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On the Directing Effect of Boronate Groups in the Lithiation of Boronated Thiophenes

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An investigation of thiophene boronates has revealed the usefulness of a metalation reaction in the synthesis of various lithiated thiophene boronates, which were further converted to functionalized thiopheneboronic derivatives. The lithiation of 2- and 3-thienylboronic *N*-butyldiethanolamine (BDEA) esters with lithium diisopropylamide and lithium 2,2,6,6-tetramethylpiperidide showed that both boronated thiophenes were readily deprotonated. In the latter case, lithiation at the 2-position adjacent both to sulfur and the borocanyl group is thermodynamically favoured due to the significant stabilizing effect of the borocanyl group. Further derivatization with a range of electrophiles followed by hydrolysis afforded various 2-substituted 3-thiopheneboronic acids. Lithiation of the corresponding thiopheneboronic "ate" complexes of the type [ThB(OR)$_3$]Li revealed that the 2-thienyl derivatives could not be effectively deprotonated, whereas the "ate" complex, [3-ThB(OEt)$_3$]Li, was selectively lithiated with *n*BuLi at C-2. This points to a directing effect of the anionic boronate moiety. The resulting bimetallic species, [(2-Li-3-Th)B(OEt)$_3$]Li, underwent ring-closing dimerization upon heating to give, after subsequent hydrolysis, 4,8-dihydro-4,8-dihydroxy-*p*-diborino[2,3-*b*:5,6-*b*′]dithiophene − a cyclic diborinic acid. A computational study of the lithiation of boronated thiophenes and furans proved that boronation decreases ring-proton acidity. This effect is much stronger for the boronic "ate" complexes than for the corresponding neutral BDEA esters. Calculations of the transition states have shown that the specific directing effect of boronate groups in 3-thienyl derivatives is due to intramolecular oxygen–lithium coordination.

Introduction

Arylboron compounds are important as versatile and convenient reagents in modern organic synthesis. They are intensively used in C–C and other cross-coupling reactions. Their applications in analytical and materials chemistry also seem promising.[1] Thus, it is highly desirable to develop new synthetic strategies that lead to new functionalized derivatives. Bimetallic lithium–boron aromatic reagents are valuable intermediates, which can be readily converted into functionalized arylboronic acids and esters,[2,3] although they have attracted limited interest to date. However, results have been recently published and reviewed by our group.[4] Despite a high demand for heteroarylboron compounds in recent years, there are essentially no reports devoted to the synthesis and reactions of heteroaryllithium–boron aromatic derivatives. In this work, we report the generation of such compounds from thiophene boronates and their conversion into functionalized thiophene boronates. It should be stressed that boronated thiophene derivatives are widely used as building blocks in Suzuki–Miyaura cross-coupling reactions that lead to a wide range of heterobiaryl systems.[5] These include conducting polymers and luminescent materials based on oligothiophene cores.[6] To the best of our knowledge, our results show for the first time that the lithiation of the aromatic ring is directed by boronate-type groups.

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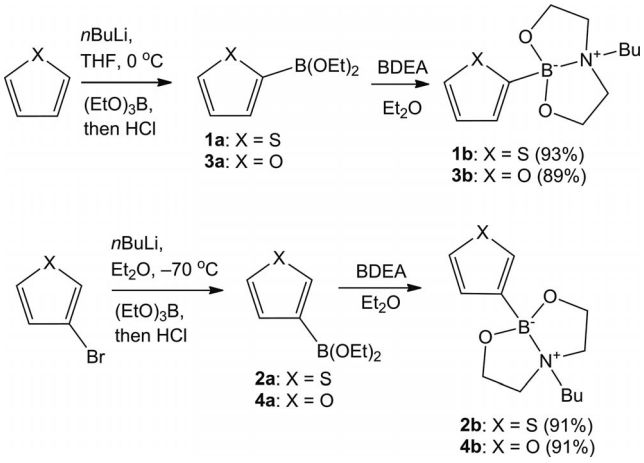
Results and Discussion

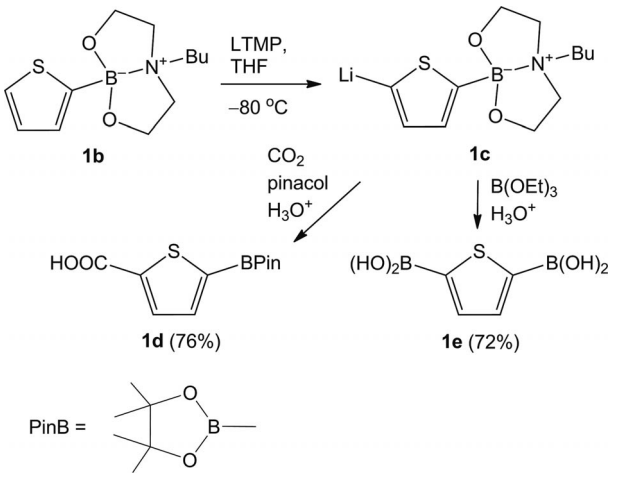
Lithiation of Thiopheneboronic BDEA Esters

The synthesis of thiopheneboronic azaesters **1b** and **2b** was accomplished using a stepwise protocol, which involved the lithiation of thiophene followed by transmetalation with trialkylborate and quenching with ethereal HCl. The resulting thiopheneboronic diethyl esters **1a** and **2a** were isolated by fractional distillation and treated with *N*-butyldiethanolamine in Et_2O to give crystalline products (Scheme 1). The same protocol was successfully applied to the synthesis of analogous furanboronic azaesters **3b** and **4b**. All products were obtained in high yields.



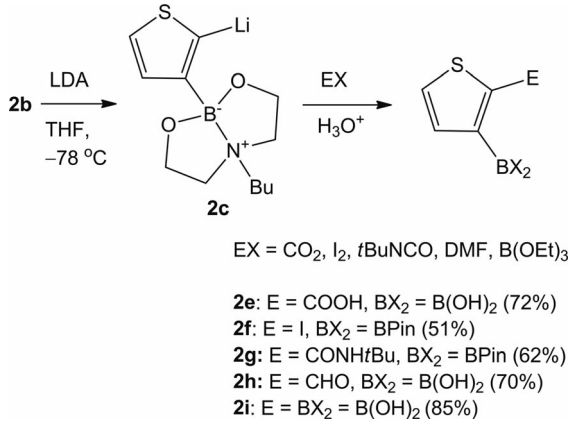
Scheme 1. The synthesis of **1b**–**4b**.

We have previously shown that halogenated phenylboronic azaesters are metalated cleanly using nonnucleophilic bases, such as lithium dialkylamides, whereas alkyllithiums can be problematic as boron alkylation occurs to some extent.[7] Thus, deprotonative lithiation of **1b** proceeded readily at C-5 using either lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LTMP) at ca. –80 °C (internal temperature), and the resulting bimetallic species, **1c**, was carboxylated by saturation with CO_2 at ca. –100 °C. The addition of pinacol and hydrolysis afforded 2-(5′-carboxy-2′-thienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1d**) in 76% yield (Scheme 2). The structural formulation of **1d** was based on its ^{1}H NMR spectrum, in which two doublets with a coupling constant of J = 3.5 Hz appear in the aromatic region. Such a value is typical of 3-H,4-H coupling in thiophene derivatives.[8] When the lithiation was performed at a slightly higher temperature using a dry ice/acetone bath (internal temperature ca. –70 °C), **1d** was isolated in a much lower yield (ca. 25%). This suggests that **1c** is thermally unstable. However, it can be effectively trapped using an internal electrophile. Thus, in situ lithiation/boronation[9] of **1b** with LDA/B(O*i*Pr)$_3$ at ca. –65 °C followed by hydrolysis gave thiophene-2,5-diboronic acid (**1e**) [10] in good yield as evidenced from its ^{1}H NMR spectrum, in which a singlet resonance of two thiophene ring protons at 7.69 ppm indicates the regioselective formation of the symmetrical structure.



Scheme 2. Lithiation of **1b**.

