

Palladium-Catalyzed C–H Perfluoroalkylation of Arenes

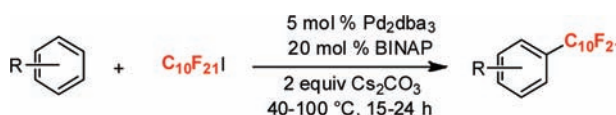
Rebecca N. Loy and Melanie S. Sanford*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States

mssanfor@umich.edu

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ABSTRACT



A new Pd-catalyzed reaction for the coupling between perfluoroalkyl iodides ($R_F I$) and simple aromatic substrates is described. The perfluoroalkylated arene products are obtained in good to excellent yields in the presence of a phosphine-ligated Pd catalyst and Cs_2CO_3 as a base. The development, optimization, scope, and preliminary mechanistic studies of these transformations are reported.

The introduction of fluorine-containing functional groups can drastically change both the biological and physical

properties of organic molecules.¹ In particular, trifluoromethyl and perfluoroalkyl (R_F) substituents are important structural features of many commercial agrochemicals, pharmaceuticals, and materials.² There are numerous methods for the construction of alkyl– R_F bonds.^{3,4} In contrast, the generation of aryl– R_F linkages (particularly aryl– CF_3) remains synthetically challenging,^{5–8} particularly via transition metal catalysis.^{6b,9–12} Several recent reports have demonstrated Cu- or Pd-catalyzed reactions for the trifluoromethylation of C–H bonds and/or aryl halides using, for example, [(*S*-trifluoromethyl)dibenzothiophene][BF_4] (**1**),¹⁰ $TESCF_3$ (**2**),¹¹ and $TMSCF_3$ (**3**)^{12a} as CF_3 sources. While these transformations represent very exciting advances, they are limited by the high cost of the reagents,¹³ the requirement for forcing reaction conditions, and/or have a modest substrate scope.^{9–12}

(1) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305.

(3) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(4) For recent reviews, see: (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (c) Prakash, G. K. S.; Chacko, S. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 793. (d) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633.

(5) Examples of stoichiometric reactions that form of aryl– R_F bonds: (a) Swarts, F. *Bull. Acad. R. Belg.* **1892**, *24*, 309. (b) McLoughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921. (c) Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. *Chem. Lett.* **1981**, *10*, 1719. (d) Chu, L.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 5060. (e) Zhang, C.-P.; Wang, Z.-L.; Chen, Q.-Y.; Zhang, C.-T.; Gu, Y.-C.; Xiao, J.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1896. (f) Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011**, *76*, 1174.

(6) For examples of stoichiometric free-radical perfluoroalkylations of aromatics with perfluoroalkyl halides, see: (a) Cowell, A.; Tamborski, C. *J. Fluorine Chem.* **1981**, *17*, 345. (b) Bravo, A.; Bjørsvik, H.-R.; Fontana, F.; Liguori, L.; Mele, A.; Minisci, F. *J. Org. Chem.* **1997**, *62*, 7128. (c) Huang, X.-T.; Long, Z.-Y.; Chen, Q.-Y. *J. Fluorine Chem.* **2001**, *111*, 107. (d) Li, Y.; Li, C.; Yue, W.; Jiang, W.; Kopecek, R.; Qu, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2374.

(7) Use of electrophilic perfluoroalkylating reagents: (a) Kiehl, I.; Eisenberger, P.; Stanek, K.; Togni, A. *Chimia* **2008**, *62*, 260. (b) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757.

(8) For examples of stoichiometric Aryl– CF_3 coupling from discrete Pd, Ni, and Cu complexes, see: (a) Grushin, V. V.; Marshall, W. J. *J. Am. Chem. Soc.* **2006**, *128*, 4632. (b) Dubinina, G. G.; Furutachi, H.; Vivic, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 8600. (c) Dubinina, G. G.; Brennessel, W. W.; Miller, J. L.; Vivic, D. A. *Organometallics* **2008**, *27*, 3933. (d) Dubinina, G. G.; Ogikubo, J.; Vivic, D. A. *Organometallics* **2008**, *27*, 6233. (e) Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 2878. (f) Ye, Y.; Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 14682.

(9) For examples of metal-catalyzed free radical perfluoroalkylations of aromatics, see: (a) Zhou, Q.-L.; Huang, Y.-Z. *J. Fluorine Chem.* **1989**, *43*, 385. (b) Huang, X.-T.; Chen, Q.-Y. *J. Org. Chem.* **2001**, *66*, 4651. (c) Kino, T.; Nagase, Y.; Ohtsuka, Y.; Yamamoto, K.; Uruguchi, D.; Tokuhisa, K.; Yamakawa, T. *J. Fluorine Chem.* **2010**, *131*, 98.

(10) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648.

(11) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.

(12) (a) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909. (b) Knauber, T.; Arikian, F.; Rösenthaler, G.; Goossen, L. J. *Chem.—Eur. J.* **2011**, *17*, 2689.

(13) Current prices for these reagents are \$23,000/mol (**1**), \$11,700/mol (**2**), \$2,200/mol (**3**), \$755/mol (CF_3I): McReynolds, K. A.; Lewis, R. S.; Ackerman, L. K. G.; Dubinina, G. G.; Brennessel, W. W.; Vivic, D. A. *J. Fluorine Chem.* **2010**, *131*, 1108.

We aimed to develop a mild Pd-catalyzed method for the perfluoroalkylation of simple arenes. In addition, our goal was to utilize relatively inexpensive perfluoroalkyl iodides as R_F precursors.^{6,9,14} We report herein that a variety of aromatic substrates undergo facile perfluoroalkylation with R_FI in the presence of a Pd⁰ catalyst, a phosphine ligand, and a base. The development, optimization, scope, site-selectivity, and mechanism of this transformation are discussed herein.

Initial studies focused on the Pd-catalyzed C–H perfluoroalkylation of benzene with C₆F₁₃I (Table 1).^{6,15} We noted that aryl iodides can participate in Pd(OAc)₂/PCy₃-catalyzed C–C coupling reactions with simple arenes.^{16,17} Fagnou and co-workers have proposed that these transformations proceed via a Pd^{0/II} mechanism initiated by oxidative addition of the aryl iodide to Pd⁰.¹⁶ Since perfluoroalkyl iodides are known to undergo related oxidative addition reactions at Pd⁰ centers,¹⁸ we reasoned that a similar transformation might be feasible with these substrates. To test this possibility, we first examined the coupling of C₆F₁₃I with benzene under Fagnou's conditions for ArI/arene coupling (10 mol % of Pd(OAc)₂/20 mol % phosphine and 2 equiv of K₂CO₃). We initially selected BrettPhos as our phosphine ligand, since it is known to facilitate Aryl–CF₃ bond-forming reductive elimination from Pd^{II} centers.¹¹ We were pleased to find that this reaction provided 9% yield of the desired C–H perfluoroalkylation product **4** (Table 1, entry 1).¹⁹

The C–H perfluoroalkylation reaction was optimized with respect to Pd precursor, phosphine ligand, and base. As shown in Table 1, Pd₂dba₃ provided significantly higher yield than Pd(OAc)₂ (entries 2 and 1, respectively). An evaluation of different phosphines revealed that BINAP was the optimal ligand examined, and the combination of 10 mol % of BINAP and 5 mol % of Pd₂dba₃ provided 57% yield of **4** under an N₂ atmosphere (entry 7). Interestingly, when the analogous transformation was conducted in air, only 2% yield of **4** was detected (entry 8). Under these conditions, ³¹P NMR spectroscopic analysis showed the formation of significant quantities of phosphine oxide. Thus, we reasoned that the use of an excess of BINAP relative to Pd might provide improved results by maintaining ligated Pd species throughout the reaction. Indeed, a 2:1 ratio of BINAP/Pd afforded significantly higher yields, without the need to exclude O₂ (entry 9). Carbonate salts were the best bases of this reaction, with Cs₂CO₃ proving optimal (entry 10).

This effect may be due to the higher solubility of Cs₂CO₃ compared to other alkali metal carbonates.²⁰ The final optimized conditions (5 mol % of Pd₂dba₃, 20 mol % of BINAP, 2 equiv of Cs₂CO₃ at 80 °C for 15 h), provided perfluoroalkylated product **4** in 81% yield (entry 10).

Table 1. Optimization of Perfluoroalkylation Reaction^a

entry	phosphine	base	yield (%) ^b
1	20 mol % BrettPhos	K ₂ CO ₃	9 ^{c,d}
2	20 mol % BrettPhos	K ₂ CO ₃	38 ^d
3	20 mol % RuPhos	K ₂ CO ₃	13 ^d
4	20 mol % PPh ₃	K ₂ CO ₃	24 ^d
5	10 mol % dppf	K ₂ CO ₃	47 ^d
6	20 mol % P ^t Bu ₃	K ₂ CO ₃	23 ^d
7	10 mol % BINAP	K ₂ CO ₃	57 ^d
8	10 mol % BINAP	K ₂ CO ₃	2
9	20 mol % BINAP	K ₂ CO ₃	67
10	20 mol % BINAP	Cs ₂ CO ₃	81

BrettPhos

RuPhos

^a General conditions: C₆F₁₃I (1 equiv), Pd₂dba₃ (5 mol %), base (2 equiv) in C₆H₆ at 80 °C for 15 h. ^b Yields determined by GC analysis. ^c Pd(OAc)₂ (10 mol %). ^d Under N₂.

The scope of this transformation was evaluated using a variety of different aromatic substrates (Table 2). A longer chain perfluoroalkyl iodide (C₁₀F₂₁I) was used to facilitate isolation of the products. Arenes containing electron-donating methyl and alkoxy substituents generally reacted to provide perfluoroalkylated products in good to excellent yields (entries 2–8). In substrates containing benzylic C–H sites, these transformations were highly selective for functionalization on the aromatic ring. In general, significantly lower reactivity was observed with aromatic substrates containing electron withdrawing substituents; however, 1,2-dichlorobenzene did undergo perfluoroalkylation in modest yield (entry 10). In addition, *N*-methylpyrrole afforded the 2-perfluoroalkylated product **15** as a single detectable isomer (entry 11).

The site selectivity of these transformations was dictated by the substitution patterns on the aromatic substrate. All of the 1,2-disubstituted arenes afforded high selectivity for functionalization at the 4-position. The 1,3-substituted substrates underwent preferential functionalization at the 4-position, which is the kinetically preferred site for electrophilic substitution.²¹ Similarly, naphthalene perfluoroalkylation proceeded

(20) Cella, J. A.; Bacon, S. W. *J. Org. Chem.* **1984**, *49*, 1122.

(21) (a) Zysman-Colman, E.; Arias, K.; Siegel, J. S. *Can. J. Chem.* **2009**, *87*, 440. (b) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Synlett* **2004**, 461.

(14) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1982**, *11*, 137.

(15) Review on fluoroalkyl radicals: Dolbier, W. R. *Chem. Rev.* **1996**, *96*, 1557.

(16) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

(17) For other recent examples of Pd-catalyzed C–H functionalization reactions with aryl or alkyl halides, see: (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. C–H Activation: (d) Yu, J.-Q., Shi, Z., Eds; *Topics in Current Chemistry* 292; Springer: Heidelberg, Germany, 2010; pp 1–76.

(18) (a) Rosevear, D. T.; Stone, F. G. A. *J. Chem. Soc. A* **1968**, 164. (b) Mukhedkar, A. J.; Green, M.; Stone, F. G. A. *J. Chem. Soc. A* **1969**, 3023. (c) Empsall, H. D.; Green, M.; Stone, F. G. A. *J. Chem. Soc., Dalton Trans.* **1972**, 96.

(19) Only trace amounts of product were obtained when the palladium, phosphine or both were excluded from the reaction. The yield was reduced to 7% when base is excluded.

Table 2. Substrate Scope of Pd-Catalyzed Perfluoroalkylation

entry	substrate	major product	NMR yield (%) ^[a] (isolated yield)	isomer ratio ^[b]
1			79 (60)	—
2			79 (76)	>20:1
3			99 (69)	17:1:2 ^[c]
4			84 (59)	—
5			80 (69)	11:1:1 ^[d]
6			76 (54)	>20:1
7			77 (55)	2.2:1
8			52 (52)	—
9			76 (34)	4.0:1
10			39 (27)	>20:1
11			99 (70)	>20:1

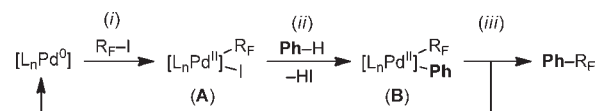
^aNMR yields obtained by ¹⁹F NMR analysis of the crude reaction mixtures. ^bSelectivity determined by ¹⁹F NMR analysis of the crude reaction mixture. ^cSelectivity determined from isolated product.

with modest selectivity for the kinetically preferred α -position.

There are several potential mechanisms for these reactions. One possibility is similar to that proposed by Fagnou for Pd-catalyzed C–H arylation with aryl iodides. This mechanism would involve: (i) oxidative addition of R_F-I to Pd^0 to generate Pd^{II} intermediate **A**, (ii) arene activation at **A** to form the diorgano Pd^{II} species **B**, and (iii) C–C bond-forming reductive elimination to release the product and regenerate the Pd^0 catalyst (Scheme 1). Notably, each step of this

(22) For examples of Pd^0 -catalyzed coupling of R_F-X with alkenes or Bu_3Sn-E ($E = ArR_2, PR_2, SeR$), see: (a) Ishihara, T.; Kuroboshi, M.; Okada, Y. *Chem. Lett.* **1986**, *15*, 1895. (b) Matsubara, S.; Mitani, M.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 5857. (c) Urata, H.; Yugari, H.; Fuchikami, T. *Chem. Lett.* **1987**, *16*, 833. (d) Chen, Q.-Y.; Yang, Z.-Y.; Zhao, C.-X.; Qiu, Z.-M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 563. (e) Rossi, R. A. *Tetrahedron Lett.* **2006**, *47*, 3511. (f) Uberman, P. M.; Lanteri, M. N.; Martin, S. E. *Organometallics* **2009**, *28*, 6927.

catalytic cycle has precedent in the literature for related systems,^{8,11,16,17,22} however, step iii is known to be challenging at most phosphine $Pd^{II}(Aryl)(CF_3)$ intermediates.^{8,11,23}

Scheme 1. C–H Activation Mechanism

An alternative mechanistic possibility would involve Pd/phosphine/base-promoted generation of free perfluoroalkyl radicals ($R_F\bullet$) that could react directly with the aromatic substrates. Such transformations also have precedent in the literature, but typically occur under quite different reaction conditions and proceed with different selectivity than the current transformations.^{6,9} For example, free radical perfluoroalkylation of veratrol via the oxidation of sodium perfluoroalkanesulfonates with $Mn(OAc)_2 \cdot H_2O$ affords a 1:1 ratio of regioisomeric products.²⁴ In contrast, this Pd-catalyzed reaction affords >20:1 selectivity (Table 2, entry 2). Caged and/or “Pd-associated” radical intermediates are a final mechanistic possibility.

Table 3. Effect of Additives on Pd-Catalyzed Perfluoroalkylation of Benzene

entry	additive	yield
1	none (ambient light)	81%
2	none (dark)	87%
3	10 mol % AIBN	71%
4	1 equiv BHT	74%
5	20 mol % hydroquinone	76%
6	20 mol % 1,4-dinitrobenzene	73%

Experimental studies showed that the yield of Pd-catalyzed benzene perfluoroalkylation is identical in the presence and absence of ambient light (Table 3, entries 1 and 2). Furthermore, the addition of azobisisobutyronitrile (AIBN) (a radical initiator), butylhydroxytoluene (BHT) or hydroquinone (radical inhibitors), and 1,4-dinitrobenzene (an ET scavenger)^{9b} all had negligible impact on the yield of this reaction (entries 3–6). This latter result is in particular contrast to Ni^0 -catalyzed free radical additions of perfluoroalkyl halides to olefins, which were dramatically inhibited by 1,4-dinitrobenzene.^{9b,25}

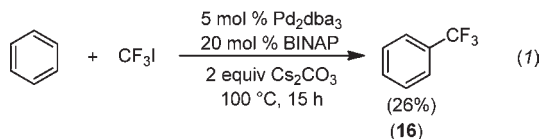
(23) Grushin, V. V.; Marshall, W. J. *J. Am. Chem.* **2006**, *128*, 12644.

(24) Huang, W.-Y.; Xie, Y. *Chin. J. Chem.* **1990**, 536.

(25) For example, the addition of 20 mol % of DNB to the $NiCl_2/PPh_3$ -catalyzed reaction of $C_6F_{13}Cl$ with 3-(allyloxy)prop-1-ene decreased the yield from 90 to 0%. See ref 9b.

These preliminary studies suggest against a purely free radical pathway, and implicate the formation of either caged radical or organometallic intermediates. Further details of the mechanism are the subject of ongoing investigations.

The most synthetically valuable perfluoroalkyl group to introduce is CF_3 ,³ and we have conducted preliminary studies to establish the viability of arene trifluoromethylation with the $\text{Pd}_2\text{dba}_3/\text{BINAP}$ catalyst system. Under our standard conditions benzene reacts with CF_3I to afford trifluorotoluene (**16**) in 26% yield as determined by gas chromatography (eq 1). This result provides promising precedent for the viability of Pd-catalyzed trifluoromethylation with CF_3I . The scope of this trifluoromethylation reaction is currently under investigation.



In conclusion, this communication describes Pd-catalyzed coupling of perfluoroalkyl iodides with simple arenes. Preliminary mechanistic investigations suggest that the reaction is not proceeding via free perfluoroalkyl radicals. The optimized conditions for C–H perfluoroalkylation were also effective for C–H trifluoromethylation. Ongoing studies are focused on probing both the mechanism and scope of this transformation in more detail.

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