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ASYMMETRIC DIELS-ALDER REACTION PROMOTED BY A CHIRAL TITANIUM REAGENT

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The asymmetric Diels-Alder reaction between prochiral dienes and dienophiles prepared from α,β-unsaturated acids and 1,3-oxazolidin-2-one proceeds by the use of a chiral alkoxy titanium(IV) to give the corresponding cycloadducts in high enantioselectivity.

Due to the preeminent utility of the Diels-Alder reaction in organic synthesis, considerable attention has been given to the exploration of intermolecular asymmetric Diels-Alder reactions. Recent progress in this area has led to the development of various highly selective asymmetric Diels-Alder reactions by employing chiral dienes or dienophiles.$^{1)}$ On the other hand, little work has been done on asymmetric Diels-Alder reactions promoted by chiral Lewis acids$^{2)}$ and this area remains as an unexplored field.

In this communication, we describe a highly enantioselective Diels-Alder reaction between prochiral dienes and dienophiles utilizing a chiral alkoxy titanium(IV).

Firstly, α,β-unsaturated acids of dienophiles were converted to the corresponding 3-acyl-1,3-oxazolidin-2-ones 1 based on the consideration that such bidentate dienophiles would form rigid complexes with a chiral Lewis acid to result in a good level of π-facial selectivity during the cycloaddition process. As a chiral Lewis acid, cyclic dialkoxy dichloro titaniums(IV) 2 were chosen and prepared in situ from various chiral 1,2- or 1,4-diols 3 and dichlorodiisopropoxytitanium(IV) according to the alkoxy exchange method.$^{3)}$

The reaction of 3-crotonoyl-1,3-oxazolidin-2-one (1a) and cyclopentadiene was examined in toluene in the presence of an equimolar amount of various chiral alkoxy titaniums 2 (Table 1). When chiral 1,1,4,4-tetraphenylbutanetetraol derivatives 3b$^{3)}$ and 3c were used as chiral auxiliaries, the endo adduct 4 was obtained in good enantioselectivity. Especially, the titanium reagent derived from 2,3-O-phenylethylidene derivative 3c$^{4)}$ was found to promote the asymmetric cycloaddition reaction in a selective manner, and the optical purity of the adduct 4a reached up to 75% ee. Moreover, by the use of 2 molar amounts of the titanium reagent 2c, the product 4a was obtained in 92% ee.

Since a high level of enantioselectivity was achieved by the employment of the chiral titanium reagent 2c, the asymmetric Diels-Alder reaction of various 1,3-oxazolidin-2-one derivatives of α,β-unsaturated acids and cyclopentadiene was studied in the presence of 2 molar amounts of the titanium reagent 2c and the results are listed in Table 2. Excepting the acryloyl derivative 1b, various dienophiles 1 were found to react with cyclopentadiene in a highly selective manner to afford the corresponding endo adducts 4 in high optical purity (80-92% ee).

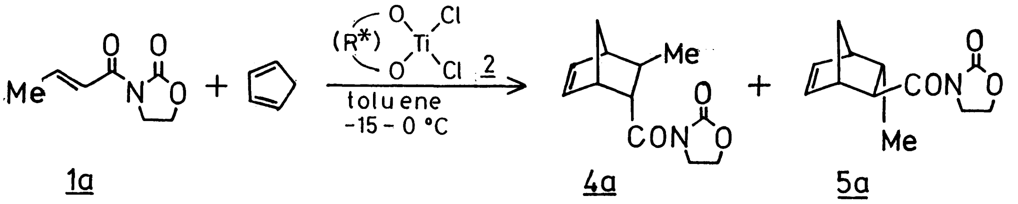
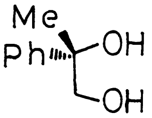
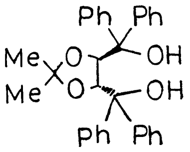
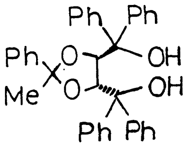


Table 1. Effect of Chiral Diols 3 in the Reaction of 1a with Cyclopentadiene

Diol 3		Yield/%[a]	endo:exo (4a:5a)	ee/% of 4[b]	Abs.config.
	3a	73	86 : 14	2	2R,3S
	3b	88	93 : 7	55	2S,3R
	3c	quant.	86 : 14	75	2S,3R
		93[c]	90 : 10	92	2S,3R

Molar ratio of dienophile : titanium reagent = 1 : 1.

a) Total yield of the endo and exo isomers which were separated by column chromatography on silica gel.

b) The product was esterified to the benzyl ester by Evans's procedure,[5] and the optical purity was determined by the optical rotation.[1d]

c) Molar ratio of dienophile : titanium reagent = 1 : 2.

