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Direct Amination of Azoles via Catalytic C−H, N−H Coupling

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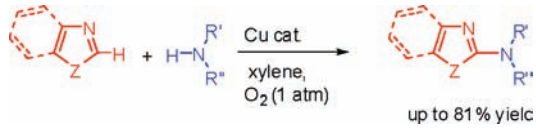
ABSTRACT



C−H, N−H Coupling of azoles takes place with several amines in the presence of a copper catalyst to undergo amination at the 2-position. The reaction of benzothiazole with *N*-methylaniline in the presence of sodium acetate and 20 mol % $Cu(OAc)_2$ in xylene under an oxygen atmosphere afforded the aminated product in 81% yield.

Transition-metal-catalyzed C−H functionalization reactions are of great interest in organic synthesis because the reaction shows an advantage in atom efficiency compared to related cross-coupling with organometallic compounds.[1] The reaction of heteroaromatic compounds is particularly important because of their wide utilities in the synthesis of biologically active molecules and advanced organic materials.[2] The catalytic carbon−carbon bond-forming reaction via C−H functionalization has been achieved by the reaction of aryl halides[3,4] or simple arenes at the carbon−hydrogen bond.[5]

In addition to such carbon−carbon bond-forming reactions, carbon−heteroatom bond formation is also an important issue, and a variety of reactions with organic halides (Buchwald−Hartwig reactions)[6] and organometallic compounds (oxidative coupling)[7] have been developed so far. In contrast, limited examples are shown for intra-[8] and

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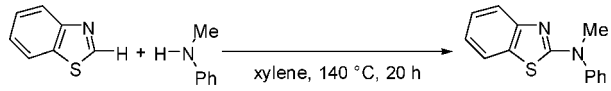
Table 1. Amination of Benzothiazole (**1**) with **2a**



1 **2a** **3a**

entry	reagents (equiv)[a]	yield[b] (%)
1	CuI (0.2), PPh_3 (0.4), NaOAc (4), O_2	0
2	$CuCl_2$ (0.2), PPh_3 (0.4), NaOAc (4), O_2	23
3	$Cu(OAc)_2$ (0.2), PPh_3 (0.4), NaOAc (4), O_2	82
4	$Cu(OAc)_2$ (0.2), NaOAc (4), O_2	39[c]
5	$Cu(OAc)_2$ (0.2), 2,2′-bipyridyl (0.2), NaOAc (4), O_2	tr
6	$Cu(OAc)_2$ (0.2), *N*,*N*′-dimethylethylenediamine (0.2), NaOAc (4), O_2	52
7	$Cu(OAc)_2$ (0.2), dppe (0.2), NaOAc (4), O_2	42
8	$Cu(OAc)_2$ (0.2), XANTPHOS (0.2), NaOAc (4), O_2	68
9	$Cu(OAc)_2$ (0.2), PPh_3 (0.4), NaOAc (4), air	46
10	$Cu(OAc)_2$ (0.2), PPh_3 (0.4), NaOAc (4), N_2	tr
11	$Cu(OAc)_2$ (0.2), PPh_3 (0.4), Na_2CO_3 (4), O_2	51
12	$Cu(OAc)_2$ (0.2), PPh_3 (0.4), $NaHCO_3$ (4), O_2	51
13	$Cu(OAc)_2$ (0.2), PPh_3 (0.4), NEt_3 (4), O_2	33
14	$Cu(OAc)_2$ (0.2), PPh_3 (0.4), NaF (4), O_2	52
15	$Cu(OAc)_2$ (0.2), PPh_3 (0.4), KF (4), O_2	29
16	$Cu(OAc)_2$ (0.1), PPh_3 (0.2), NaOAc (4), O_2	70[d]

[a] Unless noted, the reaction was performed with **1** (0.2 mmol) and **2a** (0.8 mmol) in 1 mL of xylene at 140 °C for 20 h under O_2 (1 atm). [b] Yield estimated by ^{1}H NMR analysis. [c] Reaction period of 18 h. [d] Reaction period of 40 h.

intermolecular[9] C−H functionalization with amines.[10] The reaction of azoles at the 2-position, which possess an sp^2 C−H bond, still remains to be exploited, and thereby it is intriguing whether the reaction takes place by transition metal catalysis. Herein, we report catalytic oxidative amination of azoles via C−H, N−H coupling in the presence of a copper salt as a catalyst.

