Loudon Chapter 22 Review: Enols and Enolates
Jacquie Richardson, CU Boulder – Last updated 3/9/2020

The previous three chapters were about adding things directly to the base of a carbonyl. In this chapter, we'll look at reaction that happen on the carbon next to the base of the carbonyl, the α carbon. Any hydrogens attached to this position are called α Hs. They are much easier to pull off than a regular H attached to C, because of the resonance forms you can get in the product. This makes an enolate, which looks like a deprotonated enol.

Enolate   Enolate
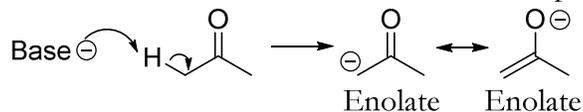
Another functional group that shows up in this chapter is the enol, which we've seen in the past. The mechanism for making it is the reverse of keto-enol tautomerism.
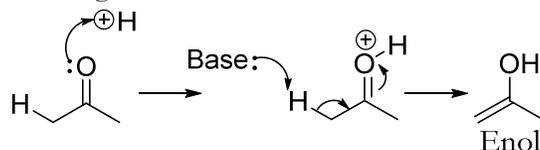
Enol

We already know that this is an equilibrium reaction that strongly favors the ketone form, but there's still a tiny bit of enol present at any given time (usually around one part in 10^6 or 10^7). In most cases, that tiny amount of enol creates the product, and then more ketone turns into enol to replace it. Some molecules can form very stable enols though. For example, phenol exists almost exclusively in its enol form, because that's the only way for it to be aromatic. And β-dicarbonyls like to form the enol, because they can hydrogen-bond to themselves and because the enol form is conjugated. If you remember decarboxylation, it looks a lot like the setup for that mechanism.

| Keto form | Enol form | Keto form | Enol form |
| Less stable | More stable | Less stable | More stable |
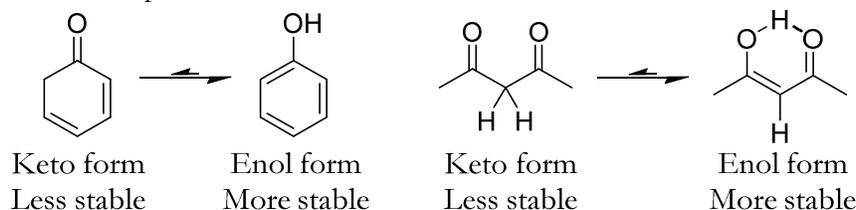
We can make enols with either acid or base, but usually if there's base around then the enolate will be the major product. So in this chapter, **reactions in acidic conditions will go via the enol, and reactions in basic conditions will go via the enolate.**

Reactions based on proton exchange
Either the enol or the enolate will slowly lose and regain its proton at the α position. Normally this doesn't change the molecule, but in some circumstances it does. For instance, if you put a molecule in an environment with deuterium, it will slowly exchange its Hs for Ds.

Another way to see this happening is to put a stereocenter at the α position. If it converts to the enol or the enolate then it loses its stereochemical information, since it has a double bond to the α carbon. This makes it form the racemic product (undergoing racemization).

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50/50 mixture of enantiomers
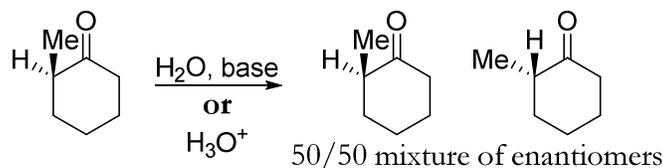
α-Halogenation

This just means removing an α H and attaching a halogen in its place. You can do this in either acid or base. In acid, you make the enol first, by the mechanism on the first page. Then it attacks a molecule of dihalogen, usually Cl_2 or Br_2.
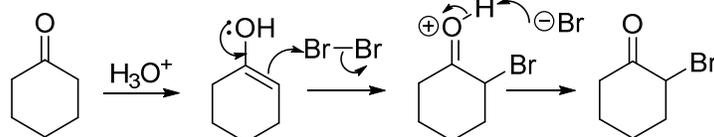
Note that having the halogen on the molecule means the reaction is less likely to happen a second time, because the bromine is creating a partial positive charge on the molecule and destabilizing the intermediates that lead to the enol form. So this reaction normally only happens once per molecule in acid.

