

# Copper(II)-Catalyzed Conversion of Bisaryloxime Ethers to 2-Arylbenzoxazoles via C–H Functionalization/C–N/C–O Bonds Formation

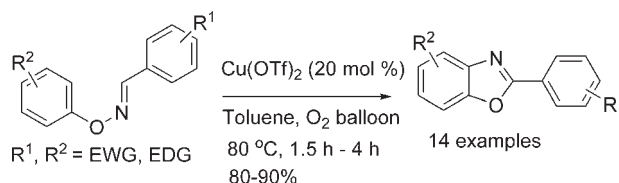
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## ABSTRACT



A copper(II)-catalyzed conversion of bisaryloxime ethers to 2-arylbenzoxazoles has been developed. The reaction involves a cascade C–H functionalization and C–N/C–O bond formation under oxygen atmosphere.

Recent advances in cross-coupling reactions by transition metal catalysis have led to the development of effective methods for the construction of carbon–carbon and carbon–heteroatom bonds.<sup>1</sup> Among these, the direct functionalization of aryl C–H bonds is a particularly valuable

tool in synthetic chemistry.<sup>2–4</sup> These reactions are usually aided by the directing groups that can coordinate to the catalyst to direct ortho functionalization via a five- or six-membered metallocycle. Herein, we wish to report a new copper(II)-catalyzed rearrangement of bisaryloxime ethers to 2-arylbenzoxazoles in the presence of molecular oxygen. This process involves a cascade C–H functionalization and C–N/C–O bond formation.

Benzoxazoles are an important class of heterocycles that are encountered in a number of biologically active natural products and medicinally significant compounds.<sup>5</sup> The common classical methods used for the construction of the benzoxazole framework start from 2-aminophenols, and often they are limited due to nonavailability of suitably substituted starting precursors and, sometimes, the requirement of harsh reaction conditions such as involvement of

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(2) For some examples on C–C cross-coupling, see: (a) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (b) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 781. (c) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830. (d) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (f) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288. (g) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. (h) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (i) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, *132*, 9602.

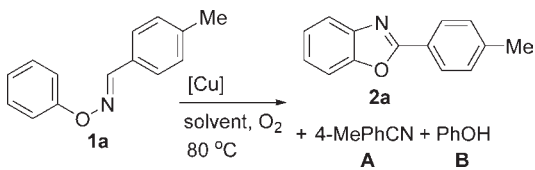
(3) For some examples on C–N cross-coupling, see: (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (b) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (c) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931.

(4) For examples on C–O cross-coupling, see: (a) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272. (b) Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415.

(5) For some examples, see: (a) Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Gonzalez, E. *Org. Lett.* **1999**, *1*, 527. (b) 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.; Sacchetti, J. C.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2758. (c) Taki, M.; Wolford, J. L.; O'Halloran, T. V. *J. Am. Chem. Soc.* **2004**, *126*, 712.

strong acids in combination with elevated temperature.<sup>6</sup> Some of these drawbacks have been recently overcome by using the cross-coupling reactions that allow the construction of the target heterocycles under relatively milder conditions.<sup>2g,4,7</sup>

**Table 1.** Screening of Reaction Conditions<sup>a</sup>



entry	[Cu]	solvent	time (h)	conv <sup>b</sup> (%)	yield (%) <sup>c</sup> <b>2a</b>	<b>A + B</b>
1	Cu(OTf) <sub>2</sub>	toluene	3	100	90	trace
2	Cu(OTf) <sub>2</sub>	xylene	4	100	88	5
3	Cu(OTf) <sub>2</sub>	DMSO	0.5	100	40	50
4	Cu(OTf) <sub>2</sub>	DMF	1.5	100	45	43
5	Cu(OTf) <sub>2</sub>	1,4-dioxane	12	70	35	32
6	Cu(OTf) <sub>2</sub>	THF	12	80	37	35
7	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	toluene	24	50	30	16
8	CuSO <sub>4</sub> ·5H <sub>2</sub> O	toluene	24	47	35	12
9	Cu(OTf) <sub>2</sub>	toluene	8	100	80	5 <sup>d</sup>
10	Cu(OTf) <sub>2</sub>	toluene	4	60	55	trace <sup>e</sup>
11	-	toluene	5	trace	-	trace

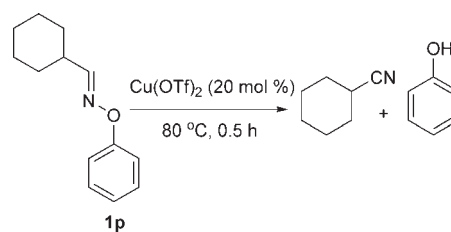
<sup>a</sup> Reaction conditions: bisaryloxime ether **1a** (0.5 mmol) and [Cu] (20 mol %) were stirred in solvent (2 mL) at 80 °C under oxygen balloon. <sup>b</sup> Determined by 400 MHz <sup>1</sup>H NMR. <sup>c</sup> Isolated yield. <sup>d</sup> Cu(OTf)<sub>2</sub> (10 mol %) used. <sup>e</sup> Reaction temperature = 70 °C.

