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Iodine-Catalyzed Amination of Benzoxazoles: A Metal-Free Route to 2-Aminobenzoxazoles under Mild Conditions

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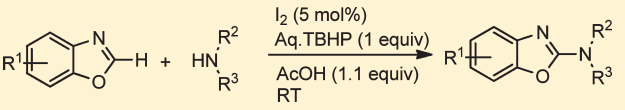
Supporting Information

ABSTRACT: A facile metal-free route of oxidative amination of benzoxazole by activation of C−H bonds with secondary or primary amines in the presence of catalytic iodine in aqueous *tert*-butyl hydroperoxide proceeds smoothly at ambient temperature under neat reaction condition to furnish the high yield of the aminated product. This user-friendly method to form C−N bonds produces tertiary butanol and water as the byproduct, which are environmentally benign. The application of the methodology is demonsrated by synthesizing therapeutically active benzoxazoles.



INTRODUCTION

Transition-metal-catalyzed C−H bond activation reactions of arenes and heteroarenes are important in synthetic organic chemistry,[1] which have been widely used in the synthesis of pharmacologically active organic compounds and natural products. C−N bond-forming reactions are traditionally accomplished by Buchwald−Hartwig-type amination,[2] Ullmann[3] and Goldberg couplings,[4] and cross-coupling reactions of boronic acids, stannanes, and siloxanes with corresponding amines.[5] The disadvantages associated with these methods are the utility of poisonous metals and expensive transition-metal catalysts or ligands. Additionally, heavy metal impurities in drug intermediates and harsh reaction conditions limit the utility of such methods. Hence, the development of environmentally benign procedures to synthesize such compounds is highly desirable. In this direction, C−H amination of heteroarenes has been achieved by using copper, silver, manganese, iron, cobalt, and other catalysts.[7] Hence, there is a huge surge in the literature to develop these methods under environmentally benign conditions.[1] However, C−H amination of heteroarenes under metal-free conditions are less known.[8,9] In this direction, stoichiometric amount of PIDA (phenyliodine diacetate) under heating condition was employed for the amination of benzoxazoles in two steps using ring-opened adduct *O*-hydroxyamidine.[8a] Apart from this, a recent report by Nachtsceim and co-workers uses tetrabutylammonium iodide along with terminal oxidant is utilized for the amination of benzoxazole.[8b]

2-Aminobenzoxazole derivatives are generally synthesized by transition-metal-catalyzed amination with *N*-chloroamines,[6a] amines,[6b] and amides[6c] or *O*-acylated hydroxylamines.[6d] The latest development for the synthesis of 2-aminobenzoxazole includes transition-metal-catalyzed amination of formamides and amines using stoichiometric amount of metal catalysts such as silver carbonates,[7a] a substoichiometric amount of $FeCl_3$,[7b] $Cu(OAc)_2 \cdot H_2O$,[7c] or $CuBr_2$[7d] using oxygen as an oxidant. Recently, Chang[7e] and co-workers reported an elegant example for the synthesis of 2-aminoxazoles by employing cobalt and manganese catalysts and *tert*-butylhydroperoxide (TBHP) as oxidant. In view of the increased attention to design environmentally benign and metal-free methods for the formation of C−N bonds and continuation of our research on green chemistry,[10] herein we report a novel and efficient metal-free method for the oxidative C−H bond activation of benzoxazoles for the formation of C−N bond using catalytic amount of I_2 and TBHP in acetic acid under solvent-free conditions.

RESULTS AND DISCUSSION

Our optimization studies began with the activation of benzoxazole (**1a**) and amination with diethyl amine (**2a**). As seen in Table 1, a variety of reaction conditions were employed to achieve the optimal conditions. Initial screening of the oxidants revealed that the oxidants such as H_2O_2 or sodium perborate are not suitable for this reaction (Table 1, entries 1 and 2). Further investigation has shown that the reaction proceeds well with aqueous TBHP (1 equiv) at room temperature in AcOH (1 equiv) (entries 3−8). Subsequent experiments revealed that the coupling reaction requires 5 mol % of I_2 (entries 5−8). However, increasing the amount of I_2 did not bring considerable change in the outcome of the reaction (entries 3 and 4). Performing the reaction in organic solvents such as dioxane, CH_3CN, or EtOAc did not enhance the yield of **3a** (Table 1, entries 3−7). The excellent yield of the product **3a** was obtained when the reaction was performed without any solvent (Table 1, entry 8). The importance of acid additive is shown in entry 9. The reaction of benzoxazole (**1a**) and diethylamine (**2a**) in the absence of AcOH resulted in low yield of **3a** (36%) indicating the significance of the acid additive in the reaction (Table 1, entry 9). TFA or TfOH as additives did not furnish the amination product (Table 1, entries 10 and 11). Amination of benzoxazole was not observed in the absence of either TBHP or iodine, indicating that I_2/TBHP combination is crucial for the reaction (Table 1, entries 12 and 13). Therefore, we decided to carry out further

