The product, α-cyclohexyl aspartate, was identified by amino acid analysis and ^{1}H NMR spectrum. ^{1}H NMR: δ 0.95–1.63 (11 H, m), 2.65–2.85 (2 H, m), 4.16–4.20 (1 H, t, J = 5.1 Hz); yield 1.3 g (60%); $[\alpha]^{25}_D$ +5.2° (c = 2.0, 1% HOAc).

Registry No. H-Asp-OH, 56-84-8; chymotrypsin, 9004-07-3; dicyclopentyl L-aspartate, 121329-69-9; dicyclohexyl L-aspartate, 121329-70-2; dicycloheptyl L-aspartate, 121329-71-3; β-cyclopentyl L-aspartate, 121329-72-4; β-cyclohexyl L-aspartate, 112259-66-2; β-cycloheptyl L-aspartate, 107164-80-7; α-cyclohexyl L-aspartate, 121329-73-5; subtilisin, 9014-01-1.

Camphoryl Sulfide as a Chiral Auxiliary and a Mediator for One-Step Synthesis of Optically Active 1,2-Diaryloxiranes

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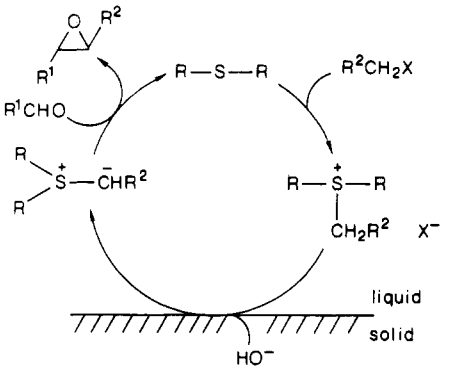
Sulfonium salts have been known to serve as either alkylating or alkylidene transfer agents after conversion to the corresponding ylides, which are widely employed in synthetic organic chemistry.[1] One advantage of sulfur ylides in organic synthesis is that the starting sulfides can be readily recovered after treatment of ylides with, e.g., carbonyl compounds and recycled to regenerate the starting ylides. Recently, we reported a convenient one-pot synthesis of oxiranes using a reaction system composed of alkyl sulfides, alkyl halides, and aldehydes in the presence of solid KOH under phase-transfer conditions.[2] In these reactions, the sulfides are converted initially to sulfonium salts and then subsequently to the corresponding ylides in situ under phase-transfer conditions. Thus, the sulfide works as a mediator that transfers an alkyl group to the aldehyde. The reaction cycle is shown in Scheme I. As a modification of this reaction, if one used an optically active sulfide as a mediator, one could obtain optically active oxiranes in one pot. We tried several optically active sulfides and found that those derived from camphorsulfonic acid work as both mediators and chiral auxiliaries for the formation of optically active oxiranes in moderate enantiomeric excess. Herein we report the results.

Results and Discussion

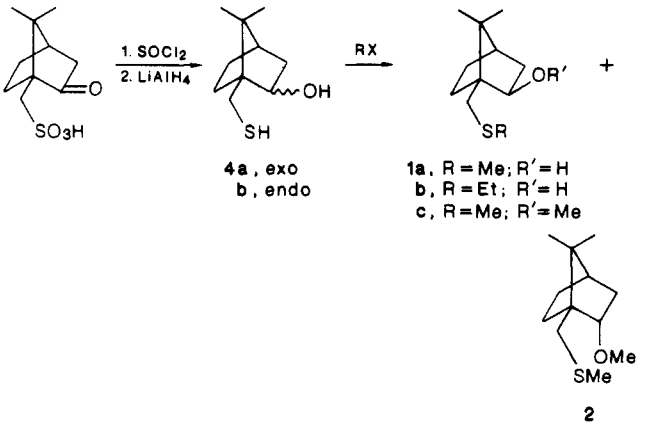
Optically active sulfides **1** and **2** used in the reactions were prepared starting from (+)-camphorsulfonic acid in three steps as shown in Scheme II.

