Enantioselective Inclusion of Methyl Phenyl Sulfoxides and Benzyl Methyl Sulfoxides by (*R*)-Phenylglycyl-(*R*)-phenylglycine and the Crystal Structures of the Inclusion Cavities

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Crystalline (*R*)-phenylglycyl-(*R*)-phenylglycine [(*R*,*R*)-**1**] includes methyl phenyl sulfoxides (**2** and **3**) and benzyl methyl sulfoxides (**4**) with high enantioselectivity. The dipeptide exhibited different stereoselectivity depending on four structural isomers of methyl tolyl sulfoxide ($C_8H_{10}OS$): *R* for methyl 2-tolyl sulfoxide, *S* for methyl 3-tolyl sulfoxide, and racemic for methyl 4-tolyl sulfoxide. A structural isomer, benzyl methyl sulfoxide, was included in racemic form. Chlorophenyl methyl sulfoxides **3** (C_7H_7ClOS) with a similar volume showed the same enantioselectivity for their recognition. By single-crystal X-ray analyses of these inclusion compounds, it was elucidated that (*R*,*R*)-**1** molecules self-assembled to form layer structures and included the sulfoxides between these layers and that the origin of the enantioselectivity based on chiral cavities was induced by conformation of the C-terminal phenyl group of the dipeptide. The relative position between the ammonio proton and the C-terminal phenyl group in one molecule of the dipeptide determined the stereochemistry of the methyl sulfinyl groups to be recognized. Various positional isomers of methyl xylyl sulfoxide having the formula of $C_9H_{12}OS$ were subjected to the enantioselective inclusion by (*R*,*R*)-**1** crystals and these results are also discussed.

Introduction

In many inclusion systems, host molecules change their conformation more or less to include guest molecules.[1,2] As for inclusion of various guest molecules, it is more important for relatively large host molecules to possess flexibility. Herbstein has reported conformational isomerism of the flexible host as a factor for molecular recognition of the tripod host molecule, that is, tris(5-acetyl-3-thienyl)methane.[3]

Our attention has been focused on dipeptide molecules that have a straight glycylglycine backbone to construct a two-dimensional layer by means of intermolecular salt formation between COOH and NH_2 groups.[4,5] To date, we have reported that (*R*)-phenylglycyl-(*R*)-phenylglycine [(*R*,*R*)-**1**] effectively affords inclusion crystals of alkyl phenyl sulfoxides with high enantioselectivity.[4,6,7] Single-crystal X-ray analyses revealed that (*R*,*R*)-**1** molecules self-assemble to form layer structures, between which the sulfoxide molecules are accommodated. Ethyl, isopropyl, and *tert*-butyl phenyl sulfoxides were included with high *S* enantioselectivity, while the stereochemistry of the preferably included methyl phenyl sulfoxide was *R*. All of these inclusion crystals have a quite similar hydrogen bonding network of the dipeptide molecules to construct a layer. The sulfoxide molecules are in the channel between the walls of the dipeptide phenyl groups which stand on the layer. There are schematically represented in Figures 1 and 2.

The central ammonio proton of the channel binds to the sulfinyl oxygen, and the phenyl groups of the wall are rotatable to create a specific cavity suitable for the inclusion of the sulfoxide. It is noteworthy that the methyl group of methyl phenyl sulfoxide is located on the right side of the inclusion void (motif A), while ethyl, isopropyl, and *tert*-butyl groups are on the left side (motif B). Hence we have investigated the inclusion of various methyl phenyl sulfoxides (**2** and **3**) and benzyl methyl sulfoxides (**4**) in (*R*,*R*)-**1** crystals from the following viewpoints: (1) whether their methyl group is always located on the right side of the void or not and (2) how the shape of the sulfoxide influences the rotation of the phenyl wall to determine the enantioselectivity.

Results and Discussion

Inclusion of Structural Isomers of Sulfoxide ($C_8H_{10}OS$ 2a−d,4a, and C_7H_7ClOS 3a−d). An inclusion compound was prepared by three methods: (a) (*R*,*R*)-**1**

(1) Molecular Inclusion and Molecular Recognition-Clathrates I and II, *Topics in Current Chemistry*; Weber, E., Ed.;. Springer-Verlag: Berlin-Heidelberg, **1987** and **1988**; Vol. 140 and 149.

(2) *Comprehensive Supramolecular Chemistry*; NacNicol, D. D., Toda, F.; Bishop, R., Eds.; Pergamon: U.K., 1996; Vol. 9.

(3) Herbstein, F. H. *Acta Crystallogr.* **1997**, *B53*, 168.

(4) (a) Akazome, M.; Noguchi, M.; Tanaka, O.; Sumikawa, A.; Uchida, T.; Ogura, K. *Tetrahedron* **1997**, *53*, 8315. (b) Ogura, K.; Uchida, T.; Noguchi, M.; Minoguchi, M.; Murata, A.; Fujita, M.; Ogata, K. *Tetrahedron Lett.* **1990**, *31*, 3331.

(5) (a) Akazome, M.; Takahashi, T.; Ogura, K. *J. Org. Chem.* **1999**, *64*, 2293. (b) Akazome, M.; Yanagita, Y.; Sonobe, R.; Ogura K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2823. (c) Akazome, M.; Sumikawa, A.; Sonobe, R.; Ogura, K. *Chem. Lett.* **1996**, 995.

(6) Optical resolution of sulfoxides using inclusion phenomena has been already reported by Toda et al. (a) Toda, F.; Tanaka, K.; Nagamatsu, S. *Tetrahedron Lett.* **1984**, *25*, 4929. (b) Toda, F.; Tanaka, K.; Mak, T. C. W. *Chem. Lett.* **1984**, 2085.

(7) As application for molecular recognition of sulfoxides, several NMR chiral shift reagents have been designed and reported for determination of the stereochemistry of sulfoxides and their enantiomeric excess: (a) Drabowicz, J.; Duddeck, H. *Sulfur Lett.* **1989**, *10*, 37. (b) Buist, P. H.; Marecak, D.; Holland, H. L.; Brown, F. M. *Tetrahedron: Asymmetry* **1995**, *6*, 7. (c) Charpin, P.; Duñach, E.; Kagan, H. B.; Theobald, F. R. *Tetrahedron Lett.* **1986**, *27*, 2989. (d) Deshmukh, M.; Duñach, E.; Juge, S.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 3467.

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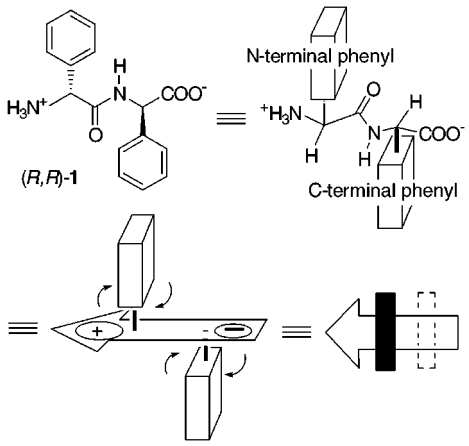


Figure 1. Structure of (*R*)-phenylglycyl-(*R*)-phenylglycine [(*R*,*R*)-**1**].

