A facile microwave-assisted Diels–Alder reaction of vinylboronates†

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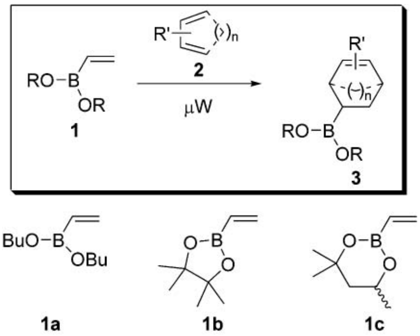
The Diels–Alder reaction of vinylboronates can be easily performed using microwave irradiation giving excellent yields of the cycloadducts. Pinacol vinylboronate was the reagent of choice due to its stability towards hydrolysis, operational simplicity and yields of Diels–Alder products. To the best of our knowledge, this is the first example of microwave-assisted Diels–Alder reaction of boron-substituted dienophiles. Subsequent *in situ* oxidation of the cycloadducts with alkaline hydrogen peroxide afforded the alcohols efficiently.

Introduction

Due to their great versatility, boron-substituted dienophiles have emerged as attractive building blocks in organic synthesis.[1,2] Unsaturated boronates exhibit poor reactivity in Diels–Alder (DA) reactions, which require temperatures as high as 200 °C and prolonged reaction times. However, unlike dialkylboranes, boronates are stable to air and moisture and can be purified by chromatography. As a result, the Diels–Alder products can be isolated, offering an interesting alternative for further elaboration of C–C, C–O and C–N bonds. Although alkynylboronates have been recently used in a number of [4+2] cycloadditions,[3] examples on the use of alkenylboronates as dienophiles are scarce.[4] In the past years, many papers on microwave-assisted reactions of boronic esters appeared in the literature.[1,5] However, this seems to be limited to cross-coupling reactions mostly. To the best of our knowledge, the possibility of using microwave irradiation to facilitate cycloadditions of boron-functionalized compounds remained unexplored. Herein we report that the Diels–Alder reaction of vinylboronates can be easily performed using microwave irradiation.

Results and discussion

We first studied the microwave-assisted reactions of commercial vinylboronates derived from n-butanol (**1a**), pinacol (**1b**) and 2-methyl-2,4-pentanediol (**1c**)[4c,6] with cyclopentadiene (**2a**) and 1,3-cyclohexadiene (**2b**), some of which have been previously carried out with conventional heating (Scheme 1).[4a–d] We were pleased to note that the reactions could be completed in short reaction times with excellent yields (Table 1, entries 1–7). Best product yields were obtained using the pinacol derivative **1b**. Also, vinylboronate **1b** and its derived products offered greater stability towards hydrolysis than **1a** and operational simplicity than **1c**, which affords complex diastereomeric mixtures due the presence of a stereogenic center. We also observed that *endo*/*exo* stereoselectivities for all dienophiles were comparable and similar to those reported for the thermal reactions. For pinacol vinylboronate (**1b**), we were able to reduce the number of equivalents of diene to three (entries 3 and 7).



Scheme 1 Microwave-assisted Diels–Alder reaction of vinylboronates.

In light of these encouraging results, we next performed the microwave-assisted Diels–Alder reactions with a series of structurally diverse dienes (**2c**–**2i**) (entries 8–14). All reactions were complete within a few hours and proceeded in good to excellent yields.[7] The tolerance of the boronic ester functionality in **1b** to the reaction temperatures is remarkable. The observed reactivity trend for the dienes was consistent with literature reports of Diels–Alder reactions with other electron-poor dienophiles such as tetracyanoethylene or maleic anhydride.[8] Inspection of the results in Table 1 also reveals that *endo*/*exo* stereoselectivities and regioselectivities varied depending on the nature of the diene.[9] Most reactions showed moderate to good *exo* selectivities (up to *endo*/*exo* 12 : 88 for **2i**, entry 14). Only the reactions with 1,3-cyclohexadiene (**2b**) showed a significant preference for the formation of the *endo* adduct (*endo*/*exo* 75 : 25, entries 6–7). In addition, for 2-substituted dienes such as isoprene (**2c**) and myrcene (**2d**) the *para* products were slightly favored (entries 8 and 9). 1-Substituted dienes showed different levels of regioselectivity: while 1-methoxy-1,3-cyclohexadiene (**2h**) showed high *ortho* selectivity (*ortho*/*meta* >80 : 20, entry 13), *trans*-pyperylene (**2e**) gave similar quantities of the *ortho* and *meta* products (entry 10).

