P, S Ligands

DOI: 10.1002/ange.200701040

N-Phosphino Sulfinamide Ligands: An Efficient Manner To Combine Sulfur Chirality and Phosphorus Coordination Behavior**

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Chiral bidentate ligands are almost ubiquitous in metal catalysis.[1] This type of ligand can be classified according to where the chiral information lies in their structures and the nature of the coordinating atoms (Figure 1). Most commonly,

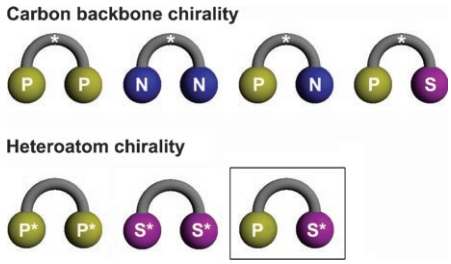
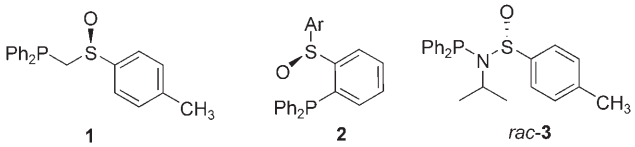


Figure 1. Chiral bidentate ligands can be classified depending on where the chirality lies in their structure.

chirality resides in the carbon backbone (for example, diop,[2] binap,[3] box,[4] phox,[5] fesulphos[6]). A smaller group of chiral bidentate ligands are based on chiral phosphorus and sulfur. Some P-chirogenic ligands (such as dipamp[7] and quinoxP*[8]) are highly effective in a variety of asymmetric processes. However, the synthesis of chiral-phosphorus ligands is often complex and difficult. In contrast, the preparation of chiral-sulfur compounds is more convenient and several chiral sulfoxides and sulfinamides are commercially available.[9] In 1997, Ellman and co-workers introduced *tert*-butylsulfinamide.[10] This chiral sulfur compound is now available in large amounts and is used as a sacrificial chiral auxiliary in a wide range of synthetic processes.[11] Conversely, there are only a few cases in which *tert*-butylsulfinamide has been used in the construction of chiral ligands. A notable example is the siam ligand, which has been successfully applied to the copper-catalyzed asymmetric Diels–Alder reaction.[12] The limited use of sulfinamides in metal catalysis is due to their poor coordination capacity with respect to phosphines and phosphites. This limitation could be addressed by the preparation of phosphine–sulfinamide ligands in which the phosphorus atom would provide metal affinity while the sulfur moiety would be the source of chirality (Figure 1).

Only a few P,S=O ligands have been described in the literature (Scheme 1). The main weakness of these ligands is



Scheme 1. Phosphine–sulfoxide and phosphine–sulfinamide ligands described in the literature.

the sulfur-to-phosphorus oxygen migration side reaction, which jeopardizes their chemical stability. Thus, when pure, compound **1** is stable towards oxygen migration, although it can only be prepared in 23% yield.[13] Hiroi and co-workers reported that ligand **2** suffers from oxygen transfer when heated in THF.[14] To our knowledge there is only one report on the synthesis of *N*-phosphino sulfinamides (**3**) in racemic form.[15] We considered this family of compounds to have a great potential as chiral ligands since they can act as monodentate or bidentate (P,S or P,O) ligands. Furthermore, we thought that they could be easily assembled from the corresponding chlorophosphine and chiral sulfinamide. Herein we report on the synthesis of novel *N*-phosphino sulfinamide (PNSO) ligands and their application in the intermolecular asymmetric Pauson–Khand reaction.

Initial trials to prepare the desired ligands failed because of the undesired oxygen migration. Phosphinylation of **4** in the presence of a base (Et_3N) in THF provided the corresponding rearranged phosphinamide **5** in quantitative yield (Scheme 2). Deprotonation with *n*BuLi at low temperature and subsequent addition of Ph_2PCl again produced **5** as a major reaction product.[16] Fortunately, the use of borane as a phosphine-protecting group allowed the synthesis of the desired compound. Quenching the phosphinylation reaction at −30 °C with the $BH_3{\cdot}SMe_2$ complex prevented oxygen rearrangement and provided the borane-protected phosphine **6**. Deprotection of **6** with DABCO at room temperature afforded the PNSO ligand **7** in good overall yield (54%). At this stage, the free ligand **7** was stable towards oxygen migration.

