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Electrochemically Initiated Oxidative Amination of Benzoxazoles Using Tetraalkylammonium Halides As Redox Catalysts

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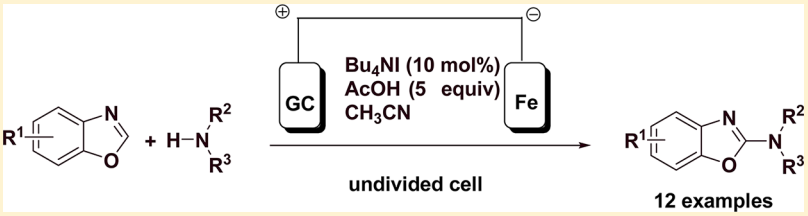
Supporting Information



ABSTRACT: An electrochemically promoted coupling of benzoxazoles and amines has been developed, leading directly to the formation of 2-aminobenzoxazoles. The chemistry utilizes catalytic quantities of a tetraalkylammonium halide redox catalyst and is carried out under constant current conditions in a simple undivided cell. The use of excess chemical oxidant or large amounts of supporting electrolyte is avoided. This greatly simplifies the workup and isolation process and leads to a reduction in waste.

1. INTRODUCTION

Oxidative cross-dehydrogenative coupling (CDC) to form new C−N bonds has proven to be of significant importance in organic chemistry since preactivation of the C−H or N−H bonds of the reaction partners is not required, and *formally*, hydrogen is the only byproduct.[1] Due to its step- and atom-economical characteristics, a variety of CDC strategies have been developed and widely employed.[2] The direct oxidative CDC amination of benzoxazole with unactivated amines to afford 2-aminobenzoxazoles has attracted much attention by virtue of the fact that 2-aminobenzoxazoles constitute an important scaffold in a number of therapeutically important molecules.[3] Although transition metal catalysts, based on Pd, Cu, Ru, Ag, or Fe, have been widely used in combination with co-oxidants to achieve C−N bond formation,[4] the toxicity of residual traces of the transition metal makes it worthwhile to devise metal-free oxidative amination processes. Hypervalent iodine reagents are versatile and powerful oxidants that have been used in this manner.[5] For example, Chang and co-workers used stoichiometric amounts of $PhI(OAc)_2$,[6] and Bhanage et al.[7] used 2-iodoxybenzoic acid (IBX) to achieve C−H bond amination of benzoxazoles. Recently, an excess of 2,2,6,6-tetramethylpiperidine-*N*-oxoammonium tetrafluoroborate ($TEMPO^+BF_4^-$) was also utilized to achieve the oxidative coupling.[8] In addition, much progress has been made through the use of a combination of an iodine source and a co-oxidant (e.g., H_2O_2, *t*-BuOOH, IBX).[9] For example, with the combination of a catalytic amount of *n*-Bu_4NI and excess H_2O_2 or *t*-BuOOH, 2-aminobenzoxazoles can be isolated in excellent yields.[10] High yields were also furnished from the oxidative amination of benzoxazole in the presence of catalytic iodine (I_2) in aqueous *t*-BuOOH under neat reaction conditions.[11] These catalytic systems overcome some of the drawbacks of using stoichiometric amounts of hypervalent iodine reagents. However, excess co-oxidant is still required, which leads to the formation of a large amount of waste and complicates the workup process.

Electrochemistry provides an alterative, environmentally benign method to achieve the C−H functionalization, either through direct electron transfer between an electrode and a substrate (direct electrolysis) or via a redox catalyst playing the role of the electron transfer agent (indirect electrolysis).[12] We are interested in oxidative activation of C−H bonds induced by redox catalysts and have developed novel redox catalysts based upon the triarylimidazole scaffold, which have been employed for the oxidative activation of benzylic C−H bonds to afford the corresponding aldehydes, ketones, and benzoates.[13] Recently, we reported the efficient synthesis of 2-substituted benzoxazoles from the electrochemical oxidation of Schiff bases or their precursors (*o*-aminophenol and aldehydes) using sodium iodide as a redox mediator, as illustrated in Figure 1.[14] The key step was proposed to be an intramolecular cyclization of Schiff base **I** to generate benzoxazoline **II**,[15] which undergoes further oxidation by I^+ (or an equivalent), formed *in situ* electrochemically, to furnish the benzoxazole adduct **III**.