Benzothiazole **1** (0.2 mmol) and *N*-mehylaniline **2a** (0.8 mmol) were first chosen as a substrate. As summarized in Table 1, the reaction was performed at 140 °C for 20 h in xylene with a copper catalyst. The reaction in the presence of copper(II) chloride (20 mol %)/PPh_3 (40 mol %) and sodium acetate (0.8 mmol) under an oxygen atmosphere afforded the amination product **3a** in 23% yield, whereas the use of copper(I) iodide (20 mol %) resulted in no reaction (entries 1 and 2). An improved yield (82%) was obtained when the catalyst was switched to $Cu(OAc)_2$ (entry 3). The addition of PPh_3 is not crucial to the amination; **3a** was afforded in slightly inferior yield when the reaction was carried out without the phosphine ligand (entry 4). Although the reaction with several bidentate nitrogen and phosphine ligands was also examined, drastic improvement in the yield was not observed (entries 5−8). It appeared to be important to carry out the reaction under oxygen. The yield was, indeed, decreased to 46% when the reaction was performed under an aerobic condition, and no reaction was observed under a nitrogen atmosphere (entries 9 and 10). The use of other organic and inorganic bases, including Na_2CO_3, $NaHCO_3$, NEt_3, NaF, and KF, was found to promote the reaction, although the yield was inferior to that using NaOAc (entries 11−15). Lower catalyst loading (10 mol %) also afforded **3a** in 70% yield with a longer reaction period (40 h, entry 16).

With the reaction conditions for the catalytic C−H amination in hand, several amines were employed for the reaction of benzothiazole **1**. As summarized in Table 2, *N*-methylaniline **2a** and diphenyl amine **2b** were found to react with **1** to afford the corresponding amination product **3** in 47−81% yield. Furthermore, sulfonamide **2c** also underwent the reaction to give **3c** in 65% yield.

In addition to benzothiazole **1**, several azoles were subjected to the amination reactions. The scope with respect to the heteroaromatic compounds is presented in Table 3. The reaction of 4,5-dimethylthiazole **4** with *N*-methylaniline **2a** afforded **5a** in 73% yield (entry 1). Benzoxazole **6** with **2a** and diphenylamine **2b** also afforoded **7a** and **7b** in 73% and 66% yield, respectively (entries 2 and 3). The reaction of **6** was found to take place with several aliphatic amines

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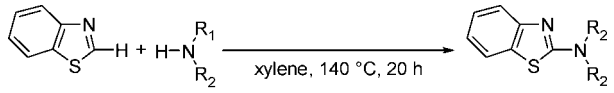
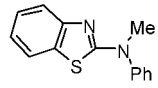
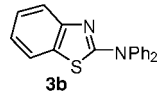
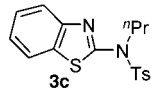
Table 2. Amination of Benzothiazole[a]



1 **2** **3**

entry	2	R^1	R^2	product	yield (%)[b]
1	**2a**	Me	Ph	 **3a**	81
2	**2b**	Ph	Ph	 **3b**	47
3	**2c**	^{n}Pr	Ts	 **3c**	65[c]

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $Cu(OAc)_2$ (20 mol %), and PPh_3 (40 mol %), under 1 atm of O_2, in 1 mL of xylene, at 140 °C for 20 h. [b] Isolated yield. [c] The reaction was carried out with 0.8 mmol of **1** and 0.2 mmol of **2c**. The yield was based on the amount of **2c**.

such as piperidine (**2d**) and diethylamine (**2e**) in 72% and 47% yields (entry 4 and 5). *N*-Methylbenzoimidazole (**8**) was found to be a favorable substrate to undergo the amination reaction with **2a**.

Although the mechanism of copper-catalyzed oxidative C−H, N−H coupling is still unclear, the reaction would proceed under a similar pathway to the reaction of terminal alkynes reported by Stahl.[9a] As shown in Scheme 1, the C−H bond of the azole would be replaced with Cu(II), to form organocopper **10**. The X group of **10** would be replaced with amine to give **11**. A following reductive elimination produces the coupling product **3** along with a copper species of the lower oxidation state, which would be oxidized to give Cu(II) by oxygen to complete the catalytic cycle.

