Palladium-Catalyzed Cross-Coupling of Arenediazonium Salts with Organoundium or Organobismuth Reagents

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Abstract

Arylindium and isolated triarylbismuth compounds generated in situ react as nucleophiles with arenediazonium salts in palladium-catalyzed cross-coupling reactions to give substituted biphenyls.

Key words palladium catalysis, cross-coupling, arenediazonium salts, organoundium compounds

Received: 17.08.2018
Accepted after revision: 07.09.2018
Published online: 11.10.2018

In spite of recent interesting developments in the synthesis of biaryl compounds, such as C–H activation,\textsuperscript{1} hydroarylations of arynes generated in situ,\textsuperscript{2} and dehydro-Diels–Alder reactions,\textsuperscript{3} transition-metal-catalyzed cross-coupling reactions remain the most general and reliable methods.\textsuperscript{4,5} The most commonly used cross-coupling reaction for this synthetic application is the Suzuki–Miyaura reaction,\textsuperscript{7} which uses arylboronic acids\textsuperscript{8} or their derivatives\textsuperscript{9} as nucleophilic partners. Less common, but still intensively investigated, are arylsilicon,\textsuperscript{10} arylzinc,\textsuperscript{11} aryltin,\textsuperscript{12} and arylmagnesium\textsuperscript{13} compounds. In most cross-coupling reactions, aryl halides have been used as the electrophilic cross-coupling partner, the phenylindium reagent, with triflates or nonaflates providing alternatives.\textsuperscript{14} A recent addition to the group of fluorinated sulfate leaving groups is the fluorosulfate group, which has also found application in cross-coupling reactions.\textsuperscript{15} Arenediazonium salts are useful but underinvestigated alternatives to aryl halides or triflates in Pd-catalyzed coupling and cross-coupling reactions.\textsuperscript{16}–\textsuperscript{19} Although the majority of Pd-catalyzed coupling reactions investigated for these reagents are Heck-type reactions,\textsuperscript{20}–\textsuperscript{25} there have also been reports on their use in cross-coupling reactions, in particular Suzuki–Miyaura couplings.\textsuperscript{19,26}–\textsuperscript{30} Apart from organoboron compounds, surprisingly few other organometallic reagents have been tested in cross-coupling reactions with arenediazonium salts.\textsuperscript{31}–\textsuperscript{34} Kikukawa et al. reported that the Stille coupling of p-toluenediazonium tetrafluoroborate with phenyl(tributyl)tin resulted in the formation of the desired cross-coupling product in fair yields, but these products were accompanied by large amounts of homocoupling products.\textsuperscript{35} Dughera investigated the same reaction, but with the less common o-benzenedisulfonimide counterion instead of tetrafluoroborate; he reported significantly higher yields of biaryls and only minor amounts of homocoupling products for this and several other examples.\textsuperscript{36} We are aware of only one report that describes a Pd-catalyzed cross-coupling of arenediazonium salts with organometallic reagents other than organoboron or organotin compounds. Dughera and co-workers found that the above-mentioned arenediazonium benzenedisulfonimides can be coupled with triarylindium reagents generated in situ to give diazenes or biaryls in the absence or presence of a Pd catalyst, respectively.\textsuperscript{27} Our interest in the synthesis of biaryls with at least one phenol or methoxybenzene ring\textsuperscript{38,39} as potential phytoalexins\textsuperscript{40} prompted us to explore arylindium\textsuperscript{41} and arylbismuth\textsuperscript{12,42} as alternatives to organoboron compounds in cross-coupling reactions with arenediazonium salts. Both classes of organometallic reagents have previously found applications in Pd-catalyzed cross-coupling reactions, but mostly with aryl, vinyl, or benzyl halides.\textsuperscript{43} We are not aware of any reports describing cross-coupling reactions of arenediazonium salts with organobismuth reagents.

We started this investigation with 4-hydroxybenzenediazonium tetrafluoroborate (3a) and 4-methoxybenzenediazonium tetrafluoroborate (3b) as test substrates. As the nucleophilic cross-coupling partner, the phenylindium reagent 2a, synthesized in situ from phenylmagnesium bromide (equimolar amount to the diazonium salt) and InCl\textsubscript{3} (0.5 equiv), was employed.\textsuperscript{37} In previous investigations on Suzuki–Miyaura-type\textsuperscript{29} and Heck-type couplings\textsuperscript{36} with arenediazonium salts, we found that the solvent and the
Table 1  Optimization of the Cross-Coupling Reaction of Diazonium Salts and Arylindium Reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazonium salt 3</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>Yielda (%) of 4</th>
<th>Yieldb (%) of 5</th>
<th>Yieldb (%) of 6</th>
<th>Yieldb (%) of 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>NaOAc (3.0)</td>
<td>MeOH</td>
<td>4a (14)</td>
<td>32</td>
<td>6a (21)</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>–</td>
<td>MeOH</td>
<td>4a (6)</td>
<td>5</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>NaOAc (3.0)</td>
<td>MeCN</td>
<td>4a (95)</td>
<td>2</td>
<td>n.d.</td>
<td>4aa (91)</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>–</td>
<td>MeCN</td>
<td>4a (8)</td>
<td>20</td>
<td>6a (12)</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>3b</td>
<td>NaOAc (3.0)</td>
<td>MeOH</td>
<td>4ab (18)</td>
<td>20</td>
<td>6b (15)</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>3b</td>
<td>–</td>
<td>MeCN</td>
<td>4ab (5)</td>
<td>10</td>
<td>6b (2)</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>3b</td>
<td>NaOAc (3.0)</td>
<td>MeCN</td>
<td>4ab (80)</td>
<td>9</td>
<td>6b (3)</td>
<td>4ab (73)</td>
</tr>
<tr>
<td>8</td>
<td>3b</td>
<td>–</td>
<td>MeCN</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
</tbody>
</table>

