Alkenylboronate Tethered Intramolecular Diels−Alder Reactions

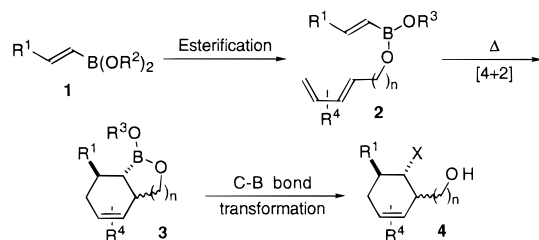Robert A. Batey,* Avinash N. Thadani, and Alan J. Lough[†]

Department of Chemistry, University of Toronto
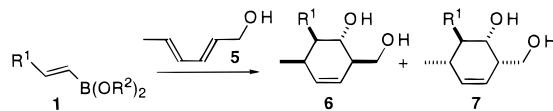*Toronto, Ontario, Canada, M5S 3H6*

The intermolecular Diels−Alder reaction[1] is a powerful method for the selective formation of functionalized cyclohexene derivatives. The adoption of an intermolecular Diels−Alder reaction in a synthetic sequence is nevertheless contingent upon electronic matching of diene and dienophile, such that cycloaddition occurs under thermal or Lewis-acid-catalyzed conditions. Many synthetically desirable intermolecular Diels−Alder reactions do not satisfy this criteria. One solution to this problem is to tether the diene and dienophile together through a temporary covalent connection.[2−4] This enables reaction between the otherwise unreactive components, since intramolecular Diels−Alder reactions (IMDA)[5] are more entropically favored than their intermolecular counterparts. In addition, the constraining effects of the tether control the regio- and stereoselectivity of the cycloaddition. The use of carbon−metal or carbon−metalloid precursors in tethered IMDA reactions is of particular interest, since the C−M bond in the product can be subsequently transformed in a sequential[6] reaction. Examples of this approach using C−Si−O,[2,3] C−Mg−O,[4] and C−Al−O[4] tethers have been previously reported. As part of a wider interest in the use of boron substituents in controlling reactivity,[7] we now report a *boron-tethered* (C−B−O) IMDA approach.[8] The general strategy that we envisaged first connects alkenyl boronic acids (or esters) **1** to a diene component to give alkenyl boronic esters **2** (Scheme 1).[9,7a] A C−B−O tethered IMDA reaction would then

* To whom correspondence may be sent. Fax: 416-978-5059. E-mail: rbatey@alchemy.chem.utoronto.ca.
[†] To whom correspondence concerning the crystallographic data should be addressed.

(1) For a review on intermolecular Diels−Alder reactions, see: Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 315−399.
(2) (a) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578−7579. (b) Sieburth, S. McN.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 7, 5279−5281.
(3) For reviews on silicon-tethered reactions including Diels−Alder reactions, see: (a) Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, 813−854. (b) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277.
(4) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595−6596.
(5) For reviews on intramolecular Diels−Alder reactions, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 513−550. (b) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187−238. (c) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183−234.
(6) For a review on sequential reactions, see: Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163.
(7) (a) Batey, R. A.; Lin, D.; Wong, A.; Hayhoe, C. L. S. *Tetrahedron Lett.* **1997**, *38*, 3699−3702. (b) Batey, R. A.; Pedram, B.; Yong, K.; Baquer, G. *Tetrahedron Lett.* **1996**, *37*, 6847−6850.
(8) Phenyl boronic acid has been elegantly used to tether a diene and a dienophile via an O−B−O linkage, see: (a) Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171−1172. (b) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634−644. (c) Shimada, S.; Osoda, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1254−1257.
(9) Intermolecular and intramolecular Diels−Alder reactions of alkenyl boranes and boronates have been described, see: (a) Lee, Y.-K.; Singleton, D. A. *J. Org. Chem.* **1997**, *62*, 2255−2258 and references therein. (b) Singleton, D. A. In *Advances in Cycloaddition*; Lautens, M., Ed.; Jai Press: Greenwich, CT, 1997; Vol. 4, pp 121−148. (c) Matteson, D. S.; Waldbillig, J. O. *J. Org. Chem.* **1963**, *28*, 366−369. (d) Evans, D. A.; Scott, W. L.; Truesdale, L. K. *Tetrahedron Lett.* **1972**, *2*, 121−124. (e) Martinez-Fresneda, P.; Vaultier, M. *Tetrahedron Lett.* **1989**, *30*, 2929−2932. (f) Singleton, D. A.; Lee, Y.-K. *Tetrahedron Lett.* **1995**, *36*, 3473−3476. (g) Lorvelec, G.; Vaultier, M. *Tetrahedron Lett.* **1998**, *39*, 5185−5188.
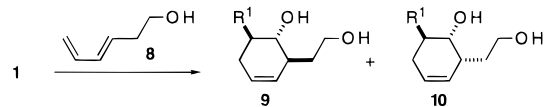
Scheme 1

