An Accessible Method for DFT Calculation of ^{11}B NMR Shifts of Organoboron Compounds

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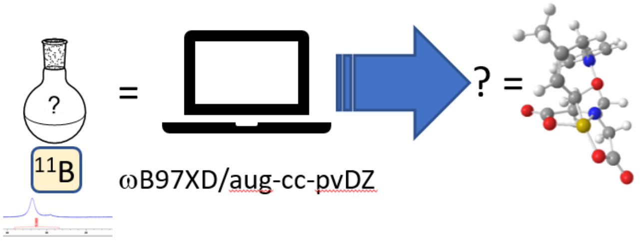
Electronic Supplementary Information (ESI) available,[16] including FAIR data for NMR spectra, computational data and synthetic procedures.



Abstract: The study of boron-mediated reactions in organic synthesis and reactions of organoboron compounds is greatly facilitated by the use of ^{11}B NMR. However, the identification and characterisation of reaction intermediates in often complex systems is far from trivial, as ^{11}B NMR does not provide any detailed structural information. Greater insight into the structures present in such systems can be obtained by using DFT chemical shift calculations to support or exclude proposed reaction intermediates. In this article, we report a rapid and accessible approach to the calculation of ^{11}B NMR shifts that is applicable to a wide range of organoboron compounds.

Introduction

Organoboron compounds are widely used in organic synthesis as important reagents for a range of transition-metal catalysed processes,[1] and they can also serve as useful precursors to a variety of organic compounds through regioselective and stereoselective conversion of the boron atom into other functional groups.[2] Furthermore, boron compounds themselves have found many applications in recent years as catalysts for industrially important reactions such as direct amidation,[3] and as radical precursors.[4] As a consequence of the importance of boron in organic chemistry, there has been considerable interest in elucidating the mechanisms of these reactions.[5] In many cases, complex reaction pathways are involved, where both the nature and the role of the boron species in the key steps can be hard to determine. Direct NMR analysis of real or simulated reaction mixtures can serve to provide insights into the boron species present, but accurate identification of the groups attached to boron is non-trivial due to the lack of detailed structural information that can be obtained from ^{11}B NMR data. As part of our ongoing interest in the study of boron-mediated reactions in organic chemistry,[6] we required a reliable method for predicting the ^{11}B NMR shifts of organoboron compounds so that the presence of proposed reaction intermediates could be supported or excluded. Whilst DFT calculation of ^{11}B NMR chemical shifts of organoboron compounds has been employed in several mechanistic studies,[7] to the best of our knowledge there has been no detailed evaluation of a DFT method using a structurally diverse set of organoboron compounds covering a wide range of chemical shift values. In this article, we describe a convenient method for DFT calculation of ^{11}B chemical shifts that is widely applicable, and which we believe will prove useful for helping to establish the likely structure of unknown intermediates in boron-mediated chemical reactions.

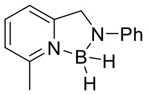
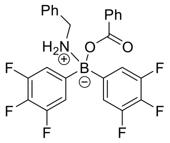
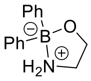
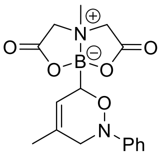
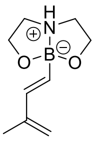
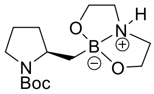
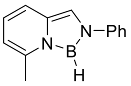
Computational procedures.

