

Asymmetric trimethylsilylcyanation of benzaldehyde catalyzed by (salen)Ti(IV) complexes derived from (*R*)- and/or (*S*)-4-hydroxy-5-formyl[2.2]paracyclophane and diamines

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Abstract: Benzaldehyde has been asymmetrically trimethylsilylcyanated, using chiral (salen)Ti(IV) catalysts **1a** and **1b**, **2a** and **2b**, **3a** and **3b** prepared *in situ* from titanium tetraisopropoxide and the Schiff's bases derived from (*R*)- or (*S*)-4-hydroxy-5-formyl[2.2]paracyclophane [(*R*)- and (*S*)-FHPC] and diaminoethane (EDA) (catalysts **1a** or **1b**); (*R*)- or (*S*)-FHPC and 1,3-diaminopropane (PDA) (catalysts **2a** or **2b**); (*R*)- or (*S*)-FHPC and (1*R*,2*R*)-1,2-diaminocyclohexane [(1*R*,2*R*)-CHDA] (catalysts **3a** and **3b**). Surprisingly, **1a** and **1b** were found to be the most efficient catalysts whereas both enantiomers of **2** were completely inactive. The maximum e.e. of 84% (*S*) at -78°C was obtained in the reaction catalysed by **1b** at 5–10 mol%. The catalyst could be precipitated with hexane from the reaction mixture and reused. © 1997 Published by 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

From the synthetic point of view trimethylsilyl derivatives of the cyanohydrins, having greater stability, are more attractive.¹ Recently, a set of catalytic systems 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 the hydrocyanation and trimethylsilylcyanation of aldehydes were elaborated.² E.e.s of the corresponding reaction products up to 96% have been reported.²

Other types of chiral Schiff's base (salen)Ti(IV) complexes derived from the tetradentate ligand (1*R*,2*R*)-[*N,N'*-bis(2'-hydroxy-3'-*t*-butyl-benzylidene)]-1,2-disubstituted-ethylenediamine and Ti(O^{*i*}Pr)₄ have been shown recently to be efficient catalysts for the asymmetric trimethylsilylcyanation of aldehydes.³ The chiral diamine moiety of the catalyst was eventually responsible for the asymmetric induction in this reaction.

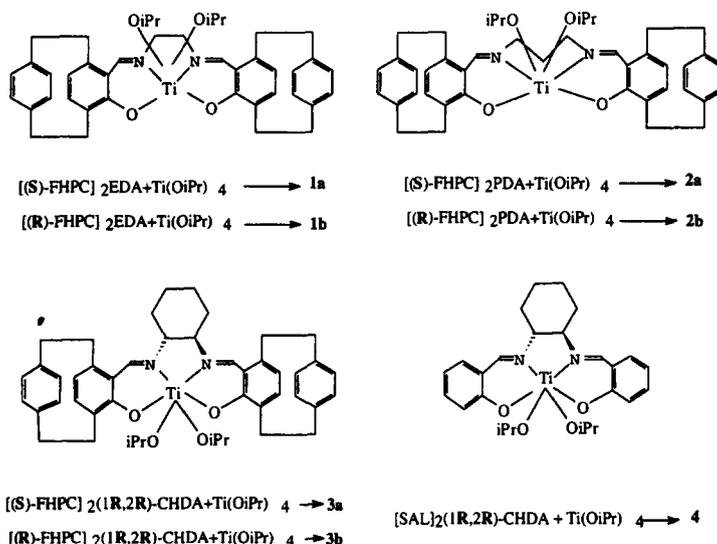
Recently, we reported synthesis, resolution and application for the asymmetric synthesis of (*R*)- and (*S*)-4-hydroxy-5-formyl-[2.2]paracyclophane, (*R*)- and (*S*)-FHPC, chiral analogues of salicylaldehyde.⁴ The compound was found to be an efficient chiral auxiliary for the asymmetric synthesis of amino acids.⁴ We supposed that the substitution of salicylaldehyde with (*S*)- or (*R*)-FHPC in the chiral (salen)Ti(IV) complexes may greatly modify the catalytic properties of the catalyst and may obviate the use of chiral diamines in the catalyst, still retaining its asymmetry inducing properties. Herein we describe the successful application of the idea.

