Pergamon

Tetrahedron Vol. 50, No. 15, pp. 4385-4398, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0077-7

Asymmetric Carbon—Carbon Bond Forming Reactions Catalyzed by Chiral Schiff Base—Titanium Alkoxide Complexes#

Masahiko Hayashi, Tetsuya Inoue, Yasunori Miyamoto, and Nobuki Oguni*

Department of Chemistry, Faculty of Science, Yamaguchi University, Yamaguchi City, Yamaguchi 753, Japan

Abstract: The enantioselective addition of trimethylsilyl cyanide to a variety of aldehydes proceeded by the aid of a catalyst prepared *in situ* from titanium tetraisopropoxide [Ti(O-*i*-Pr)4] and chiral Schiff bases and gave the corresponding cyanohydrins in high optical yield (up to 96% e.e.). A remarkable rate enhancement was brought about by the addition of the Schiff base to the titanium alkoxide mediated silylcyanation of aldehydes. This catalyst system also promoted the highly enantioselective reaction of diketene with aldehydes, which led to the formation of optically active 5-hydroxy-3-oxoesters.

Introduction

The catalytic asymmetric synthesis of optically active organic compounds from prochiral precursors using chiral metal complexes has attracted much recent attention.[1] These enantioselective additions of carbon nucleophiles to aldehydes are a fundamental operation in preparing optically active secondary alcohols. Of the numerous synthesis now known, optically active cyanohydrins, especially, are versatile intermediates for the preparation of a variety of important classes of organic compounds, such as α-hydroxy carboxylic acids, β-hydroxyamines, *etc.*[2] Therefore, several efficient methods have been reported for obtaining optically active cyanohydrins by biochemical[3] and chemical methods. Of the latter, Elliot and Johnson reported the highly diastereoselective addition of trimethylsilyl cyanide to chiral acetals,[4] and in a catalytic process, Reetz first reported that boron[5a] or titanium compounds[5b] catalyzed silylcyanation of isovaleraldehyde. The enantiomeric excess (e.e.) of each product was not, however, high. Narasaka and co-workers also reported the asymmetric hydrocyanation of aldehydes using a *stoichiometric amount* of chiral titanium complexes composed of titanium dichloride diisopropoxide [$TiCl_2$(O-*i*-Pr)2] and a tartrate-derived chiral 1,4-diol in the presence of molecular sieves (MS) 4A.[6] We found a highly enantioselective silylcyanation of a variety of aldehydes catalyzed by

Dedicated to Professors Ryoji Noyori and K. Barry Sharpless on the occasion of their receiving the Tetrahedron Prize for 1993.

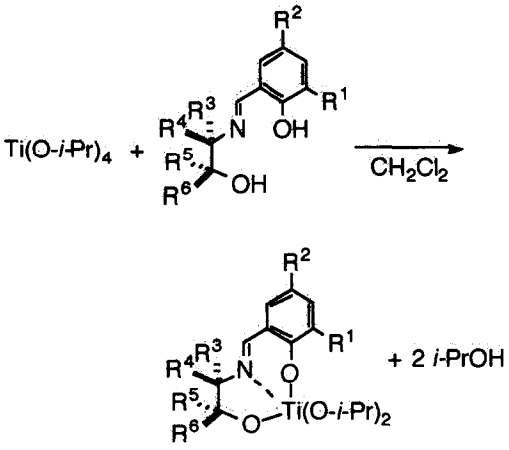
new chiral Schiff base—titanium alkoxide catalyst system.[7,8] This catalyst system was also found to be very effective for the enantioselective reaction of diketene with some aldehydes to give optically active 5-hydroxy-3-oxoesters, which can be easily converted to 6-substituted-4-hydroxy lactones. These chiral lactones are known to be a very important component of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase such as compactin and mevinolin.[9,10]

The chiral Schiff base complexes of transition metals have been found to work as very effective catalysts for asymmetric cyclopropanation,[11] epoxidation of olefins,[12] and so on.

In this paper, we describe a novel and efficient reaction of highly enantioselective addition of trimethylsilyl cyanide to aldehydes using a catalytic amount of chiral titanium complexes composed of a chiral Schiff base and titanium alkoxide, and highly enantioselective reaction of diketene with aldehydes promoted by the above complexes.

Results and Discussion

Preparation of Chiral Schiff Base—Titanium Alkoxide Catalysts. The chiral Schiff bases were synthesized by the condensation of 2-hydroxybenzaldehyde (salicylaldehyde), 3-*tert*-butyl-2-hydroxybenzaldehyde,[13] 3-*tert*-butyl-2-hydroxy-5-methylbenzaldehyde, or 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde with various chiral β-amino alcohols in methanol. The chiral Schiff base—titanium alkoxide catalyst was prepared by mixing an equimolar amount of chiral Schiff base and titanium alkoxide in dichloromethane (eq. 1). Table 1 summarizes the Schiff base used in our asymmetric reactions.



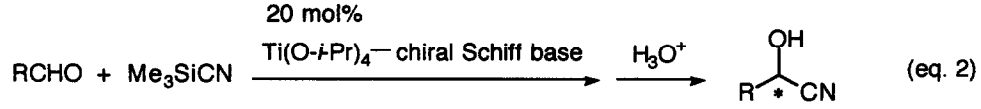
(eq. 1)

Table 1. Chiral Schiff Bases Used in Asymmetric Reaction

Schiff base	R^1	R^2	R^3	R^4	R^5	R^6
(*S*)-**1a**	H	H	*i*-Pr	H	H	H
(*S*)-**1b**	H	H	*i*-Pr	H	Ph	Ph
(*S*)-**1c**	H	H	*t*-Bu	H	H	H
(*S*)-**1d**	*t*-Bu	H	Me	H	H	H
(*R*)-**1e**	*t*-Bu	H	H	Et	H	H
(*S*)-**1f**	*t*-Bu	H	*i*-Pr	H	H	H
(*S*)-**1g**	*t*-Bu	H	*i*-Pr	H	Ph	Ph
(*S*)-**1h**	*t*-Bu	H	*t*-Bu	H	H	H
(*R*)-**1i**	*t*-Bu	H	H	Ph	H	H
(*R*)-**1j**	*t*-Bu	H	H	H	*t*-Bu	H
(*S*)-**1k**	*t*-Bu	Me	*i*-Pr	H	H	H
(*S*)-**1l**	*t*-Bu	*t*-Bu	*i*-Pr	H	H	H

Asymmetric Trimethylsilylcyanation of Some Aldehydes Catalyzed by Chiral Schiff Base—Titanium Alkoxide Complexes. First, the reaction of benzaldehyde with trimethylsilyl cyanide was examined with 20 mol% of chiral titanium catalyst prepared *in situ* from a variety of chiral Schiff bases (**1a—1m**) and Ti(O-*i*-Pr)4 (eq. 2). A remarkable rate enhancement was observed by the addition of Schiff

bases to Ti(O-*i*-Pr)4 mediated silylcyanation of aldehydes. The results for the asymmetric silylcyanation of benzaldehyde using a variety of Schiff bases—titanium isoproxide complexes are summarized in Table 2.



(eq. 2)

The product yields in Table 2 are isolated yield of mandelonitrile after hydrolysis with 1N HCl, and the e. e. was determined by HPLC analysis of the corresponding MTPA ester.[14] As shown in Table 2, the enantioselectivity was strongly influenced by the nature of chiral Schiff bases. Among the catalyst systems we examined, the combination of Ti(O-*i*-Pr)4 and the Schiff base **1f** which was prepared by the reaction between 3-*tert*-butyl-2-hydroxybenzaldehyde and (*S*)-valinol gave the product in the highest optical yield (85% e.e.). Low reaction temperature and high reaction concentrations were also an essential factor to obtain high enantioselectivity. The stereochemical outcome is of interest. As shown in entry 1 and 8, when the Schiff base prepared from (*S*)-valinol and 2-hydroxybenzaldehyde was used, (*S*)-mandelonitrile was obtained in 22% e.e., whereas the reaction using the Schiff base derived from (*S*)-valinol and 3-*tert*-butyl-2-hydroxybenzaldehyde afforded the product bearing (*R*)-configuration in 85% e.e. A similar phenomenon was observed in the reaction using Schiff bases prepared by the reaction of (*S*)-*tert*-leucinol with 2-hydroxybenzaldehyde and its *tert*-butyl substituted derivative (entry 3 and 10).

