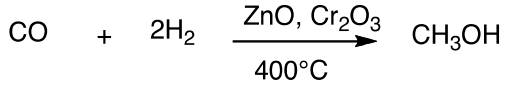
Chapter 16
Alcohol, Diols, Thiols

Alcohols are a very important functional group, which we have already seen in previous chapters. In this chapter we will review previous material and see some new ways to make alcohols (**reduction of aldehydes, ketones and carboxylic acids**) and new reactions of alcohols including **oxidation of primary and secondary alcohols.**

Sources of Alcohols

Methanol used to be produced from wood as a by-product in the production of charcoal (hence the name 'wood alcohol') but now most of it is produced by reduction of CO in the presence of H_2O.

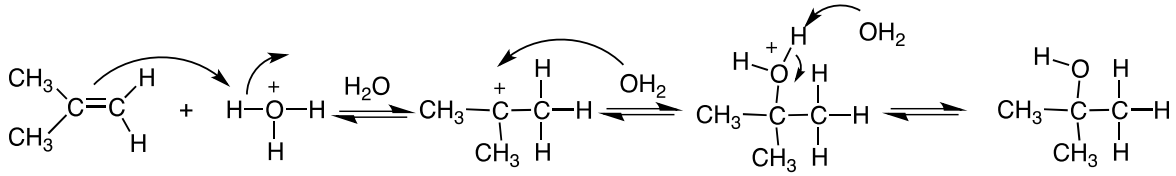


Methanol is used to make formaldehyde, which is used in resins and plastics, and to make MTBE (*t*-butyl methyl ether), which is an important additive in gasoline. Methanol is also used as a fuel. It is highly poisonous to humans, causing blindness and death.

Ethanol is formed from carbohydrates by fermentations by action of the enzymes in yeast. The maximum concentration achievable by fermentation is about 15%, since higher concentrations will kill the yeast. It is produced commercially by hydration of ethylene and from agro-products for use as fuel.

Review of Methods for Alcohol Preparation

(1) Acid-catalyzed hydration of alkenes

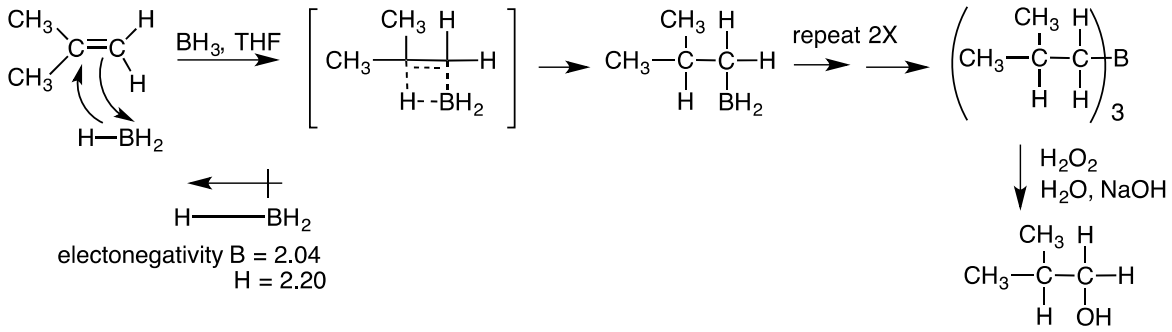


The nucleophilic π-electrons on the double bond attack the proton on H_3O^+ to form the more substituted – and more stable – carbocation as predicted by Markovnikov's rule (the proton adds to the carbon with the most H's). In the second step water attacks the carbocation and in a third, fast step the extra proton on the water is transferred to another molecule of water to regenerate the H_3O^+.

As we know, this reaction is fully reversible because we can dehydrate alcohols to alkenes using acidic conditions. We drive the equilibrium in favor of hydration by using an excess of water and we drive the equilibrium in favor of hydration by using anhydrous conditions (H_2SO_4) and removing the water as it is formed.

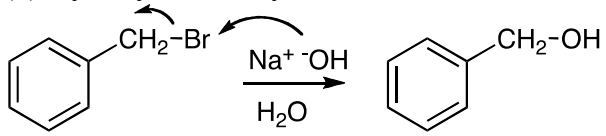
Note that we form the more substituted alcohol. To form the less substituted alcohol we use hydroboration/oxidation.

(2) Hydroboration/oxidation



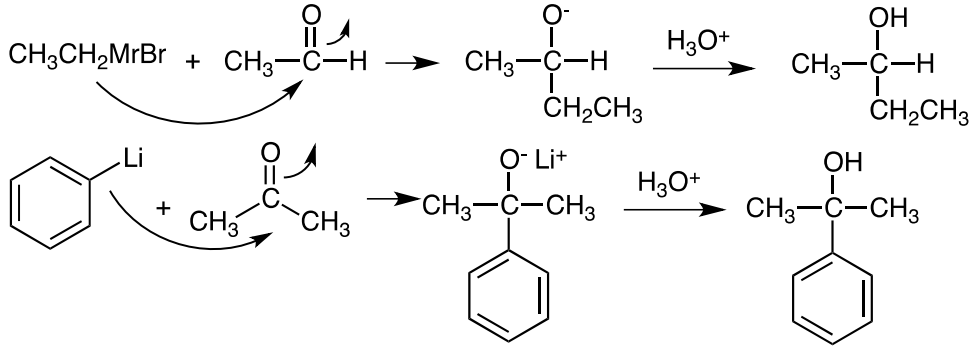
Here we get the opposite regiochemistry, which we usually describe as the anti-Markovnikov product. But is we re-phrase Markovnikov's rule into a broader statement – **the electrophile adds to the alkene so as to form the more stable carbocation** – then we see that this actually follows the rule. Here the electrophile is boron, since the hydrogen is more electronegative (2.20 v. 2.04) and so the boron has a partial plus charge and the hydrogen has a partial negative charge. The addition occurs in one step in a concerted fashion so we see syn addition. Then the boron is replaced stereospecifically to give the less substituted alcohol.

(3) Hydrolysis of Alkyl Halides



This is a simple S_N2 reaction and is most useful for primary alkyl halides or tosylates. With secondary and tertiary alkyl halides we would see mainly elimination reactions.

(4) Reaction of Grignard and organolithium reagents with aldehydes and ketones.

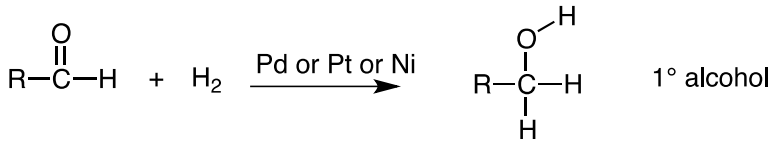


New Methods for Alcohol Formation

Reduction of Aldehydes and Ketones:
We will look at three reagents for the reduction of aldehydes and ketones: (a) catalytic hydrogenation (b) sodium borohydride and (c) lithium aluminum hydride.

(a) Catalytic hydrogenation
Use of hydrogen gas, H_2, with a catalyst such as Pd or Pt or Ni results in the reduction of aldehydes and ketones and recall from Chem. 121 that it will also reduce alkenes and alkynes.

Reduction of aldehydes gives primary alcohols.



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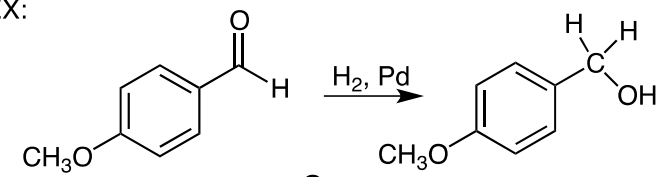
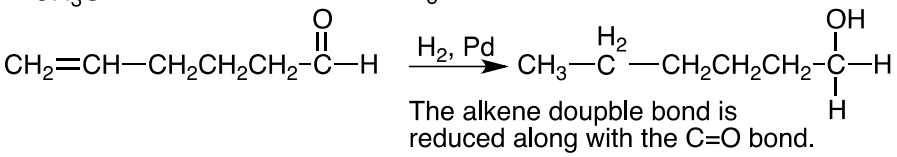
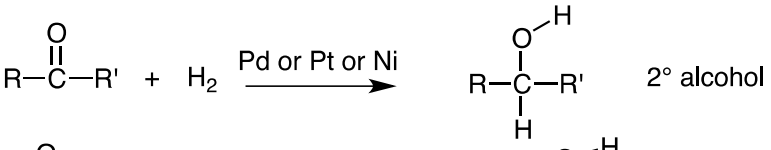
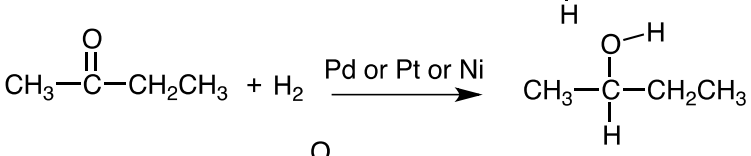


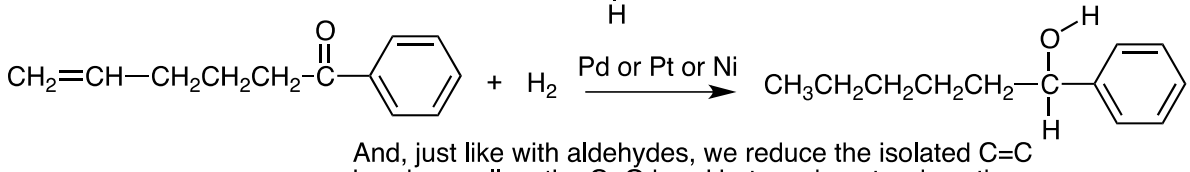


The alkene doupble bond is reduced along with the C=O bond.