The metalation of **2b** with LDA occurred smoothly at ca. –80 °C. Two isomeric products, **2c** and **2d**, could potentially be formed due to proton abstraction at C-2 and C-5, respectively. Based on previous results, we initially expected that lithiation at C-2 would be disfavoured due to the steric hindrance and electron-donating properties of the adjacent borocanyl moiety. To our surprise, the 2-lithiated intermediate **2c** was formed exclusively as evidenced by the regioselective formation of a range of 2-substituted thiophene-3-boronic acids **2e**–**2i** upon treatment with electrophiles (Scheme 3). The formation of thiophene-2,3-diboronic acid (**2i**) was confirmed by single-crystal X-ray diffraction. To the best of our knowledge, this is the first crystal structure of an *ortho*-diboronic acid. The molecular structure of **2i** is shown in Figure 1 (a). One molecule of **2i** is accompanied by 1.5 molecules of H_2O in the asymmetric part of the unit cell. Both boronic acid groups are almost coplanar with the aromatic ring. The C(1)- and C(2)-bound $B(OH)_2$ groups adopt *exo*–*exo* and *endo*–*exo* conformations, respectively. The *endo*-oriented OH group is engaged in a strong intramolecular hydrogen bond with O(2) with an O(2)···O(3) distance of 2.633(1) Å. Classical hydrogen bonded, centrosymmetric $B(OH)_2\cdots_2(HO)B$ dimers[11] are not present in the structure of **2i**. Instead, several other supramolecular motifs were formed. The most basic of which involves intermolecular O(1)–H(1)···O(4) bridges that give rise to molecular chains parallel to the [110] or [1–10] directions. Two adjacent antiparallel chains are connected through water molecules to form a double chain (Figure 1, b). The 3D supramolecular structure is reinforced by additional lateral H-bonding interactions.



Scheme 3. Lithiation of **2b** and the regioselective formation of 2-substituted thiophene-3-boronic acids **2e**–**2i**.

When the lithiation of **2b** was performed with the sterically more demanding base LTMP followed by boronation and hydrolysis, a mixture of isomeric thiophenediboronic

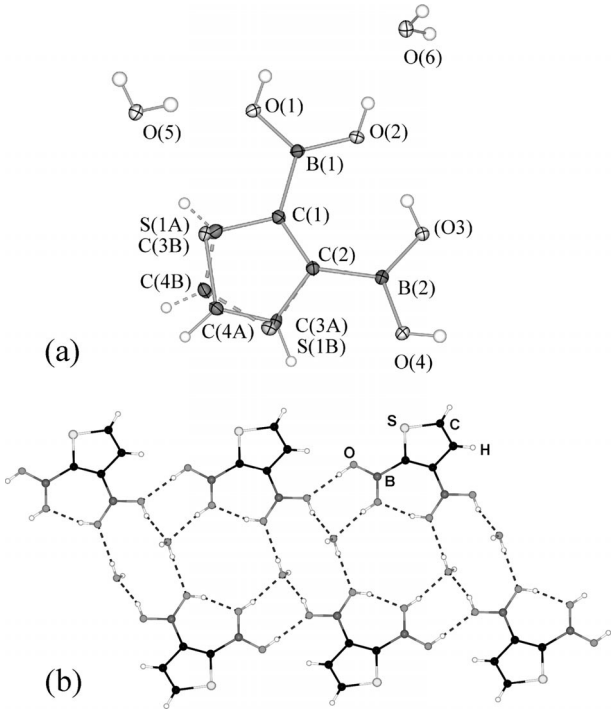
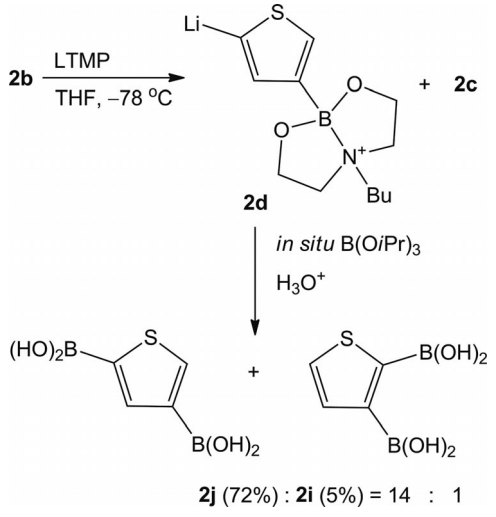


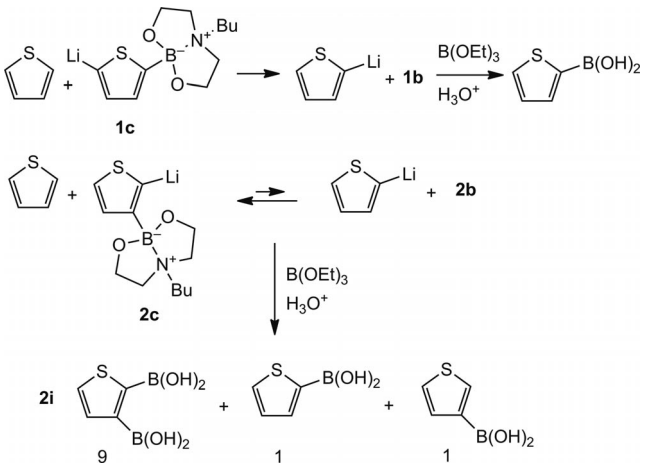
Figure 1. (a) Labelling of atoms and visualization of their atomic displacement parameters at the 50% probability level in **2i**. (b) Fragments of the crystal lattice of **2i** showing the hydrogen-bonded double chain formed between diboronic acid and water. Hydrogen bonds are shown as dashed lines.

acids was formed. The main product, **2i**, was contaminated with a significant proportion of thiophene-2,4-diboronic acid (**2j**, ca. 30%). In situ lithiation/boronation of **2b** with LTMP/B(O*i*Pr)$_3$ at ca. –80 °C followed by hydrolysis gave **2j** with only ca. 6% **2i** (Scheme 4). Compound **2j** was subsequently converted into the isomerically pure bis(pinacol) ester **2k** whose structure was confirmed by its ^{1}H NMR spectrum, which showed two separate singlets from non-equivalent BPinacol groups as well as two doublets in the aromatic region with a long-range coupling constant between the thiophene ring protons $J_{3\text{-H},5\text{-H}}$ = 1.0 Hz.[8] These results indicate that the lithiation of **2b** with LTMP is kinetically favoured at C-5 and the resulting bimetallic derivative **2d** shows a strong tendency to form a thermodynamically more stable 2-lithio isomer **2c**.

Equilibration experiments were performed to assess the relative basicities of **1c** and **2c** with respect to 2-thienyllithium. When a solution of 1 equiv. of **1c** (prepared from **1b** and LDA/THF at –80 °C) was treated with 1 equiv. of thiophene followed by the addition of (EtO)$_3$B and hydrolysis, thiophene-2-boronic acid (almost 2 equiv.) was obtained as the sole product (Scheme 5). This indicates that the complete reprotonation of **1c** with thiophene occurred to give a mixture of **1b** and 2-thienyllithium, the latter being transmetalated with (EtO)$_3$B to produce the corresponding "ate" complex. Aqueous acidic hydrolysis of both boronated thiophenes provided thiophene-2-boronic acid. A similar experiment was carried out with **2c** in combination with thiophene. In this case, after the addition of (EtO)$_3$B and hydrolysis, diboronic acid **2i** was isolated as the main product, which was contaminated with only a small amount of thiophene-2-boronic (ca. 9%) and thiophene-3-boronic (ca. 9%) acids. To summarize this point, **1c** seems to be more basic than 2-thienyllithium, which can be rationalized in terms of the σ-donor properties of the borocanyl group, which result in the decreased acidity of the thiophene ring in **1b** with respect to the parent thiophene. This effect should be even more pronounced for the **2b**/thiophene pair as the borocanyl group is closer to the deprotonation site. The increased stability of **2c** is thus somewhat confusing but it can be reasonably explained by assuming extra stabilization due to the intramolecular chelation of the lithium atom by one or two oxygen atom(s) from the borocanyl moiety. To the best of our knowledge, this is the first clear evidence of the activating and *ortho*-directing effect of the boronic ester group in aromatic lithiation. It should be noted that related intramolecular Li–F coordination has been invoked in the *ortho*-lithiation of BF_3 complexes of *N*,*N*-dimethylanilines.[12]

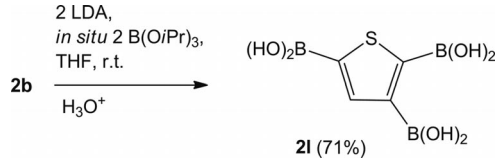


Scheme 4. Lithiation/in situ boronation of **2b**.



Scheme 5. Acid–base equilibration between thiophene and **1c**–**2c**.

Surprisingly, it was even possible to obtain thiophene-2,3,5-triboronic acid (**2l**, isolated as the trihydrate) by a double in situ lithiation/boronation of **2b** with LDA/$B(OiPr)_3$ (Scheme 6). It should be stressed that the second lithiation must involve proton abstraction from the diboronated intermediates, which are strongly electronically deactivated due the presence of the anionic boronate moiety. Nevertheless, the reaction occurred readily, and **2l** was formed in good yield.

