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Synthesis of chiral pentacyclo-undecane ligands and their use in the enantioselective alkylation of benzaldehyde with diethylzinc

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Abstract—The synthesis of a new class of chiral pentacycloundecane cage annulated bidentate ligands is reported. This class of ligands can be used in many reactions that are catalysed by amino alcohol ligands. The ability of the chiral ligands to asymmetrically catalyse the reaction between diethylzinc and benzaldehyde was investigated. The cage annulated bidentate ligands have C_1 symmetry and showed poor to good enantioselectivity with high yields compared to previous systems reported using other amino alcohol ligands. An important conclusion from the results is that both ligands should be involved in the mechanism as the bidentate ligands gives much improved enantioselectivity when compared with a single chiral source molecule. This system could be utilised as a versatile probe for examining the reaction mechanism.
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1. Introduction

The search for new chiral ligands to be used in asymmetric catalysis is of great interest in the field of synthetic chemistry.[1,2] Carbon–carbon bond forming reactions remain an active area of research.[3] A popular reaction is that of dialkylzinc with pro-chiral aldehydes[3–5] since the chiral secondary alcohols that are formed are important substrates for drug synthesis. Amino alcohols are impressive ligands for this reaction as shown by Noyori and Kitamura[1,6] The accepted mechanism for the chiral induced dialkylzinc additions to carbonyl compounds involves a dinuclear zinc chiral amino alkoxide intermediate **3** (see Fig. 1). This intermediate **3**, acts as a Lewis acid to activate the carbonyl substrate, and enhances the nucleophilicity of the alkyl group on the neighbouring zinc reagent.

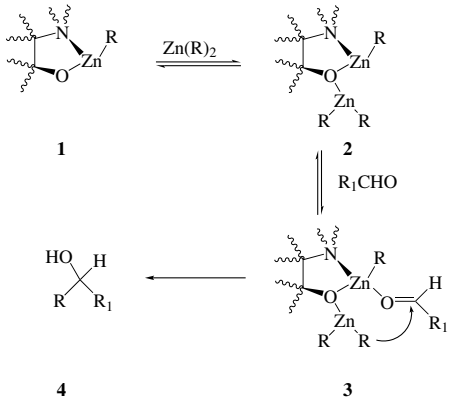

Figure 1. Proposed mechanism for chiral induced dialkylzinc reactions.[6]

Chiral pentacyclo-undecane (PCU) cage moieties were previously used as hosts for chiral ammonium ions,[7,8] but the application of a PCU-moiety in chiral ligands for asymmetric synthesis has not yet been reported. The results herein form part of a programme to investigate chiral applications of the pentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane framework attached to amino alcohols. There are a number of reasons why this programme is likely to enhance our understanding about the mechanism of the reaction: (a) the proposed PCU-ligands (see Fig. 3) are the first bidendate ligands reported with C_1 symmetry; it also offers a central ether type oxygen, which could potentially participate in the reaction, (b) the alkyl arms of the PCU-moiety can easily be varied,[9] enabling versatility to probe the mechanism of the reaction, (c) the PCU moiety enhances the lypophilicity of the ligand, which could lead to more effective recycling of the ligand and (d) the source of chirality is inexpensive amino acids.

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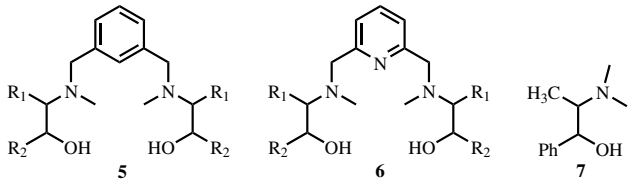


Figure 2. Examples of bidentate ligands with C_2 symmetry.[10–12]

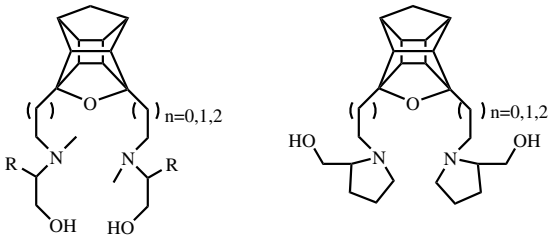


Figure 3. Possible chiral PCU ligands.

