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Diels-Alder Reactions of Pinacol Alkenylboronates: An experimental and theoretical study

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We have studied the Diels-Alder reactions of pinacol alkenylboronates with cyclopentadiene under two different conditions: thermal heating at 170 °C in a pressure tube and with catalytic TFA (5 mol%) at 80 °C. Yields varied significantly from system to system and also for the uncatalyzed and catalyzed methodologies. Moderate to excellent exo-stereoselectivities were obtained in all cases. The theoretical study of the thermal reactions shed some light into the intriguing substituent effects observed experimentally. A variety of substituted 5-norbornen-2-ols were easily generated by subsequent in-situ oxidation of the cycloadducts with alkaline hydrogen peroxide.

Introduction

The Diels-Alder (DA) reactions of boron-activated dienophiles were first described more than five decades ago. In the last years, a renewed interest in such processes arouse, both from the experimental and theoretical viewpoints. We have recently shown that the Diels-Alder reactions of vinylboronates can be easily performed using microwave irradiation giving excellent yields of the cycloadducts. Vinylboronic acid pinacol ester showed good stability towards hydrolysis, operational simplicity and yields of Diels-Alder products. The [4+2] cycloadditions of pinacol vinylboronate with a variety of cyclic and acyclic dienes under microwave irradiation generated the boronate cycloadducts in excellent yields in short reaction times (1-6 h) (Scheme 1).

For example, the reaction with cyclopentadiene was complete in 1 h at 150 °C, affording the products in quantitative yield with a 38:62 endo/exo ratio. Subsequent in-situ oxidation of the cycloadducts with alkaline hydrogen peroxide yielded the alcohols efficiently, demonstrating the utility of these intermediates for direct C-O bond-forming reactions.

As part of our continuing work in the field, we have now studied the Diels-Alder reactions of cyclopentadiene with pinacol alkenylboronates with different substitution patterns under different reaction conditions with the aims of developing new methodologies, gaining additional knowledge about the reactivity of boron-substituted dienophiles and analyzing their possible use as synthetic equivalents of substituted enols.

Results and discussion

To carry out this study we have used cyclopentadiene, which was chosen for being a reactive cyclic 1,3-diene and also for the interesting structural and synthetic properties of the bicyclo[2.2.1]heptane products. To investigate the substituent

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>endo/exo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene, 150 °C, MW, 1 h</td>
<td>100</td>
<td>38:62</td>
</tr>
<tr>
<td>2</td>
<td>Xylenes, reflux, 1 h</td>
<td>54</td>
<td>35:65</td>
</tr>
<tr>
<td>3</td>
<td>Toluene, reflux, 5 h</td>
<td>96</td>
<td>35:65</td>
</tr>
<tr>
<td>4</td>
<td>Toluene, 150 °C, 1 h, pressure tube</td>
<td>79</td>
<td>32:68</td>
</tr>
<tr>
<td>5</td>
<td>Toluene, 150 °C, 2 h, pressure tube</td>
<td>86</td>
<td>37:63</td>
</tr>
<tr>
<td>6</td>
<td>Toluene, 170 °C, 5 h, pressure tube, BHT (5 mol%)</td>
<td>92</td>
<td>40:60</td>
</tr>
<tr>
<td>7</td>
<td>Toluene, 170 °C, 1 h, pressure tube, BHT (5 mol%)</td>
<td>96</td>
<td>35:65</td>
</tr>
</tbody>
</table>

* Determined by 1H NMR.
effect on the outcome of the thermal Diels-Alder reaction, we tested a range of commercially available alkenylboronates with alkyl or aryl groups with different substitution patterns in the 1- and 2-positions of the carbon-carbon double bond. Initial screening reactions under microwave heating with the pinacol esters of trans-1-penten-1-ylboronic acid and trans-2-phenylvinylboronic acid suggested that the presence of substituents in the double bond of the substrates retarded the cycloaddition process considerably. Therefore, the use of microwave irradiation proved impractical. We then re-investigated the Diels-Alder reaction of pinacol vinylboronate with cyclopentadiene under a large number of thermal conditions using conventional heating. Table 1 summarizes the outcome of some descriptive experiments. Entry 1 shows the result previously obtained in our laboratories at 150 °C under microwave irradiation for 1 h. When the reaction was performed in refluxing xylenes under conventional heating, a 54% yield was obtained (Entry 2). We managed to get a 96% yield in refluxing toluene with a longer reaction time (Entry 3). As an alternative, use of a pressure tube at 150 °C in 1 h gave the cycloadduct in 79% yield (Entry 4), while increasing the time to 2 h raised the yield to 86% (Entry 5). If the bath temperature was set to 170 °C, a 92% yield was generated in 5 h, and a nearly quantitative yield was obtained in 1 h (Entries 6 and 7). BHT (5 mol%) was added to prevent undesired radical side reactions. The endo/exo ratios varied slightly around 38:62 for all reactions.

Having optimized the conditions for the thermal reaction of pinacol vinylboronate under conventional heating, we next turned our attention to the [4+2] cycloadditions of the substituted substrates (Table 2). All the reactions were optimized to yield the greatest amount of products. Lower temperatures or shorter reaction times afforded poorer yields while higher temperatures or longer reaction times either did not increase the yield or led to some decomposition.

