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Asymmetric Catalysis by Chiral Titanium Perchlorate for Carbonyl-Ene Cyclization

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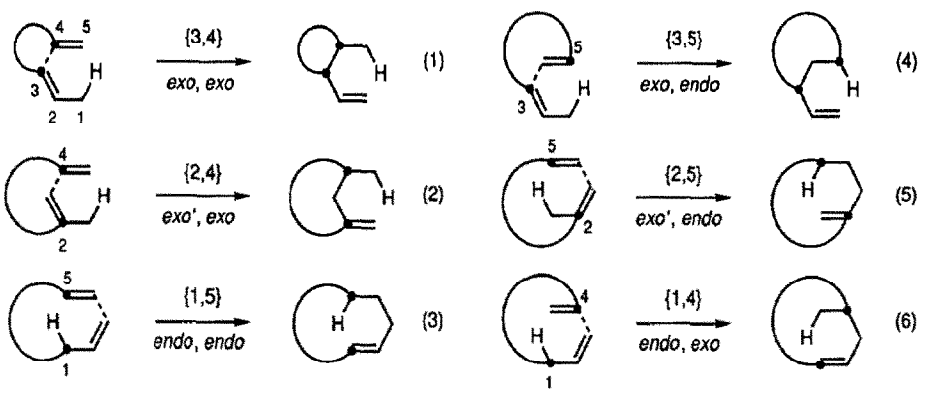
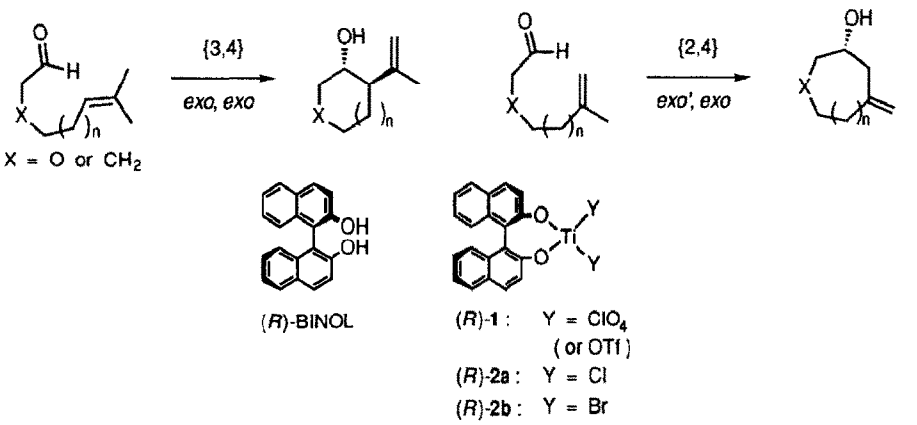
Abstract: The chiral binaphthol-derived titanium perchlorate (or triflate) is shown to serve efficiently as an asymmetric catalyst for the ene cyclization of type {3,4}*exo,exo* and {2,4}*exo',exo* involving α-alkoxy aldehyde as an internal enophile to afford the 6- and 7-membered cyclic ethers in high enantiomeric purity.

Intramolecular ene reaction (ene cyclization) has recently been recognized as an efficient method for stereocontrolled cyclization with carbon-carbon bond formation ("carbo-cyclization").[1,2] Similar to intramolecular [4+2] and [3+2] cycloadditions, ene cyclization profits from entropic advantage and exhibits synthetically useful level of regio- and stereoselectivity. Conceptually, ene cyclizations can be classified into six different modes of cyclizations (Scheme 1) according to Ziegler's notation originally proposed for the cyclic Claisen sigmatropic shifts.[3] In the ene cyclizations, the carbons to which the tether connecting the [1,5]-hydrogen shift system is attached are exemplified in {m,n} fashion. The subscripts *endo* and *exo*(') indicate the placement of the ene or enophile as a part of the tether and as an extraannular substituent, respectively.[4] Oppolzer referred to the first three modes of ene cyclizations (eq. 1-3) as type I-III, respectively.[1a] Recently, Snider found a new type of ene cyclization (eq. 4).[5] However, asymmetric catalysis for any mode of ene cyclization has never been developed. Only reported so far are the asymmetric version employing chiral internal enophiles[6,7] or using an excess amount of chiral Lewis acids such as a binaphthol-derived zinc complex[8] or a tartrate-derived titanium complex.[9,10] Reported herein is the asymmetric catalysis of ene cyclization by chiral binaphthol (BINOL)-derived titanium perchlorate (or triflate) of type (*R*)-1 (Scheme 2).[11]