Very little attention has been given to the use of bidentate type ligands in chiral dialkylzinc reactions. Ligands such as **5** and **6** have C_2 symmetry and were found[10–12] to exhibit much higher enantioselectivity (up to 90%) than the corresponding single source of chirality (36% ee for ligand **7**)[13] indicating that both arms should be involved in the dialkylzinc addition reaction (Fig. 2).

It was also demonstrated[12] that the nitrogen of the pyridine ring is involved in the mechanism as ligands of the type **6** gave opposite enantioselectivity than ligands **5**. In most cases pyridine based ligands **6** also gave higher enantioselectivity when compared to benzene based ligands **5**.

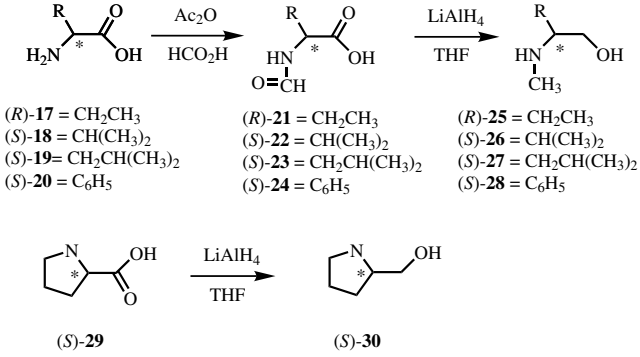
In light of the discussion above it is clear that the proposed PCU bidentate ligands are likely to enhance our understanding about this important organic reaction.

2. Results and discussion

The synthesis of ligands **8**–**12** (Scheme 1) was accomplished in respectable yields starting from the pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8,11-dione **13** (PCU-dione)[14,15] with commercially available amino acids as the source of chirality.

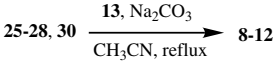
The dione was converted to the 3,5-diallyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecane **14** as described previously.[8,16] Ozonolysis of **14** followed by a reductive workup using $NaBH_4$ afforded the 3,5-(2′,2″-bis-(hydroxyethyl))-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}] dodecane **15** (90%). The diol **15** has been previously synthesised and characterised by Marchand et al. via a different method.[17] The diol **15** was treated with *p*-toluene sulfonyl chloride and solid KOH in THF to yield the PCU-ditosylate **16** (62%).[18]

The *N*-methyl amino alcohols were synthesised from their respective amino acids (Scheme 2) by treating the amino acids **17**–**20** with formic acid and acetic anhydride to give the formamides **21**–**24**, respectively.[19–21] The formamides were reduced to the corresponding *N*-methyl amino alcohols **25**–**28** via $LiAlH_4$ at ambient temperature.[20,21]



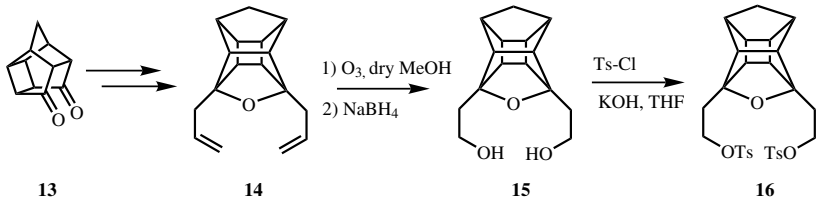
Scheme 2. Synthesis of the amino alcohols.

The reduction of (*S*)-(+)-proline **29** to (*S*)-(+)-prolinol **30** does not require the additional formamide formation step. Ligands **8**–**12** were formed by reacting the PCU-ditosylate **16** with the corresponding amino alcohols **25**–**28** and **30** (Scheme 3).



Scheme 3. Synthesis of PCU-ligands.

The catalytic activity of these ligands was investigated using the standard reaction of diethylzinc and benzaldehyde. Reactions were carried out in dry toluene at ambient temperature in the presence of 10 mol% chiral ligand



Scheme 1. Synthesis of PCU-ditosylate **16**.

