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BINOL-derived *N*-phosphino sulfoximines as ligands for asymmetric catalysis

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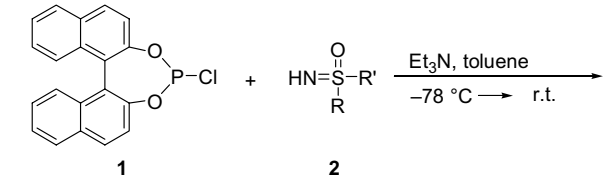
Abstract—BINOL-derived *N*-phosphino sulfoximines have been prepared for the first time and tested as ligands in asymmetric transition metal catalysis. Up to 99% ee was achieved in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins and up to 66% ee in the Pd-catalyzed allylic alkylation.

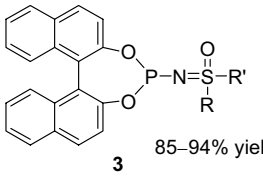
Optically active sulfoximines constitute an interesting class of auxiliaries and reagents in asymmetric synthesis.[1] However, only a few examples of phosphorylated sulfoximines as ligands in transition metal catalysis have been reported. Bolm and Müller were the first to recognize this possibility and used certain chiral *O*- and *C*-diphenylphosphino sulfoximines as ligands in such processes as Ni-catalyzed conjugate addition and Rh-catalyzed hydrosilylation reactions.[2] The application of a *C*-diphenylphosphino sulfoximine in Pd-catalyzed allylic substitution with sulfinates showed it to be far less selective than *P*,*P*- and *P*,*N*-ligands.[3] Thereafter, Tye prepared *N*-diphenylphosphino sulfoximines and used them as ligands in Cu-catalyzed conjugate addition reactions (ee up to 44%).[4] It is not clear in this case whether the ligand is monodentate at phosphorus or whether it undergoes a *P*,*O*-chelation. Along a different line BINOL-derived monodentate phosphites,[5] phosphonites[6] and phosphoramidites[7] were reported to be cheap and highly efficient ligands in asymmetric olefin-hydrogenation and several other types of reactions. A number of groups have used them and related monodentate ligands in a rapidly emerging area of research.[8]

Herein, we report the first synthesis of BINOL-derived *N*-phosphino sulfoximines and some preliminary results of their application as chiral ligands in Rh-catalyzed asymmetric hydrogenation and Pd-catalyzed allylic alkylation.

The new *N*-phosphino sulfoximines **3a**–**d** were synthesized by a straightforward one-step phosphorylation of the corresponding sulfoximines **2**, which are readily available from thioanisol,[9] with reagent **1**.[10] An alternative procedure,[11] also used for the preparation of ligand **3b**, is the phosphorylation of the nitrogen–TMS protected[12] sulfoximine (*S*)-**4** with (*S*)-**1** as phosphorylating agent (90% yield). This route requires an additional step (silylation of **2**), but it has the advantage that no salt has

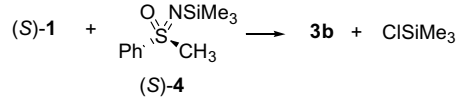


1 **2**



3 85–94% yield

a: R_{BINOL}/S_{Sulf}; R = Ph, R' = Me
b: S_{BINOL}/S_{Sulf}; R = Ph, R' = Me
c: R_{BINOL}/S_{Sulf}; R = Ph, R' = *t*-Bu
d: S_{BINOL}/S_{Sulf}; R = Ph, R' = *t*-Bu
e: R_{BINOL}; R = R' = Me
f: R_{BINOL}; R = R' = Ph



(*S*)-**4**

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to be separated from the ligands in the final step. The new BINOL-based ligands (*R*)-**3e**,**f** possessing achiral sulfoximine moieties were also prepared in order to compare their effectiveness in catalytic reactions. All of the ligands are stable under dry conditions for several months and highly soluble in common non-protic solvents.

Ligands **3a**, **3b**, **3e** and **3f** (two parts) were then treated with $[Rh(cod)_2]BF_4$ (cod = 1,5-cyclooctadiene) (one part) with formation of complexes $[Rh(cod)(\mathbf{3})_2]BF_4$, which were used as pre-catalysts in the hydrogenation of olefins **5**, **7**, **9** and **11** (solvent: CH_2Cl_2; Rh/substrate = 1:1000; 1.3 bar H_2; rt; 20 h). These are typical conditions in previous olefin-hydrogenation using BINOL-derived monodentate phosphites,[5] phosphonites[6] and phosphoramidites.[7] In the present case we likewise observed quantitative conversion in all reactions.

