Titanium(IV)(salen) and Vanadium(V)(salen) Complexes Derived from C_2- and C_1-Symmetric Diamines for Asymmetric Cyanohydrin Synthesis

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Dedicated to Sir Jack E. Baldwin on the occasion of his 70th birthday

Abstract: Titanium and vanadium salen complexes have been prepared from C_2- and C_1-symmetric acyclic diamines. All of the complexes catalysed the asymmetric addition of trimethylsilyl cyanide to benzaldehyde and the sense of asymmetric induction was determined by the nature of the substituents. The vanadium complex of a valine-derived diamine gave good results with a range of aromatic and aliphatic aldehydes.

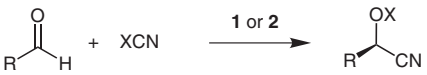
Key words: cyanohydrins, homogenous catalysis, asymmetric catalysis, Schiff bases, titanium

Over the last twelve years,[1] we have developed titanium(IV) **1** and vanadium(V) **2a**,**b** salen complexes derived from cyclohexanediamine as highly effective catalysts for the asymmetric addition of trimethylsilyl cyanide,[1,2] metal cyanides[1,3] (in the presence of an anhydride), and cyanoformates[1,4] to aldehydes (Scheme 1). Complexes **1** and **2** are active at room temperature; at substrate-to-catalyst ratios of up to 1000:1 and give products with ee >90% from a range of aromatic aldehydes. Aliphatic aldehydes are also accepted as substrates, though with reduced enantioselectivities (70–90%) and complex **1** will also catalyse the asymmetric addition of trimethylsilyl cyanide to ketones.[1,5] Complexes **1** and **2** have been commercialized[6] by NPIL under the trademark CACHy.

We have previously reported[1,2a] the influence on the enantioselectivity of the substituents on the aromatic rings of catalysts **1** and **2** (Figure 1) and shown that the presence of 3,5-di-*tert*-butyl groups gives the highest levels of asymmetric induction. However, all our previous work in this area has employed (*R*,*R*)-1,2-diaminocyclohexane as a readily available, C_2-symmetrical diamine,[7] and in every case, this resulted in addition of cyanide to the *re* face of the aldehyde. In this letter we report the synthesis of salen ligands derived from a range of acyclic diamines and discuss their catalytic activity in the asymmetric addition of trimethylsilyl cyanide to benzaldehyde.

Initially, diamines **3a**–**e** were selected as representative acyclic diamines, chosen to probe any influence of steric effects within the salen ligand. Compound **3a** is commercially available and diamines **3b**–**e** were prepared by a general literature procedure[8] as shown in Scheme 2. Diamines **3a**–**e** were condensed with 3,5-di-*tert*-butylsalicylaldehyde to give ligands **4a**–**e**. Ligand **4a** has previously been complexed to titanium(IV) isopropoxide by Jiang and the resulting in situ prepared complex (20 mol%) used to catalyse the asymmetric addition of trimethylsilyl cyanide to benzaldehyde with just 39% ee after a reaction time of 24 hours at –78 °C.[9]

Ligands **4a**–**e** were complexed to titanium tetrachloride to give dichloride complexes **5a**–**e**. Attempts to convert complexes **5a**–**e** into bimetallic complexes analogous to structure **1** were problematic due to competing ligand-hydrolysis reactions. Instead, complexes **5a**–**e** were utilised as precatalysts as they will be converted into bimetallic complexes in situ by adventitious moisture.[2a,10] Ligands



