FULL PAPERS

Enantioselective Cyanosilylation of Ketones Catalyzed by a Nitrogen-Containing Bifunctional Catalyst

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Abstract: An efficient and optically active, bifunctional tetraaza ligand (2S)-N-{(1R,2R)-2-[(S)-pyrrolidine-2-carboxamido]-1,2-diphenylethyl}pyrrolidine-2-carboxamide has been developed for the addition of trimethylsilyl cyanide (TMSCN) to ketones. The bifunctional catalyst system based on a monometallic titanium complex was found to be a highly enantioselective catalyst to provide O-TMS cyanohydrins with up to 94% ee. A possible transition state has been proposed to explain the origin of the activation and asymmetric inductivity.

Keywords: amides; bifunctional catalysts; cyanosilylation; hypervalent silicon; ketones; titanium

Introduction

The addition of TMSCN to ketones is one of the most popular strategies to afford versatile cyanohydrin trimethylsilyl ether intermediates in organic synthesis,[1,2] which can be conveniently converted into various important polyfunctionalized building blocks, including α-hydroxy carbonyl compounds and β-amino alcohols for the synthesis of many natural products and bioactive molecules.[2a] In recent years, a variety of Lewis acids and Lewis bases have been employed successfully as promoters in the cyanosilylation of carbonyl compounds and significant advances in this area have been made.[3] As methodologies for promoting the catalytic cyanosilylation of ketones, Snapper and Hoveyda's peptide-Al catalysis,[3d] Jacobsen's thiourea catalysis,[3n] and Feng's double-activation and amino acid salt catalysis[3j,o] provided particular and efficient synthetic strategies for the construction of chiral quaternary carbon centers.

In searching for new methodology, a lot of chiral bifunctional catalysts that tried to imitate natural enzymatic processes have been designed in asymmetric synthesis.[4] At least, these catalysts must contain an acid center and a basic functional group capable of simultaneously binding a basic substrate and an acidic reactant in a proper manner. Shibasaki et al. have reported a series of bifunctional catalysts derived from BINOL and natural glucose as the chiral scaffolds. Particularly, the catalysts with a phosphine oxide moiety were very efficient for the asymmetric cyanosilylation of aldehydes,[5] imines,[6] and ketones,[3b,c] as well as the addition of cyanide to quinoline or isoquinoline derivatives.[7] Other nitrogen-containing bifunctional catalysts (**A** and **B**) have also been discovered (Figure 1),[8] which could be used for the efficient enantioselective cyanosilylation of aldehydes by basic amines simultaneously activating TMSCN. Recently we reported that chiral N-oxides can effectively catalyze the asymmetric cyanosilylation of imines[9] and aldehydes[10] by activating TMSCN and chiral N-oxide titanium complexes can also effectively and dually catalyze the cyanosilylation of ketones.[3e,f,g,i]

A: R = Et (ref.[8a])
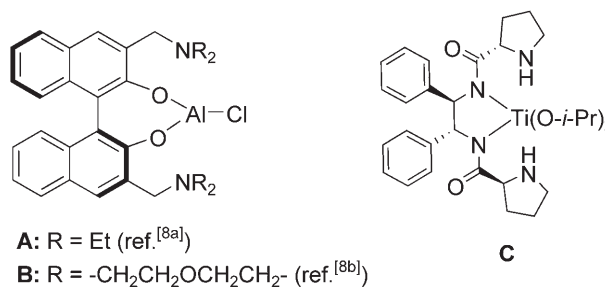**B:** R = -CH₂CH₂OCH₂CH₂- (ref.[8b])

C

Figure 1. Structures of nitrogen-containing bifunctional catalysts.

