Asymmetric Synthesis of 1,2-Diamines by the Addition of Allylic Zinc and Magnesium Reagents to *N*,*N*'-Bis[(*S*)-1-phenylethyl)]ethanediimine

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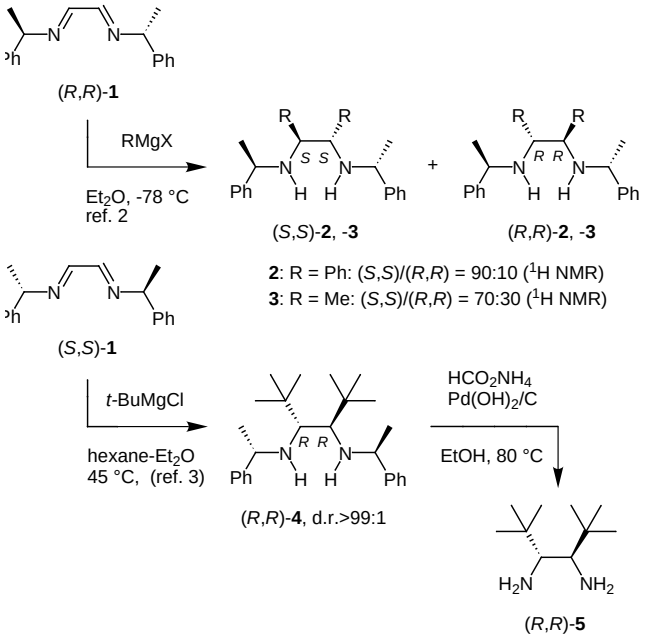
Abstract: The diimine prepared by condensation of glyoxal trimer dihydrate with (*S*)-1-phenylethylamine underwent double addition of allylic zinc compounds (2-butenyl-, 2,4-pentadienyl-, 2-methyl-2-propenylzinc bromide) in THF generally at −78 °C, with allylic inversion. The newly formed stereocentres adjacent to the nitrogen atoms had prevalently the *R* configuration. Removal of the auxiliary from the secondary 1,2-diamines with concomitant hydrogenation of the C=C double bonds afforded the primary 1,2-diamines. The reaction with 3-methyl-2-butenylzinc bromide gave almost exclusively the α-amino imine from which the α-aminoaldehyde was obtained by hydrolysis. On the other hand, 3-methyl-2-butenylmagnesium chloride reacted at 0−20 °C to give the diamine with linear-chain substituents, owing to the reversibility of the organometallic addition.

Key words: allylations, amines, asymmetric synthesis, Grignard reactions, zinc

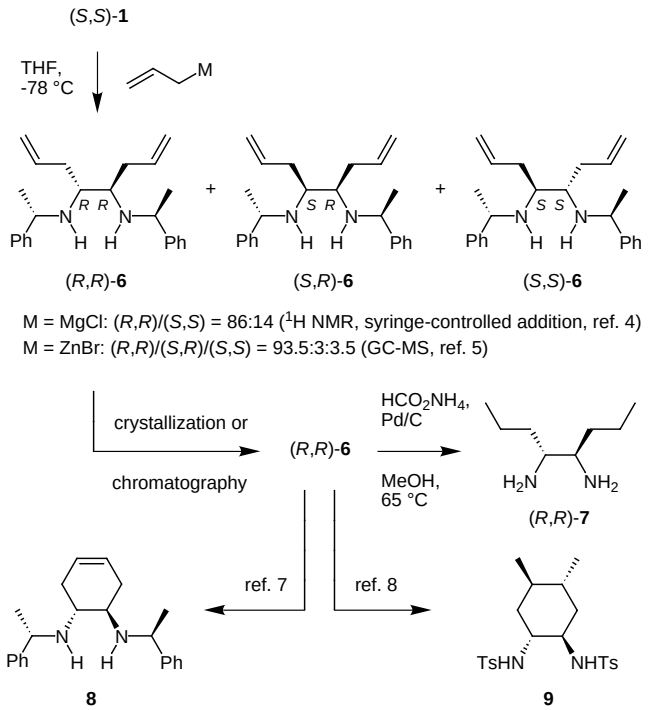


Scheme 1

The double addition of organometallic reagents to enantiomerically pure 1,2-diimines derived from glyoxal is an appealing route to C_2 symmetric 1,2-diamines.[1] The enantiomers of 1-phenylethylamine have been generally used as the chiral auxiliaries in these reactions,[2-5] but the diastereoselective addition of MeLi-$CeCl_3$ reagent to the bis-SAMP-hydrazone has been reported (yield 50%, d.e. 98%).[6] It has been claimed that the addition of Grignard reagents and alkyllithiums to the diimine (*R*,*R*)-**1** in tetrahydrofuran (THF) gave a complex mixture of products, and the reaction with phenylmagnesium chloride in diethyl ether afforded only two diastereomers of the 1,2-diamine **2** with a diastereomeric ratio (d.r.) = 90:10 (Scheme 1). The *S* configuration of the newly formed stereocenters of the main diastereomer **2** was determined by X-ray crystallographic analysis.[2] Under the same conditions, methylmagnesium bromide afforded the diamine **3**, presumably with the same sense of asymmetric induction, but with lower diastereoselectivity (d.r. = 70:30).[2]

