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Synthesis of 1,5-*P*,*N*-phosphino-sulfoximines through phospha-Michael reaction of alkenyl sulfoximines and their evaluation as ligands in palladium-catalyzed allylic alkylation

Fabien Lemasson, Hans-Joachim Gais* and Gerhardt Raabe

Institut für Organische Chemie der Rheinisch-Westfälischen Technischen Hochschule (RWTH) Aachen, Landoltweg 1, 52074 Aachen, Germany

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Abstract—We describe a modular synthesis of cyclic and acyclic 1,5-*P*,*N*-phosphino-sulfoximines by using a phospha-Michael reaction of the corresponding alkenyl sulfoximines with $HPPh_2/KO{t}Bu$ as key step, which proceeds with medium diastereoselectivity. The palladium-catalyzed allylic alkylation of racemic 1,3-diphenyl allyl acetate with malonate in the presence of a $S_SR_CR_C$-configured *N*-benzyl-substituted cyclic phosphino-sulfoximine gave the corresponding alkene with 97% ee in 98% yield. A comparative study of N-substituted phosphino-sulfoximines showed the selectivity of the Pd(0)-catalyst to be dependent not only on the chiral backbone of the ligand but also on the N-substituent and configuration of the sulfoximine group.

The palladium(0)-catalyzed allylic alkylation has emerged as a valuable method in asymmetric synthesis.[1] Of the various chiral ligands that have been developed for the Pd-atom,[1] catalysts containing bidentate P,N-ligand[2] as, for example, 1,5-*P*,*N*-phosphino-oxazolines **III**[3] show particularly high selectivity and activity. Despite the availability of several classes of P,N-ligands there is still a quest for new ligands of this type.[4] Because of our investigations of the Pd-catalyzed asymmetric allylation of S-[5] and O-nucleophiles[6] and application of sulfoximines in asymmetric synthesis,[7] we became interested in the synthesis and evaluation of cyclic and acyclic phosphino-sulfoximines of types **I** and **II**, respectively, as ligands (Fig. 1). Phosphino-sulfoximines **I** and **II**, having besides the chiral sulfoximine group also a chiral backbone, are expected to function as bidentate 1,5-*P*,*N*-ligands and form 6-membered ring chelates, the sulfoximine group of which is embedded in the ring. The variation of the substituents R^2 and R^3 of **I** and the ring size of **II** should provide a means to influence the efficiency of the ligands. Particularly yielding in this regard could be a variation of the substituent R^1 because of its close proximity to the Pd-atom. Recently, 1,4-*P*,*N*-phosphino-sulfoximines **IV**[8] and **V**[9] featuring a PCCNS connectivity had been described, which gave high enantioselectivities in the Pd-catalyzed reaction of 1,3-diphenyl-2-propenyl acetate with malonate.[8a,9] However, these P,N-ligands are in contrast to **I** and **II** not capable to form with the Pd(0)-atom N,P-chelates, the sulfoximine group of which is incorporated into the ring. Here we describe a modular synthesis of phosphino-sulfoximines **I** and **II** through a base-catalyzed phospha-Michael reaction of the corresponding alkenyl sulfoximines with $HPPh_2$ and their evaluation in Pd-catalyzed allylic alkylation.

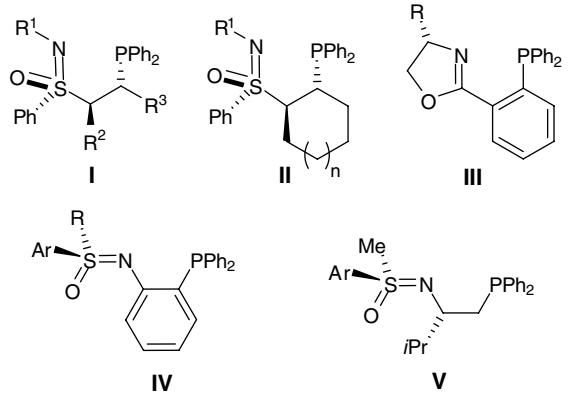

Figure 1. *P*,*N*-Phosphino-sulfoximines and *P*,*N*-phosphinooxazolines.

