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Long-Range Effects in the Metalation/Boronation of Functionalized 1,4-Dihalobenzenes

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The lithiation/boronation of 1,4-dihalobenzenes (Hal = F, Cl, Br) bearing various functional groups in the 2-position was investigated using lithium diisopropylamide (LDA) as the metalating agent and trialkyl borate $B(OR)_3$ (R = Et, *i*Pr) as the electrophile. It was demonstrated that sufficient steric hindrance precludes effective *ortho*-lithiation at the 3-position. In such cases, a strong *meta*-directing effect of an oxygen- or sulfur-based substituent (OMe, $OSiMe_3$, SMe), resulting in the preferred formation of 2,6-disubstituted 1,4-dihalobenzenes was observed. Moreover, competition experiments using 2,3-bifunctional 1,4-dihalobenzenes were performed to determine the relative *meta*-directing ability of carboxylate or fluorine in competition with a methoxy group. A significant buttressing effect is responsible for the course of metalation of 2-(dimethoxymethyl)-1,4-dihalobenzenes (Hal = Cl, Br).

Introduction

There is growing interest in the metalation of halogenated aromatics and heteroaromatics as a useful tool for their diverse functionalization.[1] Their reactivity depends strongly on the kind and number of halogens attached to the aromatic ring. Thus, halogenated fluorobenzenes are more susceptible to deprotonation than the parent compound due to an enhanced acidifying effect provided by the second halogen.[2] For instance, 1,4-difluorobenzene undergoes metalation using LTMP 80 times more rapidly than fluorobenzene.[3] Similar rules are applicable for the metalation of heavier halogen analogues,[4] e.g., lithiation of 1,4-dichlorobenzene is feasible using *n*BuLi at –78 °C, whereas chlorobenzene requires *s*BuLi to be converted into 2-chlorophenyllithium.[5] The role of long-range inductive effects in the metalation of arenes has been studied less extensively when compared to *ortho*-directed deprotonations. For instance, the lithiation of benzotrifluorides can proceed in the position *meta* or *para* with respect to a CF_3 group.[6] It is known that a bulky trialkylsilyloxy group prevents *ortho*-lithiation.[5,7] Tricarbonylchromium(0) complexes of silylated phenols and anilines are preferentially metalated at the *meta*-position of the ring, but such regioselectivity is rationalized in terms of chelation of the lithating agent by a carbonyl or an increased electron deficiency at the eclipsed ring carbons[8,9] rather than by long-range inductive effects of oxygen or nitrogen operating within the aromatic ring. Recently, we have shown that the proton abstraction from a 3-position of 1,4-dibromo-2-methoxybenzene may be problematic due to a formation of other kinetically favoured products.[10] This result has prompted us to evaluate more precisely the influence of steric and electronic factors on the regioselectivity of the metalation of 2-functionalized 1,4-dihalobenzenes with special emphasis on the role of long-range inductive effects.

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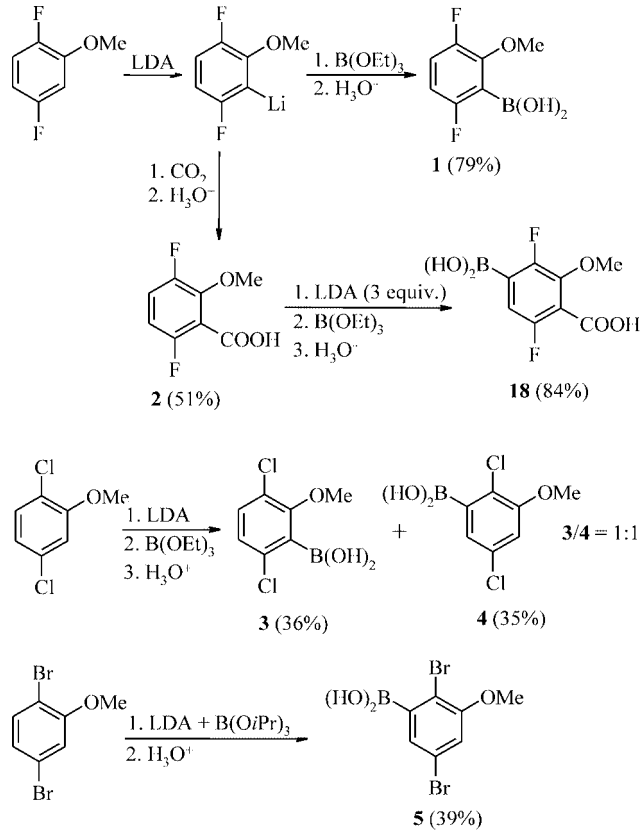
Results and Discussion

Long-Range Inductive Effects

1,4-Difluoro-2-methoxybenzene is metalated selectively at the 3-position with LDA. Treatment with $B(OEt)_3$ gave the corresponding boronic acid **1** whereas carboxylation afforded 3,6-difluoro-2-methoxybenzoic acid **2** (Scheme 1). A similar result was found previously for *n*BuLi mediated deprotonation.[11] This is not surprising since the acidifying effects of fluorines and a methoxy group are expected to cumulate to the highest extent in the 3-position which is reflected by the increased proton mobility. In order to determine the effect of a heavier halogen, we subjected the closely related 1,4-dichloro-2-methoxybenzene to LDA-mediated deprotonation followed by a $B(OEt)_3$ quench, whereas the bromo analogue was boronated using either a sequential or a modified in situ[12,13] quench with $B(O\textit{i}Pr)_3$. A progressive shift in the regioselectivity is observed as the former reaction gave an approximately equimolar mixture of substituted boronic acids **3** and **4**. We attribute this result to a substantial steric hindrance impeding the access of a lithium base to the 3-position of a substrate and thus disfavouring the formation of **3**. Accordingly, the formation of **4**, we interpret as a result of a longe-range *meta*-directing

