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Synthesis of C_2-symmetrical bis-β-amino alcohols from (*R*)-cysteine and their application in enantioselective catalysis †

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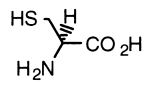
Abstract

Six new sulfur-containing C_2-symmetrical bis-β-*primary* and *sec*-amino-*tert*-alcohols have been synthesized from (*R*)-cysteine and applied successfully in the enantiocontrolled catalytic addition of diethylzinc to benzaldehyde. The resulting 1-phenyl-1-propanol could be obtained in good enantiomeric excess of up to 94%. Using the same chiral auxiliaries in the enantioselective borane reduction of acetophenone afforded 1-phenyl-1-ethanol in enantiomeric excesses of up to 82%.

1. Introduction

The stereoselective synthesis of optically active secondary alcohols is a well studied theme in organic chemistry. In this connection, the enantioselective addition of diethylzinc[1] to various aldehydes and the enantiocontrolled catalytic reduction of prochiral ketones using modified borane reagents[2] have been intensively investigated over the last decade. In both model reactions, β-amino alcohols (usually prepared from α-amino acids) are often used as chiral auxiliaries.[1,2] In the last few years sulfur-containing ligands like thioether-derivatives from (*R*)-cysteine,[3] (*R*)-cystine,[4] (*S*)-penicillamine[4] and (*S*)-methionine,[4] amino thiols[5] or sulfoxides[6] have gained more and more interest as catalysts in these stereoselective reactions.

However, to the best of our knowledge, this paper is the first report on the synthesis of bis-β-amino *tert*-alcohols, starting from (*R*)-cysteine **1**, and the application of these C_2-symmetrical sulfides in enantioselective catalysis.



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† This paper is dedicated to Heribert Offermanns on the occasion of his 60th birthday.

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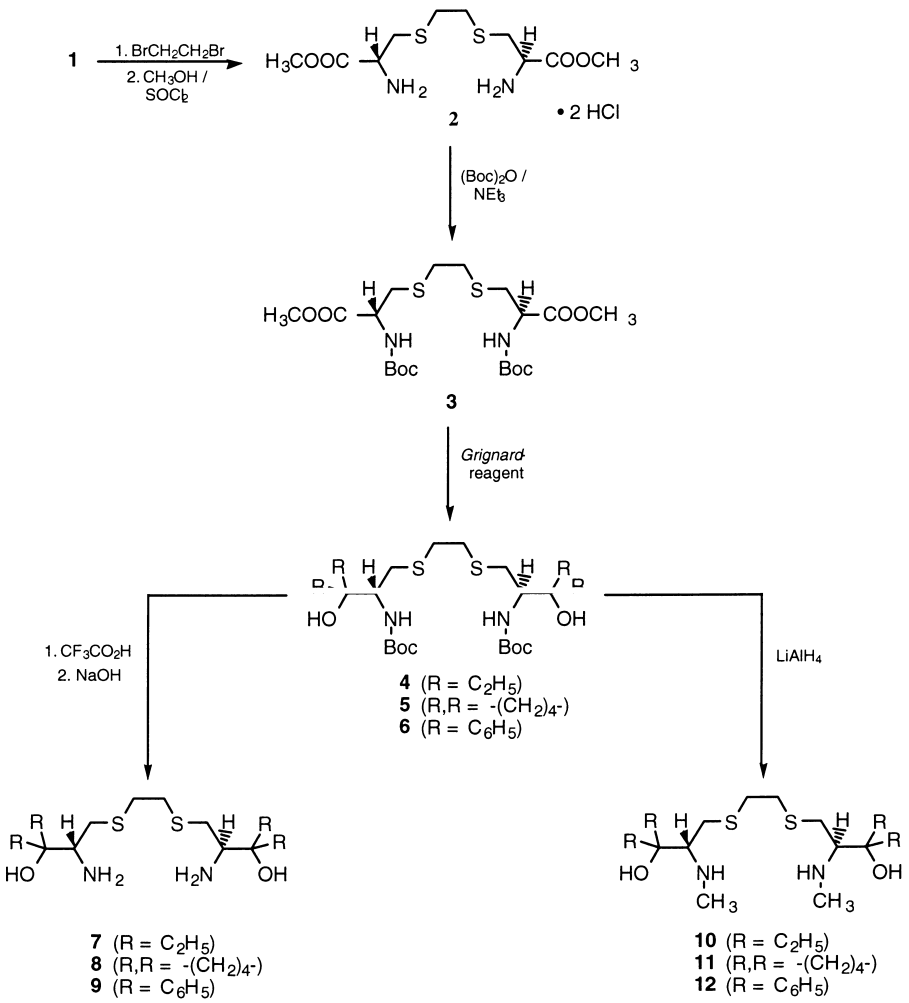
2. Results and discussion

