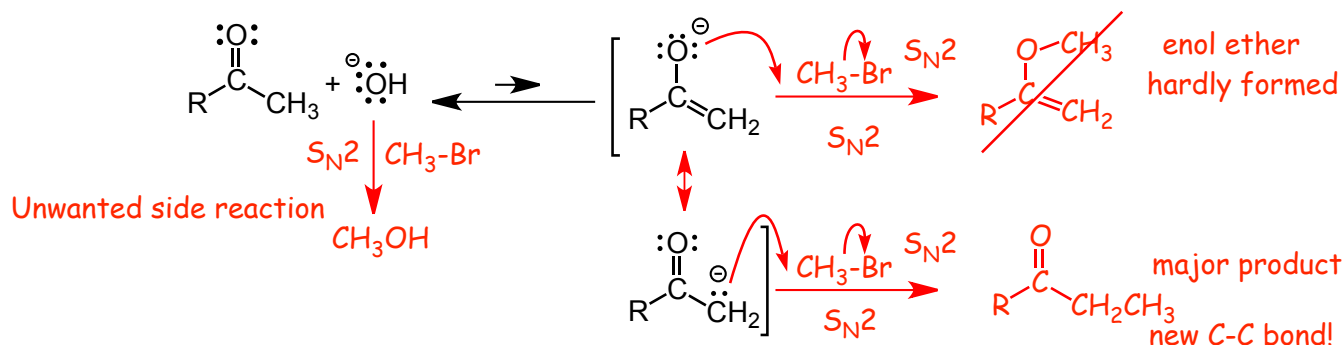
- Making C-C bonds is a very important reaction for enols, enolates and enamines.

A Basic Principle Underlying Enol/Enolate and related reactions:



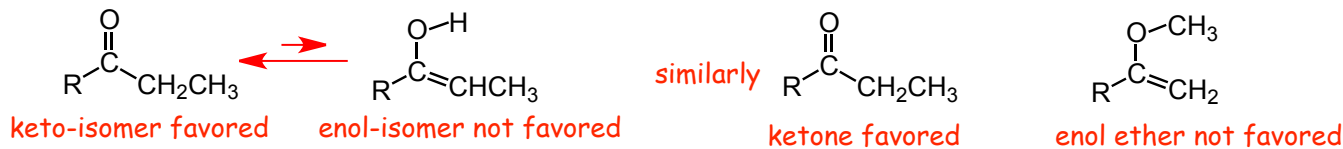
- The enamine and enolate are reactive (nucleophilic) enough to do SN2 with an appropriate alkyl halide, **and**, these reactions make new C-C bonds!

Alkylation via the Enolate Anion



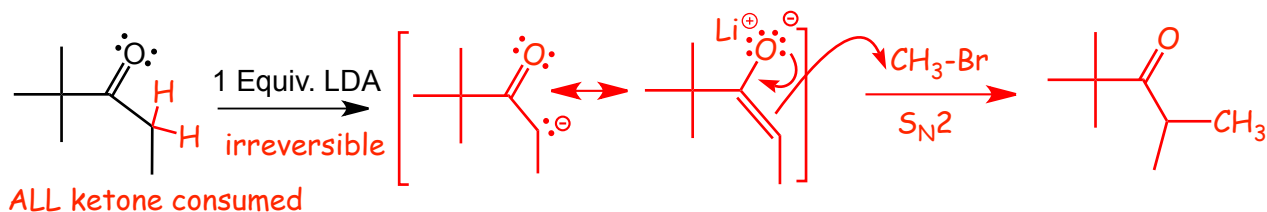
- In principle this should work, however, can't use OH^- to make the enolate because it **also** acts as a nucleophile, this problem can be fixed, see below.
- Addition occurs mainly at the **carbon** of the enolate anion rather than the oxygen.
- One way that we can understand this is that addition at oxygen forms a less stable enol ether (similar to keto/enol equilibrium, although it is actually more complicated than this).

Recall:



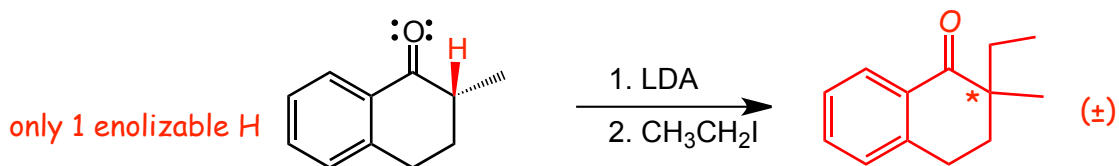
How to Fix the Problem of the base competing with the Enolate in the SN2 reaction?

- Use LDA!

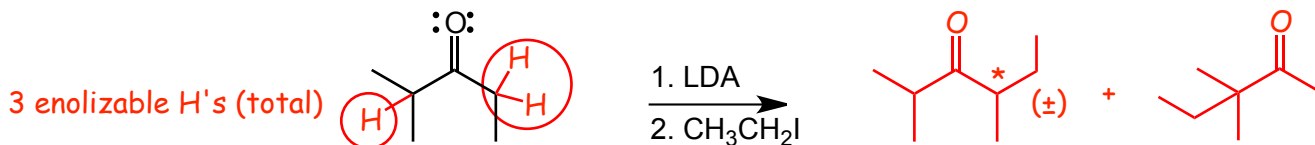


- One Equivalent of LDA completely deprotonates the carbonyl to form a lithium enolate (actually, the lithium ion may play a small role in controlling the reactions of the enolate).
- **Both** the carbonyl and the LDA are completely consumed when one equivalent is used.
- Alkyl halide should be 1° or allylic to ensure S_N2.

Examples



- Alpha-alkylation (α-alkylation) and formation of a new C-C bond is accomplished!
- It is best if there is only one **kind** of enolizable hydrogen atom or mixtures of products may result:



but 2 KINDS of enolizable H, thus two possible kinds of product

4.2 Alkylation of Aldehydes/Ketones via Enamines

- **LDA works well** if the rest of the molecule **can withstand the presence of the extremely strong base**. But in many cases we need a milder, more subtle approach, **enamines** allow such an approach.

Alkylation via an Enamine: The Stork Reaction.