Inspired by this pioneering work and our early results on asymmetric cyanosilylation using chiral bifunctional catalysts and in order to developing new catalyst systems for the addition of cyanide to ketones, we initiated a study to synthesize an efficient asymmetric amine-titanium complex **C**, structurally similar to complex **A** and **B**, as a bifunctional catalyst. It is well known that, compared to aldehydes, the lower reactivity and greater steric hindrance of ketones delay the asymmetric synthesis of tertiary cyanohydrins.[11] Moreover, the bifunctional ligand **1a** only required a two-step synthesis to give a higher yield from commercially available materials. Herein, we report its simple synthesis and its successful application in cyanohydrin synthesis.

Results and Discussion

Optimization of the Catalyst

Building on the understanding of chiral tetraaza ligands in asymmetric catalysis,[12] complexes of different metals with **1a** were used to catalyze the cyanosilylation of acetophenone as the model reaction. The results are summarized in Table 1. Ti(O-i-Pr)$_4$ gave better enantioselective inductivity than other Lewis acids. Although YbCl$_3$ · 6 H$_2$O exhibited excellent chemical efficiency, the enantioselectivity was poor (Table 1, entry 2). Ti(O-n-Bu)$_4$ could attain almost equal enantioselectivity but with

lower yield (Table 1, entry 8). Thus Ti(O-i-Pr)$_4$ was chosen to assess the following ligands.

The different diamine derivatives (**1a–h** and **2a–e**) (Figure 2) were examined, with the results listed in Table 2. The data suggested that the face selectivities of reactions depended on the configuration of the chiral diamine moiety X, R, S of X corresponding to S and R of products, respectively (Table 2, entries 1–6). The ligand containing a thiazolidine ring (**2a**) or substituted at the 4′- and 5′-positions of the pyrrolidine ring (**2b**) had a negative effect on the ee value (Table 2, entries 9 and 10). Ligands **2c**, **2d** and **2e** which contain piperidine rings or primary amine gave poor enantioselectivities (Table 2, entries 11, 12 and 13). The ligand **1a** containing a simple pyrrolidine ring was beneficial to the enantioselectivity (Table 2, entry 1).

Table 1. Asymmetric cyanosilylation of acetophenone catalyzed by Lewis acids.

Entry[a]	Lewis acids	t [h]	Yield [%][b]	ee [%][c]
1	Ti(O-i-Pr)$_4$	60	74 (69) [d]	51 (S) (38)[d]
2	YbCl$_3$ · 6 H$_2$O	60	92	1 (S)
3	AlEt$_3$	60	48	1 (S)
4	AlEt$_2$Cl	60	41	6 (S)
5	Al(O-i-Pr)$_3$	60	Trace	10 (S)
6	Zr(O-i-Pr)$_4$	60	33	8 (S)
7	TiCl$_4$	60	–	–
8	Ti(O-n-Bu)$_4$	60	18	49 (S)

[a] All reactions were carried out at 0 °C under the following condition: 0.2 M acetophenone, 20 mol % **1a** · indicated metal complex, 1.5 equivs. TMSCN in CH$_2$Cl$_2$.

[b] Isolated yield of O-TMS cyanohydrin was determined after column chromatography on silica gel.

[c] Determined by GC analysis on Chirasil DEX CB. The absolute configuration was established as S by comparison of the sign of the optical rotation value with that in the literature (ref.[3b]).

[d] After the mixture of ligand **1a** and Ti(O-i-Pr)$_4$ in CH$_2$Cl$_2$ which had been stirred for 40 min at room temperature, the solvent was not removed under vacuum.

1a: X = (1R, 2R)

1b: X = (1S, 2S)

1c: X = (1R, 2R)

1d: X = (1S, 2S)

