First planar chiral bidentate ligand based on a (η⁵-cyclopentadienyl)(η⁴-cyclobutadiene) cobalt backbone: high efficiency in enantioselective palladium-catalyzed allylic substitutions†

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The synthesis of the planar chiral (R)-[η⁵-(1-diphenylphos-phino-2-*tert*-butylsulfenyl)cyclopentadienyl](η⁴-tetraphenylcy-clobutadiene) cobalt and its high efficiency as P,S-bidentate ligand in Pd-catalyzed allylic substitutions is described.

In recent years the use of chiral bidentate ligands having strong and weak donor heteroatomic groups has proved to be a very useful tool in enantioselective catalysis.[1] Among the wide variety of chiral skeletons currently used in ligand design, planar chiral 1,2-dis-ubstituted ferrocenes with P,P- and P,N-coordination modes have become increasingly popular,[2] and even industrial applications have been developed.[3] In this field we have recently described that 1-phosphino-2-sulfenylferrocene ligands (Fesulphos), possessing planar chirality only, act as very efficient P,S-ligands in Pd-catalyzed allylic substitutions[4] and in Cu-catalyzed formal hetero Diels–Alder cycloadditions.[5] Taking into account the great interest in ferrocenes in enantioselective catalysis, it is surprising that few studies dealing with non-metallocene planar chiral ligands have been reported.[6] One of these appealing organometallic backbones is the readily available and chemically robust (η⁵-cyclopentadie-nyl)(η⁴-cyclobutadiene)cobalt moiety. With these types of com-pounds, as far as we are aware, only the chiral oxazoline-based complexes **I**[7] and a palladacycle derivative **II**,[8] reported by Richards *et al.* (Fig. 1), have been used in enantioselective catalysis.

This paper reports the synthesis of the (R)-[η⁵-(1-phosphino-2-sulfenyl)cyclopentadienyl](η⁴-tetraphenylcyclobutadiene)cobalt complex **1** (Cosulphos ligand), having solely planar chirality, and its high asymmetric efficiency as a P,S-bidentate ligand in Pd-catalyzed allylic substitutions.

We envisaged that the introduction of planar chirality at the Cp(η⁴-C₄Ph₄)Co unit could be accomplished, as previously developed by Kagan *et al.* in the case of ferrocenes,[9] by diastereoselective *ortho*-lithiation of a suitable sulfinyl derivative such as **3**, which in turn could be accessed by lithiation of complex (η⁵-C₅H₅)(η⁴-C₄Ph₄)Co (**2**) and subsequent treatment with a chiral sulfinylating agent. However, as others have noted previously,[10] the functionalization of this type of cobalt complex at the Cp ring is a challenge. For example, it has been reported that direct lithiation of complex **2** under usual conditions fails, although this metallocene was successfully functionalized through electrophilic aromatic substitution.[10] On the other hand, the diastereoselective
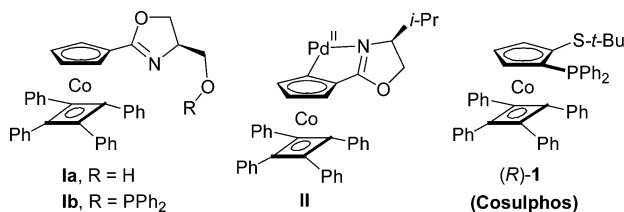
ortho-lithiation of oxazolines of type **I** with *n*-BuLi, *sec*-BuLi and *tert*-BuLi has also been reported to fail, despite the use of additives such as TMEDA and prolonged reaction times.[8b]

Initial efforts towards deprotonation of complex **2**[11] with *n*-BuLi, *sec*-BuLi or *tert*-BuLi, both alone or in combination with activating additives such as TMEDA or DMPU, followed by trapping with various electrophiles were unsuccessful. Gratifyingly, the function-alization of **2** at the Cp ring was achieved with the superbasic reagent combination of *tert*-BuLi (1.0 equiv.) and potassium *tert*-butoxide (1.0 equiv.) in a 3 : 1 mixture of THF–pentane at 0 °C.[12,13] Quenching with enantiopure (R)-S-*tert*-butyl *tert*-butanethiosulfi-nate[14] at −78 °C produced the (R)-*tert*-butylsulfoxide **3** in 36% yield (64% of starting complex **2** was recovered) and extremely high enantiopurity (ee > 99.5%, HPLC, Chiralcel OD column) as a result of the complete inversion of the configuration at sulfur (Scheme 1).

