Published in final edited form as:

J Org Chem. 2009 October 2; 74(19): 7364–7369. doi:10.1021/jo901441u.

Efficient Hydrolysis of Organotrifluoroborates via Silica Gel and Water

Gary A. Molander^{*}, Livia N. Cavalcanti, Belgin Canturk, Po-Shen Pan, and Lauren E. Kennedy Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

Abstract

A general, mild, and efficient method for the hydrolysis of organotrifluoroborates to unveil organoboronic acids using silica gel and H₂O was developed. This method proved to be tolerant of a broad range of aryl-, heteroaryl-, alkenyl-, and alkyltrifluoroborates as well as structurally diverse aminomethylated organotrifluoroborates. As anticipated, electron-rich substrates provided the corresponding boronic acids more readily than electron-poor substrates, owing to the resonance stabilized difluoroborane intermediate. The method developed was expanded further for the conversion of organotrifluoroborates to the corresponding boronate esters.

Introduction

Boronic acids¹ are most commonly employed as nucleophilic partners in synthetically valuable organic transformations, particularly in Suzuki-Miyaura cross-coupling reactions.² To a lesser extent, they have also been utilized as biological inhibitors and sensors as well as drug delivery agents.³ The recent FDA approval of the drug Velcade, a boronic acid-based proteasome inhibitor used in the treatment of multiple myeloma, has initiated immense interest in small molecules containing boronic acids in drug discovery efforts, wherein these agents can be screened for lead-like or drug-like properties (Figure 1).⁴

Even though boronic acids have been used extensively in the synthesis of organic molecules, they possess one major drawback. The tricoordinate nature of these compounds renders them susceptible to reaction with commonly employed organic reagents including bases, organic acids, nucleophiles, and oxidants, thus limiting the manner in which these valuable reagents are employed in synthetic schemes. Boronic acids are rarely carried intact through several synthetic steps;⁵ instead they are either purchased or prepared and then immediately transformed. Additionally, the late stage incorporation of boronic acids within densely functionalized molecules can be challenging because the conditions required to install boronic acids might not be compatible with the functional groups present within the molecule. One way to circumvent the problems associated with boronic acids is to utilize a more robust

gmolandr@sas.upenn.edu.

Supporting Information Available: Experimental procedures, spectral characterization, and copies of ¹H, ¹³C, ¹¹B, and ¹⁹F spectra for all compounds prepared by the method described. This material is available free of charge via the Internet at <http://pubs.acs.org>.

organoboron species that can be carried through several synthetic steps and then deprotected at an appropriate stage to unveil the boronic acid.

Over the last decade, organotrifluoroborates have received considerable attention as useful alternatives to boronic acids.⁶ Owing to their tetracoordinate nature, these organoboron species do not undergo undesirable side reactions with the commonly employed organic reagents mentioned above. Consequently, the organic substructure of simple organotrifluoroborates can be functionalized to build molecular complexity, while leaving the boron-carbon bond intact (Scheme 1). In this context, trifluoroborates have been successfully used as a protecting group for boronic acids.^{5c}

The hydrolysis of organotrifluoroborates to the corresponding boronic acids using fluorophiles (e.g., SiCl_4 , TMSCl) has been previously reported.⁷ However, these fluorophiles are either toxic, difficult to handle, or highly reactive, and therefore not ideal for use in complex molecule synthesis. Recently, Hutton and Yuen published a two-step procedure for the hydrolysis of boronate esters via the intermediate organotrifluoroborate, allowing access to boronic acids.⁸ For the hydrolysis of organotrifluoroborates, they employed either LiOH /acetonitrile or $\text{TMSCl}/\text{H}_2\text{O}$. Although these methods proved effective, the study was limited in scope because only aryltrifluoroborate substrates were examined.

Current limitations associated with the hydrolysis of organotrifluoroborates, as well as the emerging importance of boronic acids in drug discovery efforts, prompted us to investigate a general, efficient, mild, and convenient method for the late stage hydrolysis of organotrifluoroborates. Herein, we report the hydrolysis of a broad range of simple aryl-, heteroaryl-, alkenyl-, and alkyltrifluoroborates along with structurally diverse aminomethylated organotrifluoroborates to the corresponding boronic acids using silica gel and H_2O . The method developed was also extended to the direct conversion of organotrifluoroborates to the boronate esters.

