New β-Amino Alcohols as Chiral Ligands for the Catalytic Enantioselective Reduction of Prochiral Ketones and the Nucleophilic Addition of Diethylzinc to Benzaldehyde☆

Viola Peper and Jürgen Martens*

Fachbereich Chemie der Universität Oldenburg,
Carl-von-Ossietzky-Straße 9–11, D-26129 Oldenburg

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New optically active β-amino alcohols, derived from various acyclic and cyclic amino acids with alkyl groups on the carbinol carbon atom, were used in the enantioselective reduction of prochiral ketones. The attachment of alkyl groups to the nitrogen atom of the catalyst (*R*)-**1b** was shown to influence favorably the enantioselectivity of the addition of diethylzinc to benzaldehyde. In both cases the resulting secondary alcohols were obtained in moderate to high optical yields.

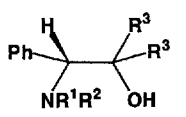
The enantioselective reduction of carbonyl groups with a variety of ligands, modified by boron and aluminum hydrides[1] and the nucleophilic addition of chelated organometallics to carbonyl compounds[2], are two of the most important asymmetric reactions.

Recently, much attention was focused on the preparation of catalysts with a β-amino alcohol structural unit. Both functionalities of the β-amino alcohol react with the hydride to give the corresponding oxazaborolidine[3]. Remarkably, most of the β-amino alcohols employed in the literature bear aromatic groups, especially on the carbinol carbon atom. Therefore, we investigated enantioselective reactions with β-amino alcohols bearing various alkyl groups on the carbinol carbon atom. The β-amino alcohols employed in this paper derive from (*R*)-phenylglycine [for (*R*)-**1a–g**], (*S*)-phenylalanine [for (*S*)-**2**], (*S*)-homophenylalanine [for (*S*)-**3**], (*S*)-*tert*-leucine [for (*S*)-**4b**], and (*S*)-indolinecarboxylic acid [for (*S*)-**5b**]. Remarkably, the catalyst (*S*)-**4b** is a purely aliphatic inductor[4].

Acetophenone and ω-chloroacetophenone were used as model substrates for the enantioselective catalytic reduction with borane.

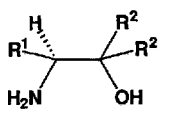
The reductions of these prochiral ketones with borane were catalyzed by the oxazaborolidines formed in situ from (*R*)-**1a–e** to (*S*)-**5b** and gave the secondary alcohols in chemical yields between 65 and 93%. The oxazaborolidines were not isolated.

The results of the reduction of the model ketones with the oxazaborolidines generated from the β-amino alcohols (*R*)-**1a–e** to (*S*)-**5b** are summarized in Table 1. The catalysts (*R*)-**1a–e** afforded alcohols with (*S*) configuration and the ligands (*S*)-**2** to (*S*)-**5b** gave alcohols with (*R*) configuration. The reductions of acetophenone were carried out by using 2 or 10 mol-% of the catalysts mentioned above. In all cases the enantioselectivity increased by increasing the amount of the catalyst. The most satisfactory results were obtained with (*R*)-**1b** as catalyst for the reduction of acetophenone with borane (88% ee with 2 mol-% and 92% ee with 10 mol-% of catalyst). It is noteworthy that the reduction of acetophenone with borane with 2 mol-% of the β-amino alcohol (*R*)-**1d** bearing a phenyl group at the stereogenic center afforded the (*S*) alcohol with 86% ee. The same reaction with 2 mol-% of the benzyl-substituted β-amino alcohol (*S*)-**2** gave the (*R*) alcohol with 78% ee. The use of the phenethyl-substituted ligand (*S*)-**3** led to the (*R*)



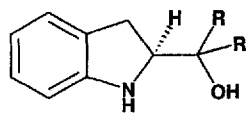
(*R*)-**1a-g**

(*R*)-1	R^1	R^2	R^3
a	H	H	Me
b	H	H	Et
c	H	H	*n*-Prop
d	H	H	*n*-Bu
e	H	H	$CH_2CH{=}CH_2$
f	H	Me	Et
g	Me	Me	Et

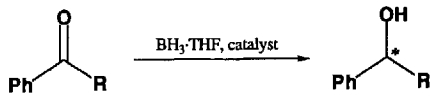


(*S*)-**2-4b**

	R^1	R^2
(*S*)-2	$PhCH_2$	*n*-Bu
(*S*)-3	$Ph(CH_2)_2$	*n*-Bu
(*S*)-4a	*tert.*-Bu	H
(*S*)-4b	*tert.*-Bu	*n*-Bu
(*S*)-4c	*tert.*-Bu	Ph



	(*S*)-5a	(*S*)-5b	(*S*)-5c
R	H	*n*-Bu	Ph



R = Me, CH_2Cl

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alcohols with only 50% ee. The optical yield of 1-phenyl-1-ethanol is influenced in the same manner when 10 mol-% of the catalysts (*R*)-**1d**, (*S*)-**2** or (*S*)-**3** were used.

