Asymmetric Cyanosilylation of Ketones Catalyzed by Bifunctional Chiral *N*-Oxide Titanium Complex Catalysts

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Keywords: Asymmetric catalysis / Asymmetric synthesis / Enantioselectivity / Ketones / N,O ligands

A new bifunctional catalytic system based on chiral *N*-oxide titanium complexes has been used for the asymmetric cyanosilylation of ketones. Screening of a variety of chiral *N*-oxide metal complexes resulted in (1*R*,2*S*)-1-(2′-pyridylmethyl)-2-(diphenylhydroxymethyl)pyrrolidine *N*-oxide titanium complex, which gave *O*-TMS cyanohydrins in good yields with enantiomeric excesses of up to 69 %. A catalytic cycle based on experimental phenomena and studies was proposed to explain the origin of the asymmetric induction.

Introduction

A number of recent studies have shown that multifunctional catalysts possess special characteristics for catalysis and asymmetric synthesis.[1] These catalysts must contain a Lewis acid moiety that activates an electrophilic substrate and a Lewis base moiety that activates a nucleophilic substrate. The positioning of the two reactive partners in close proximity and with the correct relative geometry by such a catalyst assembly facilitates a reaction in a manner similar to that of Nature's enzymatic processes. Dual coordination by such catalyst assemblies further assists the reaction by simultaneously enhancing the electrophilic character of one partner and the nucleophilic character of the other.[2]

An example of this motif can be found in heterodimetallic complexes in which the central metal atom, as a Lewis acid, has been proposed to coordinate with the electrophile, while an appropriate functionality, such as the hemilable BINOLate oxygen atoms, functions as a Lewis base to coordinate with the nucleophile. Very recently, Shibasaki et al. have reported a series of bifunctional Lewis acid/Lewis base (LALB) catalysts derived from BINOL and natural glucose as the chiral scaffold. In particular, phosphane oxide derived catalysts (Figure 1) were very efficient for the asymmetric cyanosilylation of aldehydes,[3] imines (Strecker reaction),[4] and ketones,[5] as well as for the addition of cyanide to quinoline or isoquinoline derivatives (Reissert-type reaction).[6] We have recently reported that chiral *N*-oxides can effectively activate TMSCN to catalyze the asymmetric cyanosilylation of imines[7] and that achiral and chiral *N*-oxide titanium complexes can effectively catalyze the cyanosilylation of ketones.[8] This paper describes the studies of relationships between catalyst structure and activity, substrate generality, mechanism, and limitations of asymmetric cyanosilylation of ketones catalyzed by chiral *N*-oxide titanium complexes.

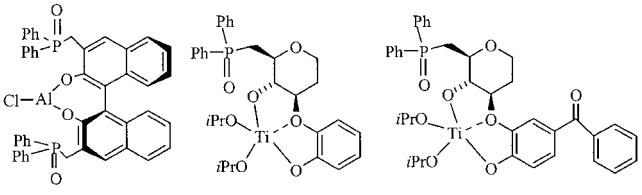

Figure 1. Structure of bifunctional catalysts

Results and Discussion

We selected Corey's reagent as a scaffold for arranging the Lewis acid and Lewis base moieties as shown in Figure 2. While the Lewis acid metal atom was connected to the hydroxy group of the hydroxymethyl function at the 2-position and an available coordinating atom at the 1-position, a Lewis base *N*-oxide moiety was located at the 1-position to promote the reaction effectively by a dual activation pathway. The following two points were considered in the design of the ligands. Ligands containing atoms with different coordinate abilities on the aryl ring at the 1-position were to be investigated for the effect of ligand−metal

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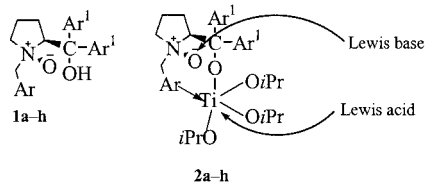
complexes on reactivity and enantioselectivity. On the other hand, the steric effects of the substituents on the hydroxymethyl group at the 2-position and the aryl ring at the 1-position were also to be considered. The ligand structures shown in Figure 2 were very flexible for optimization of the structures of the ligands by changing of the metal, the coordination abilities of coordinate atoms on the aryl ring at the 1-position and the steric effects of aryl ring and substituents on the hydroxymethyl moiety at the 2-position.

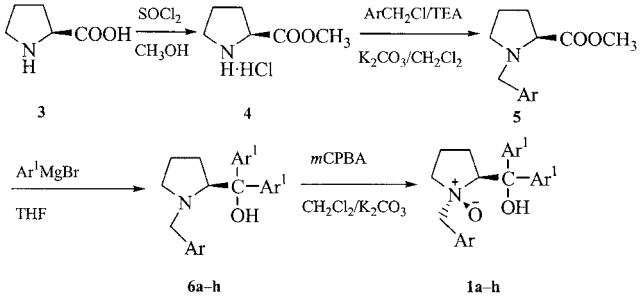


a: Ar = Ph; Ar^1 = Ph
b: Ar = 2-pyridyl; Ar^1 = Ph
c: Ar = 2-MeOC$_6$H$_4$; Ar^1 = Ph
d: Ar = 3-pyridyl; Ar^1 = Ph
e: Ar = 2-pyridyl; Ar^1 = β-naphthyl
f: Ar = 3-methyl-2-pyridyl; Ar^1 = Ph
g: Ar = quinolinyl; Ar^1 = Ph
h: Ar = 3,5-di-*tert*-butyl-2-hydroxyphenyl; Ar^1 = Ph

Figure 2. The designed Lewis acid/Lewis base catalyst

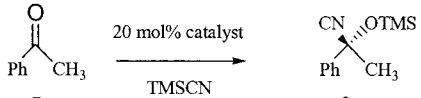
Optimization of the Catalyst

To optimize the catalytic activity of complexes **2a**−**h**, a series of amino *N*-oxides **1a**−**h** were prepared as shown in Scheme 1. Complexes of **1a**−**h** and titanium were tested for their capability to catalyze the asymmetric addition of trimethylsilyl cyanide to acetophenone at 0 °C. The results, shown in Table 1, illustrate that the structure of the ligand strongly affects the reactivity and enantioselectivity. The screening results indicate that the catalysts **2a**−**h**, with similar structures, have different enantioselective induction abilities. Complex (1*R*,2*S*)-**2a** was ineffective in promoting the enantioselective cyanosilylation of acetophenone (Table 1, Entry 1). The best result, shown in Entry 2 of Table 1, gave the *O*-TMS cyanohydrin with 51 % *ee* on application of (1*R*,2*S*)-**2b**, introduced into catalytic asymmetric reduction of ketones by O'Neil,[10] while chiral catalysts (1*R*,2*S*)-**2c**, (1*R*,2*S*)-**2d**, and (1*R*,2*S*)-**2h** gave no meaningful enantiomeric excess (Table 1, Entries 3, 4, and 8). We attempted to improve the enantiomeric excess of the product by increasing the bulk of the substituent on the hydroxymethyl moiety at the 2-position with β-naphthyl instead of phenyl, but the catalytic activity of catalyst (1*R*,2*S*)-**2e** was apparently inferior to that of catalyst (1*R*,2*S*)-**2b** (Table 1, Entry 5). When Ar = 2-pyridyl, we further explored the effects on the enantioselectivity of the *ortho* substituent of the 2-pyridyl ring. The results indicated that the *ortho*-position substituent greatly affected the enantioselectivity. Increasing bulk of the *ortho*-position substituent resulted in the *ee* value of the product being sharply decreased (Table 1, Entries 6 and 7), probably due to spatial hindrance by the substituent blocking the coordination between the nitrogen and the titanium atoms.



