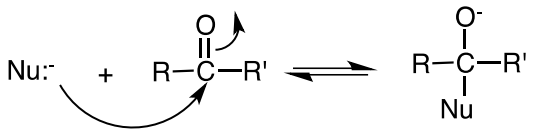
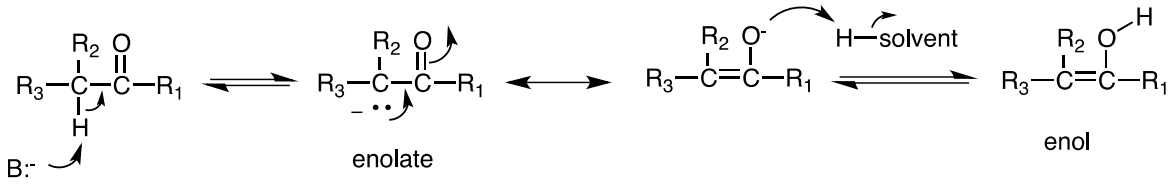
Chapter 21
Enols and Enolates

There are two major types of reactions of carbonyl compounds.
(1) Attack of nucleophiles on the carbonyl carbon.

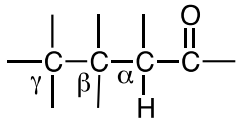


(2) Reaction at the alpha-carbon based on removal of the alpha-proton. Removal of the α-proton produces an anion at the α–carbon. The α–carbon is now a nucleophile as we shall see.



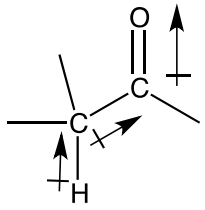
Acidity of the Alpha-Proton

Designate carbons next to the carbonyl with Greek letters.

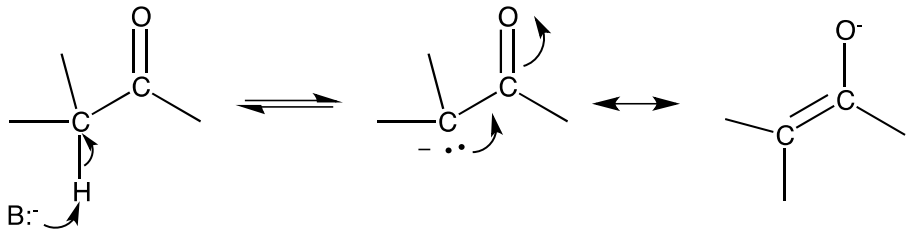


The proton at the α-carbon has increased acidity due to:

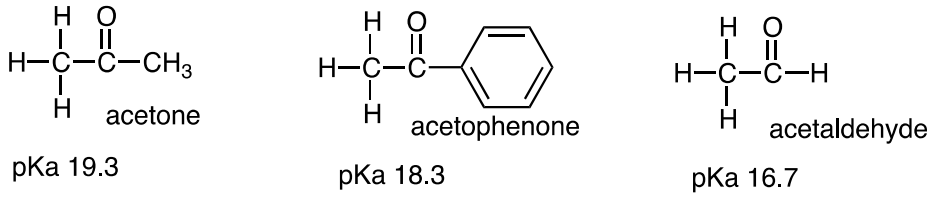
(1) The inductive effect of the carbonyl. The carbonyl group is a strong electron-withdrawing group and helps to remove electron density from the α-carbon.



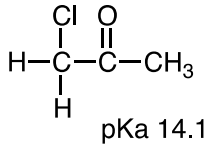
(2) Resonance stabilization of the resulting anion. The negative charge from deprotonation of the α–carbon is partially delocalized onto the carbonyl oxygen.



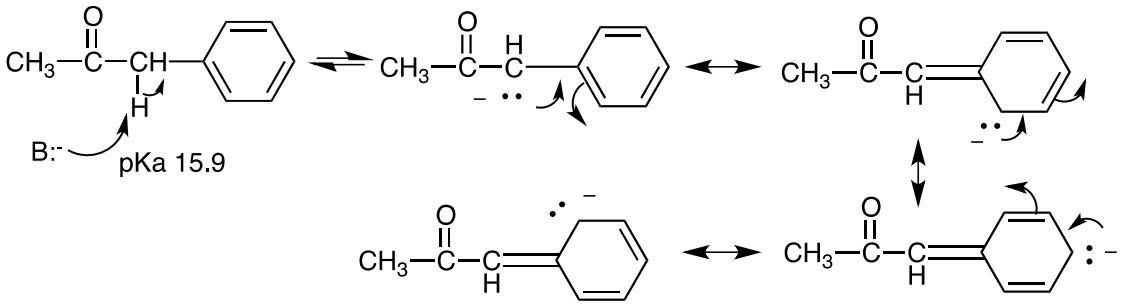
The pKa's are in the 16-20 range. Aldehydes have lower pKa's than ketones because in ketones the extra alkyl group donates electrons to make the carbonyl carbon less electron deficient and less of an electron-withdrawing group.



Electron withdrawing substituents will increase the acidity.

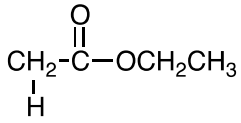


Benzene rings attached to the α-carbon also increase the acidity of the α proton by helping to stabilize the resulting anion through resonance delocalization.



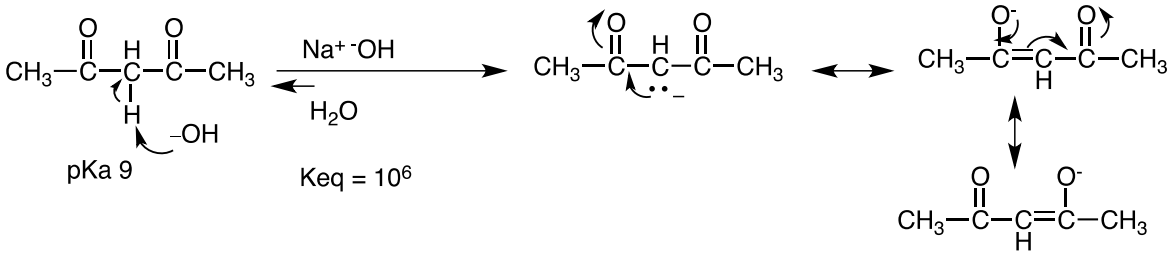
Esters can also form enolates but the α–proton of esters is much less acidic because the oxygen of the ester is an electron-donating group. The oxygen is more electronegative than

the sp^2 carbon of the carbonyl and so withdraws electrons inductively but the lone pair on the oxygen is very good at donating to the π-system of the C=O bond.

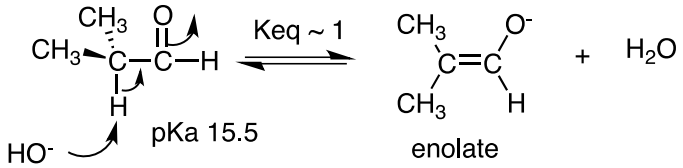


pKa 25.6

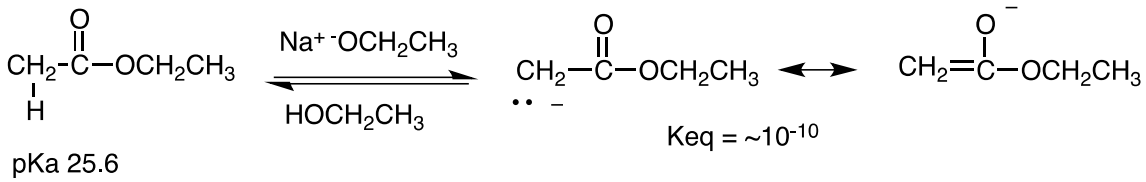
β-diketones or β–ketoesters having two carbonyl groups attached to the same carbon are much more acidic.



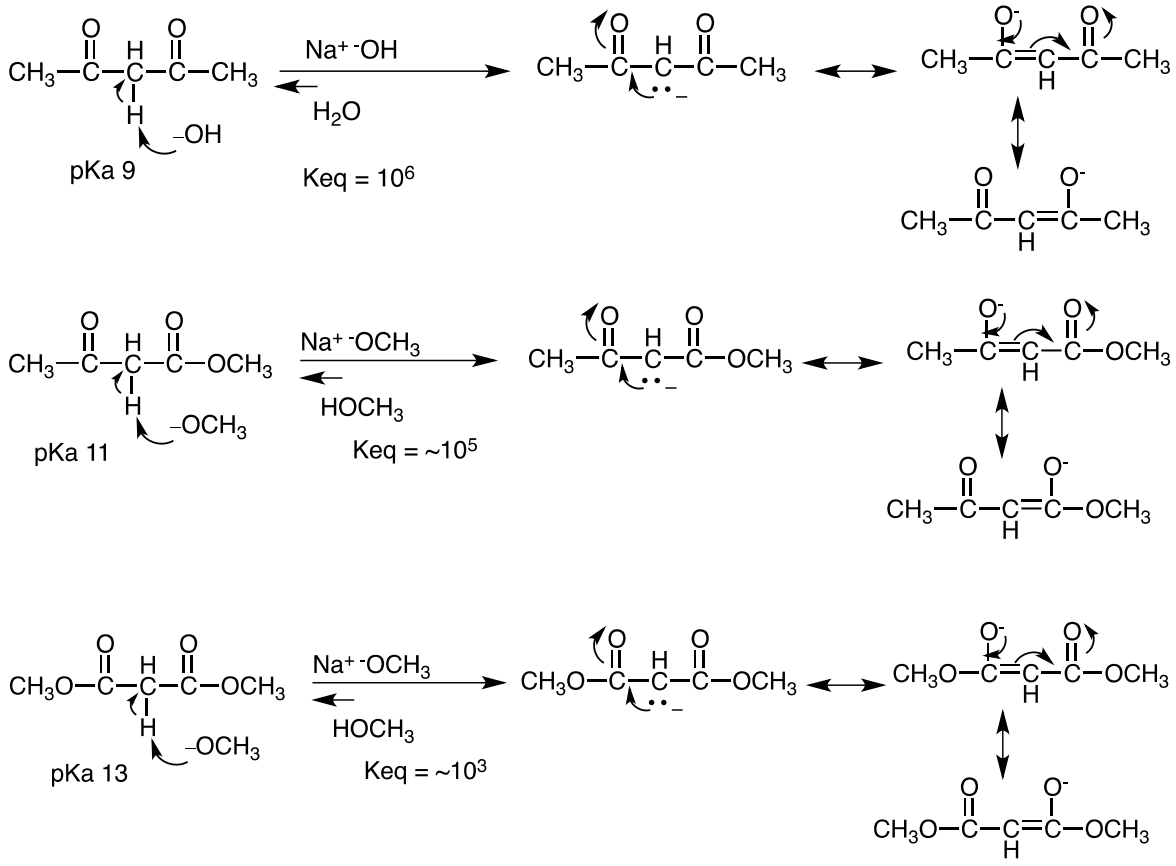
When a simple ketone or aldehyde is treated with a solution of sodium hydroxide, significant amounts of both the starting aldehyde and ketone and enolate are present at equilibrium.



With esters, the equilibrium for enolate formation is much less favorable. Some enolate is formed but its concentration at equilibrium is small.

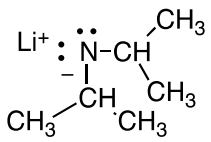


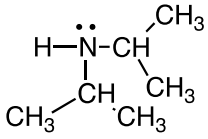
When there are two electron-withdrawing carbonyl groups attached to the same carbon, enolate concentration is much higher. It is the major species at equilibrium.



Use of LDA (Lithium Diisopropyl Amine)

Another way to drive the equilibrium full to the right is to use a very strong, non-nucleophilic base. One such example is lithium diisopropyl amine or LDA, $Li^{+}\ ^{-}N[CH(CH_3)_2]_2$.

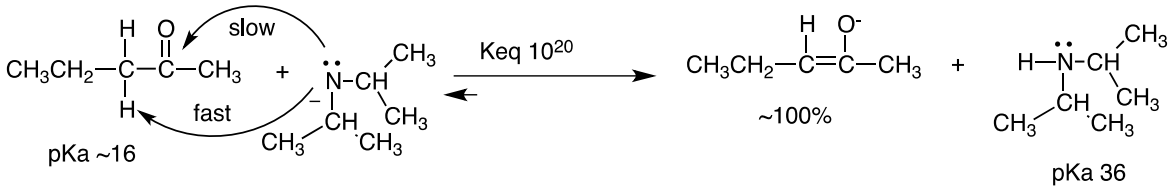




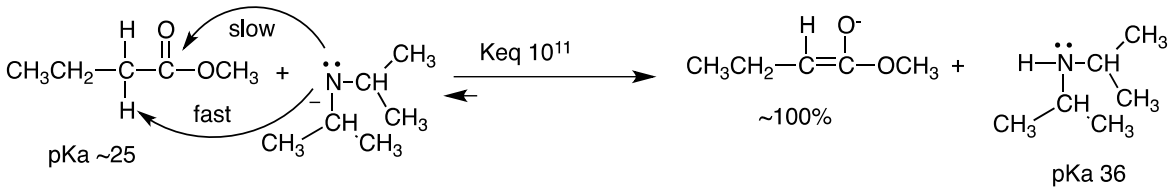
Diisopropyl amine

pKa 36

The large, bulky isopropyl groups provide a lot of steric hindrance so that it is not a good nucleophile and so will not attack the carbonyl carbon but only remove the α proton. Recall that Grignard and organolithium reagents are also very strong bases and excellent nucleophiles. We could not use a Grignard or organolithium reagent since it would preferentially attack the carbonyl carbon. Since LDA is such a strong base that it will quantitatively convert an aldehyde, ketone or ester to the enolate.