Preliminary theoretical calculations suggest that the reactions under study are normal electron-demand Diels–Alder reactions. The low reactivity of vinylboronates appears to be related to the donating effect of the oxygens on the boron atom, which increases the energy of the LUMO. To rationalize the experimental reactivities and selectivities more calculations are currently underway,

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Table 1 Microwave-assisted Diels–Alder reaction of vinylboronates

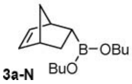
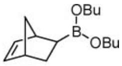
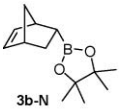
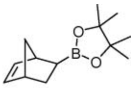
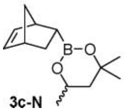
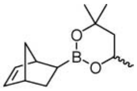
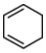
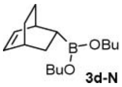
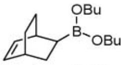
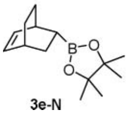
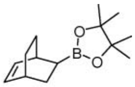
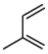
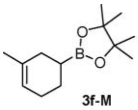
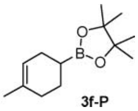
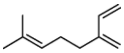
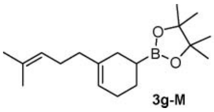
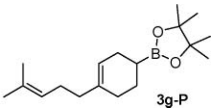
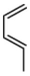
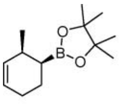
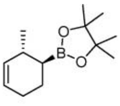
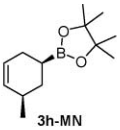
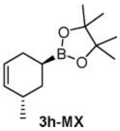
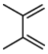
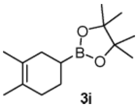
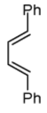
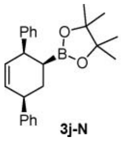
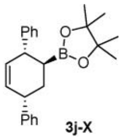
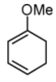
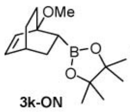
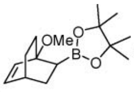
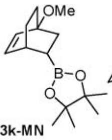
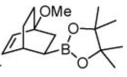
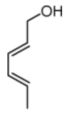
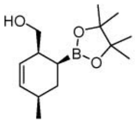
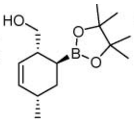
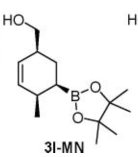
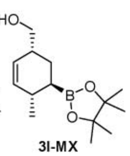
Entry	Vinylboronate	Diene	Conditions[a,b]	Yield[c] ratios[d]	Products
1	**1a**	 **2a**	10 equiv. diene dichloromethane 60 min, 150 °C	Not determined[e]	 **3a-N**  **3a-X**
2	**1b**		10 equiv. diene 60 min, 150 °C (3 × 20 min)	100% *endo*/*exo* 37 : 63	 **3b-N**  **3b-X**
3	**1b**		3 equiv. diene 60 min, 150 °C (3 × 20 min)	100% *endo*/*exo* 38 : 62	
4	**1c**		10 equiv. diene 80 min, 150 °C (4 × 20 min)	95% *endo*/*exo* 49 : 51	 **3c-N**  **3c-X**
5	**1a**	 **2b**	15 equiv. diene 1 h, 150 °C 3 h, 220 °C	Not determined[e]	 **3d-N**  **3d-X**
6	**1b**		10 equiv. diene 4 h, 220 °C (4 × 1 h)	91% *endo*/*exo* 75 : 25	 **3e-N**  **3e-X**
7	**1b**		3 equiv. diene 4 h, 220 °C (4 × 1 h)	93% *endo*/*exo* 75 : 25	
8	**1b**	 **2c**	3 equiv. diene 3 h, 220 °C	92% *meta*/*para* 33 : 67	 **3f-M**  **3f-P**
9	**1b**	 **2d**	3.4 equiv. diene 2 h, 220 °C (2 × 1 h)	94% *meta*/*para* 35 : 65	 **3g-M**  **3g-P**
10	**1b**	 **2e**	4 equiv. diene 4 h, 220 °C	83% *endo*/*exo* 39 : 61 *ortho*/*meta* 54 : 46	 **3h-ON**  **3h-OX**  **3h-MN**  **3h-MX**
11	**1b**	 **2f**	3 equiv. diene 3 h, 200 °C (3 × 1 h)	98%	 **3i**

