Top 10 Challenges for Catalysis

1. \( \text{SO}_2 \rightarrow \text{SO}_3 \)

2. \( \text{CH}_4 \rightarrow \text{CH}_3\text{OH} \)

3. \( \text{N}_x\text{O}_y \rightarrow \text{N}_2 + \text{O}_2 \)

4. alkane \( \rightarrow \) alkene

\( \text{H}_3\text{C} = \text{CH}_3 \)

\( \text{H}_2\text{C} = \text{CH}_2 \)

\( \text{current: cracking} \)

\( \text{H}_3\text{C} = \text{CH}_3 \)

\( \text{CH}_3\text{CH} = \text{CH}_3 \)

\( \text{current: nitration and Fe reduction} \)

5. \( \text{CH}_3\text{OH} \rightarrow \text{H}_2\text{C} = \text{CH}_2 \)

6. \( \text{Cyclic compound} \rightarrow \text{Cyclic compound} \)

\( \text{current:} \)

7. \( \text{H}_2 + \text{O}_2 \rightarrow \text{H}_2\text{O}_2 \)

8. \( \text{H}_2\text{C} = \text{CH}_2 \rightarrow \)

9. \( \text{Cyclic compound} \rightarrow \text{Cyclic compound} \)

10. \( \text{Cyclic compound} \rightarrow \text{Cyclic compound} \)

\( \text{current: nitration and Fe reduction} \)

\( \text{R} = \text{C} = \text{CH} \rightarrow \text{R} \text{CH} = \text{NH}_2 \)

\( \text{R} = \text{C} = \text{CH} \rightarrow \text{R} \text{CH} = \text{OH} \)
Anti-Markovnikov Intermolecular Hydroamination of Olefins and Relative Mechanism Studies

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Content

Reactions

1. Anti-Markovnikov hydroamination of olefin
   a. Alkali-metal-catalyzed/mediated (Li, Na)
   b. Transition-metal-catalyzed (Rh, Ru, Cu...)
   c. Non-catalyzed

Mechanism and Insights

2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds

3. Activation of N-H bond
1. Anti-Markovnikov hydroamination of olefin
   a. Alkali-metal-catalyzed/mediated (Li, Na)

\[
\begin{align*}
\text{R} \text{H} + \text{N} \text{H} \text{Bn} \quad \xrightarrow{nBuLi (20\, \text{mol\%})} \quad \text{R} \text{H} \text{N} \text{Bn}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Olefin/amine</th>
<th>Conv. [b]</th>
<th>Product (Yield [c] [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>2:1</td>
<td>82</td>
<td>4a (80)</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl</td>
<td>2:1</td>
<td>99</td>
<td>4b (60)</td>
</tr>
<tr>
<td>3</td>
<td>4-Me</td>
<td>2:1</td>
<td>99</td>
<td>4c (96)</td>
</tr>
<tr>
<td>4</td>
<td>4-OMe</td>
<td>2:1</td>
<td>100</td>
<td>4d (99)</td>
</tr>
<tr>
<td>5</td>
<td>4-F</td>
<td>2:1</td>
<td>98</td>
<td>4e (87)</td>
</tr>
<tr>
<td>6</td>
<td>3-Cl</td>
<td>2:1</td>
<td>94</td>
<td>4f (85)</td>
</tr>
<tr>
<td>7</td>
<td>3-Me</td>
<td>2:1</td>
<td>80</td>
<td>4g (47)</td>
</tr>
<tr>
<td>8</td>
<td>3-Br</td>
<td>2:1</td>
<td>90</td>
<td>4h (41)</td>
</tr>
<tr>
<td>9</td>
<td>3-CF₃</td>
<td>2:1</td>
<td>78</td>
<td>4i (69)</td>
</tr>
<tr>
<td>10</td>
<td>2-Br</td>
<td>1:1</td>
<td>88</td>
<td>4j (59)</td>
</tr>
<tr>
<td>11</td>
<td>3-Ph</td>
<td>2:1</td>
<td>96</td>
<td>4k (94)</td>
</tr>
<tr>
<td>12</td>
<td>4-Ph</td>
<td>2:1</td>
<td>98</td>
<td>4l (98)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 2 (2.2 mmol), olefin in THF (5 mL) in a pressure tube. [b] Determined by GC with hexadecane as internal standard (based on 2). [c] Yield of isolated product. [d] 2-Vinylnaphthalene was used.