Results and Discussion

Perrin and coworkers have reported that the rate of organotrifluoroborate solvolysis is governed by substituent groups.⁹ They pointed out that loss of a fluoride ion leads to a vacancy of the *p*-orbital on boron, providing a difluoroborane intermediate that should be stabilized by electron-rich substituent groups (Scheme 2) or destabilized by electron-withdrawing groups. Consequently, electron-rich organotrifluoroborates undergo solvolysis faster than those with electron-withdrawing groups.

Because substituent groups play a key role in the hydrolysis, we independently investigated conditions for hydrolysis of the electron-rich potassium 4-methoxyphenyltrifluoroborate and the electron-poor potassium benzothiophen-2-yltrifluoroborate substrates. Silica gel^{5e,10} was employed as a convenient, inexpensive and readily available fluorophile. Various solvents were examined including acetonitrile, acetone, DMF, DMSO, and H_2O . The reactions were monitored via ^{11}B NMR spectroscopy. Of the solvents screened, H_2O proved to be the best solvent for the hydrolysis of potassium 4-methoxyphenyltrifluoroborate and benzothiophen-2-yltrifluoroborate, as the reactions were complete in 1 and 3 h, respectively. The efficacy of H_2O in these transformations can be attributed to the enhanced solubility of 4-methoxyphenyltrifluoroborate and benzothiophen-2-yltrifluoroborate in H_2O compared to the solvents mentioned above. Because silica gel proved to be a suitable fluorophile for this study, additional screening of fluorophiles was not necessary. The most efficient hydrolysis conditions employed 1 equiv of silica gel and a substrate concentration of 0.33 M in H_2O .

The requisite potassium organotrifluoroborates were readily prepared by previously reported procedures.¹¹ Initially, a broad range of electron-rich and electron-neutral aryltrifluoroborates

was investigated (Table 1). In all cases, the hydrolysis was complete in 1 h, except for **1b** and **1i** (Table 1, entries 2 and 9), which required reaction times of 3 and 4 h, respectively. The reactivity of *para*-, *meta*-, and *ortho*-methoxyphenyltrifluoroborate and *para*-, *meta*-, and *ortho*-4-methylphenyltrifluoroborate were also examined. In both substrates, *para*-derivatives provided the desired products **1a** and **1d** in higher yields (Table 1, entries 1 and 4). Also, sterically hindered derivatives afforded the products **1c**, **1f**, and **1g** in good yields (Table 1, entries 3, 6, and 7). We demonstrated that the reaction could be scaled to 5 mmol, providing product **1a** in 83% yield (Table 1, entry 1).

Next, attention was turned to electron-poor aryltrifluoroborates. The conditions developed worked equally well for these substrates, providing the arylboronic acids in good yields (Table 2). As expected, aldehyde-, nitrile-, and nitro-containing phenyltrifluoroborates required a longer time (24 h) for complete hydrolysis (Table 2, entries 1–4). As mentioned above, the slow hydrolysis is attributed to the destabilized difluoroborane intermediate. Of note, heating the reactions at 50 °C led to the formation of protodeboronation products (boric acid was detected by ¹¹B NMR at ~18 ppm). The reactivity of 4-halophenyltrifluoroborates was investigated, and it was determined that 4-fluorophenyltrifluoroborate required 4 h for full conversion, compared to only 1 h for 4-chloro- and 4-bromophenyltrifluoroborate (Table 2, entries 5–7). However, 4-fluorophenyltrifluoroborate provided the desired product **2e** in higher yield (Table 2, entry 5).

To expand the utility of the developed conditions further, heteroaryl systems were investigated including thiophenyl-, pyrimidinyl-, pyridinyl-, benzothioyl-, and indolyl derivatives (Table 3). The heteroaryls afforded the desired boronic acids **3a–f** in moderate to good yields, except for the electron-deficient 3-pyridyl- and 4-pyridyltrifluoroborates (data not shown). A few heteroaryls required a longer reaction time (24 h) for complete hydrolysis (Table 3, entries 2–5). Interestingly, thiophene-2-yltrifluoroborate converted to the corresponding boronic acid **3a** in 3 h, while thiophene-3-yltrifluoroborate required 24 h for full conversion (Table 3, entries 1 and 2).

