Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1165–1181

TETRAHEDRON: *ASYMMETRY*

Diastereoselective $LiAlH_4$ reduction of chiral ketone hydrazones derived from (*R*)-(–)-2-aminobutan-1-ol

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Received 22 December 1999; accepted 26 January 2000

Abstract

Various chiral *N*,*N*-dialkylhydrazines were prepared in four to five steps from (*R*)-(–)-2-aminobutan-1-ol **6**. They reacted with various prochiral ketones, thus giving the corresponding hydrazones. Reduction of the latter by means of $LiAlH_4$ afforded *N*,*N*,*N*′-trisubstituted hydrazines whose d.e.s were in the range 43–100%. Interestingly, $LiAlH_4$ reduction of the four *N*-trifluoroethylhydrazones **34** and **38**–**40** yielded the hydrazines **46** and **48**–**50**, respectively, and with d.e.s = 100% by ^1H and ^{13}C NMR.

1. Introduction

As far as we know, only a few groups have examined the diastereoselective $LiAlH_4$ reduction of hydrazones derived from prochiral ketones and chiral hydrazines. Thus, starting from the SAMP reagent **1**, Enders[1] prepared the ketone hydrazones **2** (Scheme 1). Reduction of the latter with $LiAlH_4$ or catecholborane yielded the corresponding trisubstituted hydrazines **3** whose d.e.s were in the range 50–94%. $LiAlH_4$ reduction afforded the (*S*,*S*′)-hydrazine **3** as the major diastereomer, whereas catecholborane led mainly to the (*S*,*R*′)-compounds. On the other hand, Takahashi et al.[2] described the condensation of acetophenone with *N*-aminoephedrine, which gave the hydrazone **4** as an 82:18 mixture of the *E*:*Z* isomers. $LiAlH_4$ reduction of **4** furnished the trisubstituted hydrazine **5** with a d.e. = 30%.

The above authors remarked that the d.e.s of the final hydrazines **3** and **5** were dependent upon the proportions of *E*/*Z* geometrical isomers in the starting hydrazones **2** and **4**, respectively. The catalytic hydrogenation of chiral hydrazones was studied by Kiyooka et al.[3] They found that the asymmetric hydrogenolysis of the chiral hydrazones deriving from a few chiral amines and ethyl pyruvate gave optically active alanine with e.e.s in the range 0.9–46.5%.

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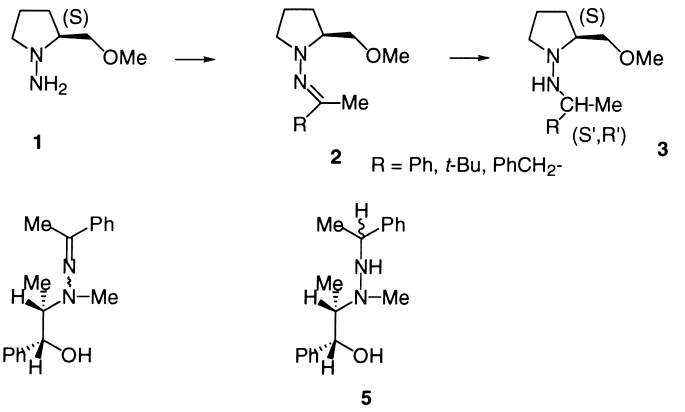
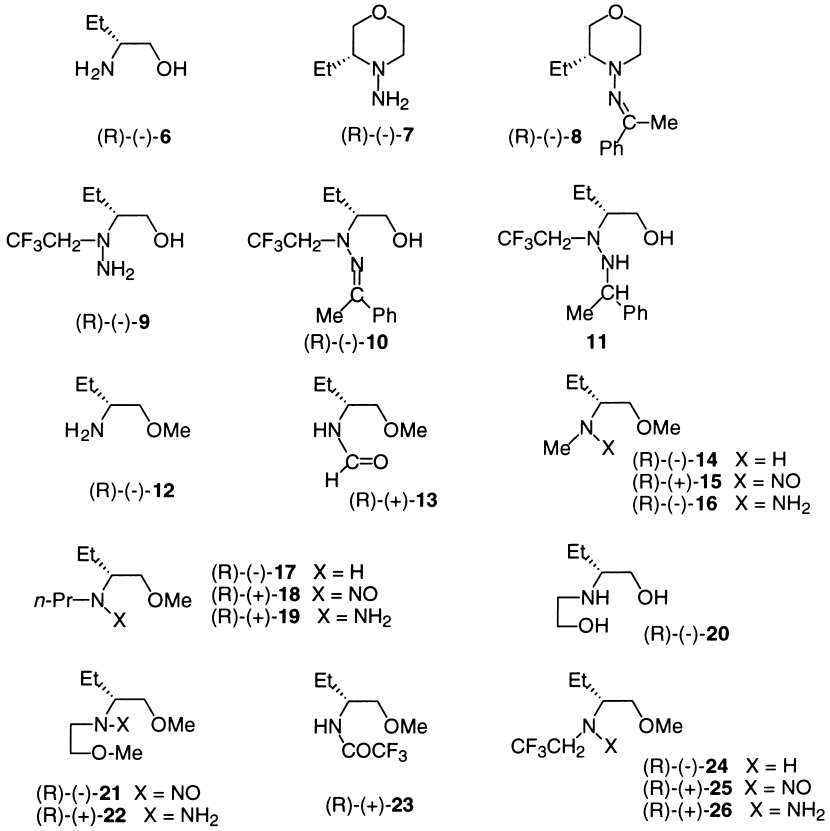
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00044-6



Scheme 1.

For some time now, we have used simple derivatives of 2-aminobutan-1-ol **6** as new chiral auxiliaries in asymmetric synthesis.[4,5] Indeed, racemic **6** is a low-molecular-weight compound which can be easily resolved on the industrial scale. In this paper we describe the $LiAlH_4$-mediated asymmetric reduction of various hydrazones derived from the aminoalcohol (*R*)-(−)-**6** (Scheme 2).



Scheme 2.

2. Results and discussion

We first synthesized the hydrazone (*R*)-(−)-**8** in ca. 88% yield from acetophenone and 4-amino-3-ethylmorpholine (*R*)-(−)-**7**.[4] However, all attempts with $LiAlH_4$ failed to reduce the double bond of (*R*)-(−)-**8**. The acetophenone hydrazone (*R*)-(−)-**10** was next obtained from the *N*,*N*-disubstituted hydrazine (*R*)-(−)-**9**,[4] as a 96:4 mixture of the *E*:*Z* geometrical isomers and in 62% yield. The reduction of the hydrazone (*R*)-(−)-**10** using 15 molar equivalents of $LiAlH_4$ in ether at room temperature led to the trisubstituted hydrazine **11** in ca. 79% yield and with a d.e. = 32% (from ^{13}C NMR).

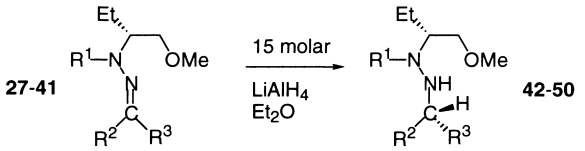
We next extended our study to other hydrazines derived from aminobutanol (*R*)-(−)-**6**, in order to assess the influence of the second *N*-substituent of the hydrazine on the diastereoselectivity of the chemical reduction of the corresponding hydrazones made from various aromatic and aliphatic ketones. The *N*-methylamine (*R*)-(−)-**14** was obtained by $LiAlH_4$ reduction of the formamide (*R*)-(+)-**13** resulting from the reaction of *O*-methylaminobutanol (*R*)-(−)-**12**[6] with ethyl formate. Treatment of the secondary amine (*R*)-(−)-**14** with aqueous nitrous acid smoothly afforded the *N*-nitrosoamine (*R*)-(+)-**15** which was in turn transformed into the hydrazine (*R*)-(−)-**16** upon reduction with $LiAlH_4$ in ether. The secondary amine (*R*)-(−)-**17** was obtained by *N*-alkylation of (*R*)-(−)-**12** with 1-bromopropane. *N*-Nitrosation of **17** gave the *N*-nitrosoamine (*R*)-(+)-**18** whose $LiAlH_4$ reduction yielded the hydrazine (*R*)-(+)-**19**. *N*-Alkylation of aminobutanol (*R*)-(−)-**6** by 2-bromoethanol led to the known aminodiol (*R*)-(−)-**20**.[7] *N*,*O*-Dimethylation of the latter was followed by nitrosation, thus yielding the intermediate (*R*)-(−)-**21** which was next smoothly reduced with $LiAlH_4$ into the hydrazine (*R*)-(+)-**22**. The *N*-trifluoroethylamine (*R*)-(−)-**24** was obtained by $LiAlH_4$ reduction of the trifluoroacetamide (*R*)-(+)-**23** resulting from the *N*-acylation of the amine **12** with trifluoroacetic anhydride. Nitrosation of the secondary amine **24**, followed by $LiAlH_4$ reduction of the resulting intermediate (*R*)-(+)-**25**, afforded the *N*,*N*-disubstituted hydrazine (*R*)-(+)-**26**.