The catalysts were synthesised from the corresponding Schiff's bases and Ti(O^{*i*}Pr)₄ *in situ*. The designations of the catalytic complexes are as follows: those derived from Schiff's base of (*S*)- or (*R*)-

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FHPC and diaminoethane (EDA) are **1a** and **1b** correspondingly, the catalysts from (*S*)- or (*R*)-FHPC and 1,3-diaminopropane (PDA) are **2a** and **2b**, those originating from (*S*)- or (*R*)-FHPC and (1*R*,2*R*)-diaminocyclohexane [(1*R*,2*R*)-CHDA] are **3a** and **3b** correspondingly. A model complex derived from salicylaldehyde and (1*R*,2*R*)-diaminocyclohexane [(1*R*,2*R*)-CHDA] is referred to as **4**.

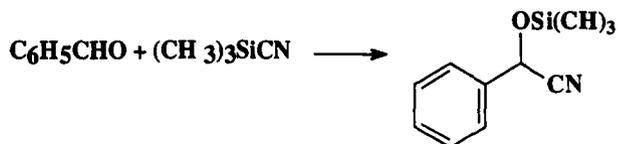
The reaction of benzaldehyde with trimethylsilyl cyanide was carried out initially, using 10% (mol) of catalysts prepared *in situ* as outlined earlier.^{3a} The reactions were monitored by TLC and, after 1–168 h, depending on the reaction conditions, the reaction mixture was put on a column of SiO₂ to separate the silyl ether of the mandelonitrile which was analysed by chiral GC, as described before.^{3a}



The data, collected in Table 1, clearly indicated that both enantiomers of **1** proved to be efficient catalysts of the reaction (Table 1, runs 1–6). **1a** and **1b** had, as the only element of chirality, two disubstituted [2.2]paracyclophane moieties and while the use of the (*S*)-FHPC derivative **1a** resulted in the synthesis of mandelonitrile of (*R*)-configuration, the (*R*)-FHPC-moiety of **1b** induced (*S*)-configuration of the final product. As could have been expected, low temperatures favoured higher e.e. of the reactions (compare Table 1, runs 1, 3 and 4). The maximum e.e. was as high as 84% at -78°C (Table 1, run 2). The catalytic complex could be recovered from the reaction mixture by precipitation with hexane and reused again (Table 1, runs 5 and 6). If the usual 10% mol ratio of the recovered catalyst were employed, no fall in the e.e. of the reaction was registered (Table 1, runs 3 and 5). 1% Of the recovered catalyst was still active (Table 1, run 6), although the asymmetric induction was somewhat lower. The preliminary experiments indicated that the catalyst could be recovered in this way and reused, at least five times without loss of its activity.

On the other hand the introduction of one more methylene link into the ethylenediamine moiety resulted in a complete loss of the catalytic activity of **2** at -78° , as compared to **1** (Table 1, runs 1, 2, 7 and 8). Although some catalytic activity seemed to be retained by **2** at 25°C (Table 1, run 9), the reaction product was racemic which indicated that the catalytic particle did not contain any chiral ligand and might be a kind of achiral Ti-containing species derived from $\text{Ti}(\text{O}^i\text{Pr})_4$ and other achiral ligands present in the reaction mixture.

The catalysts derived from both (*S*)- and (*R*)-FHPC and (1*R*,2*R*)-CHDA (**3a** and **3b**) were catalytically active, although **3a** was a disappointing performer. For example, the reaction catalysed by **3a** was only 50% complete after 120 h at -78°C (Table 1, run 11), whereas the time interval was quite sufficient for the catalysts **1a** and **1b** to bring the reaction to virtual completion under the experimental conditions (Table 1, runs 1 and 2). The e.e. of the reaction product, (*R*)-configuration, was also low (17–23%, Table 1, runs 11 and 12). Earlier^{3a} it was shown that the (1*R*,2*R*)-diaminocyclohexane moiety

Table 1. Enantioselective trimethylsilylcyanation of benzaldehyde catalysed by chiral Schiff's base-titanium complexes 1–3^a

