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Advanced Studies on the Synthesis of Organophosphorus Compounds

Dissertazione Finale

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Phosphorus ligands

Introduction

Chapter 1

GENERAL INTRODUCTION ON PHOSPHORUS CHEMISTRY

In what is perhaps the most disgusting method of discovering an element, phosphorus was first isolated in 1669 by Hennig Brand, a German physician and alchemist, by boiling, filtering and otherwise processing as many as 60 buckets of urine. Now, phosphorus is primarily obtained from phosphate rock ($Ca_3(PO_4)_2$).
Phosphorus has three main allotropes: white, red and black. White phosphorus is poisonous and can spontaneously ignite when it comes in contact with air. For this reason, white phosphorus must be stored under water and is usually used to produce phosphorus compounds. Red phosphorus is formed by heating white phosphorus to 250°C (482°F) or by exposing white phosphorus to sunlight. Red phosphorus is not poisonous and is not as dangerous as white phosphorus, although frictional heating is enough to change it back to white phosphorus. Red phosphorus is used in safety matches, fireworks, smoke bombs and pesticides. Black phosphorus is also formed by heating white phosphorus, but a mercury catalyst and a seed crystal of black phosphorus are required. Black phosphorus is the least reactive form of phosphorus and has no significant commercial uses.
The number of known phosphorus compounds probably now exceeds 10^6 and a large number of them are included in organophosphorus chemistry.

1.1 Organophosphorus Chemistry

Phosphorus can form bonds with many other elements. It can also form bonds with varying number of atoms (Coordination Number), which can vary from 1 to

6 and more. Also it can have different valencies, either 3 or 5. Also it has empty d-orbitals which readily accept electrons from any good donors.

Organophosphorus compounds are chemical compounds containing carbon-phosphorus bonds. Organophosphorus chemistry is the corresponding science exploring the properties and reactivity of organophosphorus compounds.[1] Common examples of those compound are reported in Figure 1.1.

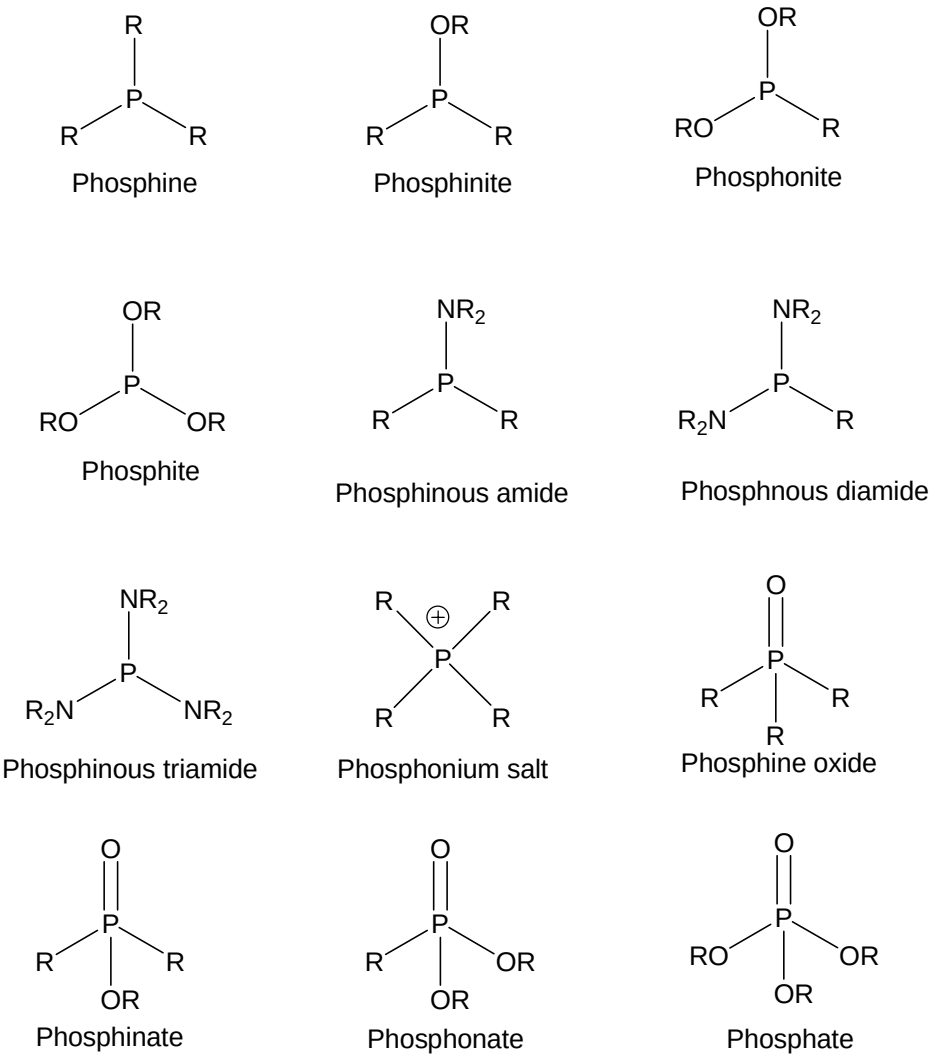


Figure 1.1 Examples of organophosphorus compounds.

The thermal stability of the P-C bond is quite high. The heat of dissociation of the 4-coordinated C-P bond is generally accepted to be about 65 Kcal/mol, and there is never any difficulty in handling most aryl and alkyl phosphorus compounds even at moderate temperatures.[2a]

1.1.1 Phosphines

Phosphanes or phosphines have oxidation state −3 and can be primary (RPH_2), secondary (R_2PH) or tertiary (R_3P). An often used organic phosphine is triphenylphosphine. Like amines, phosphines have a trigonal pyramidal molecular geometry although with larger angles. The C-P-C bond angle is 98.6° for trimethylphosphine increasing to 109.7° when the methyl groups are replaced by *tert*-butyl groups. The barrier to inversion is high for a process like inversion to occur and therefore phosphines with three different substituents can display optical isomerism. [2b]

Synthetic procedures for phosphines are:[3]

- Nucleophilic displacement of phosphorous halides with organometallic reagents such as Grignard reagents.
- Nucleophilic displacement of metal phosphides, generated by reaction of potassium metal with phosphine, as in sodium amide with alkyl halides.
- Nucleophilic addition of phosphine with alkenes in presence of a strong base (often KOH in DMSO), Markovnikov's rules apply. Phosphine can be prepared in situ from red phosphorus and potassium hydroxide. Primary (RPH_2) and secondary phospines (R_2PH) do not require a base with electron-deficient alkenes.
- Nucleophilic addition of phosphine or phosphines to alkynes in presence of base. Secondary phosphines react with electron-deficient alkynes without base.
- Radical addition of phosphines to alkenes with AIBN or organic peroxides to give anti-Markovnikov adducts.

Oxidation has been a major obstacle when working with trivalent phosphorus as phosphines. Especially alkyl-substituted phosphines oxidise readily in air making elaborating and handling of such compounds tedious. For this reason, usually phosphines are oxidized into stable compounds after their preparation, obtaining phosphine oxide, sulfide, selenide (less common) or borane complexes derivatives.[4]

- *Phosphine oxides* are obtained by simple treatment of free phosphine with an oxidizing agent such as H_2O_2,[5] O_2,[4b] *t*-BuOOH,[6] *m*-CPBA[7] (Reduction by $PhSiCl_3$,[8] $HSiCl_3$[9] with retention of configuration or $LiAlH_4$ that causes racemization).
- *Phosphine sulfides and selenides* are obtained from phosphine oxidized by elementar sulfur or selenium (Reduction by Si_2Cl_6 with retention of configuration or $LiAlH_4$ that causes racemization). [10]
- *Phosphine borane complexes* are obtained by mixing phosphines with BH_3.THF or $BH_3.Me_2S$ (decomplexation by amines, such as Et_2NH or morpholine with retention of configuration).[11]

The main reaction types of phosphines are: [3]

- as nucleophiles for instance with alkyl halides to phosphonium salts.
- as reducing agents:

Phosphines are reducing agents in the Staudinger reduction converting azides to amines and in the Mitsunobu reaction converting alcohols into esters. In these processes the phosphine is oxidized to phosphine oxide.

1.1.2 Phosphonates

Phosphonates have the general structure $R{-}P(=O)(OR)_2$. They have many technical applications and bisphosphonates are a class of drugs.
All bisphosphonate drugs share a common P-C-P "backbone":

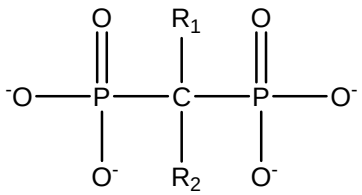


Figure 1.2 typical backbones of bisphosphonate drugs

The two PO_3 (phosphate) groups covalently linked to carbon determine both the name "bisphosphonate" and the function of the drugs. The long side chain (R_2 in the diagram) determines the chemical properties, the mode of action and the

strength of bisphosphonate drugs. The short side chain (R_1), often called the 'hook,' mainly influences chemical properties and pharmacokinetics.[12]

1.1.3 Phosphites and Phosphates

Phosphite esters or phosphites have the general structure $P(OR)_3$ with oxidation state +3. Phosphites are employed in the Perkow reaction and the Arbusov reaction. Phosphate esters with the general structure $P(=O)(OR)_3$ and oxidation state +5 are of great technological importance as flame retardant agents and plasticizers. Lacking a P−C bond, these compounds are technically not organophosphorus compounds.[3]

1.2 Uses of Organophosphorus Compounds

Organophosphorus compounds, have widespread use throughout the world, mainly in agriculture as insecticides, herbicides, and plant growth regulators.[13] They have also been used as nerve agents in chemical warfare and as therapeutic agents, such as ecothiopate used in the treatment of glaucoma.[14] In academic research organophosphorus compounds find important application in organic synthesis (Wittig, Mitsunobu, Staudinger, organocatalysis etc.).[15] The use of organophosphorus compounds as achiral or chiral ligands for transition metal-catalyzed transformations is also rapidly growing in both laboratory synthesis and industrial production.[16] Furthermore, organophosphorus compound, can be used as flame retardants for fabrics and plastic plasticising and stabilising agents in the plastics industry, selective extractants for metal salts from ores, additives for petroleum products, and corrosion inhibitors.

1.2.1 Agricultural Applications

Over the years, many organophosphorus compounds have been made and used in very large quantities in agriculture, not only as insecticides but also later as herbicides and in other applications.

Phosphorus compounds have distinct advantages in the pesticides market; they are relatively easy to make, and they biodegrade readily by hydrolysis, so that the problems of residual activity, so serious with the chlorinated hydrocarbon pesticides, are avoided.

The active compounds are normally esters, amides, or thiol derivatives of phosphoric or phosphonic acid:

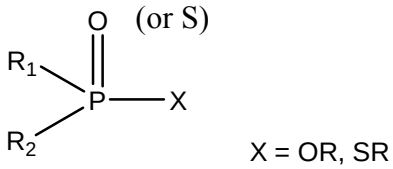


Figure 1.3 Structure of derivatives of phosphoric or phosphonic acid

Where R_1 and R_2 are usually simple alkyl or aryl groups, both of which may be bonded directly to phosphorus (in phosphinates), or linked via -O-, or -S- (in phosphates), or R_1 may be bonded directly and R_2, bonded via one of the above groups (phosphonates).

Parathion (**1**) was one of the first commercially produced insecticides; its toxicity (LD_{50}) is 55 mg/Kg, which is rather low but still requires careful handling and application in the field. It was very popular in 1960s, but after this period the interest in Parathion has greatly declined with the introduction of safer agents. Definitely, many compounds are now produced that are relatively harmless to humans yet with excellent toxicity to insects for example the well-known garden insecticide Malathion (**2**) and Phosmet (**3**) with LD_{50} up 4000 mg/Kg (Figure 1.4).

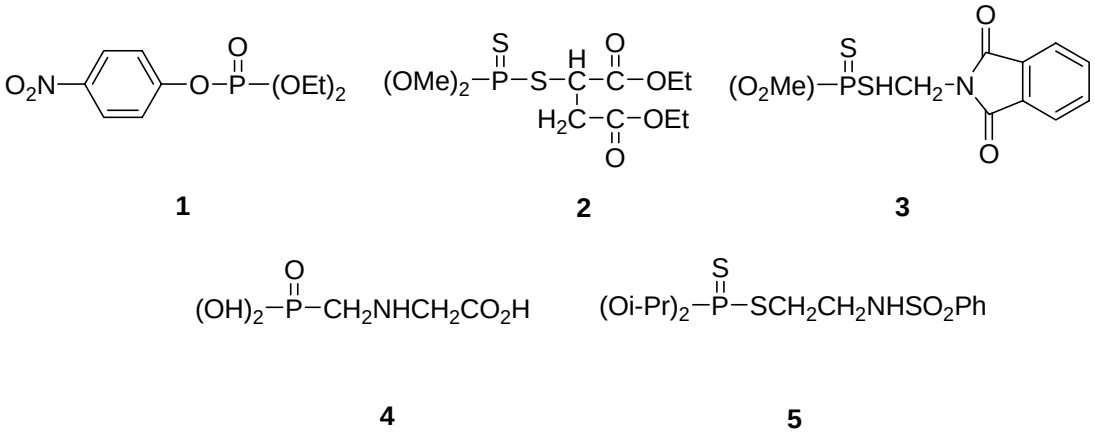


Figure 1.4 Examples of some insecticides and herbicides based on organophosphorus compounds.