Scheme 1. Synthesis of ligands

Table 1. Asymmetric cyanosilylation of acetophenone catalyzed by *N*-oxide Ti(O*i*Pr)$_4$ complexes



7a 8a

Entry[a]	Catalyst	Time [h]	Yield [%]	*ee* [%][b]	Config.[c]
1	(1*R*,2*S*)-**2a**	30	32	0.8	(*S*)
2	(1*R*,2*S*)-**2b**	30	48	51.0	(*R*)
3	(1*R*,2*S*)-**2c**	30	5	10.0	(*S*)
4	(1*R*,2*S*)-**2d**	30	27	9.0	(*S*)
5	(1*R*,2*S*)-**2e**	30	29	43.0	(*R*)
6	(1*R*,2*S*)-**2f**	48	36	7.5	(*R*)
7	(1*R*,2*S*)-**2g**	96	35	4.3	(*S*)
8	(1*R*,2*S*)-**2h**	48	11	15.5	(*S*)

[a] All reactions were carried out at 0 °C according to the experimental procedure, ligand/Ti(O*i*Pr)$_4$ = 1:1.2. [b] Determined by chiral GC assay (Chirasil DEX CB). [c] Determined by comparison of the elution order of chiral GC assay with that reported in the literature.[5,9]

To optimize the reaction conditions, a series of metals was screened in combination with ligand (1*R*,2*S*)-**1b** for catalysis of the addition of TMSCN to acetophenone (Table 2). Although the Zr and Sm catalysts showed better reactivities (Table 2, Entries 2 and 3), it was found that the Ti catalyst gave the best enantioselectivity (Table 2, Entry 4). We also examined the effects of solvent. Better results were obtained in halogenated solvents such as CH_2Cl_2 and $CHCl_3$ (Table 3, Entries 3 and 5). Although better enantioselectivity was also obtained in THF, the reactivity in THF was obviously inferior to that in CH_2Cl_2 (Table 3, Entry 4).

Table 2. Effect of combination of different metals with (1*R*,2*S*)-**1b** on the asymmetric addition of TMSCN to acetophenone

Entry[a]	M(OR)$_x$	Yield [%]	*ee* [%][b]	Config.[c]
1	Al(O*i*Pr)$_3$	19	0.8	(*S*)
2	Sm(O*i*Pr)$_3$	64	0.2	(*R*)
3	Zr(O*t*Bu)$_4$	67	1.0	(*S*)
4	Ti(O*i*Pr)$_4$	48	51.0	(*R*)

[a] All reactions were carried out at 0 °C for 30 h according to the experimental procedure. [b] Determined by chiral GC assay (Chirasil DEX CB). [c] Determined by comparison of the elution order of chiral GC assay with that reported in the literature.[5,9]

Table 3. Effects of solvent on the asymmetric addition of TMSCN to acetophenone

Entry[a]	Solvent	Yield [%]	*ee* [%][b]
1	Et_2O	51	3.5 (*R*)
2	toluene	56	14 (*R*)
3	CH_2Cl_2	48	51 (*R*)
4	THF	43	53 (*R*)
5	$CHCl_3$	66	47 (*R*)

[a] All reactions were carried out at 0 °C for 30 h according to the experimental procedure. [b] Determined by chiral GC assay (Chirasil DEX CB) and by comparison of the elution order of chiral GC assay with that reported in the literature.[5,9]

Table 4. Effects of the ratio of (1*R*,2*S*)-**1b** to Ti^{IV} on the asymmetric addition of TMSCN to acetophenone

Entry[a]	(1*R*,2*S*)-**1b**/Ti^{IV} (molar ratio)	Yield [%]	*ee* [%][b]
1	0.5:1	16	50 (*R*)
2	0.83:1	48	51 (*R*)
3	1:1	64	46 (*R*)
4	1.25:1	59	23 (*R*)
5	2:1	80	0

[a] All reactions were carried out at 0 °C for 30 h according to the experimental procedure. [b] Determined by chiral GC assay (Chirasil DEX CB) and by comparison of the elution order of chiral GC assay with that reported in the literature.[5,9]

Table 5. Effects of the concentration of acetophenone on the asymmetric addition of TMSCN to acetophenone catalyzed by (1*R*,2*S*)-**1b** Ti(O*i*Pr)$_4$ complex

Entry[a]	Concentration [mol/L]	Time [h]	Yield [%]	*ee* [%][b]
1	0.085	30	27	53 (*R*)
2	0.170	30	48	51 (*R*)
3	0.340	30	61	53 (*R*)
4	0.680	30	48	50 (*R*)

[a] All the reactions were carried out at 0 °C according to the experimental procedure. [b] Determined by chiral GC assay (Chirasil DEX CB) and by comparison of the elution order of chiral GC assay with that reported in the literature.[5,9]

The effect of the molar ratio of ligand (1*R*,2*S*)-**1b** to Ti^{IV} was then examined (Table 4), and it was found that the ratio of ligand to Ti^{IV} had a large effect on the enantioselectivity of the reaction. Increasing the ratio of ligand to Ti^{IV} produced decreases in enantioselectivity and increases in yields. The best result was obtained when the molar ratio of ligand to Ti^{IV} was 1:1.2 (Table 4, Entry 2). Further studies indicated that the concentration of acetophenone had a slight effect on the enantioselectivity, but a larger effect on the yield of the addition of TMSCN to acetophenone. The optimum concentration of acetophenone was 0.34 M (Table 5, Entry 3).

The proportion of the catalyst was an important factor for the asymmetric cyanosilylation of acetophenone. When the proportion of catalyst was 20 mol %, the reaction proceeded more efficiently at 0 °C to give the product in 48 % yield with 51 % *ee* after 30 h (Table 5, Entry 2). When the proportion of the catalyst was increased further, the yield was greatly decreased. When the catalyst was used in stoichiometric amounts, the product was obtained only in traces (Table 6, Entry 6). This was probably due to an aggregation of catalyst molecules reducing the effective quantity of the catalyst.

Only a small temperature effect was observed for the reaction in the presence of catalyst (1*R*,2*S*)-**2b**, as shown in Table 7. The reaction gave *O*-TMS cyanohydrin with 51 % *ee* in 48 % yield at 0 °C for 30 h, but the reaction carried out at −27 °C gave only trace amounts of product with 57 % *ee* after 38 h. Consequently, the best reaction conditions were found to involve 20 mol % of (1*R*,2*S*)-**1b** Ti(O*i*Pr)$_4$ (1:1.2) and 0.34 M acetophenone in CH_2Cl_2 at 0 °C.

Table 7. Effects of temperature on the asymmetric addition of TMSCN to acetophenone

Entry[a]	Temp. [°C]	Time [h]	Yield [%]	*ee* [%][b]
1	0	30	48	51 (*R*)
2	−27	38	6	57 (*R*)
3	−78	72	trace	−

[a] All the reactions were carried out according to the experimental procedure. [b] Determined by chiral GC assay (Chirasil DEX CB) and by comparison of the elution order of chiral GC assay with that reported in the literature.[5,9]

Table 6. Effects of the proportion of catalyst (1*R*,2*S*)-**2b** on the asymmetric addition of TMSCN to acetophenone

Entry[a]	Proportion of catalyst [mol %]	Temp. [°C]	Time [h]	Yield [%]	*ee* [%][b]
1	10	−27	34	trace	29 (*R*)
2	20	−27	38	trace	57 (*R*)
3	20	0	30	48	51 (*R*)
4	30	0	30	48	53 (*R*)
5	50	0	30	37	46 (*R*)
6	100	0	30	trace	−

[a] All reactions were carried out according to the experimental procedure. [b] Determined by chiral GC assay (Chirasil DEX CB) and by comparison of the elution order of chiral GC assay with that reported in the literature.[5,9]

In order to improve the enantioselectivity of the asymmetric cyanosilylation of acetophenone, we investigated the use of chiral or achiral additives such as *R*-BINOL and Ph_3PO etc. (Figure 3). Unfortunately, no effective additive was found. In addition, it was surprising that the reaction did not proceed when molecular sieves (4 Å), an effective additive in some asymmetric reactions, were used as an additive in the reaction. One possible explanation for this was the existence of a hydrogen bond between the N−O group of the *N*-oxide and the surface of the molecular sieves (4 Å), hindering the N−O group of the *N*-oxide from activating TMSCN.

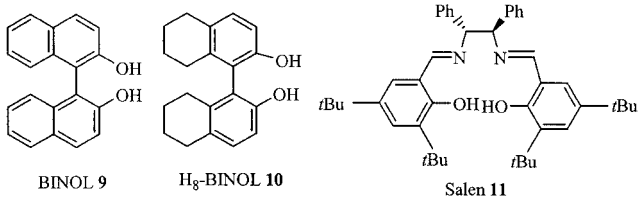


Figure 3. Additives used

Substrate Generality

Encouraged by the results from acetophenone with (1*R*,2*S*)-**2b** complex as a catalyst, we investigated the scope of the asymmetric cyanosilylation of ketones under the optimized conditions (Table 8). A summary of the results obtained is presented in Table 9. The data show that aromatic, conjugated, and aliphatic ketones afforded the corresponding products in moderate to good yields with moderate % *ee*s.

