Alcohols

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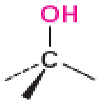
2017-2018.

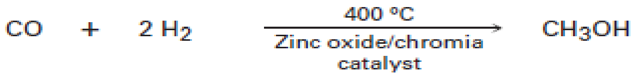
Alcohols can be thought of as organic derivatives of water in which one of the water's hydrogens is replaced by an organic group: H-O-H versus R-O-H. In practice, the group name ***alcohol*** is restricted to compounds that have their -OH group bonded to a saturated, ***sp***^{3}-hybridized carbon atom.



An alcohol

Alcohols occur widely in nature and have many industrial and pharmaceutical applications. Methanol, for instance, is one of the most important of all industrial chemicals.

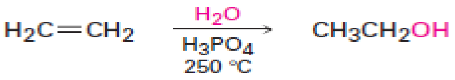
Methanol is manufactured by catalytic reduction of carbon monoxide with hydrogen gas. Methanol is toxic to humans, causing blindness in small doses (15 mL) and death in larger amounts (100–250 mL). Industrially, it is used both as a solvent and as a starting material for production of formaldehyde (CH_2O) and acetic acid (CH_3CO_2H).



$$CO + 2\,H_2 \xrightarrow[\text{Zinc oxide/chromia catalyst}]{400\ ^\circ C} CH_3OH$$

Ethanol was one of the first organic chemicals to be prepared and purified. Its production by fermentation of grains and sugars and its purification by distillation.

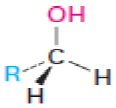
Ethanol for industrial use as a solvent or chemical intermediate is largely obtained by acid-catalyzed hydration of ethylene at high temperature.



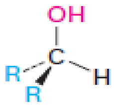
$$H_2C{=}CH_2 \xrightarrow[\substack{H_3PO_4\\250\ ^\circ C}]{H_2O} CH_3CH_2OH$$

Naming Alcohols

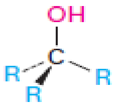
Alcohols are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of organic groups bonded to the hydroxyl-bearing carbon.



A primary (1°) alcohol



A secondary (2°) alcohol



A tertiary (3°) alcohol

Simple alcohols are named by the IUPAC system as derivatives of the parent alkane, using the suffix ***-ol.***

Rule 1

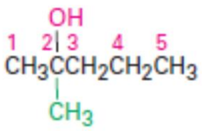
Select the longest carbon chain containing the hydroxyl group, and derive the parent name by replacing the ***-e*** ending of the corresponding alkane with ***-ol.*** The ***-e*** is deleted to prevent the occurrence of two adjacent vowels: propanol rather than propaneol, for example.

Rule 2

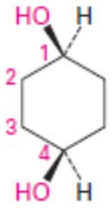
Number the alkane chain beginning at the end nearer the hydroxyl group.

Rule 3

Number the substituents according to their position on the chain, and write the name, listing the substituents in alphabetical order and identifying the position to which the -OH is bonded. Note that in naming ***cis-***1,4-cyclohexanediol, the final ***-e*** of cyclohexane is not deleted because the next letter, ***d,*** is not a vowel; that is, cyclohexanediol rather than cyclohexandiol. Also, as with alkenes, newer IUPAC naming recommendations place the locant immediately before the suffix rather than before the parent.


$$\overset{1}{CH_3}\overset{2}{C}(OH)(CH_3)\overset{3}{CH_2}\overset{4}{CH_2}\overset{5}{CH_3}$$

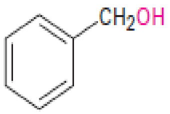
2-Methyl-2-pentanol
(New: 2-Methylpentan-2-ol)



***cis*-1,4-Cyclohexanediol**
(New: *cis*-Cyclohexane-1,4-diol)

3-Phenyl-2-butanol
(New: 3-Phenylbutan-2-ol)

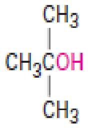
Some simple and widely occurring alcohols have common names that are accepted by IUPAC. For example:



Benzyl alcohol
(phenylmethanol)

$H_2C{=}CHCH_2OH$

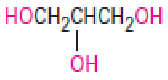
Allyl alcohol
(2-propen-1-ol)


$$CH_3\overset{CH_3}{\underset{CH_3}{C}}OH$$

tert-Butyl alcohol
(2-methyl-2-propanol)

$HOCH_2CH_2OH$

Ethylene glycol
(1,2-ethanediol)


$$HOCH_2\underset{OH}{CH}CH_2OH$$

Glycerol
(1,2,3-propanetriol)

Properties of Alcohols

Alcohols have nearly the same geometry around the oxygen atom as water. The R-O-H bond angle has an approximately tetrahedral value (108.5° in methanol, for instance), and the oxygen atom is *sp*3-hybridized. Also like water, alcohols have higher boiling points than might be expected, because of hydrogen-bonding. A positively polarized -OH hydrogen atom from one molecule is attracted to a lone pair of electrons on the electronegative oxygen atom of another molecule, resulting in a weak force that holds the molecules together **(Figure 17-1)**. These intermolecular attractions must be overcome for a molecule to break free from the liquid and enter the vapor state, so the boiling temperature is raised. For example, 1-propanol (MW = 60), butane (MW = 58), and chloroethane (MW = 65) have similar molecular weights, yet 1-propanol boils at 97 °C, compared with 20.5 °C for the alkane and 12.5 °C for the chloroalkane.

