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# Further enantioselective syntheses of α-arylalkanamines via intermediate addition of Grignard reagents to a chiral hydrazone derived from (*R*)-(−)-2-aminobutan-1-ol

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**Abstract**

Reaction of various aromatic aldehydes with the chiral hydrazine (*R*)-(−)-**2**, derived from 2-aminobutan-1-ol (*R*)-(−)-**1**, gave the corresponding hydrazones **5**–**12**. Enantioselective addition of EtMgBr or *n*-BuMgBr to **5**–**8** gave the trisubstituted hydrazines **13a**–**f** (d.e.s=100%). Catalytic hydrogenolysis (6 bar/Pd–C/110°C/5 h) of the *N*–*N* bond of the latter afforded the enantiomerically enriched α-arylalkanamines (*R*)-(+)-**14a**–**f** (e.e.s=90–93%).


## 1. Introduction

We recently described[1] the synthesis of the chiral hydrazine (*R*)-(−)-**2** in four steps from (*R*)-(−)-2-aminobutan-1-ol **1**, a readily available reagent (Scheme 1). Diastereoselective addition of Grignard reagents to the benzenecarbaldehyde hydrazone (*R*)-(−)-**3** derived from **2**, followed by catalytic hydrogenolysis of the *N*–*N* bond of the resulting trisubstituted hydrazines (d.e.s=100%), afforded the enantiomerically enriched (e.e.s=90–92%) (*R*)-(+)-α-phenylalkanamines **4a**–**g**.

## 2. Results and discussion

We next applied the above reaction scheme to the syntheses of various ring-substituted α-arylalkanamines. Thus, the hydrazones (*R*)-(−)-**5**–**12** (pure *anti*-isomers) were prepared in 63–86% yields

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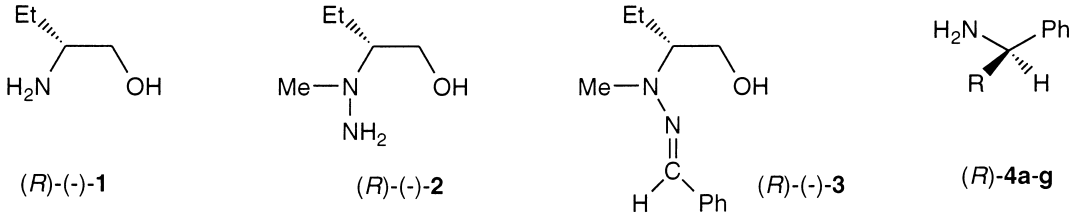



| | a | b | c | d | e | f | g |
|---|---|---|---|---|---|---|---|
| R | Et | *n*-Pr | *n*-Bu | *n*-$C_5H_{11}$ | *n*-$C_6H_{13}$ | *n*-$C_7H_{15}$ | *n*-$C_8H_{17}$ |

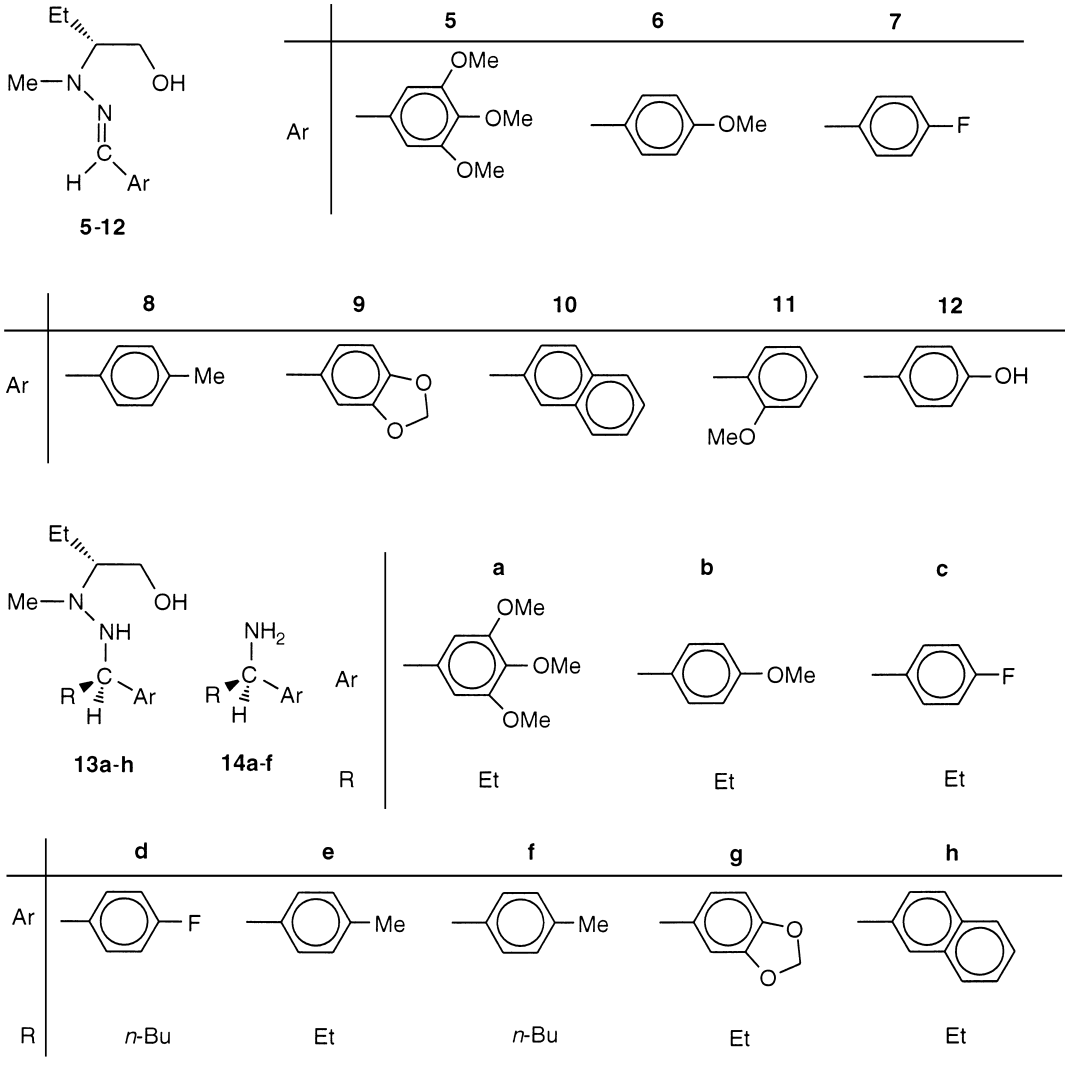
Scheme 1.

