Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1979–1984

TETRAHEDRON: *ASYMMETRY*

Enantioselective trimethylsilylcyanation of aromatic aldehydes catalyzed by titanium alkoxide–chiral *o*-hydroxyarylphosphine oxides complexes

Jean-Michel Brunel, Olivier Legrand and Gérard Buono *

Ecole Nationale Supérieure de Synthèses, de Procédés et d'Ingénierie Chimiques d'Aix Marseille, UMR CNRS 6516, Faculté de St Jérôme, Av. Escadrille Normandie Niemen, 13397 Marseille, Cedex 20, France

Received 26 April 1999; accepted 10 May 1999

Abstract

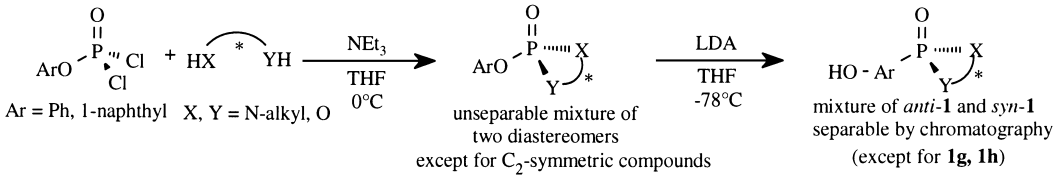
A series of new chiral titanium alkoxide–*o*-hydroxyarylphosphine oxides complexes has been used as catalysts in the asymmetric trimethylsilylcyanation of aromatic aldehydes. The corresponding cyanohydrins have been obtained in high chemical yields with good to excellent enantiomeric excesses up to 98%. The influence of the structural features of the catalysts on the enantioselectivity has been investigated.

1. Introduction

Cyanohydrins are valuable intermediates for the synthesis of various chiral compounds such as α-hydroxycarbonyl derivatives and β-aminoalcohols.[1] Although the addition of cyanide to an aldehyde or ketone is an old reaction, it has been the subject of renewed interest since Reetz's discovery that a chiral Lewis acid could be used to catalyze the asymmetric addition of trimethylsilylcyanide to isobutyraldehyde.[2] In this area, several approaches to the catalytic asymmetric synthesis of this class of compounds have been envisioned in the presence of various chiral Lewis acids. Thus, a set of catalytic systems based on Ti(IV)-tridentate Schiff's base complexes, derived from *N*-(2-hydroxy-3-*tert*-butylbenzylidene)-(*S* or *R*)-valinol (or other aminoalcohols or peptides) and Ti(O-*i*Pr)$_4$ has been elaborated[3,4] leading to the expected cyanohydrins in enantiomeric excesses (ee) up to 96%. Recently, we have reported a new general procedure for the preparation of various chiral *o*-hydroxyaryl diazaphospholidine oxides, *o*-hydroxyaryl oxazaphospholidine oxides or *o*-hydroxyaryl phosphonates.[5] This method, based on the directed metallation properties of the phosphoryl group (P-DMG), involves a stereoselective P–O to P–C rearrangement with complete retention of configuration at the phosphorus atom (Scheme 1).

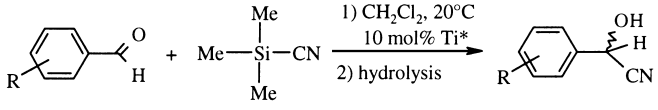
* Corresponding author. Fax: 04-91-02-77-76; e-mail: buono@spi-chim.u-3mrs.fr

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00179-2



Scheme 1.

These compounds[6] featuring a basic (P=O) and an acidic (OH) site have found application as catalysts in the asymmetric addition of diethylzinc to aromatic aldehydes[7] with enantiomeric excesses up to 95%. Due to their metal complexation properties, we envisioned the use of titanium alkoxide–chiral *o*-hydroxyarylphosphine oxide complexes in a catalytic enantioselective trimethylsilylcyanation reaction of various aromatic aldehydes (Scheme 2).



