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Synthesis and Cross-Coupling of Sulfonamidomethyltrifluoroborates

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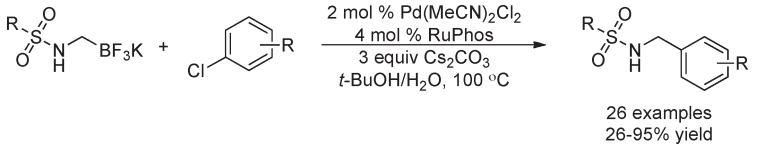
ABSTRACT



Sulfonamidomethyltrifluoroborates were successfully synthesized and cross-coupled with a wide range of aryl and heteroaryl chlorides, allowing the construction of a sulfonamidomethyl aryl linkage through a new disconnection, thus offering a new way to access such structurally interesting motifs.

Sulfonamides represent a very large and important class of drugs that can be used as antibacterials, diuretics, anticonvulsants, and hypoglycemic, anticancer, and antiviral agents.[1] Among them, arylsulfonamides are the most studied, but arylmethylsulfonamides also constitute an important class of compounds, showing potent activities in several therapeutic areas.[2] These compounds are commonly synthesized by reacting sulfonyl chlorides and arylmethanamines.[3] This method, which has proven to be efficient, is nevertheless hampered by the handling and storage of requisite sulfonyl chlorides each and every time a new sulfonamidomethyl target is required.[4] More recently, reactions starting from sulfonic acids or sulfonate esters have been reported.[5] Other alternative synthetic methods are reductive aminations of aldehydes with sulfonamides,[6] reduction of *N*-sulfonylimines,[7] or the reaction between amines and alcohols.[8] The latter is usually catalyzed by transition metal complexes via homogeneous catalysis or more recently via heterogeneous catalysis (Scheme 1, routes a and b).

Interestingly, the synthesis of sulfonamidomethyl compounds based on a cross-coupling strategy between an aryl

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(2) (a) Nirogi, R. V. S.; Daulatabad, A. V.; Parandhama, G.; Mohammad, S.; Sastri, K. R.; Shinde, A. K.; Dubey, P. K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4440. (b) Holmes, C. P.; Li, X.; Pan, Y.; Xu, C.; Bhandari, A.; Moody, C. M.; Miguel, J. A.; Ferla, S. W.; Nuria de Francisco, M.; Frederick, B. T.; Zhou, S.; Macher, N.; Jang, L.; Irvine, J. D.; Grove, J. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4336. (c) Shen, Y.; Liu, J.; Estiu, G.; Isin, B.; Ahn, Y.-Y.; Lee, D.-S.; Kapatral, V.; Wiest, O.; Oltvai, Z. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 1082. (d) Bladh, H.; Henriksson, K.; Hulikal, V.; Lepistö, M. WO 2006/046914 A1. (e) Miller, T.; Witter, D. J.; Belvedere, S. WO 2005/034880 A2. (f) Sun, D.; Perkins, E. L.; Tugendreich, S. WO 03/043578 A2.

(3) Sulfur-Containing Reagents. In *Handbook of Reagents for Organic Synthesis*; Paquette, L. A., Eds.; Wiley & Sons Ltd.: Chichester, U.K., 2009.

(4) (a) Caddick, S.; Wilden, J. D.; Wadman, S. J.; Bush, H. D.; Judd, D. B. *Org. Lett.* **2002**, *4*, 2549. (b) Caddick, S.; Hamza, D.; Wadman, S. J.; Wilden, J. D. *Org. Lett.* **2002**, *4*, 1775.

