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How big is the pinacol boronic ester as a substituent?

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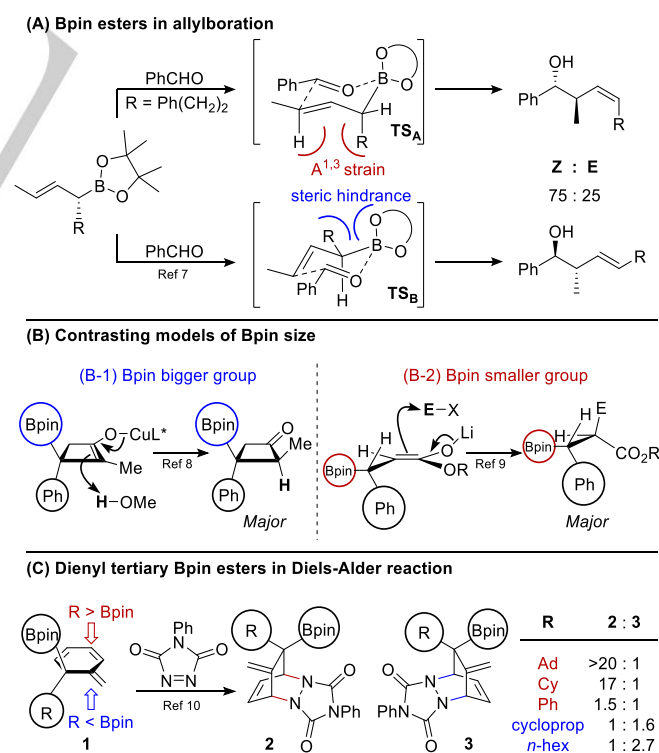
Dedicated to the memory of Prof. Dr. Stuart Warren

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Abstract: The synthetically versatile pinacol boronic ester group (Bpin) is generally thought of as a bulky moiety due to the two adjacent quaternary sp^3-hydrized carbon atoms in its diol backbone. However, recent diastereoselective reactions reported in the literature have cast doubt on this perception. Herein, we report a detailed experimental and computational analysis of Bpin and structurally related boronic esters which allows us to determine three different steric parameters for the Bpin group: the A-value, ligand cone angle, and percent buried volume. All three parameters suggest that the Bpin moiety is remarkably small, with the planarity of the oxygen–boron–oxygen motif playing an important role in minimising steric interactions. Of the three steric parameters, percent buried volume provides the best correlation between steric size and diastereoselectivity in a Diels-Alder reaction.

Boron-containing organic molecules are important building blocks in modern synthesis due to the ready transformation of the boron moiety into a wealth of different functional groups.[1,2] Of these boron-containing molecules, pinacol boronic esters (tetramethyl-1,3,2-dioxaborolanes or "Bpin esters" for short) are pre-eminent in terms of their accessibility, chemical stability, and synthetic versatility. However, despite the group's popularity in reported synthetic transformations, there is a lack of consensus in the literature regarding its size, and as a result, its impact on stereochemical pathways. With fully substituted carbons on the diol backbone, it is often perceived as a large group,[3] a perception that is supported by the behaviour of α-substituted allylboronic pinacol esters in their reaction with aldehydes. In such allylboration reactions, competing steric interactions give rise to two possible chair-like transition states (**TS$_A$** and **TS$_B$** in Scheme 1A). For pinacol boronic esters, there is poor discrimination between these two transition states when R is an alkyl group due to the competing steric interactions of the $A^{1,3}$ strain in **TS$_A$** and the significant gauche interactions which arise between equatorial R and the diol backbone in **TS$_B$** and, as a result, α-substituted allylboronic pinacol esters lead to mixtures of Z and E homoallylic alcohols with relatively low selectivity.[4-7] Smaller, less-substituted diol ligands (e.g. ethylene glycol) give much higher E selectivity (> 95:5) as a result of the reduced gauche interactions in **TS$_B$**.[7] However, two diastereoselective reactions have recently been reported, whose stereochemical outcomes are attributed to the Bpin group being in turn larger[8] *and* smaller[9] than a phenyl group (Scheme 1B). We became interested in the question of Bpin's size during a recent study which engaged the dienyl tertiary pinacol boronic ester **1** with 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione in a Diels-Alder cycloaddition reaction (Scheme 1C).[10] The facial selectivity—whether the dienophile approaches past the Bpin or

