

A promising enantioselective Diels–Alder dienophile by computer-assisted rational design: 2,5-diphenyl-1-vinyl-borolane

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Summary

Several chiral vinylboranes have been theoretically evaluated as enantioselective Diels–Alder dienophiles. Theoretical results suggest that optically pure 2,5-diphenyl-1-vinyl-borolane should be the reagent of choice for performing such transformations efficiently.

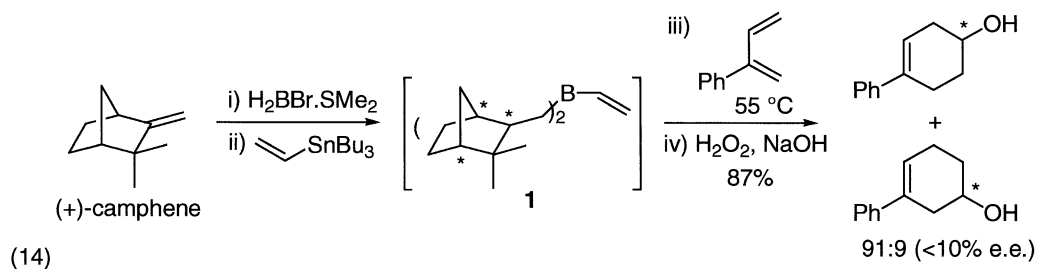
Singleton and co-workers reported the first Diels–Alder reaction of a chiral vinylborane in 1992 [1]. The reaction, which involved the use of vinylborane **1**, generated the para regioisomer almost exclusively but with poor enantiomeric excess (Scheme 1). Later on, several examples of enantioselective Diels–Alder reactions [2] and 1,3-dipolar cycloadditions [3] of chiral vinylboronates and vinylidioxaborocines were reported. However, all these compounds gave modest enantioselectivities, probably due to the distance between the stereocenters and the olefin [4]. To our knowledge, no progress on the enantioselective version of the [4 + 2] cycloadditions of dialkylvinylboranes has appeared in the literature. The borylcyclohexenes generated in these reactions can be converted into synthetically useful products which are not available through direct Diels–Alder reactions [5]. The potential of such processes as a means of obtaining versatile chiral building blocks for asymmetric synthesis could be spectacular.

Since the experimental development of reagents can be very time-consuming, we used computational methods for the rational design of chiral vinylboranes as enantioselective dienophiles. We hoped that

the results of previous theoretical studies on cycloaddition reactions of vinylboranes would help us to achieve this goal [6]. We envisioned that structurally rigid dialkylvinylboranes with stereocenters directly attached to the boron would control the selectivity efficiently. Based on this premise, we selected the ligands shown in Chart 1. In principle, compounds **2–4** could be prepared from (+)- α -pinene, (+)-2-carene and (+)-3-carene respectively, in a sequence analogous to the one used for **1** (Scheme 1). The allylboranes synthesized from these terpenes are very efficient reagents for enantioselective allylboration [7]. Although boranes **2–4** could exhibit some conformational flexibility, steric clashes between the ligands should constrain their conformations. Since cyclic dienophiles might present higher rigidity, borolanes **5** and **6** were also studied. Their C_2 symmetry further reduces the number of conformations available. Masamune [8] and Reetz [9] described the synthesis and applications of enantiomerically pure 2,5-dimethyl- and 2,5-diphenylborolane derivatives in several useful asymmetric transformations.

We started by studying the Diels–Alder reactions with cyclopentadiene because it is readily available and highly reactive, though it sometimes shows low *endo:exo* selectivities. These [4 + 2] cycloadditions can lead to four diastereoisomeric boranes which arise

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Scheme 1. Diels-Alder reaction of a chiral vinylborane.

