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Asymmetric ring opening of epoxides with cyanides catalysed by chiral binuclear titanium complexes

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ABSTRACT

A series of Schiff bases obtained from salicylaldehydes and 3,3′-diformyl-BINOL were synthesized. The complexes of these Schiff bases with Ti(IV) were active for the asymmetric ring opening of epoxides with TMSCN. A mixture of unpurified ligands was found to be as effective as the best one. The influence of temperature, solvent polarity and structural modification of the pre-catalysts on the enantioselectivity of the process has also been investigated.

1. Introduction

The design and use of bi- and polynuclear chiral Lewis acid catalysts for asymmetric catalysis is a rapidly developing area.[1] The rational design of chiral ligands capable of supporting two Lewis acid sites rigidly oriented in space is straightforward. For example, Trost's dinuclear Zn-catalysts have been used for aldol condensations.[2] Some of us have developed highly efficient homobinuclear Ti-based[3] and heteronuclear Ti/V mixed[4] chiral catalysts for the asymmetric addition of cyanides to carbonyl compounds. Such an approach has been widely used not only in asymmetric catalysis but also for polymerization reactions.[5] Also well known is that simple mixing of several single-site chiral catalysts can be extremely successful, leading to efficient heterobimetallic catalysts.[6] It is important to use very pure ligands. We previously described the binuclear titanium catalyst for cyanations of aldehydes and *meso*-epoxides, which can give high ee only when the ligand is very pure. Even if the NMR spectrum is clean, the elemental analysis could be bad, meaning that the enantiomeric excess decreased to 20–30%.[7] However, it is much easier to use ligands without any purification. Herein we report on a mixture of unpurified ligands that can be used for the asymmetric ring-opening of epoxides with TMSCN.

2. Results and discussion

Ligands **1**–**4** (see Scheme 1) were prepared as described earlier from the corresponding racemic and enantiomerically pure binaphthols[7–10] (Scheme 2). Catalysts were prepared in situ by mixing ligands with two equivalents of titanium tetraisopropoxide.

The asymmetric ring opening of cyclohexene oxide **5** with trimethylsilylcyanide (TMSCN) (Scheme 2) was chosen as a model reaction. It has previously been reported that titanium complexes can lead to a mixture of nitrile and isonitrile products in the model reaction.[11] Even the diastereomer of a ligand can change the ratio between the nitrile and isonitrile.[12] In order to check the hard and soft acid-base theory, we prepared catalysts from aluminium and zinc. The results were in agreement with the theory. Catalysts based on hard aluminium led exclusively to the nitrile product while soft zinc led only to the isonitrile product (Table 1, entries 1 and 2). When we switched the metal to the titanium tetraisopropoxide, great enantioselectivity was achieved. There were no significant differences in the activity or nitrile–isonitrile ratio in the catalysis with the pre-catalysts from ligands **1**–**3** (Table 1, entries 3, 4 and 6). However, the enantiomeric excess of the main product was slightly higher (96%) in case ligand **2** was used. Decreasing the amount of catalyst from 5 to 1 mol % did not lead to a decrease in the activity or enantioselectivity but increased the amount of isonitrile **7** (Table 1, entry 4 vs 5). Since ligand **3** is derived from the inexpensive and highly accessible salicylaldehyde, we decided to explore its catalytic ability. Decreasing the temperature from RT to −20 °C led to an increase in the enantiomeric excess of product **6** to 95% (Table 1, entry 6 vs 15). However, it also led to a decrease in the **6**:**7** ratio. The catalyst can be used several times without a loss in enantioselectivity and also with higher nitrile–isonitrile ratio (Table 1, entries 6–8). On the other hand, the chemical yield decreased. This could be due to an incorrect measurement of the amount of the catalyst after a recycle, because the structure of the catalyst could be completely different after the first recycle. Unsymmetrical Schiff bases can be unstable

