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Sulfur-containing β-amino alcohols as catalysts in enantioselective synthesis

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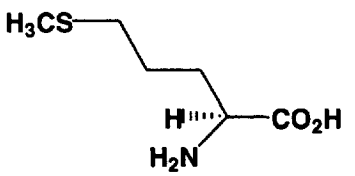
Abstract: Oxazaborolidine catalysts generated *in situ* from cyclic or acyclic sulfur containing (*R*)-cysteine, (*S*)-penicillamine and (*S*)-methionine derivates and BH_3 have been applied successfully to the enantiocontrolled, catalytic reduction of aromatic ketones. The corresponding *sec* alcohols could be obtained in excellent enantiomeric excess, up to 100% *ee*. Using these chiral auxiliaries in the enantioselective addition of diethylzinc to aldehydes afforded optically active *sec* alcohols in enantiomeric excess up to 93% *ee*.

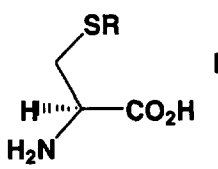
Introduction

The design of asymmetric transformation reactions is a great challenge in organic chemistry. Especially the development of enantioselective homogeneous catalysis in which a small amount of an optically active ligand can induce asymmetry for a given reaction has achieved great interest during the last years.

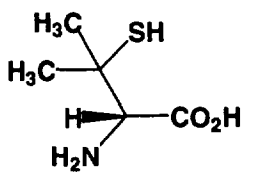
Besides the application of microbial processes[1] or heterogeneous metal catalysts[2] the enantiocontrolled hydride catalytic reduction of prochiral ketones using chirally modified borane reagents[3] and the enantioselective addition of dialkylzincs to aldehydes[4] to produce non-racemic alcohols has been intensively investigated over the last decade. Starting from (*S*)-methionine **1a**, (*R*)-cysteine **1b** or (*S*)-penicillamine **1e** new chiral ligands have been prepared. This paper reports also a detailed study of the application of the sulfur-containing β-amino alcohols **2a–e**, **3a–e**, **4a–d**, and **5** as catalysts in enantioselective catalysis. First results showed that these auxiliaries have a high ability to induce chirality in stereoselective synthesis.[5]



1a



1b (R = H)
1c (R = C_2H_5)
1d (R = *i*-C_3H_7)



1e

Results and discussion

The thioether derivatives **2a–e** and **3a–e** were synthesized according to Scheme 1: the α-amino acids **1a**, **1c** and **1d** were first converted into their ethyl carboxylates ($SOCl_2$/EtOH), which were added to the respective Grignard reagent prepared from aryl bromide (6 equiv. in dry ether, reflux). Treatment with ice cold 2 N HCl leads to the crystalline hydrochlorides of the β-amino *t*-alcohols. The free bases **2a–e** were obtained by treatment with triethylamine/aq. NaOH in dichloromethane.

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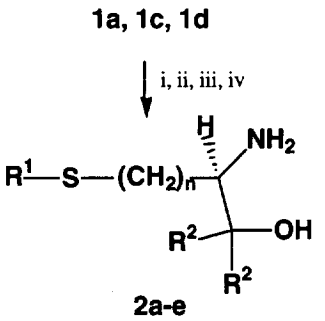
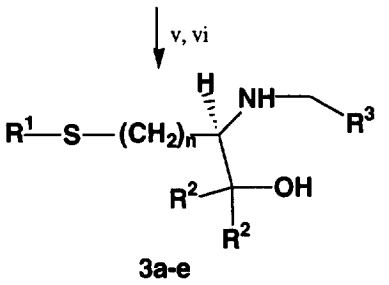


2	n	R^1	R^2
a	2	CH_3	C_6H_5
b	2	CH_3	*p*-CH_3-C_6H_4
c	2	CH_3	*p*-CH_3O-C_6H_4
d	1	C_2H_5	C_6H_5
e	1	*i*-C_3H_7	C_6H_5



3	n	R^1	R^2	R^3
a	2	CH_3	C_6H_5	CH_3
b	2	CH_3	C_6H_5	C_2H_5
c	2	CH_3	C_6H_5	*n*-C_3H_7
d	1	*i*-C_3H_7	C_6H_5	CH_3
e	1	*i*-C_3H_7	C_6H_5	C_2H_5

Reagents: i: $SOCl_2$, EtOH, reflux; ii: ArMgBr, diethyl ether, reflux; iii: aq. HCl; iv: 2N NaOH, Et_3N, CH_2Cl_2; v: acyl chloride, aq. Na_2CO_3, CH_2Cl_2, vi: $LiAlH_4$,THF, reflux.

Scheme 1.

The primary β-amino alcohols **2a** and **2e** were then acylated with the corresponding acyl chlorides in dichloromethane in the presence of aqueous sodium bicarbonate to the amides. Reduction with an excess of lithium aluminium hydride in refluxing THF afforded the *N*-alkylated ligands **3a–e**.