Since we have recently shown that the masked thiazole **12** induces catalytic C−H arylation at the 5-position of the thiazole ring to obtain 5-arylthiazole **13** after removal of the masked group by treatment of base,[11] **13** is an available thiazole derivative for catalytic C−H amination at the 2-position, which leads to the *N*-analogue of donor−acceptor-type 2,5-disubstituted thiazole.[12] Introduction of an electron-deficient aryl group to **12** following removal of the masked group was performed as reported to afford 5-arylthiazole **13**, which was reacted with *N*-methylaniline **2a** and diphenylamine **2b** at 140 °C for 3−5 h under the optimized conditions to give **14** in 68% and 48% yields, respectively. Despite the

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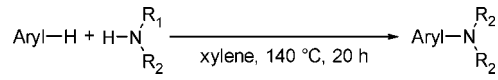
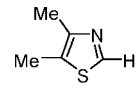
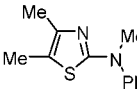
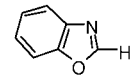
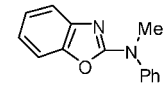
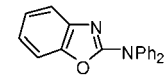
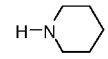
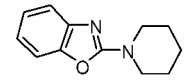
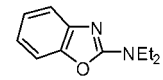
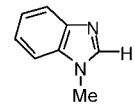
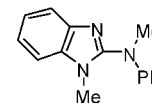
Table 3. Amination of Azoles[a]

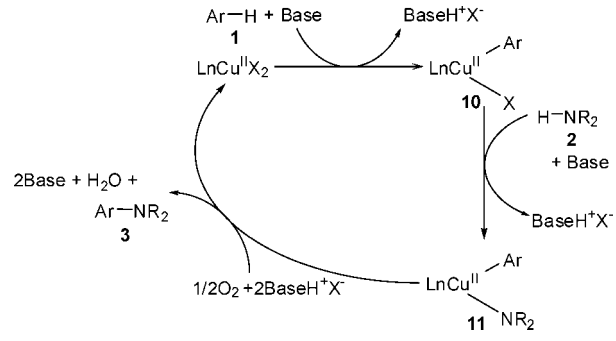


entry	Aryl–H	amine	product	yield (%)[b]
1	 **4**	**2a**	 **5a**	73
2	 **6**	**2a**	 **7a**	71
3	**6**	**2b**	 **7b**	66
4	**6**	 **2d**	 **7d**	72
5	**6**	$H\text{-}NEt_2$ **2e**	 **7e**	47
6	 **8**	**2a**	 **9a**	51

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $Cu(OAc)_2$ (20 mol %), and PPh_3 (40 mol %), under 1 atm of O_2, in 1 mL of xylene, at 140 °C for 20 h. [b] Isolated yield.

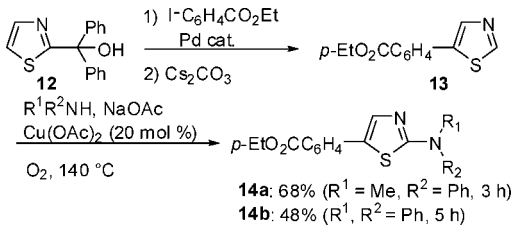
use of secondry amines, the ester group of **13** was found to be tolerant under the reaction conditions and no exchange

Scheme 1



of ester with amines was observed.[13] Spectroscopic and electronic properties of thus obtained **13** will be performed in due course (Scheme 2).

Scheme 2



In conclusion, we have demonstrated the C−H, N−H coupling of azoles with a variety of nitrogen nucleophiles in the presence of a copper catalyst. Since a number of biologically active compounds are found in azole derivatives bearing an amino substituent at the 2-position, the method is a powerful tool for synthesizing such a molecule efficiently.

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Supporting Information Available: Experimental details.[14] This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) No reaction was confirmed to take place by mixing **13** and **2a** in xylene at 140 °C for 3 h.

(14) The authors thank Nara Institute of Science and Technology, Kyoto-Advanced Nanotechnology Network, supported by MEXT for measurements of high resolution mass spectra.