Highly Efficient Double-Activation Catalysts for the Synthesis of Ketone Cyanohydrins

Fu-Xue Chen,[a] Xiaohua Liu,[a] Bo Qin,[a] Hui Zhou,[a] Xiaoming Feng,*[a] Guolin Zhang[b]

[a] Key Laboratory of Green Chemistry & Technology (Sichuan University), Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China
Fax +86(28)85418249; E-mail: xmfeng@scu.edu.cn

[b] Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, 610041, P. R. China

Received 30 April 2004; revised 24 May 2004

Abstract: Tertiary cyanohydrin trimethylsilyl ethers were synthesized in excellent chemical yields by using salen-Al complex (0.25 mol%) and *N*-oxide (0.5 mol%) without solvent at ambient temperature. The relationship between the ligand structure and catalyst efficiency is discussed. Preliminary mechanistic studies were carried out, and transition states were proposed accounting for the action of the double-activation catalysts.

Key words: addition reactions, aluminum, ketones, Schiff bases, nitriles

Tertiary cyanohydrins are versatile intermediates in the context of organic synthesis.[1] They can be easily converted into α-hydroxy carbonyl compounds, β-amino alcohols and γ-lactones. In the literature, Lewis acids, Lewis bases and bifunctional catalysts have been employed to catalyze the addition of TMS-CN to ketones.[2,3] These reports also provided useful methods to construct quaternary C centers.[4]

We have previously communicated double-activation catalysts to achieve the ketone cyanohydrins in excellent yields under low catalyst loading.[5] Our strategy involves the simultaneous activation of the substrate ketone by Lewis acid and TMS-CN by *N*-oxide Lewis base. Therefore, this reaction can be performed with less than 0.5 mol% catalysts and without solvent. In this paper, the relationship between the catalyst efficiency and structure of the ligands is described, along with substrate generality and mechanistic proposal.

In our group, salen titanium complex has been previously utilized as a Lewis acid to activate the carbonyl group in the hydrocyanation of aldehydes,[6] as well as bisquilonine *N*-oxides as Lewis base to activate the nucleophile in the addition of TMS-CN to aldoimines (Strecker reaction).[7] Combining these procedures, a double-activation catalyst system has been developed to compensate for the low reactivity of ketones. Thus, a series of salen ligands **1a**–**g**, **2a**–**b** and *N*-oxides **3** (Figure 1) were prepared and applied to the catalytic addition of TMS-CN to ketones without solvent.

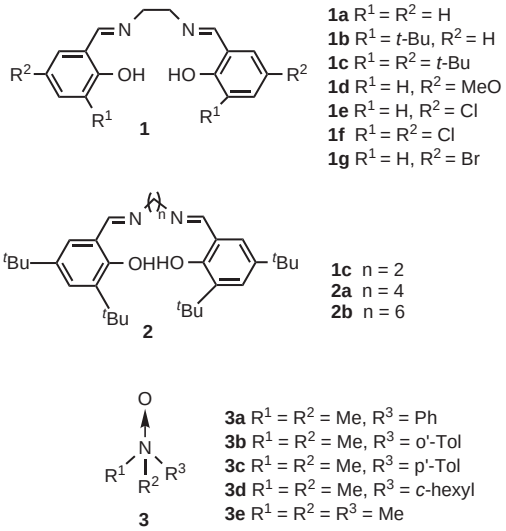


Figure 1 Ligands evaluated in this study.

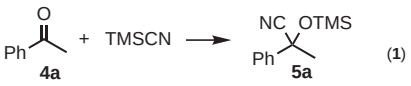
Optimization of the Catalyst

To assess the catalytic reactivity of ligands **1a**–**g** and **2a**–**b**, their complexes with Ti(O*i*-Pr)$_4$ were used to catalyze the addition of TMS-CN to acetophenone (**4a**) giving cyanohydrin trimethylsilyl ether (**5a**) as the model reaction [Equation (1)]. Results are listed in Table 1. The substituents on the salicylidene phenolic rings of the ligands played an important role on the catalyst reactivity. Two *tert*-butyl groups at the 3′,5′-positions (**1c**) showed more catalytic reactivity than 5′-*tert*-butyl- or 3′-H-substituted one (Table 1, entry 3 vs 1and 2). While the electron-donating methoxy substituted ligand gave moderate yield of the product, halogenated ones exhibited poor catalytic reactivity (Table 1, entries 4–7). Elongation of the carbon chain of **1c** led to ligands **2a**–**b** with reduced catalytic capabilities (Table 1, entries 8, 9).

Some Lewis acid metal reagents were examined, with results listed in Table 2. Complexes of alkyloxy metals with **1c** could effectively catalyze the addition of TMS-CN to acetophenone (Table 2, entries 1–3). However, complexes of **1c** with trifluoromethane sulfonates converted acetophenone in relatively low chemical yields (Table 2, entries 4–5). Curiously, Et_3Al gave the highest yield, but trace amount of the product was obtained using Et_2Zn (Table 2, entry 7 vs 8).

