Synthetic Methods

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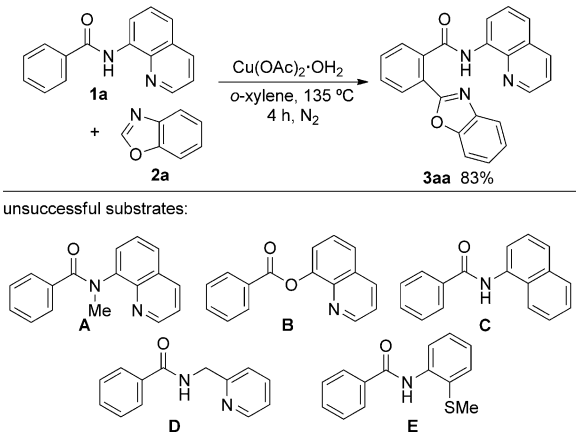
Copper-Mediated C–H/C–H Biaryl Coupling of Benzoic Acid Derivatives and 1,3-Azoles**

Mayuko Nishino, Koji Hirano, Tetsuya Satoh, and Masahiro Miura**

Over the last two decades, the use of metal-mediated direct C–H functionalization has grown rapidly as it enables the conversion of ubiquitous C–H bonds of organic molecules into diverse functional groups in a single synthetic operation.[1] In particular, since the pioneering work by Murai et al.,[2] methods involving directing groups have received significant attention because they enable the efficient and selective cleavage of the proximal C–H bond through a cyclometalation reaction. In many cases, groups containing neutral or anionic heteroatoms such as nitrogen, oxygen, and sulfur work as monodentate directing groups. Additionally, the groups of Sames,[3] Daugulis,[4] Yu,[5] and Chatani,[6] have independently developed a double coordination strategy, in which bidentate systems, including N,N and N,S systems, were used to activate otherwise unreactive C_{sp^2}–H bonds and the even more challenging C_{sp^3}–H bonds. Such a double coordination system has mainly been applied to palladium- and ruthenium-catalyzed processes.[7,8]

Meanwhile, owing to their ubiquity in biologically active compounds, natural products, and functional materials, the efficient construction of (hetero)biaryl structures is a long-standing focus for synthetic chemists.[9] In this context, direct biaryl coupling by double C–H bond cleavage of two different arenes (C–H/C–H coupling) is now a highly active research area in the metal-promoted C–H functionalization. In general, precious-metal complexes, such as palladium[10] and rhodium[11] complexes, are highly active catalysts for this type of transformation. We have recently focused on the potential of copper salts and complexes[12] as more efficient and unique promoters as well as less expensive and abundant alternatives to the above-mentioned precious metals, and thus, we have developed copper-mediated and copper-catalyzed C–H/C–H coupling of arenes and heteroarenes.[13,14] However, the substrate scope with regard to the arenes is limited to pyridine- or pyrimidine-containing arenes. Thus, there still remains a large demand for further development of copper-mediated direct biaryl couplings by using more ubiquitous and productive directing groups such as a carbonyl groups. Herein, we report a copper-mediated C–H/C–H coupling of benzoic acid derivatives and 1,3-azoles involving an amide-based double *N*,*N*-coordination strategy. The directing group is readily attachable and detachable, and parent carbonyl functional groups are easily recovered. The present reaction system is one of a few successful applications of the double coordination strategy to copper-mediated C–H functionalization of nonacidic arenes.[15]

Our optimization studies commenced with the identification of a suitable carbonyl-based directing group. After extensive screening of potential functional groups, we were pleased that an 8-aminoquinoline-containing secondary amide, which was originally developed by Daugulis and co-workers,[4] enabled the direct C–H/C–H coupling with 1,3-azoles.[16] In a typical experiment, treatment of the benzamide **1a** with benzoxazole (**2a**) in the presence of $Cu(OAc)_2 \cdot OH_2$ in *o*-xylene heated to 135 °C afforded the corresponding heterobiaryl **3aa** in 83 % yield (Scheme 1). A trace amount of the homocoupling product of **2a** was detected by GC and



Scheme 1. Screening of directing groups.

