

Transition-metal-free allylic borylation of 1,3-dienes

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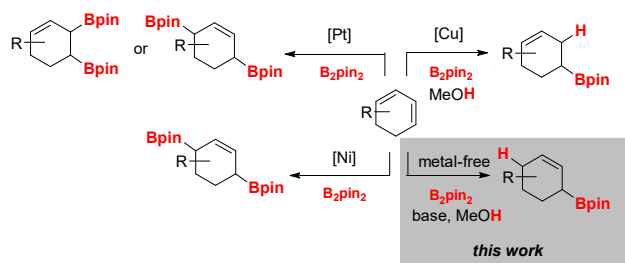
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KEYWORDS 1,3-dienes, conjugated borylation, DFT study, allylboranes, transition-metal-free

ABSTRACT: This work explains the complementary reactivity of diboron reagents with 1,3-dienes in a transition-metal-free context, compared with previous attempts using Pt, Ni or Cu complexes as catalysts. The sole addition of Na₂CO₃ (30 mol%) to bis(pinacolato)diboron in MeOH as solvent allows *in situ* formation of the Lewis acid-base adduct [MeO-Bpin-Bpin][Hbase]⁺, responsible for the 1,4-hydroboration of cyclic and non-cyclic 1,3-dienes. Electronic influence in the substrate is observed to guarantee the conjugated 1,4-hydroboration mechanism versus the competing 1,2-diboration, as well as the preferred formation of the *E* allyl boronate products in non-cyclic 1,3-dienes. Those important trends have been deeply studied under DFT calculations and a theory has been proposed to explain them. The distribution of charge in the allylic anion intermediate, which is obtained upon nucleophilic boryl addition to dienes, governs the selectivity towards 1,4-hydroboration, while the favoured *trans* configuration in diene reagents determines the preference for the *E* allyl boronate products.

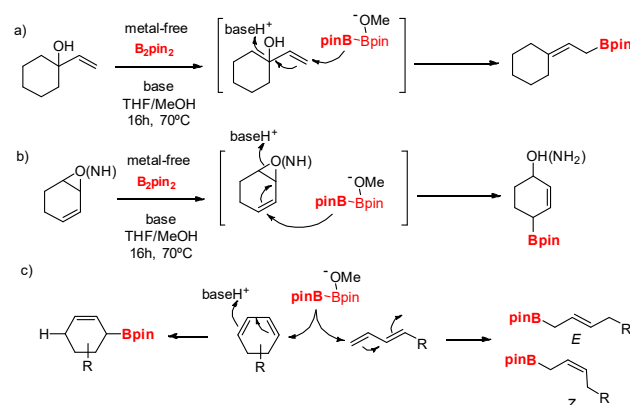
The borylation of 1,3-dienes represents a powerful synthetic tool to obtain diborated or monoborated allylic systems, depending on the transition metal catalyst employed. From Miyaoura and co-worker's breakthrough experiments on Pt(PPh₃)₄ catalyzed 1,4-diboration of 1,3-dienes to synthesize bis(allyl)boronates,¹ the field has progressed by searching different catalytic systems based on Pt, Ni and Cu. The most explored strategy uses Pt complexes to catalyse both 1,2- and 1,4-diboration of 1,3-dienes, even in an asymmetric fashion.^{2,3} Nickel complexes are also explored as catalytic systems and unlike Pt complexes, the Ni catalytic systems can catalyse the 1,4-selective diboration of even sterically hindered 1,3-dienes.⁴ Contrarily to Pt or Ni complexes, the Cu complexes catalyse the monoboration of 1,3-dienes with B₂pin₂ primarily forming the homoallyl boronate products (Scheme 1).^{5,6}



Scheme 1. Previous transition-metal-catalysed diboration and monoboration of 1,3-dienes. An alternative transition-metal-free version reported in this work.

