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Enantioselective syntheses of α-phenylalkanamines via intermediate addition of Grignard reagents to chiral hydrazones derived from (*R*)-(−)-2-aminobutan-1-ol

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Abstract

The hydrazine (*R*)-(−)-**28** was obtained in four steps from 2-aminobutan-1-ol (*R*)-(−)-**11**, and reacted with benzaldehyde to give the hydrazone (*R*)-(−)-**29**. Nucleophilic addition of various alkyl Grignard reagents to the latter yielded the corresponding trisubstituted hydrazines (*R,R*)-**30a–g** in 70–89% yields and having d.e.s=100% (^{1}H and ^{13}C NMR). Catalytic hydrogenolysis of these hydrazines afforded the corresponding (*R*)-(+)-α-phenylalkanamines (*R*)-(+)-**31a–g** having e.e.s=90–92% (chiral GPC).

1. Introduction

The enantioselective addition of organometallic reagents to chiral hydrazones, followed by hydrogenolytic cleavage of the N–N bond of the resulting hydrazine, constitutes an attractive method for the preparation of optically active amines. The general synthetic strategy disclosed by Takahashi and his coworkers[1] as early as 1979 is still in use: the chiral hydrazones are most generally derived from an enantiopure secondary amine, by *N*-nitrosation followed by reduction of the NO group into a NH_2 group and reaction with an appropriate aldehyde. Thus, the hydrazone derived from (−)-*N*-aminoephedrine and benzaldehyde reacted with organolithium or Grignard reagents to give chiral hydrazines having diastereomeric excesses (d.e.s) near 100%. Hydrogenolysis of the hydrazines yielded the corresponding (*R*)-α-phenylalkanamines in good enantiomeric purity despite the fact that some degree of racemization presumably occurred during the hydrogenolysis step. By this procedure, Takahashi and his coworkers obtained the amines **1–4** (Scheme 1), which were characterized as their crystalline *N*-salicylidene

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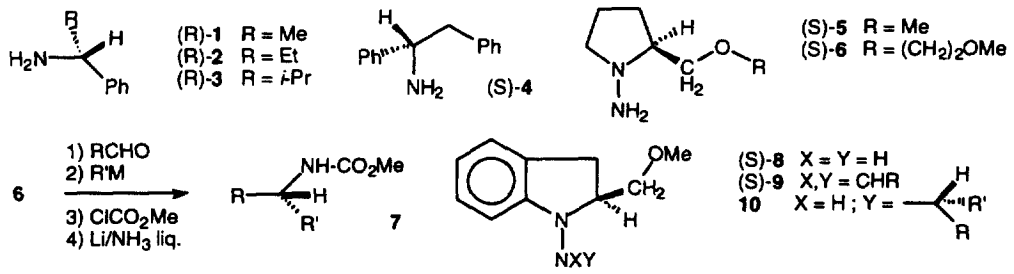
derivatives, the latter having e.e.s=97.6, 96, 76 and 40%, respectively.[1] Along similar lines, the same group used the hydrazine derived from (*S*)-*N*-methylvalinol and obtained poor yields of the amines (*S*)-**1** and (*S*)-**2**, whose crystalline salicylidene derivatives had e.e.s=99–100%.[2]



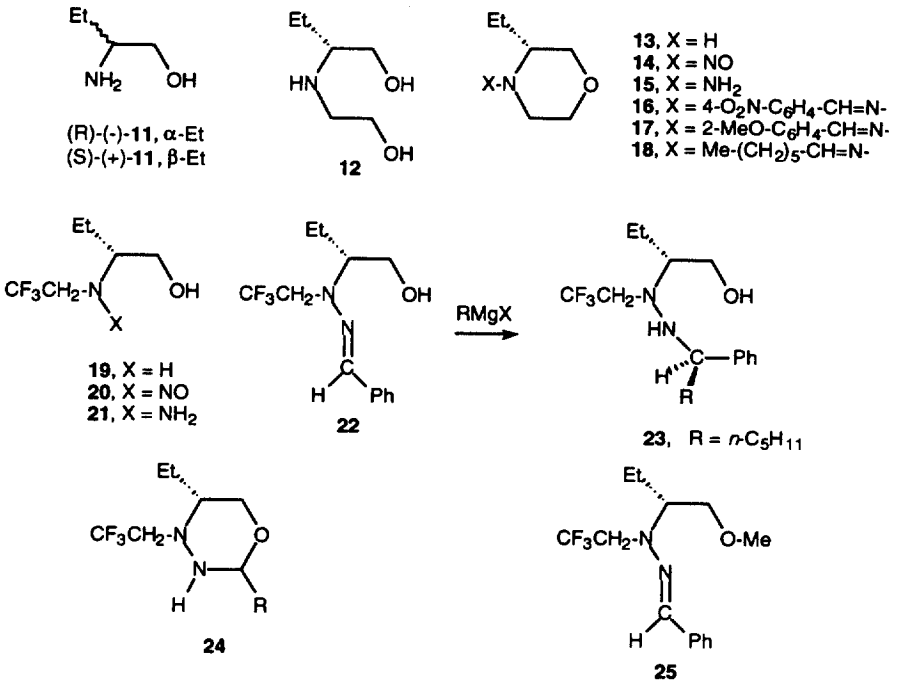
Scheme 1.

Starting from (*S*)-proline, Enders and coworkers[3] obtained the hydrazine **5** (SAMP reagent) via a 4–5 step sequence and prepared the corresponding hydrazones from diversified aromatic and aliphatic aldehydes. Addition of various organometallic (including alkyllithium) reagents to the above hydrazones, followed by hydrogenolysis using H_2/Raney nickel, afforded chiral amines whose e.e.s were within the range 81–94%. In the course of parallel studies, Denmark and coworkers[4] described the addition of organocerium reagents to the hydrazones derived from (*S*)-**6** and various aldehydes. The addition proceeded in good yields (67–81%) and with high d.e.s (>86%). Trapping the intermediate *N*-metallated hydrazine with methyl chloroformate gave carbamates whose N–N bonds were smoothly cleaved by lithium in liquid ammonia, thus affording the desired product **7** with no loss of enantiomeric purity. In 1996, Kim and Choi[5] reported the synthesis of the chiral SAMI reagent (*S*)-**8** in four steps from (*S*)-indoline-2-carboxylic acid. The hydrazones (*S*)-**9** derived from (*S*)-**8** and benzaldehyde or butanal were treated with three equivalents of an organolithium reagent (such as *n*-BuLi or PhLi) at −78°C and this afforded the corresponding hydrazines **10** in good yields (77–88%) and with high d.e.s (94–98%). The N–N bond of two trisubstituted hydrazines (amongst all those prepared) was cleaved by hydrogenation at room temperature under atmosphere using a $Pd(OH)_2$–C catalyst, in DME/H_2O containing hydrochloric acid. No racemization was observed in either of these cases.