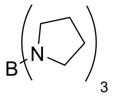
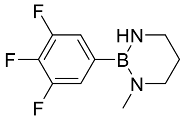
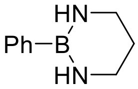
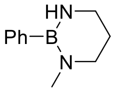
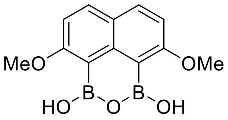
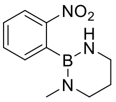
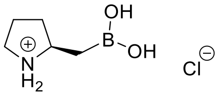
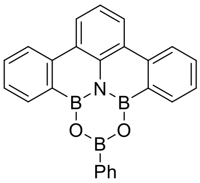
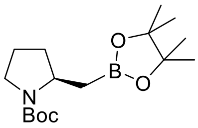
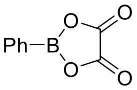
Many DFT-based methods for structure determinations based on ^{13}C and ^{1}H NMR nuclei have been reported in the last decade. A typical example was the use of such methods for structure reassignments in obtusallenes,[8] where the mPW1PW91 functional and the aug-cc-pVDZ basis set using a self-consistent reaction field correction for solvation and full optimization of the molecular geometry resulted in ^{13}C shift predictions for carbon in a wide variety of environments with a mean deviation from the observed values of 1-2 ppm. More recently, it has become customary to use functionals which also include dispersion energy corrections leading to better geometric predictions for non-rigid molecules. For ^{11}B shifts, we have evaluated two well-tested examples of such functionals; ωB97XD, for which a second-generation dispersion correction is implict[9] and the older B3LYP procedure augmented with an explicit third generation dispersion correction (B3LYP-GD3BJ).[10] For evaluation of these functionals, the relatively fast aug-cc-pVDZ basis[11] with an included continuum solvation correction was used for ^{11}B predictions relative to the computed shielding of $BF_3.OEt_2$ as the reference compound, and employing the Gaussian 09 and 16 programs.[12] The use of the relatively modest aug-cc-pVDZ basis set (compared to larger triple-ζ bases) has the direct advantage of allowing the geometries of a wide range of molecules containing up to about 125 atoms to be fully optimized and the shieldings computed with reasonable computer resources. Typically systems with < 50 atoms will complete in a few hours, whilst molecules with up to 125 atoms may take 2-4 days on 16-64 processor systems.[13] Basis sets have also been developed specifically for use in nuclear shielding calculations.[14] Here we also assessed the relatively recent double-ζ aug-pcSseg-1 basis,[14] which is both modestly larger than aug-cc-pVDZ in terms of basis functions, and computationally 2-3 times slower for the overall calculation. It is recognised that ^{1}H NMR shieldings are sensitive to the Boltzmann conformer populations and we also evaluated this sensitivity of ^{11}B shifts for one system where they might be expected to be maximal. To facilitate this, preliminary minimisation of conformer geometries was undertaken using the Avogadro program (V1.1)[15] employing the relatively crude UFF force field to pre-optimize the geometry prior to application of the full

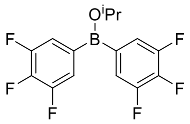
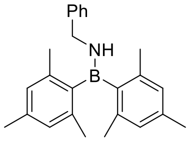
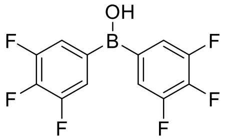
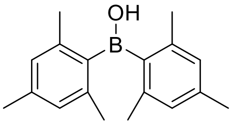
DFT procedure. An exhaustive search for the global conformational minimum for the structures reported here was not undertaken, but this could also be added to future refinements of this procedure. All the computational data and experimentally recorded ^{11}B data is available *via* a managed data repository.[16]

Results and Discussion

Table 1. Observed and Calculated ^{11}B NMR shifts for a range of boron compounds.†

Entry	Structure	δ_{obs}	δ_{calc} (ωB97XD/ aug-cc-pvDZ)	δ_{calc} (B3LYP+GD3BJ/ aug-cc-pvDZ)	δ_{calc} (ωB97XD/ aug-pcSseg-1)	Calc DOI	Expt DOI‡
1[a]	$(THF)_3LiBH_4$	-41.8[17]	-43.8	-45.5	-49.0	1929, 3675 3825	cr7n3h
2[a]	H_3BNH_3	-22[18]	-24.7	-23.7	-27.1	3894 3895 3896	ck62
3	H_3BNEt_3	-14[19]	-17.4	-18.3	-19.0	3817, 3715 3775	
4[c]		-2.6[20]	-5.6	-2.0	-8.5	3733, 3740 3867	f88f6n
5		2[6]	-1.5	-1.3	-3.4	1884, 3700 3849	chxq
6		6.4[17]	4.5	5.5	3.3	753, 3698 3847	cmm8- -
7[b]		10.1[21]	9.1	9.5	8.1	3741, 3704 3928	f7j7tt
8		10.7[21]	8.3	9.0	7.6	3920, 3706 3846	ckzz
9		12.4[17]	10.9	12.1	11.3	940, 3689 3818	cmm9
10	$B(OCH_2CF_3)_3$	17[22]	15.7 (16.5)	15.2	17.4	1617, 3708 3816	ckz2
11	$B(OPh)_3$	16.4	14.6	14.2	15.7	3877 3893 3898	ck94
12	$B(OMe)_3$	19*	17.1	16.7	19.2	1616, 3714 3815	ckz7
13[c]		19.7[20]	17.3	19.6	17.2	3735, 3739 3866	f88f6n

