

The Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Chiral (Salen)Titanium Complexes

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Received December 7, 1998

Abstract: The use of chiral (salen)TiCl₂ complexes to induce the asymmetric addition of trimethylsilyl cyanide to aldehydes has been investigated. The complexes are catalytically active at substrate-to-catalyst ratios as high as 1000:1, and the optimal catalyst (**2e**) which is derived from (*R,R*)-1,2-diaminocyclohexane and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde produces trimethylsilyl ethers of cyanohydrins with up to 90% enantiomeric excess at ambient temperature. Water plays a key role in these reactions since under strictly anhydrous conditions much lower enantiomeric excesses are produced. The role of water has been shown to be to generate dimeric complexes of the form [(salen)Ti(μ -O)]₂ (**4**) which are the real catalyst precursors. A structure for one of these complexes (**4a** derived from (*R,R*)-1,2-diaminocyclohexane and 2-hydroxybenzaldehyde) has been determined by X-ray crystallography. The dimeric complexes are more active than the dichloride precursors, and at substrate-to-catalyst ratios between 100 and 1000:1 give cyanohydrin trimethylsilyl ethers with up to 92% enantiomeric excess in less than 1 h at ambient temperature.

Introduction

Cyanohydrins are highly versatile synthetic intermediates, which can easily be converted into a wide variety of important synthetic intermediates including α -hydroxy acids, α -amino acids, and β -amino alcohols.¹ They are also components of commercially important compounds such as the pyrethroid insecticides cypermethrin and fluvalinate.² In view of their importance, there is currently considerable interest in the asymmetric synthesis of cyanohydrins, especially by methods that utilize a chiral catalyst.³ A number of catalysts for the asymmetric addition of cyanide to aldehydes have been reported, the most useful of which are enzymes,^{1,3} synthetic peptides,^{3,4} and chiral transition metal complexes.³ While impressive enantiomeric excesses have been obtained in some cases for the enzyme- and peptide-catalyzed addition of HCN to aldehydes, in other cases much lower enantiomeric excesses and/or poor chemical yields were obtained.³ The structural modification of enzymes to increase their substrate compatibility is a long

and difficult undertaking, and attempts to modify the structures of the synthetic peptides to improve their substrate tolerance have been unsuccessful.⁵ In contrast, the structural modification of chiral transition metal complexes is a straightforward undertaking, thus offering the potential for this class of asymmetric catalysts to generate any desired cyanohydrin with high enantiomeric excess.

Previous work on transition metal induced asymmetric cyanohydrin synthesis has largely concentrated on titanium complexes, though scattered reports of the use of boron,⁶ aluminum,⁷ tin,⁸ magnesium,⁹ rhenium,¹⁰ bismuth,¹¹ and lanthanide salts¹² have appeared. The chiral ligands which have previously been utilized in conjunction with titanium include the following: taddol,¹³ binol,^{7,14} tartrate esters,¹⁵ sulfoximines,¹⁶ and salicylimines.¹⁷ In each case, complexation of the ligand to a suitable titanium salt generated a chiral complex that

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induced the asymmetric addition of hydrogen and/or trimethylsilyl cyanide to aldehydes. However, all of these complexes suffer from one or more of the following limitations: need to use large amounts (10–100 mol %) of the chiral complex; need to carry out reactions at low temperatures ($-80\text{ }^{\circ}\text{C}$); poor enantiomeric excesses and/or chemical yields with many aldehydes. These characteristics have so far prevented the industrial exploitation of transition metal based catalysts for asymmetric cyanohydrin synthesis.

Inspired by the pioneering work of Jacobsen¹⁸ and Katsuki¹⁹ on asymmetric epoxidation using chiral manganese salen complexes,²⁰ we initiated a research program aimed at the development of chiral titanium salen complexes as catalysts for the asymmetric addition of cyanide to aldehydes. Early results²¹ using the readily available cyclohexane-1,2-diamine derived ligands **1a–e** and titanium tetraisopropoxide demonstrated the feasibility of our approach. However, the resulting catalysts were subject to many of the limitations that restricted the applicability of earlier catalysts, namely the need to use 20 mol % of the catalyst and the need to carry out reactions at $-80\text{ }^{\circ}\text{C}$ to obtain high enantiomeric excesses. In a recent preliminary communication,²² we have reported the use of complex **2e** derived from ligand **1e** and titanium tetrachloride as a highly active (only 0.1 mol % of catalyst required) catalyst for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde at ambient temperature. In this paper, full details of the preparation and

