Enantioselective Trimethylsilylcyanation of Some Aldehydes Catalyzed by Chiral Schiff Base–Titanium Alkoxide Complexes

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Received September 24, 1992

A variety of aldehydes (aromatic, heteroaromatic, α,β-unsaturated, and nonconjugate aliphatic aldehydes) has been trimethylsilylcyanated in highly enantiomeric excess (ee) with a catalyst prepared in situ from titanium tetraisopropoxide [Ti(O-*i*-Pr)$_4$] and chiral Schiff bases. A remarkable rate enhancement was brought about by the addition of the Schiff base into the titanium alkoxide mediated silylcyanation of aldehydes. The chemical structure of chiral Schiff base–titanium alkoxide complexes is discussed based on their ^{13}C NMR spectra, field desorption (FD) mass spectra, and molecular weights.

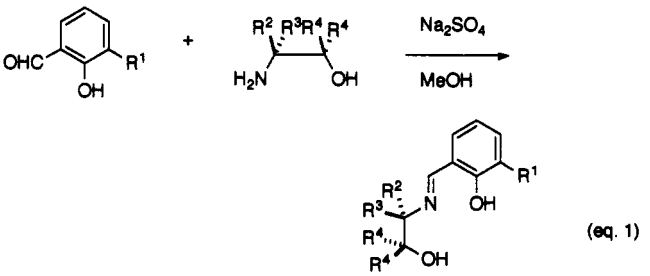
Introduction

The asymmetric synthesis of optically active organic compounds has been the focus of a great deal of research recently.[1] Of the numerous syntheses now known, optically active cyanohydrins, especially, are very versatile synthons in organic synthesis, since they give α-hydroxy carboxylic acids, β-hydroxy amines, etc. Several efficient methods have, therefore, been reported for obtaining optically active cyanohydrins by biochemical[2] and chemical methods. Of the latter, Elliot and Johnson reported the highly diastereoselective addition of trimethylsilyl cyanide to chiral acetals,[3] and in a catalytic process, Reetz first reported that boron[4a] or titanium compounds[4b] bearing chiral binaphthol and other chiral ligands catalyzed silylcyanation of isovaleraldehyde. The enantiomeric excess (ee) of each product was not, however, high. Narasaka and co-workers also reported the asymmetric hydrocyanation of aldehydes using a stoichiometric amount of an in situ prepared mixture of titanium dichloride diisopropoxide [TiCl$_2$(O-*i*-Pr)$_2$] and tartrate-derived chiral 1,4-diol in the presence of molecular sieves (MS) 4A.[5] Inoue et al. reported the enantioselective hydrocyanation of aldehydes using hydrogen cyanide catalyzed by chiral basic cyclodipeptides containing an L-histidine residue.[6] Furthermore, we recently reported highly enantioselective silylcyanation of aromatic aldehydes using catalytic amounts of modified Sharpless catalyst.[7] After those reports, many methods have been published on enantioselective hydrocyanation or silylcyanation of aldehydes by a variety of catalyst systems.[8]

On the other hand, chiral Schiff base complexes of transition metals have been found to work as very effective catalysts for asymmetric cyclopropanation,[9] epoxidation of olefins,[10] and oxidation of sulfides.[11] Here, we describe a novel and efficient procedure for highly enantioselective addition of trimethylsilyl cyanide to a variety of aldehydes catalyzed by chiral Schiff base–titanium alkoxide complexes.[12]

Results and Discussion

Preparation of Chiral Schiff Base–Titanium Alkoxide Catalysts. The chiral Schiff bases were prepared by the condensation of 2-hydroxybenzaldehyde (salicylaldehyde) (**1a**) or 3-tert-butyl-2-hydroxybenzaldehyde (**1b**) with various chiral β-amino alcohols in methanol (eq 1



(eq. 1)

2a–2h

and Table I). The chiral Schiff base–titanium isopro-

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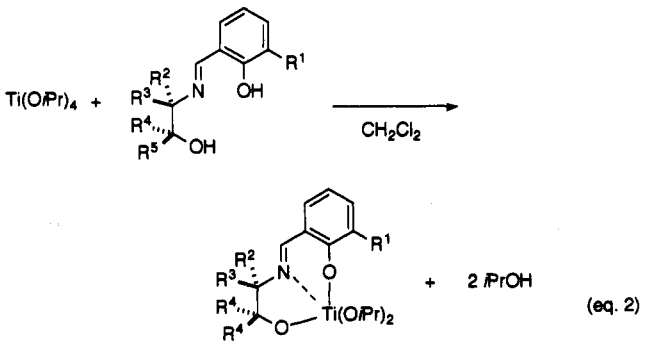
Table I. Chiral Schiff Bases Used in Asymmetric Trimethylsilylcyanation of Aldehydes

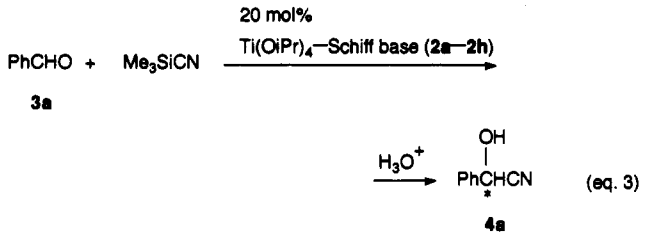
Schiff base	R^1	R^2	R^3	R^4	$[\alpha]^{24}_D$ (c, solvent)
(*S*)-**2a**	H	*i*-Pr	H	H	−26.2° (*c* 1.0, CH_3OH)
(*S*)-**2b**	H	*t*-Bu	H	H	−6.3° (*c* 0.5, C_2H_5OH)
(*S*)-**2c**	H	*i*-Pr	H	Ph	+80.7° (*c* 1.0, $CHCl_3$)
(*S*)-**2d**	*t*-Bu	Me	H	H	+44.1° (*c* 1.0, $CHCl_3$)
(*S*)-**2e**	*t*-Bu	*i*-Pr	H	H	+2.5° (*c* C_2H_5OH), −39.8° (*c* 1.0, $CHCl_3$)
(*S*)-**2f**	*t*-Bu	*t*-Bu	H	H	−3.8° (*c* 1.1, C_2H_5OH)
(*R*)-**2g**	*t*-Bu	H	Ph	H	+112.9° (*c* 1.3, $CHCl_3$)
(*S*)-**2h**	*t*-Bu	*i*-Pr	H	Ph	+84.2° (*c* 1.0, $CHCl_3$)

poxide catalyst was prepared by mixing an equimolar amount of chiral Schiff base and titanium tetraalkoxide (eq 2).



(eq. 2)

Asymmetric Trimethylsilylcyanation of Benzaldehydes Catalyzed by Chiral Schiff Base–Titanium Alkoxide Complexes. First, the reaction of benzaldehyde with trimethylsilyl cyanide was examined with a 20 mol % of the catalyst prepared in situ from a variety of chiral Schiff bases (**2a–2h**) and Ti(O-*i*-Pr)$_4$. A remarkable rate



(eq. 3)

enhancement was brought about by the addition of Schiff bases to Ti(O-*i*-Pr)$_4$-mediated silylcyanation of benzaldehyde.[13] For example, the silylcyanation of benzaldehyde catalyzed by the complex composed of Ti(O-*i*-Pr)$_4$ and chiral Schiff base **2e** proceeded several times faster than that catalyzed by Ti(O-*i*-Pr)$_4$ alone (20 mol % per aldehyde, at −25 °C, in dichloromethane), which was shown in Figure 1. The results for the asymmetric silylcyanation of benzaldehyde catalyzed by chiral Schiff bases–titanium alkoxide complexes are summarized in Table II. The product yields in the table are based on mandelonitrile isolated after hydrolysis with 1 N HCl, and the ee was determined by HPLC analysis of the corresponding MTPA ester.[14] The enantioselectivity was much influenced by the kinds of Schiff bases. Among the catalyst systems we examined, the combination of Ti(O-*i*-Pr)$_4$ and the Schiff base **2e** which was prepared by the reaction between 3-*tert*-butyl-2-hydroxybenzaldehyde (**1b**) and (*S*)-valinol gave the product in the highest optical yield (85% ee). Low reaction temperature was also an essential factor to obtain high enantioselectivity. For example, when the reaction with the above catalyst system was carried out at 0 °C in

