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Asymmetric [2+2] Cycloaddition Reaction Catalyzed by a Chiral Titanium Reagent

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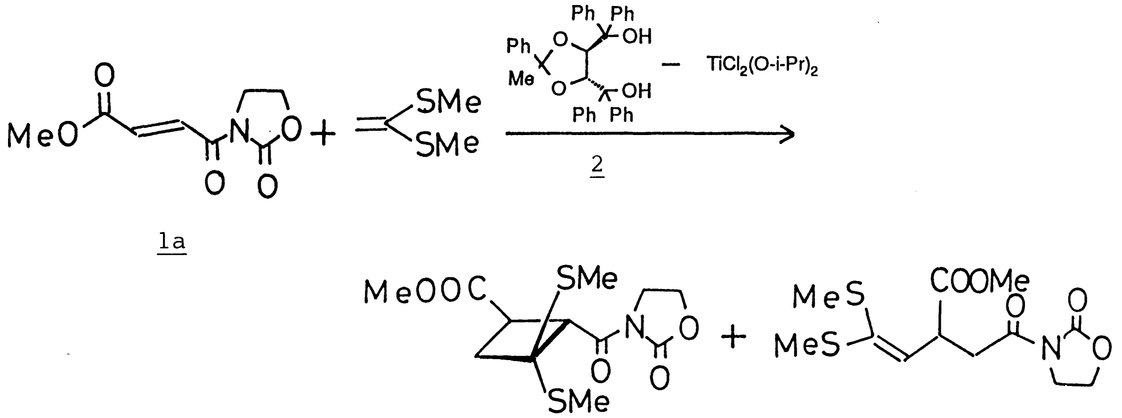
Asymmetric [2+2] cycloaddition reaction between 3-(2-acryloyl)-1,3-oxazolidin-2-one derivatives and 1,1-bis(methylthio)ethylene proceeds by the use of a catalytic amount of a chiral titanium reagent to give the corresponding cyclobutanes in high enantioselectivity.

Cyclobutane and cyclobutanone derivatives are an important class of compounds,[1)] not only because they are included as the basic structure of some natural products[2)] but also because they are converted to a variety of derivatives by further modifications such as ring enlargement and ring opening.[3)] As for the construction of cyclobutane skeleton, the photochemical [2+2] cycloaddition of olefins[4)] and the thermal [2+2] cycloaddition between electrophilic olefins and nucleophlic olefins[4,5)] have been generally employed. But there are few reports on the [2+2] cycloaddition reaction catalyzed by a Lewis acid.[6)]

We have reported that the asymmetric Diels-Alder reaction,[7)] the hydrocyanation reaction[8)] and the intramolecular ene reaction[9)] are effectively promoted by a chiral titanium reagent. In the course of our study on this chiral Lewis acid, it was found that [2+2] cycloaddition reaction was well catalyzed by the chiral titanium reagent and gave the cycloadducts in high enantioselectivity.

Firstly, the reactions of 3-[3-(methoxycarbonyl)acryloyl]-1,3-oxazolidin-2-one (1a) with electron rich olefins were examined in the presence of an equimolar amount of the chiral titanium reagent which was prepared in situ by mixing dichlorodiisopropoxytitanium and the chiral diol 2. The reaction did not proceed at all when a vinyl ether, a silyl enol ether and a ketene silyl acetal were employed. On the other hand, the reaction of 1a and 1,1-bis(methylthio)ethylene gave the cyclobutane derivative 3a in high chemical and optical yields. That is, the treatement of 1a and 1,1-bis(methylthio)ethylene with the chiral catalyst at 0 °C for 1 h in mesitylene afforded the cyclobutane derivative 3a in 93% ee[10)] along with 8% yield of the Michael product 4a.(Eq. 1)

The major product 3a was converted to the corresponding cyclobutanone derivative 6 as shown in Scheme 1. IR and ^{13}C-NMR spectra were in good agreement with the cyclobutanone structure.[11)] X-Ray crystallographic analysis of the single crystal of 5 determined the absolute configuration to be 2R, 3R as depicted in Fig. 1. In order to determine the regiochemistry of the product, X-ray analysis of the racemic 3a which gave more suitable crystal than the optically active one was performed and the structure was determined as drawn in Fig. 2.



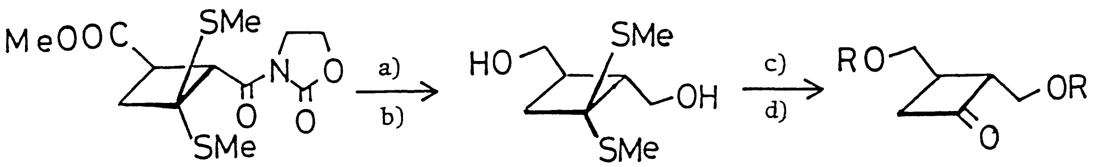
1a 3a 4a

amount of the catalyst

110% mol, 3a, 89%, 93% ee; 4a, 8% (mesitylene).

110% mol, 3a, 78%, 98% ee; 4a,11% (toluene-P. E.).

10% mol, 3a, 96%, 98% ee; 4a, 2% (toluene-P. E.).



