4S,5S-[Bis(carbethoxy)]-2-ethenyl-1,3,2-dioxaborolane: a novel enantioselective dienophile
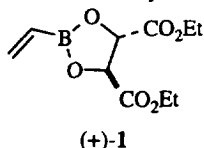
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Abstract: The novel chiral vinyl boronate (+)-**1** was utilized as a dienophile in a series of [4+2] cycloadditions. The intermediate cyclized products obtained were oxidized directly (H_2O_2, NaOH). The resulting alcohols displayed enantiomeric excesses of 7–33%. A slight preference for the endo configuration was observed, in agreement with previous results. © 1997 Elsevier Science Ltd

Introduction

The Diels–Alder reaction is of broad utility for the construction of carbocyclic ring systems.[1,2] Much effort has been expended recently in the advancement of novel concepts in diene/dienophile design, including the aspect of asymmetry.[3–5] In addition, there has also been occasion to focus on the construction of dienophiles as formal hydroxyethylene equivalents.[6–8] The use of vinyl ethers as dienophiles is often undesirable due to their unreactivity, and does not allow the stereospecific introduction of functionality. While there have been examples of "masked hydroxyethylene" strategy (such as vinyl silanes), many suffer from such obstacles as low preparative yields or harsh conditions required to effect oxidation (e.g. C–Si to C–O). We here report the development of vinyl boronate **1** as a potential solution to the introduction of a chiral hydroxyethylene moiety.
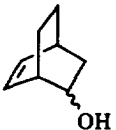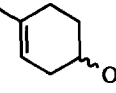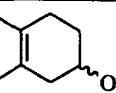

(+)-**1**

Boron-containing ligands have been employed in Diels–Alder cycloadditions, incorporated both in substrate and in a catalytic capacity.[7,9] Alkyl boranes, halo boranes, and boronates have all been utilized/studied to some degree.[7,8,10–15] However, all but the "dioxygenated" boronates suffer either from stability problems, difficulty in handling (air-sensitivity), or both. To date, chiral ligands have only been employed as such for Lewis acid *catalysis* of cycloadditions, including the use of tartrate derivatives as auxiliaries; their utility is, however, limited to engaging an appropriately polarizable substrate, such as those containing an α,β-unsaturated carbonyl. The combination of atmospheric stability and anchoring of chiral ligands directly to boron, pendant to the alkenyl dienophile, was intriguing, and prompted us to develop (+)-**1**, which was found to produce moderately enantioselective cycloadditions with a number of dienes (Table 1).

Preparation of vinyldibutylboronate as per the literature procedure[16] proceeded without event; condensation with (−)-diethyltartrate, (99+%, Aldrich) *in vacuo* provided (+)-**1** (Figure 1), $[\alpha]^{25}_D$=(+) 12.9 (c=1.8, CHCl₃) in high yield, and in accord with all spectroscopic data.

A series of typical dienes was chosen to undergo cycloaddition using (+)-**1** as dienophile. The subsequent adducts were oxidized directly to give the product alcohols. No attempt was made to

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Table 1. Diels–Alder reaction of (+)-1[a]

Diene	Product	Reaction Conditions	Yield	Optical Activity (% ee)	Optical Rotation $[\alpha]^{25}_D$
(cyclopentadiene)	(norbornene product) OH	190-200°C, 1h, 3.0 eq. diene	exo, 35% endo, 37%	exo, 0% (+)-endo, 10%	endo: (+) 11.1, c= 2.6, CHCl3
(cyclohexadiene)	(bicyclo product) OH	190-200°C, 27h, 2.0 eq. diene	exo, 14% endo, 56%	exo, 0% (+)-endo, 7%	endo: (+) 5.7, c= 5.7, CDCl3
(isoprene)	(cyclohexene product) OH	190-200°C, 10h, 2.0 eq. diene	61%[b]	33%	(+) 6.3, c= 3.4, CDCl3
(dimethylbutadiene)	(cyclohexene product) OH	190-200°C, 8.5h, 2.0 eq. diene	76%	10%	(+) 21.0, c= 2.4, CHCl3

