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STEREOCHEMICAL ASPECTS OF ASYMMETRIC DIELS-ALDER REACTION CATALYZED BY CHIRAL ALKOXYALUMINUM DICHLORIDES

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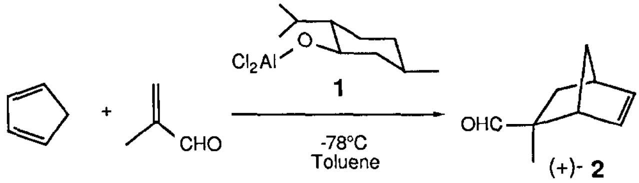
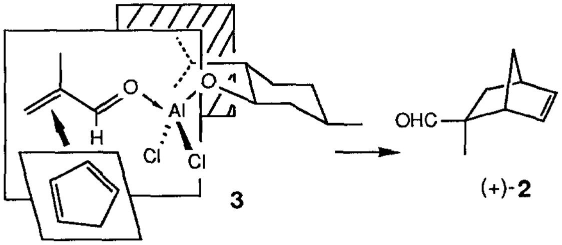
Summary: Clear stereochemical relationships were observed between the structure of chiral sources of catalysts and absolute configuration of the Diels-Alder adducts.

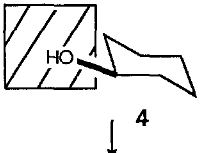
Design and application of the chiral Lewis acids to the asymmetric Diels-Alder reaction have been the current subject of substantial international interest.[1,2] However, for the purpose of designing chiral catalysts, it is highly desirable to accumulate the precise stereochemical knowledge on the transition state.

Previously we have reported the use of menthoxyaluminum dichloride (**1**)[3] in the catalytic asymmetric Diels-Alder reaction of cyclopentadiene with methacrolein.[2] To gain a more insight on the transition states, we have studied the stereochemical relationships between the structure of chiral sources of catalysts and the absolute configuration of the major product by using a variety of chiral cyclohexanol derivatives as chiral sources.



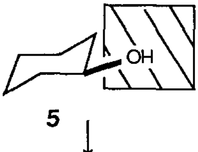
Assuming a possible transition state as shown in **3**,[4] the isopropyl substituent of menthol moiety should shield the back face of the coordinated methacrolein, resulting in the entry of





4

(+)-**2**



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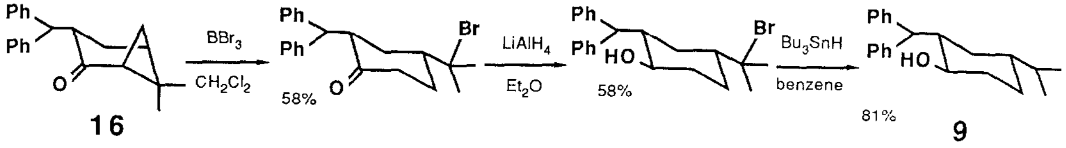
(-)- **2**

cyclopentadiene from the front face to produce the observed (+)-**2**. As a general consideration, the cyclohexanol derivatives bearing the shielding group (**4**, **5**) would afford the (+)- and (-)-**2**, respectively. And the better shielding would afford the higher enantiomeric excess (ee).

Based on the consideration above, several cyclohexanol derivatives were synthesized. The optically pure alcohol (**9**) with the fixed conformation was prepared from **16**[5] in three steps (BBr_3/CH_2Cl_2,[6] $LiAlH_4$/ether, Bu_3SnH-AIBN/benzene) as shown in Scheme I.[7] The other optically pure alcohols (**6**,[8] **8**,[5] **10**,[9] **11**,[10] **12**,[11] **13**,[9] **14**,[5] **15**[12]) were prepared according to the reported procedure.

Scheme 1



A typical experimental procedure is exemplified in the reaction using **8**. To a cooled (-78 °C) solution of **8** (0.61 g, 2.0 mmol) in a mixture of toluene and hexane (1:1, 4 ml) was added a 1 M hexane solution of ethylaluminum dichloride (1.0 ml, 1.0 mmol). After stirring at room temperature for 30 min,[13] methacrolein (distilled and stored over MS 4A) (0.6 ml, 7.3 mmol) in toluene (3 ml) was added at -78 °C. After stirring for 20 min at -78 °C, cyclopentadiene (0.7 ml, 8.5 mmol) in toluene (3 ml) was added and the whole was stirred at -78 °C for 2.5 h. The mixture was quenched with water (10 ml) and extracted with hexane. Silica gel column chromatography (ether/pentane=1/30) afforded (+)-**2** ($[\alpha]_D^{20}$ +10.5 °(c=3.80, EtOH))[2] in 45% ee and in 83% yield.

Clear correlation between the structure of the cyclohexanol derivatives used and the absolute configuration of the adducts is obvious as summarized in the Table I. It is noteworthy that cyclohexanol derivatives bearing equatorial hydroxyl group lead to the adduct with expected absolute configuration (the left and center columns in the Table I), whereas the alcohols with axial hydroxyl group and **15** with different conformation lead to the random absolute configuration (the right column). As has been expected, the alcohols having better shielding group exhibited higher ee (**6** *vs* **7**; **10**, **11** *vs* **12**).[14]

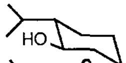
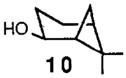
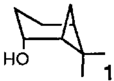
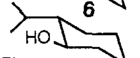
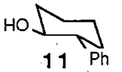
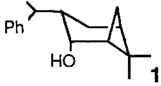
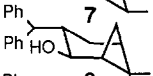
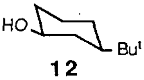
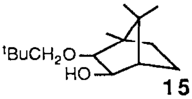
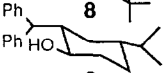
To the purpose of getting more insight on the aluminum moiety, we turned our focus on the substituent of aluminum. Substitution of one chlorine atom with bulkier alkyl group would lead to the transition state (**17**) where the alkyl group (R) on aluminum would block the approach of cyclopentadiene from the front face, resulting in the decrease of enantioselectivity.

