Catalytic Activity of Isoborneol-Derived Sulfides in Asymmetric Addition of Diethylzinc to Benzaldehyde

Yoshitsugu ARAI,* Naoya NAGATA, and Yukio MASAKI

Gifu Pharmaceutical University, 5–6–1 Mitahora-Higashi, Gifu 502, Japan.
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Enantioselective addition of diethylzinc to benzaldehyde in the presence of easily available, β-hydroxysulfides 1 was investigated. The use of a catalytic amount of 1 gave (*S*)-1-phenylpropanol in excellent yield with high enantioselectivity, ranging from 85 to 88% ee.

Key words β-hydroxysulfide; diethylzinc; catalyst; chiral ligand; (*S*)-1-phenylpropanol

Enantioselective addition of diethylzinc to prochiral aldehydes using an optically active ligand as a chiral auxiliary has been widely exploited.[1] Of the ligands used, those with two heteroatoms such as nitrogen and oxygen atoms incorporated in the 1,2-position of the chiral molecule effected highly enantioselective reactions. This is because these two heteroatoms should coordinate tightly with the zinc atom of diethylzinc, resulting in a conformationally rigid, 5-membered transition state.[2] However, little work has been done on additions using β-hydroxy sulfur-containing compounds as bidentate ligands.[2j] We focused on the use of chiral, β-hydroxysulfides as chiral ligands for the addition reaction.

We selected easily available, chiral sulfides **1** as ligands for the catalytic addition. β-Hydroxy sulfides **1a**, **b**[3] are easily obtained by the literature method,[4] which was also applied to the preparation of **1c**.

The reactions of diethylzinc and benzaldehyde were examined in the presence of **1**. The influence of the sulfur substituent and the amount of the catalyst were also investigated. The results are summarized in the table.

All the reactions were carried out by adding diethylzinc (1 M solution in hexane) to a solution of the ligand **1** in dry toluene or hexane at 0 °C. After being stirred for 30 min, the mixture was treated with benzaldehyde at −78 °C, then the resulting yellow mixture was allowed to stand for an appropriate time (shown in the table) at room temperature. Benzyl alcohol was produced as a by-product in the reaction in some cases.

As can be seen from the table, good results (85—88% ee.) were obtained by using 20 mol% of the sulfide **1** (entries 6—8), although lower optical purities of the alcohol **2** were observed with a smaller amount (5 mol%) of the ligands (entries 1—4). Furthermore, it was found that the enantioselectivity of the reaction might not depend upon the *S*-substituent on the ligand. A proper choice of solvent, *i.e.* hexane, is important for realizing high enantioselectivity. The use of toluene gave lower enantioselectivity. A longer reaction time (≥48 h) resulted in not only a decrease of the enantioselectivity, but also extensive decomposition of the ligand **1** (entries 3, 5). It is assumed that a peroxide such as $(EtO_2)_2Zn$,[5] produced from diethylzinc with a small amount of oxygen in the reaction vessel, would oxidize the sulfanyl group in ligand **1** to give rise to the corresponding sulfoxide **3**[4] in a

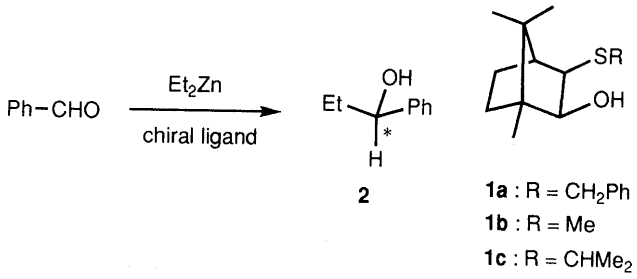


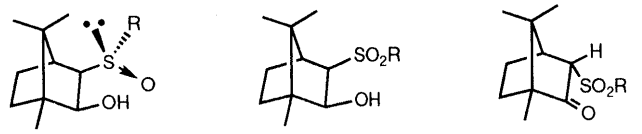
Chart 1

Table 1. Enantioselective Addition of Diethylzinc to Benzaldehyde in the Presence of the Sulfides **1a—c**