Scheme 1 Asymmetric cyanohydrin synthesis using catalysts **1** and **2**

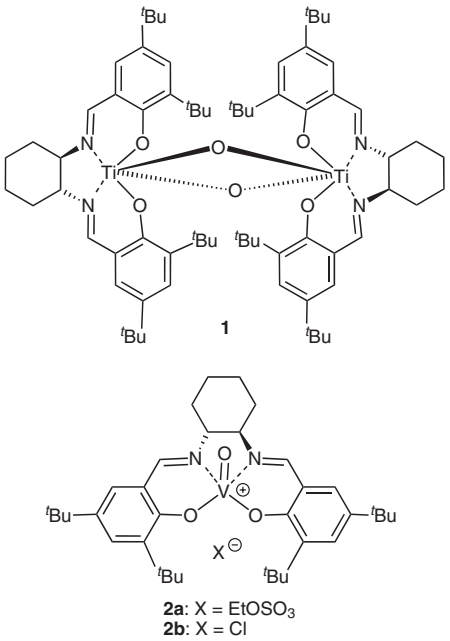


Figure 1 Salen complexes for asymmetric cyanohydrin synthesis

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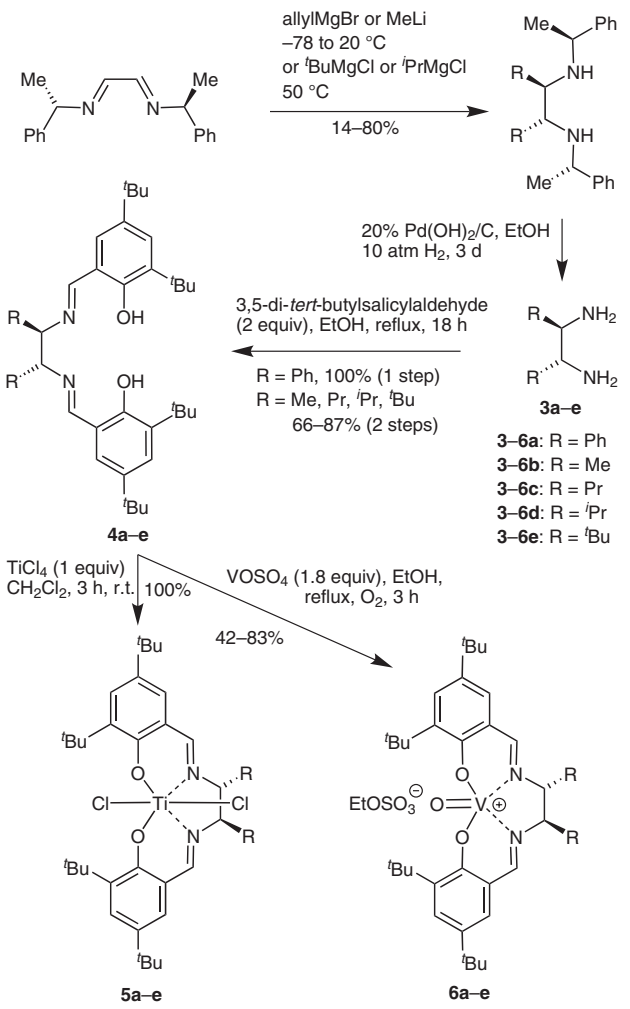


Scheme 2 Synthesis of catalysts **5a–e** and **6a–e**

4a–e were also treated with vanadyl sulfate in the presence of oxygen to give vanadium(V)(salen) complexes **6a–e**. Each of complexes **5** and **6** was evaluated as a catalyst for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde under standard conditions.[11] The results of this study are reported in Table 1.

Complex **5a** gave only moderate levels of asymmetric induction, comparable to those reported by Jiang for the titanium(IV) isopropoxide complex of the same ligand.[9] However, complex **5a** was intrinsically more active than Jiang's catalyst as only 1.0 mol% of catalyst was required to achieve 78% conversion of benzaldehyde into mandelonitrile trimethylsilyl ether. The increase in enantioselectivity as the amount of complex **5a** is reduced, mirrors the effect previously seen with the corresponding complex derived from 1,2-diaminocyclohexane and is indicative of the in situ formation of a bimetallic complex analogous to structure **1**.[2a] The corresponding vanadium complex **6a** was intrinsically more enantioselective than titanium complex **5a** as previously observed for complexes **1** and **2**.[1,2] In addition, in this case the enantioselectivity increased as the amount of catalyst was increased from 0.1 to 1.0 mol% as no in situ hydrolysis is needed to form catalytically active bimetallic species.