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(6) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

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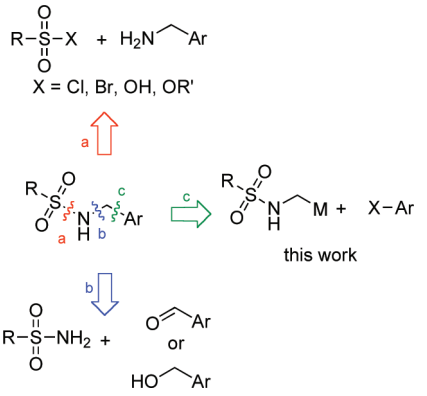
Scheme 1. Possible Disconnections To Access the Arylsulfonamidomethyl Moiety

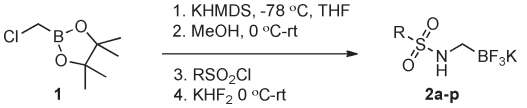


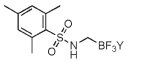
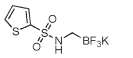
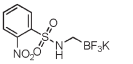
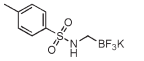
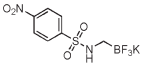
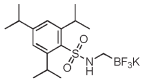
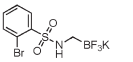
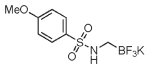
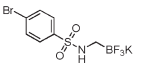
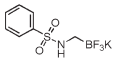
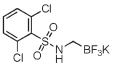
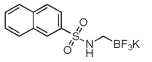
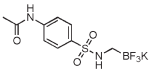
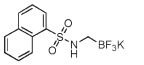
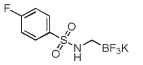
halide and a sulfonamidomethyl coupling partner has not yet been reported. This new disconnection offers an interesting and complementary alternative to existing synthetic routes by allowing the rapid and convenient introduction of a wide range of substituents and also allows enhanced efficiency in the introduction of chemical diversity (Scheme 1, route c).

The Suzuki−Miyaura reaction is one of the most efficient and widely used C−C bond-forming reactions.[9] Our research group has been involved in the synthesis and use of organotrifluoroborate salts as replacement coupling partners for boronic acids, boronate esters, or organoboranes.[10] Indeed, organotrifluoroborates offer numerous beneficial features such as being air and moisture stable salts that are easy to handle and to store. In addition, the carbon−boron bond remains intact during various chemical transformations on ancillary functional groups. Moreover, they appear to be very efficient coupling partners in Suzuki−Miyaura reactions, overcoming many of the drawbacks encountered with other reagents.[11]

In continuation of a project based on the synthesis of functionalized organotrifluoroborates using halomethyltrifluoroborates, diverse alkoxymethyl- and aminomethyltrifluoroborates have been successfully synthesized and used

Table 1. Preparation of Sulfonamidomethyltrifluoroborates



entry	product	yield[a]	entry	product	yield[a]
1	 **2a,b**	75%[b] 48%[c]	8	 **2i**	38%
			9	 **2j**	54%
2	 **2c**	63%	10	 **2k**	70%
3	 **2d**	40%	11	 **2l**	53%
4	 **2e**	65%	12	 **2m**	40%
5	 **2f**	29%	13	 **2n**	62%
6	 **2g**	67%	14	 **2o**	30%
7	 **2h**	41%	15	 **2p**	45%

[a] Isolated yield. [b] **2a**, Y = K. [c] **2b**, Y = Cs.

in cross-coupling reactions.[12] A synthetic route based on direct nucleophilic substitution of the halide of potassium halomethyltrifluoroborates proved to be efficient when using mono- or dialkylamines but failed with amides. In 2010, Hiebel and Molander developed an alternative one-pot procedure starting from halomethylboronate esters[13] and successfully accessed and coupled carboxamidomethyltrifluoroborates with aryl- and heteroaryl chlorides.[14]

In this article we report the synthesis of sulfonamidomethyl derivatives via a Suzuki−Miyaura cross-coupling reaction between sulfonamidomethyltrifluoroborates and aryl and heteroaryl chlorides.

Although the halomethyltrifluoroborate strategy also failed for the synthesis of sulfonamidomethyltrifluoroborates, even when preforming the anion of the sulfonamide, the one-pot procedure starting from the chloromethyl boronate ester **1** gave access to the desired products **2a**−**p** (Table 1).