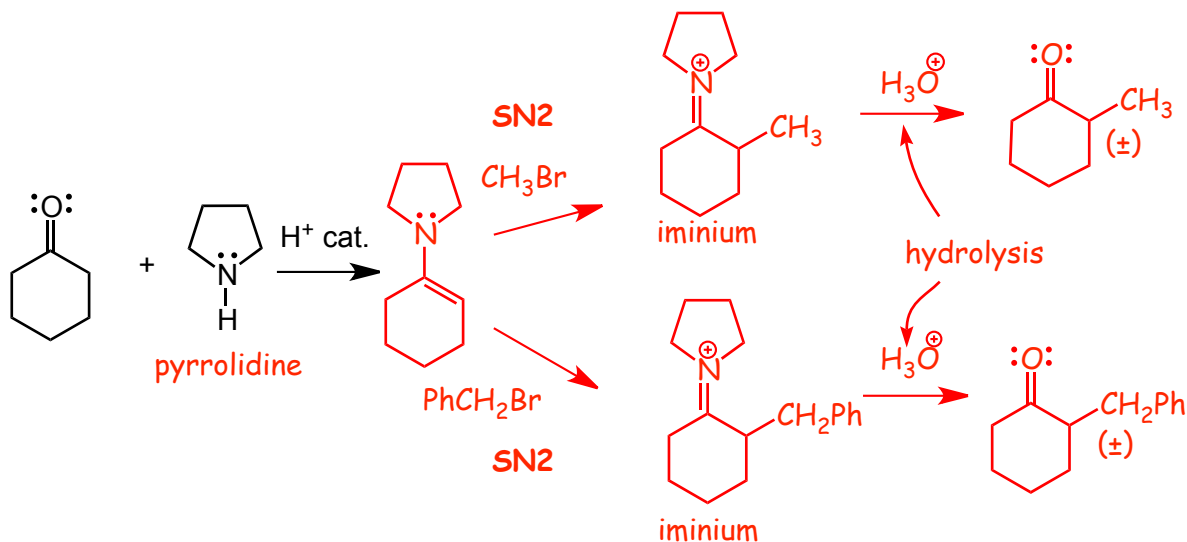
- An enamine is a stronger nucleophile than an enol, but less nucleophilic than an enolate.
- The Stork enamine alkylation reaction avoids LDA, which is a very strong base and also avoids enolate anion intermediates which are also strong Bronsted bases. As we will see, enolates can also react with the carbonyl structures they are formed from.

The Stork enamine reaction sequence: It seems a bit complicated, but it is actually relatively straightforward and is very much usually **preferred** over the LDA method.

1. Convert carbonyl to enamine.
2. React the halide with the enamine (S_N2).
3. Hydrolyze enamine to carbonyl (acid workup).

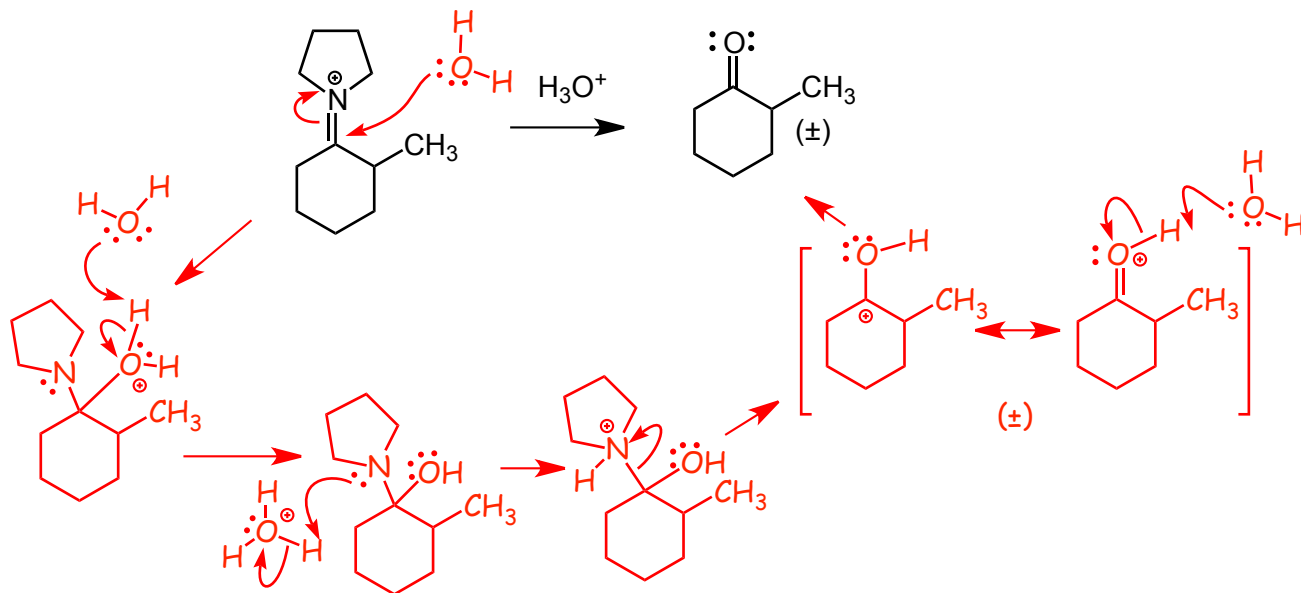
Examples:

H⁺ could be HCl, TFA, TsOH etc., any organic acid, but **not** H₃O⁺.

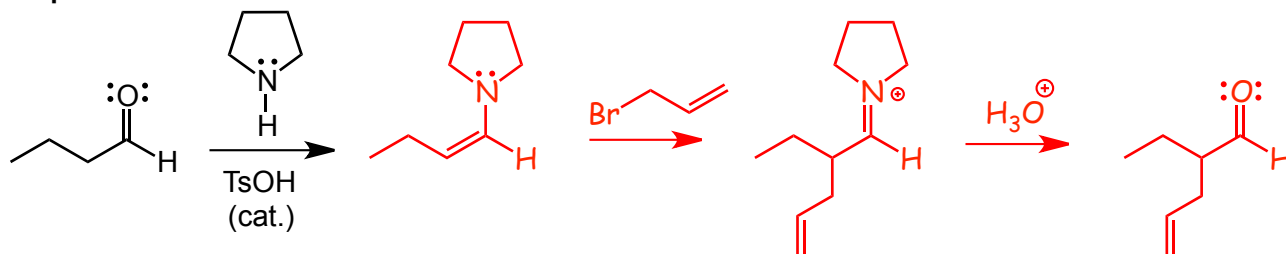


- Alkylation is accomplished after hydrolysis of the iminium salt that is formed in the SN2 reaction.
- The iminium salt has a carbon with two bonds to heteroatoms (nitrogen in this case), and we have learned previously that molecules with this structural feature can be hydrolyzed with water under acidic conditions.
- The hydrolysis mechanism is very similar to those that we have seen previously, in this case the iminium salt **starts** with a formal positive charge, and so protonation is not needed in the first step to get the reaction started, it is a strong enough LA/Electrophile to react directly with water as the weak LB/Nucleophile.

The Iminium Hydrolysis mechanism



Example



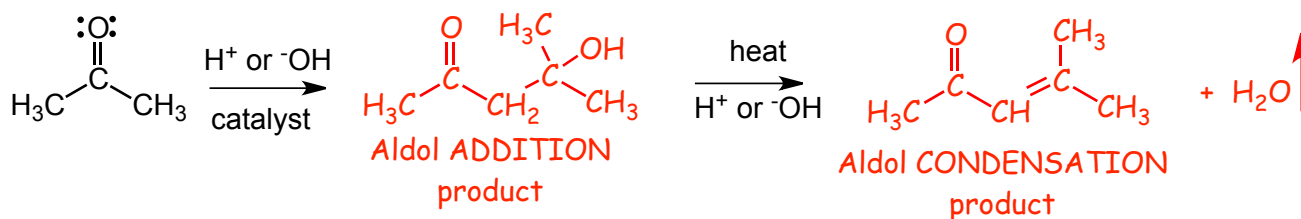
5 Aldol and Claisen Reactions of Enols/Enolates

5.1 Aldol Condensation of Aldehydes/Ketones

Definition: Condensation reaction liberates a small neutral molecule product, often water, that can be "condensed".

