Self-Activation and 1,8-Stereoinduction in a Boronate-substituted Dienophile

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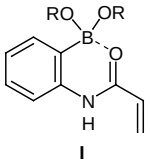
Abstract: The [4+2] cycloaddition of *ortho*-boronoanilide dienophile **4** with cyclopentadiene was found to proceed faster than both its *para* isomer **8** and the unsubstituted derivative **6**, thereby confirming that self-activation by internal coordination is operative in the case of **4**. Chiral boronic esters derivatives **9** and **10** provided a small level of remote 1,8-stereoinduction. These results show that dialkoxyboronic esters can operate as weak, internal Lewis acids and activate carbonyl-containing functionalities in cycloaddition reactions.

Key words: Lewis acids, Diels–Alder reactions, substituent effects, chiral auxiliaries, stereoselective synthesis

Dialkoxyboronic esters are a priori very weak Lewis acids.[1,2] The possibility of employing chiral diols as boronate substituents, however, constitutes a significant advantage in the use of boronic esters as Lewis acids for cycloadditions and other reactions. We were interested in investigating the potential role of a dialkoxyboronic ester as an internal activator and as a source of 1,8-stereoinduction[3,4] in a model Diels–Alder reaction using modified acrylamide dienophiles of type I (Figure 1).

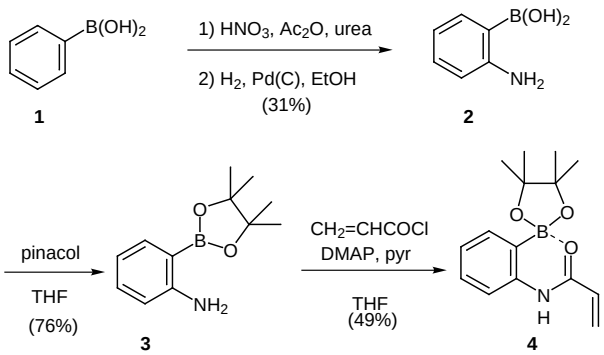


I

Figure 1

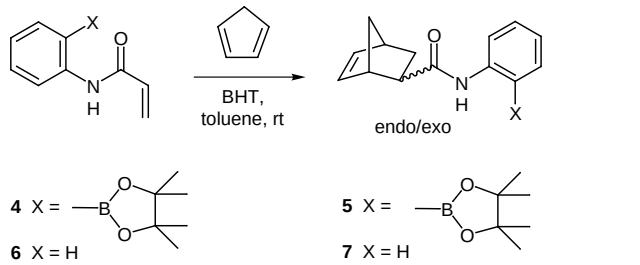
The pinacolboronate-substituted dienophile **4**[5] required for studying the carbonyl activating effect of the boronic ester was easily made in four steps from phenylboronic acid (Scheme 1).[6] The corresponding dienophile **6**[5] lacking the boronate group was also made as a reference compound for a qualitative comparison of relative reaction rates in a model Diels–Alder reaction with cyclopentadiene.

Although dienophile **4** is more sterically hindered, the data shows that it does react faster than **6** and with increased *endo*/*exo* selectivity in the resulting adducts **5** (Table).[5] These results are consistent with a small self-activation effect by internal coordination between the boronic ester and the carbonyl group in dienophile **4**. To rule out the possibility that the activation may be due to the electron-withdrawing effect of the boronate group on the reactivity of the acrylamide dienophile, a competitive kinetic experiment was performed whereby **4** and the corresponding *para*-substituted isomer **8**[5,6] were allowed to react simultaneously with excess cyclopentadiene (Scheme 2). The proportion of components in the reaction mixture confirmed the faster consumption of **4** and its consequent faster conversion into cycloadducts.[5] This result further confirms that self-activation by internal coordination is operative in the case of *ortho*-substituted dienophile **4**.



Scheme 1 Preparation of dienophile **4**

Table Relative Speed and *endo*/*exo* Ratios from Diels–Alder Reactions of **4** and **6**.[a]



	6		4	
Time (h)	s.m.:adduct	*endo*:*exo*	s.m.:adduct	*endo*:*exo*
1	no reactions		2.7:1	3.8:1
6	1:0.4	2.5:1	1.2:1	3.8:1
48	1:5	2.8:1	1:13	4.3:1

[a] Ratios of starting materials (s.m.) and cycloadducts were measured by proton NMR on the crude reaction mixtures.

