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New Chiral *o*-(Phosphinoamido)phenyl Sulfoxide Ligands in Palladium-catalyzed Asymmetric Allylic Alkylations

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Abstract: A new chiral *o*-(phosphinoamido)phenyl sulfinyl functionality was demonstrated as efficient ligands in palladium-catalyzed asymmetric allylic alkylations. Especially, chiral *o*-(phosphinoamido)phenyl 2-methoxy-1-naphthyl sulfoxide was concluded to be the most effective ligand for the asymmetric induction among the known ligands bearing a chiral organosulfur group as the sole chiral source. The mechanism of the asymmetric induction is proposed.

Much attention has been devoted in the pharmaceutical field to catalytic asymmetric synthesis for the preparation of biologically active chiral compounds with complete optical purity and high efficiency,[1] and extensive efforts have been made for the development of new advantageous chiral ligands.[2]

We have taken much interest in catalytic asymmetric synthesis with chiral organosulfur compounds, since high enantioselectivity would be expected owing to the participation of the chiral organosulfur functionality[3] to catalysts. Hitherto, we have studied the palladium- or nickel-catalyzed asymmetric reactions[4] of several particular systems bearing a chiral organosulfur function as the sole chiral source.[5] Recently, we have made much effort to develop new chiral ligands bearing a chiral sulfinyl functionality,[6] since few reports have been published using an organosulfur functionality as ligands in catalytic asymmetric synthesis, especially a chiral organosulfur group as the sole chiral function.[7] We wish to demonstrate herein the use of new chiral *o*-(phosphinoamido)phenyl sulfoxide ligands in palladium-catalyzed asymmetric alkylations, and propose the mechanism of the asymmetric induction with these new chiral sulfinyl ligands.

Chiral sulfinyl compounds were readily prepared starting from 2-bromoaniline as follows. The reaction of 2-bromoaniline with chlorodiphenylphosphine was carried out in refluxing benzene in the presence of Et_3N to give *N*-(diphenylphosphino)-2-bromoaniline (**1**). The bromo compound **1** was treated with *n*-butyllithium and the carbanion generated was reacted with (-)-menthyl (*S*)-*p*-toluenesufinate (**2a**) or (*S*)-2-methoxy-1-naphthalenesulfinate (**2b**)[8] to give (*S*)-2-(diphenylphosphinoamido)phenyl *p*-tolyl sulfoxide (**3a**) or (*R*)-2-methoxy-1-naphthyl sulfoxide (**3b**) in good yields, respectively.

The palladium-catalyzed reactions of (±)-1,3-diphenyl-2-propenyl acetate (**4**) with dimethyl malonate sodium enolate were carried out in the presence of [PdCl(π-allyl)]2 (0.06 equiv.) and the chiral ligand (*S*)-**3a** (0.12 equiv.) in THF at room temperature to give (*S*)-**5** with 45% e.e. Use of other palladium catalysts such as $Pd(OAc)_2$, $Pd(dba)_2$, and $Pd_2(dba)_3 \cdot CHCl_3$ gave (*S*)-**5** with rather low e.e. (24, 31, and 39%, respectively).

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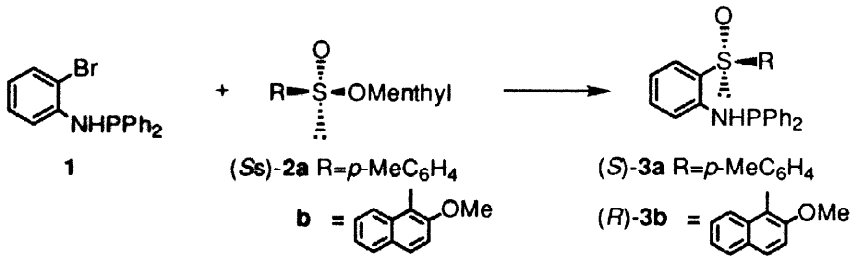
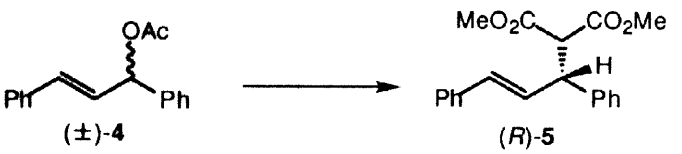


Scheme 1

The rather unequivocal solvent effects were observed in this catalytic reaction. The above reactions of (±)-**4** with sodium malonate catalyzed by [PdCl(π -allyl)]2 were carried out in DME, toluene, benzene, acetonitrile, or dimethyl sulfoxide to give (*S*)-**5** with 44, 28, 23, 19, or 8% e.e., respectively.