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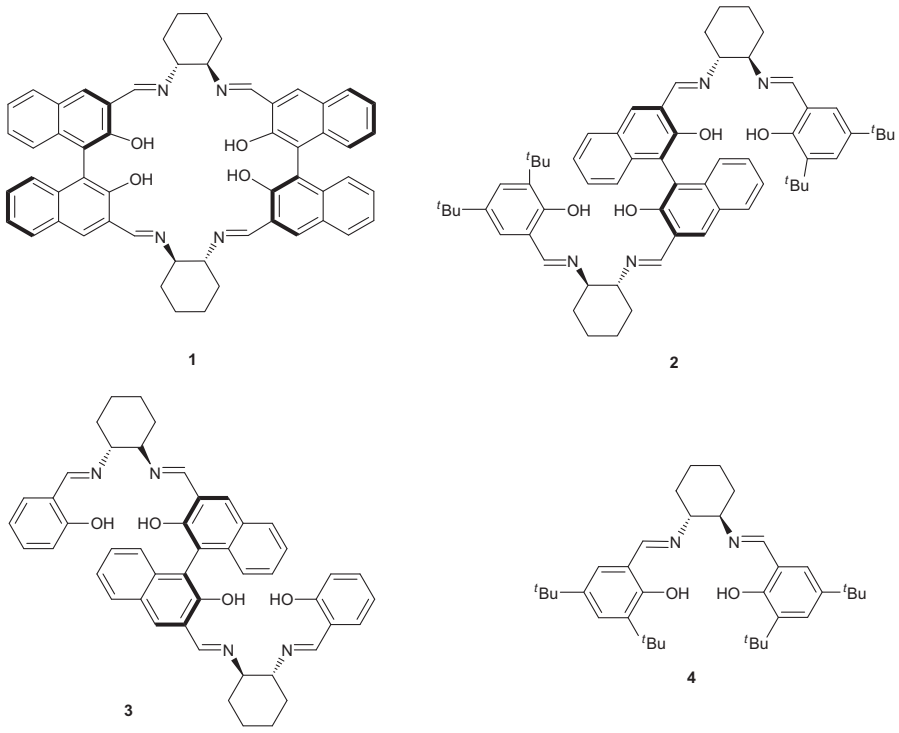
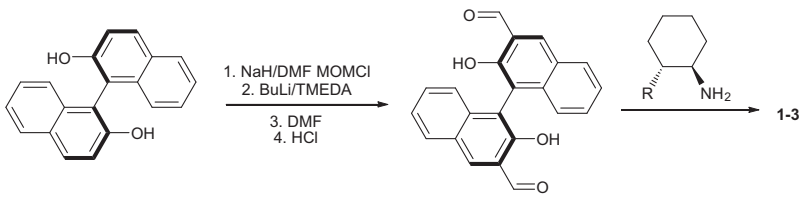


Scheme 1. Chiral ligands for catalysis.

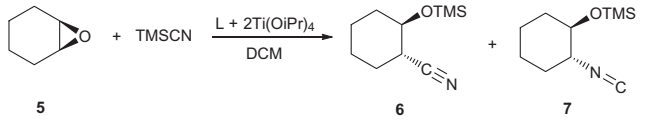


Scheme 2. Synthesis of ligands **1**–**3**.

and change equilibrium to increase entropy. We mixed ligands **1** and **2** in a 1:1 ratio. Such a system showed identical results with pure ligand **2**. During the synthesis of ligand **2**, a mixture of **1**, **2** and **4** was formed. Ligand **4** itself was the most ineffective compared to ligands **1**–**3** (Table 1, entry 11 vs 3, 4 and 6). We decided to use this unpurified mixture of Schiff bases with titanium tetraisopropoxide as the pre-catalyst. Fortunately, this mixture was very effective and led to a product with 95% ee. We found that this mixture of different ligands was very effective for the asymmetric ring-opening of epoxides with TMSCN. Since the difference in enantioselectivity was small, we decided to decrease the catalyst loading to find which ligand was the most effective. When 0.1 mol % of ligands were used, it was shown that only the catalyst based on ligand **2** remained effective (Table 1, entries 12–14). Even at 0.1 mol % of ligand **2** the yield after 24 h was 95% and the ee was 96%. The configuration of BINOL is responsible for the absolute configuration of the product. When the catalyst derived from (*R*)-BINOL was used, (1*S*,2*R*)-2-((trimethylsilyl)oxy)cyclohexane-1-carbonitrile was observed. Furthermore we decided to study the activity of ligands **2** and **3** for other *meso*-epoxides. Ligand **2** was found to be more active but slightly less regioselective than ligand **3** for the ring opening of cyclopentene oxide (Table 2, entry 1 vs 2). A similar situation was also found with cyclooctadiene oxide (Table 2, entry 3 vs 5). Ligand **3** proved to be less active but better in terms of enantioselectivity. No isonitrile was found in both cases. The catalyst based on ligand **3** was shown to be recyclable, and even led to a slight increase in the enantioselectivity (Table 2, entry 3 vs 4).

