Asymmetric trimethylsilylcyanation of aldehydes catalyzed by chiral salen Ti^{IV} complexes with the C_1 symmetry

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Asymmetric trimethylsilylcyanation of a number of aromatic and aliphatic aldehydes catalyzed by chiral Ti^{IV} complexes prepared *in situ* from $Ti(OPr^i)_4$ and (1*S*)-[*N*,*N*′-bis(2′-hydroxy-3′-*tert*-butylbenzylidene)]-1,2-diaminoalkanes gives products with (*S*)-absolute configurations.

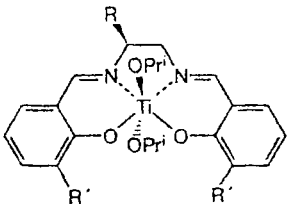
Key words: asymmetric catalysis, salen complexes, Ti^{IV}, trimethylsilylcyanation.

Asymmetric catalytic synthesis of enantiomerically pure cyanohydrins is of considerable practical interest, since they are important starting compounds for the synthesis of enantiomerically pure physiologically active β-amino alcohols[1] and pyrethroids.[2] Enzymatic[3] and chemical methods[4,5] for asymmetric synthesis of cyanohydrins are being successfully developed; however, this problem is far from being ultimately solved.

Chiral catalysts of trimethylsilylcyanation of aldehydes based on Lewis acids[5] including Ti^{IV} complexes are of particular interest in this respect, because the final reaction products, *viz.*, trimethylsilyl derivatives of cyanohydrins, can be easily converted into β-amino alcohols without racemization of the asymmetric center of the cyanohydrin.[6] In addition, there exists an infinite diversity of chiral ligands able to coordinate efficiently Ti^{IV} ions; this markedly facilitates the search for the most efficient catalyst of trimethylsilylcyanation. Recently we have shown that chiral complexes of Ti^{IV} with the C_2 symmetry prepared *in situ* from $Ti(OPr^i)_4$ and the Schiff base derived from (1*R*,2*R*)-[*N*,*N*′-bis(2′-hydroxybenzylidene)]cyclohexane-1,2-diamine acting as a tetradentate ligand are efficient catalysts of trimethylsilylcyanation of some aliphatic and aromatic aldehydes.[7] In the present study, we have shown that chiral salen complexes of Ti^{IV} having a similar structure and the C_1 symmetry are also efficient asymmetric catalysts of this reaction.

Results and Discussion

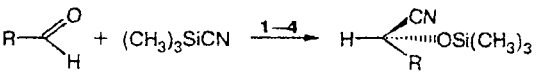
The initial chiral ligands were synthesized by the condensation of salicylaldehyde and 3-*tert*-butylsalicylaldehyde with chiral diamines prepared from the corresponding (*S*)-amino acids according to the usual scheme including synthesis of esters of amino acids, their conversion into amides, and reduction of these amides with $LiAlH_4$ to diamines.



1—4

	R	R′
1	$MeS(CH_2)_2$	H
2	$MeS(CH_2)_2$	Bu^t
3	Pr^n	Bu^t
4	Me_2CHCH_2	Bu^t

Catalysts **1—4** were obtained by mixing the tetradentate ligands with $Ti(OPr^i)_4$ in CH_2Cl_2. The products were not isolated; instead, the mixture obtained *in situ* was cooled to −78 to −80 °C, and an aldehyde and trimethylsilyl cyanide were added to it. After 120 h (at −78 °C), the reaction was completed and the mixture was applied on a column with SiO_2.



Trimethylsilyl derivatives were isolated by chromatography, and their enantiomeric compositions were analyzed by GLC (Table 1). The data presented in Table 1 indicate that all of the catalysts proved to be efficient in this reaction. An interesting feature of this type of catalyst

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is that asymmetric fragments with (*S*)-configuration induce the formation of products having also (*S*)-configurations. Reaction products with the same configuration were obtained in the presence of the catalyst prepared from $Ti(OPr^i)_4$ and a tetradentate ligand, *viz.*, the Schiff base derived from (1*R*,2*R*)-[*N*,*N*′-bis(2′-hydroxybenzylidene)]cyclohexane-1,2-diamine.

