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Remarkable Solvent Effect on the Enantioface Selectivity in the Diels-Alder Reaction Catalyzed by an Aluminum Complex of a Newly Prepared Chiral Menthol Derivative

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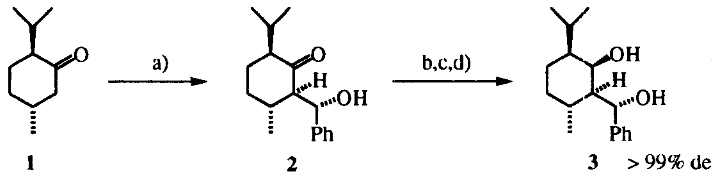
Abstract: Reversal of enantioface selectivity was observed by merely switching the solvent from CH_2Cl_2 (enantiomer ratio of the adduct = 91:9) to THF (14:86) in the asymmetric Diels-Alder reaction catalyzed by the aluminum complex of a newly prepared chiral menthol derivative. Negative nonlinear effect on the relationship between enantiomeric excesses of the reaction product and optical purities of the ligand was observed for the reaction in CH_2Cl_2 whilst linear relationship for that in THF.

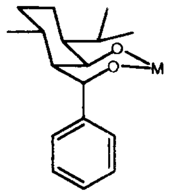
The choice of a suitable solvent is very important to perform various reactions. There have been reported several empirical parameters of solvents which facilitate the estimation of solvent effects.[1] However, it is still hard to predict the precise solvent effect in the chiral metal catalyzed asymmetric reactions. During our study on the asymmetric Diels-Alder reaction catalyzed by an aluminum complex[2] having a newly developed chiral 1,3-diol ligand (**3**), we observed an unusual reversal of enantioface selectivity merely by switching the solvent from CH_2Cl_2 to THF. Since to our knowledge such remarkable solvent effect has not been reported for asymmetric Diels-Alder reaction catalyzed by a chiral metal complex,[3] we wish to report it here along with further investigation into the nature of this effect.

The ligand **3** was prepared from (-)-menthone (**1**) as shown in Scheme 1. The aldol reaction of **1** with benzaldehyde proceeded smoothly at -78 °C to give hydroxy ketone **2** predominantly which could be readily separated from minor diastereomers by chromatography.[4] Subsequent diastereoselective reduction of the ketone in **2** was achieved by using diisobutylaluminum hydride after trimethylsilylation of the hydroxyl group. Cleavage of the silyl ether with Bu_4NF gave **3** as a single stereoisomer which was expected to form a 6-membered chelate **A** with various metal ions (M).

Scheme 1



a) LDA, benzaldehyde, 80% b) TMSCl, imidazole, 98% c) diisobutylalminum hydride d) Bu_4NF, 93% (2 steps)

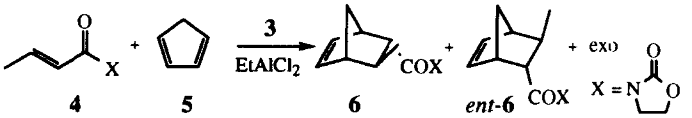


A

The Diels-Alder reaction of 3-crotonoyl-2-oxazolidone (**4**) and cyclopentadiene (**5**) producing adduct **6**,[5] was examined by using the aluminum complex prepared *in situ* from equiamount of $EtAlCl_2$ and **3**.[6] In CH_2Cl_2, the highest enantioselectivity was observed (Table 1, entry 1). Interestingly, however, the reaction in THF and dioxane showed the opposite sense of enantioface selectivity (Table 1, entries 5 and 6).

To clarify the origin of the unusual solvent effect, the relationships between the optical purities of **3** and **6** were examined. As shown in Figure 1, the plots of data obtained with the reaction in CH_2Cl_2 showed a negative nonlinear relation.[7] On the other hand, a linear relation was observed in the more polar THF with reversal of enantioface selectivity. Although the structures of the true active catalysts are quite ambiguous, it is reasonable to consider that a monomeric complex is the active species in THF and an origomeric one is the

Table 1. Solvent effect in the asymmetric Diels-Alder reaction catalyzed by the aluminum complex.[a)]



Entry	Solvent	Time(h)	Yield(%)[b)]	6 : *ent*-6[c)]
1	CH_2Cl_2	6	89	91 : 9
2	$(CH_2Cl)_2$	24	89	79 : 21
3	Toluene	20	95	57 : 43
4	Et_2O	24	77	57 : 43
5	THF	24	87	14 : 86
6	Dioxane	41	99	34 : 66

a) The reactions were conducted at 0°C as described in reference 6. b) Isolated yields of the mixture of *endo* (**6** and *ent*-**6**) and *exo* diastereomer. The isomer ratios were in the range of *endo*:*exo* = 65-77:35-23. c) The enantiomer ratios were determined by HPLC analysis using a chiral stationary phase column (Daicel chiralcel OF).

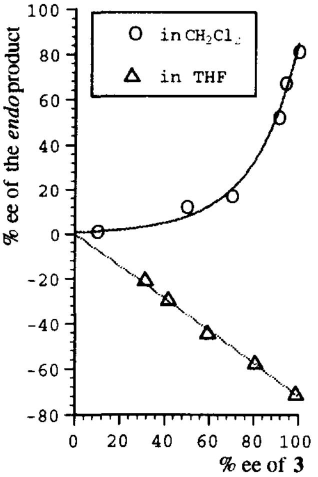


Figure 1. Nonlinear (in CH_2Cl_2) and linear (in THF) relations in the asymmetric Diels-Alder reaction.

active species in CH_2Cl_2.[8] Each complex should show the opposite sense of enantioface selectivity. Furthermore, the *negative* nonlinear effect suggests that the heterochiral oligomer possesses higher catalytic activity than the homochiral one.

The present study disclosed that the remarkable solvent effect on enantioface selectivity is strongly related to the aggregation state of the catalysts. This finding is expected to contribute to opening a new avenue to obtain both enantiomers by using the same chiral catalyst but a different solvent.

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References and Notes

This study is dedicated to Professor Dieter Seebach in celebration of his 60th birthday.

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6) Representative experiment of the reaction is as follows (Table 1, entry 1). $EtAlCl_2$ (0.15 ml, 0.15 mmol) in hexane (1.0 M) was added to **3** (40.3 mg, 0.15 mmol) in CH_2Cl_2 (2 ml) at -20°C. After stirring at rt for 1.5 h, the mixture was cooled to 0 °C. Successive addition of **4** (23.5 mg, 0.15 mmol) in CH_2Cl_2 (0.5 ml) and **5** (0.29 ml, 3.8 mmol), stirring at the same temperature for 6 h, usual work-up, and purification with column chromatography on silica gel (hexane-AcOEt 4:1) afforded **6**. $[\alpha]_D$ +145° (82% ee, c 0.35, CCl_4).
7) Guillaneux, D.; Zhao, S.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430.
8) The ^1H NMR measurement of the homochiral aluminum complex in CD_2Cl_2 showed a single set of peaks mainly while that of the heterochiral complex showed two sets of peaks mainly. On the other hand, these complexes showed similar broad peaks mainly in d_8-THF.

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