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Chiral bis(amino alcohol)oxalamides as ligands for asymmetric catalysis. Ti(IV) catalyzed enantioselective addition of diethylzinc to aldehydes

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Abstract—Several chiral bis(aminoalcohol)oxalamides with C_2-symmetry have been prepared and used as ligands for the enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes. The reaction proceeds in the presence of titanium isopropoxide to give the corresponding (*S*)-alcohols with ee up to 78%. In the absence of Ti(IV), the alcohols with the opposite configuration are obtained.

1. Introduction

The design and synthesis of new molecules able to act as chiral ligands in catalytic asymmetric reactions is one of the most important goals in modern organic chemistry.[1] For practical applications it is convenient that these ligands can be prepared through simple synthetic pathways from easily accessible starting materials and in both enantiomeric forms. Special attention has been aimed toward the synthesis of C_2-symmetric molecules since this kind of symmetry is generally considered advantageous because it reduces the number of possible transition states in enantioselective reactions.[2] Examples of widely used C_2 ligands include diols,[3] such as TADDOLs[4] and BINOLs,[5] diamines and bis-sulfonamides,[6] bis-oxazolines,[7] etc. However, the preparation of enantiopure compounds of this class is not a trivial task and requires carefully controlled synthetic strategies, and in some cases racemate separation.

Diacids such as oxalic or malonic acid derivatives are good scaffolds for the construction of C_2-symmetric multidentate ligands. Their carboxyl groups can be reacted with multiple compounds from the chiral pool providing easy access to multifunctional C_2 chiral ligands with high modularity.[8]

Herein we report the synthesis of several chiral bis(amino alcohol) oxalamides from amino alcohols derived from natural amino acids (Fig. 1). These ligands may behave as tetradentate ligands able to coordinate to a metal center through the hydroxyl and amido groups. Some of these oxalamides and their analogues have been

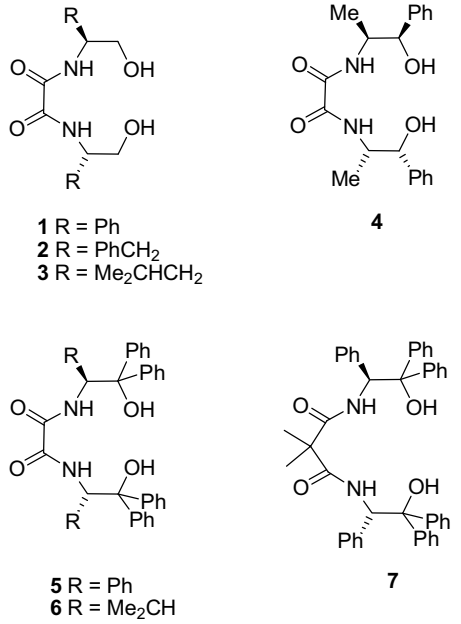

Figure 1.

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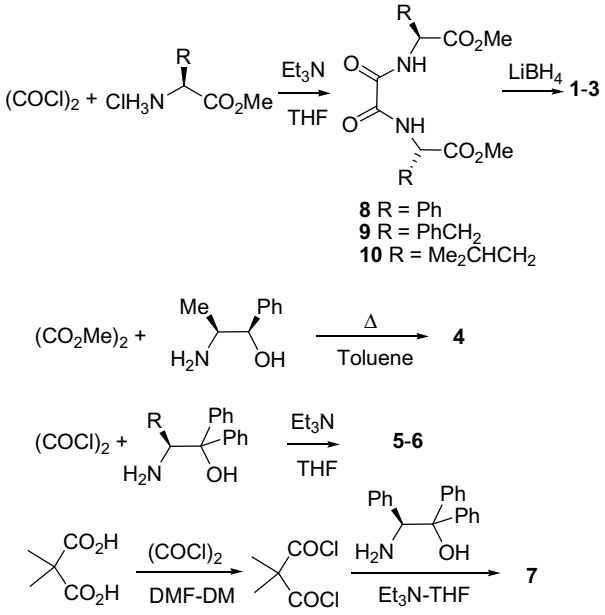
previously prepared and their gelation properties toward various organic solvents described.[9] However, no examples of their use as ligands for the asymmetric catalysis have been reported so far to the best of our knowledge. As a part of our current research on stereoselective reactions[10] we decided to investigate the efficiency of these compounds as ligands in asymmetric catalysis. The addition of diethylzinc to aldehydes, a typical catalytic asymmetric benchmark reaction was chosen for this purpose. This particular carbon–carbon bond formation reaction has been carried out in an enantioselective manner under the asymmetric induction of many different ligands.[11] In many cases the reaction involves the participation of zinc complexes with these ligands, but the use of titanium-based catalysts tends to be more efficient and selective.[12] Furthermore, the titanium-mediate addition of diethylzinc to aldehydes has previously been performed using tetradentate ligands.[8,13]

2. Results and discussion

2.1. Preparation of chiral bis(amino alcohol) oxalamide ligands

The ligands were prepared according to the synthetic routes outlined in Scheme 1. Oxalamides **1**–**3** which have primary hydroxyl groups, were prepared in two steps involving condensation of the amino acid methyl ester with oxalyl chloride in the presence of triethylamine followed by reduction of the ester group with lithium borohydride–methanol.[14] Oxalamide **4** was prepared by direct condensation of methyl oxalate and L-norephedrine in boiling toluene.[15] Oxalamides **5** and **6** bearing tertiary hydroxyl groups were obtained by condensation of the corresponding 2-substituted-2-amino-1,1-diphenylethanols[16] and oxalyl chloride. 2,2-Dimethylmalonamide **7** was obtained in a similar way.



Scheme 1. Synthesis of ligands **1**–**7**.

2.2. Asymmetric addition of diethylzinc to aldehydes

Benzaldehyde was used as test substrate for the reaction. In a preliminary survey for all the prepared ligands, the reaction was conducted at 0 °C in methylene chloride in the presence of 0.2 equiv of ligand, 3 equiv of diethylzinc (1 M solution in hexanes) and 1.4 equiv of titanium isopropoxide (Table 1). The reaction proceeded with fair to good yields and with ees ranging from 12% to 39 % with ligands **1**–**3**, which bear primary hydroxyl groups (entries 1–3). The best ee was obtained with the phenyl-substituted ligand **1** (R = Ph). The oxalamide **4** derived from L-norephedrine gave an unexpected low yield and ee, which may be due to mismatching in the asymmetric induction caused by the two stereogenic centers in the molecule. Better results were obtained with oxalamides **5** and **6**, which have a tertiary hydroxyl group. This increase in yield and ee is in agreement with the observations made by Seebach with titanium TADDOLates, which show that the bulkiness of the ligand increases the ligand exchange rate and facilitates the catalytic alkyl additions.[17] Again the phenyl substituted ligand **5** (R = Ph) gave the best result. The effect of the distance between the coordinating groups was studied with the

Table 1. Addition of diethylzinc to benzaldehyde in the presence of ligands **1**–**7**

Entry	Ligand	Conditions	Yield[a] (%)	Ee[b] (%)	Config.[c]
1	**1**	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	80	39	(*S*)-(−)
2	**2**	$Ti(OPr^i)_4$ (1.4 equiv), Et_2 Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	83	12	(*S*)-(−)
3	**3**	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	62	16	(*S*)-(−)
4	**4**	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	25	4	(*S*)-(−)
5	**5**	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	81	58	(*S*)-(−)
6	**6**	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	79	49	(*S*)-(−)
7	**7**	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	29	0	(*S*)-(−)
8	**5**	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), −30 °C, 24 h	57	43	(*S*)-(−)
9	**5**	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), rt, 24 h	80	51	(*S*)-(−)
10	**5**	Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	92	61	(*R*)-(+)
11	**5**	Et_2Zn (1 M in hexanes, 3 equiv), −30 °C, 46 h	30	24	(*R*)-(+)
12	**5**	Et_2Zn (1 M in hexanes, 3 equiv), rt, 24 h	84	56	(*R*)-(+)

[a] Isolated yields.
[b] Determined by GLC using a β-dex-225 column.
[c] Assigned by comparison of the specific rotation sign with those reported in the literature.

dimethylmalonic acid derivative ligand **7**. With this ligand, the reaction proceeded with low yield giving a racemic mixture of the addition product. This result is contradictory to previous reports using the titanium system with other tetradentate ligands, where a 1,3-separation of the coordinating groups improved yields and ees.[8] Having established that the oxalamide derivative of 2-amino-1,1,2-triphenylethanol was the most appropriate of the tested systems, we next studied the influence of the temperature with ligand **5**. Changing the temperature to −30 °C (entry 8) decreased the reaction yield and gave lower ee, while at room temperature, the reaction proceeded with good yield but with an ee somewhat lower than at 0 °C. The presence of a maximum in the plot ee versus T has been reported in many systems for the addition of dialkylzinc to aldehydes.[13e,18] This temperature effect is attributed to the existence of several competing reaction mechanisms involving monomeric and dimeric zinc species as active catalysts.[19] In our case, this could be due to a shift in the coordination mode of the ligand from tetracoordinating to tricoordinating. When the reaction was performed with ligand **5** in the absence of titanium isopropoxide at 0 °C, we obtained similar yields and ees to those obtained with titanium isopropoxide. However, the resulting alcohol presented the inverted configuration at the stereogenic carbon. This shift in the enantioselectivity of the reaction may be due to the participation of dinuclear metal complexes, bearing titanium and zinc atoms, as active catalysts. These results parallel those by Seebach[20] who found a reversal of selectivity in the addition of diethylzinc to aldehydes catalyzed by titanium TADDOLates depending on the ratio of diethylzinc and titanium isopropoxide, although in our case this reversal takes place in the total absence of titanium alkoxide.

Different aldehydes were tested (Table 2) as substrates for the enantioselective addition of diethylzinc using the best ligand **5** under the conditions described in Table 1, entry 5. Some of them were also tested in the absence of titanium isopropoxide under the conditions of Table 1, entry 10. The first remark is that, with the only exception of benzaldehyde, the presence of titanium isopropoxide increases both the yield and enantioselectivity of the reaction. A second remark is that, as in the case of benzaldehyde, in all cases opposite enantiomers were obtained depending on the presence or absence of Ti(IV).

The influence of different *para*-substituted benzaldehyde derivatives on the enantioselectivity of the reaction was also studied in order to establish whether there was any correlation between the Hammet constants[21] and the enantiomeric ratio of the secondary alcohol (Fig. 2). We found little effect with substituents with poor capability to delocalize electrons by mesomeric effect. Thus, slightly (*p*-chloro, entry 5 and *p*-bromo, entry 7) and strong (*p*-trifluoromethyl, entry 9) electron-withdrawing groups by inductive effect gave similar ees to unsubstituted benzaldehyde (entry 1). However, substituents with strong electron delocalizing capabilities by mesomeric effects, either electron-releasing (*p*-methoxy, entry 3) or electron-withdrawing (*p*-nitro, entry 11 and *p*-cyano, entry 13) gave lower ees in any case. Similar plots of ee versus the Hammet constant have been reported very recently for the addition of diethylzinc to *ortho*-substituted benzaldehydes

Table 2. Addition of diethylzinc to aldehydes in the presence of ligand **5**

Entry	Aldehyde	Conditions	Yield[a] (%)	Ee[b] (%)	Config.[c]
1	Benzaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	81	58	(*S*)-(−)
2	Benzaldehyde	Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	92	61	(*R*)-(+)
3	*p*-Methoxybenzaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	60	36	(*S*)-(−)
4	*p*-Methoxybenzaldehyde	Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	26	38	(*R*)-(+)
5	*p*-Chlorobenzaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	74	60	(*S*)-(−)
6	*p*-Chlorobenzaldehyde	Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	21	30	(*R*)-(+)
7	*p*-Bromobenzaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	41	58	(*S*)-(−)
8	*p*-Bromobenzaldehyde	Et_2Zn (1 M in hexanes, 3 equiv), 0 C, 24 h	54	50	(*R*)-(+)
9	*p*-Trifluoromethylbenzaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	89	56	(*S*)-(−)
10	*p*-Trifluoromethylbenzaldehyde	Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	36	20	(*R*)-(+)
11	*p*-Nitrobenzaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	54	46	(*S*)-(−)
12	*p*-Nitrobenzaldehyde	Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	12	5	(*R*)-(+)
13	*p*-Cyanobenzaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	77	50	(*S*)-(−)
14	*p*-Cyanobenzaldehyde	Et_2Zn (1 M in hexanes, 3 equiv), 0 C, 24 h	6	53	(*R*)-(+)
15	*o*-Methylbenzaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	19	31	(*S*)-(−)
16	*o*-Methylbenzaldehyde	Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	10	10	(*R*)-(+)
17	Decanal	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	82	66	(*S*)-(+)
18	Decanal	Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	50	41	(*R*)-(−)
19	Dihydrocinnamaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	79	74	(*S*)-(+)
20	Cyclohexanecarboxyaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	85	78	(*S*)-(−)
21	Cyclopentanecarboxyaldehyde	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), 0 °C, 24 h	80	67[d]	(*S*)-(+)
22	2-Butylhexanal	$Ti(OPr^i)_4$ (1.4 equiv), Et_2Zn (1 M in hexanes, 3 equiv), rt, 24 h	35	42[e]	(*S*)-(−)

[a] Isolated yields.
[b] Determined by GLC using a β-dex-225 column.
[c] Assigned by comparison of the specific rotation signs with those reported in the literature.
[d] Determined by ^1H and ^{19}F NMR analysis of its Mosher ester.
[e] Determined by HPLC, chiralcel ODH, hexane:*i*-PrOH 99:1, 0.5 mL/min, t_r (major) 25.9 min, t_r (minor) 28.4 min.

catalyzed by Ti(IV) complexes with C_2-symmetric bipyridyldiol ligands.[22]

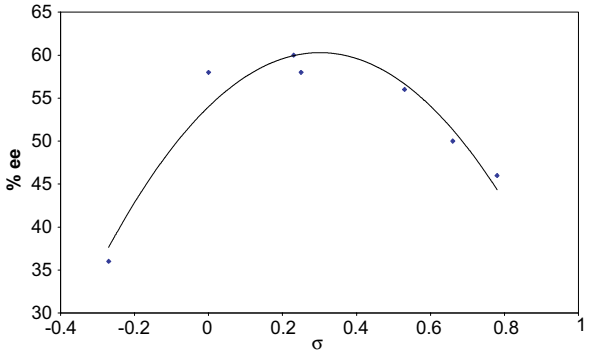


Figure 2. Correlation of substituent constants (σ_p) and the enantiomeric excesses of the alkylation of *para*-substituted benzaldehydes in the presence of Ti(IV)-5 complex.

The steric effect in the proximities of the aldehyde carbonyl group was studied with *o*-methylbenzaldehyde. In this case, low yield and ee were obtained probably due to the steric congestion caused by the four phenyl groups in the proximities of the coordinating hydroxyl groups of the ligand.

The reaction was also tested with aliphatic aldehydes (entries 17–22). In general, we observed that aliphatic aldehydes reacted more efficiently providing the corresponding alcohols with better yields and ees than the aromatic ones. In these cases ee increased until a certain level with the steric hindrance in the proximities of the aldehyde carbonyl group. A 78% ee was obtained in the case of cyclohexanecarboxyaldehyde (entry 20) and 74% in the case of dihydrocinnamaldehyde (entry 19). However when the steric hindrance was too high, a drop in the ee (42%) was observed (entry 22).

3. Conclusion

In summary, we have reported the first example of the application of tetradentate bis(hydroxy amino)oxalamides as ligands in asymmetric catalysis. These ligands are readily prepared in good yields in short synthetic sequences and allow high modularity by simply changing the amino alcohol moiety. These ligands are able to catalyze the asymmetric addition of diethylzinc to aromatic and aliphatic aldehydes in the presence of titanium isopropoxide. In general, the best results of the addition products are obtained with aliphatic aldehydes. With aromatic aldehydes better results are obtained when the aromatic ring bears substituents with weak electronic character, while strong electron-donating or withdrawing groups by a mesomeric effect diminish yield and ee. These ligands can also catalyze the reaction in the absence of titanium isopropoxide, although with lower yield and ee. Under these conditions the resulting alcohol presented an inverted configuration at the stereogenic carbon.

4. Experimental section

4.1. General

Commercial reagents were used as purchased. Dichloromethane was distilled from CaH_2 and stored over 4 Å molecular sieves. All asymmetric reactions were carried out in dry glassware under an argon atmosphere. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm. Optical rotations were measured using sodium light (D line 589 nm). IR were recorded as liquid films in NaCl for oils and as KBr discs for solids. ^{1}H NMR were run at 299.95 MHz for ^{1}H and at 50.3 MHz for ^{13}C NMR, and referenced to the solvent as the internal standard. The carbon type was determined by DEPT experiments. MS(EI) were run at 70 eV.

4.2. *N*,*N*′-Bis[(1*S*)-2-hydroxy-1-phenylethyl]ethanediamide 1

A solution of oxalyl chloride (0.79 mL, 9.3 mmol) in THF (0.5 mL) was added dropwise to a solution of (*S*)-phenylglycine methyl ester hydrochloride (3.72 g, 18.5 mmol) and triethylamine (5.2 mL, 37 mmol) in THF (250 mL) at 0 °C. After 3 h, the reaction mixture was filtered and most of the solvent evaporated under reduced pressure. The resulting solid was filtered and washed with a small portion of diethyl ether to give 4.18 g (98%) of compound **8**: Mp 180 °C; $[\alpha]_D^{25} = +226.5$ (*c* 0.83, $CHCl_3$); IR *v* 3293, 1747, 1660, 1511 cm^{-1}; MS(EI) 384 (M^+, 1), 352 (2), 325 (100); HRMS 384.1320 $C_{20}H_{20}N_2O_6$ required 384.1321; ^{1}H NMR ($CDCl_3$) δ 8.22 (2H, d, $J = 7.6$ Hz), 7.32 (10 H, s), 5.49 (2H, d, $J = 7.6$ Hz), 3.73 (6H, s); ^{13}C NMR ($CDCl_3$) δ 170.0 (s), 158.4 (s), 135.3 (s), 129.0 (d), 128.9 (d), 127.3 (d), 56.7 (d), 53.0 (q).

A solution of compound **8** (3.9 g, 10 mmol) in dry THF (170 mL) was treated with methanol (1.1 mL, 26.5 mmol) and lithium borohydride (0.57 g, 26.5 mmol). After 3 h, the reaction mixture was quenched with 2 mL of concd. HCl and anhydrous $MgSO_4$ then added. The mixture was filtered and concentrated under reduced pressure and the resulting solid was recrystallized from ethanol to give 1.8 g (54%) of compound **1**: Mp 263–265 °C; $[\alpha]_D^{25} = +87.0$ (*c* 0.1, MeOH); IR *v* 3293, 1644, 1521 cm^{-1}; MS(EI) 297 ($M^+ - CH_3O$, 73), 279 (9), 177 (67), 106 (100); HRMS 297.1238 $C_{17}H_{17}N_2O_3$ required 297.1239; ^{1}H NMR (DMSO-d_6) δ 9.00 (2H, d, $J = 8.7$ Hz), 7.4–7.1 (10H, m), 4.98 (2H, d, $J = 5.6$ Hz), 4.86 (2H, m), 3.71 (2H, dd, $J = 7.7$, 11.1 Hz), 3.61 (2H, dd, $J = 11.2$, 5.3 Hz); ^{13}C NMR (DMSO-d_6) δ 159.5 (s), 140.0 (s), 127.9 (d), 126.8 (d), 126.7 (d), 63.6 (t), 55.5 (d).

4.3. *N*,*N*′-Bis[(1*S*)-1-benzyl-2-hydroxyethyl]ethanediamide 2

Following an analogous procedure to that described for **8**, from L-phenylalanine methyl ester hydrochloride (4 g,

18.5 mmol) were obtained 3.8 g (99%) of compound **9**: Mp 194–195 °C; $[\alpha]_D^{25} = +16.2$ (*c* 0.04, MeOH); IR *v* 3283, 1736, 1660, 1521 cm^{-1}; MS(EI) 412 (M^+, 0.5), 353 (10), 178 (12), 162 (100); HRMS 412.1605 $C_{22}H_{24}N_2O_6$ required 412.1634; ^1H NMR ($CDCl_3$) δ 7.65 (2H, d, $J = 8.5$ Hz), 7.3–7.1 (6 H, m), 7.07 (4H, dd, $J = 7.5$, 2.1 Hz), 4.77 (2H, m), 3.67 (6H, s), 3.14 (2H, dd, $J = 13.7$, 5.7 Hz), 3.07 (2H, dd, $J = 13.7$, 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 170.6 (s), 158.6 (s), 135.2 (s), 129.1 (d), 128.7 (d), 127.3 (d), 53.6 (d), 52.5 (q), 37.9 (t).

Following an analogous procedure to that described for **1**, from compound **9** (3.6 g, 8.9 mmol) were obtained 2.2 g (69%) of compound **2**: Mp 253 °C; $[\alpha]_D^{25} = -43.7$ (*c* 0.03, MeOH); IR *v* 3411, 3298, 1655, 1516 cm^{-1}; MS(FAB) 357 (M^++1, 100), 339 (17), 313 (8); HRMS 357.1834 $C_{20}H_{25}N_2O_4$ required 357.1814; ^1H NMR (DMSO-d_6) δ 8.39 (2H, d, $J = 9.2$ Hz), 7.3–7.1 (10 H, m), 4.94 (2H, t, $J = 5.6$ Hz), 4.00 (2H, m), 3.42 (4H, m), 2.90 (2H, dd, $J = 13.6$, 5.5 Hz), 2.76 (2H, dd, $J = 13.6$, 8.5 Hz); ^{13}C NMR (DMSO-d_6) δ 159.2 (s), 138.5 (s), 128.7 (d), 127.8 (d), 125.7 (d), 61.9 (t), 52.7 (d), 35.8 (t).

4.4. *N*,*N*′-Bis[(1*S*)-2-hydroxy-1-isobutylethyl]ethanediamide 3

Following an analogous procedure to that described for **8**, from L-leucine methyl ester hydrochloride (4 g, 22 mmol) were obtained 3.7 g (97%) of compound **10**: Mp 119–120 °C; $[\alpha]_D^{25} = -51.9$ (*c* 0.65, MeOH); IR *v* 3344, 1742, 1665, 1516 cm^{-1}; MS(EI) 344 (M^+, 0.5), 285 (43), 225 (10), 144 (24), 86 (100); HRMS 344.1939 $C_{16}H_{28}N_2O_6$ required 344.1947; ^1H NMR ($CDCl_3$) δ 7.67 (2H, d, $J = 8.8$ Hz), 4.56 (2H, m), 3.72 (6H, s), 1.7-1.5 (6H, m), 0.92 (6H, d, $J = 6.1$ Hz), 0.91 (6H, d, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 171.9 (s), 159.0 (s), 52.5 (q), 51.1 (d), 41.4 (t), 24.7 (d), 22.7 (q), 21.7 (q).

Following an analogous procedure to that described for **1**, from compound **10** (3.4 g, 10 mmol) were obtained 1.2 g (46%) of compound **3**: Mp 174–175 °C; $[\alpha]_D^{25} = -30.2$ (*c* 1.0, MeOH); IR *v* 3375, 3283, 1655, 1527 cm^{-1}; MS(EI) 288 (M^+, 3), 257 (94), 239 (16), 86 (100); HRMS 288.2044 $C_{14}H_{28}N_2O_4$ required 288.2049; ^1H NMR (DMSO-d_6) δ 8.35 (2H, d, $J = 9.4$ Hz), 4.83 (2H, t, $J = 5.6$ Hz), 3.94 (2H, m), 3.44 (4H, m), 1.55 (4H, m), 1.40 (2H, m), 0.96 (6H, d, $J = 6.4$ Hz), 0.95 (6H, d, $J = 6.4$ Hz); ^{13}C NMR (DMSO-d_6) δ 160.1 (s), 63.7 (t), 49.9 (d), 39.9 (t), 24.6 (d), 23.6 (q), 22.2 (q).

4.5. *N*,*N*′-Bis[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]ethanediamide 4

A solution of L-(−)-norephedrine (4 g, 26.5 mmol) and diethyl oxalate (1.8 mL, 13.25 mmol) in toluene (25 mL) was refluxed for 2 h. The reaction mixture was cooled at room temperature and filtered. The solid was washed with toluene and dried to give 3.85 g (82%) of compound **4**: Mp 236–237 °C; $[\alpha]_D^{25} = +38.5$ (*c* 0.83, DMSO); IR *v* 3375, 3278, 1655, 1527 cm^{-1}; MS(EI) 338 (M^+-H_2O, 1), 320 (3), 250 (17), 231 (23), 160 (35), 118 (100); HRMS 338.1596 $C_{20}H_{22}N_2O_3$ required 338.1630; ^1H NMR (DMSO-d_6) δ 8.43 (2H, d, $J = 9.1$ Hz), 7.43–7.31 (10H, m), 5.66 (2H, d, $J = 4.5$ Hz), 4.74 (2H, t, $J = 4.5$ Hz), 4.02 (2H, m), 1.08 (6H, d, $J = 6.8$ Hz); ^{13}C NMR (DMSO-d_6) δ 159.1 (s), 143.1 (s), 128.2 (d), 127.3 (d), 126.5 (d), 74.0 (d), 51.2 (d), 14.8 (q).

4.6. *N*,*N*′-Bis[(1*S*)-2-hydroxy-1,2,2-triphenylethyl] ethanediamide 5

A solution of oxalyl chloride (0.15 mL, 1.75 mmol) in THF (1.5 mL) was added dropwise to a solution of (*S*)-2-amino-1,1,2-trifenilethanol (1 g, 3.46 mmol) and triethylamine (0.54 mL, 3.8 mmol) in THF (35 mL) at 0 °C. After 2 h, the reaction mixture was filtered and most of the solvent evaporated under reduced pressure. The resulting solid was filtered and washed with a small portion of diethyl ether to give 1.06 g (97%) of compound **5**: Mp 286–287 °C; $[\alpha]_D^{25} = -198.5$ (*c* 0.014, THF); IR *v* 3411, 3344, 1645, 1511 cm^{-1}; MS(EI) 614 (M^+-H_2O, 2), 596 (19), 432 (21), 256 (100); HRMS 614.2538 $C_{42}H_{34}N_2O_3$ required 614.2569; ^1H NMR (DMSO-d_6) δ 9.35 (2H, d, $J = 9.6$ Hz), 7.50 (4H, d, $J = 7.2$ Hz), 7.44 (4H, d, $J = 7.4$ Hz), 7.4–6.9 (26H, m), 6.63 (2H, s), 5.85 (2H, d, $J = 9.6$ Hz); ^{13}C NMR (DMSO-d_6) δ 159.0 (s), 146.6 (s), 144.8 (s), 138.5 (s), 129.3 (d), 128.3 (d), 127.6 (d), 127.2 (d), 127.1 (d), 126.9 (d), 126.5 (d), 126.1 (d), 126.0 (d), 79.5 (s), 60.0 (d).

4.7. *N*,*N*′-Bis[(1*S*)-2-hydroxy-1-isopropyl-2,2-triphenylethyl]ethanediamide 6