The scope of the general reaction conditions was extended to alkyl- and alkenyltrifluoroborates (Table 4). We successfully obtained both the 2-isobutylboronic acid (**4a**) and octylboronic acid (**4b**) in 73 and 67% yields, respectively (Table 4, entries 1 and 2). Next, the hydrolysis of alkenyltrifluoroborates was examined, and the conditions developed proved to be effective, providing the alkenylboronic acids **4c–4g** in moderate to good yields (Table 4, entries 3–7). Also, both alkyl- and alkenyltrifluoroborates were deprotected in 1 h.

Of special note, during the study we observed that arylboronic acids were more stable than the corresponding heteroaryl-, alkyl-, and alkenylboronic acid counterparts. In our hands, many of the heteroaryl-, alkyl-, and alkenylboronic acids decomposed readily (as observed by the emergence of byproducts appearing at ~18 ppm in the ¹¹B NMR spectrum), even when stored at low temperatures. To avoid extensive decomposition prior to recording of various spectra, these boronic acids were quickly isolated and dried in vacuo for several minutes. Immediate characterization was necessary to avoid contamination by various byproducts. Of the boronic acids examined, 5-indoleboronic acid (**3g**) was the most problematic substrate as it decomposed within minutes upon drying in vacuo. This study further verifies the advantages of robust potassium organotrifluoroborates, as these species could be kept indefinitely without significant decomposition.

The aminomethyl linkage is found in natural products and pharmaceutically active compounds. Recently, our group showed that aminomethyl-containing organotrifluoroborates could be accessed via the reductive amination of formyl-substituted organotrifluoroborates with a variety of amines.¹² For the reductive amination various reducing agents including potassium

formate/Pd(OAc)₂, sodium triacetoxyborohydride, and pyridine-borane were used. These reducing agents were either used in excess or in stoichiometric amounts. Slightly modifying the previous procedure and utilizing the more stable and less expensive 5-ethyl-2-methylpyridine borane (PEMB)¹³ as a reducing agent, the desired reductive amination products were obtained (Table 5). Additionally, compared to the former reducing agents, only 0.5 equiv of the PEMB was needed. Potassium *para*- and *meta*-formylphenyltrifluoroborate underwent the reductive amination successfully with 4-aminotoluene-, morpholine, and piperazine, providing the desired products **5a–f** in modest to excellent yields (Table 5).

The aminomethyl-substituted organotrifluoroborates were subsequently subjected to the hydrolysis conditions. For these reactions, using H₂O as the solvent resulted in prolonged reaction times, which in turn led to protodeboronation products. This could be attributed to the low solubility of amine-containing organotrifluoroborates in H₂O. This problem was circumvented with the use of EtOAc as a co-solvent, [H₂O:EtOAc (1:1)]. With these slightly modified conditions in hand, aminomethyl-substituted organotrifluoroborates were deprotected in 3 and 5 h, and the desired products **6a–f** were obtained in good yields (Table 6).

Boronate esters^{1a} are more stable alternatives to boronic acids, and these species have found extensive use in organic synthesis.¹⁴ Matteson and coworkers showed that organotrifluoroborates can be converted to boronate esters via the intermediate dichloroborane by treatment of organotrifluoroborates with SiCl₄ in the presence of MeOH followed by treatment with pinacol.^{6a} Owing to the important complementary physical and chemical properties of organotrifluoroborates, we sought to determine whether the conditions developed herein would be applicable to their direct conversion to boronate esters. Treatment of 4-trifluoroboratoanisole with silica gel, H₂O, and pinacol afforded the desired boronate ester **7a** in 81% yield (Table 7, entry 1). Encouraged by this result, other diols including chiral dimethyl D(–)- and L(+)-tartrates and neopentyl glycol were examined. In each case the products **7b–d** were obtained in good yields (Table 7, entries 2–4). Furthermore, octyltrifluoroborate and benzothiophene-2-yltrifluoroborate were successfully converted to boronate esters **7e** and **7f** in good yields (Table 7, entries 6 and 7).¹⁵

In conclusion, a general, mild and efficient method was developed for the hydrolysis of aryl-, heteroaryl-, alkyl-, and alkenyltrifluoroborates, along with structurally diverse aminomethylated organotrifluoroborates, to the corresponding boronic acids. The rate of hydrolysis was influenced by the substituent groups, wherein electron-rich substrates underwent hydrolysis faster than electron-poor substrates. We demonstrated that the method developed could be extended to the direct formation of boronate esters from organotrifluoroborates.