### Table 2 Thermal Diels-Alder reaction of alkenylboronates with cyclopentadiene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>1</td>
<td>96 35:65</td>
<td>2a-N 2a-X</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>24</td>
<td>78 (100) 17:83</td>
<td>2b-N 2b-X</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>24</td>
<td>89 20:80</td>
<td>2c-N 2c-X</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>24</td>
<td>88 (100) 15:85</td>
<td>2d-N 2d-X</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>24</td>
<td>29 (90) 35:65</td>
<td>2e-N 2e-X</td>
</tr>
</tbody>
</table>
As found in our initial experiments with microwave heating, longer reactions times than for the parent dienophile (1a) were needed in all cases, excluding 1h (Entry 8). However, for the latter the yield was very low and did not increase by extending the reaction time (25% in 1 h endo/exo 10:90, 21% in 12 h endo/exo 41:59). Alkyl-substituted substrates performed much better than the aromatic analogues, giving yields in the range 72-89% (Entries 2-4 and 9). We reasoned that the conjugated aromatic ring donated electron density to the carbon-carbon double bond. However, the introduction of electron-withdrawing substituents on the phenyl ring did not improve the reactivity of such systems (Entries 5-8 and 10). Regarding the stereoselectivities, the exo cycloadduct predominated in all reactions. The highest exo-stereoselectivity was observed for isopropenylboronic acid pinacol ester (1i) (endo/exo 9:91, Entry 9), while alkenylboronates with alkyl groups in the 2-position exhibited endo/exo ratios higher than 20:80 (Entries 2-4).

Table 3 TFA-catalyzed Diels-Alder reaction of alkenylboronates with cyclopentadiene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="image1" alt="Diels-Alder Reaction" /></td>
<td>24</td>
<td>20 (70)</td>
<td>2f-N, 2f-X</td>
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<tr>
<td>7</td>
<td><img src="image2" alt="Diels-Alder Reaction" /></td>
<td>24</td>
<td>19 (48)</td>
<td>2g-N, 2g-X</td>
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<tr>
<td>8</td>
<td><img src="image3" alt="Diels-Alder Reaction" /></td>
<td>1</td>
<td>25 (91)</td>
<td>2h-N, 2h-X</td>
</tr>
<tr>
<td>9</td>
<td><img src="image4" alt="Diels-Alder Reaction" /></td>
<td>24</td>
<td>72 (80)</td>
<td>2i-N, 2i-X</td>
</tr>
<tr>
<td>10</td>
<td><img src="image5" alt="Diels-Alder Reaction" /></td>
<td>12</td>
<td>Traces*</td>
<td>2j-N, 2j-X</td>
</tr>
</tbody>
</table>

*Yields based on recovered starting materials (BRSM) in parenthesis. Relative to the pinacol boronate moiety, determined by ‘H NMR. The starting material was recovered.

The aromatic compounds showed moderate exo-selectivities, similar to the one obtained with the unsubstituted system (endo/exo ~ 40:60).

In the next stage, we aimed to determine whether milder conditions could be used so we embarked in the development of the acid-catalyzed version of the reaction under study (Table 3). Many experiments were run for the Diels-Alder reactions of pinacol esters of vinylboronic acid (1a), trans-1-pentenylboronic acid (1b) and trans-2-phenylvinylboronic acid (1e) to determine the optimal conditions. Bronsted acids gave better results than Lewis acids, due to the greater polymerization of the diene in the presence of the latter. Among the Bronsted acids, we tried acetic acid, trifluoroacetic acid (TFA) and triflic acid. We tested up to 2 equivalents of Bronsted acids and 10 equivalents of cyclopentadiene, solvents like toluene, dichloromethane and water, and temperatures ranging from room temperature to

![Diels-Alder Reaction Diagram](image6)
<table>
<thead>
<tr>
<th>1</th>
<th><img src="image1.png" alt="Structure" /></th>
<th>5</th>
<th>88 (36:64)</th>
<th><img src="image2.png" alt="Structure" /> 2a-N</th>
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<td>2</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>24</td>
<td>traces&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image5.png" alt="Structure" /> 2b-N</td>
<td><img src="image6.png" alt="Structure" /> 2b-X</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>24</td>
<td>traces&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image8.png" alt="Structure" /> 2c-N</td>
<td><img src="image9.png" alt="Structure" /> 2c-X</td>
</tr>
<tr>
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<td><img src="image10.png" alt="Structure" /></td>
<td>24</td>
<td>17 (75) (14:86)</td>
<td><img src="image11.png" alt="Structure" /> 2d-N</td>
<td><img src="image12.png" alt="Structure" /> 2d-X</td>
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<tr>
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<td><img src="image13.png" alt="Structure" /></td>
<td>72</td>
<td>26 (68) (10:90)</td>
<td><img src="image14.png" alt="Structure" /> 2e-N</td>
<td><img src="image15.png" alt="Structure" /> 2e-X</td>
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<td>6</td>
<td><img src="image16.png" alt="Structure" /></td>
<td>72</td>
<td>32 (92) (17:83)</td>
<td><img src="image17.png" alt="Structure" /> 2f-N</td>
<td><img src="image18.png" alt="Structure" /> 2f-X</td>
</tr>
<tr>
<td>7</td>
<td><img src="image19.png" alt="Structure" /></td>
<td>72</td>
<td>20 (70) (36:64)</td>
<td><img src="image20.png" alt="Structure" /> 2g-N</td>
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<tr>
<td>8</td>
<td><img src="image22.png" alt="Structure" /></td>
<td>12</td>
<td>83 (6:94)</td>
<td><img src="image23.png" alt="Structure" /> 2h-N</td>
<td><img src="image24.png" alt="Structure" /> 2h-X</td>
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<tr>
<td>9</td>
<td><img src="image25.png" alt="Structure" /></td>
<td>24</td>
<td>15 (24) (9:91)</td>
<td><img src="image26.png" alt="Structure" /> 2i-N</td>
<td><img src="image27.png" alt="Structure" /> 2i-X</td>
</tr>
<tr>
<td>10</td>
<td><img src="image28.png" alt="Structure" /></td>
<td>12</td>
<td>Traces&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image29.png" alt="Structure" /> 2j-N</td>
<td><img src="image30.png" alt="Structure" /> 2j-X</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields based on recovered starting materials (BRSM) in parenthesis. <sup>b</sup>Relative to the pinacol boronate moiety, determined by $^1H$ NMR. <sup>c</sup>The starting material was recovered.
150 °C. For the reaction of 1a, we determined that best yields of the cycloadducts were obtained in 5 h at 80 °C with 5 mol % of TFA (Entry 1, 88%, endo/exo 36:64). When we run the reaction in the absence of TFA, a 20% yield was generated, with the same endo/exo ratio. Use of a pressure tube, though not necessary in toluene at 80 °C, was preferred to avoid evaporation of the small loading of the catalyst (Bp 72.4 °C). Quite unexpectedly, under catalyzed conditions only 1-phenylvinylboronic acid pinacol ester (1h) performed well (Entry 8, 83%, endo/exo 6:94). The other dienophiles gave yields below 45%. However, it is interesting to note that in this case aromatic alkenylboronates afforded better yields than the aliphatic compounds. Also, considerably higher exo-selectivities than for the uncatalyzed reactions were observed. Possibly, the acid catalyst interacts with the π electrons of the aromatic ring and therefore withdraws electron density from the conjugated unsaturated system leading to the activation of the double bond. Within the aliphatic alkenylboronates, 1d, having a possible site for protonation (oxygen atom) gave better results than 1b and 1c.

