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Optimized catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes and ketones

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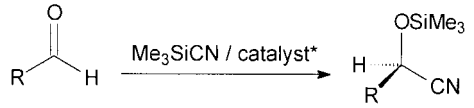
Abstract—A bimetallic titanium(IV)salen complex has been developed as an exceptionally active catalyst for the asymmetric addition of trimethylsilyl cyanide to ketones. For the corresponding addition to aldehydes, a vanadium(IV)salen complex was found to give higher levels of asymmetric induction. In both cases, additional evidence in support of the proposed catalytic cycle is presented.

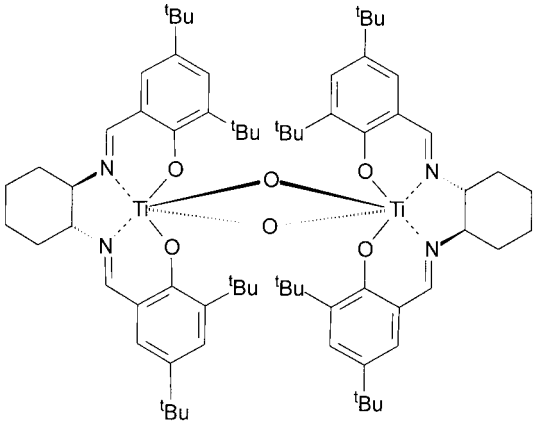
1. Introduction

Cyanohydrins are versatile synthetic intermediates which can readily be converted into a wide range of other bifunctional compounds including α-amino acids and 1,2-diamines.[1] In view of their synthetic potential, there has been considerable interest in recent years in the development of catalysts for the asymmetric addition of cyanide sources (usually trimethylsilyl cyanide) to prochiral aldehydes, leading to chiral, non-racemic cyanohydrin derivatives[2] (Scheme 1). Various catalysts have been developed including: enzymes, peptide derivatives, and transition metal complexes.[3] In contrast, there have been very few reports of the asymmetric addition of cyanide to prochiral ketones.[4]

Over recent years we have developed catalysts derived from salen ligands as catalysts for the asymmetric addition of trimethylsilyl cyanide to carbonyl compounds.[5] Our catalysts are active at room temperature and at high substrate to catalyst ratios. This work has culminated in the development of bimetallic titanium(IV)salen complex **1** as the optimal catalyst for the asymmetric addition of trimethylsilyl cyanide to ketones,[6] and vanadium(IV)salen complex **2** as the optimal catalyst for the asymmetric addition of trimethylsilyl cyanide to aldehydes.[7] We have also studied the mechanisms of these reactions, and have proposed a catalytic cycle (Scheme 2) and transition state geometry (Fig. 1) which both explains the high activity of the catalysts (simultaneous activation of both the carbonyl compound



Scheme 1.



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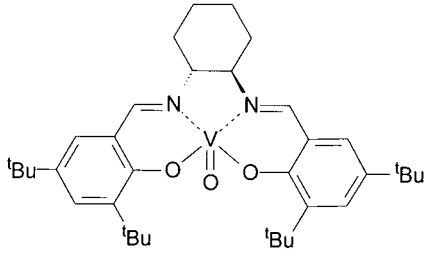

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and the trimethylsilyl cyanide) and correctly predicts the absolute configuration of the cyanohydrin silyl ethers produced during the reaction.[8] In this manuscript, we give full details of this work, and provide further evidence in support of the mechanism shown in Scheme 2 being appropriate for both titanium- and vanadium-derived catalysts.

2. Synthetic studies on the addition of trimethylsilyl cyanide to ketones using catalyst 1

Both steric and electronic effects make the addition of nucleophiles to ketones more difficult than the corresponding addition to aldehydes. This is particularly noticeable where the addition is reversible, since the reaction equilibrium may favour the starting materials. As a result of these factors, there are only scattered reports of the asymmetric catalysis of the addition of cyanide to ketones. Oxynitrilase enzymes will accept a limited range of ketones as substrates (with hydrogen cyanide as the cyanide source), but give chemical yields >15% only for methyl and ethyl ketones.[9] The only previous report of a transition metal catalyst for this reaction[4] employed a titanium triolate and was only active at high pressures (0.8 GPa). In view of the unprecedented activity of titanium(IV)salen complex **1** in

