Palladium-Catalyzed Highly Diastereoselective Oxidative Cascade Cyclization Reactions

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• Cascade Cyclization Reactions

“...The design and implementation of cascade reactions is a challenging facet of organic chemistry, yet one that can impart striking novelty, elegance, and efficiency to synthetic strategies.”

K. C. Nicolaou

Five Classifications of Cascade Cyclization Reactions:
1. Nucleophilic Cascades
2. Electrophilic Cascades
3. Radical Cascades
4. Pericyclic Cascades
5. Transition-Metal-Catalyzed Cascades

- generates molecular complexity enantioselectively
- catalytic
- bond construction unparalleled by nature
- Pd—blossomed into powerful tool over the past 25 years
- Heck is most popular Pd-catalyzed cascade reaction

• Pericyclic Diels-Alder/Schmidt cascade to stenine:

\[
\text{TMSO} - \text{Et}\n\]
\[
\text{N}_3\n\]
\[
\text{OTMS}\n\]
\[
\text{SnCl}_4, \text{CH}_2\text{Cl}_2,\n\]
\[
-78^\circ\text{C} \text{ to } -55^\circ\text{C}\n\]
\[
\text{exo-Diels-Alder reaction}\n\]
\[
\text{intramolecular Schmidt reaction + silyl ether hydrolysis}\n\]
\[
\text{70%}\n\]
\[
3:1 \text{ a:b}\n\]


Sample of Heck cyclization cascades and their weaknesses:


- **only forms 2 new bonds**
• Heck-type cascade cyclization popularity

1. preactivation of precursors leads to stoichiometric amounts of hydrohalic or triflic acids
2. palladium complexes usually contain air-sensitive phosphine ligands
3. reaction scope limited to carbon-carbon bond formation

Goal:

to refine methodology toward cascade cyclization reactions that are more atom-economical and applicable to carbon-heteroatom bond formation

• Previous work….

- used Pd(OAc)$_2$/pyridine and Pd(TFA)$_2$/(-)-sparteine as the catalyst systems
- obtain racemic and enantoenriched indoline derivatives
- free of any undesired monocyclization products even in the absence of tandem relays

• **Title Paper:** Palladium Catalyzed Highly Diastereoselective Oxidative Cascade Cyclization Reactions

- isoquinoline and quinoline as ligands *instead of* pyridine and (-)-sparteine
- Pd(OAc)$_2$/isoquinoline or quinoline as the catalyst system
- unsaturated anilides cyclize under an oxygen atmosphere (1 atm)
- furnish structurally versatile indoline derivatives
- good yields (~80%)
- make 1 C-N bond and 2 C-C bonds in a single step (one of which is a *quaternary center*)
- excellent diastereoselectivity (dr > 24:1)

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• **Synthesis of starting material (1a)**

\[
\text{aniline: $45.10$ for 500 g} \\
\text{allyl chloride: $25.60$ for 500 mL (Aldrich)}
\]

\[
\begin{align*}
\text{aniline} + \text{Cl} & \rightarrow 1. \text{(Boc)$_2$O, THF} \\
& \quad 2. \text{NaH} \\
& \quad 3. \text{HCl, H$_2$O} \\
& \quad 90\%
\end{align*}
\]


• Ligand screening

Basicity correlation with reaction conversion and product ratio

• Solvent effect and oxidant screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>NMR conversion&lt;sup&gt;a&lt;/sup&gt; / %</th>
<th>NMR combined yield&lt;sup&gt;b&lt;/sup&gt; / %</th>
<th>pdt. Ratio&lt;sup&gt;b&lt;/sup&gt; (2a : 3a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>86</td>
<td>82</td>
<td>5.6 : 1</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>85</td>
<td>72</td>
<td>3.9 : 1</td>
</tr>
<tr>
<td>3</td>
<td>1,4-dioxane</td>
<td>84</td>
<td>65</td>
<td>4.0 : 1</td>
</tr>
<tr>
<td>4</td>
<td>1,2-dichloroethane</td>
<td>46</td>
<td>44</td>
<td>2.2 : 1</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>26</td>
<td>24</td>
<td>N.D.</td>
</tr>
<tr>
<td>6</td>
<td>MeOH</td>
<td>29</td>
<td>25</td>
<td>N.D.</td>
</tr>
<tr>
<td>7</td>
<td>chlorobenzene</td>
<td>88</td>
<td>80</td>
<td>3.7 : 1</td>
</tr>
<tr>
<td>8</td>
<td>MeNO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>81</td>
<td>77</td>
<td>2.5 : 1</td>
</tr>
</tbody>
</table>

<sup>a</sup> 0.2 mmol of substrate was used.  
<sup>b</sup> Determined using nitrobenzene as the internal standard.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant (2 equiv)</th>
<th>NMR conversion&lt;sup&gt;a&lt;/sup&gt; / %</th>
<th>NMR combined yield&lt;sup&gt;b&lt;/sup&gt; / %</th>
<th>pdt. Ratio&lt;sup&gt;b&lt;/sup&gt; (2a : 3a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O&lt;sub&gt;2&lt;/sub&gt; (1 atm)</td>
<td>86</td>
<td>82</td>
<td>5.6 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Air (1 atm)</td>
<td>84</td>
<td>39</td>
<td>4.4 : 1</td>
</tr>
<tr>
<td>3</td>
<td>CuCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>12</td>
<td>&lt; 5</td>
<td>N. D.</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>36</td>
<td>29</td>
<td>1.9 : 1</td>
</tr>
<tr>
<td>5</td>
<td>Benzoquinone</td>
<td>28</td>
<td>14</td>
<td>3.1 : 1</td>
</tr>
<tr>
<td>6</td>
<td>Oxone&lt;sup&gt;x&lt;/sup&gt;</td>
<td>8</td>
<td>&lt; 5</td>
<td>N.D.</td>
</tr>
<tr>
<td>7</td>
<td>PhI(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>messy rx.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>AgOAc</td>
<td>59</td>
<td>49</td>
<td>2.2 : 1</td>
</tr>
<tr>
<td>9</td>
<td>CuCl</td>
<td>10</td>
<td>&lt; 5</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

<sup>x</sup> 0.2 mmol of substrate was used.  
<sup>b</sup> Determined using nitrobenzene as the internal standard.

