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# Transition metal-free direct amination of benzoxazoles using formamides as nitrogen sources

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An immense effort has been made to develop efficient strategies for the construction of C–N bonds of heteroaromatic compounds through the activation of C–H bonds.<sup>1</sup> During the recent years, remarkable progresses have been made in the amination of benzoxazoles which are important units for the synthesis of pharmaceuticals, natural products, functional materials, and many other biologically active molecules.<sup>2</sup> In particular, site-selective amination of azoles through C-H bond activation was recently developed.<sup>3</sup> Despite these significant advances, developing environmentally benign and economical syntheses is an area of research that is being vigorously pursued, direct installation of amino groups or their surrogates on aryl C-H bonds remains a challenge under transition metal-free conditions. Formamides are cheap, commercially available and thus can be potentially used as the ideal amination reagents.<sup>4</sup> In 2009, Chang et al. reported a stoichiometric amount of silver catalyzed direct amination using formamides as an amino group source.<sup>3a</sup> Recently, groups of Li and Yu independently disclosed Cu and Fe-catalyzed direct oxidative C-H amination of benzoxazoles with formamide derivatives (Scheme 1, path a, b, and c).<sup>3g,h</sup> However, using transition metal catalysts renders these methods increasingly unattractive and environmentally less friendly. At the present stage, C-H amination of benzoxazoles under metal-free conditions using formamides as nitrogen sources is unrevealed. If a synthetic method that allows

## ABSTRACT

A transition metal-free method for the direct amination of benzoxazoles using formamides as nitrogen sources is reported, which was mediated by an inexpensive and environmentally friendly tetrabutylammonium iodide/*tert*-butyl hydroperoxide system and gave the 2-aminobenzoxazole derivatives with moderate to good yields.

Previous work

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a) Ag<sub>2</sub>CO<sub>2</sub> (2 eg

b) Cu(OAc)<sub>2</sub> (0.2 eq

O<sub>2</sub>,130 °C

c) FeCl<sub>3</sub> (0.25 eq)

Transition metal-free

Scheme 1. Comparison of previous works with this work.

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the direct use of normally 'unreactive' formamides as nitrogen sources were to become available under transition-metal free conditions other than those procedures mediated by transition metal, a practical and environmentally friendly synthetic approach in direct amination of benzoxazoles would be opened.

A recent report by Wan suggested that nitrogen radicals can participate in TBAI (tetrabutylammonium iodide)-catalyzed acylation reactions.<sup>5</sup> Inspired by this transformation, we envisioned that aminyl radicals with persistent radical effect could react with activated benzoxazoles in situ, which would obviate the need of transition metal.<sup>6</sup> Herein, we describe a new procedure for the oxidative amination of benzoxazoles using formamides as nitrogen sources under transition metal-free conditions (Scheme 1, path d).

To optimize the amination protocol, we extensively screened various experimental parameters. Initially, benzoxazole (**1a**) and *N*,*N*-dimethylformamide (DMF) were chosen as model substrates





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#### Table 1

Screening conditions<sup>a</sup>



Entry	TBAI (mol %)	[O] (equiv)	Additive (equiv)	DMF (equiv)	Yield <sup>b</sup> (%)
1	20	TBHP (5)	_	15	20
2	20	TBHP (5)	AcOH (1.5:3:5)	15	42:58:73
3	20	TBHP (10)	AcOH (5)	15	80
4	20	TBHP (12)	AcOH (5)	15	80
5	20	TBHP (10)	AcOH (5)	10	76
6	10	TBHP (10)	AcOH (5)	15	70
7	20	TBHP (10)	AcOH (10)	15	38
8	40	TBHP (10)	AcOH (5)	15	51
9	20	TBHP (10)	PhCOOH (5)	15	46
10	20	TBHP (10)	TFA (3)	15	Trace
11	20	TBHP (10)	TfOH (3)	15	Trace
12	20	TBHP (10)	PTSA (3)	15	Trace
13	20	$H_2O_2(10)$	AcOH (5)	15	Trace
14 <sup>7</sup>	20	UHP (10)	AcOH (5)	15	22
15	20 (I <sub>2</sub> )	TBHP (10)	AcOH (5)	15	<5
16 <sup>c</sup>	20	TBHP (10)	AcOH (5)	15	Trace
17 <sup>d</sup>	20	TBHP (10)	AcOH (5)	15	43
18 <sup>e</sup>	20	TBHP (10)	AcOH (5)	15	<5
19 <sup>f</sup>	20	TBHP (10)	AcOH(5)	15	<10
20 <sup>g</sup>	20	TBHP (10)	AcOH (5)	45	<10

<sup>a</sup> Reaction conditions: A mixture of benzoxazole (**1a**, 1 mmol), DMF, Bu<sub>4</sub>NI, TBHP (70% aqueous solution) and acid additive was stirred in solvent (3.0 mL) at 90 °C for reaction, The given equivalents (equiv) are related to **1a**.

