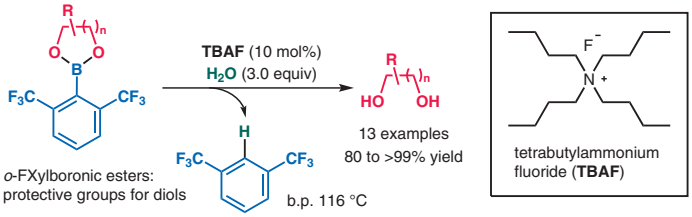
Synlett S. Urata et al. Letter

An Efficient Deprotection of 2,6-Bis(trifluoromethyl)phenylboronic Esters via Catalytic Protodeboronation Using Tetrabutylammonium Fluoride

Sari Urata
Shinya Nojima
Kazuishi Makino
Naoyuki Shimada*

Laboratory of Organic Chemistry for Drug Development and Medical Research Laboratories, Department of Pharmaceutical Sciences, Kitasato University, Tokyo 108-8641, Japan
shimadan@pharm.kitasato-u.ac.jp



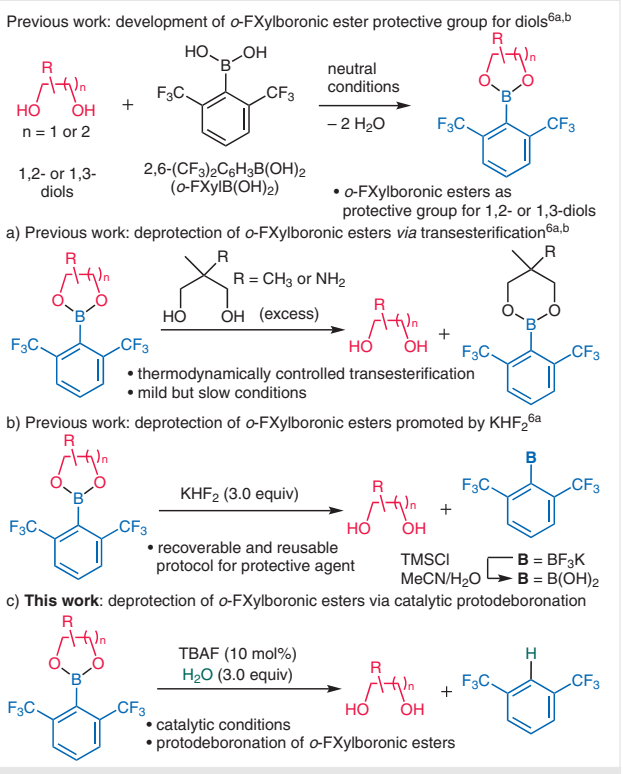
Catalytic Protodeboronation for Deprotection of o-FXylboronic Esters

Received: 20.09.2019
Accepted after revision: 16.10.2019
Published online: 30.10.2019
DOI: 10.1055/s-0039-1690236; Art ID: st-2019-u0498-l

Abstract We herein describe an efficient deprotection of 2,6-bis(trifluoromethyl)phenylboronic esters, which serve as effective protective groups for 1,2- or 1,3-diols in various organic transformations, via protodeboronation by using a catalytic amount of tetrabutylammonium fluoride (TBAF).

Key words protective groups, diols, deprotection, 2,6-bis(trifluoromethyl)phenyl boronic esters, tetrabutylammonium fluoride, protodeboronation, catalysis

Since diols are fundamental functional groups that can be found in the structure of biomolecules such as carbohydrates, nucleosides, and many other biologically active natural products, the development of effective diol protective groups still plays an indispensable role in various molecular transformations. A large number of protective groups for diols including cyclic acetals, ketals, carbonates, and siloxanes have been developed to date.[1] It is also well known that boronic acid forms covalent bonds with 1,2- or 1,3-diols to generate five- or six-membered cyclic boronic esters under mild and neutral conditions.[2,3] Therefore, boronic acids such as phenylboronic acid have been used as protective or transient masking agents for diols.[4,5] We have recently found that 2,6-bis(trifluoromethyl)phenylboronic acid (*o*-FXylB(OH)$_2$) forms highly stable cyclic boronic esters, and hence *o*-FXylboronic esters can be used as effective protective groups for 1,2- or 1,3-diols.[6a] The key features of our method are its operability in protecting the diols under neutral conditions without any additives and its applicability to a wide range of organic transformations (Scheme 1). Subsequent deprotection of *o*-FXylboronic esters can be achieved under mild conditions by thermodynamically controlled transesterification of the boronic ester with excess diols, although relatively long reaction times are required (Scheme 1, a).[6a,b] This protective group is also removable by treatment with aqueous potassium hydrogen fluoride (Scheme 1, b).[6a] In this protocol, the protective reagent *o*-FXylB(OH)$_2$ can be recovered and reused by hydrolysis of its potassium trifluoroborate salt.