3a 5 6 R=t-$BuPh_2Si$

Scheme 1. a) $Mg(OMe)_2$, b) $LiAlH_4$, c) t-$BuPh_2SiCl$, imidazole, d) $AgNO_3$, NBS.[12)]

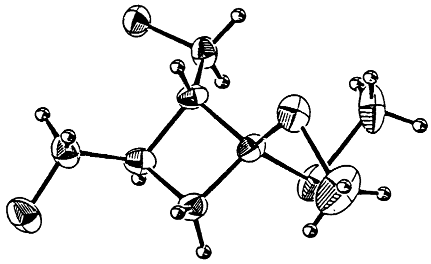


Fig. 1.

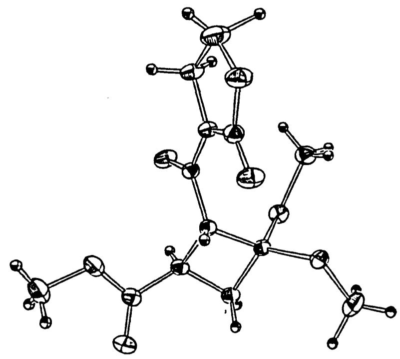


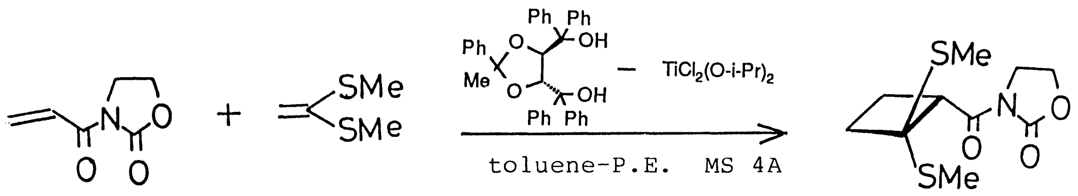
Fig. 2.

Since a remarkable solvent effect on the enantioselectivity was observed in the Diels-Alder reaction and the intramolecular ene reaction catalyzed by the chiral titanium reagent,[7c,9)] the present reaction was investigated in various solvents. The adduct 3a was obtained in high optical purity, when a solvent having small acceptor and donor properties[13)] was used. In particular, the optical purity was increased to 98% ee[10,14)] by the use of a mixture of toluene and petroleum ether (P. E.).

Even by employing 10% mol of the chiral titanium reagent and MS 4A,[7b)] this

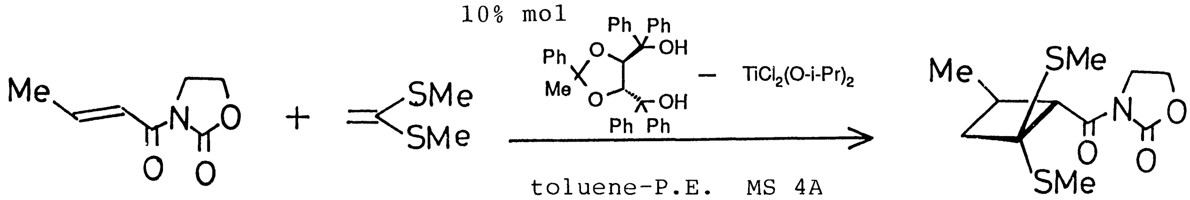
[2+2] cycloaddition reaction also proceeded in 96% yield without any loss of the optical purity (98% ee). Moreover the formation of the Michael product 4a decreased to 2% yield.

The above catalytic procedure was applied to 3-acryloyl and 3-crotonoyl oxazolidinones 1b and 1c. 3-Acryloyl-1,3-oxazolidin-2-one (1b) reacted with 1,1-bis(methylthio)ethylene at 0 °C within 1 h to afford the cyclobutane derivative 3b in 88% ee.[15,16]



1b 3b 74%, 88% ee

In the thermal [2+2] cycloaddition reaction, highly reactive and electrophilic olefins such as methyl vinyl ketone, acetylene carboxylates, and acrylates are generally used.[5] On the other hand, the present method was applicable to the common unsaturated carboxylate like 3-crotonoyl-1,3-oxazolidin-2-one (1c), which was found to react with 1,1-bis(methylthio)ethylene at r.t. for 109 h yielding the adduct 3c in 80% optical purity.[15]



1c 3c 64%, 80% ee

For the preparation of optically active cyclobutanes and cyclobutanones, there have been several precedents up to now. They are optical resolutions, syntheses from chiral building blocks, and asymmetric syntheses using substrates having chiral auxiliaries.[1,17] There has been, however, no example for the synthesis of cyclobutane and cyclobutanone derivatives by the use of an external chiral auxiliary such as a chiral catalyst. The present reaction affords the first example for the asymmetric synthesis of the cyclobutane derivatives by the use of asymmetric catalyst.

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10) The optical purity is determined by the ^{1}H-NMR analysis of the bis-MTPA ester[18] of compound 5. Two sets of the two singlet signals of methyl groups were observed in the spectrum derived from the racemate.

11) IR(neat) 1785 cm^{-1}, ^{13}C-NMR($CDCl_3$) δ = 208.8 ppm.

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14) Two recrystallization from benzene-hexane gave the optically pure 3a. $[\alpha]_D^{23}$ +11.1° (c 0.99, CH_2Cl_2)

15) The optical purities were determined by the ^{1}H-NMR of the bis-MTPA esters[18] derived from 3b and 3c. The absolute configurations are not determined, but the same sence of the enantioselection as that of 3a would be expected.

16) Two recrystallization from benzene-hexane gave the optically pure 3b. $[\alpha]_D^{24}$ +60.0° (c 1.02, CH_2Cl_2)

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