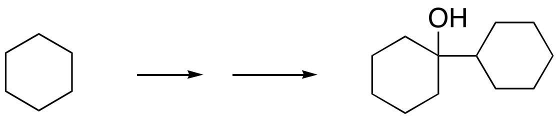
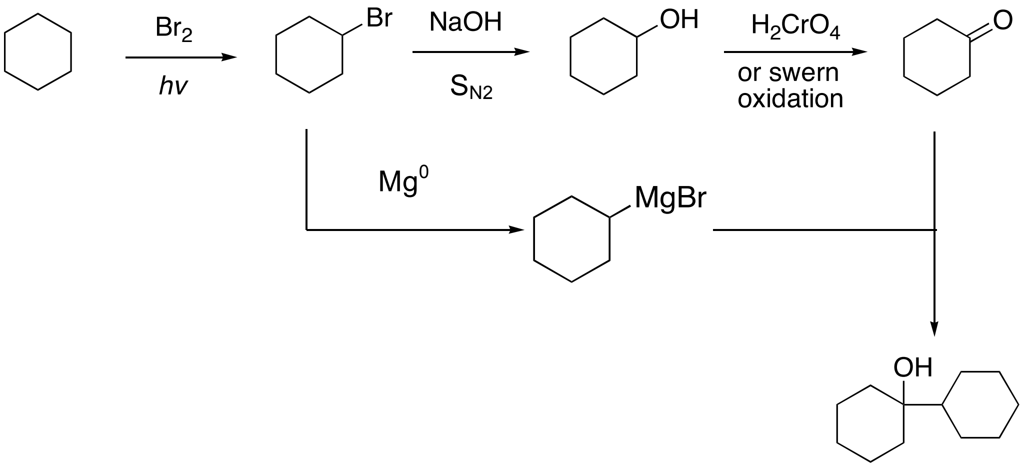
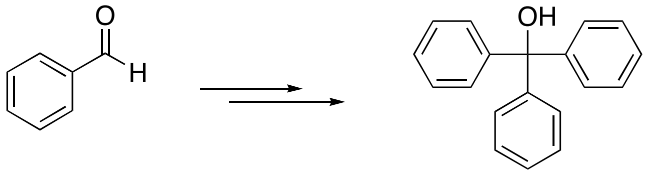
More examples:

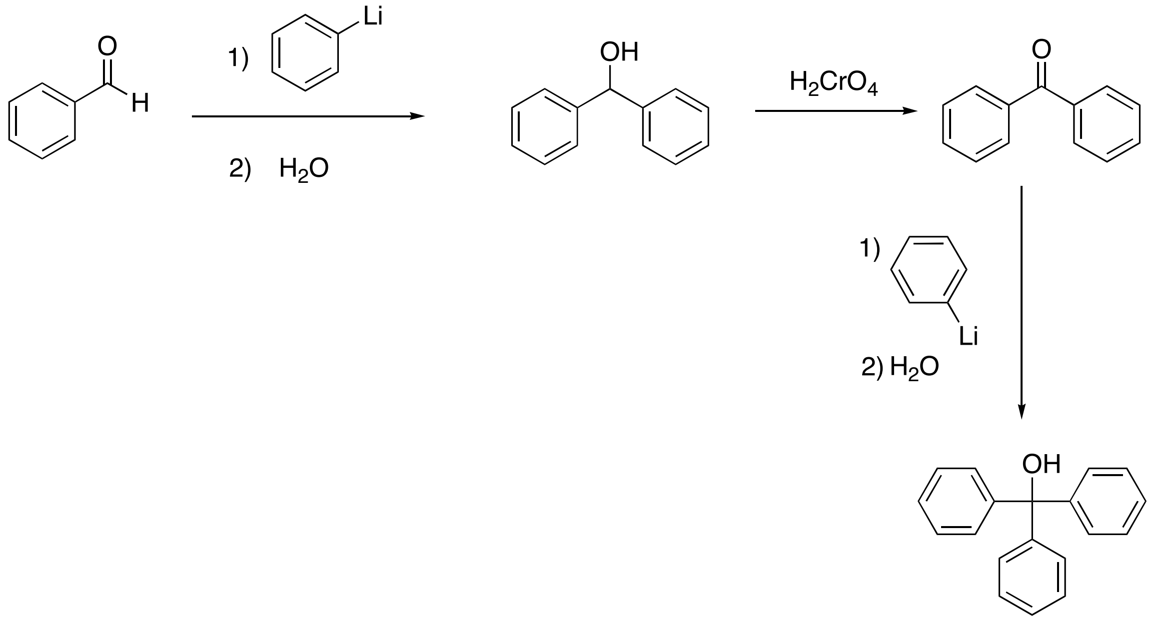
e.g.: Fill the reagents to finish the reactions (only inorganic reagents)