2. Results and discussion

For some time now, we have considered using simple derivatives of (*S*)-(+) or (*R*)-(−)-2-aminobutan-1-ol **11** (Scheme 2) as new chirality transfer reagents in asymmetric synthesis.[6] Indeed, racemic aminobutanol **11** is a cheap chemical which can be easily resolved into both its enantiomers on the industrial scale.[7] The present study is devoted to the asymmetric synthesis of chiral amines from hydrazines derived from (*R*)-(−)-2-aminobutan-1-ol (*R*)-(−)-**11**, using the general strategy disclosed in the early works of Takahashi and coworkers.[1] Firstly, the known morpholine (*R*)-(+)-**13**[8] was obtained by *N*-alkylation of aminobutan-1-ol (*R*)-(−)-**11** by 2-bromoethanol, followed by acid catalyzed intramolecular dehydration of the intermediate diol (*R*)-(−)-**12**. Treatment of (*R*)-(+)-**13** with sodium nitrite in aqueous hydrochloric acid gave the *N*-nitrosoamine (*R*)-(−)-**14** (98.8%), which was next transformed into the hydrazine (*R*)-(−)-**15** (94%) upon reduction with $LiAlH_4$ in ether. The hydrazones **16–18** were prepared in 52.8–97.7% yields by reaction of (*R*)-(−)-**15** with 4-nitrobenzaldehyde, 2-methoxybenzaldehyde and heptanal, respectively, in the presence of anhydrous $MgSO_4$ in dry dichloromethane at room temperature

for 18 hours. However, all attempts failed to obtain the required trisubstituted hydrazines upon treatment of the above hydrazones **16–18** with excess organolithium or Grignard reagents.



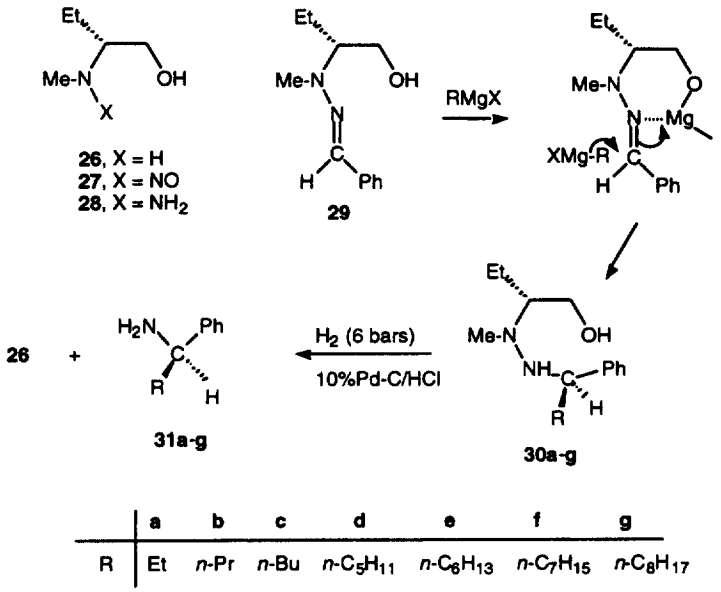
Scheme 2.

In the following study, *N*-trifluoroethyl aminobutanol (*R*)-(−)-**19**[6c] was similarly transformed into the hydrazine (*R*)-(−)-**21** via intermediate formation of the *N*-nitrosoamine (*R*)-(−)-**20**. The hydrazone (*R*)-(−)-**22** derived from (*R*)-(−)-**21** and benzaldehyde was obtained in 72.5% yield using the technique mentioned above. The hydrazone (*R*)-(−)-**22** reacted with 10 equivalents of *n*-pentylmagnesium bromide in refluxing ether and gave the desired hydrazine (+)-**23** in 79% yield. Addition of other Grignard reagents RMgX (where R=Et, *n*-Pr, *n*-Bu, *n*-hexyl) to the hydrazone (*R*)-(−)-**22** similarly gave the corresponding trisubstituted hydrazines analogous to (+)-**23**, in yields ranging from 55 to 78%. Examination of the high resolution ^{1}H and ^{13}C NMR spectra of these five hydrazines revealed that they were diastereomerically pure (d.e.=100%).[9] However, all attempts failed to cleave the N–N bond of (+)-**23** and its analogues under a wide array of hydrogenolytic procedures. These failures might be due to steric hindrance and/or to strong, stabilizing hydrogen bonding between a fluorine atom and the nitrogen-bound hydrogen atom.[10]

Reaction of the hydrazine (*R*)-(−)-**21** with aliphatic aldehydes RCHO afforded the heterocyclic compounds **24** rather than the requisite hydrazones. Reaction of compounds of type **24** with alkyl Grignard reagents led to degradation products.[9] Starting from the *O*-methyl derivative of aminobutanol (*R*)-(−)-**11**, the *O*-methyl hydrazone **25** was prepared in the usual way. However, this compound did not react with *n*-BuMgBr or *n*-BuLi/$CeCl_3$ in a variety of experimental conditions.[9] Therefore, it seems that the presence of a free hydroxy group is necessary here for the nucleophilic addition to occur.

Considering the above results, we finally extended our study to the *N*-methyl derivative (*R*)-(−)-**26**[6a] of aminobutanol (*R*)-(−)-**11** (Scheme 3). *N*-Nitrosation gave (*R*)-(+)-**27** (74.7%). Reduction of the latter with $LiAlH_4$ led to the hydrazine (*R*)-(−)-**28** (88%), which was transformed into the hydrazone (*R*)-(−)-**29** (76.4%) upon reaction with benzaldehyde in the presence of anhydrous $MgSO_4$ in dichloromethane. The hydrazone **29** was next treated with a tenfold molar excess of various *n*-alkyl Grignard reagents in

refluxing ether for 15 hours. This led to the corresponding seven trisubstituted liquid hydrazines (*R,R*)-**30a–g** in yields ranging between 70 and 89% in all cases but one. Using smaller quantities of Grignard reagents (i.e. fivefold molar excess) gave mixtures of starting hydrazone **29** and trisubstituted hydrazine **30**, the latter having rather average d.e.s. Examination of the high resolution ^{1}H and ^{13}C NMR spectra of the hydrazines **30a–g** (prepared with a tenfold excess of Grignard reagents) revealed that they were diastereomerically pure (d.e.=100% in all cases). The absolute (*R,R*) configuration of the hydrazines **30a–g** was assigned on the basis of the tentative mechanism depicted in Scheme 3.