1. Anti-Markovnikov hydroamination of olefin
   a. Alkali-metal-catalyzed/mediated (Li, Na)

\[
\text{HN} \quad + \quad \equiv \quad \xrightarrow{\text{LiNEt}_2, \text{TMEDA}} \quad \text{N} \quad \begin{array}{c}
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (ml)</th>
<th>Cat. (mol%)</th>
<th>Ligand (mol%)</th>
<th>Cat.:L ratio</th>
<th>Pressure (bar)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Toluene</td>
<td>9</td>
<td>–</td>
<td>1:0</td>
<td>20</td>
<td>80</td>
<td>18</td>
<td>23</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>5</td>
<td>10</td>
<td>1:2</td>
<td>20</td>
<td>80</td>
<td>18</td>
<td>100</td>
<td>96</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>Toluene</td>
<td>2.5</td>
<td>5</td>
<td>1:2</td>
<td>40</td>
<td>80</td>
<td>18</td>
<td>95</td>
<td>93</td>
<td>37</td>
</tr>
<tr>
<td>12</td>
<td>Toluene</td>
<td>2.5</td>
<td>5</td>
<td>1:2</td>
<td>40</td>
<td>r.t.</td>
<td>24</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>Toluene</td>
<td>2.5</td>
<td>5</td>
<td>1:2</td>
<td>40</td>
<td>40</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>Toluene</td>
<td>2.5</td>
<td>5</td>
<td>1:2</td>
<td>20</td>
<td>110</td>
<td>12</td>
<td>79</td>
<td>69</td>
<td>28</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.029 mol diethylamine, 15 ml solvent, 0.5 ml n-octane as an internal GC standard.

1. Anti-Markovnikov hydroamination of olefin
   a. Alkali-metal-catalyzed/mediated (Li, Na)

Table 3
Effect of solvent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (ml)</th>
<th>n-BuLi (mol%)</th>
<th>TMEDA (mol%)</th>
<th>Temperature (°C)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Branched amine</td>
</tr>
<tr>
<td>1</td>
<td>–</td>
<td>20</td>
<td>–</td>
<td>120</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>20</td>
<td>20</td>
<td>120</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>20</td>
<td>–</td>
<td>80</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Diethyl ether</td>
<td>20</td>
<td>–</td>
<td>80</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>MTBE</td>
<td>20</td>
<td>–</td>
<td>80</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>20</td>
<td>20</td>
<td>80</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>20</td>
<td>20</td>
<td>120</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>20</td>
<td>20</td>
<td>130</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>Toluene</td>
<td>20</td>
<td>20</td>
<td>160</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

1. Anti-Markovnikov hydroamination of olefin
a. Alkali-metal-catalyzed/mediated (Li, Na)

Table 73. Selected Examples for Alkali Metal-Catalyzed Amination of Aliphatic Olefins

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Amine</th>
<th>Product</th>
<th>Catalyst</th>
<th>Reaction conditions</th>
<th>Yield / %</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Na, Py</td>
<td>100 °C</td>
<td>80</td>
<td>455</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Na, Py</td>
<td>100 °C</td>
<td>80</td>
<td>455</td>
</tr>
<tr>
<td></td>
<td>PhNH₂</td>
<td></td>
<td>NaNH₂</td>
<td>275 °C</td>
<td>75</td>
<td>456</td>
</tr>
<tr>
<td></td>
<td>NH₃</td>
<td></td>
<td>Na</td>
<td>250 °C 800-950 bar</td>
<td>32</td>
<td>456</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Na⁺H₂</td>
<td>225 °C</td>
<td>9</td>
<td>456</td>
</tr>
<tr>
<td></td>
<td>NH₃</td>
<td></td>
<td>Na</td>
<td>250 °C 800-950 bar</td>
<td>17</td>
<td>456</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LiNEt₃/TMEDA</td>
<td>150 °C</td>
<td>18</td>
<td>457</td>
</tr>
</tbody>
</table>

