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Asymmetric Intramolecular Diels-Alder Reaction Catalyzed by the Chiral Titanium Reagent

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The highly enantioselective intramolecular Diels-Alder reaction is achieved using a catalytic amount of the chiral titanium reagent prepared from $TiCl_2(OPr^i)_2$ and the tartrate derived chiral 1,4-diol.

The intramolecular Diels-Alder reaction is one of the most useful method for the construction of polycyclic carbon frameworks with the control of relative stereochemistry, and is often employed as a key-step in the total synthesis of natural products.[1] However, asymmetric version of this reaction is not sufficiently studied compared to that of the intermolecular Diels-Alder reaction, and all of the asymmetric intramolecular Diels-Alder reactions previously reported employ substrates having chiral auxiliaries directly in the molecules.[2] Judging from the synthetic utility, it is desirable to develop the enantio-selective intramolecular Diels-Alder reaction using a chiral Lewis acid as an activator.

In previous papers,[3] we reported that the asymmetric intermolecular Diels-Alder reaction of 3-acyl-1,3-oxazolidin-2-one derivatives of α,β-unsaturated carboxylic acids and various dienes proceeds in a highly enantioselective manner by the use of the chiral titanium reagent prepared in situ from $TiCl_2(OPr^i)_2$ and the chiral 1,4-diol 1 derived from tartaric acid. Furthermore, by carrying out the reaction in the presence of Molecular Sieves (MS) 4A, almost the same level of enantioselectivity can be realized using only a catalytic amount of the titanium reagent.[3b,c,d] In this paper was reported the application of the chiral titanium reagent to the enantioselective intramolecular Diels-Alder reaction.

Firstly, the reaction of 3-acyl-1,3-oxazolidin-2-one derivative of (E,E)-2,7,9-decatrienoic acid 2 was examined. Treatment of 2 with an equimolar amount of the chiral titanium reagent in toluene at r.t. for 161 h afforded the endo-cycloadduct 3 in 78% yield as a single isomer.[4] The adduct 3 was reduced to the corresponding alcohol 4 by $LiAlH_4$, and the optical purity of 3 was determined to be 73% by ^1H NMR analysis of the MTPA ester of the alcohol 4.[5,6] The absolute configuration was assigned as shown in 3 by comparison of the optical rotation of 4 with that of the literature.[2b,e]

As a remarkable solvent effect on the enantioselectivity was observed in the asymmetric intermolecular Diels-Alder reaction,[3c,d] this reaction was examined in various solvents such as toluene, a mixture of toluene and petroleum ether (P. E.)

and mesitylene. As shown in Table 1, the same tendency on the solvent effect was observed in this reaction, and in mesitylene, the adduct 3 was obtained in 87% yield in 90% optical purity. Furthermore, the reaction proceeded without loss of enantioselectivity with 30% molar amount of the chiral titanium reagent by the combined use of MS 4A.

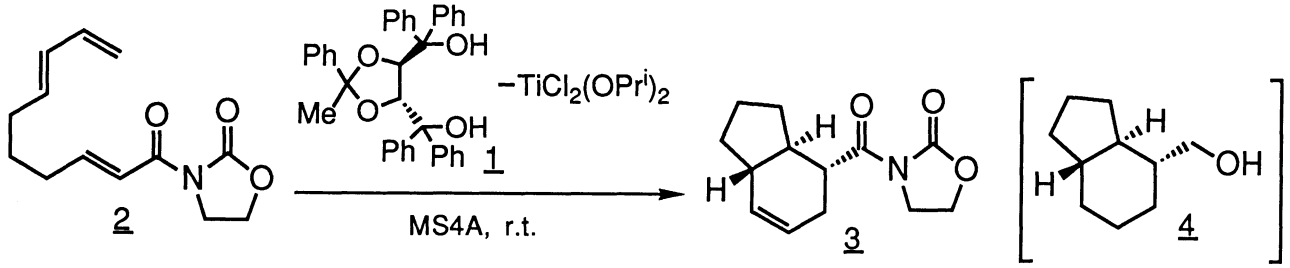
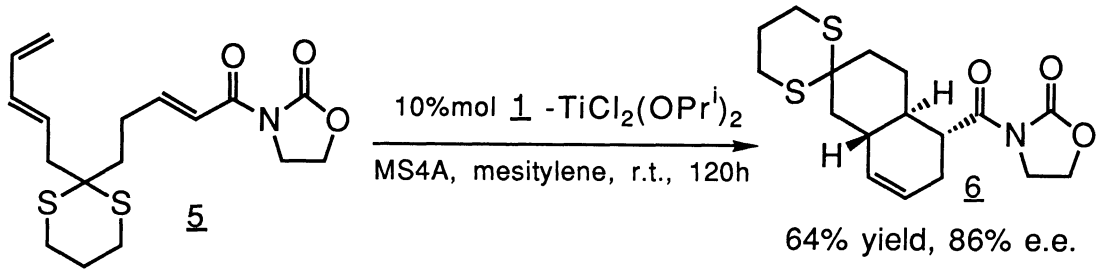


