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A Facile One-Pot Preparation of Potassium Hydroxyaryl- and (Hydroxyalkyl)aryltrifluoroborates

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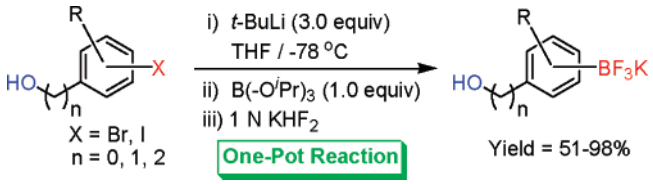
ABSTRACT



Potassium hydroxyaryl- and (hydroxyalkyl)aryltrifluoroborates have been prepared in a simple one-pot process from the corresponding hydroxy-substituted aryl halides in 51–98% yields through an in situ protection of the free hydroxyl group with *t*-BuLi. Also, we successfully performed a microwave-promoted Suzuki–Miyaura cross-coupling reaction of these substrates with aryl- and alkenyl bromides in the presence of 0.5 mol % of Pd(OAc)$_2$ catalyst without ligands.

Hydroxylated aryl- and arenylboronic acids are very useful reagents for the synthesis of pharmaceutical compounds and bioactive natural products via the Suzuki−Miyaura cross-coupling reaction.[1] Generally, these boronic acids are prepared from the corresponding aryl halides in a sequential process of lithium-halogen exchange, boration using a trialkyl borate, and hydrolysis using a strong acid. In 1996, Dupré et al. reported a direct synthesis of (hydroxymethyl)-benzeneboronic acid via the in situ protection of the hydroxy group with 2.0 equiv of *n*-BuLi.[2] However, the preparation of the (hydroxymethyl)benzeneboronic acids was not detailed in the paper. Recently, Zheng et al. described a one-pot synthesis of 4-(hydroxymethyl)benzeneboronic acid through an in situ protection of the hydroxy group with excess *n*-BuLi (3.5 equiv) followed by the addition of triisopropyl borate.[3] Unfortunately, the desired boronic acids were generated in low yields or were contaminated with butylboronic acid as

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(1) (a) Pizzirani, D.; Roberti, M.; Recanatini, M. *Tetrahedron Lett.* **2007**, *48*, 7120. (b) Antonow, D.; Cooper, N.; Howard, P. W.; Thurston, D. E. *J. Comb. Chem.* **2007**, *9*, 437. (c) Berenyi, S.; Sipos, A.; Szabo, I.; Kalai, T. *Synth. Commun.* **2007**, *37*, 467. (d) Felpin, F.-X.; Lory, C.; Sow, H.; Acherar, S. *Tetrahedron* **2007**, *63*, 3010. (e) Pla, D.; Marchal, A.; Olsen, C. A.; Francesch, A.; Cuevas, C.; Albericio, F.; Alvarez, M. *J. Med. Chem.* **2006**, *49*, 3257. (f) Taylor, S. J.; Netherton, M. R. *J. Org. Chem.* **2006**, *71*, 397. (g) Knoer, S.; Laufer, B.; Kessler, H. *J. Org. Chem.* **2006**, *71*, 5625. (h) Chordia, M. D.; Zigler, M.; Murphree, L. J.; Figler, H.; MacDonald, T. L.; Olsson, R. A.; Linden, J. *J. Med. Chem.* **2005**, *48*, 5131. (i) Tsubaki, K.; Sakakibara, M.; Nakatani, Y.; Kawabata, T. *Tetrahedron* **2006**, *62*, 10321. (j) Cousaert, N.; Toto, P.; Willand, N.; Deprez, B. *Tetrahedron Lett.* **2005**, *46*, 6529. (k) Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945.

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(3) Zheng, N.; Armstrong, J. D., III; Eng, K. K.; Keller, J.; Liu, T.; Purick, R.; Lynch, J.; Hartner, F. W.; Volante, R. P. *Tetrahedron: Asymmetry* **2003**, *14*, 3435.