After we had found that these catalysts were effective in the asymmetric ring opening of *meso*-epoxides, we decided to check their activity in the kinetic resolution of racemic epoxides. The results are summarized in Table 3. When the racemic propylene oxide was used, ligand **2** was found to be not only more active but also more regio- and enantioselective (Table 3, entry 1 vs 2). Decreasing the reaction time from 24 to 5 h did not increase the ee but the reaction became more regioselective (Table 3, entry 2 vs 3). When the reaction was carried out at −20 °C instead of room temperature, the regioselectivity and the enantiomeric excess decreased (Table 3, entry 4). When styrene oxide was used as a substrate, both ligands showed good enantioselectivity but the regioselectivity changed dramatically. When the catalyst was prepared from ligand **3** the ratio between 3-phenyl-3-((trimethylsilyl)oxy)propanenitrile and 2-phenyl-3-((trimethylsilyl)oxy) propanenitrile became 50–50 while the catalyst from ligand **2** showed an inverse ratio 10–29 (Table 3, entry 5 vs 6). When epichlorohydrin was used as a starting material, no other regioisomers were detected (Table 3, entries 7–11). When the reaction was carried out for 4 h instead of 24, the yield decreased from 38% to 20% while the enantiomeric excess increased from 55% to 63% (Table 3, entry 7 vs 8). Cooling down the reaction to −20 °C led to a slight increase in *ee* to 70% but the conversion decreases to 9% (Table 3,

Table 1
Catalysis of asymmetric ring-opening of cyclohexene oxide by TMSCN[a]

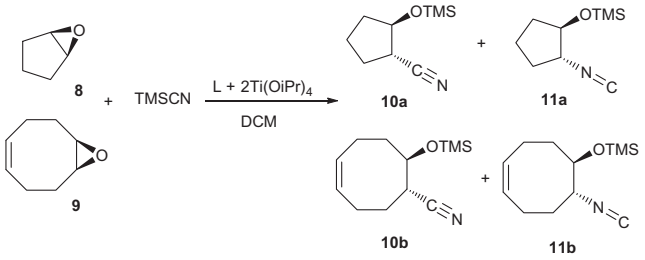


5 6 7

Entry	Ligand	mol %	Yield (%)	**6**:**7**[d]	ee (%) **6**
1	**3**+2Al(O^iPr)$_3$	10	62	100–0	23
2	**3**+2$ZnEt_2$	10	67	0–100	0
3	**1**	5	>99	90–10	92
4	**2**	5	>99	92–8	96
5	**2**	1	>99	75–25	96
6	**3**	5	>99	88–12	92
7	**3** recycle 2	5	77	96–4	91
8	**3** recycle 3	8	55	96–4	92
9	**2**+**1** 1:1	5	>99	92–8	96
10	**1**+**2**+**4** 20–60–20	5	>99	93–7	95
11	**4**	10	56	>99–1	40
12	**3**	0.1	20	77–23	54
13	**1**	0.1	22	nd	44
14	**2**	0.1	95	87–13	96
15[b]	**3**	5	>99	85–15	95

[a] Reaction conditions: **5** (0.195 mmol), TMSCN (0.390 mmol), RT, 24 h, catalyst (19.5 μmol), DCM (0.5 ml).
[b] −20 °C.
[c] 5 h.
[d] The ratio between nitrile and isonitrile was determined by NMR.