Since benzoxazoles are known to undergo ring opening in the presence of secondary amines to form *o*-hydroxyamidine adducts **IV**, especially under neat or acidic conditions,[6,7,16] we suggest that the sequence of transformations illustrated in

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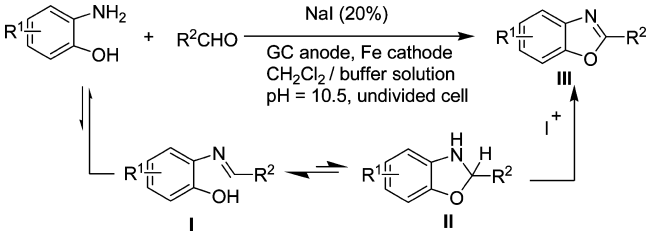


Figure 1. Electrochemical synthesis of benzoxazoles mediated by NaI.

Figure 2 may be feasible. Thus, if the intramolecular cyclization of **IV** occurs in analogy with the conversion of Schiff base **I**,

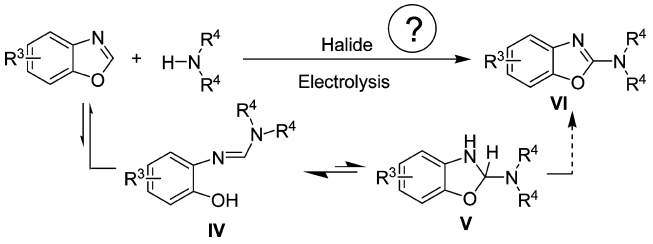


Figure 2. Proposed direct electrochemical amination for the formation of 2-aminobenzoxazoles.

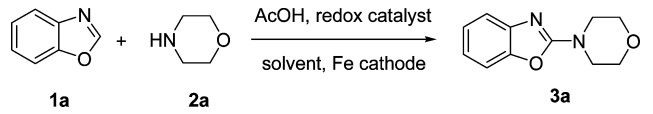
then the resulting 2-aminobenzoxazoline **V** may also undergo electrochemically initiated dehydrogenative oxidation to afford the desired 2-aminobenzoxazole **VI** (Figure 2).

Herein, we describe the electrochemically promoted oxidative amination of benzoxazoles using a catalytic amount of a tetraalkylammonium halide as a redox catalyst. The protocol features the following advantages: (1) the anode serves as a co-oxidant that is physically separated from the organic layer containing the substrate and is thus easily removed; (2) no terminal chemical co-oxidant is needed; (3) only a catalytic amount (10 mol %) of tetraalkylammonium halide is used; and (4) no additional supporting electrolyte is required, thereby simplifying the workup and isolation process and leading to a reduction in waste. In addition, the electrolysis is conveniently carried out in an undivided cell. To the best of our knowledge, this work represents the first example of the electrochemically promoted oxidative amination of benzoxazole heterocycles using a halide anion (Br^- or I^-) as a redox catalyst.

2. RESULTS AND DISCUSSION

To explore these ideas, we selected benzoxazole **1a** and morpholine **2a** as model substrates (Scheme 1). The mediated

Scheme 1. Initial Optimization of the Indirect Electrochemical Oxidation of Benzoxazole 1a and Morpholine 2a



anodic oxidation was conducted in a simple beaker-type cell equipped with an iron plate cathode and a Pt plate anode at room temperature, under constant current conditions (6 mA/cm^2). By virtue of the fact that acetic acid promotes the ring opening of the benzoxazole,[16d] 5 equiv of HOAc were included as an additive (the addition of HOAc also increases the conductivity since no additional supporting electrolyte was added). When ethanol was used as a solvent and NaI as a redox catalyst, a yellow color appeared and hydrogen gas evolution was observed on the cathode surface as the charge was consumed. After conventional workup, the desired 2-morpholinobenzoxazole **3a** was isolated in 36% chemical yield and 89% current efficiency (note Table 1, entry 1).