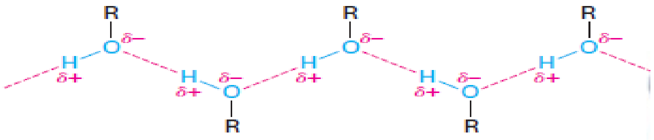
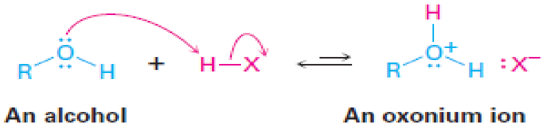
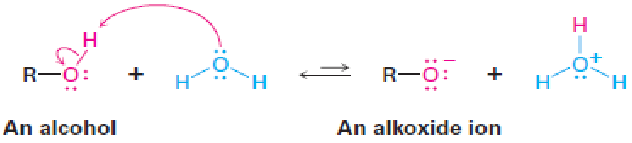


Figure 17-1 Hydrogen bonding in alcohols. Attraction between a positively polarized -OH hydrogen and negatively polarized oxygen holds molecules together. The electrostatic potential map of methanol shows the positively polarized -OH hydrogen and the negatively polarized oxygen.

Another similarity with water is that alcohols and phenols are both weakly basic and weakly acidic. As weak bases, they are reversibly protonated by strong acids to yield oxonium ions, ROH_2^+.



As weak acids, they dissociate slightly in dilute aqueous solution by donating a proton to water, generating H_3O+ and an **alkoxide ion, RO^-**.



The strength of any acid HA in water can be expressed by an acidity constant, *K*a.

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \qquad pK_a = -\log K_a$$

Compounds with a smaller *K*a and larger p*K*a are less acidic, whereas compounds with a larger *K*a and smaller p*K*a are more acidic. As shown in **Table 17-1**, simple alcohols like methanol and ethanol are about as acidic as water, but the more highly substituted *tert*-butyl alcohol is somewhat weaker. Substituent groups also have a significant effect: 2,2,2-trifluoroethanol is approximately 3700 times stronger than ethanol, for instance.

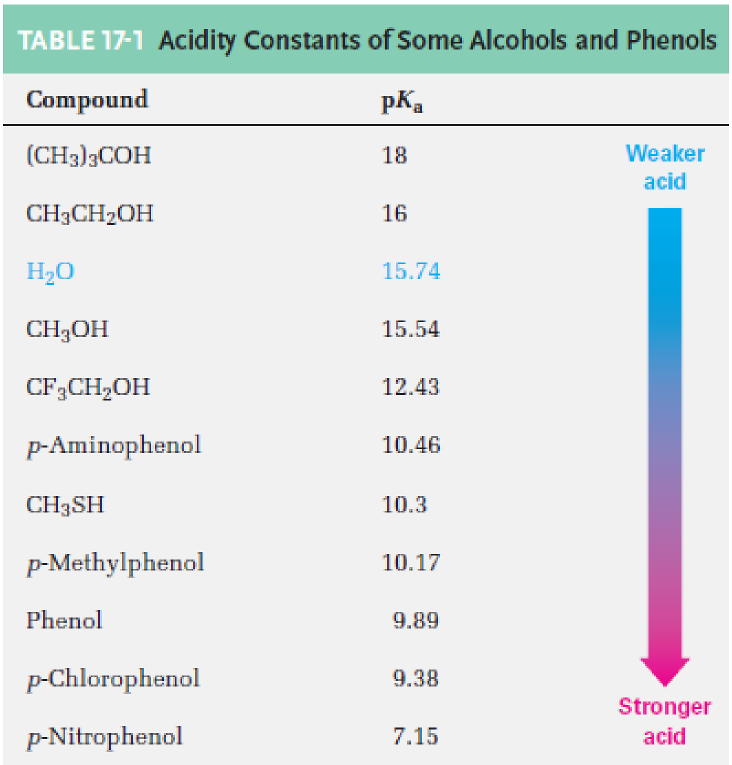
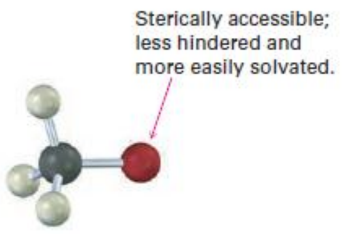


TABLE 17-1 Acidity Constants of Some Alcohols and Phenols

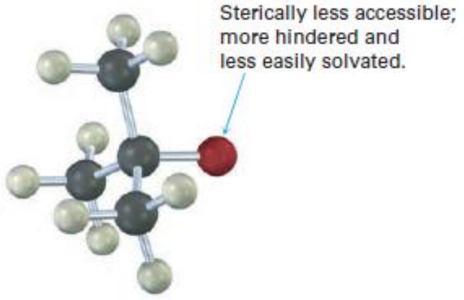
Compound	pK_a	
$(CH_3)_3COH$	18	Weaker acid
CH_3CH_2OH	16	
H_2O	15.74	
CH_3OH	15.54	
CF_3CH_2OH	12.43	
p-Aminophenol	10.46	
CH_3SH	10.3	
p-Methylphenol	10.17	
Phenol	9.89	
p-Chlorophenol	9.38	
p-Nitrophenol	7.15	Stronger acid

The effect of alkyl substitution on alcohol acidity is due primarily to solvation of the alkoxide ion formed on acid dissociation. The more readily the alkoxide ion is solvated by water, the more stable it is, the more its formation is energetically favored, and the greater the acidity of the parent alcohol. For example, the oxygen atom of an unhindered alkoxide ion, such as that from methanol, is sterically accessible and is easily solvated by water.

The oxygen atom of a hindered alkoxide ion, however, such as that from *tert*-butyl alcohol, is less easily solvated and is therefore less stable.

