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Retention of Configuration in the Ritter-type Substitution Reaction of Chiral β-Arylthio Alcohols through the Anchimeric Assistance of the Arylthio Group

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In chiral alcohols bearing a phenylthio group at the β carbon atom, the hydroxy group is replaced by nitriles through the anchimeric assistance of the phenylthio group to afford chiral amides with retention of configuration. This stereospecific Ritter-type reaction has been utilized in the conversion of chiral glycidol derivatives to chiral cyclic imino ethers such as oxazolines bearing an arylthio group.

Anchimeric assistance of the arylthio group has been widely observed in the substitution reactions at the carbon atom β to the arylthio group, the three-membered cyclic intermediate being known as an episulfonium ion.[1] Diastereoselectivity, namely the erythro-threo selectivity has been established in the substitution reactions via the episulfonium ion. Enantioselectivity, *i.e.*, the stereochemistry of the substitution reaction at the chiral carbon through the anchimeric assistance of the arylthio group (the stereochemical behavior of a chiral episulfonium ion), however, has not been studied so far.[2] We find that the chiral episulfonium ion does not racemize during the Ritter-type substitution reaction of the chiral β-phenylthio alcohols. Thus, chiral amides are produced with retention of configuration of the chiral carbon by the substitution of the hydroxy group by the nitrile through the anchimeric assistance of the phenylthio group.[3] This result shows a sharp contrast to the behavior of the homologous chiral episelenonium ion which has recently been reported to racemize quite easily.[4] We have applied this Ritter-type reaction to chiral 1,2-diol derivatives bearing the arylthio group to find that the intermediate iminium ion is trapped by the remaining hydroxy group to afford chiral cyclic imino ethers such as oxazolines.

We describe herein the details of these reactions as a new chiral pool method from readily accessible chiral oxiranes[5] to chiral amine derivatives with retention of configuration of the chiral carbon.

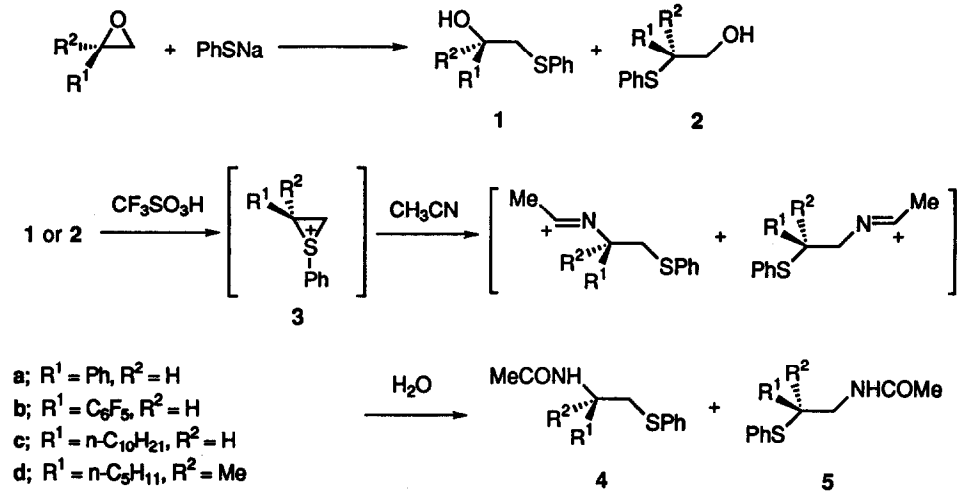
Results and Discussions

Synthesis of Chiral Phenylthio-substituted Alcohols

Chiral alcohols bearing a phenylthio group on the adjacent carbon atom (**1** and **2**) were prepared by the reaction of chiral oxiranes with sodium benzenethiolate as shown in Scheme 1. Whereas the phenylthio

group was introduced selectively to the primary carbon of alkyl-substituted oxiranes to afford **1**, aryl-substituted oxiranes afforded a mixture of regioisomers **1** and **2** which were separated by column chromatography. Optical purities of these phenylthio-substituted alcohols **1a-d**, and **2a,b** were confirmed to be same as those of chiral oxiranes based on the integrals of ^{1}H NMR spectra of their (*S*)-1-methoxy-1-trifluoromethyl-1-phenylacetates (MTPA esters).[6] This result is anticipated in the formation of **1** through the ring opening of the oxiranes without affecting the stereochemistry of the chiral carbon. On the other hand, the stereochemistry of the chiral carbon must be inverted during the conversion of the oxiranes to the primary alcohols **2**, since the episulfonium ion intermediates **3** of the same absolute configuration are produced from either **1** or **2** by the reaction with trifluoromethanesulfonic acid (*vide infra*).

Scheme 1



Stereospecificity in the Ritter-type Reaction

The reaction course and the results are summarized in Scheme 1 and Table 1, respectively. A typical reaction is as follows. By the reaction of the phenylthio-substituted benzyl alcohol **1a** (100% ee) with trifluoromethanesulfonic acid and water (1:1) (5 equiv.) in acetonitrile as solvent (-40 °C, 15 h), the hydroxy group was substituted by the nitrogen atom of the nitrile to afford, through the trapping of the iminium ion intermediate by water present in the reaction mixture, the *N*-benzylacetamide derivative **4a** in a satisfactory yield (Scheme 1). As shown in entry 2 of Table 1, the optical purity of **4a** was determined to be 100% by the liquid chromatographic analysis using chiral column, indicating that the intermediate episulfonium ion **3a** did not racemize during the reaction. When the regioisomeric primary alcohol **2a** (100% ee) was used as the starting material (10 equiv. of acid, -40 °C, 72 h), the migration of the phenylthio group was observed to afford the same amide **4a** with the same enantiomeric excess and the same absolute configuration (entry 4). These facts indicate that both reactions proceed through the same intermediate episulfonium ion **3a**, which reacts with the nitrile selectively at the carbon atom bearing the phenyl group. To confirm the absolute configuration, **4a** was desulfurized by the reaction with nickel boride[7] to give *N*-(1- phenylethyl)acetamide