Table 1. Optimization of Conditions for the Oxidative Amination of Benzoxazole[a]

Entry	Redox Catalyst (mol %)	Solvent	Anode	Yield (%)[b]	C. E. (%)[c]
1	NaI (10)	CH_3CH_2OH	Pt	36	89
2	NaI (10)	CF_3CH_2OH	Pt	trace	–
3	NaI (10)	CH_3CN	Pt	56	89
4	None	CH_3CN	Pt	53	89
5	*n*-Bu_4NI (10)	CH_3CN	Pt	66	84
6	*n*-Bu_4NI (10)	CH_3CN	graphite	70	84
7	*n*-Bu_4NI (10)	CH_3CN	GC	91	43
8	*n*-Bu_4NI (20)	CH_3CN	GC	87	49
9	*n*-Bu_4NI (5)	CH_3CN	GC	63	76
10	*n*-Bu_4NI (10)	CH_3CH_2OH	GC	34	72
11	*n*-Bu_4NI (10)	CH_2Cl_2	GC	79	80
12	Et_4NI (10)	CH_3CN	GC	80	53
13	Et_4NBr (10)	CH_3CN	GC	73	55
14	NaBr (10)	CH_3CN	GC	54	55

[a]Reaction conditions: benzoxazole **1a** (1 mmol), amine **2a** (2 mmol), and HOAc (5 mmol) as additive in 20 mL of solvent, undivided cell, Fe plate cathode, room temperature, current density of 6 mA/cm^2. [b]Isolated yield. [c]C. E.: Current efficiency.

Encouraged by this result, solvent screening was carried out in an effort to improve the yield. Only a trace amount of **3a** was detected when the electrolysis was conducted in the polar hydroxylic solvent, CF_3CH_2OH (entry 2). On the other hand, the use of acetonitrile as the solvent witnessed an increase in the chemical yield to 56% (entry 3). Notably, nearly the same yield of **3a** was isolated when the electrolysis was conducted in the absence of NaI (entry 4), which implies that benzoxazole and morpholine can undergo direct oxidative amination under electrochemical conditions, even without using iodide as an electron carrier (in this case, acetic acid served as the supporting electrolyte). Nevertheless, we continued to explore the use of a redox mediator; the efforts were rewarded.

Next, we focused our attention upon the nature of the working electrode, as well as the quantity and the nature of the redox catalyst. As shown in entry 5 of Table 1, the yield of **3a** increased from 56% using NaI to 66% using 10 mol % of *n*-Bu_4NI and a Pt anode. In general, quaternary ammonium iodides proved superior to sodium iodide, undoubtedly because of the low solubility of the latter in most organic solvents. The yield increased to 70% when a graphite rod was used (entry 6) and to 91% using a glassy carbon working electrode (entry 7). A comparable yield (87%) of **3a** was obtained when the quantity of *n*-Bu_4NI was increased to 20 mol % (entry 8), while the yield decreased to 63% when 5 mol % of *n*-Bu_4NI was employed (entry 9). Based upon these observations, we suggest an optimal use of 10 mol % of the mediator. Even then the yield of **3a** decreased substantially when the solvent was switched from acetonitrile to ethanol and dichloromethane under otherwise identical conditions (entries 10 and 11). Finally, we discovered that other quaternary ammonium

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iodides/bromides were also effective when acetonitrile was employed as the solvent. For instance, a good yield (80%) of **3a** was obtained using Et_4NI, and a 79% yield was observed when Et_4NBr was used as a redox catalyst (entries 12 and 13). The moderate yield (54%) using NaBr may result from its lower solubility in acetonitrile (entry 14).

From the results described above we conclude that the optimal reaction conditions call for using 10 mol % of tetrabutylammonium iodide as the redox catalyst, GC as the anode, and CH_3CN as the solvent. The reaction works well when conducted as a constant current electrolysis with a current density of 6 mA/cm^2 in an undivided cell.

