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Copper-Mediated Intermolecular Direct Biaryl Coupling

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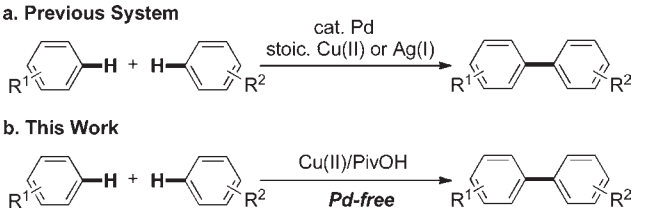
Supporting Information

ABSTRACT: Copper-mediated intermolecular direct biaryl coupling of arylazines and azoles via dual C−H bond cleavage proceeds even without palladium catalysts. The reaction system shows the high potential of copper salts in direct C−H arylation chemistry and provides a new approach to biaryl motifs, which are ubiquitous in pharmaceuticals and functional materials.

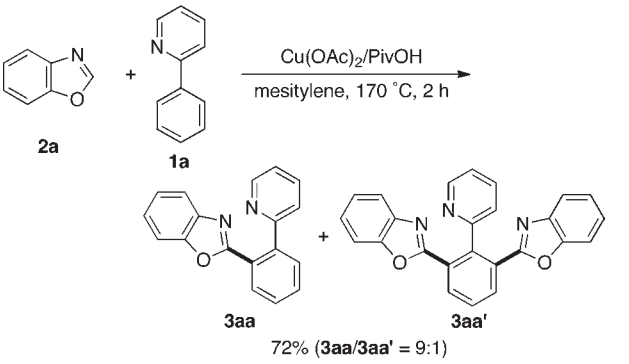
Biaryl structures are a ubiquitous motif in biological, pharmaceutical, and material sciences.[1] The transition-metal-catalyzed cross-coupling reactions of aryl halides with arylmetals, such as the Kumada−Tamao−Corriu, Suzuki−Miyaura, Negishi, Migita−Kosugi−Stille, and Hiyama couplings, rank as one of the most reliable approaches to the target molecules. On the other hand, recent advances in metal-mediated direct C−H functionalization provide an alternative and potentially more efficient synthetic methodology.[2] In particular, the direct biaryl coupling of two different arenes via dual C−H bond cleavage, though difficult to achieve in a general way, is most attractive and ideal from the viewpoint of step economy, since the tedious preactivation of the two arenes can be obviated (Scheme 1). To date, a number of successful examples of oxidative cross-coupling, including simple arene/arene[3] or heteroarene/heteroarene,[4] heteroarene/arene,[5] directing-group-containing arene/arene,[6] and electron-deficient arene/arene[7] or heteroarene,[8] have been reported. However, most precedents rely on the combination of a palladium catalyst and a stoichiometric amount of a metal oxidant based on Cu or Ag. For the realistic catalyst loading of precious palladium, further development of new reaction systems is quite appealing. Herein, we report a copper-mediated intermolecular direct biaryl coupling.[9] The reaction proceeds *without palladium catalysts* and enables an unprecedented coupling between a directing-group-containing arene and a heteroarene.

In a typical experiment, treatment of 2-phenylpyridine (**1a**)[10] with benzoxazole (**2a**)[11] in the presence of $Cu(OAc)_2$ and PivOH in heated mesitylene for 2 h afforded the corresponding biaryl **3aa** and the 1:2 coupling product **3aa′** in 72% combined yield (Scheme 2 and footnote a in Table 1).[12] The choice of Cu salts was critical: other divalent copper salts such as $CuCl_2$ and $Cu(OTf)_2$ completely failed to form **3aa**. While the reaction proceeded even without PivOH, carboxylic acid additives generally improved the reaction efficiency, with PivOH proving to be optimal. Although the full conversion required more than a stoichiometric amount of $Cu(OAc)_2$,[13] the copper salt is less expensive and has relatively low toxicity. Therefore, this palladium-free system appears

Scheme 1



Scheme 2



to be beneficial in organic synthesis.[14] The reaction scope is summarized in Table 1. Electron-donating as well as electron-withdrawing groups at the para position on the benzene ring were compatible under the reaction conditions, although the latter showed somewhat lower efficiency (**3ba**−**da**). Regardless of the electronic nature of the substituents, a small amount of 1:2 coupling product **3′** was also detected in each case. On the other hand, the 2-naphthyl-substituted pyridine **1e** resulted in the selective C−C bond formation at the less congested position, and the 1:1 coupling product **3ea** was obtained exclusively. The sterically demanding system 2-(2-methoxyphenyl)pyridine (**1f**) was also available for use (**3fa**). On the contrary, steric hindrance around the pyridine moiety was detrimental to the reaction; 2-phenylquinoline was converted to the corresponding product in only 14% GC yield (not shown), suggesting that the coordination of nitrogen to the copper center plays a pivotal role in the reaction. Among other heteroarenes tested, 5-aryloxazoles containing electronically and sterically diverse functions were found to couple with 2-phenylpyridine very smoothly under the identical conditions (**4aa**−**ah**). In addition,

