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Chiral β-Phosphino Sulfoxides as Chiral Ligands in Palladium-Catalyzed Asymmetric Allylic Nucleophilic Substitution Reactions

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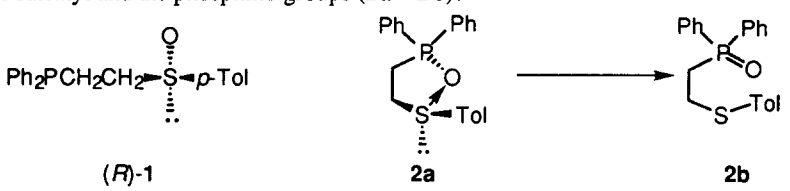
Abstract: The first attempt to use chiral β-phosphino sulfoxides as chiral ligands was successfully accomplished in a palladium-catalyzed asymmetric allylic alkylation and amination, providing extremely high enantioselectivity with chiral 2-(diphenylphosphino)phenyl 2-methoxy-1-naphthyl sulfoxide. The structure of the intermediary palladium complex chelated by the ligand was determined by the X-ray crystallographic analysis. The mechanism for the asymmetric induction is proposed on the basis of the stereochemical results obtained.

There have been published some issues related to asymmetric synthesis[1] using chiral ligands involving organosulfur functions; however, few reports have appeared concerning asymmetric synthesis with chiral ligands bearing chiral organosulfur groups[2] such as sulfinyl[3] and sulfoximine[4] functions as the sole chiral source. Hitherto, we have studied asymmetric synthesis using chiral sulfoxide ligands as the sole chiral source and developed new chiral sulfinyl compounds such as *o*-aminophenyl sulfoxides[5] and *o*-(phosphinoamino)phenyl sulfoxides.[6] Our continuous work has provided a new efficient chiral β-phosphino sulfoxide ligand, *o*-phosphinophenyl 2-methoxy-1-naphthyl sulfoxide.

Chiral β-phosphinoethyl *p*-tolyl sulfoxide (*R*)-**1** was prepared by a Michael addition of lithium diphenylphosphatide to (*R*)-*p*-tolyl vinyl sulfoxide.[7] The optical rotation of (*R*)-**1** was gradually decreased at room temperature, which would presumably arise from a rapid internal redox reaction between the sulfinyl and the phosphino groups (**2a**→**2b**).



(*R*)-**1** **2a** **2b**

Scheme 1

In contrast to (*R*)-**1**, chiral *o*-phosphinophenyl sulfoxides were obtained with retention of the chirality on the sulfinyl functions. The reason for this unexpected stability of the chirality is rationalized by the lower reactivity of the aromatic phosphino functions compared with that of the aforementioned phosphinoethyl group in (*R*)-**1**.

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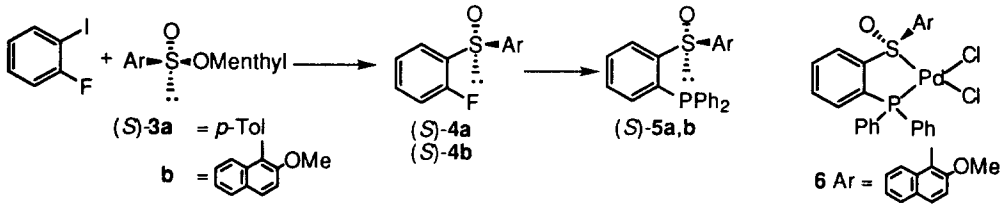
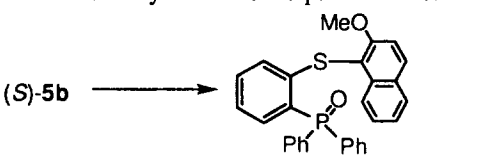
Chiral *o*-phosphinophenyl sulfoxides are obtainable from 2-fluoroiodobenzene and readily available chiral sulfinates. Lithiation of 2-fluoroiodobenzene with *n*-butyllithium followed by sulfinylation with (*S*)-**3a**[8a] or -**3b**[8b] produced (*S*)-**4a** or (*S*)-**4b**, respectively. Phosphinylation of (*S*)-**4a** or (*R*)-**4b** with potassium diphenylphosphatide[9] gave (*S*)-**5a,b**.



Scheme 2

The chiral sulfoxide (*S*)-**5b** was concluded to be very stable in THF at room temperature with complete retention of the chirality without conversion into the phosphine oxide (only a quite small amount of the corresponding phosphine oxide **7** was detected by the HPLC analysis). However, upon heating in refluxing THF, a more rapid irreversible transformation of (*S*)-**5b** into **7** was observed with almost complete retention (>96% e.e.) of the chirality as shown in Fig.1, plotted by the HPLC analysis with Chiralpak AD in accordance with the elapse of the reaction time.