Generally, the synthesis of optically active oxiranes was carried out by using an equimolar amount of aryl aldehyde (3 mmol) and benzyl bromide (3 mmol) in the presence of a half molar equivalent of the sulfide **1** (1.5 mmol) in THF or CH_3CN under liquid–solid two-phase conditions. Powdered KOH was used as a base. The products were separated and identified by NMR and IR spectra and elemental analysis. The yields and enantiomeric excess of the oxiranes thus obtained are presented in Table I. In order to elucidate the substituent effects on the chemical yields and enantiomeric excess for preparation of *trans*-1,2-diaryloxiranes, several para-substituted aryl aldehydes and benzyl bromides were reacted by using the sulfide **1a** as a mediator and the results are summarized in Table II. Recently, Sharpless and his co-workers reported a one-step synthesis of optically active oxiranes in high chemical and optical yields.[4] On the other hand, Wynberg et al. also prepared optically active oxiranes in moderate optical

Scheme I. Reaction Cycle for Formation of Oxiranes



Scheme II

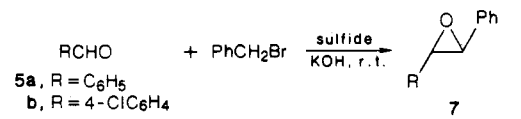


4a, exo
b, endo

1a, R = Me; R′ = H
b, R = Et; R′ = H
c, R = Me; R′ = Me

2

Table I. Preparation of Optically Active Oxiranes

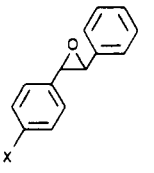


5a, R = C_6H_5
b, R = 4-ClC_6H_4

7

sulfide	RCHO	solvent	time, h	yield,[e] %	% ee[a]	confgn
1a	**5a**	CH_3CN	36	100[b]	47	(+)-*R,R*
1c	**5a**	THF	48	16[b]	14	(−)-*S,S*
1a	**5b**	THF	36	15[c]	34	(+)-*R,R*
1a	**5b**	CH_3CN	36	100[c]	43	(+)-*R,R*
1a[d]	**5b**	CH_3CN	36	230[c]	31	(+)-*R,R*
1b[d]	**5b**	CH_3CN	36	90[c]	31	(+)-*R,R*
1c	**5b**	THF	48	30	28	(−)-*S,S*
2	**5b**	THF	48	17	7	(+)-*R,R*

[a] Determined by HPLC analysis using Chiralpack OT(+) of Daicel Chemical Ind., Ltd. [b] Product is **7a**. [c] Product is **7b**. [d] Mole ratio of RCHO/$PhCH_2Br$/sulfide = 10:10:1. [e] The yields were calculated on the basis of the sulfide used in the reactions.

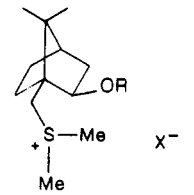


7a, X = H
b, X = Cl

(1) Trost, B. M.; Melvin, L. S. "Sulfur Ylides"; Academic Press: New York, 1975.
(2) Furukawa, N.; Okano, K.; Fujihara, H. *Nippon Kagaku Kaishi* **1987**, 1353.
(3) Eliel, E. L.; Frazee, W. J. *J. Org. Chem.* **1979**, *44*, 3598.
(4) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

