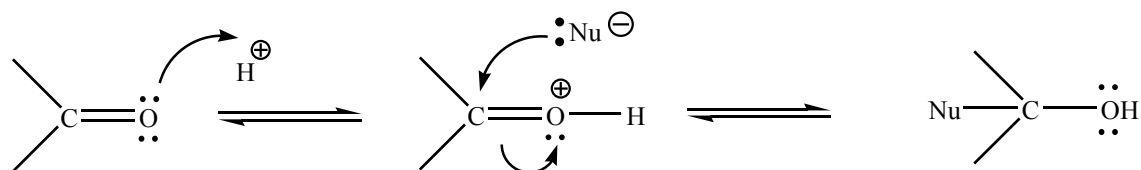


Chem 263 Section B6 – March 9, 2006 Notes

Acid Catalysis for Weak Nucleophiles



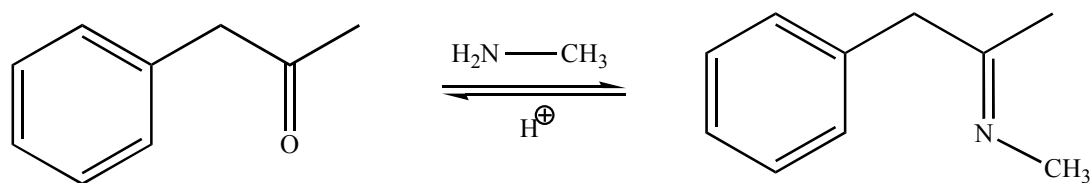
In the first step, the carbonyl oxygen uses one of its lone pairs to pick up a proton. This gives the oxygen a positive charge. Since oxygen is an electronegative atom, it does not like to have positive charge on it. It will withdraw more electron density from the carbonyl carbon. This makes the carbon more electrophilic, that is more prone to attack by nucleophile, which has a pair of electrons. The nucleophile may or may not bear a negative charge

With weak nucleophiles, the reaction is completely reversible.

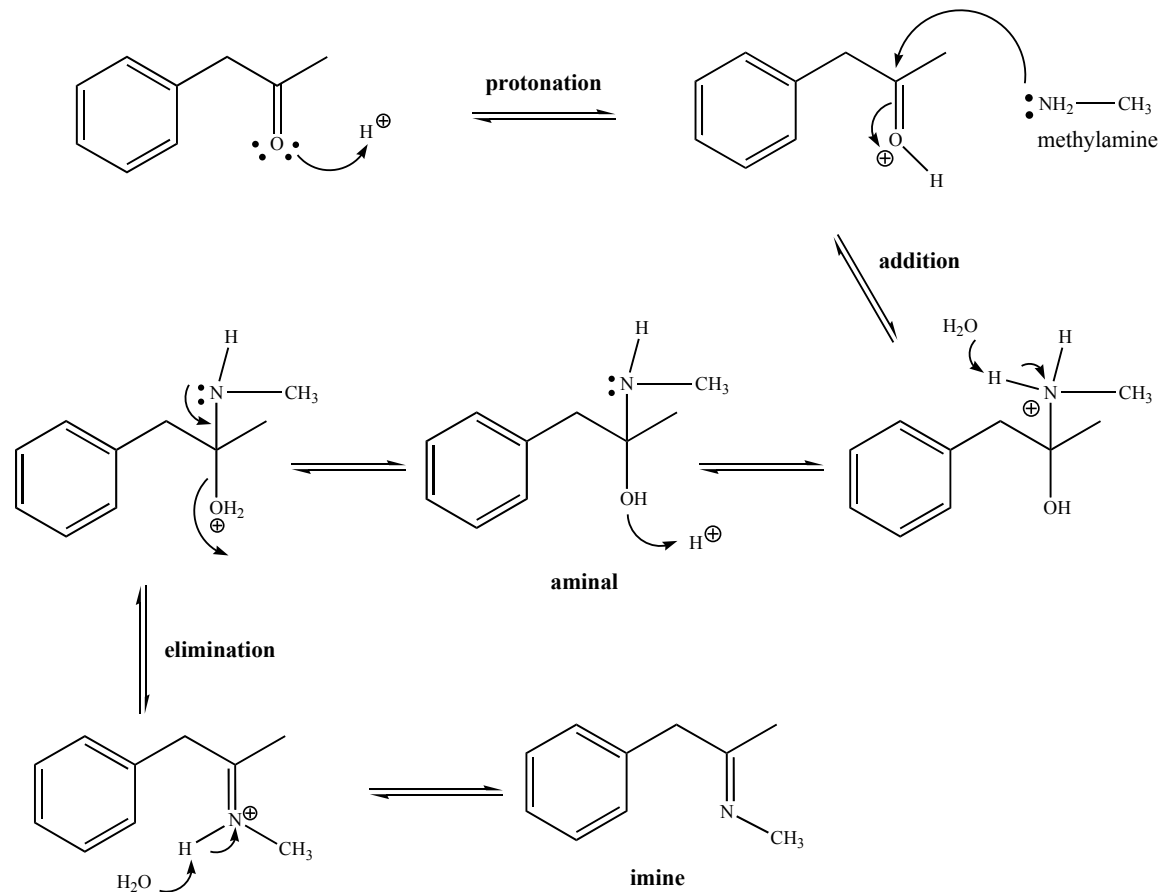
The equilibrium of the above reaction depends on:

1. Acidic or basic conditions. Acidic conditions drive the reaction to the right (to form the alcohol), whereas basic conditions favor the left side of the reaction (formation of the carbonyl)
2. Potency of the nucleophile. If there is strong nucleophile (hydride or alkyl anion), acid must follow in a second step. If acid is used, it will react with the nucleophile (to form hydrogen or corresponding alkane) instead of attacking the carbonyl.
3. Substituents on the carbonyl carbon. If the substituents are bulky, then the carbon is less likely to be attacked due to steric hinderance.

Example:



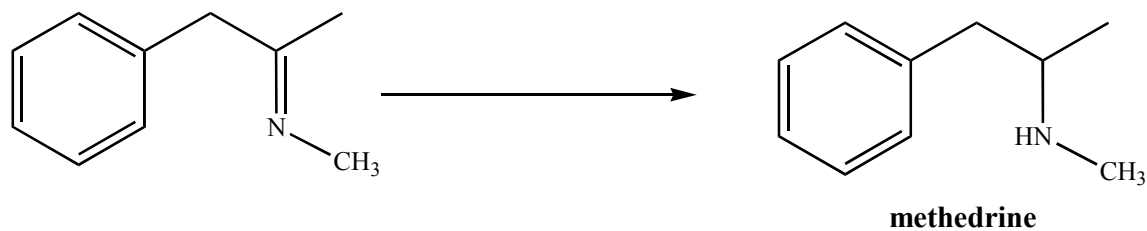
Mechanism: (lone pairs are often not shown and understood to be there)



Note that formation of the imine requires at least two hydrogens on the nitrogen of the starting amine.

For the elimination step, the amine nitrogen has a lone pair of electrons that kicks out the water molecule (which is a good leaving group). Many heteroatoms that have a lone pair can cause elimination.

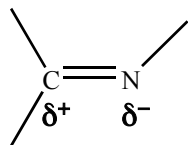
Think about the question: How do you do the reaction below? What reagent is needed?



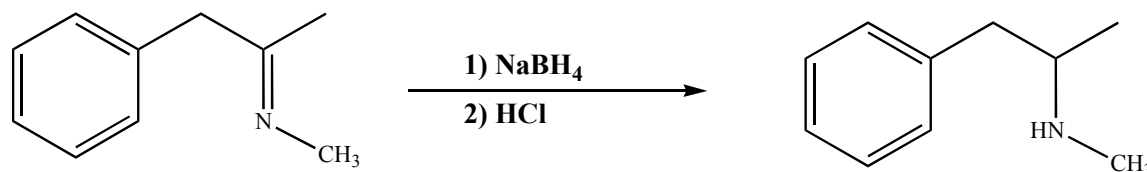
Methedrine, also known as methamphetamine. It is the common street drug: speed.

Question: Is the $\text{C}=\text{N}$ bond polarized? What atoms do you need to add ?

Answer: Yes. Like a carbonyl, the bond is polarized since nitrogen is electron withdrawing. There is partial positive charge on carbon, and partial positive charge on nitrogen. You need to add two hydrogens, one as hydride (H^-) the other as a proton (H^+).



In order to reduce the C=N (imine) bond, you would use a similar reagent as for a carbonyl.