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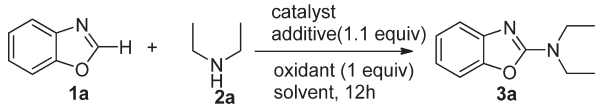
Table 1. Optimization of Amination Reactions[a]



entry	I_2 (mol %)	oxidant	additive	solvent	T (°C)	yield[b] (%)
1	20	H_2O_2	AcOH	neat	rt	nr
2	30	$NaBO_3 \cdot 4H_2O$	AcOH	dioxane	rt	<5
3	32	TBHP	AcOH	dioxane	rt	32
4	10	TBHP	AcOH	dioxane	rt	90
5	5	TBHP	AcOH	dioxane	rt	91
6	5	TBHP	AcOH	EtOAc	rt	88
7	5	TBHP	AcOH	CH_3CN	rt	90
8	5	TBHP	AcOH	neat	rt	39
9	5	TBHP	none	neat	rt	36
10	5	TBHP	TFA	neat	rt	nr
11	5	TBHP	TfOH	neat	rt	nr
12	5	none	AcOH	neat	rt	nr
13	none	TBHP	AcOH	neat	rt	nr

[a] Optimal conditions: **1a** (1 mmol), **2a** (1 mmol), I_2 (0.05 mmol), acid additive (1.1 mmol), oxidant (1 mmol). [b] Isolated yield, nr = no reaction.

reactions in the absence of the solvent. In a typical reaction, benzoxazole (**1a**, 1 equiv), diethyl amine (**2a**, 1 equiv), AcOH (1.1 mmol), I_2 (5 mol %), and aq TBHP (70% solution in water,1 equiv) were stirred at room temperature under neat reaction conditions for 12 h followed by aqueous workup furnished the amination product (**3a**) in 95% isolated yield.

Under optimized reaction conditions, a variety of amines were reacted with benzoxazoles to furnish amination products (Table 2). Benzoxazoles bearing electron-donating and electron-withdrawing functional groups underwent a smooth oxidative amination to form 2-aminobenzoxazole derivatives in good to excellent yields. Benzoxazole **1a** reacted well with cyclic amines such as morpholine (**2b**), piperidine (**2c**), and *N*-methylpiperazine (**2d**) to furnish the corresponding amination products **3b**, **3c**, and **3d** in good to excellent yields (entries 1−3). Similarly, **1a** reacted well with *N*-methylbenzylamine (**2e**), tetrahydroisoquinoline (**2f**), 1-benzhydrylpiperazine (**2g**), and dibenzylamine (**2h**) to provide the corresponding products **3e**, **3f**, **3g**, or **3h** (95%, 95%, 80%, and 95%, respectively, entries 4−7). Coupling of 5-methylbenzoxazole (**1b**) proceeded successfully with piperidine (**2c**), *N*-methylpiperazine (**2d**), thiomorpholine (**2i**), and *N*-methylhomopiperazine (**2j**) to form amination products **3i**, **3j**, **3k**, and **3l** in good to excellent yields (entries 8−11). Similarly, 5-phenylbenzoxazole (**1c**) underwent a smooth coupling with morpholine (**2b**), piperidine (**2c**), and *N*-methylbenzylamine (**2e**) to afford 2-aminobenzoxazole derivatives **3m**, **3n**, or **3o** in good yields (entries 12−14). The amination of benzoxazole that contains an electron-withdrawing group is sluggish and required heating at 60 °C in EtOAc to afford the coupled product. Hence, 6-nitrobenzoxazole (**1d**) was found to react with secondary amines such as morpholine (**2b**), piperidine (**2c**), and *N*-methylbenzylamine (**2e**) at 60 °C in ethyl acetate (12 h) to produce the corresponding amination products **3p**, **3q**, or **3r** in good yields (entries 15−17, 84%, 85%, and 80%, respectively). Similarly, benzoxazole **1a** reacted with ethyl 1-piperazinecarboxylate (**2k**) to furnish the amination product **3s** in excellent yield (95%, entry 18).

After successful demonstration of oxidative amination of benzoxazoles with secondary amines, we turned our attention to the amination of benzoxazoles with primary amines. Notably, the oxidative amination of benzoxazoles with primary amines in Cu-catalyzed coupling failed to furnish the coupled product.[7c] In light of this observation, we continued our exploration on oxidative amination of benzoxazoles with primary amines under standard reaction conditions. As expected, a variety of primary amines such as benzylamine (**2l**), 4-methylbenzylamine (**2m**), 2-phenylethylamine (**2n**), and propargylamine (**20**) underwent a smooth coupling with **1a** at room temperature to produce the corresponding amination products **3t**, **3u**, **3v**, or **3w** in good yields (Table 3).

Inspired by the versatility of this amination reaction, we diverted our attention to employ this methodology to synthesize therapeutically active benzoxazoles. A quick survey of the literature indicated that 5-chloro-7-methylbenzoxazole (**1e**) is a good precursor to react with *N*-methylpiperazine and *N*-methylhomopiperazine to afford the corresponding *N*-aminated benzaxozoles, which exhibit antidiarrhetic activity[11] and are potential radioligands for PET (positron emission tomography) imaging. Generally, these orally active benzoxazole derivatives are prepared in a multistep reaction using *O*-nitrophenol as the precursor via benzo[*d*]oxazole-2-thiol derivatives. Hence, 5-chloro-7-methylbenzoxazole **1e** was subjected to an optimized coupling reaction with cyclic diamines such as *N*-methylpiperazine (**2d**) and *N*-methylhomopiperazine (**2j**) to afford the corresponding amination products **3x** and **3y**, which exhibit antidiarrhetic activity in excellent yield (95% and 94%, respectively, Scheme 1). However, benzothiazole was inert for the amination reaction with piperidine and hence did not furnish the expected product.