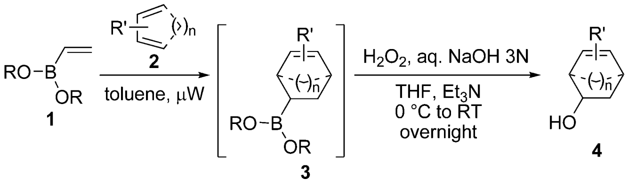
Table 1 *(Contd.)*

Entry	Vinylboronate	Diene	Conditions[a,b]	Yield[c] ratios[d]	Products
12	**1b**	 **2g**	3 equiv. diene 6 h, 220 °C (6 × 1 h)	92% *endo*/*exo* 45 : 55	 **3j-N**  **3j-X**
13	**1b**	 **2h**	3 equiv. diene 4 h, 220 °C	87% *ortho*/*meta* >80 : 20 *ortho endo*/*ortho exo* 44 : 56	 **3k-ON**  **3k-OX**  **3k-MN**  **3k-MX**
14	**1b**	 **2i**	1.5 equiv. diene 3 h, 220 °C	75% *endo*/*exo* 12 : 88 *ortho exo*/*meta exo* 47 : 53	 **3l-ON**  **3l-OX**  **3l-MN**  **3l-MX**

[a] All reactions were run in toluene, unless otherwise noted. [b] The reactions were monitored using ^{11}B NMR analysis in $CDCl_3$. Typically, the boron signal shifted 3.5 ppm downfield. As an example, the signal at δ 29.3 ppm for vinylboronate **1b** shifted to δ 33.8 ppm for the products of reaction with cyclopentadiene (**3b**). [c] Yields of isolated products after purification by chromatography on silica gel. [d] Determined by NMR integration. [e] The boronate products did not resist silica gel chromatography and hydrolysis to the boronic acids proved impractical.

though we expect that both steric and electronic effects play a significant role.

As a means to demonstrate the synthetic versatility of boronates **3**, we next investigated the functionalization of the C–B bond. We studied the sequence consisting of tandem microwave-assisted Diels–Alder reaction followed by *in situ* oxidation with alkaline hydrogen peroxide (Scheme 2, Table 2).[10] After the initial step was complete, the reaction mixtures were transferred and subjected to oxidation without isolation of the cycloadducts. It is important to remark that *no special care was taken to avoid moisture and air*. All reactions afforded the alcohols (**4a–h**) in good to excellent yields. Again, optimal yields were obtained with pinacol vinylboronate (**1b**). Furthermore, *endo*/*exo* stereoselectivities and regioselectivities did not change after oxidation, which confirmed that oxidation proceeded with retention of stereochemistry. These experiments demonstrate that vinylboronates can be efficiently employed as synthetic equivalents of vinyl alcohol in Diels–Alder reactions. The cyclohexenols thus obtained could be further transformed into structurally diverse compounds.



