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Highly enantioselective cyanosilylation of ketones catalyzed by a bifunctional Ti(IV) complex

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Abstract

A bifunctional catalyst system composed of (*S*)-prolinamide (**2a**), titanium(IV) isopropoxide, and phenolic *N*-oxide (**3f**) exhibited high catalytic efficiency in the enantioselective cyanosilylation of ketones. In the presence of 2.5 mol % catalyst, a variety of aromatic and aliphatic ketones were converted into the corresponding tertiary cyanohydrin *O*-TMS ethers in excellent yields (up to 96%) and high enantioselectivities (up to 96% ee). A proposed catalytic cycle was illustrated to explain the origin of the asymmetric induction.

Keywords: Bifunctional catalysis; Cyanosilylation; Ketone; Titanium

1. Introduction

The cyanosilylation of ketones is one of the most popular strategies to afford tertiary cyanohydrins which can be easily converted into versatile biologically active molecules and natural products.[1,2a,14b] Many synthetic methods have been developed to accomplish the asymmetric cyanosilylation of ketones successfully.[2] The majority of chiral catalysts used in this reaction are chiral metal complexes,[3–9a] cinchona alkaloid catalysts,[10] chiral oxazaborolidinium ions,[11] thiourea catalysts,[12] and amino acid salts.[13] In recent years, the synergistic activation by the combination of Lewis acids and Lewis bases is remarkable in asymmetric catalysis.[14] This dual activation concept has been successfully applied to the asymmetric addition of TMSCN to ketones, especially by Shibasaki's sugar-derivated bifunctional catalyst[2c,4] and our group's dual activation method.[7] We initiated our study on the asymmetric cyanosilylation of ketones with a bifunctional catalyst, which was composed of chiral ligand with central metal and achiral *N*-oxide. In the process of seeking for the appropriate chiral ligands, we synthesized **2a** structurally similar to **1a**[15] and **1b**[16] (Fig. 1), both of which were efficient ligands in the asymmetric cyanosilylation of aldehydes. Herein, we wish to describe the enantioselective cyanosilylation of ketones catalyzed by a bifunctional **2a**–Ti(IV)–**3f** complex.

2. Results and discussion

2.1. Catalyst survey

A series of chiral ligands **2a–j** and achiral *N*-oxides **3a–i** (Fig. 2) were synthesized according to the reported methods.[7d,9b,17] The catalyst components were screened in the

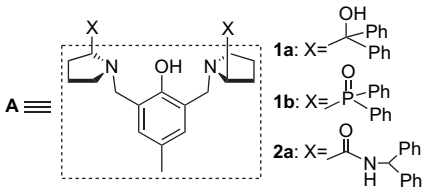

Figure 1. Structures of chiral ligands based on the backbone of **A**.

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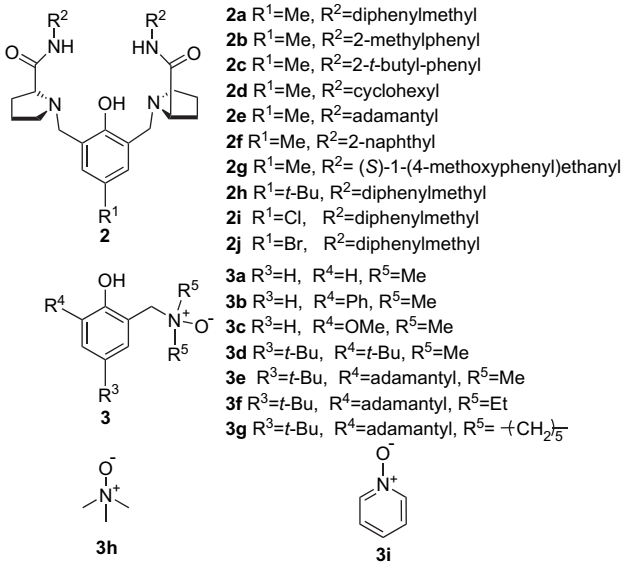
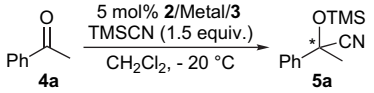


Figure 2. Structures of ligands **2** and *N*-oxides **3**.

asymmetric cyanosilylation of acetophenone **4a** (Table 1). We began our efforts to evaluate the reactivity of **2**–Ti(O^iPr)$_4$ complex. As depicted in entries 1–10 (Table 1), electronic and steric tuning of the ligand was crucial for the reactivity and enantioselectivity. The amide moiety of the ligand had a significant effect on the results (Table 1, entries 1–7). Complex **2a**–Ti(IV) containing diphenylmethylamide moiety gave the best enantioselectivity (Table 1, entry 1). Ligands derived from other amide groups, no matter bulkier ones or the ones of less steric hindrance, only gave inferior asymmetric induction (Table 1, entries 2–7). It was noteworthy that halogen and bulky *tert*-butyl moieties on the phenolic units of the ligands led to decrease in enantioselectivities (Table 1, entries 8–10).