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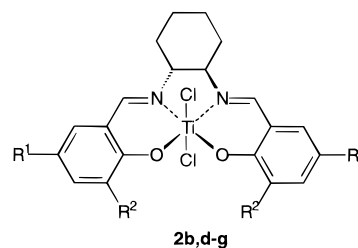
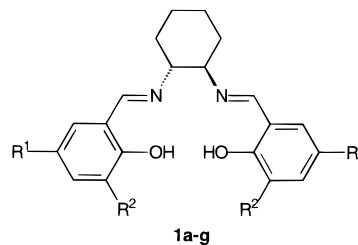
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use of complexes **2b,d–g** are reported, along with further studies culminating in the synthesis of an even more active catalyst for this reaction. The use of similar titanium salen complexes to catalyze the asymmetric addition of trimethylsilyl cyanide to aldehydes has also been reported,²³ and very recently Jacobsen has reported the use of chiral aluminum salen complexes to induce the asymmetric addition of hydrogen cyanide to imines.²⁴



- a) $R^1 = \text{H}$, $R^2 = \text{H}$
 b) $R^1 = \text{H}$, $R^2 = \text{}^t\text{Bu}$
 c) $R^1 = \text{Me}$, $R^2 = \text{}^t\text{Bu}$
 d) $R^1 = \text{OMe}$, $R^2 = \text{}^t\text{Bu}$
 e) $R^1 = \text{}^t\text{Bu}$, $R^2 = \text{}^t\text{Bu}$
 f) $R^1 = \text{CPh}_3$, $R^2 = \text{}^t\text{Bu}$
 g) $R^1 = \text{NO}_2$, $R^2 = \text{}^t\text{Bu}$

Results

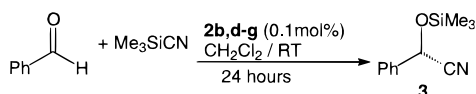
To optimize the catalytic activity of complex **2**, the effect of varying each aspect of its structure was investigated, starting with the substituents attached to the salen ligands. Catalysts **2b,d–g** were readily prepared by treating equimolar quantities of the appropriate ligand **1b,d–g** with titanium tetrachloride in dichloromethane at room temperature. In each case, the titanium complex **2** was isolated as a crystalline solid that was found by NMR studies to exist as a single species in chloroform solution. Catalyst **2e** was also analyzed by X-ray crystallography,²² and the complex was determined to have a C_2 symmetric structure with the two chlorine atoms trans to one another.²⁵ The NMR studies indicated that this C_2 symmetric structure was also present in solution. These results are in marked contrast to our earlier work with titanium tetraisopropoxide derivatives, where the catalyst had to be prepared in situ,²¹ and attempts to analyze the complex showed that a mixture of at least three species was present. The complex derived from ligand **1a** was also prepared; however, this compound was found to be highly insoluble in organic solvents which has prevented its purification and characterization.

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Scheme 1

**Table 1.** Effect of Varying the Ligand Structure on the Activity of Catalysts **2**^a

ligand ^b	enantiomeric excess (absolute configuration)
1b	63 (S)
1d	67 (S)
1e	86 (S)
1f	58 (S)
1g	21 (S)

^a All reactions were carried out using 0.1 mol % of the catalyst for 24 h at ambient temperature. ^b The unpurified complex derived from ligand **1a** gave 18% ee (S).

Table 2. Effect of Varying the Amount of Catalyst **2e** on the Enantiomeric Excess of **3**^a

mol % of catalyst	enantiomeric excess of 3	conversion
12	66	100
3	68	100
1	78	100
0.5	82	100
0.1	86	100
0.01	86	80

^a All reactions were carried out for 24 h at ambient temperature.

Each catalyst was tested for its ability to catalyze the asymmetric addition of trimethylsilyl cyanide to benzaldehyde at ambient temperature as shown in Scheme 1. As the results shown in Table 1 illustrate, the optimal catalyst was found to be compound **2e**, which is derived from the ligand-bearing ^tBu groups in the 3- and 5-positions of both aromatic rings. The enantiomeric excess of silyl ether **3** was determined by chiral GC analysis. The effect of varying the halogen ligands attached to the titanium atom was also investigated by the preparation of the titanium dibromide and titanium difluoride complexes of ligand **1e**. The difluoride complex gave similar results to complex **2e**; however, the dibromide complex proved to be rather unstable and gave inferior results to complex **2e**.

Having determined that structure **2e** was the optimal catalyst, the effect of varying the catalyst-to-substrate ratio was investigated. As Table 2 shows, the enantiomeric excess of silyl ether **3** increases as the amount of catalyst used decreases. The optimal amount of catalyst was found to be 0.1 mol % with lower amounts giving the same enantiomeric excess (86%) but lower conversions of benzaldehyde to silyl ether **3**. Since the amount of solvent used for these reactions was kept constant, the most likely explanation for this unusual relationship is that catalyst **2e** reacts with some species present in the dichloromethane solvent to produce a more reactive catalyst. Reducing the amount of catalyst **2e** will increase the relative concentration of this more active catalyst present in the reaction mixture. The cause of this effect is discussed later in this paper.

