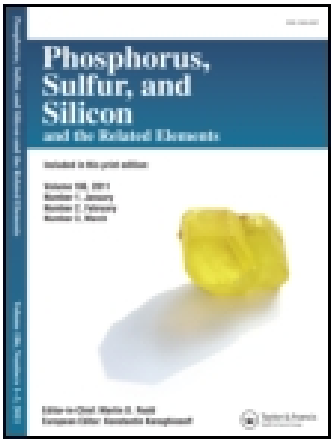


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Mixed S/P Ligands from Carbohydrates: Synthesis and Utilization in Asymmetric Catalysis

Noureddine Khiar [a] , Belén Suárez [a] , Michaela Stiller [a] , Victoria Valdivia [b] & Inmaculada Fernández [b]
[a] Instituto de Investigaciones Químicas, CSIC-Universidad de Sevilla, Isla de la Cartuja , Spain
[b] Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla , Spain
Published online: 16 Aug 2006.

To cite this article: Noureddine Khiar , Belén Suárez , Michaela Stiller , Victoria Valdivia & Inmaculada Fernández (2005) Mixed S/P Ligands from Carbohydrates: Synthesis and Utilization in Asymmetric Catalysis, Phosphorus, Sulfur, and Silicon and the Related Elements, 180:5-6, 1253-1258, DOI: 10.1080/10426500590911449

To link to this article: http://dx.doi.org/10.1080/10426500590911449

Phosphorus, Sulfur, and Silicon, 180:1253–1258, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500590911449

Taylor & Francis
Taylor & Francis Group

Mixed S/P Ligands from Carbohydrates: Synthesis and Utilization in Asymmetric Catalysis

Noureddine Khiar
Belén Suárez
Michaela Stiller
Instituto de Investigaciones Químicas, CSIC-Universidad de Sevilla, Isla de la Cartuja, Spain

Victoria Valdivia
Inmaculada Fernández
Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, Spain

New chiral mixed sulfur/phosphorus ligands derived from carbohydrates are reported. These ligands were found to be efficient catalyst precursors for palladium-catalyzed asymmetric substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate or benzylamine (up to 96% ee), and for rhodium-catalyzed methyl acetamidocinnamate hydrogenation (up to 92% ee).

Keywords Carbohydrates; P/S ligands; Pd-catalyzed; enantioselective allylic substitution; rh-catalyzed enantioselective hydrogenation

INTRODUCTION

The enormous effort in the area of enantioselective asymmetric synthesis has resulted in the accrual of structurally diverse ligands.[1] Nevertheless, the inability to predict the structural requirements of a ligand for generating efficient catalyst explains the need for new ligands that combine easy synthesis and high effectiveness. An early rationalization in this field, directed toward the restriction of the diastereomeric transition states, has resulted in the use of the C_2-symmetry as successful ligand design.[2] Nevertheless, recently, the *trans* effect resulting from the use of heterodonor ligands with different donor–acceptor properties

Received July 9, 2004; accepted October 5, 2004.
Address correspondence to Noureddine Khiar, Instituto de Investigaciones Químicas, CSIC-Universidad de Sevilla, c/. Américo Vespucio, 49, Isla de la Cartuja, 41092-Sevilla, Spain. E-mail: khiar@iiq.csic.es

of the chelating atom, has demonstrated itself as an effective control of the stereochemical restrictions needed for high enantioselectivity.[3–5] In our continuing interest in the synthesis and utilization in asymmetric synthesis of chiral sulfur compounds,[6] we have recently reported the preparation of C_2-symmetric bis-thioglycosides as new sulfur/sulfur (S/S) ligands using carbohydrates as cheap starting material.[7] These ligands were used in Pd(0)-catalyzed allylic alkylation of 1,3-diphenylpropenylacetate with dimethyl malonate affording the desired product in up to 90% enantiomeric-excess (ee). In this communication we report on the use of mixed sulfur/phosphorus (S/P) ligands derived from carbohydrates and their application in the palladium-catalyzed asymmetric substitution as well as in the Rh-catalyzed hydrogenation of enamides.

RESULTS

Our synthetic design (Figure 1) is based on the use of thioglycosides **I** having a phosphinite moiety at the 2-position of the pyranose ring.

