# Catalytic Enantio- and Diastereo-selective Addition of Diethylzinc to Racemic α-Thio- and α-Seleno-aldehydes: Asymmetric Synthesis of Optically Active Vicinal Thio- and Seleno-alcohols

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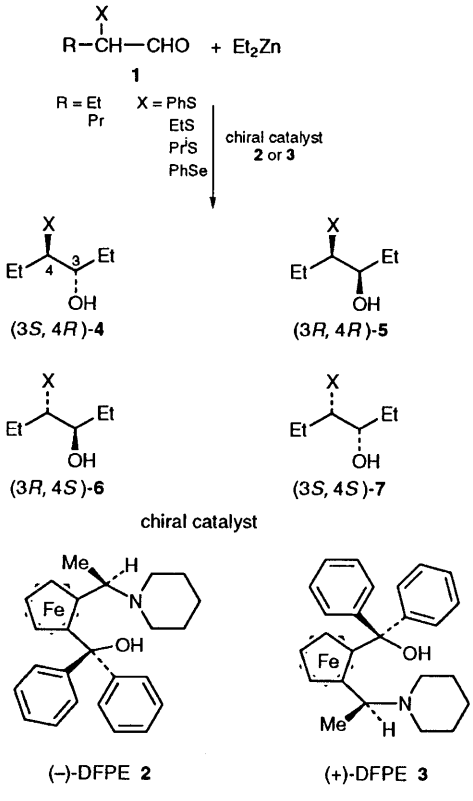
Chiral 1,2-disubstituted ferrocenyl amino alcohols **2** and **3** [(−)- and (+)-DFPE] catalysed enantio- and diastereo-selective addition of diethylzinc reagent to racemic α-thio- and α-seleno-aldehydes **1** to afford optically active vicinal thio- and seleno-alcohols **4–7**. In the presence of (*R,S*)-catalyst **2**, the *R*-enantiomer of **1** selectively reacted with diethylzinc to afford vicinal (3*S*,4*R*)-thio- and seleno-alcohols **4** with high diastereoselectivity. On the other hand, ethylation of the *S*-enantiomer of **1** proceeded with low selectivity and low yields. Similarly, the (*S,R*)-catalyst **3** [(+)-DFPE] catalysed ethylation of racemic α-thioaldehydes **1** to afford vicinal (3*R*,4*S*)-thioalcohols **6** with high stereoselectivity. The recovered unchanged aldehydes **1** were completely racemized after work-up.



The importance of optically active vicinal thio- and seleno-alcohols has been recognized in view of their potential as intermediates for enantiomerically pure epoxides, which may be used in the synthesis of more complex enantiomerically enriched compounds.[1] The synthesis of racemic vicinal thio-alcohols by way of stereoselective reduction of α-thio- and α-seleno-ketones has been reported,[2] whereas few asymmetric syntheses of highly optically active vicinal thioalcohols are known.[3]

We have reported the highly enantioselective addition of dialkylzincs to achiral aldehydes catalysed by chiral 1,2-disubstituted ferrocenyl amino alcohols which shows high enantioselectivity even in the alkylation of α-branched aliphatic aldehydes.[4] In order to develop further the characteristics of our catalysts, the ethylation of aldehydes substituted with an α-thio- and α-seleno group has been investigated.

We here disclose the asymmetric synthesis of the vicinal thio- and seleno-alcohols **4–7** based on the highly enantio- and diastereo-selective addition of diethylzinc reagent to racemic α-thio- and α-seleno-aldehydes **1**, catalysed by (−)-DFPE **2** and (+)-DFPE **3** (Scheme 1). Although the enantioselective addition of dialkylzinc reagents to achiral aldehydes using chiral catalysts has been well investigated,[5] there are no reports of the catalytic enantio- and diastereo-selective dialkylzinc addition to aldehydes with a chiral centre, except for the alkylation of α-methyl-[6,7], α-chloro-[7] and β-alkoxy-aldehydes.[8]




**Scheme 1**

## Results and Discussion

The reaction of diethylzinc with racemic α-thio- and α-seleno-aldehydes **1** was carried out in the presence of (−)-DFPE **2** or (+)-DFPE **3** (5–50 mol%) in hexane at room temperature for 12–16 h. The results are summarized in Table 1.

