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Asymmetric Trimethylsilylcyanation of Aldehydes Catalyzed by Chiral (Salen)Ti(IV) Complexes.

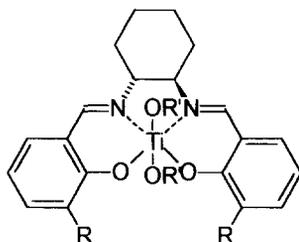
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Abstract: A set of aromatic, aliphatic and α,β -unsaturated aldehydes has been asymmetrically trimethylsilylcyanated with *e.e.*'s ranging from 40% to 80% using a chiral (salen)Ti(IV) catalyst prepared *in situ* from titanium tetraisopropoxide and (1*R*,2*R*)-[N,N'-bis(2'-hydroxy-3'-*t*-butyl-benzylidene)]-1,2-diaminocyclohexane or (1*R*,2*R*)-[N,N'-bis(2'-hydroxybenzylidene)]-1,2-diaminocyclohexane. Copyright © 1996 Elsevier Science Ltd

Enantiomerically pure cyanohydrins are versatile and important synthetic intermediates and there are several approaches to the catalytic asymmetric synthesis of this class of compounds reported in the literature.¹ Recently, N. Oguni and co-workers developed a new catalytic system based on Ti(IV)-tridentate Schiff's base complexes, derived from N-(2-hydroxy-3-*t*-butyl-benzylidene)-(S or R)-valinol (or other aminoalcohols or peptides) and Ti(O-*i*-Pr)₄, for trimethylsilylcyanation of aldehydes.² Enantiomeric excesses of the corresponding reaction products up to 96% were reported by this group.² Some experimental evidence was presented to support the reaction mechanism, including as a key step the substitution by the aldehyde carbonyl group of the isopropanol molecule in the co-ordination sphere of the catalytic complex.^{2a} A similar catalyst has recently been reported by Yaozhong *et al.*^{2d} Another type of chiral Schiff's base complexes derived from (1*R*,2*R*)-[N,N'-bis(2'-hydroxy-3'-*t*-butyl-benzylidene)]-1,2-disubstituted ethylenediamine and Mn(III) was shown by Jackobsen to be an efficient catalyst for the asymmetric epoxidation of simple olefins.³ In a further development, his group reported highly enantioselective ring opening of epoxides with Me₃SiN₃ catalysed by (salen)Cr(III) complexes of similar type.⁴ A possible mechanism involving the nucleophile delivery to the epoxide reactive group *via* co-ordination of the nucleophile with the central metal ion was tentatively suggested by the authors.⁴

We supposed that chiral (salen)Ti(IV) catalysts (**1a** and **1b**) prepared *in situ* from titanium tetraisopropoxide and (1*R*,2*R*)-[N,N'-bis(2'-hydroxybenzylidene)]-1,2-diaminocyclohexane, **1a**, {or (1*R*,2*R*)-[N,N'-bis(2'-hydroxy-3'-*t*-butyl-benzylidene)]-1,2-diaminocyclohexane, **1b**} might become efficient in the asymmetric trimethylsilylcyanation of aldehydes if the key step of the addition reaction were the cyanide co-ordination to the metal ion. Herein we describe the successful application of this idea.



1a: R= H, R'= CHMe₂

1b: R= CMe₃, R'= CHMe₂

The Schiff's bases were synthesised by the condensation of salicylaldehyde or 3-tert-butyl-2-hydroxybenzaldehyde with (**R,R**)-1,2-cyclohexanediamine in methanol, as described in the experimental section. The chiral Schiff's base-titanium complexes were obtained by mixing the corresponding chiral Schiff's base (1.3 eq.) and $\text{Ti}(\text{O}-i\text{-Pr})_4$ (1 eq.) in dichloromethane and the mixture was further used without any purification. The reaction of the aldehydes with trimethylsilyl cyanide was carried out essentially at -80 to -75°C in dichloromethane, using 20 mol% of the *in situ* prepared catalyst, as outlined by Oguni *et al.*² In addition, a special experiment was conducted to check if the free ligand was an efficient asymmetric catalyst of trimethylsilylcyanation reaction under the experimental conditions.