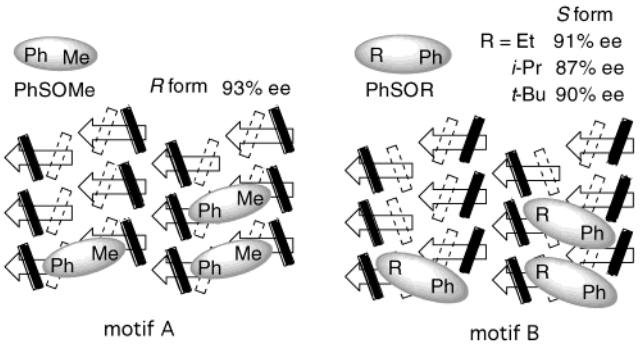


Figure 2. Schematic representation of the chiral cavities for alkyl phenyl sulfoxides.

was crystallized in the presence of the sulfoxide (method A, "crystallization"); (b) insoluble (*R*,*R*)-**1** was simply stirred in the presence of an alkyl phenyl sulfoxide and water for 24 h (method B, "sorption"); and (c) a mixture of a sulfoxide and solid (*R*,*R*)-**1** was coground in an agate mortar for 30 min (method C, "cogrinding").[8]

Results for the present inclusion are summarized in Table 1. The stereochemistry of inclusion in the dipeptide framework changes with the shape of the guest. Even if the CH_3 unit in the sulfoxides is replaced by a chlorine atom, the resulting sulfoxide isomers **3** (C_7H_7ClOS) seem to have a molecular volume comparable to that of **2** ($C_8H_{10}OS$).[9] In fact, a similar tendency was observed in their molecular recognition. The efficiency is the mole percentage of the guest molecule based on (*R*,*R*)-**1** molecule in the inclusion compound. Layer distances (L.D. in the tables) were determined by powder X-ray diffraction (PXRD). A series of the present inclusion

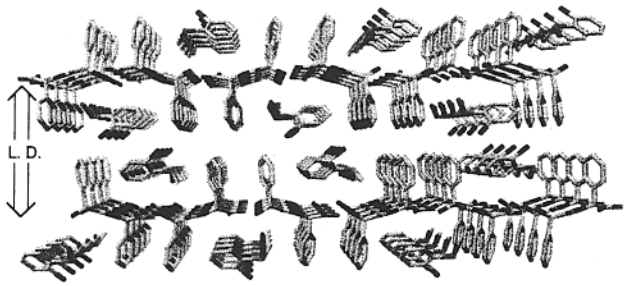


Figure 3. Perspective view of the inclusion compound of (*R*)-**3a** along the *c* axis.

compounds has a strong diffraction peak at lower 2θ range. Assignment of these layer distances was confirmed by the single-crystal structure (vide infra), because the strong peak of PXRD corresponds to the diffraction plane of the peptide backbones in the crystals.

Both 2-tolyl and 2-chlorophenyl sulfoxides (**2a** and **3a**) were recognized with high enantioselectivity of the *R* form (entries 1 and 2). In a previous paper, we reported that methyl phenyl sulfoxide is also recognized with the same enantioselectivity.[4a] Interestingly, substitution of the methyl group at the 3-position of the phenyl ring resulted in a drastic inversion of stereoselectivity. Both 3-tolyl and 3-chlorophenyl sulfoxides (**2b** and **3b**) were recognized with high *S* enantioselectivity (entries 3 and 4). However, 4-tolyl and 4-chlorophenyl sulfoxides (**2c** and **3c**) were included without the recognition of their chirality (entries 5 and 6). This phenomenon was also observed in the inclusion of benzyl methyl sulfoxide **4a** (entry 9).

Although ethyl phenyl sulfoxide **2d** was included by method A with high *S* enantioselectivity, chloromethyl phenyl sulfoxide **3d** was not included by any method (entries 7 and 8). It is likely that the terminal chlorine atom would electrically repel the π-face of the phenyl group of (*R*,*R*)-**1**,[4a] suggesting that alkyl−phenyl interaction (CH/π interaction[10]) is important for the inclusion of alkyl phenyl sulfoxides.

Irrespective of the three preparative methods, the obtained inclusion crystals showed the same PXRD pattern. Some sulfoxides were included by crystallization method A, but not by sorption method B or cogrinding method C. In the low efficiency of inclusion, especially by method C, the PXRD of the resulting crystals showed a pattern similar to that of the starting (*R*,*R*)-**1** crystal and the corresponding inclusion crystal. These results excluded the presence of other inclusion crystals.

Crystal Structures of (*R*,*R*)-1 Dipeptide Sheets in Inclusion Compounds. The crystal structures of the inclusion compounds of (*R*)-**3a** and (*S*)-**2b** were determined by single-crystal X-ray analyses. The perspective views of the inclusion compounds are shown in Figures 3 and 4. The layer distance is half of the *b* axial length of the unit cell, which corresponds to diffraction from the (020) plane.

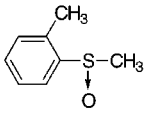
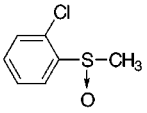
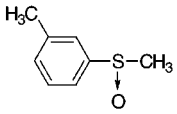
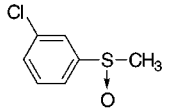
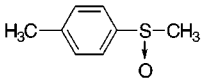
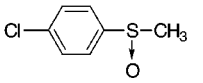
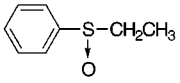
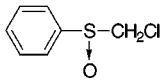
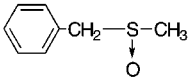
In the inclusion of **2c**, **3c**, and **4a**, optical resolution of the sulfoxide did not occur. Fortunately, we were able to obtain single crystals of the inclusion compound of **4a.** X-ray crystallographic analysis confirmed that both (*R*)- and (*S*)-enantiomers of **4a** were included in a crystal

(8) Recently, it is known that inclusion compound could be obtain by directed cogrouding in the absence of solvent: (a) Scheffer, J. R.; Wohg, Y.-F.; Patil, A. O.; Curtion, D. Y.; Paul, I. C. *J. Am. Chem. Soc.* **1985**, *107*, 4898. (b) Toda, F.; Tanaka, K.; Sekikawa, A. *J. Chem. Soc., Chem. Commun.* **1987**, 279. (c) Etter, M. C.; Frankenbach, G. M. *Chem. Mater.* **1989**, *1*, 10. (d) Hollingworth, M. D.; Brown, M. E.; Santarsiero, B. D.; Huffman, J. C.; Goss, C. R. *Chem. Mater.* **1994**, *6*, 1227. (e) Caira, M. R.; Nassimbeni, L. R.; Wildervanck, *J. Chem. Soc., Perkin Trans. 2* **1995**, 2213. (f) Pedireddi, V. R.; Jones, W.; Chorlton, A. P.; Docherty, R. *Chem. Commun.* **1996**, 987. (g) Toda, F.; Miyamoto, H.; Kanemoto, K. *J. Org. Chem.* **1996**, 61, 6490.

(9) (a) Substiuent volumes of CH_3 and Cl are 13.67 and 12.00 cm^3/mol, respectively: Bond, A. *Physical Properties of Molecular Crystals, Liquids & Glasses*; Wiley: New York, 1968. (b) Substiuent radii of CH_3 and Cl are 2.00 and 1.80, respectively: Pauling, L. *The Nature of the Chemical Bond*; Oxford: London, 1940.

(10) (a) Umezawa, Y.; Tsuboyama, S.; Honda, K.; Uzawa, J.; Nishio, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1207. (b) For a review of CH/π interaction: Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665 and references therein.