Bisaryloxime ethers were prepared from arylaldehydes and aryloxyamines.<sup>8</sup> The latter could be obtained by cross-coupling of arylboronic acids with *N*-hydroxyphthalimide followed by treatment with hydrazine monohydrate. The rearrangement of the aryloxime ethers was optimized by using bisaryloxime ether **1a** as a model substrate (Table 1). To our delight, the substrate readily underwent conversion to give 2-arylbenzoxazole **2a** along with a trace of 4-methylnitrile **A** and phenol **B** in the presence of 20 mol %

copper(II) salts under oxygen atmosphere. Screening of copper sources revealed Cu(OTf)<sub>2</sub> as the most effective catalyst, while other copper sources afforded inferior results. With Cu(OTf)<sub>2</sub> as the catalyst, we went on to screen other reaction parameters. The reaction was found to proceed more selectively in nonpolar solvents than in polar solvents, and toluene was found to be the solvent of choice (entries 1–6). The reaction in xylene required slightly longer reaction time to afford similar results. The effect of temperature was studied, and 80 °C afforded the best results. Lower catalyst loading (10 mol %) led to a slower rate of the target reaction along with increase in the yield of the byproduct (entry 9). A control experiment confirmed that in the absence of copper catalyst, for 5 h, a trace of nitrile **A** and phenol **B** were obtained along with starting material **1a**. These results reveal that the formation of **A** and **B** takes place independently due to cleavage of the N–O bond under heating and not by the copper-catalysis.<sup>8</sup>

With the optimized conditions, the scope of the reaction with various bisaryloxime ethers **1b–n** was next explored (Table 2, Scheme 1). The substrates bearing electron-withdrawing or -donating groups in the phenyl rings proceeded to react smoothly to provide the corresponding benzoxazoles **2b–j** in 80–88% yield. The structure of compound **2h** was confirmed by X-ray analysis (see the Supporting Information). Benzoxazoles **2k–n** having 2-thiophenyl-, 2-naphthyl-, and 2-quinolidinyl units could be prepared in 80–85% yield.

Using these conditions, the reaction of alkyl aryloxime ether **1p** was further studied (see below). However, no desired rearrangement was observed and the substrate underwent decomposition to give cyclohexanecarbonitrile and phenol in quantitative yield.



To reveal the practical utility of the protocol, the reaction of bisaryloxime ether **1a** was studied on a 10 mmol scale and the rearrangement readily occurred to give the desired **2a** in 86% yield.

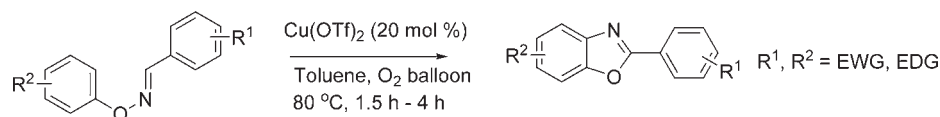
Regarding the mechanism, the bisaryloxime ether **1o** having an  $\alpha$ -methyl group does not undergo any reaction, which suggests that the imine C–H is crucial for this process. Furthermore, benzonitrile showed no reaction with phenol under similar conditions suggesting that the reaction does not involve an oxonium intermediate **3**.<sup>9</sup> In addition, the crossover experiment with a mixture of **1a** and **1m** afforded **2a** and **2m** as the only products, which suggests that the reaction involves an intramolecular

(6) For examples, see: (a) Dopp, H.; Dopp, D. In *Houben-Weyl: Methoden der Organischen Chemie*; Schumann, E., Ed.; Thieme: Stuttgart, Germany, 1993; Vol. E8a, p 1020. (b) Boyd, G. V. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Schumann, E., Ed.; Thieme: Stuttgart, Germany, 2002; Vol. 11, p 481. (c) Boyd, G. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Potts, K. T., Eds.; Pergamon Press: New York, 1984; Vol. 6, p 177.

(7) Benzoxazole synthesis: From 1,2-dihaloarenes, see: (a) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661. (b) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452. From 2-haloanilines, see: (c) Bonnamour, J.; Bolm, C. *Org. Lett.* **2008**, *10*, 2665. (d) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (e) Barbero, N.; Carril, M.; SanMartin, R.; Dominguez, E. *Tetrahedron* **2007**, *63*, 10425. (f) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (g) Saha, P.; Ali, M. A.; Ghosh, P.; Punniyamurthy, T. *Org. Biomol. Chem.* **2010**, *8*, 5692.

(8) For the synthesis and N–O cleavage of oxime ether, see: Johnson, S. M.; Petrassi, H. M.; Palaninathan, S. K.; Mohamedmohaideen, N. N.; Purkey, H. E.; Nochols, C.; Chiang, K. P.; Walkup, T.; Sacchettini, J. C.; Sharpless, K. B.; Kelly, J. W. *J. Med. Chem.* **2005**, *48*, 1576.

