

# First structurally defined catalyst for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde

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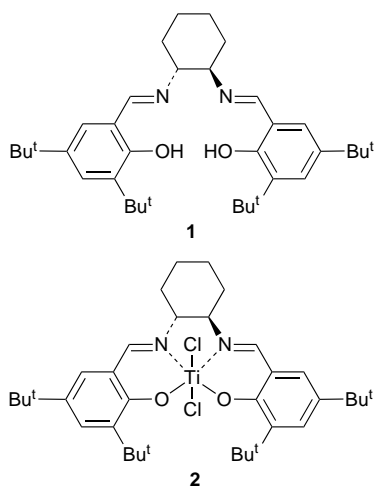
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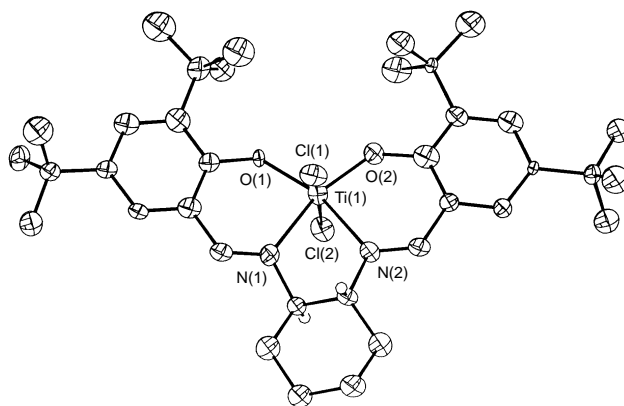
Titanium complex  $\text{TiCl}_2\text{L}$  [ $\text{H}_2\text{L} = (R,R)\text{-}N,N'\text{-bis}(3,5\text{-}di\text{-}tert\text{-butylsalicylidene)hexane-1,2\text{-}diamine$ ] **2** has been prepared, characterised by X-ray crystallography and shown to be an active catalyst for the asymmetric addition of  $\text{Me}_3\text{SiCN}$  to benzaldehyde, producing (*S*)-2-phenyl-2-trimethylsilyloxyacetonitrile in 86% ee at room temperature.

Enantiomerically pure cyanohydrins are important synthetic intermediates in the synthesis of other chiral compounds and hence are of significant industrial importance.<sup>1</sup> A number of catalytic methods have been reported for the asymmetric synthesis of cyanohydrins, including the use of enzymes, peptides and transition metal complexes.<sup>2</sup> Recently, we reported the use of chiral  $\text{Ti}^{\text{IV}}$  (salen)( $\text{OPr}^i$ )<sub>2</sub> complexes as chiral catalysts for the asymmetric addition of  $\text{Me}_3\text{SiCN}$  to aldehydes,<sup>3</sup> and related work has been reported by other workers.<sup>4</sup> Whilst some of these catalysts have given cyanohydrin silyl ethers with >90% ee, the structures of the catalysts have never been determined and this has restricted mechanistic investigations aimed at further improving the enantiomeric excesses and substrate tolerance. The catalysts have generally been prepared *in situ* by mixing a chiral ligand and titanium(IV) species. In the case of ligand **1**– $\text{Ti}(\text{OPr}^i)_4$  we have shown that at least three species can subsequently be detected by NMR spectroscopy.<sup>5</sup> Here we describe the synthesis of the first isolable and characterisable catalyst for the asymmetric addition of  $\text{Me}_3\text{SiCN}$  to benzaldehyde.



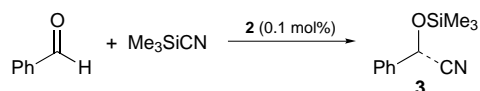
Reaction of ligand **1**<sup>6</sup> with titanium(IV) chloride in  $\text{CH}_2\text{Cl}_2$  at room temperature for 2 h followed by evaporation of the solvent *in vacuo* and washing of the solid with  $\text{Et}_2\text{O}$  and  $\text{Et}_2\text{O}$ –hexane (1:1) gave a brown solid of structure **2** which could be recrystallised from  $\text{CHCl}_3$ . The spectral ( $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR) properties of compound **2**  $\{[\alpha]_{\text{D}}^{22} +736$  (c 0.0125,  $\text{CHCl}_3$ ), mp

330 °C (decomp.)} were entirely consistent with a single species of the proposed structure, and the monomeric nature and geometry of compound **2** were proven by X-ray structure analysis<sup>‡</sup> (Fig. 1). Compound **2** has two independent molecules in the crystals, both with the *R,R* configuration and comparable geometry parameters. Each molecule adopts a slightly distorted octahedral geometry in which the two chlorine atoms are repelled by the *tert*-butyl groups (Cl–Ti–Cl bond angle  $\approx 169^\circ$ ). Although X-ray structures of similar achiral titanium complexes have been reported,<sup>7</sup> only one other example of the X-ray structure of a monomeric, chiral (salen) titanium complex has been reported,<sup>8</sup> and in that case the salen ligand did not adopt four equatorial positions around the titanium.<sup>9</sup>



**Fig. 1** Solid state structure of one independent molecule of **2**. Thermal ellipsoids are drawn at 50% probability. The structure of the other molecule is closely similar.

Compound **2** was active as a catalyst for the asymmetric addition of  $\text{Me}_3\text{SiCN}$  to benzaldehyde (Scheme 1). Thus treatment of a  $\text{CH}_2\text{Cl}_2$  solution of benzaldehyde and  $\text{Me}_3\text{SiCN}$  (2.3 equiv.) with complex **2** (0.1 mol%) at room temperature resulted after 24 h in complete conversion of the benzaldehyde to (*S*)-2-phenyl-2-trimethylsilyloxyacetonitrile **3** in 86% ee, as determined by chiral gas chromatography. It is notable that catalyst **2** is active at room temperature and at very high substrate to catalyst ratios, results which contrast with previously reported catalysts for this reactions.<sup>2–4</sup>



**Scheme 1**

Further work on the mechanism and synthetic applications of this chemistry is underway and will be reported in due course. The authors thank the EPSRC, INTAS, the EU (INCO-COPERNICUS) and the Russian Fund for Fundamental Research (grant No. 95-03-08046) for financial support.

## Notes and References

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‡ *Crystallographic data* for **2**: C<sub>36</sub>H<sub>52</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>Ti·CHCl<sub>3</sub> (FW 782.96), triclinic, space group *P*1 (No. 1); *a* = 12.032(3), *b* = 13.376(5), *c* = 14.938(5) Å,  $\alpha$  = 63.42(3),  $\beta$  = 75.75(3),  $\gamma$  = 72.92(3)<sup>o</sup>, *V* = 2036.6(11) Å<sup>3</sup>; *Z* = 2; *D*<sub>c</sub> = 1.277 Mg m<sup>-3</sup>,  $\lambda(\text{Mo-K}\alpha)$  = 0.71069 Å, *F*(000) = 824. The structure was solved by direct methods (SHELXS86) (ref. 10) using previously described procedures (ref. 11) and refined on *F*<sup>2</sup> by full-matrix least-squares (SHELXL93) (ref. 12) using all 6227 unique data corrected for Lorentz and polarisation factors but not for absorption. The structure was finally refined (823 parameters) to *R* [on *F*, *F*<sub>0</sub> > 4σ(*F*<sub>0</sub>)] and *wR* [on *F*<sup>2</sup>, all data] values of 0.0524 and 0.1013, respectively. CCDC 182/732.

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