On the other hand, you can also do this reaction in base. In this case it goes by the enolate, which attacks the dihalogen by almost the same mechanism.
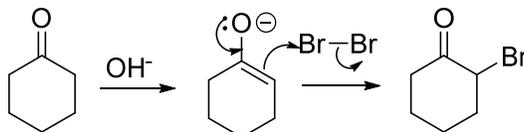
The big difference is that having a halogen makes the enolate *more* stable, since the negative charge is partially cancelled out. This means that once the reaction has happened once, it's more likely to keep happening until all Hs are replaced at that carbon. In fact, it's difficult to make this reaction stop after just one addition if it's in base.
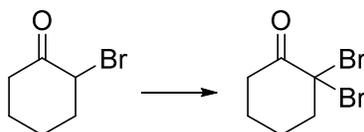
An interesting version of this happens when you have an α C with three Hs on it – in other words, the molecule is a methyl ketone. Like you'd expect, all 3 Hs get replaced.
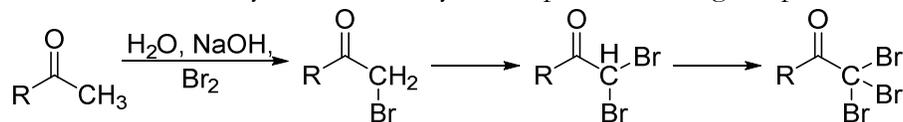
Even though carbon is usually not considered a leaving group, it turns into a pretty good leaving group once it has 3 halogens on it. So at this point you use an equivalent of OH^- to attack the base of the carbonyl and kick out the leaving group, much like in Ch. 20. This gives the carboxylic acid, which gets deprotonated immediately. To turn it back into the acid you neutralize with H_3O^+.
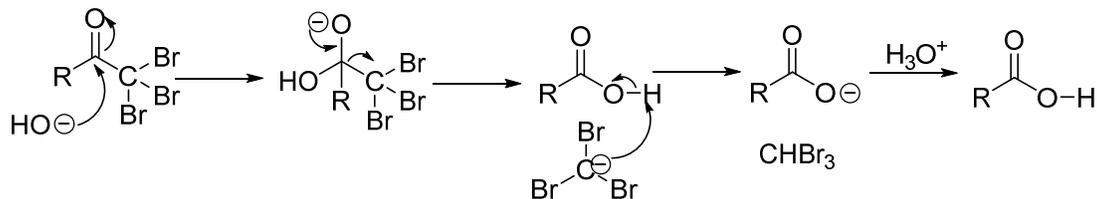
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You also make one molecule of CHX_3, which is called a haloform. The chlorine version of it, for instance, is chloroform. For this reason, this reaction is called the haloform reaction. It works with Cl, Br, or I. Overall it looks like this:
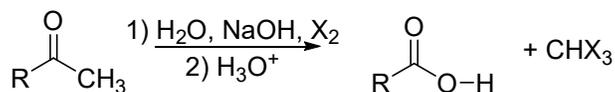
One final version of α halogenation is on a carboxylic acid. In this case, you need special conditions. You can't use base because that would just deprotonate the carboxylic acid, and you can't use acid because not enough of the molecule will form an enol at any given time. So instead, you use PBr_3 or P with Br_2 to convert the acid temporarily to the acid bromide. From there you can easily make the enol and do the same reaction as above. Then to finish it off, the molecule gets converted back to the carboxylic acid. This reaction is called the Hell-Volhard-Zelinsky reaction, or HVZ, and it only works well with Br. The overall reaction is:
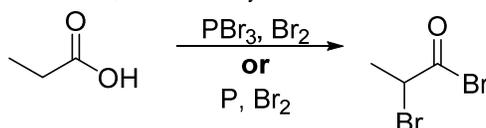
From there, you can convert back to the carboxylic acid by exposing it to water, or do any of the Ch. 21 chemistry for acid chlorides.

The products of all these reactions can undergo normal things that alkyl halides do, especially elimination and substitution reactions. If you want to attach a small, nucleophilic group at the α position this is the way to do it. You can stick on cyano groups, alkoxides, amines, or different halogens. First you halogenate the molecule with either acidic conditions (for a ketone or aldehyde) or HVZ (for an acid), then swap that halogen out for something else.
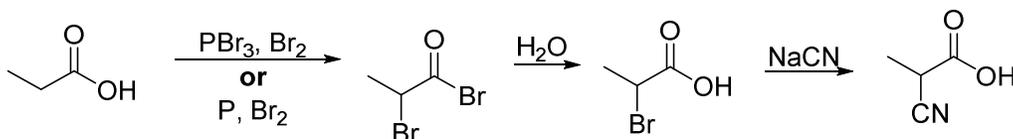
Aldol Addition and Condensation

