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Chiral sulfoxide ligands bearing nitrogen atoms as stereocontrollable coordinating elements in palladium-catalyzed asymmetric allylic alkylations[1]

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Abstract

Palladium-catalyzed asymmetric allylic alkylations were studied by using chiral sulfoxide ligands bearing nitrogen atoms as coordinating elements, such as chiral α-sulfinylacetamides, β or γ-amino sulfoxides, and β-sulfinyl sulfonamides. The effects of the chiral sulfinyl functions on the asymmetric induction were demonstrated. Use of (*S*)-2-pyrrolidinophenyl *p*-tolyl sulfoxide or (*S*)-2-(*N*-butyl-*N*-methylaminomethyl)phenyl *p*-tolyl sulfoxide as chiral ligands in the palladium-catalyzed asymmetric allylic alkylations provided the highest enantioselectivity (50 or 58% e.e., respectively) among chiral sulfoxide ligands examined by us. The participation of the sulfinyl groups in these catalytic asymmetric reactions is rationalized, and the mechanism for the asymmetric induction is proposed on the basis of the stereochemical outcome obtained.

1. Introduction

Asymmetric synthetic reactions have received much attention in recent years for the preparation of chiral biologically active compounds, and many methodologies for asymmetric carbon–carbon bond formation have been developed.[2] Quite recently, catalytic asymmetric synthesis has received much attention[3] for the practical synthesis of homochiral compounds, especially in the pharmaceutical field, and transition metal-catalyzed asymmetric reactions with many kinds of chiral ligands such as phosphines, phosphonites, amines, and alcohols have been reported.[4]

Over the course of a decade we have so far studied the stereochemistry of transition metal-catalyzed reactions of chiral systems such as chiral allyl esters[5] and cyclopropane compounds bearing chiral sulfinyl groups.[6] These continuous works have always stimulated much interest in the participation of chiral sulfinyl functionality to transition metal catalysts,[7] and successively extensive efforts have been

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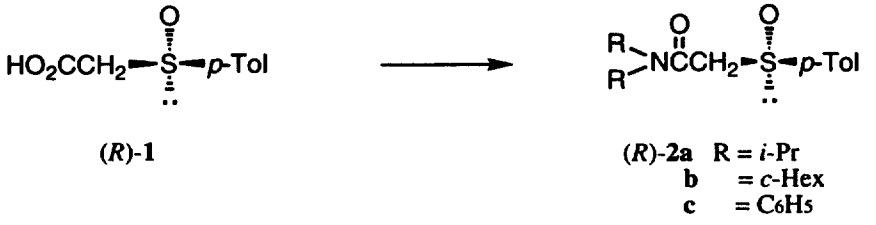
devoted to the development of new chiral ligands bearing chiral organosulfur functionalities as sole chiral sources.[8]

2. Results and discussion

Few reports have been published concerning asymmetric synthesis with chiral organosulfur ligands bearing chiral sulfinyl[9] or sulfinamide groups[10] as sole chiral sources. We describe in this article details of our studies on the palladium-catalyzed asymmetric allylic alkylations using the chiral sulfinyl functionality[11] in ligands such as chiral α-sulfinylacetamides, β or γ-amino sulfoxides, and β-sulfinyl sulfonamides.

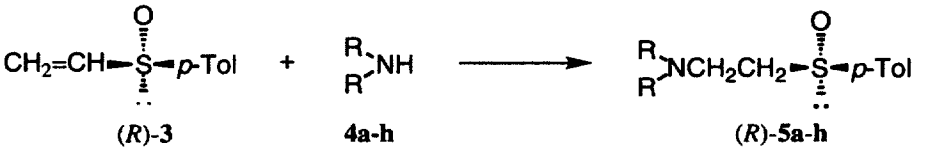
2.1. Synthesis of chiral sulfoxide ligands

Chiral sulfoxide ligands which were examined in this report were obtained as follows. Chiral 2-(*p*-toluenesulfinyl)acetamides (*R*)-**2a–c** were prepared by the amidation of (*R*)-2-(*p*-toluenesulfinyl)acetic acid **1**[12] via the corresponding methyl carbonate (Scheme 1).



Scheme 1.

Chiral β-aminoethyl sulfoxides (*R*)-**5a–h** were readily obtained in good yields (90–100%) by Michael additions[13] of the corresponding secondary amines **4a–h** to (*R*)-*p*-tolyl vinyl sulfoxide **3**[14] in MeOH at 50°C for 2 h (Scheme 2) except for *N,N*-diphenylamide (*R*)-**5h** (lithium *N,N*-diphenylamide, prepared from *N,N*-diphenylamine and *n*-butyllithium, was reacted with (*R*)-**3** in THF at room temperature). The results are listed in Table 1.



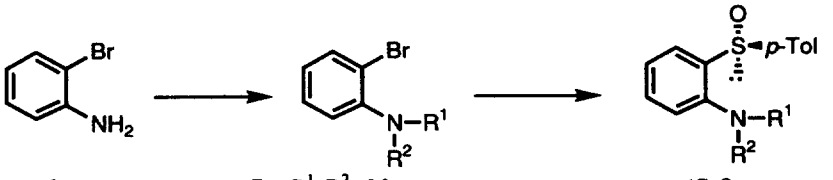
Scheme 2.

Other β-amino sulfoxides, *o*-aminophenyl sulfoxides (*S*)-**8a–d**, were prepared starting from commercially available 2-bromoaniline **6** as follows. (*S*)-2-(*N,N*-Dimethylamino)phenyl *p*-tolyl sulfoxide **8a** was obtained by reductive *N*-methylation of **6** with formaline and $NaBH_3CN$[15] followed by the sulfinylation of the carbanion (generated by treating *N,N*-dimethyl-2-bromoaniline **7a** with butyllithium) with (−)-menthyl (*S*)-*p*-toluenesulfinate (Scheme 3). Similarly, *o*-(cyclic amino)phenyl sulfoxides (*S*)-**8b,c** were synthesized via intramolecular *N,N*-dialkylation of **6** with 1,4-dibromobutane or 1,5-dibromopentane followed by the same sulfinylation of **7b,c** as described above. 2-(Sulfonamido)phenyl sulfoxides (*S*)-**8d–g** were prepared in similar sequences by *N*-sulfonylation of **6** followed by *N*-methylation and then subsequent sulfinylation of **7d–g** with (−)-menthyl (*S*)-*p*-toluenesulfinate.

Table 1
Synthesis of chiral β-amino sulfoxides (*R*)-**5a–h** by Michael additions of **4a–h** to chiral vinyl sulfoxide (*R*)-**3**[a)]

4	R, R N	Product	Yield(%) of (*R*)-5	$[\alpha]_D(CHCl_3)$ of (*R*)-5 (c,°C)
4a		5a	100	+140.3(11.4, 26)
4b		5b	90	+140.6(8.6, 28)
4c		5c	93	+140.5(1.9, 24)
4d		5d	93	+121.7(7.1, 27)
4e	Et, Et N	5e	97	+173.0(5.7, 28)
4f	c-Hex, Me N	5f	93	+149.0(3.5, 26)
4g	n-Bu, Me N	5g	93	+160.9(2.7, 26)
4h	Ph, Ph N	5h	39[b)]	+59.2(6.8, 29)

a) Chiral ligands (*R*)-**5a-g** were prepared by the reaction of secondary amines **4a-g** with vinyl sulfoxide (*R*)-**3** in MeOH at 50°C for 2 h.
b) Lithium *N*,*N*-diphenylamide, prepared from *N*,*N*-diphenylamine (**4h**) (1.2 equiv.) and *n*-butyllithium (1.2 equiv.), was reacted with (*R*)-**3** in THF at room temperature.

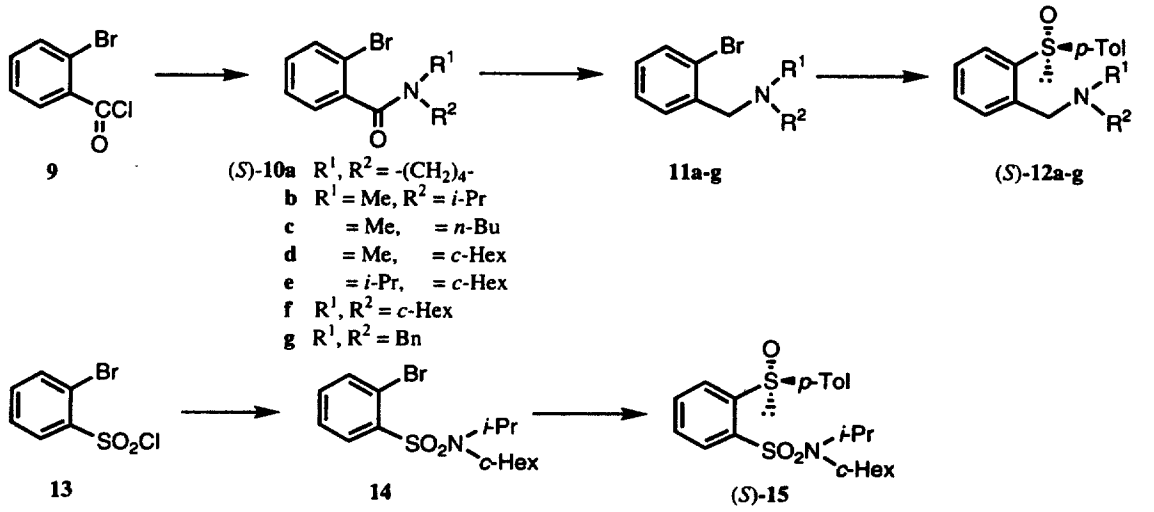


6 **7a** R^1, R^2= Me (*S*)-**8a-g**
b = -$(CH_2)_4$-
c = -$(CH_2)_5$-
d R^1= Me, R^2= $SO_2C_6H_5$
e = Me, = $SO_2C_6H_4$-CH_3-*p*
f = Me, = $SO_2C_6H_4$-OMe-*p*
g = Me, = $SO_2(\alpha)$-$C_{10}H_7$

Scheme 3.

Chiral 2-(aminomethyl)phenyl sulfoxides (*S*)-**12a–g** were prepared by amidation of readily available 2-bromobenzoyl chloride **9** with secondary amines followed by reduction of the amides **10a–g** with BH_3·THF and sulfinylation of the amines **11a–g** produced with (−)-menthyl (*S*)-*p*-toluenesulfinate in the same way as mentioned earlier (Scheme 4).

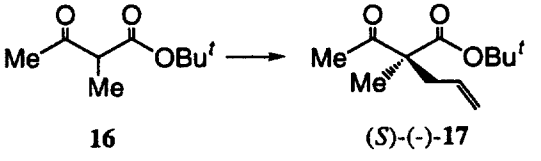
Chiral 2-(*p*-toluenesulfinyl)benzenesulfonamide (*S*)-**15** was obtained by amidation of readily available 2-bromobenzenesulfonyl chloride **13** followed by sulfinylation of sulfonamide **14** with (−)-menthyl (*S*)-*p*-toluenesulfinate.



Scheme 4.

2.2. *Palladium-catalyzed asymmetric allylations with chiral sulfoxide ligands*

Initially, palladium-catalyzed asymmetric allylations[16] of *t*-butyl 2-methylacetoacetate **16** were studied using chiral α-sulfinylacetamides (*R*)-**2a–c** as chiral ligands. The reactions of the carbanion of **16** [generated by treatment with NaH (1.0 equiv.)] with allyl acetate (1.5 equiv.) were carried out in the presence of $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.) and (*R*)-**2a–c** (0.12 equiv.) to give *t*-butyl (*S*)-2-allyl-2-methylacetoacetate **17** (Scheme 5) with considerably low enantiomeric excess (e.e.). The e.e. of the product **17** was determined on the basis of the optical rotation of **17** obtained (the optical rotation of homochiral (*S*)-(−)-**17**: $[\alpha]_D$ −22.7 ($CHCl_3$).[17] A linear relationship between the e.e. of the product **17** and its rotation was confirmed by ^{1}H-NMR analysis of the allylation product with a chiral shift reagent [europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] ($Eu(tfc)_3$)] The results are summarized in Table 2. The highest enantioselectivity (50%) was obtained with (*R*)-**2c** in 1,2-dimethoxyethane (DME).



