J|A|C|S COMMUNICATIONS

Published on Web 05/03/2010

A New Entry of Amination Reagents for Heteroaromatic C−H Bonds: Copper-Catalyzed Direct Amination of Azoles with Chloroamines at Room Temperature

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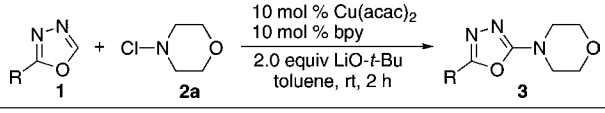
A metal-mediated sp^2 C−N bond forming reaction is of great interest in organic synthesis since the molecules containing aryl- and heteroarylamine units are prevalent in biological and pharmaceutical sciences.[1] The palladium-catalyzed amination of aryl halides, that is Buchwald−Hartwig amination,[2] as well as a copper-mediated one[3,4] is now the most powerful and reliable method for the synthesis of these target structures. On the other hand, transition-metal-catalyzed direct amination of arenes and heteroarenes has received much attention as a complementary and potentially more efficient route to the above amines. Although palladium[5] and rhodium[6] complexes are known to catalyze this type of transformations, most of them are restricted in an intramolecular fashion.[5a,c−e,6] The efforts by several groups have overcome the limitation and achieved the intermolecular versions using the copper[7] and silver[8] salts. However, these processes still suffer from harsh conditions such as higher reaction temperature[7c,d] and use of a stoichiometric amount of metal oxidant.[7a,b,8] Thus, further development for direct C−H amination is strongly desired.

Herein, we introduce chloroamine[9] as a readily available and effective nitrogen source for heteroaromatic C−H functionalization: the copper-catalyzed direct amination of azoles with chloroamines is described. Use of this type of reagent under copper catalysis enables the formation of heteroaryl−amino linkages even at room temperature so as to provide a rapid and straightforward access to the heteroarylamines of quite importance in biological and medicinal chemistry.[10]

Table 1. Copper-Catalyzed Direct Amination of Various 1,3,4-Oxadiazoles **1** with 4-Chloromorpholine (**2a**)[a]



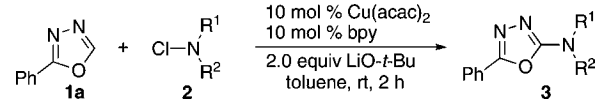
entry	R 1	3, yield (%)[b]
1	Ph (**1a**)	**3aa**, 81
2	4-MeC_6H_4 (**1b**)	**3ba**, 70
3	4-$MeOC_6H_4$ (**1c**)	**3ca**, 72
4	4-$CF_3C_6H_4$ (**1d**)	**3da**, 62
5	4-ClC_6H_4 (**1e**)	**3ea**, 84
6	1-naphthyl (**1f**)	**3fa**, 83
7	$Ph(CH_2)_2$ (**1g**)	**3ga**, 63

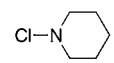
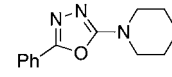
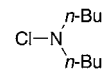
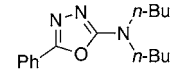
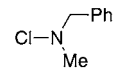
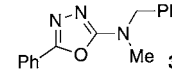
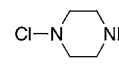
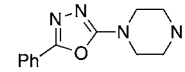
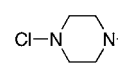
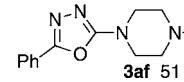
[a] A mixture of $Cu(acac)_2$ (0.050 mmol), bpy (0.050 mmol), **1** (0.50 mmol), **2a** (0.75 mmol), and LiO-*t*-Bu (1.0 mmol) in toluene (3.0 mL) was stirred at room temperature for 2 h under N_2. [b] Yield of isolated product.

Initially, we selected 2-phenyl-1,3,4-oxadiazole (**1a**) and 4-chloromorpholine (**2a**) as the starting materials because the expected product skeleton, amino-1,3,4-oxadiazole, is among the most interesting heteroarylamines exhibiting a broad spectrum of biological activity.[11] After the extensive screening of various transition metals, ligands, and bases, we were pleased to find that a combination of $Cu(acac)_2$/bpy (bpy = 2,2′-bipyridine) catalyzed the amination of **1a** with **2a** in the presence of LiO-*t*-Bu as a base to furnish **3aa** in 81% yield (Table 1, entry 1).[12] Notably, the reaction completed within 2 h even at room temperature. The oxadiazoles bearing electron-donating methyl **1b** and methoxy groups **1c** as well as the simple one underwent the amination very smoothly (entries 2 and 3). The electron-withdrawing trifluoromethyl and chloro substituents did not interfere with the reaction (entries 4 and 5). In particular, **1e** was transformed to **3ea** in good yield with the carbon−chloride moiety left intact, which could enjoy further elaboration. A bulky naphthalene motif was also compatible toward the reaction (entry 6). Moreover, the aliphatic phenethyl-substituted **1g** coupled with **2a** to form the heteroarylamine **3ga** in an acceptable yield (entry 7).

