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Undeniable Confirmation of the *syn*-Addition Mechanism for Metal-Free Diboration by Using the Crystalline Sponge Method

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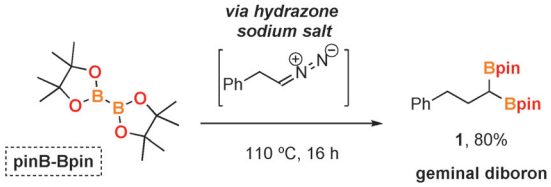
Abstract: The stereochemical outcome of the recently developed metal-free 1,2-diboration of aliphatic alkenes has, until now, only been elucidated by indirect means (e.g. derivatization). This is because classical conformational analysis of the resulting 1,2-diboranes is not viable; in the ^{1}H NMR spectrum the relevant ^{1}H resonances are broadened by ^{11}B, and the occurrence of the products as oily compounds precludes X-ray crystallographic analysis. Herein, the crystalline sponge method is used to display the crystal structures of the diboronic esters formed from internal *E* and *Z* olefins, evidencing the stereospecific *syn* addition mechanism of the reaction, which is fully consistent with the prediction from DFT calculations.

The synthesis of aliphatic 1,1- and 1,2-diboronic esters is of great interest because of their potential for selective C–B difunctionalization in Suzuki–Miyaura cross-coupling processes, for example.[1] Along with the well-known metal-catalyzed 1,1-diboration[2] and 1,2-diboration[3,4] protocols, organocatalytic diboration is emerging as an alternative, as it combines efficiency and simplicity.[5] However, the lack of a well-defined organocatalytic cycle brings about the inevitable question of the stereochemistry of the final aliphatic diboron species. Determination of the stereochemistry of these species by traditional X-ray analysis is difficult because many of them are obtained as oily products.[6] In addition, the unambiguous assignment of the configuration of aliphatic 1,2-diborated esters by ^{1}H NMR spectroscopy is nontrivial. This is due, in part, to fast quadrupolar relaxation (spin for ^{11}B = 3/2, that is, substantial peak broadening), which obfuscates the *J* coupling information.[7] Even in cases for which J_{vic} values are available, the conformational uncertainty for such species still hinders the application of the Karplus equation.[8] As a result, derivatization, mainly by oxidation to alcohols, is still one of the principal methods used to establish the stereochemistry of these species. Thus, an accurate, nondestructive and direct method for the observation of the stereochemistry of oily diboronate ester compounds would be greatly welcomed by the scientific community.

In this context, the crystalline sponge method has now been established as a reliable technique for single-crystal X-ray diffraction studies and does not require crystallization of the samples.[9] Incorporating guests into porous coordination networks causes them to become uniformly oriented, and their molecular structure can then be obtained by conventional X-ray analysis.[10] The porous network used as a crystalline sponge typically consists of pyridine-based linkers assembled around ZnI_2 nodes, and features large pores capable of binding small to medium-sized organic molecules. In this work, we report that the crystalline sponge method is a direct and convenient way to gain access to precise configurational information about 1,2-diboron compounds.

To establish a suitable inclusion method, a target diboron analyte that fulfilled certain pre-requisites was required. The analyte must be chemically inert towards Zn–pyridine-type ligand complexes, and the sizes of the pore and the diboron species would ideally be commensurate. With this in mind, a simple diboron pinacolato ester featuring a 1,1-geminal arrangement of pinacolboryl (Bpin) moieties (**1**) was chosen to check the inclusion feasibility. Interestingly, this 1,1-*gem* diboron compound has also been prepared by metal-free diboration protocols. For the synthesis of **1**, we followed the Wang procedure[5e,11] based on the insertion of B_2pin_2 (bis(pinacolato)diboron) into a diazo-derived carbene synthon, $PhCH_2CHN_2$ (Scheme 1).

A tiny, high-quality single crystal of crystalline sponge **2** with the formula $[(ZnI_2)_3(tpt)_2{\cdot}x(cyclohexane)]_n$ (tpt = 2,4,6-tris(4-pyridyl)triazine)[12] was treated with a cyclohexane solution of **1** (5 μg: 1 mg mL^{-1}, 5 μL).[10] After evaporation of the solution at 50 °C for 24 h, the resulting guest-included crystal **1·2** was subjected to X-ray diffraction analysis as a proof of concept. The crystallographic analysis of the **1·2** complex revealed the



Scheme 1. Metal-free diboration reaction to prepare compound **1**.

