Mechanistic Investigation of the Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalysed by Dinuclear Chiral (Salen)titanium Complexes

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Dedicated to Professor Gunther Wulff on the occasion of his 65th birthday

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Titanium complexes **1** derived from chiral salen ligands are highly active precatalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes and ketones. Based on spectroscopic studies and the identification of adducts between complexes **1** and carbonyl compounds or trimethylsilyl cyanide, a catalytic cycle which explains the origin of the asymmetric induction is proposed. Kinetics studies have been carried out, the results of which are consistent with the proposed catalytic cycle.

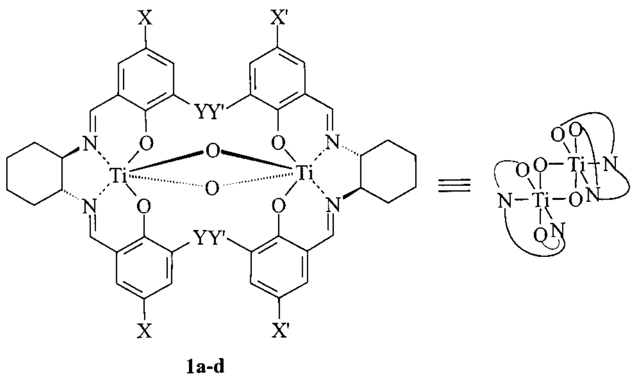
Introduction

In a previous manuscript,[1] the synthetic studies that culminated in the discovery of the dinuclear, chiral (salen)-titanium complexes **1a−c** have been described. These complexes (especially **1b**) are highly active precatalysts for the asymmetric addition of trimethylsilyl cyanide to both aromatic and aliphatic aldehydes (Scheme 1) and to ketones.[2] Amongst the favourable features of these precatalysts are their ease of preparation and stability, and the fact that trimethylsilylations employing these precatalysts can be carried out in less than one hour at ambient temperature, using high substrate to precatalyst ratios (1,000:1). The enantiomeric excesses of the cyanohydrin silyl ethers prepared in this way are 75−92% for products derived from aromatic aldehydes, >50% for aliphatic aldehydes, and 32−72% for ketones. Whilst these enantiomeric excesses compare favourably with alternative catalytic systems,[3] it would be desirable to discover a catalytic system which was capable of producing cyanohydrins with an enantiomeric excess >95%. To this end, it appeared worthwhile to investigate the mechanism of the trimethylsilylation of aldehydes catalysed by complexes **1** so that new improved catalysts could later be designed. In particular, the following questions had to be answered.

Scheme 1

1. Is the real catalyst a dinuclear or a mononuclear complex?
2. How do the coordinatively saturated complexes **1** become Lewis acids, capable of activating aldehydes?
3. Which steps of the reaction are stereo- and rate-determining?

In this manuscript we present the results of mechanistic studies, propose a reaction mechanism that is consistent with all the observed features of the reaction and propose a transition state geometry that accounts for the origin of the asymmetric induction.



1a-d

a) $X = X' = Y = Y' = H$
b) $X = X' = Y = Y' = {}^tBu$
c) $X = X' = NO_2$; $Y = Y' = {}^tBu$
d) $X = NO_2$; $X' = Y = Y' = {}^tBu$

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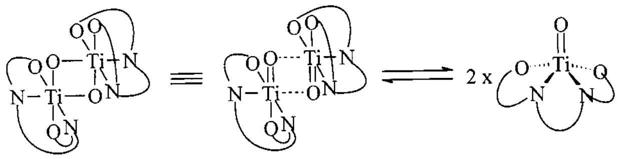
Detection of Reaction Intermediates

The X-ray crystal structure of complex **1a** showed that the central four-membered ring was rectangular rather than square.[1] Thus, two of the Ti−O bonds are significantly shorter (1.806−1.821 Å) than the other two Ti−O bonds (1.857−1.878 Å). It appeared feasible that in the reaction solution, the dimer could dissociate into monomer units (Scheme 2), and either the mononuclear or dinuclear forms of the catalyst could be the active species. To attempt to address this issue, the structures of complexes **1** were first investigated in solution in the absence of any other species that could be present in the reaction mixture. The natural abundance ^{17}O NMR spectrum of complex **1b** (in $CDCl_3$) showed a sharp peak at $\delta = 840$ which is known to be characteristic of a Ti=O group,[4] thus indicating that the equilibrium shown in Scheme 2 does exist.

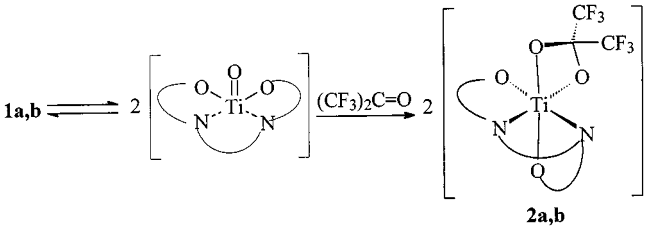


Scheme 2

Complexes **1** are only precursors of the catalytically active species, and to investigate the nature of the real catalyst, attempts were made to detect and characterise complexes formed from compounds **1a**, **b** and either trimethylsilyl cyanide or a carbonyl compound. An interaction between complexes **1** and benzaldehyde would involve the titanium acting as a Lewis acid, whilst an interaction between complexes **1** and trimethylsilyl cyanide would generate a chiral cyanide source. Literature precedent exists for both mechanisms with related titanium complexes.[5,6]