Reduction of ketones gives secondary alcohols.

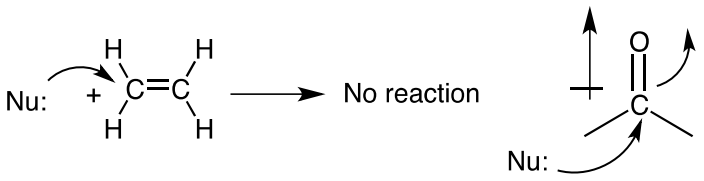




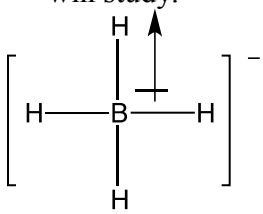


And, just like with aldehydes, we reduce the isolated C=C bond as well as the C=O bond but we do not reduce the benzene ring under these conditions.

To reduce the carbonyl C=O bond without reducing the C=C bond we need to use a polar reducing agent such as sodium borohydride or lithium aluminum hydride. Both of these reagents, as the name suggests, deliver the hydride atom, $H:^-$, which is a strong base and good nucleophile. As we know nucleophiles do not attack unactivated C=C bonds because there is no dipole moment.

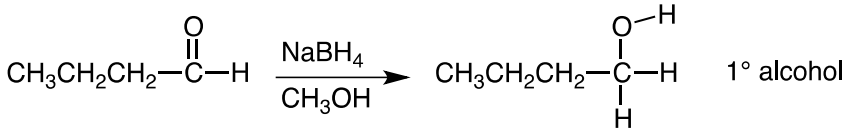


Look at sodium borohydride ($NaBH_4$) first. It is the milder of the two hydride reagents we will study.

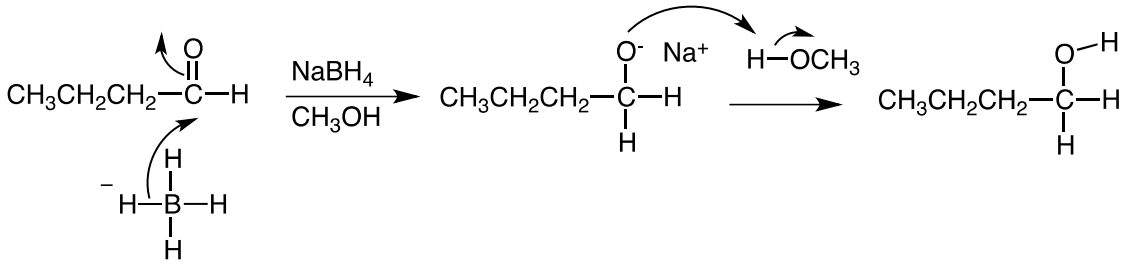


Hydrogen (2.1) is more electronegative than boron (2.0) and so the B-H bond is polarized toward the hydrogen, giving it a partial negative charge. $NaBH_4$ is a source of $H:^-$ and so it is nucleophilic and attacks the partial (+) charge at a carbonyl carbon.

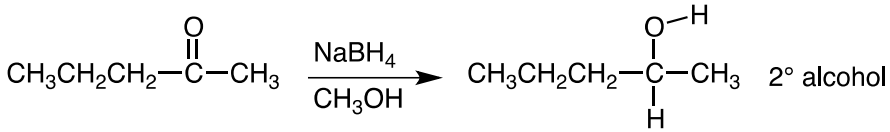
For example: With an aldehyde we get a primary alcohol just like with catalytic hydrogenation.



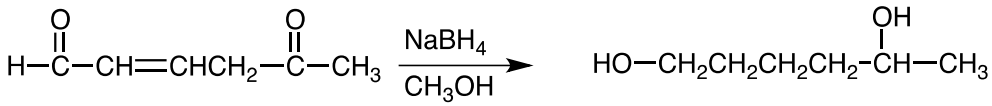
The mechanism for this reaction is shown below. It is similar to the Grignard reagent attack on carbonyls, though the $NaBH_4$, is a much weaker base. We can use CH_3OH as a solvent - it is even stable in water for a limited period of time - and this reagent provides the proton for the reduced oxygen in the second step.



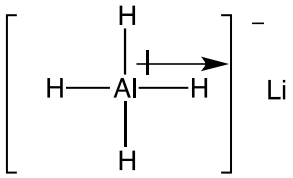
And with ketones, we get secondary alcohols.



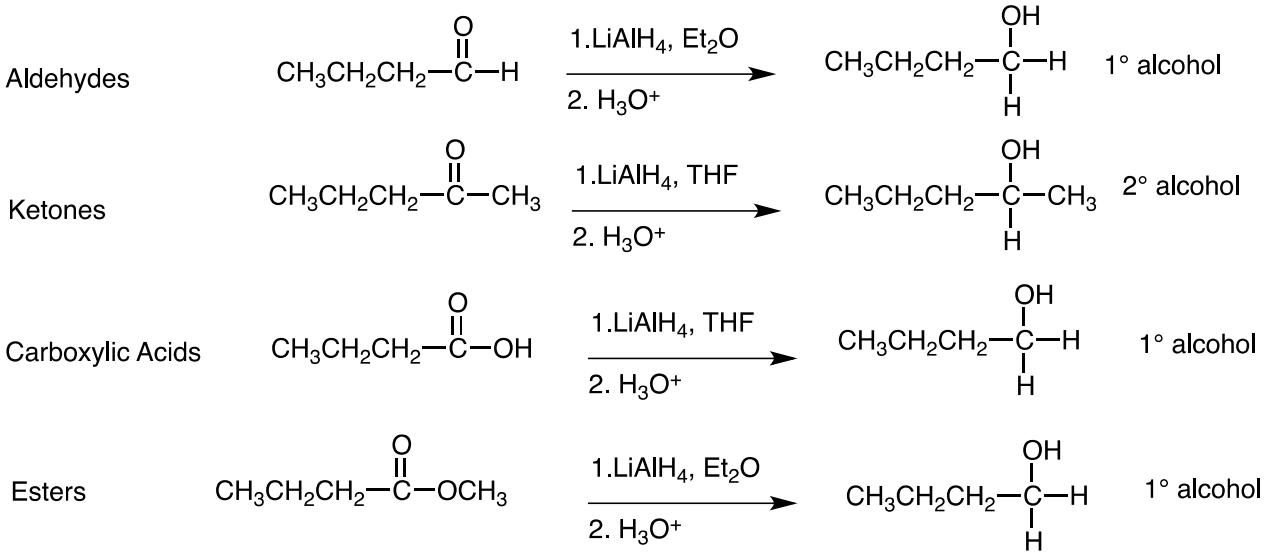
And, since $NaBH_4$ will not reduce alkenes or alkynes, we can selectively reduce aldehydes or ketones in the presence of alkenes or alkynes.



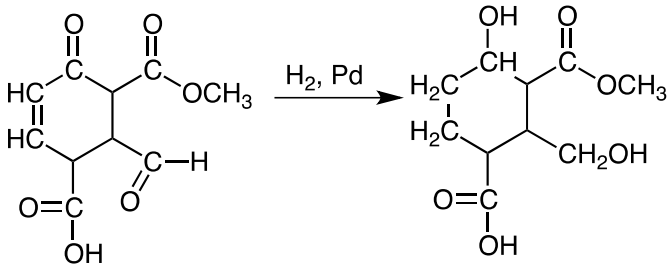
A stronger hydride reducing agent is lithium aluminum hydride ($LiAlH_4$). It is much more reactive and will reduce **ALL** carbonyl compounds to alcohols. Aluminum is right below boron in the periodic table in the same column and so it is more electropositive than boron Al = 1.5 v. B = 2.0). Therefore, the Al-H bond is even more polarized than in $NaBH_4$.



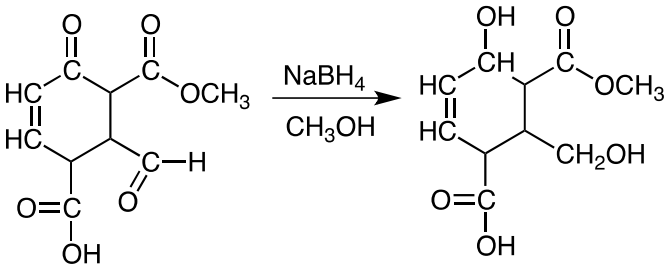
Ketones give secondary alcohols. Aldehydes, carboxylic acids and esters all give primary alcohols. We must use non-protic solvents such as diethyl ether or THF with $LiAlH_4$ since it reacts very exothermically with alcohols and water to give H_2 gas. Like $NaBH_4$, $LiAlH_4$ will not reduce double or triple bonds. The reactions for $LiAlH_4$ are shown below. Note that the proton on the alcoholic oxygen comes from the work up in aqueous acid in a separate step.



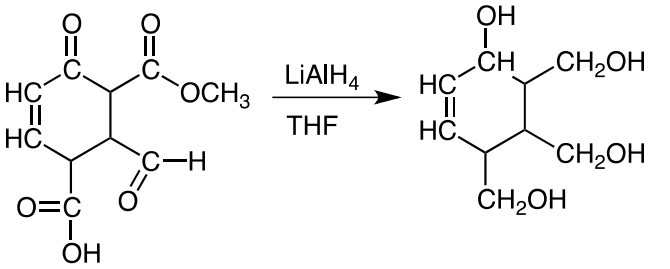
We now have three reducing agents with different reactivities so we can selectively reduce one functional group in the presence of an another functional group with a different reactivity.