Table 1
Asymmetric cyanosilylation of acetophenone catalyzed by **2**–metal–**3** complex



Entry[a]	Ligand	Central metal	*N*-Oxide	*t* (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	Ti(O^iPr)$_4$	—	48	55	51
2	**2b**	Ti(O^iPr)$_4$	—	48	39	20
3	**2c**	Ti(O^iPr)$_4$	—	48	43	24
4	**2d**	Ti(O^iPr)$_4$	—	48	42	24
5	**2e**	Ti(O^iPr)$_4$	—	48	30	40
6	**2f**	Ti(O^iPr)$_4$	—	48	40	30
7	**2g**	Ti(O^iPr)$_4$	—	48	37	28
8	**2h**	Ti(O^iPr)$_4$	—	48	33	42
9	**2i**	Ti(O^iPr)$_4$	—	48	39	47
10	**2j**	Ti(O^iPr)$_4$	—	48	33	37
11	**2a**	Ti(O^iPr)$_4$	**3a**	12	82	49
12	**2a**	Ti(O^iPr)$_4$	**3b**	12	91	45
13	**2a**	Ti(O^iPr)$_4$	**3c**	12	88	43
14	**2a**	Ti(O^iPr)$_4$	**3d**	12	88	47
15	**2a**	Ti(O^iPr)$_4$	**3e**	12	92	58
16	**2a**	Ti(O^iPr)$_4$	**3f**	12	94	62
17	**2a**	Ti(O^iPr)$_4$	**3g**	12	72	35
18	**2a**	Ti(O^iPr)$_4$	**3h**	12	36	29
19	**2a**	Ti(O^iPr)$_4$	**3i**	12	48	38
20	**2a**	Al(O^iPr)$_3$	**3f**	6	96	29

[a] Conditions: 5 mol % 1igand **2**/indicated central metal/*N*-oxide **3** (1/1/1) was used, concentration of acetophenone was 0.25 M in CH_2Cl_2, TMSCN was 1.5 equiv at −20 °C under the argon atmosphere.
[b] Isolated yield.
[c] Determined by GC on Chirasil DEX CB. The absolute configuration of the major product was *R*, determined by comparison with the reported values of optical rotation (Ref. 12).

Then, **2a**–Ti(O^iPr)$_4$ was chosen to investigate the achiral *N*-oxides **3a**–**i**. This bifunctional catalyst **2a**–Ti(IV)–**3** was prepared in situ (see Section 4 for details). To our delight, the reactivity was greatly improved by the addition of **3a**–**g** under the prescribed condition (Table 1, entries 11–17). A dramatic switching of enantioselectivity was dependent on the structure of *N*-oxides. As shown in entries 12 and 13 (Table 1), a slight erosion in enantioselectivity was observed when **3b** or **3c** was used. This demonstrated that methoxyl or phenyl substitute at *ortho* position of phenolic group was not appropriate. Improvement in the enantioselectivity could be achieved by employing **3e** and **3f**, which could be attributed to the large hindrance of adamantyl (Table 1, entries 15 and 16). 62% ee was obtained with **2a**–Ti(IV)–**3f** complex (Table 1, entry 16). The sharp decrease in enantioselectivity was observed when **3g** was employed, which could be partly due to the less flexible six-membered ring of *N*-oxide moiety (Table 1, entry 17). While simple *N*-oxides with no coordinative phenolic group were used, only poor results were obtained (Table 1, entries 18 and 19). This observation might be explained by the strong binding between Lewis acid and Lewis base resulting in the deterioration of the catalytic capability. It was found that acetophenone was converted into the corresponding product with 29% ee when Ti(O^iPr)$_4$ was replaced by Al(O^iPr)$_3$ (Table 1, entry 20 vs 16). Simultaneously, no product was observed by employing Zr(O^iPr)$_4$ or Zn(OTf)$_2$. Thus, complex **2a**–Ti(IV)–**3f** was the optimal catalyst for further investigation.

2.2. Evaluation of the molar ratio of *2a*, *3f*, and *Ti(O^iPr)$_4$*

The molar ratio of **2a**, **3f**, and Ti(O^iPr)$_4$ was finely tuned to obtain the optimum enantioselectivity. The results are summarized in Table 2. It was clearly showed that the molar ratio of 1/1/1 was crucial for both enantioselectivity and reactivity (Table 2, entry 3). Others only led to lower yields or enantioselectivity (Table 2, entries 1, 2, and 4–6).

