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## Ir-Catalyzed Preparation of SF<sub>5</sub>-Substituted Potassium Aryl Trifluoroborates via C—H Borylation and Their Application in the Suzuki—Miyaura Reaction

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## ABSTRACT



The preparation of new pentafluorosulfanyl-substituted potassium aryltrifluoroborates via Ir-catalyzed C-H borylation is reported. The utility of these novel building blocks was demonstrated in the Suzuki-Miyaura cross-coupling reaction, giving access to 3,5-disubstituted penta-fluorosulfanylbenzenes.

In recent years, the pentafluorosulfanyl group has gained increasing attention because of its particular combination of properties. The SF<sub>5</sub> is often compared to trifluoromethyl; however it is more electronegative (Hammett substituent constants: for SF<sub>5</sub>  $\sigma_I = 0.55$ , for CF<sub>3</sub>  $\sigma_I = 0.39$ )<sup>1</sup> and possesses higher intrinsic lipophilicity (Hansch hydrophobicity constants: for SF<sub>5</sub>  $\pi = 1.51$ , for CF<sub>3</sub>  $\pi = 1.09$ ).<sup>2</sup> Moreover, the SF<sub>5</sub> displays higher chemical and thermal stability.<sup>3</sup> These assets make the pentafluorosulfanyl group increasingly attractive, and several examples of its potential for various applications have been reported, such as for agrochemicals and pharmaceuticals, and also in material sciences, including polymers, liquid crystals, and energetic materials.<sup>4</sup>

The first synthesis of pentafluorosulfanylbenzene was reported by Sheppard 50 years ago by oxidative fluorination of aryl disulfides with silver difluoride.<sup>5</sup> However, yields were low and the substrate scope was limited to a few nitrosubstituted phenylsulfur pentafluorides. Improvements in the preparation of  $SF_5$ -aryl compounds were achieved recently. Notably, Umemoto developed an efficient twostep procedure, involving the synthesis of  $SF_4$ Cl-substituted aromatics, which were treated with a fluoride source, such as zinc difluoride or even hydrofluoric acid in pyridine to give  $ArSF_5$ .<sup>6</sup>

More expansive applications of the pentafluorosulfanyl group are limited by the paucity of building blocks that are generally available. Herein, we document the implementation of the Ir-catalyzed C–H borylation reaction of Hartwig, Ishiyama, and Miyaura with simple pentafluorosulfanylarenes to provide access to an expanded set of SF<sub>5</sub>-building blocks from the parent hydrocarbon. Given that the chemistry of SF<sub>5</sub>-substituted arenes is relatively unexplored, we showcase that they can be subjected to Suzuki–Miyaura cross-coupling reactions (Scheme 1).

Using the electron withdrawing effect of the pentafluorosulfanyl group, nucleophilic substitutions of halogens,<sup>7</sup>

<sup>(1)</sup> Sheppard, W. A. J. Am. Chem. Soc. 1962, 84, 3072-3076.

<sup>(2)</sup> Hansch, C.; Muir, R. M.; Fujita, T.; Maloney, P. P.; Geiger, F.;

<sup>Streich, M. J. Am. Chem. Soc. 1963, 85, 2817–2824.
(3) (a) Sheppard, W. A. J. Am. Chem. Soc. 1962, 84, 3064–3072. (b)
Bowdem, R. D.; Comina, P. J.; Greenhall, M. P.; Kariuki, B. M.; Loveday, A.; Philp, D. Tetrahedron 2000, 56, 3399–3408.</sup> 

<sup>(4) (</sup>a) Welch, J. T. Fluorine in Pharmaceutical and Medicinal Chemistry. From Biophysical Aspects to Clinical Applications; Gouverneur, V., Müller, K., Eds.; Imperial College Press: London, 2012; pp 175–207. (b) Winter, R. W., Dodean, R. A., Gard, G. A. Fluorine-Containing Synthons; ACS Symposium Series 911; Soloshonok, V. A., Ed.; American Chemical Society: Washington DC, 2005; pp 87–118.

<sup>(5) (</sup>a) Sheppard, W. A. J. Am. Chem. Soc. **1960**, 82, 4751–4752. (b) Sheppard, W. A. J. Am. Chem. Soc. **1962**, 84, 3064–3072.

<sup>(6)</sup> Umemoto, T.; Garrick, L. M.; Saito, N. *Beilstein J. Org. Chem.* **2012**, *8*, 461–471.