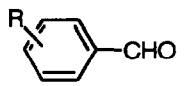
Table 2. Enantioselective Trimehylsilylcyanation of Benzaldehyde Catalyzed by a Variety of Chiral Schiff Base—Titanium Alkoxide Complexes[a]

		conditions		product	
entry	Schiff base	temp/°C	time/h	% yield[b]	% e.e.[c] (*confign*)[d]
1	(*S*)-**1a**	-80	36	69	22 (*S*)
2	(*S*)-**1b**	-78	36	28	60 (*R*)
3	(*S*)-**1c**	-78	36	40	40 (*S*)
4	(*S*)-**1d**	-80	36	60	60 (*R*)
5	(*R*)-**1e**	-80	36	72	80 (*S*)
6	(*S*)-**1f**	0	20	70	41 (*R*)
7		-30	44	90	67 (*R*)
8		-80	36	67	85 (*R*)
9	(*S*)-**1g**	-78	36	54	64 (*R*)
10	(*S*)-**1h**	-78	36	51	63 (*R*)
11	(*R*)-**1i**	-80	36	41	40 (*S*)
12	(*R*)-**1j**	-78	36	61	67 (*S*)
13	(*S*)-**1k**	-80	36	45	76 (*R*)
14	(*S*)-**1l**	-80	36	38	67 (*R*)

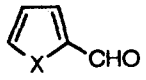
[a] All reactions were carried out in dichloromethane using 20 mol% of catalyst per benzaldehyde. [b] Isolated yield. [c] Determined by HPLC analysis of its MTPA ester. [d] Determined by comparison of the sign of optical rotation values with those in the literature.[6b]

The reaction of trimethylsilyl cyanide with a variety of aldehydes such as aromatic, heteroaromatic, α,β-unsaturated aldehydes, and aliphatic aldehydes was investigated in the presence of 20 mol% of the catalyst composed of Ti(O-*i*-Pr)4 and Schiff base **1f**, which was the best catalyst system for benzaldehyde. As shown in Table 3, most of the aromatic aldehydes were silylcyanated in good to excellent enantiomeric excesses.

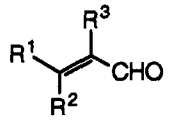
Benzaldehyde derivatives with electron-withdrawing substituents such as the cyano group (**2f**), however, provided lower e.e. values. Among the aromatic aldehydes, the highest enantiomeric excess was achieved in the silylcyanation of 4-methoxybenzaldehyde (91% e.e.). Generally, α,β-unsaturated aldehydes (**2j**—**2o**)



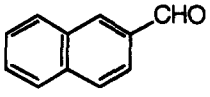
2a; R = H
2b; = *m*-OMe
2c; = *m*-OPh
2d; = *p*-Me
2e; = *p*-OMe
2f; = *p*-CN



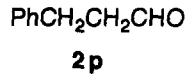
2h; X = O
2i; = S



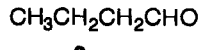
2j; $R^1 = R^2 = R^3 = H$
2k; $R^1 = R^2 = H$, $R^3 = Me$
2l; $R^1 = Me$, $R^2 = R^3 = H$
2m; $R^1 = R^2 = Me$, $R^3 = H$
2n; $R^1 = R^3 = Me$, $R^2 = H$
2o; $R^1 = Ph$, $R^2 = R^3 = H$



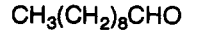
2g



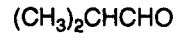
2p



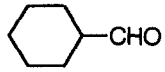
2q



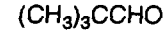
2r



2s



2t



2u

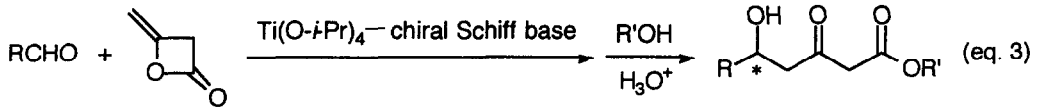
Table 3. Enantioselective Addition of Trimethylsilyl Cyanide to a Variety of Aldehydes Catalyzed by Schiff Base **1f**—Titanium Alkoxide Complex[a]

		conditions		product		
entry	aldehyde	temp/°C	time/h	% yield[b]	% e.e.[c] (*confign.*)[d]	$[\alpha]_D$ (*c*, solvent)
1	3-methoxybenzaldehyde (**2b**)	-80	36	76	56 (*R*)[e]	+22.8° (*c* 1.5, $CHCl_3$)
2	3-phenoxybenzaldehyde (**2c**)	-80	36	67	79 (*R*)[f]	+13.5° (*c* 1.5, C_6H_6)
3	4-methylbenzaldehyde (**2d**)	-78	36	68	71 (*R*)[e]	+36.4° (*c* 1.1, $CHCl_3$)
4	4-methoxybenzaldehyde (**2e**)	-78	36	62	91 (*R*)[e]	+41.7° (*c* 1.4, $CHCl_3$)
5	4-cyanobenzaldehyde (**2f**)	-80	36	60	20 (*R*)[e]	+6.5° (*c* 1.5, $CHCl_3$)
6	2-naphthaldehyde (**2g**)	-80	36	76	73 (*R*)[e]	+10.9° (*c* 1.1, EtOH)
7	2-thiophenecarboxaldehyde (**2i**)	-80	36	60	79 (*R*)[e]	+64.1° (*c* 0.6, $CHCl_3$)
8	acrylaldehyde (**2j**)	-80	36	54	63 (*R*)[g]	-3.8° (*c* 0.8, $CHCl_3$)
9	methacrylaldehyde (**2k**)	-80	36	62	85 (*R*)[h]	+5.7° (*c* 1.3, $CHCl_3$)
10	(*E*)-crotonaldehyde (**2l**)	-80	36	70	89 (*R*)[e]	-35.7° (*c* 0.3, $CHCl_3$)
11	3-methyl-2-butenal (**2m**)	-80	40	63	89 (*R*)[g]	-94.2° (*c* 0.7, $CHCl_3$)
12	*trans*-2-methyl-2-butenal (**2n**)	-80	40	68	96 (*R*)[g]	-24.8° (*c* 1.0, $CHCl_3$)
13	(*E*)-cinnamaldehyde (**2o**)	-80	36	81	72 (*R*)[e]	+19.2° (*c* 1.9, $CHCl_3$)
14	3-phenylpropionaldehyde (**2p**)	-78	36	85	40 (*R*)[i]	-2.6° (*c* 2.7, $CHCl_3$)
15	*n*-butanal (**2q**)	-78	12	73	57 (*R*)[e]	+13.1° (*c* 0.9, $CHCl_3$)
16	*n*-decylaldehyde (**2r**)	-78	36	48	66 (*R*)[i]	+6.7° (*c* 1.3, $CHCl_3$)
17	2-methylpropionaldehyde (**2s**)	-80	36	70	34 (*R*)[e]	+4.2° (*c* 1.3, $CHCl_3$)
18	cyclohexylcarboxaldehyde (**2t**)	-80	12	72	65 (*R*)[i]	+6.1° (*c* 3.8, $CHCl_3$)
19	trimethylacetaldehyde (**2u**)	-80	36	58	70 (*R*)[e]	+14.5° (*c* 1.0, $CHCl_3$)

[a] All reactions were carried out in dichloromethane using 20 mol% of chiral Schiff base **1f**—titanium isopropoxide complex. [b] Isolated yield. [c] Determined by HPLC analyses of their MTPA esters. [d] All absolute unless otherwise noted. [e] Ref. 18. [f] Ref. 8(i). [g] Determined by comparison with the retention time in HPLC analyses; former peak; *R*-isomer, latter peak; *S*-isomer. [h] Determined by the comparison of the optical rotation values after conversion into (*R*)-methyl 2-hydroxy-3-methylbutyrate; Ref. 19. [i] Ref 6(b).

were silylcyanated to afford the corresponding α-cyano allylic alcohols in high optical yield, and, in particular, (*E*)-2-hydroxy-3-methyl-pentanenitrile was obtained in 96% e.e. by silylcyanation of *trans*-2-methyl-2-butenal (tiglic aldehyde). Aliphatic aldehydes with non-conjugated hydrocarbon substituents (**2p**—**2u**) were generally silylcyanated with moderate levels of enantioselectivity. As for the stereochemistry of the products, when the reaction was carried out using the Ti(O-*i*-Pr)4—Schiff base **1f** catalyst system, the absolute configuration of the produced cyanohydrins was always *R*.

