Pergamon

Tetrahedron 57 (2001) 805–814

TETRAHEDRON

Highly enantioselective cyanosilylation of aldehydes catalyzed by a Lewis acid–Lewis base bifunctional catalyst

Yoshitaka Hamashima, Daisuke Sawada, Hiroyuki Nogami, Motomu Kanai and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received 12 May 2000; accepted 7 August 2000

Abstract—A new bifunctional asymmetric catalyst containing a Lewis acid and a Lewis base (**1**) was developed and applied to the catalytic asymmetric cyanosilylation of aldehydes. The products were obtained generally with excellent enantiomeric excess. The experiments using the control catalyst (**5**) and the catalyst containing more electron-rich phosphine oxide (**6**) suggest that the catalyst **1** should promote the reaction via a dual activation of the aldehyde by the aluminum and TMSCN by the phosphine oxide. This reaction is practical and was applied to the catalytic asymmetric total synthesis of epothilone A.

1. Introduction

It is well-established that the addition of TMSCN to aldehydes is catalyzed by Lewis acids[1] as well as Lewis bases,[2] to afford trimethylsilylated cyanohydrins. Cyanohydrins are highly versatile synthetic intermediates, which can easily be converted to various important building blocks including α-hydroxy carbonyl derivatives and β-amino alcohols. In view of their importance, there is currently considerable focus in developing methods for the asymmetric synthesis of cyanohydrins, especially using chiral catalysts.[3,4] Although impressive enantiomeric excesses have been obtained in some cases, it is highly desired to develop a more general asymmetric catalyst, applicable to a wide variety of aldehydes. During the course of our study to develop an asymmetric catalyst from the concept of multifunctional catalysis,[5] we have reported Lewis acid–Brønsted base bifunctional asymmetric catalysts, which have been applied to a wide range of reactions.[6] Inspired by the concept, we expected that a Lewis acid–Lewis base bifunctional catalyst should simultaneously activate TMSCN and an aldehyde at defined positions in the catalyst, thus providing a more general asymmetric catalyst for the cyanosilylation reaction of aldehydes. We report herein that catalyst **1** is a highly efficient catalyst for the cyanosilylation of aldehydes with broad generality, affording products in excellent chemical yields and excellent enantioselectivities.[7]

1.1. Design and synthesis of Lewis acid–Lewis base bifunctional catalyst

We selected BINOL as a scaffold for arranging the Lewis acid and Lewis base moieties as shown in Fig. 1. When the Lewis acid metal is connected to the two naphthols, it was anticipated that the Lewis base moieties should be connected to 3,3′-position of BINOL to promote the reaction efficiently via a dual activation pathway. The following two points should be important for constructing a successful bifunctional catalyst: (1) The activation ability of the Lewis acid and Lewis base moieties toward an aldehyde and TMSCN should be balanced to promote the reaction via a dual activation pathway. (2) The internal coordination of the Lewis base to the metal should be avoided. The design shown in Fig. 1 should be very flexible to optimize these points by changing the metal, the Lewis base and the linker length connecting the Lewis base and BINOL. The phosphine oxide ligand **1-L**, which finally turned out to be the best ligand, was synthesized in high yield from MOM-BINOL **7** as shown in Scheme 1.

1.2. Optimization of the catalyst

The combination of the Lewis acid metal (Al, Ga, Ti or Zr)

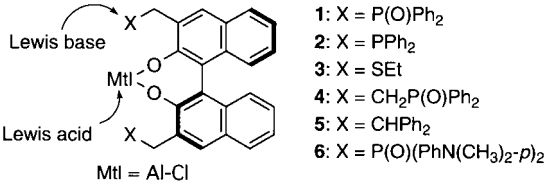
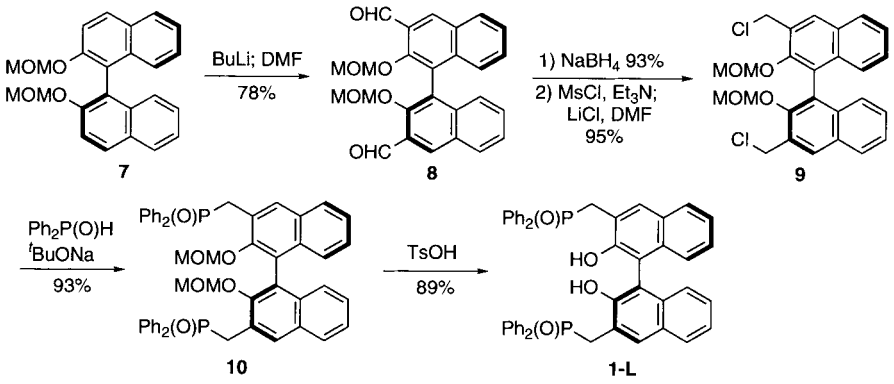


Figure 1. Design of Lewis acid–Lewis base catalysts.

Keywords: Lewis acid; Lewis base; asymmetric catalyst; cyanosilylation; epothilones.

* Corresponding author. Tel.: +81-3-5684-0651; fax: +81-3-5684-5206; e-mail: mshibasa@mol.f.u-tokyo.ac.jp

0040–4020/01/$ - see front matter
PII: S0040-4020(00)01039-5



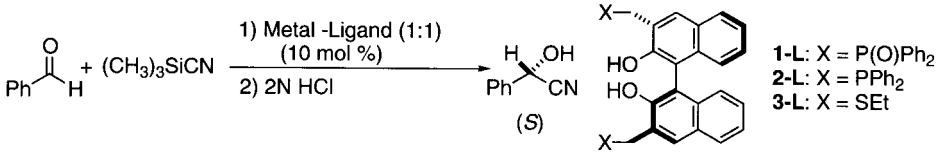
Scheme 1. Synthesis of **1-L**.

and the Lewis base (phosphorus, sulfur or phosphine oxide oxygen) was first optimized by the reaction of TMSCN with benzaldehyde, changing these two moieties independently (Table 1). It was found that the combination of aluminum chloride as a Lewis acid and a phosphine oxide as a Lewis base afforded the best catalyst in terms of reactivity as well as enantioselectivity and the product was obtained with 87% ee and 91% yield at −40°C for 37 h (entry 1). It is also important to note that ligands **2-L** and **3-L** were partially silylated during the reaction. This indicates that the chiral catalysts derived from **2-L** and **3-L** were partially decomposed under the reaction conditions, thus giving lower reactivity and lower enantioselectivity. On the other hand, no silylation of the ligand **1-L** was observed under any combination with Lewis acid metals.

To confirm the activation ability of a phosphine oxide toward TMSCN, we performed the reaction of hydrocinnamaldehyde with TMSCN in the presence or absence of $Bu_3P(O)$, without the Al catalyst **1**. Thus, in the presence of 40 mol% of $Bu_3P(O)$, the product was obtained in 81% yield at ambient temperature for 7.5 h. In the absence of the phosphine oxide, the yield was only 12% under the same conditions. At −40°C for 40 h, however, the reaction did not proceed at all even in the presence of $Bu_3P(O)$. These results appear to suggest that the internal phosphine oxide of **1** would activate TMSCN as a Lewis base if the phosphine oxide is at the defined position close to the activated aldehyde. This situation should be important to promote the reaction via a dual activation by a Lewis acid and a Lewis base.