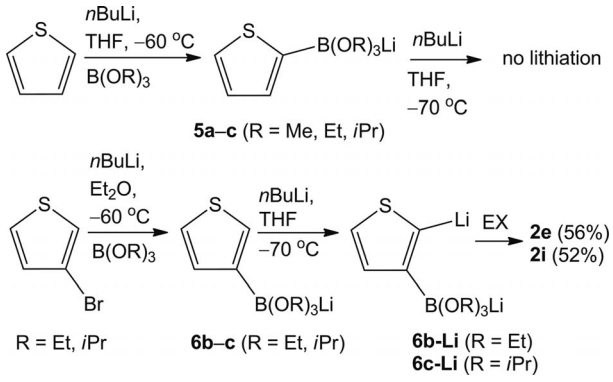


Scheme 6. Synthesis of **2l**.

Unfortunately, furanboronic azaesters **3b** and **4b** were not susceptible to metalation even using an in situ protocol that involved lithiation/boronation with LTMP/$B(OiPr)_3$ at room temperature. This is consistent with the much weaker acidity of furan (pK_a 35.6) with respect to thiophene (pK_a = 33.0) measured in tetrahydrofuran (THF).[13] LTMP is sufficiently basic to deprotonate furan (LTMP pK_a = 37.3),[13] but boronation decreases the acidity of the furan ring. Thus, the proton transfer step becomes kinetically and thermodynamically suppressed. Hence, we were unable to observe the anticipated directing effect (apparently thermodynamic in nature) of the borocanyl moiety during the attempted lithiation of **4b**.

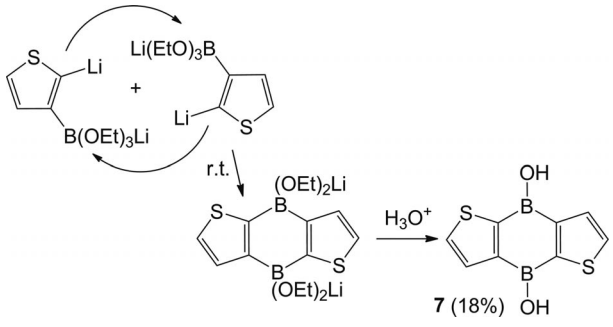
Lithiation of Lithium Thienyl(trialkoxy)borates

We next embarked on a study of the deprotonative lithiation of lithium thienyl(trialkoxy)borates. They were obtained simply by treatment of thienyllithiums with a trialkylborate and used in the key step without isolation. It has been shown previously that selected lithiated lithium phenyl(trialkoxy)borates can easily be obtained by halogen–lithium exchange from brominated or iodinated precursors.[3] However, lithium 2-thienyl(trialkoxy)borates **5a**–**c** [2-ThB$(OR)_3$Li, R = Me, Et, *i*Pr] are resistant against deprotonation using lithium amide bases even at room temperature (Scheme 7). Furthermore, the internal electrophile $B(OiPr)_3$ was employed to shift the assumed equilibrium to the product side but this approach also failed. No reaction was also observed with *n*BuLi as the metalating agent, whereas related lithium 2-thienylcarboxylate can be deprotonated at C-3 or C-5 with *n*BuLi or LDA, respectively.[14] In a simple generalization, this decreased reactivity can be rationalized in terms of the weaker acidity of aryl(trialkoxy)borates due to the strong electron-donating properties of the anionic trialkoxyborate moiety, $B(OR)_3^-$. A different situation was observed in the case of lithium 3-thienyl(trialkoxy)borates **6a**–**c**, R = Me, Et and *i*Pr, respectively, which are also unreactive towards lithium dialkylamides. Surprisingly, **6c** was lithiated with *n*BuLi (1.2 equiv.) in Et_2O/THF (ca. 3:1) at –70 °C. Quenching with $B(OR)_3$ and hydrolysis gave a mixture of diboronic acid **2i** (ca. 60%) and 3-thiopheneboronic acid (ca. 40%). The lithiation of **6b** was more effective as the crude reaction mixture contained ca. 75% **2i** and only 25% 3-thiopheneboronic acid. Similarly, the carboxylation of **6b-Li** resulted in the formation of **2e**. The extent of the lithiation of **6b** was not improved even when a large excess of *n*BuLi (1.5 equiv.) was used. Surprisingly, the related "ate" complex **6a** could not be metalated. Unlike **6b** and **6c**, **6a** underwent extensive boron alkylation as evidenced by the formation of dibutyl(methoxy)borane and tributylborane as the major products. The lithiation of **6b** and **6c** seems to proceed via the intermediate prelithiation complex formed between *n*BuLi and one (or two) oxygen atoms of the $B(OR)_3^-$ group. Thus, this is a specific example of a complex-induced proximity effect (CIPE) mechanism,[15] which involves the anionic boronate as the directing group in the aromatic lithiation. In addition, we have attempted to perform the lithiation of the analogous "ate" complex 3-FuB$(OEt)_3$Li. Unfortunately, it was totally unreactive, which is in accordance with the similar behaviour of related **4b**.



Scheme 7. Synthesis and lithiation of thiopheneboronic "ate" complexes.

We have investigated the thermal behaviour of **6b-Li**. Thus, **6b** was treated with 1.1 equiv. of *n*BuLi and warmed to room temperature. Hydrolysis and subsequent workup afforded the cyclic diborinic acid 4,8-dihydro-4,8-dihydroxy-*p*-diborino[2,3-*b*:5,6-*b*′]dithiophene (**7**) in low yield (Scheme 8). This compound is apparently formed by the ring-closing dimerization of **6b-Li**, which involves the



Scheme 8. The formation of **7**.

nucleophilic attack of the carbanionic centres at C-2 on the boron atoms at C-3′ of the partner molecule. The question of whether the process is preceded by the dissociation of anionic $B(OR)_3^-$ group to give the Lewis acidic $B(OR)_2$ group remains open.

Computational Studies

In order to obtain more information about possible deprotonation mechanisms of the studied thiophene "ate" complexes and azaesters, computational studies of the lithiated thiophene boronates as well as the appropriate transition states have been performed. Directed lithiation reactions are often supposed to proceed according to the CIPE mechanism,[15] where the directing group (e.g. amide, carbamate) brings the base close to the acidic hydrogen atom by precomplexation of the lithium atom. However, other effects should also be considered, particularly the increased/decreased acidity of the hydrogen atoms in the neighbourhood of the electron-withdrawing/donating groups or aromatic ring heteroatoms (e.g. sulfur). In the initial calculations, we compared the acidities of selected protons by calculating their deprotonation energies.

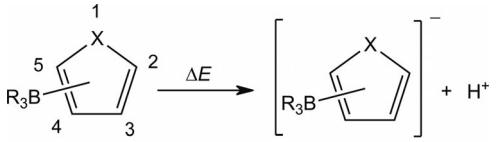
Deprotonation Energies

The deprotonation energies of hydrogen atoms can be determined by calculating the heterolytic proton dissociation energies ($AH = A^- + H^+$). Such an approach has been successfully applied in studies on the substituent additive effects on acidity in a series of oligofluorobenzenes and oligochlorobenzenes.[16] The calculations were performed at the B3LYP[17]/aug-cc-pVDZ[18] level of theory. It should be stressed that the values for the deprotonation energies do not correspond to the real energies of lithiation and are used only to compare the acidity levels of selected protons.

As expected, 2-H and 5-H are the most acidic and, therefore, more susceptible to abstraction (Table 1). It is well known that thiophene is significantly more acidic than furan. Indeed, the energy difference of proton abstraction in these two compounds from C-2 and C-3 are 41 and 38 kJ mol^{-1}, respectively. These differences are less pronounced in the case of the "ate" and "aza" derivatives. For instance, proton abstraction from C-2 in **2b** costs 12 kJ mol^{-1} less energy than that in the corresponding position in **4b**. As a result of the strong electron-donating effect of the $B(OEt)_3^-$ group and the negative charge of the molecule, the deprotonation energies of boronate derivatives **5b** and **6b** are systematically larger in comparison with their azaester analogues **1b** and **2b**. This is consistent with the experimental results as only **6b** (and its analogue **6c**) was effectively deprotonated at C-2 with *n*BuLi, whereas azaesters **1b** and **2b** were more reactive and were lithiated with less basic lithium dialkylamides.

The presence of the boronate or borocanyl group decreases the acidity of the neighbouring protons. As expected, this effect is significantly larger for the anionic boronates. For example, the differences between the energies of proton abstraction at C-2 and C-5 in **2b** and **6b** are 13 and 15 kJ mol^{-1}, respectively. Nevertheless, according to the experimental results, **6b** can only be lithiated in the vicinity of the $B(OEt)_3^-$ group, which suggests that a potent directing effect of this substituent should be considered in the metalation process. To summarize this point, the proton abstraction from thiophene and furan rings is disfavoured upon boronation (from a kinetic point of view), and this effect strongly depends on the position and type of boronate group.