To examine the scope of the process, the optimal conditions were applied to the reactions of benzoxazole **1a** with a variety of amines **2** (Scheme 2 and Table 2). As shown in Table 2,

Scheme 2. Electrochemically Oxidative Amination of Benzoxazoles

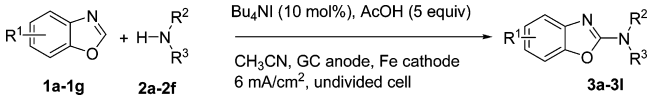
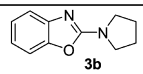
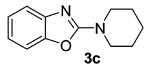
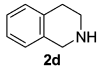
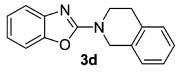
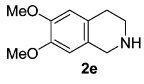
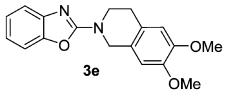
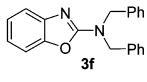


Table 2. Scope of the Secondary Amines[a]

Entry	Heterocycle	Amine	Product	Yield [b]
1	 1a	 2b	 3b	43
2	 1a	 2c	 3c	31
3	 1a	 2d	 3d	71
4	 1a	 2e	 3e	64
5	 1a	 2f	 3f	55

[a]Reaction conditions: benzoxazole **1** (1 mmol), amines **2** (2 mmol), HOAc (5 mmol), and Bu_4NI (0.1 equiv) in 20 mL of CH_3CN, beaker type undivided cell, GCE anode, Fe plate cathode, current density: 6 mA/cm^2. [b]Isolated yield. In general, decomposition of the initially formed amidine accounts for yields less than 50%.

cyclic secondary amines, such as pyrrolidine and piperidine, gave the corresponding 2-aminobenzoxazoles **3b** and **3c** in 43% and 31% yields, respectively (entries 1 and 2, Table 2). Higher yields of 2-aminobenzoxazoles **3d** (71%) and **3e** (64%) were obtained when tetrahydroisoquinoline and 6,7-dimethoxytetrahydroisoquinoline were used as the amine counterpart (entries 3 and 4, Table 2). Acyclic amines also work well. For example, the reaction of dibenzylamine and benzoxazole proceeded smoothly to give **3f** in 55% yield (entry 5, Table 2).

However, when primary amines, such as 2-phenylethanamine, benzylamine, propanamine, and cyclohexanamine were subject to the standard conditions, very complex mixtures were detected by TLC and the desired products were not isolated. Recently, Zhu et al. reported an *n*-Bu_4NI-mediated oxidative amination of benzylic C−H bonds using *tert*-butyl hydroperoxide (TBHP) as an external oxidant.[17] Inspired by this work, aromatic nitrogen-containing heterocycles and imides, such as benzoimidazole, 1*H*-benzotriazole, phthalimide, and succinimide were also tested, but no reaction was observed and the starting benzoxazole **1a** was fully recovered (note Figure 3).

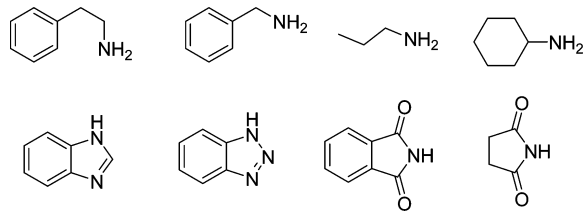
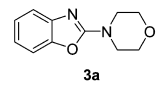
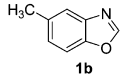
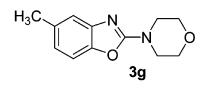
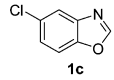
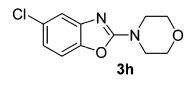
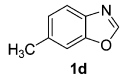
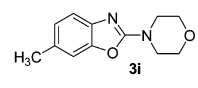
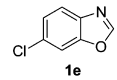
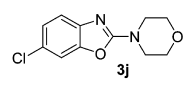
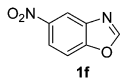
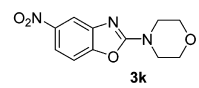
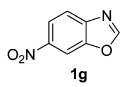
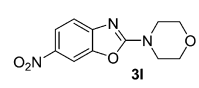


Figure 3. Molecular structures of amine partners that failed to react under the optimized reaction conditions.

