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Efficient Pd-Catalyzed Amination of Heteroaryl Halides

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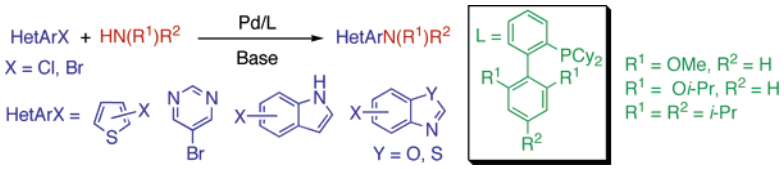
ABSTRACT



The Pd-catalyzed amination of a variety of heteroaryl halides has been accomplished by utilizing bulky electron-rich biaryl phosphine ligands. In particular, we report the first couplings of amines with chloro- and bromoindoles bearing a free NH, as well as the first Pd-catalyzed aminations of a 5-halopyrimidine.

The Pd-catalyzed formation of C−N bonds is a rapidly expanding area of research.[1] Since the first general and efficient procedures were discovered,[2] efforts toward increasing the substrate scope and efficiency have been investigated. In some cases, the use of alternative bases or solvents can be beneficial; however, electronic and steric tuning of the supporting ligand has had the most impact on increasing reactivity and efficacy in these processes.[1] A few years ago we reported the use of biaryl monophosphine ligands for a variety of Pd-catalyzed reactions.[3] These ligands have been shown to be very effective in C−N bond-forming processes.[4,5] In this paper, we describe their use in the Pd-catalyzed amination of several heteroaryl halides.

As heterocycles represent a very important class of compounds in biology and pharmaceuticals,[6] the selective functionalization of these molecules is of great interest. The use of Pd-catalyzed C−N coupling with heteroaryl substrates has been documented in many instances.[1,7−12] We sought to expand the scope of heterocyclic substrates that could be utilized, with a particular focus on employing substrates not amenable toward nucleophilic aromatic substitution.

(1) (a) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; John Wiley & Sons: Weinheim, 2004. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (c) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley-Interscience: Weinheim, 2002.

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(6) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; John Wiley & Sons: Weinheim, 1997.

(7) (a) Luker, T. J.; Beaton, H. G.; Whiting, M.; Mete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000**, *41*, 7731−7735. (b) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Chem. Commun.* **2000**, 133−134. (c) Ogawa, K.; Radke, K. R.; Rothstein, S. D.; Rasmussen, S. C. *J. Org. Chem.* **2001**, *66*, 9067−9070. (d) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861−2873.

(8) Hooper, M. W.; Hartwig, J. F. *Organometalllics* **2003**, *22*, 3394−3403.

(9) Selected examples: (a) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371−1375. (b) Kamenecka, T. M.; Lanza, T.; de Laszlo, S. E.; Li, B.; McCauley, E. D.; Van Riper, G.; Egger, L. A.; Kidambi, U.; Mumford, R. A.; Tong, S.; MacCoss, M.; Schmidt, J. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2205−2208. (c) Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611−4614.

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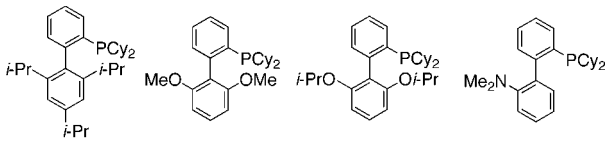
The bulky electron-rich biaryl ligands discovered within our group were employed for these reactions (Scheme 1). These ligands are commercially available[13] and air stable; the reaction setup is experimentally simple and does not require the use of a glovebox.

