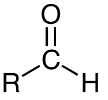
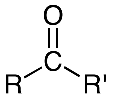
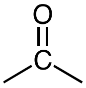
Chapter 18

Aldehydes and Ketones
Nucleophilic Addition to Carbonyls

In this chapter we will look at nucleophilic additions to aldehydes, RCHO, and ketones, RCOR’, as representative carbonyl containing compounds. The carbonyl group is one of the most versatile functional groups in all of organic chemistry. We have already seen how Grignard reagents and organolithium reagents as well as hydride reagents ($NaBH_4$ and $LiAlH_4$) will attack the carbonyl carbon. In this and subsequent chapters we will see many more reactions of these versatile and important reagents.

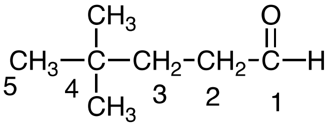

Aldehyde

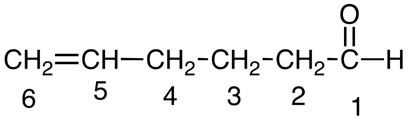

ketone

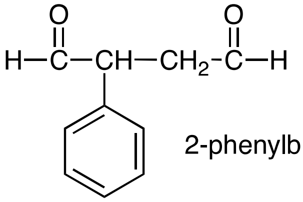

carbonyl group

Nomenclature

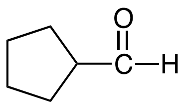
Aldehydes: Name the aldehyde so that the longest continuous chain that contains the –CHO unit is the parent. From the parent alkane, remove the ‘e’ and add –al. Number the chain so that the aldehyde unit –CHO is number 1. There is no need to specific the position of the – CHO unit since by definition it must be at the end of the chain.

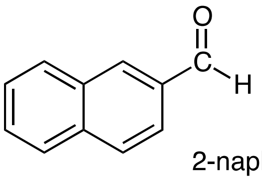

$$\underset{5}{CH_3}-\underset{4}{C}(CH_3)_2-\underset{3}{CH_2}-\underset{2}{CH_2}-\underset{1}{C}(=O)-H$$
4,4-dimethylpentanal


$$\underset{6}{CH_2}=\underset{5}{CH}-\underset{4}{CH_2}-\underset{3}{CH_2}-\underset{2}{CH_2}-\underset{1}{C}(=O)-H$$
5-hexenal

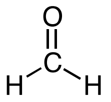

2-phenylbutanedial

When the formyl group (-CHO) is attached to a ring, the ring name is followed by the suffix “-carbaldehyde”.

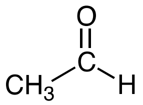

Cyclopentanecarbaldehyde


2-naphthalenecarbaldehyde

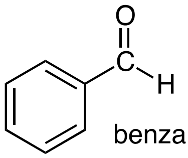
Common names:



formaldehyde

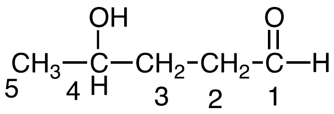


acetaldehyde
(ethanal)



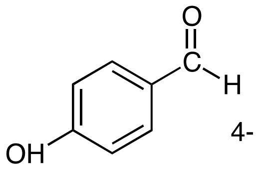
benzaldehyde
(benzenecarbaaldehyde)

Among oxygen containing groups, the higher oxidation state takes precedence over a lower one: i. e. $RCO_2H > RCOR' > ROH$.



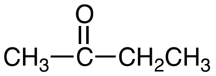
$CH_3-\overset{OH}{\underset{H}{C}}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-H$

4-hydroxypentanal



4-hydroxybenzaldehyde

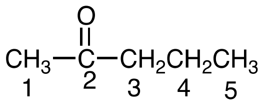
Ketones: The parent alkane is the longest continuous chain that contains the carbonyl group. Number the chain so as to give the carbonyl group the lowest number. From the parent alkane, drop the "e" and add"-one" as the suffix. The position of the carbonyl group must be specified by number.



$CH_3-\overset{O}{\overset{\|}{C}}-CH_2CH_3$

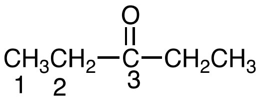
butanone

(no 2 is needed since there cannot be a 3-butanone)



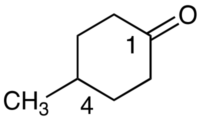
$CH_3-\overset{O}{\overset{\|}{C}}-CH_2CH_2CH_3$

2-pentanone



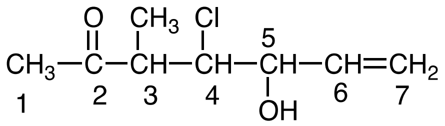
$CH_3CH_2-\overset{O}{\overset{\|}{C}}-CH_2CH_3$

3-pentanone



4-methylcyclohexanone

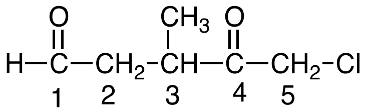
The usual rules about specifying the position of C=C bonds and the naming the substituents in alphabetical order still apply. The carbonyl substituent takes precedence over alcohols, double bonds, halogens and alkyl groups.



$CH_3-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{|}{CH}}-\overset{Cl}{\overset{|}{CH}}-\underset{OH}{\underset{|}{CH}}-CH{=}CH_2$

4-chloro-5-hydroxy-4-methyl-6-hepten-2-one

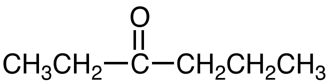
But aldehydes take precedence over ketones. A compound that contains both and aldehyde and a ketone is named as an aldehyde. The ketone substituent (the carbonyl carbon) is named as an "-oxo" group and specified by number.



$H-\overset{O}{\overset{\|}{C}}-CH_2-\overset{CH_3}{\overset{|}{CH}}-\overset{O}{\overset{\|}{C}}-CH_2-Cl$

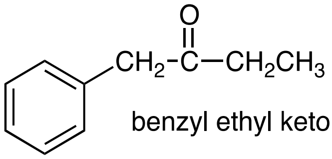
5-chloro-3-methyl-4-oxo-pentanal

Ketones are also sometimes named by functional class nomenclature as "alkyl alkyl ketones" where the alkyl groups are listed alphabetically.



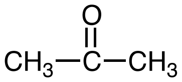
$CH_3CH_2-\overset{\overset{O}{\|}}{C}-CH_2CH_2CH_3$

ethyl propyl ketone



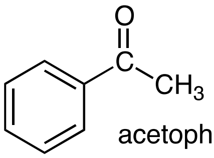
benzyl ethyl ketone

Common names:

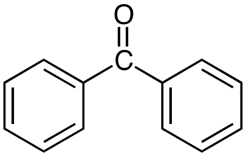


$CH_3-\overset{\overset{O}{\|}}{C}-CH_3$

acetone



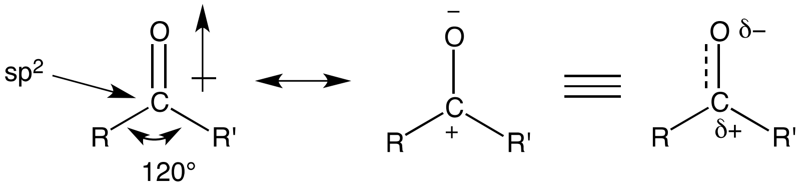
acetophenone



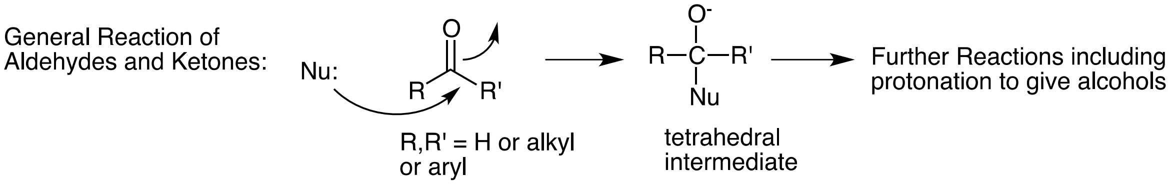
benzophenone

The Carbonyl Group: Structure and Bonding

The carbonyl carbon is sp^2 hybridized, making it trigonal and planar with angles of about 120° between the substituents. As we know, oxygen is more electronegative than carbon (3.44 v. 2.55), so the C=O bond is strongly polarized and there is a strong dipole moment, giving the carbonyl carbon a substantial partial (+) charge and the carbonyl oxygen has a substantial (-) charge. The resonance structure on the right shows this charge distribution. These charges determine much of the chemistry we will encounter with carbonyl compounds: nucleophiles will attack the carbonyl carbon with simultaneous cleavage of the C=O bond to give a tetrahedral intermediate with a full negative charge on the oxygen.

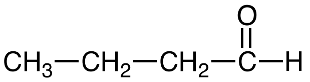


Planar: all 3 substituents on carbonyl carbon are in the same plane.



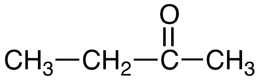
Aldehydes are more reactive than ketones since ketones are more stable. The ketone has an extra alkyl group that releases electron density to the electron-deficient carbonyl carbon to help stabilize it and lower its energy. This makes the carbonyl carbon of the ketone less

electron-deficient – it has a smaller amount of (+) charge and it will therefore be less attracted to the negatively charged nucleophile.
Compare the heats of combustion for butanal and butanone:


$CH_3-CH_2-CH_2-C(=O)-H$

butanal Δ H = 2475 Kl/mol

Higher heat of combustion,
less stable, more reactive.

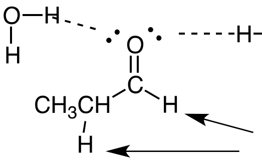

$CH_3-CH_2-C(=O)-CH_3$

butanone Δ H = 2442 Kl/mol

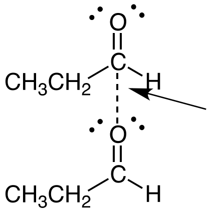
Lower heat of combustion,
more stable, less reactive.

Look at the physical properties. Aldehyde and ketones generally have higher boiling points than alkenes because they are more polar but lower boiling points than alcohols. The carbonyl oxygen can accept H-bonds but cannot donate them. This also gives them considerable solubility in water, though they are not as soluble as alcohols. Compare 1-butene, propanal and propanol.

$CH_3-CH_2-CH=CH_2$	$CH_3-CH_2-CH=O$	$CH_3-CH_2\text{-}CH_2\text{-}OH$
1-butene	propanal	propanol
b. p. -6°C	b. p. 49°C	b. p. 97°C
sol in H_2O ~0 g/100 mL	sol in H_2O 20 g/100 mL	miscible with H_2O



C-H bonds are not polarized enought for significant H-bonding.

