Boron Compound as a Trapping Reagent of α-Hydroxy o-Quinodimethanes in the Diels–Alder Reaction

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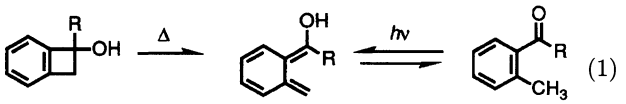
The Diels–Alder reaction of methyl 4-hydroxy-2-butenoate and α-hydroxy o-quinodimethanes, generated from 1,2-dihydrobenzocyclobuten-1-ol derivatives by thermolysis, proceeds by the use of phenylboronic acid as a template. Boron reagents trap an α-hydroxy o-quinodimethane (5-methylene-6-(1-hydroxyalkylidene)-1,3-cyclohexadiene) generated photochemically from o-tolualdehyde and the Diels–Alder reaction with methyl 4-hydroxy-2-butenoate occurs to give the cycloadducts.

The Diels–Alder reaction of o-quinodimethane (5,6-bis(methylene)-1,3-cyclohexadiene) derivatives is useful for the syntheses of some natural products[1] because tetralin skeleton can be easily constructed in one step with high regio- and stereoselectivity. Among many methods for the generation of o-quinodimethanes,[2] the thermal ring opening of 1,2-dihydrobenzocyclobutene derivatives[2] and the photochemical isomerization of o-tolylcarbonyl compounds[2] are often utilized due to the easy preparation of the starting materials (Eq. 1). o-Quinodimethanes, however, are fairly unstable and react only with highly reactive dienophiles.[3] When the reactivity of a dienophile is not so high, α-hydroxy o-quinodimethane (5-methylene-6-(1-hydroxyalkylidene)-1,3-cyclohexadiene) derivatives isomerize to give the o-tolylcarbonyl compounds or otherwise, dimerize.[2,4] This restricts the wide application of the Diels–Alder reaction of o-quinodimethane in organic synthesis.



(1)

1a R=H
1b R=CH_3 **2** **3**

We reported that phenylboronic acid (dihydroxyphenylborane) can be used as a template in the Diels–Alder reaction between anthrone or 6-hydroxy-2-pyrone and methyl 4-hydroxy-2-butenoate.[5,6] In these reactions, phenylboronic acid and the substrates smoothly form possible three types of boronates eliminating water, which are in equilibrium with each other.[7] Therefore, the reaction proceeds in an intramolecular manner via the mixed boronate consisting of both diene and dienophile components and gives the corresponding cycloadducts with high regio- and stereoselectivity.

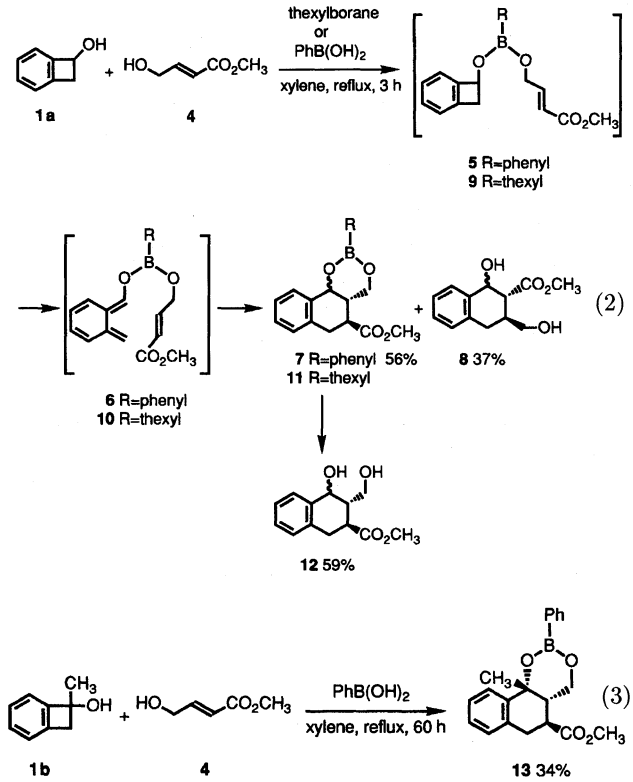
It was considered that, when boronic acid could trap both of an α-hydroxy o-quinodimethane and a dienophile as a mixed boronate, o-quinodimethane could be prevented from the isomerization to the o-tolylcarbonyl compound and the Diels–Alder reaction would proceed regioselectively in an intramolecular manner. This paper describes the investigation on the effect of boronic acid in the Diels–Alder reaction of α-hydroxy o-quinodimethane generated in situ by thermolysis or photolysis.