Definition: Aldol reaction is another nucleophilic addition to an aldehyde or ketone where the nucleophile is an enol or enolate.

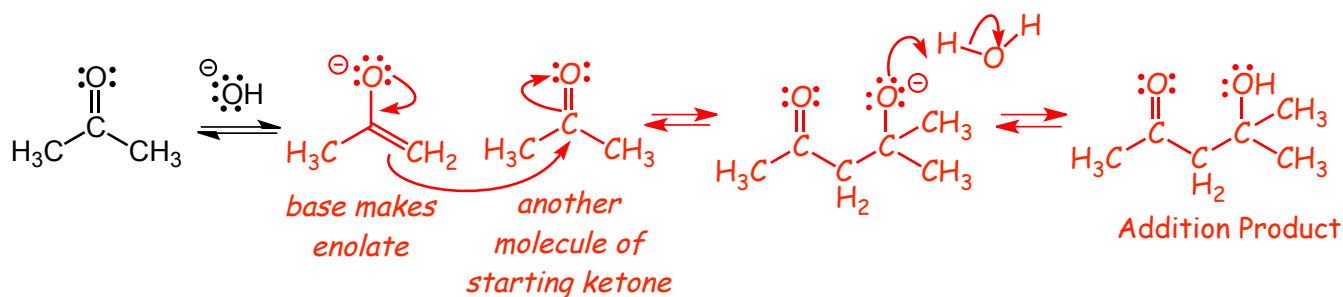
A summary of the reaction:



- The product is a conjugated "enone", formed after **elimination** of water via the (E1 or E2 mechanism).
- The water that is formed in the reaction is removed irreversibly by heating (it can subsequently be condensed).

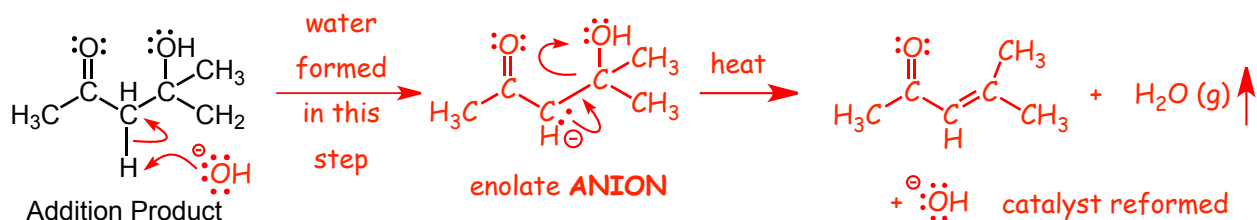
The Aldol Condensation Reaction Mechanism: Base catalyzed via the Enolate Anion

1st part: Formation of the **addition** product:

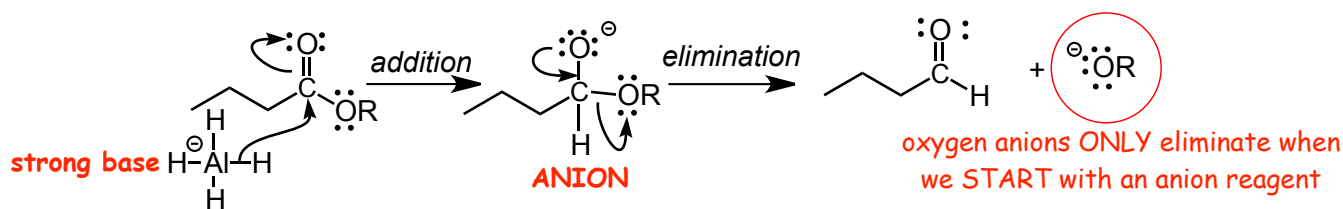


2nd part: Formation of the **condensation** product.

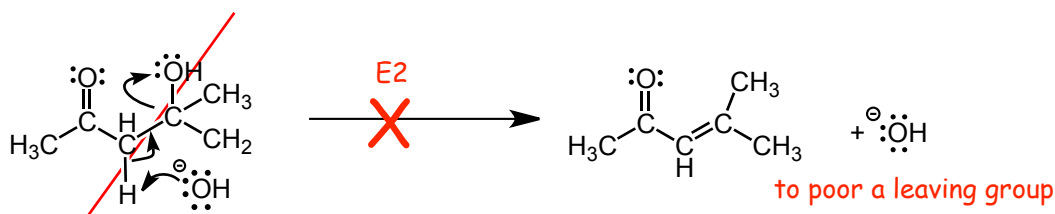
- Formation of addition product is **reversible**, **but**, formation of condensation product is **irreversible due to elimination of water**.
- The elimination can be made irreversible by physically removing the water by evaporation away from the reaction by heating. This water is often **condensed** (hence a condensation reaction), this **condensation** required to make overall reaction "go" irreversibly.
- **First**, hydroxide removes **another** enolizable proton to make another enolate anion, **then**, hydroxide leaves. This not a conventional E1 or E2 elimination, it is called an E1cb mechanism, but you don't need to know that.



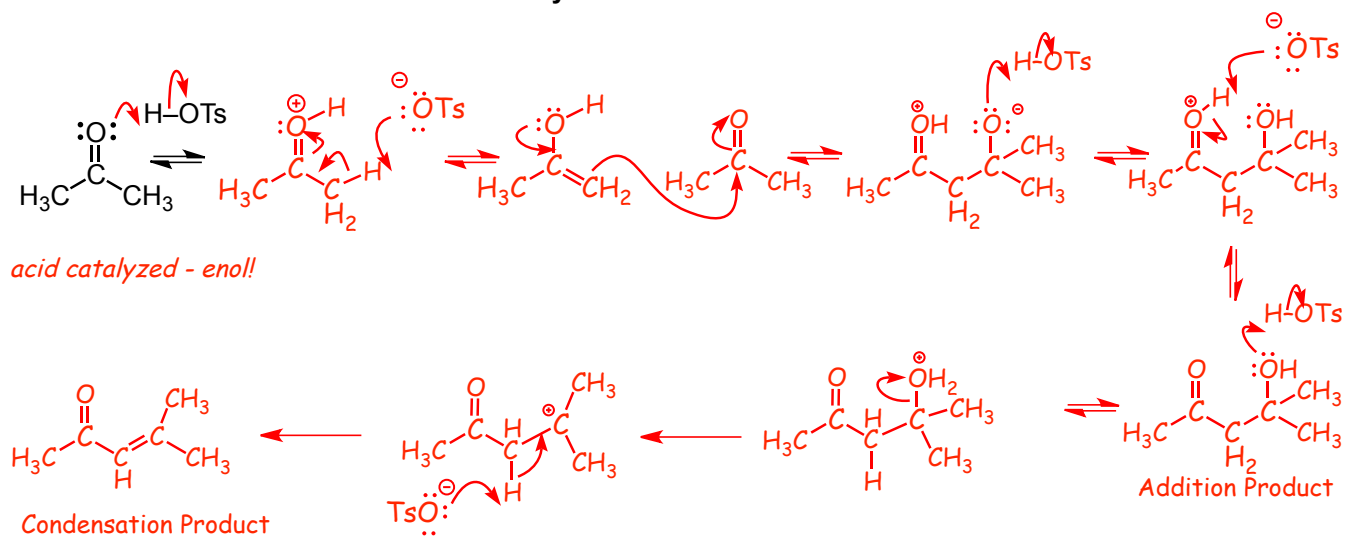
- Every time we see an oxygen anion as a leaving group the structure it leaves from is itself an anion (an enolate anion in this case), we need to get high energy electrons into the structure that "kicks out" the hydroxide (it must be an anion), and that means starting the reaction with high energy electrons, usually in the form of strong base. For example, when we reduced an ester with LiAlH_4 , the intermediate anion was able to have an oxygen anion as the leaving group, again we needed to start with a strong base.



