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Parallel Synthesis of a Library of Benzoxazoles and Benzothiazoles Using Ligand-Accelerated Copper-Catalyzed Cyclizations of *ortho*-Halobenzanilides

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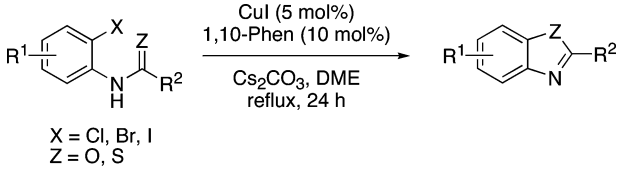

A general method for the formation of benzoxazoles via a copper-catalyzed cyclization of *ortho*-haloanilides is reported. This approach complements the more commonly used strategies for benzoxazole formation which require 2-aminophenols as substrates. The reaction involves an intramolecular C−O cross-coupling of the *ortho*-haloanilides and is believed to proceed via an oxidative insertion/reductive elimination pathway through a Cu(I)/Cu(III) manifold. The reaction is also applicable to the formation of benzothiazoles. A variety of ligands including 1,10-phenanthroline and *N*,*N*′-dimethylethylenediamine were shown to provide ligand acceleration/stabilization in the reaction. Optimal conditions for cyclization used a catalyst combination of CuI and 1,10-phenanthroline (10 mol %). The method was amenable to a parallel-synthesis approach, as demonstrated by the synthesis of a library of benzoxazoles and benzothiazoles substituted at various positions in the ring. Most examples utilized the cyclization of *ortho*-bromoanilides, but *ortho*-iodoanilides and *ortho*-chloroanilides also undergo a reaction under these conditions. The rate of reaction of the *ortho*-haloanilides follows the order I > Br > Cl, consistent with oxidative addition being the rate-determining step.

Introduction

Benz-fused azoles are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds. Benzoxazoles are found in a variety of natural products[1] and are important targets in drug discovery.[2] There are two commonly used approaches for the construction of the benzoxazole ring system, both of which employ 2-aminophenols as substrates.[3] The first approach involves the coupling of the 2-aminophenols with carboxylic acid derivatives under strongly acidic conditions, such as boric acid or polyphosphoric acid, with high reaction temperatures[4] or with microwave-assisted reaction conditions.[5] The second approach uses the reaction of 2-aminophenols with an aldehyde via the oxidative cyclization of imine intermediates.[6] The development of alternative routes to benzoxazole ring formation is an important goal because it would allow the use of milder reaction conditions, and it would overcome the requirement for using 2-aminophenols as precursors.

We have recently disclosed Pd- and Cu-catalyzed methods for the synthesis of both benzimidazoles **3**[7] and benzothiazoles **4**[8] via the intramolecular cross-coupling reaction of *ortho*-bromo- (or iodo-) substituted precursors **1** and **2** (Scheme 1).

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(1) Examples of benzoxazole natural products and their biological activities. For calcimycin (A-23187; antibiotic), see: Chaney, M. O.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932−1933. For boxazomycins (potent in vitro activity against gram-positive bacteria and anaerobes such as Staphylococcus aureus, Streptococcus pyogenes, Mycobacterium smegmatis, Clostridium difficile, and Bacterioides fragilis), see: Kusumi, T.; Ooi, T.; Walchli, M. R.; Kakisawa, H. *J. Am. Chem. Soc.* **1988**, *110*, 2954−2958. For pseudopteroxazole and *seco*-pseudopteroxazole (growth inhibitory activity against *Mycobacterium tuberculosis*), see: Rodrıguez, A. D.; Ramirez, C.; Rodrıguez, I. I.; Gonzalez, E. *Org. Lett.* **1999**, *1*, 527−530. For UK-1 (moderate cytotoxic activity against B16, HeLa, and P338 cells), see: (a) Ueki, M.; Ueno, K.; Miyadoh, S.; Abe, K.; Shibata, K.; Taniguchi, M.; Oi, S. *J. Antibiot.* **1993**, *46*, 1089−1094. (b) Shibata, K.; Kashiwada, M.; Ueki, M.; Taniguchi, M. *J. Antibiot.* **1993**, *46*, 1095−1100. (c) Reynolds, M. B.; DeLuca, M. R.; Kerwin, S. M. *Bioorg. Chem.* **1999**, *27*, 326−337. For AJI9561 (shows growth inhibitory activity against murine cancer cell line P338), see: Sato, S.; Kajiura, T.; Noguchi, M.; Takehana, K.; Kobayasho, T.; Tsuji, T. *J. Antibiot.* **2001**, *54*, 102−104.

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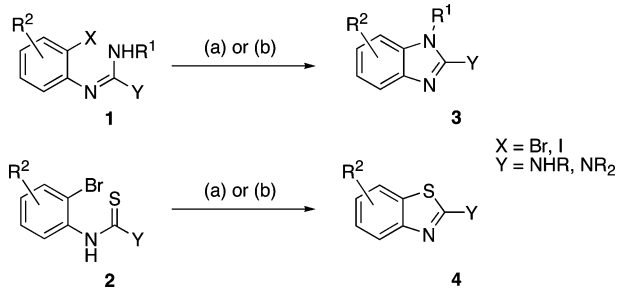
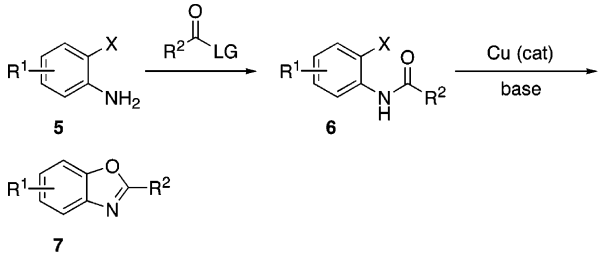
SCHEME 1. Copper- and Palladium-Catalyzed Formation of Benzimidazoles and Benzothiazoles[a]



[a] (a) CuI (5 mol %), 1,10-Phen (10 mol %), Cs_2CO_3 (2 equiv), 80 °C, DME, 16−24 h. (b) $Pd(PPh_3)_4$ (5−10 mol %), Cs_2CO_3 (2 equiv), 80 °C, DME, 16−24 h.

