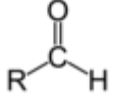
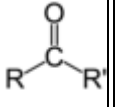
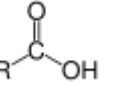
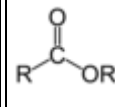
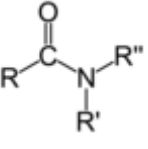
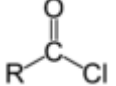
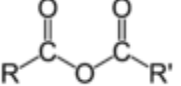


I. ALDEHYDES AND KETONES

Carbonyl compounds are everywhere. In addition to being reagents and solvents, they are constituents of fabrics, flavorings, plastics, and drugs. Naturally occurring carbonyl compounds include the proteins, carbohydrates, and nucleic acids that make up all plants and animals. Some common classes of carbonyl compounds are listed in table 1.

Table 1. Some common classes of carbonyl compounds

Class	<u>Aldehydes</u>	<u>Ketones</u>	<u>Carboxylic acid</u>	<u>Esters</u>	<u>Amides</u>	<u>Acid chlorides</u>	<u>Anhydrida acid</u>
General formula							

The simplest carbonyl compounds are aldehydes and ketones. A ketone has two alkyl (or aryl) groups bonded to the carbonyl carbon atom. An aldehyde has one alkyl (or aryl) group and one hydrogen atom bonded to the carbonyl carbon atom.

Physical properties of some carbonyl compounds

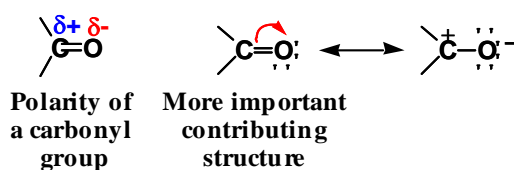
- Methanal is a gas, other lower members of aldehydes and ketones are liquids.
- Benzenecarbaldehyde is a colourless liquid with almond smell.
- Ethanal and propanone are miscible with water due to the formation of H-bond with water molecules while benzenecarbaldehyde is insoluble in water.

Structure of the carbonyl group

The carbonyl carbon atom is sp^2 hybridized and bonded to three other atoms through three coplanar sigma bonds oriented about 120° apart. The unhybridized p orbital overlaps with a p orbital of oxygen to form a pi bond. The double bond, except the carbonyl double bond is shorter

and stronger. Ketone (C=O bond length 1.23 Å, energy 178 kcal/mol), alkene (C=C bond length 1.34 Å, energy 146 kcal/mol).

Another difference between the carbonyl and alkene double bonds is the large dipole moment of the carbonyl group. Oxygen is more electronegative than carbon, and the bonding electrons are not shared equally. Oxygen is more electronegative than carbon (3.5 vs 2.5) and, therefore, a C=O group is polar. This polarization of the carbonyl group contributes to the reactivity of ketones and aldehydes. The positively polarized carbon atom acts as an electrophile (Lewis acid), and the negatively polarized oxygen acts as a nucleophile (Lewis base).

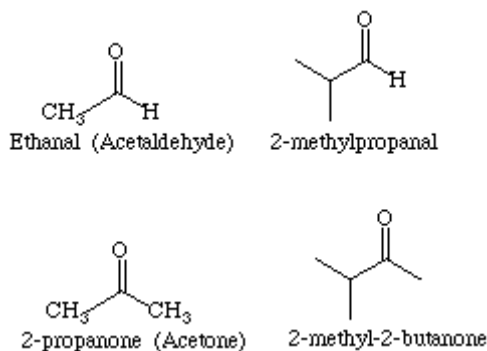


Aldehydes and ketones are polar compounds and interact in the pure state by dipole-dipole interaction. They have higher boiling points and are more soluble in water than nonpolar compounds of comparable molecular weight.

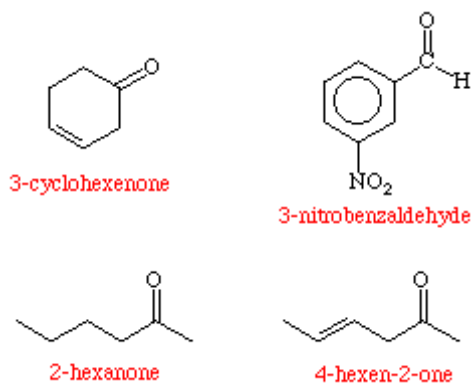
Nomenclature of aldehydes and ketones

Simple aldehydes and ketones are named using the standard rules of nomenclature which we have used in the past with the following specific changes:

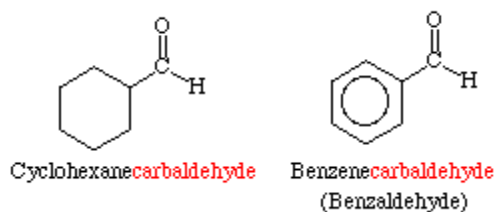
1. Aldehydes are named by replacing the terminal -e of the parent alkane with the suffix -al; the suffix for ketones is -one.



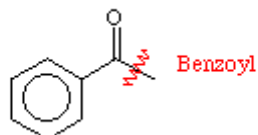
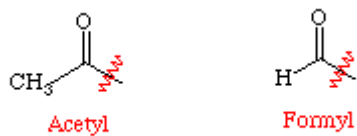
- The parent chain selected must contain the carbonyl group.
- Number the carbon chain, beginning at the end nearest to the carbonyl group.
- Number the substituents and write the name, listing substituents alphabetically.