Run No	Catalyst	t°C	time h	yield % ^b	e.e.(config) % ^c
1	1a	-78	120	90	82(R)
2	1b	-78	120	90	84(S)
3	1a	-5	72	90	48(R)
4	1a	+25	4	80	22(R)
5	1a^d	-5	72	80	49(R)
6	1b^{d,e}	-78	120	73	73(S)
7	2a	-78	120	0	0
8	2b	-78	120	0	0
9	2b	+25	35	80	0
10	3a	-78	24	0	0
11	3a	-78	120	50	17(R)
12	3a	-78	168	70	23(R)
13	3a	+25	3	90	0
14	3b	-78	24	90	35(S)
15	3b	-78	120	90	48(S)
16	3b^d	-78	120	90	49(S) ^f
17	3b	+25	1	90	44(S)
18 ^g	4	-78	120	90	60(S)

a) The reaction was conducted in CH_2Cl_2 (concentration of aldehyde 0.7 M, ratio substrate/ $(\text{Me}_3\text{Si})\text{CN}$ equal to 2-2.5); the catalyst was prepared *in situ* and used in 10% mol ratio to benzaldehyde unless indicated otherwise. b) Isolated yields, those of the Me_3Si -derivatives were determined after the purification on SiO_2 and diminished due to partial hydrolysis to cyanohydrins during the purification stage. c) Determined by enantiomeric GC analysis of the silyl-ethers, employing a chiral γ -cyclodextrine phase.^{3a} d) The catalyst was recovered from the reaction mixture by precipitation with hexane and then used repeatedly in the reaction. e) The reaction was run at the ratio. catalyst/substrate equal to 0.01 or 1% mol. f) The average of two measurements. g) Taken from Ref.3a

induced (*S*)-configuration of the final product, if the catalyst was modified in such a way, as to substitute (*S*)-FHPC in the chiral ligand with achiral salicylaldehyde or its derivatives as in (1*R*,2*R*)-[*N,N'*'-bis(2''-hydroxybenzylidene)]-1,2-diaminocyclohexane (catalyst **4**, Table 1, run 18). The observation seemed to indicate mutual compensations of the asymmetry inducing power of the chiral moieties, with the influence of the (*S*)-FHPC moiety prevailing over that of the (1*R*,2*R*)-diaminocyclohexane one. Surprisingly, **3b**, which in all three chiral moieties should have induced (*S*)-configuration of the product was not as efficient as one might expect, providing only 49% e.e of the product of (*S*)-configuration (Table 1, runs 15 and 16). As expected, the catalyst could be recovered and reused in the same way as **1a** and **1b**. Another remarkable feature of the catalysis by **3b** was evident after inspecting runs 16

and 17 of Table 1. As can be seen from the data, the temperature dependence of the reaction e.e. was almost unnoticeable with the decrease of only 5%, as the temperature varied from -78°C to $+25^{\circ}\text{C}$.

In conclusion, we believe that in spite of many enigmatic features of the catalysts derived from Ti(IV) and salen-type Schiff's bases of FHPC with diamines, their significant potential as promising Lewis acids for asymmetric catalysis is evident. We also believe that the ligands of the above mentioned type may be eventually employed for the synthesis of other types of chiral catalysts, using other metals to perform numerous asymmetric transformations.

Experimental section

^1H NMR spectra were obtained on a Bruker AMX-400 instrument at 400.13 MHz with CDCl_3 ($\delta=7.27$) as an internal standard. Optical rotations were measured with a Perkin-Elmer-241 polarimeter in a thermostated cell at 25°C . TLC-analysis were performed on silica-gel precoated plates 'Silufol UV-254' (Chemapol). Column chromatography was performed on Kieselgel 60 (Merck). Benzene was distilled prior to use from sodium. MeOH was distilled from $(\text{MeO})_2\text{Mg}$. Dichloromethane was dried over P_2O_5 and distilled prior to use. Trimethylsilyl cyanide (Fluka) was used without further purification. (1*R*,2*R*)-Diaminocyclohexane was resolved according to the literature procedures⁵ and had satisfactory elemental analyses and $[\alpha]_{\text{D}}^{25} - 15$ ($c=5$, aq. 1 N HCl), {lit.,⁶ $[\alpha]_{\text{D}}^{25} - 15.8$ }.

Schiff's base derived from (S)- or (R)-4-hydroxy-5-formyl-[2.2]paracyclophane and diaminoethane, [(S)- or (R)-FHPC]₂EDA, a general procedure

Ethylenediamine dihydrochloride (0.09 g, 0.69 mmol) and Et_3N (0.22 ml, 1.39 mmol) were added to a solution of (S)- or (R)-FHPC (0.35 g, 1.39 mmol) in a mixture of benzene (5 ml) and MeOH (2 ml). The resultant solution was refluxed for 2 h, the precipitated solid was filtered off, washed with benzene (2×20 ml), then Et_2O (20 ml) and recrystallized from acetone to yield 60% (0.22 g) of the Schiff's base.