GCMS analysis, but was readily separated from **3aa** by silica gel column chromatography. Results of control experiments with some structurally similar but monodentate directing groups suggest that an *N*,*N*-bidentate directing group is crucial for good conversion (**A**–**C**). Also notable is the inefficiency of other bidentate coordinating groups, such as (2-pyridylmethyl)amino[6a,b,e,8] and (2-methylthiophenyl)amino groups[4b,d,7e] (**D** and **E**). In addition to the bidentate nature, the relatively acidic NH in **1a** is also believed to play a pivotal role in the coupling.[17]

By using the above-mentioned bidentate directing group, we investigated the substrate scope of benzoic acid derivatives with benzoxazole (**2a**) as a coupling partner (Scheme 2).

[*] M. Nishino, Dr. K. Hirano, Prof. Dr. T. Satoh, Prof. Dr. M. Miura
Department of Applied Chemistry, Faculty of Engineering
Osaka University, Suita, Osaka 565-0871 (Japan)
E-mail: k_hirano@chem.eng.osaka-u.ac.jp
miura@chem.eng.osaka-u.ac.jp

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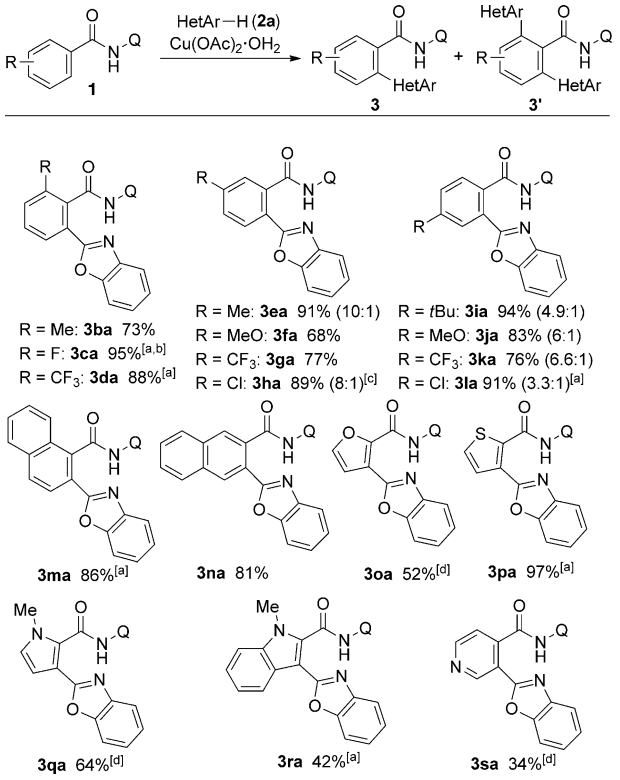
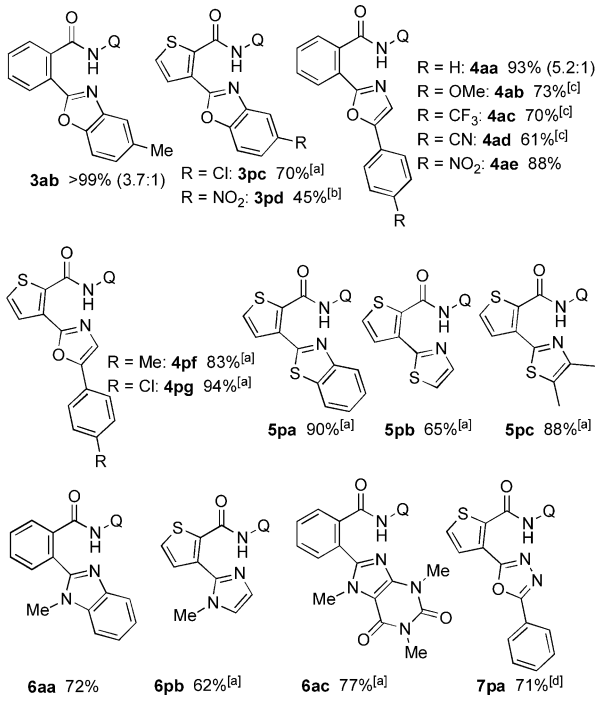


