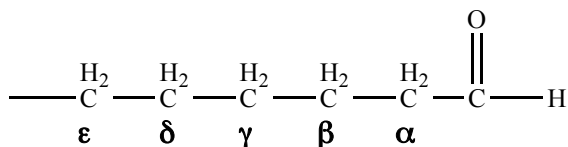


Reactions at the α -Carbon

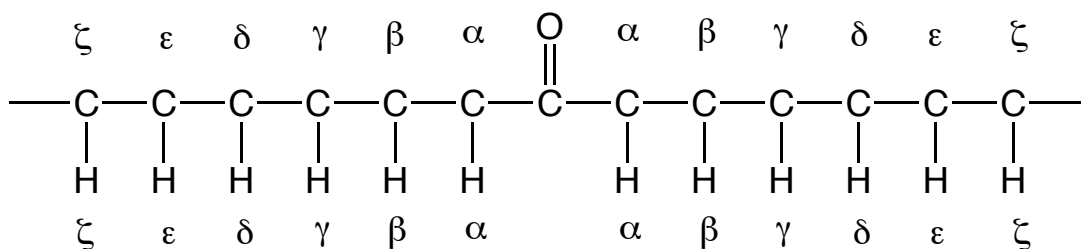
The alpha carbon is the carbon adjacent to the carbonyl carbon. Beta is the next one, followed by gamma, delta, epsilon, and so on.



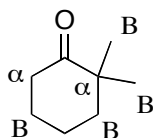
The positions of the carbons are shown in Greek letters. Similarly, the hydrogens attached to a carbon at a particular position are named the same as the carbon at that position. For example, the hydrogens attached to the alpha (α) carbon are known as alpha hydrogens, the hydrogens attached to the beta (β) carbon are called beta hydrogens, and so on.

The hydrogen attached to the carbonyl carbon in an aldehyde is called the aldehyde hydrogen or formyl hydrogen (not an alpha hydrogen). Do not get these confused.

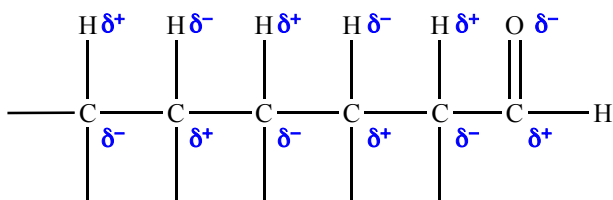
The atoms in ketones are described similarly to aldehydes:



Example:

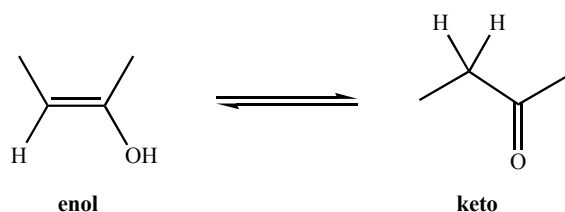


Due to polarization of the carbonyl bond, the carbons nearby have alternating partial negative and positive charge associated with them. The carbons that are farther away from the carbonyl experience less polarization than the carbon in the alpha position.



Alpha hydrogens are acidic ($pK_a \sim 20$). These hydrogens can be deprotonated to make an enolate, which can go on to react with electrophiles.

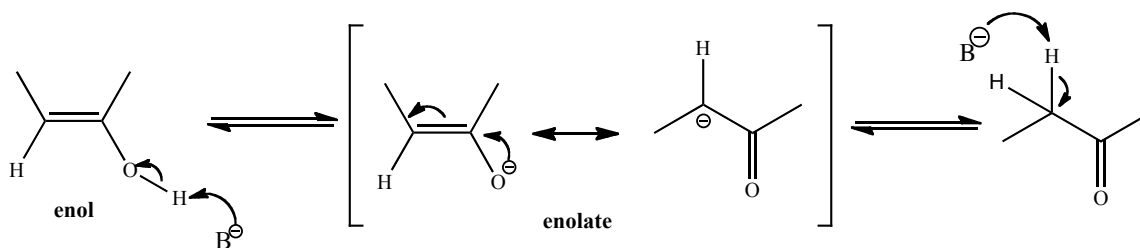
Review: Keto-enol tautomerism



The process of converting between the keto and enol forms is called **tautomerism**. Tautomers are rapidly interconverting structural isomers (different molecules because the hydrogen has moved in its position of attachment – therefore not stereoisomers).