1e: X = R

1f: X = S

1g: X =

1h: X =

2a: Y =

2b: Y =

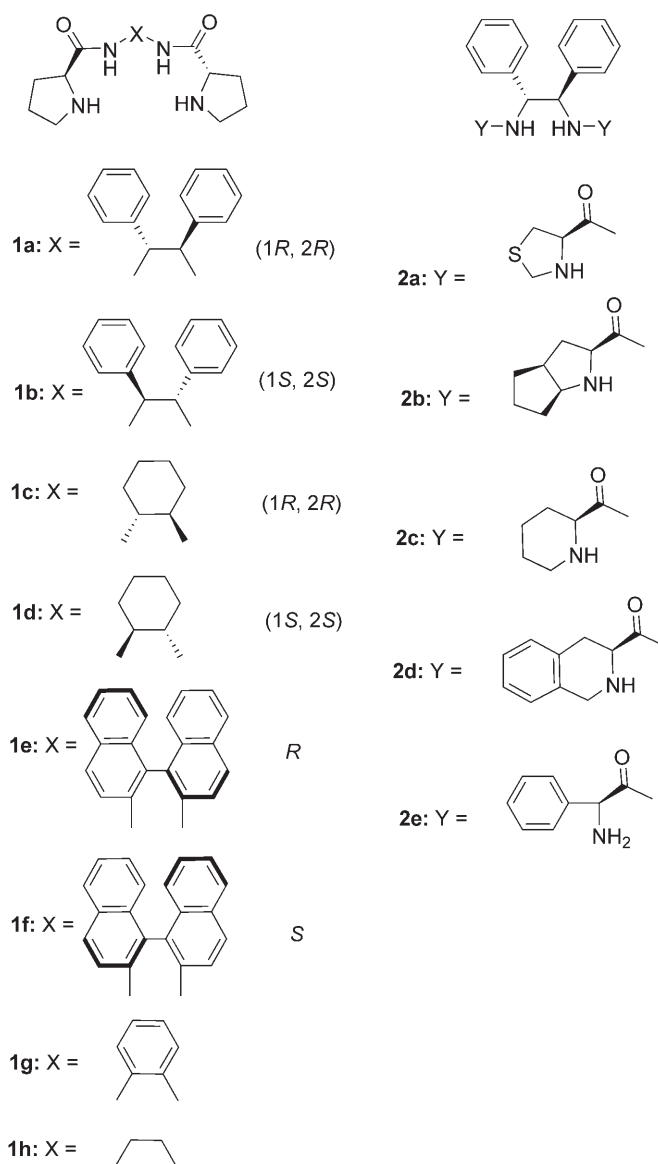**2c:** Y =

2d: Y =

2e: Y =

Figure 2. Ligands evaluated in this study.

Table 2. Effect of the ligand structure on the yield and enantioselectivity.

Entry[a]	Ligand	t [h]	Yield [%][b]	ee [%][c]
1	**1a**	60	74	51 *(S)*
2	**1b**	60	46	30 *(R)*
3	**1c**	60	81	50 *(S)*
4	**1d**	60	74	49 *(R)*
5	**1e**	60	34	16 *(S)*
6	**1f**	60	47	33 *(R)*
7	**1g**	60	26	30 *(S)*
8	**1h**	60	61	6 *(S)*
9	**2a**	60	9	19 *(S)*
10	**2b**	60	23	35 *(S)*
11	**2c**	60	25	17 *(S)*
12	**2d**	60	32	31 *(S)*
13	**2e**	60	27	21 *(S)*

[a] All reactions were carried out at $0\,^{\circ}$C under the following condition: 0.2 M acetophenone, 20 mol % indicated ligand·Ti(O-i-Pr)$_4$ complex, 1.5 equivs. TMSCN in CH$_2$Cl$_2$.
[b] Isolated yield of *O*-TMS cyanohydrin was determined after column chromatography on silica gel.
[c] Determined by GC analysis on Chirasil DEX CB. The absolute configuration was established as *S* by comparison of the sign of the optical rotation value with that in the literature (ref.[3b]).

