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Chemoselective Amination of 5-Bromo-2-chloro-3-fluoropyridine

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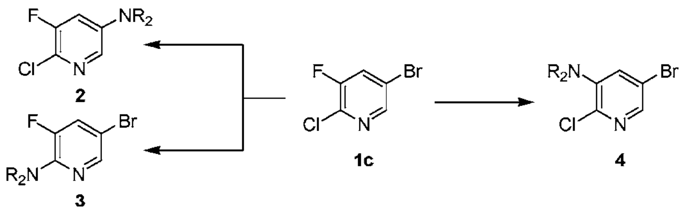
ABSTRACT



The chemoselective functionalization of 5-bromo-2-chloro-3-fluoropyridine (1c) is described. Catalytic amination conditions (Pd_2dba_3, Xantphos, base) afford exclusively the bromide substitution product (2) for both secondary amines and primary anilines. A reversal in chemoselectivity is observed under neat conditions in the absence of palladium catalysis, with substitution at the 2-chloro position preferred to generate 3. Last, selective substitution of the 3-fluoro group is achieved under S_NAr conditions to afford the dihalo adduct (4).

The construction of carbon−nitrogen bonds has garnered considerable synthetic interest in large part due to the prevalance of aromatic and heteroaromatic amines in biologically active compounds.[1] Evolution of this field has been dramatically accelerated by the discovery of efficient transition-metal-catalyzed processes pioneered by Buchwald and Hartwig.[2] With Pd- and Cu-catalyzed aminations now relied upon for increasingly complex transformations,[3] the need for chemoselective methods for amination of polyfunctionalized substrates has intensified.[4]

Ji and co-workers recently demonstrated the selective amination of 5-bromo-2-chloropyridine (**1a**) and 2,5-dibromopyridine (**1b**) via palladium catalysis (Figure 1).[5] By careful selection of supporting ligand, the regioselectivity of the amination adduct formation was optimized for the more reactive of the two halogen substituents, namely, the 5-bromo position of **1a** and the 2-bromo position of **1b**.

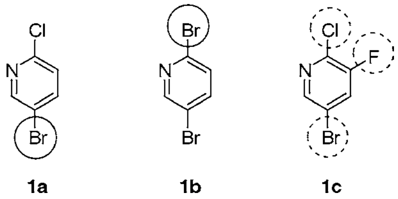


Figure 1. Observed reactivity of polyfunctional amination substrates.

As part of our interest in the properties of fluorinated bioactive molecules,[6] we became interested in the synthesis of amino pyridine derivatives bearing a fluorine atom in the pyridine ring. We recognized that commercially available 5-bromo-2-chloro-3-fluoropyridine (**1c**) represented a po-

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[1] (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Negwar, M. In *Organic-Chemical Drugs and their Synonyms: (An International Survey*), 7th ed.; Akademie Verlag: Berlin, 1994.

[2] Jiang, L.; Buchwald, S. L. In *Neuroprotection. Mechanisms and Therapies*; Bahr, M., Ed.; Wiley-VCH: Weinheim, Germany, 2004.

[3] (a) Back, T. G.; Wulff, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1268. (b) Link, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinski, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 973.

[4] For other examples of selective amination of polyhalo substrates, see: (a) Peng, Z.; Journet, M.; Humphrey, G. *Org. Lett.* **2006**, *8*, 395. (b) Kuethe, J. T.; Wong, A.; Davies, I. W. *J. Org. Chem.* **2004**, *69*, 7752. (c) Maes, B.; Loones, K.; Jonckers, T. H.; Lemiere, G.; Dommisse, R. A.; Haemers, A. *Synlett* **2002**, *12*, 1995.

[5] Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611.

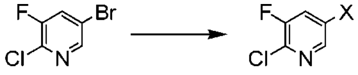
[6] Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013.

10.1021/ol070695+ CCC: $37.00

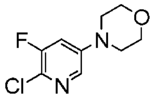
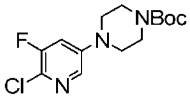
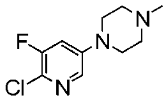
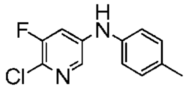
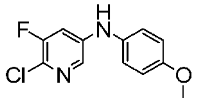
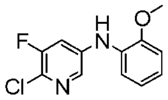
tentially versatile heterocyclic building block that could be elaborated into an array of fluorinated amino pyridine analogues.[7] During our investigation of **1c**, we discovered that in fact all three halogen positions of this substrate could serve as viable handles for synthetic transformation. The method reported herein thus constitutes a unique strategy for the assembly of topologically diverse amino pyridine cores.

For amination of the bromide substituent, we were initially concerned whether the 3-fluoro group might inductively activate the 2-chloro substituent to the extent that multiple halogen substitution pathways would be competitive. Furthermore, electron-deficient fluoroarenes are known to participate in palladium-catalyzed cross-coupling reactions.[8] In fact, the expected halogen reactivity hierarchy (Br > Cl > F) was preserved in trihaloderivative **1c** (Table 1). In addition to secondary amines (generating products **2a**−**c**), primary anilines (leading to **2d**−**f**) were also found to be selective coupling partners in this reaction. Yields were universally high for the substrates investigated, with little to no substitution at the other halogen positions observed.