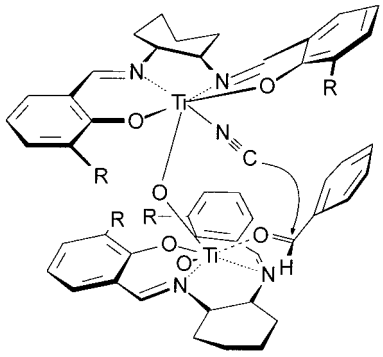
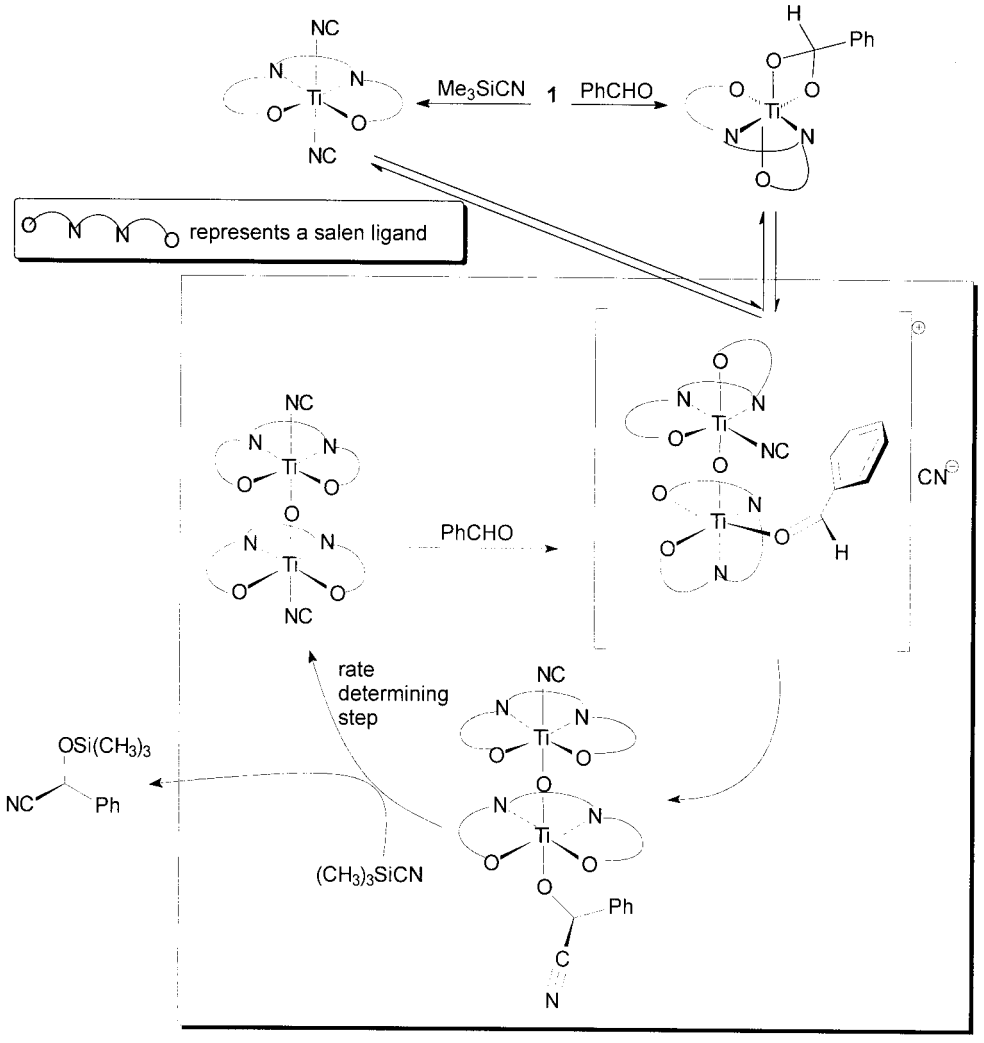


Figure 1. Proposed transition state geometry for asymmetric cyanohydrin synthesis catalyst **1**.

the asymmetric addition of trimethylsilyl cyanide to aldehydes,[5] we decided to investigate whether it could also be used to catalyse the asymmetric addition of trimethylsilyl cyanide to ketones at atmospheric pressure.[6]

Acetophenone was chosen as the test substrate since the specific rotation of the corresponding cyanohydrin had been correlated with its absolute configuration.[9] As can be seen from the data in Table 1, using 0.1 mol% of catalyst **1**



Scheme 2.

Table 1. Addition of trimethylsilyl cyanide to ketones (ArCOR)

Ar	R	**1** (mol%)	Time	Yield (%)	ee[+] (%)
Ph	Me	0.1	1 day	38	70
Ph	Me	0.5	1 day	100	66
Ph	Me	1.0	1 day	100	62
Ph	Et	0.1	2 weeks	41	32
Ph	Et	0.5	4 days	64	32
Ph	Et	1.0	4 days	100	30
Ph	^{i}Pr	0.5	no reaction		
Ph	^{t}Bu	0.5	no reaction		
4-MeC_6H_4	Me	0.1	4 days	100	52
4-MeC_6H_4	Me	0.5	1 day	100	66
2-MeOC_6H_4	Me	0.1	4 days	27	64
2-MeOC_6H_4	Me	0.5	2 days	100	72
3-MeOC_6H_4	Me	0.1	4 days	82	54
3-MeOC_6H_4	Me	0.5	1 day	100	56
4-MeOC_6H_4	Me	0.1	4 days	54	54
4-MeOC_6H_4	Me	0.5	1 day	100	60
4-F_3CC_6H_4	Me	0.1	4 days	78	60
4-F_3CC_6H_4	Me	0.5	1 day	100	56

