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Palladium-/Copper-Catalyzed Regioselective Amination and Chloroamination of Indoles

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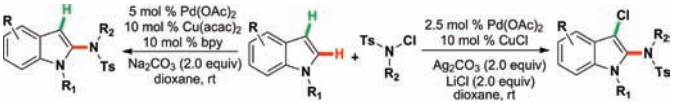
ABSTRACT



A palladium-/copper-catalyzed intermolecular C−H amination reaction of indoles has been developed. This reaction proceeds in good to excellent yields to produce a variety of 2-amino-substituted indoles and exhibits excellent regioselectivity at room temperature. Furthermore, chloroamination of indoles provides a simple method for the construction of C−N and C−Cl bonds in one step.

As a complementary methodology of Buchwald−Hartwig coupling, transition-metal-catalyzed direct C−H functionalization/amination provides a new synthetic strategy for C−N bond formation and has recently received much attention. Although intramolecular oxidative amination of arenes has been reported in the past few years,[1] direct intermolecular C−H amination of both arenes and heteroarenes has just been investigated recently.[2−5] Two major advances in this challenging transformation have been made via transition-metal-catalyzed strategies (Scheme 1): (1) direct amination of aromatic C−H bonds (eq 1);[2−4] and (2) direct C−H amination of azoles (eq 2).[5] However, intermolecular C−H amination still remains a challenge because most of the existing examples suffer from a relatively limited substrate scope. This has led us to explore a broader substrate scope for catalytic amination reactions under mild conditions. C−H arylation of

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(1) For intramolecular amidation of C−H bonds, see: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (c) Yamamoto, M.; Matsubara, S. *Chem. Lett.* **2007**, *36*, 172. (d) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (e) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (f) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (g) Neumann, J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892. (h) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (i) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (j) Kumar, R. K.; Ali, Md. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 2102. (k) Bonnamour, J.; Bolm, C. *Org. Lett.* **2011**, *13*, 2012. (l) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996.

(2) For intermolecular amination of C(aryl)−H bonds, see: (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (c) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (d) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694.

(3) For Pd-catalyzed intermolecular C−H amination with alkylamines, see: Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652.

(4) For examples of Cu(II)-catalyzed C−H amination reactions with amides and anilides, see: (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (c) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (d) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158.

(5) For C−H amination of azoles, see: (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (b) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (c) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. (d) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (e) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 2929. (f) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (g) Gu, L.; Neo, B. S.; Zhang, Y. *Org. Lett.* **2011**, *13*, 1872. (h) Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359. (i) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522. (j) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (k) For a cobalt-catalyzed C−H amination of azoles via acid-promoted nucleophilic attack, see: Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899.

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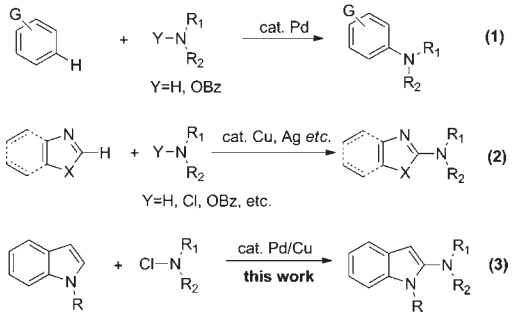
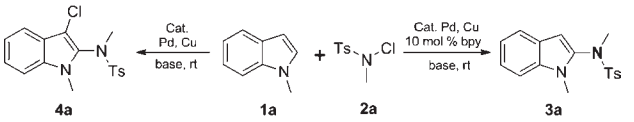
Scheme 1. Intermolecular C−H Amination



indoles has been reported; the corresponding amination is very rare.[6] Herein, we report a new palladium-/copper-catalyzed amination and chloroamination of indoles at room temperature (eq 3). This method is complementary to the synthesis of 2-amino-substituted indoles and pyrroles, which are one important class of biologically active compounds and occupy an important position in pharmaceuticals and natural products.[7] Moreover, this method offers a simple strategy for the construction of C−N and C−Cl bonds in one step.

