Note

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TEMPO-Mediated C-H Amination of Benzoxazoles with *N*-Heterocycles

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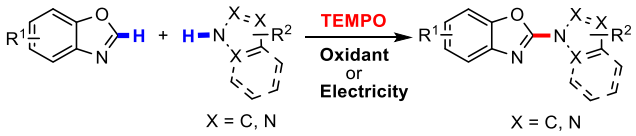
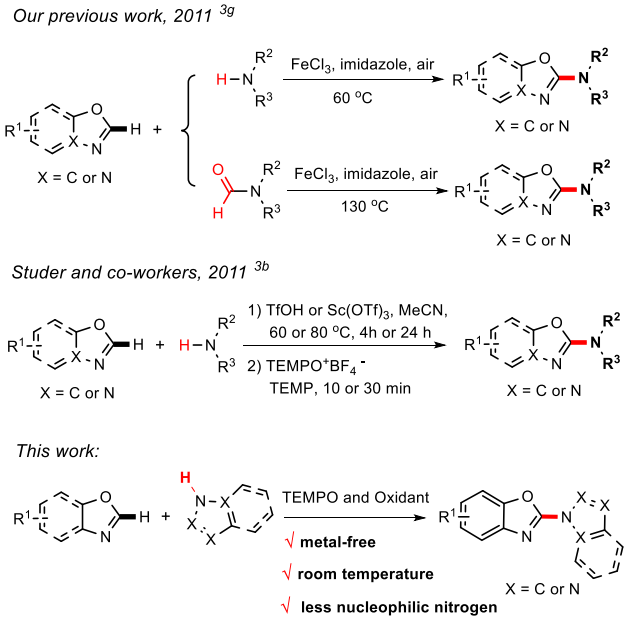


ABSTRACT: The direct amination of benzoxazoles at C2 using *N*-heterocycles as nitrogen sources has been developed for the first time. Several kinds of inexpensive oxidants and also electricity were effective for this transformation in the presence of TEMPO. This metal-free and operationally simple reaction can afford a variety of important C,N`-linked bis-heteocycles in moderate to good yields under very mild reaction conditions. The in situ generated oxoammonium salt had been proved to be important for this transformation.

Oxazole and their derivatives are privileged synthetic scaffolds due to their useful biological properties, and application as important building blocks for functional materials.[1] During the past decades, remarkable progresses have been made to develop efficient methods for their synthesis. In particular, the construction of C-N bonds through coupling reaction between C-H bond at the 2-position of oxazole and various nitrogen sources under transition-metal catalysis or metal-free conditions have attracted significant research interest (Scheme 1).[2] Among all these reported protocols for the direct C-H amination of oxazole, secondary amines were the most used nitrogen sources.[3] Primary amines and ammonia usually participated in the amination of oxazole under relatively milder conditions in comparison with secondary amines.[3f,4] Anilines generally showed lower activity than secondary amines during this amination, and therefore metal catalysts were commonly employed to active anilines through organometal intermediate.[3e,5] Formamides[3f,6] and tertiary amines[7] were able to be utilized as nitrogen sources in a one-pot domino fashion began with the dissociation of the strong C-C bonds under harsh conditions. Direct amidation of oxazole with amides was also successfully realized through a copper-mediated aerobic coupling reaction at high temperature.[8] Electrophilic amination reagent such as chloroamines[9] and *O*-acylated hydroxylamines[10] have been introduced as nitrogen sources, in which case external oxidant can be avoided.

Scheme 1. Direct C-H amination of oxazole

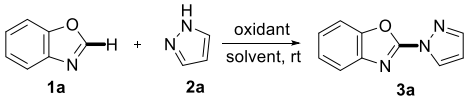


Despite great achievements, *N*-heterocycles are still undeveloped to couple with oxazole directly using reported methods. The bis-heteocycles consist of oxazole and *N*-heterocycles are biologically important,[11] and the method of connecting these two parts directly is highly desired. Herein,

we report the firstdirect amination of benzoxazoles at C2 using *N*-heterocycles as nitrogen sources under metal-free conditions.