Table 1. Optical Purities and Chemical Yields of the Amides **4** and **5** [a]

entry	alcohol (%ee)	acid [b] (equiv.)	temp. (°C)	time (h)	amide	yield [c] (%)	%ee [d]
1	**1a** (100)	1	r.t.	2	**4a**	96	74
2	**1a** (100)	5	-40	15	**4a**	74	100
3	**2a** (100)	1	r.t.	2	**4a**	68	73
4	**2a** (100)	10	-40	72	**4a**	71	99
5	**1b** (97)	5	r.t.	6	**4b**	95	97
6	**2b** (97)	5	r.t.	23	**4b**	92	97
7	**1c** (86)	2	r.t.	3	**4c**	81	85
					5c	9	86
8	**1d** (86)	5	-40	19	**4d**	92	82

a) Carried out using the alcohol (1 mmol) in acetonitrile (2-4 mL).

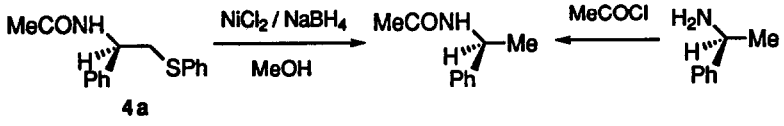
b) A mixture of trifluoromethanesulfonic acid and water (1:1 in molar ratio) was used.

c) Isolated yield by column chromatography.

d) Determined by liquid chromatography using chiral columns or from the integrals of the ^{1}H NMR spectra of the (*S*)-MTPA amides of the amines prepared by the reduction ($LiAlH_4$) of the amides (**4** or **5**).

(Scheme 2). Since the sign of the optical rotation of this compound was same as that of the authentic sample prepared from commercially available (*S*)-(1-phenylethyl)amine, the configuration of the chiral carbon in **4a** was confirmed to be *R*. As we prepared **1a** from (*R*)-phenyloxirane, the configuration of the chiral carbon in **1a** is *R*. Thus, we can conclude that the substitution of the hydroxy group in **1a** by the nitrile proceeded with overall retention of configuration. Consequently, the substitution reactions in the formation and the ring opening of the chiral episulfonium ion **3a** are elucidated to proceed with inversion of configuration (Scheme 1). It should be noted here that partially racemized **4a** was obtained from either **1a** or **2a** when this reaction was carried out at the ambient temperature (entries 1 and 3). This result indicates that the episulfonium ion **3a** is susceptible to recemization at ambient temperature. This racemization seems to proceed via the achiral open-chain carbenium ion intermediate.

Scheme 2



The regioisomeric alcohols bearing a pentafluorophenyl group **1b** and **2b** also afforded the common product **4b** regioselectively, having the same configuration (entries 5 and 6 in Table 1). Again both reactions proceeded through the same episulfonium ion intermediate **3b**. In this case the chiral episulfonium ion did not racemize at ambient temperature. It is reasonable that the less stable open-chain carbenium ion could not

intervene due to the presence of electron-withdrawing fluorine substituents.

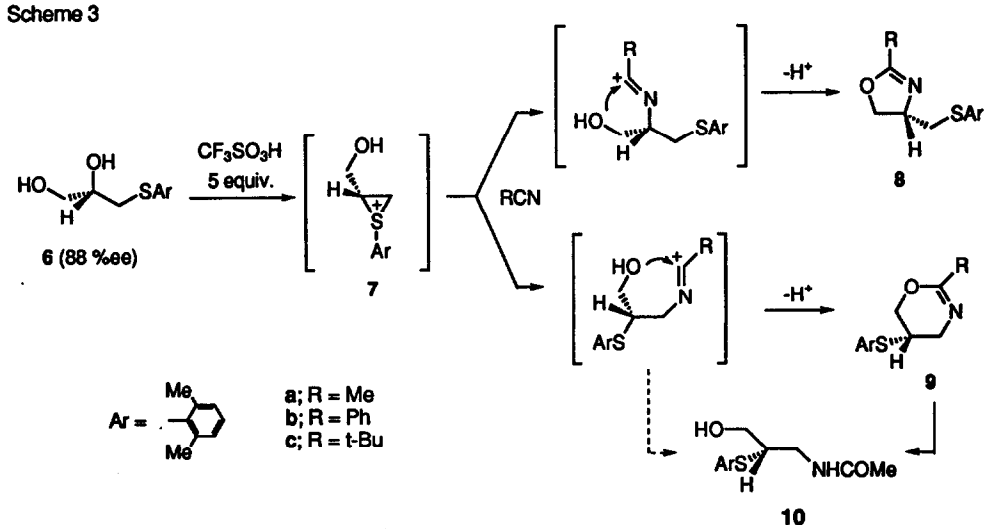
The reaction of the aliphatic secondary alcohol **1c** with trifluoromethanesulfonic acid in acetonitrile as solvent afforded a mixture of the regioisomers of the amide (**4c** + **5c**) with the same optical purities, the secondary amine derivative **4c** being the major product (entry 7). The reaction of the episulfonium ion bearing one alkyl group **3c** with the nitrile proceeded mainly at the secondary carbon, but ca. 10% of the reaction proceeded at the primary carbon. The configuration of the chiral carbon in **5c** is deduced to be *S*, since the substitution at the chiral carbon occurred only once during the conversion of **1c** to **5c** (in the formation of the chiral episulfonium ion).

The reaction of the tertiary alcohol **1d** with the acid at ambient temperature afforded an almost equal amount of the substitution product **4d** and the elimination (dehydration) products which were found to be a mixture of allylic and vinylic sulfides. By carrying out the reaction at -40 °C, the elimination was greatly suppressed and the substitution reaction proceeded selectively to afford the amide **4d** in 92 % yield (entry 8). The regioisomer of **4d** was not detected among the products. As shown in Table 1, the optical purity of this amide **4d** was slightly lower than that of the starting alcohol, indicating that the episulfonium ion **3d** racemized slowly during the reaction. It is likely that this racemization proceeds via the open-chain carbenium ion. The comparison of the results in entries 2, 4, and 8 suggests that the dialkyl-substituted episulfonium ion **3d** is more susceptible to racemization than the phenyl-substituted ion **3a**. This may be ascribed to the stability of the open-chain tertiary carbenium ion and/or to the instability of the episulfonium ion **3d** by the steric hindrance of the geminal two alkyl groups.