Next, we investigated the effect of the relative position of the Lewis acid (Al) and the Lewis base (the oxygen atom of the phosphine oxide) by changing the linker length between the phosphine oxide and the scaffolding BINOL (**1** vs **4**). Molecular modeling studies suggested that the coordination of the Lewis base to the internal aluminum seemed to be torsionally unfavorable in the case of **1**. When considering **4**, however, which has an ethylene linker, the internal coordination seemed to be quite stable without strain. Therefore, in the case of the catalyst **4**, strong intramolecular coordination of the phosphine oxide should reduce the Lewis acidity of the aluminum, therefore diminishing the catalytic efficiency of **4**. In accordance with this expectation, the reaction of TMSCN with benzaldehyde, catalyzed by **4** (9 mol%), proceeded slowly at −40°C (37 h) and gave the cyanohydrin in only 4% yield after hydrolysis. This result stands in contrast to the much higher reactivity of the catalyst **1** (91% yield under the same conditions, Table 1, entry 1). Therefore, in the case of **1**, the intramolecular binding of the phosphine oxide to the aluminum seems to be labile enough to allow the coordination of the aldehyde to the aluminum. Consequently, we investigated the best catalyst

Table 1. Optimization of the combination of the Lewis acid and the Lewis base



Entry	Metal	Ligand	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ee (%)	Conf.
1	Me_2AlCl	**1-L**	CH_2Cl_2	−40	37	91	87	*S*
2	Me_3Al	**1-L**	Toluene	0	36	97	33	*S*
3	$Ga(O^iPr)_3$	**1-L**	CH_2Cl_2	0	60	100	0	–
4	$Ti(O^iPr)_4$	**1-L**	CH_2Cl_2	rt	46	trace	–	–
5	$Zr(O^iPr)_4$	**1-L**	CH_2Cl_2	−20	46	100	3	*S*
6	Et_2AlCl	**2-L**	CH_2Cl_2	−40	71	27	5	*S*
7	Me_3Al	**2-L**	CH_2Cl_2	0	36	92	2	*S*
8	$Ti(O^iPr)_4$	**2-L**	Toluene	−40	192	75	29	*S*
9	Et_2AlCl	**3-L**	CH_2Cl_2	−20	110	27	24	*R*
10	Me_3Al	**3-L**	Toluene	−40	60	trace	–	–
11	$Ti(O^iPr)_4$	**3-L**	Toluene	−40	60	trace	–	–
12	$Zr(O^iPr)_4$	**3-L**	CH_2Cl_2	−20	216	80	3	*R*

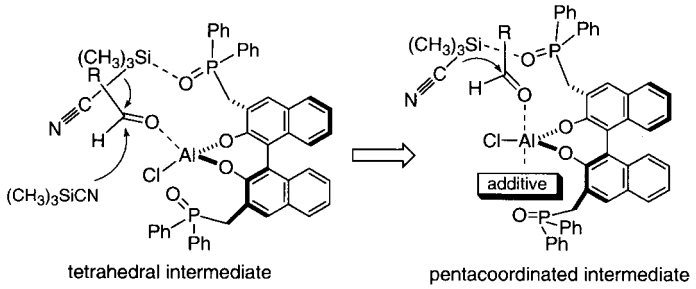


Figure 2. Assumption for the improvement of the enantioselectivity by an additive.

1, in which the aluminum acts as a Lewis acid and the oxygen atom of the phosphine oxide acts as a Lewis base with the methylene linker to connect the Lewis base and the scaffolding BINOL.

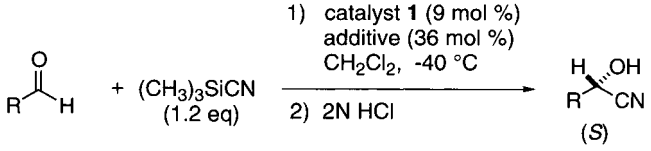
A preliminary evidence of the bifunctional catalysis by **1** was obtained by the control experiment using catalyst **5**, which contains only a steric bulkiness (diphenylmethyl group), but not a Lewis base, at the 3,3′-position of BINOL. Thus, **5** (9 mol%) gave the cyanohydrin **12h** of benzaldehyde **11h** in 50% yield and with 12% ee (−40°C, 37 h). The absolute configuration of **12h** was the opposite (*R*) to that obtained by **1**. The reversal of the absolute configuration of the products (**12a** and **12c**) was generally observed, using either **1** or **5**. In the case of **5**, it would be reasonable to assume that TMSCN attacks the activated aldehyde, coordinating to the aluminum, from the less hindered side (the opposite to the diphenylmethyl group). Then, in the case of **1**, TMSCN appears to attack the aldehyde from the side of the phosphine oxide. This can be explained if we assume TMSCN, which is activated by the phosphine oxide would react with the aldehyde.

1.3. Catalytic asymmetric cyanosilylation of various aldehydes

Encouraged by the result of benzaldehyde using catalyst **1**, we next investigated the reaction of aliphatic aldehydes. Surprisingly, aliphatic aldehydes afforded very low ee's: hydrocinnamaldehyde **11a** gave *S*-**12a** in 90% yield and in 9% ee; isobutylaldehyde **11c** gave *S*-**12c** in 80% yield and in 25% ee. We anticipated that there would be a competition between two reaction pathways in the case of the more reactive aliphatic aldehydes. The desired pathway involves the dual interaction between the Lewis acid and the aldehyde and between the Lewis base and TMSCN, whereas the undesired pathway involves mono-activation by the Lewis acid. We assumed that these two pathways could differ more significantly if the Lewis acidity of the catalyst would be decreased, and so we investigated the effect of additives which coordinate to the aluminum to reduce its Lewis acidity. Moreover, the additive could change the geometry of the aluminum from tetrahedral to trigonal bipyramidal,[8] which should allow the phosphine oxide to get into a more favorable position relative to the aldehyde (Fig. 2).

After several attempts, we found that electron donating phosphine oxides had a beneficial effect on the ee. In the case of hydrocinnamaldehyde **11a**, the ee values of **12a** significantly increased from 9% to 41% and 56% by the addition of 36 mol% of $CH_3P(O)Ph_2$ and $Bu_3P(O)$ respectively. Further improvement of ee (up to 97%) was achieved by the slow addition of TMSCN (10 h), via syringe pump, in the presence of $Bu_3P(O)$ (Table 2, entry 6). In the case of benzaldehyde **11h**, however, addition of $Bu_3P(O)$ resulted in

Table 2. Additive effect



Entry	R	Aldehyde	Product	Additive	Time (h)	Yield (%)	Ee (%)
1	$PhCH_2CH_2$	**11a**	**12a**	none	20	90	9
2	$PhCH_2CH_2$	**11a**	**12a**	$Ph_3P(O)$	36	98	2
3	$PhCH_2CH_2$	**11a**	**12a**	$CH_3P(O)(OCH_3)_2$	62	88	27
4	$PhCH_2CH_2$	**11a**	**12a**	$Ph_2P(O)CH_3$	36	78	41
5	$PhCH_2CH_2$	**11a**	**12a**	$Bu_3P(O)$	36	60	56
6[a]	$PhCH_2CH_2$	**11a**	**12a**	$Bu_3P(O)$	37	97	97
7	$PhCH_2CH_2$	**11a**	**12a**	$(octyl)_3P(O)$	36	67	40
8	$(CH_3)_2CH$	**11c**	**12c**	none	36	80	25
9	$(CH_3)_2CH$	**11c**	**12c**	$Bu_3P(O)$	36	58	72
10[a]	$(CH_3)_2CH$	**11c**	**12c**	$Bu_3P(O)$	45	96	90
11	Ph	**11h**	**12h**	none	36	91	87
12	Ph	**11h**	**12h**	$Ph_2P(O)CH_3$	96	98	96
13	Ph	**11h**	**12h**	$Bu_3P(O)$	200	trace	–

[a] TMSCN was added dropwise over 10 h.

