Asymmetric Reactions of Enamines with Methyl (*E*)-4-Oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenoate by the Use of a Chiral Titanium Reagent

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Asymmetric Michael and [2+2] cycloaddition reactions between enamines and methyl (*E*)-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenoate proceed with a chiral titanium reagent generated in situ from dichlorodiisopropoxytitanium and a tartrate-derived chiral 1,4-diol. In the presence of excess amounts of the chiral titanium reagent, good to moderate enantioselectivity is attained. The reactions are also well catalyzed even with a catalytic amount of the titanium reagent.

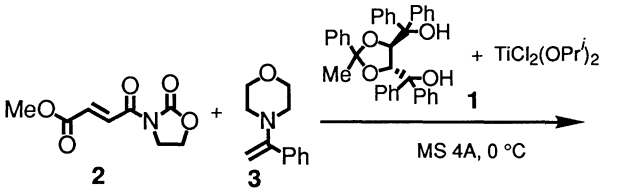
Michael reaction, one of the most versatile carbon–carbon bond forming reactions, is an indispensable tool in organic synthesis and the asymmetric version of this reaction has been intensively examined.[1] A variety of asymmetric Michael reactions have been devised by the use of chiral Michael acceptors or donors such as chiral enamines[2] or chiral vinyl sulfoxides.[3] Furthermore, in this decade, several good results have been reported on the enantioselective Michael reaction of prochiral substrates,[4] but only a few examples are known for the asymmetric Michael reactions by the use of a catalytic amount of chiral auxiliaries.[5]

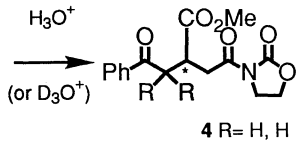
We have reported the preparation and properties of a chiral titanium reagent which is prepared in situ from dichlorodiisopropoxytitanium and optically active 1,1,4,4-tetraphenyl-2,3-(1-phenylethylidene)dioxy-1,4-butanediol (**1**) derived from dimethyl tartrate.[6] This reagent promotes the inter- and intra-molecular Diels–Alder reactions,[7] the [2+2] cycloaddition reaction,[8] the intramolecular ene reaction[9] and the hydrocyanation,[10] in which very high enantioselectivities are attained. For another application of this chiral titanium reagent, the Michael reaction of enamines[11] was investigated by employing the chiral titanium reagent as a reaction promoter.

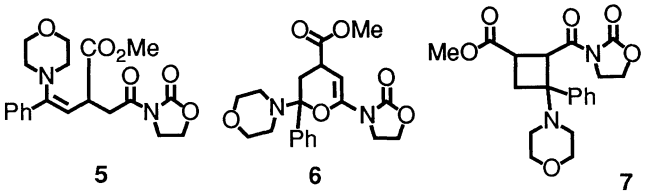
Results and Discussion

Methyl (*E*)-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenoate (**2**) which was a suitable dienophile in the above asymmetric Diels–Alder reaction[7a] was chosen as a Michael acceptor, and the reaction with enamines was examined in the presence of the chiral titanium reagent prepared by mixing dichlorodiisopropoxytitanium and the chiral (2*R*, 3*R*)-1,4-diol **1**. When **2** and 4-(1-phenylethenyl)morpholine (**3**) was treated with an equimolar amount of the chiral titanium reagent at 0 °C for 24 h in the presence of Molecular Sieves 4A (MS 4A) in CH_2Cl_2, the Michael adduct **4** was obtained in 61% yield in 22% ee after hydrolysis of the reaction mixture. The reference reaction of **2** and **3** without the Lewis acid proceeded very slowly under the same reaction conditions to give the product **4** in only 6% yield.

After screening the amino moiety of acetophenone enamines and the reaction solvents, **4** was found to be obtained in 51% yield with 58% ee when the morpholino enamine **3** reacted with **2** in ether in the presence of an equimolar amount of the titanium reagent. The enantioselectivity was further improved to 73% ee by the use of excess amounts (2 molar amounts) of the chiral titanium reagent (54% yield). Moreover, even by a catalytic use (20% molar amount) of the chiral titanium reagent, the reaction proceeded with slight loss of the optical purity (68% yield, 55% ee), which indicates that the catalyst is regenerated during the course of the reaction. The product before hydrolysis[12] is considered to be the enamine **5**,[12b] the dihydropyran **6**,[12c,d] or the cyclobutane derivative **7**.[12e,f]