from the hydrazine (*R*)-(−)-**2** and the corresponding substituted aromatic aldehydes, using the experimental conditions (anhydrous $MgSO_4$/TsOH/$CH_2Cl_2$/20°C/17 h) which we previously described (Scheme 2).[1]

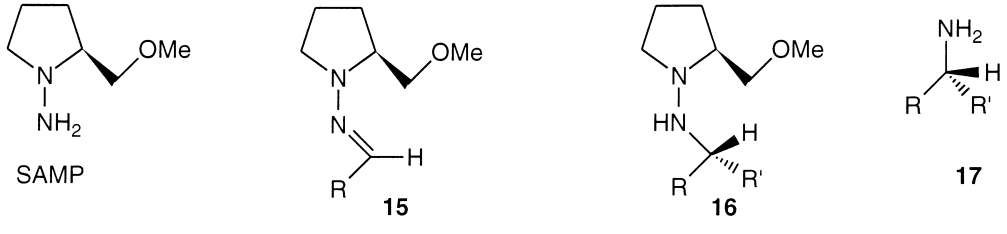
The addition of *n*-BuLi to the hydrazone **5** was attempted first. A total lack of reactivity was observed when adding 2, 4 or 6 equivalents of *n*-BuLi to the hydrazone **5** in ether at 0°C for 17 h. However, using 8 equivalents of *n*-BuLi did afford the expected trisubstituted hydrazine but in low yields (35%) and with a low d.e. (41%, from $^1$H NMR). For this reason, we decided to limit ourselves to the use of organomagnesium reagents. Thus, the addition of Grignard reagents to the hydrazones **5**–**12** was carried out as previously described[1] (10 equiv. RMgX/$Et_2O$/reflux/17 h). The eight trisubstituted hydrazines (*R*,*R*)-**13a**–**h** were thus obtained in 51–83% yields and with d.e.s=100% in all cases (as evidenced by $^1$H and $^{13}$C NMR). The addition of EtMgBr to the hydrazones **11** and **12** could not be carried out to completion and gave inseparable mixtures of trisubstituted hydrazine and starting hydrazone.

None of the ring-substituted hydrazines **13a**–**h** could be hydrogenolyzed under the conditions which we previously developed for the hydrazines **4a**–**g** ($H_2$, 6 bar/HCl/EtOH/60°C/17 h).[1] Increasing the pressure to 25 bar at 60°C gave no better results. It was eventually found that the temperature was the determining factor: indeed, hydrogenolysis of the hydrazines **13a**–**f** at 110–120°C, in the presence of a 10% Pd–C catalyst and conc. HCl in EtOH, under 6 bar for 5 h, afforded the corresponding (*R*)-α-arylalkanamines (*R*)-(+)-**14a**–**f** in 35–47% yields after purification by chromatography. Under the same conditions, hydrogenolysis of the hydrazines **13g** and **13h** gave inseparable mixtures. The e.e.s of the three amines **14a**,**d**,**f** were found to be within the range 90–93% by means of chiral GPC using a Restek β dex column. The other three amines **14b**,**c**,**e** could not be resolved using this and other chiral columns, or by running the $^1$H NMR spectra in the presence of the shift reagent Eu(hfc)$_3$. It can be assumed that the e.e.s of the amines **14b**,**c**,**e** are also in the range 90–93%, and that the six amines **14a**–**f** all belong to the *R*-series, analogously with the α-phenylalkanamines **4a**–**g**, and in agreement with the addition mechanism which we previously put forth.[1] The α-arylalkanamines (*R*)-**14a**–**d** were known in racemic form only. The amines (*R*)-**14e**,**f** are new compounds.

As early as 1979, Takahashi and his coworkers[2] described a synthesis of α-phenylalkanamines, involving the enantioselective addition of Grignard reagents to the hydrazone derived from *N*-aminoephedrine and benzaldehyde, followed by hydrogenolytic cleavage of the *N*–*N* bond of the resulting trisubstituted hydrazine. Later on, Enders and his coworkers[3] developed the chiral SAMP hydrazine, which they used for the syntheses of aldehyde hydrazones of type **15** (Scheme 3). Diastereoselective addition of lithium alkyls to **15** gave the corresponding trisubstituted hydrazines **16**. Catalytic hydrogenolysis of the latter using Raney nickel led to the corresponding amines **17** having e.e.s within the range 81–94%. A similar study was carried out by Denmark and coworkers.[4]




Scheme 2.




