Hydroamination of Alkenes: A Desirable Transformation

CHALLENGES

- High activation energy
- Repulsion between amine n.b. pair and olefin $\pi$-system
- Nearly thermoneutral (intermolecular)
- Regioselectivity

55 review articles on hydroamination since 1989! Mostly concern reactions of alkynes

Intermolecular Alkene Hydroamination

Major limitations: poor alkene scope, poor amine scope, functional group compatibility, sensitivity or cost of catalysts, harsh reaction conditions, thermodynamics

**Acid Catalysis Is Not Compatible with Basic Amines**

**Oxygen Nucleophiles:** acid-catalysis is efficient

\[ \text{H}^+ \rightarrow \text{H}_2\text{O} \rightarrow \text{OH}^- \]

**Nitrogen Nucleophiles:** *acid-catalysis is not efficient*

\[ \text{H}^+ \rightarrow \text{X}^- \rightarrow \text{R} \]

Two problems:
- The acid reacts with the amine to form a much weaker acid
- Amines cannot act as nucleophiles when protonated

**SOLUTIONS:**
- Use non-basic nitrogen nucleophiles (sulfonamides, amides, etc.)
- Generate more basic alkene
The Cope Elimination in Reverse: A Concerted Hydroamination

Bifunctional amines (RNHXH) could undergo concerted amination/protonation

— syn-elimination

— Microscopic reverse is a hydroamination!

For a review of the Cope Elimination, see: DePuy et al. Chem. Rev. 1960, 60, 431
**Cope-Type Hydroamination: A Metal-Free Hydroamination Method**

- **Key Contributions:** House, Ciganek, Oppolzer, Knight, O'Neil

**Intramolecular** referred to as "Reverse Cope Cyclization"

- Significantly activated by Thorpe-Ingold effect
- Best if $R = \text{Me}$, $R = \text{H}$: much slower

- Reactivity vs. ring size:
  - 5-membered = facile
  - 6-membered = difficult
  - 7-membered = very difficult

**Intermolecular** reactivity hampered by redox and other reactions (opportunity!)

For a review of the reverse Cope Cyclization: Cooper; Knight *Tetrahedron* 2004, 60, 243
**Intermolecular Alkyne Hydroamination w/ NH₂OH: Substrate Scope**

R\(-\equiv-\)R′

\[ \text{aq. NH}_2\text{OH (2.5 equiv.), dioxane, sealed tube, 113 °C} \]

or

\[ i-\text{PrOH, 140 °C (µw)} \]

73% yield (15%)  
72% yield (3%)  
86% yield (2%)  
72% yield (21%)

87% (5%)  
83% (3%)  
8% (5%)  
45% (11%)  
75% (2%)  
65% (3%)

8%  
45% (11%)  
75% (2%)  
65% (3%)

**Angew. Chem. Int. Ed. 2008, 47, 1410**
**N-Alkylhydroxylamine Scope with Alkenes**

RHN\_R \xrightarrow{\text{NaCNBH}_3, \text{n-PrOH}} \xrightarrow{\text{sealed tube, 110 °C, 18h}} \text{N-Alkylhydroxylamine}

<table>
<thead>
<tr>
<th>R</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>91 (67)</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>99 (18)</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>75 (8) (1:1 dr)</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>72</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>7</td>
</tr>
</tbody>
</table>

Without NaCNBH\_3, Drastic additive effect!
BnNHOH: Unstrained Alkene Scope

R \rightarrow \text{BnNHOH (2 equiv)} \xrightarrow{140 \, ^\circ \text{C}} \text{R-N-Bn} + \text{R'-N-Bn}