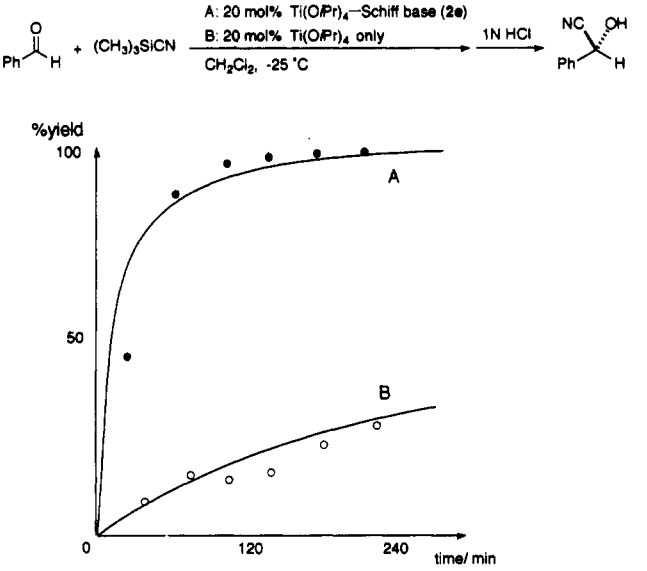


Figure 1. Rate of trimethylsilylcyanation of benzaldehyde catalyzed by Ti(O-*i*-Pr)$_4$ (○) and Ti(O-*i*-Pr)$_4$–Schiff base (**2e**) complex (●).

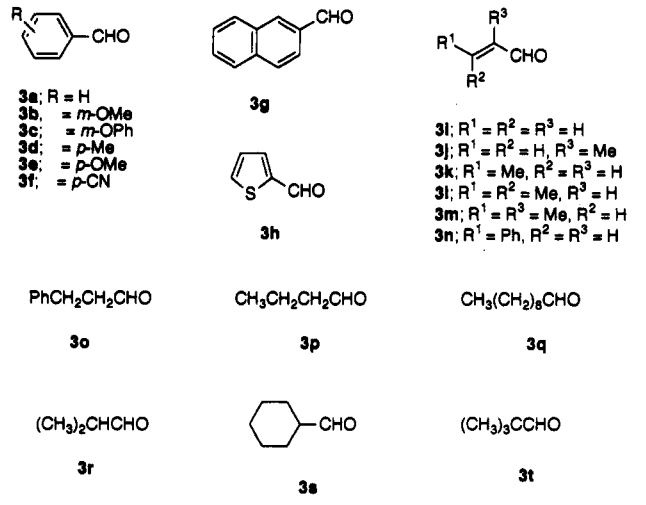


Figure 2.

Table II. Enantioselective Trimethylsilylcyanation of Benzaldehyde Catalyzed by Chiral Schiff Base–Titanium Alkoxide Complexes[a]

		condns		product	
entry	Schiff base	temp/°C	time/h	% yield[b]	% ee[c] (confign)[d]
1	(*S*)-**2a**	−80	36	69	22 (*S*)
2	(*S*)-**2b**	−78	36	40	40 (*S*)
3	(*S*)-**2c**	−78	36	28	60 (*R*)
4	(*S*)-**2d**	−80	36	60	60 (*R*)
5	(*S*)-**2e**	0	20	70	41 (*R*)
6		−30	44	90	67 (*R*)
7		−80	36	67	85 (*R*)
8	(*S*)-**2f**	−78	36	51	63 (*R*)
9	(*R*)-**2g**	−80	36	41	40 (*S*)
11	(*S*)-**2h**	−78	36	54	64 (*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.[4b]

(13) The rate enhancement brought by the addition of Schiff base was also observed in titanium tetraalkoxide catalyzed ring opening reaction of epoxides with trimethylsilyl cyanide: Hayashi, M.; Tamura, M.; Oguni, N. *Synlett* **1992**, 663.

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Table III. Enantioselective Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Schiff Base 2e–Titanium Alkoxide Complex[a]

		condns		product		
entry	aldehyde	temp/°C	time/h	% yield[b]	$[\alpha]_D$ (c, solvent)	% ee[c] (confign)[d]
1	3-methoxybenzaldehyde (**3b**)	−80	36	76	+22.8° (c 1.5, $CHCl_3$)	56 (*R*)[e]
2	3-phenoxybenzaldehyde (**3c**)	−80	36	67	+13.5° (c 1.5, C_6H_6)	79 (*R*)[f]
4	4-methylbenzaldehyde (**3d**)	−78	36	68	+36.4° (c 1.1, $CHCl_3$)	71 (*R*)[e]
5	4-methoxybenzaldehyde (**3e**)	−78	36	62	+41.7° (c 1.4, $CHCl_3$)	91 (*R*)[e]
6	4-cyanobenzaldehyde (**3f**)	−80	36	60	+6.5° (c 1.5, $CHCl_3$)	20 (*R*)[e]
7	2-naphthaldehyde (**3g**)	−80	36	76	+10.9° (c 1.1, C_2H_5OH)	73 (*R*)[e]
8	2-thiophenecarboxaldehyde (**3h**)	−80	36	60	+64.1° (c 0.6, $CHCl_3$)	79 (*R*)[e]
9	acrolein (**3i**)	−80	36	54	−3.8° (c 0.8, $CHCl_3$)	63 (*R*)[g]
10	methacrolein (**3j**)	−80	36	62	+5.7° (c 1.3, $CHCl_3$)	85 (*R*)[h]
11	(*E*)-crotonaldehyde (**3k**)	−80	36	70	−35.7° (c 0.3, $CHCl_3$)	89 (*R*)[e]
12	3-methyl-2-butenal (**3l**)	−80	40	63	−94.2° (c 0.7, $CHCl_3$)	89 (*R*)[g]
13	*trans*-2-methyl-2-butenal (**3m**)	−80	40	68	−24.8° (c 1.0, $CHCl_3$)	96 (*R*)[g]
14	(*E*)-cinnamaldehyde (**3n**)	−80	36	81	+19.2° (c 1.9, $CHCl_3$)	72 (*R*)[e]
15	3-phenylpropionaldehyde (**3o**)	−78	36	85	−2.6 (c 2.7, $CHCl_3$)	40 (*R*)[i]
16	*n*-butylaldehyde (**3p**)	−78	12	73	+13.1° (c 0.9, $CHCl_3$)	57 (*R*)[e]
17	*n*-decylaldehyde (**3q**)	−78	36	48	+6.7° (c 1.3, $CHCl_3$)	66 (*R*)[i]
18	2-methylpropionaldehyde (**3r**)	−80	36	70	+4.2° (c 1.3, $CHCl_3$)	34 (*R*)[e]
19	cyclohexylcarboxaldehyde (**3s**)	−80	12	72	+6.1° (c 3.8, $CHCl_3$)	65 (*R*)[i]
20	trimethylacetaldehyde (**3t**)	−80	36	58	+14.5° (c 1.0, $CHCl_3$)	70 (*R*)[e]

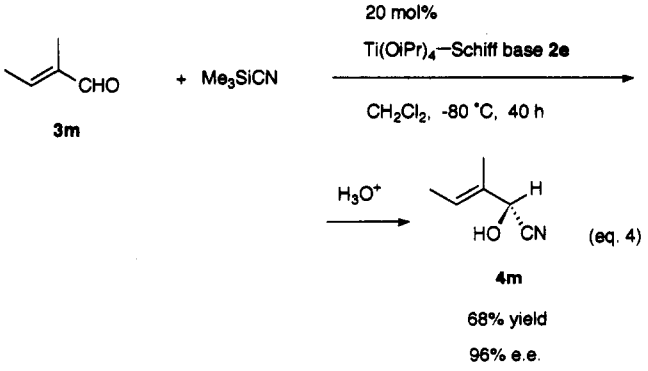
[a] All reactions were carried out in dichloromethane using 20 mol % of chiral Schiff base (**2e**)–titanium isopropoxide complex. [b] Isolated yield. [c] Determined by HPLC analyses of their MTPA esters. [d] All absolute configurations were determined by comparison of the sign of optical rotation values with those in the literature unless otherwise noted. [e] Reference 17. [f] Reference 8f. [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 18. [i] Reference 5b.

dichloromethane, the optical yield of the product was only 41% ee, whereas reaction at −30 °C increased the ee of the product up to 67% ee; furthermore, 85% ee was obtained by the reaction at −78 °C. The optimum amount of chiral titanium catalyst was 20 mol % per aldehyde. Interestingly, the use of an equimolar amount (100 mol %) of chiral titanium complex caused a decrease in enantioselectivity (22% ee), although the reaction rate increased.

