Copper-Catalyzed Reaction of Alkyl Halides with Cyclopentadienylmagnesium Reagent

\[
\begin{align*}
R^+Br & \quad + \quad \text{catal. Cu(OTf)}_2 \quad \text{tPr}_2O, \quad 25 \degree C, \quad 3 \text{ h} \\
& \quad \text{2) H}_2, \quad \text{PtO}_2 \\
\hline
& \quad \text{R}^+ \quad \text{cyclopentyl} \\
\end{align*}
\]

Masahiro Sai, Hidenori Someya, Hideki Yorimitsu, and Koichiro Oshima

Wipf Group Current Literature
Jennie Kravchenko - 05/31/08
Copper-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Primary Alkyl Halides

**Alkyl Bromides:**

*Tetrahedron* 2000, 56, 2737

\[
\begin{align*}
\text{RMgCl} & \quad \text{(cat. Li}_2\text{CuCl}_4, \ 20 ^\circ \text{C)} \\
\text{Alkyl-Br} & \quad \rightarrow \quad \text{Alkyl-R}
\end{align*}
\]

**Alkyl Fluorides:**

*J. Am. Chem. Soc.* 2003, 125, 5646

\[
\begin{align*}
\text{R-F} + \text{R'}-\text{MgX} & \quad \rightarrow \quad \text{R-R'} \\
\text{(cat. CuCl}_2 \ 1,3\text{-butadiene)} \\
\text{R = alkyl} & \quad \text{R' = alkyl, aryl}
\end{align*}
\]

**Alkyl Chlorides:**

*Angew. Chem. Int. Ed.* 2007, 46, 2086

\[
\begin{align*}
\text{Alkyl-Cl} + \text{R-MgX} & \quad \rightarrow \quad \text{Alkyl-R} \\
\text{(cat. Ph=C=Me \ THF)}
\end{align*}
\]
Cobalt-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Secondary and Tertiary Alkyl Halides

Substrate Scope:

\[
\begin{array}{ccc}
R-X & \text{cat. } [\text{CoCl}_2(\text{dppp})] & H_2C=CHCH_2MgCl \\
\text{Ph} & \text{H}_3C & \text{C}_6H_{11} & \text{cat. } [\text{CoCl}_2(\text{dppp})] & \text{CH}_3 \\
\text{t-C}_4H_9 & \text{Br} & 0 & 76 \\
\text{n-C}_8H_{17} & \text{Cl} & 20 & 31 \\
\text{n-C}_6H_{13} & \text{Br} & -40 & 76 \\
\end{array}
\]

- [CoCl\textsubscript{2}(dppp)] effectively catalyzes such reactions of secondary and tertiary alkyl halides with allylic Grignard reagents

- Treatment of substrate with allyl Grignard reagent in the presence of [CoCl\textsubscript{2}(dppp)] furnished the ring-opening product

- Existence of radical intermediates account for such ring opening

Cobalt-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Secondary and Tertiary Alkyl Halides

Proposed Mechanism:

1) Single-electron transfer from cobalt complex
2) Recombination of alkyl radical and cobalt complex
3) Reductive elimination

- π-Allyl ligands may prevent the formation of the vacant coordination sites necessary for β-elimination, which enables allylation of tertiary and secondary alkyl halides as well as of alkyl halides having β-alkoxy groups
Silver-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Secondary and Tertiary Alkyl Halides

Substrate Scope:

- Silver-catalyzed conditions were applicable to benzylation, as well as allylation and methallylation of secondary and tertiary alkyl halides

- Analogous radical pathway was proposed

Organic Letters 2008, 10, 971
Copper-Catalyzed Cyclopentadienylation of Secondary and Tertiary Alkyl Halides Followed by Hydrogenation

General Reaction:

\[
\begin{align*}
1a & \quad + \quad \text{MgBr} \quad \rightarrow \quad 2a \\
\text{\text{\text{n-C}_8\text{H}_{17}}} & \quad + \quad \text{MgBr} \\
\text{\text{\text{n-C}_8\text{H}_{17}}} & \quad \rightarrow \quad \text{\text{\text{n-C}_8\text{H}_{17}}} \\
& \quad + \quad \text{MgBr} \\
\end{align*}
\]

- Initially formed 2a undergoes isomerization into 3a and 3a' due to the high acidity of the hydrogen on the cyclopentadienyl ring.

