Highly Enantioselective Cyanosilylation of Aldehydes Catalyzed by Novel β-Amino Alcohol−Titanium Complexes

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The β-amino alcohol **1b**−Ti(O*i*-Pr)$_4$ complex has been shown to catalyze the enantioselective cyanosilylation of aldehydes efficiently. In the presence of 5 mol % of **1b**−Ti(O*i*-Pr)$_4$ complex catalyst, the aromatic, conjugated, heteroaromatic, and aliphatic aldehydes were converted to their corresponding trimethylsilyl ethers of cyanohydrins in 90−99% yields with up to 94% ee under mild conditions.

The synthesis of optically active cyanohydrins, a type of versatile reagent in organic synthesis and good precursors to some important insecticides and medicines, via asymmetric cyanosilylation of aldehydes catalyzed by metal complexes with chiral auxiliary ligands constitutes an area of increasing interest.[1] A number of synthetic methods have been reported employing enzymes,[2] synthetic peptides,[3] and chiral metal complexes. Of chiral metal complexes reported so far, titanium-based Lewis acids have attracted the most interest, and the chiral ligands used include sulfoximines,[4] *o*-hydroxyarylphosphine oxide,[5] BINOLs,[6] TADDOL,[7] and others.[8] Among those catalysts reported, the Ti(O*i*-Pr)$_4$−Schiff base system first reported by Oguni and co-workers received special attention.[9] Extensive studies on these systems by employing a variety of Schiff bases derived from different chiral amino alcohols or diamine compounds revealed that the enantioselective cyanosilylation of aldehydes is highly dependent on the type of Schiff base used.[10] In the meantime, chiral amino alcohol ligands have also been extensively employed in asymmetric syntheses, including the enantioselective cyanosilylation of aldehydes.[11] A family of novel β-amino alcohol ligands can be easily achieved from these Schiff bases, which have been successfully used in asymmetric Strecker reactions.[12] Due to the similar mechanistic aspects of cyanosilylation of imines and aldehydes, the asymmetric cyanosilylation of aldehydes catalyzed by chiral β-amino alcohol−Ti(O*i*-Pr)$_4$ complexes was investigated. Herein, we wish to report a full description of the synthesis of chiral β-amino alcohol ligands derived from some Schiff bases and the results obtained for the asymmetric cyanosilylation of aldehydes catalyzed by chiral β-amino alcohol−Ti(IV) complexes.

Results and Discussion

The synthetic strategy described in the literature provides a tremendous pool of various β-amino alcohols via variation of chiral amine R^1 and R^2 groups (Scheme 1).[12, 13]

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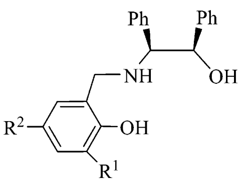
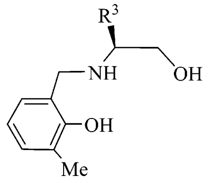
SCHEME 1. Chiral Ligands Employed for Asymmetric Induction



(1*R*, 2*S*)-**1**



(*S*)-**2**

1a:	R^1 = H	R^2 = H
1b:	R^1 = Me	R^2 = H
1c:	R^1 = *t*-Bu	R^2 = H
1d:	R^1 = H	R^2 = OMe
1e:	R^1 = H	R^2 = Cl
1f:	R^1 = H	R^2 = Br
1g:	R^1 = H	R^2 = NO_2
1h:	R^1 = *t*-Bu	R^2 = *t*-Bu
1i:	R^1 = Br	R^2 = Br
1j:	R^1= adamantanyl	R^2 = *t*-Bu

2a:	R^3 = Me
2b:	R^3 = *i*-Pr
2c:	R^3 = CH_2Ph

With these new *β*-amino alcohol ligands in hand, we took the first trial that complexes of different metals with **1b** were used to catalyze the cyanosilylation of benzaldehyde at −20 °C with 2 equiv of trimethylsilyl cyanide (TMSCN) with respect to benzaldehyde as the model reaction. The results are summarized in Table 1. Ti(O-*i*Pr)$_4$ gave more promising enantioselectivity than other Lewis acids (Table 1, entry 4). Ti(O-*i*Pr)$_4$ was thus chosen to assess the following ligands.

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

entry	Lewis acid	catalyst loading (mol %)	time (h)	yield[b] (%)	ee[c] (%)	absolute configuration
1	$AlEt_3$	10	42	65	11	*R*
2	$AlEt_2Cl$	10	42	44	19	*R*
3	Al(O*i*-Pr)$_3$	10	42	99	10	*R*
4	Ti(O*i*-Pr)$_4$	10	23	94	85	*S*

[a] Reaction was carried out with **1b**−Lewis acid (1:1) at −20 °C, concentration of benzaldehyde = 0.2 M in CH_2Cl_2. [b] Isolated yield of the corresponding cyanohydrin trimethylsilyl ether. [c] Determined by HPLC on a Chiralcel OD column, after being converted to the corresponding acetate. The absolute configuration was *S* by comparison of the reported optical rotation.