1. Anti-Markovnikov hydroamination of olefin (aromatic)
b. Transition-metal-catalyzed

\[
\text{PhCH} = \text{CH} + \text{HNR}_2 \xrightarrow{[\text{Rh(cod)}_2\text{BF}_4/2\text{PPh}_3]} \text{THF reflux} \rightarrow \text{PhCH} = \text{CNR}_2 + \text{PhC} = \text{CNR}_2 + \text{PhCH}_2 \text{CH}_2 \text{NR}_2
\]

1a - 8a
1b - 8b

Figure 1. Time/concentration diagram for the reaction of 2-vinylpyridine and piperidine

1. Anti-Markovnikov hydroamination of olefin
b. Transition-metal-catalyzed

Table 1. Rhodium-catalyzed reaction of 2-vinylpyridine and piperidine\[a\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin/Amine</th>
<th>Catalyst (mol-%)</th>
<th>Solvent, reaction time</th>
<th>Amine product (%)</th>
<th>Enamine (%)</th>
<th>Ethylpyridine (%)</th>
<th>Amine product/Enamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4:1</td>
<td>[Rh(cod)\textsubscript{2}]BF\textsubscript{4}/2 PPh\textsubscript{3} (2.5)</td>
<td>THF, reflux, 20 h</td>
<td>53</td>
<td>47</td>
<td>42</td>
<td>1.1</td>
</tr>
<tr>
<td>2</td>
<td>4:1</td>
<td>[Rh(cod)\textsubscript{2}]BF\textsubscript{4}/2 PPh\textsubscript{3} (2.5)</td>
<td>Toluene, reflux, 20 h</td>
<td>61</td>
<td>30</td>
<td>24</td>
<td>2.0</td>
</tr>
<tr>
<td>3</td>
<td>4:1</td>
<td>[Rh(cod)\textsubscript{2}]BF\textsubscript{4}/2 PPh\textsubscript{3} (2.5)</td>
<td>DMAC, 140 °C, 20 h</td>
<td>44</td>
<td>&lt; 0.1</td>
<td>21</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>4:1</td>
<td>[Rh(cod)\textsubscript{2}]BF\textsubscript{4}/2 PPh\textsubscript{3} (1.0)</td>
<td>THF, reflux, 20 h</td>
<td>47</td>
<td>8</td>
<td>7</td>
<td>5.9</td>
</tr>
<tr>
<td>5</td>
<td>4:1</td>
<td>[Rh(cod)\textsubscript{2}]BF\textsubscript{4} (2.5)</td>
<td>THF, reflux, 20 h</td>
<td>97</td>
<td>2</td>
<td>2</td>
<td>48.5</td>
</tr>
<tr>
<td>6</td>
<td>2:1</td>
<td>[Rh(cod)\textsubscript{2}]BF\textsubscript{4}/2 PPh\textsubscript{3} (2.5)</td>
<td>THF reflux, 20 h</td>
<td>16</td>
<td>82</td>
<td>46</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\[a\] The yield was determined by GC with hexadecane as internal standard and is referred to amine.
Scheme 6. Reaction of [Rh(cod)(2-vinylpyridine)$_2$]CF$_3$SO$_3$ (12) with morpholine
1. Anti-Markovnikov hydroamination of olefin

b. Transition-metal-catalyzed

\[
\text{苯乙烯} + \text{HNC}_5\text{H}_{12} \xrightarrow{5\% [\text{Rh(COD)}(\text{DPEphos})] BF_4} \text{产物 (1)}
\]

\[
\text{DPEphos} = \begin{array}{c}
\text{Ph}_2\text{P} \\
\text{PPh}_2
\end{array}
\]