On the other hand, the phosphorus compounds were late entries in the fields of organic herbicides, and to this date only a few compounds have attained major commercial importance. Glyphosphate (**4**) was the first discovered and is still used (Figure 1.4). Its is known to act by the inhibition of the plant enzyme 5-enolpyruvoyl-shikimate-3-phosphate synthetase, which is involved in the biosynthesis of aromatic aminoacids and other aromatic compounds in plants. Many other phosphorus compounds show herbicidal activity, and much current research effort is going on in this area. In addition to the phosphorus-containing amino acid derivatives, other structural types are of interest, such as is seen in Betasan (**5**) (Figure 1.4).

1.2.2 Catalysis

Between various types of enantiomerically pure ligands used for catalytic asymmetric reactions, chiral tertiary phosphines have established their position as the most effective ligands for most homogeneous transition-metal catalyses.

Homogeneous asymmetric hydrogenation started with modest results (ee 15%) in 1968 using chiral monophosphine **6** (MPPP) (Figure 1.5) as ligand.[17] Neomenthyldiphenylphosphine **7** (NMDPP) and menthyldiphenylphosphine **8** (MDPP) were prepared in 1971 by Morrison *et al*,[18] giving up to 61% ee in some cases. Knowles *et al* also published some interesting results in 1972 (ee 90%) with chiral phosphines **9** (PAMP) and **10** (CAMP).[19] At the same time

alkyldimenthylphosphines **11** were used by Wilke, Bogdanovic *et al*. as ligands of nickel complexes in the catalysis of alkene codimerization and alkene-1,3-dienes codimerization.[20] In 1971-1972 we demonstrated that a chelating chiral C2-symmetric diphosphine **12** (DIOP) without asymmetric phosphorus atoms was an excellent enantioselective catalyst (ee 88%).[21] A multitude of chelating diphosphines are presently known (of C1 or C2-symmetry), some of them are patented because of industrial applications.[22] One of the most effective chiral biphosphine ligands is BINAP **13**,[23] which has exhibited its high enantioselectivity in several asymmetric reactions including rhodium- or ruthenium-catalyzed hydrogenation. Another important class of chelating biphosphine ligand is ferrocenylbiphosphines BPPF-X **14**,[24] which had been demonstrated to be effective for palladium-catalyzed allylic substitution reactions, gold- or silver-catalyzed aldol reactions, and so on.

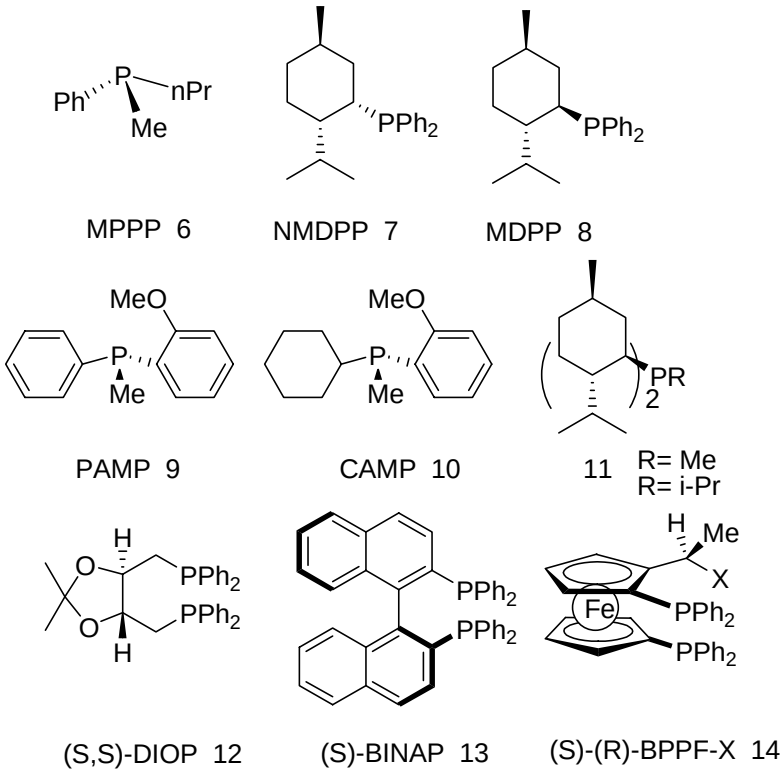
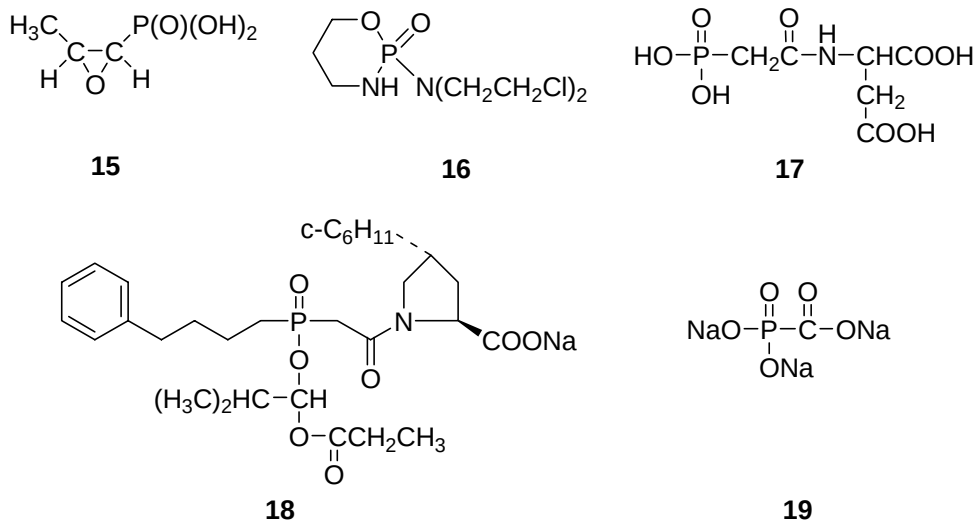


Figure 1.5 Examples of ligands for homogeneous catalysis.

1.2.3 Organophosphorus Conpounds in Medicine

A source of C-P compounds of natural origin was first recognised in 1969.[25] From the products in a fermentation broth of the bacterium *Streptomyces fradiae* a new phosphoric acid that had the properties of an antibacterial antibiotic was isolated. The compound was named *Fosfomycin* **15** (figure 1.6) and its discovery was an extremely important event in phosphorus chemistry. Phosphorus compounds had been largely ignored by medicinal chemists seeking new agents against infectious disease. *Fosfomycin* is active against both Gram-positive Gram-negative bacteria, and its effectiveness is comparable to that of the well-known antibiotics Tetracycline.[2c]

High-level anticancer activity has been found in a large number of phosphorus compounds of quite different structural types, and there is much current research in this field. Probably the first organophosphorus compound to receive acclaim as a valuable chemotherapeutic agent is the anticancer drug cyclophosphamide **16** (figure 1.6). Its activity was discovered in 1958,[26] and remains in clinical use to this day.[2c]



15 **16** **17**

18 **19**

Figure 1.6 Organophosphorus compounds in medicine.

In the design of anticancer drugs, rationales were done. An obvious one is that an exact phosphonate replica of a known biologically active phosphate could inhibit the process in which the phosphate is involved. The CH_2 group attached to P has a

very similar size and bond angle with an O atom of a phosphate. The high stability of P-C bond would block any important natural processes involving hydrolysis of a phosphate ester group. A second rationale is that a phosphonic acid designed to be similar to a naturally occurring carboxylic acid might inhibit the biochemical work of acid.[12c] Using those concepts a large amount of phosphonic acids has been synthesized and thus had useful chemotherapeutic properties. Some examples of the above rationalization are, the *PALA* (N-phosphonoacetyl-L-aspartic acid (**17**) which is a potent anticancer drug and the *Fosinopril* (**18**) which has an antihypertensive activity.[2c]

Phosphorus compounds can also have antiviral activity, the first active compound to be discovered had the very simple structure of trisodium phosphonoformiate. Its activity was discovered[27] in 1978, and is still in clinical use under the name *Foscarnet* **19**. It inhibits viral DNA polymerase, and it is a useful agent in the treatment of Herpes and is also active against HIV.

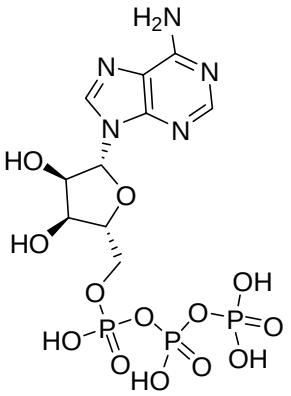
1.2.4 Phosphorus in Biological Compounds

Phosphorus is present in plants and animals. There is over 454 grams of phosphorus in the human body. It is a component of fundamental living compounds. It is found in complex organic compounds in the blood, muscles, and nerves, and in calcium phosphate, the principal material in bones and teeth. Phosphorus compounds are essential in the diet. Organic phosphates, ferric phosphate, and tricalcium phosphate are added to foods. Especially, phosphoric acid is essential in many biological derivatives such as nucleotides, nucleic acids, phospholipids and sugar phosphates.

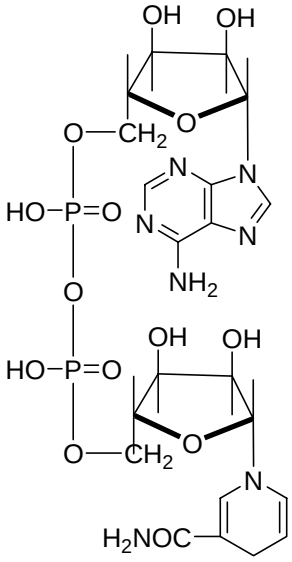
Nucleotides are monomers consisting of a phosphate group, a five carbon sugar (either ribose or deoxyribose) and a one or two ring nitrogen containing base.

Nucleotides are the monomers of nucleic acids, with three or more bonding together in order to form a nucleic acid. The genetic material (DNA) is a polymer of four different nucleotides. The genetic information is coded in the sequence of nucleotides in a DNA molecule. Nucleotides and related compounds are also

important "energy carrying" compounds. Among the ones commonly encountered are ATP (**20**), and NADH (**21**) (Figure 1.7).[28a]



adenosine triphosphate ATP **20**



Nicotinamide adenine dinucleotide dehydrogenase NADH **21**

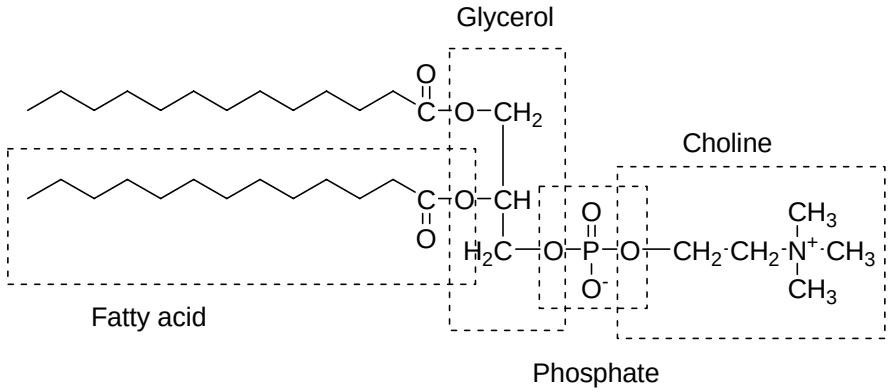
Figure 1.7 Structures of ATP and NADH.

Certain phosphoric acid derivatives play a major role in driving some processes by "energy release" that accompanies the cleavage of a phosphate group and transfer to a nucleophilic substrate. The best known of the "energy-rich" phosphates is adenosine triphosphates ATP (**20**, Figure 1.7), which can transfer the terminal phosphate group to a substrate with the release of significant energy.[2c]

Actually the phosphoryl group transfer mechanism, in "energy-rich" phosphate substrates, is explained by intervention of pentacoordinated phosphorus in the transition state species. In particular the formation of cyclic pentacoordinated phosphorus species on the reactive phosphate group facilitate the attainment of the required transition state or intermediate allowing to obtain a fast and selective reaction.[29]

A phospholipid molecule consists of a hydrophilic polar head group and a hydrophobic tail (**22** figure 1.8). The polar head group contains one or more phosphate groups. The hydrophobic tail is made up of two fatty acyl chains. When many phospholipid molecules are placed in water, their hydrophilic heads tend to

face water and the hydrophobic tails are forced to stick together, forming a bilayer. Phospholipids are a major component of all biological membranes, along with glycolipids and cholesterol.[28b]



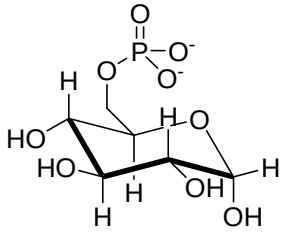
22

Figure 1.8 Typical structure of phospholipids.