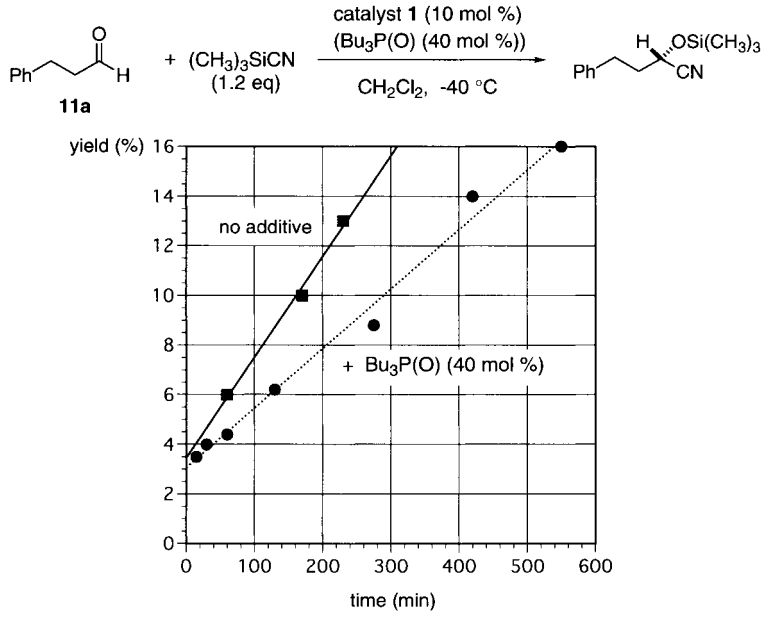


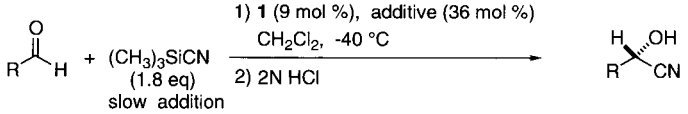
Figure 3. Initial reaction rate in the absence (■) and presence (●) of the additive.

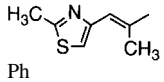
a very sluggish reaction, affording only a trace amount of the product. However, the reaction proceeded in 98% yield and in 96% ee in the presence of $CH_3P(O)Ph_2$ (entry 12). Therefore, we used $Bu_3P(O)$ as the additive for aliphatic and α,β-unsaturated aldehydes, and $CH_3P(O)Ph_2$ as the additive for aromatic aldehydes.

To confirm the origin of the beneficial effect of the additive phosphine oxide, we measured the initial kinetics of the reaction of hydrocinnamaldehyde **11a** in the absence or presence of the additive $Bu_3P(O)$. The result is shown in Fig. 3. The initial reaction rate in the presence of $Bu_3P(O)$ was 0.6 times slower than in the absence of $Bu_3P(O)$. This result can be explained from the lower Lewis acidity of the pentacoordinated aluminum in the presence of the additive phosphine oxide. Thus, the additive phosphine oxide should finely tune the balance of the Lewis acidity and the Lewis basicity of the bifunctional catalyst, as well as tuning the relative position of the activated aldehyde and TMSCN in the transition state. Since the reaction pathway involving the activation by the external phosphine oxide is negligible at −40°C, only the internal phosphine oxide can function as an activator of TMSCN as mentioned above, because the phosphine oxide exists at the appropriate position close to TMSCN in the reactive complex.

This catalyst is practical and has a broad generality with respect to the variety of aldehydes that can be used (Table

Table 3. Catalytic asymmetric cyanosilylation of various aldehydes under the optimized conditions



Entry	R	Aldehyde	Product	Additive	Time (h)	Yield (%)	Ee (%)[a]	*S/R*
1	$Ph(CH_2)_2$	**11a**	**12a**	$Bu_3P(O)$	37	97	97	*S*
2	$CH_3(CH_2)_5$	**11b**	**12b**	$Bu_3P(O)$	58	100	98	*S*
3	$(CH_3)_2CH$	**11c**	**12c**	$Bu_3P(O)$	45	96	90	*S*
4	$(CH_3CH_2)_2CH$	**11d**	**12d**	$Bu_3P(O)$	60	98	83	*S*
5	*trans*-$CH_3(CH_2)_3CH{=}CH_2$	**11e**	12e	$Bu_3P(O)$	58	94	97	–[e]
6	PhCH=CH	**11f**	**12f**	$Bu_3P(O)$	40	99	98	*S*
7[b]		**11g**	**12g**	$Bu_3P(O)$	50	97	99	*S*
8[c]	Ph	**11h**	**12h**	$CH_3P(O)Ph_2$	96	98	96	*S*
9	*p*-$CH_3C_6H_4$	**11i**	**12i**	$CH_3P(O)Ph_2$	79	87	90	*S*
10[d]		**11j**	**12j**	$CH_3P(O)Ph_2$	70	86	95	*S*

[a] Determined by HPLC after the appropriate conversion. The absolute configuration was assigned by comparison with optical rotation reported in literature.
[b] 5 mol% of **1** was used.
[c] TMSCN was added over 1 min.
[d] 18 mol% of **1** and 72 mol% of additive were used.
[e] The absolute configuration has not been determined yet.

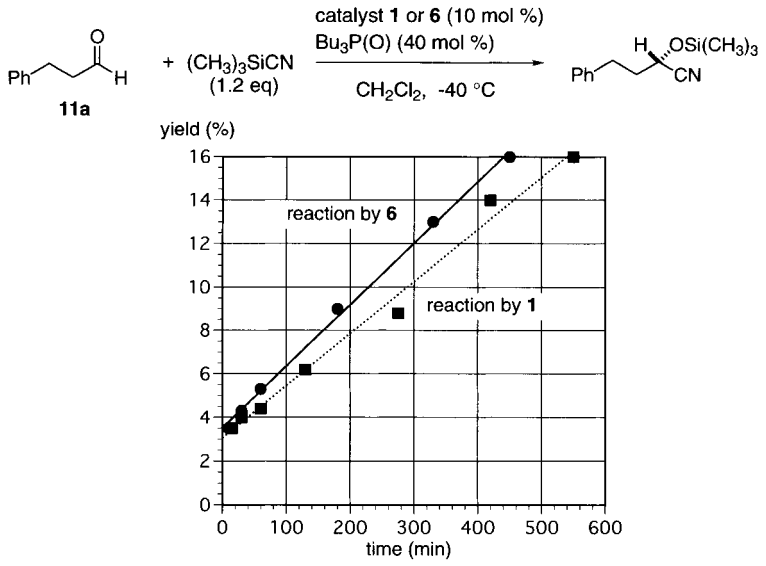


Figure 4. Initial reaction rate using **1** (■) and **6** (●).

3). Specifically, the aldehyde **11g** was converted to the cyanohydrin **12g**, which is a key intermediate for the asymmetric synthesis of the antineoplastic natural product epothilones.[9]

1.4. Preliminary mechanistic studies

To elucidate the origin of the excellent enantioselectivity with wide generality, as a bifunctional catalysis of **1**, we planned kinetic studies comparing the initial reaction rate using **1** and **6**, containing the more electron-rich phosphine oxide. The initial reaction rate using **6** (10 mol%) was 1.2 times faster than using **1** (10 mol%) (k_6/k_1=1.2) (Fig. 4), reflecting the higher Lewis basicity of the phosphine oxide in the reaction of hydrocinnamaldehyde **11a** in the presence of $Bu_3P(O)$ (40 mol%). Furthermore, by the one-portion addition of TMSCN, catalyst **6** (10 mol%) gave *S*-**12a** in 86% yield and in 68% ee in the presence of $Bu_3P(O)$ (40 mol%) (−40°C for 36 h), whereas **1** gave *S*-**12a** in 60% yield and in 56% ee under the same conditions.[10] The increased reaction rate and enantioselectivity by **6** is consistent with the dual activation mechanism of these catalysts. More electron-rich phosphine oxide should activate TMSCN more efficiently, thus facilitating the desired dual activation pathway.