- A conventional one-step E2 elimination does **not** occur because the hydroxide oxygen anion is too poor a leaving group.

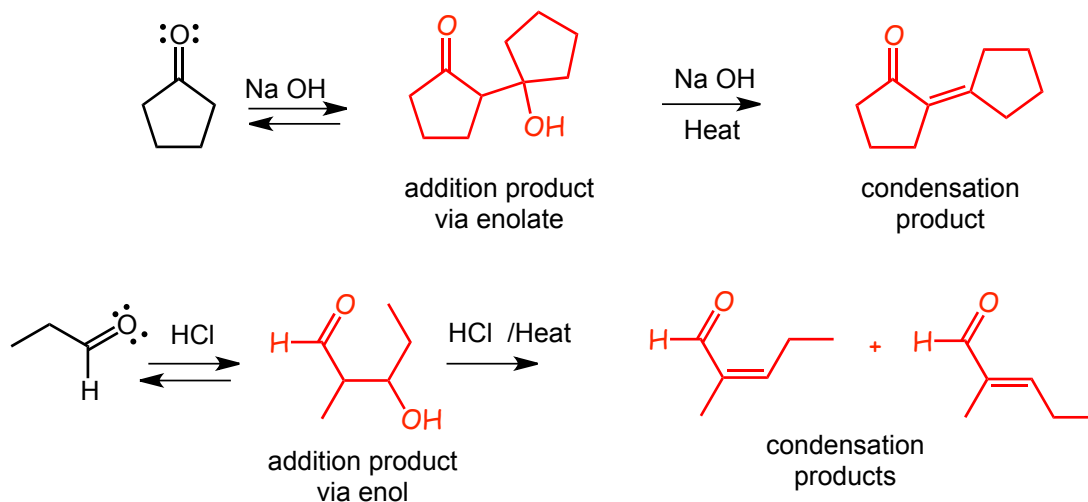


Aldol Condensation Mechanism: Acid catalyzed via the enol:



- The acid catalyzed reaction proceeds via the **enol**.
- The water elimination reaction could proceed via either the E1 or the E2 mechanism (E1 shown here).

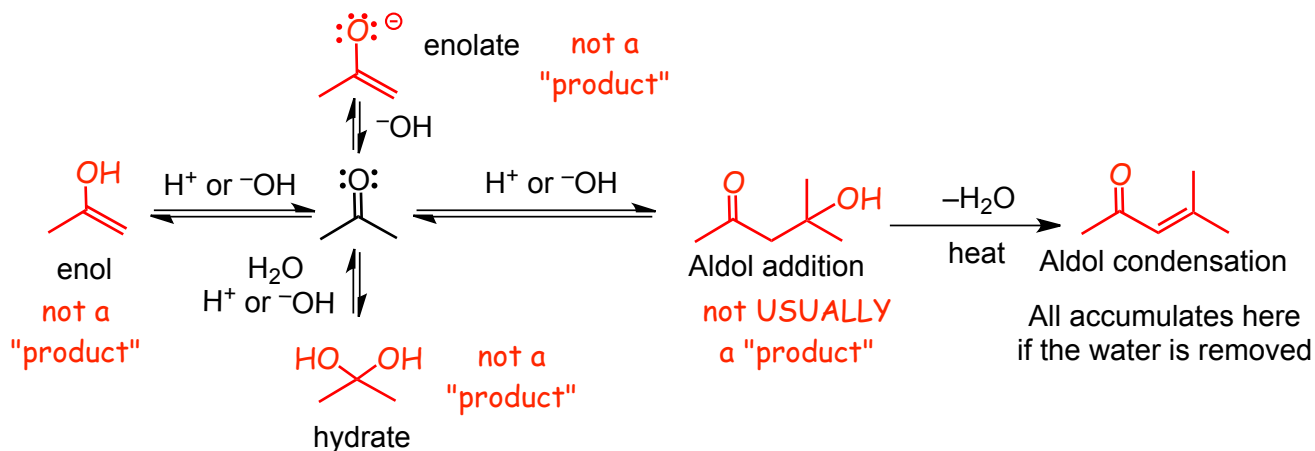
Examples



- In **base catalyzed** reactions, the reaction proceeds **via the enolate anion**.
- In **acid catalyzed** reactions, the reaction proceeds **via the enol**.

5.2 Rationalizing the Various Possible Products, How do Carbonyls Know What to do?

- So far we have seen the following acid and base catalyzed reactions for carbonyl compounds"



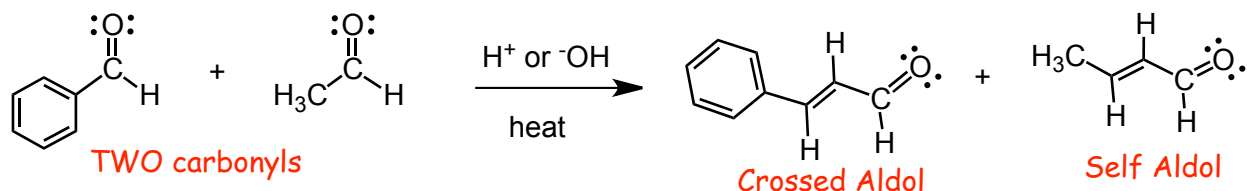
How does the carbonyl know which one to do?

Answer: It doesn't, so it does them all! Depending upon the amount of water, acid and bases catalyst, we would expect some unreacted carbonyl, some enolate, some enol, some hydrate and some Aldol addition product, **all** in equilibrium (all are formed reversibly). However, if the water is removed (for example by heating), then everything can eventually be "driven" towards the Aldol condensation product, which is formed **irreversibly**.

- Note that the enolate can only be made in the presence of base, but **both** enol and enolate (and also hydrate) can form in the presence of acid and base, **however**, in the presence of base, the enol has to be formed VIA the enolate, in other words both enol and enolate are present in base, and the enolate is considerably more reactive than the enol, which is why the enolate is the active Lewis base/nucleophile under basic conditions, under acid conditions the reactive Lewis base/nucleophile is the enol.

