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Copper-Catalyzed Domino Annulation Approaches to the Synthesis of Benzoxazoles under Microwave-Accelerated and Conventional Thermal Conditions

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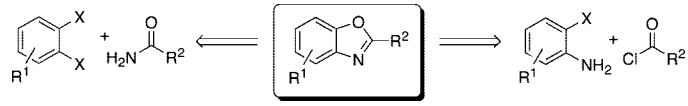

Two domino annulation approaches for benzoxazole synthesis have been developed. In the first approach, copper-catalyzed intermolecular cross-coupling of 1,2-dihaloarenes with primary amides initially forms the Ar−N bond of the benzoxazole ring, followed by copper-catalyzed intramolecular cyclization to form the Ar−O bond. Benzoxazoles were formed in good yields for the reaction of 1,2-dibromobenzene, but the reaction was not regioselective for the reaction of 3,4-dibromotoluene. Furthermore, the method is limited by the availability of 1,2-dihaloarenes. As a result of these limitations, an alternative more versatile one-pot domino annulation strategy was developed involving reaction of 2-bromoanilines with acyl chlorides in the presence of Cs_2CO_3, catalytic CuI, and the non-acylatable ligand 1,10-phenanthroline. Under these conditions initial acylation of the aniline is followed by copper-catalyzed intramolecular cyclization of the resultant 2-haloanilide to form the Ar−O bond of the benzoxazole ring. Optimized conditions using microwave irradiation achieved much shorter reaction times than conventional heating (i.e., 210 °C for 15 min versus 95 °C for 24 h) and were applied to the synthesis of a small library of benzoxazoles. These copper-catalyzed approaches complement existing strategies for benzoxazole synthesis, which typically utilize 2-aminopheonls as precursors.

Introduction

Benzoxazoles are an important class of heterocycles that are encountered in a number of natural products and are used in drug and agrochemical discovery programs, as well as for a variety of other purposes (Figure 1). For example, the benzoxazole core structure is found in a variety of cytotoxic natural products, such as the antimycobacterial pseudopteroxazole,[1] UK-1,[2] AJI9561,[3] and salvianen.[4] Recent medicinal chemistry applications[5] of benzoxazoles include the cathepsin S inhibitor **1**,[6] 5-HT_3 receptor agonist **2**,[7] HIV reverse transcriptase inhibitor L-697,661,[8] estrogen receptor-β agonist ERB-041,[9] selective peroxisome proliferator-activated receptor γ antagonist JTP-426467,[10] anticancer agent NSC-693638,[11] and orexin-1 receptor antagonist SB-334867.[12] Other applications of benzoxazoles include their use as herbicides, such as Fenoxaprop, and as fluorescent whitening agent dyes such as bisbenzoxazolyl ethylenes and arenes (e.g., **3**).[13]

Classical methods for the synthesis of benzoxazoles **4** involve the formation of the O1−C2 and N3−C2 bonds, via the

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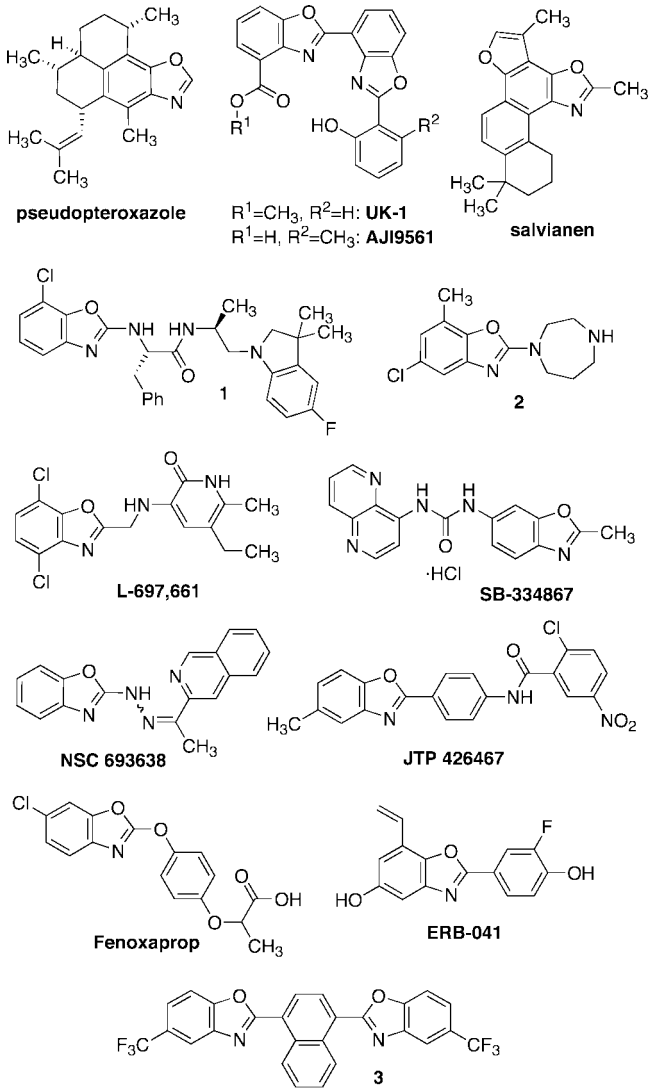

FIGURE 1. Benzoxazole natural products and medicinal/agrochemical applications of benzoxazoles.

condensation of a 2-aminophenol **5** with either a carboxylic acid derivative under strong acid/high temperature conditions or an aldehyde, followed by oxidation (Figure 2a and b).[14] Such reactions have also been applied in automated sequential synthesis, such as Player's report of the microwave-accelerated coupling of 2-aminophenols with acyl chlorides (210 °C for 15 min).[15] In the interest of broadening the scope of starting materials that can be elaborated into benzoxazoles **4** under milder conditions, we have recently reported a method in which the O1−C7a bond of **4** is formed via an intramolecular copper-catalyzed cross-coupling reaction[16–18] of a 2-haloanilide precursor **6** (Figure 2c), making the ultimate disconnection to a 2-haloaniline rather than to a 2-aminophenol.[19] Similar copper- and palladium-catalyzed approaches have also been applied to the synthesis of benzothiazoles[20] and benzimidazoles.[21]

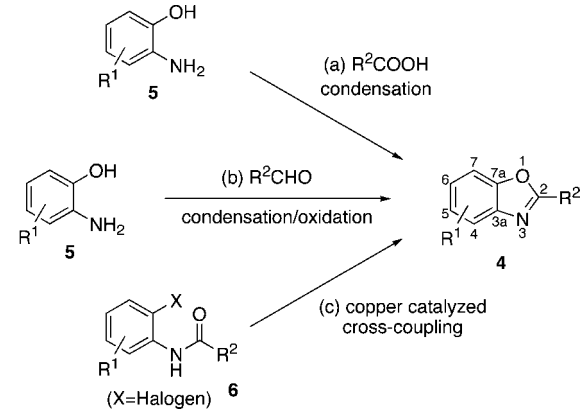

FIGURE 2. (a,b) Classical reactions for benzoxazole synthesis from 2-aminophenols **5**. (c) Intramolecular cross-coupling-based route to benzoxazoles from 2-haloanilides **6**.