More recently, the preparation of (*R*,*R*)-3,4-diamino-2,2,5,5-tetramethylhexane ((*R*,*R*)-**5**) has been described,[3] involving the addition of the diimine (*S*,*S*)-**1** to *tert*-butylmagnesium chloride in hexane/ether mixture at 45 °C to give almost exclusively the secondary diamine (*R*,*R*)-**4** (for sake of simplicity, only the configuration of the newly formed stereocentres of the secondary diamines are indicated), and the subsequent hydrogenolysis step (Scheme 1). The diastereoselectivity therein obtained was surprising, considering the relatively high temperature at which the reaction was performed and the low diastereoselectivities generally observed in the additions of *tert*-butyl organometallic reagents to chiral bidentate imines derived from 2-pyridinaldehyde.[7]

Moreover, it was described that the carefully controlled addition of allylmagnesium chloride to either (*R*,*R*)- or (*S*,*S*)-**1** in THF at −78 °C gave mixtures of two diastereomeric homoallylic diamines **6** with d.r. = 86:14 (Scheme 2).[4] We successively demonstrated that the addition to (*S*,*S*)-**1** afforded mainly (*R*,*R*)-**6** in that reaction, and furthermore improved the diastereoselectivity by using allylzinc bromide. In fact, we obtained the three diastereomers with d.r. = 93.5:3:3.5, and then prepared optically pure (*R*,*R*)-4,5-diaminooctane ((*R*,*R*)-**7**) by removal of the auxiliary.[5] Moreover, we have recently reported the transition metal-catalyzed cyclization reactions of the diamine (*R*,*R*)-**6** to give 1,2-diamino-4-cyclohexene and 1,2-diamino-4,5-dimethylcyclohexane derivatives **8**[8] and **9**,[9] respectively.

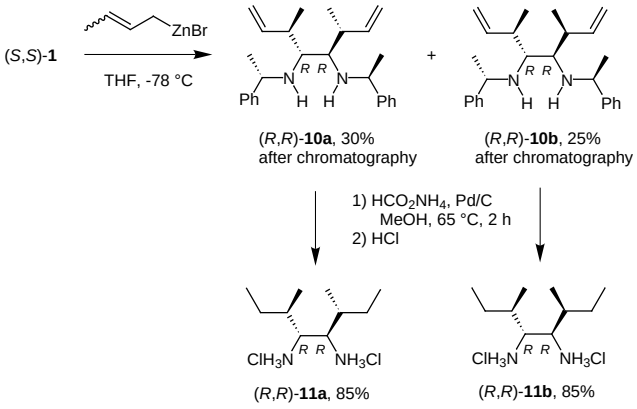


Scheme 2

We did not succeed in further improving the diastereoselectivity in the preparation of the diamine **6** by using (allyl)$_2$Zn-MgCl$_2$, (allyl)Et$_2$ZnMgCl,[5] allylPbBr-MBrCl,[10,11] (allyl)$_3$Al$_2$Br$_3$,[10] and (allyl)Bu$_3$Sn-TiCl$_4$. Only with allylSnCl$_2$I[11] we achieved a high diastereoselectivity (d.r. = 95:5), but only 80% conversion of the diimine was observed by GC−MS analysis despite the use of 5 molar equivalents of allylmetal compound, and this caused the difficult purification of the product.

Since allylzinc bromide appeared to be the reagent of choice, we successively investigated the reactivity, regioselectivity and diastereoselectivity of substituted allylzinc bromides, aiming at the same time to prepare novel 1,2-diamines having sterically demanding alkyl substituents on the chain connecting the nitrogen atoms. Here we report the outcomes of the addition reactions of the imine (*S*,*S*)-**1** with 2-butenylzinc bromide,[12] 2,4-pentadienylzinc bromide,[13] 2-methyl-2-propenylzinc bromide[12] and 3-methyl-2-butenylzinc bromide.[14] All the reagents were prepared by the direct reaction of the corresponding allylic bromide with zinc powder in anhydrous THF in nitrogen atmosphere. Alternatively, since the preparation of 2,4-pentadienylzinc bromide was not readily reproducible owing to Wurtz coupling reaction,[13c] we prepared 2,4-pentadienylzinc chloride via metallation of 1,4-pentadiene with *n*-BuLi in hexane/Et$_2$O mixture,[15] followed by transmetallation with the ZnCl$_2$-TMEDA complex.[16]

Crotylzinc bromide quickly reacted at −78 °C in THF to give the diamine **10** in high yield by a double addition process with allylic rearrangement (Scheme 3). Since four stereocentres were formed in this reaction, nine diastereomers could be obtained, and all were detected by GC−MS analysis of the crude reaction mixture. However, two diastereomers were highly predominant, accounting for 90% of the whole mixture. We separated them by column chromatography and observed by ^{1}H and ^{13}C NMR spectroscopy that the first eluted isomer had C$_2$-symmetry while the second one had C$_1$-symmetry. For both compounds the (*R*,*R*)-configuration of the newly formed stereocentres at C4 and C5 (adjacent to the nitrogen atoms) was supposed by analogy with the known asymmetric induction observed in the formation of the diamine **6**. The complete assignment of the stereochemistry of the C$_2$-symmetric diamine (*R*,*R*)-**10a** was achieved by the X-ray spectroscopic analysis of the corresponding bis-hydrochloride (*R*,*R*)-**10a**·**2HCl**. In fact, the structure depicted in Figure 1 (see Supporting Material) shows the *R* configuration of C4 and C5 and the *S* configuration of C3 and C6. The structure is analogous to that of (*R*,*R*)-**6**, described in our previous work.[5] The molecular symmetry is C$_2$ with a staggered arrangement of the phenyl and allyl groups with respect to the diazaoctane chain.