Scheme 3.

Being rather unstable, the hydrazines **30a–g** were used directly in the following step without purification. Thus hydrogenolysis of the crude colourless hydrazines **30a–g** was carried out in the presence of concentrated hydrochloric acid and 10% Pd–C catalyst under hydrogen (6 bar) at *ca.* 60°C for 16 hours. This afforded the crude amines (*R*)-**31a–g** which were purified by chromatography over silica gel in the presence of triethylamine in order to avoid racemization.[11] The amines (*R*)-(+)-**31a**,[12] (*S*)-(−)-**31b**[13] and (*S*)-(−)-**31c**[14] are known compounds, which enabled us to confirm the (*R,R*) absolute configuration allotted to the starting hydrazines **30**. We assume that the other amines **30d–g** also have the (*R*) configuration. The latter amines were described in racemic form only.[15] Gas chromatography using a chiral column revealed that the e.e.s of the amines **31a,c–g** were in the range 90–92%, which implies that some racemization must have occurred during the final hydrogenolysis step.[1a]

3. Experimental section

3.1. General

IR spectra were recorded with Nicolet 5DX and Genesis (Mattson) spectrophotometers. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker AC 400 spectrometer, using Me_4Si as an internal standard. Melting points were determined with a Reichert microscope. Optical rotations were measured at 26°C with a Perkin–Elmer 241 micropolarimeter. Elemental analyses were

carried out at the I.C.S.N. (C.N.R.S., Gif-sur-Yvette). Chiral CPG experiments were carried out with a Hewlett Packard HP 6890 chromatograph equipped with a Restek beta DEX-sm 30 m column. (*R*)-(−)-2-Aminobutan-1-ol, $[\alpha]_D$ −10.0 (neat), was kindly provided by SmithKline Beecham Laboratories (Mayenne).

3.2. (R)-(−)-2-[(2-Hydroxyethyl)amino]-butan-1-ol (R)-(−)-12

2-Bromoethanol (15.6 g; 125 mmol) in toluene (45 ml) was added dropwise to (*R*)-(−)-2-aminobutan-1-ol (*R*)-(−)-**11** (11.12 g; 125 mmol) in toluene (45 ml). After heating under reflux for 18 h, solid Na_2CO_3 (26.5 g; 250 mmol) was added. After refluxing for a further 18 h, the mixture was filtered through Celite, the solid material was extracted with dichloromethane and the combined organic phases were evaporated under reduced pressure. Vacuum distillation of the residue gave the diol (*R*)-(−)-**12** as a very viscous colourless oil (8.70 g; 52.4%), b.p.$_{0.5}$=110–120°C and $[\alpha]_D$ −25.0 (c 1.2, MeOH). Lit.[8] $[\alpha]_D$ −17.85 (c 2.8, MeOH). ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, 3H); 1.30–1.60 (m, 2H); 2.52–2.58 (m, 1H); 2.67–2.86 (m, 2H); 3.34–3.42 (dd, 1H); 3.63–3.70 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 9.94 (q), 23.35 (t), 48.07 (t), 59.96 (d), 60.66 (t), 62.42 (t).

3.3. (R)-(+)-3-Ethylmorpholine (R)-(+)-13

Concentrated sulphuric acid (8.9 mmol) was slowly added to the diol (*R*)-(−)-**12** (12.12 g; 91 mmol) at 0°C (ice bath). After heating at 160°C for 5 h, the mixture was cooled, diluted with a little water and made basic by cautious addition of sodium hydroxide pellets. The crude morpholine was recovered by continuous extraction with ether. Distillation gave the purified morpholine (*R*)-(+)-**13** as a colourless oil (7.90 g; 75.8%), b.p.$_{10}$=50–55°C and $[\alpha]_D$ +9.8 (c 0.87, MeOH). Lit.[8] $[\alpha]_D$ −2.8 (neat). ^{1}H NMR ($CDCl_3$) δ: 0.92 (t, 3H); 1.10–1.40 (m, 2H); 1.70 (s, 1H); 2.68 (m, 1H); 2.80–3.00 (m, 2H); 3.13 (t, 1H); 3.45–3.52 (m, 1H); 3.80 (d, 2H). ^{13}C NMR ($CDCl_3$) δ: 10.57 (q), 26.03 (t), 46.87 (t), 56.87 (d), 68.20 (t), 73.18 (t).

3.4. (R)-(−)-3-Ethyl-4-nitrosomorpholine (R)-(−)-14

Sodium nitrite (18.78 g; 0.27 mol) in water (20 ml) was added dropwise to a mixture of 3-ethylmorpholine (*R*)-(+)-**13**,[8] $[\alpha]_D$ +9.8 (c 0.87, MeOH) (10.45g; 90 mmol), concentrated hydrochloric acid (14 ml) and crushed ice (17 g). After stirring for a further 14 h at room temperature, dichloromethane (40 ml) was added, and the separated aqueous phase was extracted three more times with dichloromethane (3×20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure, thus giving the nitrosomorpholine (*R*)-(−)-**14** (12.97 g; 98.8%) as a yellow oil, $[\alpha]_D$ −116.7 (c 0.98, MeOH) which was directly used in the next reduction step, without further purification. This compound was pure enough to give satisfactory microanalytical data. Anal. calc. for $C_6H_{12}N_2O_2$: C, 49.99; H, 8.39; N, 19.43. Found: C, 49.78; H, 8.17; N, 19.06. IR (film): 1444 (NO) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: major conformer, 0.96 (t, 3H); 1.40–2.10 (m, 2H); 3.08–3.15 (m, 1H); 3.37–4.62 (m, 6H); minor conformer, 0.84 (t, 3H); 1.40–2.10 (m, 2H); 3.37–4.62 (m, 6H); 4.90–4.93 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: major conformer, 9.82 (q), 22.24 (t), 36.84 (t), 60.34 (d), 65.53 (t), 69.60 (t); minor conformer, 9.92 (q), 21.04 (t), 46.34 (t), 49.96 (d), 66.93 (t), 67.82 (t).

