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Enantioselective addition of diethylzinc to benzaldehyde in the presence of sulfur-containing pyridine ligands

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Abstract

Diastereomerically pure hydroxy and thiol derivatives of (5*S*,7*S*)-5,7-methane-6,6-dimethyl-2-phenyl-5,6,7,8-tetrahydroquinoline were prepared and assessed in the enantioselective addition of diethylzinc to benzaldehyde: enantioselectivities up to 62% were obtained.

1. Introduction

Chiral ligands with pyridine sp^2-nitrogen donors are gaining an important role in homogeneous catalytic asymmetric reactions.[1] In this contest only few examples of sulphur-containing pyridine ligands have been described[2] and to our knowledge no data has been reported on the use of chiral pyridine-thiols.[3] Continuing our interest in the synthesis and in the application in asymmetric synthesis of chiral pyridine derivatives,[4] we have been evaluating the potential utility of chiral pyridine-thiols as ligands for metal complexes in enantioselective catalysis, also on account of the very good results obtained by the related amino thiols.[5]

Recently, it has been reported that the aminopyridines **1**[6] and the related alcohols **2**[7] gave moderate to excellent enantioselectivity in the addition of diethylzinc to benzaldehyde. Moreover, the phenylthiopyridines **3** were effective ligands in palladium catalysed allylic substitutions.[2a] Since these compounds were prepared from the same intermediate, 5,7-methane-6,6-dimethyl-2-phenyl-5,6,7,8-tetrahydroquinoline **4**, we decided to use this compound as a starting point for the synthesis of chiral pyridine thiols.

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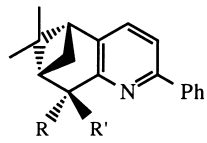


1a: R= NH_2, R'= H **2a**: R= OH, R'= H **3a**: R= SPh, R'= H **4**: R= R'= H
1b: R= H, R'= NH_2 **2b**: R= H, R'= OH **3b**: R= H, R'= SPh

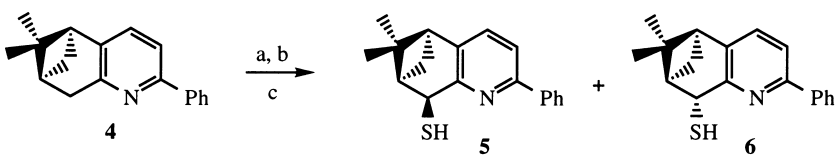
This paper is concerned with the preparation of some diastereomerically pure thiol derivatives of the tetrahydroquinoline **4** and their application in the enantioselective addition of diethylzinc to benzaldehyde.[8]

2. Results and discussion

It is appropriate to note at this point that the ligands **1**–**3** provided a level of stereodifferentiation depending on the configuration at the C_8 carbon. In the enantioselective addition of diethylzinc to benzaldehyde, the *cis*-alcohol **2a** gave a better enantioselectivity than its *trans*-epimer,[6] whereas a reverse result was obtained in the palladium catalysed allylic substitution. In this case, the best stereochemical outcome was obtained by the *trans*-phenylthiopyridine **3b**.[2a] Therefore, we devoted our efforts to obtaining both epimers of the thiol derivatives of **4**.

Initially, we decided to prepare the 8-thiol-5,6,7,8-tetrahydroquinolines **5** and **6** which are the corresponding thiol derivatives of pyridyl carbinol **2**. These compounds would be expected to be very promising ligands since amino thiols gave improved enantioselectivity over the corresponding amino alcohol counterparts in the addition of diethylzinc to benzaldehyde[9] and in the nickel(II) catalysed conjugate addition of diethylzinc to chalcone.[10] Moreover, they appear to be more readily accessible from **4** than **1** and **2**.

Indeed, ligands **5** and **6** were obtained in a one-step procedure (Scheme 1). The red solution of lithiated **4**, obtained by treatment with butyllithium containing TMEDA at −78°C for 1 h and then 2 h at −30°C, was quenched with elemental sulphur at −78°C to give a 1:3 mixture of **5** and **6** which were separated by flash chromatography.



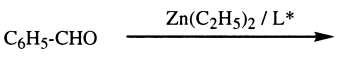
a: BuLi, TMEDA, THF, 1h at -78 °C then 2h at -30 °C; b: S_8, THF, -78 °C then slowly r.t., 70%
c: chromatographic separation

Scheme 1.