From these mechanistic studies, the enantioselctivity of the reaction catalyzed by **1** may be explained by the working model depicted as **14** in Fig. 5, with the external phosphine oxide coordinating to the aluminum, thus giving a

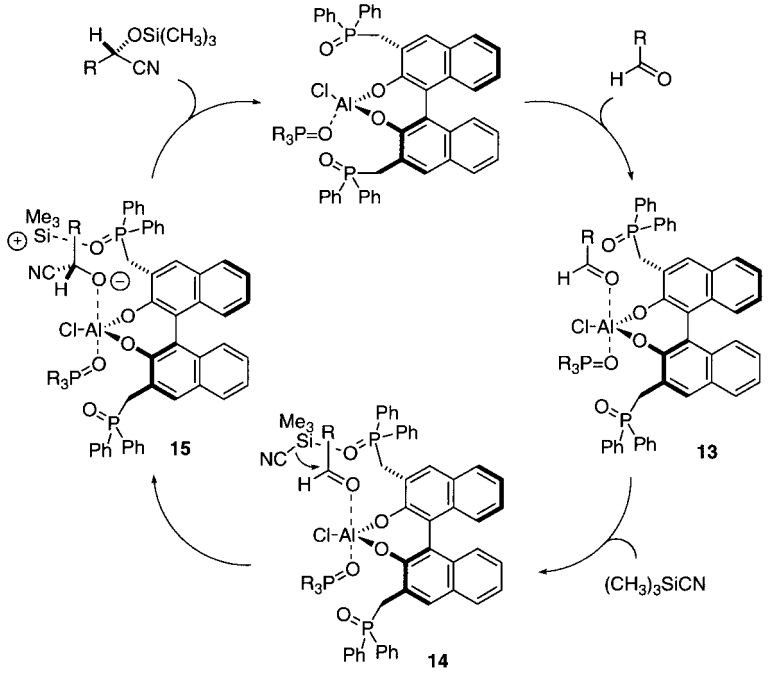


Figure 5. Proposed catalytic cycle.

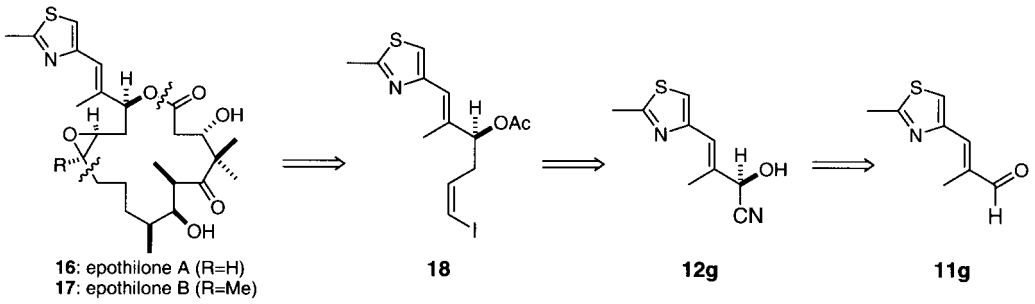


Figure 6. Retrosynthetic analysis of epothilones.

pentavalent aluminum. This geometry would allow the aldehyde to position itself at the apical site close to the internal phosphine oxide. TMSCN, interacting with the internal phosphine oxide, could then transfer cyanide to the aldehyde thus giving the observed *S*-product.[11]

1.5. Application to the catalytic asymmetric total synthesis of epothilone A

Epothilones (A: **16**, B: **17**) show a potent antitumor activity by binding and stabilizing the microtubles in the same way as taxol, and they are promising drug candidates. Recently, highly efficient total syntheses of epothilones were disclosed by Danishefsky, Nicolaou, Schinzer and Shibasaki *et al*.[12] Our retrosynthesis is shown in Fig. 6. The catalytic asymmetric cyanosilylation was utilized for the synthesis of fragment **18**. Fine tuning of the standard reaction conditions was necessary to apply this reaction to a large scale reaction using the aldehyde **11g**. Taking the high functionality of **11g** into account, the cyanosilylation of **11g** (70 mg) was initially performed using 20 mol% of the (*S*)-**1**, 80 mol% of $Bu_3P(O)$ and 3 equiv. of TMSCN. Then, the product **12g** was obtained (42 h at −40°C, including 10 h slow addition of TMSCN) in 95% yield and with 99% ee after hydrolysis with trifluoroacetic acid. However, when 300 mg of **11g** was used, the reaction became much slower and **12g** was obtained in lower yield of 83% (98% ee) after 86 h. Interestingly, when the amount of TMSCN was reduced to 1.8 equiv. from 3 equiv., the reaction proceeded smoothly again to afford **12g** in 97% yield with 99% ee (51 h). It appeared that keeping the concentration of TMSCN low enough was important in the case of aldehyde **11g**. This situation is special for the aldehyde **11g** (Fig. 6) containing a thiazole moiety. We anticipate that the excess TMSCN would be activated by the coordination of the thiazole to Si, causing deactivation of the catalyst **1** by exchange of the aluminum chloride to aluminum cyanide.[13] Gratifyingly, it was found that the amount of the catalyst **1** could be reduced to 5 mol% using 20 mol% of $Bu_3P(O)$ and slowly adding 1.2 equiv. of TMSCN for 48 h to give **12g** in 97% yield with 99% ee (50 h including the slow addition time). A catalytic asymmetric total synthesis of epothilone A using the cyanosilylation as a key step was achieved[9] and details will be reported as a full paper elsewhere.

2. Conclusion

A new bifunctional asymmetric catalyst containing a Lewis acid and a Lewis base (**1**) was designed and applied to the catalytic asymmetric cyanosilylation of aldehydes. The products were obtained generally with excellent enantiomeric excesses. This reaction is the most general catalytic asymmetric cyanosilylation of aldehydes reported to date. The absolute configuration of the products as well as experiments using the control catalyst (**5**) and the catalyst containing more electron-rich phosphine oxide (**6**) suggest that the catalyst **1** should promote the reaction via a dual activation of aldehyde by the aluminum and TMSCN by the phosphine oxide. This reaction is practical and was applied to the catalytic asymmetric total synthesis of epothilone A.

3. Experimental

3.1. General

NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, at 500 MHz for ^1H NMR, 125.65 MHz for ^{13}C NMR, and 202 MHz for ^{31}P NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (=0) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (77.00 ppm for ^{13}C NMR) as an internal reference. ^{31}P NMR were carried out with phosphinic acid (85%) as an external standard. Optical rotations were measured on a JASCO P-1010 polarimeter. Column chromatography were performed with silica gel Merck 60 (230–400 mesh ASTM). The enantiomeric exess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 nm; column, DAICEL CHIRALPAK AS, AD, or DAICEL CHIRALCEL OJ, OD; mobile phase, hexane-2-propanol; flow rate, 0.5–1.0 mL/min. In general, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Diethylaluminium chloride in hexane (1 M) was purchased from KANTO CHEMICAL. CO., INC., 2–8, Nihonbashi, Honcho 3-chome, Chuo-ku, Tokyo, 103-0023, Japan (fax: +813-3667-6892). Other reagents were purified by usual methods.

3.2. Synthesis of (*R*)-3,3′-bis(diphenylphosphinoylmethyl)-1,1′-binaphthol (1-L)

3.2.1. (*R*)-3,3′-Diformyl-2,2′-bis(methoxymethy)-1,1′-binaphthol (8). To a stirred solution of MOM-protected (*R*)-binaphthol **7** (10 g, 26.7 mmol) in Et_2O (400 mL) was

added *n*-BuLi (53.1 mL, 85.5 mmol, 1.61 M in hexane) at room temperature. The mixture was stirred for 2 h at the same temperature. After cooling down to 0°C, DMF (7.24 mL, 93.5 mmol) was dropped over 15 min. The mixture was then warmed up to room temperature and stirred for further 2 h. Sat. aq NH_4Cl was added to the reaction. After neutralization, the reaction mixture was extracted with ethyl acetate several times. The combined organic layer was washed with water and brine, and then dried over Na_2SO_4. Flash column chromatography (hexane/ethyl acetate=10:1 to 5:1) was performed carefully after the concentration to give **8** (9.0 g, 78%) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.55 (s, 2H), 8.62 (s, 2H), 8.08 (dd, *J*=8.2, 1.2 Hz, 2H), 7.52 (ddd, *J*=9.2, 7.05, 1.20 Hz, 2H), 7.43 (ddd, *J*=8.2, 7.05, 1.50 Hz, 2H), 7.22 (dd, *J*=9.2, 1.50 Hz, 2H), 4.71 (d, *J*=6.1 Hz, 2H), 4.69 (d, *J*=6.1 Hz, 2H), 2.88 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 190.6, 154.0, 136.7, 132.3, 130.3, 129.6, 128.9, 126.3, 126.1, 125.9, 100.6, 57.0.