With cat. hydrogenation we reduce the ketone, the aldehyde and the double bond but do not reduce the ester or the carboxylic acid.



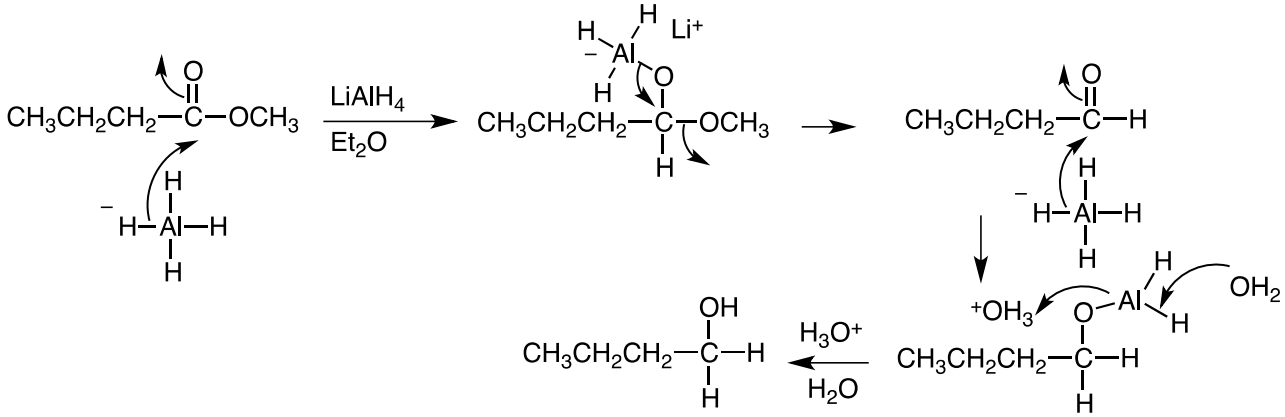
With sodium borohydride we reduce the ketone, the aldehyde but NOT the double bond, the ester or the carboxylic acid.



With lithium aluminum hydride we reduce the ketone, the aldehyde, the ester and the carboxylic acid but not but NOT the double bond.

The mechanism for ester and carboxylic acid reduction is shown below. Don't worry about the aluminum. It is a strong Lewis acid and binds to the oxygen anion in step one and step three and then is lost in the aqueous acidic workup when the alcoholic oxygen is protonated. The important thing to remember with carboxylic acids and esters is that two equivalents of the hydride ($H:^-$) are added and one of the oxygens is lost as HO^- or CH_3O^- to give a primary alcohol.

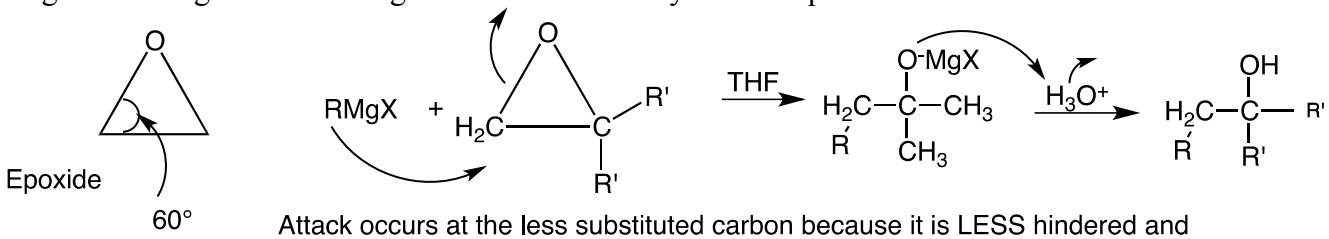
Since aldehydes are more easily reduced (we will learn why in a later chapter) than esters or carboxylic acids, we cannot isolate the aldehyde intermediate.



Alcohols from Epoxides

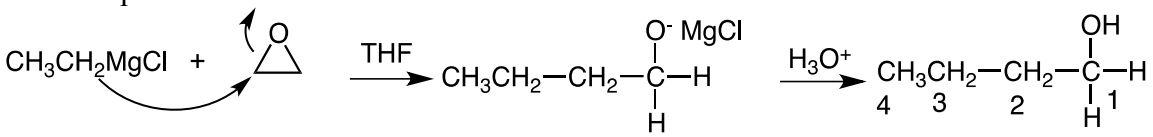
Epoxides are three-membered ring ethers and we will study them more extensively in the next chapter. For now, we should note that epoxides will react with Grignard reagents and organolithium reagents at the less substituted (and less hindered) carbon to give alcohols with formation of a new C-C bond.

As we will see, most do not react with ethers but epoxides are highly strained three-membered rings with bond angles of 60° and will undergo ring opening not only with Grignards or organolithium reagents but with a variety of nucleophiles.

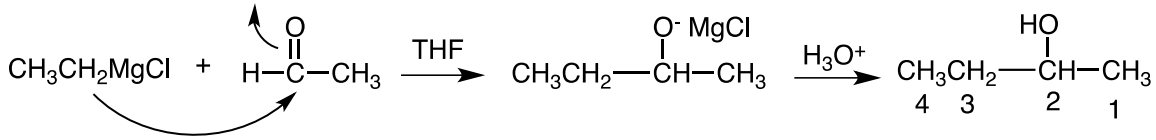


Attack occurs at the less substituted carbon because it is LESS hindered and more accessible to the nucleophile. Attack at the less substituted carbon by a nucleophile is faster than at the more substituted carbon and therefore forms the major product.

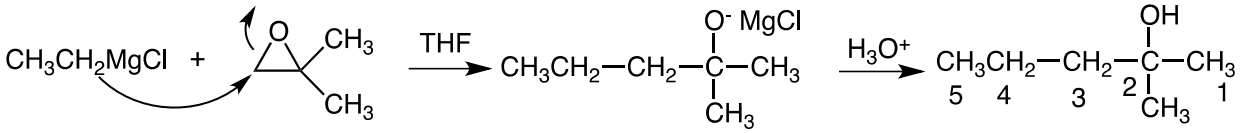
For example:



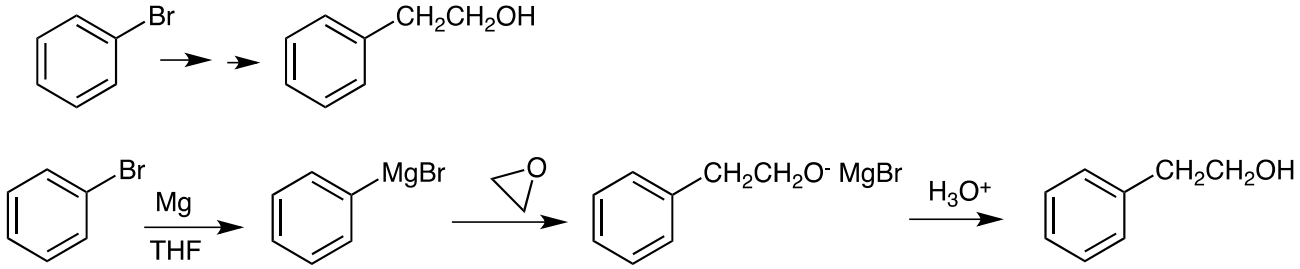
So we have added a two-carbon unit and the alcohol ends up on the second carbon away from the nucleophile, in this case carbon 1. Contrast this with the Grignard attack on an aldehyde or ketone. In this example the alcohol oxygen ends u on the carbon next to the Grignard, in this case carbon 2.



Another example:

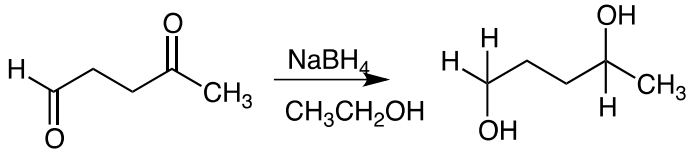


And a synthesis example:



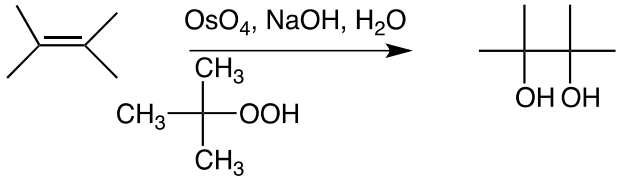
Preparation of Diols:

(1) Reduction of Carbonyls

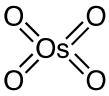


(2) To make vicinal or 1,2-diols use osmium tetraoxide in conjunction with a co-oxidant such as *tert*-butyl peroxide and aqueous base.