Table 1. Enantioselective Inclusion of Structural Isomers ($C_8H_{10}OS$ and C_7H_7ClOS) by (*R*,*R*)-1

Entry	Sulfoxide		A(crystallization) ee/%	A Ef.[a]/%	B(sorption) ee/%	B Ef.[a]/%	C(cogrinding) ee/%	C Ef.[a]/%	L.D.[b]/ Å
1		2a	94(*R*)	98	92(*R*)	54	N. I.[c]		12.3
2		3a	99(*R*)	97	48(*R*)	100	N. I.[c]		12.4
3		2b	93(*S*)	98	92(*S*)	78	75(*S*)	87	13.3
4		3b	97(*S*)	100	92(*S*)	87	N. I.[c]		13.4
5		2c	Rac.[d]	93	18(*R*)	98	15(*R*)	88	12.4
6		3c	Rac.[d]	96	Rac.[d]	27	N. I.[c]		12.5
7[e]		2d	91(*S*)	95	N. I.[c]		N. I.[c]		13.3
8		3d	N. I.[c]		N. I.[c]		N. I.[c]		—
9		4a	Rac.[d]	100	Rac.[d]	100	Rac.[d]	42	12.8

[a] Ef. is the abbreviation for "efficiency" and is the mol % of guest based on (*R*,*R*)-**1** in the inclusion complex. [b] L.D. is a layer distance measured by XRD. [c] N.I. means no inclusion complex formed. [d] Rac. means enantioselectivity within 10%. [e] In ref 4a.

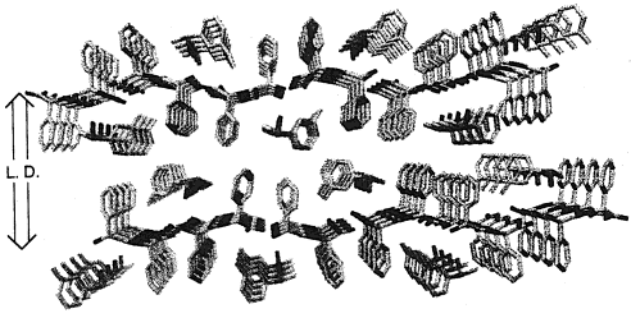


Figure 4. Perspective view of the inclusion compound of (*S*)-**2b** along the *c* axis.

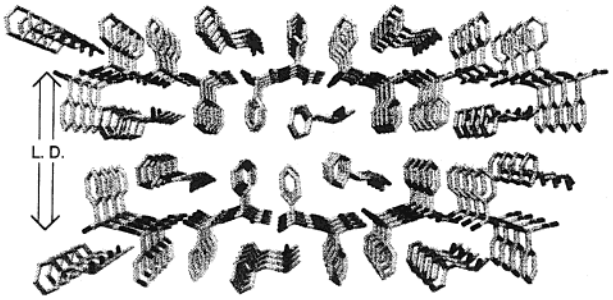


Figure 5. Perspective view of the inclusion compound of racemic **4a** along the *c* axis.

lattice of (*R*,*R*)-**1** (Figure 5). Interestingly, there are two conformers of (*R*,*R*)-**1** which construct a layer (vide infra). The *S* form of **4a** was included in the upper side cavity of the layer and the *R* form of **4a** in the lower side cavity of the same layer, but the side view is very similar to that of the two inclusion compounds mentioned above. In the PXRD analysis, this crystal also shows a layer distance that corresponds to a strong peak from the (010) plane, since this crystal has a *P*1 space group. The dipeptide sheets of the inclusion compound pile up to form a stacked layer structure in parallel.

To compare these methyl sulfoxides (**3a**, **2b**, and **4a**), the previously reported inclusion compound of (*S*)-ethyl phenyl sulfoxide (**2d**) is also shown in Figure 6.[4a] This arrangement of the dipeptide is very similar to the

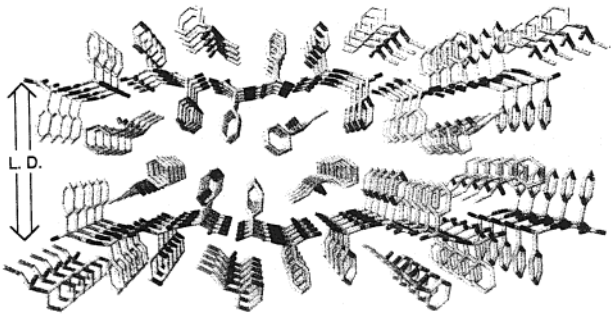
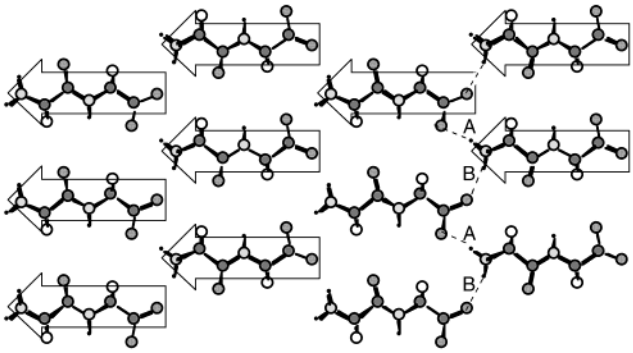


Figure 6. Perspective view of the inclusion compound of (*S*)-**2d** along the *c* axis.



		A N•••O	B N•••O	H-G N•••O
2-ClC$_6$H$_4$SOMe	**3a**	2.72	2.79	2.77
3-TolSOMe	**2b**	2.67	2.79	2.75
BnSOMe	**4a**	2.75	2.73	2.78
		2.73	2.73	2.73
PhSOEt	**2d**	2.74	2.75	2.76

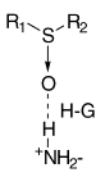


Figure 7. Dipeptide backbone and atomic distances between hydrogen bonds.

inclusion compound of (*S*)-**2b**, but the phenyl and the ethyl groups of (*S*)-**2d** replaced each other in position to realize *S* chirality. Judging from the inclusion of various methyl sulfoxides in (*R*,*R*)-**1** crystals, the methyl groups were always close to the C-terminal phenyl groups of (*R*,*R*)-**1**, which constructed the right wall of the void.

The hydrogen-bonding distances between $^+NH_3$ group and COO^- groups are summarized in Figure 7. In all of these inclusion crystals, the dipeptide backbones are very similar to each other. As for hydrogen-bonding distances between the sulfinyl oxygen and the ammonio group, these values are almost the same as the reported distances: 2.758(2) and 2.781(1) Å for SO···O of binaphthol[6] and 2.85(2) Å for SO(sulfinyl)···N(amide).[7c]

Crystal Structures of Chiral Cavities of (*R*,*R*)-1 for Enantioselective Inclusion. CPK models of the inclusion cavities are illustrated in Figures 8−10. Sheet structures are colored in black, guest sulfoxides in gray, and the phenyl groups of dipeptides in white. One molecule of the sulfoxide was deleted to clarify the inclusion cavity and the position of the ammonio group. These cavities are four motifs (A, B, pseudo-B, and C), which were characterized by the conformation of the phenyl groups of (*R*,*R*)-**1**.

