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One-Pot Generation of Lithium (Lithiophenyl)trialkoxyborates from Substituted Dihalobenzenes (Hal = Br, I) and Their Derivatization with Electrophiles

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Keywords: Lithium / Borates / Arylboronic acids / Lithiation / Substituent effects / Dihalobenzenes

The simple one-pot approach to synthetically useful phenyltrialkoxyborates bearing lithium at the phenyl ring has been developed starting with 1,3- and 1,4-diiodobenzene, as well as several activated dibromobenzenes and bromoiodobenzenes. The general sequence of transformations involves halogen–lithium exchange by using *n*BuLi and subsequent boronation with a trialkylborate. The resulting lithium (halophenyl)trialkoxyborates were then subjected to halogen–lithium exchange in situ with a second equivalent of *n*BuLi to give dianionic lithium (lithiophenyl)trialkoxyborates. Treatment with selected electrophiles afforded substituted arylboronic acids and/or their pinacol esters as final products in moderate-to-good yields.

Introduction

Recently, arylboronic acids and esters have become very popular as they are versatile building blocks in organic synthesis; they have also found applications in other fields.[1] There is a growing interest in novel functionalized derivatives. Hence, the development of new simple general synthetic routes to arylboronic acids is an important task. The classical synthetic routes to arylboronic acids involving transmetalation of aryllithium[2] or arylmagnesium[3] compounds with trialkylborates suffer from limited access to these organometallics as they do not tolerate many popular functional groups attached to the aryl ring. Very recently, a significant progress in the use of arylmagnesium reagents was achieved.[4] Many difficulties have been overcome with a discovery of palladium-catalyzed coupling of aryl halides with diboron derivatives[5] or hydroboranes.[6,7] In this context, the CuI-catalyzed coupling of iodoarenes with pinacolborane is the novel interesting alternative.[8] Aryl derivatives of silicon, mercury,[9] tin,[10] and thalium[11] have also been used in combination with borane or tribromoborane.[12] Alternative strategies relying on a structural modification of simple arylboronic acids were less explored in the past years; classical examples include nitration of phenylboronic acid and regiochemical oxidation of tolylboronic acids.[13,14] Recently, a more advanced general protocol has been developed: it involves immobilization of substituted arylboronic acids onto diethanolaminomethyl polystyrene[15] followed by derivatization of a remaining active substituent (formyl, bromomethyl, carboxy, amino groups). Furthermore, *N*-methyliminodiacetic acid[16] and 1,8-diaminonaphthalene[17] have been employed as boron-masking reagents in the Pd-catalyzed arylation of haloarylboronic acids. The conversion of arylboronic acids into azaesters by using *N*-alkyldiethanolamines was used for the introduction of lithium to the boronated aromatic ring.[18] The synthesis and reactivity of closely related boron–lithium bimetallic reagents, that is, potassium 3- and 4-lithiophenyltrifluoroborates,[19] as well as magnesiated arylboronic pinacol esters were reported.[20] Our work deals with another class of lithiated tetravalent arylboron complexes, which can be easily converted into various functionalized arylboron derivatives.

Results and Discussion

In our first attempts, consecutive reactions were performed starting with 1,3- and 1,4-diiodobenzene: they involved lithiation with *n*BuLi (1 equiv.), transmetalation with $B(O\textit{i}Pr)_3$ (1 equiv.), and then the second lithiation (1.1 equiv.) followed by addition of the electrophile (1.2 equiv.) (Scheme 1). To avoid a potential coupling of 1-iodobutane byproduct with iodophenyllithium and/or (lithiophenyl)triisopropoxyborate intermediates, diethyl ether was used as a solvent. After carboxylation and acidic hydrolysis, we isolated 4- and 3-carboxyphenylboronic acids, **1** and **3**, respectively, in ca. 50% yield by simple solvent evaporation and washing the crude products with water and ether (Scheme 1). It should be noted that the precise control of stoichiometry during the first two steps (i.e., the first I–Li exchange and boronation) is critical for a selective generation of lithium (iodophenyl)triisopropoxyborates, which is in line with the desired removal of unreacted diiodobenzene

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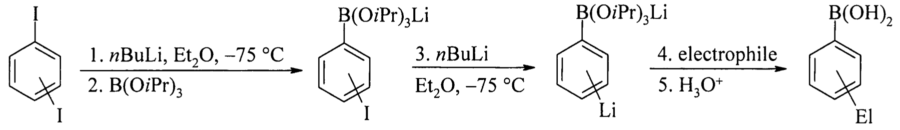


electrophile	El
CO_2	4-COOH (**1**), 3-COOH (**3**)
2-$MeOC_6H_4CHO$	4-(2-$MeOC_6H_4CHOH$) (**2**), 3-(2-$MeOC_6H_4CHOH$) (**4**)

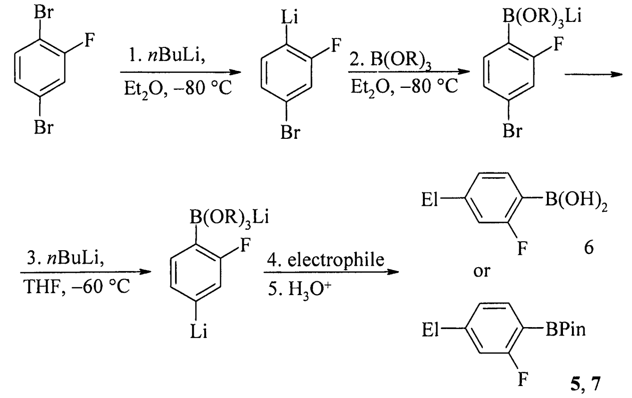
Scheme 1. The one-pot synthesis of *meta*- and *para*-substituted arylboronic acids from 1,3- and 1,4-diiodobenzene.

or iodophenyllithium from the reaction mixture. Derivatization of lithium–boron reagents with appropriate electrophiles may provide access to variously functionalized arylboronic acids that are otherwise not easily accessible. Thus, upon treatment with 2-methoxybenzaldehyde, boronated carbinols **2** and **4** were isolated in moderate yields.