Initially, we examined the direct amination of *N*-methylindole (**1a**, 0.5 mmol) with *N*-chloro-*N*,4-dimethyl-benzenesulfonamide (**2a**, 0.75 mmol) using $Pd(OAc)_2$ (5 mol %), $Cu(acac)_2$ (10 mol %), 2,2′-bipyridine (10 mol %), and Ag_2CO_3 (2.0 equiv) in toluene at room temperature. The corresponding amination product **3a** was obtained in 18% isolated yield (Table 1, entry 1). Encouraged by this preliminary result, we then screened different solvents and found that 1,4-dioxane was the most suitable candidate for this transformation (Table 1, entries 2 and 3). When the amount of **2a** was increased to 1.8 equiv, a 50% yield of **3a** was obtained (Table 1, entry 4). Further research showed that the reaction with Na_2CO_3 as the base afforded the amination product **3a** in 92% yield (Table 1, entry 5). A comparable reaction efficiency was presented by $NaHCO_3$ (Table 1, entry 6). Notably, in the absence of $Pd(OAc)_2$ or $Cu(acac)_2$, the desired product was isolated in 62% and 21% yield, respectively (Table 1, entries 7 and 8). These results indicate that the copper catalyst should play a predominate role in this catalytic system and $Pd(OAc)_2$ as the cocatalyst would increase the reactivity. No amination product was detected in the absence of 2,2′-bipyridine (Table 1, entry 9). To our surprise, with the amount of **2a** increased to 3.0 equiv, we found that treating **1a** with $Pd(OAc)_2$ (5 mol %), $Cu(acac)_2$ (10 mol %), and Ag_2CO_3 (2.0 equiv) would furnish 37% of chloroamination product **4a** (Table 1, entry 10).[8] Other silver salts such as AgOAc and Ag_2O were ineffective (Table 1, entries 11 and 12). In our further screening of copper sources and additives, optimal results were observed with 2.5 mol % $Pd(OAc)_2$, 10 mol % CuCl, 2.0 equiv of Ag_2CO_3, and 2.0 equiv of LiCl in dioxane at room temperature (Table 1, entries 13−19).

Table 1. Optimization for Palladium-/Copper-Catalyzed C2 Amination and Chloroamination of *N*-Methylindoles (**1a**) with *N*-Chloro-*N*,4-dimethylbenzenesulfonamide (**2a**)[a]



					3a	4a
entry	$Pd(OAc)_2$ (mol %)	Cu	base	solvent	yield (%)[b]	
1	5	$Cu(acac)_2$	Ag_2CO_3	toluene	18	–
2	5	$Cu(acac)_2$	Ag_2CO_3	THF	22	–
3	5	$Cu(acac)_2$	Ag_2CO_3	dioxane	35	–
4	5	$Cu(acac)_2$	Ag_2CO_3	dioxane	50	–
5	**5**	**$Cu(acac)_2$**	**Na_2CO_3**	**dioxane**	**92**	–
6	5	$Cu(acac)_2$	$NaHCO_3$	dioxane	82	–
7	–	$Cu(acac)_2$	Na_2CO_3	dioxane	62	–
8	5	–	Na_2CO_3	dioxane	21	–
9[c]	5	$Cu(acac)_2$	Na_2CO_3	dioxane	0	–
10[c,d]	5	$Cu(acac)_2$	Ag_2CO_3	dioxane	–	37
11[c,d]	5	$Cu(acac)_2$	AgOAc	dioxane	–	0
12[c,d]	5	$Cu(acac)_2$	Ag_2O	dioxane	–	0
13[c,d]	5	$CuCl_2$	Ag_2CO_3	dioxane	–	7
14[c,d]	5	$CuBr_2$	Ag_2CO_3	dioxane	–	<5
15[c,d]	5	CuBr	Ag_2CO_3	dioxane	–	<5
16[c,d]	5	CuCl	Ag_2CO_3	dioxane	–	43
17[c,e]	2.5	CuCl	Ag_2CO_3	dioxane	–	62
18[c,f]	**2.5**	**CuCl**	**Ag_2CO_3**	**dioxane**	–	**85**
19[c,f]	–	CuCl	Ag_2CO_3	dioxane	–	30

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.9 mmol), Cu (10 mol %), bpy (10 mol %), base (2 equiv), solvent (2 mL), rt, 14 h, N_2. [b] Isolated yield. [c] In absence of bpy. [d] **2a** (1.5 mmol) was used. [e] LiCl (1.0 equiv) was used. [f] LiCl (2.0 equiv) was used.

