Convenient Copper-Mediated Chan-Lam Coupling of 2-Aminopyridine: Facile Synthesis of *N*-arylpyridin-2-amines

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Graphical Abstract

Copper-Mediated Chan-Lam Coupling of 2-Aminopyridine: Facile Synthesis of *N*-arylpyridin-2-amines

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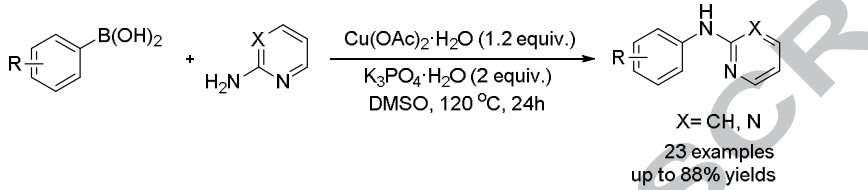
Jianbin Chen,[a] Kishore Natte,[a] Nikki Y. T. Man,[b] Scott G. Stewart,[b] and Xiao-Feng Wu*[a]



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Convenient Copper-Mediated Chan-Lam Coupling of 2-Aminopyridine: Facile Synthesis of *N*-arylpyridin-2-amines

Jianbin Chen,[a] Kishore Natte,[a] Nikki Y. T. Man,[b] Scott G. Stewart,[b] and Xiao-Feng Wu*[a]

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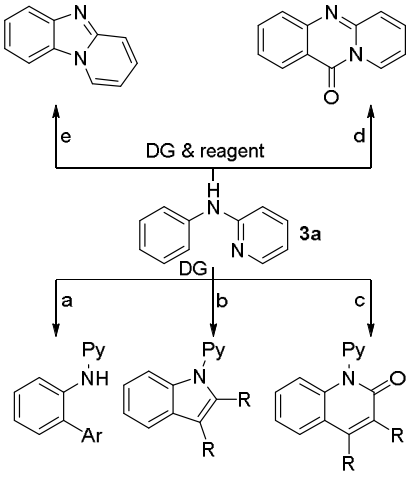
ABSTRACT

A new and practical process for the synthesis of *N*-arylpyridin-2-amine derivatives has been developed. Under the assistance of copper, the desired products were produced from commercially available 2-aminopyridine and aryl boronic acids in moderate to good yields with good functional group tolerance.

1. Introduction

Nitrogen-containing motifs are an important class of molecules which are frequently encountered in pharmaceuticals and biologically active compounds.[1] Among them, pyridine-rings not only hold unique biologically activities, taking nicotine as an example,[2] but also have been exploited as directing groups in transition metal-catalyzed C-H activations because of the excellent coordination ability of the nitrogen atom to the metal center.[3] Among them, *N*-arylpyridin-2-amines are interesting molecules. The pyridyl core bearing two functions: directing group in the C-H activation and/or reaction reagent (Scheme 1). More recently examples included: Chu et. al. developed a palladium-catalyzed arylation of **3a** (Scheme 1, procedure a);[4] it's annulation reaction with alkyl resulting indoles was reported by Li[5] and Ackermann[6] with palladium, rhodium, ruthenium or nickel as the catalysts, independently (Scheme 1, procedure b). Interestingly, our group investigated the carbonylative C-H annulation with alkynes for the quinolin-2(1*H*)-ones core synthesis (Scheme 1, procedure c).[7] We also successfully developed a heterogeneous palladium catalyzed cyclization of alkynes with **3a** to give indoles synthesis (Scheme 1, procedure b).[8] Additionally, the usage of the pyridyl group both as directing group and reaction reagent with the hypervalent iodine(III)[4a, 9] or transition-metals[10] as the catalysts were developed as well (Scheme 1, procedures d and e) and some other organic transformations of **3a** were also developed.[11]

Although many transformations of *N*-arylpyridin-2-amines have been developed, unfortunately, only very few of these substrates are commercially available. And very scarcely synthetic methods were documented to access them. In 2010, Li and co-workers demonstrated a palladium-catalyzed amination of 2-bromopyridine[5a] and a similar process for amination of 2-chloropyridine was reported by Maes in 2011.[10b] The S_NAr of 2-chloropyridine at 160 °C for the *N*-arylpyridin-2-amines production was reported as well.[10b] In 2014, Wang established a



