[**S U M M A R Y   A N D   R E V I E W   T O O L S**]

Some Synthetic Connections of Alkenes, Alkynes, Alcohols, Alkyl Halides, and Ethers

OH OH
| |
—C—C—
| |

(1) OsO$_4$
(2) NaHSO$_3$
(syn)

H$_2$O, HA or HO$^-$
(anti)

H$_2$, Ni$_2$B (syn)
or
(1) Li, EtNH$_2$
(2) NH$_4$$^+$
(anti)

—C≡C—

\C=C/
/   \

RCO$_3$H
(a peroxy acid)

O
/ \
—C—C—
| |

Nu:
(under acidic or
basic conditions)

OH
|
—C—C—
| |
Nu

Markovnikov
(1) Hg(OAc)$_2$,
THF/H$_2$O
(2) NaBH$_4$
or
H$_2$O, HA cat.

—C—C—OTBS

HA,
heat

Anti-Markovnikov
(1) BH$_3$:THF
(2) H$_2$O$_2$, HO$^-$

F$^-$

TBSCl,
imidazole

RO$^-$, E2 elim.
(best if RX is
2° or 3°, or
use bulky RO$^-$)

—C—C—OH

Oxidation/Reduction (Chapter 12)

O
‖
—C—C
| \
Y

Y = H, R, or OH
(also by alkene
oxidation, see
Chapter 8)

NaH or Na°, K°

TsCl or
MsCl, etc.
pyr

—C—C—O$^-$

HX
(Markov.)

HO$^-$
(1° RX)
or
H$_2$O
(3° RX)

I. HX
(1° or 3°)
or if 1° or 2°
II. PBr$_3$
or
III. SOCl$_2$

HBr, ROOR,
Δ (Anti-
Markov.)

—C—C—OTs (or Ms or Tf)

RX or ROTs
(if RX or ROTs is 1°)

—C—C—H

Br$_2$, $h\nu$ or Δ
(best if RH is 3°)

—C—C—X

R'O$^-$ (if RX or ROTs is 1°)

—C—C—OR'

• Alkynes to alkenes
• Alkenes and alcohols
• Alcohols and alkyl halides
• Alkenes and alkyl halides
• Alcohols and ethers
• Alkenes, epoxides, and 1,2-diols
• Alkanes to alkyl halides
• Alcohol silyl protecting group
• Alcohols to carbonyl compounds

Alcohols from Carbonyl Compounds

OXIDATION–REDUCTION AND ORGANOMETALLIC COMPOUNDS

Ask organic chemists about their favorite functional group, and a good percentage of them will name a group that contains a carbonyl group. Why? Because carbonyl groups are at the heart of many key functional groups, including aldehydes, ketones, carboxylic acids, amides, and more. Moreover, carbonyl groups are versatile, serving as a nexus for interconversions between many other kinds of functional groups. Add to these attributes two additional types of mechanistically related reactions—nucleophilic addition and nucleophilic addition-elimination—and you have one blockbuster group in terms of its chemistry.

As we have seen in earlier chapters, carbonyl groups are essential components of many natural compounds, they are intrinsic to some important synthetic materials, such as nylon, and they are central to the organic chemistry of life, whether in the form of carbohydrates or DNA, or in key biochemical processes.

IN THIS CHAPTER WE WILL CONSIDER:

- the structure and reactivity of carbonyl compounds
- the interconversion of carbonyl functional groups and alcohols through oxidation-reduction reactions
- the formation of new C—C bonds by reaction of certain carbonyl groups with organometallic reagents
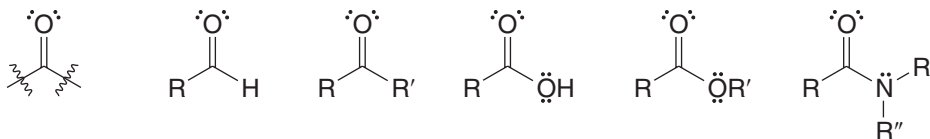
[WHY DO THESE TOPICS MATTER?] At the end of the chapter, we will see how the simple change from an alcohol to a ketone and back can fundamentally change the properties and uses of a molecule by looking at a few cases where such reactions occur in nature.

12.1 STRUCTURE OF THE CARBONYL GROUP

Carbonyl compounds are a broad group of compounds that includes aldehydes, ketones, carboxylic acids, esters, and amides.
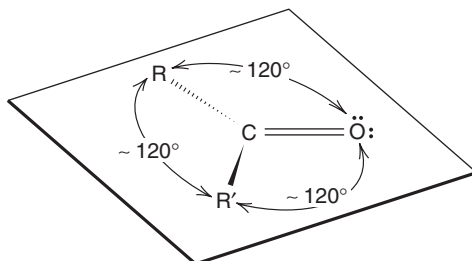
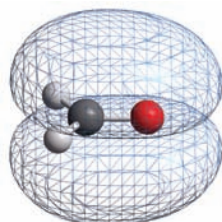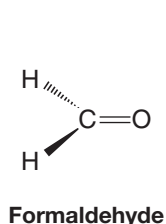**The carbonyl group**   **An aldehyde**   **A ketone**   **A carboxylic acid**   **An ester**   **An amide**

The carbonyl carbon atom is sp^2 hybridized; thus, it and the three atoms attached to it lie in the same plane. The bond angles between the three attached atoms are what we would expect of a trigonal planar structure; they are approximately 120°:

The carbon–oxygen double bond consists of two electrons in a σ bond and two electrons in a π bond. The π bond is formed by overlap of the carbon p orbital with a p orbital from the oxygen atom. The electron pair in the π bond occupies both lobes (above and below the plane of the σ bonds).
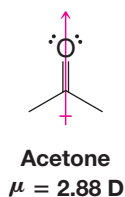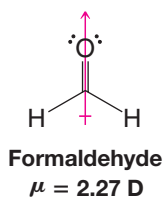
Formaldehyde

The π bonding molecular orbital of formaldehyde. The electron pair of the π bond occupies both lobes.

- The more electronegative oxygen atom strongly attracts the electrons of both the σ bond and the π bond, causing the carbonyl group to be highly polarized; the carbon atom bears a substantial positive charge and the oxygen atom bears a substantial negative charge.

Polarization of the π bond can be represented by the following resonance structures for the carbonyl group:

Resonance structures for the carbonyl group   or   **Hybrid**

Evidence for the polarity of the carbon–oxygen bond can be found in the rather large dipole moments associated with carbonyl compounds.

Formaldehyde
$\mu = 2.27$ D
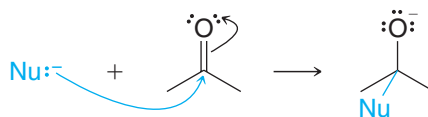
Acetone
$\mu = 2.88$ D

An electrostatic potential map for acetone indicates the polarity of the carbonyl group.

12.1A Reactions of Carbonyl Compounds with Nucleophiles

One of the most important reactions of carbonyl compounds is **nucleophilic addition to the carbonyl group**. The carbonyl group is susceptible to nucleophilic attack because, as we have just seen, the carbonyl carbon bears a partial positive charge.
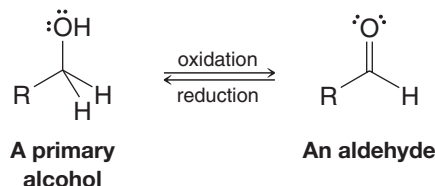
- When a nucleophile adds to the carbonyl group, it uses an electron pair to form a bond to the carbonyl carbon atom and an electron pair from the carbon–oxygen double bond shifts out to the oxygen:

As the reaction takes place, the carbon atom undergoes a change from trigonal planar geometry and sp^2 hybridization to tetrahedral geometry and sp^3 hybridization.

- Two important nucleophiles that add to carbonyl compounds are **hydride ions** from compounds such as $NaBH_4$ or $LiAlH_4$ (Section 12.3) and **carbanions** from compounds such as RLi or RMgX (Section 12.7C).

Another related set of reactions are reactions in which alcohols and carbonyl compounds are **oxidized** and **reduced** (Sections 12.2–12.4). For example, primary alcohols can be oxidized to aldehydes, and aldehydes can be reduced to alcohols:
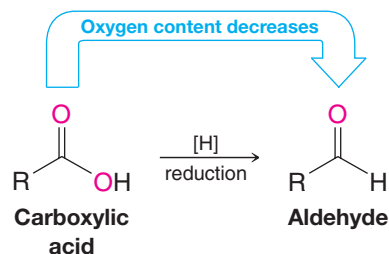
A primary alcohol   **An aldehyde**

Let us begin by examining some general principles that apply to the oxidation and reduction of organic compounds.
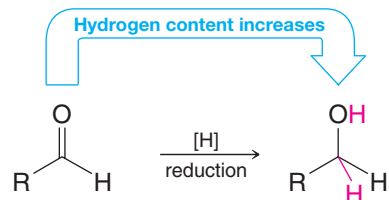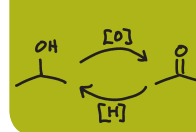
12.2 OXIDATION–REDUCTION REACTIONS IN ORGANIC CHEMISTRY

- **Reduction** of an organic molecule usually corresponds to increasing its hydrogen content or to decreasing its oxygen content.

For example, converting a carboxylic acid to an aldehyde is a reduction because the oxygen content is decreased:
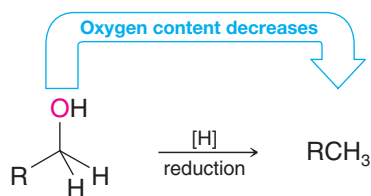
Carboxylic acid   **Aldehyde**

Converting an aldehyde to an alcohol is a reduction:

Converting an alcohol to an alkane is also a reduction:

Oxygen content decreases

$$\underset{R \quad \underset{H}{\overset{}{\vert}} \quad H}{\overset{\text{OH}}{\vert}} \xrightarrow[\text{reduction}]{\text{[H]}} RCH_3$$

In these examples we have used the symbol [H] to indicate that a reduction of the organic compound has taken place. We do this when we want to write a general equation without specifying what the reducing agent is.
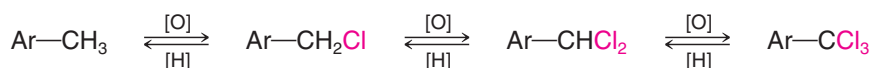
• The opposite of reduction is **oxidation**. Increasing the oxygen content of an organic molecule or decreasing its hydrogen content is an **oxidation**.

The reverse of each reaction that we have just given is an oxidation of the organic molecule, and we can summarize these oxidation–reduction reactions as shown below. We use the symbol [O] to indicate in a general way that the organic molecule has been oxidized.

$$R\text{CH}_3 \underset{\text{[H]}}{\overset{\text{[O]}}{\rightleftharpoons}} \underset{R \quad \overset{\vert}{\underset{H}{}} \quad H}{\overset{\text{OH}}{\vert}} \underset{\text{[H]}}{\overset{\text{[O]}}{\rightleftharpoons}} \underset{R \qquad H}{\overset{\text{O}}{\parallel}} \underset{\text{[H]}}{\overset{\text{[O]}}{\rightleftharpoons}} \underset{R \qquad \text{OH}}{\overset{\text{O}}{\parallel}}$$

Lowest oxidation state   **Highest oxidation state**

• Oxidation of an organic compound may be more broadly defined as a reaction that increases its content of any element more electronegative than carbon.

For example, replacing hydrogen atoms by chlorine atoms is an oxidation:

$$Ar-CH_3 \underset{\text{[H]}}{\overset{\text{[O]}}{\rightleftharpoons}} Ar-CH_2Cl \underset{\text{[H]}}{\overset{\text{[O]}}{\rightleftharpoons}} Ar-CHCl_2 \underset{\text{[H]}}{\overset{\text{[O]}}{\rightleftharpoons}} Ar-CCl_3$$

Of course, when an organic compound is reduced, something else—the **reducing agent**—must be oxidized. And when an organic compound is oxidized, something else—the **oxidizing agent**—is reduced. These oxidizing and reducing agents are often inorganic compounds, and in the next two sections we shall see what some of them are.

> **Helpful Hint**
>
> Note the general interpretation of oxidation–reduction regarding organic compounds.

12.2A Oxidation States in Organic Chemistry

One method for assigning oxidation states in organic compounds is similar to the method we used for assigning formal charges (Section 1.7). We base the assignment on **the groups attached to the carbon (or carbons) whose oxidation state undergoes change in the reaction we are considering**. Recall that with formal charges we assumed that electrons in covalent bonds are shared equally. *When assigning oxidation states to carbon atoms we assign electrons to the more electronegative element* (see Section 1.4A and Table 1.2). For example, a bond to hydrogen (or to any atom less electronegative than carbon) makes that carbon negative by one unit (-1), and a bond to oxygen, nitrogen, or a halogen (F, Cl, and Br) makes the carbon positive by one unit ($+1$). A bond to another carbon does not change its oxidation state.

