Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantioselective alkylation of aromatic aldehydes with (+)-camphoric acid derived chiral 1,3-diamine ligands

M. Elisa Silva Serra *, Dina Murtinho, Victória Paz

CQC and Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal

ARTICLE INFO

Article history:
Received 3 January 2017
Revised 12 January 2017
Accepted 19 January 2017
Available online xxxx

ABSTRACT

A series of chiral 1,3-diamine ligands derived from (+)-camphoric acid were prepared from the reaction of 1,3-diamino-1,2,2-trimethylcyclopentane with aromatic aldehydes, followed by reduction of the corresponding diimines. These newly synthesized ligands were tested in the enantioselective alkylation of benzaldehyde with diethylzinc, giving 1-phenyl-1-propanol with enantiomeric ratios of up to 86:14. Our most selective ligand, derived from 2-methoxybenzaldehyde, was also tested in the alkylation of several aromatic aldehydes and product alcohols with enantiomeric ratios of up to 93.5:6.5 being observed in 2 h at room temperature in the presence of 5 mol % ligand.

1. Introduction

Chiral secondary alcohols have found widespread application in many areas such as fine chemistry, pharmaceuticals, perfumes, herbicides and pesticides, among others, because they incorporate many structures with biological activity. Thus, reactions which allow the efficient synthesis of these compounds are of major importance in organic chemistry. The direct synthetic utility of chiral alcohols is no less significant, since the hydroxyl group is an excellent precursor for many other functional groups. Among the methods for obtaining optically active secondary alcohols, special interest has been placed upon the enantioselective alkylation of aldehydes with organozinc reagents in the presence of chiral ligands. This reaction allows the creation of a new stereogenic center from the carbonyl carbon atom and, simultaneously, a lengthening of the carbon chain in the alcohol product relatively to the parent aldehyde.[1–9] Additionally, the use of organozinc reagents with different alkyl or aryl groups allows obtaining a wide variety of optically active products to be obtained.

While many types of structurally diverse ligands have been used in enantioselective alkylations,[10–15] those with two *N*-donor atoms have not received widespread attention, although there are several examples of efficient ligands of this type. It should also be noted that 1,3- and 1,4-bidentate ligands have been relatively less studied than 1,2-bidentate ligands.[16–25]

Our continued interest in the use of (+)-camphoric acid derived (1*R*,3*S*)-1,3-diamino-1,2,2-timethylcyclopentane, a 1,3-diamino chiral backbone,[26–29] led us to prepare some new chiral secondary diamine ligands to test in the enantioselective alkylation of aldehydes with diethylzinc.

2. Results and discussion

2.1. Ligand synthesis

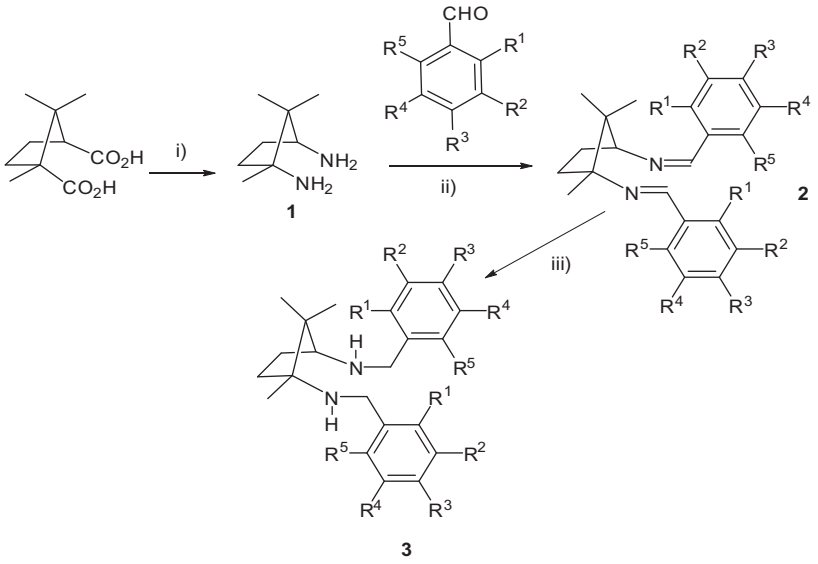
Scheme 1 illustrates the synthetic sequence used for obtaining the camphoric acid derived secondary diamines **3**: the reaction of (1*R*,3*S*)-1,3-diamino-1,2,2-trimethylcyclopentane **1**, prepared according to our previously described procedure,[26] with aromatic aldehydes, originates from diimines **2**, which are subsequently reduced to the chiral secondary diamines.

For the synthesis of diimines **2**, we initially carried out the reaction with benzaldehyde, using various reaction conditions (reflux in ethanol or toluene, acid and base catalysis, the use of water sponges, ultrasound irradiation, microwave irradiation). Microwave irradiation has been described for the synthesis of imines under different reaction conditions, so we decided to try this technique in the synthesis of our diimines.[30–33]

From the different methods tested, we found that the most favorable one was using microwave irradiation. Using this method, the products were formed in short reaction times and tedious work-up was not necessary, since the products precipitated directly from the reaction medium upon cooling. Our studies led to the following optimized conditions: the reaction of the diamine with 2 equivalents of aldehyde, in ethanol and in the presence of a

* Corresponding author. Tel.: +351 39854480.
E-mail addresses: melisa@ci.uc.pt (M. Elisa Silva Serra), dmurtinho@ci.uc.pt (D. Murtinho), victoriapatriciopaz@hotmail.com (V. Paz).

http://dx.doi.org/10.1016/j.tetasy.2017.01.013
0957-4166/



Scheme 1. Synthesis of the chiral diamine ligands. Reagents and conditions: (i) H_2SO_4, NaN_3, $CHCl_3$, 55–65 °C, overnight; (ii) ethanol, microwave radiation, 30 min. (iii) $NaBH_4$, MeOH/$CHCl_3$ 1:1, rt.

