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Synthesis and Transformations of Functionalized Benzosiloxaboroles

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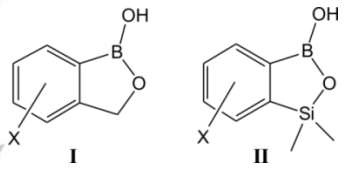
Abstract: The synthesis and characterization of a series of fluorinated benzosiloxaboroles bearing the synthetically useful formyl and cyano groups is reported. These compounds have been obtained by multistep syntheses starting with simple halogenated benzenes. The general synthetic protocol was based on the generation *ortho*-boronated aryldimethylsilanes which undergo dehydrogenative cyclization upon hydrolytic workup due to the activation of the Si–H bond by the adjacent boronic group. In some cases the synergy of adjacent boron- and silicon-based functionalities resulted in an unexpected hydrosilylation of CHO group under mild aqueous conditions. The reduction of a benzosiloxaborole derivative bearing the formyl at the ortho position with respect to the boron atom resulted in the structural transformation reflecting the higher stability of the carboxaborole heterocycle with respect to its silicon counterpart. Thus, a unique heterocyclic system featuring a central 10-membered ring comprising two borasiloxane linkages was isolated.

Introduction

Benzoxaboroles (**Chart 1, I**) are a group of boracyclic compounds known for 70 years.[1] However, they have attracted a renewed and considerable attention only in the last decade. This is mainly due to the discovery of potent antimicrobial activity of functionalized derivatives,[2,3] amply demonstrated by the recent approval of Tavaborole (trade name Kerydin),[4] for the treatment of onychomycosis - a fungal infection of the nail and nail bed. Mechanistic studies on the interaction of benzoxaboroles with biomolecules allowed for a rational design of other systems, that are currently under clinical trials.[5] Importantly, benzoxaboroles are stronger Lewis acids than corresponding arylboronic acids,[6] which is beneficial for the solubility in water at neutral pH. In general, this is also in line with their higher affinity and specificity for binding biological relevant molecules bearing 1,2-diol moiety such as saccharides, nucleosides and catechol derivatives (e.g., dopamine), which was exploited for sensing applications.[7] The importance and potential wide applicability of benzoxaboroles has prompted us to develop the synthetic routes to their analogues: pyridoxaboroles[8] and benzosiloxaboroles (**Scheme 1, II**).[9] The latter heterocycles can be defined as silicon analogues of benzoxaboroles and can be conveniently obtained by a facile intramolecular dehydrogenative condensation of arylboronic acids bearing a $SiHR_2$ group at the *ortho* position in the presence of water. This is due to the activation of the Si–H bond in arylsilanes by the adjacent boronic group.[10] In our search for novel functionalized benzosiloxaboroles as potential antimicrobial agents we have undertaken the synthesis of derivatives bearing formyl or cyano groups attached at various positions of the benzene ring. These studies resulted also in the discovery that the activation of Si–H bond by the boronic group enables hydrosilylation[11] of the formyl group under mild aqueous conditions.



Scheme 1. General structures of benzoxaborole and benzosiloxaborole.

Results and Discussion

Synthesis of formyl-substituted benzosiloxaboroles.

Our initial goal was to synthesize a series of formyl-substituted benzosiloxaboroles. The general synthetic approach to these compounds consisted of several steps (**Scheme 2**). In the first one the starting polyhalogenated benzenes were converted into corresponding benzaldehydes **1a-e** via Br/Li exchange (**1a**, **1b**, **1d**) or deprotonative lithiation (**1c**, **1e**) followed by the addition of DMF and hydrolysis. Obtained products were protected with $HC(OMe)_3$/MeOH/cat. H_2SO_4 to give the appropriate dimethyl acetals **2a-e**. The next step involved their deprotonative lithiation with LDA followed by the addition of $Me_2Si(H)Cl$ resulting in the introduction of the dimethylsilyl group (**3a-e**). In all cases the reaction occurred regioselectively at the position between fluorine and bromine atoms in agreement with the cumulated *ortho*-acidifying effect of two halogen substituents.[12] Having silylated acetals **3a-3e** in hand, we have embarked on their conversion into respective benzosiloxaboroles. Some optimization of reaction conditions was performed. Thus, the Br/Li exchange was accomplished with *t*-BuLi in Et_2O at –100 °C followed by trapping a generated aryllithium intermediate with $B(OMe)_3$ and hydrolysis with dilute aqueous H_2SO_4. It was proposed that the formation of the siloxaborole heterocycle relies on the activation of the Si–H bond due to the interaction of H atom with the adjacent boron atom.[9,10] Corresponding

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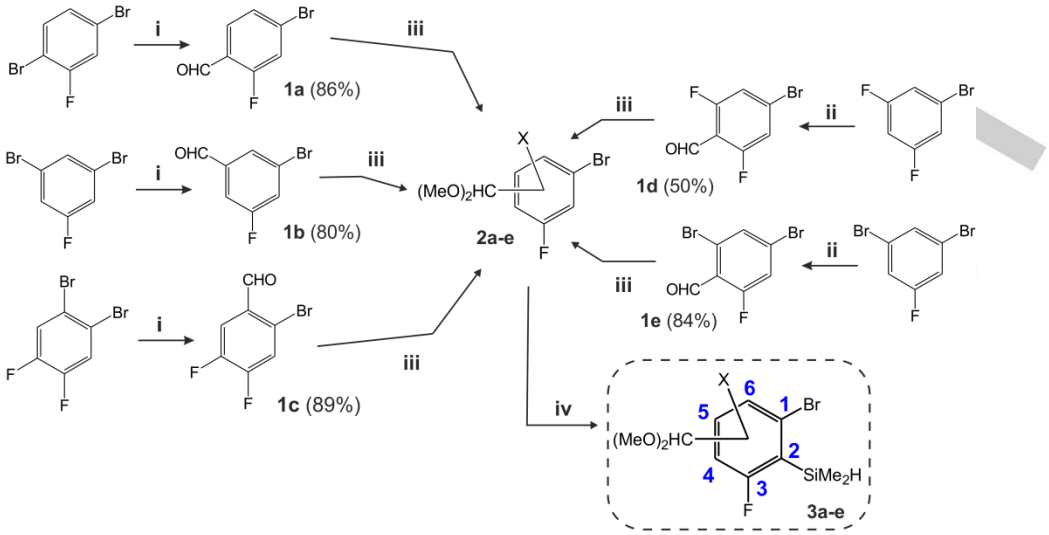
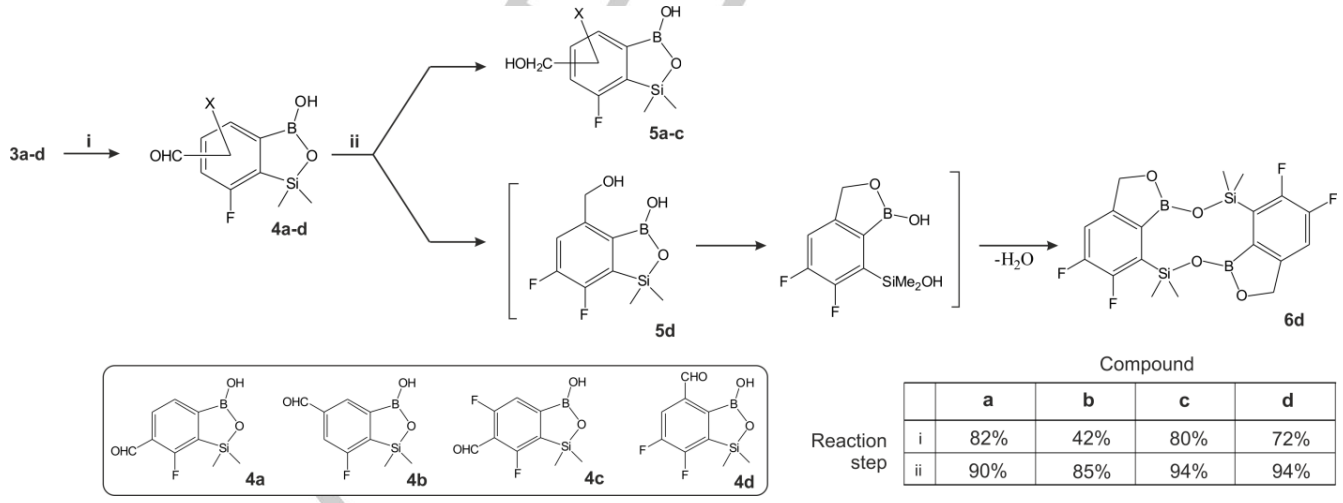


Position:	3a	3b	3c	3d	3e
4	$CH(OMe)_2$	H	$CH(OMe)_2$	F	$CH(OMe)_2$
5	H	$CH(OMe)_2$	F	H	Br
6	H	H	H	$CH(OMe)_2$	H
iii	95%	96%	93%	91%	95%
iv	85%	82%	88%	90%	83%

Substitution pattern

Yield

Scheme 2. Synthesis of silylated acetals **3a-3e**. Reaction conditions – i: (1) *n*-BuLi, Et_2O, -78 °C, (2) DMF, -78 °C, (3) H_3O^+; ii: (1) LDA, THF, -78 °C, (2) DMF, -78 °C, (3) H_3O^+; iii: $HC(OMe)_3$, MeOH, H_3O^+, reflux; iv: (1) LDA, THF, -78 °C, (2) $Me_2Si(H)Cl$, -78 °C.