Scheme 1. Access to SF5-ArBF3K via C-H Borylation

Ishiyama-Miyaura-Hartwig Borylation



nitro group,<sup>8</sup> or hydrogen<sup>9</sup> have been described. Despite the increasing interest in exploring and diversifying the chemistry of aryl-SF<sub>5</sub> compounds, their utility as substrates in a number of modern metal-catalyzed transformations remains underexplored. Knochel prepared magnesium reagents, by Br/Mg exchange using *i*PrMgCl·LiCl and by directed metalation using TMP<sub>2</sub>Mg·2LiCl. The handful of examples underwent further transformations, such as cross-coupling reactions.<sup>10</sup> However, the current portfolio of basic building blocks incorporating SF<sub>5</sub> remains limited. Indeed, in most of the synthesis work, the routes can be traced back to the same set of starting materials: para- or meta-(pentafluorosulfanyl)nitrobenzene. Because of our interest in providing greater access to novel building blocks for drug discovery,<sup>11</sup> we have been exploring ways of developing new approaches to SF<sub>5</sub> compounds.

Hartwig, Ishiyama, and Miyaura developed a powerful catalytic system for the *meta*-directed C–H borylation of 1,3-disubstituted arenes using  $[{Ir(OMe)(cod)}_2]$  and

(10) Frischmuth, A.; Unsinn, A.; Groll, K.; Stadtmuller, H.; Knochel, P. *Chem.*—*Eur. J.* **2012**, *18*, 10234–10238.

4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy).<sup>12</sup> This reaction allowed the access to various functionalities via one-pot sequences, such as halogenation, cyanation, alkylation, hydroxylation, or amination.<sup>13</sup> Additionally, one-pot synthesis of 3,5-disubstituted potassium aryltrifluoroborates via Ircatalalyzed C–H borylation followed by treatment with KHF<sub>2</sub> has been reported, but not for SF<sub>5</sub>-aryl substrates.<sup>14</sup>

Compared to other boron reagents, organotrifluoroborate salts are exceptionally stable toward air and moisture. Moreover, they are easily isolated, usually by simple precipitation or recrystallization from acetone with diethyl ether, and they show comparable reactivity to boronic acids in many reactions, such as Suzuki–Miyaura crosscoupling.<sup>15,16</sup> Consequently, we decided to examine the borylation reaction for the introduction of trifluoroborates onto SF<sub>5</sub>-containing scaffolds.

In prospecting experiments we were delighted to note that the pentafluorosulfanyl group displayed excellent compatibility with Ir-catalyzed C-H borylation conditions of Hartwig, Ishiyama, and Miyaura. After complete conversion of the precursor, direct addition of water and KHF<sub>2</sub> to the reaction mixture converted the resulting boronic ester into the corresponding aryltrifluoroborate (Table 1). To the best of our knowledge, this is the first example of the C-H activation reaction with a pentafluorosulfanyl-containing aryl system. Thus, from readily available *meta*-substituted SF<sub>5</sub>-aryl compounds,<sup>17</sup> we were able to provide access to this novel class of buildings blocks. Several examples with various substituents in meta-position of the SF<sub>5</sub>-group were obtained in good to high yields, such as methoxy, methyl ester, or halogens. Interestingly, contrary to most of the potassium organotrifluoroborates, SF<sub>5</sub>-ArBF<sub>3</sub>K are soluble in diethyl ether, emphasizing the lipophilicity of the pentafluorosulfanyl group. Therefore, isolation was achieved by precipitation from acetone with chloroform or dichloromethane. The pinacol coproduct could be removed by additional washing of the solids to afford the SF<sub>5</sub>-substituted potassium aryltrifluoroborates in high purity, according to <sup>19</sup>F and <sup>1</sup>H NMR spectra. The simplicity of the approach is underscored in a preparative scale reaction that was conducted to give more than 3 g of 2a from a meta-methoxy precursor in 92% yield.

In order to demonstrate the usefulness of these  $SF_5$ building blocks, we set out to explore their reactivity in the

<sup>(7) (</sup>a) Sipyagin, A. M.; Bateman, C. P.; Tan, Y. T.; Thrasher, J. S. *J. Fluorine Chem.* **2001**, *112*, 287–295. (b) Sipyagin, A. M.; Enshov, V. S.; Kashtanov, S. A.; Bateman, C. P.; Mullen, B. D.; Tan, Y. T.; Thrasher, J. S. *J. Fluorine Chem.* **2004**, *125*, 1305–1316.

