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

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Abstract

Cationic oxazaborolidine **1** affords Diels-Alder adducts of α,β -unsaturated acetylenic ketones with cyclic and acyclic dienes in excellent yields and enantioselectivities. Importantly, dienophiles lacking the typical hydrogen bonding motif as required for other oxazaborolidinium mediated reactions also provide uniformly high levels of asymmetric induction. Subsequently, mechanistic studies of this reaction were undertaken through X-ray crystallographic and computational studies of BF_3 -acetylene complexes which both indicate a strong preference for *syn*-coordination geometry of the Lewis acid relative to the alkyne. Thus, we postulate *syn*-coordination of the acetylene by **1** is operative, which precludes the necessity for hydrogen bonding and maintains close proximity of the reactive sp carbon centers to the chiral environment of the catalyst, ensuring high enantioselectivities.

The catalytic, enantioselective Diels-Alder reaction is one the most extensively studied transformations in the field of asymmetric catalysis.¹ This attention is justified and is further reinforced in view of the myriad of natural product syntheses making use of this reaction.² The current state of asymmetric Diels-Alder catalysis, however, is certainly impressive. Lewis and Bronsted acid activation of α,β -unsaturated aldehydes, ketones, esters, and amides as well as simple carbonyl and imino compounds have provided cycloadducts derived from various diene partners in excellent yields and enantioselectivities.^{1,3} Despite these advances, dienophiles are still mostly limited to sp^2 hybridized reactive centers. In 1997 Corey and our group independently disclosed the first asymmetric Diels-Alder reaction of cyclic dienes and α,β -unsaturated acetylenic aldehydes using boron-based catalysts. Recently, Ishihara has reported a copper catalyzed asymmetric Diels-Alder reaction of cyclic dienes and propiolamides. Besides these studies, development of asymmetric [4+2] cycloaddition reactions of acetylenes has remained nearly non-existent, leaving a tremendous gap in an otherwise robust field of

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Supporting Information Available: Complete ref.⁹, experimental procedures, spectra data, GC and HPLC chromatograms, computational methods, Cartesian coordinates of complexes in calculation, and X-ray crystallographic data. This material is available free of charge via the internet at <http://pubs.acs.org>.

chemistry. We herein describe a highly regio- and enantioselective Diels-Alder reaction of both cyclic and acyclic dienes with α,β -acetylenic ketones catalyzed by chiral cationic oxazaborolidine Lewis acid **1**. Furthermore, crystallographic and computational studies of BF_3 -acetylene complexes provide insight into the geometry and energetics of Lewis acid coordination of these unique electrophiles.

Initially, ethyl ketone **2**, containing an α -proton, was selected as a potentially suitable substrate for activation by catalyst **1**.⁴ This choice was based on an understanding, supported by our own work as well as findings by Corey for his proline-derived oxazaborolidine system, that the presence of an acidic aldehydic, vinylic, or α -proton on the electrophile capable of hydrogen bonding with the oxygen atom of the catalyst was necessary to maintain a highly ordered transition state.^{2a, 5} Use of 5 mol% of **1** with **2** and cyclopentadiene at -78°C in CH_2Cl_2 provided the corresponding cycloadduct **3a** in 96% yield and 74% ee. Thereafter, phenyl acetylenic ketone **5**, lacking an α -proton, was subjected to the same reaction conditions. Unexpectedly, the corresponding cycloadduct **3b** was obtained in 90% yield and 71% ee. This nearly identical result suggested that both acetylenes may coordinate in a related fashion and thus the presence of an α -proton was unnecessary.⁶

For both ethyl and phenyl acetylenes, enantioselectivities of adducts from cyclopentadiene could be improved to 95 and 90%, respectively, by replacing TMS with the bulkier TBS group. Since *exo* or *endo* approach by the diene will give opposite enantiomers, it was postulated that structural features of both diene and dienophile might play a decisive role in determining selectivities for *exo/endo* transition states. Based on this hypothesis, cycloaddition reaction of dienes containing varying substitution patterns and TMS-acetylenes **2** and **5** catalyzed by 5–10 mol% **1** were investigated (Table 1). In all cases adducts of both **2** and **5** are isolated in good to excellent yields as single regioisomers in 99% ee. Utilization of Dane's diene as well as related 3-vinylindene with **2** and **5** gave corresponding cycloadducts as single isomers resulting from electrophilic attack at the terminal methylene.⁷ Further, open chain and non-aromatic inner-outer ring dienes could also be applied in this reaction. X-ray crystallographic analysis indicated that the regio- and absolute stereochemistry of brominated derivatives of **7b**, **9a** and **9b** were identical. Finally, reaction of the less bulky 1-phenyl-2-propyn-1-one and diene **10** under the standard reaction conditions provided the corresponding cycloadduct in 90% yield and 99% ee (Scheme 2). Thus, the large terminal TMS group may not be essential to obtain high levels of asymmetric induction.

