Synlett J. Gu, C. Cai Letter

Copper-Catalyzed Direct Amination of Benzoxazoles Using Primary Amines as Nitrogen Sources

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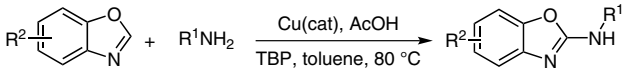

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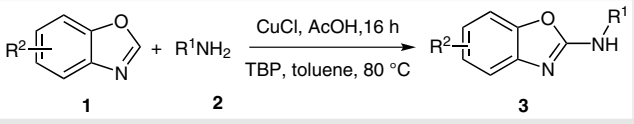
Abstract A facile, efficient, and simple protocol for direct oxidative C–H amination of benzoxazoles with primary amines through copper-catalyzed C–H bond activation using *tert*-butyl peroxide (TBP) as oxidant under air has been developed. The reaction proceeds smoothly at ambient temperature to furnish the products. A variety of substituted aminobenzoxazoles were synthesized with good to excellent yields.

Key words C-H activation, amination, copper catalysis, benzoxazole

The transition-metal-catalyzed selective C–N bond formation of azoles is an important reaction in synthetic chemistry, because the molecules containing heteroarylamine units are ubiquitous in biological, pharmaceutical and material sciences.[1] Many traditional methods have been developed to synthesize this skeleton, including palladium-catalyzed Buchwald–Hartwig coupling, copper-catalyzed Ullmann and Goldberg couplings, and cross-coupling reactions of boronic acids, stannanes, and siloxanes with corresponding amines.[2] Although rapid and straightforward access to heteroaryamines are provided by the methods mentioned above, there remain some disadvantages, such as high reaction temperature, high loading of noble metals, and special ligands.[1b,3] To find greener and more efficient methods, direct C–H amination has been investigated because of its high atom efficiency compared with the reported cross-coupling reactions, and because of its wide range of applications in the synthesis of biologically active compounds and organic intermediates.[4]

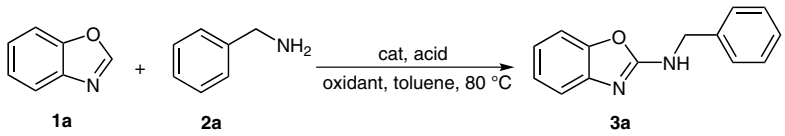
Seminal works on the direct C–H amination of heteroarenes have been reported; for example, Mori and Schreiber successfully developed a copper-catalyzed amination of azoles by using secondary amines as nitrogen sources.[5] Miura developed a copper-catalyzed reaction that allowed access to heteroarylamines with chloroamines instead of the parent amines.[6] Chang reported silver-catalyzed direct amination of benzoxazoles.[7] Hong achieved a copper-catalyzed C–H amination of polyfluorobenzenes with an array of primary aromatic amines for the first time.[8] However, these reported protocols have some drawbacks such as the use of stoichiometric amounts of catalyst, a large amount of strong base, and toxic ligand. Many groups have accomplished excellent results that address the drawbacks mentioned above. Duan and Yu independently provided a copper-catalyzed and iron-catalyzed amination of azoles with formamides or secondary amines.[9] Huang developed a copper-catalyzed route to heteroarylamines by using tertiary amines as nitrogen sources[10] and then they developed aerobic oxidative C–H amination of azoles with secondary amines at room temperature under cooperative catalysis with aldehydes and copper.[11] In these methods, the nitrogen sources are usually secondary or tertiary amines and the reaction does not occur when primary amines are used. In this context, we have developed a facile, efficient, and simple protocol for direct oxidative C–H amination of benzoxazoles with primary amines through copper-catalyzed C–H bond activation (Scheme 1).



Scheme 1 Copper-catalyzed direct amination of benzoxazoles with primary amines

The copper-catalyzed oxidative C–H amination of benzoxazole (**1a**) with benzylamine (**2a**) was chosen as a model reaction to optimize the reaction conditions. Copper catalysts such as $CuBr_2$, $Cu(OAc)_2$, CuCl, and CuI were screened for the C–H amination reaction (Table 1, entries 2–5). CuCl showed good catalytic activity among the above catalysts screened, furnishing **3a** in 69% yield (entry 5). Subsequent experiments revealed that the reaction requires 20 mol% CuCl. However, increasing the amount of CuCl further did not bring significant change in the yield of the reaction (entries 5 and 6). The use of acid as an additive was essential; the addition of 0.8 equivalent acetic acid (AcOH) greatly improved the reaction yield, and **3a** was obtained in 94% yield (entry 9). Other acids such as HCOOH and PhCOOH, were less effective than AcOH (entries 7 and 8). Ag_2CO_3, TBHP and TBP were tested and when TBP was employed as oxidant, the yield was enhanced to 94% (entries 9–11). Am-