Here, in this work, we present the results of the borylation of 1,3-dienes in a transition-metal-free context, with the sole addition of MeOH and base to generate the corresponding methoxide and form the adduct [MeO-Bpin-Bpin][Hbase]⁺ (Scheme 1,

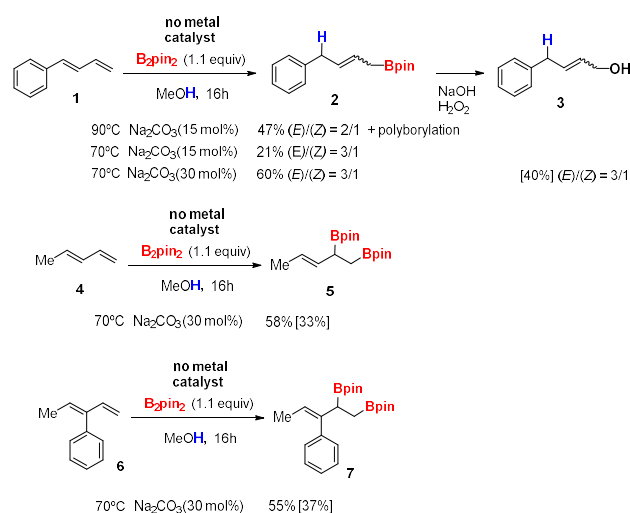
bottom right). Transition-metal-free borylation reactions have emerged within this decade as a convenient synthetic methodology towards selective C-B bond formation.⁷ Our group have previously explored the allylic borylation of tertiary allylic alcohols⁸ (Scheme 2a) as well as the allylic borylation of vinyl epoxides and vinyl aziridines⁹ (Scheme 2b) by the addition of the acid-base Lewis adduct [MeO-Bpin-Bpin][Hbase]⁺ through S_N2'-type mechanisms. To the best of our knowledge, the borylation of 1,3-dienes without metal catalysts was only preceded through the uncatalyzed diboration of 1,3-butadiene using the highly reactive B₂Cl₄ or B₂F₄ producing 1,4-bis(dihalo-boryl)-2-butene compounds.^{10,11}



Scheme 2. Transition-metal-free allylic borylations of a) tertiary allylic alcohols, b) vinyl epoxides and vinyl aziridines and c) hypothetic conjugative borylation of *cis*- and *trans*-1,3-dienes towards 1,4-hydroboration (this work)

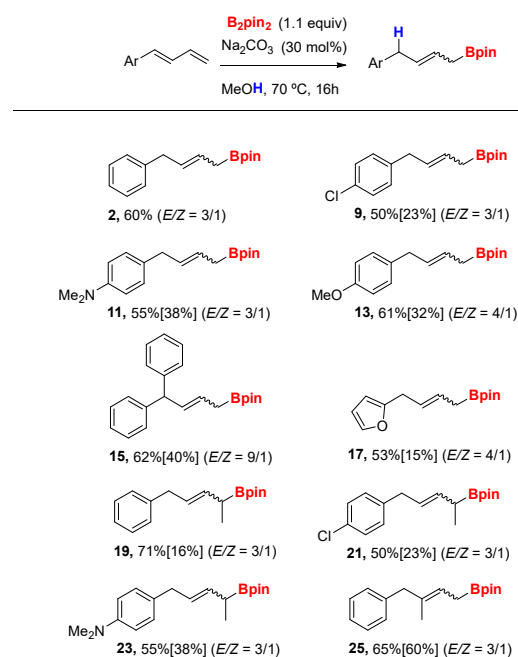
Now, the transition-metal-free borylation of 1,3-dienes generates questions about why the conjugated borylation might be favoured versus 1,2-diboration, as well as whether the *E* allyl boronate products can be preferentially formed versus the *Z* products in non-cyclic systems (Scheme 2c).