* Corresponding author. Tel.: +49 2418094686; fax: +49 2418092665; e-mail: gais@rwth-aachen.de

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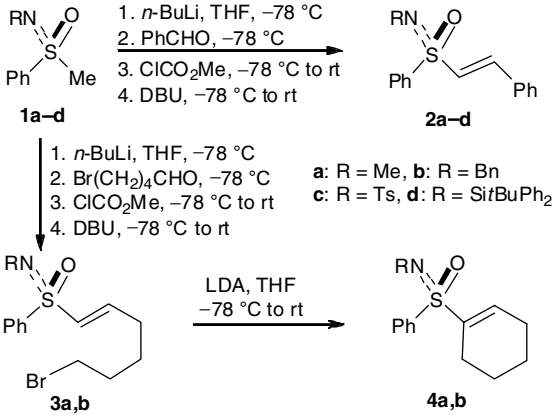


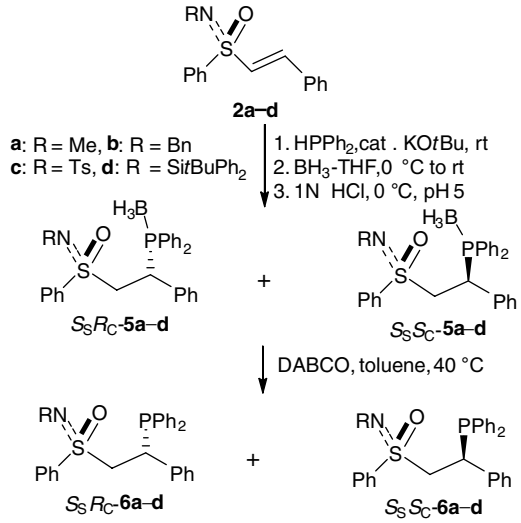
Scheme 1. Synthesis of alkenyl and cycloalkenyl sulfoximines.

Acyclic alkenyl sulfoximines **2a**–**d**[10] were synthesized by a one pot addition–elimination route[11] starting from the enantiopure N-substituted *S*-methyl sulfoximines **1a**–**d**.[12] Sulfoximines **1a**–**d** in turn are readily accessible from *S*-methyl-*S*-phenylsulfoximine[13] through reaction with CH_2O/HCO_2H, $PhCH_2Br$, TsCl, and $ClSitBuPh_2$, respectively. Thus, the successive treatment of sulfoximines **1a**–**d** with *n*-BuLi, PhCHO, $ClCO_2Me$, and 1,8-diaza-bicyclo[5.4.0]-undec-7-ene (DBU) gave the alkenyl sulfoximines **2a**–**d** in very good overall yields as single *E*-isomers (Scheme 1, Table 1).

Cycloalkenyl sulfoximines **4a**,**b** were synthesized by a two-step route. The successive treatment of sulfoximines **1a** and **1b** with *n*-BuLi, 5-bromopentanal, $ClCO_2Me$, and DBU furnished the methyl- and benzyl-substituted acyclic ω-bromo-alkenyl sulfoximines **3a** and **3b**, respectively. Treatment of **3a** and **3b** with lithium diisopropylamide (LDA) led to a lithiation at the α-position[14] followed by a cyclization of the corresponding ω-bromo-α-lithio alkenyl sulfoximines and gave cycloalkenyl sulfoximines **4a** and **4b**, respectively, in good overall yields.[15]