Esters are also quantitatively converted to the enolate.



As we will see, LDA is a very useful reagent for alkylation and acylation of aldehydes, ketones and esters.

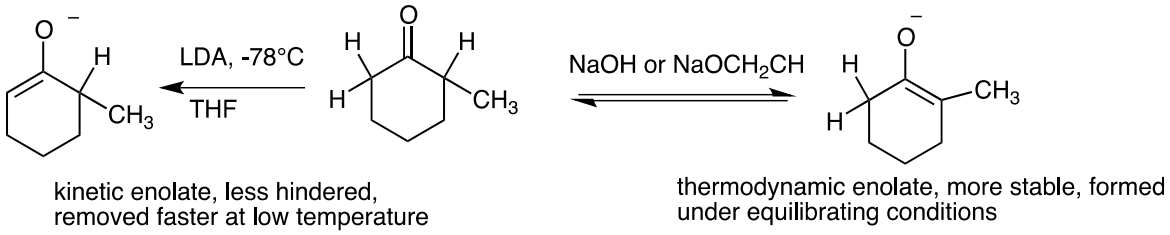
Enolate Regiochemistry

With aldehydes and esters there is only one α–carbon but ketones have two and deprotonation can occur at either of them. When the ketone is not symmetrical both positions must be considered. Two possible enolates are possible.

If there is a difference in steric hindrance between the two possible enolates, it is possible to control which enolate forms by controlling the reaction conditions.

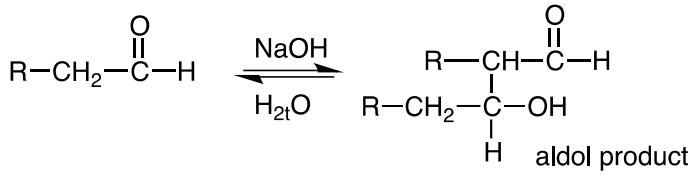
In general the less hindered α-proton can be removed by using a strong non-hindered base such as LDA at low temperatures, typically -78°C, the temperature of dry ice (solid carbon dioxide) and an acetone bath. The less hindered proton will be removed faster and using a very strong base such as LDA ensures that the reaction is irreversible. This is called kinetic control.

And the more substituted proton can be preferentially removed under conditions, which allow for equilibration since removal of the more substituted α-proton leads to the formation of the more substituted enolate. This is the more stable enolate and this is called thermodynamic control. A weaker base such as an alkoxides or hydroxide is used in conditions in which the reaction is readily reversible.



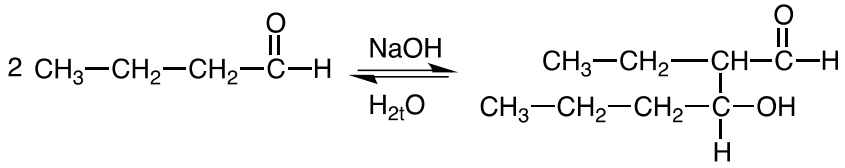
Aldol Condensation

When aldehydes and ketones with α-hydrogens in the pKa range 16-20 are treated with a base such as hydroxide or alkoxide, significant amounts of enolates are produced. The enolate can react with the starting aldehyde or ketone to give the aldol product.

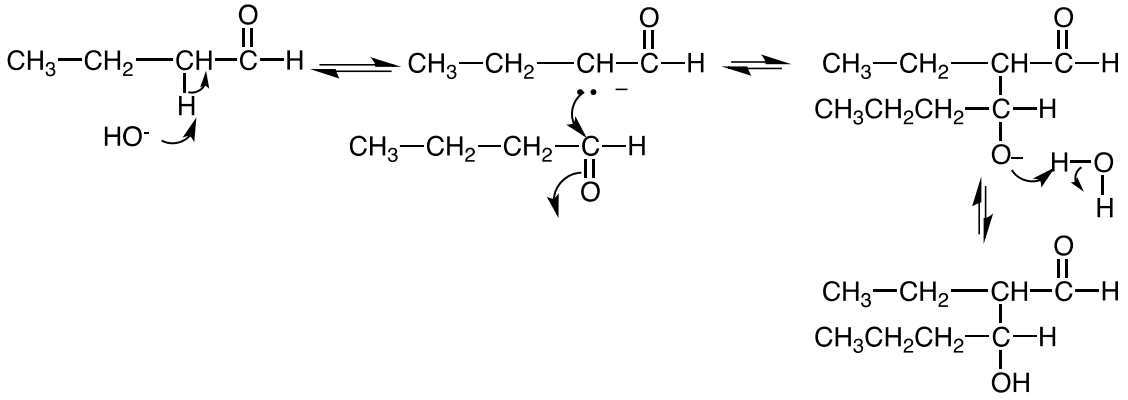


This is called a condensation because two molecules of the starting material combine to give one molecule of product. This is called the aldol product because it contains an aldehyde (ald-) and an alcohol (-ol).

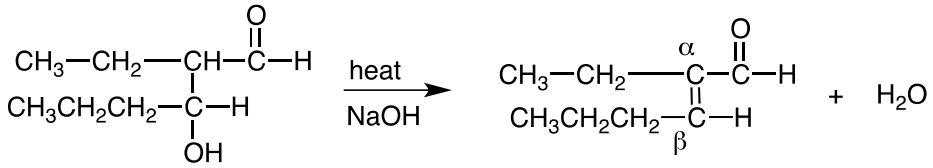
For example:



The mechanism is as shown below. At equilibrium, both the enolate and starting aldehyde are present. The enolate is a nucleophile and will attack the carbonyl carbon of another molecule of starting material.



If the initial aldol product is heated in the basic reaction conditions, the molecule will dehydrate to give an α,β–unsaturated carbonyl.

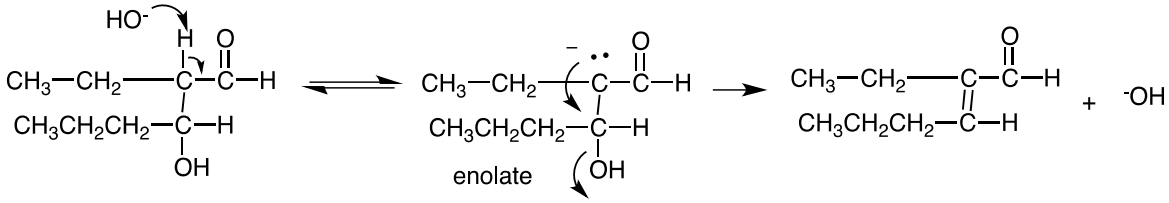


Note here that the new double bond is conjugated with the carbonyl group, making this a particularly stable double bond.

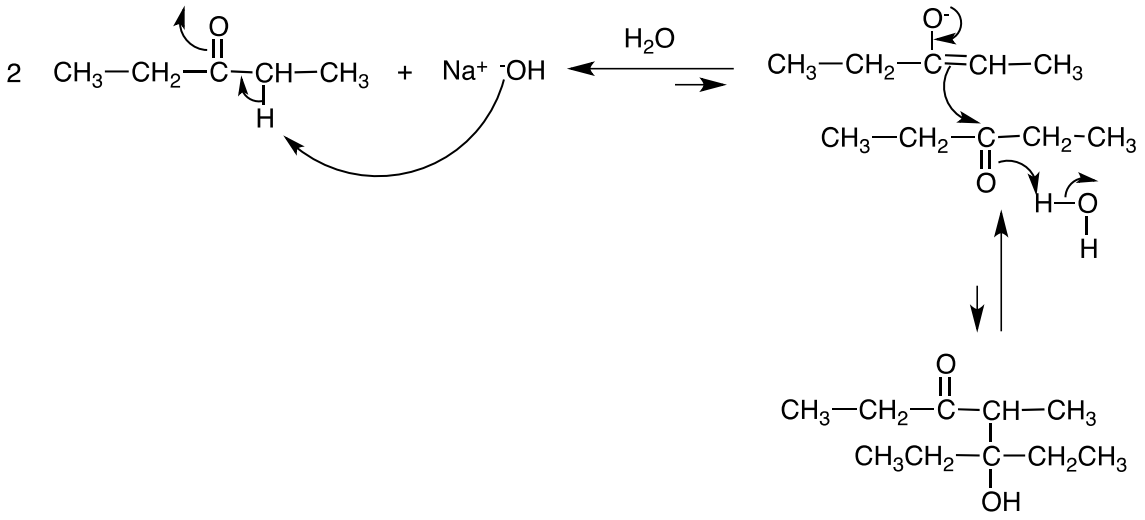
Usually dehydration does not occur in basic conditions but it does here for two reasons:

(1) The α–proton next to the carbonyl is quite acidic.
(2) The new double bond is conjugated with the carbonyl.

The reaction occurs in two steps. First the enolate forms and then loss of hydroxide, HO^-, occurs to give the α,β–unsaturated carbonyl.

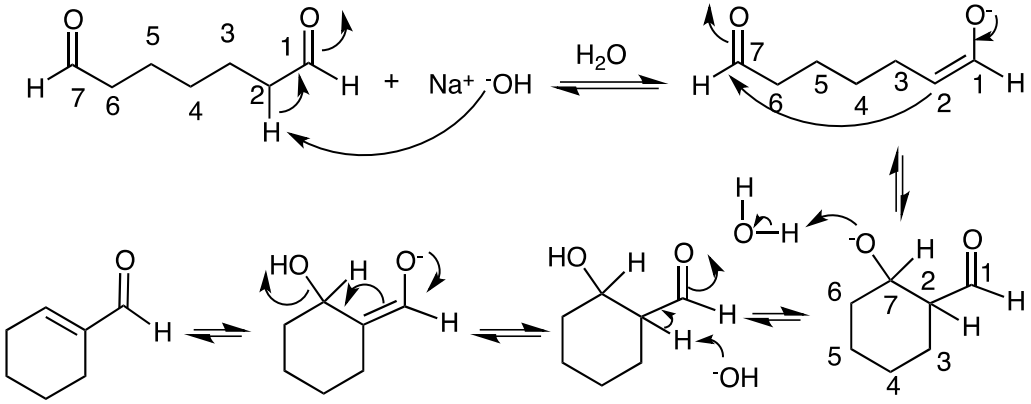


The aldol reaction is reversible and the equilibrium for aldol reactions with ketones are much less favorable than they are for aldehydes. The equilibrium generally favors the starting ketone rather than the aldol product. Recall that ketones are less reactive than aldehydes. (1) They form a lower concentration of enolate and (2) the carbonyl carbon of the ketone is less electrophilic than it is for aldehydes. This is due both to steric hindrance and to the electron-donating ability of the extra alkyl group of the ketone.

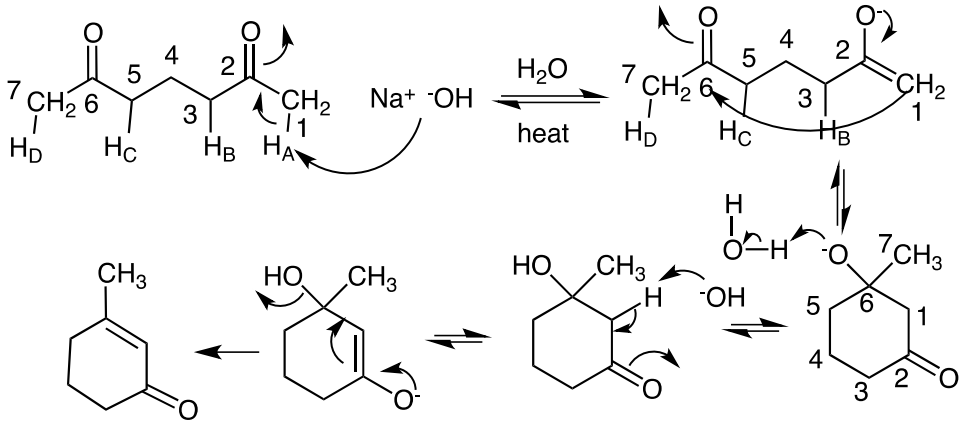


Ketones can, however, successfully undergo the aldol reaction provided that special precautions are used to remove the aldol product as it forms.