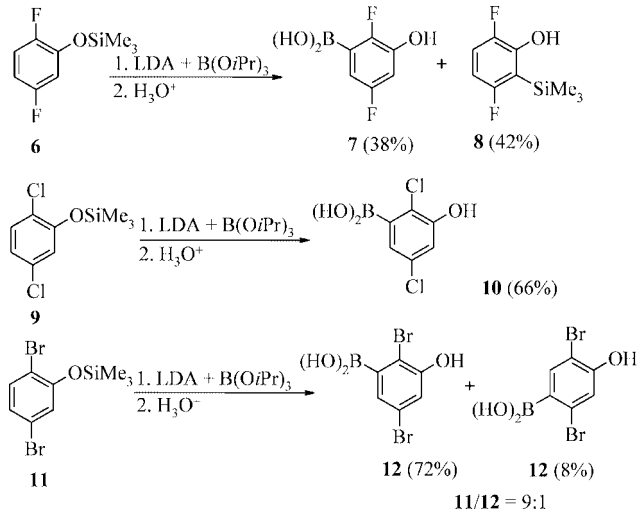
effect (i.e. in a 6-position) of the methoxy group as an isomeric acid resulting from the metalation in the 5-position, was not found to a detectable extent. In the case of 1,4-dibromo-2-methoxybenzene, the only acid isolated upon workup of the reaction mixture was 2,6-dibromo-3-methoxyphenylboronic acid **5**, although the yield was moderate (39%). This is in line with our recent results concerning the synthesis of 2,5-dibromo-3-methoxybenzaldehyde,[10] and indicates that the 6-position is preferentially metalated. As we proposed previously, these results can be rationalized assuming conformational restrictions of the methoxy group imposed by an adjacent halogen atom. This effect leads to an increased stability of an *anti*-conformation of the methoxy group, thus making in turn an approach by the bulky deprotonating agent more difficult. This is an interpretation involving kinetic control conditions, i.e., it can be applicable in a case when an internal electrophile, immediately reacting with aryllithium, is used. However, in the absence of a trapping electrophile, LDA-mediated deprotonations are generally able to reach a thermodynamic equilibrium. If so, a composition of the reaction mixture must reflect a relative stability of aryllithium isomers. It is plausible that, a thermodynamic stability of 3-lithio-1,4-dihalo-2-methoxyanisoles (Hal = Cl, Br) is decreased by conformational restrictions of the methoxy group due to their lower aggregation state and/or solvent stabilization. Hence, despite the assumed higher thermodynamic acidity of a hydrogen in the 3-position (i.e., a more negative ΔG of formation of a corresponding carbanion under gas phase conditions), a 6-lithiated species can be formed to a significant extent or even as a major product. However, at this point we have to stress that there is no evidence that LDA-mediated lithiation of 1,4-dihalo-2-methoxyanisoles is actually controlled by thermodynamics.

Results concerning the metalation of 2,5-dihaloanisoles have prompted us to investigate the reactivity of related 1,4-dihalo-2-(trimethylsilyloxy)benzenes. It is known that trialkylsilyloxy groups effectively prevent *ortho*-lithiation.[14] Indeed, the metalation of 1,4-difluoro-2-(trimethylsilyloxy) benzene **6** with LDA using a $B(OiPr)_3$ internal quench afforded 2,5-difluoro-3-hydroxyphenylboronic acid **7** (Scheme 2) in 38% yield resulting from lithiation at a less hindered *meta*-position with respect to the Me_3SiO group. A substantial amount of 3,6-difluoro-2-(trimethylsilyl)phenol **8** (42%) was isolated too. However, when a stepwise protocol was employed, i.e., the lithiation was performed followed by trapping with the electrophile [$B(OEt)_3$, DMF] and hydrolysis, no trapping products were found, and the only isolated product was the phenol **8**. In another experiment LDA (1.1 equiv.) was added to a solution of **6** in the presence of TMSCl as the electrophile (1.2 equiv.). GC/MS analysis revealed that comparable amounts of 3- and 6-silylated derivatives of **6** were formed (both ca 20%) together with a substantial amount (27%) of 2,5-difluoro-1,4-bis(trimethylsilyl)-3-(trimethylsilyloxy)benzene and unreacted **6** (15%). These results suggest unequivocally that the LDA-mediated metalation proceeds with comparable rates *ortho* and *meta* to the Me_3SiO group. In the absence of an internal electrophile, aryllithium intermediates undergo a reversible reprotonation with the byproduct diisopropylamine and hence they can interconvert with each other but one of them (lithiated *ortho* to the Me_3SiO group) is kinetically unstable and undergoes an aromatic [1,3]retro-Brook rearrangement[15] to form a silylated phenolate via silyl group migration from the oxygen to the metalated carbon (Scheme 3). Apparently, this intramolecular reaction proceeds more rapidly than trapping with $B(OiPr)_3$, which is probably hampered by the substantial steric effect of the adjacent Me_3SiO group. The metalation/in situ boronation of the analogous dichloro derivative **10** gave the acid **11** with good purity and moderate yield (66%). In a similar reaction, a dibromo compound was converted into the acid **12**, which was contaminated with some (ca. 10%) of the isomeric acid **13**. It is clear that proton abstraction from a position between the halogen and the Me_3SiO group does not proceed effectively due to significant steric hindrance, whereas the relatively strong long-range acidifying effect of oxygen enables a preferred kinetic deprotonation at the 6-position. To summarize, the metalation/boronation of dihalogenated (trimethylsilyloxy)benzenes provides (after subsequent hydrolysis/deprotection step) access to synthetically useful boronated dihalophenols.

