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Novel tridentate ligands derived from (+)-camphoric acid for enantioselective ethylation of aromatic aldehydes

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ABSTRACT

Novel tridentate ligands were prepared from (+)-camphoric acid, using simple synthetic sequences. The synthesized ligands were used in enantioselective ethylations of benzaldehydes, showing enantioselectivities up to 92%, at room temperature. Extending the reaction to other aromatic aldehydes, very good results (almost quantitative yields and ee up to 97%, for *m*-anisaldehyde) were obtained. Structural features such as no substitution in the salicylaldehyde moiety of the Schiff base and an ethyl group in the nitrogen at the C1 position of the cyclopentane ring seem to be essential for obtaining high enantioselectivities.

1. Introduction

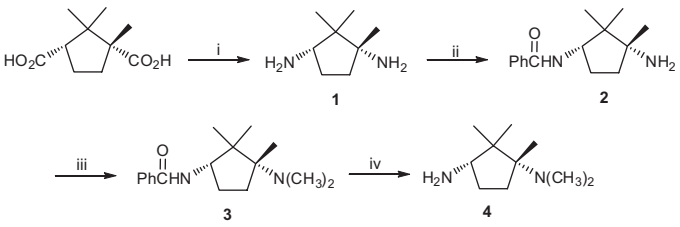
Asymmetric carbon–carbon bond formation reactions constitute one of the most important and fundamental topics of research. Among these reactions, the enantioselective ethylation of aromatic aldehydes assumes special interest since it allows for the synthesis of chiral secondary alcohols, essential components in the preparation of pharmaceuticals, agrochemicals, and perfumes, among others.[1–4]

Chiral bidentate ligands such as aminoalcohols, diamines, diols, and their derivatives are the most frequently used in alkylation reactions. Tridentate ligands have been less explored, although in recent years several examples have appeared in the literature.[5–16] Tridentate ligands are expected to form a more rigid zinc chelate in the transition state than bidentate ones, exhibiting a better discrimination between the two enantiotopic faces of the substrate and therefore may lead to a more enantioselective alkylation reaction.[10,15,16] In continuation of our studies on the enantioselective ethylation of aromatic aldehydes with diethylzinc using chiral ligands derived from (+)-camphoric acid and since very good ee were obtained with some of our ligands (ee up to 99%),[17] we decided to synthesize a new series of *N*,*N*,*O*-tridentate ligands using this chiral source. Several ligands were obtained from (1*R*,3*S*)-1,3-diamino-1,2,2-trimethylcyclopentane and used in the enantioselective addition of diethylzinc to aldehydes. In all cases *N*,*N*,*O*-chelating zinc complexes can be formed in the transition state through the reaction of the (+)-camphoric derived ligands with diethylzinc.

2. Results and discussion

2.1. Synthesis of chiral tridentate *N*,*N*,*O*-ligands

Diamine **1** [(1*R*,3*S*)-1,3-diamino-1,2,2-trimethylcyclopentane] was prepared from commercial (+)-camphoric acid, according to a previously described procedure.[18] Compounds **2** and **3** have already been described by Urabe et al. and by us.[17,19] Compound **3** can be prepared by the reaction of **1** with benzoyl chloride in ethanol to give **2**, followed by reaction with formaldehyde and formic acid in order to obtain the dimethylated product. Compound **4** was synthesized by hydrolysis of **3** with concentrated HCl (Scheme 1).



Scheme 1. Synthesis of (1*R*,3*S*)-3-amino-1-(dimethylamino)-1,2,2-trimethylcyclopentane **4**. Reagents and conditions: (i) NaN_3, H_2SO_4, $CHCl_3$, 55–60 °C, overnight, 85%; (ii), EtOH, rt, overnight, 90%; (iii) HCO_2H, HCHO, reflux, 18 h, 96%; (iv) HCl 37%, H_2O, reflux, 24 h, 77%.

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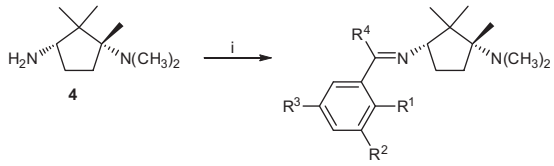
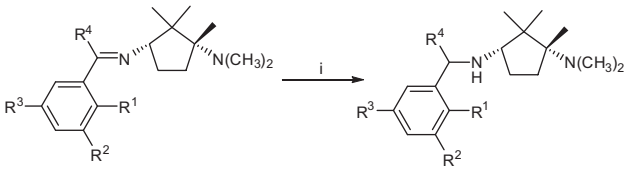
Reaction of **4** with several aldehydes using ultrasound irradiation and activated silica gel as promoter, gave the corresponding Schiff bases **5a-f** in moderate to good yields (Scheme 2).