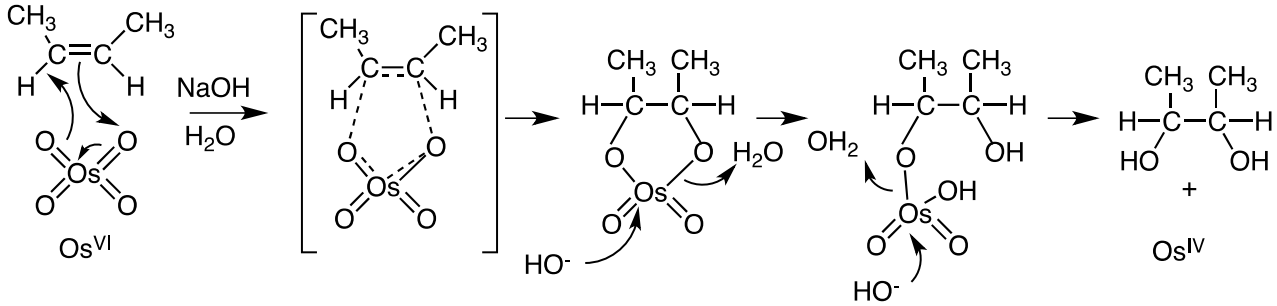
Overall Reaction



Lewis Structure of osmium teraoxide

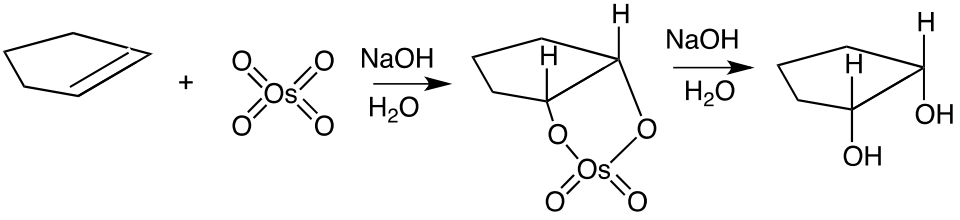


Mechanism of the addition/oxidation reaction



This is a concerted *syn*-addition with a cyclic transition state as shown. The intermediate is a cyclic osmate ester that is cleaved step-wise by the hydroxide ion in the aqueous solution. The oxygens of the diol are then protonated by water. The osmium VI of OsO_4 is reduced to Os IV and is reoxidized back to OsO_4 by the *tert*-butylperoxide.

It is important to note that since it is a concerted *syn*-addition, the two OH groups will end up *cis* to each other as in the examples below.



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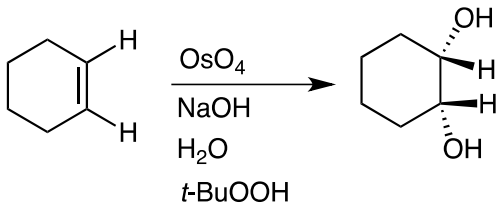


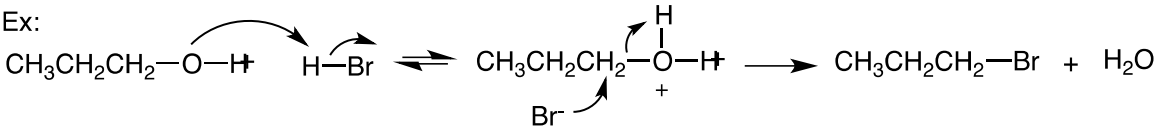
Reactions of Alcohols

Review of Previously Studied Reactions:

(1) Reaction with HX to make alkyl halides.

General reaction: $ROH + HX \longrightarrow RX + H_2O$

Ex:

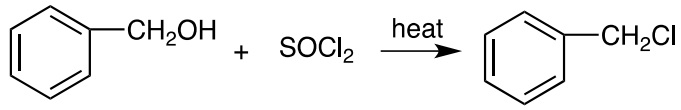


(2) Reaction with thionyl chloride to make alkyl chlorides.

This is a milder version of the reaction above and avoids the strongly acidic conditions above that can destroy sensitive organic functional groups.

General reaction: $ROH + SOCl_2 \longrightarrow RCl + SO_2 + HCl$

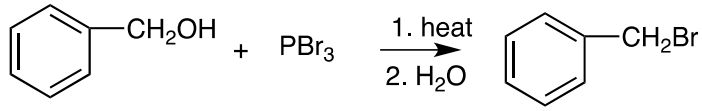
Ex:



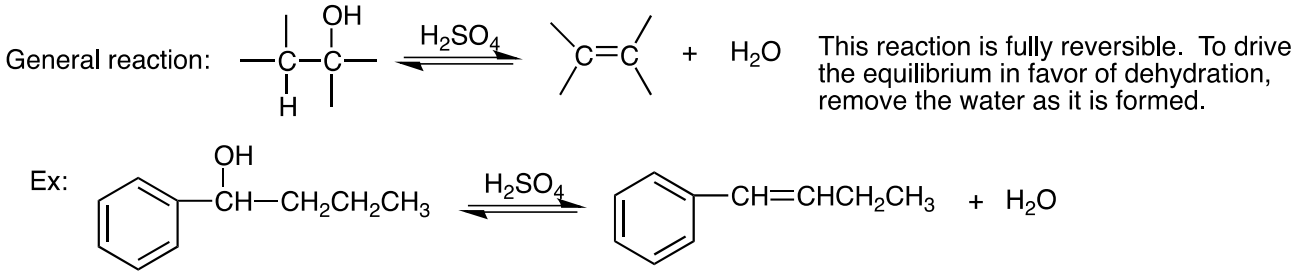
(3) Reaction of alcohols with phosphorus tribromide, PBr_3, to give alkyl bromides.

General reaction: $ROH + PBr_3 \longrightarrow RBr + H_3PO_4$ (after aqueous workup)

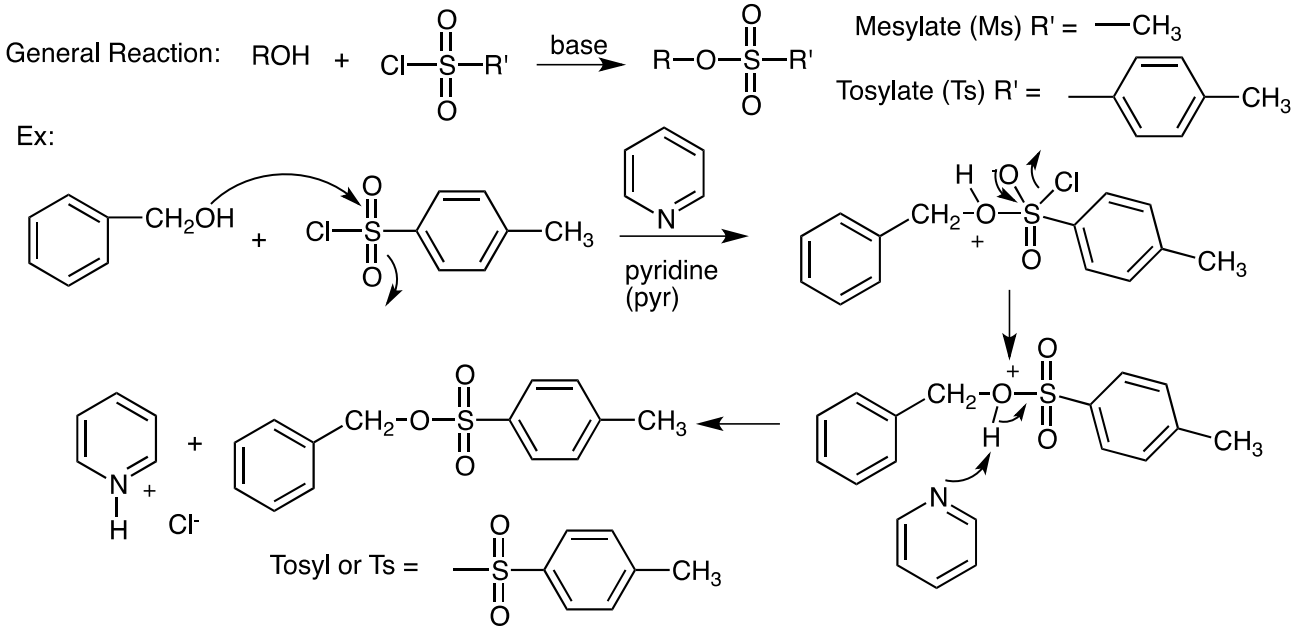
Ex:



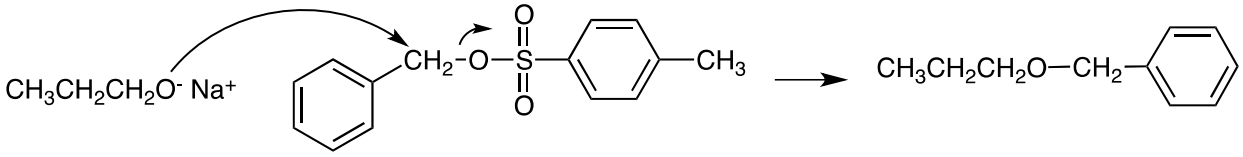
(4) Acid catalyzed dehydration of alcohols to give alkenes using strong mineral acid.



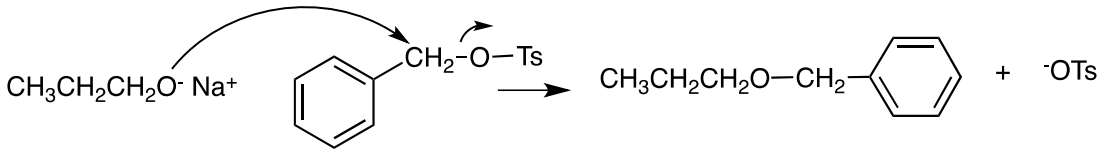
(5) Conversion of alcohols to alkyl and aryl sulfonates.



We have now converted the alcohol into a good leaving group. We can now replace the tosyl group with a basic nucleophile such as an alkoxide, RO^-. The tosyl group behaves very much like a halogen such as Br^- or Cl^- in terms of its reactivity.