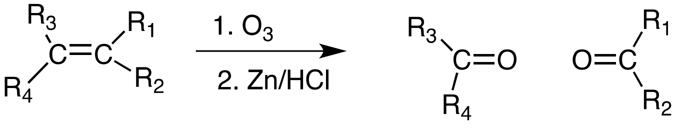


Dipole-dipole interactions between the partial positive charge on the carbonyl carbon and the partial negative charge on a carbonyl carbon.

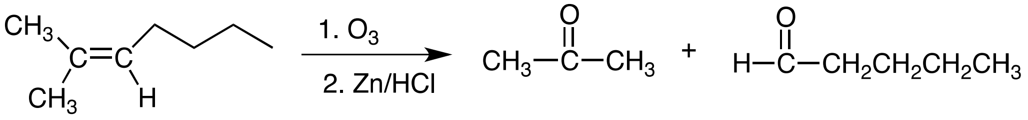
Preparation of Aldehydes and Ketones:

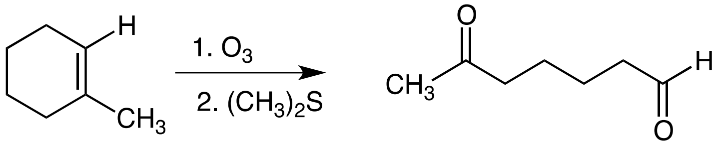
(1) Ozonolysis: this cleaves C=C bonds into aldehydes and ketones depending on the substituents on the double bond. Reductive work-up conditions are used. If we have a cyclic alkene, a linear di-carbonyl compound is obtained.

General reaction:

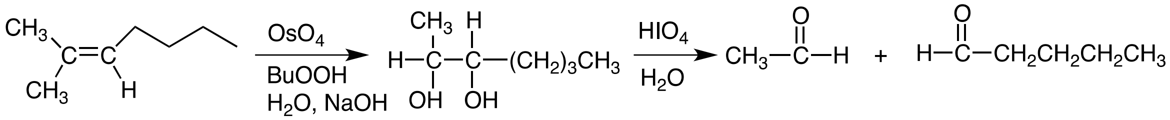


Ex.



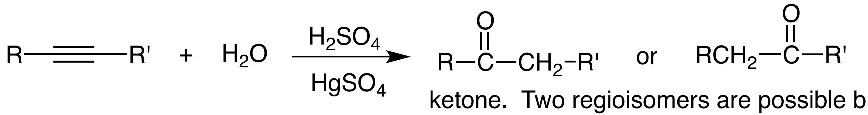


(2) Cleavage of alkenes using (i) osmium with a co-oxidant (OsO_4, BuOOH) and (ii) periodic acid (HIO_4). This method is complementary to the ozonolysis method and is sometimes more convenient. Both steps can actually be carried out in one pot at the same time.



(3) Hydration of Alkynes.

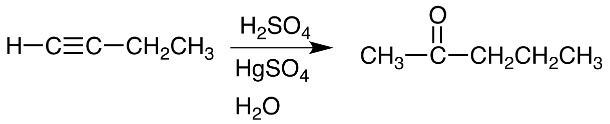
General Reaction:



$$R-C\equiv C-R' + H_2O \xrightarrow[HgSO_4]{H_2SO_4} R-\overset{O}{\overset{\|}{C}}-CH_2-R' \quad \text{or} \quad RCH_2-\overset{O}{\overset{\|}{C}}-R'$$

ketone. Two regioisomers are possible but with terminal alkynes usually get methyl ketones in accordance with Markovnikov's rule.

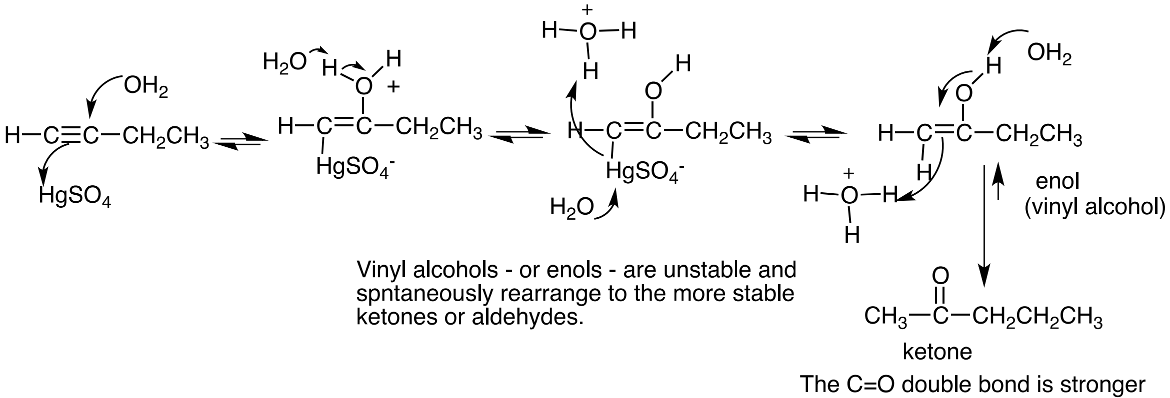
Ex



$$H-C\equiv C-CH_2CH_3 \xrightarrow[HgSO_4,\ H_2O]{H_2SO_4} CH_3-\overset{O}{\overset{\|}{C}}-CH_2CH_2CH_3$$

Here we get a methyl ketone. This reaction is eseentially acid-catalyzed Markovnikov addition to an alkyne with addition of the H^+ to the less substituted or terminal end of the alkyne and the formation of the more susbstituted carbocation intermediate, which is then attacked by the water. The role of the Hg is to help stabilize the sp^2 carbocation by acting as a Lewis acid and by donating electrons through the d-orbitals to the π-system.

The mechanism is shown below.

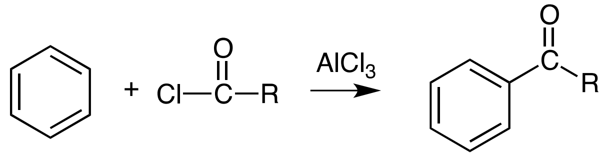


Vinyl alcohols - or enols - are unstable and spntaneously rearrange to the more stable ketones or aldehydes.

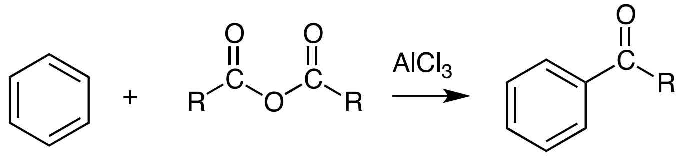
The C=O double bond is stronger than the C=C double bond.

(4) Friedel-Crafts Acylation.

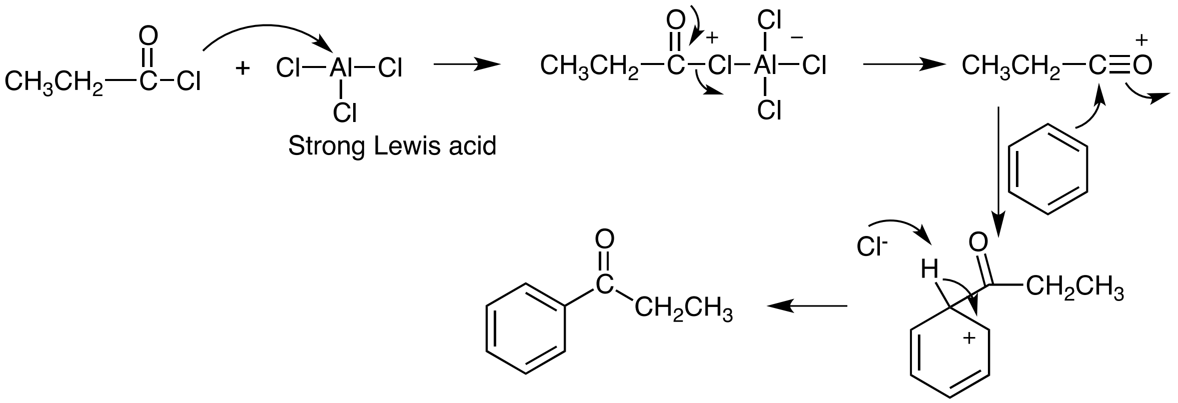
With acid chlorides



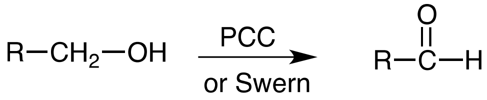
With anhydrides



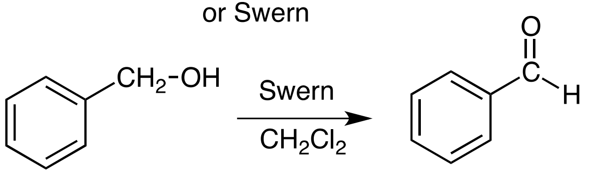
The mechanism is shown below.



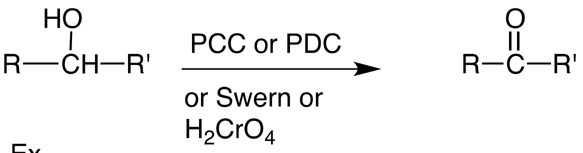
(5) Oxidation of Primary Alcohols to Aldehydes using PCC, PDC or the Swern oxidation.



Ex.



(6) Oxidation of secondary alcohols to ketones using PCC, PDC, Swern or chromic acid.



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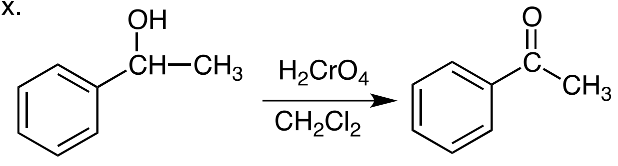
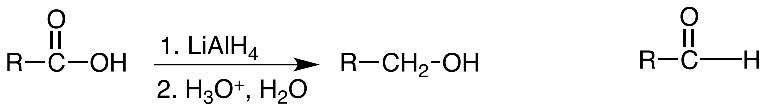
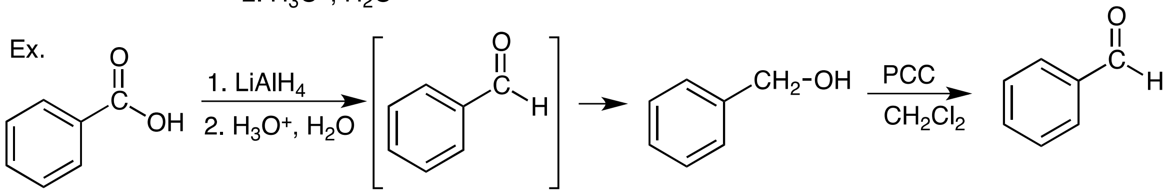


To convert a carboxylic acid to an aldehyde requires two steps (i) reduction to the primary alcohol using lithium aluminum hydride, $LiAlH_4$. (ii) oxidation back to the aldehyde with PCC or Swern.