5a R^1 = OH, R^2 = R^3 = R^4 = H
5b R^1 = OH, R^2 = OMe, R^3 = R^4 = H
5c R^1 = OH, R^2 = R^3= *t*-Bu, R^4 = H
5d R^1 = OH, R^3 = Br, R^2 = R^4 = H
5e R^1 = OH, R^2 = R^3 = H, R^4 = Me
5f R^1 = R^2 = R^3 = R^4 = H

Scheme 2. Synthesis of Schiff bases **5a**–**f**. Reagents and conditions: (i) salicylaldehydes **5a**–**d**, acetophenone **5e** or benzaldehyde **5f**, ultrasound irradiation 30–60 min, EtOH, rt, 28–78%.

Ligands **5a** and **5d** were reduced to the respective amines **6a** and **6b** using excess sodium borohydride in $CHCl_3$/MeOH (2:1) at room temperature, in 95% and 55% yields, respectively (Scheme 3).

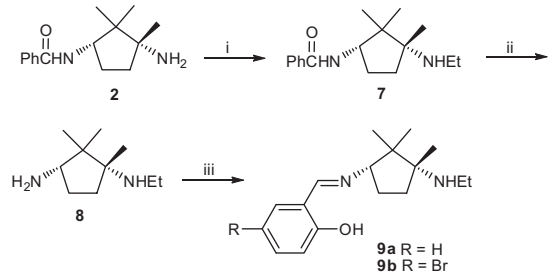


5a R^1 = OH, R^2 = R^3 = R^4 = H
5d R^1 = OH, R^3 = Br, R^2 = R^4 = H

6a R^1 = OH, R^2 = R^3 = R^4 = H
6b R^1 = OH, R^3 = Br, R^2 = R^4 = H

Scheme 3. Synthesis of amines **6a**–**b**. Reagents and conditions: $NaBH_4$, $CHCl_3$/MeOH (2:1), rt, 95% (**6a**) and 55% (**6b**).

Schiff base ligands **9a**–**b** were also prepared, according to the synthetic sequence shown in Scheme 4. Compound **2** was alkylated with ethyl iodide, in the presence of potassium carbonate to give **7**. Hydrolysis of the benzoyl group **8**, followed by reaction with salicylaldehyde or 5-bromosalicylaldehyde gave ligands **9a-b** in very good yields. Compounds **7** and **8** have already been prepared by us and reported previously.[17]



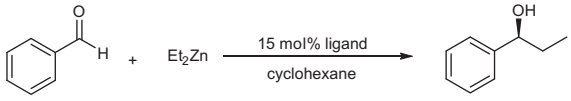
9a R = H
9b R = Br

Scheme 4. Synthesis of Schiff bases **9a**–**b**. Reagents and conditions: (i) EtI,K_2CO_3, EtOH, reflux, 24 h, 67%; (ii) HCl 37%, H_2O, reflux, 24 h, 77%; (iii) salicylaldehyde **9a**, 5-bromosalicylaldehyde **9b**, ultrasound irradiation 30–60 min, EtOH, rt, 92% both **9a** and **9b**.

2.2. Enantioselective addition of diethylzinc to aldehydes

Encouraged by the good results obtained with bidentate ligands derived from (1*R*,3*S*)-1,3-diamino-1,2,2-trimethylcyclopentane and since better results are obtained in the alkylation reactions of aldehydes when a less sterically demanding group is present in the amine moiety at C1,[17,19] we decided to prepare several tridentate ligands using dimethylated compound **4**. Also, since salen ligands are known to be relatively efficient in several asymmetric reactions, we thought that the combination of these two structural features could give several tridentate Schiff bases which could be promising ligands for enantioselective ethylations of aromatic aldehydes. Therefore, Schiff bases **5a**–**e** were synthesized via reaction of **4** with several salicylaldehydes. For comparative purposes **5f**, a bidentate ligand, was also synthesized via reaction of **4** with benzaldehyde.

Ligands **5a**–**f** were tested in the enantioselective alkylation of benzaldehyde with diethylzinc, using our previously optimized conditions (Scheme 5).[20] The reactions were carried out in dry cyclohexane at 0 °C in the presence of 15 mol% of chiral ligand. Since at 0 °C the substrate conversions were moderate (50–79% yield), the reaction temperature increased to room temperature. As can be seen from the results in Table 1, this resulted in a significant increase in the conversion (85–99%) without a significant deterioration of the enantiomeric excess.