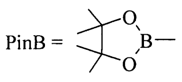
We attempted next to probe the above protocol by employing 1,3- and 1,4-dibromobenzene. Unfortunately, the corresponding lithium (bromophenyl)triisopropoxyborates do not undergo Br–Li exchange with *n*BuLi even at higher temperatures (around –20 °C) and by employing THF as a cosolvent, which is a better promoter of halogen–lithium exchange when compared to Et_2O.[21] In fact, iodine–lithium exchange proceeds generally more smoothly than bromine–lithium exchange. To give a simple example, dilithiation of 1,3- and 1,4-diiodobenzene with *n*BuLi occurs quantitatively in Et_2O at –78 °C, whereas 1,3- and 1,4-dibromobenzene can only be monolithiated.[22]

We extended our work by using dibromobenzenes bearing electron-withdrawing substituents (in terms of inductive effect), as we assumed that the better stabilization of the negative charge of the "ate" complex might be beneficial for the Br–Li interconversion. In the case of 1,4-dibromo-2-fluorobenzene, the first Br–Li exchange proceeds selectively *ortho* to the fluorine atom when performed in Et_2O at –80 °C to produce lithium (4-bromo-2-fluorophenyl)trialkoxyborate as a gelatinous material after consecutive boronation (Scheme 2, Table 1). To improve its solubility, the substantial addition of THF proved mandatory. Subsequent treatment with the next equivalent of *n*BuLi at ca –60 °C resulted in the formation of lithium (4-lithio-2-fluorophenyl)trialkoxyborate. This intermediate was trapped with selected electrophiles to give functionalized 2-fluorophenylboronic acids or their pinacol esters **5**–**7**.

A similar approach proved also successful with 1,4-dibromo-2-methoxybenzene. The sequence of first lithiation/boronation affords the "ate" complex (4-Br-2-$MeOC_6H_3$)-$B(OR)_3Li$ as a result of selective Br–Li exchange *ortho* to a methoxy group. However, to replace the remaining bromine atom with lithium a higher temperature, that is, ca. –40 °C, was necessary, as clearly evidenced by the precipitation of the lithiated "ate" complex from an almost homogeneous solution. Finally, we succeeded in the isolation of 4-substituted 2-methoxyphenylboronic acids **8**–**10** after quench with electrophiles (Scheme 3).

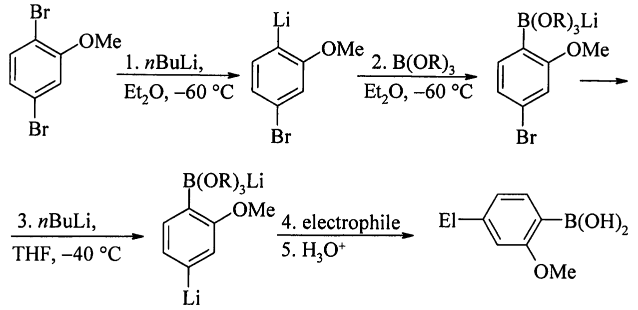


$B(OR)_3 = B(OiPr)_3$ or PinBOMe



electrophile	El
CO_2	COOH (**5**)
$(MeO)_2CO$	COOMe (**6**)
I_2	I (**7**)

Scheme 2. The one-pot synthesis of 4-substituted 2-fluorophenylboronic acids or their pinacol esters from 1,4-dibromo-2-fluorobenzene.



R = *i*Pr

electrophile	El
CO_2	COOH (**8**)
*t*BuNCO	*t*BuNHCO (**9**)
Me_2NCHO	CHO (**10**)

Scheme 3. The one-pot synthesis of 4-substituted 2-methoxyphenylboronic acids from 1,4-dibromo-2-methoxybenzene.

In 1,3-dibromo-2-alkoxybenzenes two bromine atoms gain significant activation from the adjacent alkoxy group. Hence, the Br–Li exchange in the preformed "ate" complex

$(3\text{-Br-}2\text{-ROC}_6H_3)B(OR)_3Li$ (R = Me, Pr) proceeds effectively at lower temperatures than in the previous case, that is, at ca. –60 °C, providing easy access to acids **11**–**13** (Scheme 4).

The reactivity pattern of 1-bromo-4-iodo-2-(trifluoromethyl)benzene is dictated by the tendency of iodine to be replaced much faster than bromine despite the fact that the latter is strongly activated by the adjacent strongly electron-

Table 1. The one-pot preparation of functionalized arylboronic acids and pinacol esters from dihalobenzenes.