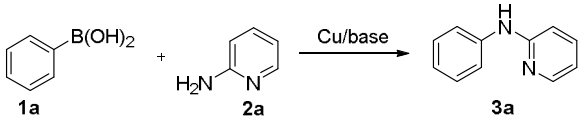
Scheme 1. *N*-phenylpyridin-2-amine as a useful building block in C-H functionalizations.

copper-catalyzed ligand free *N*-arylation of 2-aminopyridines.[12a] However, there are several drawbacks such as utilizing noble metal catalysts and expensive ligands, running at high temperature or very limited substrates scope. Moreover, over amination to give tri(hetero)arylamines is not avoidable. Thus, the development of new selective procedure under mild conditions is still highly desirable. In the past decades, Chan-Lam coupling have been regarded as one of the powerful tools for the construction of C-X (X= N, O, S) bonds.[13] Utilizing copper salts as the non-expensive catalyst and milder reaction conditions are the main advantages. Herein, we wish to report our results on the synthesis of *N*-arylpyridin-2-amines via copper-mediated *N*-arylation of 2-amino pyridine with aryl boronic acids.

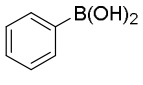
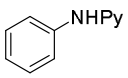
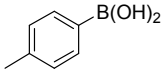
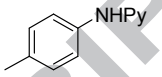
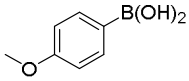
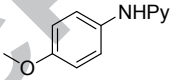
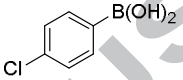
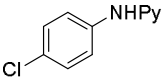
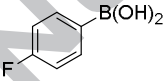
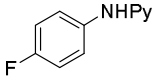
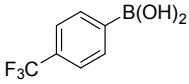
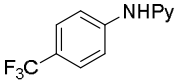
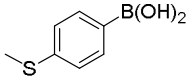
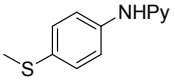
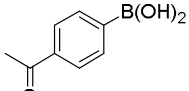
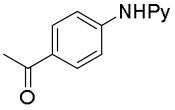
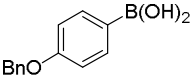
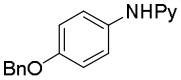
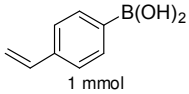
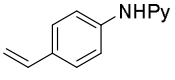
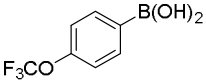
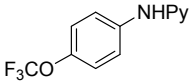
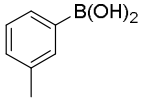
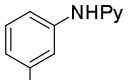
2. Discussion