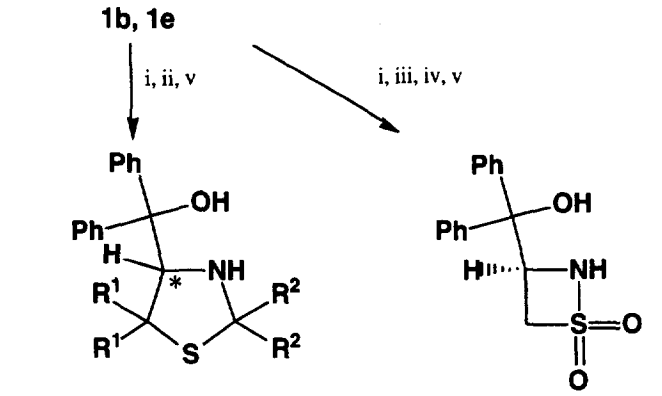
The cyclic ligand **4a–d** with a thiazolidine ring was prepared according to Scheme 2 from **1b**,**1e** in three steps. First the α amino acid was converted into its ethyl ester hydrochloride with dry HCl gas in ethanol. The condensation of the ethyl carboxylate with formaldehyde, cyclopentanone or cyclohexanone afforded (*R*)-4-thiazolidine ethyl ester hydrochloride derivates. The sulfur-containing β-amino alcolhols **4a–d**, **5** were obtained after reaction of (*R*)-4-thiazolidine ethyl carboxylates or (*R*)-β-sultame ethyl carboxylate[6] with an excess of Grignard reagent prepared from phenylbromide in diethyl ether.

An alternative synthesis is the simultaneous condensation of (*R*)-cysteine or (*S*)-penicillamine with paraformaldehyde to bicyclic thiazolidine derivates. The following treatment with phenyllithium afforded the desired compounds **4a**,**4d**. The advantages to choose this alternative route are obvious. The bicyclic thiazolidines **6a**,**b** have been prepared in a one pot reaction. The carboxyl group of the parent α-amino acid is activated in **6a**,**b** and the amino group is protected at the same time. The alternative practical two-step synthesis of **4a**,**4d** from (*R*)-cysteine **1b** and (*S*)-pencillamine **1e** respectively, is based on the addition of phenyllithium to the bicyclic lactones **6a**,**b** and is outlined in Scheme 3.

Enantioselective catalysis

Enantioselective reductions were examined with aromatic ketones. The reductions were carried out using oxazaborolidine-borane reagents[7] generated *in situ* from amino alcohols **2a–e**, **4a–d**, **5** with borane, for examples see Scheme 4. Results of the enantioselective reductions under optimized conditions are given in Tables 1 and 2.

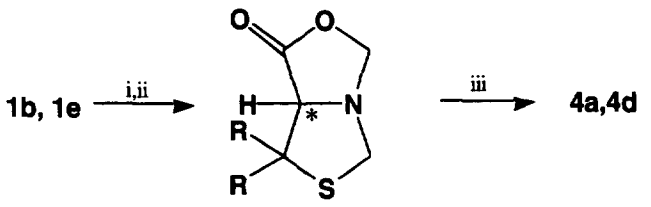
The increasing selectivity at exceptionally high temperature b.p. THF (66°C) with the cyclic derivates **4a–d**, **5** is a significant result. It seemed to be possible to raise these results with other solvents or



4	R^1	R^2	configuration
a	H	H	*R*
b	H	$(-CH_2-)_4$	*R*
c	H	$(-CH_2-)_5$	*R*
d	CH_3	H	*S*

Reagents: i: EtOH/HCl(g), r.t.; ii: HCHO or cycloalkanone; iii: Cl_2CHCl_3, 0°C; iv: NH_3, $CHCl_3$, 0°C; v: PhMgBr, diethylether, reflux.

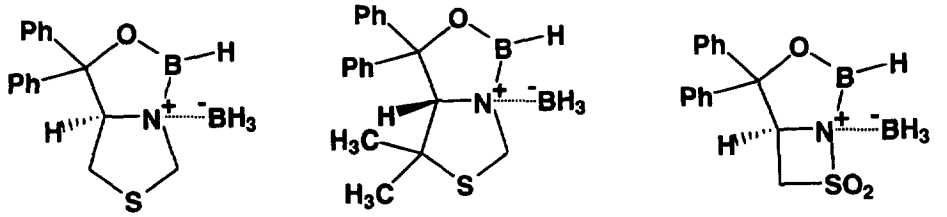
Scheme 2.



6a [R = H, (*R*)-configuration]
6b [R = CH_3, (*S*)-configuration]

Reagents: i: EtOH/HCl(g), reflux; ii: Paraformaldehyde 7 d; iii: PhLi, THF, -30°C.