The effect of solvent on enantioselectivity was also investigated. The reaction in toluene at −78 °C for 58 h gave the product in 4% ee (75% yield). The results in other solvents were as follows: diethyl ether (60% yield, 22% ee, at −78 °C, for 20 h), chloroform (32% yield, 9% ee, −78 °C, 20 h), dichloromethane (67% yield, 85% ee, −78 °C, 36 h), and acetonitrile (92% yield, 31% ee, −40 °C, 12 h). In addition to the importance of solvent effect, the selection of titanium alkoxide was also significant; that is, among the titanium alkoxide we examined, $Ti(O\text{-}i\text{-}Pr)_4$ exhibited the highest reactivity and enantioselectivity [cf. $Ti(OEt)_4$ (36% yield, 43% ee, −78 °C, 36 h), $Ti(O\text{-}t\text{-}Bu)_4$ (29% yield, 12% ee, −78 °C, 58 h)]. Furthermore, the enantioselectivity of the reaction was influenced considerably by the concentration of the reactants. That is, when higher concentrations were employed, higher optical yields were attained. These results were in quite contrast to the titanium alkoxide–chiral dialkyl tartrate system which afforded excellent enantioselectivity at very low concentration of the reactants.[7] At a substrate concentration of 1.0 M and catalyst concentration of 0.20 M, mandelonitrile was obtained in 85% ee, and in comparatively good chemical yield.

The stereochemical outcome would be very interesting. As shown in entries 1 and 7 in Table II, when the Schiff base prepared from (*S*)-valinol and 2-hydroxybenzaldehyde was used, (*S*)-mandelonitrile was obtained in 22% ee, whereas the reaction using the Schiff base deriving from (*S*)-valinol and 3-*tert*-butyl-2-hydroxybenzaldehyde afforded the product bearing (*R*)-configuration in 85% ee. A similar phenomenon was also observed in the reaction using Schiff bases prepared by the reaction of (*S*)-*tert*-leucinol with 2-hydroxybenzaldehyde and its *tert*-butyl derivative (entries 2 and 8).

Asymmetric Trimethylsilylcyanation of a Variety of Aldehydes. 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 catalyst composed of $Ti(O\text{-}i\text{-}Pr)_4$ and Schiff base **2e**, which was the best catalyst system for benzaldehyde. As shown in Table III, most aromatic aldehydes were silylcyanated in good to excellent enantiomeric excesses. Benzaldehyde derivatives with electron-withdrawing substituents such as cyano group (**3f**), however, resulted in lower ee values. Among the aromatic aldehydes, the highest enantiomeric excess was achieved in the silylcyanation of 4-methoxybenzaldehyde (91% ee). Generally, α,β-unsaturated aldehydes (**3i–3n**) were silylcyanated to afford the corresponding α-cyano allylic alcohols in high optical yield, especially (*E*)-2-hydroxy-3-methylpentanenitrile was obtained in 96% ee by silylcyanation of *trans*-2-methyl-2-butenal (tiglic aldehyde) (eq 4). Aliphatic aldehydes with



(eq. 4)

a nonconjugated hydrocarbon substituent (**3o–3t**) were generally silylcyanated in moderate level of enantioselectivity. As for the stereochemistry of the products, when the reaction was carried out using $Ti(O\text{-}i\text{-}Pr)_4$–Schiff base **2e** catalyst system, the absolute configuration of the

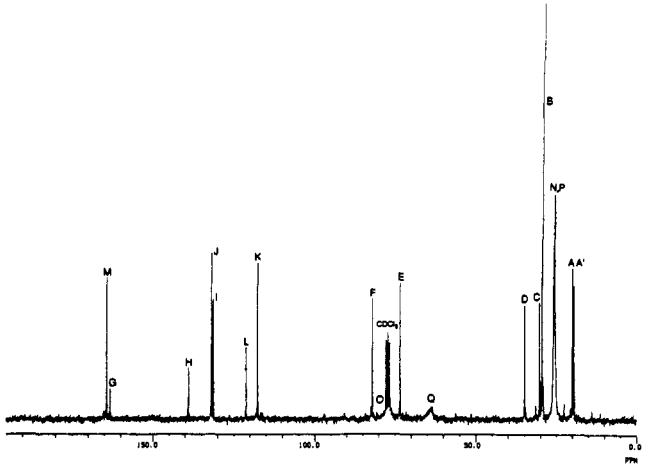


Figure 3. ^{13}C NMR spectrum of titanium isopropoxide–chiral Schiff base **2e** (1:1) complex.

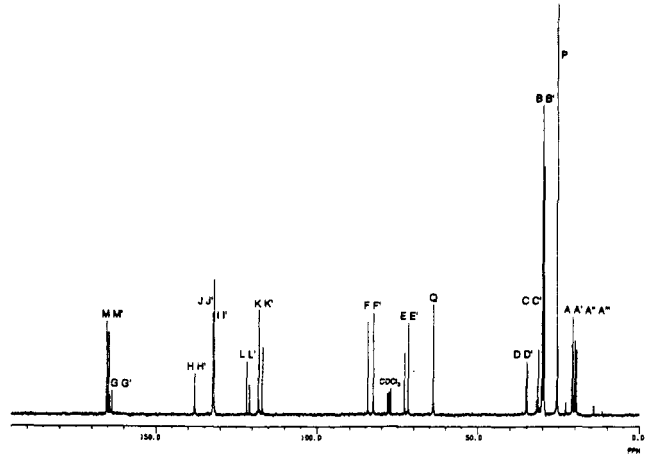
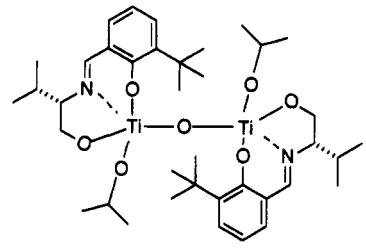


Figure 4. ^{13}C NMR spectrum of titanium isopropoxide–chiral Schiff base **2e** (1:2) complex.

cyanohydrins was always *R*, as determined by comparison of the optical rotation values (sign) of the obtained cyanohydrins or its derivatives with those in the literature (see Experimental Section).

Catalyst Structure. Sharpless and Finn reported that the dominant species in equimolar mixtures of titanium tetraalkoxide and dialkyl tartrate esters are dimeric [Ti(tartrate)(OR)$_2$]$_2$ by molecular weight determination, mass spectra of an alcohol-free compound, and other spectroscopic data.[15] In order to obtain the information on the solution structure of titanium alkoxide–Schiff base complex, we first measured the ^{13}C NMR spectra of 1:1 and 1:2 mixtures of Ti(O-*i*-Pr)$_4$ and Schiff base **2e**, which showed a single set of resonances, respectively (Figures 3 and 4). Table IV lists the peak assignments for Schiff base **2e**, titanium isopropoxide–Schiff base complex (1:1 and 1:2 ratio product).