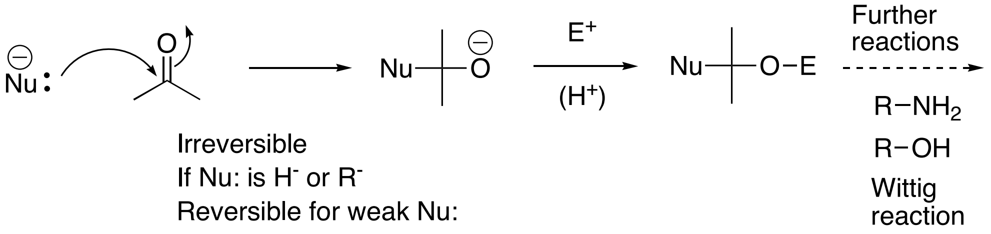
e.g. : Fill the reagents (any reagents you wish to use)





Weak Nucleophiles

Attack by weak nucleophiles on ketones and aldehydes under basic conditions is shown below with the general mechanism. The first step involves the reversible attack of the nucleophile to form the alkoxide anion, which is then protonated. The reaction is usually acid catalyzed and always reversible. In fact, most such reactions are done under acidic conditions, in which case the mechanism involves initial protonation of the oxygen as discussed in the previous class. Under basic conditions, many such reactions have an equilibrium that lies to the side of starting materials (i.e. ketone or aldehyde).

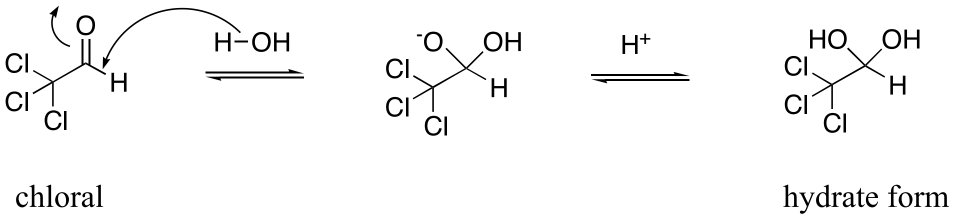


Weak nucleophiles

H_2O	$^{\ominus}OH$	Hydrate Formation		
R−OH	$^{\ominus}OR$	Hemiacetal Formation	⟶	Acetal Formation
HCN	$^{\ominus}CN$	Cyanohydrin Formation		
$R{-}NH_2$	$R{-}\underset{\ominus}{N}H$	Aminal Formation	⟶	Imine Formation

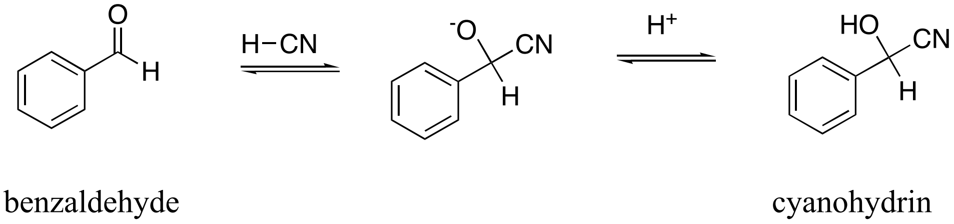
Hydrate Formation

Aldehydes and ketones react with water in a reversible fashion to yield 1,1-diols, or geminal diols. The nucleophilic addition of water to ketones and aldehydes is slow in pure water but is catalyzed by acid. An example of hydrate formation is the reversible reaction of chloral (2,2,2-trichloroethanal) with water to form the hydrated species. Due to the inductive electron-withdrawing effect of chlorine, the equilibrium in water lies to the right (hydrated form).



Cyanohydrin Formation

Aldehydes and ketones react with hydrogen cyanide (HCN) to yield cyanohydrins. Cyanohydrin formation works best with aldehydes but also works with certain ketones. An example of cyanohydrin formation is the addition of HCN to benzaldehyde to yield the cyanohydrin. Cyanide is strongly nucleophilic, and addition occurs by a typical nucleophilic addition pathway. Protonation of the anionic intermediate yields the cyanohydrin.

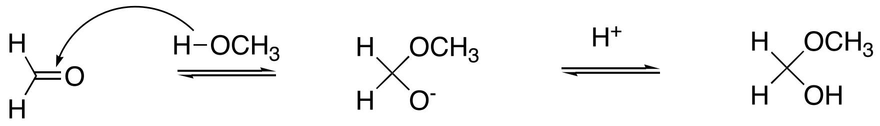


Cyanohydrin formation is particularly interesting because of the further chemistry that can be done. For example, nitriles (RCN) can be reduced with LAH to yield primary amines (RCH_2NH_2) and can be hydrolyzed by aqueous acid to yield carboxylic acids.

In order to avoid the dangers inherent in handling such a toxic gas as hydrogen cyanide (HCN), it is usually generated during the reaction by adding an acid (H_2SO_4) to a mixture of carbonyl compound and excess sodium cyanide (NaCN).

Hemi-Acetal Formation

Hemiacetal formation is similar to hydration but alcohols are used instead of water as the nucleophile. This reaction is reversible and is especially favored if you can form 5 or 6 membered rings as in sugars. An example of hemiacetal formation is the addition of methanol to formaldehyde to yield the hemiacetal.

