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(*S*)-Proline-derived new chiral ligands with phosphino, organosulfur or organoselenenyl functionality as an enantiocontrollable coordinating element

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Abstract

The synthesis of (*S*)-proline-derived chiral ligands bearing phosphino, organosulfur or selenenyl groups and their use as chiral ligands in palladium-catalyzed asymmetric allylic alkylations has been accomplished. In particular, the (*S*)-proline-derived phosphine ligands bearing alkylsulfenyl groups provided high enantioselectivity, and the degree of asymmetric induction was dependent upon the steric bulk of the alkyl substituents in sulfenyl groups. The stereochemical results are rationalized by a plausible mechanism involving the assistance of chelates formed by the participation of the two preferred heteroatoms involved.

1. Introduction

The increasing usefulness of catalytic asymmetric synthesis has been demonstrated for the synthesis of optically active compounds,[1] particularly biologically active chiral compounds, in the pharmaceutical field,[2] and as a result, the development of new efficient chiral ligands has received much attention.[3] Hitherto, various types of chiral ligands, possessing coordinating elements such as phosphorus,[4,5] nitrogen,[6] oxygen,[7] or sulfur groups,[8] have been developed. Currently, we are developing new efficient chiral ligands bearing chiral sulfinyl groups as the sole chiral source.[9] We describe in this paper (*S*)-proline-derived new chiral ligands having phosphino, organosulfur or organoselenenyl groups and demonstrate their usefulness in palladium-catalyzed asymmetric synthesis.[10] We also discuss herein the mechanism for the asymmetric induction according to the priority of the heteroatoms involved in terms of coordination ability, focused on the structure of the intermediary palladium complexes with the chelation by the phosphino, amino, sulfenyl, sulfinyl and selenenyl groups.

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2. Results and discussion

2.1. Synthesis of (S)-proline-derived chiral ligands

(*S*)-Proline-derived chiral ligands bearing heteroatoms as coordinating functions such as sulfur, selenium and phosphorus groups were obtained as follows. (*S*)-*N*-(2-Bromobenzoyl)proline derivatives **2a**,**b** were reduced with $BH_3 \cdot THF$ followed by sulfenylation with diphenyl disulfide, sulfinylation with (−)-menthyl (*S*)-*p*-toluenesulfinate,[11] selenenylation with diphenyl diselenide, phosphinylation with chlorodiphenylphosphine of (*S*)-**3a**, or sulfenylation with dimethyl or diphenyl disulfide, sulfinylation with (−)-menthyl (*R*)- or (*S*)-*p*-toluenesulfinate, or selenenylation with diphenyl diselenide of (*S*)-**3b**, producing (*S*)-**4a**, (*S*s,*S*)-**4b**, (*S*)-**4c**,**d**, (*S*)-**6a**,**b**, (*R*s,*S*)-**7a**, (*S*s,*S*)-**7b**, or (*S*)-**8**, respectively (Fig. 1).

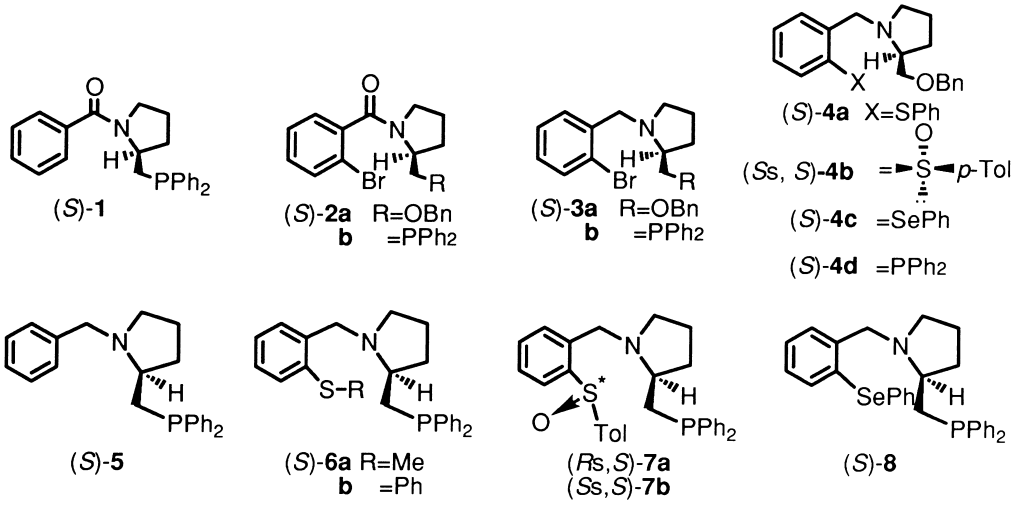
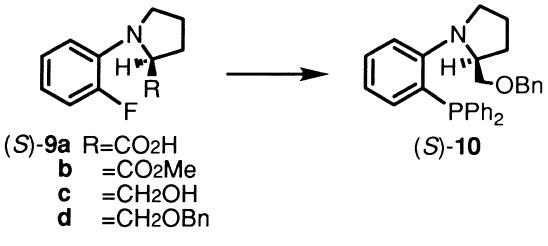


Figure 1. Synthesis of (*S*)-proline-derived ligands

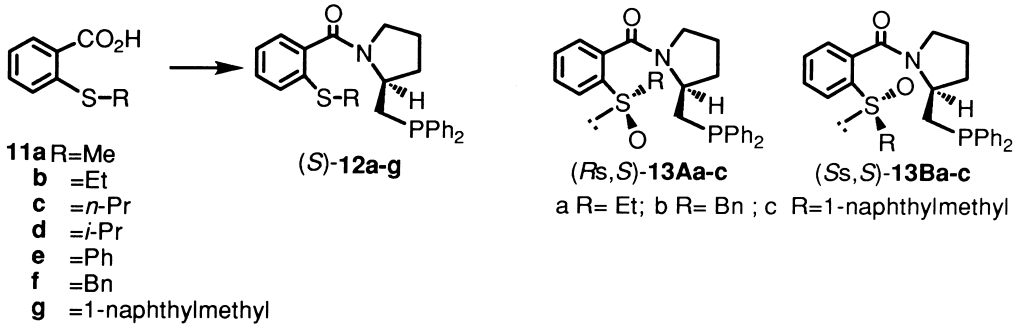
Chiral phosphine ligand (*S*)-**10** was prepared by the palladium–copper-catalyzed coupling reaction[12] of (*S*)-proline with 2-fluoroiodobenzene followed by the esterification of carboxylic acid (*S*)-**9a**, the reduction of the ester in (*S*)-**9b** with $LiAlH_4$, the benzylation of the alcohol in (*S*)-**9c**, and the phosphinylation of (*S*)-**9d** (Scheme 1).



Scheme 1.

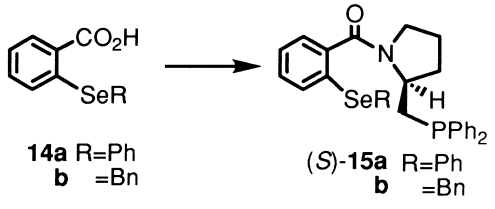
Chiral phosphine ligands (*S*)-**12a**–**g** bearing sulfenyl groups were prepared by *N*-acylation of (*S*)-2-(diphenylphosphinomethyl)pyrrolidine[13] with 2-(alkylthio)benzoic acids **11a**–**g**, which were obtained from commercially available 2-mercaptobenzoic acid, employing *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a dehydrating reagent. *N*-Acylation of (*S*)-2-(diphenylphosphinomethyl)pyrrolidine with 2-(alkylsulfinyl)benzoic acids obtained by oxidation of the sulfides **11b**,**f**,**g** with *m*-chloroperbenzoic acid (MCPBA) afforded the corresponding diastereomeric sulfoxides (*R*s,*S*)-**13Aa**–**c** and (*S*s,*S*)-**13Ba**–**c** in

a 1:1 diastereomeric ratio. The diastereoisomeric sulfoxides (*R*s,*S*)-**13Aa–c** and (*S*s,*S*)-**13Ba–c** were isolated in a 1:1 ratio by flash column chromatography over silica gel (Scheme 2).



Scheme 2.

Chiral phosphine ligands (*S*)-**15a**,**b** bearing selenenyl groups were obtainable by *N*-acylation of (*S*)-2-(diphenylphosphinomethyl)pyrrolidine with 2-(alkylselenenyl)benzoic acids **14a**,**b**, which were derived from 2-bromobenzoic acid via lithiation with *n*-BuLi and the subsequent selenenylation with diselenides (Scheme 3).



Scheme 3.