5-Methylene-6-(1-hydroxyalkylidene)-1,3-cyclohexadiene (**2a**) is known to be generated by thermolysis of 1,2-dihydrobenzocyclobuten-1-ol (**1a**) at 80 °C.[2] So, the Diels–Alder reaction of **1a**[8] and methyl 4-hydroxy-2-butenoate (**4**)[9] was examined in a refluxing benzene solution. However no Diels–Alder adduct was obtained and only o-tolualdehyde (**3a**), the isomerized product of α-hydroxy o-quinodimethane **2a**, was isolated. Then, in the presence of an equimolar amount of phenylboronic acid, a benzene solution of **1a** and **4** was refluxed with an azeotropic removal of water. After an evaporation of the solvent, the ^{1}H NMR spectrum of the crude product revealed that both alcohols **1a** and **4** were converted to the phenylboronates. Even by the successive reflux in benzene, however, the starting materials were recovered after work up. As the ring opening of a boronate of 1,2-dihydrobenzocyclobuten-1-ol (**1a**) could not occur in refluxing benzene, a mixture of **1a** and the dienophile **4** was refluxed in m-xylene in the presence of phenylboronic acid for 3 h. The cycloadduct **7** was obtained in 56% yield, along with the regioisomer **8** in 37% yield. Both of them were found to be mixtures of the *endo* and *exo* isomers (ca. 1 : 1) (Eq. 2).

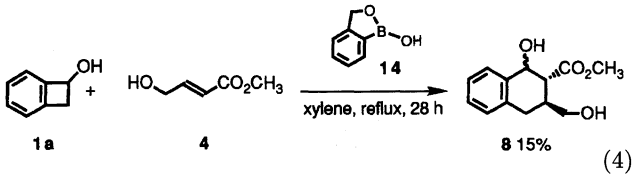
Instead of phenylboronic acid, thexylborane (1,1,3-trimethylpropylborane[10]) was used as a template. Thexylborane would form the boronates with **1a** exclusively without generation of water. A THF solution of **1a**, **4** and thexylborane was stirred for 1 h, and after evaporation of THF in vacuo, the solvent was replaced with m-xylene. The m-xylene solution was refluxed and the cycloadduct **12** was obtained in 59% yield as the hydrolyzed product of the boronate **11** during the purification. The opposite regioisomer **8** was not detected in this reaction (Eq. 2). The formation of the single regioisomer **12** confirmed that the Diels–Alder reaction proceeded completely in an intramolecular pathway via the formation of the mixed boronate **10**.

When 1,2-dihydro-1-methylbenzocyclobuten-1-ol (**1b**)[11] was employed as a quinodimethane precursor, the Diels–Alder reaction with **4** proceeded in high regio- and stereoselectivity, giving the adduct **13** as a single

regio- and stereoisomer in 34% yield (Eq. 3). The exclusive formation of **13** from **1b** suggests that the methyl-substituted *o*-quinodimethane generated from **1b** was less reactive than the *o*-quinodimethane generated from **1a** because of the steric hindrance and the intermolecular reaction did not proceed smoothly.

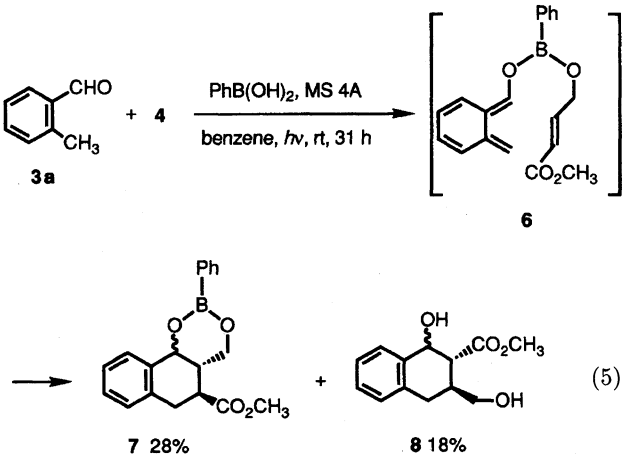


It should be noted that the cycloadducts **7**, **12**, and **13**, whose regioselectivity is not expected from the frontier orbital theory,[12] are generated predominantly over their regioisomers such as **8**. The predominant formation of **7**, **12**, and **13** in Eqs. 2 and 3 suggests the existence of the mixed boronate intermediates such as **6**, through which the Diels–Alder reactions proceeded mainly in an intramolecular manner. In order to certify the roles of boronates, the Diels–Alder reaction of 1, 2-dihydrobenzocyclobuten-1-ol (**1a**) and the dienophile **4** was examined by using 2 molar equivalents of 1-hydroxy-2-oxa-1-boraindan (**14**)[13] which could form the boronate with a single alcohol. The reaction proceeded more slowly as compared with the use of phenylboronic acid, and the cycloadduct **8** was obtained in lower yield (15%) as a sole product (Eq. 4).