We were surprised to note that the background reaction of dienophile 1h afforded a very high yield of the corresponding boronate cycloadduct (91%) with excellent exo-selectivity (endo/exo 5:95) (Scheme 2). Under the same conditions, vinylboronic acid pinacol ester (1a) gave a lower yield (45%), which was a bit unexpected since previous experiments at higher temperatures suggested that the parent compound was more reactive than 1h (Table 2).

We tested whether we could perform the catalyzed reaction of alkenylboronate 1h at room temperature using the same amount of diene, catalyst, and BHT, but we only obtained a 17% yield with a 3:97 endo/exo ratio (96% BRSM) after 12 h. Since, as commented above, prolonged exposure to the reaction conditions did not increase the yields of the products we figured that thermodynamic equilibria had been reached. Also, dienophile 1b gave a 25% (91% BRSM) in 1 h at 170 °C (Entry 8, Table 2), while the yield was much better after 12 h at 80 °C (91%, Scheme 2), so we suspected that under the initial thermal conditions the energy barrier of the Diels-Alder reaction has been surpassed and that some retro Diels-Alder might have taken place. For that reason, we submitted cycloadduct 2g (endo/exo 10:90) to the conditions of the uncatalyzed thermal reaction (Scheme 3). Indeed, the retro Diels-Alder reaction occurred, giving 76% of alkenylboronate 1g and 15% of recovered cycloadduct 2g (a mixture with a very similar composition to the one obtained when submitting the direct reaction).

Finally, we studied the tandem Diels-Alder reaction of alkenylboronates with cyclopentadiene-oxidation (Table 4).

**Table 4** Tandem Diels-Alder reaction of alkenylboronates with cyclopentadiene-oxidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Overall yield (%) endo/exo</th>
<th>Products DA + [O]</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>1a</td>
<td>93° 39:61</td>
<td>3a-N, 3a-X</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>79° 15.85</td>
<td>3b-N, 3b-X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3

3c-N 3c-X

4

3d-N 3d-X

5

3e-N 3e-X

6

3f-N 3f-X

7

3g-N 3g-X

8

3h-N 3h-X

9

3i-N 3i-X

*Determined by NMR integration. *Non TFA-catalyzed thermal conditions were used. *TFA-catalyzed conditions were used. *Conditions shown in Scheme 2 were used.

Except for the compounds with aryl groups at the 2-position (Entries 5–7), we coupled the non-catalyzed thermal conditions shown in Table 2 for the cycloaddition step with the final oxidation with alkaline hydrogen peroxide in one-pot. Overall yields for the two-step sequence were very similar to the ones obtained in the Diels-Alder reactions, which suggests that in situ transformation of the boronate cycloadducts to the corresponding alcohols occurs very efficiently. In general, the substituted 5-norbornen-2-ols were obtained with acceptable to very good yields, which demonstrated that alkenylboronic esters can be used as synthetic equivalents of substituted enols. Due to their high functionalization, the alcohol products can be foreseen as valuable synthetic intermediates towards a variety of chemical structures. We anticipate that other transformations of the cycloadduct intermediates could be developed for further elaboration of C-C, C-O and C-N bonds.

28 **Computational study**

To gain a deeper insight into the mechanism of the Diels-Alder reactions of the dienophiles under study we performed a theoretical study. In particular, we intended to examine the reversibility of such processes and whether the starting material/products distribution was determined by thermodynamic or kinetic control. Therefore, we optimized the geometries in toluene of the reactants, the transition structures and the products to compute the activation and reaction energies at 170 °C. In addition, we analyzed the geometries and the properties of the dienophiles and the transition structures with the aim of rationalizing the reactivity and selectivity trends.

