Tetrahedron 69 (2013) 6627–6633

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 2-aminobenzoxazoles via copper-catalyzed electrophilic amination of benzoxazoles with *O*-benzoyl hydroxylamines

Sirilata Yotphan *, Danupat Beukeaw, Vichai Reutrakul

Center for Catalysis and Center of Excellence for Innovation in Chemistry (PERCH-CIC), Department of Chemistry, Faculty of Science, Mahidol University, Bangkok 10400, Thailand

ARTICLE INFO

Article history:
Received 23 March 2013
Received in revised form 15 May 2013
Accepted 28 May 2013
Available online 4 June 2013

Keywords:
Copper catalysis
Electrophilic amination
C–N bond formation
Benzoxazole
O-Benzoyl hydroxylamine

ABSTRACT

An efficient copper-catalyzed electrophilic amination of benzoxazoles with *O*-benzoyl hydroxylamines is described, employing CuCl catalyst, PPh_3 ligand, and LiO^tBu base. This simple air-stable copper catalysis enables the preparation of various 2-aminobenzoxazole derivatives at room temperature in good yields.
© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

A number of 2-aminoazoles (2-*N*-substituted azoles) possess biological and pharmaceutical activities. They are employed widely as a building block for the development of promising drug candidates.[1,2] Particularly, 2-aminobenzoxazoles are ubiquitous scaffolds in a wide variety of therapeutic agents for a treatment of CNS disorders,[3] insomnia,[4] and Alzheimer's disease.[5]

Due to their significance, the development of versatile and practical protocols to achieve a variety of these 2-aminobenzoxazoles and other 2-aminoazole derivatives has been the subject of intense research effort. Over the past decade, the transition metal-catalyzed carbon–nitrogen (C–N) bond cross-coupling reactions, particularly Buchwald–Hartwig as well as Ullman couplings provide powerful, efficient, and reliable approaches for the synthesis of these structural motifs.[6] Recent methods involving the catalytic carbon–hydrogen (C–H) bond functionalization and C–N bond formation were also recognized as the potentially useful synthetic tools for these structural moieties.[7,8]

Additionally, an umpolung[9] electrophilic amination[10] using a reagent of type R_2N^+, such as halogenated amine, hydroxylamine, oxaziridine, and hydrazine, provides a practical tool to construct C–N bonds. This strategy allows the effective amination of both organometallic reagents[11] and heteroaromatic C–H bonds.[12]

Miura and co-workers recently reported the copper-catalyzed direct amination of electron-deficient heteroaryl substrates with chloroamines and hydroxylamines.[13] The use of these electrophilic amine reagents under copper catalysis enables the successful formation of heteroaryl–amino linkages at room temperature. Herein, we reported an alternative and straightforward synthetic approach to access 2-aminobenzoxazoles and their derivatives under atmospheric conditions by using the readily prepared *O*-benzoyl hydroxylamines as electrophilic amine reagents.[11d,14]

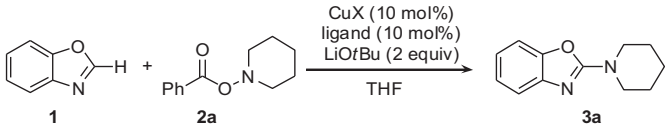
2. Results and discussion

We initiated the studies by choosing benzoxazole **1** and *O*-benzoyl hydroxylamine **2a** as substrates for the optimization under the atmospheric conditions (Table 1). To our delight, this reaction was complete within 1 h even at room temperature as monitored by GC analysis.[15] We screened various copper salts (Table 1, entries 1–7), and a combination of CuCl/PPh_3/LiO^tBu in THF showed higher catalytic activities (entry 3). No reaction was observed in the absence of copper and only 31% yield of product **3a** was obtained in the absence of PPh_3 ligand (entries 8–10). The use of phen (1,10-phenanthroline) and bipy (2,2′-bipyridine) ligands led to lower yields, 36 and 21%, respectively (entries 11 and 12).

* Corresponding author. Tel.: +662 201 5154; fax: +662 354 7151; e-mail address: sirilata.yot@mahidol.ac.th (S. Yotphan).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.05.127

Table 1
Effect of copper source and ligand[a]



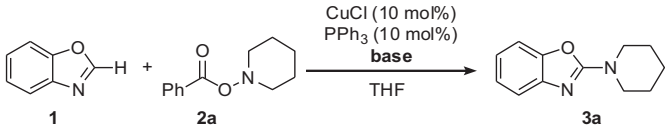
1 (1 equiv) **2a** (1.5 equiv) **3a**

Entry	Copper salt	Ligand	Yield[b] (%)
1	CuI	PPh_3	55
2	CuBr	PPh_3	40
3	*CuCl*	*PPh_3*	*60*
4	$CuBr_2$	PPh_3	17
5	$CuCl_2$	PPh_3	58
6	$Cu(OAc)_2$	PPh_3	50
7	$Cu(OTf)_2$	PPh_3	50
8	—	—	0
9	—	PPh_3	0
10	CuCl	—	31
11	CuCl	Phen	36
12	CuCl	Bipy	21

[a] Conditions: benzoxazole **1** (0.5 mmol, 1 equiv), **2a** (1.5 equiv), CuX (10 mol %), ligand (10 mol %), LiO^{t}Bu (2 equiv), THF (2 mL), rt, 1 h.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

We also studied the effect of inorganic base (Table 2, entries 1–8) and equivalency (entries 2, 9, and 10). The results in Table 2 showed that 3 equiv of LiO^{t}Bu can furnish product **3a** in very high yield (entry 10). On the other hand, other stronger bases such as NaO^{t}Bu, KO^{t}Bu, and NaOH, or weaker bases such as K_3PO_4, Cs_2CO_3, and NaOAc resulted in significantly lower yields or no reaction.

