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The Influence of Boronate Groups on the Selectivity of the Br–Li Exchange in Model Dibromoaryl Boronates

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The selectivity of the Br/Li exchange reaction of 6-butyl-2-(2,5-dibromophenyl)-1,3,6,2-dioxazaborocane (2,5-$Br_2C_6H_3B$-$(OCH_2CH_2)_2NBu$) and the analogous anionic derivatives, 2,5-$Br_2C_6H_3B(OiPr)_3Li$ and 2,5-$Br_2C_6H_3BF_3K$, was investigated using *n*BuLi as the lithiating reagent. In the case of the former compound there was a slight preference for lithiation at the 5-position. For 2,5-$Br_2C_6H_3B(OiPr)_3Li$, the lithiation occured exclusively at C5, but for 2,5-$Br_2C_6H_3BF_3K$, 2-lithiation was preferred. Calculations performed for the lithiation of *ortho*- and *meta*-brominated phenyl boronates revealed that *ortho*-lithiated aryl boronates are thermodynamically more stable, but that the Br/Li exchange is generally dictated by kinetics, which accounts for the variation of selectivity depending on the type of boronate group. In addition, the successful generation of the 2,5-dilithiophenyl boronate species 2,5-$Li_2C_6H_3B(OCH_2CH_2)_2NBu$ by a double Br/Li interconversion is reported. The Br/Li exchange in the related 6-butyl-2-[3-(2,5-dibromothienyl)]-1,3,6,2-dioxazaborocane, 2,5-Br_2-3-$ThB(OCH_2CH_2)_2NBu$, occured preferentially at the 5-position, but the product was readily transformed into the more stable 2-lithiated isomer. The use of 2 equiv. of *n*BuLi resulted in the efficient formation of the dilithiated species, 2,5-Li_2-3-$ThB(OCH_2CH_2)_2NBu$. The obtained lithiated aryl boronates were converted into functionalized arylboronic acids by treatment with selected electrophiles.

Introduction

Halogen–lithium exchange is one of the fundamental methods, and perhaps the most versatile method used to generate organolithium compounds. Its important advantage is that it is extremely rapid, even at very low temperatures, which means that it can provide a direct access to many unstable organolithium intermediates. Furthermore, this method offers a convenient route to compounds that are not accessible by directed deprotonative metalation reactions.[1] The halogen–lithium exchange reaction between polyhalobenzenes and *n*BuLi has been investigated with particular emphasis on the regiospecificity of the halolithiobenzene formation. It is known that various functional groups, such as alkoxy, amino, amido, fluoro, and CF_3 groups, increase the reactivity of neighboring halogen atoms in halogen–lithium exchange reactions.[2] The interest of our group is focused on the development of selective approaches to functionalized aryl and heteroarylboronic acids using lithiated aryl boronates as key intermediates.[3] Recently, we have found that the directing effect of boronate groups operates in the deprotonative lithiation of boronated thiophenes.[4] This study investigates the directing effects on halogen–lithium exchange with selected representative dibromoarenes, namely 1,4-dibromobenzene and 2,5-dibromothiophene containing neutral or anionic boron-based groups, i.e., $B(OCH_2CH_2)_2NBu$, $B(OR)_3Li$, or BF_3K. The experimental work has been compared with the results of theoretical calculations to shed light on the mechanistic details of the halogen–lithium exchange reactions studied.

Results and Discussion

Preliminary results on the selectivity of the low-temperature (–90 °C) halogen–lithium exchange reaction of 6-butyl-2-(2,5-dibromophenyl)-1,3,6,2-dioxazaborocane 2,5-$Br_2C_6H_3B(OCH_2CH_2)_2NBu$ (**1a**) using *n*BuLi as the lithiating reagent showed that the reaction occurs preferentially at C5, that is, the position more remote from the boronate group (Scheme 1). This was proved by the subsequent reaction with DMF and hydrolysis, which gave a 3:7 mixture of 5-bromo-2-formylphenylboronic acid (**1c**) and 2-bromo-5-formylphenylboronic acid (**1d**).[5] We repeated this lithiation at a slightly higher temperature (–80 °C), and then added MeI. After aqueous work-up, we obtained a mixture of 5-bromo-2-methylphenylboronic acid (**1e**) and 2-bromo-5-methylphenylboronic acid (**1f**) in a ratio of 4:5. Hence, it was confirmed that the borocanyl group has little impact

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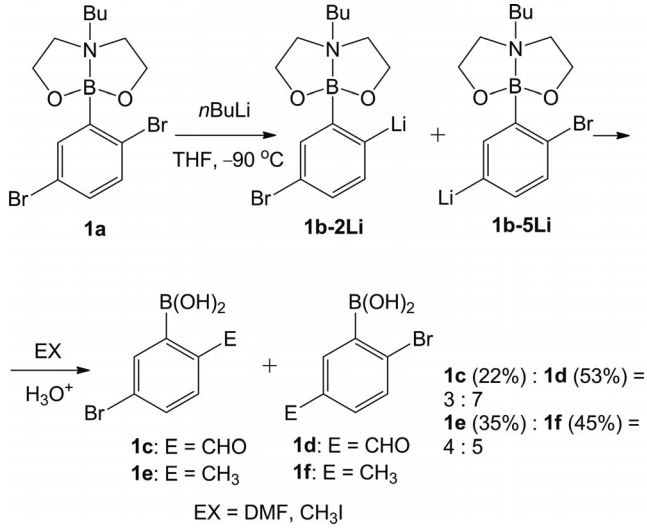
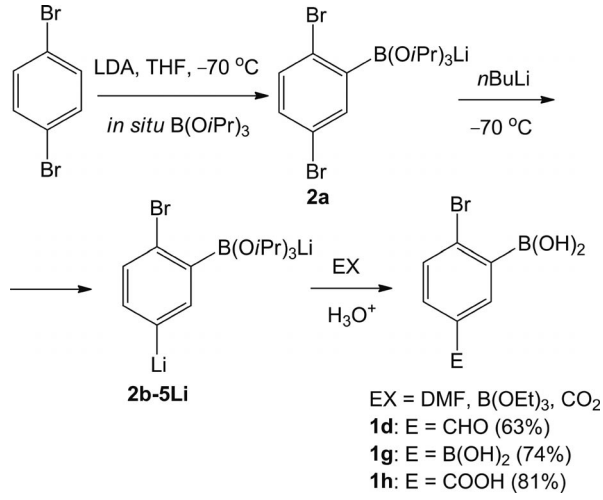
on the discrimination between the two lithiation sites upon addition of *n*BuLi. Apparently, there is no preference for the halogen–lithium exchange at C2 due to the precoordination of *n*BuLi by the oxygen atom of the adjacent borocanyl group.



Scheme 1. Lithiation of **1a** and the formation of mixtures of 5-bromo-2-substituted (**1c, 1e**) and 2-bromo-5-substituted (**1d**, **1f**) phenylboronic acids.

We also studied the reactivity of the related anionic ate complex 2,5-$Br_2C_6H_3B(OiPr)_3Li$ (**2a**) with *n*BuLi (Scheme 2). The generation of **2a** involved the in situ lithiation/boronation[6] of 1,4-dibromobenzene with LDA/$B(OiPr)_3$ in THF at –70 °C. The resulting solution of **2a** contains 1 equiv. of iPr_2NH, so it is necessary to use 2 equiv. of *n*BuLi in the subsequent reaction. The first equiv. of *n*BuLi is consumed to regenerate LDA; only the second equiv. is involved in the Br/Li exchange. The resulting lithiate was quenched with selected electrophiles to give the corresponding pure products **1d**, **1g**, and **1h** in reasonable yields. These results show that the lithiation occurs with perfect selectivity for the C5 position remote from the $B(OiPr)_3Li$ group. The relative deactivation of the 2-Br atom in **2a** towards halogen–lithium exchange can be due to strongly electron-donating properties of the adjacent anionic boronate functionality and/or steric congestion, which makes the approach of *n*BuLi to the C2 position relatively difficult.

