(*S*)-PROLINE-DERIVED CHIRAL LIGANDS BEARING ORGANOSULFUR OR -SELENENYL GROUPS AS COORDINATING ELEMENTS IN PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATIONS

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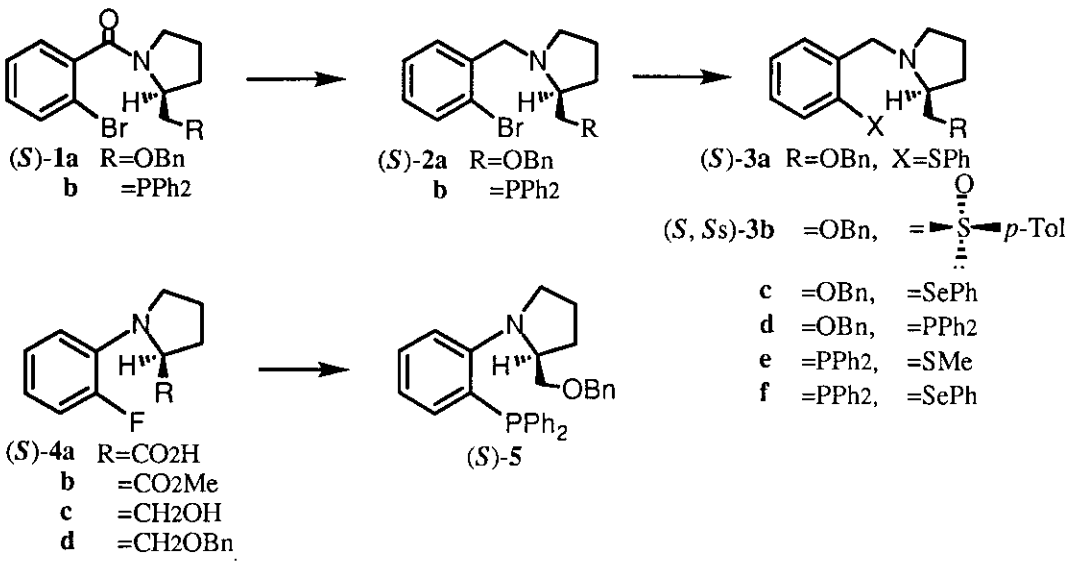
Abstract —(*S*)-Proline-derived chiral ligands bearing organosulfur or -selenenyl groups as coordinating elements were synthesized, and applied to palladium-catalyzed asymmetric allylic alkylations. These heteroatoms in the ligands played a prominent role for the stereocontrol of the conformation of the intermediary palladium complexes, and resultingly for the presentation of the high asymmetric induction in the asymmetric alkylations. The mechanism of the asymmetric synthesis using these ligands is rationalized on the basis of the stereochemical outcome observed.

Catalytic asymmetric synthesis has received much attention,[1] especially in the pharmaceutical field, as one of the synthetically most useful tools for the preparation of optically active compounds, and particularly for the practical synthesis of biologically active chiral compounds. Our recent interest has been focused on catalytic asymmetric synthesis using chiral organosulfur compounds stoichiometrically or catalytically as sole chiral sources.[2,3]

Continuing our studies on the asymmetric synthesis with organosulfur groups[4] and the stereochemical issues related to transition metal-catalyzed reactions, we report herein examples of asymmetric synthesis with (*S*)-proline-derived new chiral ligands bearing organosulfur or organoselenenyl groups in palladium-catalyzed allylic alkylations by exploiting chelate formation with the sulfur[5] or selenenyl[6] function as a stereocontrolling element.

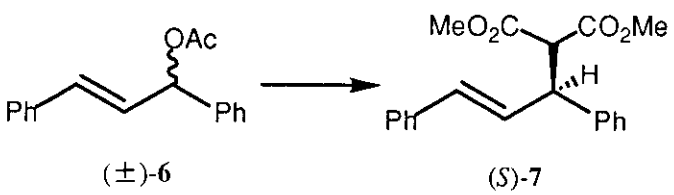
(*S*)-Proline-derived chiral ligands bearing heteroatoms as coordinating functions such as sulfur, selene, and phosphine groups were obtained as follows. (*S*)-*N*-(2-Bromobenzoyl)proline derivatives (**1a,b**) were reduced with BH_3 · THF followed by sulfenylation (with diphenyl disulfide, using *n*-BuLi in THF at 0 ℃ for 24 h), sulfinylation (with (-)-menthyl (*S*)-*p*-toluenesulfinate, using *n*-BuLi in THF at 0 ℃ for 24 h),