In the present study, we disclose the results of our efforts to extend this strategy into domino[22,23] single-pot processes in which a 2-haloanilide intermediate **6** is formed in situ via either a copper-catalyzed cross-coupling (method A) or acylation (method B) and subsequently undergoes copper-catalyzed intramolecular cyclization, resulting in an overall benzoxazole annulation procedure (Figure 3).[24] In method A, the N3−C3a bond of the benzoxazole ring is formed via intermolecular copper-catalyzed cross-coupling between a 1,2-dihaloarene **7** and a primary amide **8**, whereas in method B, the N3−C2 bond of the benzoxazole ring is first formed via intermolecular

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(22) For a review of domino reactions, see: Tietze, L F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

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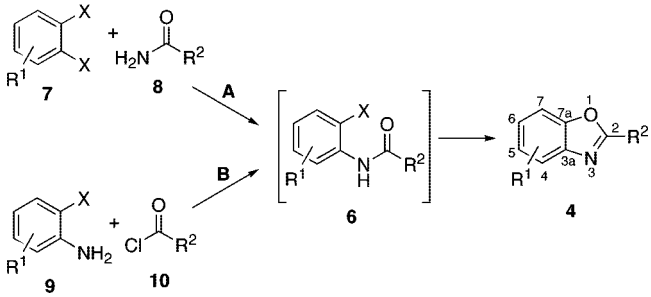


FIGURE 3. Domino approaches to the synthesis of benzoxazoles **4** via *o*-haloanilides **6**. Method A: intermolecular copper-catalyzed C−N cross-coupling, followed by intramolecular copper-catalyzed C−O cross-coupling. Method B: intermolecular N-acylation, followed by intramolecular copper-catalyzed C−O cross-coupling.

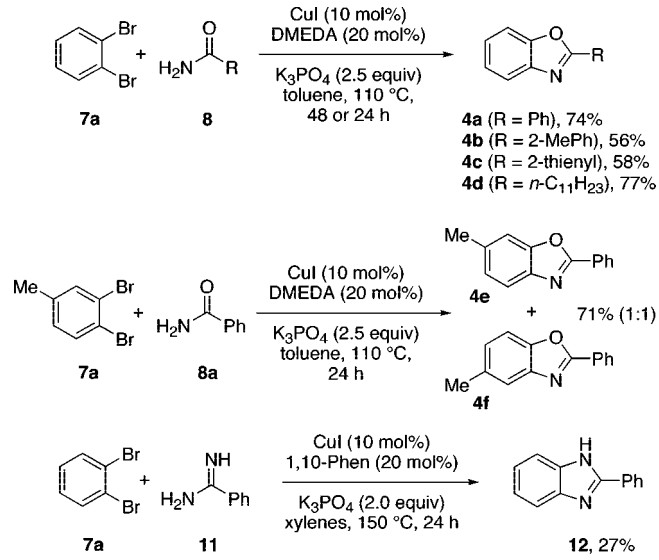
acylation of a 2-haloaniline **9** by an acyl chloride **10**. In either case, the reactions are carried out in the presence of the necessary reagents to effect the subsequent formation of the benzoxazole O1−C7a bond, converting the intermediate haloanilide **6** into benzoxazole **4** in a domino process. We also report the results of our efforts to accelerate the reactions using microwave heating and the generation of a library of benzoxazoles using automated sequential synthesis techniques.

Results and Discussion

We first focused our attention on a domino cross-coupling reaction between 1,2-dibromoarenes and primary amides (method A, Figure 3). Here the initial bond-forming event occurs by intermolecular copper-catalyzed cross-coupling to give the N3−C3a bond of the benzoxazole ring, requiring a 1,2-dihaloarene **7** and a primary amide **8** as precursors. We optimized the reaction of 1,2-dibromobenzene **7a** with benzamide **8a** only to arrive at a set of conditions that were very similar to those published by Glorius soon after we began this work (Scheme 1).[25,26] Our studies in this area did identify some important limitations to this strategy. Although Glorius reported good regioselectivity in the domino cross-coupling of primary amides with 1,2-bromochloroarenes (in every case, the carbon bearing the bromine was substituted with nitrogen in the product),[25] we found that, unsurprisingly, regioselective transformations of unsymmetrically substituted 1,2-dibromoarenes were not possible. For example, reaction of 1,2-dibromo-4-methylbenzene **7b** afforded products **4e** and **4f** in 71% combined isolated yield as an inseparable 1:1 mixture. Similar conditions applied to the annulation reaction using benzamidine **11** led to the formation of benzimidazole **12** in low yield.

In addition to the problems outlined above, there are only a few commercially available 1,2-dihaloarenes, and methods for their synthesis are neither particularly efficient nor direct.[27] Therefore, we decided to investigate a more versatile route involving a one-pot domino acylation/cross-coupling approach

SCHEME 1. Synthesis of Benzoxazoles 4 and 2-Phenylbenzimidazole 12 via Domino Intermolecular/Intramolecular Cross-Coupling



to benzoxazoles (method B, Figure 3). Here the initial bond-forming event is an acylation reaction, giving the N3−C2 bond of the benzoxazole ring. This approach has the potential advantage of using more readily available 2-haloaniline **9** and acyl chloride **10** precursors. Despite the importance of acyl chlorides as building-blocks in organic synthesis, it is noteworthy that their use in metal-catalyzed domino transformations is quite unusual.[28] In contrast, most other commonly employed synthetic building blocks have found widespread use for metal-catalyzed domino transformations. The paucity of examples of the use of acyl chlorides in such reactions can be attributed to a number of factors, including (i) their sensitivity toward hydrolysis in the presence of many of the bases commonly used in metal-catalyzed reactions, (ii) incompatibility with other functional groups, ligands, and/or metal catalysts, (iii) thermal instability, and (iv) competitive reactivity. Thus, we considered the evaluation of method B to be of interest as a test case for the use of acyl chlorides in a metal-catalyzed domino transformation.