Enantioselective Reaction of Diketene with Aldehydes Promoted by Chiral Schiff Base—Titanium Alkoxide Complexes. There are several reports of the synthesis of 5-hydroxy-3-oxoesters. Among these, one of the most efficient methods of preparing racemic compounds is the titanium tetrachloride promoted reaction of diketene with aldehydes reported by Mukaiyama *et. al.*[15] We found that the above reaction using titanium alkoxide or aluminium alkoxide gave 5-hydroxy-3-oxoesters in excellent yield under mild conditions with many aldehydes.[16] Furthermore, the chiral Schiff base—titanium alkoxide complex proved to provide excellence of enantioselection in the reaction of diketene with a variety of aldehydes (eq. 3).[17] The results of the reaction of benzaldehyde are summarized in Table 4. In this reaction, also, the enantio-



(eq. 3)

Table 4. Enantioselective Addition of Diketene to Benzaldehyde Promoted by Chiral Schiff Base—Titanium Alkoxide Complexes[a]

	conditions		product	
Schiff base	temp/°C	time/h	% yield[b]	% e.e.[c]
(*S*)-**1a**	-20	48	23	16
(*S*)-**1d**	-20	48	47	38
(*R*)-**1e**	-20	48	86	72
(*S*)-**1f**	-20	48	85	84
(*S*)-**1h**	-20	48	85	80
(*S*)-**1i**	-20	48	56	10
(*R*)-**1j**	-20	48	81	67
(*S*)-**1l**	-20	48	75	82

[a] All reactions were carried out in dichloromethane using equimolar amount of chiral titanium complexes. [b] Isolated yield. [c] HPLC analysis (CHIRALPAK AD).

Table 5. Enantioselective Addition of Diketene to Aldehyde Promoted by Chiral Schiff Base (**1f**)—Titanium Alkoxide Complexes[a]

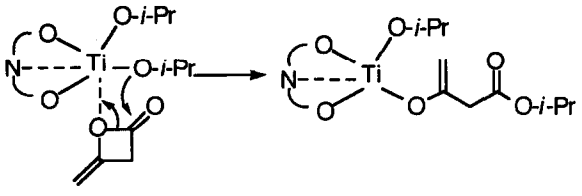
	product		
aldehyde	% yield[b]	% e.e.[c]	$[\alpha]_D^{25}$ (*c*)[d]
4-methylbenzaldehyde	90	81	-37.5° (1.2)
4-methoxylbenzaldehyde	89	67	-27.6° (1.3)
2-furfural	92	61	-18.4° (1.2)
2-thiophencarboxaldehyde	88	70	-21.8° (1.0)
methacrylaldehyde	82	68	-27.1° (1.1)
trans-2-methyl-2-butenal	73	63	-16.7° (1.1)
(*E*)-cinnamaldehyde	86	78	-11.0° (1.1)
3-phenylpropionaldehyde	69	73	-5.1° (1.1)
n-butanal	84	67	-18.4° (1.1)

[a] All reactions were carried out in dichloromethane at -20 °C for 48 h using equimolar amount of chiral titanium complexes. [b] Isolated yield. [c] HPLC analysis (CHIRALPAK AD). [d] Measured in chloroform.

selectivity was much influenced by the nature of chiral Schiff base used. The existence of a *tert*-butyl group at the 3-position was essential to achieve high enantioselection. That is, when the Schiff base **1a** without the *tert*-butyl group was used, only low levels of reactivity and enantioselectivity (23% yield, 16% e.e.) were observed, whereas, high chemical and optical yield (85% yield, 84% e.e.) were obtained by the use of Schiff base **1f** possessing a *tert*-butyl substituent at the 3-position of the benzene ring.

Unfortunately, however, the reaction using a catalytic amount of the titanium complex caused a decrease in chemical yield, even after prolonged reaction time (20 mol%, -20 °C, 88 h, 29% yield), though the enantioselectivity was not influenced by the amount of catalyst (82% e.e.). Therefore, an equimolar or more than 50 mol% of titanium complexes was necessary in order to obtain a satisfactory yield. The results obtained from the reaction of a variety of aldehydes with diketene are summarized in Table 5. In all cases, moderate to high enantioselection (61—81% e.e.) was obtained.

The reaction is assumed to proceed through an aldol type reaction between aldehydes and the titanium enolate formed by the reaction of the titanium alkoxide complex with diketene (Scheme 1). As for the stereochemical outcome of the reaction, when the Schiff base **1f** possessing the *S*-configuration was used, it was found that aldehydes were attacked from the *si* face by nucleophiles, which is consistent with the results obtained in the enantioselective addition of trimethylsilyl cyanide. The origin of the stereochemistry can be explained by consideration of the mechanism shown in Figure 1.



Scheme 1. Generation of titanium enolate

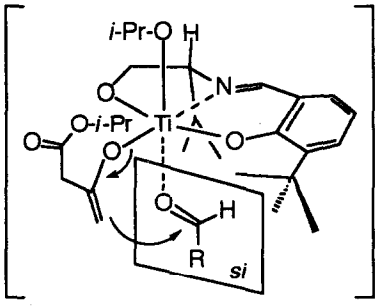


Figure 1

In conclusion, we have described a novel type of chiral titanium catalyst composed of a titanium alkoxide and a Schiff base possessing a *tert*-butyl group. This has proved to be an efficient catalyst for the enantioselective addition of trimethylsilyl cyanide or diketene to aldehydes leading to the formation of optically active cyanohydrins and 5-hydroxy-3-oxoesters, respectively, in high optical yield.

Experimental Section

General. All melting points were uncorrected. ^{1}H (250 MHz) and ^{13}C NMR (62.9 MHz) spectra were measured on a Hitachi R-250 Fourier Transfer NMR spectrometer. A high resolution mass spectra (HRMS) were recorded on a JOEL JMS SX-102A for fast atom bombardment ionization (FAB). Optical rotations were measured on a JASCO DIP-4 digital polarimeter for solutions in a 5 dm cell. Preparative column chromatography was carried out on a Wacogel-200 column. HPLC analyses were carried out with a 880-PU

liquid chromatograph with a JASCO UVIDEC 100 UV detector. The column used for HPLC analyses was YMC Packed Column A-003 S-5 120A or Daicel CHIRALPAK AD.

General Procedure for the Preparation of Chiral Schiff Base. A mixture of methanol, chiral β-amino alcohol (1 equiv.), and salicylaldehyde or its derivative (1.1—1.2 equiv.) were refluxed for 4—80 h in the presence of anhydrous Na_2SO_4. The mixture was filtered through a pad of Celite, and the filtrate was evaporated up, then the obtained residue was purified by recrystallization or flash column chromatography.

(*S*)-2-(*N*-Salicylidene)amino-3-methyl-1-butanol (1a). Yield: 1.88 g (94%). Purification: recrystallization from hexane—benzene (10:1). m.p. 107—108 °C. Yellow crystal. $[\alpha]_D^{25}$ -26.2° (*c* 1.0, CH_3OH). IR ν_{max}: 3260, 2960, 2930, 1630, 1580, 1280 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 1.6 (br s, 1H), 1.95 (sept, *J* = 6.7 Hz, 1H), 1.9—2.0 (m, 1H), 3.0—3.2 (m, 2H), 3.7—4.0 (m, 1H), 6.9—7.0 (m, 1H), 7.3—7.4 (m, 2H), 8.37 (s, 1H), 13.4 (br s, 1H). Anal. Calcd for $C_{12}H_{17}NO_2$; C, 69.54; H, 8.27; N, 6.76: Found; C, 69.53; H, 8.22; N, 6.75.

(*S*)-2-(*N*-Salicylidene)amino-3-methyl-1,1-diphenyl-1-butanol (1b). Yield: 1.15 g (82%). Purification: recrystallization from petroleum ether. m.p. 174 °C. Yellow crystalline solid. $[\alpha]_D^{23}$ +80.7° (*c* 1.0, CHCl3). IR ν_{max}: 3580, 2960, 2870, 1630, 1580, 1280 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.83 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 2.1 (sept, *J* = 6.7 Hz,1H), 2.84 (s, 1H), 4.06 (s, 1H), 6.8—7.6 (m, 14H), 8.17 (s, 1H), 12.9 (br s, 1H). Anal. Calcd for $C_{24}H_{25}NO_2$; C, 80.19; H, 7.01, N, 3.90: Found; C, 79.28; H, 7.09; N, 4.03.