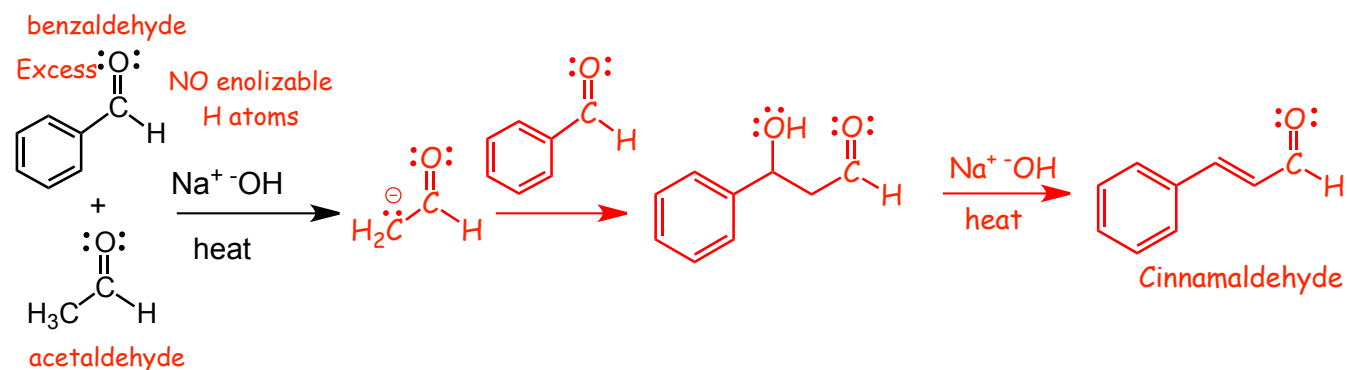
5.3 Crossed Aldol Condensations

- Aldol reactions between different carbonyl compounds have a potential major problem.....



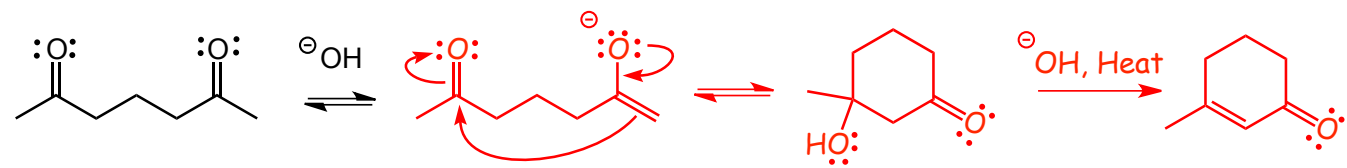
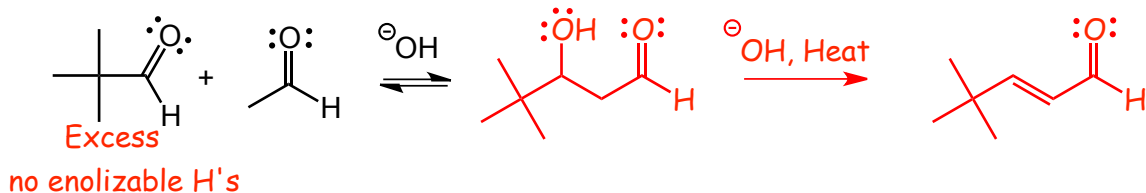
- More than one possible product, both crossed Aldol and self-Aldol reactions can occur.
- How to control these reactions and direct towards a controlled crossed Aldol reaction?

Select Appropriate Conditions:



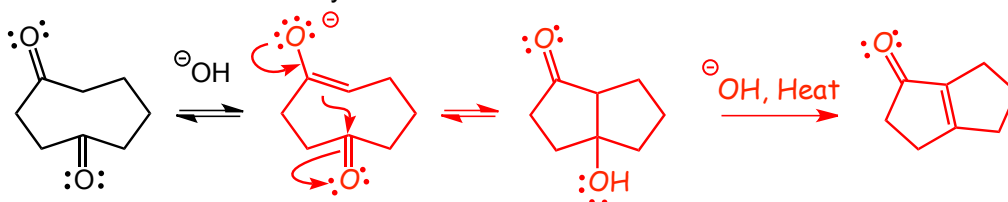
- We can't make an enolate of benzaldehyde, it can't do a self-Aldol and it can't do an Aldol with acetaldehyde
- Benzaldehyde is in excess to ensure the enolate from acetaldehyde reacts with it, and to minimize the acetaldehyde self-Aldol reaction.

Examples



- An abbreviated (incomplete) mechanism is shown above.

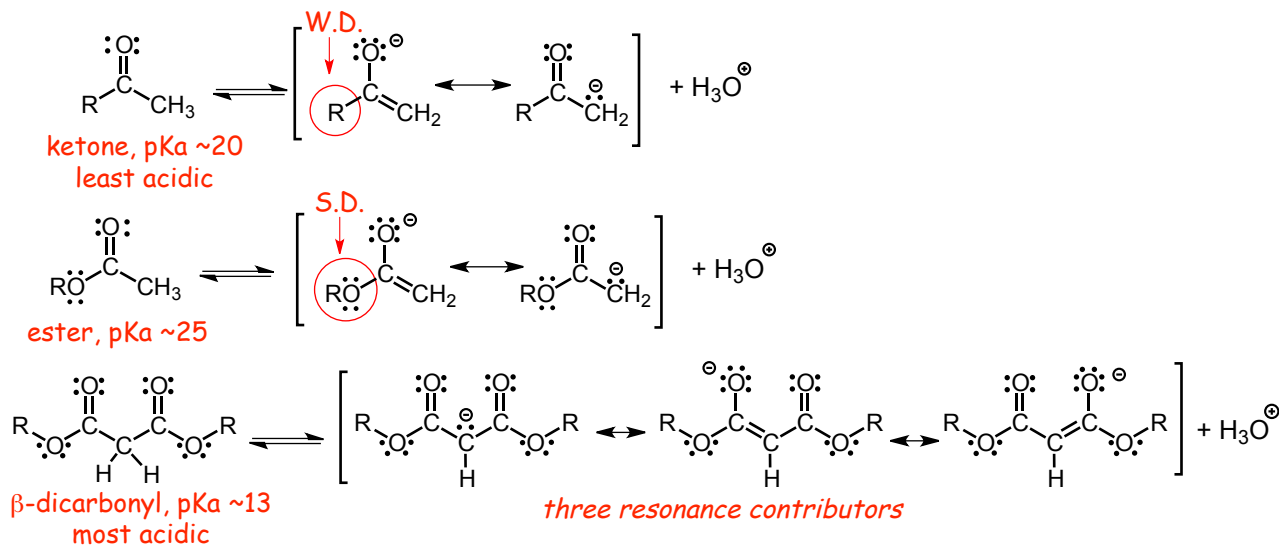
- There are two kinds of enolizable hydrogens in the molecule above, but only one gives the favored six-membered ring.
- Intramolecular reaction wins out over any intermolecular reaction.



- An abbreviated (incomplete) mechanism is shown above.