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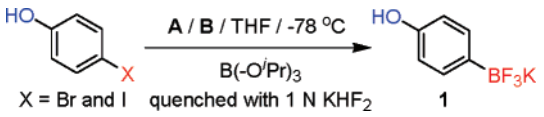
Table 1. Optimization of Reaction Conditions for the Synthesis of **1**[a]



entry	X	A (equiv)	B (equiv)	yield (%)[b]
1	Br	^{i}PrMgCl (1.0)	*n*-BuLi (1.0)	25
2	Br	^{i}PrMgCl (1.0)	*t*-BuLi (2.0)	32
3	Br	none	*n*-BuLi (2.0)	44[c]
4	I	none	*n*-BuLi (2.0)	72[c]
5	Br	none	*t*-BuLi (3.0)	61
6	I	none	*t*-BuLi (3.0)	98

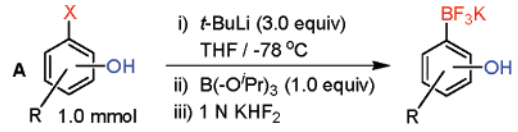
[a] All reactions were carried out on a 1.0 mmol scale. [b] Yields are given for the isolated products. [c] The products are contaminated with about 5% of potassium 1-butyltrifluoroborate as a side product.

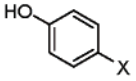
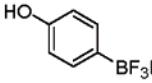
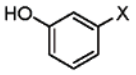
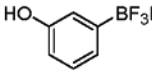
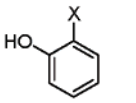
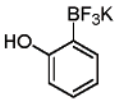
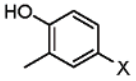
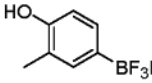
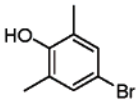
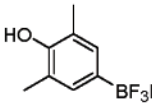
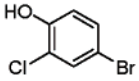
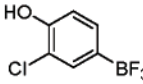
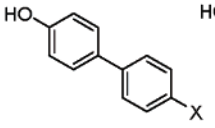
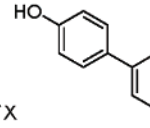
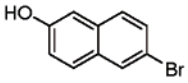
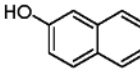
a side product. Thus, a simple and economical method for the preparation of hydroxylated organoboron compounds for use in palladium-catalyzed cross-coupling reactions remains a highly desirable goal.

Organotrifluoroborates[4] are useful synthetic intermediates for palladium-catalyzed Suzuki−Miyaura cross-coupling reactions, rhodium-catalyzed 1,4-addition reactions, and the allylation of aldehydes and *N*-toluenesulfonylimines. Potassium organotrifluoroborates have many desirable features that provide advantages over the corresponding boronic acids and boronate esters. For example, although boronic acids are often waxy solids that are difficult to isolate and purify, organotrifluoroborates are very stable crystalline solids that are easily obtained in pure form. The organotrifluoroborates provide byproducts upon coupling that are as nontoxic as other organoboron compounds. Moreover, the organotrifluoroborates are less subject to protodeborination in the Suzuki−Miyaura cross-coupling reaction when compared to the corresponding boronic acids and boronate esters, thus allowing stoichiometric amounts of these reagents to be employed in the majority of cross-coupling reactions.

During the course of our studies on the development of various organotrifluoroborates, we sought a simple one-pot method for the preparation of hydroxylated potassium aryl- and arenyltrifluoroborates from the corresponding hydroxyaryl- and (hydroxyalkyl)aryl halides. In these reactions, an appropriate organometallic reagent would serve not only as a metalating agent, but also as a base for the in situ protection of the hydroxyl group. The resulting potassium organotrifluoroborates could then be utilized as partners in the Suzuki−Miyaura cross-coupling reaction. Herein, we report our results on the development of such a transformation and the Suzuki−Miyaura cross-coupling reaction of these hydroxylated aryl- and arenyltrifluoroborates by microwave irradiation.

Table 2. One-Pot Preparation of Potassium (Hydroxyaryl)trifluoroborates from Various Halogenated Phenols[a]



entry	A	product		yield (%)[b]
1			(1)	X = Br 61 I 98
2			(2)	X = Br 28 I 98
3			(3)	X = Br 21 I 77
4			(4)	X = Br 76 I 97
5			(5)	65
6			(6)	89
7			(7)	X = Br 37 I 86
8			(8)	76

[a] All reactions were carried out on a 1.0 mmol scale. [b] Yields are given for the isolated products.

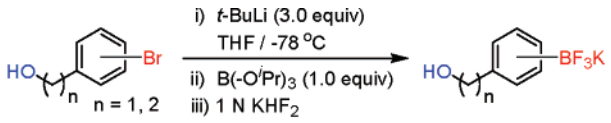
We employed both 4-bromophenol and 4-iodophenol to optimize the one-pot synthesis of potassium 4-hydroxyphenyltrifluoroborate (**1**). The results of these optimization studies are summarized in Table 1.