The structure of **1g** was confirmed by the X-ray analysis (Figure 1). It is interesting to note that in one of two crystallographically independent molecules **1g**-A, the $B(OH)_2$ group bound to the C3 atom adopts a rarely observed *anti–anti* conformation.[7] Both of the molecular structures (i.e., **1g**-A and **1g**-B) are stabilized by intramolecular OH···Br hydrogen bonds (geometrical details are given in Table 1S in the Supporting Information). The $B(OH)_2$ groups (except for the one at C9) are significantly twisted with respect to the aromatic rings, with the torsion angles ranging from 18.5(1)° to 29.5(1)°. The crystal structure of **1g** lacks centro-



Scheme 2. Lithiation of **2a** and the regioselective formation of 5-substituted-2-bromophenylboronic acids **1d**, **1g**, and **1h**.

symmetric dimeric motifs typical of most boronic acids, including diboronic acids.[8,9] Instead, **1g** is assembled to form hydrogen-bonded tetramers, which are further linked through weaker lateral hydrogen bonds to produce chains aligned parallel to the [100] direction (Figure 1, b).

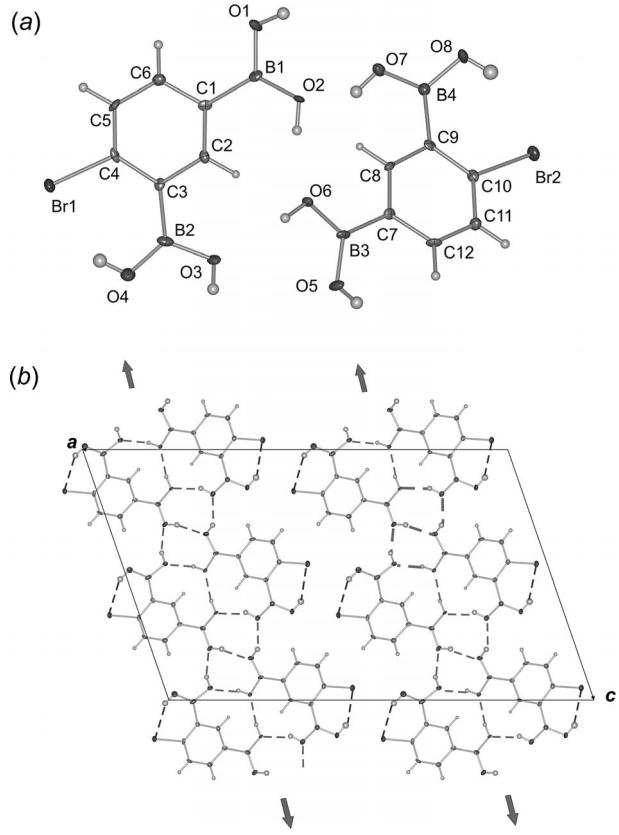
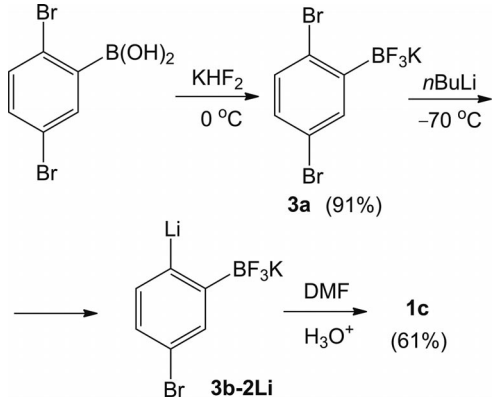


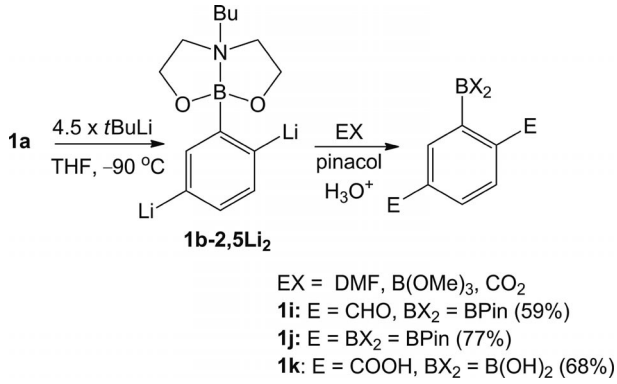
Figure 1. a) Labeling of atoms and visualization of their atomic displacement parameters (ADPs) at the 50% probability level in molecules of **1g**. b) Fragments of the crystal lattice showing the hydrogen-bonding motifs. The arrows show the directions of propagation of the chains.

We were interested comparing the behavior of **2a** in the halogen–lithium exchange with the reactivity of another anionic dibromophenyl boronate derivative: the trifluoroborate salt 2,5-$Br_2C_6H_3BF_3K$ (**3a**). Compound **3a** was prepared by the standard route,[10] involving the reaction of the appropriate arylboronic acid with KHF_2. When **3a** was treated with *n*BuLi in THF at –80 °C, the 2-Br atom was selectively exchanged with lithium as shown by the isolation of **1c** after reaction with DMF and hydrolysis (Scheme 3). This points to a significant *ortho*-directing ability of trifluoroborate group, which could be due to its smaller size and the possible precomplexation of *n*BuLi by F···Li coordination, which was recently invoked in the deprotonative lithiation of BF_3-complexed anilines and pyridines.[11] Furthermore, the trifluoroborate group should be a much weaker electron donor than trialkoxyborate, and hence it should be much less effective in the electronic deactivation of the neighboring 2-Br atom. More detailed theoretical studies into the mechanism of the lithiation processes are discussed below.



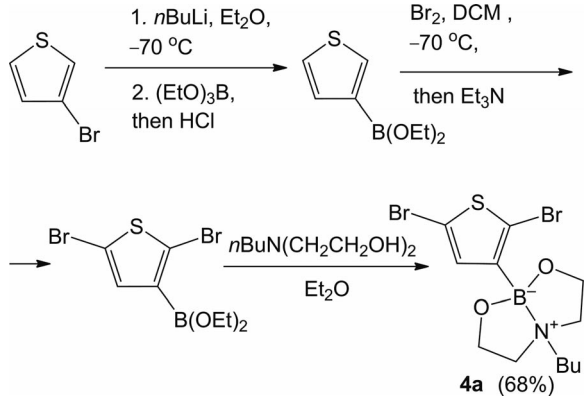
Scheme 3. Lithiation of **3a** and formation of 5-bromo-2-formylphenylboronic acid (**1c**).