To obtain the optimal reaction conditions, solvent effect, reaction temperature and the catalyst loading were studied, with the results summarized in Table 3. The use of polar solvents such as Et$_2$O and THF reduced the enantioselectivities (Table 3, entries 2 and 3). In moderately polar solvents, CH$_2$Cl$_2$ and CH$_2$ClCH$_2$Cl, this

transformation proceeded with comparable enantioselectivities, but the reaction rate was higher in CH$_2$Cl$_2$ (Table 3, entries 4 and 8). The reactions in toluene and under solvent-free conditions gave higher yields, but the ee values were lower (Table 3, entries 1 and 5). No reaction was observed in the protic solvent CH$_3$OH (Table 3, entry 6). Temperature clearly affected the enantioselectivity. The optimum enantioselectivity of 80% ee was obtained on decreasing the temperature from 20 to $-45\,^{\circ}$C (Table 3, entries 7–10). Further decreasing the reaction temperature increased the enantioselectivity up to 90% ee, but the yield was greatly reduced (Table 3, entry 16). The catalyst loading dramatically influenced the enantioselectivity: 30 mol % of catalyst loading was superior to lower loading in terms of catalyst efficiency (Table 3, entry 13 *vs.* 11 and 12). The further increasing catalyst loading to 40 mol % gave lower ee values (Table 3, entry 15). The practical level of catalyst loading for this reaction was 30 mol %. The lower isolated yield could be overcome to some extent by prolonging the reaction time and increasing the amount of TMSCN and fortunately the enantioselectivity was retained (Table 3, entry 14 *vs.* 13).

Substrate Generality

After establishing the optimal reaction conditions, we investigated a wide range of ketones. As depicted in Table 4, aromatic, bulky cyclic, heterocyclic, α,β-unsaturated and aliphatic ketones were converted into the corresponding *O*-TMS ethers of cyanohydrins with up to

Table 3. Asymmetric cyanosilylation of acetophenone catalyzed by **1a**·Ti(O-i-Pr)$_4$ complex under various conditions.

Entry	Solvent	T [$^{\circ}$C]	t [h]	TMSCN [equivs.]	Concentration of acetophenone [mol/L]	Catalyst loading [mol %]	Yield [%][a]	ee [%][b]
1	None	0	60	1.5	0.2	20	86	31 *(S)*
2	Et$_2$O	0	60	1.5	0.2	20	46	12 *(R)*
3	THF	0	60	1.5	0.2	20	65	19 *(S)*
4	CH$_2$ClCH$_2$Cl	0	60	1.5	0.2	20	65	48 *(S)*
5	toluene	0	60	1.5	0.2	20	78	37 *(S)*
6	CH$_3$OH	0	60	1.5	0.2	20	–	–
7	CH$_2$Cl$_2$	20	60	1.5	0.2	20	59	12 *(S)*
8	CH$_2$Cl$_2$	0	60	1.5	0.2	20	74	51 *(S)*
9	CH$_2$Cl$_2$	-20	60	1.5	0.2	20	50	68 *(S)*
10	CH$_2$Cl$_2$	-45	60	1.5	0.2	20	45	80 *(S)*
11	CH$_2$Cl$_2$	-45	60	2.5	2.0	10	15	81 *(S)*
12	CH$_2$Cl$_2$	-45	60	2.5	2.0	20	62	82 *(S)*
13	CH$_2$Cl$_2$	-45	60	2.5	2.0	30	56	92 *(S)*
14	CH$_2$Cl$_2$	-45	100	2.5	2.0	30	77	92 *(S)*
15	CH$_2$Cl$_2$	-45	60	2.5	2.0	40	48	76 *(S)*
16	CH$_2$Cl$_2$	-78	60	1.5	0.2	20	9	90 *(S)*

[a] Isolated yield of *O*-TMS cyanohydrin was determined after column chromatography on silica gel.
[b] Determined by GC analysis on Chirasil DEX CB. The absolute configuration was established as *S* by comparison of the sign of the optical rotation value with that in the literature (ref.[3b]).

Table 4. Enantioselectivity cyanosilylation of ketones catalyzed by **1a**·Ti(O-i-Pr)$_4$ complex.