Thus, various sulfonyl chlorides, bearing either electron-donating or -withdrawing substituents, have been successfully used to afford the trifluoroborates with modest to

(9) (a) Miyaura, N. *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds.; Wiley-WCH: Weinheim, 2004; pp 41−123. (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

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(11) (a) For reviews on organotrifluoroborate salts, see: (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (c) Stefani, H. A.; Cella, R.; Adriano, S. *Tetrahedron* **2007**, *63*, 3623. (d) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288. For mechanistic details on the advantages of trifluoroborates over other boron reagents in the Suzuki reaction, see:(e) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156.

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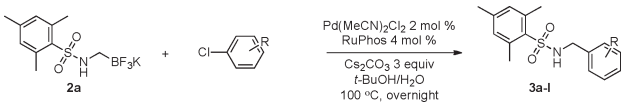
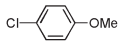
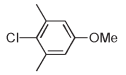
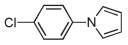
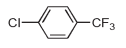
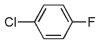
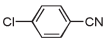
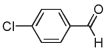
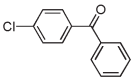
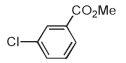
(13) For reviews on α-haloboronate esters see: (a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. (b) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (c) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.

(14) Molander, G. A.; Hiebel, M.-A. *Org. Lett.* **2010**, *12*, 4876.

Table 2. Cross-Coupling of **2a** with Aryl Chlorides



entry	electrophile	product	yield[a] (conv)
1		**3a**	95%
2		**3b**	78%, 80%[b] 87%[c]
3		**3c**	91%, 91%[d]
4		**3d**	78% 48% (57%)[c, e]
5		**3e**	91%
6		**3f**	91%
7		**3g**	61% 76%[c]
8		**3h**	87%
9		**3i**	77%
10		**3j**	51%
11		**3k**	55% 60%[c]
12		**3l**	44%

[a] Isolated yield. Reaction conditions: 1.0 equiv of aryl chloride, 1.2 equiv of trifluoroborate, 3 equiv of Cs_2CO_3, L/Pd = 2, *t*-BuOH/H_2O: 1/1, 100 °C, overnight (14−18 h). [b] Reaction performed with the cesium trifluoroborate **2b**. [c] XPhos (4 mol %) and NaO*t*-Bu (3 equiv) instead of RuPhos and Cs_2CO_3. [d] Reaction performed on a 3.13 mmol scale using 1 mol % of $Pd(MeCN)_2Cl_2$, 2 mol % of RuPhos and a 1/1 ratio of trifluoroborate/electrophile. [e] 4 mol % of Pd(II) and 8 mol % of ligand used.

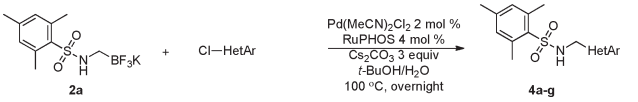
good yields. The products are all solids that can be stored without particular precautions for several weeks until used in cross-coupling reactions. **2a** has been recrystallized, and an X-ray structure has been obtained (see Supporting Information). The cesium analog (**2b**) of the potassium trifluoroborate **2a** has also been prepared by quenching the boronate ester with a solution of cesium hydrogen fluoride ($CsHF_2$) as described by Matteson et al.[15] to determine whether the nature of the cation has any influence during the cross-coupling reaction (Table 1, entry 1).