3.2.2. (*R*)-3,3′-Bis(hydroxymethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthol. $NaBH_4$ (700 mg, 18.6 mmol) was added to a solution of dialdehyde **8** (4.0 g, 9.29 mmol) in methanol (140 mL) at 0°C. After 30 min, sat. aq NH_4Cl was added and the reaction mixture was halfway concentrated. The residue was diluted with ethyl acetate (50 mL), and the organic layer was washed with water. The water layer was extracted with ethyl acetate (60 mL×4) and combined organic layer was washed with brine (50 mL×1). The further purification was performed by flash chromatography on silica gel (hexane/acetone=3:1) to afford the diol in 92.6% as a white solid; IR (KBr) ν 3387, 2936, 1622, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 2H), 7.91(m, 2H), 7.43 (ddd, *J*= 8.25, 6.7, 0.9 Hz, 2H), 7.27(ddd, *J*=8.25, 7.0, 1.5 Hz, 2H), 7.15 (m, 2H), 4.98 (d, *J*=12.8 Hz, 2H), 4.85 (d, *J*=12.8 Hz, 2H), 4.48 (d, *J*=6.1 Hz, 2H), 4.45 (d, *J*=6.1 Hz, 2H), 3.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 153.1, 134.6, 133.7, 130.9, 129.7, 128.2, 126.8, 125.7, 125.4, 125.2, 99.3, 61.9, 57.1;MS *m/z* 434 (M^+); Anal. Calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 71.51; H, 6.20.

3.2.3. (*R*)-3,3′-Bis(chloromethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthol (9). A toluene (60 mL) solution of bis(hydroxymethyl)binaphthol (3.64 g, 8.38 mmol) was cooled down to 0°C. To this solution, MsCl (3.24 mL, 41.9 mmol) and Et_3N (8.17 mL, 58.6 mmol) were added successively. After 1 h, the reaction mixture was treated with LiCl (1.78 g, 41.9 mmol) and DMF (60 mL) and stirred at room temperature until the starting material disappeared. The mixture was washed with water (20 mL×2). The separated aqueous layer was extracted with ethyl acetate (80 mL×3). The combined organic layer was washed with brine (80 mL), and then dried over Na_2SO_4. Solvent was evaporated under reduced pressure, and the residue was chromatographed (hexane/acetone=4:1) to give **9** (3.76 g, 95%): IR (neat) ν 1622, 1597, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 2H), 7.90 (d, *J*=8.25 Hz, 2H), 7.43 (m, 2H), 7.28 (m, 2H), 7.17 (d, *J*=8.5 Hz, 2H), 4.99 (d, *J*=11.9 Hz, 2H), 4.94 (d, *J*= 11.9 Hz, 2H), 4.63, (dd, *J*=5.5, 0.6 Hz, 2H), 4.52 (dd, *J*= 5.5, 0.6 Hz, 2H), 2.97 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.2, 134.2, 131.2, 130.9, 130.6, 128.1, 127.2, 126.0, 125.5, 99.5, 56.9, 42.3; MS *m/z* 470 (M^+), 472 (M^++2), 474 (M^++4); Anal. Calcd for $C_{26}H_{24}O_4$: C, 66.25; H,5.13. Found: C, 65.98; H, 5.28.

3.2.4. (*R*)-3,3′-Bis(diphenylphosphinoylmethyl)-2,2′-bis(methoxymethyl)-1,1′binaphthol (10). To a solution of diphenylphosphine oxide (2.93 g, 13.3 mmol) in THF (40 mL) was added NaO^{t}Bu (1.4 g, 15 mmol) in THF (20 mL) at 0°C. After stirring for 30 min at room temperature, the clear solution changed to a white suspension. To this suspension, **9** (2.5 g, 5.3 mmol) in THF (30 mL) was added at −40°C and the reaction mixture was gradually warmed up to room temperature. After the completion of reaction, sat. aq NH_4Cl was added, and the reaction mixture was concentrated to the half, followed by dilution with ethyl acetate (80 mL). The organic layer was washed with water (50 mL×2). Separated aqueous layer was carefully extracted with ethyl acetate (50 mL×3). The combined organic layer was washed with brine (50 mL×2). After the removal of the solvent, further purification was carried out by flash chromatography (CH_2Cl_2: MeOH=30: 1) to give **10** (3.95 g, 93%): ^{1}H NMR δ 8.30 (d, *J*=2.45 Hz, 2H), 7.92–7.76 (m, 10H), 7.52–7.41 (m, 12H), 7.35 (m, 2H), 7.15 (m, 2H), 6.85 (d, *J*=8.55 Hz, 2H), 4.21 (d, *J*=6.5 Hz, 2H), 4.20 (d, *J*=6.5 Hz, 2H), 4.15 (dd, *J*=13.5, 13.5 Hz, 2H), 4.01 (dd, *J*=13.5, 13.5, 2H), 2.84 (s, 6H).

3.2.5. (*R*)-3,3′-Bis(diphenylphosphinoyl)-1,1′-binaphthol (1-L). 10 (3.8 g, 4.73 mmol) was dissolved in the mixture of methanol/CH_2Cl_2 (40 mL/40 mL). A catalytic amount of TsOH (monohydrate) was added and stirred at 40°C over night. Most of the solvent was removed and the residue was diluted with ethyl acetate. The solvent was washed with water (30 mL×2) and the aqueous layer was extracted with ethyl acetate (80 mL×3). The combined organic layer was washed with brine and dried over Na_2SO_4. The crude product was further purified by recrystallization (CH_2Cl_2–Et_2O) to give **1-L** (3.0 g, 89%): IR (KBr) ν 3433, 1437, 1160, 746, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.80–7.67 (m, 12H), 7.53–7.41 (m, 12H), 7.24 (m, 2H), 7.14 (t, *J*= 7.65 Hz, 2H), 6.88 (d, *J*=8.55 Hz, 2H), 4.06 (dd, *J*=14.4, 14.4 Hz, 2H), 3.92 (dd, *J*=14.4, 14.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 151.4, 151.3, 133.2, 132.1 (d, *J*=3.13 Hz), 132.1 (d, *J*=2.13 Hz), 131.9, 131.7, 131.5, 131.4, 131.1 (d, *J*=7.13 Hz), 131.0 (d, *J*=7.13 Hz), 130.9, 129.0 (d, *J*= 2.0 Hz), 128.7 (d, *J*=3.13 Hz), 128.6 (d, *J*=2.0 Hz), 127.7, 126.4, 124.8, 123.6, 121.6, 121.5, 117.1, 34.0 (d, *J*= 66.8 Hz); ^{31}P NMR ($CDCl_3$) δ 37.94; MS *m/z* 714 (M^+). ^{31}P NMR spectrum is concentration-dependent; $[\alpha]^{23}_D$= +131.5° (*c*=1.0, CH_3OH); Anal. Calcd for $C_{46}H_{36}O_4P_2{\cdot}0.67H_2O$: C, 76.02; H, 5.27. Found: C, 76.02; H, 5.10.