Scheme 1. Bulky Biaryl Electron-Rich Ligands Used in the Amination of Heterocycles

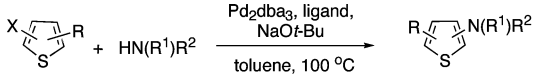


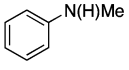
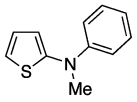
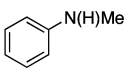
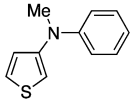
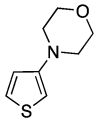
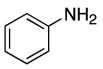
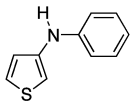
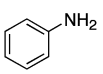
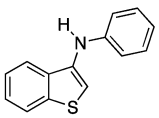
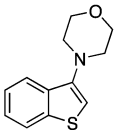
1 2 3 4

We began by investigating the amination of bromo- and chlorothiophenes, a topic that has been examined by several groups.[7] However, the substrate scope remains limited, and only reactions with bromothiophene derivatives have afforded products in acceptable yields. Although **1** has been employed in various C−N bond-forming processes, its use for the amination of 2- and 3-chlorothiophene as well as 3-bromothianaphthene provided only moderate yields of products. By utilizing **2** or **3**, higher conversions and yields were obtained (Table 1). At 0.5−1 mol % Pd, **3** proved to be superior to **2**. Anilines and cyclic secondary amines were viable substrates. However, reactions with acyclic secondary amines afforded low yields of desired products, as extensive amounts of hydro-dehalogenated material were formed. This result is consistent with the recent proposal that reductive elimination is the problematic step for reactions of these classes of substrates.[8] Curiously, this paper also suggests, on the basis of stoichiometric model studies, that the coupling of aniline with halothiophenes should be inefficient. The result shown in entry 5 (Table 1) is in conflict with this supposition.

Although chloro- and bromopyridines have been employed as effective coupling partners in Pd-catalyzed amination reactions,[9] simple 5-bromopyrimidines have, to the best of our knowledge, not been used. Utilizing **1**−**3**, a number of amines could be coupled with 5-bromopyrimidine in good to excellent yields (Table 2). In particular, functionalized anilines were viable coupling partners in the presence of a weak base, K_3PO_4 (Table 2, entries 2−4).

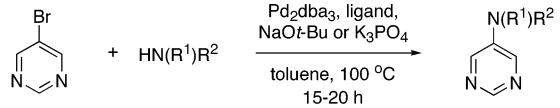
Table 1. Pd-Catalyzed Amination of Thiophenes[a]

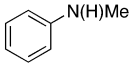
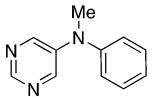
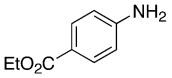
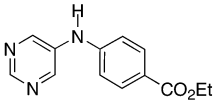
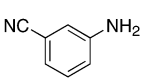
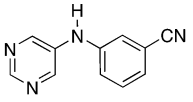
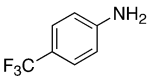
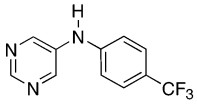
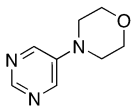
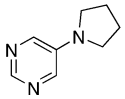


entry	heteroaryl halide	amine	ligand	product	% yield[b,c]
1			2		84[d]
2			3		98
3			2		82
4			3		82
5			3		86
6			3		70

[a] Reaction conditions: 1 mol % Pd_2dba_3, 4 mol % ligand, 1.4 equiv of NaO*t*-Bu, 1.2 equiv of amine in toluene at 100 °C. [b] Yields are an average of two runs. [c] General procedure 1 (Supporting Information) was used. [d] $Pd(OAc)_2$ was used in place of Pd_2dba_3.