In our previous work, we had demonstrated that $FeCl_3$ could mediate direct amination of azoles using formamides or amines as nitrogen sources in air (Scheme 1).[3g] *N*-heterocycles such as imidazole worked as ligand instead of nitrogen sources in this reaction. Therefore, we want to know whether the *N*-heterocycles could work as nitrogen sources to couple with oxazole. Inspired by the report of Nicewicz and coworkers,[12] pyrazoles have been widely used as nitrogen sources in the direct amination of C-H bonds.[13] Here we used pyrazole as a representative *N*-heterocyclic nitrogen source to react with benzoxazole. The results of reaction optimization are summarized in Table 1. Recently, TEMPO (2,2,6,6-tetramethyl-piperidine-*N*-oxyl) frequently appeared in the intramolecular oxidative C-H/N-H coupling reactions due to its versatile catalytic ability, such as hydrogen abstraction, single or double electron transfer, and trapping of active radical.[14] Therefore, we envisioned that the combination of TEMPO and external oxidant would also be a utility redox system for intermolecular oxidative cross-coupling reactions. Studer and co-workers reported using $TEMPO^+BF_4^-$ as organic oxidant in direct amination of benzoxazoles with secondary amines (Scheme 1).[3b] However, *N*-heterocycles was not reported here as nitrogen sources. *N*-heterocycles show lower activity than secondary amines during this kind of amination reactions, which was supported by our previous work[3g] and Little`s report[3d]. Benzoxazole may decompose in the presence of abundant $TEMPO^+$ when *N*-heterocycles are unable to attack benzoxazole quickly. The in-situ generation of $TEMPO^+$ may address this problem. Only TEMPO cannot trigger this oxidative reaction although TMEPO own some oxidizing property (entry 1). So, we began to screen a lot of oxidants in the presence of stoichiometric TEMPO. When the relatively strong oxidants were used, moderate yields of cross-coupling product **3a** were obtained (entries 2–5). Conditions with milder oxidant NCS (*N*-Chlorosuccinimide) can also form the product (entry 6). We found $PhI(OAc)_2$ was the best oxidant which can gave 86% yield together with TEMPO (entry 7). The quantity of TEMPO and $PhI(OAc)_2$ cannot be reduced or the yield will decreased significantly (entries 8–11). It has been known that $PhI(OAc)_2$ is a typical secondary oxidant in the TEMPO-involved oxidation reactions which usually go through classical oxoammonium cation mechanism.[15] Therefore, we used one stable oxoammonium salt (Bobbitt`s Salt) to oxidize the starting materials directly, but only achieved a low yield (entry 12). Considering the merit of electrochemical methods in organic synthesis and the widely use of TEMPO in electrochemical

Table 1. Optimization of the reaction conditions[a]

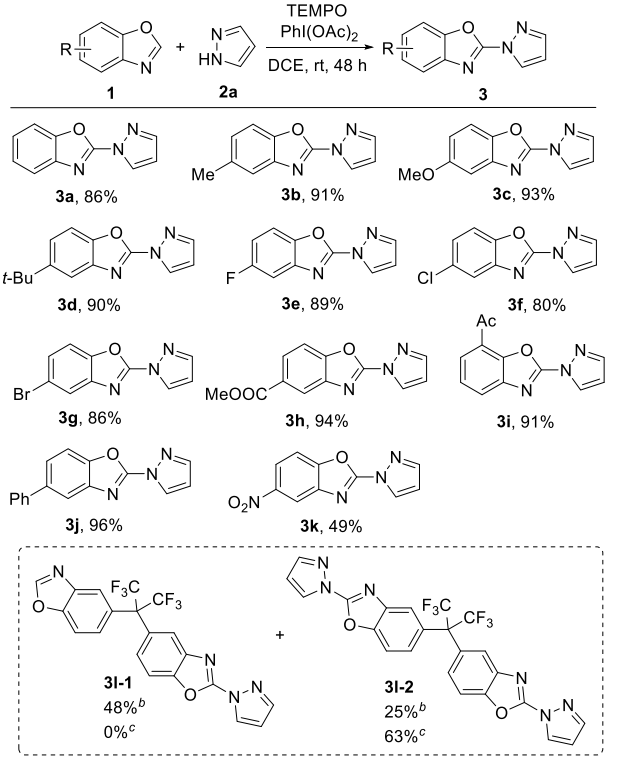


1a 2a 3a

entry	oxidant (equiv)	additive (equiv)	yield (%)
1	None	TEMPO (1.0)	0
2	$K_2S_2O_8$ (2.0)	TEMPO (1.0)	41
3	$(NH_4)Ce(NO_3)_6$ (2.0)	TEMPO (1.0)	43
4	Selectfluor (2.0)	TEMPO (1.0)	57
5	NFSI (2.0)	TEMPO (1.0)	48
6	NCS (2.0)	TEMPO (1.0)	15
7	$PhI(OAc)_2$ (2.0)	TEMPO (1.0)	86
8	$PhI(OAc)_2$ (2.0)	TEMPO (0.5)	73
9	$PhI(OAc)_2$ (1.2)	TEMPO (0.5)	45
10[b]	$PhI(OAc)_2$ (2.0)	TEMPO (0.5)	48
11	$PhI(OAc)_2$ (2.0)	TEMPO (0)	trace
12[c]	Bobbitt`s Salt (2.0)	None	29
13[d]	Pt(+) - Pt(-), 1.2 V	TEMPO (2.0)	51
14[d]	Pt(+) - Pt(-), 1.5 V	TEMPO (2.0)	38
15[e]	Pt(+) - Pt(-), 1.2 V	TEMPO (2.0)	0
16[f]	Pt(+) - Pt(-), 1.2 V	TEMPO (2.0)	9
17[d]	RVC(+) - RVC(-), 1.2 V	TEMPO (2.0)	24

