Organometallic Compounds
(Chapter 15)

- Organometallic compound: a compound that contains a carbon-metal bond
- The focus will be on organometallic compounds of Mg, Li, and Cu
  - these classes illustrate the usefulness of organometallics in modern synthetic organic chemistry
  - the use of organometallics can bring about transformations that cannot be accomplished in any other way
Organometallic reagents have two general types of reactions:

1. As strong bases (Bronsted-Lowry)
2. As nucleophilic reagents.

Regard the alkyl group as “R-”

Grignard Reagents

- Grignard reagent: an organomagnesium compound
  - prepared by addition of an alkyl, aryl, or alkenyl (vinyllic) halide to Mg metal in diethyl ether or THF
Preparation of Grignard reagents:

\[
\text{1-Bromobutane} + \text{Mg} \xrightarrow{\text{ether}} \text{Butylmagnesium bromide}
\]
(an alkyl Grignard reagent)

\[
\text{Bromobenzene} + \text{Mg} \xrightarrow{\text{ether}} \text{Phenylmagnesium bromide}
\]
(an aryl Grignard reagent)

• Grignard reagents dissolve as coordination compounds solvated by ether
  – ethylmagnesium bromide, EtMgBr
Organolithium reagents

- Organolithium reagents
  - prepared by reaction of an alkyl, aryl, or alkenyl halide with lithium metal

\[
\begin{align*}
\text{1-Chlorobutane} & \quad + \quad 2 \text{ Li} \\
\text{pentane} & \quad \rightarrow \\
\text{Butyllithium} & \quad + \quad \text{LiCl}
\end{align*}
\]

The carbon-metal bonds in RMgX and RLi are polar covalent

<table>
<thead>
<tr>
<th>C-M Bond</th>
<th>Difference in Electronegativity</th>
<th>Percent Ionic character*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Li</td>
<td>2.5 - 1.0 = 1.5</td>
<td>60</td>
</tr>
<tr>
<td>C-Mg</td>
<td>2.5 - 1.2 = 1.3</td>
<td>52</td>
</tr>
<tr>
<td>C-Al</td>
<td>2.5 - 1.5 = 1.0</td>
<td>40</td>
</tr>
<tr>
<td>C-Zn</td>
<td>2.5 - 1.6 = 0.9</td>
<td>36</td>
</tr>
<tr>
<td>C-Sn</td>
<td>2.5 - 1.8 = 0.7</td>
<td>28</td>
</tr>
<tr>
<td>C-Cu</td>
<td>2.5 - 1.9 = 0.6</td>
<td>24</td>
</tr>
<tr>
<td>C-Hg</td>
<td>2.5 - 1.9 = 0.6</td>
<td>24</td>
</tr>
</tbody>
</table>

*Percent ionic character = \( \frac{E_C - E_M}{E_C} \times 100 \)

Increasing Ionic Character

Stronger Nucleophile
• Reaction with proton donors:
  – RMgX and RLi are strong bases

\[
\begin{array}{c}
\text{CH}_3\text{CH}_2\text{-MgBr} \quad \text{Stronger base} \\
\quad \quad \quad \text{pK}_a 15.7 \\
\text{H-OH} \quad \text{Stronger acid} \\
\quad \quad \quad \text{pK}_a 51 \\
\text{CH}_3\text{CH}_2\text{-H} \quad \text{Weaker acid} \\
\quad \quad \quad \text{Weaker base} \\
\text{pK}_a \text{ eq} = -35
\end{array}
\]

– they react readily with these proton acids

<table>
<thead>
<tr>
<th>R₂NH</th>
<th>RC≡CH</th>
<th>ROH</th>
<th>HOH</th>
<th>ArOH</th>
<th>RSH</th>
<th>RCOOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° and 2° Amines</td>
<td>Terminal alkynes</td>
<td>Alcohols</td>
<td>Water</td>
<td>Phenols</td>
<td>Thiols</td>
<td>Carboxylic acids</td>
</tr>
</tbody>
</table>

This is often an undesired side reaction— to be avoided!!

Organometallic reagents have 2 general types of reactions:
1. As Strong bases (Bronsted-Lowry)
2. As nucleophilic reagents:

\[
\text{C H}_3\text{C H}_2\text{C H}_2 \ominus \text{M g B r}
\]

Regard the alkyl group as “R⁻”
• RMgX and RLi are valuable in synthesis as nucleophiles
  – the carbon bearing the halogen is transformed from an electrophile to a nucleophile
  – their most valuable use is addition to the electrophilic carbon of C=O groups of aldehydes, ketones, carboxylic esters, and acid chlorides to form a new carbon-carbon bonds

**General Reactions of Grignard Reagents**
Organic Lecture Series

• Reaction with oxiranes (epoxides)
  – reaction of RMgX or RLi with an oxirane
    followed by protonation gives a primary
    alcohol with a carbon chain two carbons
    longer than the original chain

\[
\text{Butylmagnesium bromide} + \text{Ethylene oxide} \rightarrow \text{1-Hexanol}
\]

\[
\text{MgBr} + \text{O} \overset{\text{MgBr}}{\longrightarrow} \text{OH}
\]

• Reaction with oxiranes (epoxides)
  – the major product corresponds to SN2 attack
    of RMgX or RLi on less hindered carbon of
    the epoxide

\[
\text{Phenylmagnesium bromide} + \text{Methyloxirane (Propylene oxide)} \rightarrow \text{1-Phenyl-2-propanol (racemic)}
\]

\[
\text{MgBr} + \text{O} \overset{\text{MgBr}}{\longrightarrow} \text{OH}
\]

\[
\text{Phenyl-} \overset{\text{O}}{\text{MgBr}}^+ \overset{\text{HCl}, \text{H}_2\text{O}}{\longrightarrow} \text{1-Phenyl-2-propanol (racemic)}
\]
A Simple Example:

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Li} + \text{Cul} \xrightarrow{\text{diethyl ether or THF}} \left(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\right)_2\text{Cu}^- \text{Li}^+ + \text{Lil}
\]

Gilman reagents

- Lithium diorganocopper reagents, known more commonly as Gilman reagents
  - prepared by treating an alkyl, aryl, or alkenyl lithium compound with Cu(I) iodide
Coupling within organohalogen compounds
– form new carbon-carbon bonds by coupling with alkyl chlorides, bromides, and iodides

\[
R'\text{Br} + \text{R}_2\text{CuLi} \xrightarrow{\text{diethyl ether or THF}} R'-\text{R} + \text{RCu} + \text{LiBr}
\]

Coupling within organohalogen compounds
– form new carbon-carbon bonds by coupling with alkenyl chlorides, bromides, and iodides

\[
\text{R'\text{R}} + \text{R}_2\text{CuLi} \xrightarrow{\text{ether or THF}} \text{R'\text{R}}
\]

1. Li, pentane
2. CuLi

1-Iododecane

\[
\text{Br}
\]

2-Methyl-1-dodecene

\[
\text{CuLi}
\]
coupling with a vinylic halide is stereospecific: the configuration of the carbon-carbon double bond is retained.

\[
\text{trans-1-iodo-1-nonene} + \text{(diethyl ether or THF) Li dibutylcopper} \rightarrow \text{trans-5-Tridecene}
\]

- A variation on the preparation of a Gilman reagent is to use a Grignard reagent with a catalytic amount of a copper(I) salt.

\[
\begin{align*}
\text{CH}_3\left(\text{CH}_2\right)_{7} \text{C} = \text{C} \text{H} & \quad + \quad \text{CH}_3\left(\text{CH}_2\right)_{4} \text{MgBr} \\
\text{(Z)-1-Bromo-9-octadecene} & \quad + \quad \text{(Z)-9-Tricosene} \\
\text{CH}_3\left(\text{CH}_2\right)_{7} \left(\text{CH}_2\right)_{12} \text{CH}_3 & \quad \xrightarrow[\text{Cu}^+ \text{THF}]{} \\
\text{(Muscalure)}
\end{align*}
\]
Carbenes & Carbenoids

- **Carbene**, \( R_2C \): a neutral molecule in which a carbon atom is surrounded by only six valence electrons
- Methylene, the simplest carbene
  - prepared by photolysis or thermolysis of diazomethane

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{N} \equiv \text{N}^+ \\
\text{hv} & \quad \rightarrow \\
\text{H}_2\text{C}^- & \quad + \text{N} \equiv \text{N}\
\end{align*}
\]

Methylene (the simplest carbene)

- methylene prepared in this manner is so nonselective that it is of little synthetic use

---

Carbenes & Carbenoids

**Dichlorocarbene**

- prepared by treating chloroform with potassium *tert*-butoxide

\[
\text{CHCl}_3 + (\text{CH}_3)_3\text{CO}^-\text{K}^+ \rightarrow \text{Cl}_2\text{C}: + (\text{CH}_3)_3\text{COH} + \text{K}^+\text{Cl}^-
\]

<table>
<thead>
<tr>
<th>Trichloromethane (Chloroform)</th>
<th>Potassium <em>tert</em>-butoxide</th>
<th>Dichlorocarbene <em>tert</em>-Butyl alcohol</th>
</tr>
</thead>
</table>
**Dichlorocarbene**

reacts with alkenes to give dichlorocyclopropanes

\[
\text{Cl}_2\text{C:} + \text{ cis-3-Hexene} \rightarrow \text{cis-1,1-Dichloro-2,3-diethylcyclopropane}
\]

---

**Simmons-Smith reaction**

– a way to add **methylene** to an alkene to form a cyclopropane

– generation of the Simmons-Smith reagent

\[
\text{CH}_2\text{I}_2 + \text{Zn(Cu)} \xrightarrow{\text{diethyl ether}} \text{ICH}_2\text{ZnI}
\]

– this organozinc compound reacts with a wide variety of **alkenes to give cyclopropanes**

(Prepared by: Zn dust; CuCl & heat)
Simmons-Smith reaction:
the organozinc compound reacts with an alkene by a concerted mechanism*

\[
\begin{align*}
\text{CH}_2\text{I} & \quad \text{ZnI}_2 + \text{H}_2\text{C} \\
\text{I} & \quad \text{Zn} \\
\end{align*}
\]

*concerted mechanism-one in which there is simultaneous bond breaking and bond formation.

Uses of the Simmons-Smith reagent:

\[
\begin{align*}
\text{CH}_2\text{I}_2 & \quad \text{Zn(Cu)} \\
\text{diethyl ether} & \quad \text{ZnI}_2 \\
\end{align*}
\]

Methylene-cyclopentan e
Spiro[4.2]heptane

\[
\begin{align*}
\text{O} & \quad \text{H} \quad \text{CH}_2 \\
\text{2-Cyclohexenone} & \quad \text{Bicyclo[4.1.0]heptan-2-one} \\
\end{align*}
\]
Example of a drug which has a cyclopropane moiety:

- Sedation
- Analgesia
- Euphoria
- Constipation (GI)
- Respiratory depression
- Addiction liability

Naltrexone

opioid receptor antagonist used primarily in the management of alcohol dependence and opioid dependence.