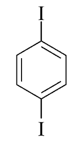
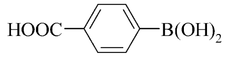
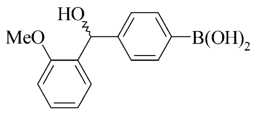
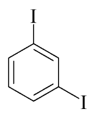
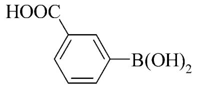
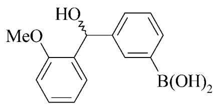
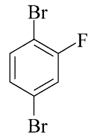
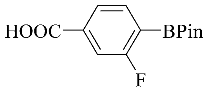
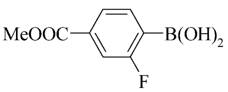
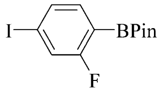
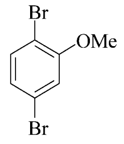
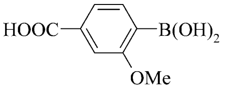
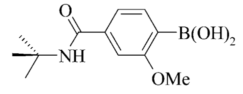
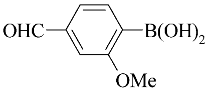
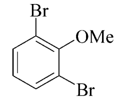
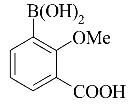
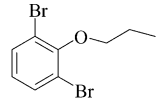
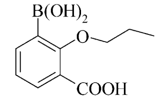
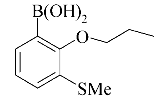
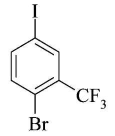
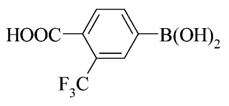
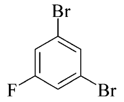
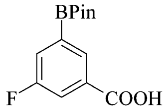
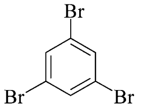
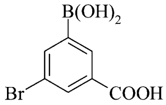
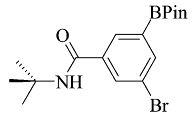
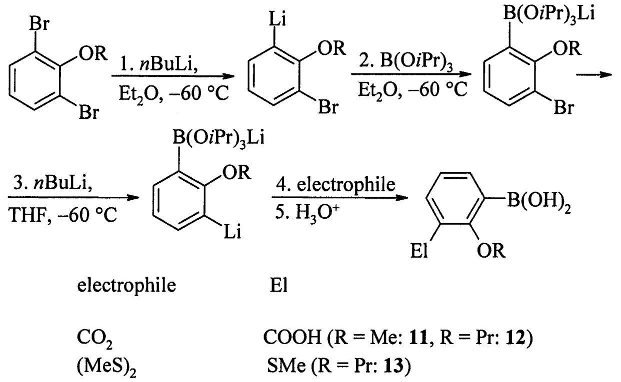
Starting material	Solvent, temperature	Boron reagent electrophile	Product	Compd. no.	Yield [%]
	Et_2O, –75 °C, then –60 °C[a]	$B(OiPr)_3$ CO_2		**1**	52
		$B(OiPr)_3$ 2-MeOC_6H_4CHO		**2**	65
	Et_2O, –75 °C, then –60 °C[a]	$B(OiPr)_3$ CO_2		**3**	50
		$B(OiPr)_3$ 2-MeOC_6H_4CHO		**4**	55
	Et_2O, –80 °C, then THF,[b] –60 °C[a]	PinBOMe CO_2		**5**	83
		$B(OiPr)_3$ $(MeO)_2CO$		**6**	68
		PinBOMe I_2		**7**	74
	Et_2O, –60 °C, then THF,[b] –40 °C[a]	$B(OiPr)_3$ CO_2		**8**	86
		$B(OiPr)_3$ tBuCNO		**9**	54
		$B(OiPr)_3$ Me_2NCHO		**10**	66
	Et_2O, THF,[b] –60 °C	$B(OiPr)_3$ CO_2		**11**	72
	Et_2O, THF,[b] –60 °C	$B(OiPr)_3$ CO_2		**12**	85
		$B(OiPr)_3$ MeSSMe		**13**	64

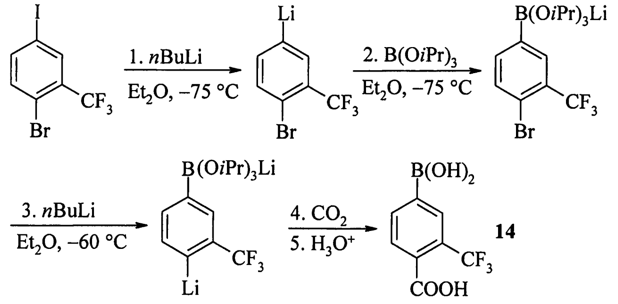
Table 1. *(Continued)*

Starting material	Solvent, temperature	Boron reagent electrophile	Product	Compd. no.	Yield [%]
	Et_2O, –75 °C, then –60 °C[a]	$B(OiPr)_3$ CO_2		**14**	61
	Et_2O, –75 °C, then THF,[b] –50 °C[a]	PinBOMe CO_2		**15**	46
	Et_2O, –75 °C, then THF,[b] –50 °C[a]	$B(OiPr)_3$ CO_2		**16**	82
		PinBOMe *t*BuCNO		**17**	55

[a] Lithiation of the halophenyl "ate" complex. [b] Used as a cosolvent.



Scheme 4. The one-pot synthesis of 3-substituted 2-alkoxyphenylboronic acids from 1,3-dibromo-2-alkoxybenzenes.



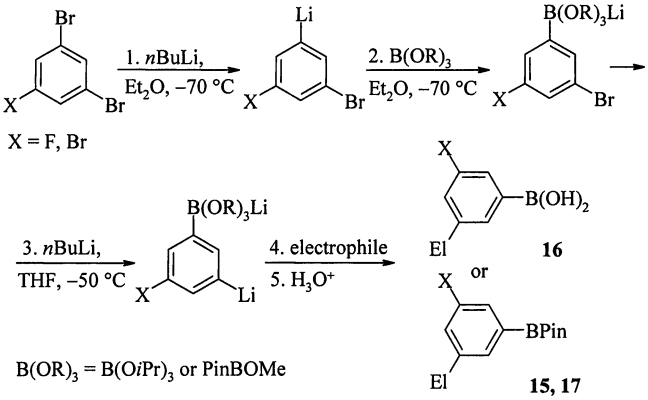
Scheme 5.

withdrawing trifluoromethyl group. Thus, the iodine–lithium exchange proceeds cleanly in Et_2O (importantly, THF must be completely avoided, as a mixture of products is formed[23]) in the first step to give the "ate" complex (4-Br-3-$CF_3C_6H_3$)B(O*i*Pr)$_3$Li after consecutive boronation. This complex undergoes facile bromine–lithium exchange at ca. –70 °C without any activation by the addition of THF. The resultant lithiated species was carboxylated to give 4-carboxy-3-(trifluoromethyl)phenylboronic acid (**14**) after acidic hydrolysis (Scheme 5).

