Carbonyl Compounds

We have already seen a number of carbonyl compounds

\[ \text{Ketone} \quad \text{two R groups} \]
\[ \text{Aldehyde} \quad \text{one R, one H} \]
\[ \text{Amide} \quad \text{one R, one N} \]
\[ \text{Acid} \quad \text{one R, one OH} \]
\[ \text{Ester} \quad \text{one R, one OR} \]
\[ \text{Acid chloride} \quad \text{one R, one Cl} \]

Ketone and aldehydes, reactions are primarily simple additions to \( \pi \) bond

Carboxylic acid derivatives, Have heteroatom attached to carbonyl -heteroatom changes type of reactions

In this chapter, the focus is on the reactivity of ketones and aldehydes
Carbonyl Compounds

Nomenclature of Ketones and Aldehydes

Many of the same IUPAC rules already learned apply

With ketones: suffix is –one
With aldehydes: suffix is -al

In numbering, the carbonyl takes precedence over previous functional groups learned

\[
\begin{align*}
\text{2-butanoine} & \quad \text{4-hydroxy-2-butanoine} & \quad \text{propanal} \\
& \quad \text{(carbonyl precedence} \quad & \quad \text{(do not need to write 1)} \\
& \quad \text{over alcohol)}
\end{align*}
\]
Carbonyl Compounds

Common Names

In addition to the IUPAC naming, many ketones and aldehydes have common names

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{O} & \quad \text{O} \\
\text{acetone} & \quad \text{methyl ethyl ketone} & \quad \text{formaldehyde}
\end{align*}
\]

(name two alkyl groups)

The aceto- common name is consistent amongst many compounds

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{aceto-} & \quad \text{acetic acid} & \quad \text{ethyl acetate}
\end{align*}
\]
Carbonyl Compounds

The properties of ketones and aldehydes are dependent on the structure. The carbonyl double bond is a result of a $\pi$ bond between the carbon and oxygen, similar to an alkene double bond is a result of a $\pi$ bond between two carbons.

Due to electronegativity of oxygen, however, this double bond is more polarized than an alkene with a greater electron density on the oxygen than carbon.

Due to this polarization, the orbitals are no longer symmetrical for an aldehyde or ketone as they are for an alkene – there is more electron density on oxygen in HOMO and more electron density on carbon in LUMO.
Carbonyl Compounds

The increase in proportion of charged structures in resonance hybrids causes two effects:

1) Carbonyl carbon is more electrophilic (compared to alkene)
2) Oxygen is more nucleophilic (compared to alkene)

Realize that when a nucleophile reacts with a ketone or aldehyde, the HOMO of the nucleophile reacts with the LUMO of the carbonyl.

In the LUMO of the carbonyl, the orbital is larger on the carbon and thus the nucleophile will preferentially react at the carbonyl carbon.

In resonance forms would obtain same result due to the increased proportion of resonance form with positive charge on carbon.
Carbonyl Compounds

Reactions on ketones/aldehydes occur either with strong nucleophiles in basic conditions or with weaker nucleophiles on protonated carbonyls in acidic conditions.

With strong nucleophiles, the HOMO of the nucleophile reacts with the LUMO of the electrophilic carbon.

When Grignard reagents react with ketones or aldehydes, an alcohol is generated after work-up as the nucleophilic carbon of the Grignard reacts with the electrophilic carbon of the carbonyl compound.
Carbonyl Compounds

Protonation of carbonyl creates more electrophilic carbon

Carbonyl carbon is much more electrophilic upon protonation due to resonance

Protonation thus allows a much weaker nucleophile to react at carbonyl carbon
Hydration Reactions

A carbonyl can become “hydrated” by reaction with water

Occurs in acidic conditions where carbonyl is first protonated

\[
\begin{align*}
\ce{H2O} & \quad \ce{H+} & \quad \ce{H2O} & \quad \ce{H+} \\
\ce{O} & \quad \ce{H} & \quad \ce{H} & \quad \ce{H} & \quad \ce{H} & \quad \ce{H} & \quad \ce{H}
\end{align*}
\]

Oxygen is more nucleophilic

Weaker water nucleophile can react at protonated carbonyl

Each step in mechanism is reversible, therefore equilibrium is dependent on concentration of each form

Ketone is more stable in carbonyl form

Aldehyde has relatively more hydrated form than ketone

Formaldehyde has a higher concentration of hydrated form
Hydration Reactions

The equilibrium in hydration reactions is dependent upon the reactivity of the carbonyl.