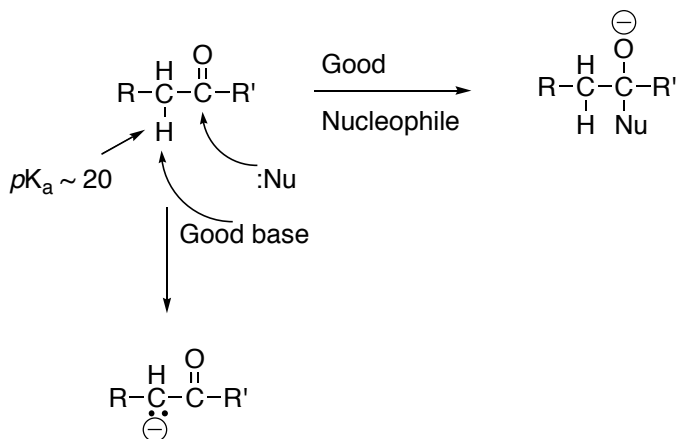
For most molecules, the equilibrium lies on the right, with the keto form being the more stable form.

Enolates are the conjugate bases of enols and can be prepared using a strong base:

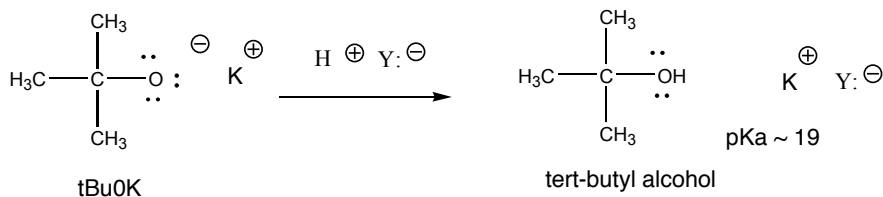
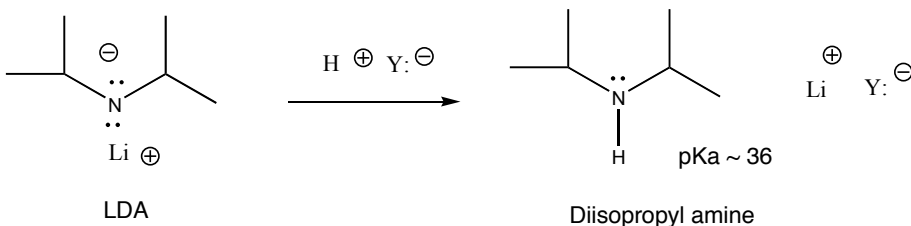


The two structures shown above of the enolate are resonance forms (different pictures of the same molecule; no atom has moved and only the positions of the electrons have been moved). Many bases can be used, but a common base used to irreversibly form an enolate at low temperature is lithium diisopropyl amide (LDA). The pK_a of diisopropyl amine (conjugate acid of LDA) is around 36. Potassium *tert*-butoxide ($KO-t\text{-Bu}$ or $t\text{-BuOK}$) can also be used, but this reaction is reversible as the pK_a of *tert*-butyl alcohol is 19.

In general, a good nucleophile is likely to attack the carbonyl group to form a tetrahedral intermediate. On the other hand, a good base deprotonates the alpha hydrogen as shown below:



Below are the structures of LDA and *t*-BuOK, two common strong bases.