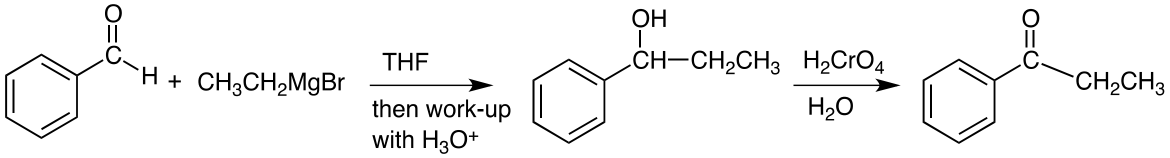
$$R-\overset{O}{\overset{\|}{C}}-OH \xrightarrow[2.\ H_3O^+,\ H_2O]{1.\ LiAlH_4} R-CH_2-OH \qquad R-\overset{O}{\overset{\|}{C}}-H$$

Ex.



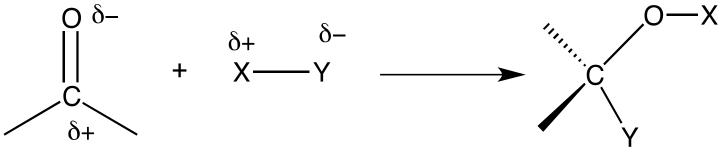
The aldehyde intermeiate in the reduction is
easier to reduce than the carboxylic acid so it
continues to react and cannot be isolated.

(7) Ketones can often be made by a process of C-C bond formation using a Grignard and subsequent oxidation of the resulting secondary alcohol to the ketone.



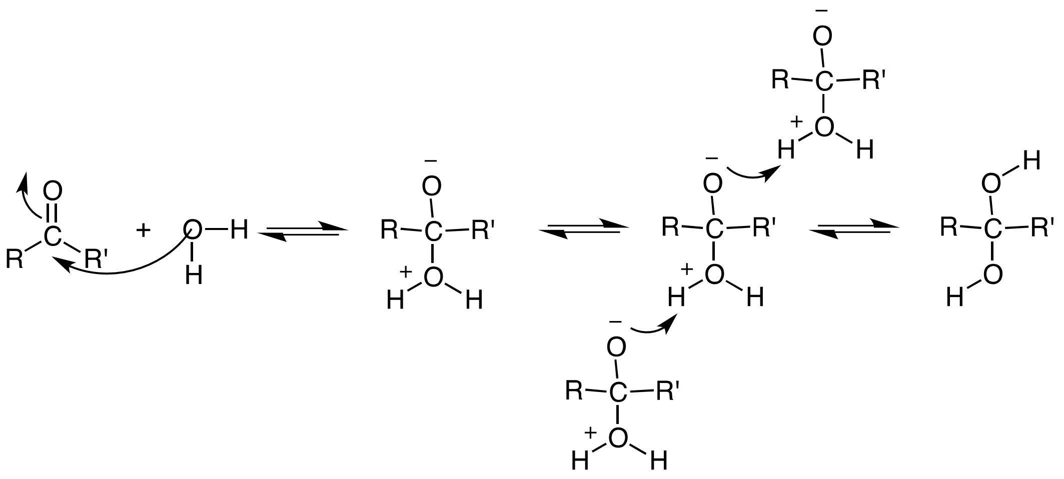
Reactions of Aldehydes and Ketones

The general reaction: aldehydes and ketones are attacked at the carbonyl carbon with cleavage of the C=O bond.

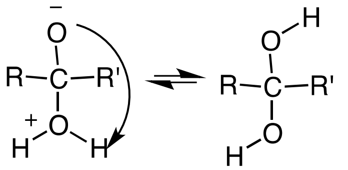


EX: RMgX, RLi, $LiAlH_4$, $NaBH_4$

Hydration:
Both aldehydes and ketones react with water to form the geminal, 1,1-diol called the hydrate. The hydrate cannot usually be isolated and so this is not a useful synthetic transformation but a description of what happens when these species are added to water. In general, when the water is removed the hydrate reverts back to the more stable carbonyl form.



Note: we can also show the final proton transfer step as occurring intra-molecularly. This is a convenient way to write the mechanism and saves time even if it is strictly not correct. It is most likely not the same proton that is on the hydronium ion (+ charge) that is transferred to the alkoxide ion (- charge). But remember that there is hydrogen bonding between all these species and the proton transfer steps are so fast as to be instantaneous. As soon as the water starts to attack the carbonyl carbon and develop a (+) charge another molecule of water starts to take its extra proton and as the carbonyl carbon double bond starts to break the oxygen starts to form a new O-H bond, getting a proton from water.

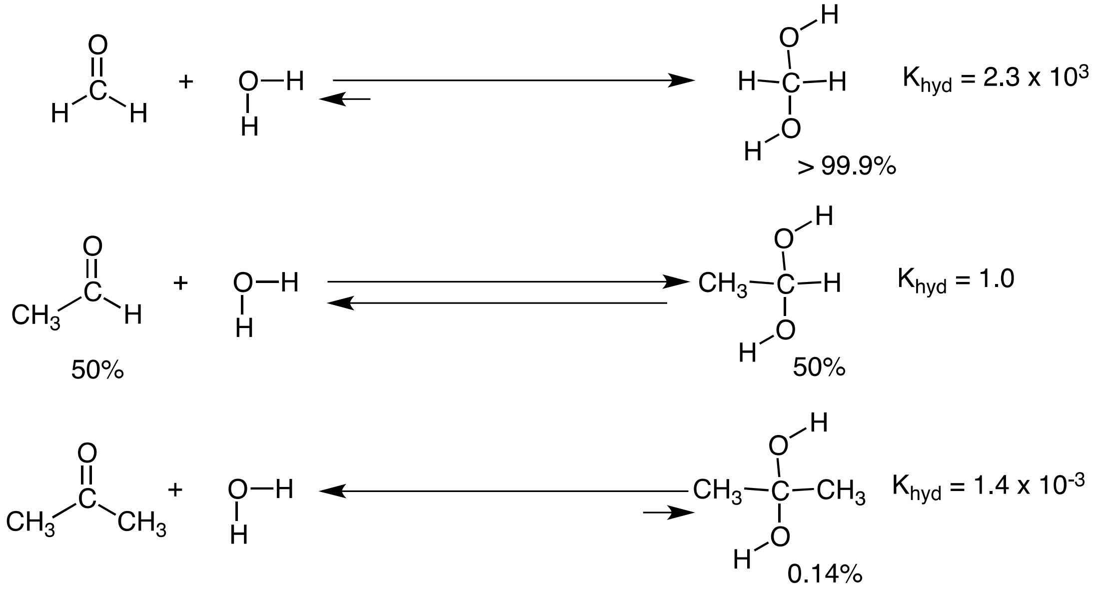


This is an acceptable representation.

This is an addition reaction and it is a rapid equilibrium. The equilibrium constant is given by:

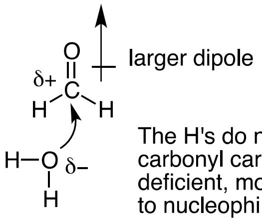
$$K_{hyd} = \frac{[\text{hydrate}]}{[\text{carbonyl compound}]}$$

Look at the following hydration equilibria:

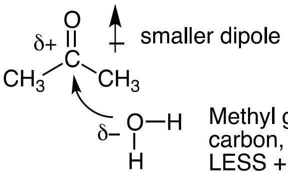


The position of the equilibrium depends on what groups are attached to the carbonyl. There are two effects: (1) electronic effect, (2) steric effect. Both are important but the electronic effect is more important.

(1) Electronic effect: As we see for formaldehyde, it has the greatest concentration of hydrate, more than 6-orders of greater than for acetone. Formaldehyde has two H's attached to the carbonyl carbon while acetone has two electron donating methyl groups. These electron donating groups decrease the amount of (=) charge on the carbonyl carbon, making it less electron deficient and less subject to attack by the water.

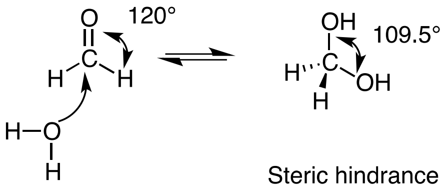


The H's do not donate eletrons; carbonyl carbon is more electron deficient, more +, more reactive to nucleophiles.



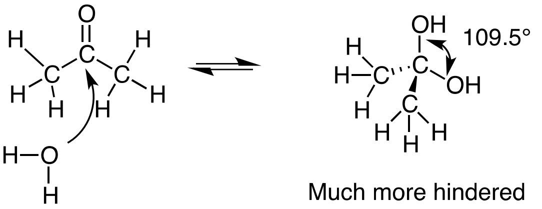
Methyl groups donate electrons to carbonyl carbon, making it LESS electron deficient, LESS +, less reactive to nucleophiles.

(2) The steric effect: the extra alkyl group of a ketone as compared to an aldehyde makes the carbonyl carbon of the ketone more sterically hindered than that of the aldehyde. It is more difficult for the nucleophile, water, to attack the carbonyl of an aldehyde than a carbon.



Less hindered approach for the nucleophile.

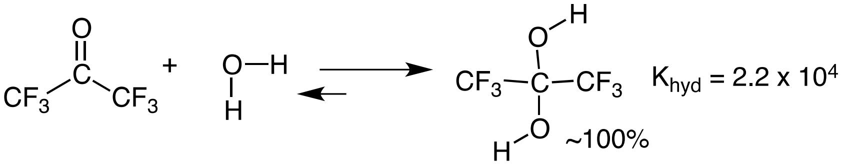
Steric hindrance in the product is not as severe as for acetone.



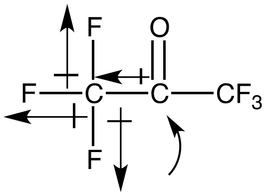
More hindered approach for the nucleophile.

Much more hindered product as the hybridization changes from sp^2 to sp^3 and the bond angles get smaller.

Which effect is more important, the steric effect or the electronic effect? To answer this question look at the K_{hyd} for hexafluoroacetone.



Carbonyl carbon is very electron deficient due to the strong elctron withdrawing effect of the two CF_3 groups.

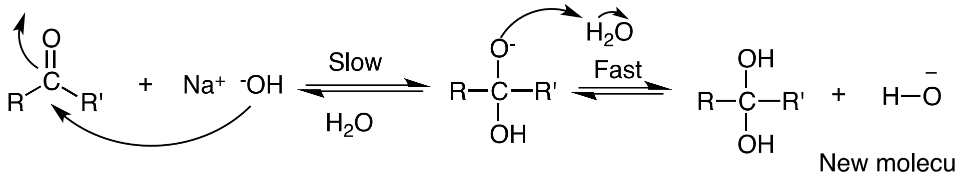


Fluorines are only slightly larger than hydrogen atoms, so the steric effect is only slighter larger in hexafluoroacetone than in acetone. This should dis-favor the hydrate formation but we see that the equilibrium constant for hydration is about 10^7 times larger. This is due to the strong electron withdrawing effect of the fluorines, making the carbonyl carbon in hexafluoroacetone very electron deficient and therefore very reactive.

