Reaction of Cis Hydroxy Epoxide 63 with Dimsylpotassium. Preparation of (1S*,1'S*,3'R*,8'S*)-1-(2',7'-Dioxabicyclo[4.4.0]decan-3'-yl)-2-propanol (65) and Its Acetate (65a). The bicyclic compound **65** was prepared from compound **63** (19.8 mg, 0.1 mmol) by the same procedure used to convert **61** to **64**. Flash chromatography (silica, 40% ether in petroleum ether) gave compound **65** (19.0 mg, 96%). Compound **65** also can be prepared from compound **63** (19.8 mg, 0.1 mmol) by the same procedure used to convert **61** to **62** via acid catalysis. (9.0 mg, 45% after flash column chromatography). **65**: oil; R_f = 0.47 (silica, 60% ether in petroleum ether); $[\alpha]^{23}_D$ +7.0° (*c* 0.1, CH_2Cl_2); IR (neat) ν_{max} 3440 (s, OH), 2940, 2838, 1438, 1262, 1100, 962, 842 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.78 (m, 1 H, C*H*=CH_2), 5.33 (d, *J* = 17.1 Hz, 1 H, CH=CH_2), 5.20 (d, *J* = 10.5 Hz, 1 H, CH=CH_2), 3.84 (m, 2 H, C*H*O, =CHC*H*O), 3.48 (m, 1 H, C*H*O), 3.25 (m, 1 H, C*H*O), 2.99 (m, 2 H, C*H*O), 2.75 (br s, 1 H, O*H*), 2.18-1.38 (m, 8 H, CH_2); HRMS calcd for $C_{11}H_{22}O_3N$ $(M + NH_4)^+$ 216.1599, found 216.1582. Acetylation of **65** with Ac_2O and DMAP under standard conditions led to acetate **65a** in 97% yield. **65a**: oil; R_f = 0.48 (silica, 30% ether in petroleum ether); $[\alpha]^{23}_D$ +21.67° (*c* 0.3, CH_2Cl_2); IR (neat) ν_{max} 2950, 2859, 1750 (s, Ac), 1452, 1378, 1242, 1100, 970, 848 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.82 (m, 1 H, C*H*=CH_2), 5.25 (m, 3 H, CH=CH_2), and C*H*OAc), 3.88 (m, 1 H, CH_2O, equatorial), 3.48 (m, 1 H, C*H*O), 3.38 (m, 1 H, C*H*O), 2.95 (m, 2 H, C*H*O), 2.18 (s, 3 H, OCH_3), 2.08-1.80 (m, 8 H, CH_2); HRMS calcd for $C_{13}H_{21}O_4$ $(M + H)^+$ 241.1440, found 241.1465.

(1'S*,3'R*,8'S*)-1-(2',7'-Dioxabicyclo[4.4.0]decan-3'-yl)-2-propen-1-one (66). Manganese dioxide (87 mg, 1.0 mmol) was added in one protion to a solution of **64** or **65** (19.8 mg, 0.1 mmol) in dry CH_2Cl_2 (3 mL) at 25 °C. The reaction mixture was stirred at room temperature for 2 h before the solid was removed by filtration through a Celite pad. Solvent removal followed by flash column chromatography (silica, 20% ether in petroleum ether) gave pure **66** (14.7 mg, 75%) and recovered starting material, **64** (4.2 mg, 21%) or **65** (4.0 mg, 20%). **66**: oil; R_f = 0.5 (silica, 20% ether in petroleum ether); $[\alpha]^{23}_D$ -11.0° (*c* 0.1, CH_2Cl_2); IR (neat) ν_{max} 2910, 2842, 1705 (s, ketone), 1610, 1460, 1095, 968 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 10.6, 17.3 Hz, 1 H, C*H*=CH_2), 6.54 (d, *J* = 17.3 Hz, 1 H, CH=CH_2), 5.45 (d, *J* = 10.6 Hz, 1 H, CH=CH_2), 3.85 (m, 2 H, C*H*O), 3.24 (m, 1 H, C*H*O), 2.98 (m, 1 H, C*H*O), 2.92 (m, 1 H, C*H*O), 2.10-1.50 (m, 8 H, CH_2); HRMS calcd for $C_{11}H_{17}O_3$ $(M + H)^+$ 197.1178, found 197.1181.

Acknowledgment. We wish to express our many thanks to Drs. George Furst and John Dykins of this department for their superb NMR and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health, Merck Sharp and Dohme, Hoffmann-La Roche, and Smith Kline Beckman, USA.

Supplementary Material Available: Data for compounds **15b-40** (R_f values, $[\alpha]_D$, IR, ^1H NMR, and MS data) (10 pages). Ordering information is given on any current masthead page.

Asymmetric Diels-Alder Reaction Catalyzed by a Chiral Titanium Reagent

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Abstract: A highly enantioselective Diels-Alder reaction has been developed by employing a chiral titanium reagent generated in situ from dichlorodiisopropoxytitanium and the chiral diol **1d**, which is easily derived from tartaric acid. With a catalytic amount of the titanium reagent, various acyloxazolidinone derivatives of α,β-unsaturated carboxylic acids react smoothly with dienes in the presence of 4A molecular sieves to give the corresponding optically active cycloadducts. Examination of the solvents revealed that the enantioselectivity and the reactivity of this reaction are widely dependent on the acceptor and donor properties of the solvents. By utilizing mesitylene, $CFCl_3$, or a mixed solvent of toluene and petroleum ether (or hexane), high enantioselectivity is achieved, and various synthetically useful chiral intermediates are obtained by a simple reaction procedure.

The Diels-Alder reaction has long been recognized as one of the most important methods for construction of cyclohexene derivatives. Due to the concerted and secondary orbital controlled reaction pathway, usually high, predictable stereoselectivity can be realized, making this reaction particularly useful in the stereoselective synthesis of various useful synthetic intermediates.