Table 1. Deprotonation energies (ΔE) of the boronated thiophene and furan derivatives. The positions of the boron-containing functional group BR_3 and the deprotonation site are assigned according to the scheme.



X = S **1b**, **2b**, **5b**, **6b** X = O **3b**, **4b**

R_3B = $B(OEt)_3^-$ ("ate") or $B(OCH_2CH_2)_2NBu$ ("aza")

Substrate	ΔE [kJ mol^{-1}]			
	2	3	4	5
Thiophene	1640	1673	–	–
1b	"aza"	1731	1722	1690
2b	1713	"aza"	1737	1700
5b	"ate"	2010	1979	1948
6b	1995	"ate"	2001	1945
Furan	1681	1701	–	–
3b	"aza"	1753	1729	1703
4b	1725	"aza"	1743	1713

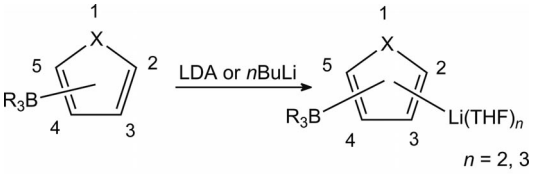
Lithiation of Thiopheneboronic BDEA Esters – Transition State Calculations

We next turned our attention to the lithiation reaction mechanism. There are several possible reaction pathways for metalation with *n*BuLi and LDA. In the two most common and frequently considered pathways, deprotonation occurs by dimeric ([*n*BuLi·2THF]$_2$, [LDA·2THF]$_2$) or monomeric bases (*n*BuLi·3THF, LDA·3THF). Intensive studies of benzene deprotonation by *n*BuLi/tetramethylethylenediamine and *n*BuLi/(*R*,*R*)-*trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexanediamine conducted by Collum[19] and Strohmann,[20] respectively, concluded that the mechanisms that proceed via monomer- and dimer-based transition states shows similar energy barriers. We decided to investigate the reactions using a monomer-based approach.

Metalation of **1b** and **2b** proceeded with monomeric LDA·3THF. Collum et al.[21] have shown that this form dominates in the in situ prepared LDA solution in THF. The intermediate prelithiated complexes are similar in energies to the reactants. The kinetically controlled regioselectivity of the lithiation of **2b** is dominated by the strong activating effect of the sulfur atom together with a significant contribution of the steric effect of the borocanyl group. We found that the disolvated structure of **2b**–**2Li** is the most

stable in the **2b-Li** series (Table 2). However, calculations of the transition state structures show that the formation of the **2b-5Li** isomer is kinetically more favoured. The energy barrier for lithiation at C-5 is 45.1 kJ mol^{-1}, whereas the formation of the **[2b-5Li]**‡ transition state requires 55.5 kJ mol^{-1} (Figure 2). The transition state structures of **[2b-2Li]**‡ and **[2b-5Li]**‡ are depicted in Figure 3 (a and b). This finding is in agreement with the calculated relative deprotonation energies at C-2 and C-5 (Table 1). For sterically more demanding bases, such as LTMP, lithiation at C-5 could be even more favoured. Indeed, experiments showed that the lithiation of **2b** with LTMP followed by boronation with B(O*i*Pr)$_3$ and hydrolysis led to the preferential formation of **2j**.

Table 2. Lithiation energies (ΔE) for thiophene and furan boronates. The positions of the boron-containing functional group BR_3 and the lithium atom are assigned according to the scheme.



X = S **1b**, **2b**, **5b**, **6b** X = O **3b**, **4b**

R_3B = $B(OEt)_3^-$ ("ate") or $B(OCH_2CH_2)_2NBu$ ("aza")

Substrate	Li agent	ΔE [kJ mol^{-1}] 2	3	4	5
Thiophene	*n*BuLi	–115.5	–82.8	–	–
Thiophene	LDA	–23.2	9.5	–	–
1b	LDA	"aza"	23.1	34.0	–6.5
2b	LDA	–27.4	"aza"	31.5	–6.8
5b	*n*BuLi	"ate"	–69.1	–33.3	–61.9
6b	*n*BuLi	–76.1	"ate"	–49.2	–47.9
3b	LDA	"aza"	16.9	27.0	7.3
4b	LDA	13.4	"aza"	30.3	7.8

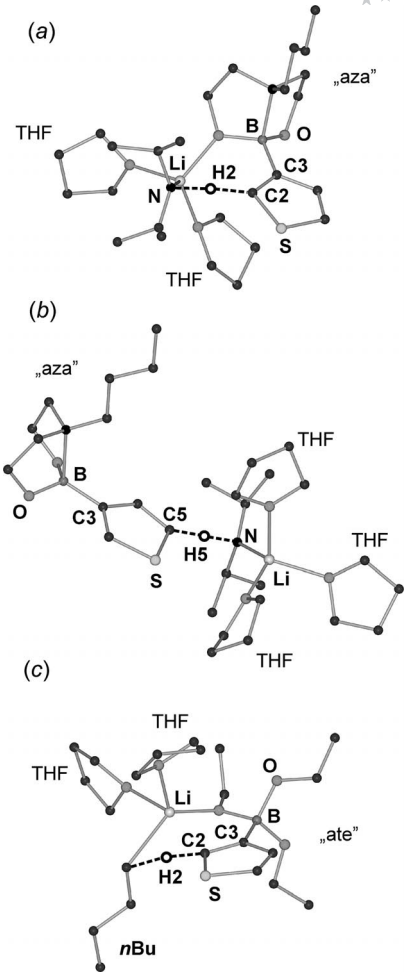


Figure 3. Calculated transition structures of (a) **[2b-2Li]**‡, (b) **[2b-5Li]**‡ and (c) **[6b-2Li]**‡. Hydrogen atoms are omitted for clarity. Boron-containing functional group "ate" = $B(OEt)_3^-$; "aza" = $B(OCH_2CH_2)_2NBu$.

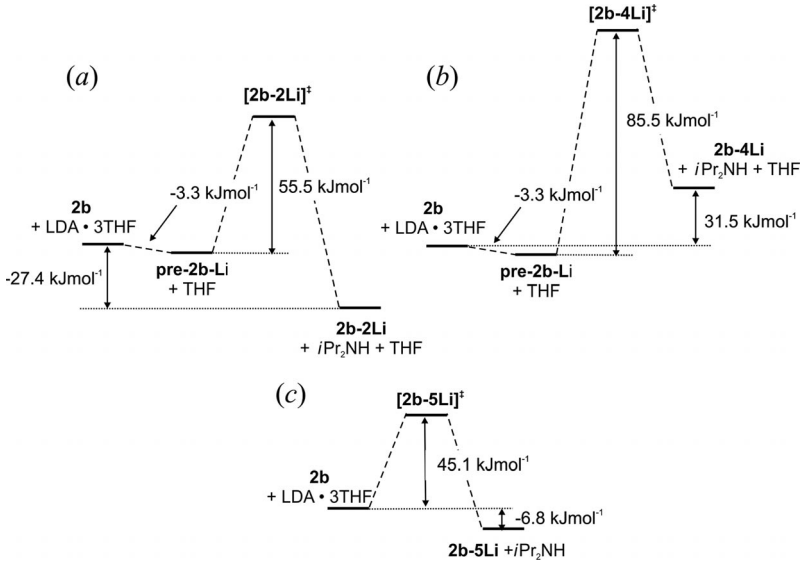


Figure 2. Reaction pathways for the lithiation of **2b** with LDA at (a) C-2, (b) C-4 and (c) C-5. [B3LYP/6-31+G(d)].

Theoretical calculations show that the borocanyl group activates the metalation process by the chelation effect, which involves intramolecular Li–O coordination and results in the increased stability of **2b-2Li** compared to **2b-5Li**. Moreover, if one compares the metalation of unsubstituted thiophene and **2b**, one can conclude that the formation of **2b-2Li** is also more favoured in this case. The activating effect of the borocanyl group was observed even in the presence of an additional $B(OR)_3^-$ group. Thus, the lithiation energy of diboronic complex **2b-5B** (formed upon in situ metalation of **2b**) is 11.6 kJ mol^{-1} lower than the metalation of the analogous borocanyl-free 2-thienyl(triisopropoxy)borate (**5c**, Figure 4). This is consistent with the formation of the triboronic acid **2l** upon in situ double lithiation/boronation of **2b**. We believe that a plausible mechanism for this process is similar to that described for **2b**. The first lithiation yields **2b-5Li**, which is immediately boronated, and the consecutive lithiation of the resulting mixed diboronic complex **2b-5B** would occur analogously as proposed for the formation of **2b-2Li**.