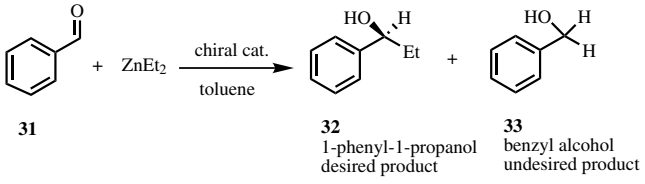
and monitored by chiral gas chromatography.[3] When complete conversion of the aldehyde was detected (approximately 5 h) the reaction was stirred for a further 48 h. Previous reports[4,5] indicate that the reaction should be quenched when there is no more aldehyde present, but with the PCU-ligands, this early workup resulted in lower yields of the desired product and the formation of benzyl alcohol[5,22] as the major by-product. After the desired reaction time, the reaction was quenched with 10% HCl and extracted with diethyl ether. The organic phase was dried, the solvent evaporated and the product purified via preparative thin layer chromatography (TLC). All reactions were repeated three times and an average of the yields are reported. The reaction was also carried out at 0 °C and this required reaction times in excess of 90 h with no appreciable increase in the % ee observed.

The results in Table 1 show that in the presence of the ligands **8**–**12**, diethylzinc reacts cleanly with benzaldehyde providing 1-phenyl-1-propanol in high yields. Only ligand **10** gave good results with respect to % ee results (Scheme 4).

Table 1. Results from the addition of diethylzinc to benzaldehyde catalysed[a] by ligands **8**–**12**

Ligand	Time (h)[b]	Yield[c] %	% ee[d]	Configuration[e]
8	30	92	—	—
9	30	90	15	*S*
10	30	84	90	*S*
11	30	60	10	*S*
12	30	92	—	—

[a] Ratio of 0.125 mmol ligand: 0.5 benzaldehyde: 0.125 diethylzinc.
[b] Quenching the reaction as soon as benzaldehyde is no longer detectable, results in benzylalcohol as a major by-product.
[c] Product was isolated by preparative TLC.
[d] Determined by chiral GC as described in Section 4.
[e] Determined by optical rotation.



Scheme 4. Chiral addition of diethylzinc to benzaldehyde.

The source of chirality in **10** is leucinol; leucinol on its own, catalyses this reaction with an ee of 48% (96% chemical yield);[23] this indicates that the cage moiety has a positive effect on the enantioselectivity of the reaction and that both arms should be involved in the reaction mechanism rather than each arm performing a separate catalytic conversion. The results for ligand **10** suggest that the intrinsically chiral PCU-unit serves to position two leucinol units in a favourable chiral orientation. These results complement previous data,[11,12] which found that bidentate ligands such as **5** and **6** exhibit much higher enantioselectivity compared to a single chiral source molecule.

3. Conclusion

A new class of chiral bidentate ligands has been synthesised. They exhibit high yields as catalysts, but with poor to good enantioselectivity. It is clear that incorporation of the PCU cage into such ligands warrants further investigation as it significantly enhances the enantioselectivity of simple chiral amino alcohols such as leucinol. The bidentate cage system will be utilised in future as a flexible mechanistic probe since the dentate arm lengths can be conveniently modified.[9] Interestingly it is difficult to envisage a Noyori[6,24] type transition state for bidentate ligands especially if the central oxygen (or nitrogen) atom of the linker between the ligands is also participating in the reaction. As predicted, the PCU-moiety enhances the lypophilicity of the ligand and effective recycling of the ligand is possible (see Section 4).

4. Experimental

Melting points are uncorrected. Optical rotations were taken on a Perkin–Elmer 341 polarimeter. All mass spectrometric analyses were carried out on a VG70-70E mass spectrometer. FAB mass spectra were obtained by bombardment of samples with xenon atoms (1 mA at 8 keV). *m*-Nitrobenzyl alcohol was used as the matrix. NMR spectra were recorded on a Varian Unity Inova-300 MHz spectrometer. Elemental microanalyses were obtained at the University of KwaZulu-Natal using a LECO CHNS-932 for carbon, hydrogen and nitrogen, and LECO VTF-900 for oxygen. The enantiomeric excess of the products were determined by GC (SGE Cydex-B chiral column, 25 m × 0.22 mm, inlet pressure 12 psi, injection volume 0.1 μL, isothermal 110 °C, $T_1 = 25.4$, $T_2 = 26.2$). Toluene was freshly distilled on sodium benzophenone ketyl under a nitrogen atmosphere prior to its use. Commercially available amino acids and diethylzinc (1.0 M solutions in hexane) was directly used.