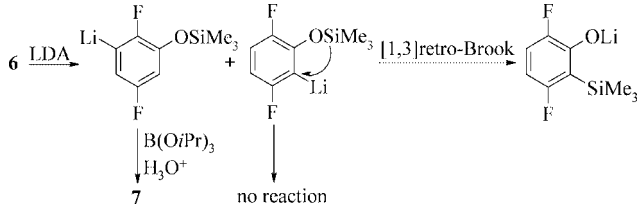


Scheme 1. Lithiation/boronation of 1,4-dihalo-2-methoxybenzenes.

The effect of the replacement of a methoxy group with a related methylthio group was subsequently studied employing 1,4-dichloro-2-(methylthio)benzene **7** and its bromo analogue **8**. It is known that SMe has weaker *ortho*-direct-

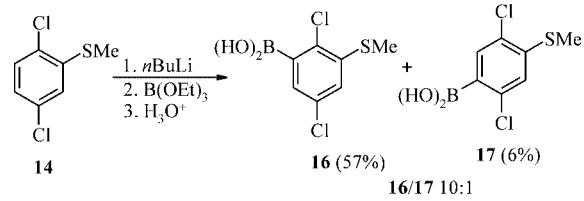


Scheme 2. Lithiation/boronation of 1,4-dihalo-2-(trimethylsilyloxy)benzenes.



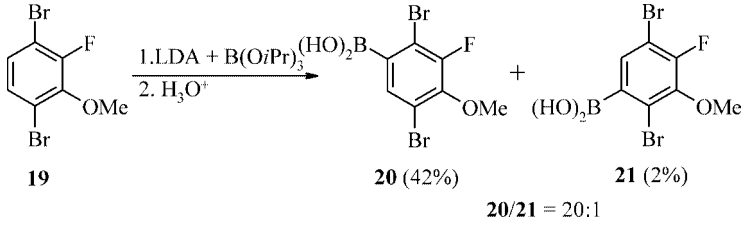
Scheme 3. LDA-induced rearrangement of 1,4-difluoro-2-(trimethylsilyloxy)benzene.

ing properties when compared to the methoxy group[16] and may undergo α-deprotonation to a significant extent.[17] Indeed, the latter was a major reaction pathway for the LDA-mediated deprotonations of **14** and **15** as the in situ Me_3SiCl trapping (1.1 equiv.) gave, in both cases, non-resolved mixtures of isomeric SMe-silylated and disilylated dihalothioanisoles. Whereas, with internal $B(OiPr)_3$ most of the starting material was recovered, presumably due to the hydrolytic cleavage of a boron–carbon bond in a SMe-boronated product during aqueous workup. With *n*BuLi, however, it was possible to lithiate **14** at the ring preferentially (Scheme 4). The selectivity of ring metalation is again influenced by a combination of steric and electronic effects imposed by the SMe group. Its steric parameters are remarkably different to those of the methoxy group; C_{arom}–S bond lengths in thioanisoles are longer by ca. 0.3 Å with respect to C_{arom}–O bond lengths in anisoles, while the C–S–C angle is significantly smaller than the corresponding C–O–C angle.[18] As a result, the lithiation at the 3-position is impeded by steric hindrance and the major product is the acid **16** resulting from a preferred lithiation at the less crowded 6-position. However, the formation of the isomeric acid **17**, albeit not exceeding 10% with respect to **16**, points to a difference in acidities of 6-H and 5-H (*meta* and *para* with respect to SMe) is not large enough to provide a perfect regioselectivity. Nevertheless, it is clear that a methylthio group does acidify aromatic hydrogen atoms in the *meta*-position by long-range inductive effects to an extent not expected for such a weak *ortho*-director.

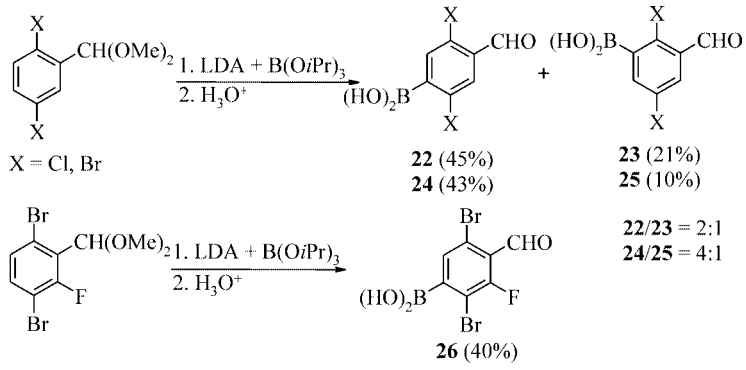


Scheme 4. Lithiation/boronation of 1,4-dichloro-2-(methylthio)-benzene.

We have extended our study by performing long-range effect competition experiments. We were interested in the comparison of the *meta*-directing power of methoxy and carboxylate groups. The *ortho*-directed metalation of related 2-methoxybenzoic acid was studied recently; it was demonstrated that with LTMP or *s*BuLi/TMEDA it proceeds *ortho* to a carboxylate whereas the superbase *n*BuLi/*t*BuOK deprotonates *ortho* to a methoxy group.[19] In our protocol the related 3,6-difluoro-2-methoxybenzoic acid **2** was subjected to a double deprotonation using a threefold excess of LDA. A quench with $(EtO)_3B$ gave 4-carboxyl-2,5-difluoro-3-methoxyphenylboronic acid **18** selectively with good yield (84%) as shown in Scheme 1. Based on conclusions concerning metalation of 2-methoxy- and 2-(trimethylsilyloxy)-1,4-dihalobenzenes we believe that the orientation in the reaction is dictated by the *meta*-directing methoxy group acting by a long-range negative inductive effect. A contribution from a positive long-range inductive effect of electron-rich carboxylate reducing the relative proton mobility in a *meta*-position with respect to this anionic group may also be taken into account. Presumably, the well-known kinetic activation of the aromatic ring by a carboxylate[20] is purely due to the precomplexation of the lithiating agent, which obviously is limited to the adjacent *ortho*-position. In another experiment, 1,4-dibromo-2-fluoro-3-methoxybenzene **19** was subjected to lithiation/in situ boronation with LDA/$B(OiPr)_3$. In this case, we found that fluorine outperforms the methoxy group in its *meta*-direct-



Scheme 5. Lithiation/boronation of 1,4-dibromo-2-fluoro-3-methoxybenzene.