We first examined the ethylation of α-phenylthiobutyraldehyde in the presence of various catalytic amounts of (−)-DFPE **2** or (+)-DFPE **3** (entries 1–7). Although the yield and the diastereoselectivity increased with increased amounts of the catalyst up to 25 mol% (entry 3 and 6), the use of 50 mol% of the catalyst showed no enhanced activity (entry 7). When **2** was used, the diastereoisomer ratio (**4**/**5**) attained for ethylation of the *R*-enantiomer of **1** was much superior to that (**6**/**7**) for the *S*-enantiomer of **1**, as well as for the ratio of non-catalysed ethyl Grignard reaction (entry 8). The *R*-enantiomer was consumed faster than the *S* (**4** + **5**/**6** + **7**), but the recovered aldehyde **1** was not *S* enriched but completely racemized owing to the presence of highly acidic α-hydrogen. Similarly, the enantio- and diastereo-selective addition of diethylzinc to racemic α-ethylthio- and α-isopropylthio-butyraldehydes was examined (entries 9–14). The diastereoselectivity was somewhat lower than that for the reaction of the aldehyde with a phenylthio substituent. The ethylation of (α-phenylthio)valeraldehyde in the presence of 25 mol% of **2** afforded 100% d.e. for the *R*-enantiomer and the largest reactivity ratio between the *R*- and *S*-enantiomers was attained (entry 17). The ethylation of (α-phenylseleno)butyraldehyde with **2** showed similar high

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**Table 1** Enantio- and diastereo-selective addition of diethylzinc to racemic α-thio- and α-seleno-aldehydes **1** using (−)-DFPE **2** or (+)-DFPE **3**[a]

| | Aldehyde **1** | | | Product | | | |
|---|---|---|---|---|---|---|---|
| Entry | R | X | Catalyst (mol %) | Yield[b] (%) | **4**/**5**[c] | **6**/**7**[c] | **4** + **5**/**6** + **7**[c] |
| 1 | Et | PhS | **2** (5) | 23 | 96:4 | 61:39 | 82:18 |
| 2 | Et | PhS | **2** (10) | 34 | 99:1 | 58:42 | 87:13 |
| 3 | Et | PhS | **2** (25) | 49 | 99:1 | 46:54 | 87:13 |
| 4[d] | Et | PhS | **2** (5) | 30 | 96:4 | 55:45 | 80:20 |
| 5 | Et | PhS | **3** (5) | 18 | 59:41 | 94:6 | 17:83 |
| 6 | Et | PhS | **3** (25) | 53 | 35:65 | 98:2 | 18:82 |
| 7 | Et | PhS | **3** (50) | 46 | 27:73 | 99:1 | 22:78 |
| 8[e] | Et | PhS | – | 88 | 82:18 | 82:18 | 50:50 |
| 9 | Et | EtS | **3** (5) | 39 | 63:37 | 96:4 | 19:81 |
| 10 | Et | EtS | **3** (10) | 19 | 57:43 | 94:6 | 21:79 |
| 11 | Et | EtS | **3** (25) | 24 | 57:43 | 96:4 | 14:86 |
| 12[e] | Et | EtS | – | 90 | 80:20 | 80:20 | 50:50 |
| 13 | Et | Pr$^i$S | **3** (10) | 20 | 48:52 | 88:12 | 25:75 |
| 14 | Et | Pr$^i$S | **3** (25) | 14 | 41:59 | 93:7 | 17:83 |
| 15[e] | Et | Pr$^i$S | – | 85 | 80:20 | 80:20 | 50:50 |
| 16 | Pr | PhS | **2** (5) | 15 | 98:2 | 56:44 | 84:16 |
| 17 | Pr | PhS | **2** (25) | 38 | 100:0 | 45:55 | 90:10 |
| 18[e] | Pr | PhS | – | 92 | 86:14 | 86:14 | 50:50 |
| 19 | Et | PhSe | **2** (5) | 10 | 98:2 | 64:36 | 89:11 |
| 20 | Et | PhSe | **2** (25) | 68 | 98:2 | 42:58 | 67:33 |
| 21[e] | Et | PhSe | – | 93 | 92:8 | 92:8 | 50:50 |

[a] Unless otherwise noted, the reaction was carried out in hexane at room temperature with 1.6 equiv. of diethylzinc to aldehydes. [b] Isolated yield. [c] Determined by $^{19}$F NMR spectrum analysis of the corresponding (*S*)-MTPA ester: see Experimental section. [d] 2.5 Equiv. of diethylzinc to aldehyde was used. [e] The reaction was conducted with EtMgBr.