Using this method the carbon atom of methane, for example, is assigned an oxidation state of -4, and that of carbon dioxide, $+4$.
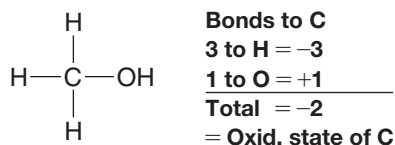
> **Helpful Hint**
>
> A method for balancing organic oxidation–reduction reactions is described in the Study Guide that accompanies this text.
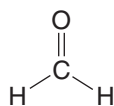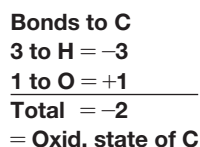
●●● SOLVED PROBLEM 12.1

Using the method just described, assign oxidation states to the carbon atoms of methanol (CH_3OH), formaldehyde ($HCHO$), and formic acid (HCO_2H) and arrange these compounds along with carbon dioxide and methane (see above) in order of increasing oxidation state.

STRATEGY AND ANSWER: We calculate the oxidation state of each carbon based on the number of bonds it is forming to atoms more (or less) electronegative than carbon.
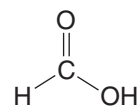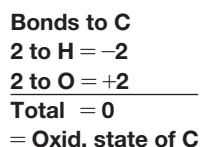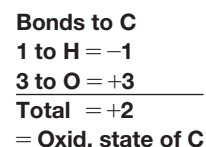
(continues on next page)

Methanol

Bonds to C
3 to H = −3
1 to O = +1
Total = −2
= Oxid. state of C

Formaldehyde

Bonds to C
2 to H = −2
2 to O = +2
Total = 0
= Oxid. state of C

Formic acid

Bonds to C
1 to H = −1
3 to O = +3
Total = +2
= Oxid. state of C

The order overall, based on the oxidation state of carbon in each compound, is

$$CH_4 = -4 < CH_3OH = -2 < HCHO = 0 < HCOOH = +2 < CO_2 = +4$$

Lowest
Oxid. state
of carbon

Highest
Oxid. state
of carbon

PRACTICE PROBLEM 12.1

Ethanol [O]→ **Acetaldehyde** [O]→ **Acetic acid**

Assign oxidation states to each carbon of ethanol, acetaldehyde, and acetic acid.

PRACTICE PROBLEM 12.2 **(a)** Although we have described the hydrogenation of an alkene as an addition reaction, organic chemists often refer to it as a "reduction." Use the method described in Section 12.2A for assigning oxidation states to explain this usage of the word "reduction."

$$\xrightarrow[\text{Pt}]{H_2}$$

(b) Provide a similar analysis for this reaction:

$$\xrightarrow[\text{Ni}]{H_2} \quad \text{OH}$$

12.3 ALCOHOLS BY REDUCTION OF CARBONYL COMPOUNDS
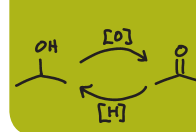
Unless special precautions are taken, lithium aluminum hydride reductions can be very dangerous. You should consult an appropriate laboratory manual before attempting such a reduction, and the reaction should be carried out on a small scale.

Primary and secondary alcohols can be synthesized by the **reduction** of a variety of compounds that contain the carbonyl group. Several general examples are shown here:
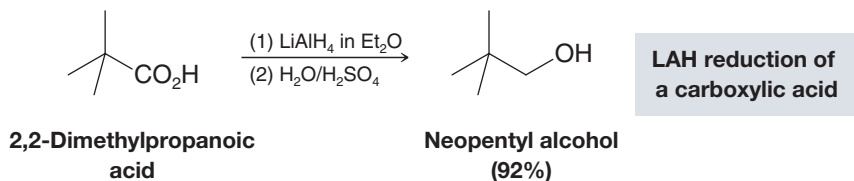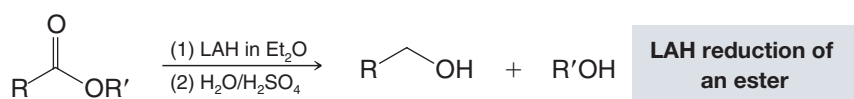
Carboxylic acid —[H]→ **1° Alcohol**

Ester —[H]→ **1° Alcohol** (+ R′OH)

Aldehyde —[H]→ **1° Alcohol**

Ketone —[H]→ **2° Alcohol**

12.3A Lithium Aluminum Hydride

- Lithium aluminum hydride ($LiAlH_4$, abbreviated LAH) reduces carboxylic acids and esters to primary alcohols.

An example of lithium aluminum hydride reduction is the conversion of 2,2-dimethylpropanoic acid to 2,2-dimethylpropanol (neopentyl alcohol).

2,2-Dimethylpropanoic acid → **Neopentyl alcohol (92%)**

LAH reduction of a carboxylic acid

LAH reduction of an ester yields two alcohols, one derived from the carbonyl part of the ester group, and the other from the alkoxyl part of the ester.

LAH reduction of an ester

Carboxylic acids and esters are more difficult to reduce than aldehydes and ketones. LAH, however, is a strong enough **reducing agent** to accomplish this transformation. Sodium borohydride ($NaBH_4$), which we shall discuss shortly, is commonly used to reduce aldehydes and ketones, but it is not strong enough to reduce carboxylic acids and esters.

Great care must be taken when using LAH to avoid the presence of water or any other weakly acidic solvent (e.g., alcohols). **LAH reacts violently with proton donors to release hydrogen gas**. Anhydrous diethyl ether (Et_2O) is a commonly used solvent for LAH reductions. After all of the LAH has been consumed by the reduction step of the reaction, however, water and acid are added to neutralize the resulting salts and facilitate isolation of the alcohol products.

12.3B Sodium Borohydride

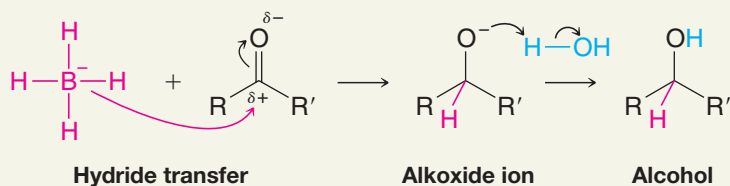- Aldehydes and ketones are easily reduced by sodium borohydride ($NaBH_4$).

Sodium borohydride is usually preferred over LAH for the reduction of aldehydes and ketones. Sodium borohydride can be used safely and effectively in water as well as alcohol solvents, whereas special precautions are required when using LAH.

Butanal → **1-Butanol (85%)**

$NaBH_4$ reduction of a aldehyde

Butanone → **2-Butanol (87%)**

$NaBH_4$ reduction of an ketone

Aldehydes and ketones can be reduced using hydrogen and a metal catalyst, as well, and by sodium metal in an alcohol solvent.

The key step in the reduction of a carbonyl compound by either lithium aluminum hydride or sodium borohydride is the transfer of a **hydride ion** from the metal to the carbonyl carbon. In this transfer the hydride ion acts as a *nucleophile*. The mechanism for the reduction of a ketone by sodium borohydride is illustrated here.

A MECHANISM FOR THE REACTION — Reduction of Aldehydes and Ketones by Hydride Transfer

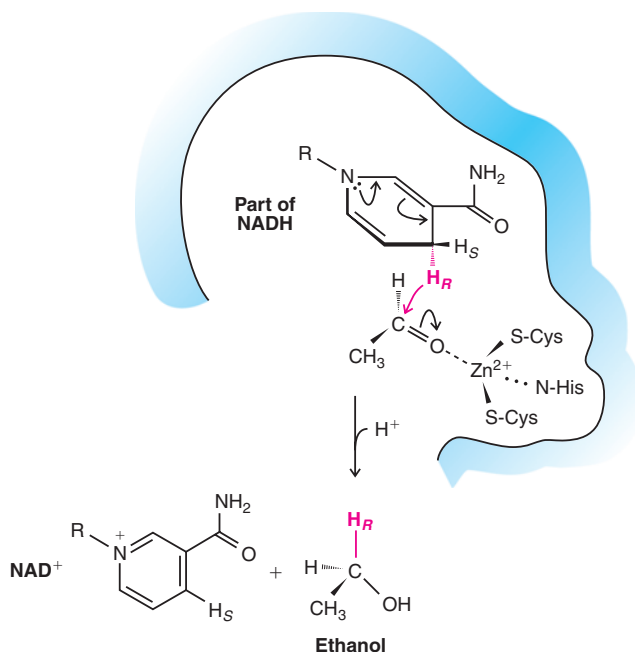**Hydride transfer**   **Alkoxide ion**   **Alcohol**

These steps are repeated until all hydrogen atoms attached to boron have been transferred.

THE CHEMISTRY OF... Alcohol Dehydrogenase—A Biochemical Hydride Reagent

When the enzyme alcohol dehydrogenase converts acetaldehyde to ethanol, NADH acts as a reducing agent by transferring a hydride from **C4** of the nicotinamide ring to the carbonyl group of acetaldehyde. The nitrogen of the nicotinamide ring facilitates this process by contributing its nonbonding electron pair to the ring, which together with loss of the hydride converts the ring to the energetically more stable ring found in NAD$^+$ (we shall see why it is more stable in Chapter 14). The ethoxide anion resulting from hydride transfer to acetaldehyde is then protonated by the enzyme to form ethanol.

Although the carbonyl carbon of acetaldehyde that accepts the hydride is inherently electrophilic because of its electronegative oxygen, the enzyme enhances this property by providing a zinc ion as a Lewis acid to coordinate with the carbonyl oxygen. The Lewis acid stabilizes the negative charge that develops on the oxygen in the transition state. The role of the enzyme's protein scaffold, then, is to hold the zinc ion, coenzyme, and substrate in the three-dimensional array required to lower the energy of the transition state. The reaction is entirely reversible, of course, and when the relative concentration of ethanol is high, alcohol dehydrogenase carries out the oxidation of ethanol by removal of a hydride. This role of alcohol dehydrogenase is important in detoxification. In "The Chemistry of… Stereoselective Reductions of Carbonyl

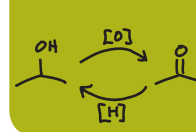Groups" we discuss the stereochemical aspect of alcohol dehydrogenase reactions.

12.3C Overall Summary of LiAlH$_4$ and NaBH$_4$ Reactivity

Sodium borohydride is a less powerful reducing agent than lithium aluminum hydride. Lithium aluminum hydride reduces acids, esters, aldehydes, and ketones, but sodium borohydride reduces only aldehydes and ketones:
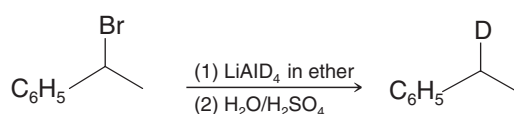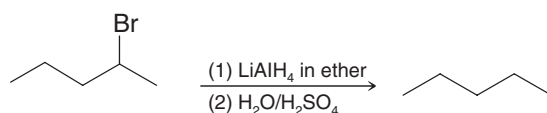
Lithium aluminum hydride reacts violently with water, and therefore reductions with lithium aluminum hydride must be carried out in anhydrous solutions, usually in anhydrous ether. (Ethyl acetate is added cautiously after the reaction is over to decompose excess $LiAlH_4$; then water is added to decompose the aluminum complex.) Sodium borohydride reductions, by contrast, can be carried out in water or alcohol solutions.
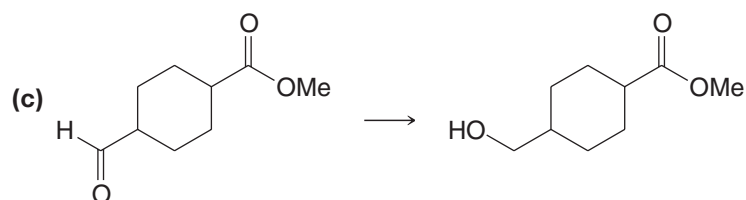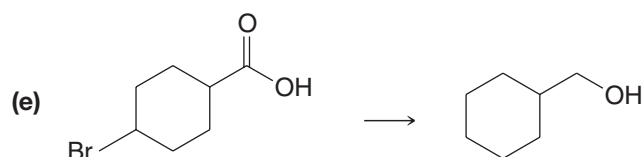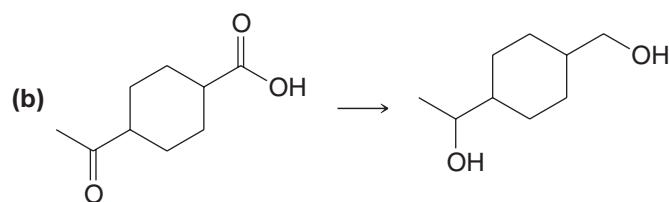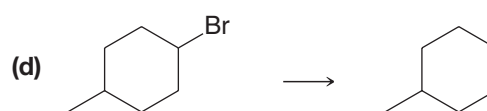
12.3D Reduction of Alkyl Halides to Hydrocarbons: RX $\longrightarrow$ RH

Replacement of the halogen atom of an alkyl halide by hydrogen can be accomplished by treating the alkyl halide with lithium aluminum hydride (Section 12.3A). Because a halogen atom with a higher oxidation state is replaced by a hydrogen atom with a lower oxidation state, this reaction is a reduction. Almost all types of alkyl halides (primary, secondary, tertiary) can be reduced by $LiAlH_4$. $LiAlD_4$ can be used to replace the halogen atom with a deuterium atom.

Which reducing agent, $LiAlH_4$ or $NaBH_4$, would you use to carry out the following transformations?

