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# A new functionalized, chiral disulfide derived from L-cysteine: (*R*,*R*)-bis[(3-benzyloxazolan-4-yl)-methane] disulfide as a catalyst in the diethylzinc addition to aldehydes

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**Abstract**

A new, easily accessible, chiral disulfide **3** was prepared from L-cysteine in a short synthetic sequence (Scheme 1) and applied successfully as a highly efficient catalyst for the enantioselective addition of diethyl zinc to aromatic and aliphatic aldehydes to afford the product alcohols in up to more than 99% ee. In contrast to the more common amino alcohols used in similar reactions, catalyst **3** does not have a protic hydrogen in the form of a free hydroxy group. 

## 1. Introduction

The stereoselective synthesis of optically active secondary alcohols is a well studied topic in organic chemistry.[1] In some cases, high enantiomeric excesses have been obtained. Commonly, asymmetric induction is achieved by the application of non-racemic chiral ligands, which complex with one or more participants in metal-ion centered reactions.[2] The asymmetric nucleophilic addition of dialkyl zinc reagents to carbonyl groups has been extensively studied, especially since this process has been found to be catalytic in the chiral ligands.[3] Mainly chiral β-amino alcohols have proven to be highly effective catalysts. Superior catalysts incorporating amino and sulfur or selenium groups have also been reported recently.[4–6]

These impressive findings together with the availability of a wide variety of diorganozinc reagents carrying labile functionality[7] ensure the continued importance for the development of improved catalysts

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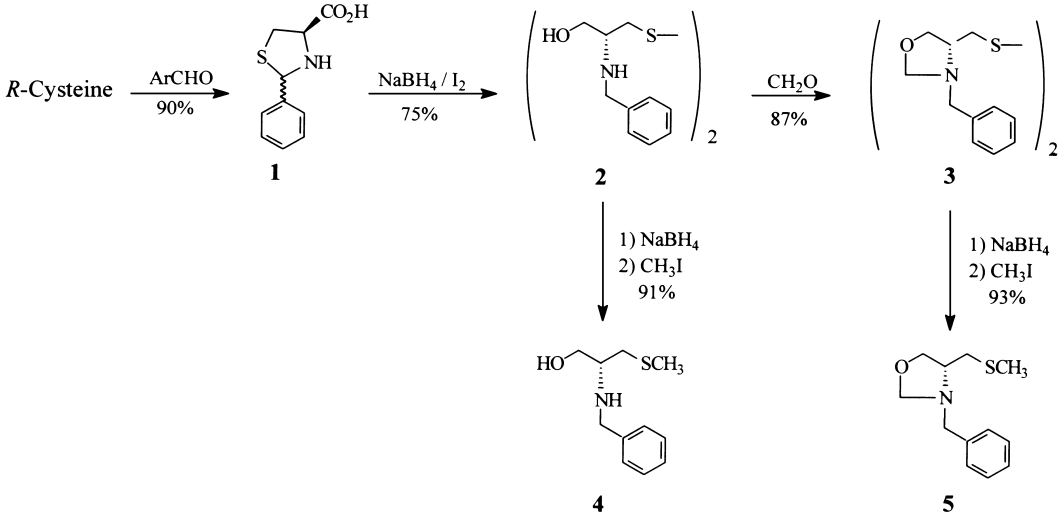
derived from non-toxic and inexpensive starting materials. With this aim, together with our interest in obtaining sulfur and selenium containing catalysts, we report the synthesis of the new chiral disulfide **3** derived from L-cysteine ((*R*)-cysteine), that proved to be a highly effective catalyst for the enantioselective addition of diethylzinc to aldehydes, including aliphatic ones.

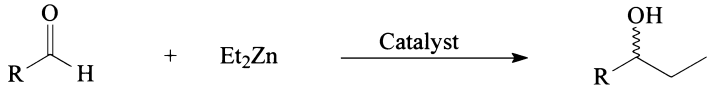
## 2. Results and discussion

The chiral disulfide **3** is readily prepared from (*R*)-cysteine in a three step synthesis (Scheme 1). In the first step, (*R*)-cysteine was cyclized with benzaldehyde leading to **1**.[8] The resultant thiazolidine was reduced with $NaBH_4/I_2$ to give the disulfide amino alcohol **2**. Oxazolidine **3** was obtained by treatment of the disulfide **2** with paraformaldehyde. Disulfides **2** and **3** were reduced with $NaBH_4$ and alkylated with MeI to give methyl-thioethers **4** and **5**. It is important to mention that the yields of most steps were around 90% and none were below 75% without much optimization.




Scheme 1.

