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Enantio- and Diastereoselective Catalysis of Addition Reaction of Allylic Silanes and Stannanes to Glyoxylates by Binaphthol-derived Titanium Complex†

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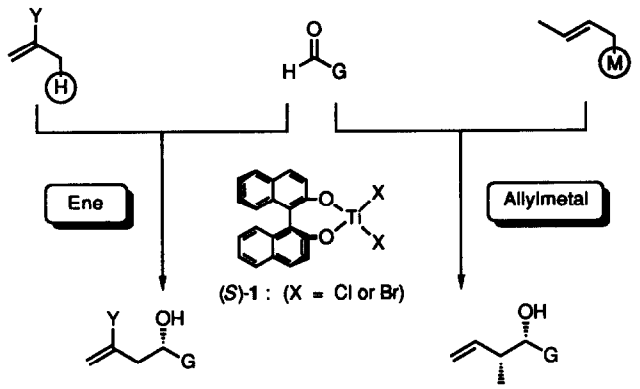
Key Words: Asymmetric catalysis; Enantiocontrol; Diastereocontrol; Allylic silane; Allylic stannane; Carbonyl-addition reaction; Carbonyl-ene reaction; Glyoxylate; Binaphthol-derived titanium dihalide; Chiral titanium complex

Abstract: *Chiral titanium complex (1), prepared in situ from optically pure binaphthol and diisopropoxytitanium dihalide in the presence of molecular sieves, is shown to catalyze the addition reactions of crotylsilanes and -stannanes to glyoxylates to afford (syn)-α-hydroxy-β-methyl esters in highly scalemic forms with high diastereoselectivity.*

The development of asymmetric catalysis, particularly for carbon-carbon bond formation, is one of the most challenging and formidable endeavor in organic synthesis.[2] The ene reaction involving carbonyl enophiles (carbonyl-ene reaction)[3] constitutes an efficient alternative to the carbonyl-addition reaction of allylmetals which has now become one of the most useful methods for carbon-carbon bond formation with diastereocontrol (Scheme 1).[4] Recently, we have reported that the enantioselective carbonyl-ene reaction with prochiral glyoxylate (G = CO_2R) catalyzed by the chiral titanium complex **1**,[5] prepared *in situ* from (i-PrO)$_2$TiX$_2$ and optically pure binaphthol (BINOL) in the presence of molecular sieves (MS 4A), provides a practical access to highly scalemic α-hydroxy esters of synthetic and biological importance.[6] However, the asymmetric catalytic glyoxylate-ene reaction has been so far restricted to 1,1-disubstituted alkenes as ene components. Herein we wish to report the asymmetric catalysis of a complementary process, namely diastereoselective carbonyl-addition reaction of crotylsilane[4b,h] and -stannane[4c,d] as activated ene counterparts.

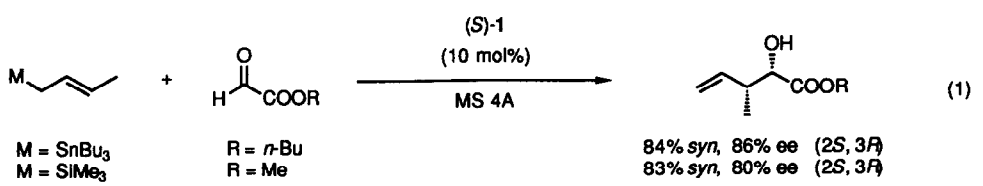
† In honor of the 77th birthday (ki-jyu in Japanese) of Professor Shun-ichi Yamada.



Scheme 1.