Formation of Chiral Cyclic Imino Ethers

We tried to displace the hydroxy group by the nitrogen atom of the nitrile at the chiral carbon of the diol derivative **6** with retention of configuration by the utilization of the anchimeric assistance of the sulfur group described above. By the reaction of the sulfur-substituted diol **6** with trifluoromethanesulfonic acid in nitrile

Scheme 3



as solvent, the substitution reaction proceeded to afford, through the trapping of the iminium ion intermediate by the remaining hydroxy group, cyclic imino ethers such as oxazolines **8** and dihydrooxazines **9** (Scheme 3). The regioselectivity in the reaction of the chiral episulfonium ion **7** with the nitrile was much lower than that expected from the results of the monoalkyl-substituted **3c**. As shown in Table 2, a mixture of almost equal amount of oxazoline **8** and dihydrooxazine **9** was produced, indicating that the nitrogen atom of the nitrile attacks on the secondary and primary carbons of the episulfonium ion **7** equally.[8] We utilized the participation of the 2,6-xylylthio group, since the yield of cyclic imino ethers was not satisfactory in the reactions through the participation of the phenylthio group. The electron-donating 2,6-xylyl group seems to be necessary for the formation of the episulfonium ion intermediate **7** in the presence of the electron-withdrawing hydroxy group on the adjacent carbon atom. The total yields of the cyclic imino ethers were good in the reactions at room temperature for all nitriles examined. In the reaction with acetonitrile, 1,3-amino alcohol derivative **10a** was obtained instead of the dihydrooxazine, presumably due to the hydrolysis of the dihydrooxazine under the reaction conditions. The optical purities of these cyclic imino ethers or amino alcohol were slightly lower than that of the diol **6**. Better results were obtained by the reactions at lower temperatures, but still we could not completely suppress the partial racemization. The configurations of the chiral carbon in **8-10** were deduced as those depicted in Scheme 3 from the consideration of the reaction mechanism described above.

Table 2. Optical Purities and Yields of Products [a]

RCN	temp. (°C)	time (h)	product; yield (%ee) [b]	
MeCN	r.t.	1	**8a**; 30 (83)	**10a**; 26 (—) [c]
MeCN	0	20	**8a**; 21 (85)	**10a**; 19 (86)
PhCN	r.t.	20	**8b**; 39 (81)	**9b**; 39 (81)
PhCN	0	20	**8b**; 31 (84)	**9b**; 31 (84)
t-BuCN	r.t.	1	**8c**; 26 (—) [c]	**9c**; 26 (—) [c]

a) Carried out using the diol **6** (0.5 mmol) and a mixture of trifluoromethanesulfonic acid and water (1:1, 2.5 mmol) in nitrile (2 mL)
b) Determined by liquid chromatography using chiral column.
c) Not yet determined.

In the expectation of the selective formation of the oxazoline, we studied the similar cyclization of the diol **12** bearing an alkyl group on the central carbon atom. The results are summarized in Scheme 4 and Table 3. As expected, the oxazoline **14** was obtained as a sole product by the reaction of **12** with trifluoromethanesulfonic acid in nitriles as solvent. Thus, in spite of the presence of the hydroxy group in the side chain, the nitrogen atom of the nitrile attacks on the tertiary carbon of the episulfonium ion **13** selectively. With this substrate, the yields of the oxazoline **14** were satisfactory for all nitriles examined through the participation of the phenylthio group. It should be noted that the optical purities of the oxazolines were same as that of the starting oxirane. These results indicate that the dialkyl-substituted episulfonium ion **13** is less susceptible to racemization as compared to the similar episulfonium ion **3d**. This difference may be ascribed to the presence of the hydroxy group in **13** which would destabilize the open-chain tertiary carbenium ion by the electron-withdrawing effect.

The result in Scheme 4 is equivalent to the ring opening of the oxirane **11** by the nitrogen nucleophile at the central carbon atom with retention of configuration of the chiral carbon. The chiral oxirane **11** can be

prepared by the asymmetric epoxidation of the allyl alcohol derivatives and are often utilized in the construction of chiral building blocks by the introduction of nitrogen functional groups into the terminal carbon atom.[5] The introduction of the nitrogen functional group into the central carbon atom, however, has been unexplored and would be valuable. As the oxazolines are easily hydrolyzed to amino alcohols and the phenylthio group would allow the further manipulation at the carbon atom bearing the sulfur substituent, the phenylthio-substituted oxazolines **14** may be valuable chiral building blocks.

Scheme 4

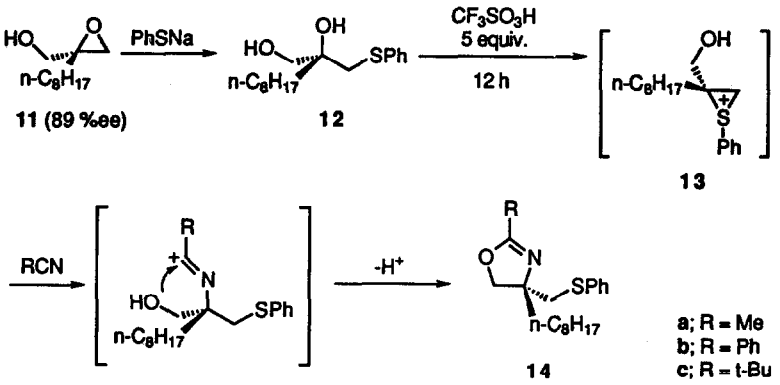


Table 3. Optical Purities and Chemical Yields of the Oxazolines **14** [a]

RCN	temp.(°C)	14	yield (%) [b]	ee(%) [c]
MeCN	-20	**14a**	82	89
PhCN	-20	**14b**	79	89
t-BuCN	r.t.	**14c**	71	89

a) Carried out using the diol **12** (0.5 mmol) and a mixture of trifluoromethanesulfonic acid and water (1:1, 2.5 mmol) in nitrile (4 mL) for 12 h.
b) Isolated yield by column chromatography.
c) Determined by liquid chromatography using chiral column.