4.1. 3,5-(2′,2″-Bis(hydroxyethyl))-4-oxahexacyclo-[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane 15

A solution of the diene **14** (5.0 g, 20.3 mmol) in dry methanol (150 mL) was cooled to −78 °C via application of an external dry ice-acetone bath and then was purged with argon for 20 min. Ozone was bubbled into the mixture until a blue-purple colour persisted, thereby indicating the presence of excess ozone and completion of reaction. Excess ozone was flushed from the reaction vessel with a stream of argon, and the reaction mixture was transferred to a 2 L flask. Sodium borohydride (3 g, 81.0 mmol) was added over 1 h to a stirred, ice bath cooled mixture of the ozonide. The resulting mixture was stirred at ambient temperature for 12 h. The reaction mixture was concentrated in vacuo, excess sodium borohydride was quenched with 10% HCl (200 mL) and extracted with ethyl acetate to give pure **15**[17] (4.4 g, 89%) obtained as a colourless microcrystalline solid: mp 153–153.5 °C; IR (KBr): ν_{max} 3320 (m), 2980 (s) cm^{-1}; ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 1.52 (d, $J = 10.3$ Hz, 1H), 1.70–2.05 (m, 4H), 2.28–2.69 (m,

9H), 3.50–3.86 (m, 6H); ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 34.3 (t), 41.4 (d), 43.5 (t), 44.1 (d), 47.7 (d), 58.2 (d), 60.0 (t), and 92.4 (s).

4.2. Synthesis of PCU ditosylate 16[18]

To a solution of **15** (5.0 g, 20.1 mmol) and *p*-toluene sulfonyl chloride (11.5 g, 60.3 mmol) in THF (200 mL) was added finely powdered KOH (17.0 g, 300 mmol). This mixture was stirred under nitrogen and monitored via TLC (50 hexane:50 ethyl acetate). When no more diol ($R_f = 0.5$) and no more mono-tosylated product ($R_f = 0.2$) is detected by TLC, water (100 mL) is added to the reaction vessel and the layers are separated. The aqueous layers were extracted with ethyl acetate and the combined organic layers were dried over anhydrous $MgSO_4$. The product was concentrated in vacuo and purified via column chromatography (20 ethyl acetate:80 hexane) to give the product **16** as a colourless microcrystalline solid; ^{1}H NMR [$CDCl_3$, 300 MHz]: δ_H 1.43 (AB, $J_{AB} = 10.5$ Hz, 1H), 1.77 (AB, $J_{AB} = 10.5$ Hz, 1H), 2.03 (t, $J = 7.0$ Hz, 4H), 2.29–2.50 (m, 8H), 2.69 (s, 6H), 4.04 (t, $J = 7.0$ Hz, 4H), 7.29 (AB, $J_{AB} = 8.1$ Hz, 4H), 7.72 (AB, $J_{AB} = 8.4$ Hz, 4H).

4.3. General procedure for preparing *N*-formyl amino acids 21–24[19–21]

Acetic anhydride (30 equiv) was added dropwise to a stirred solution of the amino acid (1 equiv) dissolved in formic acid (approx. 50 mL/g amino acid) at 0 °C. After addition of the acetic anhydride, the solution was stirred at room temperature overnight. The solution was treated with water (half volume of solution). The solvent was removed under reduced pressure to yield a white residue. This residue was recrystallised from water to yield the pure product.

(*R*)-(−)-2-*N*-Formylamino-butyric acid **21**:[25] yield 63%, mp 153–155 °C; ^{1}H NMR (DMSO, 300 MHz) δ_H 0.87 (t, $J = 8.1$ Hz, 3H, 1.50–1.85 (m, 2H), 4.22 (m, 1H), 8.02 (s, 1H, CHO), 8.34 (d, $J = 7.1$ Hz, 1H).

(*S*)-(+)-*N*-Formyl valine **22**:[19] yield 72%, ^{1}H NMR (DMSO, 300 MHz) δ_H 1.0 (d, $J = 6$ Hz, 6H), 1.6 (m, 1H), 4.8 (m, 1H), 5.9 (d, $J = 8$ Hz, 1H, NH), 8.2 (s, 1H, CHO).

