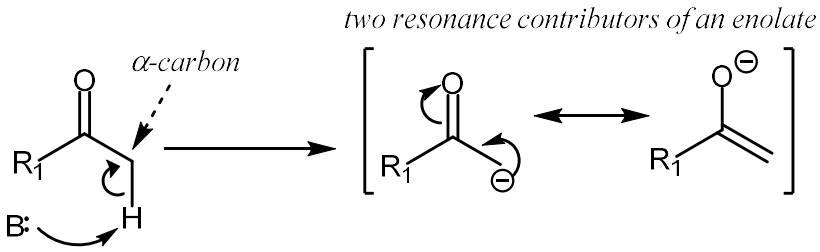
Lesson VI.15. Preparation of Enolates and Alkylation

Lesson VI.15.1 Introduction to Enolates

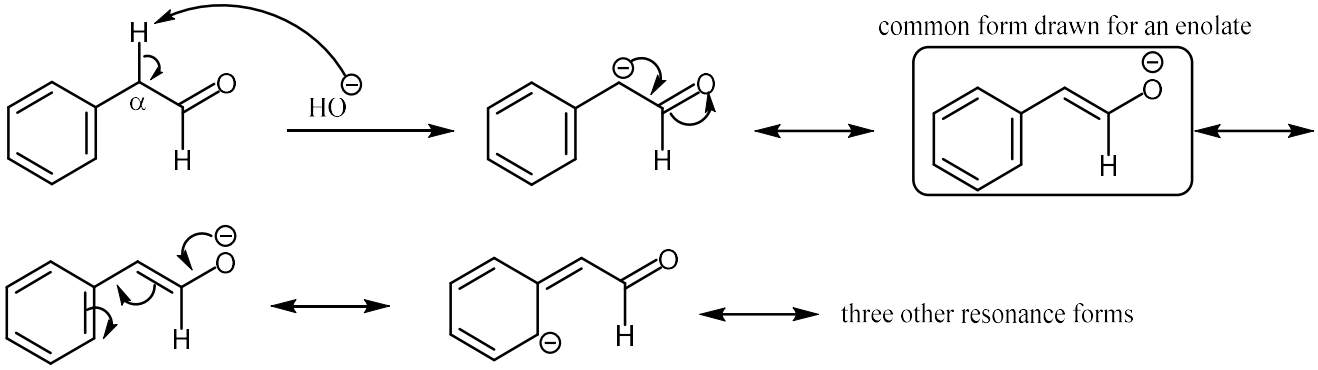
Enolates are molecules formed by treating carbonyl compounds with strong bases. The strong base removes a proton form the carbon adjacent to the carbonyl carbon – called the α-carbon (read "alpha carbon"). Enolates are characterized by negatively-charged oxygen next to a C–C double bond. Enolates are stabilized by delocalization of electrons (resonance forms). They are reactive nucleophiles, as we will see as we study the various reactions they can facilitate.



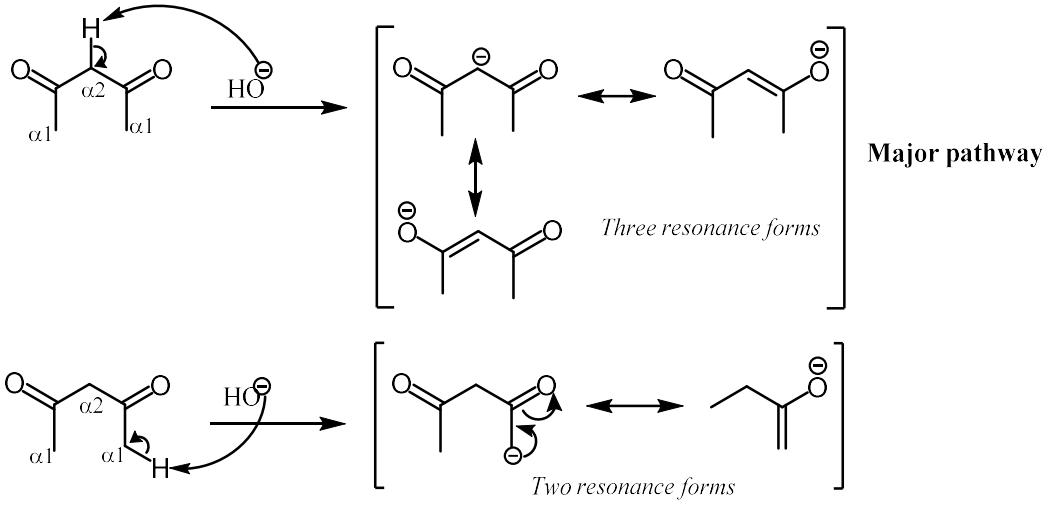
R_1 = -H, alkyl, aryl, alkenyl, -OR, or -SR

Lesson VI.15.2 Enolates of Ketones and Aldehydes

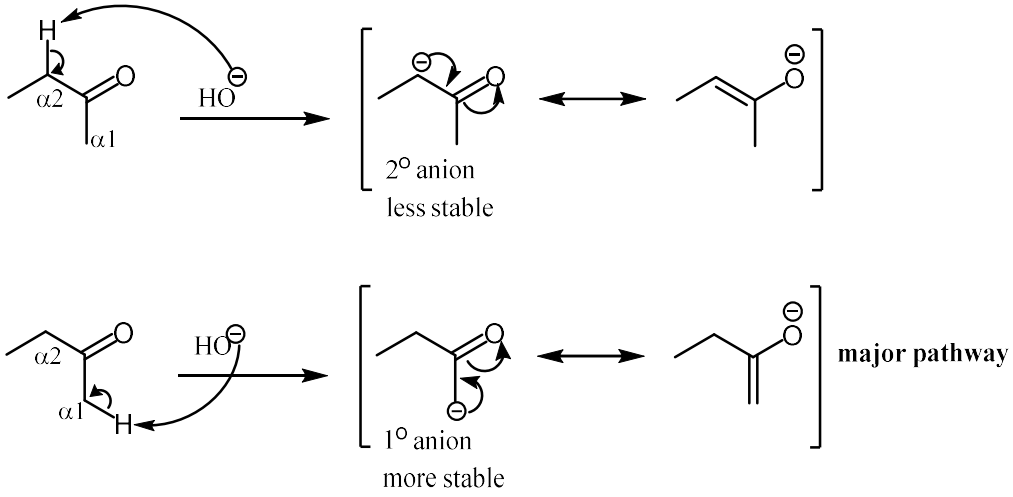
When a ketone or an aldehyde is treated with a strong base, the α-hydrogen will be removed to leave a negative charge on the α-carbon. The carbanion is resonance-stabilized by delocalization of charge onto the O as well. The stability of the enolate depends on how many resonance contributors can be formed (more resonance contributors = more stable). Treating phenyl acetaldehyde with base, for example, will lead to formation of a very stable enolate due to the resonance contributors possible by delocalizing the charge onto the adjacent benzene group:



When a compound has an sp^3-carbon between two carbonyl groups, deprotonation of the "doubly α" site will lead to a more resonance-stabilized species, and this site will therefore be deprotonated selectively over the "singly α" sites, as illustrated for 2,4-pentadione:



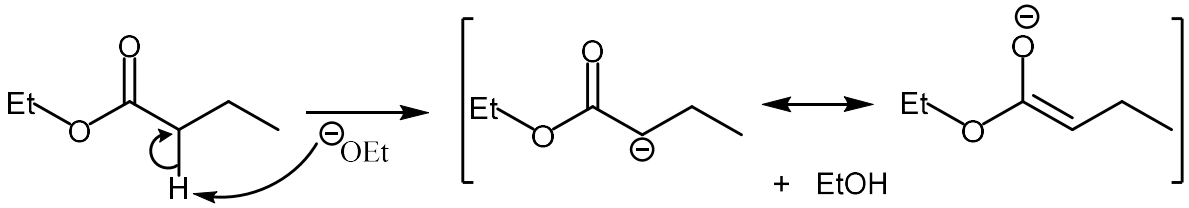
Some molecules will contain two inequivalent α-carbon positions beside the same carbonyl group, whereby deprotonation at either position affords an anion with the same extent of resonance stabilization. In these cases, we must consider inductive effects to determine which enolate anion is more stable. Consider the case of 2-butanone:



Anions are more stable on less substituted carbon atoms due to less repulsion by adjacent σ-bonds (an example of a repulsive inductive effect, see Lesson I.10 in OC1 Primer). This makes the deprotonation of α1 more thermodynamically favorable, and therefore yields the major enolate in this case. Note that this inductive effect is **secondary** to resonance effects in determining the predominant deprotonation site.

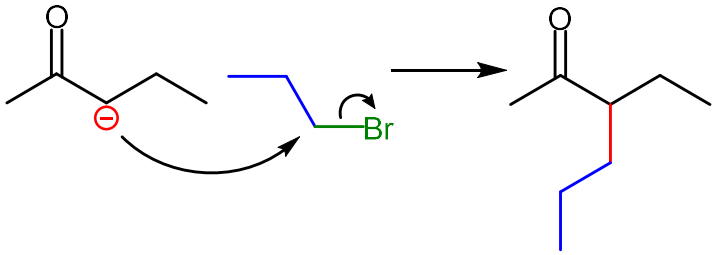
Lesson VI.15.3 Enolates of Esters

An ester enolate can be generated by deprotonation of an ester with a base like an alkoxide ($^{-}$OR). Note that the alkoxide base used should contain the same alkyl group as the ester O-substituent to prevent undesired nucleophilic addition or substitution reactions. For example, to prepare the ester enolate of ethyl butanoate (see below) we should use ethoxide as the base (added as NaOEt salt). In this reaction, the predominant net pathway is one in which the alkoxide will act as a base rather than as a nucleophile and it will deprotonate the most acidic hydrogen in the ester, similar to what we saw for aldehydes and ketones:



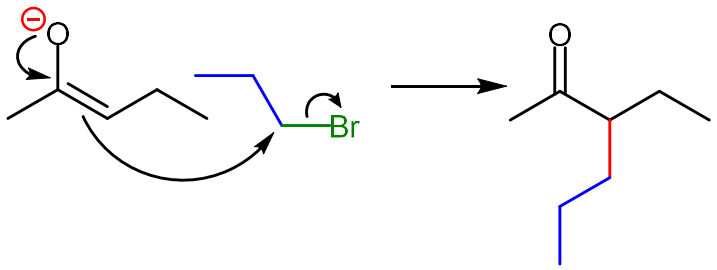
Lesson VI.15.4 Enolates as Nucleophiles for S_N2 Reaction: α-Alkylation

Once an enolate forms, it can be used as a nucleophile in an S_N2 reaction:



The net result of this reaction is adding an alkyl group to the α-carbon of a carbonyl. For this reason, this reaction is often called **α-alkylation**. In the next several lessons, we will see other reactions that employ the enolate as a nucleophile.

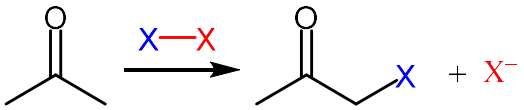
It is also important to note that some people draw the enolate in its other resonance form for mechanisms. If we do this to represent the exact same S_N2 reaction we saw above, it would look like this:



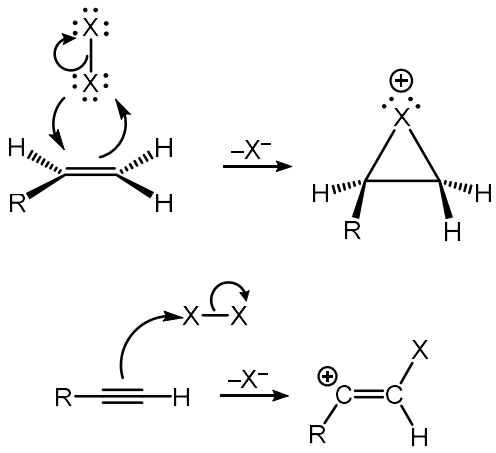
Lesson VI.16. Alpha-Halogenation and Haloform Reactions

VI.16.1 Alpha Halogenation

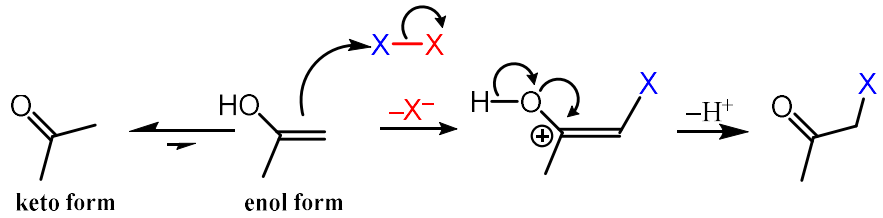
When a carbonyl species reacts with X_2 (X = Cl or Br), the result is **α-halogenation**:



To figure out how the α-halogenation reaction works, we can think back to two other halogenation reactions we have seen. We have seen (Lessons III.6 and III.12 in OC1 Primer) that in alkene or alkyne halogenation, a π-bond can act as a nucleophile in a reaction with X_2 ($X = Cl_2$ or Br_2):



