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Design, synthesis, and application of novel chiral ONN ligands for asymmetric alkylation

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Abstract Starting from easily available chiral pool amino alcohols, a set of novel chiral ONN ligands was synthesized and their catalytic potential was examined in asymmetric alkylation. Ligands with a secondary central NH group and *N*-methylated ONN ligands were successfully applied as catalysts in the addition of diethyl zinc to various aromatic aldehydes, yielding secondary alcohols in excellent yields of up to 99 % ee.

Keywords Chirality · Asymmetric synthesis · Ligands · Diethyl zinc · Organometallic compounds · Amino alcohols

Introduction

Pioneering work by Oguni and Omi provided the starting point for numerous improvements in the enantioselective synthesis of optically active alcohols for use as chiral building blocks and intermediates in the preparation of biologically active compounds [1, 2]. The successful application of diamino alcohols as ligands in organolithium additions by Mukayama, as well as Sato's work on the addition of diethyl magnesium to aldehydes, has aroused great interest in this type of reaction [3, 4]. Since the initial report from Oguni and Noyori of their discovery of (2*S*)-*exo*-(dimethylamino)isoborneol (DAIB), which is an excellent catalyst in the asymmetric diethyl zinc alkylation of aldehydes, this C–C bond-forming reaction has been greatly refined over the last few decades ([5–7]; for a review, see [8]). Ligands with two coordinating heteroatoms are widely used as catalysts, and β-amino alcohols are among the best catalysts, allowing diethyl zinc alkylation in good yields and with high enantiomeric excesses [9]. The aim of our work was to design and synthesize ligands that possess three different nucleophilic centers capable of binding organometallic reagents. Such ONN ligands could potentially play an important role in C–C bond-forming reactions, as they have a third site that can coordinate to the metal atom, in contrast to amino alcohols [10, 11]. The behavior of these tridentate ONN ligands is rather difficult to predict in comparison to their parent NO ligands; they may conserve [12], enhance [13], or even reverse [14] selectivity, or decrease the enantiomeric excess [15]. The few examples of diethyl zinc alkylation catalyzed by tridentate ligands reported in the literature tend to be polymer-supported reactions, or afford the alkylated product in low enantiomeric excess [16–19]. Therefore, new easily accessible and effective chiral ligands for use in a variety of asymmetric reactions are still desirable.

Starting from chiral pool derived amino alcohols, we developed a straightforward synthetic protocol for a new type of chiral ONN ligand that can be applied in general to any primary or secondary amino alcohol. The introduction of a third nitrogen functionality in close proximity to the 1,2-amino alcohol functionality provides an additional possible coordination site, and thus three different nucleophilic centers within a distance of 3–4 bond lengths are available for direct interactions with metals or substrates (Fig. 1).

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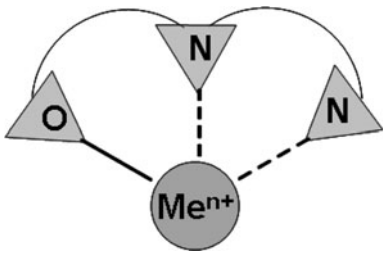


Fig. 1 Scheme for a chelating chiral ligand with three centers for coordination with a metal ion

Herein, we report the synthesis and characterization of several new ONN ligands, as well as the first results and enantioselectivities achieved using these ligands in the asymmetric diethyl zinc alkylation of various aromatic aldehydes.

