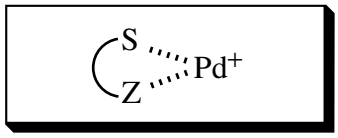

II.2.4 Pd(0) and Pd(II) Complexes Containing Sulfur and Selenium Ligands

KUNIO HIROI

A. INTRODUCTION

The reactivity of π-allylpalladium complexes is dependent on the nature of the ligands coordinated to them. In general, strongly π-accepting ligands such as phosphines generate highly reactive palladium complexes, whereas electron-donating ligands such as amines provide less reactive species.

Various types of chiral ligands incorporating organosulfur groups and other different donor atoms have been designed, in which only one of the donor atoms could behave as a π-acceptor. So it should be desirable in asymmetric synthesis that a catalyst involving a chiral ligand enables one to discriminate two allyl termini, since a nucleophile would preferentially attack the allyl terminus *trans* to the better π-acceptor. Therefore, it should be very useful for the prediction of the stereochemistry of the product in Pd-catalyzed asymmetric reactions with ligands to determine the order of preference of the electronic property for the π-acceptor of various coordinatable elements, particularly sulfur atoms, in the ligands.

With chiral sulfoxides as ligands, there are two possibilities in the formation of chelates with palladium: chelates by coordination of sulfinyl sulfur and oxygen atoms (**Scheme 1**).

B. CHIRAL LIGANDS CONTAINING SULFENYL GROUPS

B.i. Oxazoline Ligands

Enantiomerically pure ligands containing a 4,5-dihydrooxazole moiety tethered to an auxiliary sulfur donor have been developed, providing enantioselectivities of 40–96%[1] (**Scheme 2**).

The reaction of **1** with dimethyl sodiomalonate in THF at reflux in the presence of catalytic amounts of [Pd(π-allyl)Cl]$_2$ and the ligands **3**,[2,3] **4**,[4] and **5**[4–6] afforded the substitution product (*S*)-**2**. The enantioselectivity is summarized in **Table 1**.

Use of 4,5-dihydrooxazoles **6a** and **6b** in the above reaction provided (*R*)-**2** with 56% and 88% ee, respectively.[4]

Chiral phenylsulfenyl derivatives of ferrocenyl-oxazoline were used as chiral ligands in the Pd-catalyzed alkylation of **1**. The highest ee (98%) of (*R*)-**2** was obtained with **7** as a ligand[7] (**Scheme 3**).

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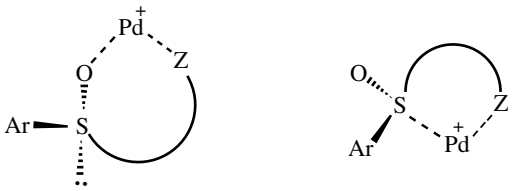
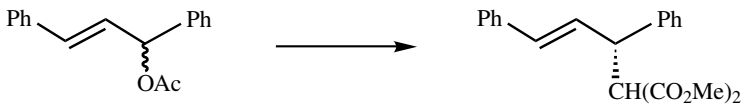
TABLE 1. Palladium-Catalyzed Asymmetric Alkylations of 1[a]

Ligand	R^1	R^2	Solvent	Pd:L	Yield of **2**	ee (%) of (*S*)-**2**
3a	Me	Ph	THF	1:2	56	6
3b	CH_2Ph	H	THF	1:2	68	24
3c	Pr^i	H	THF	1:10	89	81
3d	Ph	H	THF	1:2	Trace	—
3e	Bu^t	H	THF	1:2	Trace	—
3f	CH_2OH	Ph	THF	1:2	65	5
3g	CH_2OCPh_3	Ph	THF	1:2	Trace	—
4a	Me	Me	THF	1:2	68	51
4b	CH_2Ph	Me	THF	1:2	56	40
4c	Pr^i	Me	THF	1:2	74	70
4d	Ph	Me	THF	1:2	67	60
4e	Bu^t	Me	THF	1:4	69	75
4f	Pr^i	Ph	CH_2Cl_2	1:2	52	76
4g	Bu^t	Ph	THF	1:2	0	—
5a	Me	Me	THF	1:2	91	40
5b	CH_2Ph	Me	THF	1:2	90	52
5c	Pr^i	Me	THF	1:2	98	58
5d	Ph	Me	THF	1:2	84	66
5e	Bu^t	Me	THF	1:2	86	80
5f	Pr^i	Ph	CH_2Cl_2	1:2	96	90
5g	Bu^t	Ph	CH_2CL_2	1:2	92	96

[a]The reactions of **1** with dimethyl sodiomalonate were carried out in the presence of a catalytic amount of $[Pd(\pi\text{-allyl})Cl]_2$ and ligands **3**–**5**.



