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Tetrahedron: *Asymmetry* 17 (2006) 449–454

Chemoenzymatic syntheses of novel ligands derived from *trans*-cyclohexane-1,2-diamine: application in the enantioselective addition of diethylzinc to aromatic aldehydes

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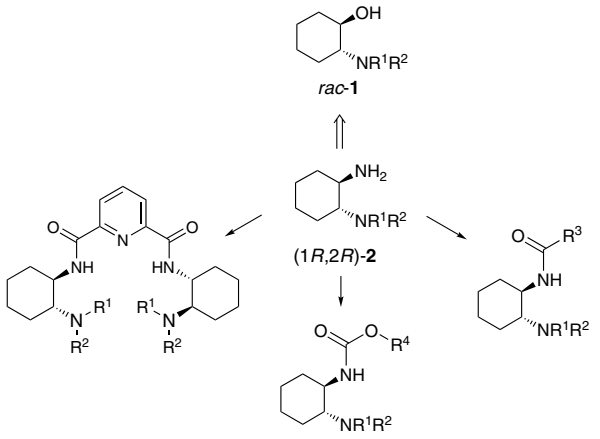
Received 16 December 2005; accepted 3 January 2006
Available online 2 February 2006

Abstract—Enantiopure (1*R*,2*R*)-cyclohexane-1,2-diamine derivatives, easily prepared from the corresponding (±)-*trans*-2-dialkylaminocyclohexanols through a chemoenzymatic route, have been employed as ligands in the enantioselective addition of diethylzinc to aromatic aldehydes. Of all the ligands tested, C_2-symmetric bisaminoamides derived from pyridine-2,6-dicarboxylic acid proved to be the most efficient.

1. Introduction

The development of novel and efficient catalysts for enantioselective reactions is one of the most challenging goals in modern organic chemistry.[1] In this sense, optically active cyclohexane-1,2-diamine derivatives are specially attractive, as can be deduced from their wide range of applicability.[2] Thus, some C_2-symmetric ligands, such as bisulfonamides and tetraza derivatives have been used to catalyze the addition of organozinc reagents to carbonyl compounds. However, their use was mainly limited to those ligands easily prepared from commercially available optically active *trans*-cyclohexane-1,2-diamine.[3] This can be due to the preparation of optically active nonsymmetric ligands from this diamine being a more complex task, involving additional steps of protection, which often takes place with low yields.[4]

In a very recent publication,[5] we described a highly efficient chemoenzymatic preparation of a variety of optically active *N*,*N*-disubstituted *trans*-cyclohexane-1,2-diamines **2** (Scheme 1) from the corresponding (±)-*trans*-2-dialkylaminocyclohexanols **1**. The easy accessibility of these diamine encouraged us to prepare some derivatives, such as carbamates and amides, some of which had C_2-symmetry (Scheme 1), and investigate their application as chiral ligands in the addition of diethylzinc to benzaldehyde. This class of ligands, which has been scarcely investigated in this reaction,[6] mimics the very successful chiral β-amino alcohol-based ligands[7] because the alcohol, amide and carbamate protons have similar pK_a values.[8] Moreover, the transformation of the primary amino group into different functions as well as the presence of different substituents in the tertiary amino group could modulate the ligand activity.



Scheme 1.

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0957-4166/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2006.01.003

2. Results and discussion

All ligands described herein were obtained from the corresponding enantiopure diamines (1*R*,2*R*)-**2a**–**d** (Fig. 1), which were prepared by enzymatic resolution of *rac-trans*-**2a**–**d** according to Ref. 5.

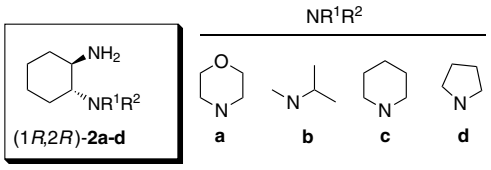
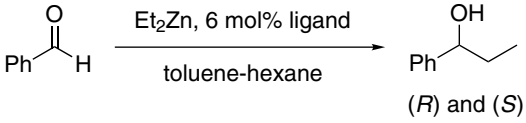


Figure 1. Chemoenzymatically prepared diamines (1*R*,2*R*)-**2a**–**d**.

In a recent paper,[9] we studied the efficiency of enantiopure 2-dialkylaminocyclohexanols (1*R*,2*R*)-**1** (Scheme 1) to catalyze the enantioselective addition of diethylzinc to benzaldehyde. In all cases 1-phenylpropan-1-ol was obtained with very good yields but with moderate enantiomeric excesses, these being dependent of the substituent on the amino group. Based on these results, we started choosing diamines (1*R*,2*R*)-**2a**,**b**, because they are structurally analogous to the β-amino alcohols that yielded the most interesting results in the ethylation of benzaldehyde.