In order to answer all these questions raised above, we selected the model substrate *trans*-1-phenyl-1,3-butadiene (**1**) and we carried out the borylation with 1.1 equiv of B₂pin₂ in the presence of 15 mol% of Na₂CO₃ and MeOH as solvent (1 mL) at 90°C. The analysis of the unpurified reaction mixture by ¹H NMR spectroscopy established 47% conversion towards the 1,4-hydrobored product **2** (*E/Z* = 2/1) (Scheme 3, top) and 22% of polyborylated products¹² without the consumption of all the starting material. Decreasing the temperature at 70°C and increasing the amount of base to 30 mol%, allowed the formation of **2** in 60% (*E/Z* = 3/1) minimizing the by-product formation. The purification of the allyl boronate product **2**, as the corresponding alcohol **3** allowed its isolation in 40% with a *E/Z* ratio of 3/1, respectively (Scheme 3). Remarkably, this is the first attempt to borylate 1,3-dienes in a transition-metal-free context and the results seem to be complementary to Huang and co-workers' work,¹³ where the same substrate **1** underwent 1,4-hydroboration with HBpin in the presence of iminopyridine Fe complexes, but forming principally the secondary (*Z*)-allylboronate. When *trans*-1-methyl-1,3-butadiene (**4**) reacted with 1.1 equiv of B₂pin₂, 1,2-diboration of the terminal alkene took place instead, to form product **5** in 58% NMR yield, (33% isolated) (Scheme 3). It seems that the competing 1,2-diboration is favoured versus 1,4-hydroboration for alkyl substituents at the C₁ position,^{14,15} in contrast to the Fe-Mg catalyzed 1,4-hydroboration of 1-alkyl-substituted 1,3-dienes or 2-alkyl-substituted 1,3-dienes, observed by the groups of Huang and Ritter respectively.^{13,16} Just to confirm the previous observation, we conducted the transition-metal free borylation of (*Z*)-penta-1,3-dien-3-ylbenzene (**6**) and as it was expected, the 1,2-diborated product **7** was also formed despite the presence of the phenyl group at the C₂ position (Scheme 3).



Scheme 3. Transition-metal-free 1,4-hydroboration of *trans*-1-phenyl-1,3-butadiene (**1**) and 1,2-diboration of *trans*-1-methyl-1,3-butadiene (**4**) and (*Z*)-penta-1,3-dien-3-ylbenzene (**6**). % NMR yields calculated in ¹H NMR spectra with naphthalene as internal standard, [% Isolated yields].

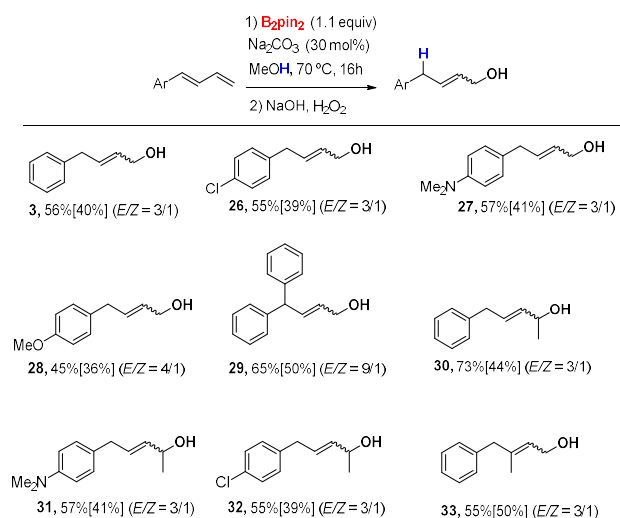
To extend the conjugative borylation on *trans*-1-aryl-1,3-butadiene type of substrates, we carried out a systematic study with the optimized reaction conditions based on the addition of B₂pin₂ (1.1 equiv) to a solution of MeOH that contains the substrate and 30 mol% of Na₂CO₃. As can be seen in Scheme 4, *trans*-1-aryl-1,3-butadienes that contain electron donating and electron withdrawing substituents in the aryl group do not affect to the reaction outcome (allyl boronates **2**, **9**, **11** and **13** in Scheme 4). However a slight increase in the *E/Z* ratio up to 4/1 was observed for product **13**. It is worth mentioning that substrate buta-1,3-diene-1,1-diylidbenzene **14** was borylated with similar success but the enhanced *E/Z* ratio (up to 9/1) indicated the preference for the *E* isomer in compound **15** when the two aryl groups are located at the terminal position (Scheme 4). We were also able to conduct the transition metal-free 1,4-hydroboration of (*E*)-2-(buta-1,3-dien-1-yl)furan **16**, towards the desired allyl boronate product **17**, demonstrating the compatibility with other conjugated systems (Scheme 4). The general method was also applied to internal 1,3 dienes such as ((1*E*,3*E*)-penta-1,3-dien-1-yl)benzene **18** and related substrates **20** and **22**. To our delight the 1,4-hydroboration took place towards the formation of the desired allylic boronates **19**, **21** and **23** without any reduction in the yield or the *E/Z* ratio. The internal substitution in (*E*)-(2-methylbuta-1,3-dien-1-yl)benzene **24**, also proved not to be influential to the reaction outcome as product **25** was formed with similar conversion.