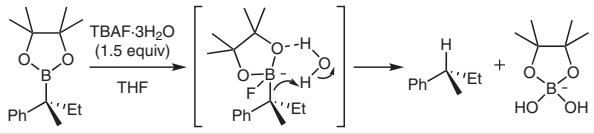


Scheme 1 2,6-Bis(trifluoromethyl)phenylboronic ester (*o*-FXylboronic ester) as protective group for diols and its deprotection conditions

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

To expand this synthetic strategy using organoboron-based diol protective groups, we herein report an alternative method for the deprotection of *o*-FXylboronic esters using a catalytic amount of tetrabutylammonium fluoride (TBAF; Scheme 1, c).

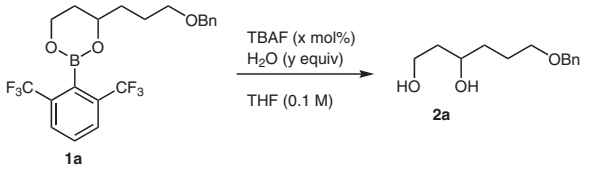
We focused on protodeboronation reactions[7,8] as a novel deprotection method. Although the base-promoted protodeboronation[9] has been known as a side reaction in Suzuki–Miyaura coupling reactions, a few recent reports have revealed that the protodeboronation of organoboron compounds promoted by acid[10] or complexes containing metals, such as gold,[11] silver,[12] copper,[13] and bismuth,[14] can be applied in synthetic organic transformations.[15] Aggarwal[16,17] reported the protodeboronation of tertiary boronic esters with essentially complete retention of configuration, promoted by a stoichiometric amount of CsF,H_2O- or TBAF·3H_2O (Scheme 2). They suggest that the protodeboronation of boronic esters proceeds via protonation of a tetracoordinated borate intermediate generated by coordination of a fluoride anion to the boron atom of the boronic esters. On the basis of this result, we considered that the protodeboronation reaction using easily handled TBAF could be applicable to the deprotection of *o*-FXylboronic esters.



Scheme 2 TBAF-promoted protodeboronation of tertiary boronic esters with essentially complete stereocontrol, reported by Aggarwal (2010)[16]

We initially examined the deprotection of boronic ester **1a** with TBAF[18] (Table 1). In the presence of a stoichiometric amount of TBAF (120 mol%),[19] the reaction proceeded smoothly at room temperature in THF within 0.2 h. After completion of the reaction, the reaction mixture was filtered through a short pad of amino silica gel to give diol **2a** in quantitative yield (entry 1).[20] Encouraged by this result, we next attempted the catalytic use of TBAF. However, the use of 20 mol% of TBAF resulted in a slight drop in conversion yield (90%) even after a longer reaction time of 24 h (entry 2). To achieve completion of the reaction under catalytic conditions, we evaluated the effect of water as an additive. Gratifyingly, the addition of 1.0 equivalent of water improved the reaction rate, providing **2a** within 13 h (entry 3). Although the same excellent yield within a shorter reaction time (11 h) was maintained even increasing the water amount to 3.0 equivalents (entry 4), the addition of excess water (10.0 equivalents) was deleterious to the reaction (entry 5).[21] In an attempt to further reduce the amount of TBAF to 10 mol%, the reaction was carried out in the presence of 3.0 equivalents of water in THF at room temperature, affording a satisfactory level of product yield (92%) within 24 h (entry 6). It is noteworthy that the deprotection reaction of boronic ester derived from simple phenylboronic acid and **2a** hardly proceeded under the same conditions.[22] These results indicate that the highly electron-deficient trifluoromethyl groups at 2,6-positions effectively promote the catalytic deprotection reaction.[23] Elevating the reaction temperature improved the reaction rates and product yields, affording **2a** in quantitative yield within 8.5 h at 50 °C (entry 7) and within 2 h under reflux conditions (entry 8). Attempts to further reduce the catalyst amount of TBAF to 5 mol% required longer reaction time (24 h), resulting in a slightly lower yield (96%, entry 9).[24]