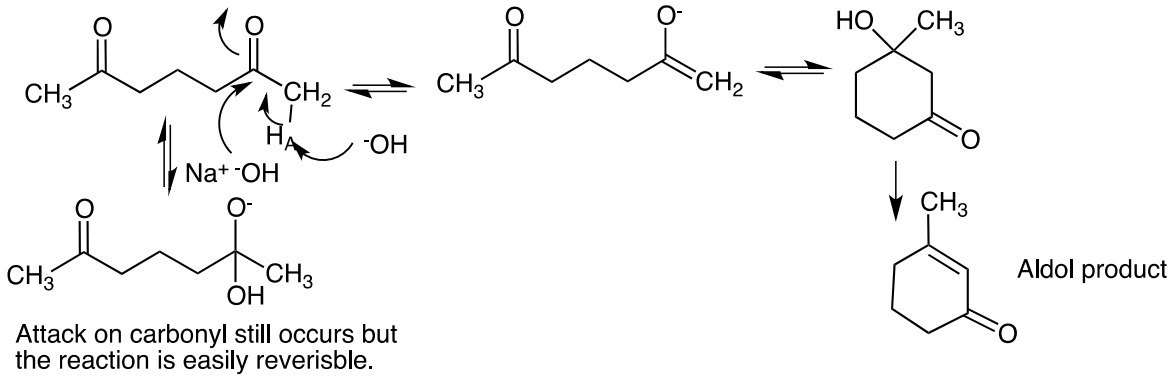
Intramolecular aldol condensations are favorable when there is the possibility of forming a five- or six-membered ring. When a five- or six-membered ring can be formed, the intramolecular aldol is faster than the intramolecular reaction. In the intramolecular case, even diketones will undergo the reaction in good yields.



In the next example with two ketones, four enolates are possible (protons H_A, H_B, H_C, H_D). since the molecule is symmetrical, H_a and H_D and H_B and H_C are the same. Deprotonation of H_B (or H_C) would give and enolate that is only four carbons away from a carbonyl carbon. An aldol condensation would form a four-membered ring, which would be unstable, and the equilibrium would be very unfavorable for this ring closure. Deprotonation of H_A (or H_D) would lead to a stable six-membered ring and this is the major
Deprotonation of H_A (or H_D) would lead to a stable six-membered ring and this is the major pathway of the reaction.

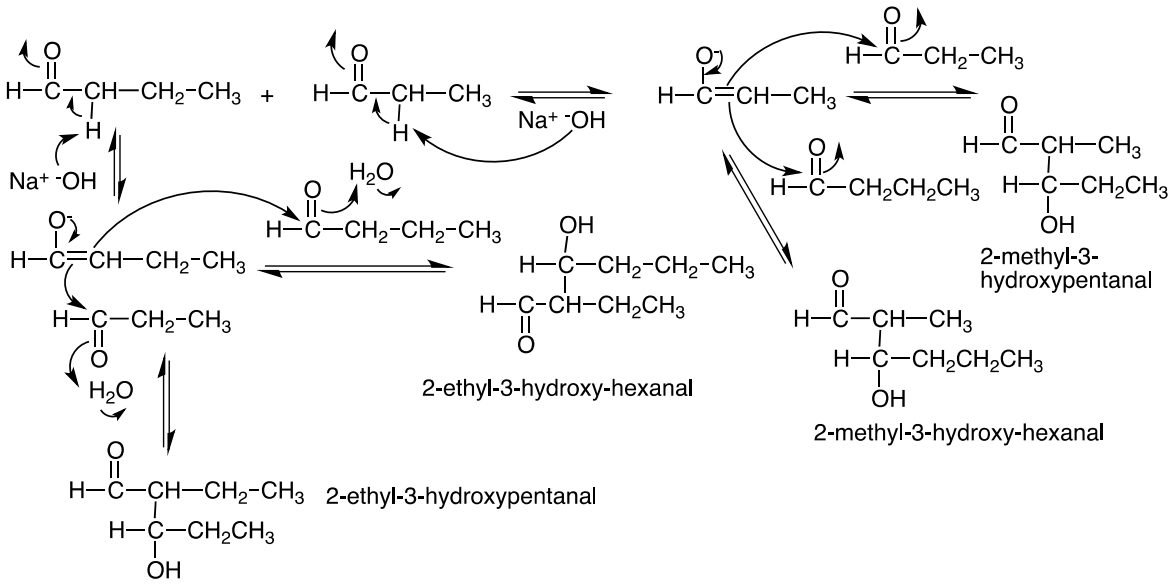


It should be pointed out that attack at the carbonyl carbon by the nucleophilic hydroxyl group still occurs as a side reaction. This just forms the hydrate, which is unstable and cannot be isolated. The hydrate is converted back to the aldehyde or ketone, which then reacts to form the aldol product.

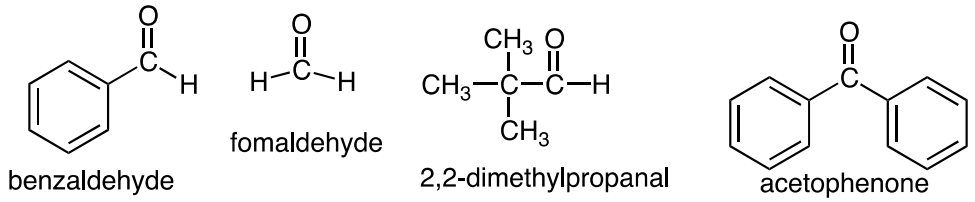


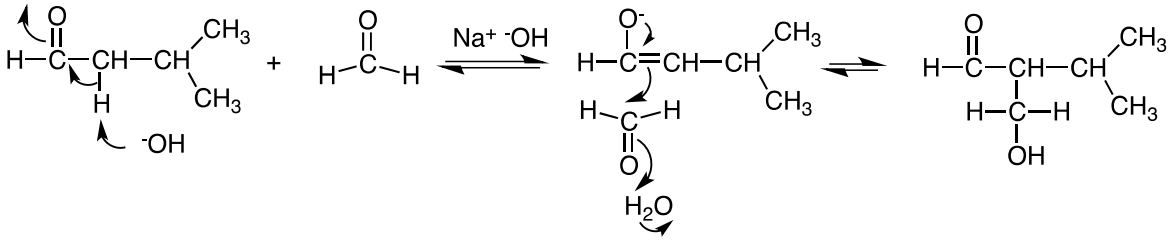
Mixed Aldol Reactions

It is generally not a synthetically useful procedure to attempt an aldol condensation between two different aldehydes or ketones unless one of them cannot form an enolate. If both can enolize then up to four products will be formed.



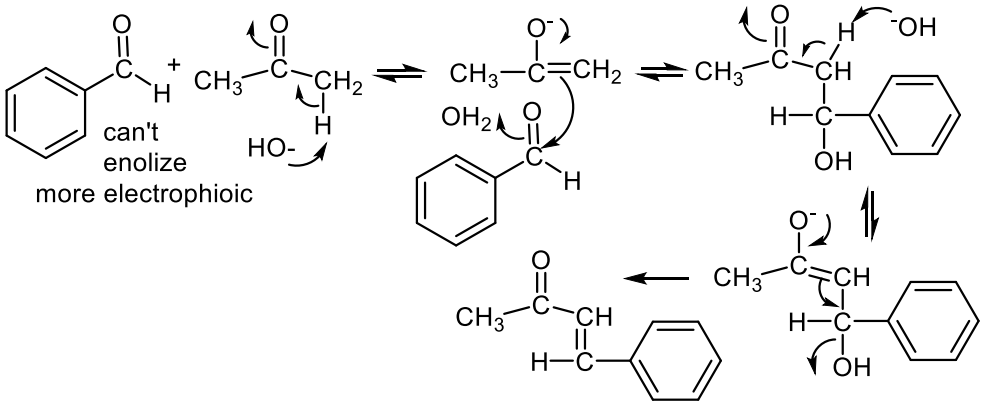
The reaction is synthetically useful and gives one major product if (1) one of the substrates cannot form an enolate or (2) one of the reactants is much more electrophilic (i.e. more reactive to nucleophiles) than the other reagent. Formaldehyde is an example of a reagent that is highly reactive to nucleophiles like enolates. The following are examples of aldehydes and ketones that do not have α-protons and cannot enolize:



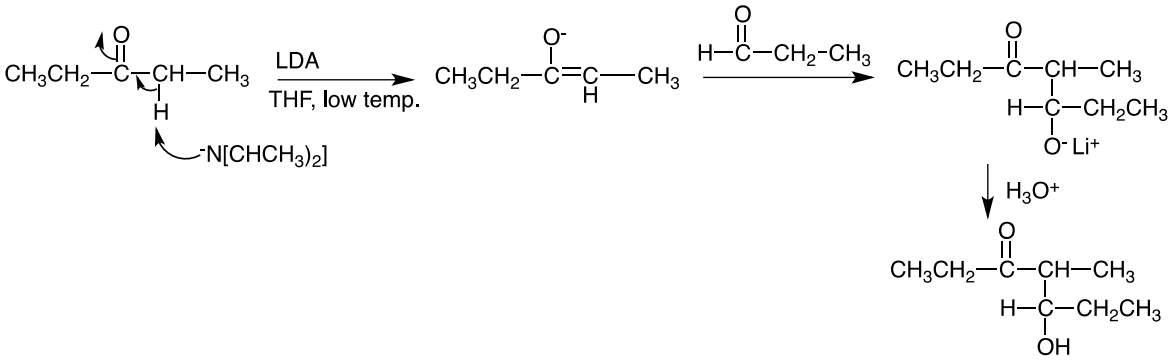


A reaction of a ketone, which does not readily undergo self-condensation, with an aromatic aldehyde, which cannot enolize, is a very useful and high yielding reaction. In this case, dehydration will be very favorable since the new double bond is conjugated with both the carbonyl group and with the benzene ring.

Mixed aldol condensations in which a ketone reacts with an aromatic aldehyde are known as Claisen-Schmidt reactions.

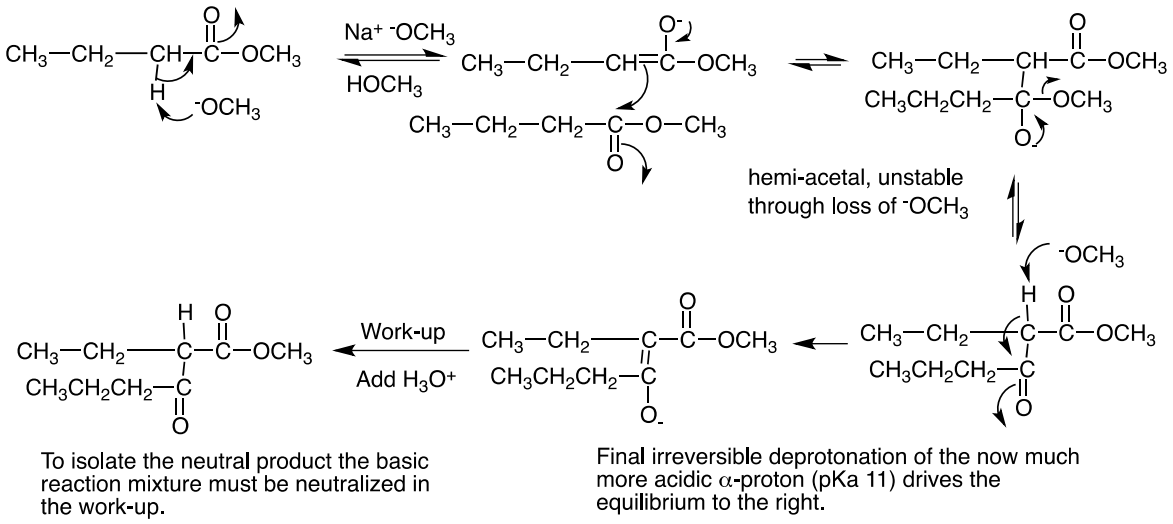


Another way to ensure that only one of the condensation partners forms the enolate is to use LDA. This will convert the starting aldehyde or ketone rapidly and quantitatively to the enolate. The will ensure that this species acts as the nucleophile. A second aldehyde or ketone can then be added as the electrophile.



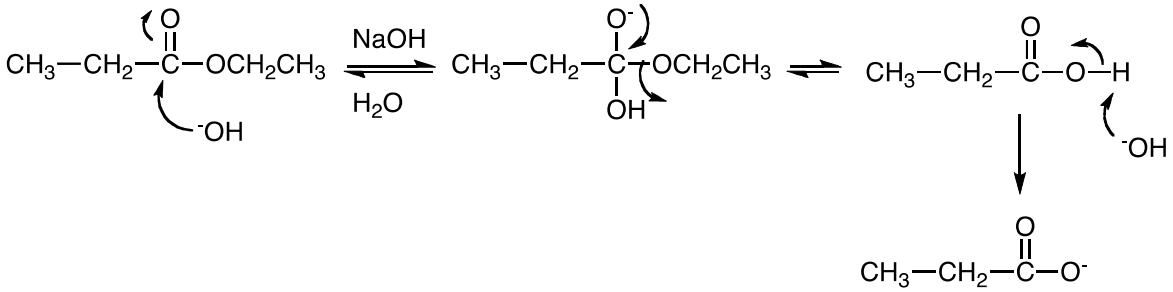
The Claisen Condensation of Two Esters

As we mentioned, esters can also form enolates, though in smaller concentrations than aldehydes or ketones. These enolates can then react with unreacted starting material in a condensation reaction that is exactly analogous to the aldol reaction. This condensation reaction of esters is called the Claisen condensation, after the early German chemist, Ludwig Claisen, who developed the reaction.