Scheme 6. Lithiation/boronation of 1,4-dihalo-2-(dimethoxymethyl)benzenes.

ing ability as the major product 2,5-dibromo-3-fluoro-4-methoxyphenylboronic acid **20** was contaminated with only a small amount (ca 5%) of the regioisomeric byproduct **21** (Scheme 5). This shows that the long-range inductive effect of fluorine is significantly stronger than that of oxygen, which is in line with the lithiation results of isomeric 1,2-dibromo-4-fluoro-5-methoxybenzene by means of Li/Br exchange.[21] For comparison, *n*BuLi/THF slowly deprotonates the parent 2-fluoroanisole *ortho* to the methoxy group, whereas a selective metalation *ortho* to fluorine requires a superbase such as *n*BuLi premixed with PMDTA or KO*t*Bu.[22]

The Impact of Buttressing Effects

The lithiation/in situ boronation of 1,4-halo-2-(dimethoxymethyl)benzenes (Hal = Cl, Br) using LDA/B(O*i*Pr)$_3$ showed that the metalation does not proceed selectively as mixtures of corresponding 2,5-dihalo-4-formyl- and 2,5-dihalo-3-formylphenylboronic acids were formed (Scheme 6). We rationalize the preferred formation of compounds **22** and **24** in terms of two factors. Standard steric hindrance precludes deprotonation *ortho* to a dimethoxymethyl CH(OMe)$_2$ group. A secondary but still significant buttressing effect exerted by the CH(OMe)$_2$ group on the adjacent halogen seems to be operative in decreasing the extent of the metalation at the *meta*-position with respect to it. The concept of a buttressing effect is not new[23] but it was employed only recently to explain the reduced mobility of a proton located *ortho* to a halogen in some fluoro- (albeit to a small extent),[24] chloro- and bromoarenes bearing adjacent bulky groups such as iodine[25] and trialkylsilyl.[25,26] More advanced studies revealed that this is a purely kinetic phenomenon[27] whose synthetic potential is remarkable.[28] As expected, a comparison of product distributions **22/23** (2:1) and **24/25** (4:1) shows that this effect is more pronounced for the dibromo compound due to the increased van der Waals radius of this halogen. However, when the dibromo acetal was replaced with its more bulky diethyl analogue, the regioselectivity was not improved in favour of the product **23** due to a potential enhancement of the buttressing effect. In this context it is also interesting to note that the metalation of related 1,3-dichloro-2-(dimethoxymethyl)benzene with *s*BuLi/THF at –100 °C gives an approximately equimolar mixture of *ortho*- and *meta*-lithiated species as comparable proportions of corresponding boronic acids were obtained after trapping with (EtO)$_3$B.[29] The buttressing effect caused by dimethoxymethyl groups is not as strong as that observed for trialkylsilyl groups, and hence it is of a lower synthetic value. However, in conjunction with the strong *meta*-directing effect of fluorine it was used to convert 1,4-dibromo-2-(dimethoxymethyl)-3-fluorobenzene into 2,5-dibromo-3-fluoro-4-formylphenylboronic acid **26** free of its regioisomer in 40% yield (Scheme 6).

Conclusion

In conclusion, the metalation of functionalized 1,4-dihalobenzenes proceeds with varying regioselectivity. Deprotonation of functionalized 1,4-dichloro- and dibromobenzenes at the 3-position is generally sluggish and occurs preferably at the less hindered 6-position, which gains an additional activation when compared to the 5-position due to long-range inductive effects exerted by heteroatom-based substituents (OMe, OSiMe$_3$, SMe, F). On the other hand, the buttressing effect of the dimethoxymethyl group leads to a reversal of such regioselectivity. In many cases a combination of various effects proved synthetically useful and gave selective access to novel dihalophenylboronic acids bearing valuable functionalities (OH, OMe, CHO, COOH) with satisfactory yields. There is also potential for a broad range of other dihalogenated aromatics by employing various electrophilic reagents.

Experimental Section

General Comments: All reactions involving air and moisture sensitive reagents were carried out in an argon atmosphere. THF was stored with sodium wire before use. All starting materials: 2,5-dihalophenols, 2,5-dibromoanisole, 2,5-dihalobenzaldehydes, 3,6-dibromo-2-fluorophenylboronic acid, and other important reagents including hexamethyldisilazane HN(SiMe$_3$)$_2$, dimethyl sulfate, trimethyl orthoformate, diisopropylamine, *n*-butyllithium (10 M solution in hexanes), triethyl and triisopropyl borates were received from Aldrich. 2,5-Difluoroanisole,[11] 2,5-dichloroanisole,[30] 1,4-dichloro-2-(dimethoxymethyl)benzene,[31] 1,4-dibromo-2-(dimeth-

oxymethyl)benzene,[21] 1,4-dibromo-2-(dimethoxymethyl)-3-fluorobenzene[21] have been prepared according to literature procedures. The NMR chemical shifts are given relative to TMS using known chemical shifts of residual proton (^{1}H) or carbon (^{13}C) solvent resonances. In the ^{13}C NMR spectra of aryl boronic acids, the resonances of boron-bound carbon atoms were not observed due to their broadening by a quadrupolar boron nucleus. New compounds gave satisfactory elemental analyses except for the acid **7**, presumably due to formation of an air-stable hydrate. In addition, for mixtures **3**–**4**, **12**–**13**, **16**–**17**, **20**–**21**, **22**–**23** and **24**–**25** a characterization by their ^{1}H NMR spectra in [D$_6$]acetone (with ca 5 wt.-% D_2O added to simplify spectra by exchanging ^{1}H from boronic groups) is provided.