Table 1. The Asymmetric Intramolecular Diels-Alder Reaction of 2

Solvent	Amount of the Ti reagent/% mol	Reaction time/h	Yield of 2/%	Optical purity of 2/%
toluene	100	161	78	73
mesitylene	100	161	87	90
toluene-P.E. (2:1)	100	162	83	86
mesitylene	30	257	87	87

In order to prepare synthetically useful intermediates, we next examined the reaction of the 3-acyl-1,3-oxazolidin-2-one derivatives of trienoic acid having 1,3-dithiane group on the connecting carbon chain. (E,E)-2,8,10-Undecatrienoic acid derivative 5 having 1,3-dithiane moiety at 6-position was treated with an equimolar amount of the titanium reagent at r.t. for 70 h, and the corresponding endo-cycloadduct 6 was obtained in 78% yield as a single isomer.[7] The optical purity of 6 was determined to be 91% by the Mosher's method.[5,8] It was also found that only 10% molar amount of the titanium reagent was sufficient to achieve the high enantioselectivity.



On the other hand, when (E,E)-2,8,10-undecatrienoic acid derivative 7, which has no dithiane moiety onto the connecting chain, was treated with an equimolar amount of the titanium reagent at r.t. for 120 h, the cycloadduct 8 was obtained in low yield as a mixture of the endo and exo isomers. Thus, the introduction of

1,3-dithiane group not only accelerated the reaction but also enhanced the endo-selectivity. It is assumed that the introduction of geminal substituents in the side chain accelerates the reaction due to the geminal dialkyl effect[9] and the enhancement of the endo-selectivity would be due to the unfavorable non-bonded interactions in the exo transition state as shown in Fig. 1.

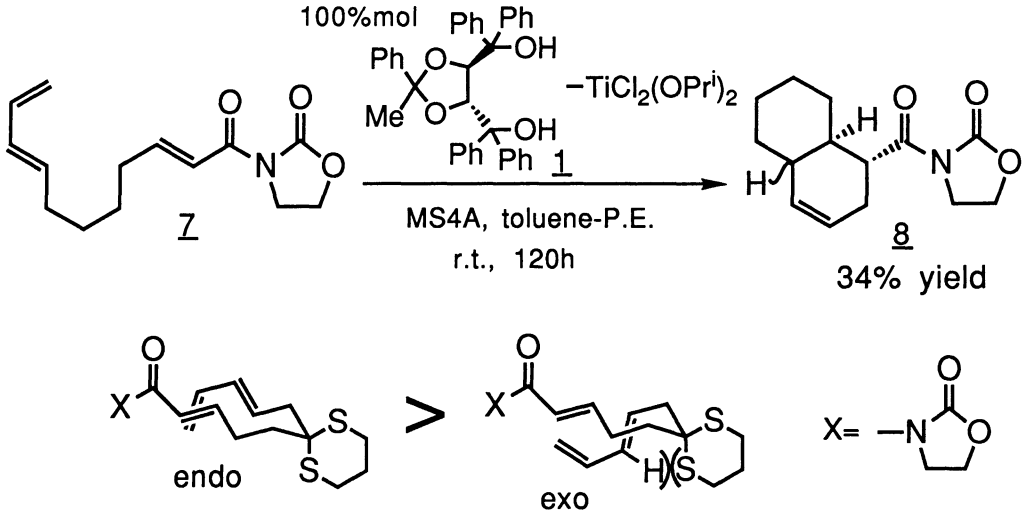
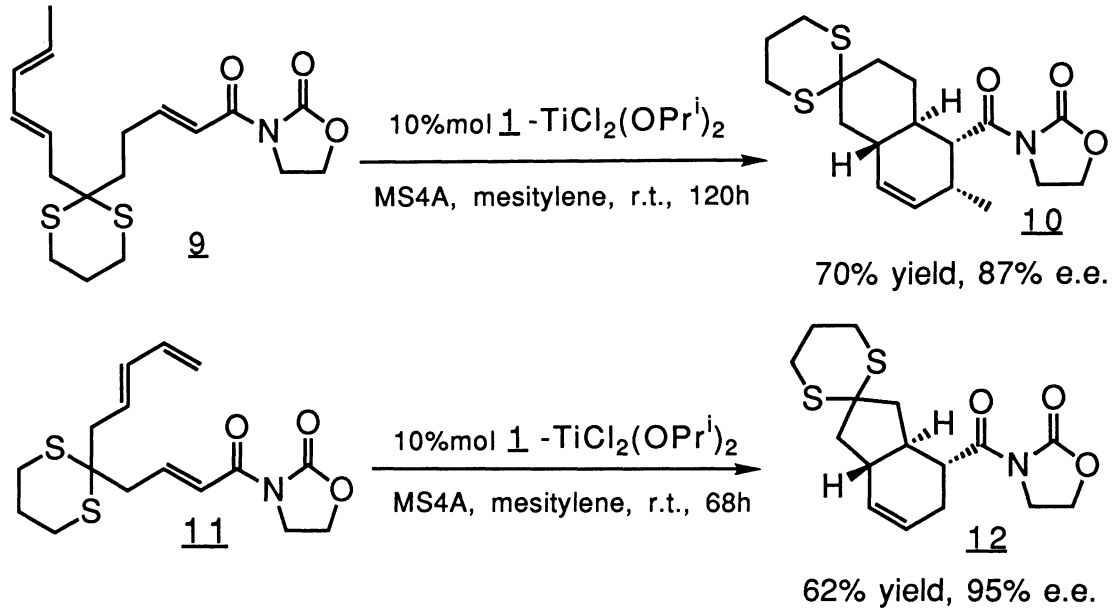