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[**] This work was supported by MEC-MYCT (CTQ2005-623). X.V. thanks the DURSI for "Distinció per a la Promoció de la Recerca Universitaria". J.S. thanks the DURSI and Universitat de Barcelona for a fellowship.

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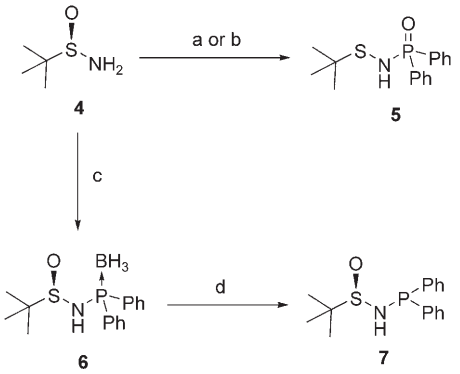
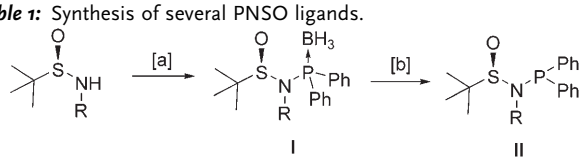


Scheme 2. Synthesis of *N*-phosphino *tert*-butylsulfinamide **7**. Reagents and conditions: a) Ph_2PCl, NEt_3, THF, 99%; b) BuLi, Et_2O, −78°C, then Ph_2PCl, reflux; c) BuLi, THF, −78°C, Ph_2PCl, then quenching with $BH_3{\cdot}SMe_2$ at −30°C, 66%; d) 1,4-diazabicyclo[2.2.2]octane (DABCO), toluene, RT, 83%.

Table 1: Synthesis of several PNSO ligands.



Entry	R	Yield of **I** [%][c]	Yield of **II** [%][c]	Ligand[d]
1	H	66	83	**7**
2	CH_3	83	96	**8**
3	Bn	86	95	**9**
4	*p*-F-$C_6H_4CH_2$	88	88	**10**
5	*p*-MeO-$C_6H_4CH_2$	81	90	**11**

[a] BuLi, THF, −78°C, Ph_2PCl, then $BH_3{\cdot}SMe_2$ at −30°C. [b] DABCO, toluene, RT. [c] Yields of isolated product after flash chromatography. [d] Ligands **7**–**11** correspond to structure **II**.

Subsequent to this procedure and taking several *N*-substituted sulfinamides as starting material, we synthesized a family of *N*-diphenylphosphino *tert*-butylsulfinamides (Table 1).[17] Thus, *N*-methyl and a number of *N*-benzyl ligands were prepared in good to excellent yields. PNSO ligands **8**–**11** are highly crystalline solids. Most interestingly, the synthesis we developed provided ligands which are stable towards internal oxygen transfer in the solid state or in solution. Finally, the stereochemical integrity of these ligands was examined by chiral HPLC and no racemization was found to take place during the synthesis.

During recent years our group has explored the use of bidentate P,S ligands in the asymmetric Pauson–Khand reaction.[18–21] Thus, to take advantage of our experience in this field, we began to study the coordination behavior of PNSO ligands towards dicobaltcarbonyl–alkyne complexes. Heating the ligands with the dicobalthexacarbonyl complex of 2-methyl-3-buyn-2-ol at 65–70°C in toluene provided a diastereomeric mixture of bridged complexes (Table 2, entries 1–3). Most interestingly, the *N*-benzyl ligand **9** gave enhanced reaction yields and diastereoselectivities (Table 2, entry 3). To determine whether the PNSO ligands acted as P,S or P,O ligands, an X-ray analysis of the major diastereomer **14a** was carried out (Figure 2). We found that the sulfinamide moiety was bound to the metal center through the sulfur atom, the Co–S bond length being 2.19(1) Å. Reaction with other dicobalt–alkyne complexes provided even higher yields and diastereoselectivities (up to >20:1). Most diastereomeric mixtures were