\text{NaCNBH}_3 \quad n-\text{PrOH}

<table>
<thead>
<tr>
<th>\text{Substrate}</th>
<th>\text{Yield}</th>
<th>\text{Diastereomeric Ratio}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylethylene</td>
<td>58%</td>
<td>(&gt; 20 : 1)</td>
</tr>
<tr>
<td>3-Me Phenylethylene</td>
<td>54%</td>
<td>(&gt; 20 : 1)</td>
</tr>
<tr>
<td>4-Me Phenylethylene</td>
<td>51%</td>
<td>(&gt; 20 : 1)</td>
</tr>
<tr>
<td>2,4-Me Phenylethylene</td>
<td>33%</td>
<td>(&gt; 20 : 1)</td>
</tr>
<tr>
<td>3-Methylbenzene</td>
<td>36%</td>
<td>(&gt; 20 : 1)</td>
</tr>
<tr>
<td>3-Bromobenzene</td>
<td>79%</td>
<td>(1 : 1.1)</td>
</tr>
<tr>
<td>2,4-Difluorobenzene</td>
<td>49%</td>
<td>(4.6 : 1)</td>
</tr>
<tr>
<td>4-Fluorobenzene</td>
<td>49%</td>
<td>(2.1 : 1)</td>
</tr>
<tr>
<td>2,4-Difluorobenzene</td>
<td>59%</td>
<td>(1 : 2.7)</td>
</tr>
<tr>
<td>2,3,4,5,6-Pentafluorobenzene</td>
<td>66%</td>
<td>(&lt; 1 : 20)</td>
</tr>
<tr>
<td>2,4,5,6-Tetrafluorobenzene</td>
<td>71%</td>
<td>(&lt; 1 : 20)</td>
</tr>
<tr>
<td>2,6-Dimethoxybenzene</td>
<td>79%</td>
<td>(1 : 1.1)</td>
</tr>
<tr>
<td>2,6-Dimethoxybenzene</td>
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</tr>
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</tr>
</tbody>
</table>

Yields, DFT calculations and crossover experiments are consistent with ~thermonuclear reaction thermodynamics (Hartwig et al. JACS 2006, 128, 9306, J. Am. Chem. Soc. 2008, 130, 17893)
Difference Between Intra- and Intermolecular Reactions

• Intramolecular ‘Reverse Cope-Elimination’ reactions sometimes occur at room temperature on unactivated alkenes

• The intermolecular versions that we developed require heating between 80-140 C and only work with biased alkenes

• Why the huge difference?

• Can we “trick” intermolecular reactions into thinking they are intramolecular?
**Disposable or Temporary Tethers**

Typical approach for difficult intermolecular reactions: "temporary" intramolecularity via a stepwise, stoichiometric approach

**Catalytic Tethering**

Advantages

- Good atom and step economy
- Allows chiral catalytic tethers to enforce sterochemical control
- Can target a variety of difficult intermolecular reactions

For a review on induced intramolecularity, see: Tan, *ACS Catal.* 2011, 1, 877
Proposed Catalytic Cycle

Optimization of the Catalytic Tether

1% (100 mol%)  
41% (100 mol%)  
0% (100 mol%)  
22% (100 mol%)  
94% (100 mol%)  
12% (20 mol%)  
77% (20 mol%)  

■ No reaction in the absence of aldehyde  
■ Mild!

J. Am. Chem. Soc. 2011, 133, 20100
Organocatalytic Hydroamination: Substrate Scope

\[
\text{R}_1\text{N} - \text{CH} = \text{CH} \quad \text{HO-N}_3
\]

1.5 equiv

\[
\text{1 equiv} \quad \text{HO-N}_3 \quad \text{BnO-C=O} \quad \text{20 mol%} \quad \text{C}_6\text{D}_6 \text{ or CHCl}_3, 22^\circ\text{C}, 24 \text{ h}
\]

\[
\text{R}_1\text{N} - \text{CH} = \text{CH} - \text{N}_3\text{R}_3
\]

83%

82%

51%

\[
\text{J. Am. Chem. Soc. 2011, 133, 20100}
\]
Asymmetric Catalysis with (R)-Glyceraldehyde Ketals

Second generation catalysts have been developed for >95% ee!

J. Am. Chem. Soc. 2011, 133, 20100
Summary

A metal-free, thermal intermolecular hydroamination method.

Catalysis *only* through temporary intramolecularity

14 examples
*up to 87% ee*
A Deep Question: How and Why Did Chemistry Become Biology?

How: We have no idea, but lots of hypotheses.

Why: Life is chemistry, so the answer must be because life solves a thermodynamic problem - it enables a breakdown of pent up chemical energy.

Must have had a constant supply of building blocks and energy.