The ability of the new ligands to provide asymmetric induction in the enantioselective addition of diethylzinc to benzaldehyde was examined. All reactions were carried out in hexane–toluene solution in the presence of 6 mol% of the ligands at 25°C (Table 1). Disappointing results were obtained with both epimers **5**,**6** (*vide infra*). Next, we decided to examine the possibility of preparing 1–3 SH–N ligands so that the zinc derivative can form a six-membered chelating ring rather than a five-membered one as in the case of that formed by **5** or **6**. Therefore the synthesis of **12** and **15** was planned.

The lithium derivative of **4** was treated with DMF at −60°C to give the enol **7** which was reduced with sodium borohydride to give a 3:7 mixture of diastereomeric alcohols **8** and **9** (Scheme 2). These

Table 1
Enantioselective addition of diethylzinc to benzaldehyde[a]



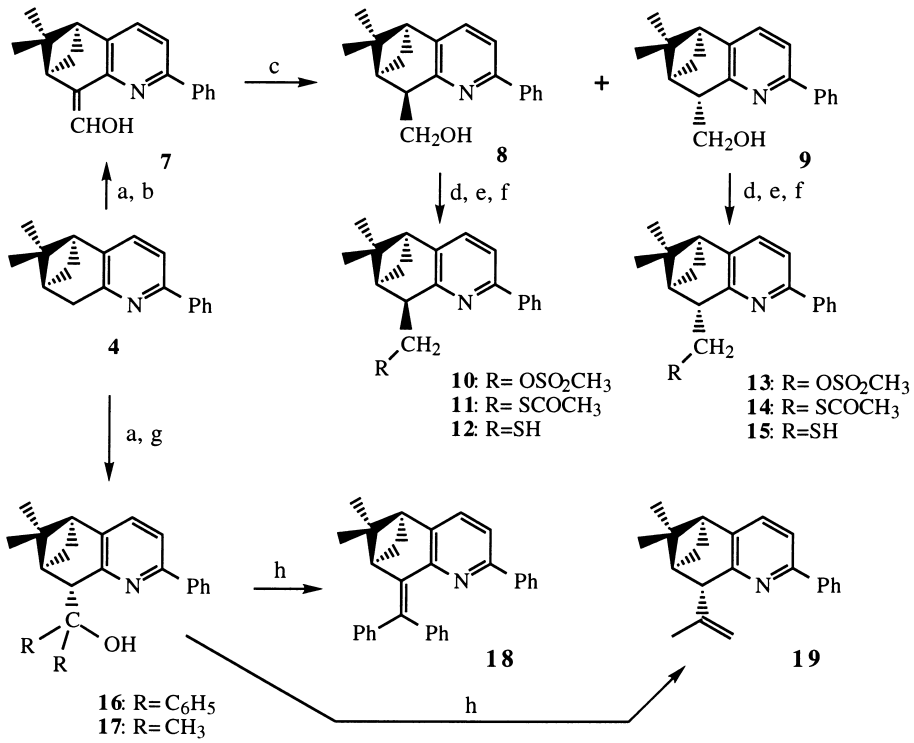
Ligand	Time (h)	Yield.[b] (%)	Ee (%)[c]	Conf.[d]
5	44	87	12	S
6	60	78	5	S
8	48	77	13	R
9	48	83	28	S
12	3	88	51	R
15	7	76	51	S
16	3	89	46	S
17	1.5	92	62	R

[a]Reaction carried out at room temperature in hexane/toluene with a molar ratio Et_2Zn/aldehyde/ligand= 2/1/0.06. [b]Isolated. [c]Determined by chiral GC. [d]Determined from the specific rotation of *(S)*-1-phenylpropanol: $[\alpha]^{25}_D$ -47.6 ($CHCl_3$): Kitamura, M., Suga, S., Kawai, R., Noyori, R. *J. Am. Chem. Soc.*, **1986**, *108*, 6071.