Sugar phosphates are present in the human body as intermediates in the many important processes like glucose metabolism. One example is the glucose 6-phosphate **23** (figure 1.9).

It is glucose sugar phosphorylated on carbon 6. This compound is very common in cells as the vast majority of glucose entering a cell will become phosphorylated in this way. Because of its prominent position in cellular chemistry, glucose 6-phosphate has many possible fates within the cell. It lies at the start of two major metabolic pathways: the Glycolysis and Pentose phosphate pathway

In addition to these metabolic pathways, glucose 6-phosphate may also be converted to glycogen or starch for storage. This storage, in the form of glycogen, is in the liver and muscles for most multicellular animals, and in intracellular starch or glycogen granules for most other organisms.[28c]



glucose-6-phosphate **23**

Figure 1.9 Structure of glucose 6-phosphate.

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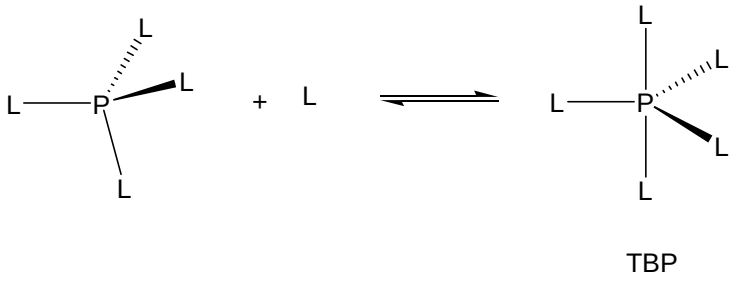
Chapter 2

THE HYPERCOORDINATE STATES OF PHOSPHORUS

One of the special properties of phosphorus that is of importance is its ability to accept more than the usual complement of 8 bonding electrons, thus acquiring 5-coordinate character with 10 electrons, or 6-coordinate with 12 electrons. This property of phosphorus was not firmly established until 1948, when the compound Ph_5P was synthesized and characterized by Wittig and Rieber.[1] Now there are many compounds known with this structural feature, which is also known to appear frequently in reactions mechanism as a transient intermediate or transition state. [2]

2.1 The 5-Coordinate State of Phosphorus

Phosphorus can undergo rapid and reversible changes between a four-coordinate and a five-coordinate state (Scheme 2.1). The preferred skeletal geometries of this states correspond to the tetrahedron and the trigonal bipyramid (TBP), respectively.[2]



Scheme 2.1 convertion between a four-coordinate and a five-coordinate state.

Molecules with five-coordinate phosphorus are essential to life[3] and the recognition of the role played by the five-coordinate state of the element in biochemistry has spurred interest in this field. On this basis, a consistent interpretation has been made of a number of significant problems of biochemistry,[4] for example: the transfer of the terminal phosphoryl group from adenosine triphosphate to nucleophiles under basic conditions; the enzymatic transformation of mevalonic acid into isopentyl diphosphate by ATP and metal ions or the role of ATP in the biological reduction of nitrogen to ammonia (nitrogen-fixation).

Pentacoordinated phosphorus compounds are not only present as reaction intermediates in biological reactions or chemical reactions as Arbusov, Perkov and Wittig,[4b] but they can be isolated as stable compounds.[5]

2.2 Pentacoordinated structures and their non rigid character

The development of structural principles for pentacoordinated species, was centered on the trigonal bipyramid geometry. These principles have been applied with considerable success in the construction of reaction intermediates. The systematic application of mechanistic criteria for postulating the most likely pentacoordinated intermediates has led to a consistent rationalization of a large number of information on phosphorus reactions. Certain principles emerged that govern conformational preferences regarding the positioning of ligands in a TBP structure. They are listed as follows in order of importance:[6]

1. Four- or five- membered cyclic systems preferentially span axial-equatorial positions;
2. The most electronegative ligands preferentially occupy axial sites;
3. P-bonding donor ligands, in general, are positioned at equatorial sites.
4. Steric effects are minimized by locating bulky groups in equatorial positions.

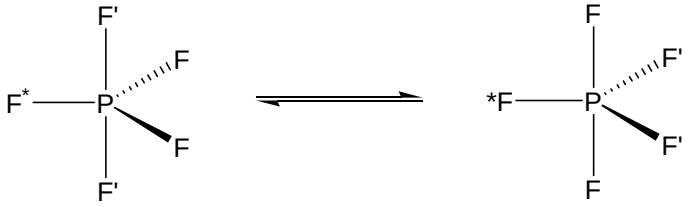
The stability of phosphoranes (pentavalent phosphorus) is markedly increased by the presence of four- anf five-membered rings, and to a lesser extent, by six-membered rings, since cyclization decreases intramolecular crowding relative to the comparable acyclic situation.[7] This assistance from intramolecular growding can outweigh any strain resulting from the deformation of bond angles within the ring. Nevertheless, ring-strain rather than intramolecular crowding is the main factor in determining the stability of tetracoordinate phosphorus. Consequently, a five membered cycle loses in stability while the corresponding cyclic phosphorane gains in stability relative to the corresponding compounds in which the phosphorus is not incorporated in rings.[8] These is thermodynamic and kinetic advantage in adding a nucleophile such as alkoxide or water to four-coordinate phosphorus to form a phosphorane intermediate when a five-membered ring is present in the phosphate, or when such a ring is easily formed during a reaction. This is in accord with Westheimer and co-workers[7,9] found studying the acid hydrolysis of cyclic esters, in fact their experimental results reported that a five-membered cyclic phosphate esters hydrolyze much more rapidly (10^5-10^8 times) than their open chain analogous in either acid or base.

2.3 Permutational isomerization

The permutational isomerization of the phosphoranes can occur by bond deformations (regular process) and by bond breaking and recombinations (irregular process). The regular permutational isomerizations of acyclic phosphanes can take place by either Berry pseudorotation[10, 11] (BPR) or turnstile rotation[10b, 11, 12] (TR) or by both of these mechanism.

2.3.1 Berry pseudorotation

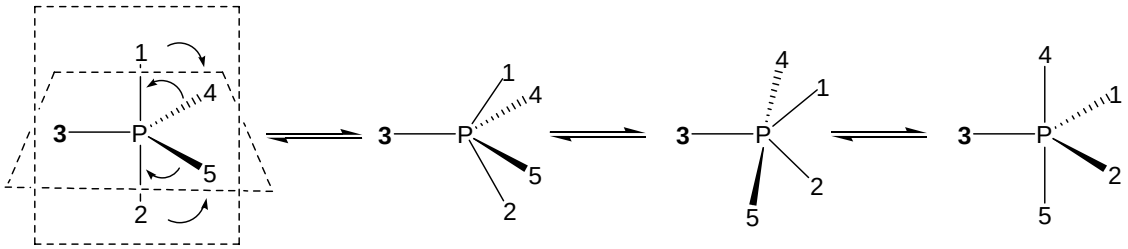
In 1960, R. S. Berry[10] suggested that the position exchange of the fluorine atoms of PF_5 occurs by a regular bond-deformation mechanism which he called pseudorotation (scheme 2.2).



Scheme 2.2 Exchange of the fluorine atoms of PF_5, consequence of BPR.

In general, this Berry pseudorotation (BPR) can be described as shown in Scheme 2.3. A pair of equatorial ligands, for istance 4 and 5, move in a plane and the two apical ligands move in another plane, perpendicular to the first. The fifth ligand, the pivot (3), does not move at all. The synchronous expansion of the original 120° diequatorial angle 4-P-5 leads to an angle of 150° in the idealized barrier situation; this angle reaches 180° in the new TBP. Similarly, the synchronous contraction of the original 180° diapical angle 1-P-2, leads to 150° in the idealized barrier situation and 120° in the new TBP. During this bending motions, the bond distances adjust to the new TBP skeletal arrangement. After the BPR, the new TBP is oriented as if the entire molecule had rotated by 90° about the pivotal bond, even though, in fact, neither a rotation of the whole molecule, and not a rotation of a ligand subsisted, for this reason the name rotation.[11]

Therefore in other words, the BPR mechanism realizes of two apical and two equatorial ligands, and the retention of the equatorial position of the pivot.



Scheme 2.3 Berry pseudo rotation with ligand 3 as pivot.[11]

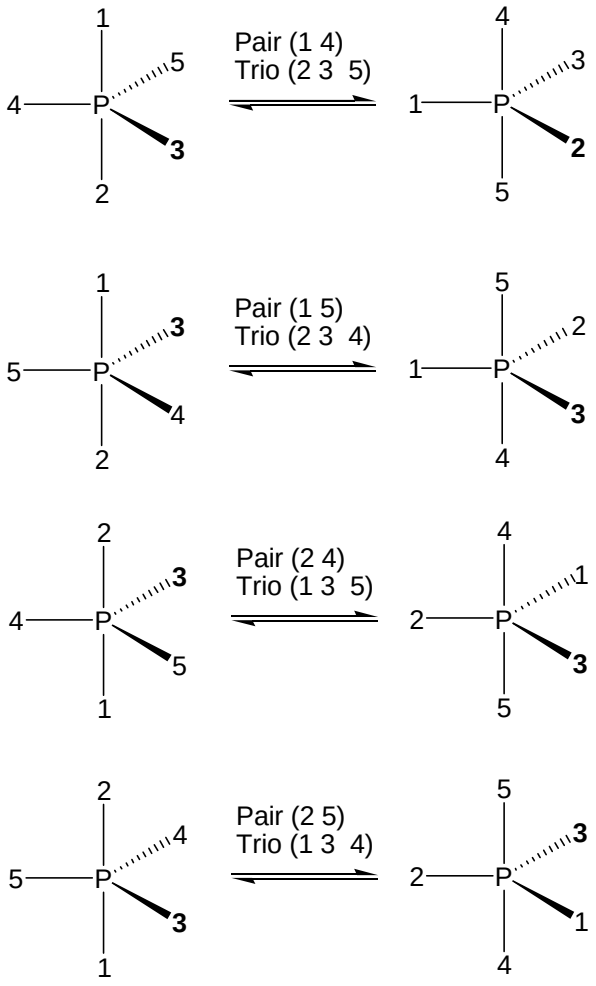
2.3.2 Turnstile rotation

About 10 years later than the Berry pseudo rotation was formulated, another theory was proposed, the turnstile rotation[12] (TR). The turnstile rotation consist in a permutation of the ligands among skeletal positions of the TBP which, in general takes the form shown in scheme 2.4.

The first TR process of scheme 2.4 corresponds to the ligand permutation (1 4) (2 3 5), which means ligand 1 replaces ligand 4 and ligand 4 replaces ligand 1, while ligand 2 replaces ligand 3, 3 replaces 5 and 5 replaces 2. The second, third and fourth equivalent TR processes correspond, respectively, to the ligand permutations (1 5) (2 3 4), (2 4) (1 3 5), (2 5) (1 3 4). It should be noted that the five ligands have been partitioned into a pair, which always contains one apical and one equatorial ligand and a trio.[11]

Obviously, the TR and the BPR processes correspond to different types of permutations of the ligands among the skeletal positions of the TBP, but the same isomerization of it can be achieved by one BPR process or by four TR process.

The differences between the two processes in the case of certain acyclic phosphoranes are not so evident, this means that the potential surface for permutational isomerization does not contain high barriers between the BPR barrier model and the TR barrier model.[10b] When two or more ligands participate in cyclic structures, the situation changes. In fact, for regular isomerizations of acyclic phosphoranes existed two mechanistic possibilities, BRP and TR, but for the case of regular isonerizations of cyclic phosphanes the only mechanistic possibility is the TR process, with the four- and the five- membered ring always as the pair of the TR pair-trio combination.



Scheme 2.4 Four equivalent turnstile processes showing the pairs and trios of ligands which effects the same isomerization as Berry pseudorotation with ligand 3 as pivot.[11]

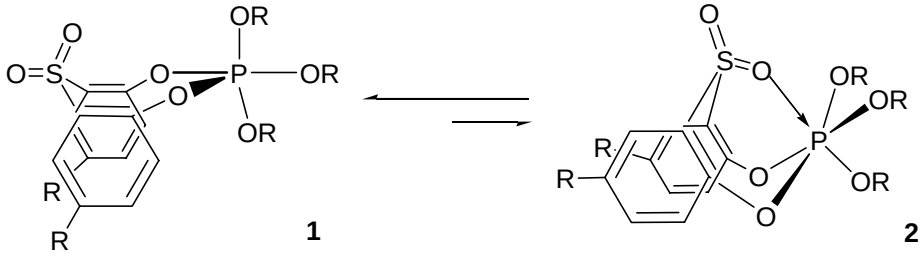
2.4 The 6-Coordinate State of Phosphorus

The chemistry of hexacoordinated phosphorus compounds has received much less attention than that of the pentacoordinated state. In recent years many stable compounds have been made in which phosphorus has six attached groups.[13,14] In general the octahedral structure, with two apical and four equatorial bonds, is adopted. In this coordination state, phosphorus is known in neutral, anionic and cationic forms. Many of the known compounds can be considered as Lewis salts

obtaining from the interaction between a donor group (neutral or ionic) with five-coordinated phosphorus.