As the electrophilicity increases, the equilibrium favors the hydrated form.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{CH}_3 & \quad \text{CH} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

Less “donating” alkyl substituents make carbonyl more electrophilic.

Inductively withdrawing chlorine substituents make carbonyl more electrophilic.

<table>
<thead>
<tr>
<th>Equilibrium for hydration (K)</th>
<th>0.002</th>
<th>1.06</th>
<th>2300</th>
<th>28000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less “donating” alkyl substituents make carbonyl more electrophilic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inductively withdrawing chlorine substituents make carbonyl more electrophilic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hydration Reactions

Another factor affecting the equilibrium is the sterics involved in the mechanism.

As the substituents on the carbonyl carbon become larger, there is a greater preference for the carbonyl form than the hydrated form due to less sterics.

As alkyl groups increase in size, the sterics will favor the carbonyl form more.
Addition of Cyanide

Cyano groups (nitriles) can also add to carbonyls

Cyanide reacts in a basic mechanism

Caution – do not acidify cyanide solution, it will create hydrogen cyanide

\[ \text{CN}^{-} + \text{H}^+ \rightarrow \text{HCN} \]
Hydrolysis of Nitrile

An advantage with cyanohydrins is that the nitrile can be hydrolyzed to an acid

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{OH} \\
\text{CH}_3 & \quad \text{CN} \\
\end{align*}
\quad \xrightarrow{\text{H}^+, \text{H}_2\text{O}}
\begin{align*}
\text{H}_3\text{C} & \quad \text{OH} \\
\text{CH}_3 & \quad \text{CO}_2\text{H}
\end{align*}
\]

Depending upon the conditions used to protonate the alkoxide in the previous step, both reactions can occur in same step

One of the easiest methods to create an α-hydroxy acid (analogs of α-amino acids)
In nature this reaction is used as a biodefense mechanism.

The formation of cyanohydrins is reversible.

\[
\text{OH} \quad \text{H} \quad \text{CN} \quad \text{H} \\
\text{O} \quad \text{H} \quad \text{H} \quad \text{CN}
\]

Insects store this cyanohydrin as a defense, if predators eat the insects they ingest the cyanohydrin which can break down to generate HCN.

The HCN will kill the predator and thus act as a deterrent.
Acetals

Acetals are related to hydrates, instead of geminal dialcohols have geminal ethers

\[
\begin{align*}
    &\text{H}_3\text{C} \quad \text{CH}_3 \\
\rightarrow &\text{ROH} \quad \text{H}^+ \\
\rightarrow &\text{RO} \quad \text{OR} \\
    &\text{H}_3\text{C} \quad \text{CH}_3
\end{align*}
\]

Originally if geminal ether came from a ketone it was called a ketal, if geminal ether came from an aldehyde it was called an acetal (now any carbonyl that forms a gem-diether is called an acetal)

This process is once again an equilibrium process

Aldehydes (which are more reactive than ketones) typically favor acetals
Cyclic Acetals

When both alcohols to form an acetal are intramolecular (on same molecule) then a cyclic acetal is formed

\[
\begin{align*}
\text{H}_3\text{C} & \text{CHO} + \text{HOCH}_2\text{OH} \xrightleftharpoons[\text{H+}]{\text{H}_3\text{C} \text{CH}_2\text{OH}} \text{H}_3\text{C} \text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3
\end{align*}
\]

Cyclic acetals are often used because they have a higher equilibrium for the acetal form

Entropy favors two molecules condensing to one more than when three molecules condense to one
Acetals

Acetals and hemiacetals are common with sugar compounds

While the open chain forms are often drawn for sugar molecules, in solution they often adopt a closed ring form

The closed ring forms have acetal or hemiacetal ring junctions
Protecting Groups

Protecting groups are extremely important in organic synthesis.

Acetals are stable under basic conditions, but will revert to aldehyde under acidic conditions. Thus acetals can be used as a protecting group for the carbonyl and allow reactions that would not be possible otherwise.

\[
\begin{align*}
\text{Br-} & \quad \text{Mg} \\
\text{BrMg} & \quad \text{H}
\end{align*}
\]

Cannot form this compound, will react intramolecularly.
Protecting Groups

Using acetal, however, the Grignard can be formed

\[
\begin{align*}
\text{Br-} & \quad \text{H} \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[+\]

With no carbonyl present, the Grignard reagent is stable

\[
\begin{align*}
\text{BrMg} & \quad \text{O} \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

Reaction is not possible without acetal protecting group
Protecting Groups

Acetals can also be used as protecting groups for alcohols in addition to carbonyl compounds.