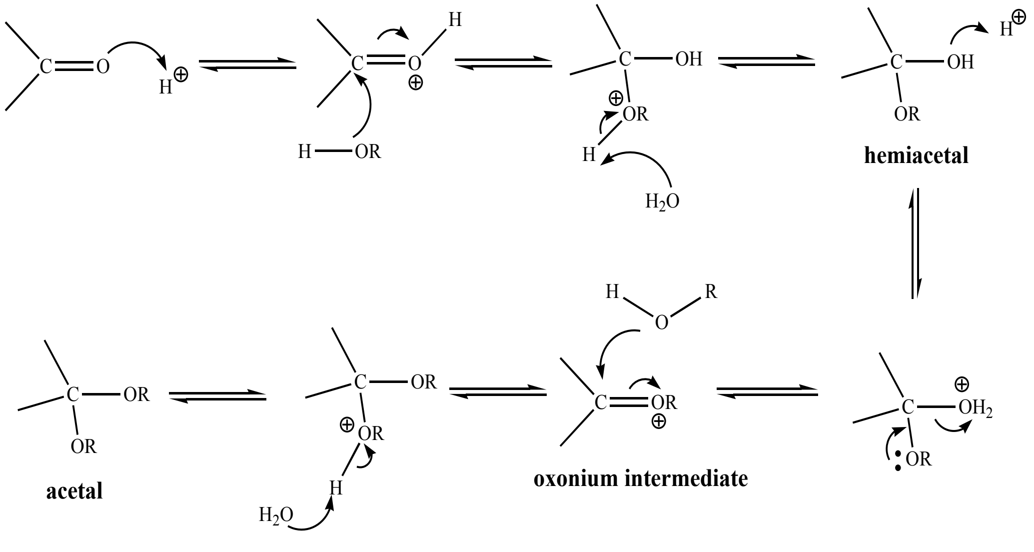


acetone hemi acetal

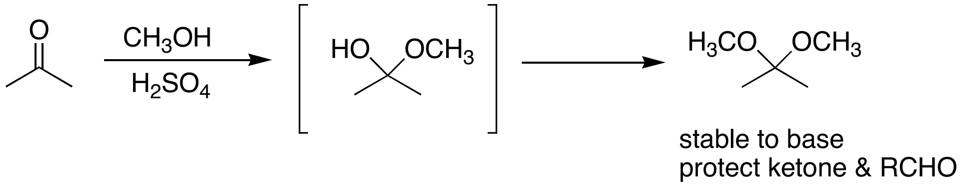
Acetal Formation

Hemiacetals can be converted to Acetals: two OR groups instead of one OR and OH
Addition then Elimination then 2nd Addition reaction

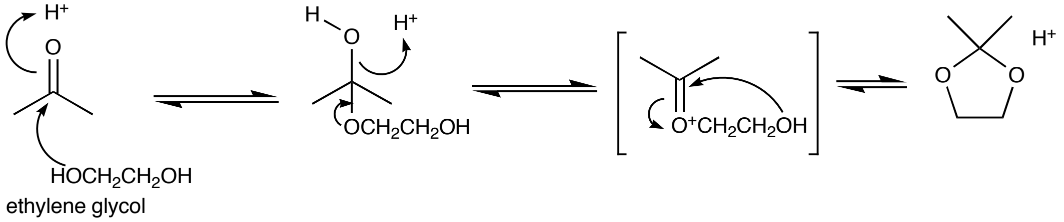
Mechanism:

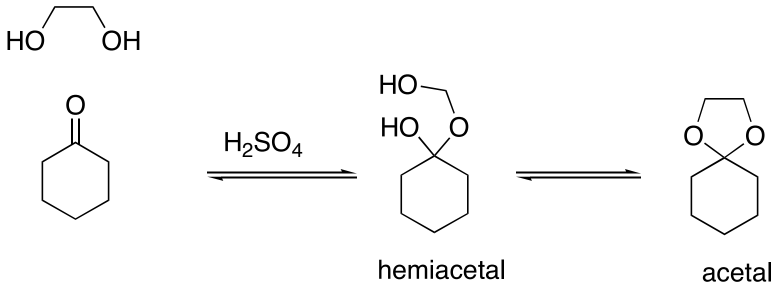


Examples:



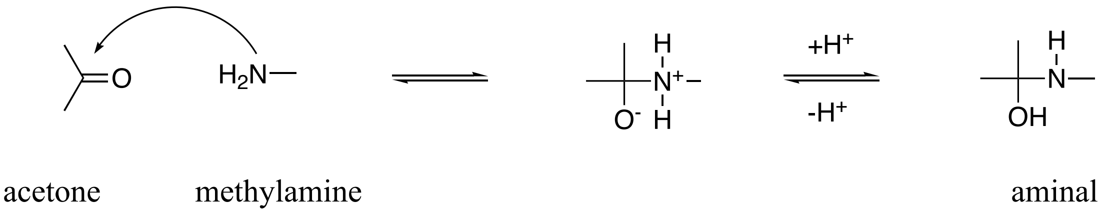
stable to base
protect ketone & RCHO



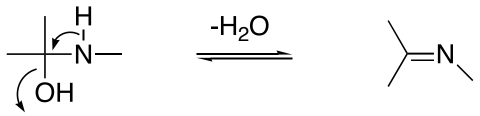


Aminal Formation

Aminal formation is similar to that of hydration except the nucleophile is an amine functionality. An example is the addition of methylamine to acetone to yield the aminal product in a reversible fashion.