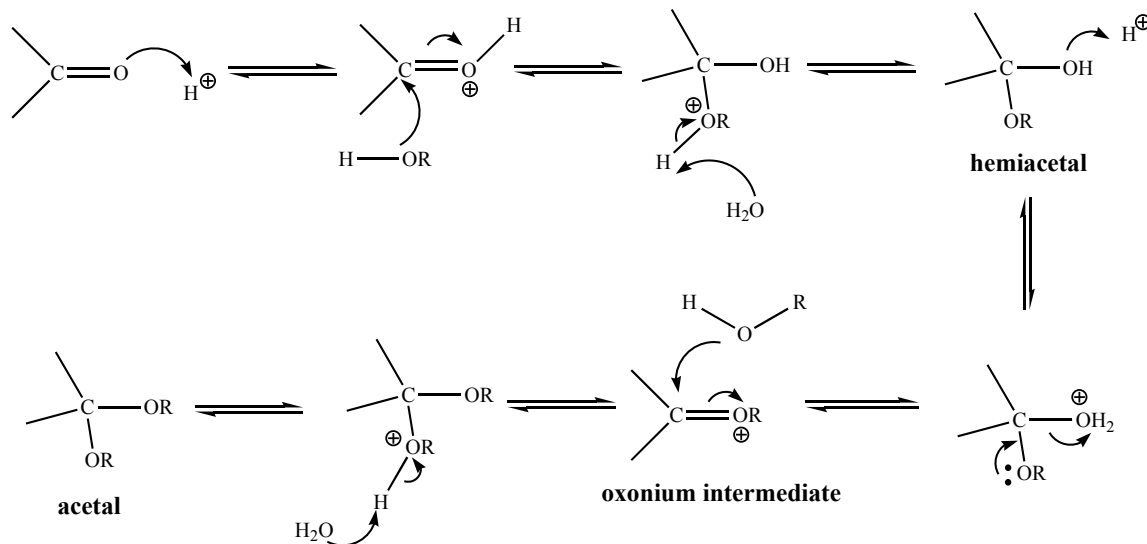


Alternatively, you could use 1) LiAlH_4 ; 2) HCl , or alternatively, H_2/Pd to reduce an imine to an amine.

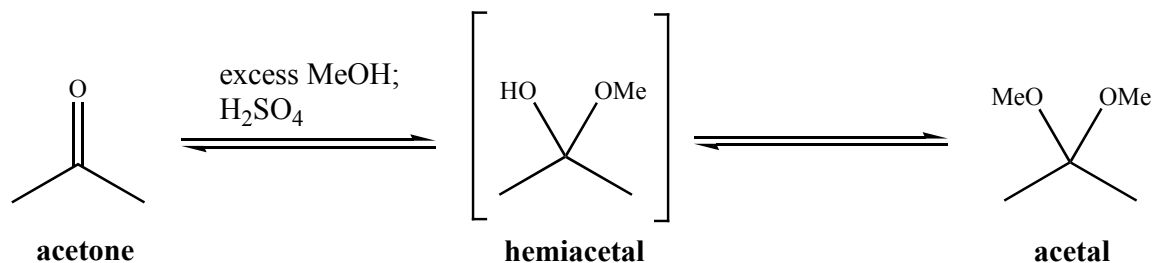
Acetal Formation (an addition-elimination reaction)

This type of reaction is very common in carbohydrate chemistry.

General mechanism:

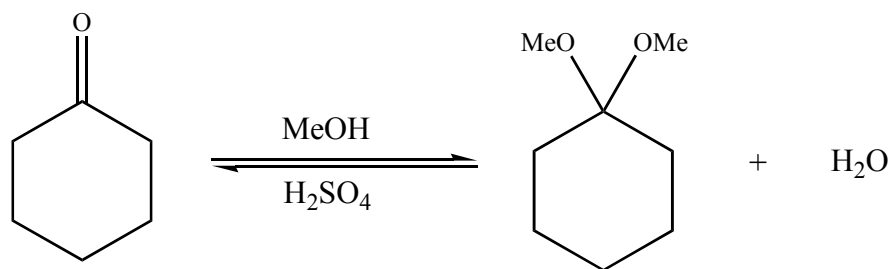


Example:



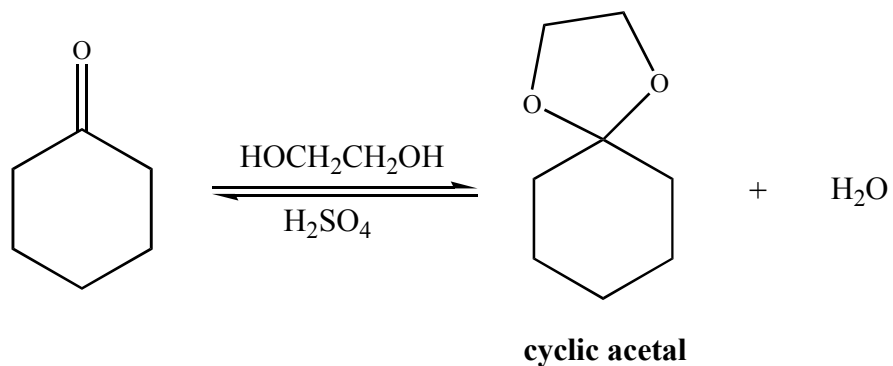
Sometimes, the acetal is formed to protect the carbonyl group from attack by nucleophiles.

Example:



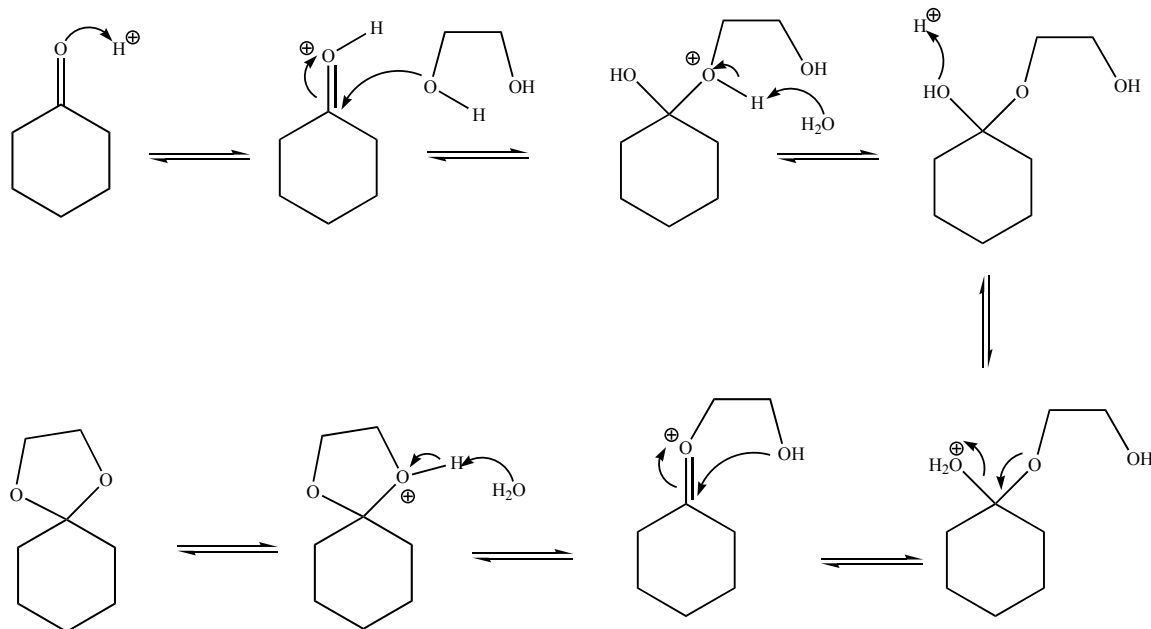
The mechanism of this reaction is the same as above.

Example:



$\text{HOCH}_2\text{CH}_2\text{OH}$ is a diol known as ethylene glycol. It is a component of anti-freeze. It is also widely used as a protecting group for carbonyl.