Experimental Section

The IR spectra were taken with a JASCO IR-810 spectrometer. ^1H NMR spectra were recorded with Varian VXR-200 (200 MHz) instrument in $CDCl_3$ using $CHCl_3$ as internal standard (δ 7.25 ppm). Melting points were determined with Shimadzu MM-2 and Yanaco MP-S3 micro melting point determination apparatus and were uncorrected. Liquid chromatographic analyses were carried out with a Waters HPLC system equipped with a 6000A solvent delivery system, a Model 440 absorbance detector (at 254 nm), and a chiral column such as Daicel Chiralpak AD, AS or Chiralcel OD, OJ. Optical rotations were measured by a JASCO DIP-370 digital polarimeter in chloroform or ethanol solutions.

Materials. Diethyl ether, THF, and DME were dried over sodium benzophenone ketyl and were

distilled just before use. Dichloromethane was dried over calcium hydride and was distilled just before use. (*S*)-2-(Hydroxymethyl)-2-octyloxirane (**11**) was prepared by the reported procedure.[9] All other organic and inorganic materials were commercial products and were used without further purification.

Preparation of (R)-1-Phenyl-2-(phenylthio)ethanol* (1a) *and (S)-2-Phenyl-2-(phenylthio)ethanol* (2a). *A General Procedure. Benzenethiol (2.1 ml, 20 mmol) was added to a solution of sodium borohydride (1.18 g, 31.3 mmol) in ethanol (50 mL) with cooling by ice bath under nitrogen atmosphere. The resulting solution was warmed up to room temperature and stirred for 0.5 h. (*R*)-Phenyloxirane (2.2 mL, 19 mmol) was added into the solution and the resulting solution was stirred for further 2 h. The reaction mixture was quenched by water (50 mL) and the products were extracted with chloroform (50 mL x 3). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to leave a light yellow oil (6.9 g). The column chromatography of this oil [silica gel, hexane / ethyl acetate (10:1) as eluant] afforded **1a** (2.55 g, 11.1 mmol, 58 %) and **2a** (1.76 g, 7.7 mmol, 41 %). (*R*)-1-Phenyl-2-(phenylthio)ethanol (**1a**): colorless liquid; R_f 0.29 [hexane / ethyl acetate (5:1)]; IR (liquid film) 3410, 1585, 740, 700 cm^{-1}; ^1H NMR δ 2.85 (1H, d, J = 2.6 Hz, OH), 3.09 (1H, dd, J = 13.8, 9.4 Hz), 3.32 (1H, dd, J = 13.8, 3.6Hz), 4.72 (1H, ddd, J = 9.4, 3.6, 2.6 Hz), 7.20-7.45 (10H, m); $[\alpha]_D^{25}$ +47.5 ° (*c* 1.13, EtOH) (100 %ee). Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13. Found: C, 73.04; H, 6.20. The optical purity of **1a** was determined by ^1H NMR spectrum of its MTPA ester. (*S*)-2-Phenyl-2-(phenylthio)ethanol (**2a**): colorless liquid; R_f 0.20 [hexane / ethyl acetate (5:1)]; IR (liquid film) 3400, 1590, 765, 700 cm^{-1}; ^1H NMR δ 2.06 (1H, t, J = 6.8 Hz, OH), 3.89 (1H, dt, J = 11.5, 6.8 Hz), 3.92 (1H, dt, J = 11.5, 6.8 Hz), 4.31 (1H, t, J = 6.8 Hz), 7.20-7.40 (10H, m), $[\alpha]_D^{26.6}$ +206 ° (*c* 1.12, EtOH) (100 %ee). Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13. Found: C, 73.25; H, 6.31. The optical purity of **2a** was determined by ^1H NMR spectrum of its MTPA ester.

Spectral and analytical data of other β-arylthio-substituted alcohols are as follows.

(R)-1-(Pentafluorophenyl)-2-(phenylthio)ethanol (**1b**). Isolated by flash column chromatography [silica gel, hexane / benzene (1:4) as eluant]; yield 42 %; white crystals; mp 60.0-60.5 °C; R_f 0.16 [hexane / ethyl acetate (10:1)]; IR (KBr) 3420, 1650 cm^{-1}; ^1H NMR δ 2.73 (1H, d, 6.2 Hz, OH), 3.32 (1H, dd, J = 13.7, 5.8 Hz), 3.42 (1H, dd, J = 13,7, 7.6 Hz), 5.11 (1H, q, J = 6.7 Hz), 7.20-7.40 (5H, m); $[\alpha]_D^{22}$ +48.8 ° (*c* 1.07, $CHCl_3$) (97 %ee). Anal. Calcd for $C_{14}H_9OF_5S$: C, 52.50; H, 2.83. Found: C, 52.48; H, 2.79. The optical purity of **1b** was determined by HPLC analysis [Chiralcel OJ, hexane / 2-propanol (10:1) as eluant].

(S)-2-(Pentafluorophenyl)-2-(phenylthio)ethanol (**2b**). Isolated by flash column chromatography [silica gel, hexane / benzene (1:4) as eluant]; yield 39 %; white crystals; mp 61.0 °C; R_f 0.16 [hexane / ethyl acetate (10:1)]; IR (KBr) 3450, 1660 cm^{-1}; ^1H NMR δ 2.14 (1H, dd, J = 7.6, 5.2 Hz, OH), 3.95-4.18 (2H, m), 4.59 (1H, t, J = 7.6 Hz), 7.25-7.42 (5H, m); $[\alpha]_D^{21}$ +184 ° (*c* 1.08, $CHCl_3$) (97 %ee). Anal. Calcd for $C_{14}H_9OF_5S$: C, 52.50; H, 2.83. Found: C, 52.55; H, 2.82. The optical purity of **2b** was determined by HPLC analysis [Chiralcel OJ, hexane / 2-propanol (7:1) as eluant].

