ORGANIC LETTERS
2008
Vol. 10, No. 16
3607−3609

Copper-Mediated C−H Bond Arylation of Arenes with Arylboronic Acids

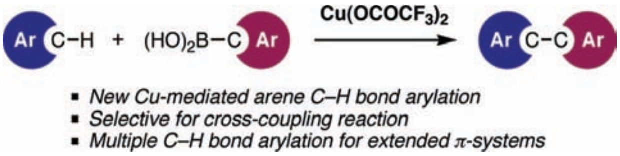
Ikuya Ban,[†] Tomoko Sudo,[†] Tadashi Taniguchi,[#] and Kenichiro Itami*[,†,‡]

Department of Chemistry, Graduate School of Science, Nagoya University, Nagoya 464-8602, Japan, and PRESTO, Japan Science and Technology Agency (JST)

itami@chem.nagoya-u.ac.jp

Received June 19, 2008

ABSTRACT



- *New Cu-mediated arene C–H bond arylation*
- *Selective for cross-coupling reaction*
- *Multiple C–H bond arylation for extended π-systems*

A new copper-mediated cross-coupling of arenes and arylboronic acids is described. Under the influence of Cu(OCOCF$_3$)$_2$, the C−H bond arylation of electron-rich arenes with arylboronic acids takes place to afford a range of biaryls in good yields. The reaction is selective for cross-coupling; no homocoupling product arising from arenes or arylboronic acids is detected. Multiple C−H bond arylation is possible with indoles and pyrroles furnishing interesting extended π-systems.

The development of efficient methods for making the privileged biaryl motif has been a topic of immense scientific importance in chemical synthesis.[1] Among a myriad of metal promoters, copper has played a pivotal role in aryl−aryl bond formation. Historically, the first methodologically important breakthrough was undoubtedly the reductive coupling of two haloarenes by the action of Cu(0) reported by Ullmann in 1901.[1] Conversely, the Cu-catalyzed oxidative coupling of arenes is of great utility in the preparation of binaphtols and related biaryls.[1] Copper has also contributed to modern methodology for the cross-coupling of different aromatic nuclei. In the cross-coupling reactions of metalated arenes and haloarenes, where palladium is usually the first catalyst of choice, it has been reported that copper complexes can function as copromoters or as catalysts.[1] This is also true in the emerging field of biaryl synthesis through C−H bond functionalization.[2–4] For example, copper salts can promote the palladium-catalyzed cross-coupling of arenes and haloarenes.[5] More recently, it was found that a copper complex alone can catalyze such cross-coupling of arenes and haloarenes.[6] Often, in the palladium-catalyzed oxidative cross-coupling of two different arenes[7] or arenes and metalated arenes,[8] a stoichiometric amount of Cu(II) salts

---

[†] Nagoya University.
[#] Shimadzu Corporation, Analytical Applications Department.
[‡] PRESTO, Japan Science and Technology Agency (JST).

(1) An extensive review on aryl−aryl bond formation including Cu-mediated and Pd-catalyzed processes: Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev* **2002**, *102*, 1359.

(2) Reviews on catalytic C−H bond functionalization: (a) Dyker, G., Ed. *Handbook of C-H Transformations*; Wiley-VCH: Weinheim, Germany, 2005. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(3) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200.

(4) Recent progress in C−H bond functionlization catalyzed or mediated by Cu: (a) Li, C.-J.; Li, Z. *Pure Appl. Chem.* **2006**, *78*, 935. (b) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (c) Baslé, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (d) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (e) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (f) Usui, S.; Hashimoto, Y.; Morey, J. V.; Wheatley, A. E. H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 15102. (g) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (h) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (i) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (j) Xifra, R.; Ribas, X.; Llobet, A.; Poater, A.; Duran, M.; Solà, M.; Stack, T. D. P.; Benet-Buchholz, J.; Donnadieu, B.; Mahía, J.; Parella, T. *Chem. Eur. J.* **2005**, *11*, 5146.

(5) (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. (b) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700. (c) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.* **2006**, 693.

(6) (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (c) Yoshizumi, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2008**, *49*, 1598.