3.5. (R)-(−)-4-Amino-3-ethylmorpholine (R)-(−)-15

A suspension of $LiAlH_4$ (0.790 g; 20.8 mmol) in dry ether (150 ml) was cooled down to −10°C and treated with dropwise addition of the nitrosoamine (*R*)-(−)-**14** (1.0 g; 6.9 mmol) in dry ether (25 ml). After stirring at room temperature for 6 h, the mixture was quenched with methanol (2.1 ml) and water (4.1 ml). The suspension was filtered and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure, thus giving the hydrazine (*R*)-(−)-**15** as a colourless oil (0.843 g; 94%), $[\alpha]_D$ −44 (c 1.12, MeOH) which was directly used in the next step without further purification. ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3H); 1.11–1.41 (m, 1H); 1.82–2.0 (m, 1H); 2.03–2.10 (m, 1H); 2.43 (dt, 1H); 2.99–3.0 (dt, 3H); 3.24–3.29 (dd, 1H); 3.63–3.68 (dt, 1H); 3.80–3.87 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 9.96 (q); 21.43 (t); 59.68 (t); 67.25 (t); 67.70 (d); 70.61 (t).

3.6. General procedure for the preparation of hydrazones derived from (R)-(−)-15

A mixture of hydrazine (*R*)-(−)-**15** (1–4 mmol), aldehyde (1 equiv.) and anhydrous $MgSO_4$ (1 molar equiv.) in dry dichloromethane (5 ml) was stirred overnight at room temperature. The suspension was filtered and the filtrate was treated with aqueous saturated sodium bisulphite solution for 2 h under stirring. The hydrazone was extracted with dichloromethane and the crude product was purified by column chromatography on silica gel (eluent: cyclohexane/ether 9/1 and elution gradient).

3.7. Hydrazone (R)-(−)-16 derived from 4-nitrobenzaldehyde

Yellow crystals (52.8% yield), m.p.=74–76°C and $[\alpha]_D$ −45.3 (c 1.0, MeOH). Anal. calc. for $C_{13}H_{17}N_3O_3$: C, 59.34; H, 6.51. Found: C, 59.47; H, 6.69. IR (Nujol): 3106–3079 (CH=); 1594 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.98 (t, 3H); 1.70–1.90 (m, 2H); 3.10–3.16 (m, 1H); 3.26–3.31 (sext, 1H); 3.32–3.38 (m, 1H); 3.71–3.75 (dd, 1H); 3.84–3.94 (m, 3H); 7.44 (s, 1H); 7.68 (d, 2H); 8.18 (d, 2H).

3.8. Hydrazone (R)-(−)-17 derived from 2-methoxybenzaldehyde

Pale yellow oil (74% yield), $[\alpha]_D$ −6.9 (c 1.0, MeOH). Anal. calc. for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.81; H, 8.33; N, 11.14. IR (film): 3106–3079 (CH=) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.96 (t, 3H); 1.64–1.96 (m, 2H); 2.97–3.03 (quint, 1H); 3.10–3.14 (m, 1H); 3.28–3.34 (quint, 1H); 3.64–3.69 (dd, 1H); 3.84 (s, 3H); 3.85–3.90 (m, 3H); 6.86–6.88 (d, 1H); 6.94 (t, 1H); 7.24 (m, 1H); 7.87–7.89 (dd, 1H); 7.93 (s, 1H).

3.9. Hydrazone (R)-(+)-18 derived from heptanal

Orange oil (97.7% yield), $[\alpha]_D$ +143 (c 1.70, MeOH). Anal. calc. for $C_{13}H_{26}N_2O$: N, 12.38. Found: N, 12.21. IR (film): 1654 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.88 (t, 3H); 0.90 (t, 3H); 1.25–1.80 (m, 10H); 2.22–2.28 (dt, 2H); 2.75–2.81 (m, 1H); 2.84–2.89 (m, 1H); 2.94–2.99 (m, 1H); 3.54–3.59 (dd, 1H); 3.81–3.86 (m, 3H); 7.07 (t, 1H).

3.10. (R)-(−)-N-Nitroso-N-(2,2,2-trifluoroethyl)-2-aminobutanol-1-ol (R)-(−)-20

Sodium nitrite (1.84 g; 27 mmol) in water (2 ml) was added dropwise at 0°C and under vigorous stirring to a mixture of trifluoroethylamine (*R*)-(−)-**19**,[6c] $[\alpha]_D$ −10.2 (c 1.02, MeOH) (1.52 g; 9.0

mmol), concentrated hydrochloric acid (1.3 ml) and crushed ice (5 g). After stirring overnight at room temperature, dichloromethane (10 ml) was added, and the separated aqueous phase was extracted twice more with dichloromethane (2×10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Chromatography of the residue over silica gel (eluent: cyclohexane/ether 9/1 and elution gradient) gave the *N*-nitrosamine (*R*)-(−)-**20** as a yellow oil (1.70 g; 94.4%), $[\alpha]_D$ −37.6 (c 2.7, MeOH). Anal. calc. for $C_6H_{11}F_3N_2O_2$: C, 36.00; H, 5.54; N, 14.00. Found: C, 35.79; H, 5.48; N, 13.91. IR (film): 3300 (OH) and 1444 (N=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.99 (t, 3H); 1.80–2.05 (m, 2H); 2.54 (t, 1H); 3.90–4.05 (m, 2H); 4.10 (dq, 1H); 4.26–4.32 (m, 1H); 4.50 (dq, 1H). ^{19}F NMR ($CDCl_3$) δ: −70.16 (conformer A, 11.75%); −68.01 (conformer B, 88.25%).