Table 8. The effects of different chiral and achiral additives on the asymmetric addition of TMSCN to acetophenone catalyzed by (1*R*,2*S*)-**2b** complex

Entry[a]	Additive [mol %]	Time [h]	Yield [%]	ee [%][b]
1	molecular sieves (4 Å)	30	–	–
2	salen **11** [20]	30	65	49 (*R*)
3	(*S*)-**10** [20]	30	69	0 (*R*)
4	$Ph_3P{=}O$ [20]	36	64	7 (*R*)
5	(*R*)-**10** [20]	41	64	1 (*R*)
6	isoquinoline *N*-oxide [109	41	51	1 (*R*)
7	calix[4]arene [10]	30	64	0 (*R*)
8	*ortho*-ethoxyphenol [10]	30	93	0 (*R*)
9	(*R*)-**9** [20]	41	57	2 (*R*)
10	(*S*)-**9** [20]	30	40	11 (*R*)
11	$CH_3Ph_2P{=}O$ [20]	44	53	2 (*R*)
12	$CH_3Ph_2P{=}O$ [40]	44	48	12 (*R*)

[a] All the reactions were carried out at 0 °C according to the experiment procedure. [b] Determined by chiral GC assay (Chirasil DEX CB) and by comparison of the elution order of chiral GC assay with that reported in the literature.[5,9]

The experimental results indicated that the *ee* values obtained were strongly dependent on the ketones used (i.e., the nature of the substrates strongly influenced the reactivity and enantioselectivity). Ketones with substituents in *ortho* positions were most notable; 2′-fluoroacetophenone, for example, gave the product in 47 % yield with 55 % *ee*. This was the first example of asymmetric cyanosilylation of 2′-fluoroacetophenone. Interestingly, benzylacetone and *trans*-4-phenyl-3-buten-2-one as substrate gave the products in 68 % *ee* and 25 % *ee*, respectively. These results are different from those of Shibasaki.[5]

Preliminary Mechanistic Studies

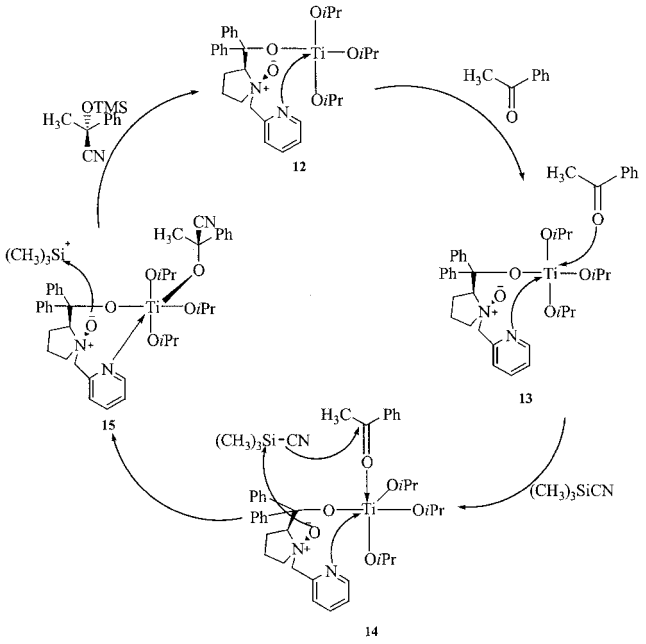
Mechanistic studies provided a proposed mechanism (Scheme 2) and a proposed transition state accounting for

Table 9. Asymmetric cyanosilylation of ketones catalyzed by (1*R*,2*S*)-**2b** complex

Entry[a]	Ketone	Time [h]	Yield [%][b]	*ee* [%]	Config.[c]
1	acetophenone	96	78	54[d]	(*R*)
2	β-acetonaphthanone	96	73	69[e]	(*R*)
3	*trans*-4-phenyl-3-buten-2-one	96	77	25[e]	(*R*)
4	benzylacetone	120	87	68[d]	(*R*)
5	α-tetralone	120	61	37[d]	(*R*)
6	4′-methylacetophenone	96	63	41[d]	(*R*)
7	3′-chloroacetophenone	120	76	33[d]	(*R*)
8	2′-fluoroacetophenone	96	47	55[d]	(*R*)
9	4′-fluoroacetophenone	120	67	33[d]	(*R*)
10	β-tetralone	120	74	26[d]	(*R*)
11	2-acetylthiophene	120	35	20[d]	(*R*)

[a] All reactions were carried out at 0 °C according to the experimental procedure, (1*R*,2*S*)-**1b**/$Ti(OiPr)_4$ = 1:1.2. [b] The yields given are for the isolated *O*-TMS cyanohydrins after chromatographic purification; satisfactory spectroscopic (^1H NMR, ^{13}C NMR, IR) and elemental analysis data were obtained for new compounds. [c] Determined by comparison of the elution order of chiral GC and HPLC (see refs.[5,9]). [d] Determined by chiral GC assay (Chirasil DEX CB). [e] Determined by chiral HPLC assay (Chiralcel OJ).

the origin of the asymmetric induction in cyanosilylation of ketones catalyzed by chiral (1*R*,2*S*)-**2b** (ligand/titanium = 1:1.2 ratio) complex.



Scheme 2. Proposed catalytic cycle

To investigate whether the N−O moiety of the catalyst *N*-oxide was coordinated to the central titanium ion, a comparison of different procedures for the preparation of catalyst for asymmetric cyanosilylation of acetophenone was undertaken. Were the N−O group of ligand *N*-oxide coordinated to the titanium ion in the preparation of the catalyst, the coordination of the titanium ion would be saturated and other coordinating groups would not change its coordination. Hence, the enantioselectivity of the cyanide addition to ketones would be similar in cases in which the solvent was evaporated in vacuo and in which the solvent was not removed after the preparation of the catalyst. In fact, the observed enantiomeric excesses (49 and 0%, respectively) were surprisingly different. This suggested that the small amount of 2-propanol produced by the preparation of the catalyst had a large effect on the enantioselectivity of the reaction and that the presence of 2-propanol changed the coordination of the catalyst. On the other hand, when additives with coordinated atoms were employed, we found that they produced deleterious enantioselectivities (Table 8). This also indicated that the *N*-oxide N−O group was not coordinated to the titanium ion of the catalyst. Another feature also supports this conclusion. When the proportion of the catalyst was increased, the yield was decreased to trace amounts (Table 6). This indicated that aggregation among catalyst molecules should be present; otherwise a positive effect of loading of a catalyst would have been expected for the reaction.

A mechanistic hypothesis consistent with all of the observations discussed above is shown in Scheme 2. Thus, the combination of complex **13** with TMSCN would generate the key intermediate **14**.

Intermediate **14** is made up of both an activated ketone and activated TMSCN. Intramolecular transfer of cyanide within **14** would generate a complex **15** containing a titanium ion bound to cyanohydrin. Subsequent intramolecular trimethylsilylation would give product *O*-TMS cyanohydrin and complex **12**. Ketone coordinated to complex **12** would regenerate complex **13**. This catalytic cycle also correctly predicted the sense of asymmetric induction, coordination of the acetophenone so as to minimize interactions between the acetophenone and the phenyl group of the ligand (Figure 4) resulting in an orientation in which the *si* face of the acetophenone would be exposed to intramolecular attack by the cyanide of activated TMSCN, producing the (*R*) enantiomer of the *O*-TMS cyanohydrin.

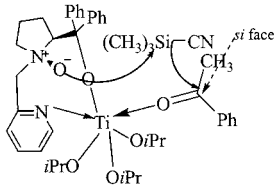


Figure 4. Representation of the transition state for reaction between a ketone and trimethylsilyl cyanide catalyzed by intermediate **14**

Conclusions

In summary, we have synthesized a new chiral *N*-oxide titanium complex to promote the asymmetric cyanosilylation of ketones. The reaction is mechanistically interesting as the first asymmetric cyanosilylation of ketones achieved by an *N*-oxide titanium approach. The experiments suggest that the (1*R*,2*S*)-**2b** [ligand/Ti(O*i*Pr)$_4$ = 1:1.2] complex should promote the reaction through dual activation of ketones by the titanium ion and TMSCN by the N−O group of the *N*-oxide. Importantly, the ligand of (1*R*,2*S*)-**2b** was readily prepared from an inexpensive and readily available chiral amino acid. Additional notable features of the reaction included the simplicity and practical aspects of the method. These features should provide potential for development of this kind of fine-tuning catalyst. Future efforts will be devoted to further searching for effective catalysts for the asymmetric cyanosilylation of ketones.