Table 2
Catalysis of asymmetric ring-opening of *meso*-epoxides by TMSCN[a]



Entry	Epoxide	Ligand	Yield (%)	**10**:**11**	ee (%) **10**
1	**8**	**2**	>99	86–14	91
2	**8**	**3**	90	90–10	92
3	**9**	**3**	50	100–0	89
4	**9**	**3** recycle	40	100–0	92
5	**9**	**2**	70	100–0	85

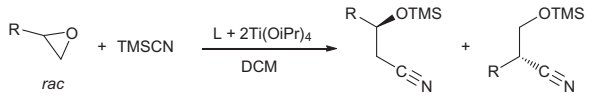
[a] Reaction conditions: meso-epoxide (0.195 mmol), TMSCN (0.390 mmol), RT, 24 h, catalyst (19.5 lmol), DCM (0.5 ml).

entry 9). When the reaction time was increased to 48 h under −20 °C, both the yield and enantioselectivity increased (Table 3, entry 10). The problem of low yield and moderate enantioselectivity was solved only when ligand **2** was used instead of ligand **3** (Table 3, entry 11). Ligand **2** showed enantioselectivity (54% *ee*) even for the highly electron deficient trifluoropropylene oxide (Table 3, entry 12).

3. Conclusion

A family of binuclear titanium(IV) catalysts based on unsymmetrical Schiff bases has been developed and their reusability has been reported on. A mixture of unpurified Schiff bases can be used directly for the preparation of highly active and stereospecific catalysts. These properties make them interesting candidates for the catalysis of other asymmetric reactions and/or polymerizations.

Table 3
Kinetic resolution of racemic epoxides with TMSCN[a]



Entry	R	Ligand	Yield (%)		ee (%)	
			2-OTMS	2-CN	2-OTMS	2-CN
1	CH_3	**3**	41	3	84	nd
2		**2**	60	9	87	nd
3[c]		**2**	50	4	86	nd
4		**2**[f]	44	14	83	nd
5	Ph	**3**	50	50	89	66
6		**2**	10	29	90	86
7[d]	$ClCH_2$	**3**	20	0	63	—
8		**3**	38	0	55	—
9[b]		**3**	9	0	70	—
10[b,e]		**3**	26	0	76	—
11		**2**	60	0	84	—
12	CF_3	**2**	23	0	54	—
13	CH_3	**1**	30	8	64	nd

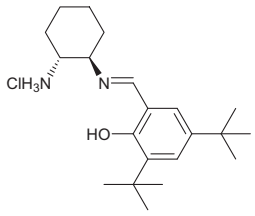
[a] Reaction conditions: epoxide (0.39 mmol), TMSCN (0.195 mmol), RT, 24 h, ligand 5 mol %, Ti(O^iPr)$_4$ 10 mol %, DCM (0.5 ml).
[b] −20 °C.
[c] 5 h.
[d] 4 h.
[e] 48 h.
[f] Recycle of the catalyst.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) and Bruker Avance 400 spectrometers. Chemical shifts were measured in the δ scale relative to the signal of residual protons of the deuterated solvent. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in a temperature maintained cell (l = 5 cm) at 25 °C. The solvent and the sample concentration in grams per 100 ml were indicated for all compounds. Elemental analyses of all the synthesized compounds were performed at the Laboratory of Elemental Analysis of the A.N. Nesmeyanov Institute of Organoelement Compounds (Russian Academy of Sciences). Silica gel Kieselgel 60 (Merck) was used. Solvents were purified according to standard procedures. Enantiomeric purities were determined with HPLC on Chiralpak IB-3 eluted with mixture hexane/^{i}PrOH (90:10 or 99:1) 1 ml/min and detected at 254 nm. The ratio between the nitrile and isonitrile was determined by NMR.