Our attempts to understand the mechanism of this reaction have not been successful. During the preparation of this manuscript, Chang[7e] and co-workers reported the cyclization of *O*-hydroxybenzamidine with PIDA to get 2-aminooxazoles in good yields. In light of this observation, we synthesized intermediate amidines 4-methyl-2-(pyrrolidin-1-ylmethyleneamino)phenol (**I**) and 4-methyl-2-(piperdin-1-ylmethyleneamino)phenol (**II**) and independently reacted them with I_2/TBHP and AcOH in EtOAc under the standard coupling conditions. In this reaction, the amination occurred successfully to produce the corresponding cyclic products **4** and **3i** in excellent yields (Scheme 2).

However, the reaction of **1a** with **2a** under the optimized conditions in the presence of BHT (2,6-bis(1,1-dimethylethyl)-4-methylphenol) furnished **3a** in 90%. This reaction indicates that the reaction may not be going through the radical intermediate. Contrary to the observation of Chang and co-workers,[7d] the reaction of 5-methylbenzoxazole with piperidine in the absence of AcOH did not furnish the ring-opened adduct amidines (Scheme 3). Nevertheless, 5-methylbenzoxazole underwent a smooth coupling with piperidine in the absence of acetic acid under the standard reaction conditions to produce the corresponding amination products **3i** in 60% yield along with starting materials in 35% (Scheme 3). However, the absence of acetic acid in the reaction of benzoxazole (**1a**) with *N*,*N*-dimethylamine (**2a**) has produced a lower yield of the product **3a** (Table 1, 36%, entry 9).

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Table 2. Oxidative Amination of Benzoxazoles with Secondary Amines[a]

entry	1	2	prodcut	yield[a]	entry	1	2	prodcut	yield[b]
1	1a	2b	3b	94	10	1b	2i	3k	60
2	1a	2c	3c	94	11	1b	2j	3l	80
3	1a	2d	3d	82	12	1c	2b	3m	92
4	1a	2e	3e	95	13	1c	2c	3n	91
5	1a	2f	3f	95	14	1c	2e	3o	93
6	1a	2g	3g	80	15	1d	2b	3p	84[c]
7	1a	2h	3h	95	16	1d	2c	3q	85[c]
8	1b	2c	3i	92	17	1d	2e	3r	80[c]
9	1b	2d	3j	82	18	1a	2k	3s	95

[a] Reaction was performed at room temperature for 12 h. [b] Isolated yield. [c] At 60 °C in EtOAC.

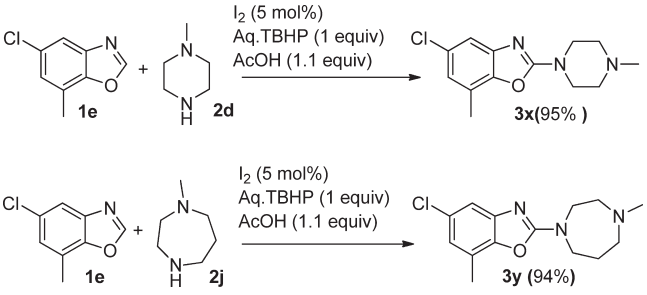
Table 3. Amination with Primary Amines[a]

entry	1	2	product	yield[b]
1	1a	2l	3t	80
2	1a	2m	3u	70
3	1a	2n	3v	65
4	1a	2o	3w	63

[a] Reaction was performed at room temperature for 12 h. [b] Isolated yield.

Recently, a metal-free approach for oxidative amination of benzoxazole using tetrabutylammoniumiodide (TBAI, 5 mol %)

Scheme 1. Synthesis of Antidiarrhetic Agents



and an aqueous solution of TBHP or H_2O_2 with acetic acid (3−5 equiv) at 80 °C in CH_3CN was reported by Nachtsheim and co-workers.[8b] In this paper, it was suggested that the reaction of quaternary ammonium iodide with H_2O_2/AcOH generates iodonium diacetate and further helps in generating I^+ source. However, we believe in our reaction, acidification of benzoxazole produces a species **III**, which reacts further with amine to furnish **IV**.[7e] Further reaction of **IV** with I_2 generates **V**, which loses a proton to generate the product, and the reaction cycle continues (Scheme 4). Further

