A New Cysteine-Derived Ligand as Catalyst for the Addition of Diethylzinc to Aldehydes: The Importance of a 'Free' Sulfide Site for Enantioselectivity

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Abstract: New chiral sulfides and disulfides were synthesized from readily available and inexpensive cysteine by straightforward methods in order to elucidate the relative importance of the various donor atoms (N, O, S) available in free or alkylated form resulting in covalent or dative bonds to the metal, respectively. Their application in the addition of diethylzinc to aldehydes provides secondary alcohols with up to 99% ee, and *S*-configuration, when catalytic amounts of disulfide ligands with the ability to form an S-Zn bond were used. In contrast to this, benzyl alcohols with the opposite absolute configuration *R* could be achieved, albeit with decreased yield and enantioselectivity, by the use of alkylated sulfide ligands.

Key words: cysteine, disulfide, chiral ligands, dialkylzinc, asymmetric synthesis

The development and functional understanding of chiral ligands for catalytic asymmetric synthesis is of increasing importance in modern synthetic chemistry.[1–4] Chiral β-amino alcohols have been shown to be versatile chiral ligands for a variety of asymmetric reactions, including the enantioselective addition of diorganozinc compounds to aldehydes.[4–38] In the last few years sulfur containing ligands have gained more and more interest as catalysts in these stereoselective reactions.[16–41] They appear especially attractive in combination with soft metal ions or late transition metals, where they are expected to either improve the ligands association to the metal, e.g. for Zn-complexation[42,43] in the presence of titanium,[16] or alter the properties of the metal center altogether through their donor properties.[21,22] Recently, we and others described the (combinatorial) synthesis and use of disulfide catalysts in combination with dialkylzinc.[17,18,22–26,36–38] Some catalysts developed by us[36–41] not only belong to the most easily available ones but also allowed the highly enantioselective addition to usually ill-behaved non-aromatic aldehydes,[15] but with a strong chain-length dependence.[36,37,41] Mechanistically it could be shown by Kellogg and others that the disulfide is reduced by the metal alkyl, and a stable Zn-S bond is formed.[17,18] Anderson synthesized amino thiolates for which a phenyl protection of the free sulfide gave significantly lower yields and no asymmetric induction at all in diethyl zinc additions.[27] Further hints on the significance of the type of Zn-S bond can be deduced from the extensive work of Martens et al.[28–32] with alkylated thiolates compared to free thiolates used e.g. by van Koten[19,20] or us;[36,37] or from Gibsons work, where sterically hindered tertiary thiolates[23] gave considerably worse results than less hindered primary ones.[25]

The significance of a covalent Zn-S bond as well as the importance of sulfur as donor in the most easily accessible cysteine derived ligands with their additional amino and alcohol moiety, however, remained unclear. In this paper we try to elucidate the relative importance of the various donors (N, O, S) available in cysteine-derived ligands in free (donor-H) or alkylated (donor-R) form for the Zn-alkyl addition, exemplified by the reaction of diethylzinc with various aldehydes, predominantly with benzaldehyde as reference compound. Thus the cysteine modifications presented in this paper do not aim at the optimization of enantiomeric excesses but at understanding the electronic effects in form of the individual donor contributions in dative or 'anionic' form.

Recently, we have described the use of highly efficient oxazol(id)ine type disulfide and diselenide catalysts for Zn-, Cu-, and Pd-mediated reactions.[36–41] The oxazol(id)ine thiols and disulfides are readily available from natural (*R*)-cysteine.[36–40,44] In order to gain some understanding of the (electronic) behavior of sulfur based catalysts without being hampered by steric or ring constraints, some simpler, linear, and more stable ligands were prepared from cysteine (see Scheme 1) and tested as catalysts in the diethylzinc addition to aldehydes.

The syntheses of disulfide **3** and sulfides **4** are shown in Scheme 1: (*R*)-cysteine (**1**) was converted into *N*,*N*′-dibenzyl disulfide **2** by treatment with benzaldehyde followed by $NaBH_4/I_2$-reduction and subsequent air oxidation.[36,44] The reaction of disulfide **2** with strong base and four equivalents of methyl iodide yielded the *N*- and *O*-methylated disulfide **3**. The sulfide amino alcohols **4a–d** were obtained in good yields by reaction with $NaBH_4$ and NaOH followed by alkylation. Selective methylation of these compounds gave the partially or fully methylated sulfides **5–7** in moderate yields.