**Computational methods.** All calculations were performed with the Gaussian 09 package. We carried out thorough conformational analyses to locate the lowest energy geometry for all the structures under study. Final geometry optimizations were carried out using MPWB1K global-hybrid meta-GGA functional together with 6-311G* basis. Solvent effects of toluene were taken into account through full optimizations using the polarizable continuum model (PCM) as developed by Tomasi’s group in the framework of self-consistent reaction field (SCRF). The vibrational frequencies were calculated to determine the nature of the stationary points and to evaluate zero-
point vibrational energy (ZPVE) and thermal corrections at 443 K (170 °C). The frontier molecular orbitals (FMOs) were computed with the same method. Intrinsic Reaction Coordinate (IRC) calculations were run to verify if the transition structures were directly connected to the reactants and the products.

Fig. 1 shows the free energy profiles for the Diels-Alder reactions of selected dienophiles with cyclopentadiene as a means to compare the reaction channels (for all the energy profiles see the ESI). Also, the optimized geometries for the corresponding transition structures with selected distances and Wiberg bond indexes are shown. Table 5 gathers the computed free energies of activation, reaction free energies and endo/exo selectivities at 170 °C in toluene for all the Diels-Alder reactions under study. All transition structures exhibit classical [4+2] geometries and are asynchronic. However, the ones corresponding to the dienophiles with aromatic substituents in CY1 (1e and 1j) are extremely asynchronic, with asynchronicities as high as 0.66 Å. Nonetheless, IRC calculations connected the transition structures with the reactants and the products, therefore all reactions were computed to be concerted.

Analysis of FMOs indicates that the reactions under study are normal electron-demand Diels-Alder reactions. From the atomic coefficients for the LUMOs of the dienophiles, it appears that the computed reversal of asynchronicity is caused by electronic effects since compounds 1e-1g have larger coefficients at CY1 than at C-2, in contrast to the rest of the dienophiles. However, we do not discard the contribution of steric effects. In addition, the transition structures of alkenylboronates with aromatic substituents in C-1 (1h and 1j) are extremely asynchronic, with asynchronicities as high as 0.66 Å. Nonetheless, IRC calculations connected the transition structures with the reactants and the products, therefore all reactions were computed to be concerted. In this case, comparison of the atomic coefficients corresponding to the LUMOs of the dienophiles suggests that the higher asynchronicity is determined by steric effects rather than electronic effects. The non-classical [4+3] carbon-boron interactions are weak (C-B distances 2.70-3.15 Å, WBI 0.04-0.02) and very similar for the endo and exo approaches. Consequently, the observed moderate to high exo-selectivities seems to be a consequence of unfavorable van der Waals interactions in the endo transition structures. Also, the short distance (ca. 2.4 Å) between one of the methylene hydrogens of the cyclopentadiene moiety and one of the oxygens of the pinacol boronate in the exo transition structures suggests...
the possibility that hydrogen bond interactions contribute to

<table>
<thead>
<tr>
<th>Dienophile</th>
<th>TS</th>
<th>$\Delta G^a_{TS}$</th>
<th>endo/exo</th>
<th>$\Delta G_{end}$</th>
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<tr>
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<td>endo</td>
<td>36.04</td>
<td>68:32</td>
<td>-5.62</td>
<td>37:63</td>
</tr>
<tr>
<td>1b</td>
<td>endo</td>
<td>36.71</td>
<td>18:82</td>
<td>-0.28</td>
<td>34:66</td>
</tr>
<tr>
<td>1c</td>
<td>endo</td>
<td>40.36</td>
<td>17:83</td>
<td>-1.09</td>
<td>61:39</td>
</tr>
<tr>
<td>1d</td>
<td>endo</td>
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<td>endo</td>
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<td>endo</td>
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<td>endo</td>
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<td>1.47</td>
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*Energies in kcal/mol.

Table 5 MPWB1K/6-311G* free energies of activation, reaction energies and endo/exo selectivities at 170 °C in toluene for the Diels-Alder reactions of pinacol alkynylboronates 1a-1j with cyclopentadiene.

Conclusions

We have investigated the Diels-Alder reactions of pinacol alkynylboronates with cyclopentadiene. The outcome of the studied transformation was shown to be very sensitive to the substitution of the dienophile both under thermal and TFA-catalyzed conditions. Theoretical calculations disclosed some interesting substituent effects for these [4+2] cycloadditions. We have found that the thermal Diels-Alder reactions of alkynylboronates with aryl groups in the 2-position give low yields because they are highly reversible. The high reactivity of 1-phenylvinylboronic acid pinacol ester (1h) was explained in terms of a stabilizing non-classical hydrogen bond between an aromatic proton and the boronate moiety. We have also synthesized a range of substituted 5-norbornen-2-ols in one-pot by performing the tandem Diels-Alder reactions - alkaline hydrogen peroxide oxidation, demonstrating the versatility of alkynylboronic esters as synthetic equivalents of substituted enols.