Table 2
Effect of inorganic base[a]



1 (1 equiv) **2a** (1.5 equiv) **3a**

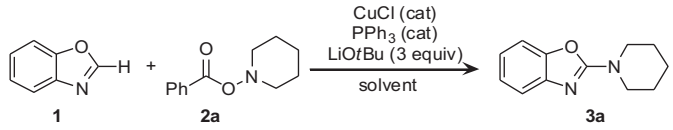
Entry	Base	Equiv	Yield[b] (%)
1	—	—	0
2	LiO^{t}Bu	2	60
3	NaO^{t}Bu	2	19
4	KO^{t}Bu	2	0
5	NaOH	2	0
6	K_3PO_4	2	<2
7	Cs_2CO_3	2	<2
8	NaOAc	2	0
9	LiO^{t}Bu	1	49
10	*LiO^{t}Bu*	*3*	*80*

[a] Conditions: benzoxazole **1** (0.5 mmol, 1 equiv), **2a** (1.5 equiv), CuCl (10 mol %), PPh_3 (10 mol %), base (1–3 equiv), THF (2 mL), rt, 1 h.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

Subsequent investigation of ratio of Cu to PPh_3 and solvent effect (Table 3, entries 1–10) established the combination of CuCl (5 mol %), PPh_3 (10 mol %), LiO^{t}Bu (3 equiv) in THF at rt for 1 h as the best catalytic conditions providing **3a** in 95% yield (Table 3, entry 5). Good yields of product **3a** can also be obtained when using 1,4-dioxane, toluene, and acetonitrile as solvent (Table 3; entries 6–8), whereas DMF and DMSO were much less effective (entries 9 and 10).

To test the generality of this protocol, reactions of benzoxazole **1** and a variety of *O*-benzoyl hydroxylamines (**2a**–**j**) were next examined for the C-2 amination under the optimized reaction

Table 3
Optimization of reaction conditions[a]



1 (1 equiv) **2a** (1.5 equiv) **3a**

Entry	CuCl (mol %)	PPh_3 (mol %)	Solvent	Yield[b] (%)
1	10	10	THF	80
2	20	20	THF	68
3	5	5	THF	88
4	2	2	THF	62
5	*5*	*10*	*THF*	*95*
6	5	10	Toluene	83
7	5	10	Dioxane	81
8	5	10	Acetonitrile	72
9	5	10	DMF	21
10	5	10	DMSO	18

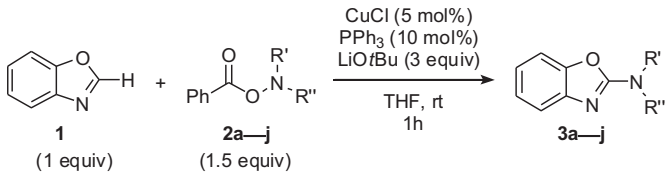
[a] Conditions: benzoxazole **1** (0.5 mmol, 1 equiv), **2a** (1.5 equiv), CuCl (cat), PPh_3 (cat), LiO^{t}Bu (3 equiv), solvent (2 mL), rt, 1 h.
[b] Yields were determined by GC integration relative to hexamethylbenzene (0.1 equiv) as the internal standard.

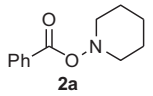
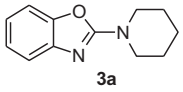
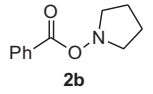
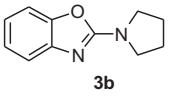
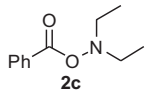
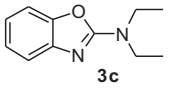
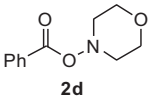
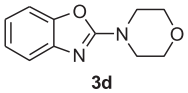
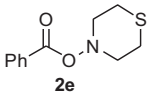
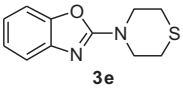
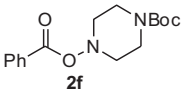
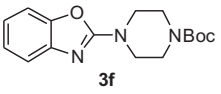
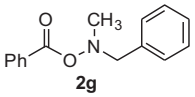
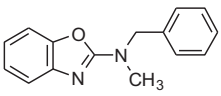
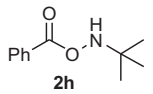
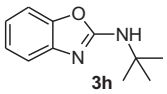
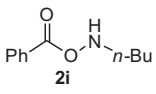
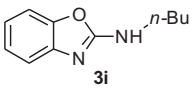
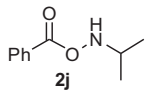
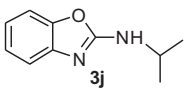
conditions (Table 4). The reactions of benzoxazole **1** with cyclic and acyclic *O*-benzoyl hydroxylamines (**2a**–**g**) derived from secondary alkylamines underwent smooth amination affording the corresponding 2-aminobenzoxazole derivatives **3a**–**g** in moderate to excellent isolated yields (entries 1–7). An additional oxygen or sulfur heteroatom in the *O*-benzoyl hydroxylamine structure is well tolerated, as shown by the successful reaction using morpholine **2d** or thiomorpholine **2e** derivatives (entries 4 and 5). The Boc **2f** and benzyl **2g** protecting groups on nitrogen are also compatible (entries 6 and 7). Therefore, further functionalization after the deprotection would be possible. On the other hand, copper-catalyzed electrophilic amination reaction of benzoxazole **1** and *O*-benzoyl hydroxylamine derived from primary amines showed somewhat lower efficiency. *O*-Benzoyl hydroxylamine **2h**, which was derived from *tert*-butylamine, provided 16% isolated yield of C-2 aminated benzoxazole product **3h** (entry 8). No reaction or only small amount of desired product was observed when using other primary amines derived *O*-benzoyl hydroxylamine reagents (e.g., entries 9 and 10).[15]

We also studied the substrate scope of benzoxazoles and other derivatives of azoles (Table 5). Under the optimized conditions, the copper-catalyzed reactions of methylbenzoxazoles (**4a** and **4b**) and *O*-benzoyl hydroxylamine **2a** afforded the corresponding C-2 aminated benzoxazole products **5a** and **5b** in high yields (86% and 73%, respectively; entries 1 and 2). In case of 5-phenylbenzoxazole substrate **4c**, excellent isolated yield of product **5c** was obtained (90%; entry 3). Moreover, the presence of chloro and nitro groups on the aromatic portion of benzoxazole substrates **4d** and **4e** did not have much significant effect in the reaction, therefore, amination reaction also proceeded without any difficulties furnishing products **5d** and **5e** in good yields (66% and 61%; entries 4 and 5). Interestingly, oxadiazole substrate **4f** can be converted to the corresponding C-2 aminated product **5f** with good efficiency (72% isolated yield; entry 6). Conversely, other azoles such as benzothiazole **4g** and *N*-methyl benzimidazole **4h** do not react under these conditions (entries 7 and 8). Only a small amount (less than 5%) of desired C-2 aminated azole was detected by GC–MS when LiO^{t}Bu was replaced by a stronger KO^{t}Bu base. This could be a result of the higher p*K*a values of the C–H bonds at C-2 position of thiazoles and imidazoles.[7a,16]