Table 1. Enantioselective catalytic reductions of prochiral ketones with the β-amino alcohols (*R*)-**1a–e** to (*S*)-**5c** and excess borane in THF

Ketone R	Catalyst	Ref.	Secondary alcohol[a] 2 mol-% of catalyst Optical yield [%][b] (abs. config.)	10 mol-% of catalyst Optical yield [%][b] (abs. config.)
Me	(*R*)-**1a**	–	56 (*S*)	91 (*S*)
Me	(*R*)-**1b**	–	88 (*S*)	92 (*S*)
Me	(*R*)-**1c**	–	53 (*S*)	91 (*S*)
Me	(*R*)-**1d**	–	86 (*S*)	90 (*S*)
Me	(*R*)-**1e**	–	49 (*S*)	68 (*S*)
Me	(*S*)-**2**	–	78 (*R*)	82 (*R*)
Me	(*S*)-**3**	–	50 (*R*)	72 (*R*)
Me	(*S*)-**4a**	5	–	80 (*R*)
Me	(*S*)-**4b**	–	68 (*R*)	82 (*R*)
Me	(*S*)-**4c**	5	–	89 (*R*)
Me	(*S*)-**5a**	6	3 (*R*)	8 (*R*)
Me	(*S*)-**5b**	–	49 (*R*)	65 (*R*)
Me	(*S*)-**5c**	6	93 (*R*)	91 (*R*)
CH_2Cl	(*R*)-**1b**	–	96 (*R*)	–
CH_2Cl	(*R*)-**1d**	–	99 (*R*)	–
CH_2Cl	(*R*)-**1e**	–	76 (*R*)	–
CH_2Cl	(*S*)-**2**	–	97 (*S*)	–
CH_2Cl	(*S*)-**3**	–	91 (*S*)	–
CH_2Cl	(*S*)-**4b**	–	60 (*S*)	–
CH_2Cl	(*S*)-**5b**	–	61 (*S*)	–

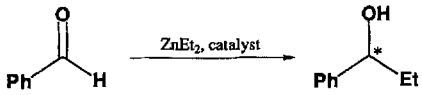
[a] Prepared according to GP I. – [b] The optical yield was calculated from the optical rotation based on the maximum rotations of each chiral alcohol: $[\alpha]_D^{20} = +43.1$ ($c = 7.19$, cyclopentane) for (*R*)-1-phenyl-1-ethanol[9], $[\alpha]_D^{20} = -48.1$ ($c = 1.73$, cyclohexane) for (*R*)-2-chloro-1-phenylethanol[10].

As can be seen from Table 1 when 10 mol-% of known (*S*)-2-amino-3,3-dimethyl-1-butanol [(*S*)-**4a**] is used as catalyst in the reduction of acetophenone Behnen et al.[5] obtained (*R*)-1-phenyl-1-ethanol with 80% ee. In the presence of 10 mol-% (*S*)-**4b** we obtained an enantioselectivity of 82% ee. Application of the (*S*)-2-amino-3,3-dimethyl-1,1-diphenyl-1-butanol [(*S*)-**4c**] as catalyst (10 mol-%) afforded the secondary alcohol with 89% ee[5]. Furthermore, (*R*)-1-phenyl-1-ethanol was obtained with 3% ee (8% ee) by using 2 mol-% (10 mol-%) of (*S*)-(indolin-2-yl)methanol [(*S*)-**5a**] as the catalyst[6]. We obtained the aromatic alcohol with an optical purity of 49% (65%) by employing 2 mol-% (10 mol-%) of (*S*)-**5b**. The *sec*-alcohol was formed with 93% ee (91% ee) from acetophenone in the presence of 2 mol-% (10 mol-%) of (*S*)-α,α-diphenyl-(indolin-2-yl)methanol [(*S*)-**5c**][6].

Furthermore, it can be seen that the optical yield of the product alcohol increases if the prochiral ketone contains the electron-withdrawing group CH_2Cl. The best result was achieved with 2 mol-% of (*R*)-**1d** (99% optical purity of the 2-chloro-1-phenylethanol).

The reductions of the two prochiral aromatic ketones with 2 or 10 mol-% of (*R*)-**1f** as the catalyst gave low optical purities (less than 10% ee).

Moreover, the efficiency of (*R*)-**1b**, (*R*)-**1f**, and the dimethylated β-amino alcohol (*R*)-**1g** was tested in the addition of diethylzinc to benzaldehyde. 1-Phenyl-1-propanol was isolated in chemical yields between 49 and 65%.