0022-3263/89/1954-4222$01.50/0

yields by using optically active quaternary ammonium salts as a chiral source under phase-transfer condition.[5] Meanwhile, optically active organosulfur compounds such as sulfoxides and sulfoximines are also utilized for synthesis of optically active oxiranes.[6] Although sulfonium salts (and ylides) have also been utilized for the preparation of oxiranes, asymmetric synthesis of optically active oxiranes by using optically active sulfonium salts has not been reported since the optical activity of the sulfonium salt is lost soon after preparation due to the facile pyramidal inversion at the sulfur center.[7] The results obtained in the present investigation provide several characteristic features for preparation of optically active oxiranes. According to the results shown in Tables I and II, the sulfide-bearing camphor moiety as a ligand gives optically active oxiranes in one-step without isolating the corresponding sulfonium salts. Although optical yields are moderate, namely, ca. 10–50%, the chemical yields are relatively high at the optimum reaction condition. The highest enantiomeric excess was obtained when the reaction was carried out in acetonitrile at room temperature by using a combination of the sulfide **1a** having an exo-OH group and benzaldehyde and benzyl bromide. Although the turnover cycle for the reaction was not examined, the chemical yields calculated on the basis of the sulfide used are quantitative and more than 100% when a large excess of the aldehyde and the benzyl bromide were subjected to the reaction conditions. Thus, this result demonstrates that the sulfide serves as a mediator in which the sulfur atom provides the reaction center for alkylation and epoxidation. As to the nature of the ligand on the sulfide, a methyl substituent gives a higher yield than the ethyl group of **1b**, suggesting that obviously the steric effect may play an important role for the intermediary formation of the corresponding sulfonium salt. Meanwhile, a large solvent effect was observed on the chemical yield of formation of the oxirane. As a comparison of CH_3CN to THF, CH_3CN gives better results since it increases the solubility of the solid KOH in solution and furthermore the ylides once generated would have highly nucleophilic activity toward the aldehyde by the formation of the naked carbanion in the solvent. Although the enantiomeric excess of the oxiranes is found to be around 10–50% depending on the nature of the substituents on the phenyl rings, the sign of optical rotation depends remarkably on the sulfides **1** employed in the reaction, particularly on the configuration of the carbon atom bearing the hydroxyl or methoxy group in the ligand. If one used the exo-OH derivative (**1a** and **1b**) as a mediator, the oxiranes having the (+) configuration were obtained, namely, (1*R*,2*R*)-oxiranes. Meanwhile, the stereochemical course for the asymmetric induction by using the methoxy derivative **1c** results preferentially in the formation of (−)-(1*S*,2*S*)-oxiranes. As shown in Table II, no general tendency to the substituent effects on both the chemical and optical yields was observed from the present experiment. However, utilization of the compound having a nitro substituent decreases both the chemical yield and optical purity. Any attempted isolation of the sulfonium salts from the reactions of the sulfide **1** and alkyl bromides was unsuccessful except in the case of **1a** and **1c** with CH_3I. Dimethylsulfonium salt **3a** or **3b** reacts with strong base, for example, LDA (lithium diisopropyl amide), in THF resulting in the formation



3a, R = H; X = BF_4^-
b, R = Me; X = I^-

of oxiranes in nearly the same chemical and optical yield as other sulfides used in the reactions. Thus, the present one-pot reaction may proceed via an initial formation of the sulfonium salt which is converted in situ to the ylide. Although the reaction center is far from the asymmetric center, the optical yields are relatively high. The configurations of the sulfur atoms in the sulfonium salts generated in the reactions were not determined. However, interestingly, in the salts **3a** and **3b**, the two *S*-methyl groups appears as two singlets in the ^1H NMR spectrum (δ 2.98 and 3.03 for **3a** and 3.35 and 3.50 for **3b**, respectively) at room temperature, indicating that the sulfur atom in the sulfonium salt does not undergo rapid pyramidal inversion even in solution. Although the stereochemical process for asymmetric induction is not understood, the configurations in the oxiranes obtained are either (1*R*,2*R* or 1*S*,2*S*, depending on the sulfides used, and neither 1*R*,2*S* nor 1*S*,2*R* was obtained.

The present procedure has several disadvantages for synthesis of optically active oxiranes. However, either by changing the structure of the sulfides[8] used or by using more reactive substrates, the method promises to be a convenient one-step synthesis of these substances.

Experimental Section

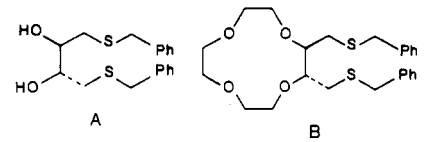
General. ^1H NMR spectra were measured on a Hitachi R-600 FT NMR spectrometer. The IR spectra were obtained on a JASCO A-3 spectrometer. The optical rotations were measured on a JASCO DIP-140 polarimeter. Elemental analyses were carried out by the Chemical Analysis Center at this University. All reagents were obtained from Wako Pure Chemical Industries, Ltd. or Aldrich Chemical Co. The reagents used as reaction solvents were further purified by general methods.