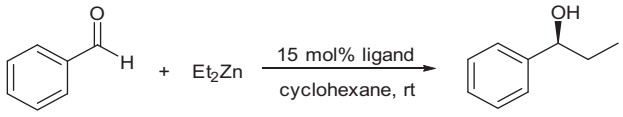
catalytic amount of *p*-toluenesulfonic acid monohydrate. The reaction was irradiated for 15 min. at 250 W (the reaction temperature reached 85–150 °C and the pressure 1–8 bar). Using these conditions, we synthesized the series of diimines **2a**–**2h**, (Table 1) with moderate yields.

In order to obtain the diamines, the corresponding diimines **2a**–**2h** were subjected to reduction with sodium borohydride, in a 1:1 mixture of MeOH/$CHCl_3$, at room temperature. In this way, diamines **3a**–**3h** were isolated, mostly in very good yields (Table 2).

2.2. Enantioselective alkylation reactions

Using benzaldehyde as the model substrate, diamine ligands **2a**–**2h** were tested in the enantioselective alkylation with diethylzinc. The reactions were initially carried out in dry cyclohexane at room temperature for 24 h, in the presence of 15 mol % of chiral ligand, our previously optimized conditions in Scheme 2.[26] The results obtained are presented in Table 3.

All of ligands tested were very efficient, with almost complete conversion in the alkylations. Moderate to good selectivity was observed, and the highest enantiomeric ratio (*er*), 86:14, was obtained in the presence of ligand **3b**. In order to analyze the effect of the reaction temperature, the most selective ligands **3b** and **3h** were additionally tested at 0 °C and −10 °C. Only a slight



Scheme 2. Asymmetric addition of diethylzinc to benzaldehyde.

Table 1
Diimines derived from camphoric acid

Ligand	R^1	R^2	R^3	R^4	R^5	Yield (%)
2a	H	H	H	H	H	52
2b	OCH_3	H	H	H	H	49
2c	CH_3	H	H	H	H	19
2d	Cl	H	H	H	H	49
2e	H	OCH_3	H	H	H	53
2f	H	H	OCH_3	H	H	52
2g	Cl	H	H	H	Cl	52
2h	CH_3	H	CH_3	H	CH_3	36

Table 2
Diamines derived from diimines **2a**–**2h**

Ligand	R^1	R^2	R^3	R^4	R^5	Yield (%)
3a	H	H	H	H	H	96
3b	OCH_3	H	H	H	H	65
3c	CH_3	H	H	H	H	97
3d	Cl	H	H	H	H	80
3e	H	OCH_3	H	H	H	88
3f	H	H	OCH_3	H	H	99
3g	Cl	H	H	H	Cl	65
3h	CH_3	H	CH_3	H	CH_3	47

Please cite this article in press as: Serra, M. E. S.; et al. *Tetrahedron: Asymmetry* (2017), http://dx.doi.org/10.1016/j.tetasy.2017.01.013

Table 3
Enantioselective alkylation of benzaldehyde catalyzed by **3a–h**[a]

Ligand	Conversion[b] (%)	1-Phenyl-1-propanol[b,c] (%)	*er* (*S*):(*R*)[b]
3a	>99	97	71:29
3b	>99	>99	86:14
3c	>99	98	73.5:26.5
3d	>99	98	71:29
3e	>99	99	71:29
3f	>99	97	71:29
3g	98	93	73:27
3h	98	88	78:22

[a] Reactions were carried out for 24 h at rt, in cyclohexane, using 15 mol % of chiral ligand, 1 mmol of benzaldehyde and 2 mmol of diethylzinc (1 M in hexane).
[b] Determined by chiral gc.
[c] Relatively to converted benzaldehyde.

improvement in selectivity was observed, but this was accompanied by much lower conversions; therefore, additional reactions were carried out at room temperature. Considering the complete conversions observed with the diamine ligands in the alkylation of benzaldehyde, we decided to analyze results after shorter reaction times, namely, conversions and product selectivity, using the most efficient ligand **3b** (Table 4).

Complete conversions were obtained, even for the short 2 h reaction time, while maintaining the selectivity of the alcohol product. These results reveal that ligand **3b** is a strongly active catalyst for the enantioselective alkylation reaction. Considering the high activity of **3b**, we studied the effect of reducing catalyst loading (Table 5). Complete conversions were observed in 2 h using 1–15 mol %. Although there was no great variation in the *er*, a slightly better result was observed when using 5 mol % of the ligand, with an *er* of 86:14 for the product.

Finally, the solvent effect was also studied and results are shown in Table 6. In all cases there was complete conversion of the benzaldehyde and no secondary product was formed. The best *er* was obtained in cyclohexane (86:14).

Using the optimized conditions, i.e. 2 h reaction time, 5 mol % ligand and cyclohexane at room temperature, we carried out the

Table 4
Enantioselective alkylation of benzaldehyde with different reaction times, in the presence of **3b**[a]

Reaction time (h)	Conversion[b,c] (%)	*er* (*S*):(*R*)[b]
24	>99	86:14
8	>99	85.5:14.5
6	>99	85.5:14.5
4	>99	85:15
2	>99	85:15

[a] Reactions were carried out at rt, in cyclohexane, using 15 mol % of chiral ligand, 1 mmol of benzaldehyde and 2 mmol of diethylzinc (1 M in hexane).
[b] Determined by chiral gc.
[c] No secondary product was observed.

Table 5
Enantioselective alkylation of benzaldehyde with different catalyst loadings of **3b**[a]

3b (mol %)	Conversion[b,c] (%)	*er* (*S*):(*R*)[b]
15	>99	85:15
10	>99	85.5:14.5
5	>99	86:14
2	>99	84.5:15.5
1	>99	83:17

[a] Reactions were carried out for 2 h at rt, in cyclohexane, 1 mmol of benzaldehyde and 2 mmol of diethylzinc (1 M in hexane).
[b] Determined by chiral gc.
[c] No secondary product was observed.

