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Copper-Catalyzed Electrophilic Amination of Heteroarenes via C−H Alumination

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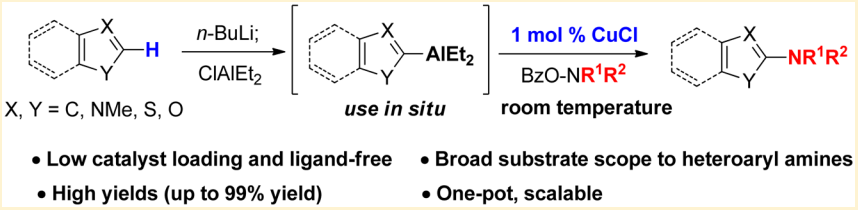
Supporting Information



ABSTRACT: A highly efficient Cu-catalyzed electrophilic amination reaction of readily available heteroarenes with *O*-benzoyl hydroxylamines via a one-pot C−H alumination is reported. The reactions were catalyzed using 1 mol % of CuCl to afford various heteroaryl amines in good to excellent yields. The direct C−H lithiation/transalumination of heteroarenes and catalytic amination sequence can be performed in a single vessel on gram scales.

INTRODUCTION

Heteroaryl amines are ubiquitous scaffolds in many natural products, biologically active molecules, and pharmaceutical targets.[1] Among the versatile synthetic approaches to form heteroaromatic C(sp^2)−N bonds, transition-metal-catalyzed amination reactions have emerged as a powerful protocol in recent decades.[2] These strategies include palladium-catalyzed Buchwald−Hartwig amination reactions[3] and copper-catalyzed Ullmann and Goldberg coupling reactions,[4] which involve heteroaryl halides, and direct oxidative C−H aminations of heteroarenes with amines in the presence of a metal catalyst and oxidants.[5] Various primary and secondary amine reagents have been used as nucleophilic nitrogen sources for these catalytic nucleophilic aminations.

An important complementary approach involves the copper-catalyzed electrophilic amination reactions of organometallic reagents with *O*-benzoyl hydroxylamines (BzO−NR_2) as an electrophilic nitrogen source.[6] In the past decade, this class of Cu catalytic systems has received great attention because of the use of low-cost and low-toxicity copper, easy handling and preparation of *O*-benzoyl hydroxylamines, and high reactivity of organocopper to electrophilic amines under mild conditions. In addition, various types of organometallic reagents based on organozinc,[7] -magnesium,[8] -boron,[9] -silicon,[10] and -aluminum[11] can be aminated with high efficiency. Despite recent advances involving Cu-catalytic C(sp^2)−N bond forming reactions with electrophilic amines, some important challenges still remain. For example, most of these methods are limited in the substrate scope to aryl amines, and the efficient synthesis of heteroaromatic amines has rarely been studied (Scheme 1). Furthermore, a practical method to prepare organometallic reagents is required; most precedents need extra manipulation and purification steps, which are derived from the metal−halogen exchange of organic halides. The use of poisonous ligands with a high catalyst loading of Cu salt is also a challenging issue. In 2014, an example of the one-pot C−H zincation/Cu-catalyzed electrophilic amination with *O*-benzoyl hydroxylamines was reported by Wang and co-workers.[12] The reaction proceeds through the direct C−H zinc metalation of heteroaromatic compounds by using Zn(tmp)$_2$ (tmp = 2,2,6,6-tetramethylpiperidine), which enabled the efficient synthesis of a range of heteroaryl amines. Nonetheless, there are compelling problems to be solved: the relatively high cost of the Zn reagent and the high catalyst loading (10 mol %). In addition, excess heteroarene substrates were required because one heteroaryl unit of diheteroaryl zinc reagents was not transferred. Very recently, Zhou and co-workers described Cu-catalyzed electrophilic amination with organoaluminum nucleophiles, affording (hetero)aryl amines in good yields (58−90%).[11] However, their limited substrate scope (aryls and heteroaryls of only thienyl and pyridyl), the use of aryl halides for the preparation of aluminum reagents, and relatively high catalyst loading (5 mol % of CuI) remained unresolved.

Herein, we demonstrate an efficient and practical route to a wide range of heteroaryl amines using the one-pot facile C(sp^2)−H alumination of heteroarenes and Cu-catalyzed electrophilic amination reactions with *O*-benzoyl hydroxylamines (eq 2 in Scheme 1). A broad range of commercially available and readily accessible heteroarenes can be directly and selectively lithiated and transmetalated with inexpensive diethylaluminum chloride to efficiently generate heteroaryl aluminum reagents, which are used *in situ* without further purification or filtration.[13] The corresponding aluminum reagents show significantly high reactivity toward electrophilic amination presumably due to high Lewis acidity of aluminums

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Scheme 1. Cu-Catalyzed C(sp^2)−N Bond Formation with *O*-Benzoyl Hydroxylamines

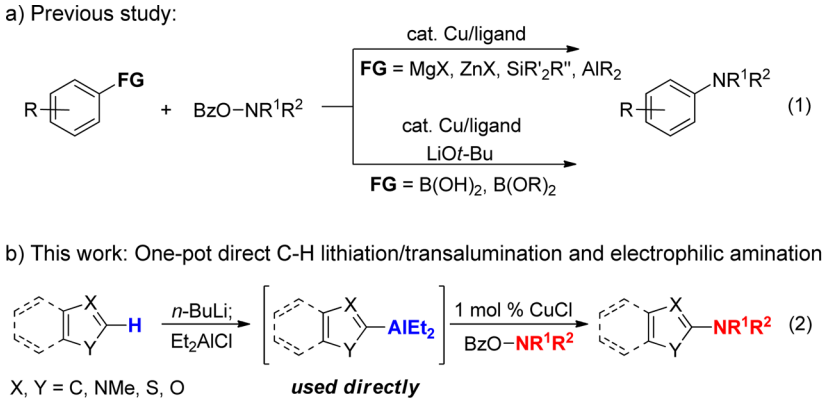
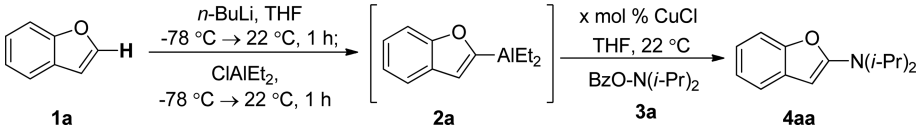