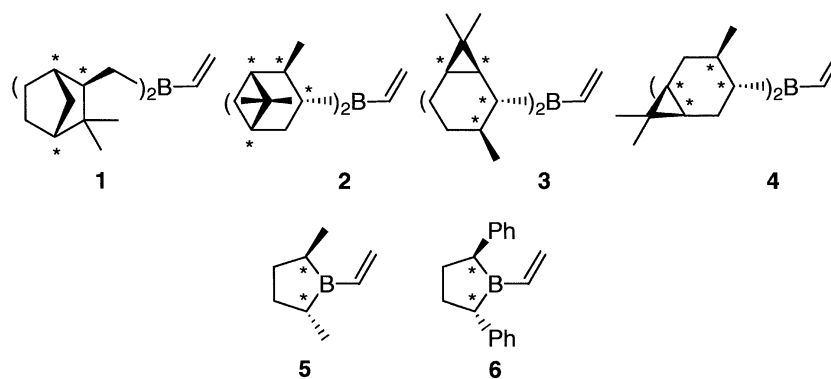
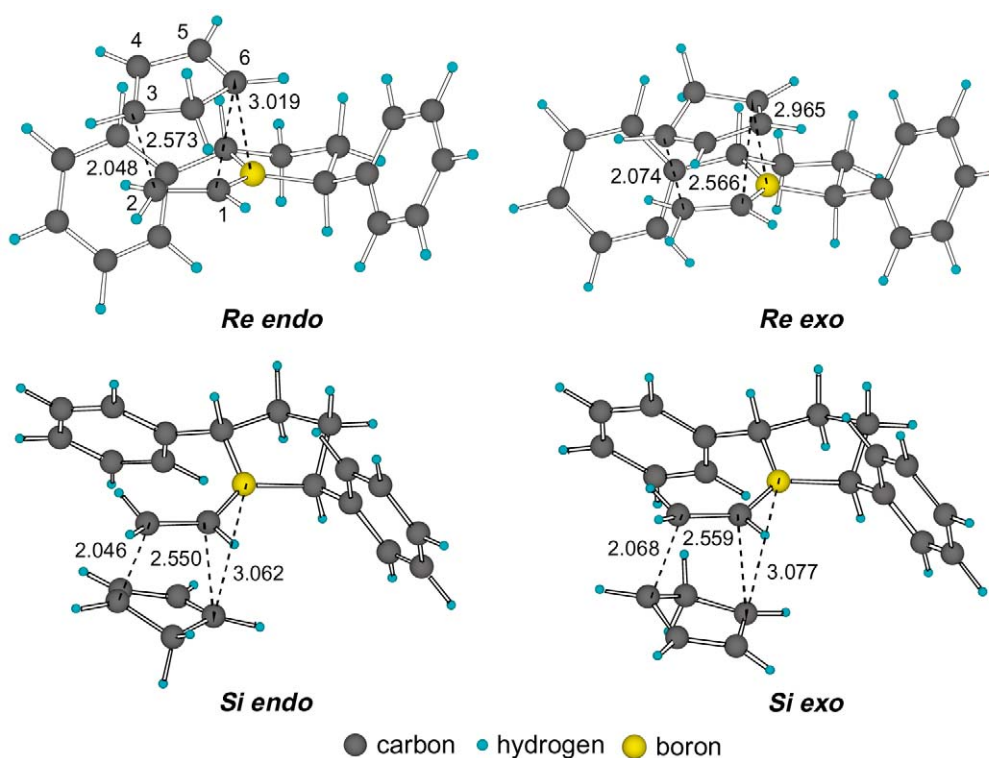


Chart 1. Chiral vinylboranes used in this study.

Figure 1. TS of the reaction between **6** and cyclopentadiene.

the methyl is oriented to the less congested position;
para regiochemistry favored