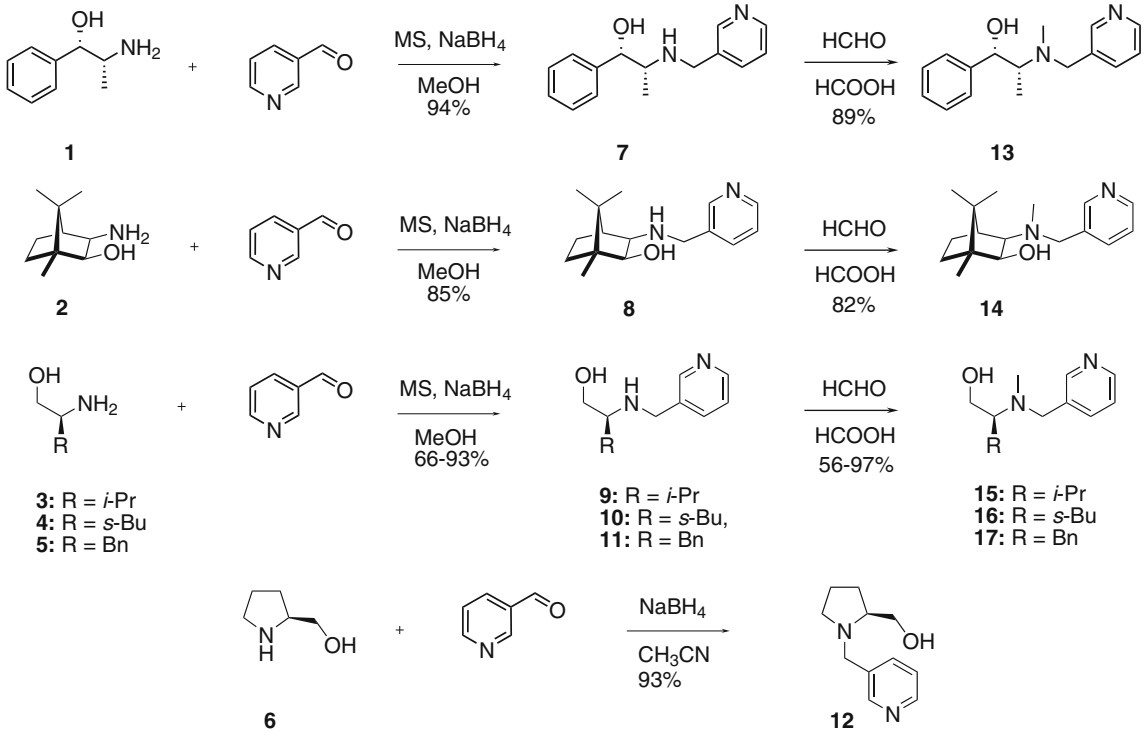
Results and discussion

We chose a set of commercially available chiral 1,2-amino alcohols from the chiral pool that have previously been used for asymmetric reactions, including amino acid derived alcohols, ephedrine, and the camphor derivative 2-aminoisoborneol [20, 21].

In a first step, reductive amination of the enantiopure amino alcohol with pyridine-3-carboxaldehyde was performed (Scheme 1). Reaction in the presence of a freshly activated molecular sieve in anhydrous methanol gave a complex and inseparable mixture of two isomeric imines and the *N*,*O*-acetal, which was reduced directly with sodium borohydride to yield the secondary amino alcohols **7**, **8**, **9**, **10**, and **11** as the sole products. In order to obtain satisfactory yields, it was necessary to use an exact stoichiometric amount of freshly distilled pyridine-3-carboxaldehyde; otherwise, it was difficult to separate out the resulting by-product pyridin-3-ylmethanol.

While the products obtained already qualify as chiral ligands, the presence of a secondary central nitrogen may limit the application of these ligands, particularly in reactions with strong nucleophiles [22]. Therefore, further *N*-methylation was implemented using classical Leuckart–Wallach conditions ($HCHO/HCO_2H$), giving the methylated ONN ligands **13**, **14**, **15**, **16**, and **17** in just two steps with a good overall yield. This general procedure employed for the primary amino alcohols **1**–**5** was slightly adapted for the secondary amino alcohol (*S*)-prolinol (**6**). (*S*)-Prolinol was simply refluxed with equimolar amounts of pyridine-3-carboxaldehyde in acetonitrile without further activation to give the cyclic *N*,*O*-acetal, which was then reduced with sodium borohydride to yield the corresponding ligand **12** in one step only.

While the ligands **14**, **15**, **16**, and **12** were obtained as light yellow oils, we were able to crystallize the phenylalanine



Scheme 1

derivative **11** and the ephedrine derivative **13**. Single crystals of **13** were grown from *n*-hexane/ethyl acetate, and the anticipated structure of **13** was confirmed by single-crystal X-ray analysis. The analysis revealed bond lengths between the three heteroatoms that should allow multiple tethering to metal cations (Fig. 2). The packing structure is dominated by an intermolecular hydrogen bond between the pyridine nitrogen and a face-to-face arrangement of pyridine and benzyl ring systems.

To examine the catalytic potential of these ligands, we investigated the enantioselective alkylation of benzaldehyde (**18**) with diethyl zinc (Scheme 2). This catalytic enantioselective addition of organometallic reagents to a carbonyl group is one of the most powerful methods for the preparation of chiral secondary alcohols and has therefore been studied extensively [8, 11, 17, 23, 24]. The utilization of several metal organyls in combination with a large number of chiral ligands has been reported, making this strategy superior to the comparable enantioselective reduction of ketones [25, 26].

A catalytic amount of ligand (10 mol%) was reacted with a 1 M solution of diethyl zinc in *n*-hexane at 0 °C. Freshly distilled benzaldehyde was added and the reaction was left to stir at room temperature for 24 h. Hydrolysis followed by standard extractive work-up gave 1-phenyl-1-propanol (**19**), which was further analyzed via chiral HPLC after chromatographic purification.

