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Copper-Catalyzed C−H Alkoxylation of Azoles

Noriaki Takemura,[†] Yoichiro Kuninobu,*[,†,‡] and Motomu Kanai*[,†,‡]

Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and ERATO, Japan Science and Technology Agency (JST), Kanai Life Science Catalysis Project, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

kuninobu@mol.f.u-tokyo.ac.jp; kanai@mol.f.u-tokyo.ac.jp

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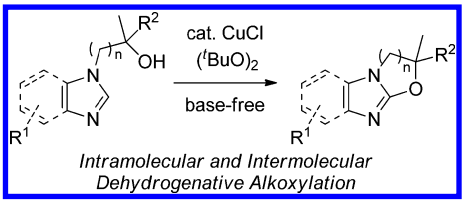
ABSTRACT



We achieved copper-catalyzed intramolecular and intermolecular alkoxylation of azoles. This reaction is a rare example of transition-metal-catalyzed C−H alkoxylation of heteroaromatic compounds. In addition, the alkoxylation reaction proceeded well even in gram scale. In most intermolecular alkoxylations, the use of an excess amount of alcohols (in some cases, alcohols are used as a solvent) is indispensable to efficiently promote the alkoxylation reaction, but this alkoxylation reaction proceeded using only 1 equiv of alcohols.

C−H transformations are attractive, effective, and ideal reactions because carbon−carbon and carbon−heteroatom bonds can be constructed directly from stable organic molecules.[1] The development of efficient and useful C−H transformations is therefore strongly desired. Carbon−oxygen bond forming reactions using alcohols as substrates via aromatic C−H bond activation, however, are rare due to both the high electronegativity of an oxygen atom and the great bond energy of metal−oxygen bonds formed in catalytic intermediates.[2] Although a metal-free oxidative coupling reaction between heterocycles and alcohols was recently reported,[3] C−C bond formation at the carbon atom adjacent to a hydroxy group of alcohols proceeded instead of C−H alkoxylation. In addition, oxidation of alcohols to aldehydes or ketones is generally more facile than carbon−oxygen bond formation under oxidative conditions.

As examples of aromatic C−H aryloxylation/alkoxylation, palladium- and copper-catalyzed synthesis of dibenzofuran derivatives through intramolecular aryloxylation,[4] iron-mediated intramolecular alkoxylation,[5] palladium-catalyzed

[†] The University of Tokyo.
[‡] Japan Science and Technology Agency (JST).

(1) For reviews, see: (a) Kakiuchi, F.; Murai, S. *Top. Organomet. Chem.* **1999**, *3*, 47. (b) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (d) Herrerías, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546. (e) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (f) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (h) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (i) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (j) Kuninobu, Y.; Takai, K. *Chem. Rev.* **2011**, *111*, 1938. (k) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (l) Borovik, A. S. *Chem. Soc. Rev.* **2011**, *40*, 1870. (m) Zhou, M.; Crabtree, R. H. *Chem. Soc. Rev.* **2011**, *40*, 1875. (n) Lu, H.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899. (o) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926. (p) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (q) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (r) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936.

(2) (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Li, W.; Sun, P. *J. Org. Chem.* **2012**, *77*, 8362.

(3) He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. *Org. Lett.* **2011**, *13*, 5016.

(4) (a) Wei, Y.; Yoshikai, N. *Org. Lett.* **2011**, *13*, 5504. (b) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250. (c) Zhao, J.; Wang, Y.; He, Y.; Liu, L.; Zhu, Q. *Org. Lett.* **2012**, *14*, 1078.

(5) Tang, L.; Pang, Y.; Yan, Q.; Shi, L.; Huang, J.; Du, Y.; Zhao, K. *J. Org. Chem.* **2011**, *76*, 2744.

(6) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203.

(7) (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (c) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476. (d) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (e) Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 9504.

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synthesis of dihydrobenzofurans through intramolecular alkoxylation,[6] and palladium-catalyzed directing-group-assisted intermolecular alkoxylation using alcohols as solvents (use of excess amounts of alcohols)[2b,7] have been reported. Heteroaromatics, however, have not been reported as substrates in C−H alkoxylations. In addition, intermolecular C−H alkoxylations are limited by the need for excess amounts of alcohol and directing groups.[2b,7] Efficient intra- and intermolecular catalytic alkoxylation of heteroaromatics has numerous potential applications to the synthesis of natural products, drugs, and organic functional materials. We are specifically interested in C−H alkoxylation of azoles for the development of new synthetic routes of delamanid, a promising drug candidate for the treatment of tuberculosis, and candesartan, a useful antihypertensive drug (Figure 1).[8,9] We report herein a copper-catalyzed intra- and intermolecular alkoxylation of azoles.

