Journal of Organometallic Chemistry 717 (2012) 135–140

Contents lists available at SciVerse ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Neutral *vs.* cationic rhodium (I) complexes of bulky *N*-phosphino sulfinamide ligands: Coordination modes and its influence in the asymmetric hydrogenation of *Z*-MAC

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ARTICLE INFO

Article history:
Received 8 May 2012
Received in revised form
28 June 2012
Accepted 8 July 2012

Keywords:
P,S and P,O ligands
Rhodium
Asymmetric hydrogenation
Sulfinamides

ABSTRACT

Here we report the synthesis of a new *N*-di-*tert*-butylphosphino-*tert*-butylsulfinamide (PNSO) ligand and its corresponding *p*-tolylsulfinamide analog. The coordination of these compounds to rhodium to form a neutral and apolar complex is described, followed by the subsequent protonation of said complexes to quantitively form the more orthodox, cationic rhodium species containing a tetrafluoroboric counterion. The crystallographic structure of the *tert*-butylsulfinamide-derived cationic species was obtained and is elucidated. It outlines coordination from the sulfinamide group to the rhodium atom and shows no preference between O- and S-coordination as both complexes can be seen in one unit cell of the crystal. The efficacies of the neutral species and the salt species were tested in the asymmetric hydrogenation of methyl (Z)-α-acetamido cinnamate (*Z*-MAC). The *p*-tolylsulfinamide-derived complexes gave no hydrogenation while the *tert*-butylsulfinamide-derived ones produced hydrogenation with complete conversion but low enantioselectivities. The stereochemical outcome of the reaction was analyzed by means of the quadrant method.

1. Introduction

Chiral bi-dentate ligands have become highly relevant in the field of asymmetric catalysis. These compounds not only increase reactivity but more importantly, they induce the high enantioselectivities currently demanded by the pharmaceutical industry [1]. Thus moving the chiral information of the ligand as close as possible to the catalyzing metal center would be the best way to efficiently confer chirality to and increase enantioselectivities of the catalytic transformations that the catalyst is mediating. This could be achieved by conferring chirality to the metal-coordinating atom. P-stereogenic bidentate diphosphine ligands are extremely proficient in asymmetric transformations [2]. In 2004 Hoge et al. reported the synthesis and efficacy of the three-hindered quadrant chiral ligand trichickenfootphos (TCFP) in the Rh-catalyzed asymmetric hydrogenations of α- and β-acetamido dehydroamino acid substrates [3]. The excellent enantioselectivities obtained suggested the C_1-symmetric, 3-hindered quadrant chiral ligand design was an excellent template to follow. MaxPHOS, an analog of the TCFP ligand, was developed in our laboratory and was first reported in 2010 [4,5]. As with TCFP, it showed excellent enantioselectivity in the asymmetric hydrogenation of α- and β-acetamido dehydroamino acid substrates. Despite the great efficiency of this type of ligand, its synthesis remains somewhat laborious [6]. In this respect, here we addressed the preparation of other cost-effective 3-hindered quadrant ligands that can be readily assembled from commercially available materials (Fig. 1).

We previously showed that the PNSO family of ligands, those containing a sulfinamide moiety bound to a phosphine group through the nitrogen atom where chirality resides on sulfur, can be highly efficient when applied to the intermolecular asymmetric Pauson–Khand reaction [7]. These ligands can be obtained in a very straightforward manner, often involving a one-step, one-pot synthesis using chiral sulfinamides that are commercially available in large amounts [8]. Also, we demonstrated that ligands such as **1** and similar analogs coordinate readily to rhodium and other metals to give either P,O or P,S bidentate coordination [9]. The positive results with these ligands in the Pauson–Khand reaction led us to test their efficacy in rhodium-catalyzed asymmetric hydrogenation of dehydroamino acids. We were willing to test whether the *N*-di-*tert*-butylphosphino-*tert*-butylsulfinamide ligand (PNSO) (**2**) could be another example of the 3-hindered quadrant chiral ligand

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http://dx.doi.org/10.1016/j.jorganchem.2012.07.008

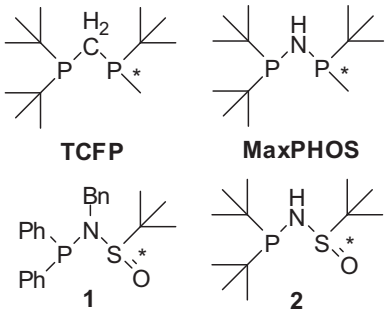


Fig. 1. C_1 symmetric diphosphine and *N*-phosphino sulfinamide (PNSO) ligands.

template, such as the TCFP and MaxPHOS ligands [10]. Thus, here we report on the synthesis of ligand **2** and its *p*-tolylsulfinamide analog, their complexation to rhodium and finally the use of the resulting complexes in asymmetric hydrogenation.