The acylatable ligand *N*,*N*′-dimethylethylenediamine, which had worked best for the domino cross-coupling protocol (method A), is clearly incompatible with the use of acyl chlorides. Instead, the use of 1,10-phenanthroline as a ligand using an anhydrous base in a one-pot route was evaluated. Treatment of either 2-chloroaniline or 2-bromoaniline **9a** with benzoyl chloride **10a** in DME for 24 h at room temperature, followed by addition of Cs_2CO_3 (2.0 equiv), CuI (5 mol%), and 1,10-

(25) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661–1664.

(26) The only differences between the conditions reported in ref 25 and those reported herein are the catalyst loading (5% vs 10%) and the choice of base (K_2CO_3 vs K_3PO_4). In addition, we initially encountered some problems with irreproducibility, which were found to be dependant upon maintaining efficient stirring during the course of the reaction, and upon the morphology of the K_3PO_4 base. Reactions were found to be reproducible only when conducted using K_3PO_4 from a new bottle, which was free-flowing, fine granular material (Fluka, catalog no. 04347). The importance of K_3PO_4 morphology in copper-catalyzed N-arylation reactions has previously been observed by Buchwald and co-workers; see: Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.

(27) In an attempt to overcome this limitation for the poor control of regioselectivity and expand the scope of available substrates, we also evaluated the use of, *o*-bromo and iodoaryl triflates, which are readily synthesized by *ortho*-halogenation and triflation of phenols. Unfortunately only trace amounts (≤5%) of the desired products were obtained, presumably because unlike Pd-catalyzed transformations, Cu does not undergo effective oxidative addition to the aryl triflate bond. The trace amounts of benzoxazole observed in these reactions may be due to a background reaction pathway not involving cross-coupling (e.g., triflate hydrolysis followed by dehydrative annulation or nucleophilic aromatic substitution).

(28) For recent examples of the use of acyl chlorides in Pd catalyzed domino transformations, see: (a) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228–3230. (b) Siamaki, A.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050–6051.

SCHEME 2. Initial Attempts at Domino Annulation Reactions Using Domino Reactions of 2-Bromoaniline with Acyl Chlorides Followed by Copper-Catalyzed Cyclization to 4

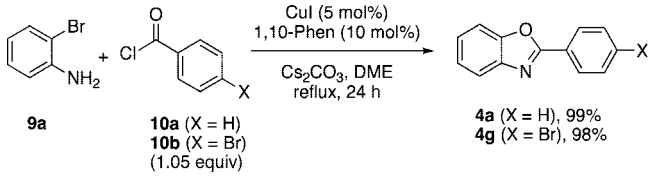
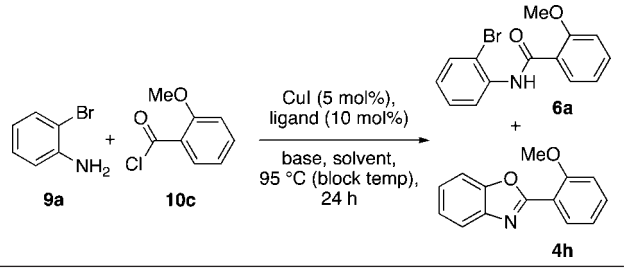


TABLE 1. Optimization of Benzoxazole 4h Synthesis via a Domino Acylation−Intramolecular Cross-Coupling Strategy Using 9a and 10c



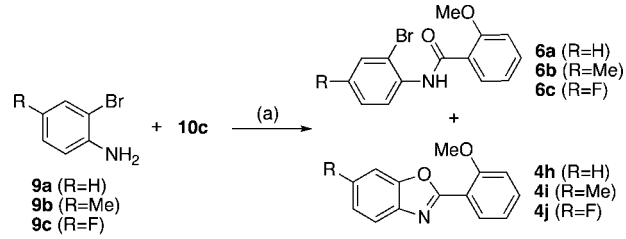
entry	solvent	[**9a**] (M)	base (equiv)	ligand[a]	**9a**:**6a**:**4h**[b]
1	DME	0.125	Cs_2CO_3 (2.2)	1,10-phen	15:80:5
2	*t*-BuOH	0.125	Cs_2CO_3 (2.2)	1,10-phen	45:25:30
3	MeCN	0.125	Cs_2CO_3 (2.2)	1,10-phen	15:25:60
4	toluene	0.125	Cs_2CO_3 (2.2)	1,10-phen	20:65:15
5	MeCN	0.125	K_3PO_4 (2.2)	1,10-phen	tr:85:15
6	MeCN	0.125	K_2CO_3 (2.2)	1,10-phen	tr:65:35
7	MeCN	0.125	KOAc (2.2)	1,10-phen	5:70:25
8	MeCN	0.125	Cs_2CO_3 (3.0)	1,10-phen	10:5:85
9	MeCN	0.25	Cs_2CO_3 (3.0)	1,10-phen	10:10:80
10	MeCN	0.125	K_2CO_3 (3.0)	1,10-phen	tr:75:25
11	MeCN	0.25	K_2CO_3 (3.0)	1,10-phen	5:45:50
12	MeCN	0.125	Cs_2CO_3 (3.0)	bipy	tr:85:15
13	MeCN	0.125	Cs_2CO_3 (3.0)	DMAP	25:65:10
14	MeCN	0.125	Cs_2CO_3 (3.0)	TMEDA	60:35:5
15	MeCN	0.125	Cs_2CO_3 (3.0)	complex	5:35:60

[a] Ligands: 1,10-phen = 1,10-phenanthroline, bipy = 2,2′-bipyridyl, DMAP = 4-dimethylaminopyridine, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, complex = preformed iodo(1,10-phenanthroline)(triphenylphosphine)copper[29] (5 mol%). [b] Reactions were performed with 1.2 equiv of **10**, and the ratio **9a**:**6a**:**4h** was determined by ^{1}H NMR analysis of the crude product (average of two runs, tr = signal was resolved from baseline noise but integrated for less than 5%).

phenanthroline (10 mol%), resulted in good conversion to 2-phenylbenzoxazole **4a** along with the presence of some of the intermediate benzanilides **6**. Modification of this protocol such that the reagents were added all at one time led to the formation of **4a** and **4g** in 99% and 98% yields, respectively (Scheme 2). Similar yields of these benzoxazoles could be obtained using 2-chloroaniline only if either the reaction times were extended to 48 h or if the catalyst/ligand loadings were doubled.

