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Pd-Catalyzed *N*-Arylation of Heteroarylamines

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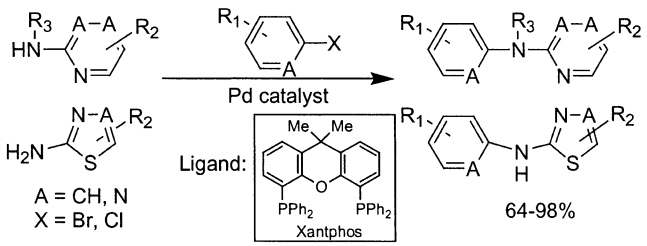
ABSTRACT



The palladium-catalyzed *N*-(hetero)arylation of a number of heteroarylamines including 2-aminopyridines, 2-aminothiazoles, and their analogues has been realized using Xantphos as the ligand. Weak bases such as Cs_2CO_3, Na_2CO_3, and K_3PO_4 were used in most cases to allow for the introduction of functional groups. Choice of the base and solvent was critical for the success of these reactions.

Pd-catalyzed arylation of amines has attracted great attention in the past few years.[1] A wide range of aryl halides can be coupled with primary and secondary amines or anilines under mild conditions with excellent functional group compatibility. However, few examples of Pd-catalyzed *N*-arylation of heteroarylamines have been reported.[2,3] Pd-catalyzed *N*-arylation of aminopyridines[2a−d] and 3-aminothiophenes[2e] has been achieved by using DPPP, BINAP, DPPF, or P(*t*-Bu)$_3$ as ligand.[4] However, the use of NaO-*t*-Bu as a strong base limited the scope of these reactions. Recently, the arylation of aminopyridines and analogous heteroarylamines using BINAP and K_2CO_3 has been reported, but a large excess (5−20 equiv) of the weak base was required.[3] The scope of the Pd-catalyzed *N*-arylation of heteroarylamines has been mostly limited to aminopyridines and analogues, and no examples with functional groups on the aryl halide or the heteroarylamine have been reported. In addition, Pd-catalyzed arylation of 2-aminothiazoles and analogues[5,6] is previously unreported despite the important biological activities of 2-arylaminothiazoles.[5,7] Here, we wish to report our progress in the Pd-catalyzed C−N bond-forming reactions between

(1) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (e) Muci, A. R.; Buchwald, S. L. Practical Palladium Catalysts for C−N and C−O Bond Formation. In *Topics in Current Chemistry*; Miyaura, N., Ed.; Springer-Verlag: Berlin, 2002; Vol. 219, p 133.

(2) (a) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. (b) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505. (c) Khan, M. M.; Ali, H.; van Lier, J. E. *Tetrahedron Lett.* **2001**, *42*, 1615. (d) Yang, J.-S.; Lin, Y.-H.; Yang, C.-S. *Org. Lett.* **2002**, *4*, 777. (e) Ogawa, K.; Radke, K. R.; Rothstein, S. D.; Rasmussen, S. C. *J. Org. Chem.* **2001**, *66*, 9067. For an example of Ni- or Cu-catalyzed couplings between a protected 5-iodouracil and heteroarylamines, see: (f) Arterburn, J. B.; Pannala, M.; Gonzalez, A. M. *Tetrahedron Lett.* **2001**, *42*, 1475.

(3) (a) Jonckers, T. H. M.; Maes, B. U. W.; Lemière, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027. (b) Košmrlj, J.; Maes, B. U. W.; Lemière, G. L. F.; Haemers, A. *Synlett* **2000**, 1581.

(4) DPPP = 1,3-bis(diphenylphosphino)propane; BINAP = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl; DPPF = 1,1′-bis(diphenylphosphino)-ferrocene.