The premise of this study is that upon coordination to the metal the stereochemistry of the sulfur in the six-member ring would be efficiently controlled through steric bias. Accordingly, the chelation of the metal through the pro *R* lp of the sulfur leads to a complex **II** where the sulfur substituent R and the endocyclic oxygen are in an unfavorable *syn* relationship. On the other hand, the chelation of the metal through the Pro-*S* lp leads to the *anti* diastereoisomer **III** presenting less steric

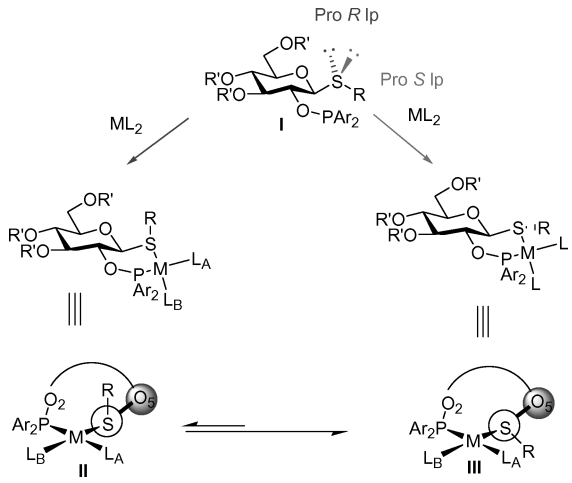
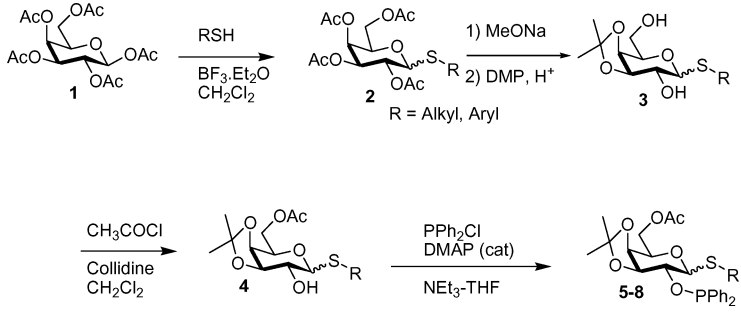


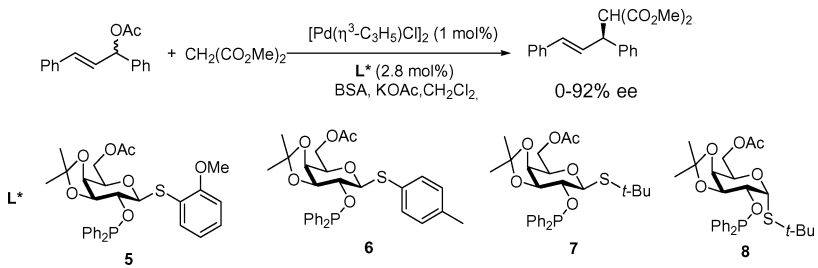
FIGURE 1 Ligand design.

interactions and thus more favored. Additionally, the strong *trans* influence of the phosphinite *vs.* the thioether places the more labile site L_A of the metal complex in the proximity of the stereogenic sulfur atom.[4] On the other hand, it is worthy of mention that ligands type **I** are highly tuneable, as the sulfur substituent, the phosphorus substituents, and the sugar backbone can all be changed easily. Another advantage of these polyhydroxylated ligands is that they can give either lipophilic or hydrophilic catalysts. The different nature of the hydroxyl groups (primary and secondaries) may be used to easily link these ligands to a solid support.

