Carbonyl Chemistry I
Carbonyl Chemistry
The Carbonyl Group

- In this and several following lectures we study the reactions of classes of compounds containing the carbonyl group, C=O
  - Aldehydes and ketones
  - Carboxylic acids
  - Derivatives of carboxylic Acids
  - Enolate anions
Resonance Description of Carbonyl Group

nucleophiles attack the carbon;

electrophiles attack the oxygen
The Carbonyl Group

- The carbonyl group consists of
  - one sigma bond formed by the overlap of sp² hybrid orbitals, and
  - one pi bond formed by the overlap of parallel 2p orbitals
Structure of Formaldehyde

The molecule is planar
bond angles: close to 120°
C=O bond distance: 1.22 Å
Bonding in Formaldehyde

Carbon and oxygen are $sp^2$ hybridized
Bonding in Formaldehyde

The $p$ orbitals on carbon and oxygen overlap to form a $\pi$ bond....

Is this the picture of such a molecular orbital?
Nomenclature-Aldehydes

- IUPAC names: select as the parent alkane the longest chain of carbon atoms that contains the carbonyl group. Subtract e and add al
  - because the carbonyl group of the aldehyde must be on carbon 1, there is no need to give it a number

- For unsaturated aldehydes, show the presence of the C=C by changing -an- to -en-
  - the location of the suffix determines the numbering pattern
Nomenclature - Aldehydes

Pentane → Pentanal

3-Methylbutanal

2-Propenal
(Acrolein)

(2E)-3,7-Dimethyl-2,6-octadienal
(Geranial)
Nomenclature of Aldehydes

when named as a substituent this is a \textit{formyl group}
when named as a suffix it is \textit{carbaldehyde}
\textit{carboxaldehyde}
Nomenclature-Aldehydes

- For cyclic molecules in which the -CHO group is attached to the ring, the name is derived by adding the suffix -carbaldehyde to the name of the ring.

- 2,2-Dimethylcyclohexanecarbaldehyde
- 2-Cyclopentene-carbaldehyde
Nomenclature of Aldehydes

- 4,4-dimethylpentanal
- 5-hexenal
- 2-phenylpropanedial
Many aldehydes and ketones occur naturally

2-heptanone (component of alarm pheromone of bees)

trans-2-hexenal (alarm pheromone of myrmicine ant)
The functional group of a ketone is a carbonyl group bonded to two carbon atoms.

- **Propanone** (Acetone)
- **Cyclohexanone**
IUPAC Nomenclature of Ketones

- $\text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_2\text{CH}_3$: 3-hexanone
- $\text{CH}_3\text{CHCHCH}_2\text{CCH}_3$: 4-methyl-2-pentanone
- H$_3$C\[\text{\Hoop{}\Hoop{}}\]\text{CO}: 4-methylcyclohexanone
Trivial Nomenclature of Ketones

- **Ethyl propyl ketone**: $\text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_2\text{CH}_3$
- **Benzyl ethyl ketone**: $\text{CH}_2\text{CCH}_2\text{CH}_2\text{CH}_3$
- **Divinyl ketone**: $\text{H}_2\text{C}≡\text{CHCCHCHCH}_2≡\text{CH}_2$
Nomenclature-Ketones

- IUPAC names:
  - select as the parent alkane the longest chain that contains the carbonyl group,
  - number to give C=O the smaller number and then subtract one and add one

Propanone (Acetone)

5-Methyl-3-hexanone

Bicyclo[2.2.1]-2-heptanone
**Nomenclature-Ketones**

Even the IUPAC system retains the common names acetone, acetophenone, and benzophenone.
Order of Precedence (Pecking order)

- For compounds that contain more than one functional group indicated by a suffix

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Suffix if Higher in Precedence</th>
<th>Prefix if Lower in Precedence</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CO₂H</td>
<td>-oic acid</td>
<td>-</td>
</tr>
<tr>
<td>-CHO</td>
<td>-al</td>
<td>oxo-</td>
</tr>
<tr>
<td>&gt;C=O</td>
<td>-one</td>
<td>oxo-</td>
</tr>
<tr>
<td>-OH</td>
<td>-ol</td>
<td>hydroxy-</td>
</tr>
<tr>
<td>-NH₂</td>
<td>-amine</td>
<td>amino-</td>
</tr>
<tr>
<td>-SH</td>
<td>-thiol</td>
<td>mercapto-</td>
</tr>
</tbody>
</table>
IUPAC Nomenclature of Ketones

3-hexanone

4-methyl-2-pentanone

ethyl propyl ketone

4-oxohexanal
Nomenclature-Ketones

- Even the IUPAC system retains the common names acetone, acetophenone, and benzophenone

- 1-Phenyl-1-pentanone

Acetone

Acetophenone

Benzophenone
Synthesis of Aldehydes and Ketones

A number of reactions already studied provide efficient synthetic routes to aldehydes and ketones.

- from alkenes
  - by ozonolysis
- from alkynes
  - by hydration (via enol)
- from arenes
  - via Friedel-Crafts acylation
The most common reaction of a carbonyl group is addition of a nucleophile to form a tetrahedral addition compound.