Scheme 5.

The low enantioselectivity observed with the above acetamide ligands would arise presumably from the rather poor coordinating ability of the amide nitrogen atom to the palladium catalyst. Therefore, it seems difficult to form chelates of (*R*)-**2a–c** with palladium. Thus, we chose chiral β-aminoethyl sulfoxides as chiral ligands, which would be expected to be more efficient for the formation of chelates owing to the increased coordination ability of the β-amino groups to palladium.

Palladium-catalyzed asymmetric allylations[18] of **16** were studied using chiral β-aminoethyl sulfoxides (*R*)-**5a–h** obtained above as chiral ligands. Studies on asymmetric allylations of the sodium enolate of **16** [generated by treatment with NaH (1.0 equiv.)] with allyl acetate (1.5 equiv.) were carried out using $[PdCl(\pi\text{-allyl})]_2$, $Pd(OAc)_2$, $Pd(dba)_2$, or $Pd_2(dba)_3 \cdot CHCl_3$ (0.03 or 0.06 equiv.) as a catalyst and (*R*)-**5a** (0.12 equiv.) as a chiral ligand in DME, tetrahydrofuran (THF), ether (Et_2O), or toluene, giving optically active allylated compound **17**[19] with a rather unexpectedly low e.e. The results are summarized in Table 3.

Table 2
Palladium-catalyzed asymmetric allylation of **16** with chiral α-sulfinylacetamide ligands (*R*)-**2a–c**[a]

Ligands	Solvent	Reaction time (h)	Yield of **17** (%)	$[\alpha]_D$ ($CHCl_3$) of **17** (c, °C)	e.e. (%) of (*S*)-**17**[b]
2a	DME	12	46	-2.7 (4.2, 24)	31
	Dioxane–THF (1:10)	12	25	-1.8 (2.3, 25)	8
2b	THF	18	64	-1.8 (5.0, 29)	8
	DME	12	18	-11.3 (2.2, 26)	50
2c	THF	20	50	-2.8 (1.1, 29)	12
	DME	12	36	-2.1 (3.8, 24)	9
	Dioxane–THF (1:10)	12	22	-5.0 (2.0, 25)	22

a) The reactions of the carbanion of **16** (generated by treating **16** with NaH (1.0 equiv.)) with allyl acetate (1.5 equiv.) were carried out at room temperature in the presence of [$PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.) and (*R*)-**2a-c** (0.12 equiv.).

b) The enantiomeric excess (e.e.) of **17** was determined on the basis of optical rotation of **17** obtained (the optical rotation of optically pure (*S*)-(-)-**17**: $[\alpha]_D$ -22.7 ($CHCl_3$))[17], which was confirmed by ^{1}H-NMR analysis with a chiral shift reagent ($Eu(tfc)_3$).

Table 3
Studies on palladium-catalyzed asymmetric allylation of **16** with a chiral β-aminoethyl sulfoxide ligand (*R*)-**5a**[a]

Catalyst	Solvent	Reaction time (h)	Yield of **17** (%)	$[\alpha]_D$ ($CHCl_3$) of **17** (c, °C)	e.e. (%) of **17**[b] (Abs. confign.)
$[PdCl(\pi\text{-allyl})]_2$	DME	20	24	-6.5 (1.0, 26)	29 (*S*)
$Pd(OAc)_2$	DME	21	17	-1.3 (1.5, 29)	6 (*S*)
$Pd(dba)_2$	DME	21	9	-3.8 (0.5, 30)	17 (*S*)
$Pd_2(dba)_3 \cdot CHCl_3$	DME	12	28	-5.4 (1.8, 28)	24 (*S*)
$[PdCl(\pi\text{-allyl})]_2$	THF	18	47	+2.5 (3.2, 27)	11 (*R*)
$[PdCl(\pi\text{-allyl})]_2$	Et_2O	20	17	-6.5 (1.1, 29)	29 (*S*)
$[PdCl(\pi\text{-allyl})]_2$	Toluene	18	15	-0.7 (1.4, 29)	3 (*S*)

a) The reactions of the carbanion of **16** (generated by treating **16** with NaH (1.0 equiv.)) with allyl acetate (1.5 equiv.) were carried out in the presence of $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.), $Pd(OAc)_2$, $Pd(dba)_2$, or $Pd_2(dba)_3 \cdot CHCl_3$ (0.06 equiv.), and (*R*)-**5a** (0.12 equiv.).

b) The enantiomeric excess (e.e.) of **17** was determined on the basis of optical rotation of **17** obtained (the optical rotation of optically pure (*S*)-(-)-**17**: $[\alpha]_D$ -22.7 ($CHCl_3$)[17], which was confirmed by ^{1}H-NMR analysis with a chiral shift reagent ($Eu(tfc)_3$).

The use of $[PdCl(\pi\text{-allyl})]_2$ in DME or Et_2O gave (*S*)-(−)-**17** with slightly higher e.e., however the allylation in THF provided (*R*)-(+)-**17**.

Use of other chiral sulfoxides (*R*)-**5b–h** as chiral ligands was carried out in the same system under similar reaction conditions with $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.) in THF or DME at 0, −20°C, or room temperature. The results obtained are summarized in Table 4. Among the chiral sulfoxide ligands examined, a slightly higher (*S*)-selectivity of the product **17** was observed with (*R*)-**5f,g**. It should be noted that the marked solvent effects on the stereochemistry of the reaction product were observed in this

Table 4
Palladium-catalyzed asymmetric allylation of **16** with chiral β-aminoethyl and *o*-aminophenyl sulfoxide ligands (*R*)-**5b–h** and **8a,b**[a]

Ligands	Solvent	Reaction temp. (°C)	Reaction time (h)	Yield of **17** (%)	$[\alpha]_D(CHCl_3)$ of **17** (c, °C)	e.e. of **17** (%)[b] (Abs. confign.)
5b	THF	0	36	33	- 1.5 (3.4, 27)	7 (*S*)
	DME	-20	20	20	- 2.7 (1.1, 26)	12 (*S*)
5c	THF	r.t.	24	11	+6.5 (1.2, 25)	29 (*R*)
	DME	r.t.	20	18	- 0.5 (2.0, 28)	2 (*S*)
5d	THF	0	36	38	- 3.3 (3.0, 27)	15 (*S*)
	DME	-20	20	28	- 2.0 (2.5, 26)	9 (*S*)
5e	DME	0	20	29	- 1.9 (1.2, 23)	5 (*S*)
5f	DME	0	20	19	- 7.6 (1.2, 30)	33 (*S*)
5g	DME	0	20	25	- 6.1 (2.6, 26)	27 (*S*)
5h	THF	0	28	18	- 0.5 (2.2, 27)	2 (*S*)
8a	THF	-20	20	33	-8.9 (1.6, 27)	39 (*S*)
	Et_2O	-20	20	25	-5.3 (1.9, 29)	23 (*S*)
	DME	-20	18	39	-10.8 (2.6, 26)	48 (*S*)
8b	THF	-20	40	25	-11.5 (1.4, 29)	50 (*S*)

a) The reactions of the carbanion of **16** (generated by treating **16** with NaH (1.0 equiv.)) with allyl acetate (1.5 equiv.) were carried out in the presence of $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.) and (*R*)-**5b-h** or **8a,b** (0.12 equiv.).

b) The enantiomeric excess (e.e.) of **17** was determined on the basis of optical rotation of **17** obtained (the optical rotation of optically pure (*S*)-(-)-**17**: $[\alpha]_D$ -22.7 ($CHCl_3$))[17], which was confirmed by ^{1}H-NMR analysis with a chiral shift reagent ($Eu(tfc)_3$).

asymmetric allylation: the allylation of **16** with (*R*)-**5b–h** in DME gave (*S*)-(−)-**17**, whereas the reaction with (*R*)-**5c** in THF afforded (*R*)-(+)-**17**.

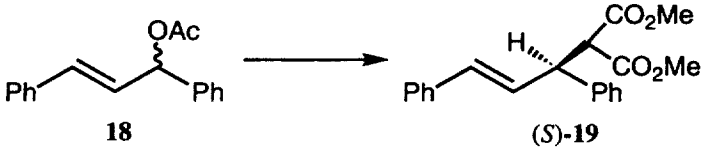
In order to improve the enantioselectivity further, stereochemical fixation of the conformation of the ligands was employed by means of introducing phenyl rings into the chiral ligand systems for the facile formation of intermediary cyclic palladium complexes mentioned later. Thus, use of chiral *o*-aminophenyl (*S*)-**8a–g**, *o*-(aminomethyl)phenyl (*S*)-**12a–g**, and *o*-(aminosulfonyl)phenyl *p*-tolyl sulfoxides (*S*)-**15** as ligands was studied in the palladium-catalyzed reactions. The allylations of sodium enolate of **16** with allyl acetate (1.5 equiv.) were carried out at −20°C in THF, Et_2O, or DME in the presence of $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.) and (*S*)-**8a,b** (0.12 equiv.) to produce (*S*)-(−)-**17**. The results obtained are summarized in Table 4. In contrast with the results with (*R*)-**5a–h**, as we expected, the rather high enantioselectivity of the product (*S*)-**17** was obtained in all cases examined with (*S*)-**8a,b**. With these ligands, solvent effects on the enantioselectivity were observed, which is quite different from the results with β-aminoethyl sulfoxides (*R*)-**5a–h**, with no change of the absolute configuration of the product **17** even in THF with (*S*)-**8b**, as shown in Table 4.

Studies on palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate **18** with dimethyl malonate sodium enolate were carried out at 50°C in the presence of $[PdCl(\pi\text{-allyl})]_2$, $Pd(dba)_2$, or $Pd(OAc)_2$ (0.06 equiv.), and chiral *o*-aminophenyl sulfoxides (*S*)-**8a–c** or chiral 2-(sulfonamido)phenyl sulfoxides (*S*)-**8d–g**. The results are summarized in Table 5. The alkylation of **18** with dimethyl malonate using chiral ligands (*S*)-**8a–c** produced (*S*)-**19** with extremely low e.e. (13–19%), whereas the reactions with sulfonamide ligands (*S*)-**8d–g** gave (*S*)-**19** with an increasing e.e. (22–38%). The e.e. of the product **19** was calculated by HPLC analysis with Chiralpak AD.[19] When the sulfonamide ligands (*S*)-**8d–g** were replaced by another sulfonamide (*S*)-**15**, the alkylation of **18** with sodium malonate afforded (*S*)-**19** with 25 and 28% e.e (Scheme 6). It seems quite understandable that despite the rather crucial difference in the stereochemical situation around the sulfonamide groups in the ligands, the degree of the asymmetric induction observed was quite similar to that with (*S*)-**8d–g**.