Scheme 4. Transition-metal-free 1,4-hydroboration of *trans*-1-phenyl-1,3-butadienes. Reaction conditions: Substrate (0.2 mmol), B₂pin₂ (1.1 eq) Na₂CO₃ (30 mol%), MeOH (1 mL), 70°C, 16h. % NMR yields calculated in ¹H NMR spectra with naphthalene as internal standard, [% Isolated yields].

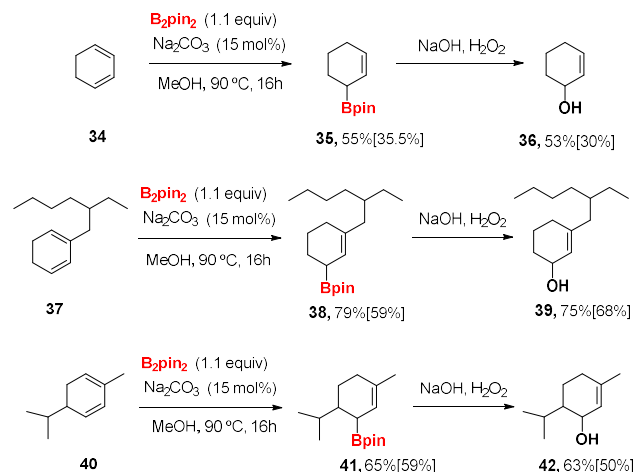
Following to the direct allylic borylation of the 1,3-dienes we carried out the *in situ* oxidative work up to provide the corresponding allylic alcohols in a transition metal-free context

(Scheme 5). The formation of allylic alcohols through borylation reactions was recently observed in the Cu-catalysed borylation of vinyl cyclic carbonates via an S_N2' mechanism, also with preference on the *E* isomer.¹⁷



Scheme 5. Transition-metal-free 1,4-hydroboration/oxidation of *trans*-1-phenyl-1,3-butadienes. Reaction conditions: Substrate (0.2 mmol), B_2pin_2 (1.1 eq) Na_2CO_3 (30 mol%), MeOH (1 mL), 70°C, 16h, followed by oxidative work up with $H_2O_2/NaOH$. % NMR yields calculated in 1H NMR spectra with naphthalene as internal standard, [% Isolated yields]

We next considered the possibility to extend the transition-metal free allylic borylation methodology to cyclic 1,3-dienes. We found that cyclohexadiene (**34**) was transformed into the corresponding allyl boronate via 1,4-hydroboration under the same reaction conditions as for non-cyclic systems except that 90°C were required (Scheme 6). This is interesting because in this substrate there is no aryl substituents that direct the conjugative borylation as in substrate **2**, and so the 1,2 diborated product could be expected to form as in the borylation of *trans*-1-methyl-1,3-butadiene (**4**) (see Scheme 3). In extension, substrate 2-(2-ethylhexyl)cyclohexa-1,3-diene (**37**) could be efficiently borylated towards the allylic boronate product **38**, despite the added steric hindrance provided by having a substituent in the internal position (Scheme 6). Even the disubstituted cyclic 1,3-diene 5-isopropyl-2-methylcyclohexa-1,3-diene (**40**) was transformed into the allylic boronate product **41**, with an *anti*- configuration of the Bpin moiety in relation to the isopropyl functional group (Scheme 6). All the cyclic allyl boronate compounds (**35**, **38** and **41**) were subsequently oxidized and the corresponding cyclic allylic alcohols (**36**, **39** and **42**) were isolated in moderate yield (Scheme 6).



Scheme 6. Transition-metal-free 1,4-hydroboration/oxidation of cyclic 1,3-dienes. Reaction conditions: Substrate (0.2 mmol), B_2pin_2 (1.1 eq) Na_2CO_3 (15 mol%), MeOH (1 mL), 90°C, 16h, followed by oxidative work up with $H_2O_2/NaOH$. % NMR yields calculated in 1H NMR spectra with naphthalene as internal standard, [% Isolated yields]

