Palladium-Catalyzed Hydroarylation of Diazocarboxylates and Diazophosphonates

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Abstract
A simple synthetic procedure for the Pd-catalyzed hydroarylation of diazoacetic ester has been previously developed in our laboratory. Now we have applied this methodology for hydroarylation of α-diazocarboxylates/α-diazophosphonates. Diazocompounds reacted with aryl iodides and formic acid to afford diarylated esters or phosphonates in yields up to 71%.

Key words hydroarylation, diazo compounds, arylacetates, palladium catalysis, cross coupling, phosphonates

The transition-metal-catalyzed transformation of α-diazocarbonyl compounds has become a standard method in organic synthesis. The approach has traditionally been used for carbene generation in reactions such as X–H insertion (X = C, N, O, S), cyclopropanation, and cycloaddition to nitrites and carbonyl compounds.1 More recently, the scope of their application was widened significantly to include Pd-catalyzed cross-coupling reactions, mostly due to the important contributions made by J. Wang and co-workers.2 Depending on the reaction conditions, two types of cross-coupling reactions can be carried out: (i) with retention of diazo group leading to formation of aryl-substituted diazo compound;3 (ii) with the loss of diazo function (Scheme 1).

In the latter case, a organopalladium intermediate that is generated can be captured with a nucleophile.4–6 The hydride ion generated from formic acid is a suitable nucleophile for this type reaction. Our research group has elaborated Pd-catalyzed three-component hydroarylation coupling: aryl iodides reacted with α-diazocarboxylates/α-diazophosphonates and formic acid to generate mono- or diarylace-2
tates and diarylphosphonates.

Recently, J. Wang and co-workers have reported Pd-catalyzed reductive coupling of ethyl diazoacetate (EDA) with aryl iodides leading to the formation of α,α-diarylacetates. Although their methodology provides high yield and wide scale of products, it requires a stoichiometric amount of silver carbonate.7

The coupling of aryl iodides with EDA in the presence of formic acid and Et3N was investigated previously by our research team (Scheme 2).8

A number of aryl iodides were subjected to three-component hydroarylation under the optimized reaction conditions. Exploration of substrates containing electron-withdrawing groups (EWG) as well as iodobenzene allowed a range of ethyl arylacetates 2 to be synthesized in respectable yields (50–85%).

In this context, we have been interested in continuing our previous studies in an attempt to extend our method to a wider range of substrates. Herein we report a solution to this issue.
The coupling of methyl 4-iodobenzoate (1a) with phenyldiazoacetate (3a) in the presence of formic acid and Et₃N was investigated as a model reaction for the preparation of diarylated products (Table 1).

### Table 1 Optimization of the Reaction Conditions in the Model Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂(PPh₃)₂</td>
<td>Et₃N</td>
<td>MeCN</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>Pd₂dba₂+PPh₃</td>
<td>Et₃N</td>
<td>MeCN</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>PdCl₂(PCy₃)₂</td>
<td>Et₃N</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄</td>
<td>Et₃N</td>
<td>MeCN</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂(PPh₃)₂</td>
<td>Et₃N</td>
<td>1,2-DCE</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh₃)₄</td>
<td>Et₃N</td>
<td>benzene</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>Pd(PPh₃)₄</td>
<td>Et₃N</td>
<td>EtOH</td>
<td>traces</td>
</tr>
<tr>
<td>8</td>
<td>Pd(PPh₃)₄</td>
<td>Et₃N</td>
<td>THF</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>Pd(PPh₃)₄</td>
<td>Et₃N</td>
<td>CHCl₃</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>PdCl₂(PPh₃)₂</td>
<td>Et₃N</td>
<td>1,2-DCE</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>PdCl₂(PPh₃)₂</td>
<td>DBU</td>
<td>1,2-DCE</td>
<td>traces</td>
</tr>
<tr>
<td>12</td>
<td>PdCl₂(PPh₃)₂</td>
<td>Py</td>
<td>1,2-DCE</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>PdCl₂(PPh₃)₂</td>
<td>DIPEA</td>
<td>1,2-DCE</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>PdCl₂(PPh₃)₂</td>
<td>K₂CO₃</td>
<td>1,2-DCE</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>PdCl₂(PPh₃)₂</td>
<td>Et₃N</td>
<td>1,2-DCE</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>PdCl₂(PPh₃)₂</td>
<td>Et₃N</td>
<td>1,2-DCE</td>
<td>31</td>
</tr>
<tr>
<td>17</td>
<td>PdCl₂(PPh₃)₂</td>
<td>Et₃N</td>
<td>1,2-DCE</td>
<td>55</td>
</tr>
</tbody>
</table>