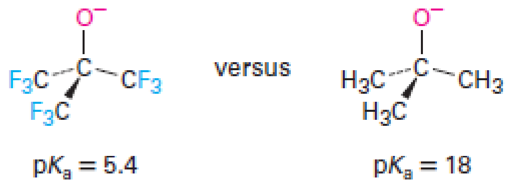


Methoxide ion, CH_3O^-
(pK_a = 15.54)



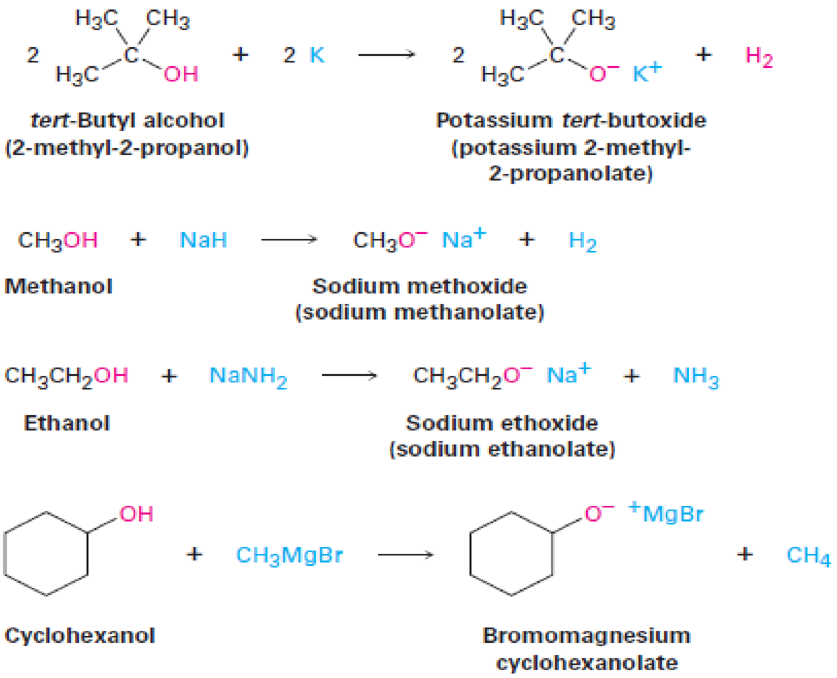
***tert*-Butoxide ion, $(CH_3)_3CO^-$**
(pK_a = 18)

Inductive effects are also important in determining alcohol acidities. Electron-withdrawing halogen substituents, for instance, stabilize an alkoxide ion by spreading the charge over a larger volume, thus making the alcohol more acidic. Compare, for example, the acidities of ethanol (p*K*a = 16) and 2,2,2-trifluoroethanol (p*K*a = 12.43), or of *tert*-butyl alcohol (p*K*a = 18) and nonafluoro-*tert*-butyl alcohol (p*K*a = 5.4).



Electron-withdrawing groups stabilize the alkoxide ion and lower the pK_a of the alcohol.

Because alcohols are weak acids, they don't react with weak bases, such as amines or bicarbonate ion, and they only react to a limited extent with metal hydroxides such as NaOH. Alcohols do, however, react with alkali metals and with strong bases such as sodium hydride (NaH), sodium amide ($NaNH_2$), and Grignard reagents (RMgX). Alkoxides are themselves bases that are frequently used as reagents in organic chemistry. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance.



***tert*-Butyl alcohol (2-methyl-2-propanol)**

Potassium *tert*-butoxide (potassium 2-methyl-2-propanolate)

Methanol

Sodium methoxide (sodium methanolate)

Ethanol

Sodium ethoxide (sodium ethanolate)

Cyclohexanol

Bromomagnesium cyclohexanolate

Preparation of Alcohols: A Review

Alcohols occupy a central position in organic chemistry. They can be prepared from many other kinds of compounds (alkenes, alkyl halides, ketones, esters, and aldehydes, among others), and they can be transformed into an equally wide assortment of compounds **(Figure 17-3)**.

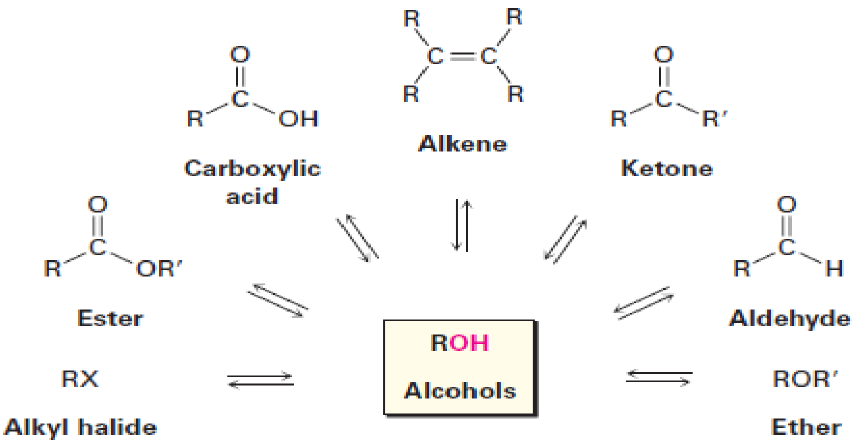
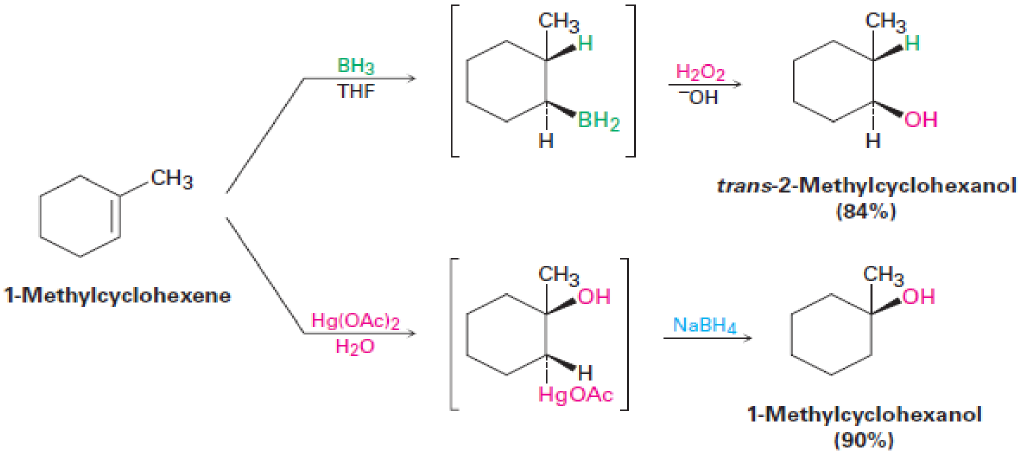


