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Selective Amination of Polyhalopyridines Catalyzed by a Palladium–Xantphos Complex

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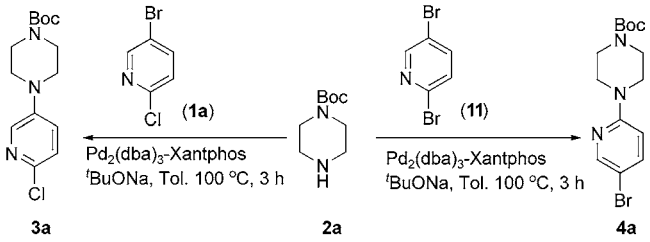
ABSTRACT



Amination of 5-bromo-2-chloropyridine (1a) catalyzed by a palladium–Xantphos complex predominately gives 5-amino-2-chloropyridine product 3a in 96% isolated yield and excellent chemoselectivity (3a/4a = 97:3). Amination of 2,5-dibromopyridine (11) under the same conditions exclusively affords 2-amino-5-bromopyridine 4a.

Synthetic approaches to aminopyridine derivatives continue to receive considerable attention due to their presence in biologically active pharmaceutical ingredients and numerous natural products.[1] Strategies for selective synthesis of aminopyridine derivatives include modification of commercially available aminopyridines,[2] selective nitration and reduction of pyridines,[3] and de novo construction of a pyridine nucleus incorporating properly disposed amino groups,[4] as well as nucleophilic substitution of halopyridines with amines under thermal conditions.[5] These methods generally require harsh reaction conditions or lengthy reaction sequences. The selective and efficient synthesis of aminopyridines under mild conditions is still regarded as a nontrivial synthetic challenge. The development of the palladium-catalyzed amination of aryl halides in the mid-1990s by Buchwald[6] and Hartwig[7] has provided a general and practical method to synthesize a wide variety of arylamines from readily available aryl halides.[8] Recently, Maes and Dommisse[9] reported that selective palladium-catalyzed amination of chloroiodo- and dichloropyridines could be accomplished with aromatic or heteroaromatic amines.[10] In connection with our medicinal

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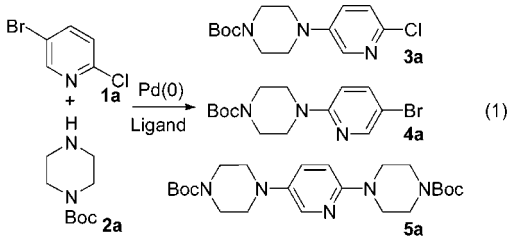
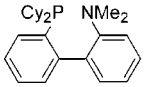
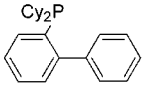
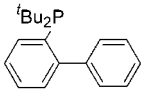
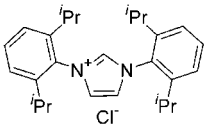
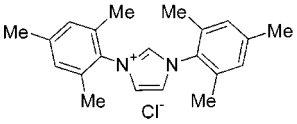
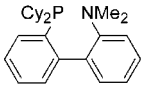
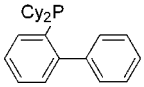
chemistry program at Abbott Laboratories, a series of aminohalopyridines was prepared. We concluded that palladium-catalyzed amination of readily available polyhalopyridines could be used to efficiently synthesize the target molecules. Here we report aminations of 5-bromo-2-chloro- and 2,5-dibromopyridine with cyclic alkylamines[11] under catalysis by a palladium−Xantphos complex with excellent levels of regioselectivity and high chemical yields.