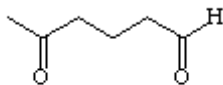
- When an aldehyde is a substituent on a ring, it is referred to as a -carbaldehyde group.



- When the -COR group becomes a substituent on another chain, it is referred to as an acyl group and the name is formed using the suffix -yl.

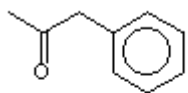


7. When the carbonyl group becomes a substituent on another chain, it is referred to as an oxo group.

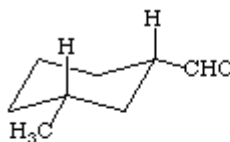


5-oxohexanal

Some Examples:



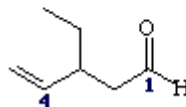
1-phenyl-2-propanone



cis-3-methylcyclohexanecarbaldehyde



pentanedial

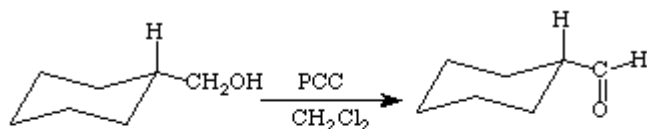


3-ethyl-4-pentenal

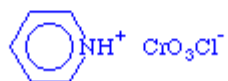
Reactions that Yield Aldehydes & Ketones

1. Oxidation of Alcohols with Pyridinium Chlorochromate

Primary and secondary alcohols are smoothly oxidized by pyridinium chlorochromate (PCC) in CH_2Cl_2 to form aldehydes and ketones, respectively. The PCC oxidation of primary alcohols to give aldehydes is a very useful reaction, since aldehydes are difficult to prepare and are easily over-oxidized to the carboxylic acid.

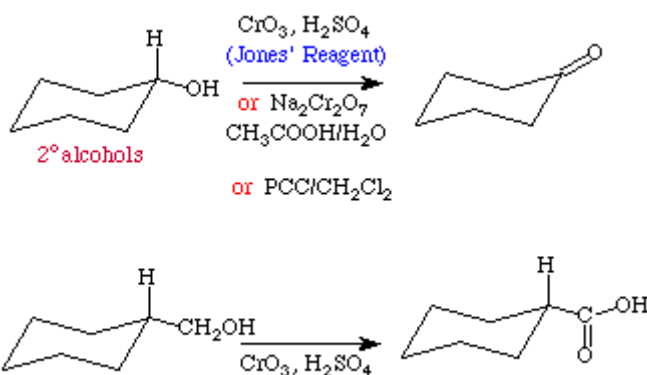


PCC: pyridinium chlorochromate



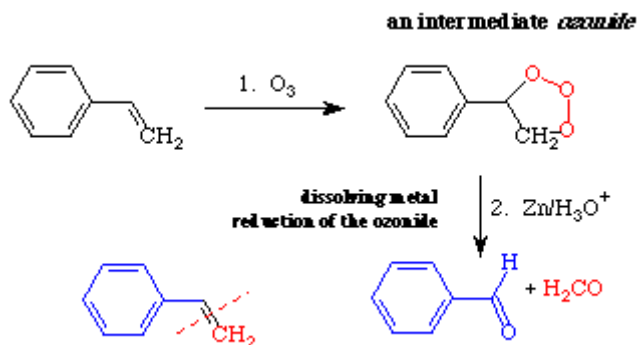
2. Oxidation of Alcohols with "Jones Reagent"

Primary and secondary alcohols are oxidized by $\text{CrO}_3/\text{H}_2\text{SO}_4$ (Jones Reagent) to form carboxylic acids and ketones, respectively; sodium dichromate in acetic acid ($\text{Na}_2\text{Cr}_2\text{O}_7$) can also be used.



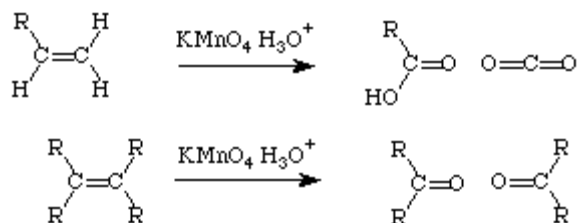
3. Ozonolysis of Alkenes

Simple alkenes are oxidized by O_3 to form an intermediate ozonide, which undergoes dissolving metal reduction with $\text{Zn}/\text{H}_3\text{O}^+$ to produce aldehydes and ketones.



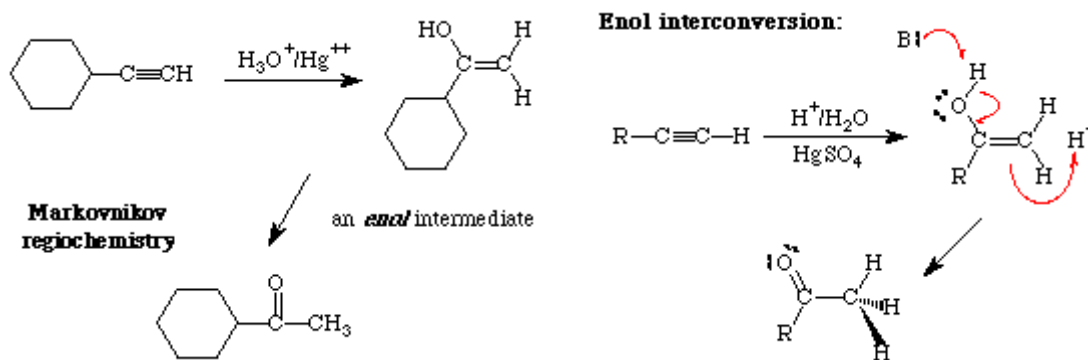
4. Oxidation of Alkenes

Simple alkenes are oxidized by MnO_4^- to produce aldehydes and ketones. Terminal alkenes yield CO_2 , while alkene carbons bearing one hydrogen form the corresponding carboxylic acid.