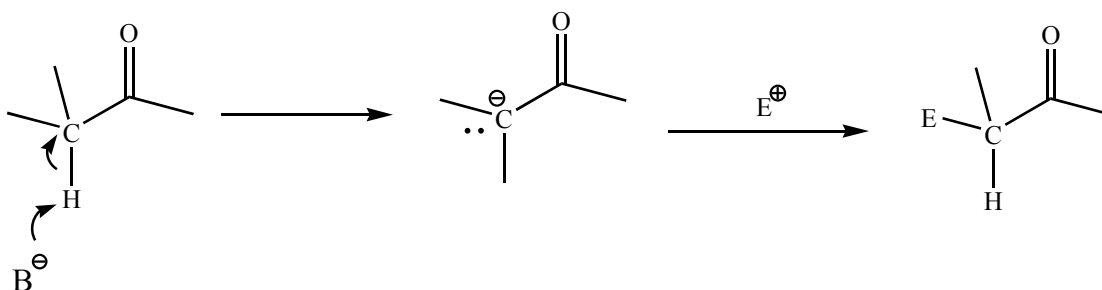


Why does LDA remove the α -hydrogen instead of attacking the carbonyl?

Answer: LDA is a bulky base. The approach to the carbonyl carbon is somewhat sterically hindered. Instead, it pulls off the hydrogen at the α position, as the α hydrogen has a partial positive charge associated with it.

Generally, nucleophiles are best if they are unhindered (not bulky). Bases are better if they are bulky, to avoid nucleophilic attack.

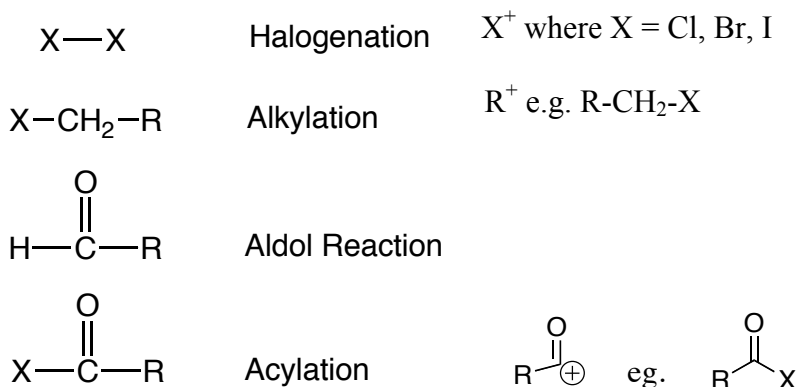
General Reaction



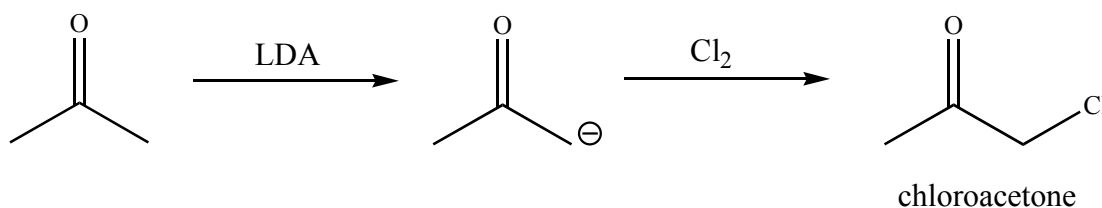
The reaction can be irreversible for both steps (depending on the conditions).

The electrophile E^+ can be X^+ from X_2 (halogens) or R^+ from alkyl halide ($R-X$), amongst other things.

Reactions of Enolates:

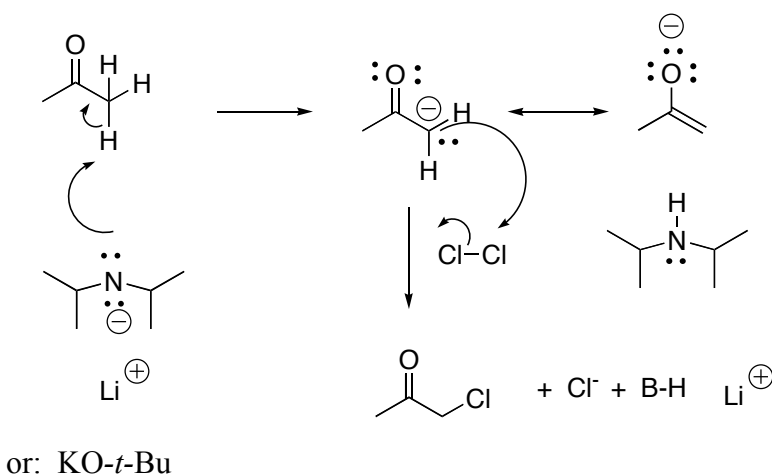


Enolate halogenation



Chloroacetone is used in tear gas.