Entry	Reaction conditions[a]			Yield[b] (%)	Recovery of ligand **1** (%)	ee[c] (%)	Configuration of **2**
	Ligand (mol%)	Solvent	Time (h)				
1	**1a** (5)	Hexane	11	92	54	46	*S*
2	**1b** (5)	Hexane	11	86	63	54	*S*
3	**1c** (5)	Toluene	48	38	0	39	*S*
4	**1c** (5)	Hexane	11	88	91	48	*S*
5	**1a** (20)	Toluene	48	83	0	77	*S*
6	**1a** (20)	Hexane	13	94	98	88	*S*
7	**1b** (20)	Hexane	12	98	74	85	*S*
8	**1c** (20)	Hexane	10	94	69	86	*S*
9	**1a** (100)	Hexane	10	76	71	86	*S*
10	**1b** (100)	Hexane	9	90	68	84	*S*
11	**1c** (100)	Hexane	13	94	78	81	*S*

a) The reaction was carried out by using a combination of 1.2 mmol of benzaldehyde and 2.4 mmol of diethylzinc. *b*) Isolated yield of **2**. *c*) Enantiomeric excess (ee) and absolute configuration of **2** were determined by comparison with an authentic sample on chiral HPLC.

* To whom correspondence should be addressed.



3a : R = CH_2Ph **4a** : R = CH_2Ph **5a** : R = CH_2Ph
3b : R = Me **4b** : R = Me **5b** : R = Me
3c : R = $CHMe_2$ **4c** : R = $CHMe_2$ **5c** : R = $CHMe_2$

Chart 2

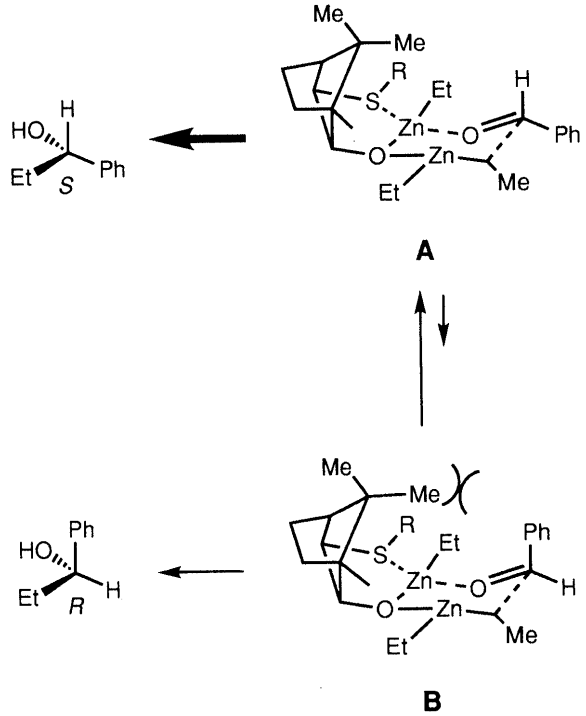


Chart 3

variable ratio. Interestingly, the oxidation of **1** to **3** proceeded diastereoselectively. In some cases, very small amounts of the sulfone **4** and the sulfonyl ketone **5** were also produced in capricious yield. The structures of **4a** and **5a** were confirmed by preparing these compounds independently from **3a** and **4a**, respectively. The structures of other by-products were tentatively assigned.

The absolute configuration of **2** obtained in the reactions of **1** was shown to be *S*. These results can be explained by the following mechanism (Chart 3), which is consistent with the observed selectivity, and also with the previous proposal by Kitamura and Noyori.[2e] The cyclic transition state **A** would be more favorable than the intermediate **B**, which is unstable due to the steric repulsion between the Me group in the bornyl residue and the phenyl group in benzaldehyde.

