Enantioselective Cyanosilylation of Ketones by a Catalytic Double-Activation Method with an Aluminium Complex and an N-Oxide

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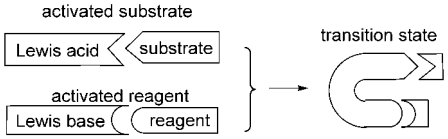
Abstract: Double-activation catalysis promises high catalytic efficiency in the enantioselective cyanosilylation of ketones through the combined use of a Lewis acid and a Lewis base. Catalyst systems composed of a chiral salen–Al complex and an N-oxide have high catalytic turnovers (200 for aromatic ketones, 1000 for aliphatic ones). With these catalysts, a wide range of aliphatic and aromatic ketones were converted under mild conditions into tertiary cyanohydrin O-TMS ethers in excellent yields and with high enantioselectivities (94% *ee* for aromatic ketones, 90% *ee* for aliphatic ones). Preliminary mechanistic studies revealed that the salen–Al complex played the role of a Lewis acid to activate the ketone and the N-oxide that of a Lewis base to activate TMSCN; that is, double activation.

Keywords: asymmetric catalysis · cyanohydrins · double activation · enantioselectivity · ketones

Introduction

Optically active cyanohydrins are versatile intermediates in organic synthesis.[1,2] Enantioselective cyanosilylation and cyanocarbonation of ketones with the aid of metal-based Lewis acids[3–6] and organic bases[7] have been reported as the common approaches for the asymmetric synthesis of non-racemic tertiary cyanohydrins. These reports provide useful methods for the enantioselective construction of quaternary stereocenters from prochiral ketones.[1] However, the development of asymmetric cyanosilylation of ketones is still a challenge in terms of catalyst efficiency and substrate generality. Here we describe an advance toward this goal through double-activation catalysis (Scheme 1).[8]

We have recently reported asymmetric Strecker reactions promoted by stoichiometric chiral N-oxides,[9] asymmetric addition of TMSCN (TMS = trimethylsilyl) to aldehydes by salen–Ti^{IV} complexes,[10a,b] and bifunctional N-oxide titanium complex-catalyzed enantioselective cyanosilylation of ketones.[10c,d] Subsequently, a double-activation catalyst system for the syntheses of racemic and non-racemic cyanohydrins has been developed.[11] Our strategy involves the simultaneous activation of the substrate ketone by Lewis acid and of the reagent TMSCN by Lewis base (Scheme 1). Guided by this hypothesis, series of metal complexes with ligands **1a–n** (Figure 1) and N-oxides **2a–e** (Figure 2) were prepared and applied to the asymmetric cyanosilylation of ketones, with high catalytic turnovers of up to 1000.



Scheme 1. General concept of the double-activation catalysis.

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Results and Discussion

Optimization of the catalysts: Building on the understanding of the catalytic capability of salen–metal complexes in the asymmetric addition of TMSCN to carbonyl compounds,[10a,11] complexes of different metals with **1a** were used to catalyze the cyanosilylation of acetophenone at −20 °C with 2 equiv TMSCN with respect to acetophenone as the model reaction. The results are summarized in

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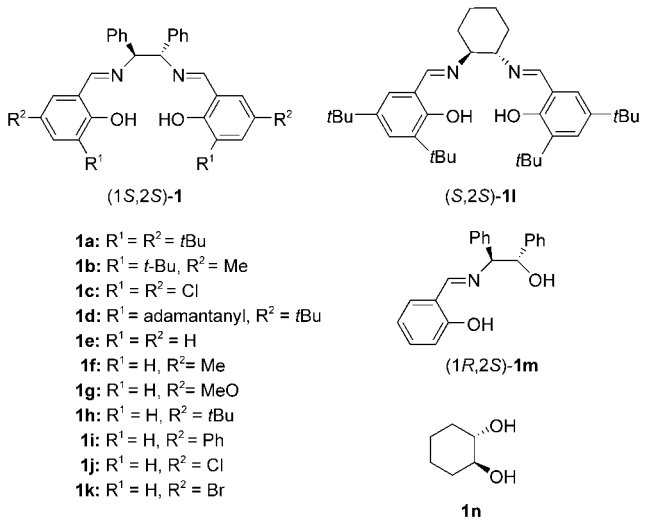


Figure 1. Ligands evaluated in this study.

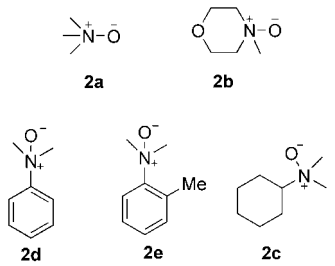


Figure 2. N-oxides assessed in this study.

Table 1. Et_3Al gave more promising enantioselectivity than $Ti(OiPr)_4$ (Table 1, entries 1 and 2). Although Et_2AlCl exhibited higher enantioselective inductivity than Et_2AlCN and $Al(OiPr)_3$, the chemical yield was poor (Table 1, entries 5 vs 3/4). Other metals such as $Ni(acac)_2$ and $Cu(OTf)_2$ catalyzed this reaction but with no enantioselectivity (Table 1, entries 7 and 8). Et_3Al was thus chosen to assess the following ligands.

Tetradentate, tridentate, and bidentate ligands (see Figure 1) were then examined for enantioselectivity, with the results listed in Table 2. The data suggested that smaller H atom at the 3′-position of the phenolic ring in the salen ligand was beneficial to the enantioselectivity (Table 2, entry 5 vs entries 1–4). The presence of the larger adamantanyl group at the 3′-position even abolished the asymmetric inductivity completely (Table 2, entry 4). Substituents at the 5′-position also had important effects on the *ee* values: it could be seen that an appropriate electron-deficient group at the 5′-position of the ligand produced a higher enantioselectivity than an electron-rich or a sterically bulky one (Table 2, entries 6–11). The catalyst derived from the 5′-bromo-substituted **1k** exhibited the highest enantioselectivity. Tetradentate analogue (**1l**) gave poor enantioselectivity (Table 2, entry 12). Selected bidentate ligands and tridentate mono-Schiff bases had no asymmetric inductivity at all (Table 2, entries 13–17).

Table 1. Asymmetric cyanosilylation of acetophenone catalyzed by Lewis acids and N-oxides.[a]

Entry	Lewis acid (mol%)	**2d** [mol%]	Yield [%]	*ee* [%][b]
1	**1a**·$Ti(OiPr)_4$ (2)	1	11	74
2	**1a**·$AlEt_3$ (2)	1	45	83
3	**1a**·$Al(OiPr)_3$ (2)	1	17	14
4	**1a**·Et_2AlCN (2)	1	36	56
5	**1a**·Et_2AlCl (2)	1	trace	87
6	**1a**·Et_2Zn (2)	1	trace	72
7	**1a**·$Ni(acac)_2$ (2)	1	trace	0
8	**1a**·$Cu(OTf)_2$ (2)	1	80	0

[a] All reactions were carried out at −20°C for 78 h with the indicated amount of the catalysts, TMSCN (2 equiv), concentration of acetophenone = 0.8 M in CH_2Cl_2. [b] Determined by chiral GC analysis on Chirasil DEX CB.