Scheme 3 **7**

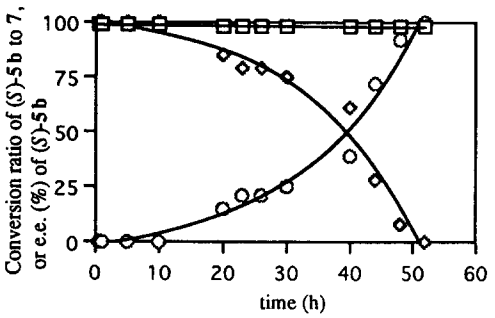


Fig.1. The conversion ratio of **5b** to **7**.
□ e.e.(%) of (*S*)-**5b**; ◇ (*S*)-**5b**; ○ **7**

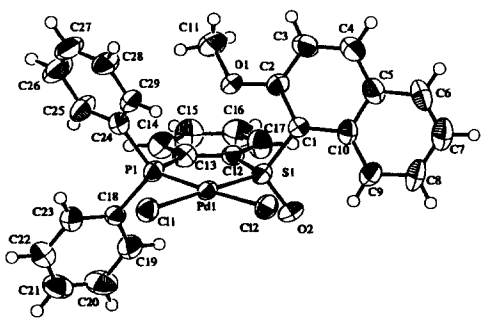
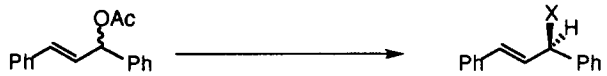


Fig.2. Molecular structure (ORTEP drawing) of **6**. Selected bond distances (Å) and angles (deg) are **6**: Pd(1)-S(1) 2.221(2), Pd(1)-P(1) 2.229 (2), Pd(1)-Cl(1) 2.313(2), Pd(1)-C1(2) 2.356 (2), S(1)-Pd(1)-P(1) 88.88(8), S(1)-Pd(1)-Cl (2) 89.13(8), P(1)-Pd(1)-Cl(1) 87.85(8).

The palladium-catalyzed asymmetric allylic alkylations of (±)-**8** with dimethyl malonate sodium enolate (generated by treating with NaH) were studied using (*S*)-**5a,b** as chiral ligands. The reactions of (±)-**8** with sodium malonate were carried out in THF, DME, CH_3CN, or DMSO at room temperature for 6-10 h in the presence of $[PdCl(\pi\text{-allyl})]_2$, $Pd(OAc)_2$, $Pd(dba)_2$, or $Pd_2(dba)_3 \cdot CHCl_3$ (0.06 equiv.) and (*S*)-**5a** (0.12 equiv.), producing (*S*)-**9a** in good yields with moderate enantiomeric excess (e.e.) (22-46%). The reaction of (±)-**8** with dimethyl malonate was accomplished also by employing *N,O*-bis(trimethylsilyl)acetamide(BSA)[10](3 equiv.) and a catalytic amount of sodium acetate, instead of sodium hydride, giving (*S*)-**9a** in 81% yield with 44% e.e..

However, a chiral sulfinyl compound (*S*)-**5b** with a bulky substituent was demonstrated to serve

as a highly efficient chiral ligand in the palladium-catalyzed reactions, providing an extremely high degree of asymmetric induction. The reactions of (±)-**8** with sodium malonate were carried out in THF at -20 or -40℃ in the presence of [PdCl(π-allyl)]2 (0.03 equiv.) and (*S*)-**5b** (0.06 equiv.) to afford (*S*)-**9a** in good yields with 75% e.e.. The use of PdCl2(CH3CN)2 (0.03 equiv) and (*S*)-**5b** (0.06 equiv.) in the reaction at -20℃ in THF improved the e.e. (82%) of the product (*S*)-**9a**. The e.e. and the absolute configuration of the product **9a** were determined by HPLC analysis with Chiralpak AD [the optical rotation of optically pure (*S*)-**9a**: $[\alpha]_D^{22}$ -17.0° (c 1.0, EtOH)].[11] The results obtained under various other reaction conditions are summarized in Table 1.



(±)-**8** → (*S*)-**9a** X = $CH(CO_2Me)_2$, (*R*)-**9b** = $NHCH_2Ph$

Table 1. The Palladium-catalyzed Asymmetric Allylic Nucleophilic Substitution Reactions of (±)-8 using (*S*)-5b[a)]