An aldol addition involves forming either the enol or the enolate and then sending it to attack on the base of another carbonyl via Ch. 19-like chemistry. In base, it uses the enolate.
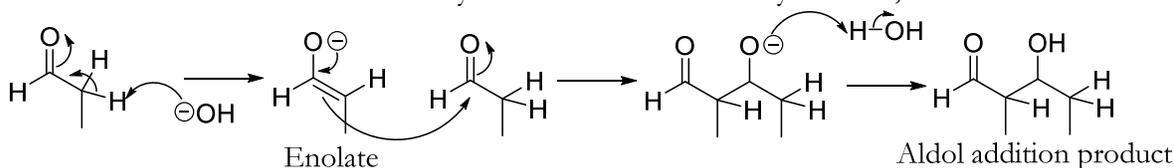
This is not always the end state. If you use stronger base or higher temperatures, you can go past the aldol *addition* product to the aldol *condensation* product. This involves eliminating a molecule of water and getting a double bond conjugated to the carbonyl. In base, this goes by a mechanism that's kind of the opposite of E1: an H gets pulled off the molecule and then the leaving group kicked off. For this reason, it's called E1$_{cb}$, for "conjugate base".
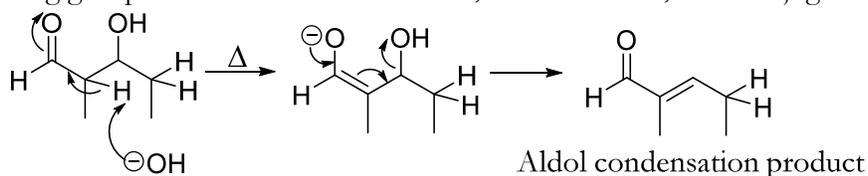
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Usually the expectation is that if heat is written on the arrow or if the product has some big benefit from being conjugated (for example see Claisen-Schmidt condensation below), you'll get the condensation product. Otherwise you get the addition product. Overall, addition and condensation in base are written like this:

You can also do this in acid, but the enol does the attacking. Like in Ch. 19, you can make the carbonyl more attackable by protonating it first. So it looks like:

Enol   Aldol addition product
                                                                              (not isolated)
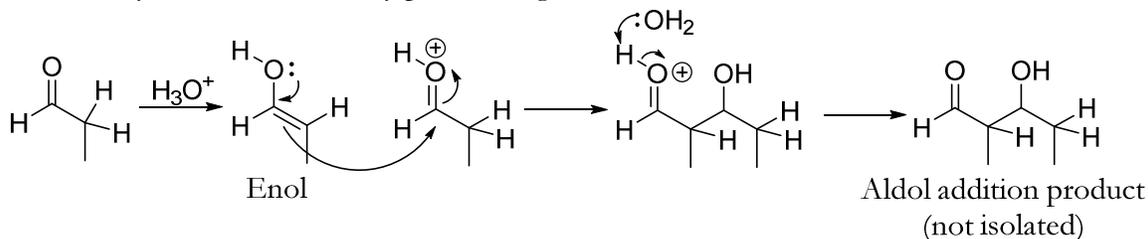
In this case heat isn't required to do the condensation – the molecule automatically goes all the way through. The mechanism is just a standard E1 elimination: protonate the OH group and drop it off first, then the H leaves.

Aldol condensation product
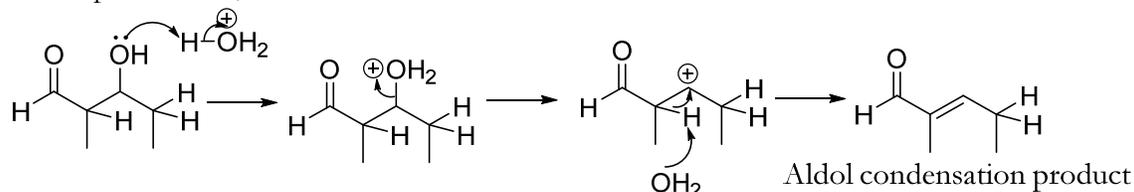
So overall, to avoid the condensation, you need three things: basic conditions, low temperature, and no conjugation.

This reaction is reversible in both acid and base. However, if you start with an aldehyde the equilibrium favors product. If you start with a ketone then the equilibrium favors starting materials.

So far we've just seen aldol happening with two identical molecules, but it's also possible to do these reactions with two molecules that are different. This is called a crossed aldol reaction. There are times when it's a bad idea, especially if both molecules can act in both roles. This can give up to four products.

A   **B**   **A** attacks **A**   **A** attacks **B**   **B** attacks **A**   **B** attacks **B**
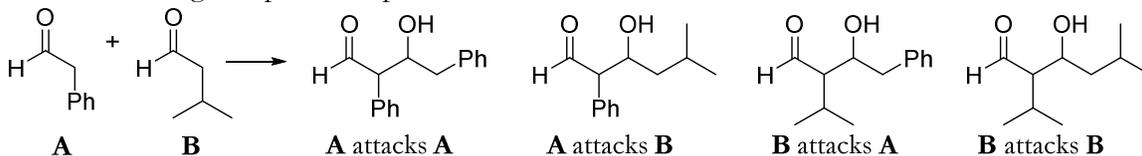
On top of this, if one molecule is an asymmetric ketone it can form the enolate on either side, which could add some more possibilities.