The hydration reaction is catalyzed by both acid and base. Though the hydration reaction is not in itself an important reaction for synthesis, the mechanism of the hydration reaction in both acid and base is very important. It involves fundamental steps that we will see again in subsequent reactions of carbonyls.

Base catalyzed hydration:

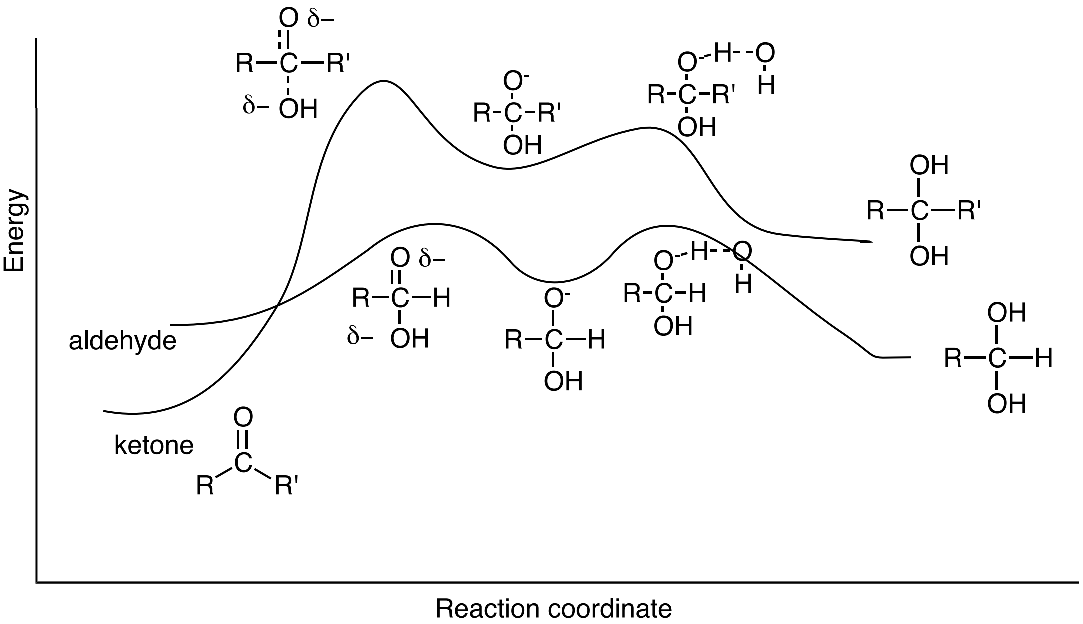
In basic hydrolysis we have a good nucleophile, -OH, and this attacks the carbonyl directly to give a tetrahedral intermediate. The hydroxide is a much better nucleophile than neutral water and so it speeds up this slow step. The alkoxide anion then gets a proton from water in a very fast step. This regenerates a new molecule of hydroxide so the hydroxide is not used up in the reaction.



Good nucleophile, direct attack on carbonyl.
This is the slow step. Protonation is very fast.

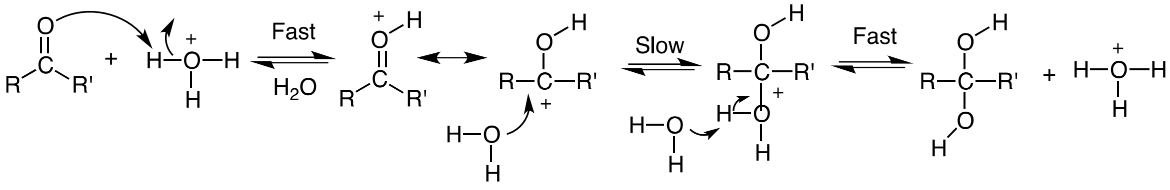
New molecule of
hydroxide is formed.

As we discussed above, aldehydes react faster than ketones. Alkyl groups at the reaction site increase the activation energy by both lowering the energy of the starting state (i.e. ketones are more stable than aldehydes) and by raising the energy of the transition state through steric crowding.



Acid catalyzed hydration:

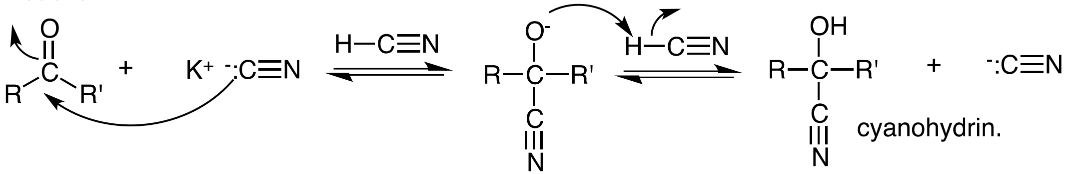
In acidic conditions, we cannot have any anions present. The strongest base (and strongest nucleophile) we can have is the neutral water. This is a weak nucleophile and will attack a neutral carbonyl very slowly. But in acidic condition we have extra protons available in the form of the hydronium cation, H_3O^+. This can give a proton to the carbonyl carbon to make it much more positive and much more electrophilic. Electron density is pulled from the C=O bond by the proton. The oxygen now has to share one of its lone pair with the proton. Note the resonance structure of the protonated carbonyl species in which there is a full (+) charge on the carbonyl carbon. The slow step is still the attack on the protonated carbonyl. Both proton transfer steps are fast. Note also that the hydronium ion, H_3O^+, is regenerated in the last step so that the overall reaction is catalytic in the acid.



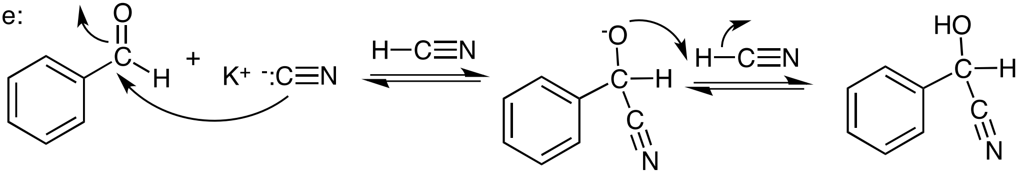
Cyanohydrin formation:

Cyanide anion can also attack a carbonyl to give, after protonation, a cyanohydrin. Cyanide anion is a strong nucleophile and attacks the carbonyl directly. These reactions are usually carried out by using a slight excess of the cyanide anion in acidic conditions. As the alkoxide is formed, it is protonated by hydrogen cyanide, a relatively weak acid (cyanic acid), to regenerate the cyanide anion.

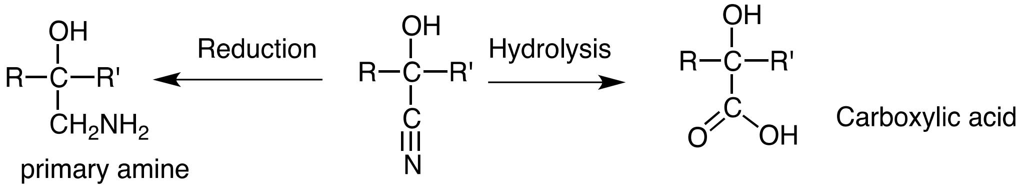
General Reaction:



Example:



Note that a new C-C bond is formed with the addition of one carbon. As we will see in later chapters, the cyano group (or nitrile) is a very useful intermediate and can be transformed into other functional groups, such as a primary amine through reduction or a carboxylic acid through hydrolysis in either basic or acidic conditions.

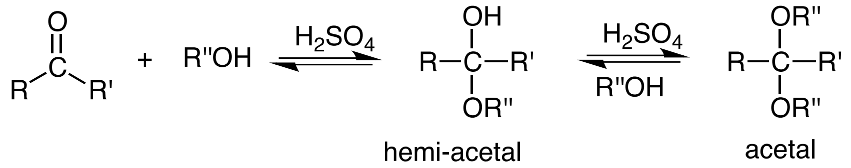


Acetal formation

Aldehydes and ketones when treated with alcohols in acidic conditions can be transformed into acetals, a new and very important functional group. Acetals are geminal diethers and like ethers are stable to the same variety of conditions. The reaction occurs by means of a hemi-acetal intermediate that is not stable and cannot be isolated. The hemi-acetal can return to the starting ketone or aldehyde (like the hydrate) to continue on to form the acetal.

It is important to note that the reaction does not occur in basic conditions.

General reaction:

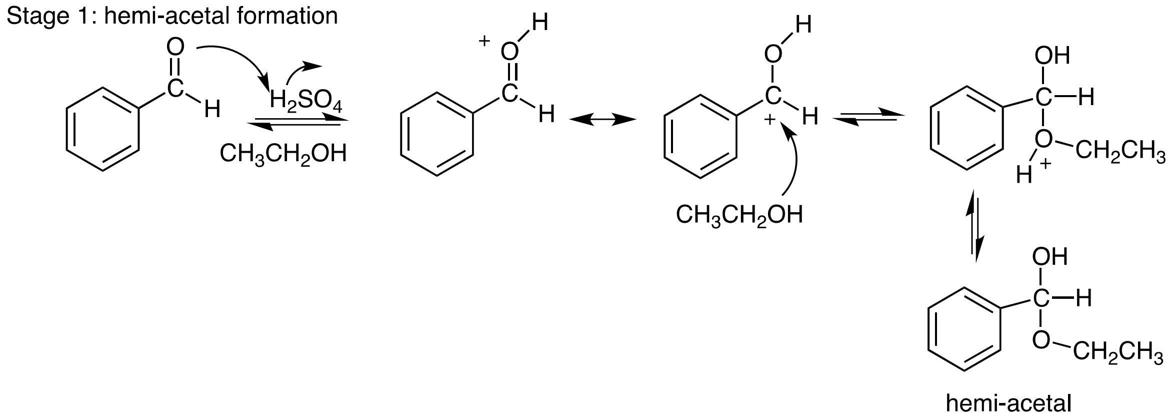


The overall mechanism is long and seems quite complex but it is actually just a series of the elementary reaction steps that we have already seen. It is useful to break the mechanism down into three parts or stages:

(1) Hemi-acetal formation: The mechanism for the formation of the hemi-acetal is identical to that for acid-catalyzed hydration except that instead of water, we have the alcohol as the nucleophile. Very often in acetal formation we use the alcohol as the solvent.