Table 1. Chemoselective Bromide Substitution of **1c**[a]

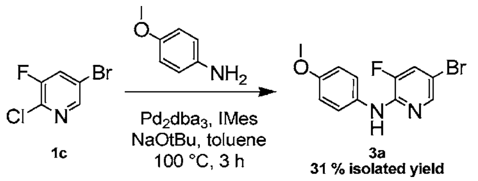


1c **2a-f**

Amine = X	2	Product	Yield[b] (%)
Morpholine	**2a**		90
N-Boc piperazine	**2b**		94
N-Me piperazine	**2c**		95
p-toluidine	**2d**		82
p-anisidine	**2e**		86
o-anisidine	**2f**		86

[a] General procedure: An equimolar mixture of **1c** and the appropriate aniline were treated with Pd_2dba_3 (0.03 equiv), Xantphos (0.04 equiv), and base and the appropriate solvent (entries a−c, NaO^tBu, 1.3 equiv in toluene; entries d−f, Cs_2CO_3, 2.0 equiv in dioxane). The heterogeneous mixture was stirred under nitrogen at 80 °C overnight. [b] Isolated yield.

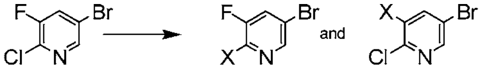
Interestingly, the N-heterocyclic carbene ligand IMes·HCl (IMes = 1,3-bis-2,4,6-trimethylphenyl imidazolium) promoted the palladium-catalyzed amination of **1c** with substitution at chloride in preference to bromide in a 5:1 ratio (eq 1). This phenomenon was also observed by Ji and co-workers with the amination of 5-bromo-2-chloropyridine (**1a**).[5] Although we do not fully understand the basis for this reversal in chemoselectivity, one can speculate that the IMES ligand confers unique nucleophilic character to the palladium complex that promotes oxidative insertion at the more electrophilic 2-chloro position of **1c**.[9]



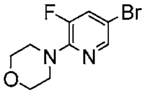
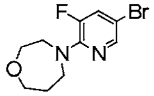
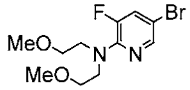
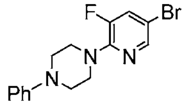
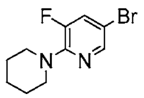
(1)

Indeed, the preference for nucleophilic substitution at the 2-chloro position of **1c** was demonstrated with secondary amines in the absence of palladium catalysis (Table 2). We initially anticipated that acidic conditions would favor addition at the 2-chloro site, but a range of Brønsted acid

Table 2. Chemoselective Chloride Substitution of **1c**[a]



1c **3b-f** **4**

Amine = X	3	Product	Ratio[c] (3 : 4)	3b-3f (%)
Morpholine	**3b**		9 : 1	82
[1,4] Oxazepine[b]	**3c**		3 : 1	36
Bis (2-methoxy ethyl) amine	**3d**		3 : 1	30
N-phenyl piperazine	**3e**		5 : 1	74
piperidine	**3f**		1 : 1	40

[a] General procedure: A neat mixture of **1c** (1.0 equiv) and excess amine was stirred at 210 °C for 10 min using microwave heating. The reaction mixture was then filtered through a plug of silica gel and purified by chromatography. [b] 5 equiv of amine hydrochloride and 5.2 equiv of *N*,*N*-diisopropylamine were used with *n*-BuOH as solvent. [c] Ratio determined by isolated yield of each analytically pure regioisomer.

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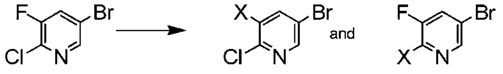
[7] For an example of carbanion addition to **1c** at elevated temperatures, see WO2005005398.

[8] (a) Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964. (b) Kim, Y. M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696.

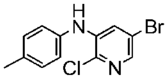
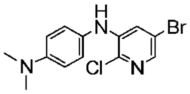
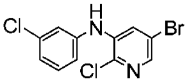
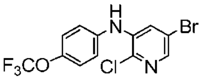
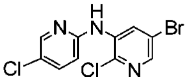
additives (concd HCl, NH_4Cl, TMSCl) were ineffective in promoting clean conversion of **1c** using morpholine as a test substrate. Instead, stirring a neat mixture of **1c** and excess amounts of the corresponding amine using microwave heating (210 °C, 10 min) afforded in most cases reasonable levels of selectivity and overall yield. Morpholine afforded the highest level of regiocontrol, with a 9:1 ratio of chloride to fluoride displacement resulting in an 82% isolated yield of adduct **3b**. Curiously, the homologue 1,4-oxazepine and the acyclic bis(2-methoxyethyl)amine were less selective (3:1 favoring **3c**), whereas piperidine was virtually nonselective. Improved levels of selectivity were observed with *N*-phenyl piperazine (5:1 favoring **3e**). A potential correlation between nucleophile and regioselectivity of halide substitution may be derived from the pK_a of the amine, as the lower pK_a nucleophiles (morpholine, *N*-phenyl piperazine) tend to react preferentially at the 2-chloro position of **1c**.[10]

We also discovered that substitution at the 3-fluoro position of **1c** could be accomplished using deprotonated amine nucleophiles (Table 3). The addition of an appropriate base (*n*-BuLi or NaH) to the amine followed by **1c** led to the clean conversion of **1c** at room temperature within 30 min to the dihalo adducts **4a**−**e**. Anilines appeared to be optimal for fluoro substitution, as *p*-MeO benzylamine afforded the bromochloro adduct in only 15% yield, albeit as a single regioisomer (data not shown).