To further explore the potential of our methodology, the reaction of morpholine with a variety of benzoxazoles was investigated; the results are summarized in Table 3. To our

Table 3. Substrate Scope with Regard to Benzoxazoles[a]

Entry	Benzoxazole	Amine	Product	Yield [b]
1	 1a	 2a	 3a	**91**
2	 1b	 2a	 3g	96
3	 1c	 2a	 3h	97
4	 1d	 2a	 3i	87
5	 1e	 2a	 3j	86
6	 1f	 2a	 3k	42
7	 1g	 2a	 3l	30
8	 1h	 2a	3m	0

[a]Reaction conditions: benzoxazoles **1** (1 mmol), morpholine **2** (2 mmol), HOAc (5 mmol), and Bu_4NI (0.1 equiv) in 20 mL of CH_3CN, beaker type undivided cell, GCE anode, Fe plate cathode, current density: 6 mA/cm^2. [b]Isolated yield.

delight, the reactions proceeded smoothly to give the desired products **3g**−**3l**. We observed that the electronic character of the substituents appended to the benzoxazole did not influence the electrochemically initiated oxidative amination reaction, except in the case of a nitro substituent. For example, an electron-donating methyl group and an electron-withdrawing chlorine atom each give >95% yields of **3g** and **3h** (entries 2 and 3). The outcome is quite similar to that observed in the

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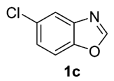
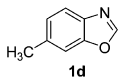
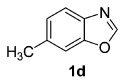
chemical oxidative amination of benzoxazole using $PhI(OAc)_2$ as the oxidant.[6] When the benzoxazole is substituted with a nitro group at either C5 or C6, substantially lower yields of corresponding 2-morpholinobenzoxazoles **3k** and **3l** were obtained (entries 6 and 7).[18]

Recently, Huang et al. reported the development of a regioselective C−N cross-coupling approach for azolation of indoles using excess amounts of iodine as the oxidant. The reaction was proposed to occur though a 3-iodoiminium intermediate.[19] Inspired by this observation, *N*-methylindole **1h** and morpholine were examined under the optimized reaction conditions. Unfortunately, adduct **3m** was not detected and *N*-methylindole **1h** was recovered fully (entry 8). The outcome suggests that our electrochemical oxidative amination may proceed through a different mechanism than that reported by Huang.[19]

As mentioned above, apart from *n*-Bu_4NI, the most effective mediator, other quaternary ammonium iodides (bromides) also mediated the amination of **1a** with **2a** (see Table 1, entries 11−13). To further demonstrate the utility of redox catalysts, the electrochemical oxidative amination of benzoxazole was investigated using other quaternary ammonium halides, and the results are summarized in Table 4. Adduct **3b** was

Table 4. Electrochemical Oxidative Amination Using Tetraethylammonium Halides[a]

Entry	Redox catalyst	Benzoxazole	Amine	Product	Yield [b] (%)
1	Et_4NI	 1a	 2b	**3b**	49 (43)[c]
2	Et_4NI	 1c	 2a	**3h**	83 (97)[c]
3	Et_4NI	 1d	 2a	**3i**	78 (87)[c]
4	Et_4NBr	 1d	 2a	**3i**	53 (87)[c]

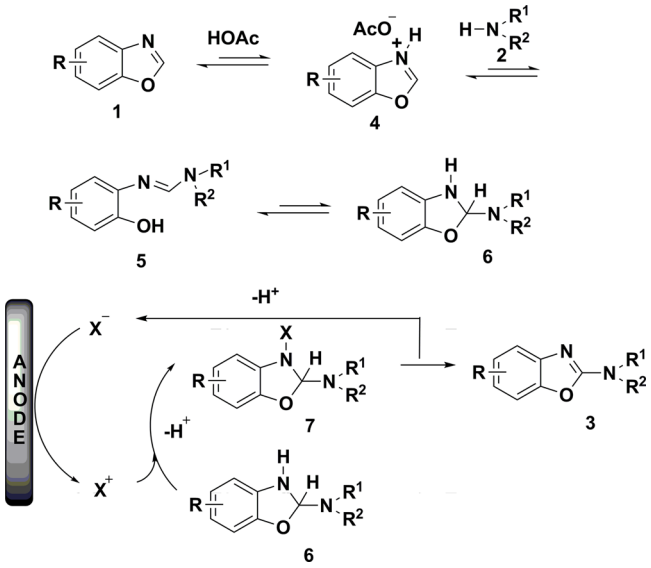
[a]Reaction conditions: benzoxazoles **1** (1 mmol), amines **2** (2 mmol), and HOAc (5 mmol) in 20 mL of CH_3CN, beaker type undivided cell, GC anode, Fe plate cathode, current density: 6 mA/cm^2. [b]Isolated yield. [c]Isolated yield using *n*-Bu_4NI as redox catalyst (see Table 1).