To fix this, there are two common strategies: either choose one molecule that doesn't have any α Hs (so it can't do the attacking), or choose one molecule that's a ketone (so it's less likely to get attacked), or both. This setup is usually called a Claisen-Schmidt condensation.

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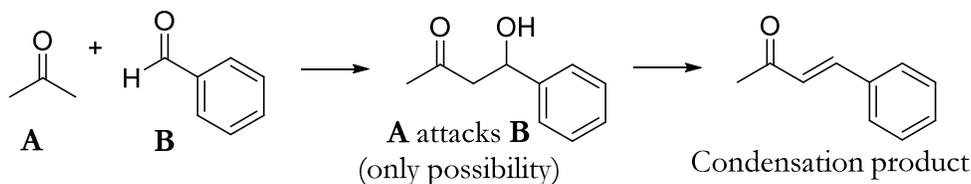
In this case the reaction goes automatically to the condensation product with or without heat, because there is a lot of benefit from the conjugation that you gain by elimination.

Another way to limit which molecule is the nucleophile (the enolate) and which is the electrophile (gets attacked by the enolate) is to use an irreversible deprotonation. This involves using much stronger bases like LDA, (lithium diisopropyl amide), which has a pKa of about 35. Normally it's used at -78°C, the temperature of dry ice in acetone. Due to its high steric bulk, LDA is a poor nucleophile and will not attack the carbonyl.
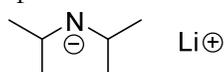
The pKa of most ketone or aldehyde enolates is about 17-20, and the pKa of OH⁻ is about 16, so this is a reversible deprotonation that favors the keto form. However, if we use a strong base like LDA, we can add it to one compound first, convert it 100% to the enolate form, and then add the second compound. This will result in a single desired aldol product.
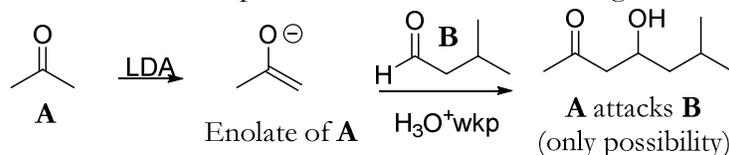
Overall, you could write this reaction as:
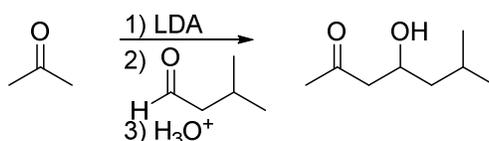
If the ketone that is being used to form the enolate has two different sides that could be deprotonated, LDA will prefer to deprotonate the less hindered side, because the protons here are more accessible to the bulky base (this is the kinetically favored enolate). Meanwhile, reversible conditions will deprotonate the more hindered side, since this gives a more substituted alkene which is more stable (this is the thermodynamically favored enolate). Note that this is similar to the difference between Zaitsev-style eliminations with most bases, and anti-Zaitsev-style eliminations with tert-butoxide.

Thermodynamic enolate

Kinetic enolate
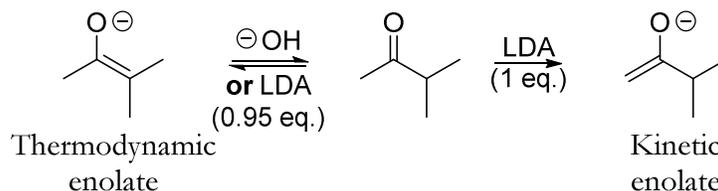
You can get reversible conditions either by using a weaker base like hydroxide, or by using slightly less than one equivalent of LDA, because then not all the ketones will get deprotonated at once and they can swap protons back and forth with each other until they all reach the thermodynamic product.

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One other complication: technically LDA doesn't work very well to make enolates out of aldehydes, since they'll do aldol chemistry to each other just as fast as the enolate forms.

A	Enolate of **A**	**A** immediately attacks **A**
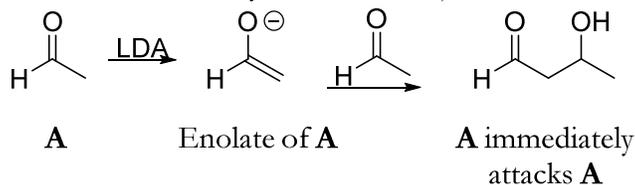
But since we're not covering the more complicated workarounds for this, we'll pretend that LDA works fine to make enolates out of aldehydes for this class.