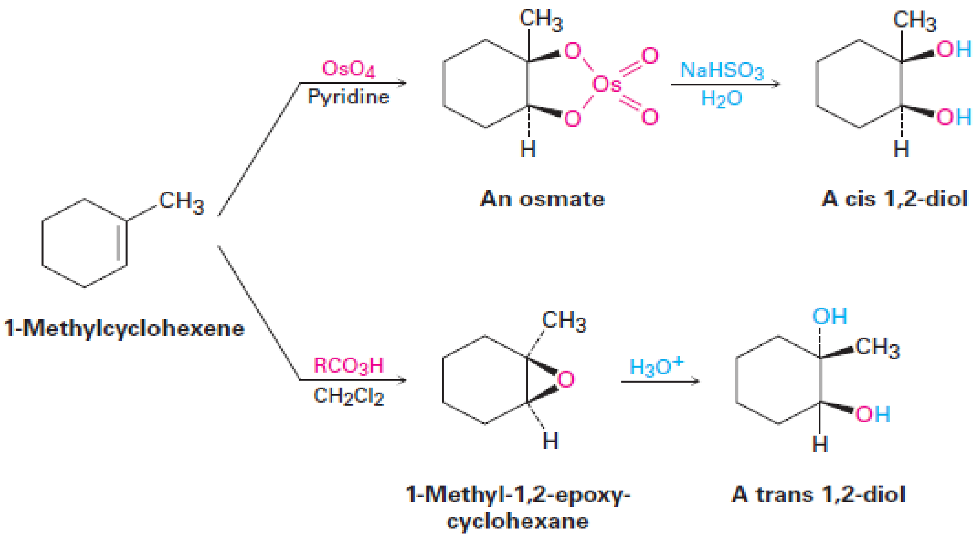
Figure 17-3 The central position of alcohols in organic chemistry. Alcohols can be prepared from, and converted into, many other kinds of compounds.

We've already seen several methods of alcohol synthesis:

- Alcohols can be prepared by hydration of alkenes. Because the direct hydration of alkenes with aqueous acid is generally a poor reaction in the laboratory, two indirect methods are commonly used. Hydroboration– oxidation yields the syn, non-Markovnikov hydration product, whereas oxymercuration–demercuration yields the Markovnikov hydration product.

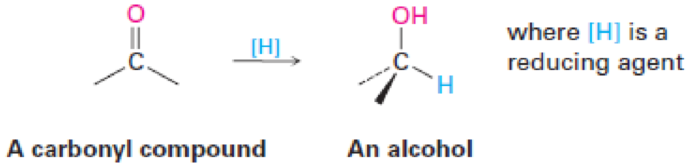


1,2-Diols can be prepared either by direct hydroxylation of an alkene with OsO_4 followed by reduction with $NaHSO_3$ or by acid-catalyzed hydrolysis of an epoxide. The OsO_4 reaction occurs with syn stereochemistry to give a cis diol, and epoxide opening occurs with anti-stereochemistry to give a trans diol.



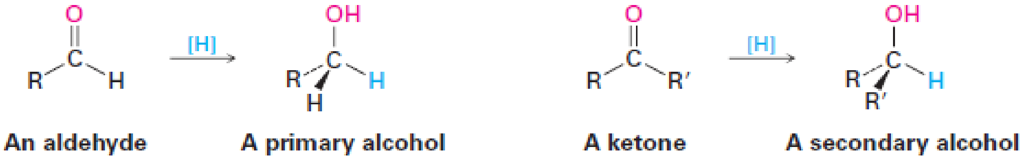
Alcohols from Carbonyl Compounds: Reduction

The most general method for preparing alcohols, both in the laboratory and in living organisms, is by the reduction of a carbonyl compound. Just as reduction of an alkene adds hydrogen to a C=C bond to give an alkane, reduction of a carbonyl compound adds hydrogen to a C=O bond to give an alcohol. Any kind of carbonyl compound can be reduced, including aldehydes, ketones, carboxylic acids, and esters.



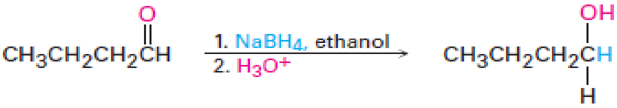
Reduction of Aldehydes and Ketones

Aldehydes are easily reduced to give primary alcohols, and ketones are reduced to give secondary alcohols.



Dozens of reagents are used in the laboratory to reduce aldehydes and ketones, depending on the circumstances, but sodium borohydride, $NaBH_4$, is usually chosen because of its safety and ease of handling. Sodium borohydride is a white, crystalline solid that can be weighed in the open atmosphere and used in either water or alcohol solution.