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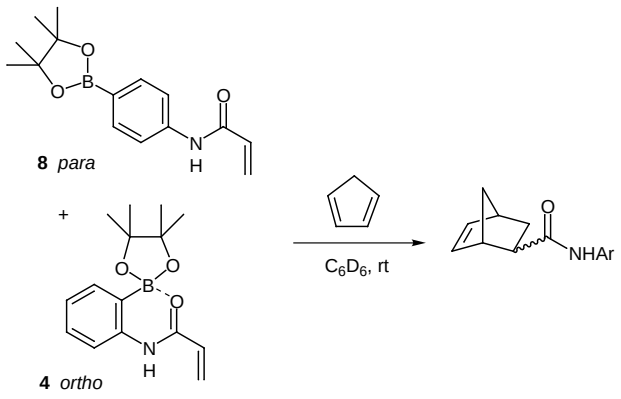


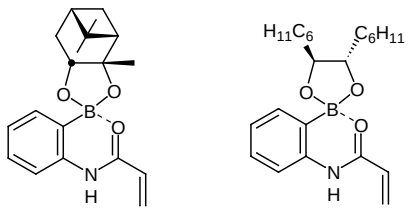
para s.m. : *ortho* s.m. : *para* adducts : *ortho* adducts (%)[a]

Start point:	55	:	45	:	0	:	0
After 17 d:	43	:	11	:	10	:	36

[a] Relative percentages of components as measured by signal integration on proton NMR spectra of the crude reaction mixtures. (s.m. = starting material)

Scheme 2 Competitive kinetic experiment between dienophiles **4** and **8**.

We then turned our attention towards the appealing possibility that internal coordination could serve at communicating stereochemistry in a long-range fashion. There are very few examples on remote stereoinduction beyond a 1,7 relative relationship between the inducing center and the reactive one.[3] In the present case, 1,8-stereoinduction could be transmitted via internal carbonyl coordination. Thus, chiral dienophiles **9** and **10** (Figure 2) were synthesized from the corresponding enantiopure diols in a manner analogous to **4**.



9 **10**

Figure 2

The level of 1,8-stereoinduction observed, however, was only minimal. The highest value of 18% diastereomeric excess originated from the *exo* cycloadduct of dienophile **10**. Inspection of the X-ray crystal structure of dienophile **9**, displayed as an ORTEP in Figure 3,[7] provides some insight on explaining the low level of 1,8-stereoinduction in these systems. Although the boronic ester is coordinated to the acrylamide carbonyl to form a tetrahedral boronate,[8] the ester substituents appear to be too distant from the dienophile to allow effective transmission of stereochemistry. Specifically in the case of **9**, which provided diastereoselectivities below 10%, Figure 3 shows that the bulkiest part of the pinanedioxy group is pushed away from the reaction center. This arrangement leaves only the C3 hydrogen and the C2 methyl as discriminating groups for effecting diastereofacial selectivity. Interestingly, this observation suggests that the presence of a bulky group at C16 (*ortho* to the boronic ester) could induce a preference for the opposite boronate configuration. Such an arrangement would place the bulk of the pinane group *syn* to the acrylamide moiety, hence in closer proximity to induce a potentially more effective transfer of chirality.

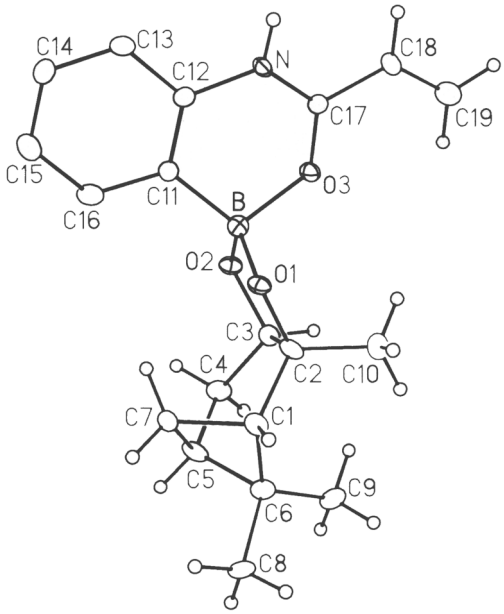


Figure 3 Computer generated ORTEP drawing from the X-ray coordinates of chiral dienophile **9**.

Although reaction acceleration and 1,8-stereoinduction were modest in this particular example of Diels–Alder cycloaddition, this work shows that non-activated dialkoxyboronic esters can operate as weak, internal Lewis acids and activate carbonyl-containing functionalities towards cycloaddition reactions.

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References

(1) Matteson, D. S.; Allies, P. G. *J. Organomet. Chem.* **1973**, *54*, 35.
(2) (a) Diaryloxy or acyloxy boronic esters are more acidic and have been used in several catalysts for asymmetric synthesis. For a noticeable example on a dialkoxyboronic ester catalyst

based on a tartrate substituent, see: Loh, T.-P.; Wang, R.-B.; Sim, K.-Y. *Tetrahedron Lett.* **1996**, *37*, 2989. (b) Tartrate boronic esters, however, are considered moderately activated by the electron-withdrawing ester groups.