The reactions were monitored by TLC and, after the disappearance of the initial aldehyde (within 24-120 h), the reaction mixture was divided into two portions. The first portion was purified on silica and the trimethylsilyl derivatives thus recovered were analysed, using ^1H NMR and polarimetry. The e.e. of some of the products were additionally checked, using chiral GC on a γ -cyclodextrin phase without any derivatization. The second portion was hydrolysed with aq. HCl and the liberated cyanohydrins were analysed by ^1H NMR and polarimetry. The e.e. of the products were additionally checked, using chiral GC on a γ -cyclodextrin phase after the derivatization of the cyanohydrins with $(\text{CF}_3\text{CO})_2\text{O}$. The results were summarised in Table 1. As can be deduced from the Table, different methods of the enantiomeric analyses (including polarimetric measurements) of the e.e. of the trimethylsilylcyanation reaction gave similar results for benzaldehyde, as a substrate (entry 4). No satisfactory enantiomeric analysis could be done on the trifluoroacetyl derivative of the cyanohydrin generated from *p*-methoxybenzaldehyde with $(\text{CF}_3\text{CO})_2\text{O}$. There is a discrepancy in e.e., as determined by chiral GC and polarimetry (entry 7) for trimethylsilylcyanation of pivaloyl aldehyde. We believe that one possible reason for that observation could be an admixture of a strongly rotating compound in the final cyanohydrin, giving higher optical rotation of the product than that originating from the enantiomerically enriched pure material.

The data, collected in Table 1, clearly indicated that the free Schiff's base ligands might serve as catalysts of the reaction but no asymmetric induction was detected in the product (entry 1). Nevertheless there were no doubts that the Ti(IV) complexes, **1a** (entries 2-7) and **1b** (entries 8-11), were both efficient asymmetric catalysts of trimethylsilylcyanation of aldehydes. As could have been expected, **1b** seemed to be a more promising catalyst, having produced a larger e.e. of the reaction (compare entries 4 and 8, 7 and 11). The temperature dependence of the e.e. of the reaction was noticeable and predictably favoured low temperatures (see entries 2 and 4), although to a lesser extent than reported by Oguni for his type of catalysts.² The influence of the electronegativity of the substituents on the enantioselectivity of the reaction seemed to be different from the case of tridentate Schiff's base-Ti(IV) complex catalysis, as the introduction of a *p*-methoxy substituent into the benzaldehyde molecule decreased the e.e. of the reaction (see entries 4 and 5, 8 and 9).

The mechanism of the catalysis by **1a** and **1b** appears to be different from that suggested by Oguni² for his tridentate ligand based catalysts. All the co-ordination sites in the complexes **1a** or **1b** are occupied either by the tetradentate ligand or by alkoxide molecules. There are no vacant sites or sites occupied by the solvent or neutral alcohol molecule left in the co-ordination sphere of the catalytic complex. The mechanism, involving the substitution of such strong ligands as alkoxide or a fragment of the tetradentate ligand by such a relatively weak base as the carbonyl group of aldehyde, looks unlikely because of the very low probability of the substitution event. We suggest that the preliminary interaction of trimethylsilyl cyanide with the complex, generating $\text{Me}_3\text{SiO}-i\text{-Pr}$ and the co-ordinated CN at the apical position of the complex, might be the first step in the catalytic cycle. The stereo differentiating step would then be nucleophilic delivery of CN from the chiral complex to the carbonyl group of the aldehyde, taking place inside the co-ordination sphere of the complex. Further discussion should be postponed until after new experimental facts emerge. The reported e.e. of the cyanosilylation reaction were not optimised and probably could be further improved by the appropriate choice of the reaction conditions. In conclusion, we believe that this work broadens the growing field of salen-type complexes, functioning as asymmetric catalysts.

Table 1 Enantioselective Trimethylsilylation of Aldehydes Catalysed by Chiral Schiff's Base-Titanium Complexes **1a** and **1b**.^a