We were also interested in whether it would be possible to perform a double halogen–lithium exchange in **1a**. The parent 1,4-dilithiobenzene is accessible in high yield by the treatment of 1,4-diiodobenzene with 2 equiv. of *n*BuLi under mild conditions.[12] However, 1,4-dibromobenzene is less reactive, and the completion of the second halogen–lithium exchange is problematic.[12,13] The use of *t*BuLi gave better conversions of dibromoarenes to the corresponding dilithioarenes.[14] We found that the attempted double lithiation of **1a** using 2 equiv. of *n*BuLi was unsuccessful, as a mixture of isomeric monolithiated intermediates **1b**-2Li and **1b**-5Li was generated. A DMF quench and hydrolysis gave a mixture of **1c** and **1d** in a ratio of 3:7, and there was no trace of the desired diformylated product. However, the use of *t*BuLi (4.5 equiv.) resulted in the efficient formation of 2,5-dilithiophenyl boronate **1b**-2,5Li_2, as proved by its subsequent reactions with electrophiles [i.e., DMF, CO_2, B(O*i*Pr)$_3$] leading to disubstituted phenylboronates **1i**–**k** in reasonable yields (Scheme 4).[15] It should be noted that the synthesis of **1j** and its analogs by the cobalt-catalyzed trimerization of borylated acetylenes has been previously reported, but these products were always obtained as minor components of inseparable mixtures, together with the isomeric 1,3,5-triboronated benzenes.[16] To the best of our knowledge, **1b**-2,5Li_2 is the first example of a boronated dilithioarene species.



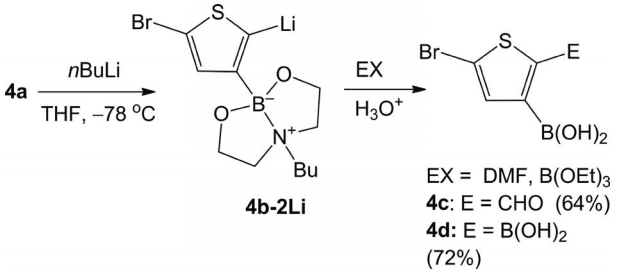
Scheme 4. Dilithiation of **1a** and the formation of 2,5-disubstituted phenylboronic acids **1i**–**k**.

Finally, we decided to compare the reactivity of (2,5-dibromophenyl)boronates with that of their heterocyclic counterpart 6-butyl-2-[3-(2,5-dibromothienyl)]-1,3,6,2-dioxazaborocane **4a**. The synthesis of **4a** is shown in Scheme 5. The addition of 1 equiv. of *n*BuLi to the solution of **4a** in THF followed by derivatization with electrophiles gave 5-bromo-2-substituted products **4c**–**d**. This means that the halogen–lithium exchange occurred at the position adjacent to the borocanyl group (Scheme 6), which is consistent with our recent results on the thermodynamically controlled deprotonative lithiation of 6-butyl-2-(3-thienyl)-1,3,6,2-dioxazaborocane with LDA.[4] However, when we performed the halogen–lithium exchange in the presence of the internal electrophile B(O*i*Pr)$_3$,[17] we obtained 5-bromothiophene-2,4-diboronic acid (**4e**) as the major product (Scheme 7). This indicates that the 5-Br atom remote from the boronate is replaced by lithium more quickly, but in the absence of an electrophile, the kinetic product (i.e., **4b**-5Li) undergoes rapid isomerization to the more stable isomer

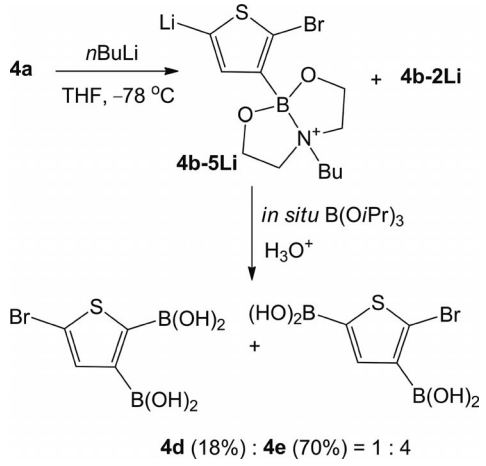


Scheme 5. The synthesis of 6-butyl-2-[3-(2,5-dibromothienyl)]-1,3,6,2-dioxazaborocane (**4a**).

(i.e., **4b**-2Li) by the halogen-dance process,[18] which occurs effectively, due to relatively strong stabilization of α-thienyl carbanions.[19]

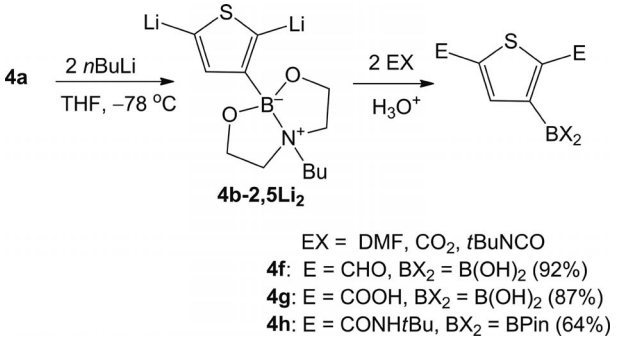


Scheme 6. Thermodynamic lithiation of **4a**, and the regioselective formation of 2-substituted 5-bromothiophene-3-boronic acids **4c**–**d**.



Scheme 7. Kinetic lithiation/in situ boronation of **4a**.

The high susceptibility of **4a** to halogen–lithium exchange was manifested by the generation of 6-butyl-2-[3-(2,5-dilithiothienyl)]-1,3,6,2-dioxazaborocane **4b**-2,5Li$_2$, which is consistent with the easy formation of the parent 2,5-dilithiothiophene from 2,5-dibromothiophene and *n*BuLi.[20] Intermediate **4b**-2,5Li$_2$ was obtained in high yield using 2.5 equiv. of *n*BuLi in THF/Et$_2$O at –75 °C. Treatment of **4b**-2,5Li$_2$ with selected electrophiles gave 2,5-disubstituted thiophene-3-boronic acids (**4f**–**h**; Scheme 8).



Scheme 8. Dilithiation of **4a** and formation of 2,5-substituted thiophene-3-boronic acids and pinacolates **4f**–**h**.

Halogen–Lithium Exchange in Bromophenyl Boronates – a Computational Approach

We were interested to see whether the origin of the observed selectivities was kinetic or thermodynamic in nature. Our intention was to compare the results with those from the deprotonation of 6-butyl-2-(3-thienyl)-1,3,6,2-dioxazaborocane with LDA, where the lithiation at the C2 position adjacent to the borocanyl moiety was found to be thermodynamically driven, but was kinetically less favored than the competitive lithiation at C5.[4] Thus, we performed theoretical calculations on the halogen–lithium exchange involving *n*BuLi, and, to simplify the calculations, the monobrominated analogs of **1a**–**3a** (2-Br, i.e., **1a′**, **2a′**, and **3a′**; and 3-Br, i.e., **1a″**, **2a″**, and **3a″**) All calculations were performed with the Gaussian09 program,[21] and the DFT method (B3LYP functional)[22] was used with the 6-31+G(d)[23] basis set. Gibbs free energies were obtained from the frequency calculations. As the experimental lithiations were performed at temperatures around –80 °C, in all calculations, the temperature was set to exactly –80 °C. It is well known that halogen–lithium exchange is hampered in nonpolar hydrocarbon solvents. Since the calculations for isolated molecules resulted in high activation energies (above 130 kJ mol^{-1}) and positive product-to-substrate energy differences,[24] the computations were performed with Thomasi's polarized continuum model,[25] using the polarizable conductor calculation model [SCRF(CPCM, solvent = THF)]. With these parameters, the activation energies were significantly lower, and products became more stable than the corresponding substrates.

In the most common and frequently considered pathway, the halogen–lithium exchange of aryl halides proceeds by polar substitution of the nucleophile at the halogen atom. Wittig suggested the formation of an intermediate ate complex rather than S$_N$2-like substitution.[26] Since the complex is stabilized by electron-withdrawing groups, it was even possible to isolate such an ate complex in the reaction of pentafluorophenyllithium and pentafluorophenyl iodide.[27] However, bromine is less likely than iodine to form hypercoordinated structures, and in the presence of electron-donating boronate groups, such intermediates should be further destabilized. This was also confirmed by calculations performed for previously located transition-state structures [**1a′**-2Li]‡ and [**1a″**-3Li]‡. These calculations showed that the Br-centered ate complexes dissociated to the substrates. Therefore, in our studies, we assumed that the activation energy corresponding to S$_N$2-like substitution is close to the energy of ate-complex formation.

