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Letters

Computational evaluation of asymmetric Diels–Alder reactions of vinylboranes with chiral dienes

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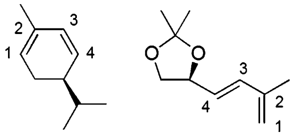
Abstract—The asymmetric Diels–Alder reactions of dichlorovinylborane and vinyl-9-BBN with two chiral dienes have been studied theoretically. Calculations suggest high reactivity and regio- and stereoselectivity could be achieved in these processes giving the *anti para endo* product. This class of reactions represents a potential stereoselective approach to a variety of chiral carbocycles.

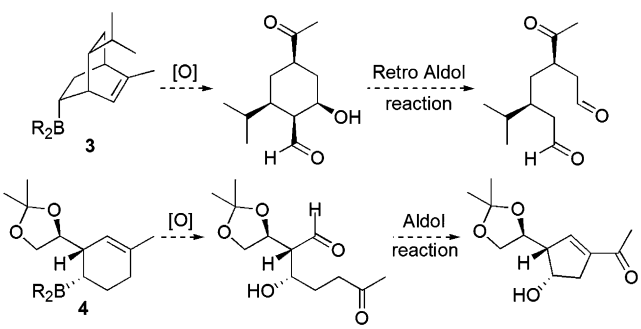
The design of novel reactions is a challenging task for organic chemists. While most methodologies are still being developed based on trial and error experiments, in the past years efforts to guide and expedite the design of novel reagents and catalysts using computers have been made.[1] The cycloaddition reactions of vinyl- and alkynylboranes have been recently investigated using experimental[2] and computational[3] techniques. These reagents constitute synthetic equivalents of a number of organic compounds such as enols, enamines, and ketenes and also exhibit striking structural properties which control their selectivity. Therefore, we believe the cycloadditions of boron-substituted alkenes and alkynes should be further explored. We have recently reported the computer-aided design of chiral vinylboranes as enantioselective dienophiles.[4] In this communication we address the theoretical evaluation of the Diels–Alder reactions of vinylboranes with chiral dienes as a possible novel transformation for the enantiospecific construction of optically pure carbocyclic building blocks. We chose (*R*)-(−)-α-phellandrene (**1**) and diene **2** as the chiral dienes (Fig. 1). These readily available compounds and related systems have been used in several Diels–Alder reactions, exhibiting variable degrees of selectivity.[5]



1 **2**

Figure 1. Chiral dienes used in this study.

The highly functionalized cyclohexenes obtained in the [4+2] cycloadditions of these dienes with vinylboranes could be transformed into useful intermediates for asymmetric synthesis (Scheme 1). For example, the oxidation of cycloadduct **3** and subsequent retro aldol reaction of the resulting β-hydroxyaldehyde could lead to a branched open chain with various carbonyls which



Scheme 1. Possible transformations for the Diels–Alder adducts.

Keywords: DFT study; Asymmetric Diels–Alder reactions; Vinylboranes.

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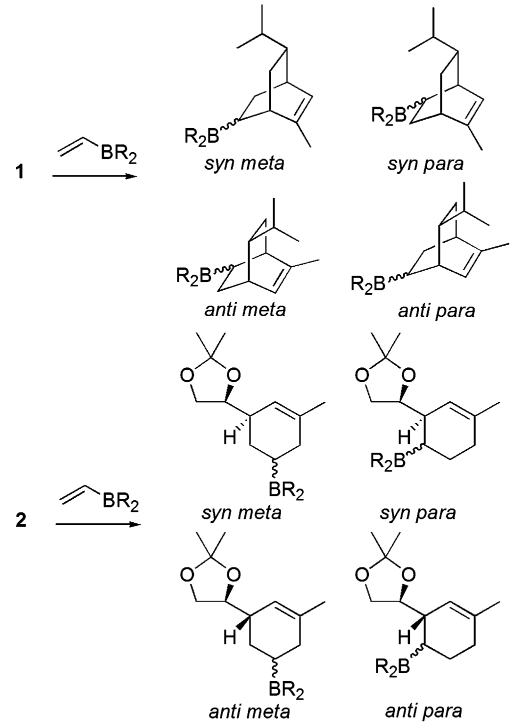
could be easily differentiated. Similar transformations, such as an oxidation followed by an aldol reaction, can be proposed for compound **4** to generate polyoxygenated carbon skeletons.