(5) Direct reaction of 2-aminothiazoles with highly activated aryl halides in refluxing PhOH or EtOH has been very limited in scope and often resulted in low yields in the absence of a 4-substituent on the thiazole. For examples, see: (a) Sarkar, B. R.; Pathak, B.; Dutta, S.; Lahiri, S. C. *J. Ind. Chem. Soc.* **1984**, *61*, 151. (b) Forlani, L.; Guastadisegni, G.; Raffellini, L.; Todesco, P. E.; Foresti, E. *Gazz. Chim. Ital.* **1990**, *120*, 493. (c) Chauhan, P. M. S.; Pratap, R.; Sharma, S. *Ind. J. Chem.* **1985**, *15B*, 1154. (d) El-Bayouki, K. A. M.; Basyouni, W. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3794. (e) Pande, A.; Pramilla, S.; Saxena, V. K.; Khan, M. N. A. A.; Verma, H. N. *Acta Pharm. Jugosl.* **1984**, *34*, 61.

(6) For a Cu-catalyzed example, see ref 2f.

(7) Kim, K. S.; Kimball, D.; Cai, Z.-w.; Rawlins, D. B.; Misra, R. N.; Poss, M. A.; Webster, K. R.; Hunt, J. T.; Ham, W.-C. U.S. Patent 6262096, 2001.

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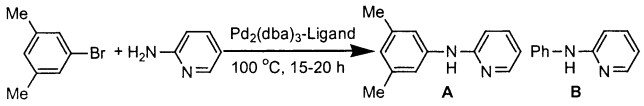
(hetero)aryl halides and heteroarylamines including 2-aminopyridines, 2-aminothiazoles, and their analogues.

The reaction between 2-aminopyridine and electron-neutral 5-bromo-*m*-xylene was first studied to establish the most effective conditions (Table 1). In addition to DPPF and BINAP, which were typically used in previous reports for this type of reaction,[2,3] Xantphos[8] was also tested as the ligand. With Xantphos as the ligand and NaO-*t*-Bu as a strong base, the reaction went smoothly without any formation of the undesired 2-anilinopyridine (**B**) (Table 1, entry 1).

Table 1. Optimization of Conditions[a]



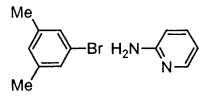
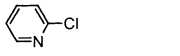
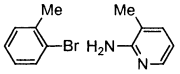
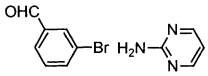
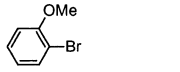
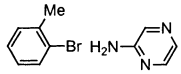
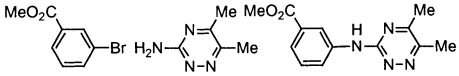
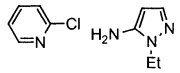
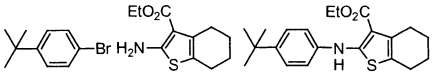
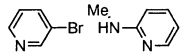
entry	% Pd	ligand	base	conv (%)	**B**/**A**[b]
1	4	Xantphos	NaO-*t*-Bu	100[c,d]	0
2	8	Xantphos	K_3PO_4	100	0.30
3	8	Xantphos	Cs_2CO_3	100	0.30
4	8	DPPF	Cs_2CO_3	46[c]	0.05
5	8	DPPF	Cs_2CO_3	67	0.04
6	8	BINAP	Cs_2CO_3	67	0.19
7	8	BINAP	Cs_2CO_3	74[e]	0.14
8	4	Xantphos	Cs_2CO_3	100	0.12
9	4	Xantphos	Cs_2CO_3	100[f]	0.08
10	1	Xantphos	Cs_2CO_3	100[f]	0.01

[a] Reaction conditions: 1.0 mmol of ArBr, 1.05 mmol of Ar′NH_2, L/Pd = 1.5, 1.2−1.4 equiv of base, 2.0−2.5 mL of dioxane, 100 °C, 15−20 h. [b] Uncorrected LC ratio. [c] Toluene as the solvent. [d] 1.2 mmol of ArBr and 1.0 mmol of Ar′NH_2 were used. [e] L/Pd = 1. [f] L/Pd = 1.1.