In general, the use of copper catalysts proved superior to that of palladium[9] in these reactions. These results follow the recent resurgence of copper-mediated reactions, beyond that of classical Ullmann etherifications[10,11] and aminations[12,13] and Goldberg amidation[14,15] reactions, through the use of ligand acceleration.[16,17] As part of our program in benzo-fused azole synthesis, we became interested in whether a similar strategy employed in the synthesis of **3** and **4** could be applied to the formation of benzoxazoles **7** (Scheme 2). This approach would remove the requirement for the use of 2-aminophenols as precursors to benzoxazoles, instead utilizing 2-haloanilines **5**, which are readily available, for example, through electrophilic aromatic substitution. Acylation of the 2-haloanilines **5** could then be used to generate the *ortho*-haloanilide substrates **6** required for the copper-catalyzed cyclization.

SCHEME 2. General Approach to the Synthesis of Substituted Benzoxazoles 7 from *ortho*-Haloanilines 5



(2) For examples of benzoxazoles in drug discovery, see: (a) Brown, R. N.; Cameron, R.; Chalmers, D. K.; Hamilton, S.; Luttick, A.; Krippner, G. Y.; McConnell, D. B.; Nearn, R.; Stanislawski, P. C.; Tucker, S. P.; Watson, K. G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2051−2055. (b) Manas, E. S.; Unwalla, R. J.; Xu, Z. B.; Malamas, M. S.; Miller, C. P.; Harris, H. A.; Hsiao, C.; Akopian, T.; Hum, W.-T.; Malakian, K.; Wolfrom, S.; Bapat, A.; Bhat, R. A.; Stahl, M. L.; Somers, W. S.; Alvarez, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 15106−15119. (c) Malamas, M. S.; Manas, E. S.; McDevitt, R. E.; Gunawan, I.; Xu, Z. B.; Collini, M. D.; Miller, C. P.; Dinh, T.; Henderson, R. A.; Keith, J. C., Jr.; Harris, H. A. *J. Med. Chem.* **2004**, *47*, 5021−5040. (d) Sun, L.-Q.; Chen, J.; Bruce, M.; Deskus, J. A.; Epperson, J. R.; Takaki, K.; Johnson, G.; Iben, L.; Mahle, C. D.; Ryan, E.; Xu, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3799−3802. (e) Lin, L. S.; Lanza, T. J.; Castonguay, L. A.; Kamenecka, T.; McCauley, E.; Van Riper, G.; Egger, L. A.; Mumford, R. A.; Tong, X.; MacCoss, M.; Schmidt, J. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2331−2334. (f) Yildiz-Oren, I.; Yalcin, I.; Aki-Sener, E.; Ucarturk, N. *Eur. J. Med. Chem.* **2004**, *39*, 291−298. (g) Gong, B.; Hong, F.; Kohm, C.; Bonham, L.; Klein, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1455−1459. (h) Sun, L.-Q.; Chen, J.; Takaki, K.; Johnson, G.; Iben, L.; Mahle, C. D.; Ryan, E.; Xu, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1197−1200. (i) Wang, B.; Vernier, J.-M.; Rao, S.; Chung, J.; Anderson, J. J.; Brodkin, J. D.; Jiang, X.; Gardner, M. F.; Yang, X.; Munoz, B. *Bioorg. Med. Chem.* **2004**, *12*, 17−21. (j) Razavi, H.; Palaninathan, S. K.; Powers, E. T.; Wiseman, R. L.; Purkey, H. E.; Mohamedmohaideen, N. N.; Deechongkit, S.; Chiang, K. P.; Dendle, M. T. A.; Sacchettini, J. C.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2758−2761. (k) Sum, P.-E.; How, D.; Torres, N.; Newman, H.; Petersen, P. J.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2607−2610. (l) Lopez-Tudanca, P. L.; Labeaga, L.; Innerarity, A.; Alonso-Cires, L.; Tapia, I.; Mosquera, R.; Orjales, A. *Bioorg. Med. Chem.* **2003**, *11*, 2709−2714. (m) Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. *Bioorg. Med. Chem.* **2002**, *10*, 3997−4004. (n) Boger, D. L.; Miyauchi, H.; Hedrick, M. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1517−1520. (o) Akahoshi, F.; Ashimori, A.; Sakashita, H.; Yoshimura, T.; Imada, T.; Nakajima, M.; Mitsutomi, N.; Kuwahara, S.; Ohtsuka, T.; Fukaya, C.; Miyazaki, M.; Nakamura, N. *J. Med. Chem.* **2001**, *44*, 1286−1296. (p) Edwards, P. D.; Zottola, M. A.; Davis, M.; Williams, J.; Tuthill, P. A. *J. Med. Chem.* **1995**, *38*, 3972−3982. (q) Tsutsumi, S.; Okonogi, T.; Shibahara, S.; Ohuchi, S.; Hatsushiba, E.; Patchett, A. A.; Christensen, B. G. *J. Med. Chem.* **1994**, *37*, 3492−3502. (r) Saari, W. S.; Wai, J. S.; Fisher, T. E.; Thomas, C. M.; Hoffman, J. M.; Rooney, C. S.; Smith, A. M.; Jones, J. H.; Bamberger, D. L.; Goldman, M. E.; O'Brien, J. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Anderson, P. S. *J. Med. Chem.* **1992**, *35*, 3792−3802. (s) Edwards, P. D.; Meyer, E. F., Jr.; Vijayalakshmi, J.; Tuthill, P. A.; Andisik, D. A.; Gomes, B.; Strimplerg, A. *J. Am. Chem. Soc.* **1992**, *114*, 1854−1863.