Table 6
Enantioselective alkylation of benzaldehyde in different solvents with **3b**[a]

Solvent	Conversion[b,c] (%)	*er* (*S*):(*R*)[b]
Cyclohexane	>99	86:14
Diethylether	>99	83.5:16.5
Toluene	>99	84.5:15.5
Dichloromethane	>99	83:17

[a] Reactions were carried out for 2 h at rt, using 5 mol % chiral ligand, 1 mmol of benzaldehyde and 2 mmol of diethylzinc (1 M in hexane).
[b] Determined by chiral gc.
[c] No secondary product was observed.

enantioselective alkylation of other aldehyde substrates with diethylzinc in the presence of **3b** in order to evaluate the scope of the reaction. The results are shown in Table 7.

All aldehydes, except for *p*-methoxybenzaldehyde, showed complete conversions to the products with *er* varying from 84.5:15.5 to 93.5:6.5. The best *er* was obtained for *m*-methoxybenzaldehyde, 93.5:6.5. We also tested an aliphatic aldehyde, cinnamaldehyde, which was completely converted into the ethylated alcohol with an *er* of 78:22, which is a promising result for this type of substrate.

Diimines **2a–2h** were also tested as ligands in the enantioselective alkylation of benzaldehyde. However, the conversions were moderate and the products were almost racemic. It is also noteworthy that we had previously synthesized structurally analogous camphoric acid derived salen and salan ligands and also tested them in the enantioselective alkylation of benzaldehyde with diethylzinc. In this case, only moderate conversions and very low selectivities were observed, which may be attributed to the tetradentate nature of these ligands as opposed to the bidentate nature of **3a–3h**.[34] Based on Noyori's model, a plausible reaction pathway for the enantioselective alkylation of benzaldehyde in the presence of **3b**, involves bidentate coordination of the ligand to the zinc, originating a tricyclic 6/4/4 transition state, as presented in Figure 1.

Table 7
Enantioselective alkylation of different aldehydes catalyzed by **3b**[a]

Aldehyde	Conversion[b] (%)	*er* (*S*):(*R*)[b]
o-Methoxybenzaldehyde	>99	91.5:8.5
m-Methoxybenzaldehyde	>99	93.5:6.5
p-Methoxybenzaldehyde	89	84.5:15.5
o-Chlorobenzaldehyde	>99	85:15
p-Chlorobenzaldehyde	>99	84.5:15.5
1-Naphthaldehyde	>99	90.5:9.5
o-Methylbenzaldehyde	>99	84.5:15.5
Cinnamaldehyde	>99	78:22

[a] Reactions were carried out for 2 h at rt, in cyclohexane, using 5 mol % of **3b**, 1 mmol of benzaldehyde and 2 mmol of diethylzinc (1 M in hexane).
[b] Determined by chiral gc.

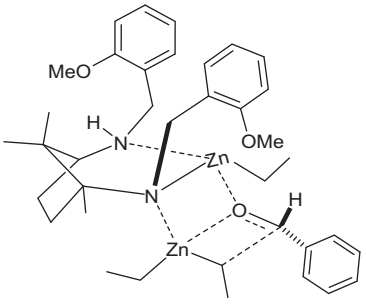


Figure 1. Possible 6/4/4 transition state for **3b**.

3. Conclusions

A new series of 1,3-chiral diamine ligands was prepared in a simple three-step synthetic sequence from (+)-camphoric acid. The ligands were tested in the enantioselective alkylation of benzaldehyde with diethylzinc, showing excellent conversions and *er* up to 86:14 in only 2 h with 5 mol % chiral ligand. Extending the reaction to other substrates using our most efficient ligand, **3b**, was also very efficient, giving products with *er* up to 93.5:6.5. Further studies are currently in progress involving the synthesis and application of similar types of diamine ligands.

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 a FALC melting point apparatus (open capillary method). Optical rotations were measured with an Optical Activity AA-5 polarimeter. NMR spectra were recorded at room temperature 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 an Agilent Technologies Cary 630 FTIR in the ATR mode. Microwave reactions were carried out in a CEM Discover S-Class instrument.

High-resolution mass spectra (HRMS) were obtained on a TOF VG Autospect M spectrometer with electrospray ionization (ESI). Elemental analyses were carried out on an Elementar Vario Micro Cube analyser. Alkylation reactions were carried out in an inert atmosphere using standard Schlenk-type techniques. Enantiomeric ratios and conversions 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 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 products.

4.2. General procedure for the synthesis of the diimine ligands

To 3 ml of ethanol in a microwave reaction tube, 6.00 mmol of diamine **2.2** (0.85 g), 0.60 mmol (10 mol %) of *p*-toluenesulfonic acid monohydrate (0.11 g) and 12.00 mmol of aldehyde were added. The tube was subjected to microwave irradiation, using a power control program (250 W) for 15 min. Subsequently, upon cooling, the product diimine crystallized directly from the reaction medium. The product was filtered and recrystallized from hot ethanol. The crystals were filtered and dried in vacuo. Upon concentration, a second crop of crystals may be collected.

4.2.1. (1*R*,3*S*)-*N*,*N*′-Bis[phenylidene]-1,3-diamino-1,2,2-trimethylcyclopentane 2a

Yield: 52%. mp: 102–105 °C. $[\alpha]_D^{20}$ = +36.2 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.92 (s, 3H); 0.97 (s, 3H); 1.23 (s, 3H); 1.75–1.82 (m, 1H); 2.02–2.09 (m, 2H); 2.28–2.36 (m, 1H); 3.58 (aprox. t, 1H, *J* = 8.4 Hz); 7.39–7.42 (m, 6H); 7.75–7.80 (m, 4H); 8.27 (s, 1H); 8.28 (s, 1H). ^{13}C NMR ($CDCl_3$), δ (ppm): 18.7; 21.0; 24.6; 27.9; 34.1; 49.1; 71.0; 77.7; 127.8; 128.2; 128.5; 128.6; 130.1; 130.3; 136.7; 137.5; 156.0; 159.1. IR (cm^{-1}): 2969, 2943, 2868, 2839, 1639, 1624, 1578, 1492, 1449, 1438, 1369, 1358, 1308, 1216, 1173, 1119, 1075, 1059, 959, 753, 90, 672. HRMS (ESI): calculated for $C_{22}H_{27}N_2$ $[M+H]^+$: 319.2169; found: 319.2163.