In fact, the catalysts (**18**, **19**) with bulkier alkyl group on aluminum lead to the poorer enantioselectivity as summarized in the Table II.[15]

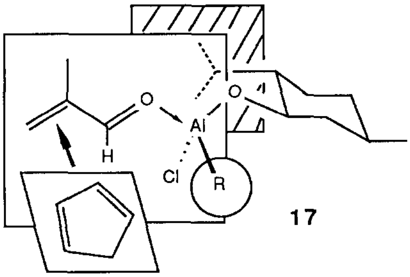
The observed stereochemical relationships between the enantioface selection and the structure of chiral sources of catalysts as well as the substituents on aluminum atom clearly indicate the high probability of the transition state **3**.

Continuing efforts to develop rationally designed chiral catalysts are in progress.

Table I. Asymmetric Diels-Alder reaction catalyzed by R*OAlCl$_2$[a]

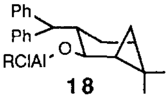
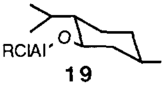
	2				2				2		
R*OH	Yield/%	ee/%	(+/-)	R*OH	Yield/%	ee/%	(+/-)	R*OH	Yield/%	ee/%	(+/-)
 **6**	80	61	(+)	 **10**	69	35	(-)	 **13**	65	20	(+)
 **7**	56	57	(+)	 **11**	56	35	(-)	 **14**	71	0	
 **8**	83	45	(+)	 **12**	67	11	(-)	 **15**	75	7	(-)
 **9**	72	36	(+)								

a) Reaction was carried out according to the typical procedure. Enantiomeric excess and absolute configuration were determined by optical rotation (see reference 2).



17

Table II. Effect of Substituent on Aluminum

		(+)-**2**	
catalyst	R	yield/%	ee/%
 **18**	Cl	83	45
	Et	70	16
	i-Bu	68	7
 **19**	Cl	56	57
	Et	57[a]	35
	i-Bu	67[a]	23

a) Yield and enantiomeric excess of the corresponding alcohol prepared by the reduction of the crude product with LiAlH$_4$.

References and Notes

1) M. Quimpère and K. Jankowsky, *J. Chem. Soc., Chem. Commun.*, **1987**, 676; G. Bir and D. Kaufmann, *Tetrahedron Lett.*, **28**, 777 (1987); K. Narasaka, M. Inoue, and T. Yamada, *Chemistry Lett.*, **1986**, 1967; M. Bednarsky, C. Maring, and S. Danishefsky, *Tetrahedron Lett.*, **24**, 3451 (1983); E. Kobayashi, S. Matsumoto, and J. Furukawa, *Polymer Bull.*, **3**, 285 (1980); M. M. Guseinov, I. M. Akhmedov, and E. C. Mamedov, *Azerb. Khim. Zhur.*, **1976**, 46 (*Chem. Ab.*, **85**, 176925z (1976)).
2) S. Hashimoto, N. Komeshima, and K. Koga, *J. Chem. Soc., Chem. Commun.*, **1979**, 437.
3) Y. Hayakawa, T. Fueno, and J. Furukawa, *J. Polymer Sci.*, **5**, 2099 (1967).
4) The simplified transition state **3** is deduced from the most stable conformation of menthyl acrylate. For the conformation of menthyl acrylate and its relation to the diastereoface differentiation in the Diels-Alder reaction, see: R. J. Loncharich, T. R. Schwartz, and K. N. Houk, *J. Am. Chem. Soc.*, **109**, 14 (1987).
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6) J. P. Konopelski and C. Djerassi, *J. Org. Chem.*, **45**, 2297 (1980).
7) All new compounds described here afforded satisfactory analytical and spectroscopic data.
8) C. Djerassi, P. A. Hart, and C. Beard, *J. Am. Chem. Soc.*, **86**, 85 (1964).
9) O. Wallach, *Ann.*, **356**, 227 (1907).
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12) W. Oppolzer, C. Chapuis, G. M. Dao, D. Reichlin, and T. Godel, *Tetrahedron Lett.*, **23**, 4781 (1982).
13) In the criteria of reproducibility, the chiral alkoxyaluminum dichlorides were prepared *in situ* and used directly in the reaction (This procedure, however, lead to somewhat poorer ee.) See reference 2.
14) At the outset of the study, it was expected that **9** would afford the better ee than **6**, **7**, and **8**. Although it is unclear why **9** afforded the lower ee than **6** and **7**, it is probable that the "effective radius" of phenyl smaller than methyl group (G. Bott, L. D. Field, and S. J. Sternhell, *J. Am. Chem. Soc.*, **102**, 5618 (1980)) would be operative. The reason of poorer ee of **9** than **8** is still unclear.
15) The catalysts (**18**, **19**) were prepared *in situ* by treating the corresponding alcohols with dialkylaluminum chloride and used directly in the reaction.

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