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# *N*-Bromosuccinimide as an oxidant for the transition-metal-free synthesis of 2-aminobenzoxazoles from benzoxazoles and secondary amines†

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A facile and transition-metal-free method was developed through merging the ring opening of benzoxazoles with secondary amines and *N*-bromosuccinimide (NBS) mediated oxidative cyclization toward the synthesis of 2-aminobenzoxazoles. NBS was selected as a powerful oxidant in the oxidative cyclization of ring-opening amidines to provide the desirable 2-aminobenzoxazoles in excellent yields (up to 94%).

## Introduction

2-Aminooxazoles are very important structural units in many natural products and widely employed in biological, pharmaceutical and materials science, such as small-molecule somatostatin receptor subtype 5 (SST5R) antagonists (Fig. 1).[1] So, the synthesis of 2-aminooxazoles has received more and more attention in recent years. Conventionally, 2-aminobenzoxazole derivatives are generally synthesized by transition-metal-catalyzed amination of compounds with pre-installation of reactive functional groups along with *N*-chloroamines, amines, and amides or O-acylated hydroxylamines at high temperatures.[2,3] As a complementary methodology of the above methods, transition metal, including Mn, Co, Ag, Fe, Cu, and Ni, catalyzed C–H direct amination has become the main strategy to construct 2-aminooxazoles.[3–8] Although significant advances have been achieved, still there are some disadvantages associated with the method, such as high temperature, long reaction time, poisonous ligands, and noneconomic effects. Hence, the development of environmentally benign procedures based on transition-metal-free catalysis to synthesize such compounds is highly desirable.

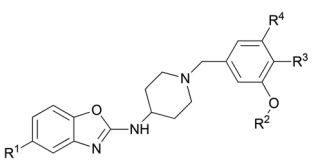


**Fig. 1** Somatostatin receptor subtype 5 antagonists.

Recently, Chang *et al*. developed a new metal-free system using iodobenzene diacetate as the oxidant for the amination of azoles with amines through a unique ring-opening and subsequent ring-closing strategy, performing in a one-pot process without isolation of the amidine intermediate (Scheme 1, (i)).[9] Studer and co-workers also reported a highly efficient system including catalytic amounts of triflic acid and a readily recyclable *N*-oxoammonium salt as an organic oxidant for direct amination of nonactivated benzoxazoles and 1,3,4-oxadiazoles with good to excellent yields (Scheme 1, (ii)).[10] And several other metal-free systems, such as catalytic iodine or tetrabutylammoniumiodide in combination with *tert*-butyl hydroperoxide (TBHP) or $H_2O_2$ as the oxidant appeared nearly at the same time for amination of benzoxazoles through activation of C–H bonds.[11] Recently, an environmentally friendly method was developed by our group through merging the ring opening of benzoxazoles with secondary amines and iron-catalyzed oxidative cyclization with $H_2O_2$ as the oxidant (Scheme 1, (iii)).[12] Attracted by the two-step strategy for amination of benzoxazoles under metal-free conditions reported by Chang *et al.* and continuing our research on the use of NBS for oxidation,[13] we herein wish to report an efficient and transition-metal-free system for the synthesis of 2-aminooxazoles, employing cheap and easily available NBS as a powerful organic oxidant for oxidative cyclization of ring-opening amidines in a biphasic system.

## Results and discussion

Our initial optimization of the model reaction between benzoxazole (**1a**) and piperidine (**2a**) is summarized in Table 1. There