Entry	Catalyst	Substrate	Chemical Yield% ^b		e.e.% ^c (config) ^d		[α] _D ²⁵ Cyanohydrin (e.e. by polarimetry)
			Me ₃ Si- ether	Cyano- hydrin	Me ₃ Si- ether	Cyano- hydrin	
1	Schiff's base ligand of 1a	Benzaldehyde	>70	>98	0	0	0
2 ^c	1a	Benzaldehyde		>98		40 (S)	
3 ^f	1a	Benzaldehyde	>90	>98	51 (S)	51 (S)	
4	1a	Benzaldehyde	>60	>98	68 (S)	68 (S)	-29.8 (67) ^g
5	1a	p-Methoxy- benzaldehyde	>40		60 (S)		
6	1a	(E)-Cinnam- aldehyde	>70	>95	70 (S)	54-60 (S) ^h	-21.5 (80) ⁱ
7	1a	Trimethyl- acetaldehyde	>86	>95	16 (S)	16 (S)	-14.5 (70) ^j
8	1b	Benzaldehyde	>68	>98	75 (S)	75 (S)	
9	1b	p-Methoxy- benzaldehyde	>70		62 (S)		
10	1b	(E)-Cinnam- aldehyde	>60		71-77 (S)		
11	1b	Trimethyl- acetaldehyde	>55	>98	77 (S)	81 (S)	

a) The experimental conditions were as described in the experimental section (-75-80°C, 24-120h) unless indicated otherwise. No changes in the enantiomeric purity of the cyanohydrins were observed within the time span of the reaction. b) Isolated yields, those of the Me₃Si-derivatives were determined after the purification on SiO₂ and diminished due to partial hydrolysis to cyanohydrins during the purification stage. c) Determined by enantiomeric GC analysis, employing a chiral γ -cyclodextrin phase. d) Determined by comparing the sign of the specific rotation of the cyanohydrins with the literature data (ref. 2). e) The reaction was run at the ambient temperature. f) The mol ratio of the chiral Schiff's base to Ti(O-*i*-Pr)₄ was 1:1.3. g) The measurements on this and other samples were carried out for their CHCl₃ solutions, $c=0.3-1$. The [α]_D²⁵ for the 100% enantiomerically pure sample of (R)-configuration was estimated as +45.5 based on literature data (see ref. 2). h) The derivatization with (CF₃CO)₂O caused partial E/Z isomerisation, the E-isomer having an e.e. of 54% and the Z-isomer of 60%. i) The [α]_D²⁵ for the 100% enantiomerically pure sample of (R)-configuration was estimated as +26.7 based on literature data (see ref. 2). j) The [α]_D²⁵ for the 100% enantiomerically pure sample of (R)-configuration was estimated as +20.7 based on literature data (see ref. 2).

Experimental Section

¹H NMR spectra were run on a Bruker WP-200-SY. Optical rotations were measured with a Perkin-Elmer-241 polarimeter in a thermostated cell at 25°C. Kieselgel 60 (Merck) was used for column chromatography and silica gel precoated plates "Silufol UV-254" (Chemapol) were used for TLC analyses. Dichloromethane was dried over P₂O₅ and distilled prior to use. Trimethylsilyl cyanide (Fluka) was used without further purification. The aldehydes were purchased from Fluka and were distilled prior to use. 3-Tert-butylsalicylaldehyde was synthesised by a modified literature procedure⁵ and purified as its Cu(II) complex; the product had b.p. 87°C/6 mm Hg (lit.^{2a} b.p. 75-77°C/5 mm Hg). (1R,2R)-diaminocyclohexane dihydrochloride was resolved, according to the literature procedures⁶ and had satisfactory elemental

analyses and $[\alpha]_D^{25} = -15$ ($c=5$, aq. 1N HCl), {lit.⁶, $[\alpha]_D^{25} = -15.8$ }. The enantiomeric analyses of trimethylsilyl-ethers and trifluoroacetyl derivatives of cyanohydrins were carried out using a GC method (chiral phase DP-TFA- γ -CD, fused silica capillary column, 32m x 0.20mm, carrier gas He). The experimental conditions were as described below for the trimethylsilyl-ethers of cyanohydrins derived from:

- a) Benzaldehyde (Temp. 125°C, 1.70 bar.); b) p-Methoxybenzaldehyde (Temp. 130°C, 2.00 bar.)
c) trans-Cinnamaldehyde (Temp. 140°C, 2.05 bar.); d) Trimethylacetaldehyde (Temp. 70°C, 1.40 bar.)

The experimental conditions were as described below for trifluoroacetyl esters derived from:

- a) Benzaldehyde (Temp. 110°C, 1.65 bar.); b) p-Methoxybenzaldehyde (Temp. 130°C, 1.60 bar (no satisfactory analytical results were obtained for this derivative because of its instability.)); c) trans-Cinnamaldehyde (Temp. 135°C, 1.67 bar.); d) Trimethylacetaldehyde (Temp. 70°C, 1.40 bar.)