Entry[a]	Ketone	3	Yield [%][b]	ee [%][c]
1	Acetophenone	**3a**	77	92[d]
2	4′-Methylacetophenone	**3b**	60	90
3	4′-Methoxyacetophenone	**3c**	48	94[e]
4	β-Acetonaphthone	**3d**	72	88[f]
5	1-Indanone	**3e**	66	92
6	α-Tetralone	**3f**	63	87
7	4′-Chloroacetophenone	**3g**	82	74
8	3′-Chloroacetophenone	**3h**	90	61
9	4′-Fluoroacetophenone	**3i**	61	83
10	3′-Fluoroacetophenone	**3j**	87	66
11	2-Acetylthiophene	**3k**	56	88
12	*trans*-4-Phenyl-3-buten-2-one	**3l**	65	64[g]
13	2-Heptanone	**3m**	89	51[d]
14	Benzylacetone	**3n**	84	51

[a] *Conditions:* **1a**·Ti(O-i-Pr)$_4$ complex (1:1, 30 mol %), 100 h, TMSCN (2.5 equivs.), $-45\,°$C, [ketone] = 2.0 M in CH$_2$Cl$_2$.
[b] Isolated yield of *O*-TMS cyanohydrin was determined after column chromatography on silica gel.
[c] Determined by GC analysis on Chirasil DEX CB.
[d] The absolute configurations were established as *S* by comparison the reported value of optical rotation (ref.[3b]).
[e] The absolute configuration was established as *S* by comparison with the reported value of optical rotation (ref.[3m]).
[f] Determined by HPLC analysis on Chiralpak OJ.
[g] Determined by HPLC analysis on Chiralpak OD.

90% yield and up to 94% ee. Introducing electron-donating groups on the *para*-position of acetophenone led to lower yields but similar enantioselectivities to acetophenone (Table 4, entries 2 and 3). Aromatic and steric cyclic ketones such as β-acetonaphthone, 1-indanone and α-tetralone afforded moderate yields and excellent enantioselectivities (Table 4, entries 4–6). The chloro-substituted ketones gave higher yields and moderate enantioselectivities, and the fluoro-substituted ones also provided moderate ee values (Table 4, entries 7–10). The reaction of 1-(thiophen-2-yl)ethanone proceeded in moderate yield and high enantioselectivity (Table 4, entry 11). The α,β-unsaturated ketone gave the corresponding product with moderate chemical yield and ee value (Table 4, entry 12). The aliphatic ketones provided relatively low enantioselectivities with good yields (Table 4, entries 13 and 14). Of practical relevance, the chiral ligand **1a** could be partly recovered in 62% yield, after column chromatography to give *O*-TMS cyanohydrins, by simple aqueous acid/base work-up on silica gel and reused (see Experimental Section).

Mechanism

Because of the similarity between **1a** and the *N,N′*-[(1*R*,2*R*)-cyclohexane-1,2-diyl]bis(trifluoromethanesulfonamide) reported[13] (see Figure 3) we considered

here that in the presence of an equivalent amount of titanium tetraisopropoxide two nitrogen atoms on amide groups probably formed N—Ti bonds with Ti(O-i-Pr)$_4$. Thus, a possible dual activation mechanism was proposed (Figure 4), in which the acidic titanium activated the ketone as a Lewis acid and the basic nitrogen atom of one of the pyrrolidinyl groups activated TMSCN as a Lewis base, respectively. Hypervalent silicon,[14] formed from an interaction between the amine group and TMSCN, was assumed to be an active cyanation intermediate which readily reacts with acetophenone to produce **4a** since the nucleophilicity of the cyano group was enhanced by the electron donation from the hypervalent silicon.