4.2.2. (1*R*,3*S*)-*N*,*N*′-Bis[2-methoxyphenylidene]-1,3-diamino-1,2,2-trimethylcyclopentane 2b

Yield: 49%. mp: 123–126 °C. $[\alpha]_D^{20}$ = -1.7 (*c* 6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.92 (s, 3H); 0.96 (s, 3H); 1.22 (s, 3H); 1.75–1.82 (m, 1H); 2.02–2.08 (m, 2H); 2.28–2.36 (m, 1H); 3.59 (aprox. t, 1H, *J* = 8.4); 3.87 (s, 3H); 3.88 (s, 3H); 6.91 (d, 2H, *J* = 8.0); 6.95–7.00 (m, 2H); 7.33–7.38 (m, 2H); 7.99–8.06 (m, 2H); 8.67 (s, 1H); 8.68 (s, 1H). ^{13}C NMR ($CDCl_3$), δ (ppm): 18.7; 20.99; 24.8; 28.0; 34.3; 49.1; 55.5; 71.3; 77.9; 110.9; 120.8; 125.2; 126.01; 127.0; 127.69; 131.1; 131.4; 152.0; 155.1; 158.6. IR (cm^{-1}): 2964, 2941, 2869, 2838, 1631, 1599, 1486, 1459, 1437, 1375, 1286, 1240, 1176, 1160, 1111, 1104, 1043, 1024, 755. HRMS (ESI): calculated for $C_{24}H_{31}N_2O_2$ $[M+H]^+$: 379.2380; found: 379.2373.

4.2.3. (1*R*,3*S*)-*N*,*N*′-Bis[2-methylphenylidene]-1,3-diamino-1,2,2-trimethylcyclopentane 2c

Yield: 19%. mp: 83–85 °C. $[\alpha]_D^{20}$ = +29.7 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.94 (s, 3H); 0.98 (s, 3H); 1.24 (s, 3H); 1.76–1.83 (m, 1H); 2.04–2.10 (m, 2H); 2.27–2.35 (m, 1H); 2.53 (s, 3H); 2.54 (s, 3H); 3.57 (aprox. t, 1H, *J* = 8.6); 7.17–7.30 (m, 6H); 7.85–7.89 (m, 2H); 8.55 (s, 2H). ^{13}C NMR ($CDCl_3$), δ (ppm): 18.9; 19.6; 19.7; 21.0; 25.0; 28.1; 34.2; 49.0; 71.5; 78.3; 126.1; 127.7; 128.1; 129.6; 129.8; 130.7; 130.8; 134.7; 135.4; 137.3; 137.4; 155.2; 158.1. IR (cm^{-1}): 2664, 2929, 2868, 1633, 1601, 1483, 1457, 1457, 1449, 1438, 1369, 1358, 1285, 1062, 1044, 959, 763, 734, 716. HRMS (ESI): calculated for $C_{24}H_{31}N_2$ $[M+H]^+$: 347.2482; found: 347.2475.

4.2.4. (1*R*,3*S*)-*N*,*N*′-Bis[2-chlorophenylidene]-1,3-diamino-1,2,2-trimethylcyclopentane 2d

Yield: 49%. mp: 91–93 °C. $[\alpha]_D^{20}$ = -7.2 (*c* 2.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.92 (s, 3H); 0.99 (s, 3H); 1.25 (s, 3H); 1.81–1.87 (m, 1H); 2.06–2.17 (m, 2H); 2.29–2.37 (m, 1H); 3.66 (aprox. t, 1H, *J* = 8.4); 7.28–7.38 (m, 6H); 8.06–8.13 (m, 2H); 8.68 (s, 2H). ^{13}C NMR ($CDCl_3$), δ (ppm): 18.8; 21.1; 24.6; 28.0; 34.4; 49.3; 71.7; 77.8; 126.9; 128.2; 128.7; 129.6; 129.7; 131.0; 131.2; 133.6; 134.3; 134.9; 135.1; 153.3; 156.0. IR (cm^{-1}): 3067, 2964, 2869, 1629, 1466, 1438, 1377, 1366, 1271, 1050, 1028, 963, 756, 709. Elemental analysis: Calcd. for $C_{22}H_{24}Cl_2N_2$ (%): C, 68.22; H, 6.25; N, 7.23. Found (%): C, 68.35; H, 6.36; N, 7.14.

4.2.5. (1*R*,3*S*)-*N*,*N*′-Bis[3-methoxyphenylidene]-1,3-diamino-1,2,2-trimethylcyclopentane 2e

Yield: 53%. mp: 120–123 °C. $[\alpha]_D^{20}$ = +45.0 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.91 (s, 3H); 0.96 (s, 3H); 1.22 (s, 3H); 1.73–1.81 (m, 1H); 2.00–2.08 (m, 2H); 2.23–2.36 (m, 1H); 3.57 (aprox. t, 1H, *J* = 8.4); 3.84 (s, 3H); 3.86 (s, 3H); 6.94–6.97 (m, 2H); 7.30–7.41 (m, 6H); 8.23 (s, 1H); 8.24 (s, 1H). ^{13}C NMR ($CDCl_3$), δ (ppm): 18.7; 21.1; 24.6; 27.9; 34.2; 49.1; 55.4; 71.0; 77.6; 111.9; 112.2; 116.3; 116.6; 121.0; 121.2; 129.5; 138.2; 139.1; 155.8; 158.9; 159.9. IV (cm-1): 2998, 2966, 2934, 2871, 2833, 1638, 1596, 1585, 1491, 1458, 1449, 1318, 1291, 1264, 1193, 1169, 1151, 1067, 1033, 959, 857, 795, 787, 690. HRMS (ESI): calculated for $C_{24}H_{31}N_2O_2$ $[M+H]^+$: 379.2380; found: 379.2374.