generated in a slightly higher yield (49% vs 43%) when Et_4NI was used as a redox catalyst in place of *n*-Bu_4NI (entry 1). Et_4NI could also mediate the reaction of **1c** and **1d** with **2a**, although slightly lower yields of **3h** and **3i** were obtained, compared with the results using *n*-Bu_4NI (entries 2 and 3). Once again, quaternary ammonium iodides were more effective than the bromide analogue. For example, when Et_4NI is replaced by Et_4NBr, the yield of **3i** decreased from a 78% to 53% yield (compare entry 4 with entry 3).

Finally, we turn attention to the mechanism. Ours is based upon precedent established independently by Chang and Studer. Previously, Chang et al. demonstrated that 2-aminobenzoxazoles can be produced using *o*-hydroxyamidines, or through a sequential two-step, one-pot procedure in which the benzoxazole was initially converted to the amidine adduct followed by the addition of $PhI(OAc)_2$.[16] Studer and coworkers observed the amidine formation by ^1H NMR for the reaction of benzoxazole and piperidine in the presence of TfOH or $Sc(OTf)_3$.[16c] We also noticed the formation of a new spot (TLC) *prior to passing charge* when benzoxazole was stirred in the presence of amine **2**; the material was isolated and identified to be the corresponding amidine.

Given this information and the results described above, we propose the mechanism illustrated in Scheme 3 for the halide-

Scheme 3. A Proposed Mechanism for the Halide-Mediated Electrochemical Synthesis of 2-Aminobenzoxazoles



mediated electrochemical oxidative amination of benzoxazoles. The sequence begins with protonation of the benzoxazole to produce **4**.[11] Its subsequent reaction with amine **2** leads to amidine **5**. Intramolecular cyclization affords the key intermediate, benzoxazoline **6**. Obviously, the formation of **6** is thermodynamically unfavorable. Meanwhile, the electrochemical oxidation of halide leads to the formation of X^+ (or an equivalent) whose reaction with **6** and loss of a proton generate structure **7**. Elimination of HX affords the aminobenzoxazole **3** and regenerates the halide anion so that it can re-enter the redox mediator cycle.

3. CONCLUSIONS

To summarize, we have developed a novel electrochemical strategy for the synthesis of 2-aminobenzoxazoles from benzoxazoles and amines. The electrochemical synthesis was performed under constant current conditions in a simple undivided cell using a catalytic amount of tetraalkylammonium halide as the redox catalyst and CH_3CN as the solvent. Following optimization of the reaction conditions, the 2-aminobenzoxazole adducts could be obtained in good-to-excellent yields. The protocol uses an electron as the initial oxidant and tetraalkylammonium halide as an electron carrier. Consequently, the use of excess chemical oxidant or large amounts of supporting electrolyte is avoided. This greatly simplifies the workup and isolation process and leads to a reduction in waste. The results further demonstrate our hypothesis that CDC reactions accomplished via the electrochemical oxidation of a variety of halide containing species can replace the use of stochiometric quantities of an organic hypervalent iodine containing oxidant, or the combination of a

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catalytic amount of iodide and an excess of external co-oxidant.[14] The application of this chemistry to other CDC reactions is underway in our laboratory.

4. EXPERIMENTAL SECTION

4.1. Instruments and Reagents. All melting points were measured using an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets. ^{1}H NMR spectra were recorded with a 400 M spectrometer (400 MHz ^{1}H frequency and 100 MHz ^{13}C frequency). Chemical shifts are given as δ values (internal standard: TMS), and coupling constants are listed in units of Hz. The benzoxazoles **1b**−**1g** were synthesized according to known procedures.[16c] Other benzoxazoles, amines, and solvents were commercially available and used without further purification.