The uniformity of enantioselectivities obtained for both **2** and **5** in Table 1 as well as the agreement in absolute configuration of **9a** and **9b** suggest that the catalyst/dienophile complexes of both **2** and **5** are quite similar. As in the case of **5**, it is conceivable that binding of **1** with **2** also lacks the typical hydrogen bonding interactions postulated for other oxazaborolidinium mediated reactions. At the onset of our work, we believed this interaction was essential in order to fix the Lewis acid in an *anti*-coordination geometry relative to the alkyne. If a highly *syn*- or *anti*-selective transition state geometry could not be obtained, low asymmetric induction would invariably arise.

To gain insight into the favored coordination mode of **1** with **2** and **5**, a series of crystallization and computational studies were undertaken.⁸ X-ray crystal structures of BF_3 complexes with aryl and ethyl ketones **12** and **13**, respectively, were obtained (Figure 1A, see Supporting Information). Importantly, both structures possess *syn*-coordination geometry of BF_3 relative to the alkyne. Furthermore, computational studies have corroborated this observation. DFT calculations at the B3LYP/6-311+G(2d,p) levels indicate that the *syn*-complex of **2**- BF_3 and **5**- BF_3 is considerably more favored by 1.23 and 4.48 kcal/mol, respectively over the *anti*-complexes.⁹ Based on this data we have proposed a transition structure **TS** in agreement with the observed absolute stereochemistry of the products. *Syn*-coordinative geometry further

allows for favorable π - π interactions of the acetylene and the *cis* aryl group of the oxazaborolidine, shielding one enantioface of the dienophile. An *exo* transition state is preferred since *endo* approach of the diene would be disfavored due to substantial steric interactions with the catalyst-dienophile complex.^{3a} Lastly, an X-ray structure of a related oxazaborole complex to catalyst **1** was obtained (Figure 1B). Importantly it supports our assumption that the dienophile should coordinate *trans* to the ring isopropyl and N-H groups.

In summary, cationic oxazaborolidine **1** is shown to catalyze Diels-Alder reactions of α,β -unsaturated acetylenic ketones with various cyclic and acyclic dienes in excellent levels of asymmetric induction. A clearer understanding of the associative nature of Lewis acid coordination with α,β -unsaturated acetylenic ketones has been gained through crystallographic and computational studies of BF_3 -acetylene complexes. Based on these results, *syn*-coordination of **2** and **5** by **1** is predicted, which maintains close proximity of the reactive sp carbon centers to the chiral environment of the catalyst, ensuring high enantioselectivities. These findings should enable more purposeful investigation of Lewis acid-mediated reactions with this oft-neglected class of electrophile.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

(A) X-ray structures BF_3 -acetylene complexes **11** & **12** indicate *syn* coordination geometries (relative to alkyne). (B) ORTEP view (50% probability level) of related oxazaborole derivative of **1**.

Figure 2.
Hypothetical Transition State (TS) (*exo* approach).

Scheme 1.

Diels-Alder Reaction of Cyclopentadiene and Acetylenic Ketones: Role of Hydrogen Bonding and Sterics.

Scheme 2.

Bulky Group at Terminus of Acetylene is Not Essential.

Table 1

Diels-Alder Reaction of Ethyl and Phenyl Acetylenic Ketones with Various Dienes.^{a,b}

Dienophile/Diene 2

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2009 November 19.

Dienophile/Diene 2

7

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96% yield
99% ee

Dienophile/Diene 2

94% yield
99% ee

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Dienophile/Diene 2

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96% yield
99% ee

Dienophile/Diene 2

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94% vie

^a See Supporting Information for details.

^b Isolated yields shown.

^c 5 mol% used for products **10a,b**. 10 mol% used for all others.

^d Use of X = OMe resulted in decomposition.

^e %Ee could not be determined by HPLC. %Ee of adduct derived from 6-bromo-3-vinyl-1*H*-indene shown.