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ASYMMETRIC DIELS-ALDER REACTION.
COOPERATIVE BLOCKING EFFECT IN ORGANIC SYNTHESIS

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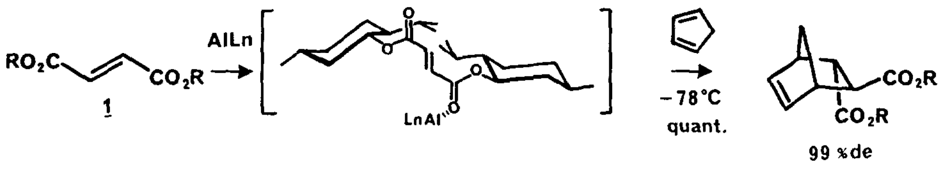
Summary: Remarkably high diastereoselectivity is observed in the organoaluminum catalyzed asymmetric Diels-Alder reaction of (-)-dimenthyl fumarate.

The title reaction, pioneered by Walborsky[1] and thoroughly developed by Helmchen and Oppolzer, has been established as one of the most important tools in modern asymmetric synthesis.[2] In their study of the influence of concave-convex topological features on asymmetric Diels-Alder reaction, they developed a number of facinating chiral auxiliary groups that in certain cases achieved levels of diastereoface differentiation significantly superior to those realized with simple menthol. Unfortunately, however, many of those methods become impractical for operation on large scale because of the limited availabilities of the chiral auxiliary groups. Readily available dimenthyl fumarate (**1**), on the other hand, appears to deserve careful reinvestigations[1] since its primitive topological feature seems to be underestimated.[3] We now describe our study on Diels-Alder reaction using dimenthyl fumarate which forms a basis for a broad range of synthetic applications.

Fortunately, by swiching from simple Lewis acid catalyst[1] to homogeneous organoaluminum reagent,[4] the diastereoselectivity of the reaction was improved dramatically (eq. 1). Furthermore, the diastereoface differentiation of the reaction of **1** with isoprene appeared to increase monotonously by lowering the reaction temperature. When the observed enantioselectivity, ln(*S*,*S*)/(*R*,*R*), was plotted against reciprocal of the temperature, 1/T (in K), a straight line was obtained at temperatures ranging from 25 to -40°C (Figure 1). Thus, a



eq 1

single reacting species may be responsible for the reaction.[5] From the line slope, the difference in activation energy of the reaction leading to the (R,R)- and (S,S)-product is estimated to be 2.3 kcal/mol under these reaction conditions. Generally, the optical yield was enhanced significantly by lowering the reaction temperature (Table 1) and the highest value, up to 99% was recorded by carrying out the reaction at -78°C (entry 10). Notably, the complex of dimenthyl fumarate and diethylaluminum chloride is reactive enough even at -78°C. Usually for the completion of the reaction at reasonable rate at lower temperature, use of 2 equiv of the reagent was required. The extent of the asymmetric induction is somewhat dependent on the nature of aluminum reagent: the less reactive diethylaluminum chloride is slightly superior to ethylaluminum dichloride. A series of dienes was then subjected to Diels-Alder reaction with organoaluminum reagent at low temperature and all the attempted reactions proceeded with excellent stereoselection.[6]

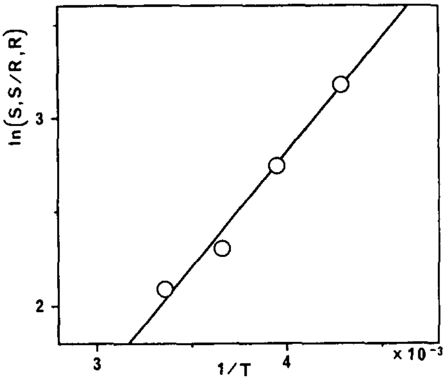
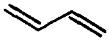
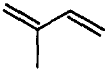
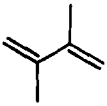
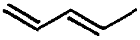
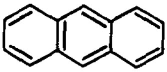
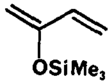


Figure 1. Temperature dependence of the diastereomeric ratio for the Diels-Alder reaction of **1** and isoprene in CH_2Cl_2.

The method is based on the strategy of forming from a relatively simple molecule a single intermediate which should have an appropriate symmetry element so as to accumulate the chiral directing capacity of prosthetic groups.[7] A similar cooperative blocking effect has been successfuly utilized for the asymmetric carbocyclization reaction previously reported from our laboratory.[3] In conclusion, the extraordinary efficiency of the cooperative blocking effect (CB effect) during the Diels-Alder process coupled with its operational simplicity opens for the first time the possibility of synthesizing a variety of chiral compounds in large amount.[8] Furthermore, it should also be noted that both enantiomers of menthol are commercially available in optically pure form, and therefore, the present method allows the synthesis of both (R,R) and (S,S) adducts with equal ease.