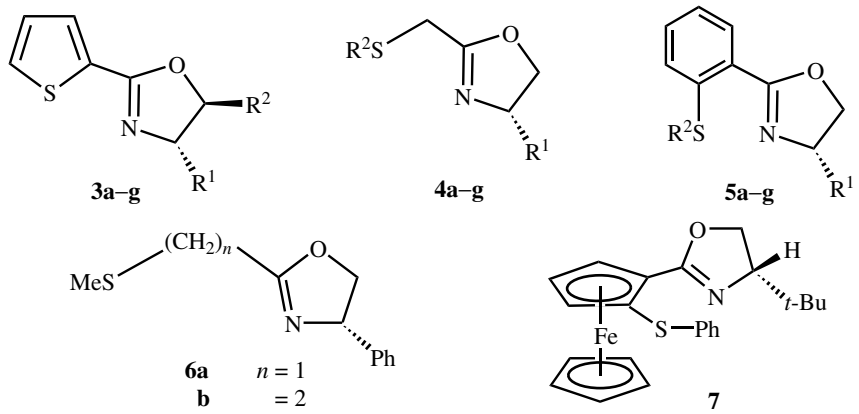
Scheme 1



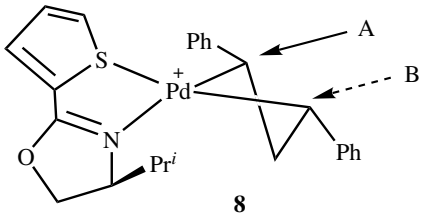
1 (*S*)-**2**

Scheme 2

The thiophene ligand as an electron-rich π-system acts as a donor and, as a result of the *trans* effect, should transfer electron density to the allylic carbon atom *trans* to the sulfur atom. The carbon atom should less willingly undergo nucleophilic attack because of the increased electron density. Thus, the favorable attack occurs by route A to give (*S*)-**2**[2,3] (**Scheme 4**).

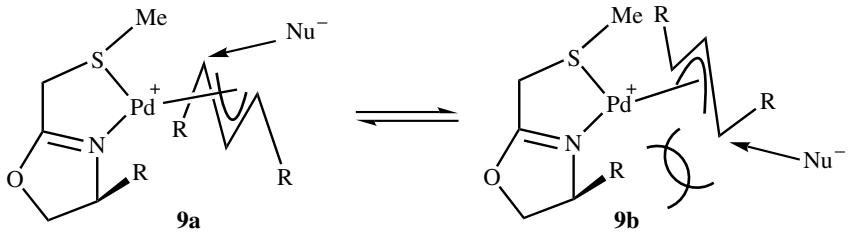


Scheme 3



Scheme 4

Comparatively, with the methylthio ligands, the reaction may occur selectively through complex **9a** and the nucleophile approaches *cis* to the better π-acceptor. Alternatively, the reaction proceeds selectively through complex **9b** and the nucleophile approaches *trans* to the better π-acceptor. Either the transition state is more distorted than represented here, or the two diastereomeric allyl complexes are in rapid equilibrium, and the reaction proceeds through the less favored, but possibly more reactive, intermediate **9b**[5] (**Scheme 5**).

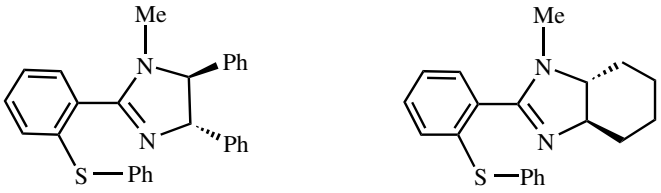


Scheme 5

B.ii. Amidine Ligands

Chiral amidine ligands bearing sulfenyl groups have been developed.[8] In these cases, more electron-rich imino groups (amidines) improve the enantioselectivity and the catalytic activity in Pd-catalyzed allylic substitution in comparison with oxazolines.