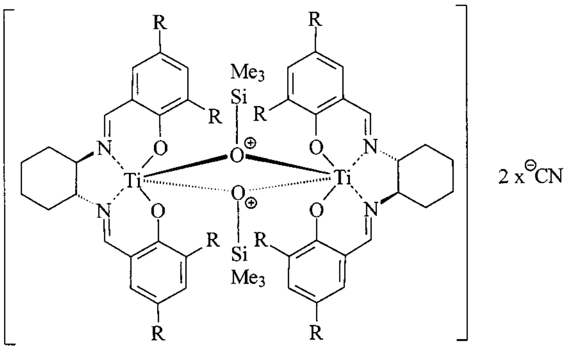
Catalyst **1a** or **1b** and benzaldehyde (30-fold excess) were mixed in dichloromethane and the resulting solution analysed by ^{1}H NMR and CD spectroscopy. No evidence for any interaction between the complex and benzaldehyde could be detected by either of these methods. Significantly, the titanium atoms in dinuclear complexes **1** are already six coordinate, so formation of a complex between the titanium and benzaldehyde would presumably only be possible if an existing bond in the complex were to break first.[7] Further evidence that complexes **1** are not capable of acting as Lewis acids was obtained during attempts to use other nucleophiles in place of trimethylsilyl cyanide. In particular, no reaction between benzaldehyde and allyl trimethylsilane,[8] allyl tributylstannane,[9] 2-silyloxypropene,[10] or trimethylsilyl azide was observed in the presence of complexes **1a**, **b**, despite the fact that the addition of the first three of these nucleophiles to aldehydes is known to be catalysed by a wide range of Lewis acids.

Nevertheless, when hexafluoroacetone was added to a solution of **1a**, **b** in CD_2Cl_2 the immediate formation of a new complex **2a**, **b** occurred. The infrared absorptions at 740 and 690 cm^{-1} associated with the Ti−(μ-O)$_2$Ti bridge of **1a**, **b** disappeared, while those of the C=N bonds (1620 cm^{-1}) were still present. It appears that complex **2a**, **b** is formed by a net [2+2] cycloaddition of the Ti=O bond of the mononuclear form of complex **1a**, **b** and the C=O bond of the electron deficient ketone (Scheme 3) to give a metallacycle, analogously to the known reaction[4] of [tmtaa]Ti=O (tmtaa = dianion of 7,16-dihydro-6,8,15,17-tetramethyldibenzo[*b*,*i*]-[1,4,8,11]tetraazacyclotetradecine). The NMR spectra of isolated complexes **2a**, **b** were also consistent with the proposed structure. Molecular weight measurements (990 by ultracentrifugation) indicate that in solution, complex **2a** may be in equilibrium with dinuclear complexes. When formaldehyde was bubbled through a solution of **1a** in $CDCl_3$, a complex analogous to **2a**, **b** was detected by ^{1}H NMR in equilibrium with complex **1a**. In particular, the ^{1}H NMR spectrum of the new complex exhibited a new set of aldimine proton resonances at $\delta = 8.29$ and 8.43, and a new set of multiplets at $\delta = 2.10$ (2 H), 2.38 (1 H), 2.57 (1 H), 3.02 (1 H), and 4.43 (1 H). It can be assumed that similar metallacycles are formed in a trimethylsilylcyanation reaction in the presence of **1** and carbonyl compounds. As most carbonyl compounds are much less electrophilic than $(CF_3)_2CO$ or formaldehyde, the concentration of such metalla-acetals will be too low to be detected.



Scheme 3

When complexes **1a**, **b** and an excess (10−30-fold) of trimethylsilyl cyanide were mixed in dichloromethane, then CD, ^{1}H NMR and ^{13}C NMR spectroscopy indicated that a new species (**3a**, **b**) was formed. Thus, ^{1}H NMR spectroscopy showed two new aldimine resonances shifted by 0.2 ppm relative to those of **1a**, or **1b** and all the other signals were also significantly shifted (vide infra). The ^{1}H NMR spectrum also showed a new signal corresponding to the protons of two $(CH_3)_3SiO$ moieties at $\delta = -0.21$. It has not proven possible to isolate a pure sample of compounds **3a**, **b** as they readily decompose, though, a dinuclear structure has been determined based upon the FAB mass spectrum ($(MH-Me_3SiCN)^+ = 1317$ for **3b**) and by ultracentrifugation (in THF) via extrapolation of the changing molecular weight of a mixture of **1b** and a 30-fold excess of trimethylsilyl cyanide to the beginning of the experiment, which gave a molecular weight of 1040 (calculated for **3b**: 1415). As the extrapolation had to be done from points obtained after the actual commencement of the reaction, the calculated zero time value of the molecular weight must be viewed with caution. It does however, show that complex **3b** is not predominantly monomeric.



3a,b
a) R = H
b) R = ^{t}Bu

The CD spectra of **3a**, **b** showed the exciton splitting[11] typical of a nonplanar salen ligand coordinated to titanium in a *cis*-β stereochemical arrangement. The ^{1}H- and ^{13}C NMR spectra of compounds **3a**, **b** suggested that the complexes retained C_2 symmetry in solution. A feature of the ^{1}H NMR spectra is a significant downfield shift of the α- and γ-protons of the cyclohexane rings (from δ = 2.7 to 3.65 and from δ = 0.9 to 1.4, respectively). These shifts suggest that the salen groups in complexes **3a**, **b** are less able to shield the α- and γ-protons of the cyclohexane rings of the other salen ligand, and hence indicate that the salen rings are further apart than in complexes **1a**, **b**.