All ligands with a secondary central NH group (**7**, **8**, **9**, **10**, and **11**) that were initially screened were able to catalyze the reaction, but only poor enantioselectivities were observed (Table 1, entries 1–5). Although excellent yields were obtained, the best enantioselectivity was a rather modest value of 45 % ee, obtained using the ephedrine derivative **7** as catalyst (entry 1). The camphor-derived (−)-DAIB analog **8** and the phenylalanine derivative **11** completely failed to induce selectivity (entries 2, 5). A change of solvent did not improve enantioselectivity; on the contrary, when *n*-hexane was used as solvent instead of toluene, the yield dropped to just 59 %. This disappointing selectivity compared to well-known ligands such as *N*-methylephedrine or (−)-DAIB [8, 27, 28] suggested that the formation of a conformationally rigid aggregate was prevented by the presence of a secondary amine.

Indeed, the *N*-methylation was observed to have a dramatic influence, with the selectivity increasing to 13 % ee for the *N*-methylated phenylalanine-derived ligand **17** (entry 11) and to 77 % ee for the *N*-methylated ephedrine derivative **13** (entry 7). Even better, almost complete enantioselectivity was obtained with the *exo*-aminoisoborneol-derived ligand **14** (entry 8), which completely failed before *N*-methylation (entry 2). However, the (*S*)-prolinol-derived ligand **12** failed even though a tertiary amine structure is present (entry 6). No

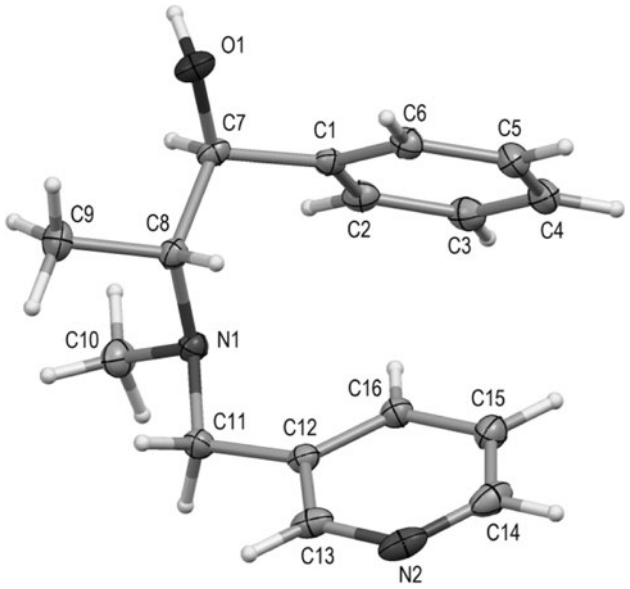
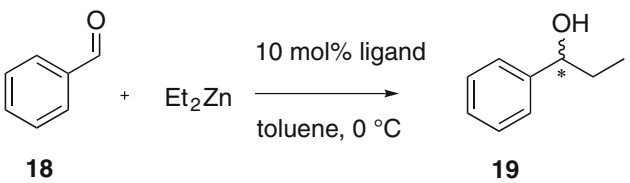


Fig. 2 Molecular structure of ephedrine derivative **13**



Scheme 2

Table 1 Asymmetric addition of diethyl zinc to benzaldehyde (**18**) catalyzed by tridentate ligands

Entry[a]	Ligand	Yield[b] **19**/%	ee[c]/%
1	**7**	94	45 (*S*)
2	**8**	85	1 (*S*)
3	**9**	93	16 (*R*)
4	**10**	84	16 (*R*)
5	**11**	95	1 (*S*)
6	**12**	93	2 (*R*)
7	**13**	79	77 (*S*)
8	**14**	94	>99 (*S*)
9	**15**	99	14 (*R*)
10	**16**	84	25 (*S*)
11	**17**	>99	13 (*S*)

[a] All reactions were performed with 2 mmol benzaldehyde, 4.4 mmol of a 1 M solution of Et_2Zn in *n*-hexane, and 0.2 mmol ligand at 0 °C for 24 h in toluene

[b] Isolated yield of **19** after flash column chromatography

[c] Determined by HPLC using a Daicel (Tokyo, Japan) Chiralcel OD-H column. Absolute configuration was determined by optical rotation and comparison with literature values [8, 11, 17, 23, 24]

significant improvement in *N*-methylation was noticed for leucinol and valinol derivatives. Surprisingly, a reversal of selectivity was observed in the case of the (*S*)-leucinol derivative **10**, which induced the (*R*)-enriched product rather than the (*S*)-enriched alcohol derived from ligand **16** (entry 4 vs. 10), suggesting a fundamentally different transition state for these tridentate ligands with a central secondary amine group. Even though they are quite similar in structure, this effect was not observed with the (*S*)-valinol derivatives **9** and **15**. In this case, *N*-methylation led to a slight decrease in selectivity but yielded a product with the same configuration as the ligand **7** (entry 3 vs. 9).

