Mild and Highly Selective Palladium-Catalyzed Monoarylation of Ammonia Enabled by the Use of Bulky Biarylphosphine Ligands and Palladacycle Precatalysts

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Mild and Highly Selective Palladium-Catalyzed Monoarylation of Ammonia Enabled by the Use of Bulky Biarylphosphine Ligands and Palladacycle Precatalysts

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Abstract

A method for the palladium-catalyzed arylation of ammonia with a wide range of aryl and heteroaryl halides, including challenging five-membered heterocyclic substrates, is described. Excellent selectivity for monoarylation of ammonia to primary arylamines was achieved under mild conditions or at room temperature by the use of bulky biarylphosphine ligands (L6, L7, and L4) as well as their corresponding aminobiphenyl palladacycle precatalysts (3a, 3b, and 3c). As this process requires neither the use of a glovebox nor high pressures of ammonia, it should be widely applicable.

Primary arylamines, including anilines and heteroarylamines, represent important structural elements found in dyes, polymers, pharmaceuticals, and agrochemicals.1 The presence of heteroarylamines and their derivatives is particularly ubiquitous in drugs as exemplified in a list of the top 200 pharmaceutical products by retail sales in 2011.2 Arylamines are traditionally prepared by the nitration of arenes followed by the reduction of the resulting nitroaromatics.3 However, the desired regioisomer of the nitroaromatics may be inaccessible via electrophilic aromatic substitution, and the use of nitric acid and strong acids often results in low functional group tolerance.3 Moreover, the reduction of nitroaromatics to arylamines may in itself pose an issue of chemoselectivity, further limiting the scope of this multistep approach. The transition metal-catalyzed cross-coupling between (hetero)aryl halides and ammonia provides a direct, regiospecific, and more atom-economical means to synthesize arylamines.4–6 Nevertheless, controlling the chemoselectivity for monoarylation of ammonia represents a significant challenge, since the resulting primary arylamine products are prone to undergo subsequent N-arylation to form undesired di- and triarylamine side-products.4,5 Ammonia surrogates have long been utilized in the synthesis of primary arylamines,7 but their use is significantly less atom-economical than the use of NH3.
A number of research groups including our own have reported the selective palladium-catalyzed arylation of NH₃ to produce primary arylamines with minimal formation of diarylamine side-products. In the case of results from our group, we demonstrated that a Pd catalyst supported by the bayliophosphine ligand, BuDavePhos (L₁, Scheme 1), is reasonably effective for the selective production of the primary arylamines.\(^5\)

Despite the considerable advances, limitations remain. These include: (1) the coupling of aryl halides bearing base-sensitive (e.g., cyano and carbonyl) groups is typically problematic or provide anilines in lower yields when utilizing NaO\(\text{Bu}\) as the base.\(^5\) While one report detailing the use of K\(_3\)PO\(_4\) has appeared,\(^5\)b it necessitates the use of high pressure of NH\(_3\). (2) The substrate scope with respect to heteroaryl halides is generally limited to pyridines and (iso)quinolines,\(^5\) and the Pd-catalyzed coupling of NH\(_3\) with more challenging heterocyclic substrates, such as diazines and five-membered heterocycles, is still unprecedented. Herein, we report the use of bulky bayliophosphine ligands and their corresponding palladium precatalysts that allow the highly selective arylation of NH\(_3\) to generate a wide range of anilines and heteroarylamines in moderate to excellent yields under mild reaction conditions.