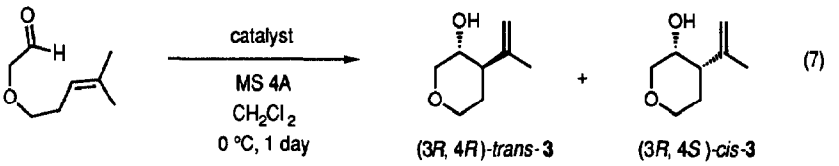
Scheme 1

Recently, we have developed an efficient asymmetric catalysis of intermolecular carbonyl-ene reactions[12] with methyl glyoxylate, which employ a chiral titanium dihalide of type (*R*)-**2** prepared *in situ* from $(i\text{-PrO})_2TiX_2$ (X=Cl or Br) and optically pure BINOL in the presence of molecular sieves (MS 4A).[13] This success prompted us to investigate the asymmetric catalysis by BINOL-derived titanium complexes for thus far-developed modes of carbonyl-ene cyclizations (Scheme 2). Chosen as the internal enophile was α-alkoxy aldehyde to give the cyclic ethers[14] in view of the high reactivity in the intermolecular version.[15] At the outset, we reasoned that the chiral titanium perchlorate (*R*)-**1** would be efficient as an asymmetric Lewis acid catalyst.[16] Thus, the chiral titanium perchlorate (*R*)-**1** was prepared by the addition of silver perchlorate (2 equiv) to the chloride (*R*)-**2a** and shown to be an efficient asymmetric catalyst for the {3,4}*exo,exo* and {2,4}*exo',exo* carbonyl-ene cyclizations. The addition of 1 equiv of $AgClO_4$ was observed to give only a similar level of enantioselectivity to that obtained with the dichloride (*R*)-**2a**. Furthermore, we found that $AgClO_4$ itself did not catalyze the ene cyclization.



Scheme 2

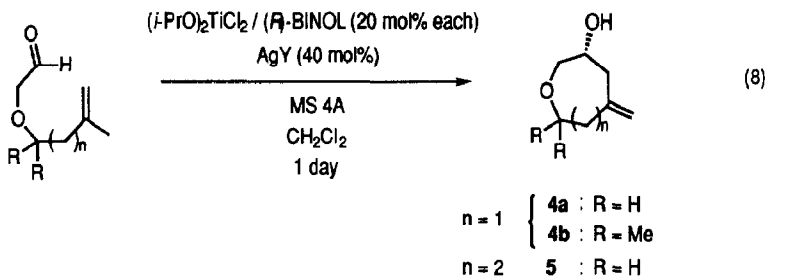
Typical experimental procedure is represented as follows (eq. 7). To a suspension of (*R*)-BINOL (29 mg, 0.1 mmol) and $AgClO_4$ (44 mg, 0.21 mmol) in CH_2Cl_2 (1.5 mL) was added $(i\text{-PrO})_2TiCl_2$ (24 mg, 0.1 mmol) in the presence of MS 4A (0.5 g) at room temperature under Ar atmosphere. After stirring for 1 h at that temperature, to the mixture was added α-alkoxy aldehyde (0.5 mmol) at 0 °C. After stirring for 1 day, the reaction mixture was poured into sat. $NaHCO_3$. Usual work up followed by column chromatography gave preferentially the *trans*-alcohol **3** in 40% isolated yield along with high enantiomeric excess. In sharp contrast, the dichloro catalyst **2a** affords an opposite sense of *cis*-selectivity and lower enantioselectivity. The absolute configuration of the cyclic alcohol was deduced by the modified Mosher method[17] after converting to its (*S*)-(-)- and (*R*)-(+)-MTPA esters. It was confirmed that this asymmetric cyclization process using the catalyst (*R*)-**1** gave rise to (3*R*,4*R*)-*trans*-alcohol. The sense of asymmetric induction is, therefore, exactly the same as observed for the glyoxylate-ene reaction catalyzed by (*R*)-**2**[13]; (*R*)-**1** provides (3*R*)-**3**.



(3*R*, 4*R*)-*trans*-**3** (3*R*, 4*S*)-*cis*-**3**

$(i\text{-PrO})_2TiCl_2$ / (*R*)-BINOL (20 mol% each) / $AgClO_4$ (40 mol%)	80 (84% ee)	:	20 (74% ee)	(50%)
$(i\text{-PrO})_2TiCl_2$ / (*R*)-BINOL (20 mol% each)	47 (70% ee)	:	53 (79% ee)	(73%)

The 6-membered cyclization of type {2,4}*exo',exo* (n=0), however, does not provide any ene product (eq. 8), presumably because of the lower ene-reactivity of the allylic ether moiety under the Lewis acid-promoted conditions.[18] By contrast, a similar 7-membered cyclization of homoallylic ether (n=1) gives the oxepane (**4**) in high enantiomeric excess (Table 1), where the "*gem*-dialkyl"[19] substituents are not essential (entries 4,5). The BINOL-derived titanium triflate is shown to give comparably high level of enantiomeric excess (92% ee) (entry 6). However, the tetrafluoroborate counterpart provides only moderate level of optical yield (entry 7). A 8-membered cyclization of bishomoallylic ether (n=2) provides oxocane (**5**) with moderate level of enantiomeric excess but in low yield (entry 8).