a GC/MS yield; determined by using 1,2-dimethoxybenzene as a standard for calibration.
b No GC/MS yields determined because TLC indicated formation of a complex mixture of products.
c Isolated yield of pure product.
d n.d.: not determined.

The successful conditions for the cross-coupling of diazonium salts 3a and 3b with the phenylindium reagent 2a were applied to four other arenediazonium tetrafluoroborates 3c–f (Scheme 1). Ketone (4ac), ester (4af), and amide groups (4ae) were well tolerated as functional groups in the arenediazonium coupling partner, but the reaction failed completely with a carboxylic acid-substituted diazonium salt (not shown). Moderate yields were obtained for 4ad and 4ba.
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Scheme 1 Examples of cross-coupling reactions of arylindium reagents with arenediazonium tetrafluoroborates

A disadvantage of arylindium reagents is that they are not isolable and, consequently, their structures and compositions are rather ill defined. For this reason, we investigated triarylbumth compounds as alternative cross-coupling partners. These are isolable and can be conveniently synthesized, purified and characterized; moreover, some are even commercially available. In addition, they are less toxic than most other heavy-metal compounds. We investigated the cross-coupling of 3b and BiPh3 (7a) as a test reaction (Table 2). The reactions were monitored by HPLC. Unfortunately, the amount of the homocoupling product biphenyl (5) could not be quantified because its retention time was identical with that of triphenylbismuth under the optimized HPLC conditions. However, an analysis of the reaction mixtures by NMR spectroscopy revealed that biphenyl (5) is indeed a byproduct of these cross-coupling reactions.

In our first experiments, a 3:1 ratio of diazonium salt 3b and BiPh3 was used with 5 mol% of Pd(OAc)2 as a precatalyst. As solvents methanol, acetonitrile, THF, 1,4-dioxane, and DMF were tested at an initial substrate concentration of 0.1 M. For each solvent, the HPLC yield was determined with and without added NaOAc. From this initial solvent screening, only the results for acetonitrile are shown in Table 2 (entries 1 and 2) because for all other solvents, the HPLC yields were lower than 30%. Addition of NaOAc is essential, as it increased the HPLC yield of 4ab from 8% (entry 1) to 51% (entry 2). We also tested several other Pd precatalysts, such as Pd(PPh3)4 (39%) or Pd2(dba)3·CHCl3 (28%), under these conditions (not shown), but we found that only Pd(acac)2 gave the product in a comparable yield and selectivity (entry 3). A wide range of alternative bases known to be efficient promoters of Suzuki–Miyaura couplings (KOAc, CsOAc, Na2CO3, K2CO3, K3PO4, KF, Bu4NF) were investigated, but none was as efficient as NaOAc. Reducing the initial substrate concentration to 0.01 M resulted in a notably lower yield of 4ab (35%) and 6b (11%), even after a reaction

Table 2 Optimization of the Cross-Coupling Reaction of BiPh3 (7a) and Arenediazonium salt 3b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>BiPh3 (equiv)</th>
<th>Catalyst (mol%)</th>
<th>Concentration (mol·L⁻¹)</th>
<th>Time (h)</th>
<th>Additive (equiv)</th>
<th>Yielda (%) of 4ab</th>
<th>Yielda (%) of 6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.33</td>
<td>Pd(OAc)2 (5)</td>
<td>0.10</td>
<td>16</td>
<td>–</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0.33</td>
<td>Pd(OAc)2 (5)</td>
<td>0.10</td>
<td>16</td>
<td>–</td>
<td>51</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>0.33</td>
<td>Pd(acac)2 (5)</td>
<td>0.10</td>
<td>16</td>
<td>–</td>
<td>49</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>0.33</td>
<td>Pd(OAc)2 (5)</td>
<td>0.01</td>
<td>48</td>
<td>–</td>
<td>35</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>0.33</td>
<td>Pd(OAc)2 (5)</td>
<td>0.10</td>
<td>16</td>
<td>TBAB (1.0)</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>0.33</td>
<td>Pd(OAc)2 (5)</td>
<td>0.10</td>
<td>16</td>
<td>TBAH (1.0)</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>0.33</td>
<td>Pd(OAc)2 (5)</td>
<td>0.10</td>
<td>16</td>
<td>TBAF (1.0)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0.50</td>
<td>Pd(OAc)2 (5)</td>
<td>0.10</td>
<td>2.5</td>
<td>–</td>
<td>50</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>1.00</td>
<td>Pd(OAc)2 (10)</td>
<td>1.00</td>
<td>18</td>
<td>–</td>
<td>55</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>1.00</td>
<td>Pd(acac)2 (10)</td>
<td>1.00</td>
<td>18</td>
<td>–</td>
<td>66f</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>–</td>
<td>Pd(OAc)2 (5)</td>
<td>0.10</td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
</tbody>
</table>