Results and Discussions

The binaphthol-derived chiral titanium (BINOL-Ti) complex **1** was prepared as previously reported[5b,e] and found to catalyze (by the 10 mol% use of **1**) the addition reaction of allylic silanes and stannanes to glyoxylates (eq. 1). The stereochemical features thus obtained are exemplified in Table 1. The most notable is that the enantiomeric excesses are so sensitive not only to the alkyl substituents but also to the geometry of the allylic metals. A high level of enantioselectivity is obtained along with a high *syn*-diastereoselectivity only by using (*E*)-crotylsilane and -stannane (entries 4, 6, and 7). By contrast, (*Z*)-crotylmetals and β-substituted (*E*)-crotylmetals show a significant decrease in enantio- and *syn*-diastereoselectivity (entries 5 and 8 ~ 11). These observations are in direct contrast to the high level of both selectivities in the chiral acyloxy borane (CAB) catalyzed carbonyl-addition reaction of allylic silanes irrespective of the olefinic geometry and β-alkyl substituents.[7] In the CAB catalyzed reaction, however, no result was reported with either geometrical isomer of crotylsilane. It should be noted here that the level of asymmetric induction with methallylstannane is quite low (entry 3), in comparison with the extremely high level of enantiomeric excess obtained in the glyoxylate-ene reaction with isobutylene.[5a,b]



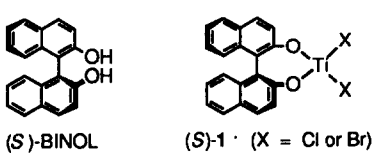
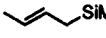
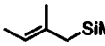
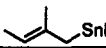


Table 1. Glyoxylate-addition reaction with allylic metals catalyzed by BINOL-Ti complex.[a)]

Entry	(*S*)-1 (X)	Glyoxylate (R)	Allylic metals (*E*/*Z*)	Yield/%	*syn*[b,c)] (% ee)[d)] / *anti*[b,c)] (% ee)[d)]	Config.[e)]
1	Br	Me		40	(30)	2*S*
2	Br	Me		35	(10)	2*S*
3	Cl	Me		70	(16)	2*S*
4	Cl	Me	 (79% *E*)	48	83 (80) / 17 (32)	2*S*,3*R*
5	Cl	Me	 (>95% *Z*)	38	61 (28) / 39 (34)	2*S*,3*R*
6	Cl	Me	 (85% *E*)	53	75 (84) / 25 (16)	2*S*,3*R*
7	Cl	Bu		64	84 (86) / 16 (28)	2*S*,3*R*
8	Cl	Me	 (>95% *Z*)	38	56 (34) / 44 (38)	2*S*,3*R*
9	Cl	Me	 (90% *E*)	44	70 (22) / 30 (8)	2*S*,3*R*
10	Cl	Me	 (>95% *Z*)	63	87 (42) / 13 (10)	2*S*,3*R*
11	Cl	Me	 (90% *E*)	80	53 (2) / 47 (2)	2*S*,3*R*

a) All reactions were carried out in dichloromethane (5 mL) at -60 °C to room temperature for 10 h period in 1 mmol of glyoxylate, 1 mmol of allylic metal and 10 mol% (0.1 mmol) of (*S*)-1 in the presence of molecular sieves 4A (0.5 g). b) The diastereomeric ratio was determined by ^{1}H NMR analysis. c) The stereochemistry was determined by the comparison of ^{1}H NMR spectrum to that of literature (see ref. 12) or the similarity seen in LIS-NMR analysis (see ref. 5b,e and 9). d) The enantiomeric excess was determined by LIS (lanthanide induced shift) NMR analysis using Eu(dppm)$_3$ as a chiral NMR shift reagent (see ref. 5b,e and 9). e) Refer to the major stereoisomers.

The present carbonyl-addition reactions of crotylmetals with or without β-alkyl substituent exhibit the *syn*-diastereoselectivity, the degree of which depends, however, dramatically on the olefinic geometry posing the antiperiplanar *vs*. synclinal problem on the transition-state conformations (Figure 1).[4b-d,8] The observed *syn*-diastereoselectivity implies that the carbonyl-addition reaction would proceed mainly through the widely accepted antiperiplanar transition state (**A**) but partially through synclinal transition state (**B**) particularly for (*Z*)- and β-alkyl substituted crotylmetals leading to *anti*-diastereomers.