1,4-Difluoro-2-(trimethylsilyloxy)benzene (6): $(Me_3Si)_2NH$ (17.05 g, 0.11 mol) was added during 1 h to 1,4-difluorophenol (26.02 g, 0.20 mol) at 170 °C. The crude liquid product was distilled in vacuo to give the title compound, b.p. 70–72 °C (2 Torr), as a colourless liquid. Yield 40.0 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96–6.89 (m, 1 H, Ph), 6.60–6.51 (m, 2 H, Ph), 0.22 (d, J = 1.0 Hz, 9 H, $SiMe_3$) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 158.5 (dd, J = 242.0, 2.5 Hz), 150.8 (dd, J = 239.5, 3.0 Hz), 143.6 (dd, J = 14.5, 11.5 Hz), 116.3 (dd, J = 22.0, 10.0 Hz), 109.7 (dd, J = 24.0, 1.5 Hz), 108.1 (dd, J = 24.0, 7.5 Hz), 0.0 (d, J = 2.0 Hz) ppm. $C_9H_{12}F_2OSi$ (202.28): calcd. C 53.46, H 5.98; found C 53.29, H 6.04.

1,4-Dichloro-2-(trimethylsilyloxy)benzene (9): This compound was prepared using procedure described for **6** starting from 2,5-dichlorophenol (8.15 g, 0.05 mol); colourless liquid, b.p. 88–91 °C (2 Torr). Yield 11.5 g (98%). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.25 (d, J = 9.2 Hz, 1 H, Ph), 6.89 (m, J = 2.4 Hz, 2 H, Ph), 0.30 (s, 9 H, $SiMe_3$) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 151.9, 132.5, 130.6, 124.3, 122.4, 121.4, 0.2 ppm. $C_9H_{12}Cl_2OSi$ (235.18): calcd. C 45.96, H 5.14; found C 46.31, H 5.23.

1,4-Dibromo-2-(trimethylsilyloxy)benzene (11): This compound was prepared using procedure described for **6** starting from 2,5-dibromophenol (12.6 g, 0.05 mol); colourless liquid, b.p. 112–115 °C (2 Tr). Yield 15.9 g (98%). ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.34 (d, J 8.0 Hz,1 H, Ph), 6.98–6.92 (m, 2 H, Ph), 0.28 (s, 9 H, $SiMe_3$) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 153.2, 134.0, 125.8, 123.8, 121.0, 114.6, 0.3 ppm. $C_9H_{12}Br_2OSi$ (324.09): calcd. C 33.33, H 3.73; found C 33.31, H 3.87.

2,5-Dichlorothioanisole (14): A solution of 1,4-dichlorobenzene (22.05 g, 0.15 mol) in THF (50 mL) was added dropwise to a solution of *n*BuLi (10 M solution in hexanes, 0.15 mol, 15 mL) in THF (100 mL) at –80 °C. The resultant solution was stirred for 15 min followed by the addition of Me_2S_2 (14.13 g, 0.15 mol). The mixture was stirred for 15 min and hydrolyzed with water. The organic phase was separated, and the water phase was extracted with diethyl ether. Evaporation of the combined organic solution left a crude solid product. The product was filtered, washed with water, and recrystallized from hexane (30 mL), to give white crystals, m.p. 64–67 °C. Yield 12.1 g (63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.5 Hz, 1 H, Ph), 7.07 (d, J = 2.5 Hz, 1 H, Ph), 7.03 (dd, J = 8.5, 2.5 Hz,1 H, Ph), 2.47 (s, 3 H, SMe) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 139.9, 133.1, 130.1, 129.6, 125.2, 124.7, 15.5 ppm. $C_7H_6Cl_2S$ (193.10): calcd. C 43.54, H 3.13; found C 43.45, H 3.52.

2,5-Dibromothioanisole (15): A solution of 1,2,4-tribromobenzene (31.5 g, 0.1 mol) in THF (50 mL) was added dropwise to a solution of *n*BuLi (10 M solution in hexanes, 0.10 mol, 10 mL) in THF/Et_2O (4:1, 150 mL) at –105 °C. The resultant solution was stirred for 15 min followed by the addition of Me_2S_2 (10.3 g, 0.11 mol) at –105 °C. The mixture was stirred for 15 min and hydrolyzed with water. The organic phase was separated, and the water phase was extracted with diethyl ether. Evaporation of the combined organic solution left a crude solid product. The product was washed with water, dried and recrystallized from ethanol (50 mL), and dried to give white crystals, m.p. 59–60 °C. Yield 14.7 g (52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.0 Hz, 1 H, Ph), 7.18 (d, J = 2.0 Hz, 1 H, Ph), 7.11 (dd, J = 8.0, 2.0 Hz, 1 H, Ph), 2.47 (s, 3 H, SMe). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 142.1, 133.6, 128.3, 127.4, 121.7, 119.8, 15.7 ppm. $C_7H_6Br_2S$ (282.00): calcd. C 29.82, H 2.14; found C 29.95, H 2.03.

