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New C_2-symmetric chiral disulfide ligands derived from (*R*)-cysteine

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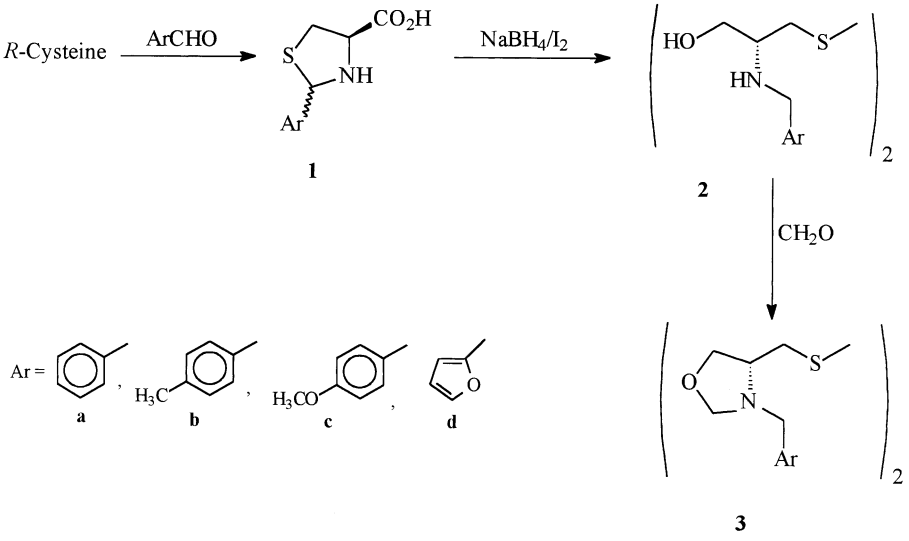
Abstract—Several sulfur-containing optically active C_2-symmetrical ligands have been synthesized from (*R*)-cysteine and applied successfully as chiral catalysts in the asymmetric addition of diethylzinc to aldehydes. The resulting secondary alcohols could be obtained in good yields and excellent enantiomeric excess.

1. Introduction

In recent years, there has been great interest in the development of transition metal catalyzed asymmetric reactions[1] and more precisely in the synthesis of ligands providing high enantioselectivity.[2] Numerous reports have shown that reagents with C_2-symmetry are efficient for asymmetric induction.[3] C_2-symmetry eliminates problems in the design of ligands connected to asymmetry. β-Amino alcohols with C_2-symmetry derived from amino acids form one of the most useful classes of such ligands, especially for the asymmetric addition of dialkylzinc nucleophiles to aldehydes.[4] C_2-symmetry, however, is usually not mandatory to achieve good enantiomeric excess. With respect to the amino acid starting materials utilized for the synthesis of such catalytically active ligands, (*R*)-cysteine has found little use compared to other members like valine, phenylalanine or serine, although it plays an important role in organic,[5] bioorganic and medicinal[6] and natural product chemistry.[7] The presence of the thiol group in this amino acid raises questions



Scheme 1.

Keywords: cysteine; disulfide; catalyst; dialkylzinc; asymmetric ligand.
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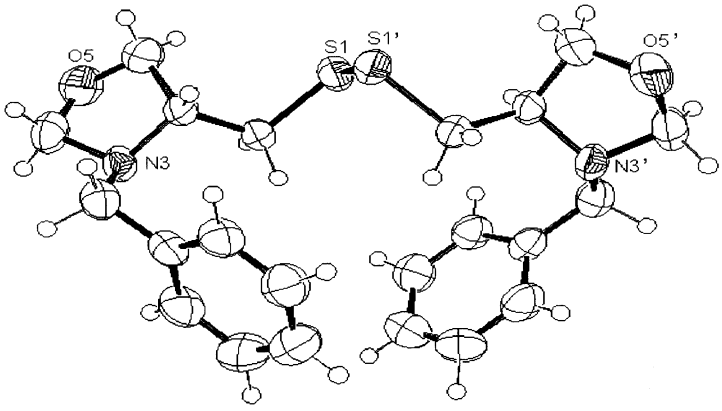