Chiral phosphine ligands (*S*)-**16** and (*S*)-**17**, possessing a pyridine or thiophene ring, were prepared in a similar way to that mentioned above by *N*-acylation with 2-pyridine- and 2-thiophenecarboxylic acid (Fig. 2).

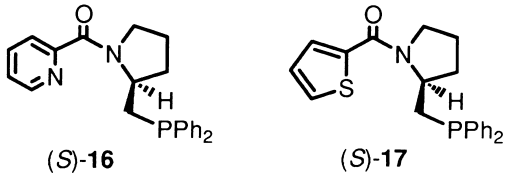
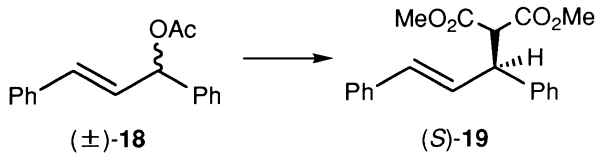


Figure 2. (*S*)-Proline-derived ligands with pyridine and thiophene rings

2.2. Palladium-catalyzed asymmetric allylic alkylation with chiral ligands

Initially, the asymmetric alkylations of (±)-1,3-diphenyl-2-propenyl acetate **18** with dimethyl malonate sodium enolate (generated by treating with NaH) using (*S*)-2-(benzyloxymethyl)pyrrolidine derivatives (*S*)-**4a–d** and (*S*)-**10** (0.12 equiv.) as chiral ligands were carried out in the presence of $[PdCl(\pi\text{-allyl})]_2$, $Pd(dba)_2$, or $Pd(OAc)_2$ (0.06 equiv.) in THF or DME at 0°C, room temperature, or 50°C to give (*S*)-**19** (Scheme 4).[14] The enantiomeric excess (e.e.) of the product **19** was calculated by HPLC analysis with a Chiralpak AD column.[14] The results obtained are summarized in Table 1.

The palladium-catalyzed reactions using (*S*)-**4a–c** provided low chemical yields of (*S*)-**19** with moderate e.e., whereas the reactions with the similar ligands (*S*)-**4d** and (*S*)-**10** bearing phosphinyl groups



(±)-**18** (*S*)-**19**

Scheme 4.

Table 1
Palladium-catalyzed asymmetric allylic alkylation of (±)-**18** with dimethyl malonate using chiral ligands (*S*)-**4a**–**d** and (*S*)-**10**[a)]

Entry	Ligand	Catalyst	Reaction temp. (°C)	Reaction time (h)	Yield (%) of (*S*)-**19**	e.e. (%) of (*S*)-**19**[b)]
1	(*S*)-**4a**	$[PdCl(\pi\text{-allyl})]_2$	rt	60	14	27
2		$Pd(OAc)_2$	50	36	31	36
3		$Pd(dba)_2$	50	48	18	31
4	(*Ss*,*S*)-**4b**	$Pd(OAc)_2$	50	60	13	-
5	(*S*)-**4c**	$Pd(OAc)_2$	50	36	12	36
6	(*S*)-**4d**	$Pd(OAc)_2$	50	14	57	36
7		$Pd(dba)_2$	0	156	10	36
8		$[PdCl(\pi\text{-allyl})]_2$	rt	1	63	36
9		$[PdCl(\pi\text{-allyl})]_2$	0	44	58	22
10		$[PdCl(\pi\text{-allyl})]_2$	50	14	84	37
11		$[PdCl(\pi\text{-allyl})]_2$	rt	2	87	39
12		$[PdCl(\pi\text{-allyl})]_2$	0	44	63	25
13	(*S*)-**10**	$[PdCl(\pi\text{-allyl})]_2$	rt	14	57	36

a) The reactions of (±)-**18** with carbanion of dimethyl malonate (generated by treating with NaH (1.2 equiv.)) were carried out in the presence of palladium catalyst (0.06 equiv.) and chiral ligands (*S*)-**4a**-**d** and (*S*)-**10** (0.12 equiv.).
b) The enantiomeric excess (e.e.) of (*S*)-**19** was determined by HPLC analysis with a Chiralpak AD.[14]

gave (*S*)-**19** in higher chemical yields with similar moderate e.e.s. This indicates that the phosphine groups in the ligands seem to play a prominent role in providing high chemical yields. Introduction of a chiral sulfinyl function on the aromatic nucleus in the place of the sulfenyl and the selenenyl groups in the ligands (*S*)-**4a**,**c** provided, unexpectedly, no asymmetric induction, presumably due to the mismatch of the two chiralities involved in the ligand (*Ss*,*S*)-**4b**.

With (*S*)-proline-derived phosphine ligands, (*S*)-**6a**,**b** and (*S*)-**8**, bearing a sulfenyl or selenenyl function as another stereocontrolling element for coordination, rather high chemical yields and extremely high e.e.s of product (*R*)-**19** were obtained as expected. The reactions of (±)-**18** with dimethyl malonate using $[PdCl(\pi\text{-allyl})]_2$ (0.06 equiv.) and (*S*)-**6a**,**b** or (*S*)-**8** (0.12 equiv.) were carried out in CH_2Cl_2 for 2 or 60 h at room temperature in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[15] (3.0 equiv.) and a catalytic amount of NaOAc to give (*R*)-**19** in 73 or 39% yield with 75 or 79% e.e., respectively. Surprisingly, introduction of a chiral sulfinyl function, instead of the sulfenyl group, into the ligands (*Ss*,*S*)-**7a** and (*Rs*,*S*)-**7b** resulted in almost no effect on the asymmetric induction, affording (*R*)-**19**. The results obtained are listed in Table 2.

However, the chiral amide ligands provided different stereochemical results depending on the ligands used. The reactions of (±)-**18** with dimethyl malonate (3.0 equiv.) under the conditions with BSA (3.0 equiv.) and a catalytic amount of NaOAc were carried out in dichloromethane in the presence of $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.) and chiral sulfenyl ligands **12a**–**d**,**f**,**g**, or a selenenyl ligand (*S*)-**15b** (0.06 equiv.) to give an alkylated product (*S*)-**19**, as summarized in Table 2. The table shows that the more bulky sulfenyl substituents in (*S*)-**12a**–**g** provided a higher degree of the asymmetric induction in proportion to the steric

Table 2
Palladium-catalyzed asymmetric allylic alkylation of (±)-**18** with dimethyl malonate using chiral ligands[a)]

Entry	Ligand	Reaction temp. (°C)	Reaction time (h)	Yield (%) of **19**	e.e. (%) of **19**[b)] (Abs. confign.)
1	(*S*)-**5**	rt	2	73	74 (*R*)
2	(*S*)-**6a**	rt	2	73	75 (*R*)
3		0	14	75	79 (*R*)
4		-20	40	76	82 (*R*)
5	(*S*)-**6b**	rt	2	75	81 (*R*)
6		0	4	76	84 (*R*)
7		-20	40	74	87 (*R*)
8	(*Rs*,*S*)-**7a**	rt	1	73	57 (*R*)
9		rt	18	69	59 (*R*)
10	(*Ss*,*S*)-**7b**	rt	18	76	78 (*R*)
11	(*S*)-**8**	rt	60	75[c)]	79 (*R*)
12		0	92	73[c)]	85 (*R*)
13	(*S*)-**1**	rt	14	69	42 (*R*)
14	(*S*)-**12a**	rt	2	65	62 (*S*)
15	(*S*)-**12b**	rt	3	72	72 (*S*)
16	(*S*)-**12c**	rt	11	68	77 (*S*)
17	(*S*)-**12d**	rt	16	54	31 (*S*)
18	(*S*)-**12e**	rt	16	42	41 (*R*)
19	(*S*)-**12f**	rt	8	76	84 (*S*)
20	(*S*)-**12g**	rt	25	59	88 (*S*)
21	(*Rs*,*S*)-**13Aa**	rt	24	72[c)]	60 (*S*)
22	(*Ss*,*S*)-**13Ba**	rt	50	51[c)]	33 (*S*)
23	(*Rs*,*S*)-**13Ab**	rt	96	53[c)]	74 (*S*)
24	(*Ss*,*S*)-**13Bb**	rt	96	58[c)]	2 (*S*)
25	(*Rs*,*S*)-**13Ac**	rt	96	58[c)]	53 (*S*)
26	(*Ss*,*S*)-**13Bc**	rt	96	-	-
27	(*S*)-**15a**	rt	42	63[c)]	74 (*R*)
28	(*S*)-**15b**	rt	70	54[c)]	86 (*S*)
29	(*S*)-**16**	rt	4	59	51 (*S*)
30	(*S*)-**17**	rt	36	44	30 (*R*)

a) The reactions of (±)-**18** with dimethyl malonate were carried out in dichloromethane in the presence of BSA[15] (3.0 equiv.), a catalytic amount of AcONa, $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.), and chiral ligands (0.06 equiv.).
b) The enantiomeric excess (e.e.) of **19** was determined by HPLC analysis with a Chiralpak AD.[14]
c) Corrected yields based on the recovered starting materials.