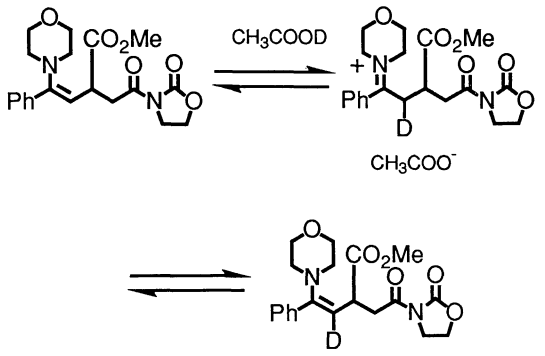




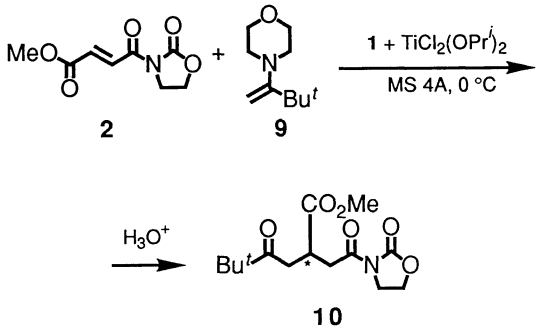


To determine which is the real intermediate, the reaction was quenched with D_2O–CH_3COOD. The Michael product was obtained in 30% yield, which consisted of d_0(**4**, 4%), d_1(24%), and d_2(**8**, 72%) deriva-

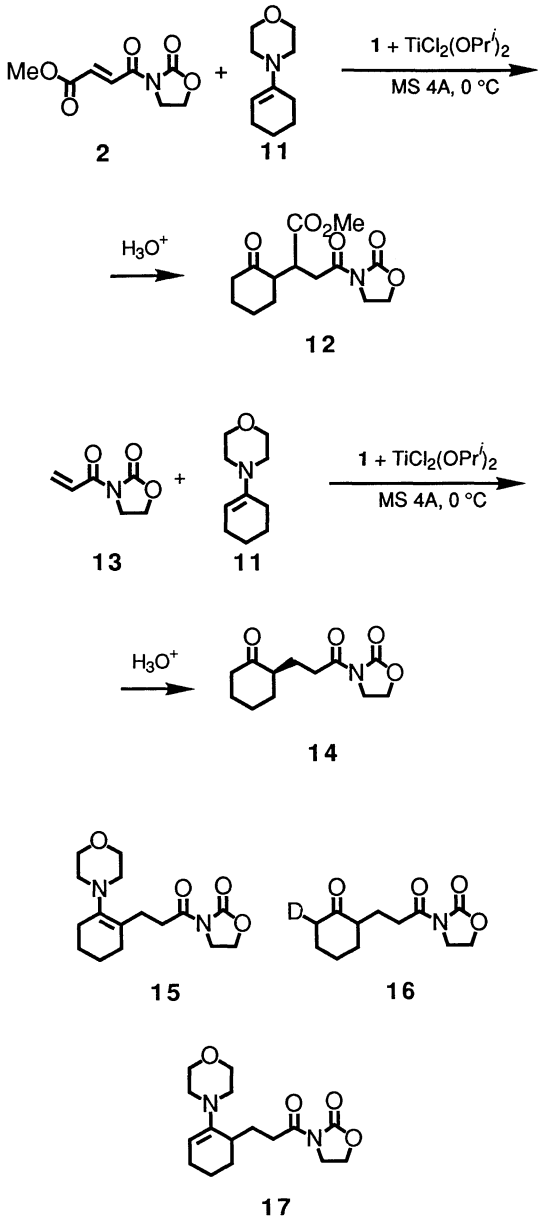
tives. The major d_2-product **8** is considered to be generated by the rapid equilibrium between the enamine and the iminium salt during the hydrolysis.[13] The selective deuteration at the α-position of the phenacyl group clearly indicates that the enamine **5** is the intermediate before hydrolysis.



The reaction of **2** and 4-(1-*t*-butylethenyl)morpholine (**9**) was also examined by varying the amount of the chiral titanium reagent. By the use of excess amount of the chiral Lewis acid, good enantioselectivity was attained (78% ee). And, in the cases of a catalytic and an equimolar use of the chiral titanium reagent, the adduct **10** was obtained with moderate optical purity (53 and 57% ee, respectively).

