Palladium-Catalyzed CS Activation/Aryne Insertion/Coupling Sequence: Synthesis of Functionalized 2-Quinolinones

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Yohan DUDOGNON, STeRéO group meeting, 24/03/2014
State of art

Synthesis of Xanthones, Thioxanthones, and Acridones by the Coupling of Arynes and Substituted Benzoates

\[
\begin{align*}
\text{R}^1\text{CO}_2\text{Me} & \quad + \quad \text{TMS}\text{R}^2 \\
\text{CsF} & \quad \rightarrow \\
\text{R}_1\text{X} & \quad \text{R}^2
\end{align*}
\]

\(X = \text{O, S, NMe}\)

J. Zhao, R. C. Larock, J. Org. Chem. 2007, 72, 583
doi: 10.1021/jo0620718

Aryl Methyl Sulfides as Substrates for Rhodium-Catalyzed Alkyne Carbothiolation: Arene Functionalization with Activating Group Recycling

\[
\begin{align*}
\text{MeS} & \quad \text{Me} \\
\text{1a} & \quad + \quad \text{2a} \\
\text{[Rh(DPEphos)-} & \quad \text{ligand)][\text{BARF}_4] \\
\text{solvent, temp, time} & \quad \rightarrow \\
\text{MeS} & \quad \text{Me}
\end{align*}
\]

doi: 10.1021/ja2108992
State of art

- Transition-metal-catalyzed CS bond activation for CC and C–heteroatom bond formation

H. Prokopcov, C. O. Kappe, Angew. Chem. 2009, 121, 2312

- Applications of arynes in cyclization reactions

Previous work of the team

Regio- and stereoselective synthesis of 2-cyclopentenones via a hydrogenolysis-terminated Heck cyclization of β-alkylthio dienones

\[
\begin{align*}
\text{Pd(PPh}_3\text{)}_2\text{Cl}_2 (10\%) & \quad \text{DMF/NEt}_3 \\
90^\circ \text{C, N}_2, 36 \text{ h} & \quad \text{X}
\end{align*}
\]


Palladium-catalyzed/copper-mediated desulfitative annulation of 2-methylthiobenzofurans with 2-hydroxyphenylboronic acids

\[
\begin{align*}
\text{RO} & \quad \text{B(OH)}_2 \\
\text{1d-j} & \quad \text{CuTC (1.5 eq.), N}_2 \quad \text{Dioxane, reflux}
\end{align*}
\]

Overview

**Strategy:**
- Take advantage of the synthetic power of functionalized ketene dithioacetals
- Take advantage of the tremendous applications of aryynes in cyclization reactions

Use Pd-catalyzed CS activation as the key to developing an annulation between aryynes and \( \alpha \)-carbamoyl ketene dithioacetals.

**Interests:**
- Effective synthesis \( 2 \)-quinolinones which have provoked great interest in chemical and biological field
- Possible versatile transformations of the 4-functionalized \( 2 \)-quinolinones

**Challenge:**
- Avoid the addition of the strongly nucleophilic sulfur atom to the aryynes and instead favoring insertion of the aryynes into the CS bond.

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_Scheme 1_. Reactions of thioorganics with benzyne.
Screening of the reaction conditions

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd</th>
<th>Ligand (mol %)</th>
<th>2a (equiv)</th>
<th>CsF (equiv)</th>
<th>Toluene/MeCN</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>$-$</td>
<td>1.5</td>
<td>3</td>
<td>0:1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>$-$</td>
<td>1.5</td>
<td>3</td>
<td>1:1</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>$-$</td>
<td>1.5</td>
<td>3</td>
<td>3:1</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>$-$</td>
<td>2</td>
<td>4</td>
<td>1:1</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)</td>
<td>$-$</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>[Pd(PPh$_3$)$_4$]</td>
<td>$-$</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>[PdCl$_2$(PPh$_3$)$_2$]</td>
<td>$-$</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>[PdCl$_2$(dppe)]</td>
<td>$-$</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$</td>
<td>dpff (15)</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$</td>
<td>dpff (15)</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>90[c]</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)$_2$</td>
<td>Xanthos (15)</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)$_2$</td>
<td>PC$_3$ (30)</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>26</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$ (30)</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>49</td>
</tr>
<tr>
<td>14</td>
<td>Pd(OAc)$_2$</td>
<td>dpff (8)</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>53[d]</td>
</tr>
<tr>
<td>15</td>
<td>Pd(OAc)$_2$</td>
<td>dpff (15)</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>28[e]</td>
</tr>
<tr>
<td>16</td>
<td>Pd(OAc)$_2$</td>
<td>dpff (15)</td>
<td>3</td>
<td>5</td>
<td>1:1</td>
<td>$&lt;5$[f]</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1a (0.3 mmol), 2a, CsF, Pd (10 mol%), toluene/MeCN (4 mL). Reaction was performed in a sealed tube at 80°C under N$_2$ for 18 h. 2a was added in six increments (3 h x 6) to avoid homocoupling of benzyne. [b] Yields of isolated products. [c] Reaction was performed in a flask with a condenser under N$_2$. [d] Used 5 mol % of Pd(OAc)$_2$. [e] At 50°C. [f] At room temperature.
Scope of the ketene dithioacetals