To choose the best model for studying the lithiation of **1a**–**3a**, we first located the transition-state structures for the halogen–lithium exchange of simple bromobenzene with *n*BuLi in the presence of one, two, or three THF molecules in the coordination sphere of lithium. Theoretical studies on the mechanism of halogen–lithium exchange in PhBr were carried out earlier by Ando.[28] In those studies, MeLi was used as the model lithiating agent, and the activation energy was found to be ca. 100 kJ mol^{-1} (B3LYP/6-31G*

level of theory, SCRF approach, THF as solvent, temperature –90 °C). It was then concluded that coordination of Me_2O to the Li atom significantly decreased the activation energy (with two Me_2O molecules, by as much as about 45 kJ mol^{-1}), and slightly stabilized the lithiation product. According to our results, the activation energy for the halogen–lithium exchange of bromobenzene with *n*BuLi in the presence of one molecule of THF amounts to 70.2 kJ mol^{-1}, i.e., the value is slightly lower than that obtained by Ando (75.7 kJ/mol). The addition of the second THF molecule decreases the activation energy to 30.9 kJ mol^{-1} (53.5 kJ mol^{-1} for Ando's results), and finally, with three molecules of THF, the activation energy becomes 36.8 kJ mol^{-1}. In turn, the Gibbs energies for the halogen–lithium exchange are equal to –16.0, –18.7, and –10.0 kJ mol^{-1} for models with one, two, and three THF molecules, respectively. The appropriate transition-state structures and reactions pathways are shown in Figure 2S in the Supporting Information.

The boronate groups can bring an alkyllithium reagent close to the Br atom by precomplexation of the lithium atom with heteroatoms (O, F) bonded to the boron atom. On the other hand, the subsequent halogen–lithium exchange can be sensitive to steric effects of the boronate groups. Based on our experience with bromobenzene, we used *n*BuLi as the lithiating agent with a four-coordinate lithium atom (two THF molecules for lithiation at C2, and three THF molecules in the case of C3-lithiation). The halogen–lithium exchange reactions at the C2 position for **1a′**, **2a′**, and **3a′** were preceded by the formation of corresponding pre-complexes with *n*BuLi (i.e., pre-**1a′**-2Li, pre-**2a′**-2Li, and pre-**3a′**-2Li). These intermediate prelithiated complexes were similar in energy to the respective reactants. The activation energies of the formation of the pre-complexes are 28.7, 10.6, and 9.1 kJ mol^{-1} for **1a′**, **2a′**, and **3a′**, respectively, and are smaller than the activation energies of the halogen–lithium exchange processes (46.2 kJ mol^{-1} for **1a′**, 70.3 kJ mol^{-1} for **2a′**, and 33.2 kJ mol^{-1} for **3a′**). This indicates that the halogen–lithium exchange is the rate-limiting step of the reaction. The reaction pathways and corresponding transition-state structures are shown in Figures 2 and 3.

The kinetically controlled regioselectivity of the halogen–lithium exchange in **1a** and **2a** is apparently dominated by the strong steric effect of the borocanyl and triisopropoxyborate groups. The lithiated structures of **1a′**-2Li and **2a′**-2Li are more stable than the corresponding isomeric C3-lithiated derivatives (i.e., **1a′′**-3Li and **2a′′**-3Li) by about 10 kJ mol^{-1}. On the other hand, the formation of 3-Li isomers is kinetically favored. The energy barriers are 37.8 kJ mol^{-1} for **1a′′** and 53.8 kJ mol^{-1} for **2a′′**, while for **1a′** and **2a′**, they are 46.2 and 70.3 kJ mol^{-1}, respectively. However, the difference of only 8 kJ mol^{-1} between the energy barriers of **1a′** and **1a′′** indicates that both isomers can be formed during the reaction. Indeed, the experiments showed that halogen–lithium exchange in **1a** followed by the addition of an electrophile led to the formation of two regioisomers, whereas in the case of **2a**, C3-lithiation was

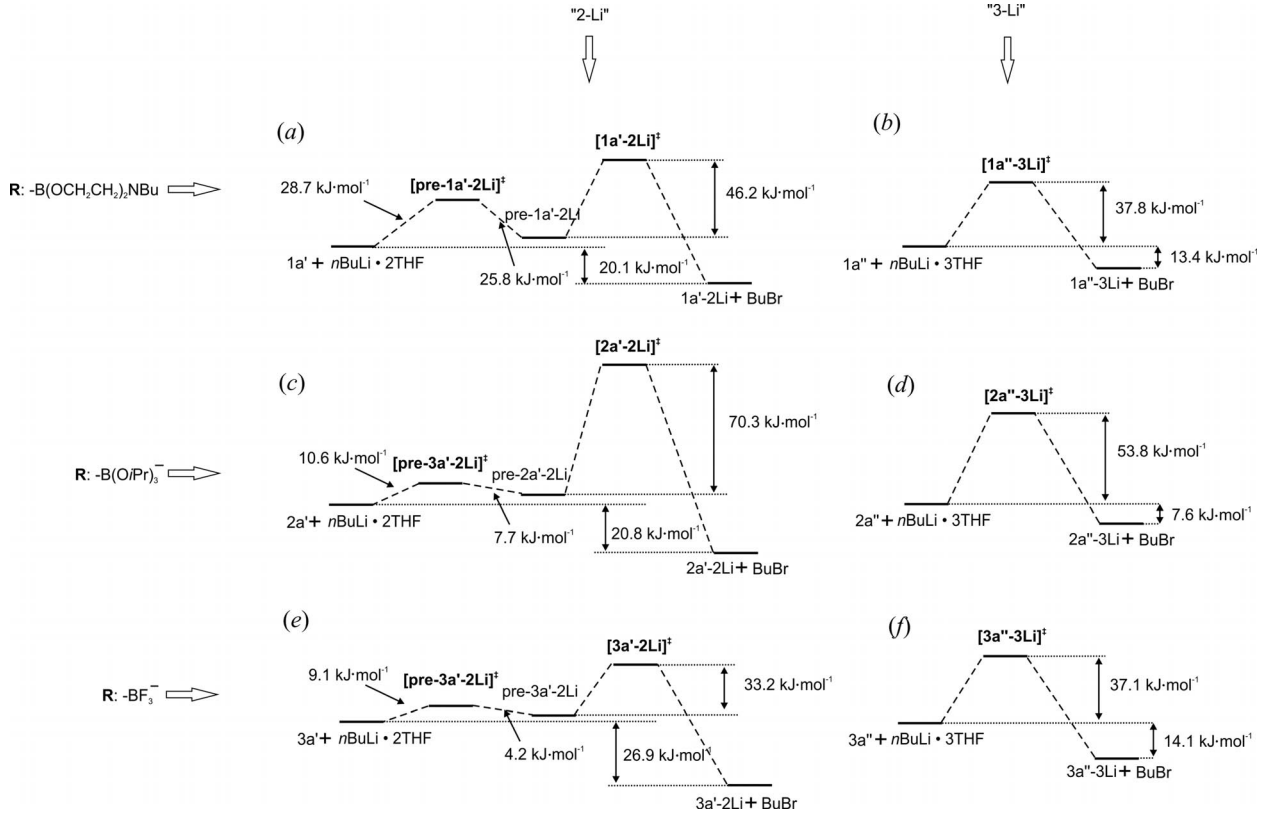


Figure 2. Reaction pathways for the lithiation of a) **1a′**; b) **1a′′**; c) **2a′**; d) **2a′′**; e) **3a′**; f) **3a′′**.