Scheme 3.

Our reaction scheme for the synthesis of enantiomerically enriched α-arylalkanamines is closely related to that used by Enders.[3] Some differences must be pointed out. We found that the presence of a free OH group in the chiral fragment of arylhydrazones of type **5** is necessary for the addition reaction to occur.[1] Besides, the addition of organolithium reagents to the hydrazones of type **5** could not be carried out using the experimental conditions described by Enders.[3] In our experience, the best results in terms

of chemical yields and diastereomeric excesses implied the use of a 10-fold excess of organomagnesium reagents.

Since 2-aminobutan-1-ol **1** is readily available in both enantiomeric forms on the industrial scale, our strategy can be applied to the syntheses of α-arylalkanamines belonging to both the *R*- and *S*-series.

## 3. Experimental

### 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. HR mass spectra were recorded at the CRMPO (Université de Rennes I) using a Varian Matt 311 spectrometer. Melting points were determined with a Reichert microscope. Optical rotations were measured at 26°C with a Perkin–Elmer 343 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 β dex column. (*R*)-(−)-2-Aminobutan-1-ol, $[\alpha]_D$ −10.0 (neat), was kindly provided by SmithKline Beecham Laboratories (Mayenne).

### 3.2. *3,4,5-Trimethoxybenzenecarbaldehyde*-N-*[(1*R*)-1-(hydroxymethyl)propyl]*-N-*methylhydrazone (*R*)-(−)-**5**

To a solution of hydrazine (*R*)-(−)-**2**[1] (1.10 g; 9.32 mmol) in anhydrous $CH_2Cl_2$ (30 ml), placed in a 100 ml flask equipped with a silica gel drying tube, 3,4,5-trimethoxybenzaldehyde (1.40 g; 7.17 mmol), anhydrous $MgSO_4$ (1.3 equiv.) and a catalytic amount of TsOH were added and the resulting mixture was stirred for 17 h at 20°C. After filtration and evaporation of the filtrate, the residue thus obtained was stirred with an aqueous solution of $NaHSO_3$ for 1 h and the mixture was extracted with $CH_2Cl_2$ (3×20 ml). The combined organic phases were dried ($MgSO_4$), evaporated under RP and the final residue was chromatographed over silica gel (eluent cyclohexane:ether, 7:3, and elution gradient) to give the hydrazone (*R*)-(−)-**5** (1.51 g, 71.2%) as a viscous colourless oil, $[\alpha]_D$ −17.0 (*c* 1.67, MeOH). Anal. calcd for $C_{15}H_{24}N_2O_4$: C, 60.79; H, 8.16; N, 9.45. Found: C, 61.22; H, 8.13; N, 9.22. IR (film): 3440 (OH) and 1589 (C=N) cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 0.94 (t, *J*=7.5 Hz, 3H), 1.50–1.75 (m, 2H), 2.86 (t, *J*=5.9 Hz, 1H), 2.96 (d, *J*=0.6 Hz, 3H), 3.24–3.30 (m, 1H), 3.85 (s, 3H), 3.88 (s, 6H), 3.83–3.88 (m, 2H), 6.76 (s, 2H), 7.17 (s, 1H); $^{13}$C NMR ($CDCl_3$): δ 10.97, 22.00, 36.71, 55.95, 60.85, 63.75, 69.58, 102.16, 130.69, 132.67, 137.46, 153.35.

### 3.3. *4-Methoxybenzenecarbaldehyde*-N-*[(1*R*)-1-(hydroxymethyl)propyl]*-N-*methylhydrazone (*R*)-(−)-**6**

Starting from 4-methoxybenzaldehyde (0.85 ml; 7.06 mmol), anhydrous $MgSO_4$ (1.3 equiv.) and TsOH (catalytic amount), and the hydrazine (*R*)-(−)-**2** (1.0 g; 8.47 mmol) in anhydrous $CH_2Cl_2$ (30 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**6** (1.33 g; 80.1%) as a viscous colourless oil, $[\alpha]_D$ −27.6 (*c* 1.3, MeOH). Anal. calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 66.17; H, 8.52; N, 12.03. IR (film): 3413 (OH) and 1608 (C=N) cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 0.93 (t, *J*=7.5 Hz, 3H), 1.40–1.70 (m, 2H), 2.93 (s, 3H), 3.02 (t, *J*=6.0 Hz, 1H), 3.16–3.22 (m, 1H), 3.81 (s, 3H), 3.84–3.87 (m, 2H), 6.87 (dt, *J*=2.4, 8.8 Hz, 2H), 7.23 (s, 1H), 7.44 (dt, *J*=2.4, 8.8 Hz, 2H); $^{13}$C NMR ($CDCl_3$): δ 11.01, 21.75, 36.95, 55.25, 63.74, 69.43, 113.97, 126.61, 129.77, 131.58, 159.07.