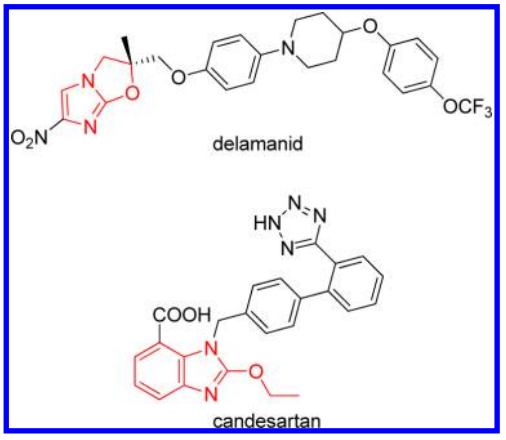
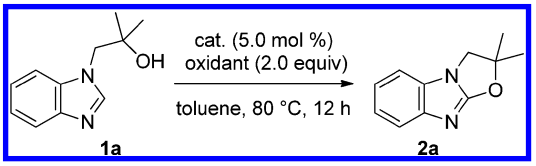


Figure 1. Pharmaceuticals that contain 2-alkoxyimidazole frameworks.

Transition-metal-catalyzed C−H functionalization (amination and C−C bond formation) of azoles is usually performed in the presence of a base.[10] Intramolecular alkoxylation of benzimidazole **1a** was first studied in the presence of several transition metal catalysts, oxidants, and bases, but the desired alkoxylation reaction did not proceed. Therefore, we next investigated base-free conditions. Treatment of **1a** with a catalytic amount of CuCl and 2.0 equiv of oxidant $(^tBuO)_2$ in toluene at 80 °C for 12 h led to an intramolecular alkoxylation reaction at the C-2 position, and benzoimidazodihydrooxazole **2a** was obtained in 98% yield (Table 1, entry 1).[11,12] Product derived from C−H alkoxylation of the benzene ring was not detected at all. This reaction was quite sensitive to reaction parameters (catalysts, oxidants, and solvents: Table 1). Changing the catalyst, CuCl, to other copper salts and complexes showed that only CuI was effective for the intramolecular oxidation (entry 3). Otherwise, **2a** was not formed or was generated in quite low yield (entries 2, 4−6).[13] Other first-row transition metal chlorides or their complexes did not promote the alkoxylation reaction (entries 7−11). The selection of an oxidant was also important. Silver carbonate Ag_2CO_3 provided **2a** in moderate yield (entry 12), whereas the use of other oxidants afforded no **2a** (entries 13−17).

Table 1. Investigation of Several Catalysts and Oxidants



entry	catalyst	oxidant	yield[a]
1	CuCl	$(^tBuO)_2$	98 (98)[b]
2	CuBr	$(^tBuO)_2$	3
3	CuI	$(^tBuO)_2$	70
4	CuCN	$(^tBuO)_2$	0
5	$Cu(OTf)(NCMe)_4$	$(^tBuO)_2$	7
6	$CuCl_2$	$(^tBuO)_2$	0
7	$MnCl_2$	$(^tBuO)_2$	0
8	$MnBr(CO)_5$	$(^tBuO)_2$	0
9	$FeCl_2$	$(^tBuO)_2$	0
10	$CoCl_2$	$(^tBuO)_2$	0
11	$NiCl_2$	$(^tBuO)_2$	0
12	CuCl	Ag_2CO_3	42
13	CuCl	$K_2S_2O_8$	0
14	CuCl	$PhI(OAc)_2$	0
15	CuCl	TBHP	0
16	CuCl	^tBuOOBz	0
17	CuCl	O_2 (1.0 atm)	0

[a] Yield was determined by ^1H NMR. [b] Isolated yield.

Next, we investigated the substrate scope and limitations of this C−H alkoxylation (Table 2). Various substituents, including electron-donating and -withdrawing groups as well as ester and amide functionalities, on the phenyl ring were tolerated (entries 1−9). Specifically, C−halogen

(8) Sasaki, H.; Haraguchi, Y.; Itotani, M.; Kuroda, H.; Hashizume, H.; Tomishige, T.; Kawasaki, M.; Matsumoto, M.; Komatsu, M.; Tsubouchi, H. *J. Med. Chem.* **2006**, *49*, 7854.

(9) Kubo, K.; Kohara, Y.; Imamiya, E.; Sugiura, Y.; Inada, Y.; Furukawa, Y.; Nishikawa, K.; Naka, T. *J. Med. Chem.* **1993**, *36*, 2182.