However, when weaker bases such as K_3PO_4 and Cs_2CO_3 were used for potential functional group compatibility (Table 1, entries 2 and 3), significant amounts of byproduct **B** formed.[9] The amount of undesired aryl group transfer product **B** decreased with decreasing amounts of Xantphos (Table 1, entries 3 and 8−10). We were pleased to find that the reaction went to completion in 15 h with just 1% of Pd and 1.1% of Xantphos, limiting the byproduct to ∼1% (Table 1, entry 10). On the other hand, even with 8% of Pd and 12% of DPPF or BINAP, the reaction only reached 67% conversion in the same amount of time (Table 1, entries 5 and 6), showing that Xantphos is a much better ligand for this reaction.[10,11]

Using the above optimized conditions, i.e., Xantphos as the ligand, Cs_2CO_3 as the base, and dioxane as the solvent, a variety of heteroarylamines was reacted with (hetero)aryl halides (Table 2). The amino group attached to a pyridine, pyrimidine, pyrazine, triazine, pyrazole, or thiophene ring could be arylated with electron-neutral (Table 2, entries 1 and 9) and electron-rich aryl bromides (Table 2, entry 5) as well as 2-, 3-, or 4-halopyridines. An ortho-substituted aryl bromide (2-bromotoluene) was also coupled with amino-

Table 2. *N*-Arylation of 2-Aminopyridines and Others[a]

entry	ArX	Ar′NH_2	product	mol%Pd	time(h)	yld(%)
1				1	15	95
2				1 (4)	15 (15)	94[b] (67)[c]
3				4	23	95
4				1	15	90
5				2	15	91
6				2	20	98
7				2	20	86
8				2	16	91[d]
9				1	23	85
10				2	20	91
11				2	16	83[d,e]

[a] Reaction conditions: 1.0 mmol of aryl halide, 1.05−1.4 equiv of Ar′NH_2, 1.4 equiv of Cs_2CO_3, 0.5−2 mol % of $Pd_2(dba)_3$ (1 mol % of Pd refers to 0.5 mol % of $Pd_2(dba)_3$), 1.1−4.4 mol % of Xantphos (L/Pd = 1.1), 4 mL (2 mL for entries 1, 2, 4, and 5) 1,4-dioxane, 100 °C, 15−23 h. Isolated yields are reported. [b] 1 mol % of BINAP was used as ligand. [c] Values in parentheses are from Xantphos. LC yield is given (82% conversion). [d] L/Pd = 1.5. [e] 1.0 equiv of KO-*t*-Bu was added to neutralize the HCl salt of 4-chloropyridine; 1.4 equiv of K_3PO_4 was used instead of Cs_2CO_3.