We envisioned a synthesis of phosphino-sulfoximines **6a**–**d**, **8a**, and **8b** through a phospha-Michael reaction of $KPPh_2$ to alkenyl and cycloalkenyl sulfoximines **2a**–**d**, **4a**, and **4b**, respectively. Although this route should result in the formation of mixtures of diastereomers, this would allow a determination of the enantioselectivity of the catalyst in dependence of the configuration of the ligand. The feasibility of a phospha-Michael reaction of alkenyl sulfoximines had been previously demonstrated in the case of the addition of $KPPh_2{\cdot}BH_3$ to a vinyl sulfoximine.[9] Treatment of the alkenyl sulfoximines **2a**–**d** with 1.1 equiv of $HPPh_2$ and 10 mol % of KO*t*Bu in absolute THF gave phosphino-sulfoximines **6a**–**d** as mixtures of diastereomers (Scheme 2, Table 2), which were isolated after treatment with BH_3–THF as borane adducts **5a**–**d** in good overall yields. The diastereomers of **5a**–**d** were separated by column chromatography. Similarly, treatment of cycloalkenyl sulfoximines **4a** and **4b** with 1.1 equiv of $HPPh_2$ and 10 mol % of KO*t*Bu in absolute THF followed by the addition of BH_3–THF gave phosphino-sulfoximines **7a** and **7b**, respectively, as mixtures of only two diastereomers (Table 3), which according to NMR spectroscopy have the trans-configuration. The direct application of $KPPh_2{\cdot}BH_3$ in the phospha Michael reaction[9] of **4** was not suitable because of a partial hydroboration of the cycloalkenyl sulfoximine (Scheme 3).

The absolute configuration of phosphine-borane adducts R_SS_C-**5a** (Fig. 2) and $S_SR_CR_C$-**7b** (Fig. 3) was determined by X-ray crystal structure analysis.[16] NMR spectroscopy of the diastereomers of **5a**–**d**, **7a**, and **7b**



Scheme 2. Synthesis of acyclic phosphino-sulfoximines.

Table 1. Synthesis of alkenyl and cycloalkenyl sulfoximines

Compound	R	Yield[a] (%)
2a	Me	88
2b	Bn	91
2c	Ts	92
2d	$SitBuPh_2$	85
4a	Me	56
4b	Bn	70

[a] Overall yields based on sulfoximines **1a**–**d**.

Table 2. Synthesis of acyclic phosphino-sulfoximines

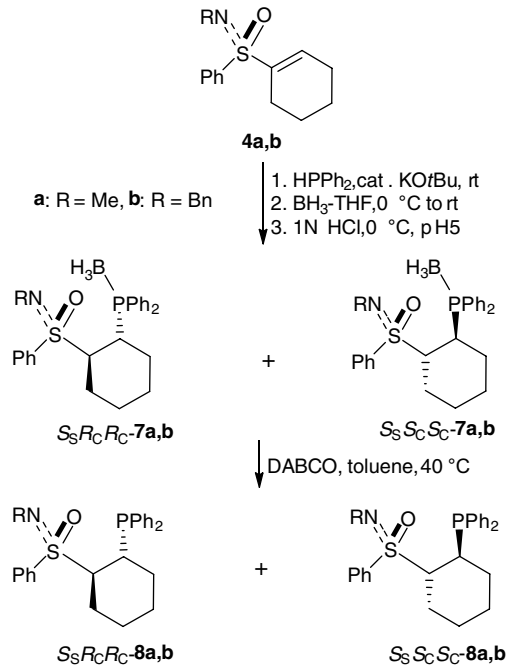
Compound	R	S_SR_C:S_SS_C	Yield[a] (%)
5a	Me	78:22	78
5b	Bn	64:36	78
5c	Ts	27:73	70
5d	$SitBuPh_2$	58:42[b]	80

[a] Overall yields based on sulfoximines **2a**–**d**.
[b] Configuration has not been assigned.

Table 3. Synthesis of cyclic phosphino-sulfoximines

Compound	R	$S_SR_CR_C$:$S_SS_CS_C$:$S_SR_CS_C$:$S_SS_CR_C$	Yield (%)[a]
7a	Me	50:50:0:0	80
7b	Bn	50:50:0:0	80

[a] Overall yields based on sulfoximines **4a** and **4b**.