Entry	Nucleophile	Solvent	Reaction temp. (℃)	Reaction time (h)	Yield (%) of **9a,b**	Product	e.e. (%) of **9a,b**[c)]
1	A	THF	0	10min	73	**9a**	65 (*S*)
2	A	THF	-20	3	75	**9a**	75 (*S*)
3	A	THF	-20	4	72	**9a**	75 (*S*)
4	A	THF	-20	8	72	**9a**	70 (*S*)
5	A	THF	-20	8	71[b)]	**9a**	82 (*S*)
6	A	THF	-45	72	59	**9a**	75 (*S*)
7	A	DME	-20	8	74	**9a**	75 (*S*)
8	A	Toluene	-20	3	73	**9a**	52 (*S*)
9	A	DMSO	r.t.	30min	64	**9a**	13 (*S*)
10	A	CH_3CN	0	10min	70	**9a**	15 (*S*)
11	B	THF	40	24	84	**9b**	74 (*R*)
12	B	THF	r.t.	96	55	**9b**	75 (*R*)
13	B	Toluene	40	20	91	**9b**	50 (*R*)
14	B	Toluene	r.t	20	85	**9b**	70 (*R*)
15	B	Toluene	0	92	51	**9b**	85 (*R*)

a) The reactions of (±)-**8** with sodium malonate (generated by treating dimethyl malonate (A) with NaH (1.2 equiv.)) or benzylamine (B) (2.0 equiv.) were carried out in the presence of $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv., except for entry 3 (0.01 equiv.) and entry 4 (0.005 equiv.)) and (*S*)-**5b** (0.06 equiv., or 0.12 equiv. for entry 11-15).

b) The catalyst $PdCl_2(CH_3CN)_2$ (0.03 equiv.) was used.

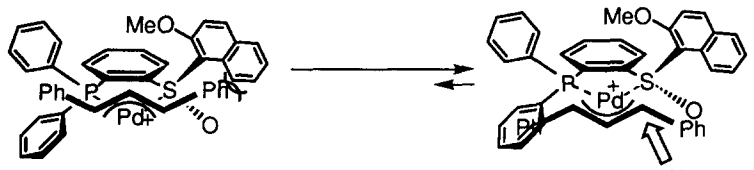
c) The e.e. of the product **9a,b** was determined by the HPLC analysis with Chiralpak AD for **9a** or Chiralcel OD for **9b**.[11, 12]

The asymmetric allylic amination of (±)-**8** under the palladium catalysis with (*S*)-**5b** provided a high degree of asymmetric induction. The reactions of (±)-**8** with benzylamine were carried out in toluene at 0℃ in the presence of [PdCl(π-allyl)]2 (0.06 equiv.) and (*S*)-**5b** (0.12 equiv.) to give (*R*)-**9b** with 85% e.e.. The e.e. and the absolute configuration of the product **9b** were determined by HPLC analysis with Chiralcel OD [the optical rotation of optically pure (*R*)-**9b**: $[\alpha]_D^{22}$ -20.6° (c 1.0, $CHCl_3$)].[12] The results obtained under various other reaction conditions are summarized in Table 1.

The intermediary palladium complex derived from (*S*)-**5b** and PdCl2(CH3CN)2 was isolated by recrystallization from CH_2Cl_2-Et_2O. The structure was determined by the X-ray crystallographic analysis[13] as shown in Fig.2. The palladium-catalyzed reactions of (±)-**8** with sodium malonate using the isolated palladium complex **6** as a catalyst gave the same result as that obtained under the normal reaction conditions (entry 5 in Table 1).

The mechanism for the asymmetric induction with (*S*)-**5a,b** is proposed on the basis of the

stereochemical results obtained and the structure of the palladium complex determined by us. As the crystallographic data clearly show, a five-membered chelated palladium complex is formed by coordination of the phosphino group and the sulfinyl sulfur function to palladium. In the conformational equilibrium of the five-membered chelated π-allylpalladium complex, a conformer **10b** would be preferred to **10a** because of the existence of steric interference between the large substituent (*p*-tolyl or 2-methoxy-1-naphthyl) on the chiral sulfoxide and the phenyl group in the allyl terminus in **10a**. Therefore, the nucleophile (sodium malonate or benzylamine) attacks preferentially the allyl terminus in **10b** *trans* to the better π-acceptor,[14] which is the phosphine group in the current case, despite the steric effect by the bulky substituent (2-methoxy-1-naphthyl), affording (*S*)-**9a** and (*R*)-**9b** in a highly enantioselective fashion, respectively.



10a Scheme 4 **10b**

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13. Crystallographic data for **6** : $C_{29}H_{23}O_2PSCl_2Pd \cdot 2CH_2Cl_2$. *Mr*=813.70, Monoclinic, Space Group P21(#4), *a*=9.466(1)Å, *b*=17.136(2)Å, *c*=11.180(1)Å, *β*=107.99(1)°, *V*=1724.9(3)Å^3, *Z*=2, *Dc*=1.567g/cm^3, *F*(000)=816.00. max2θ=54.9°, graphite monochromated MoKα(λ=0.71070Å), 2985 observations (I>3.00 (*I*)), *R*=0.038, *Rw*=0.049.
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