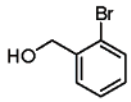
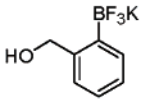
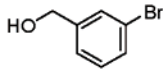
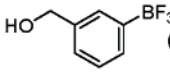
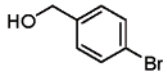
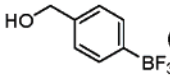
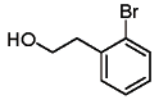
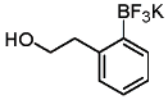
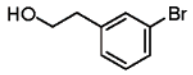
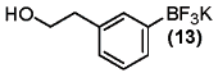
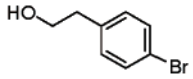
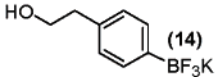
Previously, we had reported that for lithium halogen exchange reactions of halogenated hydroxy- and amine-substituted aryl halides, a Grignard reagent [isopropylmagnesium chloride (^{i}PrMgCl)], was suitable for in situ protection.[5] With this in mind, we first attempted a one-pot preparation of **1** via an in situ protection of the hydroxy group of 4-bromophenol using 1.0 equiv of ^{i}PrMgCl followed by metal-halogen exchange with 1 equiv of *n*-BuLi or 2 equiv of *t*-BuLi (Table 1, entries 1 and 2). Unfortunately, the

(4) For reviews see: (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (b) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

(5) (a) Ham, J.; Cho, S. J.; Ko, J.; Chin, J.; Kang, H. *J. Org. Chem.* **2006**, *71*, 5781. (b) Ham, J.; Kang, H. *Tetrahedron Lett.* **2005**, *46*, 6683. (c) Ko, J.; Ham, J.; Yang, I.; Chin, J.; Nam, S.; Kang, H. *Tetrahedron Lett.* **2006**, *47*, 7107.

Table 3. One-Pot Preparation of Potassium (Hydroxyalkyl)aryltrifluoroborates[a]



entry	alcohol	product		yield (%)[b]
1			(9)	60
2			(10)	83
3			(11)	90
4			(12)	51
5			(13)	68
6			(14)	73

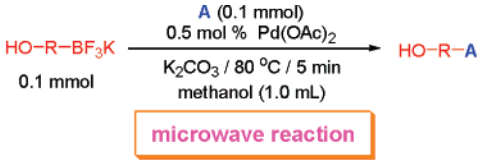
[a] All reactions were carried out on a 1.0 mmol scale. [b] Yields are given for the isolated products.

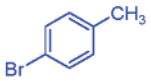
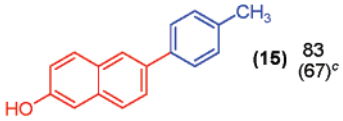
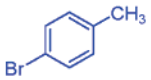
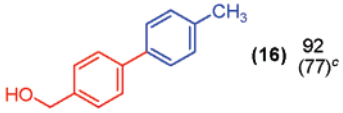
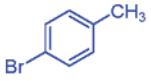
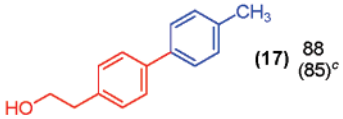
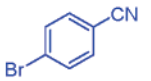
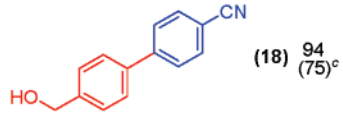
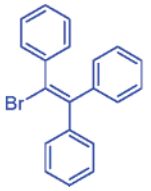
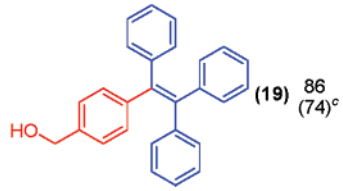
desired product in each of these cases was generated in low yields (25% and 32%, respectively).

When either 4-bromo- or 4-iodophenol were used as starting material, the desired compound **1** was obtained in 44% and 72% yields, respectively, by changing the reaction conditions from 1.0 equiv of ^{i}PrMgCl and 1.0 equiv of *n*-BuLi to 2.0 equiv of *n*-BuLi. However, the products were contaminated with potassium 1-butyltrifluoroborate (Table 1, entries 3 and 4). On the other hand, when 3 equiv of *t*-BuLi was used with either 4-bromo- or 4-iodophenol, the desired compound **1** was obtained in good yield and purity (Table 1, entries 5 and 6). These conditions served as the basis for all further studies.