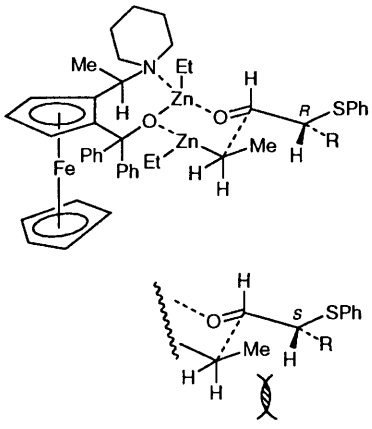


**Fig. 1**

diastereoselectivity for the *R*-enantiomer and much lower selectivity for the *S*-enantiomer.

The racemic aldehyde **1** was recovered from all the reactions after work-up. Although the EtMgBr reaction afforded good yields of the thio- and seleno-alcohols (entries 8, 12, 15, 18, 21), the addition of EtMgBr after diethylzinc reaction did not increase the thioalcohol yield. Therefore, unchanged aldehyde **1** is considered to be converted into the enolate form during the diethylzinc reaction. In addition to a marked tendency for the substrate aldehydes to enolize, the low product yields in the reactions of low catalyst concentrations may be ascribed to the strong coordination of the product bidentate alcohols that deactivate the diethylzinc–DFPE complex.

A plausible intermediate for the enantio- and diastereo-selective addition of diethylzinc to α-thioaldehyde catalysed by **2** is shown in Fig. 1. When (−)-DFPE **2** is used in the ethylation of the racemic aldehyde **1**, the *R*-enantiomer reacts faster than the *S*- and the newly produced asymmetric centre from (*R*)-**1** is of *S*-configuration.* This stereochemical property can be reasonably explained by considering the 7/6-fused bicyclic intermediate depicted. (*R*)-**1** Has a lower steric hindrance than (*S*)-**1** in the reaction complex and ethylzinc preferentially attacks from the *Si* face of (*R*)-**1** to afford the *S*-configuration. Therefore, (*R*)-**1** reacts faster than (*S*)-**1** to afford (3*S*,4*R*)-**4**.

## Experimental

*General.*—$^1$H NMR spectra were measured on a Varian XL-200 FT NMR spectrometer in $CDCl_3$. $^{19}$F NMR spectra were measured on a Hitachi R-90 FT NMR spectrometer in $CDCl_3$. Tetramethylsilane for $^1$H NMR and trichlorofluoromethane for $^{19}$F NMR were used as internal standards. IR spectra were measured on a JASCO A-102 spectrometer. HPLC analyses were carried out on a JASCO TRIROTAR-II equipped with a chiral column (Chiralcel OB, Daicel Chemical Industries) and a JASCO UVIDEC 100 UV detector. GLC analyses were carried out on a Shimazu GC-14A equipped with a PEG 20M polar 50 m capillary column. Secondary alcohols obtained by catalytic ethylation and an EtMgBr reaction were converted into (*S*)-MTPA (α-methoxy-α-trifluoromethyl-α-phenylacetic acid) esters with MTPA chloride,[9] and the diastereoisomer ratios of the corresponding (*S*)-MTPA esters were determined by $^{19}$F NMR analyses. $[\alpha]_D$ Values are given in units of $10^{-1}$ deg $cm^2$ $g^{-1}$.

*Materials.*—(−)-And (+)-DFPE (**2** and **3**)[4] and α-thio-[10] and α-seleno-aldehydes[11] were prepared according to the reported procedure. Diethylzinc in hexane was obtained from Kanto Chemical Co. (*S*)-(−)-MTPA was obtained from Nakalai Tesque and converted into the acid chloride by the literature procedure.[12] (−)-Menthyl chloroformate (MCF) was obtained from Aldrich Co. *trans*- and *cis*-3,4-Epoxyhexanes were prepared from *trans*- and *cis*-hex-3-enes with MCPBA by a conventional procedure.

*General Procedure for Enantio- and Diastereo-selective Addition of Diethylzinc to α-Thio- and α-Seleno-aldehydes.*—The

* Using (−)-DFPE **2**, $R_2Zn$ reacts from the *Si* face of achiral aldehydes to afford (*S*)-alcohols: see ref. 4.