Considering these results, the presence of a central tertiary amine in an ONN ligand appears to play a significant role in controlling chiral induction during asymmetric diethyl zinc addition. This is surprising, given that an opposite effect is reported for the asymmetric Strecker reaction, where *N*-methylated *N*-salicyl β-amino alcohol fails and the free NH group appears to control enantioselectivity [6].

Encouraged by these early results, the scope of the reaction was expanded to a series of different aldehydes, which were alkylated using a similar procedure in the presence of catalyst **14** that gave the best selectivities of all of the ligands investigated previously. The results, which are summarized in Table 2, suggest efficient coordination and activation of diethyl zinc, and prove the efficiency of ligand **14**, since the appropriate products were obtained in high yields and with good to excellent selectivities ranging from 64 to >99 % ee (Table 2).

The activity of tridentate ONN chiral ligands appears to be comparable to that of the related bidentate ON ligands bearing a benzene ring instead of a pyridine ring system. For example, when the 3-pyridyl group of ONN ligand **14** is replaced with a benzene ring to obtain a comparable bidentate system, the selectivity decreased only slightly, from >99 % ee to 95 % ee, thus indicating that a comparable transition state involving coordination with the central tertiary amino group might be present [29].

Table 2 Diethyl zinc alkylation with various aromatic aldehydes

Entry[a]	Aldehyde	Yield[b]/%	ee[c]/%
1	4-Tolylaldehyde	86	98
2	2-Tolylaldehyde	71	>99
3	3-Tolylaldehyde	87	96
4	4-*i*-Pr-benzaldehyde	91	97
5	Pyridine-3-carboxaldehyde	>99	64
6	4-Chlorobenzaldehyde	>99	>99
7	4-Bromobenzaldehyde	86	93
8	2-Chlorobenzaldehyde	84	>99
9	1-Naphthaldehyde	85	88
10	Cinnamic aldehyde	43	22

[a] All reactions were performed with 2 mmol aldehyde, 4.4 mmol of a 1 M solution of Et_2Zn in *n*-hexane, and 0.2 mmol ligand at 0 °C for 24 h in toluene

[b] Isolated yield after flash column chromatography

[c] Determined via HPLC on a Daicel Chiralcel OD-H or Chiralpak AS-H column. The corresponding racemic alcohols were prepared by the addition of an EtMgBr solution to the aldehyde and used for comparison in HPLC analysis

Conclusion

We have prepared a set of efficient ONN chiral ligands for the enantioselective addition of diethyl zinc to aldehydes. These ligands are not only easily prepared, but they permit high enantioselectivities of up to 99 % ee to be achieved with various aromatic aldehydes at moderate temperatures and a catalyst loading of 10 mol%. We anticipate that these ligands will be applicable to a wide range of asymmetric reactions, and more research in this direction is ongoing.

Experimental

Commercially available reagents and solvents were used as received from the supplier unless otherwise specified. Diethyl ether, light petrol (60–80 °C fraction), ethyl acetate, and dichloromethane were distilled prior to use. Anhydrous toluene was predried over KOH and distilled from Na/benzophenone. Anhydrous methanol was distilled from magnesium turnings and stored over a molecular sieve. ^1H and ^{13}C NMR spectra were recorded on a Bruker (Ettlingen, Germany) DPX 200 at 200 and 50 MHz or on a Bruker DRX 400 at 400 and 100 MHz, respectively, using the solvent peak or TMS as reference. ^{13}C NMR spectra were run in proton-decoupled mode. Multiplicities are referred to as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet), and m (multiplet). TLC analysis was done with precoated aluminum-backed plates (silica gel 60 F254, Merck, Darmstadt, Germany). Compounds were visualized by spraying with 5 % phosphomolybdic acid hydrate in ethanol and heating. Vacuum flash chromatography (VFC) was carried out with Merck 60 silica gel. Melting points of crystalline compounds were determined with a Kofler hot-stage apparatus. Specific rotations were measured on a PerkinElmer (Waltham, MA, USA) 241 polarimeter. Elemental analysis was carried out at the Laboratory for Microanalysis, Department of Physicochemistry, Vienna University (Währinger Str. 42, A-1090 Vienna). HPLC analysis was performed on a Thermo Finnigan (San Jose, CA, USA) Surveyor chromatograph with a PDA plus detector (190–360 nm). A Daicel Chiralcel OD-H column or Chiralpak AS-H column (250 × 4.60 mm) was used as the

stationary phase with *n*-heptane/isopropanol as solvent and a flow of 0.5–1.0 cm^3/min; detection was performed at 254 and 219 nm. X-ray diffraction analysis was carried out with a Bruker Smart APEX CCD diffractometer and Mo-Kα radiation. Structure solution and refinement were performed with the programs SHELXS97 and SHELXL9717.