Fig. 1. The endo and exo transition states of 5.

Furthermore, by the reactions of 6-(1,3-dithianyl)-2,8,10-dodecatrienoic acid derivative 9 and 5-(1,3-dithianyl)-2,7,9-decatrienoic acid derivative 11, the endo-adducts 10 and 12 were obtained in 87% and 95% optical purity by carrying out the reaction in the presence of 10% molar amount of the chiral titanium reagent.[10]



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References

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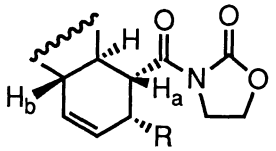

^{1}H NMR ($CDCl_3$) δ 1.15-1.26 (m, 2H), 1.66-1.73 (m, 3H), 1.76-1.80 (m, 1H), 1.83-1.89 (m, 1H), 1.97-2.00 (m, 1H, H_b), 2.20-2.26 (m, 1H), 2.46-2.52 (m, 1H), 3.89-3.95 (m, 1H, H_a), 4.03 (t, J=8.3 Hz, 2H), 4.41 (t, J=8.6 Hz, 2H), 5.56-5.60 (m, 1H), 5.85 (dd, J=1.5, 8.3 Hz, 1H) ; $[\alpha]_D^{17}$ -70° (c 1.41, CH_2Cl_2), 87 % ee. 5) J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969). 6) Two sets of dd signals of an acyloxymethyl proton were observed in the ^{1}H NMR spectrum of the MTPA esters derived from the racemic 4. 7) ^{1}H NMR ($CDCl_3$) spectrum of 6; δ 1.48-1.63 (m, 4H), 1.70-1.76 (m, 1H), 1.94-2.07 (m, 2H), 2.21-2.28 (m, 1H), 2.33-2.46 (m, 4H), 2.69-2.79 (m, 2H), 2.83-2.94 (m, 2H), 3.91-3.96 (m, 1H), 4.03 (t, J=8.0 Hz, 2H), 4.40 (t, J=8.0 Hz, 2H), 5.42 (d, J=9.9 Hz, 1H), 5.63-5.67 (m, 1H); $[\alpha]_D^{21}$ -21° (c 1.35, CH_2Cl_2), 91% ee. 8) The optical purity was determined by the integration of ^{19}F NMR signals. 9) K. Narasaka, Y. Hayashi, and S. Shimada, Chem. Lett., 1988, 1609; and references cited therein. 10) Each cycloadduct was obtained as a single isomer. Relative stereochemistry and optical purity were determined by the same methods in the case of 3 and 6. 10; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J=7.2 Hz, 3H), 1.24-1.38 (m, 2H), 1.49-1.62 (m, 2H), 1.76-1.82 (m, 2H), 1.97-2.02 (m, 2H), 2.35-2.40 (m, 3H), 2.70-2.77 (m, 3H), 2.82-2.92 (m, 2H), 3.90 (dd, J=6.0,11.3 Hz, 1H), 3.95-4.01 (m, 1H), 4.04-4.09 (m, 1H), 4.40 (t, J=8.3 Hz, 2H), 5.36 (d, J=9.8 Hz,1H), 5.58-5.61 (m, 1H); $[\alpha]_D^{25}$ -99° (c 1.53, CH_2Cl_2), 87% ee. 12; ^{1}H NMR ($CDCl_3$) δ 1.73 (q, J=12.6 Hz, 2H), 1.99-2.04 (m, 2H), 2.11-2.35 (m, 2H), 2.44-2.60 (m, 4H), 2.81-3.14 (m, 4H), 3.93 (dt, J=6.2,10.8 Hz, 1H), 4.03 (t, J=8.0 Hz, 2H), 4.42 (t, J=8.1 Hz, 2H), 5.63 (dt, J=4.9,9.8 Hz,1H), 5.79 (d, J=11.3 Hz, 1H); $[\alpha]_D^{23}$ -50° (c 1.38, CH_2Cl_2), 95% ee.

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