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Diastereo- and enantioselective synthesis of *cis*-2-hydroxycyclohexanamine and corresponding ethers by asymmetric reductive amination

Gerhard Lauktien, Franz-J. Volk and August W. Frahm *

Lehrstuhl für Pharmazeutische Chemie, Pharmazeutisches Institut, Hermann-Herder-Straße 9, D-79104 Freiburg, Germany

Abstract: A series of homochiral *cis*-2-alkoxy- and 2-aryloxycyclohexanamines **5b–5e** has been synthesised by means of asymmetric reductive amination of the corresponding racemic 2-oxygenated cyclohexanones **2** with *ee*-values ranging from 95 to >99%. The respective 2-hydroxy and 2-cyclohexyl derivatives **5g–5h** have been prepared from the 2-phenoxycyclohexanamine **4e**. Relative and absolute stereochemistry has been elucidated.

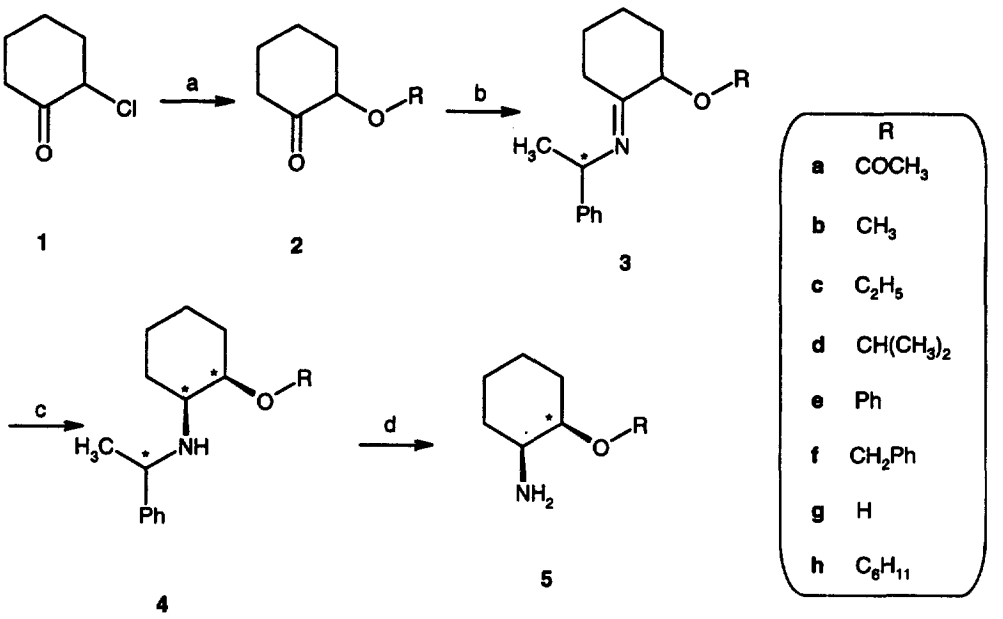
In the course of our ongoing research projects towards homochiral bioactive amines, amino acids and aminoalcohols we wanted to synthesise 2-oxygenated cyclohexanamines. Their quaternary ammonium derivatives can be regarded as constrained analogues of the parasympathomimetic cholinphenylether.[1] In a series of preceding papers we have shown that the asymmetric reductive amination[2] using optically active α-methylbenzylamine (**α-MBA**) as the chiral auxiliary[3] is a powerful tool for the synthesis of 2-monosubstituted cyclopentane-[4–6], cyclohexane-[4,6,7], and cycloheptanamines[4,6] in good chemical yields with excellent *cis*-diastereoselectivity (*de*-values >98%) and enantiomeric excesses *ee* of up to ≥99%.

Starting from the racemic ketones **2** the reaction sequence proceeds via a condensation step introducing the chiral auxiliary, a catalytic hydrogenation of the resulting imines **3** with Raney-Nickel to the secondary amines **4** and finally the catalytic hydrogenolysis of the chiral auxiliary to the primary amines **5** (Scheme 1).

The racemic 2-oxygenated cyclohexanones **2** were obtained from the commercially available 2-chlorocyclohexanone **1** either by nucleophilic substitution with potassium acetate or sodium phenolate, respectively **2a**[8]/**2e**[9,10], or by reaction of **1** with NaOH (28%) at 0°C yielding the dimeric ketal **6**[11] (Figure 1), which was then converted to the ketones **2b**, **2c** and **2d**[12–15] by refluxing in HCl gas saturated ether in the presence of a 20-fold excess of the corresponding alkanol. 2-Benzyloxycyclohexanone **2f** was obtained from **6** and benzylalcohol by azeotropic removal of water with toluene.[16]

Subsequently the ketones **2** were reacted with equimolar amounts of (*R*)-(+)- or (*S*)-(−)-α-methylbenzylamine, respectively, yielding the imines **3b–3f** in 85 to 90% as diastereomeric mixtures with *E*-α*R**,2*R**-, *E*-α*R**,2*S**-, *Z*-α*R**,2*R**- and *Z*-α*R**,2*S** configuration. The *E*/*Z* ratio derived from the respective ^{1}H NMR spectra was found to be about 3:1 with the *E*-isomers predominating, due to the lack of sterical hindrance between the N-α-methylbenzyl residue and the substituent in position 2 of the cyclohexane ring.[4] The imine **3a** could not be obtained since it rearranges *in situ* to a crystalline mixture (2:1) of the epimeric N-acetyl-2-aminoketones **7** (Figure 1). The preparation of **3f**, monitored by infrared spectroscopy, was carried out in benzene and the reaction was stopped after 2 h of refluxing. Prolonged reaction times as well as higher temperatures favoured the formation of rearranged products.[17]

* Corresponding author. Email: awfrahm@sun2.ruf.uni-freiburg.de



Scheme 1. Reaction conditions: (a) KCH_3COO/CH_3COOH, reflux (**2a**); NaC_6H_5O, benzene, reflux (**2e**); NaOH (28%) 0°C, 3 h; then ROH, HCl, reflux, 24 h (**2b–2d**); $C_6H_5CH_2OH$, toluene, 75 min (**2f**). (b) (*R*)-(+)- or (*S*)-(−)-α-MBA, toluene or benzene, reflux. (c) Raney-Ni, EtOH, 5 bar H_2, room temp., 3 weeks. (d) Pd/C (10%), EtOH, 5 bar H_2, room temp., 24 h. Compounds **5g** and **5h** have not been synthesised by means of asymmetric reductive amination. They were obtained from the secondary amine **4e**.