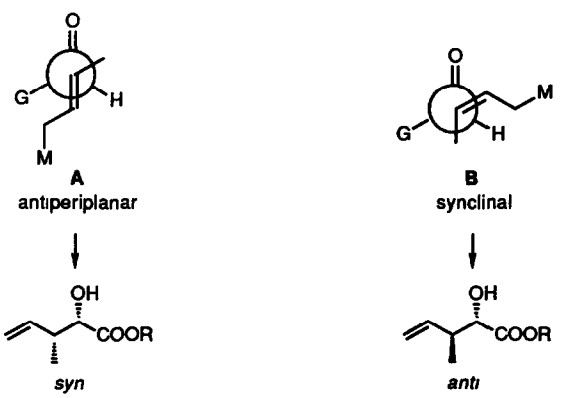
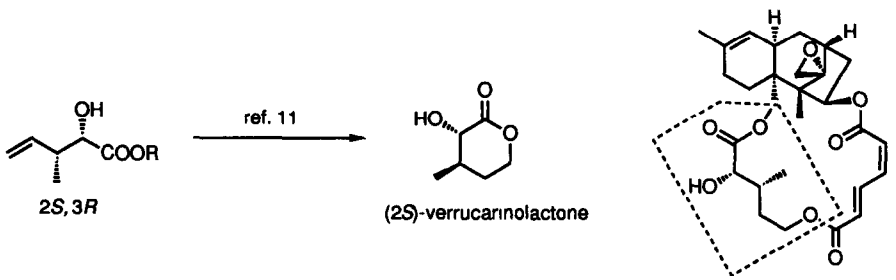


Figure 1.

The absolute configurations of the products are assigned to be 2*S*, by the LIS (lanthanide induced shift) NMR analysis using Eu(dppm)$_3$ as a chiral shift reagent,[5b,e,9] in all cases of the (*S*)-**1** catalyzed reactions. Thus, the sense of asymmetric induction is exactly the same as observed in the glyoxylate-ene reaction; (*S*)-**1** provides 2*S*-hydroxy esters. The (*syn*)-2*S*-hydroxy-3*R*-methyl-4-pentenoate, thus obtained with (*E*)-crotylsilane and -stannane by the judicious choice of the chirality of the BINOL-Ti complex (*S*)-**1**, would be transformed to the natural enantiomer of verrucarinolactone, a degradation product of verrucarin A (antitumor activity)[10] according to Roush's procedure (Scheme 2).[11]



Scheme 2.

In summary, this work has convincingly demonstrated that the binaphthol-derived chiral titanium (BINOL-Ti) complex **1** efficiently catalyze the glyoxylate-addition reactions of crotylsilane and -stannane, when properly designed in terms of the geometry and β-substituent. Thus the present enantio- and *syn*-diastereoselective catalysis provides a new, efficient method for the asymmetric synthesis of (*syn*)-α-hydroxy-β-alkyl esters. Further investigations on the asymmetric catalysis of the chiral titanium complex are in progress in our laboratory.

Acknowledgment

This research was partially supported by the Grant-in-Aid for Scientific Research on Priority Areas and for Encouragement of Young Scientist from the Ministry of Education Japan, the Asahi-Kasei Award in Synthetic Organic Chemistry Japan, Iwaki Scholarship Foundation, and the Joint Studies Program of the Institute for Molecular Science.