Experimental section

General experimental procedures. All reagents and solvents were used directly as purchased or purified according to standard procedures. Analytical thin layer chromatography was carried out using commercial silica gel plates (Merck, Silica Gel 60 F254) and visualization was effected with short wavelength UV light (254 nm) and a p-anisaldehyde solution (2.5 mL of p-anisaldehyde + 2.5 mL of H2SO4 + 0.25 mL of AcOH + 95 mL of EtOH). Column chromatography was performed with silica gel 60 H (Merck), slurry packed, run under low pressure of nitrogen. The Diels-Alder reactions were monitored using TLC and 11B NMR analysis in CDCl3. NMR spectra were recorded at 300 MHz for 1H, 75 MHz for 13C, 96 MHz for 11B and 282 MHz for 19F NMR on a Bruker Avance-300 DPX spectrometer with CDCl3 as solvent and (CH3)2Si(11B) and CDCl3 (13C, 76.9 ppm) as internal standards. 1B and 1F NMR spectra were externally
referred to BF$_3$·Et$_2$O and CFCl$_3$, respectively. Chemical shifts are reported in delta (δ) units in parts per million (ppm) and splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. Coupling constants are recorded in Hertz (Hz). Isomeric ratios were determined by 1H NMR integration. Infrared spectra were recorded on a Shimadzu IR Prestige-21 spectrometer using sodium chloride plates or potassium bromide pellets. Absorbance frequencies are recorded in reciprocal centimeters (cm$^{-1}$). The high resolution mass spectra (HRMS) were obtained with a Bruker MicroTOF-Q II instrument (Bruker Daltonics, Billerica, MA). Detection of the ions was performed with electrospray ionization (ESI), positive ion mode and Atmospheric Pressure Chemical Ionization (APCI). The structure of the products were determined by a combination of spectroscopic methods such as IR, 1D and 2D NMR (including 2-DEPT, COSY, HSQC and HMBC experiments) and HRMS. In some cases, NMR calculations were also performed to corroborate the stereochemistry and the assignment. In addition, we confirmed the structure of the Diels-Alder products by oxidation of the boronates to the alcohols, some of which were described in the literature.

Diels-Alder reactions of alkenylboronates: synthesis of boronates 2a-2i

**General procedure A:** To a pressure tube equipped with a stirring bar were added dry toluene (1.5 mL), vinylboronate 1 (typically 0.25 mmol), 2,6-di-tert-butyl-4-methylphenol (BHT, 5 mol %) and cyclopentadiene (0.75 mmol) under nitrogen atmosphere. The resulting reaction mixture was stirred at 170 ºC for the reported time (5-72 h). The solvent was removed under reduced pressure, and the crude was purified by column chromatography (hexane/AcOEt) to afford the corresponding boronate.

**General procedure B:** To a pressure tube equipped with a stirring bar were added dry toluene (1.5 mL), vinylboronate 1 (typically 0.28 mmol), 2,6-di-tert-butyl-4-methylphenol (BHT, 5 mol %), cyclopentadiene (0.84 mmol) and trifluoroacetic acid (TFA, 5 mol %) under nitrogen atmosphere. The resulting reaction mixture was stirred at 80 ºC for the reported time (5-72 h). The solvent was removed under reduced pressure, and the crude was purified by column chromatography (hexane/AcOEt) to afford the corresponding boronate.

2-Bicyclo[2.2.1]hept-5-en-2-yl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2a). 13B Boronate 2a was obtained as a mixture of diastereomers according to the general procedure A and B using vinylboronate 1a (0.28 mmol) and cyclopentadiene (0.84 mmol). A small fraction of each diastereomer could be separated and characterized.

**Procedure A:** Reaction time: 1 h. Yield: 96% (59.1 mg), endo/exo 36:65.

**Procedure B:** Reaction time: 5 h. Yield: 88% (54.2 mg), endo/exo 36:64.

4,4,5,5-Tetramethyl-2-(3-propyl-bicyclo[2.2.1]hept-5-en-2-yl)-[1,3,2]dioxaborolane (2b). Boronate 2b was obtained as a mixture of diastereomers according to the general procedure A, using allylboronate 1b (0.22 mmol) and cyclopentadiene (0.66 mmol). A small fraction of the endo diastereomer could be separated and characterized. Reaction time: 24 h. Yield: 78% (45.0 mg), endo/exo 17:83.

**Boronate 2b-N** (major compound, yellowish oil) IR (film) $v_{max}$ 2956, 2926, 2870, 2359, 2344, 1371, 1312, 1146, 978, 859, 698 cm$^{-1}$. 1H NMR (300 MHz, CDCl$_3$) δ 6.17 (dd, $J_{5,6} = 5.6$, $J_{6,7} = 2.9$ Hz, 1H, H-6), 5.87 (dd, $J_{5,6} = 5.6$, $J_{5,7} = 2.9$ Hz, 1H, H-5), 2.77 (br s, 1H, H-4), 2.74 (br s, 1H, H-1), 2.15-0.24 (m, 1H, H-3), 1.36-1.26 (m, 4H, H-7 and H-11), 1.24 (br s, 12H, H-9), 1.10-0.92 (m, 2H, H-10), 0.85 (t, $J_{1,12} = 7.3$ Hz, 3H, H-12), 0.36 (dd, $J_{3,5} = 5.3$, $J_{5,6} = 1.6$ Hz, 1H, H-2). 13C NMR (75 MHz, CDCl$_3$) δ 138.3 (CH, C-6X), 137.2 (CH, C-5X), 131.5 (CH, C-6N), 131.5 (CH, C-5N), 82.7 (2C, C-8N), 82.2 (2C, C-8X), 48.5 (CH$_2$, C-7X), 47.2 (CH$_2$, C-7N), 47.1 (CH, C-4N), 46.1 (CH, C-4X), 45.0 (CH, C-1X), 44.7 (CH, C-1N), 42.2 (CH, C-3X), 42.0 (CH, C-3N), 39.6 (CH$_2$, C-10N), 37.6 (CH$_2$, C-10X), 24.8 (2CH$_2$, C-9N), 24.7 (2CH$_2$, C-9X), 24.6 (2CH$_2$, C-9N), 21.9 (CH$_2$, C-11N), 21.8 (CH$_2$, C-11X), 14.4 (2CH$_3$, C-12X and C-12N), 2- signals missing. 1B NMR (96 MHz, CDCl$_3$) δ 34.1.

HRMS (APCI) calcd for C$_{16}$H$_{20}$O$_2$B$_3$ Na$^+$ (M+Na$^+$) 263.2177, found 263.2178.