Initial experiments focused on identifying optimal conditions for the Pd-catalyzed coupling of chlorobenzene with ammonia, utilizing 3 equivalents of NH\(_3\) and \(\text{Pd(db}a)\)\(_3\) as the Pd source in a minimal amount of solvent (0.125 M) (Table 1). Although L₁ was previously reported to be an excellent ligand for this transformation when 5 equivalents of NH\(_3\) and additional solvents were used (Scheme 1), the ratio of aniline (1) to diphenylamine (2) decreased significantly under these conditions (Table 1, entry 1). We proposed that the appropriate ancillary ligand could decrease the amount of 2, thus we proceeded to examine the effects of bayliophosphine ligands on the selectivity of arylation. We recently reported the use of sterically demanding ligands, Me\(_4\)/BuXPhos (L₂),\(^8\) AurBrettPhos (L₄),\(^8\)f and RockPhos (L₅),\(^8\)e for the efficient cross-coupling of smaller nucleophiles (hydroxide,\(^8\)a fluoride,\(^8\)b,c chloride,\(^8\)c and bromide\(^8\)c) and five-membered heterocyclic electrophiles.\(^8\)d As depicted in Table 1 (entries 2–5), ligands L₂–L₅ provided higher yields of 1 while concomitantly decreasing the formation of 2. To maximize the ratio of 1:2 further, we prepared and examined the effectiveness of new Me\(_3\)(OMe)XPhos-type ligands L₆–L₉,\(^9\) which, like L₂, contain a more conformationally rigid bayranyl backbone as a result of the 3- and 6-methyl groups. We found that the yield of 1 further increased to 92% by using L₆, which bears a dicyclohexylphosphine moiety (Table 1, entry 6). However, decreasing the size of the P-bound groups (L₇ or L₈) or increasing the size of the bottom aromatic ring (L₉) resulted in a decreased ratio of 1:2 (Table 1, entries 7–9), and thus lower yields of 1. Considering our success in using air-stable aminebiphenyl palladacycle precatalysts,\(^1\) we prepared precatalyst 3a, in which the Pd center is pre-ligated with L₆, as a source of Pd catalyst. In general, 3a was shown to be a superior Pd source as compared to the Pd\(_2\)dba\(_3\)/L₆ catalyst, providing faster reaction rates and higher yields in the coupling of NH\(_3\) with various heteroaryl halides (See Table S1 in Supporting Information for comparisons).\(^1\)

Next, we explored the scope of the Pd-catalyzed synthesis of anilines using the optimized conditions (Scheme 2). In the presence of 2 mol % 3a and 2 mol % L₆, electron-rich (4a–4c, 4f), neutral (4d), and deficient aryl chlorides (4e, 4g–4k) could be aminated with NH\(_3\) under mild conditions to afford the corresponding anilines in generally high yields and with excellent selectivity. Remarkably, the base-sensitive cyano and carbonyl groups were reasonably well-tolerated under these conditions (4e, 4g–4k). Chlorobenzenes with vinyl groups (4l) as well as heteroaryl groups (4m–4o) also represent suitable coupling partners. Additionally, the reaction protocol was applicable to the coupling of disubstituted halobenzenes (4p–4v), including the substrates bearing fluoro- and trifluoromethyl groups.

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(4r–4u) as well as unprotected NH₂ groups (4t, 4v). As expected, bromides were found to react preferentially over chlorides bonds (4s, 4u, 4v), while 3,5-dichloroanisole could undergo double amination using excess NH₃ (4w). Furthermore, at 110 °C, we demonstrated that an aryl halide could be coupled to form the aniline with less then 1 mol % precatalyst (4m).

This reaction protocol using catalyst system 3a/L₆ was also successful for the synthesis of an array of six-membered heteroarylamines with exceptionally high selectivity (Scheme 3). Various aminopyridines (5a–5f) and aminoquinolines (5g–5i) were successfully prepared under the conditions. Moreover, the NH₂ group could also be readily incorporated into benzo thiophene (5j) indole (5k), benzo thiazole (5l), benzo oxazole (5m), pyrazine (5n), quinoxaline (5o, 5p), pyrimidine (5q, 5r), pyridazine (5s), and carbazole rings (5t) as well.

Although L₆ efficiently promoted the amination of a number of (hetero)aryl halides (Schemes 2 and 3), we found that the use of L₆ resulted in incomplete conversion of more sterically hindered, ortho-substituted aryl halide and 5-chloro-8-methoxyquinoline (Scheme 4, 6a, 6b). However, high yields of various sterically hindered arylamines were obtained when a precatalyst based on its diaryl analogue L₇ was employed under otherwise identical conditions (Scheme 4).

Additionally, we found that the use of palladacycle precatalysts 3a and 3b also allowed for the coupling between (hetero)aryl halides and NH₃ at room temperature to afford a range of arylamines in high to excellent yields (Scheme 2, 4b, 4f, 4i, 4k, 4o; Scheme 3, 5n, 5p; Scheme 4, 6e), albeit at higher catalyst loading (3–5 mol %).