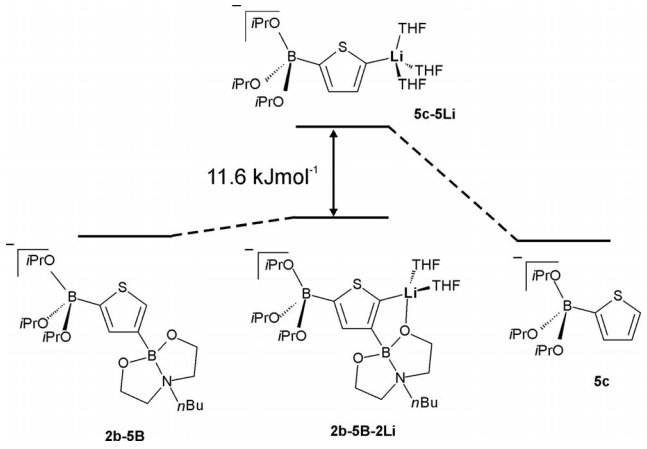


Figure 4. Comparison of lithiation of **5c** and **2b-5B**.

Because of their weaker acidity and the endoenergetic effects of lithiation, the furan derivatives **3b** and **4b** are resistant to metalation with LDA.

Lithiation of Lithium Thienyl(trialkoxy)borates – Transition State Calculations

According to the CIPE model,[15] deprotonation at the positions adjacent to the boronate functional group should be preceded by the association of **6b** with the lithiating reagent. The formation of the prelithiation complex from **6b** and *n*BuLi·3THF requires only 1.0 kJ mol^{-1}. The product of lithiation at C-2 (**6b-2Li**) is 26.9 and 28.2 kJ mol^{-1} more stable than the C-4- (**6b-4Li**) and C-5-lithiated (**6b-5Li**) derivatives, respectively (Table 2). Moreover, transition state calculations indicate that 2-lithiation exhibits a very low reaction barrier of 22.1 kJ mol^{-1} for deprotonation with *n*BuLi (Figure 5). The geometry of the [**6b-2Li**]‡ transition state structure is depicted in part c of Figure 3. Lithiations at C-4 and C-5 require considerably higher activation energies (96.8 and 91.8 kJ mol^{-1}, respectively), which totally preclude the reaction. In the series of boronate derivatives, the *ortho*-stabilizing effect of the $B(OEt)_3^-$ group has been confirmed by the hypothetical lithiation of 2-thienyl(triethoxy)borate (**5b**). The **5b-3Li** derivative is slightly more stable than **5b-5Li** (the difference between the isomers is 7.2 kJ mol^{-1}). However, due to the strong electron-donating effect of the $B(OEt)_3^-$ group, the aromatic ring acidity in **5b** is too low to effect proton abstraction. To summarize, the lithiation of anionic boronate derivatives occurs when both sufficient acidity and the boronate-group-effected stabilization criteria are fulfilled.

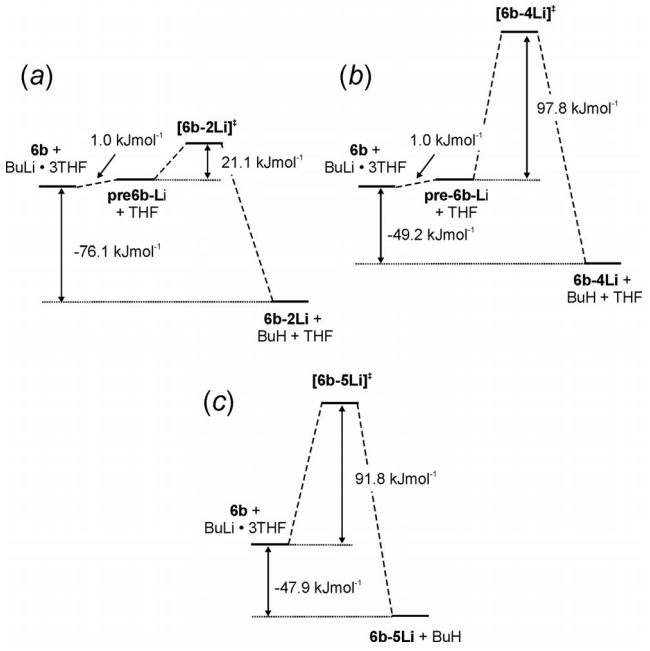


Figure 5. Reaction pathways for the lithiation of **6b** with *n*BuLi at (a) C-2, (b) C4 and (c) C-5 [B3LYP/6-31+G(d)].

Conclusions

We have developed a new method for the efficient generation of synthetically useful lithiated thiophene boronates, which were successfully employed in the synthesis of a range functionalized thiopheneboronic derivatives including hitherto unknown 2,3- and 2,4-thiophenediboronic acids and 2,3,5-thiophenetriboronic acid. This was complemented by the isolation of the thiophene-based diborinic acid **7**. The formation of 2,3-thiophenediboronic acid was confirmed by single-crystal X-ray diffraction. The significant activating effect of the borocanyl and anionic $B(OR)_3^-$ groups was found to operate in the lithiation of 3-thienyl derivatives. Theoretical calculations revealed that the proton abstraction from the thiophene and furan rings is disfavoured upon boronation. However, this is counterbalanced by the substantial chelation effect that involves intramolecular lithium–oxygen coordination, which results in the increased stability of 3-boronated 2-lithiothiophenes compared to their regioisomeric counterparts. Calculations showed that despite the fairly strong σ-donor properties of the borocanyl function, the basicity of the 2-lithiothiophene

that bears this group at the 3-position is even lower than that of the parent compound by 4.2 kJ mol^{-1}, which corresponds to the difference of the lithiation energies of **2b** and thiophene. This can be compared with the experimental value of ca. 7 kJ mol^{-1} roughly estimated based on the distribution of the products of the equilibration reaction (Scheme 5). We are currently studying the lithiation of other aryl and heteroaryl boronates. Specifically, we will try to find whether the directing effect of boronate-type groups will be observed in such systems.

Experimental Section

General Comments: All reactions involving air- and moisture-sensitive reagents were carried out under an argon atmosphere. Et_2O and THF were stored over sodium wire before use. The NMR chemical shifts are given relative to Me_4Si using the 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 the quadrupolar boron nucleus.

6-Butyl-2-(2′-thienyl)-1,3,6,2-dioxazaborocane (1b): A solution of thiophene (84 g, 1 mol) in THF (100 mL) was added to stirred solution of *n*BuLi (10 M, 100 mL, 1 mol) in THF (1.0 L) at –70 °C. The lithiate was stirred for 1 h at –70 °C followed by the dropwise addition of $(EtO)_3B$ (153 g, 1.05 mol). The mixture was stirred for 1 h and then quenched with ethereal HCl (1 L, 1.0 mol). The resultant suspension was filtered under argon and concentrated. The residue was distilled under reduced pressure. The fraction of 2-(diethoxyboryl)thiophene (**1a**) was collected, b.p. 85–90 °C (2 Torr); yield 167 g (91%). A solution of *N*-butyldiethanolamine (80.5 g, 0.5 mol) in diethyl ether (100 mL) was added to a stirred solution of **1a** (92.0 g, 0.5 mol) in Et_2O (200 mL). A white crystalline precipitate was formed rapidly, and the resulting suspension was stirred for 1 h at room temperature and cooled to –50 °C. The mixture was concentrated under reduced pressure. The crystalline product was collected by filtration, washed with Et_2O (2 × 20 mL) and dried to give **1b**; yield 118 g (93%), m.p. 121–122 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.36 (dd, J = 5.0, 1.0 Hz, 1 H, Th), 7.19 (dd, J = 3.0, 1.0 Hz, 1 H, Th), 7.07 (dd, J = 5.0, 1.0 Hz, 1 H, Th), 4.09 (m, 4 H, CH_2O), 3.01 (m, 4 H, CH_2N), 2.40 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.48 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.14 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 0.81 (t, J = 7.0 Hz, 3 H, $NCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 131.1, 127.6, 127.5, 62.7, 59.1, 56.9, 26.7, 20.1, 13.6 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 11 ppm. $C_{12}H_{20}BNO_2S$ (253.17): calcd. C 56.93, H 7.96, N 5.53; found C 56.85, H 7.84, N 5.52.