The amination of 5-bromo-2-chloropyridine (**1a**) with 1-*N*-Boc-piperazine (**2a**) in toluene at 100 °C was initially selected as a model reaction for investigating the chemoselectivities and the efficiencies of various Pd-ligand catalyst systems (eq 1).[12] A survey of several ligands that are commonly utilized for *N*-arylation is summarized in Table 1. Equimolar quantities of **1a** and **2a** were combined with 1.5 equiv of ^{t}BuONa in toluene and allowed to react in the presence of $Pd_2(dba)_3$ (2 mol %) and the test ligand (6 mol %) for 3 h at 100 °C. The chemical yields and the ratio of the products were determined by HPLC. DPPF [1,1′-bis-(diphenyl-phosphino)ferrocene] and BINAP [2,2′-bis-(diphenyl-phosphino)-1,1′-binaphthyl], which are commonly employed in *N*-arylation,[8a,12] led to coupling with relatively poor chemoselectivity providing a mixture of **3a** and **4a** in low to moderate chemical yields (Table 1, entries 1 and 2). In the case of BINAP, a small amount of diaminopyridine byproduct **5a** was also observed (Table 1, entry 2). In the presence of Xantphos, a chelating bidentate bisphosphine ligand with a wide bite angle that is widely employed in transition-metal-catalyzed couplings,[13] the reaction proceeds with excellent chemoselectivity favoring **3a**, but at the expense of increased quantities of the bis-aminated product **5a** (Table 1, entry 3). Several sterically encumbered and electron-rich monodentate phosphine ligands, such as Cy-MAP [(2′-dicyclohexylphosphanylbiphen-2-yl)dimethylamine], Cy_2P(Ph-Ph) (dicyclohexyl-2-biphenylphosphane), $^t Bu_2P$(Ph-Ph) (di-*tert*-butyl-2-biphenylphosphane),[14] and $^t Bu_3P$[15] also



(1)

Table 1. Effect of Ligands on Palladium-Catalyzed Chemoselective Amination of **2a** with 5-Bromo-2-chloropyridine (**1a**)[a]

entry	ligand	**3a** (%)[b]	**3a** : **4a** : **5a**[c]
1	DPPF	12	72 : 2 : 0
2	BINAP	72	74 : 21 : 5
3	Xantphos	70	87 : 0 : 13
4		59	81 : 0 : 19
5		64	92 : 0 : 8
6		65	96 : 4 : 0
7	$^t Bu_3P$	62[d]	99 : 0 : 1
8		79	87 : 9 : 4
9		18	23 : 76 : 1
10	Xantphos	96[e]	97 : 3 : 0
11	$^t Bu_3P$	97[d,e]	97 : 3 : 0
12		95[e]	96 : 2 : 2
13		72[e]	95 : 3 : 2

[a] General reaction conditions: Under N_2, a mixture of **1a** (1 mmol), **2a** (1 mmol), $Pd_2(dba)_3$ (0.02 mmol), ligand (0.06 mmol), and ^{t}BuONa (1.5 mmol) in toluene (0.1 M) was stirred at 100 °C for 3 h. [b] HPLC assay yield. [c] The ratio was detemined by HPLC. [d] $Pd_2(dba)_3$ (0.01 mmol) and $(^t Bu_3P)_2Pd$ (0.02 mmol) were used. [e] 1.3 mmol of **1a** was used.

provided excellent levels of chemoselectivity with moderate chemical yields (Table 1, entries 4−7). The nucleophilic heterocyclic carbene ligand[16] IPr·HCl (IPr = 1,4-bis(2,6-diisopropyl)imidazol-2-ylidene) resulted in greater than 9:1

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(14) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722 and ref 12(d).

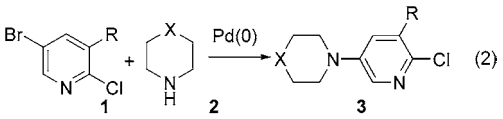
(15) Pd/$^t Bu_3P$ complex was in situ prepared by using $Pd_2(dba)_3$ (1 mol %) and $(^t Bu_3P)_2Pd$ (2 mol %): Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. Recent examples using $^t Bu_3P$ in *N*-arylation: (a) Prashad, M.; Mak, X. Y.; Liu, Y.; Repic, O. *J. Org. Chem.* **2003**, *68*, 1163. (b) Lee, M.; Jørgensen, J.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729. (c) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367.