On the basis of the observed absolute configuration of 2-phenyl-2-trimethylsilanyloxypropionitrile (Table 4, entry 1), we proposed a possible asymmetric inductivity pathway including transition state **5**. In transition state **5**, the *Re* face of the carbonyl of acetophenone is much
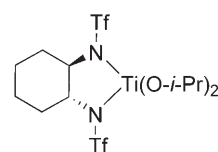

Figure 3. The complex of *N,N′*-[(1*R*,2*R*)-cyclohexane-1,2-diyl]bis(trifluoromethanesulfonamide) and Ti(O-i-Pr)$_4$.
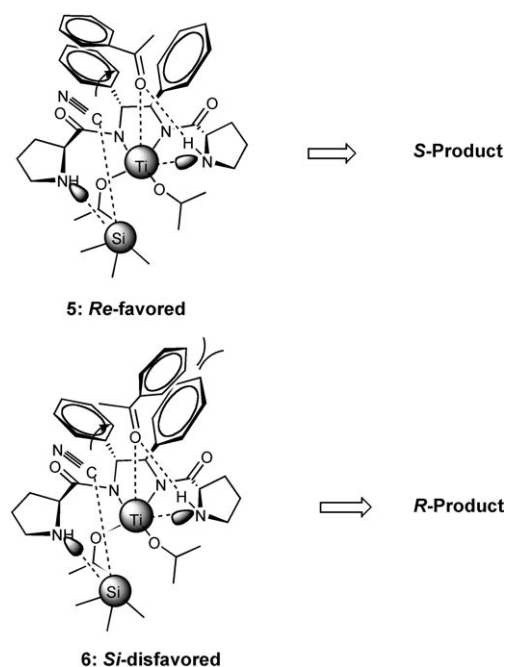
Figure 4. The proposed working model.

more accessible to a nucleophilic group CN than the *Si* face since the interaction of the *Si* face and the attacking group CN will strongly increase the repulsion between phenyl subunits as in transition state **6**. *S*-Proline is also vital to enantioselective inductivity, which causes a fit concave to define the position of the coordinated ketone at the *Re* face *syn* to the Lewis basic amine group of pyrrolidine. The activated nucleophile will attack the highly polarized C=O of acetophenone at the carbon atom from a less stereohindered direction (*Re*) to give the *S*-configuration product.

Meanwhile, preliminary studies in which the **1a**·Ti(O-*i*-Pr)$_4$ complex showed relatively low enantioselectivities for aliphatic ketones (Table 4, entries 13, 14) suggested that the existence of a weak π-π stacking interaction[15] between the aromatic ketones and (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine moiety should play a key role in the transition state of cyanation. Taking advantage of the detailed studies on the hypervalent silicon intermediate, we found that transition state **6** is less favorable because of steric repulsion and low overlap of π-π stacking resulting from the larger dihedral angle between the bulky phenyl groups. On the other hand, **5** avoids this repulsion and shows adequate π-π interaction to eventually give (*S*)-**4a**

Conclusion

In summary, the new development here is that the bifunctional catalyst used in this work is more easily accessible. The optimal ligand **1a** only requires a simple two-

step synthesis to give an excellent yield and its starting materials are commercially available. Using the bifunctional catalyst **1a**·Ti(O-*i*-Pr)$_4$ complex, we have carried out a logical development process to obtain a highly enantioselective cyanosilylation of ketones with up to 94% ee. This contribution should provide a simple and practical synthetic strategy for the construction of chiral quaternary carbon centers. Further efforts should be devoted to the optimization of the catalyst to enhance enantioselectivity and reactivity, and clarify the mechanism of this reaction.

Experimental Section

General Remarks

NMR data were obtained for ^{1}H at 300, 400 and 600 MHz, and for ^{13}C at 75 and 100 MHz. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in CDCl$_3$ solution. Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (*J*) in Hz, integration and assignment. HR-MS were recorded on a Bruker Apex-2. In each case, enantiomer ratios were determined by chiral GC analysis or chiral HPLC analysis on Chiralcel OD or OJ in comparison with authentic racemates. Optical rotation data were examined in CH$_2$Cl$_2$ solutions. Amino acids and diamines obtained from commercial sources were used directly without further purification. All ketones, TMSCN, Ti(O-*i*-Pr)$_4$ and solvents were purified by usual methods.

