J|A|C|S
COMMUNICATIONS

# $Pd(OAc)_2$-Catalyzed Oxidative C−H/C−H Cross-Coupling of Electron-Deficient Polyfluoroarenes with Simple Arenes

Ye Wei and Weiping Su*

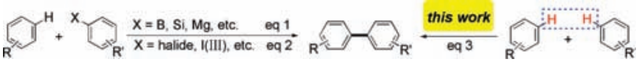
*State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Fuzhou, Fujian 350002, China*

Received September 12, 2010; E-mail: wpsu@fjirsm.ac.cn

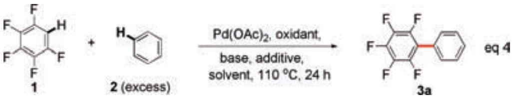
***Abstract:*** $Pd(OAc)_2$-catalyzed intermolecular C−H/C−H cross-coupling reactions between electron-deficient polyfluoroarenes and simple arenes for the synthesis of fluorinated biaryls have been developed. Deuterium-labeling experiments suggested that C−H bond cleavage of the simple arenes rather than the polyfluoroarenes is involved in the rate-limiting step.

Over the past decade, significant progress has been achieved in transition-metal-catalyzed direct aromatic C−H arylation in which a preactivated arene is required as the second coupling partner (eqs 1 and 2 in Scheme 1).[1,2] However, a far more efficient approach to nonsymmetrical biaryls would be direct oxidative cross-coupling between two non-preactivated arenes (eq 3 in Scheme 1). In this context, a few groups have recently reported their pioneering studies directed toward cross-coupling reactions between heteroarenes and arenes[3] or heteroarenes,[4] between directing-group-containing arenes and arenes,[5] and between two simple arenes.[6] Despite these advances, the reported reactions are still restricted to a narrow substrate scope. Clearly, such a dual C−H activation strategy will only be widely accepted and used in organic synthesis by synthetic chemists when a broad spectrum of (hetero)arenes can be utilized as coupling partners with high efficiency.

***Scheme 1.*** Methods for Biaryl Construction



One of the great challenges posed by the arene cross-coupling method is controlling the reaction chemoselectivity to avoid the unwanted homocoupling byproduct.[7] Inspired by the previously reported arene cross-coupling reactions,[3−6] we envisioned that Pd-catalyzed selective cross-coupling between two electronically distinctly different arenes could be achieved under suitable reaction conditions. The difference between the reactivities of the two arenes toward C−H cleavage/palladation would be capable of governing the precise sequence of two palladation steps in the catalytic cycle to selectively form the Pd intermediate containing the two cross-coupling fragments Pd(Ar)(Ar′), which is the key to achieving selective cross-coupling.[3a] For the reaction system consisting of polyfluorobenzene and simple arene, we hypothesized that the palladation of the more electron-rich simple arene would occur in the first step of catalytic cycle because of the stronger interaction between the simple arene and the Pd catalyst (i.e., the $Pd-C_{Ar}$ interaction), which would contribute to the lowering of the free energy of activation in the C−H cleavage process.[8] In the second palladation step, however, the more electron-deficient polyfluorobenzene would predominate over the simple arene because the reaction of the more electron-deficient polyfluorobenzene with the relatively electron-rich arylpalladium complex should be more facile than that of the simple arene.[2c,8] Herein, we describe the $Pd(OAc)_2$-catalyzed oxidative cross-coupling reactions of diverse electron-deficient polyfluoroarenes with benzene and substituted benzenes. This novel transformation produces fluorobiphenyls, which are of great importance in pharmaceutical[9] and materials applications,[10] with high chemoselectivity.