Comparison of the efficiencies of catalysts **1** and **2** indicates that, as should be expected, the introduction of a *tert*-butyl group into the *ortho*-position of salicylaldehyde sharply increases the enantioselectivity of the trimethylsilylcyanation of benzaldehyde from 36% to 65% *ee* (Table 1, entries 1 and 2). When the side methylthioethyl group of the diamine fragment in catalyst **2** is replaced by a propyl group, *i.e.*, in the case of catalyst **3**, the enantioselectivity of this reaction dramatically decreases: *ee* changes from 65% to 25% (Table 1, entries 2 and 8). Only the introduction of a relatively bulky isobutyl group on going to catalyst **4** makes it possible to increase again the *ee* of the reaction to 64% (Table 1, entry 9). The reason for the high efficiency of catalyst **2**, in which the side group is a nonbranched chain containing a sulfur atom, is not clear. Obviously, to clarify this point, further studies are required; however, the assumption that the sulfur atom participates in the coordination of the side group to the Ti^{IV} atom seems to be a plausible hypothesis.

It can be seen from the data listed in Table 1 (entries 3—7) that a broad range of aldehydes including aliphatic (entries 6 and 7) and aromatic (entries 3—5) derivatives can be successfully involved in the trimethylsilylcyanation catalyzed by compound **2**. Asymmetric induction for this reaction lies in the 45—76% *ee* range.

We hope that subsequent modification would make it possible to increase markedly the efficiency of simple catalysts containing tetradentate ligands with the C_1 symmetry.

Table 1. Asymmetric trimethylsilylcyanation of aldehydes RCHO catalyzed by complexes **1**—**4**

Entry[a]	Catalyst[b]	R	Yield (%)	Enantiomeric purity (*ee*) (%)[c]
1	**1**	Ph	80	36
2	**2**	Ph	80	65
3	**2**	$MeOC_6H_4$	60	76
4	**2**	PhCH=CH	75	75
5	**2**	$CF_3C_6H_4$	60	68
6	**2**	$MeCH_2CH_2$	71	60
7	**2**	Me_3C	70	45
8	**3**	Ph	80	25
9	**4**	Ph	85	64

[a] All the experiments were carried out at −78 to −80 °C in CH_2Cl_2 for 120 h; the substrate—catalyst ratio was 5 : 1, the substrate—trimethylsilyl cyanide ratio was 1 : (2—3), the concentration of the substrate was 0.73 mol L^{-1}. [b] The catalytic complex was prepared *in situ* and used without additional purification. [c] The enantiomeric purities of products and their (*S*)-absolute configurations (by a comparison with standards) were determined by GLC on a chiral phase (see Experimental).

Experimental

^1H NMR spectra were recorded on a Bruker WP-200-SY instrument (using C_6D_6 as the external standard). The optical rotation of the samples was measured on a Perkin-Elmer-241 polarimeter. The enantiomeric compositions of esters of amino acids were determined by GLC of the corresponding *N*-trifluoroacetyl derivatives on a quartz capillary column (23 m×0.22 mm) using chiral phases similar to Chirasil-Val.[8] The enantiomeric compositions of the trimethylsilyl derivatives of cyanohydrins were determined by GLC using chiral derivatives of γ-cyclodextrins as stationary phases.[7] The retention times of (*S*)-esters were longer than those for esters with the (*R*)-configuration. Column chromatography was carried out using Kieselgel 60 silica gel (Merck). Dichloromethane was distilled over P_2O_5 prior to use. Trimethylsilyl cyanide (Fluka) was used as received. Aldehydes (Fluka) were distilled before the reaction. 3-*tert*-Butylsalicylaldehyde was prepared by a procedure described previously.[9]

Esters of amino acids were synthesized by a known procedure.[10]

Methyl (S)-methioninate hydrochloride, m.p. 148—150 °C, $[\alpha]_D^{20}$ +23.8° (*c* 8, 6 *N* HCl) (lit.[11]: m.p. 150 °C, $[\alpha]_D^{19}$ +26.8° (*c* 5, H_2O)).