The control of absolute stereochemistry in the Diels-Alder reaction has been studied extensively since the first observation reported by Korolev et al. that optically active cycloadducts could be obtained by the reaction of menthyl fumarate and butadiene.[1] Another milestone was established by Walborsky, and the addition of a Lewis acid such as aluminum chloride, tin(IV) chloride, and titanium(IV) chloride was found to greatly enhance the enantioselectivity of the above reaction.[2] Since these findings, great progress has been made, and nearly complete asymmetric induction can be achieved with ingeniously designed chiral dienes or dienophiles.[3] Although these methods afford facile entry into the preparation of chiral cyclohexene derivatives, the processes for the introduction and removal of chiral auxiliary are necessitated and at least a stoichiometric amount of the chiral auxiliary is indispensable.

It is well-known that Lewis acids promote the Diels-Alder reaction,[4] but use of chiral Lewis acid to induce chirality in the Diels-Alder reaction has met with only limited success at the time when we started to study the asymmetric Diels-Alder reaction, probably due to the difficulty in designing appropriate chiral Lewis

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(3) (a) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: Orlando, 1984; Vol. 3, p 455. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, p 262. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (d) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. (e) Masamune, S.; Reed, L. A.; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441. (f) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510.
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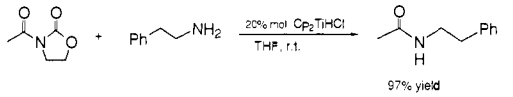
acids.[5] In this paper, we report our research in the catalytic asymmetric Diels–Alder reaction, which has enabled high enantioselectivity by the use of a chiral titanium reagent.[6]

Background

This research has been stimulated by our study concerning the exploration of new protective groups of carboxyl functionality which are stable under usual reaction conditions and can be activated by some specific reagents for the attack of nucleophiles.[7] By using these protective groups, synthetically useful condensation reactions such as macrocyclization and peptide-bond formation could be achieved without the necessity of deprotection procedures.

For example, 3-acetyl-1,3-oxazolidin-2-one (abbreviated to 3-acetyloxazolidinone), which is rather stable against the attack of primary amines, reacted smoothly with phenethylamine to give the corresponding amide by the action of titanium(IV) or zirconium(IV) reagents such as Cp_2TiHCl.[8] These facts indicate that



(1)

titanium(IV) or zirconium(IV) compounds form a rigid complex between two carbonyl groups of 3-acyloxazolidinone to activate the acyl group.

At this point, it occurred to us that the introduction of a chiral ligand to the rigid titanium(IV)–acyloxazolidinone complex would make it possible to induce an effective asymmetric induction toward the acyl part of the complex. Among various possible reactions, the Diels–Alder reaction seemed most promising, as the reaction is accelerated by a catalytic use of Lewis acid.

Then as a chiral auxiliary for the generation of chiral titanium(IV), we chose chiral diols because diols can easily be introduced to titanium(IV) by the alkoxy-exchange method[9] and also because the formation of rigid cyclic dialkoxide was expected to be effective for the asymmetric induction.

Results and Discussions

Stoichiometric Reaction. On the basis of the above considerations, we first examined the reaction of 3-crotonoyloxazolidinone (**3a**) and cyclopentadiene as a model reaction using chiral dichlorotitanium alkoxides derived from various chiral diols.

The reaction was carried out as follows: Chiral titanium complex was prepared by the azeotropic removal of 2-propanol with toluene from a mixture of a chiral diol and dichlorodiisopropoxytitanium(IV).[9] To the toluene solution of this chiral titanium reagent was added 1 molar equiv of **3a** at −15 °C and then excess cyclopentadiene was added to the reaction mixture. The mixture was slowly warmed to 0 °C and stirred overnight, and **3a**, which does not react with cyclopentadiene without Lewis acid at room temperature, was found to be activated by the titanium reagent to give cycloaddition products. Workup of the reaction mixture afforded both endo and exo cycloadducts (**4a** and **5a**, respectively) in about a 90:10 ratio in high yield. These two isomers could easily be separated by thin-layer chromatography and the optical purity of the endo isomer was determined by comparison of the optical rotation of the corresponding benzyl ester (BnOLi/THF)[10] and by the Pirkle's carbamate method.[11]

Table I. Effect of the Acetal Substituents of Chiral Diols on Enantioselectivity

compd	R^1	R^2	% yield	endo/exo[a] **4a:5a**	optical purity of **4a**/% ee[b]
1a	Me	Me	88	93:7	55
1b	Me	*n*-hex.	70	88:12	44
1c	*n*-Bu	*n*-Bu	76	86:14	27
1d	Me	Ph	quant	86:14	75
1e	Me	Ph	93	90:10	92[c]

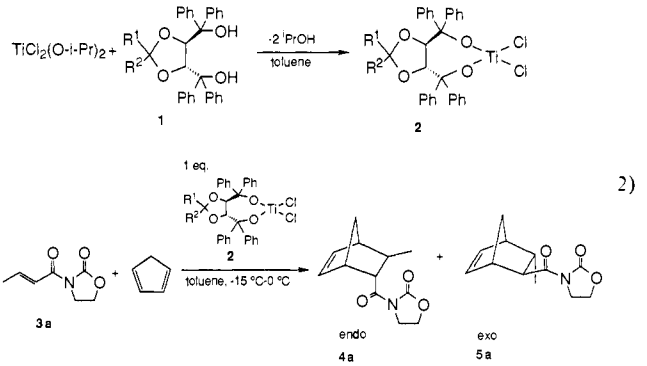
[a] These isomers were separated by silica gel chromatography. [b] Optical purity was determined by the procedure described in the text. In all cases, the 2*S*,3*R* enantiomer was obtained preferentially. [c] Two equivalents of titanium reagent was employed.

Table II. Asymmetric Diels–Alder Reaction of **3** with Cyclopentadiene by the Use of 2 molar equiv of Titanium Reagent

R (compd)	reaction temp/°C	yield/%	endo/exo[a] **4:5**	optical purity of **4**/% ee[b]
Me (**3a**)	−15	93	90:10	92 (80)[c]
Ph (**3b**)	0	97	92:8	81
n-Pr (**3c**)	−15	82	90:10	90
$CH_3CH{=}CH$ (**3d**)	room temp	77	92:8	82
H (**3e**)	−78	69	86:14	38

[a] These isomers were separated by silica gel chromatography. [b] Optical purities and absolute configurations were determined by the procedures described in the text. [c] Optical purity of the exo isomer **5a**, which was determined by converting **5a** to the corresponding MTPA ester.