Claisen and Dieckmann condensations
These are very similar to aldol reactions, but they involve making an enolate from an ester, not an aldehyde/ketone. From there you can attack on another ester molecule. The big difference is that once this happens, the carbonyl can reform by kicking out a leaving group. It only works in base, and it has to be the same base as whatever groups the ester has (often ⁻OEt).
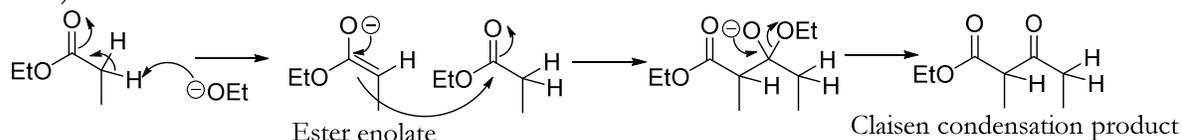
This is not actually the entire mechanism though. It turns out that the product you make is pretty disfavored – the equilibrium strongly prefers the starting materials.
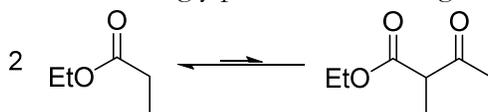
The only way to drive the reaction towards the product side is by deprotonating at the central carbon to "lock in" the product. It helps that the central carbon gets a lot more acidic when it's between two carbonyls. Then, to reverse this, you need to protonate with H_3O^+ when the reaction's done.
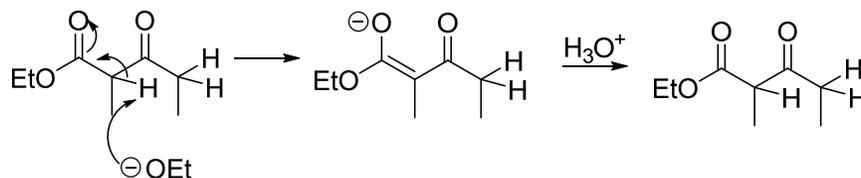
Even though this looks completely unnecessary, it's vital for making any product. Overall it means you need two α Hs on the attacking molecule: one to make the enolate, and one to lock in the product. If you don't have those you won't get any product. It also means that you need a full equivalent of base, not just a catalytic amount, since it gets used up.
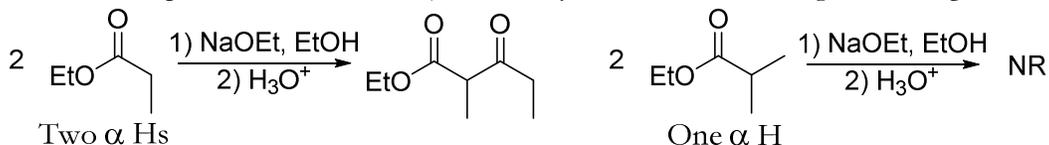
You can also do this with two ester groups in the same molecule. This is called Dieckmann condensation. It works best for 5 and 6-membered rings.
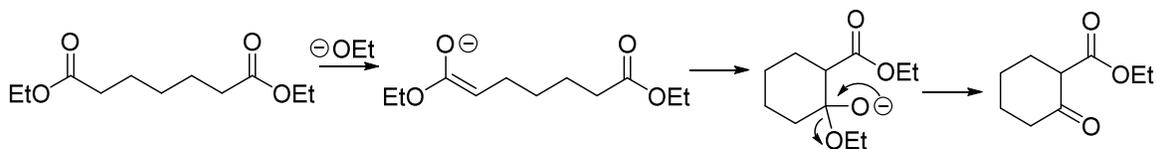
This isn't the whole mechanism – you have to show the final deprotonation and reprotonation steps like for Claisen.

