Enantioselective Trimethylsilylcyanation of some Aldehydes Catalysed by Titanium Alkoxide–Chiral Dialkyl Tartrate Complexes

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Highly enantioselective trimethylsilylcyanation of various aldehydes with trimethylsilyl cyanide has been achieved with a modified Sharpless catalyst, consisting of titanium tetraisopropoxide [$Ti(OPr^i)_4$] and chiral diisopropyl tartrate (DIPT). Asymmetric amplification was also observed in the trimethylsilylcyanation of benzaldehyde with a catalyst composed of Ti $(OPr^i)_4$ and partially resolved DIPT.

Of the numerous syntheses now known[1] those involving optically active cyanohydrins are of importance since they give α-hydroxy carboxylic acids and 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 diastereoselective addition of trimethylsilyl cyanide to chiral acetals in 90–95% d.e. (d.e. = diasteroisomeric excess)[3] and in a catalytic process, Reetz first reported that boron[4a] or titanium compounds[4b] bearing chiral binaphthol and other ligands catalysed 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 an *in situ* prepared mixture of titanium dichloride diisopropoxide [$TiCl_2(OPr^i)_2$] and tartrate-derived chiral 1,4-diol in the presence of molecular sieves (MS) 4A[5]. Further, Inoue *et al.* reported the enantioselective hydrocyanation of aldehydes by hydrogen cyanide catalysed with chiral basic cyclodipeptides containing an L-histidine residue.[6] Very recently, many reports have been published on the enantioselective hydrocyanation of aldehyde by a variety of catalyst systems.[7]

Here we describe a novel and efficient procedure for enantioselective addition of trimethylsilyl cyanide to aldehydes promoted by catalytic amounts of modified Sharpless catalyst, which consists of titanium tetraisopropoxide [$Ti(OPr^i)_4$] and chiral diisopropyl tartrate (abbreviated as DIPT) [eqn. (1)].[8]

$$RCHO + Me_3SiCN \xrightarrow[CH_2Cl_2,\ 0\ °C]{\text{chiral catalyst}} R\overset{*}{C}H(OSiMe_3)CN \qquad \text{eq. (1)}$$

1, R = Ph; **2**, R = *p*-MeC_6H_4; **3**, R = *p*-$MeOC_6H_4$; **4**, R = 2-naphthyl; **5**, 2-thienyl; **6**, C_8H_{17}

Results and Discussion

Enantioselective Trimethylsilylcyanation of Benzaldehyde **1**.—We first examined the reaction of benzaldehyde **1** with trimethylsilyl cyanide using chiral titanium complexes prepared *in situ* from $Ti(OPr^i)_4$ and L(+)-DIPT in a molar ratio of 1:1.1 (catalyst A in Table 1). In an equimolar use of catalyst, the reaction at 0 °C for 18 h gave mandelonitrile in 95% yield, whose optical yield was determined as 78% e.e. by HPLC analysis of its MTPA ester[9] after hydrolysis with 1 mol dm^{-3} HCl. However, in a catalytic system (20 mol% of chiral titanium compound per aldehyde), only 19% of mandelonitrile in 48% e.e. was obtained under the same reaction conditions as above, and the enantiomeric excess (e.e.) was also decreased. Next we examined the catalyst system in which MS 4A was added (catalyst B). The efficient use of MS 4A in an asymmetric reaction was first reported for the enantioselective epoxidation of allylic alcohols by Sharpless.[10] Subsequently, Narasaka reported a similar observation in an asymmetric Diels–Alder reaction,[11] and Yamamoto[12] and Nakai[13] also reported, independently, asymmetric ene reactions. However, in our reactions, the addition of MS 4A decreased the enantioselectivity, especially in catalytic reactions (6% e.e.). Use of freeze-dried catalyst, prepared by complete removal of isopropyl alcohol produced by the alkoxy exchange reaction between $Ti(OPr^i)_4$ and L-(+)-DIPT [eqn. (2)] (catalyst C), also resulted in low enantioselectivity. However, we found that highly enantioselective silylcyanation could be achieved by the addition of 1–2 mol equiv. of isopropyl alcohol per mol equiv. of titanium compound to the above freeze-dried system (catalyst D) even in the catalytic reactions. That is, the reaction of benzaldehyde with trimethylsilyl cyanide catalysed by 20% molar amounts of the catalyst D gave product of 91% e.e. (*R*-rich) in 84% yield. These results are summarized in Table 1.

In order to optimize the reaction, we looked for conditions under which the highest enantiomeric excess was obtained; thus, the effects of solvent, molar ratio of $Ti(OPr^i)_4$ and L-(+)-DIPT, the addition of various alcohols to the freeze-dried catalyst, and concentration of reactants and catalyst on enantioselectivity were examined. First, the asymmetric silylcyanation of benzaldehyde was investigated in various solvents. As shown in Table 2, high enantiomeric excess was achieved when chlorinated solvents such as dichloromethane and chloroform were used. A 1:1.1 ratio of $Ti(OPr^i)_4$ and L-(+)-DIPT provided optimum conditions for yield and e.e. of product, no reaction occurring at a ratio of 1:2. In examining the effect of various additive alcohols on the enantioselectivity (Table 3), we found that isopropyl alcohol was most effective for the reaction whilst *tert*-butyl alcohol decreased both the reactivity and enantioselectivity. Furthermore, the addition of water brought about a non-enantioselective reaction.

