The Grignard reaction reported in 1900 by Victor Grignard (Nobel Prize, 1912) is an important tool to connect the carbon-carbon bond.

**Preparation of Grignard**

*Alkyl Grignard* reagents are prepared by the reaction of an alkyl halide with "activated" magnesium turnings in Et₂O or THF solvent.

\[
R-X + Mg \rightarrow R-MgX
\]

*Alkenyl and phenyl Grignard* reagents are usually prepared from the corresponding bromides or iodides. The mixture of isomers was obtained during the preparation of vinyl Grignard. It can be trapped by electrophile to get the derivatives.

*Allylic Grignard* reagents, prepared from allylic halides and magnesium, are often accompanied by allylic halide coupling products. This problem can be avoided by mixing the allylic halide, the aldehyde or ketone, and magnesium in together in what is called a Barbier-type reaction. As the Grignard reagent forms, it reacts immediately with the electrophile before it has a chance to couple with unreacted allylic halide.
**Alkynyl Grignard** reagents are obtained by deprotonation of propyne using the Ethyl magnesium bromide to obtain the Grignard with evolution of ethane.

![Chemical Reaction]

**Mechanism of the Organo Grignard Preparation**

The mechanism of the Grignard preparation is not clearly understood in the last 100 years. (Not included in this notes)

**Reaction of Grignard reagent with carbonyl compound**

The Grignard reagent adds to the carbonyl compounds according to the reactivity below

Aldehyde > ketone > Ester > Amide

The Grignard reaction with aldehyde is faster than the ketone due to the reactivity of carbonyl compound.

![Chemical Reaction]

If the Grignard reagent has a hydrogen in the α-position, reduction of the carbonyl group by hydride transfer may compete with the addition reaction.

![Chemical Reaction]
The smallest-possible group for the Grignard reagent can suppress these side reactions, also the corresponding lithium reagents, which give less reduction and enolization products.

\[
\text{Product distribution (\%)}
\]

<table>
<thead>
<tr>
<th>Grignard Reagent</th>
<th>Addition</th>
<th>Enolization</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH\textsubscript{3}MgX</td>
<td>95</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(CH\textsubscript{3})\textsubscript{3}CMgX</td>
<td>0</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>(CH\textsubscript{3})\textsubscript{3}CCH\textsubscript{2}MgX</td>
<td>0</td>
<td>90</td>
<td>0</td>
</tr>
</tbody>
</table>

**Limitations**

✓ Certain functional groups present in a molecule interfere with the preparation of Grignard reagents. Thus, -NH, -OH, and -SH groups will protonate the Grignard reagent once it is formed.
✓ Carbonyl and nitrile groups attached to the electrophile containing the halogen substituent will undergo addition reactions.
✓ However, iodine-magnesium exchange reactions of functionalized aryl iodides and heteroaryl iodides recently are reported to produce functionalized Grignard reagents at low temperature.

**Organocopper Reagent**

**Homocuprate Reagents (Gilman Reagents: R\textsubscript{2}CuLi, R\textsubscript{2}CuMgX)**

Homocuprate are widely used organo copper reagents. They are prepared by the reaction of copper bromide or iodide with 2 equivalents of the appropriate lithium or Grignard reagents in ether or THF solvent.

The initially formed organocopper species (RCu)n are polymeric and insoluble in Et\textsubscript{2}O and THF but dissolve on addition of a second equivalent of RLi or RMgX. The organocuprates are prepared at low temperatures as they are thermally labile.
Heterocuprate Reagents

Since only one of the organic groups of homocuprate is usually utilized, a non-transferable group bonded to copper, such as 2-thienyl, PhS, t-BuO, R₃N, Ph₃P, is employed for the preparation of heterocuprate reagents. These cuprate are usually thermally more stable and a smaller excess of the reagent may be used.

