Mechanistic Studies of a CAB-Catalyzed Asymmetric Diels-Alder Reaction

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In recent years, a number of interesting enantioselective Diels-Alder reactions have been reported that involve α,β-enal, diene, and various chiral Lewis acids as catalysts.[1] The understanding of enantioselectivity requires a knowledge of the detailed structure and concentration of each aldehyde–Lewis acid complex present in equilibrium and the relative rates for the reaction of each with the diene. Even if the catalyst has a single fixed geometry in the complex with the α,β-enal, the proportion of *s-cis* and *s-trans* α,β-enal complexes must be known, since these will lead to enantiomeric products. One of our own investigations in this area has been in the development of a tartaric acid-derived chiral (acyloxy)borane (CAB) complex which catalyzes aldol,[2] ene,[3] and Diels-Alder reactions[1b,m,4] with excellent enantioselectivity. Our interest has focused on the sp^2–sp^2 conformational preferences in α,β-enals, where the possibility of *s-cis* or *s-trans* conformers exists in the transition-state assembly of the Diels-Alder reaction catalyzed by a Lewis acid. As a first step toward obtaining such mechanistic information, we have studied the boron-substituent-dependent enantioselectivity of the CAB-catalyzed asymmetric Diels-Alder reaction, and the results are reported herein.

CAB catalyst **1** was prepared in dry porpionitrile from the L-tartaric acid-derived chiral ligand and 1 equiv of a boron reagent like alkylboric acid (room temperature, 0.5 h), alkynyldimethoxyborane[5] (room temperature, 0.5 h), or BH_3·THF (0 °C, 15 min).

To determine an activated face of a carbonyl group in an α,β-enal–CAB complex, an aldol reaction of several α,β-enals with terminal trimethylsilyl enol ethers derived from acetophenone was conducted at −78 °C in propionitrile as solvent in the presence of 20 mol % of **1** as catalyst. The results of these experiments are summarized in Scheme I. Good yields and moderate enantioselectivities were obtained, with the predominating enantiomer being that corresponding to *re*-face attack, as anticipated. The effective steric shielding of the *si*-face of the coordinated α,β-enal is in agreement with other enantioselective reactions catalyzed by **1** previously reported.[2,3,4b] Also, the structure of the boron substituent was independent of the absolute stereochemistry of the aldol reaction.

On the basis of the above results, the Diels-Alder reaction of α,β-enal with cyclopentadiene in the presence of **1** (10–20 mol %) was examined. The results are summarized in Table I. Diels-Alder reaction of cyclopentadiene with methacrolein under catalysis by **1** gave the (2*R*)-enantiomer as major product. This result was found to hold for all boron substituents of **1**. Therefore, the stereochemistry of the reaction of an α-substituted α,β-enal like methacrolein was quite independent of the steric features of the boron substituent. Taking together the stereochemical outcome from aldol and Diels-Alder reactions of methacrolein, this substance appears to favor the *s-trans* conformation in the transition-state assembly of the catalytic Diels-Alder reaction. On the other hand, the stereochemistry of the reaction of cyclopentadiene with α-nonsubstituted α,β-enals like acrolein and crotonaldehyde was dramatically reversed by altering the structure of the boron substituent. Sterically bulky aryl boron substituents like the *o*-phenoxyphenyl group may cause the active capacity between the boron substituent and the 2,6-diisopropoxyphenyl moiety to decrease. Therefore, the *s-trans*-coordinated α-nonsubstituted acrolein which would lead to the (2*R*)-product changed inversely so that it favored the *s-cis* conformation, thereby diminishing the steric size and giving the (2*S*)-product.

We also studied the solution conformations of the CAB-complexed methacrolein and crotonaldehyde using difference NOE measurements. First, the difference NOE spectra were obtained for uncomplexed methacrolein at −95 °C. Irradiation of H^a resulted in a 6.3% NOE to H^c and no NOE to either H^b or H^d. Therefore, at −95 °C, the uncomplexed methacrolein must reside primarily in the *s-trans* conformation. The difference NOE spectra of methacrolein complexed with **1** (R = H, *o*-$PhOC_6H_4$) were then recorded. To a solution of **1** (0.050 mmol) in dichloromethane-d_2 (2.0 mL) was added methacrolein (0.036 mmol) at −78 °C. The two protons labeled H^a and H^c were individually irradiated, and the resulting NOEs were measured. Irradiation of H^a resulted in a strong NOE to H^c and no NOE to H^b and H^d. Irradiation of H^c again led to a strong NOE to H^a. These results indicate that the complex of methacrolein and **1** is primarily in the *s-trans* conformation, independent of the