Experimental Section

General: NMR spectra were recorded with Bruker 200, 300, and 400 spectrometers, at 300 and 400 MHz for ^{1}H NMR and 75 and 100 MHz for ^{13}C NMR spectroscopy, respectively. Chemical shifts in $CDCl_3$ are reported downfield from TMS (δ = 0) for ^{1}H NMR spectroscopy. For ^{13}C NMR, chemical shifts are reported relative to $CDCl_3$ (δ = 77.00 ppm for ^{13}C NMR as an internal reference). IR spectra were recorded with a Perkin−Elmer 1600 series FT-IR spectrometer. Column chromatography was performed on silica gel H 60. In general, reactions were carried out in dry solvents under nitrogen, unless otherwise noted. The enantiomeric excesses (*ee*s)

were determined by HPLC and GC analysis. HPLC was performed with Waters HPLC systems consisting of the following: pump 880-PU; detector 875-UV, 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. Chiral GC was performed with a Varian GC system: column Chirasil Dex CB. Optical rotations were recorded with a Perkin−Elmer 341 polarimeter, and are reported together with the solvent and the concentration in g/100 mL. Melting points are uncorrected. Elemental analyses were performed with a Carlo-1106 analyzer. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Other reagents were purified by conventional methods.

Methyl (*S*)-1-Arylpyrrolidine-2-carboxylates 5: Triethylamine (2.0 mL, 15.3 mmol) was added at room temperature to a solution of L-proline methyl ester hydrochloride (**4**) (1.66 g, 10 mmol) in dry DMF (10 mL) and the mixture was stirred at room temperature for 5 min. The mixture was then filtered to give a solution of L-proline methyl ester in dry DMF. The syntheses of methyl (*S*)-1-arylpyrrolidine-2-carboxylates proceeded according to ref.[12] A solution of L-proline methyl ester was added dropwise to a mixture of halomethyl aromatic compound (6.67 mmol), anhydrous K_2CO_3 (0.78 g, 5.65 mmol), and NaI (44 mg, 0.29 mmol) in dry DMF (50 mL). The mixture was kept at 50 °C, and the reaction monitored by TLC until the halomethyl aromatic compound had disappeared. The mixture was then poured into water (100 mL), the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the organic layer was washed with water (50 mL) and dried with anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure and purification of the residue by silica gel column chromatography (50 % EtOAc/petroleum ether) afforded the title compounds **5a**−**5g**, which were used for the next reaction without further purification.

(*S*)-1-Arylmethyl-2-(hydroxydiphenylmethyl)pyrrolidines 6a−6h: The syntheses of (*S*)-1-arylmethyl-2-(hydroxydiphenylmethyl)pyrrolidines **6a**−**6h** were carried out according to ref.[11] A dry, three-necked, round-bottomed flask was fitted with a pressure-equalizing dropping funnel, a condenser, a rubber septum, and a magnetic stirrer bar. The contents of the flask were placed under nitrogen, and phenylmagnesium bromide (40 mL, 8 mmol) (or β-naphthylmagnesium bromide) in THF solution was added. A solution of methyl (*S*)-1-arylpyrrolidine-2-carboxylate (**5**) (1 mmol) in THF (10 mL) was added to the phenylmagnesium bromide solution at 0 to −10 °C with ice-salt bath cooling over 1 h. After the addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stirred for 1 d. Satd. NH_4Cl was added to the reaction mixture. The resulting mixture was concentrated under reduced pressure to remove THF and the resulting aqueous mixture was extracted with diethyl ether (3 × 10 mL). The ethereal extract was washed with brine (20 mL) and dried with anhydrous sodium sulfate, and the solvents were evaporated under reduced pressure to give a solid, which was recrystallized to give the corresponding title compounds **6a**−**6h**.

(*S*)-1-Benzyl-2-(hydroxydiphenylmethyl)pyrrolidine (6a): Purification of the residue by silica gel column chromatography (5 % EtOAc/petroleum ether) afforded a solid, which was recrystallized from diethyl ether to give the title compound **6a** (246.6 mg, 72 %) as colorless crystals; m.p. 120−122 °C. $[\alpha]_D^{29}$ = +73.7 (*c* = 1.0 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62−1.80 (m, 3 H), 1.97−2.01 (m, 1 H), 2.37−2.40 (m, 1 H), 2.93−2.96 (m, 1 H), 3.06 (d, *J* = 12.6 Hz, 1 H), 3.26 (d, *J* = 12.6 Hz, 1 H), 4.01 (m, 1 H), 4.98 (br. s, 1 H), 7.06−7.36 (m, 11 H), 7.63 (m, 2 H), 7.75 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.16, 29.79, 55.52, 60.57, 70.59, 77.94, 125.54, 125.58, 126.23, 126.37, 126.83, 128.07, 128.09, 128.17, 128.58, 139.65, 146.63, 147.99 ppm. IR (film): ṽ = 703, 766, 1100, 1128, 1447, 1492, 2967, 3436 cm^{-1}. $C_{24}H_{25}NO$ (343.4): calcd. C 83.93, H 7.34, N 4.08; found C 83.79, H 7.16, N 4.07.

(*S*)-2-(Hydroxydiphenylmethyl)-1-(2′-pyridylmethyl)pyrrolidine (6b): Purification of the residue by silica gel column chromatography (50 % EtOAc/petroleum ether) afforded a solid, which was recrystallized from diethyl ether to give the title compound **6b** (255.9 mg, 74 %) as colorless crystals; m.p. 120−123 °C. $[\alpha]_D^{29}$ = +39.6 (*c* = 0.7 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.63−1.68 (m, 2 H), 1.74−1.79 (m, 1 H), 1.93−2.01 (m, 1 H), 2.48−2.55 (m, 1 H), 2.97 (m, 1 H), 3.35 (m, 1 H), 4.06 (d, *J* = 4.8 Hz, 1 H), 4.09 (d, *J* = 4.8 Hz, 1 H), 4.98 (br. s, 1 H), 7.05−7.10 (m, 3 H), 7.14−7.31 (m, 5 H), 7.57 (d, *J* = 7.2 Hz, 3 H), 7.68 (d, *J* = 7.2 Hz, 2 H), 8.42 (d, *J* = 4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.38, 29.61, 55.71, 62.23, 70.89, 78.01, 121.79, 122.44, 125.55, 125.59, 126.24, 126.37, 128.01, 128.11, 136.31, 146.36, 147.71, 148.58, 159.69 ppm. IR (film): ṽ = 704, 750, 1100, 1186, 1478, 1590, 1620, 2954, 3332 cm^{-1}. $C_{23}H_{24}N_2O$ (344.5): calcd. C 80.20, H 7.02, N 8.13; found C 80.02, H 6.91, N 8.08.

(*S*)-2-(Hydroxydiphenylmethyl)-1-(2′-methoxyphenylmethyl)-pyrrolidine (6c): Purification of the residue by silica gel column chromatography (petroleum ether/EtOAc = 10:1) afforded a solid, which was recrystallized from diethyl ether to give the title compound **6c** (283.9 mg, 76 %) as colorless crystals; m.p. 112−113 °C. $[\alpha]_D^{23}$ = +103.6 (*c* = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.62 (m, 2 H), 1.74 (m, 1 H), 1.95 (m, 1 H), 2.34 (m, 1 H), 2.90 (m, 1 H), 2.96 (d, *J* = 12.4 Hz, 1 H), 3.13 (d, *J* = 12.4 Hz, 1 H), 3.76 (s, 3 H), 3.95 (m, 1 H), 4.94 (br. s, 1 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 7.13 (m, 2 H,), 7.25−7.31 (m, 4 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.72 (d, *J* = 8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.14, 29.82, 55.18, 55.40, 59.82, 70.44, 77.93, 113.40, 125.53, 125.59, 126.19, 126.35, 128.06, 128.14, 129.70, 131.77, 146.63, 148.05, 158.43 ppm. IR (film): ṽ = 3260, 2956, 1514, 1445, 1252, 1178, 750, 704 cm^{-1}. $C_{25}H_{27}NO_2$ (373.5): calcd. C 80.40, H 7.29, N 3.75; found C 80.27, H 7.27, N 3.78.