As shown earlier,[4–6,18,19] the stereoselectivity and the chemical yield of the hydrogenation step depend mostly on the reaction time, the temperature and the amount of the Raney-Nickel catalyst used. To get the enantiomerically pure *cis*-configured secondary amines **4** from the crude imine mixtures **3b–3f** the amount of ethanol wet Raney-Nickel had to be reduced from 12.0 to 6.0 g/0.1 mol[4–6,18,19] to 4.0 g/0.1 mol. In parallel the reaction time increased from 8 to 10 days to 3 weeks. The hydrogenations were carried out in a Parr shaker at 5 bar H_2 and room temperature and yielded 70% of the secondary amine hydrochlorides **4b–4e**. Even under enforced reaction conditions (8 g Raney-Nickel per 0.1 mol; 40°C) the 2-benzyloxycyclohexanimines **3f** could not be hydrogenated to the corresponding amine **4f**, since it rearranged to the α-aminoketone **8** (Figure 1).[17]

Even though the hydrogenation of the cyclohexanimine mixtures **4b–4e** theoretically leads to four diastereomeric secondary amines, in all cases we observed only one signal set in the respective ^{13}C NMR spectra which correlated with the α*R**,1*R**,2*S** configuration. Since the chemical yields always exceeded 50% and the face controlled hydrogenation of an enamine tautomer is excluded under the given reaction conditions,[4] this can only be explained by a *cis*-diastereoselective hydrogenation of the α*R**,2*S** configured imines from the sterically less hindered *si*-face followed by an epimerisation of the α*R**,2*R** configured imines probably via an imine–enamine tautomerism or as a carbanionic intermediate.[4]

The relative stereochemistry and the conformation of the amines **4b–4e** were elucidated from the half band widths ($W_{1/2}$) of the proton signals 1-H and 2-H. As outlined in Table 1 the $W_{1/2}$ values for the 1-H signals are in the range of 20.5–21.0 Hz while those for the 2-H signals are between 10.0 and 10.5 Hz. Thus, the secondary amines **4b–4e** have to be *cis*-configured, with the alkoxy and aryloxy substituent in position 2 in the axial and the amino group in position 1 in the equatorial conformation.

In the last step the primary amines **5b–5e** were obtained by hydrogenolysis of the benzylic C–N bond of **4b–4e** on Pd/C at 5 bar H_2 and 45°C in chemical yields up to 87%. The half band widths

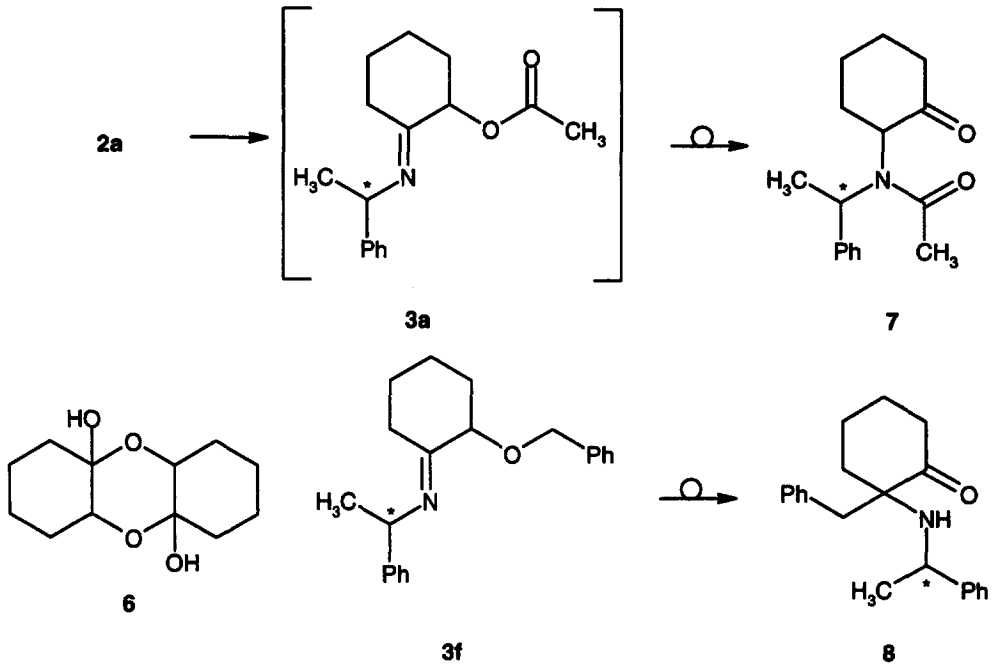


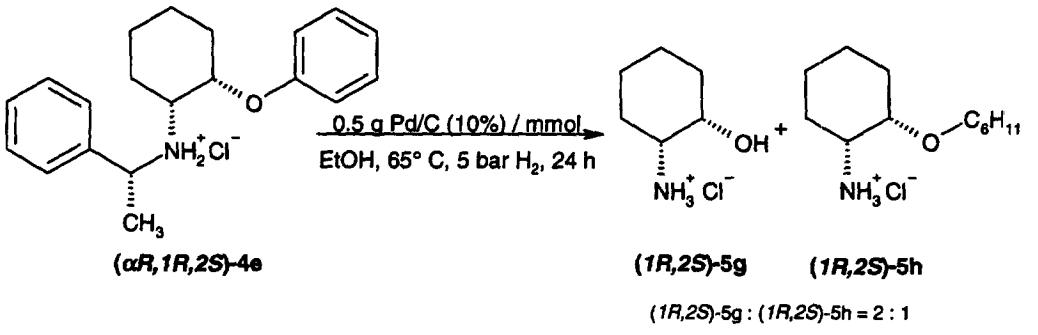
Figure 1.