With the optimized conditions in hand, we first performed a one-pot preparation of the potassium (hydroxyaryl)-trifluoroborates from the corresponding halophenols through in situ protection of the hydroxyl group with *t*-BuLi. The results are summarized in Table 2. In a test of reactivity between ortho-, meta-, and para-iodophenols, yields of the corresponding organotrifluoroborates increased in the order para > meta > ortho under the same conditions (Table 2, entries 1−3). Additionally, iodo-phenolic compounds provided the desired organotrifluoroborates in higher yield than the corresponding bromo-phenolic compounds (Table 2, entries 1−4, 7). The reaction appears to be general for a variety of substitution patterns (entries 4 and 5), and aryl chlorides are readily tolerated (entry 6).

Table 4. Suzuki-Miyaura Cross-Coupling Reaction of Potassium Hydroxy Aryl- and (Hydroxyalkyl) Aryltrifluoroborates with Aryl- and Alkenyl Bromides by Microwave Irradiation[a]



entry	A	HO–R–BF_3K		product		yield (%)[b]
1		(8)		(15)	83 (67)[c]
2		(11)		(16)	92 (77)[c]
3		(14)		(17)	88 (85)[c]
4		(11)		(18)	94 (75)[c]
5		(11)		(19)	86 (74)[c]

[a] Initial microwave irradiation of 100 W was used. [b] Yields are given for the isolated products. [c] Reactions were performed with 0.5 mol % of $Pd(OAc)_2$ and 3.0 equiv of K_2CO_3 for 1 h in methanol at refluxing temperature in an oil bath.

On the basis of the results we obtained from the preparation of potassium (hydroxyaryl)trifluoroborates, we anticipated that our method could be expanded further for the preparation of various potassium (hydroxyalkyl)aryltrifluoroborates (Table 3). As expected, all of the potassium (hydroxyalkyl)aryltrifluoroborates could be prepared from the corresponding bromides under the same reaction conditions developed for the phenols. The reactions of 3- and 4-(hydroxyalkyl)aryl bromides gave the desired trifluoroborates in good yields (Table 3, entries 2−3 and 5−6). However, both 2-bromobenzyl and 2-bromo-phenethyl alcohol gave the corresponding organotrifluoroborates in low yields (Table 3, entries 1 and 4).

We examined the Suzuki−Miyaura cross-coupling reaction of these hydroxylated aryl- and arenyltrifluoroborates with aryl- and alkenyl halides in the presence of 0.5 mol % of $Pd(OAc)_2$ without ligands[6] and 3.0 equiv of K_2CO_3 in methanol at 80 °C by microwave irradiation[7] (Table 4).

As in the previous studies of the palladium-catalyzed cross-coupling of potassium organotrifluoroborates (i.e., dihyroxylated alkyl- and arenyltrifluoroborates),[8] the free hydroxyl group was tolerated well in the general reaction conditions. Fortunately, as shown in Table 4, all hydroxylated organotrifluoroborates gave the corresponding products in good yields under the microwave-heating conditions. When potassium 6-hydroxy-2-naphthalenetrifluoroborate (**8**) was exposed to microwave irradiation at 80 °C for 5 min, the desired product **15** was obtained in 83% yield (Table 4, entry 1).

The coupling of potassium 4-(hydroxymethyl)phenyltrifluoroborate (**11**) and potassium 4-(2-hydroxyethyl)phenyltrifluoroborate (**14**) led to the target compounds in 92 and 88% yields, respectively (Table 4, entries 2 and 3). Interestingly, when 4-bromobenzonitrile containing an electron-withdrawing group (CN) was used following the same conditions, a high yield (94%) was obtained (Table 4, entry 4). Also, when triphenylethenyl bromide was utilized as a sterically hindered starting material, the compound **19** was obtained in 86% yield (Table 4, entry 5). By changing the heating source from microwave to an oil bath (Table 4, entries 1−5), product yields were slightly decreased under the same reaction conditions.

In summary, we have developed a simple one-pot synthesis of potassium hydroxyaryl- and (hydroxyalkyl)aryltrifluoroborates from the corresponding hydroxy aryl halides in 51−98% yields through an in situ protection of the free hydroxyl group with *t*-BuLi. Additionally, using the hydroxylated trifluoroborates, we successfully performed a microwave-promoted Suzuki−Miyaura cross-coupling reaction with aryl- and alkenyl bromides in the presence of 0.5 mol % of $Pd(OAc)_2$ catalyst without ligands. The cross-coupling reaction time in this process was drastically reduced.

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Supporting Information Available: Experimental procedures, spectral characterizations, and copies of NMR spectra for all compounds for which a yield is reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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