Table 1. Optimization of the Cu-Catalyzed Electrophilic Amination of Benzofuran 1a[a]



entry	Cu salts	mol % of Cu	**2a** (equiv)	time	yield (%)[b]
1	CuCl	5	1.5	10 min	95
2	CuCl	3	1.5	10 min	93
3	CuCl	1	1.5	10 min	93
4	CuCl	1	1.2	10 min	93
5	no	0	1.2	10 min	<2
6	no	0	1.2	24 h	7
7	CuI	1	1.2	10 min	79
8	CuOAc	1	1.2	10 min	73
9	CuCN	1	1.2	10 min	85
10	$Cu(OAc)_2$	1	1.2	10 min	92
11	$Cu(OTf)_2$	1	1.2	10 min	85

[a]Reactions were performed on a 0.12 mmol scale of **3a** in THF (0.3 M) under N_2. Conditions: 1.2−1.5 equiv of **2a** (**1a**/*n*-BuLi/$ClAlEt_2$ = 1:1:1.1), 1.0 equiv of $BzONR_2$ **3a** and Cu salts. [b]Determined by the ^1H NMR spectrum analysis using 1,3,5-trimethoxybenzene as an internal standard.

compared to organozincs, borons, and silicons.[11] Therefore, only 1 mol % of the CuCl catalyst was required to complete the amination at room temperature even in 10 min, which produced structurally diverse and synthetically useful heteroaryl amines including an indole, thiophene, furan, thiazole, pyrrole, or pyridine moiety with high efficiency (up to 99% yield).

RESULTS AND DISCUSSION

We selected *O*-benzoyl-*N*,*N*-diisopropylhydroxylamine **3a** and benzofuran **1a** as the model substrates to develop the reaction conditions of the copper-catalytic electrophilic amination reaction with heteroarenes (Table 1). To our delight, when benzofuran **1a** was treated with *n*-BuLi at −78 °C in tetrahydrofuran with subsequent addition of diethylaluminum chloride, the corresponding aluminum reagent **2a** was generated *in situ* and subsequently reacted with **3a** in the presence of CuCl to produce the desired heteroaryl amine **4aa**. The summarized data in Table 1 illustrate the ability of CuCl as a catalyst to promote the electrophilic amination with the aluminum reagent **2a**. With 1 mol % of CuCl, the reaction of 1.2 equiv of **2a** at room temperature proceeded to complete conversion in 10 min, affording **4aa** with 93% yield (entry 4). However, when CuCl was not used, no benzofuryl amine product **4aa** was observed in 10 min (7% yield of **4aa** after 24 h, entries 5−6). A screening of copper salts shows that CuCl represents the optimum catalyst for the amination reaction (entries 7−11). Additionally, we examined the amination of **3a** with a benzofuryl lithium reagent as an intermediate of **2a**, which was prepared from the direct C−H lithiation of **1a** with *n*-BuLi. In the case of amination with the organolithium reagent, **3a** was not converted to the desired product **4aa** even when the Cu catalyst was used in a longer reaction time (40% conversion for 24 h with <2% yield of **4aa**). These findings indicate that the combination of heteroaryl aluminums with CuCl is effective for the generation of suitable heteroaryl copper species.

Under the optimized reaction conditions, various *O*-benzoyl hydroxylamines with acyclic and cyclic *N*-alkyl substituents were applied to the Cu-catalyzed electrophilic amination with benzofuran **1a** or benzothiophene **1b** (Table 2). All transformations are rapid and highly efficient; >98% conversion was observed in 10 min−2 h with 1 mol % CuCl, which afforded the desired heteroaryl amines **4aa**−**4bd** in good to excellent yields. As shown in entries 1−5 in Table 2, *O*-benzoyl

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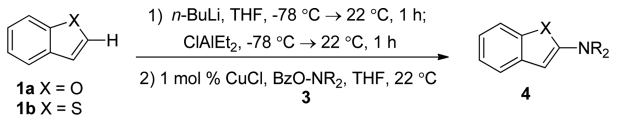
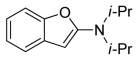
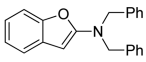
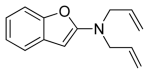
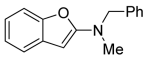
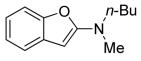
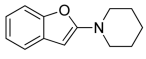
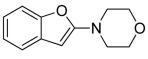
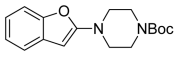
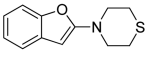
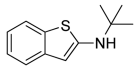
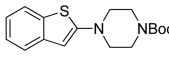
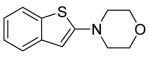
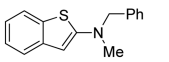
Table 2. Cu-Catalyzed Electrophilic Amination Reactions with Various *O*-Benzoyl Hydroxylamines[a]



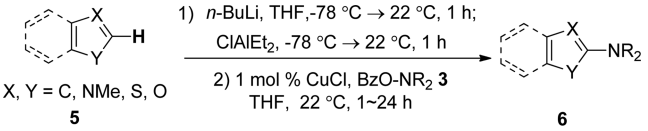
entry	product		time (h)	yield (%)[b]
1		**4aa**	10 min	88
2		**4ab**	10 min	91
3		**4ac**	30 min	92
4		**4ad**	20 min	92
5		**4ae**	15 min	63[c]
6		**4af**	10 min	78[c]
7		**4ag**	1	98
8		**4ah**	1	97
9		**4ai**	1	81
10		**4bj**	1.5	63
11		**4bh**	2	91
12		**4bg**	1.5	85
13		**4bd**	2	91

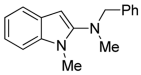
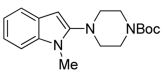
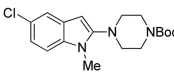
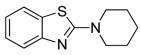
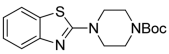
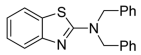
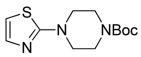
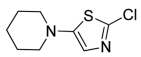
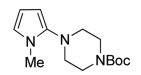
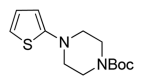
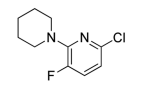
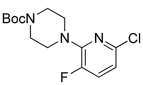
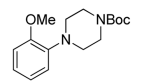
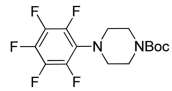
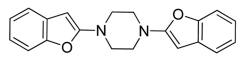
[a]Reactions typically run on a 0.4−0.5 mmol scale of **3**. Conditions: 1.2 equiv of heteroaryl-Al reagent (1.2 equiv of heteroarenes **1**, 1.2 equiv of *n*-BuLi, and 1.3 equiv of $ClAlEt_2$), CuCl (1 mol %), 1.0 equiv of $BzONR_2$ **3**, and THF (0.3 M) under N_2. [b]Yields of the isolated products. [c]Yields after acid/base workup.