Scheme 2. Copper-mediated C—H/C—H coupling of various benzoic acid derivatives **1** with benzoxazole (**2a**). Reaction conditions: $Cu(OAc)_2{\cdot}OH_2$ (0.50 mmol), **1** (0.25 mmol), **2a** (0.50 mmol), *o*-xylene (1.5 mL), 135 °C, 4 h, N_2. The combined yield of monoheteroarylated product **3** and bisheteroarylated product **3′** is given. The ratio of **3**/**3′** is in parenthesis; **3** and **3′** were readily separated by silica gel column chromatography. [a] With $Cu(OAc)_2$ instead of $Cu(OAc)_2{\cdot}OH_2$. [b] At 150 °C. [c] The protiodechlorinated bisheteroarylated product **3ha″** was obtained instead of **3ha′**, in the indicated ratio. [d] With 0.75 mmol of $Cu(OAc)_2$. HetAr = 2-benzoxazolyl, Q = 8-quinolinyl.



Scheme 3. Products of copper-mediated C—H/C—H coupling of various 1,3-azoles under the reaction conditions shown in Scheme 2. The ratio of monoheteroarylated product to bisheteroarylated product is in parenthesis. [a] With $Cu(OAc)_2$ instead of $Cu(OAc)_2{\cdot}OH_2$. [b] With 0.75 mmol of $Cu(OAc)_2$. [c] About 5% of the corresponding bisheteroarylated products **4′** were observed but not isolated. [d] With 1.0 mmol of 2-phenyl-1,3,4-oxadiazole at 110 °C.

Notably, a better result was often achieved when anhydrous $Cu(OAc)_2$ was used rather than $Cu(OAc)_2{\cdot}OH_2$. The copper-based system tolerated electronically and sterically diverse substituents at the *ortho*, *meta*, and *para* positions of benzoic acid derivatives including methyl, *tert*-butyl, methoxy, chloro, fluoro, and trifluoromethyl groups (**3ba**–**la**). For substrates that bear two potentially reactive C—H bonds, the doubly heteroarylated products **3′** were detected, and the reaction of *meta*-substituted benzoic acid derivatives occurred predominantly at the less congested site. The naphthalene ring was also compatible; 2-naphthamide reacted with **2a** regioselectively at the 3-position (**3ma** and **3na**). Moreover, some representative heteroaromatic compounds including furan, thiophene, pyrrole, indole, and pyridine were transformed into the corresponding biheteroaryls (**3oa**, **3pa**, **3qa**, **3ra**, and **3sa**, respectively) in synthetically useful yields. These reactions are particularly notable as such heteroarene-1,3-azole moieties frequently occur in biologically active natural products.[18]

Facilitated by the doubly coordinated directing group, a variety of 1,3-azoles were applicable to the direct C—H/C—H coupling (Scheme 3). Electron-rich and electron-deficient 5-aryloxazoles as well as substituted benzoxazoles underwent the arylation smoothly (**3** and **4**). In particular, cyano and nitro groups were tolerated under the reaction conditions (see **3pd**, **4ad**, and **4ae**). Biheteroaryls containing thiophene, oxazole, thiazole, imidazole, caffeine, and 1,3,4-oxadiazole were also synthesized (see **3pc**, **3pd**, **4pf**, **4pg**, **5**, **6pb**, and **7ap**). Again, the prevalence of such conjugated heteroaromatic cores in many biologically active molecules highlights the synthetic utility of this method.[9,18] Additionally, the use of the 8-aminoquinoline-based bidentate directing group broadened the scope of the 1,3-azole coupling partner as well as the arene itself. For example, thiazole, imidazole, and oxadiazole derivatives were not suitable substrates in our previous work involving the use of pyridine as a monodentate directing group.[13] The beneficial effect of the bidentate directing group can be attributed to the more rapid cyclocupration between **1** and an azolylcopper and the more rigid intermediate formed after the first cupration of 1,3-azoles (see below).