We investigated the outcome of the Diels–Alder reactions of dienes **1** and **2** with dichlorovinylborane (**a**) and vinyl-9-BBN (**b**) as the dienophiles in order to predict their reactivity and selectivity (Scheme 2). These reactions can generate eight diastereoisomeric products corresponding to the different modes of addition (*syn*/*anti*, *endo*/*exo*, and *meta*/*para*).[6]

We optimized the geometries of the reactants and the transition structures (TSs) and calculated the activation energies using GAMESS[7] with the B3LYP[8] functional and the 6-31G* basis set,[9] which gives good results for pericyclic reactions.[10]

The initial geometries of the TSs were obtained by manual distortion of the geometries of the products toward the starting materials by stretching the C1–C6 and C2–C3[11] bonds to 2.2 Å. For the more flexible diene **2** we carried out manual conformational searches for each approximation by varying the dihedral angle between C-3 and the allylic oxygen to generate new input structures which were optimized with AM1. The located TSs were then reoptimized using RHF/3-21G and B3LYP/6-31G* to find the global minimum TSs.

The computed activation energies for the processes under study are similar to the ones calculated for other Diels–Alder reactions of vinylboranes that take place under standard experimental conditions (Table 1).[2a,d,e]



Scheme 2. Diels–alder reactions of chiral dienes **1** and **2** with dichlorovinylborane (**a**) (R = Cl) and vinyl-9-BBN (**b**) (R,R = 9-BBN).

Table 1. Zero-point corrected B3LYP/6-31G* activation energies (in kcal mol^{-1}, relative energies in parentheses) for the Diels–Alder reactions of chiral dienes **1** and **2** with dichlorovinylborane (**a**) and vinyl-9-BBN (**b**)

TS	$\Delta E_0^{\ddagger}$	TS	$\Delta E_0^{\ddagger}$
1a-AMN	18.98 (2.13)	**1b-AMN**	24.38 (3.53)
1a-AMX	20.91 (4.06)	**1b-AMX**	24.47 (3.61)
1a-APN	16.84 (0.00)	**1b-APN**	20.86 (0.00)
1a-APX	18.69 (1.85)	**1b-APX**	23.95 (3.09)
1a-SMN	19.88 (3.04)	**1b-SMN**	25.76 (4.90)
1a-SMX	22.33 (5.49)	**1b-SMX**	26.59 (5.73)
1a-SPN	19.16 (2.31)	**1b-SPN**	23.72 (2.86)
1a-SPX	21.66 (4.81)	**1b-SPX**	27.39 (6.53)
2a-AMN	18.86 (1.75)	**2b-AMN**	22.30 (0.97)
2a-AMX	20.13 (3.01)	**2b-AMX**	22.82 (1.49)
2a-APN	17.11 (0.00)	**2b-APN**	21.33 (0.00)
2a-APX	17.76 (0.64)	**2b-APX**	22.73 (1.39)
2a-SMN	18.11 (1.00)	**2b-SMN**	21.63 (0.29)
2a-SMX	19.98 (2.86)	**2b-SMX**	22.69 (1.35)
2a-SPN	18.51 (1.40)	**2b-SPN**	22.06 (0.73)
2a-SPX	20.10 (2.98)	**2b-SPX**	22.52 (1.19)

This indicates reasonable rates should be expected, particularly for reactions with the more reactive dienophile dichlorovinylborane. In addition, good to excellent regio- and stereoselectivities were calculated, being the *anti para endo* approximation favored for both dienes. (R)-(−)-α-phellandrene is predicted to exhibit excellent selectivity with dichlorovinylborane (**a**) and vinyl-9-BBN (**b**). The products arising from the **1a-APN** and **1b-APN** TSs should be obtained almost exclusively (91% and 98%, respectively).[12,13] On the other hand, diene **2** is calculated to be more selective with dichlorovinylborane (**a**), giving the **2a-APN** product as the major isomer.