As can be seen from Table 2 the reactions in the presence of 10 mol-% of the catalysts (*R*)-**1b**, (*R*)-**1f**, and (*R*)-**1g** proceed with increasing enantioselectivities. We also observed that the use of the lithium alkoxides of the new chiral β-amino alcohols (*R*)-**1b** and (*R*)-**1g** as catalysts [Li-(*R*)-**1f** and Li-(*R*)-**1g**] in the reaction of diethylzinc with benzaldehyde increases the enantioselectivity. The influence of temperature on the selectivity of the reaction was also studied. Generally, the enantioselectivity slightly increases at lower temperatures (Table 2).

Table 2. Catalytic enantioselective addition of diethylzinc to benzaldehyde in the presence of 10 mol-% of the β-amino alcohols (*R*)-**1b**, (*R*)-**1f**, and (*R*)-**1g**

Entry	Catalyst	Temp. [°C]	(*S*)-1-Phenyl-1-propanol Optical yield [%][c]
1	(*R*)-**1b**[a]	0	32
2	(*R*)-**1b**[a]	–20	27
3	(*R*)-**1f**[a]	+20	34
4	(*R*)-**1f**[a]	0	42
5	(*R*)-**1f**[a]	–20	44
6	Li-(*R*)-**1f**[b]	0	76
7	Li-(*R*)-**1f**[b]	–20	81
8	(*R*)-**1g**[a]	+20	80
9	Li-(*R*)-**1g**[b]	+20	96

[a] Prepared according to GP II. – [b] Prepared according to GP III. – [c] The optical yield was calculated from the optical rotation based on the maximum rotation $[\alpha]_D^{22} = -47.6$ ($c = 6.11$, $CHCl_3$) of (*S*)-1-phenyl-1-propanol with 98% ee[11].

Further investigations are in progress regarding the catalysis and the asymmetric induction in the enantioselective reductions and nucleophilic additions of other achiral ketones and aldehydes with the optically active β-amino alcohols described above.

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Experimental

All reactions were carried out under dry argon. – Melting points (uncorrected): Linström apparatus. – IR: Beckman IR 4220, films between NaCl plates for liquids and KBr discs for solids. – ^1H and ^{13}C NMR: Bruker AM 300 (300.13 and 75.47 MHz); TMS as internal standard. Coupling constants J are given in Hertz (Hz). – Elemental analyses: CHN analyzer Carlo Erba MOD 1104. – Optical rotations: Perkin-Elmer polarimeter 241 MC. – MS: Finnigan-MAT 212 (data system SS 300) spectrometer. – Column chromatography: Silica gel 60 (particle size 0.040–0.063 mm) from Merck. – Thin-layer chromatography (TLC): Merck silica gel 60 F_{254} aluminum sheets. TLC spots were detected with UV light or with I_2. For column chromatography and TLC (determination of the R_f values) the same eluant was used.

General Procedure (GP I) for the Catalytic Enantioselective Reduction of Prochiral Ketones: The oxazaborolidine–borane reagents are prepared from 0.4 or 2 mmol of the β-amino alcohols [(*R*)-**1a** to (*S*)-**5b**] in 20 ml of dry THF and 20.4 or 22 mmol of a 1 M BH_3–THF solution at −50 °C. A solution of the ketone (20 mmol) in 20 ml of dry THF is added with stirring to this solution within 45 min at room temp. and the mixture is stirred at this temperature for 16 h. The flask is cooled to 0 °C and 50 ml of 2 N HCl is added dropwise. The resulting secondary alcohol can be isolated by extraction with ether, drying of the extract with anhydrous magnesium sulfate and removal of the ether under reduced pressure. The residue is subjected to fractional distillation under vacuum to afford the pure alcohol.

General Procedure (GP II) for the Catalytic Enantioselective Addition of Diethylzinc to Benzaldehyde: 36.5 ml (40 mmol) of a 1.1 M diethylzinc solution in toluene is added over a period of 5 min to a solution of the catalyst (2 mmol) in 40 ml of dry toluene at −40 °C. The mixture is allowed to reach the room temp. Then the mixture is treated within 10 min with 2.12 g (20 mmol) of benzaldehyde at the reaction temperature mentioned in Table 2 and stirred at this temperature for 4 h and then 16 h at room temp. The reaction is quenched with 2 N HCl, the organic layer is separated, and the aqueous layer is extracted with ether. The combinated organic layers are washed with a sodium hydrogen sulfite solution, a sodium hydrogen carbonate solution and a saturated sodium chloride solution, then dried. The solvent is evaporated under reduced pressure and the residue is subjected to fractional distillation under vacuum to afford 1-phenyl-1-propanol.