Scheme 3. Synthesis of cyclic phosphino-sulfoximines.

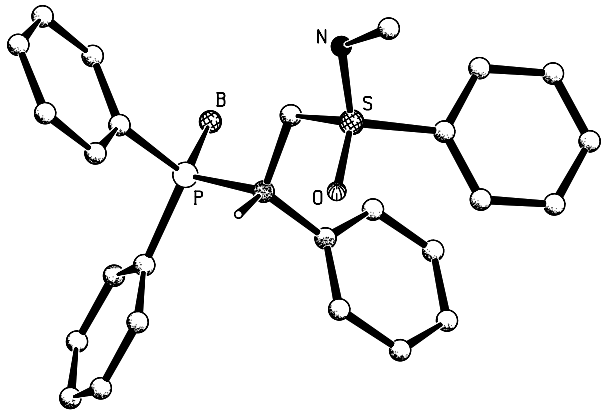


Figure 2. Structure of the phosphino-sulfoximine borane adduct R_SS_C-**5a** in the crystal. Selected bonding parameters: S–O 1.455(2), S–N 1.521(4), C–S 1.786(7), P–B 1.923(3), C–P 1.853(5).

revealed characteristic chemical shift differences, which allowed, with the exception of the *N*-silyl derivatives **5d**, in combination with the results of the crystal structure analysis a structural assignment.

Phosphanes **6a**–**d**, **8a**, and **8b** were obtained by treatment of the borane adducts **5a**–**d**, **7a**, and **7b**, respectively, with 1,4-diazabicyclo[2.2.2]octane (DABCO) in absolute toluene at 40 °C followed by a column filtration of the crude reaction mixtures under argon atmosphere in almost quantitative yields. In solution phosphanes **6a**–**d**, **8a**, and **8b** are sensitive toward oxygen.

The alkylation of malonate with racemic 1,3-diphenyl-2-propenyl acetate *rac*-**9** was selected as test reaction for ligands **6a**–**d**, **7a**, and **7b**. A mixture of 1.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone) and

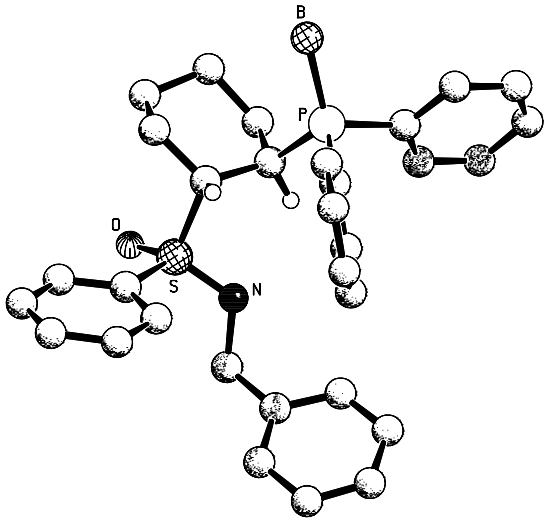
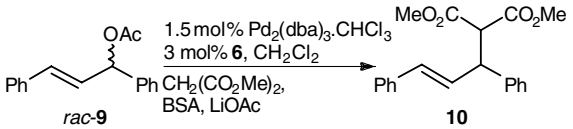


Figure 3. Structure of the phosphino-sulfoximine borane adduct $S_SR_CR_C$-**7b** in the crystal. Selected bonding parameters: S–O 1.434(4), S–N 1.492(4), C–S 1.830(4), P–B 1.927(6), C–P 1.841(4).

3 mol % of the ligand, which was heated at 40 °C under argon for 2 h, was treated with *rac*-**9**, *N*,*O*-bis(trimethylsilyl)acetamide (BSA), and a catalytic amount of LiOAc. Degassed CH_2Cl_2 was used as solvent since a screening of several solvents had shown it to be the best one in terms of activity and enantioselectivity.