Note: we can also write this same reaction as



New Reactions of Alcohols in this Chapter:

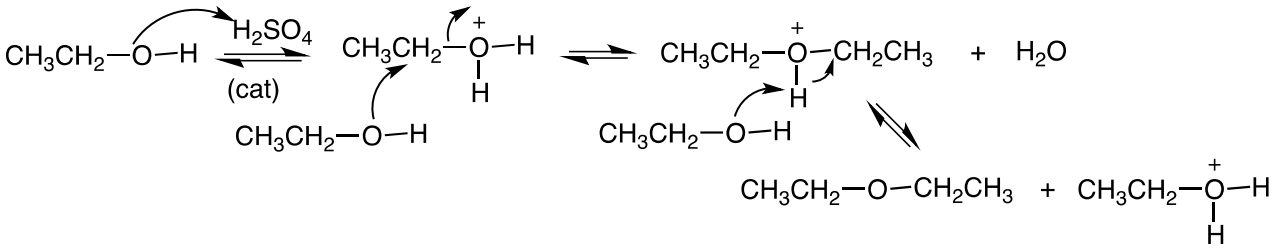
(6) Conversion of alcohols to symmetrical ethers:

Primary alcohols are converted to symmetrical ether by heating in the presence of a catalytic amount of strong acid. This is a condensation reaction and is useful only for the formation of symmetrical ethers in which both of the alkyl groups are the same.

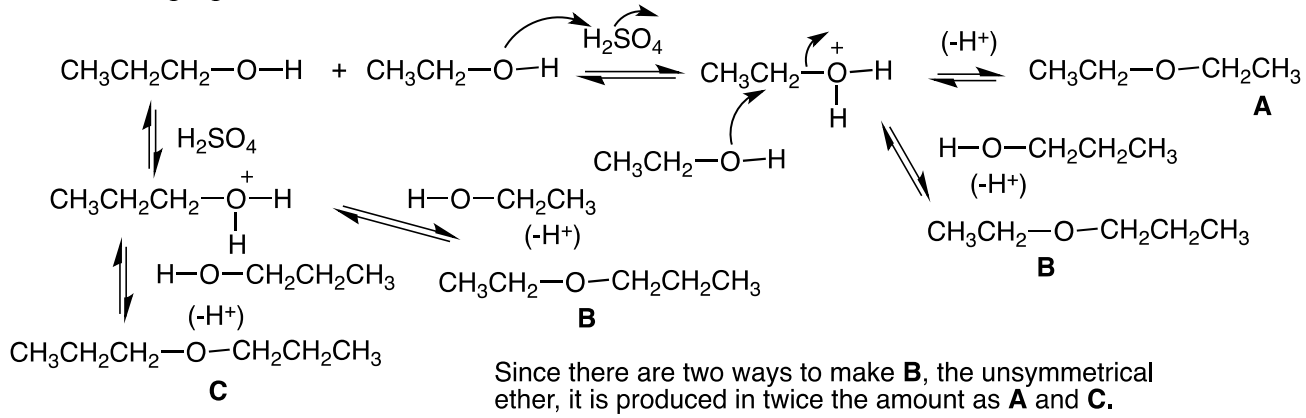
General Reaction: $2\ ROH + cat.\ H_2SO_4 \rightleftharpoons ROR + H_2O$

This is a fully reversible reaction and is driven in the direction of ether formation by the removal of the water as it is formed. We will look at the reverse reaction in the next chapter when we look at how to cleave ethers.

Ex: and Mechanism



It is only useful for primary alcohol since secondary and tertiary alcohols would give mainly dehydration. It is useful only for making symmetrical ethers. If we tried to couple two different alcohols, say ethanol and propanol, we would get a mixture of three different ethers, the symmetrical ether formed from ethanol, the mixed ether, and the symmetrical ether formed from propanol in a ratio of 1:2:1 as shown below.

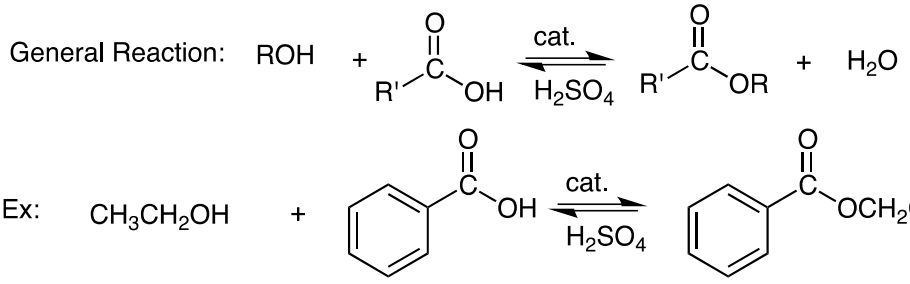


Since there are two ways to make **B**, the unsymmetrical ether, it is produced in twice the amount as **A** and **C.**

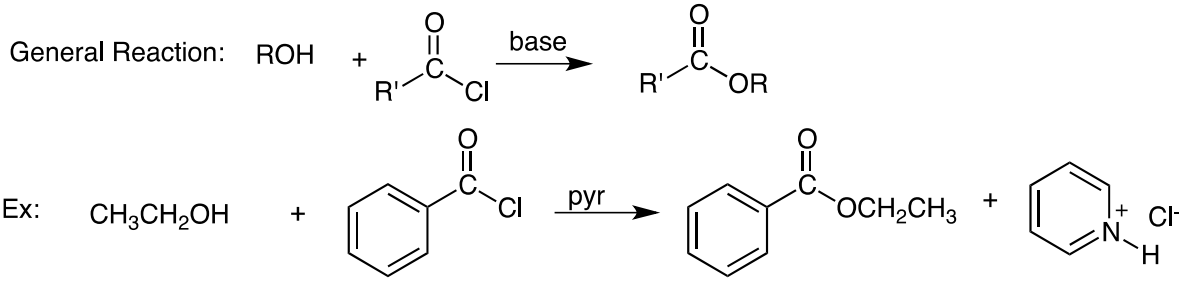
(7) Reaction of alcohols with Carboxylic acids to make esters (Esterification).

We will study this very important reaction in detail in a later section. For now we will just present the overall reaction without going into any details about the mechanism. There are three ways to make esters from carboxylic acids

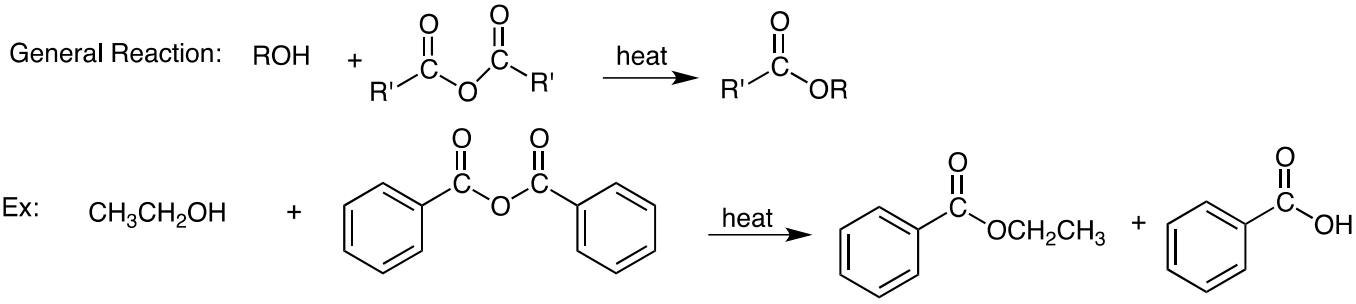
(a) Acid catalyzed esterification (also called Fischer esterification). This reaction is reversible, as we will see, and is driven toward ester formation by using an excess of the alcohol (usually it is the solvent) by removal of the water as it forms.



(b) Reaction of alcohols with acid chlorides.

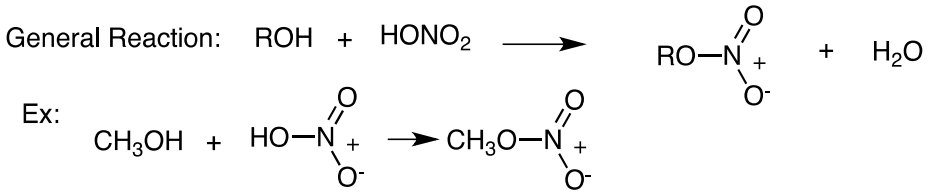


(c) Reaction of alcohols with Anhydrides.

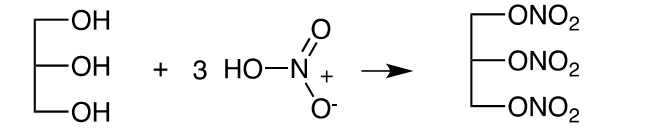


Formation of Esters from Inorganic Acids.

With nitric acid:

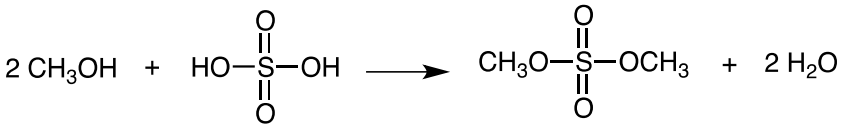


An important example of this reaction is the synthesis of trinitroglycerin from glycerin. Trinitroglycerin is the active compound in dynamite. It was Alfred Nobel, the founder of the Nobel Prizes, who first discovered a safe way to handle and package the trinitroglycerin.