It should be noted that enantioselectivity was much influenced by the concentration of the reactants, especially in the catalytic reaction (Table 4). At high concentration, only a moderate level of enantioselection (40% e.e.) was attained, a lowering of the concentration achieving higher enantioselectivity. A similar observation was made by Sharpless in the asymmetric epoxidation of allylic alcohols. Enantioselective trimethylsilylcyanation of benzaldehyde using catalytic amounts of titanium complexes was best run at a substrate concentration of 0.05 mol dm^{-3} and a catalyst concentration of 0.01 mol dm^{-3}, conditions under which silylcyanated product in 91% e.e. was obtained.

Enantioselective Trimethylsilylcyanation of a Variety of Aldehydes.—We examined the asymmetric silylcyanation of aldehydes such as *p*-tolualdehyde **2**, *p*-anisaldehyde **3**, 2-naphthaldehyde **4**, thiophene-2-carbaldehyde **5**, and nonanal

Table 1 Enantioselective trimethylsilylcyanation of benzaldehyde[a]

Catalyst system	Equimolar reaction		Catalytic reaction (20 mol%)	
	% Yield[b]	% E.e.[c,d]	% Yield[b]	% E.e.[c,d]
A: $Ti(OPr^i)_4$ L-(+)-DIPT *in situ*	95	78	19	48
B: $Ti(OPr^i)_4$–L-(+)-DIPT + MS 4A *in situ*	100	50	15	6
C: $Ti(OPr^i)_2$ [L-(+)-DIPT]	100	32	14	58
D: {$Ti(OPr^i)_2$–[L-(+)-DIPT]}–Pr^iOH (1:1)	77	86	61	68
(1:1.5)	94	91	71	75
(1:2)	63	88	84	91

[a] All reactions were carried out in dichloromethane at 0 °C for 18 h. [b] Isolated yield. [c] Determined by HPLC analysis of its MTPA ester. [d] Absolute configuration of the product was *R* by optical rotation value compared with that in the literature.[5b]

Table 2 Solvent effects on enantioselectivity in the asymmetric trimethylsilylcyanation of benzaldehyde[a]

Solvent	Conditions		Product	
	Temp. (°C)	Time (h)	% Yield[b]	% E.e.[c,d]
Hexane	0	24	79	5
Toluene	27	24	86	23
Diethyl ether	27	24	80	75
Dichloromethane	0	18	81	91
Chloroform	0	18	84	86
Acetonitrile	29	48	83	17

[a] All reactions were carried out using 20 mol% of $Ti(OPr^i)_4$ and L-(+)-DIPT. [b] Isolated yield of mandelonitrile. [c] Determined by HPLC analysis. [d] Absolute configuration was determined as *R*.

Table 3 Effect of additive alcohols to freeze-dried catalyst on enantioselectivity[a]

Entry	Additive	Product	
		% Yield[b]	% E.e.[c,d]
1	H_2O	79	2
2	MeOH	86	68
3	EtOH	80	86
4	PrOH	81	68
5	Pr^iOH	84	91
6	BuOH	83	70
7	Bu^iOH	78	54
8	Bu^tOH	40	13
9	CH_2=$CHCH_2OH$	82	75

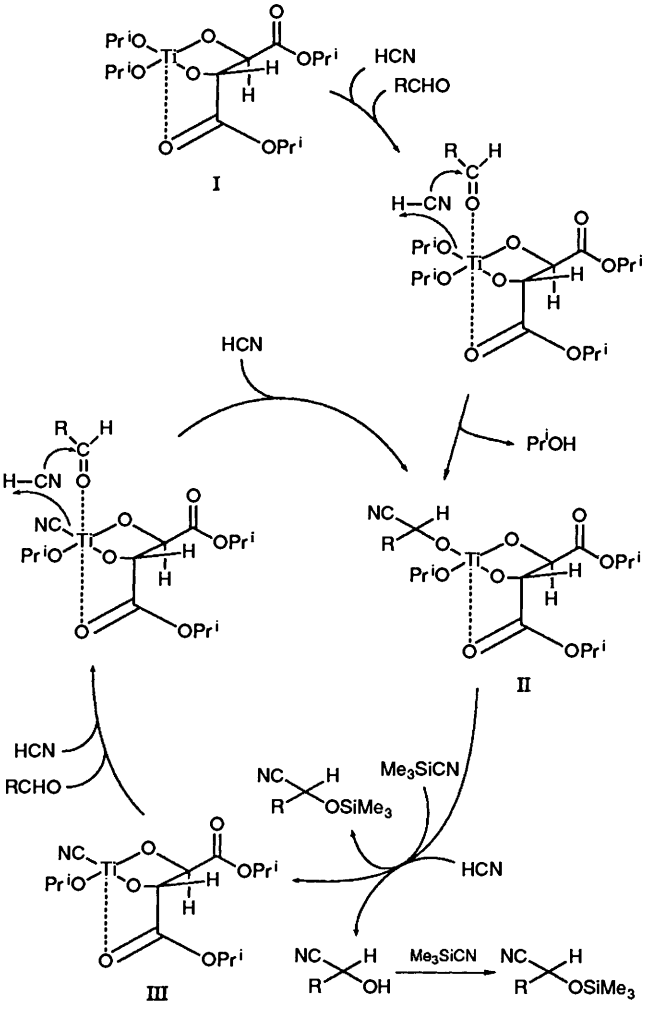
[a] All reactions were run in dichloromethane at 0 °C for 18 h using 20 mol% of titanium catalyst. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Absolute configuration was determined as *R*.