bulk, except for (*S*)-**12d**,**e**. Interestingly, the same reaction using (*S*)-**1** or (*S*)-**12e** as a ligand gave (*R*)-**19**. The (*S*)-proline-derived chiral phosphines (*S*)-**15b** and (*S*)-**16**, or (*S*)-**15a** and (*S*)-**17** provided (*S*)- or (*R*)-**19**, respectively. These results indicate that the benzylselenenyl group and the pyridinyl nitrogen served as coordinating elements, whereas the phenylselenenyl and the phenylsulfenyl or thiophene sulfur groups could not participate in the formation of a chelate of a palladium catalyst with the phosphine, because of the rather low coordination ability of the aromatic sulfenyl and selenenyl groups compared with other alkyl sulfenyl and selenenyl functions. Introduction of a chiral sulfinyl functionality [(*Rs*,*S*)-**13Aa–c** and (*Ss*,*S*)-**13Ba–c**] into the systems, instead of the sulfenyl groups, presented a little less enantioselectivity of (*S*)-**19** with a different degree of asymmetric induction depending on the diastereomers used, as listed in Table 2.

In comparison, use of amino phosphines (*S*)-**5**–**8** as ligands in the above reaction provided (*R*)-**19**. These results indicate that the organosulfur or selenenyl functionality in (*S*)-**12a**–**d**,**f**,**g**, (*S*)-**13a**–**c**, and (*S*)-**15b** served as an alternative stereocontrollable coordinating element in the above palladium-catalyzed alkylation, whereas the same groups in (*S*)-**6**–**8** could not function as coordinating elements and instead, the amino nitrogen atoms would participate in the formation of five-membered chelates with the phosphine groups, as mentioned later.

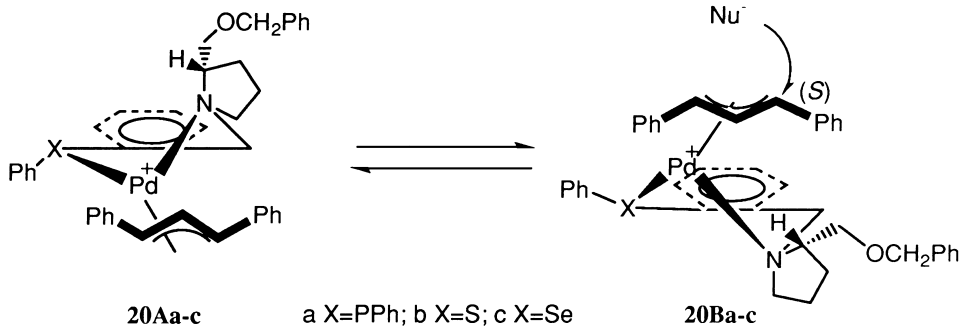
2.3. The mechanism for asymmetric induction with chiral ligands

The mechanism for the asymmetric induction with these new ligands is rationalized on the basis of the stereochemical results obtained. The (*S*)-proline-derived ligand **4d** would provide a six-membered chelate **20a** by coordination of the rather more electron-donating nitrogen groups and phosphorus groups to palladium catalysts. In the conformational equilibrium of sterically favored six-membered chelated π-allylpalladium complexes **20Aa** and **20Bb**, the palladium complex **20Bb** would be preferentially formed because of the existence of rather severe steric interference between the benzyloxymethyl group and both the axial phenyl substituent on the phosphine and the phenyl ring at the allylic site in **20Aa**. Therefore, the nucleophile (malonate anion) would attack the allylic terminus in **20Ba** *trans* to the better π-acceptor, which is the phosphine group[16] in the present case, from the back side of the palladium catalyst in the π-allyl system as designated in **20Ba**, affording (*S*)-**19**.

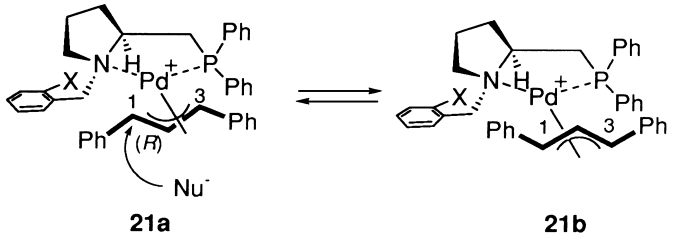
The reactions with chiral ligands (*S*)-**4a**,**c** bearing sulfenyl or selenenyl groups instead of the phosphine group are elucidated in a similar way. In the conformational equilibrium of the intermediary six-membered chelated π-allylpalladium complex **20b**,**c** coordinated by the sulfenyl or selenenyl group and the amino group in the ligands ((*S*)-**4a**,**c**), a π-allylpalladium complex **20Bb**,**c**, having the sterically preferred M-type allyl system due to the steric interaction between the two phenyl rings on the sulfur or selenenyl group and at the allylic site in the corresponding W-type one, is assumed to be a favorable isomer in preference to **20Ab**,**c**, which has the W-type allyl system based on the same steric reason, because of the steric interaction between the substituent at the stereogenic center and the phenyl group at the allylic site in **20Ab**,**c**. Thus, the nucleophile (malonate anion) would attack the allylic site *trans* to the better π-acceptor[16] which is the sulfenyl or the selenenyl function in the current case, affording (*S*)-**19**.

In the case of the amino phosphine ligands (*S*)-**5**–**8**, the formation of the intermediary nine-membered chelates with phosphino and sulfenyl groups similar to those mentioned later or six-membered chelates with amino and sulfenyl groups as mentioned earlier in Scheme 5 is not valid for the rationalization of the stereochemical results observed. Thus, the results may certainly be understandable by another plausible mechanism via five-membered chelates formed by the participation of the phosphino and the amino groups as the preferred more electron-donating elements. In the five-membered chelates, the π-allylpalladium complex **21a** is preferred to **21b**, due to the steric interference between the pyrrolidine ring and the phenyl substituent at the C_1 allyl terminus in **21b**. The nucleophile attacks the C_1 allyl terminus in **21a** *trans* to the better π-acceptor,[16] which is the phosphine group in the current case, affording (*R*)-**19** (Scheme 6).

As described earlier, the reaction using (*S*)-**1** provided (*R*)-**19**, whereas the use of (*S*)-**12a**–**d**,**f**,**g**, and (*S*)-**15b** as ligands afforded (*S*)-**19**. Therefore, with (*S*)-**12a**–**d**,**f**,**g** and (*S*)-**15b** as ligands, a nine-membered chelate formed by coordination of the organosulfur or selenenyl functionality and the phosphine group to the palladium catalyst is very crucial for the rationalization of the stereochemical results, otherwise it will be too hard to understand the absolute configuration of the product, the high enantioselectivity, and especially the steric effect of the alkyl substituents of the sulfenyl groups in the asymmetric induction, in proportion to the steric bulk as mentioned earlier. Inspection of a model of the

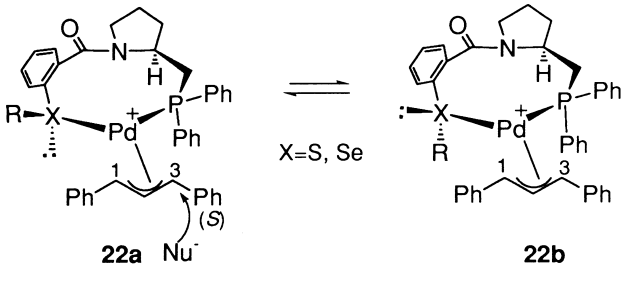


Scheme 5.



Scheme 6.

