

Efficient Pd-Catalyzed Amination of
Heteroaryl Halides

Mark D. Charles, Phillip Schultz, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139

sbuchwal@mit.edu

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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.

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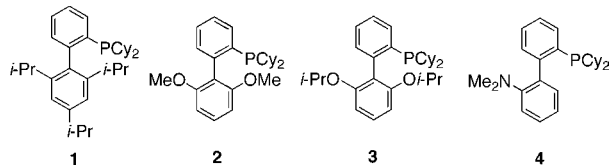
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The bulky electron-rich biaryl ligands discovered within our group were employed for these reactions (Scheme 1). These ligands are commercially available¹³ and air stable; the reaction setup is experimentally simple and does not require the use of a glovebox.

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



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-bromo-

thianaphthene 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, K₃PO₄ (Table 2, entries 2–4).

Table 1. Pd-Catalyzed Amination of Thiophenes^a

$\text{X}-\text{C}_4\text{H}_3\text{S}-\text{R} + \text{HN}(\text{R}^1)\text{R}^2 \xrightarrow[\text{toluene, 100 } ^\circ\text{C, 15-20 h}]{\text{Pd}_2\text{dba}_3, \text{ligand, NaOt-Bu}} \text{R}-\text{C}_4\text{H}_3\text{S}-\text{N}(\text{R}^1)\text{R}^2$					
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 % Pd₂dba₃, 4 mol % ligand, 1.4 equiv of NaOt-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 Pd₂dba₃.

Table 2. Pd-Catalyzed Amination of 5-Bromopyrimidine^a

$\text{Br}-\text{C}_4\text{H}_3\text{N}_2 + \text{HN}(\text{R}^1)\text{R}^2 \xrightarrow[\text{toluene, 100 } ^\circ\text{C, 15-20 h}]{\text{Pd}_2\text{dba}_3, \text{ligand, NaOt-Bu or K}_3\text{PO}_4} \text{N}(\text{R}^1)\text{R}^2-\text{C}_4\text{H}_3\text{N}_2$					
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 % Pd₂dba₃, 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 K₃PO₄ was used in place of NaOt-Bu.

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

X = O or S
R = Me, Ph or Cl

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: Pd₂dba₃/ligand ratio = 1:4, 1.4 equiv of NaOt-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 K₃PO₄ was used in place of NaOt-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 per-

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 % Pd₂dba₃, 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.

formed. 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.

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 NaOt-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 moiety¹⁶ 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.

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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*-Bu₂NH 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*-Bu₂NH resulted in competitive incorporation of an NH₂ 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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