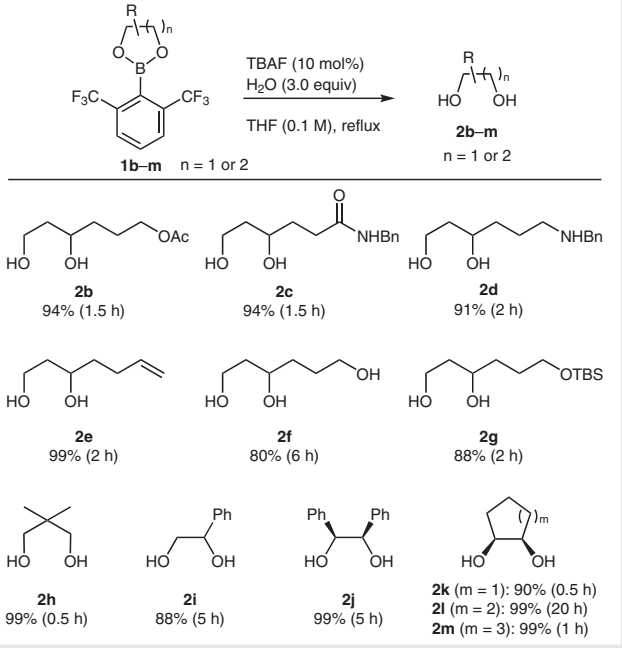
Table 1 Optimization of Deprotection Conditions via Protodeboronation[a]



Entry	TBAF (x mol%)	H_2O (y equiv)	Temp (°C)	Time (h)	Yield (%)[b]
1	120	–	rt	0.2	>99
2	20	–	rt	24	90[c]
3	20	1.0	rt	13	>99
4	20	3.0	rt	11	>99
5	20	10.0	rt	24	35[c]
6	10	3.0	rt	24	92[c]
7	10	3.0	50	8.5	>99
8	10	3.0	reflux	2	>99
9	5	1.5	reflux	24	96[c]

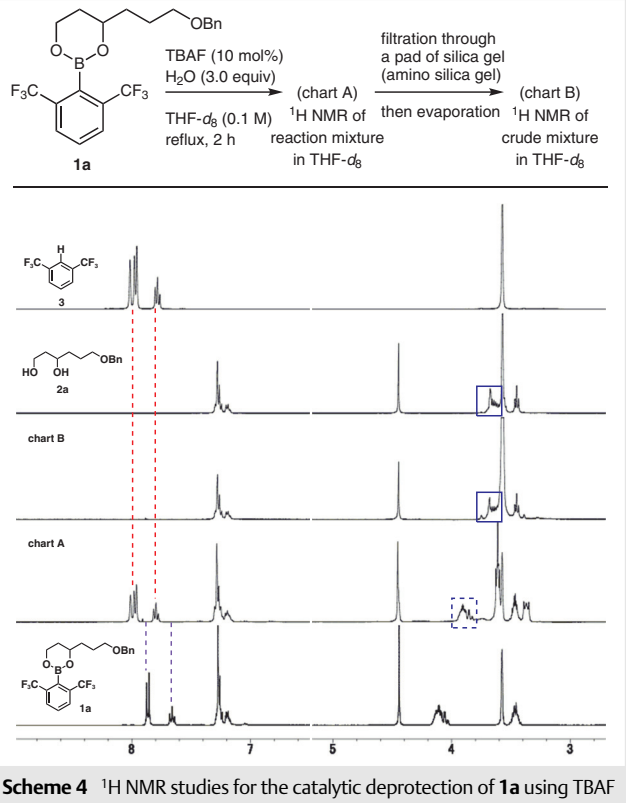
[a] Performed on 0.2 mmol scale.
[b] Isolated yield.
[c] Conversion yield determined by ^{1}H NMR spectroscopy of crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard.