14		24[*]	21.8	21.3	21.7	1619, 3692 3814	ckz8
15	B(NMe$_2$)$_3$	27[*]	26.5	26.0	26.7	1618, 3693 3776	ckz9
16		28.3[17]	26.7	26.9	31.0	755, 3755 3793	cmnb
17		28.4[17]	26.7	26.1	26.7	824 3754 3860	dvfzcf
18[d]	DanB-BPin	28.5[23] 25.2[23]	29.9 26.5	29.5 26.4	31.2 26.0	3073, 3921 3929	f2p9wj
19[c]		28.9[24]	27.5	27.1	27.6	3930, 3931 3932	bz2sz8
20	CatBH	29[*]	26.8	25.9	29.2	3879 3878 3880	f2d8f8
21		29.1[§]	27.0	26.8	27.2	3732. 3707 3865	cmnc
22		29.8[17]	29.1	28.7	28.7	757 3872 3873	cmnd
23	B$_2$Pin$_2$	30.1[*]	28.2	28.0	29.7	3069, 3709 3863	ck2b
24[e]	B$_2$Cat$_2$	30.7[25]	28.5	28.0	30.2	3068, 3712 3862	d6v9wb
25[f]		30.7[26]	29.2	29.3	31.2	3936, 3935 3934	fxfs7h
26		30.9[27] 28.7[27]	30.6 28.6	30.2 28.2	30.2 28.1	3826, 3876, 3864	f98mz3
27		33[17]	31.0	30.9	32.5	1876, 3699 3820	bz2sz8 cmnf
28		36[28]	34.4	34.4	35.2	3176, 3687 3868	ckz4
29[e]	BBr$_3$	40.5[29]	63.3	68.5	71.3	3066, 3685 3812	ckz5

30		42.2[17]	40.2	40.3	41.3	942, 3691 3819	cmng
31		43.2[30]	44.5	44.1	45.1	949, 3701 3850	b3h65j
32		43.5[17]	41.2	41.7	42.8	943, 3690 3778	cmnh
33	Ph_2BO^iPr	44.8[17]	43.0	43.1	43.8	934, 3696 3794	d6bsbf
34	Ph_2BOH	45.7[17]	43.4	43.8	45.0	719, 3695 3777	cmn2
35[g]	BCl_3	46.4[31]	48.6	49.2	52.7	3067, 3697 3798	cppdj4
36		50.2[32]	47.8	49.0	50.1	939, 3694 3813	ckz6
37[h]	Et_3B	86.5[33]	82.7	85.5	88.2	1917, 3663 3771	dbc9jq ck95

Abbreviations: Pin = Pinacolato; Dan = naphthalene-1,8-diaminato; Cat = Catecholato; [†]Data obtained in $CDCl_3$ unless otherwise stated: [a]THF; [b]Acetone; [c]Benzene; [d]MeOH; [e]CH_2Cl_2; [f]D_2O; [g]PhMe; [h]Neat. [*]NMR spectrum collected in this work using a commercial sample. [§]Novel compound, see experimental section for details. FAIR data for these calculations referenced against $BF_3.OEt_2$ are available[16] with individual entries resolved as *e.g.* https://doi.org/10.14469/hpc/1929 [‡]Short DOI resolved as *e.g.* https://doi.org/cr7n3h