n = 1 { **4a** : R = H ; **4b** : R = Me

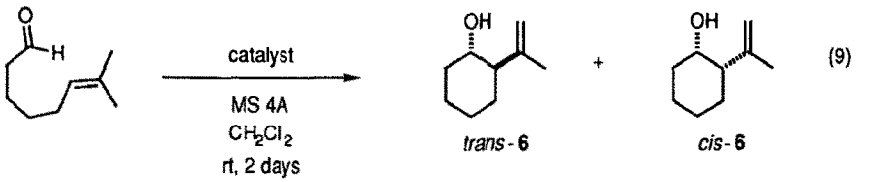
n = 2 **5** : R = H

Table 1. Ene cyclizations catalyzed by BINOL-derived Ti-complexes.[a]

entry	substrate	AgY	temperature	% ee[b]	% yield
1	n = 1, R = H	$AgClO_4$	rt	91% ee	43%
2	n = 1, R = H	none	0 °C	88% ee	64%
3	n = 1, R = H	$AgClO_4$[c]	rt	88% ee	45%
4	n = 1, R = Me	$AgClO_4$	0 °C	82% ee	40%
5[d]	n = 1, R = Me	none	0 °C	67% ee	27%
6	n = 1, R = H	AgOTf	rt	92% ee	40%
7	n = 1, R = H	$AgBF_4$	rt	55% ee	16%
8	n = 2, R = H	$AgClO_4$	rt	67% ee	16%
9	n = 2, R = H	none	rt	34% ee	12%

[a] All reactions were carried out using 0.5 mmol of α-alkoxy aldehyde and 0.1 mmol (20 mol%) of BINOL-derived titanium complex. [b] The enantiomeric excess was determined by ^1H NMR analysis after conversion to the MTPA ester. [c] 20 mol% of $AgClO_4$ was used. [d] 10 mol% of BINOL-derived titanium complex was used.

Finally, we examined the asymmetric catalytic ene cyclization of the carbon-analogue (eq. 9), which might be less reactive than the oxygen counterpart (eq. 7). Indeed, the carbonyl-ene cyclization of the carbon-analogue did proceed slowly to give the *trans*-alcohol **6** in moderate level of enantiomeric excess. It should be noted here that the observed *trans*-selectivity is not so high in view of the exclusive formation of the *trans*-alcohol **6** (but in completely racemic form) with BINOL-derived zinc reagent.[8,6b]



$(i\text{-PrO})_2TiCl_2$ / (*R*)-BINOL (20 mol% each) / $AgClO_4$ (40 mol%)	69 (55% ee)	:	31 (64% ee)	(66%)
$(i\text{-PrO})_2TiCl_2$ / (*R*)-BINOL (20 mol% each)	59 (21% ee)	:	41 (41% ee)	(54%)

The *trans*/*cis*-selectivity in the $\{3,4\}_{exo,exo}$ ene cyclizations can be explained in terms of the bicyclic transition state model (Figure 1) in which the carbonyl group adopts the *equatorial* and *axial* orientations, leading to the *trans* and *cis* alcohols, respectively. Thus, the *trans*-selectivity largely depends on the steric bulkiness of the chiral Lewis acid complexes. Furthermore, the *trans*/*cis*-selectivity may also reflect the C=O---MLn* angle (θ) which depends on the nature of the central metal.[20]

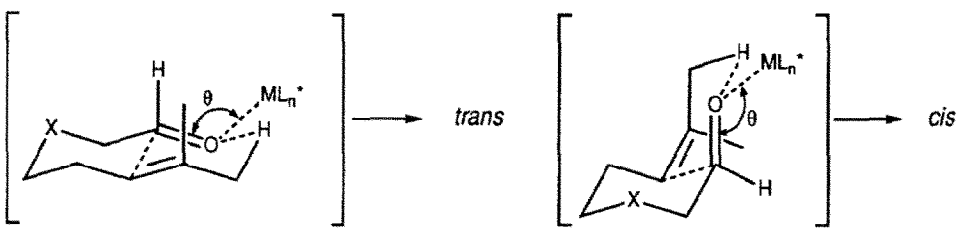


Figure 1

In summary, we have demonstrated that the chiral titanium perchlorate (or triflate) **1** thus developed efficiently serves as an asymmetric catalyst for both the chiral recognition of the enantioface of the aldehyde and the discrimination of the diastereotopic protons of the ene component in the carbonyl-ene cyclization of α-alkoxy aldehydes.