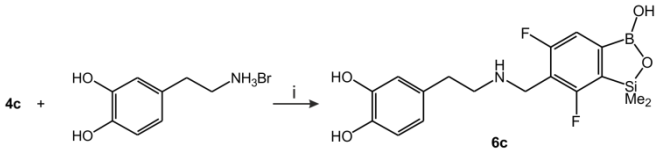


Reaction step	Compound a	b	c	d
i	82%	42%	80%	72%
ii	90%	85%	94%	94%

Scheme 3. Synthesis of formyl-substituted benzosiloxaboroles **4a-4d** and their subsequent reduction to respective hydroxymethyl derivatives **5a-5d**. Reaction conditions – i: (1) *t*-BuLi, Et_2O, -100 °C, (2) $B(OMe)_3$, -100 °C, (3) H_3O^+; ii: (1) $NaBH_4$, Et_2O, (2) H_3O^+.

benzosiloxaboroles **4a-4d** have been obtained in moderate to good yields as white microcrystalline solids soluble in common organic solvents (**Scheme 3**). Unexpectedly, the ^1H NMR spectrum of crude **4b** showed that it was contaminated with the byproduct **5b** resulting from reduction of the formyl group. The pure **4b** was isolated by crystallization from CH_2Cl_2/hexane.

Compounds **4a-4d** have been fully characterized by multinuclear NMR spectroscopy and HRMS analysis. The structural formulation of **4d** was also confirmed by the X-ray diffraction analysis (**Figure 1**). The synthetic utility of obtained formyl derivatives was demonstrated by an almost quantitative conversion of **4a-4c** to respective hydroxymethyl derivatives **5a-5c** using $NaBH_4$ in THF. Moreover, reductive amination was successfully employed for the conjugation of **4c** with dopamine (**Scheme 4**).



Scheme 4. Reaction conditions – i: (1) THF / Et_3N (2) $NaBH_4$ (3) H_3O^+.

The reduction of **4d** resulted in the structural reorganization and dimerization of an initial product **5d**. The presence of CH_2OH group at the ortho position with respect to the boron atom led to the cleavage of the siloxaborole heterocycle in favor of the formation of a carboxaborole ring. However, the liberated Me_2SiOH moiety undergoes condensation with the BOH group to give compound **6d** – a unique centrosymmetric molecule comprising a central 10-membered ring composed of two borosiloxane linkages and fused with two benzoxaborole units. The X-ray diffraction analysis of **6d** confirmed the formation of a centrosymmetric dimer with O1 oxygen atoms pointing toward the centre of a planar 10-membered heterocyclic ring (**Figure 2**). The ^{29}Si NMR spectrum of **6d** shows a signal at 2.28 ppm consistent with a significant upfield shift relative to **4d** ($\delta^{29}Si$ = 20.76 ppm) which may reflect the release of strain at the silicon atom.[9]

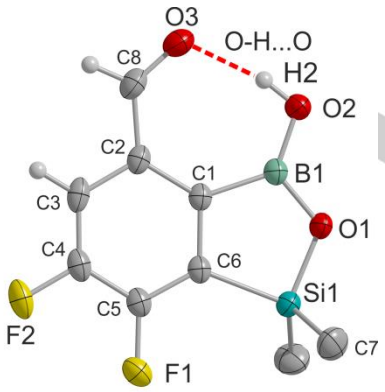


Figure 1. Crystal structure of **4d**. An intramolecular O–H…O hydrogen bond (red dashed line) is formed between the BOH and formyl groups. The hydrogen bonded centrosymmetric dimeric motif, typically found in the structures of benzoxaboroles,[2a,c] is not present in this case.

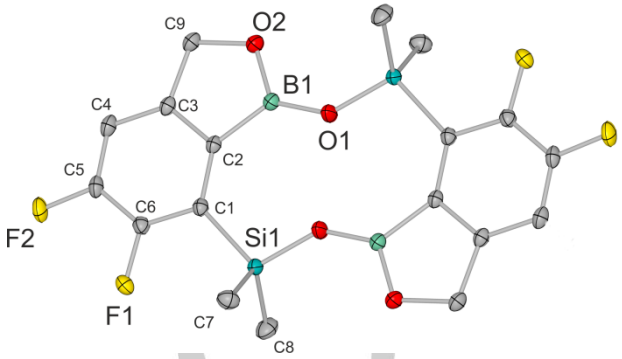
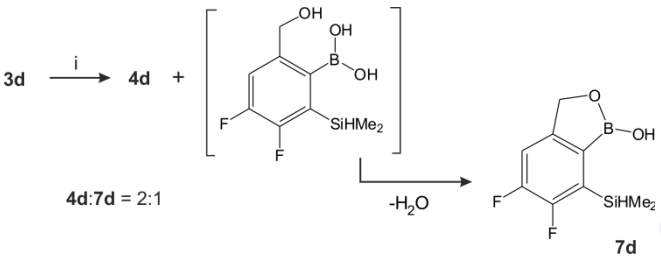


Figure 2. The crystal structure of **6d.**

Apparently, a specific mechanism accounting for the Si–H bond reactivity should be invoked for the observed reduction of the formyl group. First of all, the reduction must be preceded by the cleavage of dimethoxymethyl group. In this regard, the choice of solvent seems to be important for the reaction course. THF is much more hydrophilic than Et_2O and thus the concentration of water in this solvent is relatively high during hydrolysis. This facilitates hydrolytic cleavage of the $CH(OMe)_2$ group. In fact, when THF was added to a reaction mixture during the synthesis of **4d** prior to final hydrolysis, the mixture of products was obtained (**Scheme 5**). The major product **4d** was contaminated by a substantial amount of 7-(dimethylsilyl)-5,6-difluorobenzoxaborole **7d** (the ratio **4d/7d** was ca. 2:1). The formation of **7d** can be explained by an initial deprotection of the formyl group followed by an intermolecular hydride transfer from another molecule, which may still bear the $CH(OMe)_2$ functionality. However, the formation of **7d** could be suppressed by the addition of excess of propanal, which apparently acted as an effective hydride acceptor. The isolation of **7d** from the mixture with **4d** was accomplished by the addition of $NaBH_4$ in THF resulting in the conversion of **4d** to **6d**. Unlike **7d**, compound **6d** is essentially insoluble in a mixed solvent Et_2O/hexane (1:1) which enabled separation of these two compounds.



Scheme 5. Reaction conditions – i: (1) *t*-BuLi, THF, -100 °C, (2) $B(OMe)_3$, -100 °C, (3) H_3O^+. Note that the synthesis was performed in THF instead of Et_2O.

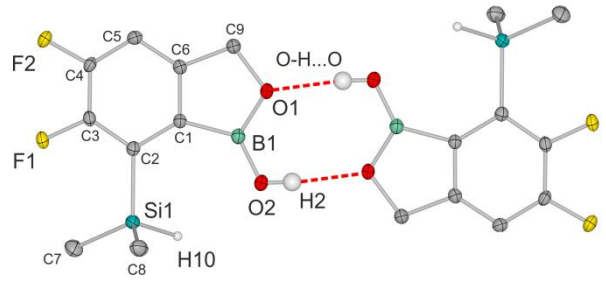
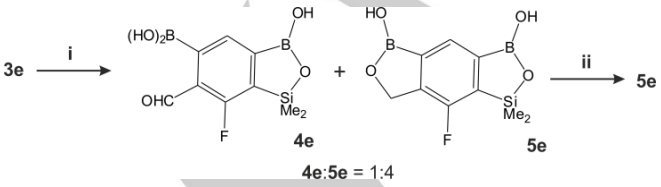


Figure 3. The crystal structure of **7d**. The formation of a centrosymmetric hydrogen-bonded dimer is presented.

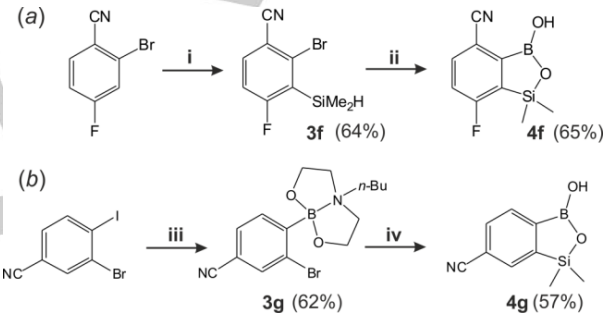
It is interesting to note that compound **7d** is relatively stable and does not eliminate dihydrogen readily. According to the DSC analysis **7d** melts at ca. 90 °C (Figure S61, ESI). Further heating is accompanied by its dehydration rather than dihydrogen elimination. This was confirmed by ^{1}H NMR spectrum which points to the formation of a dimeric anhydride featuring the B–O–B moiety and preserving Si(H)Me$_2$ group. It decomposes only at relatively high temperatures (> 200 °C). A relative inertness of the Si–H bond in **7d** is apparently due to a structural rigidity resulting from the incorporation of the boron atom into the five-membered carboxaborole ring. (**Figure 3**).