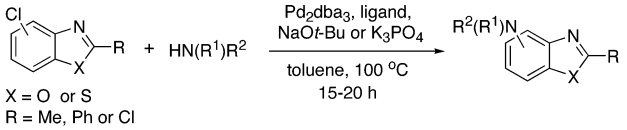
Table 2. Pd-Catalyzed Amination of 5-Bromopyrimidine[a]

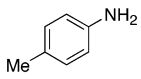
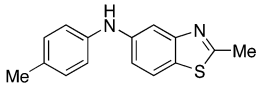
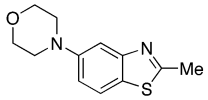
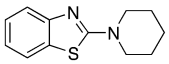
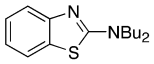
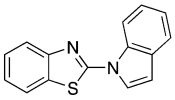
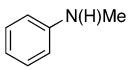
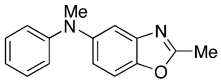
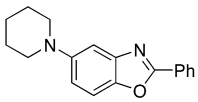
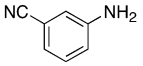
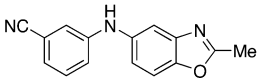


entry	amine	ligand	product	% yield[b,c]
1		1		96
2		1		89[d]
3		1		72[d]
4		1		93[d]
5		2		73
6		1		58

[a] Reaction conditions: 2 mol % Pd_2dba_3, 8 mol % ligand, 1.4 equiv of base, 1.2 equiv of amine in toluene at 100 °C. [b] Yields are an average of two runs. [c] General procedure 1 (Supporting Information) was used. [d] K_3PO_4 was used in place of NaO*t*-Bu.

Table 3. Pd-Catalyzed Amination of Benzoxazoles and Benzothiazoles[a]



entry	amine	ligand / (mol %Pd)	product	% yield [b,c]
1		**1** (4)		98
2		**1** (4)		65
3		**2** (1)		92[d]
4	$HNBu_2$	**3** (4)		97[e]
5		**1** (2)		73[f]
6		**1** (4)		83
7		**1** (4)		97
8		**1** (4)		60[g]

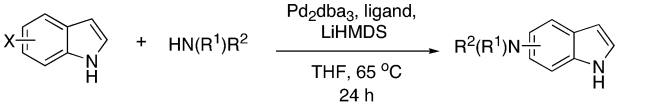
[a] Reaction conditions: Pd_2dba_3/ligand ratio = 1:4, 1.4 equiv of NaO*t*-Bu, 1.2 equiv of amine in toluene at 100 °C. [b] Yields are an average of two runs. [c] General procedure 1 (Supporting Information) was used. [d] Reaction was performed at 25 °C. [e] Reaction was performed at 50 °C. [f] Reaction was performed at 70 °C. [g] K_3PO_4 was used in place of NaO*t*-Bu.

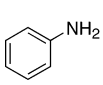
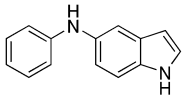
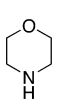
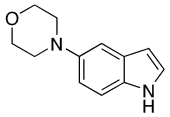
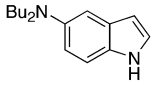
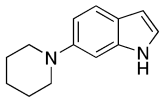
Unfortunately, the reactions of alkylamines with 5-bromopyrimidine were inefficient. We note that we have previously shown that primary amines can be coupled with 5-bromopyrimidine in high yield using a Cu catalyst.[14]

Attempts to couple 2-bromopyrimidine with various amines did not yield any of the desired product. This was a surprising result, as oxidative addition should be more rapid to 2-bromopyrimidine than to 5-bromopyrimidine.[15] The coupling of 2-chloropyrimidine with amines has been reported to occur in excellent yield utilizing the chelating ligand, Xantphos.[10]

To distinguish differences in reactivity between 2- and 5-bromopyrimidine, a competition experiment was performed. The reaction of *N*-methylaniline and an equimolar mixture of 2-bromopyrimidine and 5-bromopyrimidine with **1** yielded only a trace amount of the amination product derived from 5-bromopyrimidine. Since the coupling of 5-bromopyrimidine with *N*-methylaniline proceeds in excellent yield (Table 2, entry 1), it is likely that 2-bromopyrimidine is a catalyst poison. Although the exact mechanism of catalyst poisoning is unknown, it is possible that the oxidative addition product of 2-bromopyrimidine to the catalyst renders it inactive.