An alcohol can be reacted with dihydropyran to form an acetal.

\[
\begin{align*}
\text{Dihydropyran (DHP)} & \quad \xrightarrow{\text{acid}} \quad \text{acetal} \\
\text{OH} & \quad \xrightarrow{\text{acid}} \quad \text{H}_2\text{O} \quad \xrightarrow{\text{H}^+} \quad \text{OH} \quad \text{HO}\text{COO} \\
\end{align*}
\]

The alcohol is thus protected and can be used without worrying about the labile hydrogen.
Protecting Groups

Another common protecting group for alcohols is to form a silyl ether:

\[
\begin{align*}
\text{OH} & \quad \rightarrow \quad \text{OTBDMS} \\
\text{(H}_3\text{C)}_3\text{C} & \quad \text{Cl} \\
\text{(TBDMSCl, Tetrabutylidimethylsilyl chloride)}
\end{align*}
\]

A wide variety of silyl protecting groups are used:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{(H}_3\text{C)}_3\text{C} & \quad \text{Si} \quad \text{Cl} \\
\text{(TBDMSCl)}
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{Si} \quad \text{Cl} \\
\text{(TMS)}
\end{align*}
\]

The silyl protecting group can be removed with fluoride reagents:

\[
\begin{align*}
\text{OH} & \quad \text{TMSCl} \\
\text{TMS} & \quad \text{F} \quad \text{N(Bu)}_4 \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{TMSCl} \\
\text{TMS} & \quad \text{F} \quad \text{N(Bu)}_4 \quad \text{OH}
\end{align*}
\]
Imines

Carbonyls can also react with primary amines to create imines

Reaction occurs under an acid catalyzed mechanism

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{CH}_3
\end{align*}
\xleftrightarrow{\text{H}^+} \quad
\begin{align*}
\text{CH}_3\text{NH}_2 & \\
\text{H}_3\text{C} & \quad \text{HO} \quad \text{NHCH}_3
\end{align*}
\xrightarrow{-\text{H}_2\text{O}} \quad
\begin{align*}
\text{H}_3\text{C} & \quad \text{NCH}_3 \\
\text{H}_3\text{C} & \quad \text{CH}_3
\end{align*}
\]

Each step is reversible

The imine can therefore be converted to the carbonyl with acidic water
(Le Chatelier’s principle)
Imines are important for vision

11-cis-retinal reacts with a 1° amine in the protein opsin in the rod cells of the eye

Upon application of light, a cis/trans interconversion occurs which is converted into an electrochemical impulse by affecting the concentration of Ca²⁺ crossing a cell membrane.
Nitrogen Bases

Other substituted amines can react in a similar manner

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} & \quad \text{NH}_2\text{OH} & \quad \text{H}^+ \\
\text{H}_3\text{C} & \quad \text{C} & \quad \text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{N} & \quad \text{H}^+ \\
\text{H}_3\text{C} & \quad \text{C} & \quad \text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{N} & \quad \text{NH}_2 \\
\text{H}_3\text{C} & \quad \text{C} & \quad \text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{N} & \quad \text{NHPh} \\
\text{H}_3\text{C} & \quad \text{C} & \quad \text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{N} & \quad \text{NHPh}
\end{align*}
\]

oximes

hydrazones

Phenyl hydrazones
These condensation products are often used for identification

These condensation derivatives with substituted amines are often crystalline solids

The melting points of these solids are known

Therefore an aldehyde or ketone can be determined by comparing the melting points of its condensation products with known values

Before many spectroscopic tools were developed this was the only way to determine structure of unknowns, run reactions and systematically determine products
Secondary Amines

Secondary amines condense to form enamines

Similar process to imines
(use 2° amine instead of 1° amine)

\[
\begin{align*}
\text{H}_3\text{C} & \text{C}_2\text{H}_3 \quad \xrightarrow{\text{R}_2\text{NH}} \quad \text{H}_3\text{C} \overset{\text{CH}_3}{\underset{\text{H}}{\text{O}}} \quad \xrightarrow{-\text{H}_2\text{O}} \quad \text{H}_3\text{C} \overset{\text{C}}{\underset{\text{H}}{\text{=}}} \text{CH}_2
\end{align*}
\]

enamine

Forms carbon-carbon double bond after losing water, must lose hydrogen from α-carbon as there are no remaining hydrogens on nitrogen

Enamines have different subsequent reactivity than imines (will see more in chapter on α-substitution)
Organometallic Nucleophiles

If carbon based nucleophiles were used instead of nitrogen (which form imines and enamines) or oxygen (which form acetals or hydrates) then alcohols can be formed.