(**3a** vs **4a**) chemoselectivity in 79% yield (Table 1, entry 8). In contrast, the reaction with IMes·HCl (IMes = 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene) favored formation of **4a**[17] (Table 1, entry 9).

Despite the excellent selectivity using Xantphos and several sterically encumbered monodentate ligands (Table 1, entries 3−7), the reaction proceeded in only 59−70% chemical yields, often contaminated with the 2,5-diaminopyridine byproduct **5a**. In an attempt to improve the reaction efficiency, the effect of base was investigated. Under a standard set of conditions (equimolar quantities of **1a** and **2a** were catalyzed by $Pd_2(dba)_3$−Xantphos in toluene at 100 °C for 3 h), use of ^{t}BuONa provided **3a** in 70% yield along with **5a** (Table 1, entry 3). The stronger base ^{t}BuOK gave somewhat inferior results (**3a**, 56%; **3a**/**4a**/**5a** = 79:16:5). The reaction with Cs_2CO_3 was quite sluggish (12% conversion of **1a** over 3 h). Several other bases (K_3PO_4, K_2CO_3, DABCO, DBU, and Et_3N) were screened, but none of these led to detectable conversion of **1a**. HPLC analysis of the reactions with ^{t}BuOK and ^{t}BuONa (Table 1, entries 1−7) showed complete disappearance of starting material **1a** within 3 h. LC-MS revealed the existence of several possible bipyridines, such as 6,6′-dichloro[3,3′]bipyridine **6**.[18]

The postulated mechanism for the palladium-catalyzed *N*-arylation[19] involves oxidative addition of Pd(0) to the carbon-halo bond in **1a**,[20] exchange of **2a** for halide in the palladium complex,[21] and reductive elimination of the corresponding aza-pyridinyl-palladium complex.[22] In this scenario, the ratio of **3a**/**4a** is determined by the regioselectivity of the oxidative addition step, its reversibility, and the reactivity of the respective palladium complexes. Both **3a** and **4a** can undergo further reaction with excess **2a** to produce **5a**.[23] The presence of **5a** in the final reaction mixture obscures direct observation of the selectivity of **3a**/**4a**. Use of an excess of **1a** should diminish the production of **5a** and reveal the intrinsic chemoselectivity of the reaction. When 1.3 equiv of **1a** was employed under similar conditions, the reaction proceeded in excellent chemical yields and superior selectivity without producing **5a** by using either Xantphos or ^{t}Bu$_3$P ligand (Table 1, entries 10 and 11). Similar improvements were also seen with either CyMAP or Cy$_2$P-(Ph-Ph) ligand (Table 1, entries 12 and 13). Xantphos is a commercially available, air stable and easily handled crystalline solid. As a typical bidentate bisphosphine ligand with wide bite angle, its coordination properties and synthetic uses have been well documented.[14] The $Pd_2(dba)_3$−Xantphos combination was selected as the preferred catalytic system. Consequently, under the catalysis of $Pd_2(dba)_3$ (2 mol %) and Xantphos (6 mol %), amination of 5-bromo-2-chloropyridine (**1a**) (1.3 equiv) with 1-*N*-Boc-piperazine in toluene predominately gave 1-*N*-Boc-4-*N*-(6-chloropyridin-3-yl)piperazine **3a** in 96% yield with excellent chemoselectivity (**3a**/**4a**/**5a** = 97:3:0) at 100 °C over 3 h.