Table 1 Synthesis of Mandelonitrile Trimethylsilyl Ether Using Catalysts **5** and **6**

Catalyst (mol%)	Conversion (%)	ee (%) (config)[a]
5a (0.1)	64	52 (*S*)
5a (1.0)	78	38 (*S*)
5a (2.0)	89	31 (*S*)
5a (10.0)	100	20 (*S*)
6a (0.1)	83	68 (*S*)
6a (1.0)	100	80 (*S*)
6a (2.0)	100	77 (*S*)
5b (0.1)	7	26 (*R*)
5b (1.0)	20	26 (*R*)
5b (2.0)	34	26 (*R*)
6b (0.1)	16	28 (*R*)
6b (1.0)	58	20 (*R*)
6b (2.0)	66	20 (*R*)
5c (0.1)	12	4 (*R*)
5c (1.0)	27	6 (*R*)
5c (2.0)	42	14 (*R*)
5c (10.0)	100	30 (*R*)
6c (0.1)	78	53 (*R*)
6c (1.0)	80	62 (*R*)
6c (2.0)	84	62 (*R*)
5d (0.1)	21	2 (*R*)
5d (1.0)	37	2 (*R*)
5d (2.0)	44	2 (*R*)
6d (0.1)	12	6 (*R*)
6d (1.0)	55	23 (*R*)
6d (2.0)	59	23 (*R*)
5e (0.1)	50	27 (*R*)
5e (1.0)	62	50 (*R*)
5e (2.0)	77	41 (*R*)
6e (0.1)	57	26 (*R*)
6e (1.0)	72	52 (*R*)
6e (2.0)	77	56 (*R*)

[a] Determined by chiral GC using the conditions reported in refs. 2–4 after conversion of the mandelonitrile trimethylsilyl ether into mandelonitrile acetate by the method of Kagan.[12]

The most notable feature of catalysis by complexes **5b–e** is the inversion of enantioselectivity. This is the first time

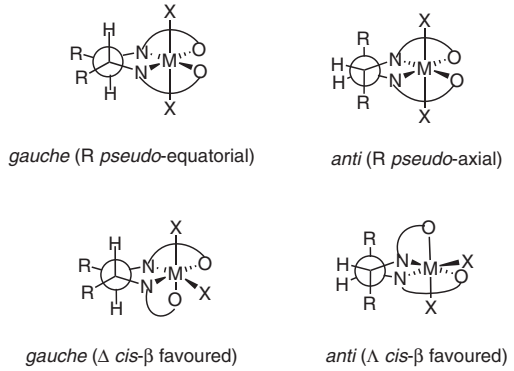


Figure 2 *Gauche* and *anti* conformations of a salen ligand

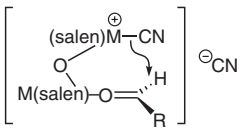
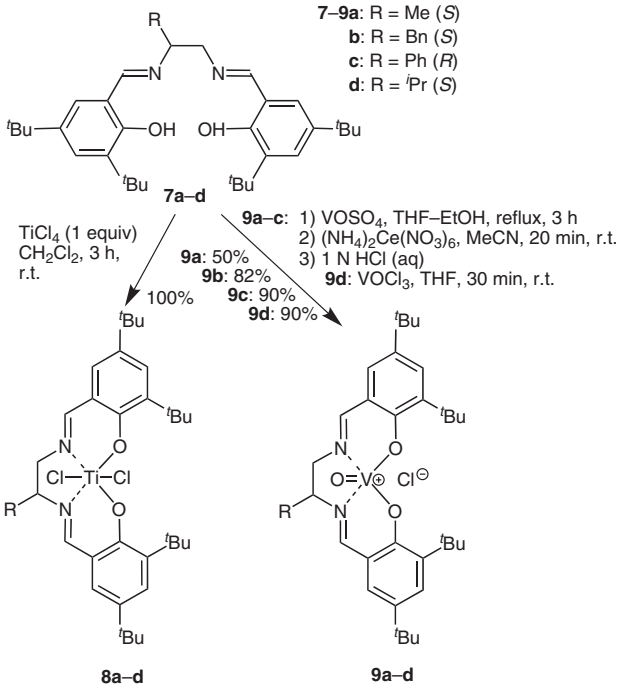