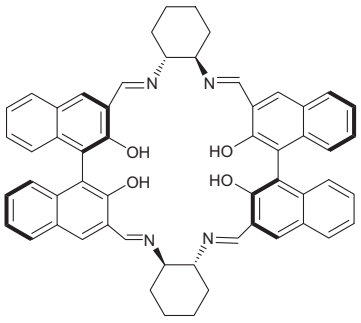
4.2. Synthesis of the Schiff base from di-*tert*-butylsalicylaldehyde and (1*R*,2*R*)-cyclohexane diamine hydrochloric salt 12



At first, 0.72 g (6.3 mmol) of (1*R*,2*R*)-cyclohexane diamine and 0.337 g (6.3 mmol) of NH_4Cl were dissolved in 30 ml of methanol. The reaction mixture was stirred for 15 min and the solvent was evaporated under vacuum. The formed solid was washed with diethyl ether and dissolved in 25 ml of methanol. A solution of

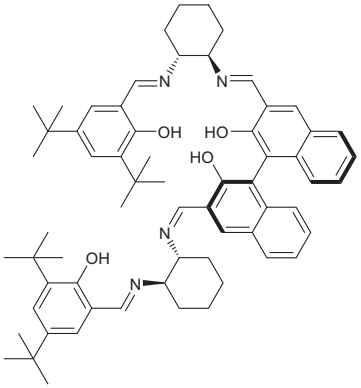
1.47 g (6.3 mmol) of 3,5-di-*tert*-butylsalycilaldehyde in 25 ml of dry methanol was added to the solution. The reaction mixture was stirred for 15 min and the solvent was evaporated under vacuum. To the formed yellow oil 10 ml of diethyl ether was added. Next, 40 ml of diethyl ether was added and white precipitate was filtered and dried. Yield 0.99 g (50%). ^{1}H NMR (400 MHz, MeOD) δ 8.60 (s, 1H), 7.43 (d, J = 2.3 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 3.20–3.40 (m, 2H), 2.10–2.22 (m, 1H), 1.80–1.95 (m, 3H), 1.60–1.75 (m, 1H), 1.45–1.60 (m, 4H), 1.43 (s, 9H), 1.31 (s, 9H).

4.3. Synthesis of ligand 1



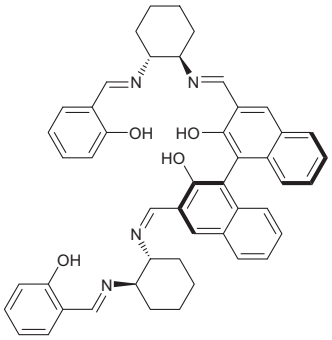
A mixture of 0.26 g (0.979 mmol) of (1*R*,2*R*)-cyclohexane diamine mono-L-tartrate and 0.27 g (1.958 mmol) of potassium carbonate was dissolved in 3 ml of 50% aqueous ethanol solution. The resulting mixture was added to a suspension of 0.335 g (0.979 mmol) of (*R*)-3,3′-diformyl-BINOL in 7 ml of ethanol. The reaction mixture was stirred at room temperature for 24 h. The resulting precipitate was filtered of and washed with ethanol and dried under vacuum. Yield of light-yellow solid was 0.5 g (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.21 (br s, 4H), 8.47 (s, 4H), 7.75 (m, 8H), 7.28 (m, 4H), 6.96 (m, 8H), 3.31 (m, 4H), 1.82–1.92 (m, 8H), 1.40–1.61 (m, 8H). $[\alpha]_D^{25} = -214$ (c 0.25, CH_2Cl_2).