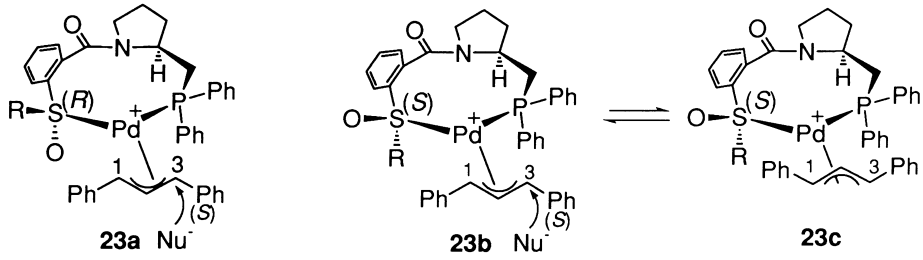
nine-membered chelated intermediary palladium complex shows that an M-type π-allylpalladium complex **22a** would be preferred to an M-type complex **22b** in the conformational equilibrium of the rather flexible nine-membered chelated π-allylpalladium complex, due to the steric 1,3-diaxial-like interaction between the substituent on the sulfenyl or selenenyl group and the phenyl ring on the phosphine group in **22b**, as illustrated in Scheme 7. The nucleophile (malonate carbanion) would attack the allyl terminus (C_3) in **22a** *trans* to the better π-acceptor,[16] which is the sulfenyl or selenenyl group in the present case, to furnish (*S*)-**19**. Increasing the size of the substituents on the sulfenyl groups resulted in enhanced enantiocontrol in the alkylation, presumably owing to the more selective alkylation at the C_3 site due to the steric reason of the large substituent for the alkylation at C_1. The rather low enantioselectivity obtained by (*S*)-**12d** is rationalized by the inaccessibility to the formation of the corresponding nine-membered chelate because of the steric effect exerted by the secondary alkyl group on the sulfenyl sulfur atom.



Scheme 7.

Thus, the high level of the asymmetric induction presented by (*S*)-**12a**–**d**,**f**,**g** is rationalized by generation of another new stereogenic center on the sulfenyl sulfur atoms in the formation of the intermediary nine-membered chelates. This rationalization is also supported by the results with diastereomeric sulfoxides (*R*s,*S*)-**13Aa**–**c** and (*S*s,*S*)-**13Ba**–**c**. One of the diastereomers, presumably (*R*s,*S*)-**13Aa**–**c**, presented a higher asymmetric induction than (*S*s,*S*)-**13Ba**–**c**; namely, the (*R*s,*S*)-**13Aa**–**c** would be a matched

pair for the formation of the sterically favorable chelate **23a** in this palladium catalysis, whereas the (*Ss*,*S*)-**13Ba–c** would be a mismatched one because of the sterical inaccessibility to the palladium catalyst for the formation of **23b**,**c** (Scheme 8). In the confomational equilibrium of **23b**,**c**, the M-type π-allylpalladium complex **23b** is slightly preferred to the W-type one (**23c**) because of the steric interference between the two phenyl rings on the phosphine group and at the C_3 allyl terminus in **23c**. Therefore, the preferential alkylation occurs at the C_3 allyl terminus in **23a** or **23b**, *trans* to the better π-acceptor,[16] which is presumably the sulfinyl group in this case, furnishing (*S*)-**19** with high or rather low enantioselectivity, respectively. The higher degree of the asymmetric induction with the sulfenyl ligands presumably also arises from the stronger coordination ability of the sulfenyl groups than the sulfinyl sulfur atoms.



Scheme 8.

Thus, in conclusion, it is worth noting that the alkyl sulfenyl groups introduced in chiral phosphine ligands derived from (*S*)-proline served as enantiocontrollable coordinating elements, providing high enantioselectivity in proportion to the steric bulk of the primary alkyl groups in the palladium-catalyzed asymmetric allylic alkylation.

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 a JEOL JNM-LA 400 (^{1}H NMR; 400 MHz) and JEOL EX-270 (^{1}H NMR; 270 MHz) high-resolution NMR spectrometer; chemical shifts are given in ppm from tetramethylsilane as an internal standard. Splitting patterns are designated as s: singlet, ss: singlet singlet, bs: broad singlet, d: doublet, dd: double doublet, dt: triple doublet, t: triplet, td: double triplet, q: quartet, 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 1:20, 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 (*S*)-*N*-benzyl-2-(benzyloxy- or diphenylphosphinomethyl)pyrrolidine derivatives*

*3.1.1. (*S*)-*N*-(2-Bromobenzoyl)-2-(benzyloxymethyl)pyrrolidine **2a***

A solution of 2-bromobenzoyl chloride (457 mg, 2.01 mmol) in acetonitrile (CH_3CN) (12 ml) was added at 0°C to a solution of (*S*)-2-(benzyloxymethyl)pyrrolidine (329 mg, 2.01 mmol) and triethylamine (Et_3N) (843 mg, 6.03 mmol) in CH_3CN (8 ml), and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then diluted with chloroform ($CHCl_3$), and the solution was 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=2:1) to give (*S*)-**2a** (465 mg, 65% yield).

The reaction of (*S*)-2-(diphenylphosphinomethyl)pyrrolidine with 2-bromobenzoyl chloride was carried out with the same procedure as described above to give (*S*)-*N*-(2-bromobenzoyl)-2-(diphenylphosphinomethyl)pyrrolidine **2b**.

(*S*)-**2a**: $[\alpha]_D$ −89 (*c*=1.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1585 (aromatic), 1625 (amide). NMR (270 MHz; $CDCl_3$) δ: 1.76–2.17 (m, 4H, $(CH_2)_2$), 3.16–3.41 (m, 2H, CH_2), 3.73–3.86 (m, 2H, CH_2), 4.45–4.54 (m, 1H, CH), 4.59 (s, 2H, CH_2), 7.15–7.36 (m, 8H, ArH), 7.52–7.57 (m, 1H, ArH). *m/z*: 373 (M^+). Exact mass determination: 373.0676 (calcd $C_{19}H_{20}NO_2Br$: 375.0677).

(*S*)-**2b**: 75% yield. $[\alpha]_D$ −110 (*c*=3.3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: NMR (270 MHz; $CDCl_3$) δ: 1.95–2.13 (m, 4H, $(CH_2)_2$), 3.16–3.24 (m, 2H, CH_2), 3.66–3.84 (m, 2H, CH_2), 4.40 (br, 1H, CH), 6.82–6.88 (m, 1H, ArH), 7.08–7.57 (m, 14H, ArH), 7.70–7.75 (m, 1H, ArH). *m/z*: 451 (M^+). Exact mass determination: 451.0667 (calcd $C_{24}H_{23}NOPBr$: 451.0700).

*3.1.2. (S)-N-(2-Bromobenzyl)-2-(benzyloxymethyl)pyrrolidine **3a***

A solution of (*S*)-**2a** (596 mg, 1.66 mmol) in THF (5 ml) was added at 0°C to a 1 M borane:THF complex solution (8 ml, 8.28 mmol), and the reaction mixture was stirred under heating at reflux for 6 h. Then after cooling, a solution of methanol (MeOH) (10 ml) and 10% aqueous potassium hydroxide (5 ml) was added to the reaction mixture. The mixture was stirred under heating at reflux for a further 1 h. The solution was concentrated to dryness in vacuo. The residue was then dissolved with $CHCl_3$, and the solution was 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 (ether:hexane=1:1) to give (*S*)-**3a** (565 mg, 98% yield).

The reduction of (*S*)-**2b** with a borane:THF complex solution was carried out in the same way as described above to give (*S*)-*N*-(2-bromobenzyl)-2-(boranatodiphenylphosphinomethyl)pyrrolidine **3b**.

(*S*)-**3a**: $[\alpha]_D$ −38 (*c*=9.2, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1585 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.59–2.02 (m, 4H, $(CH_2)_2$), 2.23–3.01 (m, 2H, CH_2), 2.86–2.93 (m, 1H, CH), 3.33–3.57 (m, 2H, CH_2), 3.59–4.19 (m, 2H, CH_2), 4.51 (s, 2H, CH_2), 7.04–7.23 (m, 1H, ArH), 7.26–7.32 (m, 6H, ArH), 7.47–7.53 (m, 2H, ArH). *m/z*: 375 (M^+). Exact mass determination: 375.0676 (calcd $C_{19}H_{22}NOBr$: 375.0657).