Only a small temperature coefficient was observed for reactions using catalyst **2e**. Thus, while reactions carried out at room temperature gave compound **3** with 86% ee, reactions carried out at -80 °C gave a 90% ee but took much longer, typically 209 h for 68% conversion. To investigate whether the catalytically active species obtained from titanium(IV) and ligands **1a–e** was monomeric or oligomeric, the relationship between the enantiomeric excess of ligand **1e** and the enantiomeric excess of silyl ether **3** was investigated for reactions

Table 3. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Catalyst **2e**^a

RCHO, R =	ee	RCHO, R =	ee
Ph	86	2,4-(MeO) ₂ C ₆ H ₃	86
2-MeC ₆ H ₄	62	3,4-(MeO) ₂ C ₆ H ₃	80
3-MeC ₆ H ₄	74	3,5-(MeO) ₂ C ₆ H ₃	84
4-MeC ₆ H ₄	72	4-F ₃ CC ₆ H ₄	50
2-MeOC ₆ H ₄	72	4-O ₂ NC ₆ H ₄	30
3-MeOC ₆ H ₄	78	Me ₃ C	46
4-MeOC ₆ H ₄	84	MeCH ₂	44

^a All reactions were carried out using 0.1 mol % of the catalyst for 24 h at ambient temperature.

carried out at -80 °C using catalyst prepared in situ from titanium tetraisopropoxide.²¹ However, no nonlinear effect²⁶ was observed, a result that is consistent with either a monomeric or oligomeric active species. Attempts to modify the metal ion have so far proved unsuccessful as the corresponding Sn(II), Sn(IV), Mn(III), and Zr(IV) complexes gave compound **3** with less than 25% ee. The use of hydrogen cyanide as an alternative to trimethylsilyl cyanide was also investigated, but no reaction occurred.

Having optimized the catalyst structure and reaction conditions, the asymmetric addition of trimethylsilyl cyanide to a range of aromatic and aliphatic aldehydes catalyzed by 0.1 mol % of catalyst **2e** was investigated. The results shown in Table 3 indicate that good enantiomeric excesses are obtained with electron-rich aromatic aldehydes, while electron-deficient aromatic aldehydes give lower enantiomeric excesses. There appears to be a relationship between the steric properties of the aromatic aldehyde and the ee of the product in these reactions as ortho-substituted aromatic aldehydes generally gave lower ee values than the meta and para isomers. The two aliphatic aldehydes that were investigated gave cyanohydrin silyl ethers with moderate ee values and did not appear to be sensitive to steric effects.

While carrying out these experiments, occasionally inconsistent results were obtained. In particular, occasionally much lower conversions and ee values were observed. The cause of this problem was eventually traced to the effect of water on the catalysts. Experiments showed that under rigorously anhydrous conditions, neither the dichloride complexes **2** nor the in situ prepared isopropoxide complexes reported earlier²¹ are effective catalysts. In the case of complexes **2**, it was also found advantageous to add triethylamine to the reaction mixture to scavenge any HCl that was generated. Representative results for both catalyst systems are shown in Table 4. The reaction between complexes **2** and water also explains the increase in ee that was observed as the concentration of catalyst **2e** was decreased as discussed earlier.

This beneficial effect of water also provides an explanation for another effect that had been observed when using the titanium tetraisopropoxide catalyst system at -80 °C. Under these conditions, the asymmetric addition of trimethylsilyl

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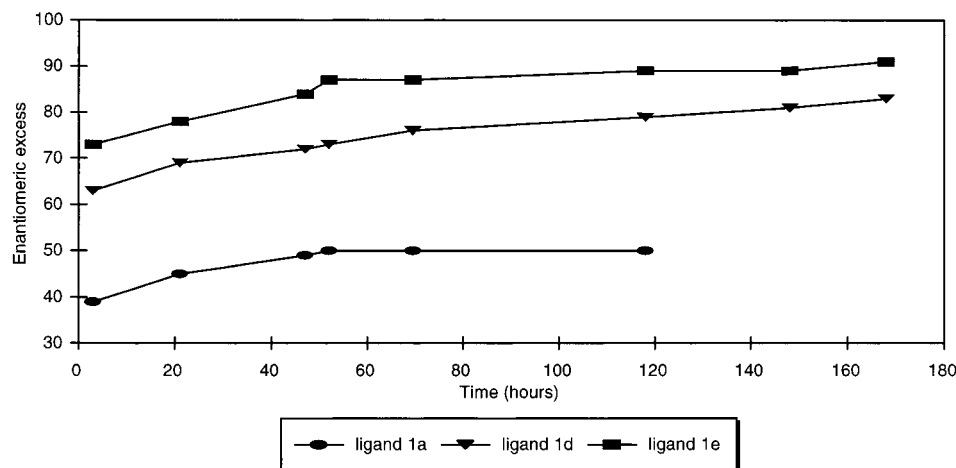


Figure 1. Variation of ee of **3** with time using ligands **1** and $\text{Ti}(\text{O}^i\text{Pr})_4$ as the catalytic system.