When chiral titanium compounds derived from chiral 1,2-diols were employed, rather poor results were obtained: however, when the chiral 1,4-diol (2*R*,3*R*)-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol (**1a**)[9] was employed as a chiral auxiliary, good asymmetric induction was achieved and the endo adduct **4a** was obtained in 55% ee. As the 1,4-diol **1a**, which would form a seven-membered chiral alkoxytitanium dichloride **2** was particularly effective for this reaction, the influence of the substituents of the acetal center was next examined on the basis of the consideration that the conformation of the five-membered acetal moiety would influence that of the seven-membered ring containing titanium. Thus, chiral 1,4-diols which have various substituents on the acetal center were synthesized and the asymmetric Diels–Alder reaction of **3a** and cyclopentadiene was examined using these diols (Table I). It was found that the optical purity of the endo cycloadduct was dramatically dependent on the acetal substituents, and use of the chiral 1,4-diol (**1d**) having a 1-phenylethylidene group gave the best result to afford the adduct **4a** in 75% ee. Furthermore, the optical purity rose up to 92% ee by the use of 2 molar equiv of the titanium reagent.



(2)

(*R*)-(+)-1,4-Diol (**1d**) was easily prepared from L-(+)-dimethyl tartrate. Dimethyl tartrate was converted to the corresponding phenylethylidene derivative by treatment with acetophenone dimethyl acetal and a catalytic amount of *p*-toluenesulfonic acid

(5) (a) Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437. (b) Bednarsky, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451. After we reported our preliminary communications,[6] the following two reports appeared concerning with the highly selective asymmetric Diels–Alder reaction using chiral catalysts: (c) Chapuis, C. Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436. (d) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.

(6) For preliminary communication of this work, see: (a) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109. (b) Narasaka, K.; Inoue, M.; Yamada, T. *Chem. Lett.* **1986**, 1967. (c) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N. *Chem. Lett.* **1987**, 2409.

(7) For example: (a) Uchimaru, T.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1981**, 1551. (b) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954.

(8) Okada, N. Master's Thesis, University of Tokyo, 1985.

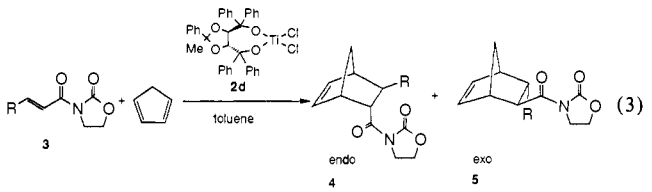
(9) (a) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods*; Scheffold, R., Ed.; John Wiley and Sons, Inc.: New York, 1983; Vol. 3, p 217. (b) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954.

(10) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(11) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904.

in refluxing benzene by removing methanol azeotropically. The phenylethylidene derivative was then converted to the diol **1d** by the reaction with excess phenylmagnesium bromide. The diol was purified by column chromatography on silica gel (benzene–hexane 2:1) and recrystallization from a mixture of hexane and 2-propanol. The crystals was obtained as an adduct of **1d** and 2-propanol and azeotropic removal of 2-propanol with benzene afforded the diol **1d** as a white amorphous solid.

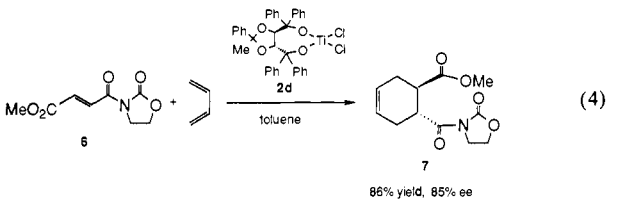
Since high enantioselectivity was achieved by employing the chiral titanium reagent prepared from **1d**, the asymmetric Diels–Alder reaction of various oxazolidinone derivatives of α,-β-unsaturated carboxylic acids **3a–e** and cyclopentadiene was



(3)

investigated in the presence of 2 molar equiv of the titanium reagent, and the results are listed in Table II. Although in the reaction of acryloyl derivatives **3e** the cycloadduct **4e** was obtained in rather poor optical purity, various other dienophiles reacted with cyclopentadiene to afford the endo adducts **4** with good optical purity.

High enantioselectivity was also attained by the application of the chiral titanium reagent to the reaction of the oxazolidinone of fumaric acid **6** with an acyclic diene such as isoprene. Thus



(4)

the titanium reagent was noted to exhibit a wide applicability to the asymmetric Diels–Alder reaction of the above prochiral dienes and dienophiles.

The optical purities and the absolute configurations of the cycloadducts were determined as follows: The cycloadducts of 3-crotonoyloxazolidinone **4a**, 3-cinnamoyloxazolidinone **4b**, 3-(2-hexenoyl)oxazolidinone **4c**, and 3-(2,4-hexadienoyl)oxazolidinone **4d** with cyclopentadiene were reduced with $LiAlH_4$ to the alcohols and then further converted to the Pirkle's carbamates, which were analyzed by HPLC. The adduct **4a** was converted to the corresponding benzyl ester ($PhCH_2OLi$–THF) and comparison of the optical rotation of this benzyl ester with that of the literature[10] determined the absolute configuration of **4a** to be 2*S*,3*R* as shown in eq 3. The absolute configurations of **4b–d** were not rigorously determined, but it is assumed that the same sense of asymmetric induction is also achieved in these cases. The cycloadduct **4e** of 3-acryloyloxazolidinone with cyclopentadiene was converted to the corresponding benzyl ester, and the optical purity and the absolute configuration were determined to be 2*S* by comparison of the optical rotation with that in the literature.[10] The cycloadduct **8** of 3-[3-(methoxycarbonyl)propenoyl]oxazolidinone with isoprene was obtained as a single regioisomer and the regiochemistry of the adduct was determined by X-ray analysis (Figure 1). The optical purity was analyzed by NMR with a chiral shift reagent, $Eu(hfc)_3$ (MeO signal separated). Furthermore, the cycloadduct itself was recrystallized several times to show a constant optical rotation, and the optical purity was also confirmed on the basis of this value. The cycloadduct **7** of 3-[3-(methoxycarbonyl)propenoyl]oxazolidinone with butadiene was converted to the dimethyl ester ($Mg(OMe)_2$–MeOH), which was analyzed by NMR with a chiral shift reagent, $Eu(hfc)_3$ (MeO signal separated). In each case (**7** and **8**), the absolute configuration was determined to be 4*R*,5*R* by comparison of the optical rotation of the corresponding dimethyl ester with that of the literature value.[2b]

