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Pd-Catalyzed Oxidative Cross-Coupling of Perfluoroarenes with Aromatic Heterocycles

Chun-Yang He, Shilu Fan, and Xingang Zhang*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

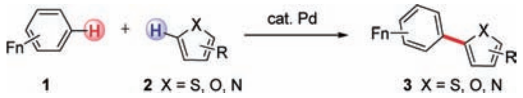
Received July 8, 2010; E-mail: xgzhang@mail.sioc.ac.cn

Abstract: A straightforward and practical method for direct $Pd(OAc)_2$-catalyzed oxidative cross-coupling of electron-deficient perfluoroarenes with aromatic heterocycles has been developed. Because of its low catalyst loading (2.5 mol %), high reaction efficiency, good chemo- and regioselectivity, and excellent functional-group compatibility, this protocol provides a useful and operationally simple access to perfluoroarene−thiophene structures of interest in functional materials for electronic devices.

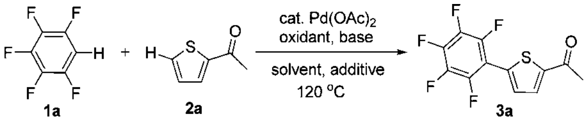
Perfluorinated aromatic rings are a prominent structural motif found in numerous functional materials of importance in various application fields.[1] In particular, because of the strong electron-withdrawing effect of perfluorinated aryl groups, which induces a significant lowering of the HOMO and LUMO energy levels with respect to the nonfluorinated counterparts,[1d,2] molecules containing the perfluoroarene−thiophene structure play a primary role as active materials in electronic devices, such as organic light-emitting diodes (OLEDs) and field-effect transistors (FETs). Generally, such a structural moiety is achieved by cross-coupling of organometallic aryls (boronic acids or stannanes) with aryl halides (ArX).[2d,3] However, this “prefunctionalization” process suffers from the tedious procedures for the preparation of the organometallic reagents, the incompatibility of important functional groups, and the use of toxic substrates (stannanes). In this context, direct transition-metal-catalyzed C−H bond functionalization of perfluoroarenes with ArX, which represents a better reaction efficiency, has recently been reported.[4] From the point of view of synthetic simplicity, the carbon−carbon bond formation obtained via twofold C−H functionalization (i.e., the oxidative cross-coupling approach) would be more straightforward. Although important progress in this field has been made,[5−7] selective oxidative cross-coupling methods are still restricted to limited substrates, and direct transition-metal-catalyzed oxidative cross-coupling of perfluoroarenes with heteroarenes has not been reported to date; this still poses a great synthesis challenge because of the difficulties in controlling the selectivity of the two C−H activation steps and in suppressing undesired homocouplings.[8] Hence, new methods to overcome these daunting limitations for widespread synthetic applications are highly desirable.

Very recently, we developed a straightforward protocol for direct olefination of perfluoroarenes that uses a Pd catalyst, which represents one of the rare examples of catalytic direct olefination of electron-deficient arenes.[9] Inspired by this preliminary study, herein we describe the first example of direct $Pd(OAc)_2$-catalyzed oxidative cross-coupling of electron-deficient perfluoroarenes with heteroarenes via twofold C−H functionalization (Scheme 1). With a low loading of Pd catalyst (2.5 mol %) and good functional-group compatibility, this straightforward protocol provides a wide range of perfluoroarene−thiophene structures with high efficiency and regioselectivity.

Scheme 1. Direct Pd-Catalyzed Oxidative Cross-Coupling of Perfluoroarenes with Aromatic Heterocycles



We began this study by choosing electron-deficient pentafluorobenzene (**1a**) and 1-(thiophen-2-yl)ethanone (**2a**) as model substrates (eq 1):



(1)

Initially, on the basis of our previous research work,[9] the reaction was carried out with **1a** (2.0 equiv), **2a** (1.0 equiv), Ag_2CO_3 (1.5 equiv), and $Pd(OAc)_2$ (10 mol %) in DMF + DMSO (5%) at 120 °C and provided a good yield (72% NMR yield) of **3a** with perfluoroaryl located only at the α position of the thiophene ring. Encouraged by this preliminary result, we further investigated the reaction parameters (see Table S1 in the Supporting Information) and found that DMSO is critical for the reaction efficiency. The absence of DMSO or use of other solvents (DMF, NMP, dioxane, HOAc) led to a lower yield or even no formation of **3a**.[10] We supposed that DMSO might function as a ligand to activate the Pd catalyst and prevent the formation of palladium black.[11] In addition, silver salts are also essential to the reaction efficiency, and a 1/1 $Ag_2CO_3/AgOAc$ mixture afforded a better yield (73% isolated yield) than the sole use of either of the silver salts. Probably, one of them serves as a base and the other as a promoter and an oxidant for the Pd(0)/Pd(II) catalytic cycle,[8a] since no reaction was observed in the absence of the silver salts. However, the roles of these silver salts remain elusive and will be addressed in the future. Further studies showed that instead of $Ag_2CO_3/AgOAc$, using 1.5 equiv of Ag_2CO_3 in conjunction with 1.0 equiv of HOAc provided a slightly higher isolated yield (77%). Other oxidants [$Cu(OAc)_2$, oxone, BQ, and $PhI(OAc)_2$] were ineffective. To our delight, further reducing the $Pd(OAc)_2$ loading to 2.5 mol % with utilization of 3.0 equiv of **1a** gave the best isolated yield (86%).

Under the optimum reaction conditions, a variety of pentafluorophenyl−thiophene structures were obtained with high efficiency (Table 1). Versatile functional groups such as methyl ketone, ester, aldehyde, amide, and chloride are compatible with the catalytic system (entries **3a**−**e** and **3j**), and these groups can easily be further functionalized utilizing traditional techniques. In particular, for compound **3e**, which is a useful building block for the synthesis of n-type organic semiconductors, a good yield was

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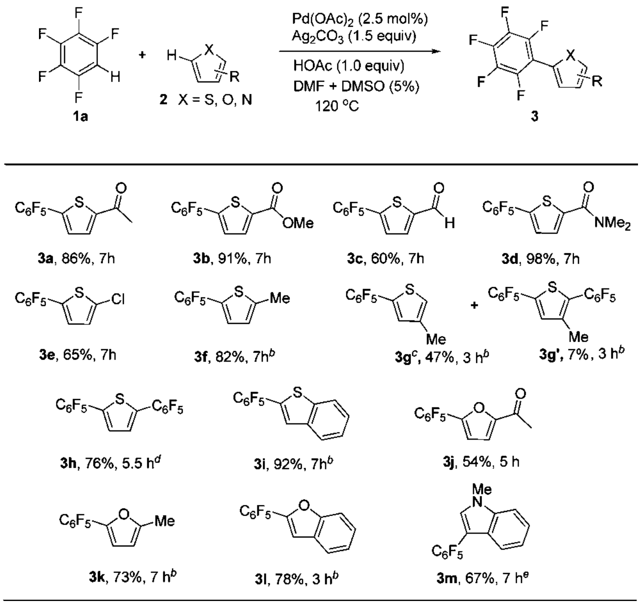
Table 1. Oxidative Cross-Coupling of Pentafluorobenzene with Various Heteroarenes[a]



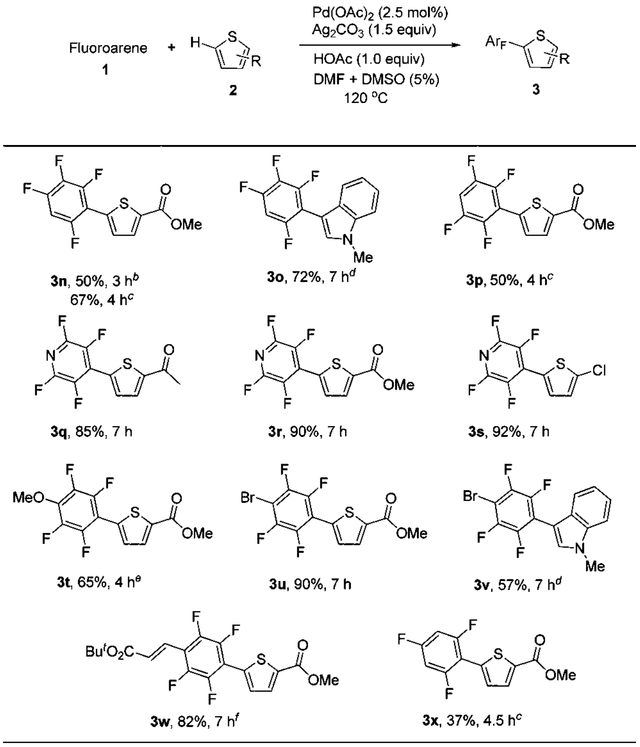
[a] Reaction conditions (unless otherwise specified): **1a** (3.0 equiv) and **2** (0.6 mmol) in DMF (2 mL) + DMSO (100 μL). All reported reaction yields are isolated yields. [b] Reaction run at 140 °C. [c] With isolation of 13% homocoupling of **3g** (see the Supporting Information). [d] Using 4.0 equiv of **1a** and 3.0 equiv of Ag_2CO_3 at 140 °C. [e] Using DMSO as the solvent.

obtained, although a small amount of homocoupling of 2-chlorothiophene was observed (entry **3e**). For 3-methylthiophene, good regioselectivity was still observed at the α-positon of the thiophene ring (entry **3g**). It is noteworthy that a symmetrical 2,5-bis(perfluorophenyl)thiophene can easily be prepared from unfunctionalized thiophene in good yield (76%) via only one step (entry **3h**), thus providing a new strategy for the efficient synthesis of this family of compounds.[2,3] Furthermore, the heteroarenes are not limited to simple thiophenes, as benzo[*b*]thiophene and other aromatic heterocycles such as furans and indole are also suitable substrates for the reaction (entries **3i**−**m**).

To further ascertain the scope of this methodology, a variety of fluoroarenes were investigated (Table 2). Although substrates bearing three or four fluorines contain more than one reaction site, reasonable yields of monothiophene- or -indole-substituted products were still observed, again with a useful functional-group tolerance (entries **3n**−**p** and **3x**). The low reactivity of 1,3,5-trifluorobenzene is probably due to the low acidity of the C−H bond to be activated (entry **3x**).[4a,12] In addition, the successful formation of **3s**, **3u**, and **3v** in good yields with intact chloride and bromide provided a good opportunity for further formation of carbon−carbon or carbon−heteroatom bonds by transition-metal-catalyzed coupling and other reactions. A large conjugated system can also be constructed using this protocol, thus allowing for the facile synthesis of a highly functionalized perfluoroarene−thiophene structure in a simple manner (entry **3w**). To demonstrate the synthetic application of this methodology, n-type organic semiconductors **6** and **7**[2d] were easily prepared in only one step without the prerequirement of preparation of aryl halides or organometallic reagents, providing even higher yields than the traditional techniques[2d,3a] (Scheme 2).

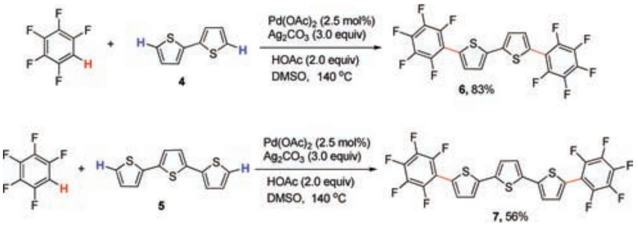
In conclusion, we have developed a straightforward and practical method for direct $Pd(OAc)_2$-catalyzed oxidative cross-coupling of electron-deficient perfluoroarenes with aromatic heterocycles via twofold C−H functionalization. Because of its low catalyst loading (2.5 mol %), high reaction efficiency, good chemo- and regioselectivity, and excellent functional-group compatibility, this protocol provides a useful and operationally simple access to perfluoroarene−thiophene structures of interest in functional materials for electronic devices. Further studies to expand the substrate scope and their applications as well as investigations of the reaction mechanism are now in progress.

Table 2. Oxidative Cross-Coupling of Fluoroarenes with Various Heteroarenes[a]



[a] Reaction conditions (unless otherwise specified): Fluoroarene (2.0−3.0 equiv) and **2** (0.6 mmol) in DMF (2 mL) + DMSO (100 μL). All reported reaction yields are isolated yields. [b] Reaction run at 140 °C. [c] Using 3.0−5.0 equiv of **1** and 5 mol % $Pd(OAc)_2$ at 140 °C. [d] Using DMSO as the solvent. [e] Using 2.0 equiv of **1** at 140 °C. [f] Using 1.0 equiv of **1** and 2.0 equiv of **2**.

Scheme 2. Syntheses of n-Type Organic Semiconductors **6** and **7**



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

References

(1) For selected recent reviews, see: (a) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119. (b) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew.*

Chem., Int. Ed. **2003**, *42*, 1210. (c) Murphy, A. R.; Fréchet, J. M. J. *Chem. Rev.* **2007**, *107*, 1066. (d) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003.

(2) For selected recent papers, see: (a) Tang, M. L.; Reichardt, A. D.; Miyaki, N.; Stoltenberg, R. M.; Bao, Z. *J. Am. Chem. Soc.* **2008**, *130*, 6064. (b) Wang, Y.; Parkin, S. R.; Watson, M. D. *Org. Lett.* **2008**, *10*, 4421. (c) Wang, Y.; Watson, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 2536. (d) Yoon, M.-H.; Facchetti, A.; Stern, C. E.; Marks, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 5792. (e) Letizia, J. A.; Facchetti, A.; Stern, C. L.; Ratner, M. A.; Marks, T. J. *J. Am. Chem. Soc.* **2005**, *127*, 13476.

(3) For selected papers, see: (a) Takimiya, K.; Niihara, N.; Otsubo, T. *Synthesis* **2005**, 1589. (b) Crouch, D. J.; Skabara, P. J.; Heeney, M.; McCulloch, I.; Coles, S. J.; Hursthouse, M. B. *Chem. Commun.* **2005**, 1465. (c) Facchetti, A.; Yoon, M.-H.; Stern, C. L.; Katz, H. E.; Marks, T. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3900.

(4) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (d) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (e) Do, H.-Q.; Daugulis, O. *Chem. Commun.* **2009**, 6433. (f) Rene, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116. (g) Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346.

(5) For stoichiometric Pd-mediated oxidative cross-coupling, see: (a) Itahara, T. *Synthesis* **1979**, 151. (b) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5272.

(6) For Pd-catalyzed oxidative cross-coupling, see: (a) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (d) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651. (f) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Chem. Soc.* **2010**, *132*, 1822. (g) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (h) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (i) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.

(7) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668.

(8) For Pd-catalyzed oxidative homocoupling of thiophenes, see: (a) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (b) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930. For Pd-catalyzed oxidative homocoupling of indolizines, see: (c) Xia, J.-B.; Wang, X.-Q.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 456. For transition-metal-catalyzed oxidative homocoupling of perfluoroarenes, see: (d) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052. (e) Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200.

(9) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506.

(10) DMSO is also a suitable solvent, but some uncertain byproducts were observed. However, for the synthesis of **3k** (Table 1), **6** and **7**, DMSO provided better reaction yields.

(11) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348, and references therein.

(12) (a) Hyla-Kryspin, I.; Grimme, S.; Buker, H. H.; Nibbering, N. M. M.; Cottet, F.; Schlosser, M. *Chem.—Eur. J.* **2005**, *11*, 1251. (b) Schlosser, M.; Marzi, E. *Chem.—Eur. J.* **2005**, *11*, 3449.

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