(1R,2R)-[N,N'-bis(2'-hydroxybenzylidene)]-1,2-diaminocyclohexane.

To a mixture of salicylaldehyde (0.7g, 5.7 mmol) and (1R,2R)-diaminocyclohexane dihydrochloride (0.5g, 2.7 mmol) in MeOH (10 ml) and EtOH (10 ml) were added 1.3 ml of 4.65N MeONa in MeOH under stirring at ambient temperature. The mixture was refluxed for 7 h, filtered and evaporated *in vacuo*, the obtained solid was taken up in dichloromethane and the solution was filtered and evaporated. The yellow residue (0.68 g, 2.1 mmol, 78%) was used without further purification. The compound had: $[\alpha]_D^{25} = -359.5$ ($c=1$, CHCl₃); ¹H NMR (CDCl₃) δ 1.1-2.0 (m, 8H), 3.30 (m, 2H), 6.7-7.4 (m, 8H), 8.30 (s, 2H), 13.35 (br. s, 2H).

(1R,2R)-[N,N'-bis(2'-hydroxy-3'-t-butyl-benzylidene)]-1,2-diaminocyclohexane.

To a mixture of 3-tert-butylsalicylaldehyde (0.48g, 2.7 mmol) and (1R,2R)-diaminocyclohexane dihydrochloride (0.25g, 1.3 mmol) in MeOH (10 ml) and EtOH (10 ml) were added 10 ml of C₆H₆ followed by 0.6 ml of 4.65N MeONa in MeOH under stirring at ambient temperature. The mixture was refluxed for 12 h with a trap to remove H₂O, then filtered and evaporated. The residue was dissolved in pentane under reflux and the hot solution was filtered to remove the adduct of one molecule of salicylaldehyde and one molecule of diamine hydrochloride which was insoluble in pentane. The procedure was repeated twice, the pentane solution was evaporated to give 0.2 g, 0.46 mmol of yellow oil which was used without further purification. The compound had: $[\alpha]_D^{25} = -396$ ($c=2$, CHCl₃); ¹H NMR (CDCl₃) δ 1.41 (s, 18H), 1.61-2.0 (m, 8H), 3.41 (m, 2H), 6.65-7.34 (m, 6H), 8.27 (s, 2H), 13.87 (br. s, 2H).

General procedure for trimethylsilylcyanation of aldehydes:

The adopted procedure closely followed one described by Oguni and coworkers.² The solution of the Schiff's base (0.55 mmol) in 2.5 ml of dichloromethane was placed into a dry flask and Ti(O-*i*-Pr)₄ was added to the solution under Ar at ambient temperature. The mixture was stirred at room temperature for 1 h, cooled to -78°C, aldehyde (2.46 mmol) and trimethylsilylcyanide (0.75 ml, 5.62 mmol) were added to the reaction mixture and it was left at -80°C. The disappearance of the aldehyde was monitored by TLC (hexane, ethyl acetate). Usually it took 48-120 h for the completion of the reaction. After this the reaction mixture was divided into two portions. The first one was evaporated *in vacuo* at ambient temperature and the residue chromatographed on a SiO₂ column (hexane/ethylacetate; 5:1) to obtain trimethylsilyl ether. The fraction containing the compound was evaporated and analysed by ¹H NMR, polarimetry and chiral GC. The second portion of the reaction mixture was quenched with aq. 1N HCl (30 ml) and the resulting emulsion was extracted with ethylacetate (50 ml x 3), the combined extracts were washed with saturated NaHCO₃ (50 ml x 4), brine (50 ml x 2) and dried over Na₂SO₄. The solution was evaporated and the cyanohydrin was analysed by ¹H NMR and polarimetry without further purification. All the cyanohydrins

and their trimethylsilyl-ethers were found to have satisfactory ^1H NMR spectra. The enantiomeric GC analyses of cyanohydrins were performed after their derivatization with $(\text{CF}_3\text{CO})_2\text{O}$ as described below.

Procedure for derivatisation of cyanohydrins:

The sample (usually 2 mg) was dissolved in 5 ml of CH_2Cl_2 and $(\text{CF}_3\text{CO})_2\text{O}$ (10 mol excess) was added into the solution at ambient temperature. After an hour at room temperature the solution was evaporated and the residue analyzed by GC. The trifluoroacetyl derivative of 2-hydroxy-2-phenylacetonitrile was found to keep its enantiomeric purity at room temperature for a month (at least).

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