2-[3-(3-Chloro-propyl)-bicyclo[2.2.1]hept-5-en-2-yl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (2c). Boronate 2c was obtained as a mixture of diastereomers according to the general procedure A, using allylboronate 1c (0.21 mmol) and cyclopentadiene (0.65 mmol). A small fraction of exo diastereomer could be separated and characterized. Reaction time: 24 h. Yield: 89% (55.5 mg), endo/exo 20:80.

**Boronate 2c-X** (major compound, yellowish oil) IR (film) $v_{max}$ 2965, 2926, 2358, 2354, 2317, 1314, 1144, 852, 669, 430, 411 cm$^{-1}$. 1H NMR (300 MHz, CDCl$_3$) δ 6.02 (dd, $J_{5,6} = 5.3$, $J_{5,7} = 3.2$ Hz, 1H, H-6), 5.88 (dd, $J_{5,6} = 5.3$, $J_{6,7} = 2.9$ Hz, 1H, H-5), 3.51 (t, $J_{1,12} = 6.9$ Hz, 2H, H-12), 2.78 (br s, 2H, H-1 and H-4), 2.14-2.04 (m, 1H, H-3), 1.75 (quintet, $J_{10,11} = 1.2$ Hz, 7.2 Hz, 2H, H-11), 1.34-1.27 (m, 2H, H-10), 1.24 (s, 12H, H-9), 1.16-1.02 (m, 2H, H-10), 0.18 (br d, $J_{2,3} = 3.2$ Hz, 1H, H-2). 13C NMR (75 MHz, CDCl$_3$) δ 138.6 (CH, C-6), 131.2 (CH, C-5), 83.8 (2C, C-8), 48.6 (CH$_2$, C-7), 46.2 (CH, C-1), 45.3 (CH$_2$, C-12), 45.0 (CH, C-3), 41.6 (CH, C-3), 32.5 (CH$_2$, C-3), 31.8 (CH, C-11), 24.7 (4CH$_2$, C-9), 2.8 (4CH$_2$, C-9N), 2.8 (C, C-12), 2- signals missing. 1B NMR (96 MHz, CDCl$_3$) δ 33.8.

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b) Procedure B: Reaction time: 72 h. Yield: 26% (15.1 mg), endo/exo 35:65.

b) Procedure B: Reaction time: 24 h. Yield: 32% (19 mg), endo/exo 17:83. Reaction time: 72 h. Yield: 38% (22.5 mg), endo/exo 17:83.

Boronates 2e-X and 2e-N (yellowish oil) IR (film) $\nu_{\text{max}}$ 2957, 2928, 2820, 1458, 1404, 1371, 1146, 853, 679 cm$^{-1}$. 1H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35-7.08 (m, 10H, ArH-X and ArH-N), 5.98 (1H, ArH-X), 5.98 (1H, ArH-N), 5.80 (3H, ArH-N, 3.12 (br s, 1H, ArH-X), 3.14 (br s, 1H, ArH-N), 2.93 (br s, 1H, ArH-X), 2.84 (t, $J_{\text{HH}} = 9.5$ Hz, 1H, ArH-N), 2.70 (br s, 1H, ArH-N), 1.24 (br s, 2H, ArH-X), 1.33 (br s, 2H, ArH-X), 1.23 (s, 12H, ArH-N), 0.88 (br d, $J_{\text{HH}} = 5.9$ Hz, 1H, ArH-N).

13C NMR (75 MHz, CDCl$_3$) $\delta$ 146.7 (C, ArYN), 145.1 (C, ArX), 138.6 (CH, C-6X), 137.6 (CH, C-5N), 136.5 (CH, C-6N), 132.1 (CH, C-5X), 128.2 (2CH, Ar-N), 128.1 (2CH, Ar-X), 127.7 (2CH, Ar-X), 127.5 (2CH, Ar-N), 125.5 (2CH, Ar-X), 125.3 (CH, Ar-N), 83.2 (2C, C-8X), 83.1 (2C, C-8N), 49.0 (CH$_2$-C-7X), 48.9 (CH$_2$-C-4X), 48.0 (CH$_2$-C-7N), 47.9 (CH, C-4N), 46.5 (CH, C-3X and C-3N), 45.9 (CH, C-1X), 45.2 (CH, C-1N), 24.9 (CH$_2$-C-9N), 24.8 (CH$_2$-C-9X), 24.7 (2CH$_2$, C-9X), 24.6 (2CH$_2$, C-9N), C-2 signals missing. 13B NMR (96 MHz, CDCl$_3$) $\delta$ 34.0. HRMS (APCI) calculated for C$_{13}$H$_{23}$B$_2$O$_3$ (M$^+$) 265.1970, found 265.1967.

Boronates 2d-X and 2d-N (yellowish oil) IR (film) $\nu_{\text{max}}$ 3055, 2979, 2927, 2889, 2688, 1403, 1399, 1145, 852, 722 cm$^{-1}$. 1H NMR (300 MHz, CDCl$_3$) $\delta$ 6.18 (dd, $J_{\text{HH}} = 5.6$, $J_{\text{HH}} = 5.6$). 3.0 Hz, 1H, H-6X, 6.10 (dd, $J_{\text{HH}} = 5.6$, $J_{\text{HH}} = 3.1$ Hz, 1H, H-5N, 5.98 (dd, $J_{\text{HH}} = 5.5$, $J_{\text{HH}} = 2.8$ Hz, 1H, H-6N, 5.96 (dd, $J_{\text{HH}} = 5.6$, $J_{\text{HH}} = 5.6$).