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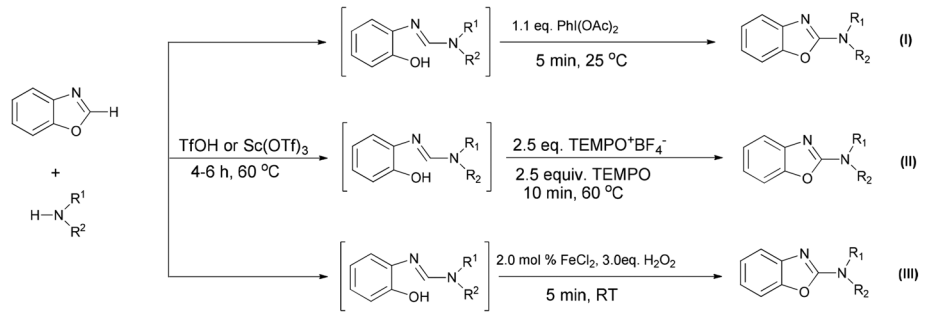
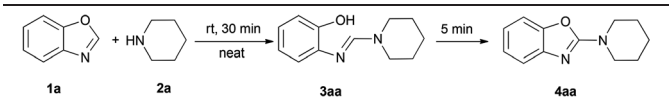



**Scheme 1** Indirect method for the amination of benzoxazoles.

**Table 1** Optimization of the oxidative cyclization reaction conditions with NBS as an oxidant[a]




| Entry | Solvent (mL) | NBS (mmol) | KOAc (mmol) | Temp. (°C) | Yield[b] |
|---|---|---|---|---|---|
| 1[c] | $CH_2Cl_2$(2) | 0.75 | No | 20 | — |
| 2 | $CH_2Cl_2$(2) | 0.75 | No | 20 | 45[d] |
| 3 | $CH_2Cl_2/H_2O$(1/1) | 0.75 | No | 20 | 47[d] |
| 4 | $CH_2Cl_2/H_2O$(1/1) | 0.75 | 0.8 | 20 | 75 |
| 5 | $CH_2Cl_2/H_2O$(1/1) | 0.75 | 0.8 | 0 | 83 |
| 6 | $CH_2Cl_2/H_2O$(1/1) | 0.75 | 0.9 | 0 | 87 |
| 7 | $CH_2Cl_2/H_2O$(1/1) | 0.75 | 0.7 | 0 | 75 |
| 8 | $CH_2Cl_2/H_2O$(1/1) | 0.65 | 0.9 | 0 | 55 |
| 9 | $CH_2Cl_2/H_2O$(1/1) | 0.85 | 0.9 | 0 | 79 |
| 10 | Toluene/$H_2O$(1/1) | 0.75 | 0.9 | 0 | 43 |
| 11 | THF/$H_2O$(1/1) | 0.75 | 0.9 | 0 | 92 |
| 12 | Dioxane/$H_2O$(1/1) | 0.75 | 0.9 | 0 | 94 |
| 13 | MeCN/$H_2O$(1/1) | 0.75 | 0.9 | 0 | 68 |

[a] Oxidative cyclization step: **3aa** (0.5 mmol), KOAc (0–0.9 mmol) in a biphasic system, and the NBS were added to the mixture and stirred at the specified temperature for 5 min. [b] Isolated yield. [c] 0.5 mmol **1a**, 1.0 mmol **2a** and 0.75 mmol NBS were added to 2.0 mL of $CH_2Cl_2$ at the same time. [d] The brominated product was observed.

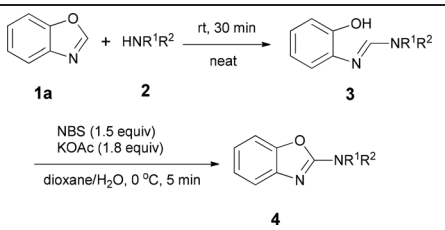
was nearly no product detected, when 1.5 equiv. of NBS along with 0.5 mmol benzoxazole and 1 mmol piperidine was added into a reaction tube at the same time using $CH_2Cl_2$ as a solvent (Table 1, entry 1). To our delight, a 45% yield was observed when NBS was added after the reaction of benzoxazole and piperidine under neat conditions for 30 min (entries 2, 3). It indicates that the present system should involve the amidine intermediate. Then, NBS serves as an oxidant to mediate the resulting oxidative cyclization.[9] However, a brominated product was always generated under the above conditions. During the study on the oxidative kinetic resolution of secondary alcohols with NBS as an oxidant, potassium acetate can be used to neutralize HBr in the enantioselective oxidation.[13] As expected, the addition of potassium acetate (KOAc, 0.8 mmol) in this reaction could not only inhibit the generation of the brominated product but also improve the yield (Table 1, entry 4 *vs.* 3). Besides, the yield would be further improved by lowering the temperature to 0 °C (Table 1, entry 5). Additionally, the amount of NBS and KOAc was also investigated. The results indicated that 0.9 mmol KOAc and 0.75 mmol NBS were the optimized conditions (Table 1, entries 6–9). Furthermore, various organic solvents were subjected to the biphasic system, and dioxane/$H_2O$ proved to be the best choice as it resulted in the desirable 2-aminooxazole **4aa** in a 94% yield (Table 1, entries 11–13).