The plausible mechanism would involve (1) an initial complexation of copper salt with phosphine and *tert*-butoxide to

Table 4
Copper-catalyzed electrophilic amination of benzoxazole **1** with various *O*-benzoyl hydroxylamines[a]

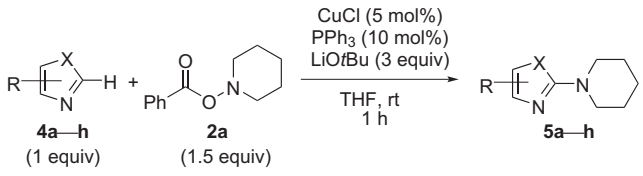


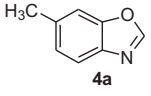
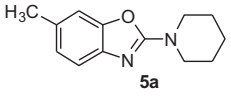
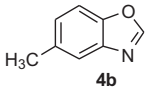
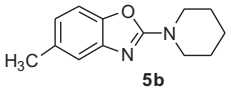
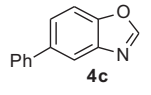
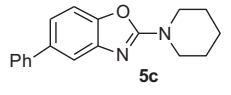
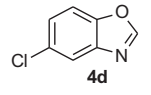
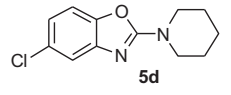
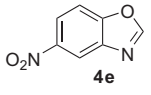
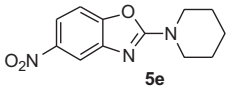
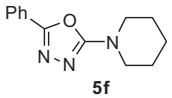
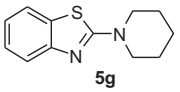
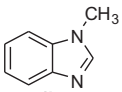
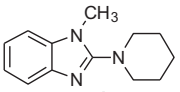
Entry	*O*-Benzoyl hydroxylamine	Product	Yield[b] (%)
1	 **2a**	 **3a**	91
2	 **2b**	 **3b**	40
3	 **2c**	 **3c**	74
4	 **2d**	 **3d**	54
5	 **2e**	 **3e**	45
6	 **2f**	 **3f**	50
7	 **2g**	 **3g**	75
8	 **2h**	 **3h**	16
9	 **2i**	 **3i**	<5[c]
10	 **2j**	 **3j**	0

[a] Conditions: benzoxazole **1** (1 mmol, 1 equiv), **2a**–**j** (1.5 equiv), CuCl (5 mol %), PPh_3 (10 mol %), LiO^tBu (3 equiv), THF (4 mL), rt, 1 h.
[b] Isolated yields after purification by chromatography.
[c] Detected by GC–MS.

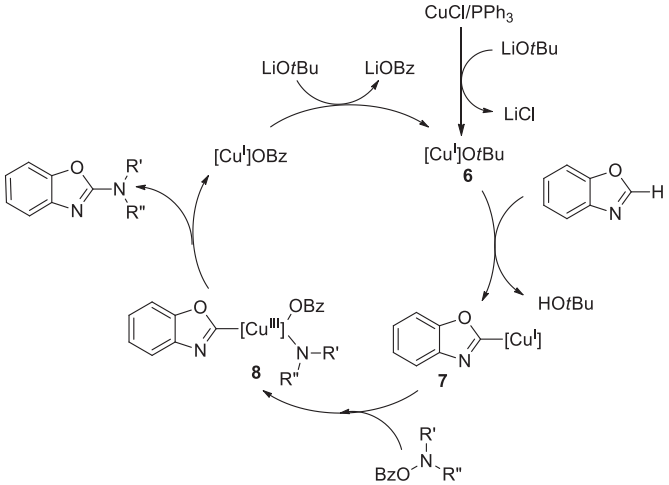
generate copper(I)-*tert*-butoxide complex **6**, (2) formation of the key intermediate azole-cuprate **7** assisted by anionic *tert*-butoxide (O^tBu) ligand,[17] (3) oxidative addition of complex **7** with *O*-benzoyl hydroxylamine by single electron transfer process to generate an intermediate **8** in higher oxidation state,[18] (4) reductive elimination of **8** to form new C–N bond of 2-aminobenzoxazole product and regenerate active copper species to resume the catalytic cycle (Scheme 1).[13b] Further efforts to study the detailed mechanism and expand the reaction scope of this chemistry are currently under investigation.

Table 5
Copper-catalyzed electrophilic amination of benzoxazole derivatives with *O*-benzoyl hydroxylamine **2a**[a]



Entry	Azole	Product	Yield[b] (%)
1	 **4a**	 **5a**	86
2	 **4b**	 **5b**	73
3	 **4c**	 **5c**	90
4	 **4d**	 **5d**	66
5	 **4e**	 **5e**	61
6	 **4f**	 **5f**	72
7	 **4g**	 **5g**	0[c]
8	 **4h**	 **5h**	0[c]

[a] Conditions: benzoxazoles **4a**–**h** (1 mmol, 1 equiv), **2a** (1.5 equiv), CuCl (5 mol %), PPh_3 (10 mol %), LiO^tBu (3 equiv), THF (4 mL), rt, 1 h.
[b] Isolated yields after purification by chromatography.
[c] No reaction was detected by TLC/GC–MS.



Scheme 1. Proposed plausible mechanism of the Cu-catalyzed electrophilic amination of benzoxazoles and *O*-benzoyl hydroxylamines.

3. Conclusion

In conclusion, we have disclosed an efficient synthetic protocol for the copper-catalyzed amination reaction of benzoxazoles and *O*-benzoyl hydroxylamines. This umpolung electrophilic amination strategy can be carried out under atmospheric conditions with good scope and functional group compatibility. This transformation allows the facile synthesis of a number of 2-aminobenzoxazole derivatives and serves as an alternative and convenient synthetic route to 2-aminobenzoxazoles, which are employed widely in medicinal chemistry.