The infrared spectra of complexes **3a**, **b** run in CH_2Cl_2 indicated the appearance of a new band centred at 2070 cm^{-1} which could be attributed to a new cyanide moiety. The CN stretching frequency for $[NEt_4]_3[Ti^{III}(CN)_6]$ occurs at 2071 cm^{-1} and is lower by approximately 40 cm^{-1} than those of other $M^{III}(CN)_6$ (M = Cr, Co, Mn, Fe, or Co) salts.[12] Notably, the stretch of the cyanide anion in water occurs at 2080 cm^{-1} and the coordination of the anion at a metal always increases the frequency of this absorption.[13] This suggests that the cyanide ligand is not significantly bonded to the Ti^{IV} centre in **3**. The infrared spectrum of **3b** run in hexane (to avoid any interference from solvent peaks) established the disappearance of the absorptions of the Ti−O−Ti bridges[13] at 690 cm^{-1} which had been present in the spectrum of **1b**. At the same time, a new absorption at 940 cm^{-1} appeared in the infrared spectrum of **3b** which can be associated with new O−Si or Ti−OSi bonds.[13]

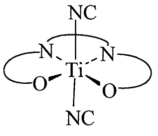
Based on the above evidence, complexes **3a**, **b** have been assigned the indicated structures. This is a C_2-symmetrical structure (which is consistent with the NMR data) containing two *cis*-β (salen)Ti moieties (consistent with the CD data) bridged by two $OSiMe_3$ groups.[14] The two cyanide groups are either weakly bonded as seventh ligands[7] or are outer-sphere anionic species, the latter being more consistent with the infrared data. The steric requirements of the trimethylsilyl groups ensures that the dinuclear complexes **3a**, **b** will have much greater distances between the two titanium atoms and their associated salen ligands, than is observed for complexes **1a**, **b**, which is consistent with the reduced shielding of protons observed in the ^{1}H NMR spectra of **3a**, **b**.

If the reaction of benzaldehyde with trimethylsilyl cyanide catalysed by **1** is conducted in the presence of an excess of trimethylsilyl cyanide, structure **3** represents the predominant form in which the titanium complex exists at the end of the reaction as judged by the ^{1}H NMR and CD spectra of the final reaction mixture. Compounds **3** are unstable and loose their C_2-symmetrical *cis*-β dinuclear structure, producing a mixture of mononuclear complexes (as determined by molecular weight determinations: the measured molecular weight of complex **3b** decreases from 880 after 1.5 hours to 690 after 4.5 hours) with a planar coordination of the salen ligand.[15] Likely structures for these products include **4**−**6**, and indeed the formation of complex **4** is needed as part of our catalytic cycle (vide infra). It is possible that complex **4** is also formed indirectly through the reaction of complexes **5** and/or **6** with trimethylsilyl cyanide. To investigate the role of compounds **3** in the catalytic cycle, the kinetics of the reaction using **3b** as catalyst were determined. As can be seen from Table 1 (run 6), the k_{obs} of the reaction is three orders of magnitude smaller than k_{obs} for the reaction using **1b** under the same conditions (Table 1, run 1).

Table 1. Observed rate constants (k_{obs}) for the addition of trimethylsilyl cyanide to benzaldehyde catalysed by complexes **1** and **3** at 20 °C

Run[a]	Solvent	Order of addition[b]	Catalyst	k_{obs} ($c^{-1} \times 10^5$)
1	CH_2Cl_2	A	**1b**	1900 ±40
2	CH_2Cl_2	A	**1c**	3 ± 1
3	CH_2Cl_2	A	**1d**	230 ± 30
4	CH_2Cl_2	B	**1b**	120 ± 50
5	CH_2Cl_2	C	**1b**	100 ± 50
6[c]	CH_2Cl_2	A	**3b**	0.3 ± 0.1
7	hexane	A	**1b**	3900 ± 100
8	C_6H_6	A	**1b**	2290 ± 10
9	THF	A	**1b**	1200 ± 100

[a] Reaction conditions: benzaldehyde 0.6347 M, trimethylsilyl cyanide 0.9676 M, catalyst $4.29 \cdot 10^{-4}$ M. − [b] A: the catalyst was added to a solution of benzaldehyde, followed by the addition of trimethylsilyl cyanide; B: the catalyst was added to a solution of trimethylsilyl cyanide followed by the addition of benzaldehyde; C: the catalyst was added to a mixture of benzaldehyde and trimethylsilyl cyanide. − [c] **3b** was prepared by mixing **1b** (0.0033 g, $2.7 \cdot 10^{-6}$ mol) and trimethylsilyl cyanide (0.01 mL, $7.66 \cdot 10^{-5}$ mol) in CH_2Cl_2 (0.6 mL). A sample of the solution (0.15 mL) was injected into a solution of benzaldehyde (0.1 mL, $9.87 \cdot 10^{-4}$ mol) in CH_2Cl_2 (1.1 mL), followed by addition of trimethylsilyl cyanide (0.2 mL, $1.53 \cdot 10^{-3}$ mol).