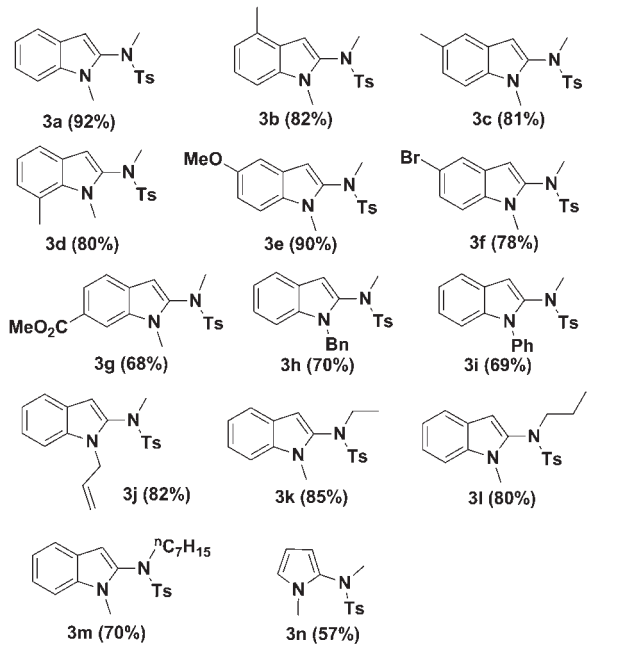
Under the optimized conditions, the substrate scope toward the amination reaction was further investigated. The amination reaction demonstrated a tolerance toward functional groups at the indoles as shown in Table 2. Indoles bearing substituents with diverse electronic properties such as electron donation (methyl or methoxy group) showed a better reactivity and gave the corresponding products in moderate to good yields (**3b**−**e**). The electron-deficient indoles (bromo or ester group) exhibited a slightly lower reactivity than their electron-donating counterparts (**3f** and **3g**). *N*-Substituted indoles such as *N*-benzylindole, *N*-phenylindole, and *N*-allylindole reacted smoothly with **2a** in good yields (**3h**−**j**). In contrast, *N*-acetylindole furnished an inextricable mixture. For different *N*-alkyl chlorosulfonamides, amides bearing long chain alkyl groups also worked well and reacted with **1a** to furnish the amination products in good yields (**3k**−**m**).

(6) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632.

(7) (a) Taylor, E. C.; Jones, R. A. *Pyrroles*; Wiley: New York, 1990. (b) *The Chemistry of Heterocyclic Compounds*, Vol. 25; Wiley Interscience: New York, 1994. (c) Sundberg, R. J. *Indoles*; Academic: New York, 1996.

(8) The structures of **3a** and **4a** were confirmed by X-ray crystallography. For details of crystal analysis data, see Supporting Information.

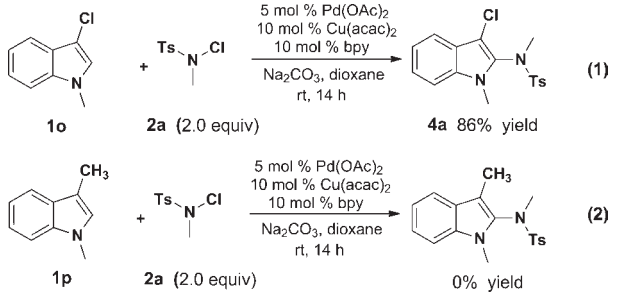
Table 2. Palladium-/Copper-Catalyzed Direct Amination and Chloroamination of Indoles[a]



[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.9 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(acac)_2$ (10 mol %), bpy (10 mol %), Na_2CO_3 (2 equiv), 1,4-dioxane (2 mL), rt, 14 h, N_2. Isolated yield.

Furthmore, the reaction of *N*-methylpyrrole with **2a** was also investigated and the desired product **3n** was isolated in 57% yield under the standard conditions. Importantly, the exclusive regioisomer was obtained in all cases.