Scheme I. Asymmetric Aldol Reaction of α,β-Enals Catalyzed by **1**

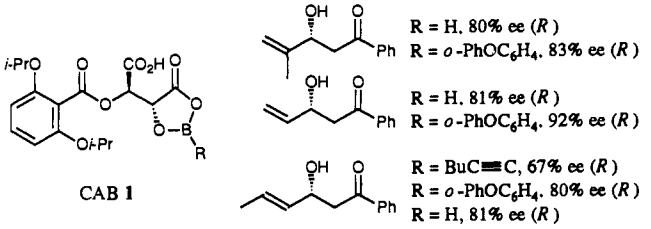
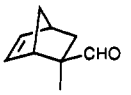
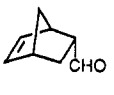
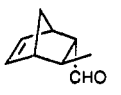


Table I. Asymmetric Diels-Alder Reaction of α,β-Enal with Cyclopentadiene Catalyzed by **1**[a]

CAB 1 R	% ee (config) 		
1-hexynyl	64 (*R*)	58 (*R*)	42 (*R*)
PhC≡C	62 (*R*)	48 (*R*)	40 (*R*)
H	87 (*R*) [96 (*R*)][b,c]	47 (*R*) [84 (*R*)][b,c]	2 (*S*) [2 (*S*)][b,c]
Me		2 (*S*)	14 (*S*)
Ph	80 (*R*)	10 (*S*) [3 (*S*)][b]	37 (*S*)
3,5-$(CF_3)_2C_6H_3$		3 (*S*)	59 (*S*)
o-$PhOC_6H_4$	93 (*R*)	57 (*S*)	67 (*S*)
o-$NpOC_6H_4$[d]		53 (*S*)	77 (*S*)

[a] Unless otherwise noted, the reaction was carried out in propionitrile for several hours using 10–20 mol % of **1** and cyclopentadiene (3 equiv) at −78 °C. [b] Dichloromethane was used in place of propionitrile. [c] (2*R*,3*R*)-2-*O*-(2,6-Dimethoxybenzoyl)tartaric acid was used as a chiral ligand.[1b] [d] *o*-Naphthoxyphenyl.

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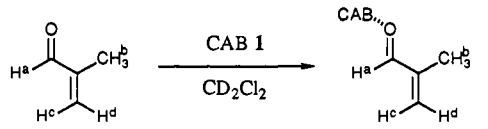
Table II. Summary of NOE Data for Methacrolein



complex	t (°C)	NOE (saturated/observed, %) H^a/H^b	H^a/H^c	H^a/H^d	H^c/H^a
methacrolein only	−95	0	6.3	0	18
methacrolein–**1**, R = H^b	−95	0	−10	0	6.3
methacrolein–**1**, R = *o*-$PhOC_6H_4$[b]	−75	0	−22	0	−33

[a] Calibrated probe temperature. [b] Complexed formed by addition of 0.72 equiv of the aldehyde to **1**.

boron substituent. All of the NOE results are collected in Table II. Next, the NOE experiments as above were done for crotonaldehyde. These results in Table III indicate that (i) uncomplexed crotonaldehyde is primarily in the *s-trans* conformation, (ii) the crotonaldehyde complexed with **1**, R = $C_4H_9C{\equiv}C$, H, is primarily in the *s-trans* conformation, and (iii) the crotonaldehyde complexed with **1** (R = 3,5-$(CF_3)_2C_6H_3$, *o*-$PhOC_6H_4$, is in the *s-cis* conformation.

Finally, it has been established by the use of difference NOE measurements that the effective shielding of the *si*-face of the CAB-coordinated α,β-enal arises from π-stacking of the 2,6-diisopropoxybenzene ring and the coordinated aldehyde.[6] Strong NOEs were obtained between protons H^m and H^p of the 2,6-diisopropoxybenzene ring and protons of the olefin subunit of α,β-enal for the **1** (R = H)–α,β-enal complex in dichloromethane-d_2 at −95 °C, as represented in Chart I.

The results obtained with NOE experiments are unambiguous in the establishment of the preferred conformation in the ground state of CAB–α,β-enal complexes. However, for precisely this reason it is essential to stress that this information should not be imported into transition-state rationalizations of CAB-catalyzed reactions according to the Curtin–Hammett principle.[7] Nevertheless, these results are in agreement with the transition-state preference for the *s-trans* or *s-cis* conformation of the α,β-enal, which is assumed from the enantioselectivities of both of the aldol and the Diels-Alder reactions catalyzed by CAB.