Here it is an acid or electrophile.

Tetrahedral carbonyl addition compound.
A second common reaction is with a proton or Lewis acid to form a resonance-stabilized cation. Protonation increases the electron deficiency of the carbonyl carbon and makes it more reactive toward nucleophiles.

Here it is a base or Nucleophile!
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Carbon Nucleophiles

- Addition of carbon nucleophiles is one of the most important types of nucleophilic additions to a C=O group; a new carbon-carbon bond is formed in the process!!!!

- We will study the addition of these carbon nucleophiles

<table>
<thead>
<tr>
<th>RMgX</th>
<th>RLi</th>
<th>RC≡C⁻</th>
<th>C≡N⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Grignard reagent</td>
<td>An organolithium reagent</td>
<td>An anion of a terminal alkyne</td>
<td>Cyanide ion</td>
</tr>
</tbody>
</table>
Victor Grignard

Shared Nobel Prize with Sabatier in 1912

“student” of Philippe Barbier
Grignard Reagents

- Given the difference in electronegativity between carbon and magnesium, the C-Mg bond is polar covalent, with C\(\delta^-\) and Mg\(\delta^+\)
  - Grignard reagents behave like a carbanions

- Carbanion: an anion in which carbon has an unshared pair of electrons and bears a negative charge
  - a carbanions are good nucleophiles and add efficiently to the carbonyl group of aldehydes and ketones
Grignard Reagents

- Addition of a Grignard reagent to formaldehyde followed by $\text{H}_3\text{O}^+$ gives a $1^\circ$ alcohol

\[
\text{CH}_3\text{CH}_2\text{MgBr}^+ \xrightarrow{\text{THF}} \text{CH}_3\text{CH}_2\text{C}^\text{=}\text{O}^- \text{MgBr}^+ \xrightarrow{\text{H}_3\text{O}^+ \text{dil.}} \text{CH}_3\text{CH}_2\text{C}^-\text{OH} + \text{Mg}^{+2}
\]

- This sequence (mechanism) is general and important!
Grignard Reagents

- Addition to any other RCHO gives a $2^\circ$ alcohol

- You may change decorations at will…review pages 263-264
  - but, be careful of acidic functions like -OH
Grignard Reagents

- Addition to CO$_2$ gives a carboxylic acid

- This is a great way to add a carbon
Grignard Reagents

- Addition to a ketone gives a 3° alcohol

- Please try this with other Grignard reagents and other ketones
Grignard Reactions

1. \[ \text{CH}_3\text{CH}_2\text{MgBr}^+ + \text{H}_3\text{O}^+ \xrightarrow{\text{THF}} \text{CH}_3\text{CH}_2\text{C}^+\text{O}^-\text{MgBr}^+ \xrightarrow{\text{H}_3\text{O}^+ \text{dil.}} \text{CH}_3\text{CH}_2\text{C}^-\text{OH} + \text{Mg}^{2+} \]

2. \[ \text{CH}_3\text{CH}_2\text{MgBr}^+ + \text{H}_3\text{O}^+ \xrightarrow{\text{THF}} \text{CH}_3\text{CH}_2\text{C}^+\text{C}^+\text{OH}^-\text{MgBr}^+ \xrightarrow{\text{H}_3\text{O}^+ \text{dil.}} \text{CH}_3\text{CH}_2\text{C}^-\text{OH} + \text{Mg}^{2+} \]

3. \[ \text{CH}_3\text{CH}_2\text{MgBr}^+ + \text{H}_3\text{O}^+ \xrightarrow{\text{THF}} \text{CH}_3\text{CH}_2\text{C}^+\text{C}^+\text{OH}^-\text{MgBr}^+ \xrightarrow{\text{H}_3\text{O}^+ \text{dil.}} \text{CH}_3\text{CH}_2\text{C}^-\text{OH} + \text{Mg}^{2+} \]
Problem: 2-phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.
Grignard Reactions

These are valuable and important reactions…
Please add to your card stock!
Salts of Terminal Alkynes

- Addition of an acetylide anion followed by $H_3O^+$ gives an $\alpha$-acetylenic alcohol.
Salts of Terminal Alkynes

An $\alpha$-hydroxyketone

A $\beta$-hydroxyaldehyde

Write the mechanism using the arrow convention
Grignard reagents react with esters

but species formed is unstable and dissociates under the reaction conditions to form a ketone.
Grignard reagents react with esters

\[
\begin{align*}
\text{R'MgX} & \quad \text{OCH}_3 \\
\text{R}_2\text{C=O} & \quad \text{CH}_3\text{O} \\
\text{RR'C} & \quad \text{OCH}_3 \\
\end{align*}
\]

this ketone then goes on to react with a second mole of the Grignard reagent to give a tertiary alcohol
Example

$$2 \text{CH}_3\text{MgBr} + (\text{CH}_3)_2\text{CHCOOCH}_3 \rightarrow$$

1. diethyl ether

2. H$_3$O$^+$

$$\text{OH}$$

$$(\text{CH}_3)_2\text{CHCCH}_3$$

CH$_3$

(73%)