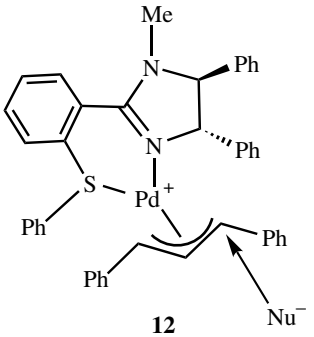
Asymmetric allylic substitution of **1** with dimethyl malonate was carried out in the presence of [Pd(π-allyl)Cl]2 (0.5–2.5 mol %), thioimidazolines **10** or **11** (2–10 mol %), and a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of LiOAc in dichloromethane, affording (*S*)-**2** or (*R*)-**2** with 93–96% or 48% ee, respectively (**Scheme 6**).



10 **11**

Scheme 6

The reaction probably proceeds through an M-type intermediate **12**. Nucleophilic attack occurs predominantly at the allyl terminus *trans* to the better π-acceptor (S >> N of imidazoline) (**Scheme 7**).



12

Scheme 7

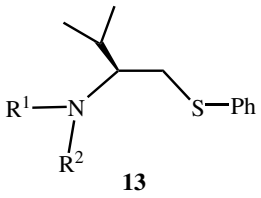
B.iii. Imine Ligands

Amino sulfides **13** were inactive, but transformation of the amino function into an imine produced ligands that made good chiral catalysts with palladium, since amine ligands afford palladium complexes of low reactivity compared to ligands containing π-accepting donor groups.

Chiral sulfur–imine ligands **14a**–**g**[9], prepared from commercially available (*S*)-valinol, have been shown to give up to 94% ee in a Pd-catalyzed allylic substitution of **1** (**Scheme 8**).

The reactions of **1** with dimethyl malonate were carried out in the presence of [Pd(π-allyl)Cl]2, **14a**–**g**, BSA, and KOAc, affording (*R*)-**2** with 82–94% ee. The *i*-propyl group on the backbone of the chelate ring can dictate the chirality at the sulfur center upon coordination.

The allylic substitutions proceed through the intermediate **15a**, which is the major diastereomer at equilibrium, affording (*R*)-**2** (**Scheme 9**).



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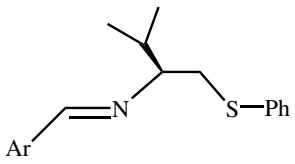
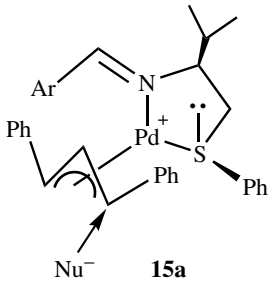


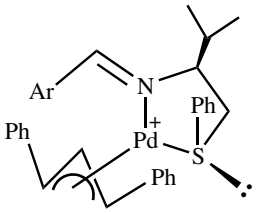
14a–g

a Ar = Ph
b = *p*-$NO_2C_6H_4$
c = *p*-$MeOC_6H_4$
d = 2,4,6-$Me_3C_6H_2$
e = 9-anthryl
f = *o*-ClC_6H_4
g = *p*-ClC_6H_4

Scheme 8



15a

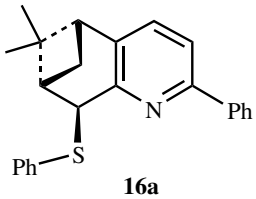


15b

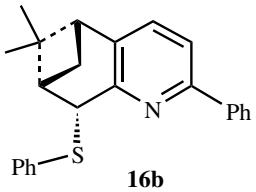
Scheme 9

B.iv. Pyridine Ligands

The sulfur-containing pyridine ligands have been prepared starting from (+)-pinocarvone.[10] The allylic alkylations of **1** with dimethyl malonate using these ligands **16a**,**b** were carried out in the presence of [Pd(π-allyl)Cl]2, BSA, and KOAc, affording (*R*)- or (*S*)-**2** with 83% or 78% ee, respectively (**Scheme 10**).