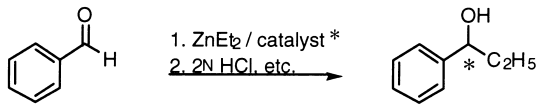
The synthesis of the C_2-symmetrical ligands **7**–**12** is shown in Scheme 1: (*R*)-cysteine **1** was first converted into the bridged bis-amino acid methyl ester **2** by treatment with 1,2-dibromoethane followed by esterification with methanol and thionylchloride.[7,8] The reaction of **2** with different Grignard reagents to give the desired chiral ligands **7**–**9** was not very successful. Low yields and the formation of by-products made it necessary to protect the primary amino groups of **2** by reaction with $(Boc)_2O$ in the presence of triethylamine, resulting in the carbamate **3**. The β-bis-amino alcohols **4**–**6** were obtained in moderate to good yields (60% to 87%, see experimental section) by addition of the respective Grignard reagent (10 equiv.) to **3**. Deprotection of the amino group by treatment with trifluoroacetic acid in dichloromethane gave the C_2-symmetrical β-*primary* amino-*tert*-alcohols **7**–**9** after basification with aq. NaOH and extractive work-up. Reduction of the *N*-Boc-protected intermediates **4**–**6** with excess $LiAlH_4$ in refluxing THF afforded the N-methylated bis-*sec*-amino-*tert*-alcohols **10**–**12**.



Scheme 1.

According to a typical procedure (see experimental section), the catalysts **7**–**12** were tested in the enantioselective addition of diethylzinc to benzaldehyde at room temperature (Scheme 2). As can be

seen from Table 1, the enantiomeric excesses of the obtained 1-phenyl-1-propanol range from 18% to 94%.



Scheme 2.

Using the β-*primary* amino alcohols **7**–**9** in the ethylation of benzaldehyde, only low excesses of one of the enantiomers (18–38%, entries 1–3) were obtained. Also, the absolute configurations of the enriched *sec* alcohols were not uniform. A predominant formation of (*S*)-1-phenyl-1-propanol was observed in the presence of the corresponding N-methylated β-*sec*-amino alcohols **10**–**12** (entries 4–8). In the case of catalysts **10** and **11** the additional N-alkylation shows no significant improvement of the enantiomeric excess, but in agreement with some of our previously published results,[3f,j] ligand **12** again clarifies the advantage of the N-methylation: with a catalyst concentration of 5 mol% the inductive efficiency strongly increased from 38% to 86% *e.e.* (entries 3 and 7). Apparently a sterically demanding α-substitution (R=phenyl) combined with a secondary amino function seems to be crucial for the enhancement of the stereocontrol. So the enantiomeric excess could be increased to 94% with **12** at a concentration of 10 mol% and, as expected, it decreased to 74% at 2.5 mol% (entries 6 and 8).

Table 2 shows the results of the homogenous catalytic reduction of acetophenone as model substrate (Scheme 3) with in situ formed oxazaborolidine catalysts derived from ligands **7**–**12**, respectively. Conversion of these bis-β-amino alcohols to oxazaborolidines was accomplished by treatment with $BH_3 \cdot THF$ and no further isolation or purification was carried out (see experimental section).

In contrast to the partially increased inductive efficiency of the ligands in the ethylation of benzaldehyde by an additional N-methylation, a drastic decrease of the enantiomeric excess was observed when the same β-*sec*-amino alcohols were used in the reduction of acetophenone (ligands **11** and **12**; entries 15 and 16). The best result was obtained with the *primary* amino alcohol **7** at a concentration of 5 mol% (82% *e.e.*; entry 10). Neither a bulky α-substitution (R=phenyl, **9** and **12**) nor a decreased conformative flexibility, caused by a rigid cyclopentanol fragment [R, R=–$(CH_2)_4$–, **8** and **11**] improved the stereocontrol in the formation of 1-phenylethan-1-ol.