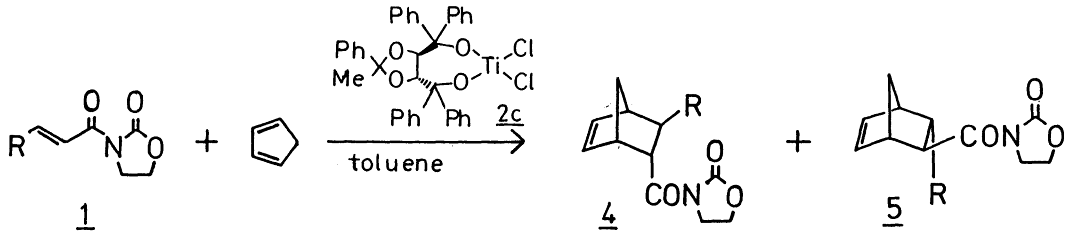


Table 2. Asymmetric Diels-Alder Reaction of 1 with Cyclopentadiene

Dienophiles R		React.temp / ℃	Yield/%[a]	endo:exo	ee/% of 4	[α]$_D$/°	Abs.config.
Me	1a	-15	93	90 : 10	92[b]	-191 (c 3.6, CCl_4)	2S,3R
H	1b	-78	69	86 : 14	38[b]	- 65 (c 1.5, $CHCl_3$)	2S
Ph	1c	0	97	92 : 8	81[c]	-143 (c 1.2, CCl_4)	
n-Pr	1d	-15	82	90 : 10	90[d]	-158 (c 2.0, CCl_4)	
	1e	r.t.	77	92 : 8	82[d]	-142 (c 3.5, CCl_4)	

Molar ratio of dienophile : titanium reagent = 1 : 2.

All the products gave satisfactory ^1H NMR and IR spectra.

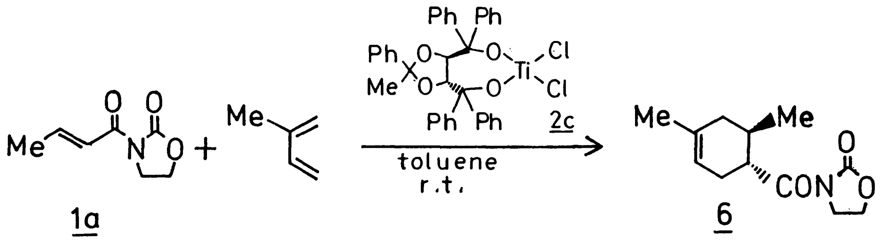
a) Total yield of endo and exo isomers. These isomers were separated by column chromatography on silica gel.

b) The products were converted to the corresponding benzyl esters by Evans's procedure,[5] and the absolute configuration and the optical purity were determined by the optical rotation.[1d]

c) The product was reduced to an alcohol with lithium aluminum hydride, and the optical purity was determined by ^{19}F NMR analysis of the corresponding chiral MTPA ester.[6]

d) The products were reduced to alcohols with lithium aluminum hydride, and the optical purity was determined by HPLC analysis of the corresponding chiral Pirkle's carbamates.[7] (Waters μPolasil, hexane : ethyl acetate = 30 : 1)

Furthermore, high enantioselectivity was observed by the application of the chiral titanium reagent 2c to the reaction of 1a and an acyclic diene such as isoprene, and the cycloadduct 6 (the absolute configuration was not determined) was obtained in 92% ee.



Thus, according to the present methods utilizing the chiral alkoxy titanium(IV), it is noted that high enantioselectivity is achieved in the asymmetric Diels-Alder reaction between prochiral dienes and dienophiles.

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4) The diol 3c was prepared from L-(+)-dimethyl tartrate. The reaction of the tartrate with 1,1-dimethoxy-1-phenylethane and a cat. amount of p-toluenesulfonic acid gave the 2,3-O-phenylethylidene derivative, which was converted to the diol 3c by treatment with excess phenylmagnesium bromide. The diol 3c was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1), and recrystalization of 3c from a mixture of hexane and 2-propanol gave the complex of 3c with 2-propanol as a white crystal (mp 111-114 °C). Then, by the azeotropic removal of 2-propanol with benzene was obtained the diol 3c as a white amorphous solid. The enantiomeric isomer of the diol 3c was not observed by HPLC analysis (Chiralpak OT(+), Daicel Chemical Industries; hexane : 2-propanol = 7 : 1).

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