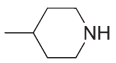
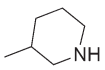
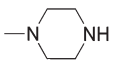
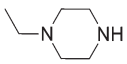
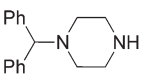
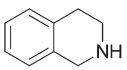
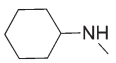
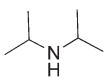
Various amines were explored to study the substrate scope of this reaction under optimized reaction conditions for the two-step oxidative amination between different types of cyclic/acyclic aliphatic secondary amines with benzoxazole. The results are summarized in Table 2. Cyclic aliphatic secondary amines such as piperidine and its derivatives, pyrrolidine, morpholine and piperazine derivatives all smoothly underwent the ring opening reaction with **1a** to provide amidine adducts **3** in excellent yields. And the subsequent cyclization of the amidines performed well at 0 °C for 5 min, leading to the corresponding compounds **4** in excellent yields (Table 2, entries 1–7). Interestingly, employing equimolar substrates of **1a** and **2h** or **2i** could directly give the desired product in about 90% yields without isolating the amidine adducts **3** (Table 2, entries 8 and 9). Additionally, the reactivities of acyclic aliphatic secondary amines were also tested. The ring opening step could occur through elevating the temperature to 80 °C and prolonging the reaction time to 8 or 10 h, and the corresponding 2-aminooxazoles **4** could be afforded in about 90% yields (Table 2, entries 10 and 11). In addition, linear aliphatic amines were also transformed into the desired 2-aminobenzoxazoles in good yields, but $Sc(OTf)_3$ should be used as the catalyst in the ring opening step according to the Studer process (Table 2, entries 12, 13).[10]

These promising results prompted us to investigate our novel method toward amination of a variety of substituted benzoxazoles with pyrrolidine. Intriguingly, nearly quantitative yields of **3** and above 90% yields of **4** were acquired employing benzoxazoles and their derivatives with substituents such as $CH_3$, OMe or Cl as the substrates (Table 3, entries 1–5). The oxidative cyclization of amidine **3** proceeded uneventfully to provide the 2-aminooxazoles **4** in excellent yields with NBS as the oxidant.

On the basis of all the results described above and the previous report,[9] a possible mechanism for the oxidative cyclization of amidines was proposed (Scheme 2). NBS may react with imine to form a 1 : 1 electron-donor–acceptor complex **I** *via* the

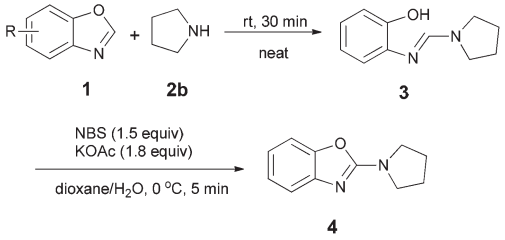
**Table 2** Scope of the oxidative C–H amination of benzoxazoles with various amines[a]




