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Chiral Ti(IV) complexes of hexadentate Schiff bases as precatalysts for the asymmetric addition of TMSCN to aldehydes and the ring opening of cyclohexene oxide

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Abstract—Chiral dinuclear titanium(IV) complexes (generated in situ from hexadentate Schiff bases and titanium tetra-isopropoxide) have been found to be more effective catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes and the ring opening of cyclohexene oxide than their mononuclear analogues. The best results were obtained for benzaldehyde (86% enantiomeric excess) and cyclohexene oxide (89% enantiomeric excess).

1. Introduction

The design and use of homo- and heterometallic polynuclear chiral Lewis acid catalysts for asymmetric catalysis is a rapidly developing area.[1] A simple mixing of several single-site chiral catalysts can be extremely successful, leading to efficient heterobimetallic catalysts, as was the case with Shibasaki's catalyst for Michael addition reactions.[2] Nevertheless, the rational design of chiral ligands capable of supporting two Lewis acid sites rigidly oriented in space seems to be more straightforward. Trost's dinuclear Zn-catalysts for aldol condensations[3] and mono and dinuclear catalysts for asymmetric binaphthol synthesis[4] are successful examples of the latter approach.

Some of us have developed highly efficient homobinuclear Ti based[5a] and heteronuclear Ti/V mixed[5b] chiral salen catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes and ketones. Both catalytic metal sites were held together in space by an oxygen atom bridge, which was found to be necessary for the catalytic activity of the binuclear system.[5c] Unfortunately, those complexes were not effective for other asymmetric C–C bond forming reactions. One reason for this seemed to be the specific mechanism of the catalysis by the coordinatively saturated systems incorporating an interaction of the bridging oxygen atom with the aldehyde carbonyl group.[5d] We believed that the use of formally unsaturated catalytically active dinuclear complexes would broaden the scope of their application whilst retaining the advantages of the dinuclear catalysis.

Herein, we report on the use of chiral binuclear Ti complexes of hexadentate Schiff bases of (*S*)-valinol and both (*S*)- and (*R*)-binaphthol derived salicylaldehydes **1** and **2**, as precatalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes and the ring opening of cyclohexene oxide. The Schiff bases of biphenol derived salicylaldehyde **3**, 2,4-di-*tert*-butylsalicylaldehyde **4** and salicyladehyde **5**, combined with (*S*)-valinol, were also prepared and tested as catalysts for the addition of trimethylsilyl cyanide to benzaldehyde, for comparison purposes.

2. Results and discussion

The synthesis of both (*S*)- and (*R*)-2,2′-diformyl-binaphthols and the corresponding 2,2′-diformyl-biphenols was achieved in three steps following the literature procedures,[6a,b] as illustrated in Scheme 1 for ligand **2**. Further condensation of the aldehydes with (*S*)-valinol furnished