(10) For several recent examples, see: (a) Fukuzawa, S.; Shimizu, E.; Atsumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374. (b) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (c) Miyasaka, M.; Hirano, K.; Satoh, T.; Kawalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359. For reviews, see: Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57.

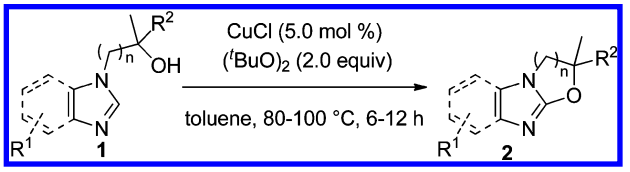
(11) Investigation of reaction temperature: 100 °C, 64%; 80 °C, 98%; 50 °C, 0%.

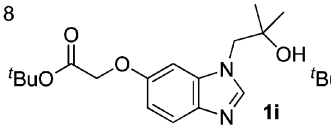
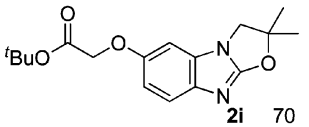
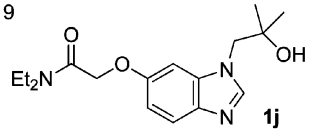
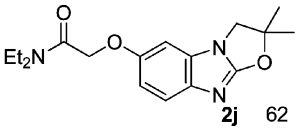
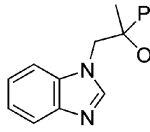
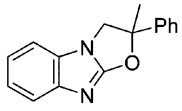
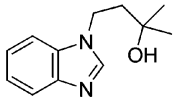
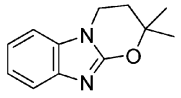
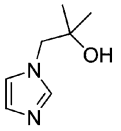
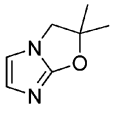
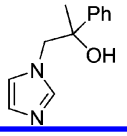
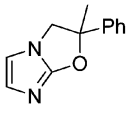
(12) Similar transformations can be achieved via two-step halogenation/nucleophilic addition (or cross-coupling) approaches. For examples, see: (a) Volpini, R.; Ben, D. D.; Lambertucci, C.; Marucci, G.; Mishra, R. C.; Ramadori, A. T.; Klotz, K.-N.; Trincavelli, M. L.; Martini, C.; Cristalli, G. *ChemMedChem* **2009**, *4*, 1010. (b) Bookser, B. C.; Dang, Q.; Gibson, T. S.; Jiang, H.; Chung, D. M.; Bao, J.; Jiang, J.; Kassick, A.; Kekec, A.; Lan, P.; Lu, H.; Makara, G. M.; Romero, F. A.; Sebhat, I.; Wilson, D.; Wodka, D. WO 2010/047982, 2010. (c) Sugimura, H.; Nitta, D. *Tetrahedron Lett.* **2012**, *53*, 4460. However, the C−H alkoxylation reaction has advantages from the viewpoint of reduced reaction steps and salt wastes.

(13) By adding tetrabutylammonium chloride to the reaction of CuBr (Table 1, entry 2), the yield of **2a** was improved to 67%. This result shows that the chloride ion is important for high reactivity.

bonds were intact (entries 5−7), allowing for further derivatizations through, for example, cross-coupling reactions. Substrate **1k**, possessing a benzylic hydroxy group, was also competent (entry 10). Intramolecular alkoxylation, however, did not proceed from primary and secondary alcohols (e.g., 2-(1*H*-benzo[*d*]imidazol-1-yl)ethanol and 1-(1*H*-benzo[*d*]imidazol-1-yl)-2-propanol). This method was also useful for six-membered ring construction (entry 11). Intramolecular alkoxylation also proceeded using monocyclic compounds such as imidazoles **1m** and **1n** (entries 12 and 13).

