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Optically Active Sulfoximines in Enantioselective Palladium Catalysis

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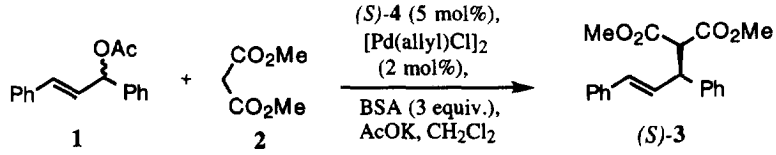
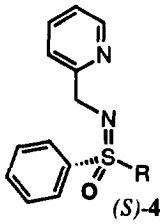
Abstract: Chiral sulfoximine/Pd-complexes catalyze enantioselective allylic alkylations. The corresponding products have been obtained in good yields with moderate enantioselectivities (up to 73% *ee*). The crystal structure of an allyl/Pd(II)-complex bearing a chelating sulfoximine is reported. Copyright © 1996 Elsevier Science Ltd

Various chelators have successfully been used as chiral ligands in palladium-catalyzed enantioselective allylic substitution reactions.[1] Among them, C_2-symmetric diphosphines[2] and P,N-oxazolines[3] gave the highest enantioselectivities. The use of dinitrogen-containing compounds[4] in palladium catalysis has also been studied.[5] The two nitrogens in these N,N-ligands were either identical (C_2-symmetric compounds) or their stereoelectronic properties were comparable. In this letter, we describe novel sulfoximine derivatives **4** having two significantly different donor atoms. Their ability to controle enantioselective Pd-catalyzed allylic substitutions has been investigated.



1 **2** *(S)*-**3**

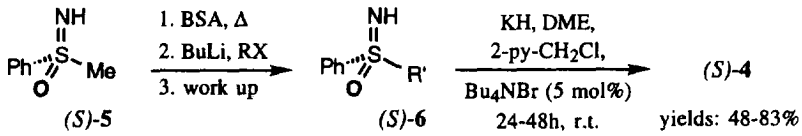


(S)-**4**

4a: R = -CH_3
4b: R = -$C_{19}H_{39}$
4c: R = -$CH(CH_3)_2$
4d: R = -$C(CH_3)_3$
4e: R = -$CH_2CH_2C_6H_5$
4f: R = -CH_2CH_2-*o*-$(CH_3O)C_6H_4$
4g: R = -CH_2CH_2-*o*-$(HO)C_6H_4$
4h: R = -$CH_2C(OH)(CH_3)_2$

Based on our previous results,[6,7] we expected sulfoximines **4** to bind to metals through the two nitrogens in a bidentate fashion. Selective coordination of the allyl fragment followed by its site-specific nucleophilic attack would then lead to the formation of optically active products.

We developed a reaction sequence by which both antipodes of **4** became available. Optically active **5** can be readily obtained by resolution of asymmetric synthesis.[8] N-silylation[9] of *(S)*-**5** followed by sequential C- and N-alkylation[8,10] gave *(S)*-**4** in moderate to good yields.



BSA = *N,O*-bis(trimethylsilyl)acetamide

The metal binding capability of sulfoximines of type **4** was revealed by the reaction of **4a** with $[Pd(allyl)Cl]_2$. A Pd(II)-π-allyl complex with one sulfoximine ligand was formed (with PF_6^- as counter ion). The molecular structure of this complex was unambiguously established by X-ray crystal structure determination.[11]

Figure 1. X-ray crystal structure of the Pd complex derived from **4a**.

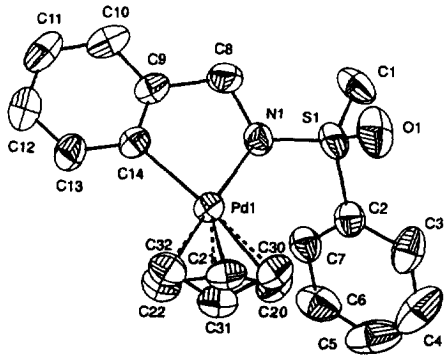


Table 1. Selected bond distances [Å].

Pd - C(20)	2.131(8)
Pd - C(21)	2.073(6)
Pd - C(22)	2.121(8)
Pd - C(30)	2.11(2)
Pd - C(31)	2.10(1)
Pd - C(32)	2.14(2)

The solid state structure of the disordered crystals shows two diastereomeric complexes which differ by the orientation of the allyl fragment (*endo* and *exo*). Both nitrogens are coordinated to the palladium center.[12] The dihedral angle between C8-N1-S1-C1 is -37.56° indicating that the orientation of the sulfoximine moity brings the S-methyl and the N-methylene groups into close proximity.[13] The Pd-N bond lenghths differ only slightly [Pd-N1: 2.096(4)Å; Pd-N2: 2.080(4)Å]. The Pd-to-C distances are listed in Table 1.