We performed DFT studies¹⁸ in order to understand the formation of the 1,4-hydroborated products in the transition metal-free borylation of cyclic and 1-aryl-substituted 1,3-dienes. Figure 1 displays the calculated potential free-energy profile for the 1,4-hydroboration of 1-*trans*-phenyl butadiene (**1**) yielding both the *E* and the *Z* stereoisomeric products. In the presence of a base (Na_2CO_3) and MeOH as solvent, the diboron compound is activated forming the acid-base Lewis adduct $[MeO-Bpin-Bpin][Hbase]^+$. Previous computational studies have demonstrated the nucleophilic character of the sp^2 boron moiety towards suitable electrophilic reagents,¹⁹ and that the electron-withdrawing substituents can favor the hydroboration over the diboration of C=C double bonds by stabilizing the anionic monoborylated intermediate.²⁰ Accordingly, the calculated free-energy barrier for the nucleophilic Bpin transfer to the terminal carbon of diene **1** is moderate (22.6 kcal·mol⁻¹) and yields a stable anionic intermediate **II-E** which lays 20.4 kcal·mol⁻¹ below the reactants. Moreover, similar to that observed for allenamides,²¹ the anionic, 3-membered boracycle intermediate opens to form a more stable allylic anion with an alkyl boronate group attached to the terminal carbon (see Figure 1). Finally, subsequent protonation of **II-E** leads to the hydroborated product.

The observed regioselective protonation of C_1 can be rationalized by performing an analysis of charge distribution in the allylic intermediate **II-E** (Figure 1). Our calculations show that the phenyl-substituted C_1 supports a larger negative charge than the allylic C_2 and C_3 . Consequently, it is more reactive towards protonation in agreement with the observed preference for 1,4-over the 3,4-hydroboration. In fact the computed free-energy barrier for the protonation at C_1 by the MeOH solvent is very low (4.2 kcal·mol⁻¹).

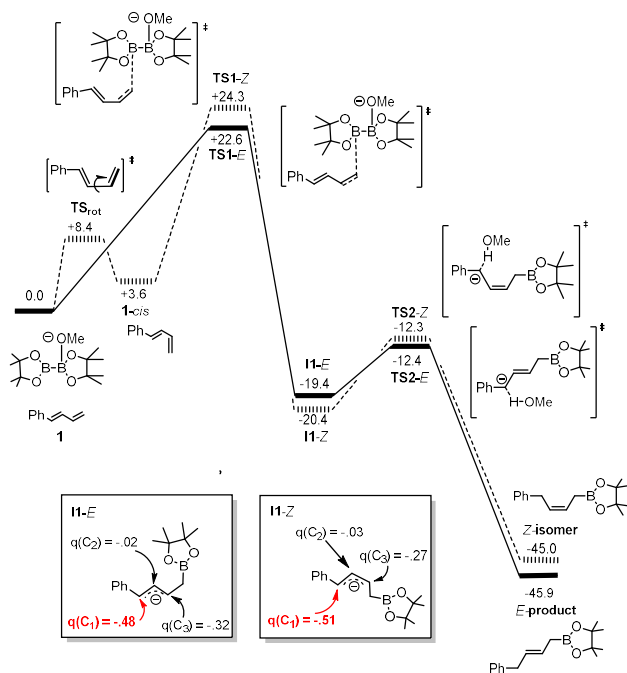


Figure 1. Potential free-energy profiles (kcal·mol⁻¹) for the 1,4-hydroboration of 1-*trans*-phenyl-1,3-butadiene (**1**) by B₂pin₂ in MeOH/base. Solid and dashed lines correspond to the paths yielding the *E* and *Z* stereoisomeric products.

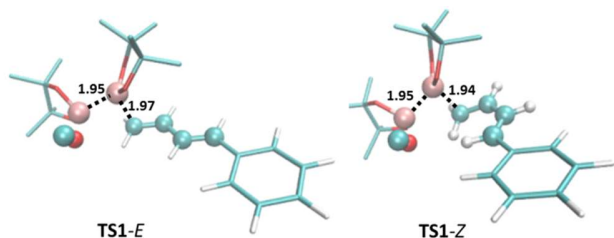


Figure 2. Molecular structures of the transition states for the *E* and *Z* paths of the nucleophilic borylation of the diene **1** (TS1-*E* and TS1-*Z*, respectively). Distances in Å.