a Reaction conditions: 1a (0.5 mmol), 2a (0.75 mmol), base (2.5 mmol), HCO₂H (0.5 mmol), Pd catalyst (0.05 mmol), reflux.

Screening of catalytic systems revealed that application of palladium catalysts Pd(PPh₃)₂ and PdCl₂(PPh₃)₂ was more effective than Pd₂dba₁ (Table 1, entries 1–3). The investigated chemical reaction appeared to be sensitive not only to the selected catalyst but also to the choice of solvent and base. The reaction afforded hydroarylated product 4a with higher yield (entries 5, 10) using 1,2-DCE as solvent. Triethylamine appeared to be the best base for this reaction; other bases such as K₂CO₃, pyridine, DIPEA or DBU were found to be ineffective or less effective in this reaction.

Reaction temperature variation was further investigated. Attempts to obtain hydroarylated product 4a at room temperature failed. Increase of reaction temperature greatly influenced the amount of synthesized product. In summary, it was found that the most favorable conditions were: PdCl₂(PPh₃)₂ as the catalyst, triethylamine as the base, 1,2-DCE as the solvent, and reflux temperature (Table 1, entry 10).

The coupling of aryl iodides 1 with α-aryl diazoacetates 3 in the presence of formic acid and triethylamine provided diarylacetas 4a–l in a yield up to 71% (Table 2). The scope of the proposed method was examined by application of ethyl α-aryl diazocarboxylates (3a–d) in the hydroarylation reaction with a series of aryl iodides 1 under the optimized reaction conditions.

### Table 2 Hydroarylation of α-Aryldiazoacetates 3 with Aryl Iodides 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ar</th>
<th>Product</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H (3a)</td>
<td>p-MeO₂CC₆H₄ (1a)</td>
<td>4a</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>H (3a)</td>
<td>m-MeO₂CC₆H₄ (1b)</td>
<td>4b</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>H (3a)</td>
<td>3-C₆H₄N (1c)</td>
<td>4c</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>H (3a)</td>
<td>p-NCC₆H₄ (1d)</td>
<td>4d</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>H (3a)</td>
<td>p-O₂NC₆H₄ (1e)</td>
<td>4e</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>H (3a)</td>
<td>p-F₃CC₆H₄ (1f)</td>
<td>4f</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>H (3a)</td>
<td>p-AcC₆H₄ (1g)</td>
<td>4g</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>H (3a)</td>
<td>m-MeC₆H₄ (1h)</td>
<td>4h</td>
<td>trace</td>
</tr>
<tr>
<td>9</td>
<td>p-CN (3b)</td>
<td>p-O₂NC₆H₄ (1e)</td>
<td>4i</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td>p-CN (3b)</td>
<td>m-MeO₂CC₆H₄ (1b)</td>
<td>4j</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>p-MeO₂C₆H₄ (3c)</td>
<td>m-MeC₆H₄ (1a)</td>
<td>4k</td>
<td>43</td>
</tr>
<tr>
<td>12</td>
<td>m-Me (3d)</td>
<td>p-NCC₆H₄ (1d)</td>
<td>4l</td>
<td>64</td>
</tr>
</tbody>
</table>

a Reaction conditions: 1 (0.5 mmol), 2 (0.75 mmol), MeCN (1.25 mmol), HCO₂H (0.5 mmol), Pd(PPh₃)₂Cl₂ (0.025 mmol), DCE, reflux for 2 h.