Table 4. Effect of Water and Triethylamine on the Catalytic Activity of the Titanium Salen Complexes

catalyst system	water/ Et_3N treatment	ee	reaction time (h)	conversion (%)
1b / $\text{Ti}(\text{O}^i\text{Pr})_4^a$	0.007% water present	56	223	100
1b / $\text{Ti}(\text{O}^i\text{Pr})_4^a$	0.12% water present	70	24	100
1b / $\text{Ti}(\text{O}^i\text{Pr})_4^a$	1 equiv of water added	74	24	100
2b ^b	anhydrous	62	24	80
2b ^b	1 equiv of water/2 equiv of Et_3N	80	24	100
2e ^b	anhydrous	40	24	42
2e ^b	1 equiv of water/2 equiv of Et_3N	86	24	100

^{a,b}All reactions were carried out at ambient temperature: (a) using 1.5 mol % of the catalyst and (b) using 0.1 mol % of the catalyst.

cyanide to benzaldehyde using 20 mol % of the catalyst is very slow, with reactions requiring 100–200 h to go to completion. Monitoring of the progress of these reactions showed that the enantiomeric excess of product **3** increased as the reaction progressed as shown in Figure 1. This effect is consistent with the initially formed anhydrous catalyst that has only low activity and gives relatively low ee values, reacting with adventitious water during the course of the reaction to generate a new, more active species which gives a higher ee.

In view of these results, it seemed likely that the same catalytically active species was being generated from both the in situ titanium tetraisopropoxide/ligand **1** catalyst system and the titanium dichloride complexes **2**. Both systems gave similar ee values with a wide range of aldehydes and required water for activation. The main difference between the two systems was the need to use 20 mol % of the in situ catalyst system and to work at $-80\text{ }^\circ\text{C}$. This could be explained by the fact that the in situ catalyst system gives a mixture of species, and the low temperature is necessary to avoid unwanted catalysis by achiral complexes such as unreacted titanium tetraisopropoxide. To prove this hypothesis, a preformed mixture of ligand **1e** and titanium tetraisopropoxide was treated with 1 equiv of water, and complex **2e** was treated with 1 equiv of water and 2 equiv of triethylamine. In both cases, the same species **4e** was obtained as a crystalline solid. Analogous complexes **4a,g** were obtained when dichloride complex **2g** was treated with water and triethylamine, and when ligand **1a** was treated with titanium tetraisopropoxide followed by water. The structure of compounds **4a,e,g** is based upon their spectral and analytical properties and the X-ray structure of complex **4a** as shown in Figure 2.

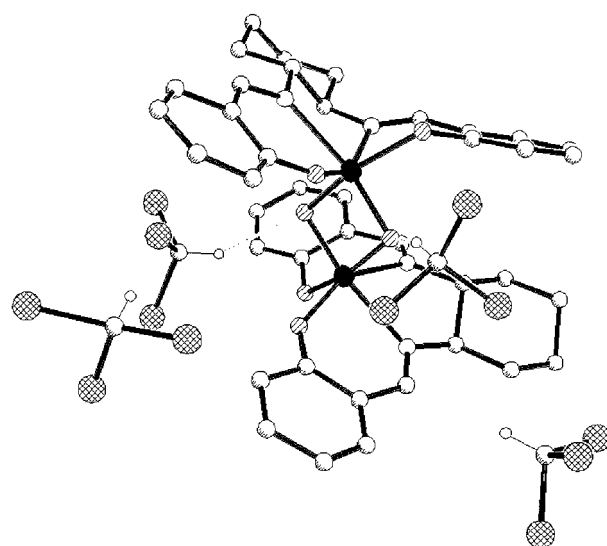
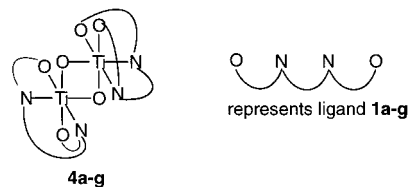


Figure 2. X-ray structure of complex **4a**· 4CHCl_3 . Titanium atoms are shown in black, oxygen atoms are striped, chlorine atoms are hashed, and nitrogen atoms are completely white.



The X-ray structure of compound **4a** suggested that complexes **4e** and **4g** are probably also dimeric with a central four-membered ring comprising two titanium atoms and two oxygen atoms. The oxygen atoms of the four-membered ring have appreciable basicity as each is hydrogen bonded to a chloroform molecule ($\text{O}-\text{H}$ distances 2.369 and 2.238 Å; $\text{C}-\text{H}-\text{O}$ angles 151.1 and 151.4°). The four bonds within the four-membered ring are not of equal length, rather there are two short $\text{Ti}-\text{O}$ bonds (1.806 and 1.821 Å) and two long $\text{Ti}-\text{O}$ bonds (1.857 and 1.878 Å). In the dimeric structure, the requirement for the two bridging oxygen atoms to adopt positions cis to one another means that the salen ligands cannot adopt a planar coordination around the titanium atoms. Rather, the salen ligands have to adopt a conformation in which one of the coordinating atoms (a phenolic oxygen) is nonplanar with the other three coordinat-

ing groups. The complex retains overall C_2 symmetry, however, since the ligands adopt a Δ -configuration around both titanium atoms.