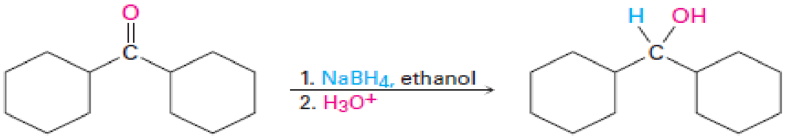
Aldehyde reduction



Butanal

1-Butanol (85%)
(a 1° alcohol)

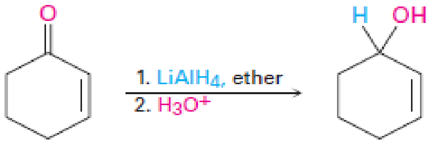
Ketone reduction



Dicyclohexyl ketone

Dicyclohexylmethanol (88%)
(a 2° alcohol)

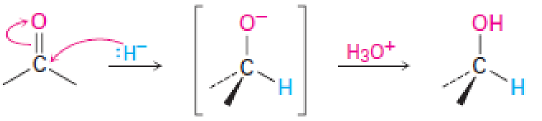
Lithium aluminum hydride, $LiAlH_4$, is another reducing agent often used for reduction of aldehydes and ketones. A grayish powder that is soluble in ether and tetrahydrofuran, $LiAlH_4$ is much more reactive than $NaBH_4$ but also more dangerous. It reacts violently with water and decomposes explosively when heated above 120 °C.



2-Cyclohexenone

2-Cyclohexenol (94%)

For the moment, we'll simply note that they involve the addition of a nucleophilic hydride ion (**:**H-) to the positively polarized, electrophilic carbon atom of the carbonyl group. The initial product is an alkoxide ion, which is protonated by addition of H_3O+ in a second step to yield the alcohol product.



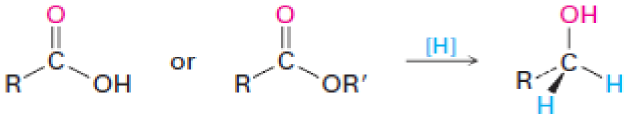
A carbonyl compound

An alkoxide ion intermediate

An alcohol

Reduction of Carboxylic Acids and Esters

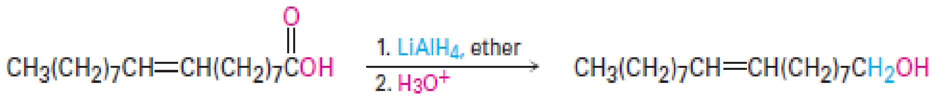
Carboxylic acids and esters are reduced to give primary alcohols.



A carboxylic acid **An ester** **A primary alcohol**

These reactions aren't as rapid as the reductions of aldehydes and ketones. $NaBH_4$ reduces esters very slowly and does not reduce carboxylic acids at all. Instead, carboxylic acid and ester reductions are usually carried out with the more reactive reducing agent $LiAlH_4$. All carbonyl groups, including acids, esters, ketones, and aldehydes, are reduced by $LiAlH_4$. Note that one hydrogen atom is delivered to the carbonyl carbon atom during aldehyde and ketone reductions but that two hydrogens become bonded to the former carbonyl carbon during carboxylic acid and ester reductions.

Carboxylic acid reduction

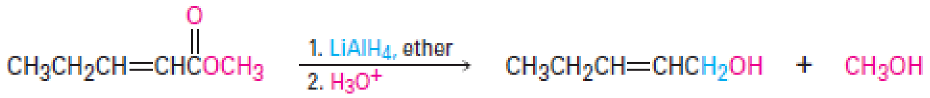


$$CH_3(CH_2)_7CH{=}CH(CH_2)_7\overset{O}{\overset{\|}{C}}OH \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4,\ ether} CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$$

9-Octadecenoic acid (oleic acid)

9-Octadecen-1-ol (87%)

Ester reduction



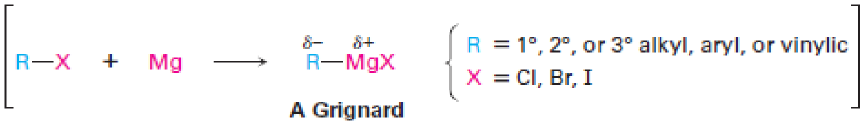
$$CH_3CH_2CH{=}CH\overset{O}{\overset{\|}{C}}OCH_3 \xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4,\ ether} CH_3CH_2CH{=}CHCH_2OH + CH_3OH$$

Methyl 2-pentenoate

2-Penten-1-ol (91%)

Alcohols from Carbonyl Compounds: Grignard Reaction

Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium, react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do. Just as carbonyl reduction involves addition of a hydride ion nucleophile to the C=O bond, Grignard reaction involves addition of a carbanion nucleophile (R:-+MgX).