Some of the concepts of the five-coordinate state are useful also in six-coordinate state. As Muetterties and Mahler[15] showed highly electronegative elements, in particular fluorine, stabilize the hexacoordinated state and their prefer the apical position. Fluxional character can be present,[16] and ^{31}P NMR shift are usual found at high field.

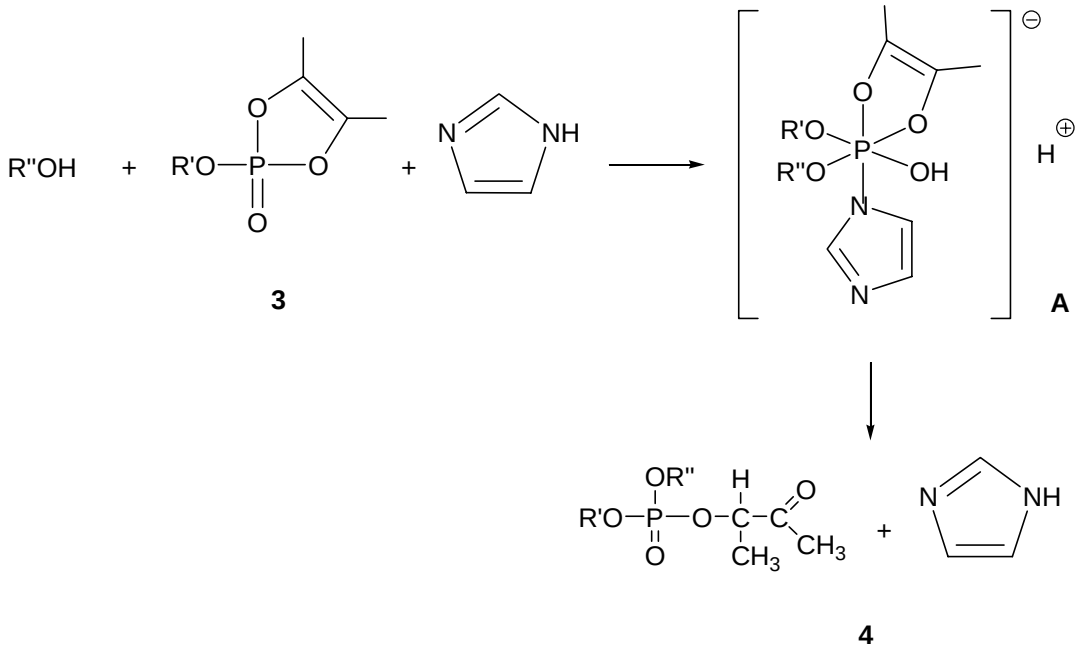
Six-coordinate compounds are receiving attention at present because they are recognised as transient intermediates in certain reactions of five-coordinate structures, adding a new dimension to considerations of reaction mechanisms. Generally, it is considered that pentacoordination to hexacoordination occurs through a square pyramidal (SP) geometry from a trigonal bipyramidal (TBP) geometry. A careful analysis of the equilibrium reported[17] in Scheme 2.5 reveals that the coordination at these sulfonyl phosphoranes **2** having a square pyramidal distortion on the pathway toward an octahedron, it is also accompanied by a change in the ring orientation. When no coordination is present, the eight-member ring occupies a diequatorial orientation, as seen in phosphorane **1**, **2** (Scheme 2.5).[18] However, it changes to an axial-equatorial orientation before distorting toward the SP geometry.



Scheme 2.5 Equilibrium from pentacoordination to hexacoordination.[17]

Other studies carried out by Ramirez[19] and others, suggested that hexacoordinated phosphorus compounds are formed during nucleophilic displacement reactions on pentacoordinated phosphorus compounds. Most of these studies have centered on oxyphosphoranes. In addition, there are studies of reactions of tetracoordinate phosphorus which have been considered to involve hexacoordinate states.[14,20] For

example, nucleophilic catalysis of the phosphorylation of alcohols by the cyclic phosphate **3** in the presence of imidazole was proposed by Ramirez et al.[20] to proceed with ring opening via the hexacoordinate intermediate **A** to give **4** (Scheme 2.6). The imidazole catalyst acts in a nucleophilic assisted attack at phosphorus by the alcohol. Ramirez and co-workers[20] infer that analogous mechanisms may be important to the behavior of some enzymes that are involved with phosphoryl group transfer whereby amino acid residues enter into the catalytic activity. The intervention of both five- and six-coordinate species is suggested.[14b,21]



Scheme 2.6 Nucleophilic catalysis of the phosphorylation of alcohols by the cyclic phosphate **3** in the presence of imidazole.

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Chapter 3

PHOSPHORUS-31 NMR SPECTROSCOPY

The phosphorus atom frequently plays a central role in the chemistry of most compounds in which it is incorporated. Without ^{31}P NMR spectroscopy, the task of sorting out the incredible changes in coordination number, and the additional stereochemical changes associated with the three-, four, five- and six- coordinate compounds world have been much slower.[1, 2]

Chemical shifts in the nuclear magnetic resonance of ^{31}P were discovered by Knight.[3] Subsequent measurements, particularly those by Gutowsky and his co-workers[4] indicate that NMR spectroscopy can became a valuable tool for chemical studies involving phosphorus compounds. Today this technique can also be used to determine the complexity of a reaction mixture or the purity of products, because different signals are almost always seen for each phosphorus compound. Many other applications of phosphorus NMR have been made, such as performing conformational analysis and studying reaction mechanisms by means of signals for intermediates.

The large use of ^{31}P NMR is due to the presence of only one natural isotope with mass 31, so strong signals can be obtained with a small quantity of compound, that render the taking of phosphorus NMR spectra easy.[2]

3.1 Chemical Shifts

Phosphorus-31 chemical shifts have been observed over a range exceeding 1000 ppm. However, many classes of phosphorus compounds give signals within quite small parts of this range. The relationship between structure and phosphorus chemical shift is often well enough established to permit quite detailed structural

inferences, even to the extent of identifying the stereochemistry in some instances. The presence of a lone pair of electrons on phosphorus tends to widen the chemical shift range, and additional information is usually required to obtain structural information. For organophosphorus compounds ^{1}H and ^{13}C NMR data can often be linked directly to the ^{31}P information. Together they form a very powerful structural tool for the chemist. Phosphorus-31 chemical shifts are reported relative to the signal for 85% phosphoric acid.[5] The acid is invariably used as an external reference due to its reactivity. Care must be taken when collecting data from the literature to establish whether the phosphorus isotope signal appears upfield or downfield of the standard, 85% phosphoric acid. There was a change in sign convention in the mid-1970s, and now positive chemical shifts are downfield of the standard.[2a]

Even if the ^{31}P NMR shifts extent in a large range, the vast majority are included in the region of about δ -200 to +300 ppm. Each type of functional group ha sits own range of shifts within this region. It should be noted that there is overlap of this functional group subregions, and it is not often possible to use only the ^{31}P shift, without other characterization for identify unambiguously a compound. Many factors have been considered to be important in effecting the shift for a particular structure. A few of this factor are reported to follow:[2b,6]

- Electron withdrawal by electronegative groups, generally considered to act by contracting the p-orbitals at P and causing deshielding.
- Resonance interactions at phosphorus with unsaturated groups that change electron density on phosphorus in either direction causing shielding.
- Chain lengthening and branching effects, which cause deshielding as the number of β-carbons to P increases or shielding as the number of γ-carbons increases.
- Changes in bond angles at phosphorus, increases in which are said to cause deshielding of 3-coordinate phosphorus and shielding in phosphates.
- Steric interaction in acyclic compounds manifested by shielding.
- Five cyclic-member compounds showed to be more deshield than the analogous six cyclic-member. This phenomena is caused by major

overlapping between dπ-pπ orbital in the five cyclic-member compounds in which the bong angle is closer to 90°.

Besides structural properties can be achieved by analysis of ^{31}P NMR spectra. In fact each P-coordinations has its range of chemical shift that covered all the ordinary range (Figure 3.1). It could be important to note that 6-coordinate compounds are also found outside their usual range; in fact they can have a positive chemical shift, as reported in the literature.[7]

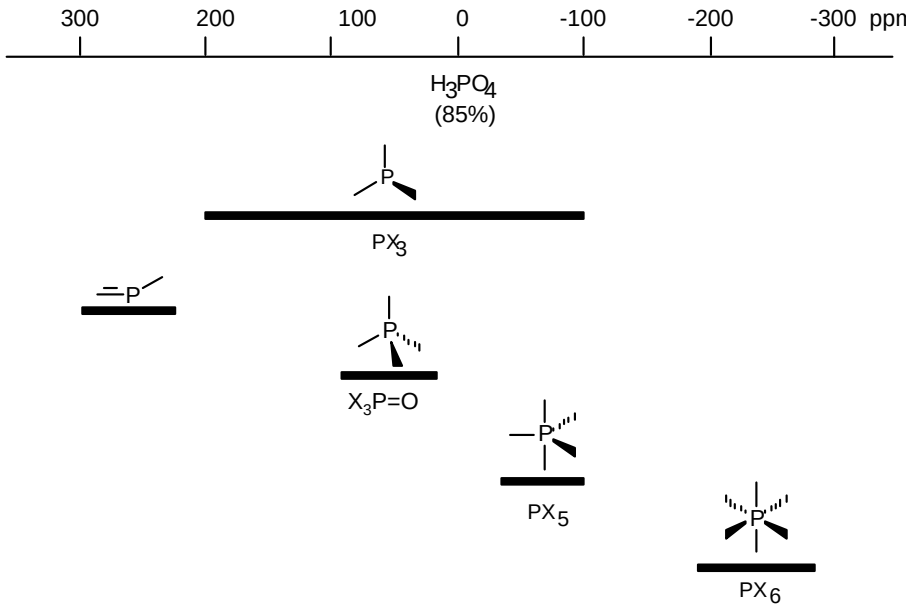

Figure 3.1 Chemical shift range for the different P-coordination.

3.2 Spin-Spin Coupling Constants

The ^{31}P nucleus coupled with ^{1}H, and both types of spectra show the effect. Couplings constants can be as small as a few Hertz or as a many as several hundred Hertz for the direct P-H bond. Because the coupling effect is commonly seen on ^{1}H spectra, but usually avoided by decoupling in ^{31}P NMR, coupling constants are usually determined from the previous spectra. Therefore couplings to neighboring protons are very useful for determining the nature and the number

of aliphatic groups bound to the phosphorus atom. The protons of aryl groups rarely produce resolvable couplings in the ^{31}P spectrum.[2c]

The lone pair effect is clearly seen in the decrease of the positive $^{1}J(^{31}P,^{1}H)$ values from PH_4^+ (546-548 Hz) to PH_3 (182-195 Hz) to PH_2^- (138-140 Hz).[8] Although there is a general increase in $^{1}J(^{31}P,^{1}H)$ with increasing oxidation states of phosphorus, the ranges for the various oxidation states overlap considerably, perhaps owing in large measure to the reduction of s character in the P-H bond as the coordination numbers increase. As expected, the loss of a P lone pair upon coordination of a phosphine to a boron Lewis acid or a transition metal results in a marked increment in coupling. The effect of electronegativity is evident in the rise of $^{1}J(^{31}P,^{1}H)$ especially when electron electronegative halogens are bound to phosphorus.[9]

A different situation prevails for the coupling of ^{31}P with ^{13}C where useful couplings to phosphorus are manifest in proton decoupled ^{13}C NMR spectra. In this case the effect is seen only on the ^{13}C NMR spectra, because the low natural abundance of ^{13}C (1.1%) in insufficient to lead to an observable number of coupled ^{31}P nuclei. Such couplings greatly aid the identification of the carbon resonances adjacent to phosphorus as well as providing important stereochemical information in many instances.[2c]

3.2.1 ^{31}P-^{11}B coupling

The one-bond coupling of ^{31}P and ^{11}B has been recorded mainly for tricovalent P ligands bonded to a BZ_3 moiety for which the range of couplings is 13-174 Hz. Most of these ^{11}B signals appear as a quartet due to the ^{31}P-^{11}B coupling. ^{1}N NMR spectra usually display a quartet (^{1}H-^{11}B coupling) which is further split into a doublet by ^{1}H-^{31}P coupling.[2c,10]

The difference between the chemical shift of the free tricoodinated phosphorus compound and the chemical shift of its borane adduct is called the coordination chemical shift (CCS), which varies depending on the nature of the groups bonded to phosphorus. Several compounds have been compared, and it appear that

trialkyl- or triarylphosphines complexation with borane results in a rather strong deshielding (CCS = 95 to 133 ppm).[11]

3.3 References

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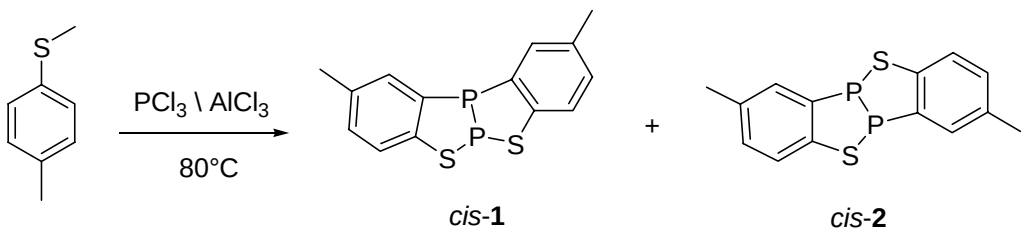
Chapter 4

THE PHOSPHORUS DONOR REAGENT

During studies on the reactivity and use of PCl_3 in organic synthesis, Baccolini and his co-workers found[1] the surprising result that fused benzo-l,2,3-thiadiphospholes (**1**) was formed by reaction of p-methylthioanisole with PCl_3 and $AlCl_3$. This synthetic procedure has been improved during recent years and now it is possible to obtain compound **1** with good yields (45%), using a one-pot three-step procedure.[2] The prevalent product isolated from the reaction was the compound *cis*-**1**, and only in trace the isomeric compound *cis*-**2** (scheme 4.1). No appreciable amount of the corresponding *trans* isomers were observed.



cis-**1** *cis*-**2**

Scheme 4.1 Synthesis of compound **1** (containing traces of **2**).