### 3.4. 4-Fluorobenzenecarbaldehyde-N-[(1R)-1-(hydroxymethyl)propyl]-N-methylhydrazone (R)-(−)-7

Starting from 4-fluorobenzaldehyde (1.05 ml; 9.8 mmol), anhydrous $MgSO_4$ (1.3 equiv.), TsOH (catalytic amount) and the hydrazine (*R*)-(−)-**2** (1.50 g; 13 mmol) in anhydrous $CH_2Cl_2$ (30 ml), the above procedure (see Section 3.2) led to the hydrazone (*R*)-(−)-**7** (1.60 g; 72.7%) as a colourless oil, $[\alpha]_D$ −18.6 (*c* 1.1, MeOH). Anal. calcd for $C_{12}H_{17}FN_2O$: C, 64.26; H, 7.63, N, 12.49. Found: C, 64.46; H, 7.77; N, 12.27. IR (film): 3409 (OH) and 1602 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.93 (t, *J*=7.5 Hz, 3H), 1.50–1.70 (m, 2H), 2.74 (s, 1H), 2.96 (s, 3H), 3.20–3.26 (m, 1H), 3.70–3.90 (m, 2H), 6.97–7.03 (m, 2H), 7.20 (s, 1H), 7.45–7.50 (m, 2H); $^{13}C$ NMR ($CDCl_3$): δ 11.04, 22.16, 36.95, 63.81, 69.75, 115.34, 115.55, 126.73, 126.81, 129.81, 133.24, 162.08.

### 3.5. 4-Methylbenzenecarbaldehyde-N-[(1R)-1-(hydroxymethyl)propyl]-N-methylhydrazone (R)-(−)-8

Starting from 4-methylbenzaldehyde (0.64 ml; 5.43 mmol), anhydrous $MgSO_4$ (1.3 equiv.), TsOH (catalytic amount) and the hydrazine (*R*)-(−)-**2** (0.77 g; 6.52 mmol) in anhydrous $CH_2Cl_2$ (30 ml), the above procedure (see Section 3.2) led to the hydrazone (*R*)-(−)-**8** (0.875 g; 73.5%) as a colourless oil, $[\alpha]_D$ −25.8 (*c* 1.1, MeOH). Anal. calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.86; H, 9.36; N, 12.65. IR (film): 3407 (OH) and 1583 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.93 (t, *J*=7.4 Hz, 3H), 1.50–1.80 (m, 2H), 2.33 (s, 3H), 2.94 (s, 3H), 3.20–3.30 (m, 1H), 3.80–3.90 (m, 2H), 7.12 (d, *J*=8.0 Hz, 2H), 7.22 (s, 1H), 7.40 (d, *J*=8.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): δ 11.53, 21.73, 22.44, 37.49, 64.33, 70.01, 125.82, 129.73, 132.03, 134.18, 137.10.

### 3.6. 1,3-Benzodioxole-5-carbaldehyde-N-[(1R)-1-(hydroxymethyl)propyl]-N-methylhydrazone (R)-(−)-9

Starting from piperonal (1.27 g; 8.46 mmol), anhydrous $MgSO_4$ (1.3 equiv.), TsOH (catalytic amount) and the hydrazine (*R*)-(−)-**2** (1.30 g; 11 mmol) in anhydrous $CH_2Cl_2$ (30 ml), the above procedure (see Section 3.2) led to the hydrazone (*R*)-(−)-**9** (1.34 g; 63.2%) as a colourless oil, $[\alpha]_D$ −22.7 (*c* 1.12, MeOH). Anal. calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.21; H, 7.41; N, 10.91. IR (film): 3401 (OH) and 1565 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.91 (t, *J*=7.5 Hz, 3H), 1.50–1.75 (m, 2H), 2.92 (s, 3H), 3.17–3.23 (m, 1H), 3.78 (dd, *J*=3.6, 11.3 Hz, 1H), 3.84 (dd, *J*=7.3, 11.3 Hz, 1H), 5.93 (s, 2H), 6.75 (d, *J*=8.0 Hz, 1H), 6.87 (dd, *J*=7.9, 1.6 Hz, 1H), 7.13 (d, *J*=1.6 Hz, 1H), 7.17 (s, 1H); $^{13}C$ NMR ($CDCl_3$): δ 11.06, 22.02, 37.04, 63.74, 69.68, 100.99, 104.58, 108.15, 120.26, 131.18, 131.79, 147.04, 148.10.

### 3.7. 2-Naphthaldehyde-N-[(1R)-1-(hydroxymethyl)propyl]-N-methylhydrazone (R)-(−)-10

Starting from 2-naphthaldehyde (1.30 g; 8.42 mmol), anhydrous $MgSO_4$ (1.3 equiv.), TsOH (catalytic amount) and the hydrazine (*R*)-(−)-**2** (1.0 g; 9.26 mmol) in anhydrous $CH_2Cl_2$ (30 ml), the above procedure (see Section 3.2) led to the hydrazone (*R*)-(−)-**10** (1.40 g; 65.1%) as pale-pink flakes, mp 80–82°C and $[\alpha]_D$ −21.2 (*c* 1.13, MeOH). Anal. calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.94; H, 8.01; N, 10.89; $^1H$ NMR ($CDCl_3$): δ 0.94 (t, *J*=7.44 Hz, 3H), 1.50–1.70 (m, 2H), 2.88 (s, 1H), 3.01 (s, 3H), 3.20–3.30 (m, 1H), 3.80–3.95 (m, 2H), 7.39–7.46 (m, 3H), 7.70–7.90 (m, 5H); $^{13}C$ NMR ($CDCl_3$): δ 11.0, 22.19, 36.99, 63.84, 69.77, 122.71, 125.06, 125.49, 126.14, 127.72, 127.75, 128.17, 131.02, 132.88, 133.60, 134.65.