(3) For a general overview of synthetic methods to benzoxazoles, see: (a) Boyd, G. V. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Schaumann, E., Ed.; Thieme: Stuttgart, 2002; Vol. 11, pp 481−492. (b) Döpp, H.; Döpp, D. In *Houben-Weyl: Methoden der Organischen Chemie*; Schaumann, E., Ed.; Thieme: Stuttgart, 1993; Vol. E8a, pp 1020−1193.

(4) (a) Terashima, M.; Ishii, M.; Kanaoka, Y. *Synthesis* **1982**, 484−485. (b) Hein, D. W.; Alheim, R. J.; Leavitt, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 427−429.

(5) (a) Bourgrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055−8064. (b) Pottorf, R. S.; Chadha, N. K.; Katkevics, M.; Ozola, V.; Suna, E.; Ghane, H.; Regberg, T.; Player, M. R. *Tetrahedron Lett.* **2003**, *44*, 175−178.

(6) Various oxidants, such as DDQ, $Mn(OAc)_3$, $PhI(OAc)_2$, thianthrene cation radical perchlorate, $BaMnO_4$, NiO_2, $Pb(OAc)_4$, and O_2 with activated carbon, as well as MnO_2/silica (under microwave conditions, see ref 5a), have been used. For examples, see: (a) Chang, J.; Zhao, K.; Pan, S. *Tetrahedron Lett.* **2002**, *43*, 951−954. (b) Varma, R. S.; Kumar, D. *J. Heterocycl. Chem.* **1998**, *35*, 1539−1540. (c) Varma, R. S.; Saini, R. K.; Prakash, O. *Tetrahedron Lett.* **1997**, *38*, 2621−2622. (d) Park, K. H.; Jun, K.; Shin, S. R.; Oh, S. W. *Tetrahedron Lett.* **1996**, *37*, 8869−8870. (e) Srivastava, R. G.; Venkataramani, P. S. *Synth. Commun.* **1988**, *18*, 1537−1544. (f) Nakagawa, K.; Onoue, H.; Sugita, J. *Chem. Pharm. Bull.* **1964**, *12*, 1135−1138. (g) Stephens, F. F.; Bower, J. D. *J. Chem. Soc.* **1949**, 2971−2972. (h) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713−3715.

(7) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133−136.

(8) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446−447.

(9) For reviews on Pd-catalyzed Buchwald−Hartwig C−N and C−O bond formation reactions, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131−209. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.

(10) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853−857.

(11) For selected examples of copper-catalyzed etherifications, see: (a) Weingarten, H. *J. Org. Chem.* **1964**, *29*, 3624−3626. (b) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*, 1007−1010. (c) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540. (d) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043−5051. (e) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315−4317. (f) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973−976. (g) Wan, Z. H.; Jones, C. D.; Koenig, T. M.; Pu, Y. J.; Mitchell, D. *Tetrahedron Lett.* **2003**, *44*, 8257−8259.

(12) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382−2384. (b) Ullmann, F.; Illgen, E. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 380−383.

(13) For selected examples of copper-catalyzed aminations, see: (a) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496−1502. (b) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459−12467. (c) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670−674. (d) Kwong, F. Y.; Klapars, A. Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581−584. (e)Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684−11688. (f) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796. (g) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987−4990. (h) Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948−9949.

(14) (a) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691−1692. (b) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 4541−4546.

At the outset of our study there were several isolated examples of such copper-promoted cyclizations of *ortho*-haloanilide substrates **6** to benzoxazoles known. In most cases, a stoichiometric or an excess amount of CuI was utilized at high temperatures in the presence of an external base, such as NaH[18−20] or *t*-BuOK.[21] Iizuka and co-workers had earlier reported the use of both stoichiometric and catalytic copper-catalyzed cyclizations.[22] For example, a CuCl (2−3 mol %)/CuO (4−5 mol %)/NaOAc (1 equiv) system was used at 200 °C for the cyclization of *ortho*-halobenzanilides.[23] In addition, they also accomplished a very early example of the use of a ligand-accelerated, catalytic, Ullmann-type coupling (e.g., Cu metal (20 mol %)/2,4-lutidine (1.5 equiv)/DMF at 142 °C). In a study on Ullmann etherification, Snieckus reported that the reaction of *N*-(2-bromophenyl)pivaloylamide using a catalytic quantity of $CuPF_6(MeCN)_2$ led to the formation of 2-*tert*-butylbenzoxazole as an undesired major product.[24] More recently, both stoichiometric and catalytic copper(I)halides were used for the synthesis of herbicidal 7-(pyrazol-3-yl)benzoxazoles (e.g., NaH/DMSO/CuBr/140 °C or pyridine/DMF/K_2CO_3 (or $KHCO_3$)/CuCl (20 mol %)/90 °C).[25] Also, during the preparation of this manuscript, Glorius reported a similar strategy to benzoxazoles using a copper-catalyzed annulation approach through the coupling of amides with 1,2-dihaloarenes.[26] Interestingly, despite the widespread use of palladium catalysts for C−X bond formation, including cyclization to benzimidazoles[7,27] and benzothiazoles,[8,28] both Castillón and Glorius have reported that Pd catalysts do not promote the cyclization of *ortho*-halobenzanilides.[26,28] Examples of benzoxazole formations from 2-haloanilides are also known that proceed via[29] aryne intermediates[30] or photochemical conditions.[31] An annulation strategy based on nucleophilic aromatic substitution was also reported by Kobayashi, using NaH/DMF at 80 °C for the coupling of hexafluorobenzene and benzamide.[32] We now report the development of a generally applicable reaction protocol using mild reaction conditions under copper catalysis.[33] In addition, conditions are established that demonstrate that the reaction can be utilized in a parallel-synthesis approach.