A survey of the Cambridge crystal structure database revealed that while there are many crystal structures of titanium complexes which contain a Ti—O—Ti—O ring system, in the vast majority of these the oxygen atoms are also bound or coordinated to additional atoms. Only a few crystal structures in which the μ -oxygens are both divalent have been reported,²⁷ and only one of these, a titanium/palladium mixed complex, contains salen ligands.²⁸ The O—Ti—O and Ti—O—Ti bond angles in these complexes do not vary significantly (82 and 98°, respectively), but the Ti—O bond varies between 1.810 and 1.923 Å depending upon the nature of the trans ligands.

The catalytic activity of the dimeric complexes **4a,e,g** was investigated using benzaldehyde as the substrate. In each case, the dimeric complexes gave the same or better enantiomeric excess to that obtained using the titanium dichloride complex under non-anhydrous conditions (56, 86, and 72%, respectively). However, the reactions with the dimeric catalysts were much faster, being complete in 1–2 h at ambient temperature as opposed to the 24 h required for catalysts **2**. If the reaction temperature was reduced then higher ee values could be obtained. Thus, catalyst **4e** gave 86% ee at ambient temperature (reaction complete in <5 min), 92% ee at 0 °C (reaction complete in <5 min), and 96% ee at –50 °C, though the latter reaction was complete after only 3 days. Similarly, catalyst **4g** gave 72% ee at ambient temperature (reaction required 2 h), 84% ee at 0 °C (reaction was complete after 18 h), and 92% ee at –50 °C, though this reaction was only 75% complete after 3 days. Significantly, however, the ee of the product observed in these reactions stayed constant throughout the course of the reaction, as would be expected if the true catalyst was present throughout the reaction. The use of catalyst **4e** to induce the asymmetric addition of trimethylsilyl cyanide to a range of aldehydes was subsequently investigated as shown in Table 5. In each case, the aldehyde was completely consumed after a 1 h reaction at ambient temperature, and in every case the enantiomeric excess obtained using catalyst **4e** was the same as or higher than the enantiomeric excess obtained using catalyst **2e**.

Finally, the dimeric complex analogous to **4e** but derived from racemic ligand **1e** was prepared. In principle, this could have given three dimeric complexes: the two enantiomeric homodimers containing two ligands both with the same absolute configuration and the heterodimer containing one ligand with the (*R,R*)-configuration and one ligand with the (*S,S*)-configuration. The latter complex would be an achiral meso compound and would be diastereomeric with the homodimers. There are further diastereomeric possibilities if the relative orientation of the two salen ligands or the configuration around the titanium atoms are allowed to vary from those shown in Figure 2. However, the ¹H and ¹³C NMR spectra of the racemic dimer were identical with those of complex **4e** derived from enantiomerically pure ligand **1e**. This indicates that for this system, the homodimer is more stable than the heterodimer, and this

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Table 5. Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Catalyst **4e**^a

RCHO, R =	ee (abs config)	RCHO, R =	ee (abs config)
Ph	86 (S)	3,4-(MeO) ₂ C ₆ H ₃	85 (S)
2-MeC ₆ H ₄	76 (S)	3,5-(MeO) ₂ C ₆ H ₃	90 (S)
3-MeC ₆ H ₄	90 (S)	4-F ₃ CC ₆ H ₄	86 (S)
4-MeC ₆ H ₄	87 (S)	4-O ₂ NC ₆ H ₄	50 (S)
2-MeOC ₆ H ₄	88 (S)	Me ₃ C	66 (S)
3-MeOC ₆ H ₄	92 (S)	Me ₂ CH	64 (S)
4-MeOC ₆ H ₄	84 (S)	MeCH ₂	52 (S)
2,4-(MeO) ₂ C ₆ H ₃	88 (S)		

^a All reactions were carried out using 0.1 mol % of the catalyst for 1 h at ambient temperature.

explains the absence of a nonlinear relationship²⁶ between the ee of the ligand and the ee of the product in trimethylsilyl cyanations carried out using ligand **1e** and titanium tetraiso-propoxide. An alternative explanation for these results—that the dimeric complexes dissociate in solution—can be discounted since the molecular weight of complex **4a** determined by ultracentrifugation showed it to be dimeric in solution. Further studies on the structure and mode of action of the catalytically active species in these reactions will be reported soon, and the synthetic utility of these and related catalysts is currently being investigated and will be reported in due course.