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effective trapping of diboron ester **1** in the network pores (Figure 1).[13] Importantly, the successful inclusion of **1** underlined the compatibility of the reactive *gem*-diboronates with the crystalline sponge system. It is noteworthy that this method required sample amounts lower than those required for regular TLC analysis.

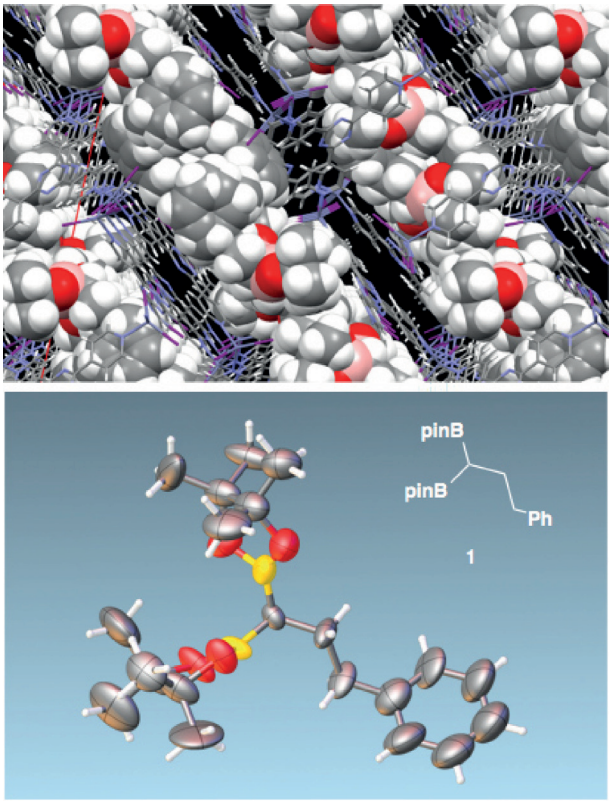
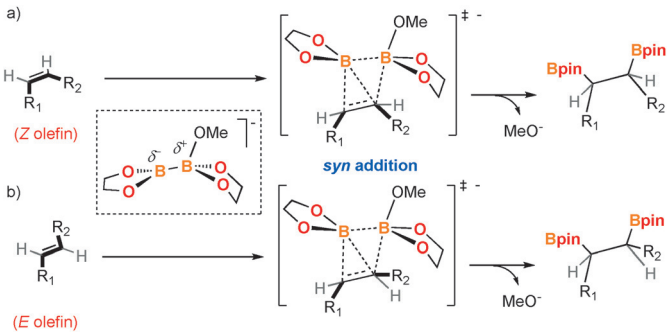


Figure 1. Top: Crystal structure of guest **1** (space-filling representation) in crystalline sponge **2** (stick representation). Hydrogen atoms and solvent molecules have been removed for clarity. Bottom: ORTEP drawing of guest **1** with 30% probability.

After having demonstrated the potential of the crystalline sponge method for the determination of the molecular structure of geminal diboronate esters, we proceeded to apply the method to 1,2-diboron species stemming from internal olefins, which posed challenges in the unambiguous assignment of their configurational structure. A technique allowing the direct observation of the X-ray structure of the 1,2-diborated products arising from a regioisomerically pure internal olefin would be particularly beneficial because it would allow mechanistic information about the stereochemical outcome of the reaction to be confirmed. For this reason, we previously conducted a comprehensive study of the metal-free 1,2-diboration of nonactivated alkenes by means of DFT calculations,[5a] and predicted stereospecific C–B bond formation by *syn* addition. Based on this theoretical prediction, the metal-free diboration of a (*Z*)-olefin would give rise to one diastereoisomer of the 1,2-*bis* pinacolato diboron ester compound (Scheme 2a), whereas the *E* olefin would provide the complementary diastereoisomer (Scheme 2b) in a stereospecific fashion.