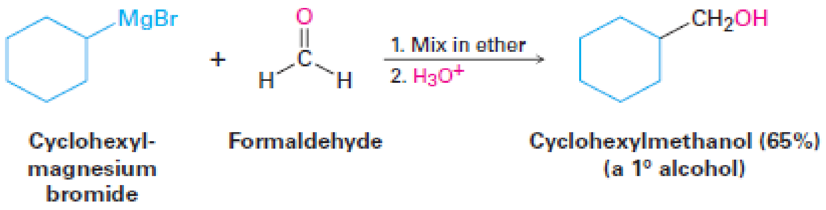
$$R{-}X + Mg \longrightarrow \overset{\delta-}{R}{-}\overset{\delta+}{MgX} \quad \left\{ \begin{array}{l} R = 1°, 2°, \text{ or } 3° \text{ alkyl, aryl, or vinylic} \\ X = Cl, Br, I \end{array} \right.$$

A Grignard reagent

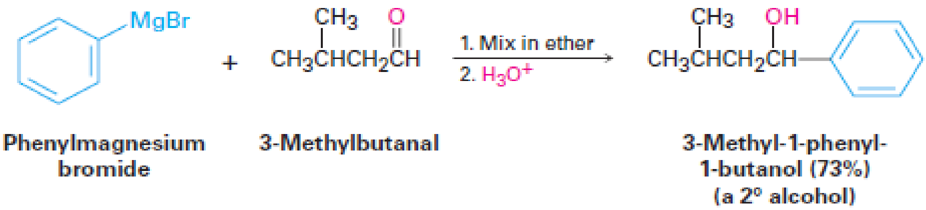
The reaction of Grignard reagents with carbonyl compounds has no direct counterpart in biological chemistry because organomagnesium compounds are too strongly basic to exist in an aqueous medium. Nevertheless, this reaction is worth understanding for two reasons. First, the reaction is an unusually broad and useful method of alcohol synthesis and demonstrates again the relative freedom with which chemists can operate in the laboratory. Second, the reaction *does* have an indirect biological counterpart, that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carbon–carbon bonds.

As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, $H_2C=O$, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols.

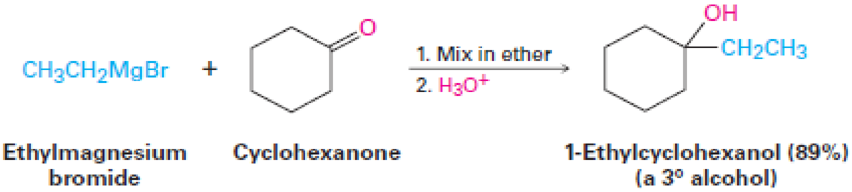
Formaldehyde reaction



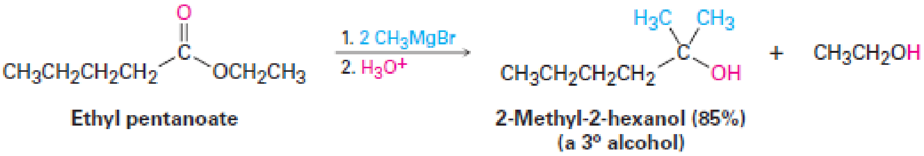
Aldehyde reaction



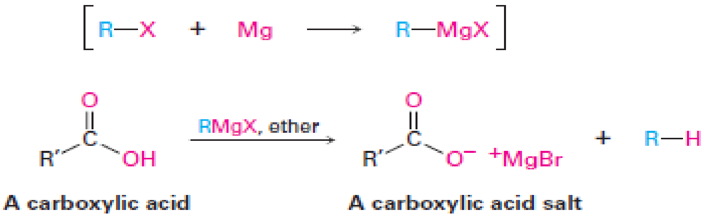
Ketone reaction



Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing carbon have come from the Grignard reagent, just as $LiAlH_4$ reduction of an ester adds two hydrogens.



Carboxylic acids don’t give addition products with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to yield a hydrocarbon and the magnesium salt of the acid.



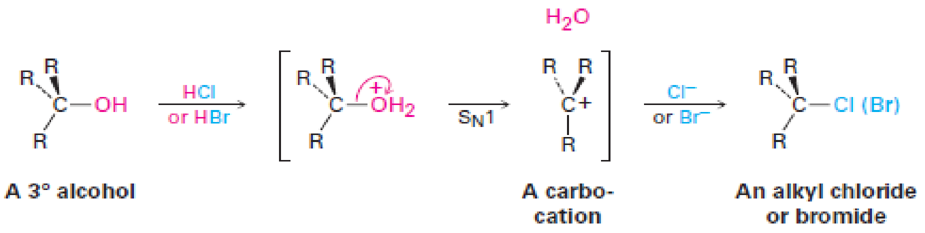
Reactions of Alcohols

Several reactions of alcohols their conversion into alkyl halides and tosylates and their dehydration to give alkenes in albeit without mechanistic details.

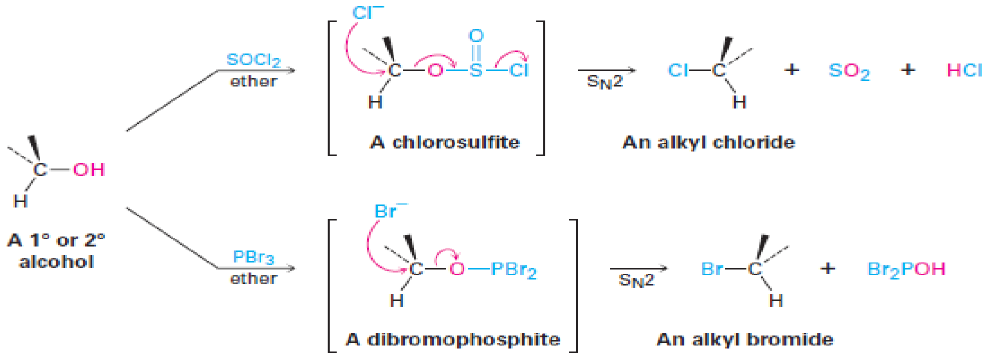
Conversion of Alcohols into Alkyl Halides

Tertiary alcohols react with either HCl or HBr at 0 °C by an S_N^1 mechanism through a carbocation intermediate. Primary and secondary alcohols are much more resistant to acid, however, and are best converted into halides by treatment with either $SOCl_2$ or PBr_3 through an S_N^2 mechanism.