**Table 2** $\delta_F$ Values for (*S*)-MTPA esters of thio- and seleno-alcohols **4–7**

| (*S*)-MTPA ester of | $\delta_F$ value (ppm) | | | |
|---|---|---|---|---|
| | (3*S*,4*S*)-**7** | (3*S*,4*R*)-**4** | (3*R*,4*R*)-**5** | (3*R*,4*S*)-**6** |
| 4-Phenylthiohexan-3-ol | −71.47 | −71.62 | −71.74 | −71.91 |
| 4-Ethylthiohexan-3-ol | −71.55 | −71.65 | −71.76 | −71.83 |
| 4-Isopropylthiohexan-3-ol | −71.62 | −71.84 | −71.90 | −71.95 |
| 4-Phenylthioheptan-3-ol | −71.42 | −71.60 | −71.70 | −71.93 |
| 4-Phenylselenohexan-3-ol | −71.52 | −71.60 | −71.74 | −71.80 |

following reaction (entry 6 in Table 1) represents the general procedure. Diethylzinc (1 mol $dm^{-3}$ hexane solution; 3.2 $cm^3$, 3.2 mmol) was added to a solution of (+)-DFPE **3** (240 mg, 0.5 mmol) in hexane (2 $cm^3$) at room temperature. After 10 min, α-phenylthiobutyraldehyde (360 mg, 2.0 mmol) in hexane (2 $cm^3$) was added and the whole mixture was stirred at room temperature for 12 h. The reaction was quenched by the addition of aqueous hydrochloric acid (1 mol $dm^{-3}$). The products were extracted with diethyl ether, and the extracts were washed with brine, dried ($Na_2SO_4$) and evaporated under reduced pressure. The residue was purified by TLC on silica gel ($CH_2Cl_2$) yielding a mixture of 4-phenylthiohexan-3-ol (**4–7**) in 53% total yield. The ratio of the isomers was analysed by the method described below. The unchanged aldehyde was also obtained in 40% recovery which showed 0% e.e. by HPLC analysis: column; Chiralcel OB, 4.6 × 250 mm; detection, 254 nm light; eluent, 0.2% propan-2-ol in hexane; flow rate 0.2 $cm^3$ $min^{-1}$; $t_R$ (min), 72.73 and 78.56.

4-*Phenylthiohexan*-3-*ol* (entries 1–8 in Table 1): [Found: C, 68.3; H, 8.7%; $M^+$, 210. $C_{12}H_{18}OS$ requires C, 68.52; H, 8.63%; *M*, 210]; $\nu_{max}$(neat)/$cm^{-1}$ 3430, 3070, 2980, 2950, 2880, 1580, 1460, 1440, 1380, 1230, 1090, 1070, 1030, 970, 820, 740 and 690; $\delta_H(CDCl_3)$ 0.97 (3 H, t, *J* 7.4), 1.12 (3 H, t, *J* 7.4), 1.43–.1.70 (3 H, m), 1.70–1.94 (1 H, m), 2.30 (1 H, br s), 3.15 (1 H, dt, *J* 4.0 and 10.0), 3.56–3.70 (1 H, m), 7.20–7.42 (3 H, m), 7.43–7.58 (2 H, m).

4-*Ethylthiohexan*-3-*ol* (entries 9–12 in Table 1): [Found: C, 59.0; H, 11.3%; $M^+$, 162. $C_8H_{18}OS$ requires C, 59.21; H, 11.18%; *M*, 162]; $\nu_{max}$(neat)/$cm^{-1}$ 3440, 2970, 2940, 2880, 1450, 1380, 1300, 1265, 1235, 1110, 1090, 1070, 1050, 970, 920, 870, 820, 760 and 730; $\delta_H(CDCl_3)$ 0.99 (3 H, t, *J* 7.2), 1.05 (3 H, t, *J* 7.2), 1.26 (3 H, t, *J* 7.5), 1.35–1.60 (3 H, m), 1.64–1.85 (1 H, m), 2.41 (1 H, d, *J* 5.0), 2.57 (2 H, q, *J* 7.2), 2.58–2.76 (1 H, m) and 3.54–3.74 (1 H, m).

4-*Isopropylthiohexan*-3-*ol* (entries 13–15 in Table 1): [Found: C, 61.05; H, 11.7; $M^+$, 176. $C_9H_{20}OS$ requires C, 61.31; H, 11.43%; *M*, 176]; $\nu_{max}$(neat)/$cm^{-1}$ 3450, 2970, 2930, 2880, 1460, 1380, 1360, 1300, 1240, 1150, 1100, 1070, 1050 and 970; $\delta_H(CDCl_3)$ 1.00 (3 H, t, *J* 7.5), 1.05 (3 H, t, *J* 7.5), 1.28 (3 H, d, *J* 4.0), 1.31 (3 H, d, *J* 4.0), 1.36–1.60 (3 H, m), 1.60–1.84 (1 H, m), 2.50 (1 H, br s), 2.64–2.78 (1 H, m), 2.86–3.06 (1 H, m), 3.58–3.68 (1 H, m).