In addition, we have attempted to convert **3e** into 4-fluoro-5-formyl-6-(dihydroxyboryl)benzosiloxaborole **4e** by a double Br/Li exchange followed by boronation and hydrolysis. Both bromine atoms in **3e** were susceptible to the interconversion with an excess of *t*-BuLi in THF at –78 °C. The obtained dilithio reagent was treated with an excess of B(OMe)$_3$. Hydrolysis and subsequent workup afforded a mixture containing the expected product **4e** as a minor component (ca. 20%). The major product was the compound **5e** resulting from the reduction of the CHO group in **4e** and comprising CH$_2$OB linkage within the fused oxaborole ring. Addition of NaBH$_4$ to the mixture of **4e** and **5e** in THF resulted in the complete reduction of the former compound affording pure **5e** after aqueous acidic workup (**Scheme 6**). The formation of **5e** can be explained by the hydride transfer from the silicon atom to the formyl group. This is consistent with the lack of dihydrogen elimination, which typically occurs during the formation of a siloxaborole ring.[9]



Scheme 6. Synthesis of **5e**. Reaction conditions – i: (1) *t*-BuLi, THF, –78 °C, (2) B(OMe)$_3$, –100 °C, (3) H_3O^+; ii: (1) NaBH$_4$, THF (2) H_3O^+.

Cyano-substituted benzoxaboroles have been previously reported to exhibit a potent activity[5b,c] and therefore we decided to synthesize related benzosiloxaboroles **4f** and **4g** (**Scheme 7**). Specifically, the presence of a substituent at the 5-position in various benzoxaborole derivatives is often beneficial for their acitivity, and therefore we decided to obtain compound **4g**. In addition there are also various possibilities of transformations involving cyano groups, which can give rise to more extended systems. The synthesis of **4f** started with 2-bromo-4-fluorobenzonitrile, which was subjected to deprotonation with LDA followed by the addition of Me$_2$Si(H)Cl. The resulting silylated derivative **3f** was reacted with *t*-BuLi in THF at –100 °C to give corresponding aryllithium, which was trapped with B(OMe)$_3$. The synthesis of **4g** involved the generation of 2-(2′-bromo-4′-cyanophenyl)-6-butyl-1,3,6,2-dioxazaborocan **3g**, which was further subjected to Br/Li exchange reaction with *n*-BuLi at –100 °C followed by the addition of Me$_2$Si(H)Cl. The hydrolytic work-up afforded the expected benzosiloxaboroles **4f** and **4g**.



Scheme 7. Preparation of functionalized benzonitriles **3f–3g** and their use for the synthesis of respective benzosiloxaboroles. Reaction conditions – i: (1) LDA, THF, –78 °C, (2) Me$_2$Si(H)Cl, –78 °C, (3) H_3O^+; ii: (1) *t*-BuLi, THF, –100 °C, (2) B(OMe)$_3$, (3) H_3O^+; iii (1) *n*-BuLi, *in situ* B(O*i*Pr)$_3$, THF/Et$_2$O (1:1), -100 °C, (2) CH$_3$SiCl, –78 °C then (3) 40 °C, (4) *N*-butyldiethanolamine, Et$_2$O, r.t.; v: (1) *n*-BuLi, THF/Et$_2$O (1:1), –90 °C, (2) B(OMe)$_3$, (3) H_3O^+.

Conclusions

In a summary, fluorinated 1,3-dihydro-1,1-dimethyl-1,2,3-benzosiloxaboroles bearing formyl, hydroxymethyl and cyano groups have been prepared by multistep protocols starting with appropriate polyhalogenated benzenes. This work was stimulated by the recent results confirming potent antimicrobial properties of fluorinated benzosiloxaboroles.[9] It should be stressed that the presence of additional functional groups opens synthetic possibilities towards creating more extended systems as exemplified by the preparation of dopamine conjugate **6c**. Such studies are currently in progress in our research group. During our work we have found that the reduction of the formyl group may occur as a subsequent reaction during final hydrolysis. The reduction is obviously consistent with a decreased selectivity and lower yields of formyl-substituted benzosiloxaboroles. On the other hand, this indicates that the *ortho*-B(OH)$_2$ group is able to activate the adjacent Si(H)Me$_2$ group toward reduction of the formyl group. In the presence of water the reaction proceeds readily at room temperature. Since

the reported preliminary observations may have a significant synthetic potential, we have undertaken further comprehensive studies on the scope and selectivity of the observed boronic group-assisted hydrosilylation supported by theoretical studies on its plausible mechanism. Those results will be reported in due course.

Experimental Section

General comments. Solvents used for reactions were dried by heating to reflux with sodium/benzophenone and distilled under argon. Starting materials including various benzene derivatives, $Me_2(H)SiCl$, $B(OMe)_3$ were used as received without further purification. In the ^{13}C NMR spectra the resonances of boron-bound carbon atoms were not observed in most cases as a result of their broadening by a quadrupolar boron nucleus. ^{1}H, and ^{13}C NMR chemical shifts are given relative to TMS using residual solvent resonances. ^{11}B, ^{19}F and ^{29}Si NMR chemical shifts are given relative to $BF_3{\cdot}Et_2O$, $CFCl_3$, and TMS, respectively. The syntheses of **1a**,[13] **1c**,[14] **1d**,[15] **2a**,[16] and **2b**[17] were reported previously. However, published procedures lack experimental and analytical details and therefore we have decided to include a full information regarding synthetic protocols and characterization for the mentioned compounds. 3-bromo-4-iodobenzonitrile was synthesised according to previously reported protocol.[18]

Synthetic procedures.

4-Bromo-2-fluorobenzaldehyde (1a):[13] A solution of 1,4-dibromo-2-fluorobenzene (25.4 g, 0.1 mol) in Et_2O (100 mL) was added dropwise to the stirred solution of *n*-BuLi (10 M, 10 mL, 0.1 mol) in Et_2O (200 mL) at –100 °C during 30 min. The mixture was stirred for 15 min followed by a dropwise addition of a solution of anhydrous DMF (8.0 g, 0.11 mol) in Et_2O (20 mL). The resulting pale yellow solution was stirred for 15 min below –90 °C and then it was allowed to warm to ca. –50 °C. 1 M aqueous H_2SO_4 (120 mL) was added with stirring. The organic phase was separated. The water phase was washed with Et_2O (2 × 50 mL). The combined organic phase was dried over anhydrous $MgSO_4$. It was filtered and evaporated under reduced pressure to leave a pale yellow solid. It was recrystallized by dissolving it in warm hexane (100 mL) followed by cooling the obtained solution to ca. -50 °C. The product was obtained as colorless crystals, m.p. 60-63 °C. Yield 17.5 g (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.76–7.72 (m, 1H), 7.45–7.41 (m, 1H), 7.39 (dd, *J* = 9.7, 1.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.03 (d, *J* = 6.2 Hz), 164.10 (d, *J* = 262.9 Hz), 130.17 (d, *J* = 9.9 Hz), 129.62 (d, *J* = 2.6 Hz), 128.39 (d, *J* = 3.8 Hz), 123.06 (d, *J* = 8.3 Hz), 120.24 (d, *J* = 23.7 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -119.79 (dd, *J* = 9.7, 7.5 Hz) ppm. Anal. Calcd for C_7H_4BrFO (203.01): C, 41.41; H, 1.99. Found: C, 41.65, H, 1.88.

3-Bromo-5-fluorobenzaldehyde (1b): This compound was obtained from 1,3-dibromo-5-fluorobenzene using the procedure described for **1a.** However, the reactions were performed at -78 °C. The product was obtained as a pale yellow solid, m.p. 40-42 °C. Yield 16.1 g (80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 – 9.84 (m, 1H, CHO), 7.82–7.74 (m, 1H, Ph), 7.58 – 7.42 (m, 2H, Ph) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.55 (t, *J* = 7.9 Hz) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 189.20 (d, *J* = 2.3 Hz), 162.81 (d, *J* = 254.4 Hz), 139.10 (d, *J* = 6.5 Hz), 128.87 (d, *J* = 3.2 Hz), 124.80 (d, *J* = 24.9 Hz), 123.57 (d, *J* = 8.8 Hz), 114.56 (d, *J* = 21.9 Hz) ppm . Anal. Calcd for C_7H_4BrFO (203.01): C, 41.41; H, 1.99. Found: C, 41.27, H, 2.06.