Table 1. Half band widths ($W_{1/2}$) for the 1-H and 2-H signals of the secondary amine hydrochlorides **4b–4e**

Compound	Proton	δ [ppm]	J [Hz]	Coupling Protons	$W_{1/2}$ [Hz]
4b	1-H	2.77	13.0, 4.0, 3.0	6-H_{ax}, 6-H_{eq}, 2-H_{eq}	21.0
	2-H	3.61	m	1-H_{ax}, 3-H_{ax}, 3-H_{eq}	10.5
4c	1-H	2.70	13.0, 4.0, 3.0	6-H_{ax}, 6-H_{eq}, 2-H_{eq}	21.0
	2-H	3.61	m	1-H_{ax}, 3-H_{ax}, 3-H_{eq}	10.0
4d	1-H	2.80	12.0, 4.0, 3.0	6-H_{ax}, 6-H_{eq}, 2-H_{eq}	20.5
	2-H	2.95	m	1-H_{ax}, 3-H_{ax}, 3-H_{eq}	10.5
4e	1-H	2.94	m	6-H_{ax}, 6-H_{eq}, 2-H_{eq}	21.0
	2-H	4.57	m	1-H_{ax}, 3-H_{ax}, 3-H_{eq}	10.0

for the 1-H signals of **5b–5e** are in the range of 18–20 Hz, whereas those for the 2-H resonances are between 10 and 12 Hz, and thus confirm the previously established *cis*-configuration at C-1 and C-2 with the C-1 substituent in the equatorial and the C-2 substituent in the axial position.

The *cis*-2-aminocyclohexanol **5g** is not accessible by means of asymmetric reductive amination of 2-hydroxycyclohexanone, since the respective imines are undergoing Voigt–Amadori rearrangement[20] to 2-aminoketones. Nevertheless, **5g** could be obtained from the 2-phenoxycyclohexylamine **4e** under modified reaction conditions for hydrogenolysis (Scheme 2). Increasing the amount of Pd/C catalyst from 1 g/20 mmol to 0.5 g/mmol resulted in a partial hydrogenation of the phenoxy residue to vinyl-, allyl-, and homoallyl ether intermediates,[21] subsequently hydrogenolysed to the aminoalcohol hydrochloride **5g** and hydrogenated to the 2-cyclohexylcyclohexanamine **5h**, respectively. Recrystallisation from Et_2O/EtOH afforded the pure 2-aminocyclohexanol.



Scheme 2.

Table 2. Retention times and *ee*-values of the diastereomeric Mosher's amides **9** on HPLC[a]

Mosher's amide	t_1 [min]	t_2 [min]	*ee* [%]	mobile phase	flow rate [mL/min]
(*1R,2S*)-**9b**	11.04	15.76	97.6	24:1	2.0
(*1S,2R*)-**9b**	15.12	11.65	96.2	24:1	2.0
(*1R,2S*)-**9c**	9.94	12.44	96.2	24:1	1.6
(*1S,2R*)-**9c**	12.40	10.35	95.8	24:1	1.6
(*1R,2S*)-**9d**	11.35	-	>99	32:1	1.7
(*1S,2R*)-**9d**	13.52	-	>99	32:1	1.7
(*1R,2S*)-**9e**	13.93	-	>99	32.1	1.7
(*1S,2R*)-**9e**	17.18	14.25	97.1	32:1	1.7

[a] The compounds are eluted with isooctane/EtOAc on LiChrosorb Si60 (Merck) 7µm, 250 x 4 mm. t_1: retention time of the major diastereomer; t_2: retention time of the minor diastereomer.

The *ee*-values were determined by means of Mosher's amide derivatisation.[22] Therefore, the primary amines **5b–5e** were reacted in pyridine with one equivalent of (*S*)-(+)-2-methoxy-2-trifluoromethylphenylethanoic acid chloride affording the amides **9** as diastereomeric mixtures. The subsequent HPLC analysis of **9** showed *ee*-values ranging from 95.1% up to greater 99% (Table 2). If it is assumed that the simultaneous hydrogenation and hydrogenolysis of the secondary amine **4e** occurs without any epimerisation, the *ee*-values for the primary amines **5g** and **5h** must be in the range of the parent compound **5e** (97.1%– >99%).

The absolute configurations were derived by comparison of the CD spectra of the 2-phenoxycyclohexanamine (**1*S*,2*R*)-5e** and of the (*1R*,2*R*)-(−)-*cis*-2-phenylcyclohexanamine.[23] Since all cotton effects for (**1*S*,2*R*)-5e** were opposite in sign to those of the reference it's absolute configuration was deduced to 1*S*,2*R*. This assignment was finally proven by X-ray analysis[24] of the 4-bromobenzamide derivative of (**1*S*,2*R*)-5e**. Thus, the results of the absolute configuration analysis confirm the previously observed 'like induction' at C-1 in asymmetric reductive amination of cycloaliphatic ketones.

Experimental

Solvents were purified according to standard procedures. Melting points are uncorrected. Analytical TLC was performed on Merck Si60 F_{254} (0.2 mm) precoated aluminia foils. CC was carried out on Merck silica gel (0.2–0.063 mm). HPLC was performed on a Waters 600 Multisolvent Delivery System equipped with Merck LiChrosorb Si60 (250×4 mm) column and a Waters 484 UV detector. The given yields are for isolated products. Infrared spectra were recorded on a Perkin–Elmer IR 298

spectrometer. The NMR spectra were obtained on a Varian XL 300 spectrometer at 300 MHz (^{1}H) and 75.4 MHz (^{13}C), respectively. Chemical shifts are reported as δ values from TMS as internal standard. CD spectra were measured on a Roussel–Jouan Dichrograph III. Optical rotation values were obtained with a Perkin–Elmer 214 polarimeter. Elemental analysis were carried out on a Perkin–Elmer DIA-CHN RS at the Analytical Laboratory, Institute for Organic Chemistry and Biochemistry, Bonn.

Dodecahydrodibenzo-1,4-dioxan-4a,9a-diol **6**

140 g of sodium hydroxide (28.5%) were added within 3 h to 132.6 g (1.0 mol) of 2-chlorocyclohexanone (**1**) whereby the reaction temperature is kept below 0°C. After the mixture was stirred for 12 h at room temperature it showed neutral reaction. The product was filtered off, freed of chloride with demineralised water, washed with EtOH (3×25 mL) and Et_2O (3×25 mL) and finally dried *in vacuo*, yielding 68.5 g (60%, 0.3 mol) of **6**: mp: 123–128°C [lit.[12]: 132.5°C]; ^{13}C NMR (CD_3OD): δ 23.5 (t), 25.5 (t), 29.0 (t), 36.6 (t), 74.1 (d), 96.4 (s).