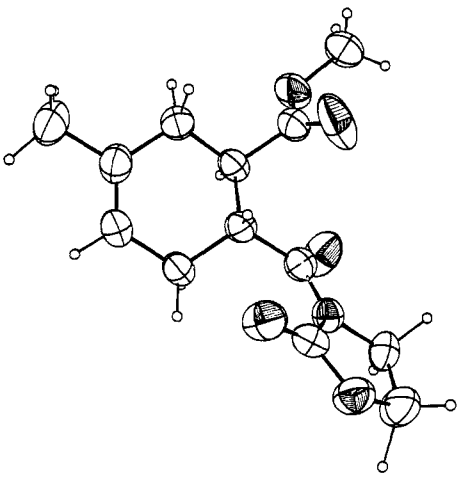
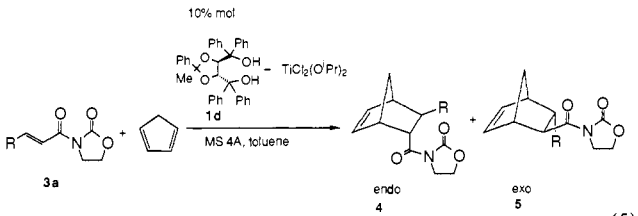


Figure 1.

Catalytic Reaction. In order to make this reaction practically useful, the amount of the reaction promoter should be reduced to a catalytic amount. However, when a catalytic amount of the titanium reagent was employed in the reaction of 3-crotonoyloxazolidinone and cyclopentadiene, the endo adduct **4a** was obtained in high yield but in low enantioselectivity. We therefore examined the possibility of using additives to achieve high enantioselectivity in this catalytic reaction. After various examinations of the additives, it was found that the presence of molecular sieves (zeolite) of A type such as 3A, 4A, and 5A in the reaction mixture greatly enhanced the enantioselectivity of the adduct **4a**.[12] Especially, the use of powdered 4A molecular sieves (MS 4A) gave the cycloadduct in 91% ee. Further examination of such zeolite type additives revealed that use of MS X (NaX) or MS Y (NaY, CaY, KY) gave much poorer results. Also addition of silica gel or aluminum oxide greatly reduced the enantioselectivity of the reaction.

We are still uncertain of the exact role of molecular sieves; however, the dehydrating ability is considered to be at least partially responsible for this success of the catalytic reaction. In fact, by the addition of a trace amount of water to the reaction mixture, even in the reaction using 2 molar equiv of titanium reagent, the optical yield of **4a** lowered dramatically.

The chiral titanium alkoxide was so far prepared by the alkoxy-exchange method by azeotropic removal of isopropanol from the refluxing toluene solution. However, in this process, slight decomposition of the chiral diol **1d** was observed by TLC. So we tried the in situ formation of the chiral titanium reagent by mixing **1d** and dichlorodiisopropoxytitanium in toluene at room temperature for 1 h, and it was found that the same level of asymmetric induction was observed in the reaction of **3a** and cyclo-



(5)

pentadiene by using this catalyst generated in situ. For example, the chiral catalyst was prepared from 11 mol % (to the dienophile) of the 1,4-diol **1d** and 10 mol % of dichlorodiisopropoxytitanium in toluene at room temperature, and then powdered MS 4A, 3-crotonoyloxazolidinone, and cyclopentadiene were added successively at 0 °C. After stirring for 24 h, the endo adduct **4a** was produced in 91% ee with the same absolute configuration as that

(12) Sharpless reported improvement of the asymmetric epoxidation to a catalytic process by the use of molecular sieves; Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

Table III. Asymmetric Diels–Alder Reaction Using a Catalytic Amount of Titanium Reagent

R	reaction temp/°C	endo/exo[a] **4**:**5**	% yield	optical purity of **4**/% ee[b]
Me	0	92:8	87	91 (83)[c]
Ph	room temp	88:12	72	64
n-Pr	0	91:9	79	72
H	−40	96:4	93	64

[a] These isomers were separated by silica gel chromatography. [b] The optical purity was determined by the procedures described in the text. [c] Optical purity of the exo isomer **5a**.

observed in the original procedure.

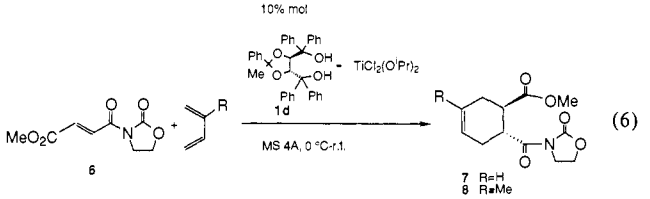
At this point, we decided to investigate the chiral titanium reagent by measuring NMR spectra. The chiral diol **1d** and dichlorodiisopropoxytitanium(IV) was mixed in toluene-d_8 and comparison of the NMR spectra of this mixture and the chiral diol **1d** itself revealed that the methyl signal shifted upfield by 0.38 ppm by complexation, while the methyne proton shifted downfield by 0.13 ppm. The ratio of the shifted methyl signal to that of **1d** was about 10:1. Furthermore, by the addition of 3-crotonoyloxazolidinone **3a** to the titanium reagent, formation of minute precipitates was observed. This new complex was isolated and NMR analysis in DMSO-d_6 indicated the formation of a 1:1 complex of **3a** and the chiral 1,4-dialkoxytitanium dichloride. Aqueous workup of this complex giving equal amounts of the diol and the acyloxazolidinone also confirmed the 1:1 complexation.

As can be seen in Table III, various oxazolidinones of β-substituted acrylic acid derivatives react with cyclopentadiene to afford the endo adducts in good to high (64–91%) enantioselectivity by the combined use of a catalytic amount of the chiral titanium reagent and MS 4A. Especially noteworthy is the fact that the reaction of 3-acryloyloxazolidinone with cyclopentadiene proceeded with higher enantioselectivity (64% ee) as compared to the stoichiometric reaction (38% ee).