(R)-1-(Phenylthio)-2-dodecanol (**1c**). Isolated by column chromatography [silica gel, hexane / ethyl acetate (5:1) as eluant]; yield 84 %; white crystals; mp 43.0-43.5 °C; R_f 0.16 [hexane / ethyl acetate (10:1)]; IR (KBr) 3400, 2920, 2850, 735, 690 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J = 6.8Hz), 1.2-1.6 (18H, m), 2.39 (1H, d, J = 3.4 Hz, OH), 2.83 (1H, dd, J = 13.8, 8.8 Hz), 3.15 (1H, dd, J = 13.8, 3.4 Hz), 3.58-3.74 (1H, m), 7.15-7.4 (5H, m); $[\alpha]_D^{25}$ -22.9 ° (*c* 1.20, $CHCl_3$) (86 %ee). Anal. Calcd for $C_{18}H_{30}OS$: C, 73.41; H, 10.27. Found: C, 73.57; H, 10.30. The optical purity of **1c** was determined by ^1H NMR

spectrum of its MTPA ester.

(R)-2-Methyl-1-(phenylthio)-2-heptanol **(1d).** Isolated by column chromatography [silica gel, hexane / ethyl acetate (5:1) as eluant]; yield 80 %; colorless liquid; R_f 0.34 [hexane / ethyl acetate (5:1)]; IR (liquid film) 3430, 2930, 2860, 736, 690 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J = 6.6 Hz), 1.24 (3H, s), 1.2-1.4 (6H, m), 1.5-1.6 (2H, m), 2.20 (1H, s, OH), 3.06 (1H, d, J = 13.2 Hz), 3.14 (1H, d, J = 13.2 Hz), 7.13-7.50 (5H, m); $[\alpha]_D^{23}$ +2.0 ° (*c* 1.13, $CHCl_3$) (86 %ee). Anal. Calcd for $C_{14}H_{22}OS$: C, 70.54; H, 9.30. Found: C, 70.57; H, 9.27. The optical purity of **1d** was determined by ^1H NMR spectrum of its MTPA ester.

(S)-3-[(2,6-Dimethylphenyl)thio]-1,2-propanediol **(6).** Isolated by column chromatography [silica gel, hexane / ethyl acetate (1:1) as eluant]; yield 90 %; white crystals; mp 62.0-63.0 °C; R_f 0.29 [hexane / ethyl acetate (1:1)]; IR (KBr) 3280, 2940, 1460, 1070, 1030, 900, 770 cm^{-1}; ^1H NMR δ 1.90 (1H, s, OH), 2.54 (6H, s), 2.65 (1H, s, OH), 2.75 (1H, dd, J = 13.2, 7.6 Hz), 2.81 (1H, dd, J = 13.2, 4.6 Hz), 3.4-3.8 (3H, m), 7.10 (3H, s); $[\alpha]_D^{29}$ +36.5 ° (*c* 1.01, $CHCl_3$) (88 %ee). Anal. Calcd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60. Found: C, 61.84; H, 7.57. The optical purity of **6** was determined by HPLC analysis [Chiralcel OD, hexane / 2-propanol (5:1) as eluant].

(S)-2-[(Phenylthio)methyl]-1,2-decanediol **(12).** The oxirane **11** was prepared from diethyl malonate in 3 steps according to the literature.[9] The compound **12** was isolated by column chromatography [silica gel, hexane / ethyl acetate (2:1) as eluant]; yield 81 % (from the oxirane **11**); colorless liquid; R_f 0.31 [hexane / ethyl acetate (2:1)]; IR (liquid film) 3400, 2940, 2860, 1590, 1480, 1440, 1070, 740, 700 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J = 6.4Hz), 1.1-1.4 (12H, m), 1.48-1.51 (2H, m), 1.8-2.0 (1H, m, OH), 2.49 (1H, s, OH), 3.14 (1H, d, J = 18.0 Hz), 3.20 (1H, d, J = 18.0 Hz), 3.52 (1H, dd, J = 11.6, 5.6 Hz), 3.54 (1H, dd, J = 11.6, 6.2 Hz), 7.15-7.44 (5H, m); $[\alpha]_D^{25}$ +1.4 ° (*c* 1.01, $CHCl_3$) (89 %ee). Anal. Calcd for $C_{17}H_{28}O_2S$: C, 68.87; H, 9.52. Found: C, 68.70; H, 9.49. The optical purity of **12** was determined by HPLC analysis [Chiralcel OD, hexane / 2-propanol (10:1) as eluant].