In summary, the presented C_2-symmetrical bis-β-amino alcohols **7**–**12** have different capabilities concerning their inductive efficiency in the addition of diethylzinc to benzaldehyde and the borane

Table 1
Enantioselective addition of diethylzinc to benzaldehyde; product: 1-phenylpropan-1-ol[a]

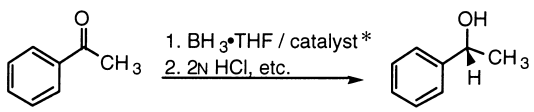
entry	catalyst *	concentration [mol%]	temperature [°C]	*e.e.* [%][b)]	configuration[c)]
1	**7**	5	21	18	*R*
2	**8**	5	23	29	*R*
3	**9**	5	23	38	*S*
4	**10**	5	21	21	*S*
5	**11**	5	23	33	*S*
6	**12**	10	23	94	*S*
7	**12**	5	23	86	*S*
8	**12**	2.5	23	74	*S*

a) Chemical yield 70-90 %; b) Enantiomeric excess determined by GC analysis (SGE Cydec-B, chiral); c) Absolute configuration was determined *via* chiral GC analysis by comparison with authentic samples.

Table 2
Enantioselective reduction of acetophenone at 25°C; product: (*R*)-1-phenylethan-1-ol[a]

entry	catalyst	concentration [mol%]	*e.e.* [%][b)]
9	**7**	2.5	32
10	**7**	5	82
11	**7**	10	50
12	**8**	5	64
13	**9**	5	68
14	**10**	5	69
15	**11**	5	14
16	**12**	5	8

a) Chemical yield 85-92 %; absolute configuration was determined *via* chiral GC analysis by comparison with authentic samples; b) Enantiomeric excess determined by GC analysis (SGE Cydec-B, chiral).



Scheme 3.

reduction of acetophenone. Noteworthy is the significant importance of a secondary amino function as well as a bulky α-hydroxy-substitution for good *e.e.*s in the ethylation of benzaldehyde and a secondary amino group combined with a less sterically demanding α-substitution in the borane reduction.

3. Experimental section

All reactions were carried out in oven-dried glassware under an argon atmosphere using anhydrous solvents. Thin layer chromatography was carried out on silica gel (60 F_{254}, Merck) and spots located with UV light or iodine vapors. Melting points were taken on a melting point apparatus according to Dr. Linström and are uncorrected. Optical rotations were measured on a Perkin–Elmer automatic polarimeter. IR spectra were recorded on a Philips PU 9706 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were registered on a Bruker AM 300 spectrometer using TMS as the internal standard. Mass spectra were recorded on a Finnigan-MAT 212 (data system 300; CI, isobutane). Elemental analyses (C, H, N, S) were performed on a Carlo Erba Stumentalione (MOD 1104) analyzer. Gas chromatography (GC) was performed using a Shimadzu (GC-15A) instrument, 25 m column: SGE Cydex-B (chiral), ω_i=0.25 mm, film thickness 0.25 μm, 1 μl product in *n*-hexane, detection: FID, carrier gas: nitrogen. The starting material (*R*)-cysteine (chemical and enantiomeric purity >99%) was obtained from Degussa AG. Borane/THF complex was supplied from Aldrich and diethylzinc from Witco GmbH. Commercially available chemicals were used.

*3.1. (2*R,9R*)-2,9-Diamino-4,7-dithia-decandiacid-methylester dihydrochloride* **2**

To a suspension of 60.5 g (0.5 mol) (*R*)-cysteine in 400 mL of 2 N NaOH and 300 mL of ethanol, 46.95 g (0.25 mol) of 1,2-dibromoethane was added slowly at r.t. After stirring for 24 h at ambient temperature

the suspension was basified cautiously (pH 10) with conc. HCl. The precipitate was filtered off, washed with cold water and ether and dried in vacuo. Without further purification and characterization, 111.4 g (0.33 mol) of the resulting bridged bis-amino acid hydrochloride was suspended in 800 mL methanol and cooled to 0°C. Under vigorous stirring, 119.1 g (1 mol) $SOCl_2$ was added over 3 h. After the reaction mixture had been allowed to warm to r.t., it was stirred for another 12 h. The solvent was evaporated in vacuo and the crude product was purified by recrystallization from methanol/methyl-*tert*-butylether. The C_2-symmetrical bis-amino acid methylester hydrochloride **2** was obtained as a yellow solid. Yield: 109.7 g (59%); m.p. 165°C; $[\alpha]_D^{20}$=+1.6 (*c*=2.18, CH_3OH); IR (KBr): ν=3300–3600 cm^{-1} (NH); 1740 (CO); ^{1}H-NMR (D_2O, 300 MHz): δ=2.87 (m, 4H, 2×CH_2S); 3.16 (dd, *J*=4.4 Hz, *J*=14.85 Hz, 2H, 2×C*H*$_2$CHN); 3.28 (dd, *J*=7.15 Hz, *J*=14.85 Hz, 2H, 2×C*H*$_2$CHN); 4.43 (dd, *J*=4.4 Hz, *J*=7.15 Hz, 2H, 2×CHN); 4.64 (s, 6H, 2×OCH_3); ^{13}C-NMR (D_2O, 75.47 MHz): δ=31.49, 31.84 (2×CH_2SCH_2); 52.82, 54.40 (2×OCH_3, 2×CHN); 169.44 (CO); MS (CI, *i*-butane): m/z (%)=297 (100) [MH^+]; anal. calc. for $C_{10}H_{20}N_2O_4S_2$ (296.4): C, 40.52; H, 6.80; N, 9.45; S, 21.64. Found: C, 40.10; H, 6.91; N, 9.42; S, 21.52.