Experimental

General. Molecular sieves 4A (activated powder) and (*S*)-(-)-1,1'-bi-2-naphthol were purchased from Aldrich Chemical Co. Ltd. Melting points and boiling point were uncorrected. ^1H and ^{13}C NMR spectra were measured on a Varian EM390 (90 MHz), GEMINI 200 (200 MHz) or 300 (300 MHz) spectrometers. Chemical shifts of ^1H NMR were expressed in parts per million downfield from tetramethylsilane as an internal standard ($\delta = 0$) in $CDCl_3$, unless otherwise noted. Chemical shifts of ^{13}C NMR were expressed in parts per million in $CDCl_3$ as an internal standard ($\delta = 77.1$), unless otherwise noted. IR spectra were measured on a JASCO FT/IR-5000 spectrometer. HPLC analyses were conducted on a Shimadzu LC-6A instrument equipped with model SPD-6A and/or RI-6A spectrometers as an UV light (at the indicated wave length) and a refractive index detector, respectively. Peak area was calculated by a Shimadzu model C-R6A as an automatic integrator. Mass spectra were recorded on a JEOL JMS AX-505H system. Analytical thin layer chromatography (TLC) were performed on glass plates and/or aluminum sheets pre-coated with silica gel (Merck, Kieselgel 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. All experiments were carried out under nitrogen or argon atmosphere. THF and diethylether were distilled over sodium benzophenone ketyl immediately prior to use. Dichloromethane was freshly distilled over CaH_2.

Preparation of Allylic Tributylstannanes.

(*E*)-Crotyltributylstannane. To a solution of diisopropylamine (2.8 mL, 20 mmol) in THF (20 mL) was added a 1.6 *N* hexane solution of *n*-BuLi (13 mL, 20 mmol) at 0 °C. After stirring for 30 min at that temperature, tributyltin hydride (5.5 mL, 20 mmol) was added into the solution. After stirring for 30 min at 0 °C, the resultant tin lithium reagent was allowed to react with crotyl methanesulfonate (3.0 g, 20 mmol) at 0 °C. The reaction mixture was quenched with ice-water and extracted with ether. The combined extracts were dried over $MgSO_4$, evaporated, and distilled under reduced pressure to give (*E*)-crotyltributylstannane (85% *E*) in 46% yield (3.14 g); bp 100 ~ 110 °C / 1 mmHg; ^1H NMR ($CDCl_3$) δ 0.70 ~ 2.00 (m, 32H), 5.10 ~ 5.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 9.2, 13.8, 17.9, 27.4, 27.5, 29.3, 120.3, 130.5.

Tributyl-2-butynylstannane. To a suspension of Mg (1.0 g, 41 mmol) in THF (50 mL) was added dropwise a solution of 2-butynylbromide (5.0g, 37.6 mmol) in THF (5 mL). After refluxed for 2 h, the resultant solution was cooled down to room temperature and then tributyltin chloride (10.2 mL, 37.6 mmol) was added into the solution. After stirring for 15 h, the reaction mixture was quenched with ice-water and the product was extracted with ether. The combined extracts were dried over $MgSO_4$, evaporated, and distilled under reduced pressure to give tributyl-2-butynylstannane in 14% yield (1.84 g); bp 110 ~ 130 °C / 0.7 mmHg; ^1H NMR ($CDCl_3$) δ 0.50 ~ 2.00 (m, 27H), 1.43 (q, $J = 3$ Hz, 2H), 1.78 (t, $J = 3$ Hz, 3H).

(*Z*)-Crotyltributylstannane. To a suspension of $Ni(OAc)_2 \cdot 4H_2O$ (0.13 g, 0.54 mmol) in ethanol (5 mL) was added a solution of $NaBH_4$ (20 mg, 0.54 mmol) in ethanol (2 mL). Ethylenediamine (0.07 mL, 1.07 mmol) and a solution of tributyl-2-butynylstannane (1.8 g, 5.4 mmol) in EtOH (2 mL) was added into the suspension. The reaction mixture was stirred under a hydrogen atmosphere. The resultant suspension was poured into water

and filtered through a pad of Celite. The filtrate was extracted with ether and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and then distilled under reduced pressure to give (*Z*)-crotyltributylstannane (>95% *Z*) in 79% yield (1.46 g); bp 100 ~ 110 °C / 1 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.43 ~ 3.30 (m, 32H), 5.96 ~ 6.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 9.4, 12.5, 13.8, 27.4, 27.5, 29.3, 118.2, 129.6.