Reaction of (R)-1-(Pentafluorophenyl)-2-(phenylthio)ethanol **(1b)** ***and Acetonitrile. A General Procedure.*** To a solution of the alcohol **1b** (0.160 g, 0.500 mmol, 97 %ee) in acetonitrile (1.0 mL) at ambient temperature was added a solution of a mixture of trifluoromethanesulfonic acid and water (1:1 in molar ratio, 442 mg, 2.63 mmol) in acetonitrile (1.0 mL) and the resulting solution was stirred for 6 h. The reaction was quenched by the addition of sat. $NaHCO_3$ aq. solution (10 mL) and the products were extracted with dichloromethane (10 mL x 3). The organic layer was washed with brine, dried ($MgSO_4$), and evaporated in vacuo to leave a pale yellow oil. Column chromatography of the oil [silica gel, hexane / ethyl acetate (1:1) as eluant] afforded (*R*)-*N*-[1-(pentafluorophenyl)-2-(phenylthio)ethyl]acetamide (**4b**) (0.171 g, 0.473 mmol, 95 %): white crystals; mp 124.0-124.5 °C; R_f 0.29 [hexane / ethyl acetate (1:1)]; IR (KBr) 3300, 1660, 745, 695 cm^{-1}; ^1H NMR δ 1.93 (3H, s), 3.25 (1H, dd, J = 14.0, 8.0 Hz), 3.36 (1H, dd, J = 14.0, 7.0 Hz), 5.56 (1H, q, J = 8.0 Hz), 6.36 (1H, d, J = 7.8 Hz), 7.20-7.40 (5H, m); $[\alpha]_D^{23}$ +3.7 ° (*c* 1.04, $CHCl_3$) (97 %ee). Anal. Calcd for $C_{16}H_{12}NOF_5S$: C, 53.19; H, 3.35; N, 3.88. Found: C, 53.09; H, 3.44; N, 3.87. The optical purity of **4b** was determined by HPLC analysis [Chiralcel OJ, hexane / 2-propanol (10:1) as eluant].

Reaction of (S)-3-[(2,6-Dimethylphenyl)thio]-1,2-propanediol **(6)** ***and Benzonitrile. A General Procedure.*** To a solution of the diol **6** (107 mg, 0.503 mmol) in benzonitrile (1.5 mL)was added a benzonitrile (0.5 mL) solution of a mixture of trifluoromethanesulfonic acid and water (1:1 in molar ratio, 418 mg, 2.49 mmol) at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 20 h. The reaction was quenched by the addition of sat. $NaHCO_3$ aq. solution and the products were extracted with

dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to leave pale yellow liquid. Column chromatography of this liquid [silica gel, hexane / ethyl acetate (20:1) as eluant] afforded a mixture of **8b** and **9b** [92 mg, 0.31 mmol, 62 % (as a mixture). A ratio of **8b** to **9b** was determined from the integral of ^{1}H NMR spectrum (**8b** / **9b** = 1:1)]. Further separation of the mixture was carried out by medium pressured column chromataography to afford the pure product each. (*S*)-4-[[(2,6-Dimethylphenyl)thio]methyl]-2-phenyloxazoline (**8b**): colorless liquid; R_f 0.27 [hexane / ethyl acetate (10:1)]; IR (liquid film) 2930, 1650, 1460, 1060, 780, 700 cm^{-1}; ^{1}H NMR δ 2.53 (6H, s), 2.63 (1H, dd, J = 12.8, 9.2 Hz), 3.14 (1H, dd, J = 12.8, 3.6 Hz), 4.24-4.37 (2H, m), 4.42-4.53 (1H, m), 7.08 (3H, s), 7.32-7.49 (3H, m),7.85-7.90 (2H, m); $[\alpha]_D^{28}$ -18.4 ° (*c* 0.581, $CHCl_3$) (84 %ee). Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.59; H, 6.39; N, 4.66. The optical purity of **8b** was determined by HPLC analysis [Chiralcel OD, hexane / 2-propanol (5:1) as eluant]. (*S*)-5-[(2,6-Dimethylphenyl)thio]-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (**9b**): colorless liquid; R_f 0.13 [hexane / ethyl acetate (10:1)]; IR (liquid film) 2950, 1660, 1130, 770, 700 cm^{-1}; ^{1}H NMR δ 2.57 (6H, s), 3.27 (1H, tdd, J = 9.2, 5.2, 4.2 Hz), 3.49 (1H, dd, J = 16.8, 9.2 Hz), 3.89 (1H, ddd, J = 16.8, 5.2, 2.4 Hz), 4.10 (1H, dd, J = 10.6, 9.2 Hz), 4.33 (1H, ddd, J = 10.6, 4.2, 2.4 Hz), 7.14 (3H, s), 7.26-7.42 (3H, m), 7.84-7.89 (2H, m); $[\alpha]_D^{29}$ +13.2 ° (*c* 0.447, $CHCl_3$) (84 %ee). Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.61; H, 6.48; N, 4.60. The optical purity of **9b** was determined by HPLC analysis [Chiralcel OD, hexane / 2-propanol (5:1) as eluant].

Reaction of (S)-2-[(Phenylthio)methyl]-1,2-decanediol* (12) *and Acetonitrile. A General Procedure. To a solution of the diol **12** (148 mg, 0.499 mmol) in acetonitrile (1.5 mL) was added a solution of a mixture of trifluoromethanesulfonic acid and water (1:1 in molar ratio, 420 mg, 2.50 mmol) at -20 °C under nitrogen atmosphere and the resulting mixture was stirred for 12 h. The reaction was quenched by the addition of sat. $NaHCO_3$ aq. solution (20 mL) and the products were extracted with dichloromethane (20 mL x 3). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to leave a pale yellow oil (145 mg). Column chromatography of the crude oil [silica gel, hexane / ethyl acetate (2:1) as eluant] afforded (*S*)-2-methyl-4-octyl-[4-(phenylthio)methyl]oxazoline (**14a**) (131 mg, 0.41 mmol, 82 %): colorless liquid; R_f 0.14 [hexane / ethyl acetate (5:1)]; IR (liquid film) 2940, 1680, 1590, 1440, 1380, 1240, 1000, 740 cm^{-1}; ^{1}H NMR δ 0.87 (3H, t, J = 6.5 Hz), 1.15-1.40 (12H, m), 1.60-1.64 (2H, m),1.94 (3H, s), 3.13 (2H, s), 3.95 (1H, d, J = 8.6 Hz), 4.18 (1H, d, J = 8.6 Hz), 7.10-7.39 (5H, m), $[\alpha]_D^{24}$ +24.3 ° (*c* 1.15, $CHCl_3$) (89 %ee). Anal. Calcd for $C_{19}H_{29}NOS$: C, 71.43; H, 9.15; N, 4.38. Found: C, 71.10; H, 9.29; N, 4.24. The optical purity of **14a** was determined by HPLC analysis [Chiralcel OD, hexane / 2-propanol (10:1) as eluant].