4. Experimental section

4.1. General methods

Unless otherwise specified, all reactions were carried out under air atmosphere. All reagents were obtained from commercial suppliers and used without further purification. Oven-dried glassware was used in all cases. Chromatography was performed on silica gel (SiO_2; 60 Å silica gel, Merck Grade, 70–230 Mesh). GC experiments were carried out with an Agilent 6890N GC-FID on chromatograph equipped with an Agilent column (HP-1, polysiloxane, 24.5 m×0.32 mm ID×0.17 μm). ^1H and ^{13}C NMR spectra were measured with Bruker AV-300 or AV-500 spectrometers in $CDCl_3$. NMR chemical shifts are reported in parts per million (ppm) relative to $CHCl_3$ (7.24 ppm for ^1H and 77.0 ppm for ^{13}C). IR spectra were recorded on an FTIR Spectrum GX (Perkin Elmer), and only partial data are listed. Melting points were determined on a Mel-Temp apparatus and are uncorrected. High-resolution mass spectroscopy analyses were carried out by Mahidol University, Department of Chemistry Micro-Mass Facility.

4.2. General procedure for the synthesis of compounds 2–5

*4.2.1. General procedure for the preparation of O-benzoyl hydroxylamines **2a**–**j**.*[11d,14] A 100-mL, one-necked, round-bottomed flask equipped with a magnetic stir bar was charged with benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv), dipotassium hydrogen phosphate (3.27 g, 18.8 mmol, 1.50 equiv), and *N*,*N*-dimethylformamide (30 mL). The suspension was stirred and amine (15.0 mmol, 1.20 equiv) was added via syringe in one portion. The flask was capped with a septum and the reaction mixture was stirred at room temperature for 1–24 h, during, which time a gradual change in coloration of the reaction mixture occurred. Deionized water (50 mL) was added and the contents were stirred vigorously for 30 min. The reaction mixture was transferred to a separatory funnel and extracted with EtOAc (1×40 mL). The organic phase was collected and washed with saturated aqueous $NaHCO_3$ solution (2×25 mL). All of the aqueous fractions were combined and extracted with EtOAc (2×25 mL). All of the organic fractions were combined and washed with 30 mL of deionized water, 25 mL of brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The resulting crude product was purified by flash column chromatography to give the corresponding *O*-benzoyl hydroxylamine **2**. All physical data of the known compounds were in agreement with those reported in the literature.[11d,11l,14,19,20]

*4.2.2. General procedure for the preparation of 6-substituted benzoxazoles (**4c** and **4e**).*[8d,21] Most of benzoxazole substrates **4** used in this study are commercially available except **4c** and **4e**.

A 100-mL, one-necked, round-bottomed flask equipped with a magnetic stir bar was charged with the corresponding 2-aminophenol derivative (5.00 mmol, 1.00 equiv) and triethyl orthoformate (8.50 mL, 60.0 mmol, 12.0 equiv). The reaction mixture was carefully heated to 150 °C for 6 h. Upon completion, the reaction mixture was cooled to room temperature and the excess orthoformate and ethanol byproduct were removed from the residue under reduced pressure. The crude product was further purified by silica gel (SiO_2) column chromatography to yield the desired substituted azole. All physical data of **4c** and **4e** were in agreement with those reported in the literature.[8d]

*4.2.3. General procedure for the synthesis of compounds **3a**–**h** and **5a**–**f**.* A 20 mL oven-dried and N_2-flushed scintillation vial equipped with a magnetic stir bar was charged with benzoxazole or azole starting material (1.00 mmol, 1.00 equiv), *O*-benzoyl hydroxylamine (1.50 mmol, 1.50 equiv), CuCl (5.0 mg, 0.05 mmol, 0.05 equiv), PPh_3 (26.0 mg, 0.10 mmol, 0.10 equiv), LiO^tBu (0.24 g, 3.00 mmol, 3.00 equiv), and tetrahydrofuran (THF) (4.00 mL, 0.25 M concentration of substrate). The vial was capped, and the reaction mixture was stirred at room temperature for 1 h. Upon completion, distilled deionized H_2O (10 mL) was added, and the mixture was extracted with EtOAc (2×15 mL). The solution was concentrated in vacuo, and the crude product was purified by SiO_2 column chromatography to afford a corresponding benzoxazole derivative. All physical data of the known compounds were in agreement with those reported in the literature.[8a,8d,13,14,22]

4.3. Analytical data for compounds 2a–j, 3a–h, 4c, 4e, 5a–f

*4.3.1. Piperidin-1-yl benzoate (**2a**).*[11d] Benzoyl hydroxylamine **2a** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and piperidine (1.28 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2a** (1.90 g, 75%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.91–7.89 (m, 2H), 7.47–7.42 (m, 1H), 7.35–7.29 (m, 2H), 3.48–3.27 (m, 2H), 2.68–2.66 (m, 2H), 1.74–1.70 (m, 4H). 1.65–1.45 (m, 1H), 1.17–1.12 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 164.8, 132.9, 129.6, 129.4, 128.3, 57.5, 25.0, 23.3. HRMS (ESI+, *m*/*z*) Calcd for $C_{12}H_{15}NO_2Na$ $[M+Na]^+$ 228.1000. Found 228.1001.

*4.3.2. Pyrrolidin-1-yl benzoate (**2b**).* Benzoyl hydroxylamine **2b** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and pyrrolidine (1.07 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2b** (1.19 g, 50%) as an off-white solid. Mp=66.2–66.6 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96–7.92 (m, 2H), 7.55–7.49 (m, 1H), 7.42–7.37 (m, 2H), 3.31–3.26 (m, 4H), 1.93 (s, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 165.2, 132.9, 129.5, 129.4, 128.3, 57.7, 22.2. IR (film): 3423, 2978, 1719, 1598, 1452, 1315, 1259, 1092, 1071, 1021, 948, 785, 719 cm^{-1}. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{13}NO_2Na$ $[M+Na]^+$ 214.0844. Found 214.0847.

*4.3.3. O-Benzoyl-N,N-diethyl hydroxylamine (**2c**).*[11d] Benzoyl hydroxylamine **2c** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and diethylamine (1.10 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2c** (1.42 g, 59%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.99–7.96 (m, 2H), 7.48–7.45 (m, 1H), 7.38–7.33 (m, 2H), 2.98 (q, *J*=7.2 Hz, 4H), 1.11 (t, *J*=7.2 Hz, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 165.6, 132.7, 129.4, 129.1, 128.1, 53.1, 11.5. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{15}NO_2Na$ $[M+Na]^+$ 216.1000. Found 216.1019.