hydroxylamines, which were derived from *N*,*N*-diisopropyl **3a**, *N*,*N*-dibenzyl **3b**, *N*,*N*-diallyl **3c**, *N*-benzyl-*N*-methyl **3d**, and *N*-*n*-butyl-*N*-methyl **3e** amines, were smoothly converted to resulting benzofuryl amines **4aa**−**4ae** in 63−92% yields. The six-membered cyclic amines **3f**−**3i** bearing a piperidine, morpholine, *N*-Boc-protected piperazine, and thiomorpholine moiety are compatible to the reaction conditions (78−98% yields in entries 6−9). An *O*-benzoyl hydroxylamine **3j**, which is prepared from primary *tert*-butylamine, can also be utilized in this protocol to furnish the desired compound **4bj**, albeit in lower yield (63% yield, entry 10). The low yield of **4bj** is presumably because **3j** was decomposed by the deprotonation of N−H bond on **3j** with the aluminum reagents. In addition, various benzothiophenyl-substituted amines **4bh**−**4bd** were efficiently synthesized with high yields (85−91% yield, entries 11−13). It is noteworthy that the allyl- and Boc-protecting groups are tolerated in this catalytic process, providing valuable protected amine intermediates, which can be further functionalized after deprotection.

Our new amination strategy greatly contributes to the efficient synthesis of a wide range of heteroaryl amines using readily accessible heteroarenes such as indole, thiazole, pyrrole, thiophene, and pyridine derivatives, as illustrated in Table 3. When the indole compounds **5a**−**b**, which belong to a rarely examined category of substrates for electrophilic amination, were used, the selective C−H alumination/amination reaction in the presence of 1 mol % CuCl successfully occurred within 3

Table 3. Substrate Scope of the Cu-Catalyzed Electrophilic Amination[a]



entry	product		time (h)	yield (%)[b]
1		**6ad**	1	99
2		**6ah**	3	86
3		**6bh**	3	98
4		**6cf**	6	86
5		**6ch**	24	93
6		**6cb**	24	68
7		**6dh**	20	96
8		**6ef**	24	95
9		**6fh**	6	89
10		**6gh**	24	97
11		**6hf**	1	97
12		**6hh**	1	92
13		**6ih**	0.3	87
14		**6jh**	24	85
15[c]		**6kk**	6	76

[a]Reactions typically run on 0.4−0.5 mmol scale of **3**. Conditions: 1.2 equiv of heteroaryl-Al reagent (1.2 equiv of heteroarenes **5**, 1.2 equiv of *n*-BuLi and 1.3 equiv of $ClAlEt_2$), CuCl (1 mol %), 1.0 equiv of $BzONR_2$ **3**, and THF (0.3 M) under N_2. [b]Yields of the isolated products. [c]Diamination conditions: benzofuran **1a** (1.5 mmol), *O*-benzoyl hydroxylamine **3k** (0.5 mmol), CuCl (1 mol %), THF (0.15 M).

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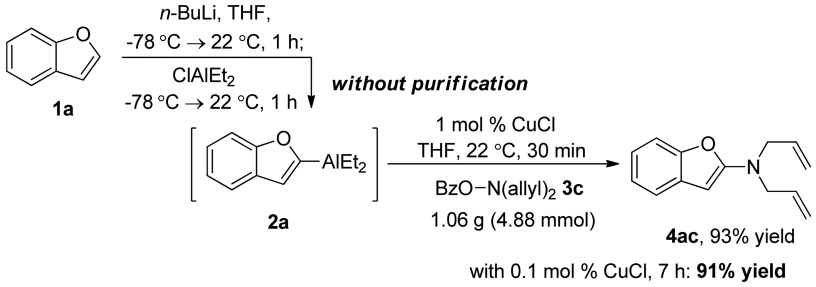
Scheme 2. Gram-Scale Synthesis of Heteroaromatic Amine 4ac



h to furnish the indole amines **6ad**−**6bh** with excellent yields (86−99%, entries 1−3). It should be noted that 5-chloroindole **5b** is compatible in this reaction and produced synthetically useful intermediate **6bh**, which can be used for Pd-catalyzed cross-coupling.[14] Benzothiazole **5c** and thiazoles **5d**−**e** were aluminated *in situ* for the subsequent reaction with *O*-benzoyl hydroxylamines in the presence of 1 mol % CuCl. The corresponding heteroaryl amines **6cf**−**6ef** were obtained in good to excellent yields, although a longer reaction time was required (6−24 h, entries 4−8). To our delight, 2-chlorothiazole **5e** can be selectively transformed to the C-5 aminated product **6ef** with a 95% yield instead of 2-amino thiazole, which is typically generated from the reaction of **5e** with a nucleophilic amine.[15] The Cu-catalyzed electrophilic aminations of pyrrole **5f** and thiophene **5g** with **3h** also smoothly occurred (entries 9−10). The presence of chloro- and fluoro-substituents on pyridine **5h** did not diminish the amination activity of **5h**, and it produced the selective C-6 aminated products **6hf** and **6hh** in 97% and 92% yields, respectively (entries 11 and 12). In addition to the Cu-catalyzed electrophilic amination with heteroarenes, we explored the functionalized arene substrates. As the data in entries 13 and 14 illustrate, the present Cu catalytic process can be used for the C−H amination of anisole **5i** and pentafluorobenzene **5j** to prepare aromatic amines **6ih** and **6jh** with high efficiency.[16] Next, the one-pot double electrophilic amination reaction of *O*-dibenzoyl hydroxylamine **3k** was evaluated. When **3k** was treated with the *in situ* generated benzofuryl aluminum reagent **2a** from 3 equiv of benzofuran **1a**, the reaction was efficiently promoted by 1 mol % of CuCl to afford the diaminated heteroaromatic compound **6kk** in 76% yield (entry 15). However, this protocol did not enable access to a benzoxazole-substituted amine (data are not shown).

The utility of this methodology is highlighted by the one-pot, gram scale synthetic procedure, as shown in Scheme 2. The direct C−H lithiation of benzofuran **1a** with *n*-BuLi and subsequent transmetalation with diethylaluminum chloride generated *in situ* aluminum reagent **2a**, which was directly treated with 1 mol % CuCl and 1.06 g of *O*-benzoyl hydroxylamine **3c** at room temperature for 30 min. The amine **4ac** was obtained in 93% yield, which was comparable to the yield of **4ac** on a smaller scale (vs 92%, entry 3 in Table 2). Even with 0.1 mol % CuCl, the reaction effectively proceeded and produced **4ac** in 91% yield. The straightforward one-pot process constitutes an important practical feature of this method.