R group—led to mixtures of diastereoisomers, **2** and **3**. Assuming that the approach is governed by steric interactions, we reasoned that the diastereoselectivities could be attributed to the relative sizes of the Bpin and R groups. To our surprise, the observed diastereoselectivities suggested that the Bpin group is considerably less sterically demanding than simple α-branched alkyl groups and that its apparent size, at least in terms of our selectivity model, lay in the order: cyclohexyl >> phenyl > Bpin > cyclopropyl > primary alkyl. Our experimental results were also supported by a computational analysis.[11] These unexpected results, along with the contradictory interpretations of experimental observations in the literature, convinced us that a comprehensive investigation of the size of the synthetically valuable Bpin group was needed. Herein, we report a broad investigation using experimental (low temperature quantitative ^{13}C NMR) and computational (DFT and common steric parameters) approaches to answer the question: how big is Bpin?

(A) Bpin esters in allylboration

(B) Contrasting models of Bpin size

(B-1) Bpin bigger group   (B-2) Bpin smaller group

(C) Dienyl tertiary Bpin esters in Diels-Alder reaction

R	2 : 3
Ad	>20 : 1
Cy	17 : 1
Ph	1.5 : 1
cycloprop	1 : 1.6
n-hex	1 : 2.7

**Scheme 1.** Literature examples for the proposed effect of the Bpin group on diastereoselective reactions.

A measure of the size of a group familiar to synthetic chemists is its "A-value": the experimental free energy difference ($\Delta G°$ in kcal/mol) between axial and equatorial mono-substituted cyclohexane conformers.[12,13] We therefore sought to determine the A-value of Bpin and other related groups.

We started our investigation by recording the ^1H and $^{13}C\{^1H\}$ NMR spectra of a CD_2Cl_2 solution of cyclohexyl pinacol boronic ester **4** (Scheme 2). At –90 °C decoalescence in the ^{13}C NMR spectrum allowed us to identify two species, characterised by signals at δ = 82.4 ppm and 82.7 ppm, which correspond to the quaternary carbon atoms of the pinacol ligand in the two conformers **C$_1$** and **C$_2$**. Integration of the two signals gave a ratio of **C$_1$**:**C$_2$** of 74:26. Based on the Arrhenius equation, this ratio represents an A-value of 0.42 kcal/mol for the Bpin group.[12] Similarly small A-values were also observed for the unsubstituted ethylene glycol boronic ester **5** and for the 6-membered ring 1,3-propanediol boronic ester **6**. Notably, replacing all the methyl groups of the pinacol with phenyl rings did not cause a significant increase in the A-value (benzopinacol boronic ester **7**). The experimentally determined A-values[14] for boronic esters **4–7** were significantly smaller than that reported for a methyl group (1.70 kcal/mol) or a hydroxy group (0.87 kcal/mol), placing them among the smallest reported A-values (see Table S2 in ESI).[12]
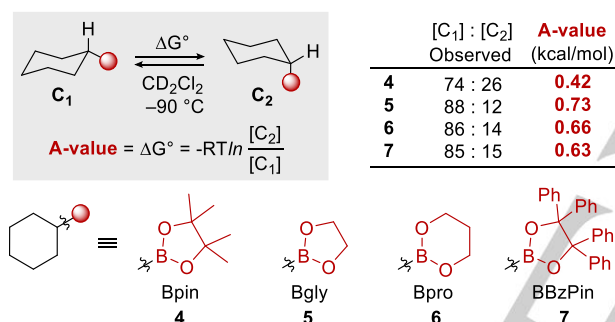
Scheme 2. Conformational analysis of mono-substituted cyclohexanes **4–7**.