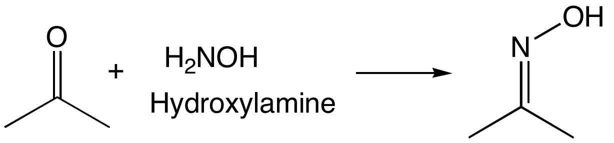


Further reaction of the aminal can take place in which the elements of water (H_2O) are eliminated to yield an imine functionality as shown below. This elimination occurs with aminals, hemiacetals and the Wittig reagent.



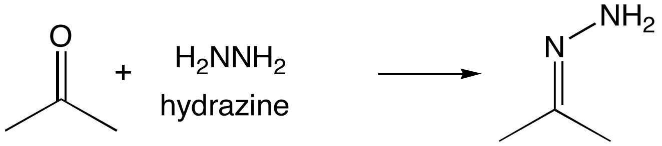
aminal imine

Examples:



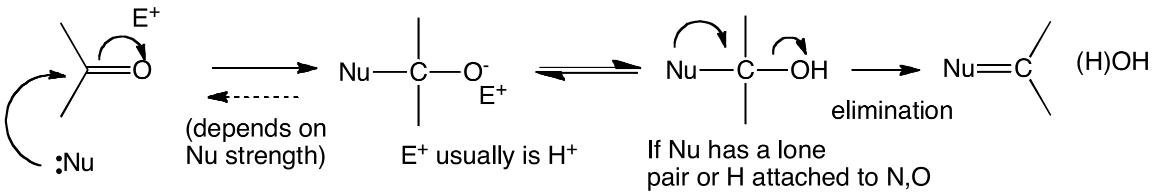
oxime

aka aldoximes or ketoximes
depending on whether they are derived
from an aldehyde or ketone

