One-Pot Synthesis of New Chiral Sulfides and Selenides Containing Oxazolidines: Catalyst in the Enantioselective Addition of Diethylzinc to Benzaldehyde

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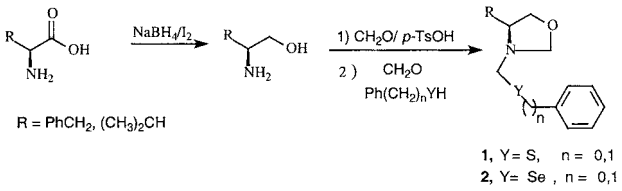
Abstract: A new easily accessible class of chiral sulfides **1** and selenides **2** containing oxazolidine was prepared from amino acids. They were used as chiral ligands in the catalytic asymmetric addition of diethylzinc to benzaldehyde to give the corresponding secondary alcohols in up to 80% ee with an *R*-configuration.

Key words: sulfur, selenium, stereoselective synthesis, asymmetric catalysis, zinc

Oxazolidines, usually obtained from amino acids, have found widespread use as chiral nonracemic ligands in asymmetric catalysis.[1] Recently, we developed oxazolidine disulfides as a new class of ligands containing a soft donor center.[2] They proved to be highly effective catalysts for the enantioselective addition of diethylzinc to aldehydes.

These findings together with the potential of chiral organochalcogen compounds as catalysts for a number of transition metal mediated carbon-carbon bond forming reactions in asymmetric synthesis,[3,4] ensure the continued importance for the development of improved catalysts derived from non-toxic and inexpensive starting materials. With this aim, together with our interest in obtaining sulfur and selenium catalysts,[2,5b] we report now the preparation of new sulfides **1** and selenides **2** containing oxazolidines (Scheme 1) for catalytic enantioselective reactions.



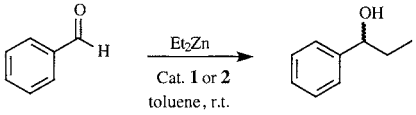
Scheme 1

The chiral sulfides **1** and selenides **2** containing oxazolidines were readily prepared from amino acids in a two step synthesis (Scheme 1). In the first step, amino acids were reduced with $NaBH_4/I_2$ or $LiAlH_4$ to give the desired amino alcohols. The reaction of amino alcohols with paraformaldehyde and the respective organochalcogenol furnished the desired chiral chalcogenides **1** or **2** in satisfactory yields (Table 1). Our ligands are stable for a long period when stored in the refrigerator.

Table 1 Preparation of Compounds **1** or **2** from Amino Alcohols

Catalyst	R	n	Yield (%)
1a	$PhCH_2$	0	59
1b	$PhCH_2$	1	61
1c	Me_2CH	1	65
2a	$PhCH_2$	0	57
2b	$PhCH_2$	1	55
2c	Me_2CH	1	41

With these ligands in hand, we chose one classical catalytic enantioselective reaction to test their behavior. Thus, ligands **1** and **2** were tested as catalysts for the diethylzinc addition to benzaldehyde (Scheme 2).



Scheme 2

With sulfide **1a** containing the SPh moiety (Table 2, entry 1), we obtained a good yield but a low enantiomeric excess. A similar result was obtained with the analogous Se compound **2a** (Table 2, entry 4). The change of the SPh-moiety into a SBn-moiety **1b** had a negative effect on the enantiomeric excess (Table 2, entry 2). The contrary was observed in the case of the Se-moiety **2b** (Table 2, entry 5). By using 10 mol% of selenide **2b** at room temperature, we obtained the desired (*R*)-1-phenylpropanol in 80% ee. At 0 °C, both the chemical yield and ee decreased. A dramatic decrease of the ee was observed when we changed the benzyl-substituent of the oxazolidine ring to an *iso*-

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propyl (Table 2, entries 5 and 6). This result is difficult to rationalize and we do not yet understand the reasons.

Although the actual catalytic active species are not determined for these ligands, the transition state model shown in Figure 1 is suggested for the enantioselective catalysts, assuming the dinuclear Zn complexes.[6]

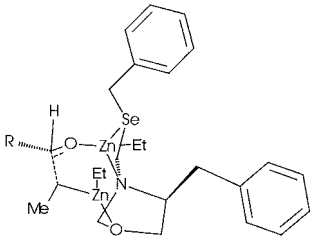
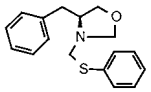
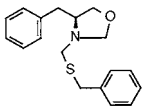
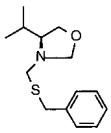
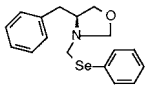
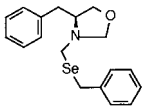
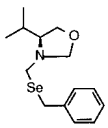