Under the same conditions, we examined the steric effect and the electronic effect based on the different structures of ligand **1** and other amino alcohol ligands **2** derived from different chiral resources (Table 2). The results indicated that the enantioselectivity was influenced by the structures of the ligands. The reaction catalyzed by the titanium(IV) complex of **1b** (R^1 = Me, R^2 = H) gave higher enantioselectivity (85% ee) (entry 2, Table 2). More or less bulky substituents all led to less enantioselectivity (entries 1−3, Table 2). Bulky R^1, such as *tert*-butyl or adamantanyl, is highly detrimental for both the enantioselectivity and the reactivity (entry 2 vs entries 3 and 10, Table 2), which is caused by the baffling interaction between R^1 and the O-*i*Pr group in the transition state (Figure 1). Then, the study of the electronic effects of substituents on ligands (**1d**−**g**) showed that neither electron-donating nor electron-withdrawing groups on the para position of the OH group could increase the enantiomeric excess (entries 4−7, Table 2). So there was no surprise that the ligands (**1h**−**j**) gave the worse results concerning both the yield and enantioselectivity (entries 8−10, Table 2). Ligands **2a**−**c** with only one stereocenter exhibited an inferior ability of chiral induction compared to **1b** with two stereocenters in this catalytic system (entries 11−13 vs entry 2, Table 2). Therefore, the correct assembly of the substituents and backbone of (1*R*,2*S*)-1,2-diphenylaminoethanol in the ligands is a key point for high reactivity and enantioselectivity of the asymmetric cyanosilylation of aldehydes.

The study of metal complexes of **1b** showed that **1b**−Ti(O*i*-Pr)$_4$ was the best catalyst for the cyanosilylation of benzaldehyde, which gave 85% ee in 10 mol % of catalyst in CH_2Cl_2. When 1.0 equiv of **1b** was used per titanium, the highest enantioselectivity was obtained. We were pleased to find that the **1b**−Ti(O*i*-Pr)$_4$ (ratio of 1:1) complex was quite effective for the enantioselectivity and reactivity of cyanosilylation of benzaldehyde. The conditions of the asymmetric cyanosilylation of benzaldehyde in the presence of **1b**−Ti(O*i*-Pr)$_4$ complexes were optimized (entries 14−21, Table 2). A preliminary solvent study showed that the best result was obtained in CH_2Cl_2 (entry 2, Table 2). Although the similar enantioselectivity also could be found in THF, the yield was

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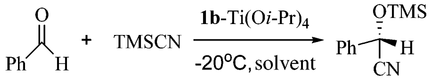
TABLE 2. Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by Different Amino Alcohol Ligands and Titanium Complexes under Various Conditions[a]



4a **5a**

entry	ligand	solvent	concn of benzaldehyde (mol/L)	tem. (°C)	yield of **5a**[b] (%)	ee of **5a**[c] (%)	absolute configuration
1	**1a**	CH_2Cl_2	0.2	−20	99	76	*S*
2	**1b**	CH_2Cl_2	0.2	−20	94	85	*S*
3	**1c**	CH_2Cl_2	0.2	−20	23	3	*R*
4	**1d**	CH_2Cl_2	0.2	−20	88	69	*S*
5	**1e**	CH_2Cl_2	0.2	−20	26	68	*S*
6	**1f**	CH_2Cl_2	0.2	−20	47	61	*S*
7	**1g**	CH_2Cl_2	0.2	−20	62	66	*S*
8	**1h**	CH_2Cl_2	0.2	−20	28	4	*R*
9	**1i**	CH_2Cl_2	0.2	−20	N.D.[d]		
10	**1j**	CH_2Cl_2	0.2	−20	N.D.[d]		
11	**2a**	CH_2Cl_2	0.2	−20	98	12	*S*
12	**2b**	CH_2Cl_2	0.2	−20	99	10	*R*
13	**2c**	CH_2Cl_2	0.2	−20	96	6	*R*
14	**1b**	$CHCl_3$	0.2	−20	95	72	*S*
15	**1b**	Et_2O	0.2	−20	76	77	*S*
16	**1b**	THF	0.2	−20	28	83	*S*
17	**1b**	toluene	0.2	−20	83	64	*S*
18	**1b**	CH_2Cl_2	0.5	−20	99	92	*S*
19	**1b**	CH_2Cl_2	1.0	−20	99	81	*S*
20	**1b**	CH_2Cl_2	0.5	0	98	90	*S*
21	**1b**	CH_2Cl_2	0.5	−40	64	87	*S*

[a] Reaction was carried out with 10 mol % ligand (**1** or **2**)−Ti(O*i*-Pr)$_4$ (1:1). [b] Isolated yield of the corresponding cyanohydrin trimethylsilyl ether. [c] Determined by HPLC on a Chiralcel OD column, after conversion to the corresponding acetate. [d] N.D. = not detected.