[(S)-FHPC]₂EDA

Mp $218-220^{\circ}\text{C}$. Found: C, 81.29; H, 6.91; N, 5.00. $\text{C}_{36}\text{H}_{36}\text{N}_2\text{O}_2$ requires C, 81.78; H, 6.86; N, 5.30%. $[\alpha]_{\text{D}}^{25} - 858$ ($c=0.3$, acetone). ^1H NMR, δ_{H} (CDCl_3) 2.53–3.52 (m, 16H, $-\text{CH}_2-\text{CH}_2-$), 3.88 (m, 2H, CH_2), 4.19 (m, 2H, CH_2), 6.18 (d, 2H, J 7.8), 6.30 (dd, 2H, J 7.8 and 1.9), 6.44 (dd, 2H, J 7.8 and 1.9), 6.49 (d, 2H, J 7.8), 6.60 (dd, 2H, J 7.8 and 1.9), 6.91 (dd, 2H, J 7.8 and 1.9), 8.32 (s, 2H, $\text{CH}=\text{N}$), 14.00 (br.s., 2H, OH).

[(R)-FHPC]₂EDA

Mp $225-226^{\circ}\text{C}$. Found: C, 81.95; H, 7.08; N, 5.13. $\text{C}_{36}\text{H}_{36}\text{N}_2\text{O}_2$ requires C, 81.78; H, 6.86; N, 5.30%. $[\alpha]_{\text{D}}^{25} + 855$ ($c=0.3$, acetone). ^1H NMR δ_{H} (CDCl_3) 2.53–3.52 (m, 16H, $-\text{CH}_2-\text{CH}_2-$), 3.88 (m, 2H, CH_2), 4.19 (m, 2H, CH_2), 6.18 (d, 2H, J 7.8), 6.30 (dd, 2H, J 7.8 and 1.9), 6.44 (dd, 2H, J 7.8 and 1.9), 6.49 (d, 2H, J 7.8), 6.60 (dd, 2H, J 7.8 and 1.9), 6.91 (dd, 2H, J 7.8 and 1.9), 8.32 (s, 2H, $\text{CH}=\text{N}$), 14.00 (b.s., 2H, OH).

Schiff's base derived from (S)- or (R)-4-hydroxy-5-formyl-[2.2]paracyclophane and 1,3-diaminopropane, [(S)- or (R)-FHPC]₂PDA, a general procedure

To a solution of (R)- or (S)-FHPC (0.21 g, 0.83 mmol) in the mixture of benzene (4 ml) and MeOH (2 ml) a solution of 1,3-propylenediamine (0.034 ml, 0.41 mmol) in benzene (1 ml) was added. The mixture was refluxed for 5 h, then the solvent was removed under reduced pressure and the residue purified by column chromatography on SiO_2 ($\text{CHCl}_3:\text{AcOEt}$, 5:1). The product was recrystallized from benzene:methanol to yield the Schiff's base in a 72% yield (0.16 g).

[(S)-FHPC]₂PDA

Mp 243–245°C. Found: C, 81.86; H, 7.32; N, 5.10. C₃₇H₃₈N₂O₂ requires C, 81.88; H, 7.06; N, 5.16%. [α]_D²⁵ –799.4 (c=1, CHCl₃). δ _H(CDCl₃) 2.18 (m, 2H, CH₂–CH₂–CH₂), 2.55–3.50 (m, 16H, –CH₂–CH₂–), 3.70 (m, 2H, CH₂–CH₂–CH₂), 3.85 (m, 2H, CH₂–CH₂–CH₂), 6.18 (d, 2H, *J* 7.8), 6.25 (dd, 2H, *J* 7.8 and 1.8), 6.42 (dd, 2H, *J* 7.8 and 1.8), 6.50 (d, 2H, *J* 7.8), 6.58 (dd, 2H, *J* 7.8 and 1.8), 2H, *J* 7.8 and 1.8), 8.28 (s, 2H, CH=N), 14.25 (b.s., 2H, OH).