Scheme 1

selenenylation (with diphenyl diselenide, using *n*-BuLi in THF at 0 ℃ for 24 h), phosphinylation (with potassium diphenylphosphatide in THF at 50 ℃ for 1h) of (*S*)-**2a**, or sulfenylation (with dimethyl disulfide) or selenenylation (with diphenyl diselenide) of (*S*)-**2b**, producing (*S*)-**3a-d** or (*S*)-**3e,f**, respectively. A chiral phosphine ligand (*S*)-**5** was prepared by the palladium-cupper-catalyzed coupling reaction[7] of (*S*)-proline with 2-fluoro-1-iodobenzene followed by the esterification of the carboxylic acid ((*S*)-**4a**), the reduction of the ester in (*S*)-**4b** with $LiAlH_4$, the benzylation of the hydroxy group in (*S*)-**4c**, and the phosphinylation of (*S*)-**4d**.

Initially, the asymmetric alkylation of (±)-1,3-diphenyl-2-propenyl acetate (**6**) with dimethyl malonate sodium enolate (generated by treating with NaH) using (*S*)-2-(benzyloxymethyl)pyrrolidine derivatives ((*S*)-**3a-d**) and ((*S*)-**5**) (0.12 equiv.) as chiral ligands was 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 ℃, room temperature, or 50 ℃ to give (*S*)-**7**.[8] The e.e. of the product (**7**) was calculated by HPLC analysis with Chiralpak AD.[8] The results obtained are summarized in Table 1.



Scheme 2

Table 1. Palladium-Catalyzed Asymmetric Allylic Alkylation of (±)-**6** with Dimethyl Malonate Using Chiral Ligands ((*S*)-**3a-f** and (*S*)-**5**)[a]

Ligands	Catalyst	Solvent	Reaction temp.(°C)	Reaction time (h)	Yield (%) of **7**	e.e. (%) of **7**[b]
(*S*)-**3a**	$[PdCl(\pi\text{-allyl})]_2$	THF	rt	60	14	27 (*S*)
	$Pd(OAc)_2$	THF	rt	36	31	36 (*S*)
	$Pd(dba)_2$	THF	rt	48	18	31 (*S*)
b	$Pd(OAc)_2$	THF	rt	60	13	—
c	$[PdCl(\pi\text{-allyl})]_2$	THF	rt	18	7	16 (*S*)
	$Pd(OAc)_2$	THF	rt	36	12	36 (*S*)
d	$Pd(OAc)_2$	THF	50	14	57	36 (*S*)
	$[PdCl(\pi\text{-allyl})]_2$	DME	rt	1	63	36 (*S*)
	$[PdCl(\pi\text{-allyl})]_2$	DME	0	44	58	22 (*S*)
	$[PdCl(\pi\text{-allyl})]_2$	THF	50	14	84	37 (*S*)
	$[PdCl(\pi\text{-allyl})]_2$	THF	rt	2	87	39 (*S*)
	$[PdCl(\pi\text{-allyl})]_2$	THF	0	44	63	25 (*S*)
e	$[PdCl(\pi\text{-allyl})]_2$	CH_2Cl_2	rt	2	73	75 (*R*)[c]
f	$[PdCl(\pi\text{-allyl})]_2$	CH_2Cl_2	rt	60	39	79 (*R*)[c]
(*S*)-**5**	$[PdCl(\pi\text{-allyl})]_2$	THF	rt	14	57	36 (*S*)