4.2. Procedure for the Synthesis of Amidine. The following procedure is similar to that used by Chang[6a] and Sun.[6b] To a 10 mL flask were added benzoxazole **1a** (0.5 mmol) and morpholine (**2a**; 1 mmol), and the mixture was stirred under neat conditions at room temperature, with monitoring by TLC. After the reaction was deemed to be complete, the desired amidine was isolated by column chromatography. The ^{1}H NMR data for the amidine derived from the reaction of **1a** and **2a** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50−3.60 (broad, 4H), 3.77−3.79 (m, 4H), 6.78−6.82 (m, 1H), 6.91−6.99 (m, 3H), 7.75 (s, 1H).

4.3. Typical Procedure for the Synthesis of Benzoxazoles 3 by Constant Current Electrolysis. A 50 mL beaker-type cell was equipped with a glassy carbon anode and a Fe plate cathode and connected to a DC regulated power supply. To the cell were added benzoxazole **1** (1 mmol), amine **2** (2 mmol), and HOAc (5 mmol) dissolved in 20 mL of CH_3CN. The mixture was electrolyzed using constant current conditions (~6 mA/cm^2) at room temperature while stirring. The electrolysis was terminated when the starting material, **1**, was consumed as determined by TLC. After the electrolysis, the solvent was removed under reduced pressure and extraction was carried out using CH_2Cl_2 (3 × 15 mL); the combined organic layers were washed with a saturated aqueous Na_2CO_3 solution and dried over $MgSO_4$. Purified product was obtained after column chromatography on silica gel using a solvent mixture of petroleum ether and acetone.

*2-Morpholinobenzo[d]oxazole (**3a**).*[16c] 186 mg, yield: 91%; mp: 86−87 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71 (t, J = 4.4, 4H), 3.84 (t, J = 4.8, 4H), 7.06 (td, J = 7.8, 1.1 Hz, 1H), 7.06 (td, J = 7.6 and 1.0 Hz, 1H), 7.29 (d, J = 6.4, 1H), 7.39 (d, J = 6.4, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.7, 66.2, 108.8, 116.5, 120.9, 124.1, 142.8, 148.7, 162.1.

*2-(Pyrrolidin-1-yl)benzo[d]oxazole (**3b**).*[16c] 81 mg, yield: 43%; mp: 121−122 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (t, J = 6.4 4H), 3.68 (t, J = 6.4, 4H), 7.01 (td, J = 7.6 and 1.1 Hz, 1H), 7.17 (td, J = 7.6 and 1.1 Hz, 1H), 7.27 (d, J = 8.0, 1H), 7.39 (d, J = 7.8, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 47.4, 108.6, 116.0, 120.0, 123.8, 143.7, 149.0, 161.0.

*2-(Piperidin-1-yl)benzo[d]oxazole (**3c**).*[16c] 63 mg, yield: 31%; mp: 69−70 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70−1.75 (b, 6H), 3.67−3.68 (b, 4H), 7.01 (t, J = 7.6 1H), 7.18 (t, J = 7.6, 1H), 7.27 (d, J = 8.4, 1H)), 7.36 (d, J = 7.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 25.2, 46.6, 108.6, 116.0, 120.3, 123.8, 143.4, 148.7, 162.5.

*2-(3,4-Dihydroisoquinolin-2(1H)-yl)benzo[d]oxazole (**3d**).*[16c] 178 mg, yield: 71%; mp: 84−85 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (t, J = 7.0, 2H), 3.98 (t, J = 7.0, 1H)), 4.88 (s, 2H), 7.05 (t, J = 7.6, 1H), 7.18−7.26 (m, 5H), 7.31 (d, J = 8.0, 1H), 7.42 (d, J = 7.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 43.1, 47.2, 108.8, 116.3, 120.6, 124.0, 126.4, 126.6, 126.8, 128.8, 132.4, 134.1, 143.2, 148.8, 162.1.