(*S*)-2-(Hydroxydiphenylmethyl)-1-(3′-pyridylmethyl)pyrrolidine (6d): Purification of the residue by silica gel column chromatography (50 % EtOAc/petroleum ether) afforded a solid, which was recrystallized from diethyl ether to give the title compound **6d** (251.8 mg, 73 %) as colorless crystals; m.p. 125−127 °C. $[\alpha]_D^{22}$ = +90.0 (*c* = 1.2 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.62−1.70 (m, 2 H), 1.76−1.83 (m, 1 H), 1.95−2.03 (m, 1 H), 2.36 (m, 1 H), 2.90 (m, 1 H), 3.07 (d, *J* = 12.8 Hz, 1 H), 3.16 (d, *J* = 12.8 Hz, 1 H), 4.00 (m, 1 H), 4.66 (br. s, 1 H), 7.09−7.20 (m, 3 H), 7.26−7.35 (m, 5 H), 7.58 (m, 2 H), 7.71 (m, 2 H), 8.25 (d, *J* = 1.6 Hz, 1 H), 8.43 (dd, *J* = 1.6, 4.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.30, 29.67, 55.63, 57.95, 70.75, 78.12, 123.20, 125.52, 125.55, 126.36, 125.52, 128.13, 128.26, 134.89, 136.11, 146.22, 147.72, 148.36, 149.87 ppm. IR (film): ṽ = 709, 749, 1166, 1480, 1578, 1683, 2976, 3255 cm^{-1}. $C_{23}H_{24}N_2O$ (344.5): calcd. C 80.20, H 7.02, N 8.13; found C 80.21, H 6.88, N 7.85.

(*S*)-2-[Hydroxybis(β-naphthyl)methyl]-1-(2′-pyridylmethyl)-pyrrolidine (6e): Purification of the residue by silica gel column chromatography (50 % EtOAc/petroleum ether) afforded the title compound **6e** (281.5 mg, 63 %) as white crystals; m.p. 78−80 °C. $[\alpha]_D^{24}$ = +170.9 (*c* = 1.13 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.73 (m, 2 H), 1.95 (m, 1 H), 2.11 (m, 1 H), 2.43 (m, 1 H),

2.97 (m, 1 H), 3.12 (d, J = 13.2 Hz, 1 H), 3.26 (d, J = 12.9 Hz, 1 H), 4.27 (m, 1 H), 5.30 (br. s, 1 H), 7.10 (m, 1 H), 7.28 (m, 1 H), 7.39−7.48 (m, 4 H), 7.70−7.90 (m, 8 H), 8.14 (m, 2 H), 8.37 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.22, 29.70, 55.59, 57.85, 70.23, 78.41, 123.07, 124.10, 124.26, 124.31, 125.89, 126.17, 127.34, 127.38, 127.79, 127.95, 128.07, 128.13, 132.00, 132.05, 133.10, 133.15, 143.38, 149.70 ppm. IR (film): ṽ = 758, 789, 858, 895, 1121, 1594, 1629, 2368, 2915, 3415 cm^{-1}. $C_{31}H_{28}N_2O$ (444.6): calcd. C 83.75, H 6.35, N 6.30; found C 83.73, H 6.46, N 6.30.

(*S*)-2-(Hydroxydiphenylmethyl)-1-(3′-methyl-2′-pyridylmethyl)-pyrrolidine (6f): Purification of the residue by silica gel column chromatography (50 % EtOAc/petroleum ether) afforded a solid, which was recrystallized from diethyl ether to give the title compound **6f** (271.4 mg, 76 %) as colorless crystals; m.p. 136−139 °C. $[\alpha]_D^{24}$ = +54.9 (c = 0.39 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62−1.81 (m, 3 H), 1.92−2.02 (m, 1 H), 2.49−2.56 (m, 4 H), 3.01 (m, 1 H), 3.38 (m, 2 H), 4.09 (s, 1 H), 5.13 (br. s, 1 H), 6.95 (m, 2 H), 7.17−7.30 (m, 6 H), 7.49 (m, 1 H), 7.61 (dd, J = 7.2, 28.5 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.28, 24.31, 29.61, 55.62, 62.12, 71.01, 77.99, 119.17, 121.24, 125.59, 125.62, 126.17, 126.30, 127.91, 128.02, 136.50, 146.39, 147.55, 157.10 ppm. IR (film): ṽ = 710, 766, 870, 1108, 1158, 1450, 1578, 2946, 3274 cm^{-1}. $C_{24}H_{26}N_2O$ (358.5): calcd. C 80.41, H 7.31, N 7.81; found C 80.22, H 7.66, N 7.37.

(*S*)-2-(Hydroxydiphenylmethyl)-1-(2′-quinolinylmethyl)pyrrolidine (6g): Purification of the residue by silica gel column chromatography (25 % EtOAc/petroleum ether) afforded a solid, which was recrystallized from diethyl ether to give the title compound **6g** (135.9 mg, 35 %) as colorless crystals; m.p. 148−149 °C. $[\alpha]_D^{23}$ = +108.3 (c = 0.60 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62−1.83 (m, 3 H), 2.01 (m, 1 H), 2.60 (m, 1 H), 2.95 (m, 1 H), 3.53 (m, 2 H), 4.16 (m, 1 H), 5.02 (br. s, 1 H), 7.05 (m, 1 H), 7.19−1.35 (m, 7 H), 7.76 (m, 6 H), 8.07 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.36, 29.60, 55.77, 62.84, 71.10, 78.04, 120.45, 125.53, 125.56, 126.03, 126.03, 126.24, 126.40, 127.20, 127.40, 128.00, 128.12, 128.43, 128.83, 129.09, 129.29, 129.55, 129.97, 136.27, 146.31, 147.19, 147.62, 160.12 ppm. IR (film): ṽ = 707, 769, 823, 871, 962, 1034, 1110, 1310, 1499, 1598, 2813, 2961, 3357 cm^{-1}. $C_{27}H_{26}N_2O$ (394.5): calcd. C 82.20, H 6.64, N 7.10; found C 81.95, H 6.66, N 7.23.

(*S*)-1-[(3′,5′-Di-*tert*-butylphenyl)methyl]-2-(hydroxydiphenylmethyl)-pyrrolidine (6h): Purification of the residue by silica gel column chromatography (17 % EtOAc/petroleum ether) afforded a solid, which was recrystallized from diethyl ether to give the title compound **6h** (329.7 mg, 70 %) as colorless crystals; m.p. 170−171 °C. $[\alpha]_D^{22}$ = +20.0 (c = 1.3 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (s, 9 H), 1.38 (s, 9 H), 1.69 (m, 2 H), 1.89 (m, 1 H), 2.07 (m, 1 H), 2.42 (m, 1 H), 2.88 (m, 1 H), 3.27 (d, J = 12.8 Hz, 1 H), 3.51 (d, J = 12.8 Hz, 1 H), 3.98 (m, 1 H), 6.69 (s, 1 H), 7.09−7.34 (m, 8 H), 7.59 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.37, 29.36, 29.44, 31.62, 34.02, 34.78, 55.17, 61.82, 72.65, 79.71, 122.11, 122.68, 123.21, 125.71, 125.87, 126.69, 126.93, 128.19, 128.41, 134.83, 140.07, 145.71, 153.34 ppm. IR (film): ṽ = 704, 748, 1242, 1448, 2958, 3424 cm^{-1}. $C_{32}H_{41}NO_2$ (471.7): calcd. C 81.48, H 8.76, N 2.97; found C 81.46, H 8.75, N, 3.14.

(1*R*,2*S*)-1-Arylmethyl-2-(hydroxydiphenylmethyl)pyrrolidine *N*-Oxides 1a−h: The syntheses of amino alcohol *N*-oxides were carried out according to ref.[12] *m*CPBA (70−74 %, 718.8 mg, 3.0 mmol) was added at −78 °C under nitrogen to a solution of amino alcohol **6** (3.0 mmol) and anhydrous K_2CO_3 (621.0 mg, 4.5 mmol) in CH_2Cl_2 (25 mL), the resulting mixture was stirred at the same temperature for 5 h, the mixture was then allowed to warm slowly to room temperature and filtered, and the solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography.