General Procedure (GP III) for the Catalytic Enantioselective Addition of Diethylzinc to Benzaldehyde with the Use of n-Butyllithium: *n*-Butyllithium (2 mmol, 1.27 ml of a 1.6 M *n*-hexane solution) is added to a solution of the catalyst (2 mmol) in 40 ml of dry toluene at −40 °C. After 10 min diethylzinc (36.5 ml, 40 mmol of a 1.1 M toluene solution) is added over a period of 5 min. The mixture is allowed to reach the room temp. The further work-up is the same as in GP II.

General Procedure (GP IV) for the Synthesis of the Chiral β-Amino Alcohols: A dried 500-ml, three-necked, round-bottomed flask is equipped with a pressure-equalizing 50-ml dropping funnel, thermometer, magnetic stirrer, and a Liebig condenser. The Grignard reagent is prepared from magnesium (333.8 mmol) and the alkyl halide (333.8 mmol) in diethyl ether (250 ml). The amino acid ethyl ester hydrochloride (41.7 mmol) is added to the alkylmagnesium halide solution in portions at −8 °C. After the addition, the cooling bath is removed and the reaction mixture is allowed to warm to room temp. The solution is heated at reflux for 2.5 h and then poured with stirring into a mixture of crushed ice (180 g) and concd. hydrochloric acid (30 ml). The organic layer is separated and the aqueous layer extracted with ethyl acetate. The combined organic layers are dried with anhydrous magnesium sulfate and concentrated.

The β-amino alcohol hydrochlorides (*R*)-**1a**-HCl[7], (*R*)-**1b**-HCl, (*R*)-**1e**-HCl, and (*S*)-**5b**-HCl are purified before the next step. The new compounds give satisfactory spectroscopic and analytical data (not mentioned in this paper). The other β-amino alcohol hydrochlorides are used without further purification for the next step:

The resulting β-amino alcohol hydrochloride is suspended in dichloromethane and the suspension is treated with a 2 N aqueous sodium hydroxide solution with vigorous stirring until the aqueous phase is alkaline. Then triethylamine (11.5 ml) is added to the resulting mixture, which is stirred for 6 h and subsequently extracted several times with dichloromethane. The combinated extracts are washed with water, dried, and the solvent is evaporated under reduced pressure. The residue is distilled under vacuum (kugelrohr).

(R)-2-(Amino-phenyl-methyl)propan-2-ol [(*R*)-**1a**]: Prepared according to GP IV. – Starting materials: 8.1 g (333.8 mmol) of magnesium, 47.4 g (333.8 mmol) of methyl iodide, 9.0 g (41.7 mmol) of (*R*)-phenylglycine ethyl ester hydrochloride. – Yield 3.2 g (46%). – Colorless needles. – M.p. 50–51 °C (ref.[7] 52–53.5 °C). – $[\alpha]_D^{20}$ = −23.9 (*c* = 1.82, $CHCl_3$) {ref.[7] $[\alpha]_D^{20}$ = −11.2 (*c* = 1.0, EtOH)}. – IR (KBr): $\tilde{\nu}$ = 3180–3580 cm^{-1} (NH, OH), 3080–2890 (=CH, CH, CH_3), 1480 (aromat.), 1450, 1370 (CH_3). – ^1H NMR ($CDCl_3$): δ = 1.05 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 2.20 (s, 3H, NH_2, OH), 3.79 (s, 1H, 1′-H), 7.25–7.38 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 24.72, 27.53 (2 × CH_3), 64.45 (C-1′), 72.15 (C-2), 127.19, 127.74, 127.93 (aromat. C), 142.47 (quat. aromat. C).

(R)-3-(Amino-phenyl-methyl)pentan-3-ol [(*R*)-**1b**]: Prepared according to GP IV. – Starting materials: 8.1 g (333.8 mmol) of magnesium, 36.4 g (333.8 mmol) of ethyl bromide, 9.0 g (41.7 mmol) of (*R*)-phenylglycine ethyl ester hydrochloride. – Yield 3.15 g (39%). – Colorless needles. – M.p. 41 °C. – $[\alpha]_D^{20}$ = −77.1 (*c* = 2.09, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3180–3560 cm^{-1} (NH, OH), 3060–2880 (=CH, CH, CH_3), 1485 (aromat.), 1450, 1375 (CH_3). – ^1H NMR ($CDCl_3$): δ = 0.81 (t, 3H, *J* = 7.5 Hz, CH_3), 0.94 (t, 3H, *J* = 7.5 Hz, CH_3), 1.18–1.27 (m, 2H, CH_2), 1.54–1.74 (m, 2H, CH_2), 2.11 (s, 3H, NH_2, OH), 3.88 (s, 1H, 1′-H), 7.22–7.36 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 7.47, 8.07 (2 × CH_3), 27.18, 27.61 (2 × CH_2), 60.03 (C-1′), 75.59 (C-3), 127.07, 127.98, 131.74 (aromat. C), 142.65 (quat. aromat. C). – MS (CI, isobutane); *m/z* (%): 194 (100) $[MH^+]$. – $C_{12}H_{19}NO$ (193.3): calcd. C 74.57, H 9.91, N 7.25; found C 74.53, H 9.83, N 6.85.