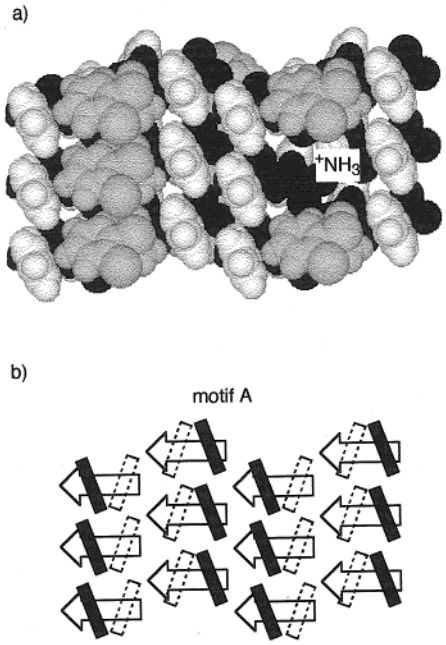


Figure 8. (a) CPK model of recognition site of (*R*)-**3a**. (b) Schematic representation of the chiral cavity (motif A).

As shown in Figure 8, (*R*)-2-chlorophenyl methyl sulfoxide **3a** is accommodated in a channel between the phenyl groups of (*R*,*R*)-**1**. It is notable that the phenyl−phenyl stacking mode of (*R*,*R*)-**1** was a "parallel stacking and displaced" mode (motif A)[11] and the methyl group of the sulfinyl was directed to the C-terminal phenyl group of the dipeptide. The 2-chlorophenyl group of **3a** was directed to the N-terminal phenyl group of the dipeptide, where "T"-mode phenyl−phenyl stacking occurred[11] (the distance between the hydrogen at the 4-position of the 2-chlorophenyl group of (*R*)-**3a** and the center of one phenyl ring of (*R*,*R*)-**1** is 2.56 Å). This motif A was also observed in the inclusion of (*R*,*R*)-bis[2-(methylsulfinyl-)benzyl] ether.[4a]

Figure 9a shows that (*S*)-methyl 3-tolyl sulfoxide **2b** was accommodated in a channel between the phenyl groups of (*R*,*R*)-**1**. These phenyl groups on the dipeptide layer interact in the "tilted T"-shaped mode and construct motif B. The methyl group of **2b** was directed to the C-terminal phenyl group of the dipeptide and the 3-tolyl group of **2b** to the N-terminal phenyl group. This cavity is very close to that of (*S*)-**2d**, but the guest molecule is arranged in a quite different manner: the ethyl group and phenyl group are directed to the phenyl groups of N-terminal and C-terminal, respectively (Figure 9b). Hence, the difference in volume between methyl and ethyl groups seems to be a crucial factor in positioning the guest sulfoxide in the cavity.

In the inclusion of racemic **4a**, there are two different recognition cavities on the upper side for its *S* enantiomer and on the lower side for its *R* enantiomer as mentioned above (Figure 5). The upper side cavity can be illustrated by motif pseudo-B, and the lower side one by motif C in

(11) Three types of interaction between two molecules of benzene ("tilted T", "T", and "parallel stacked and displaced" modes) must be taken into consideration. Jorgensen and Severance calculated these benzene dimers by the Monte Carlo method to show that they have comparable energies: Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768.

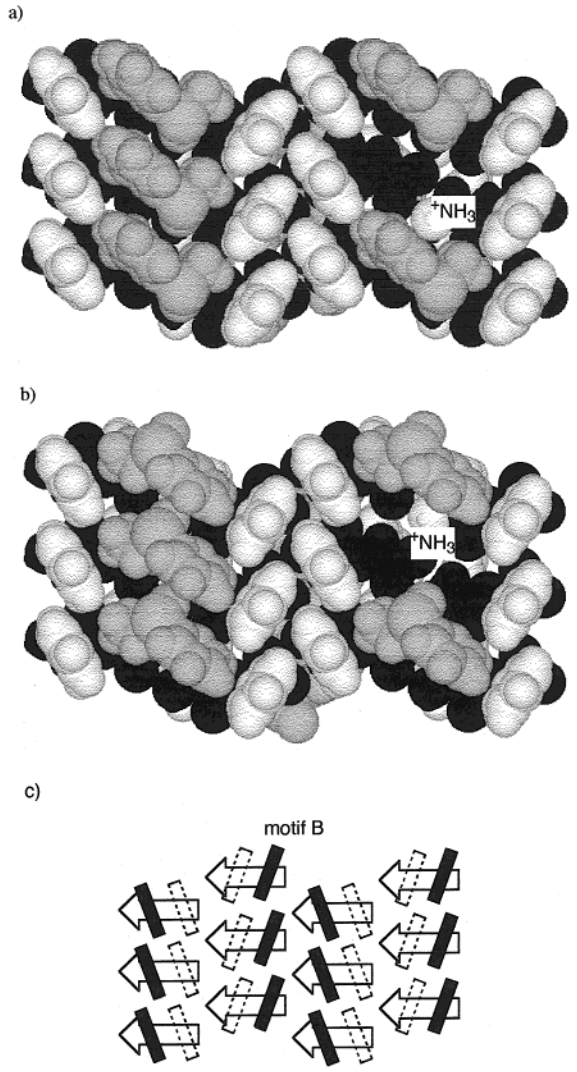


Figure 9. (a) CPK models of recognition site of (*S*)-**2b**. (b) CPK models of recognition site (*S*)-**2d**. (c) Schematic representation of the chiral cavity (motif B).

Figure 10. These cavities are just like a mirror image to each other in shape. In these cases, (*R*)- and (*S*)-benzyl methyl sulfoxides directed the methyl group and benzyl groups to the C-terminal phenyl group and to the N-terminal phenyl group, respectively. This arrangement makes the phenyl groups of (*R*,*R*)-**1** and **4a** pack tightly in the usual herringbone motif.[12,13]

From the CPK models of Figure 10, it can be assumed that, when a methyl group is introduced into the α-position of the benzyl group, the inclusion is not retarded if the methyl is located at the front site. Therefore, the (α*R**,S*S**)-isomer of methyl α-methylbenzyl sulfoxide **4b** is expected to be preferentially recognized by (*R*,*R*)-**1** crystals. According to the literature, oxidation of α-methylbenzyl methyl sulfides affords a mixture of sulfoxides, and the ratio is (α*R**, S*S**):(α*R**, S*R**) = 1:3.[14] The guest molecule (**4b**) was included by method A, but not by method B. As for the variation of the guest amount, the results of crystallization are summarized in Scheme 1. The stereochemisrty of the products was determined by comparison with authentic samples synthesized by other routes,[15] and the distributions of the diastereomers were determined by the chiral shift reagent (*S*)-MPAA.[7b]