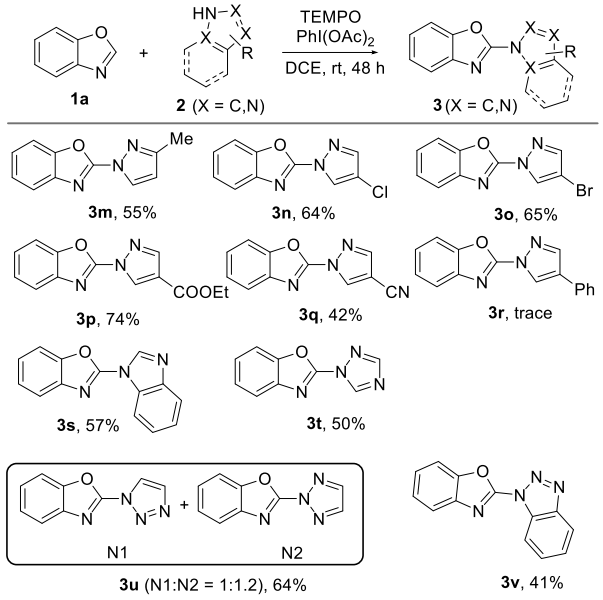
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), DCE (1 mL), rt, Air, 48 h. [b]pyrazole (0.6 mmol). [c]In CH_3CN (1 mL). [d-f]Constant cell potential, **1a** (0.5 mmol), **2a** (2.0 mmol), CH_3CN (2 mL), rt, Air, 120 h, undivided cell. [d]Bu_4NI (1.0 mmol) was used as supporting electrolyte. [e]$LiClO_4$ was used as supporting electrolyte. [f]NaI was used as supporting electrolyte. Platinum plate electrode (10 mm × 10 mm × 0.1 mm). RVC electrode (10 mm × 10 mm × 5 mm). RVC=Reticulated Vitreous Carbon.

Scheme 2. Scope of Benzoxazoles Compounds[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), TEMPO (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), DCE (1 mL), rt, Air, 48 h. [b]**1** (0.5 mmol), **2a** (2.0 mmol), TEMPO (1.0 mmol), $PhI(OAc)_2$ (2.0 mmol), DCE (2 mL), rt, Air, 72 h. [c]**1** (0.5 mmol), **2a** (5.0 mmol), TEMPO (2.5 mmol), $PhI(OAc)_2$ (5.0 mmol), DCE (5 mL), rt, Air, 7 d.

Scheme 3. Scope of *N*-heterocycles Compounds[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), TEMPO (0.5 mmol), $PhI(OAc)_2$ (1.0 mmol), DCE (1 mL), rt, Air, 48 h.

oxidation,[16] electrolytic conditions were screened for this transformation (entries 13–17). We found many factors were important for obtaining an acceptable yield by electrochemical strategy, including using Bu_4NI as supporting electrolyte, using CH_3CN as solvent, a long reaction time, and keeping the potential not too high.[17] At last, we also tried to improve the yield by adding AcOH under Bobbitt`s Salt conditions and electrolytic conditions because it was reported that AcOH was able to active benoxazole,[3c,3d] but no good result could be obtained. More optimization of this electrochemical oxidation conditions was continued in our group.

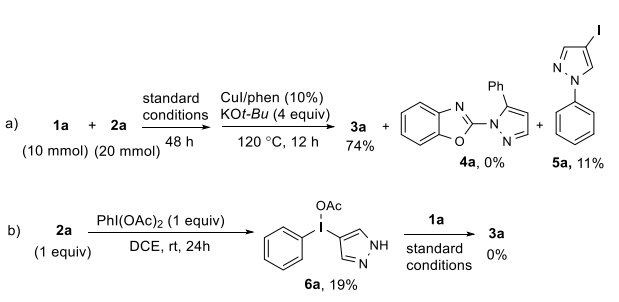
With the optimized reaction conditions in hand (Table 1, entry 7), the substrate scope of this transformation was further investigated (Scheme 2). A variety of substituted benzoxazoles were examined. We first investigated the benzoxazoles with electron-donating group at the 5-position, including methyl (**1b**), methoxy (**1c**), and tertiary butyl (**1d**). They all reacted smoothly with pyrazole to delivered high yields of products. The electron-withdrawing groups at the same position, such as F, Cl and Br, had a very slightly unfavorable effect on the yield (**3e**-**3g**). Ester, acetyl, and phenyl group could also be tolerated, and the high yield of 94%, 91% and 96% were obtained correspondingly (**3h**-**3j**). Nitro group lowered the reactivity of substrate **1**, and only a moderate yield of product **3k** was gotten. Lastly, one equivalent of 5,5`-(hexafluoroisopropylidene)bisbenzoxazolecould react with two equivalents of pyrazole successfully under a modified condition (**3l-2**).

Next, we turned to examine the scope of pyrazole derivatives and similar *N*-heterocycles in the benchmark reaction. A large number of analogues have been tried, and the successful examples are summarized in Scheme 3 (unsuccessful examples see Supporting Information). Obviously, the substituent groups on pyrazole led to a general decrease of yields (**3m**-**3q**).[18] TEMPO was replaced by other nitroxides for trying to improve the yield, but no satisfactory results could be acquired. The electrochemical methods have been also tried to improve their yields, but even worse results had been obtained. For aryl-substituted pyrazole (**2r**), only very little product (**3r**) could be isolated and many unknown impurities which may come from the decomposition of **3r** were formed. Imidazole did not react with benzoxazole under the standard condition, but benzimidazole could worked as nitrogen sources effectively under identical conditions (**3s**). Several triazoles produced 41% to 64% yields of the C-N adducts (**3t**-**3v**). 1,2,3-triazoles gave the coupling products **3u** in 1:1.2 *N*-regioisomeric ratio, while benzotriazole only formed N1 product (**3v**). At last, we explored some other substrates using similar redox system. Anisole can be aminated by pyrazole using NSFI (*N*-fluorobenzenesulfonimid) as oxidant in presence of TEMPO in 33% yield with similar regioselectivity as reported literature.[12a] Secondary amines also reacted with benzoxazole to form 2-aminated benzoxazoles in moderated yield in this standard conditions.