To confirm which isomer, equatorial **C$_1$** or axial conformer **C$_2$**, was indeed being favoured[15] we investigated the disubstituted cyclohexane geometric isomers, *trans-* and *cis*-4-hydroxy-cyclohexyl pinacol boronic esters **9** and **10** (Scheme 3A). Using a reported A-value of 0.87 kcal/mol for the hydroxy group,[12] and our experimentally determined A-value for Bpin (0.42 kcal/mol), $\Delta G°$ for the **C$_3$** to **C$_4$** equilibrium for *trans* isomer **9** can be calculated, to a first approximation, by the sum of the A-values of the two substituents, giving $\Delta G°$ = 0.87 + 0.42 = 1.29 kcal/mol.[16] For *cis* isomer **10**, the $\Delta G°$ for the **C$_{3'}$** to **C$_{4'}$** equilibrium is the difference between the substituents' A-values since the energy needed to move one substituent into the axial position is offset by the energy gained by the other group moving into the equatorial position, i.e. $\Delta G°$ = 0.87 - 0.42 = 0.45 kcal/mol.[17] These estimated $\Delta G°$ values were borne out by experiment. At –90 °C only conformer **C$_3$** was observed for **9** (predicted ratio 97:3), while compound **10** showed **C$_{3'}$** and **C$_{4'}$** in a ratio of 82:18 (predicted ratio 80:20). These results show that **10** prefers having the Bpin moiety rather than the hydroxy group in the axial position (**C$_{3'}$** *vs* **C$_{4'}$**) and thus confirms the small preference of the Bpin group for the equatorial position for monosubstituted cyclohexane **4**.
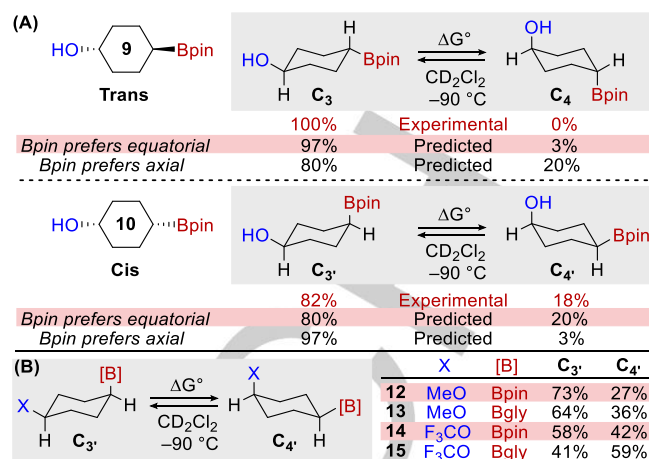
Scheme 3. Conformational analysis of 1,4-disubstituted cyclohexanes.

The surprising observation that Bgly **5** had a larger A-value than Bpin **4** warranted further exploration. We therefore prepared cis 1,4-disubstituted cyclohexanes with both Bpin and Bgly esters (Scheme 3B). As detailed in Scheme 3B, for the MeO- and F_3CO-substituted systems, the Bgly esters **13** and **15** exhibit a larger preference for placing the boron ester in the equatorial position than in the Bpin derivatives **12** and **14**. These results support the larger A-value associated with Bgly **5** reported in Scheme 2.[18] It is interesting to note that similarly counterintuitive observations have been observed for other reported systems. For example, the A-value for isopropyl carboxylate ester is smaller than that for the corresponding methyl ester.[19]