<sup>b</sup> Isolated yield after column chromatography.

<sup>c-g</sup> Reaction was carried out in dioxane, acetonitrile, dichloromethane, ethyl acetate and DMF, respectively. AcOH = acetic acid, DCE = 1,2-dichloroethane, TFA = trifluoroacetic acid, TfOH = trifluoromethanesulfonic acid, PTSA = *p*-toluenesulfonic acid.

(Table 1). Fortunately, we were pleased to observe that the desired product (**3a**) was obtained albeit in low yield when a TBAI catalyst (20 mol %) was used in the presence of *tert*-butyl hydroperoxide (TBHP) under an air atmosphere (Table 1, entry 1). Encouraged by this result, we decided to screen the reaction conditions. Gratifyingly, increasing the amount of AcOH resulted in high yields indicating the significance of the acid additive in the reaction (Table 1, entry 2). The reaction yields could be further improved to 80% when 10 equiv of TBHP was employed (Table 1, entries 3 and 4), while decreasing the amount of DMF or catalyst resulted in low yields (Table 1, entries 5 and 6). Particularly notable, excessive amounts of catalyst or additive caused the decomposition of raw material and led to a dramatically decreased conversion (Table 1, entries 7 and 8). Furthermore, various additives were investigated, compared to AcOH, PhCOOH was less effective, whereas strong acid such as TFA, TfOH, or PTSA were completely ineffective additives (Table 1, entries 9–12). Alteration TBHP with  $H_2O_2$  was proved to be less effective, although increasing the concentration of H<sub>2</sub>O<sub>2</sub> afforded slightly higher yield, due probably to H<sub>2</sub>O<sub>2</sub> poorer tendency to the formation of nitrogen-centered radicals than TBHP (Table 1, entries 13 and 14). When iodine was employed instead of our catalytic system, the corresponding reaction proceeded sluggishly presumably attributed to their poorer capability to promote the formation of aminyl radical than TBAI (Table 1, entry 14). We then surveyed the effect of different solvents: the reactions proceeded with low yields in dioxane, acetonitrile, EtOAc, DCM, and DMF (Table 1, entries 15-19), DCE was an adequate choice of solvent for the reaction to achieve a high yield.

Under these optimized conditions (Table 1, entry 3), the scope of this reaction with different formamides was investigated. The N,N-disubstituted formamides such as *N*,*N*-diethylformamide, *N*,*N*-dipropylformamide reacted smoothly, furnishing moderate yields (Table 2, entries 2 and 3). However, substrate *N*,*N*-diisopropylformamide did not give the desired product, perhaps as a result

of steric hindrance (Table 2, entry 4). Furthermore, we screened cyclic formamides such as 1-formylpyrrolidine, 1-formylpiperidine and 4-formylmorpholine that provided the highest yield of desired products (Table 2, entries 5–7). Interestingly, the N-monosubstituted formamides could be also converted to the corresponding 2-aminobenzoxazoles in moderate yield under our reaction conditions, it was observed that *N*-methylformamide gave synthetically acceptable yield (Table 2, entry 8). In addition, N-cyclopentylformamide and N-cyclohexylformamide offered an appreciable yield of the desired product (Table 2, entries 9 and 10). Notably, N-unsubstituted formamides were completely ineffective substrate (Table 2, entry 11).

Regarding the benzoxazole moiety, several functional groups including electron-donating (methyl, methoxy, phenyl, and tertbutyl) and electron-withdrawing (chloro, bromo, and nitro) substituents were tolerated well (Table 2, entries 12-22). It is noteworthy that halo-substituted benzoxazoles were compatible under standard conditions, thus leading to halo-substituted products, which could be used for further transformations (Table 2, entries 17–19). The position of the substituents on the phenyl ring of benzoxazoles affected the reaction yield slightly. Interestingly, a reaction with 5-nitrobenzoxazole (Table 2, entry 20) afforded the corresponding product with a slightly lower yield which was proved to be an ineffective substrate in FeCl3-catalyzed direct amination.<sup>3h</sup> In the case of electronic nature of the aromatic motifs, such as 5-phenylbenzoxazole, containing electron-donating substituent, increased yields of products were obtained (Table 2, entries 14–16, 21 and 22), the effect is the reverse with electron-withdrawing substituents and transformed into the desired products in synthetically acceptable yields (Table 2, entries 17-20). It is worth noting that 5-methylbenzoxazole gave only 72% yield (Table 2, entry 11), which was less effective when compared to the approach mediated by Ag<sub>2</sub>CO<sub>3</sub> or FeCl<sub>3</sub> that probably attributed to the benzylic C-H bond oxidation of the substrate