SYNTHESIS 2004, No. 14, pp 2266–2272
Advanced online publication: 13.08.2004
DOI: 10.1055/s-2004-831167; Art ID: F06404SS

Table 1 Structural Effect of Ligands on the Catalytic Cyanosilylation of Acetophenone[a]



Entry	Ligand	Yield (%)[b]	Entry	Ligand	Yield (%)[b]
1	**1a**	39	6	**1f**	trace
2	**1b**	37	7	**1g**	trace
3	**1c**	90	8	**2a**	65
4	**1d**	56	9	**2b**	67
5	**1e**	trace			

[a] Conditions: **1**/**2**-Ti(O*i*-Pr)$_4$ complex (10 mol%), **3a** (10 mol%), 0 °C, 72 h, TMS-CN (2 equiv), [$PhCOCH_3$] = 0.27 M in CH_2Cl_2.
[b] Isolated yields.

Table 2 Metal Scanning for the Cyanosilylation of Acetophenone[a]

Entry	Lewis acid	Time (h)	Yield (%)[b]
1	Ti(O*i*-Pr)$_4$	72	90
2	Zr(O*i*-Pr)$_4$	72	51
3	Al(O*i*-Pr)$_3$	72	48
4	Sc(OTf)$_3$	67	36
5	Cu(OTf)$_2$	67	NR
6	$ZrCl_4$	72	16
7	$ZnEt_2$	67	trace
8	$AlEt_3$	67	98

[a] Conditions: **1c**–M complex (10 mol%), **3a** (10 mol%), 0 °C, 67–72 h, TMS-CN (2 equiv), [$PhCOCH_3$] = 0.27 M in CH_2Cl_2.
[b] Isolated yields.

Solvents also affected the reaction rate to certain extent as illustrated in Table 3. CH_2Cl_2 and MeCN gave comparable low yields (Table 3, entries 1, 2). However, this reaction proceeded very fast when it was performed in THF or aromatic solvents. Toluene is the choice of solvent at this stage (Table 3, entry 4).

Table 3 Solvent Effect on the Addition of TMSCN to Acetophenone[a]

Entry	Solvent	Yield (%)[b]
1	CH_2Cl_2	41
2	MeCN	33
3	THF	86
4	toluene	90

[a] Conditions: **1c**–$AlEt_3$ complex (10 mol%), **3a** (10 mol%), 0 °C, 15 h, TMS-CN (2 equiv), [$PhCOCH_3$] = 0.27 M.
[b] Isolated yields.

A series of *N*-oxides and other dipolar compounds were then investigated in the cyanosilylation of acetophenone. As depicted in Table 4, *N*,*N*-dimethylaniline *N*-oxide (**3a**) showed more catalytic reactivity than *o*′-methyl (**3b**) and *p*′-methyl compounds (**3c**) (Table 4, entries 1–3). However, alkyl amine *N*-oxide **3d**–**e** converted acetophenone in relatively low yields (Table 4, entries 4, 5). It is worth noting that 0.5 mol% of NMO and 0.25 salen-Al complex showed competitive reactivity (Table 4, entry 6) with Kim's 30 mol% NMO alone in that case.[2n] Compounds containing a P=O dipolar moiety could slowly promote this conversion under these conditions (Table 4, entries 7, 8), which is in agreement with the observations by Shibasaki[3f–3h] and Denmark.[8]

Table 4 Effects of the Lewis Bases on the Addition of TMS-CN to Acetophenone[a]

Entry	Lewis base	Yield (%)[b]
1	**3a**	90
2	**3b**	25
3	**3c**	74
4	**3d**	71
5	**3e**	89
6[c]	NMO	97
7	Ph_3P=O	20
8	HMPA	41

[a] Conditions: **1c**–$AlEt_3$ complex (10 mol%), **3a** (10 mol%), TMS-CN (2 equiv), [$PhCOCH_3$] = 0.27 M in THF, 0 °C, 11 h.
[b] Isolated yields.
[c] This reaction was carried out neatly under the optimized conditions: **1c**–$AlEt_3$ complex (0.25 mol%), NMO (0.5 mol%), 11 h, TMS-CN (1.2 equiv), and see the experimental section.

The molar ratio between **1c**, $AlEt_3$ and **3a** was intensely studied with results summarized in Table 5. Increasing the amount of **3a**, the reaction was accelerated stepwise as a result of strengthened activation of the nucleophile TMS-CN (Table 5, entries 1–3). The highest reaction rate was recorded when 2 equiv **3a** with respect to **1c**–$AlEt_3$ complex was loaded (Table 5, entry 4). Further increasing the amount of **3a** yielded poor catalyst efficiency (Table 5, entry 5). In terms of chemical yield, the optimum molar ratio between the Lewis acid and the Lewis base is 1:2. Any changes to the equal molar ratio of **1c** to $AlEt_3$ resulted in a decrease in yield of **5a** to certain extent (Table 5, entries 6, 7).