(R)-4-(Amino-phenyl-methyl)heptan-4-ol [(*R*)-**1c**]: Prepared according to GP IV. – Starting materials: 8.1 g (333.8 mmol) of magnesium, 41.1 g (333.8 mmol) of *n*-propyl bromide, 9.0 g (41.7 mmol) of (*R*)-phenylglycine ethyl ester hydrochloride. – Yield 3.9 g (42%). – Colorless needles. – M.p. 58 °C. – $[\alpha]_D^{20}$ = −9.0 (*c* = 2.41, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3220–3560 cm^{-1} (NH, OH), 3070–2880 (=CH, CH, CH_3), 1490 (aromat.), 1450, 1375 (CH_3). – ^1H NMR ($CDCl_3$): δ = 0.78 (t, 3H, *J* = 6.9 Hz, CH_3), 0.95 (t, 3H, *J* = 7.2 Hz, CH_3), 1.12–1.57 (m, 8H, 4 × CH_2), 2.21 (s, 3H, NH_2, OH), 3.87 (s, 1H, 1′-H), 7.23–7.43 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 14.55, 14.68 (2 × CH_3), 16.53, 17.03 (2 × $CH_2CH_2CH_3$), 37.67, 38.46 (2 × $CH_2CH_2CH_3$), 60.76 (C-1′), 75.38 (C-4), 127.15, 128.0, 128.02 (aromat. C), 142.51 (quat. aromat. C). – MS (CI, isobutane); *m/z* (%): 222 (100) $[MH^+]$. – $C_{14}H_{23}NO$ (221.3): calcd. C 75.97, H 10.47, N 6.33; found C 75.99, H 10.32, N 5.74.

(R)-5-(Amino-phenyl-methyl)nonan-5-ol [(*R*)-**1d**]: Prepared according to GP IV. – Starting materials: 8.1 g (333.8 mmol) of magnesium, 45.7 g (333.8 mmol) of *n*-butyl bromide, 9.0 g (41.7 mmol) of (*R*)-phenylglycine ethyl ester hydrochloride. – Yield 5.3 g (51%). – Colorless solid. – M.p. 47 °C. – $[\alpha]_D^{20}$ = +6.82 (*c* = 3.52, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3240–3560 cm^{-1} (OH), 2960, 2935, 2880 (CH_2, CH_3), 1485 (aromat.), 1450, 1380 (CH_2, CH_3). – ^1H NMR ($CDCl_3$): δ = 0.74 (t, *J* = 7.5 Hz, 3H, CH_3), 0.89 (t, *J* = 7.5 Hz, 3H, CH_3), 1.04–1.58 (m, 12H, 6 × CH_2), 1.97 (s, 2H, NH_2), 3.81 (s, 1H, 1′-H), 7.16–7.30 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 13.93, 14.07 (2 × $CH_2CH_2CH_2CH_3$), 23.20, 23.35 (2 × $CHCH_2CH_2CH_3$), 25.43, 25.96 (2 × $CH_2CH_2CH_2CH_3$), 35.05, 35.81 (2 × $CH_2CH_2CH_2CH_3$), 60.74 (C-1′), 75.32 (C-5), 127.14–128.02 (aromat. C), 142.64 (quat. aromat. C). – MS (CI, isobutane); *m/z* (%): 250 (100) $[MH^+]$. – $C_{16}H_{27}NO$ (249.4): calcd. C 77.06, H 10.91, N 5.62; found C 76.58, H 11.04, N 5.55.

(R)-4-(Amino-phenyl-methyl)hepta-1,6-dien-4-ol [(*R*)-**1e**]: Prepared according to GP IV. – Starting materials: 8.1 g (333.8 mmol) of magnesium, 40.4 g (333.8 mmol) of allyl bromide, 9.0 g (41.7 mmol) of (*R*)-phenylglycine ethyl ester hydrochloride. – Yield 4.35 g (48%). – Colorless solid. – M.p. 34°C. – $[\alpha]_D^{20}$ = +12.3 (*c* = 5.05, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3240–3580 cm^{-1} (OH), 3100, 3060, 3010, 2950 (=CH, CH, CH_2), 1645 (NH), 1495 (aromat.), 1000 (CO). – ^1H NMR ($CDCl_3$): δ = 1.87–2.37 (m, 6H, 2 × CH_2-CH=CH_2, NH_2), 3.84 (s, 1H, 1′-H), 4.89–5.11 (m, 4H, olefin. H), 5.71–5.93 (m, 2H, olefin. H), 7.17–7.34 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 40.45, 41.46 (2 × CH_2-CH=CH_2), 60.77 (C-1′), 74.95 (C-4), 118.00, 118.09 (2 × olefin. C), 127.35–134.26 (aromat. C und 2 × olefin. C), 142.03 (quat. aromat. C). – MS (CI, isobutane); *m/z* (%): 218 (100) [MH^+]. – $C_{14}H_{19}NO$ (217.3): calcd. C 77.38, H 8.81, N 6.45; found C 77.13, H 8.79, N 6.09.