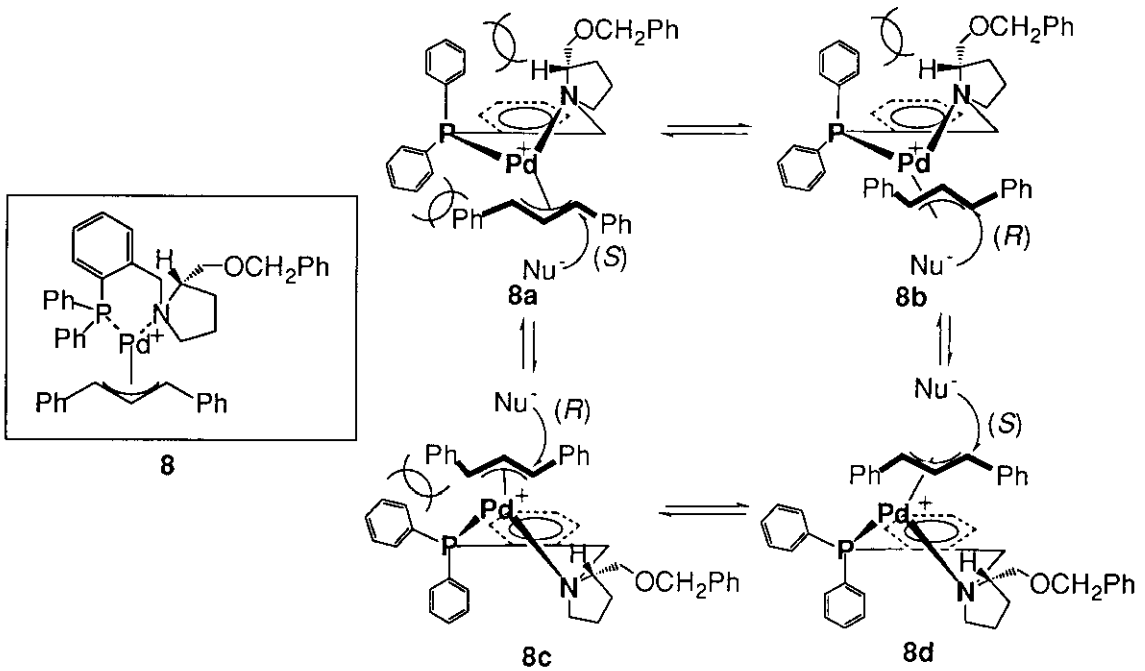
a) The reactions of **6** with carbanion of dimethyl malonate (generated by treating with NaH (1.2 equiv.)) were carried out in the presence of palladium catalyst (0.06 equiv.) and chiral ligands ((*S*)-**3a-d**) or ((*S*)-**5**) (0.12 equiv.).
b) The e.e. of **7** was calculated by HPLC analysis with Chiralpak AD.[8]
c) The reaction was carried out in the presence of BSA and a catalytic amount of NaOAc.[9]

The palladium-catalyzed reactions using (*S*)-**3a-c** provided low chemical yields of (*S*)-**7** with moderate enantiomeric excess (e.e.), whereas the reactions with the similar ligands ((*S*)-**3d**) and ((*S*)-**5**) bearing phosphinyl groups gave (*S*)-**7** in rather high chemical yields with the similar moderate e.e. It indicates that the phosphine groups in the ligands seem to play a prominent role for providing high chemical yields. Introduction of a chiral sulfinyl function in the aromatic nucleus in the place of the sulfenyl and the selenenyl groups in the ligands ((*S*)-**3a,c**) provided unexpectedly no asymmetric induction, presumably due to the unmatchedness of the two chirality involved in the ligand ((*S*, *S*s)-**3b**).

With (*S*)-proline-derived phosphine ligands ((*S*)-**3e,f**) bearing a sulfenyl or selenenyl function as another stereocontrolling element by coordination, rather high chemical yields and high e.e. of the product ((*R*)-**7**) were obtained as we expected. The reactions of (±)-**6** with dimethyl malonate using $[PdCl(\pi\text{-allyl})]_2$ (0.06 equiv.) and (*S*)-**3e,f** (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)[9] (3 equiv.) and a catalytic amount of NaOAc to give (*R*)-**7** in 73 or 39 % yield with 75 or 79 % e.e., respectively.

The mechanism for the asymmetric induction with these new ligands is rationalized on the basis of the stereochemical results obtained. The (*S*)-proline-derived phosphine ligand ((*S*)-**3d**) would provide a six-