Scheme 3.



Oxazaborolidines prepared from BH_3 and the ligands **4a**, **4d** or **5**

Scheme 4.

mixtures of solvents with higher boiling points. So it is possible to reduce less reactive prochiral ketones or analogues with high selectivity.

The resulting configuration of the *sec* alcohols are dependent on the stereochemistry of the ligand and on the modifications of its corresponding amino alcohols. We obtained the opposite configuration of

Table 1. Enantioselective reduction of acetophenone with **2a–e**, **4a–d** and **5** respectively and excess borane in THF

entry	catalyst [mol %]	temperature [°C]	chiral 1-phenylethanol[a]	
			ee[b] [%]	configuration
1	**2a** [5]	30	79	*R*
2	**2a** [10]	30	71	*R*
3	**2b** [5]	30	79	*R*
4	**2c** [5]	30	68	*R*
5	**2d** [5]	30	83	*R*
6	**2e** [5]	30	70	*R*
7	**4a** [10]	66	84	*S*
8	**4b** [10]	66	81	*S*
9	**4c** [10]	66	66	*S*
10	**4d** [10]	66	87	*R*
11	**5** [10]	66	81	*R*

[a] The isolated yields of the chiral alcohols were 80–95%.– [b] The *ee*-values of chiral secondary alcohols obtained were calculated from specific rotations based on the following maximum rotations of each alcohol: $[\alpha]_D^{20} = +43.1$ ($c = 7.19$, cyclopentane) for (*R*)-1-phenylethanol[4]

Table 2. Enantioselective reduction of aromatic ketones with **2a–e** (5 mol%, 30°C) and **4a** (10 mol%, 66°C) and excess borane in THF

entry	ketone	catalyst	chiral secondary alcohol[a]	
			ee[b] [%]	configuration
1	ω-chloroacetophenone	**2a**	95	*S*
2	methyl-2-naphthylketone	**2a**	77	*R*
3	ω-chloroacetophenone	**2b**	100	*S*
4	methyl-2-naphthylketone	**2b**	84	*R*
5	ω-chloroacetophenone	**2c**	98	*S*
6	methyl-2-naphthylketone	**2c**	85	*R*
7	ω-chloroacetophenone	**2d**	97	*S*
8	methyl-2-naphthylketone	**2d**	88	*R*
9	ω-chloroacetophenone	**2e**	100	*S*
10	methyl-2-naphthylketone	**2e**	83	*R*
11	ω-chloroacetophenone	**4a**	82	*R*
12	methyl-2-naphthylketone	**4a**	79	*S*

[a] The isolated yields of the chiral alcohols were 80–95%.– [b] The *ee*-values of chiral secondary alcohols obtained were calculated from optical rotations based on the following maximum rotations of each alcohol: $[\alpha]_D^{20} = -48.1$ ($c = 1.73$, cyclohexane) for (*R*)-2-chloro-1-phenylethanol[9], $[\alpha]_D^{20} = +55.8$ ($c = 4.8$, $CHCl_3$) for (*R*)-1-(naphth-2-yl)ethanol[10].

the *sec* alcohols by changing the catalysts from cyclic to acyclic, although the identical stereochemistry of the same precursor is used for preparation.

One reason for this result could be the fixed conformation of the cyclic compounds, which caused a rigid transition state situation in comparison to the acyclic compounds. The exception is the sulfonamide **5** with free electron pairs at the sulfone group which could gave a different complexation.

The enantioselective alkylation of prochiral carbonyl compounds such as aldehydes using e.g. optically active β-amino alcohols,[11] piperazines,[12] pyridine-based ligands[13] or ferrocenyl amino alcohols[14] as chiral catalysts received great interest during the last decade. Only a few papers report the

Table 3. Enantioselective addition of diethylzinc to benzaldehyde in the presence of 10 mol% of **2a–3e** at room temperature and **4a–d** at 0°C

		1-phenyl-1-propanol[a]	
entry	catalyst	optical yield[b] [%]	configuration
1	**2a**	5	*R*
2	**2e**	45	*R*
3	**3a**	76	*S*
4	**3b**	91	*S*
5	**3c**	63	*S*
6	**3d**	74	*R*
7	**3e**	79	*S*
8	**4a**	93	*S*
9	**4b**	84	*S*
10	**4c**	80	*S*
11	**4d**	86	*R*

[a] Chemical yield 70-90%. [b] The optical yield was calculated from the maximum rotation $[\alpha]_D^{20} = -45.45$ ($c = 5.15$, chloroform) for (*S*)-1-phenyl-1-propanol[18].