Table 2. Effect of the ligand structure on the enantioselectivity.[a]

Entry	Ligand	Yield [%]	*ee* [%][b]
1[c]	**1a**	45	83
2	**1b**	99	70
3	**1c**	99	53
4	**1d**	trace	0
5	**1e**	52	81
6	**1f**	94	75
7	**1g**	73	82
8	**1h**	99	81
9	**1i**	50	83
10	**1j**	99	73
11	**1k**	96	88
12	**1l**	45	51
13	**1m**	ND	0
14	**1n**	19	0
15	(*R*)-binol	trace	0
16	L-taddol	12	0

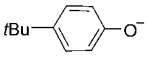
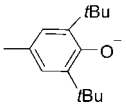
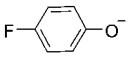
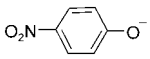
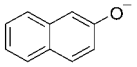
[a] All reactions were carried out with chiral Al complex (1:1, 2 mol%) and N-oxide **2d** (1 mol%) at −20°C over 24 h, TMSCN (2 equiv), concentration of acetophenone = 0.8 M in CH_2Cl_2. [b] Determined by chiral GC analysis on Chirasil DEX CB. [c] This was performed at −20°C for 120 h with the indicated amount of the catalysts, concentration of acetophenone = 0.12 M in CH_2Cl_2.

To investigate the effect of the third Et group attached to the aluminium in **1k**·Et_3Al complex, series of counterions were employed to generate the Lewis acids. The results in Table 3 demonstrate that counterions had slight effect on the enantioselectivity. Sterically hindered phenolic ions decreased the enantioselectivity slightly (Table 3, entries 1–3), but the reaction rate sharply (Table 3, entry 3). Other phenolic ions showed few effects on the *ee* values (Table 3, entries 4–6). Further, ^{13}C NMR analysis indicated that this Et group did not exchange with cyanide under the reaction conditions.[12]

Solvent effects were studied next, with the results summarized in Table 4. In moderately polar solvents, this transformation proceeded with comparable enantioselectivities (Table 4, entries 1–3). THF was the most favorable solvent for enantioselectivity (Table 4, entry 4). Use of more polar solvents, however, reduced the enantioselectivities (Table 4, entry 5). No reaction occurred in the dipolar solvent DMSO (Table 4, entry 6).

Various N-oxides[13a] and other dipolar molecules were evaluated in the model reaction, with the results listed in

Table 3. Counterion effect on the enantioselectivity.[a]

Entry	Counterion	Yield [%]	*ee* [%][b]
1	none	96	88
2		99	77
3		27	72
4		76	86
5		95	80
6		93	81

[a] All reactions were carried out with **1k**·$AlEt_3$ complex (1:1, 2 mol%) and N-oxide **2d** (1 mol%) at −20°C over 24 h, TMSCN (2 equiv), concentration of acetophenone = 0.8 M in CH_2Cl_2. [b] Determined by chiral GC analysis on Chirasil DEX CB.

Table 4. Solvent effect on the enantioselectivity.[a]

Entry	Solvent	Yield [%]	*ee* [%][b]
1	CH_2Cl_2	96	88
2	Et_2O	95	87
3	benzene	99	86
4	THF	95	90
5	CH_3CN	89	77
6	DMSO	NR	–

[a] All reactions were carried out with **1k**·$AlEt_3$ complex (1:1, 2 mol%) and N-oxide **2d** (1 mol%) at −20°C over 24 h, TMSCN (2 equiv), concentration of acetophenone = 0.8 M. [b] Determined by GC analysis on Chirasil DEX CB.

Table 5. Cyclic and acyclic tertiary amine N-oxides exhibited varying enantioselectivities (Table 5, entries 1–3). Aromatic tertiary aniline N-oxide (**2d**) was the best Lewis basic complementary catalyst (Table 5, entry 4). The presence of a methyl substituent on the phenyl ring of **2d** was not beneficial to the enantioselectivity (Table 5, entry 5). Dipolar phosphine oxide was able to promote this reaction with a moderate enantioselectivity (Table 5, entry 6) by activating the nucleophilic TMSCN.[5,14] There are a great many examples of stable complexes between N-oxides and diverse metals,[13b] but in this case N-oxides and metal complexes could be used cooperatively to catalyze the enantioselective cyanosilylation of ketones, which removed concerns relating to binding between Lewis acid and Lewis base.[8b] N-Oxides have frequently been employed in asymmetric organic synthesis.[13c–e]

The catalyst loading and ratio were investigated intensively, with the results summarized in Table 6. Higher catalyst loading (5 mol%) was inferior to lower loading (2 mol%) in terms of catalyst efficiency (Table 6, entries 1 vs 2), which might be a result of the increased possibility of binding between Lewis acid and Lewis base at higher catalyst concentrations in the reaction mixture (see Table 9, entry 4). Any deviation of the molar ratio of **1k** to $AlEt_3$ from 1:1 resulted in a certain decrease in the enantioselectivity (Table 6, entry 2 vs 3/4/5). Interestingly, a slightly higher enantioselectivity was obtained if a lower catalyst loading was applied

Table 5. Asymmetric cyanosilylation of acetophenone catalyzed by **1k**·$AlEt_3$ complex and Lewis bases.[a]

Entry	Lewis base	Yield [%]	*ee* [%][b]
1	**2a**	98	28
2	**2b**	98	65
3	**2c**	92	81
4	**2d**	95	90
5	**2e**	96	75
6	Ph_3PO	62	88

[a] All reactions were carried out with **1k**·$AlEt_3$ complex (1:1, 2 mol%) and Lewis base (1 mol%) at −20°C over 24 h, TMSCN (2 equiv), concentration of acetophenone = 0.8 M in THF. [b] Determined by chiral GC analysis on Chirasil DEX CB.

(Table 6, entries 6–8). The practical level of catalyst for this reaction is 0.5 mol%. Fortunately, the greatly reduced reaction rate caused by low catalyst loading could be overcome to some extent by increasing the concentration (Table 6, entries 7–8). It was not to be recommended that this transformation be performed with no solvent (Table 6, entry 9).

Table 6. Effects of the catalyst loading and the metal/ligand ratio on the enantioselectivity.[a]

Entry	**1k**/Et_3Al/**2d** [mol%]	[$PhCOCH_3$] [M]	*t* [h/d]	Yield [%]	*ee* [%][b]
1	5:5:2.5	0.8	24 h	41	77
2	2:2:1	0.8	24 h	95	90
3	2.5:2:1	0.8	24 h	82	86
4	2.2:2:1	0.8	24 h	97	85
5	1.8:2:1	0.8	24 h	99	88
6	1:1:0.5	0.8	36 h	98	92
7	0.5:0.5:0.25	1.5	46 h	94	93
8	0.09:0.09:0.045	2.4	16 d	99	94
9	0.01:0.01:0.005	no solvent	20 d	trace	63

[a] All reactions were carried out at −20°C in THF with TMSCN (2 equiv) under the conditions indicated. [b] Determined by GC analysis on Chirasil DEX CB.

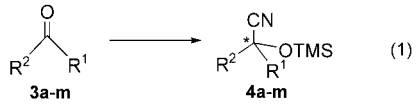
Temperature clearly affected the enantioselectivity, as shown in Table 7. The optimum enantioselectivity—of 93% *ee*—was obtained on reduction of the temperature from 0 to −20°C (Table 7, entries 1–2). Curiously, any further decrease in the reaction temperature greatly reduced the enantioselectivities (Table 7, entries 3–4).

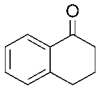
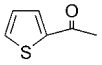
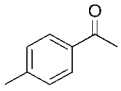
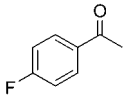
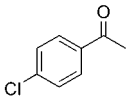
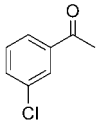
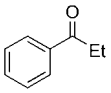
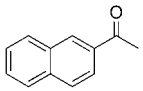
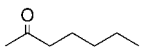
Table 7. Temperature effect on the enantioselectivity.[a]

Entry	*T* [°C]	Yield [%]	*ee* [%][b]
1	0	95	87
2	−20	94	93
3	−40	81	57
4	−78	14	66

[a] All reactions were carried out with **1k**·$AlEt_3$ complex (1:1, 0.5 mol%) and Lewis base (0.25 mol%) at −20°C over 46 h, TMSCN (2 equiv), concentration of acetophenone = 1.5 M in THF. [b] Determined by GC analysis on Chirasil DEX CB. In summary, the optimum catalyst efficiency could be achieved under these conditions: **1k**·$AlEt_3$ complex (0.1–0.5 mol%), N-oxide **2d** (0.05–0.25 mol%), TMSCN (2 equiv), [ketone] = 2.4–1.5 M in THF, −20°C.