Table 1. Enantioselective addition of Et_2Zn to benzaldehyde in the presence of ligands (1*R*,2*R*)-**3**–**5**[a]



Entry	Ligand	Yield[b] (%)	ee[c] (%)	Major enantiomer
1	**3a** (R = Bz)	51	10	*R*
2	**4a** (R = Cbz)	92	54	*R*
3	**5a** (R = Boc)	85	57	*R*
4	**3b** (R = Bz)	80	3	*S*
5	**4b** (R = Cbz)	93	25	*R*
6	**5b** (R = Boc)	86	7	*S*

[a] Reactions were carried out at 20 °C for 16 h.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC analysis (Chiralcel OD column).

First, enantiopure diamines (1*R*,2*R*)-**2a**,**b** were converted into their benzamides **3a** and **3b**, and benzyl and *tert*-butyl carbamates derivatives **4** and **5**, respectively, by conventional methods. These compounds were initially checked as ligands in the diethylzinc addition to benzaldehyde. Reactions were carried out at 20 °C using 6 mol % of ligand, diethylzinc (2.0 equiv) and a mixture of toluene-hexane as solvent. As shown in Table 1, 1-phenylpropan-1-ol was obtained with moderate to high yield in most cases, but only moderate values of enantiomeric excesses were obtained. The best ligand proved to be the Boc-derivative of **2a** (Table 1, entry 3). It is noteworthy that the enantiomeric excesses achieved with the carbamates of **2a** and the Cbz-derivative of **2b** (entries 2, 3 and 5) are very similar to those obtained with their analogous β-amino alcohols (1*R*,2*R*)-**1**.[9] This means that diamines can be used as alternative compounds to the β-amino alcohols, when they bear an NH group of similar acidity to the OH group of the alcohols.

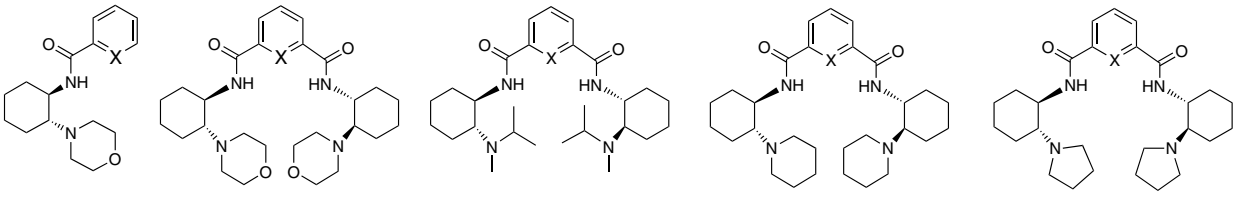
Once the utility of these diamines derivatives to catalyze the addition of diethylzinc to benzaldehyde was demonstrated, our following objective was to modify the structure of the ligand to get more enantioselective catalysts. These modifications were made by taking into account the following observations: (1) ligands can bind zinc in a tri- and tetradentate manner.[10] (2) In some cases higher enantioselectivities can be obtained with ligands bearing multiple stereocentres.[11] (3) Pyridine-based ligands are very efficient catalysts, especially those with a C_2 symmetry.[7c] Thus, starting from diamine (1*R*,2*R*)-**2a**, we prepared three derivatives, the pyridine-2-carboxamide (1*R*,2*R*)-**6a** and the C_2-symmetric benzene-1,3- and pyridine-2,6-dicarboxamides **7a** and **8a**, respectively. The syntheses of the C_2-symmetric ligands **7a** and **8a** were easily accomplished in quantitative yields by treatment of the diamine with 0.5 equiv of benzene-1,3-dicarbonyl dichloride and pyridine-2,6-dicarbonyl dichloride, respectively.

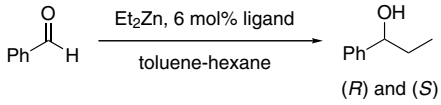
Results obtained in the reactions with these new ligands are shown in Table 2. As can be seen (Table 2, entries 1–4) the C_2-symmetric compounds **7a** and **8a** were more efficient catalysts than the corresponding derivatives **3a** and **6a** lacking symmetry. After the same reaction time, the yields of 1-phenylpropan-1-ol obtained in the reactions with **7a** and **8a** were higher that those obtained with **3a** and **6a**. Moreover, a notable increase of enantioselectivity was observed with the C_2-symmetric ligands, especially in the case of the bisaminoamide **8a** containing the pyridine unit in its structure. In addition, another interesting feature of our comparison is the reversal in enantioselectivity observed depending on the presence of a benzene or a pyridine moiety. A similar finding was previously reported by Williams et al.[12] in the addition of diethylzinc to aldehydes in the presence of C_2-symmetric β-amino alcohols containing analogous benzene and pyridine units. However, in that case, the enantioselectivities were similar with both ligands, in contrast to the strong differences observed with our pair of ligands **7a** and **8a**.

