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ORIGINAL PAPER

Exploration of 1,2-phenylenediboronic esters as potential bidentate catalysts for organic synthesis

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Abstract Recently, we described the first inverse electron demand Diels–Alder reaction of 1,2-diazene catalyzed by a bidentate Lewis acid. Herein we investigate 1,2-phenylenediboronic esters as potential catalysts for this transformation offering higher stability and easier handling than the currently used boranthracene derivatives. Different 1,2-phenylenediboronic esters were prepared and their ability to form bidentate coordination complexes with phthalazine was analyzed. Although a 1:1 complex was observed, X-ray analysis revealed binding only in a monodentate fashion.

Keywords Boron · Catalysis · Coordination chemistry · Lewis acid · NMR spectroscopy

Introduction

The development of new catalytic systems for chemical transformations is of increasing importance in view of the shortage of natural resources. Recently, we presented a bidentate Lewis acid [1] as a catalyst for the inverse electron demand Diels–Alder (IEDDA) reaction of 1,2-diazines (Scheme 1) [2, 3]. A bidentate coordination mode to the 1,2-diazene was found to be crucial for catalytic activity. In case of a monodentate interaction, the diazine does not undergo the desired IEDDA reaction [4, 5].

Currently, our bidentate Lewis acid catalyst is based on the boranthracene scaffold **6** combining the optimal geometry with a high Lewis acidity [6, 7]. However, the high sensitivity of this scaffold towards water and oxygen requires special care in handling during preparation and application. Therefore, we investigated in this report the suitability of 1,2-bisboronic esters as bidentate Lewis acid catalysts, as they show a much higher stability, which would greatly facilitate their practical use.

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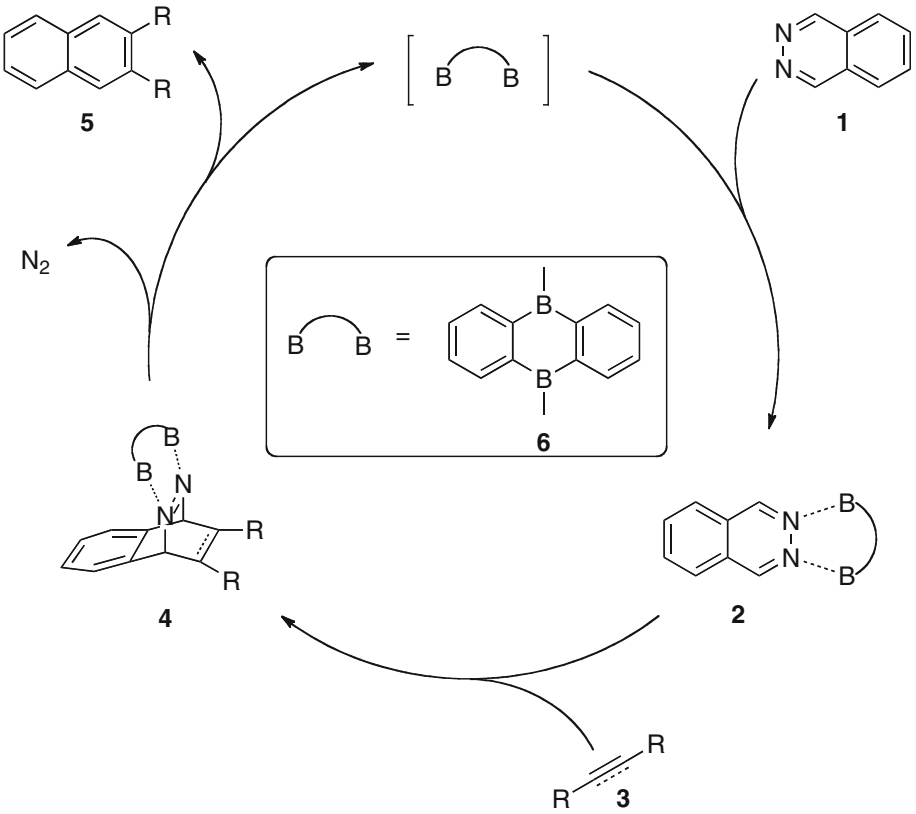
Results and discussion