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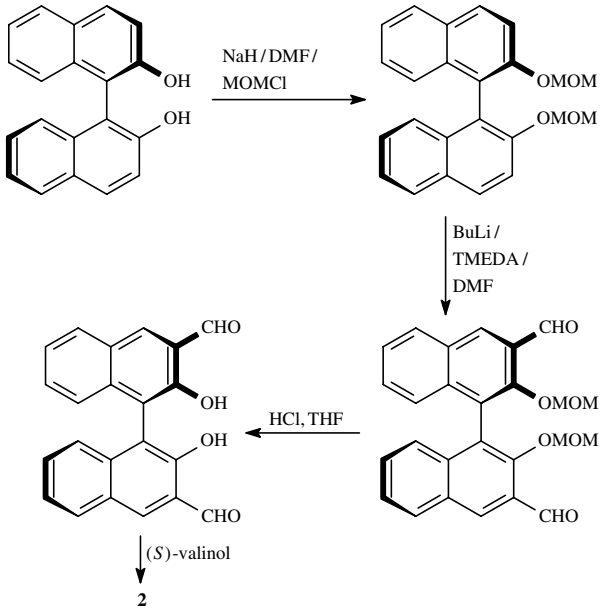
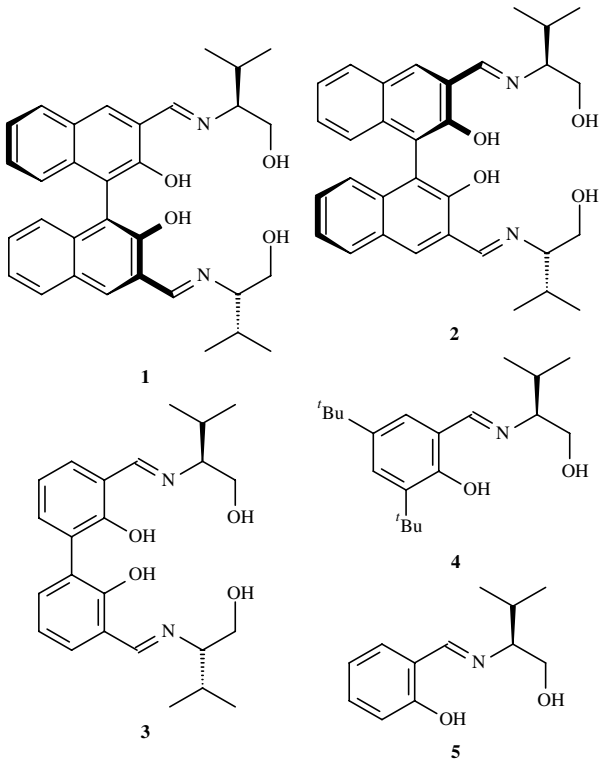
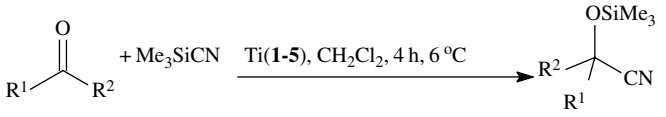


Scheme 1. Synthesis of hexadentate ligand **2**.

targets **1**–**3** (see Scheme 1). The model monomeric ligands **4** and **5** were prepared via a literature procedure.[7] The preparation of the titanium complexes was carried out in situ by mixing ligands **1**–**5** with titanium *tetra*-isopropoxide in a 1:1 molar ratio of Ti/Schiff base moieties.



The catalytic activity of the complexes was tested using the addition of trimethylsilyl cyanide to benzaldehyde[8] (Scheme 2) as a model system. The reactions were carried



Scheme 2. Addition of trimethylsilyl cyanide to carbonyl compounds catalysed by the titanium complexes of ligands **1**–**5**.

out for 4 h in CH_2Cl_2 at 6 °C using 20 mol % of the Ti-Schiff base complex. The concentration of the precatalyst was varied from 8.0×10^{-2} to 9.0×10^{-3} M. Under these conditions, all the reactions went to completion. The results of these experiments are summarised in Table 1.

Table 1. Addition of trimethylsilyl cyanide to benzaldehyde catalysed by the titanium complexes of ligands **1**–**5**[a]

Run	Ligand	Complex concentration ($M \times 10^{-2}$)	Product ee (%) (configuration)[b]
1	**5**	8.0	46 (*S*)[9]
2	**5**	1.8	27 (*S*)
3	**4**	8.0	19 (*R*)
4	**3**	4.0	28 (*R*)
5	**3**	0.9	24 (*R*)
6[c]	**2**	4.0	85–86 (*R*)
7[c]	**2**	1.6	85–86 (*R*)
8	**1**	4.0	23 (*S*)
9	**1**	0.9	28 (*S*)

[a] Reaction conditions: 6 °C in dichloromethane for 4 h, ligands **1**–**3**/Ti ratio = 1:2, ligands **4**–**5**/Ti ratio = 1:1, 20 mol % of titanium *tetra-iso*-propoxide relative to benzaldehyde.

[b] Formation of mandelonitrile trimethylsilyl ether was essentially quantitative, Ee determination was achieved by GLC on a DP-TFA-γ-cD (32 m × 0.20 mm) column.

[c] Average of several experiments.

The results of runs 1–3 in Table 1 indicate a reversal of the configuration of the product with the introduction of bulky substituents in the salicylaldehyde moiety. Thus, ligand **5** derived from unsubstituted salicyclaldehyde predominantly produces (*S*)-mandelonitrile trimethylsilyl ether, whilst ligand **4** derived from 2,4-di-*tert*-butylsalicylaldehyde generates an excess of (*R*)-mandelonitrile trimethylsilyl ether.