In this reaction, chlorine is the electrophile that reacts with the nucleophilic enolate. The first step of the reaction is the formation of the enolate by using lithium diisopropylamide (LDA) (also depicted as $:B^-$ in some cases below). LDA is a strong, bulky base, which will remove the alpha hydrogen to produce the resonance stabilized enolate anion. In the second step, the enolate attacks chlorine and breaks the weak Cl-Cl bond to form the halo ketone and the chloride anion. The Cl-Cl bond is susceptible to attack because the two electronegative chlorines pull electrons out of the bond making it weak.

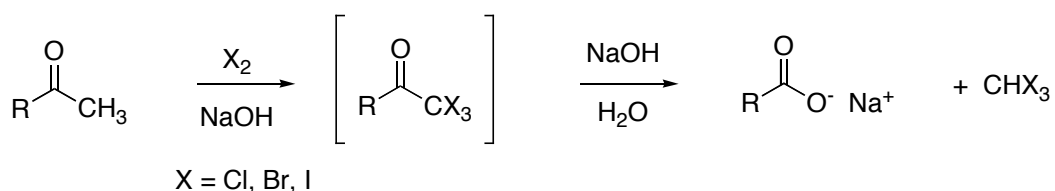


In the above example, the addition of chlorine makes the alpha hydrogens of the product (chloroacetone) even more acidic due to the electron withdrawing effect of the chlorine. Side reactions, including multiple chlorinations are possible, as shown in the next section.

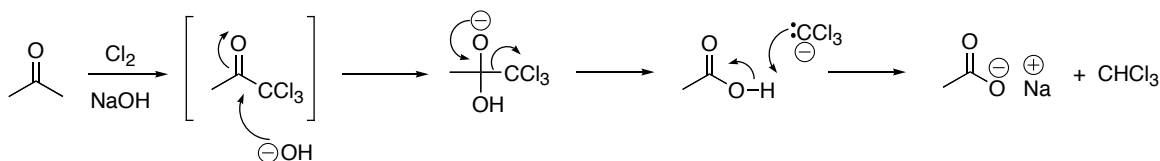
The Haloform Reaction (Not discussed in class)

A problem with doing the above reaction under basic conditions using sodium hydroxide is due to a side reaction called the **haloform** reaction. The haloform reaction converts a methyl ketone into a carboxylic acid salt and a haloform (chloroform, CHCl_3 ; bromoform, CHBr_3 ; or iodoform, CHI_3) and may be used as a qualitative test for methyl ketones.

A sample of an unknown structure (which may be a methyl ketone) is dissolved in THF or ether, and dilute solutions of aqueous NaOH and I_2 are added. Formation of a yellow precipitate of solid iodoform signals a positive test and indicates that the sample is a methyl ketone as shown below in the general example.

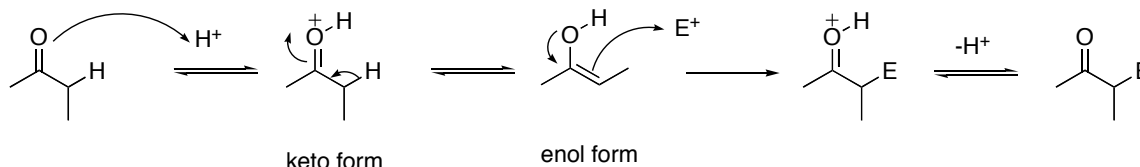


When acetone is reacted with excess Cl_2 and aqueous NaOH, multiple chlorinations occur to form trichloroacetone as shown before. This is then followed by attack of the hydroxide ion on the carbonyl to form a tetrahedral intermediate. This intermediate then displaces the $-\text{CCl}_3$ group by donation of a lone pair of electrons from the oxygen to reform the carbonyl. The CCl_3 group leaves as a stabilized anion because the three electron withdrawing chlorine atoms are capable of stabilizing the negative charge. Proton transfer then leads to the products.