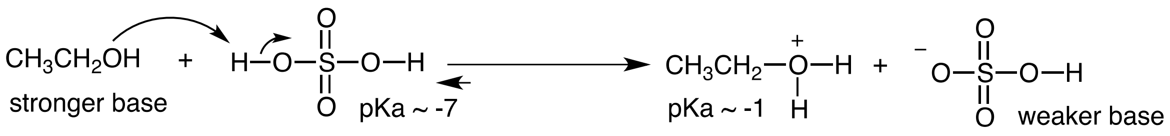
(2) Acid-catalyzed loss of water: this is just an S_N1 reaction of alcohols that we have already seen.

(3) Attack on the carbocation by the alcohol



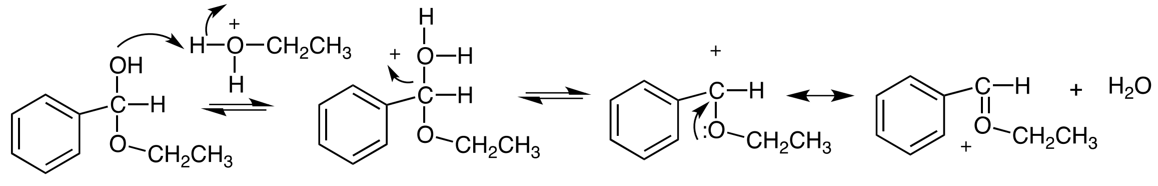
As we know, when we add H_2SO_4 to an alcohol such as ethanol, a proton is transferred from the H_2SO_4 to the ethanol. This is similar to the reaction that occurs when H_2SO_4 is added to H_2O. The reaction is very favorable thermodynamically and heat is given off. The alcohol or water is a much stronger base than the sulfate anion. Usually, for convenience, we do not show this reaction.

As we know, when we add H_2SO_4 to an alcohol such as ethanol a proton is transferred from the H_2SO_4 to the ethanol.



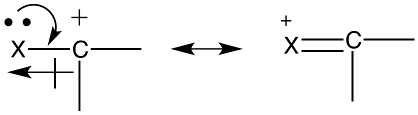
In stage 2 we protonate the alcohol to make it into a good leaving group. This is a fundamental principle that we learned in the first semester. Once it is protonated it can leave as neutral water to form a resonance stabilized carbocation.

Stage 2: loss of water



Resonance stabilized carbocation

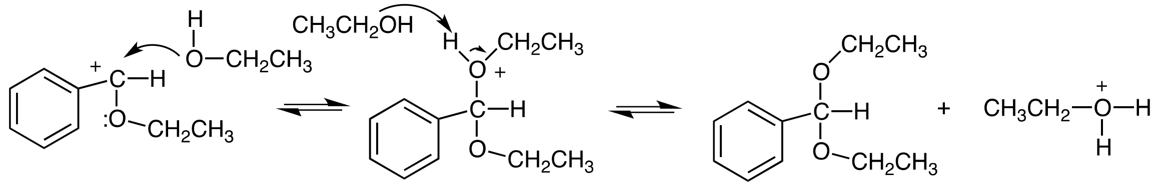
As a general rule, carbocations are stabilized by atoms that have a lone pair and can donate electrons.



X= O, N, S, I, Br, P, etc

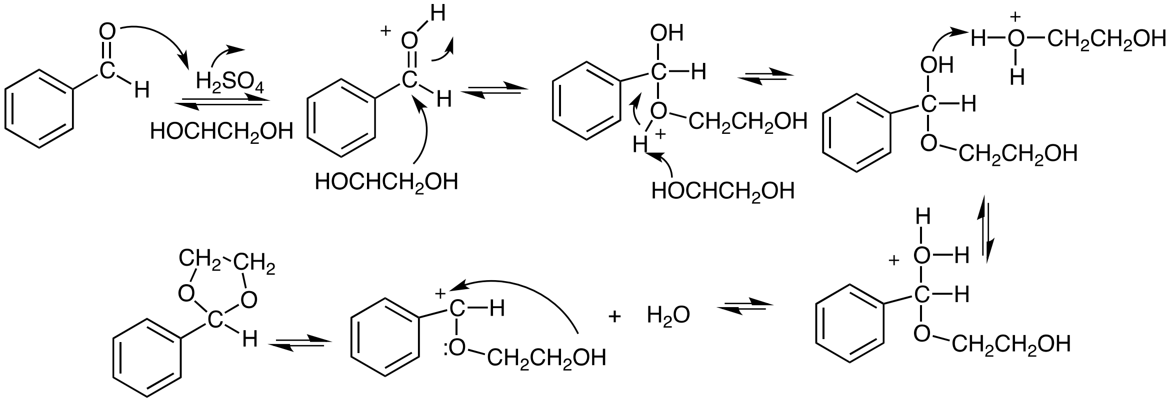
Note that there are two opposing forces operating here. The X group is more electronegative than carbon and so there is an inductive effect that withdraws electrons but there is a large resonance effect that donates electrons through the lone pair. This is the same reason that N and O containing groups are strong activating substituents on a benzene ring.

Stage 3: attack on the carbocation by the alcohol

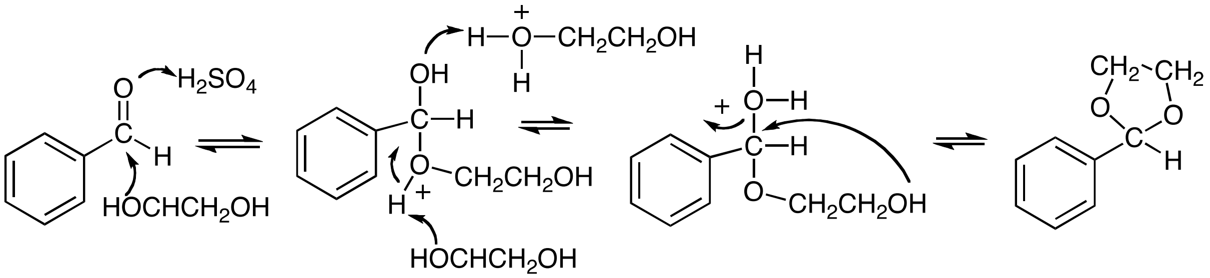


It is important to note that all steps in this reaction are reversible and as we will see we can also cleave acetals in aqueous acid. For acetal formation we drive the equilibrium to the right by using an excess of alcohol and/or removing the water as it is formed. For most aldehydes the equilibrium is favorable for acetal formation as long as an excess of alcohol is used but for most ketones it is unfavorable and we must try to remove water as it is formed. One way to do this is by distillation but this is not feasible with small molecular weight alcohols like methanol or ethanol since they have lower boiling points than water.

One way to solve this problem is to use a 1,2- or 1,3-diol. These will form cyclic 5- and 6-membered ring acetals. These form more easily than acyclic acetals and the equilibrium is more favorable since the addition of the second equivalent of the alcohol is an intramolecular reaction. Intramolecular reactions, when they form 5- and 6-membered rings, are always more favorable from an entropy considerations and also because the effective concentration of the nucleophilic alcohol is much higher since it is tethered close to the reactive site.



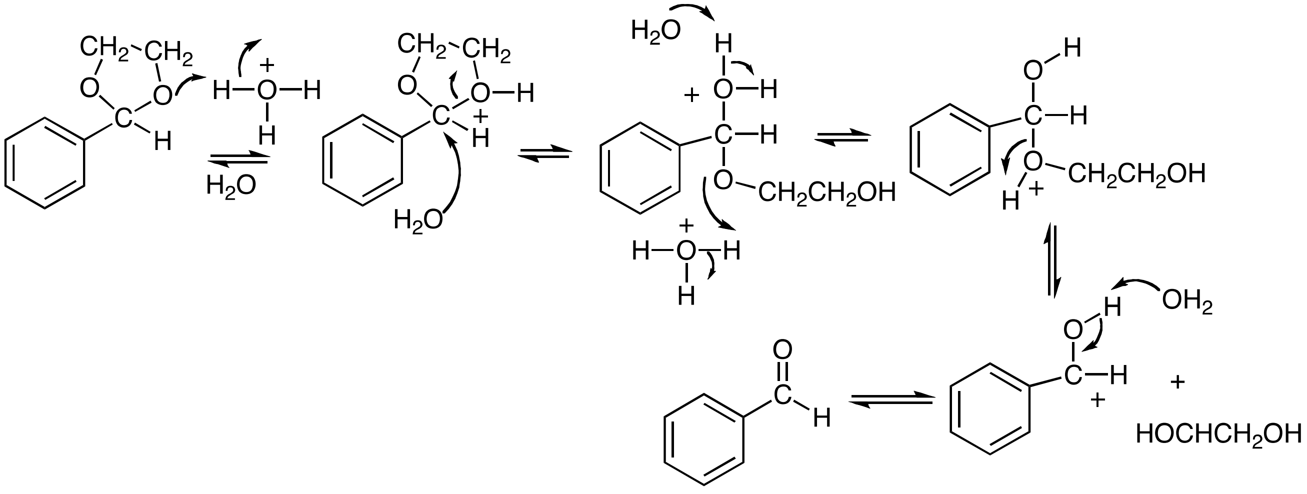
This is the complete mechanism where each step is written out. We can re-write this same mechanism is a shortened form to save time and writing. This version is shown below.



Again, this is the same mechanism but it is showing two steps happening at once. You are welcome to use this shortened form but do not attempt to shorten it further.

Acetal cleavage:

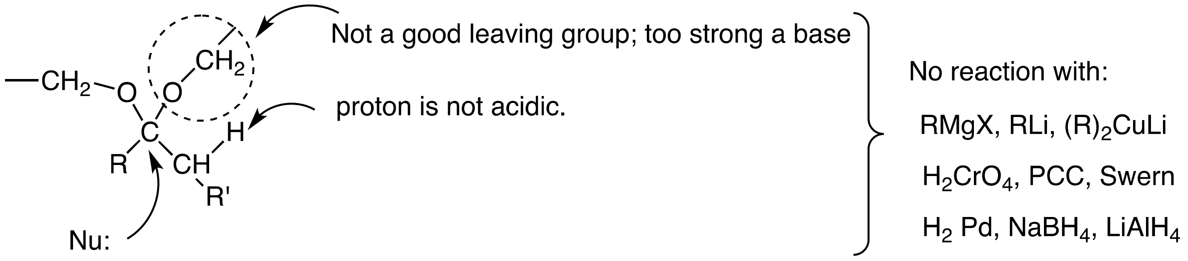
Acetals are cleaved when heated in dilute aqueous acid. The mechanism is the exact reverse of acetal formation.



To drive the equilibrium in favor of acetal cleavage, use an excess of water.

Acetals as Protecting Groups.

Acetals are very important protecting groups for ketone and aldehyde carbonyl groups. Like ethers they are stable to (1) strong bases (2) nucleophiles (3) reducing agents (4) oxidizing agents. And they are easily removed in dilute aqueous acid.