4.2.6. (1*R*,3*S*)-*N*,*N*′-Bis[4-methoxyphenylidene]-1,3-diamino-1,2,2-trimethylcyclopentane 2f

Yield: 52%. mp: 139–142 °C. $[\alpha]_D^{20}$ = +45.0 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.90 (s, 3H); 0.94 (s, 3H); 1.21 (s, 3H); 1.72–1.79 (m, 1H); 1.99–2.06 (m, 2H); 2.25–2.33 (m, 1H); 3.52 (aprox. t, 1H, *J* = 8.6); 3.84 (s, 6H); 6.90–6.94 (m, 4H); 7.69–7.74 (m, 4H);

8.20 (s, 2H). ^{13}C NMR ($CDCl_3$), δ (ppm): 18.6; 20.9; 24.7; 28.0; 34.2; 49.0; 55.4; 70.6; 113.9; 129.2; 129.6; 129.8; 130.7; 155.1; 158.3; 161.2; 161.3. IR (cm^{-1}): 2962, 2935, 2870, 2841, 1638, 1603, 1508, 1457, 1443, 1306, 1252, 1166, 1109, 1063, 1032, 837, 823. HRMS (ESI): calculated for $C_{24}H_{31}N_2O_2$ $[M+H]^+$: 379.2380; found: 379.2373.

4.2.7. (1*R*,3*S*)-*N*,*N*′-Bis[2,6-dichlorophenylidene]-1,3-diamino-1,2,2-trimethylcyclopentane 2g

Yield: 52%. mp: 117–120 °C. $[\alpha]_D^{20}$ = +4.0 (*c* 5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.08 (s, 3H); 1.09 (s, 3H); 1.32 (s, 3H); 1.82–1.88 (m, 1H); 2.10–2.17 (m, 2H); 2.38–2.45 (m, 1H); 3.70 (aprox. t, 1H, *J* = 8.0); 7.18–7.23 (m, 2H); 7.32–7.35 (m, 4H); 8.40 (s, 1H); 8.42 (s, 1H). ^{13}C NMR ($CDCl_3$), δ (ppm): 18.8; 20.6; 25.0; 27.5; 34.0; 48.9; 73.0; 79.1; 128.5; 129.8; 130.1; 133.7; 134.4; 134.5; 153.9; 155.5. IR (cm^{-1}): 2969, 2869, 1633, 1578, 1559, 1426, 1420, 1401, 1377, 1367, 1266, 1213, 1189, 1116, 1086, 1058, 943, 784, 772, 736, 715. Elemental analysis: Calcd. for $C_{22}H_{22}Cl_4N_2$ (%): C, 57.92; H, 4.86; N, 6.14. Found (%): C, 57.76; H, 4.70; N, 6.06.

4.2.8. (1*R*,3*S*)-*N*,*N*′-Bis[2,4,6-trimethylphenylidene]-1,3-diamino-1,2,2- trimethylcyclopentane 2h

Yield: 36%. mp: 124–127 °C. $[\alpha]_D^{20}$ = +25.0 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.99 (s, 3H); 1.01 (s, 3H); 1.26 (s, 3H); 1.79–1.85 (m, 1H); 2.01–2.07 (m, 2H); 2.24–2.32 (m, 1H); 2.28 (s, 6H); 2.39 (s, 6H); 2.41 (s, 6H); 3.55 (aprox. t, 1H, *J* = 8.6); 6.86 (s, 4H); 8.57 (s, 2H). ^{13}C NMR ($CDCl_3$), δ (ppm): 19.2; 20.8; 20.9; 21.0; 21.1; 21.2; 25.9; 28.1; 34.1; 48.2; 72.3; 79.4; 129.3; 131.6; 132.4; 137.0; 137.3; 138.1; 138.4; 157.6; 159.7. IR (cm^{-1}): 2960, 2955, 2917, 2868, 1629, 1609, 1565, 1559, 1457, 1449, 1438, 1429, 1396, 1374, 1364, 1359, 1114, 1067, 1032, 852, 804. HRMS (ESI): calculated for $C_{28}H_{39}N_2$ $[M+H]^+$: 403.3108; found: 403.3100.

4.3. General procedure for the synthesis of the diamine ligands

In a round bottom flask, 2.00 mmol diimine and a mixture of 20 ml of MeOH/$CHCl_3$ (1:1) were stirred for 10 min at room temperature. The mixture was placed in an ice bath and 40.00 mmol of $NaBH_4$ were slowly added with stirring. The mixture was allowed to react overnight at room temperature, then placed in an ice bath and a saturated solution of ammonium chloride was gradually added until bubbling stopped. The reaction mixture was extracted with H_2O and dichloromethane. The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated. In some cases, the products were purified by column chromatography.

4.3.1. (1*R*,3*S*)-*N*,*N*′-Dibenzyl-1,3-diamino-1,2,2-trimethylcyclopentane 3a

The product, an oil, was obtained pure. Spectroscopic details are in agreement with those previously described.[35] Yield: 96%. $[\alpha]_D^{20}$ = +47.8 (*c* 1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.95 (s, 3H); 0.97 (s, 3H); 1.10 (s, 3H); 1.41–1.51 (m, 1H); 1.52–1.67 (m, 3H); 1.85–1.92 (m, 1H); 2.00–2.09 (m, 1H); 2.83 (dd, 1H, *J* = 8.2; 5.8); 3.67 (d, 1H, *J* = 12.0); 3.71 (d, 1H, *J* = 12.0); 3.77 (d, 1H, *J* = 12.0); 3.86 (d, 1H, *J* = 12.0); 7.19–7.35 (m, 10H). ^{13}C NMR ($CDCl_3$), δ (ppm): 17.0; 20.7; 24.4; 28.4; 34.1; 47.2; 47.5; 52.6; 64.6; 66.6; 126.6; 126.7; 128.0; 128.1; 128.3; 128.4; 141.2; 142.1. IR (cm^{-1}): 3285, 3061, 3026, 2959, 2868, 2824, 2362, 2322, 1494, 1466, 1452, 1438, 1387, 1369, 1166, 1118, 1092, 1073, 1028, 730, 695. HRMS (ESI): calculated for $C_{22}H_{31}N_2$ $[M+H]^+$: 323.2482; found: 323.2470.