3,6-Dibromo-2-fluoroanisole (19): 3,6-Dibromo-2-fluorophenylboronic acid (29.8 g, 0.1 mol) was oxidized with acetic acid (50 mL)/H_2O_2 (30 wt.-% solution in water, 10.7 g, 0.11 mol) at 35–38 °C. After evaporation of solvents a crude 3,6-dibromo-2-fluorophenol was filtered and washed with a little water. Then it was dissolved in 2 M aq. NaOH (55 mL) followed by the addition of Me_2SO_4 (12.6 g, 0.10 mol). The mixture was stirred for 2 h at 70 °C and the crude product was separated as a thick, oily liquid. It was washed with 2 M aq. NaOH (10 mL) and water. Distillation in vacuo gave the title compound, b.p. 90–92 °C (2 Tr) as oil crystallizing after standing at room temperature, m.p. 42–44 °C. Yield 20.5 g (72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (dd, J = 8.5, 2.0 Hz, 1 H, Ph), 7.15 (dd, J = 8.5, 6.5 Hz, 1 H, Ph), 3.97 (d, J = 1.5 Hz, 3 H, OMe) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 153.2 (d, J = 251.5 Hz), 146.3 (d, J = 14.0 Hz), 128.3 (t, J = 4.0 Hz), 127.9, 116.3 (d, J = 2.0 Hz), 109.2 (d, J = 20.0 Hz), 61.6 (d, J = 5.0 Hz) ppm. $C_7H_5Br_2FO$ (283.92): calcd. C 29.62, H 1.77; found C 29.65, H 1.80.

3,6-Difluoro-2-methoxyphenylboronic Acid (1): A solution of 1,4-fluoro-2-methoxybenzene (2.88 g, 20 mmol) in THF (10 mL) was added dropwise to a solution of LDA freshly prepared from diisopropylamine (2.42 g, 24 mmol) and *n*BuLi (10 M solution in hexanes, 2.4 mL, 24 mmol) in THF (20 mL) at –70 °C. The resultant solution was stirred for 15 min followed by slow addition of $B(OEt)_3$ (3.50 g, 24 mmol). The mixture was stirred for 15 min and then hydrolyzed with dilute aqueous H_2SO_4. The organic phase was separated. Evaporation of the combined organic solutions left a solid that was washed with water and hexane, and dried to give white crystals, m.p. 99–101 °C. Yield 2.97 g (79%). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.13 (m, 1 H, Ph), 6.75 (m, 1 H, Ph), 3.91 (d, J = 1.5 Hz, 3 H, OMe) ppm. ^{13}C{^{1}H} NMR (100.6 MHz, [D$_6$]acetone): δ = 159.9 (d, J = 239.0 Hz), 151.2 (d, J = 242.0 Hz), 149.5 (dd, J = 14.0, 11.0 Hz), 117.4 (dd, J = 22.0, 10.5 Hz), 109.7 (dd, J = 28.0, 7.0 Hz), 60.5 (d, J = 6.0 Hz) ppm. ^{11}B NMR (64.3 MHz, [D$_6$]acetone): δ = 28 ppm. $C_7H_7BF_2O_3$ (187.94): calcd. C 44.74, H 3.75; found C 44.71, H 4.06.

3,6-Difluoro-2-methoxybenzoic Acid (2): A solution of 1,4-difluoro-2-methoxybenzene (7.2 g, 50 mmol) in THF (15 mL) was added to a solution of LDA freshly prepared from *n*BuLi (10 M solution in hexanes, 5.5 mL, 55 mmol) and diisopropylamine (5.7 g, 57 mmol) in THF (50 mL) at –60 °C. After 30 min stirring a freshly prepared solution of CO_2 in diethyl ether (50 mL) was quickly added. After hydrolysis with dilute aq. H_2SO_4 the organic phase was separated, and the water phase was extracted with diethyl ether. The organic phase was concentrated and the residue was dissolved in 2 M aq. NaOH (50 mL). The resultant solution was washed with hexane (2 × 25 mL) and acidified with dilute aq. H_2SO_4 to precipitate a solid that was filtered, washed with water (2 × 5 mL), and dried, to give the title compound as white crystals, m.p. 82–83 °C. Yield 4.75 g (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (br., 1 H, COOH), 7.20 (m, 1 H, Ph), 6.85 (td, J = 9.0, 3.5 Hz, 1 H, Ph),

4.06 (d, J = 2.0 Hz, 3 H, OMe) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 167.6, 155.9 (dd, J = 251.5, 2.5 Hz), 151.5 (dd, J = 245.0, 3.0 Hz), 146.5 (dd, J = 13.5, 5.5 Hz), 119.8 (dd, J = 21.5, 10.0 Hz), 115.9 (dd, J = 17.5, 2.5 Hz), 110.9 (dd, J = 24.0, 7.0 Hz), 62.4 (d, J = 7.0 Hz) ppm. $C_8H_6F_2O_3$ (188.13): calcd. C 51.07, H 3.21; found C 50.64, H 3.52.

2,5-Dibromo-3-methoxyphenylboronic Acid (5): A solution of LDA freshly prepared from diisopropylamine (2.42 g, 24 mmol) and *n*BuLi (10 M solution in hexanes, 2.4 mL, 24 mmol) in THF (20 mL) at –70 °C was added dropwise to a solution of 2,5-dibromoanisole (5.32 g, 20 mmol) in THF (20 mL) containing $B(OiPr)_3$ (4.51 g, 5.50 mL) at –70 °C. A resultant solution was stirred for 15 min and then hydrolyzed with dilute aq. H_2SO_4. The organic phase was separated, and the water phase was extracted with Et_2O (10 mL). Evaporation of combined organic solutions left a solid that was washed with water (2×5 mL), hexane (2×5 mL), and recrystallized from toluene (10 mL) to give white crystals, m.p. 357–360 °C. Yield 2.44 g (39%). ^1H NMR (400 MHz, [D$_6$]acetone): δ = 7.60 [broad, $B(OH)_2$], 7.17 (d, J = 2.0 Hz, 1 H, Ph), 7.14 (d, J = 2.0 Hz, 1 H, Ph),3.90 (s, 3 H, OMe), 3.10 [broad, $B(OH)_2$] ppm. $^{13}C\{^1H\}$ NMR: δ = 157.0, 128.5, 121.9, 116.3, 114.3, 56.9 ppm. ^{11}B NMR (64.3 MHz, [D$_6$]acetone): δ = 29 ppm. $C_7H_7BBr_2O_3$ (309.75): calcd. C 27.14, H 2.28; found C 27.57, H 2.60.