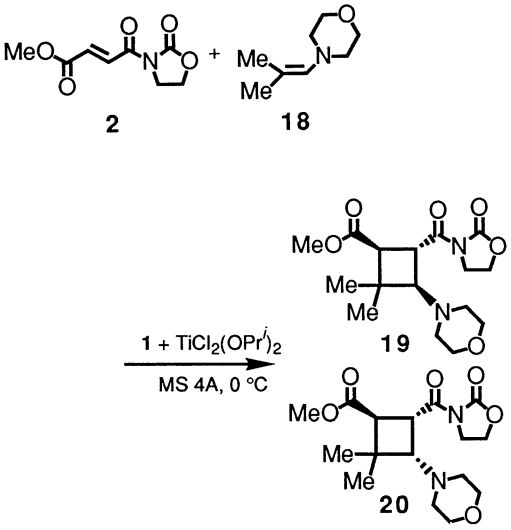


Morpholino enamine of cyclohexanone **11** also reacted in the presence of an equimolar amount of the chiral titanium reagent to afford the addition product **12** in 78% yield as a mixture of two diastereomers in a ratio of 2 : 1. Although the mixture exhibited optical rotation ($[\alpha]_D$ +17.8 (*c* 1.6, CH_2Cl_2)), the optical purity of each isomer could not be determined because of the difficulty of the separation. Accordingly, 3-acryloyl-1,3-oxazolidin-2-one (**13**), the product of which has a single chiral center, was employed as a Michael acceptor. When an ether solution of **11** and **13** was treated with an equimolar amount of the chiral reagent, the Michael product **14** was obtained in 38% yield as an optically active form (28% ee). The asymmetric induction at the chiral center is the clear evidence of the generation of a different type of intermediate from the former one **5** which should give the racemic product after hydrolysis. D_2O–CH_3COOD quenching of the reaction mixture afforded the 6-deuterated and nondeuterated cyclohexanone derivatives **16** and **14** in the ratio of 70 : 30, indicating the formation of the alternative enamine intermediate **17**. The present reaction using an enamine **11** with an α-substituent having a hydrogen is considered to proceed via the ene reaction or/and the Michael reaction followed by the successive proton transfer.[12b]

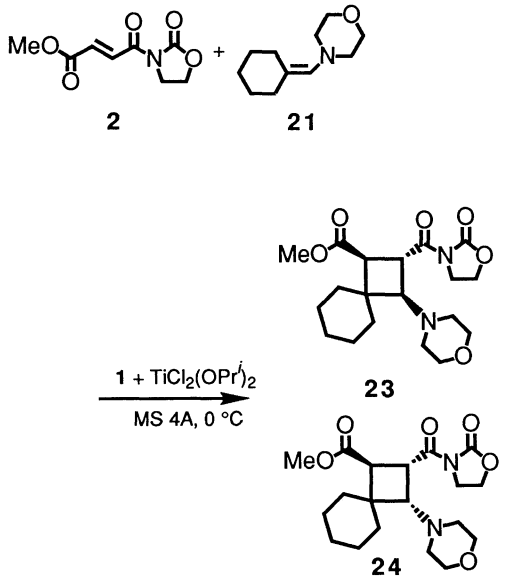


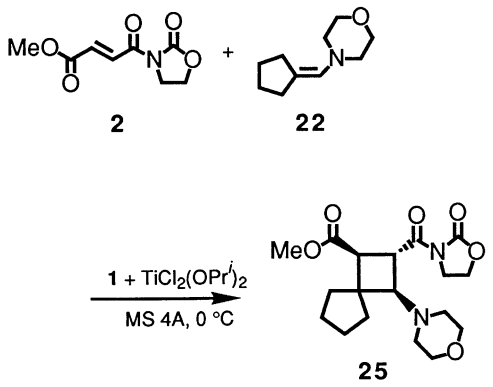
Contrary to the Michael reaction of the above enamines, the reactions of 2,2-disubstituted enamines with **2** were found to afford cyclobutanes. That is, 4-(2-methyl-1-propenyl)morpholine (**18**) reacted with **2** at 0 °C in ether by the use of an equimolar or a catalytic amount of the chiral titanium reagent to give the cyclobutane derivative **19** as a single stereoisomer in 86% and 78% yield with 53% ee and 56% ee, respectively, in which morpholino and oxazolidinylcarbonyl groups are

trans. By the usage of the excess amount of the catalyst, the *trans* isomer **19** was obtained in higher optical purity (48%, 77% ee), but a small amount (22%) of the *cis* isomer **20** was also isolated.



Since the reaction of the 2,2-disubstituted enamine **18** afforded the optically active cyclobutane, the preparation of optically active spiro compounds was next examined by employing enamines **21** and **22** prepared from cyclohexanecarbaldehyde and cyclopentanecarbaldehyde. The reactions were carried out with a catalytic amount (20% mol) of the chiral titanium reagent and the results are shown in the following equations. Two diastereomers **23** and **24** were obtained in the reaction of **21**. The optical purity of the *trans* and *cis* isomers **23**, **24** were found to be 69 and 64% ee, respectively. In the case of **22**, the *trans* isomer **25** was obtained exclusively in 71% yield with 38% ee.





Thus, in the chiral titanium catalyzed reaction, enamines react with unsaturated carboxylic acid derivatives **2** in various courses depending on their structures, which is almost the same tendency observed in the noncatalyzed reactions.[12b] As for the enantioselectivity, good asymmetric induction is attained by the use of excess amount of the chiral titanium reagent, and moderate enantioselectivity is observed in the reaction with a catalytic and an equimolar amount of the reagent. The absolute configurations of the adducts have not been determined except for **14**. In the Diels–Alder reaction[7] and the [2+2] cycloaddition reaction[8] using **2** and the chiral titanium reagent prepared from the (2*R*, 3*R*)-diol **1**, the *re*-face of the β-carbon of α,β-unsaturated acyl moiety is attacked without exception. The same sence of the enantioselection would be anticipated in these reactions with enamines.

Experimental

General. (a) NMR spectra were recorded on Hitachi R24B, and Bruker AM500 spectrometers using tetramethylsilane as the internal standard and $CDCl_3$ as a solvent. IR spectra were recorded on Hitachi 260-30 or Horiba FT-300S spectrometers. Optical rotations were measured with JASCO DIP-180 or DIP-370 digital polarimeters. Mass spectra were obtained with JEOL JMS-D300 mass spectrometer operating at 70 eV. Melting points were uncorrected.