On the other hand, the reaction of the oxazolidinone derivative **6** of fumaric acid and butadiene was found to proceed in much poorer enantioselectivity as compared with the reaction carried out in the presence of excess amounts of the chiral titanium reagent. The optical purity of the adduct **7** was 32–58% ee. In order to achieve wide applicability of this catalytic procedure, the reaction conditions were examined in detail, and a remarkable solvent effect on the enantioselectivity was found in this reaction.

Solvent Effect. To improve the optical purity of the cycloadduct **7** of the 1,3-oxazolidinone derivative of fumaric ester and butadiene, the reaction was examined in various solvents in the presence of 10 mol % of the chiral titanium reagent and powdered MS 4A. The enantioselectivity displayed by the reaction in various solvents are summarized in Table IV, indicating that alkyl substituted benzenes are suitable solvents for the present reaction. That is, the enantioselectivity is dependent on the number of methyl group on the benzene ring and the optical purity of the adduct was greatly increased in the order of benzene, toluene, xylenes, and mesitylene. Furthermore, rather high selectivity was attained by employment of hexylbenzene as the solvent, and the *trans*-4-cyclohexene-1,2-dicarboxylic acid derivative **7** was obtained in 98% yield with 85% ee.

The same tendency was observed in the reaction of **6** and isoprene, and the cycloadduct **8** was obtained in 92% ee when the



(6)

reaction was carried out in mesitylene. Furthermore, examination of other common solvents revealed that high enantioselectivity could also be realized in diethyl ether. Although the reaction in

Table IV. Solvent Effect on the Enantioselectivity in the Reaction of **6** with Butadiene or Isoprene in Various Solvents

solvent	optical purity/% ee[a]	solvent	optical purity/% ee[a]
	R = H (Butadiene)		
benzene	22	*o*-xylene	66
toluene	32–45	mesitylene	81
p-xylene	67	hexylbenzene	85
	R = Me (Isoprene)		
benzene	41	Et_2O	91
toluene	36–68	THF	*b*
mesitylene	93	CH_2Cl_2	45
$CFCl_3$	92	$CHCl_3$	52
$CF_2ClCFCl_2$	92	CCl_4	75

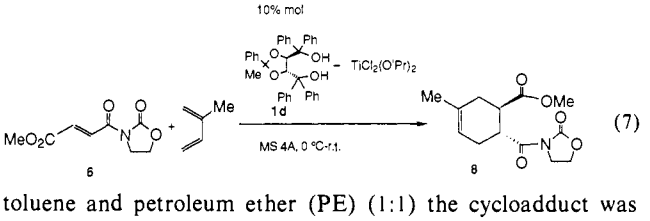
[a] Determined by the procedure described in the text. [b] No reaction.

diethyl ether gave higher enantioselectivity in some cases, the reaction rate lowered especially when rather unreactive dienophiles such as **3b** and **3d** were employed. For example, when the reaction between **3b** and cyclopentadiene was tried with 2 equiv of the chiral titanium reagent in diethyl ether, the cycloadduct was obtained in 97% yield and the optical purity of the endo adduct **4b** reached 90% ee, which is the best result yet obtained. However, when this reaction was carried out with 10 mol % of the titanium reagent, **4b** was obtained only in 30% yield in 80% optical purity under the above catalytic reaction conditions.

As for the controlling factor of this solvent effect, it was assumed that the enantioselectivity and reactivity of this reaction is dependent on the donor and acceptor ability of the solvent.[13] For example, in the solvents having large acceptor number such as dichloromethane or chloroform, the optical yield is much lower than in mesitylene. These solvents would interact with the anionic parts (chloride and alkoxyl groups) of the complex between the chiral titanium and acyloxazolidinone to bring about distortion of the complex. In THF or ether (donor number is large), the activity of the titanium reagent is decreased by the coordination of the solvents to the titanium preventing the complex formation between the dienophile and the titanium reagent. The effect of the alkyl group(s) on benzene ring might be explained by the reduced molecular interaction (such as π-stacking)[10] due to the steric repulsion. That is, to attain high synthetic and optical yields, it is necessary to carry out the reaction in a solvent having small donor and acceptor numbers, which means that the molecular interaction between the solvent and the titanium complex with a dienophile should be minimized. On the basis of this consideration, we also tried the reaction using trichlorofluoromethane or hexane as a solvent. The reaction did not proceed in hexane because of low solubility of the chiral diol **1d** and **6**, but almost the same degree of optical purity as in mesitylene was attained when trichlorofluoromethane was employed.

Although high enantioselectivity was achieved by using mesitylene or trichlorofluoromethane as a solvent, the difficulty in removing mesitylene during workup and their rather high cost prevents the application of this process to a large-scale preparation. Then, as an alternative method, we tried the reaction using a mixed solvent of toluene and alkanes such as hexane.

As shown in Table V, employment of a petroleum ether (or hexane)–toluene mixture enhanced the enantioselectivity of the reaction between **6** and isoprene, and in the mixed solvent of



(7)

toluene and petroleum ether (PE) (1:1) the cycloadduct was

(13) Gutmann, V. *The Donor-Acceptor Approach to Molecular Interactions*; Plenum Press: New York, 1978.

Table V. Enantioselectivity in the Reaction of **6** with Isoprene in Mixed Solvents

solvent	optical purity of **8**/% ee[a]	solvent	optical purity of **8**/% ee[a]
toluene	60	toluene–PE (1:1)	94
toluene–hexane (6:1)	74	toluene–2,3-dimethyl-butane (4:1)	81
toluene–hexane (8:5)	85		
toluene–PE (4:1)	80	toluene–2,3-dimethyl-butane (8:5)	85

[a] Determined by the procedure described in the text.

Table VI. Enantioselectivity in the Reaction of **6** with Butadiene in Mesitylene and a Mixed Solvent

solvent	% yield	optical purity of **7**/% ee[a]
toluene	85	32–45
mesitylene	90	85
toluene–PE (8:5)	84	91

[a] Determined by the procedure described in the text.