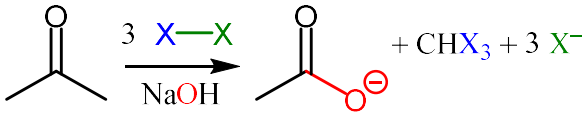
A reaction analogous to the alkyne reaction can be drawn for the reaction of a carbonyl species with X_2. When representing halogenation of the carbonyl, it is easiest to envision the reaction by considering the minor enol tautomer as the reactant, so that we can portray the π-bond attacking the halogen just like we saw for alkynes:



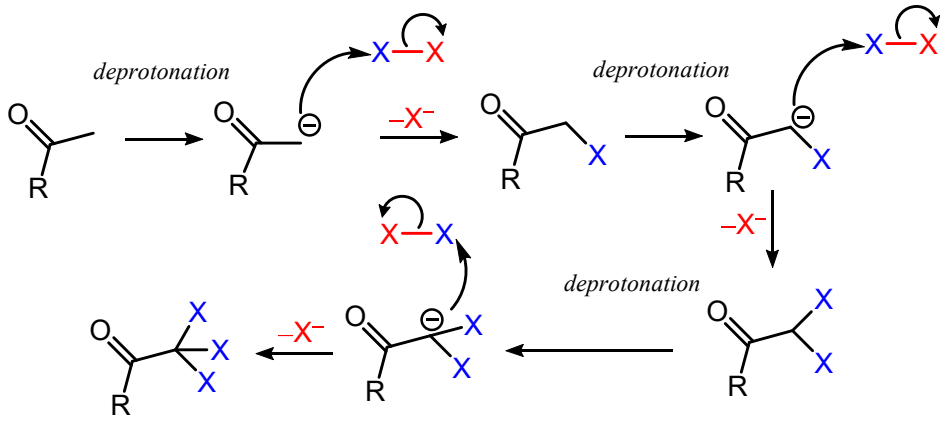
Remember that the keto-enol equilibrium is occurring constantly for a carbonyl species in solution, so if it is being consumed by reaction, eventually all of the carbonyl can be consumed to give the halogenated product. The H^+ that comes off of the O and the X^- can go together to make HX as well.

VI.16.2 The Haloform Reaction

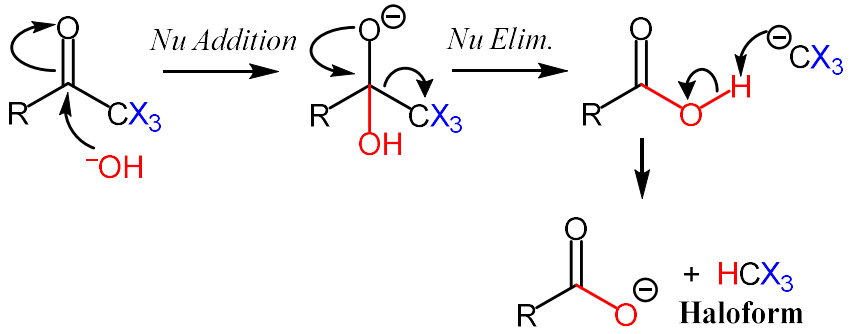
When a ketone having a methyl group on one side reacts with X_2 (X = Cl, Br or I) in the presence of NaOH, the result is formation of a haloform and a carboxylate. A haloform is a molecule with the formula CHX_3. The specific molecule is called chloroform, bromoform or iodoform when X = Cl, Br or I, respectively. This is called the **haloform reaction:**



What is a reasonable mechanism for this reaction? Well, because we have a base and a carbonyl, we can envision that the first step will be formation of the enolate. Then, the enolate can act as a nucleophile, leading to α-halogenation. The base can then deprotonate the α-carbon again, so that a second halogen can add to the α-carbon. This deprotonation-halogenation step happens a third time, and then there are no more α-hydrogens to remove from that site, and they have all been substituted for X:



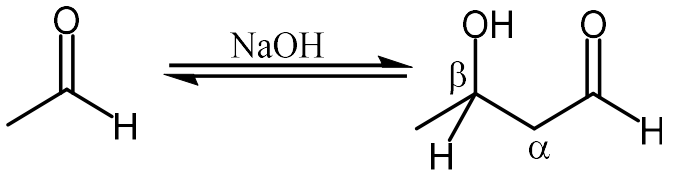
At this point, the hydroxide will act as a nucleophile for the S_NAc reaction. Generally, a carbanion would be too poor a leaving group for this reaction, but in this case the strong inductive stabilization afforded by the three attached halogens allows this to happen to some extent. As the carbanion and carboxylic acid form, the carbanion is rapidly protonated by the carboxylic acid, driving the equilibrium to the right and forming the final products:



Lesson VI.17. Aldol Addition and Condensation

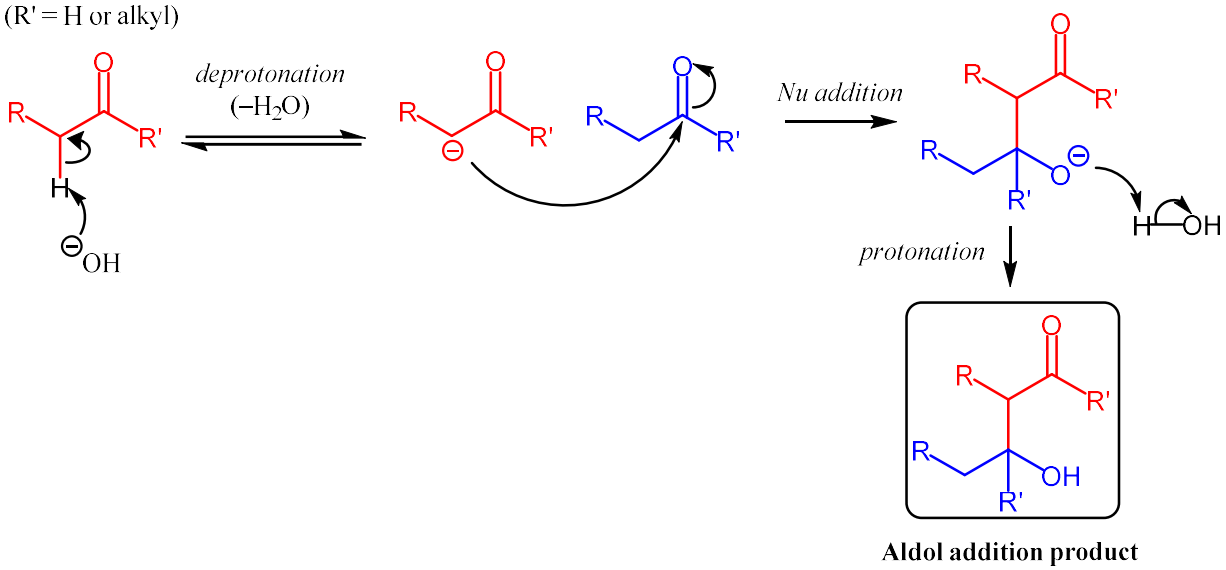
VI.17.1 Aldol Addition

Another example of a Type A reaction is **aldol addition**, so named for the **ald**ehyde and alcoh**ol** functional groups it installs in the product for some such reactions. In the aldol reaction, an enolate is generated and functions as a nucleophile that attacks the electrophilic carbonyl carbon, followed by protonation to give a β-hydroxycarbonyl product. A strong base is required to form the enolate. An example of the aldol reaction is:



β-hydroxycarbonyl

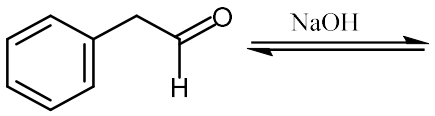
The mechanism for aldol addition is depicted in the following figure:



The aldol addition reaction is actually just a simple nucleophilic addition followed by protonation (Type A reaction) that is common for ketones and aldehydes. The only difference between this Type A reaction and those we have seen previously is that we are using the enolate as the nucleophile, so the enolate must be generated from some of the starting carbonyl itself!

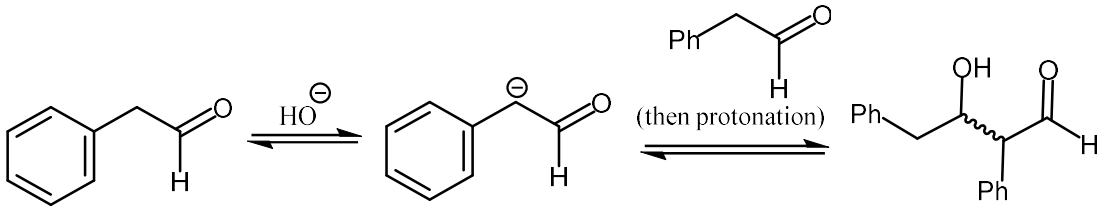
Example VI.17.1

Draw the major addition product of the following reaction



Solution VI.17.1

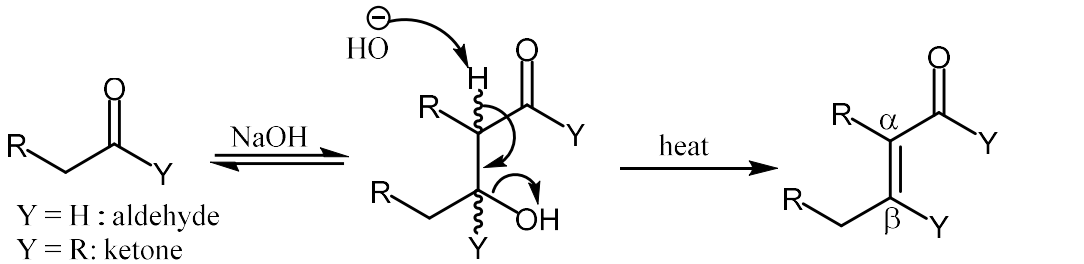
This is an aldol reaction, which is a Type A nucleophilic addition, wherein the base ($^{-}$OH) deprotonates one molecule of the reactant aldehyde to form the nucleophilic enolate, which then adds to the carbonyl carbon and breaks the C–O π-bond. Subsequent protonation affords the alcohol product. Furthermore, because the product has a chiral center but the reactant is achiral, the product will be a **racemic mixture** of both the *R* and *S* stereoisomers.



Lesson VI.17.2 Aldol Condensation

If the aldol addition product is heated in the presence of a base, further reaction will take place that leads to elimination of another molecule of water. The water often form condensation on the reaction vessel, so this additional reaction to form the elimination product is called **aldol condensation**.

The mechanism for the elimination is shown in the figure below:

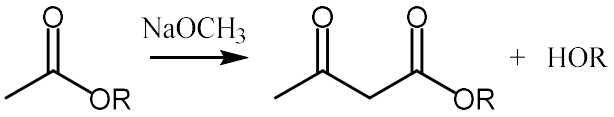


When an aldol condensation reaction has the potential to produce two geometrical isomers (for example an *E*- versus a *Z*-alkene) the more stable (thermodynamically favored) product is the major product.

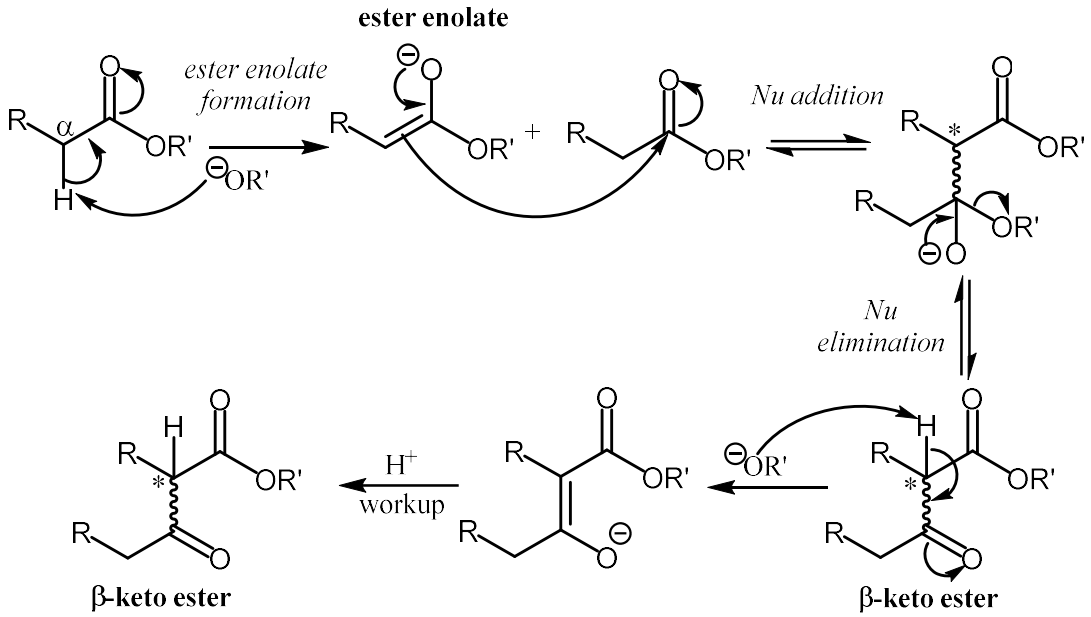
Lesson VI.18. Claisen Condensation

Lesson VI.18.1 Claisen Condensation

Claisen condensation is the nucleophilic acyl substitution of esters, in which an ester enolate (Lesson VI.15) acts as the nucleophile. This leads to β-keto esters as products:



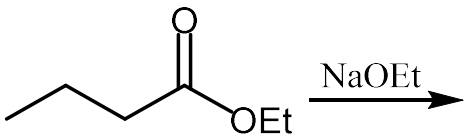
The mechanism involves making the enolate and then doing the usual S_NAc sequence:



The reaction generally produces a chiral center at the α carbon of the Claisen product, yielding a racemic mixture. The intramolecular version of the Claisen condensation is called the and **Dieckmann Condensation**.

