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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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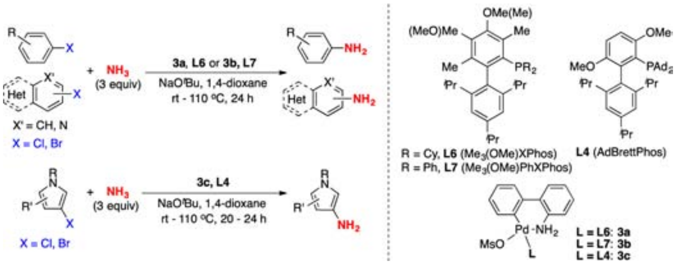
ABSTRACT



A method for the Pd-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 rt 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

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(1) (a) Travis, A. S. *Anilines: Historical background In Patai's Chemistry of Functional Groups*, Online; John Wiley & Sons, Ltd.: New York, 2009, DOI: 10.1002/9780470682531.pat0383. (b) Travis, A. S. *Manufacture and uses of the anilines: A vast array of processes and products In Patai's Chemistry of Functional Groups*, Online; John Wiley & Sons, Ltd: New York, 2009, DOI: 10.1002/9780470682531.pat0395. (c) Lawrence, S. A. *Amines: Synthesis, Properties and Application*; Cambridge University Press: Cambridge, 2004.

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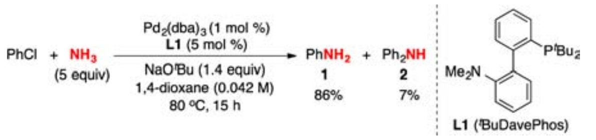
10.1021/ol401612c

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 NH$_3$.

A number of research groups including our own[5] have reported the selective Pd-catalyzed arylation of NH$_3$ 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 biarylphosphine ligand, ^{t}BuDavePhos (**L1**, Scheme 1), is reasonably effective for the selective production of the primary arylamines.[5c]

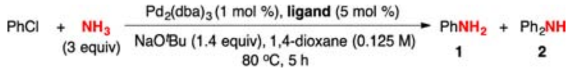
Scheme 1. Pd-Catalyzed Selective Arylation of NH$_3$



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^{t}Bu as the base.[5] While one report detailing the use of K$_3$PO$_4$ has appeared,[5b] it necessitates the use of a 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 heterocylic substrates, such as diazines and five-membered heterocycles, is still unprecedented. Herein, we report the use of bulky biarylphosphine 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.

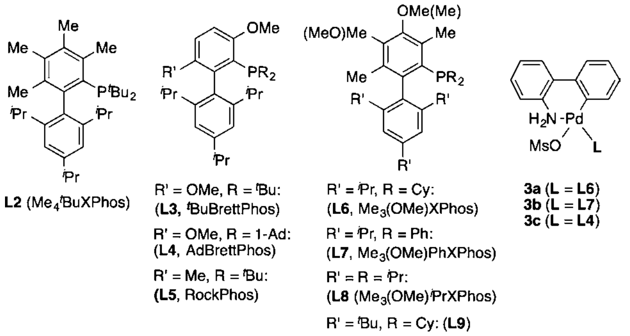
Initial experiments focused on identifying optimal conditions for the Pd-catalyzed coupling of chlorobenzene with ammonia, utilizing 3 equiv of NH$_3$ and Pd$_2$(dba)$_3$ as the Pd source in a minimal amount of solvent (0.125 M) (Table 1). Although **L1** was previously reported to be an excellent ligand for this transformation when 5 equiv 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 biarylphosphine ligands on the selectivity of arylation. We recently reported the use of sterically demanding ligands, Me$_4$^{t}BuXPhos (**L2**),[8a] ^{t}BuBrettPhos (**L3**),[8b,c] AdBrettPhos (**L4**),[8d] and RockPhos (**L5**),[8e] for the efficient cross-coupling of smaller nucleophiles (hydroxide,[8a] fluoride,[8b,e] chloride,[8c] and bromide[8c]) and five-membered heterocyclic electrophiles.[8d] 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 biaryl backbone as a result of the 3- and 6-methyl groups. We found that the

Table 1. Ligand Optimization for the Selective Pd-Catalyzed Arylation of NH$_3$[a]



entry	ligand	conv (%)[b]	yield of **1** (%)[b]	yield of **2** (%)[b]
1	**L1**	100	72	15
2[c]	**L2**	100	80	3
3	**L3**	100	89[d]	4[d]
4	**L4**	100	87	3
5	**L5**	100	80	4
6	**L6**	100	92[d]	2[d]
7	**L7**	100	76	16
8	**L8**	54	22	20
9	**L9**	43	28	7

[a] Conditions: PhCl (0.5 mmol), NH$_3$ (1.5 mmol), NaO^{t}Bu (0.7 equiv), Pd$_2$(dba)$_3$ (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.