*3.2. (2*R,*9*R*)-2,9-Di-(*tert*-butoxycarbonyl)-amino-4,7-dithia-decandiacid-methylester **3***

Under an argon atmosphere, 15.0 g (40.6 mmol) of the bis-amino acid methylester hydrochloride **2** was suspended in 400 mL anhydrous THF. Et_3N (18.04 g, 178.6 mmol) was added dropwise to the stirred reaction mixture. The resulting white suspension was cooled to 0°C and a solution of $(Boc)_2O$ (17.27 g, 79.17 mmol) in 120 mL anhydrous THF was added over 60 min. The mixture was allowed to warm to r.t. and stirred for 14 h. The solvent was removed in vacuo, and the residue portioned between Et_2O (200 mL) and water (100 mL). The aqueous phase was extracted with Et_2O (2×100 mL) and the combined organic layers were washed with 2 N HCl (2×60 mL), saturated $NaHCO_3$ (2×80 mL) and brine (60 mL). Drying ($MgSO_4$) and evaporation of the solvent under reduced pressure afforded the *N*-Boc protected bis-amino acid methylester **3** as a yellow oil which slowly crystallized at r.t. Yield: 18.70 g (93%); m.p. 58°C; $[\alpha]_D^{20}$=+17.6 (*c*=1.03, CH_2Cl_2); IR (NaCl): ν=3380 cm^{-1} (NH); 1670–1800 (CO); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=1.42 (s, 18H, 2×C(CH_3)$_3$); 2.68 (s, 4H, 2×CH_2S); 2.94 (m, 4H, 2×C*H*$_2$CHN); 3.73 (s, 6H, 2×CH_3); 4.48 (m, 2H, 2×CHN); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=28.25 (2×C(*C*H_3)$_3$); 32.45, 34.48 (2×CH_2SCH_2); 52.53, 53.41 (2×OCH_3, 2×CHN); 80.16 (2×*C*(CH_3)$_3$); 155.05 (2×CO); 171.30 (2×CO); MS (CI, *i*-butane): m/z (%)=497 (100) [MH^+]; anal. calc. for $C_{20}H_{36}N_2O_8S_2$ (496.6): C, 48.37; H, 7.31; N, 5.64; S, 12.91. Found. C, 48.29; H, 7.36; N, 5.50; S, 12.64.

*3.3. Products **4**–**6**; general procedure*

A Grignard reagent was prepared under an argon atmosphere from magnesium (200 mmol) and ethyl or phenyl bromide (200 mmol) or 1,4-dibromobutane (100 mmol) in dry THF (400 mL). The *N*-Boc-bis-amino acid methylester **3** (20 mmol in 100 mL dry THF) was added to this solution over 90 min at r.t. After complete addition the resulting solution was refluxed for 12 h, cooled and stirred for another 3 h at ambient temperature. The reaction mixture was cooled to 0°C and hydrolyzed with saturated NH_4Cl solution (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2×100 mL). The combined organic extracts were finally washed with brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude products were purified by recrystallization from dichloromethane/*n*-hexane or by column chromatography. The individual work-up is described below.