### Ligand to Pd (II) ratio and effect of Pd source

<table>
<thead>
<tr>
<th>Entry</th>
<th>Isoquinoline</th>
<th>L : Pd(II)</th>
<th>NMR conversion&lt;sup&gt;a&lt;/sup&gt; / %</th>
<th>NMR combined yield&lt;sup&gt;a&lt;/sup&gt; (2a + 3a) / %</th>
<th>pdt. Ratio&lt;sup&gt;b&lt;/sup&gt; (2a : 3a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mol%</td>
<td>1 : 1</td>
<td>41</td>
<td>29</td>
<td>1 : 1.2</td>
</tr>
<tr>
<td>2</td>
<td>20 mol%</td>
<td>2 : 1</td>
<td>76</td>
<td>65</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>3</td>
<td>40 mol%</td>
<td>4 : 1</td>
<td>86</td>
<td>82</td>
<td>5.6 : 1</td>
</tr>
<tr>
<td>4</td>
<td>60 mol%</td>
<td>6 : 1</td>
<td>88</td>
<td>78</td>
<td>4.7 : 1</td>
</tr>
<tr>
<td>5</td>
<td>80 mol%</td>
<td>8 : 1</td>
<td>86</td>
<td>73</td>
<td>9.5 : 1</td>
</tr>
</tbody>
</table>

<sup>a</sup> 0.2 mmol of substrate was used. <sup>b</sup> Determined using nitrobenzene as the internal standard.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source</th>
<th>NMR conversion&lt;sup&gt;a&lt;/sup&gt; / %</th>
<th>NMR combined yield&lt;sup&gt;a&lt;/sup&gt; (2a + 3a) / %</th>
<th>pdt. Ratio&lt;sup&gt;b&lt;/sup&gt; (2a : 3a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂(MeCN)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>N.D.</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂(COD)</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>N.D.</td>
</tr>
<tr>
<td>3</td>
<td>Pd(MeCN)&lt;sub&gt;4&lt;/sub&gt;(BF₄)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>&lt; 5</td>
<td>&lt; 5</td>
<td>N.D.</td>
</tr>
<tr>
<td>4</td>
<td>Pd(TFA)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>22</td>
<td>18</td>
<td>1 : 2.5</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>86</td>
<td>82</td>
<td>5.6 : 1</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh₃)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>60</td>
<td>43</td>
<td>4.0 : 1</td>
</tr>
<tr>
<td>7</td>
<td>Pd₂(dba)&lt;sub&gt;3&lt;/sub&gt; (10 mol%-Pd)</td>
<td>67</td>
<td>43</td>
<td>3.3 : 1</td>
</tr>
</tbody>
</table>

<sup>a</sup> 0.2 mmol of substrate was used. <sup>b</sup> Determined using nitrobenzene as the internal standard.

Scope of the cascade cyclization using quinoline and isoquinoline as ligands

1a

Pd(OAc)$_2$ (10 mol%) ligand (40 mol%) toluene, O$_2$ (1 atm), 70°C

<table>
<thead>
<tr>
<th>X</th>
<th>quinoline (2a:3a % yield)</th>
<th>isoquinoline (2a:3a % yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>60:9</td>
<td>81:3</td>
</tr>
<tr>
<td>F</td>
<td>55:7</td>
<td>70:3</td>
</tr>
<tr>
<td>OMe</td>
<td>34:29</td>
<td>55:5</td>
</tr>
</tbody>
</table>

1d

Pd(OAc)$_2$ (10 mol%) ligand (40 mol%) toluene, O$_2$ (1 atm), 70°C

<table>
<thead>
<tr>
<th></th>
<th>quinoline (% yield)</th>
<th>isoquinoline (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>exo</td>
<td>59</td>
<td>45</td>
</tr>
<tr>
<td>endo</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

• Scope of the cascade cyclization using quinoline and isoquinoline as ligands, continued

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>n</th>
<th>Quinoline (% yield)</th>
<th>Isoquinoline (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>N/A</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Key scope points:
- Quinoline and isoquinoline have similar rxn times
- Pd/(OAc)$_2$/isoquinoline resulted in better yields
- Cyclization not correlate with substrate’s electronic properties
- *endo*-olefinic products form by secondary addition of palladium hydride to the *exo* moiety

• Transition State Model

• Key nOe interactions

• Conclusions:

• new palladium-catalyzed oxidative cyclization reactions
• highly diastereoselective
• construct three new bonds and two chiral centers in a single step (one of which is a quaternary center)
• Pd(OAc)$_2$/isoquinoline and Pd(OAc)$_2$/quinoline systems are an extension of the well documented Pd(OAc)$_2$/pyridine system
• pushes past the previous reaction scope to include formation of a carbon-nitrogen bond
• overall more atom-economical and applicable in pursuit of green chemistry