epimers were separated by chromatography on a long column and then converted into the corresponding mesylates **10** and **13**, which by treatment with five equivalents of potassium thioacetate in ethanol at reflux temperature gave the thiol acetates **11** and **14**, respectively. Finally, lithium aluminium hydride reduction afforded the methanethiols **12** and **15**. With the primary thiols in hand, we examined the possibility of preparing the corresponding tertiary ones. Thus, the lithium derivative of **4** was treated with benzophenone to give the carbinol **16** as a single diastereomer. Initially, direct displacement of the hydroxy with the thiol group was attempted using the Lawesson's methodology[11] but only the dehydrated product **18** was obtained. Therefore, we decided to prepare the chloride from the parent compound **16** as an intermediate with the aim of following the above protocol and we chose thionylchloride/triethylamine as the reagent for the OH/Cl replacement reaction.[12] Once again, only the alkene **18** was obtained in this case. In order to reduce the dehydration reaction, the phenyl group was replaced by the methyl group. Thus, the carbinol **17** was prepared as a single diastereomer by treatment of the lithium derivative of **4** with acetone. In this case, the attempted conversion to the corresponding chloride gave the unsaturated compound **19**. Next, we attempted to obtain the tertiary thiol by addition of thiolacetic acid to **19**. Several experiments were carried out using $TiCl_4$[13] or $HClO_4$[14] as catalysts but all these methods proved to be unsuccessful. Finally, on account of a very recent report which describes the preparation of pyridine dithiols by base-induced addition of 2,6-lutidine to non-enolisable thioketones,[3] lithiated **4** was allowed to react with adamantanethione, but the reaction also failed in this case.

Having prepared these ligands, we studied the properties as catalysts not only of pyridine-thiols but also of the related pyridine-alcohols. The results are reported in Table 1. As mentioned before, ligands **5** and **6** gave a very low asymmetric induction and the same sense of enantioselection. It was not possible to give any sure explanation for this disappointing result (the corresponding alcohols **2a** and **2b** gave 91 and 28% ee, respectively[7]), however, this stereochemical outcome implies a probable unsuccessful coordination of the zinc atom of the initial adduct Zn–S to the pyridine nitrogen. This is not the case for ligands **12** and **15** whose zinc derivatives form a six-membered chelating ring rather than a five-membered one as in the case of **5** and **6**. Moreover, thiols **12** and **15** proved to be better catalysts than the corresponding hydroxy derivatives **8** and **9**, respectively.

It should be noted that both epimers **8** and **12**, and **9** and **15** which differ only in the C_8 carbon configuration, gave the opposite configuration of 1-phenylpropanol. But, whereas the epimeric alcohols



a: BuLi, TMEDA, THF, 1h at -78 °C then 2h at -30 °C; b: DMF at -60 °C; c: $NaBH_4$, MeOH then chromatographic separation; d: MsCl, Et_3N, DMAP, CH_2Cl_2; e: KSAc, EtOH, reflux; f: $LiAlH_4$, Et_2O; g: MeCOMe or PhCOPh; THF, -78 °C; h: $SOCl_2$, Et_3N; CH_2Cl_2, r.t.

Scheme 2.

8 and **9** gave a different level of stereodifferentiation, the epimeric thiols **12** and **15** showed the same stereodifferentiating ability. Therefore, in this case the steric course of the reaction depends on the stereogenic centre on the C_8 carbon and it is surprisingly insensitive to the other stereocentres. The two epimers behave as pseudoenantiomers. Tertiary alcohols **16** and **17** were more effective than the primary alcohol **9** with the same C_8 carbon configuration, but surprisingly **17** induced the opposite configuration in the product compared to **16** and **9** indicating a very different steric course of the reaction.

In conclusion, we have reported the synthesis of new pyridine-thiols and the first use of these type of compounds as ligands for asymmetric catalysis. Further studies aimed at the synthesis of new pyridine-thiols are in progress.

3. Experimental

Boiling points are uncorrected. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. The ^1H NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin–Elmer 240 B analyser. A 30 m Beta Dex-120 column (Supelco) was used to determine the enantiomeric excess of (*S*)- and (*R*)-1-phenylpropanol: 100°C (5 min), 5°C/min, 170°C (20 min). (5*S*,7*S*)-5,6,7,8-Tetrahydro-6,6-dimethyl-2-phenyl-5,7-methanoquinoline **4**

($[\alpha]_D^{25}$ +90.5 (*c* 1.8, $CHCl_3$)) was prepared starting from (−)-pinocarvone (obtained by MnO_2 oxidation of commercial (−)-*trans*-pinocarveol [(1*S*,3*R*,5*S*)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-ol] (Fluka A.G.)) according to reported procedures.[6,7]

*3.1. (5S,7S,8S)- and (5S,7S,8R)-5,7-Methano-6,6-dimethyl-2-phenyl-8-thiol-5,6,7,8-tetrahydroquinoline **5** and **6***