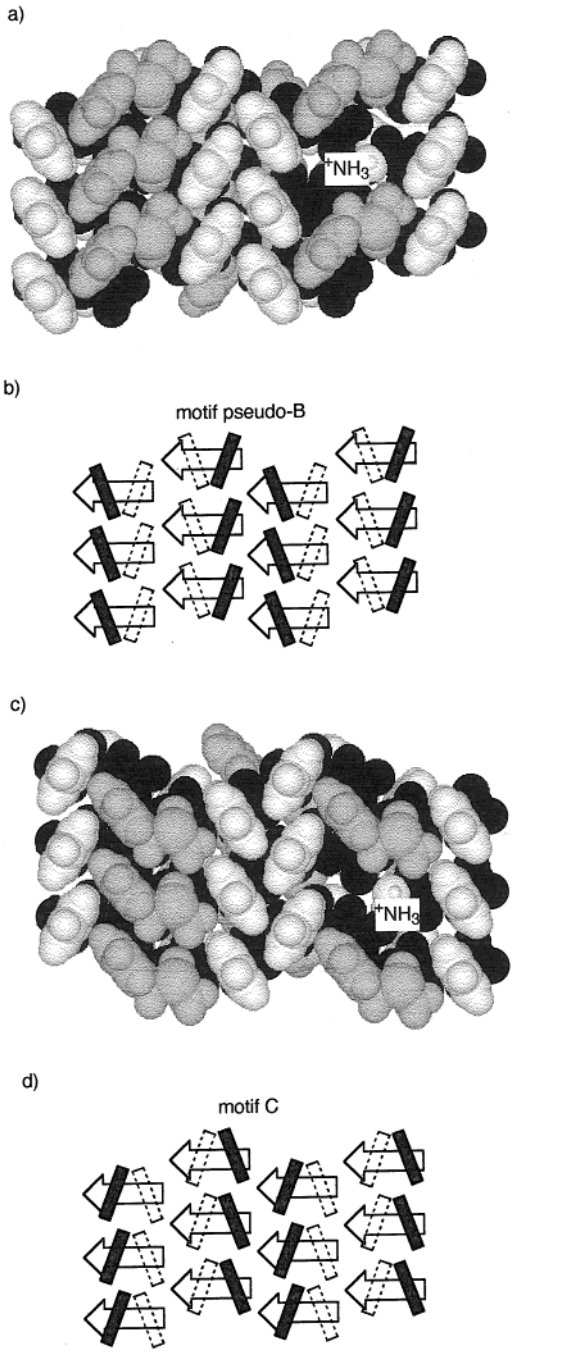


Figure 10. (a and c) CPK models of recognition sites of racemic **4a**. Recognition sites for (*S*)-**4a** (a) and (*R*)-**4a** (c). (b and d) Schematic representation of the corresponding chiral cavities (motifs pseudo-B and C).

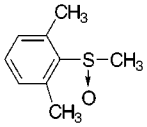
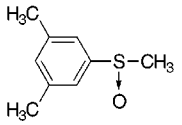
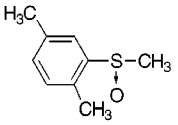
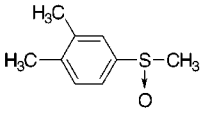
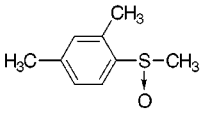
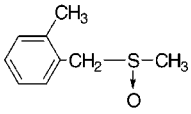
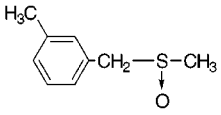
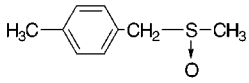
(12) (a) Swift, J. A.; Pal, R.; McBride, J. M. *J. Am Chem. Soc.* **1998**, *120*, 96. (b) Lewis, F. D.; Yang, J.-S.; Stern, C. L. *J. Am Chem. Soc.* **1996**, *118*, 12029. (c) Hunter, C. A.; Sanders, J. K. M. *J. Am Chem. Soc.* **1990**, *112*, 5525. (d) Desiraju, G. R.; Gavezzotti, A *J. Chem. Soc., Chem. Commun.* **1989**, 621. (e) Gavezzotti, A *Chem. Phys. Lett.* **1989**, *161*, 67.

(13) In proteins, $\pi-\pi$ interactions on their side chains have already been investigated to reveal the edge-to-face interaction between two benzene rings to be important: (a) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23. (b) Gould, R. O.; Gray, A. M.; Taylor, P.; Walkinshaw, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 5921. (c) Burley, S. K.; Petsko, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 7995.

(14) (a)Nishihata, K.; Nishio, M. *Tetrahedron Lett.* **1977**, *12*, 1041.

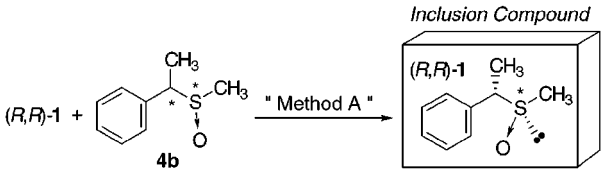
(15) (a) Nishihata, K.; Nishio, M. *Chem. Commun.* **1971**, 958. (b) Hoffmann, H. M.; Hughes, E. D. *J. Chem. Soc.* **1964**, 1244. (c) Burwell, R. L.; Shields, A. D.; Hart, H. *J. Am. Chem. Soc.* **1954**, 908.

Table 2. Inclusion of Structural Isomers with Methylsulfinyl Group ($C_9H_{12}OS$) by (*R*,*R*)-1

Entry	Sulfoxide		A(crystal.) ee/%	A(crystal.) Ef.[a]/%	B(sorption) ee/%	B(sorption) Ef.[a]/%	L.D.[b]/ Å
1		**2e**	87(*R*)	99	72(*R*)	67	14.0
2		**2f**	91(*S*)	99	77(*S*)	100	13.7
3		**2g**	73(*S*)	100	58(*S*)	85	13.6
4		**2h**	85(*S*)	91	79(*S*)	99	13.4
5		**2i**	30(*R*)	80	N. I.[c]		12.3
6		**4c**	Rac.[d]	100	Rac.[d]	100	13.0
7		**4d**	82(*R*)	100	88(*R*)	90	12.7
8		**4e**	N. I.[c]		N. I.[c]		—

[a] Ef. is the abbreviation for "efficiency" and is the mol % of guest based on (*R*,*R*)-**1** in the inclusion complex. [b] L.D. is a layer distance measured by XRD. [c] N.I. means no inclusion complex formed. [d] Rac. means enantioselectivity within 10%.

Scheme 1



Sulfoxide / mol equiv	Ef. /%	Distribution of diastereomers / % (α*S*, S*R*)	(α*R*, S*S*)	(α*R*, S*R*)	(α*S*, S*S*)
Starting material		13	13	37	37
2	69	40	33	17	10
4	87	47	32	13	8
8	100	63	21	10	6

As expected, two enantiomers (α*R**,S*S**) could be recognized and included preferably from the diastereomeric mixture in the presence of 2−4 mol equiv of **4b**. Using an 8-fold amount of **4b**, the (α*S*,S*R*)-enantiomer is recognized more predominantly than the (α*R*,S*S*)-enamtiomer. Since the stereochemistry on the sulfur atom of recognized (α*S*,S*R*)-**4b** was the *R* form, (*R*,*R*)-**1** would construct a cavity similar to that for (*R*)-**4a**.

Inclusion of Structural Isomers of One-Carbon Homologous Sulfoxides ($C_9H_{12}OS$). Results for methyl xylyl sulfoxides **2e**−**i** and methyl tolylmethyl sulfoxides **4c**−**e** ($C_9H_{12}OS$), one-carbon homologues of $C_8H_{10}OS$, are summarized in Table 2.