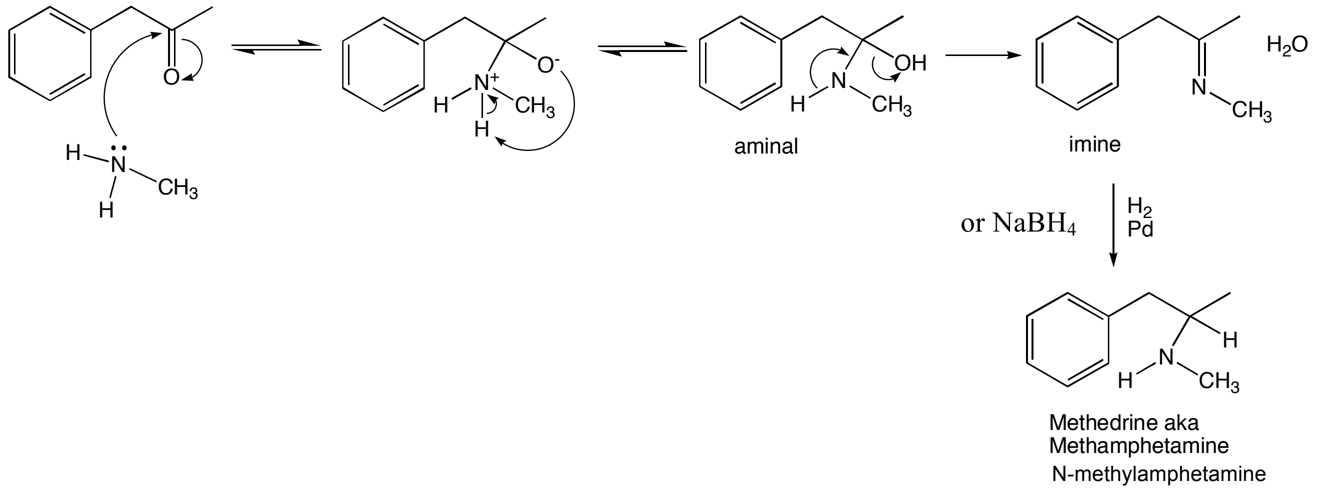


hydrazone

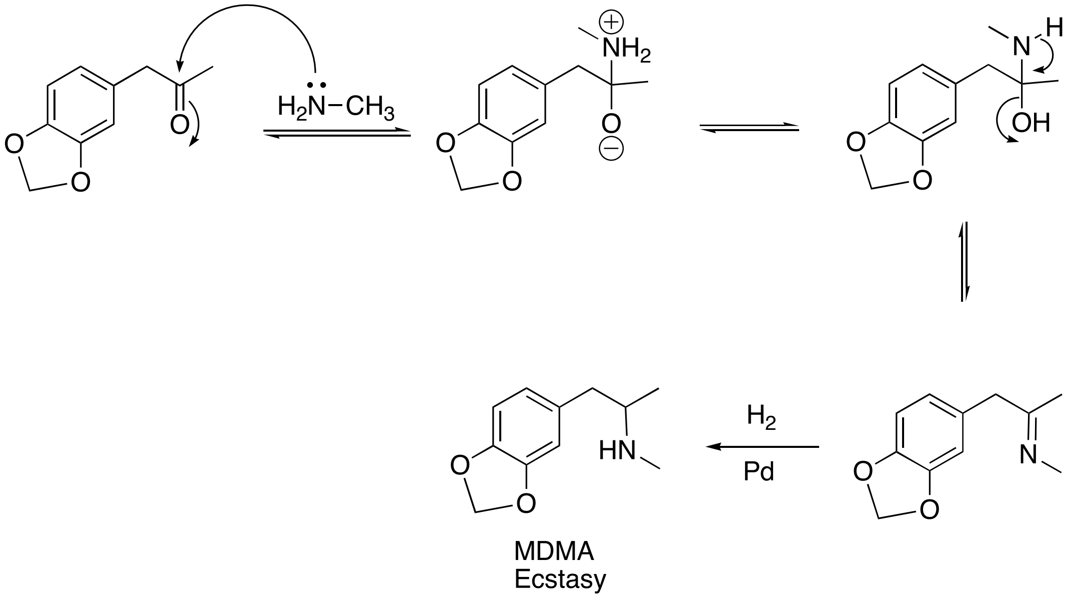
Imine Formation – addition then elimination



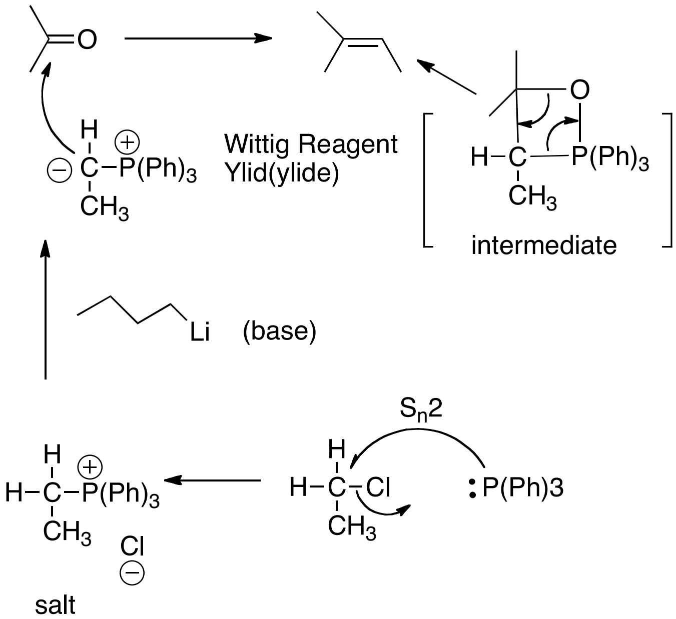
Example:



Note: Imines can be reduced to amines

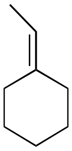


Wittig Reaction:

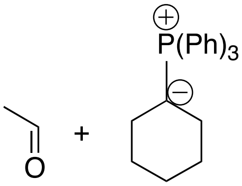


Example:

Consider how to make

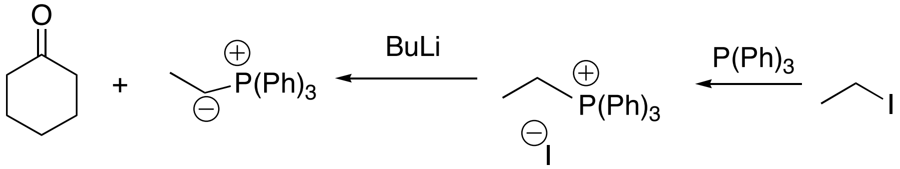


synthetic route A:



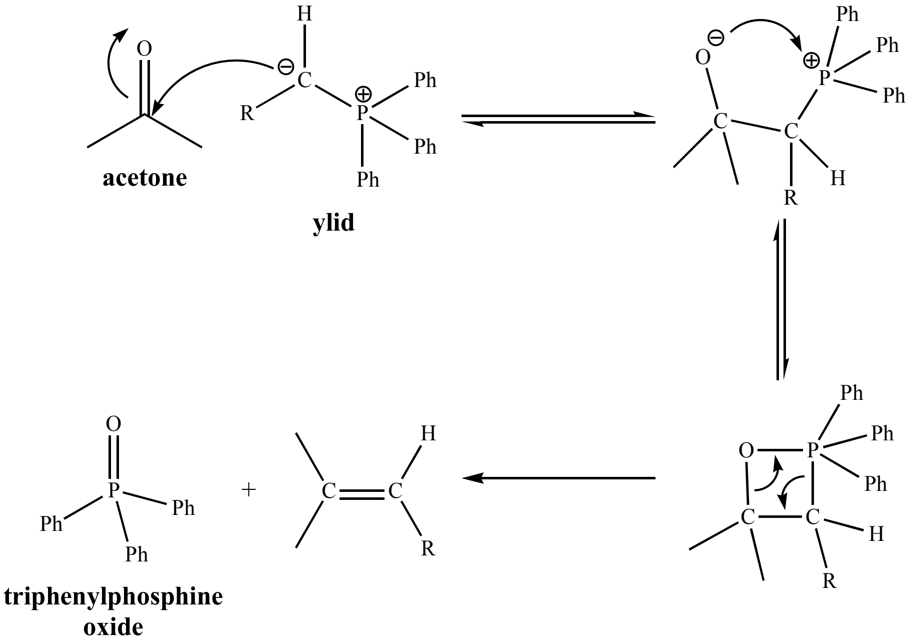
(but this wittig reagent is more hindered than the one in route B, so, route B is better)

synthetic route B:



As seen earlier, nucleophilic addition to a carbonyl can give alcohol as the product. Elimination of water follows in the case of imine formation and is also part of the mechanism of acetal formation. The Wittig reaction is an example of a carbonyl addition followed by an elimination that produces an alkene. It involves a phosphorus ylide (ylid). An ylid is a substance that has both a negative charge and a positive charge (internal salt), generally on adjacent atoms.

General mechanism:

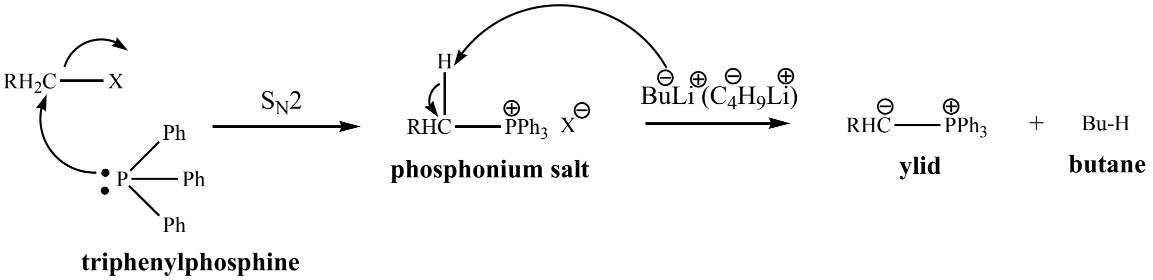


The Wittig reagent is an **ylid**, with adjacent positive and negative charges. The negatively charged carbon of the ylid is the nucleophile, and adds to the carbonyl carbon. The negatively charged oxygen generated from the first step attacks the positively charged phosphorus atom to form a four membered ring (intramolecular closure). This is possible because phosphorus can expand its valence shell to form 5 bonds. The four membered ring formed is quite strained, therefore it collapses to its constituent parts, triphenylphophine oxide and an alkene.

While the nucleophilic attack of the ylid is reversible, the last step (the collapse to an alkene) is irreversible.

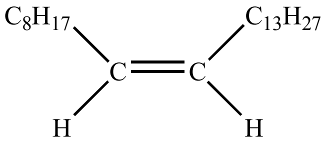
The geometry of the alkene formed is often predominantly *cis*.

Preparation of a Wittig reagent from a primary alkyl halide (S_N-2 nucleophilic substitution, followed by treatment with a base)



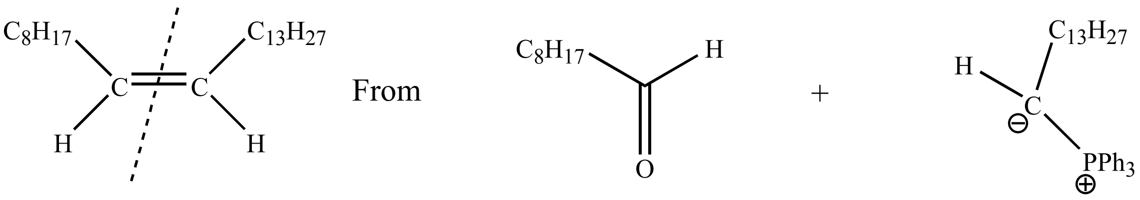
In this reaction, X is a halogen (Cl, Br, or I). Primary halides work the best for this substitution. Phosphorus is directly below nitrogen on the periodic table, and like nitrogen, it is a good nucleophile. It displaces halogen in an S_N-2 reaction. The phosphonium salt has an acidic hydrogen on the carbon adjacent to phosphorus that can be removed by strong bases (usually butyllithium = BuLi). The product of the deprotonation is an ylid. BuLi can be made by reacting butyl iodide with lithium metal.

Synthesis of housefly pheromone

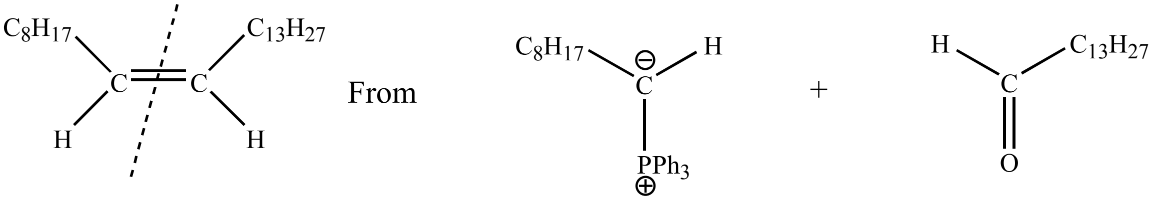


Looking at the structure, how do you make this pheromone using what you have just learned?