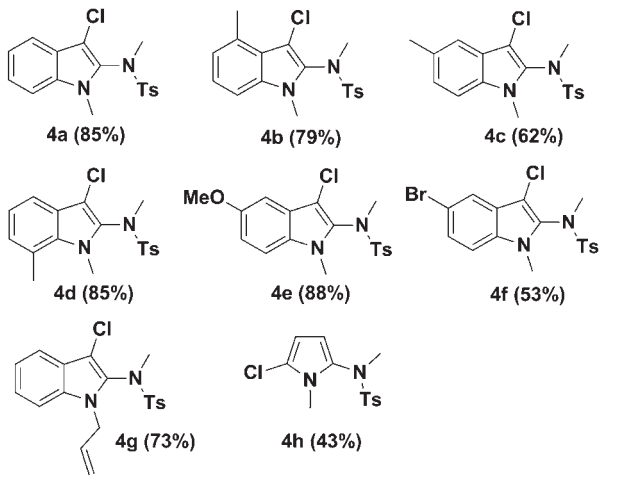
Scheme 2



The reaction of 3-chloro-1-methylindole (**1o**) with **2a** gave amination product in 86% yield (Scheme 2, eq 1). However, when 1,3-dimethylindole (**1p**) was used as the reaction partner, no corresponding product was obtained (Scheme 2, eq 2). This result indicates that the chlorine atom on the indoles improves the amination reactivity.[9]

(9) Palladium-catalyzed direct arylation of chlorine-containing heteroaromatics, see: Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

Table 3. Palladium-/Copper-Catalyzed Direct Chloroamination and Chloroamination of Indoles[a]

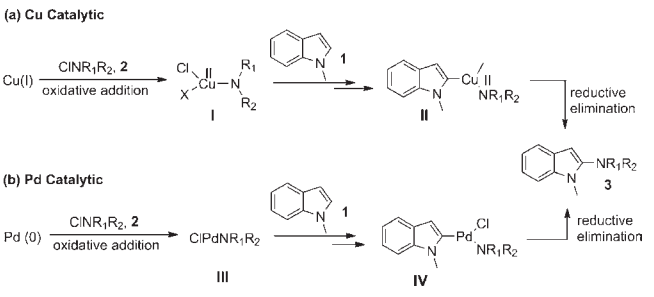


[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (2.5 mol %), CuCl (10 mol %), Ag_2CO_3 (2 equiv), LiCl (2 equiv), 1,4-dioxane (2 mL), rt, 14 h, N_2. Isolated yield.

The chloroamination of a series of substituted indoles was then studied under the optimized reaction conditions, and the results are summarized in Table 3. The electronic nature of substituents on the benzene ring of the indoles influenced the reactivity of this chloroamination reaction with the analogous tendency for amination of indoles. Compared with electron-deficient indoles, the electron-rich indoles showed a better reactivity and furnished the products in good yields (**4a**–**g**). Although, the chloroamination of *N*-methylpyrrole possessed a relatively lower reactivity with **2a** to give **4h** in 43% yield, this case gave a 2,5-disubstituted pyrrole with excellent chemo- and regioselectivity.

The detailed mechanism of the C–H amination reaction still remains unclear. A possible reaction pathway was proposed on the basis of previous studies. For the copper-catalyzed pathway (Scheme 3a): the oxidative addition of the chlorosulfonamide to the Cu(I) would generate an electrophilic Cu(II) intermediate **I**. The latter species can

Scheme 3. Possible Reaction Pathways for Copper and Palladium Catalysts



attack the C2 position[6] of indole followed by the deprotonation to give intermediate **II** (alternatively, intermediate **I** can also attack the C3 position of indole before the migration to the C2 position).[10] This step would be succeeded by reductive elimination, delivering the product **3** and reforming the Cu(I) catalyst. The palladium-catalyzed pathway is similar to the copper-catalyzed pathway (Scheme 3b): the oxidative addition of the chlorosulfonamide to the Pd(0) would generate the electrophilic Pd(II) intermediate **III**. The intermediate **III** can attack the C3 position of indole, which undergoes a C3−C2 migration to form the intermediate **IV**.[11] The subsequent reductive elimination results in the final product **3**.

(10) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

(11) (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125.

In conclusion, we have developed an intermolecular direct C−H amination and chloroamination of indoles using chlorosulfonamides as the nitrogen source. This methodology allows the synthesis of a variety of 2-amino-substituted indoles, which exhibits excellent regioselectivity and high functional group tolerance at room temperature.

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Supporting Information Available. Experimental procedures, full characterization of products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.