We examined how substitution of two methyl groups on the phenyl group of methyl phenyl sulfoxide influences the inclusion stereoselectivity. In the case of **2e**, two methyl groups at the ortho positions of the phenyl group were shown to be tolerant to the present inclusion, because its *R* form was included in the cavity with expansion of the layer distance to 14.0 Å (entry 1). In a similar manner to methyl 3-tolyl sulfoxide (**2b**), methyl 3,5-, 2,5-, or 3,4-xylyl sulfoxides (**2f**, **2g**, or **2h**) was recognized as their *S* forms (entries 2−4). Therefore, it was suggested that the methyl group at the meta position

of the phenyl group was crucial for its *S* selectivity. Since 4-tolyl sulfoxide **2c** was not enantiomerically recognized at all, the *R* enantioselectivity of 2,4-xylyl sulfoxide **2i** seems to be attributable to some degree to the 2-methyl group (entry 5).

The sulfoxides having a benzyl skeleton (**4c**−**e**) were also examined. The substitution on the 2-position did not affect the enantioselectivity of **4c**, but that of the 3-position drastically induced the enantiomeric inclusion for the *R* form of **4d** (entries 6 and 7). Two possible origins of the high *R* enantioselective inclusion can be rationalized: first, the 3-methylbenzyl group of **4d** might have a conformation like the 2,6-xylyl group of (*R*)-**2e**; second, (*R*,*R*)-**1** would construct only the *R* site of the inclusion compound of **4a**, and (*R*)-**4d** was included in it. The latter is more plausible, because the inclusion compound of (*R*)-**4d** shows a shorter layer distance (12.7 Å), which is rather comparable to that of **4a** (12.8 Å) than that of (*R*)-**2e** (14.0 Å). It should be noted that the substitution at the 4-position disturbed the inclusion of **4e** (entry 8). This is probably because **4e** is too large to be included in the void.

Conclusion Remarks

(*R*)-Phenylglycyl-(*R*)-phenylglycine [(*R*,*R*)-**1**] molecules self-assemble through intermolecular salt formation to form layers, on which an enantiomeric cavity is produced between the walls of the phenyl groups of (*R*,*R*)-**1** to recognize various sulfoxide guests. In this paper, we demonstrated the flexibility of the inclusion cavity on the lattice of crystalline (*R*,*R*)-**1** to have high potential for molecular recognition of structurally isomeric sulfoxides which have a similar volume. It was also shown that a slight difference in molecular shape induced a drastic change of conformation of (*R*,*R*)-**1** and the stereoselectivity of recognized sulfoxide molecules.

In sharp contrast to ethyl or isopropyl phenyl sulfoxide, methyl sulfoxides bearing a phenyl or benzyl group are structurally different when included: the methyl groups of sulfoxides were always directed to the C-terminal phenyl groups of (*R*,*R*)-**1**. It is important for the conformation of the C-terminal phenyl group to determine which binds to the ammonio proton via hydrogen bonding, the *R* or *S* form of the methyl sulfinyl group (Figure 11). In other words, the methyl sulfoxide induces the conformation of the dipeptide to make the shape of the recognition cavity fit for its sulfinyl group.

Experimental Section

General. (*R*)-Phenylglycine (99% ee) was purchased from Tokyo Chemical Industry. Chiral shift reagents, (*S*)-α-methoxyphenylacetic acid [(*S*)-MPAA] and (*R*)-(+)-2,2′-dihydroxy-1,1′-binaphthyl [(*R*)-BINOL], were purchased from Aldrich and Kankyo Kagaku Center, respectively.

Synthesis of (*R*)-Phenylglycyl-(*R*)-phenylglycine [(*R*,*R*)-1].[16] As for protection of the carboxylic group of (*R*)-phenylglycine, the benzyl ester *p*-toluenesulfonate was prepared in 98% yield according to a literature:[17] colorless powder; mp 191−192 °C; $[\alpha]^{25}_{D} = -35.3$ (*c* = 2.00, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 4.93 (d, 1H, 12.4 Hz), 4.96 (d, 1H, 12.4 Hz), 5.13 (s, br, 1H), 6.97 (d, 2H, 8.1 Hz), 7.00−7.28 (m, 10H), 7.51 (d, 2H, 8.1 Hz), 8.70 (s, br, 3H); IR (KBr) 3220, 3360, 1749, 1597, 1497 cm^{-1}. Anal. Calcd for $C_{22}H_{22}NO_5S$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.78; H, 5.59; N, 3.40.

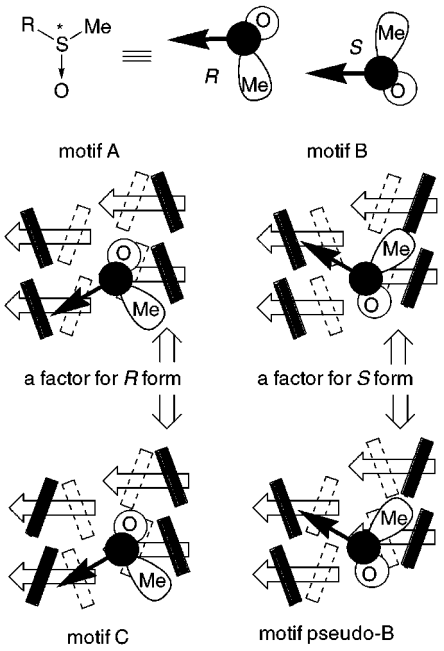


Figure 11. Schematic representation of C-terminal phenyl groups as a factor to determine the stereochemistry of the sulfoxides.

According to the DCC−HOBt method,[18] coupling between (*R*)-*N*-(benzyloxycarbonyl)phenylglycine[19] (12.8 g, 45.0 mmol) and (*R*)-phenylglycine benzyl ester *p*-toluenesulfonate (18.6 g, 45.0 mmol) provided the protected dipeptide (20.8 g, 40.9 mmol, yield 91%): mp 193.5−195 °C; $[\alpha]^{25}_{D} = -93.2$ (*c* = 2.1, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 5.09 (s, 4H), 5.40 (s, 1H), 5.53 (s, 1H), 7.13−7.45 (m, 20H); IR (KBr) 3320, 3040, 1732, 1718, 1690, 1654, 1526 cm^{-1}.

The protected dipeptide (8.50 g, 16.7 mmol) was dissolved in a mixture of MeOH (80 mL), AcOH (20 mL), and water (10 mL) and treated with hydrogen in the presence of Pd black (prepared from $PdCl_2$, 0.76 g, 4.3 mmol) overnight. The catalyst was removed by filtration, and concentration of the filtrate gave a solid. The solid was dissolved in 0.2 M aqueous HCl, the pH was adjusted to about 6.5 by the addition of 5 M aqueous NaOH. The solution was concentrated until a small amount of a solid was deposited. Then the solution was stored to precipitate crystalline (*R*,*R*)-**1** in a refrigerator overnight. Colorless powder (*R*,*R*)-**1** was collected, washed with water, and dried in vacuo (4.27 g, 15.0 mmol, yield 88%). (*R*,*R*)-**1**: mp 220−223 °C, (dec) $[\alpha]^{25}_{D} = -137.2$ (*c* = 0.99, 0.2 M HCl); ^{1}H NMR (300 MHz, DCl + D_2O) δ 5.24 (s, 1H), 5.50 (s, 1H), 7.41−7.46 (m, 5H), 7.53 (s, br, 5H); IR (KBr) 3370, 3300, 1676, 1560, 1508 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.36; H, 5.81; N, 9.81.