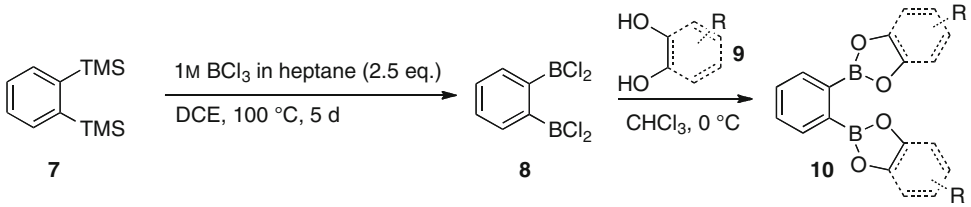
Preparation of bidentate Lewis acidic boronic esters

Our approach to access phenyl-1,2-bisboronic esters relied on tetrachloro-1,2-bisborobenzene (**8**) as a synthetic intermediate, which can be obtained by metal exchange from the corresponding 1,2-bis(trimethylsilyl)benzene (**7**) (Scheme 2) [8]. An iron-catalyzed Grignard method, developed by our group, allowed the synthesis of 1,2-bis(trimethylsilyl)benzenes on a large scale in moderate yield [9, 10]. The final transformation to the boronic ester **10** involved exchange of the chlorides in **8** with 1,2-diols **9** according to the literature method (Scheme 2) [11].

The results of the preparation of various boronic esters **10** are summarized in Table 1. The mediocre yields are rationalized by the difficulty to purify the key intermediate **8** because of its high sensitivity. Impurities as well as their reaction products had to be removed from the final product. All purifications were done under nitrogen, as some of the boronic esters might be sensitive towards water and oxygen. Purification by crystallization was troublesome for the chlorinated compounds **10c** and **10d** because they are poorly soluble in most organic solvents. For the same reasons analysis by solution-phase methods (e.g., NMR spectroscopy) was only partially successful. However, elemental analysis confirmed the purity of **10d**.

Scheme 1





Scheme 2

Properties of bidentate Lewis acidic boronic esters

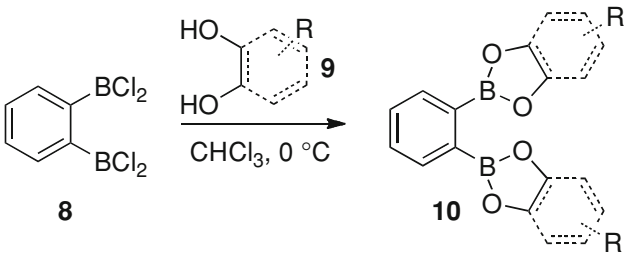
As the application of the prepared Lewis acids as bidentate catalysts was of special interest, the mode of coordination (monodentate vs. bidentate) was evaluated. For this reason, the interaction of the prepared bidentate Lewis acids with substrates such as phthalazine (**1**) was investigated, mainly with bis-boronic ester **10b**.

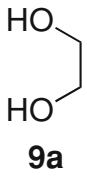
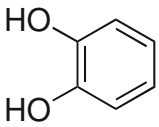
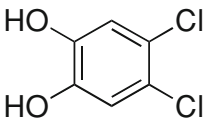
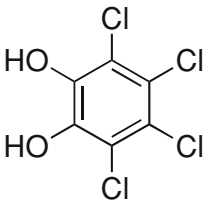
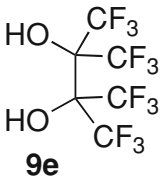
NMR studies

The Lewis acidity of the 1,2-phenylenediboronic esters is one of the crucial parameters determining their ability to form coordination bonds. In similar structures the acidity depends mainly on the electron density at the Lewis acidic centers, which can be altered by electron-withdrawing substituents. The electron density at specific atoms in a molecule can, with approximations, be correlated by NMR spectroscopy. To rank the Lewis acidity of all synthesized boronic esters, the ^{11}B NMR shifts were measured and collected in Fig. 1 [12]. Unfortunately, the solubility of compound **10d** was too low to allow the determination of its chemical shift. The fluorinated compound **10e** showed the highest chemical shift and is estimated to be the strongest Lewis acid in the series. As expected, the Lewis acidity correlated with the electron-withdrawing ability of the diol (Fig. 1).