Scheme 5. Asymmetric addition of diethylzinc to benzaldehyde.

Table 1
Enantioselective alkylation of benzaldehyde catalyzed by **5a**–**f**[a]

Ligand	Reaction temperature (°C)	Conversion[b] (%)	1-Phenyl-1-propanol[c] (%)	ee[d] (%)
5a	0	79	90	42 (*S*)
5a	rt	99	91	40 (*S*)
5b	0	50	89	18 (*S*)
5b	rt	98	98	16 (*S*)
5c	0	72	62	3 (*R*)
5c	rt	96	80	4 (*R*)
5d	0	69	82	35 (*S*)
5d	rt	99	89	31 (*S*)
5e	0	51	70	11 (*R*)
5e	rt	98	95	13 (*R*)
5f	0	55	66	12 (*R*)
5f	rt	85	82	11 (*R*)

[a] Reactions conditions: cyclohexane (4 mL), chiral ligand (0.15 mmol), benzaldehyde (1 mmol), diethylzinc solution 1 M in hexane (2 mmol), 24 h reaction.
[b] Determined by GC.
[c] Relative to converted benzaldehyde.
[d] Determined by GC on a chiral column; the major enantiomer is indicated in parenthesis.

In addition to the desired chiral alcohol, 1-phenyl-1-propanol, benzyl alcohol was also formed as a by-product. The formation of benzyl alcohol has been observed by others and is the result of a secondary process in which the benzaldehyde is reduced by the zinc alkoxide of the ethylation product, 1-phenyl-1-propanoxide.[21] An increase in the chiral alcohol yields was observed for all of the ligands at room temperature, when compared with those obtained at 0 °C.

Poor to moderate ee were obtained with ligands **5a**–**f**, wherein the best result was with ligand **5a**, [42% (*S*) at 0 °C]. It is noteworthy that ligands **5c**, **5e**, and **5f** gave products with an (*R*)-configuration, while the other ones gave products with an (*S*)-configuration.

In an attempt to improve the results, ligand **5a** was tested with other solvents and different catalyst loadings (Table 2).

Table 2
Enantioselective alkylation of benzaldehyde with **5a**[a]

Ligand	Solvent	Catalyst (mol %)	Conversion[b] (%)	1-Phenyl-1-propanol[c] (%)	ee[d] (%)
5a	Cyclohexane	15	99	91	40 (*S*)
5a	Ethyl ether	15	71	78	37 (*S*)
5a	Toluene	15	75	56	36 (*S*)
5a	Dichloromethane	15	74	69	27 (*S*)
5a	Tetrahydrofuran	15	29	67	12 (*S*)
5a	Cyclohexane	10	99	88	37 (*S*)
5a	Cyclohexane	20	99	87	39 (*S*)

[a] Reactions conditions: solvent (4 mL), benzaldehyde (1 mmol), room temperature, diethylzinc solution 1 M in hexane (2 mmol), 24 h reaction.
[b] Determined by GC.
[c] Relative to converted benzaldehyde.
[d] Determined by GC on a chiral column; the major enantiomer is indicated in parenthesis.

As it can be seen from the results in Table 2, the best solvent for the enantioselective alkylation of benzaldehyde with ligand **5a** was cyclohexane while a variation in the catalyst loading did not improve the ee of the reaction. Therefore we decide to use our best ligands **5a** and **5d** and reduce the imines to the respective amines in order to see if better results could be obtained with these less rigid ligands. The presence of an sp^3 hybridized nitrogen in ligands **6a**–**b** instead of sp^2 could lead to a more flexible complex, with a different geometry[22] and perhaps higher ee could be obtained. As can be seen from the results in Table 3, contrary to our expectations, poor ee were obtained with ligands **6a**–**b**.

Table 3
Enantioselective alkylation of benzaldehyde catalyzed by **6a**–**b** and **9a**–**b**[a]

Ligand	Conversion[b] (%)	1-Phenyl-1-propanol[c] (%)	ee[d] (%)
6a	95	81	3 (*S*)
6b	86	70	7 (*S*)
9a	>99	99	92 (*S*)
9b	>99	97	16 (*S*)

[a] Reactions conditions: cyclohexane (4 mL), chiral ligand (0.15 mmol), benzaldehyde (1 mmol), diethylzinc solution 1 M in hexane (2 mmol), 24 h reaction, room temperature.
[b] Determined by GC.
[c] Relative to converted benzaldehyde.
[d] Determined by GC on a chiral column; the major enantiomer is indicated in parenthesis.