16a

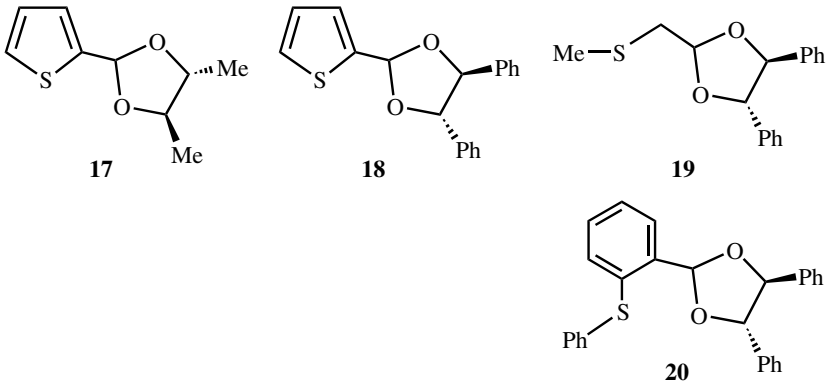


16b

Scheme 10

B.v. Acetal Ligands

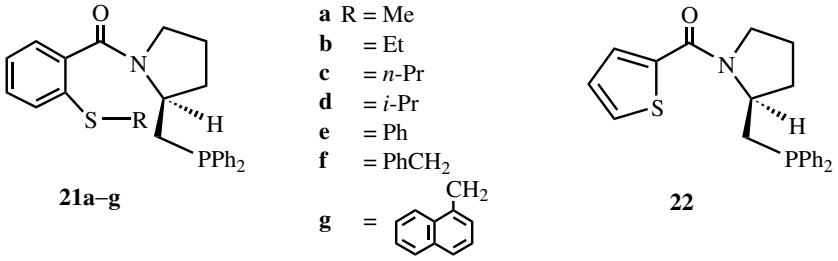
Sulfur-containing chiral acetals derived from C_2-symmetric diols have been developed.[11] Ligands **17**–**20** in which the acetals are tethered to an auxiliary donor atom (sulfur) have afforded (*S*)-**2** with <5%, 60%, 50%, or 82% ee, respectively, in the Pd-catalyzed allylic substitution reactions of **1** with dimethyl malonate using [Pd(π-allyl)Cl]2, BSA, and KOAc in dichloromethane at room temperature (**Scheme 11**).



Scheme 11

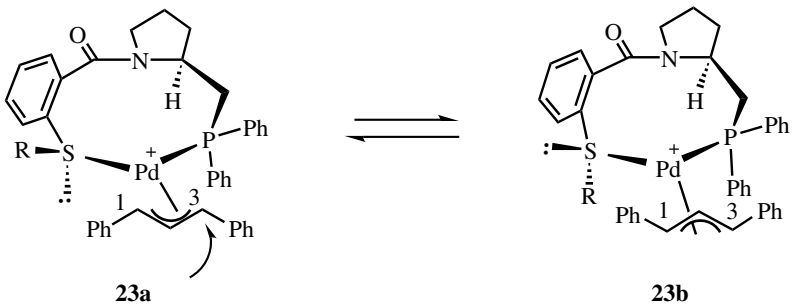
B.vi. (*S*)-Proline-Derived Phosphine Ligands

(*S*)-Proline-derived phosphines bearing various sulfenyl substituents have been developed.[12] Use of **21a**–**g** as chiral ligands provided (*S*)-**2**, except **21e** [(*R*)-**2**], with 31–88% ee in the Pd-catalyzed allylic alkylation of **1** with dimethyl malonate using [Pd(π-allyl)Cl]$_2$, BSA, and AcONa in dichloromethane at room temperature. Increasing the steric bulk of the substituents of the sulfenyl groups results in enhanced enantiocontrol (**21g**. provides 88% ee). The thiophene ligand **22** provides (*R*)-**2** with 30% ee (**Scheme 12**).



Scheme 12

Alkylthio groups, except phenylthio and thiophene substituents, coordinate to palladium in the Pd-catalyzed asymmetric allylic alkylation, forming nine-membered chelates



Scheme 13

of palladium. An M-typed π-allylpalladium complex **23a** is preferred to a W-typed one **23b** and the nucleophile attacks the allyl terminus in **23a** *trans* to the better π-acceptor, which is the sulfenyl group at the current case, to furnish (*S*)-**2** (**Scheme 13**).

C. CHIRAL LIGANDS CONTAINING CHIRAL SULFINYL GROUPS

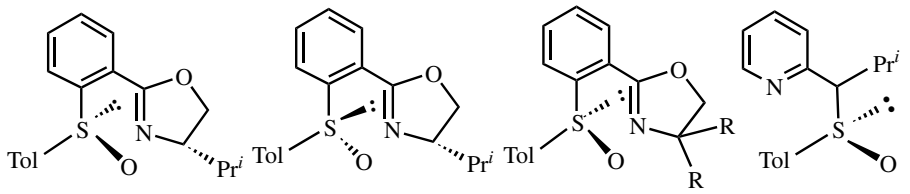
C.i. Chiral Sulfoxide Ligands Bearing Other Chiral Auxiliaries

Chiral sulfinyl functionality can be applied as another coordinating element in ligands in Pd-catalyzed reactions.