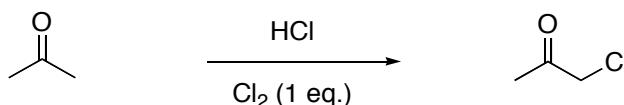


Enol Formation (Under acidic conditions)

Enols behave as nucleophiles and react with electrophiles in much the same way as enolates. The main difference between the two is that enols are formed under acidic conditions and enolates under basic conditions. The general mechanism of enol formation is shown below. Protonation of the carbonyl oxygen makes the alpha proton more acidic and deprotonation at the alpha carbon occurs to form the enol. The enol and keto forms are tautomers (interconverting structural isomers). An electron pair from the enol oxygen reforms the double bond and attacks an electrophile, forming a new carbon-electrophile bond. Loss of a proton from the oxygen yields a neutral alpha-substitution product as the carbonyl is reformed.

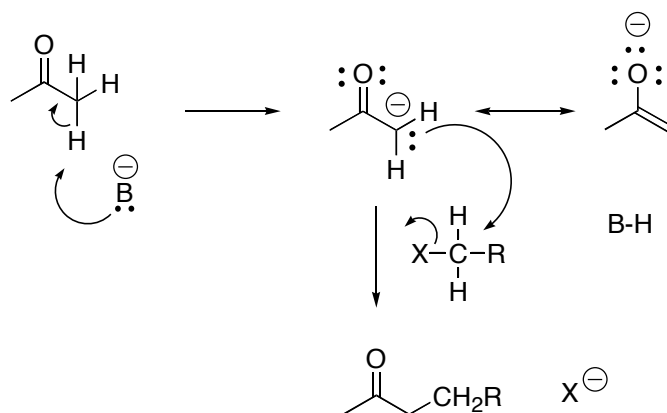


An example is the chlorination of acetone under acidic conditions. Monochlorination is hard to control under aqueous basic conditions and there is the competing haloform reaction (see above). Under acidic conditions, this is easy to do with 1 molar equivalent (1 eq.) of chlorine gas.