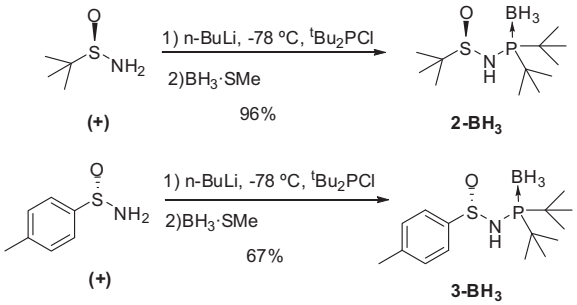
2. Results

2.1. Synthesis of the ligands

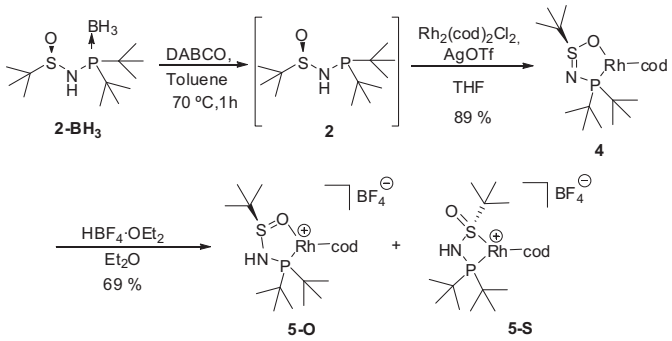
The boron-protected chiral PNSO ligand **2** was synthesized from the commercially available (+)-*tert*-butylsulfinamide in a one-pot reaction (Scheme 1). The anion of the sulfinamide was formed at low temperature with *n*-BuLi. Addition of the $^tBu_2PCl$ electrophile, which was allowed to react to completion at room temperature after warming up from −78 °C, led to total consumption of the sulfinamide starting material (easily monitored by TLC). Finally, the phosphine was protected with borane by addition of the $BH_3{\cdot}SMe_2$ complex. Borane-protected **2** was isolated in an excellent 96% yield after flash chromatography on SiO_2. The analog **3-BH$_3$** was synthesized in exactly the same manner from the commercially available dextrorotatory *p*-tolylsulfinamide. The ligands were not isolated in their borane-free form due to expected oxidation of the phosphine [7a].

2.2. Synthesis of Rh complexes

The compound **2-BH$_3$** was heated to 70 °C in toluene with an excess of DABCO to release the ligand from the boron protecting group (Scheme 2), a process which was easily monitored by TLC. When no protected form remained, the reaction was removed from the heat and allowed to cool. The source of rhodium $Rh_2(cod)_2Cl_2$/AgOTf was then added to the reaction, dissolved in THF The resulting rhodium complex derived from ligand **2** was very apolar, running high on the TLC plate in a 9:1 hexane:ethyl acetate mobile phase and also passing easily through a silica column. This behavior was not expected from a cationic complex. After stirring and later evaporation of solvents, the complex was then be purified by



Scheme 1. Synthesis of bulky BH_3-protected PNSO ligands.



Scheme 2. Synthesis of neutral and cationic rhodium complexes **4** and **5** derived from (+)-*tert*-butylsulfinamide.

column chromatography to give pure complex **4** as an orange oil, which slowly solidified.

^1H NMR analysis of complex **4** revealed a lone signal for the sulfinyl *tert*-butyl group at 1.1 ppm, a pair of overlapping doublets between 1.22 and 1.26 ppm corresponding to the phosphino *tert*-butyl groups, and a set of olefinic proton signals residing between 3.97 ppm and 5.25 ppm. These results led us to believe we had synthesized a monomeric PNSO–Rh complex that probably displayed oxygen to rhodium coordination reminiscent of complex **6**, previously synthesized by our group (Fig. 2). The sulfinyl *tert*-butyl ^1H NMR peak appeared much further downfield than that of complex **6**, which lies at 1.54 ppm and even further downfield than the sulfinyl *tert*-butyl group of complex **7**, found at 1.24 ppm. The ^1H NMR spectrum could not confirm the ligand–metal coordination mode. A reliable structural elucidation was sought by X-ray analysis; however, due to the apolar nature of **4** and its high solubility in a range of solvents from hexane to methanol, our attempts to form crystals suitable for X-ray crystallography failed time and again.

In an attempt to explain the chromatographic behavior of complex **4**, we postulated that it was not a salt but a neutral complex that resulted from deprotonation of the NH functionality in the presence of excess DABCO in the reaction mixture [11]. We hypothesized that by adding 1 eq. of acid to the complex stirring in an apolar solvent we could achieve a complex from which crystals suitable for X-ray crystallography could be formed. This hypothesis was confirmed experimentally; addition of 1 eq. of $HBF_4{\cdot}OEt_2$ to the dissolved complex in Et_2O yielded a bright yellow precipitate. This precipitate was the protonated cationic complex **5** (Scheme 2).

Crystals suitable for X-ray crystallography were formed by dissolution of the salt complex **5** in a small amount of DCM followed by the layering of an excess of Et_2O. Surprisingly, in one unit cell of the crystal (Fig. 3) we detected two distinct structures showing both sulfur coordination (P,S) and at the same time oxygen coordination (P,O) to the metal center. This finding led us to assume that in complex **5** neither O- or S- to metal coordination was greatly favored over the other. Despite of this, the crystallographic data of complex **5** gave us a unique opportunity to compare the effect of the different coordination modes on the bond lengths and bond angles of the molecule and also to analyze them with respect to comparable complexes such as **6** and **7**, previously synthesized by

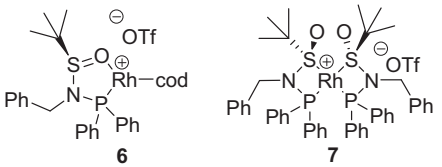


Fig. 2. Previously reported PNSO–Rh complexes.