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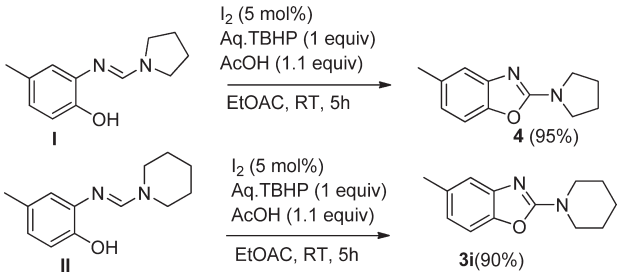
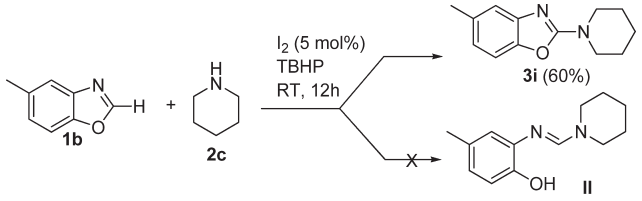
Scheme 2. Control Experiments

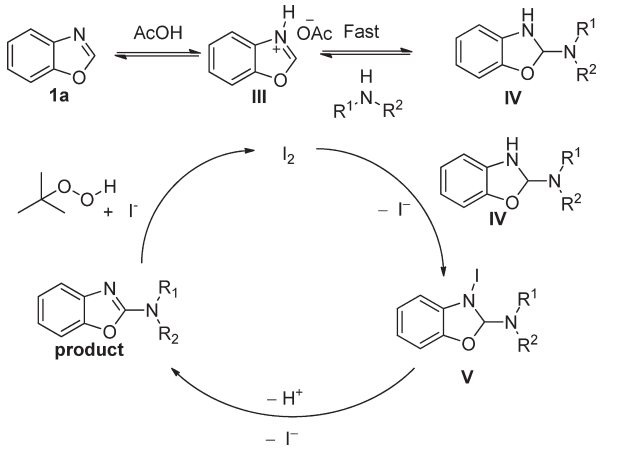


Scheme 3. Amination of Benzoxazole in the Absence of AcOH[a]



[a] Product **3i** formed along with 35% starting materials.

Scheme 4. Tentative Reaction Mechanism



work is underway in our laboratories to study the reaction mechanism.

CONCLUSION

In conclusion, we have developed a mild and efficient metal-free direct oxidative amination of benzoxazole via C−H bond activation to form a 2-aminobenzoxazole derivative under neat reaction conditions at room temperature. A wide range of benzoxazole derivative containing electron-donating and electron-withdrawing groups were coupled with both primary and secondary amines. The coupling reactions were performed using a stoichiometric amount of TBHP under solvent-free conditions. This user-friendly method produces tertiary butanol and water as the byproducts, which are environmentally benign. The present methodology constitutes a user-friendly and environmentally benign reaction for C−N bond formation of benzoxazoles. The application of the methodology is demonsrated by synthesizing therapeutically active benzoxazoles.

EXPERIMENTAL SECTION

Typical Experimental Procedure. TBHP (70% solution in water, 1 equiv, 1 mmol) was added to a well-stirred suspension of benzoxazole (**1a**, 1 mmol, 1 equiv), AcOH (1.1 mmol, 1.1 equiv), diethylamine (**2a**, 1 mmol, 1 equiv), and iodine (0.05 mmol, 0.05 equiv) at room temperature for 12 h. The reaction mixture was extracted with EtOAc (20 mL × 3) and dried over Na_2SO_4, solvent was removed under reduced pressure, and the product was purified by silica gel column chromatography to afford the amination product **3a**.

***N,N*-Diethylbenzoxazol-2-amine (3a)**[7d]**.** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−10:90): colorless liquid; yield 95%; R_f (10% EtOAc/hexane) 0.20; IR (neat, cm^{-1}) 2975, 2935, 1640, 1580, 1460, 1247, 740; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, J = 7.2 Hz, 6H), 3.57 (q, J = 7.2 Hz, 4H), 6.97 (t, J = 7.7 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H),7.34 (d, J = 7.8, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4, 42.9, 108.4, 115.7, 119.9, 123.7, 143.5, 148.7, 162.1; HRESI-MS (m/z) calcd for $C_{11}H_{14}N_2O$ (M + H) 191.1184, found (M + H) 191.1176.

2-(4-Morpholinyl)benzoxazole (3b)[7e]**.** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 20:80−30:70): pale yellow solid; yield 94%; mp 90−94 °C (lit.[7e] mp 91−94 °C); R_f (50% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 2867,1659, 1581, 1455, 1242, 1111, 798, 756, 743; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.67 (t, J = 5 Hz, 4H), 3.80 (t, J = 4.56 Hz, 4H), 7.03 (t, J = 7.9 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.26 (d, J = 8 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45. 6, 66.0, 108.7, 116.3, 120.8, 123.9, 142.6, 148.6, 161.9; HRESI-MS (m/z) calcd for $C_{11}H_{12}N_2O_2$ (M + H) 205.0977, found (M + H) 205.0977.

2-(Piperidin-1-yl)benzo[*d*]oxazole (3c)[6a]**.** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 20:80−30:70): pale yellow solid; yield 94%; mp 72−75 °C (lit.[6a] mp 74−75 °C); R_f (20% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 2867,1659, 1581, 1455, 1242, 1111, 798, 756, 743; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.68 (s, 6H), 3.66 (s, 4H), 6.97 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 8 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.1, 25.2, 46.6, 108.5, 115.9, 120.3, 123.8, 143.4, 148.7, 162.4; HRESI-MS (m/z) calcd for $C_{11}H_{12}N_2O_2$ (M + H) 203.1184, found (M + H) 203.1184.

