CHIRAL β-AMINO SULFOXIDES AS CHIRAL LIGANDS IN PALLADIUM-CATALYZED ASYMMETRIC ALLYLATIONS[1]

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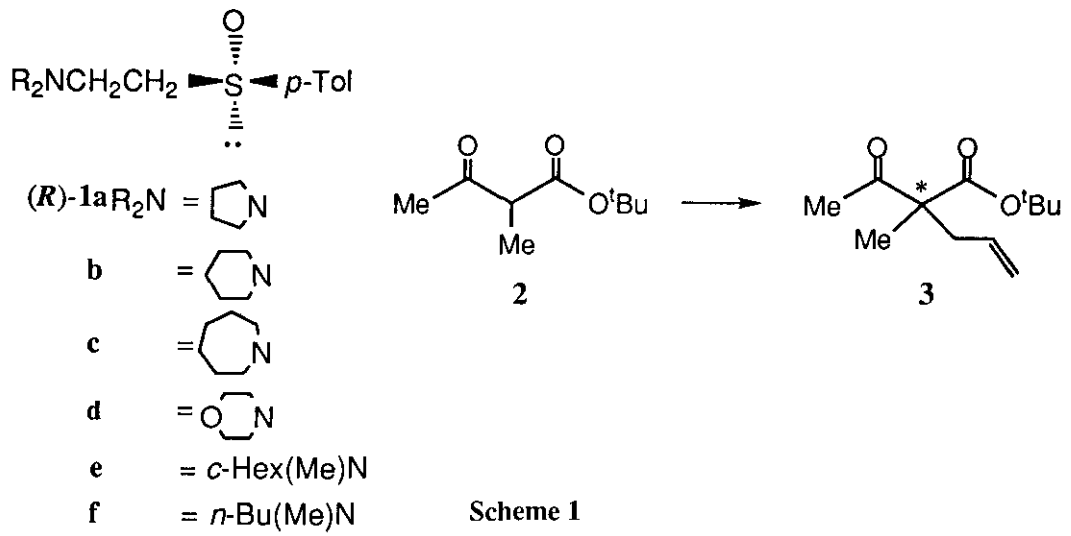
Abstract —New chiral β-amino sulfoxide ligands bearing chiral sulfinyl functionality as a sole chiral source have been deviced and palladium-catalyzed asymmetric allylations of acetoacetate with these ligands have been examined. The highest enantioselectivity (50%) was observed with **5b**. The participation of chiral sulfinyl functionality to palladium catalysts is discussed on the basis of the stereochemical outcome obtained.

Catalytic asymmetric synthesis has received much attention in recent years for practical use of optically active compounds.[2] Many methodologies for asymmetric carbon-carbon bond formation have been developed,[3] and transition metal-catalyzed asymmetric reactions with many kinds of new chiral useful ligands such as phosphines,[4] phosphonites,[5] amines,[6] and alcohols[7] have been reported.

During a past decade, we have studied on transition metal-catalyzed reactions of chiral systems such as chiral allyl esters[8] and cyclopropane compounds bearing chiral sulfinyl groups,[9] and we have taken much interest in the participation of chiral sulfinyl functionality [10] to transition metal catalysts. So we are currently studing the use of chiral ligands bearing chiral sulfinyl groups as sole chiral functionalities in palladium-catalyzed asymmetric allylations. Few reports have been published concerning asymmetric allylations with chiral sulfur ligands bearing chiral sulfinyl[11] or sulfinamide[12] groups as sole chiral sources. We wish to communicate herein palladium-catalyzed asymmetric allylations with chiral β-amino sulfinyl ligands, solvent effects on the stereochemistry of the allylations, and the rationalization of the reaction mechanism on the basis of the stereochemical results.

Chiral β-aminoethyl sulfoxides ((*R*)-**1a-f**) were readily obtained in good yields (90.3～99.7%) by Michael additions of the corresponding secondary amines to (*R*)-*p*-tolyl vinyl sulfoxide[13] in MeOH at 50 ℃ for 2 h. Palladium-catalyzed asymmetric allylations of acetoacetate (**2**) have been studied using chiral β-aminoethyl sulfoxides ((*R*)-**1a-f**) obtained above as chiral ligands. Studies on asymmetric allylations of



Scheme 1

sodium enolate of **2** (generated by treatment with NaH(1.0 equiv.)) with allyl acetate (1.5 equiv.) were carried out using $[PdCl(\pi\text{-allyl})]_2$, $Pd(OAc)_2$, $Pd(dba)_2$, or $Pd_2(dba)_3 \cdot CHCl_3$ (0.03 or 0.06 equiv.) as a catalyst and (*R*)-**1a** (0.12 equiv.) as a chiral ligand in DME, THF, ether (Et_2O), or toluene, giving optically active allylated compound (**3**).[14] The results obtained are summarized in Table 1. The use of $[PdCl(\pi\text{-allyl})]_2$ in DME and Et_2O gave (*S*)-(-)-**3** with slightly higher enantiomeric excess (ee); however, the allylation in THF provided (*R*)-(+)-**3**.