Table 2. Chemoselective Amination of Cyclic Amines **2** with 5-Bromo-2-chloropyridines (**1**) Catalyzed by a Palladium−Xantphos Complex[a]



entry	R	X	3	yield[b] (%)
1	H	NBoc	**3a**	96
2	Me	NBoc	**3b**	90
3	Cl	NBoc	**3c**	87
4	H	O	**3d**	99
5	H	CH_2	**3e**	94
6	H	MeCH	**3f**	95
7	H	PhN	**3g**	93
8	H	MeN	**3h**	87
9	H	BnN	**3i**	97

[a] General reaction conditions: Under N_2, a mixture of **1a** (1.3 mmol), **2a** (1 mmol), $Pd_2(dba)_3$ (0.02 mmol), Xantphos (0.06 mmol), and ^{t}BuONa (1.5 mmol) in toluene (0.1 M) was stirred at 100 °C for 3 h. [b] Isolated yield.

Encouraged by these results, we further explored the scope and limitations of the $Pd_2(dba)_3$−Xantphos catalyst system (eq 2). The results are summarized in Table 2. Under the standard conditions summarized in the Table, amination of **1** with a variety of cyclic amines **2** furnished 5-amino-2-chloropyridines **3** with excellent chemoselectivity and in high isolated yields. In each case, amination occurs at the more reactive C−Br bond, and the chloro substituent remains unchanged.[24] The basicity of amine **2**, as modulated by changes in substituent X, had little effect on either chemoselectivity or chemical yields (Table 2, entries 1 and 4−9).[25]

The regioselectivity for the amination of 2,5-dibromopyridine[26] (**11**) was also evaluated (eq 3). The results are

(16) (a) Arduengo, A. J., III. *Acc. Chem. Res.* **1999**, *32*, 913. Examples using heterocyclic carbene ligands in *N*-arylation: (b) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (c) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423.

(17) By using Pd-bisimidazolium (a modified IPr·HCl ligand by Trudell) complex, the reaction of 2-chloro-5-iodopyridine with 7-azabicyclo[2.2.1]-heptane was reported to give predominantly 7-(5-iodo-2-pyridinyl)-7-azabicyclo[2.2.1]heptane. See ref 11.

(18) Repetition of the experiment of entry 3 (Table 1) in absence of amine **2a** produced **6** as the major product in 56% isolated yield.

(19) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

(20) (a) Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030. (b) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373.

(21) (a) Hartwig, J. F. *Synlett* **1997**, 329. (b) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755.

(22) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232.

(23) When **2a** (2.5 mmol) reacted with **1a** (1.0 mmol) under the catalysis of by $Pd_2(dba)_3$−Xantphos with ^{t}BuONa (2.5 mmol) in toluene at 100 °C for 3 h, **5a** was obtained in 96% yield.

(24) Under the standard conditions summarized in the Table 2, amination of **2a** with 4-bromo-2-chloropyridine (**7**) and 3-bromo-2-chloropyridine (**8**) provided the corresponding 1-*N*-Boc-4-(2-chloropyridin-4-yl)-piperazine (**9**) and 1-*N*-Boc-4-(2-chloropyridin-3-yl)-piperazine (**10**) in 91% and 87% isolated yields, respectively (eq 4).

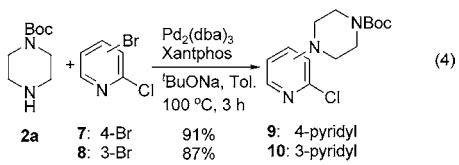
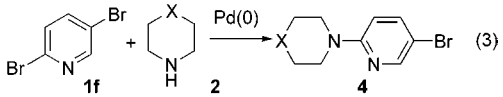


Table 3. Regioselective Amination of 2,5-Dibromopyridine (**1f**) Catalyzed by a Palladium−Xantphos Complex[a]



entry	X	4	yield[b] (%)
1	NBoc	**4a**	99
2	O	**4b**	99
3	CH_2	**4c**	98
4	MeCH	**4d**	98
5	PhN	**4e**	95
6	MeN	**4f**	99
7	BnN	**4g**	96

[a] General reaction conditions: Under N_2, a mixture of **1f** (1.3 mmol), **2a** (1 mmol), $Pd_2(dba)_3$ (0.02 mmol), Xantphos (0.06 mmol), and ^{t}BuONa (1.5 mmol) in toluene (0.1 M) was stirred at 100 °*C for 3* h. [b] Isolated yield.