CONCLUSIONS

In summary, the present studies introduce highly efficient and straightforward Cu-catalytic synthesis methods to obtain new versatile heteroaromatic amines such as furan, thiophene, indole, thiazole, pyrrole, and pyridine derivatives, which have been known to be inefficient in electrophilic amination. The corresponding amines were obtained through the one-pot electrophilic amination reactions using *O*-benzoyl hydroxylamines and the readily accessible heteroarenes with only 1 mol % CuCl via the direct C−H lithiation and transalumination. Further application of this methodology to other classes of C−N bond formation is in progress.

EXPERIMENTAL SECTION

General. Infrared (IR) spectra were recorded in reciprocal centimeters (cm^{-1}). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance as the internal standard ($CDCl_3$: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.26 ppm). High-resolution mass spectra (HRMS) were obtained using an electron ionization (EI) or an electrospray ionization (ESI) time-of-flight mass spectrometer. Melting points were determined using a melting point apparatus and are uncorrected. Unless otherwise noted, all reactions were carried out with distilled solvents under an atmosphere of dry N_2 in oven-dried (130 °C) glassware. Tetrahydrofuran was purified by distillation from sodium benzophenone ketyl immediately prior to use unless otherwise specified. All workup and purification procedures were carried out with reagent grade solvents in air. A variety of *N,N*-dialkyl-*O*-benzoyl hydroxylamines were prepared according to reported experimental procedures.[7]

Representative Experimental Procedures for Cu-Catalyzed Electrophilic Amination of Heteroarenes with *N,N*-Dialkyl-*O*-benzoyl Hydroxylamines via the Direct C−H Lithiation/Transalumination. General procedure A: Benzofuran **1a** (536 μL, 5.00 mmol) and THF (6 mL) were added to a 25 mL round-bottom flask under N_2 gas. The solution was allowed to cool to −78 °C (dry ice/acetone bath), and then *n*-BuLi (2.5 M in hexanes, 2.00 mL, 5.00 mmol) was added slowly via a syringe. The reaction mixture was allowed to warm to room temperature and stir for 1 h. After that time, the solution was allowed to cool to −78 °C (dry ice/acetone bath) and diethylaluminum chloride (690 μL, 5.50 mmol) was added slowly. After stirring at room temperature for 1 h, the resulting benzofuryl aluminum reagent **2a** (0.542 M) was directly used without further filtration and purification. To a solution of *tert*-butyl 4-(benzoyloxy)-piperazine-1-carboxylate (**3h**) (149 mg, 0.487 mmol) and CuCl (0.500 mg, 0.00490 mmol) in THF (0.5 mL) was added benzofuran-2-yldiethylaluminum solution **2a** (0.542 M, 1.10 mL, 0.584 mmol) slowly under N_2 gas. The reaction mixture was allowed to stir at room temperature for 1 h. After that time, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL) and then with a saturated aqueous solution of Rochelle's salt (1 mL). The resulting solution was allowed to stir vigorously for 10 min and washed with

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EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexanes = 1:5) to afford the desired *tert*-butyl 4-(benzofuran-2-yl)piperazine-1-carboxylate (**4ah**) (143 mg, 0.473 mmol, 97%) as a white solid.

General procedure B: Benzothiazole **5c** (545 μL, 5.00 mmol) and THF (9 mL) were added to a 25 mL round-bottom flask under N_2 gas. The solution was allowed to cool to −78 °C (dry ice/acetone bath) and then *n*-BuLi (2.5 M in hexanes, 2.00 mL, 5.00 mmol) was added slowly via a syringe. The mixture was allowed to stir at −78 °C for 1 h. After that time, the solution was allowed to cool to −78 °C (dry ice/acetone bath) and diethylaluminum chloride (690 μL, 5.50 mmol) was added slowly. After stirring at room temperature for 1 h, the resulting benzothiazoly aluminum reagent (0.409 M) was directly used without further filtration and purification. To a solution of *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**) (149 mg, 0.487 mmol) and CuCl (0.500 mg, 0.00490 mmol) in THF (0.2 mL) was added benzo[d]thiazol-2-yldiethylaluminum solution (0.409 M, 1.43 mL, 0.584 mmol) slowly under N_2 gas. The reaction mixture was allowed to stir at room temperature for 24 h. After that time, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL) and then with a saturated aqueous solution of Rochelle's salt (1 mL). The resulting solution was allowed to stir vigorously for 10 min and washed with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexanes = 1:3) to afford the desired *tert*-butyl 4-(benzo[d]thiazol-2-yl)piperazine-1-carboxylate (**6ch**) (145 mg, 0.454 mmol, 93%) as a greenish solid.

***N,N*-Diisopropylbenzofuran-2-amine (4aa).** Compound **4aa** was synthesized according to general procedure A using *O*-benzoyl-*N,N*-diisopropylhydroxylamine (**3a**, 0.453 mmol) as a white solid in 88% yield (86.7 mg, 0.399 mmol). This compound has been previously reported, and the spectra data match has been described.[9a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.08 (ddd, *J* = 7.6, 7.6, 0.8 Hz, 1H), 6.95 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 5.36 (s, 1H), 3.77 (hept, *J* = 6.8 Hz, 2H), 1.32 (d, *J* = 6.6 Hz, 12H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.3, 150.3, 131.2, 122.5, 119.0, 117.0, 109.2, 79.1, 48.1, 21.1.

***N,N*-Dibenzylbenzofuran-2-amine (4ab).** Compound **4ab** was synthesized according to general procedure A using *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**3b**, 0.453 mmol) as a white solid in 91% yield (129 mg, 0.411 mmol). Mp 85−87 °C; **IR** (neat): 3124 (w), 3063 (s), 3028 (s), 2920 (m), 2858 (m), 1952 (w), 1871 (w), 1809 (w), 1759 (w), 1608 (s), 1493 (s), 1365 (s), 1323 (s), 1254 (s), 1196 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34−7.23 (m, 12H), 7.11 (ddd, *J* = 7.5, 7.5, 0.8 Hz, 1H), 7.02−7.00 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 5.34 (s, 1H), 4.50 (s, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.5, 150.4, 137.3, 131.7, 128.7, 127.8, 127.4, 122.9, 119.5, 117.5, 109.5, 77.6, 52.0; **HRMS** (EI) *m*/*z*: $[M]^+$ Calcd for $C_{22}H_{19}NO$ 313.1467, Found 313.1438.