(*S*)-2-(*N*-Salicylidene)amino-3,3-dimethyl-1-butanol (1c). Yield: 0.13 g (50%). Purification: recrystallization from petroleum ether—benzene (5:1). m.p. 107—108 °C. Yellow crystalline solid. $[\alpha]_D^{25}$ -6.3° (*c* 0.5, C_2H_5OH). IR ν_{max}: 3290, 2970, 2870, 1630, 1580, 1280 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (s, 9H), 1.7 (br s, 1H), 2.88 (dd, *J* = 3.2 Hz, 9.2 Hz, 1H), 3.66 (dd, *J* = 11.0 Hz, 9.2 Hz, 1H), 3.87 (dd, *J* = 3.2 Hz, 11.0 Hz, 1H), 6.8—7.0 (m, 2H), 7.2—7.3 (m, 2H), 8.28 (s, 1H), 13.5 (br s, 1H). Anal. Calcd for $C_{13}H_{19}NO_2$; C, 70.56; H, 8.65; N, 6.33: Found; C, 69.90; H, 8.57; N, 6.24.

(*S*)-2-(*N*-3-*tert*-Butylsalicylidene)amino-1-propanol (1d). Yield: 1.3 g (48%). Purification: flash column chromatography (hexane—ethyl acetate (3:1)). Yellow syrup. $[\alpha]_D^{23}$ +44.1° (*c* 1.0, $CHCl_3$). IR ν_{max}: 3360, 3060, 2960, 2740, 1630, 1270 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.24 (d, *J* = 6.1 Hz, 3H), 1.44 (s, 9H), 1.6 (br s, 1H), 3.5 (m, 1H), 3.71 (d, *J* = 4.9 Hz, 2H), 6.83 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 7.3 Hz, 1H), 8.43 (s, 1H), 13.8 (br s, 1H). Anal. Calcd for $C_{14}H_{21}NO_2$; C, 79.58; H, 10.02; N, 6.63: Found; C, 79.28; H, 10.11; N, 6.70.

(*R*)-2-(*N*-3-*tert*-Butylsalicylidene)amino-1-butanol (1e). Yield: 1.8 g (72%). Purification: flash column chromatography (hexane—ethyl acetate (3:1)). $[\alpha]_D^{24}$ +20.6° (*c* 1.1, $CHCl_3$). IR ν_{max}: 3372, 2964, 2876, 1632, 1436, 1268 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.9 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 9H), 1.6—1.7 (m, 2H), 1.7 (br s, 1H), 3.1—3.3 (m, 1H), 6.8—7.5 (m, 3H), 8.4 (s, 1H), 13.8 (br s, 1H). Anal. Calcd for $C_{15}H_{23}NO_2$; C, 72.25; H, 9.30; N, 5.62: Found; C, 72.20; H, 9.55; N, 5.65.

(*S*)-2-(*N*-3-*tert*-Butylsalicylidene)amino-3-methyl-1-butanol (1f). Yield: 9.76 g (74%). Purification: recrystallization from petroleum ether. m.p. 57—58 °C. Yellow needles. $[\alpha]_D^{24}$ -39.8° (*c* 1.0, $CHCl_3$), +2.5° (*c* 1.0, C_2H_5OH). IR ν_{max}: 3250, 2960, 1630, 1270 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.4 (s, 9H), 1.6 (br s, 1H), 2.0 (m, 1H), 3.0 (m, 1H), 3.8 (m, 2H), 6.8—7.5 (m, 3H), 8.37 (s, 1H), 13.5 (br s, 1H). Anal. Calcd for $C_{16}H_{25}NO_2$; C, 72.97; H, 9.57; N, 5.32: Found; C, 73.33; H, 9.83; N, 5.32.

(*S*)-2-(*N*-3-*tert*-Butylsalicylidene)amino-3-methyl-1,1-diphenyl-1-butanol (1g). Yield: 0.52 g (64%). Purification: recrystallization from petroleum ether. m.p. 92—93 °C. Yellow crystalline solid. $[\alpha]_D^{24}$ +84.2° (*c* 1.0, $CHCl_3$). IR ν_{max}: 3600, 2960, 2870, 1630, 1490, 1260 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.81 (d, *J* = 6.7 Hz, 3H), 1.02(d, *J* = 6.7 Hz, 3H), 1.41 (s, 9H), 2.1 (m, 1H), 2.95 (s, 1H), 4.07 (s, 1H), 6.7—7.6 (m, 13H), 8.22 (s, 1H), 13.3 (br s, 1H). Anal. Calcd for $C_{28}H_{33}NO_2$; C, 80.93; H, 8.00; N, 3.37: Found; C, 80.48; H, 7.99; N, 3.29.

(*S*)-2-(*N*-3-*tert*-Butylsalicylidene)amino-3,3-dimethyl-1-butanol (1h). Yield: 0.49 g (70%). Purification: flash chromatography (hexane—ethyl acetate (5:1)). m.p. 55—57 °C. Yellow crystalline solid. $[\alpha]_D^{24}$ -3.8° (*c* 1.1, C_2H_5OH). IR ν_{max}: 3400, 2960, 2870, 1630, 1480, 1270 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.99 (s, 9H), 1.45 (s, 9H), 1.6 (br s, 1H), 2.94 (dd, *J* = 3.1 Hz, 9.2 Hz, 1H), 3.77 (t, *J* = 9.2 Hz, 1H), 3.94 (dd, *J* = 3.1 Hz, 9.2 Hz, 1H), 6.84 (t, *J* = 9.2 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 8.36 (s, 1H), 13.8 (br s, 1H). Anal. Calcd for $C_{17}H_{27}NO_2$; C, 73.61; H, 9.81; N, 5.05: Found; C, 73.27; H, 9.76; N, 5.06.

(*S*)-2-(*N*-3-*tert*-Butylsalicylidene)amino-2-phenyl-1-ethanol (1i). Yield: 8.24 g (76%). Purification: flash chromatography (hexane—ethyl acetate (5:1)). Yellow syrup. $[\alpha]_D^{24}$ +112.9° (*c* 1.3, $CHCl_3$). IR ν_{max}: 3390, 2960, 2870, 1630, 1500, 1270 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.4 (br s, 1H), 3.85 (d, *J* = 7.3 Hz, 2H), 4.40 (t, *J* = 6.1 Hz, 1H), 6.81 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.2—7.4 (m, 6H), 8.43 (s, 1H), 13.8 (br s, 1H). Anal. Calcd for $C_{19}H_{23}NO_2$; C, 76.73; H, 7.80; N, 4.71: Found; C, 76.58; H, 7.56; N, 4.85.

(*R*)-1-(*N*-3-*tert*-Butylsalicylidene)amino-3,3-dimethyl-2-butanol (1j). Yield: 0.83 g (54%). Purification: flash chromatography (hexane—ethyl acetate (5:1)). Yellow syrup. $[\alpha]_D^{24}$ -104.9° (*c* 1.0, $CHCl_3$). IR ν_{max}: 3456, 2956, 1634, 1436, 1268 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.01 (s, 9H), 1.43 (s, 9H), 1.9 (br s, 1H), 3.32 (t, *J* = 11.6 Hz, 1H), 3.61 (d, *J* = 11.6 Hz, 1H), 3.97 (d, *J* = 11.6 Hz, 1H), 6.84 (t, *J* = 7.3 Hz, 1H), 8.41 (s, 1H), 13.9 (br s, 1H). Anal. Calcd for $C_{17}H_{27}NO_2$; C, 73.61; H, 9.81; N, 5.05: Found; C, 73.27; H, 9.74; N, 5.04.

(*S*)-2-(*N*-3-*tert*-Butyl-5-methylsalicylidene)amino-3-methyl-1-butanol (1k). Yield: 11.05 g (81%). Purification: flash chromatography (hexane—ethyl acetate (7:1)). Yellow syrup. $[\alpha]_D^{24}$ -38.7° (*c* 1.3, $CHCl_3$). IR ν_{max}: 3400, 2964, 1630, 1440, 1266 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.94 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 1.43 (s, 9H), 1.5 (br s, 1H), 1.9 (m, 1H), 2.29 (s, 3H), 3.0 (m, 1H), 3.8 (m, 2H), 7.15 (s, 1H), 7.26 (s, 1H), 8.32 (s, 1H), 13.5 (br s, 1H). Anal. Calcd for $C_{17}H_{27}NO_2$; C, 73.60; H, 9.81; N, 5.05: Found; C, 73.34; H, 9.99; N; 5.02.