When we attempted to conduct the reaction of **9a** with 2-methoxybenzoyl chloride **10c** on a smaller scale and with slightly different reactant ratios and concentrations (conditions better suited to parallel synthesis in an aluminum block multiposition reactor), ^{1}H NMR analysis of the crude reaction mixture indicated only 5% conversion to the desired benzoxazole **4h**, with 80% anilide **6a** and 15% unreacted **9a** (average of two runs; Table 1, entry 1). The lower conversion in this system served as a starting point for an optimization study (Table 1). A survey of solvents conducted at the same reaction block

TABLE 2. Optimization of Benzoxazole Synthesis under Microwave Heating



entry	aniline	catalyst (mol %)	Cs_2CO_3 (equiv)	temp (°C)	time (min)	**6**:**4**
1	**9a**	5	2.4	170	5	70:30
2	**9b**	5	2.4	170	5	85:15
3	**9c**	5	2.4	170	5	80:20
4	**9a**	5	2.4	190	5	55:45
5	**9b**	5	2.4	190	5	70:30
6	**9c**	5	2.4	190	5	65:35
7	**9b**	5	2.4	200	5	50:50
8	**9b**	5	2.4	210	5	45:55
9	**9b**	5	2.4	210	10	40:60
10	**9b**	5	2.4	210	15	5:95
11	**9b**	5	2.4	210	20	10:90
12	**9b**	5	2.4	210	25	5:95
13	**9b**	5	3.0	210	15	5:95
14	**9b**	10	3.0	210	15	0:100[b]
15	**9b**	10	2.4	210	15	0:100[b]

[a] Conditions: aniline **9** (0.25 mmol), **10c** (0.30 mmol), CuI (5 or 10 mol%, relative to aniline), 1,10-phenanthroline (2 equiv relative to CuI), and Cs_2CO_3 (2.4 or 3.0 equiv relative to aniline) were dissolved in MeCN (5 mL) and heated. Conversions were determined by ^{1}H NMR analysis. In every case, ^{1}H NMR analysis revealed the aniline precursors to be completely consumed. [b] Compound **6b** not detected by ^{1}H NMR.

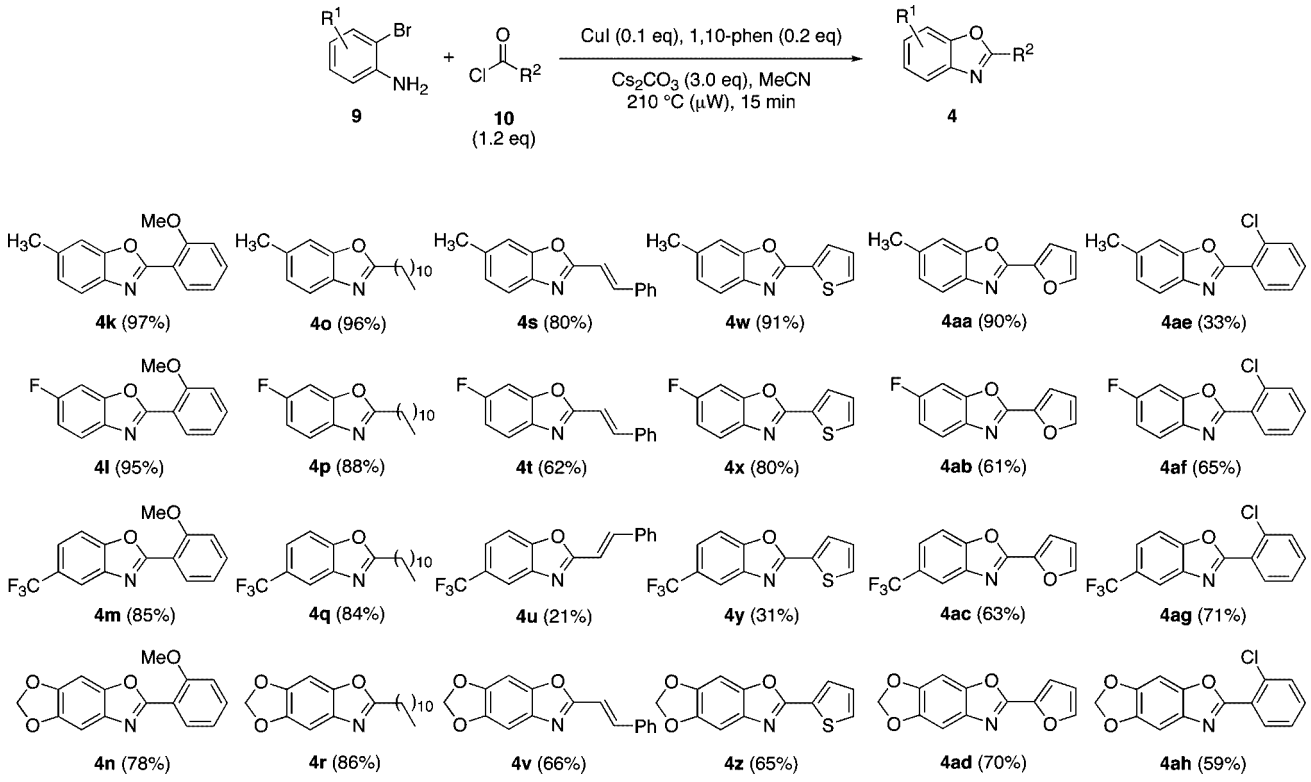
temperature (95 °C) suggested that the reaction proceeded more efficiently in MeCN, than in DME, *t*-BuOH, or toluene (entries 1–4). Using MeCN as a solvent, a limited screen of bases revealed that while K_3PO_4, K_2CO_3, and KOAc were all marginally effective at promoting the intramolecular cross-coupling, they were not as effective as the original choice, Cs_2CO_3 (entries 3, 5–7). A small increase in the amount of base used improved conversions with Cs_2CO_3 (entry 8 versus entry 3), while having a detrimental effect with K_2CO_3 (entry 10 versus entry 6). Doubling of the concentration of the reaction had little impact with Cs_2CO_3 but led to a noticeable improvement for the reaction with K_2CO_3 (entries 8–11). A screen of ligands compatible with acylation conditions reaffirmed 1,10-phenanthroline as the best choice of ligand (entries 12–15 versus entry 8).

We next set out to determine whether conversions could be further improved by conducting the reaction for a shorter time at higher temperatures in a microwave reactor (Table 2).[30] The reactions using microwave irradiation had to be carried out on a smaller scale and under more dilute conditions because of a limitation in the ability to stir the reaction mixture efficiently in the presence of a solid, insoluble base in a narrow reaction tube. Reactions with three different bromoanilines **9a**−**9c** were first screened at 170 °C for 5 min. In each case, ^{1}H NMR analysis of the crude reaction mixture indicated complete consumption of the bromoaniline but relatively low conversion

(29) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317.

(30) For a review of microwave heating in organic synthesis, see: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.