It should be noted that in all the above cases either the anionic borate moiety is stabilized by the neighboring *ortho* substituent or the halogen atom in the "ate" complex is strongly *ortho* activated (in syntheses of **11**–**14**). In addition, we were interested in evaluating whether long-range electron-withdrawing effects are sufficiently strong to activate the bromine atom, which would in turn result in lithiation of the borate. This prompted us to probe the reactivity of some 5-substituted 1,3-dibromobenzenes.

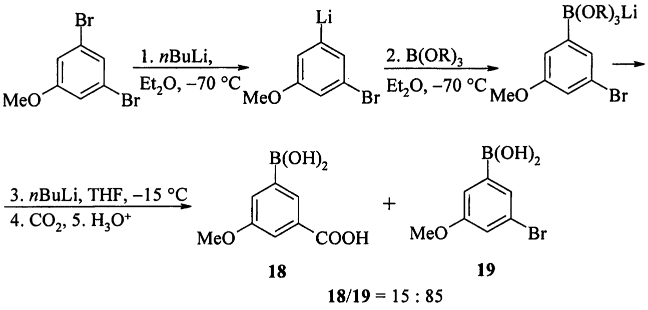
The conversion of 1,3-dibromo-5-fluorobenzene into the "ate" complexes of the type (3-Br-5-FC_6H_3)B(OR)$_3$Li was performed smoothly by using Et_2O at –70 °C as a solvent, whereas the addition of THF and a slight heating (to ca. –50 °C) were applied to induce the subsequent Br–Li interconversion. The resultant lithiated intermediate was trapped with CO_2 to give the pinacol ester of 3-carboxy-5-fluorophenylboronic acid **15** in moderate yield. This result demonstrates that fluorine is capable of activating remote *meta* positions quite strongly,[24–26] which enables an effective Br–Li exchange in the "ate" complex. An even better situation was observed for 1,3,5-tribromobenzene, where the lithiation of the "ate" complex (3,5-$Br_2C_6H_3$)B(OR)$_3$Li was observed already at –60 °C in Et_2O/THF (ca. 2:1) providing compounds **16** and **17** (Scheme 6) after derivatization. Finally, the conversion of 1,3-dibromo-5-methoxybenzene into 3-carboxy-5-methoxyphenylboronic acid (**18**;

Scheme 7) failed almost completely, as 3-bromo-5-methoxyphenylboronic acid (**19**) was identified as a major product, and it was only contaminated with a small amount (ca. 15%) of **18**. Clearly, the lithiation of the (3-Br-5-OMeC_6H_3)-$B(OR)_3Li$ complex is not effective even at higher temperatures (ca. –15 °C), which confirms the reputation of the methoxy group being only weakly activating and/or anion stabilizing when located at a remote *meta* position,[27,28] especially in comparison with fluorine.[29,30]



electrophile	El
CO_2	COOH (X = F: **15**, X = Br: **16**)
*t*BuNCO	*t*BuNHCO (X = Br: **17**)

Scheme 6. The one-pot synthesis of 3-substituted 5-halophenylboronic acids (X = F, Br) or their pinacol esters from corresponding 1,3-dibromo-5-halobenzenes.



Scheme 7.

In addition, we investigated the thermostabilities of both types of "ate" complexes existing in the reaction pathway by using VT ^{11}B NMR spectroscopy under reaction conditions. We selected 1,3-dibromo-2-methoxybenzene and 1,3,5-tribromobenzene (Table 1, compounds **11** and **16**, respectively) as starting materials. We found that lithium (3-bromo-2-methoxyphenyl)triisopropoxyborate ($\delta^{11}B$ = 4 ppm) is stable at 0 °C but decomposes quite rapidly at room temperature to give diisopropyl boronate ($\delta^{11}B$ = 27 ppm). In contrast, lithium (3,5-dibromophenyl)triisopropoxyborate is more stable under comparable conditions and does not split to form the corresponding boronate. (Lithiophenyl)triisopropoxyborates are apparently too reactive when warmed up (0–20 °C), as subsequent attempted carboxylation (at –70 °C) did not afford desired products **11** and **16**. In general, this degradation could not be easily monitored by using VT ^{11}B NMR, as only the spectra of the dianionic precursor of **11** showed changes pointing to degradation starting at ca. 0 °C, whereas for **16** they were not significantly temperature dependent.

Conclusions

The halogen–lithium interconversion in lithium (haloaryl)trialkoxyborates is straightforward by using *n*BuLi for iodides and moderately activated bromides. The resultant lithium (lithioaryl)trialkoxyborates can be regarded as equivalents of lithiated arylboronic acids or esters, which can be subsequently derivatized by the treatment with an appropriate electrophile, which provides access to a wide range of functionalized arylboronic acids and esters. It should be stressed that the proposed one-pot protocol uses readily available and relatively cheap dihalobenzenes as starting materials.

Experimental Section

General Comments: All reactions involving air- and moisture-sensitive reagents were carried out under an argon atmosphere. Et_2O and THF were stored over sodium wire before use. Starting materials: diiodobenzenes, substituted dibromobenzenes, and other important reagents including *tert*-butyl isocyanate, dimethyl carbonate, *N*,*N*-dimethylformamide, iodine, dimethyl disulfide, *n*BuLi (10 M in hexanes), triisopropoxyborane, and 2-methoxy-4,4,5,5-tetramethyl[1,3,2]dioxaborolane were received from Aldrich. 1,3-Dibromo-2-methoxybenzene, 1,3-dibromo-2-propoxybenzene, and 1-bromo-4-iodo-2-(trifluoromethyl)benzene were prepared according to literature procedures.[31,32]

The NMR chemical shifts are given relative to TMS by using known chemical shifts of residual proton (^1H) or carbon (^{13}C) solvent resonances. In the ^{13}C NMR spectra of arylboronic acids, the resonances of boron-bound carbon atoms were not observed in most cases as a result of their broadening by a quadrupolar boron nucleus. New compounds gave satisfactory elemental analyses except for acids **14** and **16**, because of the formation of air-stable hydrates.