(1*R*,2*S*)-1-Benzyl-2-(hydroxydiphenylmethyl)pyrrolidine *N*-Oxide (1a): The residue was purified by silica gel column chromatography (5 % CH_3OH/EtOAc) to give the title compound **1a** (983.3 mg, 91 %) as a white solid; m.p. 185−187 °C. $[\alpha]_D^{29}$ = +60.4 (c = 0.55 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67−1.72 (m, 1 H), 1.84−1.90 (m, 2 H), 2.05−2.11 (m, 1 H), 2.45 (m, 2 H), 3.35 (d, J = 7.6 Hz, 1 H), 3.41 (d, J = 7.6 Hz, 1 H), 3.94 (m, 1 H), 7.11−7.16 (m, 2 H), 7.24−7.34 (m, 9 H), 7.60 (d, J = 7.6 Hz, 2 H), 7.88 (d, J = 7.6 Hz, 2 H), 12.37 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.33, 26.03, 67.54, 70.43, 75.12, 77.63, 79.22, 124.63, 126.21, 126.52, 127.77, 128.00, 128.69, 131.88, 132.14, 148.05, 148.68 ppm. IR (film): ṽ = 700, 751, 806, 1375, 1490, 2957, 3426 cm^{-1}. $C_{24}H_{25}NO_2$ (359.5): calcd. C 80.19, H 7.01, N 3.90; found C 80.06, H 6.90, N 4.04.

(1*R*,2*S*)-2-(Hydroxydiphenylmethyl)-1-(2′-pyridylmethyl)pyrrolidine *N*-Oxide (1b): The residue was purified by silica gel column chromatography (9 % CH_3OH/EtOAc) to give the title compound **1b** (888.5 mg, 82 %) as a white solid; m.p. 172−175 °C. $[\alpha]_D^{29}$ = +34.0 (c = 0.6 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75−1.82 (m, 1 H), 1.99−2.09 (m, 1 H), 2.22−2.31 (m, 1 H), 2.47−2.55 (m, 1 H), 2.85−2.90 (m, 1 H), 3.53−3.60 (m, 1 H), 3.78 (d, J = 12.4 Hz, 1 H), 3.86 (d, J = 12.4 Hz, 1 H), 4.68 (t, J = 8.8 Hz, 1 H), 7.14−7.41 (m, 8 H), 7.58−7.64 (m, 3 H), 7.86 (d, J = 7.2 Hz, 2 H), 8.51 (d, J = 4 Hz, 1 H), 11.81 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.16, 26.32, 69.41, 73.08, 77.21, 78.02, 123.68, 124.77, 126.40, 126.57, 126.84, 127.69, 128.20, 136.36, 146.74, 147.48, 148.68, 151.96 ppm. IR (film): ṽ = 704, 750, 845, 1050, 1177, 1488, 1592, 2963, 3423 cm^{-1}. $C_{23}H_{24}N_2O_2$ (360.5): calcd. C 76.64, H 6.71, N 7.77; found C 76.44, H 6.66, N 7.82.

(1*R*,2*S*)-2-(Hydroxydiphenylmethyl)-1-[(2′-methoxyphenyl)-methyl]pyrrolidine *N*-Oxide (1c): The residue was purified by silica gel column chromatography (10 % CH_3OH/EtOAc) to give the title compound **1c** (1.09 g, 94 %) as a white solid; m.p. 188−190 °C. $[\alpha]_D^{24}$ = +73.0 (c = 0.40 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (m, 1 H), 2.05 (m, 1 H), 2.28 (m, 1 H), 2.51 (m, 1 H), 2.87 (m, 1 H), 3.20 (m, 1 H), 3.55 (d, J = 12.4 Hz, 1 H), 3.63 (d, J = 12.4 Hz, 1 H), 3.77 (s, 3 H), 4.47 (t, J = 8.8 Hz, 1 H), 6.81 (d, J = 8.4 Hz, 4 H), 7.14−7.36 (m, 8 H), 7.57 (d, J = 8 Hz, 2 H), 7.86 (d, J = 7.8 Hz, 2 H), 11.95 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.07, 26.88, 55.25, 68.50, 71.55, 76.68, 78.16, 113.50, 123.59, 124.83, 126.50, 126.56, 126.87, 128.20, 133.10, 146.84, 147.58, 160.14 ppm. IR (film): ṽ = 706, 746, 1178, 1264, 1516, 2930, 3424 cm^{-1}. $C_{25}H_{27}NO_3$ (389.5): calcd. C 77.09, H 6.99, N 3.60; found C 76.91, H 6.83, N 3.59.

(1*R*,2*S*)-2-(Hydroxydiphenylmethyl)-1-(3′-pyridylmethyl)pyrrolidine *N*-Oxide (1d): The residue was purified by silica gel column chromatography (17 % CH_3OH/EtOAc) to give the title compound **1d** (1.07 g, 99 %) as white crystals; m.p. 138−139 °C. $[\alpha]_D^{23}$ = +107.1 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80−1.85 (m, 1 H), 2.05−2.16 (m, 1 H), 2.25−2.32 (m, 1 H), 2.55 (m, 1 H), 2.85 (m, 1 H), 3.22 (d, J = 9.6 H_Z, 1 H), 3.27 (d, J = 9.6 Hz, 1 H), 3.62 (s, 1 H), 4.53 (t, J = 8.4 Hz, 1 H), 7.17−7.37 (m, 7 H), 7.57−7.59 (d, J = 7.6 Hz, 2 H), 7.81−7.88 (m, 3 H), 8.43 (s, 1 H), 8.56 (s, 1 H), 11.68 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.07, 26.67, 69.09, 69.11, 77.81, 78.07, 123.22, 124.76, 126.40, 126.71, 127.07, 127.52, 128.29, 128.35, 140.10, 146.65, 147.32, 150.41, 151.49 ppm. IR (film): ṽ = 704, 750, 845, 1050, 1177, 1488,

1592, 2963, 3423 cm^{-1}. $C_{23}H_{24}N_2O_2$ (360.5): calcd. C 76.64, H 6.61, N 7.77; found C 76.44, H 6.66, N 7.82.

(1*R*,2*S*)-2-[Hydroxybis(β-naphthyl)methyl]-1-(2′-pyridylmethyl)-pyrrolidine *N*-Oxide (1e): The residue was purified by silica gel column chromatography (10 % CH_3OH/EtOAc) to give the title compound **1e** (1.270 g, 92 %) as white crystals; m.p. 155−157 °C. $[\alpha]_D^{23}$ = +176.4 (*c* = 0.33 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.87 (m, 1 H), 2.19−2.37 (m, 2 H), 2.62−2.70 (m, 1 H), 2.91 (m, 1 H), 3.29−3.39 (m, 1 H), 3.77 (m, 2 H), 4.87 (t, *J* = 9 Hz, 1 H), 7.28 (m, 1 H), 7.42−7.48 (m, 4 H), 7.76−7.93 (m, 9 H), 8.12 (s, 1 H), 8.40 (s, 1 H), 8.55 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.14, 26.39, 69.37, 73.09, 76.60, 78.45, 123.37, 123.43, 123.72, 124.61, 125.26, 125.84, 125.96, 126.03, 126.15, 127.37, 127.40, 127.69, 127.89, 128.05, 128.30, 128.48, 132.13, 132.23, 133.09, 133.21, 136.41, 143.98, 144.69, 148.68, 151.79 ppm. IR (film): $\tilde{\nu}$ = 704, 750, 838, 1490, 1598, 3438 cm^{-1}. $C_{31}H_{28}N_2O_2$ (460.6): calcd. C 80.84, H 6.13, N 6.08; found C 80.69, H 6.28, N 6.26.

(1*R*,2*S*)-2-(Hydroxydiphenylmethyl)-1-[(3′-methyl-2′-pyridyl)-methyl]pyrrolidine *N*-Oxide (1f): The residue was purified by silica gel column chromatography (17 % EtOAc/CH_3OH) to give the title compound **1f** (846.3 mg, 79 %) as white crystals; m.p. 169−171 °C. $[\alpha]_D^{26}$ = +21.0 (*c* = 0.37 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.78 (m, 1 H), 2.03 (m, 1 H), 2.29 (m, 1 H), 2.51 (m, 1 H), 2.54 (s, 3 H), 2.89 (m, 1 H), 3.59 (m, 1 H), 3.80 (m, 2 H), 4.75 (t, *J* = 9.0 Hz, 1 H), 7.18−7.34 (m, 8 H), 7.52−7.61 (m, 3 H), 7.88 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.11, 24.27, 26.32, 69.26, 73.21, 77.35, 77.96, 123.13, 124.41, 124.73, 126.40, 126.47, 126.73, 128.11, 128.13, 136.58, 146.74, 147.55, 151.22, 157.40 ppm. IR (film): $\tilde{\nu}$ = 706, 750, 838, 1052, 1176, 1490, 1598, 3438 cm^{-1}. $C_{24}H_{26}N_2O_2$ (374.5): calcd. C 76.98, H 7.00, N 7.48; found C 76.78, H 6.88, N 7.30.