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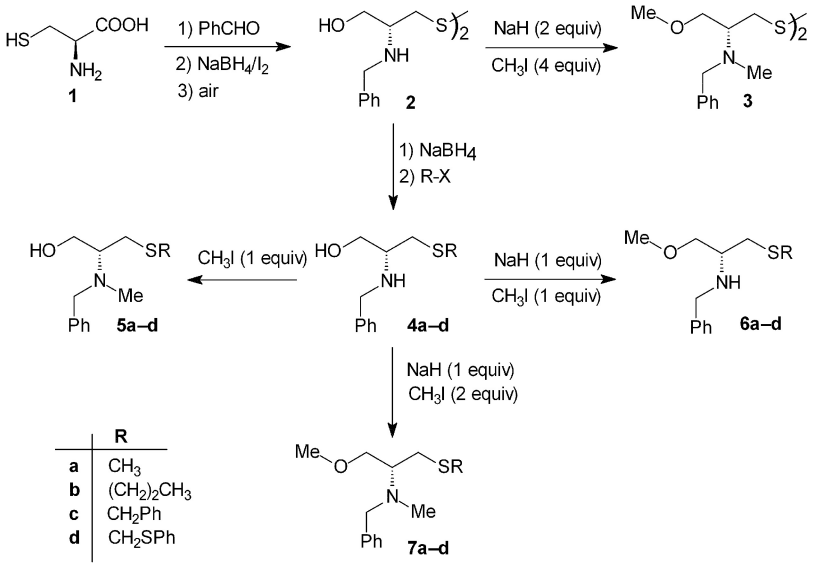
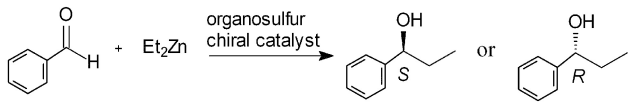


Scheme 1 Synthesis of sulfide and disulfide ligands.

The catalysts **3**–**7** were tested in the enantioselective addition of diethylzinc to benzaldehyde at room temperature (Scheme 2, Table 1). The enantiomeric excesses for 1-phenyl-1-propanol obtained with benzaldehyde ranged from 0–88%, depending on the catalyst used.



Scheme 2 Enantioselective addition of diethylzinc to benzaldehyde.

A closer analysis reveals that the disulfide ligand **3** with its potential to form covalent sulfide linkages to zinc provided much higher enantioselectivity than the *S*-methylated sulfide ligands **4**–**7**, despite the fact that in **3** the O and N atoms are fully methylated.

Of the *S*-methyl protected ligands (**4**–**7**) only sulfides **4** without any N- or O-methylation, gave very moderate enantiomeric excesses (21–41% ee, entries 3–6). In the case of the additional N- and/or O-methylated catalysts **5**–**7** no or only minimal excess of one enantiomer was obtained (entries 7–18). With increasing alkylation of the free sites the yields also decreased.

Also, the absolute configurations of the enriched *sec*-alcohols were not uniform. A predominant formation of (*S*)-1-phenyl-propanol was observed in the presence of the disulfide **3**, whereas amino alcohols **4** gave the opposite enantiomer preferentially. This appears logical if for **3** a principal S–Zn bond is assumed, formed by reductive cleavage of the labile S–S bond as reported previously.[17,18,36] For compounds **4** a principal O–Zn bond should be preferred,[8,9] and thus, since the spatial ligand orientation in the transition state complex is inverted, a preference for the opposite enantiomer is generated. Although the actual catalytically active species are not determined

Table 1 Enantioselective Addition of Diethylzinc to Benzaldehyde Using 2 mol% of the Chiral Ligands **3**, **4a–d**, **5a–d**, **6a–d** and **7a–d**[a]

Entry	Catalyst	Yield (%)[a]	ee (%) [config][b]	Free sites[c]
1	**2**	56	–	OH, NH, S–Zn[c]
2	**3**	70	88 [*S*(–)]	S–Zn (S–S)[c]
3	**4a**	67	41 [*R*(+)]	OH, NH
4	**4b**	28	33 [*R*(+)]	OH, NH
5	**4c**	29	30 [*R*(+)]	OH, NH
6	**4d**	27	21 [*R*(+)]	OH, NH
7	**5a**	43	–	OH
8	**5b**	62	–	OH
9	**5c**	55	–	OH
10	**5d**	83	–	OH
11	**6a**	33	–	NH
12	**6b**	47	–	NH
13	**6c**	32	–	NH
14	**6d**	15	–	NH
15	**7a**	59	–	–
16	**7b**	13	–	–
17	**7c**	41	–	–
18	**7d**	21	–	–