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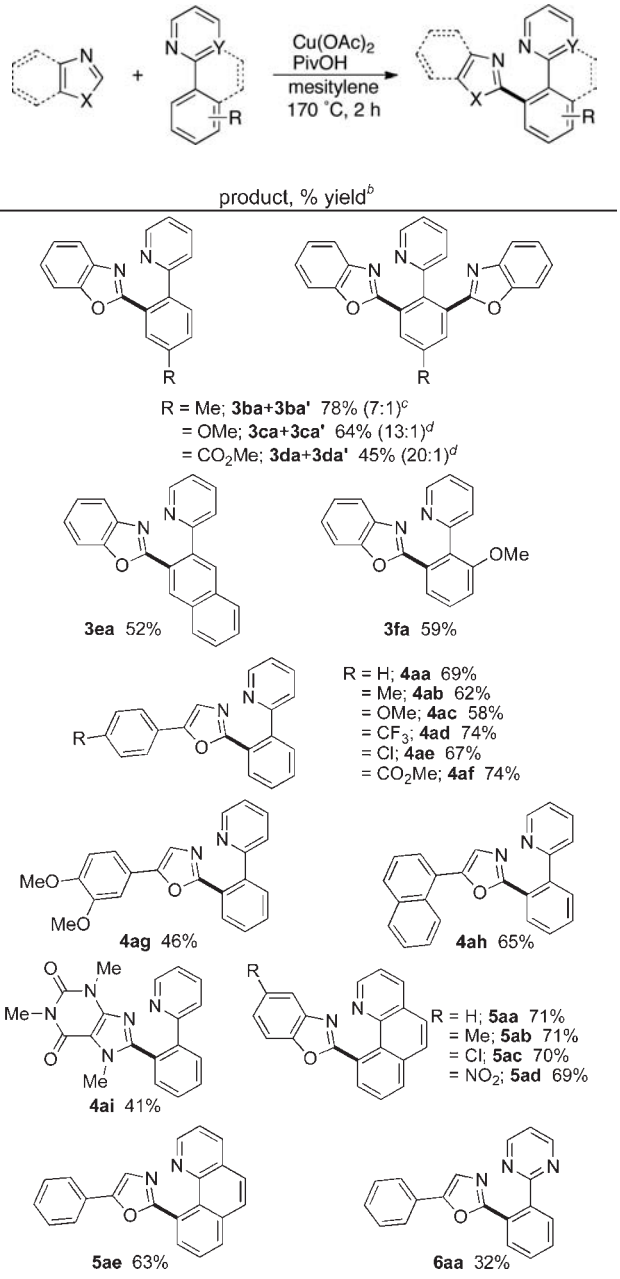
Table 1. Copper-Mediated Direct Coupling of 2-Arylazines with Azoles[a]

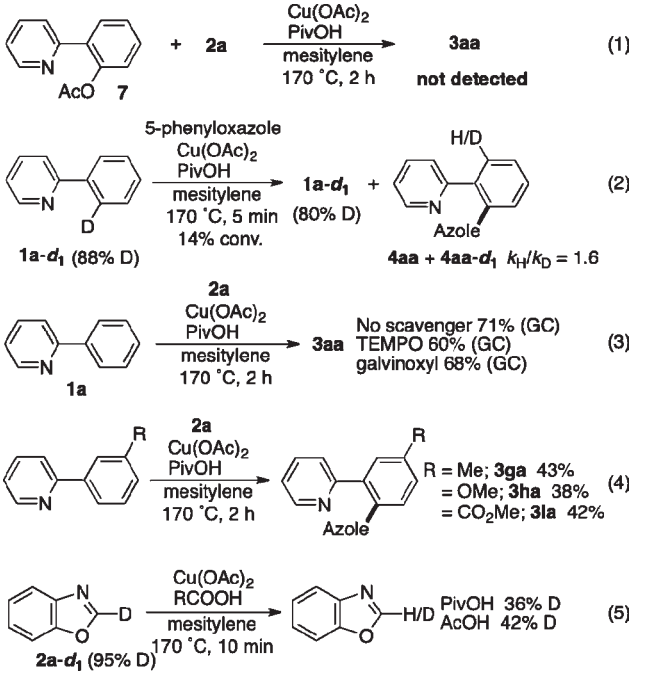


[a] A mixture of $Cu(OAc)_2$ (2.5 mmol), PivOH (0.50 mmol), 2-arylazine (0.50 mmol), and azole (1.0 mmol) in mesitylene (2.0 mL) was stirred at 170 °C for 2 h under N_2. [b] Yield of isolated product. [c] Readily separable by chromatographic purification. [d] Isolated as a mixture of **3** and **3′**.

the reaction with a highly functionalized imidazole derivative, caffeine, was possible (**4ai**).[15] As the directing-group-containing arene, benzoquinoline and 2-phenylpyrimidine also worked well, furnishing the corresponding biaryls with synthetically useful yields (**5aa**−**ae** and **6aa**).