3.0 Hz, 1H, H-5X, 3.49 (dd, $J_{\text{HH}} = 9.4$, $J_{\text{HH}} = 5.4$ Hz, 1H, H-10N), 3.34 (3H, 3H, H-11N), 3.29 (3H, 3H, H-11X), 3.22 (2$, J_{\text{HH}} = 9.5$ Hz, 1H, H-10N), 3.14 (dd, $J_{\text{HH}} = 9.5$, $J_{\text{HH}} = 5.7$ Hz, 1H, H-10X), 2.93 (br s, 2H, H-4X and H-4N), 2.84 (t, $J_{\text{HH}} = 9.5$ Hz, 1H, H-10X), 2.79 (br s, 1H, H-1X), 2.75 (br s, 1H, H-4N), 2.42 (m, 1H, H-3X), 1.81 (dt, $J_{\text{HH}} = 9.4$, $J_{\text{HH}} = 5.4$ Hz, 1H, H-10N), 1.33 (br s, 4H, H-7X and H-7N), 1.23 (s, 12H, H-9X), 1.17 (s, 12H, H-9N), 0.78 (dd, $J_{\text{HH}} = 5.2$, $J_{\text{HH}} = 3.3$ Hz, 1H, H-1N), 0.08 (br d, $J_{\text{HH}} = 5.9$ Hz, 1H, H-2X).

13C NMR (75 MHz, CDCl$_3$) $\delta$ 138.4 (CH, C-5N), 136.9 (CH, C-6X), 136.6 (CH, C-5N), 135.9 (CH, C-6N), 131.5 (CH, C-5X), 83.0 (2C, C-8X), 82.9 (2C, C-8N), 77.5 (CH$_2$-C-10N), 76.5 (CH$_2$-C-10X), 58.6 (CH$_2$-C-11X and C-11N), 48.4 (CH$_2$-C-7X), 46.7 (CH$_2$-C-7N), 44.4 (CH, C-1X), 44.2 (2CH, C-4X), 44.1 (CH, C-4N), 44.0 (CH, C-1N), 42.3 (CH, C-3N), 41.9 (CH, C-3X), 24.7 (2CH$_2$, C-9X), 24.6 (4CH$_2$, C-9N), C-2 signals missing. 13B NMR (96 MHz, CDCl$_3$) $\delta$ 33.8.

4,4,5,5-Tetramethyl-2-(3-phenylbicyclo[2.2.1]hept-5-en-2-yl)-[1,3,2]-dioxaborolane (2e). Boronate 2e was obtained as a mixture of diastereomers according to the general procedures A and B, using alkynylboronate 1e (0.20 mmol) and cyclopentadiene (0.60 mmol).
(This page contains a section of a chemical research paper discussing the preparation and characterization of boronate derivatives, including specific procedures, reaction conditions, and analytical data. The text is structured and formatted as a typical scientific document, with chemical formulas, reaction equations, and experimental procedures described in detail. The discussion includes the preparation of boronates under different conditions, their reaction conditions, yields, and characterization methods such as NMR spectroscopy and mass spectrometry. The text provides a comprehensive overview of the experimental results and conclusions drawn from the study.)
General procedure C: To a pressure tube equipped with a stirring bar were added dry toluene (1.5 mL), vinylboronate 1 (typically 0.27 mmol), cyclopentadiene (0.81 mmol) and BHT (5 mol%) under nitrogen atmosphere. Trifluoroacetic acid (5 mol%) was also added to the reactions of alkylboronates 1e, 1f and 1g. The resulting reaction mixture was stirred at the reported temperature (170/80 °C) for the reported time (5-72 h), then diluted with THF (3 mL) and transferred to a 25 mL round-bottom flask. After the addition of Et3N (1 mL) the solution was cooled to 0 °C, treated alternately with 3N NaOH (5 mL) and to warm to room temperature and stirred overnight. The reaction mixture was diluted with water (10 mL) and extracted with Et2O (3 x 15 mL). The combined organic layers were washed with NH4Cl (15 mL) and brine (15 mL) and dried over anhydrous Na2SO4. The solvent was removed under reduced pressure at 0 °C, and the crude was purified by column chromatography (pentane/Et2O for alcohols 3a and 3i and hexane/AcOEt for alcohols 3b-3h) to afford the corresponding alcohols (3a-i).

Bicyclo[2.2.1]hept-5-en-2-ol (3a). Alcohol 3a was obtained as a mixture of diastereomers according to the general procedure C, using vinylboronate 1a (0.28 mmol) and cyclopentadiene (0.84 mmol). Diels-Alder reaction step conditions: 1 h at 170 °C. Overall yield: 93% (28.6 mg), endo/exo 39:61.

3-Propyl-bicyclo[2.2.1]hept-5-en-2-ol (3b). Alcohol 3b was obtained as a mixture of diastereomers according to the general procedure C, using alkylboronate 1b (0.22 mmol) and cyclopentadiene (0.66 mmol). Diels-Alder reaction step conditions: 24 h at 170 °C. Overall yield: 79% (26.1 mg), endo/exo 15:85.