## Table 2

Synthesis of various 2-aminobenzoxazoles<sup>a</sup>



Entry	Product		Yield <sup>b</sup> (%)
1		3a	80
2		3b	39
3		3с	35
4		3d	Trace
5		Зе	70
6		3f	73
7		3g	79
8	NH NH	3h	28
9		3i	63
10		3j	71
11		3k	NR
12		31	72
13		3m	68
14	Ph	3n	87
15	Meo	30	82
16	MeO	3р	76
17		3q	62
18	CI CI N	3r	48
19	Br	3s	68
20	O <sub>2</sub> N N	3t	34
21	MeO	3u	84

Table 2 (continued)



NR = no reaction.

<sup>a</sup> Reaction conditions: benzoxazole (1.0 mmol), formamide (15 mmol), TBAI (0.2 equiv), TBHP (70% aq solution, 10 mmol) and acetic acid (2.0 equiv) in 1,2-dichloroethane (3.0 mL) at 90 °C for 12 h, also see Ref.<sup>14</sup>
<sup>b</sup> Isolated yield.

under standard conditions.<sup>8</sup> Additionally, when benzothiazole was subjected to the standard reaction conditions. 2-aminobenzothiazole was selectively obtained in modest yield (Table 2, entry 23). Encouraged by the aforementioned direct C-N bond formation of benzoxazoles, we extended the method to direct amination of benzimidazole, 1-methylbenzimidazole, 1,5,6-trimethylbenzimidazole, and 1,3,4-oxadiazoles by using formamides as the nitrogen sources. Disappointingly, the amination did not occur under standard reaction conditions. Additionally, when we treated indole derivatives (1 mmol, such as indole, 1-methylindole, 1,7-dimethylindole, or 1,4-dimethylindole) with DMF (15 equiv) in AcOH (3 mL) at 90 °C in the presence of TBAI (0.2 equiv), and TBHP (10 equiv) for 12 h, we were delighted to find that the starting materials-indole derivatives were consumed completely, but LC-MS and NMR analysis unveiled that the oxidant products-indole-2,3-dione derivatives were formed.9

To gain an insight into the reaction mechanism, the following control experiments were performed under the standard reaction conditions (Scheme 2). Firstly, ammonium hypoiodite ([Bu<sub>4</sub>N]<sup>+</sup>[- $IO]^{-}$ ) or iodite ( $[Bu_4N]^+[IO_2]^-$ ), which should be generated in situ from Bu<sub>4</sub>NOH and iodine, was not the active species (Scheme 2, Eq. a).<sup>10</sup> Secondly, when stoichiometric amount of hypervalent iodine reagent (such as ICl) was employed instead of our catalytic system, no desired product was obtained (Scheme 2, Eq. b). This result indicates that the reaction pathway is not followed in catalvsis involving in situ generated hypervalent iodine or I<sub>2</sub>–I<sup>+</sup> redox process.<sup>8,11</sup> Moreover, switching the catalyst to KI provided the desired product **3a** in 74% isolated yield (Scheme 2, Eq. c). On the other hand, when the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-N-oxyl) was added to the reaction system, the reaction was inhibited (Scheme 2, Eq. d), which implies that the reaction presumably proceed via a radical intermediate.

On the basis of the above results and previous reports,<sup>12</sup> a plausible mechanism for this reaction is illustrated in Scheme 3. Our



Scheme 2. Investigation of the reaction mechanism.



Scheme 3. A plausible mechanism for this amination.

proposed mechanism for this transformation can be divided into the radical addition and radical coupling pathway. The tert-butoxyl and tert-butylperoxyl radicals which formed by the promotion of TBAI through I<sub>2</sub>–I<sup>-</sup> redox process abstract hydrogen from the formamide to generate aminyl radical **A**.<sup>5</sup> For the radical addition case the radical **A** can react as with a reactive intermediate **B**, leading to provide radical cation C. Oxidation of an radical intermediate C can occur by electron transfer (ET) and proton transfer (PT) to give protonated 2-aminobenzoxazole D. This result does not exclude an alternative pathway, which involves C-H bond cleaving hydrogen radical abstraction (HRA) as a single-step transformation to provide the same intermediate **D**, which may be converted into the final product 3. Alternatively, the final product can be produced via the radical coupling pathway of the aminyl radical **A** and benzoxazole radical E, since when benzoxazole or N-formylmorpholine reacted, respectively, under the standard conditions the radical coupling precursor ions of  $[M+H]^+$  at m/z 237 and 173 could be detected.1

In summary, we have described the first example of a high efficient, straightforward and TBAI/TBHP mediated method for benzoxazoles amination under transition metal-free conditions using formamides as nitrogen sources. Transition-metal free and formamides as nitrogen sources make this transformation practical and environmentally friendly. Further studies to break through the limitation of benzothiazoles are ongoing in our group.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014. 02.070. These data include MOL files and InChiKeys of the most important compounds described in this article.