(1*R*,2*S*)-2-(Hydroxydiphenylmethyl)-1-(2′-quinolinylmethyl)-pyrrolidine *N*-Oxide (1g): The residue was purified by silica gel column chromatography (17 % CH_3OH/EtOAc) to give the title compound **1g** (1.08 g, 92 %) as white crystals; m.p. 155−157 °C. $[\alpha]_D^{24}$ = +8.1 (*c* = 0.12 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.82 (m, 1 H), 2.07 (m, 1 H), 2.29 (m, 1 H), 2.58 (m, 1 H), 2.92 (m, 1 H), 3.74 (m, 1 H), 4.05 (m, 2 H), 4.85 (t, *J* = 9 Hz, 1 H), 7.17 (m, 2 H), 7.28−7.35 (m, 5 H), 7.58−7.64 (m, 4 H), 7.90 (m, 3 H), 8.08 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.07, 26.23, 69.70, 73.40, 76.53, 78.18, 117.30, 119.28, 124.21, 124.73, 126.23, 126.36, 126.52, 126.81, 127.03, 127.61, 127.66, 127.94, 128.19, 129.00, 129.57, 136.00, 146.75, 147.13, 147.51, 153.04 ppm. IR (film): $\tilde{\nu}$ = 704, 750, 838, 1490, 1598, 3438 cm^{-1}. $C_{27}H_{26}N_2O_2$ (410.5): calcd. C 79.00, H 6.38, N 6.82; found C 78.88, H 6.57, N 7.08.

(1*R*,2*S*)-1-[(3′,5′-Di-*tert*-butylphenyl)methyl]-2-(hydroxydiphenylmethyl)pyrrolidine *N*-Oxide (1h): The residue was purified by silica gel column chromatography (33 % diethyl ether/petroleum ether) to give the title compound **1h** (1.40 g, 99 %) as white crystals; m.p. 154−155 °C. $[\alpha]_D^{29}$ = +10.0 (*c* = 0.60 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 9 H), 1.37 (s, 9 H), 1.83−1.87 (m, 1 H), 2.12−2.19 (m, 1 H), 2.24−2.33 (m, 1 H), 2.59 (m, 1 H), 3.14−3.19 (m, 1 H), 3.25−3.33 (m, 1 H), 3.54 (d, *J* = 13.2 Hz, 1 H), 4.01 (d, *J* = 12.8 Hz, 1 H), 4.61 (t, *J* = 8.8 Hz, 1 H), 7.14−7.35 (m, 8 H), 7.57 (d, *J* = 7.2 Hz, 2 H), 7.83 (d, *J* = 7.6 Hz, 2 H), 9.75 (br. s, 1 H), 12.68 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.65, 26.57, 29.56, 31.58, 33.99, 35.02, 69.24, 72.42, 77.81, 78.98, 118.72, 124.71, 125.65, 126.07, 126.30, 126.81, 127.32, 128.35, 128.55, 137.95, 140.12, 145.81, 146.74, 155.24 ppm. IR (film): $\tilde{\nu}$ = 704, 746, 876, 1048, 1242, 1448, 1602, 2366, 2958, 3424 cm^{-1}. $C_{32}H_{41}NO_3$ (487.7): calcd. C 78.81, H 8.47, N 2.87; found C 78.63, H 8.38, N 2.94.

General Procedure for Asymmetric Cyanosilylation of Ketones: $Ti(OiPr)_4$ (1 M in toluene, 41 μL, 0.041 mmol) was added at room temperature to a solution of (1*R*,2*S*)-**1b** (12.2 mg, 0.034 mmol) in CH_2Cl_2 (1 mL), and the mixture was stirred for 1 h. CH_2Cl_2 was evaporated under reduced pressure and the resulting residue was further dried in vacuo for 30 min. The residue was dissolved in CH_2Cl_2 (0.5 mL). The ketone (0.17 mmol) was then added to this solution, in an ice/water bath, followed by the addition of TMSCN (45 μL, 0.34 mmol) as shown in Table 9. The reaction was monitored by TLC and, after the reaction time given in Table 9, the solution was concentrated, worked up as usual, and purified by silica gel chromatography (1.6 % diethyl ether/petroleum ether) to give the product.

2-Phenyl-2-(trimethylsilyloxy)propionitrile (8a): The title compound **8a** (29.0 mg, 78 %) was obtained as a colorless oil. $[\alpha]_D^{24}$ = +12.0 (*c* = 0.10 in $CHCl_3$, 53.8 % *ee*) {ref.[5] $[\alpha]_D^{24}$ = +21.9 (*c* = 1.18 in $CHCl_3$, 93 % *ee*)}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.19 (s, 9 H, $SiMe_3$), 1.87 (s, 3 H), 7.27−7.57 (m, 5 H) ppm. GC [Varian, CP-Chirasil Dex CB (0.25 × 25 m), column temperature = 100 °C (isothermal), injector temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 5.516 × 10^4 Pa]: t_r[minor, (*S*)] = 24.87 min, t_r[major, (*R*)] = 25.87 min.

2-Naphthyl-2-(trimethylsilyloxy)propionitrile (8b): The title compound **8b** (33.4 mg, 73 %) was obtained as white crystals. $[\alpha]_D^{24}$ = +7.5 (*c* = 0.59 in $CHCl_3$, 69 % *ee*).[5] ^1H NMR (300 MHz, $CDCl_3$): δ = 0.22 (s, 9 H, $SiMe_3$), 1.97 (s, 3 H), 7.20−7.67 (s, 3 H), 7.92 (m, 3 H), 8.07 (s, 1 H) ppm. HPLC (Chiralcel OJ, *i*PrOH/hexane = 1:99, flow = 1.0 mL/min): t_r[major, (*R*)] = 5.40 min, t_r[minor, (*S*)] = 6.52 min.

2-Methyl-4-phenyl-2-(trimethylsilyloxy)but-3-enenitrile (8c): The title compound **8c** (32.1 mg, 77 %) was obtained as a colorless oil. $[\alpha]_D^{26}$ = +12.5 (*c* = 0.54 in $CHCl_3$, 25 % *ee*).[9] ^1H NMR (300 MHz, $CDCl_3$): δ = 0.27 (s, 9 H, $SiMe_3$), 1.77 (s, 3 H), 6.15 (d, *J* = 15.9 Hz, 1 H), 6.91 (d, *J* = 15.9 Hz, 1 H), 7.28−7.45 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.71, 30.83, 69.92, 120.63, 126.84, 128.54, 128.71, 129.47, 130.90, 135.06 ppm. HPLC (Chiralcel OD, *i*PrOH/hexane = 1:99, flow = 1.0 mL/min): t_r[minor, (*S*)] = 8.79 min, t_r[major, (*R*)] = 9.99 min.

2-Methyl-4-phenyl-2-(trimethylsilyloxy)butanenitrile (8d): The title compound **8d** (36.7 mg, 87 %) was obtained as a colorless oil. $[\alpha]_D^{24}$ = +7.7 (*c* = 0.39 in $CHCl_3$, 68 % *ee*).[9] ^1H NMR (300 MHz, $CDCl_3$): δ = 0.28 (s, 9 H, $SiMe_3$), 1.65 (s, 3 H), 2.06 (m, 2 H), 2.85 (m, 2 H), 7.22−7.33 (m, 5 H) ppm. HPLC (Chiralcel OD, *i*PrOH/hexane = 1:99, flow = 1.0 mL/min): t_r[minor, (*S*)] = 5.49 min, t_r[major, (*R*)] = 6.65 min.

2-(Trimethylsilyloxy)-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (8e): The title compound **8e** (25.4 mg, 61 %) was obtained as a colorless oil. $[\alpha]_D^{26}$ = +4.6 (*c* = 0.51 in $CHCl_3$, 30 % *ee*). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.24 (s, 9 H, $SiMe_3$), 2.06 (m, 2 H), 2.23 (m, 1 H), 2.35 (m, 1 H), 2.85 (m, 2 H), 7.13 (m, 1 H), 7.29 (m, 2 H), 7.67 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.27, 18.62, 28.25, 67.64, 69.79, 122.03, 126.55, 127.94, 128.98, 129.19, 135.59, 136.03 ppm. $C_{14}H_{19}NOSi$ (245.4): calcd. C 68.52, H 7.80, N 5.71; found C 68.30, H 7.70, N 6.11.GC [Varian, CP-Chirasil Dex CB (0.25 × 25 m), column temperature = 124 °C (isothermal), injector temperature = 200 °C, detector temperature = 250 °C,

inlet pressure = 5.516 × 10^4 Pa]: t_r[major, (*R*)] = 31.47 min, t_r[minor, (*S*)] = 33.53 min.