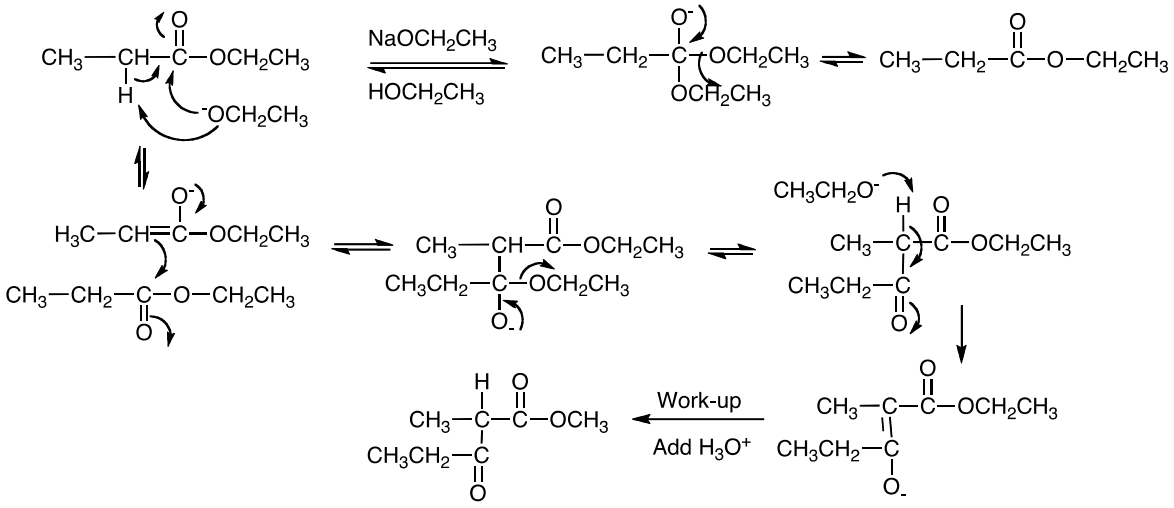


In order for the reaction equilibrium to be favorable the starting ester must have two α–protons. The first is removed to make the enolate, which undergoes the condensation reaction, and the second is removed after the initial condensation. Once the β–ketoester intermediate forms, the α–proton is now much more acidic. It has a pKa of 11 versus a pKa ~25 for the starting ester. This final deprotonation is irreversible and is essential in driving the equilibrium in favor of the aldol product.

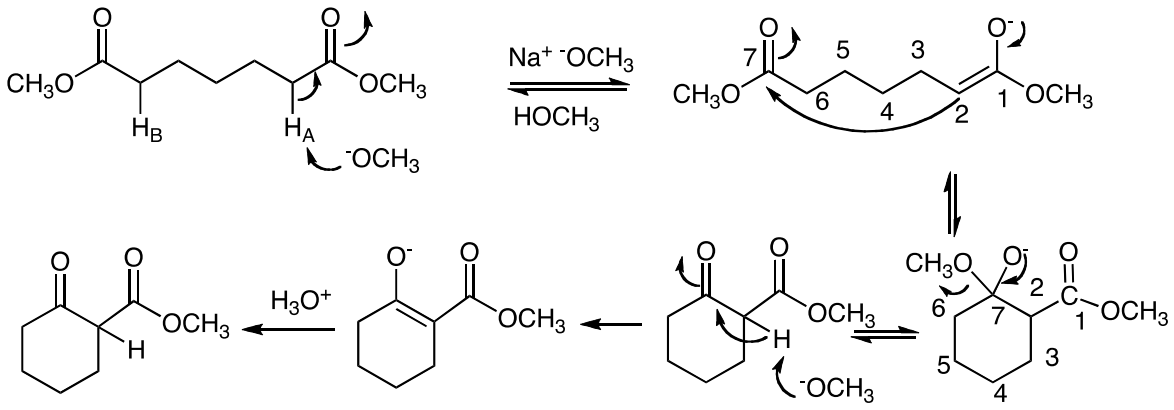
Another important aspect of the Claisen condensation is that the base portion used must be the same as the alcohol portion of the ester. If aqueous sodium hydroxide is used, irreversible ester hydrolysis will be the predominant reaction pathway.



But if sodium ethoxide is used we simply get an identity reaction. The ethoxide attacks the carbonyl carbon but the product of this reaction is simply the starting material. The other reaction that occurs is the Claisen condensation by means of enolate formation.



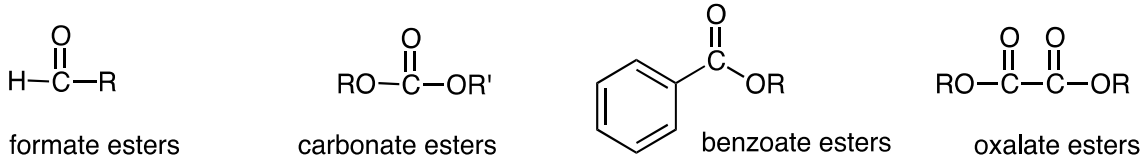
Just like with the aldol condensation, we can have intramolecular Claisen condensations with esters of dicarboxylic acids suitably positioned to form five- or six-membered rings. These reactions are called Dieckman Condensations after Walter Dieckman, an early German chemist who was a contemporary of Claisen.



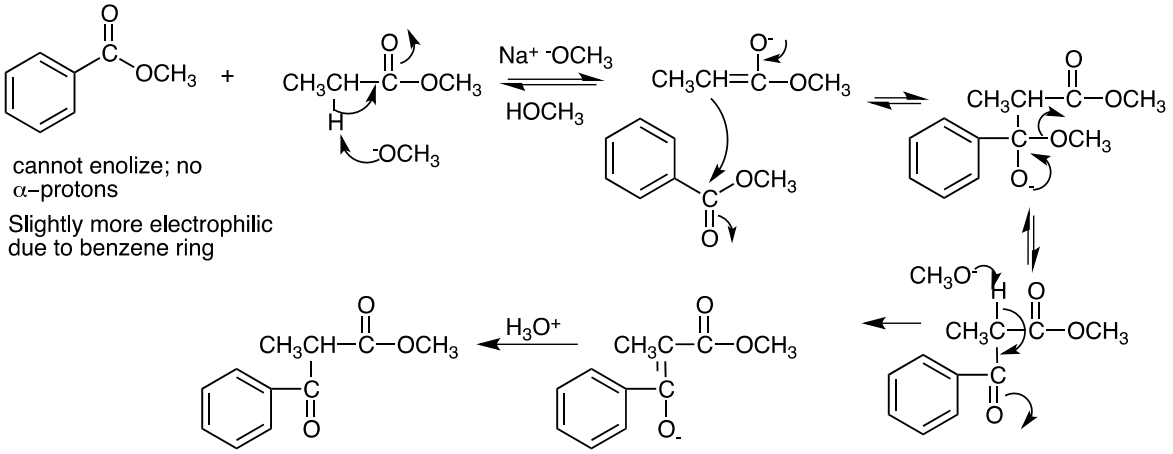
Formation of 3- and 4-membered rings is unfavorable due to ring strain and formation of larger rings (7-, 8-, etc.) becomes less favorable as the nucleophilic enolate carbon gets farther and farther from the electrophilic carbonyl carbon. Intermolecular condensations begin to compete with the intramolecular ring closure. Larger rings can be formed if the reactions are run under conditions of high dilution.

Mixed Claisen Condensations

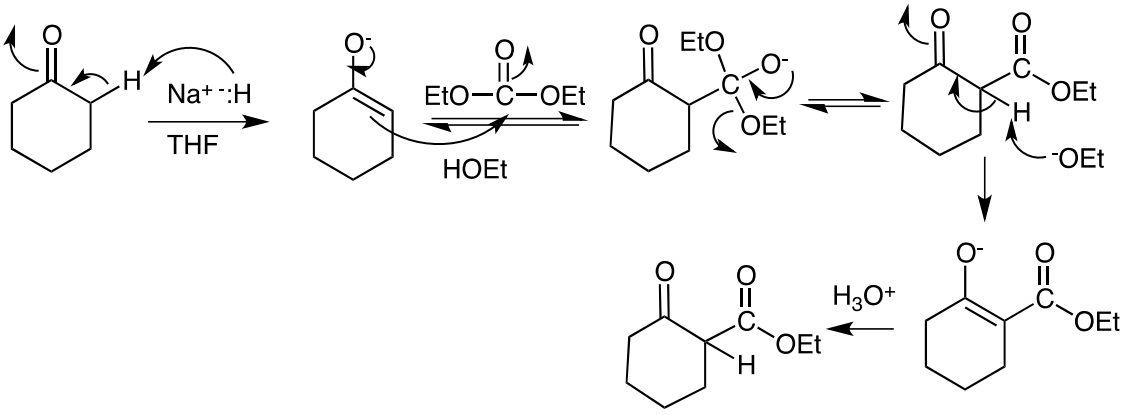
As with the aldol reaction, mixed Claisen condensations are synthetically useful only if one of the esters cannot form the enolate. Some examples of useful non-enolizable esters are:



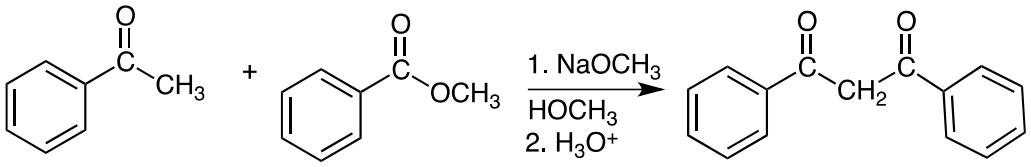
For example:



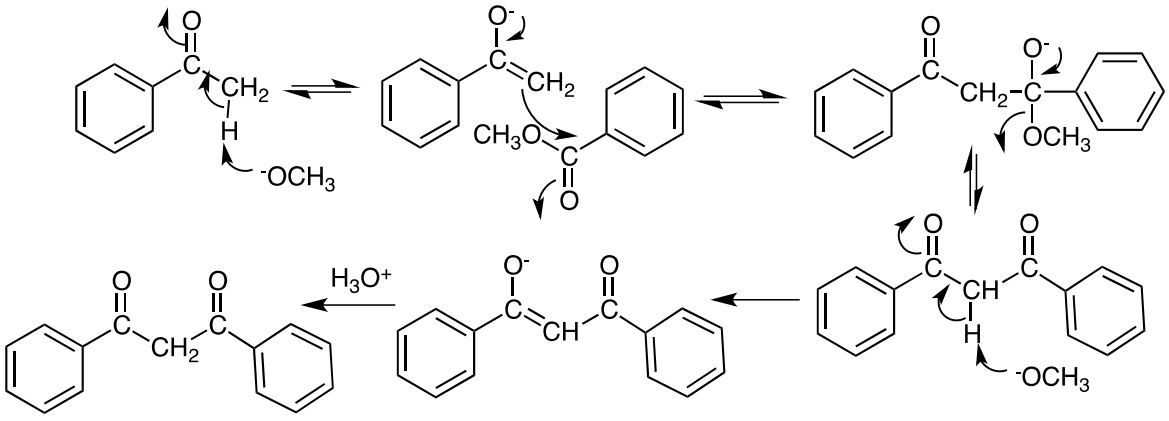
Ketones can be acylated with non-enolizable esters.



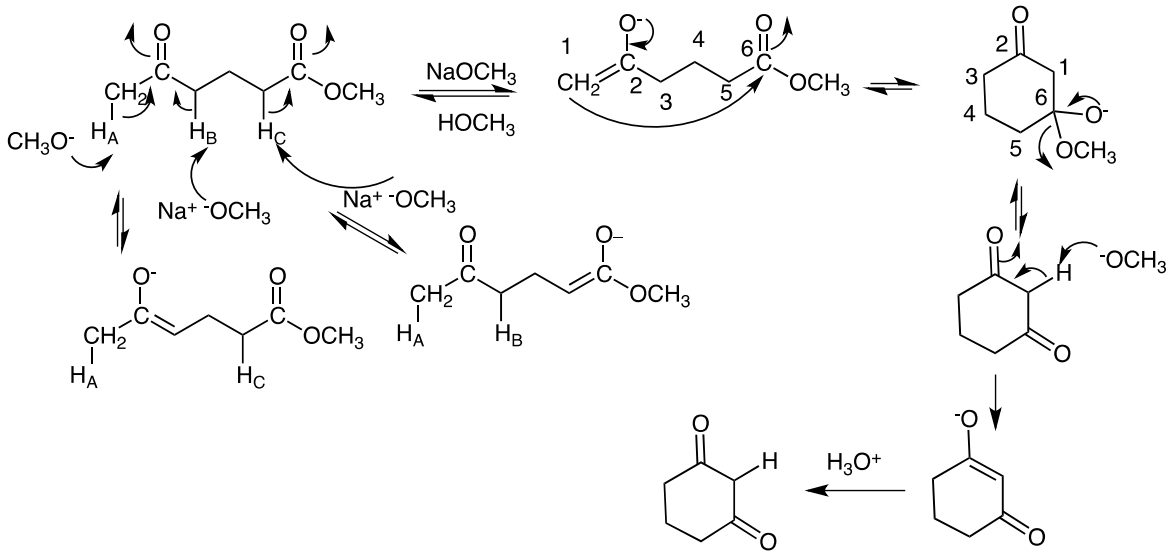
We can react a non-enolizable ester with a ketone to give a β–diketone (or 1,3-diketone).



Only the ketone can enolize. This enolate then reacts with the methyl benzoate ester. The equilibrium is driven in the desired direction by final deprotonation of the acidic β−diketone.