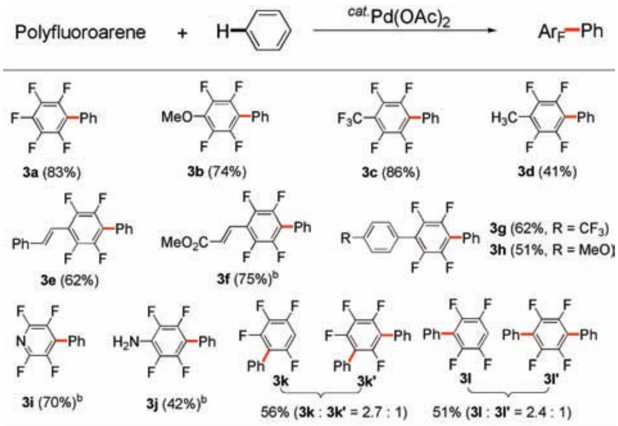


Initially, the reaction of pentafluorobenzene (**1**) with benzene (**2**) was chosen as a model reaction for optimization of the reaction conditions (eq 4; see the Supporting Information for detailed results). Preliminary results indicated that with the use of $Cu(OAc)_2$ (2 equiv) as an oxidant, $K_2CO_3$ (2 equiv) as a base, and $Pd(OAc)_2$ (10 mol %) as a catalyst, the reaction carried out in dimethylacetamide (DMA) at 110 °C for 24 h afforded the desired product **3a** in 65% yield. After screening different bases, we found that CsOPiv (1.5 equiv) gave **3a** in 74% yield. Furthermore, replacing CsOPiv with the combination of $Cs_2CO_3$ (0.75 equiv) and PivOH (1.5 equiv) gave a comparable yield (72%). Interestingly, other carboxylic acids such as AcOH were observed to be inferior to PivOH, which could be explained by the formation of more soluble CsOPiv. Although an acidic reaction medium has been observed to be beneficial to metal-mediated C−H cleavage,[5c] PivOH merely acted as the source of CsOPiv in this reaction, as evidenced by the fact that the combination of PivOH and $Cs_2CO_3$ gave rise to essentially the same yield as CsOPiv. Finally, when $Na_2CO_3$ was used in place of $Cs_2CO_3$, an 83% yield was obtained, showing the effect of the metal counterion of the base on the reaction.[11,12] Notably, only trace amounts of biphenyl and decafluorobiphenyl byproducts generated from homocoupling of the corresponding arenes were detected under the optimized conditions. Other commonly used oxidants such as Ag(I) salts, benzoquinone, and $O_2$ proved to be either less effective or totally ineffective. Although the experiments for optimizing the reaction conditions were conducted with the strict exclusion of moisture using a glovebox, further investigation showed that such strict reaction conditions were not necessary for this reaction.

With the optimal conditions in hand, we next examined the substrate scope with respect to the polyfluoroarene. As depicted in Scheme 2, tetrafluoroarenes containing additional substituents furnished fluorinated biaryls in moderate to good yields (**3a**−**j**). 1,2,3,5-Tetrafluorobenzene and 1,2,4,5-tetrafluorobenzene, each of which possesses two potential reaction sites, generated mixtures of mono- and diarylation products (**3k** + **3k′** and **3l** + **3l′**) in 56 and 51% overall yield, respectively. 2,3,5,6-Tetrafluoropyridine also participated in this reaction in 70% yield. 1,3,5-Trifluorobenzene

10.1021/ja109383e

***Scheme 2.*** Scope of Polyfluoroarenes in Pd(OAc)$_2$-Catalyzed Oxidative Arylation[a]

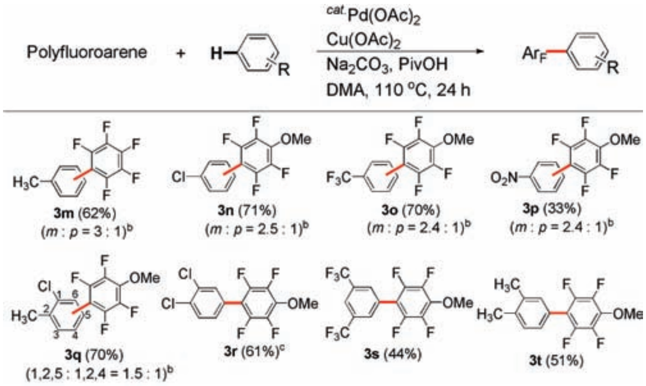


[a] Reaction conditions: polyfluoroarene (0.2 mmol), benzene (0.8 mL), Pd(OAc)$_2$ (10 mol %), Cu(OAc)$_2$ (2 equiv), Na$_2$CO$_3$ (0.75 equiv), PivOH (1.5 equiv), DMA (2 mL), 110 °C, 24 h. [b] Pd(OAc)$_2$ (20 mol %).

was less reactive, producing the mixture of mono- and diarylation products in 20% overall yield (see the Supporting Information).

Subsequently, we investigated the substrate scope with regard to the simple arene (Scheme 3). Monosubstituted benzenes underwent the reaction to generate a mixture of para and meta regioisomers regardless of electron-donating or electron-withdrawing substituents (**3m**−**p**), indicating that the electronic effects of the substituents do not affect the regioselectivity of the reaction. Good yields were obtained for these reactions, except in the case of nitrobenzene, which was deactivated by the strongly electron-withdrawing nitro group. For 1,2- or 1,3-disubstituted benzenes, the reaction selectively occurred at the less hindered C−H site. When two substitutents were identical, these reactions exhibited excellent regioselectivity (**3r**−**t**). These results indicate that the steric factors of substituents play a key role in controlling the reactivity and regioselectivity, in agreement with the observations by Sanford[5b] and Buchwald.[5d] It is noteworthy that in comparison with toluene, more electron-poor simple arenes such as 1,2-dichlorobenzene and trifluoromethylbenzene produced slightly more homocoupling byproducts, although the amounts of these byproduct were barely detectable.

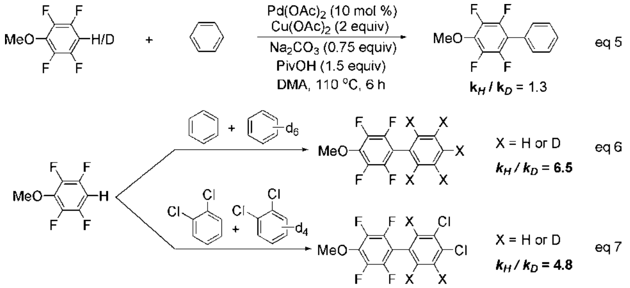
***Scheme 3.*** Scope of Simple Arenes in Pd(OAc)$_2$-Catalyzed Oxidative Arylation[a]



[a] Reaction conditions: polyfluoroarene (0.2 mmol), arene (2 mL), Pd(OAc)$_2$ (10 mol %), Cu(OAc)$_2$ (2 equiv), Na$_2$CO$_3$ (0.75 equiv), PivOH (1.5 equiv), DMA (2 mL), 110 °C, 24 h. [b] The value given in parentheses denotes the relative ratio of two regioisomers, which was calculated by GC−MS. [c] Na$_2$CO$_3$ (1.0 equiv) and PivOH (2.0 equiv).

To find out which one of the two C−H bond-cleavage processes was involved in the rate-limiting step, we determined the values of the kinetic isotope effects (KIEs) for both coupling partners (Scheme 4). An intermolecular competition reaction between 2,3,5,6-tetrafluoroanisole and deuterated 2,3,5,6-tetrafluoroanisole showed a KIE of 1.3 (eq 5 in Scheme 4; see the Supporting Information for detailed experimental procedures), illustrating that the rate-limiting step does not involve the C−H cleavage of the polyfluorobenzene. However, primary KIEs of 6.5 and 4.8 were observed for benzene (eq 6 in Scheme 4) and 1,2-dichlorobenzene (eq 7 in Scheme 4), respectively (see the Supporting Information for detailed experimental procedures). These results indicate that the C−H bond cleavage of simple arenes is significant with respect to the rate-limiting step. The importance of C−H cleavage in the rate-determining step further suggested that the C−H bond cleavage may proceed via a concerted metalation−deprotonation pathway,[2c,d,8] as the typical electrophilic aromatic substitution pathway does not involve C−H cleavage in the rate-limiting step.[13] This hypothesis for the pathway of C−H cleavage can account for the observations that the reactions of electron-poor simple arenes yielded more homocoupling byproducts than those of benzene and toluene.

***Scheme 4.*** Intermolecular Kinetic Isotope Effect



In summary, we have developed an efficient and straightforward method for the formation of aryl−aryl bonds via Pd(OAc)$_2$-mediated dual C−H bond activation. This approach represents a promising alternative to the existing C−M/C−X[14] and C−H/C−X[2c,g,h,p] coupling methods for producing fluorinated biaryls. The establishment of cross-coupling of two electronically different arenes should influence the design of new cross-coupling reactions. Our ongoing work is devoted to expanding the C−H/C−H cross-coupling reaction to a broad spectrum of substrates.

**Acknowledgment.** Financial support from the 973 Program (2006CB932903, 2009CB939803), NSFC (20821061, 20925102), “The Distinguished Oversea Scholar Project”, “One Hundred Talent Project”, the Knowledge Innovation Program of CAS, and the Key Project from CAS is greatly appreciated.

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

## References

(1) For recent reviews, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (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) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (g) Lewis, L. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (h) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (i) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (j) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.
(2) For recent examples, see: (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (d) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (e) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066.

(f) Turner, G.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996. (g) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (h) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (i) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (j) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676. (k) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (l) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925. (m) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296. (n) Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3644. (o) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12707. (p) Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346. (q) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202. (r) Liu, W.; Cao, H.; Lei, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2004.

(3) (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. (d) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050. (e) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (f) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850.

(4) (a) Kita, Y.; Morimoto, K.; Ito, M.; 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. (c) Gu, Y.; Wang, D. *Tetrahedron Lett.* **2010**, *51*, 2004.

(5) (a) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869. (b) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (c) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (d) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651. (f) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837.

(6) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973.

(7) (a) Burton, H. A.; Kozhevnikov, I. V. *J. Mol. Catal. A: Chem.* **2002**, *185*, 285. (b) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (c) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (d) Xia, J.-B.; Wang, X.-Q.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 456. (e) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052. (f) Li, Y.; Wang, W.-H.; Yang, S.-D.; Li, B.-J.; Feng, C.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 4553.

(8) Gorelsky, S.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

(9) (a) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210. (b) Zahn, A.; Brotschi, C.; Leumann, C. *Chem.—Eur. J.* **2005**, *11*, 2125. (c) Russell, M. G. N.; Carling, R. W.; Atack, J. R.; Bromidge, F. A.; Cook, S. M.; Hunt, P.; Isted, C.; Lucas, M.; McKernan, R. M.; Mitchinson, S.-A.; Wafford, K. A.; Castro, J. L. *J. Med. Chem.* **2005**, *48*, 1367.

(10) (a) Weck, M.; Dunn, A. R.; Matsumoto, K.; Coates, G. W.; Lobkovsky, E. B.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2741. (b) Sakamoto, Y.; Suzuki, T.; Miura, A.; Fujikawa, H.; Tokito, S.; Taga, Y. *J. Am. Chem. Soc.* **2000**, *122*, 1832. (c) Kitamura, T.; Wada, Y.; Yanagida, S. *J. Fluorine Chem.* **2000**, *105*, 305. (d) Nitschke, J. R.; Tilley, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 10183. (e) Tsuzuki, T.; Shirasawa, N.; Suzuki, T.; Tokito, S. *Adv. Mater.* **2003**, *15*, 1455. (f) Montes, V. A.; Li, G.; Pohl, R.; Shinar, J.; Anzenbacher, P. *Adv. Mater.* **2004**, *16*, 2001.

(11) 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.

(12) Similar reaction conditions were used by Fagnou and co-workers for Pd-catalyzed direct aromatic C−H arylation (see refs 2d and 3a, b).

(13) Zollinger, H. *Adv. Phys. Org. Chem.* **1964**, *2*, 163.

(14) Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T. *Org. Lett.* **2005**, *7*, 4915.

JA109383E