Use of other chiral sulfoxides ((*R*)-**1b-f**) as chiral ligands was carried out in the same system under the similar reaction conditions (using $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.)) in THF or DME at 0, -20℃, or room temperature. The results obtained are summarized in Table 2.

Table 1. Palladium-catalyzed Asymmetric Allylations of 2 with (*R*)-1a[a)]

Catalyst (equiv.)	Solvent	Reaction time (h)	Yield of **3** (%)	$[\alpha]_D$ ($CHCl_3$) of **2** (c, °C)	ee (%) of **3**[b)] (Abs. confign.)
$[PdCl(\pi\text{-allyl})]_2$ (0.03)	DME	20	24	-6.5° (1.0, 26)	29 (*S*)
$Pd(OAc)_2$ (0.06)	DME	21	17	-1.3° (1.5, 29)	6 (*S*)
$Pd(dba)_2$ (0.06)	DME	21	9	-3.8° (0.5, 30)	17 (*S*)
$Pd_2(dba)_3$ $CHCl_3$ (0.06)	DME	12	28	-5.4° (1.8, 28)	24 (*S*)
$[PdCl(\pi\text{-allyl})]_2$ (0.03)	THF	18	47	+2.5° (3.2, 27)	11 (*R*)
$[PdCl(\pi\text{-allyl})]_2$ (0.03)	Et_2O	20	17	-6.5° (1.1, 29)	29 (*S*)
$[PdCl(\pi\text{-allyl})]_2$ (0.03)	Toluene	18	15	-0.7° (1.4, 29)	3 (*S*)

a) The reactions of the carbanion of **2** (generated by treating **2** with NaH (1.0 equiv.)) with allyl acetate (1.5 equiv.) were carried out at 0 °C in the presence of a palladium catalyst and (*R*)-**1a** (0.12 equiv.).

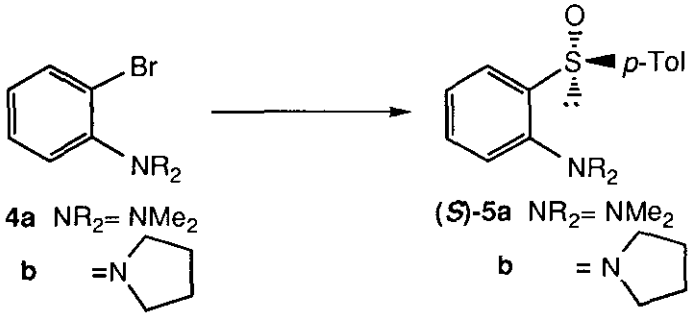
b) The enantiomeric excess (ee) of **3** was determined on the basis of optical rotation of **3** obtained (the optical rotation of optically pure (*S*)-(-)-**3**: $[\alpha]_D$ -22.7°($CHCl_3$)[14]).

Table 2. Palladium-Catalyzed Asymmetric Allylations of 2 with (*R*)-1b-f and (*S*)-5a,b[a)]

Ligands	Solvent	Reaction temp. (°C)	Reaction time (h)	Yield of 3 (%)	$[\alpha]_D(CHCl_3)$ of 3 (c, °C)	ee of 3 (%) (Abs. confign.)
1b	THF	0	36	33	- 1.5° (3.4, 27)	7 (*S*)
	DME	-20	20	20	- 2.7° (1.1, 26)	12 (*S*)
1c	THF	0	36	38	- 3.3° (3.0, 27)	15 (*S*)
	DME	-20	20	28	- 2.0° (2.5, 26)	9 (*S*)
1d	THF	rt	24	11	+6.5° (1.2, 25)	29 (*R*)
	DME	rt	20	18	- 0.5° (2.0, 28)	2 (*S*)
1e	DME	0	20	25	- 6.1° (2.6, 26)	27 (*S*)
1f	DME	0	20	19	- 7.6° (1.2, 30)	33 (*S*)
5a	THF	-20	20	33	- 8.9° (1.6, 27)	39 (*S*)
	Et_2O	-20	20	25	- 5.3° (1.9, 29)	23 (*S*)
	DME	-20	18	39	- 10.8° (2.6, 26)	48 (*S*)
5b	THF	-20	40	25	- 11.5° (1.4, 29).	50 (*S*)

a) The reactions of the carbanion of **2** (generated by treating **2** with NaH (1.0 equiv.)) with allyl acetate (1.5 equiv.) were carried out in the presence of [$PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.) and (*R*)-**1b-f** or (*S*)-**5a,b** (0.12 equiv.).