*4.3.4. Morpholino benzoate (**2d**).*[11d] Benzoyl hydroxylamine **2d** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and morpholine (1.31 g, 15.0 mmol, 1.20 equiv) following the general

procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2d** (1.97 g, 76%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J=7.5 Hz, 2H), 7.55–7.50 (m, 1H), 7.42–7.37 (m, 2H), 3.91–3.77 (m, 4H), 3.42–3.38 (m, 2H), 3.02–2.99 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.5, 133.1, 129.3, 129.0, 128.4, 65.7, 56.9. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{13}NO_3Na$ $[M+Na]^+$ 230.0793. Found 230.0794.

*4.3.5. Thiomorpholino benzoate (**2e**).* Benzoyl hydroxylamine **2e** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and thiomorpholine (1.55 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2e** (1.77 g, 69%) as an off-white solid. Mp=80.9–81.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.97 (m, 2H), 7.58–7.53 (m, 1H), 7.45–7.40 (m, 2H), 3.65 (br s, 2H), 3.22 (br s, 2H), 2.86 (br s, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.4, 133.2, 129.4, 129.1, 128.4, 57.7, 26.6. IR (film): 3439, 2961, 2925, 1732, 1598, 1452, 1317, 1267, 1247, 1183, 1090, 1067, 979, 712 cm^{-1}. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{13}NO_2SNa$ $[M+Na]^+$ 246.0565. Found 246.0567.

*4.3.6. tert-Butyl 4-(benzoyloxy)piperazine-1-carboxylate (**2f**).*[11l] Benzoyl hydroxylamine **2f** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and *tert*-butyl piperazine-1-carboxylate (2.79 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2f** (2.74 g, 72%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.95 (m, 2H), 7.58–7.49 (m, 1H), 7.46–7.36 (m, 2H), 3.99 (br s, 1H), 3.40 (br s, 2H), 3.29 (br s, 2H), 2.89 (br s, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.5, 154.4, 133.2, 129.4, 129.0, 128.4, 80.2, 55.8, 42.0, 28.3. HRMS (ESI+, *m*/*z*) Calcd for $C_{16}H_{22}N_2O_4Na$ $[M+Na]^+$ 329.1477. Found 329.1469.

*4.3.7. O-Benzoyl-N-benzyl-N-methylhydroxylamine (**2g**).*[19] Benzoyl hydroxylamine **2g** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and *N*-methyl-1-phenylmethanamine (1.93 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=9:1) to afford pure compound **2g** (1.96 g, 65%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09–8.05 (m, 2H), 7.64–7.55 (m, 1H), 7.52–7.25 (m, 7H), 4.16 (s, 2H), 2.92 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.9, 135.5, 132.8, 129.4, 129.3, 128.9, 128.4, 128.1, 127.7, 65.1, 46.1. HRMS (ESI+, *m*/*z*) Calcd for $C_{15}H_{15}NO_2Na$ $[M+Na]^+$ 264.1000. Found 264.0984.

*4.3.8. O-Benzoyl-N-(tert-butyl)hydroxylamine (**2h**).*[20] Benzoyl hydroxylamine **2h** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and *tert*-butylamine (1.10 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2h** (1.95 g, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02–8.01 (m, 2H), 7.66 (br s, 1H), 7.56–7.54 (m, 1H), 7.46–7.43 (m, 2H), 1.22 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.8, 133.2, 129.3, 129.2, 128.5, 56.1, 26.6. IR (film): 3224, 2976, 1720, 1452, 1366, 1271, 1222, 1093, 1068, 1026, 996, 708 cm^{-1}. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{16}NO_2$ $[M+H]^+$ 194.1181. Found 194.1186.

*4.3.9. O-Benzoyl-N-butylhydroxylamine (**2i**).* Benzoyl hydroxylamine **2i** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and *n*-butylamine (1.50 mL, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2i** (1.50 g, 62%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01–7.99 (m, 2H), 7.86 (br s, 1H), 7.57–7.54 (m, 1H), 7.45–7.42 (m, 2H), 3.12 (t, J=7.5 Hz, 2H), 1.62–1.56 (m, 2H), 1.45–1.38 (m, 2H), 0.93 (t, J=7.5 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.9, 133.2, 129.4, 129.3, 128.5, 52.3, 29.2, 20.2, 13.9. IR (film): 3236, 2961, 2874, 1722, 1452, 1272, 1068, 1026, 710 cm^{-1}. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{15}NO_2Na$ $[M+Na]^+$ 216.1000. Found 216.1002.

*4.3.10. O-Benzoyl-N-isopropylhydroxylamine (**2j**).* Benzoyl hydroxylamine **2j** was prepared from benzoyl peroxide (3.03 g, 12.5 mmol, 1.00 equiv) and isopropylamine (1.23 g, 15.0 mmol, 1.20 equiv) following the general procedure for the preparation of *O*-benzoyl hydroxylamines. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **2j** (1.71 g, 77%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.96 (m, 2H), 7.63 (br s, 1H), 7.50–7.48 (m, 1H), 7.41–7.35 (m, 2H), 3.31 (sep, J=6.3 Hz, 1H), 1.13 (d, J=6.3 Hz, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.6, 133.1, 129.1, 129.0, 128.4, 52.1, 19.7. IR (film): 3237, 2974, 1721, 1601, 1452, 1317, 1271, 1091, 1067, 1026, 708 cm^{-1}. HRMS (ESI+, *m*/*z*) Calcd for $C_{10}H_{13}NO_2Na$ $[M+Na]^+$ 202.0844. Found 202.0839.

*4.3.11. 2-(Piperidin-1-yl)benzoxazole (**3a**).*[8a] Compound **3a** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3a** (0.18 g, 91%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.35 (m, 1H), 7.29–7.23 (m, 1H), 7.16 (dt, J=7.8, 1.2 Hz, 1H), 7.00 (dt, J=7.8, 1.2 Hz, 1H), 3.67 (br s, 4H), 1.69 (br s, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 162.4, 148.6, 143.3, 123.8, 120.2, 115.9, 108.5, 46.5, 25.2, 24.0. HRMS (ESI+, *m*/*z*) Calcd for $C_{12}H_{15}N_2O$ $[M+H]^+$ 203.1184. Found 203.1203.