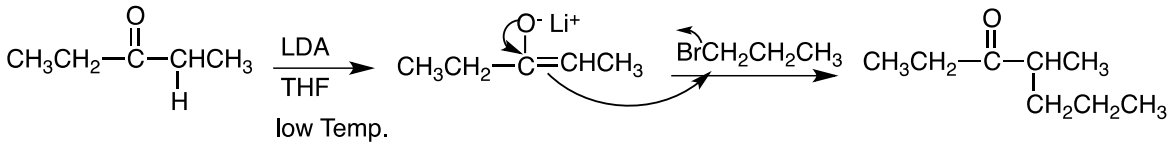
We can also have intramolecular ring closure reactions between a ketone or aldehyde and an ester to form β−diketones. In the example below, several enolates are possible but the one that leads to a favorable five- or six-membered ring will lead to the predominant species. The proton next to the ketone or aldehyde will be removed faster to form the enolate than the proton next to the ester.



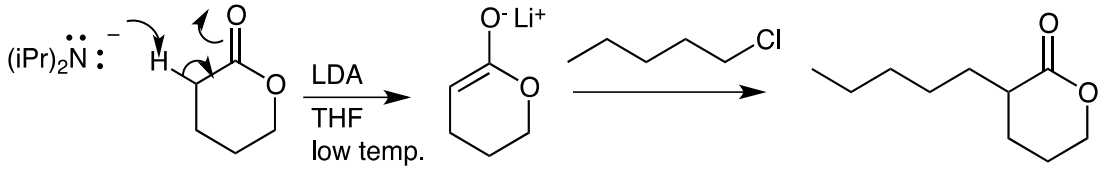
Again, three enolates are possible, H_A, H_B, H_C, and all three will form in reversible reactions but only the enolate formed at H_A will lead to a six-membered ring. The equilibrium is driven to the right by final deprotonation of the 1,3-diketone. To isolate the neutral product, the enolate must be neutralized with acid.

Alkylation of Enolates

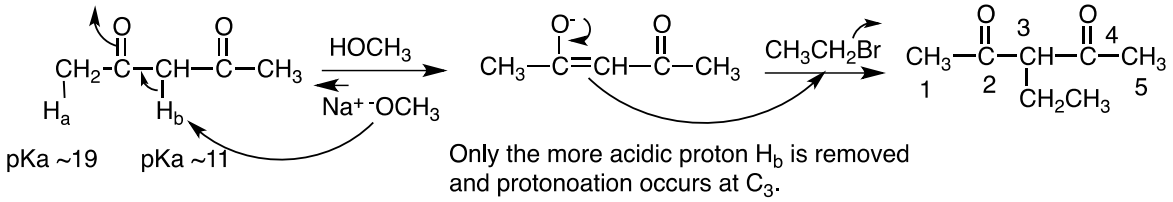
We can alkylate enolates at the α-carbon by reaction with alkyl halides. To ensure that the alkylation reaction is the predominate pathway rather than the aldol reaction (when using aldehyde and ketones) or the Claisen reaction (when using esters) it is best to use a strong, non-hindered base such as LDA to ensure that all of the starting carbonyl compound is converted to its enolate. This way there is no electrophilic carbonyl compound present and the desired electrophilic alkyl halide can be added.



With esters:



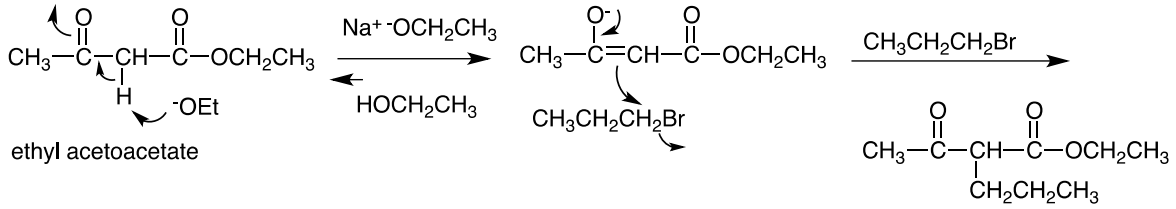
Alkylation of 1,3-dicarbonyl compounds occurs regioselectively at the more acidic position between the two carbonyl groups.



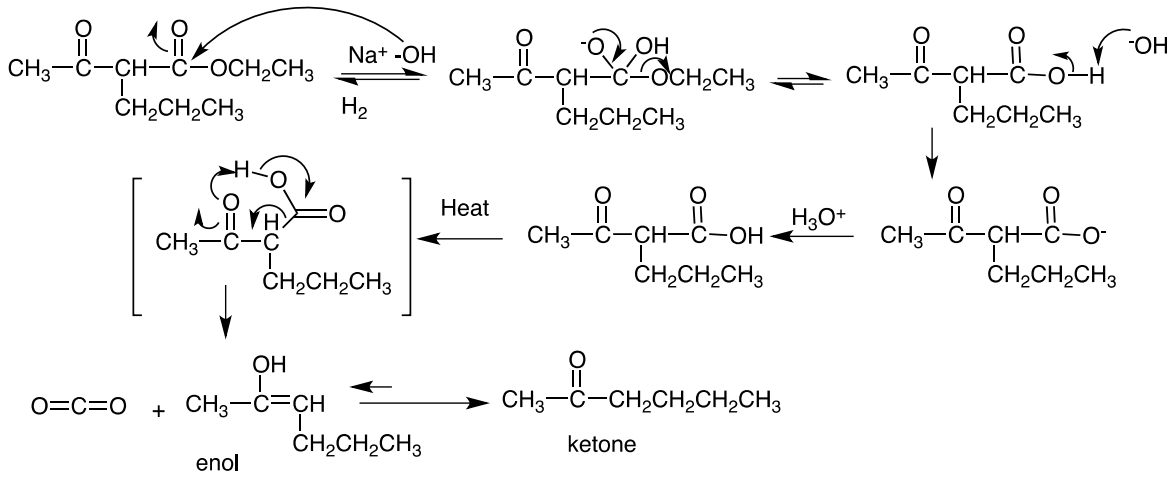
β−ketoesters and 1,3-diesters react similarly.

The Acetoacetic Ester Synthesis

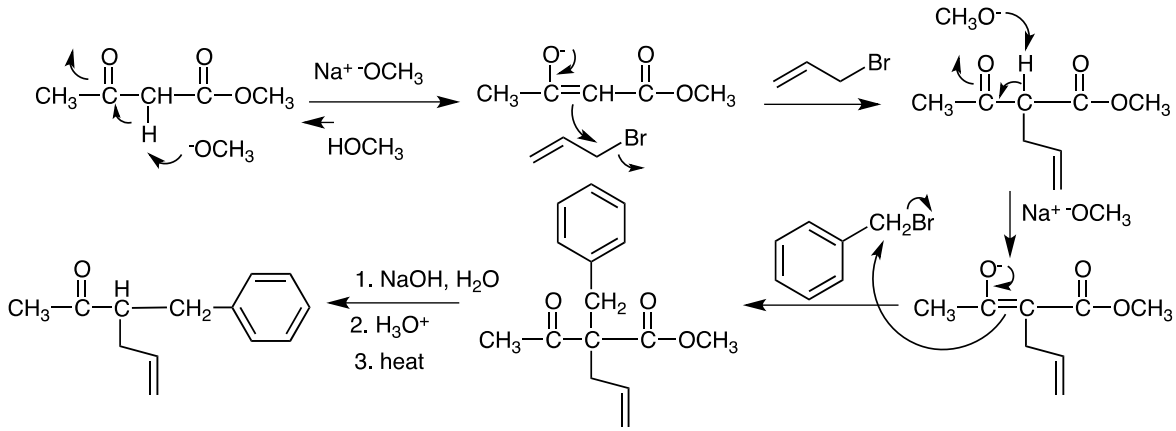
A very useful starting material for the synthesis of methyl ketone derivatives is to start with ethyl acetoacetate (an acetoacetic ester). The ethyl acetoacetate can be alkylated regioselectively at the carbon between the two carbonyls using a very mild base and then the activating ester group can be removed in a three-step sequence to give the ketone.



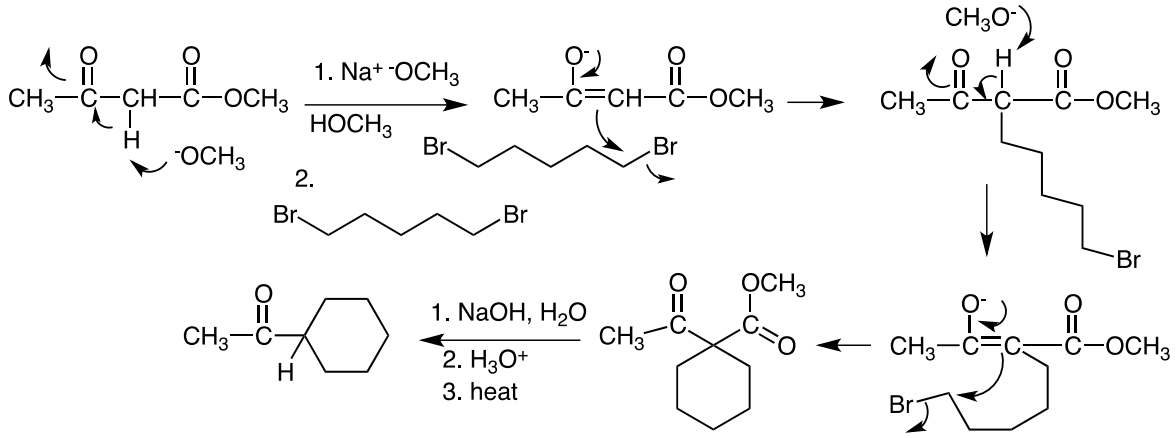
The β−ketoester can then be decarboxylated in a three-step sequence which involves (1) basic hydrolysis of the ester using aqueous sodium hydroxide (2) protonation on the carboxylate anion (3) and final heating. This sequence can all be carried in one reaction flask ("one pot").



The acetoacetic ester can be dialkylated using two different alkylating agents. This is best done step-wise, adding one equivalent base and then the first alkylating agent, then adding the second equivalent of base followed by the second alkylating agent.

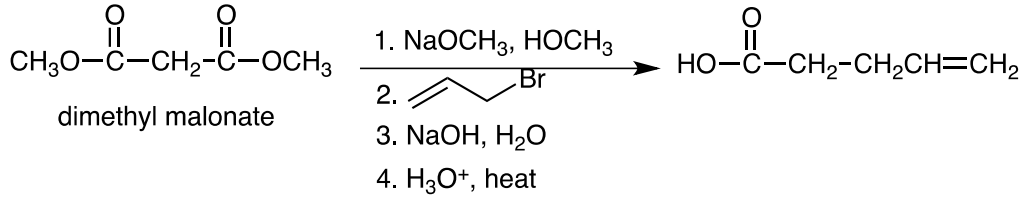


Rings can be formed using a dihaloalkane. Five- and six-membered rings are the most easily formed but four-membered rings can also be made by this method. Two equivalents of base are added at once along with the dihaloalkane. The reactions occurs in steps as in the reaction above.

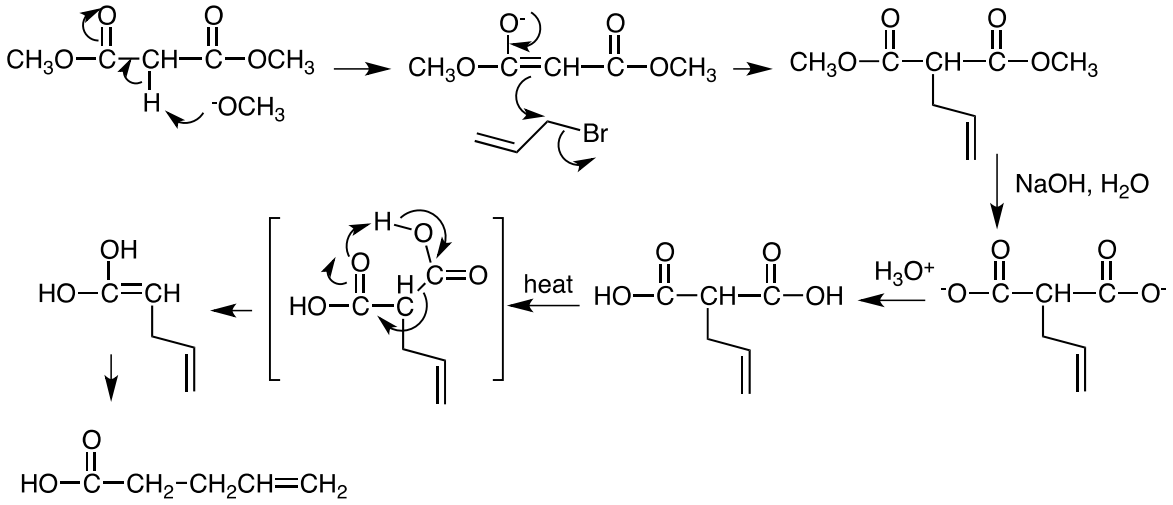


Malonic Ester Synthesis

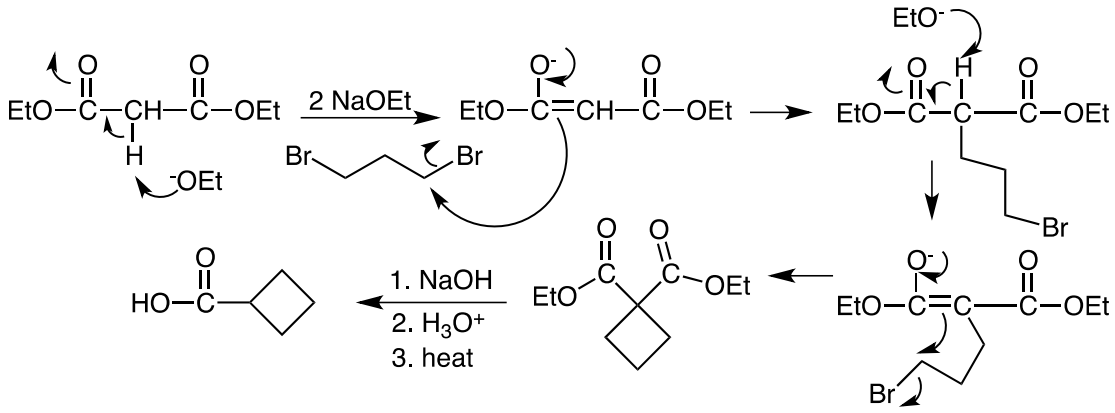
We can also start with a 1,3-diester, a derivative of malonic acid, alkylate and decarboxylate to end up with a carboxylic acid derivative.



