VIP Asymmetric Catalysis

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Cationic-Oxazaborolidine-Catalyzed Enantioselective Diels–Alder Reaction of α,β-Unsaturated Acetylenic Ketones**

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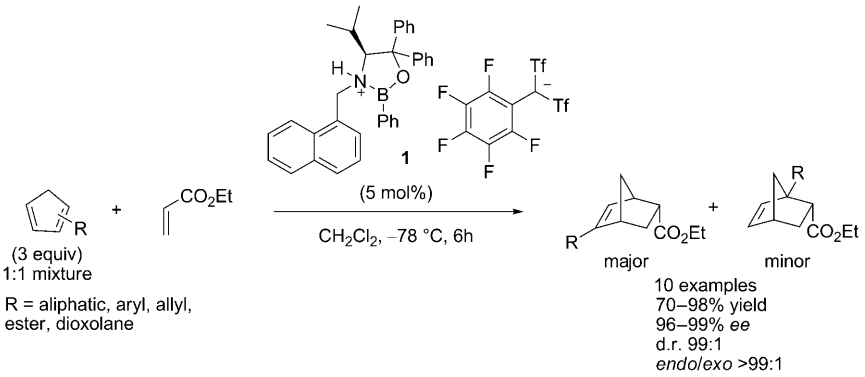
The catalytic, enantioselective Diels–Alder reaction is one the most extensively studied transformations in the field of asymmetric catalysis.[1] This attention is justified, especially in view of the myriad of natural product syntheses that make use of this reaction.[2] The current state of asymmetric Diels–Alder catalysis is certainly impressive. The Lewis and Brønsted acid activation of α,β-unsaturated aldehydes, ketones, esters, and amides, as well as simple carbonyl and imino compounds, and treatment with various dienes has provided cycloadducts in excellent yields with excellent enantioselectivities.[1,3] Despite these advances, dienophiles are still mostly limited to compounds containing sp^2-hybridized reactive centers. In 1997, Corey and Lee and our research group independently disclosed the first asymmetric Diels–Alder reactions of cyclic dienes and α,β-unsaturated acetylenic aldehydes with boron-based catalysts.[4a,b] Recently, Ishihara and Fushimi reported a copper-catalyzed asymmetric Diels–Alder reaction of cyclic dienes and propiolamides.[4f] Besides these studies, the development of asymmetric [4+2] cycloaddition reactions of acetylenes has remained nearly nonexistent, thus leaving a tremendous gap in an otherwise robust field of chemistry.[4] We herein describe a highly regio- and enantioselective Diels–Alder reaction of both cyclic and acyclic dienes with α,β-acetylenic ketones under the catalysis of the chiral cationic oxazaborolidine Lewis acid **1**.



Scheme 1. Regioselective Diels–Alder reaction catalyzed by **1** to provide adducts derived from 2-substituted cyclopentadienes. Tf = trifluoromethanesulfonyl.

We previously reported regio- and enantioselective Diels–Alder reactions of mixtures of 1- and 2-substituted cyclopentadienes with the L-valine-derived cationic oxazaborolidine catalyst **1** (Scheme 1). Notably, this catalyst system was able to discriminate between two similar regioisomeric nucleophiles.[5] We recognized that the use of a chiral catalyst to not only differentiate the enantiofaces of an electrophile but also to direct the attack of an incoming nucleophile might serve as a useful strategy in the development of new asymmetric methodologies. To demonstrate the feasibility of this approach, we sought to apply **1** to the Diels–Alder reaction of acetylenes. Unlike cycloaddition reactions of sp^2-hybridized dienophiles, *exo* and *endo* transition states of acetylenic dienophiles give opposite enantiomers. Thus, discrimination between these two modes of diene approach is vital for high levels of enantioselectivity to be attained.

We investigated the [4+2] cycloaddition reaction of acyclic dienes with varying substitution patterns and trimethylsilylacetylenes **2** and **3** in the presence of **1** (5 or 10 mol%; Table 1).[6] In all cases, the adducts were isolated in good to excellent yield as a single regioisomer with 99% *ee*. Use of Dane's diene (**4**; X = OMe) or the equivalent compound without the methoxy substituent as well as related 3-vinylindene (**5**) with **2** and **3** gave the corresponding cycloadducts as single isomers through electrophilic attack at the terminal methylene carbon atom.[7]

Open-chain dienes and non-aromatic inner–outer dienes with one endo- and one exocyclic double bond could also be applied in this reaction. X-ray crystallographic analysis indicated that the absolute configuration of brominated derivatives of **7a** and **7b** were identical. Finally, the reaction of less bulky 1-phenyl-2-propyn-1-one and diene **8** under the standard reaction conditions provided the corresponding cycloadduct in 90% yield with 99% *ee* (Scheme 2). Thus, the large terminal TMS group is not essential for high levels of reactivity or asymmetric induction.