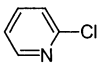
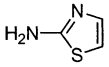
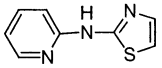
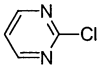
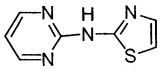
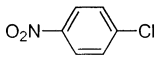
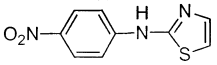
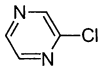
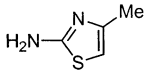
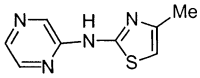
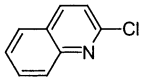
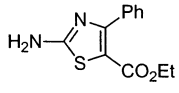
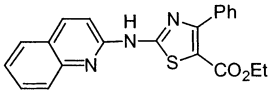
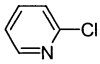
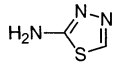
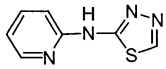
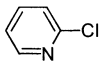
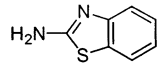
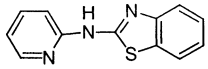
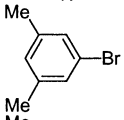
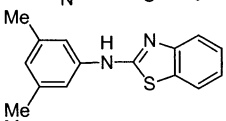
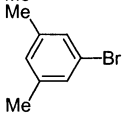
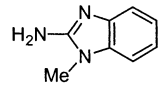
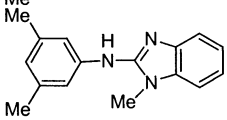
(8) First developed by van Leeuwen: (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081. For previous examples using Xantphos in Pd-catalyzed C−N bond forming reactions, see: (b) Guari, Y.; van Es, D. S.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1999**, *40*, 3789. (c) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019. (d) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35. (e) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251. (f) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. (g) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (h) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539. (i) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381. (j) Browning, R. G.; Mahmud, H.; Badarinarayana, V.; Lovely, C. J. *Tetrahedron Lett.* **2001**, *42*, 7155. (k) Anbazhagan, M.; Stephens, C. E.; Boykin, D. W. *Tetrahedron Lett.* **2002**, *43*, 4221.

(9) It formed likely via exchange between the aryl group of ArBr bound to Pd and the phenyl group of Xantphos. For similar observations, see: (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694−3703. (b) Reference 8f,g,i. For a mechanistic study, see: (c) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441.

(10) For other examples where the use of Xantphos provides better results than the use of BINAP or DPPF, see ref 8e−j.

(11) For discussions of its unique *trans*-coordination to Pd, see: (a) Reference 8g. (b) Guari, Y.; van Strijdonck, G. P. F.; Boele, M. D. K.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2001**, *7*, 475. (c) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895.

Table 3. *N*-Arylation of 2-Aminothiazoles and Analogues[a]

entry	ArX	Ar'NH$_2$	product	mol%Pd	conc(M)	base/equiv	yield(%)
1				5	0.20	Na_2CO_3/1.4	75[b]
2				2	0.25	K_3PO_4/1.4	96[c]
3				4	0.25	Na_2CO_3/1.2	91[b]
4				4	0.25	Na_2CO_3/1.4	87[b]
5				4	0.25	Na_2CO_3/1.2	98
6				8	0.125	Na_2CO_3/1.4	64[c]
7				6	0.167	Na_2CO_3/1.4	89
8				2	0.25	NaO*t*Bu/2.0	84
9				8	0.167	NaO*t*Bu/2.0	74[d]

[a] Reaction conditions: 1.0 mmol of aryl halide, 1.05−1.4 equiv of Ar′NH$_2$, 1.1−2.4 equiv of base, 1−4 mol % of $Pd_2(dba)_3$, 3−12 mol % of Xantphos (L/Pd = 1.5), toluene (4−8 mL/mmol ArX), 100 °C, 15−16 h. Isolated yields are reported. [b] 1.0 equiv of H_2O was added. [c] 1,4-Dioxane as the solvent. [d] L/Pd = 1.1.

pyrazine (Table 2, entry 6) and even 2-amino-3-methyl--pyridine (Table 2, entry 3). Relatively low levels of catalyst loading (1−2% of Pd except for the hindered substrates in entry 3) were required, which was also important to lower the amounts of the undesired *N*-phenyl heteroarylamines when inactivated aryl halides were used. With the use of just 1.4 equiv of Cs_2CO_3 as a weak base, functional groups such as aldehyde and methyl/ethyl ester groups are tolerated (Table 2, entries 4, 7, and 9). A secondary aminopyridine (2-methylaminopyridine) also underwent the cross-coupling reactions using the weak base. Interestingly, BINAP was a better ligand for the reaction between 2-aminopyridine and 2-chloropyridine (Table 2, entry 2).[12]