Table 5
Palladium-catalyzed asymmetric allylic alkylation of **18** with dimethyl malonate using chiral sulfoxide ligands (*S*)-**8a–g** or (*S*)-**15**[a)]

Ligands	Catalyst	Ratio of Pd/Ligand	Reaction Time (h)	Yield of **19** (%)	e.e. (%) of (*S*)-**19**[b)]
(*S*)-**8a**	[PdCl(π-allyl)]2	1:4	45	38	17[c)]
	[PdCl(π-allyl)]2	1:8	20	42	19
(*S*)-**8b**	[PdCl(π-allyl)]2	1:2	20	32	14
	[PdCl(π-allyl)]2	1:4	20	26	14
	[PdCl(π-allyl)]2	1:8	20	41	13
(*S*)-**8c**	[PdCl(π-allyl)]2	1:8	48	26	3
(*S*)-**8d**	[PdCl(π-allyl)]2	1:2	42	24	34
	Pd(OAc)2	1:2	26	15	38
	Pd(dba)2	1:2	26	19	38
(*S*)-**8e**	[PdCl(π-allyl)]2	1:4	20	50	24[d)]
	[PdCl(π-allyl)]2	1:4	20	51	32
	[PdCl(π-allyl)]2	1:8	48	35	14
(*S*)-**8f**	[PdCl(π-allyl)]2	1:2	20	13	22
(*S*)-**8g**	[PdCl(π-allyl)]2	1:2	36	26	24
	Pd(dba)2	1:2	36	34	41
(*S*)-**15**	[PdCl(π-allyl)]2	1:2	20	11	25
	Pd(OAc)2	1:2	20	17	28

a) The reactions of **18** with carbanion of dimethyl malonate (generated by treating with NaH (1.2 equiv.)) were carried out at 50 °C in the presence of palladium catalyst (0.06 equiv.) and chiral ligands (*S*)-**8a–g**.
b) The enantiomeric excess (e.e.) of (*S*)-**19** was calculated by HPLC analysis with chiralpak AD.[19]
c) The reaction was carried out in THF in the presence of BSA (3 equiv.) and a catalytic amount of KOAc.
d) The reaction was carried out in the presence of DME.



18 (*S*)-**19**

Scheme 6.

The use of chiral ligands (*S*)-**12a–g** bearing one-carbon longer chain substituents between the amino and the phenyl groups in the alkylation of **18** with dimethyl malonate in THF at room temperature provided (*S*)-**19** with rather low e.e. The highest enantioselectivity (58%) of (*S*)-**19** was obtained with (*S*)-**12c**, as shown in Table 6. It indicates that six-membered π-allylpalladium intermediates derived from (*S*)-**12a–g** might presumably be sterically less effective in asymmetric induction than five-membered intermediates obtained from (*S*)-**8a–g**, as mentioned later, although the coordination ability of the nitrogen groups in (*S*)-**12a–g** to the palladium catalysts would be stronger than that of the nitrogen in (*S*)-**8a–g**.

2.3. *The mechanism of the asymmetric reaction*

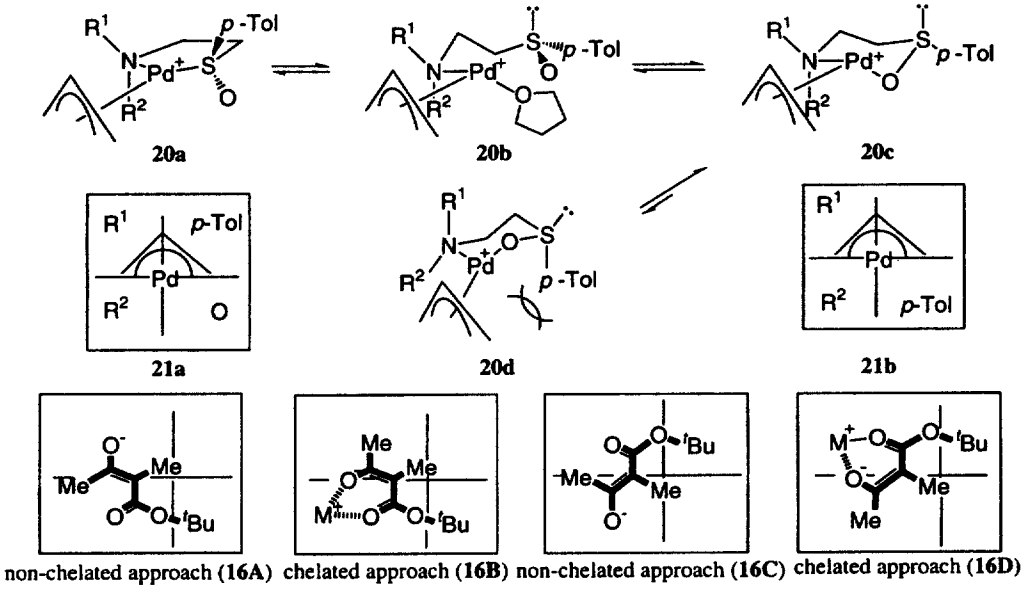
The mechanism for this asymmetric induction with these chiral sulfoxide ligands is rationalized on the basis of the stereochemical outcome obtained. A five-membered palladacyclic π-allylpalladium complex **20a** (Scheme 7) would be formed as an intermediary reactive allylating species by the participation of the sulfinyl sulfur lone pair[9] and the nitrogen atom of the chiral β-aminoethyl sulfoxides (*R*)-**5a–h** used, resulting in the creation of a new chiral environment designated in **21a**. The sodium enolate of acetoacetate **16** would react with **20a** via the nucleophilic substitution of **16A** or **16B** with **21a** (from the

Table 6
Palladium-catalyzed asymmetric allylic alkylation of **18** with dimethyl malonate using chiral sulfoxide ligands (*S*)-**12a–g**[a)]

Ligands	Reaction Time (h)	Yield(%) of **19**[b)]	e.e. (%)of (*S*)-**19**[c)]
12a	36	12 (43)	31
12b	24	14 (32)	16
12c	24	36 (64)	58
12d	48	18 (43)	17
12e	48	11 (30)	3
12f	48	15 (46)	3
12g	48	10 (64)	5

a) The reactions of **18** with carbanion of dimethyl malonate (generated by treating with NaH (1.2 equiv.)) were carried out in THF at room temperature in the presence of [PdCl(π-allyl)]$_2$ (0.06 equiv.) and chiral ligands (*S*)-**12a-g** (0.12 equiv.).
b) The corrected yields based on the recovered starting material are described in the parentheses.
c) The enantiomeric excess (e.e.) of (*S*)-**19** was calculated by HPLC analysis with chiralpak AD.[19)]

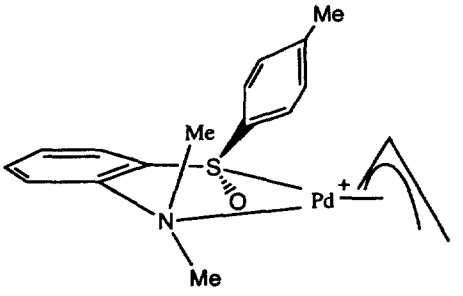
back side of the palladium catalyst) in sterically preferred fashion to give (*S*)-**17**. When THF was used as the solvent, different stereochemical results were obtained in some cases (*R*)-**5a,c**. In these cyclic amino ligands, the five-membered complexes would be transformed, via **20b** formed by the participation of the THF oxygen atom due to the steric strain induced by the five-five- or five-six-membered spiro structure, into sterically relieved six-membered intermediates **20c,d**. A six-membered π-allylpalladium complex **20c** would be preferred to **20d** because of the steric interference between the *p*-tolyl group and the allyl part in **20d**, providing the new chiral environment shown in **21b**. Thus, the reaction of sodium enolate **16** with allyl acetate in THF would proceed via the nucleophilic substitution of **16C** or **16D** with **21b** (from the back side of the palladium catalyst) in a sterically preferred manner, giving (*R*)-**17**.



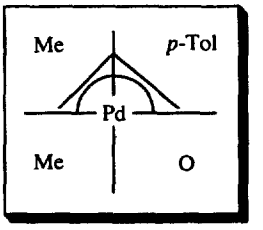
Scheme 7.

In the case of (*S*)-**8a–g**, rather higher enantioselectivity was obtained, presumably due to the sterically

fixed structure of the intermediary palladium complex **22**, which provides a chiral environment designated in **23** (Scheme 8). The reaction of the sodium enolate of **16** with this palladium complex **22** would proceed via the nucleophilic substitution of **16A** or **16B** with **23** from the back side of the palladium catalyst in sterically preferred fashion, to give (*S*)-**17**.



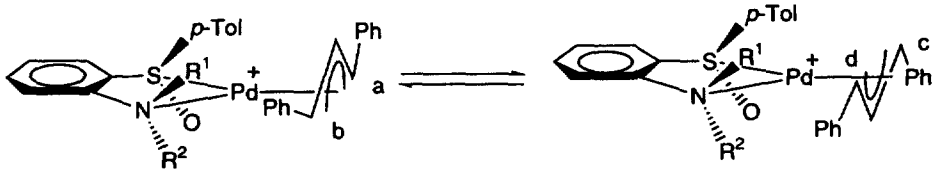
22



23

Scheme 8.

The mechanism of the asymmetric alkylations of **18** using chiral ligands (*S*)-**8a–g** or (*S*)-**12a–g** is rationalized as follows. The reactions would proceed via chiral π-allylpalladium complexes **24** (Scheme 9) involving five-membered chelates[9] derived from a palladium catalyst and (*S*)-**8a–g**. In the equilibrium of the allylic systems in the chelates, **24b** would be sterically preferred to **24a** because of the existence of the steric hindrance between the *p*-tolyl and the phenyl group in the allylic systems in **24a**. Therefore, the nucleophile (malonate sodium enolate) would attack at the allylic site (c) in **24b** from the back side of the palladium to produce (*S*)-**19**. However, the precise reason for the preference of the allyl terminus (c) in the attack of the nucleophile is not clear at the present time.



24a R^1, R^2 = Me; R^1, R^2 = $-(CH_2)_n-$ (n=4, or 5)
25a R^1 = Me, R^2 = SO_2Ar

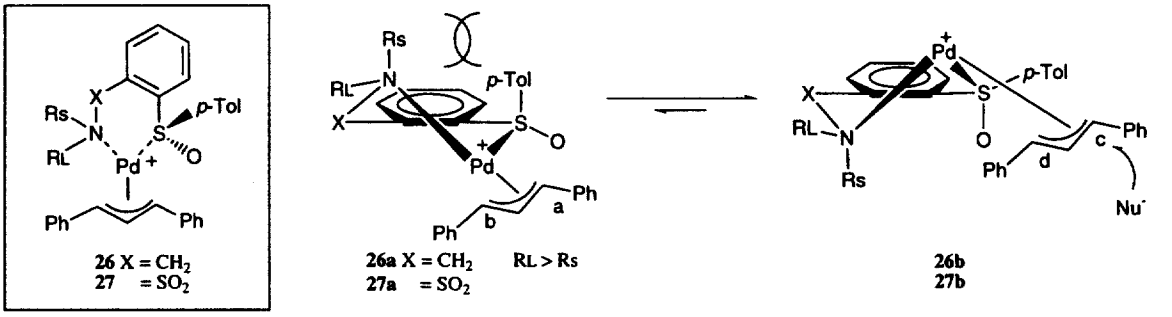
24b
25b

Scheme 9.

In the cases of sulfonamide ligands (*S*)-**8d–g** bearing bulky substituents, **25a** would be preferentially formed due to the steric repulsion between the sulfonamide substituents (R^2) and the phenyl groups at the allyl terminus in **25b**. The reaction of malonate sodium enolate would occur at the allylic site (b) in **25a** *trans* to the better π-acceptor,[20] which is the sulfinyl sulfur atom in the current case, from the back side of the palladium, affording (*S*)-**19**. This explanation would also be supported by the fact that the increasing steric bulk of the R^2 group in **25** (e.g. (*S*)-**8g**) provided the higher enantioselectivity of (*S*)-**19**.