2.3. Optimization of reaction conditions

The solvent effect was investigated and the results are listed in Table 3. The reactions proceeded more rapidly in ether solvents (Table 3, entries 1 and 2), but more sluggishly in CH_3CN (Table 3, entry 3). Toluene provided equal enantioselectivity as THF, whereas the reaction rate was lower (Table 3, entry 4 vs 2). Although the transformation proceeded better in Et_2O than in THF at −20 °C, lower temperature led to

Table 2
Effect of the molar ratio of the three components on the yield and enantioselectivity

Entry[a]	Loading of the catalyst (mol %)			Yield[b] (%)	ee[c] (%)
	2a	**3f**	$Ti(O^iPr)_4$		
1	5	2.5	2.5	76	50
2	5	5	2.5	82	57
3	5	5	5	90	62
4	5	5	10	84	52
5	5	10	5	94	60
6	5	10	10	85	55

[a] Conditions: concentration of acetophenone was 0.25 M in CH_2Cl_2, TMSCN was 1.5 equiv at −20 °C for 12 h under the argon atmosphere.
[b] Isolated yield.
[c] Determined by GC on Chirasil DEX CB. The absolute configuration of the major product was *R*, determined by comparison with the reported values of optical rotation (Ref. 12).

a dramatic decrease in reactivity (Table 3, entry 6 vs 1), while remarkable increase of enantioselectivity could be accomplished in THF at −45 °C with 90% yield and 86% ee by prolonging reaction time (Table 3, entry 7 vs 2). Further decreasing the temperature to −78 °C gave very low yield (Table 3, entry 8 vs 7). Hence, THF was the appropriate solvent.

The effect of catalyst loading was screened and the results are listed in Table 4. Increasing catalyst loading had little influence on the enantioselectivity, but it increased the reaction rate to some extent (Table 4, entries 1 and 2). When the catalyst loading was reduced to 1 mol %, the yield decreased to 67% (Table 4, entry 5). Thus the 2.5 mol % catalyst was considered to be the practical amount. The reaction concentration also had effect on the reaction rate and enantioselectivity. When the concentration of acetophenone was increased from 0.25 to 1.0 M, the yield was increased from 89 to 96% and up to 90% ee was achieved (Table 4, entries 6–8 vs 4). Additionally, further increase of the concentration of acetophenone to 1.5 M led to a slight loss of enantioselectivity (Table 4, entry 9). Consequently, the optimal working condition was 2.5 mol % **2a**/$Ti(O^iPr)_4$/**3f** (1/1/1) at the concentration of acetophenone 1.0 M in THF at −45 °C.

Table 3
Solvents evaluation on the asymmetric cyanosilylation of acetophenone

Entry[a]	Solvent	*T* (°C)	*t* (h)	Yield[b] (%)	ee[c] (%)
1	Et_2O	−20	12	99	78
2	THF	−20	12	98	72
3	CH_3CN	−20	12	32	27
4	Toluene	−20	12	75	72
5	CH_2Cl_2	−20	12	63	61
6	Et_2O	−45	48	32	85
7	THF	−45	48	90	86
8	THF	−78	48	15	85

[a] Conditions: reactions were carried out with 5 mol % **2a**/$Ti(O^iPr)_4$/**3f** complex (1/1/1), concentration of acetophenone was 0.25 M in indicated solvent, TMSCN was 1.5 equiv under the argon atmosphere.
[b] Isolated yield.
[c] Determined by Chiral GC analysis on Chirasil DEX CB. The absolute configuration of the product was *R*, determined by comparison with the reported values of optical rotation (Ref. 12).

Table 4
Effects of catalyst loading and concentration of substrate on the asymmetric cyanosilylation of acetophenone

Entry[a]	Catalyst loading (mol %)	Concentration of acetophenone (mol/L)	*t* (h)	Yield[b] (%)	ee[c] (%)
1	10	0.25	30	99	86
2	7.5	0.25	36	93	86
3	5	0.25	48	90	86
4	2.5	0.25	48	89	87
5	1	0.25	60	67	85
6	2.5	0.5	48	90	86
7	2.5	0.75	48	93	87
8	2.5	1	48	96	90
9	2.5	1.5	48	99	88

[a] Conditions: reactions were carried out with **2a**/$Ti(O^iPr)_4$/**3f** complex (1/1/1), in THF at −45 °C, TMSCN was 1.5 equiv under the argon atmosphere.
[b] Isolated yield.
[c] Determined by GC on Chirasil DEX CB. The absolute configuration of the product was *R*, determined by comparison with the reported values of optical rotation (Ref. 12).

