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C-Phosphanylated sulfoximines: synthesis and applications in asymmetric allylic substitution reactions

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Abstract—Starting from cyclic sulfonimidates, a number of C-phosphanylated enantiomerically pure sulfoximines have been prepared either as such or in protected form. Two of them, **5a** and *epi*-**5a**, have been used as ligands in palladium complex catalyzed allylic substitution reactions delivering the substitution product with up to 95% ee.

1. Introduction

Chiral bidentate P,N-ligands comprise an important class of ligands for asymmetric metal catalyzed transformations.[1] This is true, especially for systems displaying imino nitrogens and carbon-bound phosphanes as donor atoms, which in turn can be traced back to the favorable balance between the σ-donor ability of the former and the π-acceptor character of the latter binding site. Since the pioneering work of Faller on the electronic differentiation of allylic termini[2,3] in chiral molybdenum complexes, a large number of very successful ligands based on that principle have been described (Fig. 1).

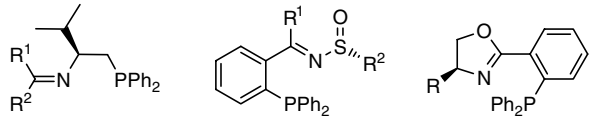
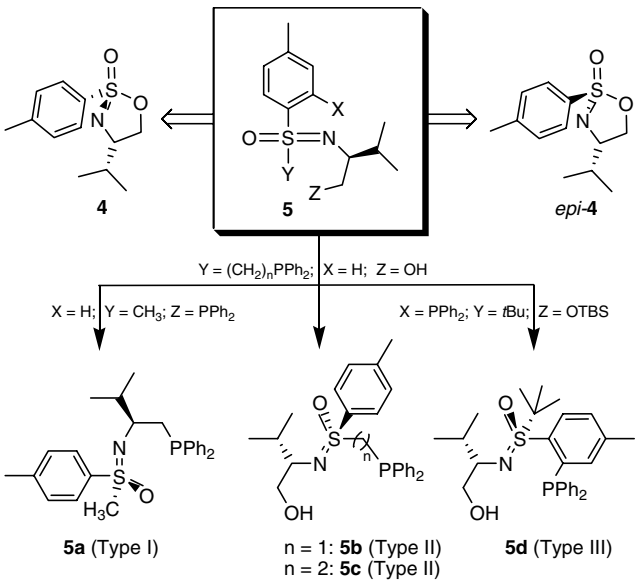


Figure 1. Important C-phosphanylated imino P,N-ligands.

Due to their structural resemblence to the ligands to be reported herein, the imino phosphanes **1**,[4–9] sulfinylimino phosphanes **2** (described by Schenkel and Ellman[10,11]) and phosphinooxazoline (PHOX) ligands **3** developed by Helmchen and Pfaltz[12] merit special attention. Amongst others, these and structurally related systems have been applied to the asymmetric allylic alkylation (AAA) reaction[13,14] and, for the PHOX ligands, their mode of action has been studied thoroughly by NMR spectroscopy.[15–19] In the course of our ongoing studies to elaborate upon enantiomerically pure sulfoximines as powerful reagents for stoichiometric asymmetric transformations,[20–24] we became struck by the idea of using these versatile compounds as ligands for asymmetric catalysis (Scheme 1).[25]



Scheme 1. C-Phosphanylated sulfoximines from cyclic sulfonimidates.

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A closer inspection of the generic structure **5** summarizing a whole class of novel C-phosphanylated sulfoximines reveals not only interesting similarities between ligands **1**–**3**, but also differences related to the interplay of the C- and S-stereogenic centers. When comparing **1** to **5a** and **5b**, it is obvious that all compounds should form five-membered ring chelates after metal complexation. However contrary to **1**, the stereogenic sulfur atoms appear as additional stereochemical control elements. Moreover, in **5a** and **5b** the position of both stereogenic centers is inverted. This raises interesting questions concerning their relative influence on the stereochemical outcome of reactions and to a possible mutual reinforcement of the asymmetric induction provoked by them. Ligands **2** and **3** are similar to **5c** and **5d** with respect to chelation (six-membered ring), but here again a concerted action of both stereogenic centers is to be expected. For these reasons and due to the fact that all four types of phosphino sulfoximines can be easily obtained by the commercially available sulfonimidates **4** and *epi*-**4**, we started a research program to explore the suitability of these ligand types for asymmetric catalysis.

