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Palladium-Catalyzed Cross-Coupling of Polyfluoroarenes with Simple Arenes

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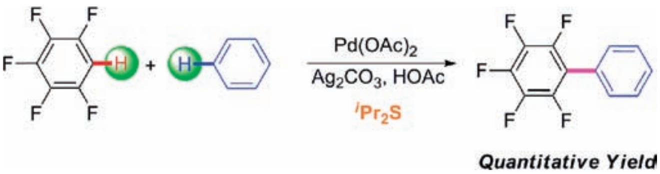
ABSTRACT



The most efficient method to construct biaryls is the direct dehydrogenative cross-coupling of two different aromatic rings. Such an ideal cross arylation starting from distinct polyfluoroarenes and simple arenes was presented. The selectivity of the cross-coupling was controlled by both of the electronic property of fluoroarenes and steric hindrance of simple arenes. Diisopropyl sulfide was essential to promote the efficacy.

The importance of polyfluorobiphenyl structures has been demonstrated by their application in medicinal chemistry[1] and numerous functional materials such as electron-transport devices and organic light-emitting diodes (OLEDs).[2] However, preparation of these important structural units is nontrivial and often requires tedious synthetic steps through traditional cross-coupling technology.[3] Direct arylation of electron-deficient polyfluoroarenes via C−H activation with aryl halides[4] or arylboronic acids[5] has been achieved, respectively, thus providing better synthetic efficiency. However, compared with using aryl halides or aryl organometallic reagents, dehydrogenative cross-coupling of aromatics would be advantageous since both arene partners do not require prefunctionalization. Recently, oxidative cross-coupling of polyfluoroarenes with terminal alkynes,[6] alkenes,[7] and electron-rich heterocycles[8] has been reported.[9] Despite the significant progress achieved in the oxidative cross-coupling of (hetero)arenes, the substrates are mainly limited to electron-rich heteroarenes and directing-group-containing arenes, typical structures that required achieving both high reactivity and selectivity. In contrast, direct cross-coupling of two simple arenes without directing group assistance, especially electron-deficient arenes, has been achieved very

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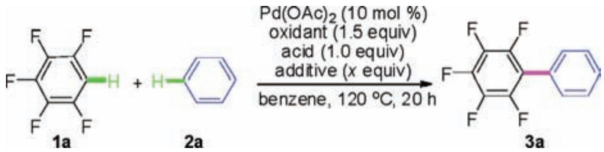
10.1021/ol102688e

Table 1. Optimization Study of Palladium-Catalyzed Cross-Coupling of Pentafluorobenzene with Benzene[a]



entry	oxidant	acid	additive (equiv)	yield (%)[b]
1	Ag_2CO_3	HOAc		<1
2	Ag_2CO_3	HOAc	DMSO (3.0)	39
3	AgOAc	HOAc	DMSO (3.0)	36
4	Ag_2O	HOAc	DMSO (3.0)	<1
5	$Cu(OAc)_2$	HOAc	DMSO (3.0)	16
6	BQ	HOAc	DMSO (3.0)	ND
7	oxone	HOAc	DMSO (3.0)	ND
8	Ag_2CO_3	HOAc	DMSO (7.0)	82
9	Ag_2CO_3	TFA	DMSO (7.0)	53
10	Ag_2CO_3	TFEol	DMSO (7.0)	62
11	Ag_2CO_3	PivOH	DMSO (7.0)	88
12	Ag_2CO_3	*tert*-butylacetic acid	DMSO (7.0)	quant
13	Ag_2CO_3	HOAc	diphenyl sulfoxide (3.0)	4
14	Ag_2CO_3	HOAc	diphenyl sulfide (3.0)	29
15	Ag_2CO_3	HOAc	diphenyl disulfide (3.0)	<1
16	Ag_2CO_3	HOAc	*tert*-butyl methyl sulfoxide (3.0)	17
17	Ag_2CO_3	HOAc	phenyl vinyl sulfoxide (3.0)	ND
18	Ag_2CO_3	HOAc	diethyl sulfide (3.0)	<1
19	Ag_2CO_3	HOAc	diisopropyl sulfide (3.0)	quant
20	Ag_2CO_3	HOAc	diisopropyl sulfide (1.0)	quant (91)

