Amination of Benzoxazoles by Visible-Light Photoredox Catalysis

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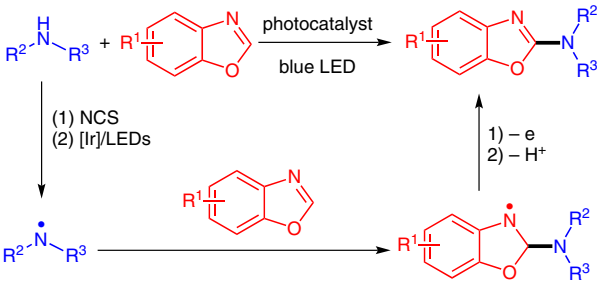
Abstract: An effective visible-light-promoted 'radical-type' coupling of benzoxazole with secondary amines has been developed. The broad substrate scope and mild reaction conditions make this procedure a practical and environmentally friendly method for the synthesis of 2-aminobenzoxazoles.

Key words: radical reaction, photochemistry, amination, heterocycles, iridium

2-Aminobenzoxazoles display high biological and pharmaceutical activities, and they are also substructures in many therapeutically important molecules,[1] such as PPAR agonist (PPAR = peroxisome proliferator-activated receptor)[2] and MK-4305 (dual orexin receptor antagonist).[3] Therefore, the construction of this kind of nitrogen-containing molecules is of great significance. Traditionally, 2-aminophenols and aldehydes are used as starting compounds, affording 2-functionalized benzoxazoles through oxidative cyclization.[4] In addition, cyclization of 2-aminophenols with other reagents have been disclosed.[5] Alternatively, they can be accessed by transition-metal-catalyzed Buchwald–Hartwig amination of aryl halide or pseudohalide under thermal conditions,[6] or direct amination of arenes and heteroarenes via aromatic C–H bond activation by transition-metal catalysis[7] and even under metal-free conditions.[8] Functionalization of benzoxazoles with the use of electrophilic amine reagents or nonactivated amines via formal C–H activation would provide a straightforward route to 2-aminobenzoxazoles.

Visible-light-promoted photoredox catalysis provides a green and sustainable process for generating radicals.[9–13] Recently, Zheng[14] reported a 'radical-type' construction of C–N bonds by visible-light-driven catalysis. Mechanistic study suggests that nitrogen-centered radical species are reactive intermediates, which are generated by direct oxidation of the corresponding amines with a photoexcited ruthenium–polypyridyl complex. Despite the advance, the direct 'radical-type' amination of heteroarenes under visible-light photoredox catalysis is still a challenge.[15] In continuing our work on coupling reactions driven by visible-light photoredox catalysis,[16] herein we report a 'radical-type' amination of benzoxazoles with in situ prepared chloroamines promoted by visible light, which provides a general and valuable method for the synthesis of 2-aminobenzoxazoles (Scheme 1).



Scheme 1 C–N coupling reaction catalyzed by an iridium complex under visible light

Initial investigations focused on the amination of benzoxazole (**1a**) with *N*-chloromorpholine (**2**, Table 1). $Ru(bpy)_3Cl_2 \cdot 6H_2O$ was employed as a photocatalyst, and 3 W blue LED were utilized as the visible-light source. The cross-coupling product 2-morpholinobenzoxazole (**3a**) was obtained with low yield at room temperature (Table 1, entry 4). Likewise, other ruthenium, copper, and organic catalysts all showed low reactivity toward this C–N coupling (Table 1, entries 5–7).

To our delight, when a more reactive iridium catalyst $[Ir(dtbpy)(ppy)_2]PF_6$ was used, the yield was increased to 80% under identical conditions (Table 1, entry 8). Solvents also play an important role in the reaction. Among the solvents surveyed, CH_2Cl_2 gave the best yield. The choice of additive amines is also critical. Amongst those tested, such as Et_3N, DIPEA, triphenylamine, and 4-methoxytriphenylamine, only triphenylamine and 4-methoxytriphenylamine promoted the reaction, furnishing 80% and 72% yield, respectively (Table 1, entries 8 and 12). It is notable that the photocatalyst, visible light, and triphenylamine are all critical for this reaction. In the absence of any of these components, no reaction product was observed (Table 1, entries 1–3).