In our previous paper[17] we observed that the presence of an ethyl group instead of two methyl groups in the nitrogen at C1 of the cyclopentane ring could be beneficial in terms of ee. With this in mind, we prepared two other ligands **9a**–**b**, with an ethyl group, according to the synthetic sequence of Scheme 4. These ligands were tested in the enantioselective alkylation of benzaldehyde and very good results were obtained with ligand **9a** (Table 3). 1-Phenyl-1-propanol was obtained in quantitative yield and 92% ee.

The efficiency of ligand **9a** was examined with a series of other aromatic aldehydes, using 15 mol% of catalyst and cyclohexane as solvent at room temperature. The obtained results are shown in Table 4.

Very good conversions were obtained with all of the aldehydes. In all cases, the absolute configuration of the major enantiomer was assigned as (*S*) by comparison of the retention times with reported values or by determining the sign of the specific rotation of the isolated reaction product.[23–25] The best ee was obtained for *m*-anisaldehyde (97%). Better ee were obtained when aromatic aldehydes with electron-donating substituents were used (88–97%). Bulky substrates, such as 1- and 2-naphthaldehyde gave moderate ee, 72% and 74%, respectively.

Table 4
Enantioselective alkylation aromatic aldehyde catalyzed by **9a**[a]

Aldehyde	Conversion[b] (%)	ee[c] (%)
o-Methylbenzaldehyde	>99	88 (*S*)
m-Methylbenzaldehyde	>99	96 (*S*)
p-Methylbenzaldehyde	>99	93 (*S*)
m-Anisaldehyde	>99	97 (*S*)
o-Chlorobenzaldehyde	>99	75 (*S*)
p-Chlorobenzaldehyde	>99	78 (*S*)
1-Naphthaldehyde	98	72 (*S*)
2-Naphthaldehyde	97	74 (*S*)

[a] Reactions conditions: cyclohexane (4 mL), chiral ligand (0.15 mmol), benzaldehyde (1 mmol), diethylzinc solution 1 M in hexane (2 mmol), 24 h reaction, room temperature.
[b] Determined by GC.
[c] Determined by GC on a chiral column; the major enantiomer is indicated in parenthesis.

3. Conclusions

A new series of tridentate ligands was synthesized from (+)-camphoric acid, using simple synthetic sequences. The ligands were tested in the enantioselective ethylation of benzaldehyde, showing enantioselectivities up to 92%, at room temperature. Structural features such as no substitution in the salicylaldehyde moiety of the Schiff base (ligands **5a** and **9a**) and an ethyl group in the C1 nitrogen of the cyclopentane ring (ligand **9a**) are essential to obtain high enantioselectivities. The best ligand, **9a**, was used in the alkylation of other aromatic aldehydes with diethylzinc, giving very good results (almost quantitative yields and ee up to 97%, for *m*-anisaldehyde). It is our objective to extend the application of these and other (+)-camphoric acid derived ligands to other asymmetric transformations.

4. Experimental

4.1. General

Commercially available compounds were used without further purification. All solvents were dried prior to use following standard procedures. Diethylzinc (Aldrich) was used as a 1 M solution in hexane. Benzaldehyde was distilled prior to use and stored over 4 Å molecular sieves. Melting points were determined using an Electrothermal melting point apparatus (values are uncorrected). Optical rotations were measured with an Optical Activity AA-5 polarimeter. NMR spectra were recorded on a Bruker Avance III 400 MHz (100 MHz for ^{13}C). TMS was used as the internal standard and chemical shifts are given in ppm. Infrared spectra were recorded on a Thermo Scientific Nicolet 6700 FTIR. Sonication was performed in a Bandelin Sonorex RK100H cleaning bath with a frequency of 35 Hz and a nominal power of 80/160 W. High-resolution mass spectra (HRMS) were obtained on a TOF VG Autospect M spectrometer with electrospray ionization (ESI). Alkylation reactions were carried out in an inert atmosphere using standard Schlenk-type techniques. Enantiomeric excesses were determined by using a chiral γ-cyclodextrin capillary column (FS-Lipodex-E, 25 m, 0.25 i.d.) from Machery-Nagel using hydrogen as carrier gas, on an Agilant 7820 instrument. The absolute configuration of the major enantiomers was determined by comparison of the retention times with reported values and by determining the sign of the specific rotation of the isolated reactions.