[a] The reactions were performed on a 0.20 mmol scale of pentafluorobenzene with 2.0 mL of benzene (110 equiv) as solvent. [b] Determined by GC with dodecane as the internal standard. The isolated yield is given in parentheses. BQ: benzoquinone. TFA: 2,2,2-trifluoroacetic acid. TFEol: 2,2,2-trifluoroethanol. PivOH: pivalic acid. ND: not detected. quant: quantitative yield.

recently by only one case after we submitted the manuscript.[11,12] Herein we described an unprecedented palladium-catalyzed oxidative cross-coupling of electron-deficient polyfluoroarenes with completely unactivated arenes.

We started to search for suitable reaction conditions for the oxidative cross-coupling of pentafluorobenzene with benzene as a model reaction system (Table 1). In the presence of 10 mol % of $Pd(OAc)_2$ as a catalyst, 1.0 equiv of HOAc as an acidic additive,[13] 1.5 equiv of Ag_2CO_3 as an oxidant, and a large excess of benzene as the solvent, the reaction carried out at 120 °C afforded only a trace amount of the desired product **3a** (entry 1). Instead, it produced biphenyl as an undesired byproduct from homocoupling. The addition of 3.0 equiv of DMSO[8,14] led to the formation of the desired coupling product in 39% yield (entry 2). Among other oxidants tested, AgOAc and $Cu(OAc)_2$ were less effective while Ag_2O, benzoquinone (BQ), and oxone were totally ineffective (entries 3−7). Moreover, increasing the amount of DMSO to 7.0 equiv led to 82% yield of the arylation product (entry 8). The influence of acid additives was also examined (entries 9−12). Generally, relatively weak acids such as HOAc and PivOH provided better results than strong acid such as 2,2,2-trifluoroacetic acid (TFA). It is noteworthy that with the assistance of *tert*-butylacetic acid, quantitative yield was achieved, although an appreciable quantity of biphenyl byproduct was also obtained (entry 12).[15] To further improve the reaction efficiency and selectivity, we tested various sulfoxides and sulfides as additives since they are known to affect the palladium-catalyzed C−H activation (entries 13−19).[8,14] Fortunately, we found that when diisopropyl sulfide was used, complete conversion was achieved and the desired product **3a** was obtained quantitatively, with only a

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(10) For selected examples, see: (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175. (b) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905. (c) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073. (d) Dwight, T. A.; Rue, N. R.; Charyk, D.; Joesselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137–3139. (e) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869–4871. (f) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254–9256. (g) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115–1118. (h) Brasche, G.; Garcia-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207–2210. (i) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720–4726. (j) Ackermann, L.; Jeyachandran, R.; Potukuchi, H. K.; Novak, P.; Buttner, L. *Org. Lett.* **2010**, *12*, 2056–2059.

(11) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973–5975.

(12) During the preparation of our manuscript, a similar report was published online: Wei, Y.; Su, W. *J. Am. Chem. Soc.* **2010**, *132*, 16377–16379.

(13) It is believed that acidic conditions might suppress undesired homocoupling in Pd-catalyzed oxidative cross-coupling reactions. For details, see: Yang, S.; Sun, C.; Fang, Z.; Li, B.; Li, Y.; Shi, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473–1476, and references cited therein.

(14) It is supposed that DMSO might function as a ligand to activate the Pd catalyst and prevent the formation of palladium black. For details, see: Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348–4355, and references cited therein.

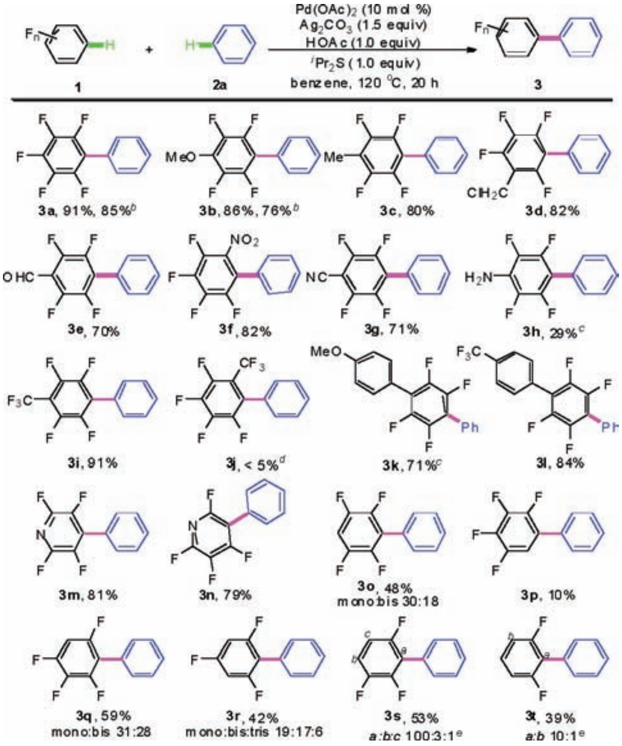
(15) The biphenyl byproduct and its quantity was detected by GC. For details, see the Supporting Information.

trace amount of biphenyl detected.[15] Decreasing the diisopropyl sulfide to 1.0 equiv did not affect the result, and the product was isolated in 91% yield (entry 20). Interestingly, using sulfide as a ligand to accelerate C−H activation is uncommon since it is well-known that sulfide tends to poison palladium catalysts.

With the optimized reaction condition in hand, a variety of polyfluoroarenes were tested as coupling partners with benzene. Tetrafluoro-, trifluoro-, and even some difluorobenzene could be selectively arylated with high efficiency (Scheme 1). For example, electron-rich or -deficient substituents such as methoxy, methyl, chloromethyl, aldehyde, nitro, cyano, and trifluoromethyl groups all could be tolerated quite well, wherever they located (**3b**−**g** and **3i**), except 2,3,4,5-tetrafluorobenzotrifluoride, probably because of the steric effect (**3j**). Those functional groups could be further transformed to other functionalities, providing the potential application of this methodology. Nevertheless, 2,3,5,6-tetrafluoroaniline converted incompletely under the standard condition, while a higher catalyst loading and longer reaction time could give a moderate yield of arylated product, accompanying the oxidation of the substrate (**3h**). Moreover, tetrafluorobenzene bearing electron-rich or -deficient phenyl ring substituents also worked very well, offering the opportunities to build up fluoroterphenyls (**3k** and **3*l***). Besides, tetrafluoropyridines were also found to be suitable partners for the coupling reactions with benzene (**3m** and **3n**). It is worth noting that reactions performed under an atmosphere of air resulted in slightly lower yields (**3a** and **3b**).

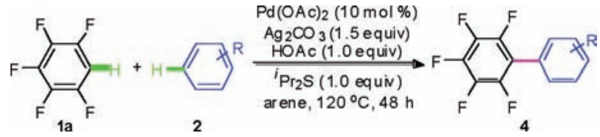
For 1,2,4,5-tetrafluorobenzene, double arylation occurred since two reaction sites were available (**3o**). Similarly, double and even triple arylation were achieved in moderate to good yields for 1,2,3,5-tetrafluorobenzene and 1,3,5-trifluorobenzene (**3q** and **3r**). Selective monoarylation of 1,2,3,4-

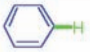
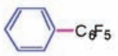
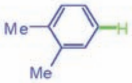
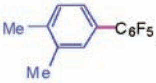
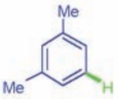
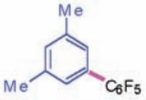
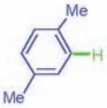
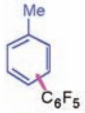
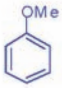
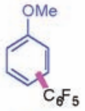
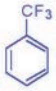
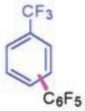
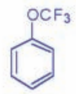
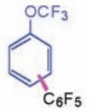
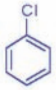
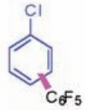
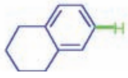
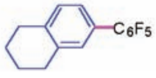
Scheme 1. Palladium-Catalyzed Oxidative Cross-Coupling of Polyfluoroarenes with Benzene[a]



[a] The reactions were performed on 0.60 mmol scales of polyfluoroarenes with 4.0 mL of benzene (75 equiv) as solvent and isolated yields are shown in the table. [b] Reactions ran under an atmosphere of air. [c] Reactions ran for 48 h with 15 mol % of Pd(OAc)$_2$. [d] Determined by GC. [e] The ratios of isomers were determined by ^{19}F NMR.

Table 2. Palladium-Catalyzed Oxidative Cross-Coupling of Pentafluorobenzene with Simple Arenes[a]



entry	arene		product		yield(%)[b]
1[c]		**2a**		**3a**	91
2		**2b**		**4b**	74
3		**2c**		**4c**	69[d]
4		**2d**		**4d**	34
5		**2e**		**4e**	83 *m*:*p* = 1.2:1
6		**2f**		**4f**	75 *m*:*p* = 2.1:1
7		**2g**		**4g**	53 *m*:*p* = 2.6:1
8		**2h**		**4h**	64 *m*:*p* = 1.8:1
9		**2i**		**4i**	61 *m*:*p*:*o* = 1.4:1.0:0.1
10		**2j**		**4j**	86

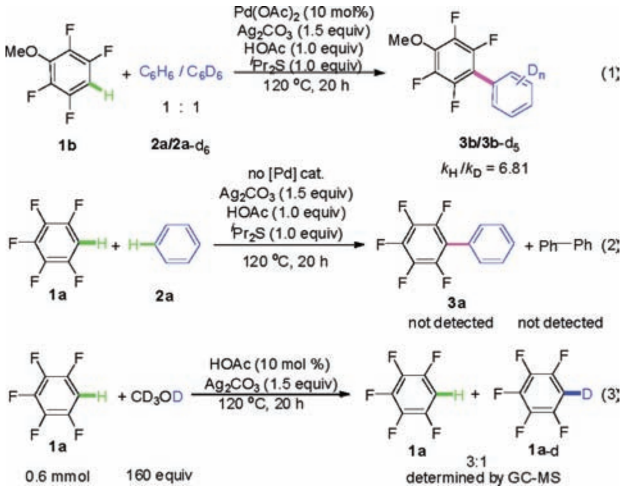
[a] The reactions were performed on a 0.60 mmol scale of pentafluorobenzene with 4.0 mL of arene as solvent. [b] Isolated yields are shown in the table and the ratios of isomers were determined by ^{19}F NMR. [c] Reaction ran for 20 h. [d] Trace quantity of isomers were detected by GC-MS.

tetrafluorobenzene was also achieved presumably due to steric hindrance of the second arylation (**3p**). The low yield showed that a C−H bond flanked with only one fluorine atom was less reactive probably due to its decreased acidity. When multiple unequal reaction sites are available, the arylation occurred preferentially at the most acidic C−H bond, which is ortho to a fluorine atom (**3s** and **3t**). The decreasing reactivity of pentafluorobenzene, 1,2,3,5-tetrafluorobenzene, 1,2,4-trifluorobenzene, 1,3,5-trifluorobenzene, 1,3-difluorobenzene, and 1,2,3,4-tetrafluorobenzene is reasonable since the fluorine atoms increase the acidity of C−H bonds, which is consistent with previous reports.[4a,10g,16]

To further probe the scope of this novel methodology, we tested various simple arenes as the coupling partners with pentafluorobenzene. All the reactions ran for 48 h to achieve complete conversion with good regioselectivity (Table 2). It is worth mentioning that these reactions were extremely sensitive to steric hindrance. For example, *o*-xylene and *m*-xylene reacted at the less hindered positions to generate single coupling products with good efficiency (entries 2 and 3). When *p*-xylene was presented as the coupling partner, only moderate yield was obtained because of the steric hindrance of the *o*-methyl group (entry 4). For monosubstituted arenes, C−H activation took place mainly at less hindered meta- and para-positions (entries 5−9). In addition, 1,2,3,4-tetrahydronaphthalene was also an excellent coupling partner with an exclusive regioselectivity (entry 10).

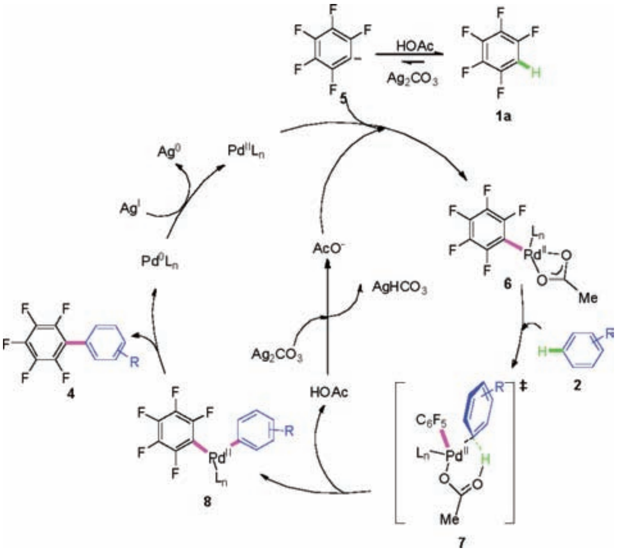
To investigate the mechanism, several control experiments were further conducted (Scheme 2). The intermolecular kinetic isotopic effect (KIE) by coupling of 2,3,5,6-tetrafluoroanisole with benzene/benzene-d_6 revealed that C−H cleavage of benzene was involved in the rate-determining step (eq 1). Although the oxidative coupling reactions did not occur in the absence of palladium catalysts (eq 2), the H/D exchange experiment indicated that for deprotonation of highly acidic pentafluorobenzene and some other polyfluorobenzenes, inorganic bases such as Ag_2CO_3 were sufficient and Pd(II) was not required (eq 3).

Scheme 2. Mechanism Investigation



On the basis of the preliminary studies, the catalytic cycle was proposed as shown in Scheme 3. Taking the coupling of pentafluorobenzene with arenes as the example, the initial deprotonation of pentafluorobenzene afforded anion **5**, followed by palladation to generate polyfluoroarylpalladium species **6**. Then C−H activation of arene **2** via concerted metalation−deprotonation (CMD)[4a,10g,16] transition-state **7** afforded biarylpalladium species **8**, which underwent reductive elimination to generate the product **4** and Pd(0) species. Finally reoxidation of Pd(0) by Ag(I) regenerated the catalytically active Pd(II) species to finish the catalytic cycle.

Scheme 3. Plausible Mechanism To Approach Oxidative Cross-Coupling of Pentafluorobenzene with Arenes



In conclusion, we have developed an unprecedented oxidative cross-coupling of polyfluoroarenes with simple arenes, providing an efficient method to build up polyfluorinated biaryls in good yields and high selectivity. The obvious effect of dialkyl sulfide was observed to promote direct C−H transformations for the first time. Remarkably, we have shown that a single palladium catalyst could activate two distinct C−H bonds through different pathways. Further studies to uncover the mechanism and apply this methodology to organic synthesis are currently underway in our lab.

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Supporting Information Available: Brief experimental details and other spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067.