General procedure A for the synthesis of ONN ligands

Freshly distilled pyridine-3-carboxaldehyde (3.54 g, 33.1 mmol) was added to a mixture of the chiral starting compound and 10 g of a 3 Å activated molecular sieve in 100 cm^3 of anhydrous methanol and refluxed for 14 h. Sodium borohydride (1.25 g, 33.1 mmol) was added in small portions and the mixture was stirred at room temperature until TLC indicated complete conversion. The reaction mixture was filtered over silica and hydrolyzed with H_2O_{dest}. Methanol was removed under reduced pressure and ethyl acetate was added to the residue. The organic layer was extracted three times with small amounts of water, dried over Na_2SO_4, filtrated and the remaining solvent was removed under reduced pressure.

[S-(R,S*)]-α-[1-[[(Pyridin-3-yl)methyl]amino]ethyl] benzenemethanol* (**7**, $C_{15}H_{18}N_2O$)
Synthesis from 5.00 g (1*S*,2*R*)-norephedrine (**1**, 33.1 mmol) according to general procedure A gave the crude product **7**, which was further purified via VFC (200 g silica, CH_2Cl_2:MeOH 40:1 + Et_3N) to yield **7** as a light yellow oil in 94 % yield. $R_f = 0.29$ (CH_2Cl_2:MeOH 30:1 + Et_3N); $[\alpha]_{589}^{20} = -13.3°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 1.00$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.68$ (d, $J = 6.5$ Hz, 3H), 2.70 (dq, $J_1 = 6.4$ Hz, $J_2 = 4.3$ Hz, 1H), 3.62/3.54 (2d, $J = 16.4$ Hz, 2H), 4.50 (d, $J = 3.9$ Hz, 1H), 7.06 (m, 6H), 7.38 (d, $J = 7.8$ Hz, 1H), 8.20 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.6$ (q), 48.3 (t), 57.7 (d), 73.7 (d), 123.4 (d), 126.1 (d), 127.0 (d), 128.0 (d), 135.4 (s), 135.7 (d), 141.5 (s), 148.2 (d), 149.2 (d) ppm.

[S-(2exo,3exo)]-1,7,7-Trimethyl-3-[[(pyridin-3-yl) methyl]amino]bicyclo[2.2.1]heptan-2-ol
(**8**, $C_{16}H_{24}N_2O$)
Preparation from 6.49 g of **2** (38.3 mmol) [30] according to general procedure A gave **8** as a colorless solid in 85 % yield. Crystallization from *n*-hexane gave colorless crystals. $R_f = 0.22$ (CH_2Cl_2:MeOH 30:1 + Et_3N); $[\alpha]_{589}^{20} = +13.9°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 1.00$); m.p.: 44–47 °C (from *n*-hexane); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.94$/0.77 (2s, 6H), 0.99 (m, 2H), 1.04 (s, 3H), 1.79–1.16 (m, 3H), 2.79 (d, $J = 7.2$ Hz, 1H), 3.43 (d, $J = 7.2$ Hz, 1H), 3.86/3.78 (2dd, $J_1 = 13.5$ Hz, 2H), 4.30 (br s, 1H, OH), 7.27 (dd, $J_1 = 7.5$ Hz, $J_2 = 5.0$ Hz, 1H), 7.66 (d, $J = 7.8$ Hz, 1H), 8.54 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 11.2$ (q), 21.2 (q), 21.8 (q), 27.0 (t), 32.7 (q), 46.5 (s), 48.7 (s), 51.4 (d), 51.8 (t), 65.6 (d), 78.6 (d), 123.4 (d), 135.0 (s), 135.6 (d), 148.6 (d), 149.4 (d) ppm.

(S)-3-Methyl-2-[[(pyridin-3-yl)methyl]amino]butan-1-ol
(**9**, $C_{11}H_{18}N_2O$)
Preparation from 4.82 g of (*S*)-valinol (**3**, 46.7 mmol) [31] according to general procedure A gave **9** as a yellow oil in 66 % yield. $R_f = 0.28$ (CH_2Cl_2:MeOH 30:1 + Et_3N); $[\alpha]_{589}^{20} = -6.5°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 1.45$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.96$/0.91 (2d, 6H, $J = 6.9$ Hz), 1.86 (m, 1H), 2.15 (br s, 2H, OH and NH), 2.74 (ddd, $J_1 = 6.5$ Hz, $J_2 = 6.3$ Hz, $J_3 = 4.0$ Hz, 1H), 3.65/3.39 (2dd, $J_1 = 10.75$ Hz, $J_2 = 4.16$ Hz, $J_1 = 10.75$ Hz, $J_2 = 6.98$ Hz, 2H), 3.85/3.76 (2d, $J = 13.3$ Hz, 2H), 7.25 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.1$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 8.49 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.6$ Hz, 1H), 8.54 (d, $J = 1.9$ Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 18.2$ (q), 19.2 (q), 28.5 (d), 48.7 (t), 60.5 (t), 63.8 (d), 123.3 (d), 135.8 (d), 136.1 (s), 148.1 (d), 149.2 (d) ppm.