(*S*)-(+)-*N*-Formyl leucine **23**:[26] yield 85%, ^{1}H NMR (DMSO, 300 MHz) δ_H 0.97 (d, $J = 6.2$ Hz, 6H), 1.70–1.92 (m, 3H), 4.10 (m, 1H), 5.95 (d, $J = 8$ Hz, 1H, NH), 8.23 (s, 1H, CHO).

(*S*)-(+)-*N*-Formyl phenylglycine **24**:[21] yield 80%, ^{1}H NMR (DMSO, 300 MHz) δ_H 5.37 (d, 1H, $J = 8$ Hz), 7.27–7.43 (m, 5H), 8.07 (s, 1H), 9.01 (d, 1H, $J = 9$ Hz).

4.4. General procedure for the synthesis of *N*-methyl amino alcohols 25–28

N-Formyl-amino acid (1 equiv) was added to a stirred solution of lithium aluminium hydride (4 equiv) in dry THF at 0 °C. The solution was allowed to gradually warm to ambient temperature overnight and stirred for a further 12 h at ambient temperature. The reaction mixture was again cooled to 0 °C and an equal volume of diethyl ether was added. The reaction was quenched with saturated Na_2SO_4 aqueous solution. The solution was filtered and the solvent removed in vacuo.

(*R*)-(−)-2-Methylamino-butan-1-ol **25**:[27] 75%, ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 0.82 (t, $J = 7.7$ Hz, 3H), 1.25–1.52 (m, 2H), 2.32 (s, 3H), 3.20–3.32 (m, 1H), 3.55 (d, $J = 3.9$ Hz, 1H), 3.51 (d, $J = 3.9$, 1H).

(*S*)-(+)-3-Methyl-2-methylamino-butan-1-o1 **26**:[28,29] yield 96%, ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 0.95 (d, $J = 7$ Hz, 6H), 1.9 (m, 1H), 2.45 (s, 3H), 3.35 (s, 2H), 3.4–3.8 (m, 3H).

(*S*)-(+)-4-Methyl-2-methylamino-pentan-1-o1 **27**:[20] yield 96%, ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 0.9 (d, $J = 7$ Hz, 6H), 1.25 (t, $J = 7$ Hz, 2H), 1.5–1.9 (m, 1H), 2.4 (s, 3H), 3.3–3.7 (m, 3H), 3.8 (s, 2H).

(*S*)-(+)-2-Methylamino-2-phenyl-ethanol **28**:[21] yield 90%, ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 2.32 (s, 2H), 2.68 (br s, 2H), 3.51–3.78 (m, 3H), 7.21–7.42 (m, 5H).

(*S*)-(+)-2-Pyrrolydinemethanol **30**:[30] yield 92%, ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 1.3–1.5 (m, 1H), 1.6–1.9 (m, 4H), 2.8–3.0 (m, 2H), 3.2–3.3 (m, 1H), 3.3–3.4 (m, 1H), 3.4–3.8 (m, 2H).

4.5. General procedure for preparing ligands 8–12

A mixture of the *N*-methyl amino alcohol (2.2 equiv), PCU ditosylate (1 equiv) and Na_2CO_3 in CH_3CN was refluxed for four days under argon. The reaction mixture was cooled, filtered and concentrated in vacuo. The residue was purified via column chromatography on silica gel (Merck 7734).

4.5.1. Ligand 8. Ligand **8** was prepared as described above. The crude product was purified by chromatography on silica gel using 88 $CHCl_3$:10 MeOH:2 NH_4OH as eluents to give the product **8** as a clear oil (52%). $[\alpha]_D^{20} = -7.8$ ($c = 5$, $CHCl_3$); IR (KBr): ν_{max} 3405 (br, s), 2961 (vs), 1220 (m), 798 (m) cm^{-1}; FAB$^+$ MS (*m*-nitrobenzyl alcohol): *m*/*z* 419 $[M + H]^+$; ^{1}H NMR [$CDCl_3$, 300 MHz]: δ_H 0.2 (t, 6H), 0.98–1.15 (m, 2H), 1.40–1.60 (m, 3H), 1.75–1.98 (m, 5H), 2.15 (s, 6H), 2.25–2.70 (m, 12H), 3.15 (t, 2H), 3.55 (d, $J = 4.4$ Hz, 2H), 3.90 (d, $J = 4.4$ Hz, 2H); ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 11.62 (q), 17.74 (t), 17.79 (t), 31.32 (t), 35.59 (q), 35.65 (q), 41.52 (d), 41.59 (d), 43.44 (t), 44.26 (d), 47.76 (d), 47.85 (d), 50.22 (t), 50.28 (t), 58.51 (d), 58.63 (d), 60.47 (t), 66.07 (d), 66.14 (d), 95.03 (s), 95.08 (s). Anal. Calcd for $C_{25}H_{42}N_2O_3$ C, 71.73; H, 10.11; N, 6.69; O, 11.47. Found C, 71.65; H, 10.21; N, 6.72; O, 11.53.