Next, we explored the substrate generality under the conditions described in Scheme 3 (10 mol% of TBAF, 3.0 equivalents of water, reflux). It was found that the reaction was applicable not only to 1,3-diol-derived boronic esters **1b–h** but also to 1,2-diol-derived boronic esters **1i** and **1j**, affording the corresponding diols **2b–j** in high to excellent yields (80–99%). Functional groups such as ester (**2b**), amide (**2c**), amine (**2d**), olefin (**2e**), and alcohol (**2f**) were compatible under the deprotection conditions. However, carboxylic acid functional group was not tolerated under the same conditions.[25] Since silyl ethers are usually deprotected by TBAF, it is noteworthy that the selective deprotection of *o*-FXylboronic ester **1g** incorporating the TBS ether proceeded to give **2g** in high yield (88%) under the catalytic conditions. Moreover, boronic esters derived from cyclic 1,2-diols were also applicable, giving diols **2k–m** in high yields (90–99%).



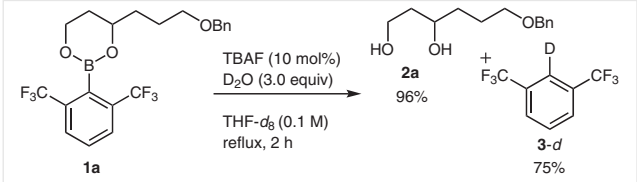
Scheme 3 Catalytic deprotection of *o*-FXylboronic esters using TBAF

To gain insights into the reaction mechanism, the deprotection reaction of **1a** was monitored by ^{1}H NMR spectroscopy in THF-d_8 (Scheme 4). After completion of the reaction, the ^{1}H NMR spectrum of the reaction mixture revealed the presence of the peak due to 1,3-bis(trifluoromethyl)benzene (**3**) and the disappearance of the peaks of the *o*-FXylboronic ester **1a** (Scheme 4, chart A). These results reveal that the deprotection reaction of **1a** proceeds through a protodeboronation mechanism. Interestingly, the new peaks observed around δ = 3.9 ppm were low-field shifted compared to those of the authentic diol **2a** (δ = 3.7 ppm, Scheme 4, chart A). This suggests that the diol interacts with boric acid in the reaction mixture. However, the ^{1}H NMR spectrum was obtained after filtration of the reaction mixture through a short pad of amino silica gel, and subsequent evaporation was in good agreement with that of the authentic diol **2a** (Scheme 4, chart B), which suggests that the boric ester is decomposed to the corresponding diol during the workup procedure using amino silica gel.



Scheme 4 ^{1}H NMR studies for the catalytic deprotection of **1a** using TBAF

For further investigation of the deprotection mechanism, the reaction was carried out using deuterated water (D_2O) as additive (Scheme 5). The result confirmed that the deprotection proceeds via a protodeboronation mechanism, since 1,3-bis(trifluoromethyl)benzene, deuterated at the 2-position (**3**-*d*), was obtained in high yield (75%) along with diol **2a**.



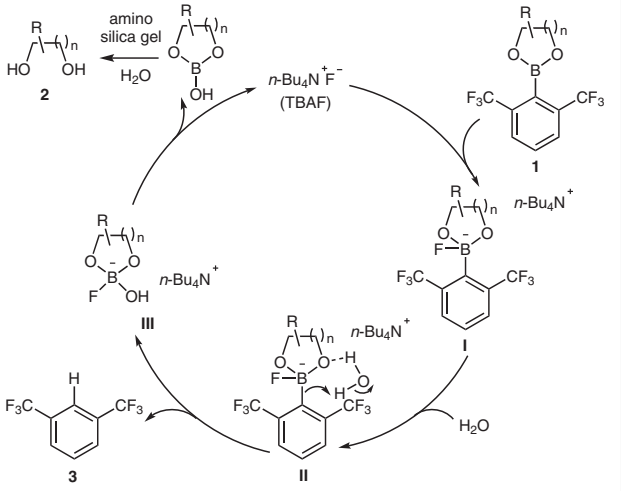
Scheme 5 Deprotection of boronic ester **1a** in the presence of D_2O