Table 4. Enantioselective addition of diethylzinc to benzaldehyde in the presence of 10 mol% of the catalysts Li-**2a–4a** at room temperature

		1-phenyl-1-propanol[a]	
entry	catalyst	optical yield[b] [%]	configuration
12	Li-**2a**	48	*S*
13	Li-**2e**	62	*R*
14	Li-**3a**	79	*S*
15	Li-**3b**	89	*S*
16	Li-**3c**	78	*S*
17	Li-**3d**	82	*S*
18	Li-**3e**	68	*S*
19	Li-**4a**	6	*S*

[a] Chemical yield 70-90%. [b] The enantiomeric excess was calculated from the maximum rotation $[\alpha]_D^{20} = -45.45$ ($c = 5.15$, chloroform) for (*S*)-1-phenyl-1-propanol[14].

application of sulfur-containing compounds as chiral precursor, namely β-hydroxysulfoxides,[15] dialkyl thiophosphoramidates[16] and sulfonamide–titanate complexes[17] in this fundamental carbon–carbon bond-forming reaction. Our results in the enantioselective alkylation of benzaldehyde using catalytic amounts of chiral thioethers are presented in Tables 3 and 4.

The low stability of cyclic N/S acetals against *n*-butyllithium could be a reason for the low selectivity observed with Li-**4a**. The decomposition products may form reactive intermediates with $ZnEt_2$ which do not react in an enantioselective manner with benzaldehyde.

Experimental section

Boiling points were uncorrected. Kugelrohr distillations were carried out with a Büchi GRK-51 apparatus. Mps were taken on a melting point apparatus according to Dr Linström and are uncorrected. Optical rotations were measured with a Perkin–Elmer automatic polarimeter in a 1 dm tube. The ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) Fourier transform spectra were registered on a Bruker AM

300 spectrometer using TMS as internal standard. Mass spectra were recorded on a Finnigan-MAT 212 (data system 300; CI, *i*-butane).

All reactions were carried out in oven dried glassware, under argon atmosphere, and using anhydrous solvents. The chiral starting material (*S*)-methionine (*S*)-penicillamine and (*R*)-cysteine (chemical and enantiomeric purity >99%) were obtained from Degussa AG. Borane–THF complex were supplied from Aldrich and diethylzinc from Witco GmbH. *S*-Ethyl-L-cysteine and *S*-isopropyl-L-cysteine were prepared according to procedures described in the literature.[19]

*Products **2a–e**; general procedure*

To stirred a solution of the α-amino acid (50 mmol) in ethanol (99%, 400 ml) at −10°C was added thionyl chloride (75 mmol). The resulting clear solution was gradually warmed to room temperature (r.t.) and refluxed for 6 h. The ethanol was evaporated under reduced pressure and the crude ethyl ester hydrochloride was recrystallized from methanol/diethyl ether. The α-amino acid ethyl ester hydrochloride (30 mmol) was added portionwise at r.t. to the Grignard reagent (180 mmol) prepared from aryl bromide in anhydrous diethyl ether (500 ml). After complete addition the resulting suspension was refluxed for 10–12 h. The reaction mixture was cooled to 0°C and hydrolyzed with cold 2 N HCl (300 ml), whereas the hydrochloride of the resulting β-amino alcohol separated as off-white solid. The crude product was isolated by suction. Separation of the organic layer and evaporation to dryness yielded an additional fraction of the desired product. The combined fractions were suspendend in dichloromethane (300 ml), triethylamine (20 ml) and 2 N NaOH (50 ml) were added and the resulting mixture was stirred for 12 h at r.t. The organic layer was separated, washed with water and brine and dried over magnesium sulfate. After removal of the solvent the free base **2a–e** was recrystallized from dichloromethane/light petroleum.

*(S)-2-Amino-1,1-diphenyl-4-(methylthio)-1-butanol **2a***

Yield: 75%; mp: 95–96°C; $[\alpha]_D^{20}=-123.0°$ (c=0.90, $CHCl_3$) [Ref.[7f]: mp: 96–98°C; $[\alpha]_D^{20}=-108.57$ (c=0.986, $CHCl_3$)].

*(S)-2-Amino-1,1-di(4-methylphenyl)-4-(methylthio)-1-butanol **2b***

Yield: 65%; mp: 69–71°C; $[\alpha]_D^{20}=-83.5$ (c=0.65, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=1.41–1.53 (m, 1H, H4), 1.63–1.74 (m, 1H, H4), 1.95 (s, 3H, SCH_3), 2.25, 2.26 (2s, 6H, 2×PhCH_3), 2.39–2.59 (m, 2H, 2×H3), 3.98–4.02 (m, 1H, H2), 7.04–7.46 (m, 8H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=15.15 (C3), 20.82 (2×PhCH_3), 29.49 (C4), 31.92 (CH_3S), 55.58 (C2), 79.12 (C1), 125.31–143.71 (Ar-C); MS (CI, *i*-butane): 316 (MH^+, 100%), 298 (MH^+-H_2O, 34%).