4-Bromo-2,6-difluorobenzaldehyde (1c):[14] The solution of LDA was prepared by the addition of diisopropylamine (10.5 g, 0.104 mol) to a solution of *n*-BuLi (10 M, 10 mL, 0,1 mol) in THF (150 mL) at -78 °C. Then a solution of 1-dibromo-3,5-difluorobenzene (19.3 g, 0,1 mol) in Et_2O (50 mL) was added dropwise at –80 °C during 30 min. The mixture was stirred for 15 min followed by a dropwise addition of a solution of anhydrous DMF (8.0 g, 0.11 mol) in Et_2O (20 mL). The resulting pale yellow solution was stirred for 15 min at –78 °C and then it was allowed to warm to ca. –50 °C. 1 M aqueous H_2SO_4 (180 mL) was added with stirring. Further workup was carried out as described for **1a**. The product was obtained as a colorless crystalline material, m.p. 75-77 °C. Yield 19.7 g (89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (t, *J* = 1.0 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.43 (t, *J* = 4.3 Hz), 162.75 (dd, *J* = 267.0, 6.8 Hz), 129.36 (t, *J* = 13.0 Hz), 116.76–116.45 (m), 113.18 (t, *J* = 11.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.27 (d, *J* = 8.1 Hz). Anal. Calcd for $C_7H_3BrF_2O$ (221.00): C, 38.04; H, 1.37. Found: C, 37.95; H, 1.34.

2-Bromo-4,5-difluorobenzaldehyde (1d):[15] This compound was obtained from 1,2-dibromo-4,5-fluorobenzene using the procedure described for **1a.** However, the reactions were performed at -110 °C and THF was used as a solvent for the preparation of a solution of *n*-BuLi. The product was isolated from the crude reaction mixture by fractional distillation under reduced pressure, b.p. 62-66 °C (1 Tr). Crystallization from hexane (50 mL) afforded a white solid, m.p. 48-50 °C. Yield 11.1 g (50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (d, *J* = 3.1 Hz, 1H), 7.78 (dd, *J* = 10.0, 8.3 Hz, 1H), 7.53 (dd, *J* = 9.1, 6.7 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.26 (t, *J* = 1.1 Hz), 153.92 (dd, *J* = 263.5, 14.0 Hz), 150.27 (dd, *J* = 253.6, 12.9 Hz), 130.57 (t, *J* = 4.0 Hz), 122.85 (d, *J* = 20.6 Hz), 121.37 (dd, *J* = 8.1, 3.5 Hz), 118.26 (dd, *J* = 19.0, 2.2 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -124.64 (dt, *J* = 20.6, 8.7 Hz), -135.61 – -135.73 (m) ppm. Anal. Calcd for $C_7H_3BrF_2O$ (221.00): C, 38.04; H, 1.37. Found: C, 37.82; H, 1.27.

2,4-Dibromo-6-fluorobenzaldehyde (1e): This compound was obtained from 1,3-dibromo-5-fluorobenzene using the procedure described for **1c.** The product was obtained as a pale beige solid, m.p. 56-59 °C. Yield 23.7 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.28–10.27 (m, 1H), 7.67 (m 1H), 7.37–7.32 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.31 (d, *J* = 2.3 Hz), 162.60 (d, *J* = 270.2 Hz), 132.86 (d, *J* = 3.9 Hz), 128.79 (d, *J* = 11.4 Hz), 125.80 (d, *J* = 3.7 Hz), 121.68 (d, *J* = 9.2 Hz), 120.12 (d, *J* = 24.6 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.48 (d, *J* = 9.7 Hz) ppm. Anal. Calcd for $C_7H_3Br_2FO$ (281.90): C, 29.82; H, 1.07. Found: C, 29.70; H, 1.14.

1-Bromo-4-(dimethoxymethyl)-3-fluorobenzene (2a):[16] The mixture of 4-bromo-2-fluorobenzaldehyde **1a** (10.2 g, 50 mmol), trimethyl orthoformate (7.0 g, 66 mmol) and methanol (5 mL) to which 1 drop of conc. H_2SO_4 was added, was refluxed for 1 hr at 60 °C (bath temp.). After neutralization with sodium methoxide (25wt% solution in MeOH) and concentration, the residue was distilled in vacuo to give the title compound as a colorless liquid, b.p. 65–68 °C (1 Tr). Yield 11.8 g (95%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.9 Hz, 1H), 7.29 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.23 (dd, *J* = 9.6, 1.7 Hz, 1H), 5.54 (s, 1H), 3.34 (s, 6H) ppm ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.26 (d, *J* = 253.3 Hz), 129.51 (d, *J* = 4.5 Hz), 127.34 (d, *J* = 3.6 Hz), 124.76 (d, *J* = 12.7 Hz), 122.89 (d, *J* = 9.6 Hz), 119.20 (d, *J* = 24.7 Hz), 98.26 (d, *J* = 2.6 Hz), 53.61 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.54 (m) ppm. Anal. Calcd for $C_9H_{10}BrFO_2$ (249.08): C, 43.40; H, 4.05. Found: C, 43.15; H, 4.14.

1-Bromo-3-(dimethoxymethyl)-5-fluorobenzene (2b):[17] This compound, b.p. 62–66 °C (1 Tr), was obtained as described for **2a** starting with **1b**. Yield 12.0 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 0.4 Hz, 1H), 7.17 (ddd, *J* = 8.0, 3.0, 1.1 Hz, 1H), 7.11 (ddd, *J* = 9.2,

1.2, 0.6 Hz, 1H), 5.33 (s, 1H), 3.29 (s, 6H). ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.64 (d, *J* = 250.6 Hz), 142.42 (d, *J* = 7.3 Hz), 125.91 (d, *J* = 3.1 Hz), 122.49 (d, *J* = 9.5 Hz), 119.01 (d, *J* = 24.5 Hz), 112.98 (d, *J* = 22.4 Hz), 101.17 (d, *J* = 2.2 Hz), 52.56 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.65 (t, *J* = 8.6 Hz) ppm. Anal. Calcd for $C_9H_{10}BrFO_2$ (249.08): C, 43.40; H, 4.05. Found: C, 43.19; H, 3.90.

1-Bromo-3,5-difluoro-4-(dimethoxymethyl)benzene (2c): This compound, b.p. 60–63 °C (1 Tr), was obtained as described for **2a** starting with **1c**. Yield 12.4 g (93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.07 (m, 2H), 5.56 (s, 1H), 3.46 (t, *J* = 0.4 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.75 (dd, *J* = 256.0, 9.0 Hz), 122.46 (t, *J* = 12.6 Hz), 115.93–115.53 (m), 113.79 (t, *J* = 16.3 Hz), 98.97 (t, *J* = 2.7 Hz), 54.94 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.49 – -111.56 (m) ppm. Anal. Calcd for $C_9H_9BrF_2O_2$ (267.07): C, 40.48; H, 3.40. Found: C, 40.25; H, 3.23.

1-Bromo-4,5-difluoro-2-(dimethoxymethyl)benzene (2d): This compound, b.p. 64–68 °C (1 Tr), was obtained as described for **2a** starting with **1d**. Yield 12.1 g (91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 11.1, 8.5 Hz, 1H), 7.38 (dd, *J* = 9.5, 7.2 Hz, 1H), 5.46–5.44 (m, 1H), 3.36 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.98 (dd, *J* = 254.0, 13.7 Hz), 149.45 (dd, *J* = 249.5, 12.3 Hz), 134.15 (dd, *J* = 4.8, 3.9 Hz), 121.61 (d, *J* = 20.1 Hz), 117.29 (dd, *J* = 19.7, 0.9 Hz), 116.03 (dd, *J* = 7.4, 3.7 Hz), 101.74, 53.67 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -134.84 – -134.98 (m), -138.00 (dddd, *J* = 21.1, 11.1, 7.3, 1.1 Hz) ppm. Anal. Calcd for $C_9H_9BrF_2O_2$ (267.07): C, 40.48; H, 3.40. Found: C, 40.37; H, 3.43.

1,5-Dibromo-2-(dimethoxymethyl)-3-fluorobenzene (2e): This compound, b.p. 93–96 °C (1 Tr), was obtained as described for **2a** starting with **1e**. Yield 15.4 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (m, 1H), 7.20 (dd, *J* = 9.9, 1.9 Hz, 1H), 5.60 (d, *J* = 1.2 Hz, 1H), 3.42 (s, 6H) ppm.^{13}C NMR (101 MHz, $CDCl_3$) δ 160.91 (d, *J* = 260.9 Hz), 131.54 (d, *J* = 3.9 Hz), 124.53 (d, *J* = 14.5 Hz), 123.85 (d, *J* = 6.4 Hz), 122.92 (d, *J* = 10.9 Hz), 119.64 (d, *J* = 26.4 Hz), 104.20, 55.44 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.84 (d, *J* = 9.9 Hz) ppm. Anal. Calcd for $C_9H_9Br_2FO_2$ (325.90): C, 32.96; H, 2.77. Found: C, 32.77; H, 2.70.