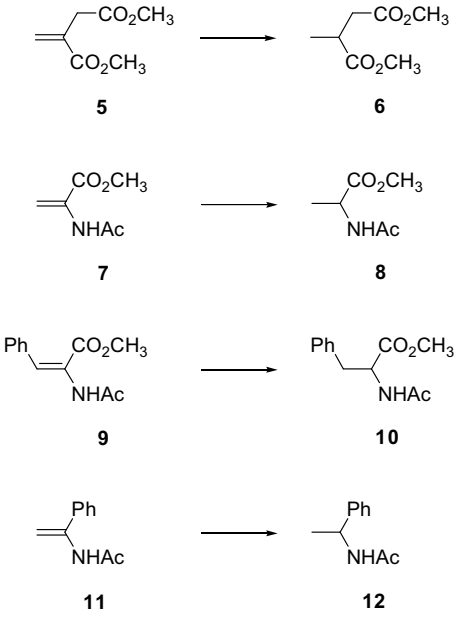


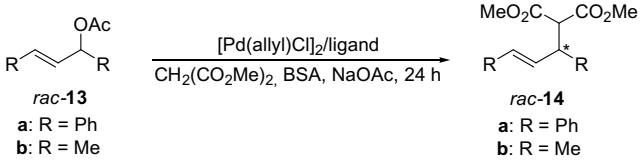
Table 1 shows that in the case of substrates **5**, **7** and **9** excellent ees are obtained and that the configuration at sulfur plays only a small role. Indeed, the ligands containing achiral sulfoximine moieties (**3e**,**f**) also lead to 94–99% ee. In contrast, in the hydrogenation of **11**, the configuration at sulfur is important. R_{BINOL}/S_{Sulf} constitutes the matched case (87.5% ee) in contrast to the mismatched combination S_{BINOL}/S_{Sulf} (76% ee). Ligands **3e**,**f** having achiral sulfoximine moieties are less effective in the hydrogenation of **11**, although in principle additional ligand tuning is possible using other achiral sulfoximines as building blocks.

Monodentate BINOL-based P-ligands have rarely been used in Pd-catalyzed allylic substitution reactions, the ees generally being moderate to poor (up to 60% ee).[13,14] Recently, Gavrilov has reported ees up to 90% in the reaction of *rac*-**13** with dimethyl malonate as the carbon nucleophile, the monodentate P-ligand being the BINOL-derived di-*n*-propyl phosphoramidite.[15] In order to see how the present ligands perform in this type of transformation, several of them were tested in the Pd-catalyzed allylic alkylation of 1,3-diphenylallyl acetate (*rac*-**13a**) and 3-penten-2-ol acetate (*rac*-**13b**) with dimethylmalonate as the *C*-nucleophile. The reactions were carried out in CH_2Cl_2 or THF at room temperature for 24 h in the presence of $[Pd(allyl)Cl]_2$ or $[Pd_2(dba)_3]CHCl_3$ using BSA (*N*,*O*-bis(trimethylsilyl)-acetamide) and a catalytic amount of sodium acetate, conditions that are applied when using classical diphosphanes as ligands.[16] The results are summarized in Table 2.

Table 1. Rh-catalyzed olefin-hydrogenation (Rh/substrate = 1:1000)

Substrate	Ligand	Configuration of product	% ee of product
5	**3a**	(*R*)	⩾99
5	**3b**	(*S*)	99.0
5	**3e**	(*R*)	⩾99
5	**3f**	(*R*)	98.0
7	**3a**	(*S*)	98.8
7	**3b**	(*R*)	98.0
7	**3e**	(*S*)	98.2
7	**3f**	(*S*)	98.2
9	**3a**	(*S*)	97.0
9	**3b**	(*R*)	94.0
9	**3e**	(*S*)	95.2
9	**3f**	(*S*)	94.0
11[a]	**3a**	(*S*)	87.5
11[a]	**3b**	(*R*)	76.0
11[a]	**3e**	(*S*)	84.5
11[a]	**3f**	(*S*)	64.0

[a] In this case Rh/substrate = 1:500.



