Asymmetric addition of trimethylsilyl cyanide to aldehydes catalysed by chiral (salen)$\mathrm{Ti}^{\mathrm{IV}}$ complexes

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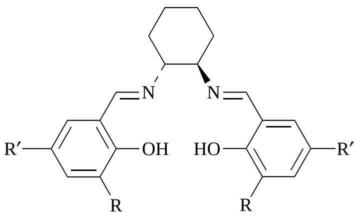
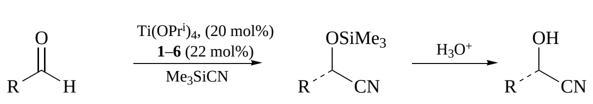
The asymmetric addition of trimethylsilyl cyanide to a range of aldehydes is catalysed by the titanium(IV) complexes of chiral salen derivatives 3–6. The enantiomeric excess of the resulting cyanohydrins is predominantly dependent upon the structure of the aldehyde, with electron-rich aromatic aldehydes giving best results. Electron-deficient aromatic aldehydes give cyanohydrins with low enantiomeric excesses, whilst ketones fail to react.

Introduction

Enantiomerically pure cyanohydrins are important synthetic intermediates in the synthesis of other chiral compounds, including α-hydroxy acids, α-hydroxy aldehydes, β-amino alcohols, α-hydroxy ketones, tetronic acids and α-amino acids, and because of these applications they are of significant industrial importance.[1] A number of catalytic methods have been reported for the asymmetric synthesis of cyanohydrins, including the use of enzymes, peptides and transition metal complexes.[2] Recently we reported the use of chiral (salen)$\mathrm{Ti}^{\mathrm{IV}}$ complexes **1** and **2** as chiral catalysts for the asymmetric addition of $\mathrm{Me_3SiCN}$ to four aldehydes as shown in Scheme 1[3] and related work has been reported by other workers.[4] Following on from these preliminary results, we initiated a research programme aimed at optimising the structure of the chiral (salen)$\mathrm{Ti}^{\mathrm{IV}}$ complex, and investigating the range of carbonyl compounds that would be compatible with these catalysts. Here we report the results of this study.



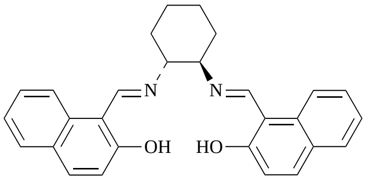
1 R = H, R′ = H
2 R = Bu^t, R′ = H
3 R = Bu^t, R′ = Me
4 R = Bu^t, R′ = OMe
5 R = Bu^t, R′ = Bu^t
6 R = Cl, R′ = Cl



Scheme 1

Results and discussion

Starting from catalyst **2**, the effect of introducing an additional substituent into the *para*-position of the aromatic rings was investigated, giving chiral ligands **3**–**6**.[5] 1-Formyl-2-naphthol derived ligand **7** was also prepared, however the titanium complex of ligand **7** was found to be highly insoluble and did not function as a catalyst. The asymmetric addition of $\mathrm{Me_3SiCN}$ to aromatic aldehydes at −80 °C in dichloromethane was investigated using the $\mathrm{Ti(OPr^i)_4}$ complex of these ligands in a 20% mole ratio as detailed in the Experimental Section. The results for catalysts **3**–**6** are shown in Table 1. The yields given in Table 1 are the isolated yields of the cyanohydrin trimethylsilyl ethers, and the enantiomeric excesses were determined by ^{1}H NMR analysis of the Mosher ester[6] derivatives after hydrolysis of the silyl ethers to the corresponding cyanohydrins. A racemic sample of each of the cyanohydrins was also converted to the Mosher ester derivative, both to confirm the identity of the resonances in the ^{1}H NMR spectrum and to prove that no kinetic resolution occurred during the formation of the diastereoisomeric derivatives. The racemic cyanohydrin of benzaldehyde is commercially available, those of *para*-methyl- and *para*-methoxy-benzaldehyde were prepared by the addition of sodium cyanide to the aldehyde in the presence of acetic acid (see Experimental section), and a racemic sample of the cyanohydrin of *para*-nitrobenzaldehyde was obtained from the reaction using ligand **3** or **4**.