[+] Determined by chiral gas chromatography of the cyanohydrin trimethylsilyl ethers. Chiral gas chromatography was carried out on a DP-TFA-γ-cyclodextrin, fused silica capillary column (32 m×0.2 mm) using helium as the carrier gas (flow rate 1.6 ml/min). In all cases, the injector temperature was 230°C and an isothermal column temperature of between 105 and 130°C was used.

at room temperature and atmospheric pressure, a moderate yield of the corresponding cyanohydrin trimethylsilyl ether could be obtained in 24 h. For comparison, under identical conditions, both aromatic and aliphatic aldehydes are converted into the corresponding cyanohydrin trimethylsilyl ethers in less than 5 min.

The enantiomeric excess of the cyanohydrin trimethylsilyl ether could be determined by chiral gas-chromatography using a γ-cyclodextrin capillary column and was found to be 70%; higher than that previously reported for the titanium triolate system under high pressure.[4] By increasing the amount of catalyst to 0.5 or 1.0 mol%, it was possible to optimize the reaction to give a quantitative conversion of acetophenone, though at the expense of a slightly reduced enantioselectivity. The cyanohydrin trimethylsilyl ether was determined to have the (*S*)-configuration (using the (*R*,*R*)-enantiomer of catalyst **1**) by hydrolysis to the known cyanohydrin,[9] which corresponds to the same sense of asymmetric induction observed for aldehyde substrates.[5]

The structure of the ketone was then modified to investigate the effect that this would have on the reaction. Variation of the alkyl substituent from methyl to ethyl, isopropyl, or *tert*-butyl was generally detrimental. Propiophenone was a substrate for the catalyst (Table 1), though the reaction was very slow and gave the corresponding cyanohydrin with only a very low enantiomeric excess. Substrates with larger alkyl groups were totally unreactive as were the aliphatic ketones 2-butanone and 3,3-dimethyl-2-butanone. Variation of the aromatic part of the ketone substrate was more successful. It proved possible to introduce substituents onto any position of the aromatic ring and to employ both electron rich and electron deficient ketones (Table 1). In general, 0.5 mol% of catalyst **1** proved to be optimal for quantitative conversion of these ketones into the corresponding cyanohydrin trimethylsilyl ethers. There is no apparent trend in the enantioselectivities of these reactions, in each case the enantiomeric excess under optimal conditions was between 56 and 72%.

3. Mechanistic implications of the addition of trimethylsilyl cyanide to ketones using catalyst 1

We have previously suggested that the transition state for asymmetric cyanohydrin synthesis using catalyst **1** is as shown in Fig. 1. In this transition state, the aldehyde is coordinated to one of the titanium ions and is oriented so that the small hydrogen atom is located near to the cyclohexanediamine unit. The larger substituent on the aldehyde is located well away from the backbone of the salen ligand. Cyanide is then delivered intramolecularly to the re-face of the coordinated aldehyde, resulting in the formation of the (*S*)-enantiomer of the product. The results obtained using ketone substrates are entirely consistent with this transition state. Thus, the only substrates are those which on one side of the carbonyl bond contain a small (methyl or ethyl) substituent which can be located close to the cyclohexanediamine unit in the transition state. Ketones with larger substituents are not able to fit into the active site of the catalyst and hence are not processed as substrates. The sense of asymmetric induction is also the same for acetophenone as for aldehydes, again consistent with a common mechanism and transition state.

To further study the mechanism of the reaction using ketones as substrates, a kinetics study of the reaction using acetophenone as substrate was undertaken. We have previously shown[8] that when benzaldehyde is used as the substrate, asymmetric cyanohydrin synthesis employing catalyst **1** shows first order kinetics described by the rate equation: rate=k_{obs}[Me_3SiCN] where k_{obs}=631[**1**]$^{1.3}$. The kinetics study using acetophenone was carried out by monitoring the disappearance of the acetophenone chromophore, and just as in the case of benzaldehyde, the reactions were found to be described by first order kinetics, showing a zero order dependence on the concentration of acetophenone and a first order dependence on the concentration of trimethylsilyl cyanide. This is shown by the first order kinetics plots ($\ln[Me_3SiCN]_t=\ln[Me_3SiCN]_0-k_{obs}t$) in Fig. 2. Each of the lines in Fig. 2 were obtained at a different catalyst concentration, and have a gradient of $-k[\mathbf{1}]^a$ where k is the