Catalyst loading, substrate concentration and reaction temperature have comprehensive effects on the reaction rate of the cyanosilylation of acetophenone. These three factors were optimized as a whole with regard to the reaction rate, with results listed in Table 6. As the catalyst loading reducing from 10 to 5, 2 and 1 mol% the reaction rate suffered a sharp decrease (Table 6, entries 1–4). Fortunately, the retarded reaction rate caused by the low cat-

Table 5 Effect of Molar Ratio Between **1c**, **3a** and $AlEt_3$ on the Cyanosilylation of Acetophenone[a]

Entry	**1c**–$AlEt_3$–**3a** (mol%)	Yield (%)[b]
1	10:10:1.5	43
2	10:10:5	89
3	10:10:10	90
4	10:10:20	93
5	10:10:30	87
6	5:10:10	78
7	12:10:10	86

[a] Conditions: indicated amount of the catalysts, 0 °C, 11 h, TMSCN (2 equiv), [$PhCOCH_3$] = 0.27 M in THF.
[b] Isolated yields.

alyst loading could be retained by increasing the substrate concentration from 0.27 up to 1.1 M (Table 6, entries 5–7). Moreover, increasing the reaction temperature from 0 °C to r.t. led to a further improvement to the reaction rate (Table 6, entry 8). At room temperature this reaction could be completed within 20 h without solvent at a level of catalyst loading down to 0.25 mol% (Table 6, entries 9, 10). And now, only 1.2 equiv TMS-CN was needed to complete the reaction. However, this transformation proceeded very slowly with 0.1 mol% of the catalysts (Table 6, entry 11). Therefore, the best catalyst efficiency can be achieved with **1c**–$AlEt_3$ complex (0.25 mol%) and **3a** (0.5 mol%) at room temperature without solvent.

Table 6 Optimization of the Catalyst Loading, Substrate Concentration and Temperature on the Addition of TMS-CN to Acetophenone[a]

Entry	**1c**–$AlEt_3$ (%)	[**4a**] (M)[b]	Temp (°C)	Time (h/d)	Yield (%)[c]
1	10	0.27	0	11 h	93
2	5	0.27	0	11 h	89
3	2	0.27	0	11 h	34
4	1	0.27	0	11 h	3
5	1	0.55	0	11 h	10
6	1	0.82	0	11 h	31
7	1	1.1	0	18 h	96
8	1	1.1	23	10 h	97
9	0.5	2.9	23	6 h	99
10[d]	0.25	–	23	11 h	99
11[d]	0.1	–	23	2 d	90

[a] All reactions were carried out with 2 equivof **3a** to the indicated amount of **1c**–$AlEt_3$ complex, and TMS-CN (2 equiv) in toluene unless otherwise indicated.
[b] Corrected concentration to the total reaction mixture volume.
[c] Isolated yields.
[d] This was performed with TSMS-CN (1.2 equiv) and no solvent.

Table 7 Cyanosilylation of Ketones Catalyzed by **1c**–$AlEt_3$ and **3a**[a]

Entry	Ketone **4**	Product **5**	Time (h)	Yield (%)[b]
1	**4a** $PhCOCH_3$	**5a**	13	99
2	**4b** 4-MeC_6H_4COMe	**5b**	15	90
3	**4c** 4-FC_6H_4COMe	**5c**	11	88
4	**4d** 3-ClC_6H_4COMe	**5d**	11	94
5	**4e** 4-$O_2NC_6H_4COMe$	**5e**	14	85
6	**4f** 2-acetonaphthone	**5f**	13	85
7	**4g** (*E*)-PhCH=CHCOMe	**5g**	11	93
8	**4h** $PhCH_2CH_2COMe$	**5h**	12	97
9	**4i** 4-phenylcyclohexanone	**5i**	11	97
10	**4j** α-tetralone	**5j**	15	89
11	**4k** α-indanone	**5k**	12	90
12	**4l** 2-octanone	**5l**	11	93
13	**4m** 2-acetylthiophene	**5m**	15	84

[a] All reactions were carried out with **1c**–$AlEt_3$ complex (0.25 mol%), **3a** (0.5 mol%), TMS-CN (1.2 equiv) and no solvent at r.t.
[b] Isolated yields.

Table 8 Control Experiments[a]

Entry	**1c**–$AlEt_3$ (mol%)	**3a** (mol%)	Yield (%)[b]
1	–	10	0
2	10	–	19
3	10	10	99
4[c]	10	10	91

[a] All reactions were carried out at 0 °C in toluene for 11 h with indicated amount of catalyst(s) and TMS-CN (2 equiv).
[b] Isolated yields.
[c] In this case, the catalysts **1c**–$AlEt_3$ and **3a** were mixed to generate the catalyst at the start of the reaction, not following the typical double-activation catalysis procedure.

Substrate Generality

Under the optimized conditions, a wide range of aliphatic, aromatic, cyclic and heterocyclic ketones **4a**–**n** was converted into corresponding cyanohydrin TMS ethers **5a**–**n**. The results in Table 7 reveal that the double-activation catalysts, composed of salen-aluminum complex and amine *N*-oxide, have a good substrate generality. Electron-deficient and electron-rich aromatic ketones (Table 7, entries 1–6), along with α,β-saturated and α,β-unsaturated ones (Table 7, entries 7, 8) exhibited a similar high reaction rate. Aliphatic, normal cyclic and sterically

hindered cyclic ketones were cyanosilylated smoothly (Table 7, entries 9–12). The double-activation catalysts also tolerated heterocyclic ketone as substrate (Table 7, entry 13).

