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Studies on Chiral Organo-Sulfur Compounds. I. Asymmetric Synthesis of Sulfoxides with Optically Active *o*-Aminoalkylphenol Derivatives[1)]

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Several kinds of optically active *o*-aminoalkylphenols were prepared and used to develop asymmetric synthetic methods for chiral sulfoxides.

The reaction of 2,3-dihydro-1,2,3-benzoxathiazine 2-oxides (derived from the *o*-aminoalkylphenols and thionyl chloride) with phenylmagnesium bromide, followed by treatment with alkyllithium, gave optically active sulfoxides with high enantiospecificity.

Among several kinds of optically active *o*-aminoalkylphenols examined, the readily available aminophenol, (*S*)-(−)-*o*-{1-((*S*)-1-α-naphthylethylamino)ethyl}phenol, was found to be the most efficient and recyclable chiral source for the asymmetric synthesis of sulfoxides.

Keywords——asymmetric synthesis; chiral sulfoxide; *o*-aminoalkylphenol; 3,4-dihydro-1,2,3-benzoxathiazine 2-oxide; thionyl chloride

Optical isomerism is observed in three-coordinate sulfur compounds such as sulfoxides, sulfinates, thiosulfinates, and sulfinamides, because of their pyramidal arrangement of ligands, and in the past decade remarkable progress has been made in the chemistry of these kinds of chiral organo-sulfur compounds.[2)] Since Andersen[3)] reported a practically useful synthetic method for the preparation of chiral sulfoxides with (−)-menthyl sulfinates, much attention has been devoted especially to the synthesis of chiral sulfoxides and to the development of their synthetic utility in organic synthesis.[4)] Many kinds of strategies have been devised for the preparation of chiral sulfoxides by means of asymmetric induction with sulfinates[5)] or sulfinamides,[6)] asymmetric oxidation of sulfides[7)] with optically active peracids[8)] or micro-organisms,[9)] partial reduction of racemic sulfoxides,[10)] and optical resolution.[11)] However these known methods have some limitations for general use and as regards enantiospecificity. Therefore, a more practically useful reagent is required for efficient preparation of optically active sulfoxides.

We wish to report herein asymmetric synthesis of sulfoxides using optically active *o*-aminoalkylphenol derivatives for enantiomeric discrimination of the two sulfur–chlorine bonds of thionyl chloride.

Preparation of Optically Active *o*-Aminoalkylphenol Derivatives

Several kinds of optically active *o*-aminoalkylphenols **4**, **7**, **8**, and **9** (starting chiral sources for this asymmetric synthesis) were prepared by condensation of optically active primary amines, (*S*)-(−)-α-phenylethylamine (**1a**) and (*S*)-(−)-α-naphthylethylamine (**1b**), and *ortho*-acylated phenols **2** and **5a**—**c**, followed by $NaBH_4$ reduction of the imines **3** and **6**.

In the preparation of *o*-{1-(1-α-naphthylethylamino)ethyl}phenol (**7**) from **1b** and 2-hydroxyacetophenone (**5a**), the main product **7a** (yield 47%) solidified and therefore could be easily separated from the other isomer **7b** (yield 25%) by recrystallization from carbon tetrachloride–hexane, giving an analytically pure sample as colorless needles of mp 141—142 °C. The other isomeric *o*-aminoalkylphenols **8a**, **b** and **9a**, **b** were isolated by benzoylation

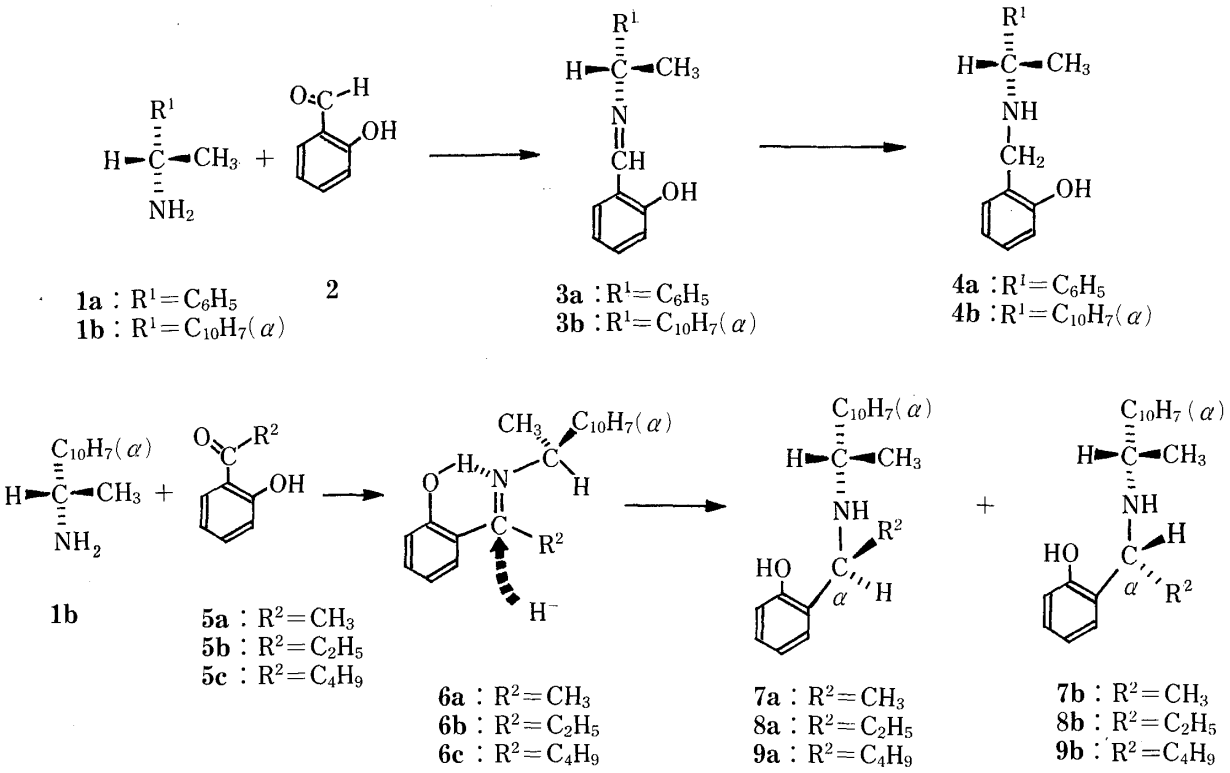


Chart 1

and subsequent hydrolysis of the separated benzoates.

Complete retention of optical activity of the chiral center in the imine during the condensation reaction was demonstrated by comparison of the optical rotation of the (*S*)-(−)-*N*-(α-naphthylethyl)acetamide, obtained by acidic hydrolysis of the imine (**3b**) followed by acetylation, with that of the authentic acetamide.

The stereochemistry of the asymmetric carbons newly created by reduction of the imine **6** can be deduced on the basis of the following mechanism. The *ortho*-hydroxy substituent in the imine would form an intramolecular hydrogen bond with the nitrogen atom of the imino group, resulting in formation of a six-membered ring system as shown in **6**.[12] Reduction of the imine **6** with $NaBH_4$ would occur mainly from the direction of the smaller group (methyl) in the most preferred conformation (**6**), in which the hydrogen atom at the chiral center would be in the same plane as the alkyl group (R^2) attached to the carbon–nitrogen double bond, as depicted in **6**. These steric considerations indicate that the stereochemistry of the asymmetric carbons newly created in the main products (**7a**, **8a**, and **9a**) and the minor ones (**7b**, **8b**, and **9b**) should be assigned as (*S*)- and (*R*)-configuration, respectively.

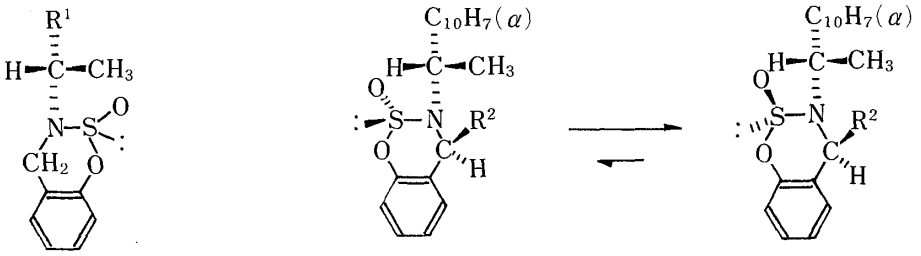
The above discussion is consistent with the preferential formation of **7b** and **9b** over **7a** and **9a** in the reaction of **3b** with methyl- and butyllithium.

Preparation of 3,4-Dihydro-1,2,3-benzoxathiazine 2-Oxide Derivatives from *o*-Aminoalkylphenols and Stereospecificity in the Nucleophilic Substitutions

Reactions of the *o*-aminomethylphenols **4a** and **4b** with thionyl chloride were carried out in the presence of triethylamine to give 3,4-dihydro-3-(1-phenylethyl)- and 3,4-dihydro-3-(1-α-naphthylethyl)-1,2,3-benzoxathiazine 2-oxide (**10a**) and (**10b**). The structures of the cyclized products **10a**, **b** were confirmed by the mass and nuclear magnetic resonance (NMR) spectral analyses.

(*S*)-*o*-{1-((*S*)-1-α-Naphthylethylamino)ethyl}phenol (**7a**) reacted with thionyl chloride (1.5 eq) in the presence of triethylamine (5 eq) at 0 °C for 4 h to give (2*R*, 4*S*)- and (2*S*, 4*S*)-3,4-

dihydro-4-methyl-3-{(*S*)-1-α-naphthylethyl}-1,2,3-benzoxathiazine 2-oxide (**11a**-I) (colorless needles of mp 98—99 °C) and (**11a**-II) (colorless needles of mp 121 °C in a ratio of about 2 : 1 in 92% yield.