*(S)-2-Amino-1,1-di(4-methoxyphenyl)-4-(methylthio)-1-butanol **2c***

Yield: 69%; mp: 82–85°C; $[\alpha]_D^{20}=-95.5$ (c=0.48, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=1.40–1.52 (m, 2H, O*H*, H4), 1.64–1.75 (m, 1H, H4), 1.96 (s, 3H, SCH_3), 2.41–2.60 (m, 2H, 2×H3), 3.73, 3.74 (2s, 6H, 2×PhOCH_3), 3.93–3.97 (m, 1H, H2), 6.78–6.86 (m, 4H, Ar-H), 7.35–7.49 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=15.02 (C3), 29.46 (C4), 31.77 (CH_3S), 54.94 (2xPhOCH_3), 55.55 (C2), 78.61 (C1), 113.19–138.68 (Ar-C); MS (CI, *i*-butane): 348 (MH^+, 100%), 330 (MH^+-H_2O, 88%).

*(R)-2-Amino-1,1-diphenyl-3-(ethylthio)-1-propanol **2d***

Yield: 60%; mp: 58–59°C; $[\alpha]_D^{20}=-166.3$ (c=0.44, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=1.18 (t, 3H, CH_3CH$_2$S), 1.69 (s, 2H, NH_2), 2.45–2.59 (m, 4H, 2×H3, CH$_3$CH_2), 4.04 (dd, J=2.4 and 10.8, 1H, H2), 4.53 (s, 1H, O*H*), 7.15–7.64 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=14.66 (CH_3CH$_2$S), 25.81 (CH$_3$CH_2S), 33.41 (C3), 55.36 (C2), 78.32 (C1), 125.23–146.73 (Ar-C); MS (CI, *i*-butane): 288 (MH^+, 100%), 270 (MH^+-H_2O, 45%).

(R)-2-Amino-1,1-diphenyl-3-(isopropylthio)-1-propanol 2e

Yield: 80%; mp.: 112–114°C; $[\alpha]_D^{20}=-160.3$ (c=0.40, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=1.14, 1.20 [2d, J=_ Hz, 6H, $(CH_3)_2CH$], 1.63 (s, 2H, NH_2), 2.36 and 2.55 (2dd, J=2.3, 10.8 and 13.5 Hz, 2H, 2×H3), 2.82–2.91 [m, 1H, $(CH_3)_2CH$], 4.00 (m, 1H, H2), 4.48 (s, 1H, OH), 7.13–7.62 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=23.2, 23.17 [$(CH_3)_2CH$], 29.31 [$(CH_3)_2CH$], 33.19 (C3), 56.92 (C2), 78.43 (C1), 125.25–144.15 (Ar-C); MS (CI, *i*-butane): 302 (MH^+, 100%), 284 (MH^+-H_2O, 10%).

Products 3a–e; general procedure

To a solution of β-amino alcohol (10 mmol) in dichloromethane (100 ml) was added sodium bicarbonate (26 mmol) dissolved in water (50 ml) and the two phase system was cooled to 0–5°C. Under vigorous stirring the acyl chloride (13 mmol) in dichloromethane (10 ml) was dropwise added, the resulting mixture was stirred further 2 h at 0–5°C and 10 h at r.t. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were successively washed with 1 N HCl, brine, saturated $NaHCO_3$-solution and brine and dried ($MgSO_4$). The clear light yellow solution was evaporated to dryness. A mixture of the obtained crude amide (5 mmol) and $LiAlH_4$ (40 mmol) in dry THF (200 ml) was refluxed under Ar for 16 h. The reaction mixture was cooled to r.t., quenched with a 10% aq. solution of potassium hydroxide and heated an additional hour to reflux. The solid was filtered off and the solvent was eliminated under vacuum. The residue was then distilled (Kugelrohr) to afford the pure *N*-alkylated products **3a–e**.

(S)-1,1-Diphenyl-2-ethylamino-4-(methylthio)-1-butanol 3a

Yield: 86%; bp: 200°C/5·10^{-3} mbar (bath temperature); $[\alpha]_D^{20}=-15.4$ (c=0.43, MeOH); ^{1}H-NMR ($CDCl_3$): δ in ppm=0.96 (t, J=7.1 Hz, 3H, 3×H2′), 1.46–1.56 (m, 1H, H4), 1.87–1.98 (m, 4H, H4, CH_3S), 2.27–2.61 (m, 4H, 2×H3, 2×H1′), 3.75–3.78 (m, 1H, H2), 7.17–7.66 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=15.21 (C3), 15.60 (C2′), 30.16 (C4), 31.80 (CH_3S), 43.25 (C1′), 63.13 (C2), 78.76 (C1), 125.45–146.95 (Ar-C); MS (CI, *i*-butane): 316 (MH^+, 100%).