![Chemical structure and reaction scheme

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products 3</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a, 3a, R^2 = Bn</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>1b, 3b, R^2 = 4-MePhCH_2</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>1c, 3c, R^2 = Ph</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>1d, 3d, R^2 = nBu</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>1e, 3e, R^2 = Cy</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>1f, 3f, R^2 = Bn</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>1g, 3g, R^2 = nBu</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>1h, 3h, R^2 = Bn</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>1i, 3i, R^2 = Ph</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>1j, 3j, R^2 = nBu</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td>1k, 3k, R^2 = Bn</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>1l, 3l, R^2 = Ph</td>
<td>79</td>
</tr>
<tr>
<td>13</td>
<td>1m, 3m</td>
<td>74</td>
</tr>
<tr>
<td>14</td>
<td>1n, 3n + 3h</td>
<td>27 + 20</td>
</tr>
<tr>
<td>15</td>
<td>1o, 3o, R^1 = 4-NO_2Ph</td>
<td>88</td>
</tr>
<tr>
<td>16</td>
<td>1p, 3p, R^1 = PhCO</td>
<td>80</td>
</tr>
<tr>
<td>17</td>
<td>1q, 3q</td>
<td>73</td>
</tr>
<tr>
<td>18</td>
<td>1r, 3r</td>
<td>&lt;15[b]</td>
</tr>
</tbody>
</table>
Scope of arynes

[Image of chemical structures and reactions]

[a] Reaction conditions: 1 (0.3 mmol), 2 (1.5 mmol), CsF (2.1 mmol), Pd(OAc)$_2$ (0.03 mmol), dppf (0.045 mmol), toluene/MeCN (4 mL, 1:1, v/v) in a sealed tube, 2 was added in six increments (0.25 mmol/3 h). Yields of isolated products. [b] Yields in parenthesis were obtained by using 0.9 mmol of 2 and 1.5 mmol of CsF. [c] The by-products 4b and 4b’ were isolated in 26% yield. [d] The ratio of two isomers, based on $^1$H NMR spectroscopy, are included within parentheses.
Mechanism

Key intermediate

Ligands omitted for clarity
Applications

• Palladium-catalyzed crosscoupling with phenylboronic acid in the presence of copper(I)-thiophene-2-carboxylate

![Chemical structure](image1)

PhB(OH)$_2$ (1.5 equiv)  
Pd(PPh)$_3$ (7 mol%)  
CuTC (2 equiv)  
1,4-dioxane, reflux  
8 h, 79%

• Direct substitution of the 4-methylthio group of with phenylmethanamine give the 4-amino quinolinone

![Chemical structure](image2)

BnNH$_2$ (1.5 equiv)  
EtOH, reflux  
24 h, 81%

• Synthesis of the pyrimidoquinolin-5-one by the condensation with acetimidamide

![Chemical structure](image3)

\[ \text{NaNH} \cdot \text{HCl} \]  
DMF, 90 °C  
10 h, 86%
Conclusion

- Development of a novel and efficient palladium-catalyzed protocol for the synthesis of 2-quinolinones

- First example for the reaction of aryynes with thioorganics based on palladium-catalyzed CS bond activation

- Functionalized 2-quinolinone as useful building blocks

- Discovery of the facile CS bond activation should lead to some new and efficient palladium-catalyzed transformations

- Work on the applications, extension of the scope, mechanistical studies are ongoing