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# Asymmetric hetero-Diels–Alder reaction of chiral pinanediol 1,3-dienylboronates with azo-compounds

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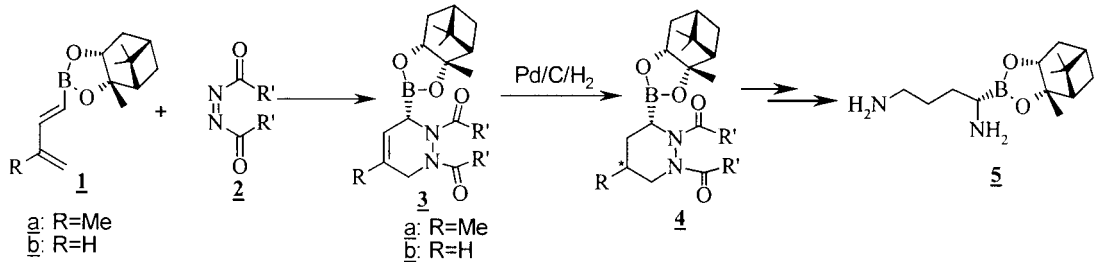
**Abstract**—The asymmetric hetero-Diels–Alder reaction of 1,3-dienylboronates **1a** and **1b** with azo-compounds was investigated. The inductive effect of the methyl in 1,3-dienylboronate **1a** resulted in an unusual product **7**, while the normal cycloadduct **8** could be obtained as the single stereoisomer by using 1,3-dienylboronate **1b**. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Vinylboronic ester derivatives are accessible and widely employed species for constructing a large number of important molecules.[1] In the past several years, the application of vinylboronic esters in asymmetric cycloaddition reactions has been well developed.[2–16] Among these cycloaddition reactions, good to excellent regio- and stereoselections could be achieved by building chiral auxiliaries into alkenylboronates or employing Lewis acid and Lewis base catalysts. As one part of our interests in the application of chiral alkenylboronic esters in asymmetric synthesis and reactions, we prepared optically active (+)-pinanediol 1,3-butadienylboronates **1a** and **1b**, and carried out their asymmetric hetero-Diels–Alder reactions. Here we describe our preliminary results.

## 2. Results and discussion

Optically active 1,3-dienylboronates are known to react with alkenyl dienophiles with very low stereoselectivity.[9,14,16] In this paper we chose to study their cycloaddition with azo-compounds as the dienophiles. Our research plan was to stereoselectively synthesize α-aminoboronate **5**, which is a key intermediate to a series of thrombin inhibitors.[7–19] As outlined in Scheme 1, the reaction of 1,3-dienylboronate **1** with an azo-compound of type **2** should give a cycloadduct of type **3**, which is the pivotal precursor to α-aminoboronate **5**. Because dienylboronate **1a** was at hand (it was prepared according to the reported procedure[11,12,16] from 2-methyl-1-buten-3-yne, which was readily prepared in our laboratory), we studied its reactivity first. After several attempts, we found that it reacted only with compounds **2a** and **2b** (Scheme 2), while other azodicarboxylate esters and azodicarbonyl dipiperidine were unreactive. To our surprise, after carrying out the cycloaddition in THF at 0°C and simple work-up, we found the isolated product was not the anticipated cycloadduct of type **6**. All the analytical data supported the structure of type **7**. Furthermore, compound **7** was always isolated as the only product,[20] no other product was observed even though the 1,3-dienylboronate **1a** was added in excess.




**Scheme 1.**

*Keywords*: Diels–Alder reaction; azo-compounds; vinylboronic ester.