We also measured field desorption (FD) mass spectra of the alkoxy exchange reaction product of Ti(O-*i*-Pr)$_4$ and Schiff base **2e** (1:1 molar ratio mixture), which showed the presence of monomeric complex **5a** (*m/z* 427) and **5b** (*m/z* 570) in an intensity of about 1.3:1 (Figure 5). This observation is inconsistent with the ^{13}C NMR spectrum which shows no peaks for the 1:2 ratio product **5b** in the spectrum of the 1:1 molar ratio mixture. So complex **5b** might be formed under the condition of measuring mass spectra. The peak at *m/z* 752 with low intensity is assumed to be originated from the compound **5c**. It should be noted



5c

m/z 752

that no peaks originating from dimeric species of **5a** were observed in the FD mass spectrum of 1:1 ratio product. Furthermore, the 1:2 molar ratio product of Ti(O-*i*-Pr)$_4$ and Schiff base **2e** showed only one peak at *m/z* 570 corresponding to **5b** in the FD mass spectrum.

We also determined the molecular weight of alcohol free Schiff base–titanium isopropoxide by a cryoscopic method in benzene. It was found that the molecular weight was not dependent on the concentration of solution and ranged from 318 to 385 for the 1:1 molar ratio product of Schiff base and Ti(O-*i*-Pr)$_4$ and from 550 to 590 for the 1:2 ratio product. These results indicate that the Schiff base–titanium alkoxide complex exists as a monomeric form in solution (Tables V and VI).

On the basis of the above spectroscopic results and the experimental fact that 1:2 molar ratio product **5b** had no catalytic activity in silylcyanation of aldehydes, we assume complex **5a** to be coordinately unsaturated in the active catalyst for asymmetric silylcyanation of aldehydes.

Reaction Mechanism. The catalytic asymmetric trimethylsilylcyanation of aldehydes is initiated by the coordination of aldehydes to coordinately unsaturated chiral Schiff base–titanium alkoxide complex **5a**. Trimethylsilyl cyanide will then react with the aldehyde coordinated to titanium. Actually, hydrogen cyanide produced by the reaction of trimethylsilyl cyanide with isopropyl alcohol is also effective as a cyanating reagent. The stereochemical outcome observed in this asymmetric silylcyanation could be reasonably explained by considering the mechanism shown in Figure 6. When Schiff base **2e**–titanium isopropoxide complex was used as a catalyst, trimethylsilyl cyanide (or hydrogen cyanide) will attack the *si* face of the activated aldehydes leading to the formation of *R*-configurational cyanohydrins, since the *re* face of aldehydes would be blocked by the *tert*-butyl substituent in **2e**. On the other hand, when Schiff base **2a** was employed for the reaction, the *si* face would be less hindered than the *re* face due to the isopropyl group in **2a**; therefore, cyanating reagent will attack from the *re* face of the aldehydes to produce the *S*-configurational cyanohydrins.

In conclusion, asymmetric silylcyanation of a variety of aldehydes with a catalyst prepared from Ti(O-*i*-Pr)$_4$ and chiral Schiff bases possessing *tert*-butyl group provides a novel and efficient method for the synthesis of optically active cyanohydrins.

Experimental Section

General. All melting points were uncorrected. ^1H and ^{13}C NMR were measured at 250 and 62.9 MHz, respectively. Field desorption (FD) mass spectra were measured on Accel Volt, 8

(15) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113.

Scheme I

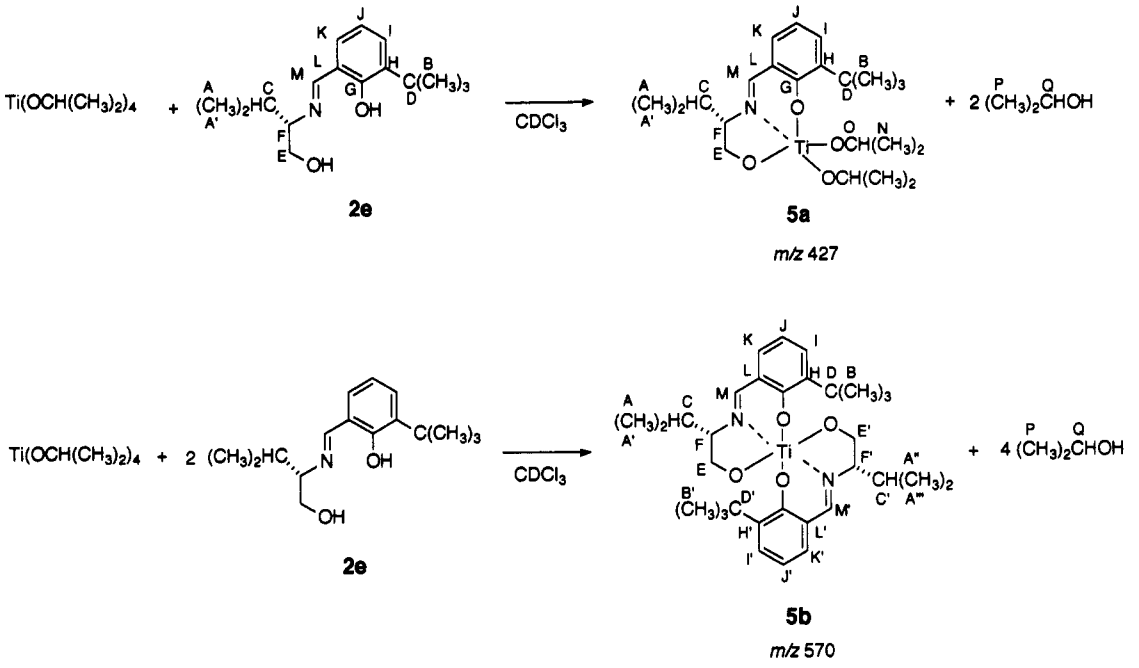


Table IV. ^{13}C NMR Data for Schiff Base (2e) and Schiff Base–Titanium Alkoxide Complexes[a]

Schiff base 2e		Ti(O-*i*-Pr)$_4$–Schiff base 2e (1:1) in situ		Ti(O-*i*-Pr)$_4$–Schiff base 2e (1:2) in situ	
carbon	δ (ppm)	carbon	δ (ppm)	carbon	δ (ppm)
A, A′	19.1, 20.4	A, A′	19.4, 19.9	A, A′, A″, A‴	19.9, 20.4, 21.1, 21.2
B	29.9	B	29.3	B, B′	30.0, 30.4
C	30.5	C	30.1	C, C′	30.9, 31.8
D	35.3	D	34.8	D, D′	35.2, 35.5
E	64.9	E	73.4	E, E′	72.1, 73.3
F	78.1	F	82.0	F, F′	83.0, 84.8
G	161.1	G	162.9	G, G′	164.1, 164.8
H	137.9	H	138.8	H, H′	138.3, 138.4
I	129.9	I	131.1	I, I′	132.5
J	130.3	J	131.7	J, J′	132.7, 132.8
K	118.3	K	117.4	K, K′	117.3, 118.4
L	119.1	L	121.0	L, L′	121.2, 122.1
M	166.9	M	164.1	M, M′	165.2, 165.8
		N	25.3		
		O	78		
		P	25.3	P	25.9
		Q	64	Q	64.3

[a] Data were recorded in $CDCl_3$ at 62.87 Hz. The δ values (parts per million downfield from Me_4Si) are referenced to the center signal of the solvent triplet ($CDCl_3$) at δ 77.00 ppm.

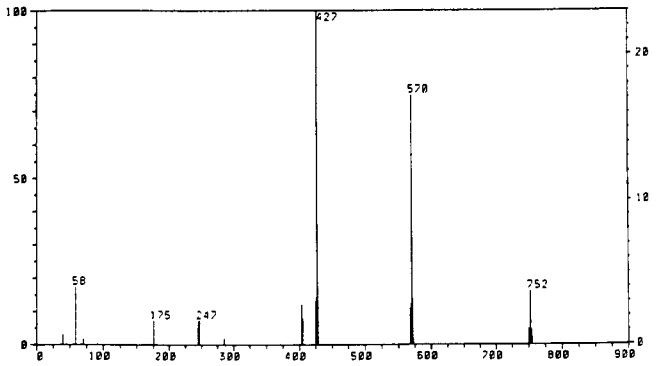


Figure 5. Field desorption (FD) mass spectrum of titanium alkoxide–chiral Schiff base **2e** (1:1) complex.

kV, emitter (carbon) current, 0–45 mA (15 mA/min). Optical rotations were measured 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 100 UV detector and a YMC Packed Column A-003 S-5 120A.