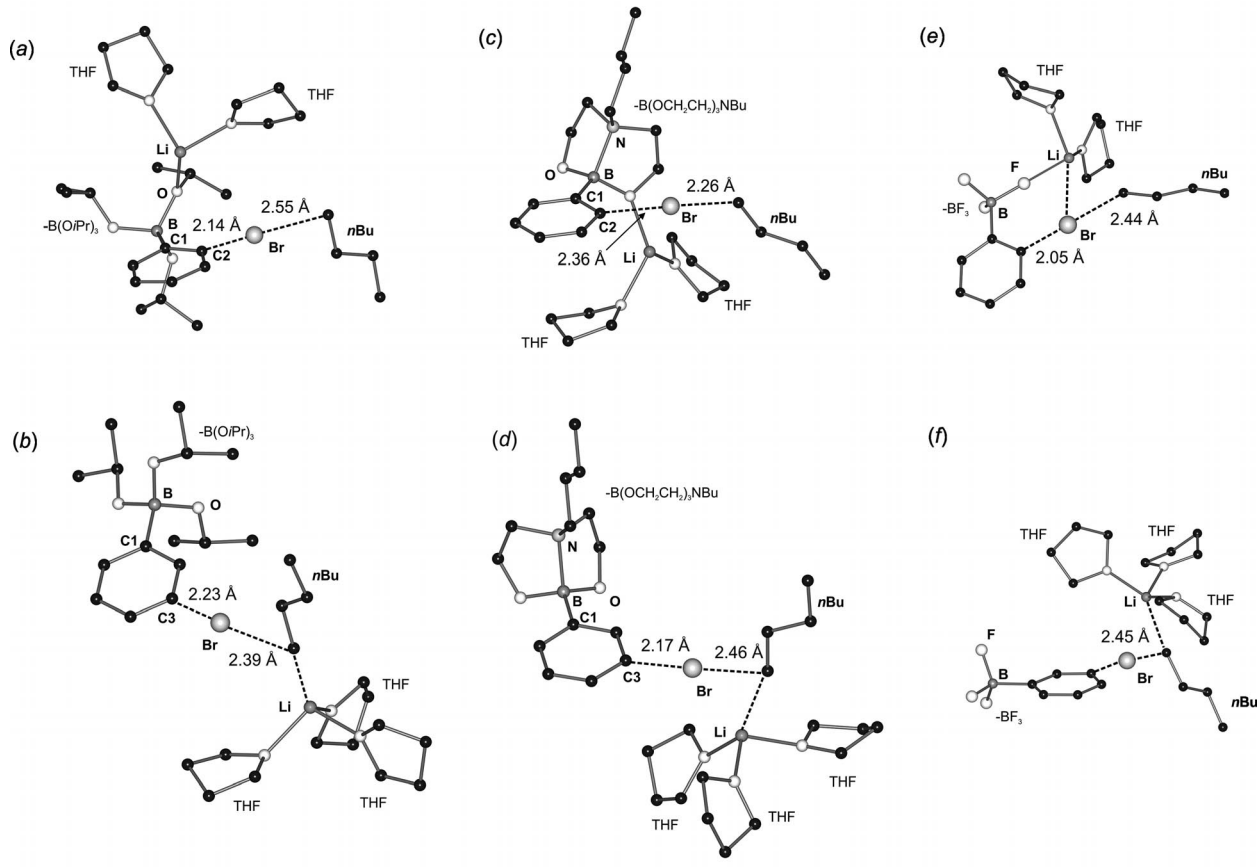


Figure 3. Transition-state structures: a) [**1a**′-2Li]‡; b) [**1a**′′-3Li]‡; c) [**2a**′-2Li]‡; d) [**2a**′′-3Li]‡: e) [**3a**′-2Li]‡; f) [**3a**′′-3Li]‡. Hydrogen atoms are omitted for clarity.

observed exclusively. The situation was different for **3a**. Theoretical calculations showed that the BF_3^- group significantly stabilizes the aryllithium derivative and promotes the metalation process (the energy difference between lithiated derivatives **3a**′-2Li and **3a**′′-3Li amounts to about 15 kJ mol^{-1}). This is presumably due to the relatively small steric requirements of this group, and also the high electronegativity of the fluorine atoms, which provides a good stabilization of the transition state for **3a**′-2Li. Therefore, the activation barrier for the *ortho*-lithiation (33.2 kJ mol^{-1}) is slightly lower than that on the pathway leading to **3a**′′-3Li (37.1 kJ mol^{-1}). These findings are consistent with the experimental results, which showed that *ortho*-lithiation is strongly preferred for **3a**.

Conclusions

In conclusion, we have evaluated and compared the directing properties of boron-based groups in halogen–lithium exchange reactions using 1,4-dibromophenyl boronates of three types as model substrates. Theoretical calculations point to the increased thermodynamic stability of *ortho*-lithiated phenyl boronates, which was recently also found for related heterocyclic analogs, namely 2-lithio-3-thienyl boronates.[4] This effect was attributed to the substantial chelation effect involving intramolecular Li–O coordination. However, the slight preference for lithiation at C5 in **1a** suggests that the reaction is dictated by kinetics, and this is strongly supported by transition-state calculations performed for halogen–lithium exchange reactions of related monobrominated analogs of **1a**. In the case of **2a**, the lithiation proceeds regioselectively at C5, apparently due to the activation barrier for the remote lithiation being much lower than that for the exchange of the 2-Br atom. Conversely, *ortho*-lithiation in **3a** is strongly favored. This is consistent with the slightly lower activation energy and the lower energy of formation of the *ortho*-lithiated phenyl trifluoroborate. The reaction of the thiophene derivative **4a** with *n*BuLi revealed that lithiation at C5, i.e., at the position remote from the borocanyl group is kinetically favored, but that the resulting product **4b**-5Li isomerizes rapidly in the absence of an internal electrophile to give the more stable (2-lithio-3-thienyl)boronate **4b**-2Li. This shows a close analogy with the behavior of the non-brominated analog of **4a** during deprotonative lithiation.[4] Studies into the selectivity of halogen–lithium exchange in boronated dibromoarenes were complemented by the successful generation of boronated dilithiobenzene and dilithiothiophene using excess *t*BuLi and *n*BuLi, respectively. These heterotrimetallic reagents conveniently gave rise to 2,5-difunctionalized phenyl- and thiophene-3-boronic acids or their pinacol esters. Currently, we are studying the metalation of

other aryl and heteroaryl boronates. Specifically, our interest will be focused on the observation of directing effects of boronate-type groups in such systems.

Experimental Section

General Remarks: 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. NMR chemical shifts are given relative to TMS, calibrated using known chemical shifts of residual proton (^1H) or carbon (^{13}C) solvent resonances. In the ^{13}C NMR spectra, the resonances of boron-bound carbon atoms were not observed in most cases, due to their broadening by a quadrupolar boron nucleus.

