

# Synthesis of 2-Arylbenzoxazoles by Copper-Catalyzed Intramolecular Oxidative C–O Coupling of Benzanilides\*\*

Satoshi Ueda and Hideko Nagasawa\*

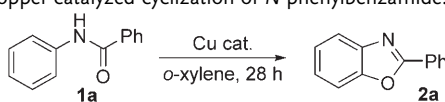
The benzoxazole moiety is an important structural motif in many biologically active natural products and pharmaceutical compounds.<sup>[1]</sup> Development of efficient methods to construct functionalized benzoxazole scaffolds is thus highly relevant for drug discovery. Traditional methods for the preparation of the benzoxazole framework include condensation reactions of 2-aminophenols with carboxylic acids in the presence of acid or the reaction of 2-aminophenols with aldehydes and subsequent oxidative cyclization of the imine intermediate.<sup>[2]</sup> Recently, general methods for the copper-catalyzed intramolecular C–O coupling reaction of 2-haloanilides were reported.<sup>[3]</sup> Although these approaches provide efficient access to benzoxazoles, they each require *ortho*-substituted anilines as starting material. We report herein the development of a straightforward and versatile method to obtain functionalized benzoxazoles by copper-catalyzed intramolecular oxidative aromatic C–O bond formation in readily available benzanilides.

Over the past decade, extensive efforts have been made to develop methodologies that directly functionalize aromatic C–H bonds to construct C–C<sup>[4]</sup> or C–N/O<sup>[5]</sup> bonds using transition-metal catalysis. Many of these reactions were aided by directing groups which typically possess a lone pair that can coordinate to the transition-metal catalyst to direct *ortho* functionalization via a five- or six-membered metallacycle.<sup>[6]</sup>

The aminoacyl group has served as the directing group in several *ortho* C–H functionalization reactions of anilides.<sup>[7]</sup> Therefore, we reasoned that, with an appropriate catalytic system, benzoxazoles could be produced through C–H bond activation and subsequent intramolecular coupling with the amide oxygen of the anilides. To develop this idea, we first optimized conditions for the conversion of benzanilide **1a** into 2-phenylbenzoxazole **2a**. Preliminary screening of a range of transition-metal catalysts (containing palladium, rhodium, or copper) showed that only the copper catalysts gave the cyclized product, albeit in small amounts. Variations in the nature of the copper catalyst, solvents, and temperature

were then explored to optimize the yields. These investigations revealed that **2a** could be obtained in 81 % yield in the presence of Cu(OTf)<sub>2</sub> (20 mol %) at 140 °C in *o*-xylene under an atmosphere of O<sub>2</sub> (Table 1, entry 1).<sup>[8]</sup> During the course of

**Table 1:** Copper-catalyzed cyclization of *N*-phenylbenzamide.<sup>[a]</sup>

				
Entry	Cu catalyst [mol %]	Gas (1 atm)	T [°C]	Yield [%] <sup>[b]</sup>
1	Cu(OTf) <sub>2</sub> [20]	O <sub>2</sub>	140	81 (77) <sup>[c]</sup>
2	Cu(OTf) <sub>2</sub> [20]	Air	140	39
3	Cu(OTf) <sub>2</sub> [20]	Air	160	89 <sup>[d]</sup> (86) <sup>[c-e]</sup>
4	Cu(OTf) <sub>2</sub> [10]	O <sub>2</sub>	140	50
5	Cu(OTf) <sub>2</sub> [20]	O <sub>2</sub>	140	22
6	Cu(OAc) <sub>2</sub> [20]	O <sub>2</sub>	140	11
7	Cu(ClO <sub>4</sub> ) <sub>2</sub> ·6 H <sub>2</sub> O [20]	O <sub>2</sub>	140	38 <sup>[f]</sup>
8	CuCl <sub>2</sub> [20]	O <sub>2</sub>	140	0 <sup>[g]</sup>
9	CuBr <sub>2</sub> [20]	O <sub>2</sub>	140	0 <sup>[h]</sup>