2-(4-Methyl-1-piperazinyl)benzoxazole (3d)[11a]**.** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−15:85): white solid; yield 82%; mp 37−39 °C (lit.[11a] mp 36−38 °C); R_f (20% EtOAc/hexane) 0.20; IR (KBr, cm^{-1}) 2817, 1638, 1581, 1459, 1303, 1290, 1001, 744; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 2.60 (t, J = 4.3 Hz, 4H), 3.76 (t, J = 4.7 Hz, 4H), 7.02(t, J = 7.7 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.27−7.24 (m, 1H), 7.35 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.0, 45.9, 53.9, 108.8, 116.3, 120.8, 123.9, 142.8, 148.7, 161.9; HRESI-MS (m/z) calcd for $C_{12}H_{15}N_3O$ (M + H) 218.1293, found (M + H) 218.1290.

***N*-Benzyl-*N*-methylbenzoxazol-2-amine (3e)**[12]**.** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 15:85−20:80): off-white solid; yield 95%; mp 50−54 °C (lit.[12] mp 51−53 °C); R_f (25% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 1646, 1580, 1460, 740; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.08 (s, 3H), 4.71 (s, 2H), 6.99 (t, J = 7.7 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.32−7.23 (m, 6H), 7.38 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.9, 53.6, 108.5, 115.9, 120.2, 123.8, 127.4, 127.5, 128. 6, 136.2, 143.3, 148.8, 162.8; HRESI-MS (m/z) calcd for $C_{15}H_{14}N_2O$ (M + H) 239.1184, found (M + H) 239.1180.

2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)benzoxazole (3f)[7a]**.** Prepared as shown in the general experimental procedure and purified on

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silica gel (EtOAc/hexane 5:95−10:90): pale yellow solid; yield 95%; mp 85−88 °C (lit.[7a] mp 83−85 °C); R_f (10% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 2843, 1658, 1581, 1460, 1399, 1372, 1261, 740; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.01 (t, J = 6.4 Hz, 2H), 3.96 (t, J = 6 Hz, 2H), 4.86 (s, 2H), 7.02 (t, J = 7.8 Hz, 1H), 7.37−7.15 (m, 6H), 7.38 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5, 43.1, 47.2, 108.7, 116.3, 120.5, 123.9, 126.4, 126.5, 126.8, 128.8, 132.4, 134.0, 143.2, 148.8, 162.0; HRESI-MS (m/z) calcd for $C_{16}H_{14}N_2O$ (M + H) 251.1184, found (M + H) 251.1183

2-(4-Benzhydrylpiperazin-1-yl)benzoxazole (3g). Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 10:90−15:85): pale yellow solid; yield 80%; mp 164−168 °C; R_f (20% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 2815, 1636, 1578, 1455, 1265, 1240, 1005, 742; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.51 (t, J = 5 Hz, 4H), 3.69 (t, J = 5 Hz, 4H), 4.28 (s, 1H), 7.00 (dt, J_1 = 1 Hz, J_2 = 7.8 Hz, 1H), 7.14 (dt, J_1 = 1 Hz, J_2 = 7.6 Hz, 1H), 7.35−7.18 (m, 8H), 7.44−7.42 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.8, 51.1, 76.0, 108.7, 116.2, 120.6, 123.9, 127.2, 127.9, 128.6, 142.1, 143.1, 148.7, 162.2. Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.24; H, 6.30; N, 11.21.

***N,N*-Dibenylbenzoxazol-2-amine (3h)[1].** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−10:90): colorless liquid; yield 95%; R_f (10% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 3027, 1640, 1577, 1456, 1401, 1241, 821, 739, 698; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.69 (s, 4H), 7.03 (t, J = 8.9 Hz, 1H), 7.22−7.16 (m, 1H), 7.35−7.25 (m, 11H), 7.40 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.3, 108.8, 116.2, 120.5, 124.0, 127.7, 127.9, 128.7, 136.2, 143.4, 148.8, 163.0; HRESI-MS (m/z) calcd for $C_{21}H_{18}N_2O$ (M + Na) 337.1317, found (M + Na) 337.1317.

5-Methyl-2-(piperidin-1-yl)benzoxazole (3i)[7e]. Prepared as shown in general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−10:90): white solid; yield 92%; mp 98−100 °C (lit.[7e] mp 94−97 °C); R_f (20% EtOAc/hexane) 0.20; IR (KBr, cm^{-1}) 2940, 2855, 1656, 1587, 1440, 1292, 1259, 1183, 1019, 889, 792; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.65 (s, 6H), 2.37 (s, 3H), 3.63 (s, 4H), 6.78 (d, J = 8 Hz, 1H), 7.08 (d, J = 8 Hz, 1H), 7.13 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 23.9, 25.1, 107.8, 116.3, 120.8, 133.3, 143.2, 146.7, 162.4; HRESI-MS (m/z) calcd for $C_{13}H_{16}N_2O$ (M + H) 217.1341, found (M + H) 217.1346 .