4-Carboxyphenylboronic acid (1): To a stirred suspension of 1,4-diiodobenzene (16.5 g, 50 mmol) in Et_2O (300 mL) was slowly added *n*BuLi (2 M in hexanes, 25 mL, 50 mmol) at –70 °C. The mixture was stirred for 30 min, followed by the dropwise addition of $B(OiPr)_3$ (8.9 g, 50 mmol). The resultant mixture was stirred for ca. 15 min and then treated with *n*BuLi (2 M in hexanes, 30 mL, 60 mmol) to give a gelatinous slurry. The mixture was stirred for 1 h at –60 °C and then poured onto freshly crushed dry ice covered with Et_2O (50 mL). After evaporation of the excess CO_2, the mixture was hydrolyzed with aqueous sulfuric acid (1.5 M, 50 mL). The organic phase was separated and concentrated under reduced pressure. The residue was filtered and washed consecutively with water (2 × 10 mL), ether (2 × 5 mL), and hexane (10 mL). Drying in vacuo afforded the title compound as a white powder. M.p. 236–237 °C (decomp.) (ref.[33] m.p. 240 °C). Yield: 4.3 g (52%). ^1H NMR (400 MHz, [D_6]acetone): δ = 7.91 (m, 4 H, Ph), 4.03 [br., 3 H, $B(OH)_2$ + COOH] ppm. ^{11}B NMR (64.2 MHz, [D_6]acetone): δ = 27.0 ppm.

4-[(2′-Methoxyphenyl)hydroxymethyl]phenylboronic acid (2): A slurry of 1,4-diiodobenzene (6.6 g, 20 mmol) in Et_2O (100 mL) was treated consecutively with *n*BuLi (2 M in hexanes, 10 mL, 20 mmol), $B(OiPr)_3$ (3.8 g, 20 mmol), and again with *n*BuLi (2 M in hexanes, 11 mL, 22 mmol) by employing a protocol similar to that described for **1**. The resultant mixture was stirred for ca. 30 min at –75 °C, and it was then treated with a solution of 2-methoxybenzaldehyde (3.25 g, 22 mmol) in Et_2O (20 mL). The mixture was stirred for 1 h at –75 °C and then hydrolyzed with aqueous sulfuric acid (1.5 M, 20 mL). The organic phase was separated and concentrated under reduced pressure. Toluene (10 mL) and hexane (10 mL) were added, and a resultant slurry was filtered and washed with water (2 × 5 mL) and hexane (2 × 5 mL). The title compound was obtained as a white powder. M.p. 126–130 °C (decomp.). Yield: 3.35 g (65%). ^1H NMR (400 MHz, [D_6]acetone + D_2O): δ = 7.76 (d, J = 8.0 Hz, 2 H, Ph), 7.49 (dd, J = 7.5, 1.5 Hz, 1 H, Ph′), 7.36 (d, J = 8.0 Hz, 2 H, Ph), 7.18 (td, J = 7.5, 1.5 Hz, 1 H, Ph′), 6.93–6.88 (m, 2 H, Ph′), 6.12 (s, 1 H, C*H*OH), 3.75 (s, 3 H, OMe) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, [D_6]acetone + D_2O): δ = 156.8, 147.9, 134.5, 134.0, 128.8, 127.5, 126.4, 121.1, 111.2, 69.7, 55.6 ppm. ^{11}B NMR (64.2 MHz, [D_6]acetone + D_2O): δ = 28.0 ppm. IR (KBr): 3460, 1608, 1316, 1244, 1032, 760 cm^{-1}. $C_{14}H_{15}BO_4$ (258.08): calcd. C 65.15, H 5.86; found C 64.81, H 5.90.

3-Carboxyphenylboronic acid (3): This compound was prepared similarly by starting with 1,3-diiodobenzene (6.6 g, 20 mmol) and obtained as a white powder. M.p. 245–247 °C (decomp.) (ref.[33] m.p. 250 °C). Yield: 1.65 g (50%). ^1H NMR ([D_6]acetone, 400 MHz): δ = 8.54 (s, 1 H, Ph), 8.10–8.06 (m, 2 H, Ph), 7.48 (t, J = 8.0 Hz, 1 H, Ph), 3.60 [br., 3 H, $B(OH)_2$] ppm. ^{11}B NMR (64.2 MHz, [D_6]acetone + D_2O): δ = 28.0 ppm.

3-[(2′-Methoxyphenyl)hydroxymethyl]phenylboronic acid (4): This compound was prepared as described for the preparation of **3** from 1,3-diiodobenzene (6.6 g, 20 mmol) and obtained as a white powder. M.p. 140–144 °C (decomp.). Yield: 2.9 g (55%). ^1H NMR (400 MHz, [D_6]acetone + D_2O): δ = 7.91 (s, 1 H, Ph), 7.67 (d, J = 7.5 Hz, 1 H, Ph), 7.50 (dd, J = 7.5, 1.5 Hz, 1 H, Ph), 7.39 (d, J = 7.5 Hz, 1 H, Ph), 7.21–7.16 (m, 2 H, Ph′), 6.91–6.87 (m, 2 H, Ph′), 6.11 (s, 1 H, C*H*OH), 3.73 (s, 3 H, OMe) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, [D_6]acetone + D_2O): δ = 156.8, 144.6, 134.2, 133.2, 129.3, 128.7, 127.7, 127.5, 121.0, 111.2, 70.0, 55.6 ppm. ^{11}B NMR (64.2 MHz, [D_6]acetone + D_2O): δ = 29.0 ppm. IR (KBr): $\tilde{\nu}$ = 3332, 1600, 1356, 1240, 1008, 756 cm^{-1}. $C_{14}H_{15}BO_4$ (258.08): calcd. C 65.15, H 5.86; found C 64.70, H 5.78.