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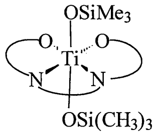

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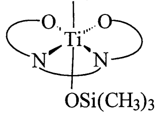

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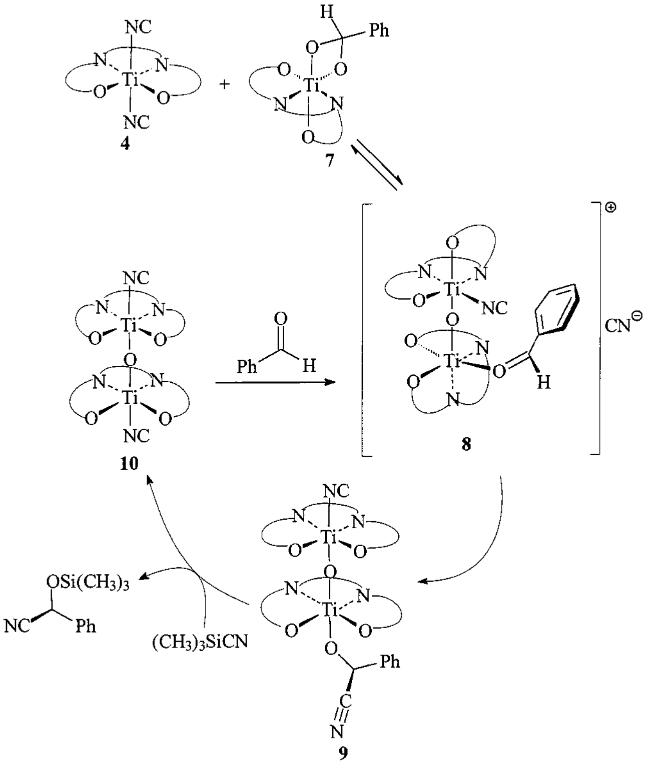
For reactions catalysed by **1b**, addition of trimethylsilyl cyanide before addition of benzaldehyde resulted in a significant decrease in k_{obs} (compare Table 1, runs 1 and 4). The same low rate constant was observed if **1b** was added to a mixture of trimethylsilyl cyanide and benzaldehyde (Table 1, run 5). Thus, it seems that the addition of benzaldehyde to catalyst **1** before the introduction of trimethylsilyl cyanide is necessary to form the catalytically active species. This can be explained if complexes **2** and **3** are both needed for the generation of the active catalyst, and if the formation of complex **3** is faster than the formation of complex **2** and is essentially irreversible.

To investigate whether the catalyst contains $(CH_3)_3SiO$ groups coordinated to titanium ions, a comparison of the use of trimethylsilyl cyanide and HCN was undertaken. The addition of HCN to benzaldehyde was catalysed by **1a** and **1b**, to give mandelonitrile with 50% and 80% *ee* respectively at ambient temperature, though the reaction was much slower than that using trimethylsilyl cyanide as the cyanide source. These values are very close to the *ee*s obtained for the addition of trimethylsilyl cyanide to benzaldehyde promoted by the same catalysts under the same conditions (50% and 78−80%, respectively). Thus, it seems that the catalyst does not contain large $(CH_3)_3SiO$ groups coordinated to titanium in the transition state of the reaction, otherwise different enantioselectivities would have been expected for reactions carried out using trimethylsilyl cyanide and HCN.

The possibility of a cyanohydrin being coordinated to titanium in the catalyst was investigated by monitoring the addition of trimethylsilyl cyanide to an equimolar mixture of benzaldehyde and *p*-CF_3-benzaldehyde catalysed by **1b**. Had a cyanohydrin been coordinated to the catalyst in the stereo-determining step, the enantioselectivity of the cyanide addition would have been different for at least one of the aldehydes from those observed for the addition of trimethylsilyl cyanide to each aldehyde separately under the same reaction conditions (78−80% for benzaldehyde and 54% for *p*-CF_3-benzaldehyde). In fact, the observed enantiomeric excesses (75% and 55% respectively) were essentially the same as those observed in separate experiments, which suggests that a cyanohydrin is not coordinated to the titanium in the stereo-determining step of the mechanism.

A mechanistic hypothesis which is consistent with all of the observations discussed above is shown in Scheme 4. Thus, combination of dicyanide complex **4** (obtained from dinuclear complex **3**) with mononuclear benzaldehyde adduct **7** (formed analogously to the hexafluoroacetone adduct **2**) generates the key intermediate, binuclear complex **8**. Complex **8** comprises both an activated aldehyde and a titanium cyanide bond. Intramolecular transfer of cyanide within complex **8** generates a complex **9** containing a titanium bound cyanohydrin. Subsequent trimethylsilylation of complex **9** would give the product and dinuclear dicyanide complex **10**. Displacement of one of the weakly bound cyanide ligands of complex **10** by benzaldehyde would regenerate complex **8**. This catalytic cycle also correctly predicts the sense of asymmetric induction. Thus, coordination of the aldehyde so as to minimize interactions between the aldehyde substituent and the cyclohexane ring of the ligand (Figure 1) results in an orientation in which the *re*-face of the aldehyde is exposed to intramolecular attack by the coordinated cyanide, leading to the (*S*)-enantiomer of the cyanohydrin trimethylsilyl ether.