a HPLC yield; determined by using 4,4'-di-tert-biphenyl for calibration.
b Reaction without added NaOAc.
c Isolated yield: 66%.
time of 48 hours (entry 4). Further attempts to improve the yield were therefore made at the higher substrate concentration. First, we tested the addition of tetraalkylammonium halides (entries 5–7), because halides are known to stabilize catalytically active Pd species. This approach turned out to be unsuccessful: addition of the bromide or chloride (entries 5 and 6) led to a lower yield of the cross-coupling product and an increased proportion of the homocoupling product 6b. Addition of fluoride led to near complete inhibition of the reaction (entry 7). Next, we tried using BiPh3 in slight excess (entry 8), but we obtained virtually identical yields of 4ab and 6b. Increasing the amount of BiPh3 to one equivalent and the amount of Pd(OAc)2 to 10 mol% resulted in an improved yield of the cross-coupling product and, more importantly, a notable reduction in that of the homocoupling product (entry 9). Replacing Pd(OAc)2 by Pd(acac)2 led eventually to the best reaction conditions, which gave 4ab in 66% HPLC yield (isolated yield 61%), together with 11% (HPLC) of 6b (entry 10).

To gain some insight into the mechanism of the formation of homocoupling product 6b, we undertook a control experiment. Diazonium salt 3b was submitted to the reaction conditions listed in Table 2, entry 1, but in the absence of the cross-coupling partner BiPh3 (entry 11). After 16 hours, the HPLC yield of 6b was only 1%. From this observation, we conclude that the homocoupling product of the arenediazonium partner is not formed through a sequence of reduction and radical dimerization, but more likely through an exchange of aryl groups between Pd–σ-aryl complexes and reductive elimination.

The optimized conditions were applied to eight other diazonium salts 3, which were successfully coupled with BiPh3 (7a) and three other triarylborane reagents 7b–d. The lowest yields were obtained with the ortho-substituted arenediazonium salt 3g (example 4ag) and the electron-deficient para-nitro-substituted arenediazonium salt 3d (examples 4ad and 4cd). Compound 4ah was obtained reproducibly in yields of less than 10% and could not be purified. All other yields were better (40–62%, Scheme 2).

In summary, we have identified conditions for the Pd-catalyzed cross-coupling of arylindium or triarylborane reagents with arenediazonium salts. The solvent, the base, and the initial substrate concentration have significant effects on the yield and selectivity of the reactions.

Funding Information

Financial support from the University of Potsdam is gratefully acknowledged.

Acknowledgment

We thank Evonik for a generous donation of solvents and Umicore (Hanau, Germany) for generous donations of precious metal catalysts.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611001.

References and Notes


(51) Methyl 4-Hydroxy-3-methoxybiphenyl-3-carboxylate (4cf); Typical Example

The diazonium salt 3f (134 mg, 0.50 mmol), triarylbismuthane 7c (265 mg, 0.50 mmol, 1.0 equiv), Pd(acac)2 (15.2 mg, 0.05 mmol, 10 mol%), and NaOAc (123 mg, 1.50 mmol, 3.0 equiv) were suspended in MeCN (0.5 mL, 1.0 M), and the mixture was stirred for 16–18 h at r.t. The mixture was then diluted with EtOAc (30 mL), washed with H2O (30 mL), dried (MgSO4), and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, PE–EtOAc) to give a colorless oil; yield: 66 mg (51%, 0.26 mmol).

IR (ATR): 2999 (bw), 1738 (w), 1675 (m), 1204 (s), 1170 (m) cm–1.

1H NMR (500 MHz, CDCl3): δ = 10.78 (s, 1 H), 8.07 (d, J = 2.2 Hz, 1 H), 7.70 (dd, J = 8.6, 2.2 Hz, 1 H, 7.35 (t, J = 7.9 Hz, 1 H), 7.13 (d, J = 7.7 Hz, 1 H), 7.09–7.03 (m, 2 H, 6.88 (dd, J = 8.2, 2.2 Hz, 1 H), 3.98 (s, 3 H), 3.87 (s, 3 H). 13C NMR (126 MHz, CDCl3): δ = 170.7, 161.2, 160.2, 141.6, 134.6, 132.4, 130.0, 128.4, 119.3, 118.2, 112.7, 112.6, 112.4, 112.4, 112.4, 55.5, 52.5. HRMS (ESI): [M + Na]⁺ calcd for C15H14NaO4: 281.0784; found: 281.0787.