[a] The reaction was carried out in 0.25 mmol scale, unless otherwise noted. [b] Yields of isolated product. [c] Gram-scale reaction in parenthesis (6.0 mmol scale). [d] 1,2-Dichlorobenzene was used as solvent. [e] Reaction time = 48 h. [f] *N*-(2-chlorophenyl)benzamide was also formed in 14 % yield. [g] *N*-(2-chlorophenyl)benzamide was formed in 10 % yield. [h] *N*-(2-cromophenyl)benzamide was formed in 6 % yield.

our present work, Buchwald and Brasche have reported impressive results on the development of intramolecular oxidative C–N coupling reactions for the synthesis of benzimidazoles using a catalytic system of Cu<sup>II</sup>/O<sub>2</sub>.<sup>[5a]</sup> However, to our knowledge, there is no precedent for amide oxygen functioning as a nucleophile in catalytic oxidative coupling reactions. Using an atmosphere of air in place of O<sub>2</sub> reduced the yield of **2a** to 39 % (Table 1, entry 2). However, the reaction at 160 °C in 1,2-dichlorobenzene achieved the best yield, even in an atmosphere of air (Table 1, entry 3).<sup>[8]</sup> On reducing the amount of catalyst to 10 mol % and reacting under an O<sub>2</sub> atmosphere, the yield was reduced to 50 % (Table 1, entry 4). The reaction also proceeded employing Cu(OTf), Cu(OAc)<sub>2</sub> or Cu(ClO<sub>4</sub>)<sub>2</sub> as catalysts, albeit in lower yield (Table 1, entries 5–7). The use of CuCl<sub>2</sub> and CuBr<sub>2</sub> gave small amounts of *o*-halogenated products and none of the desired product (Table 1, entries 8 and 9).

Substituent diversity was achieved using a variation on the optimized reaction conditions with a catalytic system of Cu(OTf)<sub>2</sub>/O<sub>2</sub> (Table 2). Reaction of benzanilides substituted at the *meta* or *para* position with electron-donating alkyl or

[\*] Dr. S. Ueda, Prof. H. Nagasawa  
Laboratory of Medicinal and Pharmaceutical Chemistry  
Gifu Pharmaceutical University  
5-6-1 Mitahora-higashi, Gifu 502-8585 (Japan)  
Fax: (+81) 58-237-8571  
E-mail: hnagasawa@gifu-pu.ac.jp

[\*\*] This work was supported in part by a Grant from The Saijiro Endo Memorial Foundation for Science & Technology and a Grant-in-Aid for Young Scientists (Start-up) (19890179) from Japan Society for the Promotion of Science (JSPS). We thank Dr. K. L. Kirk (NIDDK, NIH) for helpful suggestions.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200801240>.

**Table 2:** Synthesis of substituted 2-phenylbenzoxazoles<sup>[a]</sup>

Entry	Substrate	Product	Yield [%] <sup>[b]</sup>
1	<b>1b</b> (R = Me)	<b>2b</b>	92
2	<b>1c</b> (R = OEt)	<b>2c</b>	91
3	<b>1d</b> (R = Ph)	<b>2d</b>	72
4	<b>1e</b> (R = CO <sub>2</sub> Me)	<b>2e</b>	40 <sup>[c,d]</sup>
5	<b>1f</b> (R = COPh)	<b>2f</b>	63
6	<b>1g</b> (R = F)	<b>2g</b>	80
7	<b>1h</b> (R = Cl)	<b>2h</b>	76
8	<b>1i</b> (R = Br)	<b>2i</b>	61
9	<b>1j</b> (R = Me)	<b>2j</b>	86 (80) <sup>[e]</sup>
10	<b>1k</b> (R = OMe)	<b>2k</b>	93
11	<b>1l</b> (R = Me)	<b>2l</b>	51
12	<b>1m</b> (R = OMe)	<b>2m</b>	55
13	<b>1n</b>	<b>2n</b>	75
14	<b>1o</b>	<b>2o</b>	70
15	<b>1p</b>	<b>2p</b>	82
16	<b>1q</b>	<b>2q</b>	61 <sup>[d]</sup>

[a] The reaction was carried out in 0.25 mmol scale, unless otherwise noted. [b] Yields of isolated product. [c] With 41 % substrate recovery. [d] Reaction time = 48 h. [e] Gram-scale reaction in parenthesis (6.0 mmol scale).