Table 8. Enantioselective cyanosilylation of ketones catalyzed by **1k**·$AlEt_3$ complex and N-oxide **2d**.[a]



Entry	Ketone	3	Method	*t* [h/d]	Yield [%]	*ee* [%][b]
1		**3a**	A	46 h	94	93[c]
			B	16 d	99	94
2		**3b**	A	48 h	99	92
			B	9.5 d	99	90
3		**3c**	A	28 h	98	92
4		**3d**	A	66 h	99	90
5		**3e**	A	24 h	99	92
6		**3f**	A	32 h	99	88
			B	9 d	99	92
7		**3g**	A	40 h	99	86
			B	7 d	99	90
8		**3h**	A	36 h	95	90
			B	9 d	95	90
9		**3i**	A	40 h	92	84
			B	13 d	99	87
10		**3j**	A	3 d	96	79
			B	16 d	99	81(>99)[d]
11		**3k**	B	36 h	99	79
12		**3l**	B	36 h	95	80
13		**3m**	B	36 h	80	90

[a] *Method A*: **1k**·$AlEt_3$ complex (1:1, 0.5 mol%), **2d** (0.25 mol%), TMSCN (2 equiv), −20°C, [ketone] = 1.5 M in THF. *Method B*: **1k**·$AlEt_3$ complex (1:1, 0.1 mol%), **2d** (0.05 mol%), TMSCN (2 equiv), −20°C, [ketone] = 2.4 M in THF. [b] Determined by GC analysis on Chirasil DEX CB. [c] The absolute configuration was established as *R* by comparison of the sign of the optical rotation value with that in the literature (ref. [5c]). [d] Determined by HPLC analysis on Chiralpak OJ. The *ee* value in parentheses was obtained after recrystallization of the product from *n*-hexane.

Substrate generality: This highly efficient catalyst system tolerated a wide range of aromatic, aliphatic, heterocyclic, and sterically bulky cyclic ketones as the substrates under the optimized conditions. As depicted in Table 8, aromatic and bulky cyclic ketones were converted into the corresponding O-TMS cyanohydrins (**4a**–**m**) both in excellent chemical yields (94–99%) and with excellent enantioselectivities (90–94% *ee*; Table 8, entries 1–8). The ethyl ketone or β-acetonaphthone, however, gave smaller *ee* values than acetophenone (Table 8, entries 9, 10 vs 1). Aliphatic ketones enjoyed catalytic turnovers as high as 1000 with excellent chemical yields and moderate to excellent enantioselectivities (Table 8, entries 11–13). Notably the non-functionalized alkyl ketone **3m** was converted with such high enantioselectivity (Table 8, entry 13) for the first time.

About the mechanism: To provide insight into the mechanism, control experiments were performed. As shown in Table 9, neither **1k**·$AlEt_3$ complex nor the N-oxide **2d** on its own was effective enough to accelerate the addition of TMSCN to acetophenone (Table 9, entries 1, 2). Only when these two were used synergistically in a double-activation way could this transformation perform excellently (Table 9, entry 3). In addition, when the N-oxide was mixed with the Lewis acid at the start of the reaction, rather than by following the typical procedure (see Experimental Section), the product was obtained with comparable enantioselectivity but in low yield (Table 9, entry 4 vs. 3).

Moreover, in comparison with other dipolar molecules such as chiral N-oxides[9,13c–f] and phosphine oxide,[14] the N-oxide **2d** in this system should act as Lewis base rather than additively[15] to coordinate to, and thus activate, the nucleophile TMSCN. Entries 5 and 6 in Table 9 also collaterally provide evidence for the double-activation hypothesis with the use of (*R*)-binol titanium complex and (*R*)-3,3′-dimethyl-2,2′-biquinoline *N*,*N*′-dioxide (OBIQ).[13c] Direct evidence of the coordination of the N-oxide to TMSCN was observed by ^{1}H NMR analyses.[16] Therefore, salen–Al complex and N-oxide should work cooperatively in the model of asymmetric double-activation catalysis, the aluminium complex as a Lewis acid to activate the substrate ketone and the N-oxide as a Lewis base to activate the TMSCN.

Table 9. Control experiments.[a]

Entry	**1k** [mol%]	**2d** [mol%]	Yield [%]	*ee* [%][b]
1	0	0.25	0	–
2	0.5	0	0	–
3	0.5	0.25	94	93
4[c]	0.5	0.25	21	92
5[d]	(*R*)-binol·Ti(O*i*Pr)$_4$	(±)-OBIQ	11	43
6[d]	(*R*)-binol·Ti(O*i*Pr)$_4$	(*R*)-OBIQ	21	51

[a] Conditions: −20 °C, 46 h, TMSCN (2 equiv), [$PhCOCH_3$] = 1.5 M in THF. [b] Determined by GC analysis on Chirasil DEX CB. [c] **1k**, $AlEt_3$, and **2d** were mixed together at the start of the reaction to generate the catalyst at RT for 1 h, followed by addition of acetophenone and TMSCN. [d] This was carried out with 20 mol% of the titanium complex and 20 mol% of OBIQ at 0 °C over 84 h, [$PhCOCH_3$] = 0.12 M, OBIQ = 3,3′-dimethyl-2,2′-biquinoline *N*,*N*′-dioxide (ref. [13c]).

Consequently, the two components were activated as corresponding intermediates A and B as shown in Figure 3, in which an isocyanide species was involved.[17] The activated nucleophile and substrate attracted and approached one another, and so the transition state C was formed.[18] Formation of the more stable O–Si bond then promoted the intramolecular transfer of cyanide to carbonyl group, yielding the product cyanohydrin O-TMS ether. Further mechanistic investigations should be aimed at illustrating the actual catalytic cycle of the double-activation catalysis.

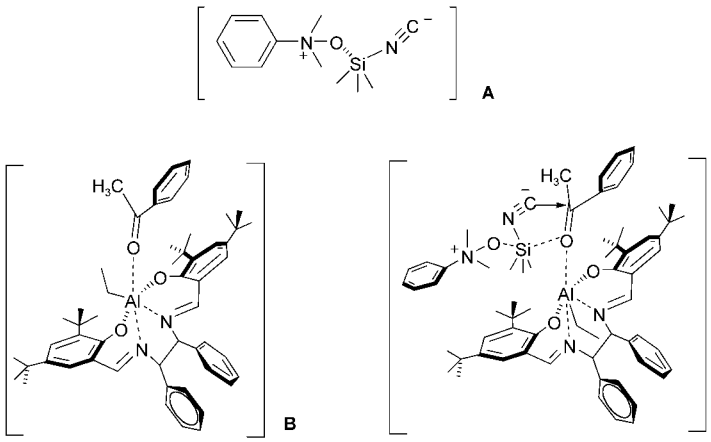


Figure 3. The proposed intermediates and transition state involved in the enantioselective cyanosilylation of ketones by double-activation catalysis.