(b) Chromatography: Flash column chromatography was conducted on silica gel (E. Merck, 7734, 70—230 mesh) and the medium pressure column chromatography was performed with the YFLC-254 system of Yamazen Corp. Preparative thin-layer chromatography (TLC) was carried out on silica gel (Wakogel B-5F).

(c) Solvents and Reagents: Toluene and petroleum ether were distilled and stored over Molecular Sieves 4A (MS 4A). Ether was freshly distilled from sodium diphenylketyl. Dichlorodiisopropoxytitanium was prepared from titanium(IV) chloride and titanium(IV) isopropoxide according to the literature method.[14] (2*R*, 3*R*)-1,1,4,4-Tetraphenyl-2,3-(1-phenylethylidene)dioxy-1,4-butanediol (**1**) was prepared according to the method in our previous paper.[7a] Methyl (*E*)-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenoate (**2**) and 3-acryloyl-1,3-oxazolidin-2-one (**13**) were prepared according to the procedure of Evans.[15] Enamines **3**,[16] **9**,[16] **11**,[17] **18**,[18] **21**,[19] and **22**[19] were prepared according to the methods in the

literatures. All the operations were performed under an argon atmosphere.

Typical Procedure for the Reaction of 2 and Enamines Using a Catalytic Amount of the Chiral Titanium Catalyst. To an ether solution (3 ml) of dichlorodiisopropoxytitanium (30.9 mg, 0.13 mmol) was added the chiral diol **1** (74.5 mg, 0.14 mmol) at room temperature. After stirring for 20 min, MS 4A (powder, 100 mg) was added and the mixture was cooled to 0 °C. Then **2** (129.6 mg, 0.65 mmol) and an ether solution (1.5 ml) of 4-(1-phenylethenyl)morpholine (**3**) (135.0 mg, 0.71 mmol) was added, and the reaction mixture was stirred for 24 h at 0 °C. The reaction was quenched with pH 7 phosphate buffer and inorganic materials were removed by filtration. The organic materials were extracted three times with ethyl acetate and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by preparative TLC (hexane : ethyl acetate, 1 : 1) to afford the Michael product **4** (140.9 mg, 0.44 mmol, 68% yield).

The procedure of the reactions using one or two equimolar amounts of the chiral titanium catalyst was identical with that described above, excepting the amount of the catalyst. Reaction conditions, chemical and optical yields are summarized in Table 1.

Spectral data and physical properties of the adducts and the determination of the optical purities were as follws.

Methyl (*R*)-2-Phenacyl-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)butyrate (4). IR (neat) 1775, 1725, 1680 cm^{-1}; ^1H NMR (500 MHz) δ=3.20—3.27 (m, 2H), 3.42 (dd, J=7.4, 18.2 Hz, 1H), 3.48—3.55 (m, 1H), 3.57—3.62 (m, 1H), 3.69 (s, 3H), 3.98 (t, J=8.1 Hz, 2H), 4.41 (t, J=8.1 Hz, 2H), 7.44 (t, J=7.4 Hz, 2H), 7.55 (t, J=7.4 Hz, 1H), 7.93 (d, J=7.4 Hz, 2H); ^{13}C NMR (125 MHz) δ=35.72, 36.52, 39.50, 42.31, 52.10, 62.18, 127.94, 128.54, 133.28, 136.30, 153.43, 171.22, 174.47, 197.15; $[\alpha]_D^{21}$ +2.07° (*c* 1.4, CH_2Cl_2), $[\alpha]_{435}^{21}$ +5.68° (*c* 1.4, CH_2Cl_2):55% ee; HRMS Found: *m/z* 319.1003. Calcd for $C_{16}H_{17}NO_6$: M, 319.1056.

The Michael product **4** was converted to the bis-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (MTPA) ester[20] **26** by the following procedure shown in Scheme 1, and the opitical purity was determined by the intergration of the signals at 30.09 (major) and 29.91 (minor) ppm of the ^{13}C NMR (125 MHz) spectrum.

Methyl (*R*)-5,5-Dimethyl-4-oxo-2-[(2-oxo-1,3-oxazolidin-3-yl)carbonylmethyl]hexanoate (10). Mp 87 °C; IR (neat) 1790, 1740, 1710 cm^{-1}; ^1H NMR (60 MHz) δ=1.1 (s, 9H), 2.7—3.0 (m, 5H), 3.6 (s, 3H), 3.8—4.6 (m, 4H); $[\alpha]_D^{24.5}$ +4.07° (*c* 1.17, CH_2Cl_2): 57% ee; Found: C, 56.06; H, 7.08; N, 4.61%. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68%.