4.2. Synthesis

Compounds **1**, **2**, **3**, **7**, and **8** are already described in the literature.[17–19]

4.2.1. (1*R*,3*S*)-N^1,N^1-Dimethyl-1,2,2-trimethylcyclopentane-1,3-diamine 4

To compound **3** (1.83 g, 6.67 mmol), water (10 mL) and conc. HCl (15 mL) were added and the reaction mixture was refluxed overnight. After cooling to room temperature, the reaction was evaporated and water and ethyl acetate were added to the residue. Next, NaOH 15% was added until basic pH and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were washed with water and brine and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent an oil, **4** was obtained and used in the next step without further purification. Yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85 (s, 3H), 0.89 (s, 3H), 0.99 (s, 3H), 1.22–1.39 (m, 3H), 1.48–1.57 (m, 1H), 1.77–2.03 (m, 2H), 2.22 (s, 6H), 2.92 (t, 1H, J = 9.4 Hz).

4.3. General procedure for the synthesis of compounds 5a–f

In a 25 mL erlenmeyer flask, compound **4** (0.51 g, 3 mmol) was dissolved in 10 mL of ethanol and the aldehyde (3 mmol) and silica gel (0.5 g, pre-activated at 200 °C during 2 h) were added. The mixture was placed in an ultrasound bath until the reaction was complete (usually 1 hour). The silica was filtered off and washed with dichloromethane. The solvent was evaporated and the crude products were purified as described below.

4.3.1. (1*R*,3*S*)-N^1,N^1-Dimethyl-N^3-salicylidene-1,2,2-trimethylcyclopentane-1,3-diamine 5a

The product was purified by silica gel column chromatography using diethyl ether as eluent to give a yellow solid. Yield: 73%; mp: 65–66 °C; $[\alpha]_D^{20}$ = +108 (*c* 1, CH_2Cl_2). IR (KBr, cm^{-1}): 2979, 2968, 2945, 2819, 2779, 1628, 1581, 1504, 1460, 1421, 1371, 1280, 1147, 1117, 1065, 1043, 966, 756. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (s, 3H); 1.00 (s, 3H); 1.07 (s, 3H), 1.64–1.70 (m, 1H); 1.83–1.97 (m, 2H); 2.03–2.11 (m, 1H); 2.25 (s, 6H); 3.41 (t, 1H, J = 9.0 Hz); 6.97 (t, 1H, J = 7.4 Hz); 6.96 (d, 1H, J = 8.4 Hz); 7.24–7.32(m, 2H); 8.26 (s, 1H); 13.83 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.30; 17.92; 22.77; 27.23; 37.99; 40.30; 48.40; 67.32; 78.30; 117.08, 118.39; 118.80; 131.14; 132.14; 161.52; 163.45. HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{26}N_2O$ $[M+H]^+$ 275.2179, found 275.2115.

4.3.2. (1*R*,3*S*)-N^1,N^1-Dimethyl-N^3-(3-methoxysalicylidene)-1,2,2-trimethylcyclopentane-1,3-diamine 5b

The product was purified by silica gel column chromatography using diethyl ether as eluent to give a yellow solid. Yield: 65%; mp: 66–68 °C; $[\alpha]_D^{20}$ = +110 (*c* 1, CH_2Cl_2). IR (KBr, cm^{-1}): 2974, 2962, 2868, 2839, 2821, 2779, 1633, 1475, 1462, 1414, 1369, 1254, 1084, 1063, 970, 850, 781, 724. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (s, 3H); 0.99 (s, 3H); 1.08 (s, 3H), 1.64–1.70 (m, 1H); 1.79–1.99 (m, 2H); 2.03–2.11 (m, 1H); 2.24 (s, 6H); 3.43 (t, 1H, J = 9.0 Hz); 6.78 (t, 1H, J = 7.8 Hz); 6.86–6.92 (m, 2H); 8.23 (s, 1H); 14.51 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.28; 17.87; 22.75; 27.19; 37.94; 40.29; 48.37; 56.01; 67.27; 77.53; 113.61, 117.42; 118.26; 122.69; 148.79; 153.13; 163.38. HRMS (ESI) *m*/*z*: calcd for $C_{18}H_{29}N_2O_2$ $[M+H]^+$ 305.2224, found 305.2220.