◆◆ THE CHEMISTRY OF... Stereoselective Reductions of Carbonyl Groups
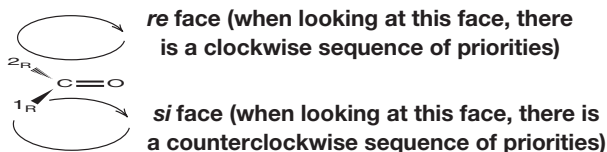
Enantioselectivity

The possibility of **stereoselective** reduction of a carbonyl group is an important consideration in many syntheses. Depending on the structure about the carbonyl group that is being reduced, the tetrahedral carbon that is formed by transfer of a hydride could be a new chirality center. Achiral reagents, like $NaBH_4$ and $LiAlH_4$, react with equal rates at either face of an achiral trigonal planar substrate, leading to a racemic form of the product. But enzymes, for example, are chiral, and reactions involving a chiral reactant typically lead to a predominance of one enantiomeric form of a chiral product. Such a reaction is said to be **enantioselective**. Thus, when enzymes like alcohol dehydrogenase reduce carbonyl groups using the coenzyme NADH (see "The Chemistry of . . . Alcohol Dehydrogenase"), they discriminate between the two faces of the trigonal planar carbonyl substrate, such that a predominance of one of the two possible stereoisomeric forms of the tetrahedral product results. (If the original reactant was chiral, then formation of the new chirality center may result in preferential formation of one diastereomer of the product, in which case the reaction is said to be **diastereoselective**.)

Thermophilic bacteria, growing in hot springs like these at Yellowstone National Park, produce heat-stable enzymes called extremozymes that have proven useful for a variety of chemical processes.
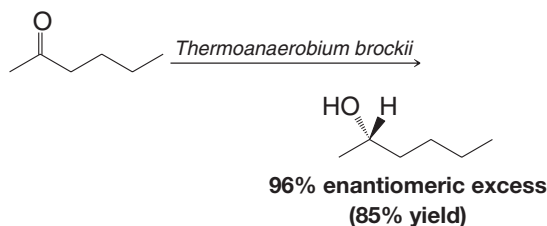
The two faces of a trigonal planar center are designated re and si, according to the direction of Cahn–Ingold–Prelog priorities (Section 5.7) for the groups bonded at the trigonal center when viewed from one face or the other (re is clockwise, si is counterclockwise):
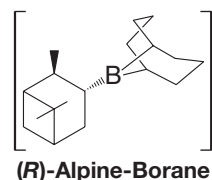

re face (when looking at this face, there is a clockwise sequence of priorities)

si face (when looking at this face, there is a counterclockwise sequence of priorities)

The re and si faces of a carbonyl group (where O > ¹R > ²R in terms of Cahn–Ingold–Prelog priorities)

The preference of many NADH-dependent enzymes for either the re or si face of their respective substrates is known. This
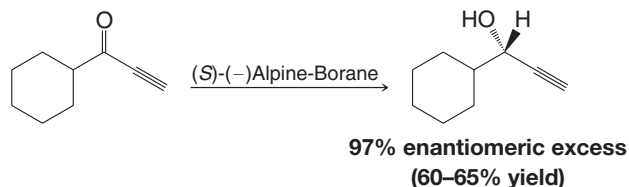
knowledge has allowed some of these enzymes to become exceptionally useful stereoselective reagents for synthesis. One of the most widely used is yeast alcohol dehydrogenase. Others that have become important are enzymes from thermophilic bacteria (bacteria that grow at elevated temperatures). Use of heat-stable enzymes (called **extremozymes**) allows reactions to be completed faster due to the rate-enhancing factor of elevated temperature (over 100 °C in some cases), although greater enantioselectivity is achieved at lower temperatures.

Thermoanaerobium brockii

**96% enantiomeric excess
(85% yield)**

A number of chemical reagents that are chiral have also been developed for the purpose of stereoselective reduction of carbonyl groups. Most of them are derivatives of standard aluminum or boron hydride reducing agents that involve one or more chiral organic ligands. (S)-Alpine-Borane and (R)-Alpine-Borane, for example, are reagents derived from diborane (B_2H_6) and either (−)-α-pinene or (+)-α-pinene (enantiomeric natural hydrocarbons), respectively. Reagents derived from $LiAlH_4$ and chiral amines have also been developed. The extent of stereoselectivity achieved either by enzymatic reduction or reduction by a chiral reducing agent depends on the specific structure of the substrate.
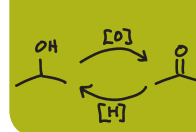

(R)-Alpine-Borane

Often it is necessary to test several reaction conditions in order to achieve optimal stereoselectivity.

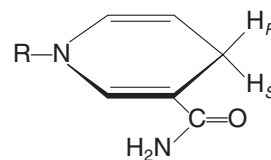(S)-(−)Alpine-Borane

**97% enantiomeric excess
(60–65% yield)**

Prochirality

A second aspect of the stereochemistry of NADH reactions results from NADH having two hydrogens at C4, either of which could, in principle, be transferred as a hydride in a reduction process. For a given enzymatic reaction, however, only one specific hydride from C4 in NADH is transferred. Just which hydride is transferred depends on the specific enzyme involved, and we designate it by a useful extension of stereochemical nomenclature. The hydrogens at C4 of NADH are said to be **prochiral**. We designate one **pro-R**, and the other **pro-S**,
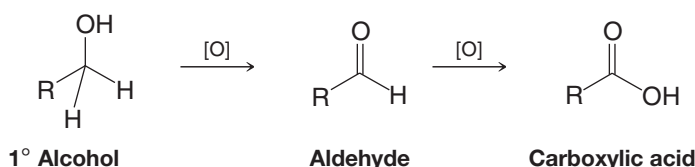
depending on whether the configuration would be *R* or *S* when, in our imagination, each is replaced by a group of higher priority than hydrogen. If this exercise produces the *R* configuration, the hydrogen "replaced" is pro-*R*, and if it produces the *S* configuration it is pro-*S*. In general, a **prochiral center** is one for which addition of a group to a trigonal planar atom (as in reduction of a ketone) or replacement of one of two identical groups at a tetrahedral atom leads to a new chirality center.
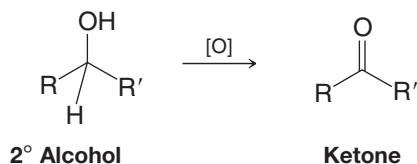
Nicotinamide ring of NADH, showing the pro-*R* and pro-*S* hydrogens

12.4 OXIDATION OF ALCOHOLS

Primary alcohols can be oxidized to aldehydes, and aldehydes can be oxidized to carboxylic acids:

1° Alcohol   **Aldehyde**   **Carboxylic acid**

Secondary alcohols can be oxidized to ketones:

2° Alcohol   **Ketone**

Tertiary alcohols cannot be oxidized to carbonyl compounds.

3° Alcohol

These examples have one aspect in common: when **oxidation** takes place, a hydrogen atom is lost from the alcohol or aldehyde carbon. A tertiary alcohol has no hydrogen on the alcohol carbon, and thus it cannot be oxidized in this way.

12.4A A Common Mechanistic Theme

Oxidations of primary and secondary alcohols, like those above, follow a common mechanistic path when certain reagents are used. These reagents, some of which we will discuss below, temporarily install a leaving group on the hydroxyl oxygen during the reaction. Loss of a hydrogen from the hydroxyl carbon and departure of the leaving group from the oxygen result in an elimination that forms the $C=O$ π bond. Formation of the carbonyl double bond essentially occurs in a fashion analogous to formation of an alkene double bond by an elimination reaction. The general pathway is shown here.

Alcohol Oxidation by Elimination
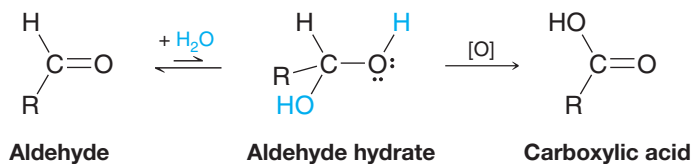

A 1° or 2° alcohol reacts with a reagent that installs a leaving group (LG) on the alcohol oxygen atom.

In an elimination step, a base removes a hydrogen from the alcohol carbon, the $C=O$ π bond forms, and the leaving group departs, resulting in the oxidized product.

Primary and secondary alcohols have the required hydrogen atom at the alcohol carbon. They also have the hydroxyl hydrogen that is lost when the leaving group is installed, as shown above.

You might ask how an aldehyde can be oxidized by this mechanism, since an aldehyde does not contain a hydroxyl group to participate as shown above. The answer lies in whether the aldehyde reaction mixture includes water or not. In the presence of water, an aldehyde can form an aldehyde hydrate (by an **addition reaction** that we shall study in Chapter 16).

Aldehyde   **Aldehyde hydrate**   **Carboxylic acid**

The carbon of an aldehyde hydrate has both a hydroxyl group and the hydrogen atom required for elimination; thus when water is present, an aldehyde can be oxidized by the mechanism shown above. Although the aldehyde hydrate may be present in low equilibrium concentration, those molecules in the hydrate form can be oxidized, drawing the reaction ultimately toward oxidation of all of aldehyde molecules to the corresponding carboxylic acid via LeChatelier's principle.

Aldehydes cannot be oxidized by the general mechanism above when water is absent. This fact proves to be useful when choosing conditions leading to specifically an aldehyde or a carboxylic acid from a primary alcohol.

Now let us consider some specific oxidation methods that hinge on the general mechanism shown above: the Swern oxidation, and oxidations involving chromate esters.

12.4B Swern Oxidation

The Swern oxidation is broadly useful for the synthesis of aldehydes and ketones from primary and secondary alcohols, respectively. The reaction is conducted in the absence of water, thus primary alcohols form aldehydes and not carboxylic acids. Secondary alcohols are oxidized to ketones.

Swern oxidation of a 1° alcohol to an aldehyde

Swern oxidation of a 2° alcohol to a ketone

The reaction is carried out in sequential operations. First, oxalyl chloride ($ClCOCOCl$) is added to dimethyl sulfoxide ($DMSO$), usually at low temperature, to generate a chlorodimethylsulfonium salt (as well as CO_2, CO, and HCl by-products). The alcohol substrate is then added to the chlorodimethylsulfonium salt, during which time a dimethylsulfonium group is installed as a leaving group on the hydroxyl oxygen. Third, an amine is added as a base to promote the elimination reaction.
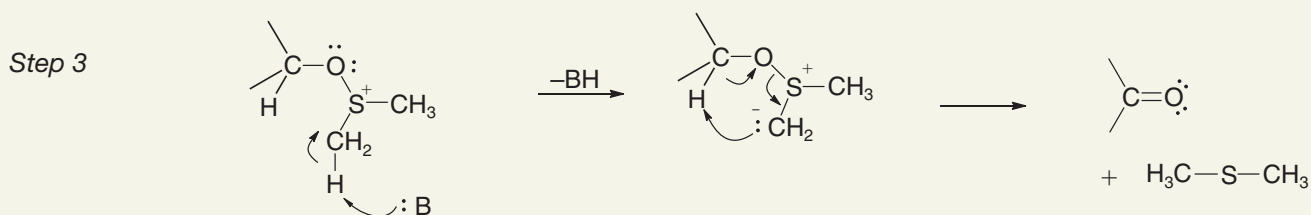
A MECHANISM FOR THE REACTION — The Swern Oxidation

Step 1

Dimethylsulfoxide (DMSO)   **Oxalyl chloride (COCl)$_2$**   **Chlorodimethylsulfonium salt** $+$ CO_2
$+$ CO

DMSO and oxalyl chloride react to form a chlorodimethylsulfonium salt.

Step 2

The 1° or 2° alcohol reacts with the sulfonium salt, installing a leaving group on the alcohol oxygen atom, along with loss of the hydroxyl proton.

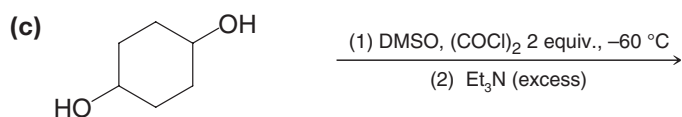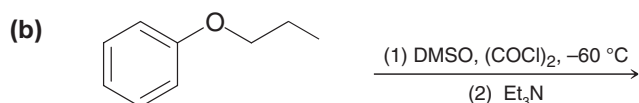The oxygen now bears a leaving group that can be lost in an elimination reaction.

Step 3

A base (usually triethylamine or diisopropylamine) removes a hydrogen from a methyl group adjacent to the positively–charged sulfur.

The anionic methyl group removes a proton from the alcohol carbon, forming the C=O π–bond. Dimethylsulfide departs as a leaving group, resulting in the oxidized product.

Reagents other than oxalyl chloride, including trifluoroacetic anhydride, have been used to generate various dimethylsulfonium salts for reaction with the alcohol.

PRACTICE PROBLEM 12.4

What oxidation product would result from each of the following reactions?

(a)

(1) DMSO, (COCl)₂, –60 °C
(2) Et₃N

(b)

(1) DMSO, (COCl)₂, –60 °C
(2) Et₃N

(c)

(1) DMSO, (COCl)₂ 2 equiv., –60 °C
(2) Et₃N (excess)

12.4C Chromic Acid (H_2CrO_4) Oxidation

Oxidations involving chromium (VI) reagents such as H_2CrO_4 are simple to carry out and have been widely used. These reactions involve formation of chromate esters, and include an elimination step similar to the general mechanisms shown in Section 12.4A. Chromium (VI) is a carcinogen and an environmental hazard, however. For this reason, methods like the Swern oxidation and others are increasingly important.