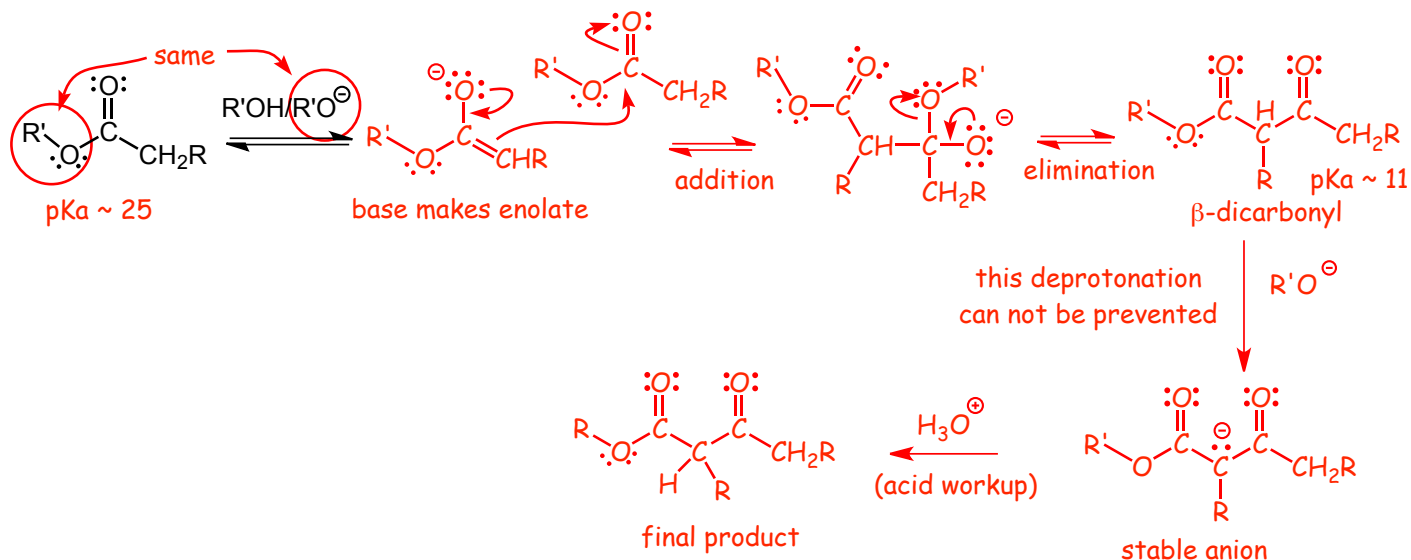
5.4 Claisen Condensations : Enolates of Esters

- Revisit acidity of carbonyl compounds:



The Claisen Reaction:

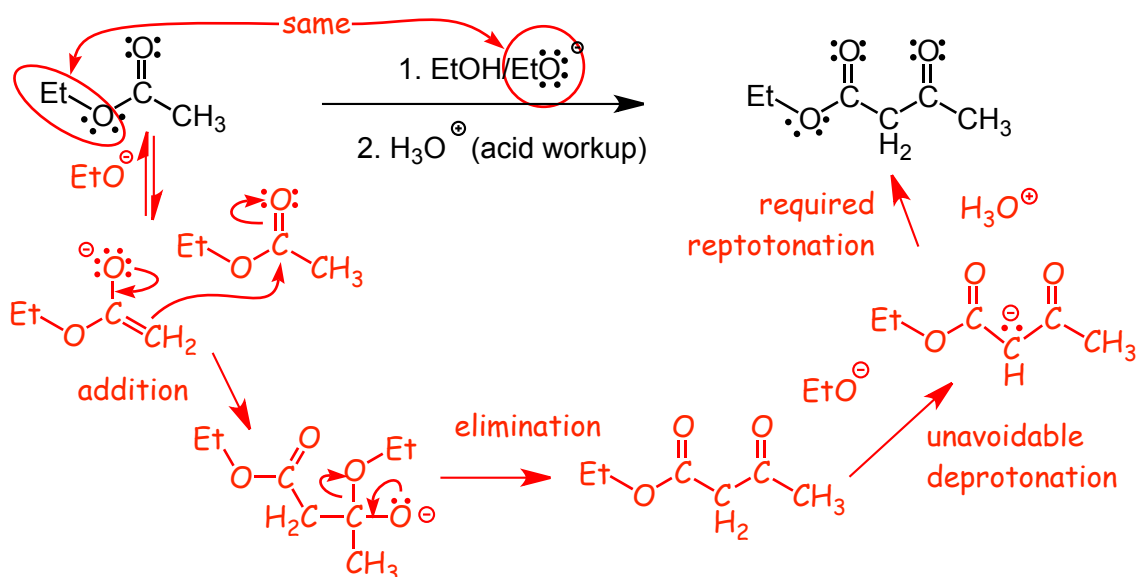
- Every time we have had a **strong nucleophile** reacting with an ester, for example a Grignard, hydroxide, hydride in the form of LiAlH_4 , etc. the reaction has always been addition/elimination.
- In the Claisen reaction an enolate is the nucleophile, which is a strong nucleophile.
- The Claisen reaction is of a strong nucleophile reaction with an ester, the mechanism, therefore, is **addition/elimination**.



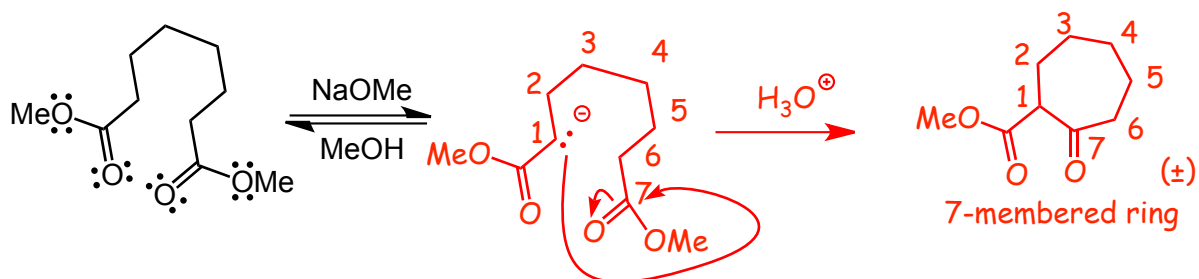
- Again, the addition/elimination mechanism.
- The pKa of $\text{R}'\text{OH}$ is ~ 15 , thus the $\text{R}'\text{O}^-$ must irreversibly deprotonate the β -dicarbonyl product that is formed initially, which has a pKa of ca. 11.

- Therefore, H_3O^+ **must** be added as a last step to reprotonate the final product. This **acid workup** step only has to protonate the β -dicarbonyl enolate, and so simple addition of aqueous acid works.
- However, this **last** deprotonation of the beta-dicarbonyl makes reaction overall **irreversible**.
- The base used is the same alkoxide of the ester ($\text{R}'\text{O}^-$) to ensure that **trans-esterification does not occur**.