Experimental Section

General Experimental Procedure for the Preparation of Organoboronic Acids. Preparation of 4-Methoxyphenylboronic Acid (**1a**).¹⁶

To a 50 mL round bottom flask containing a mixture of potassium 4-methoxyphenyltrifluoroborate (456 mg, 3.0 mmol) and silica gel (180 mg, 3.0 mmol) under N₂ was added H₂O (9 mL) in one portion. The reaction was stirred at rt until ¹¹B NMR indicated completion of the reaction (~1 h). The reaction mixture was filtered to remove silica gel, and the filter cake was thoroughly rinsed with ethyl acetate.¹⁷ The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL) (Table 2, electron-deficient arylboronic acids were washed with brine). The combined organic layers were dried (MgSO₄), filtered, concentrated, and dried *in vacuo* overnight to afford the desired pure product in 83% yield (0.38 g, 2.49 mmol) as a white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 7.82 (d,

$J = 8.4$ Hz, 2H), 6.94 (d, $J = 8.5$ Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO- d_6) δ 161.6, 137.6, 136.0, 114.0, 55.8.

General Experimental Procedure for the Preparation of Aminomethyl-substituted Potassium Trifluoroborates. Preparation of Potassium 2-Fluoro-5-[(4-tolylamino)methyl]-phenyltrifluoroborate (5a)

To a vial containing potassium 2-fluoro-5-formylphenyltrifluoroborate (200 mg, 0.87 mmol) and KHF_2 (270 mg, 3.48 mmol) in MeOH (4.4 mL) was added 4-aminotoluene (140 mg, 1.3 mmol). The reaction mixture was stirred for 3 h at rt. 5-Ethyl-2-methylpyridine borane (PEMB, 0.06 mL, 0.43 mmol) was then added, and stirring was continued for 3 h. The solvent was removed *in vacuo*, and the resulting solid was rinsed with hexane (2×5 mL). The crude solid was purified by continuous Soxhlet extraction (3 h) with acetone (125 mL). The collected solvent was concentrated and then precipitated with acetone/hexane to afford the desired pure product in 96% yield (279 mg, 0.83 mmol) as a light yellow solid. mp: $> 200^\circ\text{C}$. ^1H NMR (360.1 MHz, DMSO- d_6) δ 7.31 (s, 1H), 7.00 (s, 1H), 6.82 (d, $J = 7.2$ Hz, 2H), 6.69 (t, $J = 8.6$ Hz, 1H), 6.46 (d, $J = 8.2$ Hz, 2H), 5.78 (brs, 1H), 4.08 (d, $J = 5.7$ Hz, 2H), 2.10 (s, 3H). ^{13}C NMR (125.8 MHz, DMSO- d_6) δ 166.6, 147.6, 134.5, 134.11, 130.1, 126.9, 124.6, 114.3, 113.2, 47.6, 21.0. ^{19}F NMR (470.8 MHz, Acetone- d_6) δ -113.1, -139.8. ^{11}B NMR (128.4 MHz, Acetone- d_6) δ 2.1. FT-IR (KBr) 3393, 3020, 1616, 1478, 1274, 1156, 975 cm^{-1} . HRMS (ESI) m/z calcd. for $\text{C}_{14}\text{H}_{13}\text{BF}_4\text{N}$ (M-K) 282.1077, found 282.1074.