Interestingly, compound **10c** is an exception in this collection. The negative inductive effect of the double chloro-substituted catechol should lead to a larger electron-withdrawing effect compared to the unsubstituted catechol **10b**. Nevertheless, compound **10c** is the most high-field-shifted in this row of Lewis acids. Additionally, the chemical shifts of the protons next to the carbon–boron

Table 1 Synthesized 1,2-phenylenediboronic esters



Entry	Diol	Product	Yield/ %
1	 **9a**	**10a**	38
2	 **9b**	**10b**	48
3	 **9c**	**10c**	46
4	 **9d**	**10d**	36
5	 **9e**	**10e**	54

bond were studied, allowing a comparison with the ^{1}H NMR data of the octachlorinated compound **10d**. The results displayed the same trend, whereas an increase in chlorine substitution leads to a larger high-field shift. This behavior might originate either from a change in the paramagnetic constant or the positive mesomeric effect of the chlorine substituents. However, stronger electron-withdrawing substituents on the aromatic backbone are of special interest for the future design of more powerful Lewis acids.

Complex formation experiments

The determination of chemical shifts gave a crude estimate of the strength of the Lewis acids **10**. However, it is neither able to give a quantitative result nor to describe the complex formation ability. These parameters were studied in complexation experiments with Lewis bases such as phthalazine (**1**). Lewis acid **10b** was titrated with phthalazine (**1**) and the chemical shifts were recorded by ^{1}H NMR spectroscopy (Fig. 2, spectrum 1 represents boronic ester **10b** and spectrum 13 phthalazine). As the coordination results only in a high-field shift of the signals of **10b** and not in the development of new resonances, the complex formation has to be fast compared on the NMR timescale. Therefore, the observed shift is the average between the shift of the free acid and those of the formed complexes [13].

The ^{1}H NMR signal at $\delta = 7.65$ ppm from compound **10b** was chosen for further analysis, as it shows the strongest shift without any overlapping with other peaks. The bidentate nature of the used Lewis acids as well as the Lewis bases allows not only 1:1 complexes. To determine the stoichiometry of the complex, a Job plot of the measured shifts was calculated. The plot had a maximum at around 0.48 indicating a 1:1 complex (Fig. 3) [14].

The equilibrium constant (K) was calculated from the concentration of the reaction partners in the equilibrium based on the ^{1}H NMR signals of the boronic ester **10b** at 8.11 and 7.65 ppm. The averaged result gives an equilibrium constant of $K = 6{,}936$ dm^3/mol. As this analysis relies only on two data points it certainly includes a substantial statistical error. Nevertheless, it shows clearly that a rather strong complex is formed.

Vapor pressure osmometry (VPO)

The stoichiometry of the complex was further investigated by VPO measurements. An equimolar solution of the Lewis acid **10b** ($M = 314$ g/mol) and phthalazine ($M = 130$ g/mol) was analyzed and the average molar weight of the complex (theoretical M for 1:1 complex,

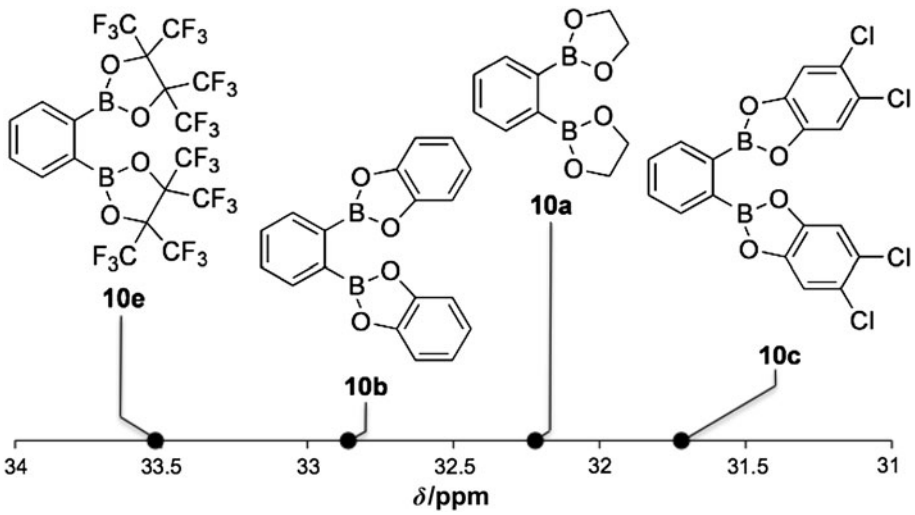


Fig. 1 ^{11}B NMR (in CD_2Cl_2) shifts of synthesized bidentate boronic Lewis acids

444 g/mol) was found to be 388 g/mol. The increased average molar mass compared to the non-complexed Lewis acid is an additional proof of the complex formation in solution. Additionally, the VPO measurement excluded the occurrence of any kind of agglomerate and oligomer.