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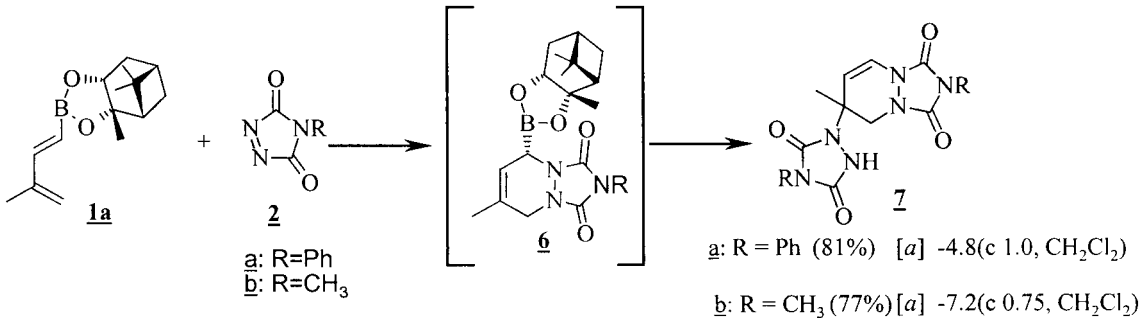
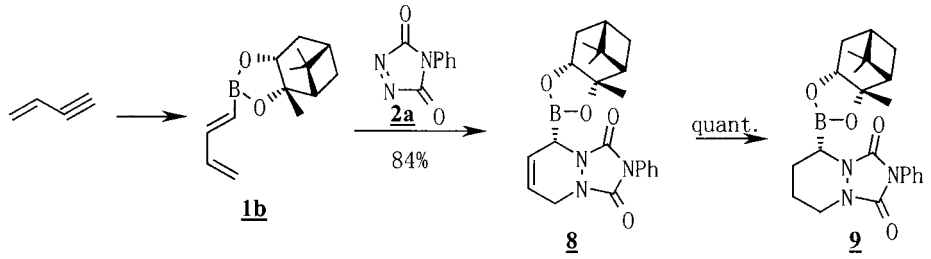



**Scheme 2.**




**Scheme 3.**

The formation of compounds **7a** and **7b** can be explained by the following mechanism. 1,3-Dienylboronate **1a** reacts with 4-phenyltriazoline-3, 5-dione **2a** or 4-methyltriazoline-3, 5-dione **2b** to give the intermediate **6a** or **6b**. Presumably, the inductive effect of the methyl group makes the double bond of the intermediate **6a** or **6b** sufficiently electron rich to react immediately with the strong electrophile **2a** or **2b** to give compound **7a** or **7b**, with loss of boronic ester group.

According to this analysis, cycloadduct **8** could be obtained by the similar hetero-Diels–Alder reaction of compound **2a** with 1,3-dienylboronate **1b**. With this idea in mind, we prepared 1,3-dienylboronate **1b** by the similar procedure starting from vinylacetylene.[11–12,16] Then the hetero-Diels–Alder reaction of compound **1b** with compound **2a** was carried out under the same reaction conditions (Scheme 3).

As expected, cycloadduct **8** was obtained as the single product with excellent stereoselectivity in 84% yield. No further reaction products or other isomers were observed. This was in sharp contrast to the reported results using carbon–carbon double bond alkenes as the dienophile.[9,14,16] Compound **8** can be rationalized to be *R*-configured *endo* cycloadduct by evaluation of the effect of the chiral (+)-pinanediol group, which blocks attack of dienophile **2a** at the *Re*-face of dienyl plane in 1,3-dienylboronate **1b** and favors attack from the *Si*-face of the dienyl plane (Fig. 1). The special structure of dienophile **2a** also makes great contribution to the excellent stereoselectivity, of course. The stereochemistry of cycloadduct **8** was confirmed by