![Chemical reaction](image)

Have already observed carbon based nucleophiles with Grignard reagents or organolithium.

![Chemical structures](image)

Due to the very high dipole of a carbon-magnesium bond (or carbon-lithium) these compounds behave like carbon anions.
Organometallic Nucleophiles

When these Grignard reagents (or organolithium) are reacted with ketones or aldehydes, alcohol products are obtained

The type of alcohol obtained is dependent upon the ketone or aldehyde used

Formaldehyde yields 1° alcohols

Aldehydes yield 2° alcohols

Ketones yield 3° alcohols
Organometallic Nucleophiles

When reacting Grignard reagents with aldehydes (to create 2° alcohols) or ketones (to create 3° alcohols), a specific alcohol can be synthesized through different routes depending upon the choice of carbonyl compound and the choice of Grignard reagent.

Desired product

\[
\text{H}_3\text{CCH}_2\text{CH}_2\text{C}^\text{\textbullet} \text{CH}_2\text{CH}_3
\]

\[
\text{H}_3\text{CCH}_2\text{CH}_2\text{C} \text{CH}_3
\]

Possibility #1

\[
\text{H}_3\text{CCH}_2\text{CH}_3
\]

\[
\text{CH}_3\text{MgBr}
\]

Possibility #2

\[
\text{H}_3\text{CH}_2\text{CH}_2\text{CCH}_2\text{CH}_3
\]

\[
\text{CH}_3\text{MgBr}
\]

Possibility #3

\[
\text{H}_3\text{CH}_2\text{CH}_2\text{CCH}_3
\]

\[
\text{MgBr}
\]
Organometallic Nucleophiles

Grignard reagents, however, have some limitations as nucleophiles

* Grignards do not have high yields when reacting with alkyl halides

When a Grignard reacts with an alkyl halide the reaction is very poor

This fact is actually fortunate because otherwise it would be difficult to form Grignard reagents since the Grignard is a result of an alkyl halide reacting with magnesium

If the Grignard reacted with the alkyl halide, as soon as some of the Grignard formed it would react with the alkyl halide used to form the Grignard

Grignard reagents can be formed in high yield, however, because they do not react with alkyl halides well
Organometallic Nucleophiles

Alkyl halides will react with organocuprates to form new carbon-carbon bonds.

Organocuprates are generated by reacting organolithium compounds with copper iodide.

$$2 \text{Li} \xrightarrow{\text{CuI}} \text{Li}_2\text{CuLi} + \text{LiI}$$

The organocuprates can then be reacted with alkyl halides to generate alkanes in high yield.

$$\text{Br} \xrightarrow{(\text{Li}_2\text{CuLi})} \text{alkane}$$
Organometallic Nucleophiles

* Another drawback of Grignard reagents is that in addition to being strong nucleophiles, they are also very strong bases

Realize Grignard reagents are a type of carbon based anions, anions on carbon have pKa values at ~50-60

These anions are thus far more basic than amines, alcohols or carboxylic acids

\[
\text{pKa} \quad 50-60 \quad \sim 35 \quad \sim 16 \quad \sim 4-5
\]

Therefore Grignard reagents can never be used with compounds that have a labile hydrogen

\[
\text{MgBr} \quad \text{HO}^\text{\textmd{C}} \quad \rightarrow \quad \text{BrMgO}^\text{\textmd{C}}
\]

Allows formation of alkanes from alkyl halides, but will undergo acid-base reaction before reacting with carbonyl
Organometallic Nucleophiles

Due to this high basicity, Grignard reagents also cannot be reacted with carboxylic acids (will undergo an acid/base reaction instead of reacting with carbonyl)

Carboxylic acids can be converted into other type of carboxylic acid derivatives (we learn this chemistry in later chapters)

Two types of carboxylic acid derivatives that are relevant for reaction with Grignard reagents are acid chlorides and esters

\[
\begin{align*}
\text{Acid} & \quad \text{Ester} & \quad \text{Acid chloride} \\
\text{one R, one OH} & \quad \text{one R, one OR} & \quad \text{one R, one Cl}
\end{align*}
\]

While carboxylic acid compounds will not react with Grignard reagents at the carbonyl, both esters and acid chloride derivatives will react at carbonyl
Organometallic Nucleophiles

Addition of one equivalent of Grignard reagent to an acid chloride (or ester) will generate a tetrahedral intermediate.