Jones reagent is one well-known source of H_2CrO_4 as the chromium (VI) oxidizing species. It can be prepared by adding CrO_3 or Na_2CrO_4 to aqueous sulfuric acid. Jones reagent is typically used by addition to solutions of an alcohol or aldehyde in acetone or acetic acid (solvents that cannot be oxidized). Primary alcohols are oxidized to carboxylic acids, via the aldehyde hydrate mentioned above. Secondary alcohols are oxidized to ketones. The following is an example of an oxidation using Jones reagent.

Cyclooctanol

**Cyclooctanol
(92–96%)**

As mentioned earlier, the chromate oxidation mechanism first involves formation of a chromate ester with the alcohol. Then a molecule of H_2CrO_3 serves as a leaving group during the elimination step that generates the $C{=}O$ bond of the carbonyl compound.

A MECHANISM FOR THE REACTION — Chromic Acid Oxidation

Formation of the Chromate Ester

Step 1

The 1° or 2° alcohol reacts with chromic acid to form a chromate ester with loss of water, installing a leaving group on the alcohol oxygen.

The oxygen now bears a leaving group that can be lost in an elimination reaction.

Oxidation by Elimination of H_2CrO_3

Step 2

A water molecule removes a proton from the alcohol carbon, forming the C=O π–bond. The chromium atom is reduced as H_2CrO_3 departs, resulting in the oxidized product.

Chromic acid solutions are orange-red in color, and the product mixture, containing Cr(III), is a greenish blue. Thus, reagents like Jones reagent can serve as a color-based functional group test. Primary or secondary alcohols and aldehydes are rapidly oxidized by Jones reagent, turning the solution an opaque greenish blue within a few seconds. If none of these groups are present, the solution remains orange-red until side reactions eventually change the color. This color change is the basis for the original **breathalyzer alcohol test**.

$$H_2CrO_4 \xrightarrow[\text{or aldehyde}]{\text{Add 1° or 2° alcohol}} H_2CrO_3 + \text{Oxidation products}$$

Clear orange-red solution   **Opaque green-blue solution**

12.4D Pyridinium Chlorochromate (PCC)

Pyridinium chlorochromate (PCC) is a $Cr(VI)$ salt formed between pyridine (C_6H_5N), HCl, and CrO_3. PCC is soluble in dichloromethane, thus it can be used under conditions that exclude water, allowing for the oxidization of primary alcohols to aldehydes because the aldehyde hydrate is not present under anhydrous conditions. Jones reagent, on the other hand, oxidizes primary alcohols to carboxylic acids because it is an aqueous reagent. The following are some general examples of PCC oxidations.

Pyridinium chlorochromate (PCC)

PCC oxidation of a 1° alcohol to an aldehyde

2-Ethyl-2-methyl-1-butanol   **2-Ethyl-2-methylbutanal**

PCC oxidation of a 2° alcohol to a ketone

12.4E Potassium Permanganate ($KMnO_4$)

Primary alcohols and aldehydes can be oxidized by potassium permanganate ($KMnO_4$) to the corresponding carboxylic acids. Secondary alcohols can be oxidized to ketones. These reactions do not proceed by the type of mechanism described above (and we shall not discuss the mechanism here). The reaction is usually carried out in basic aqueous solution, from which MnO_2 precipitates as the oxidation takes place. After the oxidation is complete, filtration allows removal of the MnO_2 and acidification of the filtrate gives the carboxylic acid.

●●● **SOLVED PROBLEM 12.2**

Which reagents would you use to accomplish the following transformations?

STRATEGY AND ANSWER:

(a) To oxidize a primary alcohol to a carboxylic acid, use (1) potassium permanganate in aqueous base, followed by (2) H_3O^+, or use chromic acid (H_2CrO_4).

(b) To reduce a carboxylic acid to a primary alcohol, use $LiAlH_4$.

(c) To oxidize a primary alcohol to an aldehyde, use the Swern oxidation or pyridinium chlorochromate (PCC).

(d) To reduce an aldehyde to a primary alcohol, use $NaBH_4$ (preferably) or $LiAlH_4$.

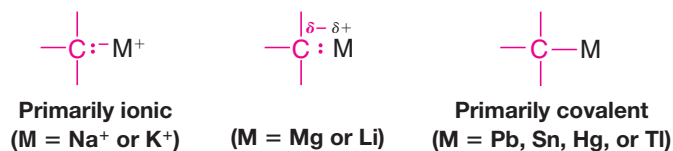**PRACTICE PROBLEM 12.5** Show how each of the following transformations could be accomplished:

(a) [cyclopentyl-CH₂OH] $\xrightarrow{?}$ [cyclopentyl-CHO]

(b) [cyclopentyl-CH₂OH] $\xrightarrow{?}$ [cyclopentyl-COOH]

(c) [cyclopentanol] $\xrightarrow{?}$ [cyclopentanone]

(d) [cyclopentene] $\xrightarrow{?}$ [pentanedial: H-CO-CH₂CH₂CH₂-CO-H]

(e) [cyclopentyl-Br] $\longrightarrow$ [cyclopentane]

12.4F Spectroscopic Evidence for Alcohols

- Alcohols give rise to broad O—H stretching absorptions from 3200 to 3600 cm^{-1} in infrared spectra.
- The alcohol hydroxyl hydrogen typically produces a broad ^1H NMR signal of variable chemical shift which can be eliminated by exchange with deuterium from D_2O (see Table 9.1).
- Hydrogen atoms on the carbon of a primary or secondary alcohol produce a signal in the ^1H NMR spectrum between δ 3.3 and δ 4.0 (see Table 9.1) that integrates for 2 and 1 hydrogens, respectively.
- The ^{13}C NMR spectrum of an alcohol shows a signal between δ 50 and δ 90 for the alcohol carbon (see Table 9.2).

12.5 ORGANOMETALLIC COMPOUNDS

- Compounds that contain carbon–metal bonds are called **organometallic compounds**.

The nature of the carbon–metal bond varies widely, ranging from bonds that are essentially ionic to those that are primarily covalent. Whereas the structure of the organic portion of the organometallic compound has some effect on the nature of the carbon–metal bond, the identity of the metal itself is of far greater importance. Carbon–sodium and carbon–potassium bonds are largely ionic in character; carbon–lead, carbon–tin, carbon–thallium, and carbon–mercury bonds are essentially covalent. Carbon–lithium and carbon–magnesium bonds lie between these extremes.

$$-\overset{|}{\underset{|}{C}}{:}^- M^+ \qquad -\overset{|}{\underset{|}{\overset{\delta-\ \delta+}{C}}}{:}\,M \qquad -\overset{|}{\underset{|}{C}}-M$$

Primarily ionic   **Primarily covalent**
(M = Na⁺ or K⁺)   **(M = Mg or Li)**   **(M = Pb, Sn, Hg, or Tl)**

The reactivity of organometallic compounds increases with the percent ionic character of the carbon–metal bond. Alkylsodium and alkylpotassium compounds are highly reactive and are among the most powerful of bases. They react explosively with water and burst into flame when exposed to air. Organomercury and organolead compounds are much less reactive; they are often volatile and are stable in air. They are all poisonous. They are generally soluble in nonpolar solvents. Tetraethyllead, for example, was once used as an "antiknock" compound in gasoline, but because of the lead pollution it contributed to the environment it has been replaced by other antiknock agents. *tert*-Butyl methyl ether is another antiknock additive, though there are concerns about its presence in the environment, as well.

Organometallic compounds of lithium and magnesium are of great importance in organic synthesis. They are relatively stable in ether solutions, but their carbon–metal bonds have considerable ionic character. Because of this ionic nature, the carbon atom that is bonded to the metal atom of an organolithium or organomagnesium compound is a strong base and powerful nucleophile. We shall soon see reactions that illustrate both of these properties.

12.6 PREPARATION OF ORGANOLITHIUM AND ORGANOMAGNESIUM COMPOUNDS

12.6A Organolithium Compounds

Organolithium compounds are often prepared by the reduction of organic halides with lithium metal. These reductions are usually carried out in ether solvents, and since organolithium compounds are strong bases, care must be taken to exclude moisture. (Why?) The ethers most commonly used as solvents are diethyl ether and tetrahydrofuran. (Tetrahydrofuran is a cyclic ether.)

Diethyl ether
(Et$_2$O)

Tetrahydrofuran
(THF)

- Organolithium compounds are prepared in this general way:

$$R{-}X \ + \ 2\,Li \ \xrightarrow{\text{Et}_2\text{O}} \ RLi \ + \ LiX$$
(or Ar$-$X)   **(or ArLi)**

The order of reactivity of halides is RI > RBr > RCl. (Alkyl and aryl fluorides are seldom used in the preparation of organolithium compounds.)

For example, butyl bromide reacts with lithium metal in diethyl ether to give a solution of butyllithium:

$$\text{Br} \ + \ 2\,Li \ \xrightarrow[-10\,°C]{\text{Et}_2\text{O,}} \ \text{Li} \ + \ LiBr$$
Butyl bromide   **Butyllithium**
                                  (80–90%)

Several alkyl- and aryllithium reagents are commercially available in hexane and other hydrocarbon solvents.

12.6B Grignard Reagents

Organomagnesium halides were discovered by the French chemist Victor Grignard in 1900. Grignard received the Nobel Prize for his discovery in 1912, and organomagnesium halides are now called **Grignard reagents** in his honor. Grignard reagents have great use in organic synthesis.

- Grignard reagents are prepared by the reaction of an organic halide with magnesium metal in an anhydrous ether solvent:

$$RX \ + \ Mg \ \xrightarrow{Et_2O} \ RMgX$$
$$ArX \ + \ Mg \ \xrightarrow{Et_2O} \ ArMgX$$

Grignard reagents

The order of reactivity of halides with magnesium is also RI > RBr > RCl. Very few organomagnesium fluorides have been prepared. Aryl Grignard reagents are more easily prepared from aryl bromides and aryl iodides than from aryl chlorides, which react very sluggishly. Once prepared, a Grignard reagent is usually used directly in a subsequent reaction.

The actual structures of Grignard reagents are more complex than the general formula RMgX indicates. Experiments have established that for most Grignard reagents there is an equilibrium between an alkylmagnesium halide and a dialkylmagnesium.

$$2 \ RMgX \ \rightleftharpoons \ R_2Mg \ + \ MgX_2$$

Alkylmagnesium halide   **Dialkylmagnesium**

For convenience in this text, however, we shall write the formula for the Grignard reagent as though it were simply RMgX.

A Grignard reagent forms a complex with its ether solvent; the structure of the complex can be represented as follows:

$$
\begin{array}{c}
R \underset{\ddots}{\overset{\cdots}{O}} R \\
\vdots \\
R - Mg - X \\
\vdots \\
R \underset{\cdots}{\overset{\ddots}{O}} R
\end{array}
$$

Complex formation with molecules of ether is an important factor in the formation and stability of Grignard reagents.

The mechanism by which Grignard reagents form is complicated and has been a matter of debate. There seems to be general agreement that radicals are involved and that a mechanism similar to the following is likely:

$$R - X \ + \ :Mg \ \longrightarrow \ R \cdot \ + \ \cdot MgX$$
$$R \cdot \ + \ \cdot MgX \ \longrightarrow \ RMgX$$

12.7 REACTIONS OF ORGANOLITHIUM AND ORGANOMAGNESIUM COMPOUNDS

12.7A Reactions with Compounds Containing Acidic Hydrogen Atoms

- Grignard reagents and organolithium compounds are very strong bases. They react with any compound that has a hydrogen atom attached to an electronegative atom such as oxygen, nitrogen, or sulfur.

We can understand how these reactions occur if we represent the Grignard reagent and organolithium compounds in the following ways:

$$\overset{\delta-}{R} \overset{\delta+}{:MgX} \quad \text{and} \quad \overset{\delta-}{R} \overset{\delta+}{:Li}$$

When we do this, we can see that the reactions of Grignard reagents with water and alcohols are nothing more than acid–base reactions; they lead to the formation of the weaker conjugate acid and weaker conjugate base.

- A Grignard reagent behaves as if it contained the anion of an alkane, *as if it contained a carbanion*:

$$\overset{\delta-}{R}-\overset{\delta+}{Mg}X \ + \ \overset{\delta+}{H}-\overset{\delta-}{\ddot{O}}-H \ \longrightarrow \ R-H \ + \ H\ddot{O}\!:^- \ + \ Mg^{2+} \ + \ X^-$$

| **Stronger base** | **Stronger acid** (pK_a 15.7) | **Weaker acid** (pK_a 40–50) | **Weaker base** | | |

$$\overset{\delta-}{R}-\overset{\delta+}{Mg}X \ + \ \overset{\delta+}{H}-\overset{\delta-}{\ddot{O}}-R \ \longrightarrow \ R-H \ + \ R\ddot{O}\!:^- \ + \ Mg^{2+} \ + \ X^-$$

| **Stronger base** | **Stronger acid** (pK_a 15–18) | **Weaker acid** (pK_a 40–50) | **Weaker base** | | |

●●● SOLVED PROBLEM 12.3

Write an equation for the reaction that would take place when phenyllithium is treated with water. Designate the stronger acid and stronger base.