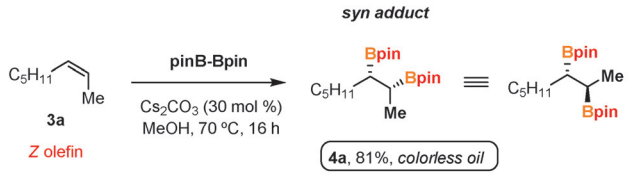


Scheme 2. DFT-supported *syn* addition mechanism for the metal-free diboration reaction. The DFT calculation was carried out with R_1 = Me and R_2 = H (ref [5a]).

Despite the theoretical prediction of the stereospecific vicinal C–B bond formation, experimental evidence had not been provided because of the ambiguity in the ^{1}H NMR spectrum. Based on the organocatalytic addition of the MeO$^-$ →bis(pinacolato)diboron adduct to (*Z*)-2-octene (**3a**) and (*E*)-2-nonene (**3b**) we synthesized the corresponding vicinal-diborated products. Our goal was to determine the relative stereochemistries of the aliphatic 1,2-diboron species by single-crystal diffraction of the products. (*Z*)-2-Octene (**3a**) was easily transformed into 2,3-bis(pinacolato) diboron ester **4a** (colorless oil) in 81% yield. A cyclohexane solution of diboron **4a** was then included into **2** under the following inclusion conditions: 1 mg mL^{-1}, 5 μL, 50 °C, 24 h. Guest **4a** was surely included in **2** as revealed by X-ray analysis.[14] In full agreement with the theoretical predictions,[5a] compound **4a** exhibited a relative 2*R**,3*S** configuration of the two C–B bonds, an outcome expected for the theoretically predicted *syn* addition (Figure 2, structure **4a·2**). The stereochemical attribution in **4a** was valid by direct observation of their molecular structure using X-ray crystallography.

Under the same organocatalytic reaction conditions, 2,3-bis(pinacolato) diboron ester **4b** was isolated as a colorless oil in 75% yield from (*E*)-2-nonene (**3b**), and was also tested using the crystalline sponge method. Diboron ester **4b** was allowed to diffuse into sponge **2**, after which guest-absorbed crystal **4b·2** was examined by X-ray analysis. As shown in Figure 3, **4b·2** presents a 2*R**,3*R** configuration that correlates with the *syn* B_2pin_2 addition to (*E*)-olefin **3b**.[15] X-ray structures of **4a·2** and **4b·2** constitute clear proof of the stereospecificity of the metal-free diboration reaction of internal olefins, and are consistent with the previously suggested mechanism.

In summary, we have demonstrated a straightforward way to characterize the stereospecific outcome of the metal-free diboration of nonactivated olefins by X-ray crystallography, and we can conclude that the mechanism is based on stereospecific *syn*-addition. The present study represents the application of the crystalline sponge method to the mechanistic study of an organic transformation, in which empirical stereochemical assignment of the products by classical NMR techniques is not obvious, and in which the products are available only as oily compounds. We truly believe that the combination of DFT calculations and the crystalline sponge method is a powerful tool for the confirmation of reaction pathways.



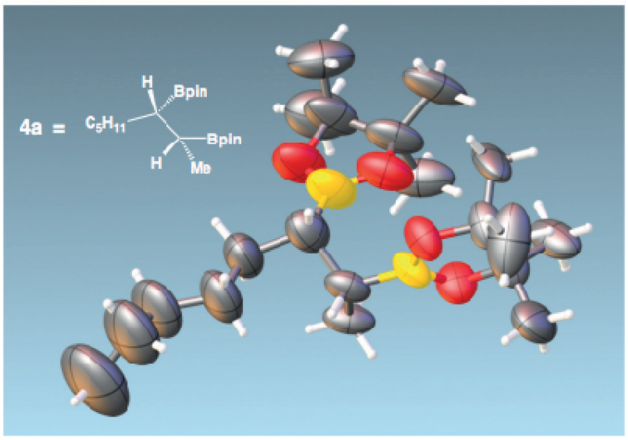


Figure 2. Top: Metal-free diboration of **3a**. Bottom: Crystal structure of 2,3-bis(pinacolato) diboron ester **4a** trapped in the pore of crystalline sponge **2** (ORTEP drawing with 30% probability).