The hydrazines (*R*)-(−)-**16**, (*R*)-(+)-**19**, (*R*)-(+)-**22** and (*R*)-(+)-**26** were treated with various prochiral phenones and aliphatic ketones to give the 15 hydrazones **27**–**41** reported in Table 1. The hydrazones **35**–**37** were obtained as mixtures of *E*/*Z* geometrical isomers, the former predominating (entries 9–11). The other 12 hydrazones were isolated as single *E*-isomers. $LiAlH_4$ reduction of the C=N bond of the hydrazones **27**–**41** was carried out next. The hydrazones **27**, **28**, **30**, **33** and **35** gave the expected hydrazines **42**, **43**, **44**, **45** and **47** with d.e.s in the range 43–87% (entries 1, 2, 4, 7 and 9). Reduction of the hydrazones **29**, **31** and **32** gave intractable mixtures of compounds (entries 3, 5 and 6). The α-tetralone hydrazone **41** could not be reduced (entry 15). We did not effect the reduction of the *E*/*Z* hydrazones **36** and **37** (entries 10 and 11), since they were not expected to give better results than the *E*/*Z* **35** (entry 9).

The hydrazones **34** and **38**–**40**, deriving from the *O*-methyl-*N*-trifluoroethylhydrazine (*R*)-(+)-**26** and various phenones, were reduced with a fifteen-fold molar excess of $LiAlH_4$ at room temperature, and afforded the corresponding hydrazines **46** and **48**–**50** as single diastereomers (d.e.s = 100%). The d.e.s of these four hydrazines were determined from their ^1H and ^{13}C NMR spectra, and their (*R*,*S*′) absolute configuration was ascribed on the basis of the following tentative mechanism, which is analogous to that which we confirmed in the case of the nucleophilic addition of Grignard reagents to the C=N bond of other similar chiral hydrazones[4,5] (Scheme 3).

The present study does show that the *N*-trifluoroethyl group plays an important part in the diastereoselectivity of the $LiAlH_4$ reduction of the C=N bond from the deriving chiral hydrazones. The reason for such a selectivity is not clear. Besides, and contrary to previous findings, it

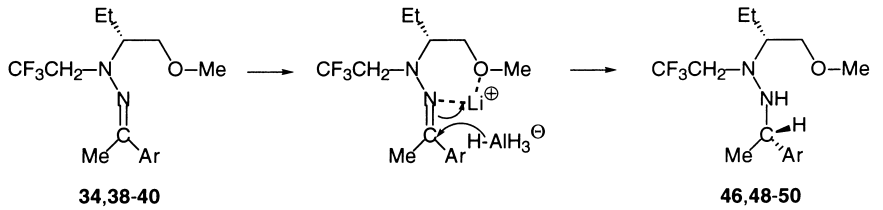
Table 1
$LiAlH_4$ reductions of the chiral hydrazones **27–41**



Entry	R^1	R^2	R^3	Hydrazones			Hydrazines		
					Yield (%)	E/Z ratio		Yield (%)	d.e. (%)
1	Me	Me	Ph	**27**	68.8	100/0	**42**	52*	43
2	Me	Me	2-HO-C_6H_4	**28**	94.4	100/0	**43**	≈100**	61.9
3	*n*-Pr	Me	Ph	**29**	76.3	100/0		Mixtures	
4	*n*-Pr	Me	2-HO-C_6H_4	**30**	30.7	100/0	**44**	71.4 **	87
5	*n*-Pr	Me	2-MeO-C_6H_4	**31**	65.7	100/0		Mixtures	
6	$MeOCH_2CH_2$	Me	Ph	**32**	52.3	100/0		Mixtures	
7	$MeOCH_2CH_2$	Me	2-HO-C_6H_4	**33**	70.5	100/0	**45**	40	48.7
8	CF_3CH_2	Me	Ph	**34**	97.5	100/0	**46**	85.4**	**100**
9	CF_3CH_2	Me	Ph-CH_2CH_2	**35**	84.2	86.5/13.5	**47**	54.7**	71-75
10	CF_3CH_2	$MeCH_2CH_2$	Ph	**36**	92.6	82/18			
11	CF_3CH_2	$MeCH_2$	Ph	**37**	89.4	85.5/14.5			
12	CF_3CH_2	Me	4-$MeOC_6H_4$	**38**	75.3	100/0	**48**	50.6	**100**
13	CF_3CH_2	Me	β–naphthyl	**39**	49	100/0	**49**	80.0	**100**
14	CF_3CH_2	Me	α–furyl	**40**	62.3	100/0	**50**	67.3	**100**
15	CF_3CH_2			**41**	41.7	100/0		no reaction	

* 20h at 20°C ; ** 72h under reflux.

appears that in the present case the OH group of the chiral auxiliary (*R*)-(−)-**6** must be protected as a methyl ether in order to achieve diastereoselective $LiAlH_4$ reduction of the corresponding hydrazones. As far as we know, the formation of the four hydrazines **46** and **48–50** represents the only reported examples of a totally diastereoselective reduction of the C=N bond of chiral *hydrazones*.



Scheme 3.

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 ICSN (CNRS, Gif-sur-Yvette). Chiral GPC 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. General procedure for the preparation of ketone hydrazones

A solution of the hydrazine, the requisite ketone (1.05–1.50 equiv.) and TsOH (catalytic amount) in dry toluene was refluxed under stirring for 12–20 h in a flask equipped with a Dean–Stark azeotropic water separator. After this the toluene was evaporated under reduced pressure and the residue was, in certain cases, purified by column chromatography on silica gel.

3.3. (3R)-3-Ethyl-N-[(E)-1-phenylethylidene]-1,4-oxazinan-4-amine (R)-(−)-8

Starting from (*R*)-(−)-4-amino-3-ethylmorpholine **7** (0.4 g, 3 mmol), acetophenone (0.24 ml, 2 mmol) and TsOH (catalytic amount) in dry toluene (30 ml), the above procedure led to hydrazone (*R*)-(−)-**8** as a colourless oil after chromatography (eluent: cyclohexane:ether, 95:5, then elution gradient) (410 mg, 88.4%), $[\alpha]_D$ −533 (*c* 1.2, MeOH). MS calcd for $C_{14}H_{20}N_2O$: M, 232.1575. Found: 232.1567. IR (film): 1610 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.85 (t, J = 7.5 Hz, 3H), 1.20–1.70 (m, 2H), 2.38 (s, 3H), 2.63 (dt, J = 2.5 and 11.3 Hz, 1H), 2.70 (td, J = 3.4 and 11.2 Hz, 1H), 2.90–3.00 (m, 1H), 3.46 (t, J = 10.8 Hz, 1H), 3.78 (td, J = 2.6 and 11.1 Hz, 1H), 3.86–3.89 (m, 1H), 3.94 (dd, J = 3.2 and 11.4 Hz, 1H), 7.37–7.78 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 9.60, 15.45, 23.08, 53.45, 64.84, 66.26, 70.12, 126.44, 128.27, 129.47, 138.90, 164.66.

3.4. (R)-(−)-2-[N′-(1-Phenylethylidene)-N-(2,2,2-trifluoroethyl)hydrazino]butan-1-ol (R)-(−)-10

Starting from (*R*)-(−)-2-[1-(2,2,2-trifluoroethyl)hydrazino]butan-1-ol **9** (3 g, 16 mmol), acetophenone (1.69 ml, 14.4 mmol) and *p*-TsOH (catalytic amount) in dry toluene (25 ml), the above

procedure led to hydrazone (*R*)-(−)-**10** as a yellow oil after chromatography (eluent: cyclohexane:ether, 9:1, then elution gradient) (2.60 g, 62.2%), $[\alpha]_D$ −16.9 (*c* 0.9, MeOH). Anal. calcd for $C_{14}H_{19}F_3N_2O$: C, 58.32; H, 6.64; N, 9.72. Found: C, 58.44; H, 6.68; N, 9.57. IR (film): 3405 (OH) and 1614 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.03 (t, J = 7.4 Hz, 3H), 1.39–1.62 (m, 2H), 2.40 (s, 3H), 2.80–3.00 (m, 1H), 3.30–3.90 (m, 4H), 7.20–7.70 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 11.40, 16.08, 21.84, 53.49, 63.45, 69.58, 123.92, 126.76, 128.07, 130.35, 137.75, 169.86. ^{19}F NMR δ: −70.3 (96.3% of the *E*-isomer) and −70.9 (3.7% of the *Z*-isomer).

3.5. 2-[2-(1-Phenylethyl)-1-(2,2,2-trifluoroethyl)hydrazino]butan-1-ol **11**

A suspension of $LiAlH_4$ (394 mg, 10.4 mmol) in dry ether (50 ml) was cooled to −10°C and treated dropwise by the hydrazone (*R*)-(−)-**10** (200 mg, 0.69 mmol) in dry ether (10 ml). After stirring at room temperature for 15 h, the mixture was quenched at −10°C by methanol and water (2 ml). After 30 min at room temperature, the suspension was filtered and the filtrate was evaporated under reduced pressure. The aqueous residue was extracted three times with ether. The organic extracts were pooled, dried ($MgSO_4$) and evaporated under reduced pressure, thus leading to the required hydrazine **11** as a colourless oil, which was used without further purification (158 mg, 78.6%), d.e. = 31% determined by ^{13}C NMR. MS calcd for $C_{14}H_{21}F_3N_2O$: M, 290.1605. Found: 290.1592. IR (film): 3409 (OH) and 3033 (CH=) cm^{-1}. ^1H NMR ($CDCl_3$) δ major diastereomer: 0.90 (t, J = 7.4 Hz, 3H), 1.25–1.52 (m, 2H), 1.31 (d, J = 6.6 Hz, 3H), 2.56–2.64 (m, 1H), 3.32–3.41 (m, 2H), 3.58 (dd, J = 7.6 and 11.2 Hz, 1H), 3.72 (dd, J = 3.1 and 11.3 Hz, 1H), 3.91 (q, J = 6.5 Hz, 1H), 7.29–7.32 (m, 5H); minor diastereomer: 0.84 (t, J = 7.4 Hz, 3H), 1.25–1.52 (m, 2H), 1.39 (d, J = 6.4 Hz, 3H), 2.65–2.70 (m, 1H), 3.15–3.42 (m, 4H), 3.91 (q, J = 6.3 Hz, 1H), 7.23–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$) δ major diastereomer: 11.14, 19.41, 21.03, 55.90, 57.32, 62.86, 66.98, 124.42, 126.63, 127.37, 128.31, 143.68; minor diastereomer: 11.06, 17.44, 20.67, 55.90, 57.51, 62.42, 66.98, 124.42, 126.63, 127.37, 128.31, 143.28.