Furthermore, boron reagents stabilize α-hydroxy *o*-quinodimethanes by forming the boronates, because no cycloadduct was obtained in the absence of boron reagents though α-hydroxy *o*-quinodimethane was generated.

Quinodimethane **2a** is also generated by photochemical isomerization of *o*-tolualdehyde (**3a**)[2] (Eq. 1). The effect of phenylboronic acid was investigated in the Diels–Alder reaction of *o*-tolualdehyde (**3a**) and the dienophile **4** under photochemical conditions. As the reference experiment, a benzene solution of *o*-tolualdehyde (**3a**) and methyl 4-hydroxy-2-butenoate (**4**) was irradiated in the absence of phenylboronic acid at room temperature, but no Diels–Alder adduct was detected. In contrast, when a benzene solution of **3a** and **4** was irradiated for 31 h in the presence of an equimolar amount of phenylboronic acid with Molecular Sieves (MS) 4A, the cycloadducts **7** (*endo*: *exo*=ca. 1:1) and **8** (*endo*: *exo*=ca. 1:1) were formed in 28% and 18% yields, respectively (Eq. 5).



In conclusion, phenylboronic acid traps unstable α-hydroxy *o*-quinodimethane (**2**) and prevents a side reaction such as the isomerization of α-hydroxy *o*-quinodimethane, and the Diels–Alder reaction with methyl 4-hydroxy-2-butenoate (**4**) proceeds preferentially in an intramolecular manner.

Experimental

Benzene and *m*-xylene were distilled and stored over MS 4A. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Benzene and *m*-xylene were degassed under reduced pressure before use. All the operations were performed under an argon atmosphere. Preparative thin-layer chromatography (TLC) was carried out on silica gel (Wakogel B-5F). IR spectra were measured with a Horiba FT-300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AM500 spectrometer.

General Procedure for the Diels–Alder Reaction of 1,2-Dihydrobenzocyclobuten-1-ols and Methyl 4-Hydroxy-2-butenoate (4) in the Presence of Phenylboronic Acid. To a benzene solution (5 ml) of 1,2-dihydrobenzocyclobuten-1-ol (**1a**) (240 mg, 2.0 mmol) and methyl 4-hydroxy-2-butenoate (**4**) (232 mg, 2.0 mmol) was added phenylboronic acid (240 mg, 2.0 mmol) and the mixture was

refluxed with azeotropic removal of water for 1 h. After evaporation of benzene, *m*-xylene (50 ml) was added and the solution was refluxed for 3 h. After evaporation of the solvent, the crude product was purified by preparative TLC (hexane–ether, 1:10) to give **7** (397 mg, 56% yield as a 1:1 mixture of the *endo* and *exo* isomers) and **8** (174 mg, 37% yield as a 1:1 inseparable mixture of the *endo* and *exo* isomers).

Methyl (10S^*,10aR^*)-1,2,3,4,4a,9,10,10a-Octahydro-3-phenyl-2,4-dioxa-3-boraphenanthrene-10-carboxylate (7): The (4aR^*) and (4aS^*)-isomers, obtained by the above experiment, were separated by preparative TLC using hexane–ether, 1:1 as an eluent.

The (4aR^*)-Isomer: Colorless oil, IR (neat) 1734, 1312 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.55—2.59 (1H, m), 2.83 (1H, ddd, J=10.5, 10.5, 6.3 Hz), 2.96 (1H, dd, J=10.5, 6.3 Hz), 2.99 (1H, t, J=10.5 Hz), 3.69 (3H, s), 3.90 (1H, dd, J=11.8, 4.4 Hz), 4.18 (1H, dd, J=11.8, 3.7 Hz), 5.17 (1H, d, J=4.4 Hz), 7.06 (2H, t, J=8.1 Hz), 7.45 (1H, dd, J=6.3, 2.7 Hz), 7.16—7.38 (4H, m), 7.71 (2H, dd, J=7.8, 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ=31.48, 37.73, 40.81, 52.09, 65.75, 72.61, 125.17, 126.69, 127.51, 127.59, 128.12, 130.88, 133.04, 135.93, 173.39. Found: C, 70.60; H, 6.06%. Calcd for $C_{19}H_{19}BO_4$: C, 70.84; H, 5.94%.

