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Diels–Alder reactions of dienylboron compounds with unactivated dienophiles: an application of boron tethering for substituted cyclohexenol synthesis

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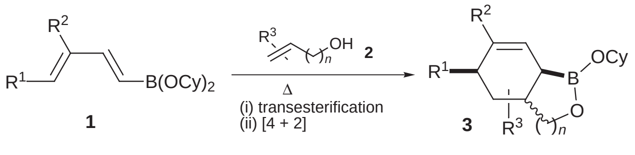
An efficient tethered intramolecular Diels–Alder reaction of 1,3-dienylboronates with various allyl and homoallyl alcohols under thermal conditions is described.

The use of Diels–Alder reactions is one of the most commonly encountered strategies for the formation of six-membered rings, particularly in natural product synthesis.[1,2] The reaction has been further augmented by using synthetic equivalents of either the diene or dienophile.[1] For instance, alkenylboron dienophiles have been used as synthetic equivalents to enols.[3–5] 1,3-Dienylboronates are versatile synthetic equivalents for hetero-subsituted dienes, since the allylboronate cycloadducts can be transformed to desirable substituted cyclohexene derivatives.[6] However, a major impediment to the use of 1,3-dienylboronate dienes in Diels–Alder reactions is the need for activated dienophile partners (*e.g. N*-phenylmaleimide or methylacrylate). Narasaka has demonstrated that phenylboronic acid can be used to create a temporary O–B–O tether between a diene and dienophile containing free hydroxy groups.[7] Inspired by Narasaka's work, we reasoned that tethering[8–10] *via* a C–B–O connection would enable the reaction of 1,3-dienylboron compounds with dienophiles containing hydroxy groups, such as allylic and homoallylic alcohols (*vide infra*). Here we report the first examples of Diels–Alder reactions of 1,3-dienylboron compounds with unactivated dienophiles.

Tethering of dienylboronate precursors **1** to a dienophilic component **2** allows *in situ* formation of mixed boronic esters, followed by intramolecular Diels–Alder reaction to the allylboracycles **3** (Scheme 1). Oxidation of the C–B bond in the adducts **3**, with retention of stereochemistry, leads to the formation of cyclohexenols, which are valuable precursors in natural porduct synthesis. Overall, **1** acts as a masked 1-hydroxydiene equivalent in the Diels–Alder reaction. In comparison to existing silicon-tethered Diels–Alder methodology, this approach uses the more readily synthesized dienylboronates as precursors. The use of a C–B–O rather than an O–B–O tether[7] is important, since in most cases O–B–O tethers are not applicable.

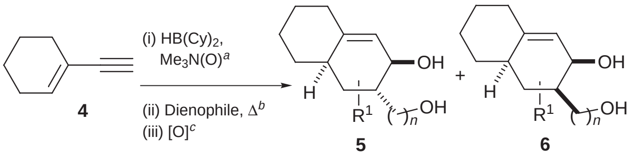
The dienylboronates **1** are formed *via* standard hydroboration methodology from the corresponding enynes. Thus, hydroboration of **4** and **7** with dicyclohexylborane afforded the corresponding dicyclohexyl(dienyl)boranes. The boron–cyclohexyl bonds were then preferentially oxidized with $Me_3N(O)$ to afford the desired dienylboronate (Table 1 and 2) without concomitant oxidation of the boron–diene bond.[6a,11] Since dienylboronates are subject to disproportionation, they were generally used *in situ* without purification. Thermal Diels–Alder reaction was conducted in the presence of an appropriate dienophile, 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 of the appropriate temperature. Oxidation with $Me_3N(O)$ or basic H_2O_2 then afforded racemic cyclohexene diols **5** and **6** in good yields (Tables 1 and 2).

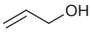
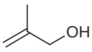
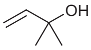
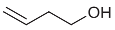
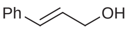
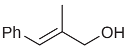
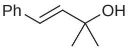
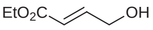
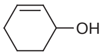
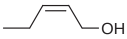


Scheme 1

The constraining effects of the tether both accelerate the rate of cycloaddition, and control the regio- and stereoselectivity of the reaction. We have not been able to isolate cycloadducts in those cases where the initial tethering step cannot occur. For instance, no cycloaddition reaction was observed between ethane-1,2-diyl dienyl boronates and cinnamyl alcohol, allyl alcohol or methyl cinnamyl ether, even after prolonged heating at 220 °C.

Table 1 Tethered Diels–Alder reactions of **4**



Entry	Dienophile	T/°C	t/h	Yield (%)[d]	Dr (**5** : **6**)[e]
1		190	48	60[f]	40 : 60
2		190	48	40	50 : 50
3		190	5	82	55 : 45
4		190	120	71	89 : 11
5		190	6	75	95 : 5
6		190	12	68	27 : 73
7		150	0.5	62	85 : 15
8		80	16	77	84 : 16
9		190	24	70	25 : 75
10		190	36	50	[g]

[a] 1 equiv. $HB(Cy)_2$, THF, 0 °C to room temp., 1 h; 2 equiv. $Me_3N(O)$, THF, 0 °C to room temp., 2 h. [b] [Boronate] = *ca*. 0.3 м, $PhCH_3$, 5 mol% BHT. [c] 5 equiv. $Me_3N(O)$, C_6H_6, 80 °C, 24 h or 3 equiv. NaOH/3 equiv. H_2O_2, $THF–H_2O$, 2 h. [d] Yields are for chromatographically purified material and are calculated from **4**. [e] The diastereomeric ratios (**5** : **6**) are based upon NMR analysis of the crude products. [f] 6% of the corresponding enone was isolated. [g] Only **5** was isolated along with 6% of a byproduct presumably derived from **6**.