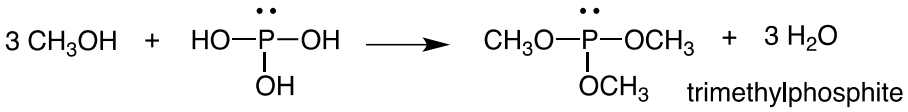


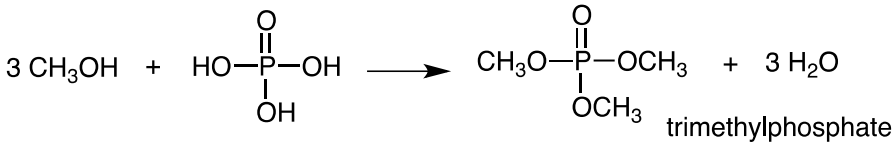
glycerin trinitroglycerin

Alkyl esters of Sulfuric acid: dialkyl sulfates. These make excellent alkylating agents.



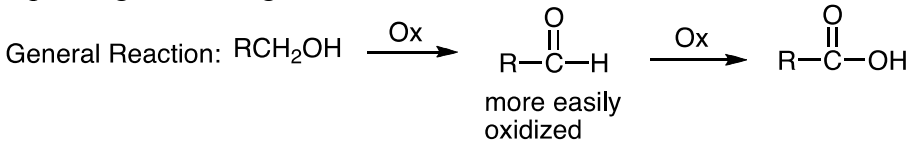
There are also esters of phosphorous acid, H_3PO_3. For example, trialkyl phosphite and esters of phosphoric acid, H_3PO_4, trialkyl phosphates. These are very important in biological systems. For example, the backbone of DNA is made up of phosphate esters.





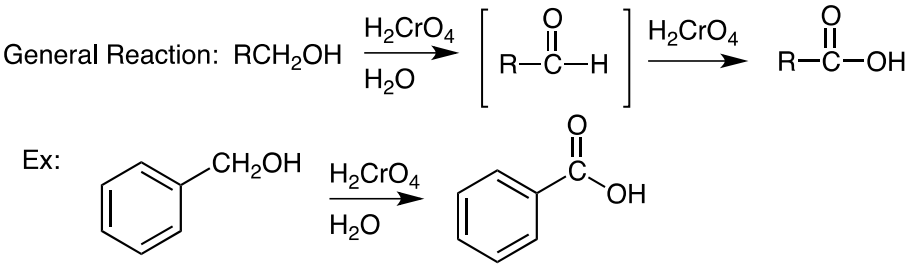
Oxidation of Alcohols:

Primary alcohols: We can oxidize primary alcohols to Aldehydes or carboxylic acids depending on the reagent.

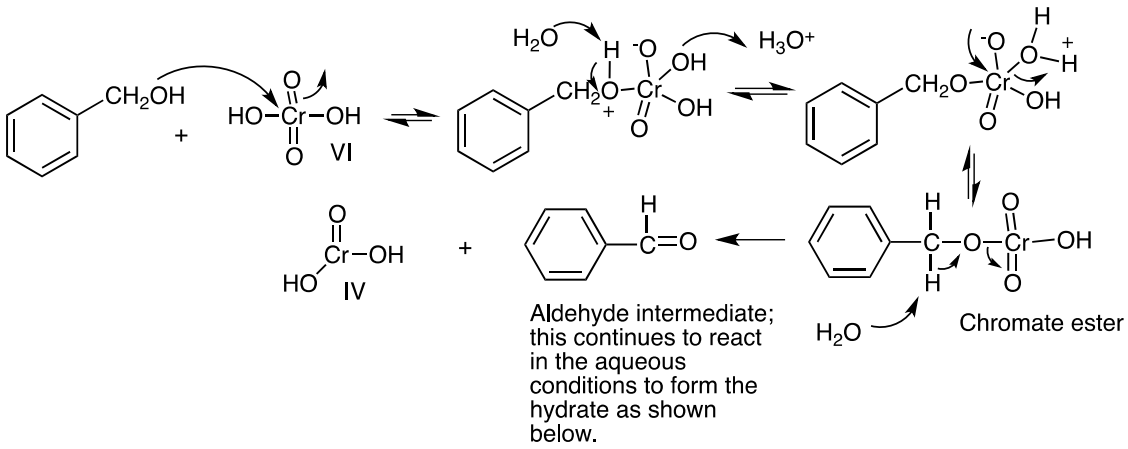


Chromic Acid, H_2CrO_4, is a good, fairly mild general oxidizing reagent that will oxidize primary alcohols to carboxylic acids. Chromic acid itself is unstable to disproportionation. It is formed *in situ* from sulfuric acid, H_2SO_4, and sodium dichromate, $Na_2Cr_2O_7$ in aqueous

solution. We will generally write it as H_2CrO_4. During the reaction, the chromium VI is reduced to chromium IV.

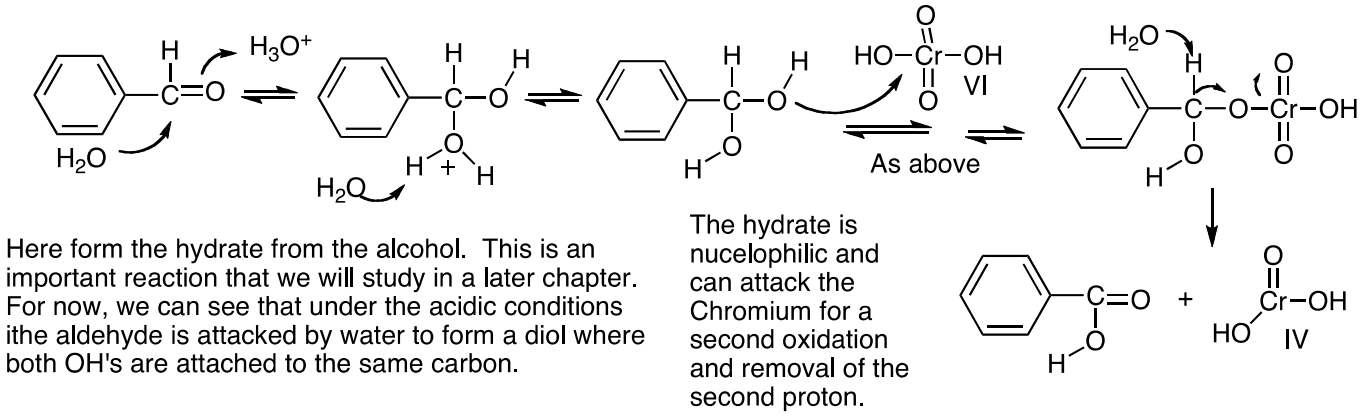


We can generally not isolate the aldehyde intermediate in aqueous solution. If we look at the mechanism you will see why. The first step is the formation of the chromate ester by attack of the alcohol hydroxyl onto the chromium with subsequent loss of water. This is an acid catalyzed esterification of an inorganic acid that we just saw with nitric acid, sulfuric acid and phosphoric acid. Once the chromate ester is formed, one of the protons is removed by water acting as a base. Note carefully how the electrons are moving. The two electrons in the C-H bond move to make the second C-O bond, forming a C=O bond and the chromium leaves with the two electrons in the C-Cr bond, thus becoming reduced by two electrons, moving from an oxidation state of +6 to +4.



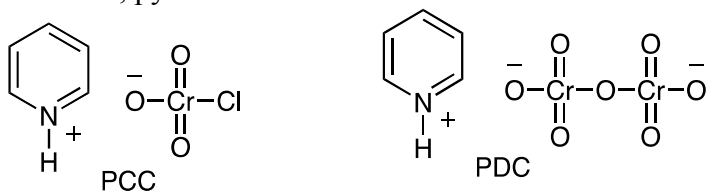
Note how the electrons are moving here. The proton is removed by water and the two electrons in the C-H bond go to make a seoond C-O bond and the chromium leaves with the two electrons in the O-Cr bond, thus becoming reduced.

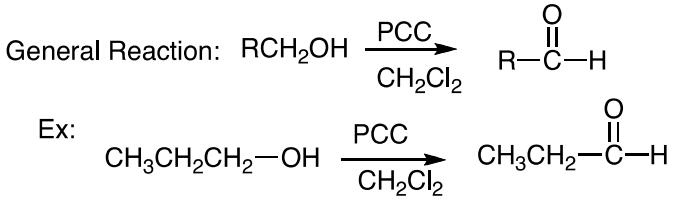
The aldehyde cannot be isolated because it immediately reacts with water in the acidic conditions to form the hydrate. This is an important reaction that we will study later in the chapter on aldehydes and ketones. For now just note that we form a geminal diol (two OH's attached to the same carbon) that is nucleophilic and can attack another molecule of chromic acid to form a second chromate ester. Removal of the second proton forms the carboxylic acid.



From this mechanism we can see that if we can prevent the aldehyde from forming the hydrate, it will not be a nucleophilic species and will not attack the chromium for a second oxidation. To do this we need to use a reducing agent that is soluble in organic solvents so that we can use anhydrous conditions.

There are several available. Two chromium reagents are PCC, pyridinium chlorochromate, and PDC, pyridinium dichromate.