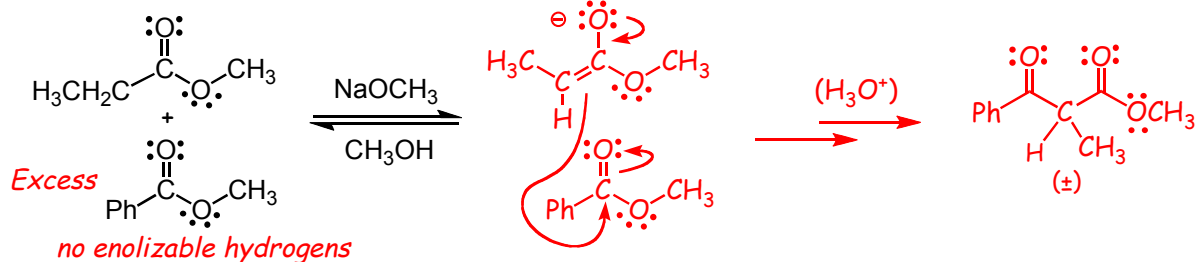
Example 1: A Self-Claisen with only 1 kind of enolizable proton:



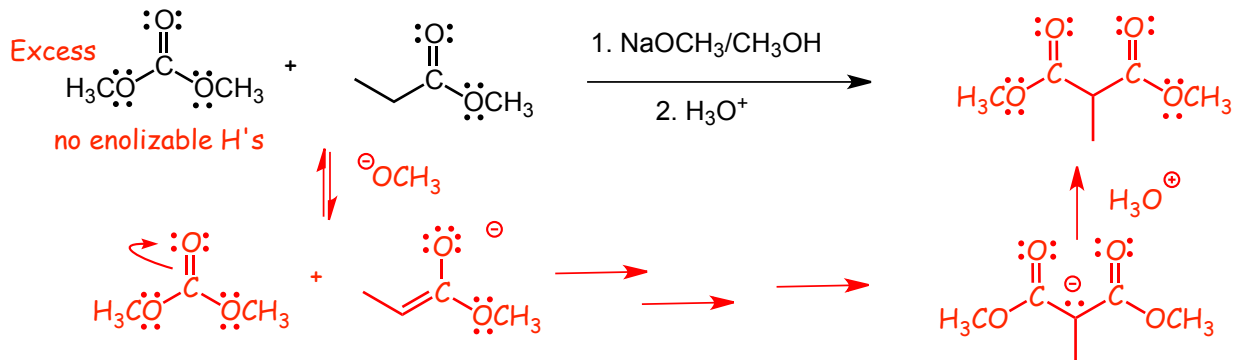
Example 2: An intramolecular Claisen (called a Dieckmann condensation) with only 1 kind of enolizable proton:



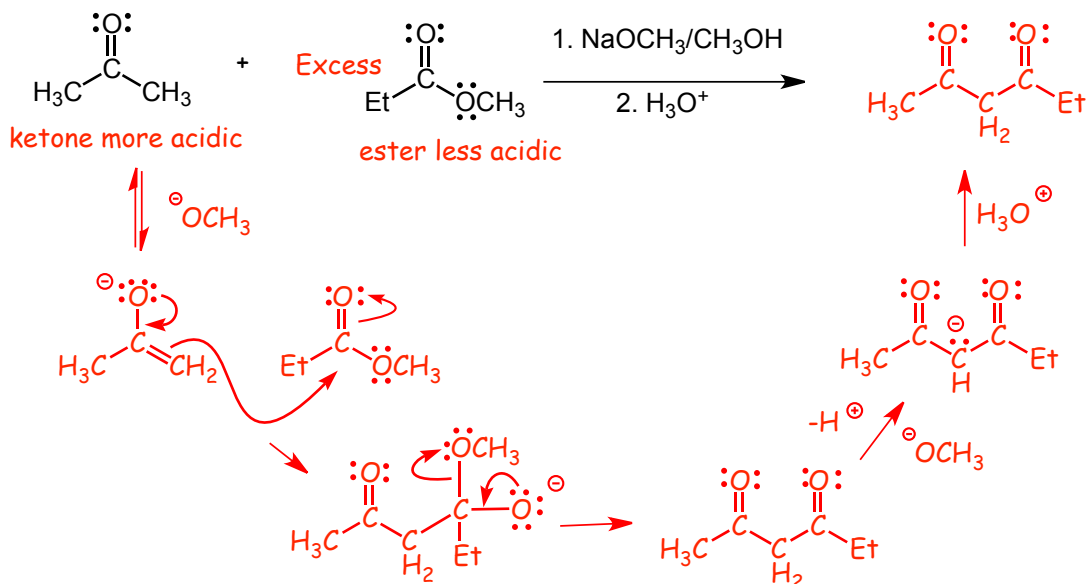
Example 3: A crossed Claisen reaction with only one kind of enolizable proton:



Example 4: A crossed Claisen with two esters:



Example 5: A crossed Claisen with a ketone:



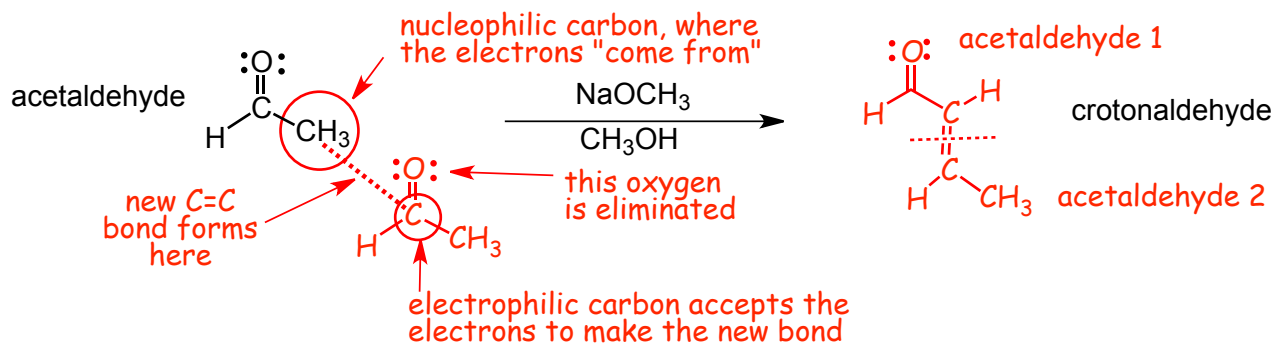
- Both structures have enolizable protons, but the ketone is more acidic, thus the enolate of the ketone forms and reacts preferentially.

5.5 Aldol and Claisen Reactions Using Heuristics

- Heuristics are skills students develop that allow them to solve the problems more quickly than by working them out from first principles, by skipping steps that become obvious.
- **Heuristics can't be taught**, each student develops their own heuristics as a result of repeatedly solving a specific type of problem.
- Nevertheless, we will now show you how some students will solve Aldol and Claisen problems heuristically. Please appreciate the context in which we tell you this. We are not trying to give you "short-cuts" or "tricks", and we definitely don't want you to start learning Aldol or Claisen reactions in this way in the hope that you can save some time by skipping the details. You still need to understand exactly how and why these reactions work, you need to know the mechanisms also! However, it is also important to understand that there is nothing "wrong" with solving problems this way, all skilled students develop them naturally, here we are just "pointing the way".

Example Aldol Problem: Aldol reaction of acetaldehyde is performed industrially on a scale of many thousands of tons annually to form crotonaldehyde, which is used in the synthesis of many useful chemicals, including sorbic acid, a food preservative. How do you draw the structure of the crotonaldehyde Aldol product without writing the entire mechanism?