Table 3. Chemoselective Fluoride Substitution of **1c**[a]



1c **4a-e** **3**

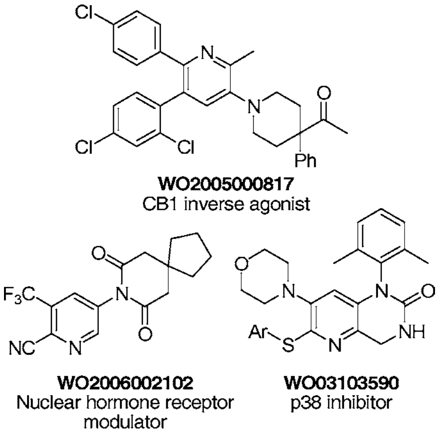
Amine = X	4	Product	Ratio[d] (4 : 3)	4a-g[e] (%)
p-toluidine[b]	4a		> 20:1	85
4-NMe_2-aniline[b]	4b		7 : 2	62
3-chloro-aniline[b]	4c		5 : 2	66
4-OCF_3-aniline[b]	4d		6 : 1	63
5-chloro-2-amino-pyridine[c]	4e		> 20:1	57

[a] General procedure: To a THF solution of amine (2.0 equiv) was added base (2.0 equiv) at −78 °C. The mixture was warmed to ambient temperature, to which was then added a THF solution of **1c** (1.0 equiv). After 30 min at rt, the reaction was quenched with MeOH and then purified by chromatography. [b] Using *n*-BuLi as base. [c] Using NaH as base. [d] Determined by HPLC analysis of crude mixture. [e] Isolated yield of analytically pure material.

Both electron-rich and electron-poor anilines were efficient reaction partners in this transformation. The choice of appropriate base appears to be dictated by both the acidity of the amino N−H and compatibility with *n*-BuLi. Amino pyridines, for instance, are sufficiently acidic to react effectively with NaH to afford adduct **4e** as a single regioisomer in reasonable yield. The compatibility of these reaction conditions with multifunctional substrates such as 5-chloro-2-aminopyridine enables further elaboration of polyhalo adducts such as **4e**.

From a mechanistic standpoint, we propose an S_NAr reaction pathway whereby the transient negative charge is inductively stabilized by the three halogen substituents on the pyridine ring. We also considered the possibility of HF elimination to generate a benzyne intermediate, but the exquisite regioselectivity and the absence of the 4-amino pyridine adduct collectively argue against this pathway. Although the regioselectivity trends of the Li^+/Na^+ base-promoted anionic pathway differ from those observed under the neutral conditions described for Table 2, clearly the reaction partners (secondary amines vs anilines) and conditions (microwave heating vs strong base at ambient temperature) are quite distinct for these two reaction pathways.

The products of the selective amination methodology described herein should allow the efficient synthesis of polyfunctional pyridines, many of which bear useful biological properties. Some examples of multisubstituted pyridines with known pharmacological activity are shown in Figure 2. By strategic selection of the various amination procedures described above, we envision rapid entry into the synthesis of these drug candidates as well as related analogues.



WO2005000817
CB1 inverse agonist

WO2006002102
Nuclear hormone receptor modulator

WO03103590
p38 inhibitor

Figure 2. Biologically active polyfunctional pyridines.

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[9] For an analogous result with 2-chloro-5-iodopyridine and a biscarbene ligand, see: Cheng, J.; Trudell, M. L. *Org. Lett.* **2001**, *3*, 1371.

[10] As reported by: Graton, J.; Berthelot, M.; Laurence, C. *J. Chem. Soc., Perkins Trans. 2* **2001**, *2*, 2130. pK_a of piperidine = 11.12; pK_a piperazine = 9.73; pK_a morpholine = 8.49. Using ACD Labs 9.0, the calculated pK_a values are in the following rank order: piperidine (11.24) > [1,4]-oxazepine > phenyl piperazine > morpholine > bis(2-methoxyethyl)amine (8.67).

In summary, we have demonstrated the ability to selectively functionalize each halogen position of 5-bromo-2-chloro-3-fluoropyridine. The reactivity of the 3-fluoro group toward nucleophilic attack[11] also suggests further opportunities for electron-poor fluoroarene and heteroarene substrates to engage in analogous transformations.

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

OL070695+

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(11) For an example of nucleophilic substitution of 3-fluoropyridine with imidazole, see: Denton, T.; Zhang, X.; Cashman, J. *J. Med. Chem.* **2005**, *48*, 224.