Preliminary Mechanistic Studies

In order to identify the double-activation catalysis, a series of control experiments were carried out with the results listed in Table 8. The cyanosilylation of acetophenone did not occur with *N*-oxide **3a** alone (Table 8, entry 1). While salen-Al complex **1c** promote this reaction in very low yield (Table 8, entry 2), additional activation of the nucleophilic TMS-CN by *N*-oxide **3a** accelerated this addition to a very fast reaction rate (Table 8, entry 3). Direct evidence of the coordination between *N*-oxide and TMS-CN was obtained from ^{1}H NMR (400 MHz, $CDCl_3$) studies. The chemical shift of free TMS-CN is located at $\delta_H = 0.35$. However, in the presence of *N*-oxide a new signal appeared at $\delta_H = 0.17$ as a result of condensed electron density around the silicon atom caused by the coordination of *N*-oxide to TMS-CN. However a weak binding between the salen-Al complex and *N*-oxide, the general concern of combined use of a Lewis acid and a Lewis base, [9,10] was observed (Table 8, entry 4). Although stable metal complexes with *N*-oxides were reported in the literature,[11] this study shows the feasibility of application of Lewis acid and Lewis base to double-activation catalysis in the cyanosilylation of ketones. These results suggested that, in this case, the catalysts worked in a double-activation model, i.e. salen-Al complex as the Lewis acid to activate the carbonyl group ([**A**], Figure 2) and *N*-oxide as the Lewis base to activate TMS-CN ([**B**], Figure 2). As [**A**] and [**B**] attract and approach each other, the transition state [**C**] is proposed and undergoes 'intramolecular' transfer of cyanide to ketone releasing the cyanohydrin TMS ether and the catalysts, salen-Al complex and *N*-oxide.

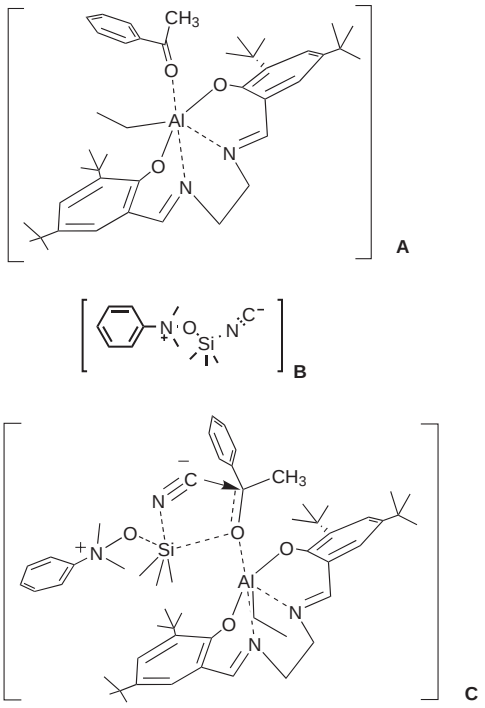


Figure 2 Proposed transition states

Practical and efficient double-activation catalysts have been developed for the addition of TMS-CN to ketones. Using salen-Al complex (0.25 mol%) and *N*-oxide (0.5 mol%) aliphatic, aromatic, cyclic and heterocyclic ketones were converted to corresponding cyanohydrin TMS ethers in good to excellent chemical yields without solvent. Preliminary mechanistic studies supported that salen-Al complex played the role of Lewis acid to activate carbonyl group and *N*-oxide the role of Lewis base to activate TMS-CN. Thus the double-activation catalysts could be loaded at such a low level with excellent catalyst efficiency. Further efforts will be directed toward the application of the double-activation catalysis to the enantioselective cyanosilylation of ketones and other reactions in this line.[12]

^{1}H NMR spectra were recorded on an INOVA 400 (400 MHz) or on a Bruker (300 MHz) instrument. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, $\delta = 7.26$). Data are listed as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (*J*, Hz), integration, and assignment. ^{13}C NMR data were collected on an INOVA 400 (100 MHz) or on a Bruker (75 MHz) apparatus. Chemical shifts are reported in ppm from the tetramethylsilane as internal standard. Elemental analyses were performed on a Carlo-1160 instrument. All ketones, TMS-CN, metal reagents and substituted salicylal were purchased from Acros, Aldrich and Fluka, and used directly without further purification.

Petroleum ether refers to the fraction with bp 60–90 °C.

***N,N′*-Bis(salicylidene)ethylene-1,2-diimine (1a)[6d]**

This kind of salen ligand was prepared according to the literature.[6d]

Yellow crystals; mp 126–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 4 H, CH_2CH_2), 6.86 (td, 7.6 Hz, 1.6 Hz, 2 H, aromatic H), 6.94 (d, 8.4 Hz, 2 H, aromatic H), 7.22 (dd, 7.6, 1.6 Hz, 2 H, aromatic H), 7.27–7.31 (m, 2 H, aromatic H), 8.31 (s, 2 H, 2CH=N), 13.22 (s, 2 H, 2 ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 59.7, 116.9, 118.58, 118.64, 131.4, 132.4, 160.9, 166.5.