[(R)-FHPC]₂PDA

Mp 244–246°C. [α]_D²⁵ +790 (c=1, CHCl₃). δ _H(CDCl₃) 2.18 (m, 2H, CH₂–CH₂–CH₂), 2.55–3.50 (m, 16H, –CH₂–CH₂–), 3.70 (m, 2H, CH₂–CH₂–CH₂), 3.85 (m, 2H, CH₂–CH₂–CH₂), 6.18 (d, 2H, *J* 7.8), 6.25 (dd, 2H, *J* 7.8 and 1.8), 6.42 (dd, 2H, *J* 7.8 and 1.8), 6.50 (d, 2H, *J* 7.8), 6.58 (dd, 2H, *J* 7.8 and 1.8), 6.87 (dd, 2H, *J* 7.8 and 1.8), 8.28 (s, 2H, CH=N), 14.25 (b.s., 2H, OH).

Schiff's base derived from (S)- or (R)-4-hydroxy-5-formyl-[2.2]paracyclophane and (1R, 2R)-diaminocyclohexane, [(S)- or (R)-FHPC]₂(1R,2R)-CHDA, a general procedure

The procedure adopted was the same as that described by Larrow *et al.*⁵ for the synthesis of other Schiff's bases of salicylaldehyde and (1R,2R)-diaminocyclohexane.

[(S)-FHPC]₂ (1R,2R)-CHDA

It was purified by column chromatography on SiO₂ (C₆H₆:AcOEt, 3:2) and recrystallized from a mixture of acetone and benzene to yield the Schiff's base (63%, 0.18 g). Mp 294°C dec. Found: C, 82.05; H, 7.41; N, 4.70. C₄₀H₄₂N₂O₂ requires C, 82.44; H, 7.26; N, 4.81%. [α]_D²⁵ –1089.3 (c=0.2, CHCl₃). δ _H(CDCl₃) 1.65 (b.m., 2H, –CH₂– CHDA), 1.90 (b.m., 2H, –CH₂– CHDA), 2.03 (b.m., 2H, –CH₂– CHDA), 2.17 (b.m., 2H, –CH₂– CHDA), 2.54 (m, 2H, –CH₂–CH₂–), 2.72 (m, 4H, –CH₂–CH₂–), 2.95–3.48 (m, 10H, –CH₂–CH₂– and –CH– CHDA), 6.09 (d, 2H, *J* 7.5), 6.23 (dd, 2H, *J* 7.8 and 1.3), 6.40 (m, 4H), 6.55 (dd, 2H, *J* 7.8 and 1.3), 6.84 (dd, 2H, *J* 7.8 and 1.3), 8.12 (s, 2H, CH=N), 14.08 (b.s., 2H, OH).

[(R)-FHPC]₂ (1R,2R)-CHDA

It was purified by column chromatography on SiO₂ (CHCl₃) and precipitated from benzene with heptane to yield the Schiff's base (0.22 g, 77%). Mp 292°C dec. Found: C, 82.63; H, 7.23; N, 4.75. C₄₀H₄₂N₂O₂ requires C, 82.44; H, 7.26; N, 4.81%. [α]_D²⁵ +601 (c=0.2, CHCl₃). δ _H(CDCl₃) 1.63 (b.m., 4H, –CH₂– CHDA), 1.90 (b.m., 2H, –CH₂– CHDA), 2.17 (b.m., 2H, –CH₂– CHDA), 2.58 (m, 2H, –CH₂–CH₂–), 2.71–3.06 (m, 6H, –CH₂–CH₂–), 3.19 (m, 4H, –CH₂–CH₂–), 3.46 (m, 4H, –CH₂–CH₂–), 3.62 (b.m., 2H, –CH– CHDA), 6.18 (d, 2H, *J* 7.8), 6.31 (dd, 2H, *J* 7.8 and 1.9), 6.45 (dd, 2H, *J* 7.8 and 1.9), 6.49 (d, 2H, *J* 7.8), 6.61 (dd, 2H, *J* 7.8 and 1.9), 6.99 (dd, 2H, *J* 7.8 and 1.9), 8.40 (s, 2H, CH=N), 14.36 (b.s., 2H, OH).

General procedure for trimethylsilylcyanation of benzaldehyde

The adopted procedure closely followed one described earlier.^{3a}

The enantiomeric analyses of trimethylsilyl ether of mandelonitrile

It was carried out using method GC (chiral phase DP-TFA-g-CD), as described before.^{3a}

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