1-Bromo-4-(dimethoxymethyl)-2-(dimethylsilyl)-3-fluorobenzene (3a): A solution of **2a** (7.5 g, 30 mmol) in Et_2O (20 mL) was added at –75 °C to a stirred solution of LDA, freshly prepared from diisopropylamine (3.2 g, 32 mmol) and *n*BuLi (10 M, 3 mL, 30 mmol) in THF (50 mL). After ca 30 min stirring at ca –75 °C $Me_2Si(H)Cl$ (3.0 g, 31.5 mmol) was added slowly. The mixture was stirred for 30 min at –75 °C and was then allowed to warm to the room temperature. Solvents were removed under reduced pressure and the residue was dissolved in hexane. The mixture was filtered under argon through a Celite pad to remove LiCl byproduct. The filtrate was concentrated and the residue was subjected to a fractional distillation under reduced pressure. The product was obtained as a colorless liquid, b.p. 102-105 °C (1 Tr). Yield 7.8 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 5.52 (s, 1H), 4.79–4.71 (m, 1H), 3.36 (s, 6H), 0.45 (dd, *J* = 3.9, 1.8 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.52 (d, *J* = 248.0 Hz), 130.74 (d, *J* = 12.4 Hz), 130.62 (d, *J* = 5.2 Hz), 128.86 (d, *J* = 3.5 Hz), 125.95 (d, *J* = 32.8 Hz), 124.25 (d, *J* = 17.4 Hz), 98.60 (d, *J* = 3.8 Hz), 53.78, -3.02 (d, *J* = 4.4 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -101.77 ppm. ^{29}Si{^{1}H} NMR (99 MHz, $CDCl_3$) δ -19.17 ppm. Anal. Calcd for $C_{11}H_{16}BrFO_2Si$ (307.23): C, 43.00; H, 5.25. Found: C, 43.12; H, 5.33.

1-Bromo-5-(dimethoxymethyl)-2-(dimethylsilyl)-3-fluorobenzene (3b): This compound, b.p. 105–108 °C (1 Tr), was obtained as described for **3a** starting with **2b**. Yield 7.6 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.06 (d, *J* = 9.4 Hz, 1H), 4.79–4.69 (m, 1H), 3.32 (s, 6H), 0.46–0.43 (m, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.08 (d, *J* = 245.8 Hz), 143.33 (d, *J* = 8.5 Hz), 130.21 (d, *J* = 12.2 Hz), 127.20 (d, *J* = 3.0 Hz), 112.54 (d, *J* = 28.4 Hz), 101.11 (d, *J* = 2.3 Hz), 52.62, -3.25 (d, *J* = 4.1 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -95.43 (m) ppm. ^{29}Si{^{1}H} NMR (99 MHz, $CDCl_3$) δ -19.42 ppm. Anal. Calcd for $C_{11}H_{16}BrFO_2Si$ (307.23): C, 43.00; H, 5.25. Found: C, 42.94; H, 5.40.

1-Bromo-3,5-difluoro-4-(dimethoxymethyl)-2-(dimethylsilyl)benzene (3c): This compound, b.p. 102–106 °C (1 Tr), was obtained as described for **3a** starting with **2c**. Yield 8.6 g (88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 9.5, 1.7 Hz, 1H), 5.54 (s, 1H), 4.79–4.70 (m, 1H), 3.47 (s, 6H), 0.45 (dd, *J* = 3.9, 1.9 Hz, 6H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.95 (dd, *J* = 250.2, 8.6 Hz), 161.58 (dd, *J* = 257.4, 9.9 Hz), 130.33 (dd *J* = 15.9, 12.3 Hz), 122.07 (d, *J* = 34.6 Hz), 117.28 (dd, *J* = 24.9, 3.1 Hz), 113.24 (dd, *J* = 21.3, 15.1 Hz), 99.37, 55.15 (d, *J* = 4.3 Hz), -3.26 (d, *J* = 4.3 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -96.50 – -96.62 (m), -110.84 – -110.95 (m) ppm. ^{29}Si{^{1}H} NMR (99 MHz, $CDCl_3$) δ -18.88 ppm. Anal. Calcd for $C_{11}H_{15}BrF_2O_2Si$ (325.22): C, 40.62; H, 4.65. Found: C, 40.47; H 4.52.

2-Bromo-4,5-difluoro-1-(dimethoxymethyl)-3-(dimethylsilyl)benzene (3d): This compound, b.p. 107–110 °C (1 Tr), was obtained as described for **3a** starting with **2d**. Yield 8.7 g (90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 10.8, 8.8 Hz, 1H), 5.50 (d, *J* = 1.2 Hz, 1H), 4.84–4.74 (m, 1H), 3.38 (s, 6H), 0.48 (dd, *J* = 3.9, 1.9 Hz, 6H) ppm. ^{13}C NMR (101 MHz $CDCl_3$) δ 154.33 (dd, *J* = 247.6, 12.3 Hz), 149.47 (dd, *J* = 251.7, 16.9 Hz) 134.81 (t, *J* = 4.0 Hz), 129.40 (dd, *J* = 27.2, 1.9 Hz), 123.61 (dd, *J* = 10.0, 3.8 Hz), 118.44 (dd, *J* = 19.8, 1.6 Hz), 102.72, 54.20, -3.06 (d, *J* = 4.6 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -120.68 – -120.88 (m), -138.48 (dd, *J* = 23.1, 10.8 Hz) ppm. ^{29}Si{^{1}H} NMR (99 MHz, $CDCl_3$) δ -18.85 (*J* = 2.6 Hz) ppm. Anal. Calcd for $C_{11}H_{15}BrF_2O_2Si$ (325.22): C, 40.62; H, 4.65. Found: C, 40.70; H, 4.43.

1,5-Dibromo-2-(dimethoxymethyl)-4-(dimethylsilyl)-3-fluorobenzene (3e): This compound, b.p. 134–137 °C (1 Tr), was obtained as described for **3a** starting with **2e**. Yield 9.6 g (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.4 Hz, 1H), 5.61 (d, *J* = 1.4 Hz, 1H), 4.75–4.67 (m, 1H), 3.46 (s, 6H), 0.43 (dd, *J* = 3.9, 1.9 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.08 (d, *J* = 255.0 Hz), 132.96 (d, *J* = 3.8 Hz), 130.77 (d, *J* = 14.2 Hz), 125.22 (d, *J* = 7.4 Hz), 123.97 (d, *J* = 19.8 Hz), 104.63, 55.90, -3.20 (d, *J* = 4.6 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.09 ppm. ^{29}Si{^{1}H} NMR (99 MHz, $CDCl_3$) δ -18.30 ppm. Anal. Calcd for $C_{11}H_{15}Br_2FO_2Si$ (386.13): C, 34.22; H, 3.92. Found: C, 34.11; H, 3.76.

2-Bromo-4-fluoro-3-(dimethylsilyl)benzonitrile (**3f**): This compound, b.p. 95-97 °C (1 Tr), was obtained as described for **3a** starting with 2-bromo-4-fluorobenzonitrile. LTMP freshly prepared from 2,2,6,6-tetramethylpiperidine and *n*-BuLi, was used as lithiating agent instead of LDA. Yield 8.3 g (62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.6, 5.8 Hz, 1H, Ph), 7.15–7.06 (m, 1H, Ph), 4.90–4.69 (m, 1H, $SiMe_2H$), 0.50 (dd, *J* = 3.9, 1.9 Hz, 6H, $SiMe_2H$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.72 (d, *J* = 255.3 Hz), 136.92 (d, *J* = 10.9 Hz), 133.66 (d, *J* = 13.2 Hz) 129.09 (d, *J* = 33.3 Hz), 117.12, 115.16 (d, *J* = 28.6 Hz), 113.31 (d, *J* = 3.8 Hz), -3.22 (d, *J* = 4.4 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.19 – -85.30 (m) ppm. ^{29}Si{^{1}H} NMR (99 MHz, $CDCl_3$) δ -19.22 ppm. Anal. Calcd for $C_9H_9BrFNSi$ (258.16): C, 41.87; H, 3.52. Found: C, 42.10; H, 3.40.