3.6. (2R)-2-Formamido-1-methoxybutane (R)-(+)-**13**

A mixture of (2*R*)-1-methoxybutan-2-amine (*R*)-(−)-**12**[6] (13.6 g, 132 mmol) and ethyl formate (50 ml, 620 mmol) was stirred under reflux for 18 h, then the excess ester was evaporated under reduced pressure. Vacuum distillation of the residue gave the formamide (*R*)-(+)-**13** as a colourless liquid (12 g, 69.4%): b.p.$_{20}$ = 120–124°C and $[\alpha]_D$ +28.3 (*c* 2.06, MeOH). MS calcd for $C_6H_{13}NO_2$: M, 131.0942. Found: 131.0946. IR (film): 1681 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) (200 MHz) δ: 0.90–1.00 (m, 3H), 1.40–1.70 (m, 2H), 3.35 (s, 3H), 3.30–3.50 (m, 2H), 3.90–4.20 (m, 1H), 5.80–6.00 (s, 1H), 8.19 (s, 1H). ^{13}C NMR (200 MHz) ($CDCl_3$) δ: 10.43, 24.67, 49.16, 59.07, 73.55, 160.98.

3.7. (2R)-1-Methoxy-N-methylbutan-2-amine (R)-(−)-**14**

A suspension of $LiAlH_4$ (9.28 g, 242 mmol) in dry ether (150 ml) was cooled to 0°C and treated dropwise by the formamide (*R*)-(+)-**13** (7 g, 53.4 mmol) in dry ether (150 ml). After stirring under reflux for 8 h, the mixture was quenched at −20°C by methanol (33 ml), followed by water (47 ml) at −15°C. After 30 min at room temperature, the suspension was filtered and the solids were extracted several times with ether. The filtrate was dried ($MgSO_4$) and distilled under atmospheric pressure, thus giving amine (*R*)-(−)-**14** as a colourless liquid (3.25 g, 52%), b.p. = 127°C and $[\alpha]_D$ −27 (*c* 1.0, MeOH). MS calcd for $C_6H_{15}NO$ $[M^{-}\cdot OCH_3]^+$: M, 86.0969.

Found: 86.0971. ^{1}H NMR ($CDCl_3$) (200 MHz) δ: 0.90 (t, J = 7.5 Hz, 3H), 1.20–1.50 (m, 2H), 2.30 (s, 1H), 2.42 (s, 3H), 2.45–2.65 (m, 1H), 3.21–3.45 (m, 2H), 3.36 (s, 3H). ^{13}C NMR (200 MHz) ($CDCl_3$) δ: 10.49, 23.98, 34.26, 59.19, 60.76, 74.80.

3.8. (2R)-1-Methoxy-N-methyl-N-nitrosobutan-2-amine (R)-(+)-15

Sodium nitrite (5.6 g, 82 mmol) in water (10 ml) was added dropwise at 0°C to a mixture of the amine (*R*)-(−)-**14** (3.2 g, 27 mmol), concentrated hydrochloric acid (4 ml) and crushed ice (15 g). After stirring for 17 h at room temperature, the mixture was extracted with dichloromethane (20 ml), the aqueous phase was saturated with NaCl then extracted three times more with dichloromethane (3×20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure, thus giving the nitrosoamine (*R*)-(+)-**15** as a yellow oil (3.4 g, 86.3%), $[\alpha]_D$ +16.9 (*c* 1.3, MeOH), which was used in the next step without further purification. MS calcd for $C_6H_{14}N_2O_2$: M, 146.1055. Found: 146.1045. IR (film): 1436 (NO) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.95 (t, J = 7.4 Hz, 3H), 1.60–1.80 (m, 2H), 3.00 (s, 3H), 3.36 (s, 3H), 3.62 (dd, J = 4.0 and 10.4 Hz, 1H), 3.68 (dd, J = 7.8 and 10.4 Hz, 1H), 4.60–4.70 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 9.48, 21.23, 27.96, 57.91, 63.56, 72.05.

3.9. 1-[(1R)-1-(Methoxymethyl)propyl]-1-methylhydrazine (R)-(−)-16

A suspension of $LiAlH_4$ (0.91 g, 23.9 mmol) in dry ether (80 ml) was cooled to 0°C and treated dropwise with the *N*-nitrosoamine (*R*)-(+)-**15** (1.0 g, 6.8 mmol) in dry ether (20 ml). After stirring overnight at room temperature, the excess hydride was destroyed by addition of methanol (3 ml) and water (5 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*)-(−)-**16** (0.9 g, 99.5%), $[\alpha]_D$ −6.0 (*c* 1.1, MeOH), which was used in the next step without further purification. ^{1}H NMR (200 MHz) ($CDCl_3$) δ: 0.95 (t, J = 7.4 Hz, 3H), 1.20–1.70 (m, 2H), 2.56 (s, 3H), 2.50–2.60 (m, 1H), 2.90–3.20 (m, 2H), 3.36 (s, 3H), 3.40–3.60 (m, 2H). ^{13}C NMR (200 MHz) ($CDCl_3$) δ: 11.69, 20.58, 46.13, 59.29, 67.79, 73.00.

3.10. (2R)-1-Methoxy-N-propylbutan-2-amine (R)-(−)-17

1-Bromopropane (4.4 ml, 48.5 mmol) in THF (25 ml) was added to (*2R*)-1-methoxybutan-2-amine (*R*)-(−)-**12**[6] (5 g, 48.5 mmol) in THF (25 ml). After heating under reflux for 18 h, solid Na_2CO_3 (5.14 g, 48.5 mmol) was added. After refluxing for a further 18 h, the mixture was filtered and the filtrate was distilled under an atmospheric pressure, thus leading to amine (*R*)-(−)-**17** as a colourless oil (3 g, 42.8%), b.p. = 130–150°C, $[\alpha]_D$ −14.8 (*c* 1.1, MeOH). MS calcd for $C_8H_{19}NO$: M, 145.1466. Found: 145.1469. ^{1}H NMR (200 MHz) ($CDCl_3$) δ: 0.90 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H), 1.20–1.50 (m, 4H), 2.00–2.80 (m, 4H), 3.35 (s, 3H), 3.10–3.60 (m, 2H). ^{13}C NMR (200 MHz) ($CDCl_3$) δ: 10.60, 12.21, 23.94, 24.58, 49.76, 59.11, 75.28.

3.11. (2R)-1-Methoxy-N-nitroso-N-propylbutan-2-amine (R)-(+)-18

Sodium nitrite (2.85 g, 41.4 mmol) in water (10 ml) was added dropwise at room temperature to a mixture of amine (*R*)-(−)-**17** (2 g, 13.8 mmol), concentrated hydrochloric acid (2 ml) and

crushed ice (8 g). After stirring for 17 h at room temperature, the mixture was extracted with dichloromethane (20 ml), the aqueous phase was saturated with NaCl then extracted several times with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: cyclohexane:ether, 9:1, then elution gradient), thus giving the nitrosoamine (*R*)-(+)-**18** as a yellow oil (1.4 g, 58.4%), $[\alpha]_D$ +0.4 (*c* 1.1, MeOH). MS calcd for $C_8H_{18}N_2O_2$: M, 174.1368. Found: 174.1365. IR (film): 1450 (NO) cm^{-1}. ^1H NMR ($CDCl_3$) δ major conformer (79%): 0.90 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H), 1.30–1.90 (m, 4H), 3.34 (s, 3H), 3.40–3.70 (m, 4H), 4.35–4.45 (m, 1H); minor conformer (21%): 0.85 (t, J = 7.4 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H), 1.30–1.90 (m, 4H), 3.28 (s, 3H), 3.40–3.70 (m, 4H), 4.80–4.95 (m, 1H). ^{13}C NMR ($CDCl_3$) δ major conformer: 10.51, 11.60, 19.65, 23.10, 45.64, 58.74, 64.74, 73.81; minor conformer: 10.75, 11.27, 21.36, 22.98, 51.52, 54.26, 58.59, 71.32.

3.12. 1-[(1R)-1-(Methoxymethyl)propyl]-1-propylhydrazine (R)-(+)-19

A suspension of $LiAlH_4$ (760 mg, 20.1 mmol) in dry ether (80 ml) was cooled to −0°C and treated dropwise with the *N*-nitrosoamine (*R*)-(+)-**18** (1 g, 5.75 mmol) in dry ether (20 ml). After stirring at room temperature for 17 h, the excess hydride was destroyed by addition of methanol and water (4 ml). After 30 min at room temperature, 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 leading to the hydrazine (*R*)-(+)-**19** (900 mg, 97.8%), $[\alpha]_D$ +3 (*c* 3, MeOH), which was used in the next step without further purification. ^1H NMR (200 MHz) ($CDCl_3$) δ: 0.91 (t, J = 7.3 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H), 1.20–1.60 (m, 4H), 2.50–2.80 (m, 3H), 3.34 (s, 3H), 3.40 (dd, J = 4.0 and 10.0 Hz, 1H), 3.59 (dd, J = 7.0 and 10.0 Hz, 1H). ^{13}C NMR (200 MHz) ($CDCl_3$) δ: 11.87, 12.01, 21.22, 21.49, 59.24, 60.09, 73.42, 66.62.