Scheme 4

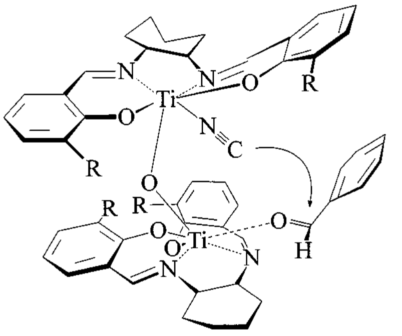


Figure 1. Representation of the transition state for reaction between an aldehyde and trimethylsilyl cyanide catalysed by complexes **1**

Kinetics Studies

Complexes **8−10** which are postulated to be the key complexes involved in the catalytic cycle could not be detected directly because of their low concentration and high reactivity within the reaction mixture. However, the kinetics of reactions carried out using precatalysts **1a−c** were consistent with the catalytic cycle shown in Scheme 4. Kinetics experiments were carried out by monitoring the decrease in absorption (at 246 nm) as the benzaldehyde was consumed. The reactions were found to be described by first order kinetics up to at least 80% conversion, the rate being first

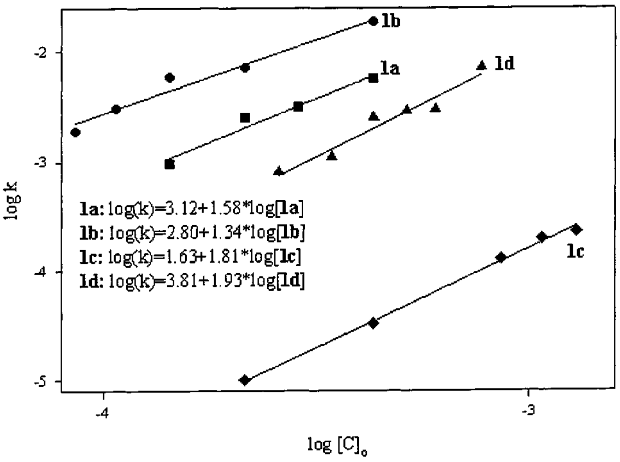


Figure 2. Plots of log *k* versus log[C]$_o$ for precatalysts **1a−d**

order with respect to the concentration of trimethylsilyl cyanide and independent of the concentration of benzaldehyde. The rate constants calculated at different initial concentrations [C]$_o$ of the precatalyst allowed the order of reaction with respect to the catalysts to be determined as 1.6±0.2 for **1a**, 1.3±0.2 for **1b**, and 1.8±0.1 for **1c** by plotting log *k* against log [C]$_o$ for **1a−c** (Figure 2). The rate equations are hence described as:

For precatalyst **1a**:
$\text{rate} = 1300\cdot[\text{C}]_o^{1.6}\cdot[\text{Me}_3\text{SiCN}]_o^{1}\cdot[\text{PhCHO}]_o^{0}$
For precatalyst **1b**:
$\text{rate} = 634\cdot[\text{C}]_o^{1.3}\cdot[\text{Me}_3\text{SiCN}]_o^{1}\cdot[\text{PhCHO}]_o^{0}$
For precatalyst **1c**:
$\text{rate} = 43\cdot[\text{C}]_o^{1.8}\cdot[\text{Me}_3\text{SiCN}]_o^{1}\cdot[\text{PhCHO}]_o^{0}$

where [C]$_o$, [Me$_3$SiCN]$_o$, and [PhCHO]$_o$ are the initial concentrations of precatalyst **1a−c**, trimethylsilyl cyanide, and benzaldehyde, respectively.

Assuming that when precatalysts **1** are dissolved in the reaction mixture, a rapid equilibrium is established between dinuclear (D) and mononuclear (M) complexes, one of which is the catalyst, then:

$$[\text{C}]_o = 0.5\cdot[\text{M}]_{eq} + [\text{D}]_{eq} \text{ and } [\text{D}]_{eq} = K_{eq}\cdot[\text{M}]_{eq}^2$$

where K_{eq} is the equilibrium constant for the dinuclear/mononuclear complex distribution and [M]$_{eq}$ and [D]$_{eq}$ are the concentrations of the mononuclear and dinuclear complexes at equilibrium. It is then possible to analyse the rate equation in terms of [M]$_{eq}$ and [D]$_{eq}$ for the four extreme cases:

a) If the mononuclear species is the catalyst so that: $\text{rate} = k'\cdot[\text{M}]_{eq}$, then:

If the mononuclear complex is the predominant species in solution so that $[\text{C}]_o \approx 0.5\cdot[\text{M}]_{eq}$ then: $\text{rate} = k'\cdot[\text{C}]_o$

If the dinuclear complex is the predominant species in solution so that $[\text{C}]_o \approx [\text{D}]_{eq}$ then: $\text{rate} = k'[\text{C}]_o^{1/2}$

b) If the dinuclear species is the catalyst so that $\text{rate} = k'[\text{D}]_{eq}$, then:

If the mononuclear complex is the predominant species in solution so that $[\text{C}]_o \approx 0.5\cdot[\text{M}]_{eq}$ then: $\text{rate} = k'\cdot[\text{C}]_o^2$

If the dinuclear complex is the predominant species in solution so that $[\text{C}]_o \approx [\text{D}]_{eq}$ then: $\text{rate} = k'\cdot[\text{C}]_o$

It is apparent from these rate equations that if the catalyst is a mononuclear species, then the order of the reaction with respect to the precatalyst cannot be greater than one. However, if the catalyst is a dinuclear species, then the order of the reaction with respect to the precatalyst will be between one and two, with the exact value depending upon the equilibrium constant K_{eq} between the mononuclear and dinuclear species. The latter is consistent with the experimental results, and indicates that the catalyst is a dinuclear complex (e.g. complexes **8−10**) in equilibrium with catalytically inactive mononuclear species (e.g. complexes **4**, **7**).