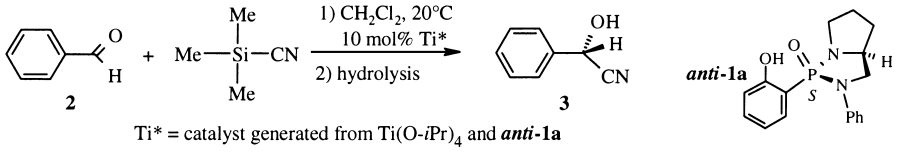
Scheme 2.

2. Results and discussion

We first examined the reaction of benzaldehyde **2** with trimethylsilylcyanide using chiral titanium complexes as catalysts prepared in situ from Ti(O-*i*Pr)$_4$ and *o*-hydroxyarylphosphine oxides **1a** (Table 1).

It clearly appears that the mode of generation of the catalyst has a dramatic influence on the outcome of the reaction in terms of enantioselectivity. Thus, the use of a catalyst prepared from Ti(O-*i*Pr)$_4$ and *anti*-**1a** in a molar ratio 1:2 or 1:4 led to the expected mandelonitrile **3** in high chemical yields but with

Table 1
Enantioselective trimethylsilylcyanation of benzaldehyde



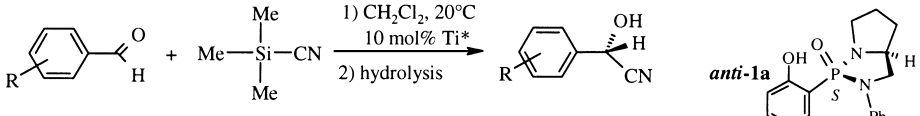
Entry[a]	Catalyst system (10 mol%)	Yield (%)[b]	ee (%)[c]
1	Ti(O-*i*Pr)$_4$ + L* (2 equiv.)	90	20 (*S*)
2	Ti(O-*i*Pr)$_4$ + L* (4 equiv.)	92	31 (*S*)
3	Ti(O-*i*Pr)$_4$ + L* (4 equiv.) - *i*PrOH	89	29 (*S*)
4	Ti(O-*i*Pr)$_4$ + L* (4 equiv.) + MS 4Å	71	15 (*S*)
5	Ti(O-*i*Pr)$_4$ + L* (4 equiv.) + *i*PrOH (1 equiv.)	95	75 (*S*)
6	**Ti(O-*i*Pr)$_4$ + L* (4 equiv.) + *i*PrOH (2 equiv.)**	**95**	**94 (*S*)**

[a] Experiment performed at 1 mmol scale. [b] Isolated yield. [c] Ee determined by ^{1}H NMR of (-)-menthyl chloroformate derivatives

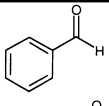
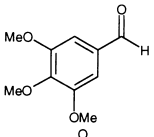
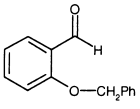
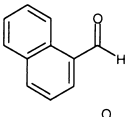
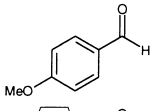
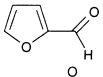
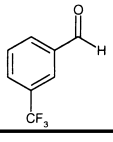
low enantiomeric excesses up to 31% (entries 1 and 2).[8] Similar results were obtained by removal of the *i*-PrOH from the reaction mixture (entry 3, 29% ee). Moreover, addition of molecular sieves (MS 4 Å) to the previously described catalytic system does not improve the enantiomeric excess of the reaction (entry 4, 71% yield and 15% ee). On the other hand, it was found that highly enantioselective reactions were initiated by addition of one or two molar equivalents of isopropyl alcohol per titanium (respectively, 75 and 94% ee, entries 5 and 6).[9]

This study has been extended to a series of aromatic aldehydes under the best previously described experimental conditions (entry 6, Table 1). The results are summarized in Table 2.