Under the optimized reaction conditions, we next investigated the substrate scope of the reaction. Firstly, we varied the structure of the benzoxazole core; both 5- and 6-substituted benzoxazoles reacted with *N*-chloromorpholine to afford the desired products (Table 2). Benzoxazoles bearing electron-donating or electron-withdrawing substituents were all aminated, affording the products **3b–g** in good to excellent isolated yields. The electronic prop-

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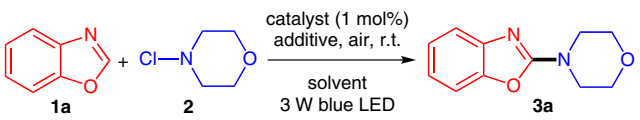
Table 1 Optimization of Visible-Light-Promoted Cross-Coupling of Benzoxazole with *N*-Chloromorpholine[a,b]



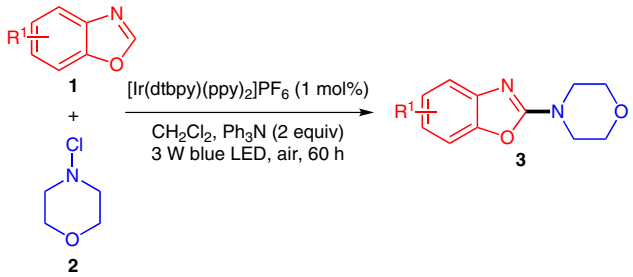
Entry	Reaction conditions	Yield (%)[b]
1	no catalyst, no light, CH_2Cl_2	n.r.
2	$Ru(bpy)_3Cl_2$, no light, CH_2Cl_2	n.r.
3	no catalyst, Ph_3N, CH_2Cl_2	trace
4	$Ru(bpy)_3Cl_2$, Ph_3N, CH_2Cl_2	10
5	$Ru(phen)_3Cl_2$, Ph_3N, CH_2Cl_2	trace
6	$Cu(dap)_2Cl$, Ph_3N, CH_2Cl_2	12
7	Eosin Y, Ph_3N, CH_2Cl_2	26
8	$[Ir(dtbpy)(ppy)_2]PF_6$, Ph_3N, CH_2Cl_2	80
9	$[Ir(dtbpy)(ppy)_2]PF_6$, Ph_3N, MeCN	62
10	$[Ir(dtbpy)(ppy)_2]PF_6$, Ph_3N, MeOH	20
11	$[Ir(dtbpy)(ppy)_2]PF_6$, Ph_3N, toluene	35
12	$[Ir(dtbpy)(ppy)_2]PF_6$, Et_3N, CH_2Cl_2	trace
13	$[Ir(dtbpy)(ppy)_2]PF_6$, DIPEA, CH_2Cl_2	trace
14	$[Ir(dtbpy)(ppy)_2]PF_6$, MOTPA, CH_2Cl_2	75

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), catalyst (1% mmol), solvents (5 mL), additives (2 equiv); DIPEA = *N*,*N*-diisopropylethylamine, MOTPA = 4-methoxytriphenylamine.
[b] Isolated yields.

erties of these substituents seem to have insignificant effect on the reaction. Notably, the chloride and bromide group survived under the mild reaction conditions and are available for further functionalization. For the arylated benzoxazole **1j**, an excellent yield was obtained for the amination product **3j**.

The chloroamines used in the coupling reactions were prepared from the corresponding amines and bleach. To simplify the synthetic procedure, we developed a convenient, direct amination sequence. Upon completion of the chlorination of morpholine with *N*-chlorosuccinimide (NCS) in CH_2Cl_2 in the first step, benzoxazole, triphenylamine, and photocatalyst were added directly to the reaction mixture at room temperature (Table 3). Delightfully, 2-morpholinobenzoxazole (**3a**) was obtained in a total yield of 75%. Such a one-pot process avoids the inconvenient purification process for chloroamines and demonstrates the potential of this new direct amination method in synthetic applications. We then focused on the substrate scope of our new amination reaction protocol. The results for the direct amination of benzoxazole with various amines are given in Table 3. In addition to morpholine, other cyclic secondary amines with varying ring sizes and substituents were coupled to benzoxazole, and the corresponding aminated products **5b–f** were isolated in good to excellent yields. Moreover, secondary aliphatic noncyclic amines also provided the desired products **5g** and **5h** in moderate yields. Unfortunately, it did not work well with primary amines or anilines. Since *N*-methylbenzylamine underwent smooth C–N coupling, different functional groups were introduced into the aryl ring, and the resulting *N*-methylbenzylamines were employed for this reaction, with acceptable yields obtained (**5i–o**). Still further, the Boc and benzyl group on the nitrogen make further functionalization possible after deprotection.