Synthesis of Sulfoxide 2, 3, and 4. Sulfides were prepared from corresponding halides and thiols by Williamson-type sulfide synthesis, except for **3d**.[20] Oxidation of sulfide was proceeded by hydrogen peroxide in acetic acid or sodium metaperiodate.[21] In the case of **3d**, methyl phenyl sulfoxide was chlorinated by our procedure.[22]

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(22) Tsuchihashi, G.; Ogura, K.; Iriuchijima, S.; Tomisawa, S. *Synthesis* **1971**, 91.

Preparation of Inclusion Compounds of Alkyl Phenyl Sulfoxide and (*R*,*R*)-1. Method A. (*R*,*R*)-**1** (1.0 mmol) was dissolved in 0.1 M aqueous HCl, then the pH was adjusted to about 6.5 by the addition of 0.1 M aqueous NaOH.[4a] After the addition of a racemic sulfoxide (**2**, **3**, or **4**) (2.0 mmol) to the aqueous solution of (*R*,*R*)-**1**, the resulting mixture was allowed to stand at an ambient temperature for several days. The deposited inclusion compound was collected by filtration and washed with water (20 mL) and $CHCl_3$ (20 mL).

Method B. Crystals of (*R*,*R*)-**1** are essentially insoluble in organic solvents and water. A suspension of (*R*,*R*)-**1** (1.0 mmol) in water (2 mL) was stirred together with a racemic sulfoxide (**2**, **3**, or **4**) (2.0 mmol) at ambient temperature for 1 day. The formed inclusion compound was collected by filtration and washed with water (20 mL) and $CHCl_3$ (20 mL).

Method C. An agate mortar and (*R*,*R*)-**1** were dried in a desiccator. A mixture of (*R*,*R*)-**1** (1.0 mmol) and a racemic sulfoxide (**2**, **3**, or **4**) (2.0 mmol) was often grounded in an agate mortar at ambient temperature for 30 min. To keep dry, the mortar was stored in a desiccator when not being used. The formed inclusion compound was washed with water (20 mL) and $CHCl_3$ (20 mL).

Determination of Efficiency, Stereochemistry, and Enantiomeric Excess in the Inclusion. After decomposition of the inclusion compound with diluted DCl in D_2O, inclusion efficiency was determined by NMR measurement. The included sulfoxide was isolated by dissolution of the inclusion compound in 0.1 M aqueous HCl (40 mL) and extraction with $CHCl_3$. The absolute stereochemistry of recognized sulfoxides was determined by comparison of the optical rotation to the value of the literature and/or by chiral shift reagents [(*R*)-(+)-2,2′-dihydroxy-1,1′-binaphthyl[7a] ((*R*)-BINOL, 1 mol equiv for the sulfoxide) and (*S*)-α-methoxyphenyl acetic acid[7b] ((*S*)-MPAA, 3 mol equiv for the sulfoxide)]. Enantiomeric excess of the sulfoxide was determined by a chiral HPLC (Daicel Chiralcel OB).

2c, **3c**, **4a**, and **4c** were not recognized enantiomerically, and **3d** and **4e** were not included at all.

2a $[\alpha]^{25}_D = +190.5$ ($c = 1.3$, acetone); 92% ee *R* by [α];[23] HPLC eluent, hexane/2-propanol (4:1), flow rate = 0.6 mL/min, $t_R(S) = 11.0$ min, $t_R(R) = 22.8$ min); ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$) δ 2.64 (s, 2.6H, *R* major), 2.65 (s, 0.4H, *S* minor), 2.36 (s, 3H), 7.19−7.61 (m, 4H).

2b: $[\alpha]^{25}_D = -120.4$ ($c = 1.0$, EtOH); 92% ee *S* by [α],[6b] HPLC eluent, hexane/2-propanol (4:1), flow rate = 0.6 mL/min, $t_R(S) = 10.7$ min, $t_R(R) = 15.4$ min); ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$) δ 2.41 (s, 3H), 2.67 (s, 0.1H, *R* minor), 2.68 (s, 2.9H, *S* major), 7.45 (s, 1H). Aromatic 3H could be not identified because of the binaphthyl group.

2c: $[\alpha]^{25}_D = +21.0$ ($c = 2.2$, acetone); 18% ee *R* by [α],[24] HPLC eluent, hexane/2-propanol (4:1), flow rate = 0.6 mL/min, $t_R(S) = 11.6$ min, $t_R(R) = 22.9$ min); ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$) δ 2.67 (s, 1.8H, *R* major), 2.68 (s, 1.2H, *S* minor), 2.41 (s, 3H), 7.32 (d, 2H 8.2 Hz), 7.52 (d, 2H, 8.2 Hz).

2d: $[\alpha]^{25}_D = -143.1$ ($c = 1.4$ EtOH); 74% ee *S* by [α],[25a,b] HPLC eluent, hexane/2-propanol (4:1), flow rate = 0.7 mL/min, $t_R(S) = 11.3$ min, $t_R(R) = 20.5$ min).

3a: $[\alpha]^{25}_D = +140.6$ ($c = 1.0$, acetone); 48% ee *R* by HPLC; HPLC eluent, hexane/2-propanol (9:1), flow rate = 0.7 mL/min, $t_R(S) = 18.5$ min, $t_R(R) = 23.6$ min); ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$) δ 2.78 (s, 2.2H, *R* major), 2.79 (S, 0.8H, *S* minor). Aromatic 4H could be not identified because of the binaphthyl group.

3b: $[\alpha]^{25}_D = -85.2$ ($c = 0.87$, acetone); 92% ee *S* by HPLC; HPLC eluent, hexane/2-propanol (9:1), flow rate = 0.7 mL/min, $t_R(S) = 18.3$ min, $t_R(R) = 27.0$ min); ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$) δ 2.69 (s, 0.1H, *R* minor), 2.70 (s, 2.9H, *S* major), 7.43−7.48 (m, 3H), 7.64−7.64 (m, 1H).

2e: $[\alpha]^{25}_D = +177.9$ ($c = 1.1$, acetone); 72% ee *R* by HPLC; HPLC eluent, hexane/2-propanol (20:1), flow rate = 0.6 mL/min, $t_R(S) = 25.7$ min, $t_R(R) = 28.2$ min); ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$) δ 2.84 (s, 2.6H, *R* major), 2.84 (s, 0.4H, *S* minor), 2.58 (s, 6H), 7.04 (d, 2H, 7.6 Hz), 7.22 (t, 1H, 7.6 Hz)

2g: $[\alpha]^{25}_D = -87.8$ ($c = 1.3$, acetone); 73% ee *S* by NMR, ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$) δ 2.63 (s, 2.60H, *R* minor), 2.64 (s, 0.40H, *S* major), 2.31 (s, 3H), 2.39 (s, 3H), 7.08 (d, 1H, 7.8 Hz), 7.14 (d, 1H, 7.8 Hz), 7.73 (s, 1H). HPLC showed no baseline separation (eluent, hexane/2-propanol (20:1), flow rate = 0.5 mL/min, $t_R(S) = 38.3$ min, $t_R(R) = 40.9$ min).

2i: $[\alpha]^{25}_D = +57.86$ ($c = 0.59$, acetone), 30% ee *R* by NMR; ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$,) δ 2.63 (s, 1.95H *R* major), 2.64 (s, 1.05H, *S* minor), 2.33 (s, 3H), 2.36 (s, 3H), 7.01 (s, 1H), 7.23 (d, 1H, 8.0 Hz), 7.80 (d, 1H, 8.0 Hz). HPLC showed no baseline separation (eluent, hexane/2-propanol (20:1), flow rate = 0.5 mL/min, $t_R(S) = 32.3$ min, $t_R(R) = 34.8$ min).