Synthesis of (R)-3-(Methylamino-phenyl-methyl)pentan-3-ol [(*R*)-**1f**]

(R)-N-(2-Ethyl-2-hydroxy-1-phenylbutyl)formamide: A solution of 5.39 g (27.9 mmol) of (*R*)-**1b** in 62 ml of methyl formate is stirred for 12 h at room temp. The solvent is evaporated and the yellow oil is crystallized from dichloromethane/*n*-hexane. The colorless crystals are dried in vacuo (40°C/20 mbar). – Yield 4.0 g (65%). – M.p. 118°C. – $[\alpha]_D^{20}$ = –79.2 (*c* = 2.52, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3140–3430 cm^{-1} (OH), 2960, 2940 (CH_2, CH_3), 1710 (C=O), 1490 (aromat.), 1420, 1360 (CH_2, CH_3), 1225 (C–N), 1090 (C–O). – ^1H NMR ($CDCl_3$): δ = 0.78 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.90 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.04–1.30 (m, 2H, CH_2CH_3), 1.63 (m, 2H, CH_2CH_3), 2.41 (s, 1H, OH), 4.99 (d, *J* = 8.8 Hz, 1H, 1-H), 7.15–7.40 (m, 5H, aromat. H), 8.08 (s, 1H, CHO). – ^{13}C NMR ($CDCl_3$): δ = 7.32, 7.91 (2 × CH_2CH_3), 27.27, 27.80 (2 × CH_2CH_3), 56.35 (C-1), 76.74 (C-2), 127.39, 128.11, 128.34 (aromat. C), 139.00 (quat. aromat. C), 160.58 (CHO). – MS (CI, isobutane); *m/z* (%): 204 (100) [$MH^+ - H_2O$]. – $C_{13}H_{19}NO_2$ (221.3): calcd. C 70.88, H 8.24, N 6.36; found C 70.28, H 8.82, N 6.37.

(R)-3-(Methylamino-phenyl-methyl)pentan-3-ol (*R*)-**1f**: To a suspension of 1.5 g (39.5 mmol) of lithium aluminum hyride in 80 ml absol. THF 3.74 g (17.0 mmol) of (*R*)-**1e** in 60 ml of absol. THF is added and the resulting reaction mixture is refluxed for 12 h. Excess $LiAlH_4$ is destroyed by addition of 2.5 ml of 10% potassium hydroxide and 2.5 ml of H_2O with cooling. The suspension is heated at reflux for 1 h and the white suspended materials are hot filtered off. The filter cake is washed with 150 ml of MTBE, the combined organic layers are dried with $MgSO_4$ and the solvent is evaporated. The resulting yellow oil is distilled under vacuum (kugelrohr: 100°C/0.003 mbar). – Yield 2.95 g (84%). – Colorless solid. – M.p. 42°C. – $[\alpha]_D^{20}$ = –58.4 (*c* = 2.12, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3320–3580 cm^{-1} (NH, OH), 2960, 2900 (CH_2, CH_3), 2810 (N–CH_3), 1495 (aromat.), 1450, 1390 (CH_2, CH_3), 1135 (C–N). – ^1H NMR ($CDCl_3$): δ = 0.86 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 0.93 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.16–1.38 (m, 2H, CH_2CH_3), 1.41–1.52 (m, 1H, CH_2CH_3), 1.68–1.77 (m, 1H, CH_2CH_3), 2.26 (s, 3H, NCH_3), 2.92 (s, 1H, OH), 3.49 (s, 1H, 1′-H), 7.20–7.37 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 7.43, 7.88 (2 × CH_2CH_3), 27.46, 27.54 (2 × CH_2CH_3), 34.81 (NCH_3), 69.95 (C-1′), 75.67 (C-3), 126.99, 127.95, 128.40 (aromat. C), 139.88 (quat. aromat. C). – MS (CI, isobutane); *m/z* (%): 208 (100) [MH^+]. – $C_{13}H_{21}NO$ (207.3): calcd. C 75.32, H 10.21, N 6.76; found C 75.18, H 10.47, N 6.74.