Exploration of EWG-containing aryl iodides and 3-iodopryidine allowed phenylarylacetates 4a–g to be synthesized in good yields (40–71%). Aryl iodide containing electron-donating groups (m-tolyl iodide) exhibited poor reactivity and provided product 4h in trace amounts (Table 2, entry 8). A significant influence of the electronic effects of substituents on the aromatic ring of the diazo compound was observed. It was opposed to that of aryl iodides: the presence of electron-withdrawing group on the benzene ring of diazo compound 3 decreased the yield of product compared with that of unsubstituted phenyldiazoacetate 3a (entries 9–11). In contrast, diazocarboxylate 3d, containing an electron-donating m-CH₃ group, provided good yield of product 4l (entry 12).

The phosphonate (PO₃²⁻) moiety is a common structural fragment that is present in a wide range of biologically active compounds. Despite structural and electronic differences between phosphonate and carboxylic functionalities (in terms of size, shape, acidity, and geometry) the
phosphonate functionality is regarded as a bioisostere of the carboxylic group. α-Diazophosphonates have received much more attention in organic synthesis in recent years; they are widely used for the preparation of derivatives of phosphonic acids.\(^{11}\)

We also applied the above procedure for the synthesis of diarylmethylphosphonates 6a–e (Table 3). Diazophosphonates 5 exhibited comparable reactivity under analogous reaction conditions yielding the corresponding α,α-diarylphosphonates 6a–e in good yield.

**Table 3** Hydroarylation of Diazophosphonates 5 with Aryl Iodides 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>R (^{1})</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-MeO</td>
<td>p-MeO,C</td>
<td>6a</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>p-O,N</td>
<td>6b</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>p-MeO,C</td>
<td>6c</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>p-NC</td>
<td>6d</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>p-Ac</td>
<td>6e</td>
<td>71</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\) Reaction conditions: 1 (0.5 mmol), 5 (0.5 mmol), Et\(_3\)N (1.25 mmol), HCO\(_2\)H (0.5 mmol), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (0.025 mmol), DCE, reflux for 4 h.

\(^{2}\) Isolated yield.

The proposed mechanism of hydroarylation is presented in Scheme 3. Palladium dichloride complex can be easily reduced by formic acid resulting in Pd(0) species. The catalytic cycle starts with oxidative addition to form arylpalladium iodide complex A. Then addition of diazo compound to this complex could generate carbene complex B,\(^{12}\) Migration of the aryl group to the carbene center, which is now described in several publications,\(^{13,14}\) would produce benzylic intermediate C. The exchange complex D can be easily produced by substitution of halogen with formate anion followed by liberation of carbon dioxide (complex E). Reductive elimination should provide the product simultaneously with regeneration of the Pd(0) species.

In conclusion, this report describes a simple method for palladium-catalyzed hydroarylation of diazocarboxylates and diazophosphonates in the presence of formic acid. The proposed reaction can serve as a pathway for the preparation of diarylated carboxylic acid and phosphonic acid derivatives that are otherwise difficult to access. A range of arylated products were synthesized in 35–71% yield by applying this methodology.

All solvents were distilled prior to use. Acetonitrile and 1,2-dichloroethane were dried by distillation over P\(_2\)O\(_5\). Chromatography was carried out using 230–400 mesh silica gel (Merck 40/60). \(^{1}H\) NMR spectra were recorded in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl\(_3\), \(\delta = 7.26\) ppm). \(^{13}C\) (\(\delta\)) NMR spectra were collected with commercial Agilent 400-MR (400 MHz) instrument. Chemical shifts are reported in ppm from tetramethylsilane. HRMS spectra were recorded with a commercial apparatus. Published procedures were applied for the synthesis of aryldiazoacetates (3)\(^{1a}\) and aryldiazophosphonates (5).\(^{1h}\)

**Pd-Catalyzed Cross-Coupling between Aryl Iodides and Aryldiazocarboxylates; Typical Procedure A**

To a mixture of aryl iodide (1a–h; 0.5 mmol), aryldiazoacetate (3a–d; 0.75 mmol), and PdCl\(_2\)(PPh\(_3\))\(_2\) (18 mg, 0.025 mmol) in a Schlenk flask under argon atmosphere, Et\(_3\)N (127 mg, 1.25 mmol) and formic acid (23 mg, 0.5 mmol) in DCE (3 mL) were added. The mixture was stirred and heated at 80 °C until 1a–h disappeared (2–4 h, monitoring by TLC). Solvent was evaporated under reduced pressure. Pure product 4 was isolated by column chromatography (EtOAc/petrol ether, 1:5 v/v).