[a] Reactions were carried out in toluene at r.t. for 24 h.
[b] Determined by GC analysis of the *N*-tosyl-prolyl ester derivatives.
[c] Free sites refer to sites enabling covalent bonding to Zn with dialkylzinc, i.e. X–H groups, or in case of sulfur also disulfides which are reductively cleaved by dialkylzinc.[17,18]

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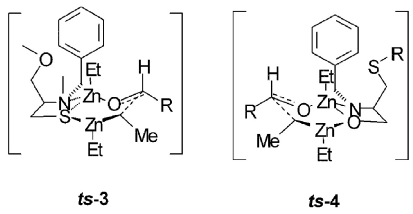
for these ligands, the transition state models shown in Figure 1 are suggested for the enantioselective catalysts, assuming the dinuclear Zn-complexes commonly accepted.[4,40,45]

Obviously, thiolate-complexation also provides improved stability and/or enhanced differences in ΔG of the diastereomeric transition state complexes, thus resulting in better enantiomeric excess – despite the fact that the second metal binding atom of the chelate ligand can only provide donor bonds, either in form of a tertiary amine or an ether-oxygen. N and O donor bonds might not add sufficient additional binding strength to give good ligand fixation in combination with thio-ether donors. i.e. of the S-alkylated ligands, only ligands **4** with their simultaneously free NH- and OH-groups, able to form covalent N–Zn and O–Zn bonds, give noteworthy ee's. Neither ligands **5** (the O equivalent of **3** with tertiary amine) nor **6** (with ether-oxygen) appear to be able to force a definite ligand geography that will result in enantio-differentiation.

Two reasons may account for this behavior of the thiolate complexes and at this moment both are very speculative: (1) Either in **ts-3** there is an additional stabilization of the second zinc (the one bound to the tertiary amine) complexed efficiently by the sulfur atom through its d-orbitals or because of its large radius; or (2) in complexes without Zn–S bond (**4**–**7**) the now free thioether sulfur competitively destabilizes the dative bonds of ether and/or tertiary amine, of which only the covalent N–Zn bond of the secondary amine and/or the covalent O–Zn bond of the primary alcohol in **4** can compete to some extent, giving rise to low ee's of inverse orientation. Other effects like the modification of Lewis acidity of the zinc ion,[21,22] other electronic donor effects,[45] or pH-dependent equilibria for ligand formation and stability[42,43] may contribute to the extent of enantioselection, but except for the latter can hardly explain a change of preference towards the other enantiomer.



ts-3 *ts*-4

Figure 1 Tentative transition state models **ts-3** and **ts-4** for ligands **3** and **4**, respectively. (The benzyl group is not shown in an conformationally ideal position but in one which allows graphical clarity).

A special case is ligand **2** with all heteroatoms as 'free' sites, which does give 0% ee[36] (entry 1). Several explanations can account for this behavior: (a) This ligand can adapt both transition states **ts-3** and **ts-4** equally well. (b) The primary sulfur coordination gives two transition states, one with oxygen as second point of coordination (6-membered complex) and one with nitrogen as second donor (cf. **ts-3**). Like in the former case, this leads to opposing stereoselection. If both transition states form equally well, or scramble rapidly, racemization results.[46] (c) Triple complexation, e.g., by expulsion of the remaining axial ethyl of the central zinc, gives a reactive complex that is either unable to enantio-differentiate or does not even bind the aldehyde at all.

The enantioselective addition of diethylzinc to various aromatic and aliphatic aldehydes using the most successful ligand, disulfide **3**, was examined more closely and the results are reported in Table 2. Most aromatic aldehydes give acceptable yields and enantiomeric ratios (entries 1–

Table 2 Addition of Diethylzinc to Various Aldehydes in the Presence of 2 mol% of Catalyst **3**

Entry	Aldehyde	Time (h)	T (°C)	Yield (%)	ee (%) [config][a]
1	Benzaldehyde	48	0	77	92 [*S*(–)]
2	4-Tolualdehyde	24	r.t.	67	81 [*S*(–)]
3	4-Tolualdehyde	48	0	53	84 [*S*(–)]
4	4-Anisaldehyde	24	r.t.	74	81 [*S*(–)]
5	4-Anisaldehyde	48	0	43	> 99 [*S*(–)]
6	Phenylacetaldehyde	24	r.t.	62	81 [*S*(+)]
7	Phenylacetaldehyde	48	0	51	91 [*S*(+)]
8	hexanal	24	r.t.	92	88[b] [*S*(+)]
9	hexanal	48	0	63	81[b] [*S*(+)]
10	decanal	24	r.t.	86	80[b] [*S*(+)]
11	decanal	48	0	55	69[b] [*S*(+)]

[a] Assigned by comparison with the optical rotations reported.[5,9,]
[b] By chiral GC analysis of the *N*-tosyl-prolyl-ester derivatives.