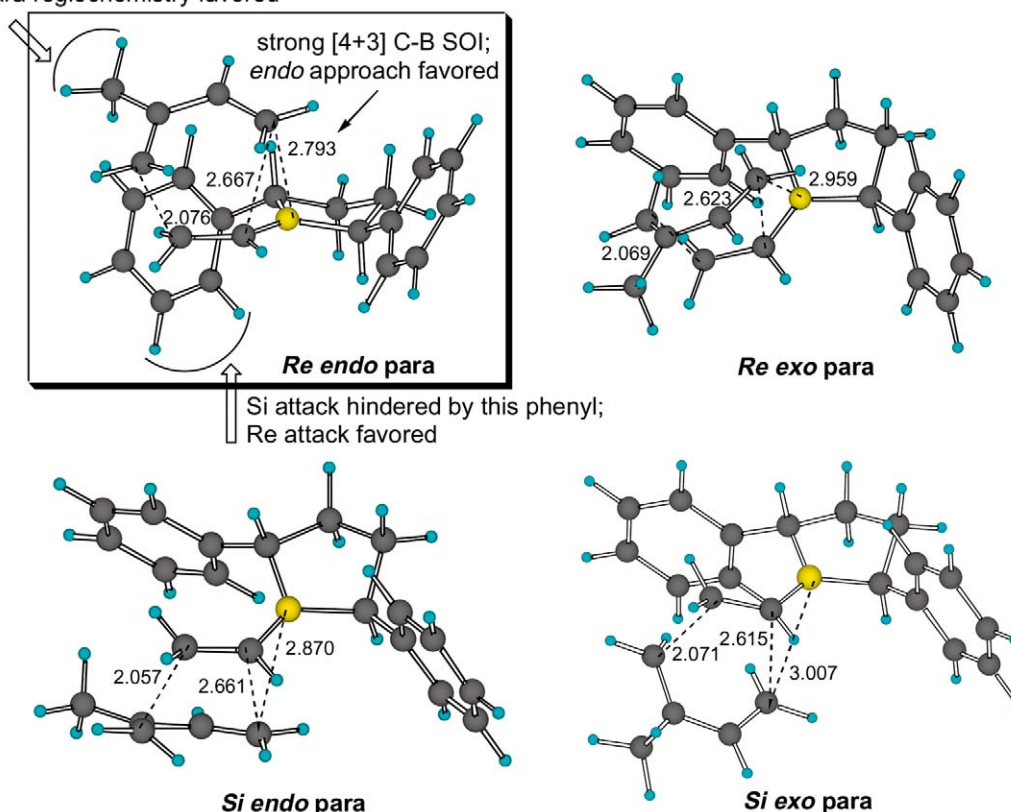


Figure 2. Para TS of the reaction between **6** and isoprene.

from the attack of the diene from either face of the dienophile (*Re* and *Si*) and with *endo* or *exo* stereochemistry. We optimized the geometries of the reactants, located the transition structures (TSs) and calculated the activation energies using Jaguar [10] with the B3LYP [11] functional and the 6-31G* basis set [12]. It is well documented that this method gives satisfactory results for pericyclic reactions in terms of geometries and energies [13]. The transition structures were located using the standard non-quadratic synchronous transit (non-QST) method following the lowest Hessian eigenvector. The initial geometries were obtained by manual distortion of the product geometries towards the starting material geometries by stretching the C1-C6 and C2-C3 bonds to 2.2 Å.

The TSs for the reactions of vinylboranes **1–6** with cyclopentadiene were very asynchronous, showing longer C1-C6 distances than C2-C3. In addition, relatively long C6-B distances were observed, suggesting that non-classical [4 + 3] C-B Secondary Orbital Interactions (SOIs) would be weak. Figure 1 shows the

TSs for the reaction of 2,5-diphenyl-1-vinyl-borolane (**6**).

Approximate selectivities were computed based on the zero-point energy corrected activation energies, assuming identical Arrhenius prefactors for all isomeric pathways. Theoretical results indicated that compounds **2–6** would present better facial selectivities than known **1** (Table 1). Good to very good *Re/Si* ratios were computed for **3**, **5** and **6**. However, the *endo:exo* selectivities for all the dienophiles were low, as expected from the C6-B distances in the TSs. With the aim of analyzing whether the removal of the methylene of cyclopentadiene could improve the *endo:exo* ratios and also evaluating the regioselectivity of these dienophiles, we then studied the [4 + 2] cycloadditions with isoprene. For these reactions there are four meta and four para TSs. The *endo* and *exo* approaches from the same face give rise to the same product. Therefore, only four diastereomeric boranes can be generated, which after oxidation are converted into one pair of enantiomeric meta al-

Table 1. B3LYP/6-31G* activation energies (relative energies in parentheses) including zero-point energy (ZPE) corrections (in kcal mol⁻¹) and calculated selectivities^a for the Diels–Alder reactions between vinylboranes **1–6** and cyclopentadiene.

Vinylborane	ΔE_0^\ddagger (kcal mol ⁻¹) ^b	Calcd. <i>Re/Si</i> facial selectivity	Calcd. <i>endo/exo</i> selectivity	
			<i>Re</i>	<i>Si</i>
1	18.93 (0.32)	36:64	56:44	55:45
	19.09 (0.48)			
	18.61 (0.00)			
	18.73 (0.12)			
2	20.55 (0.36)	74:26	35:65	0:100
	20.20 (0.00)			
	22.66 (2.46)			
	20.55 (0.36)			
3	20.87 (0.41)	84:16	33:66	81:19
	20.46 (0.00)			
	21.34 (0.88)			
	22.13 (1.67)			
4	20.59 (0.20)	81:19	42:58	16:84
	20.39 (0.00)			
	22.06 (1.67)			
	21.03 (0.64)			
5	19.41 (0.42)	85:15	33:67	60:40
	18.99 (0.00)			
	20.12 (1.13)			
	20.28 (1.30)			
6	18.15 (0.13)	96:4	45:55	75:25
	18.02 (0.00)			
	19.76 (1.74)			
	20.08 (2.06)			

^aSelectivity ratios calculated from the Boltzmann factors are of qualitative value only.