The described reaction path (solid lines in Figure 1) relates to the *E*-stereoisomer of the 1,4-hydroborated product. The borylation of the *trans* diene through transition state TS1-*E* (Figure 2) forms the intermediate I1-*E*, in which the alkyl boronate group is *trans* to the carbon to be protonated in the subsequent step (C₁). Thus, to explain the formation of the observed *Z* product, the *E* path has to undergo an isomerization process at some point of the catalytic cycle. The isomerization of the allylic intermediate I1 is very unlikely because the fast protonation yielding irreversibly the final product (Figure 1). Instead, we propose that the *trans* diene isomerizes to its *cis* conformation, the calculated barrier (8.4 kcal·mol⁻¹) and the energy difference (+3.6 kcal·mol⁻¹) might allow it. From the *cis* conformation the boryl addition yields intermediate I1-*Z* with the alkyl boronate group *cis* to C₁, which results in the *Z* product upon protonation (Figure 1). Interestingly, the barrier for boryl transfer for the *cis* conformer is lower than that for the *trans* isomer (22.6 vs. 24.5 kcal·mol⁻¹). The higher reactivity of the *cis* conformations of α,β -unsaturated aldehydes and ketones has

been explained from secondary orbital interactions which allow a better stabilization of the developing negative charge.²² Nevertheless, the lower stability of the *cis* isomer results in a higher energy transition state for the *Z* path, TS1-*Z*, which is 1.7 kcal·mol⁻¹ higher than the corresponding transition state for the *E* path, TS1-*E*. This result is in full agreement with the higher proportion of *E* stereoisomer found experimentally.

Finally, we analyzed whether the proposed mechanism for **1** can also explain the novel 1,4-hydroboration observed for cyclic 1,3-dienes. In this case we only need to consider one reaction path leading to the *E*-stereoisomer of the 1,4-hydroborated product. Figure 3 shows the key species in the mechanism and Figure S1 in Supporting Information depicts the potential free-energy profile for the reaction and the molecular geometries of the 1,4-hydroboration of cyclohexadiene. The nucleophilic Bpin transfer from the [MeO-Bpin-Bpin]⁺ adduct to cyclohexadiene **34** has a computed free-energy barrier of 27.4 kcal·mol⁻¹. The computed value is somewhat larger than that for 1-*trans*-phenyl butadiene but still reasonable for a reaction occurring at 90 °C (see above). In this case the absence of the phenyl substituent reduces stabilization of the allylic anion intermediate I1c, which lays only 2.2 kcal·mol⁻¹ below reactants and 2.9 kcal·mol⁻¹ above the boracycle intermediate I2c. Nevertheless, in both intermediates, I1c and I2c, the C₁ carbon supports the largest negative charge and it is the position most prone to protonation in agreement with the observed 1,4-hydroboration. We found a fast protonation route from the allylic intermediate I1c which undergoes protonation at position C₁ by methanol with a very small electronic energy barrier of 0.2 kcal·mol⁻¹.

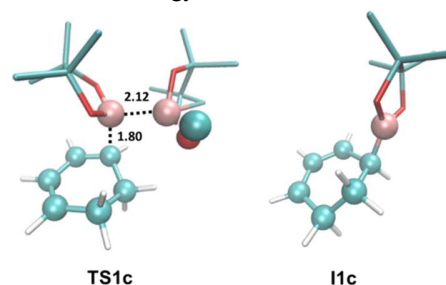


Figure 3. Molecular structures of the transition state for the nucleophilic borylation of the diene **34** (TS1c) and the resulting intermediate I1c. Distances in Å.

Through the present study, it can be concluded that transition-metal-free borylation of 1,3-dienes with the Lewis acid-base adduct [MeO-Bpin-Bpin][Hbase]⁺ takes place through an S_N2'-type mechanism with a preference for formation of the *E* stereoisomeric allylic boronate product. Furthermore, 1,4-hydroboration is favoured versus 1,2-diboration for 1-*trans*-aryl butadienes. Computational studies identify the key steps in the transition-metal-free conjugative borylation and rationalize the preference of the reactions to give 1,4-hydroborated products as well as the *E* stereoisomerism in the allylic boronate products. The electronic distribution in the allylic anion intermediate, which is obtained upon nucleophilic boryl addition to the diene, governs the regioselectivity towards the 1,4-hydroborated product over the 1,2-hydroborated one. The preferred formation of *E* allyl boronate product can be directly correlated with the favoured *trans* configuration in diene reagents. Conversely, for

cyclic dienes, in which *cis* conformation is fixed, the *Z*-stereoisomer can be obtained.

ASSOCIATED CONTENT

Supporting Information includes Experimental Procedures and Spectra data, ^1H , ^{13}C and ^{11}B spectra images, and computational Studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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