(2-Bromo-5-formylphenyl)boronic Acid (1d): A freshly prepared solution of LDA [diisopropylamine (4.84 g, 4.4 mL, 30 mmol) and *n*BuLi (10 M; 3 mL, 30 mmol) in THF (30 mL)] was added dropwise to a solution of 1,4-dibromobenzene (7.05 g, 30 mmol) in THF (70 mL) containing $B(OiPr)_3$ (5.64 g, 7.15 mL, 30 mmol) at –75 °C. The resulting white slurry was stirred for ca 30 min at –75 °C, and then *n*BuLi (10 M, 6.1 mL, 61 mmol) was added dropwise. The mixture was stirred for 1 h, and then it was quenched with DMF (7.3 g, 0.1 mol) followed by hydrolysis with H_2SO_4 (1.5 M aq., 50 mL). The aqueous phase was separated and then extracted with Et_2O (2× 15 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure. The solid residue was filtered and washed consecutively with water (2 × 10 mL) and CH_2Cl_2 (5 mL). Drying in vacuo gave the title compound (4.3 g, 63%) as a white powder, m.p. 122–124 °C. ^1H NMR ([D$_6$]acetone, 400 MHz): δ = 10.02 (s, 1 H, CHO), 8.02 (d, J = 1.6 Hz, 1 H, Ph), 7.67 (2 H, Ph) ppm. $^{13}C\{^1H\}$ NMR ([D$_6$]acetone, 100.6 MHz): δ = 192.3, 136.9, 136.4, 135.6, 133.6, 133.4, 131.4 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 28 ppm. $C_7H_6BBrO_3$ (228.84): calcd. C 36.74, H 2.64; found C 36.78, H 2.74.

(4-Bromo-1,3-phenylene)diboronic Acid (1g): This compound was prepared as described for **1d** using an excess of $B(OEt)_3$ (7.5 g, 32 mmol) as the electrophile. The product (5.5 g, 74%) was isolated as a white powder, m.p. > 300 °C. ^1H NMR ([D$_6$]acetone, 400 MHz): δ = 8.00 (d, J = 1.5 Hz, 1 H, Ph), 7.71 (dd, J = 8.0 Hz, 1 H, Ph), 7.50 (d, 1 H, Ph), 7.34 [br., 2 H, $B(OH)_2$], 7.31 [br., 2 H, $B(OH)_2$] ppm. $^{13}C\{^1H\}$ NMR ([D$_6$]acetone, 100.6 MHz): δ = 141.4, 137.2, 131.8, 128.7 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 28 ppm. $C_6H_7B_2BrO_4$ (244.64): calcd. C 29.46, H 2.88; found C 29.84, H 3.00.

(2-Bromo-5-carboxyphenyl)boronic Acid (1h): A solution of lithiate **2b**-5Li was prepared as described for **1d**. It was cooled to –100 °C and then carboxylated by passing through a stream of dried gaseous CO_2 with rapid stirring. The resulting white slurry was left to warm up to ca 0 °C to evaporate the excess of CO_2, and then a careful hydrolysis was undertaken with H_2SO_4 (2 M aq.; 50 mL). The work-up was performed as described for **1d** to give the title compound (5.95 g, 81%) as a white powder, m.p. 230–232 °C. ^1H NMR ([D$_6$]acetone, 400 MHz): δ = 11.35 (br., 1 H, CO_2H), 8.15 (d, J = 2.0 Hz, 1 H, Ph), 7.87 (dd, J = 8.0 Hz, 1 H, Ph), 7.66 (d, 1 H, Ph), 7.57 [br., 2 H, $B(OH)_2$] ppm. $^{13}C\{^1H\}$ NMR ([D$_6$]acetone, 100.6 MHz): δ = 167.9, 136.0, 132.8, 132.1, 131.6, 129.7 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 29 ppm. $C_7H_6BBrO_4$ (244.84): calcd. C 34.34, H 2.47; found C 34.46, H 2.57.

Potassium (2,5-Dibromophenyl)trifluoroborate (3a): A solution of (2,5-dibromophenyl)boronic acid (14.0 g, 0.05 mol) in MeOH (50 mL) was treated with a solution of KHF_2 (13.5 g, 0.17 mol) in water (35 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, and the resulting slurry was filtered. The filtrate was concentrated to leave a solid, which was dried in vacuo at 90 °C. The solid was extracted with boiling acetone (3× 50 mL). Et_2O (200 mL) was added to the combined extracts to precipitate a solid, which was filtered and dried in vacuo at 150 °C to give the title compound (15.5 g, 91%) as a white powder, m.p. 253–254 °C. ^1H NMR ([D$_6$]acetone, 400 MHz): δ = 7.64 (d, J = 2.5 Hz, 1 H, Ph), 7.28 (d, J = 8.5 Hz, 1 H, Ph), 7.14 (dd, 1 H, Ph) ppm. $^{13}C\{^1H\}$ NMR ([D$_6$]acetone, 100.6 MHz): δ = 137.5, 134.3, 130.9, 127.0, 120.8 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 1.5 (q, J = 50 Hz) ppm. ^{19}F NMR ([D$_6$]acetone, 376.48 MHz): δ = –141.2 (br.) ppm. $C_6H_3BBr_2F_3K$ (341.80): calcd. C 21.08, H 0.88; found C 21.28, H 0.85.

(5-Bromo-2-formylphenyl)boronic Acid (1c): *n*BuLi (10.0 M in hexane; 1.25 mL, 12.5 mmol) was added to a stirred solution of **3a** (1.71 g, 5 mmol) in THF (50 mL) at –78 °C. After stirring for 30 min at –78 °C, the mixture become brown. Then DMF (1 mL, 13 mmol) was added, and the mixture became colorless. The mixture was stirred for 30 min, and then it was hydrolyzed with H_2SO_4 (1.5 M aq.; 20 mL). The organic phase was separated and concentrated under reduced pressure. The viscous residue was triturated with hexane (5 mL) and water (5 mL) to give a yellow solid, which was filtered and washed with CH_2Cl_2 (2× 5 mL). Drying in vacuo gave a crude product containing ca 5% of **1d**. Recrystallization from toluene/acetone (5:1) gave the title compound (0.70 g, 61%) as a white powder, m.p. 161–162 °C. ^1H NMR ([D$_6$]acetone, 400 MHz): δ = 10.20 (s, 1 H, CHO), 7.95 (d, J = 1.5 Hz, 1 H, Ph), 7.87 (d, J = 8.5 Hz, 1 H, Ph), 7.81 [br., 2 H, $B(OH)_2$], 7.79 (dd, 2 H, Ph) ppm. $^{13}C\{^1H\}$ NMR ([D$_6$]acetone, 100.6 MHz): δ = 194.7, 139.7, 137.9, 133.6, 133.3, 131.4, 129.0 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 28 ppm. $C_7H_6BBrO_3$ (228.84): calcd. C 36.74, H 2.64; found C 38.78, H 3.14.

2-(2,5-Diformylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1i): *t*BuLi (1.7 M in pentane; 26.5 mL, 45 mmol) was added to THF (50 mL) at –70 °C, and the resulting yellow solution was cooled to –90 °C. Then a solution of **1a** (4.04 g, 10 mmol) in THF (10 mL) was added while the temperature was kept below –85 °C. The resulting mixture was stirred for 20 min at –85 °C, then it was cooled to –90 °C, and DMF (4 mL, 50 mmol) was added. The resulting white slurry was stirred for 30 min and hydrolyzed with H_2SO_4 (1.5 M aq.; 20 mL). The organic phase was separated, and the solvents were evaporated under reduced pressure. The viscous residue was treated with pinacol (1.34 g, 12 mmol) in Et_2O (10 mL). The solvent was evaporated to give a crude solid product, which was filtered and washed with water (2× 5 mL). It was purified by recrystallization from hexane (15 mL) to give the title compound (1.54 g, 59%) as crystals, m.p. 98–99 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 10.67 (s, 1 H, CHO), 10.13 (s, 1 H, CHO), 8.39 (s, 1 H, Ph), 8.10 (d, J = 8.0 Hz, 1 H, Ph), 8.07 (d, 1 H, Ph), 1.41 (s, 12 H, CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ = 193.9, 191.7, 145.0, 138.4, 137.7, 131.0, 128.1, 84.9, 24.9 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 31 ppm. $C_{14}H_{17}BO_4$ (260.09): calcd. C 64.65, H 6.59; found C 64.35, H 6.51.