After seeing the results obtained with ligand **8a**, we decided to modify its structure in order to improve the efficiency of the catalytic process. Thus, we prepared other C_2-symmetric ligands **7b**–**d** and **8b**–**d** (Table 2) from the optically active diamines (1*R*,2*R*)-**2b**–**d** (see Fig. 1). In addition, another focus has been in verifying if the reversal of enantioselectivity shown above also happens with these bisaminoamides.

The analysis of the results summarized in Table 2 (entries 5–10) reveals for the new ligands the same tendency

Table 2. Enantioselective addition of Et_2Zn to benzaldehyde in the presence of ligands (1*R*,2*R*)-**3a**,**6a**, **7a**–**d** and **8a**–**d**[a]





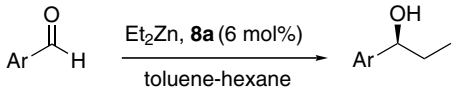
Entry	Ligand	Yield[b] (%)	ee[c] (%)	Major enantiomer
1	**3a**	51	10	*R*
2	**6a**	65	7	*S*
3	**7a**	94	21	*R*
4	**8a**	95	75	*S*
5	**7b**	90	31	*R*
6	**8b**	95	68	*S*
7	**7c**	86	11	*R*
8	**8c**	92	53	*S*
9	**7d**	90	32	*R*
10	**8d**	85	42	*S*

[a] Reactions were carried out at 20 °C for 16 h.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC analysis (Chiralcel OD column).

as for **7a** and **8a**. Thus, the major isomer obtained with all the ligands containing pyridine had an opposite absolute configuration to that observed with the ligands containing a benzene group, and with all pairs of ligands, higher enantioselectivities were achieved with the pyridine ligands. Anyway, compound **8a** was still the most efficient ligand, and a drastic influence of the selected diamine was observed over the asymmetric induction.

Further efforts to optimize the reaction with the ligand **8a** were carried out (Table 3). First, the alkylation of benzaldehyde with diethylzinc was performed after previous formation of the complex with titanium isopropoxide (entry 2). However, the new catalytic system resulted in a poor enantioselectivity of the alcohol produced, in contrast to previous reports in which an excess of the Ti reagent led to excellent enantioselectivities.[13] Similar results were achieved by employing the complex formed with nickel acetate,[14] racemic 1-phenylpropan-1-ol being obtained in this case (entry 3). Next, the loading of the catalyst was increased to 20 mol %, but a slight decrease in the enantioselectivity was noticed (entry 4). Lastly, by changing the temperature to −50 °C, the reaction rate was lower, resulting in a decrease of both the conversion and the enantioselectivity (entry 5). With the best conditions for benzaldehyde, the use of ligand **8a** was extended to the asymmetric ethylation of other aromatic aldehydes (Table 3, entries 6–8). The yields for the substituted benzaldehydes and naphthaldehyde were high, although the enantiomeric excesses continued being moderate. In all cases the configuration of the alcohol produced was *S*, established after the comparison of the elution order in HPLC analysis.[13a]

Table 3. Addition of diethylzinc to aromatic aldehydes using ligand **8a**[a]



Entry	Ar	Yield[b] (%)	ee[c] (%)	Config.
1	Ph	95	75	*S*
2[d]	Ph	75	15	*S*
3[e]	Ph	88	0	—
4[f]	Ph	81	52	*S*
5[g]	Ph	80	32	*S*
6	*p*-MeO–C_6H_4	85	46	*S*
7	*p*-Cl–C_6H_4	88	64	*S*
8	2-Naphthyl	75	60	*S*

[a] Reactions were carried out at 20 °C except that of entry 5.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC analysis (Chiralcel OD column).
[d] Using $Ti(OPr^i)_4$ (1 equiv). The catalyst was preformed prior to aldehyde addition.
[e] Using the complex formed with the metal salt $Ni(OAc)_2$.
[f] Ligand **8a** (20 mol %).
[g] Reaction was carried out at −50 °C.