6-Butyl-2-(2'-bromo-4'-cyanophenyl)-(N-B)-1,3,6,2-dioxazaborocan (3g): A *n*-BuLi solution in hexane (2.5 M, 20.0 mL, 0.050 mol) was slowly added to a stirred solution of 3-bromo-4-iodobenzonitrile[18] (15.06 g, 0.049 mol) and $B(OiPr)_3$ (11.5 mL, 0.050 mol) in THF/Et_2O (2:1, 300 mL) at -100 °C. After 30 min of stirring, the mixture was slowly warmed to -78 °C and Me_3SiCl (22.4 mL, 0.176 mol) was added dropwise. The reaction

was warmed to 40 °C, stirred for 5 h and cooled to room temperature. The precipitation of white solid (LiCl) was observed. It was removed by filtration under argon, and the solvents were evaporated from the filtrate to give a crude diisopropoxyboryl ester which was used for the next step without purification. Thus, it was dissolved in Et_2O (70 mL) followed by the addition of *N*-butyldiethanolamine (8.2 mL, 0.049 mol). The resulting dark-red solution was concentrated. The precipitated product was washed with Et_2O (ca. 40 mL) and filtered under argon to give the title compound as a white powder. Yield: 11.2 g (65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.6 Hz, 1H), 4.29 – 4.09 (m, 4H), 3.40 – 3.24 (m, 2H), 3.19 – 3.03 (m, 2H), 2.73 – 2.51 (m, 2H), 1.71 – 1.50 (m, 2H), 1.31 – 1.12 (m, 3H), 0.87 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.33, 136.17, 129.51, 129.20, 118.02, 112.83, 63.18, 58.61, 58.57, 26.92, 20.12, 13.69 ppm. ^{11}B NMR (96 MHz, $CDCl_3$) δ 11.63 ppm. Anal. Calcd for $C_{15}H_{20}BBrN_2O_2$ (350.08): C, 51.32; H, 3.74; N, 7.89. Found: C, 51.37; H, 3.79; N, 7.81. The product hydrolyzes rapidly when exposed to moist air and should be stored and handled under argon.

4-Fluoro-5-formyl-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (4a): A solution of **3a** (3.07 g, 0.01 mol) in Et_2O (15 mL) was added dropwise to a solution of *t*-BuLi (1.7 M in pentane, 12 mL, 0.02 mol) in Et_2O (30 mL) and cooled to –100 °C. After 30 min of stirring at –100 °C, $B(OMe)_3$ (2.2 mL, 0.02 mol) was added and the reaction mixture was warmed to –30 °C, quenched with 1.5 M aq. H_2SO_4 to reach the pH = 2-3 and stirred at room temperature until evolution of H_2 ceased. The aqueous phase was separated followed by the extraction with Et_2O (2 × 20 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure. Water acidified with a few drops of conc. aqueous HCl was added and the mixture was heated at ca. 60 °C under reduced pressure. The white solid precipitated during the evaporation. It was filtered, washed with CH_2Cl_2 (5 mL), hexane (2 × 5 mL) and dried *in vacuo* to give **4a**, m.p. 164–167 °C. Yield 1.85 g (82%). ^{1}H NMR (400 MHz, acetone-d_6) δ 10.38 (s, 1H), 7.94 (dd, *J* = 7.3, 6.7 Hz, 1H), 7.77 (ddd, *J* = 7.3, 1.6, 0.6 Hz, 1H), 0.49 (s, 6H) ppm. ^{13}C NMR (101 MHz, acetone-d_6) δ 188.09 (d, *J* = 5.1 Hz), 166.55 (d, *J* = 255.9 Hz), 137.57 (d, *J* = 31.2 Hz), 131.81, 128.70 (d, *J* = 3.5 Hz), 125.79 (d, *J* = 11.1 Hz), -0.74 ppm. ^{11}B NMR (96 MHz, $CDCl_3$) δ 29.3 ppm. ^{19}F NMR (376 MHz, acetone-d_6) δ -114.31 (dd, *J* = 6.7, 1.6 Hz) ppm. ^{29}Si{^{1}H} NMR (99 MHz, acetone-d_6) δ 19.94 ppm. HRMS (EI): calcd. for $C_9H_{10}BFO_3Si$ $[M]^+$ 224.0476; found 224.0477.

4-Fluoro-6-formyl-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (4b): This compound was obtained as described for **4a** starting with **3b**. White powder, m.p. 102–105 °C. Yield 0.95 g (42%). ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 10.09 (d, *J* = 2.0 Hz, 1H), 8.12 (s, 1H), 7.62 (dd, *J* = 7.0, 0.9 Hz, 1H), 0.56 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.62, 164.96 (d, *J* = 248.2 Hz), 144.5 (broad), 142.86 (d, *J* = 32.0 Hz), 140.78 (d, *J* = 5.0 Hz), 129.64, 116.36 (d, *J* = 25.4 Hz), -0.95 ppm. ^{11}B NMR (96 MHz, $CDCl_3$) δ 29.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ -103.02 ppm. ^{29}Si{^{1}H} NMR (99 MHz, $CDCl_3$) δ 22.00 ppm. HRMS (EI): calcd. for $C_9H_{10}BFO_3Si$ $[M]^+$ 224.0476; found 224.0477.

4,6-Difluoro-5-formyl-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (4c): This compound was obtained as described for **4a** starting with **3c**. White powder, m.p. 167–170 °C. Yield 1.95 g (80%). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.40–10.38 (m, 1H), 7.50 (d, *J* = 9.6 Hz, 1H), 0.50 (s, 6H) ppm. ^{13}C NMR (101 MHz, acetone-d_6) δ 184.53 (dd, *J* = 5.0, 3.5 Hz), 164.78 (dd, *J* = 264.3, 3.4 Hz), 164.01 (dd, *J* = 260.1, 5.1 Hz), 152.1 (broad), 131.42 (d, *J* = 31.9 Hz), 114.94 (dd, *J* = 18.6, 3.8 Hz), 114.78 (dd, *J* = 14.2, 11.3 Hz), -1.66 ppm. ^{11}B NMR (96 MHz, acetone-d_6) δ 29.7 ppm. ^{19}F NMR (376 MHz, acetone-d_6) δ -106.77 (d, *J* = 5.5 Hz), -114.63 (dd, *J* = 9.5, 5.5 Hz) ppm. ^{29}Si{^{1}H} NMR (99 MHz, acetone-d_6) δ 20.38 ppm. HRMS (EI): calcd. for $C_9H_9BF_2O_3Si$ $[M]^+$ 242.0382; found 242.0378.

4,5-Difluoro-7-formyl-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (4d): This compound was obtained as described for **4a** starting with **3d**. White powder, m.p. 134–137 °C. Yield 1.75 g (72%). ^{1}H NMR (300 MHz, acetone-d6) δ 10.41 (d, *J* = 1.5 Hz, 1H), 9.07 (s, 1H), 8.02 (dd, *J* = 10.9, 7.4 Hz, 1H), 0.52 (s, 6H) ppm. ^{13}C NMR (101 MHz, acetone-d_6) δ 194.53, 155.35 (dd, *J* = 253.6, 11.5 Hz), 152.25 (dd, *J* = 255.7, 16.3 Hz), 141.57 (d, *J* = 29.2 Hz), 139.22 (t, *J* = 3.5 Hz), 123.33 (d, *J* = 18.3 Hz), -0.92 ppm. ^{19}F NMR (471 MHz, acetone-d_6) δ -122.61 (dd, *J* = 23.8, 7.4 Hz), -136.53 (ddd, *J* = 23.8, 11.0, 1.7 Hz) ppm. ^{11}B NMR (96 MHz, acetone-d_6) δ 28.7 ppm. ^{29}Si{^{1}H} NMR (99 MHz, acetone-d_6) δ 20.76 ppm. HRMS (EI): calcd. for $C_9H_9BF_2O_3Si$ $[M]^+$ 242.0382; found 242.0384.

7-Cyano-4-fluoro-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (4f): This compound was obtained as described for **4a** starting with **3f**. White powder, m.p. 119–122 °C. Yield 0.28 g (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (ddd, *J* = 8.3, 4.7, 0.9 Hz, 1H, Ph), 7.19 (ddd, *J* = 8.3, 6.5, 1.0 Hz, 1H, Ph), 5.51 (br, 1H, OH), 0.52 (s, 6H, $SiMe_2$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.57 (d, *J* = 255.0 Hz), 161.35 (d, *J* = 12.7 Hz), 137.48 (d, *J* = 7.9 Hz), 134.60 (d, *J* = 11.3 Hz), 117.97 (d, *J* = 26.2 Hz), 110.83, 108.25 (d, *J* = 23.3 Hz), 103.86 (d, *J* = 25.1 Hz), -1.04 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.18 (t, *J* = 5.3 Hz) ppm. ^{29}Si{^{1}H} NMR (99 MHz, $CDCl_3$) δ 20.92 ppm. Anal. Calcd for $C_9H_9BFNO_2Si$ (221.07): C, 48.90; H, 4.10. Found: C, 49.28; H, 3.64. HRMS (EI): calcd. for $C_9H_9BFNO_2Si$ $[M]^+$ 221.0480; found 221.0484.