Figure 3 Stereochemistry inducing transition state for asymmetric cyanohydrin synthesis using metal(salen) complexes



Scheme 3 Synthesis of catalysts **8a–d** and **9a–d**

that salen ligands derived from an *R*,*R*-diamine have been found to catalyse the asymmetric addition of cyanide to the *si* face of benzaldehyde. The magnitude of the asymmetric induction using catalysts **5b–d** was very low (up to 30%), whilst complex **5e** gave more respectable enantioselectivities (up to 50%). Both the magnitude and the sense of asymmetric induction can be explained on the basis of the diamine unit within the salen ligand, which can adopt either a *gauche* or an *anti* conformation (Figure 2). Cyclic diamines such as 1,2-diaminocyclohexane can only adopt the *gauche* conformation, but for acyclic diamines the *anti* conformation is generally thermodynamically preferred as it minimises steric interactions between the R groups; and between the R groups and the imine hydrogens. Whilst a salen ligand normally prefers to be planar, it is well known that it can also adopt a *cis*-β configuration,[13] and this is necessary to allow formation of the established bimetallic transition state for asymmetric cyanohydrin synthesis in which cyanide is transferred intramolecularly to the coordinated aldehyde (Figure 3).[1]

When applied to octahedral complexes, with a salen ligand in the *cis*-β configuration, the consequence of changing the conformation of the diamine unit from *gauche* to *anti* is to change the preferred stereochemistry of the metal(salen) unit from Δ to Λ. This is due to the 'twist' of the diamine unit, which determines the overall 'twist' of the salen ligand (Figure 2). Thus, for complexes **5b–e** it appears that the salen ligand prefers to adopt the *anti* conformation, resulting in a Λ-configuration around the metal centres and thus inverting the enantioselctivity of asymmetric cyanohydrin synthesis compared to complexes **1**, **2**, **5a**, and **6a**.

The low levels of asymmetric induction observed with catalysts **5b–d** may be due to the diamine adopting a mixture of *gauche* and *anti* conformations, resulting in catalytically active complexes with both Δ- and Λ-configurations being formed. Crystal structures of copper and chromium complexes derived from ligand **4e** show that the diamine unit is locked into the *anti* conformation to avoid steric interactions between the two *tert*-butyl groups.[14] Thus in this case, exclusive formation of the Λ-configuration of the titanium(salen) unit would be predicted, consistent with the significantly higher asymmetric induction observed with this complex. Similar reasoning applies to vanadium-based complexes **6b–e**, though in this case catalyst **6c** exhibited surprisingly high reactivity and enantioselectivity and was a better catalyst even than complex **6e**.

To investigate further the influence of substituents within the diamine unit on the catalytic activity, a series of four monosubstituted diamine-derived salen ligands **7a–d** was prepared from the corresponding amino acids.[15] Ligands **7a–d** were then complexed to both titanium and vanadium to give complexes **8a–d** and **9a–d**, respectively, as shown in Scheme 3. Each of complexes **8a–d** and **9a–d** was then tested as a catalyst for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde under the standard conditions[11] (Table 2). All of the titanium complexes **8a–d** gave disappointing enantioselectivities and low conversions, neither of which was significantly improved by increasing the catalyst loading [best result 54% ee (*S*) and 61% conversion using 2 mol% of catalyst **8d**]. The vanadium(V) complexes **9a–d** gave more promising results with complex **9d** giving particularly good asymmetric induction.