Answer: This pheromone can be made using the Wittig reaction.

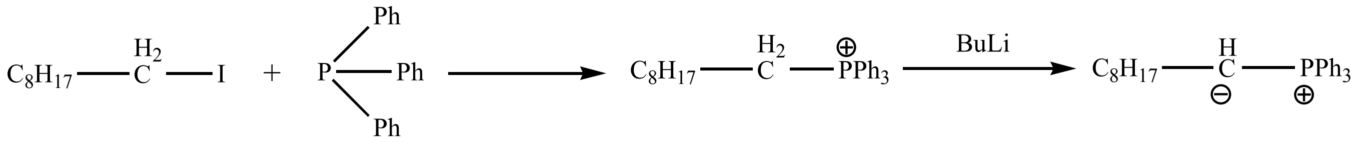


What other reagents can you use?
Answer: just reverse the sense of the ylid and aldehyde.



How would you make the ylid shown above?

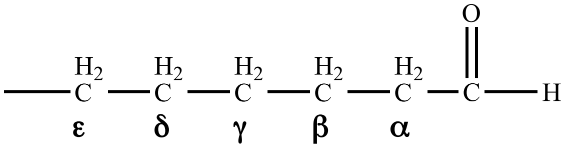
Answer: use triphenylphosphine and the corresponding halide, then treat with base (BuLi)



Note that the product of this Wittig reaction has a cis double bond.

Reactions at the α-Carbon

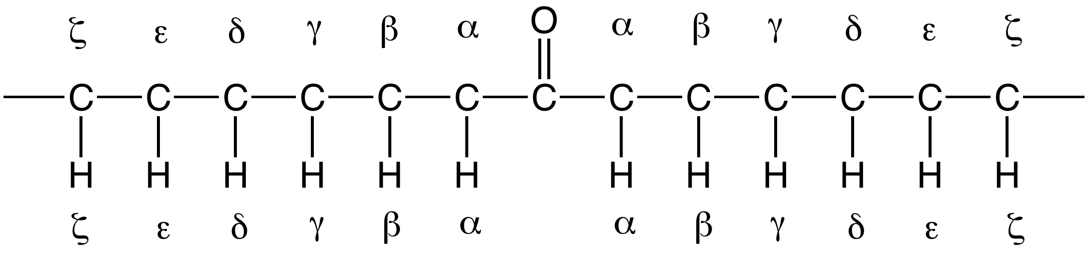
The alpha carbon is the carbon adjacent to the carbonyl carbon. Beta is the next one, followed by gamma, delta, epsilon, and so on.



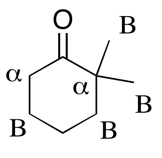
The position of the carbons are shown in Greek letters. Similarly, the hydrogens attached to a carbon at a particular position is named the same as the carbon at that position. For example, the hydrogens attached to the alpha carbon are known as alpha hydrogens, the hydrogens attached to the beta (β)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

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

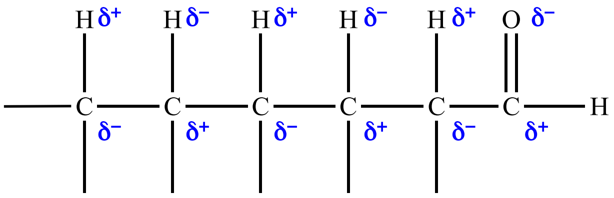
The atoms in ketones are described similarily to aldehydes:



Example:

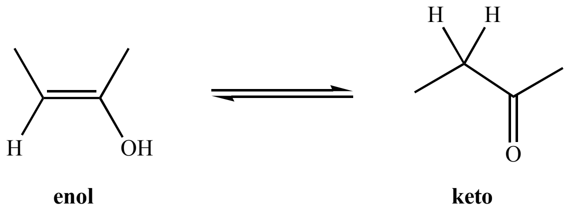


Due to polarization of the carbonyl bond, the carbons nearby have alternating partial negative and positive charge associated with them. The carbons that are farther away from the carbonyl experience less polarization than the carbon in the alpha position.



Alpha hydrogens are acidic (pKa ~ 20). These hydrogens can be deprotonated to make an enolate, which can go on to react with electrophiles.

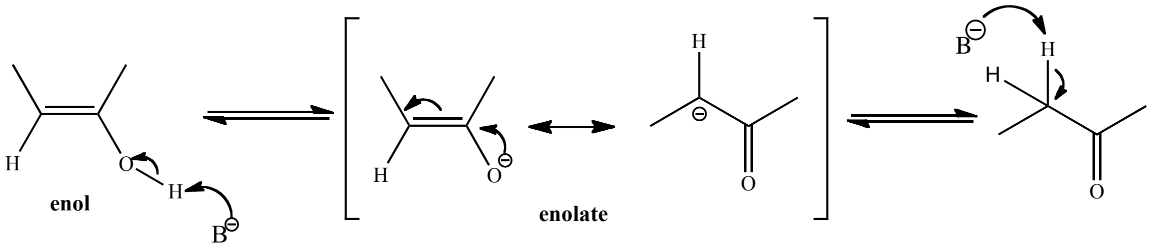
Review from last semester:



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).

