Thesis of the PhD. Dissertation

NEW SYNTHETIC ROUTES TOWARDS HYDROPHILIC PHOSPHANES

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I. INTRODUCTION

By the end of the 20th century, environmental pollution has become one of the most serious problems of mankind.

Some sectors of the chemical industry emit large quantity of waste. It is interesting that those sectors emit the largest amount of contamination which are usually regarded to be relatively "clean". For example in the course of the preparation of 1 g of medicinal drug 1000 g waste is produced on average (E ≈ 1000). Whereas, the oil industry, which is usually thought to contribute significantly to environmental pollution, is a quite clean sector: its E factor is almost zero.

Emission of large quantity of waste also means that we do not use our resources in the optimal way.

Treatment of waste in the polluting sectors should be regarded as temporary solution only. The ultimate goal is the introduction of environmentally benign chemical processes.

Aqueous and aqueous-organic two-phase organometallic catalysis can play an important role in the development of "green" chemical technologies. Water is an environmentally friendly solvent. The catalyst can be rendered water-soluble via its ligands, and in this manner it can easily be separated from the usually hydrophobic products.

As in organometallic catalysis generally, tertiary phosphanes are also the most frequently used ligands in aqueous organometallic catalysis. However, in aqueous catalytic systems, beside stabilizing the low oxidation states of the central atom, and influencing the activity/selectivity of the catalyst, the phosphane ligand has to provide the complex with sufficient water-solubility, as well.

The means of synthetic organic chemistry offer numerous ways for the preparation of hydrophilic ligands. In this dissertation two synthetic strategies have been discussed, which
provide easy access to water-soluble tertiary phosphanes. Catalytic applications of the prepared phosphanes have also been presented.

II. APPLIED EXPERIMENTAL METHODS

Preparation of intermediates and products usually required deoxygenated solvents. The syntheses were carried out in purified argon atmosphere using standard Schlenk technique. The synthesized compounds were identified and characterized by the means of NMR spectroscopy (\(^1\)H, \(^{13}\)C\(^{1}\)H), \(^{31}\)P\(^{1}\)H), \(^1\)H\(^{31}\)P), \(^1\)H-coupled \(^{13}\)C, NOESY, APT, HMQC and HMBC), mass spectroscopy (FAB, ESI), X-ray, gas chromatography, and elemental analysis. The catalytic reactions were evaluated based on the GC analysis of the product phase of the reaction mixtures.

III. NEW SCIENTIFIC RESULTS

The aim of the research was the development of new synthetic approaches for convenient preparation of water-soluble phosphanes.

1. A new synthetic route towards sulfated phosphanes - a new class of water-soluble phosphanes - has been developed.

(a) Cyclic sulfite of (2R,4R)-2,4-pentanediol (1) has been prepared via the reaction of the chiral diol and SOCl\(_2\). The cyclic sulfite has been oxidized to the corresponding sulfate (2) using the Sharpless method. The cyclic esters have been isolated. Both compounds have been identified by analytical and spectroscopical methods (GC, NMR, X-ray). The sulfated phosphane has also been prepared in a one-pot reaction, without isolating the sulfite. The reaction of the cyclic sulfate with LiPPh\(_2\) has provided a new chiral water-soluble phosphane 3. Chirality of the ligand has been established based on the most possible mechanism of the ring opening reaction. The new phosphane is hygroscopic, sensitive to oxygen, and it has an amphiphilic character.
The oxide of the phosphane (4) has been prepared and characterized. Stability of the ionic sulfate group has been investigated. The rate of the reaction of 3 and the strongly nucleophilic LiPPh₂ is not significant at room temperature. Attempts at the hydrolysis of 3 and 4 prove that the -OSO₃⁻ group is stable in neutral, as well as in slightly basic or slightly acidic aqueous solutions, even at elevated temperatures (60-90 °C). Appreciable conversions have been observed only under harsh conditions (20 % H₂SO₄, ~90 °C). The corresponding hydroxyl compounds (5, 6) have been isolated and characterized.