Results and Discussion

N-(2-Bromophenyl)benzamide **6a** was chosen as a test substrate for the initial benzoxazole studies, using the conditions previously described from our laboratory, for the synthesis of **3** and **4**.[7,8] The use of catalytic CuI (5 mol %), 1,10-phenanthroline (10 mol %), and Cs_2CO_3 (2.0 equiv) in DME at 80 °C over 16 h afforded 90% conversion of **6a** to 2-phenylbenzoxazole **7a** by ^{1}H NMR (Table 1, entry 1). The ^{1}H NMR of the product was very clean, with the starting material **6a** being the only other observable species. A variation of the ligand bound to copper can significantly alter both the solubility and the stability of the copper-ligand complexes and is an important determinant for the success of copper-promoted cross-couplings.[11,13,15,17] Several attempts were made to force the reaction to completion by screening various ligands. The use of ethylenediamine (10 mol %) as the ligand with catalytic CuI (5 mol %) and Cs_2CO_3 (2.0 equiv) in DME at 80 °C over 16 h resulted in 53% conversion, whereas the use of ethanolamine afforded 70% conversion (Table 1, entries 2 and 3). Reactions using either 10 mol % or 50 mol % of ethylene glycol afforded moderate conversion to the product **7a** and low product purity (Table 1, entries 4 and 5). The reaction of **6a** using 2-propanol as solvent led to only 25% conversion and with moderate product purity (Table 1, entry 6). Excellent conversion was, however, observed using catalytic amounts of *N*,*N*′-dimethylethylenediamine (10 mol %) as the ligand (Table 1, entry 7).

Further optimization comparing the reactivity of eight different *ortho*-bromoanilides substrates, **6**, was done using either *N*,*N*′-dimethylethylenediamine or 1,10-phenanthroline as the

(15) For selected examples of copper-catalyzed amidations, see: (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428. (c) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667−3669. (d) Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963−965. (e) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529−3533. (f) Nandakumar, M. V. *Tetrahedron Lett.* **2004**, *45*, 1989−1990. (g) Wang, S.; Sun, J.; Yu, G.; Hu, X.; Liu, J. O.; Hu, Y. *Org. Biomol. Chem.* **2004**, *2*, 1573−1574.

(16) For an excellent general review of the early literature, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456.

(17) For more reviews on more recent developments in Cu-catalyzed C−C, C−N, and C−O bond-formation reactions, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337−2364. (b) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265−555. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449. (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428−2439. (e) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469. (f) Finet, J.-P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597−626.

(18) Minami, T.; Isonaka, T.; Okada, Y.; Ichikawa, J. *J. Org. Chem.* **1993**, *58*, 7009−7015.

(19) For an example of the cyclization of 2,4,6-tribromoacetanilide using a NaH/HMPA/CuBr system, see: Kraus, G. A.; Nagy, J. O.; DeLano, J. *Tetrahedron* **1985**, *41*, 2337−2340.

(20) For the cyclization of a *N*-(3-bromoisoquinolin-4-yl) substituted amide to an oxazolo[5,4-c]isoquinoline using stoichiometric CuI and NaH, see: Brière, J. F.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Heterocycles* **2000**, *52*, 1371−1383.

(21) Bowman, W. R.; Heaney, H.; Smith, P. H. G. *Tetrahedron Lett.* **1982**, *23*, 5093−5096.

(22) Iizuka, M.; Yamamoto, M.; Matsumara, J.; Yoshida, M. U.S. Patent 3147253, 1964.

(23) For another use of a CuCl/CuO/NaOAc (or KOAc) system, see: Mitumoto, I.; Suzuki, N.; Isiguro, H. *Tokyo Kogyo Koto Senmon Gakko Kenkyu Hokokusho* **1985**, *17*, 123−126.

(24) See footnote 12, in the following: Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986−2987.

(25) Zagar, C.; Reinhard, R.; Puhl, M.; Volk, T.; Götz, N.; Hamprecht, G.; Menke, O.; Sagasser, I. World Patent WO0168644, 2001.

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

(27) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893−1895.

(28) Benedí, C.; Bravo, F.; Uriz, P.; Fernández, E.; Claver, C.; Castillón, S. *Tetrahedron Lett.* **2003**, *44*, 6073−6077.

(29) *ortho*-Fluorobenzanilides are known to undergo cyclization to benzoxazoles at a high temperature and in the presence of NaH, DBU, or BuLi. (a) Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1992**, *57*, 6351−6354. (b) Os'kina, I. A.; Vlasov, V. M.; Yakobson, G. G. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1981**, 100−109. (c) Inukai, Y.; Oono, Y.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 516−520. (d) Kyba, E. P.; Liu, S.-T.; Kannappan, C.; Reddy, B. R. *J. Org. Chem.* **1988**, *53*, 3513−3521.

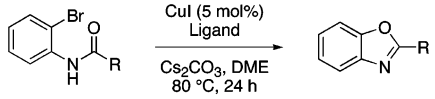
(30) For examples of cyclizations of 2-halobenzanilides under strongly basic conditions that have been proposed to proceed via addition to aryne intermediates, see: (a) Reavill, D. R.; Richardson, S. K. *Synth. Commun.* **1990**, *20*, 1423−1436. (b) El-Sheikh, M. I.; Marks, A.; Biehl, E. R. *J. Org. Chem.* **1981**, *46*, 3256−3259. (c) Hrutford, B. F.; Bunnett, J. F. *J. Am. Chem. Soc.* **1958**, *80*, 2021−2022.

(31) For photochemical cyclizations via electron-transfer mechanisms, see: (a) Park, Y.-T.; Song, M.-G.; Kim, M.-S.; Kwon, J.-H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1208−1212. (b) Park, Y.-T.; Kim, M.-S.; Kwak, Y.-W.; Lee, J.-K.; Yoh, S.-D.; Kim, W.-S. *J. Photoscience* **2000**, *7*, 135−138. (c) Mayouf, A. M.; Park, Y.-T. *J. Photoscience* **2000**, *7*, 5−8. (d) Park, Y. T.; Jung, C. H.; Kim, K.-W.; Kim, H. S. *J. Org. Chem.* **1998**, *64*, 8546−8556.