X-ray analysis

The Job plot determined the Lewis acid to substrate ratio of the complex; however, it gives no information about the number of centers involved in this coordination. One of the most accurate ways to investigate the structure of a molecule (at least in the solid state) is the measurement of an X-ray diffraction structure. Suitable crystals of Lewis acid **10b** (CCDC 903493) and its 1:1 complex with phthalazine (**1**) (CCDC 903492) were obtained from methylene chloride and subjected to X-ray analysis (Fig. 4).

For **10b**, both boron atoms are trigonal planar as expected, revealing sp^2 hybridization. One of the boronic esters lies in the same plane as the aromatic backbone. This observation might be evidence for an interaction between the different systems resulting in a higher bond order of the carbon(2)–boron(2) bond, which would be reflected in a decrease of its length; however, both carbon–boron bonds have about the same length, so this does not seem to be the case. This arrangement could also be explained by an interaction between boron(1) and oxygen(3). Such an interaction is, however, improbable, as boron(1) shows no evidence of sp^3 hybridization and lies on one line with the O(3)–C(13) bond. The planar geometry is most likely due to the crystal packing and might not be significant in solution.

Even more interesting is the structure of the complex from Lewis acid **10b** and phthalazine (Fig. 5). Most importantly, the formation of two coordination bonds between the boronic centers and the 1,2-diazenes is not observed. The X-ray structure shows clearly only one

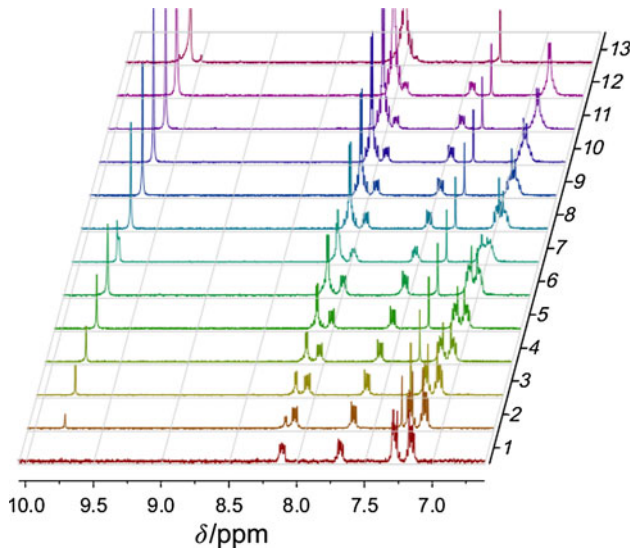


Fig. 2 ^{1}H NMR titration of boronic ester **10b** with phthalazine (**1**)

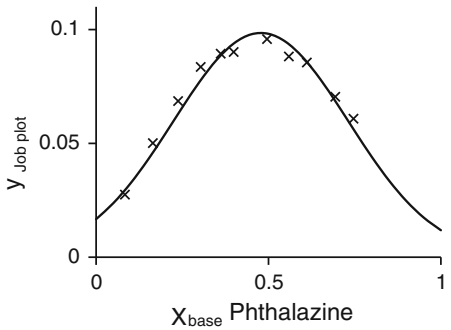


Fig. 3 Job plot with the measured data (*cross*) and the fitted bell-shaped curve (*line*)

connection between boron(1) and nitrogen(1). Boron(1) shows sp^3 hybridization; the bond to nitrogen(1) is just slightly longer than the other three bonds of boron(1) indicating the high strength of the formed bond. The reason why only one bond is formed may originate from a decrease of the acidity caused by a reduction of the electron-withdrawing effect on boron(2) through the first coordination to boron(1). Additionally, the close proximity of boron(2) and oxygen(1) indicates an additional interaction between these atoms, which results in a further weakening of the Lewis acidity. The sp^2 geometry of boron(2) is slightly distorted towards oxygen(1) allowing perfect overlap with the empty *p* orbital. Moreover, the oxygen(1) lies in one plane with B(1), B(2), C(1), and C(2). Interestingly, the monodentate complex does not exhibit any symmetry, which is in contrast to the observations by NMR spectroscopy. As already mentioned the formation of the complex is fast compared on the NMR timescale; the exchange of the different positions might be even faster. Therefore, the NMR showed the average of the different dynamic complexes.