Table V. Molecular Weight Determination of the Alcohol-Free Product of Ti(O-*i*-Pr)$_4$ and Schiff Base 2e Mixture (1:1 Molar Ratio) by Cryoscopic Method in Benzene[a]

entry	ω[b]	ΔT[c]	K_f[d]	MW[e]	AN[f]
1	7.5	0.12	5.41	326	0.76
2	9.2	0.15	5.41	333	0.79
3	14.8	0.26	5.41	318	0.75
4	17.0	0.31	5.41	298	0.70
5	22.4	0.34	5.41	356	0.81
6	29.9	0.42	5.41	385	0.90
7	31.8	0.50	5.41	347	0.81
8	38.5	0.59	5.41	353	0.83

[a] The procedure for molecular weight determination and preparation of the sample are described in the Experimental Section. [b] Weight (g) of solute in 1000 g of benzene. [c] Depression (°C). [d] Molar depression of the solvent (benzene). [e] Molecular weight. [f] AN = association number, MW = 427 (n = 1 for complex **5a**).

Materials. CH_2Cl_2, $CHCl_3$, and acetonitrile were distilled from P_4O_{10}. Toluene, diethyl ether, and benzene were distilled from sodium benzophenone ketyl under argon. The aldehydes **3a–3e, 3k, 3n,** and **3o** were purchased from Nacalai Tesque. 2-*tert*-

Table VI. Molecular Weight Determination of the Alcohol-Free Product of Ti(O-*i*-Pr)$_4$ and Schiff Base 2e Mixture (1:2 Molar Ratio) by Cryoscopic Method in Benzene[a]

entry	ω^b	ΔT^c	K_f^d	MW[e]	AN[f]
1	7.6	0.07	5.41	589	1.03
2	15.3	0.15	5.41	550	0.97
3	22.9	0.22	5.41	563	0.99
4	30.5	0.28	5.41	590	1.03
5	38.1	0.36	5.41	573	1.00

[a] The procedure for molecular weight determination and preparation of the sample are described in the Experimental Section. [b] Weight (g) of solute in 1000 g of benzene. [c] Depression (°C). [d] Molar depression of the solvent (benzene). [e] Molecular weight. [f] AN = association number, MW = 570 (n = 1 for complex **5b**).

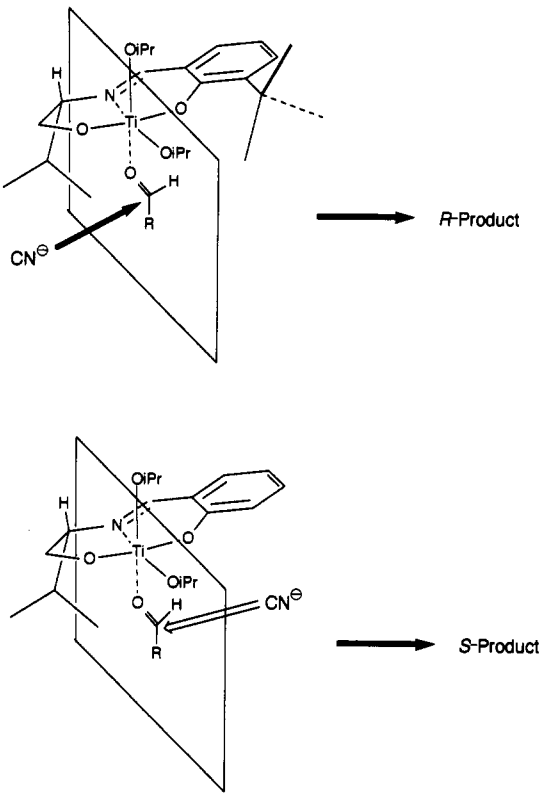


Figure 6.

Butylphenol, trimethylsilyl cyanide, and the aldehydes **3f–3j**, **3l**, **3m**, **3o–3r**, and **3t** were purchased from Tokyo Kasei Co., and aldehyde **3s** was purchased from Aldrich and distilled before use.

3-*tert*-Butyl-2-hydroxybenzaldehyde (1b). This compound was prepared according to the modified procedure reported by Casnati et al.[16] Ethyl bromide (29.18 g, 268 mmol) in ether (40 mL) was added to Mg (4.90 g, 202 mmol) and diethyl ether (200 mL), and then 2-*tert*-butylphenol (26.71 g, 178 mmol) in ether (50 mL) was added dropwise with stirring at rt. After removal of ether by distillation as completely as possible, benzene (1 L), HMPA (35.84 g, 200 mmol), and paraformaldehyde (15.03 g, 501 mmol) were added and stirred at 80 °C for 12 h. After cooling, the mixture was acidified with 10% HCl and extracted with diethyl ether (300 mL × 3). The combined extracts were washed with brine (100 mL) and then dried over Na_2SO_4. After evaporation of the volatiles, the residue was distilled (bp 75–77 °C/5 mmHg) to give **1b** (13.09 g, 41.3%): ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 6.9–7.8 (m, 3 H), 9.87 (s, 1 H), 11.79 (s, 1 H).

(*S*)-2-(*N*-Salicylideneamino)-3-methyl-1-butanol (2a). A mixture of methanol (15 mL), (*S*)-2-amino-3-methyl-1-butanol (1.00 g, 9.7 mmol), and 2-hydroxybenzaldehyde (1.48 g, 12.1 mmol) were refluxed for 4 h. The mixture was evaporated, and the obtained yellow solid was recrystallized from hexane–benzene (10:1) to give **2a** (1.88 g, 94%) as a yellow crystal: mp 107–108 °C; $[\alpha]^{25}_D$ −26.2° (*c* 1.0, CH_3OH); IR ν_{max} 3260, 2960, 2930, 1630, 1580, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.7 Hz, 3 H), 0.96 (d, J = 6.7 Hz, 3 H), 1.6 (br s, 1 H), 1.95 (sept, J = 6.7, 1 H), 1.9–2.0 (m, 1 H), 3.0–3.2 (m, 2 H), 3.7–4.0 (m, 1 H), 6.9–7.0 (m, 1 H), 7.3–7.4 (m, 2 H), 8.37 (s, 1 H), 13.4 (br s, 1 H). 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*-Salicylideneamino)-3,3-dimethyl-1-butanol (2b). A mixture of methanol (5 mL), (*S*)-2-amino-3,3-dimethyl-1-butanol (0.14 g, 1.19 mmol), 2-hydroxybenzaldehyde (0.16 g, 1.19 mmol), and anhydrous Na_2SO_4 (0.84 g) was refluxed for 2 h. The mixture was filtered off through a pad of Celite, and then the filtrates were evaporated. The obtained yellow solid was recrystallized from a mixture of petroleum ether–benzene (5:1) to give **2b** (0.13 g, 50%) as yellow crystalline solid: mp 107–108 °C; $[\alpha]^{25}_D$ −6.3° (*c* 0.5, C_2H_5OH); IR ν_{max} 3290, 2970, 2870, 1630, 1580, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 9 H), 1.7 (br s, 1 H), 2.88 (dd, J = 3.2 Hz, 9.2 Hz, 1 H), 3.66 (dd, J = 11.0, 9.2 Hz, 1 H), 3.87 (dd, J = 3.2, 11.0 Hz, 1 H), 6.8–7.0 (m, 2 H), 7.2–7.3 (m, 2 H), 8.28 (s, 1 H), 13.5 (br s, 1 H). 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.

The preparation of **2c–2h** was carried out as described for **2b**.