Preparation of Tetraaza Ligands

The ligands **1a–h** and **2a–e** listed in Figure 2 were prepared according to similar procedures (Scheme 1).
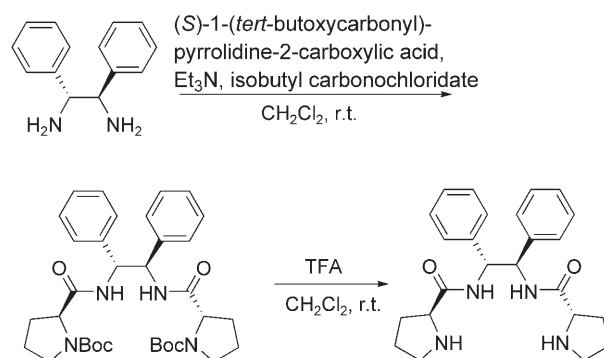
Scheme 1. The two-step synthesis of the ligand **1a**.

[C$_{24}$H$_{30}$N$_4$O$_2$] (1a)

(1) To a solution of (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (430.5 mg, 2.0 mmol) in CH$_2$Cl$_2$, triethylamine (0.31 mL, 2.2 mmol) and isobutyl carbonochloridate (0.26 mL,

2.0 mmol) were added at 0 °C under stirring. After 15 min, (1R,2R)-1,2-diphenylethane-1,2-diamine (212.3 mg, 1 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 4 h. The mixture was washed with 1 M $KHSO_4$, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated.

(2) To the residue in CH_2Cl_2, TFA (2.0 mL) was added and stirring was continued for an hour. Then the solution was concentrated under vacuum to leave a glutinous phase to which H_2O (4 mL) was added. The pH of the mixture was brought into the range of ~12 by the addition of 2 M NaOH. The aqueous phase was extracted with ethyl acetate. The ethyl acetate extracts were pooled, washed with brine, dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by flash chromatography using MeOH/EtOAc (1:2, v/v) as eluent to afford (2S)-N-{(1R,2R)-2-[(S)-pyrrolidine-2-carboxamido]-1,2-diphenylethyl}pyrrolidine-2-carboxamide (**1a**) as a white solid; yield: 374.0 mg (92%).

Optically Active Cyanohydrin Trimethylsilyl Ethers 4; Typical for the Addition of TMSCN to Acetopheone

To a solution of **1a** (24.4 mg, 0.06 mmol) in CH_2Cl_2 (0.6 mL) was added Ti(O-i-Pr)$_4$ (1 M in toluene, 60 μL, 0.06 mmol) at room temperature under an N_2 atmosphere. After the mixture had been stirred for 40 min, the solvent was removed under vacuum. This catalyst was then dissolved in CH_2Cl_2 (0.1 mL). To this solution, acetophenone (24.2 μL, 0.2 mmol) was added at −45 °C, followed by the addition of TMSCN (68.2 μL, 0.5 mmol). The reaction was monitored by TLC. After 100 h, the mixture was concentrated and then purified by flash silica gel chromatography using diethyl ether/petroleum ether (1:100 v/v) as the eluent to obtain the corresponding cyanohydrin trimethylsilyl ether **4a**; yield: 77%; 92% ee.

To recover the chiral ligand, the silica gel in the column was transferred to a flask equipped with a stirrer. Water (10 mL) and 1 M HCl (2 mL) were added, stirring was continued for about 30 min and the mixture filtered. A solution of 2 M NaOH was added dropwise to the filtrate, cooled in an ice-water bath, until pH~ 12. The mixture was extracted with ethyl acetate. The ethyl acetate extracts were pooled, washed with brine, dried over anhydrous Na_2SO_4 and evaporated under vacuum to afford chemically and optically pure **1a** (15.1 mg, 62% recovered).

Acknowledgements

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