Unlike when reacting a Grignard with a ketone or aldehyde, however, this tetrahedral intermediate has a good leaving group attached (the chlorine).

The alkoxide will reform a carbonyl (strong bond) with the good leaving group present.

Since this ketone is formed in the presence of the Grignard reagent, a second addition occurs.

Thus when either an acid chloride or ester react with a Grignard, two equivalents of Grignard are required and a 3° alcohol is obtained.
Organometallic Nucleophiles

* Another problem with Grignard reagents are that they are unselective

Grignard reagents are strong nucleophiles so they will react with any electrophilic double bond (reactivity versus selectivity)

This is good to react with carbonyl groups, but if any other reactive groups are present they will also react

Will react with various multiple bond structures

\[
\begin{align*}
R\text{C}=\text{NR} & \quad R\text{C}=\text{N} & \quad \text{O=C=O}
\end{align*}
\]

Cannot react at one site preferentially if more than one reactive site is present

A useful reaction, however, to form carboxylic acids from Grignard reagents
Metal Hydrides

When Grignard reagents are reacted with water, the initial alkyl halide has been reduced to an alkane.

\[ \text{Br} \xrightarrow{\text{Mg}} \text{MgBr} \xrightarrow{\text{H}_2\text{O}} \text{alane} \]

Another way to reduce alkyl halides to alkanes is to use lithium aluminum hydride.

\[ \text{LiAlH}_4 \]

Can consider LAH as a source of hydride “H-” nucleophiles.
Metal Hydrides

In addition to reacting with alkyl halides, lithium aluminum hydride can react with carbonyl compounds to create alcohols.

Formaldehyde reacting with LAH generates methanol.

Aldehydes reacting with LAH generate 1° alcohols.

Ketones reacting with LAH generate 2° alcohols.

Thus either methanol, 1° alcohols, or 2° alcohols can be prepared by reacting the appropriate ketone or aldehyde with LAH.
Metal Hydrides

Sodium borohydride will also reduce ketones or aldehydes to methanol, 1° alcohols, or 2° alcohols depending upon the carbonyl used.

\[
\text{NaBH}_4
\]

structure

Sodium borohydride also reacts like a hydride nucleophile on carbonyl
Metal Hydrides

While LAH and NaBH$_4$ both react like a hydride nucleophile, the reactivity is different as LAH is a much stronger nucleophile than NaBH$_4$.

Due to this increased reactivity LAH will not work in alcoholic or aqueous solvents – it reacts with the solvent before reducing the carbonyl group.

Therefore need to work-up LAH reactions in a SECOND step.

This is not true with NaBH$_4$; these reactions CAN occur in alcoholic solvents.
Metal Hydrides

Due to the increased reactivity, LAH can also reduce other carbonyl compounds that NaBH₄ cannot

\[
\begin{array}{ccc}
\text{OH} & \text{NaBH}_4 & \text{O} \\
\text{H}_3\text{C} & \text{CH}_3\text{OH} & \text{H}_3\text{C} & 1) \text{LAH} & \text{OH} \\
& & & 2) \text{H}_3\text{O}^+ & \\
\text{H}_3\text{C} & \text{CH}_3 & \text{H}_3\text{C} & \text{CH}_3 & \text{H}_3\text{C} & \text{CH}_3 \\
& & & 2) \text{H}_3\text{O}^+ & \\
\end{array}
\]

No reaction

\[
\begin{array}{ccc}
\text{NaBH}_4 & \text{O} \\
\text{CH}_3\text{OH} & \text{H}_3\text{C} & \text{OCH}_3 & 1) \text{LAH} & \text{OH} \\
& & & 2) \text{H}_3\text{O}^+ & \\
\text{H}_3\text{C} & \text{OCH}_3 & \text{H}_3\text{C} & \text{H}_3 & \text{H}_3 \\
& & & 2) \text{H}_3\text{O}^+ & \\
\end{array}
\]