To obtain some mechanistic insights, the following experiments were performed (Scheme 3). The control experiment with 2-(pyridin-2-yl)phenyl acetate (**7**) led to no formation of **3aa**, indicating that the sequential C−H oxidation/C−C bond-forming reaction would not be operative in the direct coupling (eq 1). The

Scheme 3



intramolecular kinetic isotope effect (KIE) was also investigated by using 2-(2-deuteriophenyl)pyridine (**1a**-d_1). At an early stage in the reaction, **1a**-d_1 showed a KIE of 1.6, while a minor H/D exchange reaction was observed (eq 2).[16] Addition of a radical scavenger, TEMPO or galvinoxyl, had a small effect on the reaction outcome, which runs counter to the copper-mediated single-electron-transfer mechanism proposed by Yu (eq 3).[10a] These phenomena would be consistent with an electrophilic metalation pathway.[17] However, very little electronic effect of the substituents para to the site of C−H bond cleavage was observed (eq 4).[18] On the other hand, 2-deuteriobenzoxazole (**2a**-d_1) underwent rapid H/D scrambling under the standard conditions (eq 5). PivOH rather than AcOH somewhat increased the rate, which supports the carboxylate-ligand-assisted concerted metalation−deprotonation[19] process of the relatively acidic azole C−H bond.[20]

On the basis of the above results, the copper-mediated direct biaryl coupling could consist of (i) reversible C−H cupration of the azole involving carboxylate-ligand-promoted proton abstraction, (ii) C−H metalation of the arylazine, and (iii) productive reductive elimination. In addition, in view of the necessity of a stoichiometric amount of $Cu(OAc)_2$, disproportion of Cu(II) into Cu(III) and Cu(I) might be involved as the fourth elementary step.[21] The above competitive deuterium-labeling experiments are suggestive of rate-determining reductive elimination or disproportion, but further efforts to clarify the detailed mechanism are essential.

In conclusion, we have developed a palladium-free, copper-mediated intermolecular direct biaryl coupling of arylazines and azoles. The process provides a concise access to heteroarene-containing biaryl structures of substantial utility in the areas of pharmaceuticals and functional materials. Moreover, the rare-metal-free approach is quite beneficial from an economical point of view. The development of catalytic variants and applications to other arene systems are currently underway.

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■ ASSOCIATED CONTENT

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

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■ REFERENCES

(1) (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.

(2) Recent reviews: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Campeau, L. C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (g) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (h) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (i) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (j) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395.

(3) (a) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973. (b) Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301.

(4) (a) Kita, Y.; Morimoto, K.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668. (b) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822.

(5) (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (c) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.

(6) (a) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (b) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (c) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (d) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837.

(7) Wei, Y.; Su, W. *J. Am. Chem. Soc.* **2010**, *132*, 16377.

(8) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850.

(9) Copper-mediated dehydrogenative intermolecular arylations: (a) Jia, Y.-X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636. (b) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078.

(10) Copper-mediated C−H functionalization of 2-phenylpyridines: (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (c) Mizuhara, T.; Inuki, S.; Oishi, S.; Fujii, M.; Ohno, H. *Chem. Commun.* **2009**, 3413. (d) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 632. (e) Chu, L.; Yue, X.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 1644. (f) Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415.

(11) Copper-mediated direct arylation of azoles with aryl halides: (a) Do, H.-G.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081. (c) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2009**, *11*, 1511. (d) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296. (e) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072 and references therein.

(12) A small amount (ca. 0.060 mmol) of the product of homocoupling of **2a** was observed by GC and GC−MS analyses. The byproduct was readily separated by silica gel column purification. See the Supporting Information for the detailed optimization studies.

(13) Under catalytic conditions using molecular oxygen as a co-oxidant, the oxygenation of **1a** predominantly occurred (see ref 10a). Attempts to apply other co-oxidants such as MnO_2 and $K_2S_2O_8$ remained unsuccessful.

(14) $Cu(OAc)_2$ obtained from three commercial sources mediated the coupling with similar efficiencies. The three sources were Wako Chemical Co. (>97%), Kanto Chemical Co. (95.0%), and Aldrich (99.999%). On the other hand, the addition of 10 mol % $PdCl_2$ or $Pd(OAc)_2$ decreased the yield of **3aa** by ca. 10%.

(15) The reactions of **1a** with benzothiazole, pentafluorobenzene, and 2-chlorothiophene remained unsuccessful.

(16) The KIE value was calculated by considering the partial H/D exchange reaction. The intermolecular KIE implies that C−H cleavage of 2-phenylpyridine would not be involved in the rate-determining step. See the Supporting Information for details.

(17) For reports of similar KIE values in palladium-catalyzed direct arylation and alkynylation through electrophilic C−H metalation, see: (a) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (b) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (c) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742.

(18) At this stage, the mechanism of C−H cleavage of phenylazines is not definitive. Thus, the pathway involving concerted metalation−deprotonation as well as σ-bond metathesis also could not be excluded. See: (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. (b) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651.

(19) (a) Mota, A. J.; Dedieu, A.; Bour, C.; Suffer, J. *J. Am. Chem. Soc.* **2005**, *127*, 7171. (b) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (d) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118 and references therein.

(20) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568.

(21) (a) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (b) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (c) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.