Herein we report the syntheses of **5a**, *epi*-**5a**, **5b** (as oxide), and **5c** (as borane complex) as well as applications of the first two ligands in the AAA-reaction.

2. Results and discussion

The ring opening of **4** and *epi*-**4** by MeLi delivers the methyl sulfoximines **6** and *epi*-**6** in nearly quantitative yield (Scheme 2).[22,24,26,27] The subsequent mesylation required the application of the anhydride. With mesyl chloride, variable amounts of chlorinated products were obtained, presumably via aziridinium intermediates.[25] The reaction to the mesylates **7** and *epi*-**7** was complete after 2 h at 0 °C and therefore, could be used without further purification in the phosphanylation with the potassium diphenylphosphide–borane complex. This latter compound was prepared by deprotonation of the corresponding diphenylphosphane complex using potassium *t*butanolate (KO*t*Bu) as a base. The borane protected phosphanylated sulfoximines **8** and *epi*-**8** were isolated in 90% and 73% yield from the alcohols.

Both compounds are crystalline solids, which were amenable to X-ray structural analysis (Fig. 2).[32]

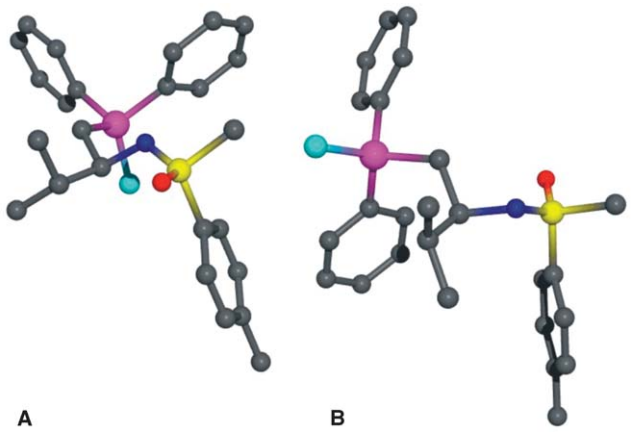


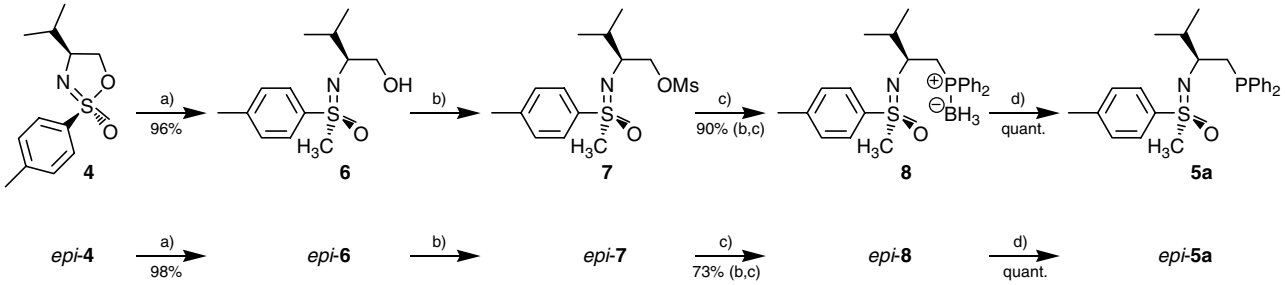
Figure 2. Crystal structures of the S-epimeric borane complexes **8** (A) and *epi*-**8** (B). Black: C; red: O; blue: N; yellow: S; magenta: P; cyan: B.

It is interesting to note that their solid state structures are quite different. Especially the NCCP torsional angle amounting 76° for **8** and 175° for *epi*-**8**, which indicates that the former might be much better suited for chelation of a metal in comparison to the latter. Due to the fact that the free phosphanes **5a** and *epi*-**5a** are rather sensitive to oxidation, their liberation from the boranes by DABCO should be part of the complexation procedure.