***N,N*-Diallylbenzofuran-2-amine (4ac).** Compound **4ac** was synthesized according to general procedure A using *N,N*-diallyl-*O*-benzoylhydroxylamine (**3c**, 0.427 mmol) as a yellow oil in 92% yield (83.9 mg, 0.393 mmol). **IR** (neat): 3086 (m), 3012 (m), 2928 (m), 1812 (w), 1720 (s), 1636 (s), 1454 (s), 1207 (s), 1157 (m), 995 (m), 930 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.12 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.00 (dd, *J* = 7.5, 7.5 Hz, 1H), 5.95−5.86 (m, 2H), 5.34 (s, 1H), 5.30−5.23 (m, 4H), 3.98 (d, *J* = 5.6 Hz, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.1, 150.4, 133.5, 131.6, 122.7, 119.3, 117.5, 117.4, 109.4, 77.1, 51.2; **HRMS** (EI) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{15}NO$ 213.1154, Found 213.1124.

***N*-Benzyl-*N*-methylbenzofuran-2-amine (4ad).** Compound **4ad** was synthesized according to general procedure A using *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine (**3d**, 0.500 mmol) as an orange oil in 92% yield (109 mg, 0.460 mmol). **IR** (neat): 3128 (w), 3059 (w), 3028 (w), 2928 (w), 2808 (w), 1608 (s), 1458 (s), 1246 (m), 1188 (w), 1099 (w), 1007 (w), 914 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38−7.29 (m, 7H), 7.14 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.02 (dd, *J* = 7.7, 7,7 Hz, 1H), 5.36 (s, 1H), 4.58 (s, 2H), 2.92 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.9, 150.5, 137.2, 131.5, 128.5, 127.6, 127.3, 121.6, 119.3, 117.3, 109.3, 76.5, 54.7, 36.0; **HRMS** (ESI) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{16}NO$ 238.1232, Found 238.1232.

***N*-Butyl-*N*-methylbenzofuran-2-amine (4ae).** Compound **4ae** was synthesized according to general procedure A using *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine (**3e**, 0.500 mmol). The resulting reaction product was purified by acid/base workup. The crude product was diluted with Et_2O (1 mL) and acidified with 1 N HCl (3 × 1 mL). The aqueous layers were combined, basified with 1 N NaOH (3 mL), and washed with Et_2O (3 × 3 mL). Then the organic layers were combined, dried over $MgSO_4$, and concentrated to afford a yellow oil in 63% yield (64.0 mg, 0.315 mmol). **IR** (neat): 3128 (w), 3055 (w), 2958 (s), 2931 (s), 2870 (m), 1608 (s), 1461 (s), 1423 (m), 1373 (m), 1246 (s), 1011 (m), 906 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.13 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 8.0 Hz, 1H), 5.27 (s, 1H), 3.37 (t, *J* = 7.3 Hz, 2H), 2.98 (s, 3H), 1.67−1.60 (m, 2H), 1.45−1.36 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.3, 150.6, 131.8, 122.6, 119.0, 117.1, 109.2, 76.0, 50.9, 36.2, 29.1, 20.0, 13.8; **HRMS** (EI) *m*/*z*: $[M]^+$ Calcd for $C_{13}H_{17}NO$ 203.1310, Found 203.1318.

1-(Benzofuran-2-yl)piperidine (4af). Compound **4af** was synthesized according to general procedure A using piperidin-1-yl benzoate (**3f**, 0.488 mmol). The resulting reaction product was purified by acid/base workup. The crude product was diluted with Et_2O (1 mL) and acidified with 1 N HCl (3 × 1 mL). The aqueous layers were combined, basified with 1 N NaOH (3 mL), and washed with Et_2O (3 × 3 mL). Then the organic layers were combined, dried over $MgSO_4$, and concentrated to afford a pale yellow solid in 78% yield (76.7 mg, 0.381 mmol). This compound has been previously reported, and spectra data match has been described.[10b] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.10 (ddd, *J* = 8.0, 8.0, 0.9 Hz 1H), 7.01−6.97 (m, 1H), 5.4 (s, 1H), 3.27 (dd, *J* = 5.5, 5.5 Hz, 4H), 1.72−1.67 (m, 4H), 1.63−1.59 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.9, 150.7, 131.1, 122.6, 119.9, 117.8, 109.5, 78.8, 48.2, 24.8, 24.1.

4-(Benzofuran-2-yl)morpholine (4ag). Compound **4ag** was synthesized according to general procedure A using *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine (**3g**, 0.487 mmol) as a white solid in 98% yield (96.5 mg, 0.475 mmol). This compound has been previously reported, and spectra data match has been described.[12a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.13 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.05 (dd, *J* = 7.5, 7.5 Hz, 1H), 5.48 (s, 1H), 3.87 (t, *J* = 4.8 Hz, 4H), 3.30 (t, *J* = 4.8 Hz, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 161.4, 151.2, 130.8, 123.1, 121.0, 118.7, 110.0, 80.0, 66.4, 47.7.

***tert*-Butyl 4-(Benzofuran-2-yl)piperazine-1-carboxylate (4ah).** Compound **4ah** was synthesized according to general procedure A using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a white solid in 97% yield (143 mg, 0.473 mmol). Mp 93 °C; **IR** (neat): 3124 (w), 3059 (w), 2978 (m), 2928 (m), 2862 (m), 1697 (s), 1601 (s), 1458 (s), 1419 (s), 1250 (s), 1169 (s), 1126 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.13 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.05 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.48 (s, 1H), 3.60 (dd, *J* = 5.1, 5.1 Hz, 4H), 3.26 (dd, *J* = 5.1, 5.1 Hz, 4H), 1.51 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.8, 154.6, 150.8, 130.4, 122.8, 120.6, 118.3, 109.6, 80.1, 80.0, 47.1, 43.2, 28.3; **HRMS** (EI) *m*/*z*: $[M]^+$ Calcd for $C_{17}H_{22}N_2O_3$ 302.1630, Found 302.1628.

4-(Benzofuran-2-yl)thiomorpholine (4ai). Compound **4ai** was synthesized according to general procedure A using thiomorpholino benzoate (**3i**, 0.500 mmol) as a white solid in 81% yield (88.8 mg, 0.405 mmol). Mp 91 °C; **IR** (neat): 3117 (w), 3055 (w), 2951 (w), 2908 (m), 2854 (m), 1604 (s), 1462 (s), 1389 (m), 1288 (m), 1261 (m), 1199 (m), 1176 (m), 976 (m), 949 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.12 (dd, *J* = 7.5, 7,5 Hz, 1H), 7.03 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.44 (s, 1H), 3.67 (dd, *J* = 5.1, 5.1 Hz, 4H), 2.76 (dd, *J* = 5.1, 5.1 Hz, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.4, 150.7, 130.7, 122.8, 120.4, 118.1, 109.6, 79.6, 49.4, 26.1; **HRMS** (EI) *m*/*z*: $[M]^+$ Calcd for $C_{12}H_{13}NOS$ 219.0718, Found 219.0715.