Conclusions

This work has resulted in the discovery of a new class of catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes. The catalysts are dimeric (salen)titanium complexes in which the titanium atoms are bridged by two oxygen atoms, and the optimum catalyst **4e** possesses *tert*-butyl substituents in the 3- and 5-positions of the aromatic rings. High levels of asymmetric induction are obtained using catalyst **4e** and aromatic aldehydes, the product cyanohydrin trimethylsilyl ethers being obtained with between 76 and 92% enantiomeric excess at ambient temperature. Aliphatic aldehydes give cyanohydrin trimethylsilyl ethers with lower enantiomeric excesses (52 to 66%). Notably, the reactions are complete within 1 h at ambient temperature.

Experimental Section

¹H NMR spectra were recorded at 250 MHz on a Bruker AM250 spectrometer fitted with a ¹H–¹³C dual probe, and were recorded at 293 K in CDCl₃. Spectra were internally referenced either to TMS or to the residual solvent peak, and peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), some combination of these, broad (br), or multiplet (m). ¹³C NMR spectra were recorded at 62.5 MHz on the same spectrometer as ¹H NMR spectra, at 293 K and in CDCl₃. Spectra were referenced to the solvent peak, and are reported in ppm downfield of TMS. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer; only characteristic absorptions are reported. Mass spectra were recorded using the FAB technique (Cs⁺ ion bombardment at 25 kV) on a VG Autospec spectrometer. Only significant fragment ions are reported, and only molecular ions are assigned. Optical rotations were recorded on an Optical Activity Ltd. Polar 2001 or a Perkin-Elmer 241 polarimeter, and are reported along with the solvent and concentration in g/100 mL. Melting points are uncorrected. Elemental analyses were performed within the Chemistry department on a Carlo Erba Model 1106 or Model 1108 analyzer. Analytical ultracentrifugation was conducted using a MOM 3180 (Hungary) ultracentrifuge with differential Philpot-Svensson's optics. Chiral GC was carried out on a DP-TFA- γ -CD, fused silica capillary column (32m \times 0.2 mm) using helium as the carrier gas.

X-ray crystallographic measurements on complex **4a** were made at 193 K using a Siemens P3/PC diffractometer, Mo K α radiation, and a

graphite monochromator. Crystal data: $C_{43}H_{43}N_4O_6Cl_2Ti_2 \cdot 4CHCl_3$ (fw 1126.66); tetragonal; space group $P4_32_12$; $a = 18.411(3)$ Å, $c = 30.568(6)$ Å; $V = 10361(3)$ Å³; $Z = 8$; $D_c = 1.445$ g cm⁻³. The structure was solved by direct methods and refined by full-matrix least-squares techniques with anisotropic approximations for non-hydrogen atoms. The crystal contains four solvate chloroform molecules, two of which are disordered. One of the two disordered molecules occupies a special position on the C_2 axis. The chlorine atoms of the disordered molecules were refined within the isotropic approximation. All hydrogen atoms in calculated positions were included in the refining with fixed positional and thermal parameters (riding model). The absorption correction was not necessary ($\mu = 0.820$ mm⁻¹) and therefore was not applied. The absolute configuration was determined by the refined Flack parameter which became equal to 0.01(1), thus confirming that the absolute structure had been determined correctly. The final divergence factors were $R_1 = 0.091$ for 2450 independent reflections with $I > 2\sigma(I)$ and $wR_2 = 0.290$ for 4093 independent reflections. All calculations were carried out using SHELXTL PLUS (PC Version 5.0) programs.²⁹

Preparation of Catalysts 2b,d–g. A mixture of ligand **1b,d–g** (1 equiv) and titanium tetrachloride (1 M solution in dichloromethane; 1 equiv) was stirred at room temperature under argon in dry dichloromethane for 2 h. The reaction was concentrated in vacuo to give a brown solid that was washed with ether and with 50% ether/50% petroleum ether. The resultant brown solid was recrystallized from chloroform to give catalysts **2b,d–g**.

2b: Yield 19%; mp 250–300 °C; $[\alpha]^{21}_D +390$ (c 0.033, $CHCl_3$); (Found: C, 59.0; H, 6.8; N, 5.2. $C_{28}H_{36}N_2O_2Cl_2Ti \cdot \frac{1}{3}CH_2Cl_2$ requires: C, 59.3; H, 6.4, N, 4.9); ν_{max} (Nujol) 1618 s, 1583 m, and 1560 cm⁻¹ m; δ_H 1.4–1.6 (2H, m), 1.53 (9H, s), 2.0–2.1 (1H, m), 2.5–2.6 (1H, m), 4.0–4.1 (1H, m), 7.01 (1H, t, $J = 7.7$), 7.41 (1H, d, $J = 7.7$), 7.58 (1H, d, $J = 7.7$), 8.31 (1H, s); δ_C 24.1, 28.4, 29.8, 35.4, 67.7, 122.2, 126.2, 133.5, 133.7, 137.6, 160.2, 161.7.