*3.3.1. (4*R,*11*R*)-4,11-Di-(*tert-*butoxycarbonyl)-amino-3,12-diethyl-6,9-dithia-tetradecan-3,12-diol* ***4***

Work-up: purification by column chromatography (silica gel 60, eluent: *n*-hexane:EtOAc=3:2, R_f-value: 0.41); yield: 7.29 g (66%); m.p. 93°C; $[\alpha]_D^{20}=-53.6$ (*c*=1.04, CH_2Cl_2); IR (KBr): ν=3500–3300 cm^{-1} (OH, NH); 1670 (CO); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=0.78–0.91 (m, 12H, 4×CH_2CH_3); 1.33–1.64 (m, 8H, 4×CH_2CH_3); 1.43 (s, 18H, 2×$C(CH_3)_3$); 2.44 (s, 2×OH); 2.53–2.97 (m, 8H, 2×CH_2SCH_2); 3.73 (m, 2H, 2×CHN); 5.03 (s, 2H, 2×NH); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=7.58, 7.79 (4×CH_2CH_3); 27.55, 27.83 (4×CH_2CH_3); 28.36 (2×$C(CH_3)_3$); 32.55, 33.04 (2×CH_2SCH_2); 76.99 (2×COH); 79.37 (2×$C(CH_3)_3$); 156.28 (2×CO); MS (CI, *i*-butane): m/z (%)=553 (96) [MH^+], 453 (100) [$MH^+-C(O)O^tBu$]; anal. calc. for $C_{26}H_{52}N_2O_6S_2$ (552.8): C, 56.48; H, 9.48; N, 5.07; S, 11.60. Found: C, 56.69; H, 9.62; N, 5.05; S, 11.32.

*3.3.2. (1*R,*8*R*)-1,8-Di-(*tert-*butoxycarbonyl)-amino-1,8-di-(1′-hydroxycyclopentyl)-3,6-dithia-octan* ***5***

Work-up: purification by column chromatography (silica gel 60, eluent: *n*-hexane:EtOAc:$CHCl_3$= 35:50:15, R_f-value: 0.68); yield: 8.24 g (60%); m.p. 150°C; $[\alpha]_D^{20}=-75.1$ (*c*=1.03, CH_2Cl_2); IR (KBr): ν=3600–3200 cm^{-1} (OH, NH); 1650 (CO); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=1.19–1.88 (m, 16H, 2×*c*-pentyl-CH_2); 1.44 (s, 18H, 2×$C(CH_3)_3$); 2.41–3.23 (m, 4H, 2×CH_2SCH_2); 3.86 (m, 2H, 2×CHN); 4.95 (m, 2H, 2×NH); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=28.38 (2×$C(CH_3)_3$); 23.53, 23.99, 30.99, 32.87, 36.14, 38.08 (8×*c*-pentyl-CH_2, 2×CH_2SCH_2); 56.15 (2×CHN); 79.63 (2×$C(CH_3)_3$); 84.41 (2×COH); 156.39 (2×CO); MS (CI, *i*-butane): m/z (%)=549 (100) [MH^+]; anal. calc. for $C_{26}H_{48}N_2O_6S_2$ (548.8): C, 56.90; H, 8.82; N, 5.10; S, 11.68. Found: C 57.03; H, 8.81; N, 5.14; S, 11.61.

*3.3.3. (2*R,*9*R*)-2,9-Di-(*tert-*butoxycarbonyl)-amino-1,1,10,10-tetraphenyl-4,7-dithia-decan-1,10-diol* ***6***

Work-up: purification by recrystallization from dichloromethane:*n*-hexane; yield: 12.98 g (87%); m.p. 193°C; $[\alpha]^{20}_D=-61.2$ (*c*=0.97, CH_2Cl_2); IR (KBr): ν=3400 cm^{-1} (NH, OH); 1660 (CO); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=1.25 (s, 18H, 2×$C(CH_3)_3$); 2.48–2.57 (m, 3H, 6×CH_2S); 2.75 (dd, *J*=3.01 Hz, *J*=13.99 Hz, 2H, 2×CH_2S); 4.08 (s, breit, 2H, 2×OH); 4.69 (m, 2H, 2×CHN); 7.08–7.47 (m, 20H, aromat.-H); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=28.25 (2×$C(CH_3)_3$); 32.17, 33.16 (2×CH_2SCH_2); 56.14 (2×CHN); 79.79 (2×COH); 81.18 ($C(CH_3)_3$); 125.29, 125.69, 126.91, 127.05, 127.88, 128.15, 128.52 (20×aromat.-C); 144.72, 144.99 (4×q.-aromat.-C); 156.05 (2×CO); MS (CI, *i*-butane): m/z (%)=745 (100) [MH^+]; anal. calc. for $C_{42}H_{52}N_2O_6S_2$ (744.6): C, 67.75; H, 7.04; N, 3.76; S, 8.61. Found: C, 67.51; H, 7.04; N, 3.78; S, 8.58.