Table 4 Effect of concentration of reactants on enantioselectivity[a]

Entry	Concentration (mol dm^{-3})		Time (h)	Product	
	Catalyst	Aldehyde		% Yield[b]	% E.e.[c]
1	0.1	0.5	18	91	40
2	0.03	0.17	18	85	77
3	0.02	0.10	18	89	87
4	0.01	0.05	18	84	91
5	0.005	0.025	36	Trace	—

[a] Reactions were run in dichloromethane at 0 °C. [b] Isolated yield. [c] Determined by HPLC analysis.

6. In the silylcyanation of aromatic aldehydes **2**–**4** and the heteroaromatic aldehyde **5** moderate to high enantioselectivity was observed (60–83% e.e.) in both equimolar and catalytic reactions. On the other hand, the reaction of nonanal with trimethylsilyl cyanide gave the silylcyanated product of only 31% e.e. in 21% yield. The results obtained are summarized in Table 5. As for the absolute configurations of the products, *R*-configurational cyanohydrins were obtained when L-(+)-DIPT was used.



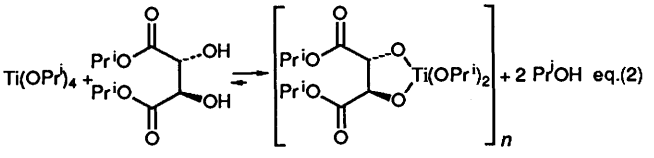
Scheme 1

Reaction Mechanism.—The catalytic asymmetric trimethylsilylcyanation of aldehydes proceeds as outlined in Scheme 1. At first, the chiral titanium species I is formed by an alkoxy exchange reaction, eqn. (2), between $Ti(OPr^i)_4$ and L-(+)-DIPT. Hydrogen cyanide produced by the reaction of tri-

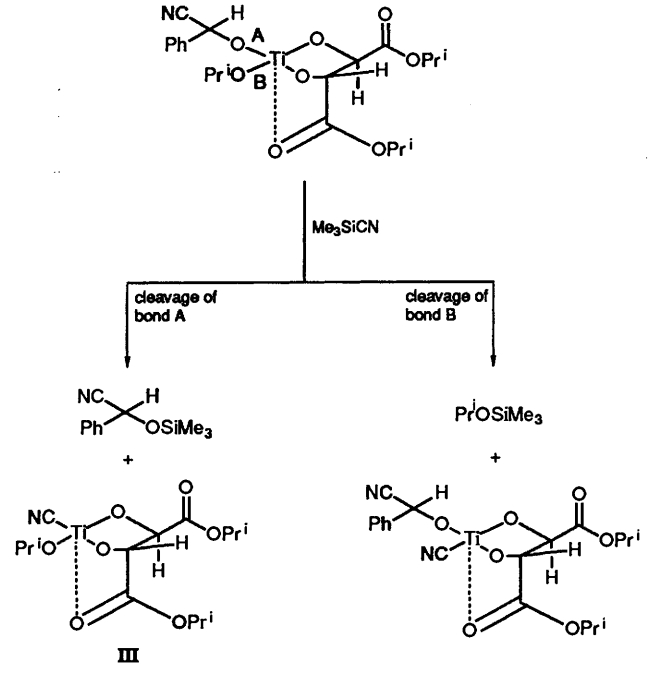
Table 5 Enantioselective addition of trimethylsilyl cyanide to some aldehydes promoted by modified Sharpless reagents[a]

Aldehyde	Equimolar reaction		Catalytic reaction (20 mol%)	
	% Yield[b]	% E.e.[c,d]	% Yield[b]	% E.e.[c,d]
p-Tolualdehyde **2**	89	77	79	65
p-Anisaldehyde **3**	90	81	88	77
2-Naphthaldehyde **4**	89	73	80	60
Thiophene-2-carbaldehyde **5**	92	81	84	83

[a] Reactions were carried out in dichloromethane at 0 °C for 18 h using L-(+)-DIPT. [b] Isolated yield. [c] Determined by HPLC analysis of MTPA esters. [d] All absolute configurations were determined as *R* by comparison of the rotation values with those in the literature (see Experimental section).