Table 2
Enantioselective trimethylsilylcyanation of aromatic aldehydes



Ti* = catalyst generated from Ti(O-*i*Pr)$_4$ and ***anti*-1a**

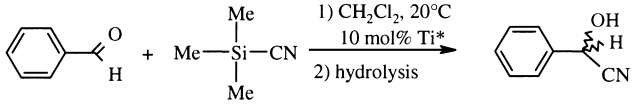
Entry[a]	Aldehyde	Yield (%)[b]	Ee (%)[b]	Configuration[c]
1		95	94	*S*
2		85	33	*S*
3		75	42	*S*
4		92	90	*S*
5		86	98	*S*
6		79	3	*S*
7		70	15	*S*

[a] Experiment performed at 1 mmol scale. [b] Isolated yield. [c] Ee determined by ^{1}H NMR of (-)-menthyl chloroformate derivatives. [c] Absolute configuration determined by comparison of reported specific rotation[4].

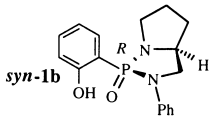
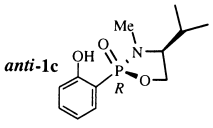
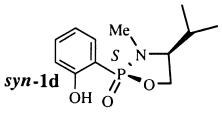
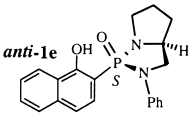
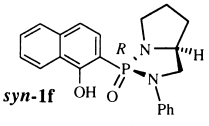
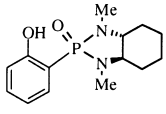
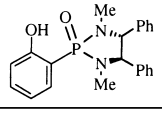
In all cases, a total conversion of the aldehydes into the corresponding cyanohydrins was obtained in yields varying from 70 to 95%. Furthermore, the (*S*)-cyanohydrin was formed as the major enantiomer whatever the substrate. On the other hand, a significant variation in enantiomeric excess was observed depending on the nature of the aldehydes; the best results being obtained with 1-naphthylaldehyde and *p*-methoxybenzaldehyde leading to 90 and 98% ee, respectively (entries 4 and 5).

On the basis of these results, compounds **1a**–**1h** have been successfully employed as ligands in the asymmetric trimethylsilylcyanation of benzaldehyde (Table 3).

Table 3
Enantioselective trimethylsilylcyanation of **2** in the presence of various *o*-hydroxyarylphosphine oxides **1a**–**1h**



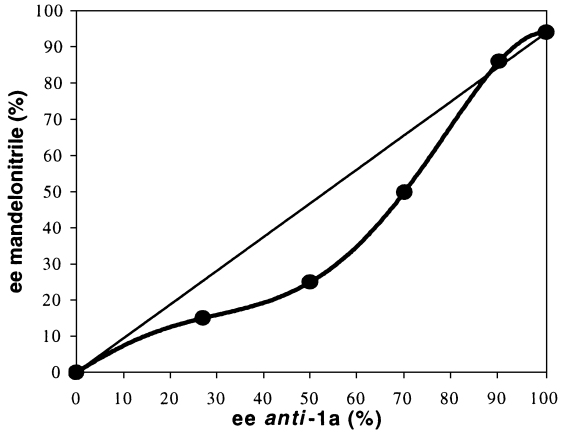
Ti* = catalyst generated from Ti(O-*i*Pr)$_4$ and **1a-1h**

Entry[a]	Ligand	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1	 *syn*-**1b**	89	98	*R*
2	 *anti*-**1c**	89	78	*S*
3	 *syn*-**1d**	85	76	*R*
4	 *anti*-**1e**	79	93	*S*
5	 *syn*-**1f**	86	92	*R*
6	 **1g**	83	52	*R*
7	 **1h**	89	47	*S*

[a] Experiment performed at 1 mmol scale. [b] Isolated yield. [c] Ee determined by ^{1}H NMR of (-)-menthyl chloroformate derivatives. [d] Absolute configuration determined by comparison of reported specific rotation[4].