3.11. (R)-(−)-2-[1-(2,2,2)-Trifluoroethyl)hydrazino]butan-1-ol (R)-(−)-21

A suspension of $LiAlH_4$ (4.0 g; 105 mmol) in dry ether (150 ml) was cooled to 0°C and treated dropwise by the *N*-nitrosoamine (*R*)-(−)-**20** (6.0 g; 30 mmol) in dry ether (150 ml). After stirring at room temperature for 6 h, the mixture was quenched at −10°C by methanol, followed by water (4 ml), 15% NaOH solution (4 ml) and finally water (12 ml). The suspension was filtered and the filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residual orange oil was distilled under atmospheric pressure, thus giving the hydrazine (*R*)-(−)-**21** (3.60 g; 64.5%), b.p.=98–103°C and $[\alpha]_D$ −3.8 (c 1.3, MeOH). IR (film): 3357 (OH and NH_2) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.96 (t, 3H); 1.40–1.54 (m, 2H); 2.60–2.68 (m, 1H); 3.29 (q, 2H); 3.63 (dd, 1H); 3.71 (dd, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.06 (q); 18.29 (t); 60.87 (t); 62.91 (t); 69.40 (d); 126.64 (s). ^{19}F NMR ($CDCl_3$) δ: −71.00 ppm.

3.12. Benzenecarbaldehyde N-[(1R)-1-(hydroxymethyl)propyl]-N-(2,2,2-trifluoroethyl)hydrazone (R)-(−)-22

A mixture of hydrazine (*R*)-(−)-**21** (2.55 g; 13.7 mmol), benzaldehyde (1.67 g; 15.7 mmol) and anhydrous $MgSO_4$ (1.60 g; 15.7 mmol) in dry dichloromethane (50 ml) was stirred overnight at room temperature. The mixture was then filtered and evaporated under reduced pressure. The oily residue was chromatographed over silica gel (eluent: cyclohexane/ether=9/1 and elution gradient), thus affording the hydrazone (*R*)-(−)-**22** as a colourless viscous oil (72.5%), $[\alpha]_D$ −135 (c 0.8, MeOH). Anal. calc. for $C_{13}H_{17}F_3N_2O$: N, 10.21. Found: N, 10.29. MS calc. for $C_{13}H_{17}F_3N_2O$: M, 274.1292. Found: 274.1292. IR (film): 3407 (OH), 3062 (CH=) and 1594–1569 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.96 (t, 3H); 1.60–1.85 (2 sept., 2H); 2.47 (s, 1H); 3.20 (dq, 1H); 3.80–4.0 (m, 4H); 7.24–7.35 (m, 3H); 7.45 (s, 1H); 7.52 (d, 2H). ^{13}C NMR ($CDCl_3$) δ: 10.27 (q); 22.95 (t); 53.52 (t); 64.58 (t); 70.38 (d); 124.15 (s); 125.93 (d); 128.16 (d); 128.63 (d); 133.31 (d); 135.95 (s). ^{19}F NMR ($CDCl_3$) δ: −70.15 ppm.

3.13. 2-[2-(1-Phenylhexyl)-1-(2,2,2-trifluoroethyl)hydrazino]butan-1-ol (+)-23 : a typical procedure for the addition of alkyl Grignard reagents to the hydrazone (R)-(−)-22

1-Bromopentane (1.36 ml; 10.9 mmol) in dry ether (15 ml) was added to magnesium chips (0.266 g; 10.9 mmol) under an inert atmosphere. After refluxing for 3 h, the mixture was cooled to 0°C and treated dropwise by the hydrazone (*R*)-(−)-**22** (0.300 g; 1.09 mmol) in dry ether (10 ml). The mixture was then refluxed for 17 h. After cooling to −10°C, water was added and the resulting medium was filtered through Celite. The aqueous phase was separated, saturated with NaCl and extracted once more with ether. The organic extracts were pooled, dried ($MgSO_4$) and evaporated under reduced pressure. The residual orange oil was chromatographed over silica gel (eluent: cyclohexane/ether=9/1 and elution gradient), thus giving

the hydrazine (+)-**23** as a pale yellow oil (0.300 g; 79%), $[\alpha]_D$ +8.14 (c 1.29, MeOH) and d.e.=100% (^{13}C and ^{19}F NMR). MS calc. for $C_{18}H_{29}F_3N_2O$: M, 346.2318. Found: 346.2238. ^1H NMR ($CDCl_3$) δ: 0.81–0.86 (m, 6H); 1.0–1.6 (m, 10H); 1.90–2.0 (m, 1H); 2.50–2.70 (m, 1H); 3.18–3.24 (dd, 1H); 3.33–3.39 (dd, 1H); 3.54–3.59 (dd, 1H); 3.69–3.76 (m, 2H); 7.10–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 10.76 (q), 13.57 (q), 17.23 (t), 22.11 (t), 25.29 (t), 31.40 (t), 33.73 (t), 55.46 (t), 62.67 (t), 63.00 (d), 66.76 (d), 127.02 (s), 125.26 (d), 127.55 (d), 128.115 (d), 142.07 (s) (single diastereomer). ^{19}F NMR ($CDCl_3$) δ: −70.268 (single diastereomer).

3.14. (R)-(+)-N-Methyl-N-nitroso-2-aminobutan-1-ol (R)-(+)-27

Sodium nitrite (10.1 g; 147 mmol) in water (20 ml) was added dropwise at 0°C to a mixture of amine (*R*)-(−)-**26**,[6a] $[\alpha]_D$ −31.7 (c 3.9, MeOH) (5.0 g; 49.0 mmol), concentrated hydrochloric acid (7 ml) and crushed ice (27 g). After stirring overnight at room temperature, the mixture was extracted with dichloromethane. The organic phase was dried ($MgSO_4$), evaporated under reduced pressure and the oily residue was chromatographed over silica gel (eluent: cyclohexane/ether=7/3 and elution gradient), thus giving the *N*-nitrosoamine (*R*)-(+)-**27** as a yellow liquid (4.83 g; 74.7%), $[\alpha]_D$ +19.9 (c 1.65, MeOH). Anal. calc. for $C_5H_{12}N_2O_2$: C, 45.44; H, 9.15; N, 21.2. Found: C, 45.44; H, 9.17; N, 21.17. IR (film): 3421 (OH) and 1461–1430 (N=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.92 (t, 3H); 1.60–1.80 (m, 2H); 3.02 (s, 3H); 3.70–3.80 (m, 2H); 4.40–4.50 (m, 1H) ^{13}C NMR ($CDCl_3$) δ: 10.46 (q), 22.07 (t), 29.38 (q), 62.91 (t), 67.46 (d).