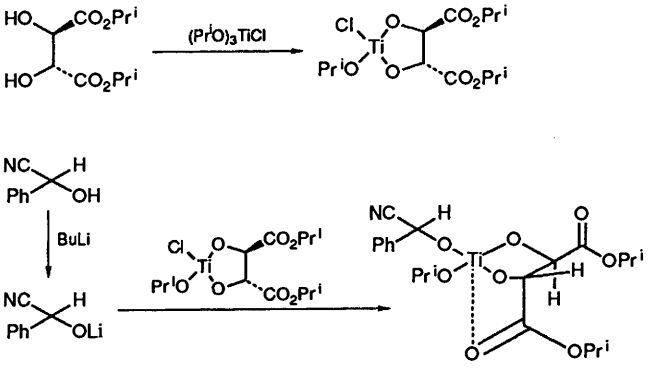


methylsilyl cyanide with isopropyl alcohol will then react with the aldehyde coordinated to titanium in **I** to form the titanium species of the cyanohydrin **II**: from a stereochemical point of view this step will be the most important. The key process to accomplish the catalytic cycle will then be cleavage of the newly produced Ti–O bond in species **II** by trimethylsilyl cyanide to produce the trimethylsilyl ether of cyanohydrin and the chiral titanium species **III**. The chiral titanium species **III** thus generated will catalyse the silylcyanation of aldehydes to afford the cyanohydrin titanium species **II** again. The following experiments support this scheme. The species **II**, prepared independently by the reaction of lithiated mandelonitrile with the titanium monochloride shown in Scheme 3, contains two



Scheme 2

Ti–O bonds (bond A and B in Scheme 2) which may be cleaved by trimethylsilyl cyanide: cleavage of bond A gave the trimethylsilyl ether of mandelonitrile with species **III** predominating. This was confirmed by a ^{1}H NMR measurement of the intensity ratio of trimethylsilyl ether of mandelonitrile [CH_3(Si), δ_H 0.23] and isopropyl trimethylsilyl ether [CH_3(Si), δ_H 0.11]. The trimethylsilyl ether of the cyanohydrin from the titanium species **II** could also be formed by reaction of hydrogen



Scheme 3

cyanide with compound **II**, followed by trimethylsilylation of the cyanohydrin by trimethylsilyl cyanide.

Asymmetric Amplification.[14]—Kagan and co-workers investigated the asymmetric epoxidation of geraniol using 1 equiv. of the Sharpless reagent [Ti(OPr^i)$_4$–L-(+)-DET/Bu^{t}OOH (1:1:2)] and diethyl tartrate (DET) of various e.e.'s, and observed that the e.e. of epoxidized product was not correlated linearly with the enantiomeric purity of DET.[15] We also examined the relationship between the e.e. of DIPT as a chiral auxiliary and of the cyanohydrin produced in trimethylsilylcyanation of benzaldehyde using the catalyst consisting of Ti(OPr^i)$_4$ and partially resolved DIPT. As shown in Table 6, the catalyst composed of DIPT of 25% e.e. gave mandolontrile of 50 e.e., whilst a product of 70% e.e. was obtained by use of DIPT of 50% e.e. These results show that a nonlinear relation between % e.e. of catalyst and of product will be common in asymmetric reactions using Sharpless reagent.

Catalyst Structure **1**: Molecular Weight Determination.—We examined the determination of molecular weight of the catalyst C which was prepared by mixing an equimolar amount of optically active and racemic DIPT with Ti(OPr^i)$_4$ in dichloromethane, followed by removal of isopropyl alcohol *in vacuo* using a freezing point depression apparatus. The molecular weight of the above titanium complexes in benzene was concentration dependent for complexes of both optically active and racemic DIPT; the ranges were 297–458 and 448–767, respectively (Table 7). These results differ from those reported by Sharpless,[16] but it was not possible to explore these differences.

Catalyst Structure **2**: ^{13}C *NMR Spectra of* 1:1 *Molar Ratio Products of* Ti(OPr^i)$_4$ *and* L-(+)-*DIPT*.—^{13}C NMR spectra of catalyst C (spectrum C in Fig. 1) and catalyst D (spectrum D) were measured in $CDCl_3$. As shown in Fig. 1, the two spectra differed in that addition of isopropyl alcohol to the freeze-dried catalyst C simplified its spectrum (see spectrum D). This implied that the freeze-dried product existed as complex associates in solution.

Table 6 Asymmetric amplification in enantioselective trimethylsilylcyanation of benzaldehyde[a]

Entry	% E.e. of DIPT[b]	Product % Yield[c]	Product %E.e.[d]
1	15	65	27
2	25	78	50
3	50	83	70

[a] Reactions were run at 0 °C for 21 h by using 1:2.3:1:1.1 molar ratio of benzaldehyde–trimethylsilyl cyanide–$Ti(OPr^i)_4$–partially resolved DIPT. [b] L-(+)-Rich DIPT was used. [c] Isolated yield. [d] HPLC analysis.