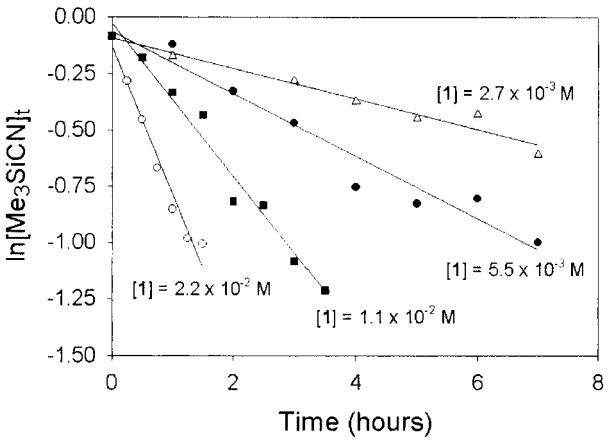


Figure 2. First order kinetics plots obtained for acetophenone at various concentrations of catalyst **1**.

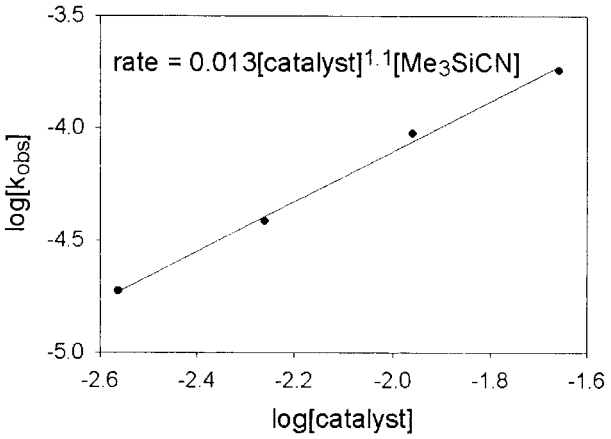
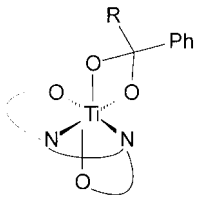


Figure 3. Plot of $\log(k_{obs})$ against $\log([\mathbf{1}])$ for reactions carried out using acetophenone as substrate.

rate constant for the reaction and a is the order with respect to catalyst **1**. Hence, $\log(-\text{gradient})=\log(k)+a.\log([\mathbf{1}])$, so from a plot of $\log(-\text{gradient})$ against $\log([\mathbf{1}])$, both a and k can be obtained. As can be seen from Fig. 3, a straight line is indeed obtained, and the gradient of this line (1.1) corresponds to the order with respect to catalyst **1**, and the intercept on the y-axis (-1.88) gives the rate constant as 0.013. Thus, reactions using acetophenone as substrate obey the rate equation: $\text{rate}=0.013[\mathbf{1}]^{1.1}[Me_3SiCN]$.

The rate equation for acetophenone differs from that for benzaldehyde in two ways. Firstly, the rate constant is much lower (0.013 as opposed to 631). This is consistent with the much lower reactivity of acetophenone compared with benzaldehyde, since the reactions take days rather than just a few minutes to reach completion. Secondly, the order with respect to the catalyst is lower for acetophenone (1.1) than for benzaldehyde (1.3). This parameter (which for a bimetallic catalyst must be between 1 and 2) is determined by the equilibrium between catalytically inactive mononuclear species and catalytically active dinuclear species in the reaction mixture.[8] A lower order for acetophenone than for benzaldehyde has two implications. Firstly, it implies that the aldehyde or ketone does react with compound **1** prior to the rate determining step of the catalytic cycle (otherwise the order would be the same for both substrates). However, this reaction cannot be part of the catalytic cycle since the concentration of the carbonyl compound would then appear in the rate equation. This is entirely consistent with the mechanism shown in Scheme 2, where only the three bimetallic species shown in the square box are actually involved in the catalytic cycle. However, the formation of these species from complex **1** involves the intermediate formation of metalloacetal complex **3a,b**, which does involve the carbonyl compound.



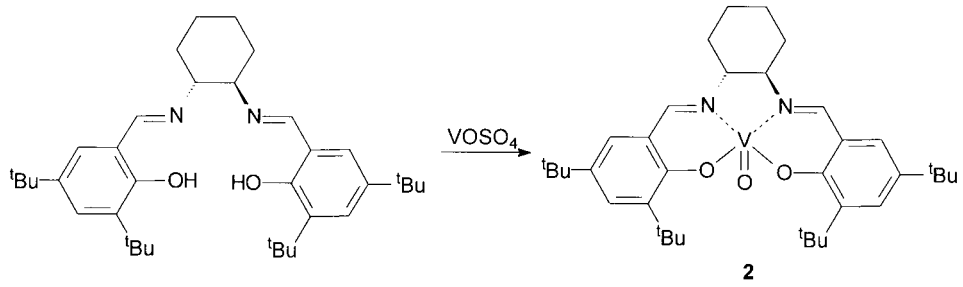
3: a R = H; **b** R= Me

The second implication is that the equilibrium between the mononuclear and dinuclear species lies more on the side of the dinuclear species for reactions involving acetophenone than for reactions involving benzaldehyde. This arises since a kinetics analysis shows[8] that the order with respect to the catalyst increases as the equilibrium concentration of the mononuclear species increases. It seems reasonable that species **3b** should have a lower equilibrium concentration than **3a** on steric grounds since acetals derived from ketones are generally less stable than those derived from aldehydes. Thus, all aspects of the asymmetric addition of trimethylsilyl cyanide to ketones catalysed by binuclear complex **1** are fully consistent with the catalytic cycle shown in Scheme 2 and the transition state geometry shown in Fig. 1.