3.15. (R)-(−)-2-(1-Methylhydrazino)butan-1-ol (R)-(−)-28

A suspension of $LiAlH_4$ (1.33 g; 35 mmol) in dry ether (100 ml) was cooled to 0°C and treated dropwise with the *N*-nitrosoamine (*R*)-(+)-**27** (1.32 g; 10 mmol) in dry ether (20 ml). After stirring overnight at room temperature, the excess hydride was destroyed by addition of methanol (4 ml) and water (7 ml). The suspension was filtered and the solids were extracted several times with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure thus affording the hydrazine (*R*)-(−)-**28** as a colourless oil (1.04 g; 88%), $[\alpha]_D$ −21.6 (c 1.1, MeOH), which was used in the next step without further purification. ^1H NMR ($CDCl_3$) δ: 0.92 (t, 3H); 1.20–1.40 (m, 2H); 2.30–2.40 (m, 1H); 2.56 (s, 3H); 3.0–3.50 (m, 2H); 3.59–3.64 (dd, 1H); 3.70–3.74 (dd, 1H). ^{13}C NMR ($CDCl_3$) δ: 10.71 (q), 17.36 (t), 47.38 (q), 63.77 (t), 68.12 (d).

3.16. Benzenecarbaldehyde N-[1-hydroxymethyl)propyl]-N-methylhydrazone (R)-(−)-29

Anhydrous magnesium sulphate (1.7 g; 16.9 mmol) was added to a solution of hydrazine (*R*)-(−)-**28** (2.0 g; 16.9 mmol) and benzaldehyde (1.7 ml; 16.9 mmol) in dichloromethane (10 ml) and the mixture was stirred overnight at room temperature. After filtration and evaporation of the solvent, the residue was stirred for 2 h with aqueous saturated sodium hydrogen sulphite solution. The hydrazone was next extracted with dichloromethane. The crude product was chromatographed over silica gel (eluent: cyclohexane/ether=9/1), thus giving the hydrazone (*R*)-(−)-**29** as a colourless oil (2.66 g; 76.4%), $[\alpha]_D$ −25.4 (c 1.04, MeOH). Anal. calc. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58. Found C, 69.85; H, 8.73; N, 13.61. IR (film): 3316 (OH) and 1585–1556 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.93 (t, 3H); 1.50–1.80 (m, 2H); 2.97 (s, 3H); 3.10–3.30 (m, 1H); 3.80–3.90 (m, 2H); 7.19–7.33 (m, 4H); 7.51 (d, 2H). ^{13}C NMR ($CDCl_3$) δ: 11.03 (q); 22.13 (t), 37.04 (q), 63.86 (t), 69.66 (d), 125.36 (2d), 127.18 (d), 128.54 (2d), 131.04 (d), 136.92 (s).

3.17. General procedure for the addition of alkyl Grignard reagents to the hydrazone (R)-(−)-29: preparation of the hydrazines 30a–g

Magnesium chips (10 equiv.) were added to an alkyl bromide (10 equiv.) in dry ether. After refluxing for 3 h, the mixture was cooled to −10°C and treated dropwise by the hydrazone (*R*)-(−)-**29** (1 equiv.) in dry ether. After stirring under reflux for 16 h, the mixture was cooled to −10°C and hydrolyzed with brine. After filtration through Celite, the aqueous phase was decanted and extracted three times more with ether. The organic extracts were pooled and evaporated under reduced pressure. The residue was treated with aqueous 50% hydrochloric acid solution. The mixture was washed three times with pentane, then made basic with 32% aqueous ammonia and finally extracted three times with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure, thus leading to the required hydrazine **30** which was used directly in the next hydrogenolysis step, without further purification. The hydrazines **30a–g** are unstable colourless oils.

3.18. (R,R)-(+)-2-[1-Methyl-2-(1-phenylpropyl)hydrazono]butan-1-ol (R,R)-(+)-30a

Starting from magnesium (0.471 g), bromoethane (1.45 ml) in ether (20 ml) and the hydrazone (*R*)-(−)-**29** (0.40 g; 1.94 mmol) in ether (5 ml), the above procedure led to the hydrazine (*R,R*)-(+)-**30a** (0.408 g; 89%), $[\alpha]_D$ +10.0 (c 1.15, MeOH) and d.e.=100% (^1H and ^{13}C NMR). ^1H NMR ($CDCl_3$) δ: 0.77 (t, 3H); 0.84 (t, 3H); 1.20–2.0 (m, 4H); 2.40 (s, 3H); 2.40–2.50 (m, 1H); 2.80–3.0 (m, 2H); 3.37–3.46 (dd, 1H); 3.60–3.66 (dd, 1H); 3.65–3.72 (dd, 1H); 7.25–7.36. ^{13}C NMR ($CDCl_3$) δ: 11.03 (q), 11.38 (q), 17.76 (t), 28.26 (t), 40.67 (q), 63.51 (t), 64.78 (d), 68.63 (d), 128.08 (d), 128.27 (2d), 128.51 (2d), 144.76 (s).

3.19. (R,R)-(+)-2-[1-Methyl-2-(1-phenylbutyl)hydrazono]butan-1-ol (R,R)-(+)-30b

Starting from magnesium (0.236 g), 1-bromopropane (0.882 ml) in ether (10 ml) and the hydrazone (*R*)-(−)-**29** (0.200 g; 0.97 mmol) in ether (2 ml), the above procedure led to the hydrazine (*R,R*)-(+)-**30b** (0.172 g; 70.8%), $[\alpha]_D$ +6.8 (c 1.33, MeOH) and d.e.=100% (^1H and ^{13}C NMR). ^1H NMR ($CDCl_3$) δ: 0.84 (t, 3H); 0.87 (t, 3H); 1.0–1.80 (m, 6H); 2.44 (s, 3H); 2.44–2.50 (m, 1H); 3.20–3.33 (m, 1H); 3.38–3.42 (dd, 1H); 3.61–3.65 (dd, 1H); 3.76–3.79 (dd, 1H); 7.10–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 10.74 (q), 13.96 (q), 17.97 (t), 19.33 (t), 36.57 (t), 39.48 (q), 62.61 (t), 62.92 (d), 67.52 (d), 127.66 (d), 127.94 (2d), 128.40 (2d), 141.36 (s).