(*S*)-**3b**: 61% yield. $[\alpha]_D$ −71 (*c*=4.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1585 (aromatic). NMR (400 MHz; $CDCl_3$) δ: 1.05–1.31 (m, 3H, BH_3), 1.32–1.39 (m, 1H, CH), 1.60–1.73 (m, 2H, CH_2), 1.82–1.91 (m, 1H, CH), 2.13–2.20 (m, 1H, CH), 2.28–2.36 (m, 1H, CH), 2.71–2.79 (m, 1H, CH), 2.84–2.96 (m, 2H,CH_2), 3.38 (d, *J*=14.1 Hz, 1H, CH), 3.94 (d, *J*=14.1 Hz, 1H, CH), 7.09 (td, *J*=7.6, 1.7 Hz, 1H, ArH), 7.22–7.26 (m, 1H, ArH), 7.37–7.53 (m, 8H, ArH), 7.66–7.44 (m, 4H, ArH). *m/z*: 452 (M^++1). Exact mass determination: 451.1188 (calcd $C_{24}H_{28}BNPBr$: 451.1236)

*3.1.3. (S)-N-[2-(Phenylthio)benzyl]-2-(benzyloxymethyl)pyrrolidine **4a***

A 1.56 M cyclopentane solution of *n*-BuLi (0.4 ml, 0.52 mmol) was added at −78°C to a solution of (*S*)-**3a** (150 mg, 0.43 mmol) in THF (3 ml), and the reaction mixture was stirred at −78°C for 1 h. A solution of diphenyl disulfide (114 mg, 0.52 mmol) in THF (4 ml) was added to the above solution, and the mixture was stirred at 0°C for 12 h. The reaction solution was diluted with ether, and the ether 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=1:5) to give (*S*)-**4a** (111 mg, 66% yield).

The substitution reactions of *ortho*-lithiated carbanions of (*S*)-**3a**,**b** obtained in the same way with (−)-menthyl (*S*)-*p*-toluenesulfinate, diphenyl diselenide or chlorodiphenylphosphine were carried out

using the procedure similar to that described above to give (*S*s,*S*)-*N*-[2-(*p*-toluenesulfinyl)-, (*S*)-*N*-[2-(phenylseleno)- or (*S*)-*N*-[2-(diphenylphosphino)benzyl]-2-(benzyloxymethyl)pyrrolidine **4b**–**d**, respectively.

(*S*)-**4a**: $[\alpha]_D$ −66 (*c*=1.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1580 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.64–2.06 (m, 4H, $(CH_2)_2$), 2.17–3.25 (m, 2H, CH_2), 2.82–2.84 (m, 1H, CH), 3.34–3.60 (m, 2H, CH_2), 3.62–4.23 (m, 2H, CH_2), 4.49 (s, 2H, CH_2), 7.12–7.31 (m, 13H, ArH), 7.49–7.51 (m, 1H, ArH). *m/z*: 389 (M^+). Exact mass determination: 389.1848 (calcd $C_{25}H_{27}NOS$: 389.1813).

(*S*s,*S*)-**4b**: 30% yield. $[\alpha]_D$ +68 (*c*=4.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1595 (aromatic), 1032 (SO). NMR (270 MHz; $CDCl_3$) δ: 1.37–1.76 (m, 4H, $(CH_2)_2$), 1.87–1.98 (m, 1H, CH), 2.01–2.16 (m, 1H, CH), 2.33 (s, 3H, CH_3), 2.52–2.58 (m, 1H, CH), 2.52–2.82 (m, 1H, CH), 3.33, 3.38 (ss, 1H, CH), 3.46 (dd, *J*=9.4, 4.8 Hz, 1H, CH), 3.63–3.72 (m, 1H, CH), 4.51 (d, *J*=7.2 Hz, 2H, CH_2), 7.14–7.45 (m, 10H, ArH), 7.51–7.59 (m, 2H, ArH), 7.89–7.92 (m, 1H, ArH). *m/z*: 420 (M^++1). Exact mass determination: 419.1960 (calcd $C_{26}H_{29}NO_2S$: 419.1919).

(*S*)-**4c**: 48% yield. $[\alpha]_D$ −29 (*c*=2.3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1580 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.43–2.02 (m, 4H, $(CH_2)_2$), 2.16–2.86 (m, 1H, CH), 3.36–3.67 (m, 2H, CH_2), 3.60–4.25 (m, 2H, CH_2), 4.49 (s, 2H, CH_2), 7.01–7.34 (m, 13H, ArH), 7.48–7.52 (m, 1H, ArH). *m/z*: 437 (M^+). Exact mass determination: 437.1254 (calcd $C_{25}H_{27}NOSe$: 437.1258).

(*S*)-**4d**: 29% yield. $[\alpha]_D$ −35 (*c*=3.9, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1580 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.09–1.82 (m, 4H, $(CH_2)_2$), 1.99–2.78 (m, 2H, CH_2), 2.55–2.61 (m, 1H, CH), 3.20–3.26 (m, 2H, CH_2), 3.59–3.67 (m, 2H, CH_2), 4.49 (dd, *J*=12.0, 21.2 Hz, 2H, CH_2), 6.86–6.91 (m, 1H, ArH), 7.10–7.35 (m, 18H, ArH). *m/z*: 465 (M^+). Exact mass determination: 465.2251 (calcd $C_{31}H_{32}NOP$: 465.2221).

*3.1.4. (*S*)-N-[2-(Methylthio)benzyl]-2-(diphenylphosphinomethyl)pyrrolidine **6a***

The reaction of an *ortho*-lithiated carbanion of (*S*)-**3b** (84 mg, 0.23 mmol), obtained in the same way as described above, with dimethyl or diphenyl disulfide, (−)-menthyl (*R*s)- or (*S*s)-*p*-toluenesulfinate or diphenyl diselenide, was carried out with the procedure similar to that described above (Section 3.1.3) to give (*S*)-*N*-(2-methylthiobenzyl)-, (*S*)-*N*-[2-(phenylthio)benzyl]-, (*R*s,*S*)- or (*S*s,*S*)-*N*-[2-(*p*-toluenesulfinyl)benzyl]- or (*S*)-*N*-[2-(phenylseleno)benzyl]-2-(boranatodiphenylphosphinomethyl)pyrrolidine, respectively.

1,4-Diazabicyclo[2.2.2]octane (DABCO) (26 mg, 0.23 mmol) was added to a solution of the crude products (0.23 mmol), obtained as above, in toluene (5 ml). The reaction mixture was stirred for 2 h at 40°C. The solution was concentrated in vacuo. The crude product was subjected to preparative TLC (ether:hexane=1:1) to give (*S*)-*N*-[2-(methylthio)benzyl]-, (*S*)-*N*-[2-(phenylthio)benzyl]-, (*R*s,*S*)- or (*S*s,*S*)-*N*-[2-(*p*-toluenesulfinyl)benzyl]- or (*S*)-*N*-[2-(phenylseleno)benzyl]-2-(diphenylphosphinomethyl)pyrrolidine **6a**,**b**, **7a**,**b** or **8**, respectively.

(*S*)-**6a**: 77% yield. $[\alpha]_D$ −165 (*c*=1.1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}:1595 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.62–1.77 (m, 4H, $(CH_2)_2$), 1.97–2.18 (m, 4H, 2×CH_2), 2.43 (s, 3H, CH_3), 2.49–2.68 (m, 1H, CH), 2.76–2.90 (m, 1H, CH), 2.92–2.95 (m, 1H, CH), 3.28 (d, *J*=13.5 Hz, 1H, CH), 4.05 (d, *J*=13.5 Hz, 1H, CH), 7.04–7.09 (m, 1H, ArH), 7.17–7.39 (m, 9H, ArH), 7.40–7.48 (m, 4H, ArH). *m/z*: 406 (M^++1). Exact mass determination: 405.1692 (calcd $C_{25}H_{28}NPS$: 405.1680).

(*S*)-**6b**: 74% yield. $[\alpha]_D$ −71 (*c*=2.8, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1595 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.62–1.76 (m, 4H, $(CH_2)_2$), 1.97–2.12 (m, 4H, 2×CH_2), 2.46–2.65 (m, 2H, CH_2), 2.91–2.96 (m, 1H, CH), 3.39 (d, *J*=13.7 Hz, 1H, CH), 4.06 (d, *J*=13.7 Hz, 1H, CH), 7.12–7.48 (m, 1H, CH). *m/z*: 468 (M^++1). Exact mass determination: 467.1857 (calcd $C_{30}H_{30}NPS$: 467.1837).

(*R*s,*S*)-**7a**: 72% yield. $[\alpha]_D$ +36 (*c*=2.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1595 (aromatic), 1032 (SO). NMR

(270 MHz; $CDCl_3$) δ: 1.40–2.10 (m, 6H, $(CH_2)_3$), 2.34 (s, 3H, CH_3), 2.51–2.54 (m, 2H, 2×CH), 2.74 (dt, *J*=13.2, 3.3 Hz, 1H, CH), 3.04 (d, *J*=12.7 Hz, 1H, CH), 4.33 (d, *J*=12.7 Hz, 1H, CH), 7.18–7.21 (m, 2H, ArH), 7.25–7.48 (m, 14H, ArH), 7.58–7.61 (m, 2H, ArH), 7.94 (d, *J*=7.6 Hz, 1H, ArH). *m/z*: 498 (M^++1). Exact mass determination: 497.1950 (calcd $C_{31}H_{32}NOPS$: 497.1942).