10.1021/ol8013717 CCC: $40.75

Scheme 1

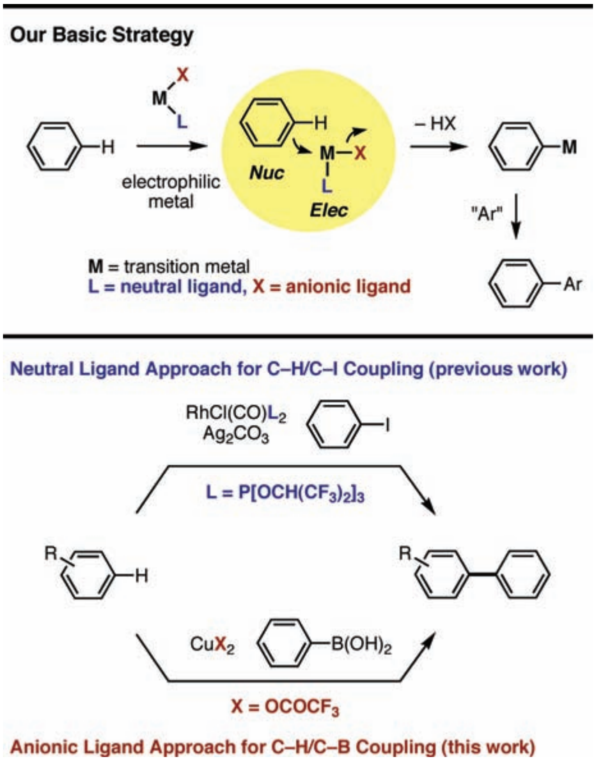
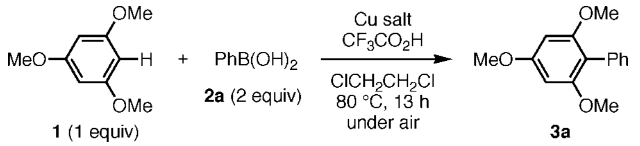


Table 1. Cu-Mediated Cross-Coupling of **1** and **2a**[a]



entry	Cu (equiv)	CF_3CO_2H (equiv)	yield (%)[b]
1	$Cu(OCOCF_3)_2$ (1.0)	0	51
2	$Cu(OCOCH_3)_2$ (1.0)	0	<1
3	$Cu(OTf)_2$ (1.0)	0	<1
4	$CuCl_2$ (1.0)	0	<1
5[c]	$Cu(OCOCF_3)_2$ (1.0)	0	14
6	$Cu(OCOCF_3)_2$ (1.0)	1.0	68
7	$Cu(OCOCF_3)_2$ (1.0)	5.0	63
8[d]	$Cu(OCOCF_3)_2$ (1.0)	1.0	45
9[e]	$Cu(OCOCF_3)_2$ (1.0)	1.0	75
10	$Cu(OCOCF_3)_2$ (0.3)	1.0	45

[a] Conditions: **1** (0.40 mmol), **2a** (0.80 mmol), Cu (0.40 mmol), CF_3CO_2H, $ClCH_2CH_2Cl$ (3 mL), 80 °C, 13 h, under air. $Cu(OCOCF_3)_2$ was employed as a hydrate salt. [b] Yield of **3a** determined by NMR, using internal standard. [c] Reaction under argon atmosphere. [d] 1.0 equiv of **2a** was employed. [e] 4.0 equiv of **2a** was employed.

(considered as an oxidant for $Pd^0 \rightarrow Pd^{II}$ process) is required. We herein report that $Cu(OCOCF_3)_2$ can facilitate the C−H bond arylation of arenes with arylboronic acids.

The metalation of the C−H bond is a key step in the C−H bond arylation of aromatic compounds. Our strategy has been to establish a distinct nucleophile−electrophile interaction between an arene and a transition metal, thereby promoting electrophilic arene metalation (Scheme 1). Previous work from our laboratory demonstrated that a rhodium complex bearing extremely π-accepting $P[OCH(CF_3)_2]_3$ as a supporting ligand can catalyze the C−H bond arylation of arenes with iodoarenes.[9] As an alternative to using a neutral ligand, we surmised that the use of electron-withdrawing anionic ligand would also facilitate aromatic C−H bond arylation (Scheme 1).[10] After an extensive screening of metal salts based on such a scenario, we found that $Cu(OCOCF_3)_2$ promotes the cross-coupling of electron-rich arenes and arylboronic acids.[8,11]