The catalyst derived from ligand **3** also formed (*R*)-mandelonitrile trimethylsilyl ether (Table 1: runs 4 and 5). The highest enantioselectivity was achieved with the catalyst obtained from ligand **2** (Table 1: runs 6 and 7), which produced (*R*)-mandelonitrile trimethylsilyl ether with up to 86% enantiomeric excess. A catalyst derived from the diastereomeric ligand **1** gave (*S*)-mandelonitrile trimethylsilyl ether with a low enantiomeric excess (Table 1: runs 8 and 9). These results indicate that the configurations of both the binaphthyl unit and the valinol groups have an influence on the enantioselectivity of the reaction, and the combination of (*R*)-binaphthyl and (*S*)-valinol is optimal to maximise the asymmetric induction.

In the case of the catalyst derived from ligand **5**, a two-fold decrease in the enantiomeric excess of the product was observed when the reaction mixture was diluted (Table 1: runs 1 and 2). However, no concentration dependence of the asymmetric efficiency of the catalysts was

observed in the case of the titanium complexes of **3** (Table 1: runs 4 and 5), **2** (Table 1: runs 6 and 7) and **1** (Table 1: runs 8 and 9). These data are consistent with a catalytically active dinuclear complex catalysing the reaction in the case of the catalysts derived from ligands **1**–**3**. In contrast, for the catalyst derived from ligand **5**, there are no catalytically active dinuclear complexes present in the reaction solution, although the catalysis still requires two metal ions. Therefore, the catalysis occurs by two mononuclear complexes acting together and the catalytic efficiency decreases as the concentration decreases. In the case of catalysis by the titanium complex of ligand **4**, the enantiomeric excess of the mandelonitrile trimethylsilyl ether was found to decrease significantly with time (Fig. 1). No such effect was observed with the corresponding reactions carried out using ligand **2**. This observation is also consistent with the formation of a single type of catalytical active complexes in the case of ligand **2**, but a time dependent formation of a manifold of complexes with differing catalytic activities in the case of the titanium complex of ligand **4**.

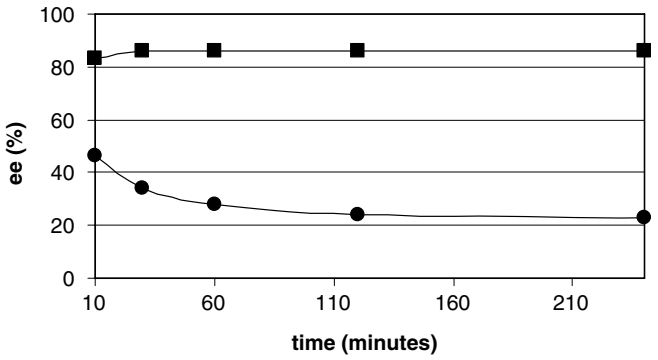


Figure 1. Time dependence of the enantiomeric excess of mandelonitrile trimethylsilyl ether formed using the titanium catalyst of ligand **2** (squares) and ligand **4** (circles).

The ratio of titanium to ligand **2** greatly influenced the enantiomeric excess of the mandelonitrile trimethylsilyl ether, as shown by the data in Table 2. As expected for the formation of a bimetallic complex, a titanium to ligand ratio of 2:1 gave the highest enantioselectivity (Table 2, run 1). Decreasing the titanium to ligand ratio to 1:1 resulted in a dramatic decrease in the enantiomeric excess of the product (Table 2: runs 2–4). Significantly, under these conditions, the enantiomeric excess of the product was around 20%, which is similar to that obtained using mononucleating ligand **4** under similar reaction conditions (Table 1: run 3).

Table 2. The effect of changing the titanium to ligand **2** ratio on the enantiomeric excess of the mandelonitrile trimethylsilyl ether[a]

Run	$Ti(O^i\text{-}Pr)_4$/**2**	ee (%)
1	2:1	86
2	1.2:1	49
3	1:1	15
4	0.8:1	24

[a] Experimental conditions were the same as for Table 1 except that the concentration of **2** was kept at 1.8×10^{-2} M.

Further optimisation of the reaction conditions proved that neither decreasing nor increasing the reaction temperature affected the enantioselectivity observed using the catalyst derived from ligand **2**. The addition of water or phosphine oxide[10] to the reaction mixture did, however, lead to a significant decrease in both the activity and stereoselectivity of the catalyst. Under the optimal reaction conditions, two other aldehydes and acetophenone were also substrates for the reaction, although with a lower enantioselectivity as shown in Table 3.