Cyclopentadiene was also investigated as a substrate for this reaction. The use of **1** (5 mol%) with **2** or **3** and cyclopentadiene at −78 °C in CH_2Cl_2 provided the corresponding cycloadducts **9a** and **9b** in 88% yield with 74% *ee* and in 90% yield with 71% *ee*, respectively. When the TMS

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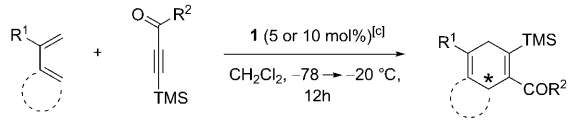
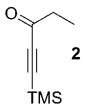
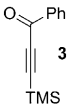
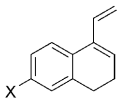
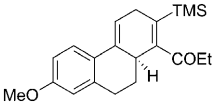
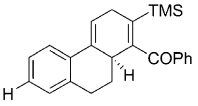
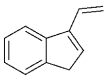
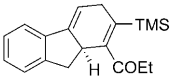
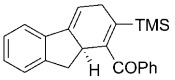
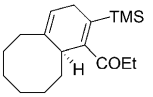
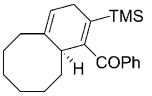
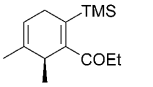
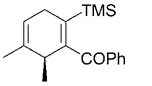
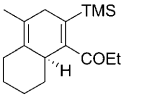
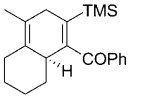
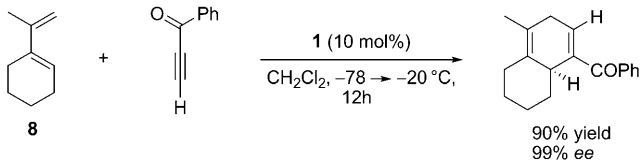
Table 1: Diels–Alder reaction of ethyl and phenyl acetylenic ketones with various dienes.[a,b]



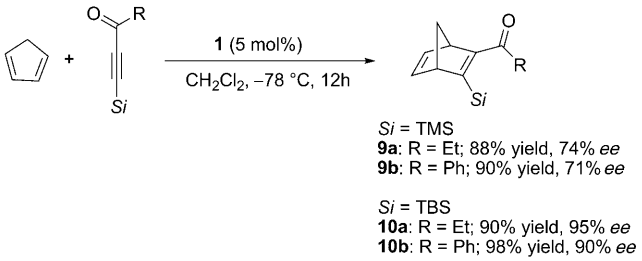
Diene	Product of the reaction with	
	 **2**	 **3**
 **4**	 **4a** 73% yield, 99% *ee*	 **4b**[d] 96% yield, 99% *ee*
 **5**	 **5a**[e] 96% yield, 99% *ee*	 **5b** 85% yield, 99% *ee*
 **6**	 **6a** 94% yield, 99% *ee*	 **6b** 93% yield, 99% *ee*
 **7**	 **7a** 96% yield, 99% *ee*	 **7b** 96% yield, 99% *ee*
 **8**	 **8a** 94% yield, 99% *ee*	 **8b** 88% yield, 99% *ee*

[a] See the Supporting Information for details. [b] Yields of the isolated product are given. [c] In the reactions to form **8a**,**b**, 5 mol% of the catalyst was used; for all other reactions, 10 mol% of the catalyst was used. [d] The use of **4** with X = OMe resulted in decomposition. [e] The *ee* value could not be determined by HPLC. The *ee* value of the adduct derived from 6-bromo-3-vinyl-1*H*-indene is given. TMS = trimethylsilyl.



Scheme 2. Diels–Alder reaction of an acetylenic ketone without a terminal silyl group.

group was replaced with the larger *tert*-butyldimethylsilyl (TBS) group, the enantioselectivity was increased to up to 95% *ee* (Scheme 3). Since *exo* or *endo* transition states give



Scheme 3. Effect of the silyl group in Diels–Alder reactions with cyclopentadiene.

opposite enantiomers, we postulate that an increase in the bulk of the dienophile leads to greater selectivity between the two sterically similar transition states formed from cyclopentadiene and the catalyst–dienophile complex. In the case of acyclic dienes, the size of the dienophile is less important, as the steric requirements of the *exo* and *endo* modes of approach are significantly different. In accord with our previous study on Diels–Alder reactions of 1- and 2-substituted cyclopentadienes, these results further demonstrate the important role that interactions between the nucleophile and catalyst–substrate complex may have in determining which of several possible transition states is favored.