Table 4. Pd-Catalyzed Amination of Haloindoles[a]



entry	indole	amine	ligand	product	% yield [b,c]
1	X = 5-Br		**4**		96
2	X = 5-Br		**4**		90
3	X = 5-Br	$HNBu_2$	**1**		51
4	X = 6-Cl		**1**		66

[a] Reaction conditions: 1 mol % Pd_2dba_3, 4 mol % ligand, 2.2 equiv of LiHMDS, 1.2 equiv of amine in THF at 65 °C. [b] Yields are an average of two runs. [c] General procedure two was used.

Our next focus was on the amination of benzothiazoles and benzoxazoles. Although activated benzothiazoles and benzoxazoles have been used as coupling partners in Pd-catalyzed amination processes,[9a,14] no examples of aminations with the nonactivated counterparts are known.

These substrates were effectively coupled with a variety of amines in good to excellent yields (Table 3). One exception includes the reactions of 2-methyl benzothiazole and benzoxazoles with alkylamines. In these cases, lower yields resulted (Table 3, entry 2), which we attribute to the deprotonation of the 2-methyl substituent by NaO*t*-Bu followed decomposition or formation of unidentified side products. For example, the reaction of 2-methyl-5-chlorobenzoxazole with piperidine proceeded to full conversion, but only a 50% yield of product was isolated. Replacing the 2-methyl group with a phenyl moiety[16] in the benzoxazole suppressed any side reactions; the reaction of 2-phenyl benzoxazole with piperidine proceeded to nearly quantitative yield (Table 3, entry 7).

(13) Ligands used in this report are commercially available from Strem and Aldrich.

(14) Kwong, F. K.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796.

(15) See ref 12, pp 375−376.

(16) 2-Phenyl-5-chlorobenzoxazole was synthesized in 53% isolated yield in an analogous fashion to a published procedure, using trimethyl orthobenzoate in place of trimethyl orthoformate. Kunz, K. R. *Org. Prep. Proc. Int.* **1990**, *22*, 613−618.

The products from the coupling of 2-chlorobenzothiazole with piperidine, dibutylamine, and indole were isolated in 92, 97, and 73% yield, respectively (Table 3, entries 3−5). In fact, the reaction of piperidine with 2-chlorobenzothiazole proceeded to full conversion at room temperature. However, it is important to note that when this reaction is conducted under the same conditions, in the absence of catalyst, a 62% yield of product is obtained via a nucleophilic aromatic substitution pathway. As shown (Table 3, entry 8), a functionalized aniline could be used if K_3PO_4 was employed.

Finally, 5-bromoindole and 6-chloroindole, both possessing a free NH, were viable coupling partners with anilines and acyclic and cyclic secondary alkylamines (Table 4). These transformations are particularly useful, as extra protection/deprotection steps are not required. Using a procedure we reported a few years ago,[17] in these examples 2.2 equiv of a strong base, LiHMDS, were employed. The use of weaker bases such as Cs_2CO_3 was found to be ineffective. Best results were obtained by utilizing **4** for the reactions with 5-bromoindole with aniline and morpholine (Table 4, entries 1 and 2). The more difficult reaction with *n*-Bu_2NH afforded 51% of the desired product. However, acceptable yields for the coupling of 6-chloroindole with piperidine were only obtained with **1**. Attempts to effect the amination of 5-chloroindole with amines such as *n*-Bu_2NH resulted in competitive incorporation of an NH_2 group derived from the LiHMDS.

In conclusion, we have expanded the scope of the Pd-catalyzed amination to include a range of activated and nonactivated heteroaryl chlorides and bromides. 5-Bromopyrimidine and unactivated benzoxazoles and benzothiazoles are viable substrates. Additionally, we have demonstrated the first aminations of 5- and 6-haloindoles containing a free indolic NH group.

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Supporting Information Available: Detailed experimental procedures and characterization data of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885−2888.