***N,N′*-Bis(3′-*tert*-butylsalicylidene)ethylene-1,2-diimine (1b)[6d]**

Yellow crystals; mp 147–148 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 18 H, 2 *t*-Bu), 3.93 (s, 4 H, CH_2CH_2), 6.80 (t, 7.8 Hz, 2 H, aromatic H), 7.09 (dd, 7.6, 1.6 Hz, 2 H, aromatic H), 7.31 (dd, 8.0 Hz, 1.6 Hz, 2 H, aromatic H), 8.38 (s, 2 H, 2 CH=N).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3, 34.8, 59.5, 117.8, 118.5, 129.5, 129.8, 137.3, 160.3, 167.2.

***N,N′*-Bis(3′,5′-di-*tert*-butylsalicylidene)ethylene-1,2-diimine (1c)[6d]**

Yellow crystals; mp 186–187 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 18 H, 2 *t*-Bu), 1.43 (s, 18 H, 2 *t*-Bu), 3.92 (m, 4 H, CH_2CH_2), 7.06 (d, 2.4 Hz, 2 H, aromatic H), 7.36 (d, 2.4 Hz, 2 H, aromatic H), 8.38 (s, 2H, 2 CH=N), 13.65 (s, 2 H, 2ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4, 31.4, 34.1, 35.0, 59.6, 117.8, 126.0, 127.0, 136.6, 140.0, 158.0, 167.6.

***N,N′*-Bis(5′-methyoxysalicylidene)ethylene-1,2-diimine (1d)[6b]**
Yellow crystals; mp 164–165 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 6 H, 2 MeO), 3.93 (s, 4 H, CH_2CH_2), 6.73 (d, 2.8 Hz, 2 H, aromatic H), 6.87 (d, 8.8 Hz, 2 H, aromatic H), 6.90 (dd, 8.8, 2.8 Hz, 2 H, aromatic H), 8.29 (s, 2 H, 2 CH=N), 12.71 (s, 2 H, 2 ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 59.8, 114.8, 117.6, 118.2, 119.4, 151.9, 155.0, 166.2.

***N,N′*-Bis(5′-chlorosalicylidene)ethylene-1,2-diimine (1e)[6b]**
Yellow crystals; mp 179–181 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (s, 4 H, CH_2CH_2), 6.95 (d, 9.2 Hz, 2 H, aromatic H), 7.22 (dd, 11.2, 2.4 Hz, 2 H, aromatic H), 7.26 (d, 0.8 Hz, 2 H, aromatic H), 8.30 (s, 2 H, 2 CH=N), 13.14 (s, 2 H, 2 ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 59.6, 118.6, 119.2, 123.3, 130.6, 132.3, 159.6, 165.4.

***N,N′*-Bis(3′,5′-dichlorosalicylidene)ethylene-1,2-diimine (1f)[6b]**
Yellow crystals; mp 211–212 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.01 (s, 4 H, CH_2CH_2), 7.15 (d, 2.4 Hz, 2 H, aromatic H), 7.40 (d, 2.4 Hz, 2 H, aromatic H), 8.28 (s, 2 H, 2 CH=N), 13.97 (s, 2 H, 2ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 59.0, 119.3, 122.7, 123.1, 129.2, 132.5, 156.1, 165.3.

***N,N′*-Bis(5′-bromosalicylidene)ethylene-1,2-diimine (1g)[6b]**
Yellow crystals; mp 193–195 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (s, 4 H, CH_2CH_2), 6.85 (d, 8.8 Hz, 2 H, aromatic H), 7.36 (dd, 8.8, 2.4 Hz, 2 H, aromatic H), 7.39 (d, 2.4 Hz, 2 H, aromatic H), 8.29 (s, 2 H, 2 CH=N), 13.16 (s, 2 H, 2 ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6, 110.2, 119.0, 119.9, 133.6, 135.2, 160.0, 165.3.

***N,N′*-Bis(3′,5′-di-*tert*-butylsalicylidene)butylene-1,4-diimine (2a)[6e]**
Yellow crystals; mp 144–145 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 18 H, 2 *t*-Bu), 1.44 (s, 18 H, 2 *t*-Bu), 1.81 (s, 4 H, CH_2CH_2), 3.63 (s, 4 H, 2 CH_2), 7.08 (d, 2.0 Hz, 2 H, aromatic H), 7.37 (d, 2.0 Hz, 2 H, aromatic H), 8.36 (s, 2 H, 2 CH=N), 13.89 (s, 2 H, 2 ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 29.4, 31.5, 34.4, 35.0, 59.3, 117.8, 125.8, 126.7, 136.6, 139.9, 158.1, 165.9.

***N,N′*-Bis(3′,5′-di-*tert*-butylsalicylidene)hexylene-1,6-diimine (2b)[6e]**
Yellow crystals; mp 120–122 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 18 H, 2 *t*-Bu), 1.45 (s, 22 H, 2 *t*-Bu, CH_2CH_2), 1.72 (t, 6.0 Hz, 4 H, 2 CH_2), 3.57 (t, 6.4 Hz, 4 H, 2 CH_2), 7.08 (d, 2.4 Hz, 2 H, aromatic H), 7.37 (d, 2.0 Hz, 2 H, aromatic H), 8.34 (s, 2 H, 2 CH=N), 13.98 (s, 2 H, 2 ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8, 29.4, 30.7, 31.5, 34.1, 35.0, 59.4, 117.8, 125.7, 126.6, 136.6, 139.8, 158.2, 165.6.