(*E*)-Tributyl-(β-methylcrotyl)stannane. The titled compound (90% *E*) was prepared in a similar manner as described in the preparation of (*E*)-crotyltributylstannane; bp 100 ~ 115 °C / 0.7 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.40 ~ 1.90 (m, 35H), 4.88 ~ 5.35 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 9.5, 13.8, 18.2, 22.1, 27.5, 29.1, 29.3, 114.2, 136.0.

Preparation of Allylic Trimethylsilanes.

(*E*)-Trichlorocrotylsilane. A 100-mL three necked flask was charged with ether (30 mL) and triethylamine (10 mL, 72 mmol) and CuCl (200 mg, 2.0 mmol). To the resultant suspension was added dropwise an ether (10 mL) solution of crotylchloride (5.9 mL, 60 mmol) and trichlorosilane (8.5 mL, 84 mmol) over 15 min at room temperature. After stirring for 3 h at that temperature, the resultant mixture was filtered through a pad of Celite to remove Et_3NHCl salt. The filtrate was concentrated and distilled under atmospheric pressure to give trichlorocrotylsilane in 66% yield (7.52 g); bp 110 °C / 760 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.75 (d, *J* = 6.0 Hz, 3H), 2.30 (d, *J* = 7.0 Hz, 2H), 5.15 ~ 6.05 (m, 2H).

(*E*)-Crotyltrimethylsilane. To an ether (40 mL) solution of trichlorocrotylsilane (7.5 g, 40 mmol) as obtained above was added a 1 N ether solution of MeMgI (200 ml, 200 mmol) at -30 °C. The reaction mixture was gradually warmed up to room temperature over 12 h period. The resultant mixture was quenched with ice-water. Organic materials were extracted with ether and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under atmospheric pressure and the residue was distilled to give crotyltrimethylsilane (79% *E*) in 47% yield (2.41 g); bp 110 °C / 760 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9H), 1.40 (d, J = 6.0 Hz, 2H), 1.67 (d, J = 5.0 Hz, 3H), 5.10 ~ 5.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ -2.0, 18.1, 22.7, 123.5, 127.4.

(*Z*)-Crotyltrimethylsilane. To a suspension of $Ni(OAc)_2 \cdot 4H_2O$ (1.0 g, 4.2 mmol) in ethanol (20 mL) was added a solution of $NaBH_4$ (0.16 g, 4.2 mmol) in ethanol (10 mL). Ethylenediamine (0.6 mL, 8.4 mmol) and 2-butynyltrimethylsilane (5.3 g, 42 mmol) was added into the suspension. The reaction mixture was stirred under a hydrogen atmosphere. The resultant solution was extracted with ether and the combined organic layers were dried over $MgSO_4$. The solvent was removed under atmospheric pressure and then distilled under reduced pressure to give (*Z*)-crotyltrimethylsilane (>95% *Z*) in 71 %yield (3.80 g); bp 65 ~ 70 °C / 150 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9H), 1.33 ~ 1.70 (m, 5H), 5.28 ~ 5.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ -1.8, 12.7, 18.1, 121.6, 126.9.

(*E*)-Trichloro-(β-methylcrotyl)silane. The titled compound was prepared in a similar manner as described in the preparation of (*E*)-crotyltrichlorosilane; bp 160 ~ 167 °C / 760 mmHg; ^{1}H NMR ($CDCl_3$) δ 1.66 (d, *J* = 7.0 Hz, 3H), 1.78 (s, 3H), 2.34 (s, 2H), 5.37 (q, *J* = 7 0 Hz, 1H).