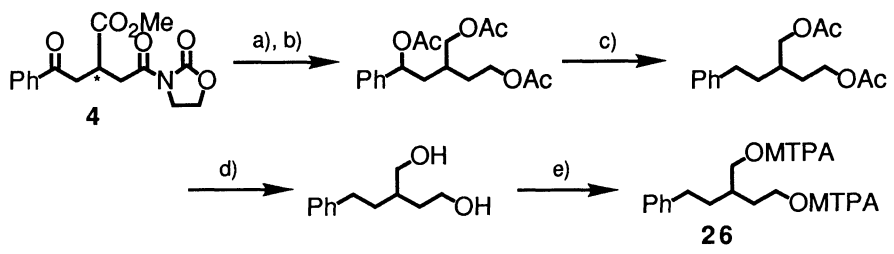
The enantiomeric excess of the Michael adduct **10** was determined by the ^1H NMR analysis of the compound **10** with the existence of a chiral reagent, Eu(hfc)$_3$,[21] in which *t*-Bu group was sufficiently separated.

(*R*)-3-[(3-(2-Oxocyclohexyl)propanoyl]-1,3-oxazolidin-2-one (14). IR (neat) 1775, 1705 cm^{-1}; ^1H NMR (500 MHz) δ=1.32—1.41 (m, 1H), 1.47—1.54 (m, 1H), 1.58—1.67 (m, 2H), 1.78—1.84 (m, 1H), 1.97—2.11 (m, 3H), 2.21—2.28 (m, 1H), 2.30—2.37 (m, 2H), 2.82—2.92 (m, 2H), 3.94 (t, J=8.2 Hz, 2H), 4.35 (t, J=8.2 Hz, 2H); ^{13}C NMR (125 MHz) δ=24.08, 25.01, 27.95, 32.92, 34.15, 42.10, 42.47, 49.70, 62.00, 153.50, 173.22,

Table 1. Asymmetric Reaction between **2** and Enamines

Enamine	Product	Amount of the catalyst/mol%	Time/h	Yield/%	Optical purity/%ee
3	**4**	200[a]	23	54	73
		110[a]	29	51	58
		20[a]	24	68	55
9	**10**	200[a]	41	16	78
		110[a]	30	37	57
		20[a]	108	36	53
18	**19, 20**	200[b]	19	48, 22	77[e]
		110[a]	15	86[d]	53[e]
		20[a]	72	78[d]	56[e]
21	**23, 24**	20[b]	70[c]	41, 23	69, 64
22	**25**	20[b]	70[c]	71	38

a) Ether was used as solvent. b) Toluene-petroleum ether (1:1) was used as solvent. c) The reaction time is 70 h at 0 °C, then 24 h at r.t. d) **20** was not obtained. e) The optical purity is that of **19**.



Scheme 1. a) $LiAlH_4$, b) Ac_2O, Pyridine, c) H_2, Pd/C, d) LiOH/H_2O-MeOH, e) (+)-MTPACl, Pyridine.

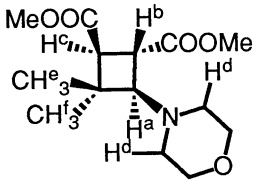
212.60; $[\alpha]_D^{26}$ +1.38° (*c* 0.755, CH_2Cl_2); HRMS Found: *m/z* 239.1178. Calcd for $C_{12}H_{17}NO_4$: M, 239.1158. The optical yield and the absolute configuration was determined by the comparison of the optical rotation of methyl 3-(2-oxocyclohexy)propionate derived from **14** with that of the literature; $[\alpha]_{435}^{27}$ +4.65° (*c* 1.55, MeOH), 27% ee (lit, $[\alpha]_{436}^{20}$ +17.13° (*c* 5.1, MeOH), 97% ee).[22]

Methyl (1*S*, 3*R*, 4*S*)-2,2-Dimethyl-3-morpholino-4-(2-oxo-1,3-oxazolidin-3-ylcarbonyl)cyclobutanecarboxylate (19). IR (neat) 1775, 1735, 1690 cm^{-1}; ^1H NMR (500 MHz) δ=1.08 (s, 3H), 1.33 (s, 3H), 2.22—2.28 (m, 2H), 2.29—2.35 (m, 2H), 2.75 (d, *J*=9.7 Hz, 1H), 2.76 (d, *J*=8.8 Hz, 1H), 3.67 (s, 3H), 3.63—3.70 (m, 4H), 4.03 (t, *J*=8.2 Hz, 2H), 4.35—4.44 (m, 2H), 4.75 (dd, *J*=8.8, 9.7 Hz, 1H); $[\alpha]_D^{23}$ −8.71° (*c* 0.81, CH_2Cl_2): 56% ee; Found: C, 58.70; H, 8.07; N, 4.81%. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.13; N, 4.91%.

The relative stereochemistry of morpholino and oxazolidinylcarbonyl groups was determined after conversion of the latter to the methoxycarbonyl group. The procedure is as follows; dry methanol (2 ml) and a drop of carbon tetrachloride was added to metal magnesium (15.75 mg, 0.648 mmol) at 0 °C to generate magnesium methoxide. After the magnesium dissolved completely, a THF solution (1.5 ml) of **19** (52.45 mg, 0.154 mmol) was added and stirred for 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution and the organic materials were extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by TLC (hexane:ethyl acetate, 1 : 1) to afford dimethyl (1*S*, 2*S*, 3*R*)-4,4-dimethyl-3-morpholino-1,2-cyclobutanedicarboxylate 24.25 mg (55%).