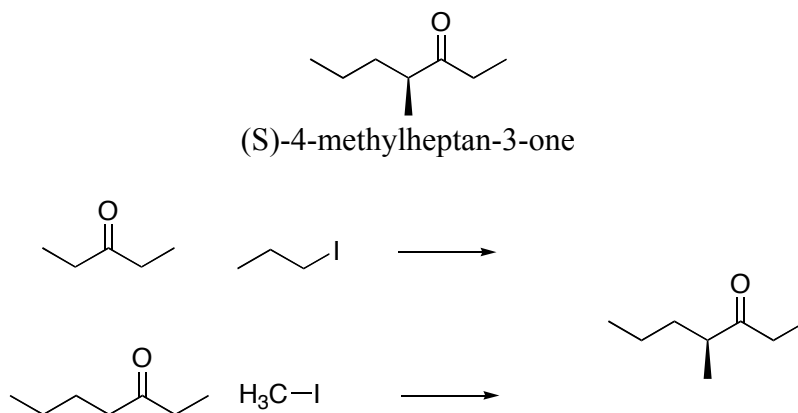
Enolate Alkylation Reactions

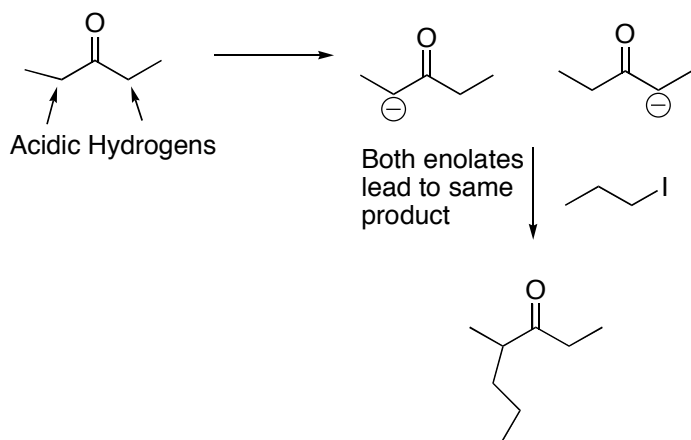
An important reaction of enolate ions is their alkylation by treatment with an alkyl halide. The alkylation reaction is useful because it forms a new C-C bond. Alkylation occurs when a nucleophilic enolate ion reacts with the electrophilic alkyl halide in an $\text{S}_{\text{N}}2$ reaction and displaces the leaving group by backside attack as shown in the general mechanism below.



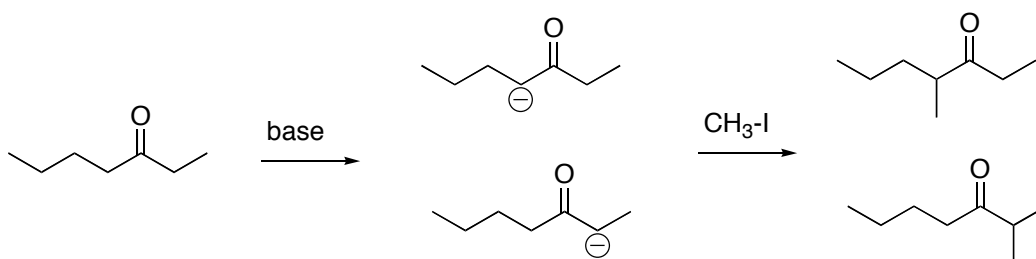
Alkylation reactions are subject to all the rules that affect all S_N2 reactions. The leaving group X in the alkylating agent can be chloride, bromide, iodide, or tosylate. The alkyl halide works best if it is primary and preferably allylic or benzylic. Secondary halides react poorly, and tertiary halides don't react at all because of competing $E2$ elimination. Vinylic and aryl halides are also unreactive, because S_N2 attack is sterically prevented.

The below example shows the ant alarm pheromone, (S)-4-methylheptan-3-one. This compound is synthesized using the alkylation reaction of an enolate. There are two possible enolates that can be used in this reaction. The first possibility is the use of the enolate of 3-pentanone and reaction with 1-iodopropane. The second possibility is the use of the enolate of 3-heptanone and reaction with methyl iodide.

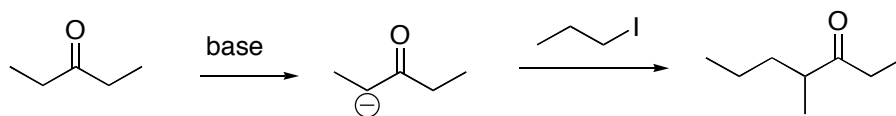




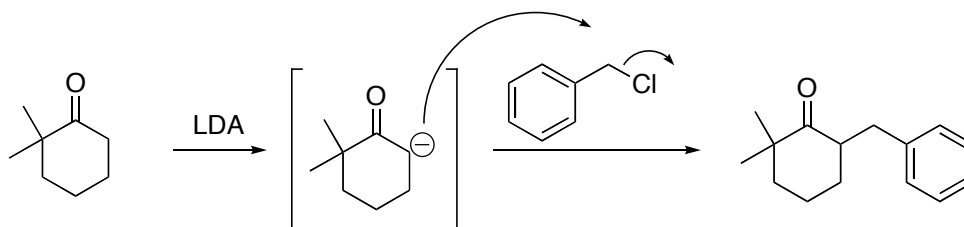
The alkylation of 3-heptanone with methyl iodide is a poor choice for this synthesis. Upon enolate formation of 3-heptanone, two possible enolates can be formed because the molecule is unsymmetrical. Therefore, alkylation can occur at the 2 and 4 positions of 3-heptanone.