2f: $[\alpha]^{25}_D = -102.59$ ($c = 0.925$, acetone); 77% ee *S* by HPLC; HPLC eluent, hexane/2-propanol (9:1), flow rate = 0.6 mL/min, $t_R(S) = 16.8$ min, $t_R(R) = 23.5$ min); ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$) δ 2.37 (s, 6H), 2.67 (s, 0.3H, *R* minor), 2.68 (s, 2.7H, *S* major), 7.11 (s, 1H), 7.23 (s, 2H).

2h: $[\alpha]^{25}_D = -111.33$ (c =0.98, acetone); 79% ee *S* by HPLC; HPLC eluent, hexane/2-propanol (9:1), flow rate = 0.6 mL/min, $t_R(S) = 20.8$ min, $t_R(R) = 41.3$ min); ^{1}H NMR (with (*R*)-BINOL in $CDCl_3$, 75% ee *S*) δ 2.304 (s, 3H), 2.309 (s, 3H), 2.648 (s, 0.4H, *R* minor), 2.662(s, 2.6H, *S* major). Aromatic 3H could be not identified because of the binaphthyl.

4b starting material (major/minor = 3:1):[15a] ^{1}H NMR ($CDCl_3$) (major, α*R**,*SR**) δ 1.75 (d, 3H, 7.1 Hz), 2.30 (s, 3H), 3.76 (q, 1H, 7.1 Hz), 7.08−7.44 (m, 5H), (minor, α*R**,*SS**) δ 1.73 (d, 3H, 7.1 Hz), 2.18 (s, 3H), 3.86 (q, 1H, 7.1 Hz), 7.08−7.44 (m, 5H). ^{1}H NMR (with (*S*)-MPAA in $CDCl_3$) (major, α*S*,*SS*) δ 1.72 (d, 3H, 7.1 Hz), 2.34 (s,3H), 3.93 (q, 1H, 7.1 Hz), (major, α*R*,*SR*) 1.69 (d, 3H, 7.1 Hz), 2.35 (s, 3H), 3.95 (q, 1H, 7.1 Hz), (minor, α*R*,*SS*) 1.69 (d, 3H, 7.1 Hz), 2.24 (s,3H), 3.99 (q, 1H, 7.1 Hz), (minor, α*S*,*SR*) 1.68 (d, 3H, 7.1 Hz), 2.26 (s, 3H), 4.12 (q, 1H, 7.1 Hz). Aromatic H could be not identified because of (*S*)-MPAA.

4d: $[\alpha]^{25}_D = -55.7$ ($c = 1.1$, acetone), 81% ee *R* by NMR; ^{1}H NMR (with (*S*)-MPAA in $CDCl_3$) δ 2.33 (s, 3H), 2.49 (s, 0.27H, *S* minor), 2.51 (s, 2.72H, *R* major), 3.94 (d, 0.91H J = 12.7 Hz, *R* major), 3.95 (d, 0.09H, $J = 12.7$ Hz, S minor), 4.17 (d, 1H, $J = 12.6$ Hz), 7.23 (t, 1H 7.6 Hz), 7.14 (d, 1H, 7.6 Hz), 7.06 (s, 1H), 7.04 (d, 1H, 7.6 Hz). HPLC showed no baseline separation (eluent, hexane/2-propanol (9:1), flow rate = 0.6 mL/min, $t_R(S) = 29.4$ min, $t_R(R) = 33.4$ min).

X-ray Analyses. X-ray powder diffractions were obtained with a MAC Science MXP diffractometer using graphite-monochromated Cu Kα radiation (40 kV, 300 mA). The spectra were measured at room temperature between 2° and 50° in the 2θ scan mode with steps of 0.01° in 2θ and 4°/min.

Crystallographic Data for the Inclusion Compounds. To the solution of (*R*,*R*)-**1** was added a methanol solution of the guest (**3a**, **2b**, or **4a**) directly in a vial, then the lid of the vial was loosely closed for evaporation of the solvent. The samples were allowed to stand for several days to form the desirable single crystals. Data of an inclusion complex with **2d** were already reported in our previous paper.[4a] Data collection was performed on a Mac Science MXC18 four-circle diffractometer with graphite-monochromated Cu Kα ($\lambda = 1.541$ 78) radiation using the $2\theta-\omega$ scan technique, and the X-ray intensities were measured up to $2\theta = 140°$ at 298 K. The structures were solved by a direct method SIR 92[26] and refined by a computer program package, CRYSTAN-GM ver. 6.2.1 or maXus ver. 1.1 from MAC Science Co. Ltd. Hydrogen atoms are calculated in the appropriate position.

The inclusion compound of 3a (2-chlorophenyl methyl sulfoxide): $C_{23}H_{23}ClN_2O_4S$, $M = 459.00$, crystal dimensions 0.15 × 0.10 × 0.05 mm, orthorhombic, $P2_12_12_1$, $a = 16.226(4)$ Å, $b = 24.679(6)$ Å, $c = 5.635(2)$ Å, $V = 2256.5(9)$ Å^3, $Z = 4$,

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$\rho_{calcld} = 1.35$ g cm^{-3}, 2594 reflections measured, 2268 independent, $R = 0.085$ (1291 reflections with $I > 1.00\sigma(I)$), $R_w = 0.068$, 297 parameters, with heavy atoms refined anisotropically, residual electron density 0.44/−0.36.

The inclusion compound of 2b (methyl 3-tolyl sulfoxide): $C_{24}H_{26}N_2O_4S$, $M = 438.55$, crystal dimensions 0.10 × 0.05 × 0.05 mm, orthorhombic, $P2_12_12_1$, $a = 15.953(4)$ Å, $b = 26.586(6)$ Å, $c = 5.628(2)$ Å, $V = 2234.2(9)$ Å^3, $Z = 4$, $\rho_{calcld} = 1.30$ g cm^{-3}, 4911 reflections measured, 3951 independent, $R = 0.131$ (2251 reflections with $I > 1.00\sigma(I)$), $R_w = 0.077$, 150 parameters. This very small crystal afforded weak diffraction, so heavy atoms refined isotropically except for the sulfur atom, residual electron density 0.41/−0.42.

The inclusion compound of 4a (benzyl methyl sulfoxide): $C_{24}H_{26}N_2O_4S$, $M = 438.55$, crystal dimensions 0.40 × 0.15 × 0.05 mm, triclinic, $P1$, $a = 5.446(2)$ Å, $b = 13.908(3)$ Å, $c = 16.164(3)$ Å, $\alpha = 69.815(15)$, $\beta = 88.028(22)$, $\gamma = 79.457(21)$, $V = 1129.2(5)$ Å^3, $Z = 2$, $\rho_{calcld} = 1.29$ g cm^{-3}, 4911 reflections measured, 3951 independent, $R = 0.067$ (2251 reflections with $F > 3.00\sigma(F)$); $R_w = 0.074$, 632 parameters, with heavy atoms refined anisotropically, residual electron density 0.33/−0.41.

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Supporting Information Available: Tables of atomic coordinates and thermal parameters, bond lengths and angles, and ORTEP views of inclusion compounds of (*R*)-**3a**, (*S*)-**2b**, and racemic **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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