10a : $R^1 = C_6H_5$
10b : $R^1 = C_{10}H_7(\alpha)$

11a-I : $R^2 = CH_3$
11b-I : $R^2 = C_2H_5$
11c-I : $R^2 = C_4H_9$

11a-II : $R^2 = CH_3$
11b-II : $R^2 = C_2H_5$
11c-II : $R^2 = C_4H_9$

Chart 2

It is necessary to form one of the diastereomeric 3,4-dihydro-1,2,3-benzoxathiazine 2-oxides **11a**-I and **11a**-II stereoselectively by means of isomerization of the amidosulfite moiety in order to develop a valuable method for asymmetric synthesis of chiral organo-sulfur compounds using this system. For this purpose and also for assignment of the stereochemistry of this compound, isomerization of the amidosulfite group in **11a** was studied using acidic catalysts such as hydrogen chloride, boron trifluoride etherate, trifluoroacetic acid, acetic acid, and aluminum chloride.[13]

It was observed, unexpectedly, that the use of excess thionyl chloride in the preparation of **11a** provided **11a**-II preferentially over **11a**-I, presumably due to the equilibrium transformation of **11a**-I into **11a**-II by hydrogen chloride generated by hydrolysis of excess thionyl chloride; *e.g.* the reaction of **7a** with thionyl chloride (2.5 eq)-triethylamine (5 eq) gave **11a** in a 2 : 3 ratio of **11a**-I and **11a**-II.

In fact, the isomerization of the amidosulfite function in **11a**-I was induced by treatment with a hydrogen chloride–toluene solution of low concentration as described in Table I. The ratios of the diastereoisomers **11a**-I and **11a**-II obtained at various times in the equilibrium reaction were determined by integrating the C_4 methine peaks of both isomers in the NMR spectra, and are listed in Table I, which indicates the optimum condition is to treat **11a**-I with a 0.032 N hydrogen chloride–toluene solution at 0 °C for 2 h. The isomerization of **11a**-I with other acidic catalysts was carried out in the same way, and the results are summarized in Table II. Inspection of Table II shows that the amidosulfite moiety in **11a**-I could be easily isomerized with Lewis acids and carboxylic acids as well as hydrogen chloride under

TABLE I. Studies on Isomerization of **11a**-I with Hydrogen Chloride[a]

Concentration of hydrogen chloride in toluene	Reaction time (h)	Yield of **11a** (%)	Ratio of **11a**-I to **11a**-II[b]	
			11a-I	: **11a**-II
0.016 N	2.0	84	33	67
0.032 N	0.5	88	87	13
0.032 N	1.0	86	39	61
0.032 N	2.0	81	4	96
0.032 N	3.0	73	3	97

a) The reactions were carried out in toluene at 0 °C.
b) Calculated by NMR analysis.

TABLE II. Studies on Isomerization of **11a**-I with Acidic Catalysts[a]

Catalysts	(eq)	Reaction time (h)	Yield of **11a** (%)	Ratio of **11a**-I to **11a**-II[b]	
				11a-I	: **11a**-II
$BF_3 \cdot OEt_2$	0.04	3.0	71	46	54
$BF_3 \cdot OEt_2$	0.07	1.0	91		100
CF_3CO_2H	0.07	3.0	70	33	67
CF_3CO_2H	0.12	1.5	66		100
CH_3CO_2H	0.20	4.0	62	25	75
CH_3CO_2H	0.60	14.0	57		100
$AlCl_3$	0.07	14.0	66	50	50
$AlCl_3$	0.20	1.0	55		100

a) Toluene (2 ml) was used with 0.45 mmol of **11a**-I. Reacted at 0 °C.
b) Calculated by NMR analysis.

extremely mild conditions to provide the other isomer **11a**-II almost quantitatively.

These results indicate that the isomer **11a**-II might be thermodynamically more stable than the other one, **11a**-I, as shown in Chart 2. This is consistent with NMR spectral analyses based on the anisotropy effect of the sulfinyl function[6b] as follows; the methine proton ($CH_3C\underline{H}$–C_6H_4) *syn* to the sulfinyl group in **11a**-I is deshielded and thus appears at a lower chemical shift (δ 4.60) as a quartet than that of **11a**-II (δ 3.90), and the methyl protons ($C\underline{H}_3CH$–C_6H_4) *anti* to this group in **11a**-I appear at higher field (δ 1.55) as a doublet than those of **11a**-II (δ 1.67). Thus, the stereochemistry of the sulfur atoms in **11a**-I and **11a**-II was unequivocally determined as (2*S*)-**11a**-I and (2*R*)-**11a**-II.

It is well known that normally a nucleophilic substitution reaction on acyclic chiral tricoordinated tetravalent sulfur compounds such as sulfoxides and sulfinates occurs highly stereospecifically with inversion of configuration at the sulfur atoms.[3,14] However, few papers have appeared on the stereochemistry in the nucleophilic substitution of amidosulfite functions. Therefore we carried out the stereochemical studies on the nucleophilic substitution of a 3,4-dihydro-1,2,3-oxathiazine 2-oxide system, in order to evaluate this system for asymmetric synthesis of chiral organo-sulfur compounds.

Compound **11a**-I reacted with phenylmagnesium bromide at −78 °C for 2 h to give *N*-[(*S*)-1-(*o*-hydroxyphenyl)ethyl]-*N*-[(*S*)-1-α-naphthylethyl]phenylsulfinamide (**12a**) and (**12b**) as colorless needles of mp 154—155 °C and mp 132—134 °C in a ratio of 92:8 (84% yield), respectively. Analogously, the reagent reacted with the other isomer **11a**-II under the same conditions to produce **12a** and **12b** in a ratio of 8:92 (98% yield). The sulfinamides **12a** and **12b** reacted with butyllithium at −78 °C for 2 h to afford (*R*)-(+)- and (*S*)-(−)-butyl phenyl sulfoxide (**15b**)[15] in 98 and 99% enantiomeric excess, respectively. Accordingly, the absolute configurations of these compounds are assigned as (S^R)-**12a** and (S^S)-**12b**, provided that the nucleophilic substitution reaction of **12** with butyllithium occurs with inversion of configuration, as reported.[3,14]

Other nucleophilic substitutions of **11a**-I and **11a**-II were performed analogously using other nucleophiles such as methylmagnesium bromide and methyl- or butyllithium. Reaction of **11a**-I with methylmagnesium bromide and methyllithium or butyllithium provided *N*-[(*S*)-1-(*o*-hydroxyphenyl)ethyl]-*N*-[(*S*)-1-α-naphthylethyl]methylsulfinamide (**13**) with 90:10 and 93:7 ratios of **13a** and **13b**, or *N*-[(*S*)-1-(*o*-hydroxyphenyl)ethyl]-*N*-[(*S*)-1-α-naphthylethyl]butylsulfinamide (**14**) with an 87:13 ratio of **14a** and **14b**, respectively. Analogous nucleophilic substitution of the other stereoisomer **11a**-II gave similar results with reversed product ratios as shown in Table III.

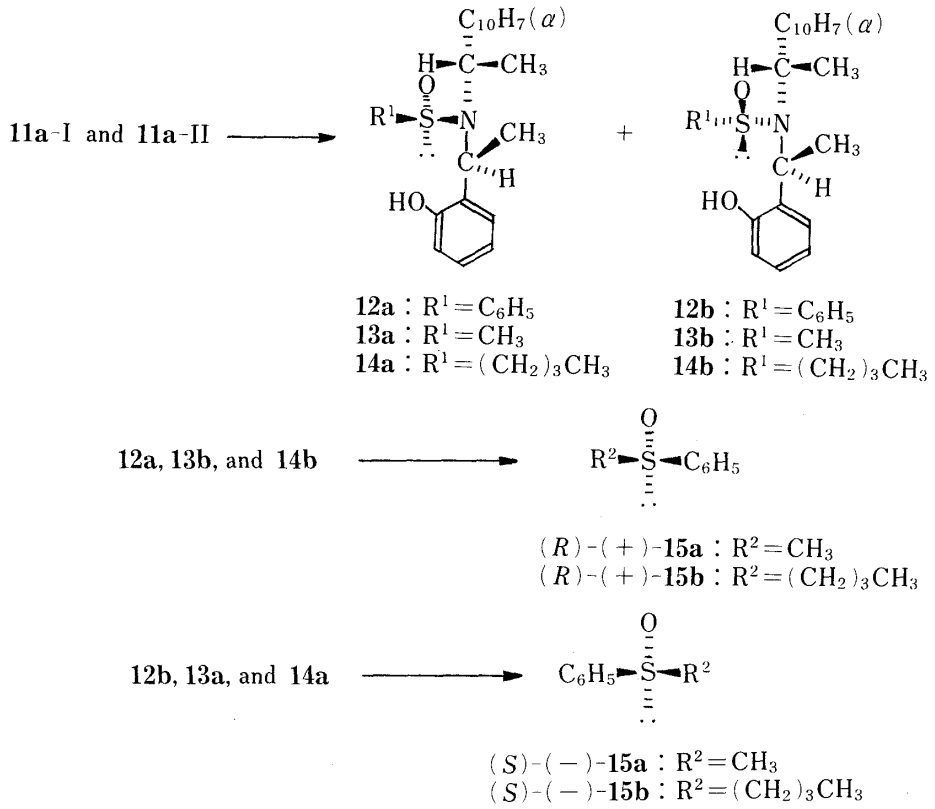


Chart 3

TABLE III. Stereospecificity in the Nucleophilic Substitution of **11a**-I and **11a**-II[a]

Nucleophiles	**11a**	Reaction time (h)	**12**—**14**	R^1	Product **12**—**14**		
					Yield of **12**—**14** (%)	**12a**—**14a** : **12b**—**14b**[b] (%)	
C_6H_5MgBr	**11a**-I	2.5	**12**	C_6H_5	84	92	8
C_6H_5MgBr	**11a**-II	2.5	**12**	C_6H_5	98	8	92
CH_3MgBr	**11a**-I	3.0	**13**	CH_3	75	90	10
CH_3MgBr	**11a**-II	3.0	**13**	CH_3	90	10	90
CH_3Li	**11a**-I	2.0	**13**	CH_3	43	93	7
CH_3Li	**11a**-II	2.0	**13**	CH_3	35	7	93
BuLi	**11a**-I	2.0	**14**	Bu	44	83	17
BuLi	**11a**-II	2.0	**14**	Bu	37	17	83

a) All reactions were carried out at −78 °C in THF.
b) The ratios were obtained by isolation of the isomers by preparative TLC.