3.4. Products ***7***–***9****; general procedure*

A portion of the respective *N*-Boc-protected amino alcohol **4**–**6** (10 mmol) was dissolved in 10 mL CH_2Cl_2, 15 mL CF_3CO_2H was added at 0°C, and the resulting mixture was stirred overnight at r.t. All volatile materials were removed in vacuo, the residue was taken up in 40 mL of 2 N NaOH and after stirring for 15 min the resulting suspension was extracted with CH_2Cl_2 (4×25 mL). The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation in vacuo afforded the crude bis-amino alcohol which was purified by column chromatography or recrystallization (see below for individual work-ups).

*3.4.1. (4*R,*11*R*)-4,11-Diamino-3,12-diethyl-6,9-dithia-tetradecan-3,12-diol* ***7***

Starting material: 1.27 g (2.3 mmol) **4**; work-up: purification by column chromatography (silica gel 60, eluent: methanol:*n*-hexane=13:0.5, R_f-value: 0.46); yield: 0.63 g (78%); $[\alpha]_D^{20}=-115.2$ (*c*=1.08, CH_2Cl_2); IR (NaCl): ν=3600–3000 cm^{-1} (OH, NH); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=0.87 (t, *J*=7.57

Hz, 6(3)H, 2×CH_2CH_3); 0.88 (t, *J*=7.52 Hz, 6(3)H, 2×CH_2CH_3); 1.28–1.62 (m, 8H, 4×CH_2CH_3); 2.34–2.43 (m, 2H, 2×CHN); 2.71–2.92 (m, 8H, 2×CH_2SCH_2); 3.46 (s, 2H, OH); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=7.53, 7.63 (4×CH_2CH_3); 26.41, 27.99 (2×CH_2CH_3); 32.33, 35.40 (2×CH_2SCH_2); 54.51 (2×CHN); 74.68 (2×COH); MS (CI, *i*-butane): m/z (%)=353 (100) [MH^+]; anal. calc. for $C_{16}H_{36}N_2O_2S_2$ (352.6): C, 54.50; H, 10.29; N, 7.94; S, 18.19. Found: C, 54.32; H, 10.18; N, 7.85; S, 18.26.

*3.4.2. (1*R,*8*R*)-1,8-Diamino-1,8-di-(1′-hydroxycyclopentyl)-3,6-dithia-octan* ***8***

Starting material: 4.60 g (8.36 mmol) **5**; work-up: purification by recrystallization from dichloromethane:*n*-hexane; yield: 2.83 g (98%); m.p. 86°C; $[\alpha]_D^{20}=-110.9$ (*c*=1.22, CH_2Cl_2); IR (KBr): ν=3600–3100 cm^{-1} (OH, NH); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=1.2–1.87 (m, 16H, 8×*c*-pentyl-CH_2); 2.22 (s, 4H, 2×NH_2); 2.43 (dd, *J*=10.59 Hz, *J*=12.87 Hz, 2H, 2×CHN); 2.63–2.95 (m, 8H, 2×CH_2SCH_2); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=23.61, 23.92, 31.99, 35.47, 35.84, 38.96 (8×*c*-pentyl-CH_2, 2×CH_2SCH_2); 57.50 (2×CHN); 83.11 (2×COH); MS (CI, *i*-butane): m/z (%)=349 (100) [MH^+]; anal. calc. for $C_{16}H_{32}N_2O_2S_2$ (348.6): C, 55.13; H, 9.25; N, 8.04; S, 18.40. Found: C, 55.08; H, 9.26; N, 7.99; S, 18.39.

*3.4.3. (2*R,*9*R*)-2,9-Diamino-1,1,10,10-tetraphenyl-4,7-dithia-decan-1,10-diol* ***9***

Starting material: 7.45 g (10 mmol) **6**; work-up: purification by recrystallization from dichloromethane:*n*-hexane; yield: 4.05 g (74%); m.p. 128°C; $[\alpha]_D^{20}=-175.5$ (*c*=1.03, CH_2Cl_2); IR (KBr): ν=3100–3600 cm^{-1} (OH, NH); 1590 (C–C aromat.); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=2.40 (dd, *J*=10.74 Hz, *J*=13.51 Hz, 2H, 2×CH_2CHN); 2.57 (m, 6H, 2×CH_2CHN, 4×CH_2S); 4.02 (dd, *J*=2.4 Hz, *J*=10.2 Hz, 2H, 2×CHN); 7.17–7.64 (3m, 20H, aromat.-H); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=31.66, 33.89 (2×CH_2SCH_2); 55.53 (2×CHN); 78.33 (2×COH); 125.12, 125.55, 126.69, 126.91, 128.28, 128.54 (20×aromat.-C); 143.65, 146.40 (4×q.-aromat.-C); MS (CI, *i*-butane): m/z (%)=545 (100) [MH^+]; anal. calc. for $C_{32}H_{36}N_2O_2S_2$ (544.8): C, 70.55; H, 6.66; N, 5.14; S, 11.77. Found: C, 70.48; H, 6.67; N, 5.08; S, 11.91.