Evaluation of three different DFT methods (Table 1) using 37 organoboron compounds from the literature, as well as more structurally complex compounds isolated as part of our mechanistic study into boron-catalysed direct amidation,[6, 34] revealed that calculations were accurate and consistent over a wide range of chemical shifts (-42 to +87 ppm). The regression analyses including all 39 sets of chemical shifts are shown in Table 2. Excluding compounds BBr_3 and BCl_3 (Entries 29 and 35), for which the errors in the calculated chemical shifts can be directly attributed to spin-orbit coupling effects,[8] reduces the standard deviations significantly. We conclude that for the ωB97XD/aug-cc-pvDZ method, the remaining systematic error can be simply attributed to the computed value for the reference compound $BF_3.OEt_2$ and that a correction of +1.83 ppm to the calculated shift can be applied. There is also little difference between the two functionals, with ωB97XD being the slightly more accurate. At the ωB97XD/aug-pcSseg-1 basis set level, the systematic errors are relatively large for the first five entries; if these are also excluded the regression improves, but is still inferior to the ωB97XD/aug-cc-pvDZ method. There is therefore no substantial advantage in using such a basis set; rather these are really designed to facilitate extrapolation to complete basis set limits (CBS), which due to the sizes of many of the molecules reported here is not feasible. Because ^{11}B peaks tend to be broad, the measured shifts themselves are likely to be accurate to only ±1ppm, resulting from effects such as variation in phasing, concentration, solvent and reference procedures used. Given this variation, an accuracy of 1-2 ppm for the predicted shifts is sufficiently useful, and we suggest it can be considered a useful adjunct for identifying unknown boron species in solution. At this stage trying to achieve further reductions in the predictive ^{11}B shift errors by systematic variation in the density functional used or optimising the basis set was not attempted; rather we consider these results as a benchmark that further work should strive to improve upon.

Table 2. Regression analysis for ^{11}B NMR shifts.

Method	Regression slope with standard error.	Regression intercept with standard error.
ωB97XD/aug-cc-pvDZ	1.032 ± 0.031	-1.79 ± 1.01
ωB97XD/aug-cc-pvDZ	1.007 ± 0.009[a]	-1.83 ± 0.30
B3LYP+GD3BJ/aug-cc-pvDZ	1.046 ± 0.036	-1.77 ± 1.20
B3LYP+GD3BJ/aug-cc-pvDZ	1.016 ± 0.009[a]	-1.87 ± 0.30
ωB97XD/aug-pcSseg-1	1.113 ± 0.039	-3.03 ± 1.28
ωB97XD/aug-pcSseg-1	1.079 ± 0.011[a]	-3.13 ± 0.36
ωB97XD/aug-pcSseg-1	1.043 ± 0.016[b]	-1.83 ± 0.53

[a] Excluding BCl_3 and BBr_3. [b] Excluding BCl_3 and BBr_3 and entries 1-5.

Specific examples

1. Entry 10, $B(OCH_2CF_3)_3$, was selected for conformational exploration, since the orientation of the C-CF_3 bond with respect to the B-O bond should be expected to exhibit a maximal electronic effect. The variation between 15.7 (all *anti* conformer) and 16.3-16.5 ppm (all *gauche* conformers of higher energy) for the ^{11}B shift is <1 ppm, which is less than the accuracy of the calculated predictions.
2. Entry 9 contains an eight-membered ring which can exist in at least two conformations, one a boat with a transannular B-N interaction (1.72 Å, Figure 1a) and an alternate chair conformation in which the transannular interaction is absent (Figure 1b) for which the calculated free energy ΔG_{298} is 6.1 kcal/mol higher indicating no significant Boltzmann population of this form. The calculated ^{11}B shifts in these forms differ substantially, 10.9 ppm for the former and 34.0 ppm for the latter, despite the relatively long B-N bond in the first. A search of the Cambridge structural database[35] for tetracoordinate boron containing one attached carbon, two oxygens and one nitrogen produces a histogram of distances (Figure 2) ranging from 1.54 to 1.76 Å, which in turn suggests that ^{11}B shifts may be useful diagnostics for strength of the B-N interaction in such systems. The B-N bond length for the compound in entry 9 is at the top end of the range indicated by the crystal structure bond length distribution, suggesting a relatively weak interaction which is reflected in the relatively high ^{11}B chemical shift compared to the compounds shown in entries 7-8.