(S)-1,1-Diphenyl-4-(methylthio)-2-propylamino-1-butanol 3b

Yield: 73%; bp: 190–200°C/5·10^{-3} mbar (bath temperature); $[\alpha]_D^{20}=-15.7$ (c=0.66, MeOH); ^{1}H-NMR ($CDCl_3$): δ in ppm=0.76 (t, J=5.5 Hz, 3H, 3×H3′), 1.28–1.53 (m, 4H, 2×H4, 2×H2′), 1.87–1.96 (m, 4H, H3, CH_3S), 2.17–2.23 (m, 1H, H3), 2.39–2.55 (m, 3H, 2×H1′, NH), 3.72–3.76 (m, 1H, H2), 7.17–7.64 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=11.54 (C3′), 15.30 (C3), 23.53 (C2′), 30.25 (C4), 31.80 (CH_3S), 50.85 (C1′), 63.31 (C2), 78.90 (C1), 125.82–146.94 (Ar-C); MS (CI, *i*-butane): 330 (MH^+, 100%).

(S)-2-Butylamino-1,1-diphenyl-4-(methylthio)-1-butanol 3c

Yield: 65%; bp: 190–200°C/5·10^{-3}; $[\alpha]_D^{20}=-16.9$ (c=1.28, MeOH); ^{1}H-NMR ($CDCl_3$): δ in ppm=0.82 (t, J=7.1 Hz, 3H, 3×H4′), 1.17–1.34 (m, 5H, 2×H2′, 2×H3′, NH), 1.47–1.52 (m, 1H, H4), 1.88–1.95 (m, 4H, H4, CH_3S), 2.22–2.26 (m, 1H, H3), 2.39–2.56 (m, 3H, H3, 2×H2′), 3.74 (dd, J=3.1 und 7.5 Hz, 1H, H2), 4.60 (s, 1H, OH), 7.18–7.65 (m, 10H, aromat.-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=13.82 (C4′), 15.32 (CH_3S), 20.15 (C3′), 30.34 (C2′), 31.90 (C4), 32.63 (C3), 48.70 (C1′), 63.39 (C2), 78.87 (C1), 125.83–128.73 (aromat.-C), 144.90, 147.00 (q. aromat.-C); MS (CI, *i*-butane): 344 (MH^+, 100%).

(R)-1,1-Diphenyl-2-ethylamino-3-(isopropylthio)-1-propanol 3d

Yield: 76%; mp: 170–175°C/5·10^{-3} mbar (bath temperature); $[\alpha]_D^{20}=-54.7$ (c=1.01, MeOH); ^{1}H-NMR ($CDCl_3$): δ in ppm=0.93 (t, J=7.1 Hz, 3H, 3×H2′), 1.19 [d, J=4.0 Hz, 3H, 1×$(CH_3)_2CH$], 1.21 [d, J=4.0 Hz, 3H, 1×$(CH_3)_2CH$], 2.03–2.12 [m, 1H, $(CH_3)_2CH$], 2.30 (dd, J=10.1 and 13.5 Hz, 1H, H3), 2.39–2.47 (m, 1H, H1′), 2.75 (dd, J=2.7 and 13.6 Hz, 1H, H3), 2.80–2.89 (m, 1H, H1′),

3.73 (dd, *J*=2.7 and 10.1 Hz, 1H, H2), 5.04 (s, 1H, OH), 7.16–7.33 (m, 6H, aromat.-H), 7.55–7.69 (m, 4H, aromat.-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=15.47 (C2′), 23.37 [2×(CH_3)$_2$CH], 32.95 (C3), 35.14 [(CH_3)$_2$*C*H], 44.19 (C1′), 63.73 (C2), 77.95 (C1), 125-49-128.15 (aromat.-C), 144.86, 147.41 (q. aromat.-C); MS (CI, *i*-butane): 330 (MH^+, 100%).

(R)-1,1-Diphenyl-3-(isopropylthio)-2-propylamino-1-propanol ***3e***

Yield: 83%; bp: 170–175°C/$5 \cdot 10^{-3}$ mbar (bath temperature); $[\alpha]_D^{20}$=−63.0 (*c*=0.58, MeOH); ^{1}H-NMR ($CDCl_3$): δ in ppm=0.76 (t, *J*=7.6 Hz, 3H, 3×H3′), 1.17–1.40 [m, 9H, H3, OH, (CH_3)$_2$*CH*, (*CH*$_3$)$_2$CH], 1.95–2.06 (m, 1H, H3), 2.16 (s, 1H, N*H*), 2.28–2.45 (m, 2H, 2×H2′), 2.73–2.90 (m, 2H, 2×H1′), 3.68–3.74 (m, 1H, H2) (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=11.47 (C3′), 23.21 [(CH_3)$_2$*C*H], 23.34 [(*C*H$_3$)$_2$CH], 32.86 (C3), 35.17 (C2′), 51.56 (C1′), 63.83 (C2), 78.05 (C1), 125.48–147.18 (Ar-C); MS (CI, *i*-butane): 344 (MH^+, 100%).