2-Acetoxycyclohexanone **2a**

A solution of 25.0 g (0.26 mol) of anhydrous potassium acetate and 33.0 g (0.25 mol) of 2-chlorocyclohexanone in 60 mL of acetic acid is heated to reflux. The acetic acid is evaporated *in vacuo* and the residue is taken up in 60 mL of H_2O. The aqueous layer is extracted with Et_2O (3×25 mL). The combined organic layers are dried with $MgSO_4$, the solvent is evaporated and the residue distilled *in vacuo* with a Vigreux column, yielding 25.0 g (64%, 0.16 mol) of **2a**: bp_{11}: 110°C [lit.[8]: bp_{12}: 120–123°C]; mp: 32–34°C [lit.[8]: 36–38°C]; IR (film):1750, 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.58 (m, 1H, 5-H_{ax}), 1.70 (m, 2H, 3-H_{ax}, 4-H), 1.91 (m, 1H, 4-H), 2.05 (m, 1H, 5-H_{eq}), 2.09 (s, 3H, CH_3), 2.25 (m, 1H, 3-H_{eq}), 2.37 (m, 1H, 6-H_{ax}), 2.45 (m, 1H, 6-H_{eq}), 5.12 (ddd, *J* 11.0, 6.5, 1.5 Hz, 1H, 2-H_{ax}); ^{13}C NMR ($CDCl_3$): δ 20.81 (q), 23.85 (t), 27.25 (t), 33.16 (t), 40.76 (t), 76.58(d), 169.88 (s), 204.39 (s).

General procedure for the ketones **2b, 2c and 2d**

A solution of 34.3 g (0.15 mol) of **6**, 3 mol of the respective alcanol (MeOH, EtOH or 2-PrOH) and 10 mL of HCl gas saturated ether was refluxed for 24 h. The solvent was evaporated and the residue distilled *in vacuo*.

2-Methoxycyclohexanone **2b**

Yield: 27.9 g (73%, 0.22 mol); bp_{18}: 78°C [lit.[12]: bp_{14}: 72–75°C]; IR (film): 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.64 (m, 3H), 1.89 (m, 2H), 2.21 (m, 2H), 2.45 (m, 1H), 3.36 (s, 3H, CH_3), 3.67 (m, 1H, 2-H_{ax}); ^{13}C NMR ($CDCl_3$): δ 22.99 (t), 27.54 (t), 34.07 (t), 40.44 (t), 57.50 (q), 84.10 (d), 209.85 (s).

2-Ethoxycyclohexanone **2c**

Yield: 29.1 g (68%, 0.21 mol); bp_{14}: 83°C [lit.[12]: bp_{14}: 81.5°C]; IR (film): 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.20 (t, *J* 7.0 Hz, 3H, CH_3), 1.70 (m, 2H, 4-H, 5-H), 1.75 (m, 1H, 3-H_{eq}), 1.90 (m, 2H, 4-H, 5-H), 2.18 (m, 1H, 3-H_{ax}), 2.26 (m, 1H, 6-H), 3.40 (dq, *J* 9.0, 7.0 Hz, 1H, $-CH_2CH_3$), 3.64 (dq, *J* 9.0, 7.0 Hz, 1H, $-CH_2CH_3$), 3.78 (ddd, *J* 10.0, 5.5, 1.5 Hz, 1H, 2-H_{ax}); ^{13}C NMR ($CDCl_3$): δ 15.21 (q), 23.02 (t), 27.61 (t), 34.49 (t), 40.40 (t), 65.24 (t), 82.46 (d), 209.96 (s).

2-Isopropoxycyclohexanone **2d**

Yield: 28.1 g (60%, 0.18 mol); bp_{11}: 81–85°C [lit.[14]: bp_{10}: 73–76°C]; IR (film): 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 1.08 (d, *J* 7.0 Hz, 3H, CH_3), 1.15 (d, *J* 7.0 Hz, 3H, CH_3), 1.50–2.70 (m, 8H, 3-H_2, 4-H_2, 5-H_2, 6-H_2), 3.60 (sept., *J* 7.0 Hz, 1H, $CH(CH_3)_2$), 3.84 (ddd, *J* 9.5, 5.5, 1,5 Hz, 1H, 2-H_{ax}); ^{13}C NMR ($CDCl_3$): δ 21.54 (q), 22.71 (q), 22.92 (t), 27.60 (t), 34.98 (t), 40.83 (t), 70.84 (d), 80.11 (d), 210.69 (s).

2-Phenoxycyclohexanone ***2e***

To a suspension of 23.2 g (0.2 mol) of sodium phenolate in 50 mL of benzene 26.4 g (0.2 mol) of 2-chlorocyclohexanone were added, and the mixture was then refluxed for 4 h. The cooled solution was alkalised with 30 mL of Na_2CO_3 (5%) and extracted with Et_2O (3×30 mL). The organic layer was washed with H_2O and dried with $MgSO_4$. The Et_2O was evaporated and the residue distilled *in vacuo* with a Vigreux column. The pink coloured product crystallised spontaneously. Recrystallisation from petrol ether gave 15.6 g (41%, 0.082 mol) of the colourless ketone **2e**: $bp_{0.3}$: 97–102°C; mp: 65°C [lit.[9]: 64.5°C]; IR (KBr): 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.78 (m, 2H, 4-H, 5-H), 2.03 (m, 3H, 3-H, 4-H, 5-H), 2.33 (m, 2H, 3-H, 6-H), 2.60 (m, 1H, 6-H), 4.65 (ddd, *J* 9.5, 5.5, 1.5 Hz, 1H, 2-H_{ax}), 6.8–7.3 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 23.00 (t), 28.02 (t), 34.60 (t), 40.64 (t), 80.69 (d), 115.51 (d), 121.42 (d), 129.43 (d), 157.51 (s), 208.11 (s).

2-Benzyloxycyclohexanone ***2f***

A solution of 22.8 g (0.1 mol) of **6** and 32.4 g (0.3 mol) of benzylalcohol in 40 mL of toluene and 10 mL of conc. hydrochloric acid was refluxed for 75 min on a Dean–Stark Apparatus. The reaction was stopped, toluene was evaporated and the oily residue was distilled *in vacuo*, affording 28.0 g (68%, 0.14 mol) of the ketone **2f**: bp_1: 136–138°C [lit.[16]: $bp_{0.5}$: 110–112°C]; IR (film): 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.65 (m, 1H, 4-H), 1.70 (m, 1H, 5-H), 1.75 (m, 1H, 3-H), 1.95 (m, 2H, 4-H, 5-H), 2.20 (m, 1H, 3-H), 2.25 (m, 1H, 6-H), 2.52 (m, 1H, 6-H), 3.87 (ddd, *J* 10.0, 5.5, 1.5 Hz, 1H, 2-H_{ax}), 4.47 (d, *J* 10.0 Hz, 1H, $CH_2C_6H_5$), 4.75 (d, *J* 10.0 Hz, 1H, $CH_2C_6H_5$), 7.32 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 22.69 (t), 27.18 (t), 34.14 (t), 40.19 (t), 71.16 (t), 81.30 (d), 127.62 (d), 127.67 (d), 128.31 (d), 137.90 (s), 209.61 (s).