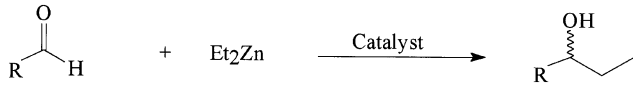
Figure 1. An ORTEP drawing of the molecular structure of (*R*,*R*)-**3a** as determined by X-ray crystallography.

related to the application of well-developed synthetic methodologies which work for other amino acids. In this context, some sulfur-containing C_2-symmetrical β-amino alcohols have been synthesized from (*R*)-cysteine and applied successfully in the enantiocontroled catalytic addition of diethylzinc to benzaldehyde.[8,9]

Recently, we have described the use of a highly efficient catalyst derived from (*R*)-cysteine, oxazoline disulfide **3** (Scheme 1, Ar=Ph), for the enantioselective addition of diethylzinc to aldehydes to afford the product alcohols in up to more than 99% ee.[9] Hence, we set out to extend this study for the synthesis of other similar ligands. In this paper we give a full account of our efforts towards the synthesis and the use as catalysts for the enantioselective addition of diethylzinc to benzaldehyde, of a series of new chiral disulfides with C_2-symmetry derived from (*R*)-cysteine.

2. Results and discussion

The synthesis of the C_2-symmetrical disulfides **3a–d** is shown in Scheme 1. The chiral disulfides are readily prepared from (*R*)-cysteine in three straightforward steps.



Scheme 2.

(*R*)-Cysteine was first converted into the thiazolidine carboxylic acids **1** by treatment with different aldehydes.[10] The resultant thiazolidines were reduced with $NaBH_4/I_2$[11] to the disulfide amino alcohols **2**. Oxazolidines **3** were obtained by treatment of the disulfide **2** with paraformaldehyde. The yields of most steps are higher than 75% and usually around 90%. All disulfide oxazolidines **3** were obtained as only one stereoisomer, with the relative configuration confirmed by X-ray analysis of **3a**. Fig. 1 shows its molecular structure.[12] Products **3a–d** were tested as catalysts for the diethylzinc addition to aldehydes (Scheme 2). As described in our previous paper,[9] good results were obtained when 2 mol% of the oxazolidine **3a** were used (Table 1, entries 2 and 3). Thus, ligand **3a** catalyzed the addition of diethylzinc to benzaldehyde at 0°C to give (1*S*)-phenylpropanol with >99% ee in 81% yield (entry 3). However, for the aliphatic aldehydes, the yields and the enantiomeric excesses were moderate (entries 4 and 5), with the exception of hexanal (>99% ee). Ligands **3b–d** were evaluated under the same experimental conditions. In the diethylzinc addition to benzaldehyde (entries 6, 9 and 12) the catalysts **3b–d** provided comparable chemical yields than **3a** (90% to quant.), but the enantioselectivity was lower (84–92% ee). Most important, the additon of diethylzinc to aliphatic aldehydes in the presence of catalysts **3b–d** proceeded in most cases better than with **3a**. The

Table 1. Asymmetric addition of diethylzinc to aldehydes using chiral ligands **3a–d** (2 mol%)