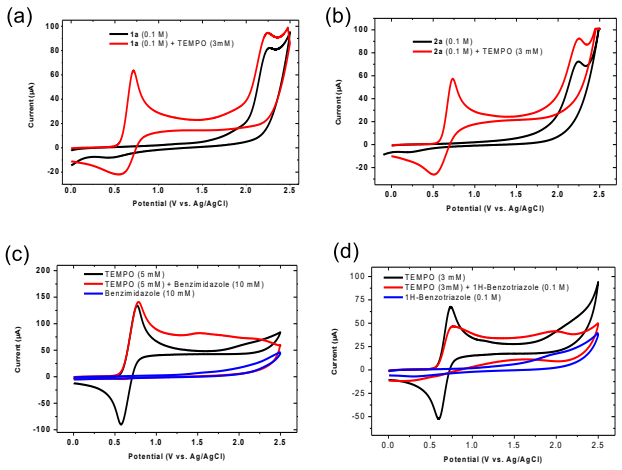
$PhI(OAc)_2$ does not oxidize TEMPO to $TEMPO^+$ directly,[19] however, the disproportionation of TEMPO would initiate the formation of $TEMPO^+$.[15] We also detected hydroxyamine and oxoammonium salt by mass spectrometry in this reaction (see Supporting Information). Consequently, the formation of $TEMPO^+$ in our reaction is highly possible. Furthermore, the mild oxidant NCS and the low potential electricity which were not powerful enough to activate benzoxazole and pyrazole directly, but they were effective to make the reaction get nonnegligible yields in the presence of TEMPO (Table 1, entry 6 and 13). Thus, the easily in situ generated $TEMPO^+$ which was usually regarded as one strong oxidant should be the real oxidant during this reaction. Different to using of stoichiometric Bobbitt`s Salt, the slowly releasing of $TEMPO^+$ in the combination of TEMPO and $PhI(OAc)_2$ may be the reason for the high yield.

During the research of exploiting the synthetic utility of this reaction, when we tried to couple the by-product iodobenzene with **3a** in one pot after the large-scale reaction in order to acquire the arylated bis-heteocycles (Scheme 4a), **5a** was isolated in 11% yield unexpectedly. We speculated **5a** came from the pyrazole-4-phenyliodonium acetate (**6a**) which was formed as shown in Scheme 4b, and this was supported by literature.[20] The iodonium compound **6a** cannot react with **1a** in the standard condition. So **6a** is another major by-product in the standard reaction, which may account for the decrease of yield in Scheme 4c and why two equivalents of pyrazole was need in the standard reaction. Additionally, because many other oxidants except $PhI(OAc)_2$ were also effective in this reaction, initially

Scheme 4. Reaction of Pyrazole with $PhI(OAc)_2$



Scheme 5. Cyclic voltammograms of 1a, 2a, 2s and 2v in MeCN

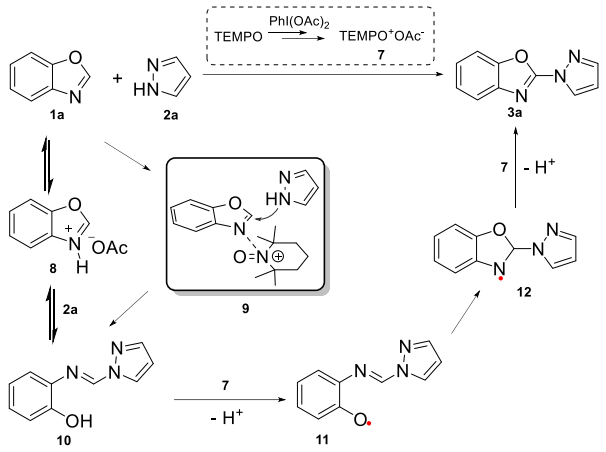


activation of pyrazole by formation a highly reactive N-I bond in pyrazole was exclude.[4a]

In the oxidative C-N coupling between pyrazole and aromatic or heteroaromatic compounds, pyrazole usually undergo nucleophilic attack of radical cation intermediate of aryl compounds which derived from single-electron oxidation processes.[12,13a-c] To verify the possibility of single-electron oxidation during our reaction, we then studied the interaction between $TEMPO^+$ and the substrates by investigating the redox behavior of them by voltammetric analysis. As shown in Scheme 5, both benzoxazole and pyrazole displayed a weak irreversible oxidation wave (**1a** at E_{ox}=2.27 V vs Ag/AgCl, **2a** at E_{ox}=2.24 V vs Ag/AgCl), and they had no interaction with $TEMPO^+$ in the voltammetric analysis (Scheme 5a and 5b). It means $TEMPO^+$ cannot react with **1a** or **2a** directly by single electron transfer. When we continued to check other substrates by voltammetric analysis, it was found that benzimidazole and 1H-benzotriazole could weaken the reduction wave of TEMPO significantly (Scheme 5c and 5d), and this indicated the quickly consumption of the $TEMPO^+$ from the electrode surface via reaction with benzimidazole and 1H-benzotriazole.[21] It means $TEMPO^+$ may react with **2s** or **2v** directly by single electron transfer to form radical cation species of **2s** or **2v** in our system. However, both yield of them were significantly lower than the yield of pyrazole. So, we thought the single-electron oxidation was side reaction here, and no single-electron oxidation of substrates was involved in the formation of products.