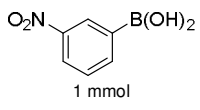
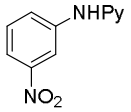
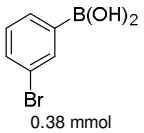
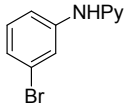
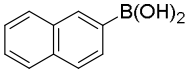
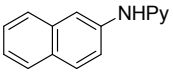
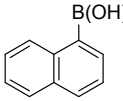
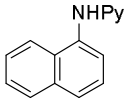
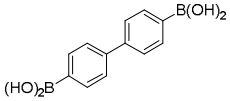
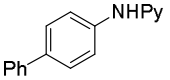
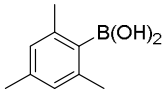
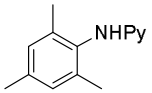
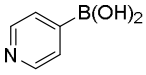
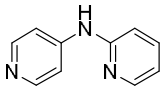
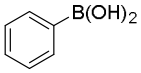
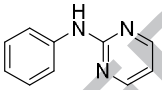
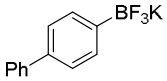
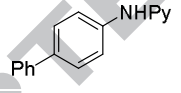
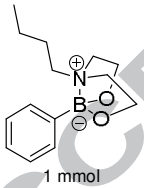
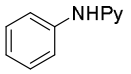
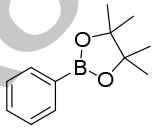
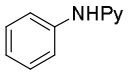
We started our optimization with phenyl boronic acid **1a** and 2-aminopyridine **2a** as the model substrates. After careful reaction conditions variation, the best results can be realized in 71% isolated yield in the presence of: 1.2 equivalents of $Cu(OAc)_2 \cdot H_2O$ as the promoter, 2 equivalents of $K_3PO_4 \cdot H_2O$ as the base in DMSO, at 120 °C for 24h. Unfortunately, low yields were observed when 10-20 % amount of copper salt was applied. With the best system in hand, we focused on the generality and limitation testing of this method.[14] As shown in Table 1, a series of functional groups can be tolerated. For the electron effect of the substrates, taken the methyl and methoxy as the examples of electron-donating group, good yields were obtained under optimized conditions (Table 1, entries 2 and 3). The substrates bearing electron-withdrawing groups such as the fluoro, chloro and trifluoromethyl provide the desired products also in good yields (Table 1, entries 4-6). Interestingly, the methylthio group which could be oxidized under the oxidative conditions was untouched under our aerobic system and gives the desired product in acceptable yield (Table 1, entry 7). The (4-acetylphenyl)boronic acid and (4-(benzyloxy)phenyl)boronic acid gave the targeted products in good yields as well (Table 1, entries 8 and 9). Importantly, the vinyl group was successfully incorporated into the final products in 84% yield which provide the possibility for further modification *via* the Heck reaction (Table 1, entry 10). Compared to the substrate-bearing trifluoromethyl group, the trifluoromethoxy group-substituted arylboronic acid resulted in moderate yield (Table 1, entry 11). Substrates with *meta* substitutions such as methyl, bromo and nitro worked as well although low yields for (3-nitrophenyl)boronic acid and (3-bromophenyl)boronic acid were given (Table 1, entries 12-14). However, the yield can be improved by simply decreasing the reaction temperature to 60 °C. It should be noted that 1- or 2-naphthylboronic acid run smoothly in our systems too (Table 1, entries 15 and 16). Notably, when using the symmetrical [1,1'-biphenyl]-4,4'-diyldiboronic acid as the starting material, only *N*-([1,1'-biphenyl]-4-yl)pyridin-2-amine was obtained because of deboronication reaction (Table 1, entry 17). Unfortunately, low yield was observed while sterically bulk arylboronic acid was applied in our system (Table 1, entry 18). To our delight, the heteroaryl boronic acid which is less stable compared to the aryl boronic acid analogues can provided the desired product in moderate yield under low temperature (Table 1, entry 19). 2-Aminopyrimidine can also serve as the coupling partner and resulted in moderate yield (Table 1, entry 20). Moreover, aryl boronic acid derivatives such as potassium aryltrifluoroborate, phenylboronic acid *N*-butyldiethanolamine ester and phenylboronic acid pinacol ester could deliver the desired products without any further optimizations (Table 1, entries 21-23).

Table 1. Substrate Scope for the Synthesis of *N*-arylpyridin-2-amines.[a]



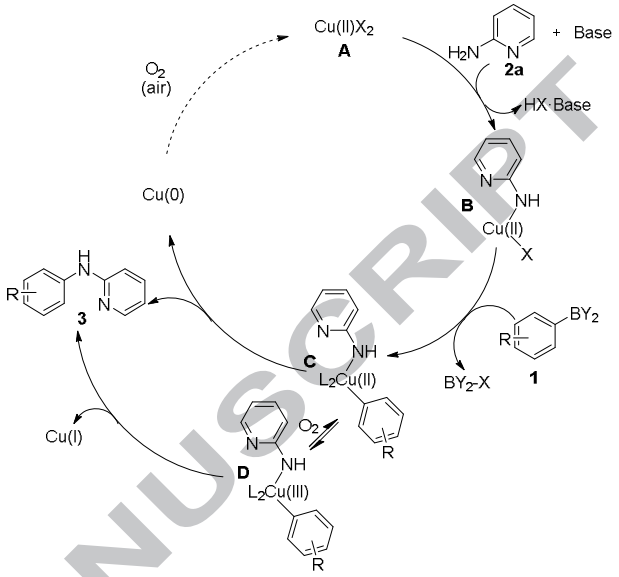
1a 2a 3a

Entry	Substrate	Product	Yield[b]
1	 2 mmol		71%
2	 0.5 mmol		83%
3	 0.5 mmol		77%
4	 0.5 mmol		61%
5	 0.8 mmol		79%
6	 0.5 mmol		82%
7	 2 mmol		54%
8	 0.5 mmol		75%
9	 2 mmol		88%
10	 1 mmol		84%
11	 2 mmol		41%
12	 0.5 mmol		73%

13	 1 mmol		17% 35%[c]
14	 0.38 mmol		24%
15	 1 mmol		61%
16	 1 mmol		15%[d]
17	 0.5 mmol		47%[e]
18	 2 mmol		8%
19	 1 mmol		2% 52%[d]
20	 2 mmol		68% 6%[c]
21	 2 mmol		17%
22	 1 mmol		45%[f]
23	 2 mmol		59%[f]

[a] Reaction conditions: Aryl boronic acid (1 equiv.), 2-amino-pyridine (1 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1.2 equiv.), $K_3PO_4 \cdot H_2O$ (2 equiv.), DMSO as solvent, 120 °C, 24h; For 2 mmol scale, 5 mL of DMSO was used while for others 3 mL of DMSO was used; Isolated yields. [b] Isolated yields. [c] 60 °C. [d] 40 °C. [e] 40 °C, 2-amino-pyridine (2 equiv.). [f] GC yields.

