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Asymmetric Catalytic Cyanosilylation of Aldehydes Using a Chiral Binaphthol-Titanium Complex

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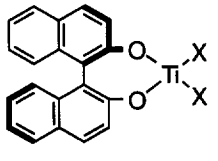
Abstract: *The asymmetric catalytic cyanosilylation of aliphatic aldehydes with Me_3SiCN using (R)-BINOL-Ti(O-i-Pr)$_2$ as an asymmetric precatalyst is shown to proceed smoothly in dichloromethane to afford the cyanohydrins in relatively high enantioselectivity (up to 75% ee).* © 1997 Elsevier Science Ltd.

Recently, much interest has been focused on asymmetric catalysis by (*R*)- or (*S*)-1,1'-bi-2-naphthol (BINOL)-derived chiral titanium complexes.[1] In an effort to develop new BINOL-derived asymmetric catalysts, we have currently been developing new asymmetric catalyses by using (*R*)-BINOL-Ti(O-*i*-Pr)$_2$ (**A**)[2] as an asymmetric *pre*catalyst that is easily accessible by simply mixing commercially available (*i*-PrO)$_4$Ti and (*R*)-BINOL. Reported so far are the asymmetric catalyses of the glyoxylate-ene reaction by complex **B** prepared via complete hydrolysis of complex **A**[3] and of the hydrosilylation of ketones by complex **C** generated *in situ* from complex **A** and $(EtO)_3SiH$.[4] In a continuation of these studies, we now wish to report the asymmetric catalytic cyanosilylation of aldehydes with trimethylsilyl cyanide (TMSCN) using complex **A** as an asymmetric *pre*catalyst, wherein the chiral dicyano complex **E** *in situ* formed, not the initially postulated monocyano complex **D**, is likely to serve as the actual asymmetric catalyst.[5]



A, X, X=O-*i*-Pr (dimer)
B, X_2=O (dimer)
C, X=H, X=O-*i*-Pr
D, X=CN, X=O-*i*-Pr
E, X, X=CN

At the outset, we studied the reaction of an aliphatic aldehyde, nonanal, with TMSCN using a stoichiometric or catalytic amount of complex **A** under various conditions (eq. 1). Table I summarizes the results thus obtained. While the use of a stoichiometric amount of complex **A** in toluene was found to provide a reasonably high % ee (78%) and chemical yield (entry 1), its catalytic use in toluene resulted in the formation of the racemic product in a much lower yield (entry 4). Interestingly, when dichloromethane was used as the solvent, the reaction proceeded catalytically at 0 ℃ to afford, after hydrolysis, the cyanohydrin in 72% ee (entry 5). Unfortunately, the reaction did not proceed catalytically at -30 ℃, while the reaction at room temperature exhibited a lower % ee (entry 6). The use of propionitrile as the solvent also resulted in a lower % ee (entry 7). Thus, the catalytic cyanosilylation is best run at 0 ℃ by using dichloromethane as the solvent.[6,7]

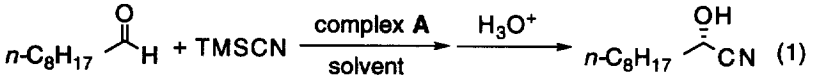


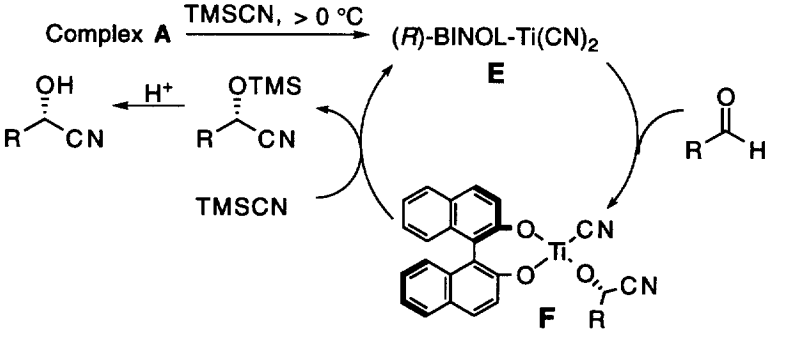
Table I. Asymmetric Cyanosilylation Using Complex **A**.

entry	A(mol%)	conditions	% yield [a]	% ee [b] (*config.*) [c]
1	100	toluene / -30 °C / 18 h	72	78 (*S*)
2	100	toluene / 0 °C / 24 h	80	32 (*S*)
3	100	CH_2Cl_2 / -30 °C / 18 h	71	64 (*S*)
4	20	toluene / r.t. / 4 d	43	0
5	20	CH_2Cl_2 / 0 °C / 18 h	92	72 (*S*)
6	20	CH_2Cl_2 / r.t. / 16 h	98	63 (*S*)
7	20	C_2H_5CN / 0 °C / 16 h	93	23 (*S*)

[a]Isolated yield. [b]Determined by ^1H NMR assay of the MTPA esters.[c]The configuration was assigned by comparison of the optical rotation with the literature value (ref 5).