The small A-values of the boronic esters suggest that 1,3-diaxial interactions are limited in the axial conformation. Computational studies on cyclohexyl pinacol boronic ester **4** were thus performed to understand the origin of these weak 1,3-diaxial interactions. DFT calculations were performed with the ORCA program[20a] using the B3LYP/def2-TZVP[20b,20c] level of theory, in combination with Grimme's D3BJ dispersion correction.[20d] A conformational search found four possible conformers for Bpin ester **4** (Figure 1): one with the Bpin group in the axial position (**4A**) and three in which the Bpin occupies the equatorial position (**4E$_{1-3}$**). In all conformers, hyperconjugation involving the empty p-orbital of the boron and an adjacent filled σ_{C-H} or σ_{C-C} bond (shown in red) is observed. Notably, all structures have similar energies, with the calculated $\Delta G°$ between **4A** and a weighted average of **4E$_{1-3}$** being 0.61 kcal/mol, which is in line with the experimentally measured A-value of 0.42 kcal/mol.
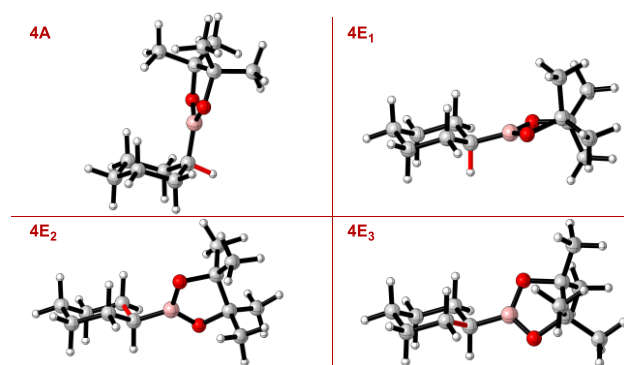
Figure 1. Computational conformational analysis of **4**.

The computationally derived structure for the axial conformer, **4A**, did not reveal any agostic interactions between the axial CHs and boron that might account for the higher than expected concentration of the axial isomer, but does clearly demonstrate that 1,3-diaxial interactions with the Bpin group are reduced due to the planar oxygen–boron–oxygen motif. These sp[2]-hybridised atoms limit the projection of steric bulk over the cyclohexane ring and thus reduce steric interactions with the axial hydrogen atoms. Furthermore, the four methyl groups of the tetramethyl-1,2-ethane bridge are held far above the cyclohexane axial hydrogens and do not contribute to destabilising steric interactions. The small A-value for Bpin, both experimentally and computationally determined, thus reflects the essentially planar structure of the group close to the cyclohexane ring, with the sterically demanding methyl groups held further away. These structural factors also explain the similar A-values for boronic ester moieties with markedly different diol ligands: the steric nature of the diol bridge is immaterial to the A-value, where steric interactions close to the cyclohexane ring are the determining factor. It is instructive to compare the Bpin group to another group with an analogous hybridisation motif: an ester, which has an sp[2]-hybridised carbon and then two sp[2]-hybridised oxygen atoms. The methyl ester group also has a small A-value (1.27 kcal/mol,[12] calculated 1.21 kcal/mol), although it is higher than that of the Bpin group. The planar O–C–O motif minimises 1,3-diaxial interactions, and the slightly larger ester A-value is attributed to the shorter C–C vs C–B bond length (calculated $C[sp^3]$-CO_2Me = 1.51 Å vs $C[sp^3]$-Bpin = 1.57 Å),[21] which brings the steric bulk of the ester closer to the cyclohexane ring.[22] For comparative purposes, a set of A values of boronic esters and common substituents is shown in Figure 2.

These experimentally and computationally determined A-values, however, are not in complete agreement with observations regarding the size of Bpin in the Diels-Alder reaction described in Scheme 1C.[10] An A-value of 0.42 kcal/mol places Bpin as considerably smaller than a methyl group, and our results clearly indicate that the Bpin group reacts in such a way that it can be considered as smaller than α-branched alkyl groups but larger than simple primary alkyl groups. These observations indicate that while the A-value does capture the comparatively small size of the Bpin group, it fails to fully account for the stereochemical influence of the group on the Diels-Alder reaction.

We thus turned our attention to other steric descriptors, in the hope of identifying alternative parameters better able to describe the influence of the Bpin group on the Diels-Alder reaction. Extensive work has been done in organometallic chemistry to quantify and compare the size of ligands, and relate this to the properties and reactivities of organometallic complexes.[23] In particular, parameters such as ligand cone angle[24] first described by Tolman (typically used for P-donor ligands of approximately C_3 symmetry) and percent buried volume developed by the groups of Nolan and Cavallo[25] (suitable for carbenes with approximately C_2 symmetry) have been introduced to rank ligands based on their steric hindrance (Figure 2). Thus, we calculated these parameters for Bpin and a series of linear/α-branched alkyl groups, treating them as ligands (L) bound to a metal centre (M).