The ring-opened adduct *o*-hydroxyamidine had been proved to be a usual intermediate in the C-H amination of benzoxazole, especially when using secondary amines as nitrogen sources under metal-free conditions.[3a,3b,3d] However, the nucleophilicity of pyrazole was too weak to open the cycle of benzoxazole directly. Therefore, on the basis of related literatures[3a,3b,22] and previous experiments, a possible mechanism for the transformations was proposed (Scheme 6). Initially, $TEMPO^+$ is generated in the presence of $PhI(OAc)_2$ or electricity. Then, benzoxazole could be activated by $TEMPO^+$. The activation by AcOH which could be generated from $PhI(OAc)_2$ cannot be ruled out else, although it did not help when we used it to improve the yields

Scheme 6. Proposed Reaction Mechanisms



under Bobbitt`s Salt conditions and electrolytic conditions. The activated benzoxazole is attacked by pyrazole to form *o*-hydroxyamidine compound **10**. Then, $TEMPO^+$ oxidizes **10** to radical **11**, followed by deprotonation, intramolecular cyclization, another single-electron oxidation and deprotonation, finally affords product **3a**.

In summary, a new oxidation system for direct amination of benzoxazoles with *N*-heterocycles was developed for the first time. Only TEMPO and $PhI(OAc)_2$ were used in this convenient method. A variety of important C,N`-linked bisheteocycles in moderate to good yields under this reaction conditions were obtained. We have undertaken detailed investigations of the reaction mechanism, and we concluded that the in situ generated oxoammonium salt should be the key mediator during the whole reaction process.

EXPERIMENTAL SECTION

General Information. Proton nuclear magnetic resonance (^{1}H-NMR, 600 MHz) and carbon-13 nuclear magnetic resonance (^{13}C-NMR, 150 MHz) spectra were measured on a JNM-ECZ600R/S1 (JEOL, Tokyo, Japan) with $CDCl_3$ as solvent and recorded in ppm relative to an internal tetramethylsilane standard. High resolution mass spectra (HRMS) were recorded on a 6520 Q-TOF MS system (Agilent, Santa Clara, CA, USA) using an electrospray (ESI) ionization source. Low resolution mass spectra were obtained on an Agilent 1260-6120 ESI-LC/MS. Known compounds were confirmed by ^{1}H-NMR spectra according to literatures. The instrument for electrolysis is multi-channel potentiostat (A-BF SS-3305D) (made in China). The dimension parameter of platinum plate electrode and reticulated vitreous carbon electrode are 10 mm×10 mm×0.1 mm, and 10 mm × 10 mm × 5 mm. Cyclic voltammetry measurements were performed in dry CH_3CN on a CHI 610E electrochemical analyzer with a three-electrode cell, using 0.1 M Bu_4NPF_6 as supporting electrolyte, AgCl/Ag as reference electrode, platinum disk as working electrode, Pt wire as counter electrode, and scan rate at 100 mV/s. Unless otherwise noted, reagents were purchased from Aldrich Chemical Co. (Darmstadt, Germany), Adamas-beta (Shanghai, China) and Energy Chemical (Shanghai, China) and used without further purification. Benzoxazole derivatives[3f,23] and pyrazole derivatives[24] are prepared according to the literature.

General Procedure for Amination of Benzoxazoles with *N*-heterocycles. A glass tube equipped with a magnetic stir bar charged with benzoxazole derivative (0.5 mmol, 1.0 equiv),

TEMPO (78 mg, 0.5 mmol, 1.0 equiv), *N*-heterocycles (2.0 equiv), 1,2-dichloroethane (1 ml), then $PhI(OAc)_2$ (322 mg, 1.0 mmol, 2.0 equiv) was added. After stirring of the solution at room temperature for 48 h under an air atmosphere. The mixture was then diluted with DCM, washed with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography. The identity and purity of the unknown product was confirmed by HRMS, ^{1}H-NMR and ^{13}C-NMR. Known compounds **3a**, **3s**, and **3v** were confirmed by ^{1}H-NMR spectra according to literatures.[11]

Electro-Oxidative Amination of Benzoxazole with Pyrazole. A solution of benzoxazole (60 mg, 0.5 mmol), pyrazole (136 mg, 2.0 mmol), TEMPO (156 mg, 1.0 mmol) and Bu_4NI (369 mg, 1.0 mmol) in CH_3CN (2 ml) was stirred at 25 °C under air atmosphere in glass tube which was equipped with platinum plate electrodes (1.0 cm×1.0 cm×0.1 mm) as both the anode and cathode. The reaction mixture was stirred and electrolyzed at a constant cell potential of 1.2 V for 120 hours. The reaction mixture was directly concentrated in vacuo, then diluted with DCM, washed with water and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford pure product.

A Large-Scale Synthesis for Amination of Benzoxazole with Pyrazole. A flame-dried round-bottom flask equipped with a stir bar was evacuated and filled with nitrogen. The flask was then charged with benzoxazole (2.38 g, 20.0 mmol, 1.0 equiv), TEMPO (3.12 g, 20.0 mmol, 1.0 equiv), pyrazole (2.72 g, 40.0 mmol, 2.0 equiv), dry 1,2-dichloroethane (50 ml), and placed in an ice bath. To this solution was added $PhI(OAc)_2$ (12.88 g, 40.0 mmol, 2.0 equiv) with stirring, and was strirred at 0 °C for 0.5 h. After stirring of the solution at room temperature for another 48 h. The mixture was then diluted with DCM, washed with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford **3a** (2.99g, 81%).