Scheme 2 Tandem microwave-assisted Diels–Alder reaction of vinylboronates-oxidation.

Conclusions

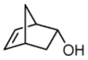
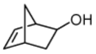
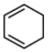
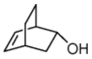
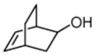
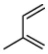
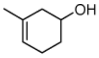
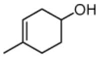
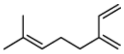
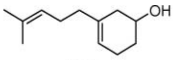
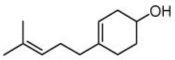
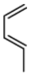
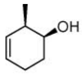
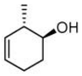
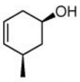
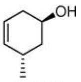
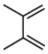
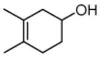
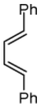
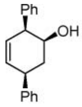
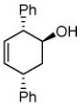
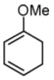
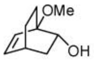
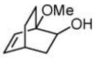
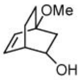
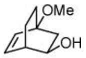
We have shown that the Diels–Alder reactions of vinylboronates can be easily performed using microwave irradiation giving excellent yields of the cycloadducts. Pinacol vinylboronate was the reagent of choice due to its stability towards hydrolysis, operational simplicity and yields of Diels–Alder products. To the best of our knowledge, this is the first example of microwave-assisted Diels–Alder reaction of boron-substituted dienophiles. Subsequent *in situ* oxidation of the cycloadducts with alkaline hydrogen peroxide afforded the alcohols efficiently, demonstrating the utility of these intermediates for C–O bond-forming reactions. We hope this investigation promotes further research on microwave-assisted boronate cycloadditions.

Experimental section

Typical procedure for the microwave-assisted Diels–Alder reaction of vinylboronates (Table 1). Synthesis of 2-bicyclo[2.2.1]hept-5-en-2-yl-4,4,5,5-tetramethyl-[1,3,2]di-oxaborolane (3b)[11]

To an oven-dried 10 mL pressure-rated reaction vial equipped with a stirring bar were added dry toluene (0.5 mL), vinylboronate **1b** (85 μL, 0.5 mmol) and diene **2a** (42 μL, 0.5 mmol) under argon atmosphere. The resulting reaction mixture was stirred at 150 °C in the microwave for 20 min. Two more runs were conducted after addition of extra portions of diene (2 × 0.5 mmol of **2a** followed by 20 min at 150 °C). The solvent was removed under reduced pressure, and the crude was purified by column chromatography

Table 2 Tandem microwave-assisted Diels–Alder reaction of vinylboronates-oxidation

Entry	Vinylboronate	Diene	Yield DA + [O][a] ratios[b]	Products DA + [O]
1	**1a**	 2a	91% *endo/exo*: 41 : 59	 4a-N  4a-X
2	**1b**		92% *endo/exo*: 37 : 63[c]	
3	**1c**		86% *endo/exo*: 44 : 56	
4	**1a**	 2b	77% *endo/exo*: 73 : 27	 4b-N  4b-X
5	**1b**		96% *endo/exo*: 73 : 27[d]	
6	**1b**	 2c	99% *meta/para* 34 : 66	 4c-M  4c-P
7	**1b**	 2d	90% *meta/para* 33 : 67	 4d-M  4d-P
8	**1b**	 2e	68% *endo/exo* 39 : 61 *ortho/meta* 54 : 46	 4e-ON  4e-OX  4e-MN  4e-MX
9	**1b**	 2f	92%	 4f
10	**1b**	 2g	92% *endo/exo* 47 : 53	 4g-N  4g-X
11	**1b**	 2h	51% *ortho/meta* >95 : 5 *ortho endo/ortho exo* 49 : 51	 4h-ON  4h-OX  4h-MN  4h-MX

[a] Yields of isolated products after purification by chromatography on silica gel. [b] Determined by NMR integration. [c] Conditions for the DA reaction are the same as reported in Table 1, entry 3. [d] Conditions for the DA reaction are the same as reported in Table 1, entry 7.