Methyl (*S*)-norvalinate hydrochloride, m.p. 85 °C, $[\alpha]_D^{20}$ +21.8° (*c* 1, MeOH) (lit.[12]: $[\alpha]_D^{20}$ +25° (*c* 1.7, $CHCl_3$)). Found (%): C, 43.12; H, 8.58; N, 8.30. $C_6H_{14}ClNO_2$. Calculated (%): C, 42.99; H, 8.42; N, 8.36. ^1H NMR ($CDCl_3$), δ: 1.02 (t, 3 H, J = 7.2 Hz); 1.5 (m, 2 H); 1.98 (m, 2 H); 3.9 (s, 3 H); 4.1 (t, 1 H, J = 6.4 Hz); 4.8 (br.s, 3 H). Enantiomeric composition (GLC) 94.5% *ee*.

Methyl (*S*)-leucinate, m.p. 89 °C (28 Torr), $[\alpha]_D^{20}$ +12.5° (*c* 2, H_2O) (lit.[13]: b.p. 79 °C (12 Torr), $[\alpha]_D^{20}$ +13° (*c* 2, H_2O)). Enantiomeric composition 99% *ee* (GLC).

Amides of amino acids were prepared by a previously reported procedure.[14]

(*S*)-Methionine amide hydrochloride, $[\alpha]_D^{21}$ +13.8° (*c* 1, H_2O) (lit.[14]: $[\alpha]_D$ +16.3° (*c* 1, H_2O)).

(*S*)-Norvaline amide hydrochloride, m.p. 278 °C, $[\alpha]_D^{20}$ +19.2° (*c* 1, MeOH). Found (%): C, 39.53; H, 8.61; N, 18.43. $C_5H_{13}ClN_2O$. Calculated (%): C, 39.35; H, 8.59; N, 18.35. ^1H NMR (D_2O), δ: 1.0 (t, 3 H, J = 7.2 Hz); 1.5 (m, 2 H); 1.9 (m, 2 H); 4.1 (t, 1 H, J = 6.5 Hz).

(*S*)-Leucine amide, m.p. 90 °C (**hydrochloride:** m.p. 242 °C), $[\alpha]_D^{25}$ +9.6° (*c* 5, H_2O) (lit.[15] **hydrochloride**, m.p. 254 °C, $[\alpha]_D^{25}$ +10° (*c* 5, H_2O)). ^1H NMR (CD_3OD), δ: 0.91—0.96 (both d, 6 H, J = 4.5 Hz); 1.4—1.5 (m, 2 H); 1.8 (m, 1 H); 3.3 (m, 1 H); 4.7 (s, 4 H).

Preparation of diamines (general procedure). A fourfold excess of $LiAlH_4$ was suspended in anhydrous THF and a hydrochloride of an amino acid amide (0.05 mmol) was added in small portions with vigorous stirring. The mixture was stirred and refluxed for 12 h. After the appropriate workup, the precipitate of $xAl_2O_3 \cdot yH_2O$ was filtered off, the filtrate was concentrated, and the residue was distilled *in vacuo*.

(*S*)-1,2-Diamino-5-thiahexane, b.p. 100—102 °C (2 Torr) (lit.:[14] b.p. 129 °C (10 Torr)). ^1H NMR ($CDCl_3$), δ: 1.40 (m, 2 H); 1.84 (s, 4 H); 1.88 (s, 3 H); 2.35 (m, 2 H); 2.53 (m, 2 H); 3.36 (m, 1 H).

(*S*)-1,2-Diaminopentane, b.p. 55 °C (2 Torr), $[\alpha]_D^{20}$ +8.1° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 0.75 (t, 3 H); 1.45 (s, 4 H); 1.30 (m, 4 H); 2.45 (m, 1 H); 2.60 (m, 2 H). **Dipicrate,**

m.p. 220 °C. Found (%): C, 36.94; H, 3.75; N, 19.98. $C_{17}H_{20}N_8O_{14}$. Calculated (%): C, 36.44; H, 3.60; N, 20.00.