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The data given in Table 1 show that ligand **5** gives consistently good enantiomeric excesses with all of the aldehydes investigated, whereas although ligands **3** and **4** gave good results in some cases, with other aldehydes they were inferior to ligand **5**. Hence, further studies were conducted mainly using ligand **5**, which is also commercially available. The manganese complex of this ligand is also the most effective catalyst for the asymmetric epoxidation of alkenes.[7]

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Table 1 Comparison of ligands **3**–**6** in the asymmetric addition of Me_3SiCN to aromatic aldehydes

Aldehyde	Ligand	Yield[a] (%)	Ee[b] (%)
PhCHO	**3**	84	60 (*S*)
PhCHO	**4**	95	76 (*S*)
PhCHO	**5**	89	72 (*S*)
PhCHO	**6**	30	69 (*S*)[c]
4-MeC_6H_4CHO	**3**	50	76
4-MeC_6H_4CHO	**4**	98	46
4-MeC_6H_4CHO	**5**	40	88
4-$MeOC_6H_4CHO$	**3**	20	60
4-$MeOC_6H_4CHO$	**4**	31	94
4-$MeOC_6H_4CHO$	**5**	40	84
4-$O_2NC_6H_4CHO$	**3**	42	0
4-$O_2NC_6H_4CHO$	**4**	43	0
4-$O_2NC_6H_4CHO$	**5**	60	10

[a] Yields are for isolated cyanohydrin trimethylsilyl ethers. All reactions were carried out at least twice. [b] Enantiomeric excess. Determined by ^1H NMR analysis of the diastereoisomeric Mosher esters. The experimental error in the enantiomeric excesses is approximately 5%. [c] Enantiomeric excess determined by chiral GC as described in ref. 3.

Table 2 Asymmetric addition of Me_3SiCN to aldehydes and ketones catalysed by ligand **5** and $Ti(OPr^i)_4$

Aldehyde	Yield[a] (%)	Ee[b] (%)
3-MeC_6H_4CHO	81	92
2-MeC_6H_4CHO	90	80
PhCH=CHCHO	100	54
4-$MeO_2CC_6H_4CHO$	43	7
4-$CF_3C_6H_4CHO$	58	3
CH_3CH_2CHO	100	58
Me_2CHCHO	100	48
Me_3CCHO	100	36
PhCOMe	0	—
MeCOPr	0	—
Heptan-2-one	0	—

[a] Yields are for isolated cyanohydrin trimethylsilyl ethers. All reactions were carried out at least twice. [b] Enantiomeric excess. Determined by ^1H NMR analysis of the diastereoisomeric Mosher esters. The experimental error in the enantiomeric excesses is approximately 5%.

The effect of varying the solvent and titanium ligand was next investigated, using benzaldehyde as the substrate. Changing the titanium(IV) species to $Ti(OEt)_4$ resulted in no significant change in the yield or enantiomeric excess of the cyanohydrin produced from benzaldehyde when used with ligand **5**, although significantly lower enantiomeric excess were obtained with both *para*-methoxybenzaldehyde [44 compared to 84% with $Ti(OPr^i)_4$] and pivaldehyde [15 compared to 36% with $Ti(OPr^i)_4$]. The use of $Ti(OPr^i)_2Cl_2$ (0% yield) or $Al(OPr^i)_3$ [10% yield, 10% ee of the (*S*)-enantiomer] in conjunction with ligand **2** and benzaldehyde gave very poor results. Changing the solvent to toluene [with ligand **5** and $Ti(OPr^i)_4$] resulted in a small increase in both the yield and enantiomeric excess (100% yield and 78% ee), but was less consistent and experimentally more difficult than using dichloromethane as the reaction solvent. The use of diethyl ether (20% yield, 33% ee) or THF (49% yield, 56% ee) gave markedly inferior results. A similar reduction in enantiomeric excess was also observed when ligand **6** was used in diethyl ether or THF (46 and 56% ee respectively).

Finally, the asymmetric addition of Me_3SiCN to a range of aromatic and aliphatic aldehydes and ketones using ligand **5** and $Ti(OPr^i)_4$ in dichloromethane was investigated, the results being shown in Table 2. Analysis of the data in Tables 1 and 2 shows that moderate to excellent enantiomeric excesses were obtained for electron-rich and aliphatic aldehydes, but that highly electron-deficient aromatic aldehydes gave only low levels of asymmetric induction, whilst ketones did not react at all under the reaction conditions. The low enantiomeric excesses observed for electron-deficient cyanohydrins may be due to poor asymmetric induction during the silylcyanation, or to facile racemisation of these cyanohydrins during the hydrolysis and derivatisation steps. It is also not possible to directly compare the enantiomeric excesses reported here for catalysts **3**–**5** with those previously reported for catalysts **1** and **2**, as the latter were determined by chiral gas chromatography on the silyl ethers rather than on the cyanohydrins.[3]

In summary, a new catalyst composed of ligand **5** and $Ti(OPr^i)_4$ has been developed for the asymmetric addition of Me_3SiCN to aldehydes. This catalyst system is simple and convenient to operate, and uses only commercially available chemicals. Further work in this area is continuing and will be reported in due course.