Spectral and analytical data of other amides, oxazolines, and dihydrooxazines are as follows.

***(R)-N-[1-Phenyl-2-(phenylthio)ethyl]acetamide* (4a).** Isolated by column chromatography [silica gel, hexane / ethyl acetate (1:1) as eluant]; yield 74 %; white crystals; mp 85.0-86.5 °C; R_f 0.24 [hexane / ethyl acetate (1:1)]; IR (KBr) 3290, 1650, 1550, 740, 690 cm^{-1}; ^{1}H NMR δ 1.92 (3H, s), 3.28 (1H, dd, J = 13.5, 6.4 Hz), 3.38 (1H, dd, J = 13.5, 7.0 Hz), 5.17 (1H, q, J = 7.0 Hz), 6.22 (1H, d, J = 7.0 Hz), 7.15-7.4 (10 H, m); $[\alpha]_D^{25}$ -41.6 ° (*c* 1.03, $CHCl_3$) (100 %ee). Anal. Calcd for $C_{16}H_{17}NOS$: C, 70.82; H, 6.31; N, 5.16. Found: C, 70.73; H, 6.20; N, 5.02. The optical purity of **4a** was determined by HPLC analysis [Chiralcel OD, hexane / 2-propanol (10:1) as eluant].

***(R)-N-[1-(Phenylthio)dodecan-2-yl]acetamide* (4c).** Isolated by column chromatography [silica gel, hexane / ethyl acetate (2:1) as eluant]; yield 81 %; white crystals; mp 68.5-69.0 °C; R_f 0.10 [hexane / ethyl acetate (3:1)]; IR (KBr) 3320, 2920, 2850, 1652, 1548, 735, 690 cm^{-1}; ^{1}H NMR δ 0.87

(3H, t, J = 6.0 Hz), 1.2-1.4 (16H, m), 1.4-1.7 (2H, m), 1.84 (3H, s), 3.10 (1H, dd, J = 13.6, 5.0 Hz), 3.13 (1H, dd, J = 13.6, 5.0 Hz), 4.15 (1H, tq, J = 8.4, 5.0 Hz), 5.39 (1H, d, J = 8.6 Hz), 7.1-7.45 (5H, m): $[\alpha]_D^{27}$ +12.7 ° (*c* 0.490, $CHCl_3$) (85 %ee); Anal. Calcd for $C_{20}H_{33}NOS$: C, 71.59; H, 9.91; N, 4.17. Found: C, 71.87; H, 10.09; N, 4.16. The optical purity of **4c** was determined by ^1H NMR spectrum of its MTPA amide.

(S)-N-[2-(phenylthio)dodecan-1-yl]acetamide (**5c**). Isolated by column chromatography [silica gel, hexane / ethyl acetate (2:1) as eluant]; yield 9 %; colorless liquid; R_f 0.10 [hexane / ethyl acetate (3:1)]; IR (liquid film) 3290, 2930, 2850, 1650, 1560, 740, 695 cm^{-1}; ^1H NMR δ 0.86 (3H, t, J = 6.8 Hz), 1.15-1.4 (14H, m), 1.4-1.6 (4H, m), 1.90 (3H, s), 3.1-3.3 (2H, m), 3.4-3.6 (1H, m), 5.93 (1H, s), 7.2-7.45 (5H, m); $[\alpha]_D^{25}$ +13.1 ° (*c* 3.91, $CHCl_3$) (86 %ee). Anal. Calcd for $C_{20}H_{33}NOS$: C, 71.59; H, 9.91; N, 4.17. Found: C, 71.39; H, 10.05; N, 4.09. The optical purity of **5c** was determined by HPLC analysis [Chiralcel OD, hexane / 2-propanol (10:1) as eluant].

(R)-N-[2-Methyl-1-(phenylthio)heptan-2-yl]acetamide (**4d**). Isolated by column chromatography [silica gel, hexane / ethyl acetate (1:1) as eluant]; yield 92 %; colorless liquid; R_f 0.20 [hexane / ethyl acetate (3:1)]; IR (liquid film) 3290, 2930, 2860, 1650, 1550, 740, 690 cm^{-1}; ^1H NMR δ 0.85 (3H, t, J = 6.6 Hz), 1.15-1.35 (6H, m), 1.33 (3H, s), 1.5-1.7 (1H, m), 1.74 (3H, s), 1.8-2.0 (1H, m), 3.21 (1H, d, J = 13.0 Hz), 3.56 (1H, d, J = 13.0 Hz), 5.38 (1H, s), 7.1-7.4 (5H, m); $[\alpha]_D^{23}$ + 1.28 ° (*c* 9.75, $CHCl_3$) (82 %ee). Anal. Calcd for $C_{16}H_{25}NOS$: C, 68.77; H, 9.01; N, 5.01. Found: C, 68.59; H, 9.01; N, 4.87. The optical purity of **4d** was determined by ^1H NMR spectrum of its MTPA amide.

(S)-2-Methyl-4-[[(2,6-dimethylphenyl)thio]methyl]oxazoline (**8a**). Isolated by column chromatography [silica gel, hexane / ethyl acetate (2:1) as eluant]; yield 21 %; colorless liquid; R_f 0.31 [hexane / ethyl acetate (2:1)]; IR (liquid film) 2940, 1680, 1460, 1240, 990, 920, 780 cm^{-1}; ^1H NMR δ 1.94 (3H, s), 2.52 (6H, s), 2.56 (1H, dd, J = 12.6, 8.6 Hz), 3.06 (1H, dd, J =12.6, 4.0 Hz), 4.01-4.33 (3H, m), 7.08 (3H, s); $[\alpha]_D^{28}$ -5.3 ° (*c* 0.339, $CHCl_3$) (85 %ee). The optical purity of **8a** was determined by HPLC analysis [Chiralcel OD, hexane / 2-propanol (10:1) as eluant].