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Experimental Section

General. Molecular sieves (MS 4A, activated powder) was purchased from Aldrich Chemical Co. (*R*)-1,1'-bi-2-naphthol was purchased from Wako Pure Chemical Industries Ltd. ^1H and ^{13}C NMR spectra were measured on a Varian EM390, GEMINI 300, or JEOL GSX-500 spectrometer. IR spectra were measured on a JASCO FT/IR-5000 spectrometer. Optical rotations were measured on a JASCO DIP-370. All experiments were carried out under an argon atmosphere. Dichlorometane was freshly distilled from CaH_2.

Preparation of the Ene Substrate. α-Alkoxy aldehydes were prepared by reduction of the corresponding α-alkoxy esters, which were prepared by etherification of alcohols as follows.

Preparation of 1,1,3-Trimethyl-3-buten-1-ol. To a suspension of magnesium (5.35 g, 220 mmol) in ether (5 mL) was added dropwise 1,2-dibromoethane (1 mL) with vigorous stirring. The mixture was cooled down to -10 °C and diluted with ether (120 mL). To the mixture was added dropwise a solution of 3-chloro-2-methylpropene (18.1 g, 200 mmol) in ether (80 mL) at that temperature. After stirring for 30 min, a solution of acetone (5.81 g, 100 mmol) in ether (20 mL) was added dropwise to the mixture at that temperature. After stirring for 12 h at room temperature, the reaction mixture was poured into sat. NH_4Cl (100 mL) at 0 °C and extracted with ether. The combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation under reduced pressure, the concentrated solution was distilled under reduced pressure (57 ~ 60 °C / 45 mmHg) to give 1,1,3-trimethyl-3-buten-1-ol in 52% yield (5.89 g): ^1H NMR ($CDCl_3$) δ 1.25 (s, 6H), 1.61 (bs, 1H), 1.85 (s, 3H), 2.22 (s, 2H), 4.72 (s, 1H), 4.90 (s, 1H).

Preparation of 4-Methyl-4-penten-1-ol. To a solution of 2-methyl-2-propen-1-ol (21.6 g, 300 mmol) in triethyl orthoacetate (275 mL, 1.5 mol) was added 2,6-dimethylphenol (2.57 g, 21 mmol). After refluxed for 12 h at 150°C with removal of ethanol, the reaction mixture was evaporated under reduced pressure to give the crude ester, which was reduced without purification. The crude material in ether (30 mL) was added dropwise to a suspension of $LiAlH_4$ (22.8 g, 600 mmol) in ether (300 mL) at 0 °C. After stirring for 1 day at room temperature, sat. Na_2SO_4 solution was added to the reaction mixture. After dried over Na_2SO_4, the mixture was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to give the crude alcohol (4-methyl-4-penten-1-ol): ^1H NMR ($CDCl_3$) δ 1.34 (m, 2H), 1.72 (s, 3H), 2.10 (m, 2H), 3.55 (m, 3H) 4.69 (s, 2H).

General Procedure for the Preparation of α-Alkoxy Ester. Methyl 6-Methyl-3-oxa-6-heptenoate. To a suspension of NaH containing 50% ash (23.0 g, 480 mmol) in THF (300 mL) was added dropwise a THF (70 mL) solution of 3-methyl-3-buten-1-ol (17.2 g, 200 mmol). The mixture was refluxed for 2 h and cooled to 0 °C. To the solution was added dropwise a THF (70 mL) solution of bromoacetic acid (27.8 g, 200 mmol) at 0 °C. After refluxed for 1 h, the resultant solution was poured into water at 0 °C and washed with ether (100 mL). The aqueous layer was acidified with conc. HCl at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$. The solution was evaporated under reduced pressure to give the crude acid, which was esterified without purification.

The crude material was dissolved in MeOH (20 mL) and trimethyl orthoformate (21.2 g, 200 mmol). Conc. H_2SO_4 (0.5 mL) was added dropwise to the solution at 0 °C. After stirring for 12 h at room temperature, the reaction mixture was poured into 5% $NaHCO_3$ solution (50 mL) and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. After evaporation under reduced pressure, the resultant concentrate was distilled under reduced pressure (77 ~ 78 °C / 8.5 mmHg) to give methyl 6-methyl-3-oxa-6-heptenoate in 72% yield (22.8 g): ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H), 2.36 (t, J = 6.9 Hz, 2H), 3.66 (t, J = 6.9 Hz, 2H), 3.76 (s, 3H), 4.11 (s, 2H), 4.76 (s, 1H), 4.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5, 37.5, 51.7, 68.1, 70.0, 111.6, 142.2, 170.7; IR (neat) 2956, 1758, 1653, 1439, 1210, 1141, 988, 890 cm^{-1}.