**Table 1.** Ligand Effects on the Reaction of Styrene with Morpholine in the Presence of Catalysts Containing DPEphos and Related Ligands

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>amine yield(^b) (%)</th>
<th>enamine yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DPEphos (eq 1)</td>
<td>62</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>PPh(_3)</td>
<td>17</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>DPPE(^c)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>DPPB(^d)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>DPPPent(^e)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Xantphos (1)</td>
<td>trace</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>DBFphos (2)</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>BIPHEphos (3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Anti-Markovnikov Hydroamination of Vinylarenes with Secondary Amines\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>vinylarene</th>
<th>time (h)</th>
<th>yield\textsuperscript{b} (%)</th>
<th>amine/enamine\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>48</td>
<td>71</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2b</td>
<td>48</td>
<td>72</td>
<td>79:21</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2c</td>
<td>48</td>
<td>71</td>
<td>85:15</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2d</td>
<td>48</td>
<td>70</td>
<td>78:22</td>
</tr>
<tr>
<td>5\textsuperscript{e}</td>
<td>1a</td>
<td>2e</td>
<td>72</td>
<td>48</td>
<td>60:40</td>
</tr>
<tr>
<td>6\textsuperscript{e,f}</td>
<td>1a</td>
<td>2f</td>
<td>72</td>
<td>41</td>
<td>57:43</td>
</tr>
<tr>
<td>7\textsuperscript{g}</td>
<td>1b</td>
<td>2a</td>
<td>72</td>
<td>57</td>
<td>63:37</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>2d</td>
<td>48</td>
<td>66</td>
<td>77:23</td>
</tr>
<tr>
<td>9\textsuperscript{g}</td>
<td>1c</td>
<td>2a</td>
<td>72</td>
<td>58</td>
<td>86:14</td>
</tr>
<tr>
<td>10</td>
<td>1d</td>
<td>2a</td>
<td>72</td>
<td>53</td>
<td>96:4</td>
</tr>
<tr>
<td>11\textsuperscript{g,h}</td>
<td>1e</td>
<td>2a</td>
<td>72</td>
<td>51\textsuperscript{k}</td>
<td>76:24</td>
</tr>
<tr>
<td>12</td>
<td>1f</td>
<td>2c</td>
<td>48</td>
<td>62\textsuperscript{l}</td>
<td>72:28</td>
</tr>
<tr>
<td>13\textsuperscript{i}</td>
<td>1g</td>
<td>2b</td>
<td>72</td>
<td>50\textsuperscript{d}</td>
<td>54:46</td>
</tr>
<tr>
<td>14\textsuperscript{i,j}</td>
<td>1g</td>
<td>2d</td>
<td>72</td>
<td>74</td>
<td>82:19</td>
</tr>
<tr>
<td>15\textsuperscript{i}</td>
<td>1g</td>
<td>2g</td>
<td>48</td>
<td>79\textsuperscript{d}</td>
<td>90:10</td>
</tr>
</tbody>
</table>

\begin{tikzpicture}
\node at (0,0) {\textbf{HNRR':} 2,5-Me\textsubscript{2}-morpholine};
\node at (3,0) {\textbf{vinylarene=}};
\node at (0,-1.5) {1e:};\node at (1.5,-1.5) {2,5-Me\textsubscript{2}-morpholine};
\node at (0,-2) {1a: X = O};
\node at (0,-2.5) {1b: X = CH\textsubscript{2}};
\node at (0,-3) {1c: X = N-Ph};
\node at (0,-3.5) {1d: X = N-CO\textsubscript{2}Bu};
\node at (3,-1.5) {2a: R = H};
\node at (3,-2) {2b: R = 4-Me};
\node at (3,-2.5) {2c: R = 4-MeO};
\node at (3,-3) {2d: R = 3,4-MeO};
\node at (3,-3.5) {2e: R = 4-Cl};
\node at (3,-4) {2f: R = 3-CF\textsubscript{3}};
\node at (3,-4.5) {2g: 2-vinylpyridine};
\end{tikzpicture}

Substrates limitation: Primary aliphatic amine and aromatic amine did not react.