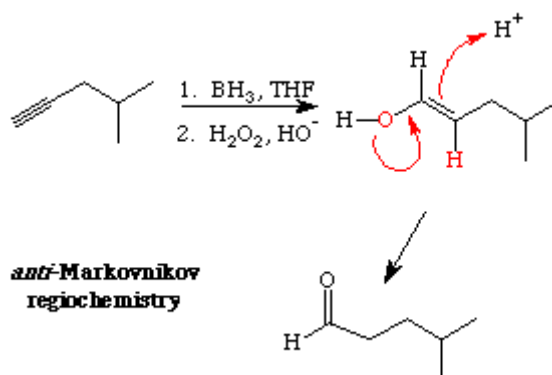
5. Hydration of Alkynes

Acid-catalyzed hydration of alkynes in the presence of Hg^{+2} yields an intermediate enol, which rapidly equilibrates with the corresponding carbonyl compound. The regiochemistry of the reaction is "Markovnikov"; that is, hydroxide anion will bond to the most stable potential carbocation center of the alkyne.



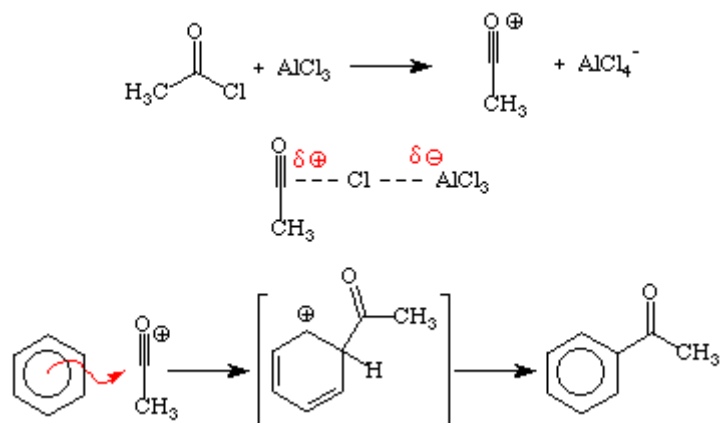
6. Hydroboration of an Alkyne, with Oxidative Work-up

Reaction of an alkyne with BH_3 results in the *syn*-addition of the boron and a hydrogen across the triple bond. Rearrangements do not occur and the hydrogen will bond to the carbon of the alkyne which would form the most stable carbocation center (overall *anti*-Markovnikov's addition). The driving force for the regiochemistry may actually be more steric than electronic, but viewing the reaction as a concerted, but polar transition state, easily rationalizes the observed product distribution. On oxidative work-up, the borane is converted to the enol, which rapidly equilibrates with the corresponding carbonyl compound.



7. Friedel-Crafts Acylation

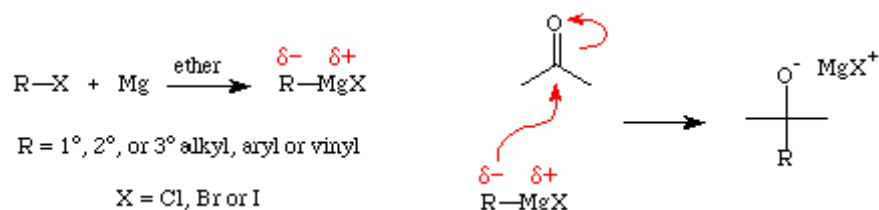
Arenes react with acid halides and acid anhydrides in the presence of AlCl_3 to form aryl ketones. This is an example of electrophilic aromatic substitution, and the reaction does not proceed well on rings which are strongly deactivated.



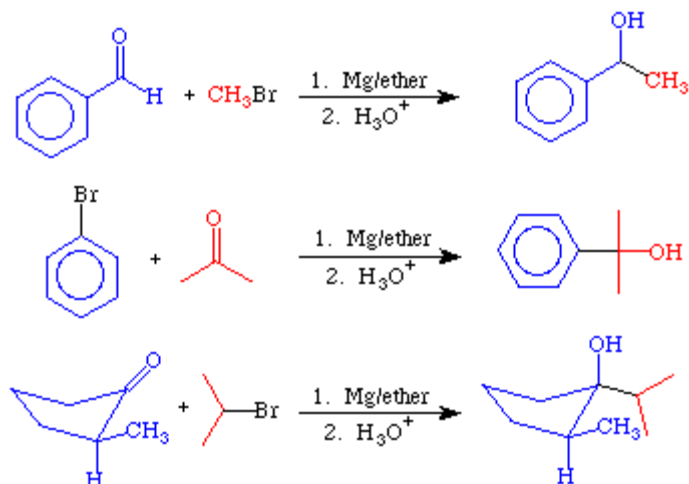
Reactions of Aldehydes & Ketones

1. The Grignard Reaction

The reaction of an alkyl, aryl or vinyl halide with magnesium metal in ether solvent, produces an organometallic complex of uncertain structure, but which behaves as if it has the structure R-Mg-X and is commonly referred to as a **Grignard Reagent**.