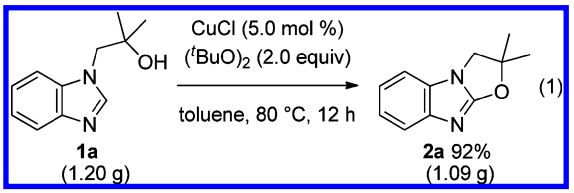
Table 2. Investigation of Several Substrates[a]



entry	substrate		product	yield / %
1	R = 5-Me	**1b**	**2b**	74
2	6-Me	**1c**	**2c**	77
3	6-MeO	**1d**	**2d**	70
4	5-CF_3	**1e**	**2e**	73
5[b]	5-F	**1f**	**2f**	64
6	5-Cl	**1g**	**2g**	75
7[b]	5-Br	**1h**	**2h**	71
8		**1i**		**2i** 70
9		**1j**		**2j** 62
10		**1k**		**2k** 88
11		**1l**		**2l** 83
12		**1m**		**2m** 45
13		**1n**		**2n** 38

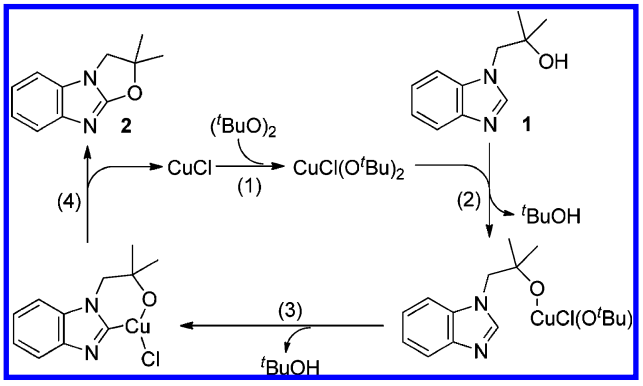
[a] Reaction temperature and time are reported in the Supporting Information. [b] 1,2-Dichloroethane was used as a solvent.

The reaction can be performed in gram scale. Treatment of 1.20 g of **1a** with a catalytic amount of CuCl and oxidant (^{t}BuO)$_2$ produced 1.09 g of **2a** in 92% yield (eq 1), which is comparable to the yield in Table 1, entry 1 (48 mg scale).



To gain some insights into the reaction mechanism if any radical intermediates are generated, the reaction in Table 1, entry 1 was carried out in the presence of a radical scavenger, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO: 5.0 mol %). As a result, the yield of **2a** was not affected (87%). This result suggests that this alkoxylation does not proceed via a radical pathway. The proposed mechanism for the intramolecular alkoxylation is as follows (Scheme 1):[14] (1) oxidation of CuCl with (^{t}BuO)$_2$;[15] (2) formation of an alkoxycopper intermediate via elimination of ^{t}BuOH;[15] (3) formation of a cyclic alkoxycopper intermediate via C−H bond activation;[16] (4) reductive elimination[17,18] to give the desired product **2** and regenerate the copper catalyst (Scheme 1).

Scheme 1. Proposed Mechanism for the Alkoxylated Products **2**



Interestingly, the reaction pattern switched dramatically when a base was added. When LiO^{t}Bu was added to the reaction mixture in Table 1, entry 1, intramolecular

(14) Copper-catalyzed oxidative C−H bond amidation of aromatic compounds have been reported. The present proposed mechanism is based on the following reports, see: Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632.

(15) For a recent example of oxidation of heteroarylcopper intermediates and formation of copper-heteroatom bonds, see: Chen, L.; Li, C.; Bi, X.; Liu, H.; Qiao, R. *Adv. Synth. Catal.* **2012**, *354*, 1773.

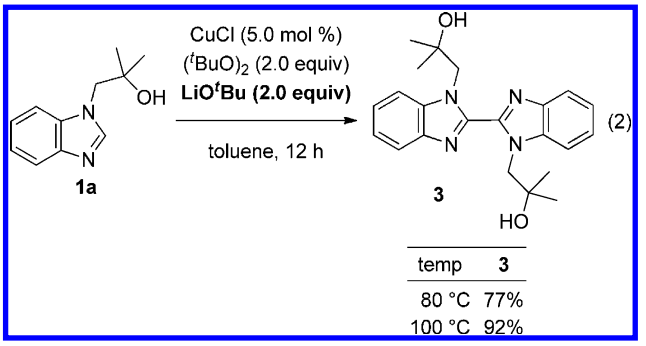
(16) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. See also: Reference 10a.

(17) For an example of formation of alkoxylated products by reductive elimination of a copper catalyst, see: Reference 4c.

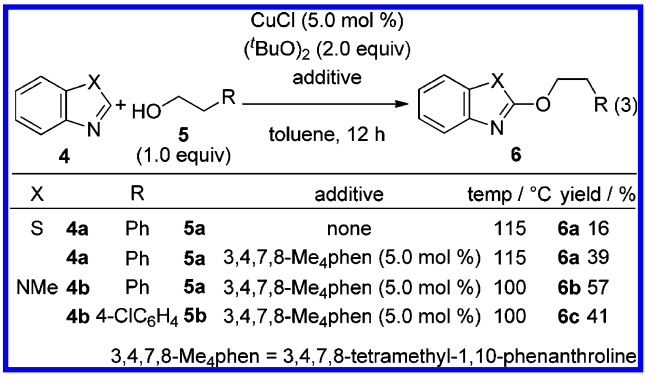
(18) For an example of formation of carbon−heteroatom bonds by reductive elimination of a copper catalyst, see: Reference 15.