6-Butyl-2-(3′-thienyl)-1,3,6,2-dioxazaborocane (2b): 3-(Diethoxyboryl)thiophene (**2a**) was obtained as described for **1a** starting with 3-bromothiophene (163 g, 1.0 mol) and using Et_2O as the solvent; yield 163 g (89%), b.p. 88–92 °C (2 Torr). Compound **2b** was prepared as described for **1b** starting with **2a** (92.0 g, 0.5 mol); yield 115 g (91%), m.p. 120–121 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.41 (dd, J = 3.0, 1.0 Hz, 1 H, Th), 7.23 (dd, J = 5.0, 3.0 Hz, 1 H, Th), 7.41 (dd, J = 5.0, 1.0 Hz, 1 H, Ph), 4.09 (m, 4 H, CH_2O), 2.99 (m, 4 H, CH_2N), 2.34 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.47 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.13 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 0.81 (t, J = 7.0 Hz, 3 H, $NCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 131.9, 129.4, 124.2, 62.7, 59.1, 57.1, 26.7, 20.1, 13.7 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 10 ppm. $C_{12}H_{20}BNO_2S$ (253.17): calcd. C 56.93, H 7.96, N 5.53; found C 56.71, H 7.93, N 5.57.

6-Butyl-2-(2′-furyl)-1,3,6,2-dioxazaborocane (3b): 2-(Diethoxyboryl)furan **3a** was obtained as described for **1a** starting with furan (13.6 g, 0.2 mol). The lithiation step was performed at 0 °C; yield 31 g (92%), b.p. 48–52 °C (2 Torr). Compound **3b** was prepared as described for **1b** starting with **3a** (17.0 g, 0.1 mol); yield 21 g (89%), m.p. 119–121 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (m, 1 H, Fu), 6.46 (d, J = 3.0 Hz, 2 H, Fu), 6.21 (m, 1 H, Fu), 3.98 (m, 4 H, CH_2O), 2.94 (m, 4 H, CH_2N), 2.40 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.43 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.09 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 0.76 (t, J = 7.0 Hz, 3 H, $NCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 143.9, 115.6, 109.0, 62.5, 58.0, 56.8, 26.3, 19.9, 13.4 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 10 ppm. $C_{12}H_{20}BNO_3$ (237.10): calcd. C 60.79, H 8.50, N 5.91; found C 60.72, H 8.75, N 5.92.

6-Butyl-2-(3′-furyl)-1,3,6,2-dioxazaborocane (4b): 3-(Diethoxyboryl)furan **4a** was obtained as described for **2a** starting with 3-bromofuran (29.4 g, 0.2 mol); yield 30 g (90%), b.p. 50–53 °C (2 Torr). Compound **4b** was prepared as described for **1b** starting with **4a** (17.0 g, 0.1 mol); yield 21.5 g (91%), m.p. 126–128 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (m, 2 H, Fu), 6.31 (dd, J = 1.5, 1.0 Hz, 1 H, Fu), 3.97 (m, 4 H, CH_2O), 2.92 (m, 4 H, CH_2N), 2.42 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.46 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 1.13 (m, 2 H, $NCH_2CH_2CH_2CH_3$), 0.80 (t, J = 7.0 Hz, 3 H, $NCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 146.3, 141.9, 113.4, 62.4, 59.2, 56.9, 26.6, 20.0, 13.5 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 10 ppm. $C_{12}H_{20}BNO_3$ (237.10): calcd. C 60.79, H 8.50, N 5.91; found C 60.86, H 8.61, N 5.97.

2-(5′-Carboxy-2′-thienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1d): A solution of **1b** (5.06 g, 20 mmol) in THF (20 mL) was added to a stirred solution of LDA freshly prepared from diisopropylamine (2.2 g, 22 mmol) and *n*BuLi (10 M, 2.2 mL, 15 mmol) in THF (30 mL) at –80 °C. After ca. 30 min stirring at ca. –80 °C (internal temperature), the mixture containing the lithiate was carboxylated by passing a stream of dried gaseous CO_2 through it with rapid stirring. After saturation, a solution of pinacol (2.36 g, 20 mmol) in Et_2O (10 mL) was added. The mixture was left to warm to ca. 0 °C to evaporate the excess CO_2 followed by careful hydrolysis with aqueous sulfuric acid (1.5 M, 50 mL). The organic phase was separated and concentrated under reduced pressure. The crude product was washed with water (3 × 10 mL) and hexane (10 mL) to give **1d** as a white powder; yield 3.8 g (76%), m.p. 172–174 °C. ^1H NMR ([D$_6$]acetone, 400 MHz): δ = 7.81 (d, J = 3.5 Hz, 1 H, Th), 7.56 (d, J = 3.5 Hz, 1 H, Th), 1.33 (s, 12 H, Me) ppm. ^{13}C NMR ([D$_6$]acetone, 100.6 MHz): δ = 162.9, 141.1, 138.0, 134.8, 85.3, 25.0 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 29 ppm. $C_{11}H_{15}BO_4S$ (254.11): calcd. C 51.99, H 5.95; found C 51.75, H 5.66.

Thiophene-2,5-diboronic Acid (1e): A solution of LDA freshly prepared from diisopropylamine (2.2 g, 22 mmol) and *n*BuLi (10 M, 2.2 mL, 22 mmol) in THF (30 mL) was added to a stirred solution of **1b** (5.06 g, 20 mmol) in THF (20 mL) containing $B(OiPr)_3$ (4.5 g, 24 mmol) at –70 °C. The mixture was stirred for 30 min at –75 °C and then hydrolyzed with 2 M aqueous H_2SO_4 (10 mL). The aqueous phase was separated and extracted with diethyl ether (2 × 15 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure. The solid residue was collected by filtration and washed with water (2 × 10 mL) and toluene (10 mL). Drying in vacuo afforded **1e** as a white powder; yield 3.0 g (72%), m.p. > 375 °C (dec.). ^1H NMR ([D$_6$]acetone, 400 MHz): δ = 7.69 (s, 2 H, Th), 7.41 [broad, 4 H, $B(OH)_2$], 3.20 [broad, 4 H, H_2O] ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 27 ppm.

2-Carboxythiophene-3-boronic Acid (2e): A solution of **2b** (5.06 g, 20 mmol) in THF (20 mL) was added to a stirred solution of LDA freshly prepared from diisopropylamine (2.2 g, 22 mmol) and *n*BuLi (10 M, 2.2 mL, 15 mmol) in THF (30 mL) at –75 °C. After ca. 30 min stirring at ca. –80 °C (internal temperature), the mixture containing **2c** was carboxylated by passing a stream of dried gaseous CO_2 through it with rapid stirring. The mixture was left to warm to ca. 0 °C to evaporate the excess CO_2 followed by a careful hydrolysis with aqueous sulfuric acid (1.5 M, 50 mL). The organic phase was separated and concentrated under reduced pressure. The crude product was washed with water (3 × 10 mL) and acetone (10 mL) to give **2e** as a white powder; yield 3.0 g (72%), m.p. 196–197 °C (dec.). ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 8.60 [broad, 3 H, COOH + B(OH)$_2$], 7.76 (d, J = 5.0 Hz, 1 H, Th), 7.32 (d, J = 5.0 Hz, 1 H, Th) ppm. ^{13}C{^{1}H} NMR ([D$_6$]DMSO, 100.6 MHz): δ = 166.2, 145.1, 138.3, 135.0, 132.1 ppm. ^{11}B NMR ([D$_6$]DMSO, 64.16 MHz): δ = 28 ppm. $C_5H_5BO_4S$ (171.97): calcd. C 34.92, H 2.93; found C 34.76, H 2.74.

2-(2′-Iodo-3′-thienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2f): A solution of **2c** (obtained as described as part of the synthesis of **2e**) was quenched with a solution of I_2 (5.1 g, 22 mmol) in THF (20 mL) at –90 °C. The mixture was stirred for 30 min at –75 °C and then hydrolyzed with 2 M aqueous H_2SO_4 (10 mL). The water phase was separated and extracted with diethyl ether (2 × 15 mL). The extracts were added to the organic phase, which was washed with 10 wt.-% aqueous $Na_2S_2O_5$ (20 mL) and concentrated under reduced pressure. The residue was treated with pinacol (2.36 g, 20 mmol) in Et_2O (20 mL). The resulting solution was washed with water and concentrated. The crude product was recrystallized from hexane (10 mL) to give **2f** as almost colourless crystals; yield 3.4 g (51%), m.p. 78–80 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (d, J = 5.0 Hz, 1 H, Th), 7.09 (d, J = 5.0 Hz, 1 H, Th), 1.35 (s, 12 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 134.1, 131.1, 84.5, 84.0, 24.5 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 27 ppm. $C_{10}H_{14}BIO_2S$ (336.00): calcd. C 35.75, H 4.20; found C 35.42, H 3.98.