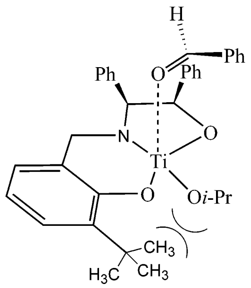
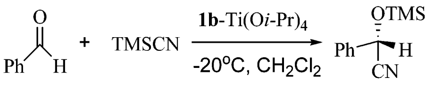


FIGURE 1. Effect of R^1 and O*i*-Pr group in the transition state.

obviously inferior to that in CH_2Cl_2 (entry 16 vs entry 2, Table 2). Further studies indicated that the concentration of benzaldehyde had an important effect on the enantioselectivity. When the concentration of benzaldehyde was 0.5 M, the enantioselectivity increased to 92% ee (entry 18, Table 2). Further increasing the concentration to 1.0 M led to a lower ee value (entry 19, Table 2). The temperature effect was also obvious. Higher or lower temperature than −20 °C disadvantaged this reaction (entries 18, 20, and 21, Table 2).

To obtain the optimal reaction conditions, the effect of the amount of catalyst on the enantioselectivity and yield of cyanosilylation of benzaldehyde was studied. The catalyst loading also dramatically influenced the enantioselectivity and yield. When the amount of catalyst was 5 mol % and the concentration of benzaldehyde was 0.5 M, the optimal enantioselectivity (94% ee) and yield (98%) were obtained (entry 3, Table 3). Extensive screening showed the optimized catalytic system as 5 mol % of **1b**−Ti(*Oi*-Pr)$_4$, 0.5 M aldehydes, and 2 equiv of TMSCN, at −20 °C.

TABLE 3. Effect of Varying the Amount of Catalyst 1b/Ti(IV) on the Enantiomeric Excess of 5a[a]



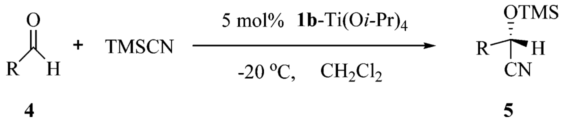
4a **5a**

entry	catalyst loading (mol %)	time (h)	yield of **5a**[b] (%)	ee of **5a**[c] (%)
1	20	20	94	88
2	10	22	99	92
3	5	20	98	94
4	1	44	33	80

[a] Reaction was carried out with **1b**−Ti(Oi-Pr)$_4$ (1:1) in CH_2Cl_2 at −20 °C; concentration of benzaldehyde = 0.2 M. [b] Isolated yield of the corresponding cyanohydrin trimethylsilyl ether. [c] Determined by HPLC on a Chiralcel OD column, after conversion to the corresponding acetate. The absolute configuration was *S* by comparison of the reported optical rotation.

Encouraged by the result obtained for the benzaldehyde, in the presence of 5 mol % of **1b**-Ti(O*i*-Pr)$_4$ complex, the asymmetric cyanosilylation of aromatic, conjugated, heteroaromatic, and aliphatic aldehydes proceeded smoothly as well under the optimized reaction conditions to provide corresponding O-TMS ethers of cyanohydrins in high yields with moderate to excellent enantioselectivities (Table 4). Aldehydes with substituents on the aromatic ring gave similar ee values with benzaldehyde (entries 1−9, Table 4). However, 2-chlorobenzaldehyde only gave 76% ee, probably because of the steric hindrance of the chlorine atom on the ortho position (entry 7, Table 4). Besides, 4-cyanobenzaldehyde

TABLE 4. Asymmetric Cyanosilylation of Aldehydes Catalyzed by the 1b/Ti(IV) Complex[a]



entry	aldehydes	time (h)	yield[b] (%)	ee[c] (%)
1	benzaldehyde (**4a**)	22	99	94
2	4-methylbenzaldehyde (**4b**)	15	90	93[d]
3	3-methylbenzaldehyde (**4c**)	16	99	88[d]
4	4-methoxybenzaldehyde (**4d**)	14	98	93
5	3-methoxybenzaldehyde (**4e**)	16	99	90[d]
6	4-fluorobenzaldehyde (**4f**)	14	94	92[d]
7	2-chlorobenzaldehyde (**4g**)	15	99	76[d]
8	3-chlorobenzaldehyde (**4h**)	20	98	90[d]
9	4-chlorobenzaldehyde (**4i**)	15	98	87[d]
10	4-cyanobenzaldehyde (**4j**)	20	93	80
11	1-naphthaldehyde (**4k**)	16	99	82
12	2-naphthaldehyde (**4*l***)	20	98	75
13	2-furaldehyde (**4m**)	16	98	89[d]
14	(*E*)-cinnamaldehyde (**4n**)	14	96	82[d]
15	(*E*)-crotonaldehyde (**4o**)	16	99	82[d]
16	*n*-hexaldehyde (**4p**)	16	99	57[d]
17	2-phenylacetaldehyde (**4q**)	14	98	72[d]
18	2-methylpropionaldehyde (**4r**)	16	99	60[d]