<sup>(8)</sup> Beier, P.; Pastýříková, T.; Vida, N.; Iakobson, G. Org. Lett. 2011, 13, 1466–1469.

<sup>(9) (</sup>a) Beier, P.; Pastyrikova, T.; Iakobson, G. J. Org. Chem. 2011, 76, 4781–4786. (b) Beier, P.; Pastyrikova, T. Tetrahedron Lett. 2011, 52, 4392–4394. (c) Pastyrikova, T.; Iakobson, G.; Vida, N.; Pohl, R.; Beier, P. Eur. J. Org. Chem. 2012, 2123–2126. (d) Vida, N.; Beier, P. J. Fluorine Chem. 2012, 143, 130–134. (e) Beier, P.; Pastyrikova, T. Beilstein J. Org. Chem. 2013, 9, 411–416.

<sup>(11) (</sup>a) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. Angew. Chem., Int. Ed. 2006, 45, 7736–7739. (b) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M.; Märki, M.; Godel, T.; Fischer, H.; Wagner, B.; Parrilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. Angew. Chem., Int. Ed. 2008, 47, 4512–4515. (c) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. J. Med. Chem. 2010, 53, 3227–3246. (d) For a review, see: Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K. J. Med. Chem., Int. Ed. 2010, 49, 9052–9067. (e) Li, D. B.; Rogers-Evans, M.; Carreira, E. M. Org. Lett. 2011, 13, 6134–6136. (f) Li, D. B.; Rogers-Evans, M.; Carreira, E. M. Org. Lett. 2013, 15, 4766–4769.

<sup>(12) (</sup>a) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. J. Am. Chem. Soc. **2002**, 124, 390–391. (b) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. Angew. Chem., Int. Ed. **2002**, 41, 3056–3058. (c) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. J. Am. Chem. Soc. **2005**, 127, 14263–14278.

<sup>(13)</sup> For a review, see: Mkhalid, I. A. I.; Barnard, J. H.; Marder,
T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* 2010, *110*, 890–931.
(14) Murphy, J. M.; Tzchucke, C. C.; Hartwig, J. F. *Org. Lett.* 2007,

<sup>(14)</sup> Murphy, J. M.; Tzchucke, C. C.; Hartwig, J. F. Org. Lett. 2007, 9, 757–760.

<sup>(15) (</sup>a) Molander, G. A.; Biolatto, B. Org. Lett. 2002, 4, 1867–1870.
(b) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. J. Am. Chem. Soc. 2008, 130, 9257–9259. (c) Sandrock, D. L.; Jean-Gérard, L.; Chen, C. Y.; Dreher, S. D.; Molander, G. A. J. Am. Chem. Soc. 2010, 132, 17108–17110. For review, see: (d) Molander, G. A.; Ellis, N. Acc. Chem. Res. 2007, 40, 275–286.

<sup>(16) (</sup>a) Darses, S.; Genêt, J. P.; Brayer, J. L.; Demoute, J. P. *Tetrahedron Lett.* **1997**, *38*, 4393–4396. (b) Darses, S.; Michaud, G.; Genêt, J. P. *Tetrahedron Lett.* **1998**, *39*, 5045–5048. (c) Darses, S.; Michaud, G.; Genêt, J. P. *Eur. J. Org. Chem.* **1999**, 1875–1883. For a review, see: (d) Darses, S.; Genêt, J. P. *Chem. Rev.* **2008**, *108*, 288–325.

<sup>(17)</sup> Most of these starting materials are commercially available, but in the present case, they were prepared in our laboratory. See Supporting Information for detailed preparations.

**Table 1.** One-Pot Synthesis of  $SF_5$ -Substituted PotassiumAryltrifluoroborates<sup>a</sup>

R	$ \begin{array}{c} \begin{array}{c} 1) \operatorname{pin}_2B_2, \ \operatorname{cat. Ir}_3\\ \\ \hline \\ \operatorname{cat. dtbpy, TH}\\ \end{array} \\ \hline \\ 2) \ \operatorname{KHF}_2, \ \operatorname{THF/H}_2\\ \operatorname{SF}_5\\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} $	F, 80 °C 20, rt	BF <sub>3</sub> K SF <sub>5</sub> <b>2</b>
entry	R	2	yield (%)
1	OMe	2a	94
2	CN	<b>2b</b>	88
3	$\rm CO_2Me$	2c	65
4	$\rm NMe_2$	2d	81
5	Cl	<b>2e</b>	89
6	Br	<b>2f</b>	76
7	Ι	$2\mathbf{g}$	$72^b$

<sup>*a*</sup> Reaction conditions: 1,  $pin_2B_2$  (0.7 equiv), {[Ir(OMe)(cod)]\_2} (0.75 mol %), dtbpy (1.5 mol %), THF, 80 °C, 24 h. Then KHF<sub>2</sub> (5.7 equiv), THF/H<sub>2</sub>O (5:3), rt, 6 h. <sup>*b*</sup> 48 h were needed for the C–H borylation.