2.4. Scope of the substrates

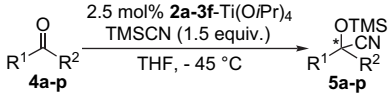
As described in Table 5, **2a**–$Ti(O^iPr)_4$–**3f** was proved to be general for the enantioselective cyanosilylation of a wide range of ketones under the optimized conditions. The *ortho* and *para* fluoro-substituted aromatic ketones gave the same enantioselectivity as acetophenone (Table 5, entries 2 and 3 vs 1). Moreover, 4-chloroacetophenone and 4-methoxyacetophenone were converted into the desired products in 89% ee with 90 and 88% yields, respectively (Table 5, entries 5 and 7). The electronic character of *ortho* or *para* substituent of acetophenone was not crucial for the enantioselectivity (Table 5, entries 2, 3, and 5–7). 3-Chloroacetophenone afforded higher enantioselectivity (Table 5, entry 4 vs 1). When heterocyclic ketone **4h** was subjected to the reaction, up to 92% ee was attained (Table 5, entry 8). Steric bulkier ketones such as β-acetonaphthone and α-tetralone afforded the corresponding cyanohydrin ethers with 96 and 85% ee, respectively (Table 5, entries 9 and 10). α,β-Unsaturated ketone **4k** was well tolerated and gave 1,2-addition product exclusively in 92% yield with 91% ee. Moreover, simple aliphatic and α,β-saturated ketones afforded the desired products in high yields with good enantioselectivities (Table 5, entries 12–16).

2.5. Mechanism investigation

Nonlinear effects in asymmetric synthesis and stereoselective reactions reflect molecular interactions and complexity in reaction mechanism.[18] NLE study manifested that a double-shape curve was apparent from the experimental data in **2a**–$Ti(O^iPr)_4$–**3f** complex catalytic system (Fig. 3). Here, we considered that the different catalyst species including monomeric species (Fig. 4, model **B**), dimeric species (Fig. 4, model **C**), and other higher order species might coexist in the catalytic process. Either **B** or **C** could act as a bifunctional catalyst through a similar dual activation pathway.

Therefore, a simplified asymmetric catalytic cycle with a bifunctional pathway is illustrated in Scheme 1. Tridentate

Table 5
Scope of enantioselective cyanosilylation of ketones



Entry[a]	Ketone **4**		Product **5**	*t* (h)	Yield[b] (%)	ee[c] (%)	Conf.[g]
1		**4a** R=H	**5a**	48	96	90	*R*
2		**4b** R=*o*-F	**5b**	36	93	90	
3		**4c** R=*p*-F	**5c**	36	90	90	
4		**4d** R=*m*-Cl	**5d**	36	93	94	*R*
5		**4e** R=*p*-Cl	**5e**	48	90	89	*R*
6		**4f** R=*p*-Me	**5f**	60	91	86	*R*
7		**4g** R=*p*-OMe	**5g**	60	88	89	*R*
8		**4h**	**5h**	60	78	92	*R*
9		**4i**	**5i**	60	89	96[d]	*R*
10		**4j**	**5j**	60	80	85	
11		**4k**	**5k**	36	92	91[e]	*R*
12		**4l**	**5l**	48	92	89	*R*
13		**4m**	**5m**	36	89	62	
14		**4n**	**5n**	36	95	82	*R*
15		**4o**	**5o**	36	92	75	
16		**4p**	**5p**	36	90	71[f]	*R*

[a] Conditions: reactions were carried out with 0.5 mmol of ketone, 0.75 mmol of TMSCN in 0.5 mL THF for 36–60 h at −45 °C catalyzed by 2.5 mol % **2a**/Ti(O^{i}Pr)$_4$/**3f** (1/1/1) complex under the argon atmosphere.
[b] Isolated yield.
[c] Unless other specified, enantiomeric excess was determined by GC on Chirasil DEX CB.
[d] Determined by HPLC on Chiralcel OJ.
[e] Determined by HPLC on Chiralcel OD.
[f] Determined by HPLC on Chiralcel AD; ee was determined after conversion to the corresponding benzyl carboxylate (Ref. 4a).
[g] The absolute configurations were determined by comparison with the reported values of optical rotation (Refs. 5, 7e, and 12).

ligand **2a** could coordinate with Ti(O^{i}Pr)$_4$ through oxygen atom and two amide moieties, meanwhile, **3f** could assemble with titanium through phenolic group to form **7**. Titanium(IV) could act as a Lewis acid to activate carbonyl group and *N*-oxide moiety could act as Lewis base to activate TMSCN, simultaneously. In transition state **9**, the large steric hindrance