Acyclic ligands **6a**–**d** were first tested. The reaction in the presence of the *R*-configured *N*-methyl-substituted ligand S_SR_C-**6a** gave the allyl derivative *R*-**10** with 65% ee (Table 4). Interestingly, the use of the *S*-configured ligand S_SS_C-**6a** afforded *S*-**10** with only 10% ee. This shows that not only the stereogenic C-atom but also the stereogenic S-atom plays an important role in the selectivity and activity of ligand **6a**. The substituent at the N-atom has also a significant effect on the selectivity of the catalyst. While the reaction in the presence of the *N*-methyl-substituted ligand S_SR_C-**6a** gave *R*-**10** with 65% ee, that with the *N*-benzyl substituted ligand S_SR_C-**6b** furnished *R*-**10** with 82% ee. Interestingly, experiments with the *N*-silyl- and *N*-tosyl-substituted sulfoximines **6c** and S_SR_C-**6d**, respectively, revealed very

Table 4. Acyclic 1,5-*P*,*N*-phosphino-sulfoximines in Pd-catalyzed alkylation



6	R	Confn	*T* (°C)	10		
				Yield (%)	ee[a] (%)	Confn
a	Me	S_SR_C	rt	90	65	*R*
a	Me	S_SS_C	rt	40	10	*S*
b	Bn	S_SR_C	rt	98	82	*R*
c	Ts	S_SS_C	rt	17	5	*S*
d	Si*t*BuPh$_2$	S_SR_C[b]	rt	5	15	*R*

[a] Determined by HPLC: Chiralpack-IA, *n*-heptane/isopropanol, 95:5, 0.75 ml/min, 35 bar.

[b] Configuration has not been assigned.

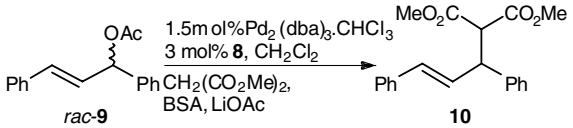
low enantioselectivities and activities of these catalysts. It is proposed that the striking difference between **6a**,**b** and **6c**,**d** is due to a different coordination of the Pd-atom by the ligands. While the *N*-alkyl-substituted sulfoximines **6a** and **6b** most likely act as bidentate P,N-ligands, the *N*-tosyl/silyl-substituted sulfoximines **6c** and **6d** function as monodentate P-ligands. Support for this notion comes from the reactivity of sulfoximines toward electrophiles and Lewis acids. While *N*-alkyl sulfoximines easily react with both at the N-atom, *N*-silyl and *N*-tosyl sulfoximines do not engage in such reactions.[17,18]

Having obtained promising results with the acyclic phosphino-sulfoximines, we investigated the Pd-catalyzed reaction of *rac*-**9** with malonate by using the cyclic phosphino-sulfoximines. The reaction of *rac*-**9** in the presence of the *N*-methyl-substituted ligand $S_SR_CR_C$-**8a** gave *R*-**10** with 86% ee (Table 5). With diastereomer $S_SS_CS_C$-**8a**, having the opposite configuration at the C-atoms, the reaction showed a reduced enantioselectivity and afforded the *S*-configured alkene *S*-**10** with only 73%. Thus, the catalysts containing cyclic ligands $S_SR_CR_C$-**8a** and $S_SS_CS_C$-**8a** exhibit a higher enantioselectivity than those derived from the acyclic ligands perhaps because of a higher rigidity. These results show furthermore that not only the chiral backbone but also the stereogenic S-atom of the cyclic ligands has a profound influence upon the selectivity.

The *N*-benzyl-substituted sulfoximine $S_SR_CR_C$-**8b** turned out to be the best ligand in terms of selectivity and activity of the catalyst. The Pd-catalyzed reaction of *rac*-**9** (0.5 mmol) with malonate in the presence of $S_SR_CR_C$-**8b** (3 mol %) gave *R*-**10** with 97% ee in 98% yield within 50 min. The corresponding reaction of *rac*-**9** in the presence of diastereomer $S_SS_CS_C$-**8b** afforded the *S*-configured alkene *S*-**10** with only 79% ee. The in situ generation of $S_SS_CS_C$-**8b** from borane adduct $S_SS_CS_C$-**7b** with DABCO did not diminish enantioselectivity of the Pd-catalyzed alkylation of *rac*-**9**.