General procedure for the imines ***3b–3f***

0.05 mol of the respective ketone **2** were taken up in 100 mL of toluene (5×) (**3b**, **3c**, **3d**) or benzene (5×) (**3e**, **3f**), respectively, and refluxed on a Dean–Stark extractor with (*R*)-(+)- or (*S*)-(−)-α-MBA (6.06 g, 0.05 mol) for 8 h **3b**, **3c**, **3d**, 16 h **3e** or 2 h **3f**, respectively. The solvent was evaporated *in vacuo* and the residue dried at the oil pump for one hour. The crude product was further reacted without purification. (The complex analytical data of the imine mixtures are not reported herein. For further information see Ref. 25.)

General procedure for the 2-oxygenated secondary amine hydrochlorides ***4b–4e***

0.05 mol of the crude imine mixtures **3** were taken up in 100 mL of absol. EtOH and hydrogenated on a Parr apparatus with 2.0 g ethanol wet Raney-Nickel under 5 bar H_2 at room temperature. After 3 weeks the catalyst was filtered off and the residue washed with EtOH (2×20 mL). The filtrate was concentrated and the crude residue was purified by flash chromatography on silica gel eluted with EtOAc. The obtained free amines were precipitated with HCl gas saturated Et_2O and recrystallized from $(H_3C)_2CO/Et_2O$, affording the secondary amine hydrochlorides **4b–4e**.

(αR,1R,2S)-2-Methoxy-N-(α-methylbenzyl)cyclohexanamine hydrochloride ***(αR,1R,2S)-4b***

Yield: 10.4 g (77%); mp: 193–195°C; $[\alpha]^{25}_D$=+70.1 (c=1.5, EtOH); Anal. calcd. for $C_{15}H_{24}NOCl$: C 66.8, H 8.97, N 5.2; Found: C 66.7, H 9.10, N 5.2; ^1H NMR ($CDCl_3$): δ 0.93 (dddd, *J* 15.0, 13.0, 4.0, 2.0 Hz, 1H, 3-H_{ax}), 1.06 (ddddd, *J* 13.0, 13.0, 13.0, 4.0, 3.5 Hz, 1H, 5-H_{ax}), 1.26 (m, 1H, 4-H_{eq}), 1.42 (ddddd, *J* 13.0, 13.0, 13.0, 4.0, 4.0 Hz, 1H, 4-H_{ax}), 1.65 (m, 1H, 5-H_{eq}), 1.95 (d, *J* 7.0 Hz, 3H, $CHCH_3$), 1.96 (dddd, *J* 13.0, 13.0, 12.5, 4.0 Hz, 1H, 6-H_{ax}), 2.05 (m, 1H, 3-H_{eq}), 2.17 (dddd, *J* 12.5, 4.0, 4.0, 3.5 Hz, 1H, 6-H_{eq}), 2.77 (ddd, *J* 13.0, 4.0, 3.0 Hz, 1H, 1-H_{ax}), 3.40 (s, 3H, OCH_3), 3.61 (m, 1H, 2-H_{eq}), 4.27 (q, *J* 7.0 Hz, 1H, $CHCH_3$), 7.3–7.8 (m, 5H, aromatic H), 9.6 (s(b), 1H, $^+NH_2$), 9.8 (s(b), 1H, $^+NH_2$); ^{13}C NMR ($CDCl_3$): δ 18.6 (t), 21.3 (q), 24.0 (t), 24.9 (t), 25.9 (t), 55.9 (q), 56.0 (d), 56.8 (d), 71.7 (d), 127.8 (d), 128.8 (d), 129.2 (d), 136.9 (s).

(αS,1S,2R)-2-Methoxy-N-(α-methylbenzyl)cyclohexanamine hydrochloride ***(αS,1S,2R)-4b***

Yield: 10.1 g (75%); mp: 193–195°C; $[\alpha]^{25}_D$=−70.2 (c=1.5, EtOH); Anal. calcd. for $C_{15}H_{24}NOCl$: C 66.8, H 8.97, N 5.2; Found: C 66.5, H 9.03, N 5.2.

(αR,1R,2S)-2-Ethoxy-N-(α-methylbenzyl)cyclohexanamine hydrochloride ***(αR,1R,2S)-4c***

Yield: 11.6 g (82%); mp: 206–207°C; $[\alpha]^{25}_D$=+76.7 (c=1.5, EtOH); Anal. calcd. for $C_{16}H_{26}NOCl$: C 67.7, H 9.23, N 4.9; Found: C 67.8, H 9.08, N 5.2; ^{1}H NMR ($CDCl_3$): δ 0.92 (dddd, *J* 15.0, 13.0, 4.0, 2.0 Hz, 1H, 3-H_{ax}), 1.03 (ddddd, *J* 13.0, 13.0, 13.0, 4.0, 3.5 Hz, 1H, 5-H_{ax}), 1.26 (m, 1H, 4-H_{eq}), 1.31 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.44 (ddddd, *J* 13.0, 13.0, 13.0, 4.0, 4.0 Hz, 1H, 4-H_{ax}), 1.61 (m, 1H, 5-H_{eq}), 1.96 (d, *J* 7.0 Hz, 3H, $CHCH_3$), 1.96 (dddd, *J* 13.0, 13.0, 12.5, 4.0 Hz, 1H, 6-H_{ax}), 2.0 (m, 1H, 3-H_{eq}), 2.17 (dddd, *J* 12.5, 4.0, 4.0, 3.5 Hz, 1H, 6-H_{eq}), 2.70 (ddd, *J* 13.0, 4.0, 3.0 Hz, 1H, 1-H_{ax}), 3.57 (dq, *J* 9.0, 7.0 Hz, 1H, CH_2CH_3), 3.69 (dq, *J* 9.0, 7.0 Hz, 1H, CH_2CH_3), 3.61 (m, 1H, 2-H_{eq}), 4.27 (q, *J* 7.0 Hz, 1H, $CHCH_3$), 7.2–8.0 (m, 5H, aromatic H), 9.4 (s(b), 1H, $^+NH_2$), 10.0 (s(b), 1H, $^+NH_2$); ^{13}C NMR ($CDCl_3$): δ 15.5 (q), 18.6 (t), 21.4 (q), 23.9 (t), 24.8 (t), 26.4 (t), 55.7 (d), 56.4 (d), 63.8 (t), 69.7 (d), 127. 7 (d), 128.6 (d), 129.1 (d), 136.9 (s).