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***N*-(*tert*-Butyl)benzo[b]thiophen-2-amine (4bj).** Compound **4bj** was synthesized according to general procedure A using *O*-benzoyl-*N*-(*tert*-butyl)hydroxylamine (**3j**, 0.534 mmol) as a yellowish oil in 63% yield (69.2 mg, 0.337 mmol). **IR** (neat): 3387 (br), 3063 (w), 2970 (s), 1713 (w), 1566 (s), 1539 (s), 1443 (s), 1365 (s), 1215 (s), 1068 (w), 1018 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.60 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.26 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.12 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 6.33 (s, 1H), 3.84 (brs, 1H), 1.38 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 150.9, 140.1, 133.5, 124.3, 121.5, 121.4, 120.8, 104.3, 53.2, 29.4; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{15}NS$ 205.0925, Found 205.0926.

***tert*-Butyl 4-(benzo[b]thiophen-2-yl)piperazine-1-carboxylate (4bh).** Compound **4bh** was synthesized according to general procedure A using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a slightly pink solid in 91% yield (141 mg, 0.444 mmol). Mp 106−107 °C; **IR** (neat): 2978 (w), 2854 (w), 1697 (s), 1535 (m), 1423 (m), 1365 (w), 1250 (m), 1173 (m), 1126 (m), 999 (w), 825 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.25 (dd, J = 8.1, 8.1 Hz, 1H), 7.12 (ddd, J = 7.8, 7.8, 0.9 Hz, 1H), 6.24 (s, 1H), 3.61 (t, J = 5.2 Hz, 4H), 3.23 (t, J = 5.0 Hz, 4H), 1.50 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 157.5, 154.6, 140.4, 132.9, 124.6, 121.7, 121.6, 121.1, 100.2, 80.2, 50.8, 42.4, 28.3; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{22}N_2O_2S$ 318.1402, Found 318.1414.

4-(Benzo[b]thiophen-2-yl)morpholine (4bg). Compound **4bg** was synthesized according to general procedure A using using *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine (**3g**, 0.487 mmol) as a white solid in 85% yield (90.5 mg, 0.413 mmol). This compound has been previously reported, and spectra data match has been described.[12a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.26 (ddd, J = 8.1, 8.1, 1.0 Hz, 1H), 7.12 (ddd, J = 7.6, 7.6, 1.2 Hz 1H), 6.24 (s, 1H), 3.88 (t, J = 4.9 Hz, 4H), 3.26 (t, J = 4.9 Hz, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 157.8, 140.4, 132.7, 124.6, 121.7, 121.6, 121.1, 99.5, 66.3, 50.9.

***N*-Benzyl-*N*-methylbenzo[b]thiophen-2-amine (4bd).** Compound **4bd** was synthesized according to general procedure A using *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine (**3d**, 0.500 mmol) as a slightly pink solid in 91% yield (116 mg, 0.456 mmol). Mp 179−180 °C; **IR** (neat): 3063 (w), 3028 (w), 2885 (w), 2804 (w), 1952 (w), 1890 (s), 1809 (w), 1774 (w), 1543 (s), 1454 (s), 1419 (s), 1362 (m), 1304 (m), 1065 (m), 1018 (w), 926 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59 (d, J = 7.3 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.37−7.32 (m, 5H), 7.23 (dd, J = 7.8, 7.8 Hz, 1H), 7.05 (dd, J = 7.6, 7.6 Hz, 1H), 6.03 (s, 1H), 4.54 (s, 2H), 3.00 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 157.2, 141.6, 137.3, 132.1, 128.9, 127.5, 127.5, 124.6, 121.4, 120.4, 120.1, 96.4, 59.2, 39.5; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{15}NS$ 253.0925, Found 253.0925.

***N*-Benzyl-*N*,1-dimethyl-1*H*-indol-2-amine (6ad).** Compound **6ad** was synthesized according to general procedure A using *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine (**3d**, 0.420 mmol) as a slightly pink solid in 99% yield (105 mg, 0.419 mmol). Mp 45−46 °C; **IR** (neat): 3055 (w), 3028 (w), 2951 (w), 2839 (w), 2796 (w), 1551 (s), 1469 (s), 1335 (m), 1311 (m), 1092 (m), 1011 (w), 949 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.8 Hz, 1H), 7.47−7.41 (m, 4H), 7.38−7.35 (m, 1H), 7.32−7.30 (m, 1H), 7.22 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H), 7.16 (ddd, J = 7.3, 7.3, 1.0 Hz, 1H), 6.04 (d, J = 0.8 Hz, 1H), 4.21 (s, 2H), 3.75 (s, 3H), 2.76 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 151.0, 137.8, 135.4, 128.5, 128.4, 127.7, 127.4, 120.1, 119.5, 119.2, 108.7, 87.7, 60.8, 41.1, 29.2; **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{19}N_2$ 251.1548, Found 251.1543.

***tert*-Butyl 4-(1-Methyl-1*H*-indol-2-yl)piperazine-1-carboxylate (6ah).** Compound **6ah** was synthesized according to general procedure A using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.426 mmol) as a white solid in 86% yield (115 mg, 0.366 mmol). Mp 142 °C; **IR** (neat): 3055 (w), 2978 (m), 2928 (w), 2862 (w), 2827 (w), 1697 (s), 1551 (m), 1473 (m), 1423 (m), 1365 (m), 1250 (s), 1173 (s), 1130 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 7.5, 1H), 7.20 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.13 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.98 (s, 1H), 3.68−3.67 (m, 7H), 3.02 (t, J = 4.9, 4H), 1.57 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 154.8, 149.8, 135.2, 127.4, 120.4, 119.6, 119.4, 108.7, 87.1, 79.9, 52.2, 43.2, 28.7, 28.3; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{25}N_3O_2$ 315.1947, Found 315.1938.

***tert*-Butyl 4-(5-Chloro-1-methyl-1*H*-indol-2-yl)piperazine-1-carboxylate (6bh).** Compound **6bh** was synthesized according to general procedure A using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a slightly yellow solid in 98% yield (167 mg, 0.476 mmol). Mp 132−133 °C; **IR** (neat): 2978 (m), 2924 (w), 2858 (w), 1697 (s), 1547 (s), 1473 (s), 1423 (s), 1250 (s), 1173 (s), 1130 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (m, 1H), 7.14−7.07 (m, 2H), 5.86 (s, 1H), 3.64−3.61 (m, 4H), 3.61 (s, 3H), 2.97 (t, J = 5.1 Hz, 4H), 1.50 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 154.8, 151.0, 133.8, 128.6, 125.3, 120.5, 118.8, 109.7, 87.0, 80.1, 52.2, 43.2, 29.2, 28.4; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{24}ClN_3O_2$ 349.1557, Found 349.1562.