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5; yield 43–77%; ee 81% to > 99%); most above values were obtained with other S/N or S/O ligands.[16–38]

Although for most aromatic aldehydes these values are not yet competitive to those from sulfur-free catalysts, we believe that the functional information presented here can significantly aid the development of problem adapted and more stable ligands, based on cheap starting materials like cysteine, penicillamine etc. In addition, the findings may allow developing catalysts for the synthesis of both enantiomeric products based on non-racemic starting material with only one natural configuration available.

Again, a very interesting feature was observed with aliphatic aldehydes, which are normally much less well behaved with traditional Noyori-type catalysts. Our non-optimized catalyst **3** furnished good chemical yields and even competitive enantioselectivities (entries 6–11; 80–91% ee). For the purely aliphatic aldehydes an inverse temperature-effect was observed (cf. entries 8–11, higher ee at higher temperature), but no detailed study of this uncommon but not unknown[47,48] behavior was done to allow a generalization, e.g. for other alkanals or temperature profiles.

We have demonstrated the ready synthesis of a set of easily accessible ligands from natural cysteine, which are useful to probe the importance of the S-, O-, or N-binding site(s). This was demonstrated for the diethylzinc addition to aldehydes, in which a covalent donor-Zn bond proved to be crucial, and where a thiolate S–Zn bond was mandatory for good enantioselectivity. Although there is no immediate need for more standard ligands for dialkyl zinc additions, there is always a demand to improve the concept of ligand design, to rationalize the process in addition to evident steric requirements,[45] for ligands with ready and cheap synthetic access,[37,40] and for ligands with special properties, e.g. ligands which can selectively bind to zinc in the presence of other metal ions[16] as is the case with thiolates. We expect that the results of this study will help to direct and support the development of even better, readily available, sulfur (and selenium) based ligands, which will also be applicable for other reactions involving late transition metals.[39,40,49]

Optical rotations were measured on a Perkin-Elmer 341 Polarimeter. The ^{1}H and ^{13}C NMR spectra were registered on Bruker DPX 200 and Bruker DPX 400 spectrometers using TMS as an internal standard. Elemental analyses (C, H) were performed on a Vario El and Perkin-Elmer CHN 2400 analyzer. Gas chromatography (GC) was performed using a Varian 3800 gas chromatograph with (2,6-Me-3-Pe)-β-cyclodextrin column as chiral stationary phase for ee determination of the secondary alcohols obtained.[37]

(*R*,*R*′)-*N*,*N*′-Dibenzylcystinol (2)

In a 100 mL two necked round-bottomed flask equipped with a reflux condenser and an addition funnel, anhyd THF (85 mL), $NaBH_4$ (3.24 g, 85.5 mmol) and 2-phenyl-thiazolidin-4-carboxylic acid (34.2 mmol), obtained from (*R*)-cysteine and benzaldehyde,[44] were introduced under Ar atmosphere. Under stirring, iodine (8.68 g, 34.2 mmol) dissolved in THF (30 mL) was added slowly. After complete addition, the reaction mixture was heated to reflux for 20 h and then cooled to r.t. MeOH was added until a clear solution was obtained which was stirred under air for several minutes. The solvent was removed in vacuo and the residue was dissolved in a 20% aq K_2CO_3 solution (70 mL), stirring thereafter for 4 h at r.t. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the organic layer dried with $MgSO_4$ and filtered, the solvent was removed in vacuo. Yield: 75%; mp 106 °C; $[\alpha]_D^{20}$ –29.0 (*c* = 1.0, CH_3OH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.30–7.17 (m, 10 H), 3.74 (s, 4 H), 3.44–3.37 (m, 4 H), 2.90–2.74 (m, 6 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 40.90, 50.31, 57.90, 61.82, 126.53, 127.90, 128.07.

Anal. Calcd for $C_{20}H_{28}N_2O_2S_2$: C, 61.19; H, 7.19. Found: C, 61.45; H, 7.08.