3.2.6. (*R*)-3,3′-Bis(bis(*p*-*N*,*N*-dimethylaminophenyl)phosphinoylmethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthol. To a solution of bis(*N*,*N*-dimethylaminophenyl)phosphine oxide (1.84 g, 6.36 mmol) in THF (120 mL) was added NaO^{t}Bu (0.96 g, 7.14 mmol) in THF (15 mL) at 0°C. This solution was allowed to stir for 30 min at room temperature. Again, the reaction mixture was cooled down to 0°C, and **9** (1.2 g, 2.55 mmol) in THF (4 mL) was added at the same temperature, followed by stirring at ambient temperature until the reaction completed. To this reaction mixture, sat. aq NH_4Cl was added to quench. Keeping the mixture pH 8–9 with sat. aq $NaHCO_3$, the same work-up procedure in the case of **10** was performed. Further purification was carried out by flash chromatography (CH_2Cl_2/MeOH=40:1∼20:1) to give

the product (1.34 g, 52.4%) as the white powder: ^{1}H NMR ($CDCl_3$) δ 8.3 (s, 2H), 7.8 (d, J=8.25 Hz, 2H), 7.68 (dd, J=8.85, 10.7 Hz, 4H), 7.57 (dd, J=8.85, 10.7 Hz, 4H), 7.31 (dt, J=0.95, 6.73 Hz, 2H), 7.10 (t, J=7.35 Hz, 2H), 6.92 (d, J=8.55 Hz, 2H), 6.70 (dd, J=2.1, 8.85 Hz, 4H), 6.64 (dd, J=2.1, 8.85 Hz, 4H), 4.25 (d, J=11 Hz, 2H), 4.23 (d, J=11 Hz, 2H), 4.01 (t, J=15 Hz, 2H), 3.89 (t, J=15 Hz, 2H), 2.96 (s, 24H), 2.78(s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.5 (d, J=15 Hz), 152 (d, J=9.3 Hz), 152 (d, J= 9.3 Hz), 133, 132.4 (d, J=10 Hz), 132.2 (d, J=10 Hz), 131.3, 131.2, 130.6, 130.6, 128, 127 (d, J=6.3 Hz), 126 (d, J=4.1 Hz), 125.3, 124.7, 111.3 (d, J=10 Hz), 111.2 (d, J=11 Hz), 40, 40, 31.5 (d, J=68 Hz); ^{31}P NMR ($CDCl_3$) δ 35.2 ppm.

3.2.7. (*R*)-3,3′-Bis(bis(*p*-*N*,*N*-dimethylaminophenyl)phosphinoylmethyl)-1,1′-binaphthol (6-L). The MOM protected **6-L** (1.34 g, 1.38 mmol) was dissolved in the mixture of methanol/CH_2Cl_2 (12 mL/12 mL). A catalytic amount of TsOH (monohydrate) was added and the mixture was stirred at 40°C over night. Most of the solvent was removed and the residue was diluted with ethyl acetate (10 mL). The solvent was washed with sat. aq $NaHCO_3$ (10 mL×2) and the aqueous layer was extracted with ethyl acetate (10 mL×3). The combined organic layer was washed with brine and dried over Na_2SO_4. The crude product was further purified by recrystallization to give **6-L** (0.8 g, 66%): IR (KBr) ν 3518, 1597, 1517, 1364, 1117 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.9 (s, 2H), 7.59 (d, J=7.9 Hz, 2H), 7.54 (d, J=2.2 Hz, 2H), 7.50 (dd, J=8.8, 8.8 Hz, 2H), 7.48 (dd, J=8.6, 8.6 Hz, 2H), 7.13 (dt, J=0.9, 6.7 Hz, 2H), 7.05 (t, J=7.7 Hz, 2H), 6.93 (d, J=8.3 Hz, 2H), 6.6 (d, J=8.9 Hz, 8H), 3.91 (dd, J=14.7, 14.7 Hz, 2H), 3.70 (dd, J=14.4, 14.4 Hz, 2H), 2.90 (s, 12H), 2.9 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 152.3, 152.0, 152.0, 111.3, 111.2, 133.4, 132.5, 132.4, 130.9, 130.9, 128.3, 127.5, 125.7, 125.0, 123.3, 123.2, 122.9, 118.2, 39.9, 35.8 (d, J=66.9 Hz); ^{31}P NMR ($CDCl_3$) δ 39.8; $[\alpha]^{21.1}_D$=−99.1° (c=1.87, CH_2Cl_2).

3.3. General procedure for the preparation of the catalyst

Into a flame dried flask, an achiral phosphine oxide (15 mg, 68.8 μmol) was added and dried at 65°C for 2 h under the reduced pressure. 0.1 mL of dichloromethane was added, followed by the addition of diethylaluminium chloride (18 μL, 17.28 μmol, 0.96 M in hexane) under argon atmosphere. After stirring for 10 min, the chiral ligand (13 mg, 18.2 μmol) in dichloromethane (0.35 mL) was added at room temperature. The resulting mixture was stirred at the same temperature for 1 h to give a clear solution. This solution can be used directly as the catalyst in catalytic asymmetric trimethysilylcyanation reactions.

3.4. General procedure for the catalytic asymmetric trimethylsilylcyanation reactions of aldehydes

To a stirred solution of the catalyst (0.45 mL, 17.28 mmol, 0.0384 M) was added an aldehyde (0.192 mmol) at −40°C. After 30 min, TMSCN (46 μL, 0.346 mmol) was slowly added over 10 h using a syringe pump. (Be careful! TMSCN should be added dropwise from the top of the flask, where the temperature may be above 15°C. Because the melting point of TMSCN is 11–12°C.) The reaction mixture was allowed to stir for the time shown in Table 1 at the same temperature. 2N HCl (1.0 mL) was added, and the mixture was stirred vigorously at room temperature for 1 h to hydrolyze the trimethylsilylether of the product. After the addition of ethyl acetate (3.0 mL), the mixture was stirred for further 30 min. The organic layer was separated and washed with water. The aqueous layer was extracted with ethyl acetate (20 mL×2). The combined organic layer was washed with brine and dried over Na_2SO_4. The crude product was further purified by flash chromatography (hexane/ethyl acetate=10:1) to give a cyanohydrin (**12a**–**12j**) in more than 86%. The enantiomeric excesses of the products were determined after the conversion to acetylester, benzoylester, *p*-nitrobenzoylester, ethylcarbonate, and *t*-butyldimethylsilylether by usual methods.

3.4.1. (2*S*)-2-Hydroxy-4-phenylbutanenitrile (12a). This product was found to be identical with the reported compound by analytical data: $[\alpha]^{24}_D$=+6.6° (c=0.68, $CHCl_3$) (97% ee) [lit.[14] $[\alpha]^{24}_D$=−2.6° (c=2.7, $CHCl_3$) for *R* enantiomer in 40% ee]. The enantiomeric excess was determined by HPLC after the conversion to TBDMS–ether: IR (neat) ν 3086, 3064, 3028, 1255, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32–7.29 (m, 2H), 7.24–7.18 (m, 3H), 4.42 (t, J=6.4 Hz, 1H), 2.81 (m, 2H), 2.12 (m, 2H), 0.90 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 140.0, 128.7, 128.4, 126.4, 119.9, 61.2, 37.9, 25.6, 18.1, −0.51, −5.32; MS m/z 218 ($M^+-{}^t$Bu); Anal. Calcd for $C_{16}H_{25}ONSi$: C, 69.76; H,9.15; N, 5.08. Found: C, 69.66; H, 8.98; N, 5.04; HPLC (DAICEL CHIRALCEL OD, hexane/2-propanol 99/1, 1.0 mL/min) t_R 8.4 min and 10.7 min.