The X-ray crystal structure determination of *cis*-**1**[1] and *cis*-**2**[3] compounds showed that both of the molecules exhibit a 'butterfly' arrangement with the phosphorus electron lone pairs in an eclipsed conformation (Figure 4.1). As this conformation is unusual for a molecule containing a P(III)-P(III) single bond, a solid state ^{31}P-NMR study was performed. The changes in $^{1}J(P,P)$ and $\delta^{31}P$ observed from solution to solid state indicated that crystal packing effects force of two “wings” of the butterfly molecule to open slightly in the solid state.[4]

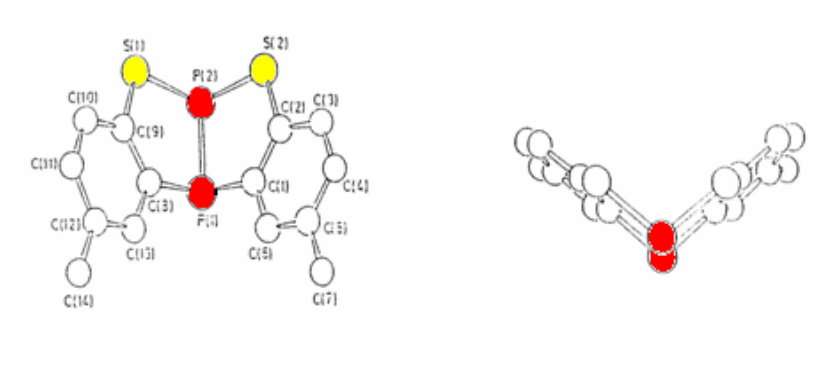
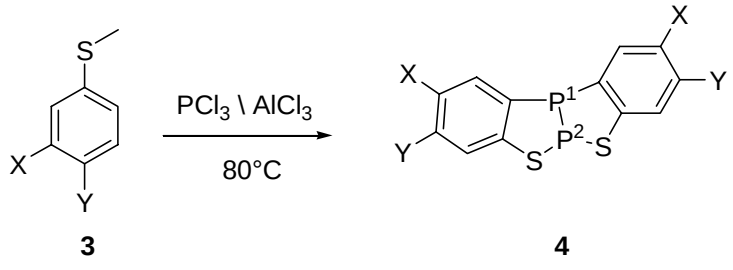


Figure 4.1 X-ray crystal structure of *cis*-**1**[1], where yellow indicates sulfur atoms and red indicates phosphorus atoms.

This method has also been generalized employing several alkyl aryl sulphides, providing in this way the corresponding fused benzo-l,2,3-thiadiphospholes, such as *cis*-**1**, but with a decrement of the obtained product.[5] In particular the tioanisoles (**3**) and PCl_3 and $AlCl_3$ were allowed to reflux in the absence of solvent for *ca*. 2h. and the products were purified by filtration on Florisil column. In the scheme 4.2 reports the products (**4**) are obtained by reaction of different alkyl- substituted tioanisoles (**3**) with PCl_3 and $AlCl_3$. The best results were obtained using a ratio (**3**)- PCl_3- $AlCl_3$ of 1:3:0.75. The yields of products (**3**) were also dependent on the starting sulphide. The substrate **3b** provided the higher yield. Compounds **4** were stable to air and moisture and for this reason easy to purify. The reaction appeared to be favoured when the methyl group occupied the *para*-position, presumably reducing the by-products arising from the electrophilic substitution of PCl_3 in that position. In addition the *ortho*-substituent does not allow the formation of **4** probably because of the steric hindrance of the methyl group.[5]



3 **4**

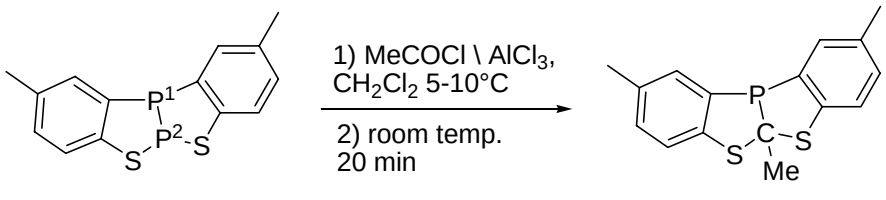
	X	Y	Yield%
a:	H	H	22
b:	Me	H	38
c:	H	Me	20
d:	Me	Me	35
e:	Et	H	30
f:	^{t}Bu	H	11

Scheme 4.2 Generalization of the method.

Exploiting the reactivity of the heterocycle **1** in order to synthesize other phosphorus and sulphur heterocycles, different reactions were carried out.[6, 7]

This new system showed to be highly unstable in the conditions under which phosphines normally react, i.e. formation of phosphonium salts with alkyl halides, oxidation with H_2O_2 reaction with diethyl azodicarboxylate (DEAD)[8]/catechol or with phenyl azide. In such cases, rather than the corresponding salts, oxides, spiro derivatives or phosphazenes[9] of **1**, decomposition products were obtained, presumably deriving from P-S and P-P bond cleavage.

Studying this instability of **1**, a Friedel-Crafts acylation with acetyl chloride and $AlCl_3$[6] was carried out and surprisingly, a highly stereospecific replacement of the phosphorus P^2 with the carbonyl carbon atom of acetyl chloride was obtained. This phosphorus-carbon exchange occurred under mild conditions in a one-pot reaction, and gave the cis-6-R-[1,3]benzothiaphospholo[2,3-b][l ,3]benzothiaphosphole derivative **5** in very good yields (scheme 4.3).

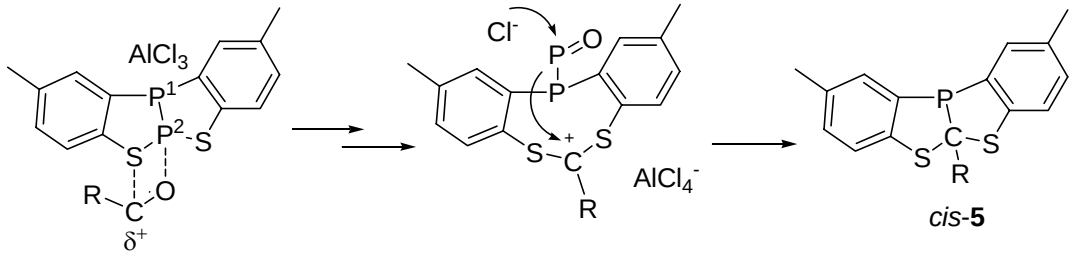


cis-**1** *cis*-**5**

Scheme 4.3 Exchange of P^2 by the carbonyl carbon atom of acetyl chloride.

A possible generalization of the reaction with other acyl chlorides was tried in order to obtain information about the mechanism involved in this phosphorus-carbon exchange.[6b] In all the reactions performed, the corresponding compound **5**-like were isolated in very good yields. In contrast, when acyl chlorides with R = ^{t}Bu, Ph, *p*-ClC_6H_4, CCl_3 were used, the starting material **1** disappeared to give formation of unidentified products. Only traces of the corresponding fused l,3-benzothiaphospholes were detected by GC-MS analysis. From these simple results it was possible to deduce that this exchange reaction was dependent on the steric factors associated with the acyl chloride. In fact, with a more forced R group, it was very likely that the cleavage of P-S and/or P-P bonds did occur, but the ring closure is disfavoured presumably because of steric congestion.

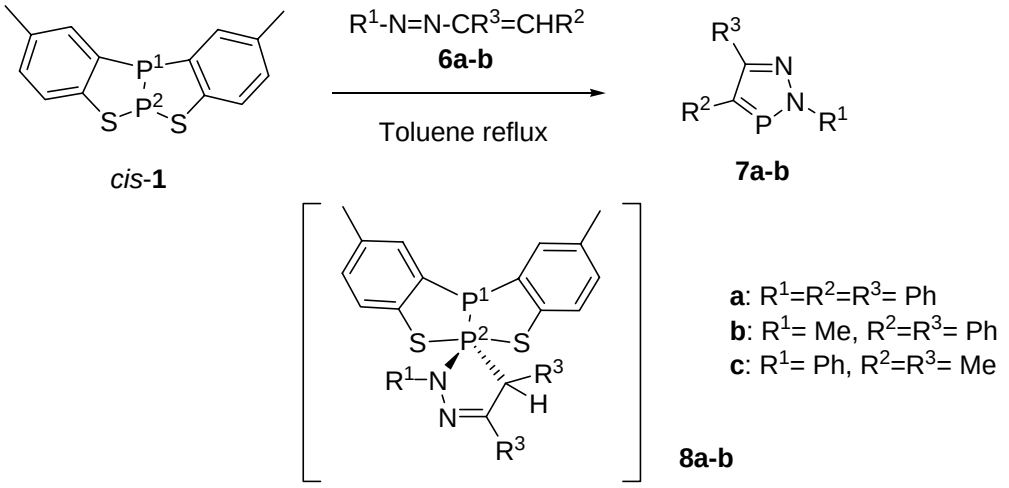
In scheme 4.4 a mechanism[6b] for the reactions is illustrated; it is based on the lability of the P-S bond, the affinity of the phosphorus for the oxygen atom, and the observed stereospecificity with inversion of configuration in the initial reaction. As depicted, it was supposed that initially a concerted breaking of the P-S bonds occurs with formation of C-S and P-O bonds; in the final step there is a ring closure, which is favoured when the R group is relatively small; this is in accord with the above experimental data.



Scheme 4.4 Proposed mechanism of the phosphorus-carbon exchange.

With the intention of continuing to explore the peculiar reactivity of compound **1**, the reaction with conjugated azoalkenes was investigated.[7] They are known to react with phosphorus halides[10] and phosphates,[11] but not with trisubstituted phosphines. Unexpectedly, all the isomers of phenylazostilbene **6a** reacted with **1** to afford the previously unknown diazaphosphole **7a**, and this procedure represents a new route for obtaining diazaphosphole derivatives (scheme 4.5).

Unfortunately, all attempts to obtain or to characterize an intermediate adduct were unsuccesful. However, it is possible to hypothesise a spirocyclic adduct **8** with pentacoordinate P^2 atom, in probable equilibrium with different ionic forms. Its decomposition gave **7a-c**, presumably by a reductive elimination[12] mechanism. Unfortunately, it was not possible to identify other by-products in order to confirm the above hypothesis.