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- MS data were recorded on Finnigan LCQ<sup>DECA</sup> ion-trap mass spectrometer (San Jose, CA, USA) with electrospray ionization sources operated in positive ion mode. 2,2'-Bibenzoxazole m/z at 237, 4,4'-bimorpholine m/z at 173, and 1,2dimorpholinoethane-1,2-dione m/z at 229 could be detected.
- General experimental procedure: Benzoxazole (1.0 mmol), N,N-disubstituted formamide (15 mmol), TBAI (0.2 equiv/74 mg), TBHP (70% aqueous solution, 10 mmol/1.37 mL), and acetic acid (5.0 equiv) in 1,2-dichloroethane (3.0 mL)

were added to a reaction vessel in air. The reaction mixture was heated in an oil bath at 90 °C for 12 h. After completion of the reaction, the mixture was quenched by addition of a saturated solution of sodium disulfite (4.0 mL, for removal of excess TBHP) and a saturated solution of sodium hydrogen carbonate (4.0 mL). Then the mixture was extracted with ethyl acetate  $(3 \times 15 \text{ mL})$ , combined organic phases were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the organic solvent was removed under vacuum. The crude residue was purified by chromatography on a silica gel column affording the desired product. Analytical data for some representative compounds: Compound 3a: petroleum ether/ethyl acetate 5:1; yellow solid (yield 80%); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  = 7.35 (d, J = 7.2 Hz, 1H), 7.24 (d, J = 6.0 Hz, 1H), 7.15–1.13 (m, 1H), 7.00–6.97 (m, 1H), 3.19 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 163.1, 149.1, 143.6, 123.9, 120.2, 116.0, 108.6, 37.7. ESI-HRMS *m/z* calcd for [C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O + H]<sup>+</sup>: 163.0871, found 163.0865. Compound 3f: petroleum ether/ ethyl acetate 4:1; yellow solid (yield 73%); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>, ppm): δ = 7.35 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 3.86 (m, 4H), 1.69 (br s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 162.0, 148.2, 142.9, 123.4, 119.8, 115.5, 108.1, 46.1, 24.8, 23.6. ESI-HRMS m/ z calcd. For  $[C_{12}H_{14}N_2O + H]^+$ : 203.1184, found 202.1179. Compound 3j: petroleum ether/ethyl acetate 4:1; yellow solid (yield 71%); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  = 7.37 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.17–7.13 (m, 1H), 7.03–7.00 (m, 1H), 4.99 (d, *J* = 7.2 Hz, 1H), 3.78–3.73 (m, 1H), 2.16–2.12 (m, 2H), 1.80–1.76 (m, 2H), 1.72–1.64 (m, 1H), 1.50–1.42 (m, 2H), 1.34–1.21 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 161.2, 148.2, 143.0, 123.6, 120.4, 116.0, 108.4, 51.8, 33.3, 25.3, 24.6. ESI-HRMS *m/z* calcd for [C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O + H]<sup>+</sup>: 217.1341, found 217.1337. *Compound* **3***I*: petroleum ether/ethyl acetate 5:1; slight white solid (yield 72%); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  = 7.14 (s, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 3.18 (s, 6H), 2.38 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 163.3, 147.3, 143.7, 133.5, 120.8, 116.4, 107.9, 37.7, 21.5. ESI-HRMS *m/z* calcd for [C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O + H]<sup>+</sup>: 177.1028, found 177.1032. *Compound* **30**: petroleum ether/ethyl acetate 5:1; slight white solid (yield 82%); <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  = 7.12 (d, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.56 (dd, *J<sub>1</sub>* = 8.4 Hz, *J<sub>2</sub>* = 2.4 Hz, 1H), 3.80 (s, 3H), 3.17 (s, 371. ESI-HRMS *m/z* calcd for [C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> + H]<sup>+</sup>: 193.0977, found 193.0970. *Compound* **3***g*: petroleum ether/ethyl acetate 5:1; slight yellow solid (yield 62%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  = 7.29 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 163.8, 147.7, 145.0, 129.2, 120.0, 116.1, 109.1, 37.7. ESI-HRMS *m/z* calcd for [C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> + H]<sup>+</sup>: 193.0977, found 193.0970. *Compound* **3***g*: petroleum ether/ethyl acetate 5:1; slight yellow solid (yield 62%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  = 7.29 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.19 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  = 7.29 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.19 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, pm):  $\delta$  = 7.29 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.19 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, pm):  $\delta$  = 163.8, 147.7, 145.0, 129.2, 120.0, 116.1,