4. Synthetic studies on the addition of trimethylsilyl cyanide to aldehydes using catalyst 2

Catalyst **1** is a highly active catalyst for the asymmetric addition of trimethylsilyl cyanide to both aldehydes[5] and ketones.[6] However, the enantiomeric excesses of the cyanohydrins derived from aldehydes do not exceed 90%, suggesting scope for further improvement in the catalyst. Our previous studies have optimized the structure of the salen ligand in catalyst **1** on a trial and error basis.[5] However, recently we have developed the mechanistic understanding of the reaction shown in Scheme 2.[8] Given this appreciation of both the catalytic cycle and origin of asymmetric induction, we set about rationally designing a new catalyst which would give higher levels of asymmetric induction.

The key feature of the mechanism shown in Scheme 2 is that the catalytically active species are bimetallic complexes which are in equilibrium with catalytically inactive mononuclear complexes. Reactions carried out using 0.1 mol% of catalyst **1** at room temperature are very rapid, complete conversion of an aldehyde to the corresponding cyanohydrin trimethylsilyl ether being observed in about 5 min. This suggested that catalyst **1** is too reactive, and that a modified catalyst with lower reactivity should be more selective. One way of reducing the activity of the catalyst would be to alter the equilibrium between the bimetallic and monometallic complexes in favour of the latter. Hence, it appeared that if the titanium ions in complex **1** could be changed to another metal ion which is capable of forming salen complexes but which has a greater propensity for the formation of mononuclear species, then a less reactive and more selective catalyst may be generated. A survey of the Cambridge crystal structure database revealed that whilst in the solid state, oxo-titanium(IV)salen complexes are always di- or polynuclear,[5,10,11] this is not the case for oxo-vanadium(IV)salen complexes. There are numerous examples of crystal structures of mononuclear oxo-vanadium(IV)salen complexes,[12–14] and also examples of polynuclear complexes.[13–15] One particularly intriguing example showed that it was possible to isomerize a (salen)V=O complex in the solid state from monomeric to polymeric by heating or treatment with acetonitrile vapour, whilst the reverse transformation could be accomplished by grinding the polymeric crystals or treating them with chloroform vapour.[13] Another example[14] had a disordered solid state structure in which



Scheme 3.

80% of the molecules were mononuclear and 20% were polymeric. In view of this solid state precedent, it seemed reasonable that mononuclear oxo-vanadium(IV)salen complexes may also be more stable in solution than the corresponding titanium species and hence give rise to a less reactive and more selective catalyst. Thus we decided to investigate the use of oxo-vanadium(IV)salen complexes as catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes.

Catalyst **2** was prepared by reaction of the corresponding salen ligand with vanadyl sulphate (Scheme 3) and was obtained as a green solid. The di-*tert*-butyl salen ligand was chosen to allow a direct comparison between catalysts **1** and **2**, and the green colour of complex **2** suggests that it has a mononuclear structure in the solid state[13,16] as polynuclear vanadium(IV)salen complexes tend to be orange. Complex **2** was tested as a catalyst for the asymmetric addition of trimethylsilyl cyanide to a range of aldehydes under identical conditions to those previously employed[5] for catalyst **1** (0.1 mol% of catalyst, room temperature, dichloromethane), and the results are compared in Table 2. In each case, the reactions gave quantitative conversions of the aldehyde to the corresponding cyanohydrin trimethylsilyl ethers, and the ee's of the products were determined by chiral gas chromatography as previously described.[5]

Comparison of the enantioselectivities obtained using catalysts **1** and **2** clearly shows that the goal of increasing the enantioselectivity of the catalyst had been achieved since the enantioselectivities observed using catalyst **2** were always higher than those obtained using catalyst **1**. For electron-rich aromatic aldehydes, catalyst **2** consistently gives products with enantiomeric excesses of 90% or higher. Electron deficient aromatic aldehydes and aliphatic aldehydes give lower enantioselectivities, but still higher than those obtained using catalyst **1**. In all cases, both catalysts predominantly gave the (*S*)-enantiomer of the cyanohydrin derivative. Other than the difference in enantioselectivities, the main difference between the two catalysts is the time required to achieve quantitative conversion: <5 min for catalyst **1**, but 18 h for catalyst **2**. An attempt to use complex **2** to catalyse the asymmetric addition of trimethylsilyl cyanide to acetophenone was less successful, after 7 days of reaction, only a 16% conversion was observed and the enantiomeric excess of the product was only 22%. Thus it appears that our goal of achieving a more selective catalyst by reducing its reactivity has been achieved.