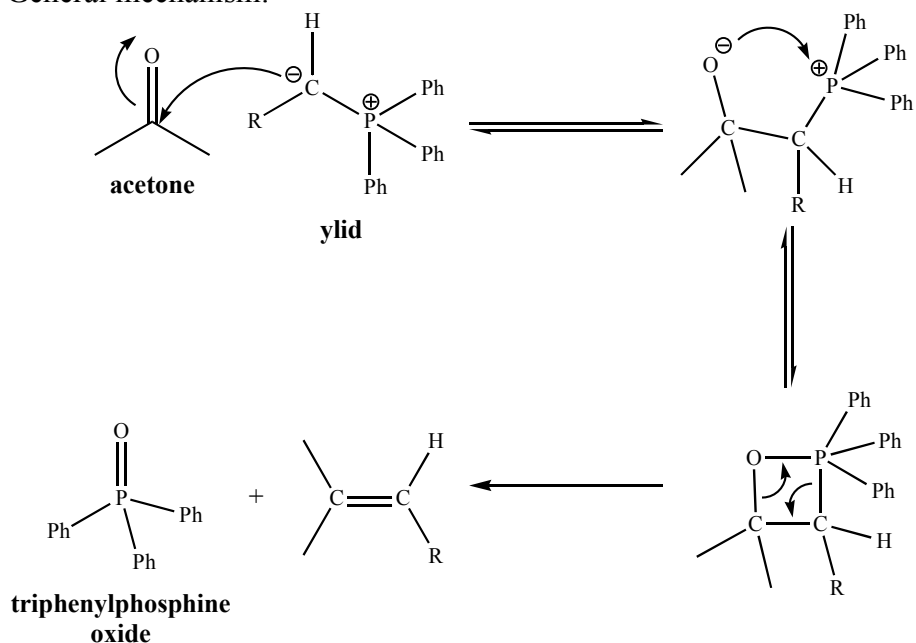
Mechanism:



Wittig Reaction

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 alkenes. It uses a phosphorus ylide (ylid). An ylid is a substance that has both a negative charge and a positive charge, generally on adjacent atoms.

General mechanism:



The Wittig reagent is an **ylid**. It has a negative charge and a positive charge next to each other. The carbon of the ylid is the nucleophile, and adds to the carbonyl double bond.

Phosphorus can expand its valence shell to form 5 bonds.

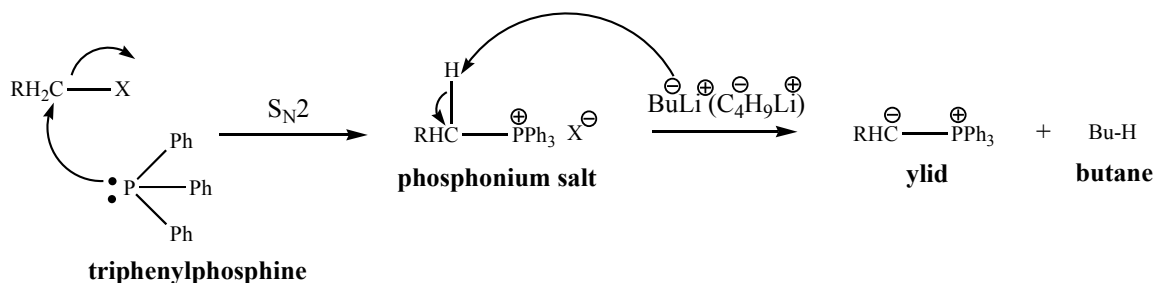
The negatively charged oxygen generated from the first step attacks the positively charged phosphorus atom to form a four membered ring (intramolecular closure).

The four membered ring formed is quite strained, therefore it collapse to its constituent parts, triphenylphosphine oxide and alkene.

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

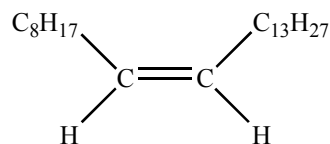
The geometry of the alkene formed is often predominantly *cis*.

Preparation of Wittig reagent from primary alkyl halide (S_N2 nucleophilic substitution, followed by base treatment)



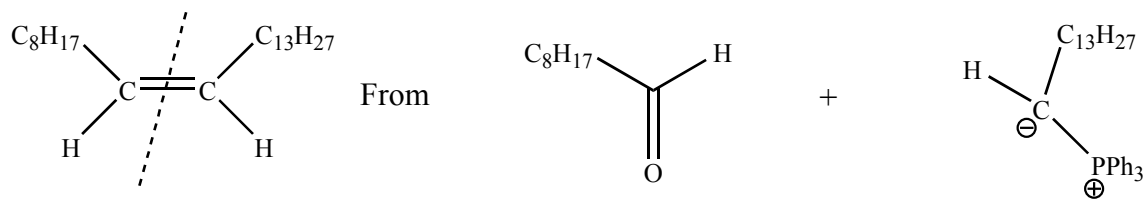
In this reaction, X is halogen (Cl, Br, or I). Primary halide works the best for this substitution. Phosphorus sits right below nitrogen in the periodic table, and like nitrogen, it is a good nucleophile. It displaces halogen in S_N2 fashion. The phosphonium salt has an acidic hydrogen on the carbon adjacent to phosphorus that can be removed by strong bases (usually butyllithium = BuLi). The product is the ylid. BuLi can be made by reacting butyl iodide with lithium metal.