Further evidence that the catalytically active species was not mononuclear was obtained by the preparation of complex **1d**. Thus, when equimolar amounts of complexes **1b** and **1c** were mixed in chloroform, quantitative formation of complex **1d** occurred as judged by ^{1}H- and ^{13}C NMR spectroscopy. In particular, complex **1d** does not possess C_2 symmetry and so shows resonances corresponding to four different aromatic rings and four different imines. These are distinct from the resonances corresponding to complexes **1b** and **1c**. The quantitative formation of complex **1d** from the equilibration of complexes **1b** and **1c** may be due to the mixed complex being less sterically hindered than **1b** and less electron deficient than **1c**.

The catalytic activity of complex **1d** was compared with the catalytic activity of complexes **1b** and **1c.** A kinetics analysis of the reaction promoted by the mixed complex **1d** gave a reaction order of 1.9±0.2 and an observed rate constant ($k_{obs} = k\cdot[\text{C}]_o^x$) of $(2.3\pm0.3) \times 10^{-3}\ c^{-1}$ (Table 1, run 3); which differ from those found for **1b** and **1c**. It is apparent from this data that precatalyst **1d** gives much greater reaction rates than precatalyst **1c** (k_{obs} for **1c** is $(3\pm1) \times 10^{-5}\ c^{-1}$; Table 1, run 2) and has a much smaller rate constant than **1b** (k_{obs} for **1b** is $(1.9\pm0.04) \times 10^{-2}\ c^{-1}$; Table 1, run 1). Thus, if a mononuclear complex derived from **1d** was to be the active catalyst, it would be expected that the rate of reaction would be virtually identical to that obtained using complex **1b**. However, the observed rate constant for complex **1d** is almost ten times lower than that of complex **1b**. Hence, the experimental evidence suggests that whilst the catalytically active species derived from complexes **1** do exist in the reaction mixtures as an equilibrium mixture of mononuclear and dinuclear forms, it is the dinuclear form of the complex that is the catalyst.

The last question to be addressed is which of the stages of the reaction is the rate determining step. As the concentration of the aldehyde does not enter the rate equation, the most likely rate limiting step is that of silylation of the coordinated cyanohydrin with the formation of the product and complex **10**. The negligible dependence of the rate of the reaction on the dielectric constant of the solvent (Table 1, runs 1, 7−9) supports this as during this step no charges are lost or created. The low catalytic activity of **1c** can also be attributed to the increase of the positive charge on the titanium centres induced by the electron-withdrawing NO$_2$ groups with the accompanying stabilization of the coordinated cyanohydrin Ti−O bond.

Conclusions

A possible mechanistic cycle and transition state structure for the asymmetric addition of trimethylsilyl cyanide to aldehydes catalysed by precatalysts **1** is presented. The mechanistic cycle is based on complexes which can readily be formed from species detected during the interaction of precatalysts **1** with carbonyl compounds or trimethylsilyl cyanide. The remarkable activity of precatalysts **1** is also explained by their ability to simultaneously activate both the aldehyde and cyanide components of the reaction. The catalytic cycle is entirely consistent with the kinetics of the reaction, and the transition state structure correctly predicts which enantiomer of the product will be formed. Ongoing work is aimed at the development of new catalysts displaying enhanced enantioselectivity and based on the mechanistic cycle presented in this manuscript. Results in this area will be reported in due course.

Experimental Section

General experimental details were reported in a previous manuscript.[1] – Infrared spectra of solutions were measured with a Nicolet Magna-750 Fourier-transform spectrometer with a resolution of 2 cm^{-1}. The spectra were recorded using a 0.06 mm KBr cell. Solvent spectra were subtracted from solution spectra using the OMNIC Nicolet program. – ^1H NMR spectra were recorded on a Bruker AMX-400 spectrometer (400.13 MHz) with CH_2Cl_2 ($\delta = 5.3$) as an internal standard.

Kinetic Experiments: Kinetic experiments were carried out at 20±0.5 °C. Standard solutions ($2.66{\cdot}10^{-3}$ mol/L) of complexes **1b** and **1c** or $1.33{\cdot}10^{-3}$ mol/L of complex **1a** were prepared in dry dichloromethane. A sample of this solution was injected into a solution of benzaldehyde (0.1 mL, 0.1 mmol) in an appropriate volume of CH_2Cl_2 (the total volume of benzaldehyde, dichloromethane and the solution of the complex was 1.35 mL), followed by addition of trimethylsilyl cyanide (0.2 mL, 1.5 mmol). The initial ($t = 0$) absorption of the benzaldehyde solution at 246 nm in dichloromethane was determined from a solution containing just the appropriate concentration of benzaldehyde and catalyst and no trimethylsilyl cyanide. 10 µL Samples were taken at appropriate intervals as the reaction progressed. These samples were immediately diluted into 5 mL of dry dichloromethane. The samples were then analysed by UV spectrophotometry at maximum benzaldehyde absorption (246 nm in dichloromethane). The absorption data were used to determine the concentration of benzaldehyde. Observed first order rate constants (k_{obs}) were determined from the slope of a plot of $\ln[Me_3SiCN]_t$ against time. These plots were linear for at least three half lives.