For a fantastic lecture, see: https://www.youtube.com/watch?v=ElMqwgkXguw
Another Deep Question: Why Is Biochemistry What It Is?
The Evolution of Catalytic Reaction Networks

Iterative Synthesis

Multicatalysis

Multicatalysis with Network Autocatalytic Topology (This work)
The Reductive Tricarboxylic Acid Cycle (rTCA)

- A network autocatalytic cycle at the universal core of metabolism
- Stabilized by continuous input of AcCoA (Wood-Ljungdahl pathway)
- Likely the oldest carbon-fixing pathway (Braakman, PLoS ONE 2014)
- Suspected as starting point for origin of life (Smith, PNAS 2004, 13168)
**Five Reasons that an Abiotic rTCA Cycle is Possible**

1. No bimolecular reactions between intermediates
2. 6 total reaction types, 2 carbon-fixing reactions
3. Simple, mutually compatible inputs: Carbon source: CO$_2$ or CO; Reductants: H$_2$ or CO; Dehydrating agent: Anhydride or CO
4. Possible *Substrate-Directed Catalysis* in the rTCA Cycle

- Directed C-M Bond Formation
- Directed Reduction (β-Ketoacid)
- Directed Dehydration (Alcohol)
- Directed Reduction (α, β-unsaturated acid)
- Directed Succinate Activation
- Intramolecular Catalysis of Retro-Aldol
5. Powerful Carbon Fixing Reactions with CO

- We are developing “double carbonylation” from activated acyl species

\[
\text{X} \text{Me} + \text{CO} \rightarrow \text{X} \text{Me CO}
\]

\[
\text{n-OctBr} \rightarrow \text{LiOH} \rightarrow \text{HO\text{Me CO n-Oct}} \quad 84\% \text{ yield}
\]

*J. Prakt. Chem. 1992, 334, 335*

\[
\text{Ar} \rightarrow \text{Pd(t-Bu}_3\text{P})_2 \rightarrow \text{R}_2\text{R}_1\text{N CO Ar} \quad 56\% \text{ yield}
\]

*Chem. Commun. 2006, 1739*

\[
\text{NHR}_1\text{R}_2 \rightarrow \text{K}_3\text{PO}_4 \rightarrow \text{R}_2\text{R}_1\text{N CO Ar} \quad 56\% \text{ yield}
\]

*Chem. Commun. 2006, 1739*

- We are developing oxidative carbonylation of pyruvic acid and its derivatives

\[
\text{X} \text{Me} \rightarrow \text{CO, [O]} \rightarrow \text{X} \text{Me CO}
\]

\[
\text{PdCl}_2 \rightarrow \text{CO (1 atm)} \rightarrow \text{MeOH, r.t.} \rightarrow \text{78\% yield of pimelate}
\]

*J. Org. Chem. 2001, 66, 180*

\[
\text{Pd(MeCN)}_2\text{(OTs)}_2 \rightarrow \text{CO (1 atm)} \rightarrow \text{BQ, TsOH} \rightarrow \text{up to 90\% yield}
\]

*Angew. Chem. Int. Ed. 2009, 48, 1830*
• A chemically plausible artificial metabolic cycle very similar to modern biochemistry
• Could the first metabolic cycle have looked like this? Let’s try to build it!
Project Organization

1) Reductive Carboxylation (CO₂)
   Carbonylation (CO)

   1 Postdoc, 1 PhD

   \[ \begin{align*}
   &\text{X} &\text{Me} \\
   \rightarrow &\text{X} &\text{Me} \\
   \end{align*} \]

2) Carboxylation/Reduction/Dehydration/Reduction (CO₂)
   Oxidative Carbonylation/Reduction/Dehydration/Reduction (CO)

   1 Postdoc, 1 PhD

   \[ \begin{align*}
   &\text{X} &\text{Me} &\text{O} \\
   \rightarrow &\text{X} &\text{Me} &\text{O} \\
   \text{X} &\text{O} &\text{X} &\text{O} \\
   \rightarrow &\text{X} &\text{Me} &\text{O} \\
   \end{align*} \]

3) Activation of X and Retro-Aldol

   1 Postdoc, 1 PhD

   \[ \begin{align*}
   &\text{X} &\text{X} &\text{O} &\text{O} &\text{X} &\text{O} &\text{OH} \\
   \rightarrow &\text{Me} &\text{X} &\text{O} &\text{X} &\text{CO} &\text{O} &\text{X} \\
   \end{align*} \]

4) Merge
Acknowledgements