Likewise when using (*S*)-**12a–g** as chiral ligands, π-allylpalladium complexes **26** (Scheme 10) involving six-membered chelates[9] would be formed. In the equilibrium of these six-membered palladium complexes **26a,b**, **26b** would be preferred to **26a** due to the steric interference between the *p*-tolyl and the substituents (Rs) on the amino groups. The nucleophile (sodium malonate) would react at the allyl terminus (c) affording (*S*)-**19**. In the case of the sulfonamide ligand (*S*)-**15**, presumably, the π-allylpalladium complex **27** involving a similar six-membered chelate with the sulfinyl sulfur and the sulfonamide nitrogen atom[21] would be created, instead of formation of the palladium complex chelating with the sulfinyl sulfur atom and the sulfonyl oxygen atom (if the reaction proceeds via the chelates, the

predicted stereochemistry of the product is in conflict with that observed). Similarly, the stereoisomer **27b** would be preferred to **27a** in the equilibrium of the palladium complex **27a,b** because of similar steric reasons to those mentioned above. The preferential attack of the nucleophile at the allyl terminus (c) would result in the formation of (*S*)-**19**.



Scheme 10.

The precise reason for the preference of the allyl terminus (c) in the attack of the nucleophile is not so clear at the present time, however, presumably it will be due to the steric interference of the large substituents at the nitrogen group in the reaction of the nucleophile at the allyl terminus (d).

Thus, the new chiral sulfoxides described herein were demonstrated to serve as chiral ligands in the palladium-catalyzed reactions of **16** and **18**, giving optically active products **17** and **19** with moderate enantioselectivity.

3. Experimental

Infrared (IR) spectra were obtained in the indicated state with a JASCO DR-81 Fourier transform IR spectrometer. NMR spectra were determined in the indicated solvent with JEOL JNM-LA 400 (^{1}H-NMR; 400 MHz, ^{13}C-NMR; 100 MHz) and JEOL EX-270 (^{1}H-NMR; 270 MHz, ^{13}C-NMR; 67.8 MHz) high-resolution NMR spectrometers; chemical shifts are given in ppm from tetramethylsilane as an internal standard. Splitting patterns are designated as s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; quint, quintet; m, multiplet. Mass spectra were taken on a JEOL JMS-DX 303/JMA-DA 5000 system. High performance liquid chromatography (HPLC) was performed with a Tosoh UV-8010 CCPM (column: Daicel Chiralpak AD, hexane:*i*-PrOH=20:1, 0.5 ml/min, 254 nm). Optical rotations were measured with a JASCO DIP-370 polarimeter. Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh). Thin layer or thick layer plates (preparative TLC) were made of Merck silica gel 60PF-254 activated by drying at 140°C for 3.5 h.

3.1. Synthesis of chiral 2-(p-toluenesulfinyl)acetamide derivatives

3.1.1. (R)-N,N-Diisopropyl-2-(p-toluenesulfinyl)acetamide **2a**

Methyl chloroformate (1.39 g, 13.8 mmol) was added to a solution of (*R*)-*p*-toluenesulfinylacetic acid **1** (911 mg, 4.6 mmol) and triethylamine (1.39 g, 13.8 mmol) in THF (15 ml) at 0°C, and the reaction mixture was stirred at 0°C for 2 h. The reaction solution was diluted with ether and filtered. The filtrate was evaporated *in vacuo*. A solution of the crude product obtained in THF (2 ml) was added at 0°C to a solution of diisopropyl amine (768 mg, 7.6 mmol) and triethylamine (697 mg, 6.9 mmol) in THF (5 ml) and the reaction mixture was stirred at room temperature for 12 h. The reaction solution was then diluted

with ether, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was subjected to preparative TLC (chloroform:methanol=10:1) to give (*R*)-**2a** (277 mg, 21% yield).

The reactions of the methyl carbonate derived from (*R*)-**1** (4.6 mmol) with diphenylamine (1.28 g, 7.6 mmol), or dicyclohexylamine (1.38 g, 7.6 mmol) were carried out using the same procedure as described above to give (*R*)-*N*,*N*-diphenyl-, or *N*,*N*-dicyclohexyl-2-(*p*-toluenesulfinyl)acetamide **2b**,**c**, respectively.

2a: $[\alpha]_D$ +95 (c=0.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1634 (amide), 1595 (aromatic), 1042 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.06 (d, *J*=6.6 Hz, 3H, CH_3), 1.18 (d, *J*=6.8 Hz, 3H, CH_3), 1.33 (dd, *J*=10.4, 6.8 Hz, 6H, $(CH_3)_2$), 2.41 (s, 3H, $C_6H_4CH_3$), 3.44–3.52 (m, 2H, CH), 3.85 (quint, *J*=6.8 Hz, 1H, CH), 3.70 (d, *J*=13.7 Hz, 1H, CH), 4.03 (d, *J*=13.7 Hz, 1H, CH), 7.47 (AB system, *J*=8.0 Hz, 4H, $C_6H_4CH_3$). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 20.4, 20.9, 21.1, 21.4, 46.4, 49.7, 64.1, 124.6, 129.8, 163.1. *m/z*: 281 (M^+). Exact mass determination: 281.1450 (calcd $C_{15}H_{23}NO_2S$: 281.1405).

2b: 42% yield. $[\alpha]_D$ +45 (c=4.1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1633 (amide), 1600 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 0.98–1.46 (m, 12H, $(CH_2)_3\times2$), 1.52–1.77 (m, 8H, $(CH_2)_2\times2$), 2.20–2.30 (m, 2H, CH×2), 2.41 (s, 3H, $C_6H_4CH_3$), 3.73 (d, *J*=13.7 Hz, 1H, CH), 4.05 (d, *J*=13.7 Hz, 1H, CH), 7.29–7.33 (m, 2H, ArH), 7.62–7.65 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 20.4, 23.1, 23.7, 24.1, 24.2, 24.3, 24.5, 25.3, 25.5, 28.8, 29.8, 63.3, 123.6, 128.8, 163.1. *m/z*: 361 (M^+). Exact mass determination: 361.2105 (calcd $C_{21}H_{31}NO_2S$: 361.2076).

2c: 18% yield. $[\alpha]_D$ +92 (c=3.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1664 (amide), 1595 (aromatic), 1049 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 2.43 (s, 3H, $C_6H_4CH_3$), 3.68 (d, *J*=13.7 Hz, 1H, CH), 4.03 (d, *J*=13.7 Hz, 1H, CH), 7.05–7.34 (m, 10H, $(C_6H_5)_2$), 7.46 (AB system, *J*=8.2 Hz, 4H, C_6H_4). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.5, 63.1, 126.1, 126.7, 128.85, 128.9, 130.0, 164.2. *m/z*: 349 (M^+). Exact mass determination: 349.1114 (calcd $C_{21}H_{19}NO_2S$: 349.1158).

3.2. Synthesis of β-amino sulfoxide derivatives

3.2.1. (R)-2-(Pyrrolidino)ethyl p-tolyl sulfoxide 5a

A solution of (*R*)-*p*-tolyl vinyl sulfoxide **3** (220 mg, 1.3 mmol) in methanol (10 ml) was added at 0°C to a solution of pyrrolidine (188 mg, 2.6 mmol) in methanol (2 ml) and the reaction mixture was stirred at 50°C for 2 h. The reaction solution was concentrated *in vacuo*. The crude product was subjected to preparative TLC (chloroform:methanol=15:1) to give (*R*)-**5a** (162 mg, 99% yield).

Michael additions of other secondary amines **4b–g** to (*R*)-**3** were carried out using the same procedure as described above to give (*R*)-2-piperidino-, (*R*)-2-(hexamethyleneamino)-, (*R*)-2-morpholino-, (*R*)-2-(*N*,*N*-diethylamino)-, (*R*)-2-(*N*-methyl-*N*-cyclohexylamino)-, and (*R*)-2-(*N*-methyl-*N*-butylamino)ethyl *p*-tolyl sulfoxide **5b–g**, respectively.

(*R*)-**5a**: $[\alpha]_D$ +140 (c=11.4, acetone). IR ν_{max}^{film} cm^{-1}: 1600 (aromatic), 1040 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.73–1.84 (m, 4H, $(CH_2)_2$), 2.42 (s, 3H, CH_3), 2.50–2.58 (m, 4H, CH_2NCH_2), 2.61–3.04 (m, 4H, $(CH_2)_2$), 7.43 (AB system, *J*=7.9 Hz, 4H, C_6H_4). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.4, 23.5, 49.0, 54.0, 56.9, 124.2, 129.9. *m/z*: 237 (M^+). Exact mass determination: 237.1187 (calcd $C_{13}H_{19}ONS$: 237.1193).

(*R*)-**5b**: 90% yield. $[\alpha]_D$ +141 (c=8.6, acetone). IR ν_{max}^{film} cm^{-1}: 1597 (aromatic), 1043 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.40–1.59 (m, 6H, $(CH_2)_3$), 2.22–2.45 (m, 4H, CH_2NCH_2), 2.47–2.81 (m, 2H, NCH_2), 2.86–3.83 (m, 2H, CH_2S), 7.42 (AB system, *J*=7.9 Hz, 4H, C_6H_4). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 20.7, 23.6, 25.2, 51.0, 53.6, 54.4, 123.5, 129.2. *m/z*: 251 (M^+). Exact mass determination: 251.1323 (calcd $C_{14}H_{21}NOS$: 251.1344).

(*R*)-**5c**: 93% yield. $[\alpha]_D$ +141 (c=1.9, acetone). IR ν_{max}^{film} cm^{-1}: 1597 (aromatic), 1044 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.57–1.61 (m, 8H, $(CH_2)_4$), 2.41 (s, 3H, CH_3), 2.62–2.66 (m, 4H, CH_2NCH_2), 2.67–3.01 (m, 4H, $(CH_2)_2$), 7.42 (AB system, *J*=7.9 Hz, 4H, C_6H_4). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.2, 26.8, 50.6, 54.9, 56.0, 124.0, 129.7. *m/z*: 265 (M^+). Exact mass determination: 265.1534 (calcd $C_{15}H_{23}ONS$: 265.1500).

(*R*)-**5d**: 93% yield. $[\alpha]_D$ +122 (c=1.9, acetone). IR ν_{max}^{film} cm^{-1}: 1600 (aromatic), 1040 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.42–1.64 (m, 4H, CH_2NCH_2), 2.37–2.51 (m, 4H, CH_2OCH_2), 2.42 (s, 3H, CH_3), 2.53–2.92 (m, 2H, NCH_2), 3.00–3.04 (m, 2H, SCH_2), 7.32 (d, *J*=7.9 Hz, 2H, ArH), 7.54 (d, *J*=8.2 Hz, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.4, 24.0, 25.6, 51.6, 54.3, 54.6, 124.2, 130.0. *m/z*: 253 (M^+). Exact mass determination: 253.1061 (calcd $C_{13}H_{19}NO_2S$: 253.1037).

(*R*)-**5e**: 97% yield. $[\alpha]_D$ +173 (c=5.7, acetone). IR ν_{max}^{film} cm^{-1}: 1597 (aromatic), 1043 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.01 (t, *J*=7.0 Hz, 6H, CH_3×2), 2.41 (s, 3H, CH_3), 2.54 (q, *J*=6.9 Hz, 4H, CH_2×2), 2.65–2.93 (m, 4H, $(CH_2)_2$), 7.32 (d, *J*=7.9 Hz, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 11.5, 21.2, 27.6, 45.5, 46.7, 55.2, 123.9, 129.7. *m/z*: 239 (M^+). Exact mass determination: 239.1378 (calcd $C_{13}H_{21}NOS$: 239.1344).

(*R*)-**5f**: $[\alpha]_D$ +149 (c=3.5, acetone). IR ν_{max}^{film} cm^{-1}: 1558 (aromatic), 1046 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.04–1.79 (m, 10H, $(CH_2)_5$), 2.26 (s, 3H, NCH_3), 2.36–2.45 (m, 1H, CH), 2.40 (s, 3H, CH_3), 2.60–3.06 (m, 4H, $(CH_2)_2$), 7.31 (d, *J*=6.9 Hz, 2H, ArH), 7.54 (dd, *J*=8.2, 1.2 Hz, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.2, 25.7, 25.8, 26.1, 28.1, 28.7, 37.4, 46.6, 56.6, 62.8, 123.9, 129.7. *m/z*: 279 (M^+). Exact mass determination: 279.1692 (calcd $C_{16}H_{25}NOS$: 279.1657).