Complex 1d: Complex **1b** (0.01 g, 0.08 mmol) and complex **1c** (0.01 g, 0.08 mmol) were stirred together in dichloromethane (5 mL) at room temperature for 30 minutes. The dichloromethane was removed in vacuo to leave complex **1d** (0.02 g, 97%) as a light orange powder. M.p. >320°C (decomp.); $[\alpha]_D^{22} = -450$ ($c = 0.0125$, $CHCl_3$). – $C_{64}H_{86}N_6O_{10}Ti_2$ calcd. C 64.32, H 7.25, N 7.03; found C 64.12, H 7.23, N 7.04. – $\nu_{max}(CH_2Cl_2)$: 2964 s, 2866 m, 1632 s, 1595 s, 1562 cm^{-1} m. – δ_H: 1.10 (s, 9 H, *t*Bu), 1.15 (s, 9 H, *t*Bu), 1.30 (s, 9 H, *t*Bu), 1.35 (s, 9 H, *t*Bu), 1.45 (s, 9 H, *t*Bu), 1.50 (s, 9 H, *t*Bu), 1.8–1.9 (m, 4 H, CH_2CH_2), 1.9–2.0 (m, 4 H, CH_2CH_2), 2.4–2.5 (m, 4 H, CH_2CH_2), 2.9–3.0 (m, 4 H, CH_2CH_2), 3.8–3.9 (m, 2 H, 2 × NCH), 4.2–4.3 (m, 2 H, 2×NCH), 7.15 (s, 1 H, ArCH), 7.45 (s, 1 H, ArCH), 7.61 (s, 1 H, ArCH), 7.95 (s, 1 H, ArCH), 8.05 (s, 1 H, ArCH), 8.28 (s, 2 H, ArCH), 8.30 (s, 1 H, ArCH), 8.35 (s, 2 H, HC=N), 8.40 (s, 2 H, HC=N). – δ_C: 24.0, 24.4, 24.6, 27.8, 28.9, 29.4, 29.6, 30.0, 31.4, 31.6, 34.2, 35.0, 35.3, 35.7, 35.9, 65.9, 67.1, 69.6, 70.5, 121.8, 125.7, 125.9, 126.2, 127.1, 127.7, 129.0, 129.3, 129.4, 136.1, 137.0, 137.9, 139.1, 139.8, 140.5, 140.8, 142.4, 156.4, 156.9, 157.8, 159.7, 160.7, 161.4, 161.7, 167.8. For the kinetic experiments, a standard solution of complex **1d** was prepared by mixing standard solutions of complexes **1b** and **1c** (in ratio 1:1 by volume).

Asymmetric Addition of Hydrogen Cyanide to Benzaldehyde Catalysed by Complexes 1a, b: Benzaldehyde (0.14 mL, 1.38 mmol), complex **1a**, **b** ($1.0{\cdot}10^{-3}$ g, $1.3{\cdot}10^{-3}$ mmol) and a 1.1 N solution of hydrogen cyanide in dichloromethane (2 mL) were stirred together under an argon atmosphere at room temperature for 2 hours. The reaction mixture was then purified by flash chromatography, eluting with a solution of ethyl acetate/hexane 1:5. Concentration in vacuo gave 2-phenyl-2-hydroxyacetontrile (30%) which had 50% *ee* (using **1a** as catalyst) or 80% *ee* (using **1b** as catalyst) as determined by chiral GC as reported previously.[16]

Complex 2a: Hexafluoroacetone (1.0 mL, 9.6 mmol) was added to a vigorously stirred suspension of complex **1a** (0.50 g, 0.65 mmol) in CH_2Cl_2 (20 mL). The resulting orange solution was allowed to warm to room temperature and stirred for 30 minutes. Solvent was evaporated in vacuo and benzene (50 mL) was added. The resulting precipitate was filtered, washed with benzene, and added to CH_2Cl_2. Impurities were removed by filtration and evaporation of the solvent in vacuo gave 0.25 g (30%) of complex **2a**. M.p. 264 °C (decomp.); $[\alpha]_D^{25}$ −491.67 (c = 0.0125, $CHCl_3$). – $C_{23}H_{20}N_2O_4F_6Ti \cdot 0.5\,H_2O$ calcd. C 49.4, H 3.8, N 5.01; found C 49.0, H 3.54, N 5.13. – $\nu_{max}(CH_2Cl_2)$: 1625 s, 1613 m, 1600 m, 1555 cm^{-1} m. – δ_H: 1.2–1.55 (m, 4 H, CH_2CH_2), 1.8–2.0 (m, 2 H, CH_2), 2.4–2.5 (m, 1 H, CH_2), 2.6–2.7 (m, 1 H, CH_2), 3.4–3.6 (m, 1 H, NCH), 4.45–4.55 (m, 1 H, NCH), 7.0–7.2 (m, 4 H, ArCH), 7.5–7.8 (m, 4 H, ArCH), 8.25 (s, 1 H, CH=N), 8.44 (s, 1 H, CH=N). – δ_F: −6.36 (s). For the molecular weight determination, (0.04 g, 0.04 mmol) of complex **2a** was dissolved in thf (8 mL). The measured molecular weight was 990 (calculated: for mononuclear complex 550, for dimeric complex 1100).