| Entry | Amine **2** | Yield of **3**[b] [%] | Yield of **4**[c] [%] |
|---|---|---|---|
| 1 |  | 99 | 93(**4aa**) |
| 2 |  | 99 | 92(**4ab**) |
| 3 |  | 99 | 92(**4ac**) |
| 4 |  | 99 | 93(**4ad**) |
| 5 |  | 99 | 92(**4ae**) |
| 6 |  | 99 | 91(**4af**) |
| 7 |  | 99 | 90(**4ag**) |
| 8[d] |  | — | 91(**4ah**) |
| 9[d] |  | — | 91(**4ai**) |
| 10[d] |  | — | 89(**4aj**) |
| 11 |  | 95 | 86(**4ak**) |
| 12 |  | 90[e] | 83(**4al**) |
| 13 |  | 89[f] | 82(**4am**) |

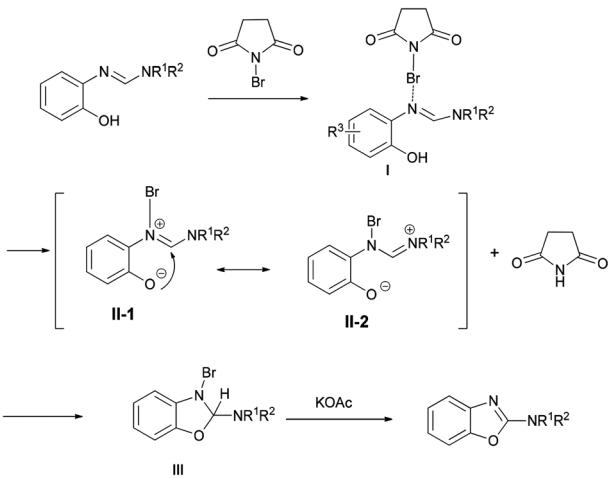
[a] Ring-opening step: benzoxazole (0.5 mmol) and secondary amine (1 mmol) were stirred at rt for 30 min. Ring-closing step: NBS (0.75 mmol, 1.5 equiv.) and KOAc (0.9 mmol, 1.8 equiv.) were added to the solution of **3** (0.5 mmol) in 1 mL of $H_2O$ and 1 mL of dioxane, and then the mixture was stirred at 0 °C for 5 min. [b] Isolated yield. [c] Isolated yield based on the two steps. [d] Benzoxazole (0.5 mmol) and piperidine (0.5 mmol) were stirred in 1 mL of dioxane for certain time (**2i**: at rt for 2 h; **2j**: at 80 °C for 10 h; **2k**: at 80 °C for 8 h), the mixture was cooled to 0 °C and NBS (0.75 mmol, 1.5 equiv.), KOAc (0.9 mmol, 1.8 equiv.) in 1 mL of $H_2O$ was stirred at 0 °C for 5 min. [e] Ring-opening step was conducted according to the method reported by Studer:[10] benzoxazole **1a** (0.5 mmol), **2l** (0.75 mmol) and 5.0 mol% of $Sc(OTf)_3$ under an Ar atmosphere at 80 °C for 2 hours in MeCN (1.0 mL). [f] Ring-opening step: benzoxazole **1a** (0.5 mmol) and **2m** (1.0 mmol) under an Ar atmosphere at 80 °C for 12 hours in MeCN (1.0 mL).

**Table 3** Scope of the benzoxazole derivatives[a]




| Entry | Benzoxazoles (R) | Yield of **3**[b] [%] | Yield of **4**[c] [%] |
|---|---|---|---|
| 1 | H, **1a** | 99 | 93(**4ab**) |
| 2 | 5-Me, **1b** | 99 | 92(**4bb**) |
| 3 | 6-Me, **1c** | 99 | 93(**4cb**) |
| 4 | 5-OMe, **1d** | 99 | 91(**4db**) |
| 5 | 5-Cl, **1e** | 99 | 90(**4eb**) |

[a] Ring-opening step: benzoxazoles 1 (0.5 mmol) and pyrrolidine (1 mmol) were stirred at rt for 30 min; Ring-closing step: NBS (0.75 mmol, 1.5 equiv.) and KOAc (0.9 mmol, 1.8 equiv.) were added to the solution of **3** (0.5 mmol) in 1 mL of $H_2O$ and 1 mL of dioxane, and then the mixture was stirred at 0 °C for 5 min. [b] Isolated yield. [c] Isolated yield based on the two steps.