STRATEGY AND ANSWER: Recognizing that phenyllithium, like a Grignard reagent, acts as though it contains a carbanion, a very powerful base ($pK_a = 40$–50), we conclude that the following acid–base reaction would occur.

$$\overset{\delta-}{Ar}-\overset{\delta+}{Li} \ + \ H\!:\!\ddot{O}H \ \longrightarrow \ Ar-H \ + \ H\ddot{O}\!:^- \ + \ Li^+$$

| **Stronger base** | **Stronger acid** | **Weaker acid** | **Weaker base** |

●●● PRACTICE PROBLEM 12.6

Predict the products of the following acid–base reactions. Using pK_a values, indicate which side of each equilibrium reaction is favored, and label the species representing the stronger acid and stronger base in each case.

(a)

+ H$_2$O ⇌

(b)

+ MeOH ⇌

(c)

+ ⇌

(d)

+ ⇌

●●● PRACTICE PROBLEM 12.7

Provide the reagents necessary to achieve the following transformations.

(a)

(D = deuterium)

(b)

Grignard reagents and organolithium compounds remove protons that are much less acidic than those of water and alcohols.

- Grignard reagents react with the terminal hydrogen atoms of 1-alkynes by an acid–base reaction, and this is a useful method for the preparation of alkynylmagnesium halides and alkynyllithiums.

The fact that these reactions go to completion is not surprising when we recall that alkanes have pK_a values of 40–50, whereas those of terminal alkynes are ~25 (Table 3.1).

Not only are Grignard reagents strong bases, they are also *powerful nucleophiles*.

- Reactions in which Grignard reagents act as nucleophiles are by far the most important and we shall consider these next.

12.7B Reactions of Grignard Reagents with Epoxides (Oxiranes)

- Grignard reagents react as nucleophiles with epoxides (oxiranes), providing convenient synthesis of alcohols.

The nucleophilic alkyl group of the Grignard reagent attacks the partially positive carbon of the epoxide ring. Because it is highly strained, the ring opens, and the reaction leads to the alkoxide salt of an alcohol. Subsequent acidification produces the alcohol. (Compare this reaction with the base-catalyzed ring opening we studied in Section 11.14.) The following are examples with oxirane.

- Grignard reagents react primarily at the less-substituted ring carbon atom of a substituted epoxide.

12.7C Reactions of Grignard Reagents with Carbonyl Compounds

- The most important synthetic reactions of Grignard reagents and organolithium compounds are those in which they react as nucleophiles and attack an unsaturated carbon—*especially the carbon of a carbonyl group*.

We saw in Section 12.1A that carbonyl compounds are highly susceptible to nucleophilic attack. Grignard reagents react with carbonyl compounds (aldehydes and ketones) in the following way:

A MECHANISM FOR THE REACTION — The Grignard Reaction

Reaction

$$R-MgX \ + \ \text{(carbonyl)} \quad \xrightarrow[\text{(2) } H_3O^+ \ X^-]{\text{(1) ether*}} \quad \text{(alcohol)} \ + \ MgX_2$$

Mechanism

Step 1

Grignard reagent   **Carbonyl compound**   **Halomagnesium alkoxide**

The strongly nucleophilic Grignard reagent uses its electron pair to form a bond to the carbon atom. One electron pair of the carbonyl group shifts out to the oxygen. This reaction is a nucleophilic addition to the carbonyl group, and it results in the formation of an alkoxide ion associated with Mg^{2+} and X^-.

Step 2

Halomagnesium alkoxide   **Alcohol**

In the second step, the addition of aqueous HX causes protonation of the alkoxide ion; this leads to the formation of the alcohol and MgX_2.

*By writing "(1) ether" over the arrow and "(2) H_3O^+ X^-" under the arrow, we mean that in the first laboratory step the Grignard reagent and the carbonyl compound are allowed to react in an ether solvent. Then in a second step, after the reaction of the Grignard reagent and the carbonyl compound is over, we add aqueous acid (e.g., dilute HX) to convert the salt of the alcohol (ROMgX) to the alcohol itself. If the alcohol is tertiary, it will be susceptible to acid-catalyzed dehydration. In this case, a solution of NH_4Cl in water is often used because it is acidic enough to convert ROMgX to ROH while not allowing acid-catalyzed reactions of the resulting tertiary alcohol.

12.8 ALCOHOLS FROM GRIGNARD REAGENTS

Grignard additions to carbonyl compounds are especially useful because they can be used to prepare primary, secondary, or tertiary alcohols:

1. Grignard Reagents React with Formaldehyde to Give a Primary Alcohol

Formaldehyde   **1° Alcohol**

2. Grignard Reagents React with All Other Aldehydes to Give Secondary Alcohols

Higher aldehyde   **2° Alcohol**

3. Grignard Reagents React with Ketones to Give Tertiary Alcohols

Ketone   **3° Alcohol**

4. Esters React with Two Molar Equivalents of a Grignard Reagent to Form Tertiary Alcohols When a Grignard reagent adds to the carbonyl group of an ester, the initial product is unstable and loses a magnesium alkoxide to form a ketone. Ketones, however, are more reactive toward Grignard reagents than esters. Therefore, as soon as a molecule of the ketone is formed in the mixture, it reacts with a second molecule of the Grignard reagent. After hydrolysis, **the product is a tertiary alcohol with two identical alkyl groups**, groups that correspond to the alkyl portion of the Grignard reagent:

Ester   **Initial product (unstable)**

Ketone   **Salt of an alcohol (not isolated)**   **3° Alcohol (with two or three identical R groups)**

Specific examples of these reactions are shown here.

Grignard Reagent	**Carbonyl Reactant**		**Final Product**

Reaction with Formaldehyde

Phenylmagnesium bromide   **Formaldehyde**   **Benzyl alcohol (90%)**

Reaction with a Higher Aldehyde

Ethylmagnesium bromide   **Acetaldehyde**   **2-Butanol (80%)**

Reaction with a Ketone

Butylmagnesium   **Acetone**   **2-Methyl-2-hexanol**
bromide   **(92%)**

Reaction with an Ester

Ethylmagnesium   **Ethyl acetate**
bromide

3-Methyl-3-pentanol
(67%)

●●● SOLVED PROBLEM 12.4

How would you carry out the following synthesis?

STRATEGY AND ANSWER: Here we are converting an ester (a cyclic ester) to **a tertiary alcohol with two identical alkyl groups** (methyl groups). So, we should use two molar equivalents of the Grignard reagent that contains the required alkyl groups, in this case, methyl magnesium iodide.

●●●

PRACTICE PROBLEM 12.8

Provide a mechanism for the following reaction, based on your knowledge of the reaction of esters with Grignard reagents.

12.8A **HOW TO** Plan a Grignard Synthesis

We can synthesize almost any alcohol we wish by skillfully using a Grignard synthesis. In planning a Grignard synthesis we must simply choose the correct Grignard reagent and the correct aldehyde, ketone, ester, or epoxide. We do this by examining the alcohol we wish to prepare and by paying special attention to the groups attached to the carbon atom bearing the —OH group. Many times there may be more than one way of carrying out the synthesis. In these cases our final choice will probably be dictated by the availability of starting compounds. Let us consider an example.

Suppose we want to prepare 3-phenyl-3-pentanol. We examine its structure and we see that the groups attached to the carbon atom bearing the —OH are a *phenyl group* and *two ethyl groups*:

3-Phenyl-3-pentanol

This means that we can synthesize this compound in several different ways:

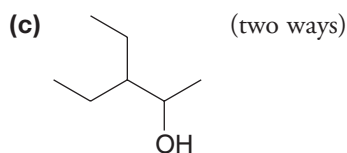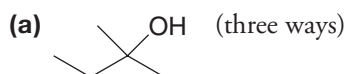1. We can use a ketone with two ethyl groups (3-pentanone) and allow it to react with phenylmagnesium bromide:

Retrosynthetic Analysis

Synthesis

| **Phenylmagnesium bromide** | **3-Pentanone** | **3-Phenyl-3-pentanol** |

2. We can use a ketone containing an ethyl group and a phenyl group (ethyl phenyl ketone) and allow it to react with ethylmagnesium bromide:

Retrosynthetic Analysis

Synthesis

| **Ethylmagnesium bromide** | **Ethyl phenyl ketone** | **3-Phenyl-3-pentanol** |

3. We can use an ester of benzoic acid and allow it to react with two molar equivalents of ethylmagnesium bromide:

Retrosynthetic Analysis

Synthesis

All of these methods will likely give us our desired compound in high yields.

●●● **SOLVED PROBLEM 12.5**

ILLUSTRATING A MULTISTEP SYNTHESIS: Using an alcohol of no more than four carbon atoms as your only organic starting material, outline a synthesis of **A**:

ANSWER: We can construct the carbon skeleton from two four-carbon compounds using a Grignard reaction. Then oxidation of the alcohol produced will yield the desired ketone.

Retrosynthetic Analysis

Retrosynthetic disconnection

Synthesis

We can synthesize the Grignard reagent (**B**) and the aldehyde (**C**) from isobutyl alcohol:

● ● ●   **SOLVED PROBLEM 12.6**

ILLUSTRATING A MULTISTEP SYNTHESIS: Starting with bromobenzene and any other needed reagents, outline a synthesis of the following aldehyde:

ANSWER: Working backward, we remember that we can synthesize the aldehyde from the corresponding alcohol by the Swern oxidation or PCC (Sections 12.4B, D). The alcohol can be made by treating phenylmagnesium bromide with oxirane. [Adding oxirane to a Grignard reagent is a very useful method for adding a —CH$_2$CH$_2$OH unit to an organic group (Section 12.7B).] Phenylmagnesium bromide can be made in the usual way, by treating bromobenzene with magnesium in an ether solvent.

Retrosynthetic Analysis

Synthesis

● ● ●

PRACTICE PROBLEM 12.9 Provide retrosynthetic analyses and syntheses for each of the following alcohols, starting with appropriate alkyl or aryl halides.

(a) OH (three ways)

(b) OH (three ways)

(c) (two ways)
OH

(d) (three ways)
OH

(e) OH (two ways)

(f) OH (two ways)

● ● ●

PRACTICE PROBLEM 12.10 Provide a retrosynthetic analysis and synthesis for each of the following compounds. Permitted starting materials are phenylmagnesium bromide, oxirane, formaldehyde, and alcohols or esters of four carbon atoms or fewer. You may use any inorganic reagents and oxidizing conditions such as Swern oxidation or pyridinium chlorochromate (PCC).

(a) OH

(b) O H

(c) OH

(d) OH

12.8B Restrictions on the Use of Grignard Reagents

Although the Grignard synthesis is one of the most versatile of all general synthetic procedures, it is not without its limitations. Most of these limitations arise from the very feature of the Grignard reagent that makes it so useful—its *extraordinary reactivity as a nucleophile and a base*.

> *The Grignard reagent is a very powerful base;* in effect it contains a carbanion.

- It is not possible to prepare a Grignard reagent from a compound that contains any hydrogen more acidic than the hydrogen atoms of an alkane or alkene.

We cannot, for example, prepare a Grignard reagent from a compound containing an —OH group, an —NH— group, an —SH group, a —CO₂H group, or an —SO₃H group. If we were to attempt to prepare a Grignard reagent from an organic halide containing any of these groups, the formation of the Grignard reagent would simply fail to take place. (Even if a Grignard reagent were to form, it would immediately be neutralized by the acidic group.)

- Since Grignard reagents are powerful nucleophiles, we cannot prepare a Grignard reagent from any organic halide that contains a carbonyl, epoxy, nitro, or cyano (—CN) group.

If we were to attempt to carry out this kind of reaction, any Grignard reagent that formed would only react with the unreacted starting material:

Grignard reagents cannot be prepared in the presence of these groups because they will react with them.

Helpful Hint

A protecting group can sometimes be used to mask the reactivity of an incompatible group (see Sections 11.11D, 11.11E, and 12.9).

> *This means that when we prepare Grignard reagents, we are effectively limited to alkyl halides or to analogous organic halides containing carbon–carbon double bonds, internal triple bonds, ether linkages, and —NR₂ groups.*

Grignard reactions are so sensitive to acidic compounds that when we prepare a Grignard reagent we must take special care to exclude moisture from our apparatus, and we must use an anhydrous ether as our solvent.

As we saw earlier, acetylenic hydrogens are acidic enough to react with Grignard reagents. This is a limitation that we can use, however.

- We can make acetylenic Grignard reagents by allowing terminal alkynes to react with alkyl Grignard reagents (cf. Section 12.7A).