### 3.8. *2-Methoxybenzenecarbaldehyde*-N-*[(1*R*)-1-(hydroxymethyl)propyl]*-N-*methylhydrazone (*R*)-(−)-**11**

Starting from 2-methoxybenzaldehyde (0.74 g; 5.43 mmol), anhydrous $MgSO_4$ (1.3 equiv.), TsOH (catalytic amount) and the hydrazine (*R*)-(−)-**2** (0.77 g; 6.52 mmol) in anhydrous $CH_2Cl_2$ (30 ml), the above procedure (see Section 3.2) led to the hydrazone (*R*)-(−)-**11** (1.10 g; 85.9%) as a colourless oil, $[\alpha]_D$ −33 (*c* 1.78, MeOH). Anal. calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 66.62; H, 8.22; N, 11.23. IR (film): 3409 (OH) and 1596 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.93 (t, *J*=7.5 Hz, 3H), 1.50–1.80 (m, 2H), 2.96 (s, 3H), 3.15–3.32 (m, 1H), 3.26 (s, 1H), 3.85 (s, 3H), 3.85–3.89 (m, 2H), 6.87 (d, *J*=8.2 Hz, 1H), 6.93 (t, *J*=7.5 Hz, 1H), 7.19 (td, *J*=1.6, 7.8 Hz, 1H), 7.54 (s, 1H), 7.69 (dd, *J*=1.6, 7.7 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): δ 11.44, 22.32, 37.52, 55.79, 64.31, 69.90, 111.26, 121.21, 125.57, 125.75, 127.65, 128.51, 156.31.

### 3.9. *4-Hydroxybenzenecarbaldehyde*-N-*[(1*R*)-1-(hydroxymethyl)propyl]*-N-*methylhydrazone (*R*)-(−)-**12**

Starting from 4-hydroxybenzaldehyde (0.86 g; 7.06 mmol), anhydrous $MgSO_4$ (1.3 equiv.), anhydrous TsOH (catalytic amount) and the hydrazine (*R*)-(−)-**2** (1.0 g; 8.47 mmol) in anhydrous $CH_2Cl_2$ (30 ml), the above procedure (see Section 3.2) led to the hydrazone (*R*)-(−)-**12** (1.0 g; 63.7%) as a colourless viscous oil, $[\alpha]_D$ −34.8 (*c* 1.35, MeOH). MS calcd for $C_{12}H_{18}N_2O_2$: M, 222.1368. Found: M, 222.1379. IR (film): 3413 (OH) and 1608 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.95 (t, *J*=7.4 Hz, 3H), 1.50–1.70 (m, 2H), 2.93 (s, 3H), 3.05–3.20 (m, 1H), 3.90–4.05 (m, 2H), 4.45 (s, 1H), 6.80 (dt, *J*=2.5, 8.6 Hz, 2H), 7.19 (s, 1H), 7.23 (s, 1H), 7.36 (dt, *J*=2.4, 8.6 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): δ 11.55, 21.74, 38.05, 64.60, 69.03, 116.32, 127.56, 128.55, 156.59.

### 3.10. *General procedure for the addition of alkyl Grignard reagents to the hydrazones* ***5*****–*****12****: preparations of the trisubstituted hydrazines* ***13a*****–*****h***

An alkyl bromide (10 equiv.) in dry ether was added to magnesium chips (10 equiv.). After refluxing for 3 h, the mixture was cooled to −10°C and treated dropwise by the requisite hydrazone (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 combined ethereal extracts were evaporated under reduced pressure and the residue was treated with aqueous 50% HCl 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 trisubstituted hydrazine which was used directly in the next hydrogenolysis step, without further purification. The hydrazines **13a**–**h** are unstable colourless oils.

### 3.11. *(2*R*)-2-{1-Methyl-2-[(1*R*)-1-(3,4,5-trimethoxyphenyl)propyl]hydrazino}butan-1-ol (*R,R*)-(+)-**13a**

Starting from magnesium (0.369 g; 15.2 mmol), bromoethane (1.13 ml; 15.2 mmol) in ether (20 ml) and the hydrazone (*R*)-(−)-**5** (0.3 g; 1.01 mmol) in ether (5 ml), the above procedure (see Section 3.10) led to the hydrazine **13a** (0.240 g; 72.9%) as a colourless oil, $[\alpha]_D$ +13.4 (*c* 1.9, MeOH) and d.e.=100% ($^1H$ and $^{13}C$ NMR). $^1H$ NMR ($CDCl_3$): δ 0.80 and 0.86 (2t, *J*=7.4, 7.5 Hz, 6H), 1.20–2.00 (m, 4H), 2.47 (s, 3H), 2.47–2.52 (m, 1H), 3.48 (dd, *J*=7.6, 10.9 Hz, 1H), 3.61 (dd, *J*=4.9, 8.9 Hz, 1H), 3.68 (dd, *J*=2.7,

11.0 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 6H), 6.50 (s, 2H); $^{13}$C NMR ($CDCl_3$): δ 10.39, 10.67, 17.14, 27.78, 40.22, 55.68, 55.76, 60.50, 62.86, 64.39, 67.91, 104.21, 137.10, 138.53, 153.08.