4.3.2. (1*R*,3*S*)-*N*,*N*′-Bis(2-methoxybenzyl)-1,3-diamino-1,2,2-trimethylcyclopentane 3b

The product was purified by column chromatography using silica gel and ethyl ether/NEt_3 80:2 to give a white solid. Yield: 65%. mp: 68–71 °C. $[\alpha]_D^{20}$ = +39.4 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.96 (s, 3H); 0.97 (s, 3H); 1.11 (s, 3H); 1.35–1.45 (m, 1H); 1.55–1.62 (m, 1H); 1.80–1.88 (m, 3H); 1.91–2.00 (m, 1H); 2.77–2.82 (m, 1H); 3.67–3.72 (m, 2H); 3.78–3.83 (m, 2H); 3.80 (s, 3H); 3.81 (s, 3H); 6.81–6.92 (m, 4H); 7.17–7.34 (m, 4H). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.8; 20.9; 23.8; 28.2; 34.8; 42.3; 47.2; 48.1; 55.2; 64.5; 66.2; 110.1; 120.4; 120.5; 127.6; 127.8; 129.3; 129.4; 157.4; 157.6. IR (cm^{-1}): 3277, 2952, 2932, 2878, 2831, 2798, 1599, 1588, 1489, 1459, 1449, 1442, 1438, 1433, 1420, 1374, 1284, 1237, 1192, 1171, 1156, 1091, 1083, 1050, 1027, 749, 716. HRMS (ESI): calculated for $C_{24}H_{35}N_2O_2$ $[M+H]^+$: 383.2693; found: 383.2684.

4.3.3. (1*R*,3*S*)-*N*,*N*′-Bis(2-methylbenzyl)-1,3-diamino-1,2,2-trimethylcyclopentane 3c

The product, an oil, was obtained pure. Yield: 97%. $[\alpha]_D^{20}$ = +44.9 (*c* 1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.96 (s, 6H); 1.15 (s, 3H); 1.25–1.52 (m, 3H); 1.61–1.69 (m, 1H); 1.91–1.97 (m, 1H); 2.04–2.13 (m, 1H); 2.30 (s, 3H); 2.34 (s, 3H); 2.87 (dd, 1H, *J* = 8.0; 6.0); 3.60–3.80 (m, 4H); 7.08–7.16 (m, 6H); 7.23–7.32 (m, 2H). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9; 19.0; 20.5; 24.3; 28.5; 33.9; 44.9; 47.6; 50.7; 64.6; 67.2; 125.8: 125.9; 126.7; 126.8; 128.2; 128.5; 130.1; 136.5; 136.6. IR (cm^{-1}): 3292, 3064, 3017, 2957, 2868, 2821, 1491, 1458, 1453, 1449, 1438, 1386, 1369, 1104, 1086, 1048, 1034, 739, 703, 696. HRMS (ESI): calculated for $C_{24}H_{35}N_2$ $[M+H]^+$: 351.2795; found: 351.2788.

4.3.4. (1*R*,3*S*)-*N*,*N*′-Bis(2-chlorobenzyl)-1,3-diamino-1,2,2-trimethylcyclopentane 3d

The product was purified by column chromatography using silica gel and ethyl ether as eluent to give an oil. Yield: 80%. $[\alpha]_D^{20}$ = +37.0 (*c* 1.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.88 (s, 3H); 0.92 (s, 3H); 1.04 (s, 3H); 1.36–1.45 (m, 1H); 1.49–1.59 (m, 3H); 1.81–1.88 (m, 1H); 1.89–1.99 (m, 1H); 2.74 (dd, 1H, *J* = 8.0; 6.0); 3.68–3.83 (m, 4H); 7.05–7.14 (m, 4H); 7.22–7.26 (m, 2H); 7.30–7.33 (m, 1H); 7.37–7.40 (m, 1H). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.9; 20.5; 24.3; 28.4; 34.0; 44.6; 47.6; 50.1; 64.7; 66.7; 126.7; 126.8; 127.8; 127.9; 129.2; 129.3; 129.8; 129.9; 133.5; 133.6; 138.5; 139.4. IR (cm^{-1}): 3278, 3063, 2959, 2868, 2376, 2324, 1466, 1441, 1438, 1420, 1371, 1164, 1126, 1092, 1048, 1036, 746, 697, 679. HRMS (ESI): calculated for $C_{22}H_{29}Cl_2N_2$ $[M+H]^+$: 391.1702; found: 391.1694.

4.3.5. (1*R*,3*S*)-*N*,*N*′-Bis(3-methoxybenzyl)-1,3-diamino-1,2,2-trimethylcyclopentane 3e

The product was purified by column chromatography using silica gel and ethyl ether/NEt_3 80:2 to give an oil. Yield: 88%. $[\alpha]_D^{20}$ = +43.5 (*c* 1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.95 (s, 3H); 1.00 (s, 3H); 1.11 (s, 3H); 1.42–1.51 (m, 1H); 1.59–1.66 (m, 1H); 1.87–1.94 (m, 1H); 1.99–2.08 (m, 1H); 2.83 (dd, 1H, *J* = 8.2; 6.2); 3.62–3.85 (m, 4H); 3.76 (s, 3H); 3.77 (s, 3H); 6.74–6.92 (m, 6H); 7.18–7.24 (m, 2H). ^{13}C NMR ($CDCl_3$), δ (ppm): 17.0; 20.7; 24.3; 28.5; 34.2; 47.2; 47.5; 52.4; 55.1; 55.2; 64.6; 66.4; 112.0; 112.2; 113.3; 113.6; 120.3; 129.2; 129.3; 142.9; 143.8; 159.7; 159.8. IR (cm^{-1}): 2954, 2870, 2834, 1596, 1585, 1487, 1465, 1457, 1453, 1437, 1434, 1420, 1369, 1261, 1152, 1118, 1087, 1042, 909, 775, 731, 691. HRMS (ESI): calculated for $C_{24}H_{35}N_2O_2$ $[M+H]^+$: 383.2693; found: 383.2685.