(*Ss*,*S*)-**7b**: 65% yield. $[\alpha]_D$ −122 (*c*=2.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1595 (aromatic), 1030 (SO). NMR (270 MHz; $CDCl_3$) δ: 1.53–1.89 (m, 4H, $(CH_2)_2$), 1.92–2.08 (m, 2H, CH_2), 2.21 (dt, *J*=13.2, 3.5 Hz, 1H, CH), 2.32 (s, 3H, CH_3), 2.44–2.48 (m, 1H, CH), 2.82–2.87 (m, 1H, CH), 3.46 (d, *J*=13.7 Hz, 1H, CH), 3.79 (d, *J*=13.7 Hz, 1H, CH), 7.14–7.49 (m, 17H, ArH), 8.03 (d, *J*=1.2 Hz, 1H, ArH). *m/z*: 497 (M^+). Exact mass determination: 497.1989 (calcd $C_{31}H_{32}NOPS$: 497.1942).

(*S*)-**8**: 46% yield. $[\alpha]_D$ −26 (*c*=1.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1603 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.54–1.86 (m, 4H, $(CH_2)_2$), 2.05–2.15 (m, 1H, CH), 2.25–2.35 (m, 1H, CH), 2.60–2.90 (m, 3H, CH, CH_2), 3.23 (d, *J*=13.0 Hz, 1H, CH), 3.93 (d, *J*=13.0 Hz, 1H, CH), 7.22–7.51 (m, 15H, ArH), 7.61–7.74 (m, 4H, ArH). *m/z*: 516 (M^++1). Exact mass determination: 515.1331 (calcd $C_{30}H_{30}NPSe$: 515.1281).

*3.2. Synthesis of (*S*)-*N*-2-substituted phenylprolinol derivative*

*3.2.1. (*S*)-*N*-(2-Fluorophenyl)-2-proline methyl ester* ***9b***

A mixture of (*S*)-proline (1.0 g, 8.70 mmol), 2-fluoroiodobenzene (1.9 g, 8.70 mmol), bis(triphenylphosphine)nickel(II) chloride $[Ni(PPh_3)_2Cl_2]$ (284 mg, 0.44 mmol), copper iodide (CuI) (82 mg, 0.44 mmol), potassium carbonate (1.2 g, 8.70 mmol), benzyltriethylammonium chloride (TEBA) (298 mg, 1.31 mmol), Et_3N (2.3 g, 23.00 mmol), *N*,*N*-dimethylformamide (16 ml) and water (2 ml) was heated at 100°C for 22 h.[12] A solution of 6 N HCl was added to adjust the pH to 2–3 and the mixture was then diluted with ethyl acetate. The organic layers were combined, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Thionyl chloride (3 ml, 34.80 mmol) was added at 0°C to a solution of the crude product obtained in MeOH (20 ml), and the reaction mixture was stirred under heating at reflux for 2 h. The reaction solution was concentrated in vacuo. It was then diluted with $CHCl_3$, and the solution 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 (*S*)-**9b** (969 mg, 50% yield).

(*S*)-**9b**: $[\alpha]_D$ −78 (*c*=6.7, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1748 (ester), 1615 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.90–2.35 (m, 6H, $(CH_2)_3$), 3.37–3.46 (m, 1H, CH), 3.58–3.66 (m, 1H, CH), 3.69 (s, 3H, CH_3), 4.50–4.56 (m, 1H, CH), 6.61–6.70 (m, 2H, ArH), 6.89–7.01 (m, 2H, ArH). *m/z*: 223 (M^+). Exact mass determination: 223.0994 (calcd $C_{12}H_{14}NO_2F$: 223.1009).

*3.2.2. (*S*)-*N*-(2-Fluorophenyl)-2-prolinol* ***9c***

Lithium aluminum hydride (169 mg, 6.04 mmol) was added at 0°C to a solution of (*S*)-**9b** (672 mg, 3.02 mmol) in THF (20 ml), and the reaction mixture stirred at room temperature for 4 h. The reaction solution was diluted with ether, and 10% aqueous sodium hydroxide (5 ml) was added to the solution. The solution was filtered, and the filtrate was dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was subjected to preparative TLC (ether:hexane=1:1) to give (*S*)-**9c** (497 mg, 85% yield).

(*S*)-**9c**: $[\alpha]_D$ +27 (*c*=1.1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3350 (OH), 1610 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.79–2.12 (m, 5H, $(CH_2)_2$, OH), 3.13–3.22 (m, 1H, CH), 3.53–3.69 (m, 3H, CH, CH_2), 3.93–4.04 (m, 1H, CH), 6.68–6.84 (m, 2H, ArH), 6.94–7.02 (m, 2H, ArH). *m/z*: 195 (M^+). Exact mass determination: 195.1053 (calcd $C_{11}H_{14}NOF$: 195.1059).

3.2.3. (S)-N-(2-Fluorophenyl)-2-(benzyloxymethyl)pyrrolidine ***9d***

A 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar, and containing sodium hydride (50% oil dispersion; 197 mg, 4.10 mmol) was flushed with argon, and maintained under a positive pressure of argon. A solution of (*S*)-**9c** (667 mg, 3.42 mmol) in THF (15 ml) was added to the above flask. The reaction mixture was stirred at 0°C for 30 min. A solution of benzyl bromide (567 mg, 4.10 mmol) in THF (5 ml) was added to the above solution, and the reaction mixture was stirred at room temperature for 36 h. The reaction solution was diluted with ether, washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo. The crude product was subjected to preparative TLC (ether:hexane=1:3) to give (*S*)-**9d** (809 mg, 83% yield).

(*S*)-**9d**: $[\alpha]_D$ −44 (*c*=2.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1610 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.87–2.06 (m, 4H, $(CH_2)_2$), 3.19–3.34 (m, 2H, CH_2), 3.54–3.59 (m, 2H, CH_2), 4.12–4.16 (m, 1H, CH), 4.44 (d, *J*=3.6 Hz, 2H, CH_2), 6.62–6.76 (m, 2H, ArH), 6.91–7.00 (m, 2H, ArH), 7.24–7.34 (m, 5H, ArH). *m/z*: 286 (M^++1). Exact mass determination: 285.1512 (calcd $C_{18}H_{20}NOF$: 285.1529).

3.2.4. (S)-N-[2-(Diphenylphosphino)phenyl]-2-(benzyloxymethyl)pyrrolidine ***10***

A 0.5 M THF solution of potassium diphenylphosphatide ($KPPh_2$)[17] was added at room temperature to a solution of (*S*)-**9d** (809 mg, 2.84 mmol) in THF (34 ml), and the reaction mixture was stirred at reflux for 38 h. The reaction mixture was diluted with ether and filtered. The filtrate was concentrated in vacuo. The crude product was subjected to preparative TLC (ethyl acetate:hexane=1:15) to give (*S*)-**10** (144 mg, 11% yield).

(*S*)-**10**: $[\alpha]_D$ −62 (*c*=3.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1582 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.62–1.80 (m, 3H, CH, CH_2), 2.06–2.17 (m, 1H, CH), 2.71–2.77 (m, 1H, CH), 2.83 (dd, *J*=9.3, 8.1 Hz, 1H, CH), 7.17 (dd, *J*=9.3, 4.1 Hz, 1H, CH), 3.47–3.55 (m, 1H, CH), 3.78–3.85 (m, 1H, CH), 4.27 (dd, *J*=18.5, 12.0 Hz, 2H, CH_2), 6.78–6.82 (m, 1H, ArH), 6.91–6.95 (m, 1H, ArH), 7.15–7.35 (m, 17H, ArH). *m/z*: 452 (M^++1). Exact mass determination: 451.2069 (calcd $C_{30}H_{30}NOP$: 451.2065).

3.3. Synthesis of (S)-N-benzyloxy-2-(diphenylphosphinomethyl)pyrrolidine derivatives

3.3.1. (S)-N-[2-(Methylthio)benzoyl]-2-(diphenylphosphinomethyl)pyrrolidine ***12a***

A solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (119 mg, 0.64 mmol) in CH_2Cl_2 (2 ml) was added at 0°C to a solution of 2-methylthiobenzoic acid **11a** (130 mg, 0.70 mmol) in CH_2Cl_2 (1 ml), and the reaction mixture was stirred at room temperature for 15 min. A solution of (*S*)-2-(diphenylphospinomethyl)pyrrolidine (156 mg, 0.58 mmol) in Et_3N (293 mg) was added to the above solution, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with ether and filtered. The filtrate was concentrated in vacuo. The crude product was subjected to preparative TLC (ether:hexane=2:1) to give (*S*)-**12a** (63 mg, 28% yield).