- Isomers were subjected to hydrogenation in order to simplify analysis of products.
Solvent Effect and Catalyst Screening:

- Choice of solvent and copper catalyst greatly altered overall yield of products

- Bulky ethers (diisopropyl ether and tert-butyl methyl ether) proved to be most suitable

- Copper(II) halides as well as copper(I) halides exhibited modest catalytic activity

- Silver(I) nitrate, found to be effective in the cross-coupling reaction of tertiary alkyl halides with allyl or benzyl Grignard reagents, was less effective than copper(II) triflate

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>catalyst</th>
<th>combined yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Pr₂O</td>
<td>Cu(OTf)₂</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOMe</td>
<td>Cu(OTf)₂</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>Cu(OTf)₂</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>diethyl ether</td>
<td>Cu(OTf)₂</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>dioxane</td>
<td>Cu(OTf)₂</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>Cu(OTf)₂</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>c-C₅H₁₁OMe</td>
<td>Cu(OTf)₂</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>Bu₂O</td>
<td>Cu(OTf)₂</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>i-Pr₂O</td>
<td>CuF₂</td>
<td>77</td>
</tr>
<tr>
<td>10</td>
<td>i-Pr₂O</td>
<td>CuCl₂</td>
<td>59</td>
</tr>
<tr>
<td>11</td>
<td>i-Pr₂O</td>
<td>CuCl</td>
<td>44</td>
</tr>
<tr>
<td>12</td>
<td>i-Pr₂O</td>
<td>CuBr</td>
<td>57</td>
</tr>
<tr>
<td>13</td>
<td>i-Pr₂O</td>
<td>CuI</td>
<td>31</td>
</tr>
<tr>
<td>14</td>
<td>i-Pr₂O</td>
<td>CuOAc</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>i-Pr₂O</td>
<td>CuCN</td>
<td>26</td>
</tr>
<tr>
<td>16</td>
<td>i-Pr₂O</td>
<td>CuOTf·0.5 C₆H₆</td>
<td>27</td>
</tr>
<tr>
<td>17</td>
<td>i-Pr₂O</td>
<td>AgNO₃</td>
<td>26</td>
</tr>
</tbody>
</table>
Substrate Scope:

$$\text{Alkyl-X } 1 + \text{MgBr} \xrightarrow{\text{5 mol % Cu(OTf)$_2$, i-Pr$_2$O, 25 °C, 3 h}} \text{Alkyl-X 3 + Alkyl-X 3'}$$

$$\text{10 mol % PtO$_2$, 0.1 MPa H}_2 \xrightarrow{\text{AcOH, reflux, 12 h}} \text{Alkyl-X 4}$$

- Phenylsulfanyl and methoxyl groups were compatible in such reaction conditions without deactivation of the copper catalyst.

- Surprisingly, tertiary alkyl fluoride participated in cyclopentadienylation as well.

<table>
<thead>
<tr>
<th>alkyl-X</th>
<th>combined yield of 3 and 3' (%)</th>
<th>overall yield of 4 from 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$-C$<em>8$H$</em>{17}$Cl</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>MeO$_5$Br</td>
<td>90</td>
<td>84</td>
</tr>
<tr>
<td>PhS$_5$Br</td>
<td>95</td>
<td>50</td>
</tr>
<tr>
<td>$n$-C$<em>6$H$</em>{13}$Br</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Ph$_2$F</td>
<td>69</td>
<td>61</td>
</tr>
</tbody>
</table>

Stoichiometric Reactions:

- Reaction mechanism was studied using the following halide with stoichiometric copper reagents and varying amounts of CpMgBr.
- Copper reagent that is active for this reaction might be [Cp₃Cu]MgBr⁶ or a more complex cuprate.
- Experiments have been conducted to examine the intermediacy of alkyl radicals in the reaction, however they failed to support the intermediacy.

<table>
<thead>
<tr>
<th>amount of Grignard reagent</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 equiv</td>
<td>0%</td>
</tr>
<tr>
<td>2.0 equiv</td>
<td>15%</td>
</tr>
<tr>
<td>3.0 equiv</td>
<td>86%</td>
</tr>
</tbody>
</table>
Conclusions and Future Directions

- Copper(II) triflate proved to efficiently catalyze the reaction of tertiary alkyl halides with cyclopentadienyl Grignard reagent.

- With the following hydrogenation of the cyclopentadienyl ring with hydrogen under Pt$_2$O catalysis, the overall transformation represents formal cyclopentylation of tertiary alkyl halides.

- Future work could include extension of the methodology to other stabilized organometallic reagents, as well as application of this method to functionalized molecules of interest.