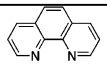
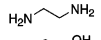
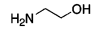
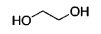
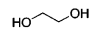
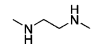
(32) Inukai, Y.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2657−2660.

(33) Evindar, G. Ph.D. Thesis, University of Toronto, 2004.

TABLE 1. Ligand Screening in Copper-Catalyzed Benzoxazole Formation

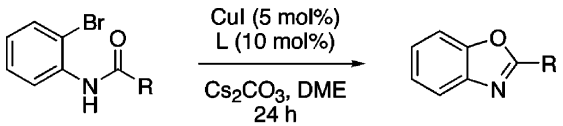


6a **7a**

Entry	Ligand	mol%	Conversion (%)[a] (isolated yield [%])
1		10	90 (90)
2		10	53
3		10	70
4		10	59
5		50	59
6	2-propanol	solvent	25
7		10	≥ 99 (99)

[a] Reaction conversion was determined by ^{1}H NMR analysis.

TABLE 2. Temperature and Ligand Optimization with *N,N′*-Dimethylethylenediamine (Method A) or 1,10-Phenanthroline (Method B)



6 **7**

			method A		method B	
entry	R	product	temp[a] (°C)	conversion[b] (%)	temp[a] (°C)	conversion[b] (%)
1	Ph	**7a**	80	≥99	reflux	≥99
2	4-Cl—Ph	**7b**	80	≥99	reflux	≥99
3	4-Br—Ph	**7c**	80	85	reflux	≥99
4	4-CN—Ph	**7d**	80	≥99[c]	reflux	95
5	4-NO_2—Ph	**7e**	80	60[c]	80	70[c]
6	(*E*)-CH═CHPh	**7f**	80	90	reflux	98
7	Et	**7g**	80	27	80	21
8	Et	**7g**	reflux	<5	reflux	≥99
9	*i*-Pr	**7h**	80	20	80	≥99

[a] Oil-bath temperature. [b] Reaction conversion was determined by ^{1}H NMR analysis. [c] The crude products were contaminated by uncharacterized impurities.

ligand (10 mol %), with catalytic CuI (5 mol %), and Cs_2CO_3 (2.0 equiv) in DME at 80 °C, or reflux, over 24 h (Table 2). For complete conversion, within 24 h, of **6** to benzoxazoles **7**, heating at reflux was generally required using 1,10-phenanthroline as the ligand, whereas heating at 80 °C was sufficient with *N,N′*-dimethylethylenediamine as the ligand. Various substitutions on the benzamide ring were well-tolerated under both reaction conditions, with the final products being obtained in high purities (Table 2, entries 1−5). Higher conversions were obtained using 1,10-phenanthroline as the ligand in the case of 4-bromobenzamide, **6c**, and the 3-phenyl acrylamide substrate, **6f**, giving 15 and 8% higher conversions, respectively (Table 2, entries 3 and 6). The reaction of the *para*-nitrobenzamide, **6e**, gave complex reaction mixtures and poor conversions using either ligand (Table 2, entry 5). Both ligands gave poor overall conversions using the propionamide, **6g**, at 80 °C (Table 2, entry 7). However, increasing the reaction temperature to reflux gave complete conversion using 1,10-phenanthroline, while the conversion suffered dramatically using *N,N′*-dimethylethylenediamine as the ligand (Table 2, entry 8). Similar results were obtained in the case of isobutyramide, **6h** (Table 2, entry 9). A partial amide hydrolysis or the presence of enolizable protons for **6g** and **6h** may lead to side reactions in the formation of 2-alkyl-substituted benzoxazoles, particularly when *N,N′*-dimethylethylenediamine is used as the ligand. Finally, screening for the optimal amount of base, using 1,10-phenanthroline as the ligand, revealed that 1.5 equiv of Cs_2CO_3 gave similar conversions in every case as those obtained with 2.0 equiv.

On the basis of these studies, we elected to use 1,10-phenanthroline as the optimal ligand in a parallel-synthesis approach (Table 3). The optimal conditions employed for the parallel synthesis were CuI (5 mol %), 1,10-phenanthroline (10 mol %), and Cs_2CO_3 (1.5 equiv) in refluxing DME over a period of 24 h. The synthesis of the *ortho*-haloanilide **6** precursors was, in most instances, readily accomplished through the coupling of *ortho*-haloanilines **5** with the corresponding acid chlorides.[34] In some cases, **6** was synthesized by the coupling of **5** with the corresponding carboxylic acids, either using a 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide/hydroxybenzotriazole coupling protocol[35] or by a one-pot procedure involving an in situ formation of the acid chloride using oxalyl chloride with a catalytic amount of DMF, followed by the addition of **5**.[36] The parallel synthesis was conducted on a 1.0 mmol scale in groups of 12 reactions in glass tubes with screw-top seals, stirred under an inert atmosphere (nitrogen). Following each reaction, water and CH_2Cl_2 were added to the reaction mixtures, and purification was achieved by phase separation through a hydrophobic membrane (the denser DME/CH_2Cl_2 layer flows through the hydrophobic membrane, while the aqueous layer remains in the reservoir). Any traces of copper salts, ligand, remaining starting materials, or byproducts were removed by passage through a short silica gel column.