To gain more insight into the mechanism, we conducted the following experiments with deuterium-labeled benzamide $[D_5]$-**1a** and benzoxazole $[D_1]$-**2a**. At an early stage in the reaction (10 min), a rapid H/D exchange reaction of $[D_1]$-**2a** was observed in both the absence and presence of benzamide **1a** [Eq. (1)]. On the other hand, $[D_5]$-**1a** did not undergo H/D scrambling in the presence of benzoxazole (**2a**), although in the absence of **2a**, a significant loss of deuterium content occurred [Eq. (2)]. These outcomes suggest that the C—H

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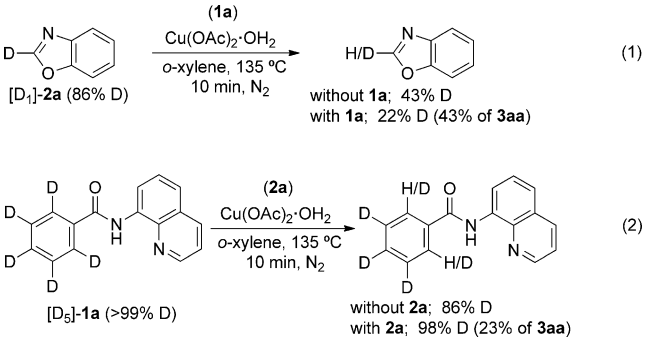
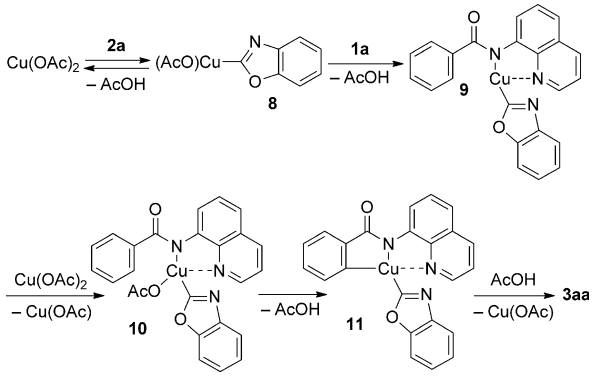
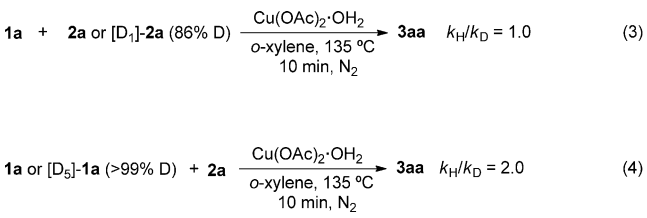


bond cleavage of benzoxazole (**2a**) occurs reversibly, whereas that of benzamide (**1a**) is an irreversible process under these reaction conditions, also the C–H bond cleavage of **2a** occurs much more readily than that of **1a**. Based on the above considerations and the necessity for two equivalents of $Cu(OAc)_2$ to achieve a good conversion, we propose the following mechanism for the reaction of **1a** and **2a** (Scheme 4). An initial acetate-ligand-assisted cupration[19] of

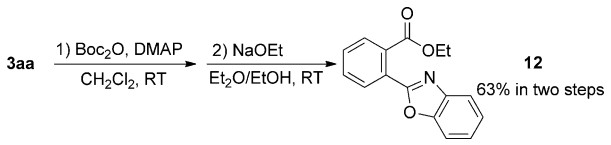


Scheme 4. Plausible reaction mechanism.

the relatively acidic C–H of **2a**[20] generates azolylcopper intermediate **8**;[21] this step is believed to be reversible, as indicated by the result shown in Equation (1). Subsequent ligand exchange with **1a** occurs to form anionic and neutral doubly *N,N*-chelated complex **9**. The corresponding heterobiaryl **3aa** is formed after an additional $Cu(OAc)_2$-promoted, oxidation (disproportionation) induced C–H cupration of the benzene ring[22] and reductive elimination via Cu^{III} complexes **10** and **11**.[23] Such a tight double coordination can allow relatively unreactive thiazoles and imidazoles to be used in this type of coupling; in the absence of this double coorodination the reverse protonation is favored over the subsequent oxidation and C–H cupration processes. The postulated order of metalation is supported by the results shown in Equations (1) and (2). The highly electron-withdrawing nature of the azolyl ligand in **8**[24] is believed to be the key to the cross-coupling occurring in preference to the homocoupling, although the exact reason is not clear at the present.[25] Kinetic studies with [D_1]-**2a** and [D_5]-**1a** provided kinetic isotope effect (KIE) values of 1.0 and 2.0, respectively [Eqs. (3) and (4)],[26] thus indicating the rate-limiting C–H cleavage of **1a**.[27]