Table 1. C−B−O Tethered [4 + 2] Reaction of **5**

entry	R[1]	method[a]	d.r.[b]	time, h	yield, %[c]
1	*n*Pr	A	65:35	48	66
2	*n*Bu	A	65:35	48	68
3	Ph	A	90:10	3	84
4	4-MeC$_6$H$_4$	A	90:10	4	83
5	4-MeOC$_6$H$_4$	A	85:15	6	78
6	3,4-(OCH$_2$O)C$_6$H$_3$	A	85:15	6	75
7	*n*Bu	B	70:30	48	65
8	Ph	B	90:10	3	83

[a] Method A: (i) **1** (R^2 = H) (1 equiv), **5** (2 equiv), THF, 4 Å mol. sieves, rt, o/n. (ii) PhCH$_3$, 5 mol % BHT, 190 °C. (iii) Me$_3$N(O), C$_6$H$_6$, 80 °C, 24 h; H$_2$O, 60 °C, 0.5 h. Method B: (i) **1** (R^2 = *i*-Pr) (1 equiv), **5** (1 equiv), PhCH$_3$, 5 mol % BHT, 190 °C. (ii) Me$_3$N(O), C$_6$H$_6$, 80 °C, 24 h; H$_2$O, 60 °C, 0.5 h. [b] The diastereomeric ratios (**6:7**) are based upon NMR analysis of the crude products. [c] Yields are for chromatographically purified material and are calculated from **1**.

provide the boracycles **3**. Transformation of the carbon−boron bond in **3**, using standard organoborane technology,[10] would then form a variety of functionalized cyclohexene derivatives **4**.

The requisite *E*-alkenyl boronic acids or esters **1** for this preliminary study, were readily synthesized via standard hydroboration methodology from the corresponding alkynes,[11] and oxidation of the C−B bond of **3**, with retention of stereochemistry, was carried out as a representative transformation. Sorbic alcohol **5** and 3,5-hexadiene-1-ol **8**[12] were used as prototypical diene components (Tables 1 and 2, respectively). The initial protocol (Method A) employed for the tethered IMDA reactions was to attach 2 equiv of diene per 1 equiv of dienophile. Thus, reaction of 2 equiv of the dienyl alcohol **5** with **1** (R$_2$ = H) in THF, in the presence of molecular sieves, provided the corresponding IMDA precursors **2** which were used without further purification (Table 1, entries 1−6). The key IMDA reaction was then accomplished in a degassed toluene solution, with 5 mol % of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a free radical inhibitor, using a sealed tube and a heating-bath temperature of 190 °C. Oxidation with trimethylamine-*N*-oxide and final hydrolysis then afforded the diastereomeric cyclohexene diols **6** and **7**, which were readily separable by column chromatography on a preparative scale. The reactions occur with complete regiocontrol, with the *endo* product **6** as the predominant diastereomer.[13] The presence of an activating aryl group on the dienophile results in faster and more highly

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(11) (a) Brown, H. C.; Campbell, J. B., Jr. *J. Org. Chem.* **1980**, *45*, 389−395. (b) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249−5255. (c) Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, 103−106.
(12) Martin, S. F.; Tu, C.; Chou, T. *J. Am. Chem. Soc.* **1980**, *102*, 5274−5279.