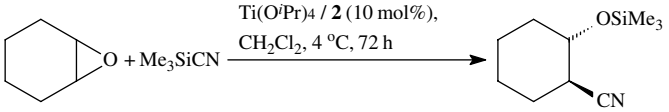
Table 3. The asymmetric addition of trimethylsilyl cyanide to carbonyl compounds catalysed by ligand **2** and titanium *tetra*-isopropoxide[a]

R^1	R^2	Time (h)	Yield[d] (%)	ee (%)
o-Cl–C_6H_4	H	4	100	74[b]
$(CH_3)_3C$	H	7	100	27[b,c]
C_6H_5	CH_3	24	36	15[b]

[a] Reaction conditions: temperature +2 to +6 °C, CH_2Cl_2, 2:1 ratio of $Ti(O^i\text{-}Pr)_4$ to **2**, 20 mol % of $Ti(O^i\text{-}Pr)_4$ with respect to carbonyl compound.
[b] Ee determination was by GLC on a DP-TFA-γ-cD column (32 m × 0.20 mm).
[c] Ee determination was carried out on the *O*-acetyl derivative.[11]
[d] Determined by NMR analysis.

Whilst the asymmetric addition of trimethylsilyl cyanide to aldehydes has been extensively studied, the corresponding reaction between trimethylsilyl cyanide and a *meso*-epoxide to form a β-hydroxy-nitrile has received only scant attention. A number of achiral catalysts[12] for the ring opening of epoxides by trimethylsilyl cyanide have been reported, and it is known that the reaction can be complicated by the competing formation of the corresponding isocyanide[13] There are, however, only two previous reports of asymmetric catalysts for the asymmetric ring opening of *meso*-epoxides by trimethylsilyl cyanide. Hoveyda reported the use of titanium-based complexes,[14] whilst Jacobsen has reported the use of lanthanide(pybox) complexes.[15]

The ring opening of cyclohexene oxide with trimethylsilyl cyanide was also catalysed by the dinuclear titanium complex derived from ligand **2** at a substrate to catalyst ratio of 10:1, as shown in Scheme 3. At 4 °C in dichloromethane, the β-hydroxy nitrile was obtained in a 60% yield after 72 h. The ^1H and ^{13}C NMR spectra of the product confirmed that the product was cyanide rather than the isocyanide[13] and the specific rotation and chiral GC of the product corresponded to 89% enantiomeric excess. In contrast, the use of a 1:1 mixture of titanium *tetra*-isopropoxide and ligand **4** gave a racemic product for this reaction.



Scheme 3. Addition of trimethylsilyl cyanide to cyclohexene oxide catalysed by the titanium complex of ligand **2**.

3. Conclusions

A new family of chiral Schiff base ligands has been constructed. When complexed to titanium to form binuclear species, enantioselectivities of up to 86% have been achieved in the asymmetric addition of trimethylsilyl cyanide to aldehydes. The ligands, which can form binuclear complexes are significantly more enantioselective than previously reported similar ligands, which can only form mononuclear complexes. The stereoselective ring opening of a *meso*-epoxide with trimethylsilyl cyanide, catalysed by the binuclear complex, is a novel extension of the catalyst reactivity.

4. Experimental

4.1. General

Optical rotations were measured on a Perkin–Elmer 241 polarimeter and specific rotations are reported as follows: $[\alpha]_{\lambda}^{T}$ (concentration in g/100 mL, solvent). Enantiomeric excesses were determined by HPLC analysis using a Kromasil column (0.25 m × 46 mm) with UV detection at 254 nm or by GC analysis using a DP-TFA-γ-cD column (32 m × 0.20 mm).

^{1}H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer and are reported in parts per million using the solvent as the internal standard. The data are reported as s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hertz, integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker Avance 300 (75.5 MHz) spectrometer and are reported in parts per million using the solvent as an internal standard. The melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were carried out by the laboratory of Microanalysis of INEOS RAS.

THF was freshly distilled from sodium/benzophenone under argon. Dichloromethane was distilled under argon from P_2O_5 and dried over 3 Å molecular sieves (7.4 g sieves on 7 mL dichloromethane). Benzaldehyde was distilled in vacuo under argon prior to use. All reagents were purchased from Aldrich or Acros, and used without purification unless otherwise stated.