Table 2 Amination of Various Benzoxazoles with 4-Chloromorpholine[a]

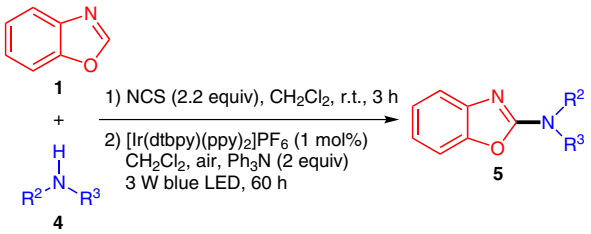


Entry	Product	Yield (%)[b]
1	**3a**	80
2	**3b**	75
3	**3c**	70
4	**3d**	73
5	**3e**	78
6	**3f**	72
7	**3g**	42
8	**3h**	48
9	**3i**	85
10	**3j**	90

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), [Ir(dtbpy)(ppy)$_2$]PF$_6$ (1% mmol), Ph_3N (1 mmol, 2 equiv), CH_2Cl_2 (5 mL), under air, r.t., 60 h.
[b] Isolated yield.

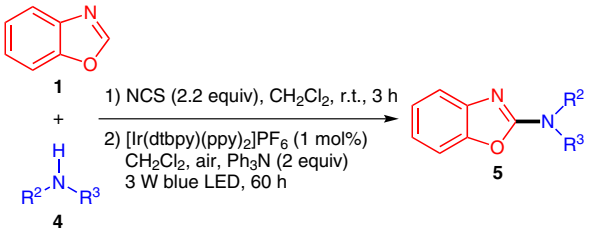
To demonstrate further the utility of this new C–N coupling method, we applied it to the synthesis of a coumarin derivative **6**, which displays potent anti-HIV and antitumor activities.[17] Using commercially available 4-bromomethyl-7-methoxycoumarin, 1-Boc-piperazine, and benzoxazole, the desired product **6** was obtained with 42% total yield in two steps under mild conditions (Scheme 2).

Table 3 One-Pot, Two-Step Amination of Benzoxazoles with Various Amines[a]



Entry	Product	Yield (%)[b]
1	**3a**	75
2	**5b**	60
3	**5c**	34
4	**5d**	63
5	**5e**	58
6	**5f**	51
7	**5g**	67
8	**5h**	60
9	**5i**	58
10	**5j**	52
11	**5k**	44

Table 3 One-Pot, Two-Step Amination of Benzoxazoles with Various Amines[a] (continued)