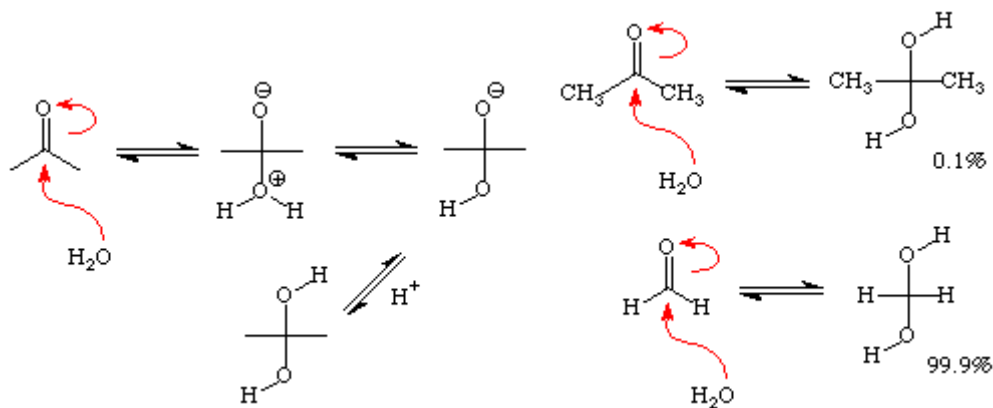


The "R" group in this complex (alkyl, aryl or vinyl), acts *as if* it was a **stabilized carbanion** and Grignard reagents react with water and other compounds containing acidic hydrogens to give hydrocarbons (just as would be expected for a well-behaved, highly basic carbanion). In the absence of acidic hydrogens, the Grignard reagent can function as a powerful nucleophile, and is most often used in addition reactions involving carbonyl compounds, as shown above. The product of these addition reactions is typically a secondary or tertiary alcohol (primary alcohols can be formed by reaction with formaldehyde), as shown in the examples below; in these the carbonyl and halide portions of the molecules have been colored blue and red, respectively, to assist in understanding the component parts of the final products.



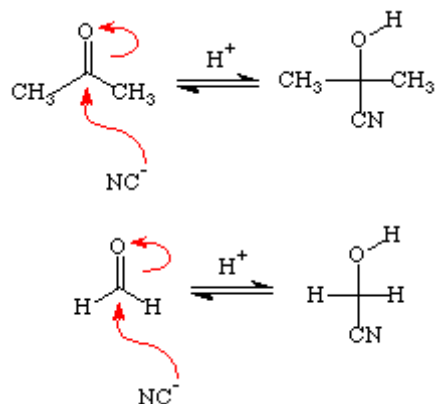
2. Hydration of Aldehydes & Ketones

The hydration of carbonyl compounds is an equilibrium process and the extent of that equilibrium generally parallels the reactivity of the parent aldehyde or ketone towards nucleophilic substitution; aldehydes are more reactive than ketones and are more highly hydrated at equilibrium.



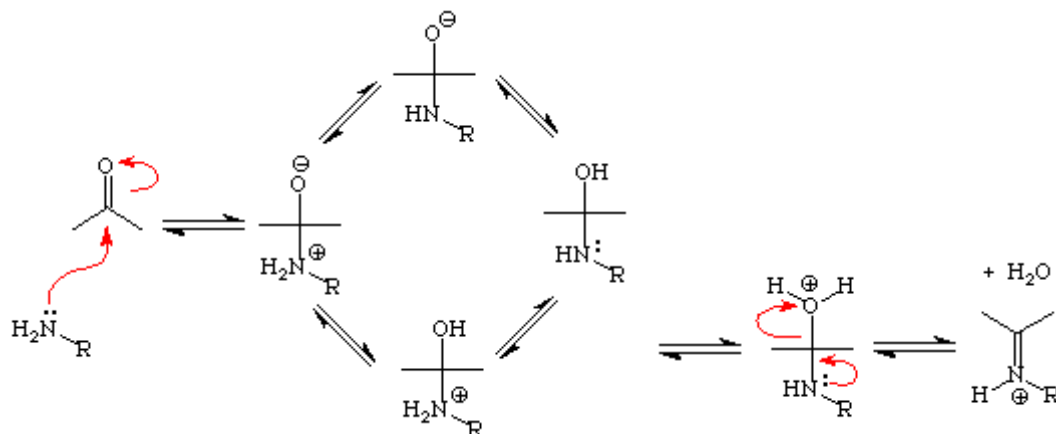
3. Formation of Cyanohydrins

The reaction of carbonyl compounds with HCN is an equilibrium process and, again, the extent of that equilibrium generally parallels the reactivity of the parent aldehyde or ketone towards nucleophilic substitution.