We can then use these acetylenic Grignard reagents to carry out other syntheses. For example,

(52%)

- When we plan a Grignard synthesis, we must also take care that any aldehyde, ketone, epoxide, or ester that we use as a substrate does not also contain an acidic group (other than when we deliberately let it react with a terminal alkyne).
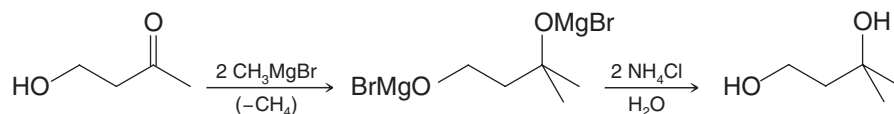
If we were to do this, the Grignard reagent would simply react as a base with the acidic hydrogen rather than reacting at the carbonyl or epoxide carbon as a nucleophile. If we were to treat 4-hydroxy-2-butanone with methylmagnesium bromide, for example, the reaction that would take place is

4-Hydroxy-2-butanone

rather than

If we were prepared to waste one molar equivalent of the Grignard reagent, we can treat 4-hydroxy-2-butanone with two molar equivalents of the Grignard reagent and thereby get addition to the carbonyl group:

This technique is sometimes employed in small-scale reactions when the Grignard reagent is inexpensive and the other reagent is expensive.

12.8C The Use of Lithium Reagents

Organolithium reagents (RLi) react with carbonyl compounds in the same way as Grignard reagents and thus provide an alternative method for preparing alcohols.

| Organo-lithium reagent | Aldehyde or ketone | Lithium alkoxide | Alcohol |

Organolithium reagents have the advantage of being somewhat more reactive than Grignard reagents although they are more difficult to prepare and handle.

12.8D The Use of Sodium Alkynides

Sodium alkynides also react with aldehydes and ketones to yield alcohols. An example is the following:

●●● **SOLVED PROBLEM 12.7**

ILLUSTRATING MULTISTEP SYNTHESES: For the following compounds, write a retrosynthetic scheme and then synthetic reactions that could be used to prepare each one. Use hydrocarbons, organic halides, alcohols, aldehydes, ketones, or esters containing six carbon atoms or fewer and any other needed reagents.
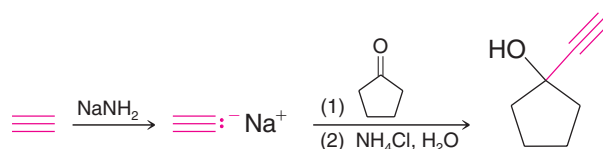
(a) OH

(b) OH

(c) HO

ANSWERS:

(a)

Retrosynthetic Analysis

OH $\Longrightarrow$ O + MgBr $\Longrightarrow$ Br $\Longrightarrow$ OH

Synthesis

OH $\xrightarrow{\text{PBr}_3}$ Br $\xrightarrow[\text{Et}_2\text{O}]{\text{Mg}}$ MgBr $\xrightarrow[\text{(2) NH}_4\text{Cl, H}_2\text{O}]{\text{(1)}}$ OH

(b)

Retrosynthetic Analysis

OH $\Longrightarrow$ OMe + 2 MgBr $\Longrightarrow$ Br

Synthesis

Br $\xrightarrow[\text{Et}_2\text{O}]{\text{Mg}}$ MgBr $\xrightarrow[\text{(2) NH}_4\text{Cl, H}_2\text{O}]{\text{(1)}}$ OH

(c)

Retrosynthetic Analysis

HO $\Longrightarrow$ O + $\equiv$:$^-$ Na$^+$ $\Longrightarrow$ $\equiv$

Synthesis

$\equiv$ $\xrightarrow{\text{NaNH}_2}$ $\equiv$:$^-$ Na$^+$ $\xrightarrow[\text{(2) NH}_4\text{Cl, H}_2\text{O}]{\text{(1)}}$ HO

12.9 PROTECTING GROUPS

- A **protecting group** can be used in some cases where a reactant contains a group that is incompatible with the reaction conditions necessary for a given transformation.

For example, if it is necessary to prepare a Grignard reagent from an alkyl halide that already contains an alcohol hydroxyl group, the Grignard reagent can still be prepared if the alcohol is first protected by conversion to a functional group that is stable in the presence of a Grignard reagent, for example, a *tert*-butyldimethylsilyl (TBS) ether (Section 11.11E). The Grignard reaction can be conducted, and then the original alcohol group can be liberated by cleavage of the silyl ether with fluoride ion (see Problem 12.36). An example is the following synthesis of 1,4-pentanediol. This same strategy can be used when an organolithium reagent or alkynide anion must be prepared in the presence of an incompatible group. In later chapters we will encounter strategies that can be used to protect other functional groups during various reactions (Section 16.7C).

●●● SOLVED PROBLEM 12.8

Show how the following synthesis could be accomplished using a protecting group.

STRATEGY AND ANSWER: First protect the —OH group by converting it to a *tert*-butyldimethylsilyl (TBS) ether (Section 11.11E), then treat the product with ethyl magnesium bromide followed by dilute acid. Then remove the protecting group.

[WHY Do These Topics Matter?

CHANGING PROPERTIES BY CHANGING OXIDATION STATE

Although you have now learned several tools to interconvert primary and secondary alcohols into aldehydes, ketones, and carboxylic acids, what you may not have fully realized is how those operations can alter a compound's properties. Specifically, we mean changes other than the standard ones of melting or boiling points, polarity, and physical appearance (i.e., solid versus a liquid) that are true of any functional group alteration. Indeed, moving from a hydroxyl group to a carbonyl group or vice versa causes many molecules to have completely different biochemical profiles as well, something that occurs frequently in nature. Here we will consider just a few examples.

Codeine, a natural compound found in opium poppies, is currently prescribed as a medication to treat mild or moderate pain (i.e., as an analgesic). If its secondary alcohol is oxidized to a ketone, however, a compound known as codeinone results. While it also can serve as a pain medication, it is only 33% as effective as codeine. Similarly, pregnenolone is a steroid used in the body largely as a key synthetic precursor to progesterone. In the needed oxidation event, it turns out that not only is the alcohol oxidized, but the neighboring double bond moves into conjugation as well, a phenomenon that will make more sense once

© NHPA/Photoshot Holdings Ltd.

you have read Chapter 13. For now, however, what is important to note is that the new molecule that is created plays a critical role in the menstrual cycle and in pregnancy. In fact, progesterone is currently prescribed in many different forms, particularly to support a woman's effort to become pregnant during procedures such as *in vitro* fertilization (IVF). Pregnenolone itself does not appear to have such important properties, though intriguingly at least one derivative of its alcohol function can promote the generation of neurons in the hippocampus, a region of the brain that is affected by Alzheimer's disease.

Codeine   **Codeinone**   **Pregnenolone**   **Progesterone**

As a final example, consider the structure of borneol, a compound found in several plant species and used in some traditional Chinese medicines. This compound is a component of several essential oils and is a natural insect repellant. When it is oxidized, a new natural product results—camphor. Camphor has many additional uses, from serving as a plasticizer, to being a flavorant in several foods, as well as being an active ingredient in products such as Vicks VapoRub®. Interestingly, an attempt to reduce the alcohol within camphor with a simple reagent such as **NaBH₄** creates isoborneol rather than borneol because the steric bulk of the methyl groups on the upper carbon bridge ensures that hydride adds from the bottom face. Isoborneol, in fact, is quite similar to camphor in its properties. Overall, it is pretty amazing what some small adjustments in oxidation state can do!

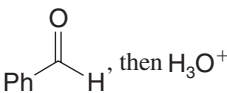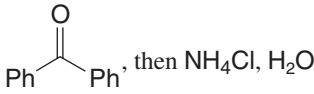**Borneol**   **Camphor**   **Isoborneol**
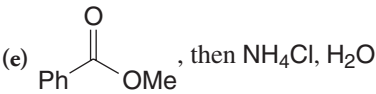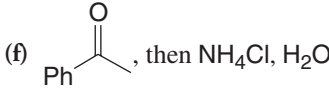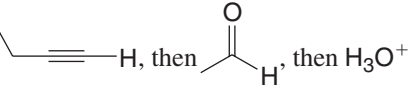
SUMMARY AND REVIEW TOOLS

The study aids for this chapter include key terms and concepts (which are hyperlinked to the Glossary from the bold, blue terms in the *WileyPLUS* version of the book at wileyplus.com) and Synthetic Connections summaries of oxidation, reduction, and carbon–carbon bond-forming reactions related to alcohol and carbonyl compounds.
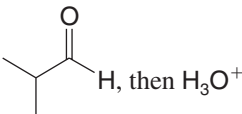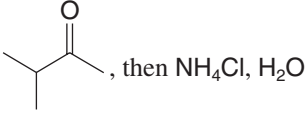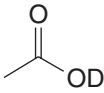
PROBLEMS

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

REAGENTS AND REACTIONS

12.11 What products would you expect from the reaction of ethylmagnesium bromide (CH₃CH₂MgBr) with each of the following reagents?

(a) H_2O

(b) D_2O

(c) Ph–CHO (with H), then H_3O^+

(d) Ph–CO–Ph, then NH₄Cl, H₂O

(e) Ph–CO–OMe, then NH₄Cl, H₂O

(f) Ph–CHO, then NH₄Cl, H₂O

(g) alkyne—H, then acetaldehyde, then H_3O^+

12.12 What products would you expect from the reaction of propyllithium (CH₃CH₂CH₂Li) with each of the following reagents?

(a) isobutyraldehyde H, then H_3O^+

(b) methyl isopropyl ketone, then NH₄Cl, H₂O

(c) 1-Pentyne, then acetone, then NH₄Cl, H₂O
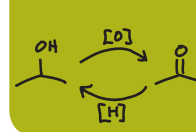
(d) Ethanol

(e) CH₃—CO—OD

12.13 What product (or products) would be formed from the reaction of 1-bromo-2-methylpropane (isobutyl bromide) under each of the following conditions?

(a) HO⁻, H₂O

(b) NC⁻, ethanol

(c) *t*-BuOK, *t*-BuOH

(d) MeONa, MeOH

(e) (1) Li, Et₂O; (2) acetone; (3) NH₄Cl, H₂O

(f) Mg, Et₂O, then CH₃CH (with O), then H_3O^+

(g) (1) Mg, Et₂O; (2) acetic ester OMe; (3) NH₄Cl, H₂O

(h) (1) Mg, Et₂O; (2) ethylene oxide; (3) H_3O^+

(i) (1) Mg, Et₂O; (2) H—CO—H; (3) NH₄Cl, H₂O

(j) Li, Et₂O; (2) MeOH

(k) Li, Et₂O; (2) H——H

12.14 Which oxidizing or reducing agent would you use to carry out the following transformations?

(a)

(b)

(c)

(d)

(e)

12.15 Write reaction conditions and the product from Swern oxidation of the following compounds.

(a)

Myrtenol

(b)

Chrysanthemyl alcohol

12.16 Predict the products of the following reactions.

(a)

(1) EtMgBr (excess)
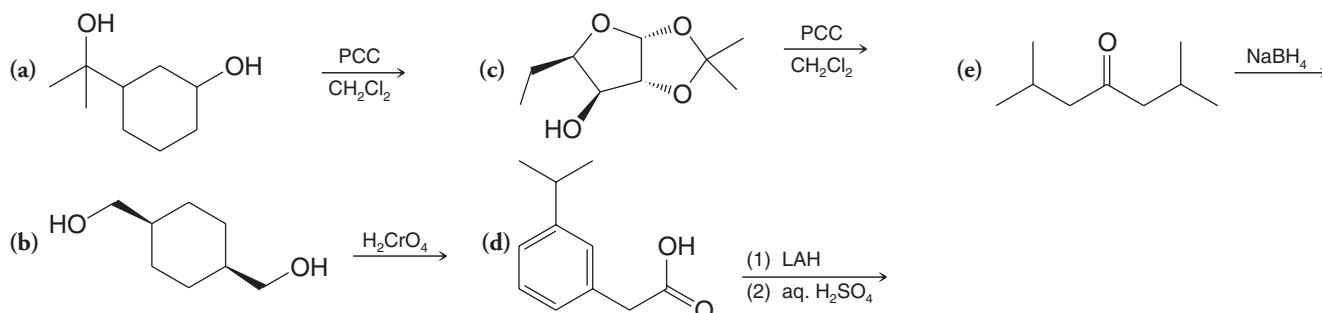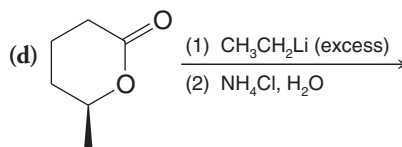(2) NH₄Cl, H₂O

(b)

(1) EtMgBr (excess)
(2) NH₄Cl, H₂O

12.17 Predict the organic product from each of the following reduction reactions.

(a)

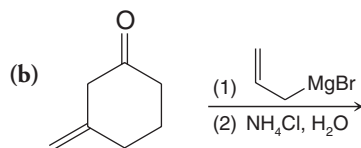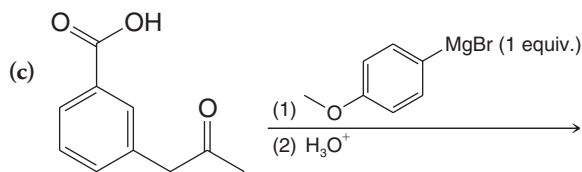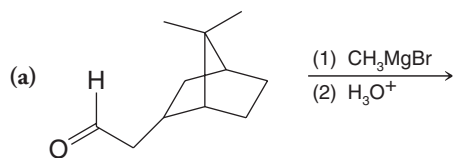NaBH₄

(b)

(1) LiAlH₄
(2) aq. H₂SO₄

(c)

NaBH₄

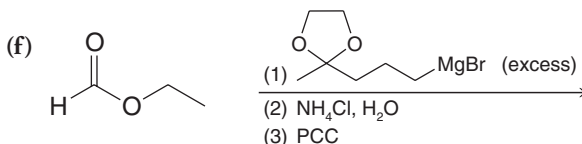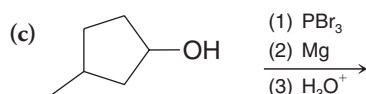**12.18** Predict the organic product from each of the following oxidation reactions.