IR (neat) 1735 cm^{-1}; ^1H NMR (500 MHz) δ=0.99 (s, $3H^e$), 1.30 (s, $3H^f$), 2.23—2.36 (m, 2H), 2.36—2.43 (m, $2H^d$), 2.61 (d, *J*=9.4 Hz, H^a), 2.74 (d, *J*=9.6 Hz, H^c), 3.17 (dd, *J*=9.4, 9.6 Hz, H^b), 3.65—3.68 (m, 4H), 3.69 (s, 3H), 3.70 (s, 3H).

The relative stereochemistry was determined as shown below by the NOESY spectrum, because NOEs were observed between H^a and H^d, H^b and H^d, H^b and H^e, H^a and H^c, H^a and H^f, H^c and H^f.



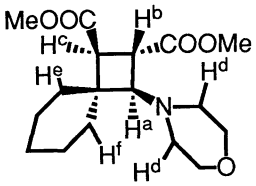
The determination of the optical purity is as follows; the cyclobutane derivative **19** was converted to the bis-(+)-MTPA esters[20] by the following sequence; 1) $Mg(OMe)_2$, 2) $LiAlH_4$, 3) (+)-MTPA-Cl, pyridine, cat. DMAP. The two sets of two singlet signals due to the methyl group appeared at 0.953, 0.934 (major) and 0.940, 0.910 (minor) ppm by 500 MHz ^1H NMR, and the optical yield was determined by the integration of these signals.

Methyl (1*S*, 2*S*, 3*R*)-3-Morpholino-2-(2-oxo-1,3-oxazolidin-3-ylcarbonyl)spiro[3.5]nonane-1-carboxylate (23) and Methyl (1*S*, 2*S*, 3*S*)-3-Morpholino-2-(2-oxo-1,3-oxazolidin-3-ylcarbonyl)spiro[3.5]nonane-1-carboxylate (24). **23** and **24** were obtained as a mixture. IR (neat) 1785, 1730, 1695 cm^{-1}; Found: C, 59.71; H, 7.50; N, 7.16%. Calcd for $C_{19}H_{28}N_2O_6$: C, 59.99; H, 7.42; N, 7.36%. ^1H NMR of the major isomer **23**; (500 MHz) δ=0.98—1.86 (m, 9H), 1.96—2.02 (m, 1H), 2.28—2.51 (m, 4H), 2.70 (d, *J*=9.5 Hz, 1H), 2.75 (d, *J*=9.2 Hz, 1H), 3.63—3.69 (m, 4H), 3.67 (s, 3H), 3.99 (t, *J*=8.1 Hz, 2H), 4.24—4.46 (m, 2H), 4.87 (dd, *J*=9.2, 9.5 Hz, 1H). The distinguishable peaks of the minor isomer **24** were as follows; δ=3.19 (d, *J*=9.7 Hz, 1H), 3.48 (d, *J*=9.7 Hz, 1H), 3.66 (s, 3H).

The mixture of spirononanes **23** and **24** was treated with $Mg(OMe)_2$ in THF to afford the corresponding dimethyl esters, which were separated by TLC (hexane:ethyl acetate, 3:2). The physical data of these dimethyl esters are as follows.

Dimethyl (1*S*, 2*S*, 3*R*)-3-morpholinospiro[3.5]nonane-1,2-dicarboxylate; IR (neat) 1729 cm^{-1}; ^1H NMR (500 MHz) δ=0.91—1.02 (m, 1H), 1.08—1.18 (m, 1H), 1.37 (dt, *J*=4.0, 13.6 Hz, 1H), 1.48—1.63 (m, 5H), 1.74—1.81 (m, H^e), 1.88-1.94 (m, H^f), 2.33—2.46 (m, $4H^d$), 2.58 (d, *J*=9.4 Hz, H^a), 2.69 (d, *J*=10.0 Hz, H^c), 3.32 (dd, *J*=9.4, 10.0 Hz, H^b), 3.65—3.71 (m, 4H), 3.67 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (125 MHz) δ=22.06, 22.44, 25.84, 26.25, 40.18, 41.51, 45.93, 46.42, 51.88, 52.00, 66.69, 68.96, 172.46, 173.70; $[\alpha]_D^{27}$ −6.58° (*c* 1.02, CH_2Cl_2).

The relative stereochemistry was determined as shown below by the NOESY spectrum, because NOEs were observed between H^b and H^e, H^b and H^d, H^a and H^f, H^a and H^d, H^c and H^f, and H^a and H^c.