Table 2. Addition of trimethylsilyl cyanide to aldehydes catalysed by complexes **1** and **2**

Aldehyde	ee using catalyst **1**[+]	ee using catalyst **2**[+]
PhCHO	82	94
$4MeOC_6H_4CHO$	84	90
$2MeC_6H_4CHO$	76	90
$3MeC_6H_4CHO$	90	95
$3MeC_6H_4CHO$	87	94
$4O_2NC_6H_4CHO$	50	73
CH_3CH_2CHO	52	77
Me_3CCHO	66	68

[+] Determined by chiral gas chromatography of the cyanohydrin trimethylsilyl ethers. Chiral gas chromatography was carried out on a DP-TFA-γ-cyclodextrin, fused silica capillary column (32 m×0.2 mm) using helium as the carrier gas (flow rate 1.6 ml/min). In all cases, the injector temperature was 230°C and an isothermal column temperature of between 70 and 155°C was used.

5. Mechanistic aspects of the addition of trimethylsilyl cyanide to aldehydes using catalyst 2

To verify the reason for the increased enantioselectivity of catalyst **2** and to obtain further mechanistic information on the reaction, a kinetics study was undertaken using catalyst **2** and benzaldehyde. The kinetics of the reaction could be monitored by observing the decrease in the benzaldehyde absorption as previously described[8] for kinetics studies involving catalyst **1**. The reactions were again found to obey first order kinetics, with a first order dependence on the trimethylsilyl cyanide concentration and a zero order dependence on the benzaldehyde concentration (Fig. 4). The order with respect to the catalyst was found to be 1.45 and the rate constant was 76 (Fig. 5).

Compared with the corresponding reaction catalysed by complex **1**,[8] the rate constant for the reaction using catalyst **2** is almost a factor of ten lower (76 versus 634), consistent with the much slower reactions observed using catalyst **2**. The order of reaction with respect to the catalyst is also higher for catalyst **2** (1.45) than for catalyst **1** (1.3). As discussed earlier, the magnitude of this component of the rate equation is determined by the equilibrium between the mononuclear and binuclear species present in solution. A number nearer to two corresponds to an increase in the equilibrium concentration of the catalytically inactive mononuclear species at the expense of the catalytically active binuclear species as intended from the design of catalyst **2**. Hence, it appears that catalysts **1** and **2** operate by the same mechanism (since they have the same form of rate equation), and all aspects of this mechanism are consistent

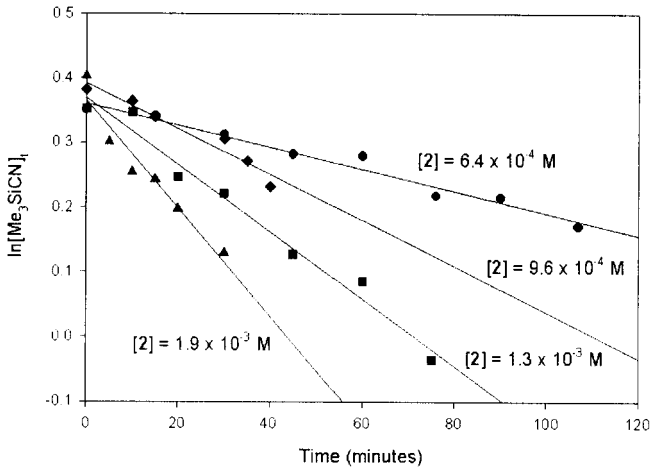


Figure 4. First order kinetics plots obtained for benzaldehyde at various concentrations of catalyst **2**.

with that shown in Scheme 2. Catalyst **2** is less reactive and correspondingly more enantioselective than catalyst **1** since it contains a lower equilibrium concentration of the catalytically active binuclear species.

6. Conclusions

Bimetallic titanium(IV)salen complex **1** is the only effective transition metal based catalyst currently available for the asymmetric addition of trimethylsilyl cyanide to aromatic methyl ketones. These reactions obey a similar rate equation to that previously determined for reactions involving catalyst **1** and benzaldehyde, suggesting a common reaction mechanism. Both the rate equation and the substrate specificity are entirely consistent with the mechanism shown in Scheme 2. Complex **1** is too reactive to be an optimal catalyst for the asymmetric addition of trimethylsilyl cyanide to aldehydes. However, based on the mechanistic understanding of the reaction, it was possible to develop vanadium(IV)salen complex **2** as a catalyst which exhibits higher enantioselectivities for aldehydes. The kinetics of reactions involving catalyst **2** and benzaldehyde are again consistent with the mechanism shown in Scheme 2, and suggest that within the reaction solution, catalyst **2** gives a higher equilibrium concentration of catalytically inactive mononuclear species than catalyst **1**.