(S)-4-Methyl-2-[[(pyridin-3-yl)methyl]amino]pentan-1-ol
(**10**, $C_{12}H_{20}N_2O$)
Preparation from 8.38 g of **4** (71.5 mmol) [32] according to general procedure A gave **10** as a colorless liquid in 65 % yield. $R_f = 0.17$ (CH_2Cl_2:MeOH 30:1 + Et_3N); $[\alpha]_{589}^{20} = +14.8°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 1.02$); m.p.: 40–42 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.91$/0.88 (2d, 6H, $J = 2.9$ Hz), 1.34 (m, 2H), 1.62 (m, 1H), 2.11 (br s, 2H, OH and NH), 2.74 (ddd, $J_1 = 13.4$ Hz, $J_2 = 6.3$ Hz, $J_3 = 3.9$ Hz), 3.67/3.31 (2dd, $J_1 = 10.9$ Hz, $J_2 = 3.8$ Hz/ $J_1 = 10.8$ Hz, $J_2 = 6.3$ Hz), 3.85/3.77 (2d, $J = 13.3$ Hz), 7.26 (dd, $J_1 = 8.1$ Hz, $J_2 = 4.4$ Hz, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 8.49 (dd, $J_1 = 4.9$ Hz, $J_2 = 1.6$ Hz, 1H, H-12), 8.54 (d, $J = 2.0$ Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 22.5$ (q), 22.8 (q), 24.7 (d), 40.8 (t), 48.1 (t), 56.3 (d), 63.1 (t), 123.3 (d), 135.7 (s), 135.8 (d), 148.1 (d), 149.2 (d) ppm.

(S)-β-[[(Pyridin-3-yl)methyl]amino]benzenepropanol
(**11**, $C_{15}H_{18}N_2O$)
Preparation from 8.81 g of **5** (58.2 mmol) [31] according to general procedure A and recrystallization from *n*-hexane/ethyl acetate gave **11** as a white solid in 93 % yield. $R_f = 0.22$ (CH_2Cl_2:MeOH 30:1 + Et_3N); $[\alpha]_{589}^{20} = -14.0°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 0.07$); m.p.: 67–68 °C (from *n*-hexane/ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.41$ (m, 2H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.29–7.05 (m, 6H), 3.72 (s, 2H), 3.60 (dd, $J_1 = 10.7$ Hz, $J_2 = 3.7$ Hz, 1H), 3.32 (dd, $J_1 = 8.0$ Hz, $J_2 = 5.2$ Hz, 1H), 2.88 (m, 1H), 2.75 (s, 1H), 2.71 (d, 1H), 1.92 (bs, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 37.9$ (t), 48.6 (t), 59.6 (d), 62.7 (d), 123.6 (d), 126.7 (d), 128.6 (2d), 129.1 (2d), 135.2 (s), 135.7 (d), 138.2 (s), 148.6 (d), 149.6 (d) ppm.

(S)-1-[(Pyridin-3-yl)methyl]pyrrolidine-2-methanol (**12**, $C_{18}H_{16}N_2O$)