4.4. Synthesis of ligand 2



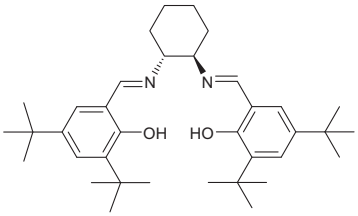
To a solution of 0.2 g (0.6 mmol) of (*R*)-3,3′-diformyl-BINOL and 0.4 ml (2.8 mmol) of triethylamine in 15 ml of dry dichloromethane was added 0.52 g (1.4 mmol) of **12** at 0 °C under argon. The reaction mixture was warmed up to 25 °C and stirred for 48 h, until no starting dialdehyde was found on TLC. The reaction mixture was worked up with a saturated solution of ammonium chloride in water, and then extracted with DCM. The organic layer was dried over anhydrous sodium sulfate, evaporated under vacuum and purified by column chromatography. R_f = 0.34 (hexane–ethyl acetate–triethylamine 9:1:0.1). Yield 0.14 g (24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.79 (br s, 2H), 13.12 (br s, 2H), 8.55 (s, 2H), 8.20 (s, 2H), 7.84 (s, 2H), 7.75 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 2.4 Hz, 2H), 7.21 (t, J = 7.4 Hz, 2H), 7.15 (t, J = 7.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 2.4 Hz, 2H), 3.35–3.47 (m, 2H), 3.16–3.30 (m, 2H), 1.80–2.05 (m, 4H), 1.60–1.80 (m, 4H), 1.35–1.50 (m + s, 13H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 165.2, 158.0, 154.5, 140.0, 136.4, 135.1, 133.6, 128.7, 128.2, 127.5, 126.9, 125.9, 124.7, 123.2, 120.7, 117.8, 116.3, 73.3, 71.7, 35.0, 34.0, 33.3, 32.8, 31.4, 29.7, 29.4, 24.3, 22.7. $[\alpha]_D^{25} = -386$ (c 0.5, $CHCl_3$).

4.5. Synthesis of ligand 3



^{1}H NMR (300 MHz, $CDCl_3$) δ 13.20 (br s, 4H), 8.51 (s, 2H), 8.18 (s, 2H), 7.99 (s, 2H), 7.75–8.05 (m, 4H), 7.33–7.16 (m, 4H), 7.01 (dd, J = 14.2, 7.9 Hz, 4H), 6.92 (d, J = 8.2 Hz, 2H), 6.78 (t, J = 7.4 Hz, 2H), 3.30 (m, 4H), 2.03–1.37 (m, 16H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.20 (s, 4H), 8.50 (s, 2H), 8.18 (s, 2H), 7.85 (s, 2H), 7.81 (d, J = 7.8 Hz, 2H), 7.31–7.16 (m, 6H), 7.01 (dd, J = 12.4, 8.0 Hz, 4H), 6.90 (d, J = 8.2 Hz, 2H), 6.78 (t, J = 7.4 Hz, 2H), 3.41–3.30 (m, 2H), 3.29–3.18 (m, 2H), 2.00–1.34 (m, 16H). $[\alpha]_D^{25} = -352$ (c 0.62, $CHCl_3$).

4.6. Synthesis of ligand 4



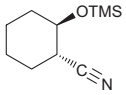
Ligand **4** was synthesized according to the literature procedure.[13] The binuclear titanium complex was also synthesized according to the literature procedure.[3]

4.7. Asymmetric ring-opening of *meso*-epoxides with TMSCN (general procedure)

At first, Ti(O-*i*-Pr)$_4$ (11.4 μl, 39.0 μmol) was added to a solution of ligands **1**–**3** (19.5 μmol) in absolute DCM (0.5 ml) under an argon atmosphere. The reaction mixture was stirred for 1 h at room temperature. A clear solution was formed in the case of the complex from ligand **2**, while a suspension was formed in the case of the complex from ligands **1** or **3**. An epoxide (195 mmol) was then added to the reaction mixture. After 15 min TMSCN (390 μmol) was added. The colour of the reaction mixture changed to dark orange. After the indicated time, hexane (or petroleum ether) (3 ml) was added. The precipitated complex was filtered off and used for the recycle. The solution was filtered through silica

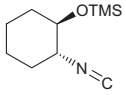
gel and evaporated under vacuum. The reaction mixture was analysed by GC to determine the enantiomeric excess of the nitrile.