(*S*)-2-(*N*-Salicylideneamino)-3-methyl-1,1-diphenyl-1-butanol (2c). A mixture of methanol, (*S*)-2-amino-1,1-diphenyl-3-methyl-1-butanol, 2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 10 h. After evaporation the obtained yellow solid was recrystallized from petroleum ether to give **2c** (1.15 g, 82%) as a yellow crystalline solid: mp 174 °C; $[\alpha]^{23}_D$ +80.7° (*c* 1.0, $CHCl_3$); IR ν_{max} 3580, 2960, 2870, 1630, 1580, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (d, J = 6.7 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 2.1 (sept, J = 6.7 Hz, 1 H), 2.84 (s, 1 H), 4.06 (s, 1 H), 6.8–7.6 (m, 14 H), 8.17 (s, 1 H), 12.9 (br s, 1 H). 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*-(3′-*tert*-Butylsalicylidene)amino]-1-propanol (2d). A mixture of methanol, (*S*)-2-amino-1-propanol, 3-*tert*-butyl-2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 60 h. After evaporation, the residue was chromatographed on silica gel [eluent, hexane–ethyl acetate (3:1)] to give **2d** (1.3 g, 48%): $[\alpha]^{23}_D$ +44.1° (*c* 1.0, $CHCl_3$); IR ν_{max} 3360, 3060, 2960, 2740, 1630, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 6.1 Hz, 3 H), 1.44 (s, 9 H), 1.6 (br s, 1 H), 3.5 (m, 1 H), 3.71 (d, J = 4.9 Hz, 2 H), 6.83 (t, J = 7.3 Hz, 1 H), 7.13 (d, J = 7.3 Hz, 1 H), 7.35 (d, J = 7.3 Hz, 1 H), 8.43 (s, 1 H), 13.8 (br s, 1 H). 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.

(*S*)-2-[*N*-(3′-*tert*-Butylsalicylidene)amino]-3-methyl-1-butanol (2e). A mixture of methanol, (*S*)-2-amino-3-methyl-1-butanol, 3-*tert*-butyl-2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 63 h. After evaporation, the residue was chromatographed on silica gel [eluent, hexane–ethyl acetate (5:1)], followed by recrystallization from petroleum ether to give **2e** (9.76 g, 74%) as yellow needles: mp 57–58 °C; $[\alpha]^{24}_D$ −39.8° (*c* 1.0, $CHCl_3$), +2.5° (*c* 1.0, C_2H_5OH); IR ν_{max} 3250, 2960, 1630, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 6.7 Hz, 3 H), 0.97 (d, J = 6.7 Hz, 3 H), 1.4 (s, 9 H), 1.6 (br s, 1 H), 2.0 (m, 1 H), 3.0 (m, 1 H), 3.8 (m, 2 H), 6.8–7.5 (m, 3 H), 8.37 (s, 1 H), 13.5–14.0 (br s, 1 H). 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]-3,3-dimethyl-1-butanol (2f). A mixture of methanol, (*S*)-2-amino-3,3′-dimethyl-1-butanol, 3-*tert*-butyl-2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 18 h. After evaporation, the residue was chromatographed on silica gel [eluent, hexane–ethyl acetate (5:1)] to give **2f** (0.49 g, 70%) as a yellow crystalline solid: mp 55–57 °C; $[\alpha]^{24}_D$ −3.8° (*c* 1.1, C_2H_5OH); IR ν_{max} 3400, 2960, 2870, 1630, 1480, 1270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 9 H), 1.45 (s, 9 H), 1.6 (br s, 1 H), 2.94 (dd, J = 3.1, 9.2 Hz, 1 H), 3.77 (t, J = 9.2 Hz, 1 H), 3.94 (dd, J = 3.1, 9.2 Hz, 1 H), 6.84 (t, J = 9.2 Hz, 1 H), 7.15 (d, J = 7.9 Hz, 1 H), 7.36 (d, J = 7.9 Hz, 1 H), 8.36 (s, 1 H), 13.8 (br s, 1 H). 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.

(16) Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, A.; Puglia, G.; Sartori, G.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 319.

(*S*)-2-[*N*-(3′-*tert*-Butylsalicylidene)amino]-2-phenyl-1-ethanol (2g). A mixture of methanol, (*S*)-2-amino-2-phenyl-1-ethanol, 3-*tert*-butyl-2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 72 h. After evaporation, the residue was chromatographed on silica gel [eluent, hexane–ethyl acetate (5:1)] to give **2g** (8.24 g, 76%) as yellow oil: $[\alpha]^{24}_D$ +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, 9 H), 2.4 (br s, 1 H), 3.85 (d, J = 7.3 Hz, 2 H), 4.40 (t, J = 6.1 Hz, 1 H), 6.81 (t, J = 7.9 Hz, 1 H), 7.15 (d, J = 7.9 Hz, 1 H), 7.2–7.4 (m, 6 H), 8.43 (s, 1 H), 13.8 (br s, 1 H). 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.

(*S*)-2-[*N*-(3′-*tert*-Butylsalicylidene)amino]-3-methyl-1,1-diphenyl-1-butanol (2h). A mixture of methanol, (*S*)-2-amino-1,1-diphenyl-3-methyl-1-butanol, 3-*tert*-butyl-2-hydroxybenzaldehyde, and anhydrous Na_2SO_4 was refluxed for 69 h. After evaporation, the residue was chromatographed on silica gel [eluent, hexane–ethyl acetate (5:1)] followed by recrystallization from petroleum ether to give **2h** (0.52 g, 64%) as yellow crystalline solid: mp 92–93 °C; $[\alpha]^{24}_D$ +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, 3 H), 1.02 (d, J = 6.7 Hz, 3 H), 1.41 (s, 9 H), 2.1 (m, 1 H), 2.95 (s, 1 H), 4.07 (s, 1 H), 6.7–7.6 (m, 13 H), 8.22 (s, 1 H), 13.3 (br s, 1 H). 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.

Determination of the Cyanohydrin Enantiomeric Excess (ee). The ee for each of the cyanohydrin trimethylsilyl ethers was determined by HPLC analysis of the corresponding (*R*)-(+)-MTPA (α-methoxy-α-(trifluoromethyl)phenylacetic acid) esters[14] after hydrolysis by 1 N HCl. The procedure for the preparation of MTPA esters was as follows: To a CH_2Cl_2 (1 mL) solution of cyanohydrin (10 mg) was added (*R*)-(+)-MTPACl (10 mg) and pyridine (10 mg) at rt. The mixture was stirred at this temperature for 1 h after which it was poured into the mixture of ethyl acetate (10 mL) and 1 N HCl solution (10 mL × 2) and extracted with ethyl acetate (10 mL × 2). The combined extracts were washed with brine (10 mL) and concentrated, and then the residue was chromatographed on a silica gel column [eluent, benzene] to afford the corresponding cyanohydrin MTPA esters, which were analyzed by HPLC.

2-Hydroxy-2-phenylacetonitrile (4a). In a flame-dried Schlenk tube were placed Schiff base **3e** (145 mg, 0.55 mmol) and CH_2Cl_2 (2.5 mL). To this solution was added $Ti(O\text{-}i\text{-}Pr)_4$ (0.15 mL, 0.50 mmol) at rt and and the resulting solution stirred for 1 h, and then the mixture was cooled to −80 °C. Freshly distilled benzaldehyde (**3a**) (261 mg, 2.46 mmol) and trimethylsilyl cyanide (0.75 mL, 5.62 mmol) were added to the solution, and the whole was stored for 36 h at this temperature. After this, the mixture was poured into a mixture of 1 N HCl (30 mL) and ethyl acetate (150 mL) and stirred vigorously for 6 h at rt. The mixture was then extracted with ethyl acetate (50 mL × 3), and the combined extracts were washed with saturated $NaHCO_3$ (50 mL × 4) and brine (50 mL × 2), dried over Na_2SO_4, and then evaporated. The residue was column chromatographed on silica gel [eluent, hexane–ethyl acetate (5:1)] to give *R*-rich-**5a** (219 mg, 67%): $[\alpha]^{24}_D$ +36.8° (*c* 2.0, $CHCl_3$) [lit.[5] $[\alpha]^{21}_D$ +45.5° (*c* 3.53, $CHCl_3$) for *R*-enantiomer in 96% ee]; IR ν_{max} 3430, 2260, 1700, 1600, 1490, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.9 (br s, 1 H), 5.55 (s, 1 H), 7.4–7.6 (m, 5 H). The ee of the product was determined as 85% ee by HPLC analysis of its MTPA ester as described above: t_R of *R*-isomer, 13 min; t_R of *S*-isomer, 15 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

The reaction was carried out as described for **3a** and was performed for aldehydes **3b–3t** (2.5 mmol scale).