4.5.2. Ligand 9. Ligand **9** was prepared as described above. The crude product was purified by chromatography on silica gel using 93 $CHCl_3$:5 MeOH:2 NH_4OH

as eluents to give the product **9** as a clear oil (64%). $[\alpha]_D^{20} = -9.0$ ($c = 2.3$, $CHCl_3$); IR (KBr): γ_{max} 3343 (br s), 2952 (vs), 1454 (m), 1056 (m) cm^{-1}; FAB^+ MS (*m*-nitrobenzyl alcohol): *m/z* 446 $[M + H]^+$; ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 0.70 (d, $J = 6.6$ Hz, 6H), 0.85 (d, $J = 6.6$ Hz, 6H), 1.48 (AB, $J_{AB} = 10.5$ Hz, 1H), 1.62–1.93 (m, 5H), 2.1–2.9 (m, 22H), 3.0–3.12 (m, 2H), 3.46–3.50 (m, 2H), 4.1 (br s, 2H, deuterium exchangeable); ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 19.83 (q), 22.20 (q), 27.87 (q), 31.06 (t), 34.91 (q), 35.07 (q), 41.28 (d), 41.45 (d), 43.39 (t), 44.02 (d), 44.11 (d), 46.83 (d), 48.32 (d), 52.49 (t), 52.63 (t), 57.45 (d), 58.87 (d), 59.31 (t), 71.22 (d), 71.29 (d), 95.08 (s), 95.18 (s). Anal. Calcd for $C_{27}H_{46}N_2O_3C$, 72.60; H, 10.38; N, 6.27; O, 10.75. Found C, 72, 31; H, 10.35; N, 6.35; O, 10.69.

4.5.3. Ligand 10. Ligand **10** was prepared as described above. The crude product was purified by chromatography on silica gel using 93 $CHCl_3$:5 MeOH:2 NH_4OH as eluents to give the product **10** as a clear oil (62%). $[\alpha]_D^{20} = +23.2$ ($c = 5$, $CHCl_3$); IR (KBr): γ_{max} 3411 (br s), 2954 (vs), 1464 (m), 1057 (m), 1032 (m) cm^{-1}; FAB^+ MS (*m*-nitrobenzyl alcohol): *m/z* 475 $[M + H]^+$; ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 0.85 (t, 12H), 0.91–1.05 (m, 2H), 1.19–1.32 (m, 2H), 1.48–1.52 (m, 3H), 1.79–1.98 (m, 5H), 2.15 (s, 6H), 2.25–2.80 (m, 16H), 3.10–3.21 (m, 2H), 3.35–3.45 (m, 2H); ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 22.15 (q), 23.74 (q), 25.30 (d), 25.35 (d), 31.31 (t), 33.73 (t), 33.78 (t), 35.64 (q), 35.72 (q), 41.52 (d), 41.58 (d), 43.46 (t), 44.25 (d), 47.88 (d), 49.83 (t), 58.55 (d), 58.59 (d), 61.11 (t), 62.05 (d), 62.09 (d), 95.03 (s), 95.08 (s). Anal. Calcd for $C_{29}H_{50}N_2O_3C$, 73.37; H, 10.62; N, 5.90; O, 10.11. Found C, 73.25; H, 10.56; N, 6.00; O, 10.15.