***N,N*-Dimethylaniline *N*-Oxide (3a)[13]**
These *N*-oxides were prepared by oxidization of the corresponding amines according to the literature report.[12] Most of them could be recrystallized from diethyl ether.
Mp 66–69 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 6 H, CH_3), 7.39–7.50 (m, 3 H, aromatic H), 7.93 (d, 8.0 Hz, 2 H, aromatic H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.7, 119.7, 129.1, 129.3, 153.6.

***N,N*-Dimethyl-*N*-(2′-methylphenyl)amine *N*-Oxide (3b)[13]**
Mp 46–48 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.73 (s, 3 H, CH_3), 3.46 [s, 6 H, $(CH_3)_2N$)], 7.22–7.27 (m, 3 H, aromatic H), 8.10 (d, 7.6 Hz, 2 H, aromatic H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.7, 61.6, 120.6, 126.4, 128.5, 130.8, 133.7.

***N,N*-Dimethyl-*N*-(4′-methylphenyl)amine *N*-Oxide (3c)[13]**
Mp 102–106 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.08 (s, 3 H, CH_3), 2.32 [s, 6 H, $(CH_3)_2N$], 7.25 (d, 8.4 Hz, 2 H, aromatic H), 7.93 (d, 8.4 Hz, 2 H, aromatic H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.4, 62.7, 120.2, 129.1, 138.1, 152.4.

***N*-Cyclohexyl-*N,N*-dimethylamine *N*-Oxide (3d)[13]**
Mp 96–98 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.03–2.09 (m, 1 H, cyclic H), 2.16–2.35 (m, 4 H, cyclic H), 2.55–2.58 (m, 1 H, cyclic H), 2.77–2.81 (m, 2 H, cyclic H), 3.20–3.23 (m, 2 H, cyclic H), 3.49 (s, 1 H, cyclic H), 3.93 [s, 6 H, $(CH_3)_2N$)].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.99, 25.03, 26.5, 55.1, 76.6.

***N,N,N*-Trimethylamine *N*-Oxide (3e)[13]**
Mp 79–83 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.31 (s, 9 H, 3 CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 61.2.

Cyanosilylation of Ketones; Standard Experimental Procedure
$AlEt_3$ (8.0 μL, 2 M in hexane, 0.0016 mmol) was stirred with **1c** (8.0 mg, 0.0016 mmol) in anhyd toluene (0.1 mL) at r.t. for 1 h under an N_2 atmosphere. To the resulting catalyst (20 μL) was added acetophenone (0.14 mL, 1.2 mmol), followed by the addition of a solution of **3a** (0.8 mg, 0.0006 mmol) in TMS-CN (1.4 mmol, 1.2 equiv). The reaction was performed at 23 °C. At completion, the reaction mixture was purified (silica gel column; Et_2O–petroleum ether, 1:100) to give the pure product. The desired 2-phenyl-2-trimethylsilyloxy-propanenitrile (**5a**) was obtained.

Yield: 263 mg (99%); colorless oil.

2-Trimethylsilyloxy-2-phenylpropanenitrile (5a)[2m]
Yield: 99%; colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.19 [s, 9 H, $(CH_3)_3Si$], 1.87 (s, 3 H, CH_3), 7.38–7.58 (m, 5 H, aromatic H).

2-Trimethylsilyloxy-2-(4′-methylphenyl)propanenitrile (5b)[2m]
Yield: 57%; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.16 [s, 9 H, $(CH_3)_3Si$], 1.84 (s, 3 H, CH_3), 2.36 (s, 3 H, ArCH_3), 7.21 (m, 2 H, aromatic H), 7.43 (m, 2 H, aromatic H).

Anal. Calcd for $C_{13}H_{19}NOSi$: C, 66.90, H, 8.21; N, 6.00. Found: C, 66.78; H, 8.03; N, 6.39.

2-Trimethylsilyloxy-2-(4′-fluorophenyl)propanenitrile (5c)
Yield: 88%; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.18 [s, 9 H, $(CH_3)_3Si$], 1.84 (s, 3 H, CH_3), 7.08 (m, 2 H, aromatic H), 7.52 (m, 2 H, aromatic H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.0, 33.5, 71.0, 115.6 (d, $^2J_{CCF}$ = 21.9 Hz), 121.4, 126.5 (d, $^3J_{CCCF}$ = 8.5 Hz), 138.0, 162.2 (d, $^1J_{CF}$ = 246.4 Hz).

2-Trimethylsilyloxy-2-(3′-chlorophenyl)propanenitrile (5d)
Yield: 94%; colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 [s, 9 H, $(CH_3)_3Si$], 1.86 (s, 3 H, CH3), 7.34–7.55 (m, 4 H, aromatic H).

^{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.