The (4aS^*)-Isomer: Colorless oil, IR (neat) 1733, 1309 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.55—2.33 (1H, m), 2.68 (1H, ddd, J=11.0, 10.5, 6.0 Hz), 3.03 (1H, dd, J=10.6, 6.0 Hz), 3.15 (1H, dd, J=10.6, 10.5 Hz), 3.68 (3H, s), 3.94 (1H, dd, J=11.8, 3.7 Hz), 4.23 (1H, dd, J=11.8, 4.5 Hz), 4.92 (1H, d, J=10.4 Hz), 7.16—7.38 (7H, m), 7.81 (2H, dd, J=8.1, 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ=31.62, 37.20, 40.98, 52.13, 63.32, 69.70, 126.85, 127.66, 128.29, 128.93, 130.81, 133.71, 133.94, 136.44, 174.89. Found: C, 70.84; H, 6.05%. Calcd for $C_{19}H_{19}BO_4$: C, 70.84; H, 5.94%.

Methyl (2R^*,3S^*)-1-Hydroxy-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (8): The (1R^*) and (1S^*)-isomers were obtained as a mixture ((1R^*) : (1S^*)=1 : 1), and were not separated by preparative TLC. Each signals of aliphatic protons were separated in the NMR spectrum and the relative structure of the (1R^*) and (1S^*)-isomers was determined by the coupling constants of benzylic protons: white solid, IR (KBr) 1720, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) aliphatic protons of the (1R^*)-isomer: δ=2.63—2.69 (1H×0.5, m), 2.70 (1H×0.5, dd, J=16.2, 7.0 Hz), 2.76 (1H×0.5, dd, J=10.5, 2.8 Hz), 2.98 (2H×0.5, dd, J=16.2, 5.1 Hz), 3.69 (1H×0.5, dd, J=11.2, 4.8 Hz), 3.73 (1H×0.5, dd, J=11.2, 4.5 Hz), 3.74 (3H×0.5, s), 4.98 (1H×0.5, d, J=2.8, Hz), aliphatic protons of the (1S^*)-isomer: δ=2.21—2.26 (1H×0.5, m), 2.58 (1H×0.5, t, J=9.5 Hz), 2.79 (2H×0.5, d, J=7.9 Hz), 3.58 (2H×0.5, d, J=5.0 Hz), 3.74 (3H×0.5, s), 5.05 (1H×0.5, d, J=9.5 Hz); aromatic protons: δ=7.05 (1H×0.5, d, J=7.2 Hz), 7.10 (1H×0.5, d, J=7.2 Hz), 7.13—7.23 (4H×0.5, m), 7.33 (1H×0.5, d, J=8.7 Hz), 7.50 (1H×0.5, d, J=7.6 Hz); ^{13}C NMR ($CDCl_3$) δ=31.43, 33.90, 38.43, 47.53, 52.14, 52.17, 52.25, 52.28, 65.22, 65.36, 68.60, 70.93, 126.11, 126.41, 128.43, 126.55, 127.60, 128.40, 128.91, 129.16, 134.72, 135.33, 135.99, 137.64, 174.78, 175.5. Found: C, 66.03; H, 6.66%. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%.

Methyl (4aR^*,10S^*,10aR^*)-1,2,3,4,4a,9,10,10a-Octahydro-4a-methyl-3-phenyl-2,4-dioxa-3-boraphenanthrene-10-carboxylate (13): IR (KBr) 1734, 1356 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.71 (3H, s, C$\underline{H}_3$–C(4a)), 2.56 (1H, ddd, J=4.0, 5.9, 8.1 Hz, $\underline{H}^a$–C(10a)), 2.74 (1H, ddd, J=6.0, 8.1, 10.5 Hz, $\underline{H}^b$), 3.00 (1H, dd, J=16.1, 6.0 Hz), 3.14 (1H, dd, J=16.1, 10.5 Hz), 3.77 (1H, dd, J=5.9, 11.9 Hz), 3.78 (3H, s), 4.26 (1H, dd, J=11.9, 4.0 Hz), 7.11 (1H, d, J=7.5 Hz), 7.21—7.24 (1H, m), 7.28—7.39 (3H, m), 7.39—7.46 (1H, m), 7.72 (1H, d, J=7.9 Hz), 7.81 (2H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ=30.1, 31.2, 39.0, 43.1, 52.2, 62.3, 72.6, 126.4, 127.1, 127.4, 127.5, 128.1, 130.7, 132.5, 133.9, 140.8, 175.1. Found: C, 71.31; H, 6.25%. Calcd for $C_{20}H_{21}BO_4$: C, 71.45; H, 6.30%. Relative stereochemistry was determined by the NOESY spectrum, in which NOE between CH_3–C (4a) and H^a–C (10a) was observed (Chart 1).