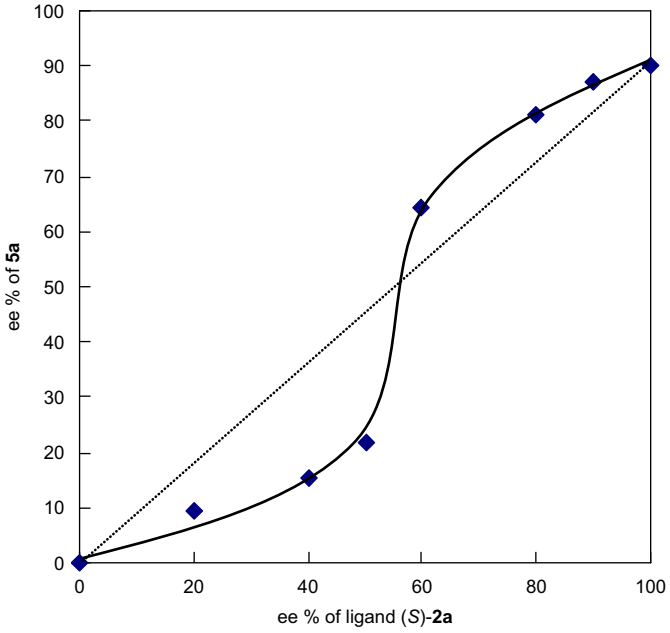


Figure 3. NLE study in the asymmetric cyanosilylation of acetophenone catalyzed by **2a**–Ti(O^{i}Pr)$_4$–**3f**.

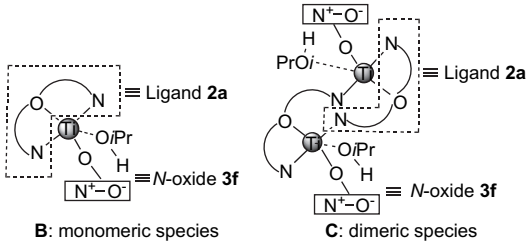
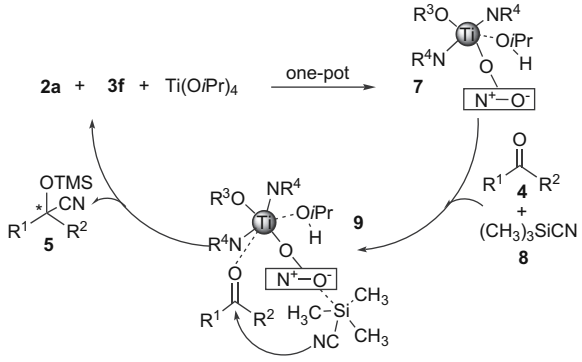


Figure 4. Hypothesis of two species.

between R group of the ketone and two phenyl groups of the amide might direct the activated CN attacked the carbonyl group from the less hindered side. Then the corresponding *O*-TMS ethers **5** could be released with the regeneration of the catalyst.

3. Conclusion

In summary, we have developed a new strategy for asymmetric cyanosilylation of ketones using a new bifunctional



Scheme 1. Proposed asymmetric catalytic cycle.

catalyst. Attractive features of the reaction are the high enantioselectivity (up to 96% ee), the low catalyst loading (2.5 mol %), and the ease of catalyst preparation. Based on the experimental results, catalyst species in this reaction and a plausible catalytic cycle were proposed. The applications of this bifunctional catalyst system in other asymmetric catalytic reactions are currently under investigations.

4. Experimental

4.1. General remarks

^{1}H NMR spectra were recorded on a 300 or 400 MHz spectrometer. Chemical shifts are reported in parts per million with the solvent reference as the internal standard ($CHCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a 75 or 100 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million with the solvent reference as the internal standard ($CHCl_3$: δ 77.2 ppm). Melting points were measured on a Mel-Temp apparatus and were uncorrected. Enantiomeric excesses (ee) were determined by HPLC or GC. Optical rotations were reported as follows: $[\alpha]_D^T$ (c=g/100 mL, in solvent). HRMS was recorded on a commercial apparatus (ESI Source). All reagents were commercially available and used directly, except for acetophenone and TMSCN, which were distilled under argon. Solvents were all purified by the usual methods. The chiral ligands **2a–j** and achiral *N*-oxides **3a–i** were synthesized according to the reported methods.[7d,9b,17]

4.2. Physical data of ligand *2a* and N-oxide *3f*

4.2.1. (2*S*,2′*S*)-1,1′-(2-Hydroxy-5-methyl-1,3-phenylene)bis-(methylene)bis(N-benzhydrylpyrrolidine-2-carboxamide) (*2a*)

White powder, mp: 84–86 °C. $[\alpha]_D^{25}$ −33.4 (c 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.59–7.61 (d, J=8.4 Hz, 2H), 7.18–7.30 (m, 20H), 6.71 (s, 2H), 6.25–6.28 (d, J=8.4 Hz, 2H), 3.99–4.03 (d, J=12.8 Hz, 2H), 3.34–3.38 (d, J=12.8 Hz, 2H), 3.18–3.22 (m, 2H), 2.91–2.96 (m, 2H), 2.35–2.41 (m, 2H), 2.34 (s, 3H), 1.69–2.03 (m, 8H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 172.77, 153.58, 141.71, 141.64, 129.35, 128.58, 128.41, 127.51, 127.44, 127.31, 127.14, 123.47, 66.68, 56.41, 53.09, 30.16, 23.34, 20.40 ppm. HRMS (ESI) calcd for $C_{45}H_{48}N_4O_3$ $(M+H)^+$: 693.3799, found: 693.3790.