Substitution of sulfinamides **13a** and **13b**, or **14a**, and **14b** with phenyllithium produced (*S*)-(−)- and (*R*)-(+)-methyl phenyl sulfoxide (**15a**),[16] or (*S*)-(−)- and (*R*)-(+)-**15b** with exceedingly high stereospecificity (95—97%), respectively. Therefore the absolute configurations of these sulfinamides were also assigned in the same way as (S^R)-**13a**, (S^S)-**13b**, (S^R)-**14a**, and (S^S)-**14b**.

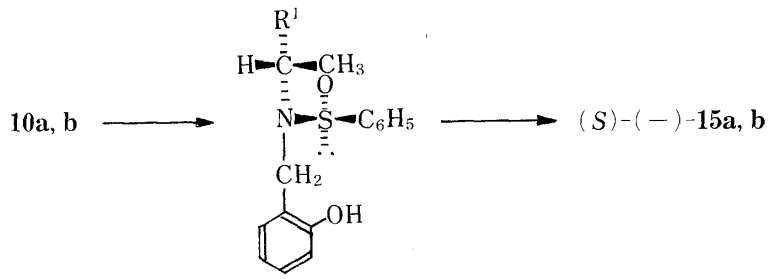
Thus, from the stereochemistry of **11a** and the stereochemical results in the nucleophilic substitutions of **11a** mentioned above, it should be concluded that the nucleophilic substitution of the 3,4-dihydro-1,2,3-benzoxathiazine 2-oxide system, a six-membered amidosul-

fite, proceeds with an extremely high degree of stereospecificity, with inversion of configuration.

This efficient stereochemical outcome suggests that this six-membered ring system involving an amidosulfite moiety should be useful for the asymmetric synthesis of various kinds of organo-sulfur compounds as a potential chiral director.

Asymmetric Synthesis of Sulfoxides through 3,4-Dihydro-1,2,3-benzoxathiazine 2-Oxide Derivatives

The 3,4-dihydro-1,2,3-benzoxathiazine 2-oxides **10a** and **10b**, prepared under various reaction conditions in the yields listed in parentheses in Table IV, reacted with phenylmagnesium bromide in tetrahydrofuran (THF) at −78 °C for 2.5 h to give *N*-(2-hydroxybenzyl)-*N*-((*S*)-1-phenylethyl) and *N*-((*S*)-1-α-naphthylethyl)phenylsulfinamide (**16a**) and (**16b**), respectively. Treatment of these products with methyl- or butyllithium at −78 °C for 2 h in THF gave (*S*)-(−)-**15a** or **15b** in the optical yields shown in Table IV. The results indicate



16a : $R^1 = C_6H_5$
16b : $R^1 = C_{10}H_7(\alpha)$

Chart 4

that the α-naphthyl substituent is rather efficient for this asymmetric synthesis, and that toluene is the most effective solvent fot the asymmetric formation of **10a**, **b** among several kinds of solvent examined in the reaction of **4a**, **b** with thionyl chloride.

In order to improve the optical yield in this asymmetric synthesis, other *o*-aminoalkylphenols derived from **1b**, bearing alkyl groups at the C_α position were examined. The crude cyclized product **11a** [obtained by reaction of **7a**, bearing a methyl group at the C_α position, with thionyl chloride (1.5 eq)-triethylamine (3.6—5.0 eq)] was treated with phenylmagnesium bromide at −78 °C for 2.5 h followed by addition of methyllithium (−78 °C, 2 h) to furnish (*R*)-(+)-**15a** in 33% optical and 42% chemical yields (based on **7a** used). In contrast, the crude product **11a**, obtained under the conditions described above, was treated with a 0.032 N hydrogen chloride–toluene solution at 0 °C for 2 h followed by the same sequence (phenylmagnesium bromide, −78 °C, 2.5 h and methyl- or butyllithium, −78 °C, 2 h) to produce (*S*)-(−)-**15a** or (*S*)-(−)-**15b** (42 or 40% yield from **7a** used) in high optical yield (75 or 81%), respectively. This means that the isomer **11a**-I was initially formed preferentially over **11a**-II in the reaction of **7a** with thionyl chloride and the subsequent hydrogen chloride treatment of the crude product (enriched with **11a**-I) caused an acid-catalyzed equilibrium reaction to convert the isomer **11a**-I into the thermodynamically more stable isomer **11a**-II.

In the reaction of **7a** with excess thionyl chloride (3 eq) in the presence of triethylamine (5 eq), the direct equilibrium transformation of **11a**-I into **11a**-II could be accomplished during this reaction, presumably due to the effect of hydrogen chloride generated by hydrolysis of excess thionyl chloride, yielding (*S*)-(−)-**15a**, **b** in the same procedure. The results obtained by these sequences, using several kinds of solvent in order to reveal solvent effects on the asymmetric cyclization of **7a** with thionyl chloride, are summarized in Table V.

TABLE IV. Asymmetric Synthesis of (*S*)-(−)-**15a, b** with **4a, b**

Reaction conditions for preparation of **10a, b**[a]					(*S*)-(−)-**15a, b**[b]			
4	Solvent	Reaction temp. (°C)	Reaction time (h)	(Yield %)	**15**	Yield[c] (%)	$[\alpha]_D$[d]	Optical[15,16] yield (%)
4a	THF	−78	5	(56)	**15a**	41	−15.5° (*c*=0.30)[e]	10
4a	THF	−78	5	(56)	**15b**	41	−13.9° (*c*=0.21)[f]	9
4a	THF	−20	7.5	(76)	**15a**	53	−18.3° (*c*=0.45)[e]	12
4a	THF	−20	7.5	(76)	**15b**	52	−11.9° (*c*=0.29)[f]	8
4a	THF	0	5	(90)	**15a**	61	−21.0° (*c*=0.37)[e]	14
4a	THF	0	6	(90)	**15b**	62	−20.5° (*c*=0.38)[f]	13
4a	THF	Room temp.	3	(82)	**15a**	56	−19.1° (*c*=0.54)[e]	13
4a	THF	Room temp.	3	(82)	**15b**	55	−15.1° (*c*=0.21)[f]	10
4a	DME	0	4	(90)	**15a**	60	−27.1° (*c*=0.80)[e]	18
4a	Dioxane	Room temp.	4	(79)	**15a**	55	−23.8° (*c*=0.80)[e]	16
4a	Toluene	−78	6.5	(51)	**15a**	37	−19.9° (*c*=0.45)[e]	13
4a	Toluene	−78	8.5	(56)	**15b**	40	−19.1° (*c*=0.31)[f]	12
4a	Toluene	0	5	(76)	**15a**	44	−26.2° (*c*=0.44)[e]	18
4a	Toluene	0	4	(70)	**15b**	49	−24.1° (*c*=0.33)[f]	15
4a	CCl_4	0	2	(60)	**15a**	42	−27.4° (*c*=0.83)[e]	18
4a	$CHCl_3$	0	4	(79)	**15a**	54	−20.5° (*c*=0.30)[e]	14
4b	THF	0	4	(76)	**15a**	55	−52.0° (*c*=0.20)[e]	35
4b	THF	0	4	(76)	**15b**	53	−42.9° (*c*=0.27)[f]	27
4b	Toluene	−20	5	(61)	**15a**	42	−30.5° (*c*=0.74)[e]	21
4b	Toluene	0	4	(73)	**15a**	44	−49.7° (*c*=0.34)[e]	33

a) Compounds **10a** and **10b** were prepared by reaction of **4a** and **4b** with thionyl chloride (1.5 eq)–triethylamine (3.6 eq) and the yields are given in parentheses.
b) Compounds **10a** and **10b** were reacted with phenylmagnesium bromide (−78 °C, 2.5 h, in THF), followed by treatment with methyl- or butyllithium (−78 °C, 2 h, in THF).
c) Yields based on **4a, b** used.
d) Measured at 17—25 °C.
e) Measured in EtOH.
f) Measured in MeOH.

TABLE V. Asymmetric Synthesis of **15a, b** with **7a**

Reaction conditions for preparation of **11a**[a]			Product **15**				
$SOCl_2$ (eq)	Et_3N (eq)	Solvent	**15**	Yield[b] (%)	$[\alpha]_D$ (EtOH) (Abs. config.)		Optical[15,16] yield (%)
1.5	3.6—5.0	Toluene	**15a**	42[c]	+48.6° (*c*=0.83, 21 °C)	(*R*)	33
1.5	5.0	Toluene	**15a**	42[d]	−111.0° (*c*=5.00, 17.5 °C)	(*S*)	75
1.5	5.0	Toluene	**15b**	40[d]	−128.0° (*c*=0.75, 23.5 °C)[e]	(*S*)	81
3.0	5.0	Toluene	**15a**	43[c]	−106.6° (*c*=0.50, 26 °C)	(*S*)	72
3.0	5.0	THF	**15a**	46[c]	−84.5° (*c*=0.63, 24 °C)	(*S*)	57
3.0	5.0	DME	**15a**	45[c]	−86.6° (*c*=0.58, 26 °C)	(*S*)	58
3.0	5.0	$CHCl_3$	**15a**	36[c]	−91.1° (*c*=0.49, 18.5 °C)	(*S*)	61
3.0	5.0	CCl_4	**15a**	35[c]	−96.0° (*c*=0.46, 26 °C)	(*S*)	64

a) Reacted at 0 °C for 4 h.
b) Based on **7a** used.
c) Without treatment with hydrogen chloride.
d) Treated with a 0.032 N hydrogen chloride–toluene solution at 0 °C for 2 h in the preparation of **11a**.
e) Measured in MeOH.