4-*Phenylthioheptan*-3-*ol* (entries 16–18 in Table 1): [Found: C, 69.4; H, 9.2%; $M^+$, 224. $C_{13}H_{20}OS$ requires C, 69.59; H, 8.98%; *M*, 224]; $\nu_{max}$(neat)/$cm^{-1}$ 3440, 3060, 2970, 2940, 2880, 1580, 1470, 1450, 1440, 1380, 1300, 1220, 1080, 1020, 970, 740 and 690; $\delta_H(CDCl_3)$ 0.94 (6 H, t, *J* 7.2), 1.36–1.90 (6 H, m), 2.36 (1 H, br s), 3.14–3.34 (1 H, m), 3.46–3.70 (1 H, m), 7.16–7.40 (3 H, m) and 7.40–7.60 (2 H, m).

4-*Phenylselenohexan*-3-*ol* (entries 19–21 in Table 1): [Found: C, 56.4; H, 7.2%; $M^+$, 258. $C_{12}H_{18}OSe$ requires C, 56.03; H, 7.05%; *M*, 258]; $\nu_{max}$(neat)/$cm^{-1}$ 3430, 3050, 2970, 2940, 2880, 1580, 1480, 1460, 1440, 1375, 1300, 1230, 1180, 1105, 1065, 1040, 1020, 1000, 960, 900, 800, 740 and 690; $\delta_H(CDCl_3)$ 0.96 (3 H, t, *J* 7.4), 1.11 (3 H, t, *J* 7.2), 1.40–1.94 (5 H, m), 3.25 (1 H, dt, *J* 4.0 and 9.6), 3.50–3.64 (1 H, m), 7.20–7.38 (3 H, m) and 7.52–7.68 (2 H, m).

*Determination of the Diastereoisomer Ratio of Ethylated Products* **4–7**.—*erythro*-4-Phenylthiohexan-3-ol (**4** and **6**) and *threo*-4-phenylthiohexan-3-ol (**5** and **7**) were prepared from *trans*- and *cis*-3,4-epoxyhexene, respectively, by the literature procedure[13] and converted into the (*S*)-MTPA esters with MTPA chloride.

MTPA ester of *erythro*-4-phenylthiohexan-3-ol (**4** and **6**): $\delta_F(CDCl_3)$ −71.62 and −71.91.

MTPA ester of *threo*-4-phenylthiohexan-3-ol (**5** and **7**): $\delta_F(CDCl_3)$ −71.47 and −71.74.

The diastereoisomer ratios of the MTPA esters of the ethylated products **4–7** determined by $^{19}F$ NMR analyses are shown in Table 1. The $\delta_F$ values of each MTPA ester are summarized in Table 2.

*Assignment of the Configuration*.—In a manner similar to the procedure for ethylation of α-thio- and α-seleno-aldehydes, enantioselective addition of diethylzinc to butyraldehyde with 5 mol% of **2** was carried out for 3 h to afford (*S*)-hexan-3-ol.

(S)-*Hexan*-3-*ol*: yield, 88% $[\alpha]_D^{22}$ +4.92 (*c* 7.62 in EtOH) [lit.,[14] $[\alpha]_D^{20}$ −8.21 (*c* 11.5 in EtOH) for *R* isomer]. This alcohol was converted into the menthyl carbonate with (−)-MCF by the reported procedure[15] and the optical purity was determined as 58% e.e. by GLC analysis: detection, flame ionization detector; carrier gas, $N_2$ (1.5 kg $cm^{-2}$); column temperature, 150 °C; $t_R$ (min), *S* isomer 29.5, *R* isomer 30.2.

4-Phenylselenohexan-3-ol from entry 20 in Table 1 was converted into the menthyl carbonate with (−)-MCF and then deselenized with tributyltin hydride and AIBN by the reported procedure[16] yielding (*S*)-hexan-3-ol menthyl carbonate ester whose optical purity was determined to be 64% e.e. From this result and the diastereoisomer ratio determined by $^{19}F$ NMR spectroscopy, the ratio of (3*S*,4*R*)-**4**, (3*R*,4*R*)-**5**, (3*R*,4*S*)-**6** and (3*S*,4*S*)-**7** was determined as 65.7, 1.3, 13.9 and 19.1. The configuration of other thioalcohols was assigned from above results.

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