Interestingly, the diastereoselective functionalization at C-2 was smoothly achieved by simple treatment of (R)-**3** with 1.2 equiva-lents of *tert*-BuLi (THF, −78 °C) and subsequent addition of Ph₂PCl. The phosphine (R_S,R_p)-**4** was obtained in 84% yield as the only product detected by NMR in the crude reaction mixture. Once the central (R) chirality of the sulfinyl directing group was applied to the generation of the (R) planar chirality, the sulfoxide **4** was reduced to the desired sulfide ligand (R)-**1** by treatment with HSiCl₃–Et₃N in refluxing toluene (86% yield). As expected, optical purity of (R)-**1** was proved to be higher than 99.5% ee (HPLC, Chiralpak AD column).

The efficiency of this new ligand was tested in the asymmetric Pd-catalyzed allylic substitution reaction. Table 1 shows the results obtained in the reaction of 1,3-diphenylpropenyl acetate with a variety of nucleophiles in the presence of (R)-**1**. Typically the reactions were performed using a combination of [Pd(η³-C₃H₅)Cl]₂ (2 mol%) and ligand **1** (4 mol%) as catalyst at temperatures from −20 °C to room temperature. After a brief search of solvents, it was found that THF and CHCl₃ provided the best results in terms of both reactivity and enantioselectivity, the former being optimal in the case of malonate (entries 1–5) and benzylamine, and the latter was found to be the best solvent for the reaction with potassium phthalimide (entries 6–7). Interestingly, good yields and excellent enantioselectivities (97–99% ee) were achieved with all nucleo-philes.

The bidentate character of **1** as a P,S-ligand was demonstrated by an X-ray crystallographic study of the complex (**1**)PdCl₂[15] (Fig. 2), readily obtained as a single epimer at sulfur by the reaction of **1** with Pd(CH₃CN)₂Cl₂ in CH₂Cl₂ at room temperature (82% yield).

Fig. 1 Chiral (η⁵-C₅H₅)(η⁴-C₄Ph₄)Co-based catalysts used in enantiose-lective catalysis.
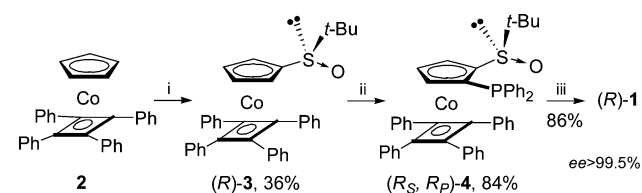
Scheme 1 Reagents and conditions: i. *t*-BuLi (1.0 equiv.)–K-*t*-BuO (1.0 equiv.), THF–pentane (3 : 1), −78 °C; (R)-*t*-BuS(O)-S-*t*-Bu. ii. *t*-BuLi (1.0 equiv.), THF, −78 °C; Ph₂PCl. iii. HSiCl₃, Et₃N, toluene, 110 °C.