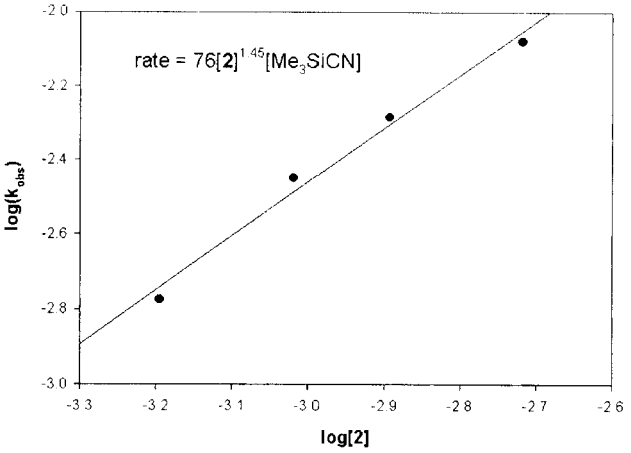


Figure 5. Plot of $\log(k_{obs})$ against $\log([\mathbf{2}])$ for reactions carried out using benzaldehyde as substrate.

Our work on the asymmetric addition of cyanide to carbonyl compounds is continuing and further results will be reported in due course.

7. Experimental

General experimental details have been reported elsewhere.[5]

7.1. Asymmetric addition of trimethylsilyl cyanide to ketones catalysed by complex 1

To a solution of trimethylsilyl cyanide (0.19 ml, 1.38 mmol) and catalyst **1** (0.1–1.0 mol%) in dry dichloromethane (1.5 ml) was added a ketone (1.25 mmol). The resulting solution was stirred under an inert atmosphere, and the progress of the reaction was followed by gas chromatography. Once the reaction was complete (1–4 days), the solution was poured onto a pad of silica gel and eluted with EtOAc/hexane (1:5). The resulting solution was evaporated in vacuo to give the trimethylsilyl ethers of cyanohydrins whose physical and analytical data was consistent with those reported in the literature,[17] except for the adducts of 2-methoxy and 3-methoxy-acetophenone, which are new compounds.

7.1.1. 2-(2-Methoxyphenyl)-2-trimethylsilyloxy-propanonitrile: Colourless liquid; δ_H ($CDCl_3$): 0.22 (9H, s, $Si(CH_3)_3$), 1.82 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 6.8–7.5 (4H, m, ArH); ^{13}C NMR ($CDCl_3$): 1.35 ($Si(CH_3)_3$), 30.14 (CH_3), 55.51 (OCH_3), 111.58 (ArCH), 111.67 (CN), 120.59 (ArCH), 125.78 (ArCH), 128.32 (ArC), 129.87 (ArCH), 147.83 (ArC); m/z (FAB) 250 (MH^+).

7.1.2. 2-(3-Methoxyphenyl)-2-trimethylsilyloxy-propanonitrile: Colourless liquid; δ_H ($CDCl_3$): 0.11 (9H, s, $Si(CH_3)_3$), 1.77 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 6.75–7.5

(4H, m, ArH); ^{13}C NMR ($CDCl_3$): 1.10 (Si(CH_3)$_3$), 33.68 (CH_3), 55.40 (OCH_3), 110.59 (Ar*C*H), 113.91 (Ar*C*H), 116.96 (Ar*C*H), 125.00 (*C*N), 130.22 (Ar*C*H), 134.47 (Ar*C*), 143.51 (Ar*C*); *m/z* (FAB) 250 (MH^+).

7.1.3. (*S*)-2-Hydroxy-2-phenyl-propanonitrile: (*S*)-2-(Trimethyl-silyloxy)-2-phenyl-propanonitrile (100 mg, 0.46 mmol) was stirred at room temperature with 1 M HCl (2 ml) for 2 h. The solution was then extracted with dichloromethane (3×5 ml) and the combined organic extracts dried ($MgSO_4$) and evaporated in vacuo to leave (*S*)-2-hydroxy-2-phenyl-propanonitrile as a colourless oil. Yield 57 mg (85%). $[\alpha]_D^{25}$ − 1.3 (*c*=3.0, $CHCl_3$) (lit.[9] $[\alpha]_D^{25}$ − 1.8 (*c*= 9.8, $CHCl_3$) for a sample of the (*S*)-enantiomer of 90% enantiomeric excess). Other data was consistent with that reported in the literature.[18]

7.2. Kinetics studies using catalyst 1 and acetophenone

A typical procedure employed a dry dichloromethane solution (2.5 ml total volume), comprising trimethylsilyl cyanide (0.9 M), catalyst **1** (5.5 mM) and acetophenone (0.8 M). This was stirred at 23°C under an inert atmosphere. At hourly intervals, a 10 μl sample was withdrawn from the reaction, diluted with dry dichloromethane (25 ml) and analysed by UV spectrophotometry. From the intensity of the λ_{max} (240 nm), the concentration of acetophenone was determined and used to calculate the concentration of trimethylsilyl cyanide remaining in the solution. This provided the data for the graphs shown in Figs. 2 and 3, from which the kinetic parameters of the reaction could be determined.