3.13. (2R)-1-Methoxy-N-(2-methoxyethyl)-N-nitrosobutan-2-amine (R)-(−)-21

A suspension of sodium hydride (60% in oil, 2.8 g, 70 mmol) (previously washed with pentane) in dry ether (50 ml) was treated dropwise by (*2R*)-2-[(2-hydroxyethyl)amino]butan-1-ol (*R*)-(−)-**20**[7] (4.2 g, 32 mmol) in dry ether (20 ml). After stirring under reflux for 15 h, a solution of methyl iodide (4.32 ml, 64 mmol) in dry ether (20 ml) was added. The mixture was stirred under reflux for a further 5 h then quenched at −10°C by brine. The aqueous phase was decanted and extracted three times with ether (3×100 ml). The organic extracts were pooled, dried ($MgSO_4$) and evaporated under reduced pressure. The colourless residue (3 g, 18.6 mmol) was directly treated with concentrated hydrochloric acid (2.7 ml), crushed ice (10.9 g) and sodium nitrite (3.9 g, 56 mmol) in water (5 ml) and the mixture was stirred for 17 h at room temperature. Extraction with dichloromethane and purification of the residue by column chromatography on silica gel (eluent: cyclohexane:ether, 9:1, and elution gradient) led to nitrosoamine **21** as a yellow oil (1.6 g, 24%), $[\alpha]_D$ −11.0 (*c* 1.1, MeOH). MS calcd for $C_8H_{18}N_2O_3$: M, 160.1337. Found: 160.1345. IR (film): 1450 (NO) cm^{-1}. ^1H NMR ($CDCl_3$) δ major conformer (88.5%): 0.94 (t, J = 7.4 Hz, 3H), 1.80–2.00 (m, 2H), 3.30 and 3.34 (2s, 6H), 3.80–3.90 (m, 6H), 4.45–4.53 (m, 1H); minor conformer: 0.84 (t, J = 7.4 Hz, 3H), 1.50–1.70 (m, 2H), 3.29 and 3.38 (2s, 6H), 3.38–4.20 (m, 6H), 4.80–4.90 (m, 1H). ^{13}C NMR ($CDCl_3$) δ major conformer: 10.47, 23.12, 44.00, 58.54, 58.60, 65.07, 68.35, 73.84; minor conformer: 10.67, 21.27, 49.15, 58.54, 58.72, 54.15, 70.92, 71.18.

3.14. 1-(2-Methoxyethyl)-1-[(1R)-1-(methoxymethyl)propyl]hydrazine (R)-(+)-22

Starting from $LiAlH_4$ (1.0 g, 26.7 mmol) in dry ether (100 ml) and the *N*-nitrosoamine (*R*)-(−)-**21** (1.45 g, 7.63 mmol) in dry ether (30 ml), the above procedure [see (*R*)-(+)-**19**)] led to hydrazine (*R*)-(+)-**22** as a colourless oil (1.3 g, 97.0%), $[\alpha]_D$ +4.5 (*c* 1, MeOH), which was used in the next step without further purification. ^1H NMR ($CDCl_3$) δ: 0.95 (t, J = 7.5 Hz, 3H), 1.32–1.58 (m, 2H), 2.69–2.75 (m, 1H), 2.78–2.90 (m, 2H), 3.34 and 3.36 (2s, 6H), 3.45 (dd, J = 3.6 and 10.0 Hz, 1H), 3.56–3.61 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 11.39, 21.10, 56.41, 58.76, 58.85, 67.00, 71.70, 72.90.

3.15. (1R)-N-[1-(Methoxymethyl)propyl]trifluoroacetamide (R)-(+)-23

Trifluoroacetic anhydride (34.3 ml, 243 mmol) in dry ether (120 ml) was added dropwise at −10°C to (*R*)-1-methoxybutan-2-amine (*R*)-(−)-**12**[6] (25.0 g, 243 mmol) in dry ether (120 ml) for 1 h. At the end of addition, solid Na_2CO_3 (43.2 g, 407 mmol) was added. After stirring for 1 h at −10°C and 2 h to reach room temperature, the mixture was filtered through Celite, the solid material was extracted with ether and the combined organic phases were pooled, dried ($MgSO_4$) and evaporated under reduced pressure. Vacuum distillation of the residue gave the amide (*R*)-(+)-**23** as a colourless oil (39.4 g, 82.5%), $b.p._{.90}$ = 117–119°C, $[\alpha]_D$ + 23.5 (*c* 1.55, MeOH). Anal. calcd for $C_7H_{12}F_3NO_2$: C, 42.21; H, 6.07; N, 7.03. Found: C, 42.94; H, 6.05; N, 7.11. IR (film): 1704 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.94 (t, J = 7.5 Hz, 3H), 1.55–1.75 (m, 2H), 3.37 (s, 3H), 3.20–3.50 (m, 2H), 3.90–4.00 (m, 1H), 6.51 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 10.28, 24.34, 51.36, 59.10, 72.50, 115.89, 156.85. ^{19}F NMR δ: −76.5.

3.16. (2R)-1-Methoxy-N-(2,2,2-trifluoroethyl)butan-2-amine (R)-(−)-24

A suspension of $LiAlH_4$ (9.92 g, 261 mmol) in dry ether (200 ml) was cooled to −10°C and treated dropwise by the amide (*R*)-(+)-**23** (17.2 g, 86 mmol) in dry ether (50 ml). After stirring for 1 h at room temperature then 10 h under reflux, the mixture was quenched at −15°C by methanol (34 ml), followed by water (50 ml). After stirring for 30 min at room temperature, the suspension was filtered through Celite and the solid material was extracted several times with ether. The filtrate was dried ($MgSO_4$) and distilled under atmospheric pressure. The residue was distilled under reduced pressure, thus giving amine (*R*)-(−)-**24** as a colourless oil (12.9 g, 80.9%), $b.p._{.40}$ = 54–56°C and $[\alpha]_D$ −9.4 (*c* 1.3, MeOH). Anal. calcd for $C_7H_{14}F_3NO$: C, 45.40; H, 7.62; N, 7.56. Found: C, 45.39; H, 7.61; N, 7.49. ^1H NMR ($CDCl_3$) δ: 0.92 (t, J = 7.5 Hz, 3H), 1.30–1.50 (m, 2H), 2.71–2.77 (m, 1H), 3.10–3.32 (m, 2H), 3.35 (s, 3H), 3.36–3.50 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 10.02, 24.13, 48.18, 57.97, 58.87, 74.92, 125.62. ^{19}F NMR δ: −72.6.

3.17. (2R)-1-Methoxy-N-nitroso-N-(2,2,2-trifluoroethyl)butan-2-amine (R)-(+)-25

Sodium nitrite (24.0 g, 348 mmol) in water (20 ml) was added dropwise at room temperature to a mixture of amine (*R*)-(−)-**24** (21.5 g, 116 mmol), concentrated hydrochloric acid (17 ml) and crushed ice (52.2 g). After stirring for 17 h at room temperature, the mixture was extracted with dichloromethane (20 ml), the aqueous phase was saturated with NaCl then extracted several times with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure, thus affording the nitrosoamine (*R*)-(+)-**25** (22.7 g, 91.5%), $[\alpha]_D$ +2.14 (*c* 1.2, MeOH), which was used in the next step without further purification. A sample was

chromatographed (eluent: cyclohexane:ether, 9:1, then elution gradient) for elemental analysis. Anal. calcd for $C_7H_{13}F_3N_2O_2$: C, 39.25; H, 6.12; N, 13.08. Found: C, 39.16; H, 5.99; N, 12.93. IR (film): 1475 (NO) cm^{-1}. ^1H NMR ($CDCl_3$) δ major conformer: 0.99 (t, J = 7.4 Hz, 3H), 1.80–2.10 (m, 2H), 3.32 (s, 3H), 3.60–3.75 (m, 2H), 3.92 (dd, J = 9.1 and 14.8 Hz, 1H), 4.30–4.43 (m, 1H), 4.67 (dd, J = 9.0 and 14.8 Hz, 1H); minor conformer: 0.86 (t, J = 7.4 Hz, 3H), 1.50–1.70 (m, 2H), 3.29 (s, 3H), 3.60–3.75 (m, 2H), 3.86–3.98 (m, 1H), 4.61–4.74 (m, 1H), 4.75–4.86 (m, 1H). ^{13}C NMR ($CDCl_3$) δ major conformer: 10.46, 23.38, 44.31, 58.99, 65.55, 75.45, 122.51. ^{19}F NMR δ: −69.0 (88.1%), −70.2 (11.9%).

3.18. *1-[(1R)-1-(Methoxymethyl)propyl]-1-(2,2,2-trifluoroethyl)hydrazine (R)-(+)-**26***

A suspension of $LiAlH_4$ (1.9 g, 50 mmol) in dry ether (100 ml) was cooled to 0°C and treated dropwise with the *N*-nitrosoamine (*R*)-(+)-**25** (4.28 g, 20 mmol) in dry ether (100 ml). After stirring at room temperature for 6 h, the excess hydride was destroyed at −10°C by methanol (5 ml) and water (10 ml). After 30 min at room temperature, 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 leading to the hydrazine (*R*)-(+)-**26** (2.8 g, 70%), $[\alpha]_D$ +7.4 (*c* 1.4, MeOH), which was used in the next step without further purification. ^1H NMR ($CDCl_3$) δ: 0.96 (t, J = 7.3 Hz, 3H), 1.19–1.52 (m, 2H), 2.60–2.80 (m, 1H), 3.34 (s, 3H), 3.30–3.46 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 10.76, 21.93, 58.67, 60.37, 67.38, 72.94, 125.51. ^{19}F NMR δ: −71.6.