4.3.3. (1*R*,3*S*)-N^1,N^1-Dimethyl-N^3-(3,5-di-*t*-butylsalicylidene)-1,2,2-trimethylcyclopentane-1,3-diamine 5c

The product was purified by silica gel column chromatography using diethyl ether/triethylamine (80:2) as eluent to give a yellow solid. Yield: 68%; mp: 185–188 °C; $[\alpha]_D^{20}$ = +75 (*c* 1, CH_2Cl_2). IR (KBr, cm^{-1}): 3124, 2960, 2871, 2819, 2773, 1630, 1466, 1439, 1392, 1369, 1273, 1252, 1070. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (s, 3H); 1.00 (s, 3H); 1.08 (s, 3H), 1.31 (s, 9H); 1.45 (s, 9H); 1.63–1.70 (m, 1H); 1.85–1.92 (m, 2H); 2.05–2.10 (m, 1H); 2.25 (s, 6H); 3.38 (t, 1H, J = 9.0 Hz); 7.09 (d, 1H, J = 2.0 Hz); 7.38 (d, 1H, J = 2.0 Hz); 8.27 (s, 1H); 13.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.36, 17.90, 22.70, 27.25, 29.44, 31.51, 34.12, 35.05, 37.96, 40.31, 48.34, 67.39, 78.60, 117.87, 125.78, 126.74, 136.71, 139.85, 158.30, 164.63. HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{43}N_2O$ $[M+H]^+$ 387.3370, found 387.3365.

4.3.4. (1*R*,3*S*)-N^1,N^1-Dimethyl-N^3-(5-bromosalicylidene)-1,2,2-trimethylcyclopentane-1,3-diamine 5d

The product was purified by silica gel column chromatography using diethyl ether as eluent to give a yellow solid. Yield: 78%; mp: 89–91 °C, $[\alpha]_D^{20}$ = +60 (*c* 1, CH_2Cl_2). IR (KBr, cm^{-1}): 2960, 2871, 2821, 2777, 1631, 1572, 1483, 1371, 1277, 1184, 1063, 827. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.89 (s, 3H); 0.93 (s, 3H); 0.98 (s, 3H), 1.58–1.64 (m, 1H); 1.75–1.85 (m, 2H); 1.95–2.01 (m, 1H); 2.18 (s, 6H); 3.35 (t, 1H, J = 8.8 Hz); 6.79 (d, 1H, J = 8.4 Hz) 7.29–7.31 (m, 2H); 8.11 (s, 1H); 13.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.30; 16.87; 21.74; 26.12; 36.91; 39.27; 47.47; 66.33; 77.21; 108.74, 118.13; 119.08; 132.26; 133.79; 159.70; 161.19. HRMS (ESI) *m*/*z*: calcd for $C_{17}H_{26}BrN_2O$ $[M+H]^+$ 353.1223, found 353.1219.

4.3.5. (1*R*,3*S*)-N^1,N^1-Dimethyl-N^3-(2-hydroxyacetophenylidene)-1,2,2-trimethylcyclopentane-1,3-diamine 5e

The product was recrystallized in diethyl ether/hexane to give a yellow solid. Yield: 72%; mp: 131–133 °C, $[\alpha]_D^{20}$ = +145 (*c* 1, CH_2Cl_2). IR (KBr, cm^{-1}): 2974, 2966, 2939, 2814, 2771, 1612, 1577, 1504, 1450, 1439, 1369, 1309, 754, 744. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (s, 3H); 1.03 (s, 3H); 1.20 (s, 3H), 1.61–1.71 (m, 2H); 1.93–2.10 (m, 2H); 2.25 (s, 6H); 2.36 (s, 3H); 3.97 (t, 1H, J = 9.0 Hz); 6.74 (t, 1H, J = 7.4 Hz); 6.92 (d, 1H, J = 8.0 Hz); 7.28 (t, 1H, J = 7.2 Hz); 7.50 (d, 1H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.50; 14.40; 17.90; 23.18; 26.83; 37.77; 40.24; 48.63; 66.96; 67.35; 116.50, 119.01; 119.21; 128.06; 132.63; 165.25; 170.77. HRMS (ESI) *m*/*z*: calcd for $C_{18}H_{29}N_2O$ $[M+H]^+$ 289.2274, found 289.2271.

4.3.6. (1*R*,3*S*)-N^1,N^1-Dimethyl-N^3-(phenylidene)-1,2,2-trimethylcyclopentane-1,3-diamine 5f

The product was purified by silica gel column chromatography using diethyl ether/triethylamine (80:2) as eluent to give a white solid. Yield: 28%; mp: 57–59 °C; $[\alpha]_D^{20}$ = +85 (*c* 1, CH_2Cl_2). IR (KBr, cm^{-1}): 2972, 2873, 2819, 2781, 1641, 1448, 1371, 1060, 1035, 960, 752, 692. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (s, 3H); 1.00 (s, 3H); 1.11 (s, 3H), 1.64–1.70 (m, 1H); 1.79–1.96 (m, 2H); 2.05–2.15 (m, 1H); 2.27 (s, 6H); 3.39 (t, 1H, J = 9.0 Hz); 7.39–7.41 (m, 3H); 7.74–7.76 (m, 2H); 8.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ:11.43; 17.98; 22.83; 26.80; 38.25; 40.35; 48.90; 67.60; 79.21; 128.16, 128.51; 130.31; 136.65; 159.23. HRMS (ESI) *m*/*z*: calcd for $[M+H]^+$ $C_{17}H_{26}N_2$ 259.2169, found 259.2167.