TABLE 3. Microwave-Accelerated Automated Sequential Synthesis of a Benzoxazole Library



of the intermediate bromobenzanilide **6** to the benzoxazole **4** (entries 1–3). Increasing the temperature to 190 °C caused an increase in this conversion, with the same trend among the three substrates (entries 4–6). Since 2-bromo-4-methylaniline **9b** exhibited the lowest conversion among the three substrates, it was chosen for further optimization. Further increases in temperature to 200 and 210 °C caused modest increases in conversion (entries 7 and 8). At 210 °C, the reaction pressure was near the upper limit for the microwave reactor (20 bar), and so further temperature increases could not be explored. Instead the reaction time was extended to 10, 15, 20 and 25 min (entries 9–12). A conversion over 90% was achieved at 15 min reaction time, with little significant change in conversion occurring upon further extending the reaction time. Increasing the amount of base from 2.4 to 3.0 equiv resulted in a slight improvement to 95% conversion, but quantitative conversion was only observed when the CuI loading was increased from 5 to 10 mol % (entries 13–15).

With microwave-accelerated conditions established, we next set out to determine the scope and practicality of the method through the synthesis of a small library of benzoxazoles with diverse substituents arising from every combination of four 2-bromoanilines and six acyl chlorides. Thus, using automated sequential synthesis techniques a library of 24 benzoxazoles **4k**–**4ah** was generated (Table 3). By combining the short reaction times achieved using microwave irradiation with rapid product purification by semi-automated flash chromatography, it was possible to completely process reactions (from mixing reagents to isolating clean dry products) in less than 2 h on a 0.25 mmol scale. The unoptimized isolated yields of the benzoxazole products ranged from 21% to 97%, with an average yield of 72%. This approach is suitable for medicinal chemistry screening campaigns, and further optimization is anticipated to lead to improvement in yields for individual reactions (as for Table 2).

In summary, two domino annulation strategies for benzoxazole synthesis have been investigated. In the first approach, the benzoxazole ring is constructed via domino inter/intramolecular copper-catalyzed cross-coupling using 1,2-dihaloarenes and primary amides. In this method the benzoxazole C−N bond is formed initially by an intermolecular copper-catalyzed cross-coupling by the amide, followed by a second copper-catalyzed cross-coupling, intramolecularly leading to C−O bond formation. Problems of accessibility of 1,2-dihaloarenes as well as controlling the regioselectivity of the reaction with unsymmetrical substrates led us to an alternative domino annulation approach. In the second approach, a one-pot domino acylation of 2-bromoanilines with acyl chlorides and subsequent intramolecular copper-catalyzed C−O cross-coupling lead to the benzoxazole ring. 1,10-Phenanthroline was the optimal ligand for this approach rather than DMEDA, which can undergo competitive acylation. Substantially better results were obtained under microwave-accelerated conditions, which were applied to the synthesis of a small focused library of benzoxazoles. The second method was found to be more practical than the first, given the accessibility of the necessary precursors, and the convenience of the one-pot protocol. This approach using 2-haloanilines compliments existing approaches to benzoxazoles that instead rely upon the use of 2-aminophenols. Further applications of this method and studies on related approaches to heterocycle formation will be reported in due course.

Experimental Section

General Procedure for Preparation of Benzoxazoles via Domino Intermolecular−Intramolecular Cross-Coupling (Scheme

1). A 25 mm reaction tube with a magnetic stirrer bar was charged with primary amide **8** (2.0 mmol), CuI (38 mg, 0.20 mmol) and K_3PO_4 (1.06 g, 5.0 mmol). The tube was sealed, evacuated, and backfilled with nitrogen three times before injecting toluene (3 mL), 1,2-dihaloarene **7** (0.24 mL, 2 mmol), and *N*,*N*′-dimethylethylendiamine (43 μL, 0.4 mmol) through the septum. The block temperature was maintained at 110 °C, and the mixture was vigorously stirred for 48 h (for **4a**, **4b**, and **4c**) or 24 h (for **4d**, **4e**, and **4f**). The reaction mixture was then cooled to room temperature, filtered through a pad of celite, evaporated, and purified by silica gel column chromatography to afford the desired benzoxazole **4** in the yields reported in Scheme 1.

Procedure for Preparation of Benzoxazoles from 9a and 10a/b (Scheme 2). To a mixture of 2-bromoaniline **9a** (1.89 mmol, 1.0 equiv), CuI (18 mg, 0.095 mmol, 0.05 equiv), 1,10-phenanthroline (34 mg, 0.19 mmol, 0.10 equiv), and Cs_2CO_3 (1.24 g, 3.78 mmol, 2.0 equiv) was added DME (20 mL) at room temperature, under a nitrogen atmosphere. To the reaction mixture was added acyl chloride **10a** or **10b** (1.98 mmol, 1.05 equiv). The reaction mixture was refluxed for 24 h then allowed to cool to room temperature. The reaction mixture was then diluted with EtOAc (50 mL) and washed with H_2O (2 × 50 mL) and brine (1 × 25 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was passed through a thin layer of silica gel using CH_2Cl_2 eluent.

Optimization of Benzoxazole Synthesis via Domino Acylation−Intramolecular Cross-Coupling with Conventional Heating (Table 1). A 25 mm reaction tube with a magnetic stirrer bar was charged with base (2.2 or 3.0 mmol) and CuI (9.5 mg, 0.05 mmol). The tube was sealed, evacuated, and backfilled with nitrogen three times before injecting a stock solution containing 2-bromoaniline **9a** and ligand (0.33 and 0.033 M, respectively, 3 mL = 1 mmol **9a** and 0.1 mmol ligand), followed by a stock solution of 2-methoxybenzoyl chloride **10c** (1.2 M, 1 mL = 1.2 mmol). In most cases (aside from Table 1, entries 9 and 11) an additional 4 mL of solvent was added before commencing heating (block temperature 95 °C) and vigorous stirring. After 24 h, the reaction mixture was cooled to room temperature and partitioned between CH_2Cl_2 (16 mL) and water (16 mL), and the organic phase was dried over $MgSO_4$ and evaporated in vacuo. The ratio of unreacted **9a** to intermediate **6a** to product **4h** was determined by ^{1}H NMR analysis of this crude material, comparing ratios of integrations of signals corresponding to one proton in each species: **9a**, 6.75 ppm; **6a**, 8.68 ppm; **4h**, 8.13 ppm. Values in Table 1 are the averages of two runs.