(*S*)-2-(*N*-3,5-di-*tert*-Butylsalicylidene)amino-3-methyl-1-butanol (1l). Yield: 9.76 g (74%). Purification: flash chromatography (hexane—ethyl acetate (10:1)). m.p. 107—108 °C. Yellow crystals. $[\alpha]_D^{24}$ -34.3° (*c* 1.3, $CHCl_3$). IR ν_{max}: 3584, 2964, 2872, 1632, 1494, 1280 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.94 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 1.31 (s, 9H), 1.45 (s, 9H), 1.6 (br s, 1H), 1.90 (q, *J* = 6.7 Hz, 1H), 3.0 (m, 1H), 3.8 (m, 2H), 7.14 (s, 1H), 7.41 (s, 1H), 8.38 (s, 1H), 13.5 (br s, 1H). Anal. Calcd for $C_{20}H_{33}NO_2$; C, 75.19; H, 10.41; N, 4.38: Found; C, 75.11; H, 10.22; N, 4.55.

General Procedure for Asymmetric Silylcyanation of Aldehydes. In a flame-dried Schlenk tube were placed Schiff base **1f** (145 mg, 0.55 mmol) and CH_2Cl_2 (2.5 mL). To this solution was added Ti(*O-i*-Pr)4 (0.50 mmol) at room temperature and stirred for 1 h, then the mixture was cooled to -80 °C. Freshly distilled aldehyde **2a**—**2u** (2.5 mmol) and trimethylsilyl cyanide (5.6 mmol) were added to it and the whole

stirred for 12—36 h at this temperature. After this, the mixture was poured into a mixture of 1N HCl (30 mL) and ethyl acetate (150 mL) and stirred vigorously for 6 h at room temperature. The mixture was then extracted with ethyl acetate (50 mL x 3), and the combined extracts were washed with satd. $NaHCO_3$ (50 mL x 4), brine (50 mL x 2), and dried over Na_2SO_4, then evaporated. The residue was column chromatographed on silica gel [eluent, hexane—ethyl acetate (5:1)] to give cyanohydrins **3a—3u**. The e. e. for each of the cyanohydrin trimethylsilyl ethers was determined by HPLC analysis [eluent, hexane—ethyl acetate (100:5), 1.0 mL/min] of the corresponding (*R*)-(+)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) esters[14] after hydrolysis with 1 N HCl.

2-Hydroxy-2-phenylacetonitrile (3a). *R*-rich-**3a**: 219 mg (67%). $[\alpha]_D^{24}$ +36.8° (*c* 2.0, $CHCl_3$). IR ν_{max}: 3430, 2260, 1700, 1600, 1490, 1460 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.9 (br s, 1H), 5.55 (s, 1H), 7.4—7.6 (m, 5H). [lit.[6] $[\alpha]_D^{21}$ +45.5° (*c* 3.53, $CHCl_3$) for *R*-enantiomer in 96% e.e.]. The e.e. of the product was determined as 85% e.e. by HPLC analysis of its MTPA ester as described above. t_R of *R*-isomer: 13 min; t_R of *S*-isomer: 15 min.

2-Hydroxy-2-(3-methoxyphenyl)acetonitrile (3b). *R*-rich-**3b**: 306 mg (76%). $[\alpha]_D^{24}$ +22.8° (*c* 1.5, $CHCl_3$). [lit.[18] $[\alpha]_D^{25}$ +36.9° (*c* 1.6, $CHCl_3$) for *R*-enantiomer in 90% e.e.]. IR ν_{max}: 3440, 3010, 2940, 2250, 1600, 1490 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.1 (br s, 1H), 3.83 (s, 3H), 5.51 (s, 1H), 6.9—7.4 (m, 4H). The e.e. of the product was determined as 56% e.e. by HPLC analysis. t_R of *R*-isomer: 30 min; t_R of *S*-isomer: 37 min.

2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile (3c). *R*-rich-**3c**: 375 mg (67%). $[\alpha]_D$24 +13.5° (*c* 1.5, C_6H_6). [lit [8i] $[\alpha]_D^{25}$ -17.5° (*c* 0.8, C_6H_6) for *S*-enantiomer in 96.8% e.e.]. IR ν_{max}: 3430, 3070, 2250, 1960, 1690, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.6 (br s, 1H), 5.47 (s, 1H), 7.0—7.4 (m, 9H). The e.e. of the product was determined as 79% e.e. by HPLC analysis. t_R of *R*-isomer: 19 min; t_R of *S*-isomer:22 min.

2-Hydroxy-2-(4-methylphenyl)acetonitrile (3d). *R*-rich-**3d**: 250 mg (68%). $[\alpha]_D^{24}$ +36.4° (*c* 1.1, $CHCl_3$). [lit.[18] $[\alpha]_D^{25}$ +47.4° (*c* 1.8, $CHCl_3$) for *R*-isomer in 92% e.e.]. IR ν_{max}: 3440, 3030, 2920, 2250, 1680, 1610 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 3.2 (br s, 1H), 5.39 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H). The e.e. of the product was determined as 71% e.e. by HPLC analysis. t_R of *R*-isomer: 11 min; t_R of *S*-isomer: 12 min.

2-Hydroxy-2-(4-methoxylphenyl)acetonitrile (3e). *R*-rich-**3e**: 253 mg (62%). $[\alpha]_D^{24}$ +41.7° (*c* 1.4, $CHCl_3$). [lit.[18] $[\alpha]_D^{25}$ +36.3° (*c* 1.0, $CHCl_3$) for *R*-isomer in 83% e.e.]. IR ν_{max}: 3430, 3010, 2940, 2840, 2250, 1710, 1610 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.7 (br s, 1H), 3.84 (s, 3H), 5.49 (s, 1H), 6.96 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H). The e.e. of the product was determined as 91% e.e. by HPLC analysis. t_R of *R*-isomer: 17 min; t_R of *S*-isomer: 20 min.

2-Hydroxy-2-(4-cyanophenyl)acetonitrile (3f). *R*-rich-**3f**: 237 mg (60%). $[\alpha]_D^{24}$ +6.5° (*c* 1.5, $CHCl_3$). [lit.[18] $[\alpha]_D$ +16.6° (*c* 0.8, $CHCl_3$) for *R*-isomer in 52% e.e.]. IR ν_{max}: 3460, 2920, 2230, 1610, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.2 (br s, 1H), 5.65 (s, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H). The e.e. of the product was calculated as 20% e.e by comparison of the rotation values in the literature.[18]

2-Hydroxy-2-naphthylacetonitrile (3g). *R*-rich-**3g**: 343 mg (76%). $[\alpha]_D^{24}$ +10.9° (*c* 1.1, C_2H_5OH). [lit [18] $[\alpha]_D$ +26.4° (*c* 0.522, $CHCl_3$) for *R*-isomer in 86% e.e.]. IR ν_{max}: 3480, 3060, 2930, 2390, 2250, 1360 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.0 (br s, 1H), 5.70 (s, 1H), 7.5—7.6 (m, 3H), 7.8—8.0 (m,

3H), 8.05 (s, 1H). The e.e. of the product was determined as 73% e.e. by HPLC analysis. t_R of *R*-isomer: 13 min; t_R of *S*-isomer: 15 min.

2-Hydroxy-2-(2-thienyl)acetonitrile (3i). *R*-rich-**3i**: 206 mg (60%). $[\alpha]_D^{24}$ +64.1° (*c* 0.6, $CHCl_3$). [lit.[18] $[\alpha]_D$ +46.8° (*c* 2.5, $CHCl_3$) for *R*-isomer in 58% e.e.]. IR ν_{max}: 3440, 3110, 2960, 2900, 2250, 1880, 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.1 (br s, 1H), 5.74 (s, 1H), 7.0—7.1 (m, 1H), 7.3—7.4 (m, 1H), 7.4—7.5 (m, 1H). The e.e. of the product was determined as 79% e.e. by HPLC analysis. t_R of *R*-isomer: 15 min; t_R of *S*-isomer: 17 min.

2-Hydroxy-3-butenenitrile (3j). *R*-rich-**3j** : 112 mg (54%). $[\alpha]_D^{24}$ -3.8° (*c* 0.8, $CHCl_3$). IR ν_{max}: 3430, 3000, 2250, 1420, 1380 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3,9 (br s, 1H), 5.0 (ddd, *J* = 4.0 Hz, 1.2 Hz, 1.2 Hz, 1H), 5.4 (ddd, *J* = 1.2 Hz, 9.0 Hz, 1.2 Hz, 1H), 5.6 (ddd, *J* = 1.2 Hz, 17.0 Hz, 1.2 Hz, 1H), 6.0 (ddd, *J* = 9.0 Hz, 17.0 Hz, 4.0 Hz, 1H). The e.e. of the product was determined as 63% e.e. by HPLC analysis. t_R of *R*-isomer: 18 min; t_R of *S*-isomer: 24 min.