The reaction of a tertiary alcohol with HX takes place by an S_N^1 mechanism when acid protonates the hydroxyl oxygen atom. Water is expelled to generate a carbocation, and the cation reacts with nucleophilic halide ion to give the alkyl halide product.



The reactions of primary and secondary alcohols with $SOCl_2$ and PBr_3 take place by S_N^2 mechanisms. Hydroxide ion itself is too poor a leaving group to be displaced by nucleophiles in S_N^2 reactions, but reaction of an alcohol with $SOCl_2$ or PBr_3 converts the -OH into a much better leaving group, either a chlorosulfite (-OSOCl) or a dibromophosphite (-$OPBr_2$), which is readily expelled by backside nucleophilic substitution.



One of the most important reasons for using tosylates in S_N^2 reactions is stereochemical. The S_N^2 reaction of an alcohol via an alkyl halide proceeds with *two* inversions of configuration one to make the halide from the alcohol and one to substitute the halide and yields a product with the same stereochemistry as the starting alcohol.

The S_N2 reaction of an alcohol via a tosylate, however, proceeds with only one inversion and yields a product of opposite stereochemistry to the starting alcohol. **Figure 17-5** shows a series of reactions on the *R* enantiomer of 2-octanol that illustrates these stereochemical relationships.

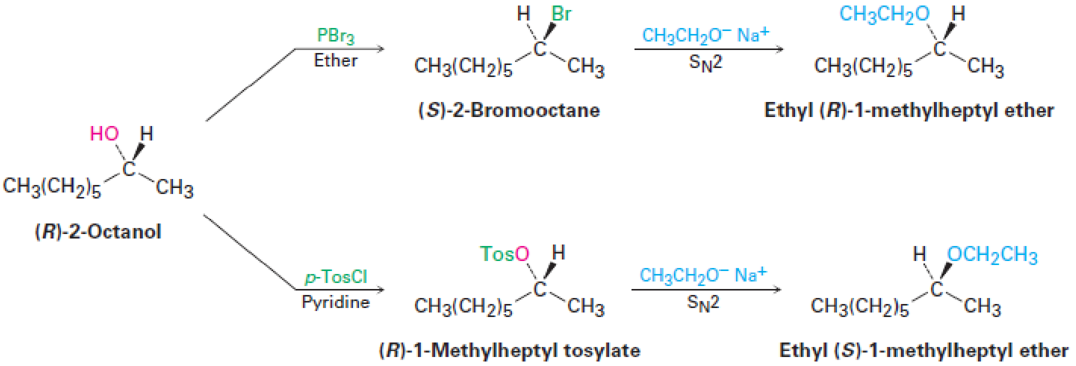
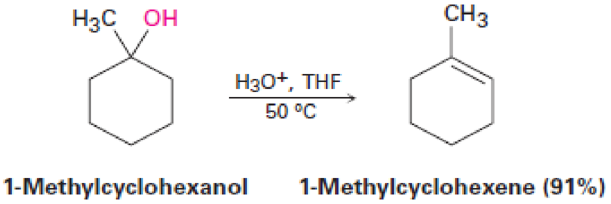


Figure 17-5 Stereochemical consequences of S_N2 reactions on derivatives of (*R*)-2-octanol. Substitution through the halide gives a product with the same stereochemistry as the starting alcohol; substitution through the tosylate gives a product with opposite stereochemistry to the starting alcohol.

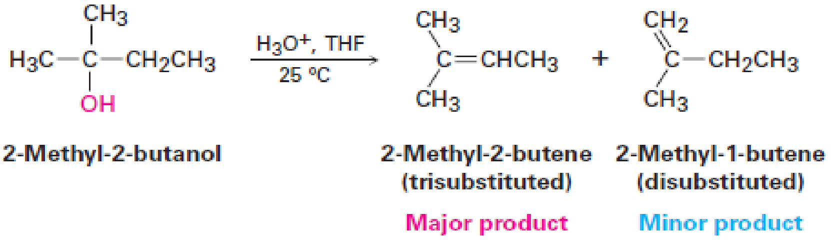
Dehydration of Alcohols to Yield Alkenes

A third important reaction of alcohols, both in the laboratory and in biological pathways, is their dehydration to give alkenes. Because of the usefulness of the reaction, a number of ways have been devised for carrying out dehydrations.

One method that works particularly well for tertiary alcohols is the acid catalyzed reaction. For example, treatment of 1-methylcyclohexanol with warm, aqueous sulfuric acid in a solvent such as tetrahydrofuran results in loss of water and formation of 1-methylcyclohexene.

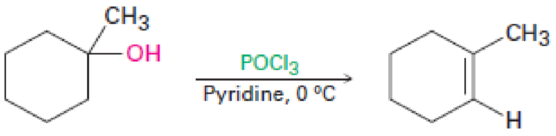


Acid-catalyzed dehydrations usually follow Zaitsev's rule and yield the more stable alkene as the major product. Thus, 2-methyl-2-butanol gives primarily 2-methyl-2-butene (trisubstituted double bond) rather than 2-methyl-1-butene (disubstituted double bond).



This reaction is an E_1 process and occurs by the three step mechanism. Protonation of the alcohol oxygen is followed by unimolecular loss of water to generate a carbocation intermediate and final loss of a proton from the neighboring carbon atom to complete the process. As with most E_1 reactions, tertiary alcohols react fastest because they lead to stabilized, tertiary carbocation intermediates.