Complexes **8b–d** and **9a–d** all catalysed the addition of cyanide to the *re* face of benzaldehyde, giving (*S*)-mandelonitrile trimethylsilyl ether. However, complexes **7c** and

Table 2 Synthesis of Mandelonitrile Trimethylsilyl Ether Using Catalysts **8** and **9**

Catalyst (0.1 mol%)	Conversion (%)	ee (%) (config)[a]
8a	9	30 (*R*)
8b	20	4 (*S*)
8c	27	20 (*S*)
8d	31	46 (*S*)
9a	57	4 (*S*)
9b	24	62 (*S*)
9c	53	32 (*S*)
9d	100	81 (*S*)

[a] Determined by chiral GC using the conditions reported in refs. 2–4 after conversion of the mandelonitrile trimethylsilyl ether into mandelonitrile acetate by the method of Kagan.[12]

Table 3 Synthesis of Cyanohydrin Trimethylsilyl Ethers Using Catalyst **9d** (0.1 mol%)

Aldehyde	Conversion (%)	ee (%) (config)[a]
3-MeC_6H_4CHO	86	78 (*S*)
4-MeC_6H_4CHO	90	78 (*S*)
4-$MeOC_6H_4CHO$	100	45 (*S*)
4-$F_3CC_6H_4CHO$	100	77 (*S*)
CyCHO	91	73 (*S*)
$C_8H_{17}CHO$	93	73 (*S*)
Me_2CHCHO	85	73 (*S*)
Me_3CCHO	100	45 (*S*)

[a] Determined by chiral GC using the conditions reported in ref. 2–4 after conversion of the mandelonitrile trimethylsilyl ether into mandelonitrile acetate by the method of Kagan.[12]

8c were derived from (*R*)-phenylglycine whilst all of the other complexes were derived from *S*-amino acids. There is only limited structural information available on complexes derived from ligands **7a**,**c** and none on the complexes of ligands **7b**,**d**. However, whilst the only crystal structure of a salen complex derived from phenylglycinamine shows that the phenyl ring adopts a pseudo-equatorial position,[16] crystal structures of vanadium(salen) complexes derived from 2,3-diaminopropane indicate that the methyl group can adopt either a pseudo-axial or a pseudo-equatorial position.[17] Thus, the inversion of enantioselectivity observed for complexes **7c** and **8c** may again be due to a change in the preferred conformation of the salen ligand.

The high catalytic activity of complex **9d** can be accounted for by the chloride counterion as we have previously shown that this has a significant influence on the catalytic activity of the vanadium-based catalysts.[2d] However, the high level of asymmetric induction obtained using catalyst **9d** was surprising given the poor results obtained with catalysts **5d**, **6d**, and **8d** which also contain isopropyl substituents. Therefore, catalyst **9d** was screened with eight other aldehydes as shown in Table 3. With the exception of the electron-rich 4-methoxybenzaldehyde, all of the aromatic aldehydes studied gave enantioselectivities of 77–81%. Similarly, with the exception of the sterically hindered pivaldehyde, all of the aliphatic substrates gave a cyanohydrin derivative with 73% ee. This trend in reactivity is the same as that previously reported for catalyst **2a**.[2b,c]

In conclusion, it has been shown that the nature of the substituent(s) within the diamine of a salen ligand influences on which one of the two enantiotopic faces of an aldehyde the reaction occurs during metal(salen)-catalysed asymmetric cyanohydrin synthesis. This effect can be traced back to the preferred configuration of the salen ligand around the metal ion.

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(11) Benzaldehyde (0.10 mL, 0.98 mmol) and catalyst **5**, **6**, **8**, or **9** (0.1–10 mol%) were dissolved in freshly distilled CH_2Cl_2 (5 mL). Trimethylsilyl cyanide (0.14 mL, 1.08 mmol, 1.1 equiv) was added, and the reaction was stirred at r.t. overnight. The resulting solution was filtered through a pad of SiO_2 using CH_2Cl_2 as eluent. Solvent was removed in vacuo to give mandelonitrile trimethylsilyl ether as a yellow oil. The conversion was determined by ^1H NMR spectroscopy. The mandelonitrile trimethylsilyl ether and $Sc(OTf)_3$ (1 mol%) were then dissolved in MeCN (5 mL), and Ac_2O (2.0 equiv) was added. The reaction mixture was stirred at r.t. for 20 min, then filtered through a pad of SiO_2 using CH_2Cl_2 as eluent. Solvent was removed in vacuo to give mandelonitrile acetate as a yellow oil which was analysed by chiral GC to determine its ee.

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