Concentration of olefin affected the amine:enamine ratio very much.
1. Anti-Markovnikov hydroamination of olefin  
   b. Transition-metal-catalyzed  

\[
\begin{align*}
\text{DPPPent} &= 1, 5\text{-bis(diphenylphosphino)pentane} \\
&\text{96\% isolated yield}
\end{align*}
\]

Table 2. Ruthenium-Catalyzed Hydroamination of Vinylarenes with Alkylamines

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>yield</th>
<th>entry</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>96%</td>
<td>8</td>
<td><img src="image2.png" alt="Structure 8" /></td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Structure 2" /></td>
<td>91%</td>
<td>9</td>
<td><img src="image4.png" alt="Structure 9" /></td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Structure 3" /></td>
<td>64%</td>
<td>10</td>
<td><img src="image6.png" alt="Structure 10" /></td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Structure 4" /></td>
<td>90%</td>
<td>11</td>
<td><img src="image8.png" alt="Structure 11" /></td>
<td>91%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Structure 5" /></td>
<td>82%</td>
<td>12</td>
<td><img src="image10.png" alt="Structure 12" /></td>
<td>71%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Structure 6" /></td>
<td>65%</td>
<td>13</td>
<td><img src="image12.png" alt="Structure 13" /></td>
<td>51%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Structure 7" /></td>
<td>63%</td>
<td>14</td>
<td><img src="image14.png" alt="Structure 14" /></td>
<td>40%</td>
</tr>
</tbody>
</table>

*a* Amine/vinylarene/Ru/DPPPent/TfOH = 1:2:0.05:0.07:0.10 (1 mmol of amine) in 0.50 mL of dioxane.  
*b* Isolated yield.  
*c* 4 mmol of vinylarene was used.  
*d* 80 °C.  
*e* 48 h.  
*f* 0.25 mL of dioxane.  
*g* 110 °C.  
*h* DippF was used as ligand.  
*i* 1.5 mmol of vinylarene was used.  
*j* 72 h.

Scheme 1

```
(COD)Ru

(1.4 eq.)
DPPPent
TfOH (2 equiv)
THF, rt

(32 eq.)
styrene
THF, 80 °C
30 min

(32 eq.)
cymene
THF, 80 °C
30 min
```

\[
\begin{array}{c}
\end{array}
\]
Scheme 4

\[ \text{Scheme 4} \]

\[ \begin{align*}
\text{3a (NR}_2 = \text{morpholino)} & \quad \text{40 equiv styrene} \\
\text{Ph}_2\text{P} \quad \text{Ru} \quad \text{PPh}_2 & \quad \text{dioxane-NMP} \\
100^\circ \text{C} & \quad k_{obs} = 5.6 \times 10^{-3} \text{ s}^{-1} \\
\text{Ph}_2\text{P} \quad \text{Ru} \quad \text{PPh}_2 & \quad \text{Ph}
\end{align*} \]

Scheme 5

\[ \text{Scheme 5} \]

\[ \begin{align*}
\text{Nucleophilic addition} & \quad \text{3a (NR}_2 = \text{morpholine)} \\
\text{Ph}_2\text{P} \quad \text{Ru} \quad \text{PPh}_2 & \quad \text{HN} \\
\text{O} & \quad \text{Ph}
\end{align*} \]

1. Anti-Markovnikov hydroamination of olefin
b. Transition-metal-catalyzed

![Chemical Reaction Diagram]

Fig. 2 Challenges of the formal anti-Markovnikov hydroamination methodology.