For the synthesis of a protected form of ligand **5b** we first tried to react the lithiated borane complexed methyl phosphane **9a** with the sulfonimidate **4** (Scheme 3).

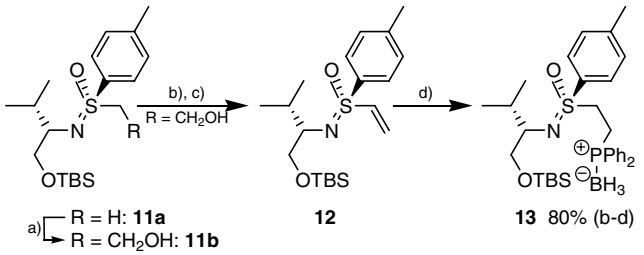
Scheme 3. Type II ligands.

To our surprise no product could be isolated and we therefore next used oxide **9b** in our second attempt. This time the desired phosphanylated sulfoximine **10b** was obtained in 31% yield, after 12 h of reaction time within



Scheme 2. Synthesis of **5a** and *epi*-**5a**. Reagents and conditions: (a) MeLi, THF, −78 °C; (b) methanesulfonyl anhydride, NEt_3, CH_2Cl_2, 0 °C; (c) $KPPh_2(BH_3)$, THF, rt; (d) DABCO, toluene, 65 °C.

which the temperature was slowly raised from −50 °C to rt. Finally we tried to gain access to phosphino sulfoximines incorporating a PCCSN bond path, as found in structures **5c** and **5d**. In fact, we were successful in preparing the latter compound via *ortho*-lithiation of the corresponding phosphane free precursor. However the product turned out to be very sensitive to oxidation and especially to acidic conditions.[28] Therefore, we synthesized **13** as an alternative (Scheme 4).

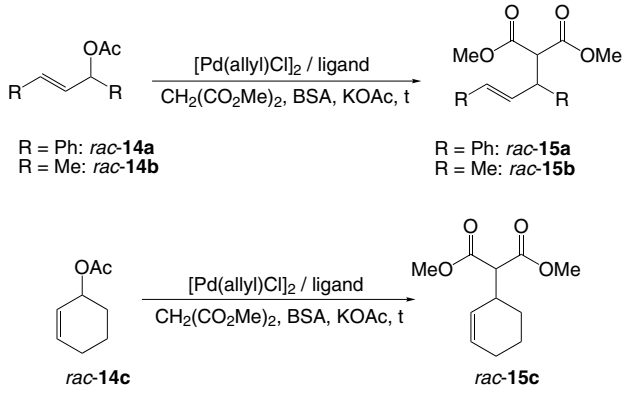


Scheme 4. Reagents and conditions: (a) *n*BuLi, THF, −78 °C then CH_2O; (b) *n*BuLi, THF, −78 to 0 °C then $ClCO_2Me$; (c) KO*t*Bu, THF, 0 °C rt; (d) $HPPh_2(BH_3)$, KO*t*Bu, THF, rt then **12**.

Hydroxyalkylation of the lithiated methyl sulfoximine **11a**[24–26] with gaseous formaldehyde (generated from paraformaldehyde by heating) followed by acylation with methyl chloroformate and KO*t*Bu induced elimination furnished vinyl sulfoximine **12**. Conjugate addition of $KPPh_2(BH_3)$ delivered the borane complexed phosphino sulfoximine **13**, which was fully characterized by 2D NMR and high resolution mass spectroscopy. Whereas the three-step sequence from alcohol **11b** to the target compound worked with an 80% overall yield without purification of intermediates, the reaction of metalated **11a** with formaldehyde turned out to be rather unsatisfactory (30%). To our surprise it was not possible to prepare **12** directly, via ring opening of **4** with vinyl lithium.

2.1. Pd-complex catalyzed allylic substitutions

Next we turned our attention to the application of **5a** and *epi*-**5a** in the palladium complex catalyzed allylic substitution reaction (Scheme 5).



Scheme 5. Reagents and conditions used for the AAA reactions.