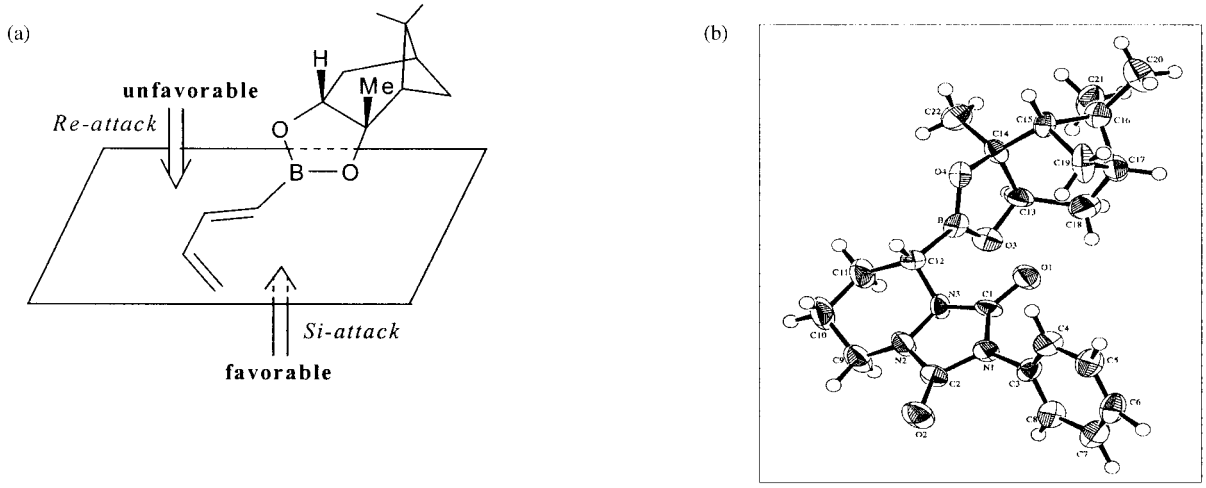
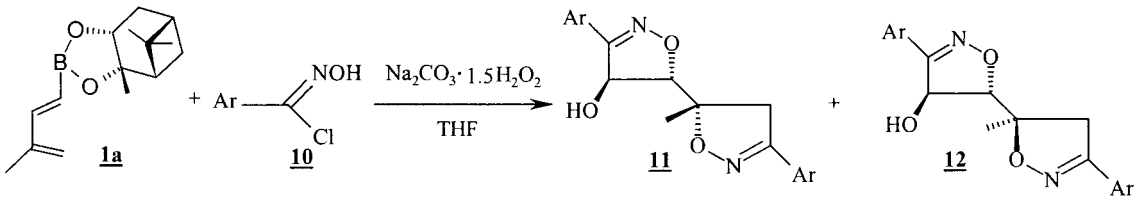



**Figure 1.** (a) Probable mechanism for the formation of compound **8**. (b) X-Ray analysis of compound **9**.




**Scheme 4.**

the X-ray analysis of compound **9**, obtained by hydrogenation of compound **8** over palladium/carbon.

As mentioned in Scheme 1, to complete the synthesis of α-aminoboronate **5**, we must cleave the N–N bond in compound **9**. But to date, this has been unsuccessful.

We also tried the asymmetric 1,3-dipolar cycloaddition of (+)-pinanediol 3-methyl-1,3-butadienylboronate **1a** with nitrile oxides. The bi(isoxazolines) products **11** and **12**, in which both of the double bonds in compound **1a** were involved in the cycloaddition, but the stereoselectivity was less than 20% (Scheme 4).[21]

## 3. Conclusions

In summary, the asymmetric hetero-Diels–Alder reaction of 1,3-dienylboronates **1a** and **1b** with azo-compounds was investigated. The inductive effect of the methyl in 1,3-dienylboronate **1a** resulted in an unusual product **7**, while the reaction of 1,3-dienylboronate **1b** with azo-dienophile **2a** gave the *R*-configured *endo* cycloadduct **8** as the single stereoisomer.