Products **2**, **3**, **4**, and **5** were tested as catalysts for the diethyl zinc addition to benzaldehyde (Scheme 2). Most likely, the active catalyst is the corresponding ethylzinc thiolate, obtained from disulfide cleavage by diethyl zinc as described by Kellogg et al.[4] However, this likely process was not rigorously proven for our catalysts, but offers the future prospect of cutting the amount of catalyst required in half, if the reduced thiol-form is applied. When catalysts **2**, **4**, or **5** were used, the results showed low excesses of one of the enantiomers (0–41%, Table 1, entries 2, 6 and 7). However, excellent results were obtained when 2 mol% of the oxazolidine **3** (Table 1, entry 3 and 5) was used. Thus (1*S*)-phenylpropanol was obtained in 81% yield and >99% ee at 0°C (or in 98% yield and 80% ee at room temperature).




Scheme 2.

$Et_2Zn$ was added to some substituted benzaldehydes in the presence of the best catalyst (**3**, see Scheme 1 and Table 2). In this small selection, satisfactory yields and enantiomeric ratios were obtained, the latter being much better at 0°C. The electronic nature of the substituents seems to exhibit a small

Table 1
Asymmetric addition of diethylzinc to benzaldehyde using chiral ligands **2–5** (2 mol%)

| Entry | Catalyst | t (h) | T (°C) | Yield (%) | ee (%) [config] |
|---|---|---|---|---|---|
| 1 | - | 16 | r.t. | 17 | 0 |
| 2 | (*R*,*R*)-**2** | 16 | r.t. | 56 | 0 |
| 3 | (*R*,*R*)-**3** | 16 | r.t. | 98 | 80 [*S* (-)] |
| 4[a] | (*R*,*R*)-**3** | 30 | 0 | 43 | 76 [*S* (-)][a] |
| 5 | (*R*,*R*)-**3** | 30 | 0 | 81 | >99 [*S* (-)] |
| 6 | (*R*)-**4** | 16 | r.t. | 67 | 41[*R* (+)] |
| 7 | (*R*)-**5** | 16 | r.t. | 57 | 40 [*S* (-)] |

a) 1 mol% (*R*,*R*)-**3** was used.

effect, as increased electron density in the aromatic ring appears to result in slight decreases in yield and enantiomeric excess (entries 3–6, Table 2). However, ees are often better than those reported with other (disulfide) catalysts,[5] distinctly so for aliphatic aldehydes like phenylacetaldehyde and hexanal at low temperatures (entries 8 and 10, respectively). The extraordinary increase in ee at 0°C with hexanal (and phenacetaldehyde) in comparison to decanal remains unexplained. However, the experiment has been repeated successfully, and as a control, racemate was synthesized in order to check for an accidental misinterpretation of the GC data.

## 3. Conclusion

In summary, several inexpensive chiral disulfides and sulfides were prepared in a short and easy synthetic route from commercial L-cysteine as the starting material. Oxazolidine disulfide **3** proved to be the best catalyst for the $Et_2Zn$ addition to aldehydes. This disulfide catalyzes the highly enantioselective ethylation of various aldehydes, including aliphatic ones, with up to >99% ee.

Further studies dealing with the preparation of new chiral dichalcogenides and their application in catalytic as well as stoichiometric reactions are in progress.

## 4. Experimental

All aldehydes used are commercially available and were distilled before use. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. The $^1H$ and $^{13}C$ NMR spectra were registered on a Bruker AC 200 spectrometer 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)-$\beta$-cyclodextrin column as chiral stationary phase for ee determination of the secondary alcohols obtained.

Table 2
Addition of diethylzinc to various aldehydes in the presence of 2 mol% of catalyst (*R,R*)-**3**

| Entry | Aldehyde | t (h) | T (°C) | Yield (%) | ee (%) [config][b] |
|---|---|---|---|---|---|
| 1 | Benzaldehyde | 16 | r.t. | 98 | 80 [*S* (-)] |
| 2 | Benzaldehyde | 30 | 0 | 81 | >99 [*S* (-)] |
| 3 | 4-Tolualdehyde | 16 | r.t. | 65 | 70 [*S* (-)] |
| 4 | 4-Tolualdehyde | 36 | 0 | 71 | 86 [*S* (-)] |
| 5 | 4-Anisaldehyde | 16 | r.t. | 67 | 36 [*S* (-)] |
| 6 | 4-Anisaldehyde | 36 | 0 | 65 | 70 [*S* (-)] |
| 7 | Phenylacetaldehyde | 16 | r.t. | 34 | 55 [*S* (+)] |
| 8 | Phenylacetaldehyde | 36 | 0 | 38 | 92 [*S* (+)] |
| 9 | Hexanal | 16 | r.t. | 34 | 36[a] [*S* (+)] |
| 10 | Hexanal | 36 | 0 | 58 | >99[a] [*S* (+)] |
| 11 | Decanal | 16 | r.t. | 56 | 34[a] [*S* (+)] |
| 12 | Decanal | 36 | 0 | 50 | 40[a] [*S* (+)] |

a) By CG analysis of its *N*-tosyl-prolyl-ester derivatives

b) Assigned by comparison of the sign of optical rotation reported[3]