Galactose with *cis* hydroxyl groups at the 3 and 4 positions offers an ideal platform for the rapid construction of these ligands. Accordingly, the synthesis of phosphinite thioglycosides has been carried out in only five high-yielding steps starting from commercially available galactose pentaacetate **1** (Scheme 1). Condensation of a thiol with **1** in the presence of boron trifluoride afforded the corresponding thioglycoside **2** in high chemical yields (85–90%). Surprisingly, while this reaction is generally highly diastereoselective, leading to the 1,2-*trans*-thioglycoside, we found that the use of *tert*-butanethiol as glycosyl acceptor afforded the corresponding α- and β-thioglycosides in a 2:1 ratio. On the other hand, taking into account that this reaction is under a thermodynamic control and that both anomers are easily separable by column chromatography, α- and β-anomers can be prepared in high yield at will. A Zemplen deacetylation, followed by acid-catalyzed acetallation with 2,2-dimethoxy propane (DMP), afforded the 3,4-acetal **3** in 75–80% yield. A regioselective acetylation of primary alcohol using collidine as base at -78°C afforded the monoalcohol **4** in 80–85% yield. The installation of the phosphinite moiety has been carried out in a 1:1 mixture THF:NEt_3, using DMAP as catalyst in 80–90% yield. Thus in only five high-yielding steps the phosphinite thioglycosides were obtained in a multigram scale.



SCHEME 1



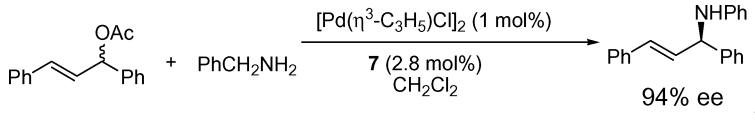
SCHEME 2

Application of Phosphinite Thioglycosides to Palladium-Catalyzed Allylic Substitution

The ability of the prepared phosphinite thioglycosides (**5–8**) to act as chiral ligands in asymmetric catalysis was first assayed in palladium-catalyzed allylic alkylation of 1,3-diphenyl propenyl acetate with dimethyl malonate (Scheme 2). The reactions were conducted under Trost's conditions in ethylene chloride using 2 mol% of the Pd and 2.8 mol% of ligands, and stopped upon completion of the reaction. The desired calculated product was always obtained in high chemical yield and in variable ee, depending mainly on the stereochemistry of the anomeric center and on the substituent of the sulfur substituent atom. Significantly, while β-thioglycosides **5–7** afforded the desired product with good yield and variable ee, α-thioglycoside **8** lead to the racemic product.

The aromatic thioglycosides, either hindered **5** or unhindered **6**, afforded the same moderate enantioselectivity around 60% ee. Bulkier alkyl thioglycosides, such as the *tert*-butyl thioglycoside **7**, afforded the desired product in 92% ee.

The optimization of the reaction conditions shows that using 2 mol% of the palladium, 2.8% of the ligand in methylene chloride at -20°C afforded the allylic alkylation product in 96% ee. Using the same condition and benzylamine as nucleophile afforded the allyl amine product in 94% ee and quantitative yield, Scheme 3. At the onset of this study was the determination of the sulfur stereocontrol upon coordination to the metal. To address this problem we synthesized the corresponding Pd(II)

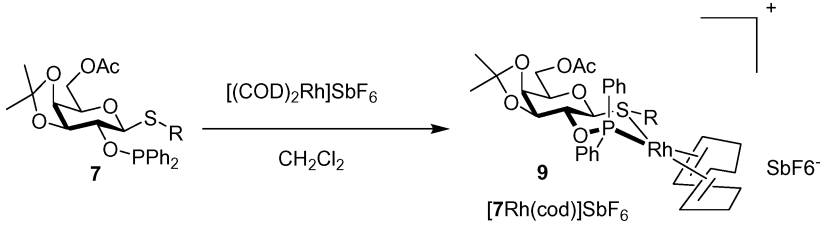


SCHEME 3

complex by treatment of **7** with palladium bis-chloro bis-acetonitrile. The complex was obtained in 90% yield as a single isomer, as shown by dynamic proton and phosphorus nuclear magnetic resonance (NMR) study, indicating an efficient control of the sulfur chirality. The nuclear overhauser effect spectroscopy (NOESY) study of the complex shows that, beside the usual NOE contacts between the H_1-H_3-H_5 that indicate a $^4C_1$ conformation of the pyranose ring, there is an intense NOE contact between the anomeric proton and the *tert*-butyl group. Additionally, as no NOE contact between *tert*-butyl group and the H-2 proton was detected, we conclude that sulfur configuration is *S* as predicted.