(3) For a review on remote stereoinduction, see: Mikami, K.; Shimizu, M.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917.

(4) For a recent example of remote asymmetric induction using chiral boronates, see: Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3362.

(5) (a) All compounds reported herein were obtained in a high state of purity and exhibited spectral data (NMR, MS) in accord with proposed structures. Characterization data for dienophile substrates **4**, **6**, **8**: Pinacol *ortho*-boronoanilide **4**: white solid, mp: 168–170 °C; ^{1}H NMR (Acetone-d_6, 400 MHz): δ = 10.34 (br s, 1 H), 8.06 (m, 1 H), 7.67 (d, *J* = 8 Hz, 1 H), 7.37 (m, 1 H), 7.10 (apparent t, *J* = 8 Hz, 1 H), 6.38 (m, 2 H), 5.82 (dd, *J* = 7 Hz, 5 Hz, 1 H), 1.38 (s, 12 H); ^{13}C NMR (Acetone-d_6, 100 MHz): δ = 164.1, 143.6, 136.0, 135.9, 132.2, 131.8, 131.7, 127.9, 127.8, 124.6, 124.5, 119.0, 84.1, 84.0, 25.6, 25.5; ^{13}C NMR (Benzene-d_6, 100 MHz): δ = 163.2, 145.3, 136.4, 133.1, 132.8, 125.8, 123.4, 119.6, 83.9, 24.8. A very slight peak duplication effect, ca. 0.05 ppm, was observed for arene carbons in acetone. This may be due to a slow competing effect from this coordinating solvent. ^{11}B NMR (Benzene-d_6, 64 MHz): δ = 30.1; IR (CH_2Cl_2 cast, cm^{-1}): 3316 (m, N-H), 3058 (w, C*sp*^{2}-H), 2970 (s, C*sp*^{3}-H), 1646 (s, C=O), 731 (s, *o*-sub Ar); HRMS (EI): *m/z* calcd for $C_{15}H_{20}NO_3{}^{11}B$: 273.15363; found: 273.15376. Acrylanilide **6**:[5b] ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.58 (m, 2 H), 7.31 (m, 2 H), 7.18 (br s, 1 H), 7.10 (m, 1 H), 6.43 (d, *J* = 17 Hz, 1 H), 6.25 (dd, *J* = 17 Hz, 10.2 Hz, 1 H), 5.78 (d, *J* = 10 Hz, 1 H). ^{13}C ($CDCl_3$, 75 MHz): δ = 164.0, 140.2, 132.8, 129.5, 126.9, 124.4, 120.3. Pinacol *para*-boronoanilide **8**: ^{1}H NMR (Acetone-d_6, 300 MHz): δ = 7.75 (AB, *J* = 9 Hz, 2 H), 7.68 (AB, *J* = 9 Hz, 2 H), 6.46 (dd, *J* = 17 Hz, 10 Hz, 1 H), 6.34 (dd, *J* = 16 Hz, 3 Hz, 1 H), 5.70 (dd, *J* = 10 Hz, 3 Hz, 1 H), 1.31 (s, 12 H); ^{13}C NMR (Acetone-d_6, 100 MHz): δ = 164.1, 142.8, 136.3, 136.2 (broad weak signal, C-B), 132.7, 127.4, 119.2, 84.3, 25.2; ^{11}B NMR (Benzene-d_6, 64 MHz): δ = 30.8; IR (CH_2Cl_2 cast, cm^{-1}): 3303 (m, N-H), 3102 (w, C*sp*^{2}-H), 2978 (m, C*sp*^{3}-H), 1667 (s, C=O), 1635 (s, C=C alkyl), 1593 (s, C=C aromatic), 1361 (vs, B-O), 860 (m, *p*-sub Ar); HRMS (EI): *m/z* calcd for $C_{15}H_{20}NO_3{}^{11}B$: 273.15363, found: 273.15381. (b) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *10*, 3583.

(6) *ortho*-Aminophenylboronic acid can be obtained from various commercial sources or prepared according to: (a) Nitration: Seaman, W.; Johnson, J. R. *J. Am. Chem. Soc.* **1931**, *53*, 711. (b) Hydrogenation: Groziak, M. P.; Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc.* **1994**, *116*, 7597; the *para*-aminophenylboronic acid was obtained from Combi-Blocks.

(7) X-ray crystallographic data have been deposited to the Cambridge Crystallographic Data Centre (file number: CCDC 166880).

(8) For an example of internally coordinated alpha-acetamidomethylboronate, see: Matteson, D. S.; Michnick, T. J.; Willet, R. D.; Patterson, C. D. *Organometallics* **1989**, *8*, 726.