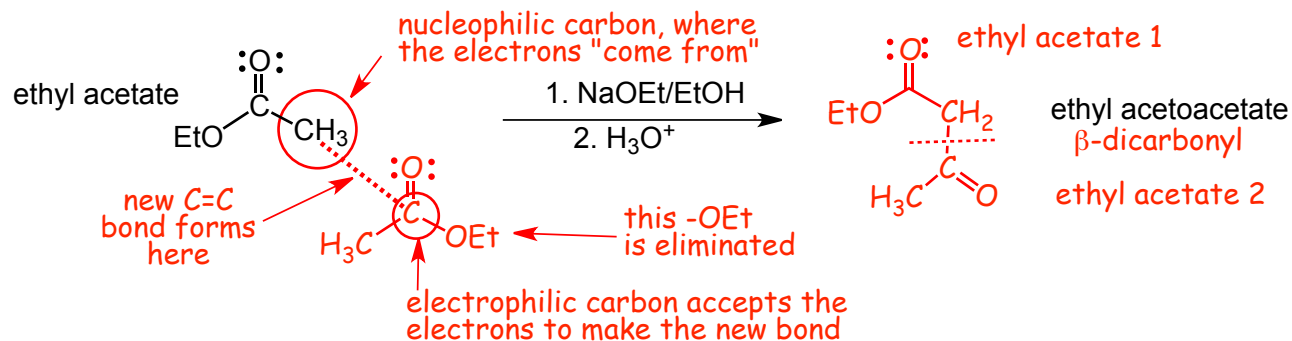
- **First**, no other organic structures are involved, the aldehyde must react with itself, so **draw another molecule**.



- **Identify** the two carbons involved in the bond-forming reaction, don't forget basic Lewis acid/base nucleophile/electrophile principles! The electrons come from the carbon with the enolizable hydrogens. These electrons make the new bond to the $\text{C}=\text{O}$ carbon.
- **Eventually a $\text{C}=\text{C}$ bond forms** between these two carbons so eliminate atoms as necessary. The product should be a conjugated enone.

Example Claisen Problem: Claisen reaction of ethyl acetate forms ethyl acetoacetate, which is used in the synthesis of many useful chemicals, including dyes, perfumes and plastics. How do you draw the structure of the ethyl acetoacetate Claisen product without writing the entire mechanism?

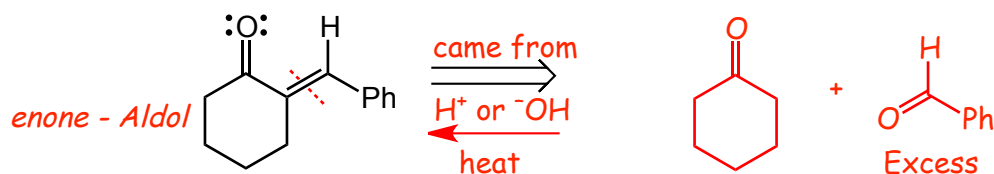
• **First**, no other organic structures are involved, the ethyl acetate must react with itself, so **draw another one**.



- **Identify** the two carbons involved in the bond-forming reaction. The electrons come from the carbon with the enolizable hydrogens. These electrons make the new bond to the C=O carbon.
- The mechanism is **addition/elimination**, therefore, eliminate the -OEt on the electrophilic carbon.
- The product should be a β -dicarbonyl

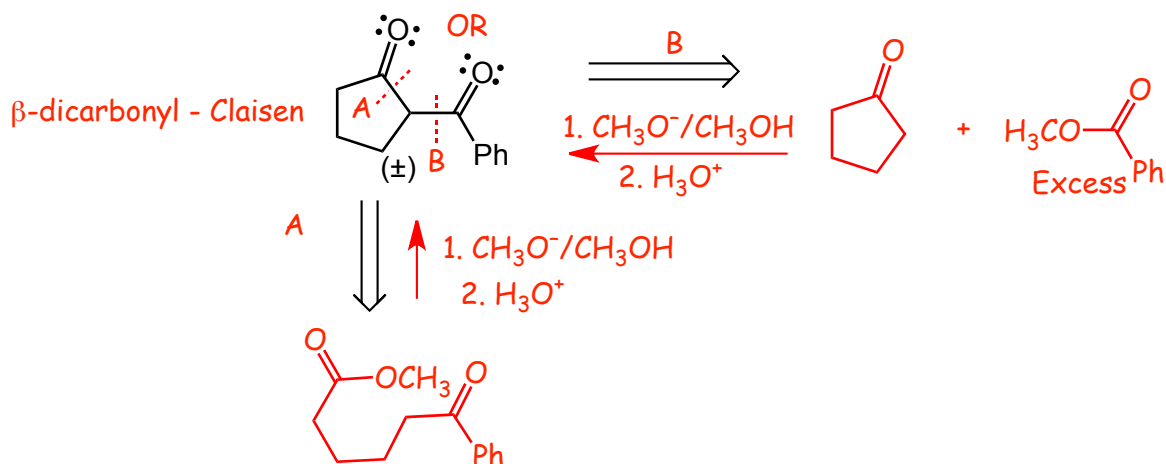
5.6 Aldol/Claisens in Reverse

Example 1:

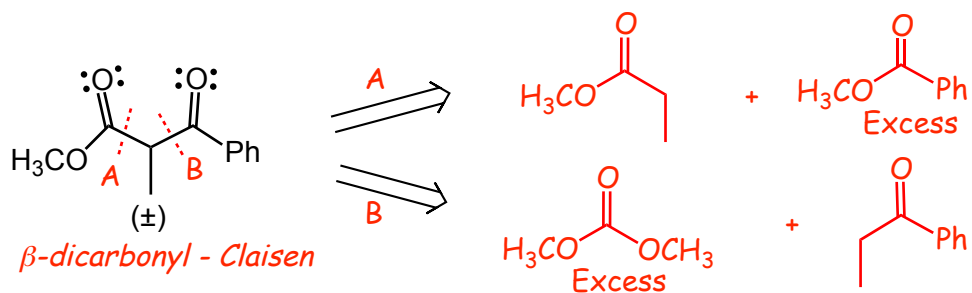


- The bond that is made in the Aldol condensation is the C=C bond, disconnect this C=C bond (pull it apart) to determine the structures of the reacting fragments.

Example 2:



- The bond that is made in the Claisen reaction is one of the central C-C bonds between the two C=O.
- Therefore, there are almost always two ways of generating a Claisen reaction product, sometimes one of these is preferred over the other.
- Disconnect each of the two C-C bonds (pull them apart) to determine the two possible sets of structures of the reacting fragments.
- Reaction **B** is slightly better because there is only one set of enolizable hydrogens in the reactants.
- Reaction **A** is still OK, since the ketone "end" is much more acidic than the ester "end" and thus the desired reaction will probably occur to give the desired product.

Example 3:

- There are almost always two ways of generating a Claisen reaction product, sometimes one of these is preferred over the other. In this case neither is preferred, either method could be used

5 Summary of Reactions of Enols/Enolates

Do not start studying by trying to memorize the reactions here!

Work as many problems as you can, with this list of reactions in front of you if necessary, so that you can get through as many problems as you can without getting stuck on the reagents/conditions, and so that you can learn and practice solving reaction problems.