On the basis of these results, we propose the catalytic cycle shown in Scheme 6. Tetracoordinated borate intermediate **I** is formed initially by the coordination of fluoride anion to the boron atom of *o*-FXylboronic ester **1**. Subsequently, C–B bond cleavage and protonation at the *ipso*-position occur from intermediate **II**[16] by the reaction of **I** with water. As a result, an ionic pair **III** and 1,3-bis(trifluoromethyl)benzene (**3**) having a newly formed C–H bond are generated. Finally, TBAF is regenerated for the next catalytic cycle, and the hydrolysis of boric ester gives deprotected diol **2**.

In conclusion, we describe a new method for the deprotection of 2,6-bis(trifluoromethyl)phenylboronic esters (*o*-FXylboronic esters) via protodeboronation using commercially available TBAF. To the best of our knowledge, this is the first example of the catalytic use of TBAF for the protodeboronation of boronic esters. In this catalytic method with easy protocol,[26] the deprotection proceeds more rapidly compared to the previously reported methods.[6]

Funding Information

Japan Society for the Promotion of Science [JSPS KAKENHI Grant 19K07000 (N.S.) for Scienfic Research (C)], Japan Society for the Promotion of Science [JSPS KAKENHI Grant 17K08218 (K.M.) for Scienfic



Scheme 6 Proposed reaction mechanism for the catalytic deprotection using TBAF

Research (C)], Sasakawa Scientific Research Grant from The Japan Science Society (S.U.), and Kitasato University Research Grant for Young Researchers (N.S.).

Acknowledgment

We thank Dr. K. Nagai and Ms. M. Sato at Kitasato University for instrumental analyses.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690236.