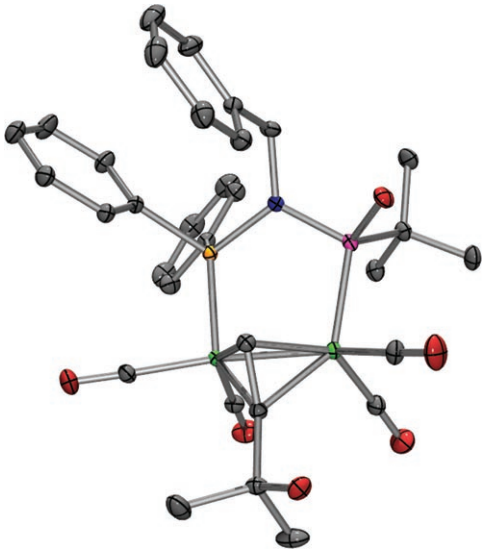
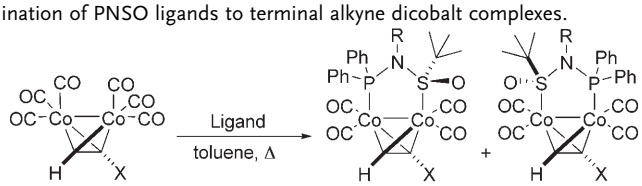


Figure 2. ORTEP plot of crystal structure **14a**. Thermal ellipsoids are shown at 50% probability; Co green, P yellow, N blue, S magenta, O red, C gray.

Table 2: Coordination of PNSO ligands to terminal alkyne dicobalt complexes.



Entry	X	L	R	Conditions	Yield [%][a]	d.r.[b]	Complex
1	$C(CH_3)_2OH$	**7**	H	70°C, 10 h	20[d]	1:1	**12a/12b**
2	$C(CH_3)_2OH$	**8**	Me	65°C, 16 h	92	1.5:1	**13a/13b**
3	$C(CH_3)_2OH$	**9**	Bn	65°C, 16 h	95	7:1	**14a/14b**
4	TMS	**9**	Bn	70°C, 16 h	78	12:1	**15a/15b**
5	Ph	**9**	Bn	65°C, 5 h	81	8:1	**16a/16b**
6	$CH_2OTBDPS$	**9**	Bn	65°C, 6 h	85	10:1	**17a/17b**
7	CH_2OH	**9**	Bn	65°C, 5 h	50	>20:1	**18a/18b**
8	TMS	**10**	*p*-F-$C_6H_4CH_2$	65°C, 40 h	99	10:1	**19a/19b**
9	TMS	**11**	*p*-MeO-$C_6H_4CH_2$	65°C, 24 h	75	12:1	**20a/20b**

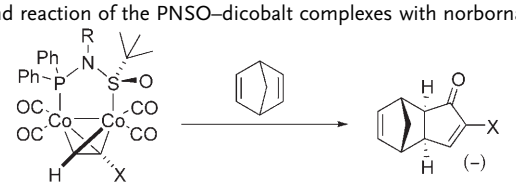
[a] Diastereomeric mixture, yield of isolated product after purification by flash chromatography. [b] Diastereomeric ratio determined by ^1H NMR analysis. [c] Yield estimated by ^1H NMR analysis of the resulting reaction mixture. TMS = trimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

crystalline and hence the major diastereomer was conveniently purified by crystallization. To our knowledge this is the first example in which a sulfonamide or a sulfoxide has been reported to bind to cobalt through sulfur. In this system the chiral center is adjacent to the metal center, and this fact could be the origin of the high selectivity observed. Furthermore, the substituent on the nitrogen atom would act as a relay element, transmitting the chiral information throughout the ligand. The improved stereocontrol obtained with *N*-benzyl with respect to *N*-H and *N*-methyl ligands confirms this mode of action.