4.4. General procedure for the synthesis of compounds 6a–b

To a solution of **5a** or **5d** (1 mmol) in $CHCl_3$/MeOH (2:1, 7.5 mL), placed in a 25 mL round bottom flask, $NaBH_4$ (0.38 g, 10 mmol) was added in small portions at 0 °C, with stirring. The reaction was then stirred at room temperature and the progress of reaction monitored by TLC. After completion, the reaction mixture was cooled to 0 °C and quenched with saturated ammonium chloride. The reaction mixture was extracted three times with dichloromethane and the combined organic phases were dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated and the crude products were purified as described below.

4.4.1. (1*R*,3*S*)-N^1,N^1-Dimethyl-N^3-(2-hydroxybenzyl)-1,2,2-trimethylcyclopentane-1,3-diamine 6a

The product was purified by silica gel column chromatography using diethyl ether as eluent to give a white solid. Yield: 95%; mp:

85–86 °C; $[\alpha]_D^{20}$ = +65 (*c* 1, CH_2Cl_2). IR (cm^{-1}): 3263, 2993, 2962, 2868, 2829, 2790, 1591, 1471, 1408, 1261, 1080, 1038, 964, 750. ^1H NMR ($CDCl_3$): 0.89 (s, 3H); 0.94 (s, 3H); 1.10 (s, 3H), 1.35–1.45 (m, 1H); 1.56–1.63 (m, 1H); 1.86–1.94 (m, 1H); 2.05–2.15 (m, 1H); 2.21 (s, 6H); 2.85 (t, 1H, *J* = 8.8 Hz); 3.82 (d, 1H, *J* = 13.6 Hz); 4.06 (d, 1H, *J* = 13.6 Hz); 6.77 (t, 1H, *J* = 7.4 Hz); 6.84 (d, 1H, *J* = 8.0 Hz); 6.98 (d, 1H, *J* = 7.2 Hz); 7.17 (t, 1H, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$): 11.01; 16.90; 23.34; 26.73; 37.14; 40.23; 46.91; 51.69; 66.67; 66.96; 116.43, 118.94; 122.97; 128.12; 128.78; 158.41. HRMS (ESI) m/z: calcd for $[M+H]^+$ $C_{17}H_{29}N_2O$ 277.2274; found 277.2272.

4.4.2. (1*R*,3*S*)-*N*^{1},*N*^{1}-Dimethyl-*N*^{3}-(5-bromo-2-hydroxybenzyl)-1,2,2-trimethylcyclopentane-1,3-diamine 6b

The product was purified by silica gel column chromatography using diethyl ether/triethylamine (80:2) as eluent to give a white solid. Yield: 55%; mp: 77–79 °C; $[\alpha]_D^{20}$ = +40 (*c* 1, CH_2Cl_2). IR (cm^{-1}): 3313, 3299, 2964, 2871, 2821, 2781, 1485, 1477, 1444, 1261, 1099, 1082, 1022, 955, 810, 802. ^1H NMR ($CDCl_3$): 0.82 (s, 3H); 0.87 (s, 3H); 1.01 (s, 3H), 1.27–1.36 (m, 1H); 1.50–1.57 (m, 1H); 1.80–1.88 (m, 1H); 1.97–2.06 (m, 1H); 2.15 (s, 6H); 2.75 (t, 1H, *J* = 8.2 Hz); 3.71 (d, 1H, *J* = 14.0 Hz); 3.96 (d, 1H, *J* = 14.0 Hz); 6.64 (d, 1H, *J* = 8.4 Hz); 7.03 (s, 1H); 7.18 (m, 1H). ^{13}C NMR ($CDCl_3$): 9.99, 15.89, 22.33, 25.64, 36.05, 39.22, 45.91, 50.08, 65.57, 65.91, 109.59, 117.20, 123.83, 129.70, 130.41, 156.60. HRMS (ESI) m/z: calcd for $[M+H]^+$ $C_{17}H_{28}BrN_2O$ 355.1380, found 355.1379.