Alcohols 3c-X and 3c-N (yellowish oil) IR (film) νmax 3404, 2957, 2922, 2851, 2358, 1717, 1024, 849, 667 cm⁻¹. H NMR (300 MHz, CDCl3) δ 6.48 (dd, J3,8 = 5.7, J5,6 = 3.1 Hz, 1H, H-5N), 6.11 (dd, J3,8 = 5.7, J5,6 = 3.1 Hz, 1H, H-6X), 6.09 (m, 1H, H-6N), 6.02 (dd, J5,6 = 5.7, J3,8 = 3.1 Hz, 1H, H-6X), 3.91 (br s, 1H, H-2N), 3.33 (br s, 1H, H-2X), 2.89 (br s, 1H, H-1N). 1H NMR (300 MHz, CDCl3) δ 141.1 (CH, C-5N), 137.0 (CH, C-5X), 134.2 (CH, C-6X), 131.8 (CH, C-6N), 79.6 (CH, C-2N), 78.8 (CH, C-2X), 51.0 (CH, C-4X), 50.2 (CH, C-3N), 49.8 (CH, C-3X), 48.3 (CH, C-1N), 47.4 (CH, C-4N), 46.6 (CH, C-7X), 45.2 (CH2, C-7N), 45.1 (CH2, C-10X and C-10N), 44.5 (CH, C-1), 31.8 (CH, C-8N), 31.5 (2CH2, C-9X and C-9N), 30.7 (CH2, C-8X), 1.75 (br s, 1H, OH), 1.66 (dd, J7a,7b = 8.5, J7a,7b = 1.6 Hz, 1H, H-7X). 13C NMR (75 MHz, CDCl3) δ 137.1 (CH, C-5), 134.4 (CH, C-6), 76.2 (CH, C-2), 75.8 (CH2, C-8), 58.8 (CH2, C-9), 50.7 (CH, C-3), 50.5 (CH, C-1), 46.7 (CH2, C-7), 43.1 (CH, C-4). HRMS (APCI) calcd for C16H18ClO (M+H+) 269.1275, found 269.1273.

3-Chloro-propyl-bicyclo[2.2.1]hept-5-en-2-ol (3c). Alcohol 3c was obtained as a mixture of diastereomers according to the general procedure C, using alkylboronate 1c (0.21 mmol) and cyclopentadiene (0.63 mmol). A small fraction of exo diastereomer could be separated and characterized. Diels-Alder reaction step conditions: 24 h at 170 °C. Overall yield: 82% (32.1 mg), endo/exo 14:86.

Alcohols 3d-X and 3d-N (yellowish oil) IR (film) νmax 3415, 3059, 2972, 2872, 2850, 1109, 1033, 717 cm⁻¹. H NMR (300 MHz, CDCl3) δ 6.11 (dd, J5,6 = 5.7, J3,8 = 2.7 Hz, 1H, H-5), 3.43 (br s, 1H, H-2), 3.33 (s, 3H, H-9), 3.22 (dd, Jgem = 14.4, J5,6 = 8.0 Hz, 1H, H-8), 3.19 (dd, Jgem = 14.4, J5,6 = 7.9 Hz, 1H, H-8), 2.78 (br s, 1H, H-1), 2.19 (br s, 1H, H-1), 1.90 (m, 1H, H-3), 1.85 (br d, J3,8 = 8.5 Hz, 1H, H-7b), 1.75 (br s, 1H, OH), 1.66 (dd, J7a,7b = 8.5, J7a,7b = 1.6 Hz, 1H, H-7a). 13C NMR (75 MHz, CDCl3) δ 137.1 (CH, C-5), 134.4 (CH, C-6), 76.2 (CH, C-2), 75.8 (CH2, C-8), 58.8 (CH2, C-9), 50.7 (CH, C-3), 50.5 (CH, C-1), 46.7 (CH2, C-7), 43.1 (CH, C-4).
58.8 (C, C-9X), 50.8 (CH, C-3N), 50.7 (CH, C-3X), 50.5 (CH, C-1X), 48.0 (CH, C-1N), 46.7 (CH₃, C-7X), 45.2 (CH₂, C-7N), 44.9 (CH, C-4N), 43.1 (CH, C-4X). HRMS (APCI) caiied for C₉₀H₁₃O₂ (M+H+H₂O⁺) ± 137.0961, found 137.0938.

3-Phenylbicyclo[2.2.1]hept-5-en-2-ol (3e). Alcohol 3e was obtained as a mixture of diastereomers according to the general procedure C, using alkenylboronate 1e (0.20 mmol) and cyclopentadiene (0.60 mmol). Diels-Alder reaction step conditions: TFA (5 mol %), 72 h at 80 °C. Overall yield: 37% (0.17 mmol).

3-(4-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-ol (3f) and 3-(4-Chlorophenyl)bicyclo[2.2.1]hept-5-en-2-ol (3g). Alcohol 3f was obtained as a mixture of diastereomers according to the general procedure C using alkenylboronate 1h (0.17 mmol) and cyclopentadiene (0.51 mmol). A small fraction of endo diastereomer could be separated and characterized. Diels-Alder reaction step conditions: 12 h at 80 °C. Overall yield: 100% (28.8 mg), endo/exo 6:94.

Alcohol 3h was obtained as a mixture of diastereomers according to the general procedure C using alkenylboronate 1i (0.17 mmol) and cyclopentadiene (0.51 mmol). Alcohols 3i-X and 3i-N were obtained as a mixture of diastereomers according to the general procedure C using alkenylboronate 1j (0.17 mmol) and cyclopentadiene (0.51 mmol). The yields and diastereomeric ratios are reported as follows:

- **Alcohol 3i**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3j**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3k**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3l**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3m**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3n**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3o**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3p**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3q**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3r**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
- **Alcohol 3s**: Overall yield: 100% (28.8 mg), endo/exo 6:94.
2-Methyl-bicyclo[2.2.1]hept-5-en-2-ol (3). 55–48 Alcohol 3i was obtained as a mixture of diastereomers according to the general procedure C using alkylboronate 1i (0.5 mmol) and cyclopentadiene (1.5 mmol). Diels-Alder reaction step conditions: 24 h at 170 °C. Overall yield: 66% (40.9 mg). 

**Notes and references**