2-(Piperidin-1-yl)benzo[d]thiazole (6cf). Compound **6cf** was synthesized according to general procedure B using piperidin-1-yl benzoate (**3f**, 0.488 mmol) as a green solid in 86% yield (91.8 mg, 0.420 mmol). This compound has been previously reported, and spectra data match has been described.[17] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.25 (dd, J = 8.0, 8.0 Hz, 1H), 7.02 (dd, J = 8.0 Hz, 1H), 3.56 (m, 4H), 1.65 (brs, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 168.9, 153.0, 130.6, 125.8, 121.0, 120.5, 118.7, 49.5, 25.1, 24.1.

***tert*-Butyl 4-(Benzo[d]thiazol-2-yl)piperazine-1-carboxylate (6ch).** Compound **6ch** was synthesized according to general procedure B using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a greenish solid in 93% yield (145 mg, 0.454 mmol). This compound has been previously reported, and spectra data match has been described.[12a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.33−7.27 (m, 1H), 7.10 (dd, J = 8.0, 8.0 Hz, 1H), 3.56 (d, J = 6.4 Hz, 8H), 1.45 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 168.7, 154.6, 152.6, 130.7, 126.1, 121.7, 120.7, 119.3, 80.3, 48.1, 42.9, 28.3.

***N*,*N*-Dibenzylbenzo[d]thiazol-2-amine (6cb).** Compound **6cb** was synthesized according to general procedure B using *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**3b**, 0.453 mmol) as a yellowish solid in 68% yield (101 mg, 0.307 mmol). Mp 119−120 °C; **IR** (neat): 3055 (w), 2984 (w), 1539 (m), 1442 (m), 1267 (s), 1207 (w), 893 (w), 733 (s), 703 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63−7.60 (m, 2H), 7.37−7.30 (m, 11H), 7.11 (dd, J = 7.5, 7.5 Hz, 1H), 4.76 (s, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 169.2, 153.1, 136.3, 131.1, 128.8, 127.8, 127.8, 126.1, 121.3, 120.7, 119.0, 53.2; **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}N_2S$ 331.1269, Found 331.1266.

***tert*-Butyl 4-(Thiazol-2-yl)piperazine-1-carboxylate (6dh).** Compound **6dh** was synthesized according to general procedure B using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a slightly yellow solid in 96% yield (126 mg, 0.469 mmol). Mp 111−113 °C; **IR** (neat): 2974 (w), 2931 (w), 2858 (w), 1697 (s), 1520 (m), 1419 (m), 1365 (w), 1234 (s), 1169 (s), 1138 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.21 (d, J = 3.6 Hz, 1H), 6.60 (d, J = 3.6 Hz, 1H), 3.56−3.54 (m, 4H), 3.48−3.45 (m, 4H), 1.47 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 172.2, 154.7, 139.6, 107.8, 80.2, 48.4, 42.7, 28.3; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{19}N_3O_2S$ 269.1198, Found 269.1199.

2-Chloro-5-(piperidin-1-yl)thiazole (6ef). Compound **6ef** was synthesized according to general procedure B using piperidin-1-yl benzoate (**3f**, 0.488 mmol) as slightly yellow solid in 95% yield (93.9 mg, 0.463 mmol). Mp 37−38 °C; **IR** (neat): 2939 (w), 2858 (w), 2820 (w), 1527 (w), 1450 (w), 1385 (w), 1238 (w), 1034 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.64 (s, 1H), 3.04 (t, J = 5.3 Hz, 4H), 1.73−1.67 (m, 4H), 1.60−1.54 (m, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 156.9, 138.3, 119.9, 53.2, 25.0, 23.4; **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_8H_{12}ClN_2S$ 203.0410, Found 203.0408.

***tert*-Butyl 4-(1-Methyl-1*H*-pyrrol-2-yl)piperazine-1-carboxylate (6fh).** Compound **6fh** was synthesized according to general procedure A using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a slightly yellow solid in 89% yield (115 mg, 0.434 mmol). Mp 62−63 °C; **IR** (neat): 3055 (w), 2974 (w), 2923 (w), 2854 (w), 1697 (s), 1551 (m), 1462 (m), 1419 (m), 1365 (m),

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J. Org. Chem. 2015, 80, 10244−10251

1250 (s), 1173 (s), 1126 (m), 999 (w), 768 (w), 744 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.41−6.40 (m, 1H), 6.04 (dd, J = 3.4, 3.4 Hz, 1H), 5.68−5.67 (m, 1H), 3.54 (t, J = 4.9 Hz, 4H), 3.51 (s, 3H), 2.82 (t, J = 4.9 Hz, 4H), 1.49 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 154.8, 142.8, 117.1, 105.9, 94.9, 79.7, 53.0, 43.4, 31.7, 28.3; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{14}H_{23}N_3O_2$ 265.1790, Found 265.1777.

***tert*-Butyl 4-(Thiophen-2-yl)piperazine-1-carboxylate (6gh).** Compound **6gh** was synthesized according to general procedure A using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a white solid in 97% yield (127 mg, 0.474 mmol). Mp 51−53 °C; **IR** (neat): 2974 (w), 2823 (w), 1697 (s), 1531 (m), 1419 (m), 1365 (w), 1246 (m), 1169 (m), 1126 (w), 833 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.80 (dd, J = 5.4, 5.4 Hz, 1H), 6.66 (d, J = 5.4 Hz, 1H), 6.18 (d, J = 5.4 Hz, 1H), 3.58 (t, J = 5.0 Hz, 4H), 3.10 (t, J = 4.7 Hz, 4H), 1.48 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 159.1, 154.6, 126.0, 113.1, 106.4, 79.9, 51.7, 43.3, 28.3; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{13}H_{20}N_2O_2S$ 268.1245, Found 268.1233.

6-Chloro-3-fluoro-2-(piperidin-1-yl)pyridine (6hf). Compound **6hf** was synthesized according to general procedure B using piperidin-1-yl benzoate (**3f**, 0.488 mmol) as a colorless oil in 97% yield (101 mg, 0.471 mmol). **IR** (neat): 2939 (m), 2854 (w), 1597 (s), 1493 (s), 1450 (w), 1385 (w), 1250 (m), 1223 (m), 1099 (w), 953 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 (d, J = 6.8 Hz, 1H), 6.69 (d, J = 6.8 Hz, 1H), 3.27 (t, J = 5.1 Hz, 4H), 1.72−1.64 (m, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 151.9, 149.5, 147.5 (d, J = 6.6 Hz), 147.2 (d, J = 2.5 Hz), 136.9 (d, J = 28.1 Hz), 111.5 (d, J = 2.5 Hz), 49.8 (d, J = 5.8 Hz), 25.4, 24.0; **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{13}ClFN_2$ 215.0751, Found 215.0748.