4.3.6. (1*R*,3*S*)-*N*,*N*′-Bis(4-methoxybenzyl)-1,3-diamino-1,2,2-trimethylcyclopentane 3f

The product, an oil, was obtained pure. Yield: 99%. $[\alpha]_D^{20}$ = +40.0 (*c* 1.1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$), δ (ppm): 0.95 (s, 3H); 1.03 (s, 3H); 1.15 (s, 3H); 1.43–1.58 (m, 1H); 1.62–1.70 (m, 1H); 1.93–2.08 (m, 2H); 2.85 (dd, 1H, *J* = 7.4; 5.4); 3.56–3.69 (m, 2H); 3.73–3.84 (m, 2H); 3.79 (s, 3H); 3.80 (s, 3H); 6.81 (d, 2H, *J* = 4.2); 6.83 (d, 2H, *J* = 4.2); 7.15 (d, 2H, *J* = 8.4); 7.26 (d, 2H, *J* = 8.4). ^{13}C NMR ($CDCl_3$),

δ (ppm): 17.1; 20.0; 24.4; 27.7; 33.8; 46.5; 47.6; 51.6; 55.2; 65.5; 66.4; 113.7; 113.8; 129.2; 129.4; 132.3; 132.9; 158.6. IR (cm^{-1}): 2954, 2834, 1610, 1584, 1509, 1491, 1458, 1438, 1420, 1369, 1299, 1242, 1172, 1105, 1032, 1012, 817, 734, 701. HRMS (ESI): calculated for $C_{24}H_{35}N_2O_2$ $[M+H]^+$: 383.2693; found: 383.2685.

4.3.7. (1*R*,3*S*)-*N*,*N*′-Bis(2,6-dichlorobenzyl)-1,3-diamino-1,2,2-trimethylcyclopentane 3g

The product was purified by column chromatography using silica gel and $CHCl_3$/MeOH 90:10, giving a white solid. Yield: 65%. mp: 86–89 °C. $[\alpha]_D^{20}$ = +30.0 (*c* 1, CH_2Cl_2). ^1H NMR ($CDCl_3$), δ (ppm): 0.91 (s, 3H); 0.96 (s, 3H); 1.19 (s, 3H); 1.34–1.43 (m, 1H); 1.51–1.69 (m, 3H); 1.81–1.88 (m, 1H); 1.93–2.02 (m, 1H); 2.83 (aprox. t, 1H, *J* = 7.8); 3.93–4.10 (m, 4H); 7.07–7.13 (m, 2H); 7.25–7.28 (m, 4H). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.5; 20.7; 23.6; 28.7; 34.9; 42.8; 47.3; 48.2; 64.5; 66.9; 128.3; 128.4; 128.5; 128.6; 135.9. IR (cm^{-1}): 2962, 2863, 1561, 1457, 1434, 1420, 1374, 1169, 1111, 1085, 1053, 1019, 771, 760, 735, 693. HRMS (ESI): calculated for $C_{22}H_{27}Cl_4N_2$ $[M+H]^+$: 459.0923; found: 459.0918.

4.3.8. (1*R*,3*S*)-*N*,*N*′-Bis(2,4,6-trimethylbenzyl)-1,3-diamino-1,2,2-trimethylcyclopentane 3h

The product was purified by column chromatography using silica gel and $CHCl_3$/MeOH 90:10 as eluent to give an oil. Spectroscopic details are in agreement with those previously described.[36] Yield: 47%. $[\alpha]_D^{20}$ = +34.1 (*c* 1, CH_2Cl_2). ^1H NMR ($CDCl_3$), δ (ppm): 0.82 (s, 3H); 0.93 (s, 3H); 1.19 (s, 3H); 1.39–1.49 (m, 1H); 1.64–1.72 (m, 1H); 1.88–1.98 (m, 1H); 2.08–2.19 (m, 1H); 2.24 (s, 6H); 2.31 (s, 6H); 2.34 (s, 6H); 2.85 (dd, 1H, *J* = 8.2; 7.0); 3.53 (d, 1H, *J* = 12.0); 3.60 (d, 1H, *J* = 12.0); 3.71 (d, 1H, *J* = 12.0); 3.76 (d, 1H, *J* = 12.0); 6.80 (s, 2H); 6.81 (s, 2H). ^{13}C NMR ($CDCl_3$), δ (ppm): 16.7; 19.4; 20.6; 20.9; 23.8; 28.8; 34.1; 40.8; 47.3; 47.4; 64.3; 68.0; 128.8; 128.9; 134.4; 134.7; 136.1; 136.2; 137.0; 137.1. IR (cm^{-1}): 2949, 2915, 2863, 1613, 1482, 1473, 1466, 1457, 1442, 1438, 1420, 1386, 11369, 1162, 1109, 1085, 1071, 1047, 1032, 1013, 849, 747, 715, 690. HRMS (ESI): calculated for $C_{28}H_{43}N_2$ $[M+H]^+$: 407.3421; found: 407.3413.

4.4. General procedure for enantioselective alkylations

To the appropriate amount of chiral ligand (0.15–0.01 mmol) and aldehyde (1 mmol) under an inert atmosphere, 4 mL of dry solvent were added. The temperature of the reaction mixture was lowered to 0 °C and diethylzinc (2 mmol, 2 mL, as a 1 M hexane solution) was added. The reaction was stirred for 10 min at 0 °C and then at the required temperature for the required time. Subsequently, a saturated ammonium chloride solution (1 mL) was added, followed by 2 M HCl (1 mL) and the reaction mixture was extracted with diethyl ether. The joint 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 *er* of the products.