Dimethyl (1*S*, 2*S*, 3*S*)-3-morpholinospiro[3.5]nonane-1,2-dicarboxylate; IR (neat) 1733 cm^{-1}; ^1H NMR (500 MHz) δ=1.07—1.76 (m, 10H), 2.33—2.50 (m, 4H), 3.05 (dd, *J*=9.6, 9.8 Hz, 1H), 3.13 (d, *J*=9.6 Hz, 1H), 3.17 (d, *J*=9.8 Hz, 1H), 3.64—3.73 (m, 4H), 3.64 (s, 3H) 3.68 (s, 3H); $[\alpha]_D^{27}$ −1.18° (*c* 1.18, CH_2Cl_2).

The dimethyl ester derived from cycloadduct **23** was converted to the corresponding bis-(+)-MTPA ester[20] and the optical purity was determined by the integration of the signals (CH_2OMTPA) at 3.98 (dd, *J*=3.4, 11.7 Hz, major) and 4.13 (dd, *J*=3.8, 11.6 Hz, minor) ppm by the 500 MHz ^1H NMR.

The dimethyl ester derived from cycloadduct **24** was converted to the corresponding (+)-MTPA ester[20] and the optical purity was determined by the integration of the signals at 2.47 (m, 1H, major) and 2.58 (m, 1H, minor) ppm by the 500 MHz ^1H NMR.

Methyl (1*S*, 2*S*, 3*R*)-3-Morpholino-2-(2-oxo-1,3-oxazolidin-3-ylcarbonyl)spiro[3.4]octane-1-carboxylate (25). IR (neat) 1780, 1725, 1690 cm^{-1}; ^1H NMR (500 MHz) δ=1.43—1.97 (m, 8H), 2.22—2.35 (m, 4H), 2.87 (d, *J*=9.9 Hz, 1H), 2.98 (d, *J*=8.9 Hz, 1H), 3.66 (s, 3H), 3.62—3.71 (m, 4H), 3.97—4.07 (m, 2H), 4.35—4.46 (m, 2H), 4.63 (dd, *J*=8.9, 9.9 Hz, 1H); $[\alpha]_D^{24}$ −1.53° (*c* 0.806, CH_2Cl_2). 38% ee. The elemental analysis was performed after conversion to the corresponding dimethyl ester. Found: C, 61.58; H, 8.06; N, 4.47%. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H; 8.09, N; 4.50%.

The cycloadduct **25** was converted to the corresponding (+)-MTPA ester.[20] By the 500 MHz ^1H NMR, one of the four ester methylene protons (CH_2OMTPA) of the major distereomer appeared at 4.07 (dd, *J*=3.6, 11.7 Hz) ppm with the integration of 0.69 proton, which indicated the optical purity to

be 38% ee.

The D_2O Quenching of the Reactions 2 with 3, and 13 with 11. The reactions between **2** and **3**, and **13** and **11** were performed by the use of a catalytic amount of the chiral titanium reagent as described previously and were quenched by adding a mixture of D_2O (1 ml) and CH_3COOD (0.5 ml) at 0 °C. After stirring for 30 min at 0 °C, pH 7 phosphate buffer was added and the inorganic materials were filtered off. The organic materials were extracted with ethyl acetate and the purification was carried out by the same procedure as described before. Methyl 4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-[α,α-$^2H_2$]phenacylbutanoate (**8**) was obtained by the reaction between **2** and **3** as a mixture with the mono- and nondeuterated adduct (d_2:d_1:d_0=72:24:4). The products ratio was determined by the mass spectrum of the mixture.

Spectral data of **8** is as follows; ^1H NMR (500 MHz) δ=3.24 (dd, J=5.5, 18.1 Hz, 1H), 3.44 (dd, J=7.3, 18.1 Hz, 1H), 3.60 (dd, J=5.5, 7.3 Hz, 1H), 3.69 (s, 3H), 3.98 (t, J=8.1 Hz, 2H), 4.41 (t, J=8.1 Hz, 2H), 7.44 (t, J=7.7 Hz, 2H), 7.55 (t, J=7.4 Hz, 1H), 7.93 (d, J=7.2 Hz, 2H); ^{13}C NMR (125 MHz) δ=35.62, 36.50, 39.20 (quintet), 42.32, 52.13, 62.18, 127.94, 128.57, 133.30, 136.35, 153.43, 171.25, 174.49, 197.24; HRMS Found: m/z 321.1151. Calcd for $C_{16}H_{15}D_2NO_6$: M, 321.1181.

The quintet of the carbon at 39.2 ppm indicates that the two deuteriums were attached at the same carbon, which was a secondary carbon by the DEPT measurement and it was also assigned as an α position of the phenacyl group because deuterium effect was observed at the carbonyl carbon of the benzoyl group.

(*R*)-3-[(2-Oxo[3-^2H]cyclohexyl)propanoyl]-1,3-oxazolidin-2-one (**16**) was obtained by the reaction of **13** and **11** as a mixture with the nondeuterated product **14** (**16**:**14**=70:30). Spectral data of **16** is as follows; ^1H NMR (500 MHz) δ=1.32—1.41 (m, 1H), 1.47—1.54 (m, 1H), 1.58—1.67 (m, 2H), 1.78—1.84 (m, 1H), 1.97—2.11 (m, 3H), 2.21—2.28 (m, 1H), 2.30—2.37 (m, 1H), 2.82—2.92 (m, 2H), 3.94 (t, J=8.2 Hz, 2H), 4.35 (t, J=8.2 Hz, 2H); ^{13}C NMR (125 MHz) δ=24.07, 25.01, 27.86, 32.90, 34.15, 41.77 (t, J=10.3 Hz), 42.45, 49.70, 62.00, 153.50, 173.21, 212.64.