2-Hydroxy-2-(3-methoxyphenyl)acetonitrile (4b). *R*-rich-**4b** (306 mg, 76%): $[\alpha]^{24}_D$ +22.8° (*c* 1.5, $CHCl_3$) [lit.[17] $[\alpha]^{25}_D$ +36.9° (*c* 1.6, $CHCl_3$) for *R* enantiomer in 90% ee]; IR ν_{max} 3440, 3010, 2940, 2250, 1600, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.1 (br s, 1 H), 3.83 (s, 3 H), 5.51 (s, 1 H), 6.9–7.4 (m, 4 H). The ee of the product was determined as 56% ee by HPLC analysis of its MTPA ester: The t_R of *R*-isomer, 30 min; t_R of *S*-isomer, 37 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min)].

2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile (4c). *R*-rich-**4c** (375 mg, 67%): $[\alpha]^{24}_D$ +13.5° (*c* 1.5, C_6H_6) [lit.[8f] $[\alpha]^{25}_D$ −17.5° (*c* 0.8, C_6H_6) for *S* enantiomer in 96.8% ee]; IR ν_{max} 3430, 3070, 2250, 1960, 1690, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6 (br s, 1 H), 5.47 (s, 1 H), 7.0–7.4 (m, 9 H). The ee of the product was determined as 79% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 19 min; t_R of *S*-isomer, 22 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-2-(4-methylphenyl)acetonitrile (4d). *R*-rich-**4d** (250 mg, 68%). $[\alpha]^{24}_D$ +36.4° (*c* 1.1, $CHCl_3$) [lit.[17] $[\alpha]^{25}_D$ +47.4° (*c* 1.8, $CHCl_3$) for *R* isomer in 92% ee]; IR ν_{max} 3440, 3030, 2920, 2250, 1680, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 3.2 (br s, 1 H), 5.39 (s, 1 H), 7.15 (d, J = 8.5 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H). The ee of the product was determined as 71% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 11 min; t_R of *S*-isomer, 12 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-2-(4-methoxyphenyl)acetonitrile (4e). *R*-rich-**4e** (253 mg, 62%): $[\alpha]^{24}_D$ +41.7° (*c* 1.4, $CHCl_3$) [lit.[17] $[\alpha]^{25}_D$ +36.3° (*c* 1.0, $CHCl_3$) for *R* isomer in 83% ee]; IR ν_{max} 3430, 3010, 2940, 2840, 2250, 1710, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7 (br s, 1 H), 3.84 (s, 3 H), 5.49 (s, 1 H), 6.96 (d, J = 8.5 Hz, 2 H), 7.46 (d, J = 8.5 Hz, 2 H). The ee of the product was determined as 91% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 17 min; t_R of *S*-isomer, 20 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-2-(4-cyanophenyl)acetonitrile (4f). *R*-rich-**4f** (237 mg, 60%): $[\alpha]^{24}_D$ +6.5° (*c* 1.5, $CHCl_3$) [lit.[17] $[\alpha]_D$ +16.6° (*c* 0.8, $CHCl_3$) for *R* isomer in 52% ee]; IR ν_{max} 3460, 2920, 2230, 1610, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.2 (br s, 1 H), 5.65 (s, 1 H), 7.67 (d, J = 8.5 Hz, 2 H), 7.75 (d, J = 8.5 Hz, 2 H). The ee of the product was calculated as 20% ee by comparison of the rotation values in the literature.[17]

2-Hydroxy-2-naphthylacetonitrile (4g). *R*-rich-**4g** (343 mg, 76%): $[\alpha]^{24}_D$ +10.9° (*c* 1.1, C_2H_5OH) [lit.[17] $[\alpha]_D$ +26.4° (*c* 0.522, $CHCl_3$) for *R* isomer in 86% ee]; IR ν_{max} 3480, 3060, 2930, 2390, 2250, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.0 (br s, 1 H), 5.70 (s, 1 H), 7.5–7.6 (m, 3 H), 7.8–8.0 (m, 3 H), 8.05 (s, 1 H). The ee of the product was determined as 73% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 13 min; t_R of *S*-isomer, 15 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-2-(2-thienyl)acetonitrile (4h). *R*-rich-**4h** (206 mg, 60%): $[\alpha]^{24}_D$ +64.1° (*c* 0.6, $CHCl_3$) [lit.[17] $[\alpha]_D$ +46.8° (*c* 2.5, $CHCl_3$) for *R* isomer in 58% ee]; IR ν_{max} 3440, 3110, 2960, 2900, 2250, 1880, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.1 (br s, 1 H), 5.74 (s, 1 H), 7.0–7.1 (m, 1 H), 7.3–7.4 (m, 1 H), 7.4–7.5 (m, 1 H). The ee of the product was determined as 79% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 15 min; t_R of *S*-isomer, 17 min [hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-3-butenenitrile (4i). *R*-rich-**4i** (112 mg, 54%): $[\alpha]^{24}_D$ −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, 1 H), 5.0 (ddd, J = 4.0, 1.2, 1.2 Hz, 1 H), 5.4 (ddd, J = 1.2, 9.0, 1.2 Hz, 1 H), 5.6 (ddd, J = 1.2, 17.0, 1.2 Hz, 1 H), 6.0 (ddd, J = 9.0, 17.0, 4.0 Hz, 1 H). The ee of the product was determined as 63% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 18 min; t_R of *S*-isomer, 24 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-3-methyl-3-butenenitrile (4j). *R*-rich-**4j** (150 mg, 62%): $[\alpha]^{24}_D$ +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, 3 H), 4.9 (br s, 1 H), 4.88 (s, 1 H), 5.1 (m, 1 H), 5.3 (m, 1 H). The ee of the product was determined as 85% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 12 min; t_R of *S*-isomer, 16 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min]. The absolute configuration was determined as *R* by comparison of the optical rotation values after conversion into (*R*)-methyl 2-hydroxy-3-methylbutyrate.[18]

(*E*)-2-Hydroxy-3-pentenenitrile (4k). *R*-rich-**4k** (170 mg, 70%): $[\alpha]^{24}_D$ −35.7° (*c* 0.3, $CHCl_3$) [lit.[16] $[\alpha]_D$ −4.9° (*c* 2.3, $CHCl_3$) for *R*-enantiomer in 11% ee]; IR ν_{max} 3430, 3040, 2980, 2250, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (dd, J = 6.1, 1.2 Hz, 3 H), 3.7 (br s, 1 H), 4.92 (dd, J = 1.2, 6.1 Hz, 1 H), 5.63 (m, 1 H), 6.1 (m, 1 H). The ee of the product was determined as 89% ee by HPLC

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analysis of its MTPA ester: t_R of *R*-isomer, 13 min; t_R of *S*-isomer, 17 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-4-methyl-3-pentenenitrile (4l). *R*-rich-**4l** (175 mg, 63%): $[\alpha]^{24}_D$ -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, 3 H), 1.80 (d, J = 1.2 Hz, 3 H), 3.5 (br s, 1 H), 5.1 (d, J = 8.5 Hz, 1 H), 5.4 (m, 1 H). The ee of the product was determined as 89% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 12 min; t_R of *S*-isomer, 15 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