3. Conclusion

In conclusion, we have carried out the chemoenzymatic synthesis of a new class of C_2-symmetric bisaminoamide

ligands derived from *N*,*N*-disubstituted *trans*-cyclohexane-1,2-diamine with promising applications in asymmetric catalysis. Thus, we have demonstrated the utility of these bisaminoamides catalyzing the enantioselective addition of diethylzinc to aldehydes, finding an interesting reversal of the asymmetric induction, with only a slight modification of the ligand structure.

4. Experimental

4.1. General

All reactions were performed under a nitrogen atmosphere. IR spectra were recorded on an Infrared FT spectrophotometer using KBr pellets (for solids) or neat (for liquids). Chiral HPLC analyses were performed using Chiralcel OD (Daicel), at 20 °C. ^{1}H, ^{13}C NMR and DEPT were recorded using AC-200 (^{1}H, 200.13 MHz and ^{13}C, 50.3 MHz), and AC-300 or DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) spectrometers using $CDCl_3$ as solvent. The chemical shifts are given in delta (δ) values and the coupling constants (J) in hertz (Hz). EI or ESI^{+} were used to record mass spectra (MS).

4.1.1. *N*,*N*-Disubstituted (1*R*,2*R*)-cyclohexane-1,2-diamines 2a–d. Enantiopure diamines (1*R*,2*R*)-**2a**–**d** were obtained by basic hydrolysis (3 M aq NaOH, reflux, 12 h, 93–95% yield) of their corresponding acetamide derivatives, which in turn were prepared by enzymatic resolution according to Ref. 5. Spectroscopic data and specific rotation values are in agreement with the published data for *rac*-**2a**–**d** and (1*S*,2*S*)-**2a**–**d**, respectively.[5]

4.2. General procedure for the synthesis of benzamides (1*R*,2*R*)-3a,b

To a solution of the corresponding diamine (1*R*,2*R*)-**2a**,**b** (0.25 mmol) and DMAP (15 mg) in dichloromethane (5 mL), benzoyl chloride (0.35 mmol) was added. After 24 h at room temperature, the solvent was evaporated and the resulting crude purified by flash chromatography (mixtures of hexane–ethyl acetate).

4.2.1. (1*R*,2*R*)-*N*-[2-(Morpholin-4-yl)cyclohexyl]benzamide (1*R*,2*R*)-3a. Yield: 92%; mp 197–199 °C; $[\alpha]_D^{20} = -93.7$ (*c* 0.70, $CHCl_3$), >99% ee; IR (neat) 3288, 1632 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.05–1.45 (m, 4H), 1.65–2.10 (m, 3H), 2.35–2.45 (m, 3H), 2.60–2.75 (m, 3H), 3.55–3.80 (m, 5H) 6.87 (br s, 1H, NH), 7.40–7.55 (m, 3H, Ph), 7.75–7.80 (m, 2H, Ph); ^{13}C NMR (75.5 MHz): δ 23.12 (CH_2), 24.54 (CH_2), 25.41 (CH_2), 32.65 (CH_2), 48.21 (CH_2), 50.58 (CH), 67.52 (CH_2), 67.57 (CH), 126.70 (CH), 128.45 (CH), 131.12 (CH), 135.13 (C), 167.53 (C=O). MS (ESI^{+}) *m*/*z* (rel. intensity): 289.2 [(M+H)$^{+}$, 100], 311.2 [(M+Na)$^{+}$, 25], 327.2 [(M+K)$^{+}$, 5].

4.2.2. (1*R*,2*R*)-*N*-[2-(*N*′-Isopropyl-*N*′-methylamino)cyclohexyl]benzamide (1*R*,2*R*)-3b. Yield: 90%; mp 101–103 °C; $[\alpha]_D^{20} = -13.1$ (*c* 0.70, $CHCl_3$), >99% ee; IR (neat) 3406, 1635 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.01 (d, 6H, $J = 6.5$ Hz, $2CH_3$), 1.05–1.40 (m, 4H), 1.60–1.85 (m, 3H), 2.13 (s, 3H, CH_3), 2.54 (m, 1H), 2.70–2.80 (m, 1H) 2.85 (hept, 1H, $J = 6.5$ Hz, N–CH), 3.51 (m, 1H), 7.10 (br s, 1H, NH), 7.30–7.45 (m, 3H, Ph), 7.70–7.80 (m, 2H, Ph); ^{13}C NMR (75.5 MHz): δ 20.85 (CH_3), 21.53 (CH_3), 24.43 (CH_2), 25.48 (CH_2), 25.63 (CH_2), 30.76 (CH_3), 32.26 (CH_2), 50.94 (CH), 51.48 (CH), 63.82 (CH), 126.65 (CH), 128.21 (CH), 130.85 (CH), 135.13 (C), 167.48 (C=O). MS (ESI^{+}) *m*/*z* (rel. intensity): 275.2 [(M+H)$^{+}$, 100].