Table 7 Molecular weight determination of freeze-dried products of optically pure and racemic DIPT and $Ti(OPr^i)_4$ (1:1 molar ratio) by cryoscopically in benzene[a]

Entry	ω^c	ΔT^d	K_f^e	M^f	AN[g]
1 (OA)	7.2	0.14	5.97	308	0.8
2 (OA)	11.2	0.17	5.97	393	1.0
3 (OA)	15.9	0.32	5.97	297	0.7
4 (OA)	24.7	0.33	5.97	447	1.1
5 (OA)	26.5	0.42	5.97	382	1.0
6 (OA)	39.3	0.54	5.97	435	1.1
7 (OA)	39.5	0.52	5.97	458	1.2
8 (R)	10.5	0.14	5.97	448	1.1
9 (R)	19.9	0.16	5.97	767	1.9
10 (R)	28.0	0.24	5.97	711	1.8
11 (R)	36.2	0.40	5.97	547	1.4

[a] The procedure for molecular weight determination and preparation of the sample are described in the Experimental section. [b] OA = $Ti(OPr^i)_4$–L-(+)-DIPT (optically pure) complex; R = $Ti(OPr^i)_4$-racemic DIPT. [c] Weight (g) in 1000 g of benzene. [d] Depression (°C). [e] Molar depression of the solvent (benzene). [f] Molecular weight. [g] AN = association number, M = 398 (n = 1 for $[Ti(OPr^i)_2(DIPT)]_n$).

In conclusion, asymmetric silylcyanation of aromatic aldehydes with trimethylsilyl cyanide using a modified Sharpless catalyst provides a new, efficient method for the synthesis of optically active cyanohydrins.

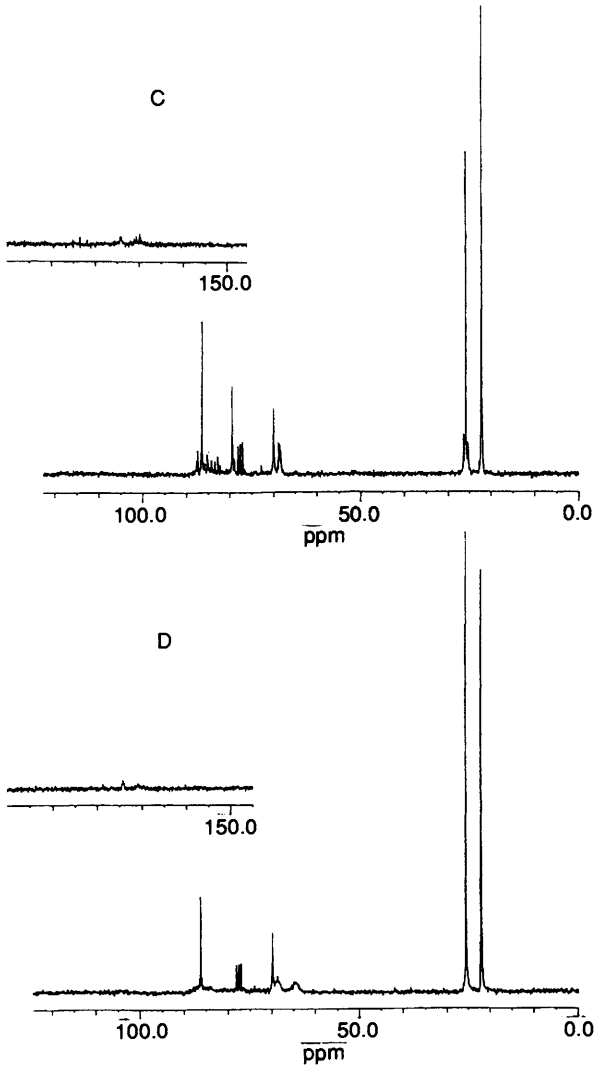


Fig. 1 ^{13}C NMR spectra of catalyst C and catalyst D.

Experimental

General.—^1H NMR (250 MHz) and ^{13}C NMR spectra (62.87 MHz) were measured on a Hitachi R-250 Fourier Transfer NMR spectrometer (250 MHz) with [^2H]chloroform as solvent and recorded in ppm relative to internal tetramethylsilane. J Values are given in Hz. Optical rotations were measured on a JASCO DIP-4 digital polarimeter for solutions in a 5 dm cell; [α] values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Preparative column chromatography was carried out on a Wacogel-200. HPLC analyses were carried out on a JASCO 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.

Materials.—Dichloromethane, carbon tetrachloride, chloroform, 1,2-dichloroethane, and acetonitrile were distilled from P_4O_{10}. Toluene, hexane, diethyl ether and benzene were distilled from sodium benzophenone ketyl under argon. Trimethylsilyl cyanide was purchased from Tokyo Kasei Co., and distilled before use. The aldehydes **1**–**5** were purchased from Nacalai Tesque, and the aldehyde **6** was purchased from Aldrich and distilled before use.