The position of deuterium was assigned as follows; the carbon at 41.77 ppm, which was connected with deuterium, was assigned as a secondary carbon and α to the carbonyl group of cyclohexanone by the chemical shift of ^{13}C NMR, DEPT measurement, and the deuterium effect observed at the carbonyl carbon of cyclohexanone.

References

1) Reviews; K. Tomioka and K. Koga, "Noncatalytic Additions to α,β-Unsaturated Carbonyl Compounds," in "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Inc., New York (1983), Vol. 2, Chap. 7; M. Norgradi, "Stereoselective Synthesis," VCH Verlagsgesellschaft, Weinheim (1987), p. 221.

2) D. Seebach, R. Imwinkelried, and T. Weber, "EPC Synthesis with C, C Bond Formation via Acetals and Enamines," in "Modern Synthetic Methods 1986," ed by R. Scheffold, Springler-Verlag, Berlin (1986); Y. Hirai, T. Terada, and T. Yamazaki, *J. Am. Chem. Soc.*, **110**, 958 (1988); S. L. Schreiber and H. V. Meyers, *ibid.*, **110**, 5198 (1988); and the references cited therein.

3) Review; G. H. Posner, "Addition of Organometallic Reagents to Chiral Vinylic Sulfoxides," in "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Inc., New York (1983), Vol. 2, Chap. 8.

4) Review; K. Tomioka, *Synthesis,* **1990**, 541.

5) H. Wynberg and R. Helder, *Tetrahedron Lett.*, **1975**, 4057; D. J. Cram and G. D. Y. Sogah, *J. Chem. Soc., Chem. Commun.*, **1981**, 625; T. Yura, N. Iwasawa, K. Narasaka, and T. Mukaiyama, *Chem. Lett.*, **1988**, 1025; K. Soai, T. Hayasaka, and S. Ugajin, *J. Chem. Soc., Chem. Commun.*, **1989**, 516.

6) N. Iwasawa, Y. Hayashi, H. Sakurai, and K. Narasaka, *Chem. Lett.*, **1989**, 1581.

7) a) K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989); b) N. Iwasawa, J. Sugimori, Y. Kawase, and K. Narasaka, *Chem. Lett.*, **1989**, 1947; c) K. Narasaka, H. Tanaka, and F. Kanai, *Bull. Chem. Soc. Jpn.*, **64**, 387 (1991).

8) Y. Hayashi and K. Narasaka, *Chem. Lett.*, **1989**, 793; **1990**, 1295; Y. Hayashi, S. Niihata, and K. Narasaka, *ibid.*, **1990**, 2091; Y. Ichikawa, A. Narita, A. Shiozawa, Y. Hayashi, and K. Narasaka, *J. Chem. Soc., Chem. Commun.*, **1989**, 1919.

9) K. Narasaka, Y. Hayashi, and S. Shimada, *Chem. Lett.*, **1988**, 1609.

10) H. Minamikawa, S. Hayakawa, T. Yamada, N. Iwasawa, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, **61**, 4379 (1988).

11) Lewis acid catalyzed Michael reaction of enamines, see; Y. Hashimoto, S. Machida, K. Saigo, J. Inoue, and M. Hasegawa, *Chem. Lett.*, **1989**, 943.

12) a) As for the mechanism of the α,β-unsaturated carbonyl compounds and enamines, see; H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Inc., Menlo Park (1972), p. 616; b) G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963); c) G. Opitz and I. Loschmann, *Angew. Chem.*, **72**, 523 (1960); d) W. Schroth and G. Fischer, *Angew. Chem., Int. Ed. Engl.*, **2**, 394 (1963); e) I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, **1964**, 2165; f) D. E. Heitmeier, J. T. Hortenstine, Jr., and A. P. Gray, *J. Org. Chem.*, **36**, 1449 (1971), and the references cited therein.

13) S. K. Malhotra and F. Johnson, *Tetrahedron Lett.*, **1965**, 4027; J. P. Scaefer and D. S. Weinberg, *ibid.*, **1965**, 1801.

14) C. Dijkgraaf and J. P. G. Rousseau, *Spectrochim. Acta, Part A.*, **24**, 1213 (1968).

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

16) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).

17) S. Hünig, E. Lucke, and W. Brenninger, *Org. Synth.*, Coll. Vol. V, 808 (1973).

18) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

19) L. Citerio, D. Pocar, R. Stradi, and B. Gioia, *J. Chem. Soc., Perkin Trans. 1,* **1978**, 309.

20) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).

21) Eu(hfc)$_3$=tris[3-heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III).

22) C. Stetin, B. D. Jeso, and J-C, Pommier, *J. Org. Chem.*, **50**, 3863 (1985).