Preparation of *exo*-2-Hydroxy-10-(methylthio)bornane (1a). To the thiol **4a**[3] (5.23 g, 28.4 mmol) in THF (200 mL) solution were added NaH (1.50 g, 34.1 mmol) under an N_2 stream and then CH_3I (2.10 mL, 34.1 mmol) with cooling and stirring. After 4 h excess NaH was decomposed by addition of EtOH. The solution was extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was evaporated and the residue was column chromatographed on silica gel (eluant benzene/hexane, 1:1) to give the compound **1a**. **1a**: yield 93%; $[\alpha]_D$ = −61.7° (*c* = 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.90 (m, 1 H), 2.79 (d, 1 H, *J* = 11 Hz), 2.53 (d, 1 H, *J* = 11 Hz), 2.16 (s, 3 H), 1.93–1.15 (m, 7 H), 1.06 (s, 3 H), 0.84 (s, 3 H); IR (neat, cm^{-1}) 3480. ***exo*-2-Hydroxy-10-(ethylthio)bornane (1b)**: $[\alpha]_D$ = −61.0° (*c* = 2.78, $CHCl_3$); ^1H NMR δ 3.90 (m, 1 H), 2.94–2.42 (m, 4 H), 2.12–1.48 (m, 7 H), 1.29 (t, 3 H), 1.07 (s, 3 H), 0.85 (s, 3 H); IR (neat, cm^{-1}) 3450.

Compounds **1c** and **2** were prepared directly from the corresponding mercapto alcohols **4a** and **4b** using 2 equiv of NaH and MeI under the above conditions.

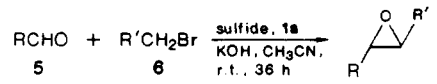
(5) Wynberg, H.; Greijdanus, B. *J. Chem. Soc., Chem. Commun.* **1978**, 427.
(6) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418.
(7) Andersen, K. K. In *The Chemistry of the Sulphonium Group*; Stirling, C. J. M., Patai, S., Eds.; John Wiley & Sons: New York, 1981; Chapter 10.

(8) We prepared many other optically active sulfides such as acyclic sulfides **A** and the corresponding crown ether **B** and subjected them to the reaction. However, both the chemical and optical yields were low upon treatment with similar substrates described in this paper. The detailed results will be published elsewhere.



A **B**

Table II. Preparation of Optically Active Oxiranes

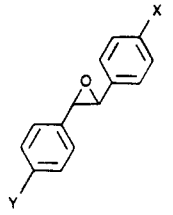


5 6

a, C_6H_5; b, 4-ClC_6H_4; c, 4-MeC_6H_4; d, 4-$NO_2C_6H_4$

RCHO	$R'CH_2Br$	yield, %	product[a]	% ee	confgn
5b	**6a**	100	**7b**	43	(+)-*R,R*
5a	**6b**	114	**7b**	32	
5c	**6a**	78	**7c**	43	(+)-*R,R*
5a	**6c**	94	**7c**	29	
5d	**6a**	22	**7d**	15	(+)-*R,R*
5a	**6d**	35	**7d**	8	
5b	**6c**	90	**8**	30	(+)
5c	**6b**	81	**8**	21	
5b	**6b**	74	**9**	24	(+)

[a] [b]Determined by HPLC analysis using Chiralpack OT(+) of Daicel Chemical Ind., Ltd.