Our previous studies with **1**, as well as studies by Corey and co-workers with their proline-derived oxazaborolidine system, indicated that the presence on the electrophile of an acidic formyl, vinylic, or α hydrogen atom capable of hydrogen bonding with the oxygen atom of the catalyst was necessary for a highly ordered transition state to be maintained.[3b,5,8] The uniformity of the enantioselectivities observed for **2** and **3** in Table 1 and the agreement in the absolute configuration of **7a** and **7b** suggest that both acetylenes may coordinate in a related fashion, and that the presence of an α hydrogen atom is unnecessary. As in the case of **3**, it is conceivable that the binding of **1** with **2** also lacks the typical hydrogen-bonding interactions postulated for other oxazaborolidinium-mediated reactions. At the onset of our investigation, we believed this interaction was essential to fix the Lewis acid in an *anti* coordination geometry relative to the alkyne. However, if catalyst/dienophile complexation does not involve hydrogen bonding, *syn* or *anti* coordination modes of the dienophile are both plausible.[9,10]

The X-ray crystal structure of an oxazaborole complex related to catalyst **1** (Figure 1)[11] suggests that the dienophile should coordinate *trans* to the isopropyl group and N–H atom. In this case, the absolute configuration of the products can be rationalized on the basis of an *endo* or *exo* transition state of the *anti*- or *syn*-coordinated catalyst–dienophile complex, respectively.

In summary, the cationic oxazaborolidine **1** has been shown to catalyze Diels–Alder reactions of acetylenic ketones with various cyclic and acyclic dienes with excellent levels of asymmetric induction.[12] These findings will hopefully stimulate more studies of Lewis acid mediated reactions with this oft-neglected class of electrophiles. Furthermore, our results demonstrate that the exploitation of interactions between the nucleophile and the catalyst–substrate complex may serve as

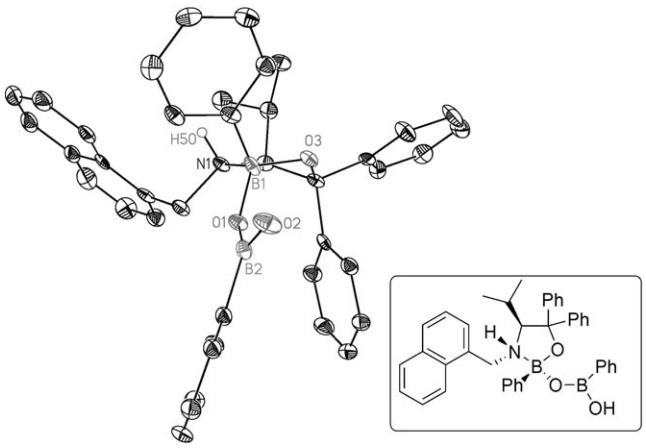


Figure 1. ORTEP view (50% probability level) of an oxazaborole complex related to **1**.

a useful approach in the development of new asymmetric methodologies. Current investigations in our laboratory are focused on the geometry and energetics of the Lewis acid coordination of acetylenic electrophiles.

Experimental Section

General Procedure: CH_2Cl_2 (1.4 or 1.95 mL) and a solution of the oxazaborolidine in CH_2Cl_2 (0.1M; 600 μL, 0.06 mmol or 300 μL, 0.03 mmol) were placed in a dried Schlenk flask under an inert atmosphere. This solution was cooled to −78 °C, and a solution of 1-(bis(trifluoromethanesulfonyl)methyl)-2,3,4,5,6-pentafluorobenzene in CH_2Cl_2 (0.1M; 500 μL, 0.05 mmol or 250 μL, 0.025 mmol) was added dropwise. The resulting slightly cloudy mixture was stirred for 15 min at this temperature, and then a solution of the acetylenic ketone (0.5 mmol) in a minimal amount of CH_2Cl_2 was added dropwise. The mixture was stirred for a further 1–2 min, and then a solution of the diene (0.65 mmol, 1.3 equiv) in a minimal amount of CH_2Cl_2 was added dropwise. The resulting mixture was allowed to warm to −20 °C. It was stirred for a total of 12 h, and then the reaction was quenched with aqueous saturated $NaHCO_3$ (5 mL) at −20 °C. The reaction mixture was allowed to warm to room temperature and was then extracted three times with Et_2O. The combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography with hexanes/ethyl acetate (20:1)

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[11] The X-ray crystal structure does not indicate the presence of a hydrogen bond between O2–H and O3.
[12] Acetylenic esters were screened as dienophiles with various cyclic and acyclic dienes. However, presumably as a result of their lower reactivity, no product was detected.