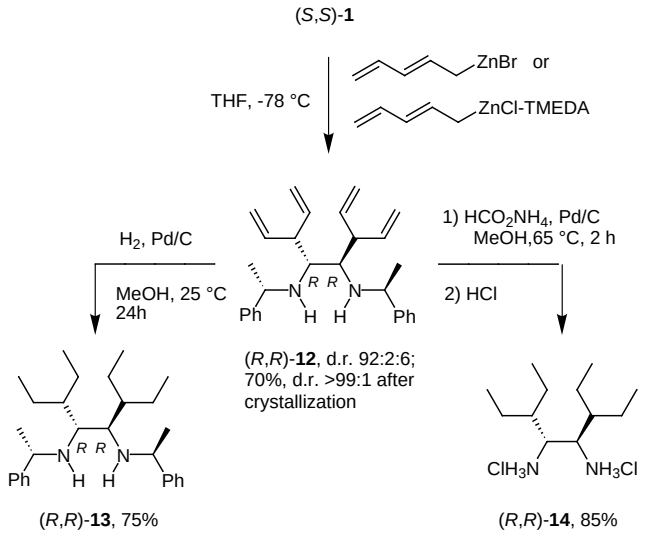


Scheme 3

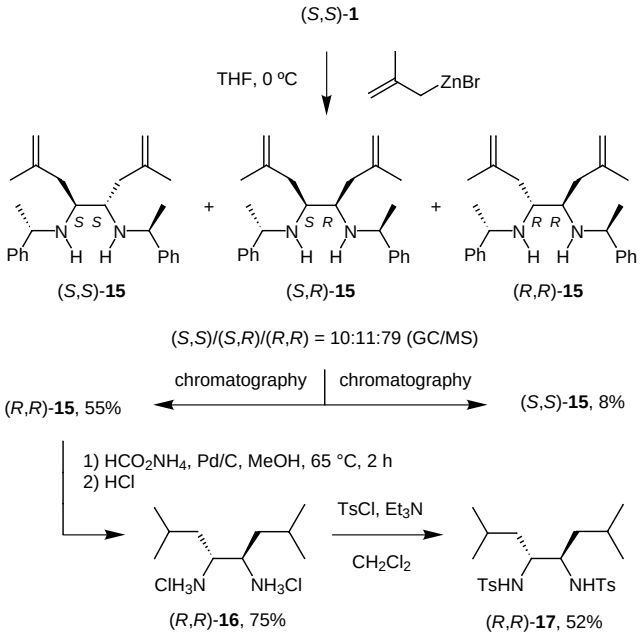
Suitable crystals were not obtained for the other isolated diastereomer, but we are confident that it has the same *R* configuration of C4 and C5, consistent with the degree of diastereoselectivity demonstrated in the previous and following reactions involving allylic zinc reagents. This implies that the same auxiliary-induced and substrate-induced diastereoselectivities occurred in the addition of crotylzinc bromide and only the simple (*syn*/*anti*) diastereoselectivity was not controlled, being dependent on the geometry of the C = C double bond in the organometallic reagent.[17] Hence, we presume that the other diastereomer has the structure depicted for (*R*,*R*)-**10b**, differing from (*R*,*R*)-**10a** only for the configuration of the stereocentres at C3 and C6. After hydrogenolysis and concomitant hydrogenation of the C=C double bonds of (*R*,*R*)-**10a,b**, the bis-hydrochlorides of the saturated primary diamines (*R*,*R*)-**11a**,**b** were obtained, both having positive values of optical activity.

It is noteworthy that 2,4-pentadienylzinc bromide or chloride reacted exclusively at C3 of the pentadienyl moiety to give the branched amine with high yield and diastereoselectivity (Scheme 4). Only reactions with carbonyl compounds were previously described,[13] and the ratio of branched to linear addition products was found to be dependent on the steric and electronic factors of the carbonyl substituent(s) as well as the solvent and the temperature. In our reaction, the main diastereomer (*R*,*R*)-**12** accounted for 92% of the mixture (GC−MS analysis) and was easily obtained pure with 75% yield by chromatography, or with 70% yield by crystallization from methanol. The secondary diamine (*R*,*R*)-**12** was in part submitted to hydrogenation on Pd/C in MeOH to obtain the saturated secondary diamine (*R*,*R*)-**13**, and in part converted to the primary diamine (*R*,*R*)-**14** by hydrogenation-hydrogenolysis using ammonium formate and Pd/C in refluxing MeOH. The positive sign of the optical rotation power of the dihydrochloride of the diamine (*R*,*R*)-**14** demonstrated the assigned configuration by comparison with the dihydrochloride of (4*R*,5*R*)-diaminooctane (*R*,*R*)-**7**[5] and (*R*,*R*)-**11a.**

The addition of 2-methyl-2-propenylzinc bromide to (*S*,*S*)-**1** occurred only at 0 °C and produced the three diastereomers of the diamine **15** with a ratio 10:11:79, in the order of elution by GC−MS analysis, suggesting the opposite configuration of the newly formed stereocenters (Scheme 5). Instead, the prevalent diastereomer was separated by column chromatography and then converted to the saturated primary diamine, whose dihydrochloride had a positive value of optical rotation power, and consequently the *R* configuration of the newly formed stereocenters as depicted for (*R*,*R*)-**16**. This compound was then converted to the ditosylamide (*R*,*R*)-**17**, which crystallized nicely from MeOH. Two independent molecules are present in the asymmetric unit, differing only in the value of the N1-C1-C2-N2 torsion angle (174.07° and 176.55° for the two molecules, respectively). One of the two minor diastereomers of the secondary diamine (*S*,*S*)-**15** was isolated by column chromatography, but was not converted to the corresponding primary diamine.