Scheme 2

Table 1. The Palladium-catalyzed Asymmetric Alkylation of **4** with (*S*)-**3b**[a)]

Solvent	Ratio of Pd/ligand	Reaction temp. (°C)	Reaction time (h)	Yield (%)[b)] of **5**	e.e.(%) of **5**[c)] (Abs. config.)
THF	1: 1	0	110	26 (59)	67 (*R*)
THF	1: 2	0	110	29 (82)	73 (*R*)
THF	1: 2	r.t.	48	41 (87)	53 (*R*)
THF	1: 4	0	110	33 (94)	70 (*R*)
THF	1: 8	0	132	49 (90)	97 (*R*)
DME	1: 2	0	40	41 (92)	75 (*R*)
DME	1: 2	r.t.	76	46 (80)	71 (*R*)
Toluene	1: 4	0	110	26 (67)	81 (*R*)
Toluene	1: 4	r.t.	35	34 (51)	67 (*R*)
DMSO	1: 2	r.t.	3	83	11 (*S*)

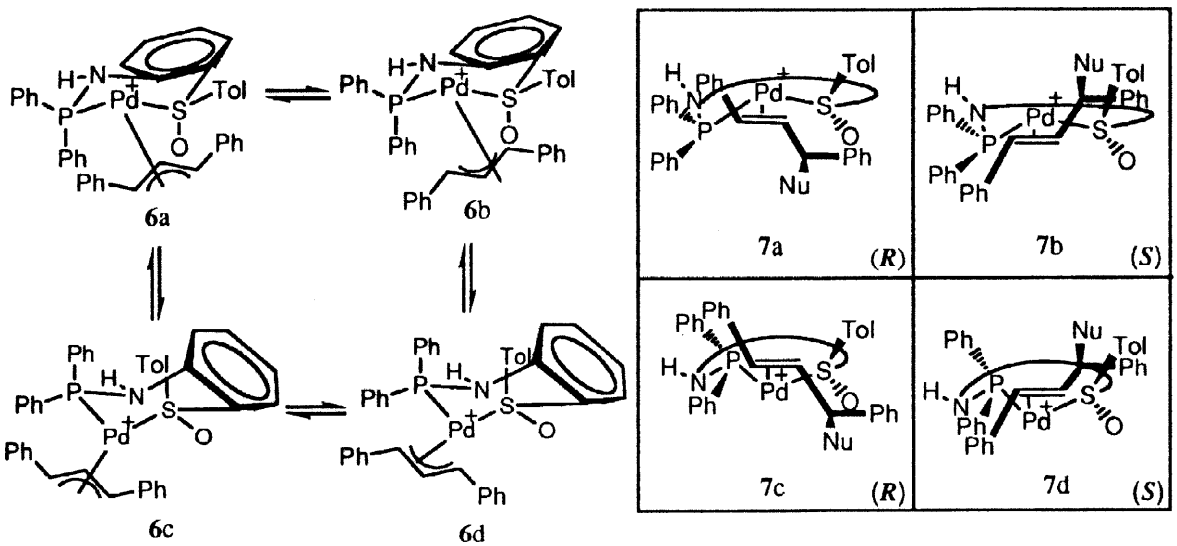
a) The reactions of **4** with dimethyl malonate sodium enolate (generated by treating with NaH (1.2 equiv.)) were carried out in the presence of [PdCl(π-allyl)]$_2$ (6 mol%) and a chiral ligand (*S*)-**3b**.
b) The corrected yields of **5** based on the recovered starting material are given in parentheses.
c) The enantiomeric excess (e.e.) of **5** was calculated by HPLC analysis with CHIRALPAK AD.

The effect of the molar ratio of [PdCl(π -allyl)]2 to (*S*)-**3a** was studied in the reaction of (±)-**4** with sodium malonate in THF at room temperature. The 1: 4 to 1: 8 molar ratios of [PdCl(π -allyl)]2 to (*S*)-**3a** provided higher enantioselectivity (43 and 49 %, respectively) of (*S*)-**5**.