4.2.2. N,N-Diethyl-(2-hydroxyl-3-adamantyl-5-tert-butylbenzyl)amine N-oxide (*3f*)

White powder, mp: 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 7.31 (m, 1H), 6.84 (m, 1H), 4.37 (s, 2H), 3.25–3.30 (q, 4H), 2.19 (m, 6H), 2.05 (m, 3H), 1.72–1.81 (m, 6H), 1.34 (s, 9H), 1.29–1.33 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 157.48, 139.37, 138.42, 126.28, 116.92, 69.01, 59.13, 45.23, 40.34, 37.21, 34.07, 31.66, 29.16, 18.23, 8.83 ppm. HRMS (ESI) calcd for $C_{25}H_{39}NO_2$ $(M+H)^+$: 386.3054, found: 386.3053.

4.3. Typical procedure for the catalytic cyanosilylation of ketones

The catalyst was prepared on a 0.0125 mmol scale by mixing $Ti(O^iPr)_4$ (1 M in toluene, 12.5 μL), **2a** (8.7 mg), and **3f** (4.8 mg) in a molar ratio of 1/1/1 in THF under an argon atmosphere at 35 °C. After cooling to 23 °C, the corresponding ketone (0.5 mmol) was added to this solution, followed by the addition of TMSCN (187 μL, 4 M in THF, 0.75 mmol) at −45 °C. The contents were stirred at −45 °C and the reaction was monitored by TLC. The residue was purified by silica gel column chromatograghy (petroleum ether/diethyl ether, 100/1, v/v) to afford the corresponding cyanohydrin trimethylsilyl ether.

4.3.1. 2-Trimethylsilyloxy-2-phenylpropanenitrile (*5a*)

Yield 96%, 90% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.19 (s, 9H), 1.87 (s, 3H), 7.38–7.58 (m, 5H) ppm. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 105 °C, 7.5 psi): t_R (minor)=23.9 min, t_R (major)=24.7 min. $[\alpha]_D^{22}$ +20.5 (c 0.325, CH_2Cl_2, 90% ee). [Lit.[12] $[\alpha]_D^{24}$ −22.3 (c 1.0, $CHCl_3$, 97% ee)].

4.3.2. 2-Trimethylsilyloxy-2(2′-fluorophenyl)propanenitrile (*5b*)

Yield 90%, 90% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.26 (s, 9H), 1.94 (s, 3H), 7.07–7.12 (m, 1H), 7.16–7.20 (m, 1H), 7.33–7.38 (m, 1H), 7.56–7.60 (m, 1H) 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 analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 105 °C, 7 psi): t_R (minor)=27.9 min, t_R (major)=28.5 min. $[\alpha]_D^{22}$ +14.7 (c 0.196, CH_2Cl_2, 90% ee). [Lit.[7b] $[\alpha]_D^{26}$ −12.7 (c 1.18, $CHCl_3$, 76% ee)].

4.3.3. 2-Trimethylsilyloxy-2(4′-fluorophenyl)propanenitrile (*5c*)

Yield 90%, 90% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 9H), 1.84 (s, 3H), 7.06–7.10 (m, 2H), 7.51–7.54 (m, 2H) 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 analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 115 °C, 8 psi): t_R (minor)=16.6 min, t_R (major)=17.2 min. $[\alpha]_D^{22}$ +17.2 (c 0.276, CH_2Cl_2, 90% ee). [Lit.[7e] $[\alpha]_D^{22}$ +17.6 (c 2.7, CH_2Cl_2, 92% ee)].

4.3.4. 2-Trimethylsilyloxy-2(3′-chlorophenyl)propanenitrile (*5d*)

Yield 93%, 94% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.22 (s, 9H), 1.86 (s, 3H), 7.34–7.55 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 1.0, 33.4, 70.9, 121.0, 122.7, 124.8, 128.8, 129.9, 134.6, 144.0 ppm. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 105 °C, 7.5 psi): t_R (minor)=70.4 min, t_R (major)=71.9 min. $[\alpha]_D^{22}$ +22.5 (c 0.214, CH_2Cl_2, 94% ee). [Lit.[7e] $[\alpha]_D^{26}$ +19.6 (c 2.88, CH_2Cl_2, 90% ee)].