(*R*,*R*′)-Bis[2-(*N*-benzyl-*N*-methyl-amino)-3-methoxy-propyl]disulfide (3)

To a suspension of NaH (48 mg, 2 mmol) in anhyd THF (10 mL), (*R*,*R*)-*N*,*N*′-dibenzylcystinol (**2**, 392 mg, 1 mmol) was added at 0 °C under Ar atmosphere. After 15 min, methyl iodide (568 mg, 4 mmol) was added and the mixture was stirred for 6 h at r.t. Then, water (10 mL) was added and the resulting solution extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOac, 9:1) to give the *N*/*O*-methylated disulfide **3** as a yellow oil (215 mg, 48%); $[\alpha]_D^{20}$ –33 (*c* = 0.72, CH_2Cl_2).

IR (neat): 2924, 1452, 1117, 734, 698 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 10 H), 3.70–3.59 (m, 6 H), 3.53–3.47 (m, 2 H), 3.34 (s, 6 H), 3.16–3.29 (m, 4 H), 2.82 (dd, *J* = 12.6, 6.9 Hz, 2 H), 2.22 (s, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.13, 38.23, 58.30, 58.48, 61.36, 71.23, 126.45, 127.8, 128.29, 139.52.

Anal. Calcd for $C_{24}H_{36}N_2O_2S_2$: C, 64.25; H, 8.09. Found: C, 63.84; H, 8.04.

***S*-Alkyl-*N*-benzyl (*R*)-Cysteinols 4; General Procedure**

To a solution of disulfide **2** (1.0 g, 2.55 mmol) in EtOH (10 mL), NaOH (204 mg, 5.1 mmol) and $NaBH_4$ (208 mg, 5.5 mmol) were added at 0 °C. After 30 min the alkyl halide, e.g. methyl iodide (852 mg, 6 mmol) was added and the mixture was stirred for approx 4 h at r.t. The exact reaction time depends on the alkylating agent and can be determined by TLC. The solvent was removed in vacuo and the residue dissolved in water (10 mL) and CH_2Cl_2. After the mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the organic layer dried with $MgSO_4$, the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 9:1).

4a (R = Me, from MeI)

Yield: 91%; $[\alpha]_D^{20}$ –12 (*c* = 1.0, CH_2Cl_2).

IR (neat): 3315, 2915, 1454 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 3.81–3.83 (m, 2 H), 3.77 (dd, *J* = 11.0, 3.9 Hz, 1 H), 3.43 (dd, *J* = 11.0, 4.5 Hz, 1 H), 2.91–2.8 (m, 1 H), 2.67–2.59 (m, 2 H), 2.22–2.09 (m, 2 H), 2.0 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.30, 35.79, 50.73, 55.87, 62.06, 126.79, 127.81, 128.13, 139.44.

Anal. Calcd for $C_{11}H_{17}NOS$: C, 62.52; H, 8.11. Found: C, 62.17; H, 8.33.

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4b (R = Propyl, from PrI)
Yield: 78%; $[\alpha]_D^{20}$ –42 (*c* = 0.56, CH_2Cl_2).

IR (neat): 3315, 2959, 1454 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.2 (m, 5 H), 3.85–3.66 (m, 3 H), 3.41 (dd, *J* = 10.0, 4.7 Hz, 1 H), 2.74–2.66 (m, 2 H), 2.40–2.33 (m, 3 H), 2.36 (t, *J* = 7.3 Hz, 2 H), 1.55 (sext, *J* = 7.3 Hz, 2 H), 0.94 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.23, 22.69, 33.92, 34.21, 50.92, 56.61, 62.29, 126.95, 127.97, 128.29. 139.66.

Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8.84. Found: C, 65.44; H, 8.61.

4c (R = Benzyl, from BnBr)
Yield: 85%; $[\alpha]_D^{20}$ –33 (*c* = 1.34, CH_2Cl_2).

IR (neat): 3390, 3028, 2924, 1953, 1453 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.23–7.15 (m, 10 H), 3.69–3.44 (m, 5 H), 3.33 (dd, *J* = 11.0 Hz, *J* = 4.9 Hz, 1 H), 2.79–2.63 (m, 3 H), 2.50–2.47 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.78, 35.97, 50.62, 56.23, 62.07, 126.70, 126.76, 127.82, 128.12, 128.50, 137.78, 139.51.

Anal. Calcd for $C_{17}H_{21}NOS$: C, 71.04; H, 7.36. Found: C, 71.28; H, 7.14.