Methyl 7-Methyl-3-oxa-6-octenoate. ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3H), 1.71 (s, 3H), 2.34 (q, J = 7.1 Hz, 2H), 3.51 (t, J = 7.1 Hz, 2H), 3.76 (s, 3H), 4.10 (s, 2H), 5.13 (t, J = 7.1 Hz, 1H); bp 81 ~ 85 °C / 5 mmHg.

Methyl 4,4,6-Trimethyl-3-oxa-6-heptenoate. ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 6H) 1.79 (s, 3H), 2.20 (s, 2H), 3.70 (s, 3H), 4.01 (s, 2H), 4.68 (s, 1H), 4.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.2, 25.3, 48.0, 51.7, 60.4, 76.6, 114.4, 142.5, 171.4; IR (neat) 2976, 1767, 1644, 1439, 1207, 1120, 1029, 891 cm^{-1}; bp 111 ~ 114 °C / 29 mmHg.

Methyl 7-Methyl-3-oxa-7-octenoate. ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3H), 1.77 (m, 2H), 2.10 (t, J = 7.2 Hz, 2H), 3.53 (t, J = 6.6 Hz, 2H), 3.76 (s, 3H), 4.09 (s, 2H), 4.69 (s, 1H), 4.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.4, 27.4, 33.9, 51.7, 68.2, 71.4, 110.0, 145.0, 170.8; IR (neat) 2954, 1760, 1653, 1439, 1210, 1141, 888 cm^{-1}; bp 85 ~ 90 °C / 9 mmHg.

General Procedure for the Preparation of α-Alkoxy Aldehyde. 6-Methyl-3-oxa-6-heptenal. To a solution of methyl 6-methyl-3-oxa-6-heptenoate (2.37 g, 15 mmol) in hexane (75 mL) was added a 1 *N* hexane solution of DIBAL-H (15.8 mL, 15.8 mmol) at -78 °C. After stirring for 30 min at that temperature, the reaction mixture was poured into water at 0 °C and stirred for 30 min. 1 *N* HCl was added to the mixture at 0 °C until the turbidity was disappeared. The mixture was extracted with ether and organic layer was washed with brine and dried over $MgSO_4$. After evaporated under reduced pressure, the concentrated solution was distilled by using kugelrohr apparatus (85 °C / 7 mmHg) to give 6-methyl-3-oxa-6-heptenal in 35% yield (0.68 g): ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H), 2.37 (t, J = 6.9 Hz, 2H), 3.67 (t, J = 6.9 Hz, 2H), 4.10 (s, 2H), 4.76 (s, 1H), 4.82 (s, 1H), 9.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 37.6, 70.3, 76.2, 111.8, 142.1, 200.9.

7-Methyl-3-oxa-6-octenal. ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 3H), 1.71 (s, 3H), 2.34 (q, J = 7.0 Hz, 2H), 3.53 (t, J = 7.0 Hz, 2H), 4.09 (s, 2H), 5.14 (m, 1H), 9.74 (s, 1H); bp 85 ~ 90 °C / 4 mmHg.

4,4,6-Trimethyl-3-oxa-6-heptenal. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6H), 1.85 (s, 3H), 2.24 (s, 2H), 3.98 (s, 2H), 4.71 (s, 1H), 4.86 (s, 1H), 9.71 (s, 1H); bp 110 ~ 115 °C / 8 mmHg.

7-Methyl-3-oxa-7-octenal. ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3H), 1.78 (m, 2H), 2.11 (t, J = 7.6 Hz, 2H), 3.54 (t, J = 6.4 Hz, 2H), 4.07 (s, 2H), 4.69 (s, 1H), 4.73 (s, 1H), 9.74 (s, 1H); bp 95 ~ 100 °C / 9 mmHg.