**Example:** -

Copper-catalysed reactions of RMgX reagents is often the method of choice since they are readily available.

\[
\text{RMgCl} \xrightarrow{\text{a. Cul (0.2 eq)}} \text{C7H15} \\
\text{b. } n-C_7H_{15}I (\text{Br, OTs}) \xrightarrow{\text{THF, 0° C}} \text{C7H15}
\]

The Cu-catalysed alkylation of Organomagnesium reagents by alkyl bromides and iodides in the presence of NMP (N-methylpyrrolidinone, a nontoxic, polar, aprotic solvent) represents an attractive alternative to the classical cuprate alkylation reaction. Only a slight excess of the Grignard reagent is required, and the reaction tolerates keto, ester, amide and nitrile groups. Used for large-scale.

**Reactions of Organocuprates**

1. **Substitution of Alkyl Halides**

The reaction of a primary alkyl iodide with a heterocuprate is more economical than homocuprate.
homocuprate reacts with primary halides. However, cyanocuprates undergo substitution reactions even at inactivated secondary halides.

The mechanism for the substitution reaction is complex, depending on the nature of the cuprate reagent, the substrate, and the solvent used. The reaction may proceed via a SN$_2$ displacement or via an oxidative addition followed by reductive elimination.

2. Substitution of Allylic Halides

Alkylation of allylic halides with organocuprates usually produces mixtures of products due to competing SN2 and SN2' reactions. Substitution with complete allylic rearrangement (SN2' reaction) is observed with RCuBF$_3$ as the alkylating agent.
Alternatively, iron-catalysed alkenylation of Organomagnesium compounds provides a highly stereo- and chemoselective synthesis of substituted alkene.

\[
\text{RBr} + \text{MgCl} \rightarrow \text{R} = \text{CH}_2\text{R}
\]

In the presence of a catalytic amount of Cul, Grignard reagents convert acid chlorides chemo selectively to the corresponding ketones via a rapidly formed cuprate reagent, which reacts competitively with the initial Grignard reagent.

3. 1,2-Additions to Aldehydes and Ketones
Organocuprates undergo 1,2-additions to aldehydes, ketones, and imines. These reactions are often highly diastereoselective.

4. Epoxide Cleavage Reactions
\(\text{R}_2\text{Cu(CN)Li}_2\) reagents are among the mildest and most efficient reagents available for generating carbon-carbon bonds by way of epoxide cleavage using organocopper chemistry. The nucleophilic addition occurs at the less sterically
hindered carbon of the oxirane ring. Stereospecific S,2 opening of cyclic epoxides with cyanocuprates furnishes, after workup, the trans-2-hydroxy-alkylated products.

\[ \text{O} \quad \text{a. n-Bu}_2\text{Cu(CN)Li}_2(1.3 \text{ eq}) \quad \text{THF, } -20 \degree \text{C, 2 h} \quad \text{b. NH}_4\text{Cl, NH}_4\text{OH} \]

98%

**Regioselectivity in addition of RLi, RMgX, and Organocuprate reagents to α, β-unsaturated carbonyl compounds**

1,4-Addition is most successful with "soft" (relatively non-basic) nucleophiles such as RNH₂, R₂NH, RSH, enolates derived from P-dicarbonyl compounds, and organocuprates.

1,2-Addition is most successful with "hard" (relatively basic) nucleophiles such as hydride, organolithiums, and Grignard reagents.

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>1,2-Addition</th>
<th>1,4-Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLi</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>RMgX</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>R₂CuLi</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>RMgX.CuX</td>
<td>-</td>
<td>✓</td>
</tr>
</tbody>
</table>

1,2-addition

\[ \text{Nu}^- \quad \text{Nu}^- \quad \text{Nu}^- \]

1,4-addition

\[ \text{Y=H, R, OR, Halogen} \quad \text{Enolate anion} \]

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The organocopper reagents used for conjugate additions to enones are homocuprate, heterocuprate, higher-order cuprate, and Grignard reagents in the presence of catalytic amounts of copper salts (CuX).

In the bicyclic system shown below, the addition is chemoselective, involving the less hindered double bond of the dienone. The reaction is also stereoselective in that introduction of the "Me" group occurs preferentially from the less hindered side of the molecule.