Table 1 Optimizing the Reaction Conditions[a]



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

Entry	Catalyst	Acid (equiv)	Oxidant (equiv)	Yield (%)[b]
1	–	–	–	n.r.
2	$CuBr_2$	HCOOH (0.4)	TBP (2)	39
3	$Cu(OAc)_2$	HCOOH (0.4)	TBP (2)	n.r.
4	CuI	HCOOH (0.4)	TBP (2)	9
5	CuCl	HCOOH (0.4)	TBP (2)	69
6	CuCl[c]	HCOOH (0.4)	TBP (2)	68
7	CuCl	HCOOH (0.8)	TBP (2)	80
8	CuCl	PhCOOH (0.8)	TBP (2)	30
9	CuCl	AcOH (0.8)	TBP (2)	94
10	CuCl	AcOH (0.8)	TBHP (2)	34
11	CuCl	AcOH (0.8)	Ag_2CO_3 (2)	13
12	CuCl	–	–	7
13	CuCl	HCOOH (0.8)	–	25
14	CuCl	–	TBP (2)	13

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), CuCl (20 mol%), toluene (2.0 mL), 16 h, 80 °C.
[b] Determined by GC analysis.
[c] CuCl (30 mol%).

ination of benzoxazole was not observed in the absence of copper source, indicating that copper was crucial for the reaction (entry 1).

Under the optimized conditions, the scope of this oxidative C–H amination reaction was investigated with a range of amines (Table 2).[12] Benzylamines substituted with either electron-withdrawing or electron-donating groups reacted with benzoxazole to give the desired products **3a**–**d** in good yield. Other primary amines, such as *n*-butylamine, *tert*-butylamine, and cyclohexylamine were tested for the oxidative C–H amination reaction to give the corresponding products **3e**–**g** in 88–91% yield.

The scope of this reaction was then investigated with respect to azole under the optimized conditions (Table 2). Alkyl- and halogen-substituted benzoxazoles were aminated effectively in good yield (**3l**–**n**). Unfortunately, no desired product was obtained when benzoxazole containing electron-withdrawing groups such as nitro was employed. In contrast to benzoxazoles, benzothiazole and benzimidazole did not afford the corresponding products **3p** and **3q** under the reaction conditions. The lower reactivity of the latter two substrates may be caused by their lower acidity.

To expand the substrate scope, cyclic secondary amine piperidine and tertiary amines **2i**–**k** were tested with benzoxazole under the optimized conditions (Table 3). When piperidine was used for this oxidative amination procedure, the desired product **3h** was obtained in 94% yield. Alkyl tertiary amines **2i**, **2j**, and **2k** provided the desired products **3i**, **3j**, **3j′**, **3k**, and **3k′** in moderate yields (Table 3, entries 2–4).

In conclusion, a facile, efficient protocol for direct oxidative C–H amination of benzoxazoles with primary amines through copper-catalyzed C–H bond activation has been developed in good to excellent yields. This catalytic system was also suitable when the nitrogen sources were secondary and tertiary amines, and the desired products were synthesized in moderate yield. The ambient reaction temperature, inexpensive copper catalyst, and easily handled TBP oxidant make this C–H amination protocol useful for future applications, and provides a powerful tool for the synthesis of substituted aminobenzoxazole derivatives.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379886.

References and Notes

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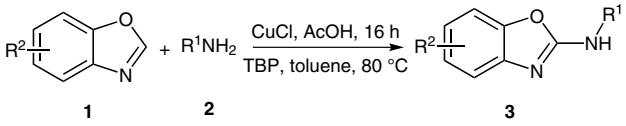
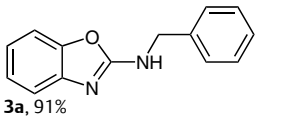
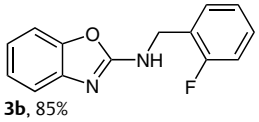
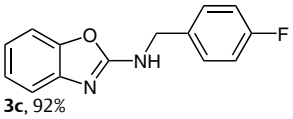
Table 2 Substrate Scope of the Reaction with Amines and Azoles[a,b]