TABLE VI. Asymmetric Synthesis of (*S*)-(−)-**15a, b** with *o*-(1-α-Naphthylethylaminoalkyl)phenols (**7a**, **8a**, and **9a**)[a]

Aminophenols		Product **15**			
7—9	R^2	**15**	Yield (%)[b]	$[\alpha]_D$	Optical[15,16] yield (%)
7a	CH_3	**15a**	43	−106.6° (c=0.50, 26 °C)[d]	72
7a	CH_3	**15b**	40[c]	−128.0° (c=0.75, 23.5 °C)[e]	81
8a	CH_2CH_3	**15a**	48	−66.9° (c=0.27, 22 °C)[d]	45
8a	CH_2CH_3	**15b**	48[c]	−69.0° (c=1.50, 19 °C)[e]	44
9a	$(CH_2)_3CH_3$	**15a**	26	−54.2° (c=1.20, 18 °C)[d]	36
9a	$(CH_2)_3CH_3$	**15b**	30	−59.9° (c=2.79, 20 °C)[e]	38

a) Compounds **11a—c**, prepared by reaction of **7a**, **8a**, and **9a** with thionyl chloride (3.0 eq)–triethylamine (5.0 eq) (0 °C, 4 h, in toluene), were reacted with phenylmagnesium bromide (−78 °C, 2.5 h, in THF) and methyl- or butyllithium (−78 °C, 2 h, in THF).
b) Yields based on **7a**, **8a**, and **9a** used.
c) Treated with a 0.032 N hydrogen chloride–toluene solution at 0 °C for 2 h in the preparation of **11**.
d) Measured in EtOH.
e) Measured in MeOH.

TABLE VII. Asymmetric Synthesis of (*R*)-(+)-**15a, b** with *o*-(1-α-Naphthylethylaminoalkyl)phenols (**7b**, **8b**, and **9b**)[a]

Aminophenols		Product (*R*)-(+)-**15**			
7—9	R^2	**15**	Yield (%)[b]	$[\alpha]_D$ (EtOH)	Optical[15,16] yield (%)
7b	CH_3	**15a**	42	+38.8° (c=0.24, 19.5 °C)	26
8b	CH_2CH_3	**15a**	45	+21.2° (c=0.44, 20 °C)	14
9b	$(CH_2)_3CH_3$	**15b**	30	+29.2° (c=0.26, 22 °C)[c]	18

a) The sulfoxides (*R*)-(+)-**15a, b** were obtained by reaction of **7b**, **8b**, and **9b** with thionyl chloride (3 eq)–triethylamine (5 eq) (0 °C, 4 h, in toluene) followed by nucleophilic substitution with phenylmagnesium bromide (−78 °C, 2.5 h, in THF) and methyl- or butyllithium (−78 °C, 2 h, in THF).
b) Yields based on **7b**, **8b**, and **9b** used.
c) Measured in MeOH.

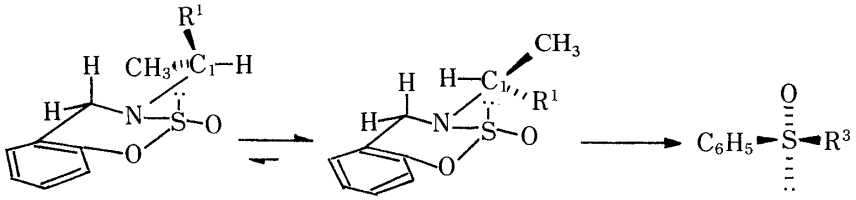
It should be noted, as shown in Table V, that toluene was the most effective in this asymmetric synthesis among the solvents examined, analogously to the case of **10a** and **10b** mentioned earlier. Furthermore, the starting *o*-aminoalkylphenol **7a** was recyclable in these asymmetric syntheses, since it was recovered without any racemization with high efficiency (87% recovered yield). Accordingly, it appeared likely that the substituents at the C_α position might greatly affect this asymmetric synthesis. Therefore the effects of substituents were investigated by replacing the methyl group with an ethyl or butyl substituent. The results obtained from the *o*-aminoalkylphenol derivatives **8a** and **9a** of *S*-configuration, possessing ethyl and butyl substituents at the C_α position, respectively, are summarized in Table VI.

It should be noted that the substituents R^2 in **11**, contrary to our expectation, affected the asymmetric induction by the degree of their decreasing steric bulkiness.

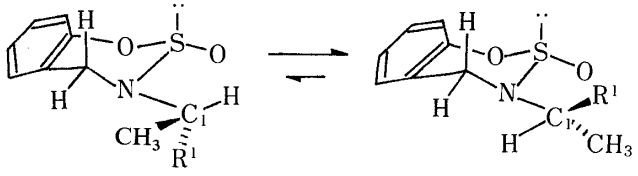
Other stereoisomeric *o*-aminoalkylphenol derivatives **7b**, **8b**, and **9b** of *R*-configuration at the C_α position were also employed in this asymmetric induction reaction and afforded the sulfoxides of inverted configuration, (*R*)-(+)-**15a, b**; the results are listed in Table VII.

Thus, it is concluded that the readily available optically active *o*-aminoalkylphenol **7a** affording high enantiospecificity can serve as a highly efficient and recyclable chiral source for asymmetric synthesis of sulfoxides.

In a consideration of these stereochemical results, the most plausible mechanistic pathway for this asymmetric induction may be as follows. As model considerations show, it seems apparent that among the stereoisomers (**17** and **18**) of **10a, b** having an oxygen atom of the sulfinyl group occupying an equatorial position, the most preferred isomer by virtue of rotation about the C_1–N bond should be **17b**, due to steric interference between the largest group (R^1) and the lone pair of the sulfur atom in **18b**, conforming the methyl and phenyl or naphthyl groups at the C_1 position on the less sterically hindered side of an oxygen atom of the sulfinyl group. Therefore a Grignard reagent would attack this favored conformer **17b** stereospecifically with inversion of configuration, followed by reaction of alkyllithium also with inversion of configuration, to yield (*S*)-(−)-**15a, b**.



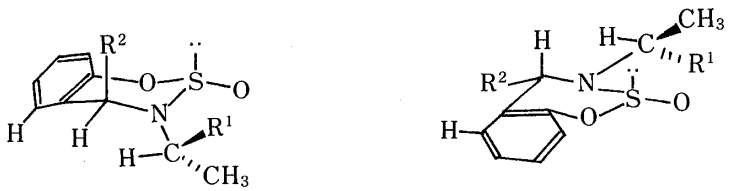
17a **17b** (*S*)-(−)-**15a, b**



18a **18b**

Chart 5

In the case of **11a**, the preferred conformer would apparently be **20** having *cis* configuration of the R^2 group (methyl) and the oxygen of the sulfinyl group, both occupying equatorial positions, since the *trans* isomer **19**, in which the lone pairs of the sulfur and nitrogen atoms are both orientated in the stereoelectronically more stable *trans* diaxial form, has 1,3-diaxial-like steric interaction between the R^2 group and a lone pair of the sulfur atom. A Grignard reagent would react stereospecifically with this preferred conformer (**20**), resulting in an excellent optical yield of **15a, b**.



19 **20**

Chart 6

On the other hand, inspection of Dreiding models of **11b, c** possessing ethyl and butyl groups at the C_α position, suggests that considerable steric hindrance exists between the substituent R^2 and a hydrogen atom at the *peri*-position of the benzene ring. This steric compression in **20** would increase the proportion of **19** in **11b, c** a little more than in **11a**, leading to much smaller optical yields of **15a, b**.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Thin-layer or preparative thick layer plates were made of E. Merck silica gel 60PF-254 activated by drying at 140 °C for 3.5 h.

Infrared (IR) spectra were obtained in the indicated state with a Hitachi 215 spectrometer. NMR spectra were determined in the indicated solvent with a Hitachi R-24B high resolution NMR spectrometer; chemical shifts are given in ppm from tetramethylsilane. Splitting patterns are designated as d, doublet; t, triplet; q, quartet: m, multiplet. Mass spectra were taken on a Hitachi RMU-6MG or RMU-7M spectrometer. Optical rotations were measured on a Union-Giken PM-101 polarimeter.

Preparation of Optically Active Aminophenol Derivatives

(*S*)-*o*-(1-Phenylethylaminomethyl)phenol (4a)——A solution of 1.00 g (8.3 mmol) of (*S*)-(−)-α-phenylethylamine (**1a**) and 1.00 g (8.3 mmol) of salicylaldehyde (**2**) in 30 ml of benzene was refluxed for 3 h using a Dean–Stark apparatus. Evaporation of the solvent gave 1.91 g of imine **3a** in quantitative yield [IR ν_{max}^{film} cm^{-1}: 1625 (C=N)][12a,c]

Sodium borohydride (0.32 g, 8.5 mmol) was added to a solution of the imine **3a** (1.91 g) in 20 ml of ethanol at 0 °C. The reaction mixture was stirred at room temperature for 4 h and concentrated to dryness under reduced pressure. The residue was diluted with ether, and the ethereal extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 1.92 g of **4a** in quantitative yield. $[\alpha]_D^{23}$ −60.7° (*c*=0.56, EtOH). IR ν_{max}^{film} cm^{-1}: 3700—3400 (OH), 1600, 1590 (phenyl). NMR (CCl_4) δ: 1.30 (3H, d, *J*=6 Hz, $CHC\underline{H}_3$), 3.30—3.80 (3H, m, CH and CH_2), 5.70—7.80 (11H, m, NH, OH, C_6H_4, and C_6H_5). *O,N*-Dibenzoyl derivative: colorless needles of mp 141—142 °C (recryst. from CCl_4–hexane). MS *m/e*: 435 (M^+). *Anal.* Calcd for $C_{29}H_{25}NO_3$: C, 79.97; H, 5.79; N, 3.22. Found: C, 79.93; H, 5.76; N, 3.21.