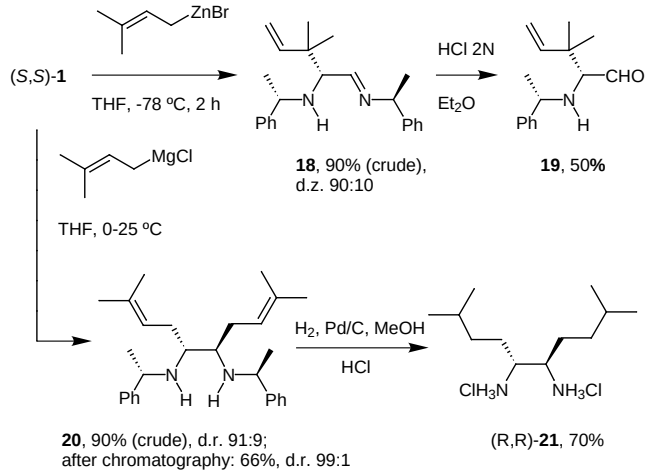
Scheme 4



Scheme 5

The reaction of the diimine (*S*,*S*)-**1** with one equivalent of 3-methyl-2-butenylzinc bromide occurred even at −78 °C (Scheme 6) and afforded the mono-addition product, i.e. the α-amino imine **18**, presumably having the *R* configuration of the newly formed stereocenter in the main diastereomer (d.r. = 90:10 by GC and ^{1}H NMR analysis). On the other hand, when the reaction was performed with 2.5 equivalents of the reagent, one product coming from a double addition process was formed in trace amounts. The yield, however, did not increase by raising the temperature to 25 °C, as observed by GC−MS analysis of the reaction mixture. Moreover, by heating the reaction mixture at reflux a complex mixture of diastereomeric bis-adducts was formed. The imine function of the product **18** underwent hydrolysis during the chromatographic purification on SiO_2 column and the optically pure α-amino aldehyde **19** was isolated with 45−50% yield. It should be considered that imine **18** and aldehyde **19** are promising intermediates for the preparation of asymmetrically substituted 1,2-diamines and 1,2-aminoalcohols by nucleophilic additions to the unsaturated functional groups.

Differing from the corresponding zinc reagent, 3-methyl-2-butenylmagnesium chloride added to the diimine (*S*,*S*)-**1** at 0−25 °C to give the double addition product **20** with high diastereoselectivity (d.r. = 91:9 by GC−MS analysis). Both the diastereomers had linear alkyl substituents, as shown by ^{1}H NMR analysis of the crude product.



Scheme 6

However, the course of the reaction performed in the temperature range −78 to 25 °C could be followed by GC–MS analysis. In this way, we demonstrated the intermediacy of the branched α-amino imine **18** and a number of intermediate double addition products, one of which had the same retention time as that of the minor product previously detected in the organozinc reaction. We can reasonably assume that the linear double addition product **20** was formed through a series of *retro*-addition and re-addition processes. The secondary diamine **20** was then converted to the bis-hydrochloride of the primary diamine (*R*,*R*)-**21** by routine procedure. In this case H_2 rather than HCO_2NH_4 was used as the reducing agent, and the expected *R* configuration was confirmed by the positive value of the optical rotation power.

General methods and the procedure for the preparation of the imine were described previously.[5] The allylic zinc reagents were prepared from the corresponding allylic bromides according to the described procedures,[12-14] and the clear solutions were taken by a syringe after decantation of unreacted zinc powder.

Preparation of 2,4-Pentadienylzinc Chloride-TMEDA Complex from Penta-1,4-diene

Penta-2,4-dienyllithium was prepared according to the reported procedure.[15] Penta-1,4-diene (3.6 mL, 3.5 mmol), pre cooled at 0 °C owing to its volatility, was added slowly to a solution of BuLi (1.6 M in hexane, 18.8 mL, 30 mmol) in THF (10 mL) at −78 °C. The temperature was allowed to rise to 0 °C and two phases were formed. THF (3 mL) and $ZnCl_2$-TMEDA complex (7.57 g, 30 mmol) were added at the same temperature, and the mixture was stirred by a magnetic bar for 1 h. The orange colour of the organic phase became yellow and a white precipitate was formed. The clear solution was taken up by a syringe after decantation.

Reactions of the Imine (*S*,*S*)-1 with Allylic Zinc Reagents. Preparation of Secondary 1,2-Diamines

A solution of the allylic zinc reagent (30 mmol) was added slowly (15 min) to a solution of the imine (2.65 g, 10 mmol) in THF (30 mL) at −78 °C (0 °C for **15**). The mixture was stirred for 1.5–3 h, during which the progress of the reaction was followed by TLC or GC–MS analysis. Then the mixture was quenched with 20 mL of a 1:1 mixture of 1 M NH_4Cl and 30% NaOH. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The collected organic layers were dried (Na_2SO_4) and concentrated at reduced pressure. The residue was chromatographed on a SiO_2 column at medium pressure eluting with cyclohexane/Et_2O mixtures. The yields of the pure compounds reported below refer to chromatographed compounds. Alternatively, the products were isolated with slightly lower yields when the crude reaction products were extracted with MeOH and allowed to crystallize.

3,6-Dimethyl-4(*R*),5(*R*)-di-[1(*S*)-phenylethylamino]octa-1,7-diene [(*R*,*R*)-10a,b]

These compounds were isolated by column chromatography on SiO_2 column eluting with cyclohexane/Et_2O (95:5), in the following order of elution.