A possible reaction mechanism is given in Scheme 2. Firstly, the ligand exchange of copper(II) complex **A** between **2a** with the aid of base forms the intermediate **B** followed by transmetallation of arylboronic acid producing complex **C**; Then reductive elimination of specie **C** delivers the target products and copper(0). At the same time, the oxidation of complex **C** in the presence of ambient oxygen from air generates the copper(III) species **D** which provides the products and copper(I) via reductive elimination is also possible. At last, the copper(0) or copper(I) could be oxidized to the active copper(II) species if the coupling proceeds through a catalytic manner.



Scheme 2. Proposed reaction mechanism.

In conclusion, a practical procedure for the synthesis of *N*-arylpyridin-2-amine analogues has been developed. The reaction go through copper-promoted Chan-Lam coupling of 2-aminopyridine with aryl boronic acids. The desired products were isolated in moderate to good yields with good functional group tolerance.

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References and notes

1. Schmeltz, I.; Hoffmann, D. *Chem. Rev.* **1977**, *77*, 295-311.
2. a) Eberle, M. K.; Houlihan, W. J. *Chem. Abstr.* **1971**.; b) Wertz, D. L.; Winters, A.; Craft, T.; Holloway, J. *Energy Fuels* **2006,** *20*, 239-244; c) Bell, T. W.; Khasanov, A. B.; Drew, M. G. B. *J. Am. Chem. Soc.* **2002,** *124*, 14092-14103; d) Wahlberg, G.; Adamson, U.; Svensson, J. *Diabetes-Metab. Res. Rev.* **2000,** *16*, 33-42; e) Lee, A.-C.; Xu, X.; Colombini, M. *J. Biol. Chem.* **1996,** *271*, 26724-26731; f) Tritz, G. J. *Vol. 6*, Peeters Press, **1992**, pp. 3-7; g) Kim, S. G.; Philpot, R. M.; Novak, R. F. *J. Pharmacol. Exp. Ther.* **1991,** *259*, 470-477; h) Kaplan, N. O. *Curr. Top. Cell. Regul.* **1985,** *26*, 371-381; i) Putilina, F. E. *Nervnaya Sistema* **1978**, 39-53; j) Zarkowsky, H.; Lipkin, E.; Glaser, L. *Biochem. Biophys. Res. Commun.* **1970,** *38*, 787-793; k) Michelazzi, L. *Minerva Med.* **1955,** *II*, 1842-1844; m) Gutmann, H. R.; Jandorf, B. J.; Bodansky, O. *J. Biol. Chem.* **1947,** *169*, 145-152.
3. a) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009,** *11*, 3120-3123; b) Ye, Z.; Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *Org. Lett.* **2009,** *11*, 3974-3977; c) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org: Lett.* **2009,** *11*, 4716-4719; d) Wang,

W.; Luo, F.; Zhang, S.; Cheng, J. *J: Org. Chem.* **2010,** *75*, 2415-2418; e) Jia, X.; Yang, D.; Wang, W.; Luo, F.; Cheng, J. *J. Org. Chem.* **2009,** *74*, 9470-9474; f) Chen, X.; Dobereiner, G.; Hao, X.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Tetrahedron* **2009,** *65*, 3085-3089; g) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006,** *128*, 12634-12635; h) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006,** *128*, 6790-6791; i) Lei, Z.-Q.; Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Sun, J.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2012,** *51*, 2690-2694; j) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010,** *110*, 1147-1169.