(b) Versatility of the synthetic approach has been shown changing the structure of the diol. Cyclic sulfite (7) of neopentanediol has been prepared and oxidized to the corresponding sulfate (8). New sulfated phosphane (8) has been prepared via the reaction of 8 with LiPPh₂. The intermediates and the new ligand have been isolated and fully characterized.
(c) The structure of the sulfated phosphanes can also be varied by changing the structure of the phosphide. A phosphide prepared via the reaction of dibenzophosphol and lithium was used as nucleophilic in the ring opening reaction of 2. The product (10), weaker σ-donor analogue of 3, was isolated and fully characterized.

(d) In order to prepare a sulfated diphosphane, a tetraol (pentaeritritol) has been functionalized. Due to the strongly polar, protic character of the pentaeritritol, preparation of the bicyclic sulfite (11) and sulfate (12) requires modification of the Sharpless method. Reaction of the bicyclic sulfate and LiPPh₂ provided the disulfated diphosphane 13, sulfated derivative of the well-known DPPP.
(e) Reactions of 3 and 13 with [Rh(COD)Cl]₂ and Pt(PhCN)₂Cl₂ have been studied. The reactions have been monitored by ³¹P{¹H}-NMR spectroscopy. Eight phosphane complexes have been identified. Their structures have usually been established based on their ³¹P{¹H}-NMR data and their chemical behavior, however, in some cases, ¹⁹⁵Pt-NMR and FAB-MS experiments also confirm the suggested structures.

(f) Two sulfated phosphanes (3, 13) have been tested in rhodium-based aqueous-organic two-phase hydroformylations. The phosphane/[Rh(COD)Cl]₂ systems catalyze the hydroformylation of styrene and octene-1 in water-toluene two-phase medium. In the course of the reactions – presumably due to the surfactant nature of the phosphanes – application of additives is not necessary. The chemoselectivity of the reactions was 100% in each case; hydrogenation of the olefins did not take place. Good regioselectivities (branch/normal) have been obtained in the case of styrene, while regioselectivity of the hydroformylation of octene-1 (normal/iso) has been rather moderate. In the course of hydroformylation of styrene no optical induction could be obtained using the chiral monotertiary phosphane 3. This observation can be explained by either the monodentate nature of the ligand or the strongly polar, protic character of the solvent that can cause racemization of the branched aldehyde via its enol-type tautomer.

2. A new synthetic approach has been suggested for the preparation of sulfonated triarylphophanes. The hydrophilic ligands can be prepared under the usual conditions of direct sulfonation. The reaction times are short, the sulfonation is selective, the products are free of oxide. The water-solubility, as well as electronic and steric nature of the ligands can be fine-tuned.

(a) Since the reason for the difficulties at the preparation of sulfonated triphenylphophanes is the deactivating effect of the protonated phosphorus, it has been reasoned that this effect can be compensated by introduction of electron-donating groups into appropriate positions of the phenyl rings. The optimal position of the activating groups (ortho, para) has been determined by simple theoretical considerations. It has been established that the substituents in these positions influence markedly the electronic and steric character of the phosphanes.
(b) Preparation of trisulfonated triphenylphosphane – the most frequently used hydrophilic phosphane in the industry – lasts several days and is accompanied with oxidation of the ligand. Three derivatives of triphenylphosphane bearing electron releasing groups in ortho and para positions of the aryl rings have been designed and prepared. The triarylphosphanes – tris(para-anisyl)phosphane (14), tris(2,4-xylyl)phosphane (15), tris(2,6-xilyl)phosphane (16) – have been sulfonated in 20-30 % oleum. Complete conversions have been obtained in three hours, and the new sulfonated phosphanes (17-19) have been isolated in outstanding yields and free of oxides. All the products have been fully characterized. Interpretation of $^1$H- and $^{13}$C-$^1$H-NMR data has partly been based on $^1$H-$^{31}$P-NMR, $^1$H-coupled $^{13}$C-NMR, APT, NOE, HMQC, and HMBC experiments.