Figure 2 shows the most stable TSs for the reaction of **1** with dichlorovinylborane (**a**) and vinyl-9-BBN (**b**). As has been found before, the geometries of the located TSs are highly asynchronous with longer C1–C6 than C2–C3 distances. The *anti* facial diastereoselectivity can be rationalized by considering the approach of the dienophile from the less congested face of the diene π system, that is, *anti* to the bulky isopropyl group of **1**. In addition, the lower energy of *endo* TSs is in accordance with stronger non-classical [4+3] C6-B secondary

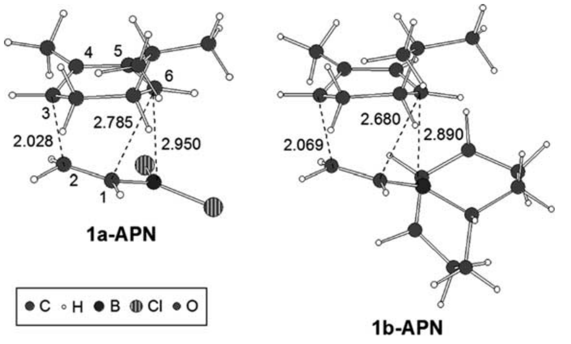


Figure 2. *anti para endo* TSs for the reactions of **1** with dichlorovinylborane (**a**) and vinyl-9-BBN (**b**).

orbital interactions (SOIs), which are supported by the calculated C6-B NBOs (see Supplementary data).[14] For instance, for **1a-APN** and **1b-APN** TSs, C6-B NBOs are 0.08 and 0.09, respectively, which are significantly higher than the typical values corresponding to *exo* TSs (ca. 0.04). The factors controlling the regiochemistry of these reactions are not obvious. The analysis of the close contacts suggests that the *meta* pathways are destabilized by repulsive steric interactions between the ligands on the boron atom and the atoms in the diene. FMO also support the calculated *para* selectivity since coefficients on the molecular orbitals indicate C-1 of the diene and the β carbon of the vinylborane should exhibit the stronger bonding interaction in the TSs.

For diene **2**, the facial diastereoselectivity seems to result from a fine combination of electronic and steric effects. In agreement with previous theoretical studies,[15] we have found that the facial selectivity cannot always be predicted based on the conformation of the ground states of the reactants. It is thus essential to locate all the TSs in order to anticipate the outcome of the reaction and investigate the origin of the selectivity. In our case, the diene moiety is predicted to experience a conformational switch during the course of the reaction, adopting different conformations in the TSs depending on which face the dienophile approaches. The most stable TS for each approximation (*anti* and *syn*) are depicted in Figure 3 for the reaction with dichlorovinylborane (**a**).

To minimize steric clashes, in the *anti para endo* TS (**2a-APN**) the dihedral angle between the allylic oxygen and C-3 is 12°, while for the *syn meta endo* TS (**2a-SMN**) it is −170°. In all the TSs for this reaction the allylic oxygen is approximately in the plane of the diene, being nearly '*syncoplanar*' in *anti* TSs and '*anticoplanar*' in *syn* TSs. In this way, the less sterically demanding group on the allylic carbon (hydrogen) is always pointing toward the incoming dienophile, allowing the π system of the diene to be attacked from the less hindered face. Figure 4 shows a schematic representation of such situation. These data suggest both steric and electronic effects contribute to favor the *anti* reaction pathways of this reaction.