(*S*)-*o*-(1-α-Naphthylethylaminomethyl)phenol (4b)——The same procedure as described for **4a**, using 500 mg (2.92 mmol) of (*S*)-(−)-α-naphthylethylamine (**1b**) and 357 mg (2.92 mmol) of **2**, gave 800 mg of **4b** in quantitative yield. $[\alpha]_D^{19}$ +11.1° (*c*=10.0, EtOH). IR ν_{max}^{film} cm^{-1}: 3500—3400 (OH), 1600, 1590 (phenyl). NMR (CCl_4) δ: 1.41 (3H, d, *J*=7 Hz, CH_3), 3.60 (2H, d, *J*=2 Hz, N–CH_2), 4.50 (1H, q, *J*=7 Hz, $C\underline{H}CH_3$), 6.20—8.00 (13H, m, NH, OHC_6H_4, and $C_{10}H_7$). *O,N*-Dibenzoyl derivative: colorless needles of mp 172—173 °C (recryst. from CCl_4–hexane). MS *m/e*: 485 (M^+). *Anal.* Calcd for $C_{33}H_{27}NO_3$: C, 81.62; H, 5.61; N, 2.88. Found: C, 81.59; H, 5.71; N, 2.83.

(*S*)- and (*R*)-*o*-{1-((*S*)-1-α-Naphthylethylamino)ethyl}phenol (7a) and (7b)——A solution of 1.00 g (5.8 mmol) of **1b** and 0.80 g (5.8 mmol) of *o*-hydroxyacetophenone (**5a**) in 30 ml of benzene was refluxed in the presence of a catalytic amount of *p*-toluenesulfonic acid using a Dean–Stark apparatus for 24 h. The reaction mixture was concentrated under reduced pressure, and the resulting imine **5a** (1.90 g) was reduced with 0.25 g (6.6 mmol) of sodium borohydride in 40 ml of ethanol by stirring at room temperature for 20 h. Work-up as described above, followed by recrystallization of the crude product from CCl_4–hexane, gave 0.80 g (47% yield) of **7a** as colorless needles of mp 141—142 °C. The mother liquor was concentrated *in vacuo* and the residual oil was subjected to preparative thin layer chromatography (TLC) with ether–hexane (1 : 1) to afford 0.42 g (25% yield) of **7b**.

7a: $[\alpha]_D^{25}$ +25.6° (*c*=0.45, EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3700—3300 (OH), 1620, 1600 (phenyl). NMR (CCl_4) δ: 1.30 (3H, d, *J*=7 Hz, $C\underline{H}_3$–CH–C_6H_4), 1.50 (3H, d, *J*=7 Hz, $C\underline{H}_3$–CH–$C_{10}H_7$), 3.22 (1H, q, *J*=7 Hz, CH_3–$C\underline{H}$–C_6H_4), 4.20 (1H, q, *J*=7 Hz, CH_3–$C\underline{H}$–$C_{10}H_7$), 6.00—7.60 (13H, m, OH, NH, C_6H_4, and $C_{10}H_7$). MS *m/e*: 291 (M^+). *Anal.* Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.36; H, 7.23; N, 4.89.

7b: $[\alpha]_D^{22}$ +9.7° (*c*=1.3, EtOH). IR ν_{max}^{film} cm^{-1}: 3700—3300 (OH), 1620, 1600 (phenyl). NMR (CCl_4) δ: 1.30 (3H, d, *J*=7 Hz, $C\underline{H}_3$–CH–C_6H_4), 1.46 (3H, d, *J*=7 Hz, $C\underline{H}_3$–CH–$C_{10}H_7$), 3.90 (1H, q, *J*=7 Hz, CH_3–$C\underline{H}$–C_6H_4), 4.52 (1H, q, *J*=7 Hz, CH_3–$C\underline{H}$–$C_{10}H_7$), 6.00—8.60 (13H, m, OH, NH, C_6H_4, and $C_{10}H_7$). MS *m/e*: 291 (M^+). *O,N*-Dibenzoyl derivative: colorless plates of mp 188—189 °C (recryst. from CCl_4–hexane). *Anal.* Calcd for $C_{34}H_{29}NO_3$: C, 81.74; H, 5.85; N, 2.80. Found: C, 81.82; H, 5.81; N, 2.79.

(*S*)- and (*R*)-*o*-{1-((*S*)-1-α-Naphthylethylamino)propyl}phenol (8a) and (8b)——A solution of 2.00 g (11.7 mmol) of **1b** and 1.75 g (11.7 mmol) of 2-hydroxypropiophenone (**5b**) in 30 ml of benzene was refluxed for 30 h in the presence of a catalytic amount of *p*-toluenesulfonic acid using a Dean–Stark apparatus. The crude imine **5b**, obtained by evaporation of the solvent, was reduced with 0.47 g (12.5 mmol) of sodium borohydride in 36 ml of ethanol (at room temperature, 14 h). Work-up as described above, followed by preparative TLC (ether–hexane 1 : 1), gave a diastereomeric mixture of **7a, b** (2.80 g). *O*-Benzoylation of **8a, b** (2.80 g, 9.2 mmol) thus obtained with 1.29 ml (11.0 mmol) of benzoyl chloride was carried out in 6 ml of pyridine by stirring at room temperature for 16 h. Usual work-up, followed by preparative TLC (benzene–ether 10 : 1), gave the *O*-benzoates of **8a** (1.15 g) and **8b** (0.46 g).

Hydrolysis of both *O*-benzoates was carried out by heating in 10% KOH–MeOH for 5 h to afford 0.80 g (23% yield from **1b**) of **8a** and 0.32 g (9% yield from **1b**) of **8b**.

8a: $[\alpha]_D^{19}$ +21.1° (*c*=0.38, EtOH). IR ν_{max}^{film} cm^{-1}: 3500—3300 (OH), 1620, 1600, 1590 (phenyl). NMR (CCl_4) δ: 0.70 (3H, t, *J*=6 Hz, CH_2CH_3), 1.50 (3H, d, *J*=6 Hz, $CHCH_3$), 1.40—1.90 (2H, m, $CHCH_2CH_3$), 3.29 (1H, t, *J*=6 Hz, $CHCH_2$), 4.55 (1H, q, *J*=6 Hz, $CHCH_3$), 6.40—8.00 (13H, m, OH, NH, C_6H_4, and $C_{10}H_7$). MS *m/e*: 305 (M^+). *O*-Benzoyl derivative: IR ν_{max}^{film} cm^{-1}: 1760 (ester), 1590, 1580 (phenyl). NMR (CCl_4) δ: 0.73 (3H, t, *J*=7 Hz, CH_2CH_3), 1.30 (3H, d, *J*=7 Hz, $CHCH_3$), 1.66 (2H, q, *J*=7 Hz, CH_2Ch_3), 3.56 (1H, t, *J*=7 Hz, $CHCH_2$), 4.40 (1H, q, *J*=7 Hz, $CHCH_3$), 7.10—8.20 (17H, m, NH, C_6H_4, C_6H_5, and $C_{10}H_7$). *O,N*-Dibenzoyl derivative: colorless needles of mp 192—194 °C (recryst. from CCl_4–hexane). *Anal.* Calcd for $C_{35}H_{31}NO_3$: C, 81.84; H, 6.08; N, 2.73. Found: C, 81.76; H, 6.03; N, 2.71.

8b: IR ν_{max}^{film} cm^{-1}: 3500—3300 (OH), 1620, 1600, 1590 (phenyl), NMR (CCl_4) δ: 0.60 (3H, t, *J*=6 Hz, CH_2CH_3), 1.50 (3H, d, *J*=6 Hz, $CHCH_3$), 1.30—1.80 (2H, m, CH_2CH_3), 3.70 (1H, t, *J*=6 Hz, $CHCH_2$), 4.60 (1H, q, *J*=6 Hz, $CHCH_3$), 6.40—8.00 (13H, m, OH, NH, C_6H_4, and $C_{10}H_7$). *O*-Benzoyl derivative: colorless needles of mp 196—198 °C (recryst. from CCl_4–hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (ester), 1590, 1580 (phenyl). NMR (CCl_4) δ: 0.80 (3H, t, *J*=7 Hz, CH_2CH_3), 1.38 (3H, d, *J*=7 Hz, $CHCH_3$), 1.20—1.80 (2H, m, CH_2CH_3), 3.90 (1H, t, *J*=7 Hz, $CHCH_2$), 4.49 (1H, q, *J*=7 Hz, $CHCH_3$), 7.00—8.20 (17H, m, NH, C_6H_4, C_6H_5, and $C_{10}H_7$). *Anal.* Calcd for $C_{28}H_{27}NO_2$: C, 82.12; H, 6.65; N, 3.42. Found: C, 82.16; H, 6.72; H, 3.46.

(*S*)- and (*R*)-*o*-{1-((*S*)-1-α-Naphthylethylamino)pentyl}phenol (9a) and (9b)——The same procedure as described for **8**, using 0.96 g (5.6 mmol) of **1b** and 1.00 g (5.6 mmol) of 2-hydroxypentanophenone (**5c**), gave 0.31 g of **9a** and 0.13 g of **9b** (24% yield).

9a: $[\alpha]_D^{24.5}$ +46.8° (*c*=0.5, EtOH). IR ν_{max}^{film} cm^{-1}: 3400—3300 (OH), 1620, 1590 (phenyl). NMR (CCl_4) δ: 0.70 (3H, t, *J*=7 Hz, CH_2CH_3), 0.90—1.98 (6H, m, $(CH_2)_3$), 1.50 (3H, d, *J*=4 Hz, $CHCH_3$), 3.35 (1H, t, *J*=7 Hz, $CHCH_2$), 4.50 (1H, q, *J*=4 Hz, $CHCH_3$), 6.28—7.92 (13H, m, OH, NH, C_6H_4 and $C_{10}H_7$). MS *m/e*: 333 (M^+). *O,N*-Dibenzoyl derivative: colorless needles of 191—192 °C (recryst. from CCl_4–hexane). *Anal.* Calcd for $C_{37}H_{35}NO_3$: C, 82.04; H, 6.51; N, 2.59. Found: C, 82.11; H, 6.61; N, 2.36.