4d (R = CH_2SPh, from $ClCH_2SPh$)
Yield: 80%; $[\alpha]_D^{20}$ –11 (*c* = 1.08, CH_2Cl_2).

IR (neat): 3306, 3059, 2916, 1479 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.11 (m, 10 H), 3.84–3.58 (m, 5 H), 3.43–3.36 (m, 1 H), 2.83–2.71 (m, 5 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.82, 37.62, 50.55, 56.26, 62.06, 126.48, 126.70, 127.77, 128.04, 128.54, 129.91, 134.58, 139.37.

Anal. Calcd for $C_{17}H_{21}NOS_2$: C, 63.91; H, 6.63. Found: C, 63.59; H, 6.75.

***S*-Alkyl-*N*-benzyl-*N*-methyl-(*R*)-cysteinols 5; General Procedure**
To sulfide **4** (1 mmol) in anhyd THF (10 mL), methyl iodide (142 mg, 1 mmol) was added under Ar atmosphere. The mixture was stirred for 6 h at r.t. Then, water (10 mL) was added and the resulting solution extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 9:1).

5a (R = Me)
Yield: 78%; $[\alpha]_D^{20}$ –12 (*c* = 0.90, CH_2Cl_2).

IR (neat): 3424, 2915, 1452 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.06–6.95 (m, 5 H), 3.52–3.42 (m, 2 H), 3.32–3.06 (m, 2 H), 2.74–2.64 (m, 2 H), 2.49 (dd, *J* = 13.0, 4.6 Hz, 1 H), 2.02 (dd, *J* = 13.0, 9.2 Hz, 1 H), 1.93 (s, 3 H), 1.80 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.29, 30.21, 35.68, 58.21, 60.67, 62.71, 127.30, 128.44, 128.81, 138.

Anal. Calcd for $C_{12}H_{19}NOS$: C, 63.96; H, 8.50. Found: C, 64.11; H, 8.32.

5b (R = Pr)
Yield: 61%; $[\alpha]_D^{20}$ –8 (*c* = 0.88, CH_2Cl_2).

IR (neat): 3454, 2960, 1453, 1029 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.29–6.86 (m, 5 H), 3.82–3.73 (m, 2 H), 3.61–3.36 (m, 2 H), 3.04–2.97 (m, 2 H), 2.85–2.76 (m, 1 H), 2.47 (t, *J* = 7.3 Hz, 2 H), 2.38–2.27 (m, 1 H), 2.22 (s, 3 H), 1.62–1.55 (sext, *J* = 7.3 Hz, 2 H), 0.98 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.32, 22.71, 27.87, 34.89, 35.62, 58.17, 60.67, 63.17, 127.16, 128.32, 128.69, 138.68.

Anal. Calcd for $C_{14}H_{23}NOS$: C, 66.36; H, 9.15. Found: C, 66.15; H, 9.21.

5c (R = Bn)
Yield: 54%; $[\alpha]_D^{20}$ +44 (*c* = 1.04, CH_2Cl_2).

IR (neat): 3435, 2927, 1452, 1028 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.39–7.37 (m, 10 H), 3.77 (m, 4 H), 3.61–3.42 (m, 2 H), 3.27 (s, 1 H), 3.11–2.98 (m, 1 H), 2.79–2.75 (m, 1 H), 2.41–2.30 (m, 1 H), 2.23 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.86, 36.30, 37.34, 58.60, 61.21, 63.62, 127.68, 128.89, 129.01, 129.24, 129.41, 137.05, 139.10.

Anal. Calcd for $C_{18}H_{23}NOS$: C, 71.72; H, 7.69. Found: C, 71.28; H, 7.21.

5d (R = CH_2SPh)
Yield: 60%; $[\alpha]_D^{20}$ +84 (*c* = 1.1, CH_2Cl_2).

IR (neat): 3437, 2931, 1479, 1025, 736 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.41–7.18 (m, 10 H), 3.96 (s, 2 H), 3.77–3.65 (m, 3 H), 3.63–3.59 (m, 1 H), 3.07–2.93 (m, 3 H), 2.51–2.39 (m, 1 H), 2.20 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.16, 35.63, 38.47, 58.10, 60.50, 62.45, 126.91, 127.10, 128.26, 128.62, 128.82, 130.46, 134.69, 138.48.

Anal. Calcd for $C_{18}H_{23}NOS_2$: C, 64.83; H, 6.95. Found: C, 64.71; H, 7.17.