2,5-Difluoro-3-hydroxyphenylboronic Acid (7): This compound was prepared using a procedure described for **5**, starting from 1,4-difluoro-2-(trimethylsilyloxy)benzene (4.04 g, 20 mmol). Evaporation of the combined organic solution obtained after acidic hydrolysis and extraction of the water phase gave a crude solid product and an oily residue. Hexane (5 mL) was added and the mixture was filtered. The solid product was washed with water (2×5 mL) and toluene (2×5 mL), and dried to give the title compound as white crystals, m.p. 179–183 °C. Yield 1.32 g (38%). ^1H NMR (400 MHz, [D$_6$]acetone): δ = 6.80–6.74 (m, 2 H, Ph), 3.14 (broad, 3 H, OH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, [D$_6$]acetone): δ = 159.2 (d, J = 240.0 Hz), 152.4 (d, J = 233.5 Hz), 145.1 (d, J = 27.0 Hz), 110.8 (dd, J = 22.0, 7.5 Hz), 107.2 (d, J = 27.5 Hz) ppm. ^{11}B NMR (64.3 MHz, [D$_6$]acetone): δ = 28 ppm.

The toluene filtrate was concentrated under reduced pressure and distilled in vacuo to give 3,6-difluoro-2-(trimethylsilyl)phenol (**8**), b.p. 75–80 °C (2 Torr), as a colourless liquid. Yield 0.85 g (42%). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.98 (m, 1 H, Ph), 6.46 (m, 1 H, Ph), 5.30 (broad, 1 H, OH), 0.37 (dd, J = 5.0, 3.0 Hz, 9 H, $SiMe_3$) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 162.8 (d, J = 237.0 Hz), 148.1 (dd, J = 30.0, 13.0 Hz), 147.2 (dd, J = 233.0, 3.5 Hz), 116.4 (dd, J = 21.0, 11.5 Hz), 114.3 (d, J = 36.0 Hz), 106.7 (dd, J = 31.0, 6.0 Hz), 0.2 (d, J = 4.0 Hz) ppm. $C_9H_{12}F_2OSi$ (202.28): calcd. C 53.46, H 5.98; found C 53.13, H 6.24.

2,5-Dichloro-3-hydroxyphenylboronic Acid (10): This compound was prepared using the procedure described for **5** starting from 1,4-dichloro-2-(trimethylsilyloxy)benzene (7.05 g, 30 mmol) as a white powder, m.p. 241–246 °C. Yield 4.10 g (66%). ^1H NMR (400 MHz, [D$_6$]acetone): δ = 7.00 (d, 1 H, J = 2.5 Hz, Ph), 6.97 (d, 1 H, J = 2.5 Hz, Ph), 3.12 (s, 3 H, OH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, [D$_6$]acetone): δ = 154.3, 132.7, 124.8, 122.9, 117.4 ppm. ^{11}B NMR (64.3 MHz, [D$_6$]acetone): δ = 28 ppm. $C_6H_5BCl_2O_3$ (206.82): calcd. C 34.84, H 2.44; found C 35.20, H 2.25.

4-Carboxy-2,5-difluoro-3-methoxyphenylboronic Acid (18): A solution of LDA freshly prepared from diisopropylamine (3.03 g, 30 mmol) and *n*BuLi (10 M solution in hexanes, 3 mL, 30 mmol) in THF (30 mL) at –70 °C was added dropwise to a solution of 3,6-difluoro-2-methoxybenzoic acid (1.88 g, 10 mmol) in THF (10 mL). The resultant solution was stirred for 15 min followed by the addition of $B(OEt)_3$ (2.92 g, 20 mmol). The mixture was stirred for 15 min and then hydrolyzed with dilute aq H_2SO_4. The organic phase was separated, and the water phase was extracted with diethyl ether. Evaporation of the combined organic solution left a solid that was washed with acidic water (2×5 mL) and hexane (2×5 mL), and dried to give white crystals, m.p. 140–143 °C. Yield 1.82 g (84%). ^1H NMR (200 MHz, [D$_6$]acetone): δ = 7.13 (dd, J = 9.0, 4.0 Hz, 1 H, Ph), 3.92 (d, J = 1.0 Hz, 3 H, OMe), 3.47 (s, 3 H, OH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, [D$_6$]acetone): δ = 163.9 (d, J = 2.5 Hz), 155.9 (dd, J = 243.5, 3.0 Hz), 154.9 (d, J = 248.5 Hz), 145.9 (dd, J = 15.0, 6.0 Hz), 121.1 (d, J = 20.5 Hz), 116.1 (dd, J = 21.5, 9.0 Hz), 62.5 (d, J = 5.5 Hz) ppm. ^{11}B NMR (64.3 MHz, [D$_6$]acetone): δ = 28 ppm. $C_8H_7BF_2O_5$ (231.95): calcd. C 41.43, H 3.04; found C 40.98, H 2.90.