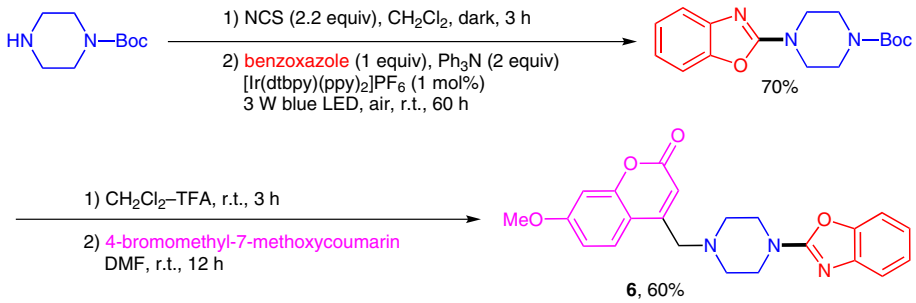


Entry	Product	Yield (%)[b]
12	**5l**	47
13	**5m**	40
14	**5n**	55
15	**5o**	45

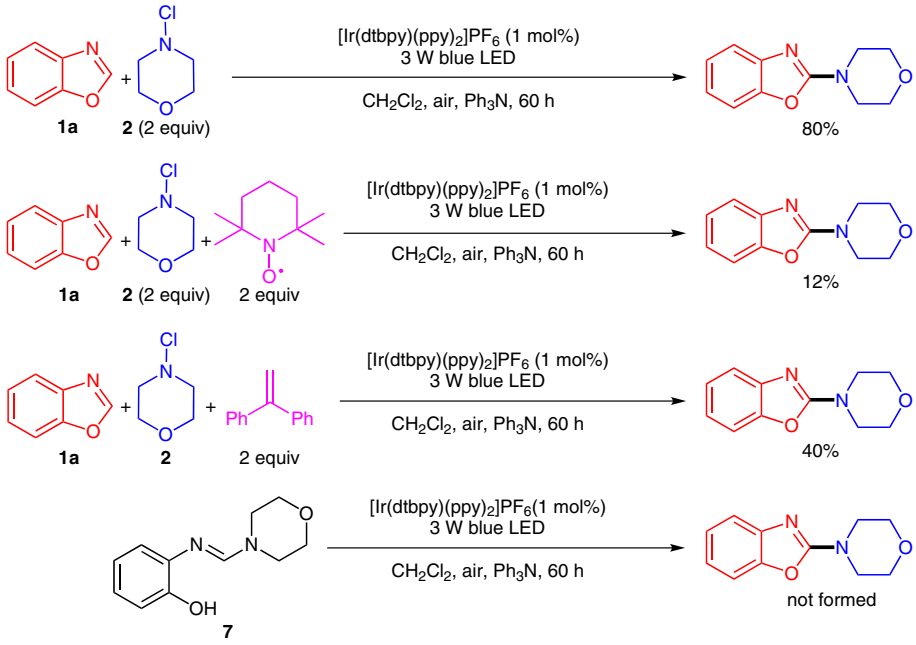
[a] Reaction conditions for the chlorination step: **4** (1 mmol), NCS (1.1 mmol), CH_2Cl_2 (5 mL) at r.t. in the dark, 3 h. The conditions for the second step were the same as above.
[b] Isolated yield.

Although the reaction mechanism is not yet clear, it is envisioned to be a radical process, which is supported by the radical trapping experiments (Scheme 3). Thus, when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added as a radical scavenger, the product **3a**[19] was obtained in only 12% yield. Similarly, 1,1-diphenylethylene, another efficient radical trapping agent, also suppressed the amination process; in its presence, yield decreased to 42%. Unlike the literature's results,[7o,8e] when amidine **7** was subjected to the standard conditions, no desired product was observed, which shows that amidine **7** is not the intermediate for this amination and our methodology proceed via a different pathway. We also studied the effect of visible light to the reaction. When the reaction was irradiated with visible light, the reaction went well. When the light was switched off, the reaction also stopped. The reaction worked again, when the light was switched on (Scheme 4). These experiments suggest that the reaction did not proceed via a radical-chain reaction mechanism.

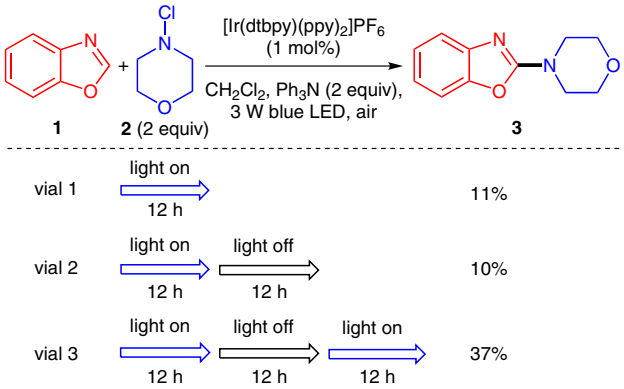
A plausible mechanism is shown in Scheme 5 on the basis of the above experiments and literature reports.[15,16] There are three key steps: (1) Irradiation of the catalyst at the ground state **A**, generating the excited $[Ir(dtbpy)(ppy)_2]^{III*}$ **B**; (2) the excited catalyst is then quenched by triphenylamine via electron transfer to form the ammo-