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(5) For Pd chemistry, see: (a) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028. (b) Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049. (c) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354. (d) Schulz, T.; Torborg, C.; Enthaler, S.; Schäffner, B.; Dumrath, A.; Spannenberg, A.; Neumann, H.; Börner, A.; Beller, M. *Chem.—Eur. J.* **2009**, *15*, 4528. (e) Dumrath, A.; Lübbe, C.; Neumann, H.; Jackstell, R.; Beller, M. *Chem.—Eur. J.* **2011**, *17*, 9599. (f) Lundgren, R. J.; Sappong-Kumankumah, A.; Stradiotto, M. *Chem.—Eur. J.* **2010**, *16*, 1983. (g) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4071. (h) Alsabeh, P. G.; Lundgren, R. J.; McDonald, R.; Johansson Seechurn, C. C. C.; Colacot, T. J.; Stradiotto, M. *Chem.—Eur. J.* **2013**, *19*, 2131.

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(9) We have reported the synthesis of Me$_3$(OMe)^{t}BuXPhos from inexpensive 2,3,6-trimethylphenol; see: Ueda, S.; Ali, S.; Fors, B. P.; Buchwald, S. L. *J. Org. Chem.* **2012**, *77*, 2543. See SI for details of the synthesis of **L6**−**L9**.

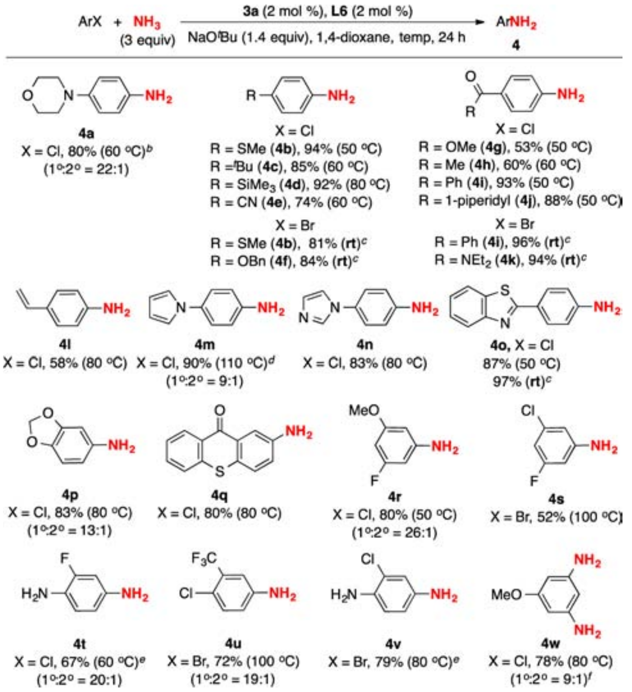
yield of **1** further increased to 92% by using **L6**, which bears a dicyclohexylphosphine moiety (Table 1, entry 6). However, decreasing the size of the P-bound groups (**L7** or **L8**) or increasing the size of the bottom aromatic ring (**L9**) resulted in a decreased ratio of **1:2** (Table 1, entries 7–9), and thus lower yields of **1**. Considering our success in using air-stable aminobiphenyl palladacycle precatalysts,[10] we prepared precatalyst **3a**, in which the Pd center is preligated with **L6**, as a source of the Pd catalyst. In general, **3a** was shown to be a superior Pd source as compared to the Pd_2dba_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 (SI) for comparisons).[11]

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 (**4r**–**4u**) as well as unprotected NH_2 groups (**4t**, **4v**). As expected, bromides were found to react preferentially over chloride bonds (**4s**, **4u**, **4v**), while 3,5-dichloroanisole could undergo double amination using excess NH_3 (**4w**). Furthermore, at 110 °C, we demonstrated that an aryl halide could be coupled to form the aniline with < 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 NH_2 group could also be readily incorporated into benzothiophene (**5j**), indole (**5k**), benzothiaole (**5l**), benzoxazole (**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).

Scheme 2. Coupling with Aryl Halides[a]



[a] Conditions: ArX (1 mmol), NH_3 (3 mmol), NaO^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°) determined by ^1H NMR. [b] **3a** and **L6** (2.5 mol %). [c] **3a** and **L6** (3–5 mol %), dioxane (0.143 M), 24–36 h. [d] **3a** and **L6** (0.7 mol %), dioxane (12 mL). [e] NaO^tBu (2.2 mmol). [f] NH_3 (6 mmol), NaO^tBu (2.8 mmol), dioxane (13 mL); 2° amine identified to be 3,3′-diamino-5,5′-dimethoxydiphenylamine.

Additionally, we found that the use of palladacycle precatalysts **3a** and **3b** also allowed for the coupling between (hetero)aryl halides and NH_3 at rt 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 a higher catalyst loading (3–5 mol %).

