Direct Oxidative Heck Cyclizations: Intramolecular Fujiwara-Moritani Arylations for the Synthesis of Functionalized Benzofurans and Dihydrobenzofurans

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Current Literature
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Why is this Article Significant?

- Heck reaction is ubiquitous for the forming C-C bonds in synthetic molecules
  - uses halogenated arenes which requires an additional synthetic step
  - a base is needed to remove the generated hydrohalic acid

- C-H activation of arenes eliminates the need for halogens

- Demonstrates the first use of catalytic Pd for oxidative intramolecular C-H activation of arenes and the addition into unactivated olefins (Heck reaction)

- Illustrates that mechanism of cyclization follows the pathway of a Fujiwara-Moritani/oxidative Heck cyclization

- Synthesize benzofuran and dihydrobenzofuran structures, which are important components of numerous biologically active compounds
Examples of Biologically Active Benzofurans

- Antifungal activity against *Candida albicans* (a pathogenic fungi)
  

- An oxytocin antagonist
  

- A serotonin release enhancer
  
Examples of Biologically Active Dihydrobenzofurans

- A tubulin polymerization inhibitor
  (GI_{50} of <10 nM against some breast cancer cell lines)

- An anti-inflammatory and analgesic drug

- An acyl-Co A: cholesterol acyltransferase inhibitor
Pd-Catalyzed Oxidative Heck Reaction

_Fujiwara-Moritani arylation (1967)_

\[
\text{Catalytic intermolecular reaction with activated olefins}
\]

Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *1119-1122*

Mechanism of Arene Insertion into Activated Esters and Reoxidation of Catalyst

\[
\begin{align*}
\text{Pd}(0) & \xrightarrow{[O] / \text{Pd(II)}} \text{Pd(OAc)}_2 \\
\text{Ar}-\text{PdOAc} & \xrightarrow{-\text{OAc}} \text{[PdOAc]}^+ \\
\text{Ar-PdOAc} & \xleftarrow{\text{Ar-H}} \text{CO}_2\text{R} \\
\end{align*}
\]
Pd-Catalyzed Reactions of Arenes with Alkynes

Carboxylation of Arenes and Ru-Catalyzed Oxidative Heck Reactions

\[
\text{C}_6\text{H}_6 + \text{CO} \underset{\text{RT, 20h}}{\rightarrow} \text{C}_6\text{H}_5\text{CO}_2\text{H} \approx 100\%
\]


\[
\text{B(OH)}_2 + \text{CH}_2\text{=CHCO}_2\text{Bu} \underset{\text{2.5 mol% Ru-cat. (1)}}{\rightarrow} \text{B(OH)}_2\text{CH}_2\text{CHCO}_2\text{Bu}
\]

98% GC, 60% isolated

* need prefunctionalized arene to facilitate reaction

Palladium-Promoted Oxidative Heck Cyclization in Total Synthesis

1 equiv. Pd(OAc)$_2$, AcOH:dioxane:H$_2$O, 1 atm O$_2$, 25 °C, 16h

44%

Okaramine N

First Example of Pd-Catalyzed Oxidative Annulations of Indoles

\[
Pd(OAc)_2 (10 \text{ mol\%}), \ O_2 (1 \text{ atm}) \quad \text{pyridine ligand (40 mol\%)}, \quad 0.1 \text{ M solvent}, \ 24 \text{ h}, \ 80 \ ^\circ \text{C}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyridine ligand</th>
<th>( \text{pKa(pyrH}^+ )</th>
<th>conversion (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>4-OMe</td>
<td>6.47</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>4-t-Bu</td>
<td>5.99</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>unsub.</td>
<td>5.25</td>
<td>23</td>
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<tr>
<td>4</td>
<td>4-CO_2Et</td>
<td>3.45</td>
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<tr>
<td>* 5</td>
<td>3-CO_2Et</td>
<td><strong>3.35</strong></td>
<td><strong>76</strong></td>
</tr>
<tr>
<td>6</td>
<td>3-COCH_3</td>
<td>3.18</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>3-F</td>
<td>2.97</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>3-CN</td>
<td>1.39</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>3,5-di-Cl</td>
<td>0.90</td>
<td>22</td>
</tr>
</tbody>
</table>

**Best result:**
40 mol\% ethyl nicotinate*, 0.1M tert-amyl alcohol/AcOH (4:1), 99% conversion, 82% isolated yield

Screening of Oxidants for the Catalytic Intramolecular Oxidative Heck Cyclization

Pd(OAc)$_2$ (10 mol%), oxidant, ethyl nicotinate (40 mol%), t-AmOH:AcOH (4:1), 24 h, 80 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant [1 equiv.]</th>
<th>Yield [%] by GC</th>
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<tbody>
<tr>
<td>1</td>
<td>O$_2$</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>benzoquinone</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)$_2$</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>AgOAc</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>Ti(OCOCF$_3$)$_3$</td>
<td>&lt;10</td>
</tr>
<tr>
<td>6</td>
<td>K$_2$S$_2$O$_8$</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>H$_2$NC(S)NH$_2$</td>
<td>&lt;10</td>
</tr>
<tr>
<td>8</td>
<td>PhCO$_3$Bu</td>
<td>42</td>
</tr>
</tbody>
</table>

Examples of Oxidative Benzofuran Synthesis

Pd(OAc)$_2$ (10 mol%), NaOAc (20 mol%),
eethyl nicotinate (20 mol%),
benzoquinone (1 equiv.),
0.1M t-AmOH:AcOH (4:1), 100 $^\circ$C

Synthesis of Quaternary Carbon-Containing Dihydrobenzofurans via Oxidative Cyclization

Pd(OAc)_2 (10 mol%), NaOAc (20 mol%), ethyl nicotinate (20 mol%), benzoquinone (1 equiv.), 0.1M t-AmOH:AcOH (4:1), 100 °C


2.3:1 diastereomers
Mechanistic Probe for the Oxidative Heck Cyclization

Pd(OAc)$_2$ (10 mol%), NaOAc (20 mol%), ethyl nicotinate (20 mol%), benzoquinone (1 equiv.), t-AmOH:AcOH (4:1), 100 °C

1 not observed

60% yield

anti nucleophilic attack

arene palladation

syn B-hydride elimination

syn B-hydride elimination

HPdL$_n$(OAc)

B-hydride elimination

HPdL$_n$(OAc)

Erick Iezzi @ Wipf Group 12/2/04
Future Work

- Develop catalysts to facilitate oxidative C-H activation of electron-poor arenes

- Develop method of synthesizing ether rings of six-members and greater