(a)

(1) KMnO₄, HO⁻, Δ
(2) H₃O⁺

(c)

(1) DMSO, (COCl)₂
(2) Et₃N

(e)

H₂CrO₄

(b)
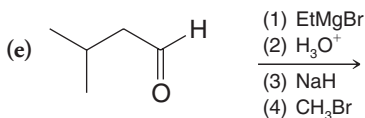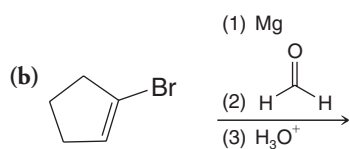

PCC
CH₂Cl₂

(d)

H₂CrO₄

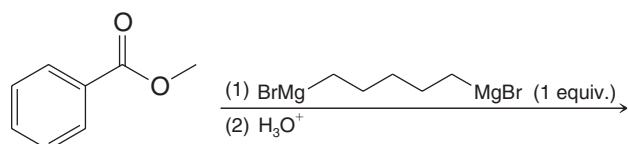**12.19** Predict the organic product from each of the following oxidation and reduction reactions.

(a)

PCC
CH₂Cl₂

(c)

PCC
CH₂Cl₂

(e)

NaBH₄

(b)

H₂CrO₄

(d)

(1) LAH
(2) aq. H₂SO₄

12.20 Predict the major organic product from each of the following reactions.

(a)

$$\frac{(1)\ \ CH_3MgBr}{(2)\ \ H_3O^+}$$

(b)

$$\frac{(1)\ \ \ \ \ \ \ \ \ \ MgBr}{(2)\ \ NH_4Cl,\ H_2O}$$

(c)

$$\frac{(1)\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ MgBr\ (1\ equiv.)}{(2)\ \ H_3O^+}$$

(d)

$$\frac{(1)\ \ CH_3CH_2Li\ (excess)}{(2)\ \ NH_4Cl,\ H_2O}$$

12.21 Predict the major organic product from each of the following reaction sequences.

(a)

$$\frac{(1)\ \ MeMgBr\ (excess)}{(2)\ \ NH_4Cl,\ H_2O}$$

(b)

$$\begin{array}{l}(1)\ \ Mg\\ (2)\ \ H{-}CHO\\ (3)\ \ H_3O^+\end{array}$$

(c)

$$\begin{array}{l}(1)\ \ PBr_3\\ (2)\ \ Mg\\ (3)\ \ H_3O^+\end{array}$$

(d)

$$\begin{array}{l}(1)\ \ PCC\\ (2)\ \ \ \ \ \ \ \ \ \ MgBr\\ (3)\ \ H_3O^+\end{array}$$

(e)

$$\begin{array}{l}(1)\ \ EtMgBr\\ (2)\ \ H_3O^+\\ (3)\ \ NaH\\ (4)\ \ CH_3Br\end{array}$$

(f)

$$\begin{array}{l}(1)\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ MgBr\ \ (excess)\\ (2)\ \ NH_4Cl,\ H_2O\\ (3)\ \ PCC\end{array}$$

12.22 Predict the product of the following reaction.

$$\frac{(1)\ \ BrMg\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ MgBr\ (1\ equiv.)}{(2)\ \ H_3O^+}$$

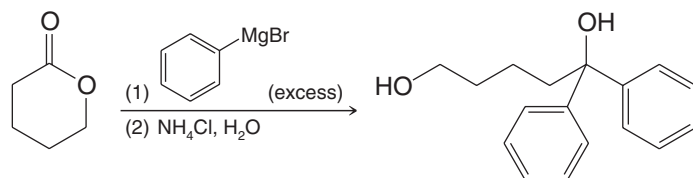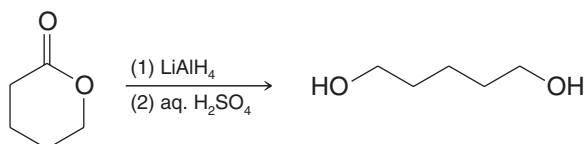**MECHANISMS**

12.23 Synthesize each of the following compounds from cyclohexanone. Use D to specify deuterium in any appropriate reagent or solvent where it would take the place of hydrogen.
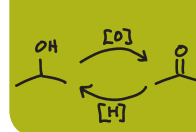
12.24 Write a mechanism for the following reaction. Include formal charges and curved arrows to show the movement of electrons in all steps.

$$\frac{(1)\ \ \ \ \ \ \ \ \ \ \ \ \ MgBr\ \ \ \ \ \ (excess)}{(2)\ \ NH_4Cl,\ H_2O}$$

12.25 Write a mechanism for the following reaction. You may use H^- to represent hydride ions from LiAlH$_4$ in your mechanism. Include formal charges and curved arrows to show the movement of electrons in all steps.

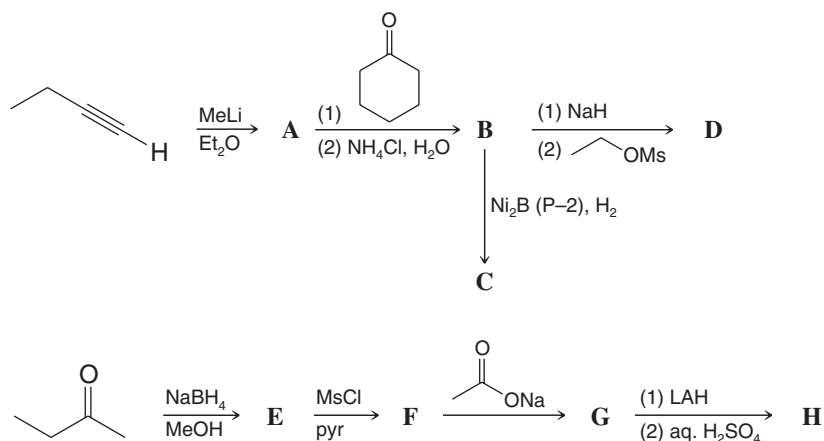$$\frac{(1)\ \ LiAlH_4}{(2)\ \ aq.\ H_2SO_4}$$

12.26 Although oxirane (oxacyclopropane) and oxetane (oxacyclobutane) react with Grignard and organolithium reagents to form alcohols, tetrahydrofuran (oxacyclopentane) is so unreactive that it can be used as the solvent in which these organometallic compounds are prepared. Explain the difference in reactivity of these oxygen heterocycles.
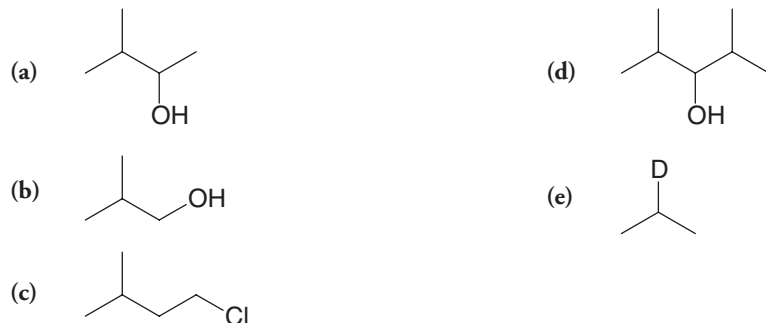
12.27 Studies suggest that attack by a Grignard reagent at a carbonyl group is facilitated by involvement of a second molecule of the Grignard reagent that participates in an overall cyclic ternary complex. The second molecule of Grignard reagent assists as a Lewis acid. Propose a structure for the ternary complex and write all of the products that result from it.

SYNTHESIS

12.28 What organic products **A–H** would you expect from each of the following reactions?
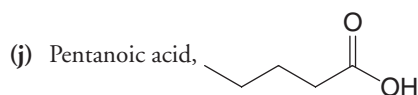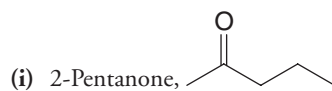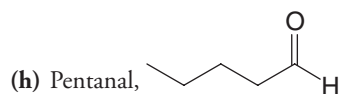

12.29 Outline all steps in a synthesis that would transform 2-propanol (isopropyl alcohol) into each of the following:
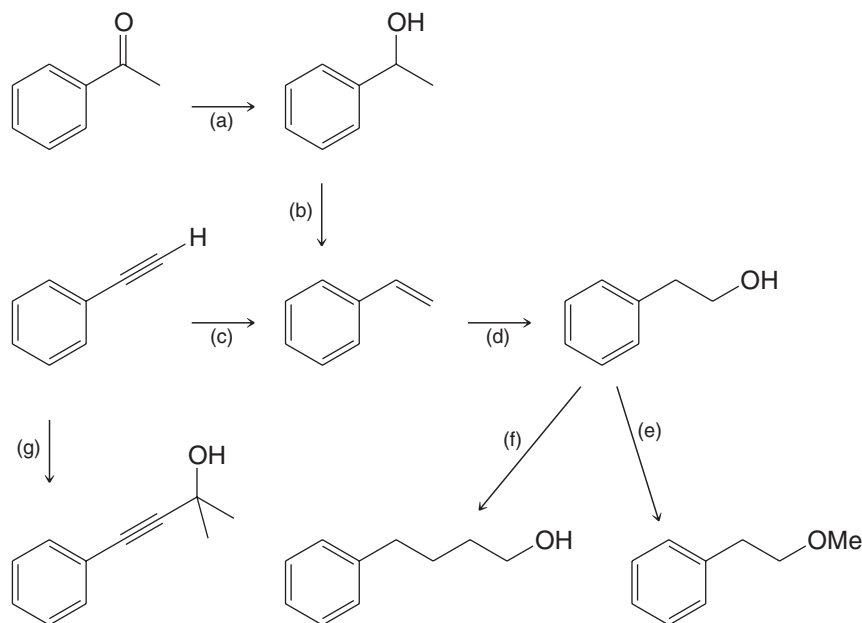

12.30 Show how 1-pentanol could be transformed into each of the following compounds. (You may use any needed inorganic reagents and you need not show the synthesis of a particular compound more than once.)

(a) 1-Bromopentane
(b) 1-Pentene
(c) 2-Pentanol
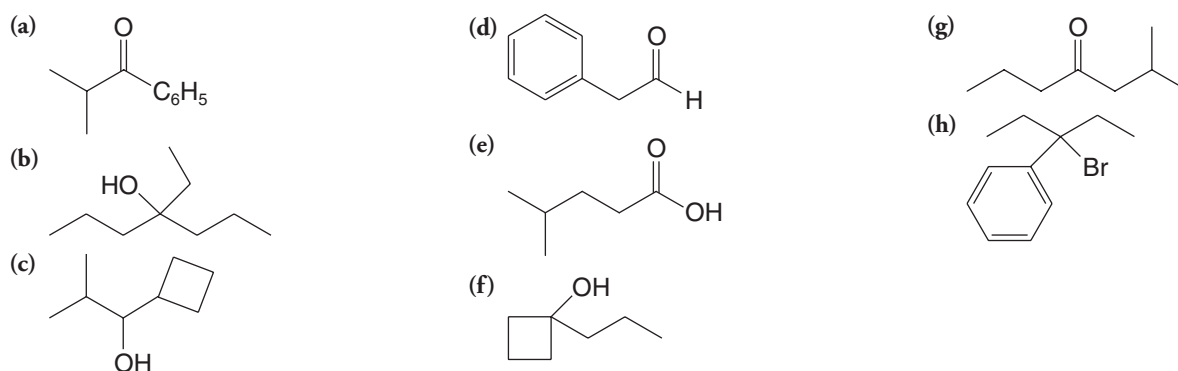(d) Pentane
(e) 2-Bromopentane
(f) 1-Hexanol
(g) 1-Heptanol

(h) Pentanal,

(i) 2-Pentanone,

(j) Pentanoic acid,

(k) Dipentyl ether (two ways)
(l) 1-Pentyne
(m) 2-Bromo-1-pentene
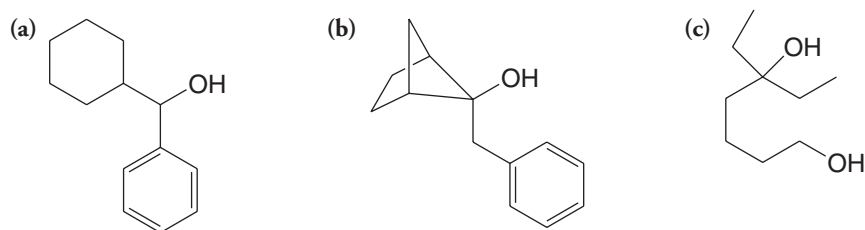(n) Pentyllithium
(o) 4-Methyl-4-nonanol