4. a) Chu, J.-H.; Huang, H.-P.; Hsu, W.-T.; Chen, S.-T.; Wu, M.-J. *Organometallics* **2014,** *33*, 1190 - 1204; b) Chu, J.-H.; Lin, P.-S.; Lee, Y.-M.; Shen, W.-T.; Wu, M.-J. *Chem. Eur. J.* **2011,** *17*, 13613 - 13620.
5. a) Chen, J.; Pang, Q.; Sun, Y.; Li, X. *J. Org. Chem.* **2011,** *76*, 3523 - 3526; b) Chen, J.; Song, G.; Pan, C.-L.; Li, X. *Org. Lett.* **2010,** *12*, 5426 - 5429.
6. a) Song, W.; Ackermann, L. *Chem. Commun.* **2013**, *49*, 6638 - 6640; b) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764 - 767.
7. Chen, J.; Natte, K.; Spannenberg, A.; Neumann, H.; Beller, M.; Wu, X.-F. *Chem. Eur. J.* **2014**, *20*, 14189-14193.
8. Chen, J.; He, L.; Natte, K.; Neumann, H.; Beller, M.; Wu, X.-F. *Adv. Synth. Catal.* **2014,** *356*, 2955-2959.
9. a) Kutsumura, N.; Kunimatsu, S.; Kagawa, K.; Otani, T.; Saito, T. *Synthesis* **2011**, 3235 - 3240; b) He, Y.; Huang, J.; Liang, D.; Liu, L.; Zhu, Q. *Chem. Commun.* **2013,** *49*, 7352 - 7354; c) Chu, J.-H.; Hsu, W.-T.; Wu, Y.-H.; Chiang, M.-F.; Hsu, N.-H.; Huang, H.-P.; Wu, M.-J. *J. Org. Chem.* **2014,** *79*, 11395 - 11408; d) Qian, G.; Liu, B.; Tan, Q.; Zhang, S.; Xu, B. *Eur. J. Org. Chem.* **2014,** 4837 - 4843; e) Rao, D. N.; Rasheed; Vishwakarma, R. A.; Das, P. *RSC Adv.* **2014,** *4*, 25600 – 25604; f) Manna, S.; Matcha, K.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 8163-8166; g) Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, 5769-5804.
10. a) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010,** *132*, 13217 - 13219; b) Masters, K.-S.; Rauws, T. R. M.; Yadav, A. K.; Herrebout, W. A.; Van Der Veken, B.; Maes, B. U. W. *Chem. Eur. J.* **2011,** *17*, 6315 - 6320.
11. a) Güell, I.; Ribas, X. *Eur. J. .Org. Chem.* **2014,** *2014*, 3188-3195; b) Huang, X.; Xu, S.; Tan, Q.; Gao, M.; Li, M.; Xu, B. *Chem. Commun.* **2014,** *50*, 1465-1468.
12. a) Wang, D.; Kuang, D.; Zhang, F.; Liu, Y.; Ning, S. *Tetrahedron Lett.* **2014,** *55*, 7121-7123; b) Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, 6084-6088; c) Kim, A. Y.; Lee, H. J.; Park, J. Chan, Kang, H.; Yang, H.; Song, H.; Park, K. H. *Molecules* **2009**, *14*, 5169-5178; d) Robin, M.; Faure, R.; Périchaud, A.; Galy, J. P. *Synth. Commun.* **2002**, *32*, 981-988.
13. a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998,** *39*, 2933-2936; b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998,** *39*, 2941-2944; c) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998,** *39*, 2937-2940; d) Chan, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003,** *44*, 3863-3865; e) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003,** *44*, 4927-4931; f) Ye, Z.; Qian, P.; Lv, G.; Luo, F.; Cheng, J. *J. Org. Chem.* **2010,** *75*, 6043-6045; g) Zhang, L.; Zhang, G.; Zhang, M.; Cheng, J. *J. Org. Chem.* **2010,** *75*, 7472-7474; h) Qin, C.; Wu, H.; Chen, J.; Liu, M.; Cheng, J.; Su, W.; Ding, J. *Org. Lett.* **2008,** *10*, 1537-1540; for selected reviews on copper-catalyzed coupling of amines, see i) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400-5449; j) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; k) Finet, J. P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597–626; l) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954-6971; m) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13-31.
14. General Procedure for the Synthesis of *N*-arylpyridin-2-amine Analogues: An oven-dried 25 mL sealed tube with stirring bar was charged with aryl boronic acid (1 equiv.), 2-amino pyridine (1 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1.2 equiv.), $K_3PO_4 \cdot H_2O$ (2 equiv.) and 3 or 5 mL of DMSO and then closed the sealed tube. The reaction mixture was heated at 120 °C for 24 h. After the reaction finished, the product was extracted with ethyl acetate (5 × 3 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to yield the crude reaction mixture. The purification was done by combi flash machine flash chromatography on silica gel (eluent: heptanes:EtOAc = 3:2).