(R)-3-(Dimethylamino-phenyl-methyl)pentan-3-ol (*R*)-**1g**: To a boiling solution of 3.65 g (17.6 mmol) of (*R*)-**1f** in 10.1 ml of formic acid and 2.3 ml of H_2O is added 7.6 ml of formaldehyde (37% in H_2O). After the addition, the reaction mixture is refluxed for further 12 h. The solution is cooled to room temp. and treated with a concd. sodium hydroxide solution with vigorous stirring until the reaction mixture is alkaline (pH 11). This basic solution is extracted three times with 30 ml of dichloromethane each, the combined extracts are dried with anhydrous magnesium sulfate and the solvent is evaporated under reduced pressure. The resulting yellow oil is purified by column chromatography on silica gel 60 with *n*-hexane/ethyl acetate (8:2) as the eluant to afford the corresponding colorless oil. – Yield 2.2 g (56%). – (TLC: R_F value = 0.21). – $[\alpha]_D^{20}$ = –22.70 (*c* = 1.62, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3330–3550 cm^{-1} (NH, OH), 2950, 2920 (CH_2, CH_3), 2820 (N–CH_3), 1490 (aromat.), 1460, 1380 (CH_2, CH_3). – ^1H NMR ($CDCl_3$): δ = 0.65 (t, *J* = 7.5 Hz, 3H, CH_3), 0.81 (t, *J* = 7.5 Hz, 3H, CH_3), 1.13–1.36 (m, 2H, CH_2), 1.61–1.79 (m, 2H, CH_2), 2.26 [s, 6H, $N(CH_3)_2$], 3.36 (s, 1H, CHN), 7.15–7.34 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 7.61, 8.31 (2 × CH_3), 28.24, 28.32 (2 × CH_2), 44.22 [2 C, $N(CH_3)_2$], 73.29 (CHN), 78.52 (C-3), 126.90, 127.44, 131.24 (aromat. C), 135.10 (quat. aromat. C). – MS (CI, isobutane), *m/z* (%): 222 (100) [MH^+]. – $C_{14}H_{23}NO$ (221.3): calcd. C 75.96, H 10.48, N 6.33; found C 75.97, H 10.38, N 6.31.

(S)-5-(1-Amino-2-phenylethyl)nonan-5-ol[8] (*S*)-**2**: Prepared according to GP IV. – Starting materials: 8.1 g (333.8 mmol) of magnesium, 45.7 g (333.8 mmol) of *n*-butyl bromide, 9.6 g (41.7 mmol) of (*S*)-phenylalanine ethyl ester hydrochloride. – Yield 4.8 g (44%). – Colorless viscous oil. – $[\alpha]_D^{20}$ = –12.8 (*c* = 7.18, CH_2Cl_2). – IR (NaCl): $\tilde{\nu}$ = 3230–3550 cm^{-1} (OH, NH), 3030, 2950, 2925, 2850 (=CH, CH_2, CH_3), 1490 (aromat.), 1460, 1370 (CH_2, CH_3). – ^1H NMR ($CDCl_3$): δ = 0.86–1.04 (m, 6H, 2 × $CH_2CH_2CH_2CH_3$), 1.25–1.66 (m, 12H, 2 × $CH_2CH_2CH_2CH_3$), 1.70–1.98 (s, 2H, NH_2), 2.27–2.38 (m, 1H, CHN), 2.89–3.04 (m, 2H, $PhCH_2$), 7.15–7.36 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 14.04 (2 × $CH_2CH_2CH_2CH_3$), 23.37, 23.51 (2 × $CH_2CH_2CH_2CH_3$), 25.46, 25.50 (2 × $CH_2CH_2CH_2CH_3$), 34.40, 35.99, 38.01 (2 × $CH_2CH_2CH_2CH_3$, $PhCH_2$), 57.81 (CHN), 74.18 (C5), 126.20, 128.51, 129.02 (aromat. C), 139.98 (quat. aromat. C).

(S)-5-(1-Amino-3-phenylpropyl)nonan-5-ol (*S*)-**3**: Prepared according to GP IV. – Starting materials: 8.1 g (333.8 mmol) of magnesium, 45.7 g (333.8 mmol) of *n*-butyl bromide, 10.2 g (41.7 mmol) of (*S*)-homophenylalanine ethyl ester hydrochloride. – Yield 4.95 g (43%). – Colorless viscous oil. – $[\alpha]_D^{20}$ = –21.3 (*c* = 3.98, CH_2Cl_2). – IR (NaCl): $\tilde{\nu}$ = 3250–3540 cm^{-1} (OH, NH), 3040, 2960, 2925, 2860 (=CH, CH_2, CH_3), 1485 (aromat.), 1455, 1375 (CH_2, CH_3). – ^1H NMR ($CDCl_3$): δ = 0.84–1.00 (m, 6H, 2 × $CH_2CH_2CH_2CH_3$), 1.06–2.07 (m, 16H, 2 × $CH_2CH_2HH_2CH_3$, $PhCH_2CH_2$, NH_2), 2.54–2.68 (m, 2h, $PhCH_2CH_2$), 2.82–2.94 (m, 1H, CHN), 7.17–7.38 (m, 5H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 13.97 (2 × $CH_2CH_2CH_2CH_3$), 23.29, 23.49 (2 × $CH_2CH_2CH_2CH_3$), 25.14, 25.31 (2 × $CH_2CH_2CH_2CH_3$), 33.49, 34.04, 34.55, 35.72 (2 × $CH_2CH_2CH_2CH_3$, $PhCH_2CH_2$), 56.07 (CHN), 74.32 (C-5), 125.81, 128.23, 128.29 (aromat. C), 141.78 (quat. aromat. C). – MS (CI, isobutane); *m/z* (%): 278 (100) [MH^+], 555 (80) [DH^+]. – $C_{18}H_{31}NO$ (277.5): calcd. C 77.91, H 11.27, N 5.05; found C 77.93, H 11.26, N 5.19.