General Experimental Procedure for the Preparation of Aminomethyl-substituted Boronic Acids. Preparation of 2-Fluoro-5-[(4-tolylamino)methyl]phenylboronic Acid (6a)

To a 20 mL vial containing a mixture of potassium 2-fluoro-5-[(4-tolylamino)methyl]-phenyltrifluoroborate (60 mg, 0.187 mmol) and silicon dioxide (11 mg, 0.187 mmol) was added H_2O :ethyl acetate (1.1 mL:1.1 mL) in one portion. The reaction was stirred at rt until ^{11}B NMR indicated completion of the reaction (6 h). The reaction mixture was filtered to remove silica gel, and the filter cake was thoroughly rinsed with ethyl acetate. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (2×5 mL), and the combined organic layers were dried (MgSO_4), filtered, concentrated, and dried *in vacuo* to afford the desired pure product in 73% yield (35.3 mg, 0.14 mmol) as a white solid. mp: 96–99 $^\circ\text{C}$. ^1H NMR (360 MHz, Acetone- d_6) δ 7.76 (m, 1H), 7.46 (m, 1H), 7.05 (s, 2H), 6.99 (t, $J = 9.5$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 2H), 6.56 (d, $J = 8.3$ Hz, 2H), 5.65 (brs, 1H), 4.30 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (90.5 MHz, Acetone- d_6) δ 136.6, 136.5, 132.9, 132.8, 130.8, 116.2, 115.9, 114.3, 48.5, 21.0. ^{19}F NMR (470.8 MHz, Acetone- d_6) δ -110.7. ^{11}B NMR (128.4 MHz, Acetone- d_6) δ 27.9. FTIR (neat) 3422, 2977, 1689, 1611, 1423, 1004 cm^{-1} . HRMS (ESI) m/z calcd. for $\text{C}_{14}\text{H}_{16}\text{BFNO}_2$ (MH^+) 260.1258, found 260.1248.

General Experimental Procedure for the Preparation of Boronate Esters. Preparation of 2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7a)

To a 50 mL round bottom flask containing a mixture of potassium 4-methoxyphenyltrifluoroborate (456 mg, 3.0 mmol), pinacol (350 mg, 3.0 mmol) and silicon dioxide (180 mg, 3.0 mmol) under N_2 was added H_2O (9 mL) in one portion. The reaction was stirred at rt until ^{11}B NMR indicated completion of the reaction (~ 30 min). The reaction mixture was filtered to remove silica gel, and the filter cake was thoroughly rinsed with ethyl acetate. The aqueous and the organic layers were separated, and the aqueous layer was extracted with ethyl acetate (3×15 mL), and the combined organic layers were dried (MgSO_4), filtered, concentrated, and dried *in vacuo* overnight to afford the desired pure product in 81% yield (0.57 g, 2.42 mmol) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 3.80 (s, 3H), 1.36 (s, 12H). ^{13}C NMR (125.8 MHz, CDCl_3) δ 162.2, 136.5, 113.3, 83.4, 54.9, 24.8. ^{11}B NMR (128.4 MHz, CDCl_3) δ 29.19. FT-IR 2978, 1606,

1360, 831, 655 cm^{-1} . HRMS (ESI) m/z calcd. for $\text{C}_{13}\text{H}_{20}\text{BO}_3$ (MH^+) 235.1506, found 235.1509.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

This work was generously supported by the National Institutes of Health (GM086209, GM035249), BASF, a Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) Graduate Research Fellowship to L.N.C., and the ACS Division of Organic Chemistry (Summer Undergraduate Research Fellowship, sponsored by Wyeth) to L.E.K. We also acknowledge Aldrich, BoroChem, and Frontier Scientific for their donation of the boronic acids. Dr. Rakesh Kohli (University of Pennsylvania) is acknowledged for obtaining HRMS data. We thank Dr. Noel Ellis and Professor Donna Huryn (University of Pennsylvania) for helpful discussions.

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15. To determine if the boronate esters were generated during the course of the reaction or during the removal of water, the reaction was monitored by ^{11}B and ^1H NMR spectroscopy. Unfortunately, we

were unable to discern spectroscopically the difference between the boronic acid and boronate ester under these conditions. Stirring **1a** and pinacol in ethyl acetate, concentrating in vacuo, did not provide the corresponding boronate ester **7a**, which perhaps suggests that the boronate esters are formed during the course of the reaction in aqueous media.

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17. For the extraction of sensitive substrates, a low boiling solvent (Et₂O) was employed to facilitate rapid isolation of the product at low temperatures and thereby avoid decomposition.

Figure 1.
The anticancer agent Velcade® (bortezomib)

Scheme 1.

Scheme 2.