4.3. General procedure for the synthesis of carbamates (1*R*,2*R*)-4a,b and (1*R*,2*R*)-5a,b

A solution of the corresponding diamine (1*R*,2*R*)-**2a**,**b** (0.25 mmol) in dichloromethane (5 mL) was treated with Cbz–Cl (0.30 mmol) or di-*tert*-butyl dicarbonate (0.30 mmol). After 7 h of reaction at room temperature, the solvent was evaporated and the resulting crude was purified by flash chromatography (mixtures of hexane–ethyl acetate). Spectroscopic data and specific rotation values for benzyl carbamates (1*R*,2*R*)-**4a**,**b** are in agreement with the published data for (1*S*,2*S*)-**4a**,**b**.[5]

4.3.1. *tert*-Butyl (1*R*,2*R*)-*N*-[2-(morpholin-4-yl)cyclohexyl]carbamate (1*R*,2*R*)-5a. Yield: 93%; mp 77–79 °C; $[\alpha]_D^{20} = -51.6$ (*c* 0.80, $CHCl_3$), >99% ee. IR (neat) 3358, 1711 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.04–1.25 (m, 4H), 1.30–1.50 (m, 10H), 1.60–1.90 (m, 4H), 2.13 (dt, 1H, $J = 10.8$ Hz), 2.30–2.45 (m, 3H), 2.60–2.75 (m, 2H), 3.29 (m, 1H), 3.60–3.75 (m, 4H), 5.03 (br s, 1H, NH); ^{13}C NMR (75.5 MHz) δ 23.16 (CH_2), 24.64 (CH_2), 25.34 (CH_2), 28.41 (CH_3), 33.31 (CH_2), 48.39 (CH_2), 50.71 (CH), 67.49 (CH_2), 67.79 (CH), 78.75 (C), 156.15 (C=O). MS (ESI^{+}) *m*/*z* (rel. intensity): 285.2 [(M+H)$^{+}$, 65], 307.1 [(M+Na)$^{+}$, 40].

4.3.2. *tert*-Butyl (1*R*,2*R*)-*N*-[2-(*N*′-isopropyl-*N*′-methylamino)cyclohexyl]carbamate (1*R*,2*R*)-5b. Colourless oil; yield: 83%; $[\alpha]_D^{20} = -112.5$ (*c* 0.70, $CHCl_3$), >99% ee; IR (neat) 3375, 1716 cm^{-1}; ^{1}H NMR (300 MHz): δ 0.94 (d, 3H, $J = 6.5$ Hz, CH_3), 0.97 (d, 3H, $J = 6.5$ Hz, CH_3), 1.10–1.25 (m, 2H), 1.30–1.45 (m+s, 11H), 1.55–1.75 (m, 3H), 2.10 (s, 3H, CH_3), 2.20–2.30 (m, 1H), 2.35–2.45 (m, 1H) 2.76 (hept, 1H, $J = 6.5$ Hz, N–CH), 3.11 (m, 1H), 5.20 (br s, 1H, NH); ^{13}C NMR (75.5 MHz): δ 20.45 (CH_3), 21.51 (CH_3), 24.47 (CH_2), 25.54 (CH_2), 25.64 (CH_2), 28.28 (CH_3), 31.09 (CH_3), 33.05 (CH_2), 50.30 (CH), 51.85 (CH), 63.99 (CH), 78.39 (C), 156.43 (C=O). MS (ESI^{+}) *m*/*z* (rel. intensity): 271.2 [(M+H)$^{+}$, 100].

4.4. Synthesis of (1*R*,2*R*)-*N*-[2-(morpholin-4-yl)cyclohexyl]pyridine-2-carboxamide (1*R*,2*R*)-6a

The method was the same as for the synthesis of the benzamides except that DMAP was not used. Yield: 91%; mp 134–136 °C; $[\alpha]_D^{20} = -79.2$ (*c* 0.50, $CHCl_3$), >99% ee; IR (neat) 3379, 1675 cm^{-1}; ^{1}H NMR (300 MHz): δ 1.10–1.40 (m, 4H), 1.60–1.90 (m, 3H), 2.30–2.50 (m, 4H), 2.55–2.75 (m, 2H), 3.40–3.85 (m, 5H), 7.40 (t, 1H, $J = 6.1$ Hz), 7.83 (t, 1H, $J = 7.2$ Hz), 8.17 (d, 1H, $J = 7.7$ Hz), 8.39 (br s, 1H, NH), 8.55 (d, 1H, $J = 4.3$ Hz); ^{13}C NMR (75.5 MHz): δ 23.66 (CH_2), 24.68 (CH_2), 25.32 (CH_2), 32.74 (CH_2), 48.40 (CH_2), 50.08