Entry	Catalyst	Aldehyde	*t* (h)	*T* (°C)	Yield (%)	ee (%) [config]
1	–	Benzaldehyde	16	rt	17	0
2	(*R*,*R*)-**3a**	Benzaldehyde	16	rt	98	80 [*S* (−)]
3	(*R*,*R*)-**3a**	Benzaldehyde	30	0	81	>99 [*S* (−)]
4	(*R*,*R*)-**3a**	Hexanal	36	0	58	>99 [*S* (−)]
5	(*R*,*R*)-**3a**	Decanal	36	0	50	40 [*S* (−)]
6	(*R*,*R*)-**3b**	Benzaldehyde	30	0	quant.	92 [*S* (−)]
7	(*R*,*R*)-**3b**	Hexanal	48	0	82	28 [*S* (−)]
8	(*R*,*R*)-**3b**	Decanal	48	0	64	>99 [*S* (−)]
9	(*R*,*R*)-**3c**	Benzaldehyde	30	0	83	84 [*S* (−)]
10	(*R*,*R*)-**3c**	Hexanal	48	0	81	>99 [*S* (−)]
11	(*R*,*R*)-**3c**	Decanal	48	0	86	94 [*S* (−)]
12	(*R*,*R*)-**3d**	Benzaldehyde	30	0	85	90 [*S* (−)]
13	(*R*,*R*)-**3d**	Hexanal	48	0	52	30 [*S* (−)]
14	(*R*,*R*)-**3d**	Decanal	48	0	53	18 [*S* (−)]

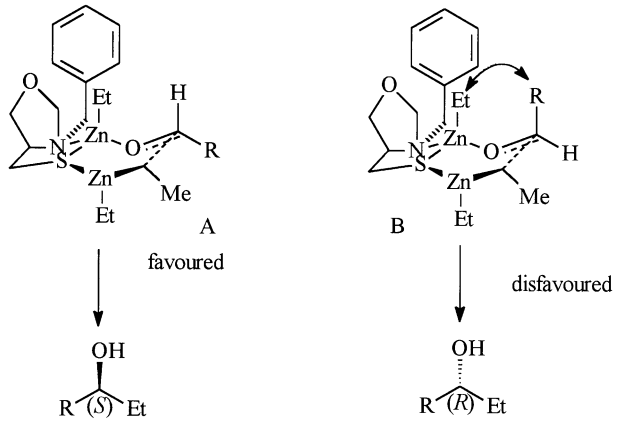


Figure 2. Transition state model.

best result was obtained with the catalyst **3c**, leading to good yields (80–90% range) and excellent enantiomeric excesses (>94% ee, entries 10 and 11). These results suggest that the benzylic substituent at the nitrogen atom plays a critical role in the enantioselection of the addition reaction. The observation also serves as a starting point for the future development of catalysts with even better ees with aliphatic aldehydes, a long standing drawback of most current ligands.

It should be mentioned that the ligand in the active catalyst likely does not retain C_2-symmetry. The disulfide bond of the C_2-ligand is probably cleaved in situ by diethylzinc to result in two corresponding identical oxazolmethylsulfides, which form the real catalytically active ligand.[13] However, for synthetic application purposes the disulfides are much easier to obtain and to handle.

Although the actual active species are unclear, the transition state model shown in Fig. 2 is suggested, based on the dinuclear Zn complexes proposed by Noyori.[1c] Transition state structure **A** is favored over **B** because it avoids axial positioning of the aldehyde R-group and a destabilizing 1,3 interaction between diethylzinc and the oxazolidinyl group.

3. Conclusions

In summary, several chiral disulfides were efficiently prepared from commercial (*R*)-cysteine as the starting material and they were found to promote the enantioselective alkylation of aldehydes to afford the corresponding secondary alcohols in excellent yields and enantiomeric excess. Considerable progress was achieved to improve ees of aliphatic aldehydes. Further studies dealing with the application of this type of ligands in catalytic, as well as stoichiometric, reactions are in progress.

4. Experimental

4.1. General

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, N) 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.

4.1.1. Thiazolidine-4-carboxylic acid (1). To a solution of (*R*)-cysteine hydrochloride hydrate (8.75 g; 50 mmol) in water (75 mL) was added sodium acetate (7.60 g; 56 mmol). After a solution was obtained, 95% ethanol (75 mL) was added followed immediately by the aldehyde (50 mmol), added in one portion. The product thiazolidine **1** soon began to crystallize. The reaction was kept at 25°C for 3 h and an additional 3 h at 0°C. The product was filtered, washed with ethanol, and dried to afford the thiazolidine **1**.