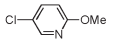
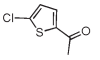
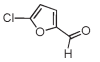
Once synthesized, the sulfonamidomethyltrifluoroborates were tested in Suzuki−Miyaura cross-couplings using aryl chlorides as electrophiles. The conditions were optimized using the mesitylsulfonamidomethyltrifluoroborate **2a** and 4-chloroanisole. Surprisingly, none of the previously reported reaction conditions for aminomethyltrifluoroborates proved to be effective or lead to full conversion. This might be explained by the very low solubility of the sulfonamidomethyltrifluoroborates, which require protic solvents (e.g., using the best conditions for amidomethyltrifluoroborates, a CPME/H_2O or THF/H_2O mixture led to 9 and 43% conversion after 24 h, respectively).[16] Extensive screening of solvent, temperature, Pd source, and ligand led to the following conditions: a 1/1 *t*-BuOH/H_2O solvent mixture, a temperature of 100 °C, $Pd(MeCN)_2Cl_2$ (2 mol %) as the metal precursor, RuPhos (4 mol %) and Cs_2CO_3 (3 equiv), which provided **3b** in 78% isolated yield (Table 2, entry 2). Further optimization showed that replacing the ligand and the base by XPhos and NaO*t*-Bu, respectively, increased the yield to 87%. However, those conditions proved to be less general and only improved the yields in a few cases (Table 2).

To investigate the method further, both electron-rich (Table 2, entries 1−6) and electron-poor (Table 2, entries 7−12) aryl chlorides were examined. All of these substrates were found to cross-couple, providing the sulfonamidomethylated products with yield of 44−95%. A large array of functional groups was tolerated, although the yields tended to decrease with delicate substrates such as aldehydes or esters (Table 2, entries 10 and 12).

The effects of steric hindrance were tested with mono- or di-ortho substituted electrophiles (Table 2, entries 3, 4, 5). The standard conditions proved to be very efficient, as shown by the good yield (78%) in the reaction of 2-chloro-5-methoxy-1,3-dimethylbenzene, which is a difficult substrate owing to the presence of two ortho substituents. Yet, XPhos and NaO*t*-Bu did not provide full conversion, and their use resulted in a 48% yield even after increasing the catalyst loading (Table 2, entry 4). Hindered and electron-rich 2-chloroanisole was used to perform the reaction on a larger scale. On a 1 g scale, lowering the catalyst loading to

Table 3. Cross-Coupling Reaction of **2a** with Heteroaryl Chlorides



entry	heteroaryls	product	yield[a]
1		**4a**	89%
2		**4b**	72% conv[b] 92%
3		**4c**	88%
4		**4d**	62%
5		**4e**	83%
6		**4f**	83%
7		**4g**	26%

[a] Isolated yield. Reaction conditions: 1.0 equiv of aryl chloride, 1.2 equiv of trifluoroborate, 3 equiv of Cs_2CO_3, RuPhos/Pd = 2, *t*-BuOH/H_2O: 1/1, 100 °C, overnight (14−18 h). [b] Obtained using XPhos (4 mol %) and NaO*t*-Bu (3 equiv).

(15) Matteson, D. S.; Malakial, D.; Pharazyn, P. S.; Kim, B. J. *Synlett* **2006**, *20*, 3501.

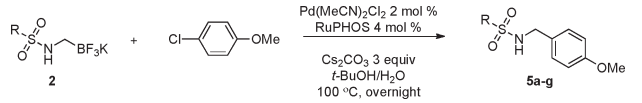
(16) See Supporting Information for more details.

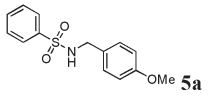
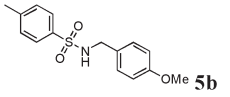
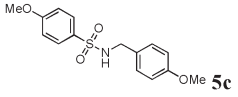
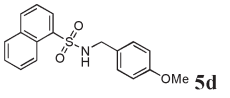
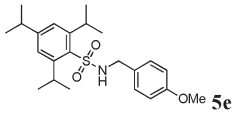
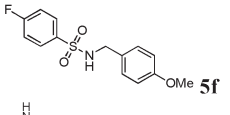
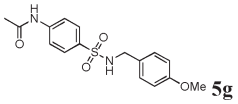
1 mol % of Pd and 2 mol % of ligand and using a 1/1 trifluoroborate/electrophile ratio afforded the expected product **3c** with an excellent isolated yield of 91%, emphasizing the robustness of the method (Table 2, entry 3). The cesium organotrifluoroborate **2b** was also successfully coupled with 4-chloroanisole in a similar yield, showing that the presence of both potassium and cesium ions had no effect on the course of the reaction (Table 2, entry 2).