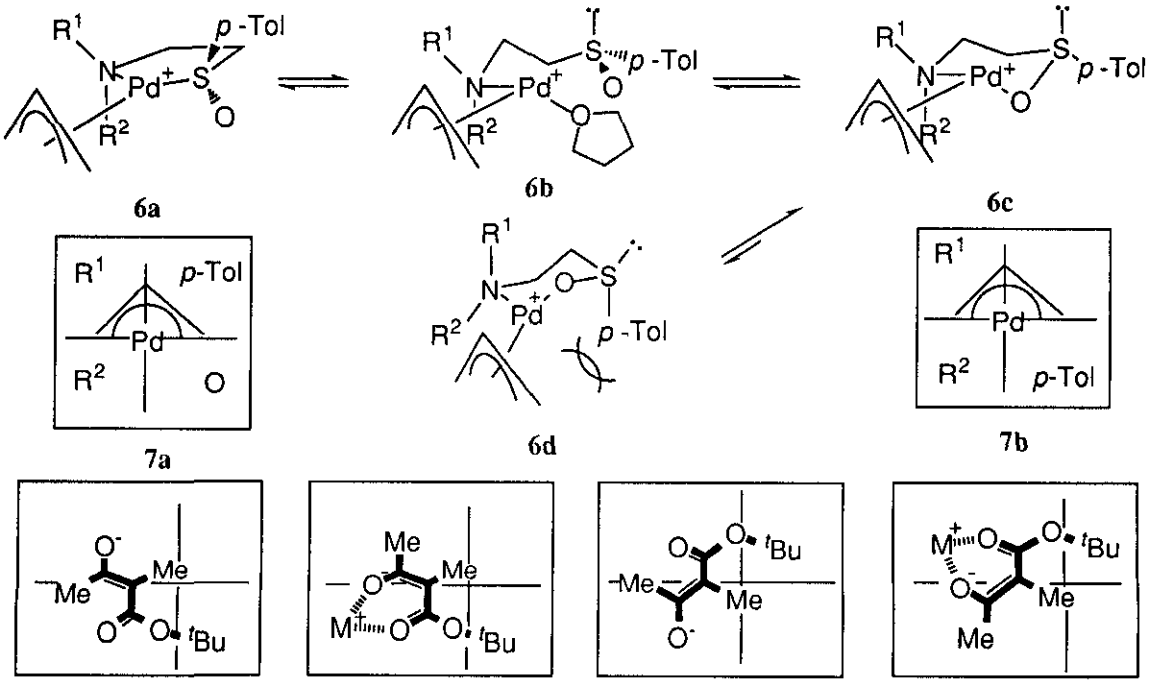
Among chiral sulfinyl ligands examined, slightly higher (*S*)-selectivity of the product (**3**) was observed with (*R*)-**1e,f**. It should be noted that marked solvent effects on the stereochemistry of the reaction product were observed in this asymmetric allylations: the allylations of **2** with (*R*)-**1b-f** in DME gave (*S*)-(-)-**3**, however that of **2** with (*R*)-**1d** in THF afforded (*R*)-(+)-**3**.



Scheme 2

In order to improve the enantioselectivity, introduction of phenyl rings into chiral ligand systems was deviced for the stereochemical control of the conformation of intermediary cyclic palladium complexes mentioned later. Chiral *o*-aminophenyl sulfoxide ((*S*)-**5a**) was prepared by reductive *N,N*-dimethylation of 2-bromoaniline with formaldehyde and $NaBH_3CN$ followed by sulfinylation of **4a** upon treatment with *n*-butyllithium and (-)-menthyl (*S*)-*p*-toluenesulfinate. *N,N*-Dialkylation of 2-bromoaniline with 1,4-dibromobutane followed by sulfination of **4b** in the same way produced (*S*)-**5b**.

The allylations of sodium enolate of **2** (generated as described earlier) with allyl acetate (1.5 equiv.) were carried out at -20 ℃ in THF, Et_2O, or DME in the presence of $[PdCl(\pi\text{-allyl})]_2$ (0.03 equiv.) and (*S*)-**5a,b** (0.12 equiv.) to produce (*S*)-(-)-**3**. The results obtained are summarized in Table 2. In comparison with the results with (*R*)-**1a-f**, rather high enantioselectivity of the product ((*S*)-**3**) was obtained in all cases



Scheme 3

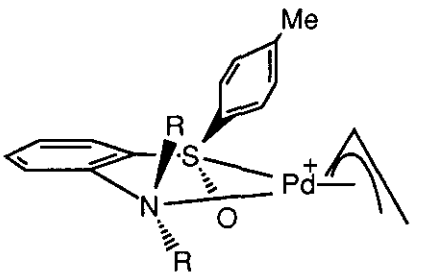
examined with (*S*)-**5a,b**. With these ligands, slightly effective solvent effects on the enantioselectivity were observed, however with no change of the absolute configuration of the product (**3**).