Table 1. Asymmetric Diels-Alder Reaction of Dimenthyl Fumarate with Dienes[a]

Entry	Diene	Lewis Acid (equiv)	Conditions		------ Adduct --------		
			^{o}C	Solvent	Yield(%)	%de	Confign[b]
1		*i*-Bu$_2$AlCl (2.0)	-40	Hexane	56	95	*S*,*S*
2		AlCl$_3$ (1.0)	-20	Toluene	60	66	
3		*i*-Bu$_2$AlCl (1.0)	-20	Hexane	94	95	
4		*i*-Bu$_2$AlCl (2.0)	-40	Hexane	80	97	
5		Et$_2$AlCl (1.0)	-40	CH$_2$Cl$_2$	32	92	
6		Et$_2$AlCl (2.0)	-20	Toluene	78	92	
7		Et$_2$AlCl (1.0)	-20	Toluene	95	93	*S*,*S*
8		EtAlCl$_2$ (1.0)	-20	Toluene	91	86	
9		Et$_2$AlCl (1.0)	-20	Toluene	100	91[c]	*S*,*S*
10		Et$_2$AlCl (1.0)	-78	Toluene	100	99	
11		None	25	Toluene	100	2	
12		Et$_2$AlCl (1.0)	-20	Toluene	70	96	
13		None	60	Benzene	68	-12	*R*,*R*
14		Et$_2$AlCl (1.0)	-20	Toluene	39[d]	94[c]	
					23[e]	92	
15		EtAlCl$_2$ (2.0)	25	Toluene	81	99[f]	*S*,*S*
16		AlCl$_3$ (2.0)	25	Toluene	92	99	
17		None	110	Toluene	70	3	
18		Et$_2$AlCl (2.0)	-20	Toluene	92	94[g]	
19		None	reflux	Toluene	67	0	

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[a] Yields are for isolated products. All new compounds gave appropriate analytical and spectral data. Unless otherwise specified, the diastereomeric ratio (%de) was determined on the basis of GC analyses of the adducts. [b] Determined by conversion to diol. [c] Determined by GC analysis after hydrogenation of the double bond. [d] 2,3-cis isomer. The stereochemical assignments are based on the observation in the base catalyzed trans-cis isomerization and also NMR analyses. [e] 2,3-trans isomer. [f] Determined by HPLC analysis of the adduct and further confirmed by HPLC analysis of MTPA ester derived from the adduct after reduction-esterification sequence.[9] [g] Determined by HPLC analysis after conversion of the adduct to the corresponding MTPA esters by acetalization-reduction-esterification sequence.

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References and Notes

(1) (a) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.*, **1961**, *26*, 4778. (b) *Idem*, *Tetrahedron*, **1963**, *19*, 2333.

(2) Recent review: L. A. Paquette, in "Asymmetric Synthesis, Vol. 3," ed by Morrison, J. D., Academic Press, Inc., Orlando, Florida.

(3) Recent report from our laboratories showed the high asymmetric induction using two menthyl ligands; Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.*, **1985**, *107*, 3343.

(4) Other new synthetic reactions using organoaluminum reagents from our laboratory, Maruoka, K.; Yamamoto, H. *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 668.

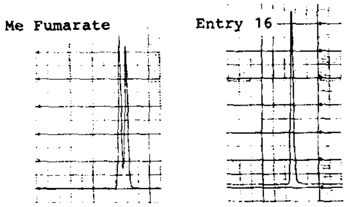
(5) The Lewis acid coordinated fumarate is considered to exist in the *s-trans* form predominantly. Thus, the two (-)-menthyl groups should cooperatively cover the *re* face of the molecule. In the thermal reaction, on the other hand, the free fumarate is regarded to exist as an equilibrium mixture of *s-trans* and *s-cis* conformations.

(6) In contrast to the previous report of Tolbert and Ali,[7] the reaction with anthracene revealed a complete diastereoselection even by aluminum chloride catalysis at ambient temperature.

(7) Tolbert and Ali had proposed a concept of cooperativity in connection with the synchronisity of the concerted reactions. Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.*, **1981**, *103*, 2104. *Idem ibid.*, **1984**, *106*, 3806. *Idem ibid.*, **1982**, *104*, 1742. *Idem ibid.*, **1985**, *107*, 4589. Recently, Masamune et al. described the usefulness of the concept of double asymmetric induction in organic synthesis. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 1.

(8) The following procedure illustrates the method: A solution of (-)-dimenthyl fumarate (9.42 g, 24 mmol) in toluene (144 ml) was treated with diethylaluminum chloride (24 ml of a 1 M hexane solution) at -78°C under nitrogen. The mixture was stirred for 15 min and to the resulting orange solution was added cyclopentadiene (5.85 ml, 72 mmol) dropwise at the same temperature. Acidic workup was conducted and the product was isolated by column chromatography on silica gel (11.0 g).

(9) The MTPA esters of diols derived from the Diels-Alder adducts of dimethyl fumarate (both thermal and aluminum chloride catalyzed reactions) showed two peaks (1 : 1) on HPLC analysis.



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