*4.3.12. 2-(Pyrrolidin-1-yl)benzoxazole (**3b**).*[8a] Compound **3b** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and pyrrolidin-1-yl benzoate **2b** (0.29 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3b** (0.08 g, 40%) as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.36 (m, 1H), 7.29–7.25 (m, 1H), 7.16 (dt, J=7.8, 1.2 Hz, 1H), 7.00 (dt, J=7.8, 1.2 Hz, 1H), 3.70–3.64 (m, 4H), 2.07–2.03 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 161.0, 149.0, 143.6, 123.8, 120.0, 115.9, 108.5, 47.4, 25.6. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{13}N_2O$ $[M+H]^+$ 189.1028. Found 189.1055.

*4.3.13. N,N-Diethylbenzoxazole-2-amine (**3c**).*[8a] Compound **3c** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and *O*-benzoyl-*N*,*N*-diethyl hydroxylamine **2c** (0.29 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3c** (0.14 g, 74%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.36 (m, 1H), 7.28–7.24 (m, 1H), 7.16 (dt, J=7.8, 1.2 Hz, 1H), 6.99 (dt, J=7.8, 1.2 Hz, 1H), 3.60 (q, J=7.2 Hz, 4H), 1.30 (t, J=7.2 Hz, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 162.2, 148.8, 143.6, 123.7, 119.9, 115.8, 108.4, 42.9, 13.4. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{15}N_2O$ $[M+H]^+$ 191.1184. Found 191.1210.

*4.3.14. 2-Morpholinobenzoxazole (**3d**).*[8a] Compound **3d** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and morpholino benzoate **2d** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3d** (0.11 g, 54%) as a pale yellow solid. ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.41–7.38 (m, 1H), 7.30–7.28 (m, 1H), 7.20 (dt, *J*=7.8, 1.2 Hz, 1H), 7.06 (dt, *J*=7.8, 1.2 Hz, 1H), 3.86–3.83 (m, 4H), 3.73–3.70 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.1, 148.7, 142.7, 124.1, 120.9, 116.4, 108.8, 66.2, 45.7. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{13}N_2O_2$ $[M+H]^+$ 205.0977. Found 205.0998.

*4.3.15. 2-Thiomorpholinobenzoxazole (**3e**).*[22] Compound **3e** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and thiomorpholino benzoate **2e** (0.33 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3e** (0.10 g, 45%) as a pale yellow solid. Mp=90.5–91.4 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.27 (m, 1H), 7.19–7.17 (m, 1H), 7.10 (dt, *J*=7.8, 1.2 Hz, 1H), 6.95 (dt, *J*=7.8, 1.2 Hz, 1H), 3.94–3.89 (m, 4H), 2.68–2.64 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 161.7, 148.7, 142.9, 124.0, 120.7, 116.3, 108.7, 48.0, 26.7. IR (film): 3436, 2921, 1655, 1578, 1460, 1401, 1263, 1149, 969, 879, 796, 754, 741, 570, 425 cm^{-1}. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{13}N_2OS$ $[M+H]^+$ 221.0749. Found 221.0741.

*4.3.16. tert-Butyl 4-(benzoxazol-2-yl)piperazine-1-carboxylate (**3f**).*[8d] Compound **3f** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate **2f** (0.46 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3f** (0.15 g, 50%) as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.38 (m, 1H), 7.30–7.27 (m, 1H), 7.22–7.17 (m, 1H), 7.09–7.03 (m, 1H), 3.71–3.68 (m, 4H), 3.60–3.57 (m, 4H), 1.51 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.0, 154.6, 148.7, 142.8, 124.1, 120.9, 116.4, 108.8, 80.4, 45.4, 28.4. HRMS (ESI+, *m*/*z*) Calcd for $C_{16}H_{21}N_3O_3Na$ $[M+Na]^+$ 326.1481. Found 326.1478.

*4.3.17. N-Benzyl-N-methylbenzoxazol-2-amine (**3g**).*[8a] Compound **3g** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine **2g** (0.36 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=7:1) to afford pure compound **3g** (0.18 g, 75%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.25 (m, 7H), 7.18 (t, *J*=6.6 Hz, 1H), 7.01 (t, *J*=6.6 Hz, 1H), 4.75 (s, 2H), 3.12 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.9, 148.9, 143.5, 136.3, 128.6, 127.6, 127.5, 123.8, 120.3, 116.0, 108.6, 53.8, 35.0. HRMS (ESI+, *m*/*z*) Calcd for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.1184. Found 239.1195.

*4.3.18. N-(tert-Butyl)benzoxazol-2-amine (**3h**).*[23] Compound **3h** was prepared from benzoxazole **1** (0.12 g, 1.00 mmol, 1.00 equiv) and *O*-benzoyl-*N*-(*tert*-butyl)hydroxylamine (**2h**) (0.29 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **3h** (0.03 g, 16%) as an off-white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J*=7.5 Hz, 1H), 7.17 (d, *J*=7.5 Hz, 1H), 7.09–7.06 (m, 1H), 6.96–6.94 (m, 1H), 5.20 (br s, 1H), 1.43 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.8, 148.1, 143.2, 123.7, 120.6, 116.4, 108.5, 52.0, 29.2. HRMS (ESI+, *m*/*z*) Calcd for $C_{11}H_{14}N_2ONa$ $[M+Na]^+$ 213.1004. Found 213.1015.

*4.3.19. 5-Phenylbenzoxazole (**4c**).*[8d] Compound **4c** was prepared from 2-amino-4-phenylphenol, 90% Aldrich technical grade (1.00 g, 5.00 mmol, 1.00 equiv) and triethyl orthoformate (8.50 mL, 60.0 mmol, 12.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=3:1) to afford pure compound **4c** (0.39 g, 79%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.99 (s, 1H), 7.66–7.57 (m, 4H), 7.50–7.31 (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 152.9, 149.4, 140.7, 140.6, 138.6, 128.7, 127.5, 127.2, 125.1, 118.9, 110.8. HRMS (ESI+, *m*/*z*) Calcd for $C_{13}H_{10}NO$ $[M+H]^+$ 196.0762. Found 196.0760.