Not a good leaving group; too strong a base

proton is not acidic.

No reaction with:

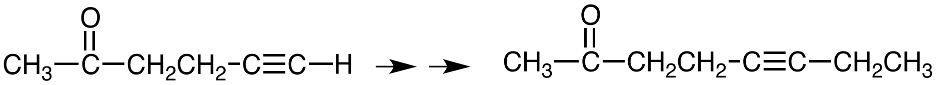
RMgX, RLi, $(R)_2CuLi$

H_2CrO_4, PCC, Swern

H_2 Pd, $NaBH_4$, $LiAlH_4$

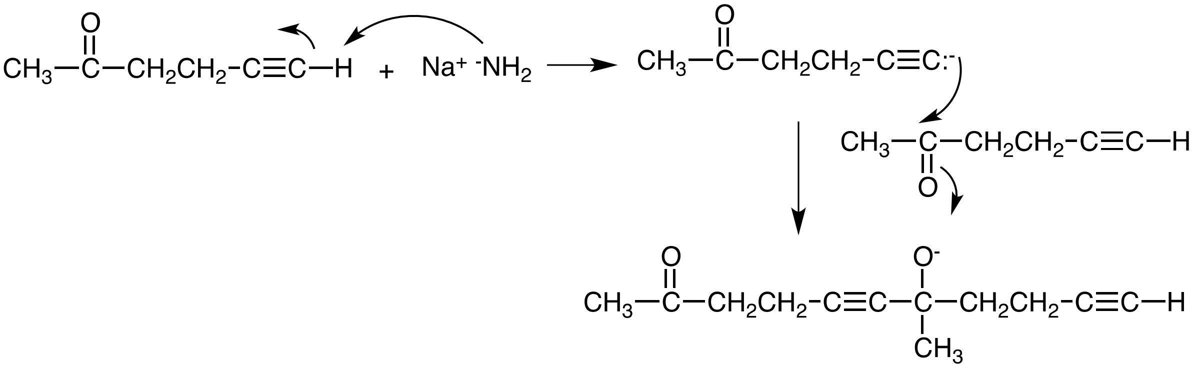
So we can put on an acetal to protect a sensitive carbonyl group in an aldehyde or ketones that does react with all of these reagents and then remove it when we are done.

For example, say we want to do the following synthesis:

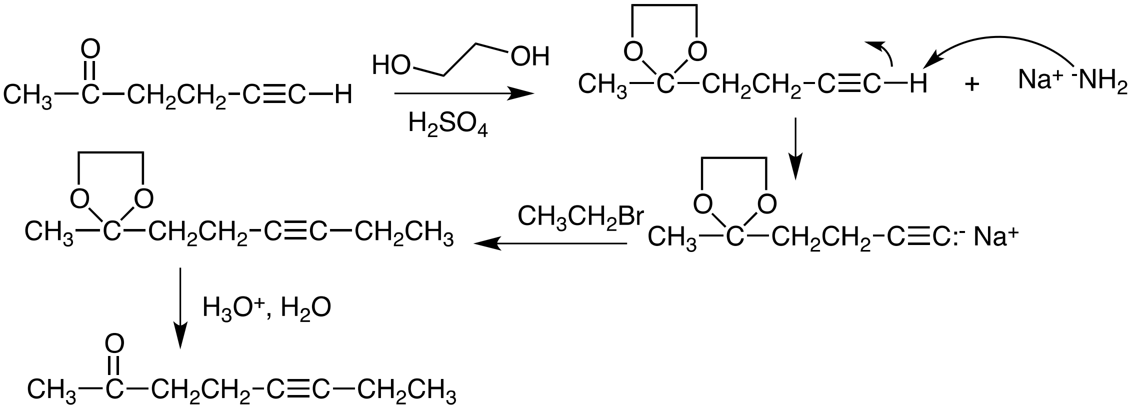


$$CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2CH_2-C\equiv C-H \longrightarrow\longrightarrow CH_3-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2CH_2-C\equiv C-CH_2CH_3$$

We know that we can remove the proton on the acetylenic carbon to form the nucleophilic acetylide anion if we use a strong enough base and then alkylate with ethyl bromide. The problem, however, is that the acetylide anion is a good nucleophile and would also react with the carbonyl group as shown below.

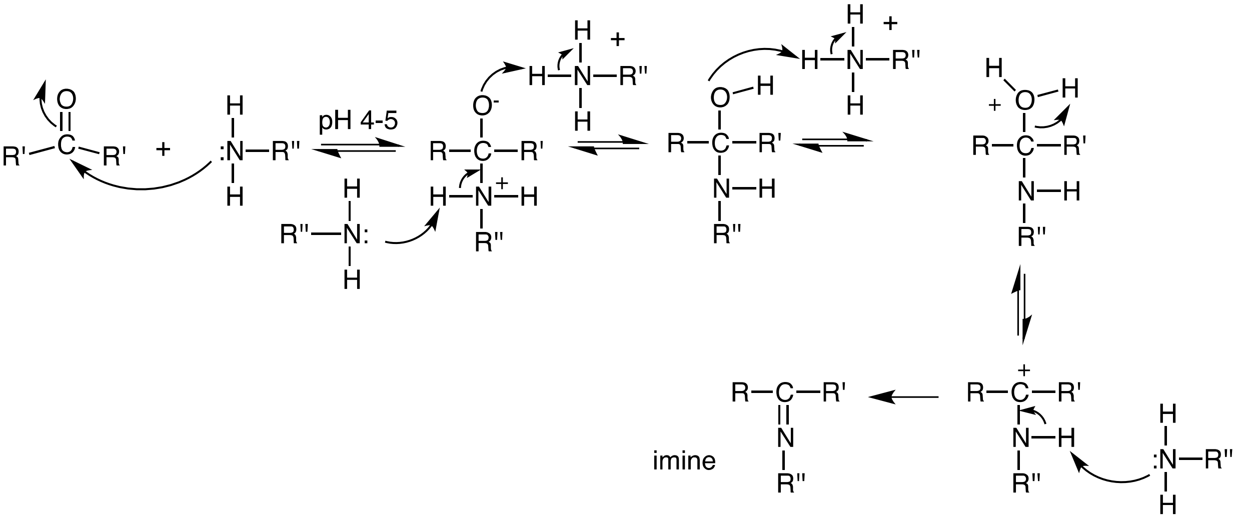


Clearly we have to protect the carbonyl as the acetal before we deprotonate. Then we alkylate and deprotect.

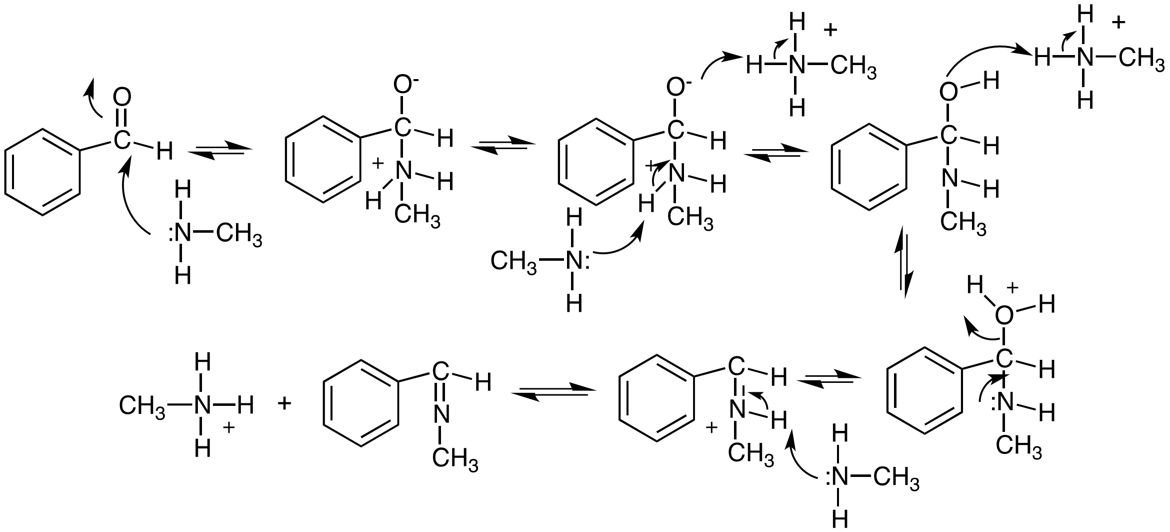


Reaction of Carbonyls with Primary Amines: Imines

Primary amines will also attack carbonyls. Dehydration (loss of water) from the initial tetrahedral adduct then gives an imine that has a C=N bond in place of the C=O bond. Generally the reaction is done at pH 4-5 so have a slightly acidic solution in order to provide enough protons to facilitate the dehydration step. As we know, protonating an OH group makes it into a much better leaving group.



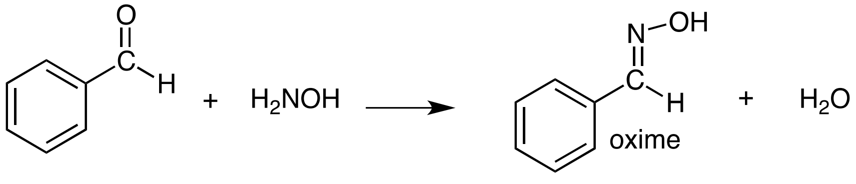
Example:



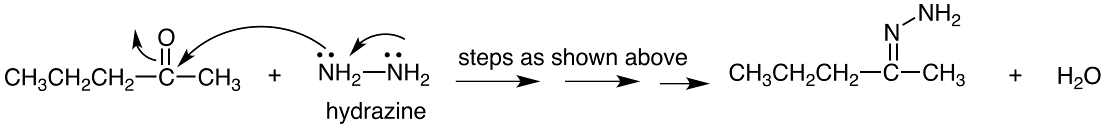
The dehydration is the rate-determining step when the reaction is carried out in acidic conditions. But you do not want too much acid since the amine would be fully protonated, making it into a weak nucleophile and making the first step very slow. Therefore, the optimum pH is around 5. At this pH there is some acid present to aid in protonating the hydroxyl group for dehydration but not enough to fully protonate all of the amine.

There are a variety of derivatives of amines that also form imine-like derivatives. Some important ones are:

(1) Hydroxyl amines, H_2NOH, react with ketones and aldehydes to form oximes.