To the best of our knowledge, this is the first application of C-phosphanylated sulfoximines in asymmetric allylic substitutions. In fact there is only one other application of this type of compounds in asymmetric catalysis. In a very recent paper, Bolm et al. described Ir-catalyzed hydrogenation reactions of imines using diphenylphosphanyl sulfoximines as ligands.[29] As substrates we used 1,3-diphenylallyl acetate *rac*-**14a**, (*E*)-3-penten-2-ol acetate *rac*-**14b** and cyclohexenyl acetate *rac*-**14c**. The C-nucleophile was prepared from dimethylmalonate using the BSA (*N*,*O*-bis(trimethylsilyl)acetamide) method in the presence of a catalytic amount of potassium acetate.[30] The reactions were carried out in either CH_2Cl_2, THF, or toluene at room temperature for reaction times as indicated in Table 1 at a substrate concentration of 0.15 M. The catalysts were generated by first deboranating **8** and *epi*-**8** with DABCO in toluene for 4 h at 65 °C followed by addition of $[Pd(allyl)Cl]_2$ as the palladium source. The first three entries in Table 1 clearly indicate that CH_2Cl_2 is the best solvent for the process, delivering (*R*)-**15a** in an almost quantitative yield with 93% ee in only 10 min.

The other solvents, especially THF, led to a drastic reduction of the reaction rate, although the ee remained almost constant. A 10-fold reduction of the catalyst load in the privileged solvent was possible (90% yield, 91% ee) but entailed unacceptably long reaction times (entry 4). To gain insight into the interplay of the different sources of chirality in the ligand, we inverted the absolute configuration at the sulfur without changing the one at carbon. Unsurprisingly this change had no effect on the absolute configuration of the product (entry 5). Moreover, only a minor (if any) effect on the stereoselectivity was observed (95% ee), which is a strong hint that the asymmetric induction is mainly governed by the C-stereogenic center as part of the assumed five-membered ring chelate being formed after complexation. Similar results were obtained with monodentate BINOL derived *N*-phosphino sulfoximines.[31] Although a little bit more pronounced than in our case, the absolute configuration at sulfur plays only a minor role in these systems too. The only recognizable significant change was on reactivity. With *epi*-**5a** as ligand, the reaction proceeded at least 6 times slower than with **5a**, which might be a consequence of the unfavorable conformational preferences of the former prior to complexation (Fig. 2). Unfortunately, aliphatic substrates **14b** and **14c** gave only unsatisfying stereoselectivites (entries 6 and 7). If one assumes that the stereochemical outcome of the reaction is governed by similar factors as found with the PHOX-ligands, this result is not very surprising.[12]

3. Conclusions

C-phosphanylated, enantiomerically pure sulfoximines of types I and II (Scheme 1) have been prepared for the first time by applying the commercially available sulfonimidates **4** and *epi*-**4** as common precursors. After deboranation of **8** and *epi*-**8** the resulting sulfoximino phosphanes can be used as ligands in the palladium

Table 1. Palladium complex catalyzed allylic substitution reactions as illustrated in Scheme 5[a]

Entry	R	Ligand	Solvent	Pd (mol %)	Temp (°C)	Time (t)	Yield (%)[b]	ee (%)[c]	Config.[d]
1	Ph	**5a**	CH_2Cl_2	10	20	10 min	99	93	*R*
2	Ph	**5a**	Toluene	10	20	4.5 h	97	91	*R*
3	Ph	**5a**	THF	10	20	192 h	74	89	*R*
4	Ph	**5a**	CH_2Cl_2	1	20	193 h	90	91	*R*
5	Ph	*epi*-**5a**	CH_2Cl_2	10	20	60 min	95	95	*R*
6	Me	**5a**	CH_2Cl_2	10	20	20 min	89	15	*R*
7	$-[CH_2]_3-$	**5a**	CH_2Cl_2	10	20	4 h	82	36	*S*

[a] All catalyses were run with a ligand:Pd ratio of 1:1. The concentration of the substrates was 0.15 M in all cases.
[b] Isolated yield.
[c] Determined by integration of the ^{1}H NMR resonances of the low-field OMe protons in the presence of 20 mol % $Eu(hfc)_3$.
[d] By comparison of the sign of specific rotation with those reported in the literature.