12.31 Provide the reagents needed to accomplish transformations (a)–(g). More than one step may be necessary.
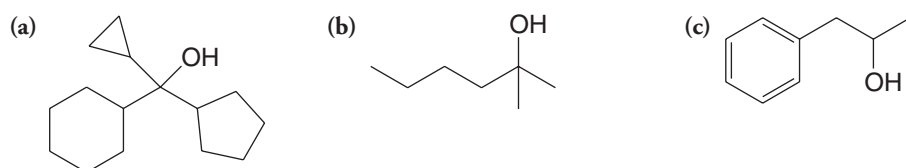

12.32 Assuming that you have available only alcohols or esters containing no more than four carbon atoms, show how you might synthesize each of the following compounds. Begin by writing a retrosynthetic analysis for each. You must use a Grignard reagent at one step in the synthesis. If needed, you may use oxirane and you may use bromobenzene, but you must show the synthesis of any other required organic compounds. Assume you have available any solvents and any inorganic compounds, including oxidizing and reducing agents, that you require.
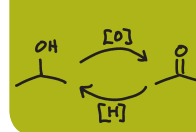

12.33 For each of the following alcohols, write a retrosynthetic analysis and synthesis that involves an appropriate organometallic reagent (either a Grignard or alkyllithium reagent).
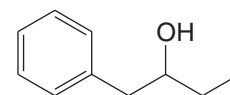

12.34 Synthesize each of the following compounds starting from primary or secondary alcohols containing seven carbons or less and, if appropriate, bromobenzene.
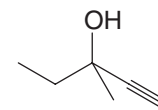
12.35 The alcohol shown here is used in making perfumes. Write a retrosynthetic analysis and then synthetic reactions that could be used to prepare this alcohol from bromobenzene and 1-butene.
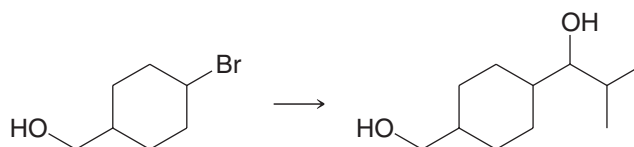
12.36 Write a retrosynthetic analysis and then synthetic reactions that could be used to prepare racemic Meparfynol, a mild hypnotic (sleep-inducing compound), starting with compounds of four carbon atoms or fewer.
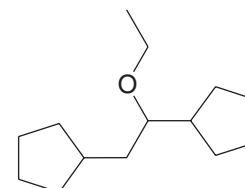
Meparfynol

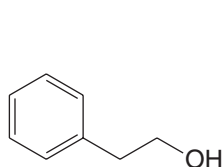**12.37** Write a retrosynthetic analysis and synthesis for the following transformation.

12.38 Synthesize the following compound using cyclopentane and ethyne (acetylene) as the sole source of carbon atoms.
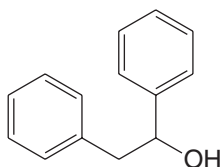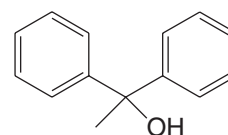
CHALLENGE PROBLEMS

12.39 Explain how ^1H NMR, ^{13}C NMR, and IR spectroscopy could be used to differentiate among the following compounds.
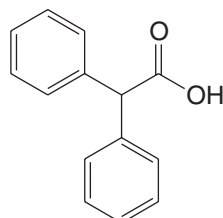
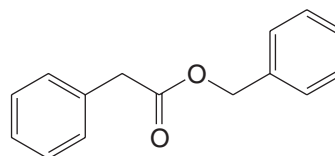**2-Phenylethanol**   **1,2-Diphenylethanol**   **1,1-Diphenylethanol**
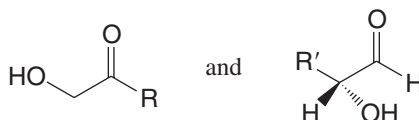
2,2-Diphenylethanoic acid   **Benzyl 2-phenylethanoate**

12.40 When sucrose (common table sugar) is treated with aqueous acid, it is cleaved and yields simpler sugars of these types:
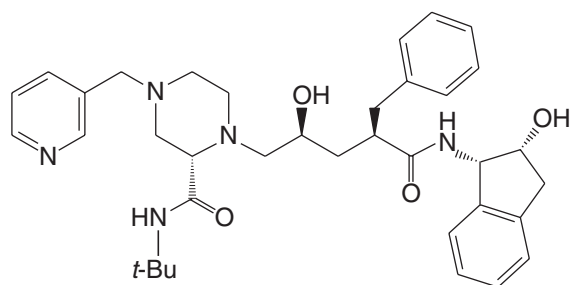
and

For reasons to be studied later, in the use of this procedure for the identification of the sugars incorporated in a saccharide like sucrose, the product mixtures are often treated with sodium borohydride before analysis. What limitation(s) does this put on identification of the sugar building blocks of the starting saccharide?

12.41 An unknown **X** shows a broad absorption band in the infrared at 3200–3550 cm^{-1} but none in the 1620–1780 cm^{-1} region. It contains only C, H, and O. A 116-mg sample was treated with an excess of methylmagnesium bromide, producing 48.7 mL of methane gas collected over mercury at 20 °C and 750 mm Hg. The mass spectrum of **X** has its molecular ion (barely detectable) at 116 *m/z* and a fragment peak at 98. What does this information tell you about the structure of **X**?

LEARNING GROUP PROBLEMS

The problem below is directed toward devising a hypothetical pathway for the synthesis of the acyclic central portion of Crixivan (Merck and Company's HIV protease inhibitor). Note that your synthesis might not adequately control the stereochemistry during each step, but for this particular exercise that is not expected.

Crixivan

Fill in missing compounds and reagents in the following outline of a hypothetical synthesis of the acyclic central portion of Crixivan. Note that more than one intermediate compound may be involved between some of the structures shown below.

LG = some leaving group

(R would be H initially. Then, by reactions that you do not need to specify, it would be converted to an alkyl group.)

SUMMARY OF REACTIONS

Summaries of reactions discussed in this chapter are shown below. Detailed conditions for the reactions that are summarized can be found in the chapter section where each is discussed.

[S U M M A R Y   A N D   R E V I E W   T O O L S]

Synthetic Connections of Alcohols and Carbonyl Compounds

1. Carbonyl Reduction Reactions

- Aldehydes to primary alcohols
- Ketones to secondary alcohols
- Esters to alcohols
- Carboxylic acids to primary alcohols

Substrate		Reducing agent	
		$NaBH_4$	$LiAlH_4$ (LAH)

Aldehydes, Ketones, Esters, Carboxylic acids reduction schemes

(Hydrogen atoms in blue are added during the reaction workup by water or aqueous acid.)

2. Alcohol Oxidation Reactions

- Primary alcohols to aldehydes
- Primary alcohols to carboxylic acids
- Secondary alcohols to ketones

Substrate		Oxidizing agent [O]		
		Swern/PCC	aq. H_2CrO_4	aq. $KMnO_4$

Primary alcohols, Secondary alcohols, Tertiary alcohols oxidation schemes

[**S U M M A R Y   A N D   R E V I E W   T O O L S**]

Synthetic Connections of Alcohols and Carbonyl Compounds
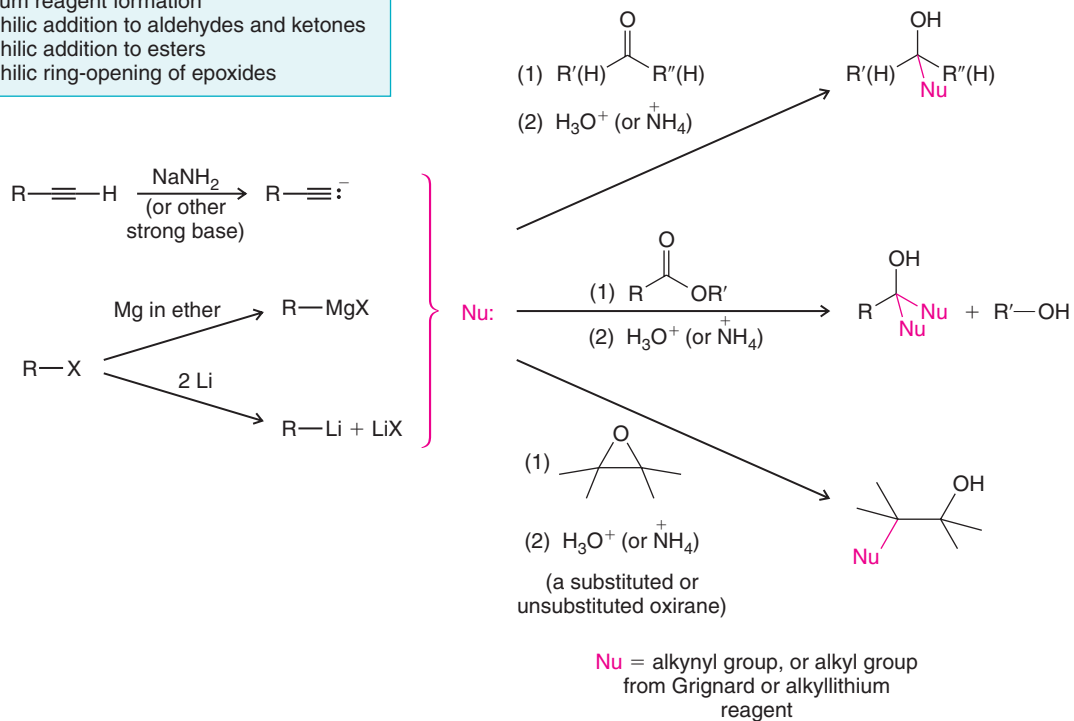
3. Carbon-Carbon Bond Forming Reactions

• Alkynide anion formation
• Grignard reagent formation
• Alkyllithium reagent formation
• Nucleophilic addition to aldehydes and ketones
• Nucleophilic addition to esters
• Nucleophilic ring-opening of epoxides

$$R\!-\!\!\!\equiv\!\!\!-H \xrightarrow[\substack{(or\ other) \\ strong\ base}]{NaNH_2} R\!-\!\!\!\equiv\!\!:^-$$

$$R\!-\!X \xrightarrow{Mg\ in\ ether} R\!-\!MgX$$

$$R\!-\!X \xrightarrow{2\ Li} R\!-\!Li + LiX$$
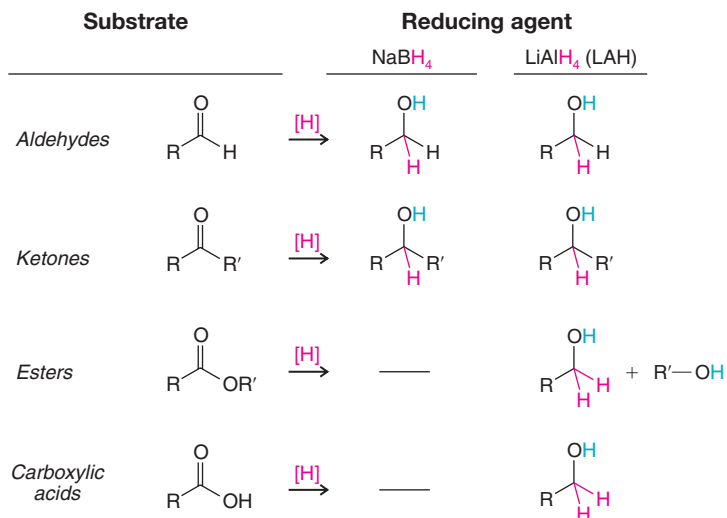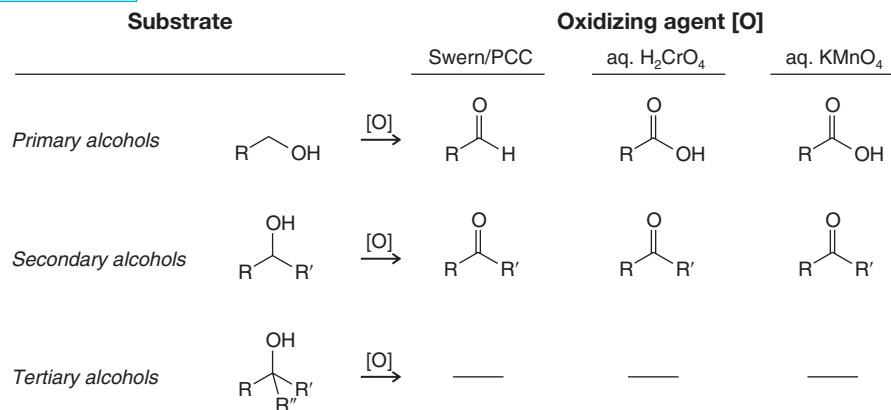
Nu:

(1) $R'(H) \overset{O}{\underset{}{\|}} R''(H)$

(2) H_3O^+ (or $\overset{+}{N}H_4$)

→ $R'(H) \overset{OH}{\underset{Nu}{|}} R''(H)$

(1) $R \overset{O}{\underset{}{\|}} OR'$

(2) H_3O^+ (or $\overset{+}{N}H_4$)

→ $R \overset{OH}{\underset{Nu}{|}} Nu$ + $R'\!-\!OH$

(1) (epoxide)

(2) H_3O^+ (or $\overset{+}{N}H_4$)

(a substituted or unsubstituted oxirane)

→ (product with OH and Nu)

Nu = alkynyl group, or alkyl group
from Grignard or alkyllithium
reagent

PLUS See *First Review Problem Set* in *WileyPLUS*