(*E*)-Trimethyl-(β-methylcrotyl)silane. The titled compound (90% *E*) was prepared in a similar manner as described in the preparation of (*E*)-crotyltrimethylsilane; bp 110 ~ 136 °C / 760 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9H), 1.50 (d, *J* = 7.0 Hz, 3H), 1.60 (s, 5H), 4.83 ~ 5.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ -1.3, 13.6, 18.4, 29.9, 116.5, 133.6.

General Procedure for BINOL-Ti Catalyzed Addition Reaction of Allylic Metals.

Methyl 2-Hydroxy-3-methyl-4-pentenoate.[12] To a suspension of activated powder molecular sieves 4A (0.5 g) in dichloromethane (5 mL) was added a 0.3 *M* toluene solution of diisopropoxytitanium dichloride (0.33 mL, 0.10 mmol) and (*S*)-(-)-binaphthol (28.6 mg, 0.10 mmol) at room temperature under an argon atmosphere. After stirring for 1 h at room temperature, the mixture was cooled to -60 °C. To the suspension was added a 1 N solution of methyl glyoxylate in dichloromethane (1.0 mL, 1.0 mmol) and a (*E*)-crotyltributylstannane (349 mg, 1.0 mmol). The reaction mixture was gradually warmed to room temperature for 10 h period. The solution was poured into saturated $NaHCO_3$ (10 ml). Molecular sieves 4A was filtered off through a pad of Celite and the filtrate was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The resultant residue was purified with silica gel chromatography (hexane/ethyl acetate = 20 : 1) to give methyl 2-hydroxy-3-methyl-4-pentenoate in 53% yield (83 mg); IR (neat) 3400, 2965, 1710, 1620, 1415 cm^{-1}; HPLC (Zorbax SIL, eluent, hexane/ethyl acetate = 10 : 1, flow rate 1.0 mL/min, detection RI), t_R of *syn*-isomer 24 min and *anti*-isomer 23 min. ***syn*-Isomer**: ^{1}H NMR ($CDCl_3$) δ 1.00 (d, *J* = 7.2 Hz, 3H), 2.43 ~ 2.83 (m, 1H), 2.53 (bs, 1H), 3.80 (s, 3H), 4.20 (d, *J* = 5.0 Hz, 1H), 5.0 ~ 5.2 (m, 2H), 5.87 (m, 1H); ***anti*-Isomer**: ^{1}H NMR ($CDCl_3$) δ 1.14 (d, *J* = 7.2 Hz, 3H), 2.50 (m, 1H), 2.53 (bs, 1H), 3.77 (s, 3H), 4.13 (d, *J* = 5.0 Hz, 1H), 5.0 ~ 5.2 (m, 2H), 5.5 ~ 5.6 (m, 1H).

Butyl 2-Hydroxy-3-methyl-4-pentenoate. IR (neat) 3472, 2968, 1734, 1642, 1462, 1419, 1381, 1214, 1133, 1071, 1023, 919 cm^{-1}; HRMS (CI) for $C_{10}H_{19}O_3$ (M + H) calcd. 187.1334, found 187.1344; ***syn*-Isomer**: ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.40 (m, 2H), 1.64 (m, 2H), 2.69 (m, 1H), 2.71 (bs, 1H), 4.18 (m, 2H), 4.20 (d, *J* = 4.2 Hz, 1H), 5.07 (m, 1H), 5.13 (m, 1H), 5.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 16.4, 19.2, 30.7, 41.8, 65.6, 74.0, 115.5, 139.5, 174.4; ***anti*-Isomer**: ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.4 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.40 (m, 2H), 1.64 (m, 2H), 2.65 (m, 1H), 2.71 (bs, 1H), 4.11 (d, *J* = 3.2 Hz, 1H), 4.18 (m, 2H), 5.06 (m, 1H), 5.07 (m, 1H), 5.75 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 16.4, 19.2, 30.7, 42.0, 65.6, 74.4, 116.4, 137.7, 174.4.