(CH), 67.43 (CH_2), 67.54 (CH), 121.94 (CH), 125.75 (CH), 137.11 (CH), 147.96 (CH), 150.39 (C), 164.18 (C=O). MS (ESI^+) *m/z* (rel. intensity): 290.1 [$(M+H)^+$, 100], 312.1 [$(M+Na)^+$, 25], 328.1 [$(M+K)^+$, 10].

4.5. Synthesis of bisaminoamides. General procedure

To a solution of diamine (1*R*,2*R*)-**2a–d** (0.26 mmol) in dichloromethane (5.0 mL), the corresponding acid dichloride (0.13 mmol) was added under a nitrogen atmosphere. After stirring to room temperature for 4 h, the solvent was evaporated and the resulting crude purified by flash chromatography (mixtures of hexane–ethyl acetate).

4.5.1. (1′*R*,1″*R*,2′*R*,2″*R*)-*N*,*N*′-Bis-[2-(morpholin-4-yl)-cyclohexyl]benzene-1,5-dicarboxamide 7a. Yield: 95%; mp 85–87 °C; $[\alpha]_D^{20} = -98.9$ (*c* 0.67, $CHCl_3$), >99% ee; IR (neat) 3462, 3322, 1643 cm^{-1}; ^1H NMR (300 MHz): δ 1.10–1.35 (m, 8H), 1.65–2.05 (m, 6H), 2.35–2.75 (m, 12H), 3.45–3.80 (m, 10H), 7.06 (br s, 2H, NH), 7.49 (t, 1H, $J = 7.7$ Hz), 7.89 (d, 2H, $J = 7.7$ Hz), 8.28 (s, 1H); ^{13}C NMR (75.5 MHz): δ 23.13 (CH_2), 24.51 (CH_2), 25.26 (CH_2), 32.62 (CH_2), 48.17 (CH_2), 50.47 (CH), 67.33 (CH_2+CH), 125.44 (CH), 128.72 (CH), 129.44 (CH), 135.22 (C), 166.65 (C=O). MS (EI^+) *m/z* (rel. intensity): 498.5 [M^+, 37], 468.5 (33), 167.1 (100).

4.5.2. (1′*R*,1″*R*,2′*R*,2″*R*)-*N*,*N*′-Bis-{2-[isopropyl(methyl)-amino]cyclohexyl}benzene-1,5-dicarboxamide 7b. Yield: 95%; mp 80–82 °C; $[\alpha]_D^{20} = -111.1$ (*c* 0.50, $CHCl_3$), >99% ee; IR (neat) 3358, 1642 cm^{-1}; ^1H NMR (300 MHz): δ 0.90–1.55 (m, 20H), 1.65–2.00 (m, 6H), 2.23 (s, 6H), 2.55–2.80 (m, 4H), 2.98 (hept, 2H, $J = 6.3$ Hz), 3.70 (m, 2H), 7.49 (t+br s, 1H+2NH, $J = 7.8$ Hz), 7.90 (dd, 2H, $J = 7.8$ and 1.6 Hz), 8.30 (s, 1H); ^{13}C NMR (75.5 MHz): δ 20.39 (CH_3), 21.31 (CH_3), 24.52 (CH_2), 25.58 (CH_2), 31.13 (CH_3), 32.50 (CH_2), 51.29 (CH), 51.41 (CH), 64.38 (CH), 125.47 (CH), 128.49 (CH), 129.74 (CH), 135.11 (C), 166.78 (C=O). MS (ESI^+) *m/z* (rel. intensity): 471.5 [$(M+H)^+$, 30].