Benzene-1,2,4-triboronic Tris(pinacolate) (1j): This compound was prepared as described for **1i** using an excess of $B(OiPr)_3$ as the electrophile. The crude benzene-1,2,4-triboronic acid was treated with pinacol (3.6 g, 30 mmol) in acetone (15 mL). The solvent was removed in vacuo, and the crude product was washed with water (2× 5 mL) and recrystallized from hexane to give the title compound (3.53 g, 77%) as a white powder, m.p. 214–215 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.08 (s, 1 H, Ph), 7.79 (dd, J = 7.0, 1.5 Hz,

1 H, Ph), 7.61 (dd, J = 1.0 Hz, 1 H, Ph), 1.36 (s, 24 H, Pin), 1.33 (s, 12 H, Pin) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ = 139.5, 135.3, 132.4, 83.85, 83.78, 83.66, 24.92, 24.87, 24.84 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 31 ppm. $C_{24}H_{39}B_3O_6$ (456.00): calcd. C 63.21, H 8.62; found C 62.39, H 8.49.

(2,5-Dicarboxyphenyl)boronic Acid (1k): A mixture containing lithiate **1b**-2,5Li_2 was prepared from **1a** (2.46 g, 6.0 mmol) as described for **1i**. It was cooled to –110 °C, and then it was carboxylated by passing through a stream of dried gaseous CO_2 with rapid stirring. The resulting white slurry was left to warm up to ca 0 °C to evaporate the excess of CO_2. Then it was subjected to careful hydrolysis with H_2SO_4 (2 M aq.; 30 mL). The work-up was performed as described for **1i** to give the title compound (0.85 g, 69%) as a white powder M.p. > 300 °C (dec). ^1H NMR ([D_6]acetone + D_2O, 400 MHz): δ = 8.12 (b, 1 H, Ph), 7.94 (d, J = 8.0 Hz, 1 H, Ph), 7.82 (1 H, Ph) ppm. $^{13}C\{^1H\}$ NMR ([D_6]acetone + D_2O, 100.6 MHz): δ = 171.3, 168.4, 146.2, 138.7, 133.8, 131.7, 129.7, 127.1 ppm. ^{11}B NMR ([D_6]acetone + D_2O, 64.16 MHz): δ = 28 ppm. $C_8H_7BO_6$ (209.95): calcd. C 45.77, H 3.36; found C 45.73, H 3.61.

6-Butyl-2-[3-(2,5-dibromothienyl)]-1,3,6,2-dioxazaborocane (4a): A solution of thiophene-3-boronic diethyl ester (36 g, 0.2 mol) in CH_2Cl_2 was cooled to –60 °C, and then a solution of Br_2 (64 g, 0.2 mol) in CH_2Cl_2 was added dropwise. The temperature was kept below –50 °C during the addition. The resulting yellow solution was warmed up to 0 °C to complete the reaction. Then it was cooled to –60 °C and diluted with Et_2O (100 mL), and then Et_3N (42 g, 0.42 mol) was added dropwise. The resulting thick slurry was diluted with hexane (100 mL) and filtered under an argon atmosphere. The white precipitate of the ammonium salt by-product (Et_3NHBr) was washed with Et_2O. The yellow filtrate was concentrated to give an oily residue, which was subjected to fractional vacuum distillation to give crude 2,5-dibromothiophene-3-boronic diethyl ester (55 g, 0.161 mol), b.p. 135–140 °C. This material was dissolved in Et_2O, and a solution of *N*-butyldiethanolamine (27 g, 0.168 mol) in Et_2O (80 mL) was added in one portion. The formation of a white crystalline precipitate was observed after a few minutes. The resulting slurry was cooled to –50 °C and filtered. The solid was washed with Et_2O (2 × 50 mL) and dried in vacuo to give the final product (56 g, 68%), m.p. 86–88 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.01 (s, 1 H, Th), 4.08 (m, 4 H, CH_2O), 3.11 (m, 2 H, CH_2N), 3.04 (m, 2 H, CH_2N), 2.57 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.54 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.22 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 0.87 (t, J = 7.0 Hz, 3 H, $NCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 136.7, 115.0, 109.4, 62.8, 58.5, 57.6, 26.8, 20.2, 13.7 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 11 ppm. $C_{12}H_{18}BBr_2NO_2S$ (410.96): calcd. C 35.07, H 4.41, N 3.41; found C 35.40, H 4.64, N 3.48.

(5-Bromo-2-formyl)thiophene-3-boronic Acid (4c): A solution of **4a** (4.12 g, 10 mmol) in THF (15 mL) was added to a stirred solution of *n*BuLi (10 M; 1.0 mL, 10 mmol) in THF (15 mL) at –85 °C. After ca 15 min stirring at ca. –80 °C (internal temperature), the mixture containing lithiate **4b**-2Li was quenched with DMF (1.1 g, 15 mmol) in Et_2O (5 mL). The mixture was stirred for 30 min, and then it was hydrolyzed with sulfuric acid (1.5 M aq.; 10 mL). The aqueous phase was separated, then it was extracted with diethyl ether (2 × 15 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure. The crude product was washed with water (3 × 10 mL) and CH_2Cl_2 (10 mL) to give the title compound (1.5 g, 64%) as a pale yellow powder, m.p. > 155 °C (dec). ^1H NMR (400 MHz, [D_6]acetone): δ = 10.21 (s, 1 H, CHO), 8.00 [br, 2 H, $B(OH)_2$], 7.56 (s, 1 H, Th) ppm. ^{13}C NMR ([D_6]acetone, 100.6 MHz): δ = 185.5, 152.8, 139.3, 122.8 ppm. ^{11}B NMR ([D_6]acetone, 64.16 MHz): δ = 27 ppm. $C_5H_4BBrO_3S$ (234.87): calcd. C 25.57, H 1.72; found C 25.31, H 1.71.

5-Bromothiophene-2,3-diboronic Acid (4d): A solution containing lithiate **4b**-2Li (obtained as described for **4c**) was quenched with a solution of $B(OMe)_3$ (1.2 g, 11.5 mmol) in Et_2O (5 mL). Work-up was carried out as described for **4c**. The title compound (1.8 g, 72%) was obtained as a white powder, m.p. 114–115 °C. ^1H NMR ([D_6]acetone, 400 MHz): δ = 8.33 [s, 2 H, $B(OH)_2$], 8.24 [s, 2 H, $B(OH)_2$], 7.57 (s, 1 H, Th) ppm. $^{13}C\{^1H\}$ NMR ([D_6]acetone, 100.6 MHz): δ = 139.5, 116.6 ppm. ^{11}B NMR ([D_6]acetone, 64.16 MHz): δ = 27 ppm. $C_4H_5B_2BrO_4S{\cdot}H_2O$ (268.69): calcd. C 17.88, H 2.63; found C 18.26, H 2.71.