We have been particularly interested in transition metal-catalyzed processes with five- membered heterocyclic coupling partners due to the ubiquity of these heterocycles in pharmaceuticals. Thus, we proceeded to study the coupling of NH₃ with 4-bromo-1-(4-fluorophenyl)pyrazole as a test substrate (Scheme 5, 7a). While incomplete conversion and poor yields were observed when either L₆ or L₃ was used, with L₄ (with the larger adamantyl group as the substituent on phosphorus) complete conversion was achieved to provide 4-aminopyrazole in 78% yield. In fact, using a catalyst derived from 3c/L₄ (Scheme 5), the selective amination of a wide range of 5-membered heteroaryl halides was readily accomplished to provide various amino-substituted benzothiazoles (7b), indazoles (7c), imidazoles (7d), and pyrazoles (7e, 7f). While 3c/L₄ was less effective for the coupling of 4-bromo-1,3,5-trimethylpyrazole, the use of a catalyst derived from 3b/L₇ provided 4- amino-3,5-dimethylpyrazoles (7g, 7h) in good yields. Of note, the coupling of heterocyclic electrophiles with NH₃ represents a convenient alternative method to synthesize five- membered heteroarylamines, since conventional methods, including cyclizations or annulations, typically involve the use of strong oxidizing agents or acids. To our knowledge, these examples represent the first Pd-catalyzed couplings between NH₃ and five-membered heteroaryl halides, and particularly, challenging and important pyrazole and imidazole substrates.

In summary, we have developed improved catalytic systems for the selective arylation of NH₃ by using L₄ and the new biarylphosphine ligands (L₆ and L₇). These reaction protocols allow for the synthesis of a broad range of functionalized arylamines, including six- and five-membered heteroarylamines, under relatively mild conditions and with an exceptionally high selectivity for monoarylation. We anticipate that this chemistry will be applicable to the general and convenient synthesis of biologically active molecules bearing arylamine functional motifs.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References


9. We have reported the synthesis of Me₃(OMe)³BuXPhos from inexpensive 2,3,6-trimethylphenol, see: Ueda S, Ali S, Fors BP, Buchwald SL. J Org Chem. 2012; 77:2543. See Supporting Information for details of the synthesis of L₆-L₉. [PubMed: 22313416]

11. The use of Pd$_2$dba$_3$ (1 mol %)/L$_6$ (4 mol %) and 3a (2 mol %)/L$_6$ (2 mol %) were compared. See Supporting Information for details.

Scheme 1.
Pd-catalyzed selective arylation of NH$_3$. 

\[
\text{PhCl} + \text{NH}_3 \xrightarrow{\text{Pd}_2(\text{dba})_3 (1 \text{ mol} \%) \atop \text{L1} (5 \text{ mol} \%) \atop \text{NaO}^\text{Bu} (1.4 \text{ equiv}) \atop 1,4\text{-dioxane (0.042 M)} \atop 80 \text{ C, 15 h}} \text{PhNH}_2 + \text{Ph}_2\text{NH} \\
1 \atop 86\% \atop 2 \atop 7\%
\]

L1 (\text{BuDavePhos})
Scheme 2.
Coupling with aryl halides

\[ \text{ArX} + \text{NH}_3 + 3a \text{ (2 mol %), L6 (2 mol %)} \rightarrow \text{ArNH}_2 \]

\[ \text{NaO}^+\text{Bu (1.4 equiv), 1,4-dioxane, temp, 24 h} \]

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<th>Z</th>
<th>C</th>
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<td>(80 °C)</td>
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\[ X = \text{Br} \]
\[ R = \text{SMe (4b), 81% (rt)} \]
\[ R = \text{OBn (4f), 84% (rt)} \]

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<td>(50 °C)</td>
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\[ X = \text{Br} \]
\[ R = \text{Ph (4i), 96% (rt)} \]
\[ R = \text{NEt}_2 (4k), 94% (rt) \]

\[ X = \text{Cl}, 58% (80 °C) \]
\[ X = \text{Cl}, 90% (110 °C) \]
\[ (1:2 = 9:1) \]

\[ X = \text{Cl}, 83% (80 °C) \]
\[ (1:2 = 9:1) \]

\[ X = \text{Br}, 72% (100 °C) \]
\[ (1:2 = 19:1) \]

\[ X = \text{Cl}, 67% (60 °C) \]
\[ (1:2 = 20:1) \]

\[ X = \text{Br}, 72% (100 °C) \]
\[ (1:2 = 19:1) \]

\[ X = \text{Cl}, 87% (50 °C) \]
\[ 97% (rt) \]

\[ X = \text{Cl}, 83% (80 °C) \]
\[ (1:2 = 13:1) \]

\[ X = \text{Cl}, 80% (80 °C) \]
\[ (1:2 = 26:1) \]

\[ X = \text{Br}, 52% (100 °C) \]

\[ NaO^+\text{Bu (2.2 mmol)} \]
\[ \text{NH}_3 (6 mmol), \text{NaO}^+\text{Bu (2.8 mmol)}, \text{dioxane (13 mL)}; 2° \text{amine} \]
\[ \text{identified to be 3,3'-diamino-5,5'-dimethoxydiphenylamine.} \]

\[ \text{Org Lett. Author manuscript; available in PMC 2014 July 19.} \]
Scheme 3.
Coupling with heteroaryl halides\(^a\)