Two of the groups attached to the tertiary carbon come from the Grignard reagent.
Grignard reagents react with:

- formaldehyde to give primary alcohols
- aldehydes to give secondary alcohols
- ketones to give tertiary alcohols
- esters to give tertiary alcohols
- CO$_2$ to give acids
- epoxides
Organolithium Reagents

H₂C=CHLi + CH₃C=CH₂

1. diethyl ether

2. H₃O⁺

CHCH=CH₂

(76%)
Addition of an acetylide anion followed by H$_3$O$^+$ gives an $\alpha$-acetylenic alcohol.
Addition of HCN

- Mechanism of cyanohydrin formation

\[ \begin{align*}
\text{N≡C}^- & \quad \xrightarrow{\text{THF}} \quad \text{N≡C} \quad \xrightarrow{\text{H}_3\text{O}^+} \quad \text{N≡C} \quad \\
& \quad \text{C} \quad \text{O}^- \quad \text{C} \quad \text{O}^- \quad \text{C} \quad \text{OH} \quad \text{Mg}^{+2}
\end{align*} \]
Cyanohydrins

- The value of cyanohydrins is for the new functional groups into which they can be converted
  - acid-catalyzed dehydration of the $2^\circ$ alcohol gives a valuable monomer

\[
\begin{align*}
\text{OH} & \quad \text{acid catalyst} \quad \text{CH}_2 = \text{CHC}≡\text{N} \quad + \quad \text{H}_2 \text{O} \\
\text{CH}_3 \quad \text{CHC}≡\text{N} & \quad \text{2-Hydroxypropanenitrile} \\
& \quad \text{(Acetaldehyde cyanohydrin)} \\
\end{align*}
\]
Cyanohydrins

- acid-catalyzed hydrolysis of the cyano group gives an $\alpha$-hydroxycarboxylic acid

\[
\begin{align*}
\text{Benzaldehyde cyanohydrin (Mandelonitrile)} & \quad \text{acid catalyst} \quad \text{2-Hydroxy-2-phenyl-ethanoic acid (Mandelic acid)} \\
\text{OH} & \quad \text{HO} \\
\text{CHC\equiv N} & \quad \text{CHCOH} \\
\text{+ H}_2\text{O} & \\
\end{align*}
\]
Cyanohydrins

- catalytic reduction of the carbon-nitrogen triple bond converts the cyano group gives a 1° amine

\[
\text{Benzaldehyde cyanohydrin} + 2 \text{H}_2 \xrightarrow{\text{Ni}} \text{2-Amino-1-phenylethanol}
\]

LiAlH\(_4\) also works well...

But…what about Pd/C and H\(_2\)
The Wittig reaction is a very versatile synthetic method for the synthesis of alkenes from aldehydes and ketones.

\[
\text{A phosphonium ylide} \quad \text{Methylene-cyclohexane} + \text{Triphenyl-phosphine oxide}
\]
Phosphonium Ylides

- **Ylide**: a molecule which, when written in a Lewis structure showing all atoms with complete valence shells, has positive and negative charges on adjacent atoms.

- **Phosphonium ylides** are formed in two steps:
  1. treatment of triphenylphosphine with a 1° or 2° alkyl halide to form a phosphonium salt followed by
  2. treatment of the phosphonium salt with strong base, typically butyllithium
Phosphonium Ylides

\[ \text{Triphenylphosphine} \quad \text{Butyllithium} \]

\[ \text{An alkyltriphenylphosphonium iodide} \]

\[ \text{A phosphonium ylide} \quad \text{Butane} \]
Wittig Reaction

- Phosphonium ylides react with the C=O group of aldehydes or ketones to give alkenes.

An oxaphosphetane

Triphenylphosphine oxide

An alkene
Wittig Reaction

- Examples:

\[
\begin{align*}
\text{O} & \\
\text{CH}_3 \text{CCH}_3 & + \text{Ph}_3 \text{P-CH(CH}_2\text{)}_3 \text{CH}_3 & \rightarrow \\
\text{CH}_3 & \\
\text{CH}_3 \text{C=CH(CH}_2\text{)}_3 \text{CH}_3 & + \text{Ph}_3 \text{P-O}^- \\
\text{2-Methyl-2-heptene}
\end{align*}
\]
Wittig Reaction

- More examples

\[ \text{PhCH}_2\text{CH} + \text{Ph}_3\text{P-CHCH}_3 \rightarrow \text{PhCH}_2\text{CH}=\text{CHCH}_3 + \text{Ph}_3\text{P-O}^- \]

1-Phenyl-2-butene
(87% Z isomer; 13% E isomer)

Don’t plan to control the E/Z ratio…you get generally get a mixture
The Wittig Reaction

- See... sometimes you can control it but... we won’t try in this class

\[
\text{PhCH}_2\text{CH} + \text{Ph}_3\text{P-CHCOCH}_2\text{CH}_3 \rightarrow \text{PhCH}_2\text{H} + \text{Ph}_3\text{P-O}^-
\]

Ethyl (E)-4-phenyl-2-butenoate
(only the E isomer is formed)