The first step is deprotonation followed by alkylation as before. In the hydrolysis step it is generally not possible to hydrolyze only one of the esters. Both are cleaved by the aqueous sodium hydroxide to give the 1,3-dicarboxylic acid derivative after protonation. Then, one of the carboxylic acid derivatives is removed on heating.



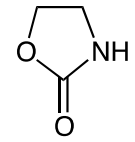
As with acetoacetic esters, dialkylation is also possible and we can also form rings using dihaloalkanes.



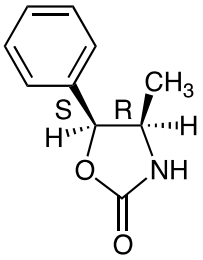
Alkylation of Chiral Enolates

Enolate alkylation can be carried out stereoselectively to give mainly one enantiomer. One very useful way to do this is to use a chiral auxiliary. This is an enantiomerically pure compound that can be reversibly attached to a carboxylic acid derivative to control the direction of alkylation at the α–carbon and then removed when it is no longer needed.

Many such chiral auxiliaries have been developed. One class of these compounds is based on the heterocyclic compound, 2-oxazolidinone. Chiral derivatives of 2-oxazoidinone can be prepared as single enantiomers from naturally occurring enantiomerically pure compounds.

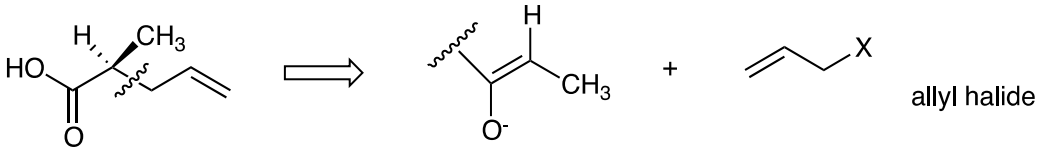


2-oxazolidinone



(4R,5S)-4-methyl-5-phenyl-2-oxazolidinone

The chiral auxiliary can be used in the synthesis of enantiomerically pure carboxylic acid derivatives such as (S)-2-methyl-4-pentenoic acid. Working backward from the product, it can be seen that it can be synthesized by alkylation of a propanoyl group with an allyl halide.

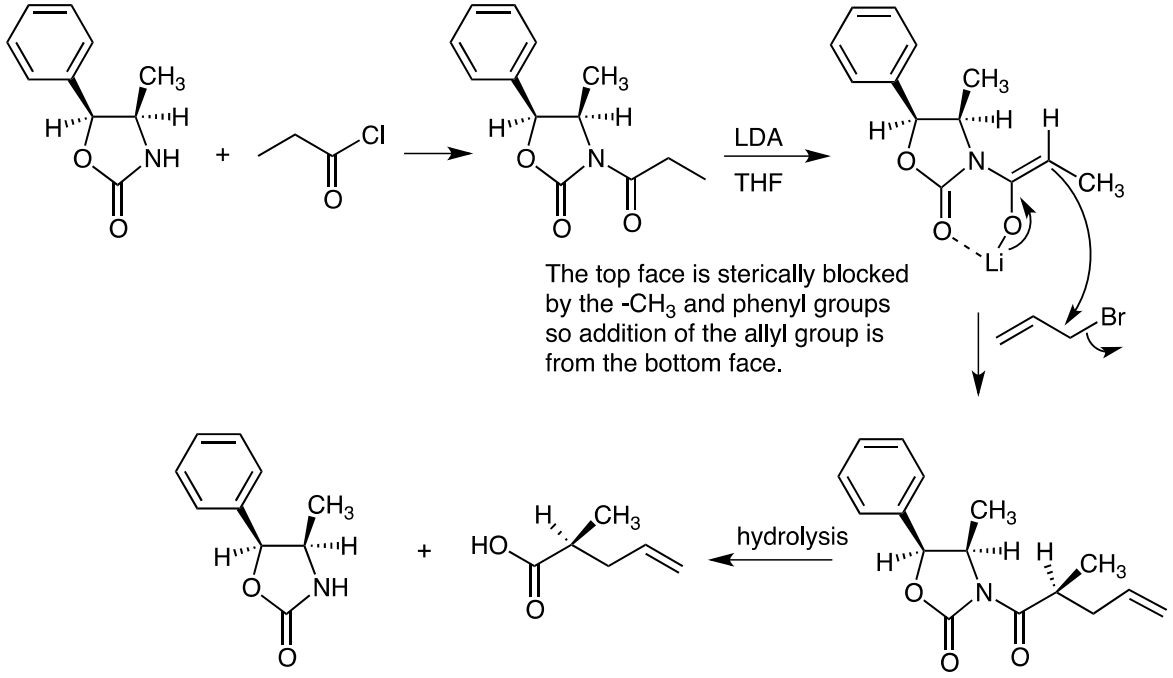


(S)-2-methyl-4-pentenoic acid

enolate of a propanoyl group

allyl halide

To control the stereochemistry, the chiral auxiliary was added first using propanoyl chloride and the chiral (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone to give a chiral amide. The enolate was form using LDA at low temperature. The carbonyl oxygen of the oxazolidinone coordinates the lithium counterion, forming a fairly rigid enolate structure. Attack on the allyl bromide electrophiles occurs from the side away from the large phenyl and methyl substituents on the oxazolidinone ring to give the (S) enantiomer as the major product. Hydrolysis of the chiral amide gives the desired carboxylic acid and the chiral auxiliary which can be recovered and reused.



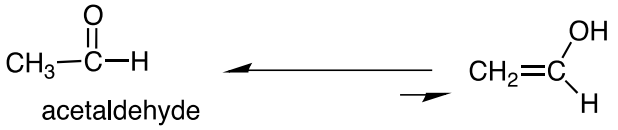
Enolzation and Enol Content

Enols are the conjugate acids of enolates. Enolates, as we have seen are very useful in organic synthesis. Enols are generally present in very small concentration in equilibrium with the keto form. The keto form is more stable than the enol form by 45-60 KJ/mol (11-14 Kcal/mol) because the C=O bond is more stable than the C=C bond of he enol. The enol and keto form are called tautomers. For normal esters, ketones and aldehydes, the enol form is present in very small amount amounts.

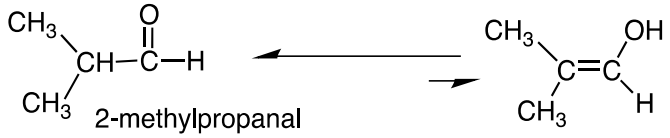
acetic acid Keq ~ 10^{-20}

ethyl acetate Keq ~ 10^{-19} to 10^{-24}

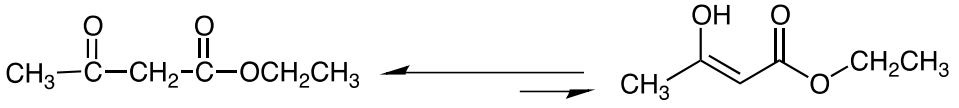
acetone Keq 6 X 10^{-9}



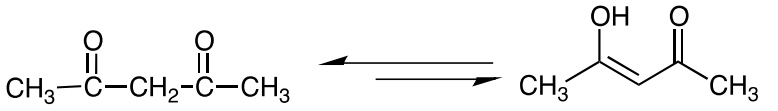
acetaldehyde Keq 6 X 10^{-7}



2-methylpropanal Keq 1.4 X 10^{-4}

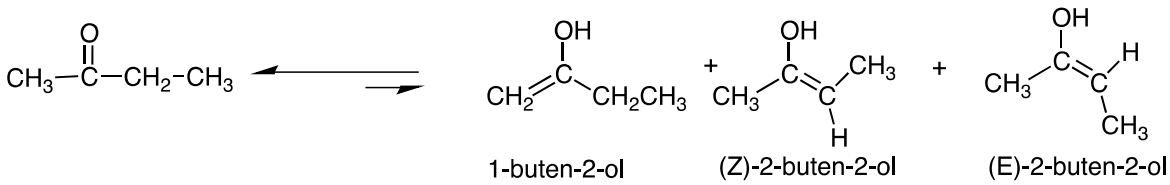


ethyl acetoacetate Keq 7 X 10^{-2}



2,4-pentandione Keq 2 X 10^{-1}

For unsymmetrical ketones, enolization can occur on either side of the carbonyl and can result in E- or Z- stereoisomers.

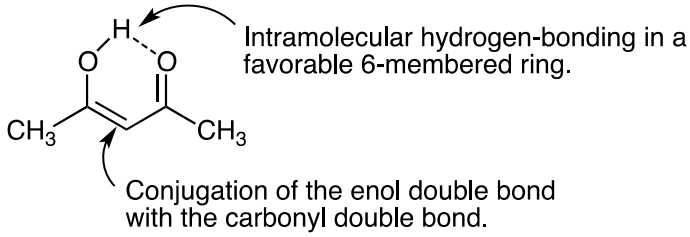


Esters and carboxylic acids contain less enol content than do aldehydes and ketones. This is due to electron donation to the carbonyl group by the oxygen.

But for 1,3-dicarbonyl (β−dicarbonyl) the enol content is much higher. There are two main reasons for this:

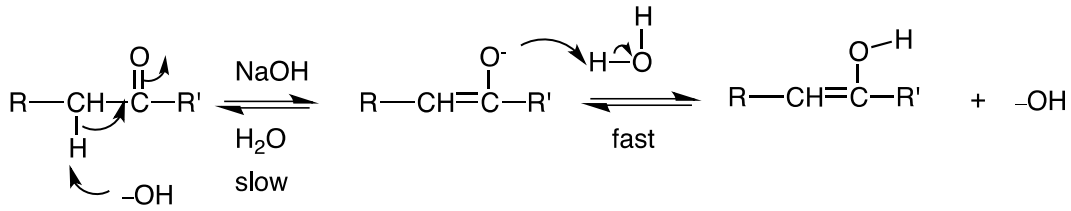
(1) The new double bond that is formed is conjugated with the carbonyl C=O bond.

(2) There is intramolecular hydrogen-bonding of the enol OH group with the carbonyl oxygen.

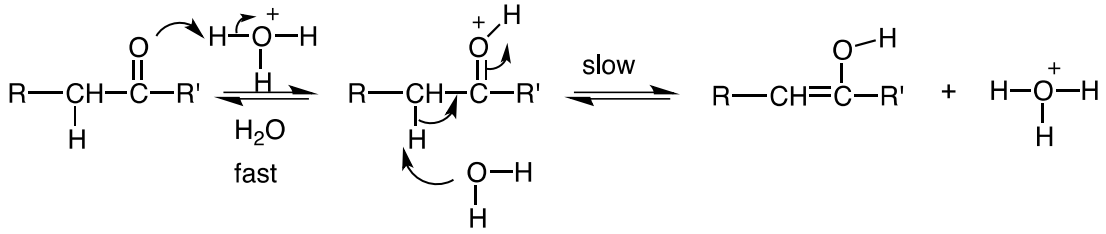


The keto enol tautomerization occurs spontaneously but is very slow in the absence of catalysts. The reaction is speeded by up either acid or base.

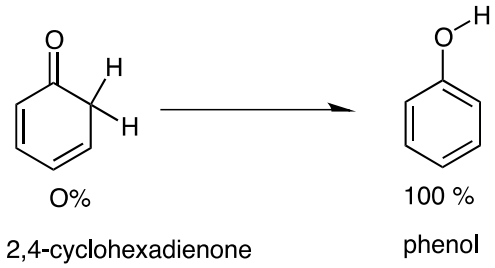
Basic catalysis:



Acid catalysis:



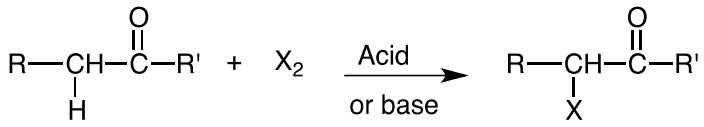
Stabilized enols: In some cases the enol form is more stable than the keto form. One important example is phenol.