Products ***4a–d****; general procedure*

To a stirred solution of the α-amino acid (50 mmol) in ethanol (99%, 400 ml) at 0°C was added dry HCl gas. The resulting clear solution was gradually warmed to room temperature (r.t.) and stirred for 8 h. The ethanol was evaporated under reduced pressure and the ethyl ester hydrochloride was recrystallized from methanol/diethyl ether. The (*R*)-4-thiazolidine carboxylic acid ethyl ester hydrochloride and its derivates are obtained by cyclisation with the corresponding aldehydes or ketones. 50 mmol of the respect ester were added in small portions to a solution of Grignard reagent (400 mmol) prepared from phenylbromide in dry diethyl ether (200 ml). The reaction mixture was heated to reflux for 2 h und stirred for further 24 h at ambient temperature. The reaction was quenched with ice cold saturated NH_4Cl-solution, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure left a yellow oil, which solidified upon standing. Recrystallisation from dichloromethane/light petroleum.

(R)-Diphenyl-(thiazolidin-4-yl)-methanol ***4a***

Yield: 64%; mp=90°C; $[\alpha]_D^{20}$=−302.8 (*c*=1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=2.35 (dd, *J*=9.6 and 14.3 Hz, 1H, H5), 2.85 (dd, *J*=2.2 and 14.0 Hz, 1H, H5), 3.15, 3.48 (2d, 2H, H2), 4.01 (dd, *J*=2.2 and 9.6 Hz, 1H, H4), 4.61 (s, 1H, NH), 7.30 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=39.28 (C5), 53.88 (C-OH), 62.51 (C4), 78.17 (C2), 125–128, (Ar-C), 144.14, 146.94 (q.-Ar-C); MS (CI, *i*-butane): 272 (MH^+, 100%).

(R)-Diphenyl-2-(1-thia-4-aza-spiro[4.4]nonan-3-yl)methanol ***4b***

Yield: 42%; mp=95°C; $[\alpha]_D^{20}$=−83.1 (*c*=1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=1.60–2.25 (m, 8H, cyclopentane-CH_2), 2.55 (dd, *J*=5.7 Hz, *J*=10.5 Hz, 1H, H2), 2.90 (m, 1H, H2), 3.26 (s, 1H, NH), 4.34 (dd, *J*=5.7 Hz, *J*=10.1 Hz, 1H, H3), 7.35 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=24.19, 25.20, 33.72, 41.28, 41.43, (cyclohexane-CH_2), 67.77 (C2), 77.01 (C-OH), 77.25 (C3), 78.35 (C5), 125.32, 126.338, 126.74, 127.06, 128.02, 128.23 (Ar-C), 145.06, 146.44 (Ar-C); MS (CI, *i*-butane): 326 (MH^+, 100%).

(R)-Diphenyl-(1-thia-4-aza-spiro[4.5]decan-3-yl)methanol ***4c***

Yield: 53%; mp=110°C; $[\alpha]_D^{20}$=−76.0 (*c*=0.95, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=1.75 (m, 10H, cyclohexane-CH_2), 2.43 (dd, *J*=5.6 Hz, *J*=10.6 Hz, 1H, H2), 2.85 (m, 1H, H2), 4.51 (dd, *J*=5.2 Hz, *J*=9.8 Hz, 1H, H3),7.25 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=24.19, 25.20, 33.72, 41.28, 41.43, (cyclohexane-CH_2), 67.77 (C2), 77.01 (C-OH), 77.25 (C3), 78.35 (C5), 125.32, 126.338, 126.74, 127.06, 128.02, 128.23 (Ar-C), 145.06, 146.44 (Ar-C); MS (CI, *i*-butane): 340 (MH^+, 100%).

(S)-(5,5)-Dimethyl-thiazolidin-4-yl)-diphenyl-methanol ***4d***

Yield: 54%; mp=103°C; $[\alpha]_D^{20}$=+90.7 (*c*=0.91, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=0.72 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.91 (s, 1H, NH), 3.98 (s, 1H, H4), 4.09 (s, 2H, H2), 7.30 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm=27.87 (CH_3), 28.60 (CH_3), 47.60 (C2), 56.45 (C5), 73.64 (C4), 77.69 (C-OH), 125–128, (Ar-C), 143.69, 149.09 (q.Ar-C); MS (CI, *i*-butane): 300 (MH^+, 100%).

(R)-Diphenyl-(1,1-dioxo[1,2]thiazetidin-3-yl)-methanol ***5***

Yield: 55%; mp=173–181°C; $[\alpha]_D^{20}$=−39.3 (*c*=0.72, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=3.72 (s, 1 H, NH), 3.90 (m, 1 H, H4), 4.27 (m, 1H, H4), 4.72 (m, 1 H, H3), 5.61 (s, 1H, OH), 7.35 (Ar); ^{13}C-NMR ($CDCl_3$): δ in ppm=46.84 (C4), 60.56 (C3), 76.57 (C-OH), 125.24–128.90 (Ar-C), 141.51, 143.79 (q. Ar-C); MS (CI, *i*-butane): 272 (MH^+, 100%).