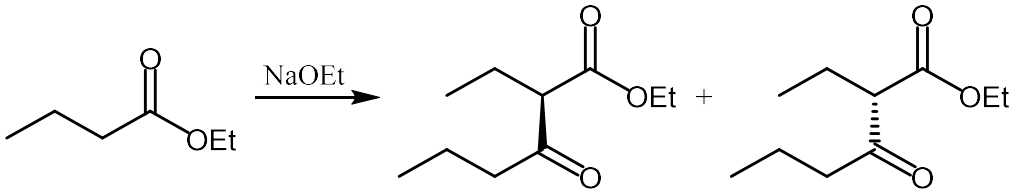
Example VI.18.1

Give the product of the following Claisen condensation reaction



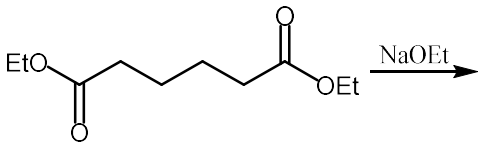
Solution VI.18.1

The ethoxide ion will produce the ester enolate, which will react with the carbonyl in another ester molecule as a nucleophile, to produce the β-keto ester. Since we will have a chiral center at the α-carbon then we will have a racemic mixture of the two enantiomers:



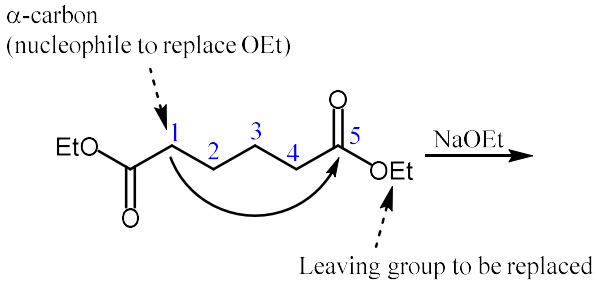
Example VI.18.2

Give the product of the following reaction:

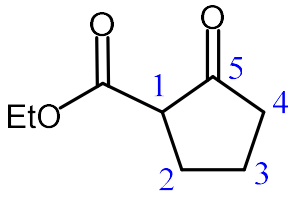


Solution VI.18.2

Both esters are attached to the same chain, so this will be a Dieckmann Condensation. We identify the α-carbon that will be the nucleophile once deprotonated, and simply attach it in place of the OEt on the other end (the usual S_NAc reaction):



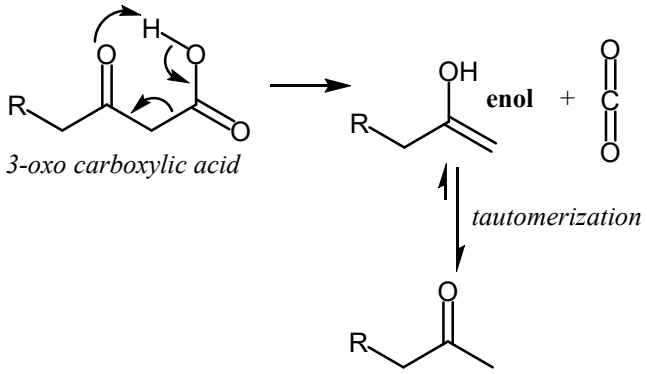
We can see that the ring we will form has five carbon atoms in it. It is helpful to number the carbons that will form the ring to be certain, as in the structure above. The final product then is:



Lesson VI.19. Decarboxylation and Synthetic Applications

Lesson VI.19.1 Decarboxylation of 3-oxo Carboxylic Acids

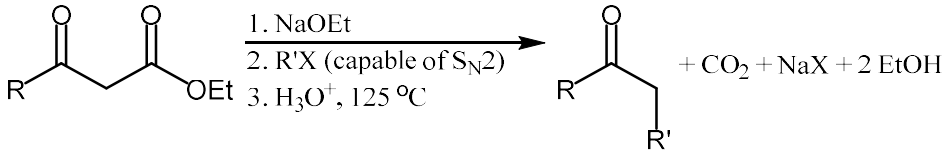
Carbonyls are typically relatively stable upon heating to moderate temperatures, but 3-oxo carboxylic acids decompose to release CO_2 if they are heated to above 120 °C. This is a process called **decarboxylation**. An arrow-pushing mechanism for the process is:



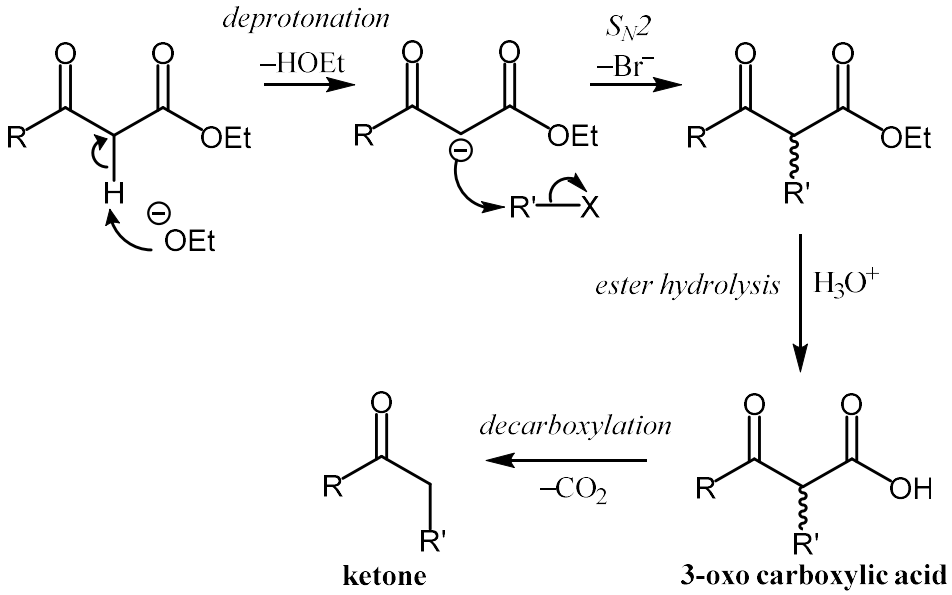
Decarboxylation is specific to 3-oxo carboxylic acids (or carboxylates at higher temperature) and is a useful way to remove a carbon from a molecule. Some especially useful synthetic procedures that employ decarboxylation as a step are discussed in the remainder of this lesson.