Unfortunately, under the above optimized conditions, the reactions between 2-chloropyridines and 2-aminothiazoles gave very little products. In addition, reactions between 2-chloropyridine and 2-aminothiazole/2-aminobenzothiazole did not proceed at all under previously reported conditions (EtOH, NEt$_3$, 100 °C, 16 h) for direct nucleophilic attack of 2-aminothiazoles to highly activated aryl halides without catalysts.[5c,d] After an extensive screening of reaction variables including the base, solvent, additive, and ligand, we found Xantphos was still the best ligand among those commonly used for Pd-catalyzed aminations. The key to the success of these reactions, however, was to use Na_2CO_3 or K_3PO_4 instead of Cs_2CO_3 as the base and toluene as the solvent in many cases. The results of arylation of 2-aminothiazoles and analogues are summarized in Table 3.[13]

2-Aminothiazoles with various substituents reacted with 2-chloropyridines, 2-chloropyrimidine, chloropyrazine, 2-chloroquinoline, and 4-nitrochlorobenzene in good to excellent yields (Table 3, entries 1−5). No 4-substituents on the thiazole were required for a successful reaction (Table 3, entries 1−3).[5] Functional groups such as nitro and ester groups were tolerated. 2-Amino-1,3,4-thiadiazole and 2-aminobenzothiazole also reacted with 2-chloropyridine under these conditions (Table 3, entries 6 and 7). In a few reactions, 0.5−1 equiv of H_2O was added to help push the reaction to completion (Table 3, entries 1, 3, and 4).[14] Relatively higher levels of catalyst loading (2−8% of Pd) were required, and it was necessary to run these reactions at lower concentrations

(12) In this work, we found that BINAP was a better ligand only for reactions between 2-halopyridines and 2-aminopyridine/pyrimidines.

(13) **Typical Procedure** (Table 3, Entry 4). A re-sealable Schlenk tube was charged with $Pd_2(dba)_3$ (18.4 mg, 0.02 mmol, 4 mol % Pd), Xantphos (34.7 mg, 0.06 mmol), 2-amino-4-methylthiazole (140 mg, 1.2 mmol), Na_2CO_3 (*fine powder*, 149 mg, 1.4 mmol), chloropyrazine (0.091 mL, 1.0 mmol), and degassed toluene (4 mL). While the mixture was being stirred, H_2O (18 mg, 1.0 mmol) was added dropwise. The Schlenk tube was capped and carefully subjected to three cycles of evacuation−backfilling with N_2. It was then sealed and immersed into a 100 °C oil bath. After 15 h, the mixture was cooled, diluted with THF, filtered, concentrated, and chromatographed on an SiO_2 flash column to give a crude product. It was then sonicated in 3 mL of toluene−hexanes (1:1), filtered, and dried to give the pure product as a white solid (167 mg, 87%).

(14) The exact role of water is unclear. One possibility is that it helped solubilize the inorganic base to increase the reaction rate.

(4−8 mL of solvent/mmol ArX).[15] When an electron-neutral aryl halide was used, 2-aminothiazole itself failed to give the desired reaction under various conditions, but 2-aminobenzothiazole and 2-amino-1-methylbenzimidazole were arylated using NaO-*t*-Bu as the base (Table 3, entries 8 and 9).

In summary, we have developed a protocol for the *N*-(hetero)arylation of a number of heteroarylamines including 2-aminopyridines and their analogues using Xantphos as the ligand, Cs_2CO_3 as the base, and dioxane as the solvent. Aryl halides with various electronic and steric properties could be used, and functional groups were well tolerated. The first Pd-catalyzed arylation of 2-aminothiazoles and analogues was also accomplished with the use of Xantphos as the ligand. Na_2CO_3 and K_3PO_4 had to be used instead of Cs_2CO_3 for the reactions with activated (hetero)aryl halides, and NaO-*t*-Bu was required for inactivated aryl halides.

(15) For a discussion of the concentration effect, see ref 8g.

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Supporting Information Available: Experimental procedures and characterization data for arylation products (Tables 2 and 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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