Amination of Anisole with Pyrazole. A glass tube equipped with a magnetic stir bar was evacuated and filled with nitrogen. The tube was then charged with anisole (54 mg, 0.5 mmol, 1.0 equiv), TEMPO (78 mg, 0.5 mmol, 1.0 equiv), pyrazole (68 mg, 1.0 mmol, 2.0 equiv), 1,2-dichloroethane (1 ml), then NFSI (315 mg, 1.0 mmol, 2.0 equiv) was added at 0 °C. After stirring of the solution at room temperature for another 48 h. The mixture was then diluted with DCM, washed with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford the product (29 mg, 33%). The identity and purity of the product was confirmed by ^{1}H-NMR spectra according to literatures.[12a]

Amination of Benzoxazole with Morpholine. A glass tube equipped with a magnetic stir bar charged with benzoxazole (60 mg, 0.5 mmol, 1.0 equiv), TEMPO (78 mg, 0.5 mmol, 1.0 equiv), morpholine (87mg, 1.0 mmol, 2.0 equiv), 1,2-dichloroethane (1 ml), then $PhI(OAc)_2$ (322 mg, 1.0 mmol, 2.0 equiv) was added. After stirring of the solution at room temperature for 48 h under an air atmosphere. The mixture was then diluted with DCM, washed with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography to afford the product (59 mg, 58%). The identity and purity of the product was confirmed ^{1}H-NMR spectra according to literatures.[3c]

5-methyl-2-(1H-pyrazol-1-yl)benzo[d]oxazole ***(3b)****.* White solid (91 mg, 91%); mp 83-85 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.38 (d, J = 2.7 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.47 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.13 (dd, J = 8.3, 0.9 Hz, 1H), 6.58-6.56 (m, 1H), 2.47 (s, 3H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 153.8, 147.60, 144.4, 140.9, 135.2, 129.8, 125.8, 119.6, 110.1, 109.6, 21.6; HRMS (ESI): $[M+H]^+$ calcd. for $C_{11}H_9N_3O$: m/z = 200.0818; found, 200.0816.

5-methoxy-2-(1H-pyrazol-1-yl)benzo[d]oxazole ***(3c)****.* White solid (100 mg, 93%); mp 82-84 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.35 (d, J = 2.7 Hz, 1H), 7.85 (s, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.16 (d, J = 2.5 Hz, 1H), 6.89 (dd, J = 8.9 Hz, 2.4, 1H), 6.56-6.54 (m, 1H), 3.84 (s, 3H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ (150 MHz, $CDCl_3$) d=158.0, 154.4, 144.5, 144.0, 141.7, 129.8, 112.8, 111.0, 109.7, 103.3, 56.1; HRMS (ESI): $[M+H]^+$ calcd. for $C_{11}H_9N_3O_2$: m/z = 216.0768; found, 216.0765.

5-(tert-butyl)-2-(1H-pyrazol-1-yl)benzo[d]oxazole ***(3d)****.* White solid (108 mg, 90%); mp 68-70 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.38 (d, J = 2.6 Hz, 1H), 7.87 (s, 1H), 7.70 (s, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 6.57-6.56 (m, 1H), 1.38 (s, 9H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 154.0, 149.1, 147.5, 144.5, 140.7, 129.9, 122.5, 116.4, 110.0, 109.7, 35.1, 31.9; HRMS (ESI): $[M+H]^+$ calcd. for $C_{14}H_{15}N_3O$: m/z = 242.1288; found, 242.1283.

5-fluoro-2-(1H-pyrazol-1-yl)benzo[d]oxazole ***(3e)****.* Pale pink solid (90 mg, 89%); mp 135-137 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (d, J = 2.7 Hz, 1H), 7.88 (s, 1H), 7.49 (dd, J = 8.9, 4.2 Hz, 1H), 7.36 (dd, J = 8.2, 2.6 Hz, 1H), 7.05 (td, J = 9.1, 2.5 Hz, 1H), 6.59-6.56 (m, 1H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 160.6 (d, J = 241.5 Hz), 155.1, 145.8, 144.9, 141.8 (d, J = 13.3 Hz), 130.1, 112.4 (d, J = 26.1 Hz), 111.2 (d, J = 10.1 Hz), 110.1, 106.6 (d, J = 26.2 Hz); HRMS (ESI): $[M+H]^+$ calcd. for $C_{10}H_6FN_3O$: m/z = 204.0568; found, 204.0566.

5-chloro-2-(1H-pyrazol-1-yl)benzo[d]oxazole ***(3f)****.* White solid (88 mg, 80%); mp 128-131 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.38 (d, J = 2.7 Hz, 1H), 7.90 (s, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.32 (dd, J = 8.6 Hz, 2.1, 1H), 6.60-6.59 (m, 1H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 154.8, 148.0, 145.0, 142.0, 130.9, 130.1, 125.2, 119.8, 111.6, 110.2; HRMS (ESI): $[M+H]^+$ calcd. for $C_{10}H_6ClN_3O$: m/z = 220.0272; found, 220.0269.