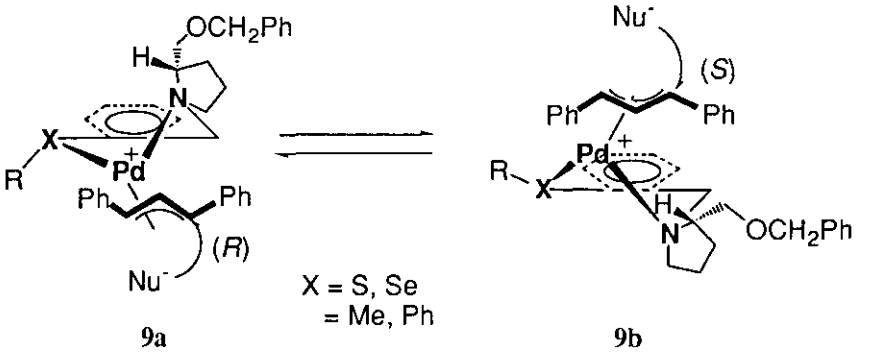
membered chelate (**8**) by the coordination of the rather more electrondonating phosphine and nitrogen groups to palladium catalysts. In the conformational equilibrium of four six-membered-chelated π-allylpalladium complexes (**8a-d**), the palladium complex (**8d**) would be preferably formed because of the existence of rather severe steric interference between the phenyl group on the phosphine and the benzyloxymethyl group in **8a** and **8b**, and between both the phenyl groups on the phosphine and at the allylic site in **8a** and **8c**. Therefore, the nucleophile (malonate anion) would attack to the allylic terminus *trans* to the better π-acceptor, which is the phosphine group[10] in the present case, from the back side of the palladium catalyst in the π-allyl system as desginated in **8d**, affording (*S*)-**7**.



scheme 3

In the conformational equilibrium of the intermediary six-membered-chelated π-allylpalladium complex (**9**) coordinated by the sulfenyl or selenenyl group and the amino group in the ligands ((*S*)-**3a,c**), **9b** is assumed to be a favorable isomer in preference to **9a** because of the steric interference between the substituent at the chiral center and the phenyl group at the allylic site in **9a**. Thus, the nucleophile (malonate anion) would attack to the allylic site *trans* to the better π-acceptor which is the sulfenyl or the selenenyl funcdon in the current case, affording (*S*)-**7**.

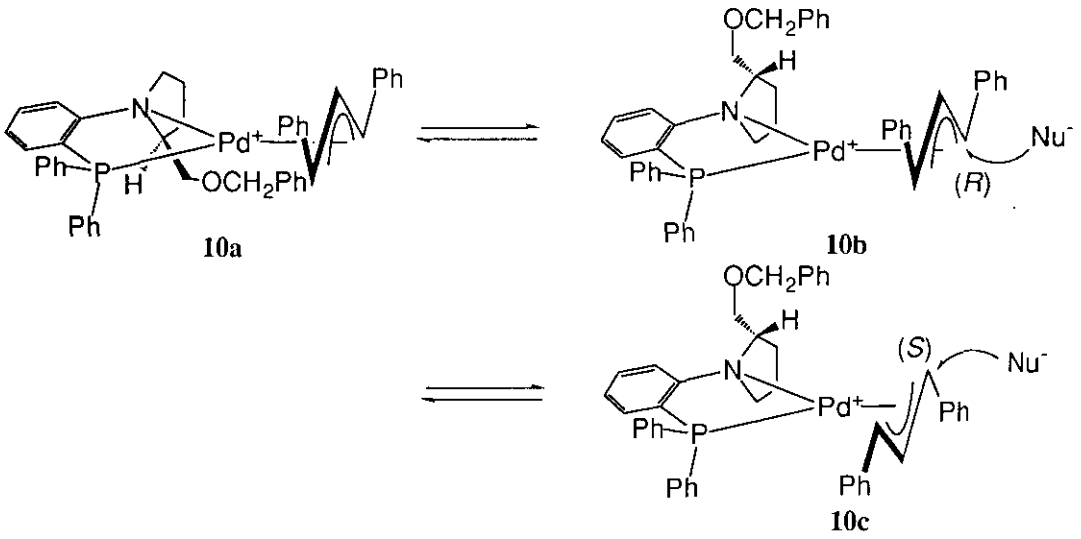
In the case of (*S*)-**5**, the five-membered-chelated π-allylpalladium complex (**10**) would be formed. The chelate (**10a**) has a steric hindrance, particularly, to the access of the nucleophile to the allylic site *trans* to



9a 9b

Scheme 4

the phosphine group. The chelate (**10c**) would be formed in preference to **10b**, due to the steric effect of the substituent at the chiral center on the allylic site in **10b**. Thus, the nucleophile would react at the allyl terminus *trans* to the phosphine group, giving (*S*)-**7**. Presumably, the small conformational energy difference between these isomers (**10a-c**) and the drop in basicity of the amino function arising from the adjacent aromatic ring led to the rather low optical yield of (*S*)-**7**.



Scheme 5

The mechanism for the asymmetric induction using (*S*)-**3e,f** is not clear at the present time, since they have three functional groups which are capable of serving as coordinating elements to palladium. We are now under progress for determing the precise mechanism of the asymmetric synthesis with these ligands.

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