Following a similar procedure to that described for the preparation of **5** from 0.5 g (1.96 mmol) of (*S*)-2-amino-2-isopropyl-1,1-diphenylethanol were obtained 390 mg (70%) of compound **6**: Mp 266–267 °C; $[\alpha]_D^{25} = -71.8$ (*c* 0.04, MeOH); IR *v* 3426, 3350, 1660, 1516 cm^{-1}; MS(EI) 546 (M^+-H_2O, 1), 528 (70), 486 (6), 220 (100); HRMS 546.2924 $C_{36}H_{38}N_2O_3$ required 546.2882; ^1H NMR (DMSO-d_6) δ 8.53 (2H, d, $J = 10.4$ Hz), 7.48 (4H, d, $J = 7.5$ Hz), 7.35 (4H, d, $J = 7.5$ Hz), 7.28 (4H, t, $J = 7.5$ Hz), 7.13 (4H, t, $J = 7.5$ Hz), 7.04 (2H, t, $J = 7.5$ Hz), 6.33 (2H, s), 4.80 (2H, dd, $J = 10.4$, 2.1 Hz), 1.78 (2H, m), 0.86 (6H, d, $J = 6.8$ Hz), 0.65 (6H, d, $J = 6.8$ Hz); ^{13}C NMR (DMSO-d_6) δ 159.7 (s), 147.0 (s), 146.0 (s), 128.0 (d), 127.7 (d), 126.2 (d), 126.1 (d), 125.1 (d), 125.0 (d), 80.1 (s), 58.9 (d), 28.5 (d), 23.1 (q), 18.1 (q).

4.8. *N*,*N*′-Bis[(1*S*)-1,2,2-triphenyl-2-hydroxyethyl]-2,2-dimethylpropanodiamide 7

To a solution of dimetilmalonic acid (460 mg, 3.46 mmol) in dichloromethane (15 mL) was added oxalyl chloride (0.37 mL, 4.3 mmol) and 2 drops of DMF. The reaction mixture was stirred for 1 h and then the solvent was evaporated under reduced pressure. The resulting acid dichloride was dissolved in dry THF (1 mL) and injected into a solution of (*S*)-2-amino-1,1,2-triphenylethanol (1 g, 3.46 mmol) and triethylamine

(0.54 mL, 3.85 mmol) in THF (34 mL) at 0 °C. After 2 h, the reaction mixture was filtered, concentrated and the resulting solid washed with diethyl ether to give 1.1 g (98%) of compound **7**: Mp 255–256 °C; $[\alpha]_D^{25} = -175.4$ (*c* 0.02, MeOH); IR *v* 3421, 3350, 1644, 1490 cm^{-1}; MS(EI) 656 (M^+-H_2O, 2), 638 (34), 473 (23), 256 (100); HRMS 656.3048 $C_{45}H_{40}N_2O_3$ required 656.3039; ^1H NMR (DMSO-d_6) δ 7.98 (2H, d, $J = 8.8$ Hz), 7.54 (4H, d, $J = 7.5$ Hz), 7.34 (4H, t, $J = 7.5$ Hz), 7.30–7.05 (14H, m), 7.03 (4H, t, $J = 7.5$ Hz), 6.92 (4H, d, $J = 7.5$ Hz), 6.25 (2H, s), 5.90 (2H, d, $J = 8.8$ Hz), 0.81 (6H, d, $J = 6.8$ Hz); ^{13}C NMR (DMSO-d_6) δ 171.7 (s), 146.2 (s), 144.8 (s), 138.9 (s), 129.0 (d), 127.6 (d), 127.3 (d), 126.6 (d), 126.4 (d), 126.2 (d), 126.1 (d), 125.9 (d), 125.8 (d), 79.9 (s), 59.2 (d), 48.6 (s), 23.4 (q).

4.9. General procedure for the enantioselective addition of diethylzinc to aldehydes

To a solution of the corresponding ligand (0.2 mmol) in dry CH_2Cl_2 (5 mL) under Ar was added $Ti(OPr^i)_4$ (0.42 mL, 1.4 mmol). After 1 h, the reaction mixture was cooled to 0 °C and a 1 M solution of diethylzinc in hexane (3 mL, 3 mmol) was added. After 30 min, the aldehyde (1 mmol) was added and stirring continued at this temperature for 24 h. Then, the reaction mixture was quenched with 1 M HCl (20 mL), filtered and extracted with ether (3×15 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography on silica gel eluting with hexane–diethyl ether mixtures gave the corresponding alcohol. Yields and ee are included in Tables 1 and 2.

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