5-Methyl-2-(4-methyl-1-piperazinyl)benzoxazole (3j)[11a]. Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 10:90−20:80): white solid; yield 82%; mp 65−67 °C (lit.[11a] mp 63−64 °C); R_f (20% EtOAc/hexane) 0.20; IR (KBr, cm^{-1}) 2919, 2850, 2803, 1645, 1574, 1449, 1281, 1268, 1171, 1147, 1003, 803; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.38 (s, 3H), 2.51 (t, J = 5.1 Hz, 4H), 3.71 (t, J = 5 Hz, 4H), 6.80−6.82 (m, 1H), 7.15−7.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 45.5, 46.2, 54.2, 108.0, 116.7, 121.3, 133.6, 143.2, 146.9, 162.6; HRESI-MS (m/z) calcd for $C_{13}H_{17}N_3O$ (M + H) 232.1450, found (M + H) 232.1454.

5-Methyl-2-thiomorpholinobenzoxazole (3k). Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−7:93): colorless liquid; yield 60%; R_f (10% EtOAc/hexane) 0.40; IR (KBr, cm^{-1}) 2916, 1633, 1583, 1260, 1180, 956; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H), 2.72 (t, J = 5 Hz, 4H), 3.98 (t, J = 5 Hz, 4H), 6.82 (d, J = 8 Hz, 1H), 7.15−7.10(m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 26.0, 48.0, 108.0, 116.7, 121.4, 133.7, 142.9, 146.8, 161.8; HRESI-MS (m/z) calcd for $C_{12}H_{14}N_2OS$ (M + H) 235.0905, found (M + H) 235.0907.

5-Methyl-2-(4-methyl-1,4-diazepan-1-yl)benzoxazole (3l). Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 25:75−40:60): gray solid; yield 80%; mp 66−70 °C; R_f (50% EtOAc/hexane) 0.20; IR (KBr, cm^{-1}) 2945, 2788, 1638, 1584, 1181, 791; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.03−2.09 (m, 2H), 2.38 (s, 3H), 2.41 (s, 3H), 2.67−2.64 (m, 2H), 2.79−2.76 (m, 2H), 3.80−3.76 (m, 2H), 3.86−3.84 (m, 2H), 6.79 (d, J = 8.1 Hz), 7.14−7.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 27.1, 46.3, 46.9, 47.1, 57.3, 58.0, 107.9, 116.33 120.8, 133.5, 143.4, 146.9, 162.4; HRESI-MS (m/z) calcd for $C_{14}H_{19}N_3O$(M + Na) 268.1426, found (M + Na) 268.1425.

2-(4-Morpholinyl)-5-phenylbenzoxazole (3m)[7e]. Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 15:85−20:80): beige solid; yield 92%; mp 106−110 °C (lit.[7e] 105−110 °C); R_f (20% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 2915, 2955,2969, 2856, 1638, 1579, 1465, 1446, 1425, 1385, 1357, 1303, 1274, 1258, 1207, 1191, 1069, 1058, 981, 894, 761, 699, 591, 515; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.66 (s, 6H), 3.65 (s, 6H), 7.29−7.21 (m, 3H), 7.40 (t, J = 7.4 Hz, 2H), 7.58−7.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.6, 66.0, 108.7, 115.0, 120.2, 126.8, 127.2, 128.6, 137.8, 141.4, 143.4, 148.2, 162.4; HRESI-MS (m/z) calcd for $C_{17}H_{16}N_2O_2$ (M + H) 281.1290, found (M + H) 281.1299.

5-Phenyl-2-(piperidin-1-yl)benzoxazole (3n)[7a]. Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 15:85−20:80): pink solid; yield 91%; mp 117−121 °C (lit.[7a] mp 118−120 °C); R_f (20% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 2938, 2922, 2854, 1647, 1638, 1578, 1466, 762; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.67 (q, J = 2 Hz, 4H), 3.76 (q, J = 4.4 Hz, 4H), 7.32−7.23 (m, 3H), 7.41 (t, J = 7.4 Hz, 2H), 7.59−7.56 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9, 25.1, 46.5, 108.4, 114.5, 119.6, 126.7, 127.1, 128.5, 128.7, 137.5, 141.5, 143.7, 148.2, 162.6; HRESI-MS (m/z) calcd for $C_{18}H_{18}N_2O$ (M + H) 279.1497, found (M + H) 279.1497.

2-(*N*-Benzyl-*N*-methylamino)-5-phenylbenzoxazole (3o)[7e]. Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 10:90−15:85): beige solid; mp yield 93%; mp 97−100 °C (lit.[7e] mp 96−100 °C); R_f (20% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 3028, 1641, 1580, 1416, 1394, 1253, 1202, 1115, 812, 758, 697; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.14 (s, 2H), 4.77 (s, 2H), 7.25−7.23 (m, 1H), 7.36−7.29 (m, 7H), 7.44−7.40 (m, 2H), 7.60−7.58 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.2, 53.8, 108.6, 114.8, 119.8, 126.8, 127.3, 127.6, 127.7, 128.7, 128.7, 136.3, 137.7, 141.6, 144.0, 148.6, 163.4; HRESI-MS (m/z) calcd for $C_{21}H_{18}N_2O$ (M + H) 315.1497, found (M + H) 315.1499.