(*R*)-**5g**: 93% yield. $[\alpha]_D$ +161 (c=2.7, acetone). IR ν_{max}^{film} cm^{-1}: 1597 (aromatic), 1046 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 0.88–0.93 (m, 3H, CH_3), 1.26–1.46 (m, 4H, $(CH_2)_2$), 2.23 (s, 3H, NCH_3), 2.33–2.39 (m, 2H, NCH_2), 2.42 (s, 3H, CH_3), 2.54–2.95 (m, 4H, $(CH_2)_2$), 7.30 (d, *J*=7.9 Hz, 2H, ArH), 7.54 (dd, *J*=8.2, 2.0 Hz, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 14.0, 20.5, 21.4, 29.3, 42.0, 50.4, 55.6, 57.3, 124.2, 129.9. *m/z*: 253 (M^+). Exact mass determination: 253.1491 (calcd $C_{14}H_{23}NOS$: 253.1500).

3.2.2. (R)-2-(N,N-Diphenylamino)ethyl p-tolyl sulfoxide **5h**

A 1.5 M hexane solution of *n*-butyllithium (0.5 ml, 0.72 mmol) was added at 0°C to a solution of *N,N*-diphenylamine (122 mg, 0.72 mmol) in THF (2 ml). The mixture was stirred at 0°C for 30 min. Then, a solution of (*R*)-**3** (100 mg, 0.6 mmol) in THF (2 ml) was added to the above solution. The reaction mixture was stirred at room remperature for 20 h. The reaction solution was diluted with ether, 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=3:1) to give (*R*)-**5h** (135 mg, 39% yield).

(*R*)-**5h**: $[\alpha]_D$ +59.2 (c=6.8, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1040 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 2.41 (s, 3H, CH_3), 2.93–3.18 (m, 2H, NCH_2), 3.94–4.29 (m, 2H, SCH_2), 6.93–6.99 (m, 6H, ArH), 7.22–7.32 (m, 6H, ArH), 7.45–7.47 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.4, 45.2, 54.0, 121.2, 122.0, 123.9, 129.5, 130.0. *m/z*: 345 (M^+). Exact mass determination: 335.1340 (calcd $C_{21}H_{21}NOS$: 335.1389).

3.3. Synthesis of chiral 2-(amino- or 2-sulfonamido)phenyl sulfoxide derivatives

3.3.1. N-(2-Bromophenyl)pyrrolidine **7b**

A solution of 2-bromoaniline **6** (100 mg, 0.59 mmol) in toluene (2 ml) was added to a solution of 1,4-dibromopentane (153 mg, 0.71 mmol) and triethylamine (175 mg, 1.77 mmol) in toluene (1 ml) and the reaction mixture was stirred at reflux for 6 h. It was then diluted with ether, 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=1:5) to give **7b** (77 mg, 57% yield).

The reaction of **6** (100 mg, 0.59 mmol) with 1,5-dibromobutane (163 mg, 0.71 mmol) was carried out using the same procedure as described above to give *N*-(2-bromophenyl)piperidine **7c**.

7b: IR ν_{max}^{film} cm^{-1}: 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.91–1.96 (m, 4H, $(CH_2)_2$), 3.32–3.37 (m, 4H, $N(CH_2)_2$), 6.70–6.76 (m, 1H, ArH), 6.89–6.92 (m, 1H, ArH), 7.15–7.21 (m, 1H, ArH), 7.48–7.51 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 25.0, 51.2, 117.9, 121.2, 127.7, 134.5. *m/z*: 225 (M^+). Exact mass determination: 225.0194 (calcd $C_{10}H_{12}NBr$: 225.0153).

7c: 58% yield. IR ν_{max}^{film} cm^{-1}: 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.52–1.60 (m, 2H, CH_2), 1.70–1.78 (m, 4H, $(CH_2)_2$), 2.92–2.96 (m, 4H, $N(CH_2)_2$), 6.82–6.87 (m, 1H, ArH), 7.00–7.03 (m, 1H, ArH), 7.20–7.26 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 24.2, 26.2, 53.3, 120.9, 123.8, 128.1, 133.7. *m/z*: 239 (M^+). Exact mass determination: 239.0310 (calcd $C_{11}H_{14}NBr$: 239.0301).

3.3.2. N-*(2-Bromophenyl)benzenesulfonamide*

Benzenesulfonyl chloride (1.23 g, 6.98 mmol) was added to a solution of **6** (1.00 g, 5.81 mmol) and pyridine (1.17 g, 17.44 mmol) in dichloromethane (5 ml) at 0°C, and the reaction mixture was stirred at 0°C for 1 h. The reaction solution was diluted with ether, washed with saturated aqueous $NaHCO_3$ and 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 *N*-(2-bromophenyl)benzenesulfonamide (1.44 g, 79% yield).

The reactions of **6** (1.00 g, 5.81 mmol) with *p*-toluenesulfonyl chloride (1.33 g, 6.98 mmol), 4-methoxybenzenesulfonyl chloride (1.44 g, 6.98 mmol), or 1-naphthalenesulfonyl chloride (1.58 g, 6.98 mmol) were carried out using the same procedure as described above to give the corresponding sulfonamides.

IR ν_{max}^{film} cm^{-1}: 3220 (NH), 1590 (aromatic), 1465, 1160 (SO_2NH). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.59 (bs, 1H, NH), 6.94–7.00 (m, 2H, ArH), 7.25–7.31 (m, 2H, ArH), 7.38–7.45 (m, 4H, ArH), 7.51–7.69 (m, 2H, ArH), 7.73–7.78 (m, 4H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 122.9, 126.5, 127.3, 128.6, 129.0, 132.6, 133.3. *m/z*: 311 (M^+). Exact mass determination: 310.9631 (calcd $C_{12}H_{10}NO_2SBr$: 310.9616).

3.3.3. N-*(2-Bromophenyl)*-p-*toluenesulfonamide*

31% yield. IR ν_{max}^{film} cm^{-1}: 1597 (aromatic), 1381, 1169 (SO_2NH). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.58 (bs, 1H, NH), 2.47 (s, 3H, CH_3), 7.08–7.11 (m, 1H, ArH), 7.27–7.29 (m, 2H, ArH), 7.31–7.35 (m, 2H, ArH), 7.61–7.64 (m, 1H, ArH), 7.85–7.88 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.6, 127.8, 129.0, 129.1, 131.4, 133.7, 134.1. *m/z*: 325 (M^+). Exact mass determination: 324.9801 (calcd $C_{13}H_{12}NO_3SBr$: 324.9772).

3.3.4. N-*(2-Bromophenyl)-4-methoxybenzenesulfonamide*

82% yield. IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1370, 1160 (SO_2NH). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 3.80 (s, 3H, OCH_3), 6.84–6.89 (m, 3H, ArH), 6.92–6.98 (m, 1H, NH), 7.22–7.29 (m, 1H, ArH), 7.40 (dd, *J*=8.1, 1.5 Hz, 1H, ArH), 7.63–7.71 (m, 3H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 55.6, 114.2, 115.8, 122.7, 126.3, 128.5, 129.5, 130.3, 132.6, 134.8. *m/z*: 341 (M^+). Exact mass determination: 340.9709 (calcd $C_{13}H_{12}NO_3SBr$: 340.9721).

3.3.5. N-(2-Bromophenyl)-1-naphthalenesulfonamide

77% yield. IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1330, 1160 (SO_2NH). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.58 (bs, 1H, NH), 6.83–6.89 (m, 1H, ArH), 7.21–7.30 (m, 2H, ArH), 7.46–7.49 (m, 1H, ArH), 7.55–7.68 (m, 3H, ArH), 7.88–8.05 (m, 2H, ArH), 8.21–8.26 (m, 1H, ArH), 8.65–8.68 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 114.9, 121.4, 124.0, 124.4, 125.8, 127.0, 128.4, 129.1, 130.4, 132.6, 135.0. *m/z*: 361 (M^+). Exact mass determination: 360.9770 (calcd $C_{16}H_{12}NSBr$: 360.9772).

3.3.6. N-(2-Bromophenyl)-N-methylbenzenesulfonamide 7d

A 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing sodium hydride (50% oil dispersion; 133 mg, 2.78 mmol) was flushed with argon, and maintained under a positive pressure of argon. A solution of *N*-(2-bromophenyl)benzenesulfonamide (433 mg, 2.78 mmol) in THF (4 ml) was added to the above flask. The mixture was stirred at 0°C for 30 min. A solution of iodomethane (394 mg, 2.78 mmol) in THF (4 ml) was added the above solution, and the mixture was stirred at room temperature for 4 h. The reaction solution was diluted with ether, 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 **7d** (331 mg, 79% yield).

The *N*-methylation of other sulfonamide derivatives was carried out using the same procedure as described above to give *N*-(2-bromophenyl)-*N*-methyl-*p*-toluenesulfonamide **7e**, *N*-(2-bromophenyl)-*N*-methyl-4-methoxybenzenesulfonamide **7f**, or *N*-(2-bromophenyl)-*N*-methyl-1-naphthalenesulfonamide **7g**, respectively.

7d: IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1340, 1175 (SO_2). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 3.20 (s, 3H, CH_3), 7.11–7.27 (m, 3H, ArH), 7.51–7.63 (m, 4H, ArH), 7.78–7.82 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 38.3, 124.7, 126.9, 127.8, 128.2, 128.9, 129.8, 130.7, 132.8, 134.0, 139.0. *m/z*: 325 (M^+). Exact mass determination: 324.9791 (calcd $C_{13}H_{12}NO_2SBr$: 324.9772).

7e: 97% yield. IR ν_{max}^{film} cm^{-1}: 1593 (aromatic), 1165 (SO_2). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 2.44 (s, 3H, $C_6H_4CH_3$), 3.18 (s, 3H, NCH_3), 6.92–6.99 (m, 1H, ArH), 7.11–7.38 (m, 4H, ArH), 7.59–7.78 (m, 3H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.6, 38.3, 122.5, 126.3, 127.3, 128.7, 129.7, 130.5, 132.6, 134.0. *m/z*: 339 (M^+). Exact mass determination: 338.9958 (calcd $C_{14}H_{14}NO_2SBr$: 338.9929).

7f: 81% yield. IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1340, 1160 (SO_2). ^{1}H-NMR (400 MHz; $CDCl_3$) δ: 3.17 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 6.88 (dd, *J*=6.8, 2.2 Hz, 1H, ArH), 6.96–6.98 (m, 2H, ArH), 7.11–7.20 (m, 1H, ArH), 7.25–7.30 (m, 1H, ArH), 7.37–7.42 (m, 1H, ArH), 7.60–7.76 (m, 2H, ArH). ^{13}C-NMR (100 MHz; $CDCl_3$) δ: 38.3, 55.6, 114.1, 115.8, 122.6, 124.8, 126.3, 128.2, 129.5, 130.1, 132.6, 134.0. *m/z*: 357 (M^+). Exact mass determination: 356.9854 (calcd $C_{14}H_{14}NO_3SBr$: 356.9857).

7g: 78% yield. IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1345, 1180 (SO_2). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 3.25 (s, 3H, CH_3), 7.11–7.31 (m, 3H, ArH), 7.45–7.67 (m, 4H, ArH), 7.88–7.91 (m, 1H, ArH), 8.18 (dd, *J*=7.4, 1.3 Hz, 1H, ArH), 8.58 (dd, *J*=6.6, 1.6 Hz, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 38.7, 124.0, 125.9, 126.8, 127.8. 128.1, 128.6, 129.7, 130.7, 131.7, 133.9, 134.5. *m/z*: 375 (M^+). Exact mass determination: 374.9959 (calcd $C_{17}H_{14}NO_2SBr$: 374.9929).