7c, X = H; Y = CH_3
d, X = H; Y = NO_2
8, X = CH_3; Y = Cl
9, X = Y = Cl

***exo*-2-Methoxy-10-(methylthio)bornane (1c)**: $[\alpha]_D$ = -62.2° (*c* = 1.7, $CHCl_3$); ^1H NMR δ 3.40 (m, 1 H), 3.25 (s, 3 H), 2.86 (d, 1 H, *J* = 12 Hz), 2.38 (d, 1 H, *J* = 12 Hz), 2.14 (s, 3 H), 1.88-1.11 (m, 7 H), 0.99 (s, 3 H), 0.84 (s, 3 H); IR (neat, cm^{-1}) 1100, 1310.

***endo*-2-Methoxy-10-(methylthio)bornane (2)**: $[\alpha]_D$ = +53.1° (*c* = 2.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.80 (t, 1 H), 3.33 (s, 3 H), 2.63 (d, 2 H), 2.10 (s, 3 H), 2.02-1.04 (m, 7 H), 0.95 (d, 6 H); IR (neat, cm^{-1}) 1100.

Preparation of *exo*-2-Methoxy-10-(dimethoxysulfonio)-bornane Iodide (3b). To the sulfide **1c** (500 mg, 2.3 mmol) dissolved in CH_2Cl_2 (30 mL) was added MeI (2 mL). After 10 h at room temperature, the solvent was evaporated and then a small amount of anhydrous Et_2O was added to the solution. Colorless crystals obtained were recrystallized from CH_2Cl_2/Et_2O. **3b**: yield 72.6%; mp 136.5-138 °C. $[\alpha]_D$ = -46.26° (*c* = 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.00 (d, 1 H, *J* = 12 Hz), 3.52 (s, 3 H), 3.41 (m, 1 H), 3.36 (s, 3 H), 3.35 (d, 1 H, *J* = 12 Hz), 3.22 (s, 3 H), 2.06-1.13 (m, 7 H), 1.06 (s, 3 H), 1.00 (s, 3 H). Anal. Calcd for $C_{13}H_{25}IOS$: C, 43.95; H, 6.81. Found: C, 43.90; H, 7.23.

Preparation of *exo*-2-Hydroxy-10-(dimethylsulfonio)-bornane Tetrafluoroborate (3a). To the sulfide **1a** (398 mg, 2.0 mmol) dissolved in the presence of $AgBF_4$ (400 mg, 2.37 mmol) in CH_2Cl_2 (20 mL) was added MeI (150 L, 2.37 mmol) at 0 °C. After 8 h at 0 °C, the solvent was evaporated and then a small amount of anhydrous Et_2O was added to the solution. Colorless crystals obtained were recrystallized from CH_2Cl_2/Et_2O. **3a**: yield 50%; mp 178-180 °C; $[\alpha]_D$ = -50.30° (*c* = 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.95 (m, 1 H), 3.69 (d, 1 H, *J* = 14.4 Hz), 3.29 (d, 1 H, *J* = 14.4 Hz), 3.03 (s, 3 H), 2.98 (s, 3 H), 2.17-1.29 (m, 7 H), 1.11 (s, 3 H), 0.93 (s, 3 H). Anal. Calcd for $C_{12}H_{23}BF_4OS$: C, 47.69; H, 7.67. Found: C, 47.42; H, 7.80.

Preparation of (*R,R*)-1-(*p*-Chlorophenyl)-2-phenyloxirane (7b). Sulfide **1a** (257 mg, 1.3 mmol) and powdered KOH (250 mg) were added to CH_3CN (10 mL). To this solution was added a mixture of benzyl bromide (340 μL, 2.86 mmol) and *p*-chlorobenzaldehyde (347 mg, 2.47 mmol) with vigorous stirring for 36 h. After the reaction, the product was separated by preparative liquid chromatography and its structure identified by ^1H NMR and elemental analysis. Yield was 235 mg based on the sulfide **1a**. **7b**: mp 91-93 °C (lit.[9] mp 100 °C); $[\alpha]_D$ = +92.5° (*c* = 0.43, EtOH); ee = 43%. The %ee was determined by HPLC analysis using Chiralpack OT(+) from Daicel Chemical Ind., Ltd. ^1H NMR ($CDCl_3$): δ 7.48-7.18 (m, 9 H), 3.83 (d, 2 H). Anal. Calcd for $C_{14}H_{11}ClO$: C, 72.89; H, 4.80. Found: C, 72.58; H, 4.81.