Finally, we tested the tetracarbonyl complexes in the asymmetric intermolecular Pauson–Khand reaction with norbornadiene (NBD). The resulting chiral cyclopentenones, by means of a retro-Diels–Alder reaction sequence, are interesting building blocks for the synthesis of deoxyphytoprostanes.[22] Reaction of diastereomerically pure complexes **14a**–**20a** with NBD produced a highly stereoselective cyclocarbonylation (Table 3). Thus, with complex **14a**, either thermal or *N*-oxide-promoted conditions provided the corresponding Pauson–Khand adduct **21** in an excellent yield and for the first time in 92–93% enantiomeric excess (Table 3, entries 1 and 2).[23] The corresponding complexes **16a** and **17a** reacted smoothly with the alkene at room temperature to give quantitatively cyclopentenones with 99% and 92% *ee*, respectively (Table 3, entries 4 and 5). From a synthetic point of view, compounds **24** and **25** are of great interest since the hydroxymethyl moiety is suitable for further elaboration. In this regard, diastereomeric complexes **18a**/**18b** could not be separated by crystallization, and the resulting mixture of diastereomers (with d.r. > 20:1) was used as such (Table 3, entry 6). This reaction provided **25** with 73% *ee*. Finally, the use of substituted *N*-benzyl ligands provided some clues about the electronic effects that occur in this process. The reaction of **20a**, bearing a *p*-MeO-benzyl group, provided complete stereocontrol in the cyclization (Table 3, entry 7), while the reaction of **19a** with an electron-withdrawing *p*-F-benzyl group showed a decrease in selectivity (Table 3, entry 8). This behavior can be explained on the basis that electron-deficient phosphines are more prone to isomerization within the bimetallic complex, thus jeopardizing the stereochemical integrity of the initial dicobalt–PNSO complex.

In summary, we describe the synthesis of *N*-phosphino *tert*-butylsulfinamides, which represent a novel class of chiral ligands. These compounds can be conveniently assembled from the corresponding commercially available chiral *tert*-butylsulfinamide in two steps. This procedure represents an efficient manner to combine the easily accessible sulfur chirality with the phosphorus coordination abilities. Our study of the coordination behavior of the PNSO ligands towards bimetallic cobalt–carbonyl complexes indicates that they work as bidentate P,S ligands. This work represents the first example of a chiral sulfur atom coordinated to a cobalt center. Finally, intermolecular Pauson–Khand reaction of the corresponding complexes occurred with unprecedented stereoselectivity. Given their unique structure, we conclude that PNSO ligands have a rich coordination chemistry which could be relevant for further applications in asymmetric synthesis and catalysis.

Table 3: Pauson–Khand reaction of the PNSO–dicobalt complexes with norbornadiene.



21–25

Entry	Complex	R	X	Conditions[a]	Yield [%][b]	*ee* [%][c]	Product
1	**14a**	Bn	$C(CH_3)_2OH$	A, 1 h	95	92	**21**
2	**14a**	Bn	$C(CH_3)_2OH$	B, 16 h	87	93	**21**
3	**15a**	Bn	TMS	B, 16 h	99	97	**22**
4	**16a**	Bn	Ph	C, 4 h	99	99	**23**
5	**17a**	Bn	$CH_2OTBDPS$	C, 5 h	99	92	**24**
6	**18a**/**18b**[d]	Bn	CH_2OH	B, 16 h	65	73	**25**
7	**20a**	*p*-MeO-$C_6H_4CH_2$	TMS	B, 40 h	99	> 99	**22**
8	**19a**	*p*-F-$C_6H_4CH_2$	TMS	B, 48 h	99	78	**22**

[a] A: Toluene, 70 °C; B: 6 equiv *N*-methylmorphonline *N*-oxide, CH_2Cl_2, RT; C: toluene, RT. [b] Yield of isolated product after purification by flash chromatography. [c] Enantiomeric excess determined by either chiral HPLC or GC. [d] > 20:1 (^{1}H NMR) diastereomeric mixture of complexes was used.

Received: March 8, 2007
Published online: May 24, 2007

Keywords: asymmetric synthesis · cobalt · P ligands · Pauson–Khand reaction · S ligands

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