2,5-Dibromo-3-fluoro-4-formylphenylboronic Acid (26): This compound was prepared using procedure described for **5**, starting form 1,4-dibromo-2-dimethoxymethyl-3-fluorobenzene (6.58 g, 20 mmol). Evaporation of the combined organic solution left an oily residue that was heated at 60 °C with water acidified with a few drops aq. HCl in order to cleave a dimethoxymethyl group. The resultant solid was filtered and washed with water (2×5 mL) and toluene (2×5 mL), and dried to give white crystals, m.p. 231–234 °C. Yield 2.25 g (40%). ^1H NMR (400 MHz, [D$_6$]acetone): δ = 10.23 (d, J = 1.0 Hz, 1 H, CHO), 7.61 (d, J = 1.5 Hz,1 H, Ph), 3.13 (s, 2 H, OH) ppm. $^{13}C\{^1H\}$ NMR (100.6 MHz, [D$_6$]acetone): δ = 188.3, 159.1 (d, J = 264.0 Hz), 134.6 (d, J = 4.5 Hz), 124.3, 123.5, 113.2 (d, J = 20.0 Hz) ppm. ^{11}B NMR (64.3 MHz, [D$_6$]acetone): δ = 28 ppm. $C_7H_4BBr_2FO_3$ (325.72): calcd. C 25.81, H 1.24; found C 25.84, H 1.55.

3,6-Dichloro-2-methoxyphenylboronic Acid (3) and 2,5-Dichloro-3-methoxyphenylboronic Acid (4): The procedure described for **1** was employed starting from 1,4-dichloro-2-methoxybenzene (3.54 g, 20 mmol). Yield 3.12 g (71%), **3/4** = 1:1. ^1H NMR (400 MHz, [D$_6$]acetone + D_2O): δ = 7.35 (d, 1 H, J = 8.0 Hz, **3**), 7.11–7.09 (m, **3** & **4**), 7.18 (s, 1 H, **17**), 3.91 (s, 3 H, **3**), 3.87 (s, 3 H, **4**) ppm.

2,5-Dibromo-3-hydroxyphenylboronic Acid (12, major component) and 2,5-Dibromo-4-hydroxyphenylboronic Acid (13, minor component): The procedure described for **5** was employed starting from **11** (9.75 g, 30 mmol). Yield 7.1 g (80%), **12/13** = 9:1. ^1H NMR (400 MHz, [D$_6$]acetone + D_2O): δ = 7.69 (s, 1 H, **13**), 7.17 (s, 1 H, **13**), 7.11 (d, 1 H, J = 2.0 Hz, **12**), 7.02 (d, 1 H, J = 2.0 Hz, **12**) ppm.

2,5-Dichloro-3-(methylthio)phenylboronic Acid (16, major component) and 2,5-Dichloro-4-(methylthio)phenylboronic Acid (17, minor component): A solution of **14** (3.86 g, 20 mmol) in THF (15 mL) was added dropwise to a solution of *n*BuLi (10 M solution in hexanes, 2 mL, 20 mmol) in THF (30 mL) at –80 °C. The resultant slurry was stirred for 15 min followed by the addition of $(EtO)_3B$ (3.2 g, 22 mmol). The mixture was stirred for 15 min and hydrolyzed 1.5 M aq. H_2SO_4. The organic phase was separated, and the water phase was extracted with diethyl ether. Evaporation of the combined organic solution left a crude solid product. The product was filtered, washed with water (2×5 mL) and toluene (2×5 mL). Yield 2.95 g (63%), **16/17** = 10:1. ^1H NMR (400 MHz, [D$_6$]acetone + D_2O): δ = 7.57 (s, 1 H, **17**), 7.23 (d, 1 H, J = 2.0 Hz, **16**), 7.19 (d, 1 H, J = 2.0 Hz, **16**), 7.18 (s, 1 H, **17**), 2.54 (s, 3 H, **17**), 2.52 (s, 3 H, **16**) ppm.

2,5-Dibromo-3-fluoro-4-methoxyphenylboronic Acid (20, major component) and 2,5-Dibromo-4-fluoro-3-methoxyphenylboronic Acid (21, minor component): The procedure described for **5** was employed starting from **19** (2.84 g, 10 mmol). Yield 1.42 g (44%), **20/21** = 20:1. ^1H NMR (400 MHz, [D$_6$]acetone + D_2O): δ = 7.51 (d, 1 H,

J = 2.0 Hz, **20**), 7.45 (d, 1 H, J = 8.0 Hz, **21**), 3.94 (d, 3 H, J = 1.5 Hz, **20**),3.90 (d, 3 H, J = 1.0 Hz, **21**) ppm.

2,5-Dichloro-4-formylphenylboronic Acid (22, major component) and 2,5-Dichloro-3-formylphenylboronic Acid (23, minor component): The procedure described for **26** was employed starting from 1,4-dichloro-2-(dimethoxymethyl)benzene (4.42 g, 20 mmol). Yield 2.9 g (66%), **22/23** = 2:1. ^{1}H NMR (400 MHz, [D$_6$]acetone + D$_2$O): δ = 10.41 (s, 1 H, CHO, **23**), 10.35 (s, 1 H, CHO, **22**), 7.77–7.75 (m, **22** & **23**), 7.67 (s, 1 H, **22**) ppm.

2,5-Dibromo-4-formylphenylboronic Acid (24, major component) and 2,5-Dibromo-3-formylphenylboronic Acid (25, minor component): The procedure described for **26** was employed starting from 1,4-dibromo-2-(dimethoxymethyl)benzene (3.10 g, 10 mmol). Yield 1.6 g (53%), **24/25** = 4:1. ^{1}H NMR (400 MHz, [D$_6$]acetone + D$_2$O): δ = 10.29 (s, 1 H, CHO, **25**), 10.21 (s, 1 H, CHO, **24**), 7.89 (s, 1 H, **24**), 7.85 (d, 1 H, J = 2.0 Hz, **25**), 7.79 (d, 1 H, J = 2.0 Hz, **25**), 7.78 (s, 1 H, **24**) ppm.

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