CHEMISTRY LETTERS, pp. 1609-1612, 1988.

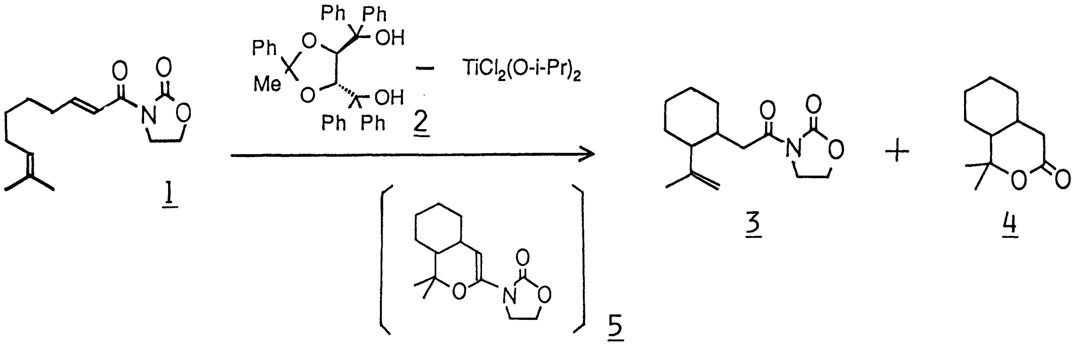
Asymmetric Intramolecular Ene Reaction Catalyzed by a Chiral Titanium Alkoxide

Koichi NARASAKA, Yujiro HAYASHI, and Satoru SHIMADA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Asymmetric intramolecular ene reaction proceeds by employing a chiral titanium alkoxide as a Lewis acid, and cyclohexane derivatives are prepared in high enantioselectivity from 1,3-oxazolidin-2-one derivatives of 2,8-dienoic acids.

Ene reaction is one of the typical pericyclic reactions and has been widely employed in organic synthesis for constructing various carbon skeletons.1) But as for an asymmetric ene reaction, there have been only a few successful precedents, most of which are diastereoselective reactions using chiral enophiles.2) Furthermore, little work has been done on catalytic asymmetric ene reaction,3) though Lewis acids have been known to effectively promote ene reactions. We have already reported that the asymmetric Diels-Alder reaction4) and hydrocyanation reaction5) are effectively promoted by a chiral titanium alkoxide prepared from a chiral diol 2 and dichlorodiisopropoxytitanium. Since this chiral titanium reagent is expected to be applied as a chiral Lewis acid to various reactions, we next investigated an intramolecular ene reaction6) employing this reagent, by which various cyclic compounds would be prepared in an enantioselective manner.

3-(9-Methyl-2,8-decadienoyl)oxazolidin-2-one(1) was treated with the chiral titanium alkoxide prepared by mixing the chiral 1,4-diol 2 and dichlorodiisopropoxytitanium in toluene in the presence of Molecular Sieves 4A. Though the reaction was slow and the starting material still remained after 20 d at 0 °C, the desired ene product 3 was obtained in 17% yield, along with a bicyclic lactone 4 in 37% yield. This lactone is supposed to be obtained by the hydrolysis of an intermediate 5, which is generated by a hetero Diels-Alder reaction.7) The



cyclohexanes **3** and **4** were isolated as mixtures of cis and trans isomers, and the optical purity was not able to be determined.

It is known that some intramolecular cyclization reactions are accelerated when geminal disubstituents are introduced on the main chain (so called the geminal dialkyl effect).8) In order to enhance the reactivity of the intramolecular ene reaction, we made an oxazolidone derivative of 2,8-dienoic acid **6** which has 5,5-dimethyl groups, and tried the reaction using the chiral titanium reagent in toluene. In fact, the reaction was completed within 4 d at 0 °C and gave the ene product **7** and the hetero Diels-Alder product **8** in 39% and 36% yield, respectively. Each of them was obtained as a single trans isomer,9) with 82%10) and 92%11) optical purity.

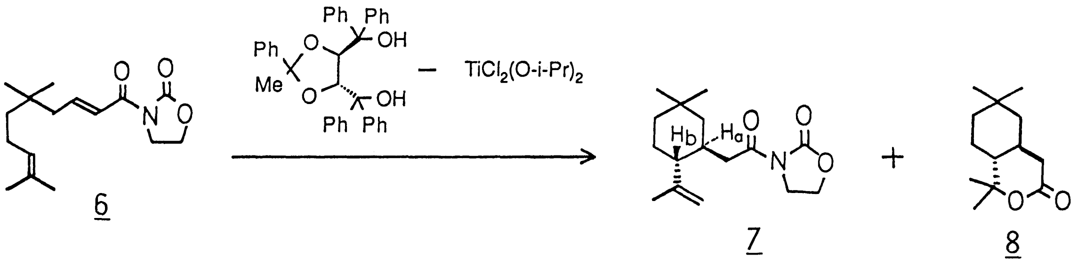
As remarkable solvent effect on the enantioselectivity was observed in the asymmetric Diels-Alder reaction,12) the above reaction was further examined in various solvents. The enantioselectivity and the ratio of the ene adduct and the hetero Diels-Alder product were found to be greatly influenced by solvents. When the ene reaction was carried out in 1,3,5-trimethylbenzene, the hetero Diels-Alder product **8** was formed in more than 98% ee, and in 1,1,2-trichloro-1,2,2-trifluoroethane the ene product **7** was obtained predominantly(63%) in more than 98% ee.