Optimization of Benzoxazole Synthesis by Method B Using Microwave Irradiation (Table 2). Reaction vials with stirrer bars were charged with CuI (0.013 or 0.025 mmol) and Cs_2CO_3 (0.60 or 0.75 mmol). Under a stream of nitrogen, a solution containing bromoaniline **9a**, **9b**, or **9c** (0.25 mmol) and 1,10-phenanthroline (0.025 or 0.050 mmol) in MeCN (2.5 mL) was added, followed by a solution of acyl chloride **10c** (0.3 mmol) in MeCN (2.5 mL). The vials were crimped and heated by microwave irradiation at the temperatures and times given in Table 2. After cooling to room temperature, the mixtures were diluted with MeCN (25 mL) and filtered through a short pad of silica gel, rinsed with additional MeCN (15 mL), and evaporated in vacuo. The ratio of amide:benzoxazole (**6**:**4**) was determined by ^{1}H NMR analysis of this crude material, comparing ratios of integrations of signals corresponding to one proton in each species: **6a**, 8.68 ppm; **4h**, 8.13 ppm; **6b**, 8.53 ppm; **4m**, 8.11 ppm; **6c**, 8.65 ppm; **4n**, 8.09 ppm (in every case, **9** was not detected in the crude NMR spectrum).

General Procedure for Preparation of a Library of Benzoxazoles via Microwave-Accelerated Automated Sequential Synthesis (Table 3). Reaction vials with stirrer bars were charged with CuI (5 mg, 0.025 mmol) and Cs_2CO_3 (245 mg, 0.75 mmol). Under a stream of nitrogen, dry MeCN stock solutions containing bromoanilines **9** and 1,10-phenanthroline (0.10 and 0.02 M, respectively, 2.5 mL = 0.25 mmol **9** and 0.05 mmol ligand) and then acyl chlorides **10** (0.12 M, 2.5 mL = 0.3 mmol **10**) were added. The vials were crimped and heated by microwave irradiation to 210 °C for 15 min. After cooling to room temperature, the mixtures were diluted with MeCN (25 mL) and filtered through a short pad of silica gel, rinsing with additional MeCN (15 mL). A small amount of silica gel was added to the filtrate, and the mixture was evaporated in vacuo. The products **4** were isolated by semi-automated flash chromatography (Biotage SP-1, 12 mm × 25 cm silica gel columns, eluted with 10% EtOAc/hexanes).

Characterization Data for Library Members. 2-(2-Methoxyphenyl)-6-fluorobenzoxazole (4l). The product was isolated as a white solid in 95% yield (58 mg). Mp = 85–87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (dd, 1H, J = 8.0 Hz, J = 2.0 Hz), 7.73 (dd, 1H, J = 9.0 Hz, J = 5.0 Hz), 7.52–7.46 (m, 1H), 7.30 (dd, 1H, J = 8.0 Hz, J = 2.0 Hz), 7.12–7.05 (m, 3H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1, 160.5 (d, J = 242.0 Hz), 158.3, 150.2 (d, J = 14.5 Hz), 138.4 (d, J = 1.5 Hz), 132.8, 131.1, 120.7, 120.4 (d, J = 10.0 Hz), 115.8, 112.2 (d, J = 23.5), 98.4 (d, J = 28.0 Hz), 56.1 (1 carbon signal missing: C-2); HRMS (EI) calculated for $C_{14}H_{10}FNO_2$ (M^+) 243.0696; observed 243.0700.

2-(2-Methoxyphenyl)-5-trifluoromethylbenzoxazole (4m). The product was isolated as a white solid in 85% yield (62 mg). Mp = 71–73 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (dd, 1H, J = 8.0 Hz, J = 2.0 Hz), 8.09 (s, 1H), 7.68–7.50 (m, 3H), 7.13–7.08 (m, 2H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.3, 158.6, 152.1, 142.2, 133.4, 131.4, 127.0 (q, J = 32.5 Hz), 124.3 (q, J = 270.5 Hz), 122.1 (q, J = 4.0 Hz), 120.7, 117.6 (q, J = 4.0 Hz), 112.1, 110.8, 56.1 (1 carbon signal missing: C-2); HRMS (EI) calculated for $C_{15}H_{10}F_3NO_2$ (M^+) 293.0664; observed 293.0663.

2-(2-Methoxyphenyl)-5,6-methylenedioxybenzoxazole (4n). The product was isolated as an off-white solid in 78% yield (51 mg). Mp = 159–160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07–8.04 (m, 1H), 7.48–7.42 (m, 1H), 7.21 (s, 1H), 7.09–7.04 (m, 3H), 6.01 (s, 2H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9, 157.9, 146.1, 145.3, 145.3, 136.1, 132.1, 130.6, 120.6, 116.3, 111.9, 101.5, 99.6, 92.3, 56.1; HRMS (ESI-QStar) calculated for $C_{15}H_{12}NO_4$ ($M + H)^+$ 270.0760; observed 270.0769.

6-Methyl-2-undecylbenzoxazole (4o). The product was isolated as yellow oil in 96% yield (69 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (d, 1H, J = 8.0 Hz), 7.27 (s, 1H), 7.09 (d, 1H, J = 8.0 Hz), 2.89 (t, 2H, J = 7.5 Hz), 2.46 (s, 3H), 1.87 (tt, 2H, J = 7.5 Hz, J = 7.5 Hz), 1.41–1.25 (m, 16H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.1, 139.2, 134.6, 125.1, 118.8, 110.4, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 28.6, 26.7, 22.6, 21.6, 14.1 (2 carbon signal missing: C-2 and 1 × aliphatic); HRMS (EI) calculated for $C_{19}H_{29}NO$ (M^+) 287.2249; observed 287.2243.

6-Fluoro-2-undecylbenzoxazole (4p). The product was isolated as a white solid in 88% yield (64 mg). Mp = 47–48 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (dd, 1H, J = 9.0 Hz, J = 5.0 Hz), 7.19 (dd, 1H, J = 8.0 Hz, J = 2.5 Hz), 7.07–7.00 (m, 1H), 2.90 (t, 2H, J = 7.5 Hz), 1.87 (tt, 2H, J = 7.5 Hz, J = 7.5 Hz), 1.50–1.26 (m, 16H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.9 (d, J = 3.5 Hz), 160.2 (d, J = 243.0 Hz), 150.7 (d, J = 14.5 Hz), 137.6 (d, J = 1.5 Hz), 119.6 (d, J = 10.0 Hz), 111.8 (d, J = 24.5 Hz), 98.3 (d, J = 28.0 Hz), 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 28.6, 26.6, 22.6, 14.1 (1 carbon signal missing: aliphatic); HRMS (ESI-QStar) calculated for $C_{18}H_{27}FNO$ ($M + H)^+$ 292.2071; observed 292.2063.