2-Hydroxy-3-methyl-3-butenenitrile (3k). *R*-rich-**3k**: 150 mg (62%). $[\alpha]_D^{24}$ +5.7° (*c* 1.3, $CHCl_3$). IR ν_{max}: 3430, 2250, 1660, 1460, 1440 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.90 (s, 3H), 4.9 (br s, 1H), 4.88 (s, 1H), 5.1 (m, 1H), 5.3 (m, 1H). The e.e. of the product was determined as 85% e.e. by HPLC analysis: t_R of *R*-isomer: 12 min; t_R of *S*-isomer: 16 min. The absolute configuration was determined as *R* by comparison of the optical rotation values after conversion into (*R*)-methyl 2-hydroxy-3-methylbutyrate.[19]

(*E*)-2-Hydroxy-3-pentenenitrile (3l). *R*-rich-**3l**: 170 mg (70%). $[\alpha]_D^{24}$ -35.7° (*c* 0.3, $CHCl_3$). [lit.[18] -4.9° (*c* 2.3, $CHCl_3$) for *R*-enantiomer in 11% e.e.]. IR ν_{max}: 3430, 3040, 2980, 2250, 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.79 (dd, *J* = 6.1 Hz, 1.2 Hz, 3H), 3.7 (br s, 1H), 4.92 (dd, *J* = 1.2 Hz, 6.1 Hz, 1H), 5.63 (m, 1H), 6.1 (m, 1H). The e.e. of the product was determined as 89% e.e. by HPLC analysis. t_R of *R*-isomer: 13 min; t_R of *S*-isomer: 17 min.

2-Hydroxy-4-methyl-3-pentenenitrile (3m). *R*-rich-**3m**: 175 mg (63%). $[\alpha]_D^{24}$ -94.2° (*c* 0.7, $CHCl_3$). IR ν_{max}: 3430, 3000, 2950, 2250, 1680, 1450, cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.76 (d, *J* = 1.4 Hz, 3H), 1.80 (d, *J* = 1.2 Hz, 3H), 3.5 (br s, 1H), 5.1 (d, *J* = 8.5 Hz, 1H), 5.4 (m, 1H). The e.e. of the product was determined as 89% e.e. by HPLC analysis. t_R of *R*-isomer: 12 min; t_R of *S*-isomer: 15 min.

(*E*)-2-Hydroxy-3-methyl-3-pentenenitrile (3n). *R*-rich-**3n**: 189 mg (68%). $[\alpha]_D^{24}$ -24.8° (*c* 1.0, $CHCl_3$). IR ν_{max}: 3430, 2980, 2940, 2250, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.76 (d, *J* = 2.9 Hz, 3H), 1.81 (d, *J* = 8.5 Hz, 3H), 3.5 (br s, 1H), 5.10 (d, *J* = 8.5 Hz, 1H), 5.40 (m, 1H). The e.e. of the product was determined as 96% e.e. by HPLC analysis. t_R of *R*-isomer: 11 min; t_R of *S*-isomer: 14 min.

(*E*)-2-Hydroxy-4-phenyl-3-butenenitrile (3o). *R*-rich-**3o**: 322 mg (81%). $[\alpha]_D^{24}$ +19.2° (*c* 1.9, $CHCl_3$). [lit.[18] +5.7° (*c* 1.4, $CHCl_3$) for *R*-enantiomer in 11% e.e.]. IR ν_{max}: 3370, 3030, 2920, 2250, 1490 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.7 (br s, 1H), 5.16 (dd, *J* = 5.7 Hz, 1.1 Hz, 1H), 6.25 (dd, *J* = 15.8 Hz, 5.7 Hz, 1H), 6.93 (dd, *J* = 15.8 Hz, 1.1 Hz, 1H), 7.3—7.5 (m, 5H). The e.e. of the product was determined as 72% e.e. by HPLC analysis. t_R of *R*-isomer: 18 min; t_R of *S*-isomer: 21 min.

2-Hydroxy-4-phenylbutanenitrile (3p). *R*-rich-**3p**: 343 mg (85%). $[\alpha]_D^{24}$ -2.6° (*c* 2.7, $CHCl_3$). [lit.[18] $[\alpha]_D$ -6.79° (*c* 2.04, $CHCl_3$) for *R*-enantiomer in 89% e.e.]. IR ν_{max}: 3430, 3050, 2980, 2250, 1720, 1610 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.0—2.2 (m, 2H), 2.8—2.9 (m, 2H), 4.1 (br s, 1H), 4.43 (t, *J* = 6.7 Hz, 1H), 7.2—7.4 (m, 5H). The e.e. of the product was determined as 40% e.e. by HPLC analysis. t_R of *R*-isomer: 16 min; t_R of *S*-isomer: 21 min.

2-Hydroxypentanenitrile (3q). *R*-rich-**3q**: 181 mg (73%). $[\alpha]_D^{24}$ +13.1° (*c* 0.9, $CHCl_3$). [lit.[18] $[\alpha]_D$ +5.5° (*c* 3.4, $CHCl_3$) for *R*-enantiomer in 26% e.e.]. IR ν_{max}: 3450, 2970, 2880, 2250, 1720, 1470 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.99 (t, *J* = 7.3 Hz, 3H), 1.3—2.1 (m, 4H), 3.8 (br s, 1H), 4.48 (t, *J* = 6.7 Hz, 1H). The e.e. of the product was determined as 57% e.e. by HPLC analysis. t_R of *R*-isomer: 12 min; t_R of *S*-isomer: 15 min.

2-Hydroxyundecanenitrile (3r). *R*-rich-**3r**: 220 mg (48%). $[\alpha]_D^{24}$ +6.7° (*c* 1.3, $CHCl_3$). [lit.[6b] $[\alpha]_D$ +7.9° (*c* 4.03, $CHCl_3$) for *R*-enantiomer in 85% e.e.]. IR ν_{max}: 3460, 2930, 2860, 2250, 1710 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.2—1.8 (m, 19H), 2.8 (br s, 1H), 4.47 (t, *J* = 6.7 Hz, 1H). The e.e. of the product was determined as 66% e.e. by HPLC analysis. t_R of *R*-isomer: 7 min; t_R of *S*-isomer: 8 min.

2-Hydroxy-3-methylbutanenitrile (3s). *R*-rich-**3s**: 174 mg (70%). $[\alpha]_D^{24}$ +4.2° (*c* 1.3, $CHCl_3$). [lit.[18] $[\alpha]_D$ +2.7° (*c* 3.9, $CHCl_3$) for *R*-enantiomer in 17% e.e.]. IR ν_{max}: 3450, 2970, 2880, 2250, 1710, 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 2.0 (m, 1H), 3.6 (br s, 1H), 4.3 (m, 1H). The e.e. of the product was determined as 34% e.e. by HPLC analysis. t_R of *R*-isomer: 13 min; t_R of *S*-isomer: 18 min.

2-Cyclohexyl-2-hydroxyacetonitrile (3t). *R*-rich-**3t**: 251 mg (72%). $[\alpha]_D^{24}$ +6.1° (*c* 3.8, $CHCl_3$). [lit.[6b] $[\alpha]_D$ +5.45° (*c* 2.96, $CHCl_3$) for *R*-enantiomer in 58% e.e.]. IR ν_{max}: 3450, 2930, 2860, 2250, 1710, 1450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.0—1.4 (m, 5H), 1.6—2.0 (m, 6H), 2.8 (br s, 1H), 4.27 (d, *J* = 6.1 Hz, 1H). The e.e. of the product was determined as 65% e.e. by HPLC analysis. t_R of *R*-isomer: 10 min; t_R of *S*-isomer: 13 min.

2-Hydroxy-3,3-dimethylbutanenitrile (3u). *R*-rich-**3u**: 108 mg (38%). $[\alpha]_D^{24}$ +14.5° (*c* 1.0, $CHCl_3$). [lit.[18] $[\alpha]_D$ +4.5° (*c* 1.5, $CHCl_3$) for *R*-enantiomer in 29% e.e.]. IR ν_{max}: 3460, 2970, 2880, 2250, 1710, 1480 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.00 (s, 9H), 2.7 (br s, 1H), 4.05 (s, 1H). The e.e. of the product was determined as 70% e.e. by HPLC analysis. t_R of *R*-isomer: 8 min; t_R of *S*-isomer: 11 min..