Chiral oxazoline ligands **24a**,**b**[13] bearing a chiral sulfinyl group provided enantioselectivity of (*S*)-**2** with 88% or 55% ee, respectively, in the Pd-catalyzed alkylation of **1** with dimethyl malonate using [Pd(π-allyl)Cl]2, BSA, and KOAc in dichloromethane at −20 °C.

The usefulness of chirality of sulfoxide as a sole chiral source was demonstrated. Use of chiral sulfoxides **25a**,**b** afforded (*S*)-**2** with 56% and 49% ee, respectively.

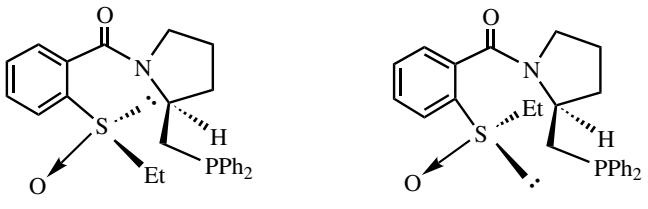
A chiral sulfoxide ligand (−)-**26**[14] bearing a pyridinyl group provided (*S*)-**2** with 34% ee. The stereochemistry of the stereogenic carbon center in (−)-**26** was unknown (**Scheme 14**).



24a **24b** **25a** **b** **26**

Scheme 14

(*S*)-Proline-derived phosphines **27a**,**b**[12] bearing chiral sulfinyl groups were used as chiral ligands in Pd-catalyzed allylic alkylations of **1** with dimethyl malonate using $[Pd(\pi\text{-allyl})Cl]_2$, BSA, and AcONa, affording (*S*)-**2** with 60% and 33% ee, respectively (**Scheme 15**).



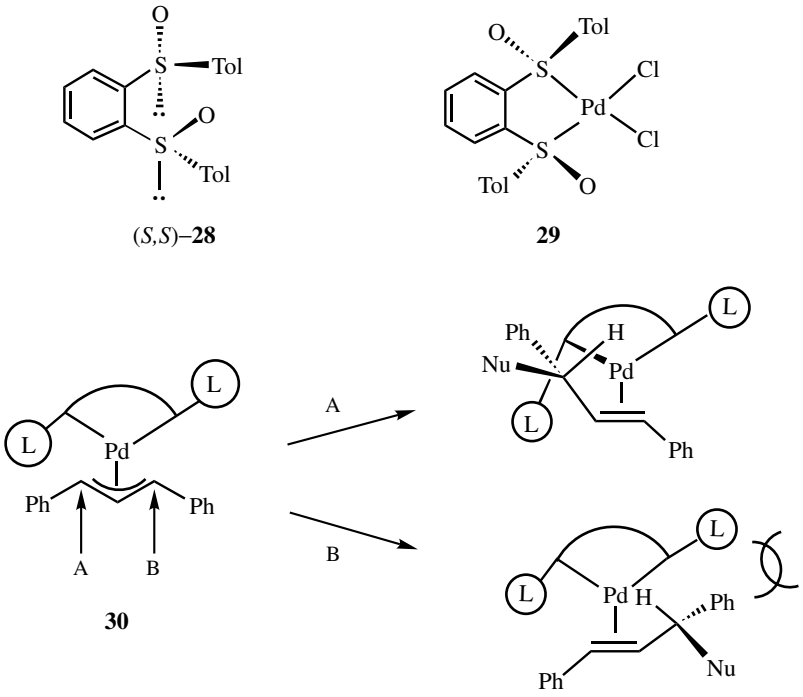
27a **27b**

Scheme 15

C.ii. Ligands Bearing Sulfinyl Groups as Sole Chiral Sources

A chiral bis-sulfoxide ligand **28** has been developed as a new ligand bearing a sulfinyl group as a sole chiral source.[15]

The structure of a palladium complex derived from **28** was determined as a C_2-symmetric five-membered chelate **29** by coordination of the sulfinyl sulfur atoms by the X-ray crystallographic analysis. The allylic alkylations of **1** with dimethyl malonate were carried out in dichloromethane at 25 °C in the presence of [Pd(π-allyl)Cl]$_2$, (*S,S*)-**28**, BSA, and AcONa, affording (*S*)-**2** with 64% ee. The nucleophile attacks the allyl terminus at position A in **30** to avoid the steric interaction between the phenyl group and a large substituent L (**Scheme 16**).