Scheme 4.5 Reaction with conjugated azoalkenes.[7]

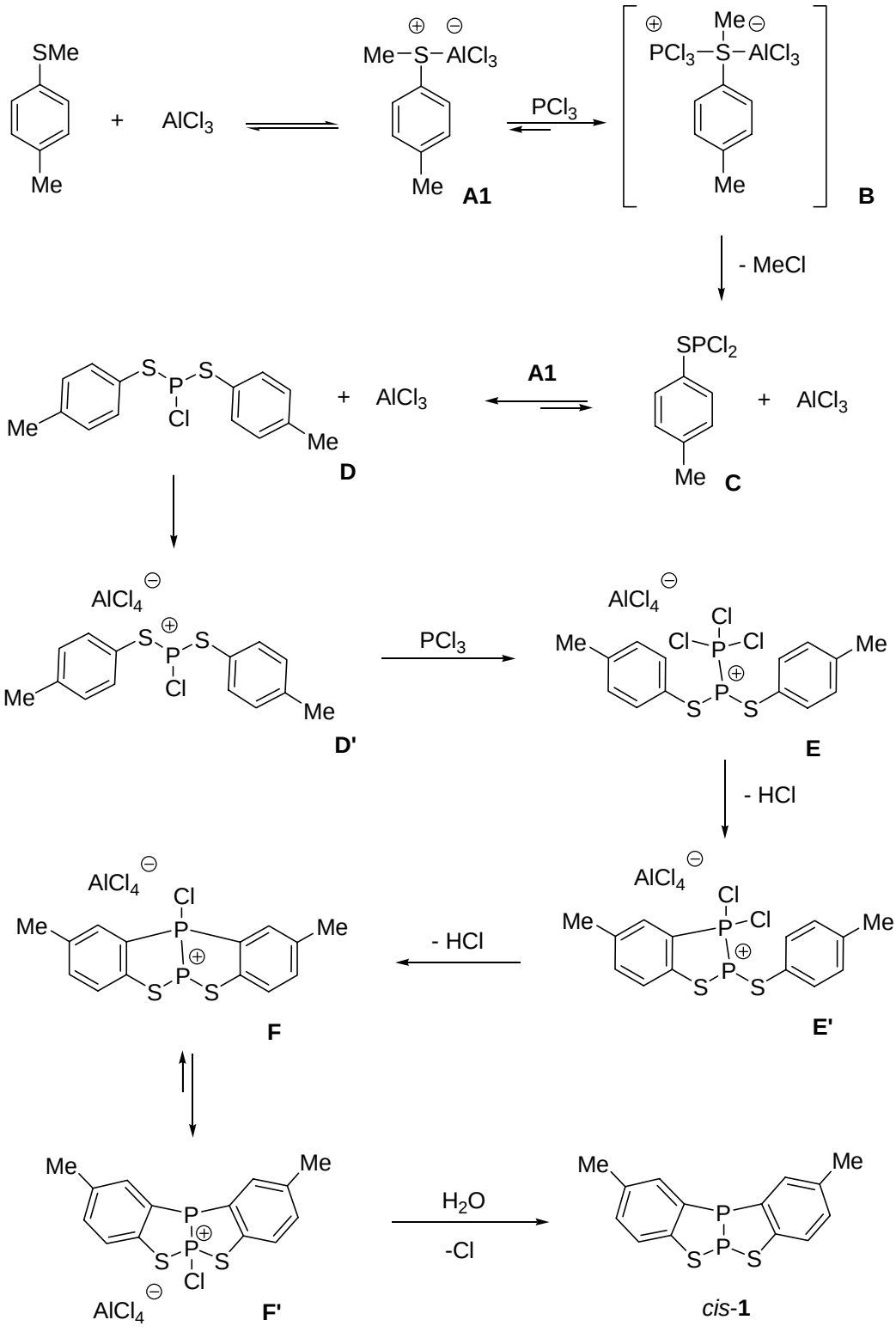
Since the formation of this heterocycle, the fused benzo-l,2,3-thiadiphosphole (**1**) from the reaction of *p*-methyl tioanisole, PCl_3 and $AlCl_3$ resulted unusual, its formation mechanism has been studied.[13] The principal problem was the complexity of the cyclization reaction, but fortunately the separation and the characterization of the prevalent product (*cis*-**1**) was very easy.

The breaking of two S-Me bonds, the formation of two C-P bonds, two P-S bonds, and one P-P bond are involved in this cyclization, and several pathways could be hypothesised, but due to a lack of data it had not been possible to determine an unequivocal reaction pathway. In order to determine the most probable pathway, it was necessary to uncover some information regarding the demethylation process, the *ortho*- and S-phosphorylation, the P-P linkage formation and, if it was possible, to have some explanation for the facile regioselective and stereoselective formation of *cis*-**1**.

It is well documented in the literature[14] that when a diphenyl sulfide is caused to react with $AlCl_3$, a sulfonium salt or complex is formed in a reversible manner, and evidence for methyl phenyl sulfide-$AlCl_3$ complex formation has also been reported.[15] In addition, when this complex is treated with other reagents, a cleavage of the C-S bond occurs presumably via a tetracovalent sulfur compound.[14-16] Furthermore, benzyl phenyl sulfide is known[16] to form a complex with $AlCl_3$, which undergoes reaction with water to give thiophenol and benzyl chloride.

In consideration of the above-mentioned observations reported in the literature, a multi-step mechanism was proposed as depicted in Scheme 4.6.

In order to obtain supporting evidence for the above-proposed multistep mechanism, a series of reactions using various conditions were conducted (different reagent ratios and various temperatures). Aliquots of the reaction mixtures were analyzed by ^{31}P- and ^{1}H-NMR spectroscopy and by GC-MS determinations .[13] The ^{31}P chemical shifts and P-P and P-H coupling constants found,[13] were in good agreement with the formulation of intermediates reported in the Scheme 4.6.

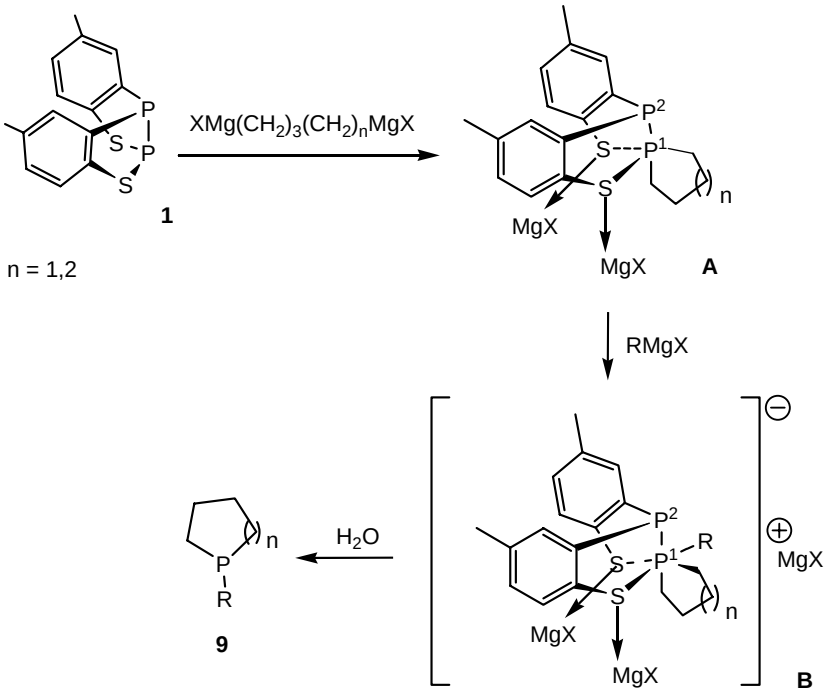


Scheme 4.6 Proposed mechanism of formation of fused benzo-l,2,3-thiadiphospholes (*cis*-**1**).[13]

After the mechanism study, an improved synthetic procedure was formulated, and now, as reported above, it is possible to obtain the compound *cis*-**1** in moderate yields.

The increment in the yield has permitted the development of the studies on the reactivity of this new heterocycle. As reported above, in both reactions[6,7] carried out on the compound **1**, the molecule reacted losing a phosphorus atom P^2.

Its reactivity was also studied using Grignard reagents, demonstrating that compound **1** could react with those reagents in an unusual manner. In particular the simultaneous addition of an equimolar mixture of a bis-Grignard (n = 1, 2) and a mono-Grignard RMgBr to an equimolar amount of **1** at room temperature, which gave the cyclic tertiary phosphines **9** as the prevalent product after quenching with water.[17]

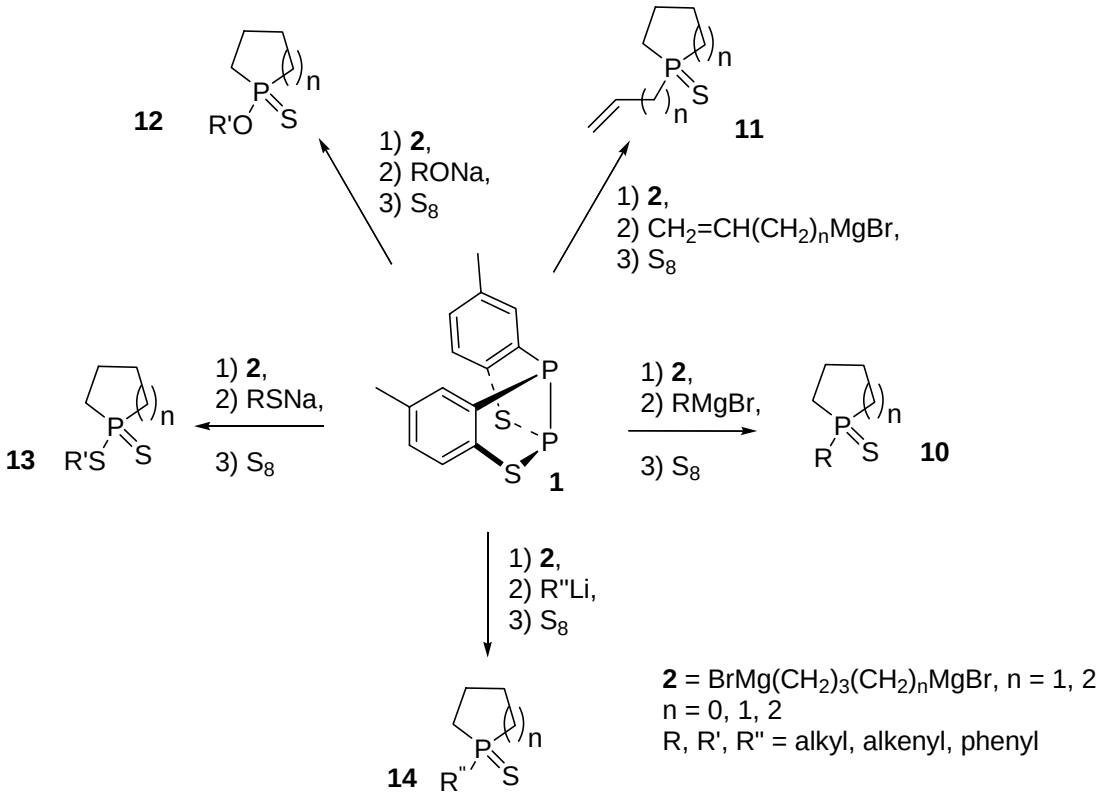


Scheme 4.7 Reaction between reagent **1** and bis- and mono-Grignard reagents.

These results were explained by the presumed intervention of hypervalent phosphorus intermediates penta- and hexacoordinates such as **A** and **B,** in which the dibenzo-butterfly moiety of reagent **1** might favour their formation. This observed favored cyclization might be in accord with a hypervalent intermediate

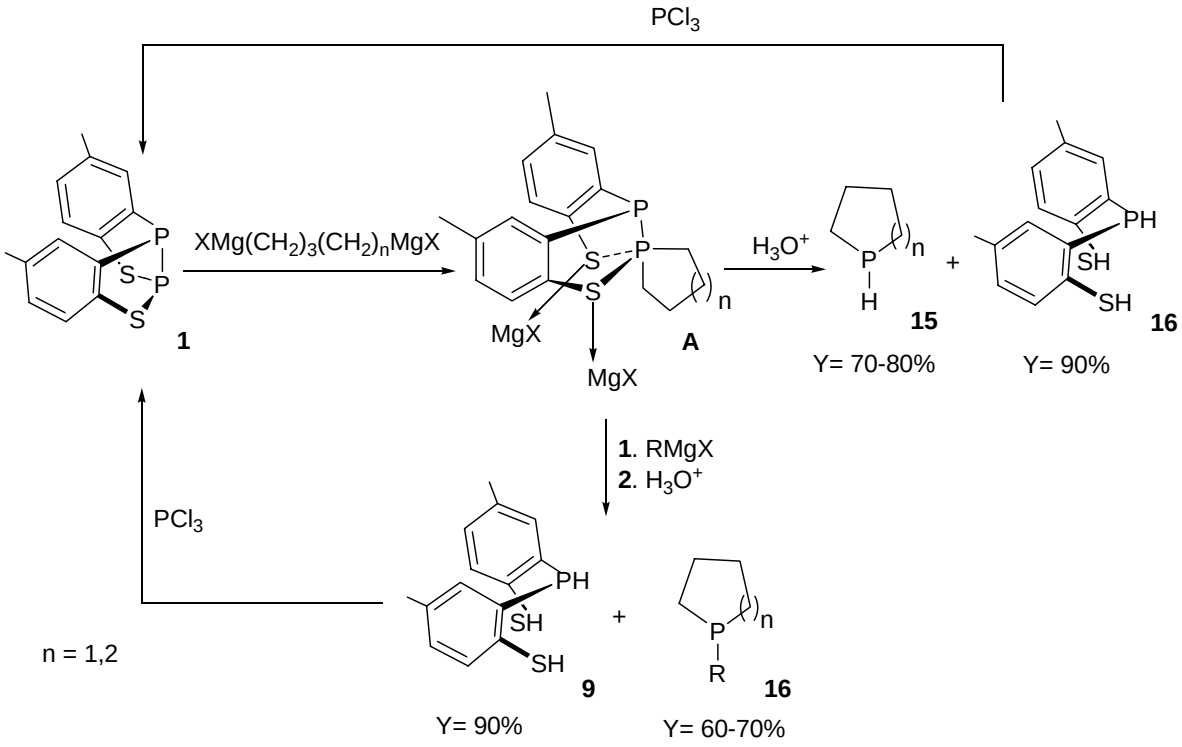
in which the formation of a cyclic form is favored by a larger factor (10^5–10^8) with respect to an acyclic form (as reported in the Chapter 2). With the aim of obtaining information about the stability of the hypothetical intermediate **A**, the reaction was carried out in a three-step procedure between bis-Grignard reagents and **1** monitoring the progress of the reaction by ^{31}P NMR spectroscopy. [18] A few minutes after mixing the reagents the disappearance of the two doublets of **1** was noted [δ = 88.3 (d, P^1), 65.4 (dt, P^2, ^3JPH = 7.8 Hz), ^1JPP = 211.5 Hz] and the concomitant appearance of two new doublets [δ = -43.3 (dm, P^1, JPP = 188 Hz); δ = -47.0 (dt, P^2 JPH = 7 Hz), JPP = 188 Hz)], tentatively assigned to the intermediate **A** (Scheme 4.7). The large P-P coupling constant indicates that intermediate **A** has a P-P bond again; the doublet of triplets observed for P^2 indicates that this P atom is bonded to two phenyl groups, while the doublet of multiplets suggests that P^1 is bonded to alkyl groups. This intermediate **A** is very stable. Only after the addition of a mono-Grignard reagent and quenching with water, the disappearance of these signals and the appearance of new signals corresponding to the phosphine **9** were observed.[18] After the study on the reaction mechanism, the reaction was carried out in a one-pot, two-step procedure, where the addition in two steps of equimolar amounts of a bis-Grignard reagent and a mono-Grignard reagent RMgBr to one equivalent of **1** at room temperature, gave the cyclic phosphine **9**, after quenching with water. In this manner the yield was improved, with a better control of the final products (Scheme 4.7).