The crystal structure of (**1**)PdCl$_2$ confirmed the (*R*) planar configuration previously established on chemical considerations.
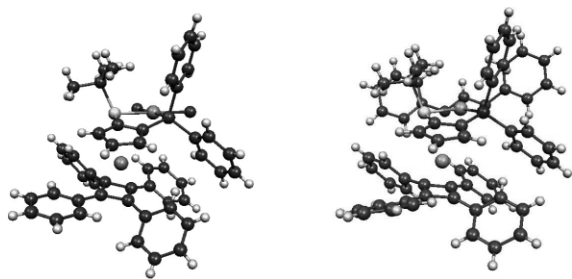
To obtain additional mechanistic evidence of the reasons for the high asymmetric performance of **1**, the key cationic π-allyl palladium intermediate complex **5** was prepared by reaction of stoichiometric amounts of the (*trans*-1,3-diphenylpropenyl) palladium dichloride dimer and **1** in the presence of AgSbF$_6$ (85% yield, as a 3 : 1 mixture of isomers). X-Ray quality crystals of complex **5** were obtained from an EtOAc solution at room temperature. Fig. 2 shows the ORTEP drawing of complex **5a**,[15] in which the allylic moiety adopts a W-type configuration. As expected, the bond between Pd and the terminal allylic carbon atom which is *trans* to phosphorus was longer (Pd–C = 2.259 Å) than that which is *trans* to sulfur (Pd–C = 2.183 Å), indicating the stronger *trans* effect of the phosphine moiety compared to the thioether.[4,16] NMR studies of complex **5** in CD$_2$Cl$_2$ allowed the unambiguous assignment of the major isomer **5a** as W-configuration, mainly based on several critical NOE contacts.[17] Besides, the terminal allylic carbon atom *trans* to phosphorus appears at much lower field (101.0 ppm) than that which is *trans* to sulfur (77.7 ppm), reflecting the much higher electrophilicity of the former.[4,16] Therefore, the high enantioselectivity achieved in these reactions (97–99% ee) could be readily explained by the attack of the nucleophile *trans* to phosphorus on the complex **5a** (Fig. 3), which should exist in a fast equilibrium with the isomer of M-configuration **5b** (Curtin–Hammet conditions).

In summary, the first bidentate chiral ligand based on a stereoselective 1,2-heteroatomic disubstitution on a Cp(η^4-tetra-pheny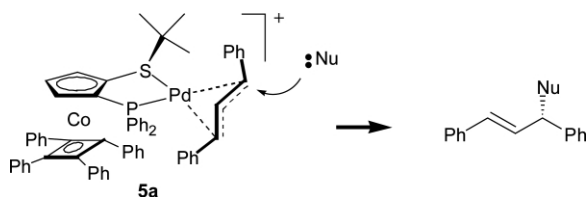lcyclobutadiene)cobalt complex has been prepared. The readily available P,S-bidentate ligand (*R*)-**1** (Cosulphos) provides very high enantioselectivities in Pd-catalyzed allylic substitutions with both carbon and nitrogen nucleophiles. The extension of this methodology to the preparation of related planar cosulphos ligands is underway.

Notes and references

† Electronic supplementary information (ESI) available: crystal data and experimental details. See http://www.rsc.org/suppdata/cc/b4/b405342g/

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Table 1 Pd-catalyzed reaction of 1,3-diphenyl-2-propenyl acetate with nucleophiles in the presence of ligand (*R*)-**1**

Entry	Nu	Solvent	T/h	Yield (%)^a	Ee (%)^b
1^c	(CO$_2$Me)$_2$CH$_2$	CHCl$_3$	48	61	95
2^c	(CO$_2$Me)$_2$CH$_2$	THF	1	99	98
3	BnNH$_2$	CHCl$_3$	48	65^e	90
4	BnNH$_2$	THF	3	96	97
5^d	BnNH$_2$	THF	48	45^e	98
6	KPhth	CHCl$_3$	48	70	98
7^d	KPhth	CHCl$_3$	48	80	99

^{a} In pure product after chromatography. ^{b} Determined by HPLC (Chiralcel OD and AD). ^{c} In the presence of BSA and 10 mol% of Bu$_4$NCl. ^{d} Reaction performed at −20 °C. ^{e} Conversion yield (determined by NMR).

Fig. 2 ORTEP drawings of complexes (**1**)PdCl$_2$ (left) and **5a** (right, SbF$_6^-$ anion has been omitted for clarity).

Fig. 3 Proposed model for the asymmetric allylic substitutions.