(*R*,*R*)-**10a** (1.50 g, 30%, **10a**:**10b** = 93:7); $[\alpha]^{20}_D$ −57.4 (*c* 1.32, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.40–7.20 (m, 10H, Ph), 5.65–5.45 (m, 2H, C*H* = CH_2), 4.85–4.60 (m, 4H, CH = C*H*$_2$), 3.76 (q, 2H, PhC*H*Me), 2.30–2.15 (m, 4H, NC*H*C*H*Me), 1.5 (broad, 2H, NH), 1.25 (d, 6H, *J* = 7.0 Hz, PhCH*Me*), 0.71 (d, 6H, *J* = 7.0 Hz, CHCH*Me*).

MS: *m/z* (%) = 105 (100) [PhCHMe], 188 (60) [M^+/2], 84 (45), 321 (11) [$M^+-C_4H_7$], 79 (11), 77 (8), 161 (7), 266 (3, $M^+-2\ C_4H_7$).

The diamine (*R*,*R*)-**10a** was converted to the bis-hydrochloride (*R*,*R*)-**10a**·**2HCl**, which nicely crystallized from MeOH): mp 208 °C (dec.); $[\alpha]^{20}_D$ −6 (*c* 0.35, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.1, 9.9 and 1.6 (br, 4H, NH_2), 7.78 (m, 4H, Ph), 7.48 (m, 6H, Ph), 4.88 (m, 2H, C*H* = CH_2), 4.53 (d, 2H, *J* = 10.2 Hz, CH = C*H*$_2$), 4.43 (q, 2H, NC*H*Me), 3.51 (d, 2H, *J* = 17.4 Hz, CH = C*H*$_2$), 2.76 (m, 4H, NC*H*C*H*Me), 2.04 (d, 6H, *J* = 6.6 Hz, NCH*Me*), 1.33 (d, 6H, *J* = 5.1 Hz, NCHCH*Me*).

(*R*,*R*)-**10b** (1.25 g, 25%, **10b**:**10a** 93:7); $[\alpha]_D^{20}$ −44.8 (*c* 1.23, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.35–7.15 (m, 10H, Ph), 5.65–5.43 (m, 2H, C*H* = CH_2), 4.85–4.50 (m, 4H, CH = C*H*$_2$), 3.76 and 3.68 (2 q, 2H, PhC*H*Me), 2.25–2.10 (m, 4H, NC*H*C*H*Me), 1.50 (br, 2H, NH), 1.25 and 1.22 (2 d, 6H, *J* = 7.0 Hz, PhCH*Me*), 0.75 and 0.63 (2 d, 6H, *J* = 7.0 Hz, CHCH*Me*).

3,6-Diethenyl-4(*R*),5(*R*)-di-[1(*S*)-phenylethylamino]octa-1,7-diene [(*R*,*R*)-12]

Yield: 2.80 g (70%) after crystallization from MeOH; mp 59 °C; $[\alpha]^{20}_D$ −2.5 (*c* 2.24, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.30–7.13 (m, 10H, Ph), 5.69–5.55 (m, 2H, C*H* = CH_2), 5.40–5.27 (m, 2H, C*H* = CH_2), 4.88–4.68 (m, 6H, CH = C*H*$_2$), 4.27–4.18 (m, 2H, CH = C*H*$_2$), 3.67 (q, 2H, C*H*Me), 2.70 (q, 2H, NCHC*H*), 2.19 (d, 2H, *J* = 6.8 Hz, NC*H*CH), 1.48 (br, 2H, NH), 1.22 (d, 6H, *J* = 6.6 Hz, CH*Me*).

^{13}C NMR (300 MHz, $CDCl_3$): δ = 146.1, 139.6, 139.1, 128.0, 127.8, 126.8, 115.5, 114.6, 57.5, 56.2, 52.3, 24.2.

MS: *m/z* (%) = 105 (100) [PhCHMe], 200 (26) [M^+/2], 266 (18), 79 (17), 161 (16), 77 (12), 106 (11), 96 (9), 103 (8), 333 (8) [$M^+-C_5H_7$].

2,7-Dimethyl-4,5-di-[1(*S*)-phenylethylamino]octa-1,7-diene [(*R*,*R*)-15 and (*S*,*S*)-15)]

The crude reaction product, obtained as a yellowish solid, was chromatographed to obtain pure diastereomers as oily compounds, in the following order of elution:

(*S*,*S*)-**15**: 0.300 g (8%); $[\alpha]^{20}_D$ −90.1 (*c* 0.56, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40–7.20 (m, 6H, Ph), 7.10 (m, 4H, Ph), 4.85 (s, 2H, C = CH_2), 4.73 (s, 2H, C = CH_2), 3.54 (q, 2H, C*H*Me), 2.74 and 2.43 (2 d, 4H, *J* = 10.7, 14.2 Hz, CHC*H*$_2$), 1.81 (t,

2H, NCHCHN), 1.47 (s, 6H, CH_2 = C*Me*), 1.44 (s, 2H, NH), 1.21 (d, 6H, *J* = 6.7 Hz, CH*Me*).

MS: *m/z* (%) = 105 (100), 188 (72) [M^+/2], 84 (40), 79 (15), 77 (11), 321 (4) [M^+- C_4H_7].