In all cases, a total conversion of benzaldehyde into mandelonitrile and enantioselectivities varying from good to excellent (entries 1–7, 47 to 98% ee) were encountered. Ligands with a stereogenic phosphorus center appeared to be more efficient than ligands possessing a C_2-symmetrical unit (76–98% ee vs 47–52% ee, respectively, Table 3). It is noteworthy that depending on the configuration assigned at the phosphorus atom of the considered diastereomer used, the reaction afforded the expected cyanohydrins with *R* or *S* absolute configuration, respectively.

Nonlinear effects have often been observed in such reactions using Lewis acids as catalysts.[10] In order to test this hypothesis in our case, a series of experiments was carried out where benzaldehyde was reacted in the presence of a catalyst generated from Ti(O-*i*Pr)$_4$ and the considered ligand *anti*-**1a** of varying enantiopurity. A pronounced negative nonlinear relationship was observed and could be explained by the action of heterochiral aggregates for which dissociation occurs more easily than for the homochiral dimers (Scheme 3).



Scheme 3.

3. Conclusion

In this paper, we have clearly demonstrated that chiral *o*-hydroxyarylphosphine oxides are a new class of efficient ligands for the titanium enantioselective trimethylsilylcyanation of aromatic aldehydes. Further investigations of their catalytic ability including modifications to aldehyde and ligand design are still in progress.

4. Experimental

^{1}H NMR spectra were recorded on a Bruker AC200 spectrometer in $CDCl_3$ as solvent. The chemical shifts (ppm) were determined relative to Me_4Si. All aldehydes and Ti(O-*i*Pr)$_4$ were distilled or crystallized and stored under argon prior to use.

4.1. General procedure for catalytic asymmetric trimethylsilylcyanation of benzaldehyde

To a solution of *anti*-**1a** (170 mg, 0.54 mmol) in dichloromethane (5 mL) was added Ti(O-*i*Pr)$_4$ (37.2 μL, 0.13 mmol) at 20°C. After the mixture had been stirred for 1 h at room temperature, isopropyl alcohol (15.6 μL, 0.26 mmol) and dichloromethane (2 mL) were added and these were followed by trimethylsilylcyanide (200 μL, 1.6 mmol) and benzaldehyde (142 mg, 1.34 mmol). The mixture was stirred for 12 h at this temperature and then poured into 1 M HCl (30 mL). After extraction with ethylacetate (3×20 mL), the combined extracts were dried over Na_2SO_4, filtered and evaporated under reduced pressure. Flash chromatography on silica gel (eluent: petroleum ether:ethyl acetate, 5:1) afforded the expected mandelonitrile in 95% yield and 94% ee.

4.2. Determination of the enantiomeric excess of cyanohydrins

(1*R*,2*S*,5*R*)-(−)-Menthyl chloroformate (0.025 mL, 0.012 mmol) was added to a solution of cyanohydrin (0.057 mmol) in toluene (0.5 mL). Pyridine (0.015 mL, 0.019 mmol) was added and the reaction stirred at room temperature for 12 h. The mixture was concentrated in vacuo and analyzed by ^{1}H NMR. The diastereomeric excess was determined by ^{1}H NMR analysis of methine signals near δ 6, corresponding to the methine proton α to the cyano group of each diastereomer of the cyanohydrin menthyl carbonate.

