Aryne Insertions into $\sigma$-Bonds

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Background

- Formal triple bond of aryne is highly strained - powerful electrophile
- Nucleophilic addition to aryne generates carbanion that can be trapped by an electrophile

For useful reviews on insertion reactions see:
Peña & Guitián, *ACIE*, 2006, 45, 3579

For an exhaustive review on aryne chemistry see:
Insertions reactions were not that well exploited until a mild method to generate benzyne was reported by Kobayashi.

Many examples

\( \sigma \)-Bond Insertions

- Examples of the insertion of benzyne into \( \sigma \)-bonds (Nu = heteroatom)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>X–Y</th>
<th>Cat.</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R_2N\text{CONR}_2 )</td>
<td>N–C</td>
<td>–</td>
<td><img src="#" alt="Product" /></td>
</tr>
<tr>
<td>( \text{ArS–SnR}_3 )</td>
<td>S–Sn</td>
<td>–</td>
<td><img src="#" alt="Product" /></td>
</tr>
<tr>
<td>( R_2N\text{SiMe}_2\text{Ph} )</td>
<td>N–Si</td>
<td>–</td>
<td><img src="#" alt="Product" /></td>
</tr>
<tr>
<td>( \text{PhHN–CF}_3 )</td>
<td>N–C</td>
<td>–</td>
<td><img src="#" alt="Product" /></td>
</tr>
<tr>
<td>( \text{PhHN–S–CF}_3 )</td>
<td>N–S</td>
<td>–</td>
<td><img src="#" alt="Product" /></td>
</tr>
</tbody>
</table>

Peña & Guitián, *ACIE*, 2006, 45, 3579
**σ-Bond Insertions**

- Examples of the insertion of benzyne into σ-bonds (Nu = carbon)

<table>
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<tr>
<th>Substrate</th>
<th>X–Y</th>
<th>Cat.</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>R¹COOR²</td>
<td>C–C</td>
<td>–</td>
<td>![Product Image]</td>
</tr>
<tr>
<td>R¹COCR²</td>
<td>C–C</td>
<td>–</td>
<td>![Product Image]</td>
</tr>
<tr>
<td>R¹COCN</td>
<td>C–C</td>
<td>–</td>
<td>![Product Image]</td>
</tr>
<tr>
<td>Ph₂P=CN</td>
<td>C–P</td>
<td>–</td>
<td>![Product Image]</td>
</tr>
</tbody>
</table>

Peña & Guitián, *ACIE*, 2006, 45, 3579
### σ-Bond Insertions

- Examples of the insertion of benzyne into σ-bonds (catalytic palladium)

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<th>Cat.</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂Si−SiMe₂</td>
<td>Si−Si</td>
<td>Pd</td>
<td><img src="image1" alt="Product" /></td>
</tr>
<tr>
<td>R₃Sn−SnR₃</td>
<td>Sn−Sn</td>
<td>Pd</td>
<td><img src="image2" alt="Product" /></td>
</tr>
<tr>
<td>R₃Sn−SnR₃</td>
<td>Sn−Sn</td>
<td>Pd</td>
<td><img src="image3" alt="Product" /></td>
</tr>
<tr>
<td>Bu₃Sn−≡R</td>
<td>Sn−C</td>
<td>Pd</td>
<td><img src="image4" alt="Product" /></td>
</tr>
</tbody>
</table>

*Peña & Guitián, ACIE, 2006, 45, 3579*
Mechanism

- Plausible mechanistic cycles for Pd-catalysed insertion reactions - both cycles have been invoked

Proposal

- Is it possible to insert directly into the C-H $\sigma$-bond?

\[
\begin{align*}
\text{OTf} & \quad \text{F}^- \quad \text{F}^- \quad \text{H} \quad \text{C} \\
\text{SiMe}_{3} & \quad \text{C} \quad \text{H} & \quad \text{Insertion} \\
\end{align*}
\]
Proposal

- Is it possible to insert directly into the C-H σ-bond?

\[
\begin{align*}
\text{OTf} & \quad \text{F}^- \\
\text{SiMe}_3 & \quad [\text{benzene}] \\
\text{H} & \quad \text{C} \\
\end{align*}
\]