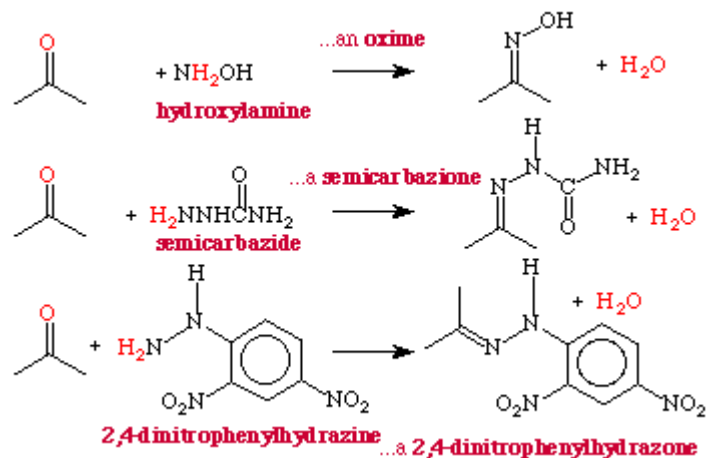


4. Reaction with Amines

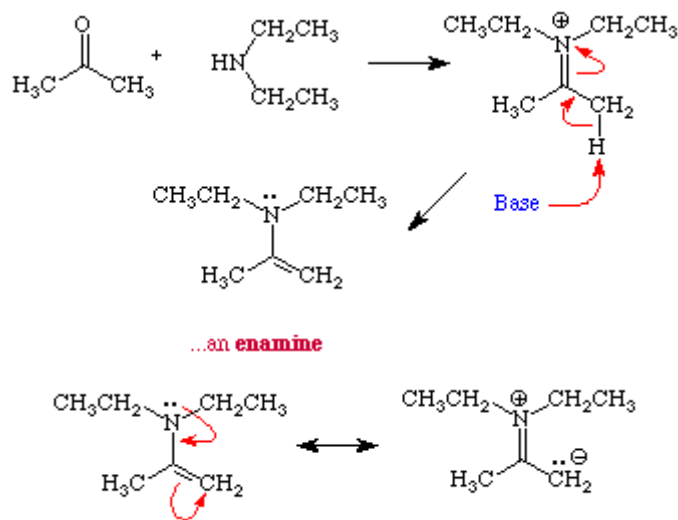
The reaction of carbonyl compounds with amines involves the formation of an intermediate **carbinolamine** which undergoes dehydration to form an **immonium cation** which can lose a proton to form the neutral **imine**.



Some examples of common imine-forming reactions are given below:

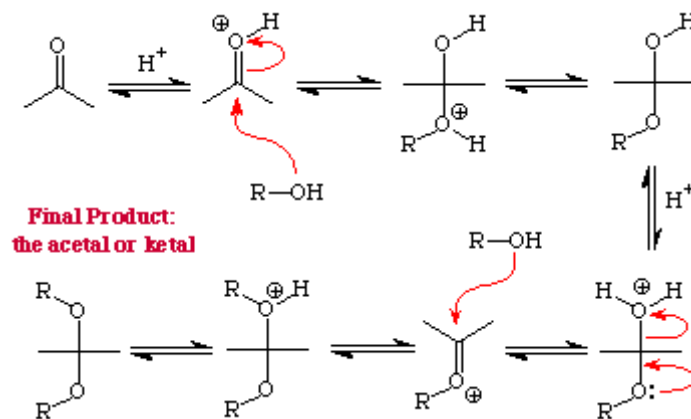


Imines formed from secondary amines can lose a proton from the α -carbon to form an **enamine**. Because of resonance, enamines maintain a partial carbanion character on the α -carbon and can be utilized as nucleophiles, as will be discussed in the section on "alpha alkylations".

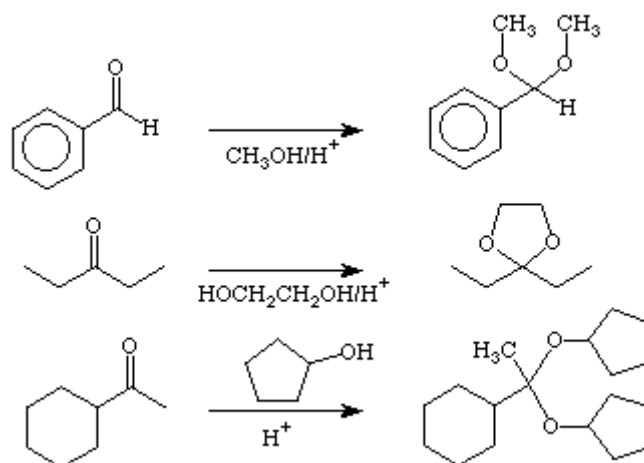


5. Ketal and Acetal Formation

Ketones and aldehydes react with excess alcohol in the presence of acid to give **ketals and acetals**, respectively. The mechanism of acetal formation involves equilibrium protonation, attack by alcohol, and then loss of a proton to give the neutral hemiacetal (or hemiketal). The hemiacetal undergoes protonation and loss of water to give an oxocarbenium ion, which undergoes attack by another mole of alcohol and loss of a proton to give the final product; note that acetal (or ketal) formation is an **equilibrium process**.