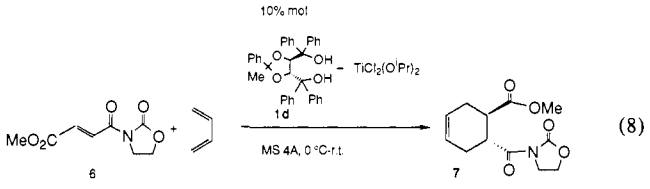
Table VII. Asymmetric Diels–Alder Reaction Using a Catalytic Amount of Titanium Reagent in Mesitylene and a Mixed Solvent

R	solvent	% yield	exo/endo[a] **4:5**	optical purity of **4**/% ee[b]
Me	toluene	87	92:8	91
	mesitylene	90	91:9	91
	toluene–PE (1:1)	91	87:13	94 (85)[c]
Ph	toluene	72	88:12	64
	mesitylene	97	92:8	82
	toluene–hexane (8:5)	76	92:8	80
Pr	toluene	79	91:9	72
	mesitylene	75	85:15	75
	toluene–PE (1:1)	72	91:9	75

[a] These isomers were separated by silica gel chromatography. [b] Determined by the procedure described in the text. [c] Optical purity of the exo isomer **5a**.

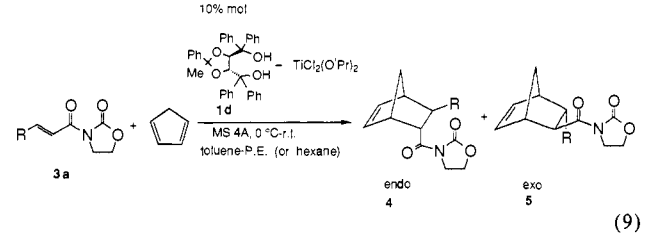
obtained in 94% ee, which is nearly identical with the result obtained using mesitylene as a solvent.

The generality of the use of the mixed-solvent system (toluene–PE) on enantioselectivity was examined in the following several examples. In the reaction of fumaric acid derivative **6** and butadiene, higher optical purity was realized by carrying out the



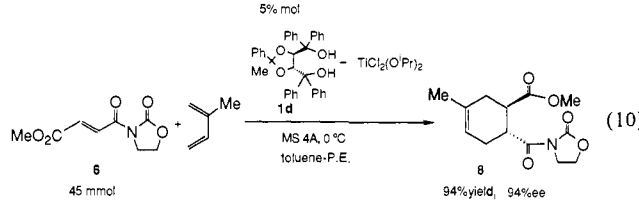
(8)

reaction in the mixed solvent as shown in Table VI. Also, nearly the same or higher level of enantioselectivity was achieved in the reaction of β-substituted acrylic acid derivatives **4** and cyclopentadiene as compared with the reaction in mesitylene (Table VII).



(9)

The reactions so far were usually carried out on a small scale (ca. 1-mmol scale) in the presence of 10 mol % of the titanium catalyst. Then, to examine the application to a large-scale preparation, we tried the reaction between **6** and isoprene in 45-mmol scale using 5 mol % of the titanium catalyst in a toluene–PE mixed solvent. The reaction proceeded with the same



(10)

efficiency, and the adduct was obtained in 94% yield in 94% optical purity. One recrystallization from ethyl acetate–hexane afforded the optically pure product **8** in 64% yield.

Conclusion

A highly enantioselective Diels–Alder reaction has successfully been developed by employing the chiral titanium reagent prepared from the chiral 1,4-diol **1d** and dichlorodiisopropoxytitanium. Even with a catalytic amount of the titanium reagent, various acyloxazolidinone derivatives of α,β-unsaturated carboxylic acids react with dienes in the presence of MS 4A in mesitylene or trichlorofluoromethane or especially a toluene–PE mixture, giving the corresponding cycloadducts in high optical purity. Furthermore, this chiral titanium reagent has found successful applications to the intramolecular ene reaction[14] and the hydrocyanation of aldehydes[15] as a chiral Lewis acid.

Experimental Section

Melting points and boiling points are uncorrected. Dichlorodiisopropoxytitanium was prepared from titanium(IV) chloride and titanium(IV) isopropoxide according to the literature method.[16] Toluene and benzene were washed twice with cold concentrated H_2SO_4, once with water, once with aqueous 5% $NaHCO_3$, and again with water and then distilled from P_2O_5 and from CaH_2 and stored over MS 4A. Xylenes, mesitylene, hexylbenzene, and cumene were distilled from $LiAlH_4$ and stored over MS 4A. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl.

NMR spectra were recorded on a Hitachi R24B or Varian EM390 spectrometer. IR spectra were recorded on a Hitachi 260-30 spectrometer. Optical rotations were measured with a JASCO DIP-180. Mass spectra were obtained with a JEOL JMS-D300 mass spectrometer.

Preparation of 3-Acyl-1,3-oxazolidin-2-one. 3-Acyl-1,3-oxazolidin-2-ones of various α,β-unsaturated carboxylic acids were prepared according to the procedure of Evans.[10] Spectral data and physical properties are as follows.

3-((*E*)-2-Butenoyl)-1,3-oxazolidin-2-one (3a). bp 115 °C (bath temperature) (0.1 mmHg); IR (neat) 1775, 1680, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (dd, 3 H, *J* = 1.5 Hz, 5.0 Hz), 3.7–4.4 (m, 4 H), 6.6–7.2 (m, 4 H). Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.03; H, 5.83; N, 8.98.

3-((*E*)-2-Cinnamoyl)-1,3-oxazolidin-2-one (3b). mp 151.0–152.5 °C; IR (KBr) 1765, 1675, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.9–4.6 (m, 4 H), 7.2–7.7 (m, 5 H), 7.9 (s, 2 H). Anal. Calcd for $C_{12}H_{10}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.30; H, 5.01; N, 6.23.

3-((*E*)-2-Hexenoyl)-1,3-oxazolidin-2-one (3c). bp 120 °C (bath temperature) (0.05 mmHg); IR (neat) 1760, 1675, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, *J* = 4.6 Hz), 1.1–1.8 (m, 2 H), 1.9–2.4 (m, 2 H), 3.7–4.1 (m, 2 H), 4.2–4.6 (m, 2 H), 6.7–7.5 (m, 2 H). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.85; H, 7.32; N, 7.53.

