Iridium-Catalyzed Regioselective Silylation of Secondary Alkyl C–H Bonds for the Synthesis of 1,3-Diols

Bijie Li, Matthias Driess, and John F. Hartwig.


dx.doi.org/10.1021/ja5026479
**Aliphatic C-H Activation**

- One the greatest challenges in complex-molecules synthesis
- Inherently reactive C-H bond (Benzylic position and etc.)
- Directing group not present in desired target.

---

Si-H Directing Group

* Hydrosilane as a directing group.

\[ \text{[Ir(COD)Cl]}_2, \text{dtbpy, B}_{2}\text{pin}, 80^\circ\text{C} \]

\[ X= \text{CH}_2, \text{O, NR} \]

Si-H Directing Group

* Recent example:

\[ \text{[Ir(COD)OMe]}_2, \text{Me}_4\text{phen} \]
\[ B_2\text{pin}_2, 80^\circ\text{C} \]

\[ X = \text{CH}_2, \text{O, NR} \]
Intramolecular C-H Silylation

* Platinum as catalyst:

\[ \text{TpMe}_2\text{Pt(Me)}_2(\text{H}) \]

\[ \begin{align*}
\text{Ph-SiMe}_2\text{H} & \xrightarrow{TpMe}_2\text{Pt(Me)}_2(\text{H}) \quad 200^\circ\text{C}, 48\text{h} \\
& \rightarrow \text{SiMe}_2
\end{align*} \]

70%

\[ \begin{align*}
\text{HSi(\text{Me})}_3 & \xrightarrow{TpMe}_2\text{Pt(Me)}_2(\text{H}) \quad 200^\circ\text{C}, 72\text{h} \\
& \rightarrow \text{Bu}_2\text{Si}
\end{align*} \]

80-88%


Yongzhao Yan @ Wipf Group
Intramolecular C-H Silylation

* Iridium catalyzed ortho-silylation

Aliphatic C-H Silylation

1,3-diol formation sequence

\[
\begin{align*}
R_2 & \quad \text{OH} \\
& \quad \text{Et}_2\text{SiH}_2 \\
\text{[Ir]} & \quad \text{R}_1 \\
& \quad \text{Si} \\
& \quad \text{Et} \\
& \quad \text{Et} \\
\text{[O]} & \quad \text{OH} \\
\end{align*}
\]

Ligand screening

\[
\begin{align*}
\text{[Ir(COD)OMe]}_2 & \quad 0.5 \text{ mol\%}/\text{ligand} 1.2 \text{ mol\%} \\
\text{norbornene (1.2 equiv.)} & \quad 80^\circ\text{C} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Ligand, L</th>
<th>Conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>phen</td>
<td>77%</td>
</tr>
<tr>
<td>b</td>
<td>dtbpy</td>
<td>83%</td>
</tr>
<tr>
<td>c</td>
<td>4,7-Cl\textsubscript{2}phen</td>
<td>13%</td>
</tr>
<tr>
<td>d</td>
<td>4,7-(HO)\textsubscript{2}phen</td>
<td>33%</td>
</tr>
<tr>
<td>e</td>
<td>4,7-Ph\textsubscript{2}phen</td>
<td>82%</td>
</tr>
<tr>
<td>f</td>
<td>4,7-Me\textsubscript{2}phen</td>
<td>94%</td>
</tr>
<tr>
<td>g</td>
<td>4,7-(MeO)\textsubscript{2}phen</td>
<td>94%</td>
</tr>
<tr>
<td>h</td>
<td>3,4,7,8-Me\textsubscript{4}phen</td>
<td>100%</td>
</tr>
</tbody>
</table>

Aliphatic C-H Silylation

* Examples in complex molecules synthesis


**Example 1:**

- **(+)-camphor**
  - 1 kg/$50
  - Total yield 66%

**Example 2:**

- **(+)-Ketopinic acid**
  - 1 g/$40
  - Total yield 51%

---

**Reactions:**

- Ir-catalyzed silylation
- KHCO₃, H₂O₂
- Then Ac₂O, Et₃N

**Yield:**

- Total yield 64%

---

**Figures:**

- (+)-camphor
- (+)-Ketopinic acid
- methyl glycyrrhetinate

---

Aliphatic C-H Silylation

Application in sugar synthesis

**Silylation of Secondary Alkyl C-H**

* Ligand screening

![Chemical structure diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>ligand</th>
<th>conv (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Pr</td>
<td>Et</td>
<td>L1</td>
<td>83</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>n-Pr</td>
<td>Et</td>
<td>L2</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>n-Pr</td>
<td>Et</td>
<td>L3</td>
<td>88</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>n-Pr</td>
<td>Et</td>
<td>L4</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Et</td>
<td>L4</td>
<td>92</td>
<td>&lt;10</td>
</tr>
<tr>
<td>6</td>
<td>n-Pr</td>
<td>Me</td>
<td>L4</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>n-Pr</td>
<td>i-Pr</td>
<td>L4</td>
<td>12</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

120°C higher than 80°C