4.2. Synthesis of methoxymethyl protected phenols

4.2.1. 2,2′-Bis-(methoxymethoxy)biphenyl.[6a] Prepared by the literature procedure[6a] in 51% yield as a colourless oil. $R_f = 0.4$ (hexane/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 6H), 5.08 (s, 4H), 7.06–7.11 (m, 2H), 7.21–7.36 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 95.2, 115.6, 121.8, 128.7, 131.53.

4.2.2. (*R*)-2,2′-Bis-(methoxymethoxy)-1,1′-binaphthyl.[6b] Prepared by the literature procedure[6b] in 85% yield as colourless crystals. $R_f = 0.17$ (hexane/ethyl acetate 3:1); $[\alpha]_D^{25} = +98$ (*c* 1, THF); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 6H), 4.98 (d, *J* 6.6 Hz, 2H), 5.09 (d, *J* 6.6 Hz, 2H), 7.14–7.26 (m, 6H), 7.35 (d, *J* 8.9 Hz, 2H), 7.58 (d, *J* 9.0 Hz, 2H), 7.88 (d, *J* 8.1 Hz, 2H), 7.96 (d, *J* 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 95.1, 117.2, 121.2, 124.0, 125.5, 126.3, 127.8, 129.4, 129.8, 134.0, 152.6.

4.2.3. (*S*)-2,2′-Bis-(methoxymethoxy)-1,1′-binaphthyl.[6b] The title compound was prepared in the same way as the (*R*)-enantiomer starting from (*S*)-BINOL.

4.3. Synthesis of dialdehydes

4.3.1. 3,3′-Diformyl-2,2′-bis(methoxymethoxy)biphenyl.[6a] Prepared by the literature procedure[6a] in 57% yield as colourless crystals. $R_f = 0.13$ (hexane/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 6H), 4.81 (s, 4H), 7.37 (dd, *J* 0.9, 8.4 Hz, 2H), 7.67 (dd, *J* 1.8, 7.5 Hz, 2H), 7.93 (dd, *J* 1.8, 7.8 Hz, 2H), 10.43 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.6, 101.2, 125.0, 129.2, 130.3, 132.7, 138.0, 158.2, 190.3.

4.3.2. (*R*)-3,3′-Diformyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl.[6a] Prepared by the literature procedure[6a] in 68% yield as white crystals. $R_f = 0.17$ (hexane/ethyl acetate 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (s, 6H), 4.69 (d, *J* 6.6 Hz, 2H), 4.73 (d, *J* 6.3 Hz, 2H), 7.22 (d, *J* 8.7 Hz, 2H), 7.42 (ddd, *J* 0.9, 7.5, 8.1 Hz, 2H), 7.52 (ddd, *J* 0.9, 6.9, 7.8 Hz, 2H), 8.08 (d, *J* 8.1 Hz, 2H), 8.62 (s, 2H), 10.55 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.0, 100.6, 125.9, 126.1, 126.3, 128.8, 129.6, 130.1, 130.3, 132.29, 136.7, 154.0, 190.6.

4.3.3. (*S*)-3,3′-Diformyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl.[6a] The title compound was prepared by the literature procedure[6a] as described for the (*R*)-enantiomer in Section 4.3.2.

4.4. Deprotection of MOM-groups

4.4.1. 3,3′-Diformyl-2,2′-dihydroxy-1,1′-biphenyl.[6a] Prepared by the literature procedure[6c] in 88% yield as yellow crystals. $R_f = 0.26$ (hexane/ethyl acetate 6:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11–7.15 (m, 2H), 7.32–7.36 (m, 4H), 7.93–7.97 (m, 2H), 8.31 (s, 2H), 10.13 (s, 2H), 10.53 (s, 2H). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.41; H, 4.11.