5-Cyano-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (**4g**): A solution of **3g** (2.04 g, 6 mmol) in THF (15 mL) was slowly added to a stirred solution of *n*-BuLi (1.6 M, 3.8 mL, 6 mmol) in THF (20 mL) at –90 °C. After 1 h of stirring the solution of $Me_2Si(H)Cl$ (0.65 mL, 6 mmol) in THF (5 mL) was added dropwise. The solution was warmed to –30 °C and hydrolyzed with 1.5 M H_2SO_4. After the hydrogen evolution ceased the water phase was separated followed by extraction with Et_2O (20 mL), the organic phase was washed with 0.5 M H_2SO_4 and brine (20 mL). Organic phases were combined and concentrated under reduced pressure. The solid residue was crystallized from hexane/ chloroform (10:10 ml). White powder, m.p. 129–130 °C. Yield 0.67 g (57%).^{1}H NMR (300 MHz $CDCl_3$) δ 7.93 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.90 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.74 (dd, *J* = 7.6, 1.5 Hz, 1H), 0.48 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.12, 133.89, 132.80, 131.70, 119.03, 114.32, -0.78 ppm.^{11}B NMR (96 MHz, $CDCl_3$) δ 29.3 ppm. ^{29}Si{^{1}H} NMR (99 MHz, $CDCl_3$) δ 22.34 ppm. Anal. Calcd for $C_9H_9BFNO_2Si$ (203.08): C, 53.23; H, 4.96; N, 6,90. Found: C, 53.19; H, 4.80; N, 6,75. HRMS (EI): calcd. for $C_9H_{10}BNO_2Si$ $[M]^+$ 203.0574; found 203.0577.

4-Fluoro-5-(hydroxymethyl)-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (5a). Compound **4a** (230 mg, 1.03 mmol) was dissolved in THF (5 mL). The solution was cooled to 0 °C. Then $NaBH_4$ (50 mg, 1.25 mmol) was added and a vigorous evolution of H_2 was observed. The mixture was stirred for 30 min at room temperature and hydrolyzed with 1.5 M aq. H_2SO_4. The aqueous phase was separated followed by the extraction with Et_2O (2 × 20 mL). The extracts were added to the organic phase, which was dried with $CaCl_2$ and concentrated to leave a white solid. It was washed with acetone (2 × 5 mL) and dried *in vacuo* to give **5a**, m.p. 285–290 °C. Yield 205 mg (90%). ^{1}H NMR (300 MHz, dmso-d_6+D_2O) δ 9.23 (s, 1H), 7.62 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.57 (t, *J* = 7.1 Hz, 1H), 4.57 (s, 2H), 0.40 (s, 6H) ppm. ^{13}C NMR (101 MHz, dmso-d_6+D_2O) δ 161.79 (d, *J* = 243.3 Hz), 143.08, 134.47 (d, *J* = 31.4 Hz), 132.09 (d, *J* = 3.4 Hz), 131.22 (d, *J* = 17.6 Hz), 128.20 (d, *J* = 3.0 Hz), 57.15 (d, *J* = 3.4 Hz), -0.20 ppm. ^{19}F NMR (282 MHz, dmso-

d_6+D_2O) δ -111.01 ppm. $^{29}Si\{^1H\}$ NMR (99 MHz, dmso-d_6+D_2O) δ 19.58 ppm. HRMS (EI): calcd. for $C_9H_{12}BFO_3Si$ $[M]^+$ 226.0633; found 226.0639.

4-Fluoro-6-(hydroxymethyl)-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (5b). This compound was obtained as described for **5a** starting with **4b**. White powder, m.p. 278–281 °C. Yield 190 mg (85%). ^1H NMR (300 MHz, acetone-d_6+D_2O) δ 7.64–7.58 (m, 1H), 7.16–7.09 (m, 1H), 4.65 (s, 2H), 0.38 (s, 6H) ppm. ^{13}C NMR (101 MHz, acetone-d_6+D_2O) δ 164.82 (d, J = 243.0 Hz), 148.32 (d, J = 5.4 Hz), 132.69 (d, J = 31.2 Hz), 125.53 (d, J = 2.6 Hz), 114.73 (d, J = 25.1 Hz), 62.85 (d, J = 1.9 Hz), -1.38 ppm. ^{19}F NMR (282 MHz, acetone-d_6+D_2O) δ -106.01 ppm. $^{29}Si\{^1H\}$ NMR (99 MHz, acetone-d_6+D_2O) δ 21.37 ppm. HRMS (EI): calcd. for $C_9H_{12}BFO_3Si$ $[M]^+$ 226.0633; found 226.0635.

4,6-Difluoro-5-(hydroxymethyl)-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (5c). This compound was obtained as described for **5a** starting with **4c**. The product contains acetone (ca 1.5wt%) used for final crystallization which could not be removed even under reduced pressure at 90 °C. White powder, m.p. 330–335 °C. Yield 225 mg (94%). ^1H NMR (400 MHz, dmso-d_6+D_2O) δ 7.43 (d, J = 8.6 Hz, 1H), 4.51 (s, 2H), 0.40 (s, 6H) ppm. ^{13}C NMR (101 MHz, dmso-d_6+D_2O) δ 163.63 (dd, J = 251.0, 6.2 Hz), 163.00 (dd, J = 247.0, 7.7 Hz), 144.71 (broad), 130.24 (d, J = 32.8 Hz), 118.87 (t, J = 21.5 Hz), 114.64 (dd, J = 19.8, 3.3 Hz), 51.09 (t, J = 3.6 Hz), -0.29 ppm. ^{19}F NMR (282 MHz, dmso-d_6+D_2O) δ -106.48 (d, J = 9.3 Hz), -113.03 (d, J = 9.3 Hz) ppm. $^{29}Si\{^1H\}$ NMR (99 MHz, dmso-d_6+D_2O) δ 19.25 ppm. HRMS (EI): calcd. for $C_9H_{11}BF_2O_3Si$ $[M]^+$ 244.0539; found 244.0538.

4,6-Difluoro-5-{*N*-[2-(3,4-dihydroxyphenyl)ethyl]aminomethyl}-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (6c). Compound **4c** (242 mg, 1 mmol) and 3-hydroxytyramine hydrobromide (245 mg, 1.03 mmol) were suspended in THF (10 mL) followed by the addition of Et_3N (303 mg, 3.0 mmol). A mixture was stirred for 1 h at 50 °C and a grayish viscous oil separated at the bottom of the flask. The mixture was cooled to 5 °C and $NaBH_4$ (120 mg, 3 mmol) was added in a few portions. The resulting mixture was stirred for 1 h at ambient temperature and concentrated under reduced pressure. A white waxy residue was triturated with Et_2O (10 mL) and the obtained suspension was hydrolyzed by a dropwise addition 1.5 M H_2SO_4 so that the final pH was adjusted to ca. 4-5. The precipitated product was filtered, washed with water and acetone (2 × 5 mL), and dried in vacuo. The obtained material contained a small amount of Et_3N which could not be removed by repeated washing and drying under reduced pressure. White powder, m.p. 225–227 °C. Yield 276 mg (73%). ^1H NMR (400 MHz, dmso-d_6+CF_3SO_3D+D_2O) δ 8.93 (broad, 1H), 7.54 (d, J = 8.3 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 2.1 Hz, 1H), 6.48 (dd, J = 8.0, 2.1 Hz, 1H), 4.26 (broad, 2H), 3.15 (broad, 2H), 2.78–2.71 (m, 2H). 0.42 (s, 6H) ppm. ^{13}C NMR (101 MHz, dmso-d_6+CF_3SO_3D+D_2O) δ 163.56 (d, J = 250.2 Hz), 163.01 (d, J = 251.0 Hz), 147.85 (broad), 145.65, 144.48, 130.56 (d, J = 32.0 Hz), 127.89, 122.67, 119.77, 119.46, 116.25 (d, J = 31.4 Hz), 114.90 (d, J = 19.2 Hz), 49.06 (t, J = 8.7 Hz), 38.30, 31.26, -0.22 ppm. ^{19}F NMR (376 MHz, dmso-d_6+CF_3SO_3D+D_2O) δ -102.43, -108.95 ppm. $^{29}Si\{^1H\}$ NMR (99 MHz, dmso-d_6+CF_3SO_3D+D_2O) δ 18.95 ppm. HRMS (EI): calcd. for $C_{17}H_{20}BF_2NO_4Si$ $[M]^+$ 379.1223; found 379.1221.

Compound 6d. This compound was obtained as described for **5a** starting with **4d**. White powder, m.p. 195–197 °C. Yield 212 mg (94%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.10 (m, 2H), 4.99 (s, 4H), 0.62 (d, J = 2.2 Hz, 12H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.28 (dd, J = 240.6, 11.9 Hz), 152.09 (dd, J = 255.6, 18.2 Hz), 151.41 (dd, J = 5.9, 2.2 Hz), 131.85 (d, J = 23.5 Hz), 111.24 (d, J = 17.4 Hz), 69.64 (d, J = 2.3 Hz), 1.62 (d, J = 2.9 Hz) ppm. ^{11}B NMR (96 MHz, $CDCl_3$) δ 30.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ -127.98– -128.10 (m), -133.79 (dd, J = 22.0, 9.7 Hz) ppm. $^{29}Si\{^1H\}$ NMR (99 MHz, $CDCl_3$) δ 2.28 (dd, J = 10.0, 4.3 Hz) ppm. HRMS (EI): calcd. for $C_{18}H_{18}B_2F_2O_4Si_2$ $[M]^+$ 452.0866; found 452.0869.