TABLE 1

Hydrolysis of Electron-rich and Electron-neutral Potassium Aryltrifluoroborates^a

entry	product	reaction isolated time (h) ^b yield (%)		
1		1a	1	86 (83) ^c
2		1b	3	83
3		1c	1	67

entry	product	reaction time (h)	isolated yield (%)
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4

1d 1 76

entry	product	reaction time (h)	isolated yield (%)
5		1e	67

entry	product	reaction time (h)	isolated yield (%)
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6		1	61
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7		1	81
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8		1	63
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entry	product	reaction time (h)	isolated yield (%)
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9

1i 4 65

^a All reactions were carried out using 3 mmol of aryltrifluoroborate, 3 mmol of silica gel, and 9 mL of H_2O

^b Based on ^{11}B NMR

^c 5 mmol scale.

TABLE 2

Hydrolysis of Electron-poor Potassium Aryltrifluoroborates^a

entry	product	reaction isolated time (h) ^b yield (%)		
1		2a	24	64
2		2b	24	88
3		2c	24	66
4		2d	24	86
5		2e	4	80
6		2f	1	60

entry	product	reaction time (h)	isolated yield (%)	
7		2g	1	71

^a All reactions were carried out using 3 mmol of aryltrifluoroborate, 3 mmol of silica gel, and 9 mL of H₂O

^b Based on ¹¹B NMR.

TABLE 3

Hydrolysis of Potassium Heteroaryltrifluoroborates^a

		$\text{HetAr-BF}_3\text{K} \xrightarrow{\text{conditions}} \text{HetAr-B(OH)}_2$		
entry	product	reaction time(h)	isolated yield (%)	
1		3a	3	81
2		3b	24	79 ^c
3		3c	24	73
4		3d	24	63
5		3e	24	53
6		3f	3	79 ^c
7		3g	1	62

entry	product	reaction time(h)	isolated yield (%)
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8		3h	1	80
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^a All reactions were carried out using 2 mmol of heteroaryltrifluoroborate, 2 mmol of silica gel, and 9 mL of H₂O.

^b Based on ¹¹B NMR.

^c 3 mmol scale.

TABLE 4

Hydrolysis of Potassium Alkyl- and Alkenyltrifluoroborates^a

entry	product	isolated yield (%)
1		73
2		67
3		81
4		82 ^c

entry	product	isolated yield (%)
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5		4e 63
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6		4f 62
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entry	product	isolated yield (%)
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7

4g 89^d

^a All reactions were carried out using 3 mmol of organotrifluoroborate 3 mmol of silica gel, and 9 mL of H₂O; reaction time 1 h, based on ¹¹B NMR.

^c Scale 2 mmol.

^d Scale 1.5 mmol.

TABLE 5

Substituted Organotrifluoroborates^a

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<p>1. Amine (1.5 equiv) KHF₂ (4.0 equiv) MeOH, 3 h, rt</p> <p>2. PEMB (0.5 equiv), rt</p>		product	reaction time (h)	isolated yield (%)
5a	96
5b	71

product

reaction isolated
time (h)^a yield (%)

BF_3K

5e 12 50

product

reaction isolated
time (h) yield (%)

BF_3K

5f 12 83

TABLE 6

Hydrolysis of Aminomethyl-substituted Organotrifluoroborates

entry	product	reaction time	isolation (h) ^b
1		6a	5
2		6b	5
3		6c	3
4		6d	3
5		6e	3

entry	product	reaction time	isolation (h) ^b
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6		6f	3
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^a All reactions were carried out using 3.0 mmol of aryltrifluoroborate, 3 mmol of silica gel, and H_2O : EtOAc (1:1).

^b Based on ^{11}B NMR.

TABLE 7

Conversion of Potassium Organotrifluoroborates to Boronate Esters^a

$R^1-BF_3K + HO \begin{array}{c} \text{R}^2 \\ \diagup \quad \diagdown \\ \text{OH} \quad \text{OH} \end{array} \xrightarrow{\text{conditions}}$	
entry	diol
1
2

MeO

entry

diol

3

4

MeO

MeO

entry	diol
5	
6	

^a All reactions were carried out using 3 mmol of organotrifluoroborate, 3 mmol of silica gel, 3 mmol of diol, and 9 mL of H₂O; reaction time 0.5 h, based on ¹¹B NMR.