(*E*)-2-Hydroxy-3-methyl-3-pentenenitrile (4m). *R*-rich-**4m** (189 mg, 68%): $[\alpha]^{24}_D$ -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, 3 H), 1.81 (d, J = 8.5 Hz, 3 H), 3.5 (br s, 1 H), 5.10 (d, J = 8.5 Hz, 1 H), 5.40 (m, 1 H). The ee of the product was determined as 96% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 11 min; t_R of *S*-isomer, 14 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

(*E*)-2-Hydroxy-4-phenyl-3-butenenitrile (4n). *R*-rich-**4n** (322 mg, 81%): $[\alpha]^{24}_D$ +19.2° (*c* 1.9, $CHCl_3$) [lit.[17] $[\alpha]_D$ +5.7° (*c* 1.4, $CHCl_3$) for *R*-enantiomer in 11% ee]; IR ν_{max} 3370, 3030, 2920, 2250, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7 (br s, 1 H), 5.16 (dd, J = 5.7, 1.1 Hz, 1 H), 6.25 (dd, J = 15.8, 5.7 Hz, 1 H), 6.93 (dd, J = 15.8, 1.1 Hz, 1 H), 7.3–7.5 (m, 5 H). The ee of the product was determined as 72% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer 18 min; t_R of *S*-isomer, 21 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-4-phenylbutanenitrile (4o). *R*-rich-**4o** (343 mg, 85%): $[\alpha]^{24}_D$ -2.6° (*c* 2.7, $CHCl_3$) [lit.[5b] $[\alpha]_D$ -6.79° (*c* 2.04, $CHCl_3$) for *R* enantiomer in 89% ee]; IR ν_{max} 3430, 3050, 2980, 2250, 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0–2.2 (m, 2 H), 2.8–2.9 (m, 2 H), 4.1 (br s, 1 H), 4.43 (t, J = 6.7 Hz, 1 H), 7.2–7.4 (m, 5 H). The ee of the product was determined as 40% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 16 min; t_R of *S*-isomer, 21 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxypentanenitrile (4p). *R*-rich-**4p** (181 mg, 73%): $[\alpha]^{24}_D$ +13.1° (*c* 0.9, $CHCl_3$) [lit.[17] $[\alpha]_D$ +5.5° (*c* 3.4, $CHCl_3$) for *R* enantiomer in 26% ee]; IR ν_{max} 3450, 2970, 2880, 2250, 1720, 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 7.3 Hz, 3 H), 1.3–2.1 (m, 4 H), 3.8 (br s, 1 H), 4.48 (t, J = 6.7 Hz, 1 H). The ee of the product was determined as 57% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer 12 min; t_R of *S*-isomer, 15 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxyundecanenitrile (4q). *R*-rich-**4q** (220 mg, 48%): $[\alpha]^{24}_D$ +6.7° (*c* 1.3, $CHCl_3$) [lit.[5b] $[\alpha]_D$ +7.9° (*c* 4.03, $CHCl_3$) for *R* enantiomer in 85% ee]; IR ν_{max} 3460, 2930, 2860, 2250, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–1.8 (m, 19 H), 2.8 (br s, 1 H), 4.47 (t, J = 6.7 Hz, 1 H). The ee of the product was determined as 66% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 7 min; t_R of *S*-isomer, 8 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-3-methylbutanenitrile (4r). *R*-rich-**4r** (174 mg, 70%): $[\alpha]^{24}_D$ +4.2° (*c* 1.3, $CHCl_3$) [lit.[17] $[\alpha]_D$ +2.7° (*c* 3.9, $CHCl_3$) for *R* enantiomer in 17% ee]; IR ν_{max} 3450, 2970, 2880, 2250, 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (d, J = 6.7 Hz, 3 H), 1.11 (d, J = 6.7 Hz, 3 H), 2.0 (m, 1 H), 3.6 (br s, 1 H), 4.3 (m, 1 H). The ee of the product was determined as 34% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 13 min; t_R of *S*-isomer, 18 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Cyclohexyl-2-hydroxyacetonitrile (4s). *R*-rich-**4s** (251 mg, 72%): $[\alpha]^{24}_D$ +6.1° (*c* 3.8, $CHCl_3$) [lit.[5b] $[\alpha]_D$ +5.45° (*c* 2.96, $CHCl_3$) for *R* enantiomer in 58% ee]; IR ν_{max} 3450, 2930, 2860, 2250, 1710, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.4 (m, 5 H), 1.6–2.0 (m, 6 H), 2.8 (br s, 1 H), 4.27 (d, J = 6.1 Hz, 1 H). The ee of the product was determined as 65% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 10 min; t_R of *S*-isomer, 13 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

2-Hydroxy-3,3-dimethylbutanenitrile (4t). *R*-rich-**4t** (108 mg, 38%): $[\alpha]^{24}_D$ +14.5° (*c* 1.0, $CHCl_3$) [lit.[17] $[\alpha]_D$ +4.5° (*c* 1.5, $CHCl_3$) for *R* enantiomer in 29% ee]; IR ν_{max} 3460, 2970, 2880, 2250, 1710, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 2.7 (br s, 1 H), 4.05 (s, 1 H). The ee of the product was determined as 70% ee by HPLC analysis of its MTPA ester: t_R of *R*-isomer, 8 min; t_R of *S*-isomer, 11 min [eluent, hexane–ethyl acetate (100:5), 1.0 mL/min].

General Procedure for ^{13}C NMR Spectroscopic Study. Samples for ^{13}C NMR study were prepared as follows: In a dry Schlenk tube were placed Schiff base **2e** (263 mg, 1.0 mmol) and $CDCl_3$ (1 mL). Ti(O-*i*-Pr)$_4$ (0.30 mL, 1.0 mmol) was added dropwise and stirred for 1 h at room temperature, after which it was transferred to a dry 5-mm NMR tube under argon atmosphere and the tube was covered by a Teflon cap.

General Procedure for FD Mass Spectroscopic Study. Samples for FD mass spectra were prepared as follows: To a mixture of Schiff base **2e** (525 mg, 2.02 mmol) and dichloromethane (2 mL) in a dry Schlenk tube was added Ti(O-*i*-Pr)$_4$ (0.60 mL, 2.02 mmol) and stirred for 1 h at room temperature, after which it was subjected to FD mass spectra measurement.

Molecular Weight Determinations. The determination of molecular weights of the alcohol free product of chiral Schiff base–titanium alkoxide was carried out using a freezing point depression apparatus. Molecular weight was calculated according to the following equation; $\Delta T = K_f\omega/MW$, where ΔT = depression of the solvent (benzene), ω = weight (g) of solute in 1000 g of benzene, MW = molecular weight. K_f value of this apparatus was calculated to be 5.41 on the basis of the depression of benzene (13.11 g) solution of naphthalene (130.7–382.4 mg). The procedure for the molecular weight determination of the product was as follows: In a flame-dried Schlenk tube were placed Schiff base **2e** (527 mg, 2.0 mmol) and dichlorcmethane (5 mL). After the mixture was cooled to 0 °C, Ti(O-*i*-Pr)$_4$ (569 mg, 2.0 mmol) was added dropwise and stirred for 1 h. The volatiles were removed in vacuo, and then benzene (10 mL) was added. By three freeze–thaw cycles a pale yellow slurry was afforded, which was used for the molecular weight determination. A dry Schlenk-type cryoscopy cell was evacuated and filled with argon, benzene (K_f = 5.41, 13.11 g, 15 mL), and the above-prepared 1:1 compound of Schiff base **2e** and Ti(O-*i*-Pr)$_4$ (0.10 g). The apparatus was imersed into an ice–salt bath, and the temperature was measured by a Beckmann thermometer at 20-s intervals until the solution froze. After the solution was warmed to room temperature, the same procedure was repeated three times. Since the averaged ΔT value obtained from four runs was 0.12 (entry 1 in Table V), the molecular weight (MW) of this compound was calculated to be 326 (AN = 0.76). The molecular weights and other parameters were summarized in Tables V and VI.

Acknowledgment. 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 measurement of FD mass spectra.