Lesson VI.19.2 Acetoacetic Ester Synthesis

The **acetoacetic ester synthesis** involves several steps, all of which we have seen throughout this book. The net reaction is:

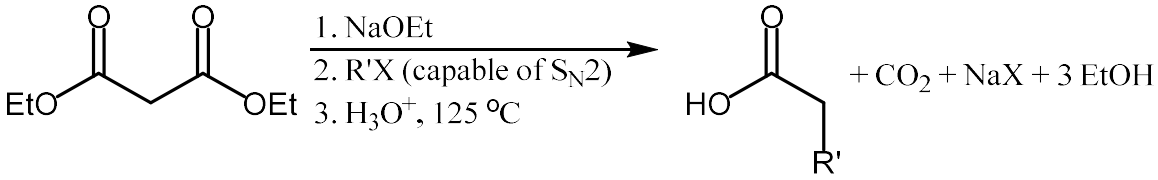


Let us walk through all of the steps (see the scheme on the following page). First, the added base will deprotonate the doubly-α carbon between the two carbonyl units to form an enolate nucleophile. The enolate nucleophile then participates in an S_N2 reaction with the alkyl halide (R'X) that is added in step 2. Once this reaction is complete, the compound is heated in the presence of acid and water (H_3O^+). We saw in Lesson VI.11 that these conditions lead to acid-catalyzed ester hydrolysis, converting the ester into a carboxylic acid. Upon further heating at elevated temperature, this species will undergo decarboxylation to yield a ketone. The **acetoacetic ester synthesis is a convenient synthetic route to ketones** with a variety of chain compositions:



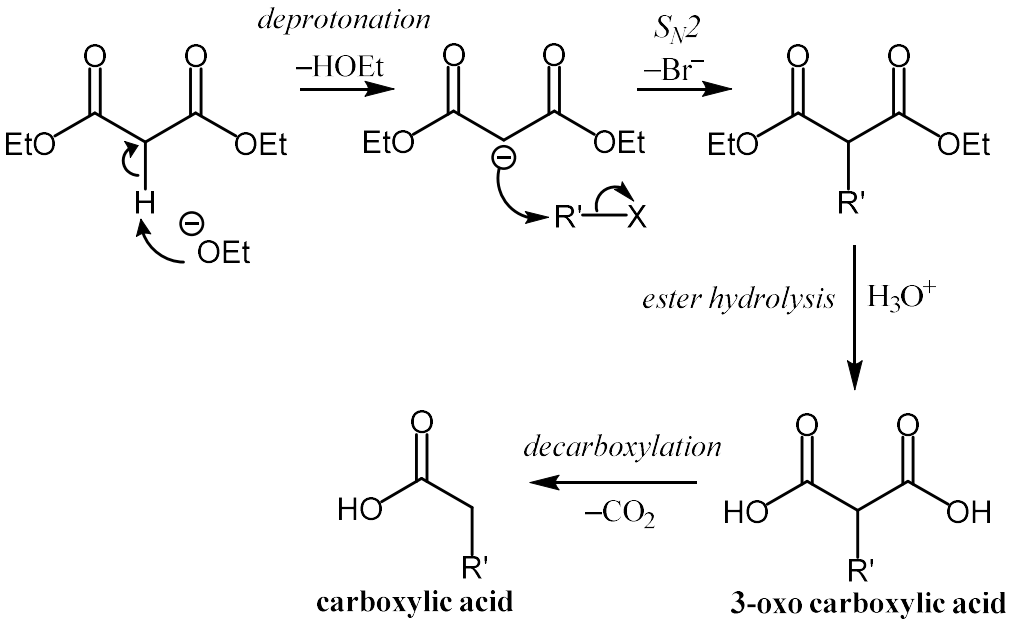
Lesson VI.19.3 Malonic Ester Synthesis

The malonic ester synthesis is another important industrial process that makes use of several reactions that we have seen. The net reaction is:



The steps are fundamentally the same as for the acetoacetic ester synthesis. First, the added base will deprotonate the doubly-α carbon between the two carbonyl units to form an enolate nucleophile. The enolate nucleophile then participates in an S_N2 reaction. The S_N2 product is heated in the presence of acid and water (H_3O^+), causing ester hydrolysis. In this case, both of the ester units are converted into carboxylic acids, giving a 3-oxo carboxylic acid. Upon further heating at elevated temperature, this species will undergo decarboxylation to yield a carboxylic acid.

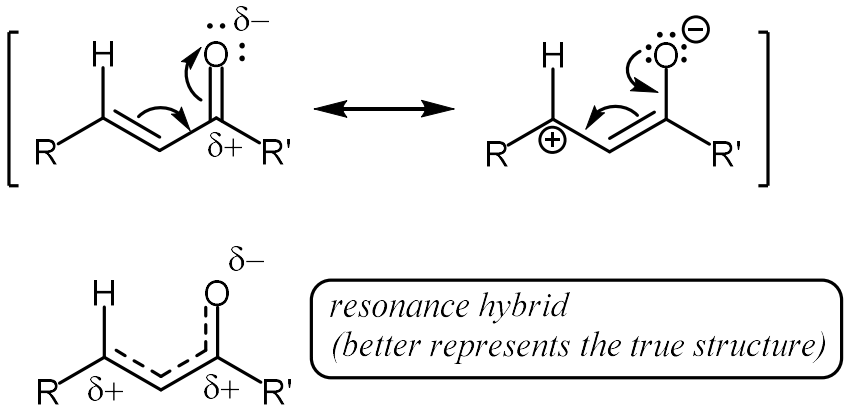
The **malonic ester synthesis is a convenient synthetic route to carboxylic acids** with a variety of chain compositions. The complete mechanism is given as:


deprotonation
–HOEt
S_N2
–Br⁻
EtO
OEt
H
OEt
R'
X
ester hydrolysis
H_3O^+
decarboxylation
$-CO_2$
HO
OH
carboxylic acid
3-oxo carboxylic acid