5-bromo-2-(1H-pyrazol-1-yl)benzo[d]oxazole ***(3g)****.* Pale pink solid (113 mg, 86%); mp 130-132 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.34 (d, J = 2.7 Hz, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.42-7.41 (m, 2H), 6.57-6,55 (m, 1H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 154.5, 148.4, 145.0, 142.4, 130.1, 127.8, 122.7, 118.1, 112.0, 110.1; HRMS (ESI): $[M+H]^+$ calcd. for $C_{10}H_6BrN_3O$: m/z = 263.9767; found, 263.9767.

methyl 2-(1H-pyrazol-1-yl)benzo[d]oxazole-5-carboxylate ***(3h)****.* white solid (114 mg, 94%); mp 151-153 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.37-8.33 (m, 1H), 8.11-8.04 (m, 1H), 7.89 (s, 1H), 7.65-7.54 (m, 1H), 6.59 (d, J = 1.3 Hz, 1H), 3.95 (s, 3H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 166.5, 154.7, 152.4, 145.0, 141.1, 130.2, 128.0, 126.9, 121.6, 110.6, 110.2, 52.5; HRMS (ESI): $[M+H]^+$ calcd. for $C_{12}H_9N_3O_3$: m/z = 244.0717; found, 244.0713.

1-(2-(1H-pyrazol-1-yl)benzo[d]oxazol-7-yl)ethan-1-one ***(3i)****.* white solid (103 mg, 91%); mp 152-154 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.39 (d, J = 2.7 Hz, 1H), 7.93-7.84 (m, 3H), 7.47-7.41 (m, 1H), 6.60 (dd, J = 2.6 Hz, 1.4, 1H), 2.87 (s, 3H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 194.4, 154.3, 148.1, 145.1, 142.1, 130.2,

125.4, 125.3, 124.6, 122.1, 110.2, 30.4; HRMS (ESI): $[M+H]^+$ calcd. for $C_{12}H_9N_3O_2$: m/z = 228.0768; found, 228.0764.

5-phenyl-2-(1H-pyrazol-1-yl)benzo[d]oxazole ***(3j)****.* white solid (125 mg, 96%); mp 130-132 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.40 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 11.6 Hz, 2H), 7.61 (d, J = 6.9 Hz, 3H), 7.57-7.53 (m, 1H), 7.47 (dd, J = 11.1, 3.9 Hz, 2H), 7.37 (dd, J = 10.9, 4.1 Hz, 1H), 6.58 (d, J = 1.7 Hz, 1H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 154.3, 149.0, 144.7, 141.5, 140.9, 139.4, 130.0, 129.0, 127.6, 124.4, 118.2, 110.8, 109.9; HRMS (ESI): $[M+H]^+$ calcd. for $C_{16}H_{11}N_3O$: m/z = 262.0975; found, 262.0970.

5-nitro-2-(1H-pyrazol-1-yl)benzo[d]oxazole ***(3k)****.* white solid (56 mg, 49%); mp 183-185 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.54 (d, J = 2.0 Hz, 1H), 8.40 (d, J = 2.7 Hz, 1H), 8.29 (dd, J = 8.9, 2.1 Hz, 1H), 7.92 (s, 1H), 7.68 (d, J = 8.9 Hz, 1H), 6.64-6.62 (m, 1H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 155.9, 152.9, 146.0, 145.6, 141.5, 130.5, 121.0, 115.9, 111.1, 110.7; HRMS (ESI): $[M+H]^+$ calcd. for $C_{10}H_6N_4O_3$: m/z = 231.0513; found, 231.0509.

5-(2-(benzo[d]oxazol-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-yl)-2-(1H-pyrazol-1-yl)benzo[d]oxazole ***(3l-1)****.* white solid (108 mg, 48%); mp 156-159 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.37 (d, J = 2.7 Hz, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.89 (s, 1H), 7.81 (s, 1H), 7.57 (t, J = 8.4 Hz, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 6.59 (dd, J = 2.5 Hz, 1.3, 1H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 154.8, 153.7, 150.1, 149.5, 145.0, 141.0, 140.2, 131.1, 130.3, 130.2, 128.0, 127.1, 124.3 (d, J = 285.2 Hz), 123.2, 122.1, 110.9, 110.6, 110.2, 65.0 (p, J = 25.2 Hz); HRMS (ESI): $[M+H]^+$ calcd. for $C_{20}H_{10}F_6N_4O_2$: m/z = 453.0781; found, 453.0771.

5,5'-(perfluoropropane-2,2-diyl)bis(2-(1H-pyrazol-1-yl)benzo-[d]oxazole) ***(3l-2)****.*white solid (163 mg, 63%); mp 195-197 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.38 (d, J = 2.7, 2H), 7.90 (d, J = 1.1, 2H), 7.83 (s, 2H), 7.57 (d, J = 8.8, 2H), 7.35 (d, J = 8.7, 2H), 6.61-6.57 (m, 2H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 154.8, 149.5, 145.1, 141.0, 131.0, 130.2, 127.1, 124.3 (d, J = 285.3 Hz), 122.1, 110.6, 110.4, 65.0 (p, J = 25.7 Hz); HRMS (ESI): $[M+H]^+$ calcd. for $C_{23}H_{12}F_6N_6O_2$: m/z = 519.0999; found, 519.0987.