2-(4′-Carboxy-2′-fluorophenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (5): To a stirred solution of *n*BuLi (10 M in hexanes, 5 mL, 50 mmol) in Et_2O (50 mL) was slowly added a solution of 1,4-dibromo-2-fluorobenzene (12.7 g, 50 mmol) in Et_2O (30 mL) at –80 °C. The mixture was stirred for 30 min, followed by the dropwise addition of PinBOMe (7.9 g, 50 mmol). The resultant gelatinous mixture was diluted with THF (70 mL) and stirred for ca. 30 min at –70 °C to give an almost clear solution. It was then treated with *n*BuLi (2 M in hexanes, 27 mL, 54 mmol) to give a gelatinous slurry. The slurry was stirred for 30 min at ca. –65 °C. After cooling to –80 °C, the mixture was carboxylated by passing through a stream of dried gaseous CO_2 with rapid stirring. After saturation, the mixture was left to warm up to ca. 0 °C to evaporate the excess CO_2, followed by the careful hydrolysis with aqueous sulfuric acid (1.5 M, 50 mL). The organic phase was separated and concentrated under reduced pressure. The crude product was washed with water (3 × 10 mL) and hexane (10 mL) to give the title compound as a white powder. M.p. 193–195 °C. Yield: 11.0 g (83%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, J = 7.5, 1.0 Hz, 1 H, Ph), 7.84 (dd, J = 8.0, 5.5 Hz, 1 H, Ph), 7.75 (dd, J = 9.5, 1.0 Hz, 1 H, Ph) 1.38 (s, 12 H, Me) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 170.9 (d, J = 2.5 Hz), 166.8 (d, J = 250 Hz), 137.0 (d, J = 8.5 Hz), 133.8 (d, J = 8.5 Hz), 125.0 (d, J = 3.0 Hz), 116.7 (d, J = 26.0 Hz) 84.4, 24.8 ppm. ^{11}B NMR (64.2 MHz, $CDCl_3$): δ = 25.4 ppm. $C_{13}H_{16}BFO_4$ (266.08): calcd. C 58.68, H 6.06; found C 58.45, H 6.27.

4-Methoxycarbonyl-2-fluorophenylboronic acid (6): This compound was prepared as described for the preparation of **5** by using $B(OiPr)_3$ (8.9 g, 50 mmol) for the boronation and an excess amount of dimethyl carbonate (6.8 g, 75 mmol) as the electrophile (added below –80 °C). The crude product was washed with water (3 × 10 mL) and toluene (2 × 5 mL) to give the title compound as a white crystalline material. M.p. 137–140 °C. Yield: 6.7 g (68%). ^1H NMR (400 MHz, [D_6]acetone): δ = 7.85–7.76 (m, 2 H, Ph), 7.58 (dd, J = 10.0, 1.5 Hz, 1 H, Ph), 7.50 [br., 2 H, $B(OH)_2$], 3.89 (s, 3 H, CO-OMe) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, [D_6]acetone): δ = 167.1 (d, J = 244 Hz), 166.1 (d, J = 3.0 Hz), 137.0 (d, J = 9.0 Hz), 134.7 (d, J = 8.0 Hz), 125.3 (d, J = 3.0 Hz), 116.1 (d, J = 26.5 Hz), 52.6 ppm. ^{11}B NMR (64.2 MHz, [D_6]acetone): δ = 28.0 ppm. $C_8H_8BFO_4$ (197.96): calcd. C 48.54, H 4.07; found C 48.67, H 4.10.

2-(2′-Fluoro-4′-iodophenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (7): This compound was prepared as described for the preparation of **5** by using iodine (12.7 g, 50 mmol) as the electrophile dissolved in THF (30 mL) at –80 °C. After hydrolysis with aqueous sulfuric acid (1.5 M, 50 mL), the organic phase was consecutively separated, washed with water (50 mL) and aqueous $Na_2S_2O_3$ (20 wt.-%, 30 mL), and concentrated under reduced pressure. The oily residue was diluted with hexane and washed with water (2 × 10 mL). After removal of hexane, the residue was distilled under reduced pressure to give the crude product as an oil. B.p. 95–105 °C (0.5 Torr). Recrystallization from hexane (30 mL) at –40 °C afforded the title compound as colorless crystals. M.p. 56–58 °C. Yield: 10.4 g (60%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (dd, J = 8.0, 1.5 Hz, 1 H, Ph), 7.45–7.41 (m, 2 H, Ph), 1.34 (s, 12 H, Me) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 166.3 (d, J = 256 Hz), 137.7 (d, J = 8.0 Hz), 133.0 (d, J = 3.0 Hz), 124.7 (d, J = 26.5 Hz), 98.1 (d, J = 8.0 Hz), 84.0, 24.7 ppm. ^{11}B NMR (64.2 MHz, $CDCl_3$): δ = 25.3 ppm. $C_{12}H_{15}BFIO_2$ (347.96): calcd. C 41.42, H 4.35; found C 41.55, H 4.65.

4-Carboxy-2-methoxyphenylboronic acid (8): This compound was prepared as described for **6** from 1,4-dibromo-2-methoxybenzene (5.32 g, 20 mmol) except the higher temperature (–40 °C) was applied to perform the lithiation of the “ate” complex. The crude product was washed with water (2 × 10 mL), ether (2 × 10 mL), and hexane (10 mL) to give the title compound as a white crystalline material. M.p. 181–182 °C. Yield: 3.4 g (87%). ^1H NMR (400 MHz, [D_6]DMSO): δ = 7.94 [br., 2 H, $B(OH)_2$], 7.58 (d, J = 7.5 Hz, 1 H, Ph), 7.51 (dd, J = 7.5, 1.0 Hz, 1 H, Ph), 7.43 (s, 1 H, Ph), 3.83 (s, 3 H, OMe) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, [D_6]DMSO): δ = 167.4, 162.9, 134.9, 133.4, 128.1 (br.), 121.2, 110.3, 55.3 ppm. ^{11}B NMR (64.2 MHz, [D_6]DMSO): δ = 29.8 ppm. $C_8H_9BO_5$ (195.97): calcd. C 49.03, H 4.63; found C 48.63, H 4.70.