Table 2. C−B−O Tethered [4 + 2] Reaction of **8**

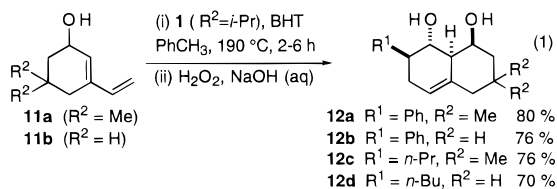| entry	R_1	method[a]	d.r.[b]	yield, %[c]
1	^nBu	A	25:75	80
2	CH_2OBn	A	20:80	83
3	Ph	A	20:80	80
4	^nBu	B	25:75	84
5	^iPr	B	20:80	80
6	Ph	B	20:80	85

[a] Method A: (i) **1** (R^2 = H) (1 equiv), **8** (2 equiv), THF, 4 Å mol. sieves, rt, o/n. (ii) $PhCH_3$, 5 mol % BHT, 190 °C, 3−4 h. (iii) $Me_3N(O)$, C_6H_6, 80 °C, 24 h; H_2O, 60 °C, 0.5 h. Method B: (i) **1** (R^2 = i-Pr) (1 equiv), **8** (1 equiv), $PhCH_3$, 5 mol % BHT, 190 °C, 3−4 h. (ii) $Me_3N(O)$, C_6H_6, 80 °C, 24 h; H_2O, 60 °C, 0.5 h. [b] Diastereomeric ratios (**9**:**10**) are based upon on NMR analysis of the crude products. [c] Yields are for chromatographically purified material and are calculated from **1**.

diastereoselective reactions (Table 1, entries 3−6). Overall, the *E*-alkenyl boronic ester acts as a masked *E*-enol dienophile. In comparison to existing tethered Diels−Alder methodology,[2−4] this approach uses the more air- and water-stable alkenyl boronic acids as precursors and leads to more synthetically versatile cycloadducts.

One drawback to the use of Method A is that 2 equiv of the diene per 1 equiv of dienophile are necessary. This limitation is readily overcome using a "dummy group" on the boronic ester precursors. Thus, in the second IMDA protocol (Method B), *direct* treatment of 1 equiv of diisopropyl boronates **1** (R^2 = i-Pr)[14] with 1 equiv of **5** in a sealed tube at 190 °C, and subsequent oxidation provides diols **6** and **7** (Table 1, entries 7 and 8). The yields and selectivity obtained in the two protocols are comparable.

The use of a longer tethering chain is exemplified by the use of 3,5-hexadiene-1-ol **8**, as the dienyl alcohol precursor (Table 2). For both Methods A and B, the IMDA reactions are more facile (3−4 h at 190 °C) than the examples shown in Table 1, and the diastereoselection is reversed, favoring formation of the *exo* products **10**.[13]

It is noteworthy that the reactions are readily amenable to scale-up, and can be run at relatively high concentrations (ca. 1 M). The utility of this methodology was also demonstrated for the formation of bicyclic diols **12**, with control of four contiguous stereogenic centers (eq 1). Thus, using diene **11**[15] and a modified
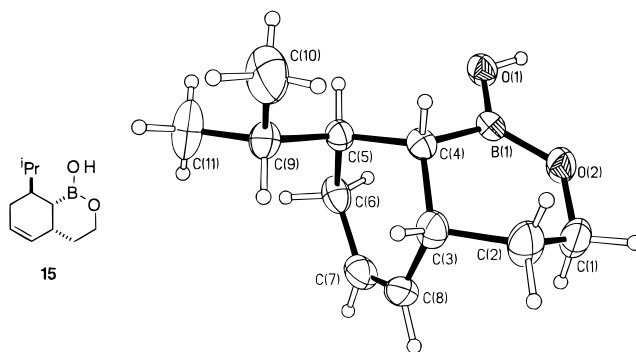

11a (R^2 = Me)
11b (R^2 = H)

12a R^1 = Ph, R^2 = Me   80 %
12b R^1 = Ph, R^2 = H   76 %
12c R^1 = n-Pr, R^2 = Me   76 %
12d R^1 = n-Bu, R^2 = H   70 %