2-(3-methyl-1H-pyrazol-1-yl)benzo[d]oxazole ***(3m)****.* white solid (55 mg, 55%); mp 100-102 °C; the regioselectivity is supported by an X-ray crystallographic structure determination, see Supporting Information; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (d, J = 2.6 Hz, 1H), 7.64 (d, J = 7.4 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.29 (td, J = 7.9, 1.1 Hz, 1H), 6.35 (d, J = 2.7 Hz, 1H), 2.42 (s, 3H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 154.6, 153.9, 149.4, 141.0, 130.5, 125.3, 124.6, 119.5, 110.7, 110.3, 13.9; HRMS (ESI): $[M+H]^+$ calcd. for $C_{11}H_9N_3O$: m/z = 200.0818; found, 200.0816.

2-(4-chloro-1H-pyrazol-1-yl)benzo[d]oxazole ***(3n)****.* white solid (70 mg, 64%); mp 116-118 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (d, J = 0.4 Hz, 1H), 7.80 (s, 1H), 7.70-7.67 (m, 1H), 7.57 (dd, J = 7.4, 1.5 Hz, 1H), 7.40-7.34 (m, 2H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 153.0, 149.5, 143.3, 140.6, 127.4, 125.6, 125.2, 119.9, 115.1, 110.9; HRMS (ESI): $[M+H]^+$ calcd. for $C_{10}H_6ClN_3O$: m/z = 220.0272; found, 220.0271.

2-(4-bromo-1H-pyrazol-1-yl)benzo[d]oxazole ***(3o)****.* white solid (85 mg, 65%); mp 115-117 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.40 (d, J = 2.6 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 7.68 (dd, J = 7.2, 1.4 Hz, 1H), 7.60-7.53 (m, 1H), 7.41-7.32 (m, 2H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$) *δ:* 152.9, 149.5, 145.2, 140.7, 129.7, 125.6, 125.3, 120.0, 110.9, 98.6; HRMS (ESI): $[M+H]^+$ calcd. for $C_{10}H_6BrN_3O$: m/z = 263.9767; found, 263.9766.

ethyl 1-(benzo[d]oxazol-2-yl)-1H-pyrazole-4-carboxylate ***(3p)****.* white solid (95 mg, 74%); mp 132-135 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.84 (d, J = 1.2 Hz, 1H), 8.21 (s, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.39-7.36 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 161.8, 152.9, 149.6, 144.9, 140.6, 132.9, 125.7, 125.5, 120.1, 118.9, 111.0, 61.1, 14.4; HRMS (ESI): $[M+H]^+$ calcd. for $C_{13}H_{11}N_3O_3$: m/z = 258.0873; found, 258.0871.

1-(benzo[d]oxazol-2-yl)-1H-pyrazole-4-carbonitrile ***(3q)****.* white solid (44 mg, 42%); mp 188-190 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.13 (s, 1H), 7.77-7.71 (m, 1H), 7.64-7.59 (m, 1H), 7.45-7.40 (m, 2H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 152.1, 149.7, 145.4, 140.3, 134.9, 126.1, 126.0, 120.5, 111.7, 111.2, 97.0; HRMS (ESI): $[M+H]^+$ calcd. for $C_{11}H_6N_4O$: m/z = 211.0614; found, 211.0613

2-(1H-1,2,4-triazol-1-yl)benzo[d]oxazole ***(3t)****.* white solid (47 mg, 50%); mp 127-130 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.05 (s, 1H), 8.21 (s, 1H), 7.73 (dd, J = 5.3, 1.8 Hz, 1H), 7.60 (dd, J = 5.1, 1.5 Hz, 1H), 7.44-7.37 (m, 2H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 154.2, 151.2, 149.5, 144.1, 140.2, 125.9, 125.8, 120.4, 111.1; HRMS (ESI): $[M+H]^+$ calcd. for $C_9H_6N_4O$: m/z = 187.0614; found, 187.0612

2-(1H-1,2,3-triazol-1-yl)benzo[d]oxazole, 2-(2H-1,2,3-triazol-2-yl)benzo[d]oxazole ***(3u)****.* white solid (60 mg, 64%); mp 84-88 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.49 (d, J = 1.1 Hz, 0.86H), 8.03 (s, 2 H), 7.90 (s, 0.86H), 7.79-7.75 (m, 1.86H), 7.65-7.61 (m, 1.86H), 7.44-7.40 (m, 3.72H). ^{13}C {^{1}H} NMR (150 MHz, $CDCl_3$): δ 152.6, 151.4, 149.7, 149.6, 140.6, 140.1, 138.7, 134.6, 126.2, 126.2, 125.9, 125.9, 125.8, 123.5, 120.7, 120.5, 111.3, 111.1; HRMS (ESI): $[M+H]^+$ calcd. for $C_9H_6N_4O$: m/z = 187.0614; found, 187.0612

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, analytical data, mass spectrum, cyclic voltammogram, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(17) Lower cell potentials than 1.2 v cannot afforded products; Using Bu_4NPF_6 as supporting electrolytes cannot afforded products.

(18) Single crystal of **3m** could be obtained by slow solvent evaporation from ethyl acetate solution. CCDC 2000018 contains the supplementary crystallographic data for **3m**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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