Application of Phosphinite Thioglycosides to Rhodium-Catalyzed Asymmetric Hydrogenation

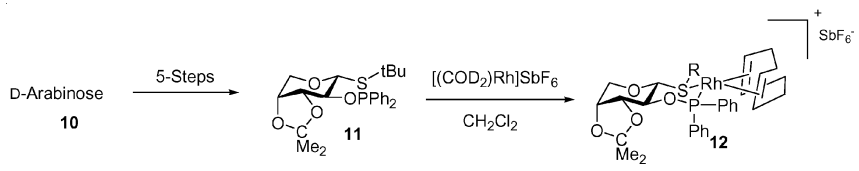
Owing to the good results of the ligand **7** in asymmetric allylic substitution, we decided to evaluate its activity in asymmetric hydrogenation of enamides. The Pd and Rh complexes employed in these processes are structurally homologous square planar d^8 metals complexed by a common ligand family. Accordingly, the origins of the setereoinduction may be owed to the interplay of the *trans* influence and metal-induced sulfur chirality. The model reaction we chose was the hydrogenation of methylacetamido cinnamate, leading to the protected phenylalanine. A large number of effective chiral bis-phosphines are available for this transformation. Nevertheless mixed ligands have been scarcely used, all of which lead to low reactivity or selectivity or both. To start this study we developed a well-defined catalyst precursor. Treatment of 1 equiv. of **7** with 1 equiv. of $[(cod)_2Rh]SbF_6$ afforded the cationic complex **9** in 90% yield (Scheme 4).



SCHEME 4

The utilisation of 1 mol% of **9** in THF at room tempertaure (rt) under only 1 atm of hydrogen afforded the (*S*)-acetamido-phenyl alanine methyl ester in quantitative yield and in 92% ee. The use of more hydrogen pressure (4 atm) afforded the product with the same enantiomeric excess.

One of the drawbacks when using carbohydrates in asymmetric synthesis in general, and as chiral ligands in asymmetric catalysis, is the difficulties to accede to the other enantiomer. Accordingly, although the price of D-glucose is low (1.2 Eu/mol), L-glucose is prohibitively expensive (8650 Eu /mol), ruling out any possibility of using L-sugars even in catalytic processes. In order to solve this problem we have noticed that α-D-arabinose 10, a cheap commercially available D-pentopyranose, which exists mainly in the $^1C_4$ conformation, is a quasi-mirror image of β-galactose. The synthesis of 2-phosphinite *tert*-butyl-thioarabinoside **11** has been carried out in four high-yielding steps from arabinose tetraacetate (Scheme 5). Using 2 mol% of the palladium, 2.8% of the



SCHEME 5

ligand in methylene chloride at -20°C afforded the opposite enantiomer of the allylic alkylation product in 96% ee. Additionally the use of 1 mol% of the cationic Rh(I) complex **12** in the hydrogenation of methylcinnamate afforded the *R*-isomer in 92% ee. Thus even though belonging to the D-serie, ligand **7** and ligand **11** behave as enantiomers.

REFERENCES

[1] E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Vol. I–III (Springer: Berlin, 1999) .
[2] J. K. Whitesell, *Chem. Rev.*, **89,** 1581 (1989).
[3] a) T. G. Appleton, H. C, Clark, and L. E. Manzer, *Coord. Chem. Rev.*, **10,** 335 (1973); b) S. Murray and F. Hartley, *Chem. Rev.*, **81,** 365 (1981).
[4] A. Albinati, J. Eckert, P. Pregosin, H. Ruegger, R. Salzmann, and C. Stossel, *Organometallics*, **16,** 579 (1997).
[5] D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael, and M. R. Gagné, *J. Am. Chem. Soc.*, **122,** 7905 (2000).
[6] I. Fernández and N. Khiar *Chem. Rev.*, **103,** 3651 (2003).
[7] N. Khiar, C. S. Araújo, E. Alvarez, and I. Fernández, *Tetrahedron Lett.*, **44,** 3401 (2003); b) N. Khiar, C. S. Araújo, B. Suárez, E. Alvarez, and I. Fernández, *Chem. Commun.*, 714 (2004).