4.7.1. 2-((Trimethylsilyl)oxy)cyclohexane-1-carbonitrile



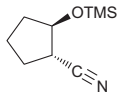
^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), 1.25–1.33 (m, 3H), 1.55–1.75 (m, 3H), 1.90–2.07 (m, 1H), 2.08–2.11 (m, 1H), 2.38–2.44 (m, 1H), 3.64–3.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 0.18, 23.3, 23.9, 28.2, 34.7, 37.7, 71.1, 121.6. Chiral GC column β-DM 30 m, *T*(column) = 120 °C, He 15 psi, split ratio 75:1 *T*(evaporator) = 200 °C, *T*(detector) = 200 °C, T_r (minor) = 15.0 min, T_r (major) = 15.8 min. The absolute configuration was determined by chiral GC and compared to our previous work.[12] When the catalyst derived from (*R*)-BINOL was used the (1*S*,2*R*)-2-((trimethylsilyl)oxy)cyclohexane-1-carbonitrile was observed; with the catalyst derived from (*S*)-BINOL the (1*R*,2*S*)-2-((trimethylsilyl)oxy)cyclohexane-1-carbonitrile was observed in all cases.

4.7.2. 2-((Trimethylsilyl)oxy)cyclohexane-1-isonitrile



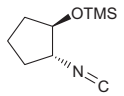
^{1}H NMR ($CDCl_3$) δ 0.2 (s, 9H), 1.25–1.33 (m, 3H), 1.55–1.75 (m, 3H), 1.90–2.07 (m, 1H), 2.08–2.11 (m, 1H), 3.30–3.35 (m, 1H), 3.60–3.65 (m, 1H); ^{13}C ($CDCl_3$) 0.27, 23.0, 23.2, 31.3, 33.4, 58.7, 72.9, 155.1.

4.7.3. 2-((Trimethylsilyl)oxy)cyclopentane-1-carbonitrile



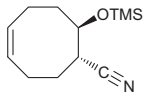
^{1}H NMR ($CDCl_3$) δ 0.15 (s, 9H), 1.40–2.30 (m, 6H), 2.55–2.70 (m, 1H), 4.36 (dd, *J* = 11.7, 5.7 Hz, 1H); Chiral GC column β-DM 30 m, *T*(column) = 100 °C, He 15 psi, split ratio 75:1 *T*(evaporator) = 200 °C, *T*(detector) = 200 °C, T_r (minor) = 18.8 min, T_r (major) = 19.9 min. The absolute configuration was assigned by analogy with 2-((trimethylsilyl)oxy)cyclohexane-1-carbonitrile.

4.7.4. 2-((Trimethylsilyl)oxy)cyclopentane-1-isonitrile



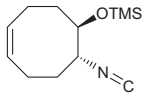
^{1}H NMR ($CDCl_3$) δ 0.14 (s, 9H), 1.30–2.20 (m, 6H), 3.55–3.65 (m, 1H), 4.15–4.25 (m, 1H).

4.7.5. 8-((Trimethylsilyl)oxy)cyclooct-4-ene-1-carbonitrile



^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H); 1.80–2.40 (m, 8H); 3.00–3.09 (m, 1H); 3.89 (td, *J* = 7.90, 3.33 Hz, 1H); 5.50–5.62 (m, 1H); 5.68–5.79 (m, 1H). Chiral GC column β-DM 30 m, *T*(column) = 150 °C, He 15 psi, split ratio 75:1 *T*(evaporator) = 200 °C, *T*(detector) = 200 °C, T_r (minor) = 17.2 min, T_r (major) = 19.5 min. The absolute configuration was assigned and by analogy with 2-((trimethylsilyl)oxy)cyclohexane-1-carbonitrile.

4.7.6. 8-((Trimethylsilyl)oxy)cyclooct-4-ene-1-isonitrile

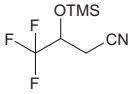


^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H); 1.50–2.60 (m, 8H); 3.77–3.88 (m, 1H); 3.90–4.00 (m, 1H); 5.49–5.70 (m, 2H).

4.8. Asymmetric kinetic resolution of epoxides with TMSCN (general procedure)

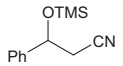
At first, Ti(O-*i*-Pr)$_4$ (11.4 μl, 39.0 μmol) was added to a solution of the ligands **1**–**3** (19.5 μmol) in absolute DCM (0.5 ml) under an argon atmosphere. The reaction mixture was stirred for 1 h at room temperature. A clear solution was formed in the case of the complex from ligand **2**, a suspension was formed in the case of the complex from ligands **1** or **3**. An epoxide (390 mmol) was then added to the reaction mixture. After 15 min, TMSCN (195 μmol) was added. The colour of the reaction mixture is changed to dark orange. After the indicated time, hexane (or petroleum ether) (3 ml) was added. The precipitated complex was filtered off and used for the recycle. The solution was filtered through celite and evaporated under vacuum. The reaction mixture was analysed by GC to determine the enantiomeric excess of the nitrile.