(*S*)-1,2-Diamino-4-methylpentane, b.p. 73 °C (20 Torr) (lit.:[16] b.p. 95 °C (15 Torr)), $[\alpha]_D^{20}$ +1.8° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$ + CD_3OD), δ: 0.86 (d, 6 H, J = 5.8 Hz); 1.12 (m, 2 H); 1.80 (m, 1 H); 2.25 (m, 1 H); 2.80 (m, 2 H); 3.50 (s, 4 H).

Preparation of Schiff bases from (*S*)-1,2-diamino-5-thiahexane was carried out either by a previously reported procedure[14] (for salicylaldehyde) or by analogy with this procedure (for 3-*tert*-butylsalicylaldehyde). For the rest of diamines, the following procedure was used: 3-*tert*-butylsalicylaldehyde (4 mmol) was added to a solution of diamine (4 mmol) in 10 mL of dry benzene. The mixture was refluxed with $MgSO_4$ for 9 h and concentrated, and the residue (oil) was dried *in vacuo* at 50 °C for 3 h.

(*S*)-[*N,N'*-Bis(salicylidene)]-1,2-diamino-5-thiahexane, m.p. 54—56 °C, $[\alpha]_D^{20}$ +129° (*c* 0.4, MeOH) (lit.:[14] m.p. 59 °C, $[\alpha]_D$ +144° (*c* 10^{-2} mol L^{-1}, MeOH). ^1H NMR ($CDCl_3$), δ: 1.81 (m, 5 H); 2.29 (m, 2 H); 3.52 (m, 2 H); 3.67 (m, 1 H); 6.67—7.10 (m, 8 H); 8.08 (s, 1 H); 8.16 (s, 1 H); 12.90 (br.s, 2 H).

(*S*)-[*N,N'*-Bis(2'-hydroxy-3'-*tert*-butylbenzylidene)]-1,2-diamino-5-thiahexane, $[\alpha]_D^{20}$ +131.4° (*c* 1, MeOH). Found (%): C, 71.40; H, 8.36; N, 6.21. $C_{27}H_{38}N_2O_2S$. Calculated (%): C, 71.33; H, 8.42; N, 6.16. ^1H NMR ($CDCl_3$), δ: 1.42 (s, 18 H); 2.50—2.60 (m, 2 H); 3.70 (m, 2 H); 3.47 (m, 1 H); 6.77—7.32 (m, 6 H); 8.07 (s, 1 H); 8.19 (s, 1 H); 13.79 (s, 2 H).

(*S*)-[*N,N'*-Bis(2'-hydroxy-3'-*tert*-butylbenzylidene)]-1,2-diaminopentane, $[\alpha]_D^{20}$ +195.8° (*c* 1, $CHCl_3$). Found (%): C, 77.01; H, 9.07; N, 6.11. $C_{27}H_{38}N_2O_2$. Calculated (%): C, 76.74; H, 9.06; N, 6.63. ^1H NMR ($CDCl_3$), δ: 0.97 (t, 3 H, J = 6.9 Hz); 1.43 (s, 18 H); 1.43—1.46 (m, 2 H); 1.45 (m, 2 H); 3.70 (m, 3 H); 6.50—7.50 (m, 6 H); 8.29 (s, 1 H); 8.32 (s, 1 H); 14.0 (s, 2 H).

(*S*)-[*N,N'*-Bis(2'-hydroxy-3'-*tert*-butylbenzylidene)]-1,2-diamino-4-methylpentane, $[\alpha]_D^{20}$ +284.2° (*c* 1, $CHCl_3$). Found (%): C, 77.66; H, 9.08; N, 6.09. $C_{28}H_{40}N_2O_2$. Calculated (%): C, 77.02; H, 9.23; N, 6.42. ^1H NMR ($CDCl_3$), δ: 0.87 (d, 6 H, J = 6.0 Hz); 1.40 (s, 18 H); 1.90 (m, 3 H); 3.70 (m, 2 H); 3.90 (m, 1 H); 6.60—7.50 (m, 6 H); 8.22 (s, 1 H); 8.30 (s, 1 H).

Trimethylsilylcyanation of aldehydes was carried out by a procedure reported previously.[7] The structures of the resulting trimethylsilyl ethers of cyanohydrins were confirmed by the ^1H NMR spectra; their optical purity was checked using chiral GLC by a comparison with authentic samples. The results are presented in Table 1.

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