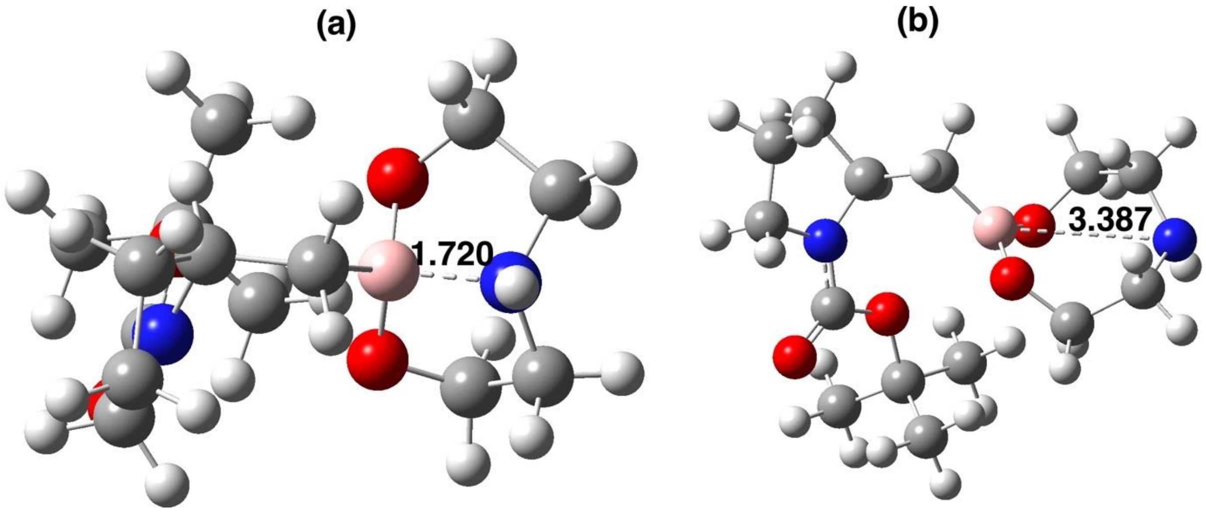


Figure 1. Calculated structures at the wB97XD/aug-cc-pVDZ/SCRF=chloroform level for system 8 as (a) a boat conformation and (b) a chair conformation, with the length of the B-N interaction shown, in Å.