Next, we investigated the catalytic properties of the palladium complexes formed *in situ* from sulfoximines **4** and $[Pd(allyl)Cl]_2$. In the presence of 5 mol% of *(S)*-**4** and 2 mol% of the Pd-π-allyl-dimer, the reaction of 1,3-diphenyl-2-propenyl acetate (**1**) and the nucleophile generated from dimethyl malonate (**2**) by treatment with BSA and a small quantity of potassium acetate[14] afforded substitution product *(S)*-**3** in good yield with moderate enantiomeric excess (*ee*) (Table 2).

In all cases, the *(S)*-configurated product was obtained in excess. The enantioselectivity in the formation of **3** depends on various parameters: 1. *The substituent R at sulfur.* Linear and α-branched aliphatic R-groups (Table 2, entries 1-4) gave only low *ee* values (20-45%). The use of phenylethyl and substituted derivatives

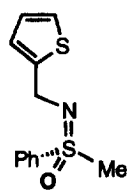
Table 2. Enantiomeric excesses of **3** resulting from asymmetric allylic alkylations of **1** using various sulfoximine/Pd(II)-complexes.

Entry	Sulfoximine	Temp. [°C]	Solvent	% Yield [a]	% *Ee* [b]	Config[c]
1	*(S)*-**4a**	r. t.	CH_2Cl_2	89	39	(*S*)
2	*(S)*-**4b**	r. t.	CH_2Cl_2	90	45	(*S*)
3	*(S)*-**4c**	r. t.	CH_2Cl_2	65	39	(*S*)
4	*(S)*-**4d**	r. t.	CH_2Cl_2	24	20	(*S*)
5	*(S)*-**4e**	r. t.	CH_2Cl_2	80	52	(*S*)
6	*(S)*-**4f**	r. t.	CH_2Cl_2	73	51	(*S*)
7	*(S)*-**4f**	r. t.	toluene	82	54	(*S*)
8	*(S)*-**4f**	-20	toluene	22	63	(*S*)
9	*(S)*-**4g**	r. t.	toluene	50	65	(*S*)
10	*(S)*-**4g**	-5	toluene	77	73	(*S*)
11	*(S)*-**4h**	r. t.	CH_2Cl_2	62	56	(*S*)

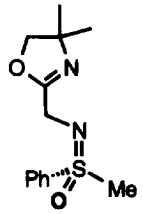
[a] Isolated by column chromatography. [b] *Ee* determ. by HPLC analysis using a chiral column (Chiralcel OD-H). [c] Abs. configuration determ. by comparison of optical rotations with literature value.

of this kind lead to better enantioselectivies (entries 5-11). The highest *ee* value was obtained with sulfoximine **4g** bearing a phenolic hydroxyl group.[15] Compared to that result the tertiary alcohol **4h** showed reduced enantioselectivity. 2. *The reaction temperature.* Most reactions were performed at room temperature. A decrease in temperature to -20°C led to an improved enantioselectivity, however, the product yield was lower due to reduced conversion of the starting materials. The best result (entry 10) was achieved in a reaction run at -5°C using **4g** as ligand. 3. *The solvent.* Reactions in toluene gave better results than those performed in dichloromethane or acetonitrile (For **4f**: 54%, 51%, 49% *ee*, respectively). 4. *The ligand-to-palladium ratio.* This effect is minor. Increasing the ratio of sulfoximine **4h** and Pd from 1:1 to 10:1 gave almost identical results (82% yield / 54% *ee* versus 88% yield / 56% *ee*).

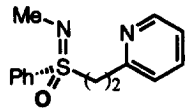
We also tested other sulfur-containing compounds such as sulfoximines **7**-**11** and sulfoxide **12** in this catalysis.[16,17] The *in situ* generated complexes were either inactive or gave **3** with very low *ee*. Yields and *ee* values are given below.



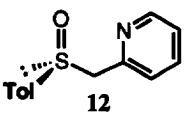
7
(no reaction)



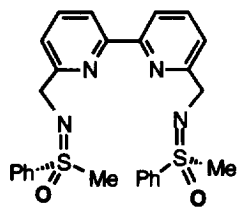
8
99% (35% *ee*)



9
11% (13% *ee*)



12
(no reaction)



11
56% (13% *ee*)

In conclusion, we have demonstrated that sulfoximines of type **4** can be used as chiral ligands in Pd-catalyzed allylic substitution reactions giving the product with moderate to good enantiomeric excess.

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