3.20. (R,R)-(+)-2-[1-Methyl-2-(1-phenylpentyl)hydrozono]butan-1-ol (R,R)-(+)-30c

Starting from magnesium (0.471 g), 1-bromobutane (2.08 ml) in ether (20 ml), and the hydrazone (*R*)-(−)-**29** (0.400 g; 1.94 mmol) in ether (5 ml), the above procedure led to the hydrazine (*R,R*)-(+)-**30c** (0.360 g; 70.3%), $[\alpha]_D$ +5.0 (c 1.08, MeOH) and d.e.=100% (^1H and ^{13}C NMR). ^1H NMR ($CDCl_3$) δ: 0.83 (t, 3H); 0.84 (t, 3H); 1.0–1.80 (m, 8H); 2.44 (s, 3H); 2.30–2.50 (m, 1H); 3.38–3.42 (dd, 1H); 3.61–3.64 (dd, 1H); 3.74–3.77 (dd, 1H), 7.10–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 10.91 (q), 13.95 (q), 17.41 (t), 22.72 (t), 28.42 (t), 34.70 (t), 40.15 (q), 62.86 (d), 63.08 (t), 68.20 (d), 127.25 (d), 127.76 (2d), 128.25 (2d), 143.05 (s).

3.21. (R,R)-(−)-2-[1-Methyl-2-(1-phenylhexyl)hydrazono]butan-1-ol (R,R)-(−)-***30d***

Starting from magnesium (0.471 g), 1-bromopentane (2.4 ml) in ether (20 ml), and the hydrazone (*R*)-(−)-**29** (0.400 g; 1.94 mmol) in ether (5 ml), the above procedure led to the hydrazine (*R,R*)-(−)-**30d** (0.44 g; 81.4%), $[\alpha]_D$ −0.8 (c 1.2, MeOH) and d.e.=100% (^{1}H and ^{13}C NMR). ^{1}H NMR ($CDCl_3$) δ: 0.82 (t, 3H); 0.83 (t, 3H); 1.0–1.80 (m, 10H); 2.43 (s, 3H); 2.47–2.50 (m, 1H); 3.34–3.44 (dd, 1H); 3.59–3.66 (dd, 1H); 3.72–3.79 (dd, 1H); 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 10.89 (q), 13.95 (q), 17.38 (t); 22.47 (t), 25.89 (t), 31.84 (t), 34.92 (t), 40.16 (q), 62.86 (d), 63.08 (t), 68.17 (d), 127.24 (d), 127.75 (2d), 128.24 (2d), 143.02 (s).

3.22. (R,R)-(−)-2-[1-Methyl-2-(1-phenylheptyl)hydrazono]butan-1-ol (R,R)-(−)-***30e***

Starting from magnesium (0.238 g), 1-bromohexane (1.36 ml) in ether (10 ml), and the hydrazone (*R*)-(−)-**29** (0.200 g; 0.97 mmol) in ether (2 ml), the above procedure led to the hydrazine (*R,R*)-(−)-**30e** (0.128 g; 45.2%), $[\alpha]_D$ −4.3 (c 0.8, MeOH) and d.e.=100% (^{1}H and ^{13}C NMR). ^{1}H NMR ($CDCl_3$) δ: 0.82–0.86 (m, 6H); 1.10–2.0 (m, 12H); 2.43 (s, 3H); 2.40–2.50 (m, 1H); 3.37–3.41 (dd, 1H); 3.61–3.64 (dd, 1H); 3.74–3.77 (dd, 1H); 7.10–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 10.39 (q), 13.48 (q), 16.92 (t), 22.02 (t), 25.70 (t), 28.81 (t), 34.47 (t), 39.65 (q), 62.38 (d), 62.58 (t), 69.12 (d), 126.76 (d), 127.25 (2d), 127.75 (2d), 143.27 (s).

3.23. (R,R)-(−)-2-[1-Methyl-2-(1-phenyloctyl)hydrazono]butan-1-ol (R,R)-(−)-***30f***

Starting from magnesium (0.238 g), 1-bromoheptane (1.35 ml) in ether (10 ml), and the hydrazone (*R*)-(−)-**29** (0.200 g; 0.97 mmol) in ether (2 ml), the above procedure led to the hydrazine (*R,R*)-(−)-**30f** (0.208 g; 70%), $[\alpha]_D$ −2.8 (c 1.07, MeOH) and d.e.=100% (^{1}H and ^{13}C NMR). ^{1}H NMR ($CDCl_3$) δ: 0.83 (t, 3H); 0.85 (t, 3H); 1.10–1.90 (m, 14H); 2.43 (s, 3H); 2.40–2.50 (m, 1H); 3.37–3.41 (dd, 1H); 3.61–3.64 (dd, 1H); 3.74–3.77 (dd, 1H); 7.10–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 10.91 (q), 14.03 (q), 17.44 (t), 22.57 (t), 26.27 (t), 29.15 (t), 29.64 (t), 31.75 (t), 35.00 (t), 40.18 (q), 62.90 (d), 62.96 (t), 68.22 (d), 127.27 (d), 127.78 (2d), 128.27 (2d), 143.06 (s).

3.24. (R,R)-(−)-2-[1-Methyl-2-(1-phenylnonyl)hydrazono]butan-1-ol (R,R)-(−)-***30g***

Starting from magnesium (0.471 g), 1-bromooctane (3.35 ml) in ether (20 ml), and the hydrazone (*R*)-(−)-**29** (0.400 g; 1.94 mmol) in ether (5 ml), the above procedure led to the hydrazine (*R,R*)-(−)-**30g** (0.437 g; 70.4%), $[\alpha]_D$ −2.8 (c 1.1, MeOH) and d.e.=100% (^{1}H and ^{13}C NMR). ^{1}H NMR ($CDCl_3$) δ: 0.84 (t, 3H); 0.86 (t, 3H); 1.10–1.90 (m, 16H); 2.43 (s, 3H); 2.40–2.50 (m, 1H); 3.37–3.41 (dd, 1H); 3.61–3.64 (dd, 1H); 3.74–3.77 (dd, 1H); 7.10–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 10.33 (q), 13.47 (q), 16.82 (t), 22.00 (t), 25.67 (t), 28.60 (t), 28.84 (t), 29.07 (t), 31.19 (t), 34.40 (t), 39.59 (q), 62.90 (d), 62.53 (t), 67.63 (d), 127.68 (d), 127.78 (2d), 127.87 (2d), 143.11 (s).