2-Morpholino-6-nitrobenzoxazole (3p). Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 10:90−15:85): yellow solid; yield 84%; mp 140−144 °C; R_f (30% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 2982, 2918, 1651, 1589, 1504, 1322, 1294, 1103, 851; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.77 (t, J = 5.3 Hz, 4H), 3.85 (t, J = 4.3 Hz, 4H), 7.34 (d, J = 8.6 Hz, 1H), 8.20−8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.7, 66.0, 105.2, 115.1, 121.5, 141.6, 147.8, 149.7, 164.5; HRESI-MS (m/z) calcd for $C_{11}H_{11}N_3O_4$ (M + Na) 272.0647, found (M + H) 272.0643.

6-Nitro-2-(piperidin-1-yl)benzoxazole (3q). Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 10:90−15:85): yellow solid; yield 85%; mp 102−106 °C; R_f (30% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 2947, 2863, 1651, 1587, 1506, 1449, 1369, 1332,1320, 1291, 1024, 803; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.72 (s, 6H), 3.73 (s, 4H), 7.28 (d, J = 8.7 Hz, 1H), 8.17−8.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 25.6, 46.7, 104.7, 114.5, 121.5, 141.1, 147.8, 150.4, 164.8; HRESI-MS (m/z) calcd for $C_{12}H_{13}N_3O_3$(M + Na) 270.0855, found (M + Na) 270.0854.

***N*-Benzyl-*N*-methyl-6-nitrobenzoxazol-2-amine (3r).** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 10:90−15:85): yellow solid; yield 80%; mp 100−104 °C; R_f (20% EtOAc/hexane) 0.30; IR (neat, cm^{-1}) 1653, 1591, 1510, 1466, 1330, 1283, 1132, 819; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.19 (s, 3H), 4.80 (s, 2H), 7.39−7.31 (m, 6H), 8.19−8.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.2, 54.0, 105.0, 114.7, 121.4, 127.7, 128.1, 128.9, 135.3, 141.2, 147.9, 150.3, 165.6; HRESI-MS (m/z) calcd for $C_{15}H_{13}N_3O_3$(M + Na) 306.0855, found (M + Na) 306.0854.

Ethyl 4-(Benzo[d]oxazol-2-yl)piperazine-1-carboxylate (3s). Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−10:90): pink solid; yield 95%; mp 97−100 °C; R_f (10% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 2988, 2930, 2870, 1674, 1583, 1460, 1235, 1166, 1086, 993, 761; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, J = 7.08 Hz, 3H), 3.63−3.61 (m, 4H), 3.68−3.67 (m, 4H), 4.18 (q, J = 7.1 Hz, 2H), 7.04 (t, J = 7.7 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6, 43.0, 45.3, 61.7, 108.8, 116.4, 120.9, 124.0, 142.7, 148.6, 155.3, 161.8; HRESI-MS (m/z) calcd for $C_{14}H_{17}N_3O_3$(M + Na) 298.1168, found (M + Na) 298.1167.

***N*-Benzylbenzo[*d*]oxazol-2-amine (3t)[12].** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−10:90): white solid; yield 80%; mp 113−115 °C (lit.[12] mp 115−117 °C); R_f (5% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 1665, 1589, 1461, 1248; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.66 (s,2H), 5.49 (bs,1H), 7.02 (t, J = 7.8 Hz,1H), 7.17 (t, J = 7.6 Hz,1H), 7.25 (d, J = 8.4 Hz, 1H), 7.39−7.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.9, 108.8, 116.3, 120.9, 123.9, 127.6, 127.8, 128.8, 137.7, 142.6, 148.5, 162.0; HRESI-MS (m/z) calcd for $C_{14}H_{12}N_2O$ (M + H) 225.1028, found (M + H) 225.1025.

***N*-(4-Methylbenzyl)benzo[*d*]oxazol-2-amine (3u)[14].** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−10:90): white solid; yield 70%; mp 148−150 °C (lit.[14] mp 148−150 °C); R_f (20% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 1665, 1589, 1461, 1248; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 3H), 4.60 (s, 2H), 6.45 (br, 1H), 7.00 (t, J = 8 Hz, 1H), 7.14−7.10 (m, 3H), 7.27−7.18 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 46.7, 108.7, 116.1, 120.7, 123.8, 127.6, 129.4, 134.7, 137.4, 142.7, 148.4,162.1; HRESI-MS (m/z) calcd for $C_{15}H_{14}N_2O$(M + Na) 261.1004, found (M + Na) 261.1003.

***N*-Phenethylbenzo[*d*]oxazol-2-amine (3v)[12].** Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−10:90): white solid; yield 65%; mp 80−83 °C (lit.[12] 82−84 °C); R_f (20% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 3178, 3057, 2929, 1672, 1654, 1647, 1586, 1462, 1249, 741; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.98 (t, J = 6.8 Hz, 2H), 3.74 (t, J = 6.2 Hz, 2H), 5.21 (br, 1H), 7.02 (t, J = 7.7 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 7.25−7.21 (m, 4H), 7.37−7.29 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.7, 44.1, 108.7, 116.3, 120.8, 123.9, 126.7, 128.7, 128.8, 138.3, 142.9, 148.4, 161.8; HRESI-MS (m/z) calcd for $C_{15}H_{14}N_2O$ (M + H) 239.1184, found (M + H) 239.1185.