9b: $[\alpha]_D^{24.5}$ +9.9° (*c*=0.36, EtOH). IR ν_{max}^{film} cm^{-1}: 3700—3300 (OH), 162, 1590 (phenyl). NMR (CCl_4) δ: 0.71 (3H, t, *J*=7 Hz, $CHCH_3$), 0.90—1.90 (6H, m, $(CH_2)_3$), 1.50 (3H, d, *J*=4 Hz, $CHCH_3$), 3.80 (1H, t, *J*=7 Hz, $CHCH_2$), 4.70 (1H, q, *J*=4 Hz, $CHCH_3$), 6.40—8.10 (13H, m, OH, NH, C_6H_4, and $C_{10}H_7$). MS *m/e*: 333 (M^+). *O,N*-Dibenzoyl derivative: colorless needles of mp 184—185 °C (recryst. from CCl_4–hexane). *Anal.* Calcd for $C_{37}H_{35}NO_3$: C, 82.04; H, 6.51; N, 2.59. Found: C, 82.10; H, 6.49; N, 2.36.

Hydrolysis of (*S*)-*o*-(1-α-Naphthylethyliminomethyl)phenol (3b)——The imine **3b** (250 mg, 0.90 mmol),[12b] obtained by dehydrative condensation of **1b** and **2**, were heated at 60—70 °C for 2 h in 2 ml of 10% aqueous HCl. The mixture was neutralized with 10% aqueous NaOH under ice cooling and the separated oil was extracted with ether. Usual work-up, followed by acetylation with acetic anhydride (80 mg)–pyridine (1 ml) (at 38 °C, 18 h), gave (*S*)-(−)-*N*-(α-naphthylethyl)acetamide (110 mg) as colorless prisms of 144—145 °C: $[\alpha]_D^{22}$ −131.3° (*c*=0.58, $CHCl_3$). The IR and NMR spectra were identical with those of the authentic acetamide: $[\alpha]_D^{22}$ −129.1° (*c*=0.46, $CHCl_3$).

Preparation of 7a, b and 9a, b from 3b——A 1.6 M ether solution of methyllithium (11.5 ml, 18.0 mmol) or a 1.5 N hexane solution of butyllithium (7.26 ml, 14.4 mmol) was added to a solution of 1.00 g (3.60 mmol) of **3b** in 16 ml of THF at 0 °C and the reaction mixture was stirred at 0 °C for 5 h. The reaction solution was quenched with 10% aqueous HCl, then made weakly basic with saturated aqueous $NaHCO_3$, and extracted with ether. The extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The crude products were subjected to preparative TLC with ether–hexane (1 : 1 or 1 : 2) to give 1.00 g (95% yield) of **7** (**7a** : **7b** 1 : 2.5) and 1.21 g (91% yield) of **9** (**9a** : **9b** 1 : 3).

Preparation of 3,4-Dihydro-1,2,3-benzoxathiazine 2-Oxide Derivatives from *o*-Aminoalkylphenols 4a, b and 7a, b and Thionyl Chloride

(*S*)-3,4-Dihydro-3-(1-phenylethyl)-1,2,3-benzoxathiazine 2-Oxide (10a)——A solution of 236 mg (1.98 mmol) of thionyl chloride in 1.5 ml of THF was added to an ice-cooled solution of 300 mg (1.32 mmol) of **4a** and 0.92 ml (6.60 mmol) of triethylamine in 5 ml of THF and the reaction mixture was stirred at 0 °C for 5 h. The precipitates were filtered off and the filtrate was concentrated under reduced pressure. The resulting crude product was subjected to preparative TLC with ether–hexane (1 : 1) to afford 344 mg (95% yield) of **10a**. Compound **10a** was also obtained under the reaction conditions given in Table IV in the yields shown in parentheses in the table.

10a: IR ν_{max}^{film} cm^{-1}: 1585 (phenyl). NMR (CCl_4) δ: 1.46, 1.60 (3H, dd, *J*=7, 7 Hz, CH_3), 3.42 (1H, d, *J*=17 Hz, CH–C_6H_4), 4.05 (1H, q, *J*=7 Hz, $CHCH_3$), 4.60 (1H, d, *J*=17 Hz, CH–C_6H_4), 6.70—7.40 (9H, m, C_6H_4 and C_6H_5). MS *m/e*: 273 (M^+). Exact mass determination: 273.0861 (Calcd for $C_{15}H_{15}NO_2S$, 273.0822).

(*S*)-3,4-Dihydro-3-(1-α-naphthylethyl)-1,2,3-benzoxathiazine 2-Oxide (10b)——Reaction of 612 mg (2.21 mmol) of **4b** with 0.19 ml (2.65 mmol) of thionyl chloride was carried out in 13 ml of THF in the presence of 1.54 ml (11.05 mmol) of triethylamine at 0 °C for 4 h. Work-up as described above gave 542 mg (76% yield) of **10b**. The yields of **10b** under other reaction conditions are listed in parentheses in Table IV.

10b: IR ν_{max}^{film} cm^{-1}: 1590 (phenyl). NMR (CCl_4) δ: 1.56, 1.70 (3H, dd, *J*=7, 7 Hz, CH_3), 3.20—3.90 (1H, m,

CHCH$_3$), 4.30—5.00 (2H, m, N–CH$_2$), 6.40—8.00 (11H, m, C$_6$H$_4$ and C$_{10}$H$_7$). MS *m/e*: 323 (M$^+$). Exact mass determination: 323.0993 (Calcd for $C_{19}H_{17}NO_2S$, 323.0980).

(2*S*, 4*S*)- and (2*R*, 4*S*)-3,4-Dihydro-4-methyl-3-{(*S*)-1-α-naphthylethyl}-1,2,3-benzoxathiazine 2-Oxide (11a-I and 11a-II)——A solution of 364 mg (3.10 mmol) of thionyl chloride in 2 ml of toluene was added to a solution of 600 mg (2.06 mmol) of (*S*)-(+)-*o*-{1-((*S*)-1-α-naphthylethylamino)ethyl}phenol (**7a**) and 1.040 g (10.30 mmol) of triethylamine in 14 ml of toluene at 0 °C and the reaction mixture was stirred at 0 °C for 4 h. The precipitates were filtered off and the filtrate was concentrated under reduced pressure. The residual brown oil was subjected to preparative TLC (ether–hexane 1 : 1) to give 430 mg of **11a**-I and 208 mg of **11a**-II in 92% yield.

Reaction of 400 mg (1.37 mmol) of **7a** with 405 mg (3.43 mmol) of thionyl chloride in the presence of 692 mg (6.85 mmol) of triethylamine in 10 ml of toluene (0 °C, 4 h) gave 172 mg of **11a**-I and 248 mg of **11a**-II in 91% yield.

11a-I: Colorless needles of mp 121 °C (recryst. from CCl_4–hexane). $[\alpha]_D^{25}$ +162.6° (*c*=0.35, EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1600, 1590 (phenyl). NMR (CCl_4) δ: 1.55 (3H, d, *J*=7 Hz, CH$_3$CH–C$_6$H$_4$), 1.79 (3H, d, *J*=7 Hz, C$_{10}$H$_7$–CHCH$_3$), 4.60 (1H, q, *J*=7 Hz, CH$_3$CH–C$_6$H$_4$), 5.38 (1H, q, *J*=7 Hz, C$_{10}$H$_7$–CHCH$_3$), 6.50—8.20 (11H, m, C$_6$H$_4$ and C$_{10}$H$_7$). MS *m/e*: 337 (M$^+$). *Anal.* Calcd for $C_{20}H_{19}NSO_2$: C, 71.20; H, 5.68; N, 4.15; S, 9.49. Found: C, 71.08; H, 5.69; N, 4.06; S, 9.02.

11a-II: Colorless needles of mp 98—99 °C (recryst. from CCl_4–hexane). $[\alpha]_D^{25}$ +72.3° (*c*=0.35, EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1600 (phenyl). NMR (CCl_4) δ: 1.67 (3H, d, *J*=7 Hz, CH$_3$CH–C$_6$H$_4$), 1.74 (3H, d, *J*=7 Hz, C$_{10}$H$_7$CHCH$_3$), 3.90 (1H, q, *J*=7 Hz, CH$_3$CH–C$_6$H$_4$), 4.90 (1H, q, *J*=7 Hz, C$_{10}$H$_7$CHCH$_3$), 6.60—8.98 (11H, m, C$_6$H$_4$ and C$_{10}$H$_7$). MS *m/e*: 337 (M$^+$). *Anal.* Calcd for $C_{20}H_{19}NSO_2$: C, 71.20; H, 5.68; N, 4.15; S, 9.49. Found: C, 71.21; H, 5.71; N, 4.09; S, 9.33.

Studies on Isomerization of 11a-I with Acidic Catalysts

Isomerization with Hydrogen Chloride——A 0.32 N toluene solution of hydrogen chloride (0.1 ml) was added to a solution of 50 mg (0.13 mmol) of **11a**-I in 0.9 ml of toluene at 0 °C. The mixture was stirred at 0 °C for 0.5—3.0 h, then quenched with 1.5 ml of triethylamine, and diluted with benzene. The precipitates were filtered off and the filtrate was concentrated under reduced pressure to recover the isomerized amidosulfite **11a**. The ratios of **11a**-I to **11a**-II obtained at various times during this reaction were calculated from the NMR spectra. The ratios and the yields of recovered **11a** are listed in Table I.