With similar methods different classes of tertiary cyclic phosphines were obtained (see Scheme 4.8). In order to easily characterize the compounds, the final reaction mixture was treated *in situ* with elementar sulfur to obtain the corresponding cyclic phosphines sulfides **10**, **11**.[17, 18] If the reaction mixture is treated with water instead of S_8 the corresponding cyclic phosphines **9** are obtained. Consequently, it was discovered in the second step that a large variety of Grignard reagents and other nucleophilic reagents, such as sodium alcoholate or thiolate and lithium derivatives could be used, obtaining various 1-substitued cyclophosphine derivatives **12**, **13** and **14** respectively (Scheme 4.8).[19]



Scheme 4.8 Reaction of compound **1** with bis-Grignard reagents and mono-Grignard reagents (containing alkyl, phenyl and alkenyl groups), R'ONa, R'SNa and lithium derivatives.

The above reaction was further studied when intermediate **A**, formed by reaction of **1** with one equivalent of bis-Grignard reagent, was treated with water. Unexpectedly, in this case, secondary cyclic phosphanes **15**[20] were obtained in 70–80% yields (Scheme 4.9).[21] Moreover, if the reaction mixture was treated with acidic water instead of only water, the new compound **16**, which is the end product derived from **1**, was isolated, in very good yields (before it could only be observed by a GC-MS in the reaction mixture). These can be easily separated by treating the solution with aqueous basic solution; in this way the sodium salt of **16** dissolves in the aqueous soluton, whereas the organic phase contains almost pure cyclic secondary phosphines, which can be purified by distillation. Compound **16** can be recovered from the basic aqueous layer by acidification and extraction, and purified by distillation. Simply treating a dry solution of **16** with an equimolar amount of PCl_3 regenerates **1** in sufficiently pure form that it can be reused without further purification.[20]



Scheme 4.9 Synthesis of secondary and tertiary cyclic phosphines, with recycling of starting reagent **1**.

Following on from the results obtained with secondary phosphines **15**, the reaction to obtain tertiary cyclic phosphines **9** was carried out using the same treatment of the crude reaction mixture used to obtain secondary cyclic phosphines, and also in this case the by-product **16** was isolated.

Due to the simple isolation of **16** and its easy recycling into **1**, these syntheses can be considered atom-economic.

4.2 References

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Aim of the Thesis

AIM OF THE THESIS

As previously reported in the introduction, organophosphorus compounds are important in many fields. In particular their use as ligands in homogeneous catalysis has increased enormously in the past 50 years. From here, it is important to find new synthetic procedures that produce phosphines and organophosphorus derivatives with an easy and inexpensive approach.

The aim of the first part of this thesis (Chapter 5-10) has been to develop new synthetic procedures for the synthesis of organophosphorus compounds and in particular of phosphines. The initial intention was to find innovative methods in which it was possible to use inexpensive and not air-sensitive starting reagents, as usually happens in the reported syntheses where halogen phosphorus derivatives are employed.
For these reasons, the fused benzo-l,2,3-thiadiphosphole was chosen as the starting reagent. This was possible because previous studies on fused benzo-l,2,3-thiadiphosphole demonstrated its ability to release a phosphorus atom when it reacted with Grignard reagents and was easily recycled at the end of reaction. In addition, the fused benzo-l,2,3-thiadiphospholes is easily obtained and it is not air-sensitive and as such can be conserved for long time.
Moreover, the study of the mechanism of the reaction between fused benzo-l,2,3-thiadiphosphole and Grignard reagents was attempted in order to understand which were the hypervalent phosphorus species involved in the reaction.

The aim of the second part of this thesis (Chapter 11-12) has been to apply the knowledge, acquired during the making of the first part of this thesis, for the development of new phosphorus ligands for homogeneous catalysis.
This second part was carried out developing two different projects at the University of Warwick under the supervision of Professor Martin Wills.

Results and Discussion

Chapter 5

SYNTHESIS OF HALOALKYL PHOSPHOLANE AND PHOSPHINANE DERIVATIVES AND THEIR APPLICATION

5.1 Introduction

The synthesis of cyclic phosphine derivatives is of considerable current interest principally because these compounds are the most commonly studied ligands for application in homogeneous catalysis.[1] In fact, the development of bisphosphine and phospho-amino compounds and their application to the homogeneous catalysis and coordination chemistry have increased enormously in the past decade.[1,2]

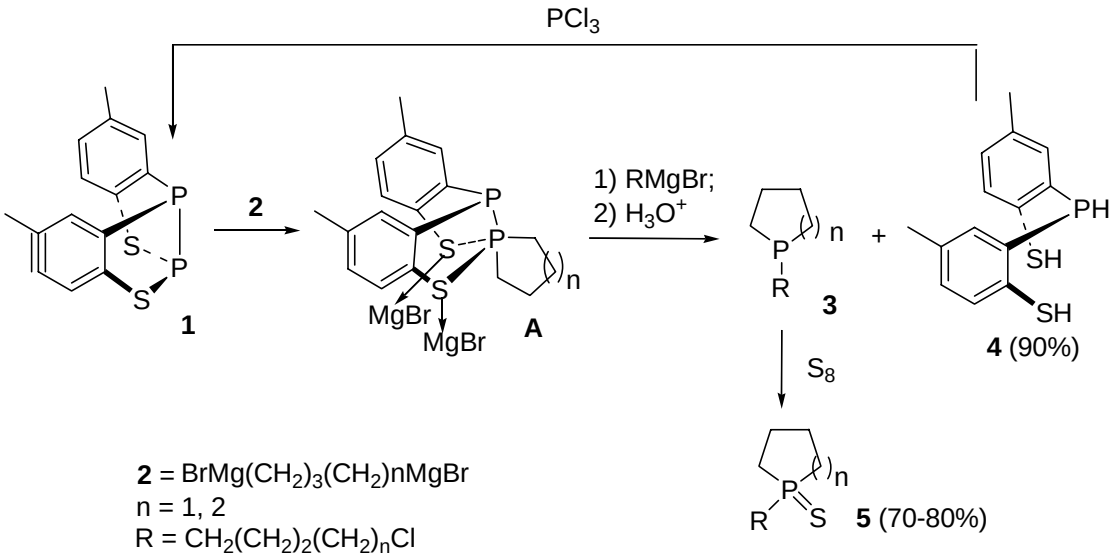
Generally, the reported syntheses of 1-substituted cyclic phosphines are related to the interaction of several reagents with halophosphines[3,4] or with primary and secondary phosphines.[4-7] However, we have noted that haloalkyl derivatives of tri-coordinate phospholane and phosphinane are still unknown. In spite of this, compounds can be used in the synthesis of bidentate ligands. A possible reason for their absence in the literature could be that primary or secondary phosphanes (RPH_2 or R_2PH) cannot be used to obtain haloalkyl derivatives of cyclic phosphanes with halogen group derivatives because of the possible reactivity of the PH group with the halogen group.[8] For this reason, it is either very difficult to obtain haloalkyl cyclic phosphine derivatives with current procedures.

5.2 Results and discussion

Recently a new synthesis[9] of tertiary cyclic phosphines, and their sulfides, was developed using the benzothiadiphosphole **1** as a starting reagent. In fact, as reported in Chapter 4, the simultaneous or the sequential addition of equimolar amounts of a bis- and a mono-Grignard reagent RMgBr (R = alkyl, phenyl, alkenyl) to one equivalent amount of **1** gave tertiary cyclic phosphines and, after the addition of elemental sulfur, their sulfides in good yields at room temperature (Chapter 4, Scheme 4.8). In particular a new class of 1-alkenyl derivatives of cyclic phosphines was obtained that was not possible or very difficult to obtain with the known procedures.

These results encouraged us to develop a synthetic method to obtain haloalkyl phospholanes and haloalkyl phosphinanes using our phosphorus-donating reagent **1** by the addition of bis- and a mono- Grignard reagents at room temperature. Consequently, we obtained the haloalkyl cyclophosphane derivatives **3** (70-80% yield) by addition to **1**, in the first step, of equimolar amounts of a bis-Grignard reagent **2** (n = 1 or 2), and in the second step, addition of a mono-Grignard reagent RMgBr (R = haloalkyl group). As reported in Chapter 4, this reaction mechanism had already been studied and explained by the intervention of hypervalent phosphorus species such as the intermediate **A** (scheme 5.1).

In addition we found that the treatment of the resulting reaction mixture with acidic (HCl) water gave the cyclic tertiary phosphines **3** and the by-product **4** in 90% yield (Scheme 5.1). These two reaction products can be separated easily by treating the organic solution with aqueous NaOH; in this way the sodium salt of compound **4** dissolves in the aqueous solution, whereas the organic phase contains almost pure phosphine **3**. Compound **4** can be recovered, as reported previously,[11] from the basic aqueous layer by acidification and extraction, and then transformed to **1** for re-use. It should be noted that phosphines **3** were analyzed only by GC-MS analysis, and were not isolated. Rather they were immediately treated with sulfur to obtain the corresponding sulfides **5** (Scheme 5.1), which are stable and thus were separated by column chromatography and fully characterized.

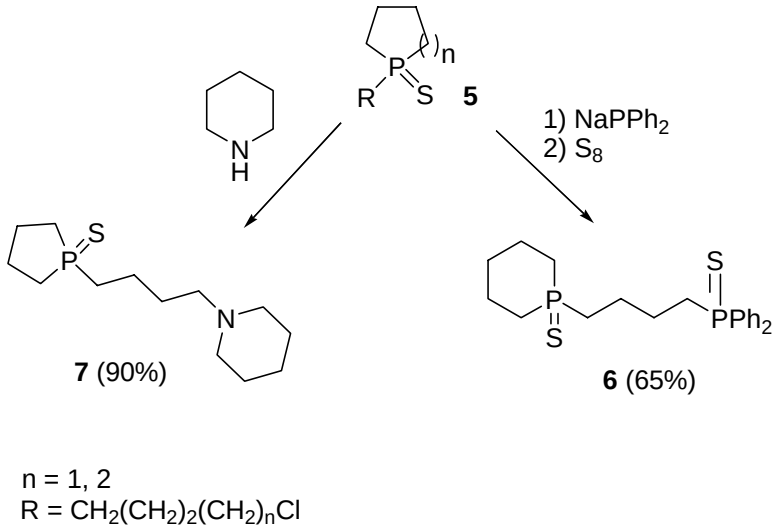


Scheme 5.1 Synthesis of haloalkyl cyclophosphane derivatives **3**, and their sulfides **5**.

As we hypothesized the presence of an halogen group in the moiety permit the use of these haloalkyl cyclophosphane derivatives **3** in the synthesis of bidentate ligands. In fact, the high reactivity of the chlorine group as a living group easily permits substitution by secondary phosphines and amines.