A recent computational study by Houk[8] showed that acrolein adopts the *s-cis* conformation upon Diels-Alder reaction with a diene, thus overriding the ground-state preference for the *s-trans* conformation.[9] Our experimental results demonstrate that the structures of both the chiral Lewis acid and the α,β-enal are very important as relative factors which control the favorable conformation of the α,β-enal in the transition-state assembly of the Diels-Alder reaction. Interestingly, the (*S*)-tryptophan-derived chiral Lewis acid catalyst system[1i,j] appears to function *via* an *s-cis*-α-substituted-α,β-enal complex, in contrast to our results that the α-substituted α,β-enal preferred the *s-trans* conformation in spite of the steric feature of the boron substituent of **1**.

(6) A colorless crystal of racemic 2-*O*-(2,6-dimethoxybenzoyl)tartaric acid was obtained by recrystallization from acetonitrile at room temperature. X-ray diffraction analysis of this compound revealed the folded structure rather than the extended structure. It is interesting that the 2,6-dimethoxybenzene ring and the terminal α-hydroxycarboxylic acid subunit are positioned close to each other. This conformer is similar to the expected structure of the CAB-α,β-enal complex suggested by NOE experiments.

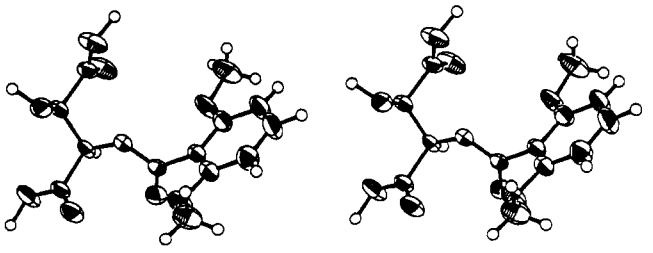


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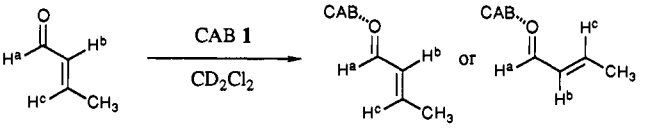
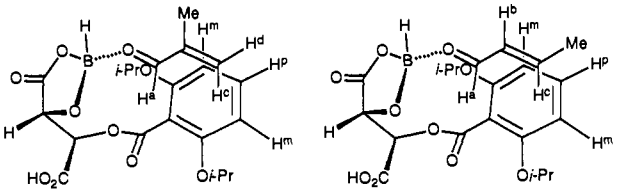
Table III. Summary of the NOE Data for Crotonaldehyde



complex	t (°C)	NOE (saturated/observed, %) H^a/H^b	H^a/H^c	H^b/H^a	H^c/H^a
crotonaldehyde only	−95	0	5.4		
crotonaldehyde–**1**, R = $C_4H_9C{\equiv}C$[b]	−75	0	6		13
crotonaldehyde–**1**, R = H^b	−95	0	18		
crotonaldehyde–**1**, R = 3,5-$(CF_3)_2C_6H_3$[b]	−75	−32	0	−48	
crotonaldehyde–**1**, R = *o*-$PhOC_6H_4$[b]	−75	−14	0	−18	

[a] Calibrated probe temperature. [b] Complex formed by addition of 0.72 equiv of the aldehyde to **1**.

Chart I



methacrolein-**1** (R = H)

NOE (saturate/observe, %) $H^c/2H^m$	H^c/H^p	$H^d/2H^m$	H^d/H^p
-32	-12	-25	-29

the same condition with Table II

crotonaldehyde-**1** (R = H)

NOE (saturate/observe, %) $H^b/2H^m$	H^b/H^p	$H^c/2H^m$	H^c/H^p
-8	-6	2	-32

the same condition with Table III

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Supplementary Material Available: Detailed data on Scheme I and Table I; ^1H NMR spectral data for **1**, methacrolein, crotonaldehyde, and the **1**–α,β-enal complexes under NOE experimental conditions and their experimental procedures; a listing of complete crystallographic data for racemic 2-*O*-(2,6-dimethoxybenzoyl)tartaric acid (17 pages); observed and calculated structure factors (6 pages). Ordering information is given on any current masthead page.

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