Anal. Calcd for $C_{12}ClH_{16}NOSi$: C, 56.79; H, 6.35; N, 5.52. Found: C, 56.61; H, 6.39; N, 5.90.

2-Trimethylsilyloxy-2-(4′-nitrophenyl)propanenitrile (5e)[2m]
Yield: 85%; white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.26 [s, 9 H, $(CH_3)_3Si$], 1.89 (s, 3 H, CH_3), 7.75 (d, 9.0 Hz, 2 H, aromatic H), 8.30 (d, 9.0 Hz, 2 H, aromatic H).

2-Trimethylsilyloxy-2-(2′-naphthyl)propanenitrile (5f)[2m]
Yield: 85%; white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 [s, 9 H, $(CH_3)_3Si$], 1.97 (s, 3 H, CH_3), 7.54–7.66 (m, 3 H, aromatic H), 7.90–7.93 (m, 3 H, aromatic H), 8.07 (d, 1.8 Hz, 1 H, aromatic H).

2-Trimethylsilyloxy-2-methyl-4-phenyl-3-butenenitrile (5g)[2m]
Yield: 93%; white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.27 [s, 9 H, $(CH_3)_3Si$], 1.77 (s, 3 H, CH_3), 6.15 (d, 15.9 Hz, 1 H, CH=), 6.91 (d, 15.9 Hz, 1 H, CH=), 7.33–7.45 (m, 5 H, aromatic H).

^{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.

2-Trimethylsilyloxy-2-methyl-4-phenylbutanenitrile (5h)[2m]
Yield: 97%; colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.29 [s, 9 H, $(CH_3)_3Si$], 1.65 (s, 3 H, CH_3), 2.02–2.08 (m, 2 H, CH_2), 2.80–2.91 (m, 2 H, CH_2), 7.22–7.33 (m, 5 H, aromatic H).

1-Trimethylsilyloxy-1-(4′-phenylcyclohexyl)-1-carbonitrile (5i)[2m]
Yield: 97%; white solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.28 [s, 9 H, $(CH_3)_3Si$], 1.76 (td, 25.8, 3.6 Hz, 2 H, cyclic H), 1.82–1.89 (m, 2 H, cyclic H), 1.98 (m, 2 H, cyclic H), 2.31 (m, 2 H, cyclic H), 2.51–2.55 (m, 1 H, cyclic H), 7.24 (m, 3 H, aromatic H), 7.32 (t, 7.8 Hz, 2 H, aromatic H).

1-Trimethylsilyloxy-1,2,3,4-tetrahydronaphthane-1-carbonitrile (5j)
Yield: 89%; colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.24 [s, 9 H, $(CH_3)_3Si$], 2.06 (m, 2 H, cyclic H), 2.23 (m, 1 H, cyclic H), 2.35 (m, 1 H, cyclic H), 2.85 (m, 2 H, cyclic H), 7.13 (m, 1 H, aromatic H), 7.29 (m, 2 H, aromatic H), 7.67 (m, 1 H, aromatic H).

^{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.

Anal. Calcd for $C_{14}H_{19}NOSi$: C, 68.52, H, 7.80; N, 5.71. Found: C, 68.30; H, 7.70; N, 6.11.

1-Trimethylsilyloxy-1-indanyl-1-carbonitrile (5k)[3j]
Yield: 90%; colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.20 [s, 9 H, $(CH_3)_3Si$], 2.43–2.47 (m, 1 H, cyclic H), 2.70–2.74 (m, 1 H, cyclic H), 2.97–3.02 (m, 1 H, cyclic H), 3.10–3.15 (m, 1 H, cyclic H), 7.28 (d, 7.2 Hz, 1 H, aromatic H), 7.31 (t, 14.4 Hz, 1 H, aromatic H), 7.36 (td, 14.4, 1.2 Hz, 1 H, aromatic H), 7.55 (d, 7.2 Hz, 1 H, aromatic H).

2-Trimethylsilyloxy-2-methyloctanenitrile (5l)[2m]
Yield: 93%; colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.24 [s, 9 H, $(CH_3)_3Si$], 0.90 (t, 13.6 Hz, 3 H, CH_2CH_3), 1.31–1.36 (m, 6 H, alkyl H), 1.43–1.46 (m, 1 H, alkyl H), 1.51–1.54 (m, 1 H, alkyl H), 1.57 (s, 3 H, CCH_3), 1.66–1.75 (m, 2 H, alkyl H).

2-Trimethylsilyloxy-2-methyl-(2′-thiophenyl)propanenitrile (5m)
Yield: 84%; colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 [s, 9 H, $(CH_3)_3Si$], 2.00 (s, 3 H, CH_3), 7.00 (m, 1 H, aromatic H), 7.21–7.34 (m, 2 H, aromatic H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 0.8, 33.4, 68.2, 120.8, 124.7, 126.0, 126.6, 146.3.

Anal. Calcd for $C_{10}H_{15}NOSiS$: C, 53.33; H, 6.66; N, 6.22. Found: C, 53.48; H, 6.94; N, 6.43.

Acknowledgment

The authors thank the NSFC (No. 20225206, 20390050 and 20372050) and the Ministry of Education, China (No. 01144, 104209 and others) for financial support. Dr. F.-X. Chen thanks China Postdoctoral Science Foundation.