Measurements of the ligand cone angle θ (at a normalized M-L bond length of 2.28 Å, using the Solid-G[26] and Exact Cone Angle[27] implementations, Figure 2 and Table S3 in ESI) predict that Bpin and methyl groups have comparable sizes, again, in contrast to the experimental observations in the Diels-Alder reaction. Interestingly, like the A-values, the ligand cone angle

appears to capture the planar oxygen–boron–oxygen motif, but not the ligand backbone.[9] The percent buried volume (%V_{Bur}) steric parameter describes the percentage of a sphere (r = 3.5 Å) around the metal center that is occupied by a given ligand and we postulated that it might better incorporate the effect of the diol backbone.[25] The percent buried volume values, using fully optimized C-R distances to capture differences in bond lengths as noted above (see Table S3 in ESI), are provided in Figure 2 and show the same trend as the experimental Diels-Alder reaction results,[10] with the Bpin group appearing bigger than unbranched primary alkyl groups (e.g. Me, Et), comparable to a phenyl ring, but significantly smaller than secondary and tertiary alkyl groups (e.g. iPr, Cy, tBu). The close agreement between the %V_{Bur} and diastereoselectivity in the Diels Alder reaction, a reaction where there is no geometric flexibility and therefore no ambiguity over the steric effects of the two groups, suggests that %V_{Bur} is likely to be the best measure of steric size. Furthermore, %V_{Bur} could also differentiate, within error, among the 5-membered boronic esters, with the benzopinacol ligand being bigger than Bpin which, in turn, is bigger than the ethylene glycol group.

Finally, Sterimol parameters[28]—recently introduced for quantitative relationships between structure and stereoselectivity—were also determined. All Sterimol data have been included in the ESI (Table S3), but, as they provide a measure of steric demand along different principal axes of substituents, the size of Bpin described by each of the individual parameters, B1, B5, and L, varied from small to one of the largest substituents in the series depending on the axis considered. So while this group of parameters seeks to capture the different dimensions of substituents, it loses the intuitive appeal of a single parameter.
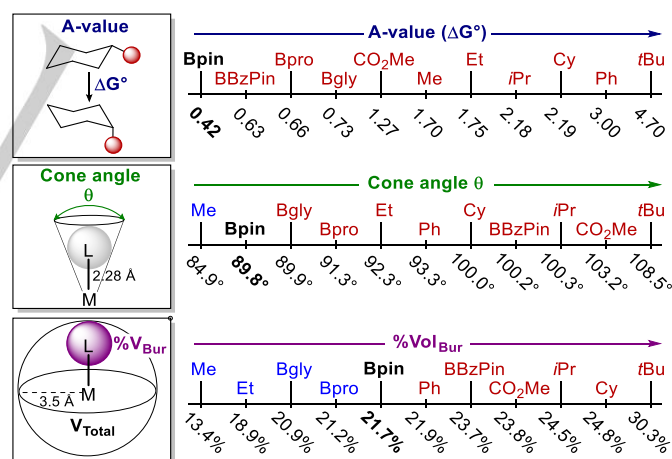

Figure 2. A-values,[12] calculated cone angle[26] and percent buried volume[25] for different substituents. See ESI for calculation details.

In conclusion, surprisingly small A-values have been measured for Bpin and other boronic esters with both considerably smaller and larger diol backbones. The A-value is primarily determined by the sp[2]-hybridized O–B–O motif and not the diol backbone since only the former is directly involved in 1,3-diaxial interactions across the cyclohexane ring. The calculated ligand cone angles are similarly small as they are also primarily determined by the planar O–B–O motif. When used to predict the stereochemical outcome of a geometrically constrained reaction

like the Diels-Alder, these two parameters underestimate the steric influence of the Bpin group with respect to other simple alkyl groups, which we attribute to their failure to fully capture the effects of the remote backbone. The percent buried volume seems to give a more accurate indication of the size of the Bpin moiety and related boronic acids; again, $\%V_{Bur}$ suggests that the Bpin group is comparatively small in size, but in contrast to the A-value and ligand cone angle, places it somewhere between a primary and secondary alkyl group, as observed experimentally in the Diels-Alder reaction. Where experimental results suggest a markedly different ordering of substituents, stereochemical outcomes may not be solely sterically controlled and other factors should perhaps be considered.