Carbonyl-Ene Cyclization Catalyzed by (*R*)-BINOL-Derived Titanium Complex ((*R*)-1). $AgClO_4$ / (*R*)-BINOL / $(i\text{-}PrO)_2TiCl_2$. (+)-3-Hydroxy-5-methylenoxepane (4a). To a solution of (*R*)-1,1'-bi-2-naphthol (28.6 mg, 0.10 mmol) in CH_2Cl_2 (1.5 mL) in the presence of molecular sieves (MS 4A, activated powder) (500 mg) was added $AgClO_4$ (43.5 mg, 0.21 mmol) at room temperature under an argon atmosphere. After stirring for 10 min at room temperature, diisopropoxy titanium dichloride (23.7 mg, 0.10 mmol) was added to the mixture. After stirring for 1 h at room temperature, 6-methyl-3-oxa-6-heptenal (64.1 mg, 0.50 mmol) was added and the mixture was stirred for 1 day. The solution was poured into sat. $NaHCO_3$ solution (5 mL). MS 4A was filtered off through a pad of Celite and the filtrate was extracted with ethyl acetate three times (totally 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Chromatographic separation by silica gel (hexane / ethyl acetate = 4 : 1 ~ 2 : 1) gave **4a** in 43% yield: ^1H NMR ($CDCl_3$) δ 2.39 (m, 2H), 2.46 (m, 1H), 2.58 (m, 2H), 3.58 (m, 2H), 3.80 (bs, 1H), 3.91 (m, 2H), 4.97 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 38.1, 42.7, 68.3, 70.7, 77.2, 116.8, 142.7; IR (neat) 3348, 3078, 2942, 1644, 1448, 1127, 1060, 895 cm^{-1}; $[\alpha]_D^{26}$ +20.0 (c 1.36, $CHCl_3$) (92% ee).

AgOTf / (*R*)-BINOL / $(i\text{-}PrO)_2TiCl_2$. The ene reaction was carried out as described above, except for the use of AgOTf instead of $AgClO_4$.

$AgBF_4$ / (*R*)-BINOL / $(i\text{-}PrO)_2TiCl_2$. The ene reaction was carried out as described above, except for the use of $AgBF_4$ instead of $AgClO_4$.

(*R*)-2a: (*R*)-BINOL / $(i\text{-}PrO)_2TiCl_2$. The ene reaction was carried out as described above but in the absence of AgY.

(+)-*trans*-3-Hydroxy-4-(1'-methyl)ethenyloxane (*trans*-3). ^1H NMR ($CDCl_3$) δ 1.68 (m, 2H), 1.75 (s, 3H), 1.87 (bs, 1H), 2.12 (ddd, J = 5.0, 10.2, 10.7 Hz, 1H), 3.10 (dd, J = 9.9, 10.7 Hz, 1H), 3.38 (dt, J = 3.2, 11.4 Hz, 1H), 3.60 (ddd, J = 4.8, 9.9, 10.7 Hz, 1H), 3.94 (ddd, J = 1.9, 4.5, 11.4 Hz, 1H), 4.08 (dd, J = 4.8, 10.7 Hz, 1H), 4.91 (s, 1H), 4.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.3, 30.0, 52.2, 67.0, 67.8, 71.8, 113.5, 144.8; IR (neat) 3276, 3078, 2924, 1649, 1437, 1120, 1083, 1017, 959, 890 cm^{-1}; $[\alpha]_D^{26}$ +11.7 (c 3.1, $CHCl_3$) (84% ee).

(+)-*cis*-3-Hydroxy-4-(1'-methyl)ethenyloxane (*cis*-3). ^1H NMR ($CDCl_3$) δ 1.45 (m, 1H), 1.82 (s, 3H), 1.85 (d, J = 4.9 Hz, 1H), 2.03 (dq, J = 4.7, 12.2 Hz, 1H), 2.23 (m, 1H), 3.44 (dt, J = 2.1, 12.2 Hz, 1H), 3.53 (dd, J = 1.1, 12.2 Hz, 1H), 3.82 (bs, 1H), 4.05 (m, 2H), 4.82 (s, 1H), 5.01 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 24.4, 45.6, 65.5, 67.9, 72.2, 111.8, 145.3; IR (neat) 3412, 3080, 2924, 1649, 1441, 1143, 1087, 1002, 891, 756 cm^{-1}; $[\alpha]_D^{25}$ +24.7 (c 1.9, $CHCl_3$) (*cis* (74% ee) / *trans* (84% ee) = 45 : 55 mixture).

(+)-6-Hydroxy-2,2-dimethyl-4-methylenoxepane (4b). ^1H NMR ($CDCl_3$) δ 1.21 (s, 3H), 1.22 (s, 3H), 2.24 (s, 2H), 2.25 (m, 1H), 2.43 (m, 1H), 2.66 (bs, 1H), 3.62 (ddd, J = 1.8, 4.2, 12.8 Hz, 1H), 3.72 (m, 1H), 3,75 (bs, 1H), 4.84 (bs, 1H), 5.01 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 27.1, 27.5, 46.3, 47.7, 65.2, 67.8, 74.6, 117.5, 141.0; IR (neat) 3342, 3078, 2976, 1649, 1446, 1091, 1064, 907 cm^{-1}; $[\alpha]_D^{26}$ +13.1 (c 1.2, $CHCl_3$) (82% ee).