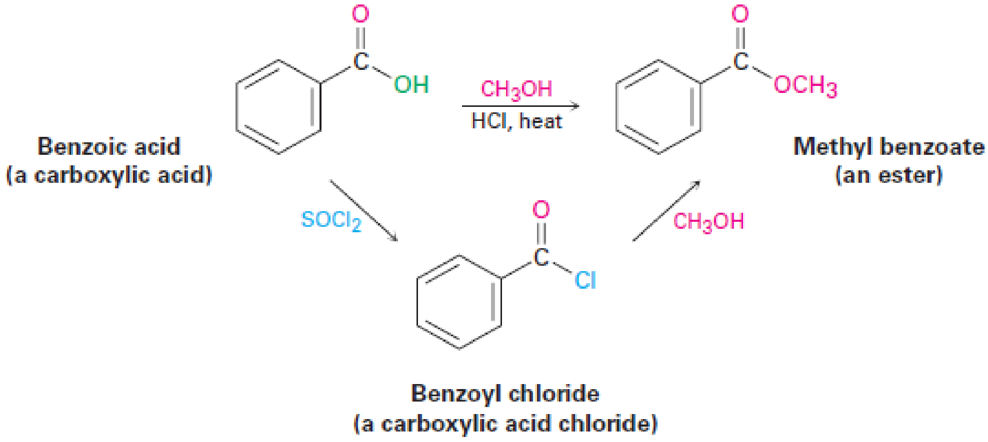
Secondary alcohols can be made to react, but the conditions are severe (75% H_2SO_4, 100 °C) and sensitive molecules don't survive. To circumvent the need for strong acid and allow the dehydration of secondary alcohols in a gentler way, reagents have been developed that are effective under mild, basic conditions. One such reagent, phosphorus oxychloride ($POCl_3$) in the basic amine solvent pyridine, is often able to effect the dehydration of secondary and tertiary alcohols at 0 °C.



1-Methylcyclohexanol **1-Methylcyclohexene (96%)**

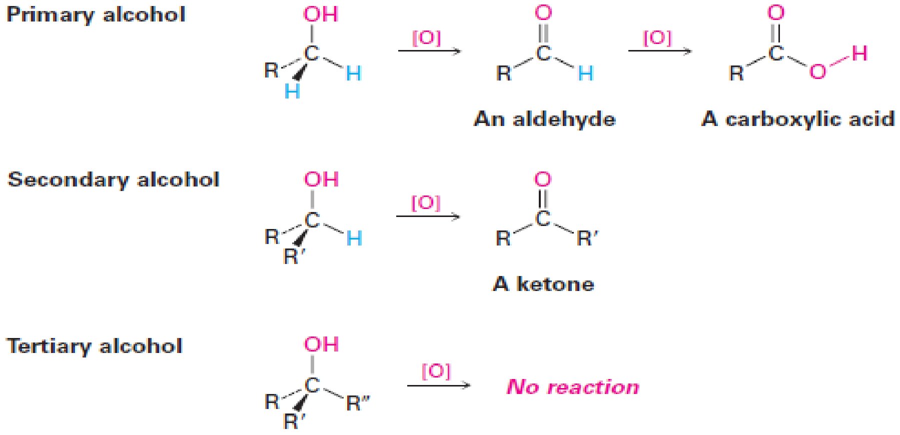
Conversion of Alcohols into Esters

Alcohols react with carboxylic acids to give esters, a reaction that is common in both the laboratory and living organisms. In the laboratory, the reaction can be carried out in a single step if a strong acid is used as catalyst. More frequently, though, the reactivity of the carboxylic acid is enhanced by first converting it into a carboxylic acid chloride, which then reacts with the alcohol.



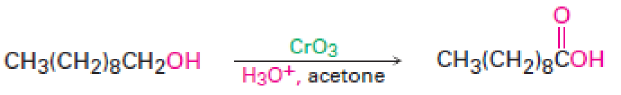
Oxidation of Alcohols

Perhaps the most valuable reaction of alcohols is their oxidation to give carbonyl compounds the opposite of the reduction of carbonyl compounds to give alcohols. Primary alcohols yield aldehydes or carboxylic acids, secondary alcohols yield ketones, but tertiary alcohols don’t normally react with most oxidizing agents.



The oxidation of a primary or secondary alcohol can be accomplished by any of a large number of reagents, including $KMnO_4$, CrO_3, and $Na_2Cr_2O_7$. Which reagent is used in a specific case depends on such factors as cost, convenience, reaction yield, and alcohol sensitivity.

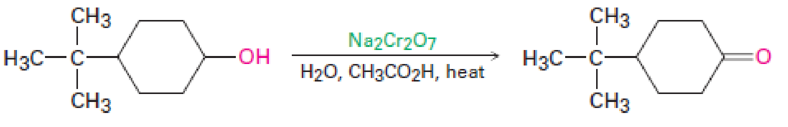
Most commonly used oxidizing agents, such as chromium trioxide (CrO_3) in aqueous acid, oxidize primary alcohols directly to carboxylic acids. An aldehyde is involved as an intermediate in this reaction but can’t usually be isolated because it is further oxidized too rapidly.



$$CH_3(CH_2)_8CH_2OH \xrightarrow[H_3O^+,\ \text{acetone}]{CrO_3} CH_3(CH_2)_8\overset{\overset{O}{\|}}{C}OH$$

1-Decanol Decanoic acid (93%)

Secondary alcohols are easily oxidized to give ketones. For a large-scale oxidation, however, an inexpensive reagent such as $Na_2Cr_2O_7$ in aqueous acetic acid might be used.



4-*tert*-Butylcyclohexanol 4-*tert*-Butylcyclohexanone (91%)