**Scheme 2** Proposed mechanism for the oxidative cyclization of amidines.

halogen bond interaction, which will be further transformed into a more electrophilic species **II-1** and **II-2**.[14,15] Then intermediate **III** is generated *via* nucleophilic substitution of imine by oxygen anions to achieve the ring-closing step. Finally, the product will be formed through removing of HBr in the presence of KOAc as a base.

## Conclusions

In conclusion, a new transition-metal-free system for the amination of benzoxazoles with aliphatic secondary amines through the ring-opening step and further oxidative cyclization was developed. The ring-opening step executed well under

neat conditions to give the amidine adducts. The subsequent ring-closing strategy was performed by oxidative cyclization of the amidine adducts employing cheap and easily available NBS as the powerful organic oxidant, which makes the protocol more practical toward the synthesis of 2-aminooxazoles. Besides, an electron-donor–acceptor complex as the intermediate was proposed in the oxidative cyclization step. Efforts are currently underway in our group to further expand the other oxidant system for the reaction or synthetic application of the current system.

## Experimental

### General remarks

NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer operating at 400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR in $CDCl_3$. The chemical shifts ($\delta$) are reported in ppm and coupling constants ($J$) are reported in Hz. High resolution mass spectra (HRMS) were recorded using a Bruker micrOTOF-Q$^{II}$ spectrometer (ESI). GC-MS was recorded using an Agilent 7890A/5975C. Column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections were on silica gel $GF_{254}$ plates. Unless otherwise stated, solvents were purchased from commercial suppliers and used without further purification. NBS, amines, benzoxazole and potassium acetate were purchased from Aldrich and used as received. Other substituted benzoxazoles were obtained according to the reported procedures.[6d]

### General procedures of ring-opening

The ring-opening step was according to the Chang's procedures: benzoxazole (0.5 mmol) and amine (1 mmol, 2 equiv.) were added to a tube and the mixture was stirred under neat conditions at the specified temperature for certain time. After the reaction detected by TLC was complete, the desired product **3** was obtained by column chromatography to give the amidines **3**.[9,10]

### General procedures for ring-closing steps

In a 10 mL tube, amidine **3** (0.5 mmol) was stirred in 1 mL of $H_2O$ and 1 mL of dioxane at 0 °C. Then KOAc (0.9 mmol, 1.8 equiv.) and NBS (0.75 mmol, 1.5 equiv.) were added directly and stirred for 5 min in air. The crude mixture was diluted with dichloromethane (10 mL), and washed with saturated NaCl solution (3 × 15 mL). Then the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the desired product **4** was obtained by column chromatography.

**2-(Piperidin-1-yl)benzoxazole (4aa).**[9] White solid; M.p. 55–57 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.36 (dd, $J$ = 10.3, 4.6 Hz, 1H), 7.28–7.21 (m, 1H), 7.15 (dd, $J$ = 15.7, 8.0 Hz, 1H), 6.99 (t, $J$ = 7.8 Hz, 1H), 3.66 (s, 4H), 1.68 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.4, 148.7, 143.3, 123.9, 120.3, 116.0, 108.6, 46.6, 25.3, 24.1. HRMS (ESI) calcd for $C_{12}H_{15}N_2O$ [M + H]$^+$: 203.1179, found: 203.1170.

**2-(Pyrrolidin-1-yl)benzoxazole (4ab).**[9] White solid; M.p. 60–62 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.37 (dd, $J$ = 12.1, 4.8 Hz, 1H), 7.28–7.21 (m, 1H), 7.19–7.08 (m, 1H), 7.04–6.86 (m, 1H), 3.79–3.51 (m, 4H), 2.11–1.93 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 161.0, 149.0, 143.6, 123.8, 120.0, 116.0, 108.6, 47.4, 25.6. HRMS (ESI) calcd for $C_{11}H_{13}N_2O$ [M + H]$^+$: 189.1022, found: 189.1017.