[a]Typical reaction conditions: a mixture of (+)-1 and diene were heated in a benzene solution in a sealed tube with 1 mol% phenothiazine as stabilizer until TLC showed no starting material remained. The mixture was then concentrated in vacuo, and dissolved in ether. Oxidation with H_2O_2/NaOH provided a mixture of product alcohols which were analyzed by GC, NMR (or both) for product composition before purification by flash column chromatography on silica gel. Enantiomeric excesses were determined on purified isomers by optical rotation, NMR with (+)-Eu(tfc)3, or both. Reaction conditions and yields are unoptimized.
[b]We estimate the regiopurity to be at least 95% by GC, but have not proved the other isomer absent.
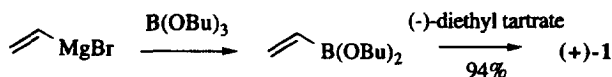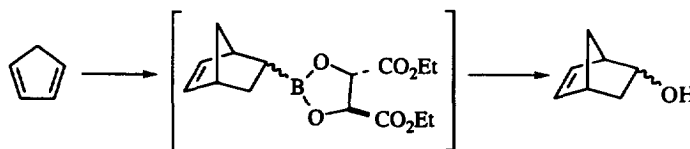

Figure 1.

Figure 2.

characterize the intermediate cycloadducts, as treatment with alkaline peroxide is known to proceed with retention of configuration. A representative cycloaddition sequence is shown in Figure 2.

Discussion

In the examples studied (Table 1), all products (except exo products) were optically active, albeit marginally in some cases. In view of the somewhat low optical purities of the endo products, the failure of the exo products to adopt any amount of optical purity was not surprising. In fact, inspection of a [4+2] transition state model shows the chirality-bearing portion of the dienophile to be of minimal steric influence. A [4+3] transition state as postulated by Singleton et al.[17] (Figure 3) brings tartrate terminus into somewhat closer proximity.

The moderate preference for the endo products is in accord with other similar examples (vinyl
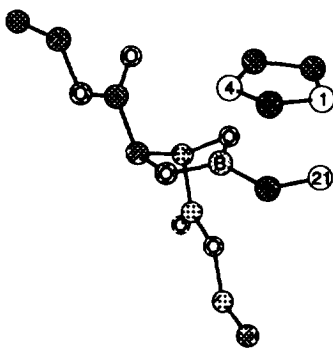
Figure 3. [4+3] **Simulated transition state for cyclopentadiene and (+)-1.** Simulated transition state generated using Sybyl 6.0 molecular modeling program.[18] Two constraints were set; B–C4 (2.2 Å), and C1–C21 (2.0 Å), to mimic the transition state proposed by Singleton et al.[17] The model is shown without hydrogens for clarity.
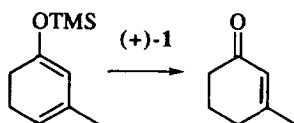

Figure 4.

dibutylboronate), and also serves to reinforce the theory that the vacant p orbital on boron has an effect on the product distribution. The reaction of (+)-1 with isoprene was observed to proceed with complete regioselectivity, in parallel with the results obtained for vinyl dibutylboronate. Attempts to cycloadd a silyl enol ether (Figure 4) yielded only recovery of the corresponding enone; this suggests that enolization of the dienophile in these cases is a competing process. This hindrance can, in principle, be overcome by the use of a non-enolizable ligand on boron.

The possibility of utilizing reduced amino acids (lacking acidic protons) such as valinol was briefly explored; unfortunately the reaction of valinol with vinyl dibutylboronate gave a complex mixture of products upon NMR analysis. We speculated that this was due to the heightened nucleophilicity of nitrogen relative to oxygen, and the possible formation of bis(aminovalinol) adducts and oligomers thereof. This was of no consequence, as MNDO calculations indicated that two nitrogen-containing groups attached to a vinylidene boron atom ($H_2C=CHB(NR)_2$) would have a significantly higher LUMO than two oxygenated groups ($H_2C=CHB(OR)_2$).[19]

Although the observed optical purities are moderate at best, these examples serve to illustrate that the concept of chiral induction can be realized through the attachment of specific ligands to boron. Perhaps more importantly, a rough correlation between enantioselectivity and distance of chirality-bearing functionality from the reaction site can be utilized to guide the design of new, improved ligands.

Acknowledgements

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19. Representative MNDO LUMO values (eV): (+)-**1**, +0.1153; $H_2C=CHB(OBu)_2$, +0.7658; $H_2C=CHB(NHMe)_2$, +1.033. Pertinent LUMO atomic coefficients for (+)-**1**: C1, −0.68; C2, +0.47; B, +0.47; C1 and C2 are the terminal and internal alkenyl carbons, respectively. Calculated with MOPAC v. 6.00 within Sybyl 6.0, Ref. 18. For a relevant discussion of FMO effects and comparative data, see Singleton, D. A.; Martinez, J. P. *J. Am. Chem. Soc.* **1990**, 7423.