\(^a\) Conditions: HetArX (1 mmol), NH\(_3\) (3 mmol), NaO\(\text{tBu}\) (1.4 mmol), 3a (2 mol %), L6 (2 mol %), dioxane (10 mL, 0.10 M), 24 h; isolated products, average of two runs; ratios of arylamine to diarylamine (1:2\(^{o}\)) determined by \(^1\)H NMR. \(^b\) \(^1\)H NMR yield of crude product. \(^c\) NaO\(\text{tBu}\) (2.2 mmol). \(^d\) 3a and L6 (3 mol %), dioxane (0.143 M). \(^e\) HetArX (2 mmol), NH\(_3\) (6 mmol), NaO\(\text{tBu}\) (2.8 mmol), dioxane (13 mL).
Scheme 4.  
Coupling with bulky (hetero)aryl halides\textsuperscript{d}  

\textsuperscript{a} Conditions: (Het)ArX (1 mmol), NH\textsubscript{3} (3 mmol), NaO\textsubscript{t}Bu (1.4 mmol), 3b (2 mol %), L7 (2 mol %), dioxane (10 mL, 0.10 M), 24 h; isolated products, average of two runs; ratios of arylamine to diarylamine (1°:2°) determined by \textsuperscript{1}H NMR.  

\textsuperscript{b} Conditions: (Het)ArX (0.25 mmol), NH\textsubscript{3} (0.75 mmol), NaO\textsubscript{t}Bu (0.35 mmol), Pd\textsubscript{2}dba\textsubscript{3} (1 mol %), L6/L7 (4 mol %), dioxane (2.5 mL, 0.10 M), 100 °C, 24 h; \textsuperscript{1}H NMR yield of crude product.  

\textsuperscript{c} 3b and L7 (5 mol %), dioxane (0.143 M).
Scheme 5.
Coupling with five-membered substrates$^a$

$^a$ Conditions: HetArX (1 mmol), NH$_3$ (3 mmol), NaO'Bu (1.4 mmol), 3c (2 mol %), L4 (2 mol %), dioxane (10 mL, 0.10 M), 20–24 h; isolated products, average of two runs. $^b$ Conditions: HetArX (0.25 mmol), NH$_3$ (0.75 mmol), NaO'Bu (0.35 mmol), Pd$_2$dba$_3$ (1 mol %), L6/L3/L4 (4 mol %), dioxane (2.5 mL, 0.10 M), 120 °C, 20 h; $^1$H NMR yield of crude product. $^c$ 3c and L4 (5 mol %), dioxane (7 mL, 0.143 M). $^d$ $^1$H NMR yield of crude product. $^e$ 3b and L7 (2 mol %).

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<td>7b</td>
<td>X = Cl</td>
<td>98% (rt)$^c$</td>
<td>79% (80 °C)</td>
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<td>7c</td>
<td>X = Cl</td>
<td>79% (80 °C)</td>
<td>Br, 90% (80 °C)</td>
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<td>7d</td>
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<td>7e</td>
<td>X = Br</td>
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<tr>
<td>7f</td>
<td>X = Br</td>
<td>50% (100 °C)</td>
<td>40% (78%$^d$ (100 °C)$^e$</td>
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<td>50% (100 °C)</td>
<td>40% (78%$^d$ (100 °C)$^e$</td>
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Table 1

Ligand Optimization for the Selective Pd-catalyzed Arylation of NH₃.°

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<td>9</td>
<td>L₉</td>
<td>43</td>
<td>28</td>
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°Conditions: PhCl (0.5 mmol), NH₃ (1.5 mmol), NaOBDu (0.7 equiv), Pd₂dba₃ (1 mol %), ligand (5 mol %), dioxane (4 mL, 0.125 M), 80°C, 5 h.

b Determined by GC.

c 13 h.

d Average of two runs.