3.19. *Acetophenone-*N-*[(1R)-1-(methoxymethyl)propyl]-*N-*methylhydrazone (R)-(−)-27*

Starting from (*R*)-(−)-**16** (0.5 g, 3.78 mmol), acetophenone (0.29 ml, 2.52 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**27** as a yellow oil after chromatography (eluent: cyclohexane then elution gradient: cyclohexane:ether) (405 mg, 68.8 %), $[\alpha]_D$ −166.6 (*c* 1.1, MeOH). MS calcd for $C_{14}H_{22}N_2O$: M, 234.1732. Found: 234.1737. IR (film): 1608 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.95 (t, J = 7.4 Hz, 3H), 1.50–1.70 (m, 2H), 2.32 (s, 3H), 2.58 (s, 3H), 2.80–2.90 (m, 1H), 3.36 (s, 3H), 3.50 (dd, J = 5.4 and 9.7 Hz, 1H), 3.77 (dd, J = 5.3 and 9.8 Hz, 1H), 7.20–7.40 (m, 3H), 7.70–7.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 11.25, 15.77, 23.19, 41.55, 59.13, 68.12, 73.53, 126.37, 127.27, 128.26, 139.47, 160.46.

3.20. *2-Hydroxyacetophenone-*N-*[(1R)-1(methoxymethyl)propyl]-*N-*methylhydrazone (R)-(−)-28*

Starting from (*R*)-(−)-**16** (0.75 g, 5.68 mmol), 2-hydroxyacetophenone (0.45 ml, 3.79 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**28** as a yellow liquid after chromatography (eluent: cyclohexane) (890 mg, 94.4%), $[\alpha]_D$ −201.8 (*c* 1.1, MeOH). MS calcd for $C_{14}H_{22}N_2O_2$: M, 250.1681. Found: 250.1674. IR (film): 3361 (OH) and 1602 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.96 (t, J = 7.4 Hz, 3H), 1.50–1.70 (m, 2H), 2.45 (s, 3H), 2.63 (s, 3H), 2.80–2.90 (m, 1H), 3.35 (s, 3H), 3.48 (dd, J = 4.8 and 9.9 Hz, 1H), 3.66 (dd, J = 5.9 and 10.0 Hz, 1H), 6.86 (td, J = 1.0 and 7.9 Hz, 1H), 6.95 (dd, J = 1.0 and 8.3 Hz, 1H), 7.26 (td, J = 1.6 and 7.7 Hz, 1H), 7.48 (dd, J = 1.5 and 7.9 Hz, 1H), 13.92 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 10.68, 13.85, 21.90, 41.53, 58.43, 66.94, 72.20, 116.96, 117.62, 119.63, 127.44, 130.59, 160.26, 168.27.

3.21. *Acetophenone*-N-*[(1*R*)-1-(methoxymethyl)propyl]*-N-*propylhydrazone* (R)-(−)-**29**

Starting from (*R*)-(+)-**19** (0.56 g, 3.5 mmol), acetophenone (0.27 ml, 2.33 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**29** as a yellow oil after chromatography (eluent: cyclohexane) (466 mg, 76.3%), $[\alpha]_D$ −220 (*c* 1.3, MeOH). MS calcd for $C_{16}H_{26}N_2O$: M, 262.2045. Found: 262.2044. IR (film): 1616 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.90 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.42–1.65 (m, 4H), 2.36 (s, 3H), 2.71–3.00 (m, 3H), 3.34 (s, 3H), 3.45 (dd, J = 6.5 and 9.5 Hz, 1H), 3.76 (dd, J = 4.6 and 9.5 Hz, 1H), 7.34–7.37 (m, 2H), 7.73–7.76 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 11.44, 11.71, 16.03, 21.68, 23.28, 55.12, 58.90, 65.24, 73.28, 126.34, 128.15, 129.00, 139.44, 163.43.

3.22. *2-Hydroxyacetophenone*-N-*[(1*R*)-1-(methoxymethyl)propyl]*-N-*propylhydrazone* (R)-(−)-**30**

Starting from (*R*)-(+)-**19** (0.40 g, 2.5 mmol), 2-hydroxyacetophenone (0.2 ml, 1.66 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**30** as a yellow liquid after chromatography (eluent: cyclohexane) (142 mg, 30.7%), $[\alpha]_D$ −268 (*c* 1.0, MeOH). MS calcd for $C_{16}H_{26}N_2O_2$: M, 278.1994. Found: 278.2004. IR (film): 3361 (OH) and 1602 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.90 (t, J = 7.4 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H), 1.40–1.60 (m, 4H), 2.50 (s, 3H), 2.70–2.90 (m, 3H), 3.33 (s, 3H), 3.41 (dd, J = 5.7 and 9.5 Hz, 1H), 3.62 (dd, J = 5.4 and 9.7 Hz, 1H), 6.83–6.87 (m, 1H), 6.95 (dd, J = 1.1 and 8.3 Hz, 1H), 7.25–7.29 (m, 1H), 7.49 (dd, J = 1.6 and 8.0 Hz, 1H), 14.33 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 10.81, 10.90, 14.06, 20.65, 21.73, 54.86, 58.23, 64.88, 71.95, 116.92, 117.32, 118.42, 127.56, 130.60, 160.81, 171.13.

3.23. *2-Methoxyacetophenone*-N-*[(1*R*)-1-(methoxymethyl)propyl]*-N-*propylhydrazone* (R)-(−)-**31**

Starting from (*R*)-(+)-**19** (0.6 g, 3.75 mmol), 2-methoxyacetophenone (0.34 ml, 2.49 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**31** as a yellow liquid after chromatography (eluent: cyclohexane:ether, 9:1, then elution gradient) (480 mg, 65.7%), $[\alpha]_D$ −48.8 (*c* 0.8, MeOH). MS calcd for $C_{17}H_{28}N_2O_2$: M, 292.2150. Found: 292.2155. IR (film): 1600 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.91 (t, J = 7.4 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H), 1.46 (sex, J = 7.4 Hz, 2H), 1.61 (quint, J = 7.2 Hz, 2H), 2.31 (s, 3H), 2.70–2.90 (m, 3H), 3.38 (s, 3H), 3.40–3.50 (m, 1H), 3.72 (dd, J = 4.4 and 9.6 Hz, 1H), 3.81 (s, 3H), 6.88–7.31 (m, 4H).

3.24. *Acetophenone*-N-*(2-methoxyethyl)*-N-*[(1*R*)-1-(methoxymethyl)propyl]hydrazone* (R)-(−)-**32**

Starting from (*R*)-(+)-**22** (0.6 g, 3.41 mmol), acetophenone (0.26 ml, 2.27 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**32** as a yellow liquid after chromatography (eluent: cyclohexane:ether, 9:1, then elution gradient) (330 mg, 52.3%), $[\alpha]_D$ −220 (*c* 1.0, MeOH). MS calcd for $C_{16}H_{26}N_2O_2$: M, 278.1994. Found: 278.2004. IR (film): 1608 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.98 (t, J = 7.4 Hz, 3H), 1.59 (quint, J = 7.4 Hz, 2H), 2.37 (s, 3H), 2.87 (quint, J = 6.1 Hz, 1H), 3.05–3.20 (m, 2H), 3.33 (s, 6H), 3.37–3.50 (m, 3H), 3.74 (dd, J = 4.8 and 9.7 Hz, 1H), 7.35–7.78 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 11.38, 15.99, 23.06, 52.63, 58.77, 58.86, 66.19, 71.37, 73.07, 126.36, 128.15, 129.16, 139.14, 164.08.

*3.25. 2-Hydroxyacetophenone-*N*-(2-methoxyethyl)-*N*-[(1*R*)-1-(methoxymethyl)propyl]hydrazone (*R*)-(−)-**33***

Starting from (*R*)-(+)-**22** (0.6 g, 3.41 mmol), 2-hydroxyacetophenone (0.27 ml, 2.27 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**33** as a yellow liquid after chromatography (eluent: cyclohexane:ether, 95:5, then elution gradient) (470 mg, 70.5%), $[\alpha]_D$ −183 (*c* 1.2, MeOH). MS calcd for $C_{16}H_{26}N_2O_3$: M, 294.194. Found: 294.195. IR (film): 1602 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.99 (t, J = 7.4 Hz, 3H), 1.50–1.60 (m, 2H), 2.51 (s, 3H), 2.89–2.95 (m, 1H), 3.08–3.21 (m, 2H), 3.32 and 3.33 (2s, 6H), 3.38–3.47 (m, 3H), 3.62 (dd, J = 5.7 and 9.8 Hz, 1H), 6.86 (td, 1.1 and 7.5 Hz, 1H), 6.96 (dd, J = 1.1 and 8.2 Hz, 1H), 7.26–7.32 (m, 1H), 7.50 (dd, J = 1.5 and 8.0 Hz, 1H), 14.14 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 10.97, 14.31, 21.93, 52.87, 58.27, 58.44, 65.95, 70.31, 72.10, 117.17, 117.64, 119.31, 127.93, 131.00, 160.75, 172.04.