**Pd-Catalyzed Cross-Coupling between Aryl Iodides and Aryldiazophosphonates; Typical Procedure B**

To a mixture of aryl iodide (1; 0.5 mmol), aryldiazophosphonate (5a–b; 0.5 mmol), and PdCl\(_2\)(PPh\(_3\))\(_2\) (18 mg, 0.025 mmol) in a Schlenk flask under argon atmosphere, Et\(_3\)N (127 mg, 1.25 mmol) and formic acid (23 mg, 0.5 mmol) in DCE (3 mL) were added. The mixture was stirred and heated at 80 °C for 3 h. Solvent was evaporated under reduced pressure. Pure product 5 was isolated by column chromatography (EtOAc/petrol ether, 1:1 v/v).
Characterization of Synthesized Products

Ethyl [4-Methoxy(phenyl)phenyl]acetate (4a)
Prepared according to general procedure A from methyl 4-iodobenzene and phenyldiazooacetate. Reaction time 2 h.
Yield: 104 mg (70%); colorless oil.

\[
\begin{align*}
\text{IR (film)}: & \ 1721, 1677, 1391, 1331, 1328, 1297, 1286, 1278, 1264, 146, 141, 1.41. \\
\text{HRMS (ESI)}: & \quad \text{m/z} [M+H]^+ \text{ calcld for } C_{18}H_{18}O_4: 299.1283; \text{ found: } 299.1278.
\end{align*}
\]

Ethyl [3-Methoxy(phenyl)phenyl]acetate (4b)
Prepared according to general procedure A from methyl 3-iodobenzene and phenyldiazooacetate. Reaction time 2.5 h.
Yield: 64 mg (53%); colorless oil.

\[
\begin{align*}
\text{IR (film)}: & \ 1730, 1600 cm^{-1}. \\
\text{HRMS (ESI)}: & \quad \text{m/z} [M+H]^+ \text{ calcld for } C_{18}H_{18}O_4: 299.1283; \text{ found: } 299.1278.
\end{align*}
\]

Ethyl (Pyridin-3-yl)(phenyl)acetate (4c)
Prepared according to general procedure A from 3-iodopyridine and phenyldiazooacetate. Reaction time 2.5 h.
Yield: 64 mg (53%); colorless oil.

\[
\begin{align*}
\text{IR (film)}: & \ 1730, 1600 cm^{-1}. \\
\text{NMR spectral data for this compound were consistent with those in the literature.}^{7}
\end{align*}
\]

Ethyl [4-(Trifluoromethyl)phenyl](phenyl)acetate (4d)
Prepared according to general procedure A from 4-trifluoromethyl-1-iodobenzene and phenyldiazooacetate. Reaction time 3 h.
Yield: 85 mg (55%); colorless oil.

\[
\begin{align*}
\text{IR (film)}: & \ 1721, 1677, 1391, 1331, 1328, 1297, 1286, 1278, 1264, 146, 141, 1.41. \\
\text{NMR spectral data for this compound were consistent with those in the literature.}^{7}
\end{align*}
\]
Ethyl 3-[(3-methoxy carbonyl)phenyl][4-cyanophenyl]acetate (4j)
Prepared according to general procedure A from methyl 4-iodobenzoate and (3-methylphenyl)diazoacetate. Reaction time 2 h.
Yield: 56 mg (35%); colorless oil.

\[ 1^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta = 7.99 (d, J = 8.0 Hz, 4 H), 7.37 (d, J = 8.0 Hz, 4 H), 5.09 (s, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 3.89 (s, 6 H), 1.24 (t, J = 7.1 Hz, 3 H). \]

\[ 1^3C\{^1H\} \text{ NMR (100 MHz, CDCl}_3\text{): } \delta = 172.1, 166.6, 142.9, 129.9, 129.4, 128.6, 61.6, 56.9, 52.1, 14.1. \]

IR (film): 1715, 1610, 1286 cm\(^{-1}\).