Determination of the Cyanohydrin Enantiomeric Excess (*e.e.*).—The e.e. for each of the cyanohydrin trimethylsilyl ethers was determined by HPLC analysis of the corresponding (*R*)-(+)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) esters after hydrolysis by 1 mol dm^{-3} HCl. The procedure for the preparation of MTPA esters was as follows. To a dichloromethane (1 cm^3) solution of the cyanohydrin (10 mg) was added (*R*)-(+)-MTPACl (10 mg) and pyridine (10 mg) at room temperature. The mixture was stirred at this temperature for 1 h after which it was poured into a mixture of ethyl acetate (10 cm^3) and 1 mol dm^{-3} HCl (10 cm^3 × 2) and extracted with ethyl acetate (10 cm^3 × 2). The combined extracts were washed with brine (10 cm^3) and concentrated and the residue was chromatographed on a silica gel column [eluent, benzene] to afford the corresponding cyanohydrin MTPA esters, which was analysed by HPLC.

Procedure for the Asymmetric Trimethylsilylcyanation of Benzaldehyde **1** *Catalysed by a Mixture of* $Ti(OPr^i)_4$ *and* L-(+)-*DIPT* (*Method A*).—In a flame-dried Schlenk tube a mixture of L-(+)-DIPT (130 mg, 0.55 mmol) and dichloromethane (5 cm^3) was cooled to 0 °C. $Ti(OPr^i)_4$ (0.15 cm^3, 0.5 mmol) was then added slowly *via* a syringe. After being stirred for 1 h at room temperature, the mixture was diluted with dichloromethane (25 cm^3) and then cooled to 0 °C again. Trimethylsilyl cyanide (0.75 cm^3, 5.62 mmol) and benzaldehyde (261 mg, 2.46 mmol) were then added to it and the whole stirred for 18 h at this temperature. After this, the mixture was poured into 1 mol dm^{-3}

HCl (30 cm^3) and stirred vigorously. The mixture was then extracted with ethyl acetate (50 cm^3 × 2) and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was then column chromatographed on silica gel [eluent, hexane–ethyl acetate (5:1)] to give *R*-rich mandelonitrile (62 mg, 19%). The e.e. of the product was determined as 48% 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 cm^3 min^{-1}]; $[\alpha]_D^{22}$ +21.6 (*c* 1.0, $CHCl_3$); $\delta_H(CDCl_3)$ 2.9 (1 H, br s), 5.55 (1 H, s) and 7.4–7.6 (5 H, m).

Procedure for Trimethylsilylcyanation of **1** *by Method B.*—To a solution of L-(+)-DIPT (130 mg, 0.55 mmol) in dichloromethane (5 cm^3) was added $Ti(OPr^i)_4$ (0.15 cm^3, 0.5 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, after which dichloromethane (25 cm^3) and MS 4A (65 mg) were added and the mixture cooled to 0 °C again. Trimethylsilyl cyanide (0.75 cm^3, 5.62 mmol) and benzaldehyde (261 mg, 2.46 mmol) were then added and stirring continued for 18 h at this temperature. Work-up was as described above to give *R*-rich **7** (49 mg, 15%). The e.e. of the product was determined as 6% by HPLC analysis.

Procedure for Trimethylsilylcyanation of **1** *by Method C.*—$Ti(OPr^i)_4$ (0.15 cm^3, 0.5 mmol) was added dropwise at 0 °C to a solution of L-(+)-DIPT (130 mg, 0.55 mmol) in dichloromethane (5 cm^3). After the mixture had been stirred for 1 h at room temperature, isopropyl alcohol was removed under reduced pressure (30–35 °C, 20 min); benzene (2 cm^3) was then added to the residue and the mixture freeze-dried (× 3). To the resulting slurry, dichloromethane (25 cm^3), trimethylsilyl cyanide (0.75 cm^3, 5.62 mmol) and benzaldehyde (261 mg, 2.46 mmol) were added at 0 °C and the mixture stirred for 18 h at this temperature. Work-up was as described above to give *R*-rich **7** (46 mg, 14%). The e.e. of the product was determined as 58% by HPLC analysis.

Procedure for Trimethylsilylcyanation of **1** *by Method D.*—To a solution of L-(+)-DIPT (130 mg, 0.55 mmol) in dichloromethane (5 cm^3) was added $Ti(OPr^i)_4$ (0.15 cm^3, 0.5 mmol) at 0 °C. After the mixture had been stirred for 1 h at room temperature, isopropyl alcohol was removed under reduced pressure (30–35 °C, 20 min) and benzene (2 cm^3) added to the residue; the mixture was then freeze-dried (× 3). Isopropyl alcohol (77 mm^3, 1.0 mmol) and dichloromethane (50 cm^3) were added to the resulting slurry, and these were followed by trimethylsilyl cyanide (0.75 cm^3, 5.62 mmol) and benzaldehyde (261 mg, 2.46 mmol) added at 0 °C; the mixture was then stirred for 18 h at this temperature. Work-up as described above gave *R*-rich mandelonitrile (275 mg, 84%). The e.e. of the product was determined as 91% by HPLC analysis of its MTPA ester; $[\alpha]_D^{25}$ +41.6 (*c* 1.1, $CHCl_3$), {lit.,[5] $[\alpha]_D^{21}$ +45.5 (*c* 3.53, $CHCl_3$) for *R*-enantiomer in 96% e.e.}.