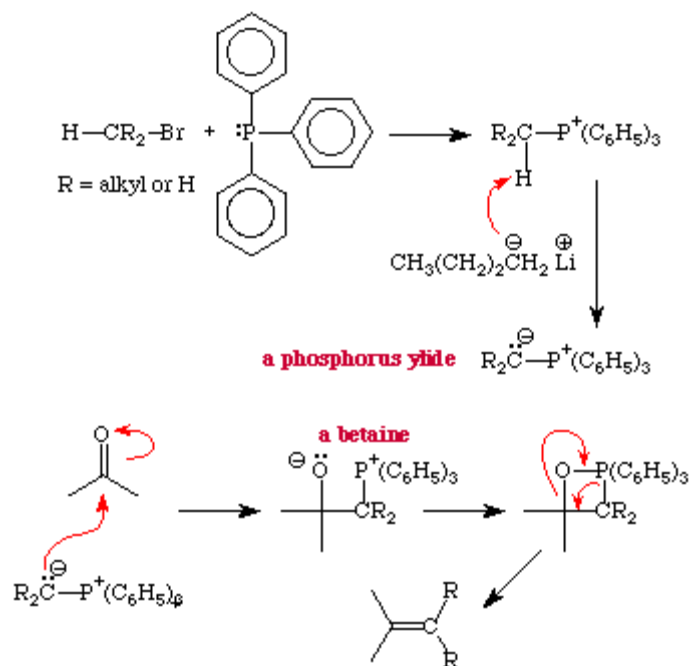


Some examples of acetal and ketal formation are given below:



6. The Wittig Reaction

Ketones and aldehydes react with **phosphorus ylides** to form alkenes. Phosphorus ylides are prepared by an S_N2 reaction between an alkyl halide and triphenylphosphine, followed by deprotonation by a strong base such as n-butyllithium. The mechanism of the Wittig reaction involves nucleophilic addition to give an intermediate **betaine**, which decomposes to give the alkene and triphenylphosphine oxide. The Wittig reaction works well to prepare mono- di- and tri-substituted alkenes; tetra-substituted alkenes cannot be prepared by this method.

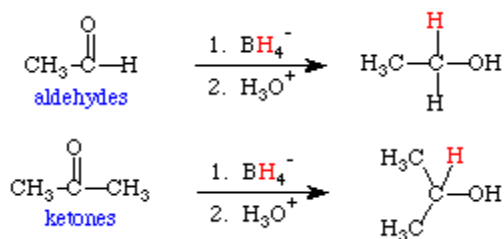


7. Reaction Oxidation & Reduction of Aldehydes and Ketones

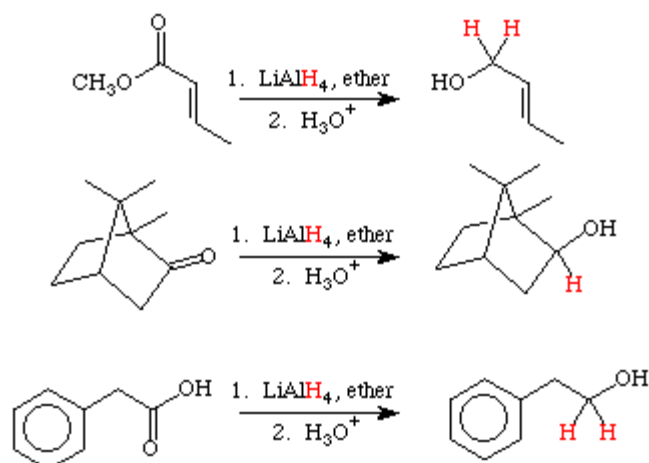
Reduction of simple aldehydes and ketones with BH_4^- yields the corresponding alcohol directly. The reaction works well for simple compounds, but reaction of BH_4^- with α - β unsaturated aldehydes and ketones can result in significant reduction of the double bond.

Reduction by BH_4^-

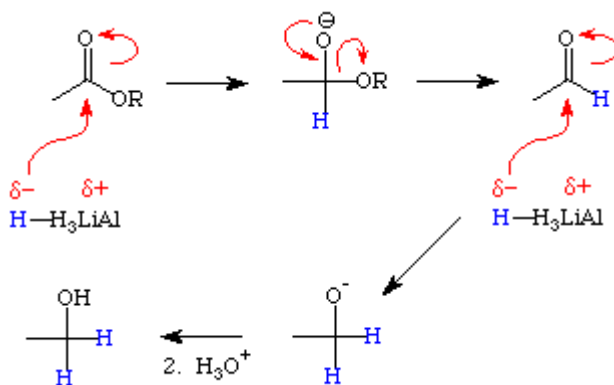
The reaction works well for simple compounds, but reaction of BH_4^- with α - β unsaturated aldehydes and ketones can result in significant reduction of the double bond.



A much more powerful reductant is LiAlH_4 , which will reduce aldehydes, ketones, esters, carboxylic acids and nitriles. Some sample reactions are shown below:

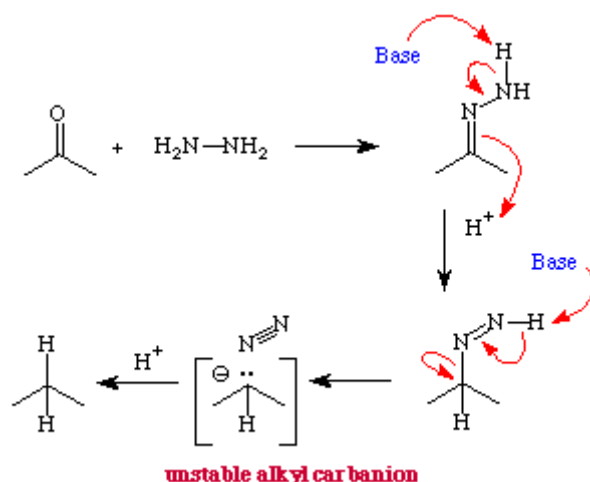


As seen in the first example, the reduction of carboxylate esters results in the addition of **two moles** of hydride to the carbonyl carbon, with loss of the alcohol portion of the ester, forming the corresponding primary alcohol.



