Stereofacial Control in Asymmetric Cyanosilylation of Aldehydes Catalyzed by Novel *S*-Proline-Derived Titanium Complexes

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Abstract: Asymmetric cyanosilylation of aryl aldehydes has been achieved utilizing catalytic amounts of novel chiral ligands. Chiral ligands of amino alcohols and aminophosphine gave *S*-configured cyanosilylated products with up to 84% ee. In contrast, C_2-symmetric ligands resulted in *R*-configured products with up to 95% ee.

Key words: asymmetric catalysis, cyanohydrin, *S*-proline derivatives, stereoselectivity, Lewis acid/base catalysis

Optically active cyanohydrins are synthetically important intermediates as they may be elaborated to give a number of valuable intermediates, including α-hydroxyacids,[1] α-hydroxyketones,[2] primary and secondary β-hydroxy amines,[3,4] α-aminonitriles,[5] α-hydroxyesters,[6] α-sulfonyloxynitriles,[7] α-fluoronitriles,[8] 3-amino-2-trimethylsilyloxy-2-alkenoates,[9] 2,3-substituted piperidines,[10] and azacycloalkan-3-ols.[11] Thus, the asymmetric cyanosilylation of aldehydes remains an important goal in organic chemistry. Intensive studies on the enantioselective cyanation of aldehydes using chiral ligands have been reported.[12] However, there are few reports about chiral ligands derived from *S*-proline and *S*-indoline amino acids. Recently, Corey's group[13] reported that cationic oxazaborolidinium with $O=PPh_3$ as an additive gave cyanohydrins with high enantiomeric excess. Chiral oxazaborolidinium salt acted as a Lewis acid and $O=PPh_3$ acted as a Lewis base. Shibasaki's group[14] also reported bifunctional catalysis in cyanosilylation. In order to understand the mechanism of asymmetric cyanosilylation regarding the structural relationships of the chiral ligands and the activity of additives novel chiral ligands have been designed and synthesized from *S*-proline (Figure 1). Their catalytic activities in enantioselective cyanosilylation have been examined. We wish to report the results on the asymmetric cyanosilylation of aldehydes catalyzed by Ti(IV)-chiral ligand complexes.

The synthesis of **1**–**5** followed the general method – coupling of *S*-proline with chiral amino alcohols or amino phosphine. In the case of **6** and **7**, the synthetic method is described in the literature.[15,16]

Firstly, the catalytic activity of different metals was examined with **6** for the catalytic cyanosilylation of benzaldehyde at –20 °C with two equivalents of trimethylsilyl cyanide (TMSCN), in the presence of two equivalents of $O=PPh_3$. The results are summarized in Table 1. Ti(O*i*-Pr)$_4$ gave more promising enantioselectivity (87% ee) than other Lewis acids (Table 1, entry 1). Therefore, Ti(O*i*-Pr)$_4$ was employed in testing a range of ligands.

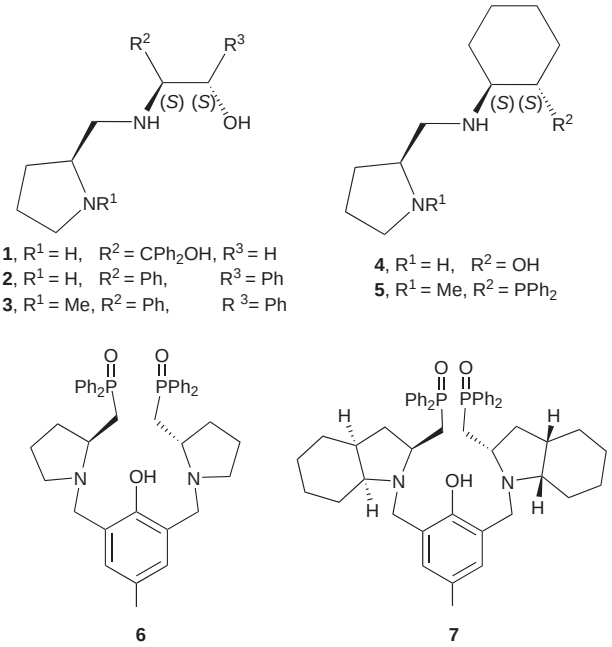

Figure 1 Chiral ligands used for asymmetric induction

Under the same reaction conditions, the asymmetric cyanosilylation was studied with ligands possessing different symmetry; **1**–**4** (amino alcohols), **5** (amino phosphine), and **6**–**7** (C_2-symmetric). The results indicated that the enantioselectivity of the reaction and configuration of the cyanohydrins were influenced by the structures and symmetry of the ligands.