The reactions of (*S*)-2-(diphenylphosphinomethyl)pyrrolidine with 2-(ethylthio)-, 2-(ethylsulfinyl)-, 2-(*n*-propylthio)-, 2-(isopropylthio)-, 2-(phenylthio)-, 2-(benzylthio)-, 2-(benzylsulfinyl)-, 2-(naphthylmethylthio)-, 2-(naphthylmethylsulfinyl)-, 2-(phenylseleno)-, 2-(benzylseleno)benzoic acid, picolinic acid or 2-thiophenecarboxylic acid were carried out using the same procedure as described above to give (*S*)-*N*-[2-(ethylthio)benzoyl]-, (*R*s,*S*)- or (*S*s,*S*)-*N*-[2-(ethylsulfinyl)benzoyl]-, (*R*s,*S*)- or (*S*s,*S*)-*N*-[2-(benzylsulfinyl)benzoyl]-, (*R*s,*S*)- or (*S*s,*S*)-*N*-[2-(naphthylmethylsulfinyl)benzoyl]-, (*S*)-*N*-[2-(*n*-propylthio)benzoyl]-, (*S*)-*N*-[2-(isopropylthio)benzoyl]-, (*S*)-*N*-[2-(phenylthio)benzoyl]-, (*S*)-*N*-[2-(benzylthio)benzoyl]-, (*S*)-*N*-[2-(benzylsulfinyl)benzoyl]-, (*S*)-*N*-[2-(naphthylmethylthio)benzoyl]-, (*S*)-*N*-[2-(naphthylmethylsulfinyl)benzoyl]-, (*S*)-*N*-[2-(phenylseleno)benzoyl]-, (*S*)-*N*-[2-(benzylseleno)benzoyl]-, (*S*)-*N*-2-picolinoyl- or (*S*)-*N*-2-thenoyl-2-(diphenylphosphinomethyl)pyrrolidine

((*S*)-**12a**–**g**, (*Rs*,*S*)-**13Aa**, (*Ss*,*S*)-**13Ba**, (*Rs*,*S*)-**13Ab**, (*Ss*,*S*)-**13Bb**, (*Rs*,*S*)-**13Ac**, (*Ss*,*S*)-**13Bc**, (*S*)-**15a**,**b**, (*S*)-**16**,**17**), respectively.

(*S*)-**12a**: $[\alpha]_D$ −170 (*c*=1.9, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1628 (amide), 1590 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.96–2.13 (m, 4H, $(CH_2)_2$), 2.45 (s, 3H, CH_3), 3.12–3.33 (m, 2H, CH_2), 3.69–3.76 (m, 2H, CH_2), 4.41–4.42 (m, 1H, CH), 6.78–6.84 (m, 1H, ArH), 7.06–7.47 (m, 12H, ArH), 7.71 (dd, *J*=4.5, 1.3 Hz, 1H, ArH). *m/z*: 420 (M^++1). Exact mass determination: 419.1451 (calcd $C_{25}H_{26}NOPS$: 419.1473).

(*S*)-**12b**: 42% yield. $[\alpha]_D$ −120 (*c*=2.9, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1628 (amide), 1588 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.26 (t, *J*=7.4 Hz, 3H, CH_3), 1.88–2.15 (m, 4H, $(CH_2)_2$), 2.93 (q, *J*=7.4 Hz, 2H, CH_2), 3.10–3.28 (m, 2H, CH_2), 3.65–3.83 (m, 2H, CH_2), 6.78–6.84 (m, 1H, ArH), 7.06–7.48 (m, 12H, ArH), 7.69–7.76 (m, 1H, ArH). *m/z*: 434 (M^++1). Exact mass determination: 433.1632 (calcd $C_{26}H_{28}NOPS$: 433.1629).

(*S*)-**12c**: 33% yield. $[\alpha]_D$ −141 (*c*=4.5, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1626 (amide), 1588 (aromotic). NMR (270 MHz; $CDCl_3$) δ: 0.90–1.01 (m, 3H, CH_3), 1.43–1.79 (m, 4H, $(CH_2)_2$), 1.91–2.20 (m, 4H, $(CH_2)_2$), 3.09–3.30 (m, 2H, CH_2), 3.61–3.83 (m, 2H, CH_2), 4.21–4.45 (m, 1H, CH), 6.81 (dd, *J*=8.1, 9.1 Hz, 1H, CH), 7.06–7.46 (m, 12H, ArH), 7.70–7.76 (m, 1H, ArH). *m/z*: 448 (M^++1). Exact mass determination: 447.1751 (calcd $C_{27}H_{30}NOPS$: 447.1786).

(*S*)-**12d:** 44% yield. $[\alpha]_D$ −128 (*c*=4.5, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1626 (amide), 1588 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.22 (dd, *J*=8.9, 6.8 Hz, 6H, $(CH_3)_2$), 1.90–2.11 (m, 4H, $(CH_2)_2$), 3.12–3.27 (m, 2H, CH_2), 3.42–3.65 (m, 1H, CH), 3.68–3.75 (m, 2H, CH_2), 4.38–4.45 (m, 1H, CH), 6.78–6.84 (m, 1H, CH), 7.06–7.47 (m, 12H, ArH), 7.72–7.75 (m, 1H, ArH). *m/z*: 448 (M^++1). Exact mass determination: 447.1786 (calcd $C_{27}H_{30}NOPS$: 447.1786).

(*S*)-**12e**: 46% yield. $[\alpha]_D$ −71 (*c*=2.8, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1622 (amide), 1576 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.54–2.25 (m, 4H, $(CH_2)_2$), 3.06–3.14 (m, 2H, CH_2), 3.39–3.52 (m, 3H, CH, CH_2), 4.40–4.42 (m, 1H, CH), 7.13–7.54 (m, 17H, ArH), 7.65–7.70 (m, 2H, ArH). *m/z*: 481 (M^+). Exact mass determination: 481.1612 (calcd $C_{30}H_{28}NOPS$: 481.1629).

(*S*)-**12f**: 37% yield. $[\alpha]_D$ −117 (*c*=5.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1616 (amide), 1588 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.66–2.40 (m, 4H, $(CH_2)_2$), 2.94–3.28 (m, 2H, CH_2), 3.66–3.76 (m, 2H, CH_2), 4.11 (s, 2H, CH_2), 4.38–4.45 (m, 1H, CH), 6.77–6.82 (m, 1H, ArH), 7.07–7.10 (m, 2H, ArH), 7.17–7.46 (m, 14H, ArH), 7.70–7.76 (m, 2H, ArH). 496 (M^++1). Exact mass determination: 495.1789 (calcd $C_{31}H_{30}NOPS$: 495.1786).

(*S*)-**12g**: 24% yield. $[\alpha]_D$ −125 (*c*=2.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1622 (amide), 1588 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.73–2.40 (m, 4H, $(CH_2)_2$), 2.82–3.27 (m, 2H, CH_2), 3.61–3.83 (m, 2H, CH_2), 4.17–4.57 (m, 3H, CH, CH_2), 6.80 (dd, *J*=14.3, 6.6 Hz, 1H, ArH), 7.02–7.50 (m, 16H, ArH), 7.59–7.84 (m, 4H, ArH). *m/z*: 546 (M^++1). Exact mass determination: 545.1943 (calcd $C_{35}H_{32}NOPS$: 545.1942).

(*Rs*,*S*)-**13Aa**: 15% yield. $[\alpha]_D$ −72 (*c*=1.7, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1622 (amide), 1589 (aromatic), 1026 (SO). NMR (400 MHz; $CDCl_3$) δ: 1.19 (t, *J*=7.6 Hz, 3H, CH_3), 1.81–2.49 (m, 4H, $(CH_2)_2$), 3.05–3.14 (m, 2H, CH_2), 3.21–3.39 (m, 4H, 2×CH_2), 6.87–6.93 (m, 1H, ArH), 7.23–7.70 (m, 12H, ArH), 7.82–7.90 (m, 1H, ArH). *m/z*: 449 (M^+). Exact mass determination: 449.1587 (calcd $C_{26}H_{28}NO_2PS$: 449.1579).