4-*tert*-Butylaminocarbonyl-2-methoxyphenylboronic acid (9): This compound was prepared as described for the preparation of **8** by using *t*BuNCO as the electrophile. The crude product was washed with water (2 × 10 mL), toluene (2 × 5 mL), and hexane (2 × 5 mL) to give the title compound as a white crystalline material. M.p. 189–191 °C. Yield: 2.7 g (54%). ^1H NMR (400 MHz, [D_6]acetone): δ = 7.76 (d, J = 7.5 Hz, 1 H, Ph), 7.42 (d, J = 1.0 Hz, 1 H, Ph), 7.39 (dd, J = 7.5, 1.0 Hz, 1 H, Ph), 7.35 (br., 1 H, NH), 3.93 [s, 2 H, $B(OH)_2$], 1.42 (s, 9 H, *t*Bu) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, [D$_6$]acetone): δ = 167.3, 165.2, 140.7, 136.9, 119.8, 109.8, 55.9, 52.0, 28.8 ppm. ^{11}B NMR (64.2 MHz, [D$_6$]acetone): δ = 28.8 ppm. $C_{12}H_{18}BNO_4$ (251.09): calcd. C 57.40, H 7.23, N 5.58; found C 57.30, H 7.23, N 5.56.

4-Formyl-2-methoxyphenylboronic acid (10): This compound was prepared as described for the preparation of **8** by using Me_2NCHO as the electrophile. The crude product was washed with water (2 × 10 mL), toluene (2 × 5 mL), and hexane (2 × 5 mL) to give the title compound as a white crystalline material. M.p. 152–155 °C. Yield: 2.4 g (67%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 10.01 (s, 1 H, CHO), 7.95 (d, J = 7.5 Hz, 1 H, Ph), 7.52 (dd, J = 7.5, 1.0 Hz, 1 H, Ph), 7.47 (d, J = 1.0 Hz, 1 H, Ph), 7.24 [s, 2 H, B(OH)$_2$], 3.98 (s, 3 H, OMe) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]acetone): δ = 193.1, 165.5, 140.6, 137.7, 123.5, 109.8, 56.0 ppm. ^{11}B NMR (64.2 MHz, [D$_6$]acetone): δ = 28.6 ppm. $C_8H_9BO_4$ (179.97): calcd. C 53.39, H 5.04; found C 53.70, H 4.83.

3-Carboxy-2-methoxyphenylboronic acid (11): This compound was prepared as described for the preparation of **6** from 1,3-dibromo-2-methoxybenzene (5.32 g, 20 mmol). The crude product was washed with water (2 × 10 mL), toluene (2 × 5 mL), and hexane (2 × 5 mL) to give the title compound as a white crystalline material. M.p. 156–159 °C. Yield: 2.8 g (72%). ^{1}H NMR (400 MHz, [D$_6$]acetone + D_2O): δ = 7.90–7.85 (m, 2 H, Ph), 7.20 (t, J = 7.5 Hz, 1 H, Ph), 3.89 (s, 3 H, OMe) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]acetone + D_2O): δ = 167.7, 165.4, 140.5, 134.6, 124.8, 124.2, 63.4 ppm. ^{11}B NMR (64.2 MHz, [D$_6$]acetone + D_2O): δ = 28.8 ppm. $C_8H_9BO_5$ (195.97): calcd. C 49.03, H 4.63; found C 49.19, H 4.73.

3-Carboxy-2-propoxyphenylboronic acid (12): This compound was prepared as described for the preparation **11** from 1,3-dibromo-2-propoxybenzene (5.88 g, 20 mmol). The crude product was washed with water (2 × 10 mL), toluene (2 × 5 mL), and hexane (2 × 5 mL) to give the title compound as a white crystalline material. M.p. 142–144 °C. Yield: 3.8 g (85%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 11.3 (br., 1 H, COOH), 7.92 (m, 2 H, Ph), 7.30 [br., 2 H, B(OH)$_2$], 7.22 (t, J = 7.5 Hz, 1 H, Ph), 4.02 (t, J = 7.0 Hz, 2 H, OCH$_2$Et), 1.82 (sextet, J = 7.0 Hz, 2 H, OCH$_2$*CH$_2$*CH$_3$), 1.00 (t, J = 7.0 Hz, 3 H, OCH$_2$CH$_2$*CH$_3$*) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]acetone): δ = 167.2, 164.5, 140.6, 134.7, 124.8, 124.3, 78.9, 24.0, 10.5 ppm. ^{11}B NMR (64.2 MHz, [D$_6$]acetone): δ = 28.8 ppm. $C_{10}H_{13}BO_5$ (224.02): calcd. C 53.62, H 5.85; found C 53.69, H 5.89.

3-(Methylthio)-2-propoxyphenylboronic acid (13): This compound was prepared as described for the preparation of **12** by using (MeS)$_2$ as the electrophile. The crude product was washed with water (2 × 10 mL), toluene (2 × 5 mL), and hexane (2 × 5 mL) to give the title compound as a white crystalline material. M.p. 97–99 °C. Yield: 2.9 g (64%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.53 (dd, J = 7.5, 1.5 Hz, 1 H, Ph), 7.31 (dd, J = 7.5, 1.5 Hz, 1 H, Ph), 7.17 [br., 2 H, B(OH)$_2$], 7.14 (t, J = 7.5 Hz, 1 H, Ph), 3.92 (t, J = 7.0 Hz, 2 H, OCH$_2$Et), 2.43 (s, 3 H, SMe), 1.82 (sextet, J = 7.0 Hz, 2 H, OCH$_2$*CH$_2$*CH$_3$), 1.04 (t, J = 7.0 Hz, 3 H, OCH$_2$CH$_2$*CH$_3$*) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]acetone): δ = 161.5, 132.8, 129.1, 125.4, 76.6, 24.1, 14.2, 10.6 ppm. ^{11}B NMR (64.2 MHz, [D$_6$]acetone): δ = 29.0 ppm. $C_{10}H_{15}BO_3S$ (226.10): calcd. C 53.12, H 6.69; found C 53.11, H 6.74.