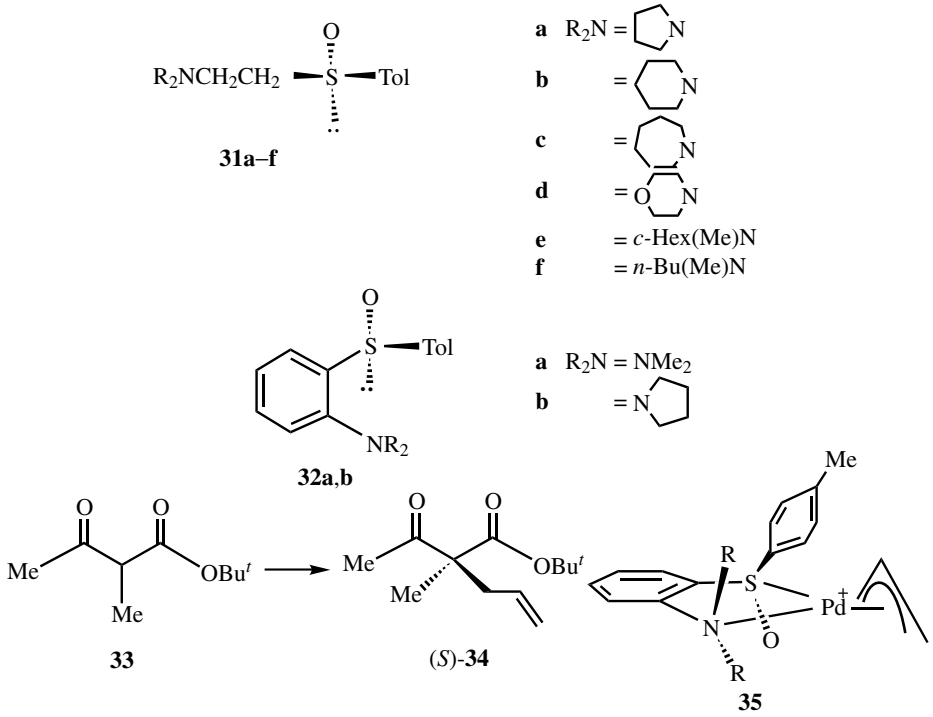


Scheme 16

Chiral β-amino sulfoxides served as chiral ligands in Pd-catalyzed allylations.[16],[17] Chiral β-aminoethyl sulfoxides **31a–f**-palladium complexes catalyzed asymmetric allylations of **33** to give (*S*)-**34** with 29% ee. *o*-Aminophenyl sulfoxides **32a**,**b** provided much higher enantioselectivity (50%), presumably due to the sterically fixed structure of the intermediary palladium complex **35** (**Scheme 17**).

A new chiral *o*-(phosphinoamino)phenyl sulfoxide has been demonstrated as an efficient ligand in the Pd-catalyzed asymmetric allylic alkylations of **1** with dimethyl sodiomalonate using [Pd(π-allyl)Cl]$_2$, affording (*S*)-**2** [45% ee with (*S*)-**36a**].[18]

In particular, (*R*)-*o*-(phosphinoamino)phenyl 2-methoxy-1-naphthyl sulfoxide (**36b**) provides the highest enantioselectivity (97%) of (*R*)-**2** among the known ligands bearing a chiral organosulfur group as a sole chiral source.



Scheme 17

Since the steric crowd by the large naphthyl group disturbs the alkylation at the allylic site *trans* to the phosphorus group in the sterically preferred **37a** in the equilibrium of **37a**,**b**, the preferential alkylation at the allylic site *syn* to the phosphorus group in **37a** gave (*R*)-**2** (**Scheme 18**).

The first attempt to use chiral β-phosphino sulfoxides as chiral ligands was successfully accomplished in Pd-catalyzed asymmetric allylic alkylations and aminations.[19]

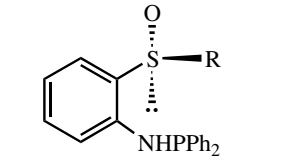
Chiral β-phosphinoethyl *p*-tolyl sulfoxide (**38**) undergoes a rapid internal redox reaction between the sulfinyl and the phosphino group. On the other hand, an aromatic phosphino sulfoxide is much more stable; a chiral sulfoxide **39a** is recovered without any racemization even though at a much higher temperature (130–140 °C).

2-Methoxy-1-naphthyl sulfoxide **39b** is stable in THF at room temperature; however, it undergoes a gradual internal redox reaction in THF at reflux, generating the corresponding phosphine oxide, presumably due to the stereoelectronic effect of the 2-methoxy-1-naphthyl substituent (**Scheme 19**).