The higher enantioselectivity was obtained by using 2-methoxy-1-naphthyl sulfoxide (*R*)-**3b**, and the results are summarized in Table 1. The reaction of (±)-**4** with sodium malonate catalyzed by [PdCl(π -allyl)]2 and (*R*)-**3b** produced (*R*)-**5** with 97% e.e. The effects of the molar ratio of the palladium catalyst to the ligand used were extremely remarkable. In particular, the 1:8 molar ratio of [PdCl(π -allyl)]2 to (*R*)-**3b** resulted in the highest enantioselectivity of (*R*)-**5**. The reason for this high efficiency is not clear at the present time. It should be also noted that the absolute configuration of the product **5** prepared by the effect of (*R*)-**3b** was inversed from that

obtained with (*S*)-**3a**. Surprisingly, however, the reaction in DMSO gave (*S*)-**5** with low e.e.. This indicates that the sulfinyl functionality would participate in this palladium-catalyzed reaction *via* coordination to the catalyst and, resultingly, control the stereochemistry of the product. This high enantioselectivity was the most highly selective example among the asymmetric synthetic methods, reported previously, by means of a chiral organosulfur ligand as the sole chiral source.

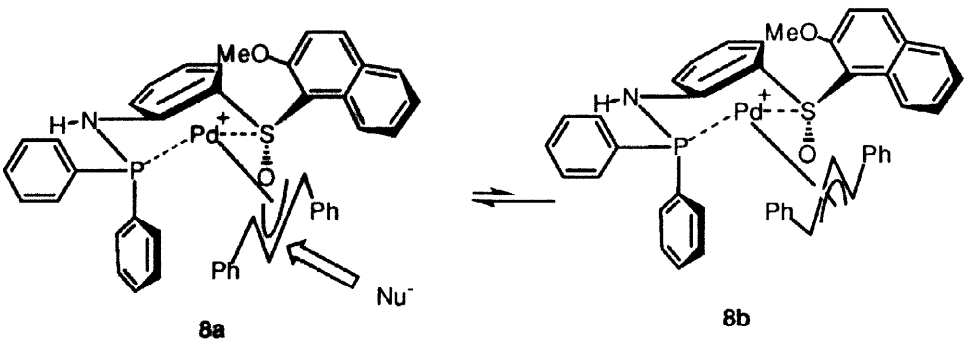
Thus, the existence of vicinal phosphinoamido functions in the chiral sulfinyl ligands was demonstrated to be extremely essential for the improvement of the enantioselectivity, in comparison with the cases of vicinal amino[6] and phosphino sulfinyl ligands.[9] This high enantioselectivity arises presumably from the formation of a sterically controllable six-membered transition state as described below.



Scheme 3

The mechanism of this asymmetic synthesis induced by the chirality of the chiral sulfinyl group is rationalized as follows. The phosphorus and sulfur atoms in the chiral ligands (*S*)-**3a,b** have rather strong coordination ability to palladium catalysts, forming six-membered π -allylpalladium intermediates **6a-d**, in which **6a,b** would be more sterically preferred to **6c,d**, because of the existence of 1,3-diaxial steric interference between the tolyl group and the phenyl group in **6c,d**. In the conformational equilibrium between **6a** and **6b**, **6b** would be preferred to **6a** which has steric interference between the tolyl group and the phenyl substituent in the allylic system. In general, nucleophilic attack would be preferred at the allyl terminus of **6a-d** *trans* to the better π -acceptor which is the phosphorus group in the current ligand,[10] resulting in the formation of the corresponding intermediates **7a-d**, respectively. The nucleophile (malonate carbanion) would preferentially attack to the allylic site *trans* to the the phosphorus group in the sterically most preferred π –allylpalladium complex **6b**, producing (*S*)-**5** *via* **7b**.

Surprisingly, the ligand with the larger substituent, 2-methoxy-1-naphthyl group, was highly effective in the asymmetric induction *via* the π -allylpalladium complex, controlling the stereochemistry of the product. Since, presumably, the steric crowd by the large naphthyl group would disturb the alkylation at the allylic site *trans* to the phosphorus group in the sterically preferred **8a**, similarly as mentioned above, in the equilibrium of **8a,b**, the preferential alkylation at the allylic site *syn* to the phosphorus group in **8a** would occur to give (*R*)-**5**.



Scheme 4

Thus, chiral 2-(phosphinoamido)phenyl sulfoxides were demonstrated to serve as extremely efficient chiral ligands in the palladium-catalyzed allylic alkylation. It should be noted that chiral 2-(diphenylphosphino-amido)phenyl 2-methoxy-1-naphthyl sulfoxide was the most efficient ligand among the known ligands bearing a chiral organosulfur functionality as the sole chiral source.

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