3.5. Products ***10***–***12****; general procedure*

To a suspension of 2.28 g (60 mmol) lithium aluminiumhydride in 100 mL THF — stirred for 1 h under reflux then cooled to r.t. — 3.0 mmol of the respective *N-tert*-butoxycarbonyl derivative **4**–**6** (dissolved in 20 mL THF) was added dropwise over 30 min at r.t. under an argon atmosphere. The reaction mixture was heated under reflux for 24 h. The heating bath was removed and aqueous KOH (10%) was added cautiously at r.t. to destroy excess reducing reagent. After an additional 2 h under reflux, the resulting white suspension was filtered, the solids were intensively washed with ethyl acetate and the combined organic layers were concentrated in vacuo to afford colourless or slightly yellow oils as crude products. In all cases further purification was accomplished by column chromatography on silica gel.

*3.5.1. (4*R,*11*R*)-4,11-Di-(monomethyl)-amino-3,12-diethyl-6,9-dithia-tetradecan-3,12-diol* ***10***

Starting material: 1.66 g (3.0 mmol) **4**; eluent: *n*-hexane:triethylamine=6:4, R_f-value: 0.15; yield: 0.84 g (74%); $[\alpha]_D^{20}=-50.1$ (*c*=1.29, CH_2Cl_2); IR (NaCl): ν=3600–3100 cm^{-1} (OH, NH); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=0.86 (t, *J*=7.54 Hz, 6(3)H, 2×CH_2CH_3); 0.88 (t, *J*=7.46 Hz, 6(3)H, 2×CH_2CH_3); 1.23–1.66 (m, 8H, 4×CH_2CH_3); 2.42–2.53 (m, 2H, 2×CHN); 2.55 (s, 6H, 2×NCH_3); 2.76–2.71 (m, 8H, 2×CH_2SCH_2); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=7.68 (4×CH_2CH_3); 27.06, 28.36 (4×CH_2CH_3); 32.95, 34.16 (2×CH_2SCH_2); 37.91 (2×NCH_3); 63.63 (2×CHN); 75.21 (2×COH); MS (CI, *i*-butane):

m/z (%)=381 (100) [MH^+]; anal. calc. for $C_{18}H_{40}N_2O_2S_2$ (380.7): C, 56.80; H, 10.59; N, 7.36; S, 16.85. Found: C, 56.85; H, 10.51; N, 7.36; S, 16.90.

*3.5.2. (1*R,*8*R*)-1,8-Di-(monomethyl)-amino-1,8-di-(1′-hydroxycyclopentyl)-3,6-dithia-octan* ***11***

Starting material: 2.74 g (5.0 mmol) **5**; eluent: MTBE:triethylamine=8:2, R_f-value: 0.17; yield: 1.23 g (65%); $[\alpha]_D^{20}=-109.9$ (*c*=1.13, CH_2Cl_2); IR (NaCl): ν=3600–3000 cm^{-1} (OH, NH); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=1.26–1.89 (m, 16H, 8×*c*-pentyl-CH_2); 2.35–2.52 (m, 8H, 2×CHN, 2×NCH_3); 2.73–2.92 (2m, 8H, 2×CH_2SCH_2); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=23.36, 23.68, 32.28, 34.23, 36.15, 37.05 (8×*c*-pentyl-CH_2, 2×CH_2SCH_2); 40.11 (2×NCH_3); 66.14 (2×CHN); 83.07 (2×COH); MS (CI, *i*-butane): m/z (%)=377 (100) [MH^+]; anal. calc. for $C_{18}H_{36}N_2O_2S_2$ (376.6): C, 57.40; H, 9.63; N, 7.44; S, 17.03. Found: C, 57.23; H, 9.62; N, 7.41; S, 17.10.