3-(2′(*E*),4′(*E*)-2,4-Hexadienoyl)-1,3-oxazolidin-2-one (3d). mp 114.5–118 °C; IR (KBr) 1760, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–1.9 (m, 3 H), 3.8–4.6 (m, 4 H), 5.9–6.4 (m, 2 H), 6.9–7.5 (m, 2 H).

3-(2-Propenoyl)-1,3-oxazolidin-2-one (3e). mp 82.0–83.0 °C; IR (KBr) 1770, 1685, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6–4.4 (m, 4 H), 5.6 (dd, 1 H, J = 1.0 Hz, 5.0 Hz), 6.2 (dd, 1 H, *J* = 1.0 Hz, 8.0 Hz), 7.2 (dd, 1 H, J = 5.0 Hz, 8.0 Hz). Anal. Calcd for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.93. Found: C, 50.80; H, 4.73; N, 9.97.

3-((*E*)-3-(Methoxycarbonyl)propenoyl)-1,3-oxazolidin-2-one (6). mp 80.5–81.0 °C; IR (KBr) 1775, 1720, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3 H), 3.8–4.6 (m, 4 H), 6.85 (d, 1 H, J = 16 Hz), 8.10 (d, 1 H, J = 16 Hz).

(14) Narasaka, K.; Hayashi, Y.; Shimada, S. *Chem. Lett.* **1988**, 1609.
(15) (a) Narasaka, K.; Yamada, T.; Minamikawa, H. *Chem. Lett.* **1987**, 2073. (b) Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379.
(16) Dijkgraaf, C.; Rousseau, J. P. G. *Spectrochim. Acta, A* **1968**, *24*, 1213.

Preparation of the Chiral Diol: Dimethyl (2*R*,3*R*)-2,3-*O*-(1-Phenylethylidene)tartrate. To a benzene solution of dimethyl (2*R*,3*R*)-tartrate (10.7 g, 60 mmol) and acetophenone dimethyl acetal (10.6 g, 60 mmol) is added a catalytic amount of *p*-TsOH, and the mixture is heated to reflux to remove the liberated methanol azeotropically with occasional addition of benzene until the boiling point reaches 80.5 °C. The mixture is washed with saturated aqueous $NaHCO_3$ solution and then with brine and is dried over Na_2SO_4. The solvent is removed under reduced pressure and the residual oil is purified by silica gel column chromatography to afford the product, which is further purified by Kugelrohr distillation to give the pure product (10.7 g, 63% yield): bp 140 °C (bath temperature) (0.15 mmHg); $[\alpha]_D$ +11° (*c* 2.6, CH_2Cl_2); IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (s, 3 H), 3.30 (s, 3 H), 3.64 (s, 3 H), 4.65 (s, 2 H), 7.0–7.7 (m, 5 H).

(2*R*,3*R*)-2,3-*O*-(1-Phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol (1d). Under an argon atmosphere, to a THF solution (50 mL) of PhMgBr (about 25 mmol) is added a THF solution (10 mL) of the above prepared acetal (1.4 g, 5 mmol) at 0 °C. After the reaction mixture is stirred at room temperature overnight, saturated NH_4Cl solution is added to the mixture. Organic materials are extracted with ethyl acetate and the organic phase is washed with brine and dried over Na_2SO_4. The solvent is removed under reduced pressure and the residue is purified by silica gel column chromatography. The separated product is dissolved in hot hexane, and a small portion of 2-propanol is added to the mixture with stirring. White precipitates (2-propanol complex) are formed slowly. The precipitates are collected and further recrystallized from hexane–2-propanol. 2-Propanol is removed azeotropically with benzene several times by evaporation under reduced pressure, and the essentially pure product is obtained as amorphous solid (1.6 g, 60% yield). $[\alpha]^{23}_D$ +83° (c 1.3, $CHCl_3$); IR (KBr) 3300, 1490, 1445, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3 H), 2.32 (s, 1 H), 2.45 (s, 1 H), 5.04 (d, 1 H, *J* = 6.0 Hz), 5.08 (d, 1 H, J = 6.0 Hz), 6.8–7.6 (m, 25 H).

The elemental analysis is performed after conversion to the corresponding bis(trimethylsilyl) ether: Calcd for $C_{42}H_{48}O_4Si_2$: C, 74.96; H, 7.19. Found: C, 74.68; H, 7.12.

Asymmetric Diels–Alder Reaction. General Procedure for the Reaction Using 2 molar equiv of the Titanium Reagent. The reaction of 3-((*E*)-3-(methoxycarbonyl)propenoyl)-1,3-oxazolidin-2-one **6** with isoprene is outlined. Under an argon atmosphere, to a toluene solution (5 mL) of dichlorodiisopropoxytitanium (140 mg, 0.59 mmol) is added a toluene solution (5 mL) of the chiral diol **1d** (354 mg, 0.67 mmol) at room temperature, and the mixture is stirred for 1 h. The mixture is cooled to 0 °C and then a toluene solution (3 mL) of the fumaric acid derivative **6** (60 mg, 0.3 mmol) is added to the reaction mixture and finally isoprene (1 mL) is added. The mixture is stirred overnight at 0 °C. Then pH 7 phosphate buffer is added and the organic materials are extracted with ethyl acetate and the combined extracts are dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude product is purified by thin-layer chromatography (AcOEt–hexane = 1:2) to give the pure product.

General Procedure for the Reaction Using a Mixed-Solvent System in the Presence of a Catalytic Amount of Titanium Reagent. To a toluene suspension (3 mL) of MS 4A (150 mg) is added a toluene solution of the chiral titanium catalyst (prepared by the same procedure described above) (about 0.07 mmol) and the mixture is cooled to 0 °C. A toluene solution (4 mL) of the fumaric acid derivative **6** (140 mg, 0.7 mmol) is added to the mixture and then hexane (5 mL) and isoprene (1 mL) are added. The mixture is stirred overnight at 0 °C, and then pH 7 phosphate buffer is added to the mixture. By the same procedure described for the stoichiometric reaction, the corresponding cycloaddition product **8** is obtained in 92% yield.

Spectral data and physical properties of the cycloadduct are as follows.