3.3.7. (S)-2-(N,N-Dimethylamino)phenyl p-tolyl sulfoxide 8a

A 1.64 M pentane solution of *tert*-butyllithium (0.8 ml, 1.3 mmol) was added at −78°C to a solution of 2-bromo-*N*,*N*-dimethylaniline **7a**[15] (253 mg, 1.2 mmol) in THF (3 ml), and the reaction mixture was stirred at −78°C for 1 h. A solution of (−)-menthyl (*S*)-*p*-toluenesulfinate (395 mg, 1.3 mmol) in THF (3 ml) was added to the above solution, and the reaction mixture was stirred at 0°C for 6 h. The reaction solution was diluted with ether, and the solution was washed with saturated aqueous NH_4Cl and

saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether:hexane=3:1) to give (*S*)-**8a** (168 mg, 52% yield).

The sulfinylation of *N*-(2-bromophenyl)pyrrolidine **7b** and -piperidine **7c** was carried out using the same procedure as described above to give (*S*)-2-(pyrrolidino)phenyl or (*S*)-2-(piperidino)phenyl *p*-tolyl sulfoxide **8b,c**, respectively.

8a: $[\alpha]_D$ −96 (c=5.5, acetone). IR ν_{max}^{film} cm^{-1}: 1588 (aromatic), 1032 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 2.33 (s, 3H, CH_3), 2.61 (s, 6H, $(CH_3)_2$), 7.08–7.20 (m, 1H, ArH), 7.25–7.38 (m, 4H, ArH), 7.40–7.48 (m, 1H, ArH), 7.53–7.56 (m, 1H, ArH), 7.94–9.97 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.3, 44.9, 120.9, 124.7, 125.1, 125.5, 129.4, 131.5. *m/z*: 259 (M^+). Exact mass determination: 259.1069 (calcd $C_{15}H_{17}NOS$: 259.1031).

8b: 31% yield. $[\alpha]_D$ −101 (c=1.0, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1020 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.83–2.03 (m, 4H, $(CH_2)_2$), 2.33 (s, 3H, $C_6H_4CH_3$), 3.11–3.19 (m, 2H, NCH_2), 3.41–3.51 (m, 2H, NCH_2), 6.84 (dd, *J*=1.0, 8.2 Hz, 1H, ArH), 6.93–6.99 (m, 1H, ArH), 7.30 (AB system, *J*=8.2 Hz, 4H, C_6H_4), 7.26–7.40 (m, 1H, ArH), 7.85 (dd, *J*=7.9, 1.6 Hz, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.3, 25.5, 52.1, 116.7, 120.1, 125.3, 126.3, 129.6, 131.7. *m/z*: 285 (M^+). Exact mass determination: 285.1187 (calcd $C_{17}H_{19}NOS$: 285. 1232).

8c: 43% yield. $[\alpha]_D$ −110 (c=1.0, acetone). IR ν_{max}^{film} cm^{-1}: 1595 (aromatic), 1020 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.55–1.70 (m, 6H, $(CH_2)_3$), 2.33 (s, 3H, $C_6H_4CH_3$), 2.44–2.52 (m, 2H, NCH_2), 3.03–3.10 (m, 2H, NCH_2), 7.08 (dd, *J*=7.7, 1.3 Hz, 1H, ArH), 7.38 (AB system, *J*=8.0 Hz, 4H, C_6H_4), 7.27–7.41 (m, 2H, ArH), 7.97–8.00 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.4, 23.9, 26.0, 121.3, 124.6, 125.3, 125.9, 129.4, 131.5. *m/z*: 299 (M^+). Exact mass determination: 299.1344 (calcd $C_{18}H_{21}NOS$: 299.1328).

3.3.8. (S)-N-Methyl-N-[2-(p-toluenesulfinyl)phenyl]benzenesulfonamide 8d

A 1.14 N cyclopentane solution of *sec*-butyllithium (1.7 ml, 1.79 mmol) was added at −78°C to a solution of *N*-(2-bromophenyl)-*N*-methylbenzenesulfonamide **7d** (292 mg, 0.90 mmol) in THF (6 ml), and the reaction mixture was stirred at −78°C for 1 h. A solution of (−)-menthyl (*S*)-*p*-toluenesulfinate (527 mg, 1.79 mmol) in THF (7 ml) was added to the above solution, and the reaction mixture was stirred at room temperature for 6 h. The reaction solution was diluted with ether and the solution was washed with saturated aqueous NH_4Cl and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether:hexane=2:1) to give (*S*)-**8d** (98 mg, 28% yield).

The sulfinylations of *N*-(2-bromophenyl)-*N*-methyl-*p*-toluenesulfonamide **7e**, *N*-(2-bromophenyl)-*N*-methyl-4-methoxybenzenesulfonamide **7f**, or *N*-(2-bromophenyl)-*N*-methylnaphthalene-1-sulfonamide **7g**, *N*-cyclohexyl-*N*-isopropyl-2-bromobenzenesulfonamide **14** were carried out using the same procedure as described above to give (*S*)-*N*-methyl-*N*-[2-(*p*-toluenesulfinyl)phenyl]-*p*-toluenesulfonamide **8e**, (*S*)-*N*-methyl-*N*-[2-(*p*-toluenesulfinyl)phenyl]-4-methoxybenzenesulfonamide **8f**, or (*S*)-*N*-methyl-*N*-[2-(*p*-toluenesulfinyl)phenyl]-1-naphthalenesulfonamide **8g**, respectively.

(*S*)-**8d**: $[\alpha]_D$ −243 (c=2.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1170 (SO_2), 1050 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 2.31 (s, 3H, $C_6H_4CH_3$), 3.30 (s, 3H, NCH_3), 7.10–7.18 (m, 4H, ArH), 7.29–7.39 (m, 3H, ArH), 7.47–7.50 (m, 1H, ArH), 7.52–7.68 (m, 3H, ArH), 7.72–7.78 (m, 1H, ArH), 8.29 (dd, *J*=1.2, 7.9 Hz, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.3, 38.6, 125.4, 125.8, 127.3, 128.2, 129.3, 129.7, 130.0, 130.7. *m/z*: 385 (M^+). Exact mass determination: 385.0795 (calcd $C_{20}H_{19}NO_3S_2$: 385.0807).

(*S*)-**8e**: 35% yield. $[\alpha]_D$ −48 (c=13.1, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1160, 1340 (SO_2), 1020 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 2.31 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.27 (s, 3H, NCH_3),

7.11–7.18 (m, 4H, ArH), 7.26–7.39 (m, 4H, ArH), 7.50–7.60 (m, 3H, ArH), 8.02 (d, *J*=0.8 Hz, 1H, ArH). 6.78–7.74 (m, 12H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.3, 21.7, 38.5, 125.2, 125.8, 127.1, 127.9, 129.1, 129.6, 131.1, 131.3. *m/z*: 385 (M^+). Exact mass determination: 385.0807 (calcd $C_{20}H_{19}NO_3S_2$: 385.0837).

(*S*)-**8f**: 29% yield. $[\alpha]_D$ −128 (c=1.7, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1580 (aromatic), 1170 (SO_2), 1050 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 2.31 (s, 3H, $C_6H_4CH_3$), 3.25 (s, 3H, NCH_3), 3.91 (s, 3H, $C_6H_4OCH_3$), 6.93 (dd, *J*=2.6, 8.7 Hz, 1H, ArH), 7.10–7.23 (m, 5H, ArH), 7.29–7.39 (m, 2H, ArH), 7.51–7.70 (m, 3H, ArH), 7.77 (dd, *J*=2.6, 4.8 Hz, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.3, 38.4, 56.0, 109.7, 110.2, 116.6, 125.6, 127.2, 128.0, 129.3, 129.8, 131.4, 132.2. *m/z*: 436 (M+1). Exact mass determination: 435.0998 (calcd $C_{24}H_{21}NO_3S_2$: 435.0963).

(*S*)-**8g**: 25% yield. $[\alpha]_D$ −37 (c=2.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1580 (aromatic), 1160 (SO_2), 1045 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 2.31 (s, 3H, $C_6H_4CH_3$), 3.30 (s, 3H, NCH_3), 6.96–7.96 (m, 11H, ArH), 7.86–8.03 (m, 1H, ArH), 8.19–8.26 (m, 1H, ArH), 8.41–8.67 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.2, 38.3, 119.9, 124.6, 125.8, 126.0, 127.6, 127.9, 128.1, 128.3, 129.3, 129.7, 130.0, 130.5, 132.4, 134.2, 134.5, 134.9, 135.2. *m/z*: 415 (M^+). Exact mass determination: 415.0902 (calcd $C_{21}H_{21}NO_4S_2$: 415.0912).

3.4. Synthesis of chiral 2-(aminomethyl)phenyl sulfoxides derivatives

*3.4.1. Bromobenzoic acid pyrrolidine amide **10a***

A solution of 2-bromobenzoyl chloride **9** (1.29 g, 5.87 mmol) in dichloromethane (10 ml) was added at 0°C to a solution of pyrrolidine (500 mg, 7.04 mmol) and triethylamine (1.19 g, 4.56 mmol) in dichloromethane (10 ml), and the reaction mixture was stirred at room temperature for 2 h. It was then diluted with chloroform, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to flash column chromatography (ether:hexane=2:1) to give **10a** (1.49 g, 97% yield).

The reactions of **9** (1.00 g, 4.56 mmol) with *N*-methylisopropylamine (399 mg, 5.47 mmol), *N*-methyl-*n*-butylamine (476 mg, 5.47 mmol), *N*-methylcyclohexylamine (618 mg, 5.47 mmol), *N*-cyclohexylisopropylamine (771 mg, 5.47 mmol), *N,N*-dicyclohexylamine (990 mg, 5.47 mmol), or *N,N*-dibenzylamine (1.08 g, 5.47 mmol) were carried out using the same procedure as described above to give 2-bromo-*N*-methyl-*N*-isopropylbenzamide **10b**, 2-bromo-*N*-methyl-*n*-butylbenzamide **10c**, 2-bromo-*N*-methyl-*N*-cyclohexylbenzamide **10d**, 2-bromo-*N*-cyclohexyl-*N*-isopropylbenzamide **10e**, 2-bromo-*N,N*-dicyclohexylbenzamide **10f**, or 2-bromo-*N,N*-dibenzylbenzamide **10g**, respectively.

10a: IR ν_{max}^{film} cm^{-1}: 1630 (amide), 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.85–2.17 (m, 4H, $(CH_2)_2$), 3.16–3.21 (m, 2H, CH_2), 3.64–3.69 (m, 2H, CH_2), 7.20–7.38 (m, 3H, ArH), 7.55–7.58 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 24.6, 25.9, 45.5, 48.0, 118.8, 127.5, 127.7, 130.2, 132.8, 139.7, 167.4. *m/z*: 253 (M^+). Exact mass determination: 253.0096 (calcd $C_{11}H_{12}NOBr$: 253.0102).

10b: 99% yield. IR ν_{max}^{film} cm^{-1}: 1637 (amide), 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.08 (d, *J*=6.6 Hz, 3H, CH_3), 1.23 (d, *J*=6.8 Hz, 3H, CH_3), 2.98 (s, 3H, NCH_3), 3.68 (quint, *J*=6.6 Hz, 1H, CH), 7.19–7.27 (m, 2H, ArH), 7.32–7.38 (m, 1H, ArH), 7.54–7.60 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 20.4, 25.5, 29.3, 49.9, 119.0, 127.5, 127.8, 129.9, 132.9, 139.3, 168.4. *m/z*: 255 (M^+). Exact mass determination: 255.0247 (calcd $C_{11}H_{14}NOBr$: 255.0259).