A solution of **4** (0.498 g, 2 mmol) in THF (2 ml) was added dropwise under an argon atmosphere to a solution of butyllithium (2.2 mmol, 1.37 ml of a 1.6 M solution in hexane) and tetramethylethylendiamine (0.31 ml, 2 mmol) in THF (16 ml) at −78°C. The resulting solution was stirred for 1 h at −78°C and for 2 h at −30°C, then a solution of sulphur (0.064 g, 2 mmol) in THF (5 ml) was added dropwise at −78°C. The solution was allowed to reach room temperature slowly, H_2O was added and the organic phase separated. The aqueous phase was extracted with ether, the combined organic phases were dried over anhydrous Na_2SO_4, the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether:ethyl acetate=95:5) to give pure thiols **5** and **6**. Compound **5**: 0.123 g (22%); m.p. 79–80°C; $[\alpha]_D^{25}$ +35.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.08 (m, 2H, Ph–H_2 and H_6), 7.50 (d, 1H, J=7.8 Hz, H_4), 7.46–7.32 (m, 3H, Ph), 7.32 (d, 1H, J=7.8 Hz, H_3), 4.83 (d, 1H, J=3.0 Hz, H_8), 3.04 (m, 1H), 2.82 (t, 1H, J=5.4 Hz), 2.64 (m, 1H), 1.67 (d, 1H, J=10.5 Hz), 1.49 (s, 3H), 1.25 (s broad, 1H, SH), 0.64 (s, 3H). Anal. calcd for $C_{18}H_{19}NS$: C, 76.83; H, 6.81; N, 4.98. Found: C, 76.58; H, 6.99; N, 5.19. Compound **6**: 0.287 g (51%); m.p. 89–90°C; $[\alpha]_D^{25}$ +90.2 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 8.05 (m, 2H, Ph–H_2 and H_6), 7.50–7.34 (m, 4H, Ph and H_4), 7.26 (d, 1H, J=7.8 Hz, H_3), 4.64 (s, 1H, H_8), 2.77 (t, 1H, J=6.0 Hz), 2.65 (dt, 1H, J=10.5, 6.0 Hz), 2.57 (d, 1H, J=6.0 Hz), 2.42 (m, 1H), 1.66 (d, 1H, J=10.5 Hz), 1.42 (s, 3H), 0.68 (s, 3H). Anal. calcd for $C_{18}H_{19}NS$: C, 76.83; H, 6.81; N, 4.98. Found: C, 76.66; H, 6.56; N, 5.12.

*3.2. (5S,7S,8S)- and (5S,7S,8R)-8-(Hydroxymethyl)-5,7-methane-6,6-dimethyl-2-phenyl-5,6,7,8-tetrahydroquinoline **8** and **9***

A solution of N,N-dimethylformamide (0.35 g, 4.8 mmol) in THF (5 ml) was added dropwise at −60°C to a solution of lithiated **4** (0.996 g, 4 mmol) under an argon atmosphere. The solution was allowed to reach room temperature slowly, treated with water and then extracted with ether. The organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue (1 g) was used in the next step without further purification (alternatively the residue was purified by flash chromatography eluting with petroleum ether:ethyl acetate=9:1). ^{1}H NMR ($CDCl_3$) δ: 7.88 (m, 2H), 7.52–7.35 (m, 5H), 6.85 (d, 1H), 2.85 (t, 1H), 2.77 (m, 1H), 2.66 (t, 1H), 1.44 (s, 3H), 1.40 (d, 1H), 0.66 (s, 3H).

Sodium borohydride (0.6 g, 16 mmol) was added portionwise to a mixture of the crude aldehyde **7** (1 g) in methanol (10 ml) and an aqueous saturated solution of Na_2CO_3. After 5 h stirring, H_2O was added, the methanol was evaporated in vacuo and the aqueous mixture was extracted with ether. The organic phase was dried over anhydrous Na_2SO_4, the solvent was evaporated and the residue purified by chromatography on a column (3×200 cm) of silica gel (32–63 microns) eluted with a mixture of methylene chloride:petroleum ether:ethyl ether=7:3:0.5 to give pure alcohols **8** and **9**. Compound **8**: 234 mg (21%); $[\alpha]_D^{25}$ −25.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H, Ph–H_2 and H_6), 7.53–7.36 (m, 4H, Ph and H_4), 7.34 (d, 1H, J=7.8 Hz, H_3), 5.91 (s broad, 1H, OH), 4.24 (t, 1H, J=10.5 Hz), 3.74 (dd, 1H, J=10.2, 4.2 Hz), 3.59 (m, 1H), 2.79 (m, 2H), 2.30 (dt, 1H, J=6.3, 2.1 Hz), 1.46 (d, 1H, J=8.7 Hz), 1.42 (s, 3H), 0.66 (s, 3H). Anal. calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.73; H, 7.41; N, 5.12. Compound **9**: 558 mg (50%); $[\alpha]_D^{25}$ +150.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.92