Table 1  Optimization of hydroamination methodology

\[
\begin{align*}
&\text{Entry} & [M] & \text{Mol% [M]} & [H] & \text{Additives (step)} & \text{Equiv. amine} & \text{Equiv. H}_2\text{O} & \text{Yield}\% \\
& 1 & 9 & 10\% & \text{Isopropyl alcohol} & \text{CuCl}_2 \text{ (ii)} & 2.5 & 1 & 15\% \\
& 2 & 9 & 10\% & 2,4-\text{Dimethyl-3-pentanol} & \text{Mol. sieves (i); CuCl (ii)} & 2.5 & 0 & 25\% \\
& 3 & 10 & 10\% & 5:2 \text{HCO}_2\text{H/TEA} & - & 2.5 & 1 & 63\% \\
& 4 & 10 & 10\% & 5:2 \text{HCO}_2\text{H/TEA} & - & 2.5 & 2 & 59\% \\
& 5 & 10 & 1\% & 5:2 \text{HCO}_2\text{H/TEA} & - & 2.5 & 1 & 65\% \\
& 6 & 10 & 10\% & 5:2 \text{HCO}_2\text{H/TEA} & - & 1.3 & 1 & 66\% \\
& 7 & 10 & 1\% & 5:2 \text{HCO}_2\text{H/TEA} & - & 1.3 & 1 & 59\%
\end{align*}
\]

\[a\] Yield determined from analysis of the \textsuperscript{1}H NMR spectrum using 1,4-dioxane as an external standard.

**Table 2** Hydroamination of styrenes with \(N\)-methyl-aniline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>3a</td>
<td>61% (56%(^b))</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>3b</td>
<td>55%</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>3c</td>
<td>55%(^c)</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>3d</td>
<td>62%</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>3e</td>
<td>65%</td>
</tr>
</tbody>
</table>

\(R \rightarrow \text{NMePh}\)

1. \(\text{PdCl}_2(\text{PhCN})_2\) (10 mol\%)
   - benzoquinone (1 equiv), \(H_2O\) (1 equiv)
   - \(t\)-BuOH, 35 °C

2. \(N\)-Me-aniline (2a, 2.5 equiv), 10 (1 mol\%)
   - 5:2 formic acid/TEA azeotrope, 85 °C

---

**Table 4** Hydroamination of aliphatic olefins with \(N\)-methyl-aniline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1k</td>
<td>3k</td>
<td>64%</td>
</tr>
<tr>
<td>2</td>
<td>1l</td>
<td>3p</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>1m</td>
<td>3q</td>
<td>40%</td>
</tr>
<tr>
<td>4</td>
<td>1n</td>
<td>3r</td>
<td>56%</td>
</tr>
<tr>
<td>5</td>
<td>1o</td>
<td>3s</td>
<td>60%</td>
</tr>
</tbody>
</table>

\(R \rightarrow \text{NMePh}\)

1. \(\text{PdCl}_2(\text{PhCN})_2\) (12 mol\%)
   - \(\text{CuCl}_2\cdot2\text{H}_2\text{O}\) (12 mol\%)
   - \(\text{AgNO}_3\) (6 mol\%)
   - \(t\)-BuOH, \(\text{MeNO}_2\), \(\text{O}_2\), rt

2. \(N\)-Me aniline (2a, 2.5 equiv)
   - 10 (10 mol\%)
   - 5:2 formic acid/TEA azeotrope argon, 85 °C

---

**Substrate limitation:** aromatic amines

1. Anti-Markovnikov hydroamination of olefin
b. Transition-metal-catalyzed

![Chemical reaction diagram]

**Figure 1.** Proposed catalytic cycle for CuH-catalyzed hydroamination of alkenes.
1. Anti-Markovnikov hydroamination of olefin
b. Transition-metal-catalyzed