(αS,1S,2R)-2-Ethoxy-N-(α-methylbenzyl)cyclohexanamine hydrochloride ***(αS,1S,2R)-4c***

Yield: 11.6 g (82%); mp: 204–207°C; $[\alpha]^{25}_D$=−76.1 (c=1.5, EtOH); Anal. calcd. for $C_{16}H_{26}NOCl$: C 67.7, H 9.23, N 4.9; Found: C 67.8, H 9.26, N 5.0.

(αR,1R,2S)-2-Isopropoxy-N-(α-methylbenzyl)cyclohexanamine hydrochloride ***(αR,1R,2S)-4d***

Yield: 8.5 g (57%); mp: 182–186°C; $[\alpha]^{25}_D$=+86.1 (c=1.5, EtOH); Anal. calcd. for $C_{17}H_{28}NOCl$: C 68.5, H 9.47, N 4.7; Found: C 68.4, H 9.39, N 4.8; ^{1}H NMR ($CDCl_3$): δ 0.92 (dddd, *J* 13.0, 13.0, 4.0, 2.0 Hz, 1H, 3-H_{ax}), 1.18 (ddddd, *J* 13.0, 13.0, 13.0, 3.5, 3.5 Hz, 1H, 5-H_{ax}), 1.27 (d, *J* 6.0 Hz, 3H, $CH(CH_3)_2$), 1.28 (d *J* 6.0 Hz, 3H, $CH(CH_3)_2$), 1.30 (m, 1H, 4-H_{eq}), 1.44 (ddddd, *J* 13.0, 13.0, 13.0, 3.5, 3.5 Hz, 1H, 4-H_{ax}), 1.69 (m, 1H, 5-H_{eq}), 1.95 (d, *J* 7.0 Hz, 3H, $CHCH_3$), 1.96 (m, 1H, 3-H_{eq}), 2.05 (dddd, *J* 13.0, 12.0, 12.0, 4.0 Hz, 1H, 6-H_{ax}), 2.20 (dddd, *J* 12.0, 4.0, 3.5, 3.5 Hz, 1H, 6-H_{eq}), 2.80 (ddd, *J* 12.0, 4.0, 3.0 Hz, 1H, 1-H_{ax}), 3.77 (sept., *J* 6.0 Hz, 1H, $CH(CH_3)_2$), 3.86 (m, 1H, 2-H_{eq}), 4.31 (q, *J* 7.0 Hz, 1H, $CHCH_3$), 7.3–7.8 (m, 5H, aromatic H), 9.2 (s(b), 1H, $^+NH_2$), 10.0 (s(b), 1H, $^+NH_2$); ^{13}C NMR ($CDCl_3$): δ 18.7 (t), 21.3 (q), 21.7 (q), 23.7 (q), 23.9 (t), 24.7 (t), 27.0 (t), 55.5 (d), 56.5 (d), 66.8 (d), 68.2 (d), 127.8 (d), 128.7 (d), 129.2 (d), 136.9 (s).

(αS,1S,2R)-2-Isopropoxy-N-(α-methylbenzyl)cyclohexanamine hydrochloride ***(αS,1S,2R)-4d***

Yield: 8.5 g (57%); mp: 183–185°C; $[\alpha]^{25}_D$=−86.2 (c=1.5, EtOH); Anal. calcd. for $C_{17}H_{28}NOCl$: C 68.5, H 9.47, N 4.7; Found: C 68.7, H 9.46, N 4.7.

(αR,1R,2S)-2-Phenoxy-N-(α-methylbenzyl)cyclohexanamine hydrochloride ***(αR,1R,2S)-4e***

Yield: 11.3 g (68%); mp: 212–215°C; $[\alpha]^{25}_D$=+111.6 (c=1.5, EtOH); Anal. calcd. for $C_{20}H_{26}NOCl$: C 72.4, H 7.90, N 4.2; Found: C 72.6, H 8.10, N 4.5; ^{1}H NMR ($CDCl_3$): δ 1.14 (m, 1H, 3-H_{ax}), 1.17 (m, 1H, 5-H_{ax}), 1.34 (m, 1H, 4-H_{eq}), 1.52 (ddddd, *J* 13.0, 13.0, 13.0, 3.5, 3.5 Hz, 1H, 4-H_{ax}), 1.74 (m, 1H, 5-H_{eq}), 1.88 (d, *J* 7.0 Hz, 3H, $CHCH_3$), 2.21 (m, 1H, 3-H_{eq}), 2.47 (m, 2H, 6-$H_{ax/eq}$), 2.94 (m, 1H, 1-H_{ax}), 4.31 (q, *J* 7.0 Hz, 1H, $CHCH_3$), 4.57 (m, 1H, 2-H_{eq}), 6.9–7.8 (m, 10H, aromatic H), 9.9 (s(b), 1H, $^+NH_2$), 10.4 (s(b), 1H, $^+NH_2$); ^{13}C NMR ($CDCl_3$): δ 18.9 (t), 21.9 (q), 23.9 (t), 25.2 (t), 27.2 (t), 55.9 (d), 56.1 (d), 68.0 (d), 115.3 (d), 127.8 (d), 128.7 (d), 128.7 (d), 129.3 (d), 129.6 (d), 136.6 (s), 156.7 (s).

(αS,1S,2R)-2-Phenoxy-N-(α-methylbenzyl)cyclohexanamine hydrochloride ***(αS,1S,2R)-4e***

Yield: 11.1 g (67%); mp: 212–215°C; $[\alpha]^{25}_D$=−111.8 (c=1.5, EtOH); Anal. calcd. for $C_{20}H_{26}NOCl$: C 72.4, H 7.90, N 4.2; Found: C 72.1, H 8.12, N 4.4.