(*R*,*R*)-**15**: 2.08 g (55%); $[\alpha]^{20}_D$ −107.2 (*c* 0.724, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$-D_2O): δ = 7.40−7.20 (m, 10H, Ph), 4.43 (s, 2H, C = CH_2), 3.95 (s, 2H, C = CH_2), 3.67 (q, 2H, C*H*Me), 2.25, 2.10 and 1.95 (3 m, 6H, NCHCH_2), 1.39 (s, 6H, CH_2 = C*Me*), 1.27 (d, 6H, *J* = 6.6 Hz, CH*Me*).

3,6-Diethyl-4(*R*),5(*R*)-di-[1(*S*)-phenylethylamino]octane [(*R*,*R*)-13)]

10% Pd/C (30 mg) was added to a solution of the diamine (*R*,*R*)-**12** (0.400 g, 1 mmol) in MeOH (15 mL) and the mixture was stirred in H_2 atm (1 atm) for 24 h. The solution was filtered through Celite, then concentrated at reduced pressure, and the residue was chromatographed on an SiO_2 column eluting with cyclohexane/EtOAc (95:5) to obtain the diamine (*R*,*R*)-**13** as an oil.

Yield: 0.300 g (75%); $[\alpha]^{20}_D$ −26 (*c* 1.33, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz,): δ = 7.35−7.15 (m, 10H, Ph), 3.85 (q, 2H C*H*Me), 2.25 (s, 2H, NCHCHN), 1.58 (br, 2H, NH), 1.29 (d, 6H, *J* = 6.6 Hz, CH*Me*), 1.40−0.90 (m, 10H, CH_2CHCH_2), 0.82 and 0.73 (2 t, 12H, CH_2*Me*).

MS: *m/z* (%) = 204 (100) [M^+/2], 105 (88) [PhCHMe], 100 (40), 205 (17), 106 (9), 79 (9), 103 (6), 77 (6), 337 (5, $M^+-C_5H_{11}$).

Anal. Calcd for $C_{28}H_{44}N_2$: C, 82.29, H, 10.85, N, 6.85. Found: C, 82.34, H, 10.87, N, 6.82.

Hydrogenation/Hydrogenolysis of the Unsaturated Secondary 1,2-Diamines; Preparation of the Saturated Primary 1,2-Diamines

To a solution of the diamine (3 mmol) in MeOH (60 mL) was added Pd/C (0.06 g) and HCO_2NH_4 (1.14 g, 18 mmol), and the mixture was heated at the reflux temperature with stirring for 2 h. After cooling, the solution was filtered off and concentrated at reduced pressure to leave an oil containing some ethylbenzene. MeOH (15 mL), 10 N HCl (0.5 mL, 6 mmol) and benzene (10 mL) were added, and the mixture was concentrated at reduced pressure. This operation was repeated another two times and finally the residues (the di-hydrochlorides of the diamines) were thoroughly washed with $CHCl_3$ until a white powder was obtained.

4(*R*),5(*R*)-Diamino-3(*R*),6(*R*)-dimethyloctane Dihydrochloride [(*R*,*R*)-11a]

Yield: 0.63 g (85%); mp 230 °C (dec.); $[\alpha]^{20}_D$ +7.5 (*c* 0.77, MeOH).

^{1}H NMR (D_2O, 300 MHz, 20 °C, MeOH as internal standard): δ = 3.57 (m, 2H, CHN), 2.0 (m, 2H, C*H*Me), 1.43 (m, 4H, CH_2Me), 0.95 (m, 12 H, Me).

^{13}C NMR (D_2O, 300 MHz, MeOH as internal standard): δ = 55.4, 33.1, 25.8, 12.2, 10.4.

Anal. Calcd for $C_{10}H_{26}Cl_2N_2$: C, 48.98, H, 10.69, N, 11.42. Found: C, 48.82, H, 10.73, N, 11.38.

4(*R*),5(*R*)-Diamino-3(*R*),6(*S*)-dimethyloctane Dihydrochloride [(*R*,*R*)-11b]

Yield: 0.63 g (85%); mp 232 °C (dec.); $[\alpha]^{20}_D$ +2.6 (*c* 0.39, MeOH).

^{1}H NMR (D_2O, 200 MHz, 20 °C, MeOH as internal standard): δ = 3.65−3.40 (m, 2H, CHN), 2.05−1.85 (m, 2H,C*H*Me), 1.60−1.30 (m, 4H, CH_2Me), 1.10−0.80 (m, 12H, Me).

^{13}C NMR (D_2O, 300 MHz, MeOH as internal standard): δ = 56.6, 55.2, 33.4, 33.2, 25.7, 22.7, 15.0, 12.9, 10.4, 10.0.

Anal. Calcd for $C_{10}H_{26}Cl_2N_2$: C, 48.98, H, 10.69, N, 11.42. Found: C, 48.77, H, 10.71, N, 11.39.

4(*R*),5(*R*)-Diamino-3,6-diethyloctane Dihydrochloride (*R*,*R*)-14

Yield: 0.70 g (85%); mp 228 °C (dec.); $[\alpha]^{20}_D$ +29.1 (*c* 1.90, H_2O).

The free amine had $[\alpha]^{20}_D$ +18.9 (*c* 2.06, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz, 20 °C): δ = 8.2 and 2.6 (br, NH_3), 4.2 (m, 2H, CHN), 1.6−1.4 (m, 2H, NCHC*H*), 1.55−1.10 (m, 8H), 0.92 (m, 12H, Me).

Anal. Calcd for $C_{12}H_{30}Cl_2N_2$: C, 52.74, H, 11.06, N, 10.25. Found: C, 52.70, H, 11.08, N, 10.23.