In summary, different 1,2-phenylenediboronic esters were prepared and their binding properties with 1,2-diazine were investigated. Analysis via NMR revealed a 1:1 complex. However, only one boron atom interacts with one nitrogen of the 1,2-diazene, as no bidentate coordination was observed by X-ray analysis. These studies give valuable information about the future design of bidentate Lewis acids as suitable catalysts for organic synthesis. Future efforts will evaluate the potential of the bidentate 1,2-phenylenediboronic esters in this context.

Experimental

All chemicals were used as received from Acros, Alfa Aesar, Fluka, Fluorochem, or Sigma-Aldrich without any prior purification. Dry solvents for the reactions were purchased from Fluka or Biosolve. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Technical grade solvents for extractions and chromatography were distilled once before usage. NMR solvents were obtained from Cambridge Isotope Laboratories (Andover, MA, USA). Air-sensitive reactions were set up in dry glassware that had previously been heated to 200 °C and dried in several evacuation–flush cycles or just flushed with nitrogen. All manipulations of air-sensitive chemicals were either done by Schlenk techniques (liquids) or in a nitrogen-filled glovebox (solids).

Bruker DPX-NMR (400 MHz) (also ^{19}F-NMR, 376 MHz) and Bruker BZH-NMR (250 MHz) instruments were used to measure the ^{1}H NMR spectra. Two-dimensional spectra were recorded on a Bruker Avance 500 (500 MHz) as well as ^{13}C NMR (100.6 MHz) and ^{11}B NMR (160 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks or tetramethylsilane; coupling constants (*J*) are given in Hertz (Hz). The measurements were done at room temperature (rt). The multiplicities are reported as s singlet, d doublet, t triplet, m multiplet, and dd doublet of a doublets. For multiplets only the chemical shift (ppm) of the center is reported. FT-IR spectra were recorded on a Shimadzu FTIR-8400S. The compounds were measured *tel quel* through a Specac Golden Gate ATR sampling system. Mass spectra were recorded on a Finnigan MAT 95Q instrument for electronic ionization (EI). GC–MS analysis was performed on a Hewlett Packard 5890 series II gas chromatography system with a Macherey–Nagel OPTIMA 1 Me2Si column (25 m × 0.2 mm × 0.35 m), at 1 cm^3/min He flow rate (split = 20:1) using a Hewlett Packard 5971 mass-selective detector (EI 70 eV). Elemental analyses (C, H) were conducted using a Perkin-Elmer 240; the results were

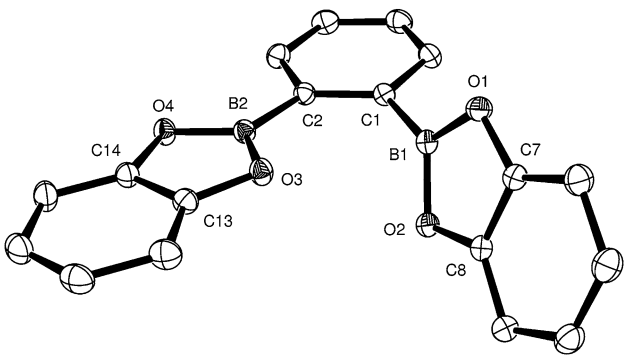


Fig. 4 Crystal structure of compound **10b**

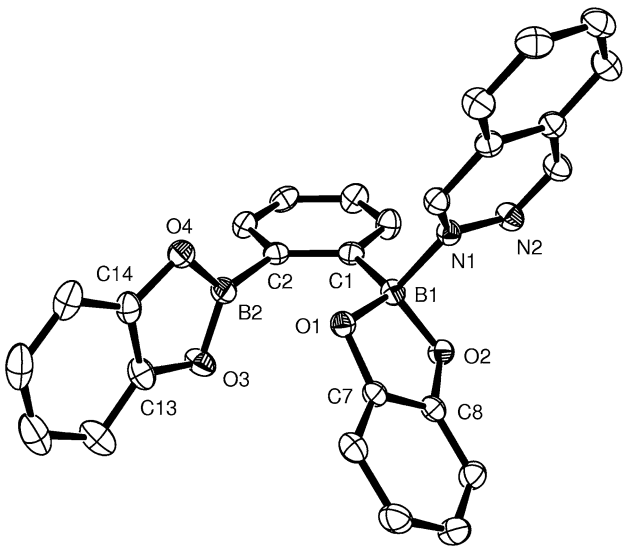


Fig. 5 Crystal structure of the complex of Lewis acid **10b** and phthalazine (**1**)