General Procedure for Asymmetric Addition of Diketene to Aldehydes Promoted by Chiral Schiff Base—Titanium Alkoxide Complexes. In a Schlenk tube were placed Schiff base **1f** (1.43 g, 5.4 mmol) and CH_2Cl_2 (5 mL). To this solution was added Ti(O-*i*-Pr)4 (4.9 mmol) at room temperature and stirred for 1 h, then the mixture was cooled to -20 °C. Freshly distilled aldehyde **2a—2q** (4.9 mmol) and diketene (9.8 mmol) were added to it and the whole storred for 48 h at this temperature. After this, isopropyl alcohol (9.8 mmol) was added to the mixturem then stirred for 3 h. The mixture was poured into a mixture of 1N HCl (50 mL) and diethyl ether (50 mL) and stirred vigorously for 24 h at room temperature. The mixture was then extracted with ethyl acetate (50 mL x 3), and the combined extracts were washed with satd. $NaHCO_3$ (50 mL x 4), brine (50 mL x 2), and dried over Na_2SO_4, then evaporated. The residue was column chromatographed on silica gel [eluent, benzene—diethyl ether (3:1)] to give 5-hydroxy-3-oxoesters **4a—4q**. The e. e. for each of the 5-hydroxy-3-oxoesters was determined by HPLC analysis (CRIRALPAK AD) [eluent, hexane—ethanol (95:5) + trifluoroacetic acid (0.01%), 1.0 mL/min].

Isopropyl 5-Hydroxy-5-phenyl-3-oxopentanoate (4a). **4a**: 1.04 g (85%). $[\alpha]_D^{24}$ -40.8° (*c* 1.0, $CHCl_3$). IR ν_{max}: 3508, 2984, 2936, 1740, 1646, 1314, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.26 (d, *J* = 6.7 Hz, 6H), 2.4 (br s, 1H), 2.94 (d, *J* = 3.7 Hz, 1H), 2.97 (d, *J* = 9.2 Hz, 1H), 3.46 (s, 2H), 5.0—5.1 (m, 1H), 5.2 (dd, *J* = 3.7 Hz, 9.2 Hz, 1H), 7.3—7.4 (m, 5H). The e.e. of the product was determined as 84% e.e. by HPLC analysis. t_R of minor-isomer: 12 min; t_R of major-isomer: 19 min. HRMS (FAB) *m/z* Calcd for $C_{14}H_{17}O_3$ (M^+-17): 233.1179. Found: 233.1209.

Isopropyl 5-Hydroxy-5-(4-methylphenyl)-3-oxopentanoate (4d). 4d: 1.17 g (90%). $[\alpha]_D^{24}$ -37.5° (*c* 1.2, $CHCl_3$). IR ν_{max}: 3492, 2988, 2936, 1716, 1646, 1314, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.25 (d, *J* = 6.1 Hz, 6H), 2.34 (s, 3H), 2.91 (d, *J* = 3.7 Hz, 1H), 2.96 (d, *J* = 8.5 Hz, 1H), 3.44 (s, 2H), 5.05 (sept, J = 6.1 Hz, 1H), 5.15 (dd, *J* = 3.7 Hz, 8.5 Hz, 1H), 7.2—7.3 (m, 4H). The e.e. of the product was determined as 81% e.e. by HPLC analysis. t_R of minor-isomer: 12 min; t_R of major-isomer: 17 min. HRMS (FAB) *m/z* Calcd for $C_{15}H_{19}O_3$ (M^+-17): 247.1335. Found: 247.1343.

Isopropyl 5-Hydroxy-5-(4-methoxylphenyl)-3-oxopentanoate (4e). 4e: 1.22 g (89%). $[\alpha]_D^{24}$ -27.6° (*c* 1.3, $CHCl_3$). IR ν_{max}: 3500, 2988, 2940, 1740, 1616, 1514, 1378, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.25 (d, *J* = 6.1 Hz, 6H), 2.5 (br s, 1H), 2.91 (d, *J* = 3.7 Hz, 1H), 2.96 (d, *J* = 9.2 Hz, 1H), 3.45 (s, 2H), 3.8 (s, 3H), 5.0 (sept, *J* = 6.1 Hz, 1H), 5.14 (dd, *J* = 3.7 Hz, 9.2 Hz, 1H), 6.8—6.9 (m, 2H), 7.2—7.3 (m, 2H). The e.e. of the product was determined as 67% e.e. by HPLC analysis. t_R of minor-isomer: 22 min; t_R of major-isomer: 33 min. HRMS (FAB) *m/z* Calcd for $C_{15}H_{19}O_4$ (M^+-17): 263.1284. Found: 263.1248.

Isopropyl 5-Hydroxy-5-(2-furyl)-3-oxopentanoate (4h). 4h: 1.08 g (92%). $[\alpha]_D^{24}$ -18.4° (*c* 1.2, $CHCl_3$). IR ν_{max}: 3472, 2988, 1734, 1318, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.26 (d, *J* = 6.1 Hz, 6H), 1.8 (m,, 1H), 2.5 (br s, 1H),3.07 (d, *J* = 3.7 Hz, 1H), 3.14 (d, *J* = 8.6 Hz, 1H), 3.48 (s, 2H), 5.0—5.1 (m, 1H), 5.2 (dd, *J* = 3.7 Hz, 8.6 Hz, 1H), 6.3—6.4 (m, 2H), 7.3—7.4 (m, 1H). The e.e. of the product was determined as 61% e.e. by HPLC analysis. t_R of minor-isomer: 15 min; t_R of major-isomer: 22 min. HRMS (FAB) *m/z* Calcd for $C_{12}H_{16}O_5$ (M^+): 240.0999. Found: 240.1014.

Isopropyl 5-Hydroxy-5-(2-thienyl)-3-oxopentanoate (4i). 4i: 1.11 g (88%). $[\alpha]_D^{24}$ -21.8° (*c* 1.1, $CHCl_3$). IR ν_{max}: 3498, 2988, 1736, 1316, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.26 (d, *J* = 6.1 Hz, 6H), 1.8 (m,, 1H), 2.5 (br s, 1H),3.07 (d, *J* = 4.3 Hz, 1H), 3.1 (d, *J* = 8.5 Hz, 1H), 3.47 (s, 2H), 5.0 (sept, *J* = 6.1 Hz, 1H), 5.4 (dd, *J* = 4.3 Hz, 8.5 Hz, 1H), 6.9—7.0 (m, 2H), 7.2—7.3 (m, 1H). The e.e. of the product was determined as 70% e.e. by HPLC analysis. t_R of minor-isomer: 14 min; t_R of major-isomer: 25 min. HRMS (FAB) *m/z* Calcd for $C_{12}H_{16}O_4S$ (M^+): 256.0770. Found: 256.0760.

Isopropyl 5-Hydroxy-6-methyl-3-oxo-6-heptenoate (4k). 4k: 860 mg (82%). $[\alpha]_D^{24}$ -27.1° (*c* 1.1, $CHCl_3$). IR ν_{max}: 3528, 2988, 1738, 1654, 1320, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.27 (d, *J* = 6.1 Hz, 6H), 1.75 (s, 3H), 2.5 (br s, 1H), 2.78 (d, *J* = 6.1 Hz, 2H), 3.47 (s, 1H), 4.54 (t, *J* = 6.1 Hz, 1H), 4.88 (s, 1H), 5.0—5.1 (m, 2H). The e.e. of the product was determined as 68% e.e. by HPLC analysis. t_R of minor-isomer: 8 min; t_R of major-isomer: 11 min. HRMS (FAB) *m/z* Calcd for $C_{11}H_{17}O_3$ (M^+-17): 197.1176. Found: 197.1184.

Isopropyl 5-Hydroxy-6-methyl-3-oxo-6-octenoate (4n). 4n: 816 mg (73%). $[\alpha]_D^{24}$ -16.7° (*c* 1.1, $CHCl_3$). IR ν_{max}: 3456, 2988, 1738, 1646, 1482, 1314, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.26 (d, *J* = 6.1 Hz, 6H), 1.61 (d, *J* = 6.7 Hz, 3H), 1.62 (s, 3H), 2.2 (br s, 1H), 2.72 (d, *J* = 3.2 Hz, 1H), 2.77 (d, *J* = 9.2 Hz, 1H), 3.46 (s, 2H), 4.5 (dd, *J* = 9.2 Hz, 3.2 Hz, 1H), 5.0—5.1 (m, 1H), 5.5—5.6 (m, 1H). The e.e. of the product was determined as 63% e.e. by HPLC analysis. t_R of minor-isomer: 8 min; t_R of major-isomer: 11 min. HRMS (FAB) *m/z* Calcd for $C_{12}H_{19}O_3$ (M^+-17): 211.1336. Found: 211.1331.