Methyl 2-Hydroxy-4-pentenoate. IR (neat) 3470, 2958, 1742, 1644, 1441, 1218, 1139, 1087, 1000, 922 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (m, 1H), 2.58 (m, 1H), 2.69 (bs, 1H), 3.79 (s, 3H), 4.29 (dd, *J* = 4.6, 6.4 Hz, 1H), 5.11 (m, 1H), 5.15 (m, 1H), 5.81 (ddt, *J* = 10.1, 17.0, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 38.7, 52.6, 70.1, 118.8, 132.5, 174.9; HRMS (CI) for $C_6H_{11}O_3$ (M + H) calcd. 131.0708, found 131.0717.

Methyl 2-Hydroxy-4-methyl-4-pentenoate. IR (neat) 3490, 2950, 1740, 1440, 1100, 905 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.80 (s, 3H), 2.35 (dd, *J* = 8.0, 14.0 Hz, 1H), 2.58 (dd, *J* = 5.0, 14.0 Hz, 1H),

2.70 (b, 1H), 3.78 (s, 3H), 4.35 (dd, J = 8.0, 5.0 Hz, 1H), 5.82 (m, 1H), 5.88 (m, 1H); $[\alpha]_D^{20}$ -1.20 ° (c 2.23, $CHCl_3$) (16% ee (*S*)); HRMS for $C_7H_{12}O_3$ calcd. 144.0786, found 144.0781.

Methyl 2-Hydroxy-3,4-dimethyl-4-pentenoate.[12] IR (neat) 3450, 1740, 1650, 1440, 1380, 895 cm^{-1}; MS for $C_8H_{14}O_3$ calcd 158.0943, found 158; ***syn*-Isomer**: ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 7.0 Hz, 3H), 1.77 (bs, 3H), 2.50 (br, 1H), 2.53 (m, 1H), 3.76 (s, 3H), 4.25 (d, J = 4.0 Hz, 1H), 4.76 (m, 1H), 4.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 21.0, 44.3, 52.5, 72.9,112.4, 146.3, 175.4. ***anti*-Isomer**: ^1H NMR ($CDCl_3$) δ 1.10 (d, J = 7.2 Hz, 3H), 1.69 (bs, 3H), 2.50 (br, 1H), 2.53 (m, 1H), 3.74 (s, 3H), 4.11 (d, J = 5.3 Hz, 1H), 4.76 (m, 1H), 4.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.7, 20.6, 45.0, 52.4, 74.1, 113.4, 145.7, 175.1.

Determination of Enantiomeric Excess of Carbonyl-Addition Reaction Products.

I. HPLC Analysis. The enantiomeric excess of methyl 2-hydroxy-4-methyl-4-pentenoate were analyzed by HPLC using chiral column (SUMICHIRAL OA-2500I, eluent, hexane/1,2-dichloroethane/ethanol = 180 : 19 : 1, flow rate 1.0 mL/min, detection 215-nm light), t_R of (*R*)-(+)-isomer 10.7 min and (*S*)-(-)-isomer 11.6 min.

II. LIS-NMR Analysis. The enantiomeric excess was determined by LIS-NMR analysis of α-hydroxy esters and/or after conversion to the corresponding α-methoxy esters using (+)-Eu(dppm)$_3$ as a chiral NMR shift reagent (30 w/v% CCl_2FCClF_2 solution).

Typical Procedure. A 15 ~ 25-μL sample of the α-hydroxy ester (or α-methoxy ester) was dissolved in 0.4 mL of $CDCl_3$ and transferred to an NMR tube. A 5-μL portion of (+)-Eu(dppm)$_3$ (30 w/v% CCl_2FCClF_2 solution) was added to the α-hydroxy ester (α-methoxy ester) sample. The mixture was shaken well, and ^1H NMR spectrum was recorded. Additional portions of the shift reagent solution were added in 8-μL portions until the methyl ether (or α-methyl ether) resonance showed baseline resolution from the two enantiomers. Totally 25 ~ 80 μL of the shift reagent solution should be required to achieve the desired shift. At that point, a chemical shift difference of the methyl esters (about 0.1 ~ 0.3 ppm) should be observed. The %ee was obtained by integration of the two methyl ester peaks (or α-methoxy peaks).