***S*-Alkyl-*N*-Benzyl-*O*-methyl-(*R*)-cysteinol (6); General Procedure**
To a suspension of THF (10 mL) and NaH (24 mg, 1 mmol), sulfide **4** (1 mmol) was added at 0 °C under Ar atmosphere. After 15 min, methyl iodide (142 mg, 1 mmol) was added and the mixture was stirred for approx 6 h at r.t. Then, water (10 mL) was added and the resulting solution extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 9:1).

6a (R = Me)
Yield: 38%; $[\alpha]_D^{20}$ –26 (*c* = 1.4, CH_2Cl_2).

IR (neat): 2917, 1453, 1117, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H), 3.84 (s, 2 H), 3.45 (d, *J* = 5.2 Hz, 2 H), 3.33 (s, 3 H), 2.96–2.75 (m, 1 H), 2.73–2.53 (m, 2 H), 2.0 (s, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.92, 36.28, 51.40, 55.27, 58.89, 73.96, 126.90, 128.08, 128.32, 140.06.

Anal. Calcd for $C_{12}H_{19}NOS$: C, 63.96; H, 8.50. Found: C, 64.22; H, 8.31.

6b (R = Pr)
Yield: 37%; $[\alpha]_D^{20}$ –20 (*c* = 1.16, CH_2Cl_2).

IR (neat): 2924, 1454, 1117, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 5 H), 3.83 (s, 2 H), 3.44 (d, *J* = 5.2 Hz, 2 H), 3.33 (s, 3 H), 2.91–2.83 (m, 1 H), 2.74–2.54 (m, 2 H), 2.41 (t, *J* = 7.3 Hz, 2 H), 2.27 (s, 1 H), 1.56 (sext, *J* = 7.3 Hz, 2 H), 0.95 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.41, 22.93, 34.11, 34.63, 51.51, 55.85, 58.93, 74.12, 126.91, 128.13, 128.36, 140.22.

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Anal. Calcd for $C_{14}H_{23}NOS$: C, 66.36; H, 9.15. Found: C, 66.70; H, 9.34.

6c (R = Bn)
Yield: 40%; $[\alpha]_D^{20}$ +15 (*c* = 1.1, CH_2Cl_2).

IR (neat): 3027, 2917, 1454, 1028 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 10 H), 3.82–3.50 (m, 4 H), 3.38 (d, *J* = 5.3 Hz, 2 H), 3.28 (s, 3 H), 2.90–2.78 (m, 1 H), 2.65–2.53 (m, 2 H), 2.12–2.07 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.27, 36.55, 51.30, 55.49, 58.79, 73.98, 126.79, 126.85, 127.03, 127.99, 128.25, 128.33, 128.61, 128.75, 138.23, 140.22.

Anal. Calcd for $C_{18}H_{23}NOS$: C, 71.72; H, 7.69. Found: C, 71.61; H, 7.47.

6d (R = CH_2SPh)
Yield: 35%; $[\alpha]_D^{20}$ +9 (*c* = 1.14, CH_2Cl_2).

IR (neat): 2919, 1454, 1113, 738, 696 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 10 H), 3.98–3.81 (m, 4 H), 3.44–3.41 (m, 2 H), 3.31 (s, 3 H), 2.98–2.78 (m, 3 H), 2.07–2.03 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.41, 38.43, 58.58, 58.82, 61.67, 71.53, 126.76, 128.11, 128.34, 128.62, 139.0.

Anal. Calcd for $C_{18}H_{23}NOS_2$: C, 64.83; H, 6.95. Found: C, 64.74; H, 6.78.

_S_-Alkyl-_N_-benzyl-_N_,_O_-dimethyl-(_R_)-cysteinols (7); General Procedure
To a suspension of THF (10 mL) and NaH (24 mg, 1 mmol), sulfide **4** (1 mmol) was added at 0 °C under argon atmosphere. After 15 min, methyl iodide (284 mg, 2 mmol) was added and the mixture was stirred for 6 h at r.t. Then, water (10 mL) was added and the resulting solution extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 9:1).

7a (R = Me)
Yield: 45%; $[\alpha]_D^{20}$ –15 (*c* = 1.36, CH_2Cl_2).