4.5.3. (1′*R*,1″*R*,2′*R*,2″*R*)-*N*,*N*′-Bis-[2-(piperidin-1-yl)cyclohexyl]benzene-1,5-dicarboxamide 7c. Yield: 94%; mp 177–179 °C; $[\alpha]_D^{20} = -130.7$ (*c* 0.50, $CHCl_3$), >99% ee; IR (neat) 3333, 1644 cm^{-1}, ^1H NMR (300 MHz): δ 1.05–2.00 (m, 26H), 2.10–2.75 (m, 12H), 3.66 (m, 2H), 7.28 (br s, 2H, NH), 7.53 (t, 1H, $J = 7.8$ Hz), 7.94 (d, 2H, $J = 7.8$ Hz), 8.27 (s, 1H); ^{13}C NMR (75.5 MHz): δ 23.01 (CH_2), 24.49 (CH_2), 24.72 (CH_2), 25.51 (CH_2), 26.73 (CH_2), 32.40 (CH_2), 49.11 (CH_2), 51.08 (CH), 67.73 (CH), 125.29 (CH), 128.61 (CH), 129.40 (CH), 135.37 (C), 166.92 (C=O). MS (ESI^+) *m/z* (rel. intensity): 495.5 [$(M+H)^+$, 100].

4.5.4. (1′*R*,1″*R*,2′*R*,2″*R*)-*N*,*N*′-Bis-[2-(pyrrolidin-1-yl)-cyclohexyl]benzene-1,5-dicarboxamide 7d. Yield: 95%; mp 120–122 °C; $[\alpha]_D^{20} = -84.9$ (*c* 0.50, $CHCl_3$), >99% ee; IR (neat) 3317, 1643 cm^{-1}; ^1H NMR (300 MHz): δ 1.05–2.00 (m, 22H), 2.10–2.75 (m, 12H), 3.66 (m, 2H), 7.15 (br s, 2H, NH), 7.45 (t, 1H, $J = 7.8$ Hz), 7.85 (d, 2H, $J = 8.0$ Hz), 8.36 (s, 1H); ^{13}C NMR (75.5 MHz): δ 22.30 (CH_2), 23.61 (CH_2), 24.33 (CH_2), 24.59 (CH_2), 32.01 (CH_2), 47.13 (CH_2), 52.29 (CH), 61.68 (CH), 125.27 (CH), 128.43 (CH), 129.66 (CH), 135.11 (C), 166.77 (C=O). MS (ESI^+) *m/z* (rel. intensity): 467.5 [$(M+H)^+$, 100].

4.5.5. (1′*R*,1″*R*,2′*R*,2″*R*)-*N*,*N*′-Bis-[2-(morpholin-4-yl)-cyclohexyl]pyridine-2,6-dicarboxamide 8a. Yield: 93%; mp 110–112 °C; $[\alpha]_D^{20} = -167.0$ (*c* 0.60, $CHCl_3$), >99% ee; IR (neat) 3453, 3354, 1663 cm^{-1}; ^1H NMR (300 MHz): δ 1.05–1.45 (m, 8H), 1.65–2.00 (m, 6H), 2.25–2.75 (m, 12H), 3.45–3.85 (m, 10H), 8.01 (t, 1H, $J = 7.8$ Hz), 8.21 (d, 2H, NH, $J = 5.7$ Hz), 8.32 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR (75.5 MHz): δ 23.44 (CH_2), 24.39 (CH_2), 25.30 (CH_2), 32.82 (CH_2), 48.33 (CH_2), 50.16 (CH), 67.39 (CH_2), 67.64 (CH_2), 124.40 (CH), 138.62 (CH), 148.91 (C), 163.48 (C=O). MS (EI^+) *m/z* (rel. intensity): 499.5 (M^+, 32), 469.5 (26), 167.1 (90).

4.5.6. (1′*R*,1″*R*,2′*R*,2″*R*)-*N*,*N*′-Bis-{2-[isopropyl(methyl)-amino]cyclohexyl}pyridine-2,6-dicarboxamide 8b. Yield: 93%; mp 116–118 °C; $[\alpha]_D^{20} = -183.8$ (*c* 0.93, $CHCl_3$), >99% ee; IR (neat) 3442, 3396, 1666 cm^{-1}; ^1H NMR (300 MHz): δ 0.90–1.50 (m, 20H), 1.60–1.95 (m, 6H), 2.22 (m, 6H), 2.45–2.70 (m, 4H), 2.93 (hept, 2H, $J = 6.3$ Hz), 3.79 (m, 2H), 7.97 (t, 1H, $J = 7.8$ Hz), 8.15 (br s, 2H, NH), 8.31 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (75.5 MHz): δ 20.81 (CH_3), 21.60 (CH_3), 24.68 (CH_2), 25.71 (CH_2), 26.60 (CH_2), 31.14 (CH_3), 33.01 (CH_2), 51.02 (CH), 51.08 (CH), 51.17 (CH), 64.30 (CH), 124.28 (CH), 138.39 (CH), 149.14 (C), 163.46 (C=O). MS (EI^+) *m/z* (rel. intensity): 471.5 (M^+, 17), 428.5 (100).