(c) In order to study the electronic and steric effects of CH$_3$ and OCH$_3$ groups, trisulfonated tris(para-anizyl)phosphane (17, T(p-A)PTS), trisulfonated tris(2,4-xylyl)phosphane (18, T(2,4-X)PTS), and trisulfonated triphenylphosphane (TPPTS) have been tested in rhodium based two-phase hydrogenation of benzaldehyde and caproaldehyde. The sterically similar TPPTS and T(p-A)PTS form stable and active catalysts. In the course of the hydrogenation of benzaldehyde the TPPTS/rhodium catalyst has been more active, while in the case of caproaldehyde the T(p-A)PTS/rhodium system has provided higher conversion. Presumably due to the steric nature of the ligand, T(2,4-X)PTS having ortho methyl groups cannot stabilize the rhodium complex: precipitation of rhodium metal has been observed.

(d) In order to characterize the steric nature of T(2,4-X)PTS, guanidinium salt of the phosphane (20) has been prepared and isolated as a single crystal. The compound has been characterized by X-ray and Tolman cone angle of the ligand has been calculated. Comparison of the obtained values (196°, 210°) and the corresponding data of TPPTS (152°, 166°) confirm
that the new ligand is significantly more demanding sterically than the trisulfonated triphenylphosphane.

(c) Considering the steric bulk of T(2,4-X)PTS, iridium complexes of the ligand as well as that of TPPTS and T(p-A)PTS have been tested in two-phase hydrogenation of benzaldehyde and caproaldehyde. It has been found that the T(2,4-X)PTS/iridium catalyst is stable and much more active than both the similar iridium systems, and the previously studied rhodium catalysts modified by TPPTS and T(p-A)PTS.
(f) Presuming that also the selectivity of direct sulfonation of arylphosphanes can be influenced applying the suggested approach, triarylphosphanes having activated (para-anizyl, 2,4-xylyl, 2,6-xylyl) and non-activated (phenyl) rings (21-25) have been prepared. The phosphanes can be sulfonated in 20 % oleum with short reaction times, and the corresponding oxide free mono- and disulfonated derivatives (21-25) have been obtained with complete selectivity and in outstanding yields (88-95 %). The new sulfonated phosphanes have been fully characterized.

(g) Due to the activating groups, the synthesis of sulfonated triarylphosphanes is more convenient and the steric nature can be varied in a wide range, however, the electronic character of the ligand can be shifted only towards higher basicity. In order to generalize the synthetic approach further, new triarylphosphane (31), having one activated (p-OCH₃) and two deactivated (p-CF₃) rings, have been designed and prepared. It has been proved that 31 is much less basic than triphenylphosphane.

(h) The novel triarylophosphate (31) can easily be sulfonated in 20 % oleum. After one hour reaction time the product can be isolated in quantitative yield and the oxidation is negligible. The new phosphane ligand (31) has a π-acceptor capacity that is outstanding among the known sulfonated triarylphosphanes.
Two basic monosulfonated phosphanes (29, 30) and the weak σ-donor, strong π-acceptor 32 have been tested in rhodium catalyzed hydrogenation of cinnamaldehyde in methanol. Under the applied conditions the chemoselectivity was complete in each case, only the C=C double bond of the substrate has been reduced. Rhodium/32 has been found to be the most active catalyst, however, in this case formation of diacetals has also been observed. The catalysts can be separated from the product by addition of hexane.

In the presence of the rhodium complex of 32 the methanol/hexane two-phase system give one phase already at 40 °C, that provides the opportunity to develop unique one-phase catalysis – two-phase separation processes. None of the other ligands has similar ability.

Application of strong base accelerates the reaction and suppresses the formation of acetals without decreasing the chemoselectivity. Under the improved conditions, rhodium complex of 32 provides remarkable reaction rates (300-600 molmol$^{-1}$h$^{-1}$).

Since application of π-acceptor type ligand and base increases the reaction rate, it can be assumed that the catalyticly active species a monohidrido rhodium complex.

**III. SIGNIFICANCE OF THE NEW SCIENTIFIC RESULTS**

Synthetic routes have been developed for the preparation of hydrophilic tertiary phosphanes. Both methods provide notable structural variability: most important features (water-solubility, electronic and steric character) of the ligands can be changed in wide range.