(hexane–AcOEt) to afford boronate **3b** (100%, 106 mg, *endo/exo* 38 : 62). HRMS calcd for $C_{13}H_{25}BNO_2$ $(M+NH_4)^+$: 238.1973, found: 238.1980. **3b-N**: IR (film) ν_{max}: 3058, 2976, 2934, 2874, 1412, 1371, 1310, 1273, 1146, 979, 856, 719, 690, 502. ^1H NMR (300 MHz; $CDCl_3$) δ: 6.00 (br s, 2H, H-5 and H-6), 3.02 (br s, 1H, H-1), 2.86 (br s, 1H, H-4), 1.83 (ddd, $J_{3n,3x} = 10.8$, $J_{2,3x} = 10.0$, $J_{3x,4} = 3.6$ Hz, 1H, H-3x), 1.40-1.32 (m, 2H, H-2 and H-7), 1.19 (s, 12H, H-9), 1.15–1.08 (m, 2H, H-3n and H-7). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 135.8 (CH, C-5), 134.4 (CH, C-6), 82.7 (2C, C-8), 50.3 (CH_2, C-7), 44.2 (CH, C-1), 42.3 (CH, C-4), 27.7 (CH_2, C-3), 24.6 ($4CH_3$, C-9), C-2 signal missing. ^{11}B NMR (96 MHz; $CDCl_3$) δ: 33.4. **3b-X**: IR (film) ν_{max}: 3056, 2975, 2931, 2871, 1370, 1313, 1232, 1146, 976, 858, 719. ^1H NMR (300 MHz; $CDCl_3$) δ: 6.09 (dd, $J_{5,6} = 5.4$, $J_{1,6} = 2.9$ Hz, 1H, H-6), 5.95 (dd, $J_{5,6} = 5.4$, $J_{4,5} = 3.0$ Hz, 1H, H-5), 2.88 (br s, 2H, H-1 and H-4), 1.71 (ddd, $J_{3n,3x} = 11.1$, $J_{2,3x} = 4.2$, $J_{3x,4} = 4.2$ Hz, 1H, H-3x), 1.25–1.06 (m, 15H, H-3n, H-7 and H-9), 0.68 (ddd, $J_{2,3n} = 9.7$, $J_{2,3x} = 4.9$, $J_{1,2} = 1.3$ Hz, 1H, H-2). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 137.0 (CH, C-6), 134.2 (CH, C-5), 82.8 (2C, C-8), 47.4 (CH_2, C-7), 44.0 (CH, C-1), 42.2 (CH, C-4), 27.6 (CH_2, C-3), 24.6 (4CH_3, C-9), C-2 signal missing. ^{11}B NMR (96 MHz; $CDCl_3$) δ: 34.1.

Typical procedure for the tandem microwave-assisted Diels–Alder reaction of vinylboronates - oxidation (Table 2). Synthesis of Bicyclo[2.2.1]hept-5-en-2-ol (4a)[12]

The microwave-assisted Diels–Alder reaction between **1b** and **2a** was performed as described above. Upon completion, the reaction mixture was diluted with THF (3 mL), and transferred to a 25 mL round-bottom flask. After the addition of Et_3N (1 mL) the solution was cooled to 0 °C and treated alternately with 3 N NaOH (3 mL) and 30% H_2O_2 (3 mL) under argon atmosphere, and then allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with saturated NH_4Cl (15 mL) and brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure at 0 °C, and the crude was purified by column chromatography (pentane–Et_2O) to afford alcohol **4a** (92%, 48.3 mg, *endo*/*exo* 37 : 63) with NMR spectra identical to the commercial material.

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