Method B, several diols **12** were formed in each case as single diastereomers.[13] As anticipated for intramolecular Diels−Alder reactions, the addition of *gem* dimethyl groups in the tethering
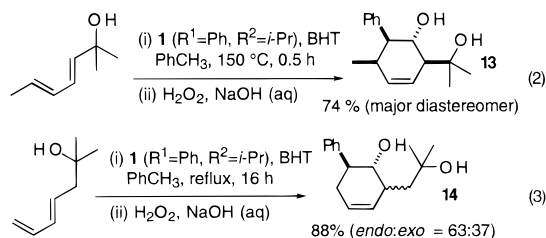

Figure 1. ORTEP diagram of **15**.

chain allowed the use of milder reaction conditions because of Thorpe-Ingold rate acceleration (eqs 2 and 3).[16]

(i) **1** (R^1=Ph, R^2=i-Pr), BHT
$PhCH_3$, 150 °C, 0.5 h
───────────────────
(ii) H_2O_2, NaOH (aq)

13
74 % (major diastereomer)   (2)

(i) **1** (R^1=Ph, R^2=i-Pr), BHT
$PhCH_3$, reflux, 16 h
───────────────────
(ii) H_2O_2, NaOH (aq)

14
88% (*endo*:*exo* = 63:37)   (3)

The tethered nature of these cycloadditions was confirmed by the absence of cycloaddition observed for alkenyl catechol or ethylene glycol boronates heated in the presence of either **5** or **8**. In this case the reduced lability of these cyclic boronates prevents tethering. Similarly, protection of **5** or **8** as their benzyl ethers and subsequent heating in the presence of alkenyl boronic acids did not result in the formation of cycloadducts. An X-ray structure[13] of a tethered boracycle **15**[17] was also obtained (Figure 1).

In summary, we have established an efficient new boron-tethered Diels−Alder reaction using alkenyl boronic esters as dienophilic components. The effect of the tether length on the efficacy and the mode of diastereoselectivity of the reaction was demonstrated. The ready availability of alkenyl boronic acids and the synthetic flexibility of the C−B bond in the cycloadducts is anticipated to provide access to a variety of functionalized cyclohexene derivatives and underscores the versatility of boronic acids as synthetic precursors. Further work on the utility of this approach, for [4 + 2] and other cycloaddition reactions of tethered boronic ester derivatives will be reported in due course.

Supporting Information Available: Experimental procedures for the preparation of **1**, **6**, **7**, **9**, **10**, **12**, **13**, **14**, and **15**. ^{1}H NMR and ^{13}C NMR spectra of **6**, **7**, **9**, **10**, **12**, **13**, **14**, and **15**. X-ray data of **6** (R_1 = n-Bu), **9** (R_1 = Ph), **12a**, and **15** (113 pages, print/PDF). X-ray crystallographic files, in CIF format, are available through the Internet only. See any current masthead page for ordering information and Web access instructions.

(13) The structures of **6** (R^1 = *n*-Bu), **9** (R^1 = Ph), **12a**, and **15** were confirmed by X-ray crystallography. The authors have deposited atomic coordinates for these compounds with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(14) Diisopropyl boronates were synthesized from the corresponding acids, see Supporting Information section.

(15) Hayakawa, K.; Aso, K.; Shiro, M.; Kanematsu, K. *J. Am. Chem. Soc.* **1989**, *111*, 5312−5320.

(16) **13** was isolated as a single diastereomer. However, crude NMR revealed the presence of presumably the *exo* diastereomer as a minor component (88:12 *endo/exo* ratio), but we were unable to isolate this compound.

(17) **15** was formed by slow hydrolysis of the corresponding boracyclic ester **3** (R^1 = R^3 = i-Pr, n = 2). Crystal Data for **15**: monoclinic, $P2_1/c$, colorless crystal, a = 10.3504(4) Å, b = 10.9465(3) Å, c = 10.9959(4) Å, β = 113.698(2)°, Z = 4, $R(F)$ = 0.0719, $R(wF^2)$ = 0.1575 for all 2328 independent reflections, [$R(F)$ = 0.0503, $R(wF^2)$ = 0.1446 for 1598 data with $F > 4\sigma(F_o)$], GOF = 1.094.