The questions thus arise whether the catalytic species actually involved is the initially postulated complex **D** and why a temperature higher than 0 ℃ is required to render the reaction catalytic. To answer the questions, ^1H NMR experiments (500 MHz) were made on a mixture of complex **A** and TMSCN (12 equiv.) in CD_2Cl_2 at variable temperatures. At -30 ℃ the methine peak due to the isopropoxy group bound to Ti was still observed around δ4.3. When the temperature was raised to 0 ℃, this peak completely disappeared, while the methine peaks due to *i*-PrOH and *i*-PrOTMS liberated were intensified. This spectral change strongly suggests that at -30 ℃ the monocyano complex **D** is predominantly formed which, however, cannot act as an efficient catalyst, but as a cyanating agent in the stoichiometric reaction, whereas at 0 ℃ the dicyano complex **E** is readily formed which can serve as an efficient catalyst. Scheme I depicts a plausible catalytic cycle for the present reaction, wherein the enantio-determining step is the addition of complex **E** to the aldehyde to give complex **F** which then reacts with TMSCN to afford the cyanohydrin silyl ether with the regeneration of complex **E**. It is interesting to note that the % ee's of the product essentially were constantly independent of % conversion, indicating that the third generation complex **F** does not act as *another* asymmetric catalyst.[8] In other words, such "enantioselective autoinduction," as previously observed for the complex **C**-catalyzed hydrosilylation of ketones with $(EtO)_3SiH$,[4,9] does not occur in the present reaction.

Scheme I.



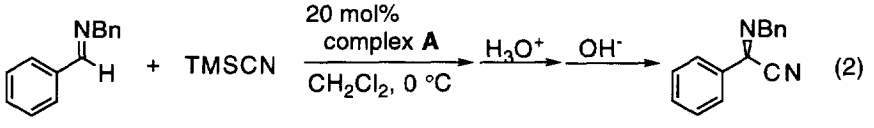
Next, the applicability of the present asymmetric catalysis to other aldehydes was studied under the optimal conditions (Table II). Of special interest is that the reactions with aliphatic aldehydes, particularly those with a long or bulky chain, provide relatively high % ee's (entries 1 and 2), whereas the reactions with aromatic aldehydes resulted in much lowered % ee's, regardless of the substituents on the phenyl group (entries 6-8). This trend is in stark contrast to the previously reported cases[5] where aromatic aldehydes generally provide higher %ee's than aliphatic aldehydes. Thus, the present catalytic method complements the existing ones.[5]

Table II. Catalytic Asymmetric Cyanosilylation of Aldehydes.[a]

entry	aldehydes	% ee[b]	entry	aldehydes	% ee[b]
1	*t*-BuCHO	75	6	PhCHO	<10
2	*n*-C_8H_{17}CHO	72	7	4-MeO-PhCHO	<10
3	*i*-PrCHO	34	8	4-Cl-PhCHO	<10
4	*c*-C_6H_{11}CHO	33			
5	EtCHO	<10			

[a]Chemical yields were >90% in every case. [b]Determined by ^{1}H NMR assay of the MTPA esters.

Finally, the present asymmetric catalysis was applied to the cyanosilylation of an imine under similar conditions. As shown in eq. 2, the reaction of the *N*-benzyl imine with TMSCN using 20 mol% of complex **A** was found to proceed catalytically to afford the α-amino nitrile in good yield but quite low % ee.



60% yield (30% ee)

$[\alpha]_D$ -21.3° (c1.00, $CHCl_3$)

In summary, we have developed a new, convenient asymmetric catalysis of the cyanosilylation of aliphatic aldehydes with TMSCN using (*R*)-BINOL and Ti(O-*i*-Pr)$_4$ as the asymmetric catalyst precursors. Further work to improve the present catalytic asymmetric process and develop more new BINOL-based asymmetric catalysts is in progress in our laboratories.

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References and Notes

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5. Reviews: North, M. *Synlett* **1993**, 807-820. For the asymmetric catalytic cyanosilylations with TMSCN using chiral Ti complexes in particular, see: (a) Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379-4383. (b) Hayashi, M.; Matsuda, T.; Oguni, N. *J. Chem. Soc. Perkin Trans. 1* **1992**, 3135-3140. (c) Hayashi, M.; Tanaka, K.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385-4398. (d) Bolm, C.; Müller, P. *Tetrahedron Lett.* **1995**, *36*, 1625-1628.
6. The following procedure is representative. A solution of (*R*)-BINOL (0.2 mmol) and (i-PrO)$_4$Ti (0.2 mmol) in CH_2Cl_2 (5 m*L*) was stirred at room temperature for 30 min. To the solution TMSCN (2.5 mmol) was added at 0 ℃. The resulting mixture was stirred for 30 min, and nonanal (1.0 mmol) was added. The resulting mixture was stirred for 17 h at that temperature, then quenched by adding 4 *N* HCl / MeOH (10 m*L*). The mixture was allowed to warm up to room temperature and stirred for 2 h, then filtrated through Celite to remove the solids formed. Usual workup followed by silica gel column chromatography afforded the cyanohydrin: $[\alpha]_D$ -2.09°(*c*1.00, CCl_4), 43% ee(*S*).
7. It should be noted that a similar use of 6, 6'-dibromo-, 3, 3'-dibromo-, 3, 3'-diphenyl-, or 3, 3'-dimethyl-BINOL in place of BINOL was found to provide a much lower % ee. These BINOL derivatives were prepared according to the literature procedures: Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253-2256.
8. The chiral complex **F**, if it acts as the catalyst, should provide a different % ee from that of complex **E**, thus the overall %ee depending, more or less, on % conversion.
9. For the concept of "enantioselective autoinduction", see: Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265-7266. For a remarkable example in the catalytic asymmetric hydrocyanation of aldehydes with HCN, see: Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740-6741.
10. Both Narasaka *et al.* (ref. 5a) and Oguni *et al.* (ref. 5b) have reported that the cyanosilylations of aromatic aldehydes give higher % ee's than those of aliphatic aldehydes.

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