In summary, we have investigated the use of easily available, camphor-derived sulfides as chiral ligands for the asymmetric addition of diethylzinc to benzaldehyde to provide (*S*)-1-phenylpropanol with good enantioselectivity. Further exploration of the addition by the use of the other sulfur-containing ligands is in progress in this laboratory.

Experimental

Melting points were taken with a Yanagimoto micro melting-point apparatus and are uncorrected. Boiling points are also uncorrected. IR spectra were measured as films or in $CHCl_3$ solution on a JASCO IRA-1 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GX270 (270 NHz) spectrometer with $CDCl_3$ as the solvent; *J* values are in hertz (Hz). Tetramethylsilane was used as an internal standard. Mass spectra were recorded with a JEOL JMS D-300 spectrometer. Optical rotations were measured on a JASCO DIP-360 digital polarimeter in $CHCl_3$ solution. All organometallic and low temperature reactions were carried out in oven-dried glassware under a slight positive pressure of argon. All solvents were distilled prior to use. Extracts were dried over anhydrous $MgSO_4$ before evaporation of solvents in a rotary evaporator. Flash column chromatography was performed with Merck 230—400 mesh silica gel. Chiral HPLC analyses were carried out on a Shimadzu LC-6A pump using a chiral column, Chiralcel OD® (Daicel Chemical Industries Ltd), with monitoring of the 254 nm. Peak ratios on HPLC were measured with a Shimadzu integrator (Chromatopac C-R3A).

(1*R*,2*S*)-*exo*-3-(Isopropylsulfanyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (1c) Di-isobutylaluminum hydride (9.8 ml, 1.02 M in toluene) was added dropwise to a solution of (1*R*)-*exo*-3-(isopropylsulfanyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (1.70 g, 7.5 mmol), prepared from (+)-camphor and isopropyl *p*-toluenesulfanylsulfonate[6] by the literature method,[4] in dry CH_2Cl_2 (25 ml) at 0 °C. The mixture was stirred at 0 °C for 3 h, then the reaction was quenched with cold 3% HCl (10 ml) and the whole was extracted with Et_2O (30 ml × 3). The extracts were washed with saturated aqueous $NaHCO_3$ (10 ml) and saturated brine (10 ml), dried, and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica (150 g) with hexane–AcOEt (15 : 1) to give **1c** (1.76 g, 97%), bp 116—124 °C/0.18 mmHg, $[\alpha]_D^{23}$ +31° (*c* = 1.1, $CHCl_3$). IR (neat): 3400, 2980, 1450, 1090, 1060 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, s, Me), 0.95 (3H, s, Me), 0.97 (3H, s, Me), 1.27 (3H, d, *J* = 6.8, Me), 1.28 (3H, d, *J* = 6.8, Me), 1.1—1.8 (4 H, m, 5-H, 6-H), 1.87 (1 H, d, *J* = 4.4, 4-H), 2.83 (1H, septet, *J* = 6.8, SCH), 2.97 (1H, d, *J* = 7.6, 3-H), 3.09 (1H, d, *J* = 3.9, OH), 3.56 (1H, dd, *J* = 7.6, 3.9, 2-H). HRMS *m/z* M^+ Calcd for $C_{13}H_{24}OS$: 228.1547. Found: 228.1561.

General Procedure for the Addition of Benzaldehyde Catalyzed by a Chiral Ligand In a flame-dried flask was placed the ligand **1** (5—100 mol %) in dry hexane or toluene (5 ml) and the mixture was sonicated for 5 min. Diethylzinc (0.98 M in hexane) was added dropwise to this solution at 0 °C. The mixture was stirred at that temperature for 0.5 h. Benzaldehyde was then added to the solution *via* a syringe at −78 °C and the mixture was allowed to warm to room temperature. The resulting mixture was stirred for an appropriate time (shown in the table), poured into aqueous NH_4Cl (10 ml) and extracted with EtOAc (5 ml × 3). The extracts were washed with 3% HCl (10 ml), saturated $NaHCO_3$ (10 ml) and saturated brine (10 ml), dried, and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica (20 g) with hexane–AcOEt (5 : 1) to give 1-phenylpropanol **2**. The ligand was also recovered after chromatography. The enantiomeric excess and the absolute configuration of the alcohol **2** obtained were determined by use of a chiral column[2h] with hexane–2-propanol (99 : 1) (flow rate 1 ml/min; t_R (*R*)-**2** 28.9 min; t_R (*S*)-**2** 34.4 min).