10c: 99% yield. IR ν_{max}^{film} cm^{-1}: 1630 (amide), 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 0.98 (t, *J*=7.2 Hz, 3H, CH_3), 1.39–1.76 (m, 6H, $(CH_2)_3$), 3.10 (s, 3H, NCH_3), 7.19–7.27 (m, 2H, ArH), 7.32–7.38 (m, 1H, ArH), 7.54–7.59 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 25.6, 27.0,

30.9, 58.5, 118.9, 119.0, 126.9, 127.3, 127.4, 127.6, 129.7, 132.6, 139.0. *m/z*: 269 (M^+). Exact mass determination: 269.0384 (calcd $C_{12}H_{16}NOBr$: 269.0415).

10d: 99% yield. IR ν_{max}^{film} cm^{-1}: 1630 (amide), 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.43–1.94 (m, 10H, $(CH_2)_5$), 3.01 (s, 3H, NCH_3), 4.56–4.65 (m, 1H, CH), 7.18–7.27 (m, 2H, ArH), 7.31–7.38 (m, 1H, ArH), 7.53–7.60 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 25.5, 25.7, 27.0, 30.7, 30.9, 58.5, 119.0, 127.3, 127.4, 127.6, 129.7, 132.7, 139.2, 168.7. *m/z*: 295 (M^+). Exact mass determination: 295.0563 (calcd $C_{14}H_{18}NOBr$: 295.0551).

10e: 99% yield. IR ν_{max}^{film} cm^{-1}: 1640 (amide), 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.05 (d, *J*=6.6 Hz, 3H, CH_3), 1.22 (d, *J*=6.6 Hz, 3H, CH_3), 1.44–2.16 (m, 10H, $(CH_2)_5$), 2.97–3.14 (m, 1H, CH), 3.58 (quint, *J*=6.6 Hz, 1H, CH), 7.14–7.22 (m, 2H, ArH), 7.27–7.34 (m, 1H, ArH), 7.53–7.56 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 20.6, 20.8, 25.2, 25.6, 26.6, 29.9, 31.1, 51.2, 118.8, 126.5, 127.5, 129.4, 132.8, 168.3. *m/z*: 323 (M^+). Exact mass determination: 323.0889 (calcd $C_{16}H_{22}NOBr$: 323.0885).

10f: 86% yield. IR ν_{max}^{film} cm^{-1}: 1635 (amide), 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.18–2.04 (m, 20H, $(CH_2)_5$×2), 2.57–2.70 (m, 2H, CH×2), 2.57–2.70 (m, 2H, CH×2), 7.39–7.49 (m, 2H, ArH), 7.75–7.83 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 22.5, 26.6, 30.0, 33.1, 52.9, 122.9, 127.4, 130.0, 132.5, 166.9. *m/z*: 363 (M^+). Exact mass determination: 363.1242 (calcd $C_{19}H_{26}NOBr$: 363.1198).

10g: 86% yield. IR ν_{max}^{film} cm^{-1}: 1630 (amide), 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 4.12–4.18 (m, 2H, CH_2), 4.29–5.32 (m, 2H, CH_2), 7.10–7.15 (m, 2H, ArH), 7.20–7.39 (m, 11H, ArH), 7.56–7.58 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 46.6, 50.8, 119.5, 127.5, 127.6. 127.7, 127.8, 128.5, 128.8, 129.0, 130.3, 133.0, 135.8, 169.7. *m/z*: 379 (M^+). Exact mass determination: 379.0619 (calcd $C_{21}H_{18}NOBr$: 379.0572).

3.4.2. N-(2-Bromobenzyl)pyrrolidine ***11a***

A solution of **10a** (743 mg, 2.93 mmol) in THF (5 ml) was added at 0°C to a 1 M borane–THF complex solution (15 ml, 15.0 mmol), and the reaction mixture was stirred at reflux for 6 h. Then, after cooling, a solution of methanol (15 ml) and 10% potassium hydroxide (5 ml) was added. The reaction mixture was stirred at reflux for a further 1 h. The solution was concentrated *in vacuo*. It was then diluted with chloroform and washed with saturated aqueous NaCl. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ethyl acetate:hexane=1:4) to give **11a** (384 mg, 55% yield).

The reduction of *N*-2-bromobenzamide derivatives **10b–g** with a borane–THF complex solution was carried out using the same procedure as described above to give *N*-methyl-*N*-isopropyl- **11b**, *N*-butyl-*N*-methyl- **11c**, *N*-cyclohexyl-*N*-methyl- **11d**, *N*-cyclohexyl-*N*-isopropyl- **11e**, *N,N*-dicyclohexyl- **11f**, or *N,N*-dibenzyl-2-bromobenzylamine **11g**, respectively.

11a: IR ν_{max}^{film} cm^{-1}: 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.78–1.82 (m, 4H, $(CH_2)_2$), 2.57–2.62 (m, 4H, $(CH_2)_2$), 3.74 (s, 2H, CH_2), 7.05–7.11 (m, 1H, ArH), 7.24–7.27 (m, 1H, ArH), 7.46–7.68 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 23.7, 54.2, 59.5, 124.0, 127.1, 128.0, 130.4, 132.4. *m/z*: 239 (M^+). Exact mass determination: 239.0348 (calcd $C_{11}H_{14}NBr$: 239.0310).

11b: 78% yield. IR ν_{max}^{film} cm^{-1}: 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.09 (d, *J*=6.6 Hz, 6H, CH_3×2), 2.18 (s, 3H, NCH_3), 2.94 (quint, *J*=6.6 Hz, 1H, CH), 3.59 (s, 3H, NCH_3), 7.04–7.10 (m, 1H, ArH), 7.23–7.29 (m, 1H, ArH), 7.47–7.52 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 18.0, 36.7, 53.8, 57.1, 127.1, 128.0, 130.6, 132.5, 139.3. *m/z*: 241 (M^+). Exact mass determination: 241.0426 (calcd $C_{11}H_{16}NBr$: 241.0466).

11c: 90% yield. IR ν_{max}^{film} cm^{-1}: 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 0.88–0.93 (m, 3H,

CH_3), 1.21–1.39 (m, 2H, CH_2), 1.41–1.57 (m, 2H, CH_2), 2.22 (s, 3H, NCH_3), 2.40–2.46 (m, 2H, NCH_2), 3.56 (s, 2H, CH_2), 7.05–7.29 (m, 1H, ArH), 7.24–7.29 (m, 1H, ArH), 7.45–7.53 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 14.1, 20.6, 29.6, 42.3, 57.8, 61.5, 127.2, 128.2, 130.8, 132.6. *m/z*: 255 (M^+). Exact mass determination: 255.0601 (calcd $C_{12}H_{18}NBr$: 255.0623).

11d: 81% yield. IR ν_{max}^{film} cm^{-1}: 1595 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.05–1.39 (m, 6H, $(CH_2)_3$), 1.79–1.98 (m, 4H, $(CH_2)_2$), 2.23 (s, 3H, NCH_3), 2.42–2.51 (m, 1H, CH), 3.65 (s, 2H, CH_2), 7.04–7.10 (m, 1H, ArH), 7.23–7.29 (m, 1H, ArH), 7.47–7.52 (m, 2H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 26.1, 26.4, 28.8, 37.6, 57.5, 63.1, 127.1, 128.0, 130.6, 132.5. *m/z*: 281 (M^+). Exact mass determination: 281.0743 (calcd $C_{14}H_{20}NBr$: 281.0779).

11e: 81% yield. IR ν_{max}^{film} cm^{-1}: 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.02 (d, *J*=6.6 Hz, 6H, CH_3×2), 1.18–1.26 (m, 6H, $(CH_2)_3$, 1.43–1.81 (m, 4H, $(CH_2)_2$), 2.47–2.55 (m, 1H, CH), 3.08 (quint, *J*=6.6 Hz, 1H, CH), 3.72 (s, 2H, CH_2), 7.00–7.06 (m, 1H, ArH), 7.22–7.28 (m, 1H, ArH), 7.45 (dd, *J*=7.9, 1.2 Hz, 1H, ArH), 7.68–7.71 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.0, 26.3, 31.7, 48.7, 49.6, 58.3, 126.9, 127.4, 130.1, 132.0. *m/z*: 309 (M^+). Exact mass determination: 309.1058 (calcd $C_{16}H_{24}NBr$: 309.1092).

11f: 90% yield. IR ν_{max}^{film} cm^{-1}: 1590 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.02–1.77 (m, 20H, $(CH_2)_5$×2), 2.52–2.59 (m, 2H, CH×2), 3.77 (s, 2H, CH_2), 7.00–7.06 (m, 1H, ArH), 7.22–7.28 (m, 1H, ArH), 7.43–7.47 (m, 1H, ArH), 7.69–7.72 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 26.2, 26.4, 31.9, 50.3, 58.4, 126.9, 127.4, 130.1, 132.0. *m/z*: 349 (M^+). Exact mass determination: 349.1406 (calcd $C_{19}H_{28}NBr$: 349.1405).

11g: 78% yield. IR ν_{max}^{film} cm^{-1}: 1600 (aromatic). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 3.60 (s, 4H, CH_2×2), 3.68 (s, 2H, CH_2), 7.06–7.19 (m, 1H, ArH), 7.21–7.50 (m, 12H, ArH), 7.69–7.73 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 57.3, 58.2, 124.2, 126.7, 126.8, 128.1, 128.6, 128.1, 128.6, 130.3, 132.5. *m/z*: 365 (M^+). Exact mass determination: 365.0774 (calcd $C_{21}H_{20}NBr$: 365.0779).

3.4.3. (S)-2-(Pyrrolidinomethyl)phenyl p-*tolyl sulfoxide* ***12a***

A 1.04 M cyclopentane solution of *sec*-butyllithium (0.5 ml, 0.50 mmol) was added at −78°C to a solution of *N*-(2-bromobenzyl)pyrrolidine **11a** (100 mg, 0.42 mmol) in THF (3 ml), and the reaction mixture was stirred at −78°C for 1 h. A solution of (−)-menthyl (*S*)-*p*-toluenesulfinate (147 mg, 0.50 mmol) in THF (3 ml) was added to the above solution, and the mixture was stirred at 0°C for 6 h. The reaction solution was diluted with ether and the solution was washed with saturated aqueous NH_4Cl and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether:hexane=3:1) to give (*S*)-**12a** (87 mg, 70% yield).

The sulfinylations of *N*-isopropyl-*N*-methyl-2-bromobenzylamine **11b**, *N*-butyl-*N*-methyl-2-bromobenzylamine **11c**, *N*-cyclohexyl-*N*-methyl-2-bromobenzylamine **11d**, *N*-cyclohexyl-*N*-isopropyl-2-bromobenzylamine **11e**, *N*,*N*-dicyclohexyl-2-bromobenzylamine **11f**, *N*,*N*-dibenzyl-2-bromobenzylamine **11g** were carried out using the same procedure as described above to give (*S*)-2-(*N*-isopropyl-*N*-methyl-, (*S*)-2-(*N*-butyl-*N*-methyl-, (*S*)-2-(*N*-cyclohexyl-*N*-methyl-, (*S*)-2-(*N*-cyclohexyl-*N*-isopropyl-, (*S*)-2-(*N*,*N*-dicyclohexyl-, or (*S*)-2-(*N*,*N*-dibenzylaminomethyl)phenyl *p*-tolyl sulfoxide **12b–g**, respectively.

(*S*)-**12a**: $[\alpha]_D$ −109 (c=4.7, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1030 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.61–1.71 (m, 4H, $(CH_2)_2$), 2.28–2.49 (m, 4H, $N(CH_2)_2$), 2.35 (s, 3H, $C_6H_4CH_3$), 3.33 (d, *J*=13.2 Hz, 1H, NCH), 3.87 (d, *J*=13.2 Hz, 1H, NCH), 7.18–7.53 (m, 7H, ArH), 8.03–8.07 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.3, 23.4, 53.2, 57.5, 128.3, 128.9, 129.5, 130.4. *m/z*: 299 (M^+). Exact mass determination: 299.1344 (calcd $C_{18}H_{21}NOS$: 299.1351).