IR (neat): 2916, 1452, 1117, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.06 (m, 5 H), 3.70 (s, 2 H), 3.63 (dd, *J* = 9.9, 6.2 Hz, 1 H), 3.5 (dd, *J* = 9.9, 6.2 Hz, 1 H), 3.34 (s, 3 H), 3.07–2.98 (m, 1 H), 2.74 (dd, *J* = 12.9, 6.4 Hz, 1 H), 2.59 (dd, *J* = 12.9, 7.5 Hz, 1 H), 2.27 (s, 3 H), 2.08 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.20, 33.52, 37.38, 58.64, 58.79, 61.45, 71.90, 126.71, 128.07, 128.59, 139.88.

Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8.84. Found: C, 64.86; H, 8.69.

7b (R = Pr)
Yield: 43%; $[\alpha]_D^{20}$ –28 (*c* = 0.90, CH_2Cl_2).

IR (neat): 2951, 1435, 1040, 699 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.30–7.13 (m, 5 H), 3.7–3.59 (m, 2 H), 3.55 (dd, *J* = 10.0, 6.3 Hz, 1 H), 3.43 (dd, *J* = 10.0, 4.8 Hz, 1 H), 3.27 (s, 3 H), 2.98–2.85 (m, 1 H), 2.69 (dd, *J* = 12.0, 6.3 Hz, 1 H), 2.51 (dd, *J* = 12.0, 7.6 Hz, 1 H), 2.39 (t, *J* = 7.4 Hz, 2 H), 2.2 (s, 3 H), 1.52 (sext, *J* = 7.4 Hz, 2 H), 0.89 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.45, 22.94, 31.11, 34.9, 37.45, 58.68, 58.82, 61.92, 71.97, 126.74, 128.11, 128.66, 139.93.

Anal. Calcd for $C_{15}H_{25}NOS$: C, 67.37; H, 9.42. Found: C, 67.56; H, 9.71.

7c (R = Bn)
Yield: 48%; $[\alpha]_D^{20}$ +23 (*c* = 1.1, CH_2Cl_2).

IR (neat): 2923, 1681, 1264 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.24–7.18 (m, 10 H), 3.62–3.58 (m, 4 H), 3.51 (dd, *J* = 10.0, 6.4 Hz, 1 H), 3.38 (dd, *J* = 10.0, 4.8 Hz, 1 H), 3.24 (s, 3 H), 2.94–2.8 (m, 1 H), 2.6 (dd, *J* = 13.0, 6.6 Hz, 1 H), 2.46 (dd, *J* = 13.0, 7.4 Hz, 1 H), 2.14 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.73, 37.04, 37.35, 58.71, 58.84, 61.71, 72.0, 126.77, 126.8, 128.15, 128.42, 128.69, 128.88, 138.59. 139.98.

Anal. Calcd for $C_{19}H_{25}NOS$: C, 72.34; H, 7.99. Found: C, 71.96; H, 7.78.

7d (R = CH_2SPh)
Yield: 52%; $[\alpha]_D^{20}$ +19 (*c* = 1.90, CH_2Cl_2).

IR (neat): 2922, 1152, 1116, 736 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.42–7.19 (m, 10 H), 4.06–3.93 (m, 2 H), 3.68–3.61 (m, 2 H), 3.59 (dd, *J* = 9.8, 5.8 Hz, 1 H), 3.44 (dd, *J* = 9.8, 5.8 Hz, 1 H), 3.31 (s, 3 H), 3.03–2.92 (m, 1 H), 2.80–2.75 (m, 2 H), 2.24 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.70, 37.12, 38.52, 58.55, 58.67, 61.54, 71.65, 126.65, 127.99, 128.52, 128.69, 130.26, 135.25, 139.50.

Anal. Calcd for $C_{19}H_{25}NOS_2$: C, 65.67; H, 7.25. Found: C, 65.49; H, 7.18.

Asymmetric Addition of Diethylzinc to Benzaldehyde; General Procedure
In a 25 mL flask with anhyd toluene (7 mL), benzaldehyde (3 mmol) and catalyst **2**–**7** (60 μmol; 2 mol%) and a 1 M hexane solution of diethyl zinc (5 mL; 5 mmol) were slowly injected under constant stirring. Stirring was continued for 24 h at r.t. Finally the temperature was adjusted to 0 °C (ice bath) and 1 N HCl (5 mL) was slowly added (10 min) with continuous stirring. The organic layer was separated and washed with 1 N HCl (2 × 8 mL). After drying over Na_2SO_4 and filtration the toluene was removed under reduced pressure. The crude alcohol was purified by bulb-to-bulb distillation under reduced pressure (ca. 0.1 mbar).

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