The enol tautomer (phenol) is stablized by resonance. Recall that the benzene ring is ~ 36 Kcal/mol more stable due to this electron delocalization of the π-electrons.

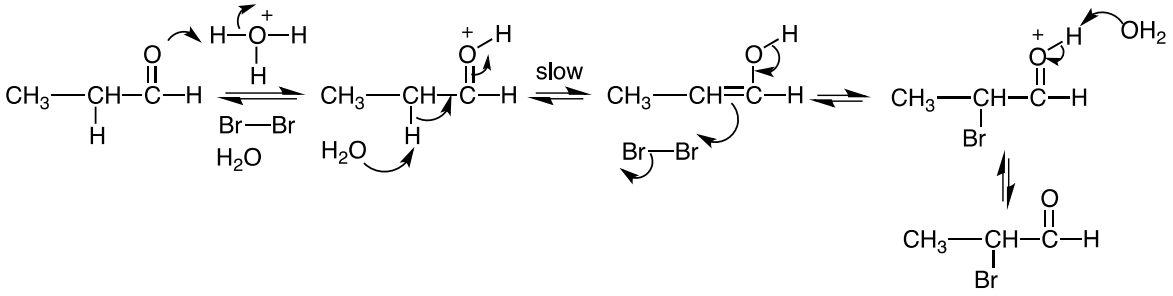
α-Halogenation of Aldehydes and Ketones

We can replace an α–proton next to a carbonyl of an aldehyde or ketone with a halogen using acidic or basic conditions.



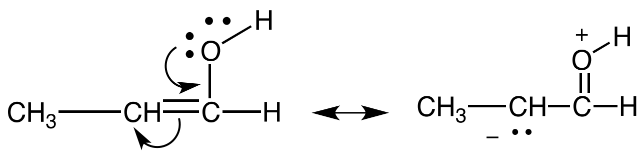
The reaction occurs through formation of the enolate or enol. This is catalyzed by acid or base.

Acidic catalysis:

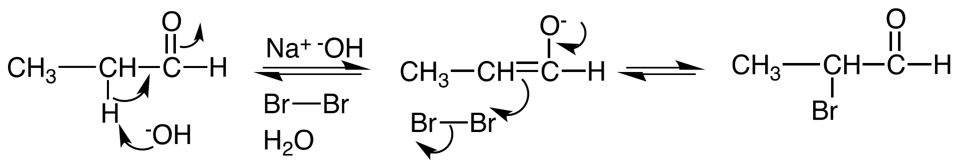


The slow step is the removal of the α–proton to form the enol. It is the overall rate limiting step so the rate for iodination, bromination and chlorination is the same. The α–carbon of the

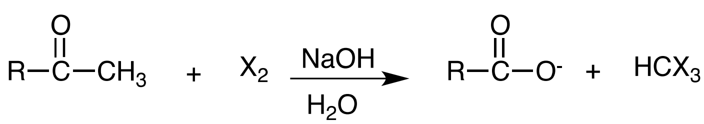
enol is nucleophilic. The enol is an electron-rich double bond and therefore nucleophilic. The oxygen activates the double bond by donating electron density.



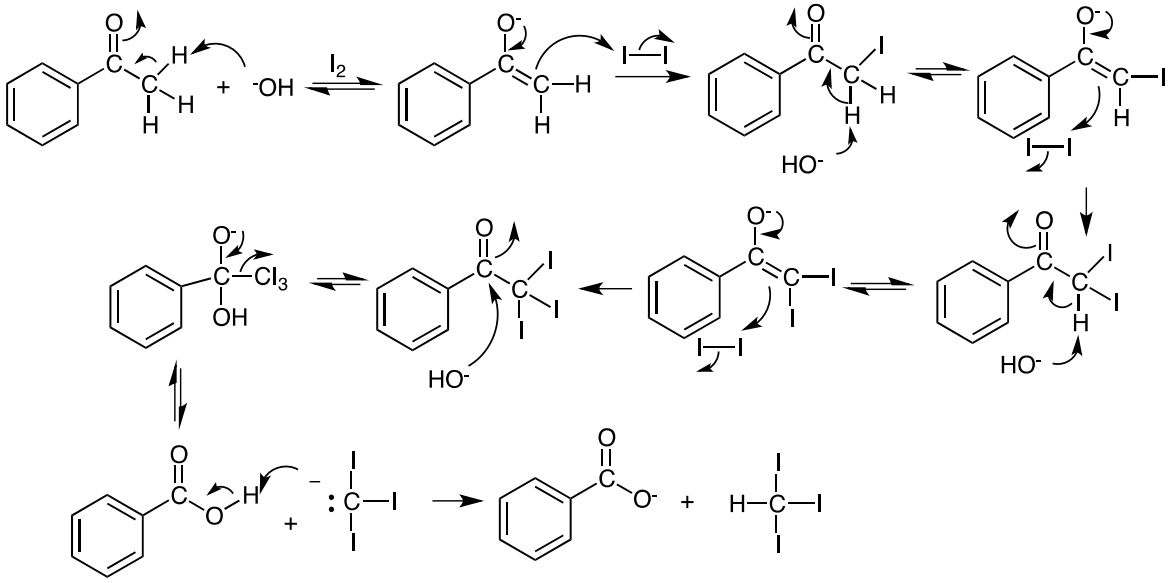
Basic conditions



If an excess of the halide (Cl_2, Br_2 I_2) is used with a methyl ketone, we get the haloform reaction.

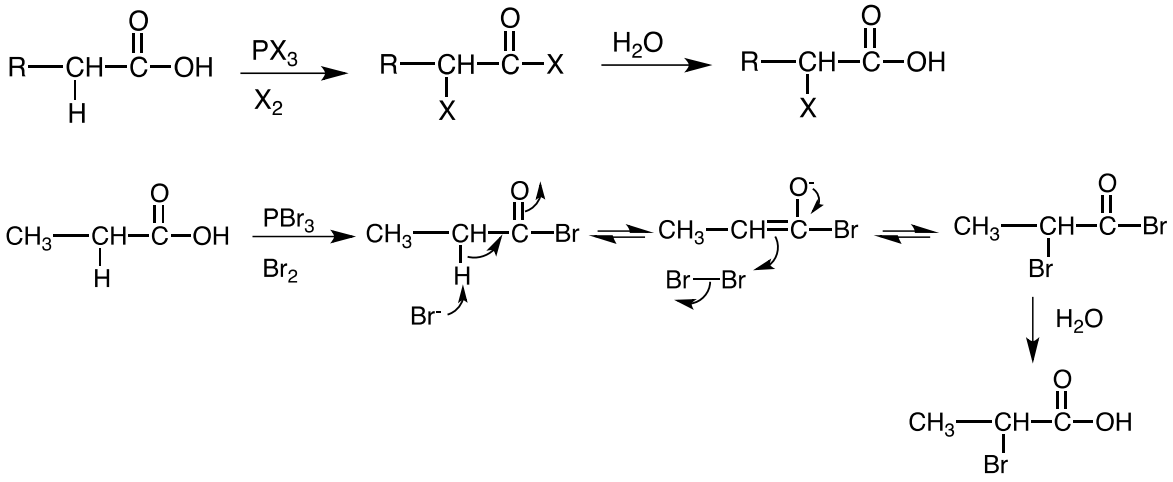


The mechanism is shown below. Note that after the addition of the first iodine, the remaining two α-[illegible] after addition of the second iodine, the third α–proton is even more acidic. The $–CI_3$ is a good leaving group and is displaced from the carbonyl carbon by hydroxide. This final step is irreversible, since the carbanion then removes a proton from the carboxylic acid.

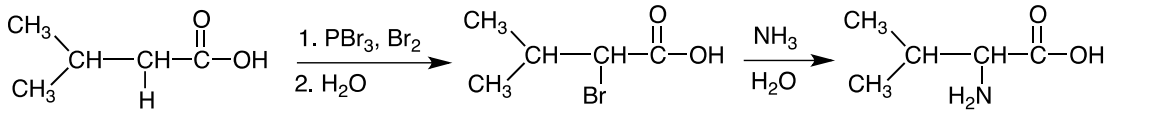


α–Halogenation of Carboxylic Acid (Hell-Volhard-Zelinsky Reaction)

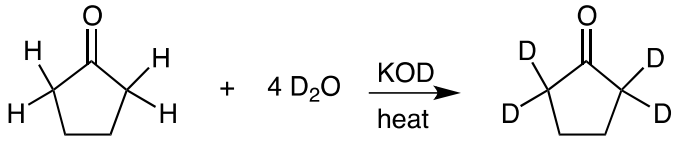
The α-proton next to the carbonyl carbon of a carboxylic acid can also be removed. Again, the enolate is involved but first the carboxylic acid halide is formed using a phosphorus trihalide reaction. Formation of the acid halide increases the acidity of the α-proton, making the enolate formation more favorable. After addition of the halide to the α–carbon, the acid halide is hydrolyzed back to the carboxylic acid during the work up.



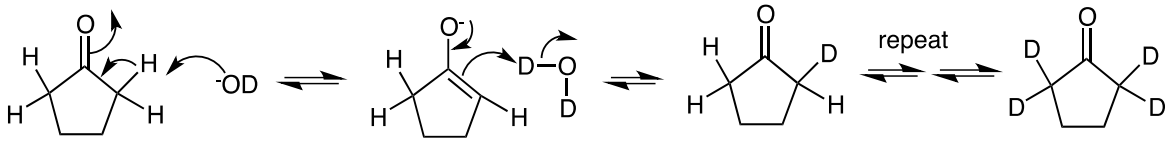
This reaction is useful for making α–amino acid.



The α–proton can be replaced by deuterium to isotopically label a molecule.

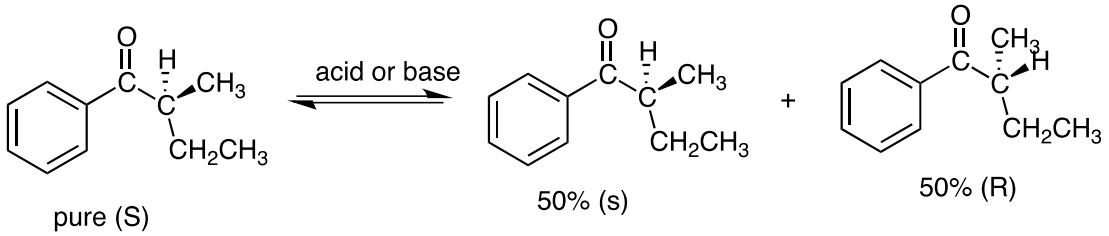


This occurs by means of the enolate.

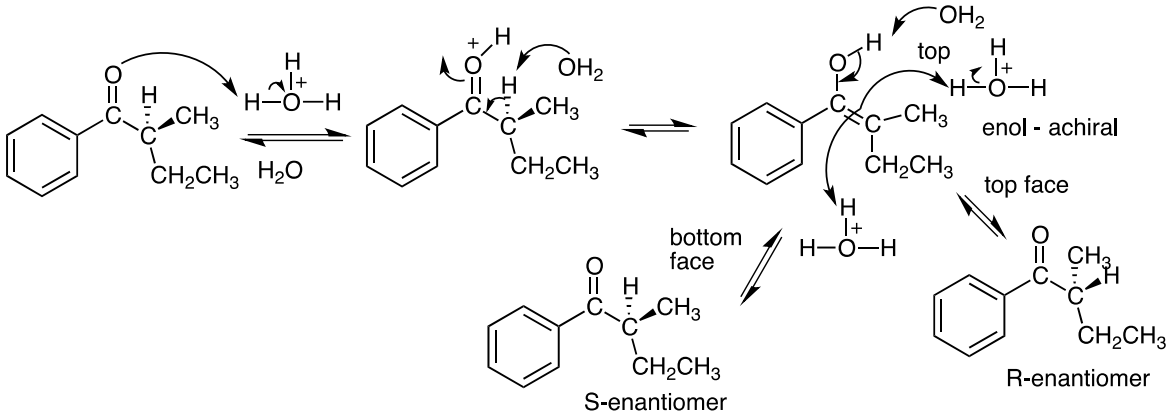


Racemization of Chiral Carbonyl Compounds

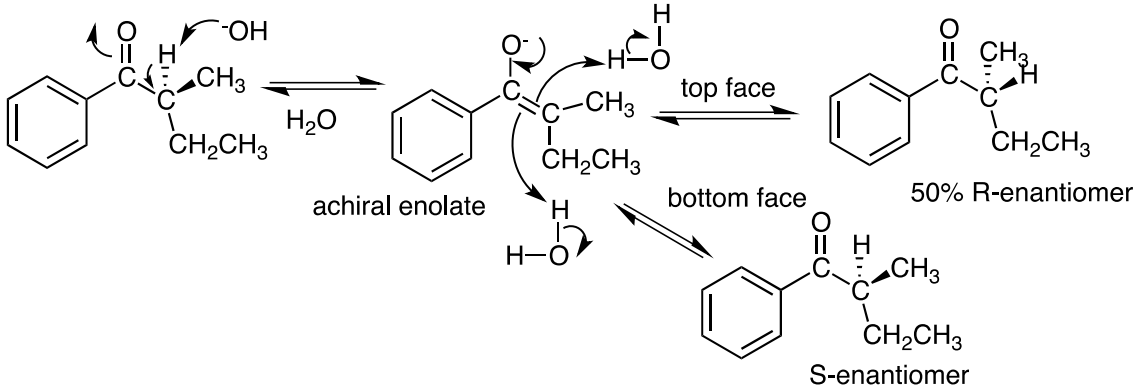
A chirality center that is next to a carbonyl group and has at least one α–proton is subject to racemization in either acidic or basic conditions.