(+)-3-Hydroxy-5-methylenoxocane (5). ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 2H), 1.72 (bs, 1H), 2.34 (m, 2H), 2.40 (m, 1H), 2.46 (m, 1H), 3.51 (m, 1H), 3.63 (m, 1H), 3.72 (m, 1H), 3.77 (m, 2H), 4.82 (s, 1H), 4.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.7, 45.6, 46.7, 71.5, 73.1, 74.0, 112.7, 145.3; IR (neat) 3356, 3076, 2930, 1638, 1446, 1102, 1048, 897, 756 cm^{-1}; $[\alpha]_D^{25}$ +1.58 (c 1.0, $CHCl_3$) (67% ee).

(+)-*trans*-2-(1'-Methyl)ethenylcyclohexanol (*trans*-6). ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 5H), 1.70 (m, 3H), 1.72 (s, 3H), 1.93 (m, 1H), 2.07 (m, 1H), 3.43 (dt, J = 4.4, 10.1 Hz, 1H), 4.86 (s, 1H), 4.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.2, 24.9, 25.6, 30.2, 34.1, 54.6, 70.7, 112.8, 146.6; IR (neat) 3384, 2932, 1647, 1452, 1067, 1017, 888 cm^{-1}; $[\alpha]_D^{25}$ +4.69 (c 0.90, $CHCl_3$) (55% ee).

(+)-*cis*-2-(1'-Methyl)ethenylcyclohexanol (*cis*-6). ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 2H), 1.46 (m, 3H), 1.64 (m, 2H), 1.75 (bs, 1H), 1.79 (s, 3H), 2.01 (m, 2H), 3.98 (bs, 1H), 4.78 (s, 1H), 4.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.7, 22.7, 23.9, 26.0, 32.2, 48.7, 65.8, 111.2, 147.6; IR (neat) 3446, 2936, 1644, 1448, 1120, 1064, 973, 893 cm^{-1}; $[\alpha]_D^{25}$ +8.34 (c 0.40, $CHCl_3$) (64% ee).

Determination of the Absolute Configuration of the Ene Cyclization Products. The absolute configurations of cyclic alcohols were deduced by the modified Mosher method after converting to the corresponding (*S*)-(-)- and (*R*)-(+)-MTPA esters.

(*S*)-(-)-MTPA ester of *trans*-3. ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3H), 1.72 ~ 1.82 (m, 2H), 2.43 (dt, J = 5.4, 10.7 Hz, 1H), 3.07 (t, J = 10.6 Hz, 1H), 3.34 (m, 1H), 3.91 ~ 3.97 (m, 1H), 4.03 (dd, J = 5.2, 10.6 Hz, 1H), 4.87 (m, 2H), 5.16 (ddd, J = 5.2, 10.6, 10.7 Hz, 1H).
(*R*)-(+)-MTPA ester of *trans*-3. ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 3H), 1.67 ~ 1.81 (m, 2H), 2.37 (dt, J = 5.2, 10.7 Hz, 1H), 3.25 (t, J = 10.2 Hz, 1H), 3.37 (dt, J = 3.0, 11.4 Hz, 1H), 3.92 ~ 3.98 (m, 1H), 4.11 (dd, J = 4.9, 10.2 Hz, 1H), 4.70 (m, 2H), 5.15 (ddd, J = 4.9, 10.2, 10.7 Hz, 1H).

(*S*)-(-)-MTPA ester of *cis*-3. ^{1}H NMR ($CDCl_3$) δ 1.55 (m, 1H), 1.78 (s, 3H), 2.02 (ddt, J = 4.4, 11.4, 12.6 Hz, 1H), 2.34 (m, 1H), 3.46 (dt, J = 2.1, 11.4 Hz, 1H), 3.58 (dd, J = 1.4, 13.1 Hz, 1H), 4.05 (m, 1H), 4.12 (m, 1H), 4.74 (bs, 1H), 4.92 (t, J = 1.4 Hz, 1H), 5.28 (bs, 1H).
(*R*)-(+)-MTPA ester of *cis*-3. ^{1}H NMR ($CDCl_3$) δ 1.51 (m, 1H), 1.65 (s, 3H), 2.02 (ddt, J = 4.7, 11.9, 13.2 Hz, 1H), 2.31 (m, 1H), 3.49 (dt, J = 2.0, 11.9 Hz, 1H), 3.60 (dd, J = 1.4, 12.9 Hz, 1H), 4.09 (m, 1H), 4.17 (m, 1H), 4.56 (bs, 1H), 4.69 (t, J = 1.4 Hz, 1H), 5.24 (bs, 1H).