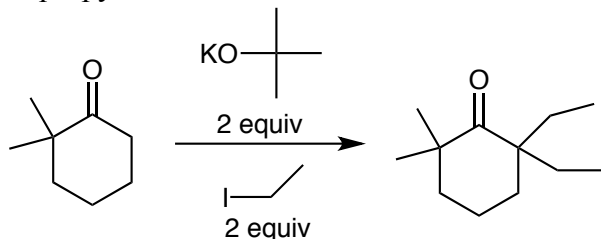
The alkylation of 3-pentanone with 1-iodopropane is the best choice because upon enolate formation, there is only one enolate formed because the molecule is symmetrical. In this reaction is important to know that the alkylation product is racemic (1:1 mixture of enantiomers) because there is no stereochemical control.



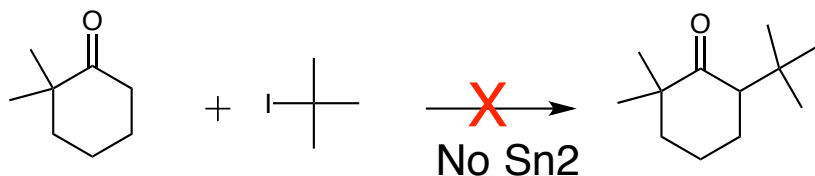
An example is the alkylation of 2,2-dimethylcyclohexanone with LDA and benzyl chloride to give the benzyl substituted product shown below. The enolate undergoes an $\text{S}_{\text{N}}2$ attack of the methylene bearing the chloride to give the final product.



An additional example of an alkylation of 2,2-dimethylcyclohexanone with LDA and isopropyl iodide.

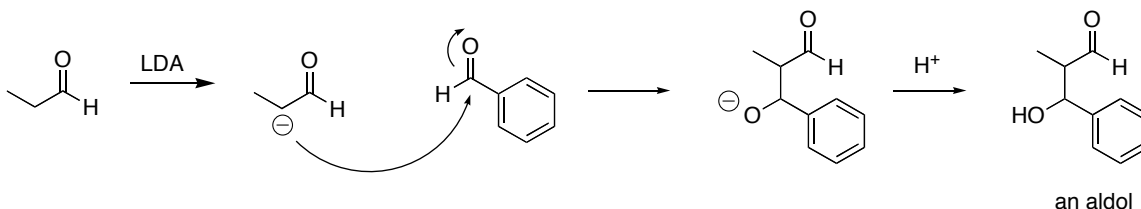


The same reaction with a tertiary alkyl halide will not proceed because it's too hindered for S_N2

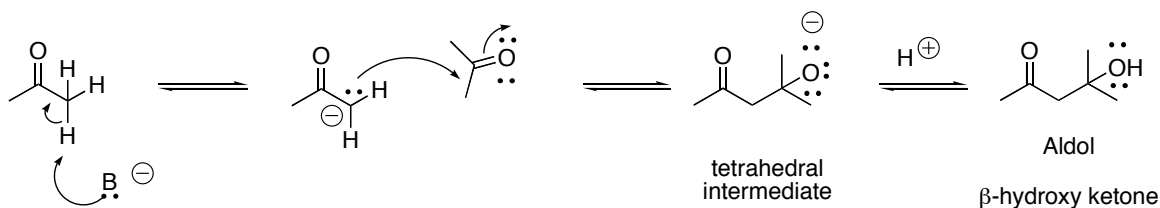


Aldol Formation

The base induced aldol formation is a general reaction for ketones and aldehydes with alpha hydrogen atoms. If the ketone or aldehyde does not have alpha hydrogens, the aldol reaction cannot occur. Aldol condensations occur by nucleophilic addition of the enolate ion of the donor molecule to the carbonyl group of the acceptor molecule, yielding a tetrahedral intermediate that is protonated to give the aldol product (a β -hydroxy carbonyl compound). This reaction is completely reversible under aqueous conditions, and can revert to the starting materials in the presence of base and water.