5,6-Difluoro-7-(dimethylsilyl)-1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole (7d). The synthesis was carried out as described for **4d** except that THF (30 mL) was added to the reaction mixture prior to hydrolysis. The crude product consisting of **4d** (ca. 65%) and **7d** (ca. 35%) was dissolved in THF (20 mL). The solution was cooled to 0 °C. Then $NaBH_4$ (100 mg) was added in a few portions. A vigorous evolution of H_2 was observed. The mixture was stirred for 1 hr at room temperature and hydrolyzed with 1.5 M aq. H_2SO_4. The standard workup gave a white solid, which was filtered washed with water (3 × 5 mL) and dried *in vacuo.* Then it was triturated with cold Et_2O/hexane (1:1, 10 mL). The resulting suspension was filtered; the white solid was washed with hexane (5 mL) and dried to give **5d** (yield 0.90 g, 40%). The filtrate was evaporated and the residue was crystallized from boiling hexane (20 mL) to afford **7d** as colorless needles, m.p. 99–101 °C. Yield 0.35 g (15%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 9.7, 7.0 Hz, 1H), 5.04 (s, 2H), 4.78–4.69 (m, 1H), 0.46 (dd, J = 3.8, 0.9 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.87 (d, J = 241.5, 11.9 Hz), 152.40 (d, J = 257.0, 18.2 Hz), 150.58 (m), 130.44 (d, J = 24.4 Hz), 111.24 (d, J = 18.2 Hz), 70.26 (d, J = 2.4 Hz), -3.24 (d, J = 2.8 Hz) ppm. ^{11}B NMR (96 MHz, $CDCl_3$) δ 32.3 ppm.^{19}F NMR (376 MHz, $CDCl_3$) δ -127.58 (d, J = 21.7 Hz), -132.78 (dd, J = 21.9, 9.7 Hz) ppm. $^{29}Si\{^1H\}$ NMR (99 MHz, $CDCl_3$) δ -22.23 (dd, J = 7.8, 3.4 Hz) ppm. HRMS (EI): calcd. for $C_9H_{11}BF_2O_2Si$ $[M]^+$ 228.0589; found 228.0582.

Compound 5e: This compound was obtained as described for **4a** starting with **3e**. The crude product containing ca. 20% of **4e** (^1H and ^{19}F NMR spectra point that **4e** exists in solution as a ca. 1:1 mixture of two tautomers: a species with free CHO and $B(OH)_2$ groups and a second cyclic form, where these groups interact to form the carboxaborole ring)[19] was dissolved in THF (20 mL). The solution was cooled to 0 °C. Then $NaBH_4$ (0.1 g) was added in a few portions. A vigorous evolution of H_2 was initially observed. The mixture was stirred for 1 hr at room temperature and hydrolyzed with 1.5 M aq. H_2SO_4. The standard workup gave a white solid, which was filtered, washed with water (2 × 5 mL), CH_2Cl_2 (5 mL) and dried *in vacuo* to give **5e** as a white powder, m.p. 164–167 °C. Yield 2.05 g (81%). ^1H NMR (400 MHz, acetone-d_6) δ 8.39 (broad, 1H), 8.17 (broad, 1H), 8.00 (d, J = 3.8 Hz, 1H), 5.11 (s, 2H), 0.45 (s, 6H) ppm. ^{13}C NMR (101 MHz, acetone-d_6) δ 159.86 (d, J = 246.1 Hz), 142.34 (d, J = 18.2 Hz), 138.08 (d, J = 29.3 Hz), 130.75 (d, J = 3.2 Hz), 68.05 (d, J = 1.6 Hz), -0.58 ppm. ^{11}B NMR (96 MHz, acetone-d_6) δ 31.8, 30.1 ppm. ^{19}F NMR (376 MHz, acetone-d_6) δ -114.01 (d, J = 3.5 Hz) ppm HRMS (EI): calcd. for $C_9H_{11}B_2FO_4Si$ $[M]^+$ 252.0597; found 252.0598.

Structural measurement and refinement details. The single crystals of was measured at 100 K on SuperNova diffractometer equipped with Atlas detector (Cu-K_α radiation, λ = 1.54184 Å). The structures of **6d**, **7d** were determined on SuperNova diffractometer equipped with an EOS measurement device type (Mo-K_α radiation, λ = 0.7107 Å). Data reduction and analysis were carried out with the CrysAlisPro program.[20] All structures were solved by direct methods using SHELXS-97[21] and refined using SHELXL-2014.[22] All non-hydrogen atoms were refined anisotropically. All structures except for **4d** were measured at 100 K. Single crystals of **4d** collapsed during cooling which is probably due to phase transition and therefore the diffraction experiment was performed at room temperature. CCDC-1047174-1047176 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4d: $C_9H_9BF_2O_3Si$, M_r = 242.06 a.u.; T = 298 K; orthorhombic space group, *Pbcm*, a = 11.7006 (7) Å, b = 14.2170 (6) Å, c = 7.0010 (5) Å, V =

1164.60 (12) Å^3, Z = 4; d_{calc} = 1.381 gcm^{-3}; μ = 1.97 mm^{-1}; F(000) = 496; crystal size = 0.07_0.07_0.01; θ range: 3.78°–67.68°; index ranges: –13 < h < 13, –16 < k <16, –8 < l < 6; absorption correction: multiscan; number of collected / independent / unique reflection (R_{int} = 3.7%) = 6210 / 1128 / 738; GooF = 1.019, R_1 / wR_1 (I ≥ 3σ(I)) = 4.5% / 12.0%; R_2 / wR_2 (all data) = 7.5% / 13.8%; $\Delta\varrho_{res}^{(min/max)}$ = −0.17 / +0.13 eÅ^{-3}.

6d: $C_{18}H_{18}B_2F_4O_4Si_2$, M_r = 452.12 a.u.; T = 100 K; monoclinic space group, $P2_1/c$, a = 8.5267 (2) Å, b = 11.5577 (2) Å, c = 10.1858 (2) Å, β = 100.476 (2) °; V = 987.07(4) Å^3; Z = 2; d_{calc} = 1.521 gcm^{-3}; μ = 0.241 mm^{-1}; F(000) = 464; crystal size = 0.10_0.09_0.09; θ range: 2.32°–32.70°; index ranges: –9 < h < 9, –13 < k <13, –14 < l < 14; absorption correction: multiscan; number of collected / independent / unique reflection (R_{int} = 4.1%) = 39804 / 4111 / 3435, R_1 / wR_1 (I ≥ 3σ(I)) = 3.8% / 10.8%, R_2 / wR_2 (all data) = 4.8% / 11.9%, $\Delta\varrho_{res}^{(min/max)}$ = −0.28 / +0.57 eÅ^{-3}.

7d: $C_9H_{11}BF_2O_2Si$, M_r = 228.08 a.u.; T = 100 K; triclinic space group, P-1, a = 6.4605 (7) Å, b = 9.2182 (7) Å, c = 9.5147 (9) Å, α = 110.238 (8) °, β = 99.365 (9) °, γ = 92.087 (8) °; V = 521.93(9) Å^3; Z = 2; d_{calc} = 1.451 gcm^{-3}; μ = 0.228 mm^{-1}; F(000) = 236; crystal size = 0.10_0.09_0.09; θ range: 2.32°–32.70°; index ranges: –9 < h < 9, –13 < k <13, –14 < l < 14; absorption correction: multiscan; number of collected / independent / unique reflection (R_{int} = 3.6%) = 10338 / 3590 / 2911,GooF = 1.054, R_1 / wR_1 (I ≥ 3σ(I)) = 5.7% / 10.9%, R_2 / wR_2 (all data) = 7.5% / 13.8%; $\Delta\varrho_{res}^{(min/max)}$ = −0.31 / +0.50 eÅ^{-3}.

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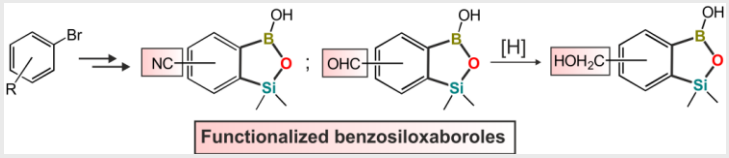

The synthesis and characterization of a series of fluorinated benzosiloxaboroles bearing the synthetically useful formyl, hydroxymethyl and cyano groups is reported. These compounds have been obtained by multistep syntheses starting with simple halogenated benzenes. In some cases the synergy of adjacent boron and silicon centres resulted in an unexpected hydrosilylation of CHO group under mild aqueous conditions.

Boracycles

Maja Czub, Krzysztof Durka, Sergiusz Luliński, Justyna Łosiewicz, Janusz Serwatowski, Mateusz Urban, Krzysztof Woźniak

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Synthesis and Transformations of Functionalized Benzosiloxaboroles