tabulated in Table 3. Under the standard conditions with 30% excess **11**, **4a** was produced in virtually quantitative yield (Table 3, entry 1) and with no trace of the regioisomeric product or the diaminated material **5a**. However, the reaction of equimolar **11** and **2a** under the catalysis by $Pd_2(dba)_3$−Xantphos afforded **4a** in only 87% yield (**4a**/**5a** = 97:3),[27] while the use of $Pd_2(dba)_3$ (2 mol %)−BINAP (6 mol %) gave a mixture of **4a** and **5a** in 40% yield (**4a**/**5a** = 84:16). In the case of $Pd_2(dba)_3$−BINAP catalytic system, use of excess **11** (1.3 mmol) gave **4a** in 72% yield with slightly improved selectivity (**4a**/**5a** = 89:11). A number of cyclic amines **2** were examined under the standard conditions of $Pd_2(dba)_3$−Xantphos catalytic system, and all provided the single aminated product **4** in excellent yield (Table 3, entries 2−7). The basicity of amine **2** was noticed again to have little effect on either selectivity or chemical yield.

In summary, we have achieved a chemoselective amination of 5-bromo-2-chloropyridine under catalysis by $Pd_2(dba)_3$−Xantphos with ^{t}BuONa in toluene at 100 °C for 3 h. The reaction predominately gives 5-amino-2-chloro-pyridine products **3** in good chemical yield and excellent chemoselectivity (**3**/**4**/**5** ≥ 97:3:0). Amination of 2,5-dibromopyridine selectively provides 2-amino-5-bromopyridines **4** in quantitative yields. Further investigations including further reaction optimization and synthetic applications will be reported shortly.

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Supporting Information Available: Experimental procedures and spectral data for the products **3**−**5**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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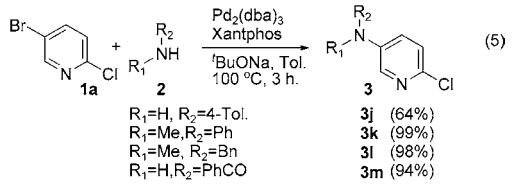
(25) Noncyclic amines also react efficiently with **1a** under these conditions (equation 5). For example, reaction of 4-methylaniline with **1a** provided **3j** in 64% isolated yield, along with 27% of the bis(arylated) byproduct *N*,*N*-bis-(6-chloropyridin-3-yl)-4-methylaniline. In this case, use of Cs_2CO_3 as base led to a much slower reaction (18 h) but greatly improved yield of **3j** (91%) owing to diminished conversion to the bis(arylated) byproduct (7%). Bis(arylation) is not an issue with the secondary amines *N*-methylaniline and *N*-methylbenzylamine, which furnished **3k** and **3l** in excellent yields under the standard conditions. Benzamide reacts smoothly to provide the monoarylated product **3m**.



(26) **2a** (2.5 mmol) reacted with **1f** (1.0 mmol) under the catalysis by $Pd_2(dba)_3$-Xantphos with ^{t}BuONa (2.5 mmol) in toluene at 100 °C for 3 h affording **5a** in 54% isolated yield.

(27) Amination of 2,5-dibromopyridine using palladium catalysts: (a) Gomtsyan, A.; Didomenico, S.; Lee, C.; Matulenko, M. A.; Kim, K.; Kowaluk, E. A.; Wismer, C. T.; Mikusa, J.; Yu, H.; Kohlhaas, K.; Jarvis, M. F.; Bhagwat, S. S. *J. Med. Chem.* **2002**, *45*, 3639. (b) Madar, D.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedeman, P. E.; Djuric, S. W. *Tetrahedron Lett.* **2001**, *42*, 3681. Amination of 2,5-dibromopyridine using copper catalysts: (c) Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251.