**2-(4-Methylpiperidin-1-yl)benzoxazole (4ac).**[11] White solid; M.p. 64–67 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.27 (dd, $J$ = 7.8, 0.6 Hz, 1H), 7.16 (d, $J$ = 7.9 Hz, 1H), 7.07 (td, $J$ = 7.7, 1.1 Hz, 1H), 6.94–6.89 (m, 1H), 4.25–4.17 (m, 2H), 2.99 (td, $J$ = 12.9, 2.8 Hz, 2H), 1.72–1.62 (m, 2H), 1.60–1.45 (m, 1H), 1.27–1.13 (m, 2H), 0.91 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 161.4, 147.7, 142.3, 122.8, 119.3, 115.0, 107.6, 45.1, 32.4, 29.6, 20.8. HRMS (ESI) calcd for $C_{13}H_{17}N_2O$ [M + H]$^+$: 217.1335, found: 217.1353.

**2-(3-Methylpiperidin-1-yl)benzoxazole (4ad).** White solid; M.p. 60–63 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.34 (dd, $J$ = 7.8, 0.6 Hz, 1H), 7.23 (d, $J$ = 7.9 Hz, 1H), 7.14 (td, $J$ = 7.7, 1.1 Hz, 1H), 6.99 (td, $J$ = 7.8, 1.2 Hz, 1H), 4.26–4.12 (m, 2H), 3.07–2.97 (m, 1H), 2.71 (dd, $J$ = 12.9, 10.8 Hz, 1H), 1.91–1.83 (m, 1H), 1.81–1.69 (m, 2H), 1.68–1.55 (m, 1H), 1.27–1.08 (m, 1H), 0.97 (d, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 162.3, 148.7, 143.3, 123.9, 120.3, 116.0, 108.6, 53.0, 46.0, 32.7, 30.7, 24.8, 18.9. HRMS (ESI) calcd for $C_{13}H_{17}N_2O$ [M + H]$^+$: 217.1335, found: 217.1341.

**2-Morpholinobenzoxazole (4ae).**[9] Colorless solid; M.p. 90–93 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.41 (d, $J$ = 1.8 Hz, 1H), 7.30 (dd, $J$ = 8.3, 1.8 Hz, 1H), 7.27 (s, 1H), 7.22 (d, $J$ = 8.3 Hz, 1H), 3.83–3.81 (m, 4H), 3.69–3.67 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 162.0, 148.7, 142.7, 124.1, 121.0, 116.5, 108.8, 66.2, 45.7. HRMS (ESI) calcd for $C_{11}H_{13}N_2O_2$ [M + H]$^+$: 205.0972, found: 205.0969.

**2-(4-Methylpiperazin-1-yl)benzoxazole (4af).**[9] White solid; M.p. 36–38 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.36 (d, $J$ = 7.8 Hz, 1H), 7.25 (d, $J$ = 8.0 Hz, 1H), 7.16 (td, $J$ = 7.7, 1.0 Hz, 1H), 7.05–6.98 (m, 1H), 3.75–3.70 (m, 4H), 2.57–2.51 (m, 4H), 2.35 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 162.2, 148.7, 143.0, 124.0, 120.8, 116.3, 108.8, 54.2, 46.2, 45.5. HRMS (ESI) calcd for $C_{12}H_{16}N_3O$ [M + H]$^+$: 218.1288, found: 218.1284.