Conclusion

In conclusion, the work in this paper has demonstrated the feasibility of the application of double-activation catalysis in asymmetric addition of TMSCN to aromatic and aliphatic ketones. It is efficient and practical. The catalyst has high catalytic turnover (200 for aromatic ketones, 1000 for aliphatic ones) and gives excellent yields (up to 99%) and competitive enantioselectivities (up to 94% *ee* for aromatic ketones, up to 90% *ee* for aliphatic ones). Further efforts should be devoted to the optimization of the catalyst to enhance both enantioselectivity and reactivity, and also to mechanistic clarification of this reaction.

Experimental Section

General: ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 machine (400 MHz) or on Bruker instruments (600, 300 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ_H = 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), integration, and assignment. ^{13}C NMR data were also collected on a Varian Unity INOVA 400 machine (100 MHz) or on Bruker instruments (150, 75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ_C = 77.0). Elemental analyses were performed on a Carlo-1160 apparatus. Enantiomer ratios were determined by chiral GC analysis on Varian Chirasil DEX CB or by chiral HPLC analysis on Daicel Chiralcel OD/OJ in comparison with the authentic racemates. Optical rotation data were recorded on a Perkin–Elmer Polarimeter-341. All ketones, TMSCN, substituted salicylal and chiral molecules [(1*S*,2*S*)-diamines, (1*R*,2*S*)-amino alcohol, (*R*)-binol, L-taddol)] were purchased from Acros, Aldrich, and Fluka, and were used directly without further purification. Solvents were purified by conventional methods.

(1*S*,2*S*)-Salen (1a):[10a] m.p. 195–197 °C (lit. 199–200 °C);[10a] $[\alpha]_D^{22}$ = +33.3 (*c* = 0.6, $CHCl_3$) [lit. $[\alpha]_D^{20}$ = +32.4 (*c* = 0.25, $CHCl_3$)];[10a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 1.6 Hz, 18H; 2×$C(CH_3)_3$), 1.42 (d, *J* = 2.0 Hz, 18H; 2×$C(CH_3)_3$), 4.73 (d, *J* = 1.6 Hz, 2H; CH–CH), 6.98 (m, 2H; aromatic H), 7.16–7.20 (m, 10H; aromatic H), 7.31 (d, *J* = 2.4 Hz, 2H; aromatic H), 8.40 (d, *J* = 1.2 Hz, 2H; 2×CH=N), 13.60 (d, *J* = 2.0 Hz, 2H; 2×ArOH, exchangeable with D_2O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4, 31.4, 34.0, 35.0, 80.1, 117.8, 126.3, 127.1, 127.4, 128.0, 128.2, 136.3, 139.8, 140.0, 157.9, 167.2 ppm.

(1*S*,2*S*)-Salen (1b):[10a] m.p. 69–71 °C; $[\alpha]_D^{22}$ = −140.4 (*c* = 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 18H; 2×*t*Bu), 2.18 (s, 6H; 2×Me), 4.68 (s, 2H; CH–CH), 6.77 (d, *J* = 1.6 Hz, 2H; aromatic H), 7.05 (d, *J* = 1.6 Hz, 2H; aromatic H), 7.17–7.21 (m, 10H; aromatic H), 8.30 (s, 2H; 2×CH=N), 13.50 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 29.3, 34.7, 80.2, 118.2, 126.5, 127.4, 128.0, 128.3, 130.0, 130.6, 136.7, 140.0, 157.9, 166.9 ppm.

(1*S*,2*S*)-Salen (1c): m.p. 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.76 (s, 2H; CH–CH), 7.09 (d, *J* = 2.4 Hz, 2H; aromatic H), 7.12–7.15 (m, 4H; aromatic H), 7.20–7.23 (m, 6H; aromatic H), 7.38 (d, *J* = 2.8 Hz, 2H; aromatic H), 8.27 (s, 2H; 2×CH=N), 14.07 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.0, 119.4, 122.5, 123.4, 127.7, 128.1, 128.7, 129.5, 132.6, 138.0, 155.6, 164.6 ppm; HRMS (ESI): calcd for $C_{28}H_{20}Cl_4N_2O_2$: 557.0352; found 557.0356 $[M+H]^+$.

(1*S*,2*S*)-Salen (1d): The precursor 3-adamantanyl-5-*tert*-butylsalicylaldehyde was synthesized similarly to the literature procedure.[19] M.p. 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 9H; *t*Bu), 1.79 (s, 6H; adamantanyl H), 2.09–2.14 (m, 9H; adamantanyl H), 7.33 (d, *J* = 1.6 Hz, 1H; aromatic H), 7.53 (s, 1H; aromatic H), 9.86 (s, 1H; CHO) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.9, 31.3, 34.3, 37.0, 37.2, 40.2, 119.9, 127.7, 132.0, 137.8, 141.7, 159.3, 197.5 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 2954, 1649, 1618, 1459 cm^{-1}.

Compound 1d: m.p. 190–192 °C; $[\alpha]_D^{22}$ = −75.0 (*c* = 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 18H; 2×*t*Bu), 1.57 (s, 4H; adamantanyl H), 1.84 (m, 10H; adamantanyl H), 2.08–2.16 (m, 16H; adamantanyl H), 4.72 (s, 2H; CH–CH), 6.97 (s, 2H; aromatic H), 7.18 (m, 10H; aromatic H), 7.26 (d, *J* = 1.2 Hz, 2H; aromatic H), 8.40 (s, 2H; 2×CH=N), 13.52 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.1, 31.4, 34.1, 37.2, 40.2, 80.1, 117.9, 126.3, 127.1, 127.3, 128.0, 128.2, 136.6, 139.8, 140.0, 158.2, 167.4 ppm; IR (KBr): $\tilde{\nu}_{max}$ = 1626 cm^{-1} (CH=N); HRMS (ESI): calcd for $C_{56}H_{68}N_2O_2$: 801.5354 $[M+H]^+$; found 801.5374 $[M+H]^+$.

(1*S*,2*S*)-Salen (1e):[10a] m.p. 155–156 °C; $[\alpha]_D^{22}$ = −12.4 (*c* = 1.37, CH_2Cl_2) {lit. $[\alpha]_D^{20}$ = −11.9 (*c* = 1.0, $CHCl_3$)}[10a]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.73 (s, 2H; CH–CH), 6.81 (dt, *J* = 8.4, 2.0 Hz, 2H; aromatic H), 6.95 (d, *J* = 8.4 Hz, 2H; aromatic H), 7.11–7.28 (m, 14H; aromatic H), 8.29 (s, 2H; 2×CH=N), 13.32 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.2, 116.9, 118.5, 118.7, 127.6, 127.8, 128.3, 131.7, 132.5, 139.3, 160.9, 166.1 ppm

(1*S*,2*S*)-Salen (1f): m.p. 55–56 °C; $[\alpha]_D^{22} = +13.0$ ($c = 1.61$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.21$ (s, 6H; 2×Me), 4.69 (s, 2H; CH–CH), 6.86 (m, 2H; aromatic H), 6.92 (m, 2H; aromatic H), 7.06–7.09 (m, 2H; aromatic H), 7.16–7.21 (m, 10H; aromatic H), 8.26 (s, 2H; 2×CH=N), 13.07 (s, 2H; 2×ArOH) ppm; HRMS (ESI): calcd for $C_{30}H_{28}N_2O_2$: 449.2224; found 449.2222 $[M+H]^+$.

(1*S*,2*S*)-Salen (1g):[10a] m.p. 91–93 °C [lit. 89–91 °C];[10a] $[\alpha]_D^{22} = +12.0$ ($c = 3.58$, CH_2Cl_2) {lit. $[\alpha]_D^{20} = +4.9$ ($c = 4.0$, CH_2Cl_2)};[10a] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.70$ (s, 6H; 2×CH_3O), 4.71 (s, 2H; CH–CH), 6.64 (s, 2H; aromatic H), 6.89 (m, 4H; aromatic H), 7.16–7.21 (m, 10H; aromatic H), 8.26 (s, 2H; 2×CH=N), 12.82 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.8$, 80.3, 114.9, 117.6, 118.1, 119.8, 127.6, 127.8, 128.4, 139.3, 152.0, 155.1, 165.9 ppm.