## 4. Experimental

### 4.1. General

NMR spectra were recorded as $CDCl_3$ solutions on a VXL-300 instrument. The $^1H$ NMR (300 MHz) chemical shifts are reported as $\delta$ values in ppm relative to tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin–Elmer 983 FT-IR spectrometer. Mass spectral measurements were performed on a Fining 4021 or Fining MAT 8403 gas chromatography/mass spectrometer at 70 eV. Elemental analyses were carried out on a MOD-1106 elemental analyzer. All solvents were purified and dried by standard techniques just before use. All reactions were monitored by thin layer chromatography (TLC) using silica gel GF254. Products were purified by chromatography on silica gel manufactured in Qingdao Marine Chemical Factory, eluting with the solvent mixture of petroleum ether (bp 60–90°C) and ethyl acetate. Optical rotations were measured using a Shanghai WZZ-1S automatic polarimeter.

### 4.2. Preparation of 1,3-dienylboronates 1a and 1b

Under an atmosphere of nitrogen, dimethyl sulfide–borane complex (21.1 mL, 0.15 mol) is dissolved in DME (300 mL). Cyclohexene (24.6 g, 0.3 mol) is added at 0°C. After 15 min, the mixture is allowed to reach room temperature. The resultant suspension of dicyclohexylborane is stirred for 1 h, then cooled to 0°C. Enyne (0.15 mol) is added and the mixture is allowed to warm to room temperature whereupon the dicyclohexylborane dissolves. After 1 h, anhydrous trimethylamine oxide (22.5 g, 0.30 mol) is added in small portions in such a manner that the solution is maintained under gentle reflux. The mixture is then cooled to room temperature, stirred for 1 h, and (+)-pinanediol (25.5 g, 0.15 mol) is added. After 12 h, the solution is filtered and the filtrate is concentrated. The residue is subjected to flash chromatography. The 1,3-dienylboronates **1a** and **1b** are obtained as viscous oils.

**4.2.1. 1,3-Dienylboronate 1a.** Yield 89%; *m/z* (EI) 246 ($M^+$, 11), 231 (22), 205 (16), 193 (23), 177 (90), 150 (54), 135 (25), 83 (100%); $\nu_{max}$ (liquid film) 3083, 2986, 2931, 2871, 1625, 1602, 1452, 1376 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.03 (1H, d, *J*=18 Hz), 5.49 (1H, d, *J*=18 Hz), 5.07 (2H, s), 4.23–4.26 (1H, m), 2.05–2.07 (6H, m), 1.77 (3H, s), 1.33 (3H, s), 1.22 (3H, s), 0.78 (3H, s); $\delta_c$ (300 MHz, $CDCl_3$) 146.44, 137.15, 116.21, 108.90, 85.26, 81.23, 58.37, 42.35, 35.78, 28.90, 25.32, 24.91, 24.37, 23.82, 20.38. HRMS (EI): $MH^+$, found 247.1854. $C_{15}H_{24}B^{11}O_2$ requires 247.1869.

**4.2.2. 1,3-Dienylboronate 1b.** Yield 78%; *m/z* (EI) 232 ($M^+$, 10), 217 (16), 179 (23), 168 (90), 135 (65), 53 (100%); $\nu_{max}$ (liquid film) 3079, 2976, 2934, 2866, 1631, 1607, 1448, 1357 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.03–7.05 (1H, m), 6.44–6.46 (1H, m), 5.59–5.61 (1H, m), 5.32–5.34 (2H, m), 4.35 (1H, s), 2.10–2.11 (5H, m), 1.40 (3H, s), 1.28 (3H, s), 1.14–1.16 (1H, m), 0.83 (3H, s); $\delta_C$ (300 MHz, $CDCl_3$) 140.21, 137.74, 116.83, 115.84, 85.37, 81.42, 58.26, 43.18, 35.81, 28.80, 25.23, 24.84, 24.77, 20.32; HRMS (EI): found 232.1634. $C_{14}H_{21}B^{11}O_2$ requires 232.1635.