No reaction

\[
\begin{array}{ccc}
\text{NaBH}_4 & \text{O} \\
\text{CH}_3\text{OH} & \text{H}_3\text{C} & \text{OH} & 1) \text{LAH} & \text{OH} \\
& & & 2) \text{H}_3\text{O}^+ & \\
\text{H}_3\text{C} & \text{OH} & \text{H}_3 & \text{H}_3 & \text{H}_3 \\
& & & 2) \text{H}_3\text{O}^+ & \\
\end{array}
\]
Metal Hydrides

Sodium borohydride is thus more selective than LAH, while LAH will reduce almost all carbonyl compounds to an alcohol, \( \text{NaBH}_4 \) will only react with ketones or aldehydes.

\[
\text{LaH will reduce both carbonyls in this compound}
\]

\[
\begin{align*}
\text{CH}_3\text{OCH}_3 & \xrightarrow{1) \text{LAH}} \text{CH}_3\text{OH} \\
\text{H}_2\text{O} & \xrightarrow{2) \text{H}_3\text{O}^+} \text{CH}_3\text{OH}
\end{align*}
\]

\[
\text{NaBH}_4 \text{ will reduce the ketone, but will not react with ester}
\]

\[
\begin{align*}
\text{LaH} & \xrightarrow{\text{CH}_3\text{OH}} \text{CH}_3\text{OH} \\
\text{NaBH}_4 & \xrightarrow{\text{NaBH}_4} \text{CH}_3\text{OH}
\end{align*}
\]
Metal Hydrides

Instead of reducing ketones or aldehydes with LAH to form alcohols, the carbonyl can first be converted into an imine or imine derivative which will reduce to an amine.

\[
\begin{align*}
\text{O} & \quad \text{NH}_2\text{OH} & \quad \text{NOH} & \quad 1) \text{LAH} & \quad \text{NH}_2 \\
\text{H}_3\text{C} - \text{CH}_3 & \quad + \quad \text{H}^+ & \quad \text{H}_3\text{C} - \text{CH}_3 & \quad \rightarrow & \quad \text{H}_3\text{C} - \text{CH}_3 \\
\text{O} & \quad \text{CH}_3\text{NH}_2 & \quad \text{NCH}_3 & \quad 1) \text{LAH} & \quad \text{NH}_2\text{CH}_3 \\
\text{H}_3\text{C} - \text{CH}_3 & \quad + \quad \text{H}^+ & \quad \text{H}_3\text{C} - \text{CH}_3 & \quad \rightarrow & \quad \text{H}_3\text{C} - \text{CH}_3
\end{align*}
\]

Oximes are reduced to 1° amines.

\[
\begin{align*}
\text{O} & \quad \text{(CH}_3\text{)}_2\text{NH} & \quad \text{H}_3\text{C}^{+} - \text{CH}_3 & \quad \text{Na(CH}_3\text{CO}_2\text{)}_3\text{BH} & \quad \text{H}_3\text{C} - \text{N} - \text{CH}_3 \\
\text{H}_3\text{C} - \text{CH}_3 & \quad + \quad \text{H}^+ & \quad \text{H}_3\text{C} - \text{CH}_3 & \quad & \quad \text{H}_3\text{C} - \text{CH}_3
\end{align*}
\]

Iminium salt

Iminium salts are unstable and must be reduced \textit{in situ}, thus a weaker reducing agent is required.
Oxidation of Alcohols

We have already observed the reduction of ketones to alcohols by reacting with LAH

The reverse of this step would be to oxidize a 2° alcohol to a ketone

\[
\begin{align*}
\text{Oxidation} & \quad \text{reduction} \\
\end{align*}
\]
Oxidation of Alcohols

Typical procedure to oxidize an alcohol is to use a chromium (VI) reagent
e.g. CrO₃, H₂Cr₂O₇, H₂CrO₄

The alcohol reacts with Cr(VI) to form a chromate ester
(similar to alcohols reacting with carbonyl compounds to form acetals)

The chromate ester then reacts with base to oxidize the alcohol
[and reduce the chromium reagent]
Oxidation of Alcohols

With 2° alcohols, oxidation with any Cr(VI) reagent will generate a ketone.

When oxidizing 1° alcohols, however, the choice of oxidizing agent will determine what product is obtained.

Under basic conditions with no water present, the 1° alcohol is oxidized to an aldehyde.

Common reagents for this transformation:

- Pyridinium chlorochromate (PCC)
- Pyridinium dichromate (PDC)
Oxidation of Alcohols

Under aqueous acidic conditions, however, the aldehyde is oxidized further to a carboxylic acid.