### *4.1. 1-(4*R*)-2-Phenylthiazolidine-4-carboxylic acid **1***

Compound **1** was prepared according to previous reports.[8] To a solution of 8.75 g (50 mmol) of (*R*)-cysteine hydrochloride hydrate in 75 mL of water was added 7.60 g (56 mmol) of sodium acetate. After a solution was obtained, 75 mL of 95% ethanol was added followed immediately by 5.1 mL (5.36 g, 50 mmol) of benzaldehyde, 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 11.0 g (90%) of the thiazolidine **1**: mp 158–159°C; IR (KBr) 2700–2400 ($NH_3^+$), 1600–1550 ($CO_2^-$), 1360 $cm^{-1}$; $^1H$ NMR (DMSO) δ=7.51–7.30 (m, 5H), 5.8 (s, 1H), 4.2 (dd, 1H), 3.5–3.0 (m, 2H).

### *4.2.* N,N′*-Dibenzyl-(*R*)-cystinol **2***

In a 100 mL two necked round-bottomed flask equipped with a reflux condensor and an addition funnel, 85 mL dry THF, 3.24 g (85.5 mmol) of $NaBH_4$ and 8.40 g (34.2 mmol) of **2** were introduced under argon. Under stirring, 8.68 g (34.2 mmol) iodine dissolved in 30 mL THF 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 combined organic layers dried with $MgSO_4$ and filtered, the solvent was removed under vacuum to yield 6.13 g (75%) of **2**: mp 105.7–106.1°C; $[\alpha]_D^{20}$ −29.0 (*c* 1.0, $CH_3OH$); $^1$H NMR (DMSO) δ=7.30–7.17 (m, 10H), 3.78–3.70 (m, 4H), 3.43–3.39 (m, 4H), 2.90–2.74 (m, 6H); $^{13}$C NMR (DMSO, 50 MHz) δ=40.90 (2×$CH_2S$); 50.31 (2×$CH_2N$); 57.90 (2×CHN); 61.82 (2×$CH_2OH$); 126.53 (2×aromat.-C); 127.90, 128.07 (10×aromat.-C). 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.

### *4.3. (*R,R*)-Bis[(3-benzyloxazolan-4-yl)methane]disulfide **3***

In a 50 mL round-bottomed flask with Dean Stark apparatus was added 30 mL benzene, 392 mg (1 mmol) of **3**, 90 mg (3 mmol) of paraformaldehyde and *p*-toluenesulfonic acid (catalytic quantities). 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 30 mL $CH_2Cl_2$, washed with 0.5 N NaOH solution, dried with $MgSO_4$, filtered, and the solvent removed under vacuum to afford 353 mg (87%) of **3**; $[\alpha]_D^{20}$ +14.8 (*c* 1.96, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ=7.34–7.19 (m, 10H), 4.29 (s, 4H), 4.08–4.00 (m, 2H), 3.76–3.73 (m, 4H), 3.51–3.45 (m, 2H), 3.28–3.28 (m, 2H), 2.81–2.71 (m, 2H), 2.53–2.43 (m, 2H); $^{13}$C NMR ($CDCl_3$, 50 MHz): δ=41.08 (2×$CH_2S$); 58.92 (2×$CH_2N$); 62.06 (2×CHN); 69.06 (2×$CH_2O$); 85.98 (2×$CH_2NO$); 127.19 (2×aromat.-C); 127.97, 128.24, 128.40, 128.60 (10×aromat.-C).

### *4.4. (*R*)-2-Benzylamino-3-methylthiopropanol **4***

To a solution of **2** (1.0 g, 2.55 mmol) and sodium hydroxide (204 mg, 5.1 mmol) in dry ethanol (10 mL) under an argon atmosphere sodium borohydride (208 mg, 5.5 mmol) was added in portions, and the mixture was stirred for 30 min at room temperature. Methyl iodide (1.42 g, 10.2 mmol) was added and the resulting mixture was stirred again for 30 min at room temperature. Ethanol was removed under vacuum and the residue was dissolved in 20 mL $CH_2Cl_2$, washed with water, dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford 461 mg (91%) of **4**; $[\alpha]_D^{25}$ −39.7 (*c* 1.12, $CH_3OH$); $^1$H NMR ($CDCl_3$) δ=7.36–7.24 (m, 5H), 3.47–3.39 (m, 2H), 2.82–2.62 (m, 3H), 3.80–3.71 (m, 2H), 1.99 (s, 3H); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ=15.59 ($CH_3S$); 36.28 ($CH_2S$); 50.99 ($CH_2N$); 56.04 (CHN); 61.82 ($CH_2OH$); 126.53 (1×aromat.-C); 127.90, 128.07 (5×aromat.-C)