(1*S*,2*S*)-Salen (1h): m.p. 188–190 °C; $[\alpha]_D^{22} = -8.3$ ($c = 1.32$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$ (s, 18H; 2×*t*Bu), 4.72 (s, 2H; CH–CH), 6.89 (d, $J = 8.8$ Hz, 2H; aromatic H), 7.12 (d, $J = 0.8$ Hz, 2H; aromatic H), 7.15–7.19 (m, 10H; aromatic H), 7.31 (dd, $J = 8.8$, 1.2 Hz, 2H; aromatic H), 8.34 (s, 2H; 2×CH=N), 13.12 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 31.3$, 33.9, 80.2, 116.3, 117.9, 127.5, 127.9, 128.2, 128.3, 129.9, 139.6, 141.4, 158.6, 166.6 ppm; HRMS (ESI): calcd for $C_{36}H_{40}N_2O_2$: 533.3163; found 533.3173 $[M+H]^+$.

(1*S*,2*S*)-Salen (1i): m.p. 188–190 °C; $[\alpha]_D^{22} = -64.8$ ($c = 1.1$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.79$ (s, 2H; CH–CH), 7.04 (d, $J = 8.8$ Hz, 2H; aromatic H), 7.20–7.24 (m, 10H; aromatic H), 7.29 (d, $J = 7.6$ Hz, 2H; aromatic H), 7.38 (t, $J = 7.6$ Hz, 6H; aromatic H), 7.45 (d, $J = 7.6$ Hz, 4H; aromatic H), 7.51 (dd, $J = 8.8$, 0.8 Hz, 2H; aromatic H), 8.38 (s, 2H; 2×CH=N), 13.38 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 80.2$, 117.4, 118.6, 126.5, 126.8, 127.7, 127.8, 128.4, 128.8, 130.1, 131.4, 132.0, 139.3, 140.1, 160.4, 166.3 ppm; HRMS (ESI): calcd for $C_{40}H_{32}N_2O_2$: 573.2537; found 573.2544 $[M+H]^+$.

(1*S*,2*S*)-Salen (1j):[10a] m.p. 101–104 °C (lit. 86–88 °C);[10a] $[\alpha]_D^{22} = -12.7$ ($c = 1.12$, CH_2Cl_2) {lit. $[\alpha]_D^{20} = -12.2$ ($c = 1.0$, CH_2Cl_2)};[10a] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.75$ (s, 2H; 2×CH–CH), 6.92 (d, $J = 8.8$ Hz, 2H; aromatic H), 7.10 (d, $J = 2.8$ Hz, 2H; aromatic H), 7.16–7.25 (m, 12H; aromatic H), 8.18 (s, 2H; 2×CH=N), 13.26 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 80.0$, 118.6, 119.2, 123.4, 127.7, 127.9, 128.6, 130.7, 132.6, 138.8, 159.5, 165.1 ppm;

(1S,2S)-Salen (1k):[10a] This kind of salen ligands was prepared according to the literature.[10a] $[\alpha]_D^{22} = -22.9$ ($c = 1.54$, CH_2Cl_2) {lit. $[\alpha]_D^{20} = -2.2$ ($c = 1.0$, CH_2Cl_2)};[10a] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.75$ (s, 2H; CH–CH), 6.87 (d, $J = 8.8$ Hz, 2H; aromatic H), 7.16–7.26 (m, 12H; aromatic H), 7.34–7.37 (m, 2H; aromatic H), 8.18 (s, 2H; 2×CH=N), 13.29 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 80.0$, 110.3, 119.0, 119.8, 127.7, 127.9, 128.6, 133.7, 135.4, 138.8, 160.0, 165.0 ppm.

(1*S*,2*S*)-Salen (1l):[20] m.p. 206–207 °C (lit. 200–203 °C);[20] $[\alpha]_D^{22} = +323.8$ ($c = 1.3$, CH_2Cl_2) {lit. $[\alpha]_D^{20} = -315$ ($c = 4.0$, CH_2Cl_2 for (1*R*,2*R*)-enantiomer)};[20] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$ (s, 18H; 2×*t*Bu), 1.41 (s, 18H; 2×*t*Bu), 1.48 (m, 2H; cyclic H), 1.72–1.96 (m, 6H; cyclic H), 3.30–3.33 (m, 2H; CH–CH), 6.98 (d, $J = 2.4$ Hz, 2H; aromatic H), 7.30 (d, $J = 2.0$ Hz, 2H; aromatic H), 8.30 (s, 2H; 2×CH=N), 13.72 (s, 2H; 2×ArOH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.3$, 29.4, 31.4, 33.3, 34.0, 34.9, 72.4, 117.8, 126.0, 126.7, 136.3, 139.8, 158.0, 165.8 ppm.

(1*R*,2*S*)-Mono-Schiff base (1m):[10b] m.p. 124–126 °C (lit. 125.6–126.0 °C);[10b] $[\alpha]_D^{22} = -16.8$ ($c = 0.55$, CH_2Cl_2) {lit. $[\alpha]_D^{20} = -17$ ($c = 0.6$, $CHCl_3$)};[10b] ^1H NMR (600 MHz, $CDCl_3$): $\delta = 2.06$ (d, $J = 2.0$ Hz, 1H; =CH–O*H*), 4.53 (d, $J = 7.0$ Hz, 1H; CHN=C), 5.06 (d, $J = 7.0$ Hz, 1H; C*H*–OH), 6.82 (s, 1H; aromatic H), 6.95 (d, $J = 7.9$ Hz; 1H; aromatic H), 7.09 (d, $J = 7.9$ Hz; 1H; aromatic H), 7.26–7.40 (m, 11H; aromatic H), 8.08 (s, 1H; CH=N), 13.15 (s, 1H; ArOH) ppm.

N-Oxide (2a):[13a] The N-oxides **2a–e** were obtained by direct oxidization of the corresponding tertiary amines,[13a] except for **2b** (NMO), which was purchased from Acros; ^1H NMR (400 MHz, [D$_6$]DMSO): $\delta = 3.31$ (s, 9H; 3×CH_3) ppm; ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 61.2$.

N-Oxide (2c):[13a] ^1H NMR (400 MHz, [D$_6$]DMSO): $\delta = 2.03$–2.09 (m, 1H; cyclic H), 2.16–2.35 (m, 4H; cyclic H), 2.55–2.58 (m, 1H; cyclic H), 2.77–2.81 (m, 2H; cyclic H), 3.20–3.23 (m, 2H; cyclic H), 3.49 (s, 1H; cyclic H), 3.93 (s, 6H; $(CH_3)_2N$)) ppm; ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 24.99$, 25.03, 26.5, 55.1, 76.6 ppm.

***N*,*N*-Dimethylaniline *N*-oxide (2d)**:[13a] ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.66$ (s, 6H; CH_3), 7.39–7.50 (m, 3H; aromatic H), 7.93 (d, $J = 8$ Hz, 2H; aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 62.7$, 119.7, 129.1, 129.3, 153.6 ppm.

N-Oxide (2e):[13a] ^1H NMR (600 MHz, [D$_6$]DMSO): $\delta = 2.08$ (s, 3H; CH_3), 2.32 (s, 6H; $(CH_3)_2N$), 7.25 (d, $J = 8.4$ Hz, 2H; aromatic H), 7.93 (d, $J = 8.4$ Hz, 2H; aromatic H) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): $\delta = 20.4$, 62.7, 120.2, 129.1, 138.1, 152.4 ppm.