complex catalyzed allylic substitution reaction. Both S-epimeric complexes proved to be very active catalysts delivering the substitution product (*R*)-**15** with nearly quantitative yield on a minutes time scale (with **5a**) and $\geqslant$93% ee. These results clearly indicate that the major source of enantioselectivity is the valine derived C-stereogenic center, whereas the electron rich imino nitrogen of the sulfoximine serves as a rate enhancer very much like the amidine moiety in the VALAP-ligand.[9] The major difference between the two epimers is the much higher reactivity of **5a**, as compared to *epi*-**5a**. The *ortho*-phosphanylated sulfoximine **5d** turned out to be too acid sensitive to be of any practical value, whereas the type II ligands were not only stable compounds, but also appeared very promising from a stereochemical point of view. Here the S-stereogenic center would be part of the metal chelate, thus a pronounced effect on the stereochemical outcome of the reaction in combination with the rate enhancing effect of the sulfoximine nitrogen can be expected. Work along these lines is currently in progress as well as solution NMR studies on the structure of the complexes.

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References

1. Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.
2. Faller, J. W.; Chao, K.-H.; Murray, H. H. *Organometallics* **1984**, *3*, 1231.
3. Adams, R. D.; Chodosh, D. F.; Faller, J. W.; Rosan, A. M. *J. Am. Chem. Soc.* **1979**, *101*, 2570.
4. Hiroi, K.; Watanabe, K. *Tetrahedron: Asymmetry* **2001**, *12*, 3067.
5. Morimoto, T.; Yamaguchi, Y.; Suzuki, M.; Saitoh, A. *Tetrahedron Lett.* **2000**, *41*, 10025.
6. Saitoh, A.; Achiwa, K.; Tanaka, K.; Morimoto, T. *J. Org. Chem.* **2000**, *65*, 4227.
7. Suzuki, Y.; Ogata, Y.; Hiroi, K. *Tetrahedron: Asymmetry* **1999**, *10*, 1219.
8. Saitoh, A.; Achiwa, K.; Morimoto, T. *Tetrahedron: Asymmetry* **1998**, *9*, 741.
9. Saitoh, A.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3567.
10. Schenkel, L. B.; Ellman, J. A. *J. Org. Chem.* **2004**, *69*, 1800.
11. Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 545.
12. Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
13. Trost, B. M.; Vranken, D. L. v. *Chem. Rev.* **1996**, *96*, 395.
14. Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817.
15. Kollmar, M.; Goldfuss, B.; Reggelin, M.; Rominger, F.; Helmchen, G. *Chem. Eur. J.* **2001**, *7*, 4913.
16. Junker, J.; Reif, B.; Steinhagen, H.; Junker, B.; Felli, I. C.; Reggelin, M.; Griesinger, C. *Chem. Eur. J.* **2000**, *6*, 3281.
17. Reif, B.; Steinhagen, H.; Junker, B.; Reggelin, M.; Griesinger, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1903.
18. Steinhagen, H.; Reggelin, M.; Helmchen, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 2108.
19. Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M. *Tetrahedron Lett.* **1994**, *35*, 1523.
20. Reggelin, M.; Junker, B.; Heinrich, T.; Slavik, S.; Bühle, P. *J. Am. Chem. Soc.*, submitted for publication.
21. Reggelin, M.; Junker, B. *Chem. Eur. J.* **2001**, *7*, 1232.
22. Reggelin, M.; Gerlach, M.; Vogt, M. *Eur. J. Org. Chem.* **1999**, 1011.
23. Reggelin, M.; Heinrich, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 2883.
24. Reggelin, M.; Weinberger, H.; Gerlach, M.; Welcker, R. *J. Am. Chem. Soc.* **1996**, *118*, 4765.
25. Reggelin, M.; Weinberger, H.; Spohr, V. *Adv. Synth. Catal.* **2004**, *346*, 1295.
26. Reggelin, M.; Weinberger, H. *Tetrahedron Lett.* **1992**, *33*, 6959.
27. Reggelin, M.; Weinberger, H. *Angew. Chem., Int. Ed.* **1994**, *33*, 444.
28. Dupas, G.; Levacher, V. *Tetrahedron* **2005**, *61*, 8138.
29. Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564.
30. Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, *109*, 1469.
31. Reetz, M. T.; Bondarev, O. G.; Gais, H. J.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 5643.
32. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 289283 and 289284. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].