2d: Yield 76%; mp 280–300 °C dec; $[\alpha]^{24}_D +153$ (c 0.01, $CHCl_3$); (Found: C, 53.4; H, 6.3; N, 4.4. $C_{30}H_{40}N_2O_4Cl_2Ti \cdot CH_2Cl_2$ requires: C, 53.5; H, 6.1, N, 4.0); ν_{max} (Nujol) 1615 s, 1594 s, and 1560 cm⁻¹ s; δ_H 1.2–1.4 (2H, m), 1.51 (9H, s), 2.0–2.1 (1H, m), 2.4–2.6 (1H, m), 3.80 (3H, s), 4.0–4.1 (1H, m), 6.85 (1H, d, $J = 3.0$), 7.16 (1H, d, $J = 3.0$), 8.25 (1H, s); δ_C (DMSO- d_6) 23.9, 29.0, 29.7, 35.1, 55.8, 67.8, 115.7, 124.8, 128.1, 138.3, 141.0, 152.2, 161.1; m/z (FAB) 692 ((M – Cl)₂ + *o*-nitrobenzyl alcohol)⁺, 100, 676 (10), 555 (12), 541 (15).

2e: Yield 95%; mp 330 °C dec; $[\alpha]^{22}_D +736$ (c 0.0125, $CHCl_3$); (Found: C, 63.8; H, 8.1; N, 4.4. $C_{36}H_{52}N_2O_2Cl_2Ti \cdot 0.7H_2O$ requires: C, 63.9; H, 8.0; N, 4.1); ν_{max} (KBr) 3449 br m, 2955 s, 1617 s, and 1561 cm⁻¹ m; δ_H 1.35 (9H, s), 1.4–1.65 (2H, m), 1.54 (9H, s), 2.05–2.1 (1H, m), 2.5–2.65 (1H, m), 4.0–4.1 (1H, m), 7.35 (1H, d, $J = 2.3$), 7.61 (1H, d, $J = 2.3$), 8.32 (1H, s); δ_C 24.1, 28.5, 29.9, 31.4, 34.5, 35.5, 67.7, 125.7, 130.1, 131.1, 136.7, 144.6, 159.7, 160.5; m/z (FAB) 663 (MH⁺, 20), 629 (100).

2f: Yield 99%; mp 280–300 °C; $[\alpha]^{21}_D +112$ (c 0.0125, $CHCl_3$); (Found: C, 73.5; H, 6.3; N, 2.6. $C_{66}H_{64}N_2O_2Cl_2Ti$ requires: C, 73.2; H, 6.0, N, 2.6); ν_{max} (Nujol) 1611 s, and 1552 cm⁻¹ m; δ_H 1.35 (9H, s), 1.5–1.7 (2H, m), 1.8–2.0 (1H, m), 2.3–2.5 (1H, m), 3.9–4.1 (1H, m), 6.9–7.4 (17H, m), 8.11 (1H, s); δ_C 24.0, 29.7, 35.4, 64.6, 67.8, 125.3, 126.2, 127.9, 131.0, 135.3, 136.3, 137.3, 140.5, 146.4, 160.0, 160.5.

2g: Yield 100%; mp 280–300 °C dec; $[\alpha]^{21}_D +268$ (c 0.0125, $CHCl_3$); (Found: C, 52.0; H, 5.7; N, 8.3. $C_{28}H_{36}N_4O_6Cl_2Ti$ requires: C, 52.3; H, 5.6, N, 8.7); ν_{max} (Nujol) 1620 s, 1592 s, and 1513 cm⁻¹ m; δ_H 1.2–1.5 (2H, m), 1.56 (9H, s), 2.1–2.2 (1H, m), 2.6–2.7 (1H, m), 4.0–4.1 (1H, m), 8.4–8.5 (3H, m); δ_C 23.9, 28.6, 29.4, 35.9, 68.4, 125.6, 128.8, 129.1, 139.7, 157.0, 159.5, 160.2.

Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Induced by Catalysts 2. To a stirred solution of the aldehyde (1.25 mmol) and catalyst **2b,d–g** (0.00125 mmol) in dry dichloromethane (1.5 mL) under an argon atmosphere was added dropwise, trimethylsilyl cyanide (1.38 mmol). The reaction mixture was stirred for 24 h and

then filtered through a pad of silica eluting with a 5/1 mixture of hexane/ethyl acetate. Concentration of the resulting solution in vacuo gave the cyanohydrin silyl ethers, the spectroscopic properties of which were consistent with those reported in the literature.^{3,6–17} The chemical yields and enantiomeric excesses of the products are given in Tables 1–3.

Synthesis of the Dimeric Complexes 4e,g from the Dichlorides 2e,g. A solution of the dichloride complex **2e,g** (1 equiv), water (1 equiv), and triethylamine (2 equiv) in dichloromethane was stirred at room temperature for 3 h. The resulting yellow solution was washed with water, dried over magnesium sulfate, and concentrated in vacuo to yield the dimeric complex **4e,g** as a yellow solid.

