Effects of the temperature and substituents in chiral Ti^{IV}(salen) catalysts on the enantioselectivity of the addition of Me_3SiCN to PhCHO

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The enantiomeric purity (*ee*) of the addition product of Me_3SiCN to PhCHO at ~20 °C catalyzed by chiral Ti^{IV} complexes, which were prepared *in situ* from $Ti(OPr^i)_4$ and the Schiff bases (condensation products of substituted salicylaldehydes with (1*R*,2*R*)-1,2-diaminocyclohexane), was, on the average, 20—30% lower than that achieved at −80 °C. The substituents at position 5 of 3-*tert*-butylsalicylaldehyde exert only the steric effect. It was shown that the stereochemical result of the reaction is controlled by the stage which involves the formation of the C—C bond rather than the transfer of the Me_3Si group.

Key words: asymmetric catalysis, chiral salen complexes, Ti^{IV}, trimethylsilylcyanation, aldehydes, enantioselectivity, temperature effect, effect of substituents.

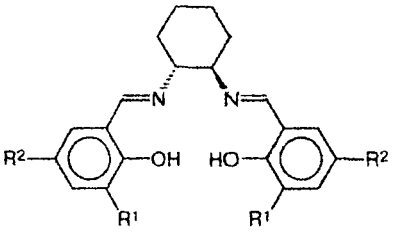
Enantiomerically pure cyanohydrins are important starting compounds in the synthesis of a broad spectrum of homochiral compounds exhibiting physiological activity.[1—4]

An efficient procedure for the asymmetric synthesis of cyanohydrins involves the addition of HCN to aldehydes catalyzed by enzymes oxynitrilases.[1,3] Since the resulting cyanohydrins are chemically unstable, they are converted into *O*-acyl- or *O*-trialkylsilyl derivatives. A two-stage chemoenzymatic procedure is used in the preparation of optically pure silyl ethers of cyanohydrins.[1]

The addition of Me_3SiCN to aldehydes catalyzed by chiral complexes is a promising procedure for the direct synthesis of optically active *O*-silyl ethers of cyanohydrins.[2] Products prepared according to this procedure contain an *O*-protective group and their optical purity can be as high as 90%.[5—10] However, virtually all the published syntheses were carried out at low temperature (at about −80 °C). Scarce data[5,6,9] indicate that the enantioselectivity of catalysis decreases substantially as the temperature increases. However, it has been reported recently that the Ti^{IV} complex with (*R*)-1,1'-bi-2-naphthol at 20 °C catalyzed the addition of Me_3SiCN to a number of aliphatic (but not aromatic) aldehydes to give products with *ee* of ~60%.[10]

Previously,[11—14] we have demonstrated that Ti^{IV} complexes formed *in situ* from $Ti(OPr^i)_4$ and enantiomerically pure tetradentate Schiff bases, *viz.*, derivatives of salicylaldehyde and diamines, efficiently catalyze the enantioselective (*ee* was up to 90%) addition of Me_3SiCN to aldehydes in the temperature range from −78 to −80 °C.

In the present work, we studied the effect of the temperature and substituents in the salicylaldehyde nucleus of ligands **1**—**6** on the enantioselectivity of the addition of Me_3SiCN to benzaldehyde catalyzed by complexes prepared *in situ* from $Ti(OPr^i)_4$ and these ligands.



	1	2	3	4	5	6
R^1	H	Bu^t	Bu^t	Bu^t	Bu^t	Bu^t
R^2	H	H	OMe	NO_2	Bu^t	CPh_3

The enantiomeric purity of product **7** was determined by GLC on a chiral stationary phase.[11]

$$PhCHO + Me_3SiCN \longrightarrow \underset{\mathbf{7}}{PhCH(CN)OSiMe_3}.$$

The data on the enantiomeric purity of product **7** at −80, −30, and +22 °C are given in Table 1.

The highest *ee* value of product **7** (>70% at 22±2 °C) is the best one on record. When Ti^{IV} complexes with

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Table 1. Enantiomeric purity of compound **7** (*ee*, %)

Ligand	Reaction conditions	
	−80 °C, 60 h	22±2 °C, 1 h
1	50	21
2	75	44
3	81	58
4	—	56
5	89	72
6	—	73

Note. In all cases, the conversion of PhCHO was quantitative according to the ^1H NMR spectra of the final products. For ligand **5** (−30 °C; the reaction time was 3 h), *ee* was 81%.

(*R*)-1,1′-bi-2-naphthol were used, the enantioselectivity of the addition of Me_3SiCN to nonanal at 22 °C was 63%,[10] while the corresponding value for aromatic aldehydes was <10%.

As can be seen from Table 1, the enantioselectivity of catalysis by Ti^{IV} complexes at −20 °C was approximately 20—30% lower than that observed at −80 °C.

The structure of the ligand affects substantially the enantioselectivity of catalysis. The introduction of the bulky Bu^t group at position 3 of salicylaldehyde (**1** → **2**) resulted in an increase in *ee* of product **7** by ~20%. The introduction of substituents at position 5 of 3-*tert*-butylsalicylaldehyde also led to an increase in the enantioselectivity of catalysis due, apparently, to a steric rather than an electronic effect (*cf.* ligands **3** and **4**).

In an analogous reaction at −80 °C catalyzed by Ti^{IV} complexes with tetradentate Schiff bases prepared from derivatives of salicylaldehyde and (1*S*,2*S*)-1,2-diphenylethylenediamine,[9] an increase in the bulkiness of the substituents resulted in a decrease in *ee* of product **7**. In addition, the substituent at position 5 of salicylaldehyde exerts a substantial electronic effect.