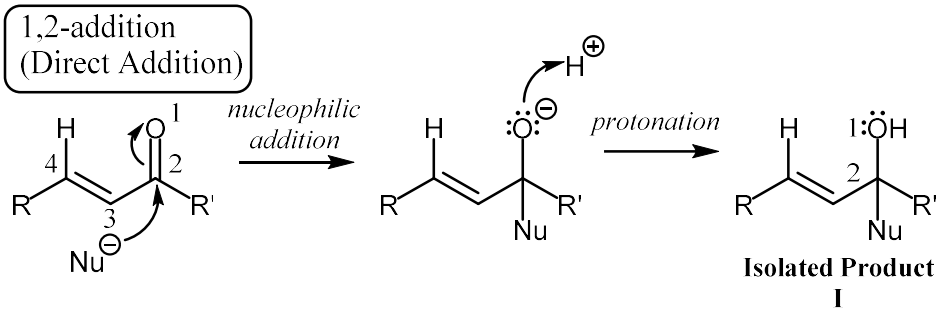
Lesson VI.20. Addition of Nucleophiles to α,β-Unsaturated Carbonyls

Lesson VI.20.1 Electrophilic Sites in α,β-Unsaturated Carbonyls

In Lesson VI.17, we learned how to prepare α,β-unsaturated carbonyls via aldol condensation. We also saw that two conjugated C=C bonds can undergo either 1,2- or 1,4-electrophilic addition reactions (Lesson IV.2). In this lesson, we will investigate how the double bonds in an α,β-unsaturated carbonyl can undergo nucleophilic addition. To understand the reactivity of α,β-unsaturated carbonyls with respect to nucleophilic addition, we must first identify which sites in an α,β-unsaturated carbonyl are electrophilic by examining the possible resonance contributors and corresponding distribution of charges within the resonance hybrid:

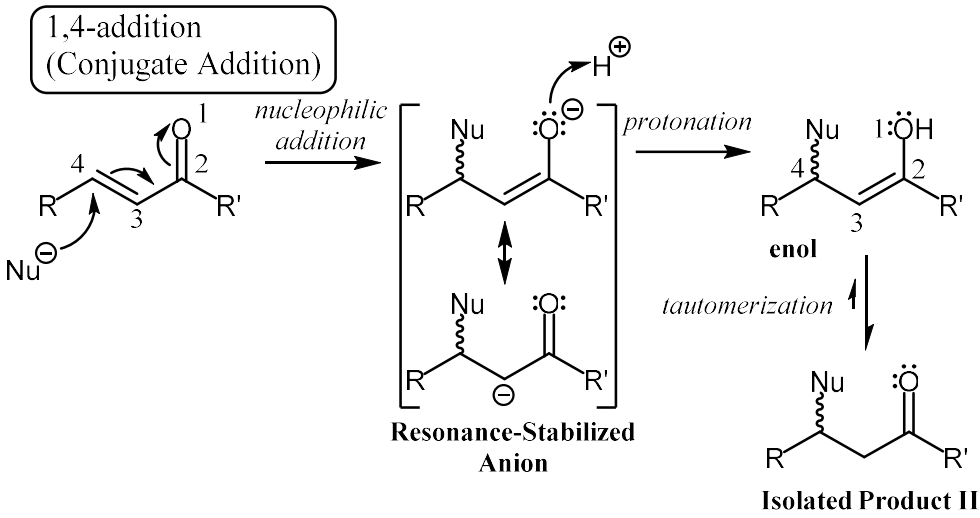


There are two electrophilic sites: the carbonyl carbon and the β-carbon. So, just as conjugated dienes can undergo 1,2- (direct) or 1,4- (conjugate) *electrophilic* addition, **α,β-unsaturated carbonyls can undergo 1,2- (direct) or 1,4- (conjugate) *nucleophilic* addition**:



The isolated product of direct addition to an α,β-unsaturated carbonyl is the same as for a ketone that is not unsaturated: it results from nucleophilic addition at the carbonyl carbon (atom 2) followed

by protonation at the carbonyl oxygen (atom 1). We have previously classified this as carbonyl reaction type A in this book.



Conjugate addition features nucleophilic addition to the β-carbon (atom 4), then protonation of the carbonyl oxygen (atom 1). Because the H and Nu have added to atoms 1 and 4, this is also called 1,4-addition. The isolated product, however, is not this 1,4-addition species itself, because we know from Lesson III.14 (OC1 Primer, reviewed in Lesson VI.15) that an enol spontaneously tautomerizes to the keto form. Conjugate addition to an α,β-unsaturated carbonyl occurs therefore affords a product like **II**.

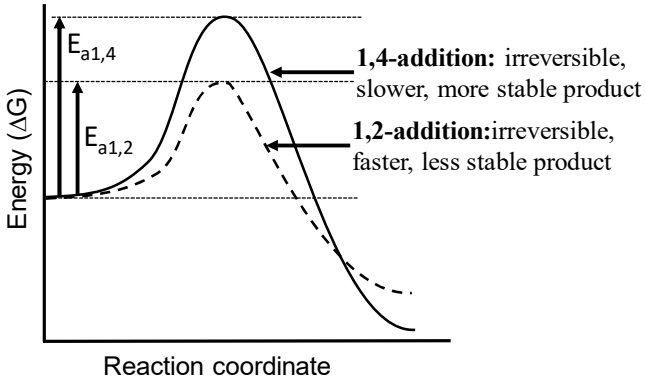
Lesson VI.20.2 Nucleophile Stability Dictates Regioselectivity

Whether 1,2-addition or 1,4-addition leads to the major product depends on how good a leaving group the nucleophile is. To understand why this is, we need to consider the thermodynamics of the nucleophilic addition step.

We first consider the case in which the **nucleophile is an unstable anion** (i.e. a strong base; CH_3O^- or less stable for this case). In this case, the nucleophile is a **bad leaving group**, so after it does nucleophilic addition, the step is **irreversible** regardless of whether the nucleophile adds to the 2-C or the 4-C of the α,β-unsaturated carbonyl. In general, a reaction that consumes a very unstable anion will favor the product side. In the current case, the anion resulting from 1,4-addition is resonance-stabilized, whereas the anion resulting from 1,2-addition is not. Finally, because there is greater δ– charge at the carbonyl C than at the β-carbon, the nucleophilic addition to the carbonyl C will be faster, meaning that the energy of activation for 1,4-addition ($E_{a1,4}$) will be higher than the energy of activation for 1,2-addition ($E_{a1,2}$). This information can be most clearly displayed on a qualitative **reaction coordinate diagram for nucleophilic addition of a strongly basic nucleophile**:

1,2-Addition Dominates

Both reactions are Irreversible:
Reaction is Under Kinetic Control
The faster reaction leads to the major product
Occurs when Nu is a poor leaving group (strong base)

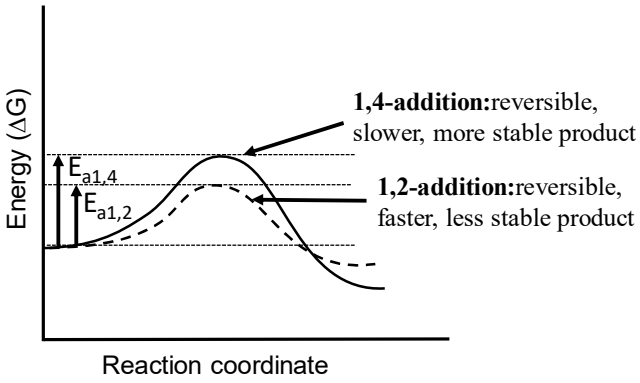


When two competing pathways are both irreversible, the faster process dominates, and the reaction is under kinetic control (Lesson IV.2). So, **when the nucleophile is a strong base, 1,2-addition is the major pathway**.