### 4.3. General procedure for the hetero-Diels–Alder reaction of 1,3-dienylboronate 1a with 4-phenyltriazoline-3,5-dione 2a or 4-methyltriazoline-3,5-dione 2b

To a solution of 1,3-dienylboronate **1a** (240 mg, 0.979 mmol) in anhydrous THF (5 mL) was added dropwise under an atmosphere of nitrogen a solution of 4-phenyltriazoline-3,5-dione **2a** (171 mg, 0.979 mmol) or 4-methyltriazoline-3,5-dione **2b** (179 mg, 0.979 mmol) in THF (4 mL) at 0°C. The resulting red solution was stirred for 50 min at 0°C and then condensed. The residue was treated with diethyl ether (15 mL) and a white solid was obtained. The crude solid product was recrystallized from diethyl

ether and hexane to give the pure product as viscous white solid.

**4.3.1. Compound 7a.** Yield 81% (based on compound **2a**); mp 209.2–210.8°C; *m/z* (EI) 418 ($M^+$, 0.2), 242 (100), 228 (20), 177 (43), 123 (27), 119 (68), 94 (31%); $\nu_{max}$ (KBr) 3473, 3163, 3103, 1774, 1710, 1648, 1503, 1418 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.41–7.43 (10H, m), 7.01 (1H, d, *J*=8.2 Hz), 5.24 (1H, d, *J*=8.2 Hz), 4.85 (1H, d, *J*=12.9 Hz), 3.59 (1H, d, *J*=12.9 Hz), 1.64 (3H, s); $\delta_C$ (300 MHz, $CDCl_3$) 153.92, 153.02, 149.98 and 145.65 (4×C=O), 130.68, 129.25, 128.56 and 125.62 (d, Ar), 119.84 (C=C), 106.54 (C=C), 58.16 (C=C–*C*), 48.09 ($CH_2$), 21.73 ($CH_3$); $[\alpha]_D$=−4.9 (*c* 1.0, $CH_2Cl_2$). HRMS (EI): found 418.1403. $C_{21}H_{18}N_6O_4$ requires 418.1390.

**4.3.2. Compound 7b.** Yield 77% (based on compound **2b**); mp 167.2–168.5°C; *m/z*(EI) 180 ($M^+$−114, 100), 166 (2), 123 (59), 115 (7), 94 (17), 80 (39%); FABMS 295 ($M^+$+1); $\nu_{max}$ (KBr) 3470, 3079, 2983, 1768, 1689, 1648, 1486, 1397 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 8.45 (br s, 1H), 7.00 (d, 1H, *J*=8.2 Hz), 5.21 (d, 1H, *J*=8.2 Hz), 4.73 (d, 1H, *J*=12.8 Hz), 3.50 (d, 1H, *J*=12.8 Hz), 3.12 (s, 3H), 3.04 (s, 3H), 1.60 (s, 3H); $\delta_C$ (300 MHz, $CDCl_3$) 155.39, 154.40, 151.27 and 146.88 (4×C=O), 119.76 and 106.13 (C=C), 57.84 (C=C–*C*), 48.16 ($CH_2$), 29.49 ($CH_3$), 25.28 ($CH_3$), 21.75 ($CH_3$); $[\alpha]_D$=−7.2 (*c* 0.75, $CH_2Cl_2$). Anal.: $C_{11}H_{14}N_6O_4$ Calcd: C, 44.89; H, 4.76; N, 28.57. Found: C, 44.91; H, 4.65; N, 28.56.