(S)-5-(1-Amino-2,2-dimethylpropyl)nonan-5-ol (*S*)-**4b**: Prepared according to GP IV. – Starting materials: 4.38 g (180 mmol) of magnesium, 24.7 g (180 mmol) of *n*-butyl bromide, 4.4 g (30.2 mmol) of (*S*)-*tert*-leucine ethyl ester. – Yield 3.25 g (47%). – Colorless oil (kugelrohr: 105°C/0.004 mbar). – $[\alpha]_D^{20}$ = +18.2 (*c* = 1.57, $CHCl_3$). – IR (NaCl): $\tilde{\nu}$ = 3240–3550 cm^{-1} (OH, NH), 2965, 2925, 2860 (CH_2, CH_3), 1450, 1390 (CH_2, CH_3). – ^1H NMR ($CDCl_3$): δ = 0.83–0.92 (m, 6H, 2 × $CH_2CH_2CH_2CH_3$), 1.00 [s, 9H, $C(CH_3)_3$], 1.17–1.72 (m, 12H, 2 × $CH_2CH_2CH_2CH_3$), 2.52

(s, 1H, CHN). – ^{13}C NMR ($CDCl_3$): δ = 14.12 (2 × $CH_2CH_2CH_2CH_3$), 23.32, 23.66 (2 × $CH_2CH_2CH_2CH_3$), 25.67, 25.99 (2 × $CH_2CH_2CH_2CH_3$), 28.74 [3 × $C(CH_3)_3$], 35.14 [$C(CH_3)_3$], 37.23, 37.82 (2 × $CH_2CH_2CH_2CH_3$), 63.23 (CHN), 75.31 (C-5). – MS (CI, isobutane); *m/z* (%): 230 (100) [MH^+]. – $C_{14}H_{31}NO$ (229.4): calcd. C 73.30, H 13.62, N 6.11; found C 73.25, H 13.42, N 6.08.

(S)-5-(2,3-Dihydro-1H-indol-2-yl)nonan-5-ol (*S*)-**5b**: Prepared according to GP IV. – Starting materials: 8.1 g (333.8 mmol) of magnesium, 45.7 g (333.8 mmol) of *n*-butyl bromide, 9.45 g (41.7 mmol) of ethyl (*S*)-2-indoline carboxylate. – Yield 5.85 g (54%). – Pale yellow solid. – M.p. 63°C. – $[\alpha]_D^{20}$ = –52.4 (*c* = 2.11, CH_2Cl_2). – IR (KBr): $\tilde{\nu}$ = 3540–3220 cm^{-1} (OH, NH), 3060–2840 (=CH, CH_2, CH_3), 1595, 1490 (aromat.), 1450, 1370 (CH_2, CH_3). – ^{1}H NMR ($CDCl_3$): δ = 0.91–1.08 (m, 6H, 2 × $CH_2CH_2CH_2CH_3$), 1.22–1.72 (m, 12H, 2 × $CH_2CH_2CH_2CH_3$), 2.86–2.99 (m, 1H, CH_2CHN), 3.07–3.12 (m, 1H, CH_2CHN), 3.90–4.02 (m, 1H, CH_2CHN), 6.67–6.84 (m, 2H, aromat. H), 7.10–7.17 (m, 2H, aromat. H). – ^{13}C NMR ($CDCl_3$): δ = 13.92, 14.00 (2 × $CH_2CH_2CH_2CH_3$), 23.32, 25.44, 25.67, 30.00, 33.93, 37.28 (2 × $CH_2CH_2CH_2CH_3$, CH_2CHN), 66.30 (CHN), 73.48 (COH), 109.74, 119.20, 124.52, 126.95, 129.36, 150.45 (aromat. C). – MS (CI, *i*-butane), *m/z* (%): 262 (100) [MH^+], 523 (28) [DH^+]. – $C_{17}H_{27}NO$ (261.4): calcd. C 78.11, H 10.41, N 5.36; found C 78.50, H 10.53, N 5.38.

☆ Dedicated to Dr. *Werner Schwarze*.

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