found to be in good agreement (±0.6 %) with the calculated values. VPO for molar mass calculations was measured on a Knauer K-7000 vapor pressure osmometer.

1,2-Di(1,3,2-dioxaborolan-2-yl)benzene (**10a**, $C_{10}H_{12}B_2O_4$)

In a dry round-bottom flask 1.19 g 1,2-bis(dichloroboryl)benzene (**8**, 4.95 mmol, 1.00 eq.) was dissolved in 10 cm^3 chloroform and cooled in an ice bath. Within 25 min 0.61 g ethylene glycol (**9a**, 0.55 cm^3, 9.9 mmol, 2.0 eq.) was slowly added. The mixture was stirred for 2 h at 0 °C and then allowed to warm to rt and stirred overnight. After 12 h the solvent and the hydrogen chloride were removed by distillation in vacuum. The resulting solid was dried in high vacuum, mixed with 3 cm^3 hexane, and heated to the boiling point. The emulsion was slowly cooled to 30 °C and stirred at this temperature overnight. First crystals emerged and the mixture was cooled to 0 °C. The liquid part was removed and the yellowish crystals were dried in high vacuum overnight to yield 0.41 g (38 %) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.69$ and 7.43 (m, AA′XX′, 4H), 4.37 (s, 8H, HO-CH_2-CH_2-O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 133.8$, 129.9, 66.6 ppm (carbon atoms bound to boron atoms were not observed); ^{11}B NMR (160 MHz, CD_2Cl_2): $\delta = 32.22$ ppm; GC–MS (70 eV): $m/z = 218$ (M^+, 90), 188 (100).

1,2-Di(benzo[d][1,3]dioxaborol-2-yl)benzene (**10b**, $C_{18}H_{12}B_2O_4$)

In a dry round-bottom flask 0.55 g 1,2-bis(dichloroboryl)benzene (**8**, 2.3 mmol, 1.0 eq.) was dissolved in 7 cm^3 chloroform and cooled in an ice bath. Solid catechol (**9b**, 0.51 g, 4.6 mmol, 2.0 eq.) was slowly added, the mixture was stirred for 2 h at 0 °C, and then warmed to rt overnight. After 16 h the solvent and the hydrogen chloride were removed by distillation in vacuum. The resulting solid was dissolved in 35 cm^3 hot acetonitrile, hot filtrated, and washed with 10 cm^3 hot acetonitrile. The filtrate was cooled to rt overnight and the crystals formed were filtered, washed with 5 cm^3 cold acetonitrile, and dried to yield 0.35 g (48 %) of the title compound as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$ and 7.65 (m, AA′XX′, 4H, H-aryl), 7.25 and 7.12 (m, AA′XX′, 4H, H-catechol) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.9$, 135.4, 131.2, 123.2, 113.0 ppm (carbon atoms bound to boron atoms were not observed); ^{11}B NMR (160 MHz, CD_2Cl_2): $\delta = 32.86$ ppm; GC–MS (70 eV): $m/z = 314$ (M^+, 100).

1,2-Bis(5,6-dichlorobenzo[d][1,3]dioxaborol-2-yl)benzene (**10c**, $C_{18}H_8B_2Cl_4O_4$)