4.4.2. (*R*)-3,3′-Diformyl-2,2′-dihydroxy-1,1′-binaphthyl. Prepared by the literature procedure[6c] in a quantitative yield as yellow crystals. $R_f = 0.35$ (hexane/ethyl acetate 4:1); Mp 285 °C; $[\alpha]_D^{25} = +249.5$ (*c* 0.8, CH_2Cl_2) {lit.[6a] $[\alpha]_D^{20} = -254$ (*c* 0.3, CH_2Cl_2) for (*S*)-enantiomer}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11–7.15 (m, 2H), 7.32–7.36 (m, 4H), 7.93–7.97 (m, 2H), 8.31 (s, 2H), 10.13 (s, 2H),10.53 (s, 2H). Ee = 98.8% determined by HPLC analysis (Kromasil 0.46 cm × 25 cm, eluent hexane/*iso*-propyl alcohol 100/4, 1 mL/min, UV detector 254 nm) t_R(major) = 22.8, t_R(minor) = 20.8 min.

4.4.3. (*S*)-3,3′-Diformyl-2,2′-dihydroxy-1,1′-binaphthyl.[6a] Prepared by the literature procedure[6c] in quantitative yield as yellow crystals. $[\alpha]_D^{25} = -267.0$ (*c* 0.5, CH_2Cl_2) {lit.[6a] $[\alpha]_D^{20} = -254$ (*c* 0.3, CH_2Cl_2)}. Ee = 100% determined by

HPLC analysis (Kromasil 0.46 cm × 25 cm, eluent hexane/*iso*-propyl alcohol 100/4, 1 mL/min, UV detector 254 nm) t_R(major) = 20.8, t_R(minor) = 22.8.

4.5. Synthesis of ligands

4.5.1. Compound 3. A solution of (*S*)-2-amino-3-methyl-1-butanol[16] (Ee = 96.6% determined by GC analysis of the trifluoroacetyl derivative) (0.52 g, 5.0 mmol) in ethanol (5 mL) and benzene (5 mL) was added to 3,3′-diformyl-2,2′-dihydroxy-1,1′-biphenyl (0.61 g, 2.5 mmol) and the reaction mixture was heated in a Dean–Stark apparatus for 10 h. The solution was concentrated and the residue purified by column chromatography on aluminium oxide eluting with hexane/dichloromethane/ethanol (20:5:1) to give compound **3** (0.98 g, 95%) as yellow crystals. $[\alpha]_D^{25} = -143.8$ (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.93 (dd, *J* 6.6, 7.8 Hz, 12H), 1.86–1.91 (m, 2H), 3.05–3.10 (m, 2H), 3.76–3.82 (m, 4H), 6.96–7.04 (m, 2H), 7.34 (dd, *J* 1.8, 7.5 Hz, 2H), 7.44 (dd, *J* 1.8, 7.5 Hz, 2H), 8.43 (s, 2H), 14.00 (br s, 2H). Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.99; H, 7.80; N, 6.75.

4.5.2. Compound 2. A solution of (*S*)-2-amino-3-methyl-1-butanol[16] (Ee = 96.6% determined by GC analysis of the trifluoroacetyl derivative) (0.19 g, 1.8 mmol) in ethanol (5 mL) and benzene (5 mL) was added to (*R*)-3,3′-diformyl-2,2′-dihydroxy-1,1′-binaphthyl (0.31 g, 0.91 mmol). The reaction mixture was heated in a Dean–Stark apparatus for 10 h. The solution was concentrated and the residue purified by column chromatography on aluminium oxide eluting with hexane/dichloromethane/ethanol (20:5:1), then the eluent was further purified by chromatography on Sephadex LH-20 eluting with benzene to give compound **2** (0.44 g, 95%) as a red solid. $[\alpha]_D^{25} = -139.8$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.91 (dd, *J* 6.6, 7.8 Hz, 6H), 1.80–1.90 (m, 2H), 2.30–2.80 (br m, 2H), 3.00–3.15 (m, 2H), 3.65–3.75 (m, 4H), 7.10–7.19 (m, 2H), 7.27–7.33 (m, 4H), 7.86–7.89 (m, 2H), 7.99 (s, 2H), 8.64 (s, 2H), 13.19 (s, 2H). Anal. Calcd for $C_{32}H_{36}N_2O_4$: C, 74.97; H, 7.08, N, 5.46. Found: C, 75.04; H, 7.41, N, 5.26.

4.5.3. Compound 1. The title compound was prepared as described in Section 4.5.2 for compound **2**, using (*S*)-3,3′-diformyl-2,2′-dihydroxy-1,1′-binaphthyl as the starting material. $[\alpha]_D^{25} = -163$ (*c* 1, $CHCl_3$).