Next, let us consider the case in which the **nucleophile is a more stable anion** (a weak base, weaker than HO^- for this case). In this case, the nucleophile is stable enough to serve as a leaving group, so addition is **reversible** and therefore it is possible to reach a state of equilibrium. In an equilibrium process, the reaction is under thermodynamic control. As we discussed above, 1,4-addition produces a more stable anion. Here is a qualitative reaction coordinate diagram for nucleophilic addition of a weakly basic nucleophile:

1,4-Addition Dominates

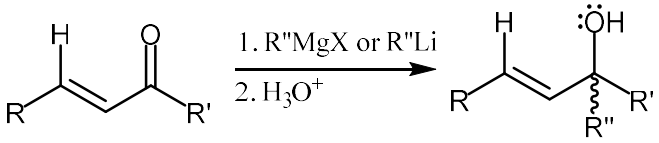
Both reactions are reversible:
Reaction is Under Thermodynamic Control
More stable product is the major product
Occurs when Nu is a good leaving group (weaker base)



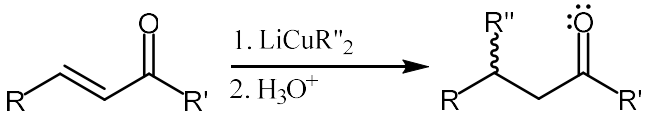
So, when the nucleophile is a weak base, 1,2-addition is the major pathway.

Lesson VI.20.3 Addition of Organometallic Reagents to α,β-Unsaturated Carbonyls

In our study of organometallic reagents (Part V), we saw that Grignard reagents and organolithium reagents are significantly more reactive (which is the same as saying they are less stable) than are Gilman reagents. We also learned that Grignard reagents and organolithium reagents are very strong bases. For this reason, **RMgX and RLi do 1,2-addition (direct addition) to α,β-unsaturated carbonyls**:



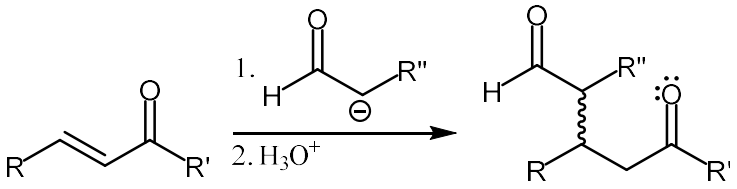
The direct addition is further driven by the strong interaction of the Li or Mg metal with the oxygen atom in the anionic intermediate. The Gilman reagents were developed as a less reactive (more stable) alternative to Grignard and organolithium reagents. They are stable enough that they **LiCuR"$_2$ undergo 1,4-addition (conjugate addition) to α,β-unsaturated carbonyls**:



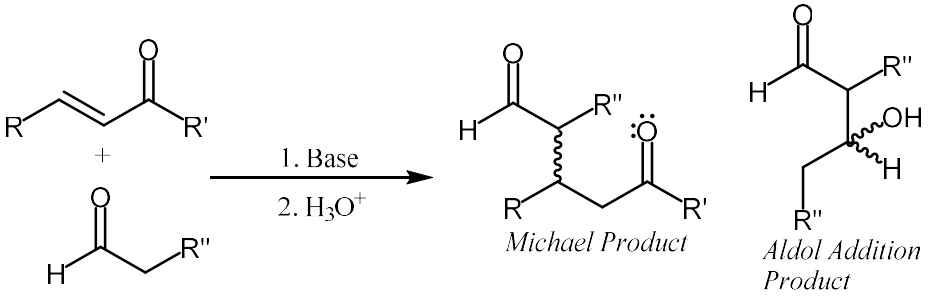
This process is also driven by the stronger interaction of the Cu with the C=C than with the C=O. The reasons for this are beyond the scope of this text.

Lesson VI.20.4 Michael Addition of Enolates to α,β-Unsaturated Carbonyls

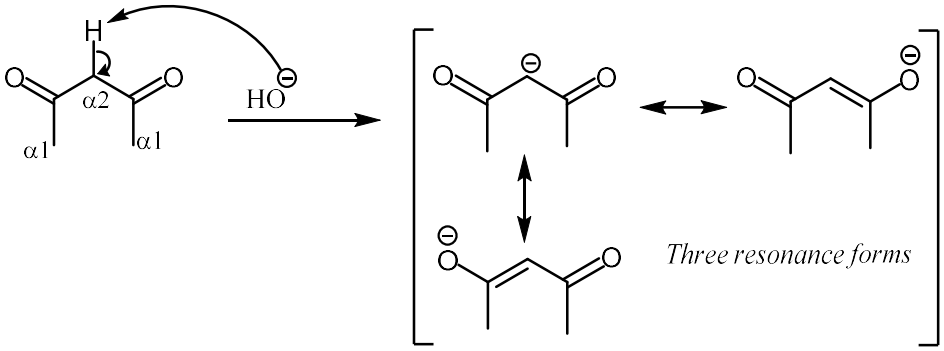
We saw in Lesson VI.15 that enolates can be generated by deprotonation at a site α- to a carbonyl. These enolates are stabilized by resonance, making them more stable than a typical alkoxide. For this reason, **enolates undergo 1,4-addition (conjugate addition) to α,β-unsaturated carbonyls**:



The conjugate addition of an enolate to an α,β-unsaturated carbonyl is called **Michael addition**. If we attempt to conduct a Michael addition by combining an α,β-unsaturated carbonyl and a ketone/aldehyde with a base (to generate the enolate), we will encounter undesired side reactions, because a ketone/aldehyde can also undergo aldol condensation under these conditions:



A better nucleophile for a Michael addition is a 1,3-dicarbonyl compound that will form a more stable enolate:



Here is an example of a Michael addition reaction using an enolate derived from a 1,3-diketone: