ORGANIC LETTERS

2013
Vol. 15, No. 19
5004–5007

Pd-Catalyzed Direct Arylation of Nitro(pentafluorosulfanyl)benzenes with Aryl Bromides

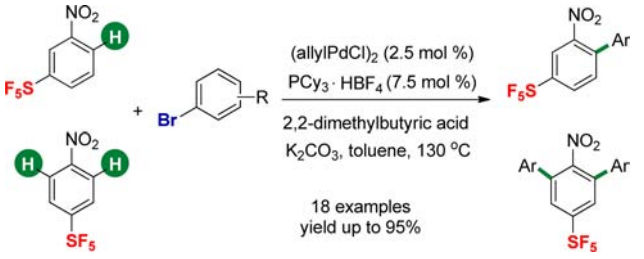
Chao Wang, Yan-Bo Yu, Shilu Fan, and Xingang Zhang*

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

xgzhang@mail.sioc.ac.cn

Received August 14, 2013

ABSTRACT



Limited methods for the synthesis of SF_5-substituted compounds significantly restrict their widespread application. A Pd-catalyzed direct arylation of nitro(pentafluorosulfanyl)benzenes with aryl bromides is reported. This protocol provides a facile and straightforward access to diversified SF_5-containing aryl derivatives. The notable features of this reaction are its synthetic simplicity, high reaction efficiency, and good regioselectivity.

Due to the important role of fluorinated compounds in life and material sciences,[1] it is of great interest to develop new and efficient methods to prepare such compounds. In the past few years, great endeavors have been devoted to fluorination and trifluoromethylation of (hetero)arenes, and it has become an intensive topic of organosynthetic chemistry.[2] However, to meet the increasing demand of life and materials, the preparation of novel fluorine-containing compounds remains highly desirable. The pentafluorosulfanyl (SF_5) group, namely, the "super-trifluoromethyl group",[3] is one of the fascinating fluorinated groups bearing specific physicochemical properties, such as its high thermal, hydrolytic, and chemical stability, high lipophilicity, high density, and strong electron-withdrawing character.[4] It is beginning to find many applications in pharmaceuticals, agrochemicals, and important functional materials.[5] However, compared to trifluoromethylation of (hetero)arenes, only a few methods for the synthesis of SF_5-substituted (hetero)aryl derivatives have been reported so far.[6] This is mainly because of the difficulty in

(1) For selected reviews, see: (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3. (b) Maienfisch, P.; Hall, R. G. *Chimia* **2004**, *58*, 93. (c) Special issue on "Fluorine in the Life Sciences": *ChemBioChem* **2004**, *5*, 557. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (f) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (g) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(2) For selected reviews, see: (a) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804. (b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (d) Ye, Y.; Sanford, M. S. *Synlett* **2012**, 2005. (e) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048. (f) Qing, F.-L. *Chin. J. Org. Chem.* **2012**, *32*, 815. (g) Wang, X.; Zhang, Y.; Wang, J. *Sci. Sin.: Chim.* **2012**, *42*, 1417.

(3) Kirsch, P. *Modern Fluoroorganic Chemistry Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, 2004.

(4) (a) Verma, R.; Kirchmeier, R.; Shreeve, J. *Advances in Inorganic Chemistry*; Elsevier: Amsterdam, 1994; pp 125–169. (b) Lentz, D.; Seppelt, K. In *Chemistry of Hypervalent Compounds*; Akiba, K.-Y., Ed.; Wiley-VCH: New York, 1999; p 295.

(5) For a review, see: (a) Altomonte, S.; Zanda, M. *J. Fluorine Chem.* **2012**, *143*, 57. For selected papers, see: (b) Kirsch, P.; Bremer, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4216. (c) Welch, J. T.; Lim, D. S. *Bioorg. Med. Chem.* **2007**, *15*, 6659. (d) Wipf, P.; Mo, T.; Geib, S.; Caridha, D.; Dow, G.; Gerena, L.; Roncal, N.; Milner, E. *Org. Biomol. Chem.* **2009**, *7*, 4163. (e) Stump, B.; Eberle, C.; Schweizer, W. B.; Kaiser, M.; Brun, R.; Kraut-Siegel, R. L.; Lentz, D.; Diederich, F. *ChemBioChem* **2009**, *10*, 79.

(6) (a) Roberts, H. L. *J. Chem. Soc.* **1962**, 3183. (b) Sheppard, W. A. *J. Am. Chem. Soc.* **1960**, *82*, 4751. (c) Sheppard, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 3064. (d) Bowden, R. D.; Comina, P. J.; Greenhall, M. P.; Kariuki, B. M.; Loveday, A.; Philp, D. *Tetrahedron* **2000**, *56*, 3399. (e) Chambers, R. D.; Spink, R. C. H. *Chem. Commun.* **1999**, 883. (f) Umemoto, T. WO 2008/118787, 2008. (g) Beier, P.; Pastyrikova, T.; Vida, N.; Iakobson, G. *Org. Lett.* **2011**, *13*, 1466. (h) Beier, P.; Pastyrikova, T.; Iakobson, G. *J. Org. Chem.* **2011**, *76*, 4681. (i) Frischmuth, A.; Unsinn, A.; Groll, K.; Stadtmuller, H.; Knochel, P. *Chem.—Eur. J.* **2012**, *18*, 10234.

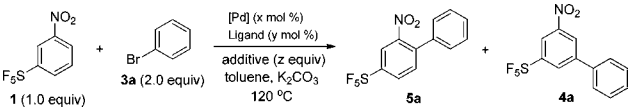
10.1021/ol4023326
Published on Web 09/20/2013

accessing pentafluorosulfanylated reagents and lack of key SF_5-substituted building blocks.[7] Hence, developing new and efficient methods to access SF_5-containing compounds for widespread applications is appealing.

The *meta*- and *para*-nitro(pentafluorosulfanyl)benzenes (**1** and **2**) are readily and commercially available and can be easily prepared through direct fluorination of bis-(nitrophenyl)disulfides on a large scale.[6d] Usually, the SF_5-substituted aryl derivatives can be accessed by reduction of the nitro group on (**1** and **2**) to amine, followed by acylation, electrophilic halogenation, or diazotization.[6d,i] Despite the utility of this method, developing new efficient and straightforward methods to access diversified structures would benefit the application of SF_5-containing compounds in life and material sciences. Considering that SF_5 and nitro groups are strong electron-withdrawing groups that can acidify their corresponding *ortho* C−H bonds, we envisioned that with the aid of a transition-metal catalyst, such as palladium, the direct arylation of **1** and **2** would be possible,[8] and thus diversified SF_5-containing aryl derivatives can be easily accessed via this strategy. Continuing our study of transition-metal-catalyzed direct functionalization of electron-deficient arenes,[9] herein we describe an efficient and straightforward method for the synthesis of SF_5-substituted aryl derivatives through palladium-catalyzed cross-coupling between nitro(pentafluorosulfanyl)benzenes and aryl bromides. The notable features of this protocol are its synthetic simplicity, high reaction efficiency, and good regioselectivity.

We began this study by choosing *meta*-nitro(pentafluorosulfanyl)benzene **1** and phenyl bromide **3a** as model substrates. Initially, a negative result was obtained with the use of $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and K_2CO_3 (1.2 equiv) in toluene at 120 °C (Table 1, entry 1). After a survey of different reaction parameters, such as phosphane ligands, solvents, and additives, it was found that the reaction is sensitive to the ligands and solvents. The use of $PCy_3 \cdot HBF_4$ **L1** and nonpolar solvent toluene in conjunction with PivOH showed better catalytic effect, albeit a mixture of **5a** and **4a** was obtained in 31 and 8% yield, respectively (Table 1, entry 2) (for details see Supporting Information). Further, to improve the reaction efficiency by investigation of different palladium sources (Table 1, entries 5−9), it turned out that $(AllylPdCl)_2$ is the optimal precatalyst with 55% yield of **5a** as the major product obtained (Table 1, entry 6). We were delighted to find that increasing the reaction temperature to 130 °C in combination with bulky carboxylic acid 2,2-dimethylbutyric acid **6** could improve the yield of **5a** to 71% without observation of **4a** (Table 1, entry 10). Further optimization revealed that 79% yield of isolated product **5a** was afforded by decreasing the $(AllylPdCl)_2$ loading to 2.5 mol % with use of $PCy_3 \cdot HBF_4$ (7.5 mol %), **6** (0.3 equiv), and K_2CO_3 (1.8 equiv) in high concentration at 130 °C (Table 1, entry 14). The use of PivOH diminished the yield (Table 1, entry 15). Without Pd catalyst or phosphane ligand, no desired product was obtained (Table 1, entries 16 and 17), thus implying that a Pd(0/II) catalytic cycle is involved in the reaction. Furthermore, the absence of additive **6** failed to afford any desired product, thus demonstrating the essential role of carboxylic acid for the reaction efficiency

Table 1. Optimization of Palladium-Catalyzed Direct Arylation of *meta*-Nitro(pentafluorosulfanyl)benzene **1** with Phenyl Bromide **3a**[a]



entry	[Pd], *x* mol %	ligand, *y* mol %	additive, *z* equiv	**5a**/**4a** yield (%)[b]
1	$Pd(OAc)_2$, 10	PPh_3, 20		NR
2	$Pd(OAc)_2$, 10	**L1**, 15	PivOH, 1	31/8
3	$Pd(OAc)_2$, 10	**L1**, 15	AcOH, 1	2/trace
4	$Pd(OAc)_2$, 10	**L1**, 15	AdOH, 1	3/2
5	$PdCl_2$, 10	**L1**, 15	PivOH, 1	38/3
6	$(AllylPdCl)_2$, 5	**L1**, 15	PivOH, 1	55/4
7	$Pd(dppf)Cl_2$, 10	**L1**, 15	PivOH, 1	51/6
8	$Pd(MeCN)Cl_2$, 10	**L1**, 15	PivOH, 1	38/4
9	$Pd(PPh_3)Cl_2$, 10	**L1**, 15	PivOH, 1	42/4
10[c]	$(AllylPdCl)_2$, 5	**L1**, 15	**6**, 1	71/0
11[d]	$(AllylPdCl)_2$, 5	**L1**, 15	**6**, 1	62/8
12[c,e]	$(AllylPdCl)_2$, 5	**L1**, 15	**6**, 0.5	(82)/(7)
13[c,f]	$(AllylPdCl)_2$, 2.5	**L1**, 7.5	**6**, 0.3	(74)/(7)
14[g]	$(AllylPdCl)_2$, 2.5	**L1**, 7.5	**6**, 0.3	(79)/(7)
15[g]	$(AllylPdCl)_2$, 2.5	**L1**, 7.5	PivOH, 0.3	61/8
16[g]		**L1**, 7.5	**6**, 0.3	NR
17[g]	$(AllylPdCl)_2$, 2.5		**6**, 0.3	NR
18[g]	$(AllylPdCl)_2$, 2.5	**L1**, 7.5		NR

[a] Reaction conditions (unless otherwise specified): **1** (0.3 mmol), **3a** (2.0 equiv), K_2CO_3 (1.2 equiv), toluene (1 mL), 8 h, 120 °C. [b] NMR yield determined by ^{19}F NMR using fluorobenzene as an internal standard (isolated yield in parentheses). [c] Reaction conducted at 130 °C. [d] Reaction conducted at 140 °C. [e] Using 2.4 equiv of K_2CO_3. [f] Using 1.8 equiv of K_2CO_3. [g] **1** (0.5 mmol), **3a** (1.5 equiv), K_2CO_3 (1.8 equiv), toluene (0.8 mL), 130 °C, 8 h. **L1**: $PCy_3 \cdot HBF_4$; **6**, 2,2-dimethylbutyric acid.

(7) SF_5Cl is presently the only commercially available "reagent" that can be used to introduce the SF_5 substituent into aliphatic compounds. However, SF_5Cl is a gaseous and highly toxic reagent. See: Ait-Mohand, S.; Dolbier, W. D., Jr. *Org. Lett.* **2002**, *4*, 3013.

(8) For selected transition-metal-catalyzed direct arylation of electron-deficient (hetero)arenes with aryl halides, see: (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (c) Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533. (d) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

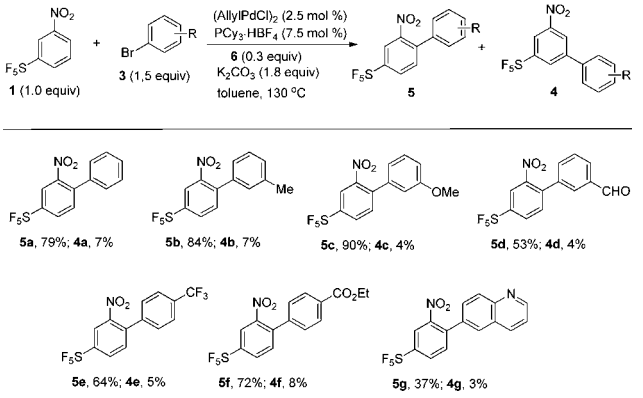
(9) (a) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506. (b) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850. (c) Fan, S.; Chen, F.; Zhang, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 5918. (d) Fan, S.; Yang, J.; Zhang, X. *Org. Lett.* **2011**, *13*, 4374. (e) Fan, S.; He, C.-Y.; Zhang, X. *Chem. Commun.* **2010**, *46*, 4926. (f) Chen, F.; Feng, Z.; He, C.-Y.; Wang, H.-Y.; Guo, Y.-l.; Zhang, X. *Org. Lett.* **2012**, *14*, 1176. (g) Chen, F.; MinQ.-Q.; Zhang, X. *J. Org. Chem.* **2012**, *77*, 2992. (h) He, C.-Y.; Min, Q.-Q.; Zhang, X. *Organometallics* **2012**, *31*, 1335. (i) Yu, Y.-B.; Fan, S.; Zhang, X. *Chem.—Eur. J.* **2012**, *18*, 14643.

(10) (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. (b) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (c) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (d) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.

(Table 1, entry 18). On the basis of previous studies, we supposed that 2,2-dimethylbutanoate generated by the reaction of **6** with K_2CO_3 may serve as a suitable base to assist the C−H cleavage for compound **1**.[10]

Under optimal reaction conditions, the substrate scope of direct arylation of *meta*-nitro(pentafluorosulfanyl)-benzene **1** was investigated (Scheme 1).

Scheme 1. Pd-Catalyzed Direct Arylation of *meta*-Nitro-(pentafluorosulfanyl)benzene **1** with Aryl Bromides **3**[a]



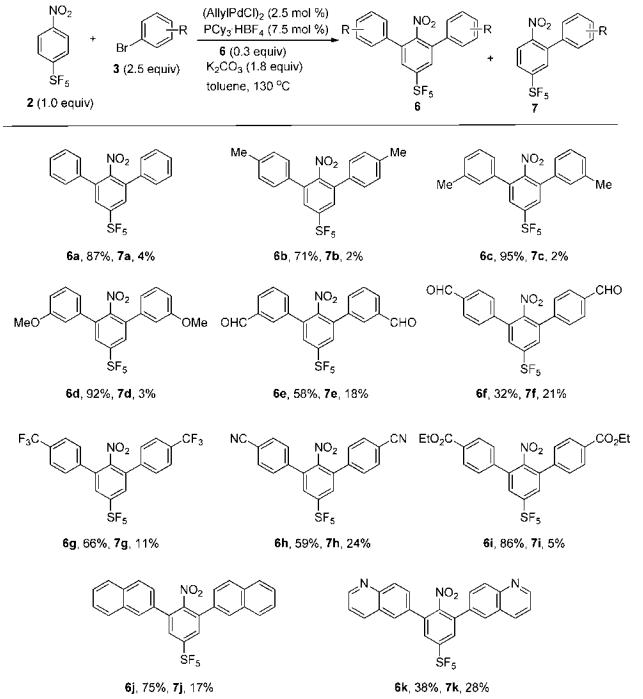
[a] Reaction conditions (unless otherwise specified): **1** (0.5 mmol, 1.0 equiv), **3** (1.5 equiv), $(AllylPdCl)_2$ (2.5 mol %), $PCy_3 \cdot HBF_4$ (7.5 mol %), K_2CO_3 (1.8 equiv), and 2,2-dimethylbutyric acid **6** (0.3 equiv) in toluene (0.8 mL) at 130 °C for 15 h.

The present method allowed the direct arylation of **1** with a variety of aryl bromides, and high regioselectivity was observed with aryl groups *ortho* to the nitro group. Generally, the reaction efficiency depends on the nature of the substituents on the aryl bromides. Substrates bearing an electron-donating group afforded higher yields than those substituted with an electron-withdrawing group. However, for the heteroaryl bromide, a reasonable yield was obtained (**5g**).

To probe the applicability of this method further, couplings of *para*-nitro(pentafluorosulfanyl)benzene **2** with aryl bromides **3** were also tested (Scheme 2). Interestingly, diarylated compounds **6** were obtained as major products when 2.5 equiv of **3** was used. Similarly, the coupling of compound **2** with electron-rich aryl bromides provided yields of compounds **6** higher than those of electron-deficient ones. The position of the substituents on the phenyl bromide also affected reaction efficiency, and *meta*-substituted phenyl bromides furnished their corresponding products in higher yields (**6c** and **6e**). For electron-deficient aryl bromides, more monoarylated **7** was afforded (**6e**−**h**). 2-Bromonaphthalene also underwent the reaction smoothly, providing **6j** in 75% yield along with a 17% yield of **7j (6j)**, but for 6-bromoquinoline, a mixture of **6k** and **7k** (**6k**/**7k** = 1.36) was obtained in moderate yield (**6k**).

To demonstrate the utility of this method, a transformation of **5c** was performed. As shown in Scheme 3, reduction of the nitro group on **5c** with iron powder and concentrated

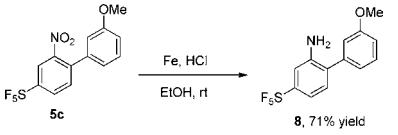
Scheme 2. Pd-Catalyzed Direct Arylation of *para*-Nitro(penta-fluorosulfanyl)benzene **2** with Aryl Bromides **3**[a]



[a] Reaction conditions (unless otherwise specified): **2** (0.2−0.3 mmol, 1.0 equiv), **3** (2.5 equiv), $(AllylPdCl)_2$ (2.5 mol %), $PCy_3 \cdot HBF_4$ (7.5 mol %), K_2CO_3 (1.8 equiv), and 2,2-dimethylbutyric acid **6** (0.3 equiv) in toluene (1 mL) at 130 °C for 15 h.

hydrochloric acid afforded SF_5-substituted aniline **8** in good yield,[11] thus providing a good opportunity for further applications of this key SF_5-substituted building block in life and materials sciences.

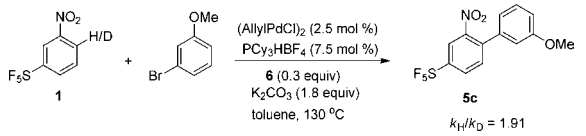
Scheme 3. Transformation of Compound **5c**



To understand the working mode of the present reaction, a kinetic isotope effect (KIE) experiment was conducted (Scheme 4). The intermolecular competition reactions between **1** and *d*-**1** showed a KIE of 1.91. Although the exact mechanism of the reaction is still not clear, on the basis of the results reported by others[10] and the preliminary kinetic data and the fact that a Pd(0/II) is involved in the catalytic cycle (Table 1, entries 16 and 17), we proposed that the catalytic cycle could be initiated from oxidation of Pd(0) to aryl bromides. The resulting Pd(II) intermediate subsequently goes through the concerted metalation−deprotonation (CMD) process[10] with **1** or **2** to form a

(11) Welch, J. T.; Lim, D. S. *Bioorg. Med. Chem.* **2007**, *15*, 6659.

Scheme 4. Kinetic Isotope Effect Study



diarylpalladium complex. Finally, reductive elimination provides the final product and releases Pd(0). However, the detailed reaction mechanism remains a point of discussion.

In conclusion, we have developed a straightforward and convenient method for Pd-catalyzed direct arylation of *meta*- and *para*-nitro(pentafluorosulfanyl)benzenes (**1** and **2**). The reaction makes direct use of simple and readily available SF_5-substituted benzenes without the requirement of several synthetic steps to prepare cross-coupling partners. Because of the high reaction efficiency, high regioselectivity, and the ease of conducting such reactions, this protocol provides a useful and facile access to SF_5-substituted aryl derivatives of interest in life and materials sciences.

Acknowledgment. The National Basic Research Program of China (973 Program) (No. 2012CB821600), the NSFC (No 21172242), and SIOC are greatly acknowledged for funding this work.

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.

The authors declare no competing financial interest.