4(*R*),5(*R*)-Diamino-2,7-dimethyloctane Dihydrochloride [(*R*,*R*)-16]

Yield: 0.54 g (75%); mp 218 °C (dec.); $[\alpha]^{20}_D$ +29.1 (*c* 1.80, MeOH).

^{1}H NMR (D_2O, 300 MHz, 20 °C): δ = 3.74 (m, 2H, CHN), 1.72 (m, 4H, NCHCH_2), 1.48 (m, 2H, C*H*Me_2), 1.0 and 0.96 (2 d, 12H, *J* = 6.3 Hz, CHMe_2).

Anal. Calcd for $C_{10}H_{26}Cl_2N_2$: C, 48.98, H, 10.69, N, 11.42. Found: C, 48.91, H, 10.71, N, 11.39.

4(*R*),5(*R*)-Diamino-2,7-dimethyloctane di-(4-methylbenzenesulfonamide) [(*R*,*R*)-17]

4-Toluenesulfonyl chloride (0.152 g, 0.80 mmol) was added to the stirred suspension of salt (*R*,*R*)-**16** (0.090 g, 0.37 mmol) and Et_3N (0.56 mL, 4.0 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The mixture was stirred overnight at r.t., filtered, washed with 2 N HCl (3 mL), then with brine. The organic phase was dried (Na_2SO_4) and concentrated to leave a solid, which was washed with Et_2O until a white solid was obtained, which was recrystallized from MeOH.

Yield: 0.090 g, 52%; mp 198−200 °C; $[\alpha]^{25}_D$ +84.5 (*c* 0.44, $CHCl_3$).

^{1}H NMR ($CDCl_3$+D_2O, 300 MHz): δ = 7.78 and 7.36 (2 d, 8H, *J* = 7.8 8.1 Hz, $SO_2C_6H_4$Me), 3.32 (t, 2H, NCHCHN), 2.40 (s, 6H, $SO_2C_6H_4$*Me*), 1.33 (m, 4H, CHCH_2CH), 0.82 (m, 2H, C*H*Me_2), 0.67 and 0.54 (2 d, 12H, *J* = 6.3, 6.0 Hz, CHMe_2).

Anal. Calcd for $C_{24}H_{36}N_2O_4S_2$: C, 59.98, H, 7.55, N, 5.83, Found: C, 59.94, H, 7.57, N, 5.81.

N-[1(*S*)-Phenylethyl]-3,3-dimethyl-2(*R*)-[1(*S*)-phenylethylamino]-4-penteneimine (18)

The solution of the zinc reagent (8 mmol) in THF (40 mL) was cooled to −78 °C, then the diimine (*S*,*S*)-**1** (0.53 g, 2 mmol) dissolved in THF (2 mL) was added during 15 min. The reaction mixture was stirred for 2 h, then quenched with 1 M HCl (6 mL) and further stirred for 20 min at 20 °C. After cooling to 0 °C, KOH pellets were added until the aq phase reached pH 11, the organic phase was separated, and the aq phase extracted with Et_2O (3 × 20 mL). The collected ethereal layers were dried (Na_2SO_4) and concentrated at reduced pressure to leave the crude imine **18** as a reddish oil.

Yield: 0.60 g, 1.8 mmol, 90%; $[\alpha]_D^{25}$ −101.8 (*c* 0.82, $CHCl_3$).

IR (neat): ν = 3304 (NH), 1666 (C = N) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.48 (d, 1H, *J* = 5.7 Hz, CH = N), 7.38−7.15 (m, 10H, Ph), 5.95−5.83 (m, 1H, C*H* = CH_2), 5.06−4.95 (m, 2H, CH = CH_2), 4.25 (q, 1H, CH = NC*H*Me), 3.65 (q, 1H, CHNHC*H*Me), 2.99 (d, 1H, *J* = 5.1 Hz, C*H*NH), 1.95 (br, 1H, NH), 1.47 (d, 3H, *J* = 6.6 Hz, C = NCH*Me*Ph), 1.29 (d, 3H, *J* = 6.6 Hz, CHNHCH*Me*Ph), 1.1 and 1.05 (2 s, 6H, CMe_2).

MS: *m/z* (%) 105 (100) [PhCHMe], 265 (25) [$M^+-C_5H_9$], 78 (13), 161 (10), 215 (10), 57 (5), 69 (2).

3,3-Dimethyl-2-[1(*S*)-phenylethylamino]pent-4-enal (19)
Compound **18** (0.50, g, 1.5 mmol) dissolved in Et_2O (4 mL) with 2 N HCl (4 mL) was stirred for 12 h, followed by treatment with NaOH to reach pH 11. Extraction (Et_2O, 2 × 5 mL) and chromatography on SiO_2 column eluting with cyclohexane/EtOAc mixture (95:5) gave the aldehyde **19** as an oil.

Yield: 0.174 g (50%); $[\alpha]^{25}_D$ −70.6 (*c* 0.51, $CHCl_3$).

IR (neat): ν = 3317 (NH), 1726 (C = O) cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.47 (d, 1H, *J* = 2.4 Hz, CHO), 7.35−7.10 (m, 5H, Ph), 6.0−5.8 (m, 1H, C*H* = CH_2), 5.15−5.0 (m, 2H, CH = C*H*$_2$), 3.68 (q, 1H, C*H*Me), 2.89 (d, 1H, *J* = 2.4 Hz, C*H*NH), 2.0 (br, 1H, NH), 1.33 (d, 3H, *J* = 6.6 Hz, CH*Me*), 1.15 and 1.07 (2 s, 6H, Me).