Isomerization with Other Acidic Catalysts——A 0.07 M toluene solution of boron trifluoride etherate (0.45 ml, 0.032 mmol) was added to an ice-cooled solution of 154 mg (0.450 mmol) of **11a**-I in 1.5 ml of toluene. The mixture was stirred at 0 °C for 1 h. The crude product was subjected to preparative TLC (ether–hexane 1 : 1) to recover 140 mg (91% recovered yield) of the starting amidosulfite **11a**, and the isomerization ratios were calculated from the NMR spectra. The results are given in Table II.

Isomerization with other acidic catalysts such as trifluoroacetic acid, acetic acid, and aluminum chloride were carried out in the same way and the results are summarized in Table II.

Nucleophilic Substitution of 11a-I and 11a-II

***N*-[(*S*)-1-(*o*-Hydroxyphenyl)ethyl]-*N*-[(*S*)-1-α-naphthylethyl] (S^R)- and (S^S)-Phenylsulfinamide (12a) and (12b)**

Reaction of 11a-II with Phenylmagnesium Bromide——A dry 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar was flushed with nitrogen and maintained under a positive pressure of nitrogen. A solution of 100 mg (0.30 mmol) of **11a**-II in 2 ml of THF was added, followed by the dropwise addition of a 2 M THF solution of phenylmagnesium bromide (0.22 ml, 0.45 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 2.5 h, then warmed to 0 °C, quenched with 10% aqueous HCl (adjusted to pH about 6), and extracted with ether. The ethereal layers were combined, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane 1 : 1) to give 10 mg of **12a** and 110 mg of **12b** in 98% yield.

12a: Colorless needles of mp 154 °C (recryst. from CCl_4–hexane). $[\alpha]_D^{22}$ −18.6° (*c*=0.52, EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1600, 1590 (phenyl). NMR (CCl_4) δ: 1.00, 1.90 (3H, 3H, dd, *J*=7 Hz, 2CH$_3$), 4.90, 5.30 (1H, 1H, qq, *J*=7, 7 Hz, 2CHCH$_3$), 6.00—8.00 (17H, m, C$_6$H$_4$OH, C$_6$H$_5$, and C$_{10}$H$_7$). MS *m/e*: 415 (M$^+$). *Anal.* Calcd for $C_{26}H_{25}NSO_2$: C, 75.16; H, 6.07; N, 3.37; S, 7.70. Found: C, 74.88; H, 6.08; N, 3.17; S, 7.27.

12b: Colorless needles of mp 132—134 °C (recryst. from CCl_4–hexane). $[\alpha]_D^{22}$ +16.1° (*c*=0.60, EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 1600, 1590 (phenyl). NMR (CCl_4) δ: 2.20, 2.30 (3H, 3H, dd, *J*=7, 7 Hz, 2CH$_3$), 5.20, 5.75 (1H, 1H, qq, *J*=7, 7 Hz, 2CHCH$_3$), 6.70—8.20 (17H, m, C$_6$H$_4$OH, C$_6$H$_5$, and C$_{10}$H$_7$). MS *m/e*: 415 (M$^+$). *Anal.* Calcd for $C_{26}H_{25}NSO_2$: C, 75.16; H, 6.07; N, 3.37; S, 7.70. Found: C, 75.13; H, 6.01; N, 3.29; S, 7.57.

Reaction of 11a-I with Phenylmagnesium Bromide——A 2 M THF solution of phenylmagnesium bromide (0.30 ml, 0.60 mmol) was added to a solution of 155 mg (0.45 mmol) of **11a**-I in 4 ml of THF at −78 °C and the reaction mixture was stirred at −78 °C for 2.5 h. Work-up as described above, followed by preparative TLC (ether–hexane 1 : 1), gave 147 mg of **12a** and 13 mg of **12b** in 84% yield. The spectral data of these products were identical with those of the compounds obtained above.

***N*-[(*S*)-1-(*o*-Hydroxyphenyl)ethyl]-*N*-((*S*)-1-α-naphthylethyl) (S^R)- and (S^S)-Methylsulfinamide (13a) and (13b)**——A dry 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar was flushed with nitro-

gen and maintained under a positive pressure of nitrogen. A solution of 181 mg (0.54 mmol) of **11a**-II in 4.5 ml of THF was added, followed by the dropwise addition of a 1 M THF solution of methylmagnesium bromide (1.34 ml, 1.34 mmol) at −78 °C. Work-up as described above, followed by preparative TLC (ether), gave 17 mg of **13a** and 155 mg of **13b** in 90% yield.

Reaction of 183 mg (0.54 mmol) of **11a**-I with methylmagnesium bromide (0.81 ml of 1 M THF solution, 0.81 mmol) was carried out in the same manner to give 129 mg of **13a** and 14 mg of **13b** in 75% yield.

13a: $[\alpha]_D^{21}$ +108.1° (c=2.23, EtOH). IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1590 (phenyl). NMR (CCl_4) δ: 1.56, 1.60 (3H, 3H, dd, J=7, 7 Hz, $2CH_3$), 2.80 (3H, s, CH_3SO), 5.16, 5.20 (1H, 1H, qq, J=7, 7 Hz, C<u>H</u>–C_6H_4, C<u>H</u>–$C_{10}H_7$), 6.00—7.90 (12H, m, OH, C_6H_4, and $C_{10}H_7$). MS m/e: 353 (M^+). Exact mass determination: 353.1441 (Calcd for $C_{21}H_{23}NSO_2$: 353.1448).

13b: $[\alpha]_D^{22}$ +59.0° (c=2.10, EtOH). IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1610, 1600 (phenyl). NMR (CCl_4) δ: 1.87 (6H, d, J=7 Hz, $2CH_3$), 2.33 (3H, s, CH_3SO), 5.30, 5.40 (1H, 1H, qq, J=7, 7 Hz, C_6H_4C<u>H</u> and $C_{10}H_7C$<u>H</u>), 6.40—8.00 (12H, m, OH, C_6H_4, and $C_{10}H_7$). MS m/e: 353 (M^+). Exact mass determination: 353.1450 (Calcd for $C_{21}H_{23}NSO_2$: 353.1449).

Reaction of **11a**-I and **11a**-II (153 mg, 0.45 mmol) with methyllithium (1.3 M ether solution, 0.45 ml) was carried out in the same way (−78 °C, 2 h) as described above. The yields and the ratios of **13a** to **13b** are listed in Table III.

***N*-[(*S*)-1-(*o*-Hydroxyphenyl)ethyl]-*N*-((*S*)-1-α-naphthylethyl) (S^R)- and (S^S)-Butylsulfinamide (14a) and (14b)**——A 1.5 M hexane solution of butyllithium (0.28 ml, 0.42 mmol) was added to a solution of 143 mg (0.42 mmol) of **11a**-I in 3 ml of THF at −78 °C and the reaction solution was stirred at −78 °C for 2 h. Work-up as described above, followed by preparative TLC (ether–hexane 3 : 2), gave 61 mg of **14a** and 12 mg of **14b** in 44% yield. Reaction of **11a**-II with butyllithium was carried out in the same way and the product ratio is listed in Table III.

14a: $[\alpha]_D^{20}$ +35.3° (c=2.07, EtOH). IR ν_{max}^{film} cm^{-1}: 3300 (OH), 1610, 1600, 1590 (phenyl). NMR (CCl_4) δ: 0.90 (3H, t, J=7 Hz, CH_2C<u>H</u>$_3$), 1.20—2.00 (10H, m, CH_2CH_2 and $2CH_3$), 2.90 (2H, t, J=7 Hz, CH_2SO), 5.10, 5.20 (1H, 1H, qq, J=7, 7 Hz, C<u>H</u>C_6H_4, C<u>H</u>$C_{10}H_7$), 6.00—7.70 (12H, m, OH, C_6H_4, and $C_{10}H_7$). MS m/e: 395 (M^+). Exact mass determination: 395.1965 (Calcd for $C_{24}H_{29}NSO_2$: 395.1919).

14b: $[\alpha]_D^{20}$ +18.4° (c=1.25, EtOH). IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1600, 1580 (phenyl). NMR (CCl_4) δ: 0.30 (3H, t, J=7 Hz, CH_2C<u>H</u>$_3$), 0.40—1.10 (4H, m, CH_2CH_2), 1.80, 1.90 (3H, 3H, dd, J=7, 7 Hz, $2CHC$<u>H</u>$_3$), 2.40 (2H, t, J=7 Hz, CH_2SO), 5.46 (2H, q, J=7 Hz, C<u>H</u>C_6H_4 and C<u>H</u>$C_{10}H_7$), 6.40—7.70 (12H, m, OH, C_6H_4, and $C_{10}H_7$). MS m/e: 395 (M^+). Exact mass determination: 395.1938 (Calcd for $C_{24}H_{29}NSO_2$: 395.1918).

Nucleophilic Substitution of 12a, b, 13a, b, and 14a, b

(*R*)-(+)- and (*S*)-(−)-Butyl Phenyl Sulfoxide (15b) from 12a, b——A 1.5 N hexane solution of butyllithium (0.67 ml, 1.00 mmol) was added to a solution of 104 mg (0.25 mmol) of **12a** in 2.5 ml of THF at −78 °C. The reaction mixture was stirred at −78 °C for 2 h, then quenched by addition of 100 mg of ammonium chloride and diluted with ether. The ethereal solution was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to preparative TLC (ether–hexane 5 : 1) to afford 36 mg (80% yield) of (*R*)-(+)-**15b**, which had an optical rotation of $[\alpha]_D^{25}$ +155.0° (c=0.28, MeOH) (98% enantiomeric excess).

Reaction of **12b** with butyllithium was undertaken in the same way to furnish (*S*)-(−)-**15b** with 99% enantiomeric excess ($[\alpha]_D^{21}$ −156.6° (c=0.24, MeOH).