1a. Yield: 90%; mp: 158–159°C; IR (KBr) 2700–2400 (NH_3^+), 1600–1550 (CO_2^-), 1360 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) Isomer A: δ 7.51–7.30 (m, 5H), 5.51 (s, 1H), 3.90 (dd, 1H, J=8.8 Hz, J=7.2 Hz), 3.39 (dd, 1H, J=10.0 Hz, J=7.2 Hz), 3.08 (dd, 1H, J=10.0 Hz, J=8.8 Hz). Isomer B: δ 7.51–7.30 (m, 5H), 5.71 (s, 1H), 4.23 (dd, 1H, J=7.2 Hz, J=4.8 Hz), 3.31 (dd, 1H, J=10.0 Hz, J=7.2 Hz), 3.15 (dd, 1H, J=10.0 Hz, J=4.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 38.11 (38.70), 65.04 (65.75), 71.13 (71.90), 126.97, 127.32, 127.61, 128.28, 128.55, 139.00, 141.40, 172.49, 175.10. Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.30; N, 6.69. Found: C, 56.97; H, 5.10; N, 6.85.

1b. Yield: 83%; mp: 163.2–163.7°C; ^{1}H NMR (400 MHz, DMSO-d_6) Isomer A: δ 7.4–7.1 (m, 4H), 5.63 (s, 1H), 4.23 (dd, 1H, J=4.6 Hz, J=6.8 Hz), 3.29 (dd, 1H, J=7.2 Hz, J=10.2 Hz), 3.13 (dd, 1H, J=4.4 Hz, J=10.2 Hz), 2.27 (s, 3H). Isomer B: δ 7.4–7.1 (m, 4H), 5.45 (s, 1H), 3.86 (m, 1H), 3.37 (dd, 1H, J=7.6 Hz, J=10.0 Hz), 3.05 (m, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) Isomer A: δ 20.80, 38.06, 65.05, 71.13, 126.95 128.83, 137.70, 138.22, 173.16. Isomer B: δ 20.74, 38.75, 65.75, 71.83, 127.21, 129.10, 135.96, 136.87, 172.55. Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.41; H, 5.69; N, 6.32.

1c. Yield: 94%; mp: 163–164°C; ^{1}H NMR (400 MHz, DMSO-d_6) Isomer A: δ 7.5–6.8 (m, 4H), 5.61 (s, 1H), 4.26 (dd, 1H, J=4.1 Hz, J=7.0 Hz), 3.71 (s, 3H), 3.29 (dd, 1H, J=7.0 Hz, J=10.1 Hz), 3.15 (dd, 1H, J=4.1 Hz, J=10.1 Hz). Isomer B: δ 7.5–6.8 (m, 4H), 5.44 (s, 1H), 3.85 (m, 1H), 3.36 (dd, 1H, J=7.4 Hz, J=9.6 Hz), 3.06 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) Isomer A: δ 38.70, 55.20, 64.96, 71.03, 113.68, 128.46, 132.81, 159.32, 173.23. Isomer B: δ 38.03, 55.24, 65.57, 71.64, 113.94, 128.73, 130.31, 158.86, 172.50. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.57; H, 4.97; N, 5.87.

1d. Yield: 87%; mp: 137–138°C; ^{1}H NMR (400 MHz, DMSO-d_6) Isomer A: δ 7.56 (s, 1H), 6.5–6.2 (m, 2H),

5.74 (s, 1H), 4.14–4.08 (m, 1H), 3.45–3.25 (m, 1H), 3.15–2.80 (m, 1H). Isomer B: δ 7.63 (s, 1H), 6.5–6.2 (m, 2H), 5.59 (s, 1H), 3.86 (dd, 1H, J=7.0 Hz, J=8.8 Hz), 3.45–3.25 (m, 1H), 3.15–2.80 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) Isomer A: δ 37.81, 63.92, 64.77, 106.34, 110.35, 142.43, 154.44, 172.54 Isomer B: δ 38.11, 64.21, 65.35, 107.52, 110.65, 142.91, 151.38, 172.20. Anal. Calcd for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.01; H, 4.43; N, 6.97.