5-Bromothiophene-2,4-diboronic Acid (4e): A solution of **4a** (4.11 g, 10 mmol) and $B(OiPr)_3$ (2.1 g, 11.2 mmol) in THF (25 mL) was added to a stirred solution of *n*BuLi (1.6 M in hexane; 6.5 mL, 10.4 mmol) at –85 °C. After ca 15 min stirring at ca –80 °C (internal temperature), work-up was carried out as described for **4c** to give crude product **4e** containing ca 20% of isomeric compound **4d**. It was purified by the addition of Et_2O/CH_2Cl_2/hexane (1:1:1, 30 mL). The resulting suspension was stirred for 30 min and then filtered to give **4e** (1.7 g, 66%) as a white powder, m.p. > 400 °C. ^1H NMR ([D_6]acetone, 400 MHz): δ = 7.68 (s, 1 H, Th), 7.45 [s, 2 H, $B(OH)_2$], 7.18 [s, 2 H, $B(OH)_2$] ppm. $^{13}C\{^1H\}$ NMR ([D_6]-acetone, 100.6 MHz): δ = 143.1, 125.3 ppm. ^{11}B NMR ([D_6]-acetone, 64.16 MHz): δ = 27 ppm. $C_4H_5B_2BrO_4S{\cdot}H_2O$ (268.69): calcd. C 17.88, H 2.63; found C 18.30, H 2.66.

2,5-Dicarboxythiophene-3-boronic Acid (4f): A solution of **4a** (4.11 g, 10 mmol) in THF (20 mL) was added to a stirred solution of *n*BuLi (10 M; 2.2 mL, 22 mmol) in THF (30 mL) at –80 °C. After ca 30 min stirring at ca –75 °C (internal temperature), the solution of lithiate **4b**-2,5Li_2 was cooled to –110 °C and then carboxylated by passing through a stream of dried gaseous CO_2 with rapid stirring. The resulting white slurry was left to warm up to ca 0 °C to evaporate the excess of CO_2, and then careful hydrolysis with H_2SO_4 (2 M aq.; 15 mL) was undertaken. Further work-up was carried out as described for **4c** to give the title compound (2.0 g, 92%) as a white powder, m.p. > 320 °C (dec). ^1H NMR ([D_6]acetone, 400 MHz): δ = 8.08 (s, 1 H, Th) ppm. $^{13}C\{^1H\}$ NMR ([D_6]DMSO, 100.6 MHz): δ = 166.9, 163.1, 144.9, 141.7, 139.1 ppm. ^{11}B NMR ([D_6]DMSO, 64.16 MHz): δ = 28 ppm. $C_6H_5BO_6S$ (215.98): calcd. C 33.37, H 2.33; found C 33.69, H 2.66.

2,5-Diformylthiophene-3-boronic Acid (4g): A solution containing dilithiate **4b**-2,5Li_2 (obtained as described for **4f**) was quenched with a solution of DMF (2.2 g, 30 mmol) in Et_2O (10 mL). Further work-up was carried out as described for **4c** to give the title compound (1.6 g, 87%) as a pale pink powder, m.p. 148–150 °C (dec). ^1H NMR (400 MHz, [D_6]acetone): δ = 10.46 (s, 1 H, CHO), 10.08 (s, 1 H, CHO), 8.29 (s, 1 H, Th), 8.08 [br, 2 H, $B(OH)_2$] ppm. ^{13}C NMR ([D_6]acetone, 100.6 MHz): δ = 187.6, 185.3, 156.0, 148.8, 143.9 ppm. ^{11}B NMR ([D_6]acetone, 64.16 MHz): δ = 27 ppm. $C_6H_5BO_4S{\cdot}0.5H_2O$ (192.99): calcd. C 37.34, H 3.13; found C 37.48, H 3.04.

2-[2,5-Bis(*tert*-butylcarboxamido-3-thienyl)]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4h): A solution containing dilithiate **4b**-2,5Li_2 (obtained as described for the synthesis of **4f**) was quenched with a solution of *t*BuNCO (2.2 g, 22 mmol) in Et_2O (20 mL) at –90 °C. The mixture was stirred for 30 min at –75 °C and then hydrolyzed with H_2SO_4 (2 M aq.; 15 mL). The aqueous phase was separated and then extracted with diethyl ether (2 × 15 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure to give a viscous residue. Pinacol (1.2 g, 10 mmol) and hexane (15 mL) were added, and the mixture was stirred for

1 h at 40 °C. The resulting white suspension was filtered. The crude product was washed with water and hexane (10 mL), dried, and recrystallized from hexane/CH_2Cl_2 (1:1, 20 mL) to give **4h** (2.6 g, 64%) as a white powder, m.p. 248–250 °C. ^{1}H NMR (400 MHz, [D_6]acetone): δ = 8.61 (br., 1 H, NH), 7.77 (s, 1 H, Th), 7.42 (br., 1 H, NH), 1.43 (s, 9 H, *t*Bu), 1.42 (s, 9 H, *t*Bu), 1.40 (s, 12 H, Pin) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 161.4, 161.2, 156.7, 144.6, 135.4, 86.1, 52.4, 52.3, 28.9, 28.8, 25.1 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 26 ppm. $C_{20}H_{33}BN_2O_4S$ (408.37): calcd. C 58.82, H 8.15, N 6.86; found C 58.79, H 7.87, N 6.80.

X-Ray Data: Suitable crystals were obtained by slow evaporation of an acetone solution of **1g**. Single crystal X-ray measurements of **1g** were performed with graphite-monochromated Mo-K_α radiation using a Kuma KM4CCD κ-axis diffractometer equipped with an Oxford Cryosystems nitrogen gas-flow apparatus. Data reduction and analysis were carried out with the Oxford Diffraction Ltd. suite of programs.[29] All structures were solved by direct methods using SHELXS-97 and refined using SHELXL-97.[30] The refinement was based on F^2 for all reflections except those with very negative F^2. All non-hydrogen atoms were refined anisotropically.

1g: $C_6H_7B_2BrO_4$; molecular weight, 244.64; T = 100(2) K; monoclinic space group *Cc*; unit cell dimensions, a = 28.918(3), b = 3.770(1), c = 16.676(2) Å, α = 90, β = 109.88(1), γ = 90°, V = 1709.7(3) Å^3; Z = 4; d_{calc} = 1.901 g cm^{-3}; absorption coefficient μ = 4.781 mm^{-1}; F(000) = 960; crystal size, 0.15 × 0.12 × 0.02 mm; τ range for data collection: 2.29–33.93°; index ranges: $-39 < h < 39$, $-5 < k < 5$, $-22 < l < 22$; reflections collected: 8066; unique: 3746 (R_{int} = 0.0615); absorption correction – multi-scan; refinement method – full-matrix least-squares on F^2; goodness-of-fit on F^2, GooF = 1.062; data/restraints/parameters 3746/2/235; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0410, wR_2 = 0.0660; R indices (all data): R_1 = 0.0538, wR_2 = 0.0623; weight: $1/[\sigma^2(F_o^2) + (0.0775P)^2 + 0.28P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$; largest diffraction peak and hole: 0.61 and –0.59 e Å^{-3}.

CCDC-917887 contains 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.

Theoretical Calculations: All geometry optimizations and frequency calculations were carried out with the GAUSSIAN 09 suite of programs[21] and Becke-style three-parameter density functional method using the Lee–Yang–Parr correlation functional (B3LYP) was applied.[22] The 6-31+G(d)[23] basis sets were used to calculate the optimal geometries. The minima were confirmed by vibrational frequency calculations [B3LYP/6-31+G(d)] within harmonic approximation (no imaginary frequencies). To optimize the structures of transition states, a synchronous transit-guided quasi-Newton approach (qst3) was applied. In this method, three input structures are needed: one corresponds to substrates, one to products and one is a guess of a transition state. To verify the structures of the transition states, frequency calculations were carried out at the B3LYP/6-31+G(d) level of theory. One imaginary frequency was found in all cases.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra, computational details, and crystallographic data as a CIF file. This material is available free of charge via the Internet at http://www.eurjoc.org.

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