(19) For copper-catalyzed dehydrogenative dimerization of heteroaromatic compounds, see: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052. (b) Monguchi, D.; Yamamura, A.; Fujiwara, T.; Somete, T.; Mori, A. *Tetrahedron Lett.* **2010**, *51*, 850. (c) Li, Y.; Jin, J.; Qian, W.; Bao, W. *Org. Biomol. Chem.* **2010**, *8*, 326. (d) Zhu, M.; Fujita, K.-i.; Yamaguchi, R. *Chem. Commun.* **2011**, *47*, 12876.

alkoxylation did not proceed at all. Instead, dehydrogenative dimerization of **1a** proceeded, affording dimer **3** in 77% yield without loss of the hydroxy groups (eq 2).[19,20] Increasing the reaction temperature to 100 °C improved the yield of **3** to 92% (eq 2). Thus, two different products (**2a** and **3**) can be selectively synthesized either in the presence or absence of a base.



The present alkoxylation conditions can be extended to an intermolecular reaction (eq 3). Treatment of benzothiazole (**4a**) with 2-phenylethanol (**5a**) in the presence of a catalytic amount of CuCl and 2.0 equiv of oxidant (^{t}BuO)$_2$ in toluene at 115 °C for 12 h gave alkoxylated product **6a** in 16% yield. When 3,4,7,8-tetramethylphenanthroline (3,4,7,8-Me$_4$phen) was added as a ligand to copper, the yield of **6a** increased to 39%. Intermolecular alkoxylation also proceeded from benzimidazole (**4b**), and the corresponding products **6b** and **6c** were obtained in 57% and 41% yields, respectively.[21−23]



X		R		additive	temp / °C	yield / %
S	**4a**	Ph	**5a**	none	115	**6a** 16
	4a	Ph	**5a**	3,4,7,8-Me$_4$phen (5.0 mol %)	115	**6a** 39
NMe	**4b**	Ph	**5a**	3,4,7,8-Me$_4$phen (5.0 mol %)	100	**6b** 57
	4b	4-ClC$_6$H$_4$	**5b**	3,4,7,8-Me$_4$phen (5.0 mol %)	100	**6c** 41

3,4,7,8-Me$_4$phen = 3,4,7,8-tetramethyl-1,10-phenanthroline

In summary, we successfully developed copper-catalyzed intra- and intermolecular alkoxylation of azoles.[24] To the best of our knowledge, this is the first example of transition-metal-catalyzed direct C−H alkoxylation of heteroaromatic compounds. It is noteworthy that only a stoichiometric amount (1 equiv) of alcohol is required, without a directing group. Key to our success was the identification of base-free conditions. The reaction pathway dramatically switched to dehydrogenative dimerization when a base was added to the reaction system. This method provides a useful and direct method of heteroaromatic C−H alkoxylation, leading to an efficient synthesis of drugs, natural products, and organic functional materials. Improvement of yields and substrate scope of intermolecular reactions is ongoing.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Product **3** exhibited a purple fluorescence by UV (254 nm) irradiation in a dichloromethane solution. Interestingly, **3** has a purple fluorescence as a solid state.

(21) The alkoxylation reaction also proceeded when isopropanol (secondary alcohol) was employed as a substrate; however, the yield of the alkoxylated benzimidazole was low (8%). The alkoxylation reaction did not proceed using *tert*-butanol. In this reaction, a complex mixture was formed. In the mixture, a dimer of **4b** was formed in 27% yield by dehydrogenative dimerization of **4b** as described in eq 2, and **4b** was recovered in 28% yield.

(22) We investigated the intermolecular reactions by increasing the amount of the alcohols, **5a** or **5b**. However, the yields of **6a**, **6b**, and **6c** were not improved.

(23) Tertiary alcohols produced higher yields than primary alcohols in the intramolecular reaction, but the tendency was opposite in the intermolecular reaction. The hydroxy group of tertiary alcohols could easily access to the reactive carbon atom of the heterocyles due to the Thorpe−Ingold effect in the intramolecular reaction; on the other hand, steric hindrance would hamper the access of the two substrates to each other in the case of the intermolecular reaction.

(24) For several examples of copper-catalyzed cross-coupling reactions to form C−O bonds, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (c) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954.

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