(9) Abramovitch, R. A.; Inbasekaran, M.; Kato, S. *J. Am. Chem. Soc.* **1973**, *95*, 5428.

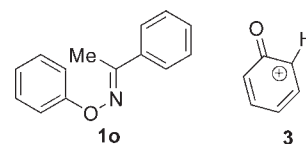
**Table 2.** Cu(OTf)<sub>2</sub>-Catalyzed Conversion of Bisaryloxime Ethers to Benzoxazoles

entry	substrate		time (h)	product	yield (%) <sup>b,c</sup>
1		<b>1a</b> R <sup>1</sup> = Me	3.0		<b>2a</b> 90
2		<b>1b</b> H	3.0		<b>2b</b> 80
3		<b>1c</b> Br	3.0		<b>2c</b> 81
4		<b>1d</b> Cl	3.5		<b>2d</b> 82
5		<b>1e</b> OMe	3.5		<b>2e</b> 85
6		<b>1f</b>	3.0		<b>2f</b> 83
7		<b>1g</b> R <sup>1</sup> = Cl; R <sup>2</sup> = Me	3.0		<b>2g</b> 88
8		<b>1h</b> R <sup>1</sup> = OMe, R <sup>2</sup> = Cl	1.5		<b>2h</b> 84
9		<b>1i</b>	3.0		<b>2i</b> 80
10		<b>1j</b>	2.0		<b>2j</b> 80
11		<b>1k</b>	4.0		<b>2k</b> 80
12		<b>1l</b>	2.5		<b>2l</b> 80
13		<b>1m</b>	2.5		<b>2m</b> 81
14		<b>1n</b>	1.5		<b>2n</b> 85

<sup>a</sup> Reaction conditions: substrate **1a–n** (0.5 mmol) and Cu(OTf)<sub>2</sub> (20 mol %) were stirred in toluene (2 mL) at 80 °C under oxygen balloon. <sup>b</sup> Isolated yield. <sup>c</sup> A ~2–5% of nitrile and phenol were obtained as determined by <sup>1</sup>H NMR of the crude reaction mixture.

process. These experimental results reveal that the reaction might involve a Lewis acid catalyzed cascade rearrangement with C–H functionalization and C–N/C–O bond formation. Thus, the substrates **1a–n** may undergo chelation with Cu(OTf)<sub>2</sub> to give an intermediate **a** that could rearrange to provide **c** via **b**. The intermediate **c** can provide the target molecules **2a–n** by reductive elimination.<sup>4a</sup> Alternatively, **c** may be oxidized by another equivalent of Cu(OTf)<sub>2</sub>, forming a copper(III) intermediate **d** that may undergo reductive elimination to give the target products **2a–n**.<sup>4b</sup> The reduced

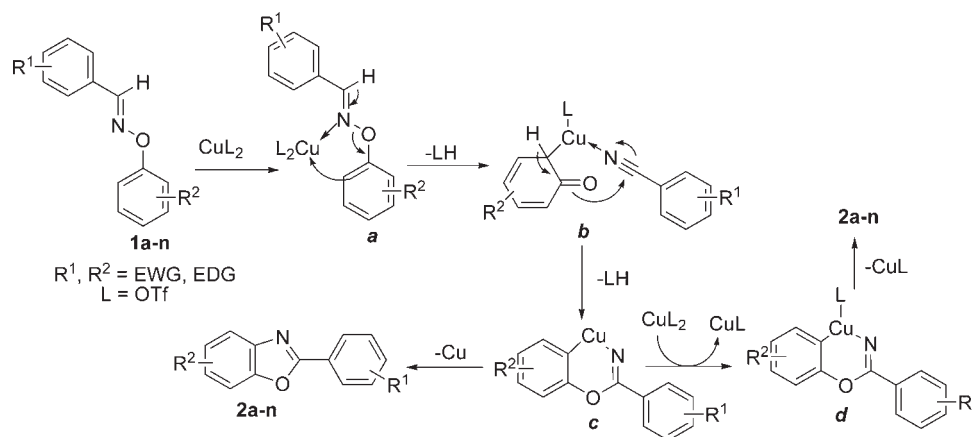
copper species may be oxidized by oxygen to complete the catalytic cycle.<sup>4,10</sup>



In conclusion, a copper(II)-catalyzed rearrangement of bisaryloxime ethers to substituted 2-arylbenzoxazoles has been developed by using molecular oxygen under neutral

(10) For example, see: Punniyamurthy, T.; Rout, L. *Coord. Chem. Rev.* **2008**, *252*, 134.

**Scheme 1.** Proposed Catalytic Cycle



conditions. The reaction affords a new route for the synthesis of substituted 2-arylbenzoxazoles. The detailed study on the mechanism is currently under investigation.

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**Supporting Information Available.** Experimental procedure, X-ray data and structure, characterization data, and NMR ( $^1H$  and  $^{13}C$ ) spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.