Complex 2b: Complex **1b** ($3.3{\cdot}10^{-3}$ g, $2.7{\cdot}10^{-6}$ mol) was dissolved in a saturated solution of hexafluoroacetone in CD_2Cl_2 (0.6 mL). ^1H NMR spectroscopy showed quantitative formation of complex **2b**. δ_H: 1.2–1.7 (m, 4 H, CH_2CH_2), 1.31 (s, 9 H, *t*Bu), 1.35 (s, 9 H, *t*Bu), 1.51 (s, 9 H, *t*Bu), 1.57 (s, 9 H, *t*Bu), 2.0–2.1 (m, 2 H, CH_2), 2.4–2.45 (m, 1 H, CH_2), 2.6–2.7 (m, 1 H, CH_2), 3.3–3.4 (m, 1 H, NCH), 4.3–4.4 (m, 1 H, NCH), 7.65 (s, 1 H, ArCH), 7.70 (s, 1 H, ArCH), 8.43 (s, 1 H, CH=N), 8.60 (s, 1 H, CH=N). – δ_F: −5.62 (1 F, s), −5.63 (1 F, s).

Complex 3b: Complex **1b** (0.15 g, 0.12 mmol) was stirred with trimethylsilyl cyanide (0.02 mL, 0.12 mmol) in dry dichloromethane (5 mL) for two hours. Concentration of the reaction mixture in vacuo yielded 0.1 g (62%) of a light brown solid, which slowly decomposed, but which could be characterized as complex **3b**. M.p. 250 °C (decomp.); $[\alpha]_D^{22}$ −194 (c = 0.0125, $CHCl_3$). – $\nu_{max}(CH_2Cl_2)$: 2927 s, 2292 m, 1625 s, 1555 m, 1537cm^{-1} m. – δ_H: −0.29 (s, 9 H, $SiMe_3$), 1.25 (s, 9 H, *t*Bu), 1.26 (s, 9 H, *t*Bu), 1.41 (s, 9 H, *t*Bu), 1.42 (s, 9 H, *t*Bu), 1.0–1.6 (m, 4 H, CH_2CH_2), 1.9–2.1 (m, 2 H, CH_2), 2.3–2.5 (m, 1 H, CH_2), 2.5–2.7 (m, 1 H, CH_2), 3.5–3.7 (m, 1 H, NCH), 3.7–3.9 (m, 1 H, NCH), 7.18 (s, 1

H, ArCH), 7.21 (s, 1 H, ArCH), 7.50 (s, 2 H, ArCH), 8.13 (s, 1 H, CH=N), 8.22 (s, 1 H, CH=N). − δ_C: 1.9, 24.1, 24.4, 28.2, 29.3, 29.7, 31.4, 34.3, 35.3, 35.4, 67.5, 68.0, 123.5, 124.1, 129.2, 129.4, 130.9, 131.1, 142.0, 142.2, 161.1, 161.7. − *m/z* (FAB): 1317 (3) [MH − $Me_3SiCN]^+$, 1290 (6), 744 (100), 609 (23). For the molecular weight determination, complex **1b** (0.05 g, $4.1 \cdot 10^{-5}$ mol) was dissolved in a solution of trimethylsilyl cyanide in thf (5 mL of 0.15 N solution). The molecular weight was measured as 880 after 1.5 hours and 690 after 4.5 hours.

Complex 3a: This was prepared in the same way as complex **3b**, though it could not be isolated since removal of solvent resulted in reversion to **1a**. $\nu_{max}(CH_2Cl_2)$: 2090 s, 1627 s, 1600 m, 1554cm^{-1} m. − δ_H: −0.21 (s, 9 H, $SiMe_3$), 1.35−1.6 (m, 3 H, CH_2CH_2), 1.6−1.7 (m, 1 H, CH_2), 2.0−2.2 (m, 2 H, CH_2), 2.4−2.5 (m, 1 H, CH_2), 2.6−2.7 (m, 1 H, CH_2), 3.6−3.7 (m, 1 H, NCH), 3.8−3.9 (m, 1 H, NCH), 6.75−6.76 (m, 2 H, ArCH), 6.93−7.1 (m, 2 H, ArCH), 7.45−7.62 (m, 4 H, ArCH), 8.27 (s, 1 H, CH=N), 8.36 (s, 1 H, CH=N).

Asymmetric Addition of Trimethylsilyl Cyanide to Benzaldehyde Catalysed by Complex 3b: The reaction was carried out under previously reported conditions and gave 2-phenyl-2-trimethylsilyloxyacetontrile with quantitative yield and 78−80% *ee* after 18 hours. For the kinetics experiments, complex **3b** was prepared in situ by mixing **1b** ($3.3 \cdot 10^{-3}$ g, $2.7 \cdot 10^{-3}$ mmol) and trimethylsilyl cyanide (0.01 mL, 0.08 mmol) in CH_2Cl_2 (0.6 mL). A ^1H NMR spectrum (in CD_2Cl_2) recorded 5 minutes after the start of the reaction showed complete conversion into complex **3b**. A sample of the solution (0.15 mL) was injected into a solution of benzaldehyde (0.1 mL, 1.0 mmol) in CH_2Cl_2 (1.1 mL), followed by addition of trimethylsilyl cyanide (0.2 mL, 1.5 mmol). After 6 hours, a sample of the kinetics solution was removed and purified for chiral GC. The chemical yield of the trimethylsilyl ether of mandelonitrile was 40% with 74% *ee.*

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