LIS-NMR Analysis of α-Hydroxy Esters.

LIS-NMR Analysis of Methyl 2-Hydroxy-3-methyl-4-pentenoate. On addition of (+)-Eu(dppm)$_3$ (75 μL) to the solution of methyl 2-hydroxy-3-methyl-4-pentenoate in $CDCl_3$ (21 mg, in 0.4 mL), the two singlets of methyl ester at δ 3.80 (*syn*) and 3.77 (*anti*) were changed into the four singlets at δ 4.51 ((2*S*,3*R*)-isomer (*syn*)), 4.42 ((2*R*,3*S*)-isomer (*syn*)), 4.36 ((2*S*,3*S*)-isomer (*anti*)), and 4.23 ((2*R*,3*R*)-isomer (*anti*)).

LIS-NMR Analysis of Methyl 2-Hydroxy-3,4-dimethyl-4-pentenoate. On addition of (+)-Eu(dppm)$_3$ (70 μL) to the solution of methyl 2-hydroxy-3,4-dimethyl-4-pentenoate. in $CDCl_3$ (15 mg, in 0.4 mL), the two singlets of methyl ester at δ 3.76 (*syn*) and 3.74 (*anti*) were changed into the four singlets at δ 4.34 ((2*S*,3*R*)-isomer (*syn*)), 4.27 ((2*R*,3*S*)-isomer (*syn*)), 4.07 ((2*S*,3*S*)-isomer (*anti*)), and 4.04 ((2*R*,3*R*)-isomer (*anti*)).

LIS-NMR Analysis of α-Methoxy Esters.

Preparation of α-Methoxy Esters. To a mixture of methyl iodide (0.3 mL) and the ene product (0.5 mmol) in ether was added Ag_2O (0.23 g). The reaction mixture was stirred for 1 day at room temperature. The resultant suspension was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure. Chromatographic purification gave the corresponding α-methoxy esters in 95-100% yield.

Methyl 2-Methoxy-4-pentenoate. ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.57 (t, J = 6.0 Hz, 2H), 3.49 (s, 3H), 3.86 (s, 3H), 3.94 (t, J = 6.0 Hz, 1H), 5.10 ~ 6.26 (m, 3H).

Methyl 2-Methoxy-4-methyl-4-pentenoate. ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.74 (s, 3H), 2.43 (d, J = 6.5 Hz, 2H), 3.38 (s, 3H), 3.73 (s, 3H), 3.90 (t, J = 6.5, 1H), 4.74 (m, 2H), 4.82 (m, 1H).

LIS-NMR Analysis of Methyl 2-Methoxy-4-pentenoate. On addition of (+)-Eu(dppm)$_3$ (50 μL) to the solution of methyl ether in $CDCl_3$ (41 mg, in 0.4 mL), the singlet of methyl ether at δ 3.49 was changed into the two singlets at δ 4.19 ((*R*)-isomer) and 4.07 ((*S*)-isomer) (relative intensity = 35 : 65).

LIS-NMR Analysis of Methyl 2-Methoxy-4-methyl-4-pentenoate. On addition of (+)-Eu(dppm)$_3$ (28 μL) to the solution of methyl ether in $CDCl_3$ (25 mg, in 0.4 mL), the singlet of methyl ether at δ 3.38 was changed into the two singlets at δ 4.60 ((*R*)-isomer) and 4.40 ((*S*)-isomer) (relative intensity = 42 : 58); the ^{1}H NMR ratio was almost identical with the HPLC ratio (42 : 58).

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