*General procedure for the 2-oxygenated primary amine hydrochlorides **5b–5e***

10% Pd/C (1.0 g) was suspended in 50 mL of dry EtOH and prehydrogenated for 30 min. 20 mmol of the secondary amine hydrochlorides **4b–4e** in 50 mL of EtOH were added and the mixture was hydrogenolysed for 24 h at 5 bar H_2 and 45°C. The catalyst was filtered off and the solvent evaporated *in vacuo*. The residue was recrystallised from EtOH/Et_2O. The primary amines **5e** were purified by column chromatography on silica gel, eluted with 2-PrOH/NH_4OH (95:5) [Rf=0.7], whereby **5g** [Rf=0.2] was obtained as a by product. The free bases were treated with HCl gas saturated Et_2O and finally recrystallised from Et_2O/EtOH (25:1).

*(1R,2S)-2-Methoxycyclohexanamine hydrochloride (**1R,2S**)-**5b***

Yield: 2.6 g (78%); mp: 150–151°C; $[\alpha]^{25}_D$=+32.7 (c=1.5, EtOH); Anal. calcd. for $C_7H_{16}NOCl$: C 50.7, H 9.74, N 8.5; Found: C 50.5, H 9.60, N 8.6; ^1H NMR ($CDCl_3$): δ 1.30 (m, 1H, 5-H_{ax}), 1.35 (m, 1H, 4-H_{eq}), 1.39 (m, 1H, 3-H_{ax}), 1.49 (m, 1H, 4-H_{ax}), 1.75 (m, 1H, 5-H_{eq}), 1.87 (m, 2H, 6-$H_{ax/eq}$), 2.05 (m, 1H, 3-H_{eq}), 3.29 (m, 1H, 1-H_{ax}), 3.39 (s, 3H, C*H*$_3$), 3.65 (m, 1H, 2-H_{eq}), 8.25 (s, 3H, $^+NH_3$); ^{13}C NMR ($CDCl_3$): δ 18.9 (t), 23.0 (t), 25.5 (t), 26.1 (t), 52.0 (d), 55.2 (q), 74.5 (d).

*(1S,2R)-2-Methoxycyclohexanamine hydrochloride (**1S,2R**)-**5b***

Yield: 2.6 g (78%); mp: 150–151°C; $[\alpha]^{25}_D$=−33.0 (c=1.5, EtOH); Anal. calcd. for $C_7H_{16}NOCl$: C 50.7, H 9.74, N 8.5; Found: C 50.4, H 9.73, N 8.4.

*(1R,2S)-2-Ethoxycyclohexanamine hydrochloride (**1R,2S**)-**5c***

Yield: 3.0 g (83%); mp: 190–192°C; $[\alpha]^{25}_D$=+51.9 (c=1.5, EtOH); Anal. calcd. for $C_8H_{18}NOCl$: C 53.5, H 10.10, N 7.8; Found: C 53.2, H 10.17, N 7.5; ^1H NMR ($CDCl_3$): δ 1.25 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.28 (m, 1H, 5-H_{ax}), 1.32 (m, 1H, 3-H_{ax}), 1.35 (m, 1H, 4-H_{eq}), 1.51 (m, 1H, 4-H_{ax}), 1.72 (m, 1H, 5-H_{eq}), 1.85 (m, 1H, 6-H_{ax}), 1.87 (m, 1H, 6-H_{eq}), 2.0 (m, 1H, 3-H_{eq}), 3.27 (ddd, *J* 11.0, 4.5, 3.0 Hz, 1H, 1-H_{ax}), 3.46 (dq, *J* 9.0, 7.0 Hz, 1H, C*H*$_2$CH$_3$), 3.60 (dq, *J* 9.0, 7.0 Hz, 1H, C*H*$_2$CH$_3$), 3.76 (dddd, *J* 3.0, 2.5, 2.5, 2.0 Hz, 1H, 2-H_{eq}), 8.25 (s, 3H, $^+NH_3$); ^{13}C NMR ($CDCl_3$): δ 15.5 (q), 19.1 (t), 23.2 (t), 25.6 (t), 27.0 (t), 52.2 (d), 64.2 (t), 72.8 (d).

*(1S,2R)-2-Ethoxycyclohexanamine hydrochloride (**1S,2R**)-**5c***

Yield: 3.0 g (83%); mp: 190–192°C; $[\alpha]^{25}_D$=−51.7 (c=1.5, EtOH); Anal. calcd. for $C_8H_{18}NOCl$: C 53.5, H 10.10, N 7.8; Found: C 53.3, H 10.17, N 7.6.

*(1R,2S)-2-Isopropoxycyclohexanamine hydrochloride (**1R,2S**)-**5d***

Yield: 2.2 g (57%); mp: 215°C; $[\alpha]^{25}_D$=+67.6 (c=1.5, EtOH); Anal. calcd. for $C_9H_{20}NOCl$: C 55.8, H 10.41, N 7.2; Found: C 55.6, H 10.61, N 7.2; ^1H NMR ($CDCl_3$): δ 1.14 (d, *J* 6.0 Hz, 3H, CH(C*H*$_3$)$_2$), 1.21 (d, *J* 6.0 Hz, 3H, CH(C*H*$_3$)$_2$), 1.30 (m, 1H, 3-H_{ax}), 1.32 (m, 1H, 4-H_{eq}), 1.50 (m, 1H, 4-H_{ax}), 1.71 (m, 1H, 5-H_{eq}), 1.75 (m, 1H, 6-H_{ax}), 1.86 (m, 1H, 6-H_{eq}), 1.90 (m, 1H, 3-H_{eq}), 3.18 (ddd, *J* 11.0, 4.5, 3.0 Hz, 1H, 1-H_{ax}), 3.67 (sept., *J* 6.0 Hz, 1H, C*H*(CH$_3$)$_2$), 3.81 (dddd, *J* 3.0, 2.5, 2.5, 2.0 Hz, 1H, 2-H_{eq}), 8.15 (s, 3H, $^+NH_3$); ^{13}C NMR ($CDCl_3$): δ 19.2 (t), 22.1 (q), 23.3 (t), 23.4 (q), 25.4 (t), 27.0 (t), 52.3 (d), 69.4 (d), 70.0 (d).

*(1S,2R)-2-Isopropoxycyclohexanamine hydrochloride (**1S,2R**)-**5d***

Yield: 2.1 g (56%); mp: 215°C; $[\alpha]^{25}_D$=−67.4 (c=1.5, EtOH); Anal. calcd. for $C_9H_{20}NOCl$: C 55.8, H 10.41, N 7.2; Found: C 55.9, H 10.36, N 7.4.