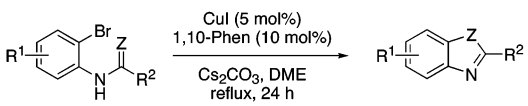
A variety of substituted benzamide groups were tolerated on **6** leading to 2-aryl-substituted benzoxazoles **7** in high yields (Table 3, entries 1−7). Additional chloro and bromo substituents were tolerated in the reaction (Table 3, entries 2−4). Particularly notable was the chemoselective reaction of **6c** to afford 92% of the corresponding benzoxazole **7c** without any observable reaction of the *para*-bromophenyl ring (Table 3, entry 4). The presence of both strongly electron-withdrawing cyano and strongly electron-donating methoxy groups were also tolerated, either at the para or at the *ortho* position of the benzamide ring in **6** (Table 3, entries 5−7). The corresponding iodo substrates, **6**−**I**, also underwent the reaction with similar yields and purities (Table 3, entries 1−3, 5, and 6). While many metal-catalyzed cross-couplings are known in which the use of iodides, rather than bromides, can lead to improved reactivity at lower temperatures, a separate study using the iodo substrate, **6a**−**I**, revealed that reaction conversions dropped at lower temperatures (75% conversion at 60 °C and 90% conversion at 80 °C for 24 h). Heterocyclic groups such as thiophen-2-yl and pyridin-3-yl rings could also be introduced at the C2 position of the benzoxazoles (Table 3, entries 8 and 9). However, not all heteroaromatic rings worked well in the reaction with both the

(34) Substrates **6a**−**6n**, **6p**−**6t**, **6v**, **6w**, **6ab**−**6ac**, **6a**−**I**, **6b**−**I**, **6d**−**I**, **6i**−**I**, **6j**−**I**, and **6a**−**Cl** were prepared from the acid chlorides.

(35) Substrates **6o**, **6u**, and **6aa** were prepared from the carboxylic acids using an EDC/HOBt coupling protocol.

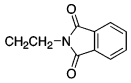
(36) Substrates **6u**, **6x**−**6aa**, and **6ad** were prepared from the carboxylic acids via a one-pot method involving the in situ formation of the acid chlorides from oxalyl chloride and DMF (cat).

TABLE 3. Parallel Synthesis of Benzoxazoles 7 and Benzothiazoles 9



6 (Z = O)
8 (Z = S)

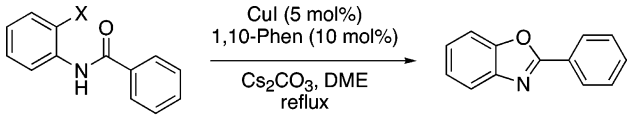
7 (Z = O)
9 (Z = S)

Entry	R^1	R^2	Z	Product	Yield (%)
1	–	Ph	O	**7a**	95 (>99)[a]
2	–	4-Cl-Ph	O	**7b**	>99 (>99)[a]
3	–	3,4-di-Cl-Ph	O	**7i**	>99 (97)[a]
4	–	4-Br-Ph	O	**7c**	92
5	–	4-CN-Ph	O	**7d**	93 (98)[a]
6	–	4-OMe-Ph	O	**7j**	>99 (>99)[a]
7	–	2-OMe-Ph	O	**7k**	99
8	–	thiophen-2-yl	O	**7l**	>99
9	–	pyridin-3-yl	O	**7m**	96
10	–		O	**7n**	–[b]
11	–		O	**7o**	–[b]
12	4-Me[c]	Ph	O	**7p**	>99
13	4-Cl[c]	Ph	O	**7q**	95
14	4-F[c]	Ph	O	**7r**	99
15	5-F[c]	Ph	O	**7s**	98
16	5-CF_3[c]	Ph	O	**7t**	75
17	–	Et	O	**7g**	>99
18	–	Bn	O	**7u**	89
19	–	*i*-Pr	O	**7h**	98
20	–	CH_2COOMe	O	**7v**	–[b]
21	–	CH_2COOEt	O	**7w**	–[b]
22	–		O	**7x**	~19[d]
23	–		O	**7y**	~33[d]
24	–		O	**7z**	90
25	–		O	**7aa**	~11[d]
26	–		O	**7ab**	62
27	–	propenyl	O	**7ac**	>99
28	–	(*E*)-CH=CHPh	O	**7f**	97
29	–	penta-1,3-dienyl	O	**7ad**	84
30	–	Ph	S	**9a**	>99
31	–	4-OMe-Ph	S	**9b**	93

[a] Yields obtained from the corresponding iodo precursors **6**–**I**. [b] Reactions afforded a complex mixture of products. [c] Substituent numbering refers to the starting material **6**. [d] These compounds were obtained in poor yields and were not analytically pure. Approximate yields are given, but full characterization was not obtained for these products.

2-chloropyridin-3-yl and the pyrrol-2-yl precursors, leading to complex reaction mixtures (Table 3, entries 10 and 11). Good to excellent yields of products were also obtained from substrates incorporating additional substitution on the *ortho*-bromoanilide ring (Table 3, entries 12–16). Simple 2-alkyl- or 2-benzyl-substituted benzoxazoles could also be obtained in excellent yields (Table 3, entries 17–19). The presence of an additional carbonyl group at the β position, however, led to complex mixtures of products (Table 3, entries 20 and 21). It was also desirable to test whether α-amino acid derived substrates could be applied in the reaction.[13b] The free proline derived precursor, **6x**, and the corresponding 9-fluorenylmethoxycarbonyl protected precursor, **6y**, both afforded low yields of adducts (Table 3, entries 22–23). However, the *N*-Cbz protected proline derived compound, **6z**, was converted to the benzoxazole, **7z**, in 90% yield (Table 3, entry 24). The presence of a neighboring NH group, as in the Cbz protected phenylalanine derived precursor, **6aa**, led to a very poor yield of **7aa** (Table 3, entry 25). A moderate yield of 62% was obtained for the alkyl phthalimide derived product, **7ab** (Table 3, entry 26). Alkenyl or dienyl substitution could also be introduced at the C2 position of the benzoxazole ring using substituted acrylamide precursors (Table 3, entries 27–29). In addition to the formation of benzoxazoles, two examples of benzothiazoles **9** were also included as part of the parallel-synthesis study. The *N*-(2-bromophenyl)-thiobenzamide **8a** and *N*-(2-bromophenyl)-4-methoxythiobenzamide **8b** starting materials were readily synthesized from the corresponding amides using Lawesson's reagent in 94 and 95%, respectively. Intramolecular C–S bond formation, using the same protocol developed for the benzoxazole chemistry, provided excellent yields of both benzothiazole **9a** and benzothiazole **9b**.