In order to compare their stereoselectivity, the results are shown in Table 2. The reactions catalyzed by the Ti(IV) complex of **1**–**3** gave lower enantioselectivities (34–67% ee) than that of complex **4** and **5**, probably due to the rigidity of the cyclic ring in **4** and **5**. It is important and valuable to achieve opposite enantioselectivity in asymmetric synthesis[17] depending on structural differences of chiral ligands. The chiral ligands (**1**–**5**) gave *S*-configured cyanated products. In contrast, C_2-symmetric ligands (**6**

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Table 1 Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Lewis Acids[a]

Entry	Lewis acids	Catalyst loading (mol%)	Yield (%)[b]	ee (%)[c,d]
1	$Ti(O\textit{i}\text{-}Pr)_4$	10	75	87
2	$TiCl_4$	10	80	80
3	$AlCl_3$	10	65	70
4	$MgCl_2$	10	40	53

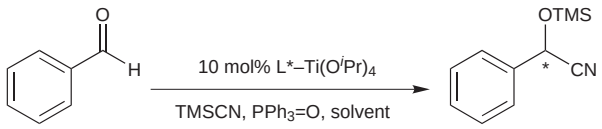
[a] Reactions were carried out with **6**/Lewis acid (1:1) at –20 °C, TMSCN (2 equiv), $O{=}PPh_3$, and CH_2Cl_2.
[b] Isolated yields of the corresponding cyanohydrin trimethylsilyl ether.
[c] Determined by HPLC on a Chiralcel OD column, after being converted to the corresponding acetate.
[d] The absolute configurations were *R* by comparison of the reported optical rotations.

and **7**) resulted in *R*-configured cyanohydrin with good to excellent enantiomeric excess. Shibasaki et al.[14] demonstrated that phosphine oxide plays an important role as a Lewis base in the cyanosilylation of aldehydes, while Corey and Ryu[13] proposed that a reactive cyanide donor intermediate, $Ph_3P(OTMS)(N{=}C{:})$, is generated from TMSCN and $Ph_3P{=}O$. The chiral ligands of amino alcohol derivatives **1**–**5** have no phosphine oxide in their structure. Thus, $Ph_3P(OTMS)(N{=}C{:})$ is initially generated during the reaction and then may attack the *re* side of the carbonyl carbon of benzaldehyde preferentially (Figure 2). In the case of **6** and **7**, phosphine oxide attached to the ligand may act as a Lewis base (Figure 3).

A study of the solvent effects showed that CH_2Cl_2 gave better enantioselectivity than toluene (Table 2, entry 6–11). Table 2 shows the results of cyanosilylation experiments with **8a** in the presence of $L^*/Ti(O\textit{i}\text{-}Pr)_4$ in CH_2Cl_2 under optimal conditions with two equivalents of $PPh_3{=}O$ to generate **8b**. Both the yield and enantioselectivity of the isolated cyanohydrin trimethylsilyl ether were good (Table 2, entry 10).

The effect of additives is shown in Table 3. When no additive was used in the reaction, enantioselectivity was very low (Table 3, entry 1). The best result was obtained with two equivalents of $O{=}PPh_3$ (Table 3, entry 5, 82%, 87% ee). In this reaction, the added $O{=}PPh_3$ acts as a ligand to titanium and the phosphine oxide attached to the 2-position of pyrrolidine may acts as a Lewis base.[14] When two equivalents of $O{=}PPh_3$ were used, the highest

Table 2 Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Different Chiral Ligands and Titanium Complexes under Various Conditions[a,18]



8a **8b**

Entry	L*	Solvent	Time (h)	Temp (°C)	Yield (%)[b]	ee (%)[c,d]
1	**1**	CH_2Cl_2	24	–20	76	34 (*S*)
2	**2**	CH_2Cl_2	24	–20	70	67 (*S*)
3	**3**	CH_2Cl_2	24	–20	68	57 (*S*)
4	**3**	CH_2Cl_2	24	–10	72	48 (*S*)
5	**4**	CH_2Cl_2	24	–20	78	80 (*S*)
6	**4**	CH_2Cl_2	36	–10	80	71 (*S*)
7	**4**	Toluene	24	–20	54	71 (*S*)
8	**5**	CH_2Cl_2	36	–20	80	84 (*S*)
9	**5**	Toluene	36	–20	65	68 (*S*)
10	**6**	CH_2Cl_2	24	–20	82	87 (*R*)
11	**6**	Toluene	24	–20	60	70 (*R*)
12	**7**	CH_2Cl_2	24	–20	74	93 (*R*)