Remember that under acidic aqueous conditions, an aldehyde has a high concentration of hydrated form present.

\[
\begin{align*}
K &= 1.06 \\
\text{H}_3\text{C}-\text{CHO} &\xrightleftharpoons{\text{H}_2\text{O}} \text{H}_3\text{C}-\text{COOH} \\
\text{H}_3\text{C}-\text{CHO} &\xrightarrow{\text{CrO}_3} \text{H}_3\text{C}-\text{COOH}
\end{align*}
\]

This hydrated form can react with the Cr(VI) reagent present and oxidize to a carboxylic acid.

The choice of chromium reagent conditions will thus determine the product with 1° alcohols.

\[
\begin{align*}
\text{H}_3\text{C}-\text{CHO} &\xrightarrow{\text{PCC}} \text{H}_3\text{C}-\text{COOH} \\
\text{H}_3\text{C}-\text{OH} &\xrightarrow{\text{H}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4, \text{H}_2\text{O}} \text{H}_3\text{C}-\text{COOH}
\end{align*}
\]
Oxidation of Alcohols

While Cr(VI) reagents are the most common to oxidize alcohols, a variety of other reagents can cause this transformation.

Manganese dioxide only oxidizes allylic or benzylic positions

Nitric acid will oxidize 1° alcohols to acids

Potassium permanganate will oxidize 1° and 2° alcohols to acids and ketones

Remember that KMnO₄ also oxidizes aromatic alkyl chains to carboxylic acids
Oxidation of Alcohols

Another convenient oxidation procedure is called the “Swern” oxidation

DMSO is reacted with an electrophile (oxalyl chloride is commonly used) to form a chlorosulfonium ion

\[
\begin{align*}
\text{DMSO} & \quad \text{Oxalyl chloride} \\
\begin{array}{c}
\text{H}_3\text{C}\
\text{S}\
\text{CH}_3
\end{array} & \quad \begin{array}{c}
\text{Cl}\
\text{O}\
\text{C}\
\text{H}_3
\end{array} & \quad \begin{array}{c}
\text{Cl}\
\text{S}\
\text{CH}_3
\end{array}
\end{align*}
\]

The chlorosulfonium is generated in the presence of an alcohol which reacts at sulfur

In the presence of a triethylamine base, the intermediate is deprotonated which then undergoes an intramolecular elimination
Oxidation of Alcohols

The Swern oxidation is convenient because it will oxidize a 1° alcohol to only the aldehyde stage.

\[
\begin{array}{c}
\text{OH} \\
\text{CH}_2\text{CH}_2\text{OH} \\
\text{DMSO} \\
\text{oxalyl chloride} \\
\text{NEt}_3 \\
\text{O} \\
\text{H} \\
\text{CH}_2\text{CH}_2\text{O} \\
\text{O} \\
\text{H}
\end{array}
\]

There are many advantages to the Swern oxidation including:
- a very mild method (often done at low temperatures),
- easy to purify products,
- and no acid product is obtained from 1° alcohols.

One of the bigger advantages, however, is that no metal catalyst was used, therefore there is no need to remove chromium or manganese impurities.
Oxidation of Vicinal Alcohols

Periodic acid will cleave vicinal diols (glycols) selectively

\[
\text{Pinacol}
\]

As seen only glycols can react as the intermediate is a cyclic periodate ester

Important reaction to determine structure of sugar molecules

Only vicinal diols cleave
Oxidation of Thiols

Thiols can be oxidized under mild conditions to form a disulfide bond

\[ \text{SH} \xrightarrow{\text{Br}_2, \text{NaHCO}_3} \text{S-S} \]

This process is used in proteins to link together cysteine amino acids

The disulfide bond thus can lock the protein in a particular shape
Oxidation of Thiols

The formation of the disulfide bridge can change the properties of the protein

Structure of Insulin

Disulfide bonds lock the two amino acid fragments in particular shape
Oxidation of Thiols

A cosmetic application of disulfide bridges

Human hair consists of a protein (keratin) that contains a large percentage of cysteine (~4 times the amount found in other proteins)
The cysteine forms disulfide bonds to keep the hair in a particular shape

To change the shape:
A reducing agent is applied which breaks the disulfide bonds

The hair is then rearranged into a desired shape (curlers or combing)

An oxidizer is added to maintain the new shape of the hair

To change straight hair to curly this is called a “permanent”
To change curly hair to straight this is called a “hair straightening”
Oxidation of Thiols