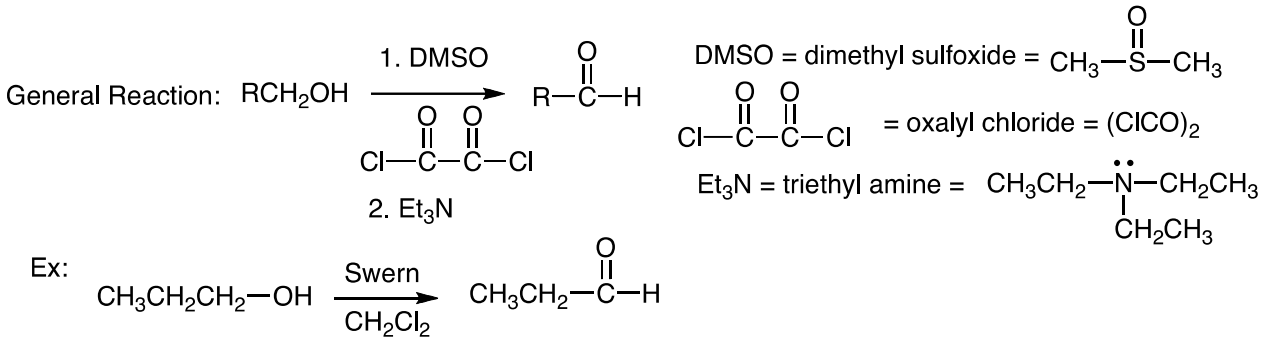




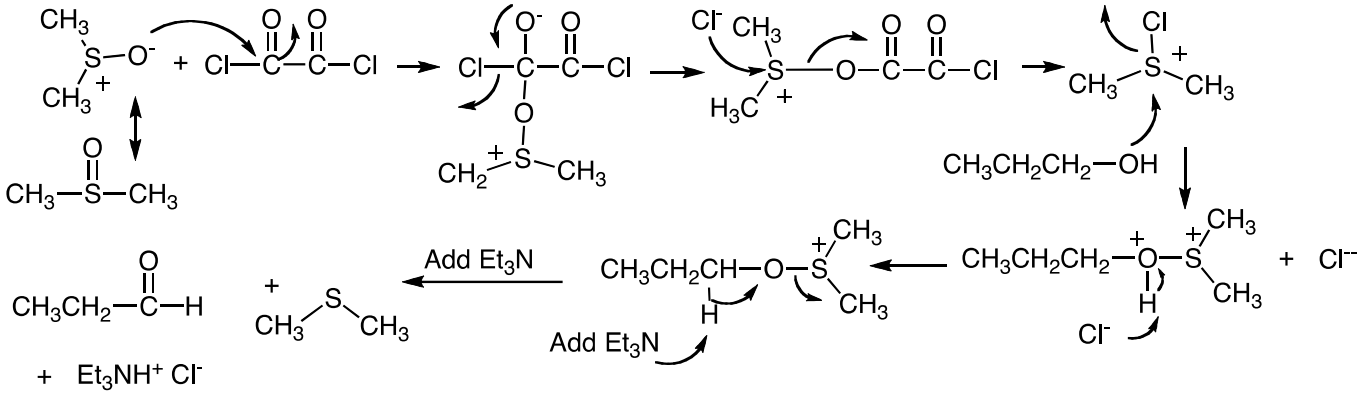
Both of these reagents are soluble in moderately polar organic solvents such as methylene chloride, CH_2Cl_2 and give good yields of aldehydes from primary alcohols.

There is a major problem, however, with these reagents and also with chromic acid. Chromic is a toxic, heavy metal and must be disposed of properly so that it does leach into the environment. This is expensive. Therefore, several alternate oxidizing agents have been developed.

One of the most popular is the Swern oxidation using the very mild and non-toxic reagents of oxalyl chloride, dimethylsulfoxide and triethyl amine.



The mechanism is quite complicated but it is elegant and worth looking at. It is given below.



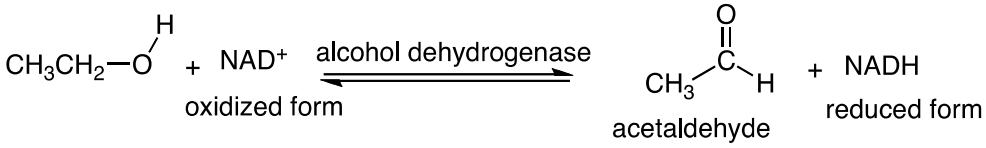
Oxalyl chloride is a highly reactive reagent. It is a dicarboxylic acid chloride and a very powerful electrophile. The electronegative chlorines withdraw electron density from the carbonyl carbon making it very electron deficient. Don't worry about the details right now. We will study the reactions of acid chlorides in great detail in a later chapter.

The purpose of the oxalyl chloride is to activate the dimethyl sulfoxide. The oxygen of the DMSO attacks the carbonyl carbon of the oxalyl chloride, releasing a Cl^- species which then attacks the sulfur of the DMSO-oxalyl chloride adduct to form a sulfur-chlorine bond. This then reacts with the alcohol to form an activated alcohol. This is the end of stage one. Then the triethyl amine is added to remove a proton and form the C=O bond. Note again how the electrons are moving in this final key step. The sulfur leaves with its electrons.

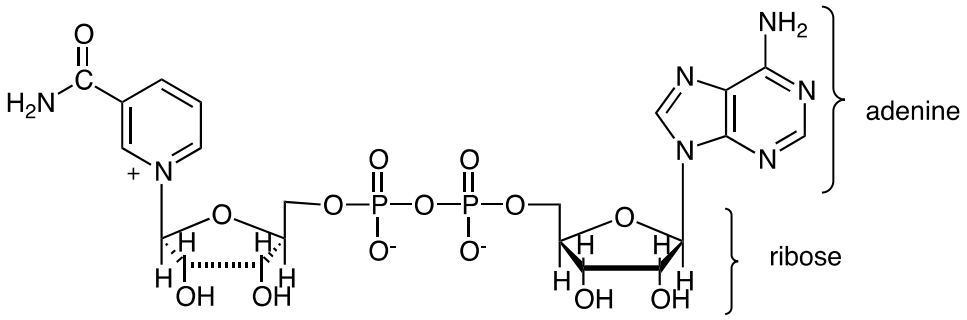
Biological Oxidation of Alcohols

Ethanol is metabolized in the liver to acetaldehyde. This reaction is catalyzed by alcohol dehydrogenase.

Alcohol dehydrogenase uses the co-enzyme NAD^+, which is reduced to NADH.

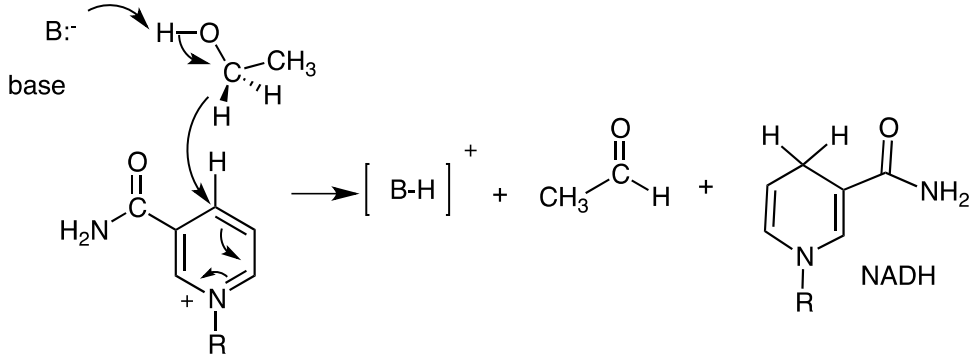


The structure of NAD^+ is shown below.



NAD^+ = nicotinamide dinucleoptide

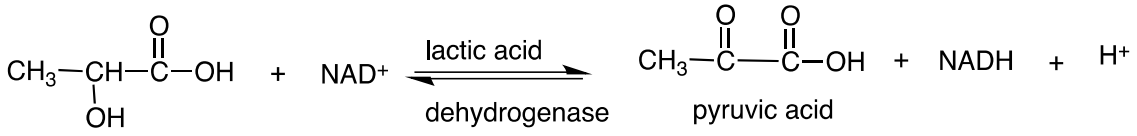
The mechanism for the reaction is as show below:



NAD^+, R = rest of molecule as shown above

NADH can also act as a reducing agent, reducing acetaldehyde to ethanol in the presence of alcohol dehydrogenase.

NAD^+ is also a co-enzyme for lactic acid dehydrogenase, which oxidizes lactic acid to pyruvic acid.

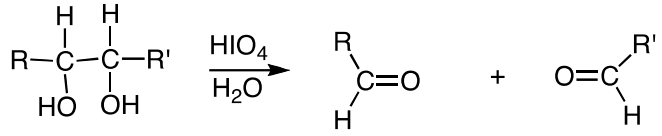


lactic acid

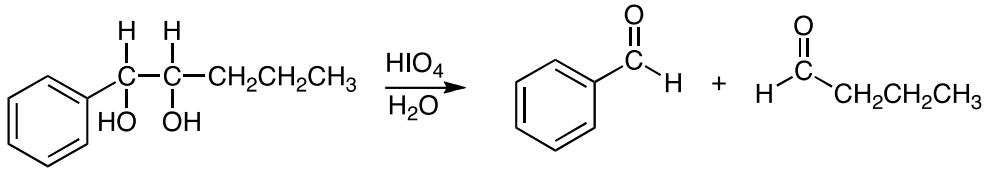
Oxidative cleavage of Vicinal Diols

We can cleave vicinal or 1,2-diols using periodic acid, a very mild oxidizing reagent to form aldehydes. The C-C bond is broken and we get two aldehyde molecules. Remember that we form the 1,2-diols from alkenes using osmium tetraoxide and so this two-step sequence provides a way to transforming an alkene into two aldehydes with ultimate cleavage of the C=C bond. This is an alternative to the ozonolysis reaction that we studied in an earlier chapter. We will not examine the mechanism for this reaction. It involves single electron transfer steps (SET).