**2-(4-Ethylpiperazin-1-yl)benzoxazole (4ag).** White solid; M.p. 44–46 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.36 (d, $J$ = 7.8 Hz, 1H), 7.25 (s, 1H), 7.16 (t, $J$ = 7.6 Hz, 1H), 7.02 (t, $J$ = 7.7 Hz, 1H), 3.78–3.70 (m, 4H), 2.60–2.55 (m, 4H), 2.49 (q, $J$ = 7.2 Hz, 2H), 1.14 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.2, 148.8, 143.1, 124.0, 120.7, 116.3, 108.7, 52.4, 52.0, 45.5, 11.9. HRMS (ESI) calcd for $C_{13}H_{18}N_3O$ [M + H]$^+$: 232.1444, found: 232.1440.

**2-(4-Benzhydrylpiperazin-1-yl)benzoxazole (4ah).**[11] White solid; M.p. 165–167 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.44 (d, $J$ = 7.5 Hz, 4H), 7.39–7.33 (m, 1H), 7.31 (t, $J$ = 7.6 Hz, 4H), 7.25–7.18 (m, 3H), 7.18–7.11 (m, 1H), 7.05–6.98 (m, 1H), 4.30 (s, 1H), 3.79–3.55 (m, 4H), 2.63–2.31 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$162.2, 148.7, 143.1, 142.1, 128.6, 127.9, 127.2, 123.9, 120.6, 116.2, 108.7, 76.1, 51.1, 45.8. HRMS (ESI) calcd for $C_{24}H_{24}N_3O$ [M + H]$^+$: 370.1914, found: 370.1911.

**2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)benzoxazole (4ai).**[11] White solid; M.p. 84–86 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.32 (d, $J$ = 7.8 Hz, 1H), 7.22 (d, $J$ = 7.8 Hz, 1H), 7.18–7.07 (m, 5H), 6.96 (td, $J$ = 7.8, 1.2 Hz, 1H), 4.80 (s, 2H), 3.90 (t, $J$ = 5.9 Hz, 2H), 2.95 (t, $J$ = 5.9 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 162.0, 148.8, 143.0, 134.0, 132.3, 128.8, 126.9, 126.6, 126.4, 124.1, 120.6, 116.3, 108.8, 47.2, 43.1, 28.5. HRMS (ESI) calcd for $C_{16}H_{15}N_2O$ $[M + H]^+$: 251.1179, found: 251.1175.

***N*-Benzyl-*N*-methylbenzoxazol-2-amine (2aj).**[7] Colorless solid; M.p. 55–56 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.35–7.15 (m, 6H), 7.10 (td, $J$ = 7.7, 1.1 Hz, 1H), 6.95 (td, $J$ = 7.8, 1.2 Hz, 1H), 4.69 (s, 2H), 3.06 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 161.9, 147.9, 142.4, 135.4, 127.7, 126.7, 126.7, 123.0, 119.4, 115.1, 107.7, 52.8, 34.2. HRMS (ESI) calcd for $C_{15}H_{15}N_2O$ $[M + H]^+$: 239.1179, found: 239.1182.

***N*-Cyclohexyl-*N*-methylbenzoxazol-2-amine (2ak).**[11] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.35 (dd, $J$ = 7.8, 0.4 Hz, 1H), 7.23 (d, $J$ = 7.9 Hz, 1H), 7.13 (td, $J$ = 7.7, 1.0 Hz, 1H), 6.97 (td, $J$ = 7.8, 1.1 Hz, 1H), 4.12 (ddd, $J$ = 11.6, 7.6, 3.6 Hz, 1H), 3.05 (s, 3H), 1.89–1.77 (m, 4H), 1.70 (d, $J$ = 13.2 Hz, 1H), 1.57–1.35 (m, 4H), 1.16–1.04 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 162.8, 148.7, 143.5, 123.8, 119.9, 115.8, 108.5, 56.8, 30.0, 29.5, 25.6, 25.5. HRMS (ESI) calcd for $C_{14}H_{19}N_2O$ $[M + H]^+$: 231.1492, found: 231.1486.