*4.3.20. 5-Nitrobenzoxazole (**4e**).*[8d] Compound **4e** was prepared from 2-amino-4-nitrophenol (0.77 g, 5.00 mmol, 1.00 equiv) and triethyl orthoformate (8.50 mL, 60.0 mmol, 12.0 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=3:1) to afford pure compound **4e** (0.42 g, 85%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.70 (d, *J*=2.4 Hz, 1H), 8.36 (dd, *J*=9.0, 2.4 Hz, 1H), 8.25 (s, 1H), 7.70 (d, *J*=9.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 155.0, 153.4, 145.4, 140.5, 121.6, 117.1, 111.2. HRMS (ESI+, *m*/*z*) Calcd for $C_7H_4N_2O_3Na$ $[M+Na]^+$ 187.0120. Found 187.0128.

*4.3.21. 6-Methyl-2-(piperidin-1-yl)benzoxazole (**5a**).*[8d] Compound **5a** was prepared from 6-methylbenzoxazole **4a** (0.13 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5a** (0.19 g, 86%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J*=7.8 Hz, 1H), 7.00 (s, 1H), 6.90 (d, *J*=7.8 Hz, 1H), 3.59 (s, 4H), 2.35 (s, 3H), 1.63 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.1, 148.6, 140.7, 130.1, 124.3, 115.1, 108.8, 46.4, 25.1, 24.0, 21.2. HRMS (ESI+, *m*/*z*) Calcd for $C_{13}H_{16}N_2ONa$ $[M+Na]^+$ 239.1160. Found 239.1162.

*4.3.22. 5-Methyl-2-(piperidin-1-yl)benzoxazole (**5b**).*[8d] Compound **5b** was prepared from 5-methylbenzoxazole **4b** (0.13 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5b** (0.16 g, 73%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.06 (s, 1H), 7.02 (d, *J*=8.1 Hz, 1H), 6.72 (d, *J*=8.1 Hz, 1H), 3.57 (s, 4H), 2.31 (s, 3H), 1.60 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.6, 146.8, 143.5, 133.4, 120.9, 116.4, 107.9, 46.6, 25.2, 24.1, 21.5. HRMS (ESI+, *m*/*z*) Calcd for $C_{13}H_{17}N_2O$ $[M+H]^+$ 217.1341. Found 239.1346.

*4.3.23. 5-Phenyl-2-(piperidin-1-yl)benzoxazole (**5c**).*[8d] Compound **5c** was prepared from 5-phenylbenzoxazole **4c** (0.20 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5c** (0.25 g, 90%) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65–7.50 (m, 3H), 7.40 (t, *J*=7.8 Hz, 2H), 7.33–7.14 (m, 3H), 3.74–3.50 (m, 4H), 1.65 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.8, 148.3, 144.0, 141.7, 137.6, 128.5, 127.2, 126.8, 119.6, 114.7, 108.4, 46.6, 25.1, 24.0. HRMS (ESI+, *m*/*z*) Calcd for $C_{18}H_{18}N_2ONa$ $[M+Na]^+$ 301.1317. Found 301.1329.

*4.3.24. 5-Chloro-2-(piperidin-1-yl)benzoxazole (**5d**).*[8d] Compound **5d** was prepared from 5-chlorobenzoxazole **4d** (0.15 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5d** (0.16 g, 66%) as a pale yellow solid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J*=2.1 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 1H), 6.94 (dd, *J*=8.4, 2.1 Hz, 1H), 3.63 (s, 4H), 1.67 (s, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 163.0, 147.3, 144.8, 129.1, 119.8, 116.0, 109.0, 46.5, 25.2, 23.9. HRMS (ESI+, *m*/*z*) Calcd for $C_{12}H_{13}ClN_2ONa$ $[M+Na]^+$ 259.0614. Found 259.0607.

*4.3.25. 5-Nitro-2-(piperidin-1-yl)benzoxazole (**5e**).*[8d] Compound **5e** was prepared from 5-nitrobenzoxazole **4e** (0.16 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol,

1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5e** (0.15 g, 61%) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J=2.1 Hz, 1H), 7.85 (dd, J=8.7, 2.1 Hz, 1H), 7.18 (d, J=8.7 Hz, 1H), 3.60 (br s, 4H), 1.63 (s, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 163.7, 152.7, 145.0, 144.4, 116.6, 111.1, 107.9, 46.6, 25.2, 23.8. HRMS (ESI+, m/z) Calcd for $C_{12}H_{13}N_3O_3Na$ $[M+Na]^+$ 270.0855. Found 270.0868.

*4.3.26. 2-Phenyl-5-(piperidin-1-yl)-1,3,4-oxadiazole (**5f**).*[8d] Compound **5f** was prepared from 2-phenyl-1,3,4-oxadiazole **4f** (0.15 g, 1.00 mmol, 1.00 equiv) and piperidin-1-yl benzoate **2a** (0.31 g, 1.50 mmol, 1.50 equiv) following the general procedure. The crude product was further purified by flash column chromatography (SiO_2, Hex/EtOAc=4:1) to afford pure compound **5f** (0.16 g, 72%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95–7.83 (m, 2H), 7.49–7.38 (m, 3H), 3.61–3.52 (m, 4H), 1.69 (br s, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 164.2, 158.9, 130.3, 128.7, 125.5, 124.7, 47.0, 24.8, 23.6. HRMS (ESI+, m/z) Calcd for $C_{13}H_{15}N_3ONa$ $[M+Na]^+$ 252.1113. Found 252.1102.

Acknowledgements

This work was financially supported by Thailand Research Fund (TRF Grant MRG5580039), Faculty of Science, Mahidol University, and Center of Excellence for Innovation in Chemistry (PERCH-CIC), Commission on Higher Education, Ministry of Education. The authors also thank Department of Chemistry and Center of Instrumental Facility (CIF) at Faculty of Science, Mahidol University for facilities.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.05.127.