[a] All reactions were carried out with TMSCN (2 equiv) and $O{=}PPh_3$ (2 equiv).
[b] Isolated yields of **8b**.
[c] Determined by HPLC on a Chiralcel OD column, after conversion to the corresponding acetate.
[d] The absolute configuration was determined by comparison with the reported optical rotations.

chemical yield and enantioselectivity were obtained (82% yield with 87% ee) due to the effect of the bifunctional catalytic system (Table 3, entry 5).

Table 3 Effect of Various Additives with **6**/Ti(IV) on the Enantiomeric Excess of **8b**

Entry	Additives[a]	Equivalent	Yield (%)[b]	ee (%)[c,d]
1	none		50	25 (*R*)
2	4Å M.S.	2	40	15 (*R*)
3	*i*-PrOH	2	36	19 (*R*)
4	$O=PPh_3$	1	75	60 (*R*)
5	$O=PPh_3$	2	82	87 (*R*)

[a] All additives were used with benzaldehyde (2 equiv).
[b] Isolated yields of **8b**.
[c] Determined by HPLC on a Chiralcel OD column, after conversion to the corresponding acetate.
[d] The absolute configuration was determined by comparison with the reported optical rotation.

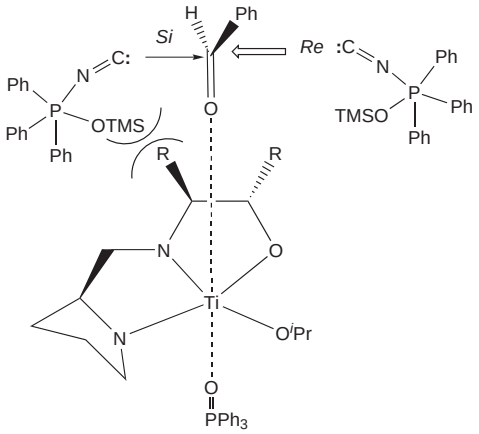


Figure 2 Possible mechanism of cyanosilylation with **1**–**5**.

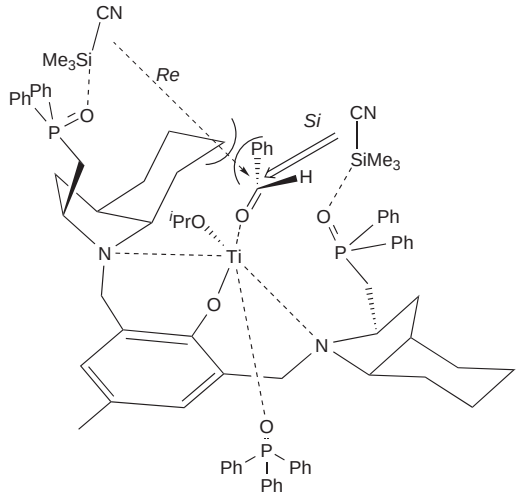
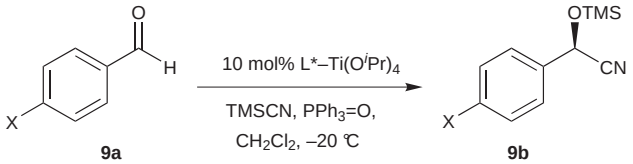


Figure 3 Possible mechanism of cyanosilylation with **6** and **7**.

Titanium may work as a Lewis acid to activate the carbonyl group, and the oxygen atom of the phosphine oxide in ligands (**6**, **7**) could act as a Lewis base to activate silylated nucleophiles in the reaction (Figure 3). In this possible mechanism, the C_2-symmetric chiral ligand **7** containing a cyclohexane ring makes *si* attack of CN more favorable, as shown in Figure 3. On the other hand, *re* attack of CN may become unfavorable due to steric repulsion between the large phenyl moiety and the cyclohexane ring.

In order to generalize the synthetic utility of this reaction, several aldehydes were tested under the optimized conditions. 4-Methyl-substituted aldehydes gave a high enantiomeric excess (91–95% ee; Table 4, entries 3–4). On the other hand, 4-cyanobenzaldehyde, substituted with a strong electron-withdrawing group (CN), gave a lower enantiomeric excess (70% ee).