(*R*)-3,3′-Dimethyl-2,2′-bisquinoline *N*,*N*′-dioxide (OBIQ):[13c] This compound was prepared and resolved by the literature procedure.[13c] m.p. 223–225 °C; $[\alpha]_D^{20} = -88.6$ ($c = 0.64$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 2.27 (s, 6H; 2×CH_3), 7.73–7.64 (m, 6H; aromatic H), 7.86 (d, $J = 7.6$ Hz, 2H; H_5 and $H_{5'}$), 8.72 (d, $J = 9.2$ Hz, 2H; H_8 and $H_{8'}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 17.7, 119.8, 125.1, 127.3, 128.9, 129.1, 130.0, 131.6, 140.1 ppm.

Asymmetric addition of TMSCN to ketones

Typical procedure for Method A (0.5 mol %): Et_3Al (9 μL, 25 wt % in hexane, 0.016 mmol) was stirred under N_2 atmosphere with **1k** (8.3 mg, 0.016 mmol) in THF (0.4 mL) at 23 °C for 1 h. After the addition of acetophenone (**3a**, 0.4 mL, 3.3 mmol), the reaction mixture was cooled to −20 °C; subsequently a solution of **2d** (1.2 mg, 0.008 mmol) was added which had been separately treated with TMSCN (0.9 mL, 6.6 mmol) in THF (0.4 mL) at 23 °C for 1 h. The reaction was allowed to proceed at −20 °C. At completion, the reaction mixture was concentrated and placed on a silica gel column to give the pure product with diethyl ether/petroleum ether (1:100 *v*/*v*) as the eluent. The desired 2-trimethylsilyloxy-2-phenylpropanenitrile (**4a**) was obtained as a colorless oil (0.7 g, 94 %). The *ee* was determined as 93 % by chiral GC analysis on Chirasil DEX CB.

Typical procedure for method B (0.1 mol %): Et_3Al (4.5 μL, 25 wt % in hexane, 0.008 mmol) was stirred with **1k** (4.2 mg, 0.008 mmol) in THF (0.2 mL) at 23 °C for 1 h under N_2 atmosphere. After the addition of acetophenone (**3a**, 1.0 mL, 8.4 mmol), the reaction mixture was cooled to −20 °C; subsequently a solution of **2d** (0.6 mg, 0.004 mmol) was added which had been separately treated with TMSCN (2.2 mL, 16 mmol) at 23 °C for 1 h. The reaction was allowed to proceed at −20 °C. At completion, the reaction mixture was concentrated and placed on a silica gel column to give the pure product with diethyl ether/petroleum ether (1:100 *v*/*v*) as the eluent. The desired 2-trimethylsilyloxy-2-phenylpropanenitrile (**4a**) was obtained as a colorless oil (1.8 g, 99 %). The *ee* was determined by chiral GC analysis on Chirasil DEX CB to be 94 %.

2-Trimethylsilyloxy-2-phenylpropanenitrile (4a): 1.80 g, 99 % yield, 94 % *ee*, colorless oil; $[\alpha]_D^{22} = +16.9$ ($c = 2.58$, CH_2Cl_2, 94 % *ee*) [lit. $[\alpha]_D^{20} = +21.9$ ($c = 1.18$, $CHCl_3$, 93 % *ee*)];[5c] ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.19$ (s, 9H; $(CH_3)_3Si$), 1.87 (s, 3H; CH_3), 7.38–7.58 (m, 5H; aromatic H) ppm; GC (CP-Chirasil DEX CB, 0.25 mm×25 m, column temperature = 110 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (minor) = 20.0 min, t_r (major) = 20.6 min.

1-Trimethylsilyloxy-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (4b): 367 mg, 99 % yield, 92 % *ee*; $[\alpha]_D^{22} = +10.1$ ($c = 1.44$, CH_2Cl_2, 92 % *ee*); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.24$ (s, 9H; $(CH_3)_3Si$), 2.06 (m, 2H; CH_2), 2.23 (m, 1H; CH_2), 2.35 (m, 1H; CH_2), 2.85 (m, 2H; CH_2), 7.13 (m, 1H; aromatic H), 7.29 (m, 2H; aromatic H), 7.67 (m, 1H; aromatic H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 1.3$, 18.6, 28.2, 37.6, 69.8, 122.0, 126.6, 127.9, 129.0, 129.2, 135.6, 136.0 ppm; elemental analysis 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; GC (CP-Chirasil DEX CB, 0.25 mm×25 m, column temperature = 130 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (major) = 46.1 min, t_r (minor) = 46.9 min.

1-Trimethylsilyloxy-(1′-indane)-1-carbonitrile (4c): 362 mg, 98 % yield, 92 % *ee*, colorless oil; $[\alpha]_D^{22} = +28.8$ ($c = 2.34$, CH_2Cl_2, 92 % *ee*) [lit. $[\alpha]_D^{20} = +31.6$ ($c = 1.52$, $CHCl_3$, 88 % *ee*)];[6a] ^1H NMR (600 MHz, $CDCl_3$): $\delta = 0.20$ (s, 9H; $(CH_3)_3Si$), 2.43–2.47 (m, 1H; cyclic H), 2.70–2.74 (m, 1H; cyclic H), 2.97–3.02 (m, 1H; cyclic H), 3.10–3.15 (m, 1H; cyclic H), 7.28 (d, $J = 7.2$ Hz, 1H; aromatic H), 7.31 (t, $J = 14.4$ Hz, 1H; aromatic H), 7.36 (td, $J = 1.2$ Hz, 14.4 Hz, 1H; aromatic H), 7.55 (d, $J = 7.2$ Hz, 1H; aromatic H) ppm; GC (Chirasil DEX CB, 0.25 mm× 25 m, column temperature = 120 °C (isothermal), inject temperature =

200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (major) = 38.4 min, t_r (minor) = 38.9 min.

1-Trimethylsilyloxy-(1′-thiophene)-1-carbonitrile (4d): 330 mg, 99% yield, 90% *ee*, colorless oil; $[\alpha]_D^{22} = +13.6$ (c = 2.13, CH_2Cl_2, 90% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.20 (s, 9H; $(CH_3)_3Si$), 2.00 (s, 3H; CH_3), 7.00 (m, 1H; aromatic H), 7.21–7.34 (m, 2H; aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 0.78, 33.40, 68.24, 120.82, 124.70, 125.97, 126.61, 146.27 ppm; elemental analysis calcd (%) for $C_{10}H_{15}NOSSi$ (225.4): C 53.29, H 6.71, N 6.21; found C 53.48, H 6.94, N 6.43; GC (Chirasil DEX CB, 0.25 mm × 25 m, column temperature = 110 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (minor) = 19.6 min, t_r (major) = 20.3 min.

2-Trimethylsilyloxy-2-(4′-methylphenyl)propanenitrile (4e): 353 mg, 99% yield, 92% *ee*; $[\alpha]_D^{22} = +22.1$ (c = 2.44, CH_2Cl_2, 92% *ee*) [lit. $[\alpha]_D^{20} = +21.3$ (c = 1.28, $CHCl_3$, 90% *ee*)];[5c] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.16 (s, 9H; $(CH_3)_3Si$), 1.84 (s, 3H; CH_3), 2.36 (s, 3H; ArCH_3), 7.21 (m, 2H; aromatic H), 7.43 (m, 2H; aromatic H) ppm; elemental analysis 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; GC (CP-Chirasil DEX CB, 0.25 mm × 25 m, column temperature = 105 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (minor) = 43.0 min, t_r (major) = 43.8 min.