rac-**13**
a: R = Ph
b: R = Me

rac-**14**
a: R = Ph
b: R = Me

The data allow the following conclusions to be made. Although the ees are better than in previous cases of using monodentate P-ligands,[13] they cannot compete with the best bidentate ligand systems reported in the literature.[16] However, interesting trends emerge. In many cases, the ratio of ligand to Pd has a profound influence on enantioselectivity. Increasing the steric demand of the aliphatic substituent R′ of the sulfoximine moiety by changing the methyl to a *tert*-butyl group improves the enantioselectivity. The best result (66% ee) was obtained with the bulkiest ligand **3c**. Moreover, in many instances a pronounced difference in the matched versus mismatched combinations becomes apparent (entries 1, 6 and 17, 22). The best case for 1,3-diphenylallyl acetate (*rac*-**13a**) involves the use of ligand **3c** prepared from (*R*)-BINOL and the (*S*)-sulfoximine, resulting in an ee-value of 63% (entry 10). 3-Penten-2-ol acetate (*rac*-**13b**) shows that this type of influence is rather pronounced, the highest enantioselectivity (63% ee) again resulting from the use of ligand **3c**.

In summary, *N*-phosphino sulfoximine ligands derived from the cheap BINOL and readily available chiral or

Table 2. Pd-catalyzed allylic alkylation using $[Pd(allyl)Cl]_2$ as precursor

Entry	Substrate	Ligand	Solvent	Ligand/Pd	Yield of **14** (%)	ee (%)
1	**13a**	**3a**	CH_2Cl_2	1/1	93	57 (*R*)
2	**13a**	**3a**	CH_2Cl_2	2/1	92	7 (*R*)
3	**13a**	**3a**	THF	1/1	76	39 (*R*)
4	**13a**	**3a**	THF	2/1	80	11 (*R*)
5	**13a**	**3a**	THF	1/1[a]	72	25 (*R*)
6	**13a**	**3b**	CH_2Cl_2	1/1	95	35 (*S*)
7	**13a**	**3b**	CH_2Cl_2	2/1	92	22 (*S*)
8	**13a**	**3b**	THF	1/1	75	15 (*S*)
9	**13a**	**3b**	CH_2Cl_2	1/1[a]	90	26 (*R*)
10	**13a**	**3c**	CH_2Cl_2	1/1	90	63 (*R*)
11	**13a**	**3c**	CH_2Cl_2	2/1	94	39 (*R*)
12	**13a**	**3c**	THF	1/1	82	42 (*R*)
13	**13a**	**3c**	THF	2/1	83	56 (*R*)
14	**13a**	**3d**	CH_2Cl_2	1/1	89	58 (*S*)
15	**13a**	**3d**	CH_2Cl_2	2/1	87	53 (*S*)
16	**13b**	**3a**	THF	1/1	86	32 (*S*)
17	**13b**	**3a**	THF	2/1	89	62 (*S*)
18	**13b**	**3a**	CH_2Cl_2	1/1	90	3 (*S*)
19	**13b**	**3a**	CH_2Cl_2	2/1	91	25 (*S*)
20	**13b**	**3a**	CH_2Cl_2	1/1[a]	83	1 (*S*)
21	**13b**	**3b**	THF	1/1	75	2 (*S*)
22	**13b**	**3b**	THF	2/1	87	3 (*S*)
23	**13b**	**3b**	CH_2Cl_2	1/1	93	7 (*S*)
24	**13b**	**3b**	CH_2Cl_2	2/1	89	10 (*S*)
25	**13b**	**3c**	THF	1/1	83	45 (*S*)
26	**13b**	**3c**	THF	2/1	85	64 (*S*)
27	**13b**	**3c**	THF	3/1	88	66 (*S*)
28	**13b**	**3c**	THF	4/1	86	64 (*S*)
29	**13b**	**3c**	CH_2Cl_2	2/1	90	57 (*S*)

[a] $[Pd_2(dba)_3]\cdot CHCl_3$.

achiral sulfoximines have been synthesized for the first time. These novel ligands show high enantioselectivity in the Rh-catalyzed hydrogenation of dimethyl itaconate and α-acetamidoacrylates (98–99% ee). They are far less selective in Pd-catalyzed allylic substitution. Further screening of these new chiral ligands in other types of reactions is currently in progress. Moreover, the question whether ligands **3** behave in a monodentate manner or whether *P*,*O*-bidentate chelation is involved, also needs to be addressed. Finally, compounds **3** can be used as components in mixtures of monodentate P-ligands, a new concept in combinatorial asymmetric catalysis.[17]

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