Table 4 Asymmetric Cyanosilylation of Aldehydes Catalyzed by **6** and **7**/Ti(IV) Complexes[a,19]



9a **9b**

Entry	X	L*	Yield (%)[b]	ee (%)[c,d]
1	H	**6**	82	87
2	H	**7**	74	93
3	Me	**6**	79	91
4	Me	**7**	74	95
5	OMe	**6**	65	81
6	Br	**6**	63	72
7	CN	**6**	60	70

[a] All reactions were carried out with TMSCN (2 equiv) and of $O=PPh_3$ (2 equiv).
[b] Isolated yields of **9b**.
[c] Determined by HPLC on a Chiralcel OD column, after conversion to the corresponding acetate.
[d] The absolute configuration (*R*) was determined by comparison with the reported $[\alpha]_D$ value.

In conclusion, asymmetric cyanosilylation of aldehydes has been achieved using 10 mol% of the chiral ligand/Ti(O*i*-Pr)$_4$ complex and good yields of the corresponding OTMS ethers of cyanohydrins were obtained with high enantioselectivities (*R*, up to 95% ee) under mild reaction conditions. The *S*-proline ligands (**1**–**5**) gave *S* product (up to 84% ee), whereas the C_2-symmetric ligands (**6**, **7**) gave *R* product (up to 95% ee). Further investigations are planned to provide additional information with regard to the scope and the precise mechanism.

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(18) **2,6-Bis[2-(diphenylphosphinoylmethyl)octahydroindol-1-ylmethyl]-4-methylphenol(7); Typical Procedure**
2,6-Bis(bromomethyl)-4-methylphenol (292 mg, 1 mmol) was added in one portion to a stirred and cooled solution of 2-(diphenylphosphinoylmethyl)octahydroindole (879 mg, 2 mmol) and K_2CO_3 (552 mg, 4 mmol) in anhyd DMF (5 mL). The ice bath was removed after the addition and the resulting solution was allowed to stir at r.t. for 24 h before it was diluted with H_2O and Et_2O. The two phases were separated and the aqueous phase was extracted with Et_2O three times and the combined organic phases were washed H_2O, brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography through a short silica gel column (EtOAc–hexane, 1:1) to give **7** in 64% yield (520 mg, yellow foam). $[\alpha]_D^{23}$ –79.8 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42–1.60 (m, 8 H), 1. 65–1.96 (m, 4 H), 2.06 (d, 2 H), 2.08–2.34 (m, 6 H), 2.12 (s, 3 H), 2.36 (t, 2 H), 2.84–2.93 (m, 4 H), 3.28 (d, 2 H), 3.38 (d, 2 H), 3.52 (s, 2 H), 3.96 (s, 2 H), 6.75 (s, 2 H), 7.31–7.38 (m, 10 H), 7.39–7.64 (m, 10 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.36, 21.97, 31.34, 31.77, 32.92, 33.63, 52.50, 53.15, 53.54, 59.40, 60.00, 123.1, 128.6, 129.6, 129.7, 131.5, 135.0, 155.3. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 29.31 (s). MS (MALDI-TOF): *m*/*z* calcd for $C_{51}H_{60}N_2O_3P_2$, 810.4079; found, 811.0474.

(19) **Asymmetric Cyanosilylation of Aldehydes (Table 4, entry 2); Typical Procedure**
To a solution of **7** (20.2 mg, 0.025 mmol) and O=PPh_3 (139 mg, 0.5 mmol) in CH_2Cl_2 (5 mL), Ti(O*i*-Pr)$_4$ (1 M in toluene, 25 μL, 0.025 mmol) was added at r.t., and the mixture was stirred at 0 °C for 30 min under an argon atmosphere. To this solution, benzaldehyde (0.25 mol) was added after the addition of TMSCN (60 μL, 0.5 mmol) in CH_2Cl_2 (1 mL) at –20 °C. The reaction was monitored by TLC, after 24 h, the mixture was concentrated and then purified by silica gel chromatography (EtOAc–hexane, 1:4) to obtain phenyltrimethylsilanyloxyacetonitrile in 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 9 H), 5.55 (s, 1 H), 7.40–7.60 (m, 5 H). After conversion to acetate, the enantiomeric excess was determined by HPLC on a Chiralcel OD column, hexane–*i*-PrOH, 99:1 (flow rate = 1.0 mL/min), t_R (*R*) 12.92 min (major), t_R (*S*) 14.80 min (minor).