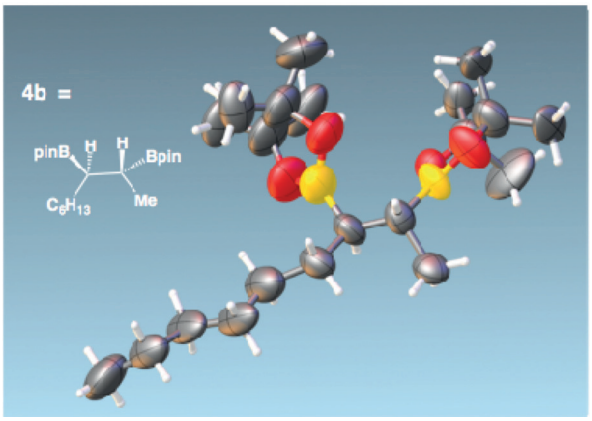


Figure 3. Top: Metal-free diboration of **3b**. Bottom: Crystal structure of 2,3-bis(pinacolato) diboron ester **4b** trapped in the pore of crystalline sponge **2** (ORTEP drawing with 30% probability).

Experimental Section

General procedure for metal-free diboration of internal olefins

An oven-dried resealable Teflon screw-cap Schlenk reaction tube was evacuated and refilled with argon. Under argon counter flow, Cs_2CO_3 (30 mol%, 1.2 mmol, 0.390 g) and bis(pinacolato)diboron (1.2 equiv, 4.8 mmol, 1.21 g) were added. Dry methanol (17 mL) was added to dissolve the mixture. Next, the corresponding alkene (4 mmol, 1 equiv) was added dropwise. The Schlenk tube was then sealed and heated at 70 °C in an oil bath for 16 h. After the reaction was cooled to room temperature, the obtained mixture was filtered over a small pad of Celite® and the solvent was gently concentrated on a rotary evaporator. After all the volatiles had been removed, the crude residue was purified by silica gel flash chromatography to afford the 1,2-diboron compounds.

General procedure for guest inclusion into crystalline sponge

To a microvial containing a piece of a rod-shaped crystal of **2** and cyclohexane (5 μL), a cyclohexane solution of the target compound (1 mg/1 mL, 22 μL) was added. The crystal-containing microvial was then capped and pierced with a needle for solvent evaporation. The microvial was kept at 50 °C and the solvent was gradually evaporated over 1 day. Typically, 5 to 10 vials were used for this procedure.

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Keywords: 1,2-diboron · configuration · crystalline sponge method · diboron inclusion · organocatalysis

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[13] Crystallographic data for **1·2**: $C_{66}H_{72.5}B_2I_6N_{12.5}O_5Zn_3$ $M=2099.99$, monoclinic $C2/c$, $a=35.3355(8)$ Å, $b=14.9646(2)$ Å, $c=30.5277(5)$ Å, $\beta=102.201(2)^\circ$, $V=15777.9(5)$ Å^3, $Z=8$, $D_{calc}=1.768$ g cm^{-3}, GoF = 1.166, $R_1=0.0482$, and $wR_2=0.1489$, CCDC 1444309 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[14] Crystallographic data for **4a·2**: $C_{56.5}H_{65}BI_6N_{12}O_2Zn_3$ $M=1912.52$, monoclinic $C2/c$, $a=34.7466(13)$ Å, $b=14.8989(3)$ Å, $c=30.5651(9)$ Å, $\beta=100.894(3)^\circ$, $V=15538.0(8)$ Å^3, $Z=8$, $D_{calcd}=1.635$ g cm^{-3}, $GoF=1.031$, $R_1=0.0725$, and w$R_2=0.2300$, CCDC 1444310 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[15] Crystallographic data for **4b·2**: $C_{63}H_{78}B_2I_6N_{12}O_4Zn_3$ $M=2046.50$, monoclinic $C2/c$, $a=35.3841(10)$ Å, $b=14.9998(2)$ Å, $c=30.4076(7)$ Å, $\beta=101.922(2)^\circ$, $V=15790.8(6)$ Å^3, $Z=8$, $D_{calc}=1.722$ g cm^{-3}, $GoF=1.043$, $R_1=0.0517$, and w$R_2=0.1364$, CCDC 1444311 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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