*(1R,2S)-2-Phenoxycyclohexanamine hydrochloride (**1R,2S**)-**5e***

Yield: 4.0 g (87%); mp: 218–220°C; $[\alpha]^{25}_D$=+75.5 (c=1.5, EtOH); Anal. calcd. for $C_{12}H_{18}NOCl$: C 63.3, H 7.97, N 6.1; Found: C 63.1, H 7.94, N 6.4; ^1H NMR ($CDCl_3$): δ 1.18 (m, 1H, 5-H_{ax}), 1.20

(m, 1H, 4-H_{eq}), 1.25 (m, 1H, 3-H_{ax}), 1.42 (m, 1H, 4-H_{ax}), 1.70 (m, 1H, 5-H_{eq}), 1.80 (m, 2H, 6-$H_{ax/eq}$), 2.05 (m, 1H, 3-H_{eq}), 3.10 (ddd, *J* 10.5, 5.5, 2.0 Hz, 1H, 1-H_{ax}), 4.70 (dddd, *J* 2.5, 2.5, 2.5, 2.0 Hz, 1H, 2-H_{eq}), 6.9–7.2 (m, 5H, aromatic H), 8.15 (s, 3H, $^{+}NH_3$); ^{13}C NMR ($CDCl_3$): δ 18.8 (t), 23.0 (t), 25.4 (t), 26.5 (t), 51.9 (d), 71.4 (d), 116.8 (d), 121.3 (d), 129.3 (d), 156.4 (s).

(1S,2R)-2-Phenoxycyclohexanamine hydrochloride (1S,2R)-5e

Yield: 4.0 g (87%); mp: 218–221°C; $[\alpha]^{25}_D$=−75.7 (c=1.5, EtOH); Anal. calcd. for $C_{12}H_{18}NOCl$: C 63.3, H 7.97, N 6.1; Found: C 63.2, H 7.86, N 6.2.

(1S,2R)-2-Aminocyclohexanol hydrochloride (1S,2R)-5g

10% Pd/C (1.0 g) was suspended in 50 mL of dry EtOH and prehydrogenated at 60°C for 30 min. A solution of 664 mg of **(αR,1R,2S)-4e** in 50 mL of 60°C warm EtOH was added and the resulting mixture was hydrogenated for 24 h at 5 bar H_2 and 65°C. The catalyst was filtered off, washed with EtOH and the filtrate was concentrated *in vacuo*. Recrystallisation from Et_2O/EtOH (1:1) gave 170 mg (54%) of the pure **(1S,2R)-5g**: mp: 225–227°C; $[\alpha]^{25}_D$=+30.2 (c=0.4, EtOH); Anal. calcd. for $C_6H_{14}NOCl$: C 47.5, H 9.31, N 9.2; Found: C 47.4, H 9.39, N 9.2; ^1H NMR (CD_3OD): δ 1.35–1.80 (m, 8H, $-(CH_2)_4-$), 3.18 (m, 1H, 1-H_{ax}), 4.0 (dddd, *J* 2.5, 2.5, 2.5, 2.5 Hz, 1H, 2-H_{eq}); ^{13}C NMR (CD_3OD): δ 20.1 (t), 24.2 (t), 26.1 (t), 32.3 (t), 54.0 (d), 66.5 (d).

(1R,2S)-2-Aminocyclohexanol hydrochloride (1R,2S)-5g

Analogously to **(1S,2R)-5g**, starting with **(αS,1S,2R)-4e**: mp: 225–227°C; $[\alpha]^{25}_D$=−30.2 (c=0.4, EtOH); Anal. calcd. for $C_6H_{14}NOCl$: C 47.5, H 9.31, N 9.2; Found: C 47.2, H 9.05, N 9.2.

(1R,2S)-2-Cyclohexylcyclohexanamine hydrochloride (1R,2S)-5h

10% Pd/C (1.0 g) was suspended in 50 mL of dry EtOH and prehydrogenated at 60°C for 30 min. A solution of 664 mg of **(αR,1R,2S)-4e** in 50 mL of 60°C warm EtOH was added, and the resulting mixture was hydrogenated for 24 h at 5 bar H_2 and 65°C. The catalyst was filtered off, washed with EtOH and the filtrate was concentrated *in vacuo*. CC of the residue on silica gel eluted with 2-PrOH/NH_4OH (95:5) yielded **(1R,2S)-5h** [Rf=0.7] as well as **(1S,2R)-5g** [Rf=0.2]. The free aminoether of **(1R,2S)-5h** was treated with HCl gas and recrystallised from Et_2O/EtOH (1:1).

Yield: 35 mg (15%); mp: 230–231°C; $[\alpha]^{25}_D$=+61.7 (c=0.9, EtOH); ^1H NMR (CD_3OD): δ 1.1–2.0 (m, 18H, $-(CH_2)_4-$, cyclohexyl), 3.2 (m, 1H, 1-H_{ax}), 3.4 (m, 1H, 1′-H_{ax}), 3.8 (m, 1H, 2-H_{eq}); ^{13}C NMR (CD_3OD): δ 20.3 (t), 24.3 (t), 25.3 (t), 25.4(t), 26.6 (t), 26.8 (t), 28.8 (t), 32.9 (t), 34.9 (t), 53.5 (d), 71.8 (d), 76.6 (d).

General procedure for the Mosher's amides 9

A solution of 0.3 mmol of the primary amine hydrochlorides **5** in 3 mL of 1 N NaOH was extracted with Et_2O (3×3 mL). The organic layers were dried over KOH, filtered and the solvent was removed *in vacuo*. The residue was taken up in 15 drops of abs. pyridine and 60 µL (0.3 mmol) of (*S*)-(+)-2-methoxy-2-trifluoromethylphenylethanoic acid chloride were added. After 24 h 3 mL of H_2O were added and the mixture was extracted with Et_2O (3×3 mL). The combined organic layers were washed with 1 N HCl (3×5 mL), saturated Na_2CO_3 (3×5 mL) and H_2O (2×5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. For HPLC analysis 2–5 µL (10% in EtOAc) of the crude residue were used. The diastereomeric amides were eluted with isooctane/EtOAc (24:1 and 32:1, respectively) at a rate of 1.6–2.0 mL/min on LiChrosorb Si 60 (Merck) 7µm, 250×4 mm. (The analytical data are not reported here. For further information see Lauktien.[25])

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