To expand the array of electrophiles, the potassium mesitylsulfonamidomethyl trifluoroborate **2a** was coupled with a variety of heteroaromatic chlorides (Table 3). RuPhos and cesium carbonate proved to be the most efficient ligand and base, respectively, as they afforded the highest yields (Table 3, entry 2). An array of these substrates was examined including pyridine, thiophene, and furan derivatives. The resulting sulfonamidomethylated heteroaromatics **4a**−**f** were obtained with good to excellent yields from 62 to 92%, while 5-chloro-2-furaldehyde coupled with a lower yield.

The scope of this method was further demonstrated by using a variety of arylsulfonamidomethyl potassium trifluoroborates as coupling substrates with 4-chloroanisole (Table 4). Both electron-rich and electron-poor arylsulfonamidomethyl trifluoroborates coupled using the previously defined conditions with 24−77% yields.

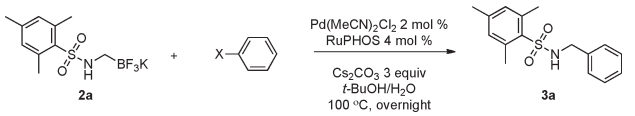
Table 4. Variation of the Trifluoroborate Moiety



entry	R	product	yield[a] (conv)[b]
1	C_6H_5	 **5a**	70% (79%)
2	*p*-MeC_6H_4	 **5b**	76% (100%)
3	*p*-MeOC_6H_4	 **5c**	70% (78%)
4	1-Naphth	 **5d**	70% (79%)
5	2,4,6-tri*i*-Pr C_6H_2	 **5e**	24% (35%)
6	*p*-FC_6H_4	 **5f**	64% (79%)
7	*p*-AcHNC_6H_4	 **5g**	42% (44%)

[a] Isolated yield. [b] Conversion measured by ^{1}H NMR.

Table 5. Electrophile Compatibility



entry	X	yield[a]
1	Cl	95%
2	Br	61%
3	I	55%
4	OTf	95%
5	OTs	70%
6	OMs	33% (46%)[b] 53%[c]

[a] Isolated yield. Reaction conditions: 1.0 equiv of aryl chloride, 1.2 equiv of trifluoroborate, 3 equiv of base, L/Pd = 2, *t*-BuOH/H_2O: 1/1, 100 °C, overnight (14−18 h). [b] Catalyst loading 5 mol %, ligand 10 mol %. [c] K_3PO_4 used instead of Cs_2CO_3.

We then proceeded to examine the electrophile compatibility using trifluoroborate **2a** (Table 5). The aryl iodide and aryl bromide gave modest yields; various amounts of reduced aryls were observed, suggesting that the transmetalation might be the rate-limiting step. The aryl triflate showed the same behavior as chlorides as it coupled with excellent yield (Table 5, entry 4). Phenyl tosylate afforded a good yield (70%), while the more difficult mesylate gave a more limited result with a promising yield (53%) after some modifications of the reaction conditions (Table 5, entry 6).

In conclusion, we have synthesized a variety of potassium arylsulfonamidomethyl trifluoroborates and demonstrated their suitability as coupling partners in Suzuki−Miyaura cross-coupling reactions with both aryl and heteroaryl chlorides. These trifluoroborates can be easily prepared through a one-pot process from 2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, providing a new means for efficiently accessing a large array of structurally diverse and significant sulfonamidomethyl-containing molecules.

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Supporting Information Available. Experimental procedures, spectral characterization and copies of ^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR spectra for all compounds, and X-ray crystallographic data for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.