Experimental

General

^1H NMR Spectra were recorded at 250 MHz on a Bruker AM250 spectrometer fitted with a ^1H-^{13}C dual probe, at 293 K in $CDCl_3$. Spectra were internally referenced either to $SiMe_4$ or to the residual solvent peak. ^{13}C NMR Spectra were recorded at 62.9 MHz on the same spectrometer at 293 K in $CDCl_3$. Spectra were referenced to the solvent peak. Peak assignments were made by DEPT editing of the spectra. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer, and UV spectra were recorded on an ATI Unicam UV4 spectrophotometer. Mass spectra were recorded using the FAB technique (Cs^+ ion bombardment at 25 kV) on a VG Autospec spectrometer, or by electron ionisation (EI) on either a VG model 12-253 quadrupole spectrometer or a VG Quattro II triple quadrupole spectrometer. High resolution mass measurements were made on a VG ZAB-E spectrometer. Optical rotations were recorded on an Optical Activity Ltd Polar 2001 polarimeter, at a concentration of 1.0 g per 100 ml in chloroform. Elemental analyses were performed within the Chemistry Department on a Carlo Erba Model 1106 or Model 1108 analyser.

General procedure for the synthesis of racemic cyanohydrins

To a stirred solution of the aldehyde (15 mmol) in ethanol (3 ml) was added a solution of sodium cyanide (22 mmol, 1.5 equiv.) in water (5 ml). To the resulting solution was added glacial acetic acid dropwise to adjust the pH to 8, after which the solution was stirred at room temperature for 4 h. The reaction mixture was then extracted with diethyl ether (2 × 25 ml) and the combined ethereal extracts washed with 2 M hydrochloric acid (2 × 20 ml), dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* to leave the racemic cyanohydrins as oils in 63–92% yield. Analytical data for these compounds were consistent with those previously reported.

General procedure for the asymmetric trimethylsilylcyanation of aldehydes

In a dry test tube under an argon atmosphere were placed Schiff's base ligand (**2**–**6**) (0.27 mmol, 0.22 equiv.) and dry, distilled (over calcium hydride) dichloromethane (1.5 ml). To this solution was added $Ti(OPr^i)_4$ (0.25 mmol, 0.2 equiv.) and the resulting solution was stirred at room temperature for 1 h. The solution was then cooled to −80 °C, and the aldehyde (1.25 mmol, 1 equiv.) and trimethylsilyl cyanide (2.85 mmol, 2.3 equiv.) were added dropwise. The solution was stirred at −80 °C for 24–100 h, after which the reaction mixture was placed on a dry silica gel flash chromatography column[8] and eluted with hexane–ethyl acetate (5:1) to give the cyanohydrin trimethylsilyl ethers. The spectroscopic and analytical data for the silyl ethers corresponded to those previously reported for these compounds.[9]

Hydrolysis of the trimethylsilyl ethers and enantiomeric excess determination

The cyanohydrin trimethylsilyl ether obtained above was added to 1 M hydrochloric acid (30 ml), and the mixture stirred vigorously at room temperature for 1–2 h. The aqueous solution was then extracted with dichloromethane (2 × 30 ml), and the combined organic layers were dried ($MgSO_4$) and the solvent evaporated *in vacuo* to leave the cyanohydrin. The spectroscopic and analytical data for the cyanohydrins corresponded to those previously reported for these compounds.[9] A sample of the cyanohydrin (5–7 mg, 1 equiv.) was immediately dissolved in chloroform (0.1 ml), and (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (12.5 mg, 1.3 equiv.), pyridine (0.1 ml) and 4-dimethylaminopyridine (2–3 mg) were added. The resulting mixture was stirred overnight at room temperature, then diluted with dichloromethane (5 ml), washed with 2 M hydrochloric acid (2 × 5 ml), dried ($MgSO_4$) and filtered through a short silica column (eluting with dichloromethane). Evaporation of the solvents *in vacuo* gave the Mosher esters as yellow oils, which were analysed by ^1H NMR spectroscopy in $CDCl_3$.

For each of the cyanohydrins, a racemic sample was also prepared and converted to the Mosher ester in the same way. In no case was there any evidence for preferential reaction of the Mosher's acid chloride with one enantiomer of the cyanohydrin, or was any separation of the diastereoisomeric Mosher esters during the preparation and purification of these compounds observed.

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