2-Trimethylsilyloxy-2-(4′-fluorophenyl)propanenitrile (4f): 1.60 g, 99% yield, 92% *ee*, colorless oil; $[\alpha]_D^{22} = 17.6$ (c = 2.7, CH_2Cl_2, 92% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.18 (s, 9H; $(CH_3)_3Si$), 1.84 (s, 3H; CH_3), 7.08 (m, 2H; aromatic H), 7.52 (m, 2H; aromatic H) ppm; ^{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) ppm; GC (CP-Chirasil DEX CB, 0.25 mm × 25 m, column temperature = 115 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (minor) = 17.0 min, t_r (major) = 17.6 min.

2-Trimethylsilyloxy-2-(4′-chlorophenyl)propanenitrile (4g): 1.80 g, 99% yield, 90% *ee*, colorless oil; $[\alpha]_D^{22} = +18.2$ (c = 2.06, CH_2Cl_2, 90% *ee*) [lit. $[\alpha]_D^{20} = +29.5$ (c = 1.04, $CHCl_3$, 92% *ee*)];[5c] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 9H; $(CH_3)_3Si$), 1.83 (s, 3H; CH_3), 7.38 (m, 2H; aromatic H), 7.48 (m, 2H; aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.0, 33.5, 71.0, 121.2, 126.1, 128.8, 134.6, 140.7 ppm; elemental analysis calcd (%) for $C_{12}ClH_{16}NOSi$: C 56.79, H 6.35, N 5.52; found C 56.82, H 6.41, N 5.93; GC (CP-Chirasil DEX CB, 0.25 mm × 25 m, column temperature = 125 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (minor) = 29.1 min, t_r (major) = 29.9 min.

2-Trimethylsilyloxy-2-(3′-chlorophenyl)propanenitrile (4h): 370 mg, 95% yield, 90% *ee*, colorless oil; $[\alpha]_D^{22} = +19.6$ (c = 2.88, CH_2Cl_2, 90% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 (s, 9H; $(CH_3)_3Si$), 1.86 (s, 3H; CH_3), 7.34–7.55 (m, 4H; aromatic H) 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; elemental analysis 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; GC (CP-Chirasil DEX CB, 0.25 mm × 25 m, column temperature = 105 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (minor) = 57.1 min, t_r (major) = 58.0 min.

2-Trimethylsilyloxy-2-phenylbutanenitrile (4i): 1.80 g, 99% yield, 87% *ee*, colorless oil; $[\alpha]_D^{22} = +15.7$ (c = 1.22, CH_2Cl_2, 87% *ee*) [lit. $[\alpha]_D^{20} = +19.4$ (c = 1.39, $CHCl_3$, 88% *ee*)];[5c] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.15 (s, 9H; $(CH_3)_3Si$), 0.99(t, J = 7.2 Hz, 3H; CH_3), 1.92–2.23(m, 2H; CH_2), 7.40(m, 3H; aromatic H), 7.50(m, 2H; aromatic H) ppm; GC (CP-Chirasil DEX CB, 0.25 mm × 25 m, column temperature = 110 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (minor) = 25.6 min, t_r (major) = 26.9 min.

2-Trimethylsilyloxy-2-(2′-naphthyl)propanenitrile (4j): 2.16 g, 99% yield, >99% *ee* (after recrystallization of the product with 81% *ee* from *n*-hexane), white solid; $[\alpha]_D^{22} = -9.5$ (c = 0.58, CH_2Cl_2, >99% *ee*) [lit. $[\alpha]_D^{20} = +12.6$ (c = 1.99, $CHCl_3$, 94% *ee*)];[5c] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.22 (s, 9H; $(CH_3)_3Si$), 1.97 (s, 3H; CH_3), 7.54–7.66 (m, 3H; aromatic H), 7.90–7.93 (m, 3H; aromatic H), 8.07 (d, J = 1.8 Hz, 1H; aromatic H) ppm; HPLC (Chiralcel OJ, *i*PrOH/*n*-hexane, 0.5:99.5 *v*/*v*, 1.0 mL min^{-1}, 23 °C, UV 254 nm): t_r (major) = 6.0 min, t_r (minor) = 7.1 min.

2-Trimethylsilyloxy-2-methylheptanenitrile (4k): 1.73 g, 99% yield, 79% *ee*, colorless oil; $[\alpha]_D^{22} = +1$ (c = 1.62, CH_2Cl_2, 79% *ee*); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.20 (s, 9H; $(CH_3)_3Si$), 2.43–2.47 (m, 1H; cyclic H), 2.70–2.74 (m, 1H; cyclic H), 2.97–3.02 (m, 1H; cyclic H), 3.10–3.15 (m, 1H; cyclic H), 7.28 (d, J = 7.2 Hz, 1H; aromatic H), 7.31 (t, J = 14.4 Hz, 1H; aromatic H), 7.36 (td, J = 1.2 Hz, 14.4 Hz, 1H; aromatic H), 7.55 (d, J = 7.2 Hz, 1H; aromatic H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 1.5, 14.2, 22.7, 24.2, 29.1, 31.7, 43.6, 69.9, 122.4 ppm; GC (Chirasil DEX CB, 0.25 mm × 25 m, column temperature = 100 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (major) = 15.4 min, t_r (minor) = 15.7 min.

2-Trimethylsilyloxy-2-methylpentanenitrile (4l): 1.30 g, 95% yield, 80% *ee* [(1R,2*R*)-**1k** was used in this case], colorless oil; $[\alpha]_D^{22} = -0.9$ (c = 1.6, CH_2Cl_2, 80% *ee*); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.23 (s, 9H; $(CH_3)_3Si$), 0.97 (t, J = 6 Hz, 3H; CH_3), 1.57 (m, 4H; CH_2CH_2), 2.18 (s, 3H; CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 1.3, 13.8, 17.7, 30.9, 45.5, 69.6, 122.2 ppm; GC (Chirasil DEX CB, 0.25 mm × 25 m, column temperature = 65 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (minor) = 11.0 min, t_r (major) = 11.2 min.

2-Trimethylsilyloxy-2-methyl-3-methylbutanenitrile (4m): 1.11 g, 80% yield, 90% *ee* [(1*R*,2*R*)-**1k** was used in this case], colorless oil; $[\alpha]_D^{22} = -1.1$ (c = 1.66, CH_2Cl_2, 90% *ee*); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.24 (s, 9H; $(CH_3)_3Si$), 1.03 (t, J = 6 Hz, 6H; $(CH_3)_2CH$), 1.53 (s, 3H; CH_3), 1.86 (hept, J = 6 Hz, 1H; $(CH_3)_2CH$) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 1.2, 17.0, 26.0, 39.1, 73.5, 121.6 ppm; GC (Chirasil DEX CB, 0.25 mm × 25 m, column temperature = 65 °C (isothermal), inject temperature = 200 °C, detector temperature = 250 °C, inlet pressure = 8 psi): t_r (minor) = 19.0 min, t_r (major) = 19.4 min.

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[1] For reviews on the enantioselective construction of quaternary stereocenters, see: a) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726–1728; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688–1690; b) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597; c) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; d) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066.

[2] For reviews on the synthesis and applications of cyanohydrins, see: a) R. J. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682; b) F. Effenberger, *Angew. Chem.* **1994**, *106*, 1609–1619; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555–1564; c) M. North, *Synlett* **1993**, 807–820; d) M. North, *Tetrahedron: Asymmetry* **2003**, *14*, 147–176.

[3] M. C. K. Choi, S. S. Chan, K. Matsumoto, *Tetrahedron Lett.* **1997**, *38*, 6669–6672.