Isopropyl 5-Hydroxy-7-phenyl-3-oxo-6-heptenoate (4o). 4o: 1.16 g (86%). $[\alpha]_D^{24}$ -11.0° (*c* 1.1, $CHCl_3$). IR ν_{max}: 3472, 2984, 2936, 1716, 1646, 1314, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.16 (d, *J* = 6.1 Hz, 6H), 2.4 (br s, 1H), 2.75 (s, 1H), 2.77 (s, 1H), 3.37 (s, 2H), 4.69 (dd, *J* = 6.1 Hz, 1.2 Hz, 1H), 4.97 (sept, *J* = 6.1 Hz, 1H), 6.1 (dd, *J* = 16.5 Hz, 6.1 Hz, 1H), 6.55 (dd, *J* = 16.5 Hz, 1.22 Hz, 1H), 7.1—7.3 (m, 5H). The e.e. of the product was determined as 78% e.e. by HPLC analysis. t_R of *R*-isomer: 16

min; t_R of *S*-isomer: 24 min. HRMS (FAB) *m/z* Calcd for $C_{16}H_{20}O_4$ (M^+): 276.1363. Found: 276.1330. Absolute configuration of the major isomer was determined as *S* by the comparison of the optical rotation value after conversion into (4*R*,6*R*)-4-hydroxy-6-benzylmethyl-2-pyrone. Ref. 10(i).

Isopropyl 5-Hydroxy-7-phenyl-3-oxoheptanoate (4p). **4p**: 941 mg (69%). $[\alpha]_D^{24}$ -5.1° (*c* 1.1, $CHCl_3$). IR ν_{max}: 3448, 2988, 2936, 1740, 1712, 1646, 1316, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.25 (d, *J* = 6.1 Hz, 6H), 1.8 (m,, 1H), 2.3 (br s, 1H),2.6—2.9 (m, 4H), 3.42 (s, 2H), 4.0—4.1 (m, 1H), 5.0—5.1 (m, 1H), 7.2—7.3 (m, 5H). The e.e. of the product was determined as 73% e.e. by HPLC analysis. t_R of *S*-isomer: 12 min; t_R of *R*-isomer: 19 min. HRMS (FAB) *m/z* Calcd for $C_{16}H_{21}O_3$ (M^+-17): 261.1492. Found: 261.1483. Absolute configuration of the major isomer was determined as *R* by the comparison of the optical rotation value after conversion into (4*R*,6*R*)-4-hydroxy-6-benzylmethyl-2-pyrone. Ref. 10(i).

Isopropyl 5-Hydroxy-3-oxooctanoate (4q). **4q**: 890 mg (84%). $[\alpha]_D^{24}$ -18.4° (*c* 1.1, $CHCl_3$). IR ν_{max}: 3524, 2984, 2936, 1742, 1644, 1316, 1106 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.0 Hz, 3H), 1.26 (d, *J* = 6.10, 6H), 1.3—1.6 (m, 4H), 2.1 (br s, 1H), 2.66 (d, *J* = 8.5 Hz, 1H), 2.71 (d, *J* = 3.1 Hz, 1H), 3.44 (s, 2H), 4.0—4.1 (m, 1H), 5.0—5.1 (m, 1H). The e.e. of the product was determined as 67% e.e. by HPLC analysis. t_R of *S*-isomer: 8 min; t_R of *R*-isomer: 11 min. HRMS (FAB) *m/z* Calcd for $C_{11}H_{19}O_3$ (M^+-17): 199.1336. Found: 199.1315. Absolute configuration was determined as *R* by the comparison of the optical rotation value after conversion into (*R*)-6-propyl-5,6-dihydro-2-pyrone. Ref. 10(h).

Acknowledgement: The present work was supported by a Grant-in-Aid from the Ministry of Education, Science and Culture of Japan (No 02453024). We also thank UBE INDUSTRIES. Ltd. for financial support and UBE Scientific Analysis Laboratory Inc. for measurement of HRMS.

References and Notes

1. (a) Morrison, J. D. Asymmetric Synthesis; Academic Press: New York, Vol. 3B, 1984. (b) Bosnich, B. Asymmetric Catalysis; Martinus Nijihoff Publishers: Dordrecht, 1986. (c) Brunner, H. *Synthesis*, **1988**, 645. (d) Noyori, R.; Kitamura, M. Modern Synthetic Method. ed. Scheffold, R. Springer: Berlin, 1989, Vol.5, p. 115. (e) Tomioka, K. *Synthesis*, **1990**, 541. (f) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.*, **1991**, *30*, 49.
2. Fuhrhop, J.; Penzlin, G. Organic Synthesis, Concepts, Methods, Starting Materials, Verlag Chemie, Weinheim, **1983**, 47.
3. (a) Becker, W.; Freund, H.; Pfeil, E., *Angew. Chem.* **1965**, *77*, 1139. (b) Ognyanov, V. I; Datcheva, V. K. Kyler, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 6992. (c) Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *Ibid.* **1991**, *113*, 9360.
4. (a) Elliot, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294. (b) Choi, V. M. F.; Elliot, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591.
5. (a) Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *39*, 4721; (b) Reetz, M. T.; Kyung, S. -H.; Bolm, C.; Zierke, *Chem. Ind.* **1986**, 824.
6. (a) Narasaka, K.; Yamada, T.; Minamikawa, H. *Chem. Lett.* **1987**, 2073; (b) H. Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379.
7. (a) Hayashi, M; Miyamoto, Y. Inoue, T. Oguni, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1752. (b) Idem, *J. Org. Chem.* **1993**, *58*, 1515.

8. Other reported methods of the optically active cyanohydrin synthesis: (a) Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc. Chem. Commun.*. **1990**, 1364. (b) Idem, *J. Chem. Soc., Perkin Trans. 1* **1992**, 3135. (c) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.*. **1990**, *55*, 181. (d) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.*. **1991**, 541; (e) Danda, H.; Chino, K.; Wake, S. *Ibid.* **1991**, 731. (f) Danda, H. *Synlett*, **1991**, 263. (g) Mori, A.; Ohno, H.; Nitta H.; Inoue, S. *Ibid.* **1991**, 563. (h) Mori, A.; Nitta, H.; Kudo, M.; Inoue, S. *Tetrahedron Lett.* **1991**, *32*, 4333. (i) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740. (j) Corey, E. J.; Wang, Z. *Tetrahedron Lett.* **1993**, *34*, 4001.
9. (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (b) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. J. *Chem. Soc., Perkin Trans 1* **1976**, 1165.
10. Reports of the asymmetric synthesis of mevinic acid and its derivatives including the chiral lactone moiety: (a) Rosen, T.; Heathcock, C. H.; *Tetrahedron* **1986**, *18*, 4909. (b) Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385. (c) Roth, B. D.; Roark, W. H. *Tetrahedron Lett.* **1988**, *29*, 1255. (d) Johnson, W. S.; Kelson, A. B.; Elliot, J. D. *Ibid.* **1988**, *31*, 3757. (e) Boquel, P.; Chapleur, Y., *Ibid.*, **1990**, *31*, 1869. (f) Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis* **1989**, 539. (g) Shao, L.; Seki, T.; Kawano, H.; Saburi, M. *Tetrahedron Lett.* **1991**, *52*, 7699. (h) Shao, L.; Kawano, H.; Saburi, M.; Uchida, Y. *Tetrahedron*, **1993**, *49*, 1997. (i) Bonini, C.; Pucci, P.; Viggiani, L. *J. Org. Chem.* **1991**, *56*, 4050.
11. (a) Nozaki, H.; Moriuchi, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, 5239. (b) Nozaki, H.; Takaya, H.; Moriuchi, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655. (c) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron. Lett.* **1975**, 1707. (d) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839.
12. (a) Zhang, W.; Loebach, J. L.; Wilson, S, R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *Ibid.* **1991**, *113*, 7063. (c) Zhang, W.; Jacobsen, E. N. *J. Org. Chem* . **1991**, *56*, 2296.
13. Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, A.; Puglia, G.; Sartori, G.; Ungaro, R. *J. Chem. Commun., Perkin Trans. 1* **1978**, 319.
14. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
15. Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1975**, 161.
16 Hayashi, M.; Watanabe, N.; Oguni, N. unpublished results.
17. For preliminary results: Hayashi, M.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* in press.
18. Matthews, B. R.; Jackson, W. R.; Jayatilake, G. S.Willshire, C.; Jacobs, H. A. *Aust. J. Chem.* **1988**, *41*, 1697.
19. Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1986**, *51*, 3396.

(*Received in USA* 6 *October* 1993; *accepted* 10 *December* 1993)