15b: bp 135 °C (bath temp.) (1 mmHg). IR ν_{max}^{film} cm^{-1}: 1585 (phenyl), 1080, 1030 (sulfoxide). NMR (CCl_4) δ: 0.96 (3H, t, J=6 Hz, CH_3), 1.23—1.83 (4H, m, CH_2CH_2), 2.60 (2H, t, J=6 Hz, S–CH_2), 7.30—7.65 (5H, m, C_6H_5). MS m/e: 182 (M^+). *Anal.* Calcd for $C_{10}H_{14}OS$: C, 65.91; H, 7.74; S, 17.56. Found: C, 66.02; H, 7.79; S, 17.40.

(*S*)-(−)- and (*R*)-(+)-Methyl Phenyl Sulfoxide (15a) from 13a, b——A 1.65 N THF solution of phenyllithium (0.51 ml, 0.81 mmol) was added to a solution of 100 mg (0.28 mmol) of **13a** in 2 ml of THF at −78 °C and the reaction mixture was stirred at −78 °C for 2 h. Work-up as described above, followed by preparative TLC (ether–hexane 7 : 1) gave 15 mg (38% yield) of (*S*)-(−)-**15a** with 94% enantiomeric excess ($[\alpha]_D^{22}$ −140.4° (c=1.00, EtOH).[16] Reaction of **13b** with phenyllithium was performed in the same manner to afford (*R*)-(+)-**15a** with 95% enantiomeric excess ($[\alpha]_D^{20}$ +142.0° (c=1.00, EtOH).

(*S*)-(−)- and (*R*)-(+)-15b from 14a, b——Treatment of **14a** and **14b** with phenyllithium as described above gave (*S*)-(−)- and (*R*)-(+)-**15b** with 97% ($[\alpha]_D^{20}$ −153.0° (c=1.00, MeOH)) and 95% ($[\alpha]_D^{21}$ +150.0° (c=1.20, MeOH)) enantiomeric excess, respectively.

Preparation of (*S*)-(−)-15a from 10a and 10b

From 10a through *N*-(2-Hydroxybenzyl)-*N*-((*S*)-1-phenylethyl)phenylsulfinamide (16a)——A 2 M THF solution of phenylmagnesium bromide (0.63 ml, 1.26 mmol) was added to a solution of 312 mg (1.14 mmol) of **10a** in 4.5 ml of THF at −78 °C. The reaction mixture was stirred at −78 °C for 2.5 h, then warmed to 0 °C, quenched with 10% aqueous HCl (adjusted to pH about 6), and extracted with ether. The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residual oil was subjected to preparative TLC (ether–hexane 1 : 1) to give 418 mg (quantitative yield) of **16a**: IR ν_{max}^{film} cm^{-1}: 3300 (OH), 1590 (phenyl). NMR (CCl_4) δ: 1.57, 1.70 (3H, dd, J=7, 7 Hz, CH_3), 3.30—4.17 (2H, m, CH_2), 4.40 (1H, q, J=7 Hz, C<u>H</u>CH_3), 6.50—7.70 (15H, m, OH, C_6H_4, and $2C_6H_5$). MS m/e: 351 (M^+). Exact mass determination: 351.1293

(Calcd for $C_{21}H_{21}NO_2S$, 351.1293).

A 2.27 M ether solution of methyllithium (1.57 ml, 3.57 mmol) was added to a solution of 418 mg (1.19 mmol) of **11a** in 4 ml of THF at −78 °C. The reaction mixture was stirred at −78 °C for 2 h, quenched with 300 mg of ammonium chloride, and diluted with ether. The solution was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual oil was subjected to preparative TLC (ether–hexane 7 : 1) to give 142 mg (85% yield) of **15a**.

From 10b through *N*-(2-Hydroxybenzyl)-*N*-((*S*)-1-α-Naphthylethyl)phenylsulfinamide (16b)——A 2 M THF solution of phenylmagnesium bromide (0.92 ml, 1.85 mmol) was added to a solution of 542 mg (1.68 mmol) of **10b** in 10 ml of THF at −78 °C and the reaction mixture was stirred at −78 °C for 2.5 h. Work-up as described above, followed by preparative TLC (ether–hexane 1 : 1), gave 650 mg (97% yield) of **16b**: IR ν_{max}^{film} cm^{-1}: 3200 (OH), 1595, 1580 (phenyl). NMR (CCl_4) δ: 1.77 (3H, d, J=7 Hz, CH_3), 3.62, 4.33 (2H, dd, J=15, 15 Hz, CH_2–N), 5.17 (1H, q, J=7 Hz, C<u>H</u>CH_3), 6.40—7.90 (17H, m, OH, C_6H_4, C_6H_5, and $C_{10}H_7$). MS *m/e*: 401 (M^+). Exact mass determination: 401.1462 (Calcd for $C_{25}H_{23}NO_2S$: 401.1449).

Reactions of 650 mg (1.62 mmol) of **16b** with methyllithium (2.27 M ether solution, 2.14 ml, 4.86 mmol) was carried out in 12 ml of THF at −78 °C for 2 h. Work-up and subsequent preparative TLC, as described above, gave 181 mg (80% yield) of **15a**.

Asymmetric Synthesis of Optically Active Methyl and Butyl Phenyl Sulfoxides (15a) and (15b)

General Procedure——A dry 25 ml two-necked flask with a septum inlet and a magnetic stirring bar was flushed with nitrogen and maintained under a positive pressure of nitrogen. A solution of an *o*-aminoalkylphenol (**4a, b, 7a, b, 8a, b,** or **9a, b**) (1.38 mmol) in 5 ml of solvent (toluene, THF, dimethoxyethane, dioxane, $CHCl_3$, or CCl_4) and triethylamine (0.69 ml, 4.97 mmol) were added followed by the dropwise addition of a solution of thionyl chloride (246 mg, 2.07 mmol) in 1.5 ml of the solvent at the temperature given in Tables IV—VII. The reaction mixture was stirred under the reaction conditions described in the tables. The precipitates were filtered off and the filtrate was concentrated to dryness *in vacuo*. A 2 M THF solution of phenylmagnesium bromide (1.04 ml, 2.07 mmol) was added to a solution of the resulting oil (**10a, b** and **11a—c**) in 4.5 ml of THF at −78 °C . The reaction mixture was stirred at −78 °C for 2.5 h, warmed to 0 °C , then quenched with 10% aqueous HCl (adjusted to pH about 6), and extracted with ether. The ethereal extracts were combined, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated to dryness *in vacuo*. Methyllithium (2.27 M ether solution, 1.82 ml, 4.14 mmol) or butyllithium (1.5 N hexane solution, 2.76 ml, 4.14 mmol) was added to a solution of the residual oil in 8 ml of THF at −78 °C. The reaction mixture was stirred at −78 °C for 2 h, then quenched with 317 mg (5.52 mmol) of ammonium chloride, and extracted with ether. The ethereal extracts were combined, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether–hexane 7 : 1) to give **15a** or **15b**.

The optical rotations and the chemical and optical yields of **15a, b** obtained under various reaction conditions are summarized in Tables IV—VII.

Asymmetric Synthesis of (*S*)-(−)-15a and 15b with 7a through Isomerization with Hydrogen Chloride——A solution of 214 mg (1.80 mmol) of thionyl chloride in 1.5 ml of toluene was added to a mixture of 350 mg (1.20 mmol) of **7a** and 436 mg (4.32 mmol) of triethylamine in 5 ml of toluene at 0 °C and the reaction mixture was stirred at 0 °C for 4 h. Work-up as described above gave a brown oil (412 mg). This crude product (**11a**) was dissolved in 5 ml of toluene and cooled at 0 °C. A 0.32 N hydrogen chloride–toluene solution (0.63 ml) was added to this solution. The mixture was stirred at 0 °C for 2 h, and quenched with 1.5 ml of triethylamine. The separated precipitates were filtered off and the filtrate was concentrated to dryness under reduced pressure. This isomerized product (**11a**) was allowed to react with phenylmagnesium bromide (2 M THF solution, 0.90 ml, 1.80 mmol) (−78 °C , 2.5 h), followed by methyllithium (2.27 M ether solution, 1.59 ml, 3.60 mmol) or butyllithium (1.5 N hexane solution, 2.40 ml, 3.60 mmol) (−78 °C, 2 h), in the same manner as described above, affording (*S*)-(−)-**15a** and (*S*)-(−)-**15b**, respectively, with recovery (87% recovered yield) of the starting aminophenol **7a**. The optical rotations, and optical and chemical yields of **15a, b** are listed in Table V.

Preparation of (*S*)-(−)-15b from (*S*)-(−)-15a——A solution of 150 mg (1.07 mmol) of (*S*)-(−)-**15a** ($[\alpha]_D^{23}$ −25.3° (*c*=0.67, EtOH), 17% optical purity)[16] in 2 ml of THF was added at 0 °C to a solution of lithium diethylamide in 1 ml of THF, prepared from diethylamine (0.17 ml, 1.61 mmol) and butyllithium (1.5 N hexane solution, 1.07 ml, 1.61 mmol). The mixture was stirred at 0 °C for 1.5 h, then a solution of 0.16 ml (1.61 mmol) of propyl iodide in 1 ml of THF was added and the whole was stirred at 0 °C for 2 h. The reaction was quenched with 10% aqueous HCl (adjusted to pH about 5—6), and extracted with ether. The ethereal extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residual oil was subjected to preparative TLC (ether–hexane 7 : 1) to give 106 mg (55% yield) of (*S*)-(−)-**15b** with the optical rotation of $[\alpha]_D^{23}$ −26.9° (*c*=1.14, MeOH). The NMR and mass spectra were identical with those of an authentic sample prepared in the normal way.[5] It was confirmed that the optical activity of the sulfoxide **15a** was completely retained in this procedure. Therefore the optical rotation of optically pure (*S*)-(−)-**15b** was calculated to be $[\alpha]_D$ −158.0° (MeOH).

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