(S)-N-[3-Hydroxy-2-[(2,6-dimethylphenyl)thio]propan-1-yl]acetamide (**10a**). Isolated by column chromatography (silica gel, ethyl acetate as eluant); yield 19 %; pale yellow crystals; mp 102.0-104.0 °C; R_f 0.29 (ethyl acetate); IR (KBr) 3300, 3250, 2940, 1650, 1570, 1460, 970, 770 cm^{-1}; ^1H NMR δ 2.02 (3H, s), 2.50 (6H, s), 2.92-3.03 (1H, m, OH), 3.30 (1H, dt, J = 14.4, 5.4 Hz), 3.47 (1H, dd, J = 12.0, 8.2 Hz), 3.57 (1H, dd, J = 12.0, 4.7 Hz), 3.82 (1H, ddd, J = 14.4, 7.4, 4.2 Hz), 4.0-4.2 (1H, m), 6.22 (1H, s), 7.09 (3H, s); $[\alpha]_D^{31}$ +60.2 ° (*c* 0.504, $CHCl_3$) (86 %ee). The alcohol **10a** was derived to the acetate whose optical purity was determined by HPLC analysis [Chiralpak AD, hexane / 2-propanol (10:1) as eluant].

(S)-2-t-Butyl-4-[[(2,6-dimethylphenyl)thio]methyl]oxazoline (**8c**). Isolated by column chromatography [silica gel, hexane / ethyl acetate (20:1) as eluant]; white crystals; yield 26 %; mp 41.0-43.5 °C; R_f 0.33 [hexane / ethyl acetate (5:1)]; IR (liquid film) 2980, 1670, 1460, 1140, 780 cm^{-1}; ^1H NMR δ 1.18 (9H, s), 2.52 (6H, s), 2.5-2.6 (1H, m), 3.03 (1H, dd, J = 12.8, 3.2 Hz), 3.99-4.16 (2H, m), 4.20-4.34 (1H, m), 7.07 (3H, s); $[\alpha]_D^{23}$ -32.8 ° (*c* 0.540, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}NOS$: C, 69.27; H, 8.36; N, 5.05. Found: C, 69.48; H, 8.23; N, 5.31.

(S)-2-t-Butyl-5-[(2,6-dimethylphenyl)thio]-5,6-dihydro-4H-1,3-oxazine (**9c**). Isolated by column chromatography [silica gel, hexane / ethyl acetate (20:1) as eluant]; yield 26 %; white crystals; mp 58.0-59.0 °C; R_f 0.39 [hexane / ethyl acetate (5:1)]; IR (liquid film) 2980, 1670, 1460, 1140, 780 cm^{-1}; ^1H NMR δ 1.11 (9H, s), 2.54 (6H, s), 3.08 (1H, tdd, J = 9.0, 5.0, 4.0 Hz), 3.25 (1H, ddd, J = 15.8, 8.4, 0.8 Hz), 3.65 (1H, ddd, J = 15.8, 5.0, 2.4 Hz), 3.83-3.93 (1H, m), 4.12 (1H, ddd, J = 10.4, 4.0, 2.4 Hz), 7.12 (3H, s); $[\alpha]_D^{23}$+24.2 ° (*c* 0.650, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}NOS$: C, 69.27; H, 8.36; N, 5.05. Found: C, 69.05; H, 8.15; N, 4.88.

Since the peaks of the enantioisomers of **8c** and **9c** were not separated completely in liquid chromatographic analyses using chiral columns listed in this Experimental Section, their enantiomeric excesses were not determined.

(S)-4-Octyl-2-phenyl-4-[(phenylthio)methyl]oxazoline (**14b**). Isolated by column chromatography [silica gel, hexane / ethyl acetate (20:1) as eluant]; yield 79 %; colorless liquid; R_f 0.42 [hexane / ethyl acetate (10:1)]; IR (liquid film) 2930, 1650, 1580, 1480, 1160, 740, 700 cm^{-1}; ^1H NMR δ 0.85 (3H, t, J = 6.5 Hz), 1.1-1.5 (12H, m), 1.7-1.9 (2H, m), 3.26 (2H, s), 4.16 (1H, d, J = 8.6 Hz), 4.38 (1H, d, J = 8.6 Hz),7.10-7.27 (3H, m), 7.33-7.51 (5H, m), 7.85-7.91 (2H, m); $[\alpha]_D^{30}$ -9.3 ° (*c* 1.19, $CHCl_3$) (89 %ee). Anal. Calcd for $C_{24}H_{31}NOS$: C, 75.55; H, 8.19; N, 3.67. Found: C, 75.48; H, 8.21; N, 3.69. The optical purity of **14b** was determined by HPLC analysis [Chiralpak AD, hexane / 2-propanol (10:1) as eluant].

(S)-2-t-Butyl-4-octyl-4-[(phenylthio)methyl]oxazoline (**14c**). Isolated by column chromatography [silica gel, hexane / ethyl acetate (20:1) as eluant]; colorless liquid; yield 71 %; R_f 0.28 [hexane / ethyl acetate (10:1)]; IR (liquid film) 2930, 1660, 1580, 1480, 1130, 990, 740, 700 cm^{-1}; ^1H NMR δ 0.86 (3H, t, J = 6.4 Hz), 1.1-1.4 (12H, m), 1.17 (9H, s), 1.55-1.70 (2H, m), 3.11 (1H, d, J = 12.8 Hz), 3.20 (1H, d, J = 12.8 Hz), 3.96 (1H, d, J = 8.6 Hz), 4.16 (1H, d, J = 8.6 Hz), 7.10-7.39 (5H, m); $[\alpha]_D^{26}$ +22.6 ° (*c* 0.982, $CHCl_3$) (89 %ee). Anal. Calcd for $C_{22}H_{35}NOS$: C, 73.08; H, 9.76; N, 3.87. Found: C, 72.82; H, 9.93; N, 3.59. The optical purity of **14c** was determined by HPLC analysis [Chiralcel OD, hexane / 2-propanol (100:1) as eluant].

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