(*Ss*,*S*)-**13Ba**: 18% yield. $[\alpha]_D$ −106 (*c*=1.3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1622 (amide), 1589 (aromatic), 1026 (SO). NMR (400 MHz; $CDCl_3$) δ: 1.29 (t, *J*=7.6 Hz, 3H, CH_3), 1.67–2.27 (m, 4H, $(CH_2)_2$), 2.44 (dd, *J*=13.9, 8.8 Hz, 1H, CH), 2.80–2.96 (m, 2H, CH_2), 4.45–4.54 (m, 1H, CH), 6.98 (dd, *J*=7.6, 1.2 Hz, 1H, ArH), 7.23–7.61 (m, 12H, ArH), 8.04 (dd *J*=7.8, 1.0 Hz, 1H). *m/z*: 449 (M^+). Exact mass determination: 449.1606 (calcd $C_{326}H_{28}NO_2PS$: 449.1579).

(*Rs*,*S*)-**13Ab**: 10% yield. $[\alpha]_D$ +41 (*c*=2.7, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1620 (amide), 1589 (aromatic), 1017 (SO). NMR (270 MHz; $CDCl_3$) δ: 1.69–2.28 (m, 4H, $(CH_2)_2$), 2.19–2.28 (m, 1H, CH), 2.97 (dt, *J*=13.7, 3.5 Hz, 1H, CH), 3.23–3.43 (m, 2H, CH_2), 4.08 (d, *J*=12.9 Hz, 1H, CH), 4.47–4.52 (m, 1H, CH),

4.55 (d, *J*=12.9 Hz, 1H, CH), 7.05–7.70 (m, 19H, aromatic). *m/z*: 512 (M^++1). Exact mass determination: 511.1779 (calcd $C_{31}H_{30}NO_2PS$: 511.1735).

(*Ss*,*S*)-**13Bb**: 11% yield. $[\alpha]_D$ −235 (*c*=1.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1620 (amide), 1590 (aromatic), 1015 (SO). NMR (270 MHz; $CDCl_3$) δ: 1.76–2.28 (m, 6H, 3×CH_2), 3.23–3.32 (m, 2H, CH_2), 3.97 (d, *J*=12.9 Hz, 1H, CH), 4.26–4.39 (m, 1H, CH), 4.44 (d, *J*=12.9 Hz, 1H, CH), 7.13–7.48 (m, 17H, aromatic), 7.65–7.78 (m, 2H, aromatic). *m/z*: 512 (M^++1). Exact mass determination: 511.1750 (calcd $C_{31}H_{30}NO_2PS$: 511.1735).

(*Rs*,*S*)-**13Ac**: 12% yield. $[\alpha]_D$ +35 (*c*=1.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1618 (amide), 1590 (aromatic), 1017 (SO). NMR (270 MHz; $CDCl_3$) δ: 1.70–2.27 (m, 4H, $(CH_2)_2$), 2.36–2.44 (m, 1H, CH), 4.73 (m, 1H, CH), 2.95–3.07 (m, 1H, CH), 4.46 (d, *J*=12.9 Hz, 1H, CH), 4.55–4.65 (m, 1H, CH), 7.10–7.58 (m, 13H, aromatic), 7.63–7.81 (m, 8H, aromatic). *m/z*: 562 (M^++1). Exact mass determination: 561.1893 (calcd $C_{35}H_{32}NO_2PS$: 561.1891).

(*Ss*,*S*)-**13Bc**: 10% yield. $[\alpha]_D$ −165 (*c*=1.5, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1620 (amide), 1590 (aromatic), 1015 (SO). NMR (270 MHz; $CDCl_3$) δ: 1.75–2.27 (m, 6H, 3×CH_2), 3.28–3.33 (m, 2H, CH_2), 4.39–4.48 (m, 1H, CH), 4.41 (d, *J*=12.9 Hz, 1H, CH), 4.63 (d, *J*=12.9 Hz, 1H, CH), 7.07–7.81 (m, 21H, aromatic). *m/z*: 562 (M^++1). Exact mass determination: 561.1895 (calcd $C_{35}H_{32}NO_2PS$: 561.1891).

(*S*)-**15a**: 48% yield. $[\alpha]_D$ −129 (*c*=1.9, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1622 (amide), 1578 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.84–2.24 (m, 4H, $(CH_2)_2$), 3.06–3.52 (m, 4H, 2×CH_2), 4.38–4.44 (m, 1H, CH), 6.80–6.90 (m, 1H, ArH), 7.08–7.54 (m, 17H, ArH), 7.64–7.68 (m, 2H, ArH). *m/z*: 529 (M^+). Exact mass determination: 529.1026 (calcd $C_{30}H_{28}NOPSe$: 529.1074).

(*S*)-**15b**: 20% yield. $[\alpha]_D$ −125 (*c*=1.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1622 (amide), 1578 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.62–1.70 (m, 2H, CH_2), 1.82–2.24 (m, 2H, CH_2), 2.91–3.09 (m, 2H, CH_2), 3.61–3.82 (m, 2H, CH_2), 4.04, 4.14 (ss, 2H, CH_2), 4.37–4.41 (m, 1H, CH), 6.77–6.83 (m, 1H, ArH), 7.06–7.56 (m, 16H, ArH), 7.69–7.75 (m, 2H, ArH). *m/z*: 544 (M^++1). Exact mass determination: 543.1202 (calcd $C_{31}H_{30}NOPSe$: 543.1230).

(*S*)-**16**: 23% yield. $[\alpha]_D$ −152 (*c*=1.3, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1624 (amide), 1587 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.82–2.21 (m, 4H, $(CH_2)_2$), 3.21–3.29 (m, 2H, CH_2), 3.46–3.89 (m, 2H, CH_2), 4.36–4.39 (m, 1H, CH), 7.11–7.44 (m, 10H, ArH), 7.67–7.82 (m, 3H, ArH), 8.55–8.58 (m, 1H, ArH). *m/z*: 375 (M^++1). Exact mass determination: 374.1580 (calcd $C_{23}H_{23}N_2OP$: 374.1548).

(*S*)-**17**: 89% yield. $[\alpha]_D$ −47 (*c*=4.6, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1624 (amide), 1580 (aromatic). NMR (270 MHz; $CDCl_3$) δ: 1.68–2.13 (m, 5H, CH, $(CH_2)_2$), 3.12–2.52 (m, 1H, CH), 3.66–3.81 (m, 3H, CH, CH_2), 4.35–4.40 (m, 1H, CH), 7.01–7.03 (m, 1H, ArH), 7.25–7.44 (m, 1H, ArH), 7.58–7.67 (m, 2H, ArH). *m/z*: 380 (M^++1). Exact mass determination: 379.1123 (calcd $C_{22}H_{22}NOPS$: 379.1160).

*3.4. Palladium-catalyzed asymmetric nucleophilic substitution reactions of 1,3-diphenyl-2-propenyl acetate **18** with chiral sulfoxide ligands*

3.4.1. General procedure A

A 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar, and containing sodium hydride (50% oil dispersion, 18 mg, 0.38 mmol), was flushed with argon, and maintained under a positive pressure of argon. A solution of dimethyl malonate (84 mg, 0.63 mmol) in THF (3 ml) was added at 0°C to the above flask. Another 25 ml two-necked flask equipped with a septum inlet and a magnetic stirring bar, and containing di-μ-chlorobis(π-allyl)dipalladium ($[PdCl(CH_2{=}CHCH_2)]_2$) (7 mg, 0.02 mmol) and chiral sulfoxide ligands (0.04 mmol), was flushed with argon, and maintained under a positive pressure of argon. A solution of (±)-1,3-diphenyl-2-propenyl acetate **18** (80 mg, 0.32 mmol) in THF (3 ml) was added at room temperature to the above solution, and the mixture was stirred at room temperature

for 30 min. The solution was added to the above solution including sodium dimethyl malonate, and the reaction mixture was stirred under the conditions listed in Table 1. The reaction solution was then diluted with ether, and the solution 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 optically active diethyl (1,3-diphenyl-2-propenyl) propanedioate **19**.[14] The e.e. and the absolute configuration of the product were determined by HPLC analysis with a chiral column, Chiralpak AD (hexane:*i*-propanol, 20:1).[14] The results obtained are listed in Table 1.

3.4.2. General procedure B

A solution of chiral sulfoxide ligands (0.04 mmol) and $[PdCl(CH_2{=}CHCH_2)]_2$ (7 mg, 0.02 mmol) in CH_2Cl_2 (2 ml) was stirred under argon for 30 min, and then a solution of (±)-**18** (80 mg, 0.32 mmol) in THF (1 ml), dimethyl malonate (84 mg, 0.63 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[15] (0.3 ml, 1.19 mmol), and a catalytic amount of anhydrous sodium acetate was added to the above solution. The reaction mixture was stirred at −20°C to room temperature for 1–92 h. The reaction mixture was then diluted with ether. The organic layer was washed with 10% aqueous sodium hydroxide 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 **19**.[14] The results obtained are listed in Table 2.

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