Similarly, other oxiranes were prepared and their spectra and elemental analyses are summarized as follows. **7a**: mp 69-70 °C (lit.[9] mp 69 °C); ^1H NMR ($CDCl_3$) δ 7.35 (s, 10 H), 3.86 (s, 2 H). Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.43; H, 6.11. **7c**: mp 55-56 °C (lit.[9] mp 62 °C); ^1H NMR ($CDCl_3$) δ 7.34-7.20 (m, 9 H), 3.83 (s, 2 H), 2.35 (s, 3 H). Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.59; H, 6.74. **7d**: mp 120.5-121 °C (lit.[9] mp 127 °C:); ^1H NMR ($CDCl_3$) δ 8.34, 7.41 (dd, 4 H, *J* = 9 Hz), 7.38 (s, 5 H), 3.97 (d, 1 H, *J* = 2 Hz), 3.86 (d, 1 H, *J* = 2 Hz). Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.61; H, 4.58; N, 5.75. **8**: mp 115-116 °C; ^1H NMR ($CDCl_3$) δ 7.30-7.17 (m, 8 H), 3.81 (d, 1 H, *J* = 2 Hz), 3.76 (d, 1 H, *J* = 2 Hz), 2.35 (s, 3 H). Anal. Calcd for $C_{15}H_{13}ClO$: C, 73.62; H, 5.35. Found: C, 73.51; H, 5.35. **9**: mp 96-97 °C; ^1H NMR ($CDCl_3$) δ 7.34 (d, 4 H, *J* = 10 Hz), 7.26 (d, 4 H, *J* = 10 Hz), 3.78 (s, 2 H). Anal. Calcd for $C_{14}H_{10}Cl_2O$: C, 63.42; H, 3.80. Found: C, 63.14; H, 3.72.

(9) Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 2505.

Enantiospecific Synthesis of L-α-Aminosuberic Acid. Synthetic Applications in Preparation of Atrial Natriuretic Factor Analogues

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L-α-Aminosuberic acid (**5c**) has been frequently utilized as a metabolically stable isostere for Cys-Cys disulfide linkage in a variety of naturally occurring cyclic hormonal peptides, such as oxytocin,[1] vasopressin,[2] somatostatin,[3] and atrial natriuretic peptides.[4] To date, there have been only two reports on the stereospecific synthesis of α-aminosuberic acid. The first method involved lengthy (18 steps) iterative extension[5a] of the side chain of L-glutamic acid via the Arndt-Eistert procedure. The second one utilized the Kolbe electrolysis[5b] of the mixture of derivatized D-glutamic and glutaric acids, upon which the desired unsymmetrical adduct (D enantiomer) was separated from the two byproduct symmetrical dimers obtained as a statistical mixture. All other syntheses[6] required resolution of racemic α-aminosuberic acid.

Herein we report on efficient and convergent synthesis of L-α-aminosuberic acid (**5c**) (Scheme I) which allows for preparation of the amino acid in an orthogonally protected form **5b**, convenient for peptide synthesis. In addition, this route provides for the novel 4,5-dehydro intermediate **4a**, which is suitable for isotopic labeling or further functionalization of the double bond.

Commercially available[7] *N*-α-t-Boc-L-aspartic acid α-(*tert*-butyl ester) (**1**) was converted to the corresponding *N*-methoxy-*N*-methylamide **2**, which was reduced with diisobutylaluminum hydride to give pure aldehyde **3** in quantitative yield. This method of obtaining α-(t-Boc-amino) aldehydes from α-(t-Boc-amino) acids has been described previously as giving products of high optical purity.[8] Subsequent Wittig condensation[9] of the aldehyde **3** with the ylide derived from (3-carboxypropyl)triphenylphosphonium bromide gave (γ,δ)-*Z*-dehydro-L-α-aminosuberic acid as the N-t-Boc, α-(*tert*-butyl ester) **4a**

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