(*S*)-Prolinol (**6**, 6.56 g, 64.9 mmol) [33] and 6.95 g of freshly distilled pyridine-3-carbaldehyde (64.9 mmol) were dissolved in 100 cm^3 of anhydrous acetonitrile and stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the crude material was dissolved in 80 cm^3 of anhydrous methanol. $NaBH_4$ was added in small portions and the mixture was stirred for 2 h at room temperature until TLC indicated complete conversion. The reaction mixture was carefully hydrolyzed with 50 cm^3 H_2O and the methanol was removed under reduced pressure. The aqueous solution was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified over silica (CH_2Cl_2:MeOH 30:1 + Et_3N) to yield **12** as a light brown oil in 93 % yield. $R_f = 0.43$ (CH_2Cl_2:MeOH 20:1 + Et_3N); $[\alpha]_{589}^{20} = +73.9°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 1.02$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.06–1.59$ (m, 4H), 2.25 (m, 1H), 2. 73 (ddd, $J_1 = 11.9$ Hz, $J_2 = 5.8$ Hz, $J_3 = 2.9$ Hz, 1H), 2.94 (m, 2H), 3.65/3.46 (2dd, $J_1 = 11.0$ Hz, $J_2 = 3.7$ Hz/ $J_1 = 11.0$ Hz, $J_2 = 2.5$ Hz, 2H), 3.99/3.35 (2d, $J = 13.3$ Hz, 2H), 7.23 (dd, $J_1 = 7.8$ Hz, $J_2 = 4.7$ Hz, 1H), 7.63 (dt, $J_1 = 7.8$ Hz, $J_2 = 1.8$ Hz, 1H), 8.47 (dd, $J_1 = 5.1$ Hz, $J_2 = 2.0$ Hz, 1H), 8.50 (d, $J = 2.7$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.1$ (t), 27.5 (t), 55.8/54.2 (2), 62.3 (t), 64.4 (d), 123.2 (d), 134.6 (s), 136.3 (d), 148.2 (d), 149.8 (d) ppm.

General procedure B

Compounds **7**–**11**, prepared according to procedure A, were dissolved in 30 cm^3 of concentrated formic acid and stirred for 30 min. Formaldehyde (25 cm^3, 37 % solution in H_2O) was added and the mixture was refluxed overnight. Remaining formaldehyde was removed under reduced pressure, 4 M NaOH solution in H_2O was added until pH >7, and the reaction mixture was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield the crude products.

[S-(R,S*)]-α-[1-[Methyl[(pyridin-3-yl)methyl]amino]-ethyl]benzenemethanol* (**13**, $C_{16}H_{20}N_2O$)

Synthesis starting from 4.30 g compound **7** (17.74 mmol) yielded crude **13**. Crystallization from *n*-hexane/ethyl acetate gave **13** as colorless crystals in 89 % yield. $R_f = 0.24$ (CH_2Cl_2:MeOH 30:1 + Et_3N); $[\alpha]_{589}^{20} = -10.5°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 1.08$); m.p.: 106–108 °C (from *n*-hexane/ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.08$ (d, $J = 6.9$ Hz, 3H), 2.19 (s, 3H), 2.92 (m, 1H), 3.59 (s, 2H), 3.67 (br s, 1H, OH), 4.83 (d, 1H, $J = 5.5$ Hz), 7.17 (dd, $J_1 = 7.8$ Hz, $J_2 = 4.9$ Hz), 7.32 (m, 5H), 7.43 (d, $J = 7.8$ Hz, 1H), 8.35 (d, $J = 2.0$ Hz, 1H), 8.43 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.5$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.6$ (q), 38.1 (q), 55.9 (t), 63.6 (d), 74.4 (d), 123.2 (d), 126.2 (d), 126.9 (d), 127.9 (d), 135.0 (s), 136.2 (d), 143.3(s), 148.0 (d), 149.6 (d) ppm.

[S-(2exo,3exo)]-1,7,7-Trimethyl-3-[methyl[(pyridin-3-yl)methyl]amino]bicyclo[2.2.1]heptan-2-ol (**14**, $C_{17}H_{26}N_2O$)

Preparation from 2.75 g of **8** (10.6 mmol) according to general procedure B gave **14** as a light yellow oil in 82 % yield. $R_f = 0.38$ (CH_2Cl_2:MeOH 30:1 + Et_3N); $[\alpha]_{589}^{20} = -3.8°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 1.14$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.92/0.72$ (2s, 6H), 0.96 (m, 2H), 1.05 (s, 3H), 1.69/1.39 (2m, 2H), 2.07 (m, 4H), 2.49 (d, $J = 7.04$ Hz, 1H), 3.43 (m, 3H), 4.13 (br s, 1H, OH), 7.22 (dd, $J_1 = 7.7$ Hz, $J_2 = 4.8$ Hz, 1H), 7.57 (d, $J = 7.8$ Hz, 1H), 8.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.6$ (q), 21.2 (q), 22.1 (q), 28.0 (t), 32.3 (t), 40.5 (br q), 46.7 (d), 46.9 (s), 49.4 (d), 59.2 (br t), 73.5 (d), 79.2 (d), 123.5 (d), 133.9 (s), 136.5 (d), 148.9 (d), 150.4 (d) ppm.