3.26. N-*(1-Methoxymethyl)propyl*-N′-*(1-phenylethylidene)*-N-*(2,2,2-trifluoroethyl)-hydrazone (*R*)-(−)-**34***

Starting from (*R*)-(+)-**26** (2.11 g, 10 mmol), acetophenone (1.1 ml, 9.5 mmol) and *p*-TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**34** as a yellow oil (2.9 g, 97.5%), $[\alpha]_D$ −151.3 (*c* 1.1, MeOH), which was used in the next step without further purification. Anal. calcd for $C_{15}H_{21}F_3N_2O$: C, 59.59; H, 7.00; N, 9.27. Found: C, 60.02; H, 7.03; N, 9.12. IR (film): 1614 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.02 (t, J = 7.4 Hz, 3H), 1.61 (quint, J = 7.3 Hz, 2H), 2.40 (s, 3H), 2.75–2.83 (m, 1H), 3.33 (s, 3H), 3.52 (dd, J = 4.5 and 9.7 Hz, 1H), 3.61 (dd, J = 4.7 and 9.8 Hz, 1H), 3.63–3.69 (m, 2H), 7.74–7.77 (m, 3H), 7.37–7.39 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 11.36, 16.11, 22.33, 54.42, 58.97, 67.64, 72.35, 125.24, 126.70, 128.28, 129.71, 138.69, 167.54. ^{19}F NMR δ: −70.9.

*3.27. 4-Phenylbutan-2-one-*N*-[(1*R*)-(1-methoxymethyl)propyl]-*N*-(2,2,2-trifluoroethyl)hydrazone (*R*)-(−)-**35***

Starting from (*R*)-(+)-**26** (2 g, 10 mmol), 4-phenylbutan-2-one (1.35 ml, 9 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) after 4 days under reflux, led to hydrazone (*R*)-(−)-**35** as a yellow–orange oil after chromatography (eluent: cyclohexane then elution gradient: cyclohexane:ether) (2.5 g, 84.2%), $[\alpha]_D$ −46.8 (*c* 1.1, MeOH). Presence of two isomers (*E*:*Z*, 86.5:13.5). Anal. calcd for $C_{17}H_{25}F_3N_2O$: C, 61.80; H, 7.63; N, 8.48. Found: C, 61.66; H, 7.29; N, 8.42. IR (film): 1604 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ major isomer: 0.90–1.00 (m, 3H), 1.40–1.50 (m, 2H), 1.97 (s, 3H), 2.40–2.90 (m, 5H), 3.33 (s, 3H), 3.30–3.60 (m, 4H), 7.00–7.30 (m, 5H); minor isomer: 0.90–1.00 (m, 3H), 1.50–1.52 (m, 2H), 2.00 (s, 3H), 2.40–2.90 (m, 5H), 3.34 (s, 3H), 3.30–3.60 (m, 4H), 7.00–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ major isomer: 11.21, 17.70, 22.00, 32.63, 40.04, 54.01, 58.80, 67.23, 71.87, 125.00, 125.95, 128.13, 141.10, 172.38. ^{19}F NMR δ: −70.9 (86.5%) and −70.7 (13.5%).

*3.28. 1-Phenylbutan-1-one-*N*-[(1*R*)-(1-methoxymethyl)propyl]-*N*-(2,2,2-trifluoroethyl)hydrazone (*R*)-(−)-**36***

Starting from (*R*)-(+)-**26** (1 g, 5 mmol), butyrophenone (667 mg, 4.5 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone

(*R*)-(−)-**36** as an orange oil (1.37 g, 92.6%), $[\alpha]_D$ −108.9 (*c* 1.05, MeOH), which was used in the next step without further purification. Presence of two isomers (*E*:*Z*, 82:18). Anal. calcd for $C_{17}H_{25}F_3N_2O$: C, 61.80; H, 7.63; N, 8.48. Found: C, 62.14; H, 7.67; N, 8.25. IR (film): 1689 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ major isomer: 0.91 (t, J = 7.3 Hz, 3H), 1.05 (t, J = 7.4 Hz, 3H), 1.37–1.80 (m, 4H), 2.49–2.97 (m, 3H), 3.33 (s, 3H), 3.54–3.77 (m, 4H), 7.29–7.70 (m, 5H); minor isomer: 0.86–1.06 (m, 6H), 1.56–1.80 (m, 4H), 2.49–2.97 (m, 3H), 3.34 (s, 3H), 3.54–3.77 (m, 4H), 7.30–8.20 (m, 5H). ^{19}F NMR δ: −70.7 (82%) and −70.6 (18%).

3.29. 1-Phenylpropan-1-one-N-*[(1*R*)-(1-methoxymethyl)propyl]*-N-*(2,2,2-trifluoroethyl)hydrazone (*R*)-(−)-**37***

Starting from (*R*)-(+)-**26** (1 g, 5 mmol), propiophenone (600 mg, 4.5 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**37** as an orange oil (1.27 g, 89.4%), $[\alpha]_D$ −96 (*c* 1.04, MeOH), which was used in the next step without further purification. Presence of two isomers (*E*:*Z*, 85.5:14.5). MS calcd for $C_{16}H_{23}F_3N_2O$: M, 316.1762. Found: 316.1759. IR (film): 1691 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ major isomer: 1.01 and 1.04 (2t, J = 7.5 and 7.3 Hz, 6H), 1.59–1.66 (m, 2H), 2.50–3.00 (m, 3H), 3.33 (s, 3H), 3.41–3.77 (m, 4H), 7.29–7.68 (m, 5H); minor isomer: 0.96–1.08 (m, 6H), 1.54–1.59 (m, 2H), 2.50–3.00 (m, 3H), 3.34 (s, 3H), 3.41–3.77 (m, 4H), 7.29–7.68 (m, 5H). ^{19}F NMR δ: −70.7 (85.5%) and −70.6 (14.5%).

3.30. 4-Methoxyacetophenone-N-*[(1*R*)-1-(methoxymethyl)propyl]*-N-*(2,2,2-trifluoroethyl)hydrazone (*R*)-(−)-**38***

Starting from (*R*)-(+)-**26** (480 mg, 2.4 mmol), 4-methoxyacetophenone (240 mg, 1.6 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**38** as a colourless oil after chromatography (eluent: cyclohexane then elution gradient: cyclohexane:ether) (0.4 g, 75.3%), $[\alpha]_D$ −121 (*c* 0.95, MeOH). Anal. calcd for $C_{16}H_{23}F_3N_2O_2$: C, 57.82; H, 6.98; N, 8.43. Found: C, 57.91; H, 7.04; N, 8.42. IR (film): 1602 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.02 (t, J = 7.4, 3H), 1.55–1.63 (m, 2H), 2.37 (s, 3H), 2.70–2.80 (m, 1H), 3.33 (s, 3H), 3.52 (dd, J = 4.8 and 9.7 Hz, 1H), 3.58–3.65 (m, 3H), 3.83 (s, 3H), 6.90 (d, J = 8.9 Hz, 2H), 7.73 (d, J = 8.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 11.33, 15.74, 22.28, 54.47, 54.92, 58.92, 67.64, 72.30, 113.54, 125.48, 128.13, 131.21, 160.95, 167.10. ^{19}F NMR δ: −70.9.

3.31. 2-Acetonaphthone-N-*[(1*R*)-1-(methoxymethyl)propyl]*-N-*(2,2,2-trifluoroethyl)hydrazone (*R*)-(−)-**39***

Starting from (*R*)-(+)-**26** (480 mg, 2.4 mmol), 2-acetylnaphthalene (272 mg, 1.6 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**39** as a viscous yellow oil after chromatography (eluent: cyclohexane then elution gradient: cyclohexane:ether) (275 mg, 49%), $[\alpha]_D$ −153 (*c* 0.8, MeOH). Anal. calcd for $C_{19}H_{23}F_3N_2O$: C, 64.76; H, 6.58; N, 7.95. Found: C, 64.63; H, 6.71; N, 7.95. IR (film): 1608 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.05 (t, J = 7.4 Hz, 3H), 1.64 (quint, J = 7.3 Hz, 2H), 2.52 (s, 3H), 2.80–2.88 (m, 1H), 3.35 (s, 3H), 3.56 (dd, J = 4.4 and 9.8 Hz, 1H), 3.64 (dd, J = 4.5 and 9.7 Hz, 1H), 3.67–3.74 (m, 2H), 7.48–7.54 (m, 2H), 7.70–7.90 (m, 3H), 8.04 (d, J = 8.7 Hz, 1H), 8.10

(s, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.36, 15.96, 22.35, 54.48, 58.98, 67.66, 72.39, 123.98, 126.24, 126.73, 126.76, 127.61, 127.79, 128.63, 132.98, 134.04, 136.14, 166.96. ^{19}F NMR δ: −70.9.

*3.32. 2-Acetylfuran-*N*-[(1*R*)-1-(methoxymethyl)propyl]-*N*-(2,2,2-trifluoroethyl)hydrazone (*R*)-(−)-**40***

Starting from (*R*)-(+)-**26** (300 mg, 1.5 mmol), 2-acetylfurane (0.1 ml, 1 mmol) and TsOH (catalytic amount) in anhydrous toluene (20 ml), the above procedure (see Section 3.2) led to hydrazone (*R*)-(−)-**40** as a yellow oil after chromatography (eluent: cyclohexane:ether. 9:1, then elution gradient) (182 mg, 62.3%), $[\alpha]_D$ −139 (*c* 2, MeOH). Anal. calcd for $C_{13}H_{19}F_3N_2O_2$: C, 53.42; H, 6.55; N, 9.58. Found: C, 53.94; H, 6.61; N, 9.79. IR (film): 1602 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.01 (t, J = 7.4 Hz, 3H), 1.58–1.66 (m, 2H), 2.32 (s, 3H), 2.72–2.78 (m, 1H), 3.32 (s, 3H), 3.55 (t, J = 4.7 Hz, 2H), 3.63–3.70 (AB, J = 9.4 Hz, 2H), 6.45 (dd, J = 1.7 and 3.4 Hz, 1H), 6.77 (d, J = 3.4 Hz, 1H), 7.50 (d, J = 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.22, 15.06, 22.14, 54.18, 58.89, 67.80, 72.09, 111.32, 118.86, 125.38, 144.18, 152.05, 159.18. ^{19}F NMR δ: −71.1.