2-(2′-*tert*-Butylcarboxamido-3′-thienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2g): A solution of **2c** (obtained as described as part of the synthesis of **2e**) was quenched with a solution of *t*BuNCO (2.2 g, 22 mmol) in THF (20 mL) at –90 °C. The mixture was stirred for 30 min at –75 °C and then hydrolyzed with 2 M aqueous H_2SO_4 (10 mL). The water phase was separated and extracted with diethyl ether (2 × 15 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure. The residue was treated with pinacol (2.36 g, 20 mmol) in Et_2O (20 mL). The resulting solution was washed with water and concentrated. The crude product was recrystallized from hexane (10 mL) to give **2g** as almost colourless crystals; yield 3.8 g (62%), m.p. 101–103 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (d, J = 5.0 Hz, 1 H, Th), 7.09 (d, J = 5.0 Hz, 1 H, Th), 1.35 (s, 12 H, Me) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 161.4, 153.3, 135.9, 128.4, 84.9, 51.9, 28.7, 24.8 ppm. ^{11}B NMR ($CDCl_3$, 64.16 MHz): δ = 26 ppm. $C_{15}H_{24}BNO_3S$ (309.23): calcd. C 58.23, H 7.82, N 4.53; found C 58.40, H 7.66, N 4.46.

2-Formylthiophene-3-boronic Acid (2h): A solution of **2c** (obtained as described as part of the synthesis of **2e**) was quenched with DMF (2.2 g, 30 mmol). The mixture was stirred for 30 min at –75 °C and then hydrolyzed with 2 M aqueous H_2SO_4 (10 mL). The water phase was separated and extracted with diethyl ether (2 × 15 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure. The solid residue was collected by filtration and washed with water (2 × 10 mL) and toluene (10 mL). Drying in vacuo afforded **2h** as a pale yellow powder; yield 2.2 g (70%), m.p. 220–222 °C (dec.). ^{1}H NMR ([D$_6$]acetone, 400 MHz): δ = 10.27 (s, 1 H, CHO), 8.22 [br., 2 H, B(OH)$_2$], 7.96 (d, J = 5.0 Hz, 1 H, Th), 7.60 (d, J = 5.0 Hz, 1 H, Th) ppm. ^{13}C NMR ([D$_6$]acetone, 100.6 MHz): δ = 186.5, 150.2, 136.9, 135.0 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 27 ppm. $C_5H_5BO_3S$ (155.97): calcd. C 38.50, H 3.23; found C 38.75, H 3.02.

Thiophene-2,3-diboronic Acid (2i): A solution of **2c** (obtained as described as part of the synthesis of **2e**) was quenched with B(OEt)$_3$ (3.2 g, 22 mmol). The mixture was stirred for 30 min at –75 °C and then hydrolyzed with 2 M aqueous H_2SO_4 (10 mL). The water phase was separated and extracted with diethyl ether (2 × 15 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure. The solid residue was collected by filtration and washed with water (2 × 10 mL) and toluene (10 mL). Drying in vacuo afforded **2i** as a white powder; yield 3.4 g (85%), m.p. 121–122 °C (dec.). ^{1}H NMR ([D$_6$]acetone, 400 MHz): δ = 8.28 [s, 2 H, B(OH)$_2$], 8.18 [s, 2 H, B(OH)$_2$], 7.65 (m, 2 H, Th), 3.21 (s, 3 H, H_2O) ppm. ^{13}C{^{1}H} NMR ([D$_6$]acetone, 100.6 MHz): δ = 136.7, 130.8 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 27 ppm. $C_4H_6B_2O_4S{\cdot}1.5H_2O$ (198.80): calcd. C 25.31, H 4.25; found C 25.05, H 4.20.

Bis(pinacol)thiophene-2,4-diboronate (2k): A solution of LTMP freshly prepared from 2,2,6,6-tetramethylpiperidine (3.1 g, 22 mmol) and *n*BuLi (10 M, 2.2 mL, 22 mmol) in THF (30 mL) was added to a stirred solution of **2b** (5.06 g, 20 mmol) in THF (20 mL) containing B(O*i*Pr)$_3$ (4.5 g, 24 mmol) at –75 °C. Hydrolysis and workup was performed as described for **2b** and afforded thiophene-2,4-diboronic acid (**2j**) contaminated with ca. 6% **2i**; yield 3.0 g. Compound **2j** was converted into the corresponding bis(pinacol) ester **2k** by treatment with pinacol (2.0 g) in acetone (10 mL). The resulting solution was evaporated, and the crude product was recrystallized from hexane (20 mL) to give **2k**; yield 4.1 g (72%). ^{1}H NMR ([D$_6$]acetone, 400 MHz): δ = 8.14 (d, J = 1.0 Hz, 1 H, Th), 8.00 (d, J = 1.0 Hz, 1 H, Th), 1.33 (s, 12 H, BPin), 1.31 (s, 12 H, BPin) ppm. ^{13}C{^{1}H} NMR ([D$_6$]acetone, 100.6 MHz): δ = 143.3, 142.9, 84.0, 83.6, 24.8, 24.7 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 27 ppm. $C_{16}H_{26}B_2O_4S$ (336.06): calcd. C 57.18, H 7.80; found C 56.98, H 7.68.

Thiophene-2,3,5-triboronic Acid (2l): A solution of LDA freshly prepared from diisopropylamine (5.05 g, 50 mmol) and *n*BuLi (10 M, 5.0 mL, 50 mmol) in THF (60 mL) was added to a stirred solution of **2b** (5.06 g, 20 mmol) in THF (20 mL) containing B(O*i*Pr)$_3$ (4.5 g, 24 mmol) at –75 °C. The mixture was warmed to room temperature and then cooled to 0 °C and hydrolyzed with 2 M aqueous H_2SO_4 (30 mL). The water phase was separated and extracted with diethyl ether (2 × 15 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure. The solid residue was collected by filtration and washed with water (2 × 10 mL). Drying in vacuo afforded **2l** as a white powder. The product was obtained as a trihydrate; yield 4.1 g (71%), m.p. > 395 °C (dec.). ^{1}H NMR ([D$_6$]acetone, 400 MHz): δ = 8.26 [s, 2 H, B(OH)$_2$], 8.12 (s, 1 H, Th), 8.10 [s, 2 H, B(OH)$_2$], 7.35 [s, 2 H, B(OH)$_2$], 3.15 (s, H_2O) ppm. ^{13}C{^{1}H} NMR ([D$_6$]acetone, 100.6 MHz): δ = 145.7 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 27 ppm. $C_4H_7B_3O_6S{\cdot}3H_2O$ (287.65): calcd. C 17.82, H 4.86; found C 17.51, H 5.00.

4,8-Dihydro-4,8-dihydroxy-*p*-diborino[2,3-*b*:5,6-*b*′]dithiophene (7): A solution of 3-bromothiophene (9.2 g, 50 mmol) in Et_2O (20 mL) was added to the stirred solution of *n*BuLi (10 M, 5 mL, 50 mmol) in Et_2O (50 mL) at –70 °C. The resulting white suspension was stirred for 30 min before the addition of $(EtO)_3B$ (7.3 g, 50 mmol). The white suspension was diluted with THF to give an almost clear

colourless solution. A solution of *n*BuLi (10 M, 5 mL, 50 mmol) in pentane (20 mL) was added at –70 °C. The resulting mixture was warmed to room temperature with stirring then cooled to ca. 0 °C and hydrolyzed with 2 M aqueous H_2SO_4 (10 mL). The water phase was separated and extracted with diethyl ether (2 × 15 mL). The extracts were added to the organic phase, which was concentrated under reduced pressure. The solid residue was collected by filtration and washed with water (2 × 10 mL) and Et_2O (2 × 5 mL). Drying in vacuo afforded **7** as a greyish powder; yield 0.5 g (18%), m.p. 160–162 °C (dec.). ^{1}H NMR ([D$_6$]acetone, 400 MHz): δ = 9.31 [s, 2 H, BOH], 7.79 (d, J = 4.5 Hz, 1 H, Th), 7.73 (d, J = 4.5 Hz, 1 H, Th) ppm. ^{13}C{^{1}H} NMR ([D$_6$]acetone, 100.6 MHz): δ = 133.1, 132.8 ppm. ^{11}B NMR ([D$_6$]acetone, 64.16 MHz): δ = 36 ppm. $C_8H_6B_2O_2S_2$ (219.89): calcd. C 43.70, H 2.75; found C 43.21, H 2.98.

X-ray Data: The single-crystal XRD analysis of **2i** was performed with a Bruker AXS Kappa APEX II Ultra diffractometer with TXS rotating anode (Mo-K_α radiation, λ = 0.71073 Å) and multilayer optics and equipped with an Oxford Cryosystems nitrogen gas-flow attachment. The data collection strategy was optimized and monitored using the appropriate algorithms applied in the APEX2 program package.[22] Data reduction and analysis were carried out with the APEX2 suit of programs (integration was performed with SAINT).[23] The data were corrected for Lorentz and polarization effects. The multiscan absorption correction, scaling and merging of reflection data were performed with SORTAV.[24] All structures were solved by direct methods using SHELXS-97[25] and refined using SHELXL-97.[25] The refinement was based on F^2 for all reflections except those with very negative F^2. All non-hydrogen atoms were refined anisotropically.