You can also do crossed Claisen reactions. Again, you want to set things up so that only one molecule can be attacked, and only one molecule can do the attacking. The molecule that forms the enolate and does the attack needs 2 or 3 α Hs, and the molecule that gets attacked needs 0 or 1 α Hs. It also helps if you use a more attackable molecule – formate esters and carbonate esters are good choices and they both have 0 α Hs.
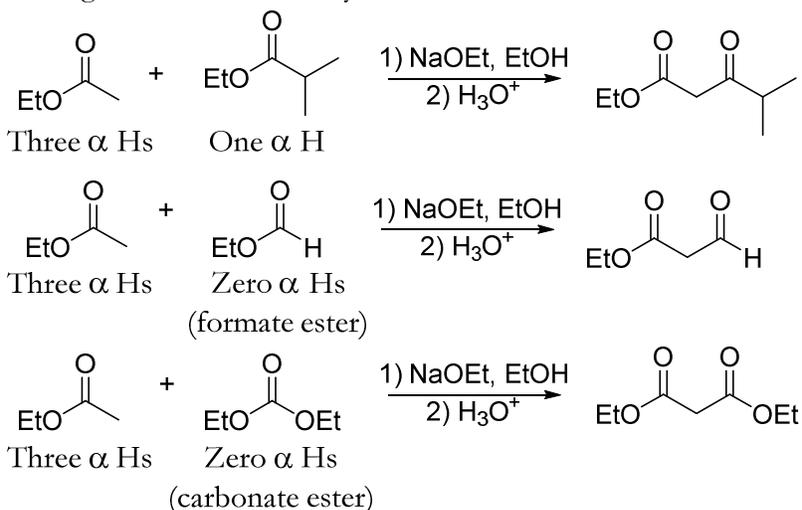
Alkylation of Ester Enolates
One other thing that ester enolates can do is attack on alkyl halides. This works best if the ester has another carbonyl, so that it's easily deprotonated on the central carbon. The two molecules that do this most often are malonic and acetoacetic esters.

When deprotonated, they can do S_N2 on a Me or 1° alkyl halide. Again, you need to use a base that matches whatever's on the ester part of the molecule.
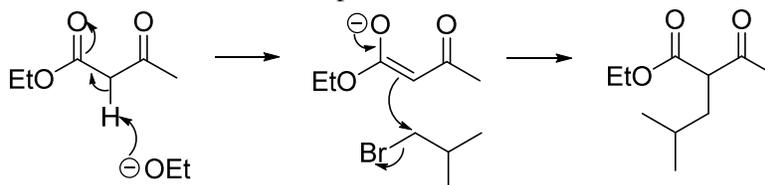
There's no need to lock in the product, since the equilibrium favors products anyway. However, if you started with two α Hs on the molecule you can deprotonate a second time and add another alkyl halide, though you have to do it as a separate step.

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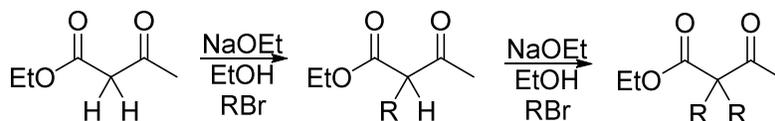
The interesting thing is what happens next. Normally at this point the molecule is exposed to aqueous base, to convert the ester to a carboxylic acid. Next it's neutralized with acid. This gives a molecule that's capable of undergoing decarboxylation, which happens at higher temperatures. This is named either the acetoacetic ester synthesis or the malonic ester synthesis, depending on which molecule you use.

Acetoacetic ester synthesis:
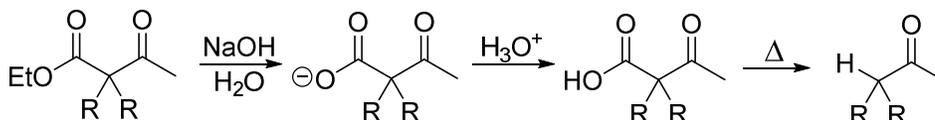
Malonic ester synthesis:
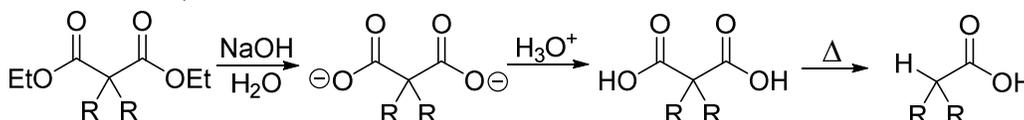
This is a good way to take an R group (or two R groups), and extend its chain by either two or three carbons. The acetoacetic ester synthesis adds three carbons in the form of a methyl ketone, while the malonic ester synthesis extends the chain by two carbons in the form of a carboxylic acid. Another option is to go straight from the one-carbonyl molecule, but the problem is that in NaOEt or similar bases the molecule will immediately undergo Claisen condensation. A workaround to this again involves using LDA to irreversibly form the enolate. This stops Claisen condensations because it converts all the ester molecules into enolates, so there's nothing left to attack.