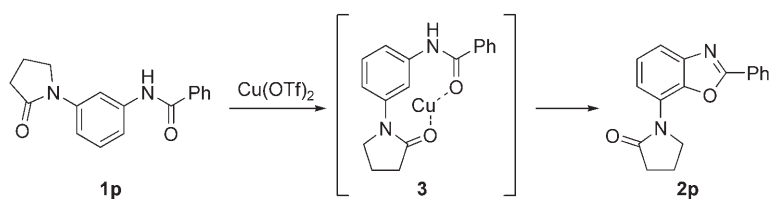
alkoxy groups gave the corresponding benzoxazoles in high yield (Table 2, entries 1, 2, 9 and 10). Sterically demanding *ortho* substituted substrates provided the corresponding benzoxazoles in moderate yield (Table 2, entries 11 and 12), indicating that steric congestion around the amide decreases the reaction efficacy. The presence of either halogen or electron-withdrawing groups was tolerated but resulted in slightly decreased reactivity and some recovered substrate (Table 2, entries 4–8 and 16). The regioselectivity of the cyclization significantly depends on the arene substituents. Thus, C–O bond formation took place exclusively at the less sterically hindered position in the reaction of *meta*-methyl- or methoxy-substituted anilides, to give 2,5-disubstituted benzoxazoles (Table 2, entries 9 and 10). *N*-(Naphthalen-2-yl)benzamide also exclusively cyclized at the less sterically hindered  $\beta$ -position (Table 2, entry 13). Conversely, the substrate with a pyrrolidin-2-one group at the *meta* position (**1p**) cyclized at the more sterically hindered position to give 2,7-disubstituted benzoxazole **2p** in 81 % yield as the

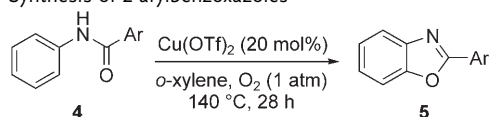
sole product (Table 2, entry 15). A similar result was obtained for the substrate with a *meta*-methoxycarbonyl substituent, which cyclized exclusively at the 2-position of the anilide to give the 2,7-disubstituted benzoxazole **2q** (Table 2, entry 16). These results demonstrated that the regioselectivity of the cyclization could be controlled by the substituent of the anilides. The *meta* substituents of **1p** and **1q** seemingly act as an additional directing group to promote the formation of doubly coordinated intermediate such as **3**, leading to selective formation of 7-substituted benzoxazoles (Scheme 1).

Substituent diversity of the 2-aryl group was achieved using the catalytic system of Cu(OTf)<sub>2</sub>/O<sub>2</sub> (Table 3). From the reactions of various substrates with substituents at *meta* and/or *para* position of the benzamide ring, the corresponding 2-arylbenzoxazoles were obtained in generally good yield. Conversely, a lower yield was observed for the substrate with an *ortho*-methyl group (Table 3, entry 11). Together with the results of the reaction of *ortho*-substituted anilides (Table 2, entries 11 and 12), these results indicate that steric congestion around the amide moiety seems to decrease the efficacy of the reaction.

The reaction mechanism is uncertain at the present time. An intramolecular competition experiment using *ortho*-deuterium labeled substrate suggested that a hydrogen-abstraction step is not involved in the rate-limiting step.<sup>[9]</sup> A possible mechanism might be analogous to those proposed for other oxidative C–N/O coupling reactions.<sup>[5]</sup>

In summary, we have developed a novel copper-catalyzed intramolecular oxidative C–O coupling reaction for the efficient synthesis of 2-arylbenzoxazoles that complements the commonly used strategies for the synthesis of benzoxazoles. Advantages of our procedure include simplicity of

**Scheme 1.** Possible route for the 7-substituted benzoxazoles.

**Table 3:** Synthesis of 2-arylbenzoxazoles<sup>[a]</sup>


Entry	Ar	Product	Yield [%] <sup>[b]</sup>
1	4-Et-Ph	<b>5a</b>	85
2	3,4-di-Me-Ph	<b>5b</b>	70
3	4-OMe-Ph	<b>5c</b>	89
4	3,4-di-OMe-Ph	<b>5d</b>	61
5	4-CO <sub>2</sub> Me-Ph	<b>5e</b>	83
6	4-F-Ph	<b>5f</b>	80
7	4-Cl-Ph	<b>5g</b>	78 (79) <sup>[c]</sup>
8	4-Br-Ph	<b>5h</b>	72
9	4-I-Ph	<b>5i</b>	81
10	Naphthalene-2-yl	<b>5j</b>	86
11	2-Me-Ph	<b>5k</b>	42 <sup>[d]</sup>
12	Thiophen-2-yl	<b>5l</b>	44 <sup>[e]</sup>