In acidic conditions: An achiral enol intermediate forms reversible. This reverts back to starting ketone by means of reprotonation from hydronium ion (H_3O^+). The proton can add to either face, protonating from the top face to give the R-enantiomer or protonation from the bottom face to give the S-enantiomer. Both are equally likely and so after a period of time a solution of pure S-enantiomer will racemize into a 50:50 mixture of enantiomers.

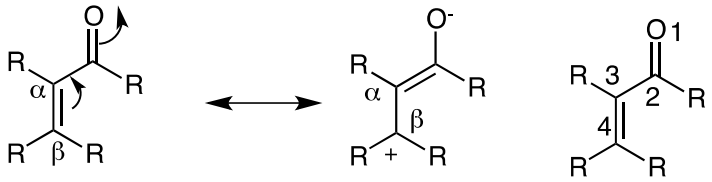


Basic conditions:



Effects of Conjugation in α,β−Unsaturated Aldehydes and Ketones

When we have a double bond directly attached to a carbonyl group the double bond becomes electron deficient at the β−carbon. This is due to the electron withdrawing effect of the carbonyl group and is illustrated by drawing a resonance structure.

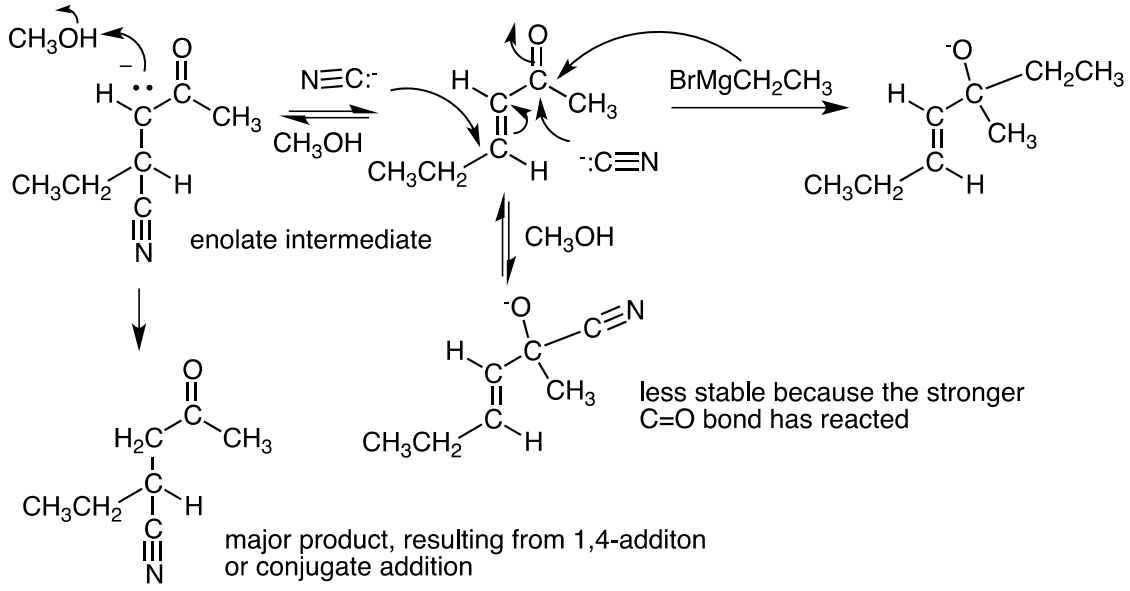


As we learned in CH. 14, Grignard reagents and organolithium reagents will attack the carbonyl carbon of aldehydes and ketones and esters. We often refer to this as 1,2-addition. Certain other nucleophiles, however, will attack the β−carbon. We call this conjugate addition or 1,4-addition.

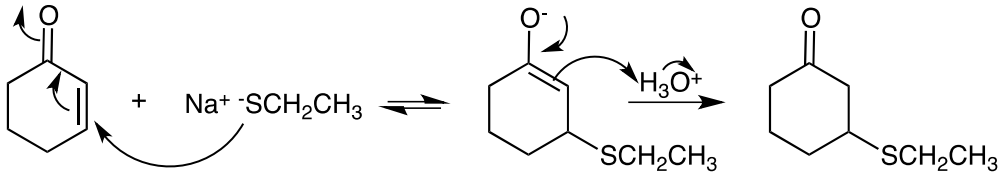
In general nucleophiles that are weaker bases and weaker nucleophiles tend to attack at the β−carbon.

The following nucleophiles attack the β−carbon: (1) thiolate anions, RS^- (2) nitriles, $^-:CN$ (3) organocuprates, $(R)_2CuLi$ (4) enolates.

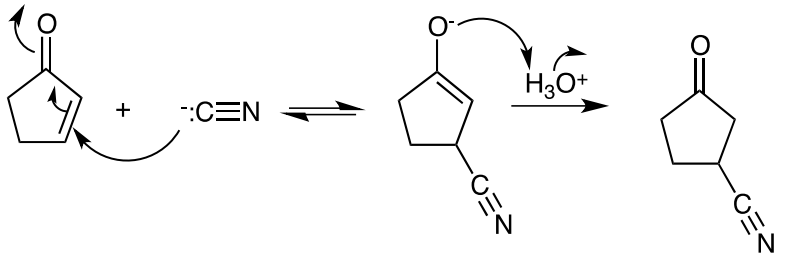
There are several explanations for this. One possible reason is that with weaker nucleophiles the reaction tends to be reversible. Attack at the β−carbon is the thermodynamic (more stable) product since the stronger C=O is still intact while the weaker C=C bond has been cleaved. Stronger nucleophiles attack the carbonyl carbon since this position is more electrophilic with a greater density of (+) charge. With stronger nucleophiles the reaction is irreversible and we get the kinetic 1,2-product.



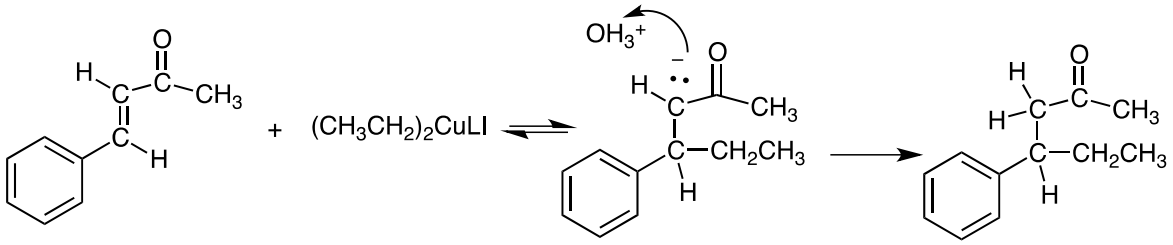
(1) Thiolate anions attack the β−carbon to form an enolate anion. This is then protonated in the work-up.



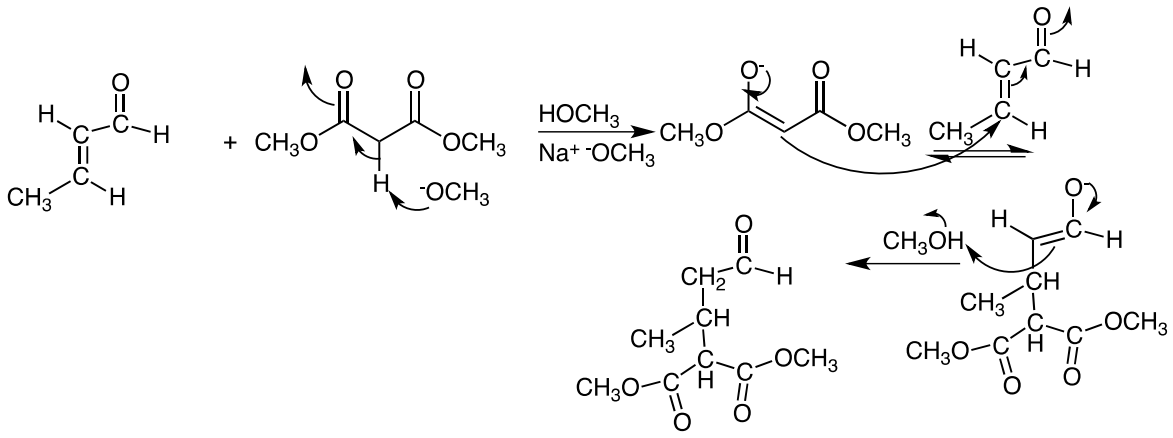
(2) Nitriles attack the β−carbon.



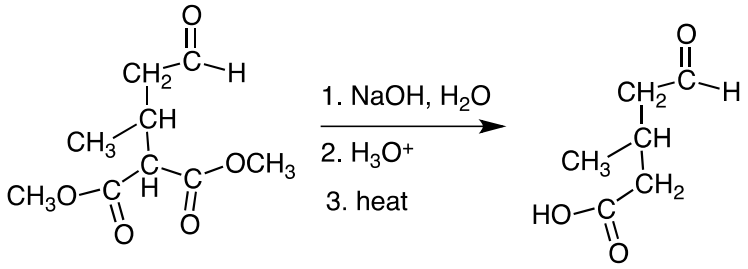
(3) Organocuprates attack the β–carbon.



(4) Enolates will attack the β–carbon. This reaction is called the Michael reaction in recognition of an early American chemist, Arthur Michael, who did much of the exploratory work on this reaction. The use of activated enolates – i.e. those having a 1,3-dicarbonyl relationship – is particularly useful in this reaction. As we have seen, the enolate can be formed quantitatively under mild conditions. The enolate then attacks the β–carbon to form a new enolate that is protonated by the solvent.

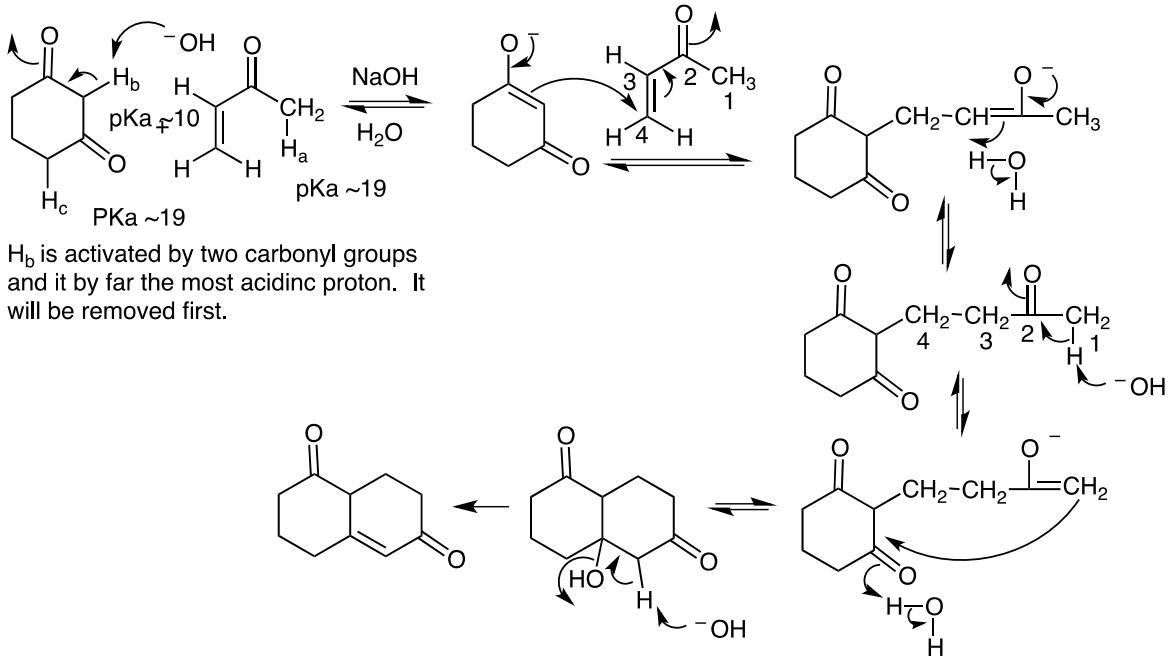


In this case we can isolate the diester or we could decarboxylate one of them through the three-step sequence of (1) basic hydrolysis (2) protonation and (3) heating.



We can use the Michael reaction to form new cyclic compounds by combining it with an intramolecular aldol reaction. This sequence is called the Robinson Annulation after Sir Robert Robinson who developed this reaction. He was awarded the Nobel Prize in 1918 for chemistry for his work.

We start with a 1,3-dicarbonyl such as cyclohexane-1,3 – dione and methyl vinyl ketone or MVK. The most acidic site is the proton between the two carbonyl groups. The enolate forms there and attacks the β–carbon of methyl vinyl ketone. Removal of a proton at C1 forms an enolate that can undergo an intramolecular aldol reaction in the second phase of the reaction. Enolization can occur at other positions but again, the enolate that allows for formation of a five- or six-membered ring will be the predominant reaction pathway.



H_b is activated by two carbonyl groups and it by far the most acidinc proton. It will be removed first.