5-Trifluoromethyl-2-undecylbenzoxazole (4q). The product was isolated as colorless oil in 84% yield (72 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (s, 1H), 7.57 (s, 2H), 2.96 (t, 2H, J = 7.5 Hz), 1.90 (tt, 2H, J = 7.5 Hz, J = 7.5 Hz), 1.46–1.26 (m, 16 H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 152.6, 141.6, 126.9 (q, J = 32.5 Hz), 124.2 (q, J = 272.0 Hz), 121.7 (q, J = 3.5 Hz), 117.2 (q, J = 4.0 Hz), 110.6, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 28.6, 26.6, 22.7, 14.1 (1 carbon signal missing: aliphatic); HRMS (ESI-QStar) calculated for $C_{19}H_{27}F_3NO$ ($M + H)^+$ 342.2039; observed 342.2040.

5,6-Methylenedioxy-2-undecylbenzoxazole (4r). The product was isolated as a white solid in 86% yield (68 mg). Mp = 69–70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (s, 1H), 6.96 (s, 1H), 5.99 (s, 2H), 2.85 (t, 2H, J = 7.5 Hz), 1.84 (tt, 2H, J = 7.5 Hz, J = 7.5 Hz), 1.42–1.23 (m, 16H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7, 145.6, 145.6, 145.1, 135.1, 101.5, 99.2, 92.3, 31.9, 29.6, 29.4, 29.3, 29.2, 29.1, 28.6, 26.8, 22.6, 14.1 (1 carbon signal missing: aliphatic); HRMS (ESI-QStar) calculated for $C_{19}H_{28}NO_3$ $(M + H)^+$ 318.2063; observed 318.2055.

6-Fluoro-2-styrylbenzoxazole (4t). The product was isolated as an off-white solid in 62% yield (37 mg). Mp = 97–100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, 1H J = 16.5 Hz), 7.65–7.56 (m, 3H), 7.44–7.37 (m, 3H), 7.24 (dd, 1H, J = 8.0 Hz, J = 2.5 Hz), 7.10–7.04 (m, 1H), 7.03 (d, 1H, J = 16.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 160.7 (d, J = 243.0 Hz), 150.4 (d, J = 14.5 Hz), 139.5, 138.5 (d, J = 1.5 Hz), 135.0, 129.8, 129.0, 127.5, 120.1 (d, J = 10.0 Hz), 113.6, 112.4 (d, J = 25.0 Hz), 98.4 (d, J = 28.0 Hz); HRMS (ESI-QStar) calculated for $C_{15}H_{11}FNO$ $(M + H)^+$ 240.0819; observed 240.0822.

2-Styryl-5-trifluoromethylbenzoxazole (4u). The product was isolated as a yellow solid in 21% yield (15 mg). Mp = 97–100 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (s, 1H), 7.84 (d, 1H, J = 16.5 Hz), 7.63–7.59 (m, 4H), 7.48–7.38 (m, 3H), 7.08 (d, 1H, J = 16.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.5, 152.2, 142.3, 140.9, 134.8, 130.2, 129.1, 127.7, 127.3 (q, J = 32.5 Hz), 124.2 (q, J = 272.0 Hz), 122.4 (q, J = 3.5 Hz), 117.5 (q, J = 4.0 Hz), 113.3, 110.7; HRMS (EI) calculated for $C_{16}H_9F_3NO$ $(M - H)^+$ 288.0636; observed 288.0639.

5,6-Methylenedioxy-2-styrylbenzoxazole (4v). The product was isolated as a yellow solid in 66% yield (44 mg). Mp = 161–162 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (d, 1H, J = 16.5 Hz), 7.57–7.54 (m, 2H), 7.42–7.34 (m, 3H), 7.10 (s, 1H), 6.99 (s, 1H), 6.98 (d, 1H, J = 16.5 Hz), 6.01 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.4, 146.4, 145.6, 145.5, 137.6, 136.2, 135.3, 129.4, 128.9, 127.3, 113.9, 101.7, 99.3, 92.3; HRMS (ESI-QStar) calculated for $C_{16}H_{12}NO_3$ $(M + H)^+$ 266.0811; observed 266.0817.

6-Methyl-2-(2-thienyl)benzoxazole (4w). The product was isolated as an off-white solid in 91% yield (49 mg). Mp = 74–76 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (dd, 1H, J = 4.0 Hz, J = 1.0 Hz), 7.58 (d, 1H, J = 8.0 Hz), 7.51 (dd, 1H, J = 5.0 Hz, J = 1.0 Hz), 7.33–7.31 (m, 1H), 7.17–7.12 (m, 2H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.5, 150.7, 139.7, 135.5, 129.8, 129.5, 128.1, 125.9, 119.1, 110.5, 21.7 (1 carbon signal missing: C-2); HRMS (EI) calculated for $C_{12}H_9NOS$ (M^+) 215.0405; observed 215.0408.

6-Fluoro-2-(2-thienyl)benzoxazole (4x). The product was isolated as a white solid in 80% yield (44 mg). Mp = 113–114 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (dd, 1H, J = 4.0 Hz, J = 1.5 Hz), 7.64 (dd, 1H, J = 9.0 Hz, J = 5.0 Hz), 7.55 (dd, 1H, J = 5.0 Hz, J = 1.0 Hz), 7.26 (dd, 1H, J = 8.0 Hz, J = 2.5 Hz), 7.17 (dd, 1H, J = 5.0 Hz, J = 4.0 Hz), 7.12–7.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6 (d, J = 243.0 Hz), 159.6 (d, J = 3.5 Hz), 150.3 (d, J = 15.0 Hz), 138.3 (d, J = 2.0 Hz), 130.3, 129.9, 129.2, 128.2, 120.0 (d, J = 10.0 Hz), 112.6 (d, J = 24.5 Hz), 98.6 (d, J = 28.0 Hz) (1 carbon signal missing: C-2); HRMS (ESI-QStar) calculated for $C_{11}H_7FNOS$ $(M + H)^+$ 220.0226; observed 220.0217.

2-(2-Thienyl)-5-trifluoromethylbenzoxazole (4y). The product was isolated as a white solid in 31% yield (21 mg). Mp = 98–101 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (s, 1H), 7.95 (dd, 1H, J = 4.0 Hz, J = 1.0 Hz), 7.65–7.61 (m, 3H), 7.21 (dd, 1H, J = 5.0 Hz, J = 3.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 152.2, 142.2, 131.2, 130.8, 128.8, 128.4, 127.5 (q, J = 32.5 Hz), 124.1 (q, J = 270.0 Hz), 122.3 (q, J = 4.0 Hz), 117.4 (q, J = 4.0 Hz), 110.8; HRMS (ESI-QStar) calculated for $C_{12}H_7F_3NOS$ $(M + H)^+$ 270.0194; observed 270.0208.