CCDC-834903 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. $C_8H_{18}B_4O_{11}S_2$, molecular weight 397.60 a.u.; T = 100(2) K; monoclinic space group $C2/c$; unit cell dimensions, a = 11.088(1) Å, b = 11.845(1) Å, c = 13.283(1) Å, α = 90°, β = 104.72(1)°, γ = 90°, V = 1687.4(2) Å^3; Z = 4; d_{calc} = 1.565 g cm^{-3}; absorption coefficient μ = 0.368 mm^{-1}; F(000) = 824; crystal size: 0.15 × 0.05 × 0.05 mm^3; θ range for data collection: 2.56°–38.93°; index ranges: $-18 < h < 17$, $-18 < k < 20$, $-20 < l < 22$; reflections collected: 18494/unique: 4770 (R_{int} = 0.0224); absorption correction: multiscan; refinement method: full-matrix least-squares on F^2; goodness-of-fit on F^2, GooF = 1.002; data/restraints/parameters 4770/14/164; final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0300, $wR2$ = 0.0814; R indices (all data): $R1$ = 0.0365, $wR2$ = 0.0793; 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: 0.626 and –0.251 e Å^{-3}. The carbon and sulfur atoms were disordered and, therefore, modelled as two partly occupied sites (the occupancy ratio of 3:2). The difference Fourier map through the B(1)–C(1)–C(2) plane is shown in Figure S1 in the Supporting Information.

Computational Details: All geometry optimizations and frequency calculations were carried out with the Gaussian 03 suite of programs[26] and the Becke-style three-parameter density functional method using the Lee–Yang–Parr correlation functional (B3LYP) was applied.[17] The 6-31+G(d)[27] basis sets were used to calculate the optimal geometries of "ate" complexes, azaesters and their lithiated derivatives. To establish the outcome of the quantum-chemical method, we performed additional calculations for **2b** at the MP2[28]/6-31+G(d) and B3LYP/aug-cc-pVDZ[18] levels of theory and obtained similar values of the lithiation energies at C-5 [–6.8 kJ mol^{-1} for the B3LYP/6-31+G(d) method, –7.9 kJ mol^{-1} for the B3LYP/aug-cc-pVDZ method and –7.6 kJ mol^{-1} for the MP2/6-31+G(d) method]. The minima were confirmed by vibrational frequency calculations [B3LYP/6-31+G(d)] within harmonic approximation (no imaginary frequencies). In the optimization processes, no symmetry constraints were applied. Deprotonation energies were calculated according to the equation:

$AH = A^- + H^+$; $\Delta E = E_{AH} - E_{A^-}$

In these computations, the B3LYP/aug-cc-pVDZ level of theory was used starting from geometries optimized with the 6-31+G(d) basis set. To optimize the structures of transition states, a synchronous transit-guided quasi-Newton approach (qst3) was applied. In this method three input structures were needed: one corresponded to substrates, one to products and one is an estimation of the 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 of new compounds, selected single-crystal XRD data for **2i** and detailed results of the computational studies.

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[1] D. G. Hall, *Boronic Acids*, 1st ed., Wiley-VCH, Weinheim, Germany, **2005**.
[2] a) Y. Yamamoto, T. Seko, H. Nemoto, *J. Org. Chem.* **1989**, *54*, 4734–4736; b) P. Vedsø, P. H. Olesen, T. Hoeg-Jensen, *Synlett* **2004**, 892–894; c) G. A. Molander, N. M. Ellis, *J. Org. Chem.* **2006**, *71*, 7491–7493; d) M. Dąbrowski, P. Kurach, S. Luliński, J. Serwatowski, *Appl. Organomet. Chem.* **2007**, *21*, 234–238.
[3] a) Q. Jiang, M. Ryan, P. Zhichkin, *J. Org. Chem.* **2007**, *72*, 6618–6620; b) P. Kurach, S. Luliński, J. Serwatowski, *Eur. J. Org. Chem.* **2008**, 3171–3178.
[4] T. Kliś, S. Luliński, J. Serwatowski, *Curr. Org. Chem.* **2010**, *14*, 2549–2566.
[5] J. J. Li, G. W. Gribble, *Palladium in Heterocyclic Chemistry*, 2nd ed., Elsevier, Oxford, **2006**, vol. 26, pp. 261–272.
[6] a) M. Jayakannan, J. L. J. van Dongen, R. A. J. Janssen, *Macromolecules* **2001**, *34*, 5386–5393; b) H. Mori, K. Takano, T. Endo, *Macromolecules* **2009**, *42*, 7342–7352; c) D. Tuncel, M. Artar, S. B. Hanay, *J. Polym. Sci. Polym. Chem. Ed.* **2010**, *48*, 4894–4899.
[7] a) K. Durka, P. Kurach, S. Luliński, J. Serwatowski, *Eur. J. Org. Chem.* **2009**, 4325–4332; b) K. Durka, R. Kamiński, S. Luliński, J. Serwatowski, K. Woźniak, *Phys. Chem. Chem. Phys.* **2010**, *12*, 13126–13136.
[8] S. Gronowitz (Ed.), *Thiophene and Its Derivatives*, part IV, Wiley-InterScience, **1991**, vol. 44, pp. 55–56.
[9] a) T. D. Krizan, J. C. Martin, *J. Am. Chem. Soc.* **1983**, *105*, 6155–6157; b) S. Caron, J. M. Hawkins, *J. Org. Chem.* **1998**, *63*, 2054–2055; c) J. Kristensen, M. Lysén, P. Vedsø, M. Begtrup, *Org. Lett.* **2001**, *3*, 1435–1437; d) S. Luliński, J. Serwatowski, A. Zaczek, *Eur. J. Org. Chem.* **2006**, 5167–5173.
[10] I. G. C. Coutts, H. R. Goldschmid, O. C. Musgrave, N. C. Oliver, *J. Chem. Soc. C* **1970**, *3*, 488–493.

[11] See, for example: a) S. J. Rettig, J. Trotter, *Can. J. Chem.* **1977**, *55*, 3071–3075; b) M. Pilkington, J. D. Wallis, S. Larsen, *J. Chem. Soc., Chem. Commun.* **1995**, 1499–1500; c) P. R. Parry, C. Wang, A. S. Batsanov, M. R. Bryce, B. Tarbit, *J. Org. Chem.* **2002**, *67*, 7541–7543.
[12] S. V. Kessar, P. Singh, K. N. Singh, P. V. Bharatam, A. K. Sharma, S. Lata, A. Kaur, *Angew. Chem.* **2008**, *120*, 4781; *Angew. Chem. Int. Ed.* **2008**, *47*, 4703–4706.
[13] R. R. Fraser, T. S. Mansour, S. Savard, *Can. J. Chem.* **1985**, *63*, 3505–3509.
[14] a) A. J. Carpenter, D. J. Chadwick, *Tetrahedron Lett.* **1985**, *26*, 1777–1781; b) D. W. Knight, A. P. Nott, *J. Chem. Soc. Perkin Trans. 1* **1983**, 791–794.
[15] M. C. Whisler, S. McNeal, V. Snieckus, P. Beak, *Angew. Chem.* **2004**, *116*, 2256; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225.
[16] I. Hyla-Kryspin, S. Grimme, H. H. Büker, N. M. M. Nibbering, F. Cottet, M. Schlosser, *Chem. Eur. J.* **2005**, *11*, 1251–1256.
[17] a) D. Becke, *Phys. Rev. A* **1988**, *38*, 3098–3100; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
[18] T. H. Dunning, *J. Chem. Phys.* **1989**, *90*, 1007–1023.
[19] D. Hoffmann, D. B. Collum, *J. Am. Chem. Soc.* **1998**, *120*, 5810–5811.
[20] C. Strohmann, V. H. Gessner, *J. Am. Chem. Soc.* **2008**, *130*, 11719–11725.
[21] A. C. Hoepker, L. Gupta, Y. Ma, M. F. Faggin, D. B. Collum, *J. Am. Chem. Soc.* **2011**, *133*, 7135–7151.
[22] *APEX2*, 2010.3-0, Bruker AXS Inc., Madison, **2010**.
[23] *SAINT*, 7.68A, Bruker AXS Inc., Madison, **2010**.
[24] a) R. H. J. Blessing, *Appl. Crystallogr.* **1989**, *22*, 396–397; b) R. H. J. Blessing, *Acta Crystallogr., Sect. A* **1995**, *51*, 33–38.
[25] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.
[26] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, N. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, revision C.02, Gaussian Inc., Wallingford, CT, **2004**.
[27] R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 650–654.
[28] C. Møller, M. S. Plesset, *Pure Appl. Chem.* **1934**, 618–622.

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