3-(((1′*S*,2′*S*,3′*R*,4′*R*)-3′-Methylbicyclo[2.2.1]hept-5′-en-2′-yl)-carbonyl)-1,3-oxazolidin-2-one (4a). IR (neat) 1775, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (d, 3 H, *J* = 7.0 Hz), 1.2–2.1 (m, 3 H), 2.46 (br, 1 H), 3.25 (br, 1 H), 3.48 (dd, 1 H), 3.8–4.6 (m, 4 H), 5.77 (dd, 1 H, J = 2.4 Hz, 5.4 Hz), 6.43 (dd, 1 H, J = 3.4 Hz, 5.4 Hz). $[\alpha]_D$ −191° (*c* 3.6, CCl_4): 92% ee. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.98; H, 6.93; N, 6.15.

3-(((1′*S*,2′*R*,3′*R*,4′*R*)-5′-Phenylbicyclo[2.2.1]hept-5′-en-2′-yl)-carbonyl)-1,3-oxazolidin-2-one (4b). IR (neat) 1770, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–2.0 (m, 2 H), 2.85 (br, 1 H), 3.6–4.4 (m, 5 H), 5.80 (dd, 1 H, *J* = 2.2 Hz, 5.4 Hz), 6.41 (dd, 1 H, *J* = 2.4 Hz, 5.4 Hz), 6.9–7.6 (m, 5 H). $[\alpha]_D$ −143° (*c* 1.2, CCl_4): 81% ee. Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.88; H, 6.20; N, 4.71.

3-(((1′*S*,2′*S*,3′*R*,4′*R*)-3′-Propylbicyclo[2.2.1]hept-5′-en-2′-yl)-carbonyl)-1,3-oxazolidin-2-one (4c). IR (neat) 1775, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7 (m, 3 H), 1.0–1.8 (m, 4 H), 2.01 (br, 1 H), 2.63 (br, 1 H), 3.27 (br, 1 H), 3.57 (dd, 1 H, *J* = 2.0 Hz, 3.0 Hz), 3.8–4.2 (m, 2 H), 5.77 (dd, 1 H, *J* = 2.0 Hz, 4.0 Hz), 6.35 (dd, 1 H, *J* = 2.0 Hz, 4.0 Hz). $[\alpha]_D$ −158° (*c* 2.0, CCl_4): 90% ee. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.14; H, 7.80; N, 5.39.

3-(((1′*S*,2′*R*,3′*R*,4′*R*)-3′-(1-Propenyl)bicyclo[2.2.1]hept-5′-en-2′-yl)carbonyl)-1,3-oxazolidin-2-one (4d). IR (neat) 1780, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.9 (m, 5 H), 2.5–3.0 (m, 2 H), 3.1–3.5 (m, 1 H), 3.78 (dd, 1 H, J = 4.0 Hz, 3.6 Hz), 3.9–4.6 (m, 4 H), 5.0–5.6 (m, 2 H), 5.88 (dd, 1 H, J = 2.8 Hz, 6.0 Hz), 6.35 (dd, 1 H, *J* = 2.8 Hz, 5.0 Hz). $[\alpha]_D$ −142° (*c* 3.5, CCl_4): 82% ee.

3-((1′*S*,2′*S*,4′*S*)-Bicyclo[2.2.1]hept-5′-en-2′-ylcarbonyl)-1,3-oxazolidin-2-one (4e). IR (neat) 1760, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–2.2 (m, 4 H), 2.97 (m, 1 H), 3.30 (m, 1 H), 3.7–4.6 (m, 5 H), 5.82 (dd, 1 H, *J* = 2.4 Hz, 5.8 Hz), 6.20 (dd, 1 H, *J* = 2.2 Hz, 5.8 Hz). $[\alpha]_D$ −65° (*c* 1.5, $CHCl_3$): 38% ee. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 62.91; H, 6.20; N, 6.44.

3-(((4′*R*,5′*R*)-5′-(Methoxycarbonyl)cyclohexen-4′-yl)carbonyl)-1,3-oxazolidin-2-one (7). IR (neat) 1785, 1725, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–3.2 (m, 6 H), 3.65 (s, 3 H), 3.7–4.7 (m, 4 H), 5.5–5.8 (m, 2 H). $[\alpha]_D$ −158° (*c* 1.5, CH_2Cl_2): 90% ee. Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.65; H, 6.03; N, 5.36.

3-(((4′*R*,5′*R*)-1′-Methyl-5′-(methoxycarbonyl)cyclohexen-4′-yl)-carbonyl)-1,3-oxazolidin-2-one (8). IR (KBr) 1775, 1745, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–1.8 (m, 3 H), 1.9–3.3 (m, 5 H), 3.63 (s, 3 H), 3.8–4.6 (m, 5 H), 5.32 (br, 1 H). $[\alpha]_D$ −161° (*c* 1.1, CH_2Cl_2): 93% ee. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42, H, 6.41; N, 5.24. Found: C, 58.21; H, 6.53; N, 5.06.

General Procedure for a Large-Scale Preparation. Under an argon atmosphere, to a toluene solution (5 mL) of dichlorodiisopropoxytitanium (540 mg, 2.3 mmol) is added a toluene solution (5 mL) of the chiral diol **1d** (1.32 g, 2.5 mmol) at room temperature, and the mixture is stirred for 1 h. This chiral titanium reagent is added to a toluene suspension (175 mL) of MS 4A (3.74 g), and the mixture is cooled to 0 °C. The fumaric acid derivative **6** (9.10 g, 46 mmol) is added to the mixture and then petroleum ether (150 mL) and isoprene (50 mL) are added. The mixture is stirred overnight at 0 °C, and then pH 7 phosphate buffer is added to the mixture. Organic materials are extracted with ethyl acetate three times and the combined extracts are dried over Na_2SO_4. After evaporation of the solvent, the crude product is purified by silica gel column chromatography (ethyl acetate–hexane = 1:4) to give the adduct **8** in 94% yield and 93% optical purity. One recrystallization from ethyl acetate–hexane gives optically pure adduct **8** in 64% yield.

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Supplementary Material Available: X-ray crystal analysis of **8** (13 pages). Ordering information can be found on any current masthead.