*3.33. 3,4-Dihydro(2*H*)naphthalen-1-one-*N*-[(1*R*)-1-(methoxymethyl)propyl]-*N*-(2,2,2-trifluoroethyl)hydrazone (*R*)-(−)-**41***

Starting from (*R*)-(+)-**26** (480 mg, 2.4 mmol), α-tetralone (234 mg, 1.6 mmol) and TsOH (catalytic amount) in anhydrous toluene (15 ml), the above procedure (see Section 3.2) after 4 days under reflux, led to hydrazone (*R*)-(−)-**41** as a yellow oil after chromatography (eluent: cyclohexane) (219 mg, 41.7%), $[\alpha]_D$ −136 (*c* 0.7, MeOH). Anal. calcd for $C_{17}H_{23}F_3N_2O$: C, 62.18; H, 7.06; N, 8.53. Found: C, 62.29; H, 6.84; N, 8.32. IR (film): 1616 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.01 (t, J = 7.4 Hz, 3H), 1.55–1.63 (m, 2H), 1.85–1.94 (m, 2H), 2.70–2.78 (m, 2H), 2.83 (t, J = 6.1 Hz, 2H), 2.94–3.00 (m, 1H), 3.33 (s, 3H), 3.50 (dd, J = 4.7 and 9.6 Hz, 1H), 3.61 (dd, J = 4.7 and 9.6 Hz, 1H), 3.62–3.68 (m, 2H), 7.13 (d, J = 7.7 Hz, 1H), 7.17–7.23 (m, 1H), 7.26–7.31 (td, J = 1.2 and 7.4 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.36, 22.32, 22.48, 27.87, 29.83, 54.47, 58.94, 67.58, 72.49, 125.12, 125.33, 126.10, 128.65, 128.85, 132.80, 140.39, 166.59. ^{19}F NMR δ: −70.0.

*3.34. 1-[(1*R*)-1-(Methoxymethyl)propyl]-1-methyl-2-(1-phenylethyl)hydrazine **42***

A suspension of $LiAlH_4$ (126 mg, 3.3 mmol) in dry ether (30 ml) was cooled to −10°C and treated dropwise by hydrazone (*R*)-(−)-**27** (54 mg, 0.22 mmol) in dry ether (10 ml). After stirring under reflux for 72 h, the mixture was quenched at −10°C by methanol and water. After 30 min at room temperature, the suspension was filtered and the filtrate was evaporated under reduced pressure. The aqueous residue was extracted three times with ether (3×10 ml). The organic extracts were pooled, dried ($MgSO_4$) and evaporated under reduced pressure, thus leading to the hydrazine **42** as a colourless and unstable oil, without further purification (28 mg, 52%), d.e. = 43% (^{1}H NMR). ^{1}H NMR (200 MHz) ($CDCl_3$) δ major diastereomer: 0.83 (t, J = 7.3 Hz, 3H), 1.10–1.60 (m, 2H), 1.29 (d, J = 6.4 Hz, 3H), 2.49 (s, 3H), 2.50–2.80 (m, 1H), 3.24 (s, 3H), 3.32 (dd, J = 5.5 and 10.3 Hz, 1H), 3.52 (dd, J = 7.6 and 9.7 Hz, 1H), 3.94 (q, J = 6.5 Hz, 1H), 7.00–7.40 (m, 5H); minor diastereomer: 0.80 (m, 3H), 1.10–1.60 (m, 5H), 2.47 (s, 3H), 2.50–2.80 (m, 1H), 3.33 (s, 3H), 3.28–3.57 (m, 2H), 3.89–3.99 (m, 1H), 7.00–7.40 (m, 5H).

3.35. N-*[(1*R*)-1-(Methoxymethyl)propyl]*-N-*methyl*-N′-*[1-(2-hydroxyphenyl)ethyl]hydrazine* ***43***

A suspension of $LiAlH_4$ (455 mg, 12 mmol) in dry ether (40 ml) was cooled to −10°C and treated dropwise by hydrazone (*R*)-(−)-**28** (200 mg, 0.8 mmol) in dry ether (20 ml). After stirring at room temperature for 20 h, the mixture was quenched at −10°C by methanol and water. After 30 min at room temperature, the suspension was filtered and the filtrate was evaporated under reduced pressure. The aqueous residue was extracted three times with ether. The organic extracts were pooled, dried ($MgSO_4$) and evaporated under reduced pressure, thus leading to the hydrazine **43** as a colourless and unstable oil, without further purification (200 mg, quantitative), d.e. = 61.9% (^{1}H NMR). ^{1}H NMR ($CDCl_3$) δ major diastereomer: 0.82 (t, J = 7.4 Hz, 3H), 1.20–1.40 (m, 2H), 1.37 (d, J = 6.8 Hz, 3H), 2.51 (s, 3H), 2.84–2.91 (m, 1H), 3.28 (s, 3H), 3.34–3.40 (m, 1H), 3.53 (t, J = 8.9 Hz, 1H), 4.14 (q, J = 6.7 Hz, 1H), 6.76 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 7.2 Hz, 1H), 7.11 (t, J = 7.7 Hz, 1H), 10.66 (s, 1H); minor diastereomer: 0.85 (t, J = 7.4 Hz, 3H), 1.20–1.40 (m, 2H), 1.34 (d, J = 6.8 Hz, 3H), 2.45 (s, 3H), 2.97–2.98 (m, 1H), 3.33 (s, 3H), 3.34–3.40 (m, 1H), 3.62 (t, J = 9.8 Hz, 1H), 4.10 (q, J = 6.7 Hz, 1H), 6.76 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 7.11 (t, J = 7.7 Hz, 1H), 10.92 (s, 1H). ^{13}C NMR ($CDCl_3$) δ major diastereomer: 10.24, 18.27, 21.14, 37.54, 56.07, 57.91, 63.31, 72.41, 115.84, 118.15, 127.04, 127.21, 129.25, 157.70; minor diastereomer: 10.53, 18.50, 20.55, 37.05, 56.01, 57.97, 62.31, 72.68, 115.77, 118.09, 127.04, 127.21, 129.25, 157.70.

3.36. N-*[(1*R*)-1-(Methoxymethyl)propyl]*-N-*propyl*-N′-*[1-(2-hydroxyphenyl)ethyl]hydrazine* ***44***

A suspension of $LiAlH_4$ (47.8 mg, 1.25 mmol) in dry ether (20 ml) was cooled to −10°C and treated dropwise by hydrazone (*R*)-(−)-**30** (70 mg, 0.25 mmol) in dry ether (10 ml). After stirring at room temperature for 20 h, the mixture was quenched at −10°C by methanol and water. After 30 min at room temperature, the suspension was filtered and the filtrate was evaporated under reduced pressure. The aqueous residue was extracted three times with ether. The organic extracts were pooled, dried ($MgSO_4$) and evaporated under reduced pressure, thus leading to the hydrazine **44** as a colourless and unstable oil, without further purification (50 mg, 71.4%), d.e. = 87% (^{1}H NMR). ^{1}H NMR ($CDCl_3$) δ major diastereomer: 0.93–0.94 (2t, J = 7.4 and 7.4 Hz, 6H), 1.10–1.70 (m, 4H), 1.38 (d, J = 6.7 Hz, 3H), 2.40–3.20 (m, 3H), 3.24 (s, 3H), 3.26–3.66 (m, 2H), 4.12 (q, J = 6.5 Hz, 1H), 6.78 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ major diastereomer: 11.67, 11.85, 18.89, 21.32, 22.63, 56.84, 58.93, 61.07, 65.80, 74.19, 116.82, 119.12, 128.05, 128.32, 156.87, 128.23.

*3.37. 2-[1-(2-Hydroxyphenyl)ethyl]-1-(2-methoxyethyl)-1-[(1*R*)-1-(methoxymethyl)propyl]hydrazine* ***45***

A suspension of $LiAlH_4$ (194 mg, 5 mmol) in dry ether (20 ml) was cooled to −10°C and treated dropwise by hydrazone (*R*)-(−)-**33** (0.1 g, 0.34 mmol) in dry ether (5 ml). After stirring at room temperature for 20 h, the mixture was quenched at −10°C by methanol and water. After 30 min at room temperature, the suspension was filtered and the filtrate was evaporated under reduced pressure. The aqueous residue was extracted three times with ether. The organic extracts were pooled, dried ($MgSO_4$) and evaporated under reduced pressure, thus leading to the hydrazine **45** as a colourless and unstable oil, without further purification (40 mg, 40%), d.e. = 48.7% (^{1}H NMR). ^{1}H NMR ($CDCl_3$) δ major diastereomer: 0.95 (t, J = 7.3 Hz, 3H), 1.25–1.33 (m, 2H),

1.38 (d, J = 6.6 Hz, 3H), 2.81–2.87 (m, 2H), 2.95–3.05 (m, 1H), 3.24 and 3.36 (2s, 6H), 3.35–3.70 (m, 4H), 4.09 (q, J = 6.6 Hz, 1H), 6.70–7.20 (m, 5H); minor diastereomer: 0.88 (t, J = 7.3 Hz, 3H), 1.25–1.33 (m, 2H), 1.35 (d, J = 6.9 Hz, 3H), 2.81–2.87 (m, 2H), 2.95–3.05 (m, 1H), 3.17 and 3.22 (2s, 6H), 3.35–3.70 (m, 4H), 4.07 (q, J = 6.9 Hz, 1H), 6.70–7.20 (m, 5H).