***N*,*N*-Diethylbenzoxazol-2-amine (2al).**[6d] Colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.35 (d, $J$ = 7.3 Hz, 1H), 7.28–7.18 (m, 1H), 7.14 (t, $J$ = 7.2 Hz, 1H), 7.02–6.91 (m, 1H), 3.58 (q, $J$ = 7.1 Hz, 4H), 1.28 (t, $J$ = 7.1 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 162.2, 148.8, 143.6, 123.7, 119.9, 115.8, 108.4, 42.9, 13.4. GC-MS (EI-MS) calcd for $C_{11}H_{14}N_2O$:190.1, found: 190.1.

***N*,*N*-Diisopropylbenzoxazol-2-amine (2am).**[6d] White solid; M.p. 52–53 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.35 (d, $J$ = 7.7 Hz, 1H), 7.25 (d, $J$ = 6.4 Hz, 1H), 7.14 (t, $J$ = 7.6 Hz, 1H), 6.98 (t, $J$ = 7.7 Hz, 1H), 4.24 (dt, $J$ = 13.4, 6.7 Hz, 2H), 1.38 (d, $J$ = 6.8 Hz, 12H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 148.5, 123.7, 119.8, 115.5, 108.4, 58.4, 47.7, 20.8, 18.4. GC-MS (EI-MS) calcd for $C_{13}H_{18}N_2O$: 218.1, found: 218.1.

**5-Methyl-2-(pyrrolidin-1-yl)benzoxazole (4bb).**[9] Brown solid; M.p. 100–102 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.16 (s, 1H), 7.11 (d, $J$ = 8.1 Hz, 1H), 6.79 (dd, $J$ = 8.1, 0.9 Hz, 1H), 3.64 (t, $J$ = 6.7 Hz, 4H), 2.38 (s, 3H), 2.07–1.96 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 161.13, 147.13, 143.59, 133.47, 120.72, 116.37, 107.93, 47.40, 25.60, 21.55. HRMS (ESI) calcd for $C_{12}H_{16}N_2O$ $[M + H]^+$: 203.1179, found: 203.1175.

**6-Methyl-2-(pyrrolidin-1-yl)benzoxazole (4cb).**[9] White solid; M.p 94–96 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.23 (d, $J$ = 7.9 Hz, 1H), 7.07 (s, 1H), 6.95 (d, $J$ = 7.7 Hz, 1H), 3.63 (s, 4H), 2.39 (s, 3H), 2.02 (s, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 160.8, 149.2, 141.2, 130.0, 124.5, 115.4, 109.2, 47.4, 25.6, 21.5. HRMS (ESI) calcd for $C_{12}H_{16}N_2O$ $[M + H]^+$: 203.1179, found: 203.1182.

**5-Methoxy-2-(pyrrolidin-1-yl)benzoxazole (4db).**[9] White solid; M.p. 72–74 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.12 (d, $J$ = 8.7 Hz, 1H), 6.94 (d, $J$ = 2.5 Hz, 1H), 6.55 (dd, $J$ = 8.7, 2.6 Hz, 1H), 3.80 (s, 3H), 3.67–3.55 (m, 4H), 2.08–1.96 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 161.7, 157.0, 144.4, 143.5, 108.4, 106.4, 101.2, 55.9, 47.4, 25.6. HRMS (ESI) calcd for $C_{12}H_{15}N_2O_2$ $[M + H]^+$: 219.1128, found: 219.1123.

**5-Chloro-2-(pyrrolidin-1-yl)benzoxazole (4db).**[9] Brown solid; M.p. 87–89 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.31 (d, $J$ = 1.9 Hz, 1H), 7.14 (d, $J$ = 8.4 Hz, 1H), 6.96–6.91 (m, 1H), 3.67–3.63 (m, 4H), 2.06–1.97 (m, 4H).$^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 161.7, 147.6, 144.9, 129.2, 119.9, 116.0, 109.1, 47.5, 25.6. HRMS (ESI) calcd for $C_{11}H_{13}ClN_2O$ $[M + H]^+$: 223.0633, found: 223.0640.

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