3.25. General procedure for the hydrogenolysis of the hydrazines ***30****: preparation of the* (R)*-1-phenyl-1-alkanamines* (R)-***31***

The trisubstituted hydrazine **30a–g** in ethanol was hydrogenolyzed in the presence of conc. HCl and 10% Pd–C under hydrogen (6 bar) at 55–65°C for 16 h. After filtration and evaporation, the residue was treated with 32% aqueous ammonia solution until basic, and the mixture was extracted three times

with ether. The ethereal solutions were pooled, dried ($MgSO_4$), filtered and evaporated, thus affording the crude amine **31** which was chromatographed over silica gel in the presence of triethylamine (eluent: cyclohexane/ether=9/1 and elution gradient).

3.26. (R)-(+)-1-Phenyl-1-propanamine (R)-(+)-31a

Starting from the hydrazine (*R,R*)-(+)-**30a**, $[\alpha]_D$ +10.0 (c 1.15, MeOH) (0.330 g; 1.39 mmol) in ethanol (26 ml), conc. HCl (0.3 ml) and 10% Pd–C (0.106 g), the above procedure led to the pure amine (*R*)-(+)-**31a** (0.066 g; 35.4%), $[\alpha]_D$ +26 (c 1.6, EtOH) and e.e.=90.5% (chiral GPC). Lit.[12] $[\alpha]_D^{30}$ +6.6 (c 1.49, EtOH). ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, 3H); 1.69 (quint, 2H); 1.95 (s, 2H); 3.79 (t, 1H); 7.10–7.30 (m, 5H).

3.27. (R)-(+)-1-Phenyl-1-butanamine (R)-(+)-31b

Starting from the hydrazine (*R,R*)-(+)-**30b**, $[\alpha]_D$ +6.8 (c 1.33, MeOH) (0.321 g; 1.28 mmol) in ethanol (25 ml), conc. HCl (0.3 ml) and 10% Pd–C (0.1 g), the above procedure led to the pure amine (*R*)-(+)-**31b** (0.130 g; 68.4%), $[\alpha]_D$ +22.7 (c 1.1, $CHCl_3$) and $[\alpha]_D$ +14.5 (c 1, EtOH), which could not be resolved by chiral GPC. Lit.[13] $[\alpha]_D$ −21.3 (c 1.3, $CHCl_3$) for the (*S*) enantiomer. ^{1}H NMR ($CDCl_3$) δ: 0.90 (t, 3H); 1.10–1.80 (m, 6H); 3.89 (t, 1H); 7.10–7.30 (m, 5H).

3.28. (R)-(+)-1-Phenyl-1-pentanamine (R)-(+)-31c

Starting from the hydrazine (*R,R*)-(+)-**30c**, $[\alpha]_D$ +5.0 (c 1.08, MeOH) (0.100 g; 0.38 mmol) in ethanol (10 ml), conc. HCl (0.08 ml) and 10% Pd–C (0.029 g), the above procedure led to the pure amine (*R*)-(+)-**31c** (0.048 g; 77.4%), $[\alpha]_D$ +11.7 (c 1.0, $CHCl_3$) and e.e.=92% (chiral GPC). Lit.[14] $[\alpha]_D$ −12.7 (c 2.50, $CHCl_3$) for the (*S*) enantiomer. ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, 3H); 1.10–1.80 (m, 8H); 3.86 (t, 1H); 7.10–7.30 (m, 5H).

3.29. (R)-(+)-1-Phenyl-1-hexanamine (R)-(+)-31d

Starting from the hydrazine (*R,R*)-(−)-**30d**, $[\alpha]_D$ −0.8 (c 1.2, MeOH) (0.400 g; 1.44 mmol) in ethanol (30 ml), conc. HCl (0.30 ml) and 10% Pd–C (0.111 g), the above procedure led to the pure amine (*R*)-(+)-**31d** (0.140 g; 54.9%), $[\alpha]_D$ +4.3 (c 1.6, EtOH) and e.e.=90.2% (chiral GPC). Lit.[15] (racemic form). ^{1}H NMR ($CDCl_3$) δ: 0.85 (t, 3H); 1.10–1.80 (m, 10H); 3.86 (t, 1H); 7.10–7.30 (m, 5H).

3.30. (R)-(+)-1-Phenyl-1-heptanamine (R)-(+)-31e

Starting from the hydrazine (*R,R*)-(−)-**30e**, $[\alpha]_D$ −4.3 (c 0.8, MeOH) (0.100 g; 0.34 mmol) in ethanol (10 ml), conc. HCl (0.08 ml) and 10% Pd–C (0.026 g), the above procedure led to the pure amine (*R*)-(+)-**31e** (0.046 g; 70.6%), $[\alpha]_D$ +9.2 (c 0.6, EtOH) and e.e.=91.3% (chiral GPC). Lit.[15] (racemic form). ^{1}H NMR ($CDCl_3$) δ: 0.85 (t, 3H); 1.10–1.80 (m, 12H); 3.89 (t, 1H); 7.10–7.40 (m, 5H).

3.31. (R)-(+)-1-Phenyl-1-octanamine (R)-(+)-31f

Starting from the hydrazine (*R,R*)-(−)-**30f**, $[\alpha]_D$ −2.8 (c 1.07, MeOH) (0.170 g; 0.55 mmol) in ethanol (16 ml), conc. HCl (0.12 ml) and 10% Pd–C (0.043 g), the above procedure led to the pure amine (*R*)-

(+)-**31f** (0.055 g; 49.1%), $[\alpha]_D$ +4.0 (c 1, EtOH) and e.e.=90% (chiral GPC). Lit.[15] (racemic form). ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, 3H); 1.10–1.80 (m, 14H); 3.86 (t, 1H); 7.10–7.40 (m, 5H).

3.32. (R)-(+)-1-Phenyl-1-nonamine (R)-(+)-31g

Starting from the hydrazine (*R,R*)-(−)-**30g**, $[\alpha]_D$ −2.8 (c 1.1, MeOH) (0.330 g; 1.04 mmol) in ethanol (20 ml), conc. HCl (0.22 ml) and 10% Pd–C (0.080 g), the above procedure led to the pure amine (*R*)-(+)-**31g** (0.110 g; 48.2%), $[\alpha]_D$ +2.3 (c 4.5, EtOH) and e.e.=91% (chiral GPC). Lit.[15] (racemic form). ^{1}H NMR ($CDCl_3$) δ: 0.86 (t, 3H); 1.10–1.80 (m, 16H); 3.89 (t, 1H); 7.20–7.40 (m, 5H).

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