MS: *m/z* (%) = 105 (100), 98 (26), 202 (13) [M^+−CHO], 77 (12), 79 (11), 162 (7), [M^+−C_5H_9].

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88, H, 9.15, N, 6.05. Found: C, 77.49, H, 9.18, N, 6.03.

2,9-Dimethyl-5(*R*),6*(R)*-di-[1(*S*)-phenylethylamino]deca-2,8-diene [(*R*,*R*)-20)]
To an approx 1 M soluion of 3,3-dimethyl-2-propenylmagnesium chloride in THF (22 mL, 22 mmol) (prepared according to the literature), cooled at 0 °C, was added the imine (*S*,*S*)-**1** (1.85, 7 mmol) dissolved in THF (10 mL). The reaction mixture was stirred at 25 °C for 90 min, then quenched with aq $NaHCO_3$, and the organic phase was extracted with Et_2O (3 x 20 mL). The collected ethereal phases were dried (Na_2SO_4) and concentrated to leave crude **20** (90 %, d.r. =99:1) which was then chromatographed on a SiO_2 column eluting with cyclohexane/EtOAc mixture (90:10) to give the pure diamine **20** as an oil.

Yield: 1.85 g (66%); $[\alpha]^{20}_D$ −116.9 (*c* 1.4, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40−7.15 (m, 10H, Ph), 4.68 (t, 2H, CH = C), 3.76 (q, 2H, C*H*Me), 2.18−1.95 (m, 6H, $NCHCH_2$), 1.55 and 1.46 (2 s, 12H, CMe_2), 1.4 (s, 2H, NH), 1.23 (d, 6H, *J* = 6.9 Hz, CH*Me*).

MS: *m/z* (%) = 105 (100) [PhCHMe], 202 (56) [M^+/2], 98 (22), 81 (14), 335 (10) [M^+−C_5H_9].

(*R*,*R*)-2,9-Dimethyl-5,6-diaminodecane Dihydrochloride [(*R*,*R*)-21]
A Parr apparatus was filled with the diamine (*R*,*R*)-**20** (1.01 g, 2.5 mmol), MeOH (40 mL) and Pd/C (100 mg), then submitted to a pressure of 45 psi H_2 for 24 h. The solution was filtered through a small pad of Celite, then concentrated to a volume of 10 mL, and 37% HCl (0.5 mL) was added. The mixture was concentrated at reduced pressure, and benzene (5 mL) and MeOH (5 mL) were added. The mixture was concentrated, and the operation was repeated. The solid residue was treated with CH_2Cl_2 (5 mL), filtered and washed with CH_2Cl_2 (5 mL), then dried at reduced pressure to give pure (*R*,*R*)-**21**.

Yield: 0.476 g, 70%; mp 204 °C (dec.); $[\alpha]^{20}_D$ +25.1 (*c* 0.94, MeOH).

^{1}H NMR (300 MHz, D_2O) δ = 3.46 (m, 2H, CHN), 1.56 (m, 4H, $NCHCH_2$), 1.45 (m, 2H, C*H*Me_2), 1.16 (m, 4H, C*H*$_2$CMe_2), 0.75 and 0.73 (2 d, 12H, *J* = 6.6 Hz, CH*Me*$_2$).

Anal. Calcd for $C_{12}H_{30}Cl_2N_2$: C, 52.74, H, 11.06, N, 10.25. Found: C, 52.53, H, 11.10, N, 10.23.

Crystal Structure Characterisation of (*R*,*R*)-10a·2HCl and (*R*,*R*)-17
All X-ray diffraction data collections were carried out on a NONIUS CAD-4 diffractometer. The intensities were reduced to F^2, and the structures were solved by direct methods followed by difference Fourier and subsequent full-matrix least-squares refinement using the computer programs SHELXL97.[18a] Fractional atomic coordinates and anisotropic displacement parameters are available as Supporting Information. SCHAKAL97[18b] was used for the graphical representation of the results. Common to all compounds: MoKα radiation, λ = 0.71069 Å, monochromator graphite, temperature 293 K. All non-H atoms were refined anisotropically. The position of the *N*-H hydrogen atoms in both (*R*,*R*)-**10a·2HCl** and (*R*,*R*)-**17** were observed in the Fourier maps and not refined, while the C-H hydrogen atoms were added in the calculated positions.

(*R*,*R*)-**10a·2HCl**: $C_{26}H_{36}Cl_2N_2$, M = 447.47, tetragonal, P 4_12_12; *a* = 13.160(5), *b* = 13,160(10), *c* = 31,28(2) Å, *Z* = 8, *V* = 5417(6) $Å^3$; ρ_{calc} = 1.097 Mg/m^{-3}, Θ-range = 3.0−23.0°, 4187 measured reflections, 3753 independent reflections used in the refinement, 247 refined parameters; R1[I>2σ(I)] = 0.0822, Rw2(all data) = 0.3174.

(*R*,*R*)-**17**: $C_{24}H_{36}N_2O_4S_2$, M = 480.67, monoclinic, $P2_1$, *a* = 10.333(3), *b* = 15.061(5), *c* = 17.252(5) Å, β = 98.36(2)°, *Z* = 2, *V* = 2656.3(14) $Å^3$; ρ*calc* = 1.202 Mg/m^{-3}, Θ-range = 3.0−5.0°; 5019 measured reflections, 4853 independent reflections used in the refinement, 529 refined parameters; R1[I>2σ(I)] = 0.0471, Rw2(all data) = 0.1385.

Tables of crystallographic data, atomic coordinates, bond distances, and angles have been deposited with the Cambridge Crystallographic Data Centre.[19]

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