7.3. Synthesis of catalyst 2

Solutions of (1*R*,2*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (1.0 g, 1.8 mmol) in THF (20 ml) and vanadyl sulphate hydrate (0.6 g, 2.2 mmol) in hot ethanol (32 ml) were mixed and stirred under reflux for 3 h, after which time the solvent was removed in vacuo. The residue was dissolved in dichloromethane and filtered. The filtrate was evaporated in vacuo and absorbed onto a plug of silica. Elution first with dichloromethane, then with EtOAc:methanol (2:1) gave catalyst **2** (0.6 g, 53%) as a green crystalline solid. $[\alpha]_D^{23}$ − 950 (*c*=0.01, $CHCl_3$); ν_{max} (nujol) 1618 m and 1560 cm^{-1} m; (Found: C, 59.0; H, 7.6; N, 3.8%. $C_{36}H_{52}N_2O_3V$. $2CH_2Cl_2$ requires: C, 58.5; H, 7.2; N, 3.6%); δ_H ($CDCl_3$): 1.39 (18H, s, 2×C(CH_3)$_3$), 1.54 (18H, s, 2×C(CH_3)$_3$), 1.7–2.2 (8H, m, 4×CH_2), 3.81 (1H, m, HCN), 4.26 (1H, m, HCN), 7.52 (1H, s, ArCH), 7.57 (1H, s, ArCH), 7.72 (1H, s, ArCH), 7.77 (1H, s, ArCH), 8.55 (1H, s, HC=N), 8.77 (1H, s, HC=N); ^{13}C NMR ($CDCl_3$): 24.57 (*C*H_2), 28.67 (*C*H_2), 29.27 (*C*H_2), 29.69 (C(*C*H_3)$_3$), 29.91 (C(*C*H_3)$_3$), 31.39 (*C*H_2), 34.49 (2×*C*(CH_3)$_3$), 35.01 (2×*C*(CH_3)$_3$), 35.46 (C(*C*H_3)$_3$), 35.64 (C(*C*H_3)$_3$), 69.98 (*C*HN), 71.00 (*C*HN), 121.06 (Ar*C*), 121.57 (Ar*C*), 127.85 (Ar*C*H), 128.36 (Ar*C*H), 131.23 (Ar*C*H), 131.89 (Ar*C*H), 134.99 (Ar*C*), 135.20 (Ar*C*), 144.18 (2×Ar*C*), 156.34 (2×Ar*C*), 161.95 (H*C*=N), 164.62 (H*C*=N); *m/z* (FAB) 611 (M^+, 100); Found: 611.3409, $C_{36}H_{52}N_2O_3V$ requires 611.3418.

7.4. Asymmetric addition of trimethylsilyl cyanide to aldehydes catalysed by complex 2

To a solution of catalyst **2** (0.78 mg, 1.28×10^{-3} mmol) in dry distilled dichloromethane (1.5 ml) under an argon atmosphere was added the aldehyde (1.28 mmol) followed by trimethylsilyl cyanide (0.38 ml, 2.85 mmol). The resulting solution was stirred for 24 h at room temperature, after which the reaction mixture was poured onto a plug of silica and eluted with hexane: EtOAc (5:1) to give the cyanohydrin trimethylsilyl ethers. The analytical data of the products were consistent with those reported previously,[5] and their enantiomeric excesses were determined by chiral gas chromatography.

7.5. Kinetics studies using catalyst 2 and benzaldehyde

Standard solutions of benzaldehyde (12.8 mM), trimethylsilyl cyanide (0.71 M) and catalyst **2** (0.64 mM) were prepared in dry dichloromethane. Samples of these solutions were diluted with dry dichloromethane as necessary to provide solutions of the concentration required for a particular experiment. The initial (*t*=0) absorption (at 243 nm) was determined from a solution containing just the appropriate concentration of benzaldehyde and no other reagents. The solutions of benzaldehyde and complex **2** were mixed and stirred under an argon atmosphere at 19–20°C, then the trimethylsilyl cyanide solution and sufficient dry dichloromethane were added such that the total reaction volume was 2.0 ml. The reaction was stirred under an argon atmosphere at 19–20°C and 10 μL samples were periodically removed and immediately diluted into dry dichloromethane (25 ml). The samples were then analysed by UV spectrophotometry at 243 nm to determine the concentration of benzaldehyde in the sample. This was used to calculate the concentration of the trimethylsilyl cyanide remaining in the solution and hence provided the data for the graphs shown in Figs. 4 and 5, from which the kinetic parameters of the reaction could be determined.

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