### 4.4. Hetero Diels–Alder reaction of 1,3-dienylboronate 1b with 4-phenyltriazoline-3,5-dione 2a

To a solution of 1,3-dienylboronate **1b** (232 mg, 1 mmol) in anhydrous THF (5 mL) at 0°C, was added a solution of 4-phenyltriazoline-3,5-dione **2a** in THF (4 mL) dropwise. After completion, the ice bath was removed. The red solution changed to pale yellow after 20 min. The solvent was removed and methanol (2 mL) was added. A white precipitate was produced. After filtration, the product **8** was obtained in 84% yield as a viscous solid. *m/z* (EI) 407 ($M^+$, 100), 392 (23), 379 (83), 330 (61), 228 (57), 179 (12), 91 (21%); $\nu_{max}$ (KBr) 3074, 1699, 1642, 1425, 1399; $\delta_H$ (300 MHz, $CDCl_3$) 7.42–7.46 (5H, m), 5.92–5.94 (2H, m), 4.37 (1H, dd, *J*=9, 2 Hz), 4.21–4.23 (3H, m), 2.27–2.29 (2H, m), 2.06 (1H, t, *J*=6 Hz), 1.87–1.89 (2H, m), 1.41 (3H, s), 1.28 (3H, s), 1.26 (2H, d, *J*=8 Hz), 0.89 (3H, s); $[\alpha]_D$=+122 (*c* 2.76, dioxane). HRMS (EI): found 407.2048. $C_{22}H_{26}BN_3O_4$ requires 407.2016. Anal.: $C_{22}H_{26}BN_3O_4$ Calcd: C, 64.86; H, 6.39; N, 10.32. Found: C, 64.91; H, 6.36; N, 10.34.

**4.4.1. Hydrogenation of compound 8.** Compound **8** (1 g, 2.46 mmol) was dissolved in a solution of anhydrous THF (150 mL) and ethyl acetate (50 mL) and palladium/carbon (10%, 0.1 g) was added. After having been degassed 3 times, the solution was hydrogenated under normal pressure for 3 h. The solid was filtered and the filtrate was concentrated. The residue was subjected to flash chromatography (diethyl ether as eluent) to afford compound **9** in 98% yield. Mp 237.1–238.4°C *m/z* (EI) 409 ($M^+$, 49), 408 (10), 381 (22), 258 (13), 220 (11), 135 (10), 119 (72), 91 (13%); $\nu_{max}$ (KBr) 3080, 2992, 1701, 1637, 1429, 1407, 1140 $cm^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 7.3–7.5 (5H, m), 4.42 (1H, dd, *J*=8.7, 2 Hz), 3.93–3.95 (1H, m), 3.44 (1H, td, *J*=8, 4 Hz), 3.28 (1H, dd, *J*=9.4, 3.6 Hz), 2.37–2.39 (1H, m), 2.23–2.25 (1H, m), 2.0–2.2 (1H, m), 1.86–1.90 (6H, m), 1.47 (3H, s), 1.30 (3H, s), 1.28 (1H, d, *J*=13.7 Hz), 0.85 (3H, s); $[\alpha]_D$=+58.8 (*c* 2.07, dioxane). HRMS (EI): found 409.2136. $C_{22}H_{28}BN_3O_4$ requires 409.2173. Anal.: $C_{22}H_{28}BN_3O_4$ Calcd: C, 64.54; H, 6.84; N, 10.27. Found: C, 64.64; H, 6.89; N, 10.33.

**4.4.2. Crystal structure determination for compound 9.** X-Ray structure determination of **9** $C_{22}H_{28}BN_3O_4$: colorless prismatic crystal (0.20×0.20×0.30 mm, grown from dichloromethane and *n*-hexane), orthorhombic, space group $P2_12_12_1$(#19), *a*=8.612(2) Å, *b*=35.10(1) Å, *c*=6.846(4) Å, *V*=2069(1) $Å^3$, *Z*=4, *D*=1.31 g $cm^{-3}$, *T*=293 K. A Rigaku AFC7R diffractometer (CCD area detector) with graphite monochromated MoKα radiation and a 12 kW rotating anode generator was used for all measurements. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using the setting angles of 18 carefully centered reflections in the range $13.65<2\theta<16.39°$. The data was collected using the $\omega$–$2\theta$ scan technique to a maximum $2\theta$ value of 45.0°. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 235 mm. A total of 1636 reflections were collected. The intensities of three representative reflection were measured after every 200 reflections. The structure was solved by direct methods using MITHRIL84 and expanded using DIRDIF92. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined.

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Center (CCDC).

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20. The determination of the enantioselective excess of compound **7a** and **7b** was unsuccessful by HPLC with chiralcel OA, OB, OC, OD, OJ or AD columns.
21. Part of the planned PhD thesis of Mr Zhang Ao.