We have been particularly interested in transition-metal-catalyzed processes with five-membered heterocyclic coupling partners[8d,10c] due to the ubiquity of these heterocyles in pharmaceuticals.[2] Thus, we proceeded to study the coupling of NH_3 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 five-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 NH_3 represents a convenient alternative

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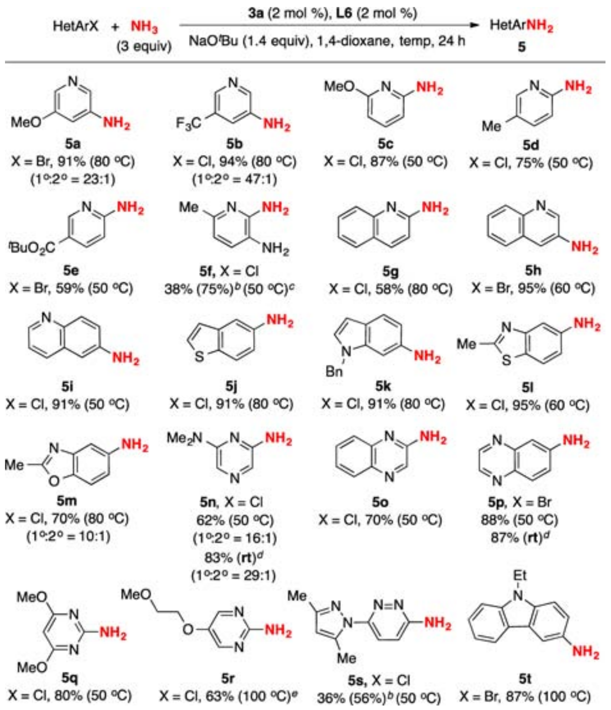
(10) (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916. (b) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876. (c) Yang, Y.; Oldenhuis, N. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *52*, 615.

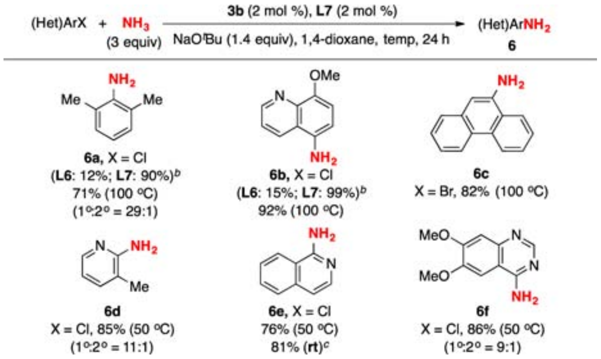
(11) The use of Pd_2dba_3 (1 mol %)/**L6** (4 mol %) and **3a** (2 mol %)/**L6** (2 mol %) were compared. See SI for details.

Scheme 3. Coupling with Heteroaryl Halides[a]



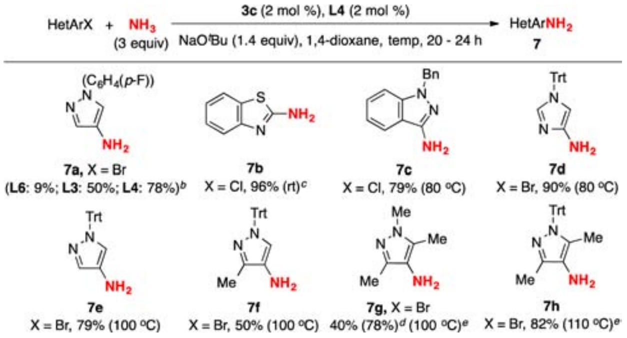
[a] Conditions: HetArX (1 mmol), NH_3 (3 mmol), NaO^{t}Bu (1.4 mmol), **3a** (2 mol %), **L6** (2 mol %), dioxane (10 mL, 0.10 M), 24 h; isolated products, average of two runs; ratios of arylamine to diarylamine (1°:2°) determined by ^{1}H NMR. [b] ^{1}H NMR yield of crude product. [c] NaO^{t}Bu (2.2 mmol). [d] **3a** and **L6** (3 mol %), dioxane (0.143 M). [e] HetArX (2 mmol), NH_3 (6 mmol), NaO^{t}Bu (2.8 mmol), dioxane (13 mL).

Scheme 4. Coupling with Bulky (Hetero)aryl Halides[a]



[a] Conditions: (Het)ArX (1 mmol), NH_3 (3 mmol), NaO^{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 ^{1}H NMR. [b] Conditions: (Het)ArX (0.25 mmol), NH_3 (0.75 mmol), NaO^{t}Bu (0.35 mmol), Pd_2dba_3 (1 mol %), **L6/L7** (4 mol %), dioxane (2.5 mL, 0.10 M), 100 °C, 24 h; ^{1}H NMR yield of crude product. [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^{t}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^{t}Bu (0.35 mmol), Pd_2dba_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 %).

method to synthesize five-membered heteroarylamines, since conventional methods, including cyclizations or annulations, typically involve the use of strong oxidizing agents or acids.[12] To our knowledge, these examples represent the first Pd-catalyzed couplings between NH_3 and five-membered heteroaryl halides and, particularly, challenging and important pyrazole and imidazole substrates.[8d,10c]

In summary, we have developed improved catalytic systems for the selective arylation of NH_3 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.

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Supporting Information Available. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare the following competing financial interest(s): M.I.T. has patents on some of the ligands and precatalysts used in this work from which S.L.B. receives royalty payments.