(S)-3-Methyl-2-[methyl[(pyridin-3-yl)methyl]amino]butan-1-ol (**15**, $C_{12}H_{20}N_2O$)

Preparation from 0.707 g of **9** (3.64 mmol) according general procedure B gave **15** as a light yellow oil in 97 % yield. $R_f = 0.33$ (CH_2Cl_2:MeOH 30:1 + Et_3N); $[\alpha]_{589}^{20} = -19.6°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 1.00$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.09/0.89$ (2d, 6H, $J = 6.5$ Hz), 1.68 (br s, 1H, OH), 1.93 (m, 1H), 2.15 (br s, 2H, OH and NH), 2.27 (s, 3H), 2.52 (ddd, $J_1 = 10.0$ Hz, $J_2 = 8.6$, $J_3 = 4.7$ Hz, 1H), 3.34 (m, 1H), 3.66 (dd, $J_1 = 10.7$ Hz, $J_2 = 5.0$ Hz, 1H), 3.88/3.74 (2d, $J = 13.5$ Hz, 2H), 7.27 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.2$ Hz, 1H), 7.63 (ddd, $J_1 = 7.8$ Hz, $J_2 = 1.9$ Hz, $J_3 = 1.9$ Hz, 1H), 8.51 (s, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 19.8$ (q), 22.1 (q), 27.8 (d), 35.9 (q), 58.9 (t), 59.4 (t), 70.7 (d), 123.4 (d), 135.2 (s), 136.2 (d), 148.3 (d), 149.8 (d) ppm.

(S)-4-Methyl-2-[methyl[(pyridin-3-yl)methyl]amino]pentan-1-ol (**16**, $C_{13}H_{22}N_2O$)

Preparation from 4.99 g of **10** (24.0 mmol) according to general procedure B gave **16** as a light yellow oil in 89 % yield. $R_f = 0.33$ (CH_2Cl_2:MeOH 30:1 + Et_3N); $[\alpha]_{589}^{20} = +3.4°$ cm^3 g^{-1} dm^{-1} (EtOH, $c = 1.01$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.93/0.60$ (2d, 6H, $J = 6.7$ Hz), 1.08 (dq, $J_1 = 13.4$ Hz, $J_2 = 4.6$ Hz, 1H), 1.45 (m, 2H), 1.45 (m, 2H), 2.75 (s, 3H), 2.86 (m, 1H), 3.41 (m, 3H), 3.70/3.50 (2d, $J = 13.3$ Hz/$J = 13.5$ Hz), 7.26 (dd, $J_1 = 7.8$ Hz, $J_2 = 4.3$ Hz, 1H), 7.64 (d, $J = 7.83$ Hz, 1H), 8.50 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 22.0$ (q), 23.5 (q), 25.1 (d), 33.8 (t), 35.5 (q), 55.1 (t), 61.1 (t), 61.7 (d), 123.3 (d), 134.6 (s), 136.3 (d), 148.5 (d), 150.0 (d) ppm.

(S)-β-[Methyl[(pyridin-3-yl)methyl]amino] benzenepropanol (**17**, $C_{16}H_{20}N_2O$)

Preparation from 5.32 g of **11** (20.8 mmol) according to general procedure B gave **17** as a light yellow oil in 56 % yield (3.14 g). $R_f = 0.16$ (CH_2Cl_2:MeOH 20:1 + Et_3N); $[\alpha]_{589}^{20} = -16.6°$ cm^3 g^{-1} dm^{-1} ($CHCl_3$, $c = 1.05$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.42$ (m, 2H), 7.55 (d, $J = 9.6$ Hz, 1H), 7.28–7.20 (m, 6H), 3.74–3.45 (dd, $J_1 = 33.5$ Hz, $J_2 = 13.4$ Hz, 2H), 3.38 (m, 2H), 3.08–2.75 (m, 3H), 2.36 (dd, $J_1 = 13.0$ Hz, $J_2 = 8.9$ Hz, 1H), 2.21 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 31.6$ (t), 35.8 (q), 55.7 (t), 60.6 (t), 65.8 (d), 123.6 (d), 126.3 (d), 128.6 (2d), 129.1 (2d), 134.4 (s), 136.5 (d), 139.0 (s), 148.7 (d), 150.1 (d) ppm.

Asymmetric diethyl zinc alkylation of aromatic aldehydes

The chiral ligand (0.2 mmol) was dissolved in 4 cm^3 of anhydrous toluene under a dry argon atmosphere and cooled to 0 °C. A solution of diethyl zinc (1.0 M in *n*-hexane, 4.4 mmol) was added slowly at 0 °C. After the reaction had been stirred for 30 min, freshly distilled aldehyde (2 mmol) was added dropwise via a microsyringe at 0 °C, and the reaction was stirred for 8 h at room temperature. The mixture was carefully hydrolyzed with 1 M HCl and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with a small amount of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (30 g silica, light petrol:diethyl ether) to yield the secondary alcohol **19**. HPLC: Chiralcel OD-H; *n*-hexane:isopropanol 98:2; 0.7 cm^3/min; 254 nm. Analytical data were in agreement with those reported in the literature [17–19].

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