2-(4′-Methylphenyl)-2-(trimethylsilyloxy)propanenitrile (8f): The title compound **8f** (25.0 mg, 63 %) was obtained as a colorless oil. $[\alpha]_D^{24}$ = +16.7 (*c* = 0.11 in $CHCl_3$, 41 % *ee*).[5] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.18 (s, 9 H, $SiMe_3$), 1.86 (s, 3 H), 2.38 (s, 3 H), 7.20−7.28 (m, 2 H), 7.44 (m, 2 H) ppm. GC [Varian, CP-Chirasil Dex CB (0.25 × 25 m), column temperature = 105 °C (isothermal), injector temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 5.516 × 10^4 Pa]: t_r[minor, (*S*)] = 38.67 min, t_r[major, (*R*)] = 39.53 min.

2-(3′-Chlorophenyl)-2-(trimethylsilyloxy)propanenitrile (8g): The title compound **8g** (32.8 mg, 76 %) was obtained as a colorless oil. $[\alpha]_D^{26}$ = +7.1 (*c* = 0.34 in $CHCl_3$, 33 % *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 (s, 9 H, $SiMe_3$), 1.86 (s, 3 H), 7.34−7.55 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.97, 33.41, 70.90, 121.03, 122.73, 124.84, 128.76, 129.83, 134.60, 144.05 ppm. $C_{12}ClH_{16}NOSi$ (421.0): calcd. C 56.79, H 6.35, N 5.52; found C 56.61, H 6.39, N 5.90. GC [Varian, CP-Chirasil Dex CB (0.25 × 25 m), column temperature = 120 °C (isothermal), injector temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 5.516 × 10^4 Pa]: t_r[minor, (*S*)] = 38.07 min, t_r[major, (*R*)] = 39.00 min.

2-(2′-Fluorophenyl)-2-(trimethylsilyloxy)propanenitrile (8h): The title compound **8h** (18.9 mg, 47 %) was obtained as a colorless oil. $[\alpha]_D^{24}$ = +9.1 (*c* = 0.10 in $CHCl_3$, 55 % *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.27 (s, 9 H, $SiMe_3$), 1.96 (s, 3 H), 7.11−7.22 (m, 2 H), 7.36 (m, 1 H), 7.60 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.0, 30.8, 68.4, 116.5, 120.6, 124.2, 126.7, 130.6, 159.4 ppm. GC [Varian, CP-Chirasil Dex CB (0.25 × 25 m), column temperature = 100 °C (isothermal), injector temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 5.516 × 10^4 Pa]: t_r[minor, (*S*)] = 31.47 min, t_r[major, (*R*)] = 32.53 min.

2-(4′-Fluorophenyl)-2-(trimethylsilyloxy)propanenitrile (8i): The title compound **8i** (27.0 mg, 67 %) was obtained as a colorless oil (33 % *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 9 H, $SiMe_3$), 1.86 (s, 3 H), 7.09 (m, 2 H), 7.54 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.0, 33.5, 71.0, 115.6, 121.4, 126.5, 138.0, 162.2 ppm. GC [Varian, CP-Chirasil Dex CB (0.25 × 25 m), column temperature = 100 °C (isothermal), injector temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 5.516 × 10^4 Pa]: t_r[minor, (*S*)] = 28.67 min, t_r[major, (*R*)] = 31.00 min.

2-(Trimethylsilyloxy)-1,2,3,4-tetrahydronaphthane-2-carbonitrile (8j): The title compound **8j** (31.0 mg, 74 %) was obtained as a colorless oil (26 % *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.28 (s, 9 H, $SiMe_3$), 2.00−2.30 (m, 2 H), 3.02−3.15 (m, 3 H), 3.34 (d, *J* = 16.5 Hz, 1 H), 7.05−7.28 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.26, 26.05, 35.58, 42.85, 68.39, 121.50, 126.20, 126.65, 128.53, 129.05, 131.19, 133.80, 131.19 ppm. GC [Varian, CP-Chirasil Dex CB (0.25 × 25 m), column temperature = 124 °C (isothermal), injector temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 5.516 × 10^4 Pa]: t_r[major, (*R*)] = 27.87 min, t_r[minor, (*S*)] = 29.93 min.

2-(Thien-2-yl)-2-(trimethylsilyloxy)propanenitrile (8k): The title compound **8k** (10.6 mg, 34.6 %) was obtained as a colorless oil (20 % *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 9 H, $SiMe_3$), 2.00 (s, 3 H), 7.00 (m, 1 H), 7.21−7.34 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.78, 33.40, 68.24, 120.82, 124.70, 125.97, 126.61, 146.27 ppm. $C_{10}H_{15}NOSSi$ (225.4): calcd. C 53.29, H 6.71, N 6.21; found C 53.48, H 6.94, N 6.43. GC [Varian, CP-Chirasil Dex CB (0.25 × 25 m), column temperature = 80 °C (isothermal), injector temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 5.516 × 10^4 Pa]: t_r[minor, (*S*)] = 27.33 min, t_r[major, (*R*)] = 29.27 min.

Acknowledgments

The authors are grateful to the National Science Foundation of China (nos. 20390050 and 20225206) and the Ministry of Education, P. R. China for the financial support.

[1] [1a] E. J. Corey, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. [1b] M. Kitamura, S. Suga, M. Niwa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842. [1c] M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236−1256. [1d] Y. S. Kim, S. Matsumaga, J. Das, A. Sekine, T. Oshima, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6506−6507 and references therein. [1e] M. P. Gample, A. R. C. Smith, M. Wills, *J. Org. Chem.* **1998**, *63*, 6068−6071. [1f] M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc.* **2000**, *122*, 1466−1478 and references therein. [1g] B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004. [1h] B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573−575 and references therein.

[2] [2a] M. Sawamura, Y. Ito, *Chem. Rev.* **1992**, *92*, 857−871. [2b] E. K. Van den Beuken, B. L. Feringa, *Tetrahedron* **1998**, *54*, 12985−13011. [2c] G. J. Rowlands, *Tetrahedron* **2001**, *57*, 1865−1882. [2d] T. Nemoto, T. Ohshima, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2725−2732. [2e] H. Steinhagen, G. Helmchen, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2339−2342.

[3] [3a] Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 2641−2642. [3b] Y. Hamashima, D. Sawada, H. Nogami, M. Kanai, M. Shibasaki, *Tetrahedron* **2001**, *57*, 805−814.

[4] M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2000**, *39*, 1650−1652.

[5] [5a] Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413. [5b] Y. Hamashima, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 691−693.

[6] M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327−6328.

[7] [7a] B. Liu, X.-M. Feng, F.-X. Chen, G.-L. Zhang, X. Cui, Y.-Z. Jiang, *Synlett* **2001**, 1551−1554. [7b] Z.-G. Jiao, X.-M. Feng, B. Liu, F.-X. Chen, G.-L. Zhang, Y.-Z. Jiang, *Eur. J. Org. Chem.* **2003**, 3818−3826.

[8] [8a] Y.-C. Shen, X.-M. Feng, Y. Li, G.-L. Zhang, Y.-Z. Jiang, *Synlett* **2002**, 793−795. [8b] Y.-C. Shen, X.-M. Feng, G.-L. Zhang, Y.-Z. Jiang, *Synlett* **2002**, 1353−1355. [8c] Y.-C. Shen, X.-M. Feng, Y. Li, G.-L. Zhang, Y.-Z. Jiang, *Tetrahedron* **2003**, *59*, 5667−5675.

[9] H.-B. Deng, P. M. Isler, M. L. Snapper, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2002**, *41*, 1009−1012.

[10] I. A. O'Neil, C. D. Turner, S. B. Kalindjian, *Synlett* **1997**, 777−779.

[11] G. Chelucci, M. Falorni, G. Giacomelli, *Tetrahedron: Asymmetry* **1990**, *1*, 843−849.

[12] I. A. O'Neil, N. D. Miller, J. V. Barkley, M. R. Low, S. B. Kalindjian, *Synlett* **1995**, 619−621.

Received July 4, 2003