4.1.2. Amino alcohol disulfide (2). In a 100 mL two necked round-bottomed flask equipped with a reflux condenser and an addition funnel, dry THF (85 mL), $NaBH_4$ (3.24 g; 85.5 mmol) and **1** (34.2 mmol) were introduced under argon 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 at reflux for 20 h and then cooled to room temperature. Methanol was added to the mixture until a clear solution was obtained. The solvent was removed under vacuum and the residue dissolved in 70 mL of a 20% aqueous K_2CO_3 solution, stirring for 4 h at room temperature. After 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.

2a. Yield: 75%; mp 105.7–106.1°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, 10H), 3.74 (s, 4H), 3.44–3.37 (m, 4H), 2.90–2.74 (m, 6H); ^{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; N, 7.14. Found: C, 60.84; H, 6.84; N, 7.13.

2b. Yield: 94%; mp 110–110.6°C; $[\alpha]_D^{20}$=−85 (c 0.62, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (d, 4H, J=8.0 Hz), 7.08 (d, 4H, J=8.0 Hz), 3.71 (s, 4H,), 3.55–3.40 (m, 4H), 2.91–2.85 (m, 4H), 2.82–2.77 (m, 2H), 2.26 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.75; 40.94; 50.19; 57.91; 61.91; 127.94; 128.73; 135.57; 137.82. Anal. Calcd for $C_{22}H_{32}N_2O_2S_2$: C, 62.82; H, 7.67; N, 6.66. Found: C, 62.68; H, 7.50; N, 6.62.

2c. Yield: 86%; mp 88.4–89°C; $[\alpha]_D^{20}$=−98 (c 0.52, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (d, 4H, J=8.1 Hz), 6.84 (d, 4H, J=8.1 Hz), 3.71 (s, 6H,), 3.67 (s, 4H), 3.50–3.41 (m, 4H), 2.91–2.80 (m, 4H), 2.78–2.72 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 40.94; 49.75; 54.95; 57.78; 61.84; 113.48; 129.08; 132.80; 158.03. Anal. Calcd for $C_{22}H_{32}N_2O_4S_2$: C, 58.38; H, 7.13; N, 6.19. Found: C, 58.30; H, 6.97.

2d. Yield: 76%; $[\alpha]_D^{20}$=−55 (c 0.80, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 2H), 6.28 (s, 2H), 6.18 (s, 2H), 3.76 (s, 4H), 3.66–3.44 (m, 4H), 2.90–2.67 (m, 4H), 2.62–2.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.73; 41.91; 58.85; 61.28; 106.54; 109.60; 141.58; 152.34. Anal. Calcd for $C_{16}H_{24}N_2O_4S_2$: C, 51.59; H, 6.49; N, 7.52. Found: C, 51.57; H, 6.45; N, 7.48.

4.1.3. Oxazolidine disulfide (3). In a 50 mL round-bottomed flask with Dean–Stark apparatus was added benzene (30 mL), **2** (1 mmol), p-formaldehyde (90 mg; 3 mmol) and p-toluenesulfonic acid (10 mg). The mixture was heated at reflux for 5 h and cooled to room temperature. The benzene was removed under vacuum and the residue dissolved in CH_2Cl_2 (30 mL), washed with 0.5N NaOH aqueous solution, dried with $MgSO_4$, filtered, and the solvent removed under vacuum to afford **3**.