2-*Hydroxy*-2-(p-*tolyl*)*acetonitrile.*—Enantioselective trimethylsilylcyanation as described for **1** by method D was performed for *p*-tolualdehyde **2** (296 mg, 2.46 mmol). After work-up, evaporation of the volatiles provided an oil, which was subjected to silica-gel column chromatography [eluent, hexane–ethyl acetate (5:1)] to afford *R*-rich title compound (286 mg, 79%). The e.e. of the product was determined as 65% by HPLC analysis of the corresponding MTPA esters. t_R of R-isomer, 11 min; t_R of *S*-isomer, 12 min [eluent, hexane–ethyl acetate (100:5), 1.0 cm^3 min^{-1}]; $[\alpha]_D^{24}$ +33.3 (*c* 2.6, $CHCl_3$) [lit.,[17] $[\alpha]_D$ +47.4 (*c* 1.8, $CHCl_3$) for *R*-enantiomer in 92% e.e.]; $\delta_H(CDCl_3)$ 2.29 (3 H, s), 3.2 (1 H, br s), 5.39 (1 H, s), 7.15 (2 H, d, *J* 8.5) and 7.31 (2 H, d, *J* 8.5).

2-*Hydroxy*-2-(4-*methoxyphenyl*)*acetonitrile.*—The reaction as described for **1** by method D was performed for *p*-anisaldehyde **3** (336 mg, 2.46 mmol) under the same conditions. After work-up, evaporation of the volatiles provided an oil, which was subjected to silica-gel column chromatography [eluent, benzene–ethyl acetate (10:1)] to afford *R*-rich title compound (353 mg, 88%). The e.e. of the product was determined as 77% by HPLC analysis of the corresponding MTPA esters; t_R of *R*-isomer, 17 min; t_R of *S*-isomer, 20 min [eluent, hexane–ethyl acetate (100:5), 1.5 cm^3 min^{-1}]. $[\alpha]_D^{24}$ +35.4 (*c* 1.5, $CHCl_3$) [lit.,[17] $[\alpha]_D$ +36.3 (*c* 1.0, $CHCl_3$) for the *R*-enantiomer in 83% e.e.]; $\delta_H(CDCl_3)$ 2.7 (1 H, br s), 3.84 (3 H, s), 5.49 (1 H, s), 6.96 (2 H, d, *J* 8.6) and 7.46 (2 H, d, *J* 8.6).

2-*Hydroxy*-2-*naphthylacetonitrile.*—The reaction as described for **1** by method D was performed for 2-naphthaldehyde **4** (384 mg, 2.46 mmol) under the same conditions. After work-up, evaporation of the volatiles provided an oil, which was subjected to silica-gel column chromatography [eluent, hexane–ethyl acetate (5:1)] to afford *R*-rich title compound (361 mg, 80%). The e.e. of the product was determined as 60% by HPLC analysis of the corresponding MTPA ester; t_R of *R*-isomer, 13 min; t_R of *S*-isomer, 15 min [eluent, hexane–ethyl acetate (100:5), 1.0 cm^3 min^{-1}]. $[\alpha]_D^{24}$ +9.0 (*c* 1.4, EtOH) [lit.,[17] $[\alpha]_D$ +26.4 (*c* 0.522, $CHCl_3$) for *R* enantiomer in 86% e.e.]; $\delta_H(CDCl_3)$ 3.0 (1 H, br s), 5.70 (1 H, s), 7.5–7.6 (3 H, m) and 7.8–8.0 (4 H, m).

2-*Hydroxy*-2-(2-*thienyl*)*acetonitrile.*—The reaction as described for **1** by method D was performed for thiophene-2-carbaldehyde **5** (276 mg, 2.46 mmol) under the same conditions. After work-up, evaporation of the volatiles provided an oil, which was subjected to silica-gel column chromatography [eluent, hexane–ethyl acetate (5:1)] to afford *R*-rich title compound (288 mg, 84%). The e.e. of the product was determined as 83% by HPLC analysis of the corresponding MTPA esters; t_R of *R*-isomer, 15 min; t_R of *S*-isomer, 17 min [eluent, hexane–ethyl acetate (100:5), 1.0 cm^3 min^{-1}]; $[\alpha]_D^{24}$ +46.5 (*c* 1.0, EtOH) [lit.,[17] +46.8 (*c* 2.5, $CHCl_3$) for the *R*-enantiomer in 58% e.e.]; $\delta_H(CDCl_3)$ 4.1 (1 H, br s), 5.74 (1 H, s), 7.0–7.1 (1 H, m), 7.3–7.4 (1 H, m) and 7.4–7.5 (1 H, m).