5,6-Methylenedioxy-2-(2-thienyl)benzoxazole (4z). The product was isolated as a white solid in 65% yield (40 mg). Mp = 184 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78 (dd, 1H, J = 3.5 Hz, J = 1.0 Hz), 7.48 (dd, 1H, J = 5.0 Hz, J = 1.0 Hz), 7.14 (dd, 1H, J = 5.0 Hz, J = 3.5 Hz), 7.12 (s, 1H), 7.01 (s, 1H), 6.02 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.6, 146.2, 145.7, 145.4, 135.9, 129.8, 129.3, 128.7, 128.1, 101.7, 99.3, 92.4; HRMS (ESI-QStar) calculated for $C_{12}H_8NO_3S$ $(M + H)^+$ 246.0219; observed 246.0215.

2-(2-Furyl)-6-methylbenzoxazole (4aa). The product was isolated as a brown solid in 90% yield (45 mg). Mp = 52–53 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.64 (dd, 1H, J = 2.0 Hz, J = 0.5 Hz), 7.61 (d, 1H, J = 8.0 Hz), 7.34–7.33 (m, 1H), 7.22 (dd, 1H, J = 3.5 Hz, J = 0.5 Hz), 7.17–7.13 (m, 1H), 6.59 (dd, 1H, J = 3.5 Hz, J = 2.0 Hz), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.8, 150.4, 145.4, 142.7, 139.4, 135.7, 126.0, 119.4, 113.7, 112.1, 110.6, 21.7; HRMS (ESI-QStar) calculated for $C_{12}H_{10}NO_2$ $(M + H)^+$ 200.0706; observed 200.0716.

2-(2-Furyl)-6-fluorobenzoxazole (4ab). The product was isolated as a pale brown solid in 61% yield (31 mg). Mp = 69–73 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70–7.65 (m, 2H), 7.30–7.24 (m, 2H), 7.14–7.07 (m, 1H), 6.61 (dd, 1H, J = 3.5 Hz, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7 (d, J = 243.0 Hz), 155.9 (d, J = 3.5 Hz), 150.1 (d, J = 15.0 Hz), 145.8, 142.2, 137.9 (d, J = 1.5 Hz) 120.3 (d, J = 10.0 Hz), 114.3, 112.8 (d, J = 25.0 Hz), 112.2, 98.7 (d, J = 28.5 Hz); HRMS (ESI-QStar) calculated for $C_{11}H_7FNO_2$ $(M + H)^+$ 204.0455; observed 204.0456.

2-(2-Furyl)-5-trifluoromethylbenzoxazole (4ac). The product was isolated as an off-white solid in 63% yield (40 mg). Mp = 102–105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (s, 1H), 7.71 (dd, 1H, J = 2.0 Hz, J = 0.5 Hz), 7.65–7.64 (m, 2H), 7.34 (dd, 1H, J = 3.5 Hz, J = 0.5 Hz), 6.66 (dd, 1H, J = 3.5 Hz, J = 2.0 Hz) ^{13}C NMR ($CDCl_3$, 75 and 125 MHz) δ 156.8, 151.9, 146.4, 142.0, 141.9, 127.8 (q, J = 32.5 Hz), 124.1 (q, J = 272.0 Hz), 122.5 (q, J = 3.5 Hz), 117.8 (q, J = 4.0 Hz), 115.5, 112.5, 111.0; HRMS (ESI-QStar) calculated for $C_{12}H_7F_3NO_2$ $(M + H)^+$ 254.0423; observed 254.0420.

2-(2-Furyl)-5,6-methylenedioxybenzoxazole (4ad). The product was isolated as an off-white solid in 70% yield (40 mg). Mp = 179–181 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 1H, J = 1.5 Hz), 7.15 (d, 1H, J = 0.5 Hz), 7.14 (s, 1H), 7.03 (s, 1H), 6.58 (dd, 1H, J = 3.5 Hz, J = 2.0 Hz), 6.03 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.9, 146.4, 145.8, 145.2, 145.1, 142.7, 135.6, 112.8, 112.1, 101.8, 99.5, 92.5; HRMS (ESI-QStar) calculated for $C_{12}H_8NO_4$ $(M + H)^+$ 230.0447; observed 230.0436.

2-(2-Chlorophenyl)-6-fluorobenzoxazole (4af). The product was isolated as a white solid in 65% yield (40 mg). Mp = 97–99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (dd, 1H, J = 7.0 Hz, J = 2.5 Hz), 7.77 (dd, 1H, J = 9.0 Hz, J = 5.0 Hz), 7.56 (dd, 1H, J = 7.5 Hz, J = 2.0 Hz), 7.47–7.38 (m, 2H), 7.33 (dd, 1H, J = 8.0 Hz, J = 2.5 Hz), 7.17–7.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.5 (d, J = 3.5 Hz), 160.9 (d, J = 243.0 Hz), 150.5 (d, J = 15.0 Hz), 138.0 (d, J = 2.0 Hz), 133.4, 132.0, 131.6, 131.4, 126.9, 125.9, 120.8 (d, J = 10.0 Hz), 112.7 (d, J = 25.0 Hz), 98.7 (d, J = 28.0 Hz); HRMS (ESI-QStar) calculated for $C_{13}H_8ClFNO$ $(M + H)^+$ 248.0272; observed 248.0274.

2-(2-Chlorophenyl)-5-trifluoromethylbenzoxazole (4ag). The product was isolated as a white solid in 71% yield (53 mg). Mp = 74–75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18–8.13 (m, 2H), 7.73–7.64 (m, 2H), 7.60–7.56 (m, 1H), 7.52–7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7, 152.3, 141.8, 133.7, 132.5, 131.9, 131.5, 127.5 (q, J = 32.5 Hz), 127.0, 125.5, 124.1 (q, J = 270.5 Hz), 122.8 (q, J = 3.5 Hz), 118.2 (q, J = 4.0 Hz), 111.2; HRMS (EI) calculated for $C_{14}H_7ClF_3NO$ (M^+) 297.0168; observed 297.0175.

2-(2-Chlorophenyl)-5,6-methylenedioxybenzoxazole (4ah). The product was isolated as an off-white solid in 59% yield (40 mg). Mp = 142–144 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10–8.06 (m, 1H), 7.55–7.52 (m, 1H), 7.43–7.35 (m, 2H), 7.23 (s, 1H), 7.08 (s, 1H), 6.04 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5, 146.9, 145.9, 135.9, 133.0, 131.5, 131.5, 131.4, 129.0, 127.0, 126.4, 101.9, 99.9, 92.6; HRMS (ESI-QStar) calculated for $C_{14}H_9ClNO_3$ $(M + H)^+$ 274.0265; observed 274.0272.

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Supporting Information Available: General experimental section, characterization data and ^{1}H NMR spectra for literature compounds, and ^{1}H and ^{13}C spectra for all compounds in Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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