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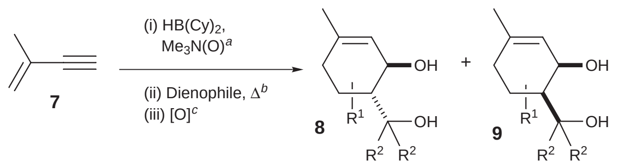
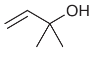
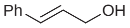
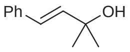
Table 2 Tethered Diels–Alder reactions of **7**



Entry	Dienophile	T/°C	t/h	Yield (%)^d	Dr (**5** : **6**)^e
1		190	1	81	55 : 45
2		190	6	65	75 : 25
3		150	0.5	62	75 : 25

^{a} 1 equiv. HB(Cy)$_2$, THF, 0 °C to room temp., 1 h; 2 equiv. Me$_3$N(O), THF, 0 °C to room temp., 2 h. ^{b} [Boronate] = *ca.* 0.3 M, PhCH$_3$, 5 mol% BHT. ^{c} 5 equiv. Me$_3$N(O), C$_6$H$_6$, 80 °C, 24 h or 3 equiv. NaOH/3 equiv. H$_2$O$_2$, THF–H$_2$O, 2 h. ^{d} Yields are for chromatographically purified material and are calculated from **7**. ^{e} The diastereomeric ratios (**8** : **9**) are based upon NMR analysis of the crude products.

Although the tethered reactions are completely regioselective, they occur with varying diastereoselectivity depending on the substituents present on the dienophile. The presence of an activating electron-withdrawing group on the dienophile results in faster reactions (Table 1, entries 5 and 7). In comparison to the reaction using allyl alcohol (Table 1, entry 1), reaction with activated *E*-allylic alcohols favours the formation of the *trans*-substituted compounds **5** (Table 1, entries 5 and 8). This is expected, since the activating phenyl or ester groups are *endo* with respect to the diene in the transition state. The use of a longer tethering chain as exemplified by homoallyl alcohol (Table 1, entry 4) results in longer reaction times compared to allyl alcohol (Table 1, entry 1), but again favours the *trans*-substituted adduct **5**. Conversely, the presence of a *gem*-dimethyl group in the tethering chain results in shorter reaction times, because of the Thorpe–Ingold effect (Table 1, entries 3 and 6). The stereochemistry of compound **5** (Table 1, entry 5)[12] and compound **6** (Table 1, entry 9)[13] were confirmed by single crystal X-ray analysis. In the latter case the dienylboronate is delivered to the same face of the cyclohexenol ring as the hydroxy group.

Dienylboronates derived from **7** were also used as Diels–Alder precursors (Table 2). The yields are slightly lower in these cases due to the greater propensity of the dienylboronate towards polymerization. One of the enantiomers of compound **8** (Table 2, entry 1) has been used as an intermediate in the synthesis of *ent*-Δ^1-tetrahydrocannabinol.[14]

In summary, we have demonstrated a new dienylboronate tethered Diels–Alder reaction, one of the few methods allowing the use of unactivated dienophiles. The effect of the substituents on the dienophile and the length of tether on the efficacy and diastereoselectivity of the reaction was investigated. The ready availability of various enynes as precursors and the synthetic flexibility of the C–B bond in the cycloadducts is anticipated to provide access to a variety of functionalized cyclohexene derivatives.

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Notes and references

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4 For examples of the use of alkenylboron compounds as dienophiles in intermolecular Diels–Alder reactions, see: D. A. Singleton, in *Advances in Cycloaddition*, ed. M. Lautens, JAI Press, Greenwich, CT, 1997, vol. 4, pp. 121–148.

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12 *Crystal data* for **5**·0.5(H$_2$O): C$_{17}$H$_{22}$O$_2$·0.5(H$_2$O), M = 267.35, orthorhombic, a = 20.2986(7), b = 5.8725(3), c = 25.2100(14) Å, U = 3005.1(2) Å^3, T = 293 K, space group $Pca2_1$ (no. 29), Z = 8, μ(Mo-Kα) = 0.077 mm^{-1}, 29314 reflections measured, 3874 unique (R_{int} = 0.064) which were used in all calculations. The final $wR(F^2)$ was 0.1610 (all data). Single crystals of **5**·0.5(H$_2$O) were obtained *via* slow evaporation of a solution of **5** in EtOAc–hexanes, mounted in inert oil and transfered to the diffractometer. The structure was solved using direct methods and refined by full-matrix least-squares on F^2.

13 *Crystal data* for **6**: C$_{14}$H$_{22}$O$_2$, M = 222.32, monoclinic, a = 6.0121(2), b = 12.1615(4), c = 16.7127(5) Å, U = 1221.96 (7) Å^3, T = 293 K, space group $P2_1/c$ (no. 14), Z = 4, μ(Mo-Kα) = 0.078 mm^{-1}, 10537 reflections measured, 2468 unique (R_{int} = 0.038) which were used in all calculations. The final $wR(F^2)$ was 0.1553 (all data). Single crystals of **6** were obtained *via* slow evaporation of a solution of **6** in EtOAc–hexanes, mounted in inert oil and transfered to the diffractometer. The structure was solved using direct methods and refined by full-matrix least-squares on F^2. CCDC 182/1161.

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