3.4.2. (2*S*)-2-Hydroxy-*n*-octanenitrile (12b). ^{1}H NMR ($CDCl_3$) 4.48 (t, J=6.7 Hz, 1H), 2.31 (bs, 1H), 1.88–1.83 (m, 2H), 1.54–1.47 (m, 2H), 1.39–1.26 (m, 6H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) 119.5, 61.5, 35.3, 31.5, 28.6, 24.4, 22.5, 14.0; $[\alpha]^{21}_D$=−13.3° (c=1.0, $CHCl_3$) (98% ee) [lit.[15] $[\alpha]^{26}_D$=+9.1° (c=2.82, $CHCl_3$) for *R* enantiomer in 66% ee]. The enantiomeric excess was determined by HPLC after the conversion to benzoylester: IR (neat) ν 1913, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.06 (m, 2H), 7.63 (m, 1H), 7.48 (m, 2H), 5.59 (t, J=6.7 Hz, 1H), 2.05 (m, 2H), 1.62–1.54 (m, 2H), 1.43–1.30 (m, 6H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 164.8, 134.0, 130.0, 128.7, 128.4, 117.0, 61.7, 32.5, 31.5, 28.5, 24.6, 22.5, 14.0; $[\alpha]^{16.3}_D$=−53.4° (c=0.48, $CHCl_3$) (97% ee); Anal. Calcd for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.22; H, 7.96; N, 5.64; HPLC (DAICEL CHIRALPAK AS, hexane/2-propanol 99/1, 0.5 mL/min) t_R 13.4 min and 14.8 min.

3.4.3. (2*S*)-2-Hydroxy-3-methylbutanenitrile (12c). This product was found to be identical with the reported compound by analytical data: $[\alpha]^{19}_D$=−15.4° (c=2.1, $CHCl_3$) (90% ee) [lit.[14] $[\alpha]^{24}_D$=+4.2° (c=1.3, $CHCl_3$) for *R* enantiomer in 34% ee]. The enantiomeric excess was determined by HPLC after the conversion to benzoylester: IR (neat) ν 2970, 1732, 1258 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08–8.05 (m, 2H), 7.51–7.47 (m, 1H), 7.56–7.61 (m, 2H), 5.45 (d, J=5.75 Hz, 1H), 2.32 (dqq, J=6.7, 6.7, 5.75 Hz, 1H), 1.21 (d, J=6.7 Hz, 3H), 1.18 (d, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.8, 134.0, 130.0, 128.7, 128.5, 116.0, 66.8, 31.4, 17.9, 17.5; MS m/z 203 (M^+); $[\alpha]^{22}_D$=−48.4°

(c=0.46,$CHCl_3$) (90% ee); HPLC (DAICEL CHIRALCEL OJ, hexane/2-propanol 9/1, 0.5 mL/min) t_R 11.7 min and 13.0 min.

3.4.4. (2*S*)-2-Hydroxy-3-ethylpentanenitrile (12d). ^{1}H NMR ($CDCl_3$) δ 4.48 (d, J=4.9 Hz, 3H), 1.68–1.41 (m, 6H), 0.98 (t, J=7.3 Hz, 3H), 0.97 (t, J=7.35 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 119.4, 64.1, 45.7, 21.7, 21.6, 11.2, 11.1; $[\alpha]^{21}_D$=−17.0° (c=1.32, $CHCl_3$) (83% ee) [lit.[15] $[\alpha]_D$=−14.2° for *S* enantiomer in 91% ee]. The enantiomeric excess was determined by HPLC after the conversion to *p*-nitrobenzoylester: IR (neat) ν 1737, 1530, 1348, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.34 (ddd, J=8.85, 2.1, 2.1 Hz, 2H), 8.23 (ddd, J=8.85, 2.1, 2.1 Hz, 2H), 5.68 (d, J=4.85 Hz, 1H), 1.90 (m, 1H), 1.74–1.57 (m, 4H), 1.05 (dd, J=7.35, 3.65 Hz, 3H), 1.03 (dd, J=7.35, 3.65 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 163.1, 151.1, 133.7, 131.1, 123.8, 115.8, 65.2, 43.9, 22.4, 22.3, 11.3, 11.2; MS m/z 276 (M^+), 277 (M^++1); $[\alpha]^{22}_D$=−38.6° (c=0.74, $CHCl_3$) (83% ee); Anal. Calcd for $C_{14}H_{16}O_4N_2$: C, 60.86; H, 5.84; N, 10.141. Found: C, 61.06; H, 5.91; N, 9.86; HPLC (DAICEL CHIRALPAK AD, hexane/2-propanol 99/1, 1.0 mL/min) t_R 22.9 min and 28.5 min.

3.4.5. (3*E*)-2-Hydroxy-3-octenenitrile (12e). ^{1}H NMR ($CDCl_3$) δ 6.08 (ddt, J=15.3, 6.7, 0.95 Hz, 1H), 5.61 (ddt, J=15.3, 6.1, 1.6 Hz, 1H), 4.94 (m, 1H), 2.47 (d, J=4.9 Hz, 1H), 2.12 (m, 2H), 1.44–1.30 (m, 4H), 0.91 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 134.1, 128.3, 118.4, 61.9, 31.6, 30.6, 22.1, 13.8; $[\alpha]^{23}_D$=+19.8° (c=1.49, $CHCl_3$) (97% ee) The absolute configuration of the product has not been determined yet. The enantiomeric excess was determined by HPLC after the conversion to benzoylester: IR (neat) ν 2958, 2930, 1731, 1601, 1246, 969 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07–8.05 (m, 2H), 7.62 (dt, J=7.4, 1.2 Hz, 1H), 7.47 (m, 2H), 6.24 (dddd, J=15.3, 6.7, 6.7, 0.9 Hz, 1H), 6.07 (dd, J=6.7, 0.9 Hz, 1H), 5.67 (dddd, J=15.3, 6.7, 1.6 Hz, 1H), 2.16 (m, 2H), 1.46–1.31 (m, 4H), 0.92 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.7, 140.9, 134.0, 130.0, 128.6, 128.4, 120.1, 115.9, 62.0, 31.8, 30.5, 22.2, 13.8; Anal. Calcd for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.91; H, 7.18; N, 5.73; HPLC (DAICEL CHIRALCEL OJ, hexane/ 2-propanol 9/1, 1.0 mL/min) t_R 5.1 min and 5.7 min.

3.4.6. (2*S*,3*E*)-2-Hydroxy-4-phenyl-3-butenenitrile (12f). This product was found to be identical with the reported compound by analytical data: $[\alpha]^{28}_D$=−24.1° (c=0.8, $CHCl_3$) 98% ee) [lit.[14] $[\alpha]^{24}_D$=+19.2° (c=1.9, $CHCl_3$) for *R* enantiomer in 72% ee]. The enantiomeric excess was determined by HPLC after the conversion to acetylester: IR (neat) ν 1751, 1654, 1213, 1020, 967 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.30 (m, 5H), 6.98 (d, J=15.9 Hz, 1H), 6.19 (dd, J=15.9, 6.7 Hz, 1H), 6.03 (dd, J=6.7, 0.9 Hz), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.9, 137.9, 134.4, 129.4, 128.9, 127.2, 118.4, 115.5, 61.5, 20.5; MS m/z 201 (M^+); $[\alpha]^{22}_D$=+54.0° (c=0.41, $CHCl_3$) (98% ee); Calcd for $C_{12}H_{11}O_2N$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.99; H, 5.65; N, 6.70; HPLC (DAICEL CHIRALPAK AS, hexane/ 2-propanol 150/1, 1.0 mL/min) t_R 22.2 min and 24.1 min.

3.4.7. (2*S*)-2-Hydroxy-2-phenylacetonitrile (12h). This product was found to be identical with the reported compound by analytical data: $[\alpha]^{27}_D$=−43.4° (c=2.5, $CHCl_3$) (92% ee) [lit.[14] $[\alpha]^{24}_D$=+36.8° (c=2.0, $CHCl_3$) for *R* enantiomer in 85% ee]. The enantiomeric excess was determined by HPLC after conversion to ethylcarbonate: IR (neat) ν 1757, 1252 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48–7.37 (m, 5H), 6.19 (s, 1H), 4.27–4.17 (m, 2H), 1.27 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 153.4, 131.2, 130.6, 129.2, 127.9, 115.7, 66.3, 65.6, 14.1; $[\alpha]^{16.4}_D$=−13.7° (c=2.8, $CHCl_3$) (74.5% ee); Anal. Calcd for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.60; H, 5.51; N, 6.69; HPLC (DAICEL CHIRALCEL OD, hexane/2-propanol 99/1, 1.0 mL/min) t_R 10.5 min and 13.0 min.