Figure 1 Possible model to account for the observed stereochemistry

Table 2 Enantioselective Addition of Diethylzinc to Benzaldehyde According to Scheme 2

	Catalyst	Temp. (°C)	Time (h)	Yield (%)	ee (%)[a,b] (Config.)
1	 **1a**	r.t.	20	97	30 [*R*-(+)]
		0	60	51	35[*R*-(+)]
2	 **1b**	r.t.	20	95	13 [*R*-(+)]
		0	60	30	14 [*R*-(+)]
3	 **1c**	r.t.	20	75	37 [*R*-(+)]
		0	60	42	35 [*R*-(+)]
4	 **2a**	r.t.	20	99	31 [*R*-(+)]
		0	60	52	30 [*R*-(+)]
5	 **2b**	r.t.	20	61	80 [*R*-(+)]
		0	60	25	45 [*R*-(+)]
6	 **2c**	r.t.	20	83	33 [*R*-(+)]
		0	60	48	32 [*R*-(+)]

[a] The ee's were determined by GC using a (2,6-Me,3-Pe)-β-CD-Column.
[b] Assigned by comparison of the sign of optical rotation reported.[4]

In summary, we have reported a new class of chiral chalcogenides ligands prepared in an easy synthesis from commercial and inexpensive amino acids. Preliminary results from their behavior as ligands to enantioselective addition of diethylzinc to benzaldehyde, showed a great catalytic potential. Further studies dealing with their application in asymmetric catalysis are in progress.

Reagents were used as received unless otherwise stated. All manipulations were carried out under N_2. The glassware was flame dried prior to use for the alkylation reactions. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 200 and 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. GC was performed using a Varian 3800 gas chromatograph with (2,6-Me-3-Pe)-β-cyclodextrin column as chiral stationary phase for ee determinations of the secondary alcohols obtained. The purity of the ligands was determined by HPLC analyses using a DAICEL CHIRALCEL OD-H column (0.46 cm ∅ × 25 cm), degassed hexane–propan-2-ol (99:1), 0.5 mL/min as the mobile phase, and detection with a UV-monitor (254).

Chalcogenides 1 and 2; General Procedure

In a 50 mL round-bottomed flask fitted with a Dean–Stark apparatus was added benzene (30 mL), the respective amino alcohol (2.19 mmol), paraformaldehyde (3.3 mmol) and *p*-toluenesulfonic acid (catalytic amount). The mixture was refluxed for 3 h. Additional amounts of paraformaldehyde (3.3 mmol) and the respective chalcogenol (3 mmol) were then added and the mixture was refluxed for an additional 3 h. The benzene was removed under vacuum and the residue was dissolved in CH_2Cl_2 (30 mL). The CH_2Cl_2 solution was washed with aq 0.5 N NaOH, dried ($MgSO_4$), filtered and the solvent was removed under vacuum. The product was purified by flash chromatography (silica gel) by eluting with EtOAc–hexane (1:9) to afford the respective compound **1** or **2**.

1a

$[\alpha]_D^{20}$ +11.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.01 (m, 10 H), 4.50 (d, 1 H, *J* = 4.44 Hz), 4.46 (d, 1 H, *J* = 4.44 Hz), 4.37 (d, 1 H, *J* = 13.04 Hz), 4.28 (d, 1 H, *J* = 13.04 Hz) 3.97–3.88 (m, 1 H), 3.55–3.40 (m, 2 H), 2.81 (dd, 1 H, *J* = 6.54, 13.34 Hz), 2.56 (dd, 1 H, *J* = 6.54, 13.34 Hz).

^{13}C NMR (50 MHz): δ = 138.42, 136.50, 131.30, 129.03, 128.99, 128.40, 126.71, 126.34, 84.43, 71.19, 61.58, 60.17, 39.33.

Anal. Calcd for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.91. Found: C, 71.57; H, 6.73; N, 4.94.

1b

$[\alpha]_D^{20}$ +13.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.28–7.13 (m, 10 H) 4.48 (d, 1 H, *J* = 5.72 Hz), 4.45 (d, 1 H, *J* = 5.72 Hz), 3.91 (m, 1 H), 3.67–3.55 (m, 4 H), 3.50–3.36 (m, 2 H), 2.84 (dd, 1 H, *J* = 7.32, 13.57 Hz), 2.62 (dd, 1 H, *J* = 7.32, 13.57 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.91, 129.76, 129.43, 128.88, 127.34, 126.87, 85.35, 70.36, 63.76, 56.64, 40.39, 34.75.