*4.3.5. 2-Trimethylsilyloxy-2(4′-chlorophenyl)propanenitrile (**5e**)*

Yield 90%, 89% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 9H), 1.83 (s, 3H), 7.37–7.39 (m, 2H), 7.47–7.49 (m, 2H) ppm. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 125 °C, 8 psi): t_R (minor)=28.4 min, t_R (major)=29.1 min. $[\alpha]_D^{22}$ +18.1 (*c* 0.225, CH_2Cl_2, 89% ee). [Lit.[7e] $[\alpha]_D^{25}$ +18.2 (*c* 2.06, CH_2Cl_2, 90% ee)].

*4.3.6. 2-Trimethylsilyloxy-2(4′-methylphenyl)propanenitrile (**5f**)*

Yield 91%, 86% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.16 (s, 9H), 1.84 (s, 3H), 2.36 (s, 3H), 7.19–7.21 (m, 2H), 7.41–7.44 (m, 2H) ppm. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 105 °C, 7.5 psi): t_R (minor)=43.2 min, t_R (major)=43.9 min. $[\alpha]_D^{22}$ +17.9 (*c* 0.173, CH_2Cl_2, 86% ee). [Lit.[7e] $[\alpha]_D^{25}$ +22.1 (*c* 2.44, CH_2Cl_2, 92% ee)].

*4.3.7. 2-Trimethylsilyloxy-2(4′-methoxyphenyl)-propanenitrile (**5g**)*

Yield 88%, 89% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 9H), 1.87 (s, 3H), 3.85 (s, 3H), 6.90–6.93 (m, 2H), 7.44–7.49 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.41, 55.33, 71.28, 113.89, 121.81, 126.06, 134.04, 159.80 ppm. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 105 °C, 7.5 psi): t_R (minor)=114.4 min, t_R (major)=116.5 min. $[\alpha]_D^{22}$ +21.8 (*c* 0.189, CH_2Cl_2, 89% ee). [Lit.[5] $[\alpha]_D^{20}$ +22.6 (*c* 1.09, $CHCl_3$, 91% ee)].

*4.3.8. 2-Trimethylsilyloxy-(1′-thiophene)-1-carbonitrile (**5h**)*

Yield 78%, 92% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.20 (s, 9H), 2.00 (s, 3H), 6.98–7.00 (m, 1H), 7.21–7.34 (m, 2H) 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. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 110 °C, 7 psi): t_R (major)=22.8 min, t_R (minor)=22.0 min. $[\alpha]_D^{22}$ +51.6 (*c* 0.196, CH_2Cl_2, 92% ee). [Lit.[12] $[\alpha]_D^{22}$ −57.6 (*c* 1.0, $CHCl_3$, 97% ee)].

*4.3.9. 2-Trimethylsilyloxy-2(2′-naphthyl)propanenitrile (**5i**)*

Yield 89%, 96% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.22 (s, 9H), 1.97 (s, 3H), 7.54–7.66 (m, 3H), 7.90–7.93 (m, 3H), 8.07 (d, *J*=1.8 Hz, 1H) ppm. HPLC (Chiralcel OJ, 2-propanol/*n*-hexane=0.5/99.5, flow: 0.5 mL/min, 254 nm): t_R (minor)=5.9 min, t_R (major)=7.9 min. $[\alpha]_D^{22}$ +14.2 (*c* 0.194, CH_2Cl_2, 96% ee). [Lit.[12] $[\alpha]_D^{20}$ −14.2 (*c* 1.0, $CHCl_3$, 97% ee)].

*4.3.10. Trimethylsilyloxy-1,2,3,4-tetrahydronaphthane-carbonitrile (**5j**)*

Yield 80%, 85% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.24 (s, 9H), 2.02–2.08 (m, 2H), 2.22–2.26 (m, 1H), 2.32–2.36 (m, 1H), 2.83–2.87 (m, 2H), 7.11–7.14 (m, 1H), 7.27–7.30 (m, 2H), 7.66–7.69 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 1.3, 18.6, 28.2, 37.6, 69.8, 122.0, 126.6, 127.9, 129.0, 129.2, 135.6, 136.0. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 120 °C, 8 psi): t_R (minor)=68.8 min, t_R (major)=70.4 min. $[\alpha]_D^{22}$ +17.2 (*c* 0.235, CH_2Cl_2, 85% ee). [Lit.[7e] $[\alpha]_D^{22}$ +12.9 (*c* 1.44, $CHCl_3$, 86% ee)].