4.5.4. Ligand 11. Ligand **11** was prepared as described above. The crude product was purified by chromatography on silica gel using 93 $CHCl_3$:5 MeOH:2 NH_4OH as eluents to give the product **11** as a waxy solid (59%). $[\alpha]_D^{20} + 28.6$ ($c = 7$, $CHCl_3$); IR (KBr): γ_{max} 3393 (br s), 2961 (vs), 1458 (m), 1026 (m), 706 (m) cm^{-1}; FAB+ MS (*m*-nitrobenzyl alcohol): *m/z* 515 $[M + H]^+$; ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 1.49 (AB, $J_{AB} = 10.5$ Hz, 1H), 1.85 (AB, $J_{AB} = 10.5$Hz, 1H), 1.89–2.05 (m, 4H), 2.15 (s, 6H), 2.25–2.70 (m, 12H), 3.05 (br s, 2H, deuterium exchangeable), 3.55–3.65 (m, 2H), 3.70–3.82 (m, 2H); 3.86–4.00 (m, 2H), 7.10–7.40 (m, 10H); [$CDCl_3$, 75 MHz]: δ_C 30.28 (t), 36.95 (q), 37.17 (q), 41.53 (d), 41.59 (t), 43.48 (t), 44.25 (d), 44.30 (d), 47.90 (d), 47.99 (d), 50.06 (t), 50.21 (t), 58.53 (d), 58.68 (d), 60.75 (t), 68.77 (d), 68.83 (d), 95.16 (s), 95.20 (s), 127.80 (d), 128.20 (d), 128.96 (d), 135.69 (s), 135.79 (s). Anal. Calcd for $C_{33}H_{42}N_2O_3$. C, 77.01; H, 8.22; N, 5.44; O, 9.33. Found C, 76.90; H, 8.18; N, 5.57, O, 9.27.

4.5.5. Ligand 12. Ligand **12** was prepared as described above. The crude product was purified by chromatography on silica gel using 93 $CHCl_3$:5 MeOH:2 NH_4OH as eluents to give the product **12** as a waxy solid (60%). $[\alpha]_D^{20} = -39.4$ ($c = 5$, $CHCl_3$); IR (KBr): γ_{max} 3405 (br m), 3148 (br s), 2954 (vs), 1370 (m), 1088 (m) cm^{-1}; FAB+ MS (*m*-nitrobenzyl alcohol): *m/z* 415 $[M + H]^+$; ^1H NMR [$CDCl_3$, 300 MHz]: δ_H 1.49 (AB, $J_{AB} = 10.5$ Hz, 1H), 1.60–2.10 (m, 13H), 2.15–2.62 (m, 16H), 2.74–2.84 (m, 2H), 3.08–3.64 (m, 6H, 2H are deuterium exchangeable); ^{13}C NMR [$CDCl_3$, 75 MHz]: δ_C 23.55 (t), 27.51 (t), 31.38 (t), 41.56 (d), 43.44 (t), 44.22 (d), 44.27 (d), 47.74 (d), 48.09 (d), 50.90 (t), 50.94 (t), 54.24 (t), 54.27 (t), 58.54 (d), 58.87 (d), 62.24 (t), 65.17 (d), 65.21 (d), 95.00 (s), 95.09 (s). Anal. Calcd for $C_{25}H_{38}N_2O_3$ C, 72.43; H, 9.24; N, 6.76; O, 11.58. Found C, 72, 35; H, 9.17; N, 6.70; O, 11.49.

4.6. General procedure for the enantioselective addition of diethylzinc to benzaldehyde promoted by enantiopure ligands 8–12[4,5]

To a solution of the ligand (0.125 mmol) in dry toluene (5 mL) under a nitrogen atmosphere at ambient temperature, was added a solution of $ZnEt_2$ in hexane (1.0 M, 1.25 mL, 1.25 mmol). The mixture was stirred for 30 min, and then benzaldehyde (60 mg, 0.5 mmol) was added. The mixture was monitored by GC analysis until no more benzaldehyde was present and stirred for a further 48 h. The reaction was quenched by adding 10% HCl and extracted with Et_2O and the organic phase was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude oil was purified via preparative TLC (hexane/ethyl acetate) and its enantiomeric excess determined by chiral GC. An average % ee of three experiments was taken.

The PCU-ligand can be effectively recovered (>90%) from the acidic aqueous phase by adjusting the pH to approximately 7.5, followed by extraction.

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