(m, 2H, Ph–H_2 and H_6), 7.55–7.36 (m, 4H, Ph and H_4), 7.34 (d, 1H, J=7.8 Hz, H_3), 5.80 (s broad, 1H, OH), 4.01 (t, 1H, J=10.2 Hz), 3.82 (dd, 1H, J=10.2, 4.5 Hz), 3.34 (m, 1H), 2.81 (t, 1H, J=5.7 Hz), 2.61 (dt, 1H, J=11.4, 5.7 Hz), 2.18 (dt, 1H, J=6, 2.4 Hz), 1.42 (s, 3H), 1.27 (d, 1H, J=9.0 Hz), 0.74 (s, 3H). Anal. calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.79; H, 7.61; N, 4.97.

3.3. (5S,7S,8S)-5,7-Methane-6,6-dimethyl-8-(mercaptomethyl)-2-phenyl-5,6,7,8-tetrahydroquinoline ***12***

Methanesulfonyl chloride (0.2 ml, 0.258 mmol) in anhydrous CH_2Cl_2 (2 ml) was added at 0°C to a solution of **8** (0.48 g, 172 mmol), Et_3N (0.65 ml), 4-(dimethylamino)pyridine (20 mg) in anhydrous CH_2Cl_2 (10 ml). The resulting solution was stirred at 0°C for 10 min and then at room temperature for 2 h. The reaction mixture was poured into a 10% $NaHCO_3$ solution, the organic phase was separated, washed with H_2O, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue (0.65 g) was used in the next step without further purification. A solution of the crude mesylate (0.65 g) and potassium thioacetate (1.08 g, 9.45 mmol) in ethanol (13 ml) was heated under reflux for 15 h. The solvent was evaporated and the residue was purified by flash chromatography (petroleum ether:ethyl acetate=9:1) to give the thiol acetate **11** (0.339 g, 52%) as a single spot on TLC (R_f=0.6; petroleum ether:ethyl acetate=9:1).

A 1 M solution of $LiAlH_4$ in Et_2O (10 ml, 10 mmol) was added dropwise under an argon atmosphere to a solution of **11** (0.339 g, 0.95 mmol) in Et_2O (5 ml) at 0°C. After stirring at room temperature for 12 h, water was added and the organic phase separated. The aqueous phase was extracted with ether, the combined organic phases dried over anhydrous Na_2SO_4, the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether:ethyl acetate=95:5) to give pure **12**: 0.21 g (75%); $[\alpha]_D^{25}$ −136.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.96 (m, 2H, Ph–H_2 and H_6), 7.43–7.24 (m, 4H, Ph and H_4), 7.22 (d, 1H, J=7.8 Hz, H_3), 3.73 (dd, 1H, J=14.4, 4.1 Hz), 2.25 (dd, 1H, J=10.3, 4.1 Hz), 2.75–2.72 (m, 4H), 1.38 (s, 3H), 1.30 (d, 1H, J=8.2 Hz), 1.16 (s broad, 1H, OH), 0.60 (s, 3H). Anal. calcd for $C_{19}H_{21}NS$: C, 77.25; H, 7.17; N, 4.74. Found: C, 77.35; H, 7.19; N, 4.78.