100% conversion – no Claisen possible

LDA
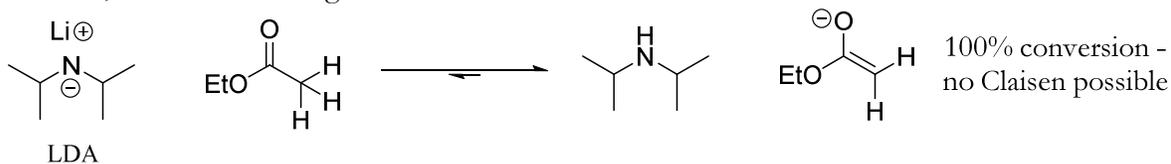
From there, you can add an alkyl halide and it will do the same sort of addition reaction as above. Overall it looks like this. You can keep replacing α Hs until you run out.
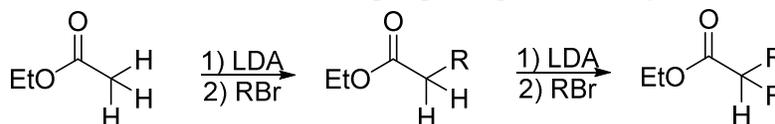
As a side note, this reaction doesn't work well for ketone enolates – they tend to get deprotonated again to make a new enolate, which then adds a second alkyl group.

Conjugate Addition Reactions
If you have an alkene conjugated to a carbonyl (an enone), it does some things that are very different from normal alkene chemistry. You can think of it as an extension of the carbonyl, because you can attack the double bond the same way. Like in Ch. 15, these are called 1,2- or 1,4-addition, and it's determined by kinetics vs. thermodynamics.

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Can attack at either   1,2-addition   1,4-addition
of these positions
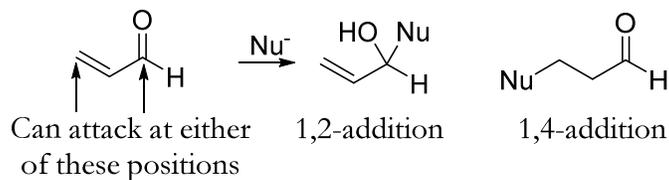
The mechanism for attacking at the carbonyl is the same as in Ch. 19 or 21 (depending on whether the carbonyl is an aldehyde/ketone or an acid derivative). The mechanism for attacking at the alkene is different.
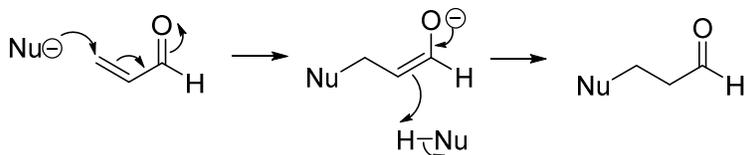
Most nucleophiles have a preference for attacking at one place over another. Usually the ones that prefer 1,4-addition are weaker bases that can't stay on the carbonyl after doing 1,2-addition because they get kicked out reversibly – in other words, they equilibrate to the thermodynamic product. The ones that prefer 1,2-addition are stronger reagents that favor the kinetic product. There are some other factors that have to do with copper acting differently that we don't get into.

1,2-addition: RLi, LiAlH$_4$ 1,4-addition: CN$^-$, RS$^-$, R$_2$NH, R$_2$CuLi,

Mixture: NaBH$_4$, RMgBr
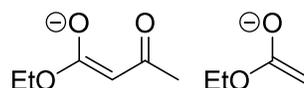
If you use an enolate, it's specifically called Michael addition.
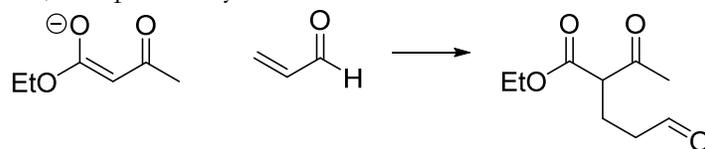
If you combine a Michael addition with a regular aldol condensation, it's called a Robinson annulation. The idea here is that one molecule does Michael addition onto a conjugated methyl ketone, and then that molecule does an aldol condensation back onto the first molecule.

Deprotonate here   Deprotonate here

Allyl methyl ketone   Michael addition   Aldol condensation
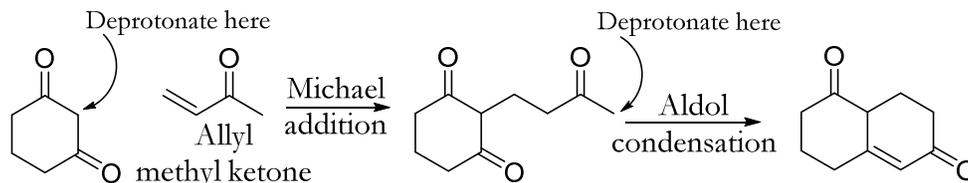
Overall, we now have ways to target each of three positions near a carbonyl:
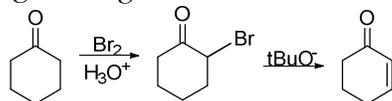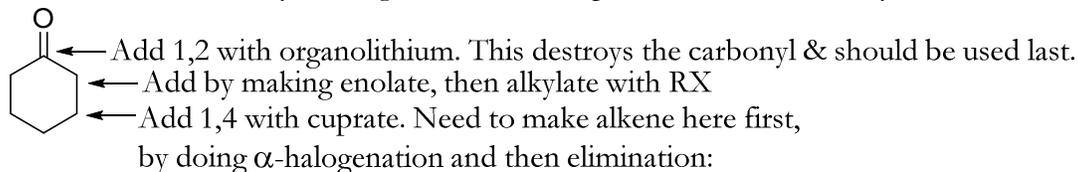
— Add 1,2 with organolithium. This destroys the carbonyl & should be used last.
— Add by making enolate, then alkylate with RX
— Add 1,4 with cuprate. Need to make alkene here first,
by doing α-halogenation and then elimination:

Br$_2$
H$_3$O$^+$ tBuO$^-$

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Retrosynthesis for Enolate Chemistry
Since there are a lot of carbonyl functional groups in this chapter, it's useful to be able to tell which group attacked which. As a general rule, **the molecule that because an enol/enolate and then attacked will stay at the same oxidation level, and the molecule that got attacked will drop by one oxidation level (or two, in a condensation).** The disconnect will always be next to the base of the molecule that got attacked. So in this product, the left half became an enolate then attacked, and the right half got attacked.

3 bonds to O: 2 bonds to O:
became enolate, got attacked
then attacked
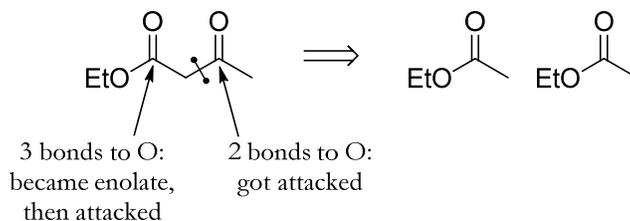
Ch. 22 Synthesis Practice
Let's try to make this compound from anything with six carbons or fewer.
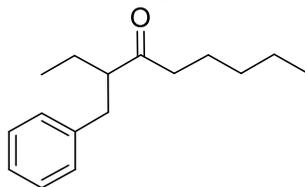
Since there's an alkyl group attached to the α position, this looks like a good candidate for α-alkylation. But how can we selectively alkylate one side over the other?
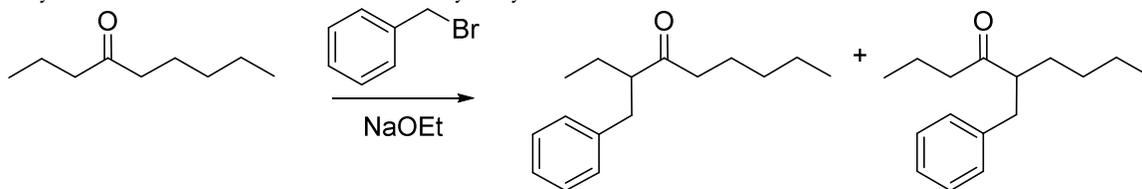
Instead, let's bring in one side of the ketone parent chain later, so that we start out with only the left side chain attached to the carbonyl. That way we can selectively alkylate the left side, then attach the right side chain via acid chloride + cuprate.
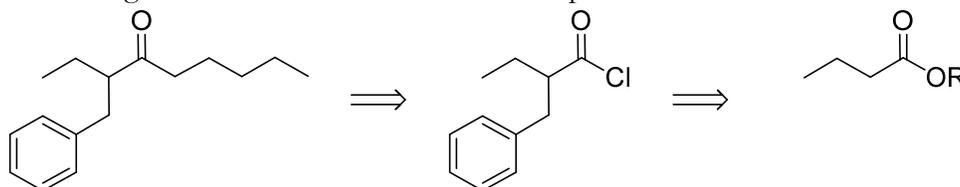
Before we start showing the main synthesis, we'll need to make the group we'll be using to alkylate (an aromatic ring plus an extra carbon), since it has 7 carbons. We'll need to bring it in as an alkyl halide if we want to attach it to the ester.
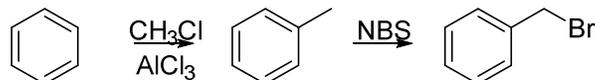
We'll also need to make the cuprate that corresponds to the right side chain, since it has more than six carbons.
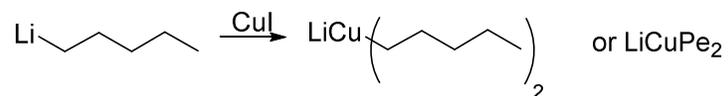
Now we can put the steps together. Note that if we want to keep this ester starting material at 6 carbons or fewer, we can use either the methyl or the ethyl ester.