***tert*-Butyl-4-(6-chloro-3-fluoropyridin-2-yl)piperazine-1-carboxylate (6hh).** Compound **6hh** was synthesized according to general procedure B using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a white solid in 92% yield (142 mg, 0.450 mmol). Mp 121−122 °C; **IR** (neat): 2978 (w), 2931 (w), 2862 (w), 1697 (s), 1597 (s), 1493 (m), 1419 (m), 1246 (s), 1169 (s), 1126 (m), 953 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (d, J = 6.6 Hz, 1H), 6.72 (d, J = 6.6 Hz, 1H), 3.58 (t, J = 4.9 Hz, 4H), 3.27 (t, J = 4.9 Hz, 4H), 1.48 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 154.6, 152.0, 149.5, 147.4 (d, J = 2.5 Hz), 147.0 (d, J = 6.6 Hz), 137.2 (d, J = 28.1 Hz), 111.8 (d, J = 2.5 Hz), 80.3, 48.4 (d, J = 5.8 Hz), 43.4, 28.3; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{14}H_{19}ClFN_3O_2$ 315.1150, Found 315.1122.

***tert*-Butyl 4-(2-Methoxyphenyl)piperazine-1-carboxylate (6ih).** Compound **6ih** was synthesized according to general procedure A using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a white solid in 87% yield (124 mg, 0.425 mmol). Mp 68−69 °C; **IR** (neat): 3063 (w), 2974 (s), 2927 (m), 2862 (m), 2816 (m), 1687 (s), 1593 (m), 1501 (s), 1458 (s), 1419 (s), 1365 (m), 1242 (s), 1173 (s), 1122 (s), 1030 (s), 1003 (m), 922 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.06−7.01 (m, 1H), 6.96−6.88 (m, 3H), 3.88 (s, 3H), 3.62 (t, J = 4.6 Hz, 4H), 3.01 (brs, 4H), 1.49 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 154.8, 152.3, 141.1, 123.3, 121.0, 118.3, 111.2, 79.6, 55.3, 50.6, 43.3, 28.3. **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{25}N_2O_3$ 293.1865, Found 293.1861.

***tert*-Butyl 4-(Perfluorophenyl)piperazine-1-carboxylate (6jh).** Compound **6jh** was synthesized according to general procedure B using *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (**3h**, 0.487 mmol) as a white solid in 85% yield (145 mg, 0.412 mmol). Mp 96−98 °C; **IR** (neat): 2997 (w), 2928 (w), 2901 (w), 2862 (w), 1678 (s), 1520 (m), 1504 (m), 1431 (m), 1261 (m), 1176 (m), 1130 (w), 991 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.55 (t, J = 5.1 Hz, 4H), 3.14 (brs, 4H), 1.49 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 154.7, 143.5 (dm, J = 248.8 Hz), 138.1 (dm, J = 249.2 Hz), 137.5 (dm, J = 248.3 Hz), 125.9 (tt, J = 12, 4.2 Hz) 80.0, 50.9, 44.2, 28.3; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{17}F_5N_2O_2$ 352.1210, Found 352.1204.

1,4-Di(benzofuran-2-yl)piperazine (6kk). Compound **6kk** was synthesized according to general procedure A using piperazine-1,4-diyl dibenzoate (**3k**, 0.487 mmol) as a slightly yellow solid in 76% yield (118 mg, 0.372 mmol). Mp 203−204 °C; **IR** (neat): 2854 (w), 1601 (m), 1454 (w), 1381 (w), 1338 (w), 1257 (w), 1207 (w), 1153 (w), 1041 (w), 972 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H) 7.15 (ddd, J = 8.0, 8.0, 0.9 Hz, 2H), 7.09−7.05 (m, 2H), 5.55 (d, J = 0.7 Hz, 2H), 3.48 (s, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.5, 150.6, 130.1, 122.6, 120.5, 119.4, 118.1, 80.1, 46.2; **HRMS** (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{18}N_2O_2$ 318.1368, Found 318.1364.

Experimental Procedure for the Synthesis of Piperazine-1,4-diyl Dibenzoate (3k):[7] Benzoyl peroxide (1.00 g, 4.13 mmol), K_2HPO_4 (982 mg, 5.64 mmol), piperazine (162 mg, 1.88 mmol), and DMF (10 mL) were added to a 25 mL round-bottom flask under N_2 gas. The reaction mixture was allowed to stir at room temperature for 7 h. After that time, the solution was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL), diluted with water (5 mL), and washed with EtOAc (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. After purification of the crude product by triturating with Et_2O, the desired white powder product was obtained (239 mg, 0.734 mmol, 39%). Mp 143−144 °C; **IR** (neat): 3066 (w), 2982 (w), 2862 (m), 1740 (s), 1501 (w), 1454 (m), 1261 (s), 1180 (w), 1088 (m), 1045 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (brs, 4H), 7.60 (dd, J = 7.4, 7.3 Hz, 2H), 7.47 (dd, J = 7.6, 7.5 Hz, 4H), 3.49 (brs, 6H), 3.29 (brs, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 164.4, 133.2, 129.3, 128.4, 54.2, 52.5; **HRMS** (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}N_2O_4$ 326.1267, Found 326.1255.

One-Pot, Gram Scale Cu-Catalyzed Electrophilic Amination Reaction. Benzofuran **1a** (632 μL, 5.86 mmol) and THF (7 mL) were added to a 25 mL round-bottom flask under N_2 gas. Then, *n*-BuLi (2.5 M in hexane, 2.30 mL, 5.86 mmol) was added slowly at −78 °C (dry ice/acetone bath). The reaction solution was allowed to warm to room temperature and stir for 1 h and then cooled to −78 °C (dry ice/acetone bath) again. Diethylaluminum chloride (0.810 mL, 6.45 mmol) was added slowly to the solution, which was allowed to stir at room temperature for 1 h. Afterward, copper chloride (4.80 mg, 0.0488 mmol) was added at 0 °C, followed by addition of *N,N*-diallyl-*O*-benzoyl hydroxylamine **3c** (1.06 g, 4.88 mmol) and THF (7 mL). The reaction mixture was allowed to stir at room temperature for 30 min. After that time, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (7 mL) and washed with EtOAc (3 × 7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexanes = 1:10) to afford the desired product *N,N*-diallylbenzofuran-2-amine **4ac** as a colorless oil (971 mg, 4.55 mmol, 93% yield).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01863.

^{1}H NMR and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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