Changing the water-solubility potential ligands can be prepared for all of those areas of organometallic catalysis which aim at separation of the catalyst from the product (aqueous-organic, organic-organic, ionic liquid-organic two-phase systems, SAP catalysis, etc.). Fine-tuning the electronic and steric nature of the phosphanes allows optimization of the catalytic performance of the complexes.
Significance of the suggested synthetic approaches might also be confirmed by the fact that ligand 18 is already being used in palladium based Heck and Suzuki couplings. A T(2,4-X)PTS/palladium systems are more active than the corresponding TPPTS/palladium catalysts. American researchers have established that 18 is the first ligand that allows aqueous phase Heck couplings under really mild conditions [1, 2].

IV. SCIENTIFIC PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS CLOSELY RELATED TO THE DISSERTATION

H. Gulyás, A. Dobó, J. Bakos:
Synthesis of sulfated mono- and ditertiary phosphines, complex chemistry and catalysis
*Canadian Journal of Chemistry* 2001, 79: 5-6: 1040
H. Gulyás, B. E. Hanson, Á. Szöllősy, J. Bakos:
A direct approach to selective sulfonation of triarylphosphines
*Tetrahedron Letters* 2002, 43, 2543
H. Gulyás, Á. Szöllősy, P. Szabó, P. Halmos, J. Bakos:
Preparation of new sulfonated triarylphosphanes: control of the selectivity by structural assistance
H. Gulyás, A. C. Bényei, J. Bakos:
Catalytic properties of water-soluble rhodium and iridium complexes: the influence of the ligand structure
*Inorganica Chimica Acta* 2004, 357, 3094

FURTHER PUBLICATIONS RELATED TO THE DISSERTATION

H. Gulyás, P. Árva, J. Bakos:
A New Route for the Synthesis of Amphiphilic and Water-soluble Ligands: Mono- and Ditertiary Phosphines Having an Alkyene Sulfate Chain.
C. Hegedűs, J. Madarász, H. Gulyás, Á. Szöllősy, J. Bakos:
One pot synthesis of a chiral diphosphine having C1 symmetry from 1,3-cyclic sulfate.
Asymmetric hydroformylation of styrene
*Tetrahedrom: Asymmetry* 2001, 12, 2867
**Publication not related to the dissertation**

I. Gergely, C. Hegedüs, H. Gulyás, Á. Szöllősy, A. Monsees, T. Riermeier, J. Bakos:
Highly Active and Enantioselective Hydrogenation Catalyzed by Rhodium Complexes of
Chiral Phosphites with Atropisomeric Moieties

**Presentations related to the dissertation**

Henrik Gulyás, József Bakos: General method for the preparation of sulfated tertiary
phosphanes. Study on the complex chemistry and catalytic behavior of the new ligands.
presentation)

Henrik Gulyás, József Bakos: A new route for the synthesis of amphiphilic and water-soluble
ligands: mono and ditertiary phosphines having an alkylene sulfate chain. *11th International
Symposium on Homogeneous Catalysis*, July 12-17, 1998, University of St Andrews,
Scotland, UK (poster)

Henrik Gulyás, József Bakos: A new route for the synthesis of amphiphilic and water-soluble
ligands: mono and ditertiary phosphines having an alkylene sulfate chain. *XVIII*th *
International Conference on Organometallic Chemistry*, August 16-21, 1998, Munich, Germany (poster)

Henrik Gulyás, József Bakos: DPPP derivative containing -CH$_2$OSO$_3$L functional groups:
preparation, complexes, catalysis. *2nd International School of Organometallic Chemistry*,
September 11-15, 1999, Camerino, Italy (poster)

Henrik Gulyás, József Bakos: Sulfonation of homologues of triphenylphosphane *XXXVI*th
*Conference on Complex Chemistry*, May 23-25, 2001, Pécs, Hungary (oral presentation)

Henrik Gulyás, József Bakos: A direct approach to selective sulfonation of triarylpseudophosphines
*Hungarian-American Workshop on Molecular Catalysis Design For Green Chemistry*, May
23-26, 2002, Budapest, Hungary (oral presentation)

Henrik Gulyás, József Bakos: A direct approach to selective sulfonation of triarylpseudophosphines.
*XX*th *International Conference on Organometallic Chemistry*, July 7-12, 2002, Danilla, Corfu,
Greece (poster)