Stronger oxidation of thiols generates sulfonic acids

With mild oxidation the thiol can be converted to a disulfide, stronger oxidation however oxidizes the sulfur to a sulfonic acid

Typically use potassium permanganate or nitric acid for this oxidation (use strong conditions, usually heat)
Oxidation of Thioethers

Thioethers can be oxidized to sulfoxides or sulfones (unlike ethers which will not be oxidized)

\[
\begin{align*}
\text{S} \quad \text{H}_2\text{O}_2 \quad \overset{\text{H}_2\text{O}_2}{\longrightarrow} \quad \text{S} \\
\text{O} \\ 
\text{sulfoxide} \\
\text{Δ} \\
\text{O} \\ 
\text{sulfone}
\end{align*}
\]

While a sulfoxide might seem structurally similar to a carbonyl compound, the sulfur of a sulfoxide is not planar

LUMO of carbonyl (C is sp\(^2\) hybridized)  Sulfoxide (S is \(\sim\)sp\(^3\) hybridized)
Wittig Reaction

Reaction converts a ketone or aldehyde into an alkene

\[
\begin{align*}
\text{H}_3\text{C}-\text{CH}_3 & \quad \xrightarrow{(\text{Ph})_3\text{P}=\text{CH}_2} \quad \text{H}_3\text{C} \equiv \text{CH}_3 \\
\end{align*}
\]

Merely looking at starting materials and product might cause confusion, but this reaction is another type of nucleophile reacting at electrophilic carbonyl

The nucleophile is the phosphorous ylide

An ylide is any compound that contains a cation adjacent to an anion

Georg Wittig
(1897-1987)
1979 Nobel prize
Wittig Reaction

typically these ylides can be prepared by reacting triphenylphosphine with alkyl halide

\[ \text{Ph} \stackrel{P}{\bigtriangleup} \text{Ph} \rightarrow \text{Ph} \stackrel{P}{\bigtriangleup} \text{Ph} \]

phosphonium salt

the methylene adjacent to phosphorous in phosphonium salt is acidic

\[ (\text{Ph})_3\text{P} \rightarrow \text{BuLi} \rightarrow (\text{Ph})_3\text{P} \]

with strong base therefore the ylide can be obtained
Wittig Reaction

The carbanion of the ylide is nucleophilic and will react with the carbonyl

\[
\text{betaine}
\]

The betaine structure will form 4-membered ring between positive phosphorous and negative oxygen

\[
\text{oxyphosphetane}
\]

The oxyphosphetane is the driving force for this reaction, strong phosphorous-oxygen bonds energetically drive reaction
Wittig Reaction

The oxyphosphetane will collapse to form a second phosphorous-oxygen bond

Overall an alkene is formed from the initial carbonyl compound

The oxygen of the initial carbonyl forms double bond to phosphorous in phosphine oxide (driving force for reaction)

Depending upon the initial phosphonium salt, different alkyl groups can be added to alkene product

Overall, the Wittig reaction is thus merely the reverse of an ozonolysis
Tollen’s Test

In this chapter we have observed a number of reactions of ketones and aldehydes.

In general, these two carbonyl compounds will undergo the same type of reactions, reactions that occur with ketones will also occur with aldehydes (there are quite different types of reactions, however, with carboxylic acid derivatives).

How does a chemist know if an unknown compound is a ketone or an aldehyde?

Often today the chemist would use the analytical tools learned earlier to distinguish, but having reactions that can distinguish the functional groups are useful.

One common test to differentiate whether an unknown compound is a ketone or an aldehyde is the so-called “Tollen’s test.”
Tollen’s Test

In this reaction, an aldehyde is oxidized to a carboxylic acid while the Ag\(^{+1}\) present is reduced to silver metal.

\[
\text{H}_3\text{C} = \text{H} + \text{Ag(NH}_3\text{)}_2^{+} + \text{KOH} \rightarrow \text{H}_3\text{C} \text{O}^- \text{K}^+ + \text{Ag} + \text{H}_2\text{O} + \text{NH}_3
\]

Clear solution

Metallic precipitate

The test is quite diagnostic because when an aldehyde is present, the clear solution forms a metallic silver precipitate (forms a silver mirror).

A ketone, however, does not react and thus the solution maintains a clear appearance, if an aldehyde is present a silver mirror forms but solution stays clear if a ketone is present.