The Pd-catalyzed allylic alkylation or amination of **1** with dimethyl sodiomalonate or benzylamine using $[Pd(\pi\text{-allyl})Cl]_2$ provided (*S*)-**2** or (*R*)-**40** with 82% or 85% ee, respectively.

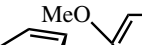
The structure of a palladium complex derived from **39b** and $PdCl_2$ was determined as a five-membered chelate **41** coordinated by the sulfinyl sulfur and phosphorus groups by X-ray crystallographic analysis.

In the conformational equilibrium of the five-membered chelated π-allylpalladium complex, a conformer **42b** is preferred to **42a** by the steric reason. The nucleophile

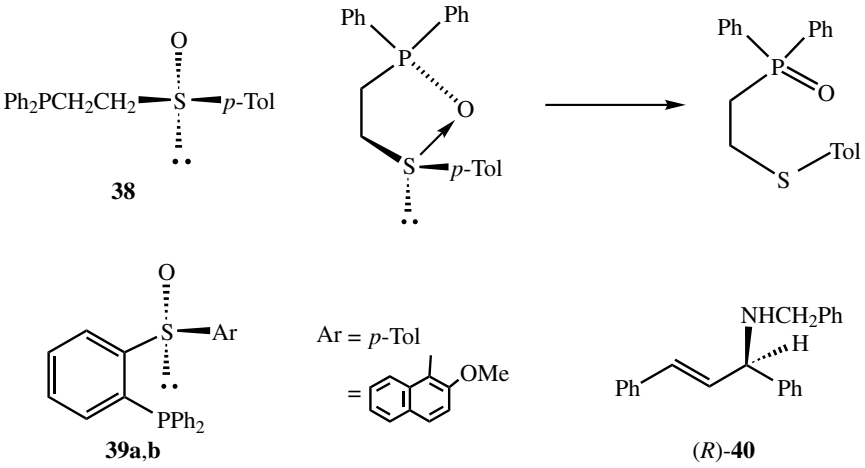


(*S*)-**36a** R = *p*-MeC_6H_4

(*R*)-**36b** =



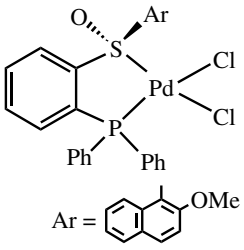
Scheme 18



Scheme 19

attacks preferentially the allyl terminus in **42b** *trans* to the better π-acceptor, which is the phosphine group in the present case, despite the steric effect by the bulky substituent (**Scheme 20**).

A chiral sulfoxide–palladium complex was determined as a chelate coordinated by the sulfinyl oxygen atom by X-ray crystallographic analysis.[20] The amino-phosphine palladium chloride **43** was transformed into **44** by chloride abstraction with $AgPF_6$. The six-membered P—O chelate structure was confirmed by crystallographic analysis (**Scheme 21**).



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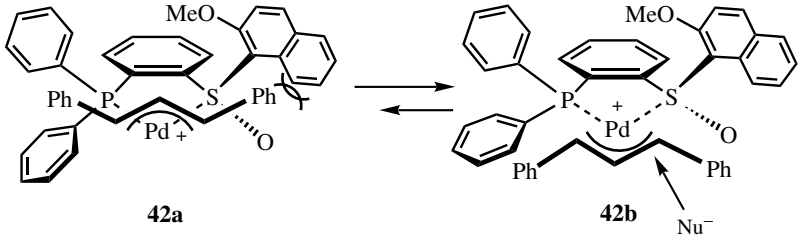
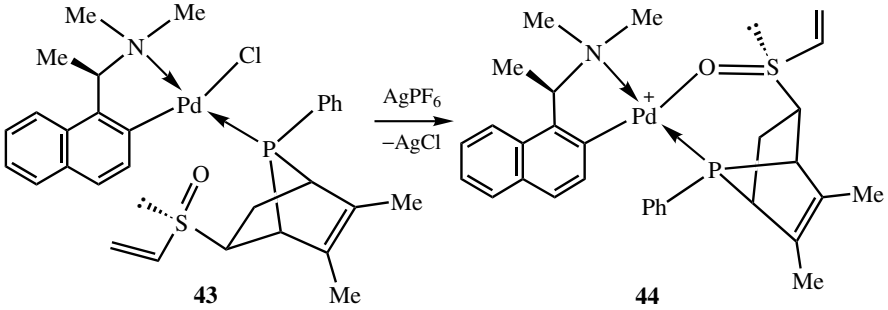