Scheme 2 Synthesis of the anti-HIV reagent **6**

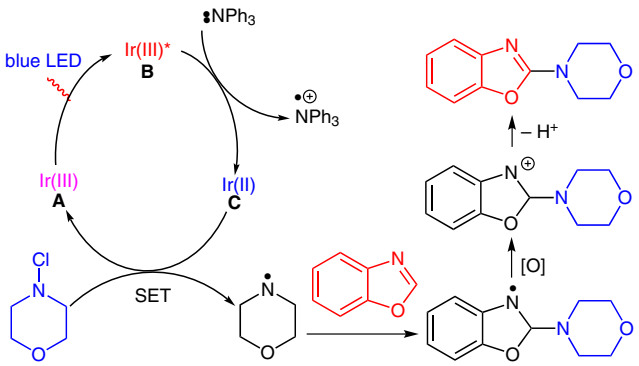


Scheme 3 Mechanistic experiments



Scheme 4 The experiments of on–off switching of visible light

nium radical cation and $[Ir(ppy)_2(dtbpy)]^{II}$ **C**; (3) the resulting $[Ir(ppy)_2(dtbpy)]^{II}$ species is capable of performing a single-electron reduction of the N–Cl bond, regenerating $[Ir(ppy)_2(dtbpy)]^{III}$ and a nitrogen-centered radical. Coupling of the radical and benzoxazole affords a new radical intermediate, which is subsequently transformed into a nitrogen-centered cation intermediate by an oxidant existed in the reaction, such as $[Ir(dtbpy)(ppy)_2]^{III}$, oxygen, or triarylammonium radical cation.[18] Finally, deprotonation of the cation intermediate regenerates the aromatic systems, furnishing the desired coupling adduct.



Scheme 5 Proposed reaction mechanism

In summary, a highly effective, visible-light-promoted 'radical-type' coupling of benzoxazoles with secondary amines has been developed. The reaction proceeds at room temperature with $[Ir(dtbpy)(ppy)_2]PF_6$ as photosensitizer and commercial LED bulb as light source. The broad substrate scope and mild reaction conditions make this procedure a practical and environmental friendly method for the synthesis of 2-aminobenzoxazoles. The reaction mechanism and further application of this new amination method are being actively explored in our group.

Acknowledgment

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(18) The catalyst Ir(III), oxygen, or triarylammonium radical cation may be responsible for the oxidation. It is not clear at this time.

(19) **One-Pot, Two-Step Amination of Benzoxazole with Various Amines**

An amine (1 mmol, 2 equiv) was added to a solution of *N*-chlorosuccinimide (149 mg, 1.1 mmol, 2.2 equiv) in CH_2Cl_2 (5 mL) at r.t. in the dark. After 3 h, $Ir(dtbpy)(ppy)_2PF_6$ (4 mg, 5 μmol, 0.01 equiv), Ph_3N (245 mg, 1 mmol, 2 equiv), and benzoxazole (60 mg, 0.5 mmol, 1 equiv) were added. The reaction rube was sealed and placed at a distance of 5 cm from 3 W blue LED and stirred for 60 h. After the reaction was complete, the solvent was evaporated under vacuo. The crude mixture was purified by flash column chromatography eluting with a mixture of PE–EtOAc.

2-(4-Morpholinyl)benzoxazole (3a)

Known compound; yellow solid; mp 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 7.6 Hz, 1 H), 7.27 (d, *J* = 6.4 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.04 (t, *J* = 7.6 Hz, 1 H), 3.82 (t, *J* = 4.4 Hz, 4 H), 3.69 (t, *J* = 5.2 Hz, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 148.7, 142.8, 124.0, 120.9, 116.4, 108.8, 66.1, 45.7.

5-Methyl-2-(4-morpholinyl)benzoxazole (3b)

Known compound; yellow solid; mp 117–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 0.8 Hz, 1 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 6.83 (dd, *J* = 8.0, 0.8 Hz, 1 H), 3.80 (t, *J* = 4.4 Hz, 4 H), 3.67 (t, *J* = 5.2 Hz, 4 H), 2.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 147.0, 143.0, 133.8, 121.6, 116.9, 108.2, 66.2, 45.8, 21.5.