Anal. Calcd for $C_{18}H_{21}NOS$. C, 72.20; H, 7.07; N, 4.68;. Found: C, 72.22; H, 7.10; N, 4.70.

1c

$[\alpha]_D^{20}$ +51.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5 H), 4.47 (d, 1 H, *J* = 5.86 Hz), 4.25 (d, 1 H, *J* = 5.86 Hz), 3.93 (t, 1 H, *J* = 8.05 Hz), 3.81 (s, 2 H), 3.76–3.71 (m, 2 H), 3.44 (dd, 1 H, *J* = 5.86, 8.05 Hz), 2.77 (dd, 1 H, *J* = 8.05, 13.53 Hz), 1.57 (m, 1 H), 0.97 (d, 3 H, *J* = 6.60 Hz), 0.84 (d, 3 H, *J* = 6.60 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 134.46, 128.88, 128.39, 126.87, 85.23, 68.23, 57.95, 34.81, 31.15, 19.97, 18.48.

Anal. Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57. Found: C, 66.92; H, 8.46; N, 5.60.

2a

$[\alpha]_D^{20}$ +10.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.57–6.96 (m, 10 H), 4.65 (d, 1 H, *J* = 11.77 Hz), 4.51 (d, 1 H, *J* = 11.77 Hz), 4.44 (d, 1 H, *J* = 3.70 Hz), 4.34 (d, 1 H, *J* = 3.70 Hz), 3.93 (m, 1 H), 3.58–3.29 (m, 2 H), 2.78 (dd, 1 H, *J* = 6.50, 13.35 Hz), 2.53 (dd, 1 H, *J* = 7.66, 13.35 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.17, 134.23, 131.52, 129.14, 128.95, 128.39, 127.07, 126.36, 85.07, 71.74, 61.27, 56.89, 38.79.

Anal. Calcd for $C_{17}H_{19}NOSe$: C, 61.45; H, 5.76; N, 4.22. Found: C, 61.41; H, 5.73; N, 4.20

2b

$[\alpha]_D^{20}$ +23.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.15 (m, 10 H), 4.40 (d, 1 H, *J* = 4.38 Hz), 4.25 (d, 1 H, *J* = 4.38 Hz), 4.15 (d, 1 H, *J* = 11.75 Hz), 4.01 (d, 1 H, *J* = 11.75 Hz), 3.92 (dd, 1 H, *J* = 7.08, 8.04 Hz), 3.73 (s, 2 H), 3.50 (dd, 1 H, *J* = 5.88, 8.04 Hz), 3.28 (m, 1 H), 2.81 (dd, 1 H, *J* = 6.96, 13.53 Hz), 2.59 (dd, *J* = 7.34, 13.53 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.63, 138.43, 128.97, 128.78, 128.47, 128.42, 126.65, 126.38, 85.33, 71.08, 62.41, 51.17, 39.21, 26.97.

Anal. Calcd for $C_{18}H_{21}NOSe$: C, 62.43; H, 6.11; N, 4.04. Found: C, 62.46; H, 6.13; N, 4.06

2c

$[\alpha]_D^{20}$ +53.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5 H), 4.29 (d, 1 H, *J* = 11.60 Hz), 4.10 (d, 1 H, *J* = 11.60 Hz), 3.95–3.87 (m, 1 H), 3.81 (s, 2 H), 3.76–3.71 (m, 2 H), 3.44 (dd, 1 H, *J* = 6.00, 8.20 Hz), 2.77 (dd, 1 H, *J* = 6.00, 13.40 Hz), 1.57 (m, 1 H), 0.97 (d, 3 H, *J* = 6.60 Hz), 0.84 (d, 3 H, *J* = 6.60 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 134.46, 128.88, 128.39, 126.87, 85.23, 68.23, 57.95, 34.81, 31.15, 19.97, 18.48.

Anal. Calcd for $C_{14}H_{21}NOSe$: C, 56.37; H, 7.10; N, 4.70. Found: C, 56.39; H, 7.13; N, 4.72.

Asymmetric Addition of Diethylzinc to Benzaldehyde; General Procedure

In a 25 mL flask containing toluene (7 mL), benzaldehyde (3 mmol, 0.32 g) and the catalyst (10 mol%) was slowly injected a 1 M solution of diethylzinc in hexane (5 mmol, 5 mL) with constant stirring. The stirring was continued for the time and the temperature indicated in Table 2. Finally, the temperature was adjusted to 0 °C (ice-bath) and aq 1 N HCl (5 mL) was slowly added (10 min) with continuous stirring. The organic layer was separated and washed with of aq 1 N HCl (2 × 8 mL). After drying (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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