The sulfoxides **3a** and **3b**, each produced as essentially a single diastereoisomer after a long reaction time, were identified by comparison with the reported spectral data.[4] The sulfoxide **3c**, sulfone **4a**, and keto sulfoxide **5a**, produced from the reaction in the presence of **1a** as by-products, were isolated after chromatography, and were identical with authentic samples obtained by oxidation of **1c**, **3a**, and **4a**, respectively. The stereochemistry of the sulfonyl group in **5a** was assigned to be *endo* with respect to the bornyl moiety, as judged from its ^{1}H-NMR spectrum, which showed a large coupling constant (*J* = 4.1 Hz) between the H-3 proton and the H-4 proton. It is thus assumed that the sulfonyl group in **5** was isomerized during the oxidation. The stereochemistries of the sulfonyl group in both **5b** and **5c** were not ascertained, but were tentatively assigned to be *endo* by analogy with **5a**.

Sulfoxide **3c**: mp 145—147 °C (from CH_2Cl_2), $[\alpha]_D^{20}$ +40° (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): 3320, 2980, 1060, 990 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s, Me), 1.00 (3H, s, Me), 1.25 (3H, s, Me), 1.28 (3H, d, *J* = 6.8, Me), 1.40 (3 H, d, *J* = 6.8, Me), 1.1—1.8 (4 H, m, 5-H_2, 6-H_2), 1.69 (1 H, d, *J* = 4.4, 4-H), 2.73 (1H, septet, *J* = 6.8, SCH), 2.93 (1H, d, *J* = 7.3, 3-H), 3.76 (1H, br, OH), 4.12 (1H, d, *J* = 7.6, 2-H). *Anal.* Calcd for $C_{13}H_{24}O_2S$: C, 63.89; H, 9.90. Found: C, 63.68; H, 9.93.

Sulfone **4a**: mp 220—221 °C (from EtOH), $[\alpha]_D^{18}$ +41° (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): 3500, 2980, 1320, 1110, 1060 cm^{-1}. ^{1}H-NMR

($CDCl_3$) δ: 0.84 (3 H, s, Me), 0.96 (3 H, s, Me), 1.30 (3 H, s, Me), 0.86—1.75 (4H, m, 5-H_2, 6-H_2), 2.23 (1 H, d, J=3.7, 4-H), 3.06 (1 H, d, J=7.6, SO_2CH), 3.06 (1H, d, J=5.8, OH), 3.92 (1 H, dd, J=7.6, 5.8, 2-H), 4.32 (2 H, s, $PhCH_2$), 7.42 (5H, m, ArH). *Anal.* Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84. Found: C, 65.92; H, 7.83.

Keto Sulfone **5a**: mp 138—139 °C (from EtOH), $[\alpha]_D^{21}$ −65° (c=0.3, $CHCl_3$). IR ($CHCl_3$): 2980, 1740, 1315, 1120, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, s, Me), 0.98 (3H, s, Me), 0.99 (3H, s, Me), 1.7—2.0 (3H, m, 5-H, 6-H_2), 2.30—2.45 (1H, m, 5-H), 2.50 (1 H, d, J=4.1, 4-H), 3.74 (1H, br d, J=4.1, SO_2CH), 4.33 (1H, d, J=13.9, PhCHH), 4.77 (1H, d, J=13.9, PhCHH), 7.3—7.5 (5H, m, ArH). *Anal.* Calcd for $C_{17}H_{22}O_3S$: C, 66.64; H, 7.24. Found: C, 66.46; H, 7.20.

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