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

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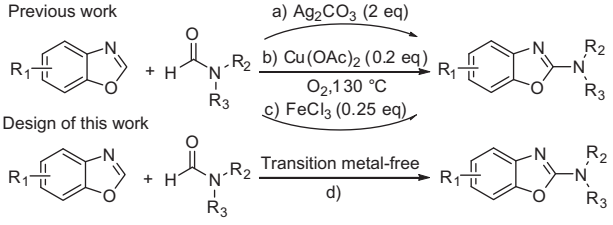
ABSTRACT

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.

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.[1] 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.[2] In particular, site-selective amination of azoles through C—H bond activation was recently developed.[3] 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.[4] In 2009, Chang et al. reported a stoichiometric amount of silver catalyzed direct amination using formamides as an amino group source.[3a] 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).[3g,h] 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 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.



Scheme 1. Comparison of previous works with this work.

A recent report by Wan suggested that nitrogen radicals can participate in TBAI (tetrabutylammonium iodide)-catalyzed acylation reactions.[5] 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.[6] 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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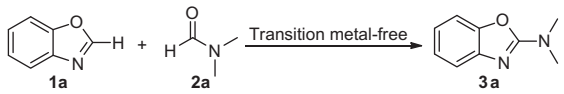
0040-4039/

Table 1
Screening conditions[a]



Entry	TBAI (mol %)	[O] (equiv)	Additive (equiv)	DMF (equiv)	Yield[b] (%)
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[7]	20	UHP (10)	AcOH (5)	15	22
15	20 (I_2)	TBHP (10)	AcOH (5)	15	<5
16[c]	20	TBHP (10)	AcOH (5)	15	Trace
17[d]	20	TBHP (10)	AcOH (5)	15	43
18[e]	20	TBHP (10)	AcOH (5)	15	<5
19[f]	20	TBHP (10)	AcOH(5)	15	<10
20[g]	20	TBHP (10)	AcOH (5)	45	<10

[a] Reaction conditions: A mixture of benzoxazole (**1a**, 1 mmol), DMF, Bu_4NI, 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**.
[b] Isolated yield after column chromatography.
[c–g] 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_2O_2 afforded slightly higher yield, due probably to H_2O_2 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 *tert*-butyl) 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 $FeCl_3$-catalyzed direct amination.[3h] 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_2CO_3 or $FeCl_3$ that probably attributed to the benzylic C—H bond oxidation of the substrate