3a. Yield: 87%; $[\alpha]_D^{20}$=+14.8 (c 1.96, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.19 (m, 10H), 4.29 (s, 4H), 4.04 (dd, 2H, J=7.0 Hz, J=8.4 Hz), 3.76–3.70 (m, 4H), 3.48 (dd, 2H, J=5.0 Hz, J=8.4 Hz), 3.36–3.21 (m, 2H), 2.76 (dd, 2H, J=5.8 Hz, J=13.2 Hz), 2.47 (dd, 2H, J=8.4 Hz, J=13.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.08; 58.92; 62.06; 69.06; 85.98; 127.19; 127.97, 128.24, 128.40, 128.60. Anal. Calcd for $C_{22}H_{28}N_2O_2S_2$: C, 63.43; H, 6.77; N, 6.72. Found: C, 63.20; H, 7.26; N, 7.10.

3b. Yield: 92%; $[\alpha]_D^{20}$=−30.32 (c 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (d, 4H, J=7.8 Hz), 7.11 (d, 4H, J=7.8 Hz), 4.32 (s, 4H), 4.05 (m, 2H,), 3.72 (m, 4H), 3.50 (dd, 2H, J=5.0 Hz, J=8.2 Hz), 3.33 (dd, 2H, J=6.30 Hz, J=13.2 Hz), 2.78 (dd, 2H, J=6.3 Hz, J=13.20 Hz), 2.50 (dd, 2H, J=8.2 Hz, J=13.2 Hz), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.02; 41.83; 58.63; 62.31; 69.09; 85.95; 128.68; 128.95; 135.53; 136.79. Anal. Calcd for $C_{24}H_{32}N_2O_2S_2$: C, 64.83; H, 7.25; N, 6.30. Found: C, 64.56; H, 7.24; N, 6.79.

3c. Yield: 93%; $[\alpha]_D^{20}$=−2 (c 0.64, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26 (d, 4H, J=8.7 Hz), 6.84 (d, 4H, J=8.7 Hz), 4.30 (s, 4H), 4.05 (dd, 2H, J=7.0 Hz, J=8.5 Hz), 3.78 (s, 6H), 3.70 (dd, 4H, J=6.0 Hz, J=8.5 Hz), 3.50 (dd, 2H, J=5.0 Hz, J=8.5 Hz), 2.79 (dd, 2H, J=6.0 Hz, J=13.2 Hz), 2.51 (dd, 2H, J=8.5 Hz, J=13.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.95, 55.16, 58.31, 62.26, 69.12, 85.88, 113.61, 129.95, 130.70, 158.83. Anal. Calcd for $C_{24}H_{32}N_2O_4S_2$: C, 60.48; H, 6.77; N, 5.88. Found: C, 60.73; H, 6.41; N, 5.49.

3d. Yield: 75%; $[\alpha]_D^{20}$=−48 (c 0.52, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39 (s, 2H); 6.33–6.23 (m, 4H); 4.45 (d, 2H, J=6.0 Hz); 4.35 (d, 2H, J=6.0 Hz); 4.12–4.01 (m, 2H); 3.78 (s, 4H); 3.55–3.33 (m, 4H); 2.83 (dd, 2H, J=6.0 Hz, J=13.4 Hz); 2.55 (dd, 2H, J=7.9 Hz, J=13.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.73; 51.14; 62.00; 69.20; 85.70; 108.53; 110.13; 142.34; 151.88. Anal. Calcd for $C_{18}H_{24}N_2O_4S_2$: C, 54.52; H, 6.10; N, 7.06. Found: C, 54.76; H, 5.93; N, 6.79.

4.2. General procedure for asymmetric addition of diethylzinc to aldehydes

In a 25 mL flask with toluene (7 mL), aldehyde (3 mmol) and catalyst (60 μmol; 2 mol%), a 1 M hexane solution of diethylzinc (5 mL; 5 mmol) was slowly injected under constant stirring. Stirring was continued for the time and at the temperature indicated in Table 1. Finally the temperature was adjusted to 0°C (ice bath) and 1N HCl (5 mL) was slowly added (10 min) with continuous stirring. The organic layer was separated and washed with 2×8 mL of 1N HCl. After drying over sodium sulfate 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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