(*S*)-**12b**: 41% yield. $[\alpha]_D$ −124 (c=3.9, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1030 (S=O). ^{1}H-

NMR (270 MHz; $CDCl_3$) δ: 0.99 (d, *J*=2.5 Hz, 3H, CH_3), 1.01 (d, *J*=2.3 Hz, 3H, CH_3), 1.96 (s, 3H, NCH_3), 2.35 (s, 3H, $C_6H_4CH_3$), 2.88 (quint, *J*=7 Hz, 1H, $CH(CH_3)_2$), 3.37 (d, *J*=13.4, 1H, CH), 3.80 (d, *J*=13.4, 1H, CH), 7.37 (AB system, *J*=8.3 Hz, 4H, C_6H_4), 7.32–7.47 (m, 3H, ArH), 7.94–7.97 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 17.3, 21.3, 34.7, 52.9, 55.7, 125.7, 125.9, 129.5, 129.6, 130.4. *m/z*: 301 (M^+). Exact mass determination: 301.1501 (calcd $C_{18}H_{23}NOS$: 301.1477).

(*S*)-**12c**: 11% yield. $[\alpha]_D$ −109 (c=1.7, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1035 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 0.87 (m, 3H, $(CH_2)_3CH_3$), 1.18–1.53 (m, 4H, $CH_2(CH_2)_2CH_3$), 2.03 (s, 3H, NCH_3), 2.28–2.34 (m, 2H, $NCH_2(CH_2)_2)_2$, 2.35 (s, 3H, $C_6H_4CH_3$), 3.28 (d, *J*=13.4 Hz, 1H, CH), 3.75 (d, *J*=13.4 Hz, 1H, CH), 7.37 (AB system, *J*=8.1 Hz, 4H, C_6H_4), 7.31–7.51 (m, 3H, ArH), 7.97–8.00 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 14.0, 20.6, 21.3, 28.8, 41.1, 57.1, 59.4, 125.6, 126.0, 128.5, 129.6, 130.5. *m/z*: 425 (M^+). Exact mass determination: 425. 1788 (calcd $C_{28}H_{27}NOS$: 425.1813).

(*S*)-**12d**: 64% yield. $[\alpha]_D$ −121 (c=8.6, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1030 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.12–1.25 (m, 6H, $(CH_2)_3$), 1.75–1.78 (m, 4H, $CH(CH_2)_2$), 2.02 (s, 3H, NCH_3), 2.34 (s, 3H, $C_6H_4CH_3$), 2.39–2.43 (m, 3H, NCH_3), 3.44, (d, *J*=13.5 Hz, 1H, CH), 3.88 (d, *J*=13.5 Hz, 1H, CH), 7.37 (AB system, *J*=8.2 Hz, 4H, C_6H_4), 7.34–7.42 (m, 3H, ArH), 7.90–7.93 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.2, 25.9, 26.2, 28.1, 35.8, 55.7, 62.5, 125.6, 125.7, 128.3, 129.4, 129.5, 130.4. *m/z*: 341 (M^+). Exact mass determination: 341.1813 (calcd $C_{21}H_{27}NOS$: 341.1800).

(*S*)-**12e**: 93% yield. $[\alpha]_D$ −27 (c=10.3, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1035 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 0.93 (d, *J*=6.6 Hz, 3H, CH_3), 0.96 (d, *J*=6.4 Hz, 3H, CH_3), 1.00–1.26 (m, 6H, $(CH_2)_3$), 1.43–1.76 (m, 4H, $CH(CH_2)_2$), 2.36 (s, 3H, $C_6H_4CH_3$), 2.98 (quint, *J*=6.6 Hz, 1H, $CH(CH_3)$), 3.52 (d, *J*=16.0 Hz, 1H, CH), 3.58 (d, *J*=16.0 Hz, 1H, CH), 7.36 (AB system, *J*=8.2 Hz, 4H, C_6H_4), 7.40–7.43 (m, 2H, ArH), 7.71 (dd, *J*=5.4, 5.6 Hz, 1H, ArH), 7.95 (dd, *J*=5.7, 3.6 Hz, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 20.1, 21.3, 31.0, 32.0, 45.4, 48.2, 57.7, 124.2, 126.1, 127.4, 128.9, 129.8, 130.6. *m/z*: 369 (M^+). Exact mass determination: 369.2126 (calcd $C_{23}H_{31}NOS$: 369.2093).

(*S*)-**12f**: 57% yield. $[\alpha]_D$ −19 (c=2.4, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1025 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 0.94–1.25 (m, 12H, $(CH_2)_3\times2$), 1.52–1.75 (m, 8H, $NCH(CH_2)_2\times2$), 2.35 (s, 3H, $C_6H_4CH_3$), 2.38–2.59 (m, 2H, NCH×2), 3.56, (d, *J*=16.0 Hz, 1H, CH), 3.89 (d, *J*=16.0 Hz, 1H, CH), 7.36 (AB system, *J*=8.2 Hz, 4H, C_6H_4). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.3, 26.1, 26.2, 26.3, 31.3, 31.6, 46.0, 57.9, 124.2, 126.2, 127.3, 128.9, 129.8, 130.6. *m/z*: 409 (M^+). Exact mass determination: 409.2439 (calcd $C_{26}H_{35}NOS$: 409.2462).

(*S*)-**12g**: 54% yield. $[\alpha]_D$ −48 (c=5.2, acetone). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1030 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 2.34 (s, 3H, $C_6H_4CH_3$), 3.39–3.73 (m, 6H, $N(CH_2)_3$), 7.24 (AB system, 4H, *J*=8.4 Hz, C_6H_4), 7.20–7.34 (m, 12H, $C_6H_5\times2$), 7.67–7.70 (m, 1H, ArH), 7.96–7.99 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.4, 54.0, 57.9, 124.6, 126.1, 127.1, 128.3, 128.9, 129.7, 129.9, 130.9, 137.7, 138.6. *m/z*: 425 (M^+). Exact mass determination: 425.1788 (calcd $C_{28}H_{27}NOS$: 425.1813).

3.5. Synthesis of chiral 2-(p-toluenesulfinyl)benzenesulfonamide derivatives

3.5.1. N-*Cyclohexyl*-N-*isopropyl-2-bromobenzenesulfonamide* ***14***

A solution of 2-bromobenzenesulfonyl chloride **13** (500 mg, 1.96 mmol) in dichloromethane (5 ml) was added to a solution of *N*-isopropylcyclohexylamine (332 mg, 2.35 mmol) and pyridine (393 mg) in dichloromethane (5 ml) at 0°C, and the reaction mixture was stirred at room temperature for 6 h. The reaction solution was diluted with ether, and washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The ethereal layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether:hexane=1:1) to give **14** (334 mg, 48% yield).

14: IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1325, 1160 (SO_2N). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.05–1.23 (m, 2H, CH_2), 1.29 (d, *J*=6.9 Hz, 6H, CH_3×2), 1.51–1.84 (m, 8H, $(CH_2)_4$), 3.44–3.55 (m, 1H, CH), 3.91 (quint, *J*=6.9 Hz, 1H, CH), 7.27–7.48 (m, 2H, ArH), 7.70 (dd, *J*=7.7, 1.5 Hz, 1H, ArH), 8.14–8.17 (m, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 22.5, 25.3, 26.6, 32.9, 49.7, 58.2, 120.1, 127.4, 131.9, 133.0, 135.6. *m/z*: 359 (M^+). Exact mass determination: 359.0576 (calcd $C_{15}H_{22}NO_2SBr$: 359.0555).

3.5.2. (S)-N-Cyclohexyl-N-isopropyl-2-(p-toluenesulfinyl)benzenesulfonamide ***15***

The reaction was carried out using the same procedure as described in Section 3.3.8.

(*S*)-**15**: 60% yield. $[\alpha]_D$ −109 (c=4.3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1590 (aromatic), 1150 (SO_2), 1040 (S=O). ^{1}H-NMR (270 MHz; $CDCl_3$) δ: 1.15–1.85 (m, 10H, $(CH_2)_5$), 1.26 (dd, *J*=6.8 Hz, 6H, $CH(CH_3)_2$), 2.32 (s, 3H, $C_6H_4CH_3$), 3.26–3.36 (m, 1H, $NCH(C_5H_{10})$), 3.76 (quint, *J*=6.8 Hz, 1H, $CH(CH_3)_2$), 7.20 (d, *J*=7.9 Hz, 2H, ArH), 7.54–7.75 (m, 4H, ArH), 7.89 (d, *J*=1.3 Hz, 1H, ArH), 8.31 (d, *J*=1.3 Hz, 1H, ArH). ^{13}C-NMR (67.8 MHz; $CDCl_3$) δ: 21.3, 21.6, 22.6, 25.2, 26.5, 32.0, 32.9, 125.7, 125.8, 129.2, 129.7, 130.9, 133.2. *m/z*: 419 (M^+). Exact mass determination: 419.1584 (calcd $C_{22}H_{29}NO_3S_2$: 419.1589).

3.6. Palladium-catalyzed asymmetric allylations of 2-methylacetoacetate ***17*** *with chiral ligands*

3.6.1. General procedure A

A 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing sodium hydride (50% oil dispersion, 21 mg, 0.34 mmol), was flushed with argon, and maintained under a positive pressure of argon. A solution of *tert*-butyl 2-methylacetoacetate **17** (100 mg, 0.58 mmol) in THF (1 ml) was added at 0°C to the above flask. The mixture was stirred at 0°C for 30 min. Another 25 ml two-necked flask equipped with a septem inlet and a magnetic stirring bar, and containing di-μ-chlorobis(π-allyl)dipalladium ($[PdCl(CH_2{=}CHCH_2)]_2$) (6 mg, 0.02 mmol), was flushed with argon, and maintained under a positive pressure of argon. A solution of allyl acetate (88 mg, 0.87 mmol) and a chiral ligand (*R*)-**2a–c**, **5a–h**, or (*S*)-**8a,b** (0.07 mmol) in THF (2 ml) was added at room temperature to the above solution and the mixture was stirred at room temperature for 1 h. The solution was added to the above solution including sodium enolate of **17**, and the reaction mixture was stirred under the conditions listed in Tables 2–4. The reaction solution was diluted with ether, and the solution was washed with saturated aqueous NH_4Cl and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ether:hexane=1:2) to give optically active *tert*-butyl 2-allyl-2-methylacetoacetate **18**.[17] The results obtained are listed in Tables 2–4.

3.6.2. General procedure B

A solution of a chiral ligand (*S*)-**8a–g**, **12a–g**, or **15** (0.038 mmol) and $[PdCl(\pi\text{-allyl})]_2$ (7 mg, 0.019 mmol) in THF (1 ml) was stirred under argon for 1 h, then a solution of racemic (*E*)-1,3-diphenyl-2-propenyl acetate **18** (80 mg, 0.32 mmol) in THF (1 ml) was added. To the mixture was added dropwise a solution of sodium dimethyl malonate in THF (3 ml), generated by treating dimethyl malonate (51 mg, 0.39 mmol) with NaH (50% oil dispersion, 18 mg, 0.38 mmol). After stirring at 50°C under argon for 20–48 h, the reaction mixture was diluted with ether. The organic layer was washed with saturated aqueous NH_4Cl and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was subjected to preparative TLC (ethyl acetate:hexane=1:7) to give (*S*)-(1,3-diphenyl-2-propenyl)propanedioate **19**.[19] The e.e. and the absolute configuration of the product **19** were determined by HPLC analysis with a chiral column, Chiralpak AD (hexane:*i*-propanol=20:1). The results obtained are listed in Tables 5 and 6.

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