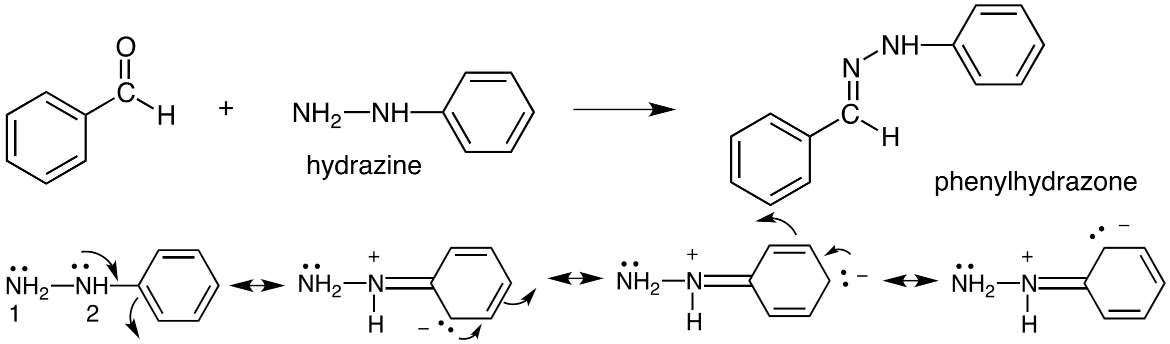
(2) Hydrazine, NH_2NH_2, reacts with aldehydes and ketones to form hydrazones. Hydrazine is an excellent nucleophile, much more reactive than ammonia, NH_3, since the lone pair on one nitrogen donates electron density to the other nitrogen.



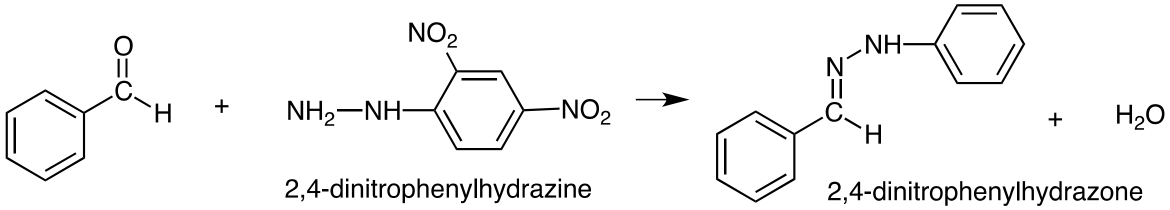
The lone pair on one nitrogen donates to the other nitrogen to increase the lectron density and to make it a better nucleophile. Another reason for the enhanced reactivity of hydrazine is relief of the electron-electron repulsion between the two adjacent lone pairs.

(3) Phenylhydrazine reacts with ketones and aldehydes to form phenylhydrazones. Notice that the phenylhydrazine reacts at N1, the nitrogen away from the benzene ring, since it is less hindered and much more electron-rich. The nitrogen lone pair is partially delocalized

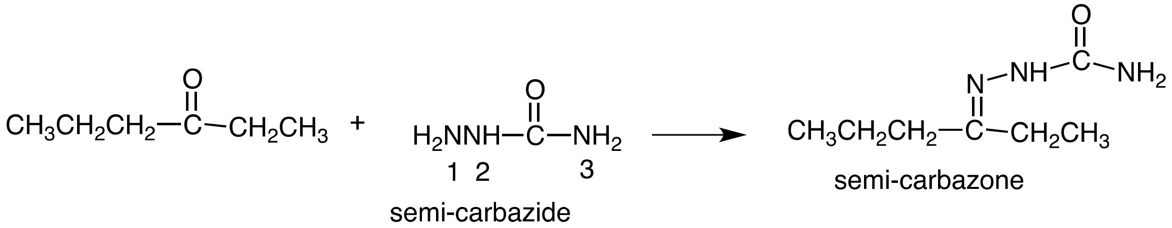
onto the benzene ring.



Substituted phenylhydrazine derivatives such as 2,4-dinitrophenylhydrazine form similar derivatives. The 2,4-dinitrophenylhydrazone derivatives are invariably solids and by means of their melting points can be used to identify particular aldehydes or ketones.

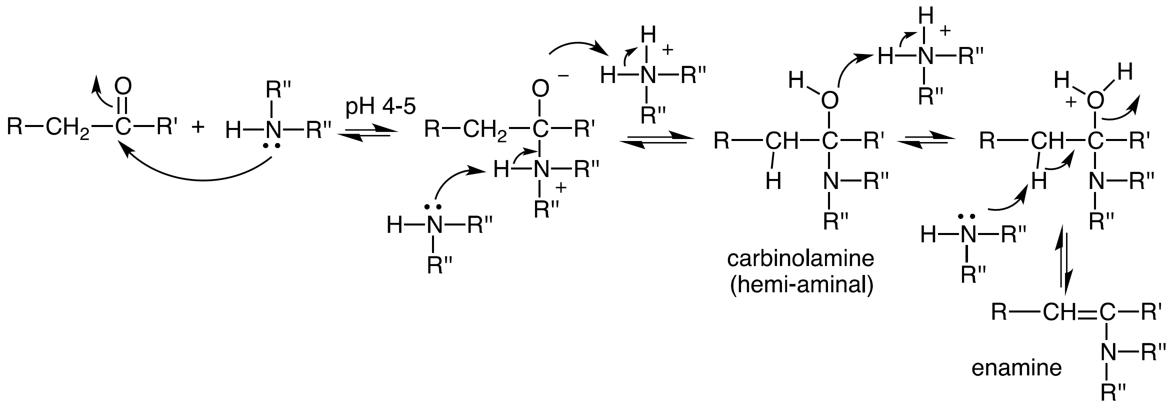


(4) Semi-carbazide reacts with aldehydes and ketones to give semi-carbazones. Note that reaction occurs on N1 since it is the most electron rich and least hindered nitrogen. The carbonyl is a strong electron withdrawing group that deactivates the lone pair of the directly attached nitrogens.

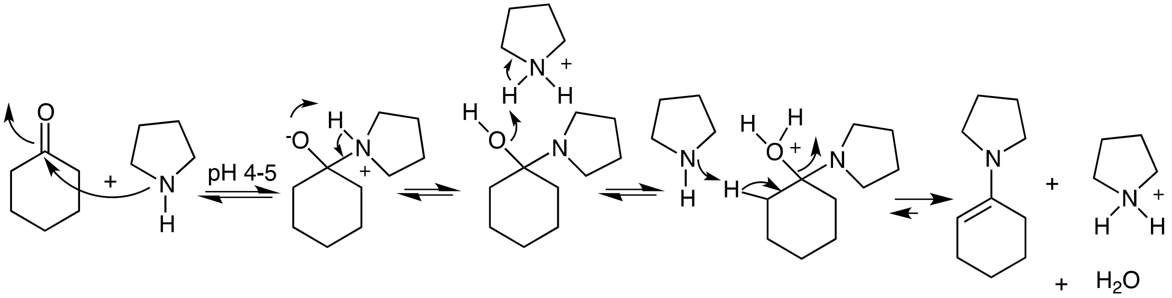


Reactions with Secondary Amines: Enamines

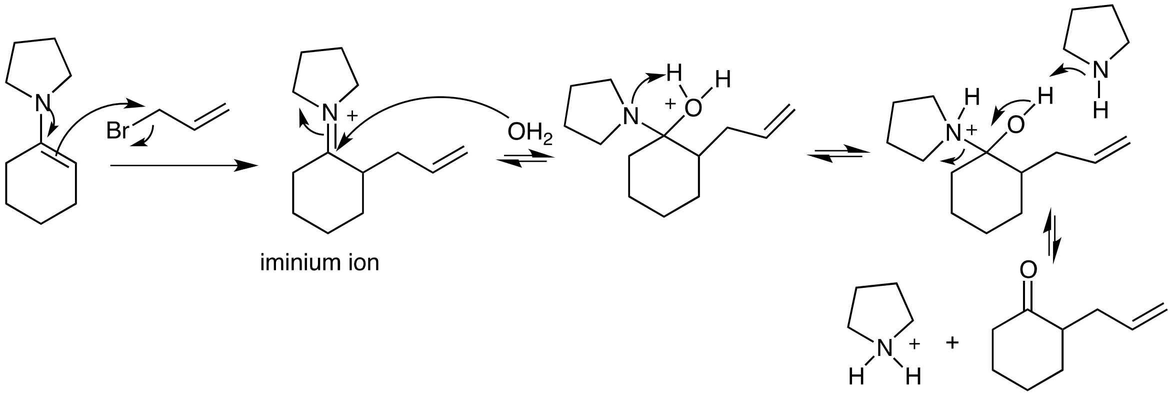
Secondary amines react with ketones and aldehydes to form enamines in which there is a C=C bond formed next to the C-N bond. A secondary amine, of course, has only one hydrogen to lose and so can not dehydrate to form a C=N bond but can dehydrate by loss of a proton from an alpha-carbon. This carbon must have at least one hydrogen.



A very convenient secondary amine to use is pyrrolidine. This is a cyclic secondary amine that is a liquid at room temperature and has a moderate boiling point so that any excess reagent can be easily removed by distillation.



Enamines are very useful compounds in organic synthesis since they are mild nucleophiles and undergo a variety of useful reactions. For example, they can be alkylated under mild conditions and then on addition of water they can be hydrolyzed to give back the original aldehyde or ketone. The whole sequence can be carried out in one pot as a single operation. This chemistry was developed by the great Belgian chemist, Gilbert Stork, working at Columbia University.

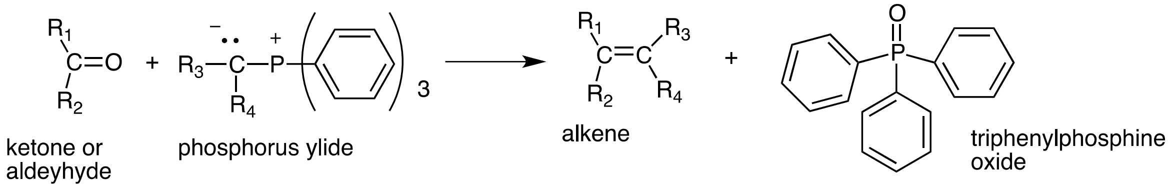


Wittig Reaction

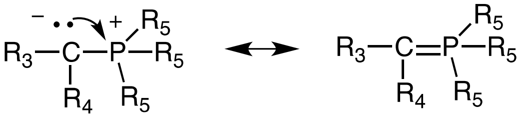
The eponymous Wittig reaction was developed by the German chemist, Georg Wittig while working at Göttingen University in Germany. He received the Nobel Prize for this work in 1979.

The Wittig reaction uses phosphorus stabilized anion, called the phosphorus ylide, as the nucleophile to attack a carbonyl to form a new C-C bond. What is unique about the Wittig reaction is that the phosphorus then acts as a dehydrating agent to make a new C=C bond. The overall reaction is thermodynamically favorable since a very strong P=O bond is being formed. The P=O bond is estimated to be > 130 Kcal/mol or 540 KJ/mol.