In Mechanism of addition of organocuprates to α,β-unsaturated carbonyl compounds may proceed via reversible copper(1)-olefin-lithium association, which undergoes oxidative addition followed by reductive elimination.

Conjugate additions of organocopper reagents is sensitive with steric bulk.

Addition of Me₃SiCl accelerates the conjugate additions of copper reagents to such enones, probably by activating the carbonyl group.
For example

3-methylcyclohexenone is basically inert to \(n\text{-Bu}_2\text{CuLi}\) at \(-70 \, ^\circ\text{C}\) in. However, in the presence of \(\text{Me}_3\text{SiCl}\) reaction worked very well.

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

\[
\begin{align*}
\text{Me}_3\text{SiCl} & \quad \text{Me}_3\text{SiCl} \\
-70 \, ^\circ\text{C}, 1 \, \text{h} & \quad -70 \, ^\circ\text{C}, 1 \, \text{h}
\end{align*}
\]

Reactions of \(\beta,\beta\)-disubstituted enones with organocuprates are often not very effective due to steric crowding of the double bond. But when, use of \(R_2\text{CuLi-BF}_3\text{.OEt}_2\) polarizes and activates the ketone by coordination and reaction get worked.

\[
\begin{align*}
\text{a. } n\text{-Bu}_2\text{CuLi, THF} & \quad \text{a. } n\text{-Bu}_2\text{CuLi, THF}
\end{align*}
\]

\[
\begin{align*}
\text{BF}_3\text{.OEt}_2 & \quad \text{BF}_3\text{.OEt}_2 \\
-70 \, ^\circ\text{C}, 1 \, \text{h} & \quad -70 \, ^\circ\text{C}, 1 \, \text{h}
\end{align*}
\]

\[
\begin{align*}
b. \text{H}^+, \text{H}_2\text{O} & \quad b. \text{H}^+, \text{H}_2\text{O}
\end{align*}
\]

Grignard reagents in the presence of CuX or in the presence of a mixture of MnCl and Cul undergo 1,4-addition to hindered enones.

\[
\begin{align*}
n\text{-BuMgBr, THF} & \quad n\text{-BuMgBr, THF}
\end{align*}
\]

\[
\begin{align*}
30\% \text{ MnCl}_2, 3\% \text{ CuI} & \quad 30\% \text{ MnCl}_2, 3\% \text{ CuI}
\end{align*}
\]

\[
\begin{align*}
\text{THF, 0 \, ^\circ\text{C}, 2 \, \text{h}} & \quad \text{THF, 0 \, ^\circ\text{C}, 2 \, \text{h}}
\end{align*}
\]

\[
\begin{align*}
94\% & \quad 94\%
\end{align*}
\]

The reaction of dialkylcuprates with \(\alpha, \beta\)-unsaturated aldehydes results in the preferential 1,2-addition to the carbonyl group. However, in the presence of \(\text{Me}_3\text{SiCl}\), conjugate addition prevails to furnish, after hydrolysis of the resultant silyl enol ether, the saturated aldehyde.
Tandem 1,4-Addition-Enolate Trapping

The formation of enolate anion in the 1,4-Addition can be trapped by using different electrophiles with regioselective manner on oxygen and carbon depends on the nature of electrophile.

\[ \text{R}_2\text{CuLi} \rightarrow \text{O-Trap} \quad \text{C-Trap} \]

- **O-trapping:** \( \text{E}^+ = \text{R}_3\text{SiCl}, (\text{RO})_2\text{P(O)Cl} \)
- **C-trapping:** \( \text{E}^+ = \text{R-X}, \text{RCHO}, \text{Halogens} \)

**Example: O-Trapping**

The enolate generated from the enones shown below reacts at oxygen with chlorotrimethylsilane in the presence of triethylamine to produce the trimethylsilyl enol ether. This intermediate can be used further for derivatisation.

\[ \text{a. Me}_3\text{SiCl, Et}_3\text{N, HMPA} \]
\[ \text{b. workup} \]
THANK YOU

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