References and Notes

(1) Wuts, P. G. M. *Greene's Protective Groups in Organic Synthesis, 5th ed*; John Wiley & Sons: Hoboken, **2014**.
(2) Hall, D. G. *Boronic Acids, 2nd ed.*; Wiley-VCH: Weinheim, **2011**.
(3) (a) Ferrier, R. J. *Methods Carbohydr. Chem.* **1972**, *6*, 419. (b) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1978**, *35*, 31.
(4) For a book, and reviews of boronic acids as protective reagents, see: (a) Wuts, P. G. M. In *Greene's Protective Groups in Organic Synthesis, 5th ed*; John Wiley & Sons: Hoboken, **2014**, 468. (b) Duggan, P. J.; Tyndall, E. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1325. (c) McClary, C. A.; Taylor, M. S. *Carbohydr. Res.* **2013**, *381*, 112.
(5) For selected examples of boronic esters as protective groups or transient masking groups, see: (a) Kaji, E.; Nishino, T.; Ishige, K.; Ohya, Y.; Shirai, Y. *Tetrahedron Lett.* **2010**, *51*, 1570. (b) Nishino, T.; Ohya, Y.; Murai, R.; Shirahata, T.; Yamamoto, D.; Makino, K.; Kaji, E. *Heterocycles* **2012**, *84*, 1123. (c) Kaji, E.; Yamamoto, D.; Shirai, Y.; Ishige, K.; Arai, Y.; Shirahata, T.; Makino, K.; Nishino, T. *Eur. J. Org. Chem.* **2014**, 3536. (d) Nakanishi, M.; Takahashi, D.; Toshima, K. *Org. Biomol. Chem.* **2013**, *11*, 5079. (e) Fenger, T. H.; Madsen, R. *Eur. J. Org. Chem.* **2013**, 5923. (f) Nakagawa, A.; Tanaka, M.; Hanamura, S.; Takahashi, D.; Toshima, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 10935. (g) Mancini, R. S.; McClary, C. A.; Anthonippillai, S.; Taylor, M. S. *J. Org. Chem.* **2015**, *80*, 8501. (h) Fukuhara, K.; Shimada, N.; Nishino, T.; Kaji, E.; Makino, K. *Eur. J. Org. Chem.* **2016**, 902. (i) Mancini, R. S.; Lee, J. B.; Taylor, M. S. *Org. Biomol. Chem.* **2017**, *15*, 132. (j) Dimakos, V.; Garrett, G. E.; Taylor, M. S. *J. Am. Chem. Soc.* **2017**, *139*, 15515. (k) Mancini, R. S.; Lee, J. B.; Taylor, M. S. *J. Org. Chem.* **2017**, *82*, 8777. (l) Manhas, S.; Taylor, M. S. *J. Org. Chem.* **2017**, *82*, 11406. (m) Kanzaki, Y.; Hirano, Y.; Mitsunuma, H.; Kanai, M. *Org. Biomol. Chem.* **2019**, *17*, 6562.
(6) (a) Shimada, N.; Urata, S.; Fukuhara, K.; Tsuneda, T.; Makino, K. *Org. Lett.* **2018**, *20*, 6064. (b) Shimada, N.; Fukuhara, K.; Urata, S.; Makino, K. *Org. Biomol. Chem.* **2019**, *17*, 7325.
(7) For review and book for protodeboronation, see: (a) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51. (b) Lee, C.-Y.; Cheon, C.-H. In *Boron Reagents in Synthesis, ACS Symposium Series 1236*; American Chemical Society: Washington DC, **2016**, 483.
(8) (a) Kuivila, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2159. (b) Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *Can. J. Chem.* **1963**, *41*, 3081. (c) Kuivil, A. H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666.
(9) For selected examples of base-promoted protodeboronation, see: (a) Lozada, J.; Liu, Z.; Perrin, D. M. *J. Org. Chem.* **2014**, *79*, 5365. (b) Ahn, S.-J.; Lee, C.-Y.; Kim, N.-K.; Cheon, C.-H. *J. Org. Chem.* **2014**, *79*, 7277. (c) Ding, Q.; Song, Q. *Org. Chem. Front.* **2016**, *3*, 14. (d) Lee, C.-Y.; Cheon, C.-H. *Adv. Synth. Catal.* **2016**, *358*, 549. (e) Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C. *J. Am. Chem. Sci.* **2016**, *138*, 9145. (f) Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. C. *J. Am. Chem. Sci.* **2017**, *139*, 13156. (g) Huang, X.; Hu, J.; Wu, M.; Wang, J.; Peng, Y.; Song, G. *Green Chem.* **2018**, *20*, 255.
(10) (a) Klingensmith, L. M.; Bio, M. M.; Moniz, G. A. *Tetrahedron Lett.* **2007**, *48*, 8242. (b) Zhang, G.; Li, Y.; Liu, J. *RSC Adv.* **2017**, *7*, 34959; see also ref. 9b.
(11) Barker, G.; Webster, S.; Johnson, D. G.; Curley, R.; Andrews, M.; Young, P. C.; Macgregor, S. A.; Lee, A.-L. *J. Org. Chem.* **2015**, *80*, 9807.
(12) (a) Fürstner, A.; Radkowski, K. *Chem. Commun.* **2002**, 2182. (b) Lacombe, F.; Radkowski, K.; Seidel, G.; Fürstner, A. *Tetrahedron* **2004**, *60*, 7315. (c) Sundararaju, B.; Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 14050. (d) Liu, C.; Li, X.; Wu, Y. *RSC Adv.* **2015**, *5*, 15354. (e) Nagao, K.; Yamazaki, A.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2018**, *20*, 1861.
(13) Liu, C.; Li, X.; Wu, Y.; Qiu, J. *RSC Adv.* **2014**, *4*, 54307.
(14) Shen, F.; Tyagarajan, S.; Perera, D.; Krska, S. W.; Maligres, P. E.; Smith, M. R. III.; Maleczka, R. E. Jr. *Org. Lett.* **2016**, *18*, 1554.
(15) Clausen, F.; Kischkewiz, M.; Bergander, K.; Studer, A. *Chem. Sci.* **2019**, *10*, 6210.
(16) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096.
(17) (a) Elford, T. G.; Nave, S.; Sonawane, R. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16798. (b) Roesner, S.; Casatejada, J. M.; Elford, T. G.; Sonawane, R. P.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 5740. (c) Scott, H. K.; Aggarwal, V. K. *Chem. Eur. J.* **2011**, *17*, 13124. (d) Aggarwal, V. K.; Ball, L. T.; Carobene, S.; Connelly, R. L.; Hesse, M. J.; Partridge, B. M.; Roth, P.; Thomas, S. P.; Webster, M. P. *Chem. Commun.* **2012**, *48*, 9230. (e) Roesner, S.; Aggarwal, V. K. *Can. J. Chem.* **2012**, *90*, 965. (f) Watson, C. G.; Aggarwal, V. K. *Org. Lett.* **2013**, *15*, 1346. (g) Roesner, S.; Blair, D. J.; Aggarwal, V. K. *Chem. Sci.* **2015**, *6*, 3718.
(18) TBAF (ca. 1 mol/L in tetrahydrofuran including maximum 10% of water) was purchased from Tokyo Chemical Industry Co., Ltd and used.
(19) In this study, maximun 6.7 equiv of water are included when 120 mol% of TBAF were used.