2-*Hydroxydecanenitrile.*—Enantioselective trimethylsilylcyanation as described for **1** by method D was performed for nonanal **6** (356 mg, 2.50 mmol) under the same conditions. After work-up, evaporation of the volatiles provided an oil, which was subjected to silica-gel column chromatography [eluent, hexane–ethyl acetate (5:1)] to afford *R*-rich title compound (87 mg, 21%). The e.e. of the product was determined as 31% by HPLC analysis of the corresponding MTPA esters; t_R of *R*-isomer, 7 min; t_R of *S*-isomer, 8 min [eluent, hexane–ethyl acetate (100:5), 1.0 cm^3 min^{-1}]; $[\alpha]_D^{24}$ +4.3 (*c* 1.0, $CHCl_3$) [lit.,[5b] $[\alpha]_D^{25}$ +12.8 (*c* 2.52, $CHCl_3$) for the *R*-enantiomer in 93% e.e.]; $\delta_H(CDCl_3)$ 0.8–1.9 (17 H, m), 2.5 (1 H, br s) and 4.48 (1 H, t, *J* 6.7).

Asymmetric Amplification Experiments.—The partially resolved DIPT was prepared as follows; [L-(+)-rich] DIPT of 15% e.e. was prepared by mixing L-(+)-DIPT (0.3 g, 1.3 mmol) and racemic DIPT (1.7 g, 7.3 mmol); DIPT of 25% e.e. was prepared by mixing L-(+)-DIPT (0.5 g, 2.1 mmol) and racemic DIPT (1.5 g, 6.4 mmol); and DIPT of 50% e.e. was prepared by mixing L-(+)-DIPT (1.0 g, 4.3 mmol) and racemic DIPT (1.0 g, 4.3 mmol).

Enantioselective Silylcyanation of **1** *by using* $Ti(OPr^i)_4$-*partially resolved* DIPT.—The reaction as described for **1** by method D was performed using, in this case, DIPT of 15% e.e.

(260 mg, 1.11 mmol), $Ti(OPr^i)_4$ (287 mg, 1.01 mmol) and **1** (104 mg, 0.98 mmol). The mixture was stirred for 21 h, worked up as described above, and the product subjected to silica-gel column chromatography to afford *R*-rich mandelonitrile (85 mg, 65%). The e.e. of the latter was determined as 27% by HPLC analysis. The reactions using DIPT of 25% e.e. and 50% e.e. were carried out under the same conditions.

Molecular Weight Determinations.—The determination of the molecular weights of the 1:1 molar ratio products of optically pure and racemic DIPT and $Ti(OPr^i)_4$ was carried out using a freezing point depression apparatus. Molecular weight was calculated according to the following equation; $\Delta T = K_f\omega/M$, where ΔT = depression of the solvent (benzene), ω = weight (g) of solute in 1000 g of benzene, and M = molecular weight. K_f Value of this apparatus was calculated to be 5.97 on the basis of the depression of benzene (13.11 g) solution of naphthalene (123.6–375.9 mg). The procedure for the molecular weight determination of the product prepared from optically pure and racemic DIPT with $Ti(OPr^i)_4$ in a 1:1 molar ratio was as follows; DIPT (609 mg, 2.6 mmol) and dichloromethane (20 cm^3) in a flame-dried Schlenk tube were cooled to 0 °C and $Ti(OPr^i)_4$ (739 mg, 2.6 mmol) was added dropwise. The mixture was stirred for 1 h after which it was evaporated and benzene (10 cm^3) added to the residue. Three freeze–thaw cycles provided a pale yellow slurry which was used for the molecular weight determination. A dry and evacuated Schlenk-type cryoscopy cell was filled with argon and then benzene (K_f = 5.97, 13.11 g, 15 cm^3) and the above prepared 1:1 compound of DIPT and $Ti(OPr^i)_4$ (0.10 g) were added to it. The apparatus was immersed in an ice–salt bath, and the temperature was measured with a Beckmann thermometer at 15-s intervals until the solution froze. After the apparatus had warmed up to room temperature, the same procedure was repeated three times. Since the averaged ΔT value obtained from four runs was 0.17 (entry 2 in Table 7), the molecular weight (M) of this compound was calculated to be 393 (n = 1.0). The molecular weights and other parameters were summarized in Table 7.

General Procedure for ^{13}C *NMR Study.*—Samples for ^{13}C NMR study were prepared as follows. L-(+)DIPT (472 mg, 2.02 mmol) and $CDCl_3$ (2 cm^3) in a dry Schlenk tube were cooled to 0 °C and $Ti(OPr^i)_4$ (0.60 cm^3, 2.02 mmol) was added dropwise. The mixture was stirred for 1 h at room temperature after which it was transferred to dry 5-mm NMR tube under argon atmosphere and the tube was covered by Teflon cap.

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Paper 2/03224D
Received 18*th June* 1992
Accepted 7*th July* 1992