The reasons for the difference in the behavior of structurally similar complexes and the nature of the steric effect of the substituent at position 5 of salicylaldehyde in the catalysts under study based on ligands **1**—**6** remain unclear.

The Ti^{IV} complexes prepared *in situ* from ligand **5** and $Ti(OPr^i)_4$ also catalyzed the addition of HCN to PhCHO. The absolute configuration and the *ee* value of mandelonitrile prepared at −80 °C are identical with those obtained with the use of Me_3SiCN under the same conditions. The reaction of (±)-PhCH(OH)CN with Me_3SiCN in the presence of the catalysts under study at −80 °C afforded racemate **7**. This suggests that the formation of a C—C bond rather than the kinetic resolution of (±)-PhCH(OH)CN (which was postulated as an intermediate in the reaction of PhCHO with Me_3SiCN [5,7,10]) upon the transfer of the Me_3Si group is the stereocontrolling stage of the reaction. Therefore, the use of Ti^{IV} complexes with ligands **5** and **6** at 22 °C made it possible to enhance the enantioselectivity up to 72—73%, which opens new avenues for the asymmetric synthesis of optically active *O*-trimethylsilyl ethers of cyanohydrins at industrially acceptable temperatures.

Experimental

All operations were carried out in preliminarily dried Schlenk vessels under an Ar atmosphere. CH_2Cl_2 was distilled over CaH_2 under an inert atmosphere.

The enantiomeric purity of product **7** was determined by GLC on a chiral stationary phase.[11]

The syntheses of ligands **1**—**6** were reported in the literature: **1**,[11] **2**,[11] **3**,[16] **4**,[17] **5**,[18] and **6**.[18]

Synthesis of cyanohydrin 7 (general procedure). The catalysts were prepared *in situ* by mixing $Ti(OPr^i)_4$ and the corresponding ligands in a ratio of 1 : 1.1 in CH_2Cl_2 (generally, 6 mL of the solvent per mmole of Ti) at ~20 °C. The reaction mixture was stirred under Ar. After 1—2 h, the vessel containing the solution of the complex was placed in a thermostat and kept for 10—15 min. Then PhCHO and Me_3SiCN (the Ti : PhCHO : Me_3SiCN ratio was 1 : 5 : 11.5) were added successively with a syringe. After certain intervals, aliquots (0.2—0.3 mL) were withdrawn and applied onto a short column (standard Pasteur pipettes were used) with SiO_2. The product was eluted from the sorbent with a 5 : 1 mixture of hexane and AcOEt (10 mL). The solvents were evaporated *in vacuo* and the residue was analyzed by ^1H NMR and GLC.

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References

1. C. G. Kruse, in *Chirality in Industry*, Eds. A. N. Collins, G. N. Sheldrake, and J. Crosby, Wiley, Chichester, 1992, Ch. 14.
2. M. North, *Synlett.*, 1993, 807.
3. F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1555.
4. F. Effenberger and J. Jager, *J. Org. Chem.*, 1997, **62**, 3868.
5. M. Hayashi, Y. Miyamoto, T. Inoue, and N. Oguni, *J. Org. Chem.*, 1993, **58**, 3515.
6. A. Abiko and G. Wang, *J. Org. Chem.*, 1996, **61**, 2264.
7. Y. Jiang, L. Cong, X. Feng, W. Hu, W. Pan, Z. Li, and A. Mi, *Tetrahedron*, 1997, **53**, 14327.
8. I. Iovel, Y. Popelis, M. Fleisher, and E. Lucevics, *Tetrahedron: Asymmetry*, 1997, **8**, 1279.
9. J. Yaozhong, Z. Xiangge, H. Wenhao, L. Zhi, and M. Aiquiao, *Tetrahedron: Asymmetry*, 1995, **6**, 2915.
10. M. Mori, H. Imma, and T. Nakai, *Tetrahedron Lett.*, 1997, **38**, 6229.

11. Yu. Belokon', N. Ikonnikov, M. Moscalenko, M. North, S. Orlova, V. Tararov, and L. Yashkina, *Tetrahedron: Asymmetry*, 1996, **7**, 851.
12. Yu. Belokon', M. Flego, N. Ikonnikov, M. Moscalenko, M. North, C. Orizu, V. Tararov, and M. Tasinazzo, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1293.
13. Yu. N. Belokon', L. V. Yashkina, M. A. Moscalenko, A. A. Chesnokov, V. S. Kublitskii, N. S. Ikonnikov, S. A. Orlova, V. I. Tararov, and M. North, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 2040 [*Russ. Chem. Bull.*, 1997, **46**, 1936 (Engl. Transl.)].
14. Yu. Belokon', M. Moscalenko, N. Ikonnikov, L. Yashkina, D. Antonov, E. Vorontsov, and V. Rozenberg, *Tetrahedron: Asymmetry*, 1997 **8**, 3245.
15. V. I. Tararov, D. E. Hibbs, M. B. Hursthouse, N. S. Ikonnikov, K. M. Abdul Malik, M. North, C. Orizu, and Yu. N. Belokon', *Chem. Commun.*, 1998, 387.
16. P. J. Pospisil, D. H. Carsten, and E. N. Jacobsen, *Chem. Eur. J.*, 1996, **2**, 974.
17. M. Paluki, N. S. Finney, P. J. Pospisil, M. L. Guler, T. Ishida, and E. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 948.
18. J. E. Larrow, E. N. Jacobsen, Y. Gao, Y. Hong, X. Nie, and C. Zepp, *J. Org. Chem.*, 1994, **59**, 1939.

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