[a] The reaction was carried out in 0.25 mmol scale, unless otherwise noted. [b] Yields of isolated product. [c] Gram-scale reaction in parenthesis (6.0 mmol scale). [d] With 35 % substrate recovery. [e] With 33 % substrate recovery.

operation, high regioselectivity, and use of readily available, inexpensive, and harmless starting materials.

Received: April 14, 2008

Published online: July 10, 2008

**Keywords:** C–H activation · C–O bond formation · copper · homogeneous catalysis · nitrogen heterocycles

[1] For selected examples, see: a) M. S. Malamas, E. S. Manas, R. E. McDevitt, I. Gunawan, Z. B. Xu, M. D. Collini, C. P. Miller, T. Dinh, R. A. Henderson, J. C. Keith, Jr., H. A. Harris, *J. Med. Chem.* **2004**, *47*, 5021; b) H. Razavi, S. K. Palaninathan, E. T. Powers, R. L. Wiseman, H. E. Purkey, N. N. Mohamedmohaideen, S. Deechongkit, K. P. Chiang, M. T. A. Dendle, J. C.

Sacchettini, J. W. Kelly, *Angew. Chem.* **2003**, *115*, 2864; *Angew. Chem. Int. Ed.* **2003**, *42*, 2758; c) M. Taki, J. L. Wolford, T. V. O'Halloran, *J. Am. Chem. Soc.* **2004**, *126*, 712; d) See also an extensive list in footnote 2 of reference [3b].

- [2] For an overview of synthetic methods for the synthesis of benzoxazoles, see [3a] and references therein.
- [3] a) R. D. Viirre, G. Evindar, R. A. Batey, *J. Org. Chem.* **2008**, *73*, 3452; b) G. Evindar, R. A. Batey, *J. Org. Chem.* **2006**, *71*, 1802; c) N. Barbero, M. Carril, R. San Martín, E. Dominguez, *Tetrahedron* **2007**, *63*, 10425.
- [4] For selected examples, see: a) L. Ackermann, A. Althammer, *Angew. Chem.* **2007**, *119*, 1652; *Angew. Chem. Int. Ed.* **2007**, *46*, 1627; b) L. Ackermann, A. Althammer, R. Born, *Angew. Chem.* **2006**, *118*, 2681; *Angew. Chem. Int. Ed.* **2006**, *45*, 2619; c) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 1128; d) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050; e) J.-P. Leclerc, K. Fagnou, *Angew. Chem.* **2006**, *118*, 7945; *Angew. Chem. Int. Ed.* **2006**, *45*, 7781; f) T. Watanabe, S. Ueda, S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Chem. Commun.* **2007**, 4516; g) J. Barluenga, M. Trincado, E. Rubio, J. M. Gonzalez, *Angew. Chem.* **2006**, *118*, 3212; *Angew. Chem. Int. Ed.* **2006**, *45*, 3140; h) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904.
- [5] a) G. Brasche, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 1958; *Angew. Chem. Int. Ed.* **2008**, *47*, 1932; b) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790; c) K. Inamoto, T. Saito, M. Katsuno, T. Sakamoto, K. Hiroya, *Org. Lett.* **2007**, *9*, 2931; d) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048; e) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560.
- [6] J.-Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041.
- [7] a) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586; b) O. Daugulis, V. G. Zaitsev, *Angew. Chem.* **2005**, *117*, 4114; *Angew. Chem. Int. Ed.* **2005**, *44*, 4046; c) X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang, Z. Shi, *J. Am. Chem. Soc.* **2006**, *128*, 7416; d) S. Yang, B. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 6066; e) V. G. Zaitsev, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 4156.
- [8] We also performed a gram-scale reaction that proceeded in good yield. See Supporting Information for the experimental details.
- [9] See Supporting Information for the measurement of the deuterium isotope effect.