### *4.5. (4*R*)-*N*-Benzyl-4-(methylthiomethyl) oxazolane **5***

To a solution of **3** (2.30 g, 5.48 mmol) and sodium hydroxide (440 mg, 10.4 mmol) in dry ethanol (20 mL) under an argon atmosphere sodium borohydride (416 mg, 11 mmol) was added in portions at room temperature. The mixture was stirred for 30 min and methyl iodide (3.09 g, 21.9 mmol) was added. After 30 min ethanol was removed under vacuum and the residue was dissolved in 30 mL $CH_2Cl_2$, washed with water, dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure to afford 1.08 g (93%) of **5**; $[\alpha]_D^{25}$ −25.9 (*c* 1.02, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ=7.36–7.24 (m, 5H), 4.38 (s, 2H), 3.76–3.58 (m, 5H), 2.78–2.70 (m, 2H), 1.99 (s, 3H); $^{13}$C NMR ($CDCl_3$, 50 MHz) δ=15.89 ($CH_3S$); 33.38 ($CH_2S$); 50.63 ($CH_2N$); 59.23 (CHN); 69.60 ($CH_2O$); 86.24 ($CH_2NO$); 126.24 (aromat.-C); 121.93, 122.27 (5×aromat.-C).

### 4.6. General procedure for asymmetric addition of diethylzinc to aldehydes

In a 25 mL flask with 7 mL toluene, 3 mmol aldehyde and 60 μmol (2 mol%) catalyst, 5 mL (5 mmol) of a 1 M solution of diethyl zinc in hexane was slowly injected with constant stirring. Stirring was continued for the time and at the temperature indicated in Tables 1 and 2. Finally the temperature was adjusted to 0°C (ice bath) and 5 mL of 1 N HCl was slowly added (10 min) with continuous stirring. The organic layer was separated and washed with 2×8 mL of 1 N HCl. After drying over sodium sulfate, and filtration, toluene was removed under reduced pressure. The crude alcohol was purified by bulb-to-bulb distillation under reduced pressure (oil pump, ca. 0.1 mbar).

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## References

1. (a) Dervant, R. M.; Radunz, H. E. In *Houben-Weyl*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E, 21 b, pp. 1314–1334. (b) Soai, S.; Niwa, K. *Chem. Rev*. **1992**, *92*, 833.
2. (a) Singh, V. K. *Synthesis* **1992**, 843. (b) Deloux, L.; Screbnik, M. *Chem. Rev*. **1993**, *93*, 743.
3. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; chapter 5. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 49. (c) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem*. **1990**, *102*, 206; *Angew. Chem., Int. Ed. Engl*. **1990**, *29*, 205. (d) Bringmann, G.; Breuning, M. *Tetrahedron: Asymmetry* **1998**, *9*, 667. (e) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 1489.
4. (a) Fitzpatrick, K.; Hulst, R.; Kellogg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 1861. (b) Kellogg, R. M.; Hof, R. P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1651.
5. (a) Gibson, C. L. *Chem. Commun*. **1996**, 645. (b) Fulton, D. A.; Gibson, C. L. *Tetrahedron Lett*. **1997**, *38*, 2019. (c) Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1409. (d) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun*. **1994**, 2009. (e) Jin, M.; Ahn, S.; Lee, K. *Tetrahedron Lett*. **1996**, *37*, 8767. (f) Rijnberg, E.; Jastrebski, J.; Janssen, M.; Boersma, J.; van Koten, G. *Tetrahedron Lett*. **1994**, *35*, 6521.
6. (a) Wirth, T. *Tetrahedron Lett*. **1995**, *36*, 7849. (b) Wirth, T.; Kulicke, K.; Fragale, G. *Helv. Chim. Acta* **1996**, *79*, 1957. (c) Wessjohann, L. A.; Sinks, U. *J. Prakt. Chem*. **1998**, *340*, 189.
7. (a) Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem*. **1992**, *57*, 1956. (b) Knochel, P.; Perea, J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
8. Confalone, P. N.; Pizzolato, G.; Baggiolini, E. G.; Lollar, D.; Uskokovic, M. R. *J. Am. Chem. Soc*. **1977**, *99*, 7020.