Typical procedure using 1,1,2-trichloro-1,2,2-trifluoroethane(Fron 113) as solvent in Table 1 is as follows: To a Fron 113 solution (1.5 mL) of dichlorodiisopropoxytitanium (0.34 mmol) was added chiral diol **2** (0.38 mmol) in Fron 113 (3 mL) at rt. After the reaction mixture was stirred at that temperature for 1 h, Molecular Sieves 4A (powder, 60 mg) was added. After 10 min, the solution (2 mL) of 3-(5,5,9-trimethyl-2,8-decadienoyl)oxazolidin-2-one (**6**, 0.30 mmol) was added at 0 °C and stirred at that temperature for 4 d. The reaction was quenched by adding aqueous sodium hydrogen carbonate and the purification by thin layer chromatography gave the ene product **7** (63%), and the hetero Diels-Alder product **8** (25%).

Table 1. Solvent Effect on Ene and Hetero Diels-Alder Reaction

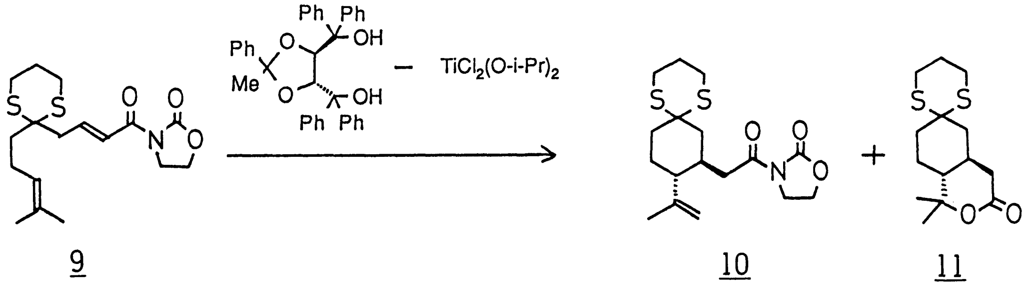
	7		**8**	
Solvent	Yield/%	Opt. Pur./% ee	Yield/%	Opt.Pur./% ee
Toluene	39	82	36	92
1,3,5-TMB[a]	32	86	37	>98[b,13]
CH_2Cl_2	34	66	20	20
$CFCl_3$	56	95	16	-[c]
$CFCl_2CF_2Cl$	63	>98[d,13]	25	-[c]
$CFCl_2CF_2Cl/CH_2Cl_2$[e]	47	97	16	-[c]

a) 1,3,5-Trimethylbenzene. b) $[\alpha]_D^{27}$ +20.7 (c 0.46, CH_2Cl_2).
c) Not determined. d) $[\alpha]_D^{19}$ -50.0 (c 0.87, CH_2Cl_2). e) 5/1 volume ratio.



J_{HaHb} = 10.8 Hz

By introducing two methyl groups at the 5-position, not only the reaction was accelerated but also the high diastereo- and enantioselectivities were attained. In order to prepare a disubstituted cyclohexanone derivative, which is a synthetically important chiral building block, trimethylene dithio group was next introduced instead of dimethyl substituents. The reaction proceeded much faster in 1,3,5-trimethylbenzene than the compound having dimethyl substituent and were completed in 2 d at 0 °C to give the corresponding trans ene **10** and the hetero Diels-Alder **11** products in 84% ee[11,14] and >98% ee,[11,15] respectively. Almost the same results were observed when a reaction was carried out in a mixed solvent ($CFCl_2CF_2Cl/CH_2Cl_2$, 5/1).



We are very grateful to Mr. Takatoshi Kawai (Eizai Co., Ltd.) for the X-ray analysis of the hetero Diels-Alder product **11**.

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7) As the ene adduct **3** was recovered unchanged by treatment with dichlorodiisopropoxytitanium in toluene at rt., the lactone **4** is not formed by the cyclization of the ene product under the present reaction conditions. L. F. Tietz, et al. reported that a hetero Diels-Alder adduct was also obtained as a side product in an intramolecular ene reaction. L. F. Tietz, and U. Beifuss, Justus Liebigs Ann. Chem., 1988, 321. Reviews of hetero Diels-Alder reaction: R. R. Schmidt, Acc. Chem. Res., 19, 250 (1986); G. Desimoni and G. Tacconi, Chem. Rev., 75, 651 (1975).

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9) The coupling constant between H_a and H_b of **7** clearly indicates the trans stereochemistry. The relative stereochemistry of the lactone **8** was confirmed as trans by the comparison with the authentic lactone prepared from **7** by iodo-lactonization and reduction. Absolute configurations of **7** and **8** are not determined.

10) The product was reduced to an alcohol with $LiAlH_4$, and the optical purity was determined by HPLC analysis of the corresponding chiral Pirkle´s carbamate.[16]

11) The opticaly purity was determined after conversion of **8**, **10**, and **11** to the corresponding MTPA esters by HPLC, ^{19}F-NMR, and 270 MHz ^{1}H-NMR analyses, respectively.

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13) The Pirkle´s carbamate of racemic **7**[10] and the MTPA ester of racemic **8**[11] showed two peaks by HPLC analysis. Only a single peak was detected when the chiral products obtained by these reactions were analyzed by the above procedure.

14) Absolute configuration is not determined. $[\alpha]_D^{21}$ -41.8 (c 0.71, CH_2Cl_2).

15) Absolute and relative configurations are determined by X-ray analysis as shown in the scheme. Two sets of two methyl singlet signals were observed in the ^{1}H-NMR spectrum of the MTPA ester of the racemate, and only a couple of methyl signals was detected for the chiral hetero Diels-Alder product.

$[\alpha]_D^{21}$ +18.9 (c 0.56, CH_2Cl_2).

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(Received June 22, 1988)