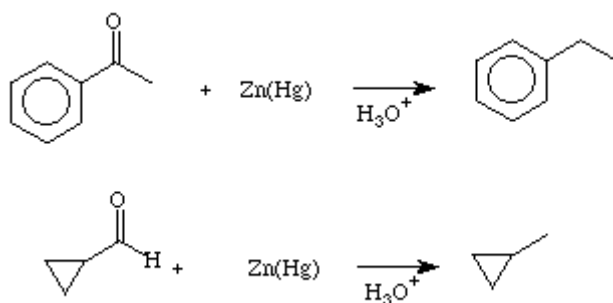
Wolff-Kishner Reduction

The imine formed from an aldehyde or ketone on reaction with hydrazine (NH_2NH_2) is unstable in base, and undergoes loss of N_2 to give the corresponding hydrocarbon.



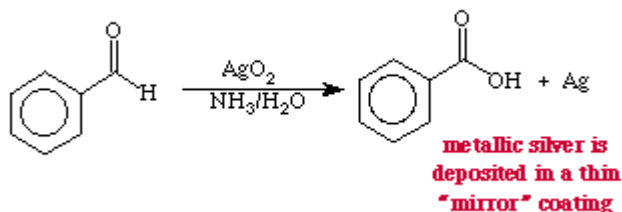
Clemmensen Reduction

Carbonyl compounds can also be reduced by the Clemmensen reduction using zinc-mercury amalgam in the presence of acid; the mechanism most likely involves free radicals.



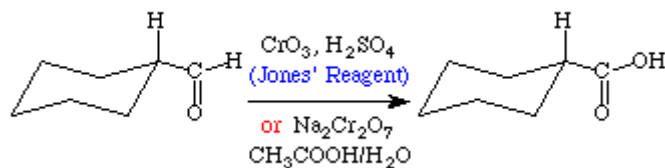
Oxidation of Aldehydes by Silver Oxide

Reaction of simple aldehydes with aqueous Ag_2O in the presence of NH_3 yields the corresponding carboxylic acid and metallic silver. The silver is generally deposited in a thin metallic layer which forms a reflective "mirror" on the inside surface of the reaction vessel. The formation of this mirror forms the basis of a qualitative test for aldehydes, called the **Tollens Test**.



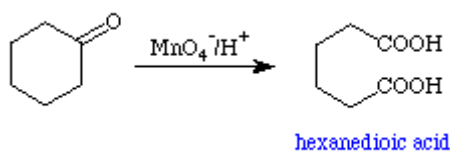
Oxidation of Aldehydes to form Carboxylic Acids

Reaction of simple aldehydes with acidic MnO_4^- , or $\text{CrO}_3/\text{H}_2\text{SO}_4$ yields the corresponding carboxylic acid. Aldehydes oxidize very easily and it is often difficult to prevent oxidation, even by atmospheric oxygen.



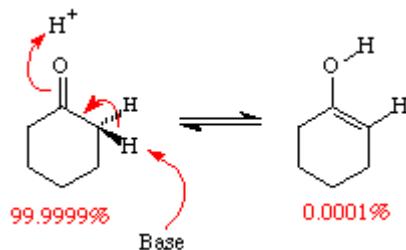
Oxidation of Ketones

Ketones are more resistant to oxidation, but can be cleaved with acidic MnO_4^- to yield carboxylic acids.

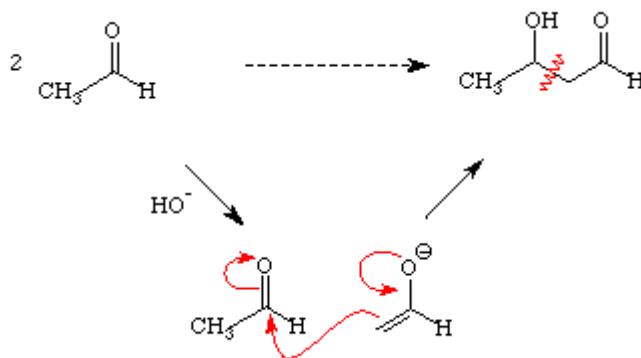


The Aldol Condensation

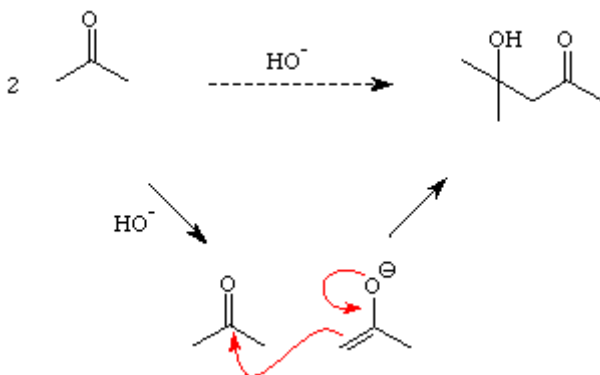
Carbonyl compounds exist in equilibrium with a very small amount of a structural isomer, termed an **enol**. An enol is formed by abstraction of a proton from the α -carbon, delocalization of the electrons onto the carbonyl oxygen, and finally, protonation of the oxygen to give an alkene bonded to an alcohol (an enol!). It is important to note that this is a true **equilibrium** and the carbonyl compound and its enol are distinct different chemical species, **not resonance forms**. Since both proton abstraction and donation are required in the isomerization, keto-enol isomerization is catalyzed by both acids and bases.