3.4.8. (2*S*)-2-Hydroxy-2-(4-methyphenyl)acetonitrile (12i). This product was found to be identical with the reported compound by analytical data: $[\alpha]^{25}_D$=−46.3° (c=1.2, $CHCl_3$) (90% ee) [lit.[14] $[\alpha]^{24}_D$=+36.4° (c=1.3, $CHCl_3$) for *R* enantiomer in 71% ee]. The enantiomeric excess was determined by HPLC after the derivatization to ethylcarbonate. ^{1}H NMR ($CDCl_3$) δ 7.43 (d, J=8.25 Hz, 2H), 7.26 (d, J=8.25 Hz, 2H), 6.20 (s, 1H), 4.28 (m, 2H), 2.39 (s, 3H), 1.33 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 153.5, 140.9, 129.9, 128.4, 127.9, 115.9, 66.3, 65.5, 21.3, 14.1; HPLC (DAICEL CHIRALCEL OD, hexane/2-propanol 99/1, 0.5 mL/min) t_R 17.5 min and 19.6 min.

3.4.9. (2*S*)-2-(2-Furyl)-2-hydroxyethanenitrile (12j). This product was found to be identical with the reported compound by analytical data: $[\alpha]^{24}_D$=−39.0 (c=0.6, $CHCl_3$) (95% ee) [lit.[16] $[\alpha]_D$=+14.0° (c=1.89, $CHCl_3$) for *R* enantiomer in 79% ee]. The enantiomeric excess was determined by HPLC after the derivatization to acetylester; ^{1}H NMR ($CDCl_3$) δ 7.51 (dt, J=1.8 Hz, 1H), 6.69 (d, J=3.4 Hz, 1H), 6.48 (s, 1H), 6.47 (dd, J=3.4, 1.8 Hz, 1H), 2.17 (s, 3H); HPLC (DAICEL CHIRALPAK AS, hexane/ 2-propanol 1.0 mL/min) t_R 8.5 min and 9.5 min.

3.4.10. Trimethylsilylcyanation reaction of aldehyde 11g using 5 mol% catalyst. Into a flame dried flask, **1-L** (64 mg, 0.0895 mmol) was added and dried at 50°C for 2 h under the reduced pressure. 3 mL of dichloromethane was added, followed by the addition of diethylaluminum chloride (93 μL, 0.0895 mmol, 0.96 M in hexane) under argon atmosphere. After stirring for 10 min, tributylphosphine oxide (78 mg, 0.358 mmol) in dichloromethane (1.2 mL) was added at room temperature. The resulting mixture was stirred at the same temperature for 1 h to give a clear solution. To this stirred solution of the catalyst was added aldehyde **11g** (300 mg, 1.79 mmol) in dichloromethane (1.4 mL) at −40°C. After 30 min, TMSCN (287 μL, 2.15 mmol) was slowly added over 48 h using a syringe pump. (Be careful! TMSCN should be added dropwise from the top of the flask, where the temperature may be above 15°C. Because the melting point of TMSCN is 11–12°C.) The reaction mixture was allowed to stir for additional 2 h at the same temperature. Trifluoroacetic acid (2.0 mL) was added at −40°C, and the mixture was stirred vigorously at room temperature for 1 h to hydrolyze the trimethylsilylether of the product. Adding ethyl acetate (30 mL), the mixture was stirred for further 30 min. After an usual workup, the crude product was further purified by flash chromatography (ethyl acetate/hexane 1:3) to give cyanohydrin **12g** in 97% yield with 99% ee.

3.4.11. (2*S*)-2-Hydroxy-3-methyl-4-(2-methyl-4-thiazolyl)-3-butenenitrile (12g). ^{1}H NMR ($CDCl_3$) δ 7.0 (s, 1H), 6.76 (s, 1H), 4.99 (s, 1H), 2.75 (s, 3H), 2.15 (s 1H); ^{13}C NMR ($CDCl_3$) δ 166.4, 150.8, 134.6, 121.5, 118.4, 117.5, 66.2, 18.9, 15.0; IR (KBr) 3039, 2821, 2694, 2361, 1508, 1450, 1381, 1277, 1197, 1166, 1091, 980, 901, 813, 743, 452 cm^{-1}; EI-MS *m/z* 194 (M^+); EI-HRMS Calcd for $C_9H_{10}N_2OS$ (M^+): 194.0514, Found: 194.0513; $[\alpha]^{16.8}_D$= −16.5° (*c*=0.7, $CHCl_3$) (99% ee); The enantiomeric excess was determined by HPLC after conversion to TBDMS ether: ^{1}H NMR ($CDCl_3$) δ 7.26 (s, 1H), 6.65 (s, 1H), 4.91 (s, 1H), 2.70 (s, 3H), 2.20 (s, 3H), 0.93 (s, 9H), 0.21 (s, 3H), 0.12 (s,3H); ^{13}C NMR ($CDCl_3$) δ 165, 152, 134, 122, 118, 118, 68, 25, 19, 18, 14, −5.27, −5.28; $[\alpha]^{16.7}_D$=−17.7° (*c*=0.845, $CHCl_3$) (97% ee); EI-MS *m/z* 308 (M^+); EI-HRMS Calcd for $C_{15}H_{24}N_2OSiS$ (M^+): 308.1379, Found: 308.1378; HPLC (DAICEL CHIRALPAK AD, hexane/2-propanol 100/1, 1.0 mL/min) t_R 6.5 min and 7.5 min.

References

1. (a) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55–56. (b) Lidy, W.; Sundermeyer, W. *Chem. Ber.* **1973**, *106*, 587–593.
2. (a) Evans, D. A.; Wong, R. Y. *J. Org. Chem.* **1977**, *42*, 350–351. (b) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, *42*, 537–540.
3. (a) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682. (b) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555–1564. (c) North, M. *Synlett* **1993**, *33*, 807–820.
4. (a) For recent interesting examples, see: (a) Belokon', Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973 (b) Hwang, C.-D.; Hwang, D.-R.; Uang, *J. Org. Chem.* **1998**, *63*, 6762–6763.
5. (a) Shibasaki, M. *Enantiomer* **2000**, *4*, 513–527. (b) Shibasaki, M. *CHEMTRACTS-Organic Chemistry* **1999**, *4*, 979–998. (c) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236–1256.
6. (a) For example: (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178. (b) Yamada, K.-i.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3504–3506. (c) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252–2260.
7. Preliminary communication: Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641–2642
8. (a) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754–5755. (b) Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997**, *119*, 11713–11714.
9. Sawada, D.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 209–213; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *43*, 10521–10532.
10. Modest ee's were attributed to the one-portion addition of TMSCN in these kinetic studies.
11. When this catalytic asymmetric cyanosilylation was applied to a larger scale reaction (5 g scale of aldehyde **11h**), it was found that the addition of a catalytic amount of proton source (5 mol% of MeOH) was necessary to reproduce the results of the smaller scale reactions shown in Table 3. Although the role of the proton source is not clear at this moment, we think that the proton source would facilitate the catalytic cycle by protonating the intermediate **15**. The free cyanohydrin **12h** was found to be silylated immediately under the reaction conditions. For a discussion about the role of a proton source in facilitating the catalytic cycle, see: Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1650–1652; *Idem, Chem. Pharm. Bull.* **2000**, *48*, 1586–1592.
12. Review: Nicolaou, K. C.; Roschangar, F.; Vourloumis, D.; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2014–2045. For other recent examples, see references cited in Ref. 9.
13. The aluminum cyanide catalyst (**1**: Mtl=Al–CN) prepared by the reaction of Et_2AlCN and **1-L** showed a lower reactivity in the reaction of **11h**.
14. Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515–1522.
15. Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 7969–7975.
16. Matthews, B.; Jackson, W.; Jayatilake, G.; Wilshire, C.; Jacobs, H. *Aust. J. Chem.* **1988**, *41*, 1697–1609.