^bValues are given in the following order: *Re endo* TS, *Re exo* TS, *Si endo* TS, *Si exo* TS.

cohols and one pair of enantiomeric para alcohols like in Scheme 1. We investigated the reactions with **1** and the three dienophiles that presented the best facial selectivities with cyclopentadiene. The located TSs showed very similar structural features to those corresponding to the reactions with cyclopentadiene. However, the C6-B distances in the *endo* TSs were shorter, which suggested that the C-B SOI would be stronger and the *endo*-selectivity would increase. The para TSs for the reaction between isoprene and 2,5-diphenyl-1-vinyl-borolane (**6**) are depicted in Figure 2. Table 2 gathers the calculated ratios of the Diels–Alder

Table 2. B3LYP/6-31G* activation energies (relative energies in parentheses) including ZPE corrections (in kcal mol⁻¹) and calculated selectivities^a for the Diels–Alder reactions between vinylboranes **1, 3, 5** and **6** with isoprene.

Vinylborane	ΔE_0^\ddagger (kcal mol ⁻¹) ^b	Calcd. meta/para regioselectivity	Calcd. <i>Re/Si</i> facial selectivity	
			meta	para
1	20.78 (1.71)	14:86	30:70	70:30
	21.51 (2.44)			
	20.15 (1.08)			
	21.77 (2.70)			
	19.07 (0.00)			
	21.01 (1.94)			
	19.56 (0.50)			
	21.19 (2.13)			
3	24.83 (2.75)	10:90	85:15	90:10
	23.16 (1.09)			
	24.60 (2.52)			
	24.60 (2.52)			
	22.08 (0.00)			
	22.38 (0.30)			
	23.36 (1.28)			
	23.85 (1.77)			
5	20.78 (0.83)	18:82	74:26	64:36
	21.98 (2.03)			
	21.79 (1.84)			
	21.67 (1.72)			
	19.95 (0.00)			
	21.35 (1.39)			
	20.40 (0.45)			
	21.06 (1.10)			
6	20.01 (1.28)	12:88	83:17	87:13
	21.23 (2.50)			
	22.70 (3.96)			
	20.93 (2.20)			
	18.73 (0.00)			
	20.44 (1.71)			
	20.44 (1.71)			
	20.09 (1.36)			

^aSelectivity ratios calculated from the Boltzmann factors are of qualitative value only.

^bValues are given in the following order: *Re endo* TS, *Re exo* TS, *Si endo* TS, *Si exo* TS for the meta regiochemistry first and then the para regiochemistry.

reactions with isoprene. Calculations nicely modeled the experimental selectivity for the reaction of dienophile **1** with 2-phenyl-1,3-butadiene (Scheme 1). In addition, they predicted better *endo*-selectivities than

with cyclopentadiene. Although dienophile **3** exhibits low *endo*-selectivity, the meta and para *Re/Si* ratios were calculated to be very good, similar to the ones corresponding to **6** and considerably higher than **1**. Dienophiles **3** and **6** are also computed to exhibit the best regioselectivities.

The geometries and electronic features of the located TSs suggest that the regio- and stereoselectivity of these cycloadditions are finely balanced. In general, steric effects seem to dominate the facial diastereoselectivity and the regioselectivity. For instance, the phenyl group closer to the double bond in **6** shields the bottom *Si* face, making the *Re* attack of the diene more favorable (Figure 2). Moreover, the close contacts between the methyl of isoprene and the ligands on boron destabilize the meta TSs relative to their para counterparts. In addition, when the steric repulsions between the diene and the dienophile are less important, such as with isoprene and **6**, the *endo:exo* selectivity is controlled by C-B SOIs. The bulky phenyl groups which convey high selectivity to **6** may also reduce the rate of the reaction. However, the calculated activation energies predict that **6** should be the most reactive of all vinylboranes under study. In summary, calculations suggest that **6** should be deemed to be a promising enantioselective Diels–Alder dienophile. The results of further experimental studies on the use of chiral vinylboranes in asymmetric cycloadditions will be reported in due course. We hope that our findings pave the way for extending the scope of this fascinating boron chemistry.

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Supporting Information available

B3LYP/6-31G* optimized geometries in cartesian coordinates, 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 transition structures.

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