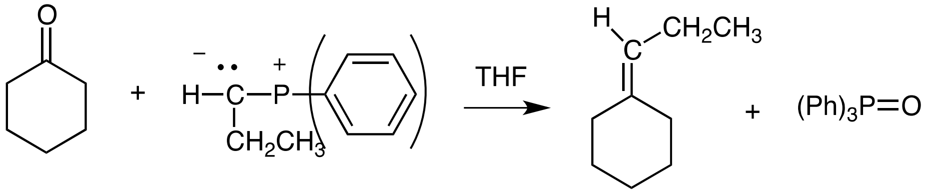
Overall Reaction:



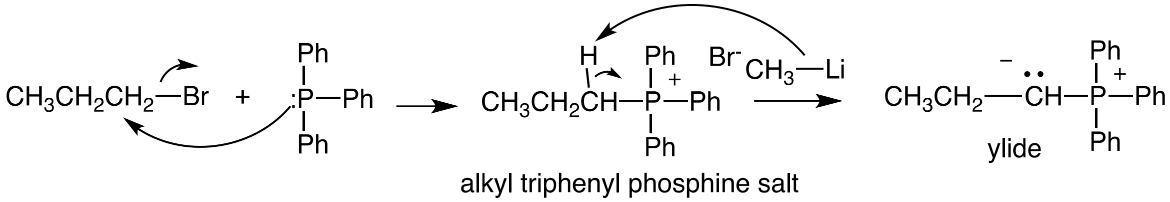
An ylide is a species which has adjacent positive and negative charges on atoms that each have an octet of electrons. It is stabilized by resonance but acts as a nucleophile at carbon.



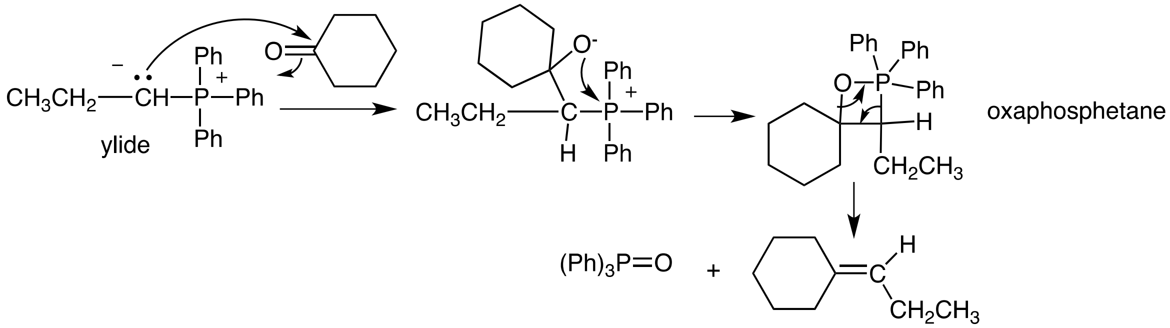
For example:



The phosphorus ylide is not a stable species and is generated *in situ* by the deprotonation of a phosphonium salt using a strong base. The phosphonium salt is made and isolated in a separate step by stirring an alkyl halide with a phosphine derivative. This is called the Arbuzov reaction and is shown below. Typically, triphenyl phosphines are used, since they are air stable solids that are easy to work with, but others are possible and sometimes alkyl phosphites are used (see below) in a modification of the original Wittig reaction. The positively charged phosphine acts as a strong electron-withdrawing group. This allows deprotonation of the attached carbon. A strong base such as methyl lithium is needed. Another commonly used base is sodium hydride in dimethyl sulfoxide (NaH in DMSO).



Again, the ylide is generated *in situ* and then the ketone or aldehyde is added to the reaction mixture, maintained at low temperature to avoid decomposition of the sensitive ylide. As we know, aldehydes are more reactive than ketones and the attack of the ylide is sensitive to steric hindrance. It is not possible to make tetra-substituted alkenes by means of the Wittig reaction but tri-substituted alkenes are possible. The mechanism is shown below.

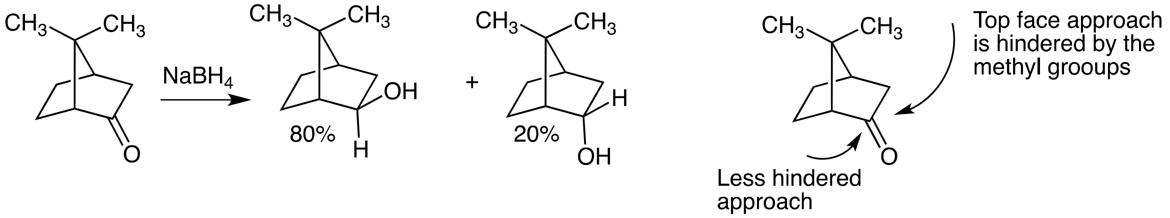


Due to the geometry of the oxaphosphetane intermediate, the less stable Z-alkene is usually obtained, though the stereochemistry of the double bond can usually be controlled thorough choice of reagents.

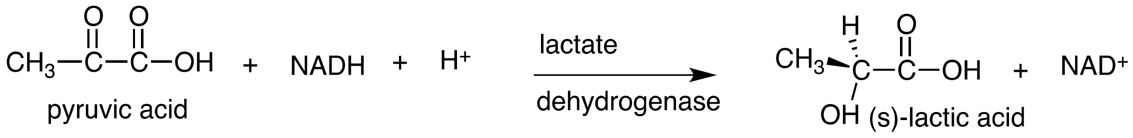
When there is an electron-withdrawing group on the ylide next to the carbanion, a more reactive phosphorus reagent is needed. This is typically a trialkyl phosphite. This is called the Wadsworth-Horner-Emmons modification. Stabilized ylides typically give the more stable E-alkene.

Stereoselective Addition to Carbonyls

Addition to carbonyls can give a mixture of isomers but often the direction of attack is controlled by steric factors. The nucleophile often approaches form the less hindered face.



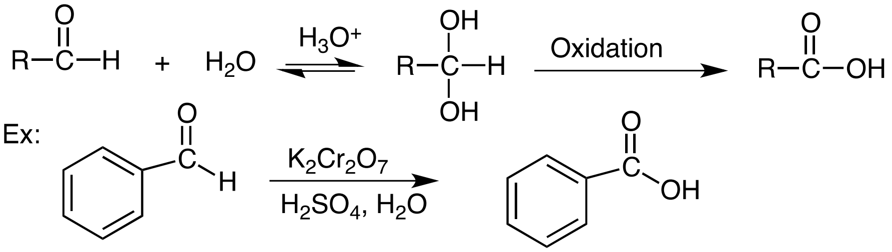
Enzymes can reduce carbonyls and are usually very stereoselctive. For example, the reduction of pyruvic acid by lactate dehydrogenase give exclusively (s)-(+)-lactic acid.



$$\mathrm{CH_3{-}\overset{\overset{\large O}{\|}}{C}{-}\overset{\overset{\large O}{\|}}{C}{-}OH + NADH + H^+ \xrightarrow[\text{dehydrogenase}]{\text{lactate}} CH_3{-}\overset{H}{\underset{OH}{C}}{-}\overset{\overset{\large O}{\|}}{C}{-}OH + NAD^+}$$

Oxidation of Aldehydes

Aldehydes are readily oxidized to carboxylic by a variety of reagents including chromic acid in aqueous solution. The reaction is similar to the oxidation of alcohols and in order to form the necessary chromate ester, the aldehyde must be in the hydrated form.

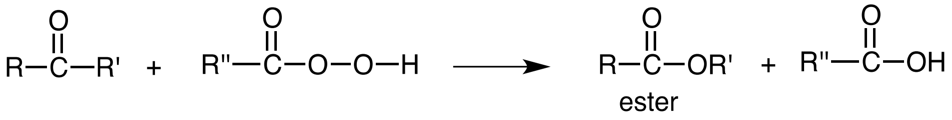


$$\mathrm{R{-}\overset{\overset{\large O}{\|}}{C}{-}H + H_2O \overset{H_3O^+}{\rightleftharpoons} R{-}\overset{OH}{\underset{OH}{C}}{-}H \xrightarrow{\text{Oxidation}} R{-}\overset{\overset{\large O}{\|}}{C}{-}OH}$$

Many reagents are capable of performing this oxidation including silver oxide (AgO). It even occurs slowly in air (O_2).

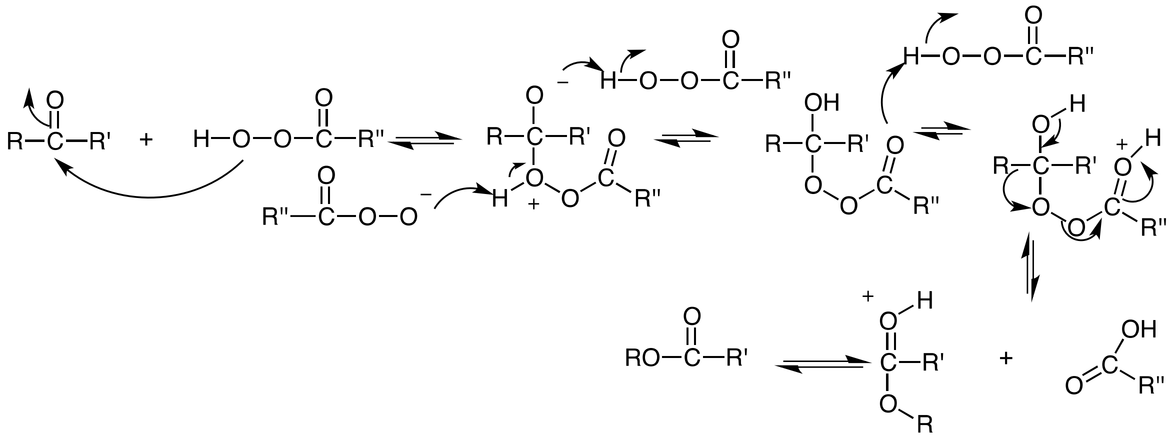
Oxidation of Ketones to Esters: Baeyer-Villiger Oxidation

Ketones, when treated with peroxyacids, RCOOOH, are oxidized to esters.



$$\mathrm{R{-}\overset{\overset{\large O}{\|}}{C}{-}R' + R''{-}\overset{\overset{\large O}{\|}}{C}{-}O{-}O{-}H \longrightarrow \underset{\text{ester}}{R{-}\overset{\overset{\large O}{\|}}{C}{-}OR'} + R''{-}\overset{\overset{\large O}{\|}}{C}{-}OH}$$

Methyl ketones give esters of acetic acid. The oxygen is inserted between the carbonyl carbon of th larger of the two groups attached to it. This occurs by means of a rearrangement reaction in which the larger – and therefore more electron rich – alkyl group migrates to an oxygen with synchronous cleavage of the weak O-O bond.



These reactions are very useful with cyclic ketones to give lactones (cyclic esters) that are one atom larger. This is a ring expansion reaction.