4.5. General procedure for the synthesis of compounds 9a–b

In a 25 mL erlenmeyer flask, compound **8** (0.51 g, 3 mmol) was dissolved in 10 mL of ethanol and the aldehyde (3 mmol) and silica gel (0.5 g, pre-activated at 200 °C during 2 h) were added. The mixture was placed in an ultrasound bath until the reaction was complete (usually 1 h). The silica was filtered off and washed with dichloromethane. The solvent was evaporated and the crude products were purified as described below.

4.5.1. (1*R*,3*S*)-*N*^{1}-Ethyl-*N*^{3}-salicylidene-1,2,2-trimethylcyclopentane-1,3-diamine 9a

The product was purified by silica gel column chromatography using diethyl ether/triethylamine (80:2) as eluent to give a yellow solid, which was recrystallized in diethyl ether/hexane. Yield: 92%; mp: 127–128 °C; $[\alpha]_D^{20}$ = +72 (*c* 1, CH_2Cl_2). IR (cm^{-1}): 3446, 3294, 2970, 2870, 1651, 1626, 1579, 1498, 1485, 1460, 1281, 1119, 758, 704. ^1H NMR ($CDCl_3$): 0.95 (s, 3H); 0.99 (s, 3H); 1.08 (s, 3H), 1.15 (t, 3H, *J* = 7.0 Hz); 1.51–60 (m, 2H), 1.97–2.06 (m, 1H); 2.25–2.34 (m, 1H); 2.50–2.63 (m, 1H); 2.65–2.73 (m, 1H); 4.30 (t, 1H, *J* = 8.4 Hz); 7.39–7.46 (m, 3H); 7.77–7.79 (m, 2H); 8.85 (d, 1H, *J* = 8.4 Hz) ^{13}C NMR ($CDCl_3$): 16.60; 16.65; 19.03; 25.32; 30.11; 31.89; 36.35; 48.58; 59.35; 65.91; 126.81, 128.35; 130.88; 135.43; 165.33. HRMS (ESI) m/z: calcd for $[M+H]^+$ $C_{17}H_{27}N_2O$ 275.2118, found 275.2116.

4.5.2. (1*R*,3*S*)-*N*^{1}-Ethyl-*N*^{3}-(5-bromosalicylidene)-1,2,2-trimethylcyclopentane-1,3-diamine 9b

The product was purified by silica gel column chromatography using diethyl ether/triethylamine (80:2) as eluent to give a yellow solid. Yield: 92%; mp: 77–78 °C; $[\alpha]_D^{20}$ = +64 (*c* 1, CH_2Cl_2). IR (cm^{-1}): 3421, 2970, 2870, 1630, 1570, 1477, 1373, 1282, 1182, 1140, 1111, 1074, 1057, 822, 625. ^1H NMR ($CDCl_3$): 0.83 (s, 3H); 0.88 (s, 3H); 1.04 (t, 3H, *J* = 7.0 Hz); 1.09 (s, 3H), 1.67–1.79 (m, 3H), 1.88–1.96 (m, 1H); 2.49–2.58 (m, 1H); 2.63–2.71 (m, 1H); 3.35–3.39 (m, 1H); 6.77 (d, 1H, *J* = 8.4 Hz); 7.28–7.31 (m, 2H); 8.08 (s, 1H). ^{13}C NMR ($CDCl_3$): 16.34; 17.62; 21.70; 22.44; 28.07; 36.47; 37.32; 48.15; 64.22; 109.49; 119.42, 119.92; 133.32; 134.92; 161.35; 161.75. HRMS (ESI) *m*/*z*: calcd for $[M+H]^+$ $C_{17}H_{26}BrN_2O$ 353.1223, found 353.1220.

4.6. General procedure for enantioselective alkylation reactions

To the chiral ligand (0.15 mmol) and benzaldehyde (1 mmol) in an inert atmosphere, 4 mL of solvent was added. The temperature of the reaction mixture was lowered to 0 °C and diethylzinc (2 mmol, as a 1 M hexane solution) was added. The reaction was stirred for 10 min at 0 °C and then for 24 h at 0 °C or room temperature. After this time a saturated ammonium chloride solution (1 mL) followed by 2 M HCl (1 mL) was added and the reaction mixture was extracted with diethyl ether. The organic phases were washed with water and brine and dried over anhydrous sodium sulfate. The resulting solution was analyzed by GC on a chiral γ-cyclodextrin capillary column in order to determine the ee of the products.[17]

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