References

1. (a) Ziegler, T.; Horsch, B.; Effenberger, F. *Synthesis* **1990**, 575. (b) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Watson, K. G. *Aust. J. Chem*. **1990**, *43*, 2045. (c) Effenberger, F.; Stelzer, U. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 873. (d) Zandbergen, P.; Brussee, J.; van der Gen, A. *Tetrahedron: Asymmetry* **1992**, *3*, 769. (e) Effenberger, F.; Eichhorn, J.; Roos, J. *Tetrahedron: Asymmetry* **1995**, *6*, 271.
2. Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett*. **1986**, *27*, 4721.
3. (a) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem*. **1993**, *58*, 1515. (b) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385. (c) Yaozhong, J.; Xiangge, Z.; Wenhao, H.; Zhi, L.; Aiqiao, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2915.
4. For significant publications dealing with asymmetric trimethylsilylcyanation reactions, see: (a) Hwang, C. D.; Hwang, D. R.; Uang, B. J. *J. Org. Chem*. **1998**, *63*, 6762. (b) Tararov, V.; Hibbs, D. E.; Hursthouse, M. B.; Ikonnikov, N.; Malik, K. M. A.; North, M.; Orizu, C.; Belokon, Y. *Chem. Commun*. **1998**, 387. (c) Jiang, Y.; Gong, L.; Feng, X.; Hu, W.; Pan, W.; Li, Z.; Mi, A. *Tetrahedron* **1998**, *53*, 14327. (d) Mori, M.; Imma, H.; Nakai, T. *Tetrahedron Lett*. **1997**, *38*, 6229. (e) Belokon, Y.; Flego, M.; Ikonnikov, N.; Moscalenko, M.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1293. (f) Choi, M. C. K.; Chan, S. S.; Matsumoto, K. *Tetrahedron Lett*. **1997**, *38*, 6669. (g) Belokon, Y.; Moscalenko, M.; Ikonnikov, N.; Yashkina, L.; Antonov, D.; Vorontsov, E.; Rosenberg, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3245. (h) Belokon, Y.; Ikonnikov, N.; Moscalenko, M.; North, M.; Orlova, S.; Tararov, V.; Yashkina, L. *Tetrahedron: Asymmetry* **1996**, *7*, 851. (i) Bolm, C.; Muller, P.; Harms, K. *Acta Chem. Scand.* **1996**, *50*, 305. (j) Qian, C.; Zhu, C.; Huang, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2131. (k) Yang, W. B.; Fang, J. M. *J. Org. Chem*. **1998**, *63*, 1356. (l) Iovel, I.; Popelis, Y.; Fleisher, M.; Lukevics, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1279. (m) Wada, M.; Takahashi, T.; Domae, T.; Fukama, T.; Miyoshi, N.; Smith, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3939. (n) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385. (o) Abiko, A.; Wang, G. Q. *J. Org. Chem*. **1996**, *61*, 2264.
5. (a) Legrand, O.; Brunel, J. M.; Constantieux, T.; Buono, G. *Chem. Eur. J*. **1998**, *4*, 1061. (b) Legrand, O.; Brunel, J. M.; Buono, G. *Eur. J. Org. Chem*. **1999**, in press.
6. These compounds may be reviewed as analogues of 1,3-diketone type ligand of various transition metals. They may form complexes with metal ions and have been used in the preparation of ligands capable of extracting ammonium compounds from aqueous to organic phases. Alberts, A. H.; Timmer, K.; Noltes, J. G.; Spek, A. L. *J. Am. Chem. Soc*. **1979**, *101*, 3375.
7. (a) Brunel, J. M.; Constantieux, T.; Legrand, O.; Buono, G. *Tetrahedron Lett*. **1998**, *39*, 2961. (b) Legrand, O.; Brunel, J. M.; Buono, G. *Tetrahedron Lett*. **1998**, *39*, 9419.
8. The use of a stoichiometric amount of titanium complexes generated from Ti(O-*i*Pr)$_4$ and *anti*-**1a** in a 1:4 molar ratio led to the formation of mandelonitrile in 91% yield and 36% ee.
9. Similar results have been previously reported by Oguni et al. using a modified Sharpless catalyst. In this case, it has been clearly demonstrated that the resulting active species are different depending on the method used for the preparation of the titanium catalyst. (a) Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3135. (b) Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc., Chem. Commun*. **1990**, 1364.
10. About nonlinear effects in asymmetric catalysis, see: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2922. (b) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc*. **1986**, *108*, 2353. (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc*. **1989**, *111*, 4028.