Finally, we attempted a removal of the 8-aminoquinoline directing group. As shown in Scheme 5, Boc protection of the secondary amide moiety of **3aa** followed by ethanolysis with



Scheme 5. Removal of directing group.

NaOEt in a Et_2O/EtOH (4:1, v/v) mixed solvent system produced the corresponding ethyl ester **12** in a good overall yield. The same reaction conditions could be applied to the reaction of substituted benzoxazole systems **3ea** and **3fa**. Ethyl benzoates and thiophenecarboxylate bearing oxazole, thiazole, and imidazole-conjugated π systems were also obtained by the same procedure (see the Supporting Information for the complete substrate scope). The resultant ester group can act as a synthetic handle for further manipulations.

In conclusion, we have developed a precious-metal-free, copper-mediated C–H/C–H coupling of benzoic acid derivatives and 1,3-azoles with the aid of 8-aminoquinoline-based double *N,N*-coordination strategy. Such a bidentate coordination system broadens the substrate scope of both nonacidic arenes and 1,3-azoles in the copper-promoted direct heterobiaryl coupling. Moreover, the directing group is easily removed after the coupling, and parent ester groups are recovered. Further elucidation of the detailed mechanism, application to other arene systems, and development of catalytic variants with copper[28] are under investigation in our laboratory.

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[1] Selected recent reviews: a) C. Liu, H. Zhang, W. Sui, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; see the Supporting Information for complete citations.
[2] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529.
[3] J. A. Johnson, D. Sames, *J. Am. Chem. Soc.* **2000**, *122*, 6321.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[4] a) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; b) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965; c) E. T. Nadres, O. Daudulis, *J. Am. Chem. Soc.* **2012**, *134*, 7; d) L. D. Tran, O. Daugulis, *Angew. Chem.* **2012**, *124*, 5278; *Angew. Chem. Int. Ed.* **2012**, *51*, 5188.

[5] R. Giri, N. Maugel, B. M. Foxman, J.-Q. Yu, *Organometallics* **2008**, *27*, 1667.

[6] a) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898; b) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 8070; c) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984; d) Y. Ano, M. Tobisu, N. Chatani, *Org. Lett.* **2012**, *14*, 354; e) K. Shibata, N. Hasegawa, Y. Fukumoto, N. Chatani, *ChemCatChem* **2012**, *4*, 1733; f) Y. Aihara, N. Chatani, *Chem. Sci.* **2013**, *4*, 664.

[7] For applications of such a bidentate directing group to palladium catalysis by other groups, see: a) B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391; b) Y. Feng, G. Chen, *Angew. Chem.* **2010**, *122*, 970; *Angew. Chem. Int. Ed.* **2010**, *49*, 958; c) Y. Feng, Y. Wang, B. Landgraf, S. Liu, G. Chen, *Org. Lett.* **2010**, *12*, 3414; d) G. He, G. Chen, *Angew. Chem.* **2011**, *123*, 5298; *Angew. Chem. Int. Ed.* **2011**, *50*, 5192; e) W. R. Gutekunst, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 19076; f) W. R. Gutekunst, R. Gianatassio, P. S. Baran, *Angew. Chem.* **2012**, *124*, 7625; *Angew. Chem. Int. Ed.* **2012**, *51*, 7507; g) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; h) S.-Y. Zhang, G. He, Y. Zhao, K. Wright, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 7313; i) G. He, C. Lu, Y. Zhao, W. A. Nack, G. Chen, *Org. Lett.* **2012**, *14*, 2944; j) Y. Zhao, G. He, W. A. Nack, G. Chen, *Org. Lett.* **2012**, *14*, 2948.