Table 2. Scope of Different Styrene Derivatives

<table>
<thead>
<tr>
<th>Substrate Scope: Styrenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical Structures]</td>
</tr>
</tbody>
</table>

DEMS: di-EtMeSiH

1. Anti-Markovnikov hydroamination of olefin
b. Transition-metal-catalyzed

**Table 4. Hydroamination of Terminal Aliphatic Alkenes***

<table>
<thead>
<tr>
<th>Alkyl</th>
<th>N-Bn</th>
<th>N-Bn</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 mol% Cu(OAc)$_2$ + 2.2 mol% (±)-DTBM-SEGPHOS + 2.0 equiv. DEMS
THF (0.5 M), 40 °C, 36 h

<table>
<thead>
<tr>
<th>5a</th>
<th>89% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>5b</td>
<td>94% yield</td>
</tr>
<tr>
<td>5c</td>
<td>90% yield</td>
</tr>
<tr>
<td>5d</td>
<td>95% yield</td>
</tr>
<tr>
<td>5e</td>
<td>88% yield</td>
</tr>
<tr>
<td>5f</td>
<td>92% yield</td>
</tr>
<tr>
<td>5g</td>
<td>90% yield</td>
</tr>
</tbody>
</table>

$^a$Isolated yields (average of two runs). 2 (1 mmol), O-benzoyl-N,N-dibenzylhydroxylamine (1.2 mmol), Cu(OAc)$_2$ (2 mol%), (±)-DTBM-SEGPHOS (2.2 mol%), DEMS (2 mmol), THF (0.5 M), 40 °C, up to 36 h. $^b$THF (1 M).

1. Anti-Markovnikov hydroamination of olefin
c. Non-catalyzed

Question 1:

Content

Reactions

1. Anti-Markovnikov hydroamination of olefin
   a. Alkali-metal-catalyzed/mediated (Li, Na)
   b. Transition-metal-catalyzed (Rh, Ru, Cu...)
   c. Non-catalyzed

Mechanism and Insights

2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds

3. Activation of N-H bond
2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds

a. Pd-N bond

Scheme 18. Proposed reaction mechanism of the palladium-catalyzed oxidative amination of norbornene. DME = dimethoxyethane, Ts = 4-toluenesulfonyl.

2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds

a. Pd-N bond

![Reaction Scheme]

**Question 3:**

![Reaction Scheme]

2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds

a. Pd-N bond

2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds

a. Pd-N bond

**Table 1.** Reactions of Ethylene and 1-Octene with Amides 2a–2e

<table>
<thead>
<tr>
<th>entry</th>
<th>complex</th>
<th>For R = H (yield)</th>
<th>for R = H $k_{obs} \times 10^3$ (s$^{-1}$)</th>
<th>For R = C$<em>8$H$</em>{13}$ (Yield)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>89%</td>
<td>0.91</td>
<td>(neat) 74%</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>-</td>
<td>-</td>
<td>(25 equiv) 69%</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>-</td>
<td>-</td>
<td>(10 equiv) 48%</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>94%</td>
<td>9.6</td>
<td>97%</td>
</tr>
<tr>
<td>5</td>
<td>2c</td>
<td>63%</td>
<td>4.3</td>
<td>64%</td>
</tr>
<tr>
<td>6</td>
<td>2d</td>
<td>60%</td>
<td>0.79</td>
<td>52%</td>
</tr>
<tr>
<td>7$^c$</td>
<td>2e</td>
<td>98%</td>
<td>0.053</td>
<td>ND$^d$</td>
</tr>
</tbody>
</table>

$^a$Conditions for reactions with 1-octene: benzene, 80 °C for 30 min. Conditions for reactions with ethylene: toluene, −10 °C for 2 h, 20 equiv of ethylene. $^b$Combined yield for all enamine isomers. $^c$Reaction at 85 °C. $^d$This reaction did not form detectable amounts of the enamine product.