42a **42b**

Scheme 20



43 **44**

Scheme 21

D. CHIRAL LIGANDS CONTAINING CHIRAL SULFOXIMINE GROUPS

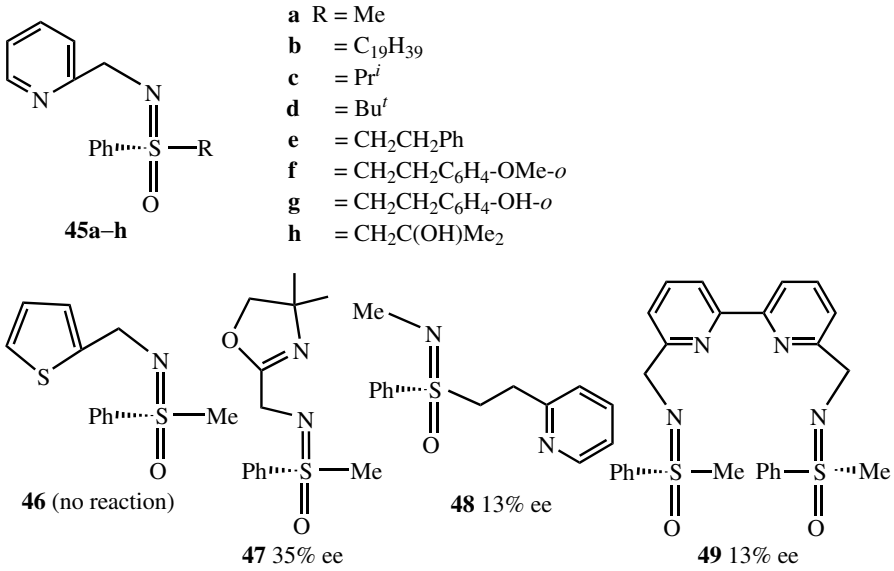
Chiral sulfoximine–palladium complexes catalyzed enantioselective allylic alkylation with moderate enantioselectivities.[21] The allylic alkylations of **1** with dimethyl malonate were carried out in dichloromethane at room temperature in the presence of $[Pd(\pi\text{-allyl})Cl]_2$ (2 mol %), BSA (3 equiv), chiral ligands **45a**–**h** (5 mol %), and AcOK, affording (*S*)-**2** with 20–73% ee.

The allylic alkylations using other chiral sulfoximines **46**–**49** provided much lower enantioselectivity (**Scheme 22**).

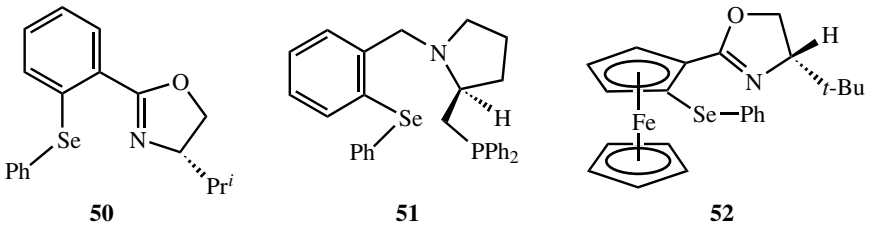
E. LIGANDS BEARING SELENENYL GROUPS

Few reports have been published so far related to chiral ligands bearing selenenyl groups. Selenenyl group-containing chiral ligands **50**[6], **51**[16], and **52**[22] provided 95%, 79%, and

98–99% enantioselectivity of (*S*)- and (*R*)-**2**, respectively, in the Pd-catalyzed allylic alkylations of **1** with dimethyl malonate using $[Pd(\pi\text{-allyl})Cl]_2$ and BSA-AcOLi or NaH (**Scheme 23**).



Scheme 22



Scheme 23

F. SUMMARY

Organosulfur functionalities, such as sulfenyl and sulfinyl groups, can serve as coordinating elements in ligands in Pd-catalyzed reactions, and normally they function as good π-acceptors.

Among chiral ligands known to contain sulfenyl groups, high enantioselectivity was obtained with chiral oxazoline, amidine, and imine ligands.

Sulfinyl functionality serves as a slightly weaker coordinating element compared with sulfenyl function. Chiral sulfoxide ligands provide rather good enantioselectivity in Pd-catalyzed allylic alkylations. (*R*)-*o*-(Diphenylphosphinoamino)phenyl 2-methoxy-1-naphthyl sulfoxide provided the highest enantioselectivity (97%) among known chiral sulfoxide ligands.

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