4e: Yield 95%; mp 315 °C dec; $[\alpha]^{22}_D -267$ (c 0.0125, $CHCl_3$); (Found: C, 70.9; H, 8.7; N, 4.8. $C_{72}H_{104}N_4O_6Ti_2$ requires: C, 71.0; H, 8.6; N 4.6); ν_{max} (CH_2Cl_2) 2962 s, 2865 m, 1625 s, and 1555 cm⁻¹ m; δ_H 1.04 (9H, m), 1.22 (9H, m), 1.31 (9H, m), 1.40 (9H, m), 1.8–1.9 (4H, m), 2.5–2.6 (4H, m), 4.0–4.1 (2H, m), 6.95 (1H, s), 7.05 (1H, s), 7.23 (1H, s), 7.42 (1H, s), 7.75 (1H, s), 8.15 (1H, s); δ_C 24.6, 24.9, 28.1, 29.7, 30.1, 31.5, 31.7, 34.1, 35.0, 35.7, 65.7, 69.8, 121.0, 121.9, 125.8, 127.5, 128.0, 128.5, 137.6, 138.0, 139.1, 139.4, 157.1, 161.3; m/z (FAB) 1217 (MH⁺, 6), 1201 (14), 744 (100), 609 (20).

4g: Yield 93%; mp >320 °C dec; $[\alpha]^{22}_D -297$ (c 0.0125, $CHCl_3$); (Found: C, 56.7; H, 5.7; N, 9.4. $C_{56}H_{68}N_8O_{14}Ti_2 \cdot 0.5H_2O$ requires: C, 56.9; H, 5.8; N 9.5); ν_{max} (CH_2Cl_2) 2949 s, 2862 m, 1727 w, 1633 s, 1596 s, 1572 m, 1552 w, and 1510 cm⁻¹ s; δ_H 1.15 (9H, s), 1.50 (9H, s), 2.5–2.6 (4H, m), 2.8–2.9 (4H, m), 3.85 (2H, m), 8.11 (1H, s), 8.26 (2H, m), 8.37 (3H, m); δ_C 23.9, 24.4, 25.328.1, 29.2, 29.5, 35.4, 35.9, 67.9, 68.9, 121.7, 122.0, 126.3, 126.9, 128.7, 137.5, 138.0, 138.9, 140.0, 141.1, 144.3, 158.0, 161.2.

Synthesis of Dimers 4a,e from in Situ Catalyst. A solution of ligand **1a,e** (1 equiv) and titanium tetraisopropoxide (1 equiv) in dry dichloromethane was stirred at room temperature under argon for 2 h. Water (1 equiv) was then added and the reaction mixture was stirred at room temperature for 3 h. The resulting yellow solution was concentrated in vacuo, and the residue was washed with dichloromethane to leave complex **4a,e** as a yellow solid.

4a: Yield 50%; $[\alpha]^{25}_D -410$ (c 0.04, $CHCl_3$); (Found: C, 61.7; H, 5.4; N, 7.3; Ti, 12.3. $C_{40}H_{40}N_4O_6Ti_2$ requires: C, 61.8; H, 5.4; N, 7.3; Ti, 12.3); δ_H 1.3–1.4 (7H, m), 1.8–1.9 (7H, m), 2.3–2.4 (2H, m), 2.7–2.8 (2H, m), 3.8–3.9 (2H, m), 6.95 (1H, s), 6.75–7.45 (16H, m), 8.07 (2H, s), 8.24 (2H, m). Molecular weight determined by analytical ultracentrifugation³⁰ 773 (c 3–6 g/L, THF, 25 °C), calculated for $C_{40}H_{40}N_4O_6Ti_2$ 768 (2% deviation).

Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Induced by Catalyst 4. To a stirred solution of the aldehyde (1.25 mmol) and catalyst **4a,e** (0.00125 mmol) in dry dichloromethane (1.5 ml) under an argon atmosphere was added dropwise trimethylsilyl cyanide (1.38 mmol). The reaction mixture was stirred for 24 h and was then filtered through a pad of silica eluting with a 5/1 mixture of hexane/ethyl acetate. Concentration of the resulting solution in vacuo gave the cyanohydrin silyl ethers, the spectroscopic properties of which were consistent with those reported in the literature.^{3,6–17} The enantiomeric excesses of the products are given in Table 5.

Acknowledgment. The authors thank the EPSRC, INTAS, the EU (INCO-COPERNICUS and SOCRATES), and the Russian Fund for Fundamental Research (Grant No. 98-03-32862) for financial support. Mass spectra were recorded by the EPSRC national mass spectrometry service.

Supporting Information Available: Tables of crystal data, structure solution and refinements, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **4a**; table of GC conditions for ee determinations; ¹H NMR spectra for complexes **2b**, **2e**, and **4g** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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