Although the structure and dynamics of the π-allyl-Pd complex(es) derived from *rac*-**9** and $S_SR_CR_C$-**8b** are not known, formation of the diastereomeric chelate complexes **VI** and **VII**, featuring a P,N-coordination of the Pd-atom, may be assumed (Fig. 4). The proposal of a formation of chelate rather than mono-dentate complexes between Pd(0) and 1,5-*P*,*N*-phosphino-sulfoximines **6a**, **6b**, **8a**, and **8b** is based on the following observations. First, the Pd-catalyzed reaction of *rac*-**9** in the presence of phosphino-sulfoximines **6c** and **6d**, the N-atoms of which have a low Lewis basicity, proceeded only with low enantioselectivities. Second, the enantioselectivity of the Pd-catalyzed reaction of *rac*-**9** in the presence of cyclic phosphino sulfoximine $S_SR_CR_C$-**8a** (86% ee) remained the same upon changing the ligand Pd(0) ratio from 2:1 to 1:1. Reaction of **VI** could be faster than that of **VII** because of a steric interaction between the allyl- and P-phenyl groups as well as between the benzyl and the allyl-phenyl group in the latter complex. This model is based on the assumption that the attack of the nucleophile at **VI** trans to the P-atom is kinetically preferred. Such a preference for a trans-P-attack had been observed in π-allyl-Pd-complexes containing phosphino-oxazoline ligand **III**[19] and other P,N-ligands.[20]

Table 5. Cyclic 1,5-*P*,*N*-phosphino-sulfoximines in Pd-catalyzed alkylation



8	R	Confn	*T* (°C)	10		
				Yield (%)	ee[a] (%)	Confn
a	Me	$S_SR_CR_C$	rt	98	86	*R*
a	Me	$S_SS_CS_C$	rt	95	73	*S*
b	Bn	$S_SR_CR_C$	rt	98	97	*R*
b	Bn	$S_SS_CS_C$	rt	96	79	*S*
b[b]	Bn	$S_SS_CS_C$	rt	96	79	*S*

[a] Determined by HPLC: Chiralpack-IA, *n*-heptane/isopropanol, 95:5, 0.75 ml/min, 35 bar.

[b] Prepared in situ from its borane adduct with DABCO.

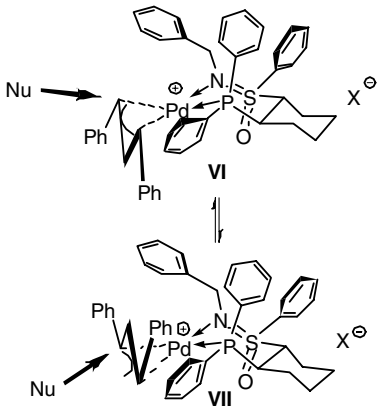


Figure 4. Alleged structures and dynamics of π-allyl-Pd-complexes containing $S_SR_CR_C$-**8b** as ligand.

In summary, we have developed a modular synthesis of acyclic and cyclic phosphino-sulfoximines of types **I** and **II**. The catalyst containing cyclic ligand $S_SR_CR_C$-**8b** showed high enantioselectivity. The asymmetric induction mainly stems from the chiral backbone of the ligand and to some extend also from the configuration of the sulfoximine group and the structure of its N-substituent. Because of the route chosen for the synthesis of phosphino-sulfoximines **6** and **8**, various derivatives should be accessible for further testing. A subject of further studies will be the enhancement of the diastereoselectivity of the phospha-Michael addition of alkenyl sulfoximines and the determination of the structure of the Pd(0)/**8** complexes.

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