2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds
   a. Pd-N bond

\[ \text{Scheme 1} \]

\[
\begin{align*}
\text{Reaction Scheme:} & \\
\text{Pd(0) + Pd(Bn)(t-Bu)_2, 7} & \rightarrow (P-C)\text{Pd-H + Ph}_2\text{N} \\
k_{\text{obs}} = k_1 k_2 [\text{ethylene}][2a] / k_{-1} [\text{THF}] & \\
\end{align*}
\]

Question 2:

\[
\begin{align*}
\text{Product Scheme:} & \\
\text{two enamine products} & \\
\end{align*}
\]

2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds
b. Pt-N bond

Scheme 21. Proposed reaction mechanism of platinum amides with acrylonitrile.

2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds
c. Ir-N bond

Scheme 22. Proposed reaction mechanism of iridium-catalyzed addition of aniline to norbornene.

2. Migratory Insertion of Olefins into Metal–Nitrogen Bonds
d. Rh-N bond

3. Activation of N-H bond

\[ \text{Ir(P} \text{Et}_3\text{)}_2(\text{C}_2\text{H}_4\text{)}_2\text{Cl} \xrightarrow{\text{NH}_3} \text{THF, 25 °C, 90\%} \xrightarrow{\text{[Ir(P} \text{Et}_3\text{)}_2(\mu-\text{NH}_2)(\text{NH}_3)\text{]}_n\text{Cl}_n} \text{pyridine, 110 °C, 50\% (quant. conv.)} \]

\[ \text{X-ray} \]

3. Activation of N-H bond


3. Activation of N-H bond

Kanzelberger, M.; Zhang, X.; Emge, T. J.; Goldman, A. S.; Zhao, J.; Incarvito, C.; Hartwig, J. F. 
3. Activation of N-H bond

3. Activation of N-H bond

3. Activation of N-H bond

Scheme 1. Proposed pathways for the iridium-catalyzed H/D exchange in C₆D₆.

3. Activation of N-H bond

\[ \text{(tBu)2P} \text{Ir} \text{P(tBu)2} + \text{H}_2\text{NPh} \xrightleftharpoons{K = 105} \text{(tBu)2P} \text{Ir}^{\text{III}} \text{P(tBu)2} + \text{HPh} \]

Only Ir(III) Adduct Observed

\[ \text{(tBu)2P} \text{Ir} \text{P(tBu)2} + \text{H}_2\text{NPh} \xrightleftharpoons{K = 188} \text{(tBu)2P} \text{Ir} \text{P(tBu)2} \text{NH}_{2}\text{Ph} + \text{C}_6\text{H}_6 \xrightleftharpoons{K = 0.1} \text{(tBu)2P} \text{Ir}^{\text{III}} \text{P(tBu)2} + \text{C}_6\text{H}_6 \]

Ir(I) \sigma - Adduct Favored

3. Activation of N-H bond

\[
\begin{align*}
\text{Sykes, A. C.; White, P.; Brookhart, M.} & \quad \textit{Organometallics} \text{ 2006, 25, 1664.}
\end{align*}
\]
3. Activation of N-H bond

3. Activation of N-H bond

4. Conclusion

a. NH$_3$ + Olefin
   Catalytic utilization of ammonia in olefin hydroamination and in coupling with arenes were listed among the top ten challenges for catalysis over a decade ago, and these remain unsolved today.

b. NHRR$'$ + Olefin
   Markovnikov + aromatic olefin
   Markovnikov + aliphatic olefin
   Anit-Markovnikov + aromatic olefin
   **Anit-Markovnikov + aliphatic olefin**

c. Any chance?

   Activation of olefin
   Activation of amine

   $$\begin{align*}
   &\text{oxidative addition} \\
   \text{M-\text{NHRR$'$}} &\rightarrow \text{NHRR$'$} \\
   \text{M-N$^R$} &\rightarrow \text{M-N$^R$} \\
   \text{Markovnikov} &
   \end{align*}$$

   deprotonation