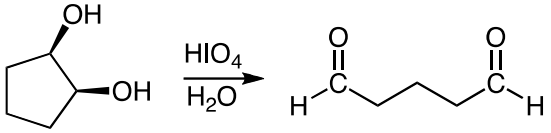
General reaction:



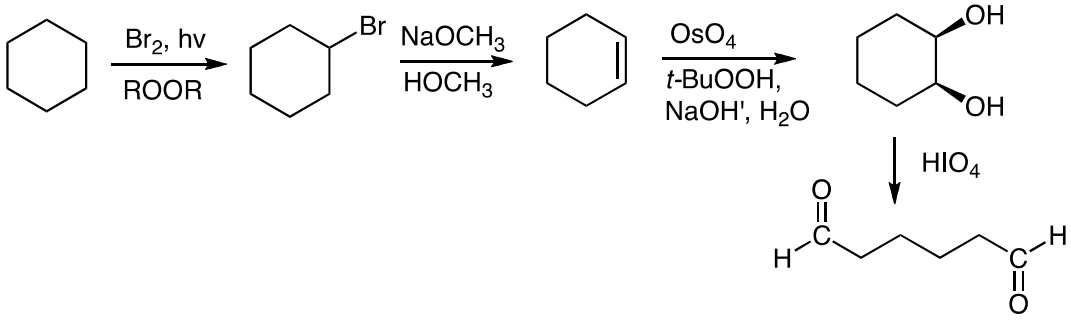
Ex:



If we have a cyclic 1,2-diol, we get linear dialdehydes that, as we will see, are very useful synthetic intermediates.

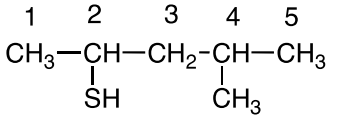


So, now we can do multi-step syntheses such as the following:
First we need to form the double bond. We can do this in two steps. As we know, the only way to react an unactivated C-H bond is through free radical chemistry. We do this using Br_2 in the presence of ultra-violet light and a peroxide. Treatment of the resulting bromocyclohexane with a strong base such as sodium methoxide results in elimination. Then comes the two-step sequence we have learned in this chapter: treatment with osmium tetraoxide to give the *cis*-1, 2-diol and subsequent cleave with periodic acid. There are procedures in which these last two steps can be done at the same time in one pot.



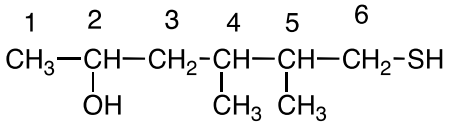
Thiols, RSH

Nomenclature: name from the parent alkane by adding the suffix –thiol. Like with diols, the 'e' of the parent alkane is retained. As always, number the chain in the direction that gives the lower number for the sulfur bearing carbon.



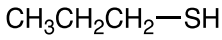
4-methyl-2-pentanethiol

When the –SH group is named as a substituent, use "mercapto-". We also sometimes use "sulfhydryl group" but this is a non-systematic name.



6-mercapto-4,5-dimethyl-2-hexanol

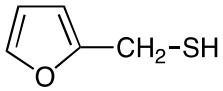
An older nomenclature is still sometimes in use. This names Thiols as alkyl mercaptans.



propyl mercaptan

Most thiols have a horrible and very distinctive smell (think: rotten eggs!). In fact methanethiol, CH_3SH, is a gas at room temperature and is used in natural gas lines in trace amounts so that the odorless natural gas, propane or butane, can be detected by smell.

One thiol, however, that is found in freshly brewed coffee does have a pleasing smell. It is 2-mercaptometylfuran and is one of the volatile compounds responsible for the wonderful aroma.



Sulfur, of course, is in the same column as oxygen and has many similarities in its reactivity but there are also large differences. It has two lone pair, like oxygen, and will form two bonds. It is an excellent nucleophile, even better than oxygen.

The differences from oxygen stem from the fact that sulfur is considerably less electronegative than oxygen (2.58 for sulfur v. 3.44 for oxygen, a difference of 25%) and it has a considerably larger covalent radius (1.02 for sulfur v. 0.73 for oxygen, a difference of 28%).

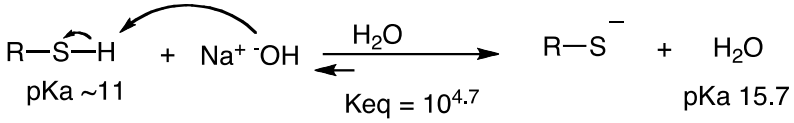
This makes the sulfur into a much better nucleophile than oxygen. Sulfur, being less electronegative, is more polarizable, meaning it donates its electrons more readily than oxygen. This is the same trend that we saw in the halogens (i.e. Cl^- is a better nucleophile than F^-).

And the S-H bond is longer and weaker than the O-H bond. The reasons are similar to those that determine the strengths of the halogen acids, H-Cl v. H-F. The sulfur atom is larger and so the H atom is farther from the sulfur nucleus and less tightly held. Since the S-H bond is

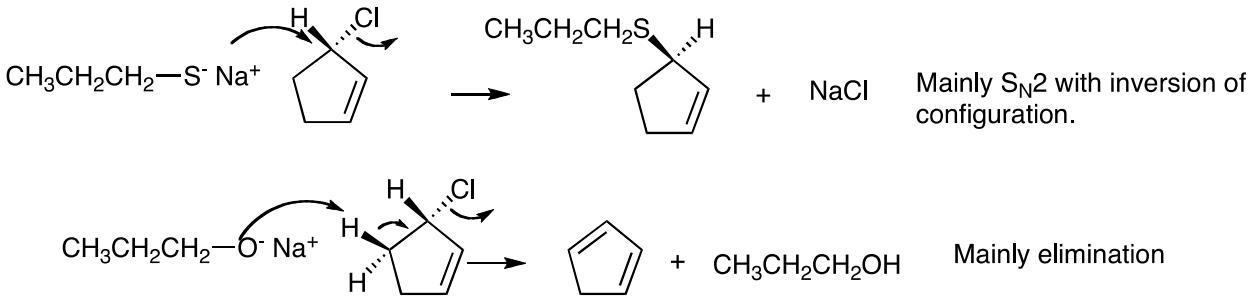
less polarized than the O-H bond, thiols are stronger acids than alcohols and have much lower boiling points since there is less intermolecular hydrogen-bonding. Compare the physical properties of methanethiol and methanol.

$CH_3—S—H$ b.p. 6°C pKa ~11 $CH_3—O—H$ b.p 65°C pKa ~16

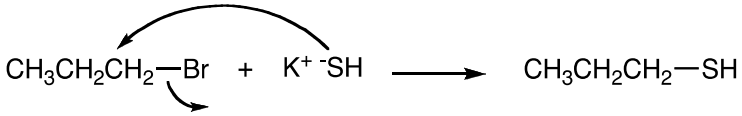
Thiols can be converted quantitatively to there conjugate bases with sodium hydroxide in aqueous solution.



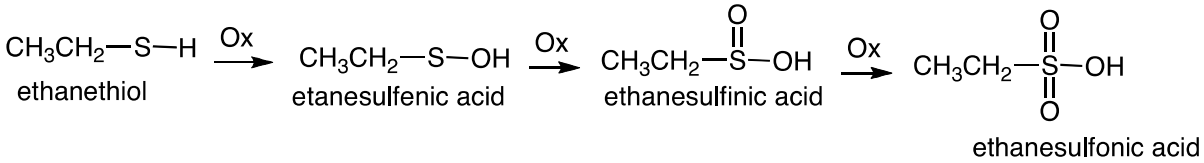
Consequently, as we mentioned, alkanethiolates are weaker bases than alkoxides and better nucleophiles. We can do S_N2 reactions on secondary alkyl halides without seeing much competing elimination. Recall, that alkoxides react with secondary alkyl halides to give mainly elimination rather than substitution. Tertiary alkyl halides will give mainly elimination even with the alkanethiolates.



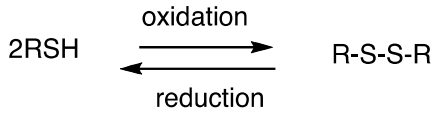
Thiols can often be prepared using the conjugate base of H_2S in reactions with primary and secondary alkyl halides.



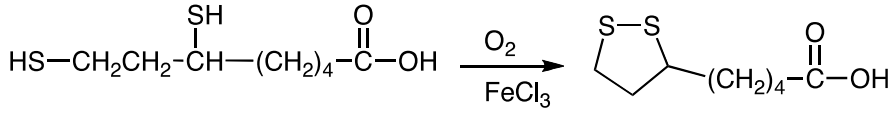
A major difference in the behavior of thiols and alcohols is in their oxidation reactions. We do not see oxidation of thiols to C=S compounds. Instead, the sulfur becomes oxidized, not the carbon.



Another reaction that is particularly important in biological systems is the oxidation of thiols to disulfides.



This occurs readily, even in air. Dithiols give cyclic disulfides as for example the co-enzyme α-lipoic acid.



Sulfur-sulfur bonds are ~220 Kcal/mol, which is intermediate between C-C, C-H bonds and hydrogen-bonds.

All mammalian cells contain a thiol called glutathione, which protects cells by scavenging harmful oxidants in the cell. It reacts with oxidants by forming a disulfide.