*3.38. N-[(1*R*)-1-(Methoxymethyl)propyl]-*N′*-(1-methyl-3-phenyl)propyl-*N*-(2,2,2-trifluoroethyl)-hydrazine* ***47***

A suspension of $LiAlH_4$ (354 mg, 9.1 mmol) in dry ether (50 ml) was cooled to −10°C and treated dropwise by hydrazone (*R*)-(−)-**35** (200 mg, 0.6 mmol) in dry ether (20 ml). After stirring at room temperature for 15 h, the mixture was quenched at −10°C by methanol (1.1 ml) and water (1.7 ml). After 30 min at room temperature, the suspension was filtered and the filtrate was evaporated under reduced pressure. The aqueous residue was extracted three times with ether. The organic extracts were pooled, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: cyclohexane:ether, 9:1, and elution gradient), thus leading to the hydrazine **47** as a colourless oil (110 mg, 54.7%), $[\alpha]_D$ +33.3 (*c* 0.9, MeOH), 71% < d.e. < 75% determined by ^{13}C NMR. Anal. calcd for $C_{17}H_{27}F_3N_2O$: C, 61.43; H, 8.19; N, 8.43. Found: C, 61.47; H, 8.47; N, 8.13. ^1H NMR ($CDCl_3$) δ major diastereomer: 0.95 (t, J = 7.3 Hz, 3H), 1.07 (d, J = 6.0 Hz, 3H), 1.10–1.30 (m, 2H), 1.40–1.60 (m, 2H), 2.60–2.65 (m, 2H), 2.79–2.88 (m, 2H), 2.82 (q, J = 6.0 Hz, 1H), 3.08 (dd, J = 9.7 and 15.2 Hz, 1H), 3.32 (s, 3H), 3.37 (dd, J = 3.9 and 9.9 Hz, 1H), 3.51 (AB system, J = 9.7 Hz, 2H), 7.17–7.29 (m, 5H); minor diastereomer: 0.91 (m, 3H), 1.01 (d, J = 6.3 Hz, 3H), 1.10–1.30 (m, 2H), 1.40–1.60 (m, 2H), 2.60–2.65 (m, 2H), 2.79–2.88 (m, 2H), 3.04–3.10 (m, 1H), 3.35–3.41 (m, 1H), 3.44–3.54 (m, 2H), 7.17–7.29 (m, 5H). ^{13}C NMR ($CDCl_3$) δ major diastereomer: 11.17, 18.93, 22.58, 32.12, 37.02, 51.43, 59.05, 63.28, 74.52, 125.39, 125.74, 125.79, 128.19, 142.36.

*3.39. 1-[(1*R*)-1-(Methoxymethyl)propyl]-2-[(1*R*)-1-phenylethyl]-1-(2,2,2-trifluoroethyl)hydrazine (*R,S*)-(+)-* ***46***

Starting from $LiAlH_4$ (1.9 g, 49.6 mmol) in dry ether (100 ml) and (*R*)-(−)-**34** (1 g, 3.3 mmol) in dry ether (50 ml), the above procedure (see Section 3.38), without chromatography, led to hydrazine **46** as a yellow oil (854 mg, 85.4%), $[\alpha]_D$ +57.4 (*c* 0.6, EtOH), d.e. = 100% determined by ^{13}C NMR and ^1H NMR. Anal. calcd for $C_{15}H_{23}F_3N_2O$: C, 59.20; H, 7.62; N, 9.20. Found: C, 59.54; H, 7.94; N, 9.43. ^1H NMR ($CDCl_3$) δ: 0.96 (t, J = 7.3 Hz, 3H), 1.16–1.23 (m, 2H), 1.33 (d, J = 6.4 Hz, 3H), 2.85–2.91 (m, 1H), 3.14 (dd, J = 9.7 and 15.1 Hz, 1H), 3.25 (s, 3H), 3.35 (dd, J = 4.1 and 9.9 Hz, 1H), 3.50–3.57 (m, 2H), 3.68 (s, 1H), 3.91 (q, J = 6.4 Hz, 1H), 7.22–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 11.20, 21.12, 22.85, 55.90, 57.16, 58.83, 63.90, 74.39, 126.02, 127.13, 127.26, 128.32, 144.00.

*3.40. N-[(1*R*)-1-(Methoxymethyl)propyl)-N′-[1-(4-methoxyphenyl)ethyl]-N-(2,2,2-trifluoroethyl)-hydrazine (*R,S*)-(+)-* ***48***

Starting from $LiAlH_4$ (438 mg, 11 mmol) in dry ether (50 ml) and (*R*)-(−)-**38** (256 mg, 0.77 mmol) in dry ether (10 ml), the above procedure (see Section 3.38), with chromatography (eluent: cyclohexane), led to hydrazine **48** as a colourless oil (130 mg, 50.6%), $[\alpha]_D$ +40.7 (*c* 1.4, MeOH), d.e. = 100% (^{13}C NMR and ^1H NMR). Anal. calcd for $C_{16}H_{25}F_3N_2O_2$: C, 57.47; H, 7.54; N, 8.38.

Found: C, 57.63; H, 7.55; N, 8.35. ^{1}H NMR ($CDCl_3$) δ: 0.97 (t, J = 7.3 Hz, 3H), 1.15–1.25 (m, 2H), 1.31 (d, J = 6.3 Hz, 3H), 2.85–2.95 (m, 1H), 3.10–3.16 (m, 1H), 3.25 (s, 3H), 3.34 (dd, J = 4.2 and 9.9 Hz, 1H), 3.49–3.63 (m, 3H), 3.79 (s, 3H), 3.86 (q, J = 6.4 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 11.22, 21.07, 22.84, 55.22, 55.79, 56.36, 59.00, 63.83, 74.39, 113.65, 125.43, 128.27, 136.85, 158.69.

3.41. N-*[(1*R*)-1-(Methoxymethyl)propyl]*-N′-*[1-(naphthalen-2-yl)ethyl]*-N-*(2,2,2-trifluoroethyl)-hydrazine (*R,S*)-(+)-**49**

Starting from $LiAlH_4$ (356 mg, 9.38 mmol) in dry ether (50 ml) and (*R*)-(−)-**39** (220 mg, 0.62 mmol) in dry ether (10 ml), the above procedure (see Section 3.38), without chromatography, led to hydrazine **49** as a yellow oil (177 mg, 80%), $[\alpha]_D$ +26.8 (*c* 1.05, MeOH), d.e. = 100% determined by ^{13}C NMR and ^{1}H NMR. Anal. calcd for $C_{19}H_{25}F_3N_2O$: C, 64.39; H, 7.11; N, 7.90. Found: C, 64.83; H, 7.19; N, 7.95. ^{1}H NMR ($CDCl_3$) δ: 0.96 (t, J = 7.3 Hz, 3H), 1.20–1.40 (m, 2H), 1.42 (d, J = 6.3 Hz, 3H), 2.90–3.10 (m, 1H), 3.17 (dd, J = 9.7 and 15.2 Hz, 1H), 3.21 (s, 3H), 3.31–3.36 (m, 1H), 3.50–3.70 (m, 2H), 4.08 (q, J = 6.3 Hz, 1H), 7.41–7.80 (m, 7H). ^{13}C NMR ($CDCl_3$) δ: 11.20, 21.60, 22.87, 55.60, 57.31, 58.95, 63.85, 74.44, 125.52 to 127.96, 126.74, 132.87, 133.41, 142.16.

3.42. N-*[1-(Furan-2-yl)ethyl]*-N-*[(1*R*)-(methoxymethyl)propyl]*-N-*(2,2,2-trifluoroethyl)hydrazine (*R,S*)-(+)-**50**

Starting from $LiAlH_4$ (325 mg, 8.56 mmol) in dry ether (50 ml) and (*R*)-(−)-**40** (167 mg, 0.57 mmol) in dry ether (10 ml), the above procedure (see Section 3.38), without chromatography, led to hydrazine **50** as a colourless oil (113 mg, 67.3%), $[\alpha]_D$ +31.4 (*c* 0.35, MeOH), d.e. = 100% determined by ^{13}C NMR and ^{1}H NMR. Anal. calcd for $C_{13}H_{21}F_3N_2O_2$: H, 7.19; N, 9.52. Found: H, 7.09; N, 9.68. ^{1}H NMR ($CDCl_3$) δ: 0.94 (t, J = 7.3 Hz, 3H), 1.00–1.30 (m, 2H), 1.36 (d, J = 6.5 Hz, 3H), 2.75–2.83 (m, 1H), 3.09–3.15 (m, 1H), 3.31 (s, 3H), 3.37 (dd, J = 4.0 and 9.9 Hz, 1H), 3.46–3.51 (AB, J = 9.4 Hz, 2H), 3.98 (q, J = 6.5 Hz, 1H), 6.15 (d, J = 3.4 Hz, 1H), 6.29 (dd, J = 1.8 and 3.1 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 11.65, 18.29, 23.44, 51.60, 55.48, 59.60, 64.39, 74.87, 106.30, 110.57, 125.45, 141.31, 157.10.

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