As a typical example, when a mixture of 1,3,5-trimethoxybenzene (**1**) and phenylboronic acid (**2a**) is treated with $Cu(OCOCF_3)_2$ in 1,2-dichloroethane at 80 °C for 13 h under air (molar ratio, **1**/**2a**/Cu = 1:2:1), biaryl **3a** is obtained in 51% yield (Table 1, entry 1). Surprisingly, the reaction is selective for cross-coupling; no homocoupling product arising from **1** or **2a** is detected. The importance of the trifluoroacetate moiety[10] has been quickly recognized, as other copper(II) salts such as $Cu(OCOCH_3)_2$, $Cu(OTf)_2$, and $CuCl_2$ do not promote the reaction at all (entries 2−4). The reaction under argon atmosphere is significantly slower than that performed under air (entry 5). The addition of CF_3CO_2H is beneficial giving rise to better yield as high as 68% (1 equiv is optimal, entry 6). The yield of **3a** can be increased to 75% at the expense of higher loading of **2a** (4 equiv) (entry 9). Reducing the amount of copper (0.3 equiv) results in a 45% yield; the reaction is limited by low TON (turnover number) with respect to copper under current conditions (entry 10).

With a first-generation procedure in hand, the scope of applicable arylboronic acids (**2**) was examined (Table 2). Various arylboronic acids (**2**) react with **1** to give the corresponding biaryls **3** in moderate to good yields.[12] In all cases, the cross-coupling product is solely detected. Notably, halogen-containing arylboronic acids undergo cross-coupling leaving carbon−halogen bonds intact (**3e**−**h**). The tolerance of the

---

(7) Oxidative cross-coupling of two arenes catalyzed by Pd and mediated by Cu or Ag: (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (c) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869. (d) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (e) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (f) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115.

(8) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (c) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554. (d) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (e) Kawai, H.; Kobayashi, Y.; Oi, S.; Inoue, Y. *Chem. Commun.* **2008**, 1464.

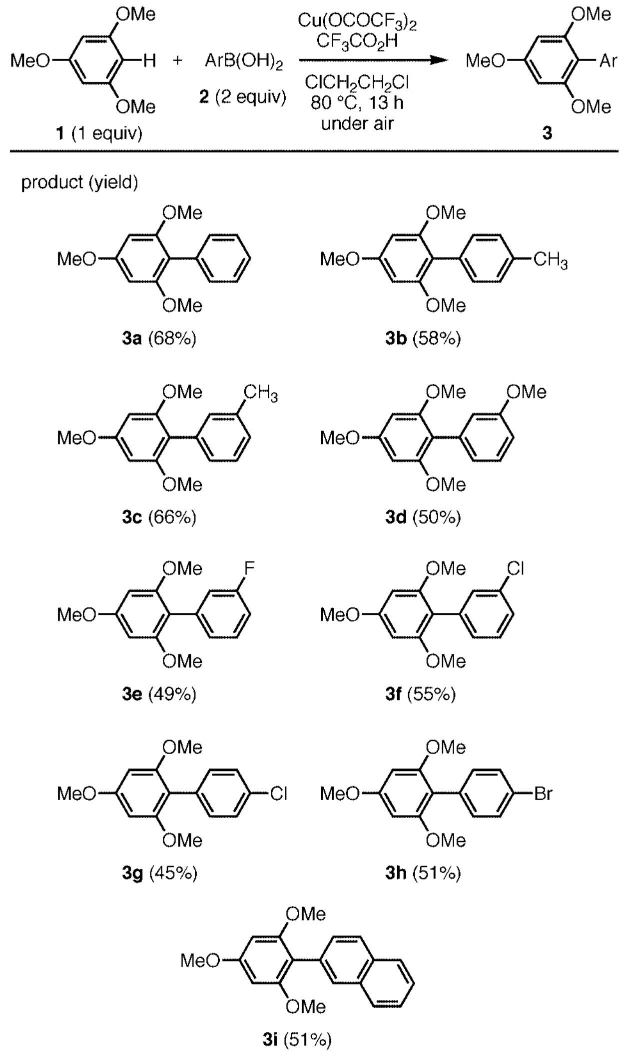
(9) (a) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748. (b) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *Tetrahedron* **2008**, *64*, 6073.

(10) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

(11) (a) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. (c) Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 129.

(12) Under current conditions, efficient cross-coupling proceeds only with electron-rich benzene derivatives; simple substrates such as benzene or toluene are unreactive. A full scope of applicable arenes and arylboronic acids will be reported in due course.