*4.3.11. 2-Trimethylsilyloxy-2-methyl-4-phenyl-3-butenenitrile (**5k**)*

Yield 92%, 91% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.27 (s, 9H), 1.77 (s, 3H), 6.15 (d, *J*=15.9 Hz, 1H), 6.91 (d, *J*=15.9 Hz, 1H), 7.33–7.45 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 1.3, 30.8, 69.9, 120.6, 126.8, 128.5, 128.7, 129.5, 130.9, 135.1 ppm. HPLC (Chiralcel OD, 2-propanol/*n*-hexane=1/99, flow: 0.5 mL/min, 254 nm): t_R (minor)=10.1 min, t_R (major)=11.6 min. $[\alpha]_D^{22}$ +58.6 (*c* 0.207, CH_2Cl_2, 91% ee). [Lit.[12] $[\alpha]_D^{25}$ −61.9 (*c* 1.0, $CHCl_3$, 96% ee)].

*4.3.12. 2-Trimethylsilyloxy-2-methyl-4-phenylbutanenitrile (**5l**)*

Yield 92%, 89% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.29 (s, 9H), 1.65 (s, 3H), 2.02–2.08 (m, 2H), 2.80–2.91 (m, 2H), 7.22–7.33 (m, 5H). GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 130 °C, 7.5 psi): t_R (major)=34.5 min, t_R (minor)=33.9 min. $[\alpha]_D^{22}$ +11.2 (*c* 0.305, CH_2Cl_2, 89% ee). [Lit.[5] $[\alpha]_D^{22}$ +9.7 (*c* 1.78, $CHCl_3$, 80% ee)].

*4.3.13. 2-Trimethylsilyloxy-2-methyl-3-methylbutanenitrile (**5m**)*

Yield 89%, 62% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.24 (s, 9H), 1.03 (t, *J*=6 Hz, 6H), 1.53 (s, 3H), 1.84–1.87 (m, 1H) ppm. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 60 °C, 8 psi): t_R (major)=17.3 min, t_R (minor)=16.9 min. $[\alpha]_D^{22}$ −1.0 (*c* 0.291, CH_2Cl_2, 62% ee). [Lit.[7e] $[\alpha]_D^{22}$ −1.1 (*c* 1.66, CH_2Cl_2, 90% ee)].

*4.3.14. 2-Trimethylsilyloxy-2-methylheptanenitrile (**5n**)*

Yield 95%, 82% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.20 (s, 9H), 2.43–2.47 (m, 1H), 2.70–2.74 (m, 1H), 2.97–3.02 (m, 1H), 3.10–3.15 (m, 1H), 7.28 (d, *J*=7.2 Hz, 1H), 7.31 (t, *J*=14.4 Hz, 1H), 7.35–7.37 (m, 1H), 7.55 (d, *J*=7.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 1.5, 14.2, 22.7, 24.2, 29.1, 31.7, 43.6, 69.9, 122.4 ppm. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 80 °C, 8 psi): t_R (minor)=35.5 min, t_R (major)=36.7 min. $[\alpha]_D^{22}$ +1.5 (*c* 0.184, CH_2Cl_2, 82% ee). [Lit.[7e] $[\alpha]_D^{22}$ +1.0 (*c* 1.62, CH_2Cl_2, 79% ee)].

*4.3.15. 2-Trimethylsilyloxy-2-methylpentanenitrile (**5o**)*

Yield 92%, 75% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.23 (s, 9H), 0.97 (t, *J*=6 Hz, 3H), 1.55–1.59 (m, 4H), 2.18 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 1.3, 13.8, 17.7, 30.9, 45.5, 69.6, 122.2 ppm. GC analysis (Varian, CP-Chirasil DEX CB, 0.25 mm×25 m, 60 °C, 8 psi): t_R (minor)=24.5 min, t_R (major)=25.3 min. $[\alpha]_D^{22}$ +1.0 (*c* 0.300, CH_2Cl_2, 75% ee). [Lit.[7e] $[\alpha]_D^{22}$ −0.9 (*c* 1.6, CH_2Cl_2, 80% ee)].

*4.3.16. 2-Cyclohexyl-2-(trimethylsilyloxy)propanenitrile (**5p**)*[4a]

Yield 90%, 71% ee. ^{1}H NMR ($CDCl_3$): δ 7.40–7.26 (m, 5H), 5.20 (s, 2H), 3.05 (s, 2H), 1.82–1.58 (m, 5H), 1.37 (s, 3H), 1.37–1.04 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 177.3, 135.4,

128.6, 128.5, 128.2, 76.9, 67.3, 45.6, 27.3, 26.3, 26.2, 26.1, 25.6. HPLC (Chiralcel AD, 2-propanol/hexane=5/95, 0.5 mL/min, 220 nm): t_R (minor)=8.06 min, t_R (major)=8.72 min. $[\alpha]_D^{22}$ +6.25 (*c* 0.170, CH_2Cl_2, 71% ee). [Lit.[4a] $[\alpha]_D^{25}$ +15.1 (*c* 1.52, $CHCl_3$, 90% ee)].

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