References

(1) For reviews, see: (a) Gregory, R. J. H. *Chem. Rev.* **1999**, 3649. (b) North, M. *Synlett* **1993**, 807. (c) Effenberger, F. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 1555. (d) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147.

(2) (a) Evans, D. A.; Carroll, G. L.; Truesdale, L. K. *J. Org. Chem*. **1974**, *39*, 914. (b) Gassman, P. G.; Talley, J. J. *Tetrahedron Lett*. **1978**, *19*, 3773. (c) Greenlee, W. J.; Hangauer, D. G. *Tetrahedron Lett.* **1983**, *24*, 4559. (d) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (e) Saravanan, P.; Vijaya, R.; Sigh, V. K. *Tetrahedron Lett*. **1998**, *39*, 3823. (f) Jenner, G. *Tetrahedron Lett*. **1999**, *41*, 491. (g) Wilkinson, H. S.; Grover, P. T.; Vandenbossche, C. P.; Bakale, R. P.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *Org. Lett*. **2001**, *3*, 553. (h) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Achille, U.-R. *Tetrahedron Lett.* **2001**, *42*, 3041. (i) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Achille, U.-R. *Eur. J. Org. Chem*. **2002**, 3243. (j) Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Synlett* **2002**, 793. (k) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2002**, *42*, 9703. (l) Bian, Z.-X.; Zhao, H.-Y.; Li, B.-G. *Polyhedron* **2003**, *22*, 1523. (m) Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Tetrahedron* **2003**, 5667. (n) Kim, S. S.; Kim, D. W.; Rajagopal, G. *Synthesis* **2004**, 213. (o) Zhou, H.; Chen, F.-X.; Qin, B.; Feng, X.; Zhang, G. *Synlett* **2004**, 1077.

(3) For asymmetric catalytic cyanosilylation of ketones, see: (a) Choi, M. C. K.; Chan, S. S.; Matsumoto, K. *Tetrahedron Lett.* **1997**, *38*, 6669. (b) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40*, 8147. (c) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; Larichev, V. S.; Lokshin, B. V.; Moscalenko, M. A.;

North, M.; Orizu, C.; Peregudov, A. S.; Timofeeva, G. I. *Eur. J. Org. Chem.* **2000**, 2655. (d) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Parsons, T.; Tararov, V. I. *Tetrahedron* **2001**, *57*, 771. (e) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timo-feeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968. (f) Hamashimia, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412. (g) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691. (h) Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2923. (i) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195. (j) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 1009. (k) Shen, Y.; Feng, X.; Zhang, G.; Jiang, Y. *Synlett* **2002**, 1353. (l) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900. (m) Shen, Y.; Feng, X.; Li, Y.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* **2004**, 129.

(4) For reviews on construction of quaternary stereocenters, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (c) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591. (d) Christoffers, J.; Baro, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1688.

(5) (a) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Synlett* **2003**, 558. (b) Chen, F.; Feng, X.; Qin, B.; Zhang, G.; Jiang, Y. *Org. Lett.* **2003**, *5*, 949.

(6) (a) Pan, W.; Feng, X.; Gong, L.; Hu, W.; Li, Z.; Mi, A.; Jiang, Y. *Synlett* **1996**, 337. (b) Dutton, J. C.; Fallon, G. D.; Murray, K. S. *Inorg. Chem.* **1988**, *27*, 34. (c) Feng, X.; Gong, L.; Hu, W.; Li, Z.; Pan, W.; Mi, A.; Jiang, Y. *Chem. J. Chin. Univ.* **1998**, *19*, 1416; (in Chinese). (d) Chen, H.; White, P. S.; Gagne, M. R. *Organometallics* **1998**, *17*, 5358. (e) Atwood, D. A.; Harvey, M. J. *Chem. Rev.* **2001**, *101*, 37.

(7) (a) Liu, B.; Feng, X.; Chen, F.; Zhang, G.; Jiang, Y. *Synlett* **2001**, 1551. (b) Jiao, Z.; Feng, X.; Liu, B.; Chen, F.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* **2003**, 3818.

(8) (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

(9) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394.

(10) For other double-activation examples, see: (a) Ristic-Petrovic, D.; Torkelson, J. R.; Hilts, R. W.; McDonald, R.; Cowie, M. *Organometallics* **2000**, *19*, 4432. (b) Chen, E. Y.-X.; Kruper, W. J.; Roof, G.; Wilson, D. R. *J. Am. Chem. Soc.* **2001**, *123*, 745. (c) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050. (d) Corey, E. J.; Wang, Z. *Tetrahedron Lett.* **1993**, *34*, 4001. (e) Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (f) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593.

(11) Karayannis, N. M.; Pytlewski, L. L.; Mikulski, C. M. *Coord. Chem. Rev.* **1973**, *11*, 93.

(12) Compound **5a** has been obtained in 94% ee using chiral salen-Al complex, which will be described in another paper.

(13) Kruger, T. L.; White, W. N.; Hartzell, S. L.; Kress, J. W.; Walter, N. *J. Org. Chem.* **1975**, *40*, 77.