Suzuki-Miyaura reaction. After screening of conditions for the cross-coupling of aryl halides and organotrifluoroborates, we identified those of Molander as promising.<sup>18</sup> In our case, slight modifications of these conditions were necessary in order to obtain satisfying yields. The choice of the method was dependent on the aryl halide used (Table 2). Thus, employing 2 mol % of PdCl<sub>2</sub>(dppf)  $\cdot$  CH<sub>2</sub>Cl<sub>2</sub> with 3 equivalents of triethylamine in EtOH at 85 °C (Method A) allowed cross-coupling of the *meta*-methoxy derivative of SF<sub>5</sub>-ArBF<sub>3</sub>K 2a with various functionalized arvl halides (Table 2, entries 1-3). The use of substrates bearing electron withdrawing groups under conditions A resulted in a decrease in yield of product (Table 2, entries 4-5). Attempts to improve the reaction by using Pd(OAc)<sub>2</sub> with  $K_2CO_3$  in MeOH at 80 °C (Method B) failed with only traces of the biaryl product being observed. However, with heteroaryl halides, the conditions of method A were not effective, whereas using method B afforded the desired cross-coupling product. For example, when 3-bromopyridine was submitted to reaction conditions B, the corresponding biaryl was obtained in excellent yield (Table 2, entry 7), whereas method A afforded less than 20% conversion. Reaction of 2a with unprotected 4- and 5-bromoindoles could be achieved in modest yield (Table 2, entries 8-9). Diheteroaryl halide 5-bromopyrimidine also participated in the reaction and gave the corresponding cross-coupling product in excellent yield (Table 2, entry 10).

In conclusion, we have described the preparation of new stable and versatile 3,5-disubstituted potassium aryltrifluoroborates bearing a pentafluorosulfanyl group. These new compounds are potential important building blocks for drug discovery and agrochemicals. Their synthesis was achieved in one-pot, involving Hartwig, Ishiyama, and Miyaura Ir-catalyzed C–H borylation. We also showed their compatibility in the Suzuki–Miyaura cross-coupling

Table 2. Cross-Coupling Reactions of $SF_5$ -ArBF <sub>3</sub> K with Aryl Halides								
R	BF	<sup>5</sup> ₃K + Ar−X <u>cat.</u> solve	Pd, ba ent, he	se R → at	Ar			
	ŚF₅ 2				SF <sub>5</sub> 3			
entry	R	Ar-X	3	method <sup>a</sup>	yield (%)			
1	OMe	O <sub>2</sub> N-Br	3a	А	93			
2	OMe	NC	3b	А	81			
3	OMe	MeO <sub>2</sub> CB	<sup>7</sup> 3c	А	85			
4	CN	O <sub>2</sub> N-Br	3d	А	41			
5	CO <sub>2</sub> Me	O <sub>2</sub> N-Br	3e	А	57			
6	OMe	N	3f	В	54			

3g

3h

3i

3j

В

в

В

R

83

42

46

95

<sup>*a*</sup> Method A: Ar–X, **2** (1.2 equiv), Et<sub>3</sub>N (3.0 equiv), PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (2 mol %), EtOH, 85 °C, 12–16 h. Method B: Ar–X, **2** (2.0 equiv), K<sub>2</sub>CO<sub>3</sub> (3.0 equiv), Pd(OAc)<sub>2</sub> (5 mol %), MeOH, 80 °C, 16 h.

7

8

9

10

OMe

OMe

OMe

OMe

reaction with aryl and heteroaryl halides, allowing the access to a library of unprecedented 3,5-disubstituted SF<sub>5</sub>-aryl compounds.

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**Supporting Information Available.** Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet http://pubs.acs.org.

<sup>(18)</sup> Molander, G. A.; Biolatto, B. J. Org. Chem. 2003, 68, 4302–4314.

The authors declare no competing financial interest.