anti-Markovnikov Hydroamination of Alkenes Catalyzed by a Two-Component Organic Photoredox System: Direct Access to Phenethylamine Derivatives

Tien M. Nguyen, Namita Manohar, and David A. Nicewicz.

Angew. Chem. Int. Ed., 2014, ASAP, April 24\textsuperscript{th} Web

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A. Manos-Turvey,
Wipf Group Current Literature
May 10\textsuperscript{th}, 2014
Anti-Markovnikov Hydroamination

In 1993, *anti*-Markovnikov Hydroamination was highlighted as one of the top 10 challenges for catalysis.

- repulsion of nitrogen by the olefin must be overcome
- regioselectivity can be difficult to control

Some Literature Examples

- Alkali-base catalysed amine activation

\[
\begin{align*}
\text{R} & \quad + \quad \text{BnNH}_2 \quad \xrightarrow{n\text{BuLi} (0.1 \text{ eq}), \text{THF, 65-120 °C}} \quad \text{R} - \text{N}\text{Bn}
\end{align*}
\]

- Organolanthanide/Titanium/Iridium or Rhodium/Ruthenium catalysed

\[
\begin{align*}
\text{La} & \quad \text{CH(TMS)}_2 \quad \xrightarrow{\text{H}_2\text{N}} \quad \text{Ph} - \text{MeHN} \quad \xrightarrow{[\text{Rh(COD)}(\text{DPPB})]BF_4, 5 \text{ mol%}, \text{THF, 80 °C}} \quad \text{Ph} - \text{MeNN}
\end{align*}
\]

J-S. Rya, G.Y. Li, T.J. Marks, *JACS*, 2003, 125, 12584-12605
The 9-Mesityl-10-methylacridinium Ion

- Donor = mesitylene portion
- Acceptor = acridinium ion
- Reorganisation energy is very small
  - charge remains the same from D|A to D+|A-

The 9-Mesityl-10-methylacridinium Ion

- absorbs in the visible region (450 nm)
  - upon photoexcitation it reaches a long lived electron transfer (ET) state
  
  ![Diagram of the 9-Mesityl-10-methylacridinium ion with a light source and reaction arrows showing electron transfer]

- 2 h at 203 K and higher energy transfer state (Acr⁺-Mes = 2.37 eV)

**Nicewicz and Anti-Markovnikov Reactions**

- *Anti*-Markovnikov Alkenol Hydroalkoxylation
  - cyclic ether formation with complete regioselectivity through intramolecular hydroalkoxylation

- *Anti*-Markovnikov Alkene Hydroacetoxylation
  - use of oxidisable *E*-olefins to react with a variety of carboxylic acids regioselectively

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Nicewicz and *Anti*-Markovnikov Reactions

- *Anti*-Markovnikov Intramolecular Hydroamination
  - achieve the formation of nitrogen containing heterocycles regioselectively

- Expansion to intermolecular *anti*-Markovnikov hydroamination of alkenes
- Focus upon β-methylstyrenes as phenethylamine derivatives are an important motif in biologically active molecules

![Chemical structures and equations](image-url)

Optimization of Reaction Conditions

All reactions irradiated with a 15 W 450 nm LED flood lamp and run on a 0.2 mmol scale.
Yields determined by 1H NMR spectroscopy using [(H₃C)₃Si]₂O as an internal standard.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Cocatalyst</th>
<th>mol %</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tf</td>
<td>thiophenol</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Tf</td>
<td>2,6-dimethylthiophenol</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Tf</td>
<td>4-nitrothiophenol</td>
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<td>58</td>
</tr>
<tr>
<td>4</td>
<td>Tf</td>
<td>phenyl disulfide</td>
<td>20</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>Tf</td>
<td>–</td>
<td>0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>Tf</td>
<td>phenyl disulfide</td>
<td>5</td>
<td>35</td>
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<td>phenyl disulfide</td>
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</tr>
<tr>
<td>10</td>
<td>Ts</td>
<td>phenyl disulfide</td>
<td>10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>11</td>
<td>Ns</td>
<td>phenyl disulfide</td>
<td>10</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>
Scope of Reaction with Styrenyl Substrates

All reactions irradiated with a 15 W 450 nm LED flood lamp and yields of isolated products (average of two trials).
Scope of Reaction with Different Alkenes

All reactions irradiated with a 15 W 450 nm LED flood lamp and yields of isolated products (average of two trials).
**Scope of Reaction with Heterocyclic Amines**

All reactions irradiated with a 15 W 450 nm LED flood lamp and yields of isolated products (average of two trials).

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Product 1" /></td>
<td>96 h, 83%</td>
<td>96 h, 80%, 2:1 (N1/N2)</td>
</tr>
<tr>
<td><img src="image2.png" alt="Product 2" /></td>
<td>96 h, 57%</td>
<td>X h, 81%, 4:1 (N1/N2)</td>
</tr>
<tr>
<td><img src="image3.png" alt="Product 3" /></td>
<td>96 h, 50% (3 eq imidazole)</td>
<td>72 h, 41%, 1.9:1 (N1/N2)</td>
</tr>
</tbody>
</table>
Proposed Reaction Mechanism

\[ \text{PhS}^+ + e^- \rightarrow \text{PhS} \]

\[ \text{PhS}^+ + \text{H}^+ \rightarrow \text{PhSH} \]

\[ \text{E}_{1/2}^{\text{red}} = +0.16 \text{ V} \]

\[ \text{E}_{1/2}^{\text{ox}} = -0.49 \text{ V} \]

\[ \text{E}_{1/2}^{\text{red}} = +2.06 \text{ V} \]
Conclusions

- Successfully demonstrated the use of an acridinium catalyst in intermolecular *anti*-Markovnikov hydroamination reactions
  - trisubstituted aliphatic alkenes and α- and β-substituted styrenes with various functional groups appear to be tolerated
  - the amine nucleophiles employed are triflylamide or heterocyclic amines
  - all carried out at rt
- Diastereoselectivity needs to be probed
- Interesting to see further extensions of this work on further substrates and additional reactions apart from hydroamination