*2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)benzo[d]-oxazole (**3e**).* 198 mg, yield: 64%; mp: 101−103 °C, ^{1}H NMR (400 MHz, $CDCl_3$): d 2.95 (t, J = 5.6, 2H), 3.89 (s, 6H), 3.97 (t, J = 6.0, 2H), 4.81 (s, 2H); 6.68 (d, J = 4.8, 2H), 7.04−7.06 (m, 1H), 7.19 (td, J = 7.6 and 1.3 Hz, 1H), 7.29 (d, J = 8.0, 1H), 7.39 (d, J = 8.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9, 43.2, 46.9, 55.9, 56.0, 108.7, 109.0, 111.5, 116.2, 120.5, 124.0, 124.1, 125.8, 143.2, 147.8, 147.9, 148.8, 162.1; HRMS (ESI) m/z calcd for $C_{18}H_{19}O_3N_2$ (M + H) 311.1396, found 311.1390.

*N,N-Dibenzylbenzo[d]oxazol-2-amine (**3f**).*[16d] 173 mg, yield: 55%; mp: 81−82 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 (s, 4H), 7.06−7.09 (m, 1H), 7.21−7.25 (m, 1H), 7.28−7.39 (m, 11H), 7.41−7.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.4, 108.9, 116.3, 120.6, 124.1, 127.8, 128.0, 128.8, 136.4, 143.6, 149.0, 163.2.

*5-Methyl-2-morpholinobenzo[d]oxazole (**3g**).*[16c] 209 mg, yield: 96%; mp: 112−113 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 3.69 (t, J = 4.8, 4H), 3.83 (t, J = 5.2, 4H), 6.86 (d, J = 8.4, 1H), 7.15 (d, J = 8.0, 1H), 7.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 45.8, 66.2, 108.2, 116.9, 121.6, 133.8, 143.0, 146.9, 162.3.

*5-Chloro-2-morpholinobenzo[d]oxazole (**3h**).*[16c] 231 mg, yield: 97%; mp: 102−103 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.701 (t, J = 5.2, 4H), 3.84 (t, J = 5.2, 4H), 7.00−7.03 (m, 1H), 7.17 (d, J = 8.4, 1H), 7.34 (d, J = 2.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.6, 66.1, 109.3, 116.5, 120.7, 129.4, 144.3, 147.3, 162.8.

*6-Methyl-2-morpholinobenzo[d]oxazole (**3i**).*[16d] 190 mg, yield: 87%; mp: 112−113 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.70 (t, J = 4.4, 4H), 3.84 (t, J = 5.2, 4H), 7.02 (d, J = 7.6, 1H), 7.11 (s, 1H), 7.28 (d, J = 7.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 45.8, 66.2, 109.4, 116.0, 124.8, 131.0, 140.4, 148.9, 161.9.

*6-Chloro-2-morpholinobenzo[d]oxazole (**3j**).*[20] 205 mg, yield: 86%; mp: 130−131 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (t, J = 4.4, 4H), 3.85 (t, J = 5.2, 4H), 7.18−7.20 (m, 1H), 7.29−7.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.6, 66.1, 109.6, 116.7, 124.4, 125.9, 141.7, 148.8, 162.3.

*2-Morpholino-5-nitrobenzo[d]oxazole (**3k**).*[21] 105 mg, yield: 42%; mp: 131−132 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (b, 4H), 3.85−3.87 (m, 4H), 7.35 (d, J = 8.8, 1H), 8.05 (d, J = 8.8, 1H), 8.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.6, 66.1, 108.5, 112.0, 117.4, 143.9, 145.2, 152.6, 163.5.

*2-Morpholino-6-nitrobenzo[d]oxazole (**3l**).*[11] 75 mg, yield: 30%; mp: 138−139 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (t, J = 4.4, 4H), 3.86 (t, J = 4.8, 4H), 7.36 (d, J = 8.8, 1H), 8.16 (d, J = 2.4, 1H), 8.19−8.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 45.7, 66.1, 105.2, 115.1, 121.5, 141.6, 147.8, 149.7, 164.5.

■ ASSOCIATED CONTENT

Supporting Information

The NMR spectra of products **3a**−**3l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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