(R)-1-Aza-3-oxa-7-thiabicyclo[3.3.0]-octan-4-one ***6a***

From (*R*)-cysteine; prepared according to the published procedure Ref.[20]

(S)-1-Aza-3-oxa-7-thiabicyclo[3.3.0]-6-dimethyl-octan-4-one ***6b***

To a suspension of (*S*)-penicillamine (1.5 g, 10 mmol), anhydrous magnesium sulphate (1.3 g, 11 mmol) in dry dichloromethane (65 ml) was added paraformaldehyde (0.3g, 11 mmol) at room temperature. After stirring for 4 d another portion paraformaldehyde (0.3 g, 11 mmol) was added and stirring was continued for 3 d. The suspension was filtered off and the removal of the solvent under reduced pressure afforded analytically pure **6b** in quantitative yield, $[\alpha]_D^{20}$=−19.4 (*c*=5.90, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ in ppm=1.59 (s, 6H, 2×CH_3), 3.42 (s, 1H, H5), 4.15 (d, J=11.2 Hz, 1H, H8), 4.43 (d, J=11.2 Hz, 1H, H8), 4.64 (d, J=5.4, 1H, H2), 5.09 (d, J=5.4, 1H, H2); ^{13}C-NMR ($CDCl_3$): δ in ppm=24.92 (CH_3), 31.38 (CH_3), 57.06 (C6), 58.24 (C8), 72.95 (C5), 86.29 (C2), 172.11 (C4); MS (CI, *i*-butane): 162 (MH^+, 100%).

Products ***4a,4d****; general procedure (alternative synthesis)*

To a stirred solution of the lactone **6a,b** in anhydrous THF (60 ml) phenyllithium (28 ml, 1.8 M, 50 mmol) was dropwise added at −30°C. The dark red solution was stirred at −30°C for 1 h and left over night at r.t. Under ice cooling the solution was hydrolyzed by treatment with saturated aqueous ammonium chloride solution. The aqueous layer were extracted with diethyl ether (3×50 ml) and washed with brine. The organic extracts, dried over magnesium sulphate, filtered and evaporated, gave a residue which crystallized from dichloromethane/n-hexane. Yield **4a**: 64%; **4d**: 54%. Spectroscopical data see above.

Enantioselective addition of diethylzinc to benzaldehyde in the presence 10 mol% catalyst

Under argon atmosphere 20 mmol of a 1.1 M solution of diethylzinc in abs. toluene (18.2 ml, 20 mmol of a 1.1 M solution) was added to a solution of the respective amount of catalyst (1 mmol) in dry toluene (15 ml) at −20°C under argon atmosphere. The mixture was allowed to reach room temperature and treated with benzaldehyde (10 mmol) in dry toluene (10 ml), then the resulting yellow mixture was stirred for 16 h at room temperature. The reaction was quenched with 2 N HCl (40 ml), the organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were extracted with sodium hydrogen sulfite solution, sodium hydrogen carbonate solution and water, before drying ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue distilled (Kugelrohr) to afford 1-phenyl-1-propanol. The optical yield was determined by specific rotation analysis.

Enantioselective addition of diethylzinc to benzaldehyde by using 10 mol% Li-salt

n-Butyllithium (2 mmol, 1.3 ml of 1.6 M hexane solution) was added to a solution of the ligand (1 mmol) in dry toluene (15 ml) at −40°C. After 15 min diethylzinc (20 mmol, 18.2 ml of 1.1 M toluene solution) was added over a period of 5 min. The mixture is allowed to reach room temperature and

treated within 10 min with benzaldehyde (10 mmol), then the resulting mixture was stirred for 16 h at room temperature. The above mentioned acidic workup afforded after Kugelrohr distillation the chiral *sec* alcohol.

Enantioselective reduction of aromatic ketones in the presence of 5 or 10 mol% chiral catalyst

In a typical procedure a mixture of the respective ketone in dry THF (10 ml) was slowly added within 45 min to a solution of the catalyst (0.5 or 1 mmol) and borane–THF complex (10 mmol, 10 ml of a 1 M of BH_3 in THF) in dry THF (15 ml) at 30°C. After stirring for 2 hours at 30°C the reaction mixture was hydrolyzed with 2 N HCl (40 ml) and extracted with diethyl ether. The combined organic layers were successively washed with 2 N NaOH and water, dried ($MgSO_4$) and concentrated under reduced pressure. The obtained crude product was distilled under *vacuo* (Kugelrohr) to afford the corresponding chiral secondary alcohol. The enantiomeric excesses were determined by specific rotation analysis.

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