[8] Recently, Chatani reported a nickel-catalyzed oxidative cycloaddition involving C–H bond cleavage with double coordination assistance: H. Shiota, Y. Ano, Y Aihara, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 14952.

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

[10] For selected recent examples, see: a) C.-Y. He, Q.-Q. Min, X. Zhang, *Organometallics* **2012**, *31*, 1335; b) M. Khoobi, M. Alipour, S. Zarei, F. Jafarpour, A. Shafiee, *Chem. Commun.* **2012**, *48*, 2985; c) K. H. Kim, H. S. Lee, S. H. Kim, J. N. Kim, *Tetrahedron Lett.* **2012**, *53*, 2761; d) J. Shao, W. Chen, M. A. Giulianotti, R. A. Houghten, Y. Yu, *Org. Lett.* **2012**, *14*, 5452; e) G. Wu, J. Zhou, M. Zhang, P. Hu, W. Su, *Chem. Commun.* **2012**, *48*, 8964; f) J. Dong, Y. Huang, X. Qin, Y. Cheng, J. Hao, D. Wan, W. Li, X. Liu, J. You, *Chem. Eur. J.* **2012**, *18*, 6158; see the Supporting Information for complete citations.

[11] a) J. Wencel-Delord, C. Nimphius, F. W. Patureau, F. Glorius, *Angew. Chem.* **2012**, *124*, 2290; *Angew. Chem. Int. Ed.* **2012**, *51*, 2247; b) K. Morimoto, M. Itoh, K. Hirano, T. Satoh, Y. Shibata, K. Tanaka, M. Miura, *Angew. Chem.* **2012**, *124*, 5455; *Angew. Chem. Int. Ed.* **2012**, *51*, 5359; c) N. Kuhl, M. N. Hopkinson, F. Glorius, *Angew. Chem.* **2012**, *124*, 8354; *Angew. Chem. Int. Ed.* **2012**, *51*, 8230; d) J. Wencel-Delord, C. Nimphius, H. Wang, F. Glorius, *Angew. Chem.* **2012**, *124*, 13175; *Angew. Chem. Int. Ed.* **2012**, *51*, 13001; e) J. Dong, D. Long, F. Song, N. Wu, Q. Guo, J. Lan, J. You, *Angew. Chem.* **2013**, *125*, 608; *Angew. Chem. Int. Ed.* **2013**, *52*, 580; f) X. Qin, H. Liu, D. Qin, Q. Wu, J. You, D. Zhao, Q. Guo, X. Huang, J. Lan, *Chem. Sci.* **2013**, DOI: 10.1039/c3sc22241a.

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

[13] a) M. Kitahara, N. Umeda, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2011**, *133*, 2160; b) M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2012**, *124*, 7099; *Angew. Chem. Int. Ed.* **2012**, *51*, 6993; also see, c) K. Hirano, M. Miura, *Chem. Commun.* **2012**, *48*, 10704.

[14] For recent developments in copper-mediated direct cross-couplings between acidic azoles, see: a) Z. Mao, Z. Wang, Z. Xu, F. Huang, Z. Yu, R. Wang, *Org. Lett.* **2012**, *14*, 3854; b) S. Fan, Z. Chen, X. Zhang, *Org. Lett.* **2012**, *14*, 4950; c) X. Qin, B. Feng, J. Dong, X. Li, Y. Xue, J. Lan, J. You, *J. Org. Chem.* **2012**, *77*, 7677.

[15] During the preparation of this manuscript, Daugulis reported a copper-mediated sulfenylation of C_{sp^2}–H bond with the same bidentate coordination group: L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237.

[16] See the Supporting Information for detailed optimization studies.

[17] The ^{1}H NMR chemical shifts of NH in **1a**, **D**, and **E** are 10.76, 7.61, and 9.26 ppm, respectively ($CDCl_3$, 25 °C).