4-Carboxy-3-(trifluoromethyl)phenylboronic acid (14): This compound was prepared as described for the preparation of **1** from 1-bromo-4-iodo-2-(trifluoromethyl)benzene (7.02 g, 20 mmol). The crude product was washed with water (2 × 10 mL), toluene (2 × 10 mL), and hexane (10 mL) to give the title compound as a white crystalline material. M.p. 253–254 °C (decomp.). Yield: 3.1 g (61%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.27 (s, 1 H, Ph), 8.18 (d, J = 8.0 Hz, 1 H, Ph), 7.85 (d, J = 8.0 Hz, 1 H, Ph), 7.7 (br., 1 H), 5.5 (br., 2 H) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]acetone): δ = 168.2, 138.6, 134.2 (q, J = 2.0 Hz), 132.6 (q, J = 5.5 Hz), 129.9, 127.7 (q, J = 31.0 Hz), 124.9 (q, J = 271 Hz) ppm. ^{11}B NMR (64.2 MHz, [D$_6$]acetone): δ = 27.9 ppm. $C_8H_6BF_3O_4 \cdot H_2O$ (255.96): calcd. C 38.14, H 3.20; found C 37.73, H 3.57.

2-(3′-Carboxy-5′-fluorophenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (15): This compound was prepared as described for the preparation of **5** from 1,3-dibromo-5-fluorobenzene (12.7 g, 50 mmol) except a slightly higher temperature (–50 °C) was applied to perform the lithiation of the "ate" complex. The crude product was washed with water (3 × 10 mL) and hexane (10 mL) to give the title compound as pale yellow crystals. M.p. 212–215 °C. Yield: 6.1 g (46%). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.34 (d, J = 1.0 Hz, 1 H, Ph), 7.86 (ddd, J = 9.0, 2.5, 1.0 Hz, 1 H, Ph), 7.73 (dd, J = 9.0, 2.5 Hz, 1 H, Ph), 1.37 (s, 12 H, Ph) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$): δ = 170.9, 162.3 (d, J = 247 Hz), 138.2 (br.), 132.1 (d, J = 2.5 Hz), 130.9 (d, J = 7.0 Hz), 126.6 (d, J = 20.0 Hz), 119.5 (d, J = 23.0 Hz), 84.5, 24.8 ppm. ^{11}B NMR (64.2 MHz, CDCl$_3$): δ = 25.6 ppm. $C_{13}H_{16}BFO_4$ (266.08): calcd. C 58.68, H 6.06; found C 58.46, H 6.06.

3-Bromo-5-carboxyphenylboronic acid (16): This compound was prepared as described for the preparation of **5** from 1,3,5-tribromobenzene (9.45 g, 30 mmol) except that *n*BuLi was added to a stirred slurry of the substrate in Et$_2$O. The crude product was washed with water (3 × 10 mL) and toluene (2 × 5 mL) to give the title compound as a white crystalline material. M.p. 260–263 °C. Yield: 6.5 g (82%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.48 (t, J = 1.0 Hz, 1 H, Ph), 8.20 (dd, J = 2.0, 1.0 Hz, 1 H, Ph), 8.17 (dd, J = 2.0, 1.0 Hz, 1 H, Ph), 7.61 [br., 2 H, B(OH)$_2$] ppm. ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]acetone): δ = 166.6, 141.8, 134.8, 134.6, 133.0, 122.6 ppm. ^{11}B NMR (64.2 MHz, [D$_6$]acetone): δ = 28.0 ppm. $C_7H_6BBrO_4 \cdot H_2O$ (262.853): calcd. C 31.99, H 3.07; found C 31.57, H 3.57.

2-[3′-Bromo-5′-(*tert*-butylaminocarbonyl)phenyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (17): This compound was prepared as described for the preparation of **16** by using PinBOMe for the boronation. The crude product was washed with water (3 × 10 mL) and recrystallized from hexane (30 mL) to give the title compound as a white powder. M.p. 217–220 °C. Yield: 6.3 g (55%). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.72 (dd, J = 7.5, 1.0 Hz, 1 H, Ph), 7.64 (dd, J = 7.5, 6.0 Hz, 1 H, Ph), 7.53 (dd, J = 9.0, 1.0 Hz, 1 H, Ph) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$): δ = 165.4, 139.9, 137.3, 133.2, 130.4, 122.8, 84.5, 51.9, 28.8, 24.8 ppm. ^{11}B NMR (64.2 MHz, CDCl$_3$): δ = 25.5 ppm. $C_{17}H_{25}BBrNO_3$ (382.11): calcd. C 53.44, H 6.59, N 3.67; found C 53.69, H 6.66, N 3.81.

3-Carboxy-5-methoxyphenylboronic acid (18): This compound was prepared as described for the preparation of **8** from 1,3-dibromo-5-methoxybenzene (5.32 g, 20 mmol) except a higher temperature (–15 °C) was applied to perform the lithiation of the "ate" complex. The crude product was washed with water (3 × 10 mL) and toluene (2 × 5 mL) to give a mixture containing the title compound as a minor component (ca. 15%) and acid **19** as the major product. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.15 (t, J = 1.5 Hz, 1 H, Ph), 7.66 (dd, J = 2.5, 1.0 Hz, 1 H, Ph), 7.59 (dd, J = 2.5, 1.5 Hz, 1 H, Ph), 3.86 (s, 3 H, OMe) ppm.

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