Table 2. Cross-Coupling of **1** and Arylboronic Acids (**2**)[a]

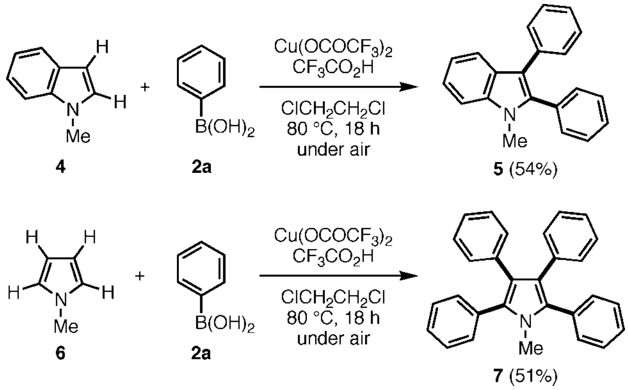


[a] Conditions: **1** (0.40 mmol), **2** (0.80 mmol), $Cu(OCOCF_3)_2$ (0.40 mmol), CF_3CO_2H (0.40 mmol), $ClCH_2CH_2Cl$ (3 mL), 80 °C, 13 h, under air. $Cu(OCOCF_3)_2$ was employed as a hydrate salt.

reaction for C−Br bonds makes it attractive for the rapid and selective assembly of arene units in combination with C−X bond cross-couplings such as the Suzuki−Miyaura reaction.

More interestingly, multiple C−H bond arylation is possible with some nitrogen heterocycles (Scheme 2). For example, when *N*-methylindole (**4**) is reacted with $PhB(OH)_2$ (**2a**) under the influence of $Cu(OCOCF_3)_2$ (molar ratio, **4**/**2a**/Cu/CF_3CO_2H = 0.51:1.5:1.0:0.05), double phenylation takes place to afford **5** in 54% yield. When *N*-methylpyrrole (**6**) is reacted with **2a** (molar ratio, **6**/**2a**/Cu/CF_3CO_2H = 0.22:1.3:1.0:0.02), quadruple phenylation takes place to afford **7** in 51% yield. It should be noted that the tetraarylpyrrole motif has been a target of interest as materials for organic electroluminescence devices[13] or as an antioxidant inhibiting microsomal lipid oxidation.[14] Also worthy of note is that such a facile multiple C−H bond arylation does not take place in the seemingly related Pd-catalyzed oxidative arene cross-coupling reactions.[7,8] These results, together with the quantitative elemental analysis of $Cu(OCOCF_3)_2$ by ICP-AES (Inductively Coupled Plasma-Atomic Emission Spectrometry) showing that the Pd concentration is less than 0.40 ppm (detection limit), implicate that the present reaction is not likely to be mediated by trace palladium.[15]

Scheme 2. Multiple C−H Bond Arylation of Nitrogen Heterocycles



In summary, a new copper-mediated C−H bond arylation of arenes with arylboronic acids is described. Although further mechanistic studies and optimization of the reaction conditions are warranted for this reaction to reach its full synthetic potential, the new reactivity finding in C−H bond functionalization is noteworthy. In particular, the successful multiple C−H bond arylation of nitrogen heterocycles highlights the potential of the present cross-coupling for further development and applications. In addition to the synthetic potential of this reaction, these results indicate that the role of stoichiometric copper salts used in Pd-catalyzed oxidative C−H bond transformations[7,8] may not always be limited to that of a reoxidant for Pd^0. The development of a catalytic protocol is the focus of ongoing research efforts.

Acknowledgment. This work was supported by the PRESTO program of Japan Science and Technology Agency (JST), a Grant-in-Aid for Scientific Research from MEXT, Japan, and the Global COE in Chemistry, Nagoya University. We thank Dr. Jean Bouffard (Nagoya University) for critical comments and discussion.

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

OL8013717

---

(13) Selected recent examples: (a) Kuo, W.-J.; Chen, Y.-H.; Jeng, R.-J.; Chan, L.-H.; Lin, W.-P.; Yang, Z.-M. *Tetrahedron* **2007**, *63*, 7086. (b) Yabe, M.; Fugono, M. Jpn. Kokai Tokkyo Koho JP2005232159; *Chem. Abstr.* **143**, 266809.

(14) Lehuédé, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J.-M. *Eur. J. Med. Chem.* **1999**, *34*, 991.

(15) To completely rule out catalysis by ultra-low levels of Pd would be precocious. A cautionary report: Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.