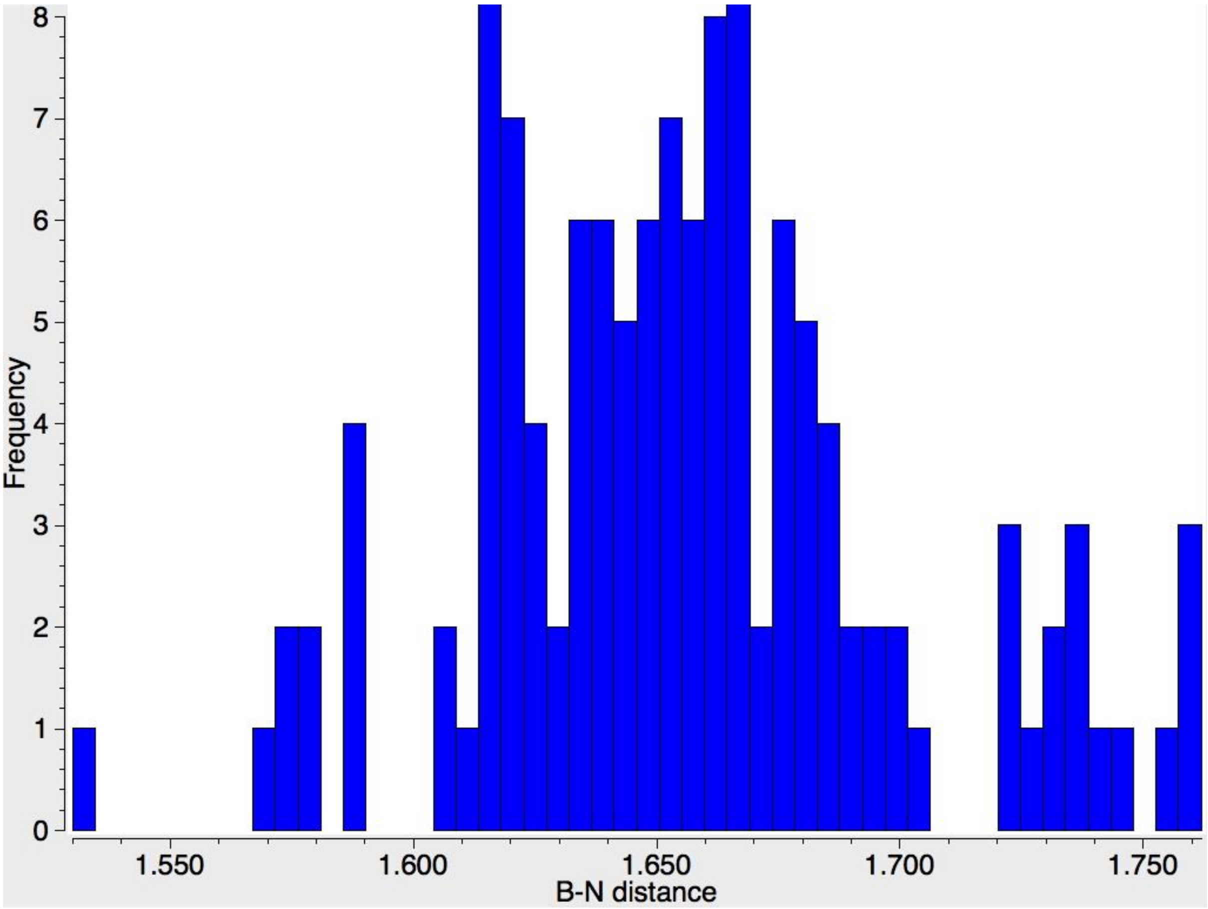
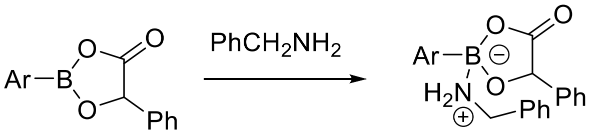


Figure 2. A crystal structure search for tetracoordinate B with B-C, two B-O and one B-N interactions, using the February 2018 version of the CSD database.

3. During our recent study of the mechanism of boron-catalysed direct amidation reactions, we evaluated the reactivity of simple acyloxyboron compounds with amines (Scheme 1). Mandelic acid derivative **1** was synthesised as reported previously,[30] and reacted with benzylamine in $CDCl_3$ solution to give a new species in the ^{11}B NMR, which we proposed was the amine adduct **2**. DFT predictions of the chemical shifts of both **1** and the amine adduct **2** were in good agreement with the proposed structures, which supports our hypothesis that trigonal acyloxyboron compounds react readily with amines at the boron atom. There was no evidence for reaction at the carbonyl group and subsequent amide formation. This serves as an illustration of the utility of this DFT method for identifying unknown species in solution.



1a Ar = *o*-ClC_6H_4 δ_{obs} 33.4 (34.4)
1b Ar = Ph δ_{obs} 33.6 (34.9)

2a Ar = *o*-ClC_6H_4 δ_{obs} 8.0 (7.6)
2b Ar = Ph δ_{obs} 9.5 (8.5)

Scheme 1. Reaction of mandelic acid boronates **1** with benzylamine to give adducts **2**. The DFT calculated ^{11}B chemical shifts (shown in parentheses) are ωB97XD/aug-cc-pvdz/scrf=chloroform, including the reference correction of +1.8 ppm. Data in the sub-collection at DOI: 10.14469/hpc/3900

Summary

^{11}B NMR spectroscopy is widely used as a tool for investigating the role of organoboron reagents in organic reaction mechanisms, but accurately identifying the structure of unknown organoboron species is non-trivial. We have evaluated a simple "one-pot" procedure for estimating the ^{11}B chemical shift of putative species in solution using a standard quantum chemical program, enabling predictions with better than 2 ppm accuracy and providing a tool for assisting with probing the mechanistic pathways of organoboron mediated reactions.