Acknowledgements

Thanks are due to Coimbra Chemistry Centre (CQC), supported by the Portuguese Agency for Scientific Research, *Fundação para a Ciência e a Tecnologia* (FCT), through Project N° 007630 UID/QUI/00313/2013, co-funded by COMPETE2020-UE. We acknowledge the UC-NMR facility for obtaining the NMR data (www.nmr-ccc.uc.pt).

References

1. Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757–824.
2. Lin, G.; Li, Y.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; John Wiley & Sons Inc: New York, 2001.
3. Naganawa, Y.; Namba, T.; Aoyama, T.; Shoji, K.; Nishiyama, H. *Chem. Commun.* **2014**, 13224–13227.
4. Karabuga, S.; Karakaya, I. *Tetrahedron: Asymmetry* **2014**, *25*, 851–855.
5. Zhang, W.; Tang, R.; Yu, H.; Gao, S. *Appl. Organomet. Chem.* **2014**, *28*, 545–551.
6. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed.* **1991**, *30*, 49–69.
7. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, 833–856.
8. Binder, C. M.; Singaram, B. *Org. Prep. Proced. Int.* **2011**, *43*, 139–208.
9. Łowicki, D.; Baś, S.; Mlynarski, J. *Tetrahedron* **2015**, *71*, 1339–1394.
10. Jarzyński, S.; Leśniak, S.; Pieczonka, A. M. *Tetrahedron: Asymmetry* **2015**, *26*, 35–40.
11. Wang, Z.; Huang, D.; Xu, P.; Dong, X.; Wang, X.; Dai, Z. *Tetrahedron Lett.* **2015**, *56*, 1067–1071.
12. Wu, H.-L.; Wu, P.-Y.; Cheng, Y.-N.; Uang, B.-J. *Tetrahedron* **2016**, *72*, 2656–2665.
13. Frensch, G.; Labes, R.; Wosch, C. L.; Munaretto, L. D. S.; Salomé, K. S.; Guerrero, P. G.; Marques, F. A. *Tetrahedron Lett.* **2016**, *57*, 420–422.
14. Lee, D.-S.; Chang, S.-M.; Ho, C.-Y.; Lu, T.-J. *Chirality* **2016**, *28*, 65–71.
15. Li, F.; Huang, H.; Zong, H.; Bian, G.; Song, L. *Tetrahedron Lett.* **2015**, *56*, 2071–2076.
16. Martins, J. E. D. *Tetrahedron: Asymmetry* **2008**, *19*, 1250–1255.
17. Burguete, M. I.; Escorihuela, S. V. L.; Lledós, A.; Ujaque, G. *Tetrahedron* **2008**, *64*, 9717–9724.
18. Cheng, Y. Q.; Bian, Z.; Kang, C. Q.; Guo, H. Q.; Gao, L. X. *Tetrahedron: Asymmetry* **2008**, *19*, 1572–1575.
19. Scarpi, D.; Occhiato, E. G. *Tetrahedron: Asymmetry* **2009**, *20*, 340–350.
20. Olsson, C.; Helgesson, S. *Tetrahedron: Asymmetry* **2008**, *19*, 1484–1493.
21. Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; Cerero, S. M.; Ruiz, P. M.; Morillo, C. D. *Tetrahedron: Asymmetry* **2007**, *18*, 742–749.
22. Zanardi, M. M.; Suárez, A. G. *Tetrahedron Lett.* **2015**, *56*, 3762–3765.
23. Asami, M.; Hasome, A.; Yachi, N.; Hosoda, N.; Yamaguchi, Y.; Ito, S. *Tetrahedron: Asymmetry* **2016**, *27*, 322–329.
24. Asami, M.; Miyairi, N.; Sasahara, Y.; Ichikawa, K. I.; Hosoda, N.; Ito, S. *Tetrahedron* **2015**, *71*, 6796–6802.
25. Csillag, K.; Szakonyi, Z. *Tetrahedron: Asymmetry* **2013**, *24*, 553–561.
26. Serra, M. E. S.; Murtinho, D.; Goth, A.; Rocha Gonsalves, A. M. d'A.; Abreu, P. E.; Pais, A. A. C. C. *Chirality* **2010**, *431*, 425–431.
27. Serra, M. E. S.; Murtinho, D.; Goth, A. *ARKIVOC* **2009**, *2010*, 64–69.
28. Murtinho, D.; Serra, M. E. S. *Tetrahedron: Asymmetry* **2010**, *21*, 62–68.
29. Murtinho, D.; Ogihara, C. H.; Serra, M. E. S. *Tetrahedron: Asymmetry* **2015**, *26*, 1256–1260.
30. Bekdemir, Y.; Efil, K. *Org. Chem. Int.* **2014**, *2014*, 1–5.
31. Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J. *Res. Chem. Intermed.* **2007**, *33*, 541–548.
32. Ramos, N. C.; Echevarria, A.; Valbon, A.; Bortoluzzi, A. J.; Guedes, G. P.; Rodrigues-Santos, C. E.; Smith, C. *Cogent Chem.* **2016**, *2*, 1207863.
33. Das, S.; Das, V. K.; Saikia, L.; Thakur, A. J. *Green Chem. Lett. Rev.* **2012**, *5*, 457–474.
34. Goth, A. Masters Thesis, Coimbra, Portugal, 2007.
35. He, K.; Zhou, Z.; Wang, L.; Li, K.; Zhao, G.; Zhou, Q.; Tang, C. *Tetrahedron* **2004**, *60*, 10505–10513.
36. Reddy, P. V. G.; Tabassum, S.; Blanrue, A.; Wilhelm, R. *Chem. Commun.* **2009**, 5910–5912.