*3.5.3. (2*R,*9*R*)-2,9-Di-(monomethyl)-amino-1,1,10,10-tetraphenyl-4,7-dithia-decan-1,10-diol* ***12***

Starting material: 5.0 g (6.7 mmol) **6**; eluent: *n*-hexane:triethylamine=7:3, R_f-value: 0.32; yield: 2.96 g (77%); m.p. 112°C; $[\alpha]_D^{20}=-103.3$ (*c*=1.69, CH_2Cl_2); IR (KBr): ν=3500–3100 cm^{-1} (OH, NH); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ=1.59, 4.74 (2s, 4H, 2×NH, 2×OH); 2.16 (s, 6H, 2×NCH_3); 2.34 (dd, *J*=9.38 Hz, *J*=13.65 Hz, 2H, 2×CHN); 2.53 (s, 4H, 2×C*H*$_2$SCH_2CHN); 2.74 (dd, *J*=2.69 Hz, *J*=13.65 Hz, 2H, 2×SC*H*$_2$CHN); 3.61 (dd, *J*=2.69 Hz, *J*=9.38 Hz, 2H, 2×SC*H*$_2$CHN); 7.16–7.36, 7.53–7.68 (2m, 20H, 4×aromat.-H); ^{13}C-NMR ($CDCl_3$, 75.47 MHz): δ=32.12, 34.20 (2×CH_2SCH_2); 36.82 (2×NCH_3); 65.56 (2×CHN); 78.21 (2×COH); 125.38, 125.75, 126.65, 126.73, 128.21, 128.29 (aromat.-C); 144.65, 146.98 (q.-aromat.-C); MS (CI, *i*-butane): m/z (%)=573 (100) [MH^+]; anal. calc. for $C_{34}H_{40}N_2O_2S_2$ (572.8): C, 71.29; H, 7.04; N, 4.89; S, 11.19. Found: C, 71.47; H, 7.03; N, 4.91; S, 11.29.

3.6. Enantioselective addition of diethylzinc to benzaldehyde (typical procedure)

Under an argon atmosphere, 10 mmol of a 1.1 M solution of diethylzinc in anhydrous toluene (9.1 mL, 10 mmol of a 1.1 M solution) was added to a solution of the respective amount of catalyst (0.1 mmol, 0.5 mmol or 1 mmol; see Table 1) in dry toluene (10 mL) at −15°C. After 30 min with stirring at constant temperature, the clear solution was allowed to warm to r.t. and then 0.53 g (5 mmol) of freshly distilled benzaldehyde, dissolved in 10 mL abs. toluene, was added over a period of 15 min. The mixture was stirred for an additional 24 h and quenched at 0°C with 20 mL of 2 N aqueous HCl. After separation of the layers, the aqueous layer was extracted with diethyl ether (3×20 mL) and the combined organic extracts were subsequently washed with 3.9% $NaHSO_3$ solution (3×20 mL), saturated aqueous $NaHCO_3$ solution and finally with brine. After drying with $MgSO_4$, the solvents were removed under reduced pressure and the residue distilled (Kugelrohr) to afford pure 1-phenyl-1-propanol. The obtained secondary alcohol was analysed by chiral gas chromatography (GC). The absolute configuration of the product was determined *via* chiral GC analysis by comparison with authentic samples. Temperature programme: 100°C, 4°C/min up to 125°C, 10 min isothermal, retention times: (*R*)-1-phenyl-1-propanol: 13.12 min, (*S*)-1-phenyl-1-propanol: 13.46 min.

3.7. Enantioselective reduction of acetophenone (typical procedure)

In a typical procedure, a mixture of 5 mmol of acetophenone in dry THF (10 mL) was slowly added to a solution of the catalyst (0.5 mmol) and borane–THF complex (5.5 mmol, 5.5 mL of a 1.0 M of BH_3 in THF) in dry THF (10 mL) within 30 min at r.t. After stirring for 4 h at 24°C the reaction mixture was hydrolysed at 0°C with 2 N HCl (20 mL) and extracted with diethyl ether (2×20 mL).

The combined organic layers were successively washed with 2 N NaOH (20 mL) and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The obtained crude product was distilled in vacuo (Kugelrohr) to afford the corresponding chiral secondary alcohol which was analysed by chiral gas chromatography (GC). The absolute configuration of the product was determined *via* chiral GC analysis by comparison with authentic samples. Temperature programme: 100°C, 5°C/min up to 140°C, 5 min isothermal, retention times: (*R*)-1-phenyl-1-ethanol: 7.98 min, (*S*)-1-phenyl-1-ethanol: 8.12 min.

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