Experimental Section.

General methods. All starting materials and solvents were obtained commercially from standard chemical suppliers and were used as received unless otherwise stated. NMR spectra were recorded using a Bruker Avance-400 MHz spectrometer at frequencies of 400, 101, 128 and 376 MHz for ^{1}H, ^{13}C, ^{11}B and ^{19}F respectively. NMR experiments were run in $CDCl_3$ unless otherwise stated and the data is reported as follows: chemical shift (δ, ppm), multiplicity, spin-spin coupling constants (J, Hz), integration and assignment, where possible. H_{na} and H_{nb} denote diastereotopic protons; H_n and $H_{n'}$ (or equivalently, C_n and $C_{n'}$), denote rotamers. Aromatic carbons next to boron atom are not reported in ^{13}C NMR. Mass spectra were obtained using ASAP (LCT Premier XE), ESI (TQD mass spectrometer with Acquity UPLC photodiode array detector) or EI (Shimadzu QP-2010-Ultra) techniques. Accurate mass values were measured on QtoF Premier mass spectrometer. IR spectra were obtained using FT1600 series or PerkinElmer UATR Two spectrometers. Elemental analysis was performed using an Exeter Analytical E-440 Elemental Analyser. Melting points were determined using an Electrothermal apparatus and were uncorrected.

4,9-Dimethoxy-1H,3H-naphtho[1,8-cd][1,2,6]oxadiborinine-1,3-diol (Entry 21)

n-Butyllithium (0.289 mL, 0.723 mmol) was added to a solution of 1,8-dibromo-2,7-dimethoxynaphthalene (0.100 g, 0.289 mmol) in dry THF (4 mL) under argon at -78 °C. The mixture was stirred for 30 minutes. Trimethyl borate (0.071 mL, 0.636 mmol) was then added quickly and the mixture slowly warmed to r.t. The mixture was stirred for 30 min, quenched with 20 % HCl (2 mL) and left to stir for 15 min. The product was extracted with EtOAc (3 x 4 mL), washed with brine (3 x 4 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The compound was recrystallised from CH_2Cl_2 – Et_2O to give the product as a white solid (10.2 mg, 14 %): ^{1}H NMR (600 MHz, $CDCl_3$): 7.96 (2H, d, J 9.1), 7.35 (2H, s), 7.19 (2H, d, J 9.0), 4.07 (6H, s); ^{13}C NMR (150 MHz, $CDCl_3$): 165.4. 144.0. 134.4. 123.7. 110.1. 56.2; ^{11}B NMR

($CDCl_3$): 29.8; m/z (ES+): 259.3 [M+H+]; HRMS: Calcd for $C_{12}H_{13}{}^{10}B_2O_5$ 257.1022, found 257.1017.

Crystal data for 4,9-dimethoxy-1H,3H-naphtho[1,8-cd][1,2,6]oxadiborinine-1,3-diol (Entry 21): $C_{12}H_{12}B_2O_5$, M = 257.84, orthorhombic, space group P bca, a = 12.4294(6), b = 12.3804(6)), c = 15.3932(7) Å, U = 2368.7(2) Å^3, F(000) = 1072.0, Z = 8, D_c = 1.446 mg m^{-3}, μ = 0.108 mm^{-1} (Mo-Kα, λ = 0.71073 Å), T = 120(1)K. 46156 reflections were collected on a Bruker D8Venture diffractometer (ω-scan, 1°/frame) yielding 3142 unique data (R_{merg} = 0.0562). The structure was solved by direct method and refined by full-matrix least squares on F^2 for all data using SHELXTL and OLEX2 software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Final $wR_2(F^2)$ = 0.1122 for all data (220 refined parameters), conventional R (F) = 0.0419 for 2297 reflections with $I \geq 2\sigma$, GOF = 1.034. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1834774.

Supporting Information: Computational full data files are available *via* a data repository,[16] with these files containing details of calculations; also included are crystallographic and NMR data for 4,9-dimethoxy-1H,3H-naphtho[1,8-cd][1,2,6]oxadiborinine-1,3-diol, and all ^{11}B NMR spectra collected in this work (in Mpublish format).[16]

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