References and notes

1. Selected references: (a) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140; (b) Veh, V. S. C.; Iyengar, R. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Pergamon: Oxford, UK, 2008; Vol. 4, p 487; (c) Sheng, C.; Xu, H.; Wang, W.; Cao, Y.; Dong, G.; Wang, S.; Che, X.; Ji, H.; Miao, Z.; Yao, J.; Zhang, W. *Eur. J. Med. Chem.* **2010**, *45*, 3531.
2. Selected references on natural products or biologically active molecules which contain substituted 1,3-azoles: imidazoles: (a) Gordon, T.; Hansen, P.; Morgan, B.; Singh, J.; Baizman, E.; Ward, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 915; (b) von Geldern, T. W.; Kester, J. A.; Bal, R.; Wu-Wong, J. R.; Chiou, W.; Dixon, D. B.; Opgenorth, T. J. *J. Med. Chem.* **1996**, *39*, 968; (c) Pridgen, L. N.; Mokhallalati, M. K.; McGuire, M. A. *Tetrahedron Lett.* **1997**, *38*, 1275 Thiazoles: (d) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301; (e) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1995**, *60*, 1224; (f) Cetusic, J. R. P.; Green, F. R.; Graupner, P. R.; Oliver, M. P. *Org. Lett.* **2002**, *4*, 1307 Oxazoles: (g) Kreisberg, J. D.; Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2001**, 627; (h) Nogle, L. M.; Marquez, B. L.; Gerwick, W. H. *Org. Lett.* **2003**, *5*, 3; (i) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87.
3. (a) Liu, K. G.; Lo, J. R.; Comery, T. A.; Zhang, G. M.; Zhang, J. Y.; Kowal, D. M.; Smith, D. L.; Kerns, E. H.; Schechter, L. E.; Robichaud, A. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1115; (b) O'Donnell, C. J.; Rogers, B. N.; Bronk, B. S.; Bryce, D. K.; Coe, J. W.; Cook, K. K.; Duplantier, A. J.; Evrard, E.; Hajos, M.; Hoffmann, W. E.; Hurst, R. S.; Maklad, N.; Mather, R. J.; McLean, S.; Nedza, F. M.; O'Neill, B. T.; Peng, L.; Qian, W.; Rottas, M. M.; Sands, S. B.; Scmidt, A. W.; Shrikhande, A. V.; Spracklin, D. K.; Wong, D. F.; Zhang, A.; Zhang, L. *J. Med. Chem.* **2010**, *53*, 1222.
4. (a) Whitman, D. B.; Cox, C. D.; Breslin, M. J.; Brashear, K. M.; Schreier, J. D.; Bogusky, M. J.; Bednar, R. A.; Lemaire, W.; Bruno, J. G.; Hartman, G. D.; Reiss, D. R.; Harrell, C. M.; Kraus, R. L.; Li, Y.; Garson, S. L.; Doran, S. C.; Prueksaritanont, T.; Li, C.; Winrow, C. J.; Koblan, K. S.; Renger, J. J.; Coleman, P. J. *Chem. Med. Chem.* **2009**, *4*, 1069; (b) Cox, C. D.; Breslin, M. J.; Whitman, D. B.; Schreier, J. D.; McGaughey, G. B.; Bogusky, M. J.; Roecker, A. J.; Mercer, S. P.; Bednar, R. A.; Lemaire, W.; Bruno, J. G.; Reiss, D. R.; Harrell, C. M.; Murphy, K. L.; Garson, S. L.; Doran, S. M.; Prueksaritanont, T.; Anderson, W. B.; Tang, C.; Roller, S.; Cabalu, T. D.; Cui, D.; Hartman, G. D.; Young, S. D.; Koblan, K. S.; Winrow, C. J.; Renger, J. J.; Coleman, P. J. *J. Med. Chem.* **2010**, *53*, 5320.
5. Pochetti, G.; Mitro, N.; Lavecchia, A.; Gilardi, F.; Besker, N.; Scotti, E.; Aschi, M.; Re, N.; Fracchiolla, G.; Laghezza, A.; Tortorella, P.; Montanari, R.; Novellino, E.; Mazza, F.; Crestani, M.; Loiodice, F. *J. Med. Chem.* **2010**, *53*, 4354.
6. Selected references: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805; (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534; (c) Ley, S. V.; Thomas, A. W. *Angew. Chem.* **2003**, *115*, 5558; (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
7. Selected references on transition metal-catalyzed C–H bond functionalization: (a) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282; (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790; (c) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607; (d) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178.
8. Selected references on metal-free C–H bond functionalization: (a) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. *J. Org. Lett.* **2011**, *13*, 3754; (b) Iamani, M.; Prabhu, K. R. *J. Org. Chem.* **2011**, *76*, 7938; (c) Wagh, Y. S.; Sawant, D. N.; Bhanage, B. M. *Tetrahedron Lett.* **2012**, *53*, 3482; (d) Wertz, S.; Shintaro, K.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11511.
9. Seebach, D.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15.
10. (a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947; (b) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, *21*, 4505; (c) Barker, T. J.; Jarbo, E. R. *Synthesis* **2011**, 3954.
11. Selected references: (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680; (b) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799; (c) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364; (d) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219; (e) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598; (f) Barker, T. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 8325; (g) Yan, X.; Chen, C.; Zhou, Y.; Xi, C. *Org. Lett.* **2012**, *14*, 4750; (h) Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 1947; (i) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918; (j) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005; (k) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414; (l) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3953; (m) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012**, *134*, 6571; (n) Xiao, Q.; Tian, L.; Tan, R.; Xia, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Org. Lett.* **2012**, *14*, 4230; (o) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449; (p) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521; (q) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516.
12. (a) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676; (b) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694; (c) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652; (d) Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 4196; (e) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2012**, *14*, 272; (f) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656; (g) John, A.; Nicholas, K. M. *Organometallics* **2012**, *31*, 7914.
13. (a) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900; (b) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860; (c) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Synthesis* **2012**, *44*, 1792.
14. Berman, A. M.; Johnson, J. S. *Org. Synth.* **2006**, *83*, 31 Coll. Vol. **2009**, *11*, 684.
15. See Supplementary data for more experimental detail.
16. (a) Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 463; (b) Massey, R.; Collett, C. J.; Lindsay, A. G.; Smith, A. D.; O'Donoghue, A. C. *J. Am. Chem. Soc.* **2012**, *134*, 20421.
17. Base-assisted cupration: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404; (b) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296; (c) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072; (d) Besseliévre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553.
18. (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196; (b) Srieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78; (c) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044.
19. Nemchik, A.; Badescu, V.; Phanstiel, O. I. V. *Tetrahedron* **2003**, *59*, 4315.
20. Heistand, R. H., II; Stahl, M. A.; Heine, H. W. *J. Org. Chem.* **1978**, *43*, 3613.
21. Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem.* **2009**, *121*, 9291 *Angew. Chem., Int. Ed.* **2009**, *48*, 9127.
22. Yotphan, S.; Beukeaw, D.; Reutrakul, V. *Synthesis* **2013**, *45*, 936.
23. Cioffi, C. L.; Lansing, J. J.; Yuksel, H. *J. Org. Chem.* **2010**, *75*, 7942.