### 3.12. (2R)-2-{2-[(1R)-1-(4-Methoxyphenyl)propyl]-1-methylhydrazino}butan-1-ol (R,R)-(+)-13b

Starting from magnesium (0.412 g; 16.9 mmol), bromoethane (1.26 ml; 16.9 mmol) in ether (20 ml) and the hydrazone (*R*)-(−)-**6** (0.40 g; 1.69 mmol) in ether (5 ml), the above procedure (see Section 3.10) led to the hydrazine **13b** (0.323 g; 71.9%) as a colourless oil, $[\alpha]_D$ +4.4 (*c* 1.34, MeOH) and d.e.=100% ($^1$H and $^{13}$C NMR). $^1$H NMR ($CDCl_3$): δ 0.76 and 0.85 (2t, *J*=7.4, 7.4 Hz, 6H), 1.20–1.90 (m, 4H), 2.45 (s, 3H), 2.45–2.50 (m, 1H), 3.45 (dd, *J*=7.6, 10.8 Hz, 1H), 3.61–3.67 (m, 2H), 3.79 (s, 3H), 6.86 (d, *J*=8.4 Hz, 2H), 7.19 (d, *J*=8.6 Hz, 2H); $^{13}$C NMR ($CDCl_3$): δ 10.67, 11.01, 17.21, 27.84, 40.55, 55.21, 63.27, 63.74, 68.15, 113.67, 128.86, 134.66, 153.86.

### 3.13. (2R)-2-{2-[(1R)-1-(4-Fluorophenyl)propyl]-1-methylhydrazino}butan-1-ol (R,R)-(+)-13c

Starting from magnesium (0.542 g; 22.3 mmol), bromoethane (1.66 ml; 22.3 mmol) in ether (20 ml) and the hydrazone (*R*)-(−)-**7** (0.50 g; 2.23 mmol) in ether (5 ml), the above procedure (see Section 3.10) led to the hydrazine **13c** (0.358 g; 63.4%) as a colourless oil, $[\alpha]_D$ +16.8 (*c* 1.42, MeOH) and d.e.=100% ($^1$H and $^{13}$C NMR). $^1$H NMR ($CDCl_3$): δ 0.76 and 0.83 (2t, *J*=7.4, 7.5 Hz, 6H), 1.20–1.90 (m, 4H), 2.44 (s, 3H), 2.40–2.50 (m, 1H), 3.37 (dd, *J*=7.9, 10.9 Hz, 1H), 3.60 (dd, *J*=2.9, 10.9 Hz, 1H), 3.67 (dd, *J*=4.9, 9.0 Hz, 1H), 6.97–7.02 (m, 2H), 7.22–7.27 (m, 2H); $^{13}$C NMR ($CDCl_3$): δ 9.84, 10.16, 17.09, 27.25, 39.51, 62.37, 62.97, 67.60, 114.24, 114.45, 128.55, 128.62, 138.49, 162.06.

### 3.14. (2R)-2-{[(1R)-1-(4-Fluorophenyl)pentyl]-1-methylhydrazino}butan-1-ol (R,R)-(+)-13d

Starting from magnesium (0.434 g; 17.8 mmol), *n*-bromobutane (1.9 ml; 17.8 mmol) in ether (20 ml) and the hydrazone (*R*)-(−)-**7** (0.40 g; 1.78 mmol) in ether (5 ml), the above procedure (see Section 3.10) led to the hydrazine **13d** (0.400 g; 79.4%) as a colourless oil, $[\alpha]_D$ +11.2 (*c* 1.12, MeOH) and d.e.=100% ($^1$H and $^{13}$C NMR). $^1$H NMR ($CDCl_3$): δ 0.82 and 0.84 (2t, *J*=7.2, 7.5 Hz, 6H), 1.00–1.90 (m, 8H), 2.43 (s, 3H), 2.43–2.50 (m, 1H), 3.34 (dd, *J*=8.0, 11.0 Hz, 1H), 3.60 (dd, *J*=2.9, 11.0 Hz, 1H), 3.75 (dd, *J*=5.2, 8.9 Hz, 1H), 6.98–7.02 (m, 2H), 7.22–7.27 (m, 2H); $^{13}$C NMR ($CDCl_3$): δ 10.78, 13.81, 17.96, 22.67, 28.36, 34.80, 40.15, 62.11, 63.10, 68.26, 114.92, 115.13, 129.16, 129.24, 138.82, 163.18.

### 3.15. (2R)-2-{1-Methyl-2-[(1R)-1-(4-methylphenyl)propyl]hydrazino}butan-1-ol (R,R)-(+)-13e

Starting from magnesium (0.221 g; 9.1 mmol), bromoethane (0.68 ml; 9.1 mmol) in ether (20 ml) and the hydrazone (*R*)-(−)-**8** (0.20 g; 0.9 mmol) in ether (5 ml), the above procedure (see Section 3.10) led to the hydrazine **13e** (0.117 g; 51.5%) as a colourless oil, $[\alpha]_D$ +3.5 (*c* 1.0, MeOH) and d.e.=100% ($^1$H and $^{13}$C NMR). $^1$H NMR ($CDCl_3$): δ 0.76 and 0.85 (2t, *J*=7.4, 7.5 Hz, 6H), 1.10–2.0 (m, 4H), 2.32 (s, 3H), 2.44 (s, 3H), 2.45–2.48 (m, 1H), 3.45 (dd, *J*=7.5, 11.0 Hz, 1H), 3.62–3.67 (m, 2H), 7.11–7.17 (m, 4H); $^{13}$C NMR ($CDCl_3$): δ 10.55, 10.94, 16.95, 20.99, 27.71, 40.26, 63.05, 63.97, 68.03, 127.62, 128.88, 136.77, 139.46.