[4] a) Y. N. Belokon, B. Green, N. S. Ikonnikov, M. North, V. I. Tararov, *Tetrahedron Lett.* **1999**, *40*, 8147–8150; b) Y. N. Belokon′, B. Green, N. S. Ikonnikov, M. North, T. Parsons, V. I. Tararov, *Tetrahedron* **2001**, *57*, 771–779; c) Y. N. Belokon′, S. Caveda-Cepas, B. Green, N. S. Ikonnikov, V. N. Khrustalev, V. S. Larichev, M. A. Moscalenko, M. North, C. Orizu, V. I. Tararov, M. Tasinazzo, G. I. Timofeeva, L. V. Yashkina, *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973.

[5] For reviews on bifunctional catalysis, see: a) H. Gröger, *Chem. Eur. J.* **2001**, *7*, 5246–5251; b) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989–1999. For examples, see: c) Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413; d) Y. Hamashima, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 691–694; e) K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 9908–9909; f) S. Masumoto, K. Yabu, M. Kanai, M.

Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 2919–2922; g) K. Yabu, S. Masumoto, M. Kanai, D. P. Curran, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 2923–2926; h) S. Masumoto, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 8647–8651.

[6] a) H. Deng, M. P. Isler, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2002**, *114*, 1051–1054; *Angew. Chem. Int. Ed.* **2002**, *41*, 1009–1012. The dipeptide catalysts have been developed and applied to other asymmetric reactions. For examples, see: b) B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776–1779; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668–1671.

[7] a) S.-K. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901; b) S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196.

[8] For other examples, see: a) E. J. Corey, Z. Wang, *Tetrahedron Lett.* **1993**, *34*, 4001–4004; b) K. Itoh, S. Kanemasa, *J. Am. Chem. Soc.* **2002**, *124*, 13394–13395; c) E. Y.-X. Chen, W. J. Kruper, G. Roof, D. R. Wilson, *J. Am. Chem. Soc.* **2001**, *123*, 745–746; d) A. H. Mermerian, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 4050–4051; e) D. Ristic-Petrovic, J. R. Torkelson, R. W. Hilts, R. McDonald, M. Cowie, *Organometallics* **2000**, *19*, 4432–4434; f) J. Kruger, E. M. Carreira, *J. Am. Chem. Soc.* **1998**, *120*, 837–838; g) M. Wadamoto, N. Ozasa, A. Yanagisawa, H. Yamamoto, *J. Org. Chem.* **2003**, *68*, 5593–5601.

[9] a) B. Liu, X. Feng, F. Chen, G. Zhang, Y. Jiang, *Synlett* **2001**, 1551–1553; b) Z. Jiao, X. Feng, B. Liu, F. Chen, G. Zhang, Y. Jiang, *Eur. J. Org. Chem.* **2003**, 3818–3826.

[10] a) Y. Jiang, L. Gong, X. Feng, W. Hu, W. Pan, Z. Li, A. Mi, *Tetrahedron* **1997**, *53*, 14327–14338; b) Y. Jiang, X. Zhou, W. Hu, L. Wu, A. Mi, *Tetrahedron: Asymmetry* **1995**, *6*, 405–408; c) Y. Shen, X. Feng, G. Zhang, Y. Jiang, *Synlett* **2002**, 1353–1355; d) Y. Shen, X. Feng, Y. Li, G. Zhang, Y. Jiang, *Eur. J. Org. Chem.* **2004**, 129–137.

[11] a) F. Chen, X. Feng, B. Qin, G. Zhang, Y. Jiang, *Synlett* **2003**, 558–560; b) F. Chen, X. Feng, B. Qin, G. Zhang, Y. Jiang, *Org. Lett.* **2003**, *5*, 949–952.

[12] ^{13}C NMR (150 MHz, $CDCl_3$) shows two signals at $\delta_C = 9.4$ and $\delta_C = 17.9$ ppm remaining unchanged both during the catalyst generation in the absence of TMSCN and during the reaction period, which suggested that the third Et attached to the Al atom of **1k**·$AlEt_3$ complex did not exchange with CN. For methyl-Al-salen complex, see: a) J. K. Myers, E. N. Jacobsen, *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960. For other examples of Al-salen complexes, see: b) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316; c) D. A. Atwood, M. J. Harvey, *Chem. Rev.* **2001**, *101*, 37, and references therein; d) D. A. Evans, J. M. Janey, N. Magomedov, J. S. Tedrow, *Angew. Chem.* **2001**, *113*, 1936–1939; *Angew. Chem. Int. Ed.* **2001**, *40*, 1884–1888; e) E. J. Campbell, H. Zhou, S. T. Nguyen, *Angew. Chem.* **2002**, *114*, 1062–1064; *Angew. Chem. Int. Ed.* **2002**, *41*, 1020–1022; f) A. Baeza, J. Casas, C. Najera, J. M. Sansano, J. M. Saa, *Angew. Chem.* **2003**, *115*, 3251–3254; *Angew. Chem. Int. Ed.* **2003**, *42*, 3143–3146; g) G. M. Sammis, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 4442–4443.

[13] Tertiary amine N-oxides were prepared by direct oxidation of the corresponding amines by literature methods. a) T. L. Kruger, W. N. White, H. White, S. L. Hartzell, J. W. Kress, N. Walter, *J. Org. Chem.* **1975**, *40*, 77–81. For a review on the coordination chemistry of N-oxides with metals, see: b) N. M. Karayannis, L. L. Pytlewski, C. M. Mikulski, *Coord. Chem. Rev.* **1973**, *11*, 93–159. For other examples, see: c) M. Nakajima, M. Saito, M. Shiro, S.-i. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420; d) B. Tao, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 353–354; e) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2002**, *124*, 4233–4235; f) T. Shimada, A. Kina, S. Ikeda, T. Hayashi, *Org. Lett.* **2002**, *4*, 2799–2801.

[14] For examples, see: a) S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*, 432–440; b) S. E. Denmark, T. Wynn, G. L. Beutner, *J. Am. Chem. Soc.* **2002**, *124*, 13405–13407; c) S. E. Denmark, J.-P. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 12021–12022; d) S. E. Denmark, T. Wynn, G. L. Beutner, *J. Am. Chem. Soc.* **2002**, *124*, 13405–13407.

[15] a) E. M. Vogl, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 1672–1680; *Angew. Chem. Int. Ed.* **1999**, *38*, 1570–1577; b) A. M. Costa, C. Jimeno, J. Gavenonis, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 6929–6941, and references therein; c) M. Bandini, M. Fagioli, P. Melchiorre, A. Melloni, A. Umani-Ronchi, *Tetrahedron Lett.* **2003**, *44*, 5843–5846.

[16] ^{1}H NMR (400 MHz, $CDCl_3$) shows that the chemical shift of TMSCN is $\delta_H = 0.35$ ppm. After it has coordinated to N-oxide **2d**, however, a new signal appears at $\delta_H = 0.17$ ppm.

[17] R. Noyori, S. Murata, M. Suzuki, *Tetrahedron* **1981**, *37*, 3899–3910.

[18] TMSCN appears to be involved in the rate-determining step because more than an equivalent quantity (2 equiv) of it relative to the ketones was needed to give the optimum reaction rate and enantioselectivity.

[19] C. M. Mascarenha, S. P. Miller, P. S. White, J. P. Morken, *Angew. Chem.* **2001**, *113*, 621–623; *Angew. Chem. Int. Ed.* **2001**, *40*, 601–603.

[20] J. F. Larrow, E. N. Jacobsen, Y. Gao, Y. Hong, X. Nie, C. M. Zepp, *J. Org. Chem.* **1994**, *59*, 1939–1942.

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