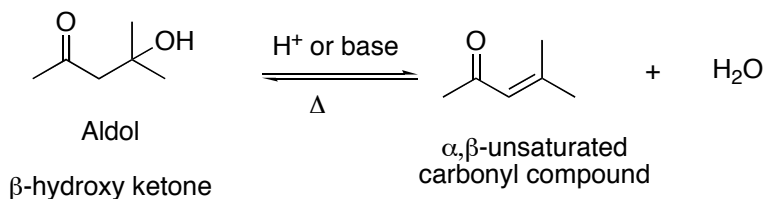


Another example:

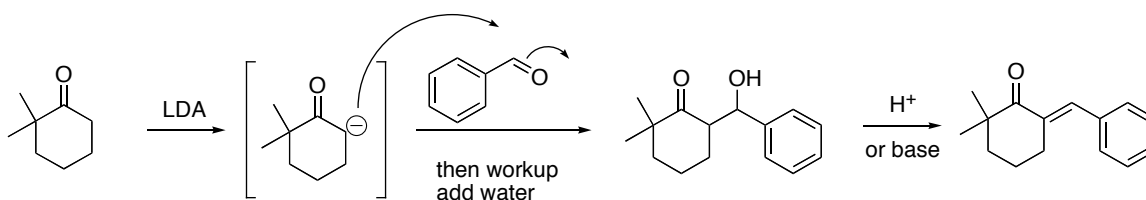


Aldol Formation with Dehydration

The β -hydroxy ketones and β -hydroxy aldehydes formed in the aldol process can easily be dehydrated ($-\text{H}_2\text{O}$) to yield conjugated enones called α,β -unsaturated carbonyl compounds by the application of heat with acid or base.



An example is the aldol condensation of 2,2-dimethylcyclohexanone with benzaldehyde. The aldol product dehydrates readily to form the extended conjugated system.

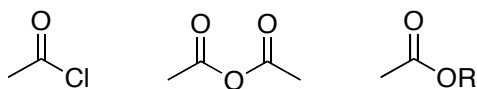


Enolate Acylation (addition of an acyl group)

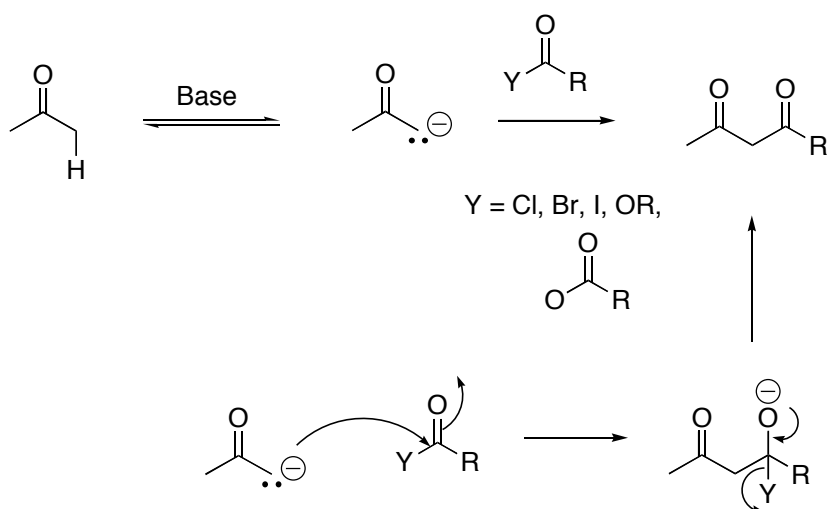
Recall that acylium groups are



and that you can add an acylium group using one of the three following reagents



Similar to above, enolates can attack an acyl group to form a tetrahedral intermediate and release a good leaving group next to the carbonyl group. The general mechanism is as shown below:



An example: Treat acetophenone with LDA first, and then with acetyl chloride to yield a diketone.