### 3.16. (2R)-2-{1-Methyl-2-[(1R)-1-(4-methylphenyl)pentyl]hydrazino}butan-1-ol (R,R)-(−)-13f

Starting from magnesium (0.442 g; 20 mmol), *n*-bromobutane (1.95 ml; 20 mmol) in ether (20 ml) and the hydrazone (*R*)-(−)-**8** (0.40 g; 1.82 mmol) in ether (5 ml), the above procedure (see Section 3.10) led to the hydrazine **13f** (0.422 g; 83.4%) as a colourless oil, $[\alpha]_D$ −4.12 (*c* 1.07, MeOH) and d.e.=100% ($^1$H and $^{13}$C NMR). $^1$H NMR ($CDCl_3$): δ 0.83 and 0.85 (2t, *J*=7.3, 7.5 Hz, 6H), 1.00–1.90 (m, 10H), 2.33 (s, 3H), 2.43 (s, 3H), 2.43–2.50 (m, 1H), 3.43 (dd, *J*=7.6, 10.9 Hz, 1H), 3.63–3.67 (m, 1H), 3.71 (dd, *J*=4.8, 9.1 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 2H), 7.16 (d, *J*=8.1 Hz, 2H); $^{13}$C NMR ($CDCl_3$): δ 11.03, 14.02, 18.04, 20.27, 21.97, 27.69, 33.91, 39.52, 61.86, 62.41, 67.35, 126.85, 128.18, 136.91, 139.99.

### 3.17. (2R)-2-{2-[(1R)-1-(1,3-Benzodioxol-5-yl)propyl]-1-methylhydrazino}butan-1-ol (R,R)-(+)-13g

Starting from magnesium (0.390 g; 16 mmol), bromoethane (1.19 ml; 16 mmol) in ether (20 ml) and the hydrazone (*R*)-(−)-**9** (0.40 g; 1.6 mmol) in ether (5 ml), the above procedure (see Section 3.10) led to the hydrazine **13g** (0.231 g; 51.6%) as a colourless oil, $[\alpha]_D$ +15.0 (*c* 1.16, MeOH) and d.e.=100% ($^1$H and $^{13}$C NMR). $^1$H NMR ($CDCl_3$): δ 0.77 and 0.86 (2t, *J*=7.4, 7.5 Hz, 6H), 1.20–1.90 (m, 4H), 2.44 (s, 3H), 2.46–2.49 (m, 1H), 3.43 (dd, *J*=7.8, 10.9 Hz, 1H), 3.60 (dd, *J*=4.8, 9.3 Hz, 1H), 3.64 (dd, *J*=2.9, 11.0 Hz, 1H), 5.94 (s, 2H), 6.70–6.79 (m, 3H); $^{13}$C NMR ($CDCl_3$): δ 11.16, 11.59, 17.79, 28.46, 40.81, 63.55, 64.72, 68.80, 101.42, 108.31, 108.43, 121.77, 136.68, 146.69, 147.66.

### 3.18. (2R)-2-{1-Methyl-2-[(1R)-1-(2-naphthyl)propyl]hydrazino}butan-1-ol (R,R)-(−)-13h

Starting from magnesium (0.296 g; 12.2 mmol), bromoethane (0.91 ml; 12.2 mmol) in ether (20 ml) and the hydrazone (*R*)-(−)-**10** (0.30 g; 1.21 mmol) in ether (5 ml), the above procedure (see Section 3.10) led to the hydrazine **13h** (0.217 g; 65.5%) as a colourless oil, $[\alpha]_D$ −2.1 (*c* 1.17, MeOH) and d.e.=100% ($^1$H and $^{13}$C NMR). $^1$H NMR ($CDCl_3$): δ 0.79 and 0.83 (2t, *J*=7.4, 7.5 Hz, 6H), 1.20–2.10 (m, 4H), 2.47 (s, 3H), 2.47–2.55 (m, 1H), 3.44 (dd, *J*=7.6, 10.9 Hz, 1H), 3.64 (dd, *J*=2.8, 10.9 Hz, 1H), 3.86 (dd, *J*=4.8, 9.2 Hz, 1H), 7.42–7.48 (m, 3H), 7.69 (s, 1H), 7.81–7.83 (m, 3H); $^{13}$C NMR ($CDCl_3$): δ 9.66, 9.96, 16.34, 26.80, 39.55, 62.13, 63.63, 67.27, 124.42, 124.57, 124.92, 126.00, 126.63, 126.70, 127.09, 132.98, 133.28, 140.11.

### 3.19. General procedure for the hydrogenolysis of the hydrazines 13: preparation of the (R)-1-arylalkanamines 14

The trisubstituted hydrazine (**13a**–**h**) in ethanol was hydrogenolyzed in the presence of conc. HCl and 10% Pd–C under hydrogen (6 bar) at 110–120°C for 5 h. After filtration and evaporation, the residue was treated with 32% aqueous ammonia 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 **14** which was chromatographed over silica gel in the presence of triethylamine to prevent racemization (eluent: cyclohexane:ether, 9:1, and elution gradient).

### 3.20. (R)-1-(3,4,5-Trimethoxyphenyl)propan-1-amine (R)-(+)-14a

Starting from the hydrazine (*R*,*R*)-(+)-**13a** (0.250 g; 0.77 mmol) in ethanol (15 ml), conc. HCl (0.16 ml) and 10% Pd–C (0.060 g), the above procedure (see Section 3.19) led to the pure amine (*R*)-(+)-**14a** (0.060 g; 34.9%), $[\alpha]_D$ +3.0 (*c* 1.85, EtOH) and e.e.=91.5% (chiral GPC). Lit.[5] (racemic form); $^1$H NMR

($CDCl_3$): δ 0.89 (t, *J*=7.4 Hz, 3H), 1.67 (quint., *J*=7.2 Hz, 2H), 1.85 (m, 2H), 3.76 (t, *J*=6.8 Hz, 1H), 3.84 (s, 3H), 3.87 (s, 6H), 6.55 (s, 2H).