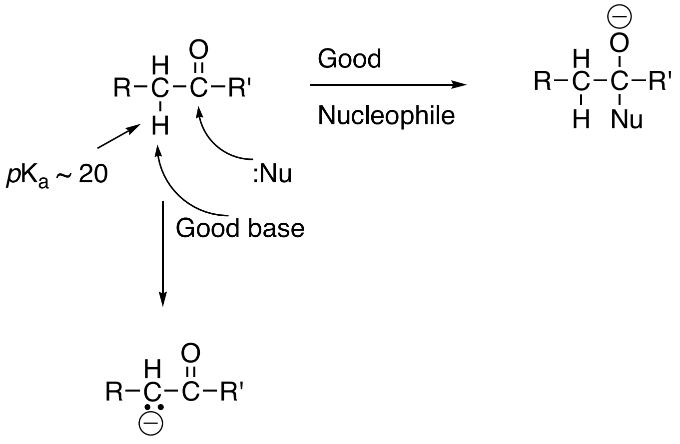
For most molecules, the equilibrium lies on the right, with the keto form being the more stable form.

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

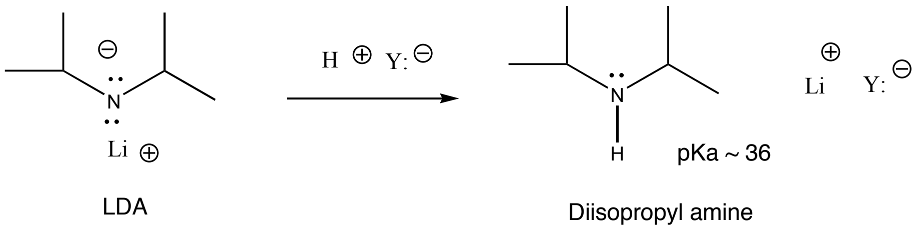


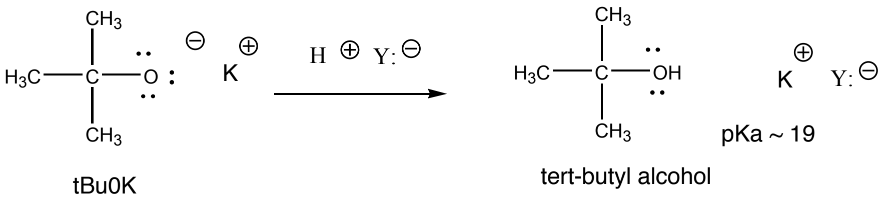
The two structures shown above of the enolate are resonance forms (different pictures of the same molecule; no atom has moved and only the positions of the electrons have been moved). Many bases can be used, but a common base used to irreversibly form an enolate at low temperature is lithium diisopropyl amide (LDA). The pKa of diisopropyl amine (conjugate acid of LDA) is around 36. Potassium tert-butoxide can also be used, but this reaction is reversible as the pKa 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 tBuOK, two common strong bases.



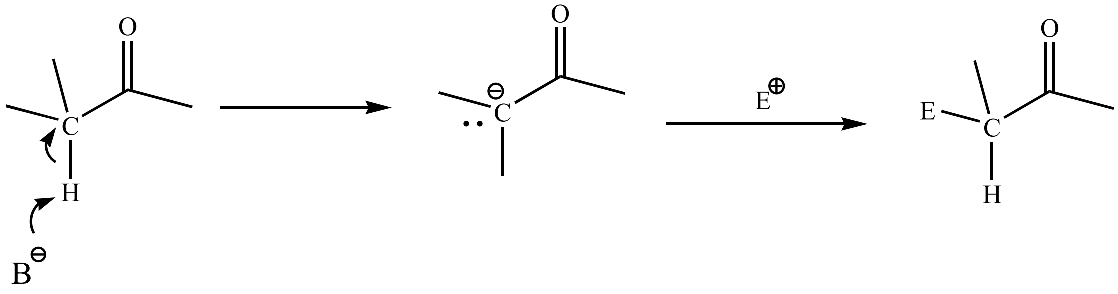


Why does LDA remove the alpha-hydrogen instead of attacking the carbonyl?

Answer: LDA is a bulky base. The approach to the carbonyl carbon is somewhat sterically hindered. Instead, it pulls off the hydrogen at the alpha position, as the alpha 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.

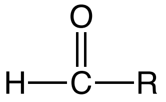
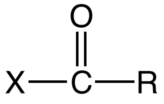
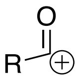
General Reaction



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:

$X-X$	Halogenation	X^+ where X = Cl, Br, I
$X-CH_2-R$	Alkylation	R^+ eg. $R-CH_2-X$
 $\mathrm{H-\overset{O \atop \|}{C}-R}$	Aldol Reaction	
 $\mathrm{X-\overset{O \atop \|}{C}-R}$	Acylation	 eg.