TABLE 4. Comparative Study on the Intramolecular Cross-Coupling of Amides 6a and 6a–Cl to Benzoxazole 7a



6a-Cl X = Cl
6a X = Br

7a

time (h)	conversion of chloride **6a–Cl**[a] (%)	conversion of bromide **6a**[a] (%)
1	12	63
3	33	99
6	59	≥99
12	94	≥99
24	98	≥99

[a] Reaction conversion was determined by ^{1}H NMR analysis.

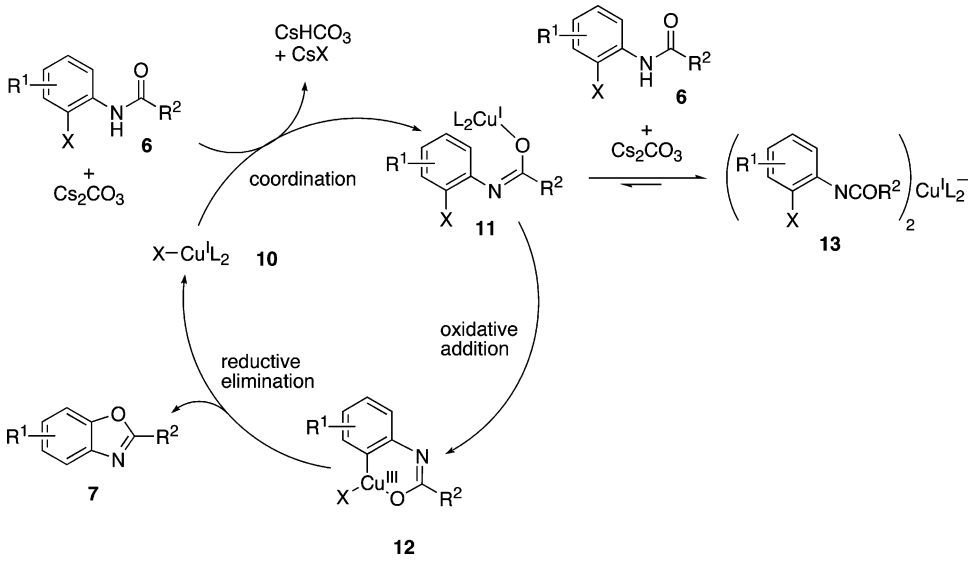
The successful synthesis of substituted benzoxazoles from bromo and iodo precursors encouraged us to evaluate the reactivity of the corresponding chloro precursors. The reaction of *N*-(2-chlorophenyl)-benzamide, under the standard reaction conditions over 48 h, gave the product **7a** in 99% yield. A more detailed comparison of the reactivity of the bromide and the reactivity of the chloride precursors revealed that intramolecular cross-coupling of both amide **6a** and amide **6a–Cl** were complete in 3 and 24 h, respectively (Table 4).

By an analogy with other Cu- and Pd-catalyzed C–X bond formations,[9,17,37,38] the most likely mechanism for the reaction involves the coordination of the amide group of **6** with **10** to give **11**, followed by an oxidative insertion to **12**, and then a reductive elimination to release product **7** with concomitant

(37) For an excellent discussion of the mechanism of Cu-catalyzed C–N bond formation from aryl halides, see: Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607–5622.

(38) See also: (a) Cohen, T.; Wood, J.; Dietz, A. G., Jr. *Tetrahedron Lett.* **1974**, *15*, 3555–3558. (b) Cohen, T.; Cristea, I. *J. Am. Chem. Soc.* **1976**, *98*, 748–753. (c) Allred, G. D.; Liebskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.

SCHEME 3. Mechanistic Proposal for the Copper-Catalyzed Formation of 7



regeneration of **10** (Scheme 3). The initial coordination to copper in **11** is supported by the lack of reactivity of the halo substituents at other positions in the ring under the copper-catalyzed conditions. Our study of benzimidazole formation revealed similar selectivity for the copper-catalyzed reactions, whereas the use of palladium catalysis led to competing debromination.[7] The chelating 1,10-phenanthroline ligand may serve to avoid multiple coordination of Cu by the amide substrate in **13**, as has been proposed by Buchwald for intermolecular Cu-catalyzed amidation reactions.[39] The greater reactivity of the bromo- over the chloro-based substrates (Table 4) lends some support to the oxidative addition being the rate-limiting step. Various studies, including our own investigations,[33] have shown that copper in its different oxidation states (Cu (bronze), Cu^{I}, or Cu^{II}) are catalytically active, presumably a result of their conversion into the same active species under the reaction conditions.[38b] It also seems likely that a Cu(I)−Cu(III) reaction manifold is involved. It is likely that reductive amination from copper(III) intermediates would proceed much faster than that from copper(II) intermediates. The requirement of atmospheric oxygen in copper-mediated C−O and C−N bond formations in the reaction of organoboron reagents with alcohols and amines has also been invoked as evidence for the involvement of copper(III) intermediates in these related cross-coupling reactions.[40]

Conclusion

The copper-catalyzed cyclization of *ortho*-haloanilides is a generally applicable approach to benzoxazole ring formation. A reaction using 5 mol % of copper(I)iodide could be achieved with either 1,10-phenanthroline or *N*,*N*′-dimethylethylenediamine as ligands, but 1,10-phenanthroline, in general, showed greater substrate tolerance. The approach is readily applied to the synthesis of substituted benzoxazoles through incorporation of appropriately positioned substituents on the *ortho*-haloanilide precursors. The reaction could also be adapted for benzothiazole formation using thioamide substrates. The high product yields and straightforward purification allowed this reaction to be adapted to a parallel-synthesis format. Overall, this approach complements the more commonly used strategies for benzoxazole formation, which require 2-aminophenols as substrates. Finally, it is noteworthy that, in comparison to the results obtained using copper catalysis, Pd catalysts do not appear to promote cyclization to benzoxazoles, as shown by previous reports[26,28] and our own observations. This observation differs from comparable cyclizations to benzimidazoles and benzothiazoles,[7,8] as well as other heterocycles,[41] where both Cu and Pd lead to good yields of cyclized products. Further studies on related reactions and their application to azole synthesis will be reported in due course.

