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Asymmetric synthesis using catalysts containing multiple stereogenic centres and a *trans*-1,2-diaminocyclohexane core; reversal of predominant enantioselectivity upon *N*-alkylation

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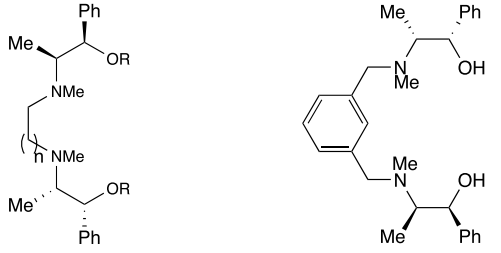
Abstract—*N*-Methylation of ligands containing a *trans*-1,2-diaminocyclohexane core and multiple stereogenic centres is shown to provide the product of the opposite configuration in significant enantiomeric excess, in the addition of diethylzinc to aldehydes. Some of the ligands were effective in an asymmetric Michael addition.

1. Introduction

Catalytic asymmetric formation of carbon–carbon bonds is a field of continuing importance in organic synthesis.[1] Ligands derived from a β-amino alcohol or a vicinal diamine are commonly found in catalysts, especially in the asymmetric addition of organometallic reagents to carbonyl compounds. In particular, the β-amino alcohol moiety has found extensive use as a ligand in the asymmetric addition of dialkylzincs to carbonyl compounds,[2–4] and mechanistic features have been thoroughly examined.[3] Catalysts incorporating a *trans*-1,2-diaminocyclohexane core have also found much use for asymmetric additions to carbonyl compounds.[5] For a ligand based upon either a β-amino alcohol or a vicinal diamine, the co-ordination geometry is reasonably well understood, leading in a number of cases to plausible models for the catalytic processes. In contrast, catalysts prepared from ligands that contain multiple stereocentres have been studied much less. Representative catalysts **1**[6] and **2**[7] (Fig. 1) were constructed from two ephedrine units linked, respectively, by an alkyl or alkylarylalkyl chain. In the addition of diethylzinc to benzaldehyde, ligands **1a** and **2** afforded (*R*)-1-phenylpropan-1-ol in 32 and 85% ee, respectively;[6] ligand **2** afforded the (*S*)-enantiomer in 80% ee.[7] Additional possibilities for intramolecular coordination of related compounds could widen the scope of catalytic asymmetric processes.



1a n=1 R=Li
1b n=2 R=H

2

Figure 1.

Recently, our research has shown that catalysts with up to four co-ordinating sites and at least as many possible coordinating atoms permit asymmetric hydrogenation of carbonyl compounds; moreover, in several instances, *N*-benzylation of the terminal amino groups resulted in reversal of the absolute configuration of the major product.[8] In our search for new catalysts for asymmetric carbon–carbon bond formation that contain multiple co-ordinating sites and stereogenic centres, a catalyst containing both a *trans*-1,2-diaminocyclohexane subunit and β-amino alcohol moiety was shown to be effective in the asymmetric addition of diethylzinc to aromatic aldehydes.[9] These ligands possess an extended array of up to six chiral centres. The preparation, further reactions and reversal, upon *N*-methylation, of the predominant enantioselection induced by such catalysts is here described.

The unadorned ligands **4** and **5** incorporating bis(β-

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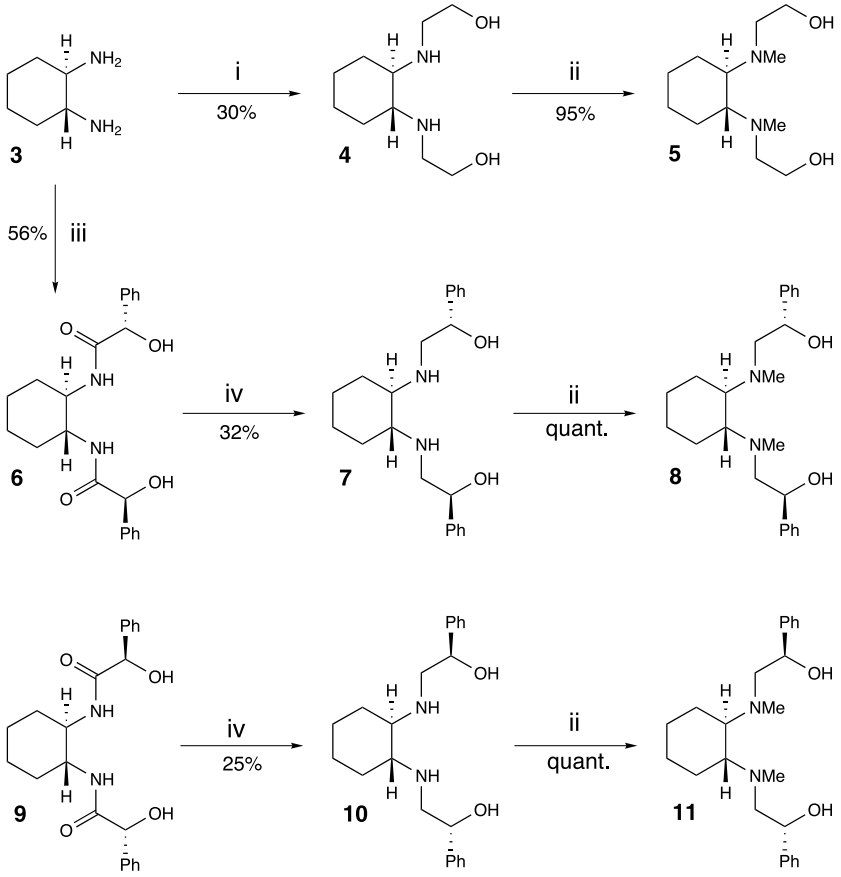
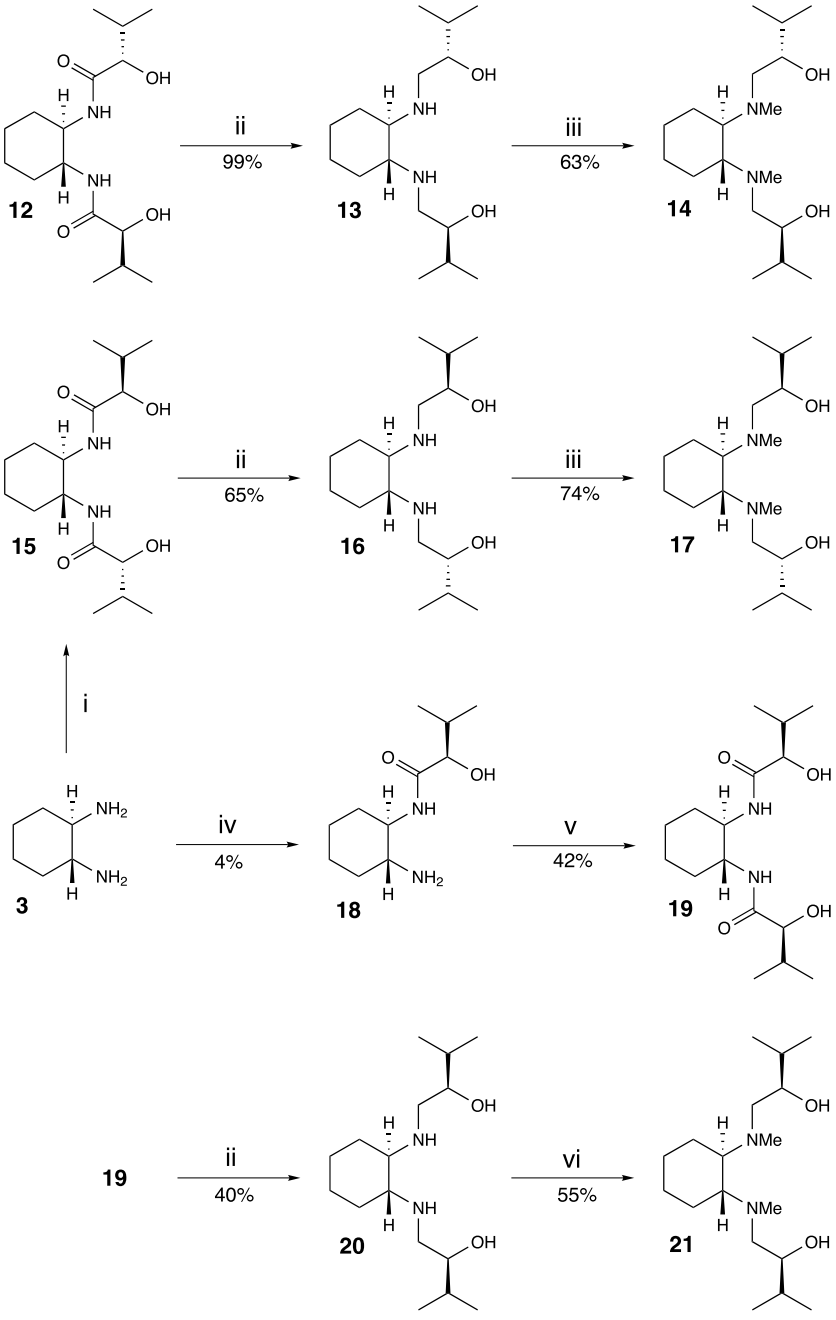
aminoalcohol) moieties were prepared according to Scheme 1. (1*R*,2*R*)-(−)-1,2-Diaminocyclohexane **3**[10] was dialkylated with 2-bromoethanol (water, reflux, 12 h) to give diol **4** (30%).[11] *N*,*N*′-Dimethylation of diol **4** to give the tertiary amino diol **5** (95%) was achieved using formaldehyde and formic acid in an Eschweiler–Clarke procedure,[12] but modified by addition of the hydrogen donor sodium formate.[13] The introduction of additional chiral centres on the β-aminoalcohol unit was found to be achieved satisfactorily by acylation followed by reduction. Activation of the requisite enantiomer of mandelic acid with dicyclohexylcarbodiimide (DCC) in the presence of *N*-hydroxysuccinimide followed by addition of the diamine **3** afforded ligands **6** and **9** in respective yields of 56% and 50%.[14] Reduction of amides **6** and **9** with $Me_2S\cdot BH_3$ gave the secondary amines **7** (32%) and **10** (25%) respectively.[15] Those amines were also subjected to Eschweiler–Clarke *N*,*N*′-dimethylation in the above manner to give the corresponding tertiary amines **8** and **11**[16] in quantitative yields.

To provide a contrast to the planarity of the phenyl substituents in the ligands **6**–**11**, isopropyl-substituted systems were also prepared (Scheme 2). Ligands **12** and **15**, (89% and 92%, respectively) were prepared by activation of the requisite enantiomer of 2-hydroxy-3-methylbutyric acid with carbonyldiimidazole in the presence of 1-hydroxybenzotriazole, followed by addition of the diamine **3**. Reduction of amides **12** and **15** gave the secondary amines **13** (99%) and **16** (65%) respectively.[15] Those amines were also subjected to Eschweiler–Clarke *N*,*N*′-dimethylation in the manner described above to give the corresponding tertiary amines **14** (63%) and **17** (74%). Since each of the above ligands possesses C_2 symmetry, it was of interest to prepare ligands with a *trans*-diaminocyclohexane core that are not C_2-symmetric, because of the presence of *N*-substituents of opposite configuration to each other. A stepwise synthesis was required and proceeded by reaction of diamine **3** with (*R*)-(−)-2-hydroxy-3-methylbutyric acid activated by carbonyldiimidazole in the presence of 1-hydroxybenzotriazole to give the amide **18** followed by subsequent reaction with (*S*)-(+)-2-hydroxy-3-methylbutyric acid and carbonyldiimidazole in the presence of 1-hydroxybenzotriazole to give the diamide **19** (42%). Reduction of **19** with $Me_2S\cdot BH_3$ afforded the diamine **20** (40%) which underwent *N*,*N*′-dimethylation with formaldehyde and formic acid to give the tetraamine **21** in 55% yield.

Lastly, amino alcohols containing six chiral centres were obtained by heating diamine **3** with cyclohexene oxide to give diamino diol **22** (30%) which was also reacted with formaldehyde and formic acid in the presence of sodium formate to give quantitatively the corresponding tertiary diamino diol **23**.[9] The relative configuration of each stereocentre in diamino diol **22** was established by X-ray



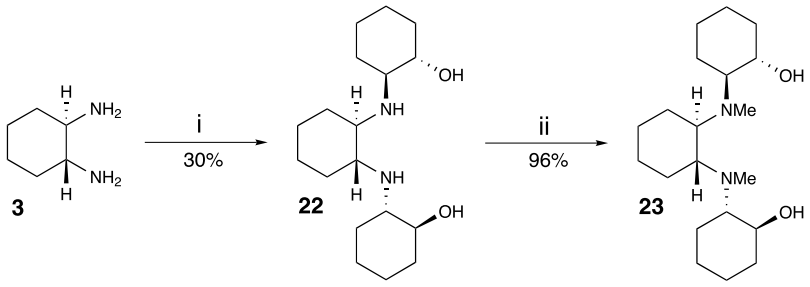
Scheme 1. Reagents and conditions. (i) 2-Bromoethanol (2 mol equiv), reflux in water; (ii) 37% HCHO (20 mol equiv), 96% HCOOH (53 equiv), HCOONa (10 mol%); (iii) (*S*)-(+)-mandelic acid (2.2 mol equiv), DCC (2.2 mol equiv), *N*-hydroxysuccinimide (2.2 mol equiv), THF; (iv) $Me_2S\cdot BH_3$ (6 mol equiv), $Et_2O\cdot BF_3$ (14 mol equiv), THF.



Scheme 2. Reagents and conditions. (i) (*R*)-(−)-2-Hydroxy-3-methylbutyric acid (2.2 mol equiv), carbonyldiimidazole (1.5 mol equiv), 1-hydroxybenzotriazole (0.14 mol equiv), THF; (ii) $Me_2S{\cdot}BH_3$ (5.5 mol equiv), $Et_2O{\cdot}BF_3$ (4 mol equiv), THF; (iii) 37% HCHO, 90% HCOOH, HCOONa (10 mol%); (iv) (*R*)-(−)-2-hydroxy-3-methylbutyric acid (0.5 mol equiv), carbonyldiimidazole (0.86 mol equiv), 1-hydroxybenzotriazole (0.1 mol equiv), THF; (v) (*S*)-(+)-2-hydroxy-3-methylbutyric acid (2.2 mol equiv), carbonyldiimidazole (1.5 mol equiv), 1-hydroxybenzotriazole (0.35 mol equiv), THF (vi) 37% HCHO, 90% HCOOH.

crystallography performed on the racemic modification.[17] A single diastereoisomer was also obtained from the reaction of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane with cyclohexene oxide, as had been found in a previous study using the racemic diamine.[17] Such directed stereochemical control is presumably assisted by hydrogen bonding networks and has features in common with adducts formed from the co-crystallisation of enantiopure 1,2-diaminocyclohexane with cyclohexane-1,2-diols (Scheme 3).[18]

Some of the new ligands were evaluated as catalysts by investigating the addition of diethylzinc to aldehydes.[2,19] This is considered as a yardstick for the efficiency and enantioselectivity of a catalyst, since the rate of the reaction in the absence of a catalyst is low but markedly increased in the presence of a suitable catalyst.[3,20] The unadorned ligands as catalysts **4** and **5** did not provide 1-phenylpropan-1-ol in either acceptable yield or enantiomeric excess (Table 1). However, all of the catalysts studied containing appended stereogenic centres (compounds **7**, **8**, **10**, **11**, **22** and **23**) showed appreciable catalysis and in some cases afforded the secondary alcohols in high ee, showing that



Scheme 3. Reagents and conditions. (i) Cyclohexene oxide (3 mol equiv), EtOH, reflux; (ii) 37% HCHO, 96% HCOOH, HCOONa.

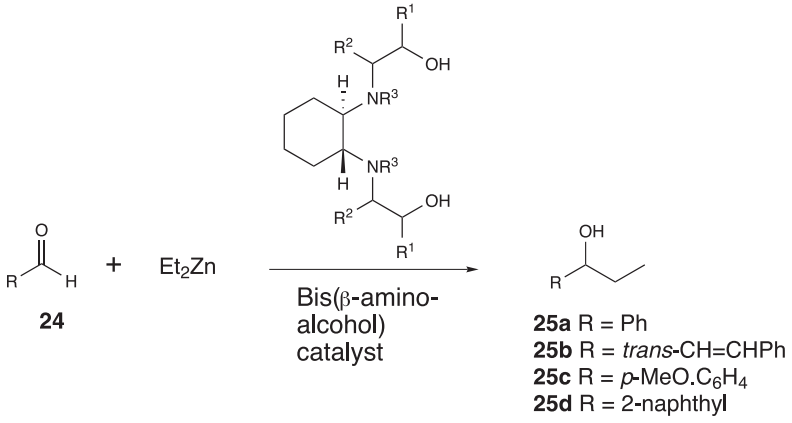
Table 1. Reaction of aldehydes with diethylzinc in toluene[a]

Entry	Ligand	Aldehyde	Temperature (°C)	Yield (%)[b]	ee (%)[c]	Configuration
1	**4**	PhCHO	−30	30	8	(*S*)
2	**5**	PhCHO	−30	0	—	—
3	**7**	PhCHO	−30	40	23	(*R*)
4	**8**	PhCHO	−30	55	54	(*S*)
5	**10**	PhCHO	−30	42	45	(*S*)
6	**11**	PhCHO	−30	51	16	(*R*)
7	**22**	PhCHO	−30	50	80	(*R*)
8	**23**	PhCHO	−30	25	92	(*S*)
9	**22**	PhCHO	0	99	64	(*R*)
10	**23**	PhCHO	0	68	75	(*S*)
11	**22**	PhCH=CHCHO	−30	41	72	(*R*)
12	**22**	*p*-MeO·C_6H_4CHO	−30	74	56	(*R*)
13	**23**	*p*-MeO·C_6H_4CHO	−30	18	52	(*S*)
14	**22**	2-Naphthaldehyde	0	95	60	(*R*)

[a] In the presence of the *trans*-1,2-diaminocyclohexane ligand (10 mol%), and 2.2 equiv of diethylzinc. Reactions were maintained at −30 or 0 °C for 4 h, then allowed to warm to 20 °C over a further 12 h.
[b] Yields were determined by ^{1}H NMR spectrometry.
[c] Enantiomeric excesses and absolute configurations of the alcohols were determined using a Chiralcel OD column.[24]

ligands with multiple stereogenic centres can indeed participate as catalysts in asymmetric carbon–carbon bond formation.

In all pairs of compounds studied (i.e., the secondary amines and their corresponding *N*-methylated derivatives), a reversal was observed in the configuration of the major enantiomer. The configuration at the carbinol carbon atom has a pronounced effect upon the asymmetric induction, and where it is (*R*), as for pairs **7** and **8** (Table 1, entries 3 and 4), and for pairs **22** and **23** (entries 7 and 8, 9 and 10, 12 and 13) the *N*-methylated derivative favours induction of the (*S*)-enantiomer, as compared with the corresponding secondary amine ligand. Conversely, for pair **10** and **11**, which possess the (*S*)-configuration at the carbinol carbon atom, the *N*-methylated derivative **11** favours induction of the (*R*)-enantiomer (entries 5 and 6). In previous work, *N*,*N*-dimethylation led to reversal of enantioselectivity but in only low ee's using secondary amine ligands.[21,22] Accordingly, it is noteworthy that the secondary amine catalyst **22** affords 80% ee (Table 1, entry 7). While the *N*-methylated catalysts **8**, **11** and **23** all give greater amounts of (*S*)-1-phenylpropan-1-ol, the effect is greatest with ligand **23**, containing six stereogenic centres. Using **23** and 2-naphthaldehyde, the aryl alcohol was not detected, presumably because of steric hindrance of approach to the



Scheme 4.

catalyst. Using a *trans*-1,2-diaminocyclohexane as part of a salen ligand, ee's of 30–70% were obtained for the addition of diethylzinc to benzaldehyde;[23] ligands such as **22** compare favourably, and show that systems based on a *trans*-1,2-diaminocyclohexane but with additional chirality can deliver significantly high ee's in the enantioselective addition to carbonyl compounds (Scheme 4).

The absolute configurations obtained with catalysts **22** and **23** might be accounted for by a catalyst with a pocket defined by the flanking wall of the aminocyclohexanol ring, and the basal plane that includes two zinc and two oxygen atoms. Interaction of the carbonyl group of the aldehyde with the zinc atom coordinated to the diamine unit, prior to alkyl transfer from the other zinc atom (presumed to be bound to the two oxygen atoms) would be consistent with previous models.[19,25] For ligand **22**, the bulk at nitrogen is sufficiently small to allow the aryl ring to reside nearby, leading to the attack of the aldehyde on its *Re*-face. Conversely, for **23**, the bulk of the *N*-methyl group is deemed to hinder location of the aryl group as above, so leading to *Si*-face addition and predominantly the (*S*)-1-arylpropan-1-ol.

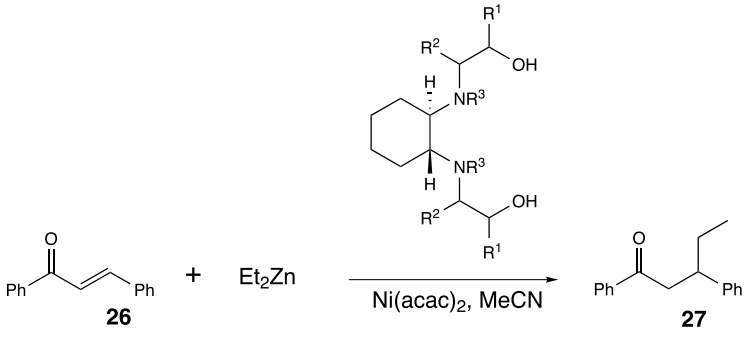
In view of the use of tetradentate amino alcohols as ligands in the asymmetric Michael addition[26] of diethylzinc to chalcone, the efficacy of some of the diamino diol ligands was briefly examined (Scheme 5). Ligand **8** (Table 2) was found to be significantly better than **14**, again showing that the stereogenic centre at the carbinol carbon atom plays a major role. In the isopropyl substituted series, ligand **14** (corresponding to **8**) gave a somewhat higher ee than the diastereoisomer **17**, but no asymmetric induction was observed using ligand **21**, containing opposite stereochemistries at the carbinol position. Again, a (modest) reversal in the configuration of the major enantiomer was observed for both the phenyl-substituted series (**8** and **11**), and the isopropyl series (**14** and **17**), indicating that similar complexation features regarding secondary and tertiary (*N*-methylated) amine ligands are likely to operate for Michael additions as well as for 1,2-additions to carbonyl compounds.

These results show that introduction of new chiral centres at the β-amino alcohol carbon atoms of the diamino diol **4** can lead to improved ee's, and that catalysts with multiple stereogenic centres can lead to significant asymmetric induction in carbon–carbon bond-forming reactions. A cyclohexane backbone, as in **22** and **23**, gave the highest ee's of those catalysts studied, as well as providing the products of the opposite configuration in high enantiomeric excess, simply by *N*,*N*′-dimethylation of the ligand.[27]

2. Experimental

2.1. General

Melting points were determined on a microscope hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer PE-983 spectrophotometer. Optical rotations were measured at 20 °C. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300 instrument operating at 300 and 75 MHz, respectively; chemical shifts are reported in δ (ppm) relative to the internal reference (tetramethylsilane or deuteriochloroform). Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualized using alkaline $KMnO_4$ spray or by ultraviolet light. Flash column chromatography was performed using Merck 0.040–0.063 mm, 230–400 mesh silica gel. Microanalytical data were obtained on a Perkin–Elmer 2400 CHN



Scheme 5.

Table 2. Reaction of chalcone with diethylzinc in toluene[a]

Entry	Ligand	Yield (%)[b]	ee (%)[c]	Configuration
1	**8**	72	37	(*R*)
2	**11**	68	10	(*S*)
3	**14**	63	13	(*R*)
4	**17**	70	8	(*S*)
5	**21**	61	0	—

[a] Reactions were conducted at −30 °C with 16 mol% of $Ni(acac)_2$ and 16 mol% of ligand.
[b] Yields were determined by ^{1}H NMR spectrometry.
[c] Absolute configurations of the conjugate ketone were determined by HPLC analysis using a Chiralcel OD column.[24]

elemental analyser. Mass spectra were obtained on a VG7070H mass spectrometer with Finigan Incos II. All solvents were reagent grade and, where necessary, were purified and dried by standard methods. Evaporation refers to the removal of solvent under reduced pressure.

The following compounds were prepared according to literature procedures: (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane;[10] (1*S*,2*S*)-(+)-*trans*-1,2-diaminocyclohexane; (*R*)-(−)-2-hydroxy-3-methylbutyric acid;[28] (*S*)-(+)-2-hydroxy-3-methylbutyric acid;[28] (1*R*,2*R*)-(−)-*N*,*N*′-bis-(1-hydroxyethyl)-*trans*-diaminocyclohexane.[29]

2.1.1. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(1-hydroxyethyl)-*trans*-diaminocyclohexane (5). (1*R*,2*R*)-(−)-*N*,*N*′-Bis-(1-hydroxyethyl)-*trans*-diaminocyclohexane (0.40 g, 2.0 mmol) was dissolved in formaldehyde (3.3 mL, 37% w/v, 41 mmol,) and formic acid (4.2 mL, 96% v/v, 107 mmol) and the resulting solution heated to 90 °C. Sodium formate (14 mg, 0.20 mmol) was then added and the mixture was kept stirring at 90 °C for 16 h. The solution was then was cooled to room temperature and made alkaline, with cooling, to pH 12 with aqueous sodium hydroxide (2 M). The mixture was extracted with diethyl ether (3×20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give amine **5** (0.43 g, 95%) as a clear oil; $[\alpha]_D=-32.8$ ($c=0.01$, $CHCl_3$); IR (film) 3628 (br), 2886, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.63 (2H, br, OH), 3.68 (4H, m, CH_2OH), 3.58 (2H, m, C*H*N), 2.84 (4H, m, CH_2N), 2.41 (6H, s, Me), 2.07–1.20 (8H, m, CH_2CH_2CHN); ^{13}C NMR ($CDCl_3$) δ 64.4 (*C*H_2OH), 53.3 (*C*H_2N), 40.7 (*C*HN), 35.9 (Me), 23.5 (*C*H_2CHN), 21.6 (*C*H_2CH$_2$CHN). HRMS (EI): calcd for $C_{12}H_{27}N_2O_2$ (MH^+) 231.2073, found 231.2081.

2.1.2. (1*R*,2*R*)-(+)-*N*,*N*′-Bis(α-hydroxy-(*S*)-phenyl)-acetamido-*trans*-1,2-diaminocyclohexane (6). L-Mandelic acid (11.7 g, 77 mmol) and *N*-hydroxysuccinimide (8.86 g, 77 mmol) were added to a stirred solution of (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (4.0 g, 35 mmol) in THF (100 mL) and the resulting mixture was stirred for 30 min at 20 °C. To this solution was added 1,3-dicyclohexylcarbodiimide (15.9 g, 77 mmol) in portions over 10 min and the resulting mixture was stirred for 48 h at 20 °C. Saturated aqueous sodium hydrogen carbonate (50 mL) was then added and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give an off-white solid that was purified by flash column chromatography (7:3 ethyl acetate/petroleum ether). Any residual urea by-product is removed in the first few fractions and is visible by its precipitation within the fraction solvent. Evaporation of the required fractions gave a white solid that was recrystallized from the elution solvent to give amide **6** (7.4 g, 56%) as white plates, mp 158–160 °C; $[\alpha]_D=+28.7$ ($c=1$, $CHCl_3$) cm^{-1}; IR ($CHCl_3$) 3185 (br), 1645, 1535, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (10H, m, phenyl), 6.38 (2H, br, NH), 4.47 (2H, s, C*H*OH), 3.67 (2H, br, OH), 3.52 (2H, m, C*H*N), 1.80–1.10 (8H, m, CH_2CH_2CHN); ^{13}C NMR ($CDCl_3$) δ 173.3 (C=O), 140.0 (*ipso*-phenyl), 129.2 (*o*-phenyl), 129.0 (*m*-phenyl), 127.1 (*p*-phenyl), 74.2 (*C*HOH), 54.2 (*C*HN), 34.3 (*C*H_2CHN), 25.3 (*C*H_2CH$_2$CHN). HRMS (EI): calcd for $C_{22}H_{26}N_2O_4$ (M^+) 382.1893, found 382.1889.

2.1.3. (1*R*,2*R*)-(+)-*N*,*N*′-Bis(ethan-(1-(*R*)-phenyl)-1-ol)-*trans*-1,2-diaminocyclohexane (7). To an oven-dried, 25 mL pear-shaped flask with an inlet capped with a septum and containing a stirrer bar (1 cm length) was attached a 4′ Vigreux column. At the top of the column was placed a distillation arm with a small condenser. Between the condenser and a 10 mL receiver flask was an outlet connected to nitrogen through a mercury bubbler. The whole system was flushed with nitrogen and the pear-shaped flask was charged with a solution of amide **6** (0.235 g, 0.62 mmol) in dry THF (5 mL). To this solution was added boron trifluoride etherate (0.312 mL, 8.61 mmol); the mixture was then heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (1.84 mL, 2 M, 3.69 mmol) was then added carefully over 15 min. The liberated dimethyl sulfide and ether were distilled and collected. After 18 h at reflux, the remaining solution was allowed to cool to room temperature and the solvent carefully removed by connecting the outlet for nitrogen to a vacuum pump. The residual amine–boron trifluoride complex was cooled to 0 °C and hydrochloric acid (10 mL, 6 M) was added dropwise for the first few mL; CAUTION: the initial reaction is very vigorous! The acidified solution was heated at reflux for 1 h to ensure complete hydrolysis. The solution was then allowed to cool to 20 °C and the non-basic components removed by extraction with diethyl ether (3× 15 mL). The aqueous layer was made alkaline by addition of aqueous sodium hydroxide (6 M, CAUTION) to pH 12 and was then extracted with diethyl ether (3×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give a clear oil that was purified by flash column chromatography (1:19 methanol/chloroform) to give amine **7** (71 mg, 32%) as a clear oil; $[\alpha]_D=+1.87$ ($c=1.55$, $CHCl_3$); IR (film) 3618 (br), 3149, 1645, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (10H, m, phenyl), 4.97 (2H, m, C*H*OH), 3.48 (2H, br, CHO*H*), 3.22 (2H, m, C*H*NH), 2.70 (4H, m, CH_2NH), 2.15–1.25 (8H, m, CH_2CH_2CHNH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.9 (*ipso*-phenyl), 128.7 (*o*-phenyl), 127.8 (*m*-phenyl), 126.3 (*p*-phenyl), 74.7 (C*H*OH), 64.3 (*C*H_2NH), 56.5 (*C*HNH), 33.4 (CH_2CHNH), 25.6 (CH_2CH$_2$CHNH). HRMS (EI): calcd for $C_{22}H_{31}N_2O_2$ (MH^+) 355.2377, found 355.2386.

2.1.4. (*R*,*R*)-(+)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(ethan-(1-(*R*)-phenyl)-1-ol)-*trans*-1,2-diaminocyclohexane (8). Amino alcohol **7** (0.25 g, 0.65 mmol) was dissolved in aqueous 37% formaldehyde (1.2 mL, 15 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (1.5 mL, 35 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was then cooled to 20 °C and made alkaline (pH 12) by addition of aqueous sodium hydroxide (2 M) with constant cooling. The aqueous layer was extracted with diethyl ether (2×25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give an oil that was purified by flash column chromatography (1:19 methanol/chloroform) to give amine **8** (0.26 g, quantitative) as a clear oil; $[\alpha]_D=-27.7$ ($c=0.76$, $CHCl_3$); IR (film) 3520 (br), 3061, 1645, 1511 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (10H, m, phenyl), 5.71 (2H, br, OH), 4.79 (2H, m, C*H*OH), 2.85

(2H, m, C*H*N), 2.43 (4H, m, CH_2N), 2.17 (6H, s, CH_3), 1.75–1.05 (8H, m, CH_2CH_2CHN)); ^{13}C NMR ($CDCl_3$) δ 143.8 (*ipso*-phenyl), 128.6 (*o*-phenyl), 127.4 (*m*-phenyl), 126.4 (*p*-phenyl), 70.6 (*C*HOH), 63.2 (*C*H_2N and *C*HN), 37.4 (*C*H_3), 25.9 (*C*H_2CHN), 24.8 (*C*H_2CH$_2$CHN). HRMS (EI): calcd for $C_{24}H_{35}N_2O_2$ (MH^+) 383.2699, found 383.2692.

2.1.5. (1*R*,2*R*)-(+)-*N*,*N*′-(α-Hydroxy-(*R*)-phenyl)-acetamido-*trans*-1,2-diaminocyclohexane (9). D-Mandelic acid (11.7 g, 77 mmol) and *N*-hydroxysuccinimide (8.86 g, 77 mmol) were added to a stirred solution of (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (4.0 g, 35 mmol) in THF (100 mL) and the resulting mixture stirred for 30 min at 20 °C. To this solution was added 1,3-dicyclohexylcarbodiimide (15.9 g, 77 mmol) in portions over 10 min and the resulting mixture was stirred for 48 h at 20 °C. The mixture was worked up as described for **6**, and after column chromatography, evaporation of the required fractions gave a white solid which was recrystallized from ethyl acetate. The white plates so obtained were filtered and dried under reduced pressure to give amide **9** (6.5 g, 50%) as plates, mp 173–174 °C; $[\alpha]_D = +17.6$ ($c=1$, $CHCl_3$); ($CHCl_3$) 3184, 1645, 1534, 1059 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.12 (10H, m, aryl), 4.88 (2H, br, NH), 4.72 (2H, s, C*H*OH), 3.48 (2H, m, C*H*N), 1.65–1.00 (8H, m, CH_2CH_2CHN); ^{13}C NMR ($CDCl_3$) δ 174.1 (C=O), 139.6 (*ipso*-phenyl), 129.0 (*o*-phenyl), 128.7 (*m*-phenyl), 127.1 (*p*-phenyl), 74.4 (*C*HOH), 53.6 (*C*HN), 32.4 (*C*H_2CHN), 25.0 (*C*H_2CH$_2$-CHN); IR (KBr pellet) 3355, 2944, 2832, 1657 cm^{-1}; FAB-MS *m*/*z* 383 (MH^+, 100%). HRMS (EI): calcd for $C_{22}H_{26}N_2O_4$ (M^+) 382.1893, found 382.1897.

2.1.6. (1*R*,2*R*)-(−)-*N*,*N*′-Bis(ethan-(1-(*S*)-phenyl)-1-ol)-*trans*-1,2-diaminocyclohexane (10). The procedure described for amine **7** was followed using a solution of amide **9** (0.404 g, 1.06 mmol) in dry THF (5 mL). To this solution was added boron trifluoride etherate (0.153 mL, 4.22 mmol) and the solution was heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (1.17 mL, 2 M, 2.33 mmol) was then added carefully over 15 min. The subsequent steps, work-up and isolation as described for amine **7** gave an oil that was purified by flash column chromatography (1:19 methanol/chloroform) to give amine **10** (94 mg, 25%) as a clear oil that solidified on cooling to 4 °C; $[\alpha]_D = -96.6$ ($c=0.5$, $CHCl_3$); IR (film) 3626, 3090, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (10H, m, phenyl), 4.76 (2H, m, C*H*OH), 3.00–2.60 (6H, m, CH_2NH and C*H*NH), 2.25 (2H, m, NH), 2.05–1.20 (8H, m, CH_2CH_2CHNH); ^{13}C NMR ($CDCl_3$) δ 143.1 (*ipso*-phenyl), 128.8 (*o*-phenyl), 127.9 (*m*-phenyl), 126.4 (*p*-phenyl), 72.6 (*C*HOH), 60.8 (*C*H_2NH), 54.4 (*C*HNH), 32.5 (*C*H_2CHNH), 25.5 (*C*H_2CH$_2$CHNH). HRMS (EI): calcd for $C_{22}H_{30}N_2O_2$ (MH^+) 355.2377, found, 355.2386.

2.1.7. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(ethan-(1-(*S*)-phenyl)-1-ol)-*trans*-1,2-diaminocyclohexane (11). Amino alcohol **10** (30 mg, 0.085 mmol) was dissolved in aqueous 37% formaldehyde (1.4 mL, 19 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (1.8 mL, 42 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was worked up and purified as described for amine **8** to give amine **11** (31 mg, quantitative) as a clear oil; $[\alpha]_D = -111.6$ ($c=0.57$, $CHCl_3$); IR (film) 3567, 2988, 1511, 1168 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 7.31 (10H, m, phenyl), 7.51 (2H, br, OH), 4.83 (2H, m, C*H*OH), 2.75 (2H, m, C*H*NH), 2.50–2.30 (10H, m, NCH_3, NCH_2, C*H*N), 2.02–1.80 (4H, CH_2CHN), 1.10 (4H, m, CH_2CH$_2$CHN); ^{13}C NMR ($CDCl_3$) δ 143.3 (*ipso*-phenyl), 128.9 (*o*-phenyl), 127.9 (*m*-phenyl), 126.6 (*p*-phenyl), 72.2 (*C*HOH), 65.0 (*C*H_2N), 60.5 (*C*HN), 42.0 (N*C*H_3), 26.0 (CH_2CHN), 23.8 (CH_2CH$_2$CHN). FAB-MS *m*/*z* 383 (MH^+, 100%), 232 (17%). HRMS (EI): calcd for $C_{24}H_{35}N_2O_2$ (MH^+) 383.2701, found 383.2699.

2.1.8. (1*R*,2*R*)-(+)-*N*,*N*′-Bis-(1-hydroxy-1-(*S*)-isopropyl-acetamido)-*trans*-1,2-diaminocyclohexane (12). A solution of carbonyldiimidazole (3.14 g, 19.4 mmol) in dry THF (10 mL) was added to a stirred solution of (*S*)-(+)-2-hydroxy-3-methylbutyric acid (2.0 g, 17.0 mmol) and 1-hydroxybenzotriazole (0.23 g, 1.7 mmol) in freshly distilled THF (60 mL) under an inert atmosphere at 20 °C, and the mixture was stirred for 1 h. A solution of (1*R*,2*R*)-(−)-*trans*-diaminocyclohexane (0.88 g, 0.77 mmol) in dry THF (2 mL) was then added dropwise. The mixture was stirred at 20 °C for 24 h, then hydrochloric acid (50 mL, 1 M) as added. The aqueous layer was extracted with diethyl ether (3×25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give an off-white solid which was purified by flash column chromatography (4:1 ethyl acetate/40–60 °C petroleum ether). Evaporation of the appropriate fractions gave a white solid that was recrystallized from isopropanol to give amide **12** as white needles (2.16 g, 89%), mp 197–198 °C; $[\alpha]_D = +32.2$ ($c=1$, MeOH); IR ($CHCl_3$) 3592, 2859, 1602 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.75 (2H, d, $J=3.5$ Hz, C*H*OH), 3.68 (2H, m, C*H*N), 2.01 (2H, m, CH_3CHCH_3), 2.00–1.75 (4H, m, CH_2CHN), 1.35 (4H, m, CH_2CH$_2$CHN), 0.97 (6H, d, $J=7.0$ Hz, CH_3CHCH$_3$), 0.83 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR (CH_3OD) δ 177.2 (C=O), 77.6 (*C*HOH), 54.2 (*C*HN), 33.7 (CH_3CHCH_3), 33.5 (*C*H_2CHN), 26.1 (*C*H_2-CH$_2$CHN), 20.1 (*C*H_3CHCH$_3$), 17.2 (CH_3CH*C*H_3); FAB-MS *m*/*z* 315 (MH^+, 100%), 215 (21%), 141 (23%), 98 (42%). Anal. calcd for $C_{16}H_{30}N_2O_4$: C, 61.10; H, 9.62; N, 8.91. Found: C, 61.09; H, 9.74; N, 8.85.

2.1.9. (1*R*,2*R*)-(−)-*N*,*N*′-Bis(ethan-(1-(*R*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (13). The procedure described for amine **7** was followed using a solution of amide **12** (0.10 g, 0.32 mmol) in dry THF (5 mL). To this solution was added boron trifluoride etherate (0.16 mL, 1.27 mmol) and the solution was heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (3 mL, 2 M, 3.18 mmol) was then added carefully over a period of 15 min. The subsequent steps, work-up and isolation as described for amine **7** gave an oil that was purified by flash column chromatography (1:49 methanol/chloroform) to give amine **13** (90 mg, 99%) as a clear oil; $[\alpha]_D = -7.2$; ($c=0.31$, $CHCl_3$); IR (film) 3202, 1556, 1383 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.91 (2H, br, OH), 3.32 (2H, m, C*H*OH), 2.88 (4H, m, CH_2NH), 2.16 (2H, m, C*H*NH), 2.00–1.15 (8H, m, CH_2CH$_2$CHNH), 1.53 (2H, m, CH_3CHCH_3), 0.87 (6H, d, $J=7.0$ Hz, CH_3CHCH$_3$), 0.83 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$) δ 76.7 (*C*HOH), 63.8 (*C*H_2NH), 51.6 (*C*HNH), 32.8 (CH_3CHCH_3), 30.4 (*C*H_2CHNH), 25.5 (*C*H_2CH$_2$CHNH), 19.1

(CH_3CHCH_3), 18.7 (CH_3CHCH_3). HRMS (EI): calcd for $C_{16}H_{35}N_2O_2$ (MH^+) 287.2699, found 287.2710.

2.1.10. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(ethan-(1-(*R*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (14). Amino alcohol **13** (29 mg, 0.10 mmol) was dissolved in aqueous 37% formaldehyde (2.8 mL, 27 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (2.0 mL, 35 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was worked up and purified as described for amine **8** to give amine **14** (20 mg, 63%) as a clear oil; $[\alpha]_D=-42.8$ ($c=1$, $CHCl_3$); IR (film) 3119, 1503, 1204 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (2H, m, C*H*OH), 2.68 (2H, m, C*H*HN), 2.44 (2H, m, C*H*N), 2.26 (2H, m, CH*H*N), 2.23 (6H, s, NCH_3), 1.77–1.10 (8H, m, CH_2CH_2-CHN), 1.55 (2H, m, CH_3CHCH_3), 0.97 (6H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.89 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$) δ 72.1 (*C*HOH), 65.9 (CH_2N), 59.2 (*C*HN), 35.5 (NCH_3), 32.4 (CH_3CHCH_3), 25.5 (CH_2CHN), 24.9 (CH_2CH_2CHN), 18.8 (CH_3CHCH_3), 18.4 (CH_3CHCH_3). HRMS (EI): calcd for $C_{18}H_{39}N_2O_2$ (MH^+) 315.3012, found 315.3009.

2.1.11. (1*R*,2*R*)-(+)-*N*,*N*′-Bis-(1-hydroxy-1-(*R*)-isopropylacetamido)-*trans*-1,2-diaminocyclohexane (15). A solution of carbonyldiimidazole (3.14 g, 19.4 mmol) in dry THF was added to a stirred solution of (*R*)-(−)-2-hydroxy-3-methylbutyric acid (3.42 g, 29.0 mol) and 1-hydroxybenzotriazole (0.46 g, 2.7 mmol) in freshly distilled THF (70 mL) under an inert atmosphere at 20 °C, and the mixture was stirred for 1 h. A solution of (1*R*,2*R*)-(−)-*trans*-diaminocyclohexane (1.50 g, 13.1 mmol) in dry THF (5 mL) was then added dropwise. The mixture was stirred at 20 °C for 24 h followed by work-up and flash column chromatography as described for **12**. Evaporation of the appropriate fractions gave a white solid that was recrystallized from ethanol to give amide **15** as white needles (3.78 g, 92%), mp 210–212 °C; $[\alpha]_D=+51.7$ ($c=1$, MeOH); IR ($CHCl_3$) 3616, 2864, 1619 cm^{-1}; ^1H NMR (CD_3OD) δ 3.84 (2H, d, $J=3.5$ Hz, C*H*OH), 3.75 (2H, m, *C*HN), 2.15 (2H, m, CH_3CHCH_3), 2.00–1.40 (8H, m, CH_2CH_2CHN), 1.03 (6H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.87 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$) δ 177.0 (C=O), 77.2 (*C*HOH), 54.1 (*C*HN), 33.8 (CH_3CHCH_3), 33.3 (CH_2CHN), 26.2 (CH_2CH_2CHN), 20.1 (CH_3CHCH_3), 16.5 (CH_3CHCH_3). Anal. calcd for $C_{16}H_{30}N_2O_4$: C, 61.10; H, 9.62; N, 8.91. Found: C, 61.14; H, 9.74; N, 8.82.

2.1.12. (1*R*,2*R*)-(−)-*N*,*N*′-Bis(ethan-(1-(*S*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (16). The procedure described for amine **7** was followed using a solution of amide **15** (0.134 g, 0.43 mmol) in dry THF (5 mL). To this solution was added boron trifluoride etherate (0.22 mL, 1.71 mmol) and the solution was heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (1.17 mL, 2 M, 2.33 mmol) was then added *carefully* over 15 min. The subsequent steps, work-up and isolation as described for amine **7** (chromatography not required) gave amine **16** (79 mg, 65%) as a clear oil; $[\alpha]_D=-29.8$ ($c=0.04$, $CHCl_3$); IR (film) 3369, 3200, 1565, 1382 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.26 (2H, m, C*H*OH), 2.51 (4H, m, CH_2NH), 2.11 (2H, m, C*H*NH), 1.99–1.08 (8H, m, CH_2CH_2CHNH), 1.54 (2H, m, CH_3CHCH_3), 0.88 (6H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.83 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 74.8 (*C*HOH), 60.9 (CH_2NH), 49.9 (*C*HNH), 32.6 (CH_3CHCH_3), 32.4 (CH_2CHNH), 25.5 (CH_2CH_2CHNH), 19.0 (CH_3CHCH_3), 18.6 (CH_3CHCH_3). HRMS (EI): calcd for $C_{16}H_{35}N_2O_2$ (MH^+) 287.2699, found 287.2696.

2.1.13. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(ethan-(1-(*S*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (17). Amino alcohol **16** (46 mg, 0.16 mmol) was dissolved in aqueous 37% formaldehyde (2.8 mL, 27 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (3.6 mL, 63 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was worked up and purified as described for amine **8** to give amine **17** (36 mg, 74%) as a clear oil; $[\alpha]_D=-67.3$ ($c=1.8$, $CHCl_3$); IR (film) 3602, 3128, 1512, 1206 cm^{-1}; ^1H NMR ($CHCl_3$, 500 MHz) δ 3.39 (2H, m, C*H*OH), 2.40–2.29 (6H, m, CH_2N and CHN), 2.14 (6H, s, CH_3N), 1.97–1.80 (4H, m, C*H*HC*H*HCHN), 1.55 (2H, m, CH_3CHCH_3), 1.12 (4H, m, CH*H*CH*H*CHN), 0.89 (6H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.85 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 73.6 (*C*HOH), 64.8 (CH_2N), 54.8 (*C*HN), 32.3 (CH_3CHCH_3), 31.2 (NCH_3), 25.8 (CH_2CHN), 23.3 (CH_2CH_2CHN), 18.8 (CH_3CHCH_3), 18.5 (CH_3CHCH_3). HRMS (EI): calcd for $C_{18}H_{39}N_2O_2$ (MH^+) 315.3012, found 315.3016.

2.1.14. (1*R*,2*R*)-(+)-*N*-(α-Hydroxy-(*R*)-isopropylacetamido)-*trans*-1,2-diaminocyclohexane (18). Carbonyldiimidazole (3.10 g, **19** mmol) was added in portions to a stirred solution of (*R*)-(−)-2-hydroxy-3-methylbutyric acid (1.30 g, 11 mmol) and 1-hydroxybenzotriazole (0.30 g, 2.2 mmol) in anhydrous THF (45 mL) under an inert atmosphere at 20 °C, and the mixture was stirred for 1 h. After this time, a solution of (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (2.50 g, 22 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise over 15 min. The mixture was stirred at 20 °C for 16 h followed by evaporation of the solvent and acidification of the residue with hydrochloric acid (1 M) to pH 2. The aqueous layer was washed with ethyl acetate (3×30 mL) and the combined organic layers discarded. The remaining aqueous layer was then made alkaline to pH 11 with aqueous sodium hydroxide (1 M) and extracted with ethyl acetate (3× 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a white solid which was recrystallized from isopropanol to give **18** as white plates (0.14 g, 4%), mp 127–128 °C; $[\alpha]_D=+83.3$ ($c=0.5$, $CHCl_3$); IR (film) 3520 (br), 1683, 1469, 1183 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.64 (1H, m, NH), 3.96 (1H, d, $J=4.0$ Hz, C*H*OH), 3.64 (1H, m, *C*HNHCO), 2.99 (3H, br, OH and NH_2), 2.49 (1H, m, *C*HNH$_2$), 2.13 (1H, m, CH_3CHCH_3), 1.95–1.35 (8H, m, CH_2CH_2CHN), 1.04 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.89 (3H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5 (C=O), 76.3 (*C*HOH), 55.4 (*C*HNH), 54.3 (*C*HNH$_2$), 35.7 (CH_2-CHNHCO), 32.7 (CH_2CHNH_2), 31.6 (CH_3CHCH_3), 25.0 (CH_2CHN), 24.9 (CH_2CH_2CHN), 19.3 (CH_3CHCH_3), 15.8 (CH_3CHCH_3). FAB-MS *m*/*z* 215 (MH^+, 100%). HRMS (EI): calcd for $C_{11}H_{23}N_2O_2$ (MH^+) 215.1760, found 215.1761.

2.1.15. (1*R*,2*R*)-(+)-*N*-(α-Hydroxy-(*R*)-isopropylacetamido)-*N*′-(α-hydroxy-(*S*)-isopropylacetamido)-*trans*-1,2-diaminocyclohexane (19). A solution of 1,1′-carbonyldiimidazole (36 mg, 0.22 mmol) in dry tetrahydrofuran (2 mL) was added via a pressure-equilibrating dropping funnel to a solution of (*S*)-(+)-2-hydroxy-3-methylbutyric acid (26 mg, 0.22 mmol) and 1-hydroxybenzotriazole hydrate (30 mg, 0.22 mmol) in dry tetrahydrofuran (10 mL) under an inert atmosphere at 20 °C, and the mixture was stirred for 1.5 h. A solution of amide **18** (40 mg, 0.19 mmol) in dry THF (2 mL) was then added dropwise via a gas-tight syringe and the resulting solution stirred for 16 h under an inert atmosphere at 20 °C. The solution was then acidified with hydrochloric acid (20 mL, 1 M) and the aqueous layer extracted with ethyl acetate (3× 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give an off-white solid that was purified *via* flash chromatography (4:1 ethyl acetate/40–60 °C petroleum ether) to give amide **19** as a white solid (25 mg, 42%), mp 182 °C; $[\alpha]_D = +5.3$ ($c=0.5$, MeOH); IR ($CHCl_3$) 3601 (br), 1689, 1694, 1465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (1H, br, CHN*H*), 7.02 (1H, br, CHN*H*), 3.92 (1H, d, $J=4.5$ Hz, C*H*OH), 3.77 (1H, d, $J=4.5$ Hz, C*H*OH), 3.75 (2H, m, C*H*NH), 2.12 (1H, m, CH_3CHCH_3), 1.91 (1H, m, CH_3CHCH_3), 1.89–1.35 (8H, m, CH_2CH_2CHN), 0.99 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.92 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.79 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.77 (3H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8 (C=O), 174.6 (C=O), 76.7 (*C*HOH), 76.0 (*C*HOH), 53.2 (*C*HNH), 52.7 (*C*HNH), 32.3 (CH_2CHNH), 32.2 (CH_2CHNH), 31.8 (CH_3CHCH_3), 31.4 (CH_3CHCH_3), 24.8 (CH_2CH_2CHN), 24.7 (CH_2CH_2CHN), 19.7 (CH_3CHCH_3), 19.4 (CH_3CHCH_3), 16.2 (CH_3CHCH_3), 15.8 (CH_3CHCH_3). HRMS (EI): calcd for $C_{16}H_{31}N_2O_4$ (MH^+) 315.2284, found 315.2273.

2.1.16. (1*R*,2*R*)-(−)-*N*-(Ethan-(1-(*S*)-isopropyl)-1-ol)-*N*′-(ethan-(1-(*R*)-isopropyl)-1-ol)-*trans*-1,2-diamino-cyclohexane (20). The procedure described for amine **7** was followed using a solution of amide **19** (22 mg, 0.07 mmol) in dry THF (2 mL). To this solution was added boron trifluoride etherate (0.04 mL, 0.27 mmol) and the solution was heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (1.17 mL, 2 M, 2.33 mmol) was then added *carefully* over 15 min. The subsequent steps, work-up and isolation as described for amine **7** (chromatography not required) gave amine **20** (8 mg, 40%) as a clear oil; $[\alpha]_D = -35.2$ ($c=0.4$, $CHCl_3$); IR (film) 3321 (br), 1566, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.27 (2H, m, C*H*OH), 2.85–2.60 (2H, m, CH_2NH), 2.50–2.25 (2H, m, CH_2NH), 2.10 (2H, m, C*H*NH), 1.56 (2H, m, CH_3CHCH_3), 2.00–1.15 (8H, m, CH_2CH_2CHNH), 0.90–0.82 (12H, m, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 76.3 (*C*HOH), 74.8 (*C*HOH), 61.4 (CH_2NH), 59.7 (CH_2NH), 51.1 (*C*HNH), 49.8 (*C*HNH), 32.6 (CH_2CHNH), 32.3 (CH_2CHNH), 31.3 (CH_3CHCH_3), 31.2 (CH_3CHCH_3), 25.4 (CH_2CH_2CHNH), 19.1 (CH_3CHCH_3), 19.0 (CH_3CHCH_3), 18.7 (CH_3CHCH_3), 18.6 (CH_3CHCH_3). HRMS (EI): calcd for $C_{16}H_{35}N_2O_2$ (MH^+) 287.2699, found 287.2694.

2.1.17. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*-(ethan-(1-(*S*)-isopropyl)-1-ol)-*N*′-(ethan-(1-(*R*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (21). Amino alcohol **20** (50 mg, 0.17 mmol) was dissolved in aqueous 37% formaldehyde (1.0 mL, 9.6 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (1 mL, 17.5 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was allowed to cool to 20 °C and made alkaline (pH 12) by addition of sodium hydroxide (2 M) with constant cooling. The aqueous layer was extracted with diethyl ether (2×25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give amine **21** (30 mg, 55%) as a clear oil; $[\alpha]_D = -18.2$ ($c=0.15$, $CHCl_3$); IR (film) 3482 (br), 1399, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.40 (2H, m, C*H*OH), 2.50–2.25 (6H, m, CH_2N and C*H*N), 2.15 (6H, s, CH_3N), 1.95–1.25 (8H, m, CH_2CH_2CHNH), 1.60 (2H, m, CH_3CHCH_3), 0.90 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.88 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.87 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.85 (3H, d, $J=7.0$ Hz, CH_3CHCH_3). HRMS (EI): calcd for $C_{18}H_{39}N_2O_2$ (MH^+) 315.3012, found 315.3025.

2.1.18. (1*R*,2*R*)-*N*,*N*′-Bis((3*S*,4*S*)-4-hydroxycyclohexyl)-*trans*-1,2-diaminocyclohexane (22). To a stirred solution of (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (4.80 g, 42.0 mmol) in anhydrous ethanol (100 mL) under an inert atmosphere at 20 °C was added cyclohexene oxide (17.3 mL, 171 mmol) *via* a pressure-equilibrated dropping funnel over a period of 20 min. Upon complete addition, the mixture was heated at reflux for 16 h. After this time, the pale yellow solution was allowed to cool to 20 °C whereupon the solvent was evaporated to give a brown oil that was acidified to pH 2 with 2 M hydrochloric acid and the aqueous layer extracted with chloroform (2×50 mL) which was discarded. The aqueous layer was then basified to pH 11 with 2 M aqueous sodium hydroxide and the aqueous layer was again extracted with chloroform (2×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The resulting yellow-orange oil was subjected to purification by flash column chromatography, initially with methanol/chloroform (1: 4 v/v), then followed by methanol/chloroform (1:19 v/v) to give a clear oil that was dissolved in hot petroleum ether (40–60 °C). On allowing to cool, small glassy needles deposited which were isolated and recrystallised from cyclohexane to give **22** (3.90 g, 30%), as small glassy needles, mp 129–130 °C; $[\alpha]_D = +11.2$ (*c* 1, $CHCl_3$); IR (film) ν_{max} 3126, 2926, 2854, 1446, 1369, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.63 (2H, br, OH), 3.49 (2H, m, C_1HOH), 2.43 (2H, m, $C_{1'}HNH$), 2.29 (2H, m, C_2HNH), 2.01 (2H, m), 1.91 (2H, m), 1.67 (6H, m), 1.64 (2H, m), 1.30–1.18 (10H, m), 0.99 (2H, m), 0.65 (2H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 77.46, 65.58, 65.44, 35.25, 33.19, 32.57, 25.59, 25.46, 24.33. HRMS calcd for $C_{18}H_{35}N_2O_2$ (MH^+) 311.2699. Found: 311.2699. FAB MS (%) 311 (MH^+, 100), 196 (52), 115 (42). Anal. calcd for $C_{18}H_{34}N_2O_2$ C, 69.62; H, 11.04; N, 9.03. Found: C, 69.42; H, 11.14; N, 8.93.

2.1.19. (1*R*,2*R*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis((3*S*,4*S*)-4-hydroxycyclohexyl)-*trans*-1,2-diaminocyclohexane (23). Diamine **22** (0.556 g, 1.80 mmol) was dissolved in formaldehyde (37% by wt., 4.0 mmol, 6.0 mL) and formic acid (96% v/v, 0.22 mol, 7.8 mL), and the resulting solution heated to 90 °C. Sodium formate (7.40 mmol, 0.50 g) was then added in one portion and the resulting solution was

stirred at 90 °C for 16 h. After this time, the solution was cooled to 20 °C and then basified, with cooling, to pH 12 with 2 M aqueous sodium hydroxide. The aqueous layer was washed with diethyl ether (3×20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a clear oil (0.58 g, 95%) that required no further purification; $[\alpha]_D = +42.2$ (*c* 0.53, $CHCl_3$); IR (film) ν_{max} 3401, 1454, 1204, 1061 cm^{-1}; ^1H NMR δ ($CDCl_3$, 300 MHz) δ 3.23 (2H, m, C_1HOH), 2.45 (2H, m, $C_{1'}HNH$), 2.30 (2H, m, C_2HNH), 2.09 (6H, s, CH_3), 2.02 (2H, m), 1.86 (2H, m), 1.75–1.63 (8H, m), 1.64–1.18 (12H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 72.59, 67.77, 66.55, 34.00, 29.31, 28.78, 27.80, 26.57, 26.33, 24.87. HRMS calcd for $C_{20}H_{38}N_2O_2$ (MH^+) 339.3012. Found: 339.3009. FAB MS (%) 339 (MH^+, 100), 210 (22), 112 (19).

2.1.20. (*R*)- or (*S*)-1-Phenylpropan-1-ol (25a). *Representative procedure*. Ligand **22** (0.06 g, 0.20 mmol, 10 mol%) was dissolved with stirring in freshly distilled toluene (9 mL) under an atmosphere of nitrogen at 20 °C. Freshly distilled benzaldehyde (0.20 mL, 2.0 mmol) was then injected by syringe and the resulting solution stirred for 15 min. The mixture was then cooled to −30 °C (cooling bath) and a solution of diethylzinc in toluene (3.5 mL, 1.1 M, 4 mmol) was injected by syringe, ensuring that the tip of the needle was below the surface of the solution. The mixture was stirred at −30 °C for 16 h. Aqueous hydrochloric acid (10 mL, 1 M) was then added slowly (CAUTION: vigorous reaction). The aqueous layer was extracted with diethyl ether (2×20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a turbid oil that was purified by flash column chromatography (3:17 ethyl acetate: 40–60 °C petroleum ether) to give **25a** (0.135 mg, 50%) as a clear oil; ^1H NMR ($CDCl_3$) δ 7.32 (5H, m, phenyl), 4.56 (1H, t, $J=7.5$ Hz, C*H*OH), 2.43 (1H, br, OH), 1.78 (2H, m, CH_2), 1.43 (3H, t, $J=7.5$ Hz, CH_3). Enantiomeric excess was determined on a Chiralcel OD column (99:1 *i*-PrOH/hexane; 1 mL min^{-1} t_R 20 min, t_S 29 min).

2.1.21. (*R*)- or (*S*)-1-Phenylpent-1-en-3-ol (25b). ^1H NMR ($CDCl_3$) δ 7.12 (5H, m, aryl), 6.40 (1H, d, $J=16.0$ Hz, aryl–C*H*=CH), 5.92 (1H, dd, $J=16.0$, 7.0 Hz, aryl–CH=C*H*), 4.08 (1H, m, C*H*OH), 1.80 (1H, br, OH), 1.51 (2H, m, CH_2), 0.82 (3H, t, $J=7.5$ Hz, CH_3). Enantiomeric excess was determined on a Chiralcel OD column (5:95 *i*-PrOH/hexane, 1 mL min^{-1}; t_R 12 min, t_S 19 min).

2.1.22. (*R*)- or (*S*)-1-*p*-Methoxyphenylpropan-1-ol (25c). ^1H NMR ($CDCl_3$) δ 7.15–6.80 (4H, m, aryl), 4.71 (1H, t, $J=$ 7.0 Hz, C*H*OH), 3.79 (3H, s, CH_3), 2.48 (1H, br, OH), 1.85 (2H, m, CH_2), 0.92 (3H, t, $J=7.0$ Hz, CH_3). ee was determined on a Chiralcel OD column (2.5: 97.5 *i*-PrOH/hexane; 0.7 mL min^{-1}; t_R 33 min, t_S 40 min).

2.1.23. (*R*)- or (*S*)-1-(α-Naphthyl)-1-propanol (25d). ^1H NMR ($CDCl_3$) δ 7.72 (7H, m, aryl), 5.35 (1H, t, $J=7.0$ Hz, C*H*OH), 2.31 (1H, br, OH), 1.99 (2H, m, CH_2), 1.02 (3H, t, $J=7.0$ Hz, CH_3). Enantiomeric excess was determined on a Chiralcel OD column (4:96 *i*-PrOH/hexane, 0.5 mL min^{-1}; t_R 31 min, t_S 27 min).

2.1.24. (*R*)- or (*S*)-Ethylchalcone 27. *Typical procedure*. Amino alcohol **8** (30.6 mg, 0.08 mmol, 8 mol%) and nickel acetonylacetonate (18 mg, 0.07 mmol, 7 mol%) in freshly distilled acetonitrile (2 mL) were heated at reflux under an atmosphere of nitrogen with stirring for 1 h. The solution was allowed to cool to 20 °C and a solution of chalcone (208 mg, 1.0 mmol) in freshly distilled acetonitrile (5 mL) was added. The mixture was cooled to −35 °C (cooling bath) and a solution of diethylzinc in toluene (1.36 mL, 1.1 M, 1.5 mmol) was added cautiously whereupon an immediate colour change from green to dark brown occurred. After stirring at −30 °C for 16 h, the solution was poured into hydrochloric acid (15 mL, 3 M) and the aqueous layer extracted with dichloromethane (3×20 mL). The combined organic layers were shaken with brine (25 mL) and then dried ($MgSO_4$), filtered and evaporated to give crude **27** which was purified by flash column chromatography; ^1H NMR ($CDCl_3$) δ 7.93 (2H, m, *o*-aryl ketone), 7.52 (3H, m, *m* and *p*-aryl ketone), 7.25 (5H, m, *phenyl*-alkyl), 3.31 (3H, m, C(O)CH_2CH), 1.75 (2H, m, CH_2CH_3), 0.88 (3H, t, $J=7.0$ Hz, CH_2CH_3). Enantiomeric excess was determined on a Chiralcel OD column (0.2: 99.8, *i*-PrOH/hexane, 1 mL min^{-1}; t_R 23 min, t_S 18 min).

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