- If metal free then essentially “C(δ+)” and “H(δ-)” (i.e. an intermolecular hydride transfer)

\[
\begin{align*}
\text{R} & \quad \text{R}' \\
\text{R}'' & \quad \text{H} \\
\text{R}^\oplus & \quad \text{R}' \\
\text{R}'' & \quad \text{H} \\
\end{align*}
\]

Suitable cation stabilising groups?
Examples of good hydride transfer compounds

- Hantzsch ester
- Nicotinamide
- 10-Methylacridin
- Benzothiazoline
Proposal

- Examples of good hydride transfer compounds

- **Hantzsch ester**  
  
- **Nicotinamide**  
  
- **10-Methylacridin**  
  
- **Benzothiazoline**  

- e.g. Possible target: Nifedipine (treats hypertension) - $1 billion drug in 1999

\[
\begin{align*}
\text{Hantzsch ester} & \quad \text{Nicotinamide} & \quad \text{10-Methylacridin} & \quad \text{Benzothiazoline}
\end{align*}
\]
Proposal

- Will any heteroatom be tolerated in substrate - competing nucleophile?
- How feasible is an *inter*molecular hydride shift? No examples onto arynes.
Two reports of *intramolecular* hydride transfer involving benzyne - **but** only as side reactions.

e.g. 1: *Tetrahedron*, 1977, 581

\[
\begin{align*}
\text{Cl} & \quad \text{Et} \\
\text{CN} & \quad \text{H}
\end{align*}
\]

\[
\xrightarrow{\text{NaNH}_2}
\]

\[
\begin{align*}
\text{CN} & \quad \text{Et} & \quad \text{H} & \quad 11\% \\
\text{NH}_2 & \quad \text{CN} & \quad \text{Et} & \quad 60\% \\
\text{H} & \quad \text{Et} & \quad \text{H} & \quad \sim1\%
\end{align*}
\]

e.g. 2: *Tetrahedron*, 1968, 6223

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{N} & \quad \text{H}
\end{align*}
\]

\[
\xrightarrow{\text{KNH}_2}
\]

\[
\begin{align*}
\text{N} & \quad \text{H} \quad \text{O} \\
\text{H} & \quad \text{N} \\
\end{align*}
\]

\[
\xrightarrow{\text{oxidation}}
\]

38 %

*Oxidation of indoline*
Proposal - Self-Oxidising Protecting Groups

- Intramolecular hydride transfer to benzyne - potential dual role:
  - alcohol oxidation (also indoline, amines etc.)
  - protecting group (can be used for regio- and chemoselective oxidation)

Protected alcohol → Oxidation of alcohol
Proposal - Self-Oxidising Protecting Groups

- Intramolecular hydride transfer to benzyne - potential dual role:
  - alcohol oxidation (also indoline, amines etc.)
  - protecting group (can be used for regio- and chemoselective oxidation)

\[ \text{Protected alcohol} \quad \xrightarrow{\text{Oxidation of alcohol}} \]


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- employed in Nicolau and Baran’s synthesis of the CP-Molecules, \textit{JACS}, 2002, 124, 2190
Proposal - Self-Oxidising Protecting Groups

- Require benzylic electrophile of the general structure:

![Chemical structure diagram]

- Synthesis?

\[
\begin{align*}
\text{Br} & \quad \text{(CHO)}_n \quad \text{PhB(OH)}_2 \\
\text{OH} & \quad 1. \text{BuLi, TMS} \\
\text{Br} & \quad 2. \text{TBAF} \\
\text{HO} & \quad \text{Tf}_2\text{O} \\
\text{TMS} & \quad \text{TfO}_{\text{OTf}}
\end{align*}
\]


or

\[
\begin{align*}
\text{Br} & \quad \text{CO}_2\text{R} \\
\text{OH} & \quad \text{Et}_2\text{NCOCl} \\
\text{CO}_2\text{R} & \quad 1. \text{BuLi then TESCl} \\
\text{NET}_2 & \quad 2. \text{LiAlH}_4 \\
\text{TES} & \quad \text{Tf}_2\text{O} \\
\text{OTf} & \quad \text{TES}_{\text{OTf}}
\end{align*}
\]
Proposal - Self-Oxidising Protecting Groups

Any suggestions, observations, criticisms etc.?

- This project:
- In general:

Further ideas for aryne insertions (C-H or otherwise)?
Different coupling partners for arynes?
Tandem processes - what concurrent reactions could F- be used for?