4.8.1. 4,4,4-Trifluoro-3-((trimethylsilyl)oxy)butanenitrile



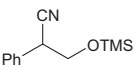
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30–4.45 (m, 1H), 2.70–2.90 (m, 2H), 0.24 (s, 9H). Chiral GC DP-TFA-γ-CD column, gas carrier N_2 1.8 atm, *T* = 100 °C. T_R = 1.24 and 1.33 min.

4.8.2. 3-Phenyl-3-((trimethylsilyl)oxy)propanenitrile



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.35 (m, 5H), 5.05 (m, 1H), 2.73 (AB-part from ABX, J_{AB} = 16.5, J_{AX} = 5.4, J_{BX} = 6.9, 2H), 0.18 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 128.5, 128.1, 127.8, 125.4, 70.6, 29.4, −0.2. Chiral HPLC: IB-3 column, 1 ml/min, UV detector 254 nm, hexane–*i*PrOH 95:5, T_r = 7.8 and 8.2 min. Chiral GC column β-DM, *T*(column) = 140 °C, He 15 psi, *T*(evaporator) = 200 °C, *T*(detector) = 200 °C, T_r (minor) = 18.1 min, T_r (major) = 18.7 min.

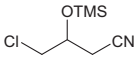
4.8.3. 2-Phenyl-3-((trimethylsilyl)oxy)propanenitrile



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.35 (m, 5H), 3.90–4.10 (m, 3H), 0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.6, 128.8, 128.3, 128.2, 127.8, 65.3, 41.0, −0.8. Chiral HPLC: IB-3 column,

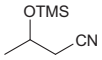
1 ml/min, UV detector 254 nm, hexane–*i*PrOH 95:5, T_r = 5.0 and 5.6 min. Chiral GC: column β-DM, *T*(column) = 140 °C, He 15 psi, *T*(evaporator) = 200 °C, *T*(detector) = 200 °C, T_r (minor) = 20.3 min, T_r (major) = 20.7 min.

4.8.4. 4-Chloro-3-((trimethylsilyl)oxy)butanenitrile



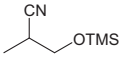
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17–4.06 (m, 1H), 3.52 (dd, *J* = 13.2, 6.7 Hz, 1H), 3.46 (dd, *J* = 13.2, 8.8 Hz, 1H), 2.71 (dd, *J* = 16.7, 4.5 Hz, 1H), 2.61 (dd, *J* = 16.7, 6.5 Hz, 1H), 0.19 (s, 9H). Chiral GC DP-TFA-γ-CD column, gas carrier N_2 1.8 atm, *T* = 100 °C. T_R = 4.48 and 5.08 min.

4.8.5. 3-((Trimethylsilyl)oxy)butanenitrile



^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16–4.06 (m, 1H), 2.45 (d, *J* = 5.9 Hz, 2H), 1.28 (d, *J* = 6.1 Hz, 3H), 0.15 (s, 9H). Chiral GC column β-DM 30 m, *T*(column) = 140 °C, He 15 psi, *T*(evaporator) = 200 °C, *T*(detector) = 200 °C, T_r (minor) = 18.1 min, T_r (major) = 18.7 min. Chiral GC Fusedsil 25 m × 0.23 mm ID column, gas carrier N_2 1.8 atm, *T* = 100 °C. T_R = 1.70 and 1.85 min.

4.8.6. 2-Methyl-3-((trimethylsilyl)oxy)propanenitrile



^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (t, *J* = 6.0 Hz, 1H), 2.55–2.50 (m, 2H), 1.36 (d, *J* = 6.2 Hz, 3H), 0.15 (s, 9H).

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