(20) The only byproduct of this reaction is 1,3-bis(trifluoromethyl)benzene (**3**) with low boiling point (b.p. 116 °C), which can be easily removed by evaporation during the workup procedure. Therefore, the desired diol at satisfactory level of purity was obtained by simple filtration of reaction mixture through a pad of basic amino silica gel eluting with EtOAc. See Supporting Information for experimental details.

(21) For a report on the effect of water in reactivity of fluoride ion, see: Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050.

(22) Deprotection of the corresponding phenylboronic ester only gave the small amount of diol **2a** (16% conversion yield) after 24 h under the conditions using 10 mol% of TBAF in the presence of 3.0 equiv of water at room temperature. See the Supporting Information for details.

(23) The Perrin and Lloyd-Jones groups independently reported that two *ortho* electron-withdrawing substituents on arylboronic acid accelerate base-catalyzed protodeboronation, see: (a) Lozada, J.; Liu, Z.; Perrin, D. M. *J. Org. Chem.* **2014**, *79*, 5365. (b) Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 13156.

(24) The reaction in the presence of 3.0 equiv of water with 5 mol% of TBAF resulted in a remarkably decreased yield (53%).

(25) Our attempt to deprotect under the optimized conditions using boronic ester derived from 4,6-dihydoroxyhexanoic acid failed, resulting in a nearly quantitative recovery of the starting material.

(26) **General Procedure for the Deprotection of the Boronic Esters with TBAF; Method A (Catalytic Conditions, Table 1, Entry 8)**

TBAF (0.20 M in THF, 100 μL, 0.0200 mmol, 10 mol%) and H_2O (6.0 M in THF, 100 μL, 0.600 mmol, 3.0 equiv) were added to a solution of **1a** (89.2 mg, 0.200 mmol, 1.0 equiv) in dry THF (1.8 mL, total 0.10 M) at room temperature. After stirring for 2 h under reflux and cooling to room temperature, the reaction mixture was filtered through a short pad of amino silica gel (800 mg) eluting with EtOAc (20 mL), and the filtrate was concentrated under reduced pressure to give **2a** (46.8 mg, 0.200 mmol, >99% yield) as a colorless oil.

Analytical Data for 2a

R_f = 0.13 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 4.53 (s, 2 H), 3.90–3.79 (m, 3 H), 3.57–3.49 (m, 2 H), 2.34 (br s, 2 H), 1.79–1.52 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.4, 127.8, 127.7, 73.1, 71.9, 70.5, 61.7, 38.3, 35.2, 26.2. IR (neat): ν = 3372, 2942, 2865, 1278, 1099 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{13}H_{20}O_3Na$ [M + Na]$^+$: 247.1310; found: 247.1311.

Method B (Stoichiometric Conditions, Table 1, Entry 1)

TBAF (1.0 M in THF, 0.24 mL, 0.240 mmol, 120 mol%) was added to a solution of **1a** (89.2 mg, 0.200 mmol, 1.0 equiv) in dry THF (1.8 mL, total 0.10 M) at room temperature. After stirring for 2 h under reflux, cooling to room temperature, the reaction mixture was filtered through a short pad of amino silica gel (800 mg) eluting with EtOAc (20 mL), and the filtrate was concentrated under reduced pressure to give **2a** (44.8 mg, 0.200 mmol, >99% yield) as a colorless oil.