Synthesis of housefly pheromone



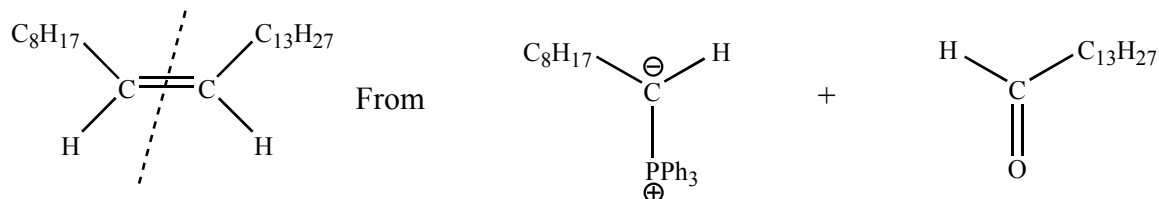
Looking at the structure, how do you make this pheromone using what you have just learned.

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



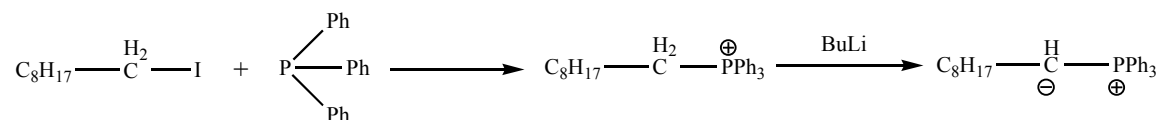
What other reagents can you use?

Answer: just reverse the sense of the ylid and aldehyde.



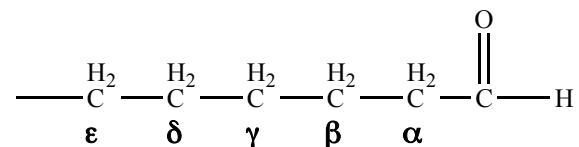
How would you make the ylid shown above?

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



Reaction at the alpha Carbon

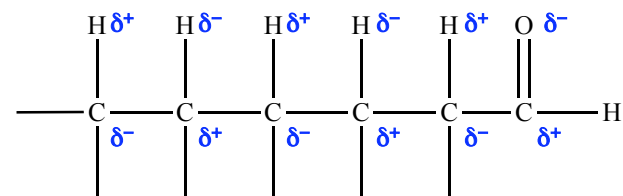
The alpha carbon is the carbon adjacent to the carbonyl carbon. Beta is the next one etc.



The carbons and their positions are shown in Greek letters. Similarly, the hydrogen attached to the carbon at that position is named the same as the 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 forth for gamma (γ), delta (δ), and epsilon (ϵ)

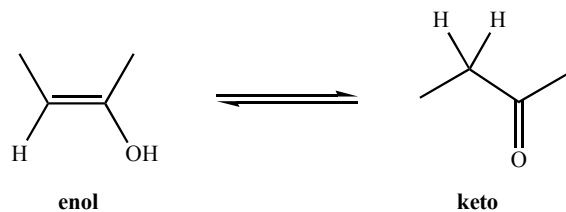
The hydrogen attached to the carbonyl carbon is called the aldehyde hydrogen (not alpha hydrogen). Do not get these two confused.

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



The alpha hydrogens are acidic ($pK_a \sim 20$). These hydrogens can be deprotonated to make an enolate, which can react with an electrophile.

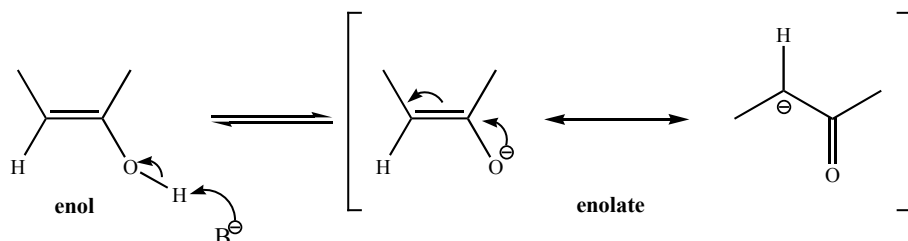
Review from last semester:



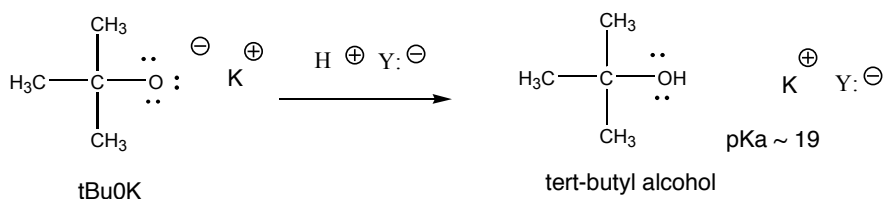
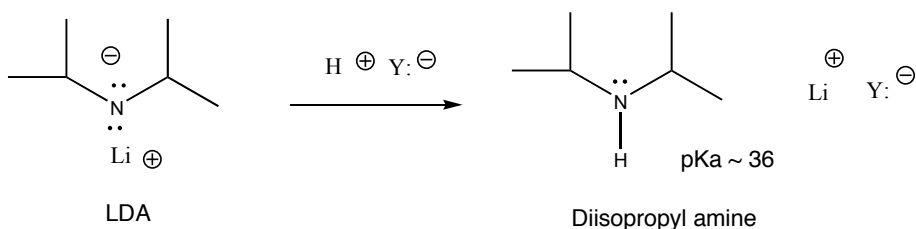
The process of converting enol and keto forms is called tautomerism. Tautomers are rapidly interconverting structural isomers (different molecules because the hydrogen has moved in its position of attachment).

For most molecules, the equilibrium lies on the right (keto is the more stable form).

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



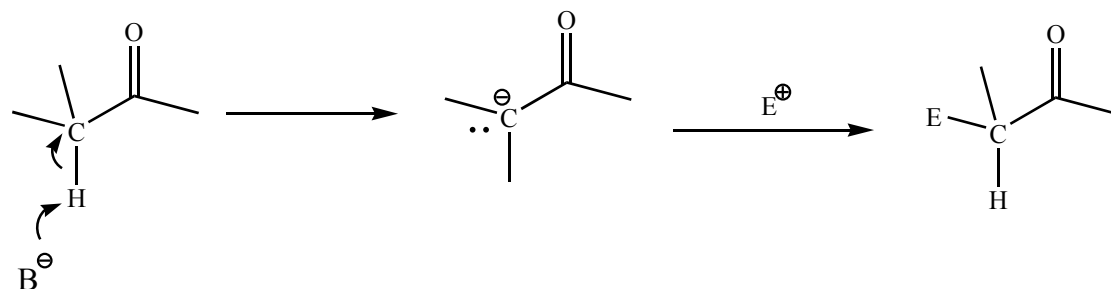
The two structures of enolate are resonance form of each other (different pictures of the same molecule since no atom has moved and only positions of electrons have been moved). Many bases can be used, but a common base used to form an enolate at low temperature irreversibly is lithium diisopropyl amide (LDA). The pKa of diisopropyl amine (protonated LDA) is ca 36. Potassium tert-butoxide can also be used, but this reaction is reversible as the pKa of tert-butyl alcohol is 19.



Why does LDA attack alpha hydrogen instead of attacking the carbonyl?

Answer: because LDA is a bulky base. It is sterically hindered to approach the carbonyl carbon. Instead, it pulls off the hydrogen at the alpha position since the alpha hydrogen has a partial positive charge associated with it.

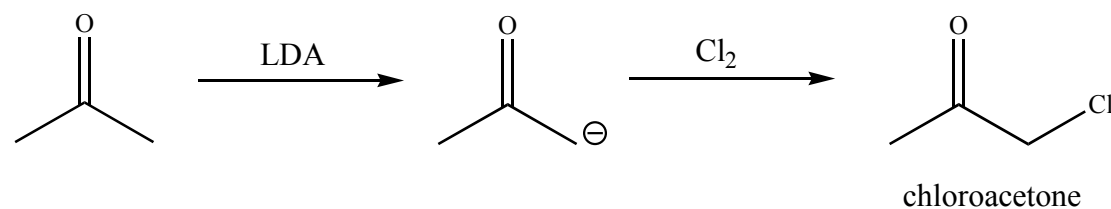
General Reaction



The reaction is irreversible for both steps.

The electrophiles E^+ can be X^+ from X_2 (halogens) or R^+ from alkyl halide ($R-X$).

Example: halogenation



Chloroacetone is used in tear gas.