Preparation of Methyl (2S^*,3R^*)-4-Hydroxy-3-hydroxymethyl-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (12) by the Use of Thexylborane. To a THF solution (5 ml) of 2,3-dimethyl-2-butene (88 mg, 1.1 mmol) was added borane–THF complex (1 equiv THF solution, 1 ml, 1 mmol) at 0 °C and stirred for 1 h. Then, 1,2-dihydrobenzocyclobuten-1-ol (**1a**) (35 mg, 0.29 mmol) and methyl 4-hydroxy-2-butenoate (**4**) (197 mg, 1.7 mmol) was added successively and stirred for 1 h. After evaporation of THF, *m*-xylene (50 ml) was added and the solution was refluxed for 8 h. After evaporation of the solvent, the crude product was obtained. In this case, the cycloadducts were hydrolyzed to **12** as a 1:1 inseparable mixture of the *endo* and *exo* isomers ((4R^*) : (4S^*)=1 : 1) during the purification by prerarative TLC (hexane–ether, 1:1). Each signals of aliphatic protons were separated in the NMR spectrum and the relative structure of the (4R^*) and (4S^*)-isomers was determined by the coupling constants of benzylic protons: Colorless oil, IR (neat) 1727, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) aliphatic protons of the (4R^*)-isomer: δ=2.15—2.18 (1H×0.5, m), 3.03 (1H×0.5, dd, J=16.1, 5.5 Hz), 3.10 (1H×0.5, dd, J=16.1, 6.0 Hz), 3.20 (1H, ddd, J=11.6, 6.0, 5.5 Hz), 3.74 (3H×0.5, s), 3.92 (1H×0.5, dd, J=11.6, 5.6 Hz), 3.98 (1H×0.5, dd, J=11.6, 8.7 Hz), 4.99 (1H×0.5, d, J=5.5 Hz); aliphatic protons of the (4S^*)-isomer: δ=2.22—2.25 (1H×0.5, m), 2.77 (1H×0.5, ddd, J=10.3, 6.0, 5.5 Hz), 2.95 (1H×0.5, dd, J=16.7, 5.5 Hz), 3.16 (1H×0.5, dd, J=16.7, 6.0 Hz), 3.78 (3H×0.5, s), 3.78 (1H×0.5, dd, J=11.0, 4.2 Hz), 3.93 (1H×0.5, dd, J=11.0, 6.5 Hz), 4.82 (1H×0.5, d, J=8.5 Hz): aromatic protons δ=7.10 (1H×0.5, d, J=7.4 Hz), 7.15 (1H×0.5, d, J=7.0 Hz), 7.20—7.30 (2H, m), 7.34 (1H×0.5, d, J=7.0 Hz), 7.55 (1H×0.5, d, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ=31.60, 32.30, 37.19, 41.00, 42.89, 46.12, 52.02, 52.05, 63.67, 63.84, 70.80, 71.20, 126.76, 126.82, 127.00, 127.57, 128.10, 128.54, 128.70, 129.12, 133.94, 134.46, 136.93, 137.97, 174.95, 175.70. Found: C, 66.22; H, 6.81%. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%.

Procedure for the Diels–Alder Reaction of *o*-Tolualdehyde (3a) by Photochemical Isomerizaion

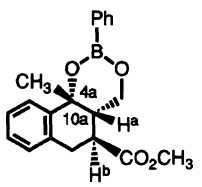


Chart 1.

and Methyl 4-Hydroxy-2-butenoate (4). A benzene solution (1.5 ml) of *o*-tolualdehyde (**3a**) (36 mg, 0.30 mmol), methyl 4-hydroxy-2-butenoate (**4**) (35 mg, 0.30 mmol), phenylboronic acid (36 mg, 0.30 mmol), and MS 4A (powder, 100 mg) was irradiated for 32 h at room temperature in a Pyrex test tube under the irradiation with the high-pressure mercury lamp. After filtration of MS 4A, the filtrate was evaporated and the residue was purified by preparative TLC (hexane–ether, 1:10) to give **7** (30 mg, 28% yield) and **8** (12 mg, 18% yield).

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