Under the standard reaction conditions, a variety of *N*,*N*-dialkylchloroamines **2** were examined for the direct amination of **1a** (Table 2). The reactions with cyclic **2b** and acyclic chloroamines **2c** proceeded without any difficulties to afford amino-1,3,4-oxadiazoles **3ab** and **3ac** (entries 1 and 2). Benzyl and Boc protections on nitrogen were tolerant so that the orthogonal additional functionalization after their appropriate deprotection would be possible (entries 3 and 4). In addition, the chloroamine **2f** containing two C−Cl bonds was also available for use (entry

Table 2. Copper-Catalyzed Direct Amination of 2-Phenyl-1,3,4-oxadiazole (**1a**) with Various Chloroamines **2**[a]



entry	2	3, yield (%)[b]
1	 **2b**	 **3ab** 68
2	 **2c**	 **3ac** 62
3	 **2d**	 **3ad** 69
4	 **2e**	 **3ae** 63
5[c]	 **2f**	 **3af** 51

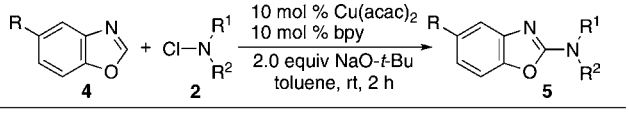
[a] See Table 1 for the reaction conditions. [b] Yield of isolated product. [c] Chloroamine **2f** as the limiting reagent. With 20 mol % of $Cu(acac)_2$/bpy, 2.4 equiv of **1a**, and 4.8 equiv of LiO-*t*-Bu.

10.1021/ja101939r

5). Thus, a symmetrical *N*,*N*′-bis(heteroaryl)piperazine **2af** was easily prepared.[13]

Next, we turned our attention to the amination of benzoxazole (**4a**) (Table 3).[14] Under the same conditions as those shown in Tables 1 and 2, **4a** reacted with **2a** sluggishly, and the desired **5aa** was detected in only 17% GC yield (entry 1). However, to our delight, the simple replacement of LiO-*t*-Bu with NaO-*t*-Bu significantly improved the reaction efficiency to afford **5aa** in 76% yield (entry 2). By using the modified protocol, benzoxazoles **4b**−**d** having the substitutions at the 5-position were aminated effectively (entries 3−5), and the piperizine and dibutylamine moieties also could be introduced to the benzoxazole core (entries 6 and 7).[15]

Table 3. Copper-Catalyzed Direct Amination of Various Benzoxazoles **4**[a]



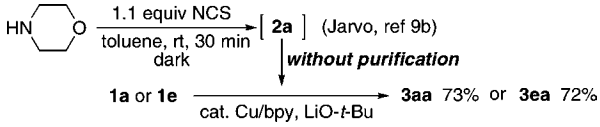
4 + **2** → **5**

entry	R **4**	**2**	**5**, yield (%)[b]
1[c]	H (**4a**)	**2a**	**5aa**, 17[d]
2	**4a**	**2a**	**5aa**, 76
3	Ph (**4b**)	**2a**	**5ba**, 62
4	Me (**4c**)	**2a**	**5ca**, 53
5	Cl (**4d**)	**2a**	**5da**, 73
6	**4a**	**2b**	**5ab**, 66
7	**4a**	**2c**	**5ac**, 38

[a] A mixture of $Cu(acac)_2$ (0.050 mmol), bpy (0.050 mmol), **4** (0.50 mmol), **2** (0.75 mmol), and NaO-*t*-Bu (1.0 mmol) in toluene (3.0 mL) was stirred at room temperature for 2 h under N_2. [b] Yield of isolated product. [c] With LiO-*t*-Bu instead of NaO-*t*-Bu. [d] GC yield.

While the present chloroamines are readily accessible from the corresponding amines and bleach,[16] a more convenient chlorination/direct amination sequence is operative.[9b] Namely, upon the exposure of **2a** generated in situ through the chlorination of morpholine with *N*-chlorosuccinimide (NCS) in toluene to a mixture of **1a**, $Cu(acac)_2$/bpy, and LiO-*t*-Bu, **3aa** was produced in a slightly lower yield (Scheme 1). Amino-1,3,4-oxazole **3ea** was also synthesized in the same manner.

Scheme 1



Although the exact reaction mechanism still remains unclear, the most plausible pathway would involve (i) base-assisted cupration of azole,[17] (ii) subsequent oxidative addition of the chloroamine to the resulting (heteroaryl)Cu(I) intermediate, and (iii) productive reductive elimination from the Cu(III) complex.[18] Ongoing work seeks to uncover the detailed mechanism and expand the reaction scope with chloroamines of high potential in direct C−H amination chemistry.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research from MEXT and JSPS, Japan.

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

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JA101939R