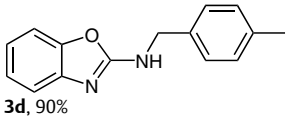


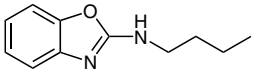
1 2 3

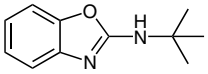

3a, 91%

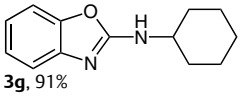

3b, 85%

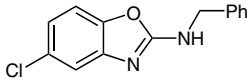

3c, 92%

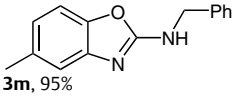

3d, 90%

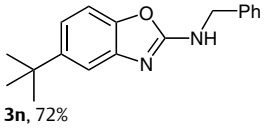

3e, 91%

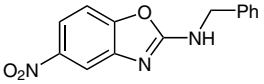

3f, 88%

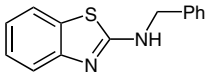

3g, 91%

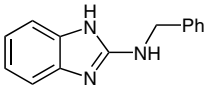

3l, 80%


3m, 95%


3n, 72%

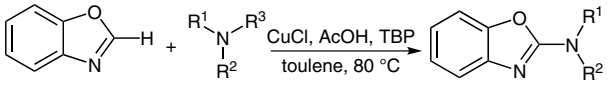

3o, 0%


3p, 0%

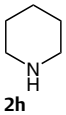
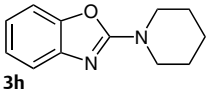
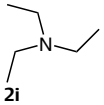
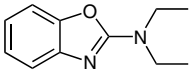
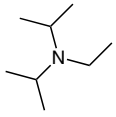
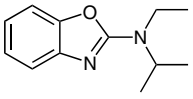
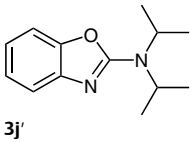
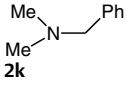
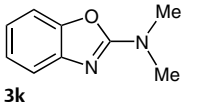
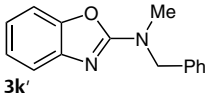

3q, 0%

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), CuCl (20 mol%), AcOH (0.8 equiv), TBP (2 equiv), toluene (2.0 mL), 16 h, 80 °C.
[b] Isolated yield.

Table 3 Substrate Scope of Secondary and Tertiary Amines[a]



1a 2 3

Entry	Amine **2**	Product **3**	Yield (%)[b]
1	 **2h**	 **3h**	94
2	 **2i**	 **3i**	67
3	 **2j**	 **3j**	33
		 **3j′**	44
4	 **2k**	 **3k**	24
		 **3k′**	47

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), CuCl (20 mol%), AcOH (0.8 equiv), TBP (2 equiv), toluene (2.0 mL), 80 °C, 16 h.
[b] Isolated yield.

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(11) Xie, Y. J.; Qian, B.; Huang, H. M. *Adv. Synth. Catal.* **2013**, *355*, 1315.
(12) (a) **Synthesis of Aminobenzoxazoles from Benzoxazoles and Amines; General Procedure:** A mixture of benzoxazole (1.0 mmol), amine (1.0 mmol), CuCl (0.2 mmol), TBP (2.0 mmol), and AcOH (0.8 mmol) in toluene (2.0 mL) was stirred at 80 °C for 16 h. Upon completion, the reaction mixture was diluted with EtOAc (4.0 mL) and filtered through a bed of silica gel. The volatiles were removed under vacuum to afford the crude product, which was analyzed by GC. The crude product was purified by column chromatography on silica gel (EtOAc–hexanes, 10:90) to afford the desired pure product **3**.
***N*-(2-Fluorobenzyl)benzo[*d*]oxazol-2-amine (3b):** Colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 7.0 Hz, 1 H), 7.23–7.14 (m, 3 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 6.99 (dd, *J* = 17.3, 8.8 Hz, 2 H), 6.93 (t, *J* = 8.6 Hz, 1 H), 6.35 (s, 1 H), 4.63 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.0 (s), 159.0 (s), 142.1 (s), 128.7 (d, *J* = 37.4 Hz), 128.2–127.8 (m), 123.9 (s), 123.2 (d, *J* = 52.9 Hz), 122.9–122.4 (m), 119.9 (s), 115.4 (s), 114.6 (s), 114.4 (s), 107.9 (s), 40.0 (s).
***N*-Benzyl-5-methylbenzo[*d*]oxazol-2-amine (3m):** Brown solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (t, *J* = 10.9 Hz, 3 H), 7.37 (d, *J* = 7.4 Hz, 2 H), 7.36–7.32 (m, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 6.92 (s, 1 H), 6.85 (d, *J* = 8.1 Hz, 1 H), 4.68 (s, 2 H), 2.40 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.7 (s), 145.9 (s), 141.9 (s), 137.0 (s), 132.6 (s), 127.8 (s), 126.7 (s), 120.4 (s), 115.5 (s), 107.2 (s), 45.9 (s), 20.5 (s)