(*S*)-(-)-MTPA ester of 4a. ^{1}H NMR ($CDCl_3$) δ 2.46 (t, J = 5.8 Hz, 2H), 2.62 (dd, J = 7.8, 13.6 Hz, 1H), 2.80 (dd, J = 4.8, 13.6 Hz, 1H), 3.64 (q, J = 5.8 Hz, 1H), 3.76 (dd, J = 2.8, 13.4 Hz, 1H), 3.78 (q, J = 5.8 Hz, 1H), 3.84 (dd, J = 2.8, 13.4 Hz, 1H), 4.92 (s, 2H), 5.17 (ddt, J = 4.8, 7.8, 2.8 Hz, 1H).
(*R*)-(+)-MTPA ester of 4a. ^{1}H NMR ($CDCl_3$) δ 2.44 (t, J = 5.8 Hz, 2H), 2.53 (dd, J = 7.4, 13.6 Hz, 1H), 2.73 (dd, J = 5.2, 13.6 Hz, 1H), 3.64 (q, J = 5.8 Hz, 1H), 3.82 (q, J = 5.8 Hz, 1H), 3.83 (dd, J = 4.2, 13.4 Hz, 1H), 3.92 (dd, J = 4.2, 13.4 Hz, 1H), 4.81 (s, 1H), 4.86 (s, 1H), 5.17 (ddt, J = 5.2, 7.4, 4.2 Hz, 1H).

(*S*)-(-)-MTPA ester of 4b. ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3H), 1.18 (s, 3H), 2.23 (d, *J* = 13.8 Hz, 1H), 2.32 (d, *J* = 13.8 Hz, 1H), 2.41 (dd, *J* = 7.8, 13.6 Hz, 1H), 2.74 (dd, *J* = 5.4, 13.6 Hz, 1H), 3.71 (d, *J* = 5.2 Hz, 2H), 4.84 (s, 1H), 5.01 (s, 1H), 5.08 (m, 1H).
(*R*)-(+)-MTPA ester of 4b. ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 6H), 2.23 (d, *J* = 14.0 Hz, 1H), 2.31 (d, *J* = 14.0 Hz, 1H), 2.32 (dd, *J* = 6.0, 13.8 Hz, 1H), 2.63 (dd, *J* = 5.2, 13.8 Hz, 1H), 3.76 (dd, *J* = 3.2, 14.0 Hz, 1H), 3.87 (dd, *J* = 6.2, 14.0 Hz, 1H), 4.80 (s, 1H), 4.93 (s, 1H), 5.06 (m, 1H).

(*S*)-(-)-MTPA ester of 5. ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.47 (dd, *J* = 9.9, 12.9 Hz, 1H), 2.71 (dd, *J* = 4.2, 12.9 Hz, 1H), 3.48 (m, 1H), 3.71 (m, 3H), 4.91 (s, 1H), 4.96 (s, 1H), 5.19 (m, 1H).
(*R*)-(+)-MTPA ester of 5. ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 2H), 2.31 (t, *J* = 6.0 Hz, 2H), 2.36 (dd, *J* = 9.5, 13.5 Hz, 1H), 2.59 (dd, *J* = 4.5, 13.5 Hz, 1H), 3.67 (dd, *J* = 7.5, 12.5 Hz, 1H), 3.68 (m, 1H), 3.78 (m, 1H), 3.79 (dd, *J* = 4.0, 12.5 Hz, 1H), 4.78 (s, 1H), 4.91 (s, 1H), 5.19 (m, 1H).

(*S*)-(-)-MTPA ester of *trans*-6. ^{1}H NMR ($CDCl_3$) δ 1.22 ~ 1.45 (m, 5H), 1.70 (s, 3H), 1.73 ~ 1.79 (m, 2H), 2.05 ~ 2.29 (m, 2H), 4.81 (s, 2H), 5.05 (dt, *J* = 4.7, 10.7 Hz, 1H).
(*R*)-(+)-MTPA ester of *trans*-6. ^{1}H NMR ($CDCl_3$) δ 1.22 ~ 1.45 (m, 5H), 1.58 (s, 3H), 1.73 ~ 1.79 (m, 2H), 2.05 ~ 2.29 (m, 2H), 4.60 (s, 1H), 4.64 (s, 1H), 5.05 (dt, *J* = 4.7, 10.7 Hz, 1H).

(*S*)-(-)-MTPA ester of *cis*-6. ^{1}H NMR ($CDCl_3$) δ 1.21 ~ 1.34 (m, 3H), 1.50 ~ 1.63 (m, 4H), 1.77 (s, 3H), 2.01 ~ 2.11 (m, 2H), 4.71 (s, 1H), 4.86 (s, 1H), 5.53 (bs, 1H).
(*R*)-(+)-MTPA ester of *cis*-6. ^{1}H NMR ($CDCl_3$) δ 1.21 ~ 1.34 (m, 3H), 1.50 ~ 1.63 (m, 4H), 1.71 (s, 3H), 2.01 ~ 2.11 (m, 2H), 4.56 (s, 1H), 4.68 (s, 1H), 5.57 (bs, 1H).

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