The mechanism of this asymmetric induction by these chiral sulfinyl ligands is rationalized on the basis of the stereochemical outcome obtained, as follows. A five-membered palladacyclic π-allylpalladium complex (**6a**) would be formed as an intermediary reactive allylating species by the participation of the sulfinyl sulfur lone pair and the nitrogen atom of the chiral β-aminoethyl sulfoxides used, resulting in the creation of a new chiral environment designated in **7a**. The sodium enolate of acetoacetate (**2**) would react with **6a** *via* the nucleophilic substitution of **2A** or **2B** with **7a** (from the back side of the palladium catalyst) in sterically preferred fashion to give (*S*)-**3**. When THF was used as solvent, different stereochemical results were obtained in some cases [(*R*)-**1a,d**]. In these cyclic amino ligands, the five-membered complexes would be transformed, *via* **6b** formed by the participation of tetrahydrofuran oxygen atom due to the steric strain induced by five-five- or five-six-membered spiro structure, into sterically-relieved six-membered intermediates (**6c,d**). A six-membered π-allylpalladium complex (**6c**) would perfer to **6d** because of steric interferene between *p*-tolyl group and the allyl part in **6d**, providing a new chiral environment shown in **7b**. Thus, the reaction of sodium enolate (**2**) with allyl acetate in THF would proceed *via* the nucleophilic substitution of **2C** or **2D** with **7b** (from the back side of the palladium catalyst) in sterically preferred

manner, giving (*R*)-(+)-**3**.

In the cases of **5a,b** rather higher enantioselectivity was obtained, presumably due to sterically-fixed structure of the intermediary palladium complex (**8**).

Thus, new chiral β-amino sulfoxides described herein served as chiral ligands in palladium-catalyzed allylations of acetoacetate (**2**) to give optically active α-allyl ester (**3**) with moderate enantioselectivity. This paper is the first example for the use of chiral β-amino sulfinyl ligands in palladium-catalyzed reactions.



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REFERENCES

1. This paper is dedicated to the memory of Professor Dr. Shun-ichi Yamada.
2. *"Catalytic Asymmetric Synthesis,"* ed. by I. Ojima, VCH Publishers Inc., New York, 1993; R. Noyori, *"Asymmetric Catalysis in Organic Synthesis,"* John Wiley & Sons Inc., New York, 1994.
3. J. Seyden-Penne, *"Chiral Auxiliaries and Ligands in Asymmetric Synthesis,"* John Wiley & Sons Inc., New York, 1995.
4. H. Brunner, *Synthesis*, **1988**, 645; T. Hayashi, *Pure & Appl. Chem.*, 1988, **60**, 7; G. Consiglio and R.M. Waymouth, *Chem. Rev.*, 1989, **89**, 257; S.L. Blystone, *ibid.* 1989, **89**, 1663; I. Ojima, N. Clos, and C. Bastos, *Tetrahedron*, 1989, **45**, 6901; M. Sawamura and Y. Ito, *Chem. Rev.*, 1992, **92**, 857; S. Otsuka and K. Tani, *Synthesis*, **1991**, 665; T. Hayashi, A. Kubo, and F. Ozawa, *Pure & Appl. Chem.*, 1992, **64**, 421.
5. U.M. Dzhemilev, R.N. Fakhretdinov, A.G. Telin, G.A. Tolstikov, A.A. Panasenko, and E.V. Vasileva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1980**, 2771(*English translation*, **1981**, 1943).
6. A. Togni and L.M. Vennanzi, *Angew. Chem., Int. Ed. Engl.*, 1993, **33**, 497; *Angew. Chem.*, 1994, **106**, 517.
7. H. Fritschi, U. Leutenegger, and A. Pfaltz, *Angew. Chem.*, 1986, **98**, 1028; *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1005.
8. K. Hiroi, J. Abe, K. Suya, S. Sato, and T. Koyoma, *J. Org. Chem.*, 1994, **59**, 203 and references cited therein.
9. K. Hiroi and Y. Arinaga, *Tetrahedron Lett.*, 1994, **35**, 153.
10. K. Hiroi, *Reviews on Heteroatom Chemistry*, 1996, **14**, 21 and references cited therein.
11. R. Tokunoh, M. Sodeoka, K. Abe, and M. Shibasaki, *Tetrahedron Lett.*, 1995, **36**, 8035.
12. C. Bolm, D. Kaufmann, M. Zehnder, and M. Neuburger, *Tetrahedron Lett.*, 1996, **37**, 3985.
13. G.A. Russel and H.-D. Becker, *J. Am. Chem. Soc.*, 1963, **85**, 3406.
14. K. Tomioka, K. Ando, Y. Takemasa, and K. Koga, *J. Am. Chem. Soc.*, 1984, **106**, 2718.

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