Experimental Section

General Procedure for the Preparation of Benzoxazoles and Benzothiazoles via an Intramolecular Process. The reactions were set up in a parallel-synthesis fashion using reaction tubes with a water-cooled head at the top of the tubes (Radleys Discovery Technologies Carousel Reaction Stations), and were performed on a 1.0-mmol scale in groups of 12 reactions. To a mixture of the bromo- (or in some cases the chloro- or iodo-) amide precursor **6** or thioamide precursor **8** (1.0 mmol), CuI (9.5 mg, 0.05 mmol), 1,10-phenanthroline (18.8 mg, 0.10 mmol), and Cs_2CO_3 (0.49 g, 1.5 mmol) was added DME (8 mL) at room temperature, under a nitrogen atmosphere. The reaction was refluxed for 24 h and then allowed to cool to room temperature. To the reaction mixture was added H_2O (8 mL) and then CH_2Cl_2 (8 mL). After stirring for 10 min, each solution was filtered through a hydrophobic membrane, with the denser DME/CH_2Cl_2 layer passing through the hydrophobic membrane and the aqueous layer remaining in the reservoir. The reservoir was washed with CH_2Cl_2 (2 × 2 mL). The combined organic layers were then evaporated under reduced pressure. The final product, **7** or **9**, was passed through a short layer of silica gel to remove any traces of copper salts, ligand, byproducts, or remaining starting material.

(2*S*)-2-Benzoxazol-2-yl-pyrrolidine-1-carboxylic Acid Benzyl Ester (7z). The product was isolated by passage through a short silica gel column (1:2, EtOAc/hexanes) as a colorless oil in 90% yield (0.290 g). TLC (1:2, EtOAc/hexanes), $R_f = 0.3$; IR (film) δ

(39) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120−4121.

(40) Chan, D. M. T.; Lam, P. Y. S. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 205−240.

(41) See, for example: Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475−14484.

3063, 3033, 2955, 2881, 1710, 1570, 1455, 1413, 1356, 1241, 1153, 1116, 1086, 766, 749, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.68−7.78 (m, 1H), 7.28−7.58 (m, 5H), 7.68−7.22 (m, 3H), 4.94−5.31 (m, 3H), 3.77−390 (m, 1H), 3.57−3.75 (m, 1H), 2.32−2.51 (m, 1H), 2.11−2.32 (m, 2H), 1.95−2.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, rotamers) δ 166.7, 166.5, 154.9, 154.4, 150.8, 150.6, 141.2, 141.1, 136.7, 136.3, 128.5, 128.2, 128.0, 127.7, 127.6, 127.5, 127.0, 124.92, 124.91, 124.4, 124.3, 120.1, 120.0, 110.7, 67.2, 67.0, 55.5, 55.1, 47.1, 46.6, 32.5, 31.4, 24.3, 23.6. MS (EI) *m*/*z*: 323 (11), 322 (37, M^+), 209 (11), 187 (18), 160 (22), 146 (23), 92 (13), 91 (100). HRMS (EI): calculated for (M^+) $C_{19}H_{18}N_2O_3$, 322.1317; observed, 322.1311.

2-(2-Benzoxazol-2-yl-ethyl)isoindole-1,3-dione (7ab). The product was isolated by passage through a short silica gel column (1:3, EtOAc/hexanes) as a colorless oil in 62% yield (0.180 g). Mp 179−180 °C; TLC (1:2, EtOAc/hexanes), R_f = 0.4; IR (film) δ 2946, 1774, 1709, 1614, 1572, 1456, 1433, 1395, 1362, 1231, 1167, 1030, 930, 768, 754, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81−7.89 (m, 2H), 7.69−7.78 (m, 2H), 7.62−7.69 (m, 1H), 7.44−7.52 (m, 1H), 7.27−7.36 (m, 2H), 4.26 (t, J = 7.1 Hz, 2H), 3.36 (t, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.9, 163.4, 150.9, 141.2, 134.2, 134.1, 132.0, 124.9, 124.3, 123.5, 123.4, 119.8, 110.4, 48.2, 35.1, 27.8. MS (EI) *m*/*z*: 293 (26), 292 (100, M^+), 160 (65), 146 (18), 145 (71), 104 (16). HRMS (EI): calculated for (M^+) $C_{17}H_{12}N_2O_3$, 292.0848; observed, 292.0851.

2-Penta-1,3-dienylbenzoxazole (7ad). The product was isolated by passage through a short silica gel column (2:1, CH_2Cl_2/hexanes) as a yellowish oil in 84% yield (0.155 g). TLC (2:1, CH_2Cl_2/hexanes), R_f = 0.5; IR (film) δ 3060, 2970, 2932, 1715, 1642, 1538, 1455, 1352, 1243, 1108, 1003, 762, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65−7.73 (m, 1H), 7.26−7.52 (m, 4H), 6.42 (dd, J = 15.6 Hz, J = 0.6 Hz, 1H), 6.26−6.38 (m, 1H), 6.08−6.21 (m, 1H), 1.90 (dd, J = 7.5 Hz, J = 0.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1, 150.4, 142.3, 140.1, 137.4, 130.7, 124.9, 124.3, 119.7, 114.8, 110.2, 18.7. MS (EI) *m*/*z*: 185 (33, M^+), 175 (19), 174 (11), 171 (13), 170 (100), 146 (30), 145 (11). HRMS (EI): calculated for (M^+) $C_{12}H_{11}NO$, 185.0841; observed, 185.0840.

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Supporting Information Available: Experimental procedures and characterization data for **6**, **6**−**I**, **6a**−**Cl**, **7**, **8**, and **9** and ^1H and ^{13}C NMR spectra of **7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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