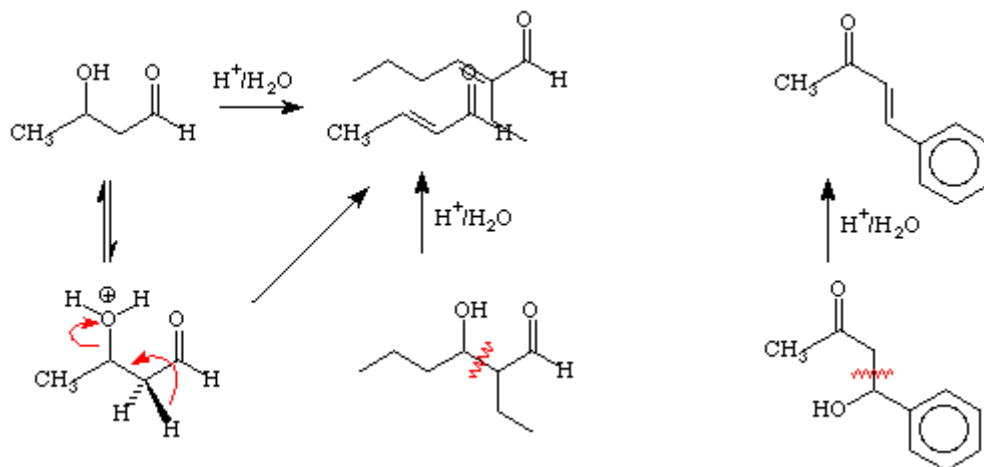
As described previously, aldehydes and ketones enolize in base to produce a small equilibrium concentration of the corresponding enolate anion. If the concentration of carbonyl compound is sufficiently high, this enolate anion can function as a nucleophile towards the carbonyl carbon of other aldehydes or ketones in the solution. The result is the formation of a bond between the α -carbon of one mole of carbonyl compound and the carbonyl carbon of a second, to give a β -hydroxy aldehyde or ketone. This condensation reaction between two moles of an aldehyde or ketone is called the **aldol condensation**.



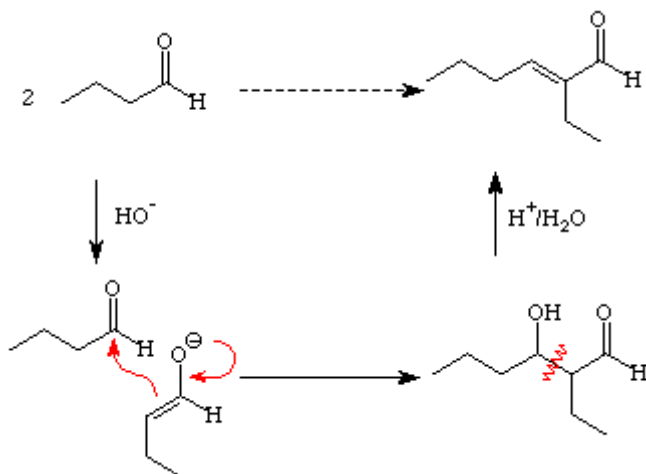
The reaction is general for both aldehydes and ketones, bearing at least one α -hydrogen.



The β -hydroxy carbonyl compounds which are formed are stable in base, but readily dehydrate in acid solution to give α - β -unsaturated carbonyl compounds.



As an example of the use of an aldol reaction in synthesis, consider the preparation of 2-ethyl-2-hexenal. This molecule is an α - β -unsaturated aldehyde. We can make these by the dehydration of β -hydroxy aldehydes in aqueous acid. The required β -hydroxy aldehyde, in turn can be prepared by the aldol condensation of two moles of butanal in aqueous base. To determine the structure of the required aldehyde, simply split the compound at the bond between the hydroxyl group and the α -carbon of the carbonyl, as shown on the right. As you can see, splitting like this breaks the molecule into two, four-carbon parts, both with an oxygen bonded to carbon #1.



Drawing the structure of the reacting enol-aldehyde pair, as shown above, the mechanism of the condensation becomes clear. It is also possible to utilize two *different* aldehydes or ketones in an aldol-type condensation reaction. In order to minimize *self*-condensations, generally one reactant is chosen which has **no α -hydrogens**, and that reactant is maintained in large excess over the second reactant (which will have α -hydrogens and can form the enolate anion). An example of this is the synthesis of 4-phenyl-3-buten-2-one, shown on the right. This α - β -unsaturated ketone can be prepared by dehydration of the β -hydroxy ketone, as shown. Splitting this between the α -carbon and the hydroxyl group, it is evident that it can be prepared by the condensation of the enol of 2-propanone (acetone) and benzaldehyde, as shown below.