[18] a) X. A. Domínguez, G. de La Fuente, A. G. Gonzalez, M. Reina, I. Timon, *Heterocycles* **1988**, *27*, 35; b) T. Ichiba, W. Y. Yoshida, P. J. Scheuer, T. Higa, D. G. Gravalos, *J. Am. Chem. Soc.* **1991**, *113*, 3173; c) E. Selva, G. Beretta, N. Montanini, G. S. Saddler, B. P. Gastaldo, P. Ferrari, R. Lorenzetti, P. Landini, F. Ripamonti, B. P. Goldstein, M. Berti, L. Montanaro, M. Denaro, *J. Antibiot.* **1991**, *44*, 693; d) J. Kettenring, L. Colombo, P. Ferrari, P. Tavecchia, M. Nebuloni, K. Vekey, G. G. Gallo, E. Selva, *J. Antibiot.* **1991**, *44*, 702; e) A. Nagatsu, H. Kajitani, J. Sakakibara, *Tetrahedron Lett.* **1995**, *36*, 4097.

[19] For p*K*a values of representative heteroarenes, see: K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron* **2007**, *63*, 1568.

[20] For the carboxylate-ligand-assisted concerted metalation/deprotonation, see: a) A. J. Mota, A. Dedieu, C. Bour, J. Suffer, *J. Am. Chem. Soc.* **2005**, *127*, 7171; b) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066; c) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754; d) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118, and references therein.

[21] Selected examples of reactions believed to proceed through analogous heteroaryl copper intermediates: a) H.-G. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404; b) L. Ackermann, H. K. Potukuchi, D. Landsberg, R. Vicente, *Org. Lett.* **2008**, *10*, 3081; c) S. Yotphan, R. G. Bergman, J. A. Ellman, *Org. Lett.* **2009**, *11*, 1511; d) D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao, J. You, *Angew. Chem.* **2009**, *121*, 3346; *Angew. Chem. Int. Ed.* **2009**, *48*, 3296; e) T. Kawano, T. Yoshizumi, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 3072; f) T. Kawano, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2010**, *132*, 6900; g) L. Zhang, J. Cheng, T. Ohishi, Z. Hou, *Angew. Chem.* **2010**, *122*, 8852; *Angew. Chem. Int. Ed.* **2010**, *49*, 8670, and references therein.

[22] The disproportionation into Cu^{III} prior to the second C–H cupration can also explain the finding that no H/D exchange of [D_5]-**1a** proceeded under the reaction conditions [Eq. (2)]; the higher reactivity of the Cu^{III} enables the irreversible C–H cupration and reductive elimination. For the rapid reductive elimination reaction of some Cu^{III} intermediates, see: A. Casitas, M. Canta, M. Solá, M. Costas, X. Ribas, *J. Am. Chem. Soc.* **2011**, *133*, 19386, and references therein. However, the detailed mechanism of C–H cleavage of **1a** is not clear at this stage.

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

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[24] A similar intermediate is proposed in the copper-mediated homocoupling reaction of 1,3-azoles; a) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2009**, *131*, 17052; b) D. Monguchi, A. Yamamura, T. Fujikawa, T. Somete, A. Mori, *Tetrahedron Lett.* **2010**, *51*, 850; c) M. Zhu, K.-i. Fujita, R. Yamaguchi, *Chem. Commun.* **2011**, *47*, 12876.

[25] Another disproportionation of Cu^{I} into Cu^{II} and Cu^{0} would not be involved as a Cu^{0} mirror (metallic copper) was not observed at the end of the reaction; see Ref. [14a].

[26] See the Supporting Information for details.

[27] Because of the possibility of an off-cycle C–H cupration of 1,3-azoles, at the present, we cannot completely exclude an alternative pathway that includes: 1) formation of an arylcopper species through double *N*,*N*-*N*,*N*-coordination assistance, 2) insertion of the C=N bond of 1,3-azoles into the C–Cu bond, and 3) oxidation leading to rearomatization of azole cores. Also see: S. Ranjit, R. Lee, D. Heryadi, C. Shen, J. Wu, P. Zhang, K.-W. Huang, X. Liu, *J. Org. Chem.* **2011**, *76*, 8999.

[28] A preliminary attempt to apply catalytic conditions (20 mol% $Cu(OAc)_2$, 4.0 equiv of AcOH, mesitylene, 170 °C, air) afforded the desired heterobiaryl **3aa** in 50% yield (71% brsm, versus Scheme 1).

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