4.5.4. (*S*)-2-(*N*-3′,5′-Di-*tert*-butylsalicylideneamino)-3-methyl-butan-1-ol. A solution of (*S*)-2-amino-3-methyl-1-butanol[16] (0.10 g, 0.97 mmol) in ethanol (5 mL) and benzene (5 mL) was added to 2,4-di-*tert*-butylsalicylaldehyde (0.23 g, 0.97 mmol). The reaction mixture heated in a Dean–Stark apparatus for 10 h. The solution was concentrated and the residue purified by column chromatography on aluminium oxide eluting with hexane/dichloromethane/ethanol (20:5:1) to give the title compound (0.30 g, 86%) as yellow crystals. $[\alpha]_D^{25} = -33.3$ (*c* 0.78, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (dd, *J* 3.9, 9.6 Hz 6H), 1.32 (s, 9H), 1.45 (s, 9H), 1.85–2.05 (m, 1H), 2.99–3.07 (m, 1H), 3.70–3.90 (m, 2H), 7.13 (d, *J* 2.4 Hz 1H), 7.40 (d, *J* 2.4 Hz 1H), 8.38 (s, 1H), 13.40–13.70 (br s, 1H). Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19 H, 10.41, N, 4.38. Found: C, 75.04; H, 10.41, N, 4.37.

4.5.5. (*S*)-2-(*N*-Salicylideneamino)-3-methyl-butan-1-ol 5.[7] Prepared by a modification of the literature procedure.[7] A solution of (*S*)-2-amino-3-methyl-1-butanol[16] (0.10 g, 0.97 mmol) in ethanol (5 mL) and benzene (5 mL) was added to salicylaldehyde (0.12 g, 0.98 mmol). The reaction mixture was heated in a Dean–Stark apparatus for 10 h. The solution was concentrated and the residue purified by column chromatography on aluminium oxide eluting with hexane/dichloromethane/ethanol (20:5:1) to give the title compound (0.19 g, 85%) as yellow crystals. Mp 104–106 °C; $[\alpha]_D^{25} = -25.0$ (*c* 0.8, MeOH) [lit.[7] = −26.2 (*c* 1, MeOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (dd, *J* 4.2, 6.9 Hz, 6H), 1.45–1.70 (br s, 1H), 1.89–2.01 (m, 1H), 3.02–3.09 (m, 1H), 3.70–3.90 (m, 2H), 6.85–7.00 (m, 2H), 7.26–7.36 (m, 2H), 8.36 (s, 1H), 13.20–13.50 (br s, 1H). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.99; H, 7.80; N, 6.75.

4.6. Catalytic reactions

4.6.1. Asymmetric cyanohydrin trimethylsilyl ether synthesis. The following procedure using benzaldehyde is a representative of that used with all carbonyl compounds: Ti(O^i-Pr)$_4$ (28 μL, 94 μmol) was added to a solution of ligand (47 μmol) in dichloromethane (1 mL) (containing 0.00046 mass % H_2O). The reaction mixture was stirred for 2 h, then freshly distilled benzaldehyde (48 μL, 471 μmol) was added. The mixture was cooled to +1 °C and trimethylsilyl cyanide (100 μL, 750 μmol) was added. The reaction was stirred at +1 to +6 °C for 4 h, then the solvent was evaporated and the residue purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) to give mandelonitrile trimethylsilyl ether.

4.6.2. Asymmetric ring opening of cyclohexene oxide. Ti(O^i-Pr)$_4$ (23.3 μL, 78 μmol) was added to a solution of ligands (39.0 μmol) in dichloromethane (1 mL) (containing 0.00046 mass % H_2O). The reaction mixture was stirred for 2 h, then cyclohexene oxide (40 μL, 390 μmol) was added. The reaction was cooled to +1 °C and trimethylsilyl cyanide (80 μL, 600 μmol) was added. The reaction was stirred in an ice bath for 4 h, then kept in a refrigerator for 20 h. The solvent was evaporated and the residue purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5:1) to give (1*R*,2*S*)-*trans*-2-hydroxy-1-cyanocyclohexene in 60% yield as a viscous oil. $[\alpha]_D^{25} = +28.0$ (*c* 0.4, CH_2Cl_2) {lit.,[15] $[\alpha]_D^{25} = -38.0$ (*c* 4, CH_2Cl_2) for the (1*S*,2*R*)-isomer}; ^{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.

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