In a dry round-bottom flask 2.08 g 4,5-dichlorocatechol (**9c**, 11.6 mmol, 2.00 eq.) was suspended in 10 cm^3 chloroform and cooled in an ice bath. A solution of 1.39 g 1,2-bis(dichloroboryl)benzene (**8**, 5.80 mmol, 1.00 eq.) in 8 cm^3 chloroform was slowly added within 20 min. The mixture was stirred for 2 h at 0 °C and then warmed to rt overnight. After that, all volatile parts were removed by vacuum distillation and the residue was dried in high vacuum. The resulting solid was dissolved in 25 cm^3 hot toluene and cooled to rt overnight. The mixture was then left unstirred for 8 h. The supernatant liquid was removed and replaced by the same quantity of toluene. This heat-up and replace procedure was repeated four times. Then, all volatile parts were removed by distillation in vacuum. The resulting solid was suspended in 30 cm^3 chloroform and filtered. The solid was dried in high vacuum to yield 1.20 g (46 %) of the title compound as a gray solid. ^{1}H NMR (400 MHz, THF-d_8): $\delta = 8.00$ and 7.61 (m, AA′XX′, 4H), 7.44 (s, 4H, H-catechol-Cl_2) ppm; ^{13}C NMR (100 MHz, THF-d_8): $\delta = 148.9$, 134.8, 130.7, 125.7, 114.0 ppm (carbon atoms bound to boron atoms were not observed); ^{11}B NMR (160 MHz, CD_2Cl_2): $\delta = 31.72$ ppm; MS (70 eV): $m/z = 452$ (100), 450 (M^+, 81).

1,2-Bis(4,5,6,7-tetrachlorobenzo[d][1,3]dioxaborol-2-yl)benzene (**10d**, $C_{18}H_4B_2Cl_8O_4$)

In a dry round-bottom flask 2.75 g 3,4,5,6-tetrachlorocatechol (**9d**, 11.1 mmol, 2.00 eq.) was suspended in 20 cm^3 chloroform and cooled in an ice bath. A solution of 1.33 g 1,2-bis(dichloroboryl)benzene (**8**, 5.55 mmol, 1.00 eq.) in 8 cm^3 chloroform was slowly added within 25 min. The mixture was stirred for 2 h at 0 °C and then warmed to rt overnight. After that, all volatile parts were removed by vacuum distillation and the residue was dried in high vacuum. The resulting solid was suspended in 30 cm^3 hot toluene and cooled to rt overnight. The mixture was then left unstirred for 8 h. The supernatant liquid was removed and replaced by the same quantity of toluene. This heat-up and replace procedure was repeated four times. The resulting suspension was filtrated and washed with 10 cm^3 toluene. The solid was dried in high vacuum to yield 1.19 g (36 %) of the title compound as a gray solid. The product is barely soluble and due to the high reactivity only aprotic solvents can be used. Therefore, all of the following analyses were done on a saturated suspension. ^{1}H NMR (400 MHz, THF-d_8): $\delta = 7.88$ and 7.50 (m, AA′XX′, 4H) ppm; ^{13}C NMR (100 MHz, THF-d_8): $\delta = 146.9$, 133.6, 129.8, 124.7, 115.2 ppm (carbon atoms bound to boron atoms were not observed); MS (70 eV): $m/z = 589$ (100), 586 (M^+, 38).

1,2-Bis[4,4,5,5-tetrakis(trifluoromethyl)-1,3,2-dioxaborolan-2-yl]benzene (**10e**, $C_{18}H_4B_2F_{24}O_4$)

In a dry round-bottom flask 0.733 g 1,2-bis(dichloroboryl)benzene (**8**, 3.06 mmol, 1.00 eq.) was dissolved in

7.5 cm^3 chloroform and cooled in an ice bath. A solution of 2.04 g hexafluoro-2,3-bis(trifluoromethyl)-2,3-butandiol (**9e**, 6.12 mmol, 2.00 eq.) in 4 cm^3 chloroform was slowly added within 15 min. The mixture was stirred for 2 h at 0 °C and then warmed to rt overnight. After 16 h all volatile parts were removed by distillation in vacuum and the residue was dried in high vacuum. The resulting solid was dissolved in 9 cm^3 hot hexane and slowly cooled to rt. No crystals emerged and the solution was lyophilized to get 1.26 g (54 %) of the title compound as a white solid in a purity of 70 % (^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.10$ and 7.75 (m, AA′XX′, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 138.2$, 133.6, 122.0, 119.1 ppm (carbon atoms bound to boron atoms were not observed); ^{11}B NMR (160 MHz, CD_2Cl_2): $\delta = 33.52$ ppm; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = 70.08$ (s) ppm; MS (70 eV): $m/z = 762$ (M^+, 69), 215 (100).

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