[a] All reactions were carried out with 5 mol % of **1b**−Ti(Oi-Pr)$_4$ (1:1), 2 equiv of TMSCN, at 0.5 M in CH$_2$Cl$_2$ at −20 °C. [b] Isolated yield of the corresponding cyanohydrin trimethylsilyl ether. [c] Determined by HPLC on a Chiralcel OD column, after conversion to the corresponding acetate. The absolute configuration was *S* by comparison of the reported optical rotation. [d] Determined by GC analysis on Chirasil DEX CB.

with a strong electron-withdrawing substituent (CN) also gave a lower ee value (80%) than benzaldehyde (entry 10, Table 4). This is in agreement with Oguni's report.[9] 1-Naphthaldehyde afforded a higher ee value than 2-naphthaldehyde (entries 11 and 12, Table 4). The reaction of a heteroaromatic aldehyde such as 2-furaldehyde took place in high yield with 89% ee (entry 13, Table 4). α,*β*-Unsaturated aldehydes gave the same enantioselectivity (entries 14 and 15, Table 4). Aliphatic aldehydes can give moderate enantioselectivities from 57% to 72% ee (entries 16−18, Table 3).

As to the reaction pathway, because of the similar structure of **1b** and the Schiff base that Oguni reported, we consider that **1b** was still a tridentate ligand coordinated with Ti(O*i*-Pr)$_4$. The only difference is that the C=N double bond of the ligand was converted to the C−N single bond. Therefore, this transformation makes the molecule of **1b** more flexible. On the basis of the observed absolute configuration of the O-TMS ethers of cyanohydrins and Oguni's transition-state model,[9a] we proposed a possible asymmetric induction pathway, which is shown in Figure 2. We suggested that the difference in the chiral induction effects comes from the formation of the N−Ti bond, and there remains only one isopropoxy on titanium instead of two. In this transition state, the *Re* face of the carbonyl of benzaldehyde is much more accessible to a nucleophile than the *Si* face since the latter is strongly shielded by the nearby phenyl subunit (Model A, Figure 2). On the other hand, benzaldehyde could not bond Ti(IV) by the other aspect of C=O, which is caused by the large steric hindrance between two phenyl subunits (Model B, Figure 2). The nucleophile of CN will attack the highly polarized C=O of benzaldehyde at the carbon atom from a less stereohindered direction (*Re*) to give the product in the (*S*)-configuration.

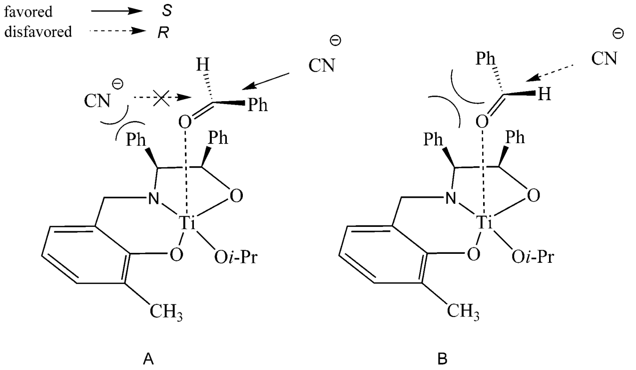


FIGURE 2. Proposed working model for asymmetric cyanosilylation of benzaldehyde.

In conclusion, the asymmetric cyanosilylation of aldehydes has been achieved by the catalysis of 5 mol % of chiral *β*-amino alcohol−Ti(O*i*-Pr)$_4$ complex giving corresponding O-TMS ethers of cyanohydrins in high yields (up to 99%) with moderate to excellent enantioselectivities (up to 94% ee) under the mild reaction conditions. The results described show that it is feasible for the **1b**−Ti(O*i*-Pr)$_4$ complex to efficiently catalyze the cyanosilylation of aldehydes with high ee. Further efforts should be directed to provide a basis for optimization of the chiral *β*-amino alcohol structure to enhance both the enantioselectivity and the catalytic ability.

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Supporting Information Available: Experimental procedure for the asymmetric cyanosilylation of aldehydes, and the characterization of ligands and products, including ^{1}H and ^{13}C NMR, HRMS data, HPLC and GC conditions, etc. This material is available free of charge via the Internet at http://pubs.acs.org.

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