Ethyl Bis[4-(methoxy carbonyl)phenyl]phenylacetate (4k)
Prepared according to general procedure A from methyl 4-iodobenzoate and (4-(methoxy carbonyl)phenyl)diazoacetate. Reaction time 2 h.
Yield: 76 mg (43%); colorless oil.

\[ 1^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta = 7.99 (d, J = 8.0 Hz, 4 H), 7.37 (d, J = 8.0 Hz, 4 H), 5.09 (s, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 3.89 (s, 6 H), 1.24 (t, J = 7.1 Hz, 3 H). \]

\[ 1^3C\{^1H\} \text{ NMR (100 MHz, CDCl}_3\text{): } \delta = 171.2, 166.6, 142.9, 129.9, 129.4, 128.6, 61.6, 56.9, 52.1, 14.1. \]

IR (film): 1725, 1610, 1280 cm\(^{-1}\).

Anal. Calcd for C\(_{32}\)H\(_{32}\)O\(_7\): C, 70.58; H, 5.30; N, 4.33. Found: C, 70.41; H, 5.34; N, 4.24.

Ethyl (3-Methylphenyl)[4-cyanophenyl]acetate (4l)
Prepared according to general procedure A from methyl 4-iodobenzoate and (4-cyanophenyl)diazoacetate. Reaction time 2 h.
Yield: 89 mg (64%); colorless oil.

\[ 1^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta = 7.61 (d, J = 8.2 Hz, 2 H), 7.44 (d, J = 8.2 Hz, 2 H), 7.52–7.48 (m, 1 H), 7.46–7.40 (m, 3 H), 5.09 (s, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 3.91 (s, 3 H), 1.26 (t, J = 7.1 Hz, 3 H). \]

\[ 1^3C\{^1H\} \text{ NMR (100 MHz, CDCl}_3\text{): } \delta = 171.5, 144.1, 138.7, 137.3, 132.3, 129.4, 129.1, 128.8, 128.5, 125.4, 118.7, 111.1, 61.6, 56.9, 21.4, 14.1. \]

IR (film): 2227, 1731, 1607 cm\(^{-1}\).

Anal. Calcd for C\(_{17}\)H\(_{14}\)N\(_2\)O\(_4\): C, 65.81; H, 4.52; N, 9.03. Found: C, 65.93; H, 4.73; N, 8.93.

Diethyl [4-(methoxycarbonyl)phenyl][phenyl]methylphosphonate (6a)
Prepared according to general procedure B from methyl 4-iodobenzoate and diethyl 1-diazo-4-methoxyphenyl)methylphosphonate.
Yield: 129 mg (66%); colorless oil.
Diethyl (4-Acetylphenyl)(phenyl)methylphosphonate (6e)
Prepared according to general procedure B from 4-iodoacetophenone and diethyl 1-diazo-phenylmethylphosphonate.

Yield: 100 mg (71%); colorless oil.

1H NMR (400 MHz, CDCl3): δ = 7.90 (d, J = 8.2 Hz, 2 H), 7.63 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 8.2 Hz, 2 H), 7.35-7.30 (m, 2 H), 7.28-7.23 (m, 1 H), 4.49 (d, J = 25.0 Hz, 1 H), 4.03–3.93 (m, 2 H), 3.92–3.77 (m, 2 H), 2.57 (s, 3 H), 1.13 (t, J = 7.1 Hz, 3 H), 1.10 (t, J = 7.1 Hz, 3 H).

13C{1H} NMR (100 MHz, CDCl 3): δ = 197.6, 142.3, 135.8, 129.6, 129.4, 129.3, 128.7, 128.5, 127.4, 62.9 (d, J = 6.6 Hz), 62.6 (d, J = 6.6 Hz), 51.2 (d, J = 138.4 Hz), 26.5, 16.1.

31P NMR (162 MHz, CDCl3): δ = 24.2.


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