2-(Propargylamino)benzoxazole (3w)[13]. Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−10:90): white solid; yield 63%; mp 120−124 °C (lit.[13] mp 118−120 °C); R_f (20% EtOAc/hexane) 0.30; IR (KBr, cm^{-1}) 3406, 3275, 1685, 1666, 1588, 1338, 1246, 741, 648; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (s, 1H), 4.28 (s, 2H), 5.80 (br, 1H), 7.06 (t, J = 7.8 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.28 (d, J = 8 Hz, 7.42 (d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.8, 72.3, 79.2, 108.9, 116.8, 121.3, 124.0, 142.5, 148.7, 161.2; HRESI-MS (m/z) calcd for $C_{10}H_8N_2O$ (M + H) 173.0715, found (M + H) 173.0715.

5-Chloro-7-methyl-2-(4-methyl-1-piperazinyl)benzoxazole (3x)[11a]. Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 25:75−35:65): yellow solid; yield 95%; mp 64−66 °C (lit.[11a] mp 62−64 °C); R_f (30% EtOAc/hexane) 0.20; IR (KBr, cm^{-1}) 1645, 1627, 1574, 1452, 1302, 895; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H), 2.39 (s, 3H), 2.58 (t, J = 5.2 Hz, 4H), 3.75 (t, J = 5.2 Hz, 4H), 6.80 (s, 1H), 7.12 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.0, 45.9, 53.9, 113.7, 119.9, 121.9, 128.8, 143.6, 146.2, 162.4; HRESI-MS (m/z) calcd for $C_{13}H_{16}ClN_3O$ (M + H) 266.1060, found (M + H) 266.1072.

5-Chloro-7-methyl-2-(4-methyl-1,4-diazepan-1-yl)benzo[*d*]oxazole (3y)[12]. Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 25:75−40:60): white solid; yield 94%; mp 112−114 °C (lit.[12] mp 116−117 °C); R_f (50% EtOAc/hexane) 0.20; IR (neat, cm^{-1}) 2940, 1644, 1626, 1572, 1459, 1172, 792; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13−2.10 (m, 2H), 2.36 (s, 3H), 2.45 (s, 3H), 2.75−2.73 (m, 2H), 2.86−2.84 (m, 2H), 3.81−3.78 (m, 2H), 3.90−3.88 (m, 2H), 6.77 (s, 1H), 7.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 26.6, 46.0, 46.4, 46.9, 57.1, 57.7, 113.4, 119.8, 121.4, 128.7, 143.8, 146.3, 162.6; HRESI-MS (m/z) calcd for $C_{14}H_{18}ClN_3O$ (M + H) 280.1217, found (M + H) 280.1215.

5-Methyl-2-(pyrrolidin-1-yl)benzoxazole (4)[8a]. Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 5:95−10:90): brown solid; yield 95%; mp 97−100 °C (lit.[8a] mp 101 °C); R_f (20% EtOAc/hexane) 0.30; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03−2.00 (m, 4H), 2.38 (s, 3H), 3.64−3.61 (m, 4H), 6.77 (d, J = 7.9 Hz, 1H), 7.14−7.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 25.5, 47.3, 107.8, 116.2, 120.6, 133.3, 143.5, 147.0, 161.0; HRESI-MS (m/z) calcd for $C_{12}H_{14}N_2O$ (M + H) 203.1184, found (M + H) 203.1186.

(*E*)-4-Methyl-2-((pyrrolidin-1-ylmethylene)amino)phenol (I)[8a]. Prepared as shown in the experimental procedure and purified on silica gel (EtOAc/hexane 15:85−40:60): gray solid; yield 92%; mp 100−104 °C (lit.[8a] mp 106 °C); R_f (50% EtOAc/hexane) 0.20; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (s, 4H), 2.24 (s, 3H), 3.51 (s,4H), 6.79−6.69 (m, 3H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 24.7, 25.2, 45.3, 112.8, 116.1, 123.6, 128.7, 137.2, 147.8, 149.2; HRESI-MS (m/z) calcd for $C_{12}H_{16}N_2O$(M + H) 205.1341, found (M + H) 205.1342.

4-Methyl-2-((piperidin-1-ylmethylene)amino)phenol (II)[8a]. Prepared as shown in the general experimental procedure and purified on silica gel (EtOAc/hexane 15:85−40:60): white solid; yield 89%; mp 100−104 °C (lit.[8a] mp 101 °C); R_f (50% EtOAc/hexane) 0.20; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.58−1.54 (m, 4H), 1.64−1.61 (m, 2H), 2.22 (s, 3H), 3.55−3.28 (br, 4H), 6.75 (d, J = 7.8 Hz, 1H), 6.69−6.67 (m, 2H), 7.62 (s, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 21.2, 24.4, 26.4, 42.9, 50.2, 112.6, 116.1, 123.4, 128.5, 136.8, 147.7,151.3; HRESI-MS (m/z) calcd for $C_{12}H_{18}N_2O$ (M + H) 219.1497, found (M + H) 219.1495.

■ ASSOCIATED CONTENT

Supporting Information. Characterization data are available (including ^{1}H and ^{13}C NMR spectra) for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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