Acknowledgements

Keywords: Boronic ester • A-value • Conformational energy • Buried Volume • Sterics

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[17] If Bpin preferred the axial position, then ΔG° = 0.87 - 0.42 = 0.45 kcal/mol for **9** and ΔG° = 0.87 + 0.42 = 1.29 kcal/mol for **10**.

[18] These counterintuitive A-values were also investigated computationally. While in the gas phase at 295 K the A-value of Bgly was higher than that for Bpin (1.15 kcal/mol and 0.29 kcal/mol, respectively), in line with the experimental observations, calculations in CH_2Cl_2 solvent at 183 K (to simulate the experimental conditions) were successful only for Bpin (A-value = 0.61 kcal/mol) but not for Bgly due to our inability to locate fully minimised structures for the equatorial conformers. Many of the structural parameters associated with the computationally optimized structures were almost identical for the two esters (e.g. charge distribution, B–O bond length, B–O–B angle), although differences were noted for the O–C–C–O torsion angle (11.1° for Bgly **5** and 27.0° for Bpin **4**) and for the O–C–C angle (104.7° for Bgly **5** and 102.2° for Bpin **4**). It is possible that these differences in the conformation of the diol backbone have subtle stereoelectronic effects, which influence the axial–equatorial equilibrium.

[19] It is common to find variations of A-values between different papers in the literature, so when comparing different groups it is necessary to find a paper where the different groups have been measured by the same protocol. In the following paper the A-value for the isopropyl and methyl carboxylate esters were measured and found to be 0.9 kcal/mol and 1.1 kcal/mol, respectively. B. J. Armitage, G. W. Kenner, M. J. T. Robinson *Tetrahedron* **1964**, *20*, 747–764.

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[22] (a) This effect is well-recognised for other A-values, where bond length can have a marked effect on their magnitude. For example, the trimethylsilyl group has an A-value of 2.50 kcal/mol, which is considerably smaller than that of *tert*-butyl (4.70 kcal/mol), despite the fact that the trimethylsilyl group occupies more space. This derives from the considerably longer C–Si bond, which holds the steric bulk away from the cyclohexane ring ($C[sp^3]$- $C[sp^3]$ = 1.54 Å *vs* $C[sp^3]$- $Si[sp^3]$ = 1.85 Å); see reference 21a and K. Min, D. Hernandez, T. Skrydstrup, *Acc. Chem. Res.* **2013**, *46*, 457−470). (b) When the C–C(=O) in the ester is stretched to 1.57 A, the calculated A-value decreases to 1.06 kcal/mol. This free energy value uses frequency calculations on structures that are not at their energy minimum and so should be treated with a bit of caution. It should also be noted that the rotational alignment of the ester at the minimum energy conformer is not the same as for the Bpin group.

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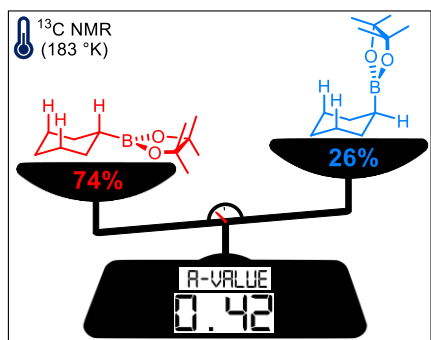
How big is Bpin as a substituent? The Bpin group is generally perceived to be a sterically bulky substituent, but here we show that it has a surprisingly small A-value (0.42 kcal/mol; cf Me is 1.7, OH is 0.87). The percent buried volume seems to give a more accurate indication of the size of the Bpin moiety, which is somewhere between a primary and secondary alkyl group.

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