4.5.7. (1′*R*,1″*R*,2′*R*,2″*R*)-*N*,*N*′-Bis-[2-(piperidin-1-yl)cyclohexyl]pyridine-2,6-dicarboxamide 8c. Yield: 90%; mp 79–81 °C; $[\alpha]_D^{20} = -186.9$ (*c* 0.50, $CHCl_3$), >99% ee; IR (neat) 3472, 3349, 1668 cm^{-1}; ^1H NMR (300 MHz): δ 1.05–1.60 (m, 20H), 1.65–2.00 (m, 5H), 2.20–2.70 (m, 13H), 3.68 (m, 2H), 8.01 (t, 1H, $J = 7.8$ Hz), 8.34 (d, 2H, $J = 7.8$ Hz), 8.57 (d, 2H, NH, $J = 3.9$ Hz); ^{13}C NMR (75.5 MHz): δ 23.46 (CH_2), 24.55 (CH_2), 24.79 (CH_2), 25.66 (CH_2), 27.04 (CH_2), 32.67 (CH_2), 49.29 (CH_2), 51.04 (CH), 67.90 (CH), 124.11 (CH), 138.53 (CH), 149.02 (C), 165.73 (C=O). MS (ESI^+) *m/z* (rel. intensity): 496.5 [$(M+H)^+$, 100], 518.5 [$(M+Na)^+$, 20].

4.5.8. (1′*R*,1″*R*,2′*R*,2″*R*)-*N*,*N*′-Bis-[2-(pyrrolidin-1-yl)-cyclohexyl]pyridine-2,6-dicarboxamide 8d. Yield: 90%; mp 94–96 °C; $[\alpha]_D^{20} = -117.8$ (*c* 0.50, $CHCl_3$), >99% ee; IR (neat) 3471, 3339, 1666 cm^{-1}; ^1H NMR (300 MHz): δ 1.00–1.90 (m, 22H), 2.40–2.65 (m, 12H), 3.70–3.90 (m, 2H), 7.98 (t, 1H, $J = 7.7$ Hz), 8.30 (d+br s, 2H+2NH, $J = 7.7$ Hz); ^{13}C NMR (75.5 MHz): δ 23.10 (CH_2), 23.81 (CH_2), 24.09 (CH_2), 24.42 (CH_2), 31.61 (CH_2), 47.60 (CH_2), 51.68 (CH), 62.09 (CH), 124.33 (CH), 138.59 (CH), 149.01 (C), 163.28 (C=O). MS (ESI^+) *m/z* (rel. intensity): 468.5 [$(M+H)^+$, 100].

4.6. Addition of diethylzinc to aldehydes. General procedure

To a solution of the optically active ligand (0.10 mmol) in toluene (1.8 mL), diethylzinc (3.2 mmol, 3.2 mL of a

1 M solution in hexane) was slowly added at 0 °C under a nitrogen atmosphere. The mixture was stirred to room temperature during 30 min and then aldehyde (1.6 mmol) was added at 0 °C. The mixture was allowed to reach room temperature and stirred during 16 h. After this time, 1 M aq HCl was added and the mixture was extracted with dichloromethane (3 × 15 mL). Evaporation of the organic solvents yielded the corresponding 1-arylpropan-1-ol.

4.7. Chiral HPLC analyses of the 1-arylpropan-1-ols

A Chiralcel OD column was used in all cases. $T = 20$ °C. UV detection, $\lambda = 210$ nm.

4.7.1. 1-Phenylpropan-1-ol. Hexane–2-propanol 97:3; 0.8 mL/min. $t_R = 14.7$ (*R*) and 16.1 (*S*) min. $R_S = 1.5$.

4.7.2. 1-(4-Methoxyphenyl)propan-1-ol. Hexane–2-propanol 97:3; 1.0 mL/min. $t_R = 18.3$ (*R*) and 20.9 (*S*) min. $R_S = 2.6$.

4.7.3. 1-(4-Chlorophenyl)propan-1-ol. Hexane–2-propanol 99:1; 0.5 mL/min. $t_R = 27.0$ (*S*) and 28.8 (*R*) min. $R_S = 1.1$.

4.7.4. 1-(2′-Naphthyl)propan-1-ol. Hexane–2-propanol 95:5; 1.0 mL/min. $t_R = 19.0$ (*S*) and 21.9 (*R*) min. $R_S = 2.3$.

Acknowledgements

We thank Novo Nordisk Co. for the generous gift of the CAL-B. This work has been supported by MEC (Spain; Project MEC-04-CTQ-04185). J.G.-S. thanks the Spanish MEC, for a predoctoral fellowship.

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