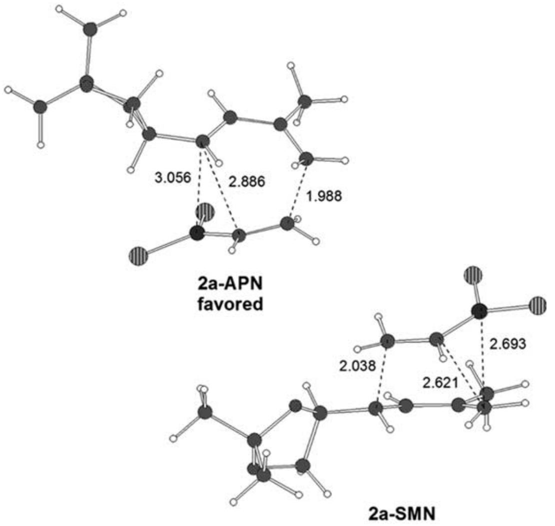


Figure 3. *anti para endo* and *syn meta endo* TSs for the reaction between **2** and dichlorovinylborane (**a**).

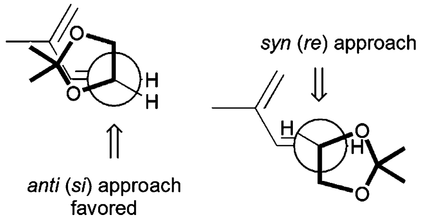


Figure 4. Preferred conformation adopted by diene **2** in the TSs for the reaction with dichlorovinylborane (**a**).

The low energy difference between the *endo* and *exo* approximations for the *anti para* TSs corresponding to diene **2** could be attributed mainly to the small difference in C6-B overlap, as calculated by the NBOs for **2a-APN** and **2a-APX** (0.07 and 0.05, respectively).

Once more, for this diene no single effect seems to dominate the predicted regioselectivities. Repulsive steric interactions between the ligands on the boron of the vinylborane and the atoms of the diene seem to be involved in *meta* TSs, making the *para* TSs more stable. In addition, HOMO/LUMO interactions agree with the computed *para* regioselectivity. A larger molecular orbital coefficient for C-1 of diene **2** suggests this atom should exhibit a stronger overlap with the terminal carbon of the vinylborane, favoring *para* TSs.

In summary, we have evaluated the Diels–Alder reactions of chiral dienes **1** and **2** with dichlorovinylborane and vinyl-9-BBN with computational DFT techniques. These reactions are predicted to show high reactivity and good to excellent regio- and stereoselectivities. The conformation of the acyclic diene **2** seems to switch depending on which face the dienophile attacks, showing that the selectivity of these reactions cannot be predicted based on the conformation of the ground state. Instead, they ought to be studied based upon transition state modeling. We hope this class of reactions prove to be useful as a novel route for the enantioselective preparation of chiral carbocycles. Further studies on the cycloaddition reactions of vinylboranes are being performed in our group and will be reported in due course.

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Supplementary data

Selected distances (in Å) and bond orders and thermochemical data (kcal/mol) for all the transition structures studied in the paper. Coordinates and absolute energies (in hartrees), including ZPE, and number of imaginary frequencies of all stationary points reported in the paper; values of imaginary frequencies of all TSs. B3LYP/6-31G* optimized geometries for all the TSs studied in the paper. Energies and atomic coefficients of the frontier molecular orbitals of the reactants. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.050.

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11. TS numbering (see Fig. 2).
12. Ratios were computed using Boltzmann factors based on the zero-point energy corrected activation energies and are of qualitative value.
13. The reaction of **1** with α-chloroacrylonitrile yielded a mixture of three isomeric ketone products in a 84:14:1 ratio (Ref. 5a), which suggests vinylboranes could be more efficient than other ketene equivalents.
14. NBO analysis was performed using the NBO 4.M program interfaced to the Jaguar 4.2 program (Jaguar 4.2, Schrodinger, Inc., Portland, Oregon, 2000).
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