### *3.21. (*R*)-1-(4-Methoxyphenyl)propan-1-amine (*R*)-(+)-**14b***

Starting from the hydrazine (*R*,*R*)-(+)-**13b** (0.256 g; 0.96 mmol) in ethanol (18 ml), conc. HCl (0.21 ml) and 10% Pd–C (0.074 g), the above procedure (see Section 3.19) led to the pure amine (*R*)-(+)-**14b** (0.056 g; 35.2%), $[\alpha]_D$ +13 (*c* 0.8, EtOH), which could not be resolved by chiral GPC. Lit.[6] (racemic form); $^1$H NMR ($CDCl_3$): δ 0.85 (t, *J*=7.4 Hz, 3H), 1.51 (s, 2H), 1.60–1.72 (m, 2H), 3.76 (t, *J*=6.8 Hz, 1H), 3.80 (s, 3H), 6.55 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.5 Hz, 2H).

### *3.22. (*R*)-1-(4-Fluorophenyl)propan-1-amine (*R*)-(+)-**14c***

Starting from the hydrazine (*R*,*R*)-(+)-**13c** (0.300 g, 1.18 mmol) in ethanol (24 ml), conc. HCl (0.25 ml) and 10% Pd–C (0.095 g), the above procedure (see Section 3.19) led to the pure amine (*R*)-(+)-**14c** (0.072 g; 40.2%), $[\alpha]_D$ +14 (*c* 0.85, EtOH), which could not be resolved by chiral GPC. Lit.[7] (racemic form); $^1$H NMR ($CDCl_3$): δ 0.85 (t, *J*=7.4 Hz, 3H), 1.60–1.70 (m, 4H), 3.80 (t, *J*=6.8 Hz, 1H), 6.90–7.00 (m, 2H), 7.24–7.30 (m, 2H).

### *3.23. (*R*)-1-(4-Fluorophenyl)pentan-1-amine (*R*)-(+)-**14d***

Starting from the hydrazine (*R*,*R*)-(+)-**13d** (0.295 g; 1.05 mmol) in ethanol (20 ml), conc. HCl (0.22 ml) and 10% Pd–C (0.081 g), the above procedure (see Section 3.19) led to the pure amine (*R*)-(+)-**14d** (0.089 g; 47.1%), $[\alpha]_D$ +13.3 (*c* 1.05, EtOH) and e.e.=90% (chiral GPC). Lit.[8] (racemic form); $^1$H NMR ($CDCl_3$): δ 0.86 (t, *J*=7.0 Hz, 3H), 1.00–1.70 (m, 8H), 3.86 (t, *J*=6.9 Hz, 1H), 6.98–7.02 (m, 2H), 7.25–7.29 (m, 2H).

### *3.24. (*R*)-1-(4-Methylphenyl)propan-1-amine (*R*)-(+)-**14e***

Starting from the hydrazine (*R*,*R*)-(+)-**13e** (0.190 g; 0.76 mmol) in ethanol (16 ml), conc. HCl (0.16 ml) and 10% Pd–C (0.063 g), the above procedure (see Section 3.19) led to the pure amine (*R*)-(+)-**14e** (0.052 g; 46%), $[\alpha]_D$ +9.5 (*c* 1.0, EtOH), which could not be resolved by chiral GPC. MS calcd for $(C_{10}H_{14}N{=}M{-}H)^+$: 148.126. Found: 148.113; $^1$H NMR ($CDCl_3$): δ 0.85 (t, *J*=7.4 Hz, 3H), 1.60–1.70 (m, 2H), 1.80–1.90 (s, 2H), 2.33 (s, 3H), 3.76 (t, *J*=6.8 Hz, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 7.19 (d, *J*=8.1 Hz, 2H); $^{13}$C NMR ($CDCl_3$): δ 11.00, 21.04, 32.35, 57.53, 126.30, 129.07, 136.39, 143.41.

### *3.25. (*R*)-1-(4-Methylphenyl)pentan-1-amine (*R*)-(+)-**14f***

Starting from the hydrazine (*R*,*R*)-(−)-**13f** (0.314 g; 1.13 mmol) in ethanol (22 ml), conc. HCl (0.24 ml) and 10% Pd–C (0.088 g), the above procedure (see Section 3.19) led to the pure amine (*R*)-(+)-**14f** (0.080 g; 40%), $[\alpha]_D$ +2.9 (*c* 1.9, EtOH) and e.e.=93% (chiral GPC). MS calcd for $C_{12}H_{19}N$: M, 177.1517. Found: M, 177.1517; $^1$H NMR ($CDCl_3$): δ 0.86 (t, *J*=7.1 Hz, 3H), 1.00–1.80 (m, 8H), 2.33 (s, 3H), 3.83 (t, *J*=6.9 Hz, 1H), 7.13 (d, *J*=8.0 Hz, 2H), 7.19 (d, *J*=8.1 Hz, 2H); $^{13}$C NMR ($CDCl_3$): δ 13.59, 20.62, 22.26, 28.39, 39.95, 55.57, 125.79, 128.66, 136.36, 143.89.

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