3.4. (5S,7S,8R)-5,7-Methane-6,6-dimethyl-8-(mercaptomethyl)-2-phenyl-5,6,7,8-tetrahydroquinoline ***15***

The procedure reported for the preparation of compound **12** was followed. Starting from compound **9** (0.208 g, 0.748 mmol) the thiol acetate **14** (0.16 g, 63%) was obtained. From **14** (0.16 g), the thiol **15** was obtained: 0.108 g (77%); $[\alpha]_D^{25}$ +36.8 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 7.94 (m, 2H, Ph–H_2 and H_6), 7.43–7.24 (m, 4H, Ph and H_4), 7.20 (d, 1H, J=7.8 Hz, H_3), 3.62 (dd, 1H, J=12.2, 4.1 Hz), 3.14 (m, 1H), 2.70 (s, 1H), 2.62–2.45 (m, 4H), 1.39 (s, 3H), 1.20 (d, 1H, J=8.2 Hz,), 0.61 (s, 3H). Anal. calcd for $C_{19}H_{21}NS$: C, 77.25; H, 7.17; N, 4.74. Found: C, 77.41; H, 7.14; N, 4.69.

3.5. (5S,7S,8R)-5,7-Methane-6,6-dimethyl-2-phenyl-8-(diphenylhydroxymethyl)-5,6,7,8-tetrahydroquinoline ***16***

A solution of benzophenone (2 mmol) in THF (5 ml) was added dropwise at −30°C to a solution of lithiated **4** (0.498, 2 mmol). The solution was allowed to reach room temperature slowly, H_2O was added and the organic phase separated. The aqueous phase was extracted with ether, the combined organic phases were dried over anhydrous Na_2SO_4, the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether:ethyl acetate=9:1) to give pure alcohol **16**: 0.733 g (85%); m.p.

105–6°C; $[\alpha]_D^{25}$ −464.3 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 10.25 (s broad, 1H, OH), 8.05 (m, 2H, 2-phenyl H_2 and H_6), 7.52 (d, 1H, J=7.8, H_4), 7.50–7.26 (m, 8H, arom), 7.24 (d, 1H, J=7.8, H_3), 7.09 (s broad, 5H, arom), 4.44 (s, 1H), 2.64 (t, 1H, J=6.0 Hz), 2.55 (t, 1H, J=6.0 Hz), 2.06 (dt, 1H, J=10.5, 6.0 Hz), 1.38 (s, 3H), 0.88 (s, 3H), −0.18 (d, 1H, J=10.5 Hz). Anal. calcd for $C_{31}H_{29}NO$: C, 86.27; H, 6.77; N, 3.25. Found: C, 86.44; H, 6.61; N, 3.27.

*3.6. (5S,7S,8R)-5,7-Methane-6,6-dimethyl-8-(dimethylhydroxymethyl)-2-phenyl-5,6,7,8-tetrahydroquinoline **17***

Compound **17** was obtained following the above procedure and using acetone (2 mmol) instead of benzophenone: 0.468 g (77%); m.p. 147–8°C; $[\alpha]_D^{25}$ −33.0 (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 8.16 (s broad, 1H, OH), 7.91 (m, 2H, Ph–H_2 and H_6), 7.55 (d, 1H, J=7.8, H_4), 7.48–7.34 (m, 3H, Ph), 7.34 (d, 1H, J=7.8, H_3), 3.26 (s, 1H, H_8), 2.78 (t, 1H, J=6.0 Hz), 2.69 (dt, 1H, J=10.5, 6.0 Hz), 2.36 (dt, 1H, J=6.0, 1.5 Hz), 1.44 (s, 3H), 1.42 (d, 1H, J=10.5 Hz), 1.34 (s, 3H), 1.13 (s, 3H), 0.72 (s, 3H). Anal. calcd for $C_{21}H_{25}NO$: C, 82.03; H, 8.20; N, 4.56. Found: C, 82.24; H, 8.31; N, 4.27.

3.7. Addition of diethylzinc to benzaldehyde: general procedure

A solution of ligand (0.37 mmol) in toluene (5 ml) was cooled at 0°C. A 1 M solution of diethylzinc in hexane (12.4 ml, 12.4 mmol) was added over a period of 5 min. The mixture was stirred at room temperature for 20 min, cooled at 0°C, benzaldehyde (0.6 ml, 0.647 g, 6.1 mmol) was added and then the mixture was stirred at room temperature for the appropriate time (see Table 1). The reaction mixture was quenched with 10% H_2SO_4 (10 ml) and extracted with ether. The organic layer was washed with 10% H_2SO_4, saturated $NaHCO_3$, and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography to afford pure 1-phenylpropanol. The enantiomeric excess was determined by capillary GC with a chiral column: (*R*)-1-phenylpropanol 15.6 min, (*S*)-1-phenylpropanol 15.7 min.

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