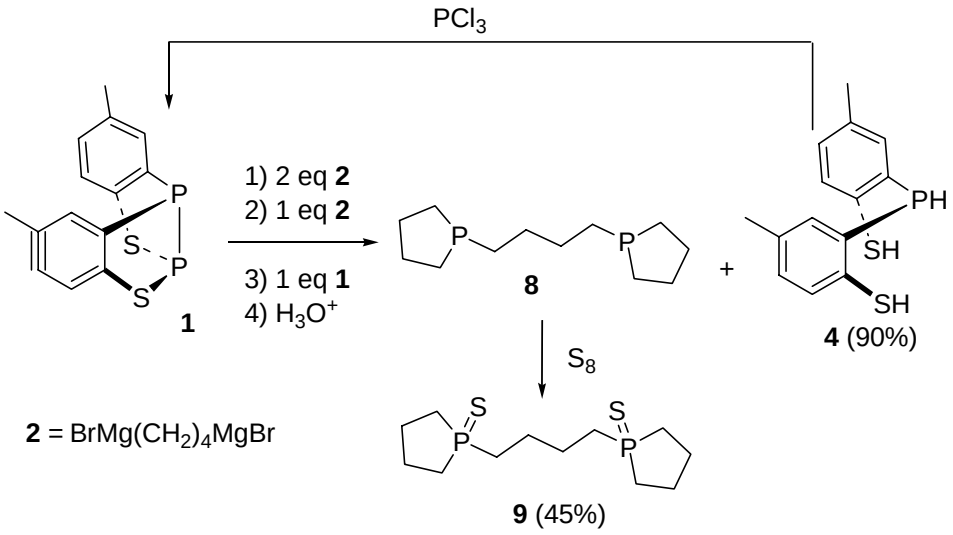
For the synthesis of the bisphosphine **6**, the compound **5b** was treated with a solution of sodium diphenyl phosphine. After treatment of the reaction mixture with elemental sulfur, compound **6** was obtained in moderate yields (65%) (scheme 5.2) and purified by column chromatography and fully characterized.

Also phospho-amino compound **7** can be synthesized using **5a** which was treated with piperidine in toluene at reflux. Compound **7** was obtained in high yield (90%) (scheme 5.2) and purified by column chromatography and fully characterized.



Scheme 5.2 Synthetic application of haloalkyl cyclophosphines.

Alternatively we optimized a one-pot three-step procedure for the synthesis of a C_2-symmetric bisphospholane compound. We obtained bisphospholane **8** by addition, in the first step, of two equimolar amounts of bis-Grignard reagent **2** to one of reagent **1**; in the second step another equimolar amount of bis-Grignard reagent **2** was added to the reaction mixture, finally in the third step, a dropwise addition of one equimolar amount of **1** was performed (scheme 5.3). After quenching the reaction mixture with acidic water we obtained the bisphospholane **8** and the end product **4** (90% yield, respect to **1**). The two compounds were easily separated as previously described. After separation, the bisphospholane **8** was immediately treated with elemental sulfur, giving the sulphide **9** in moderate yield (45%), which was purified by column chromatography and fully characterized.



Scheme 5.3 Synthesis of bisphospholane **8** and sulfide derivative **9**.

5.3 Conclusion

In conclusion, the one-pot synthesis of tertiary acyclic phosphines reported permits the production of a new class of compounds, as haloalkyl phospholanes and phoaphinanes in high yields. In this procedure, by-product **4** was recovered and transformed into the starting reagent **1**, making the process very atom-economic and environmentally friendly.

Importantly, these products could be useful in the synthesis of diphosphine and phospho-amine derivatives that have a large use in asymmetric catalysis.

5.4 Experimental section

***General*:** ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 300 (400), at 76.46 (100.56) and 120.76 (161.89) MHz, respectively. Chemical shifts are referenced to internal standard TMS (^{1}H NMR), to solvent (77.0 ppm for ^{13}C NMR) and to external standard 85% H_3PO_4 (^{31}P NMR). *J* values are given in Hz. MS spectra were recorded at an ionisation voltage of 70 eV. Flash chromatography (FC) was

performed on silica gel (0.040-0.063 mm). Melting points are uncorrected. THF was distilled from sodium benzophenone ketyl and all solvents were purified appropriately before use and degassed immediately prior to use. All Grignard reagents used, both commercially available and prepared from the corresponding alkyl halide or alkyl dihalide[12] and magnesium turnings, were titrated immediately prior to use by standard methods.[13] Air and moisture sensitive solutions and reagents were handled in a dried apparatus under a dry argon atmosphere using standard Schlenk-type techniques.

General one-step procedure for the synthesis of cyclic tertiary haloalkyl phosphine sulfides

The bis-Grignard reagent (1.1 mmol) was added to a solution of **1** (1 mmol) in THF (10 mL), at room temperature. The mixture was stirred for 15 min, then the mono-Grignard reagent (1.1 mmol) was added. The reaction mixture was stirred for 1 h after that the solvent was partially evaporated and the reaction mixture was treated with aqueous acid solution (HCl). Extraction with CH_2Cl_2 gave a mixture of phosphines and the residue **3**. The phosphines were easily separated from **3** by treating the organic solution with aqueous NaOH; after this treatment, the sodium salt of **4** was dissolved in the aqueous solution, whereas the phosphines were in the organic phase. Treatment of this layer with a slight excess of elemental sulfur gave the corresponding sulfides, which were purified by flash chromatography (dichloromethane: petroleum ether 3:2) and fully characterized. Compound **4**[10] was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, and was then purified by distillation and stored under argon. Simple treatment of a dry solution of compound **4** with an equimolar amount of PCl_3 led to the regeneration of the starting reagent **1** in almost pure form, allowing it to be reused without further purification.

1-(4-chlorobutyl) phospholane sulfide (5a): y = 80%, colourless oil, R_F = 0.44 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.58 (t, 2 H, *J*=5.6 Hz, CH_2Cl), 2.20-1.74 (m, 14 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 44.1 (s), 33.2 (d, *J*=52 Hz), 33.1 (d, *J*= 15 Hz), 32.8 (d, *J*=47 Hz), 26.0

(d, *J*=6 Hz), 20.5 (d, *J*=3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 64.5 (m) ppm; MS (70 eV, EI): *m/z* : 212 (M^+,9), 210 (26), 175 (100), 120 (99); IR: 598 (CCl), 725 (PS), 1111 (PC) cm^{-1}.

1-(4-chlorobutyl) phosphinane sulfide (5b): y = 82%, grease solid, R_F = 0.38 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.58 (t, 2 H, *J*=6.1 Hz, CH_2Cl), 2.20- 1.50 (m, 16 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 44.2 (s), 33.3 (d, *J*=15 Hz) , 30.9 (d, *J*=48 Hz), 30.0 (d, *J*=50 Hz), 26.4 (d, *J*=6Hz), 21.9 (d, *J*=6 Hz), 19.3 (d, *J*=3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 37.8 (m) ppm; MS (70 eV, EI): *m/z* : 226 (M^+, 6) 224 (18), 189 (100), 134 (53); IR: 595 (CCl), 728 (PS), 1110 (PC) cm^{-1}.

1-(5-chloropentanyl) phospholane sulfide (5c): y = 73%, grease solid, R_F = 0.43 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.56 (t, 2 H, *J*=6.6 Hz, CH_2Cl), 2.20-1.40 (m, 16 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 44.7 (s), 33.4 (d, *J*=47 Hz), 33.2 (d, *J*=52 Hz) , 32.0 (d, *J*=15Hz), 26.0 (d, *J*=6Hz), 22.4 (d, *J*=3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 64.6 (m) ppm; MS (70 eV, EI): *m/z* : 226 (M^+ , 8), 224 (24), 189 (81), 120 (100); IR: 598 (CCl), 724 (PS), 1109 (PC) cm^{-1}.

1-(5-chloropentanyl) phosphinane sulfide (5d): y = 75%, grease solid, R_F = 0.40 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.56 (t, 2 H, *J*=6.4 Hz, CH_2Cl), 2.20-1.40 (m, 18 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 44.7 (s), 32.1(s), 30.9 (d, *J*=49 Hz), 30.6 (d, *J*=51 Hz), 28.0 (d, *J*=15 Hz), 26.4 (d, *J*=6 Hz), 21.9 (d, *J*=6 Hz), 21.1 (d, *J*=3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 38.7 (m) ppm; MS (70 eV, EI): *m/z* : 240 (M^+ , 5), 238 (15), 203 (91), 134 (100).; IR: 595 (CCl), 725 (PS), 1111 (PC) cm^{-1}.

Synthesis of 1-[4-(diphenylphosphorathioyl)butyl]-phosphinane 1-sulfide (6):
To a solution of diphenyl phosphine (0.689 mmol) in THF (4 ml) was added metallic sodium (0.013 mol) at 0°C, than the mixture was stirred for 5 h at room temperature. After that the resulting orange-red solution was dropwise added

under argon to a solution of 1-(4-chlorobutyl) phosphinane sulfide (5b) (0.53 mmol) in THF (4 ml). The reaction mixture was stirred for 1 h than was treated with a slight excess of elemental sulfur to give the corresponding sulfides, which were purified by flash chromatography (dichloromethane: petroleum ether 3:2) and fully characterized.

1-[4-(diphenylphosphorathioyl)butyl]-phosphinane 1-sulfide (6): y = 65 %, yellow solid, pf = 134-136 °C, R_F = 0.14 (dichlromethane); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.86-7.78 (m, 4 H), 7.54-7.42 (m, 6 H), 2.55-2.44 (m, 2 H), 2.12-1.40 (m, 16 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 21.8 (d, $^2J_{PC}$=6.48 Hz,), 22.6 (dd, J_{PC}=17.8 Hz, J_{PP}=3.3 Hz), 23.3 (dd, J_{PC}=16.2 Hz, J_{PP}=2.4 Hz), 26.2 (d, $^2J_{PC}$= 6.5 Hz), 30.2 (d, $^1J_{PC}$= 50.2 Hz), 30.8 (d, $^1J_{PC}$= 48.6 Hz), 32.1 (d, $^1J_{PC}$= 57.0 Hz), 128.6 (d, J_{PC} =12.1 Hz), 130.9 (d, J_{PC} = 9.7 Hz), 131.5 (d, J_{PC} =3.2 Hz), 132.5 (d, J_{PC} = 80.14 Hz) ppm; ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 38.5, 43.0 ppm; IR: 716 (PS), 1439 (P-Ph), 2863 (Ph) cm^{-1}.

Synthesis of 1-[4-(1-sulfidophospholan-1-yl)butyl] piperidine (7):
A solution of 1-(4-chlorobutyl) phospholane sulphide (**5a**) (1 mmol) and piperidine (3 mmol) in toluene (10 ml) was refluxed for 20 h. After that the solvent was partially evaporated and the reaction mixture was treated with water and extracted with CH_2Cl_2. The organic layer, containing the product, was purified by flash chromatography (dichloromethane) and the product fully characterized.

1-[4-(1-sulfidophospholan-1-yl)butyl] piperidine (7): y = 90%, grease solid, R_F = 0.0 (dichlromethane); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.50-1.40 (m, 26 H, CH_2) ppm; ^{13}C NMR (76.46 MHz, $CDCl_3$, 25 °C): δ = 57.9, 54.1, 33.4 (d, *J* = 52 Hz), 33.1 (d, *J* = 47 Hz), 29.7, 26.0 (d, *J* = 6 Hz), 24.5, 23.4, 21.0 (d, *J* = 3 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 64.7 (m) ppm; MS (70 eV, EI): *m/z* : 259 (M^+, 2), 226 (13), 175 (3), 143 (13), 98 (100).

One-step procedure for the synthesis of cyclic tertiary bis-phosphine :

A solution of **1** (1 mmol) in THF (10 mL) was added drop wise to a solution of bis-Grignard reagent (2 mmol) in THF (5 ml), at room temperature. The mixture was stirred for 2 h, then again the bis-Grignard reagent (1 mmol) was added to the resulting solution. After that to the reaction mixture was added drop wise a solution of **1** (1 mmol) in THF (10 mL), and stirred for 4h. During the 4 h, the reaction was monitored by GC-MS. After that the solvent was partially evaporated and the reaction mixture was treated with aqueous acid solution (HCl). Extraction with CH_2Cl_2 gave a mixture of diphosphine and the residue **4**. The diphosphine was easily separated from **4** by treating the organic solution with aqueous NaOH; after this treatment, the sodium salt of **4** was dissolved in the aqueous solution, whereas the diphosphine was in the organic phase. Treatment of this layer with a slight excess of elemental sulfur gave the corresponding sulfides (9), which were purified by flash chromatography (dichloromethane: petroleum ether 3:2) and fully characterized. Compound **4** was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, and was then purified by distillation and stored under argon. Simple treatment of a dry solution of compound **4** with an equimolar amount of PCl_3 led to the regeneration of the starting reagent **1** in almost pure form, allowing it to be reused without further purification.

1,1'-butane-1,4-diylbis(phospholane) 1,1'-disulfide (9)[14]: y = 45%, brown solid, pf = 29°C; p.eb. = 115-120°C (0.1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.7-2.1 (m, 24 H) ppm ppm; ^{13}C NMR (75.46 MHz, $CDCl_3$, 25 °C): δ = 24.0 (2C, dd, $^2J_{PC}$ = 3 Hz, $^1J_{PC}$ = 15 Hz), 26.0 (4C, d, $^2J_{PC}$ = 6 Hz), 33.2 (2C, d, $^1J_{PC}$ = 45 Hz), 33.5 (4C, d, $^1J_{PC}$ = 52 Hz) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = 63.2 ppm; MS (70 eV, EI): *m/z* : 294 (M^+,14), 175 (66), 119 (58), 85 (27), 63 (100), 55 (59), 41 (46); IR: 715.78 (PS), 1113 (PC) cm^{-1}.

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Chapter 6

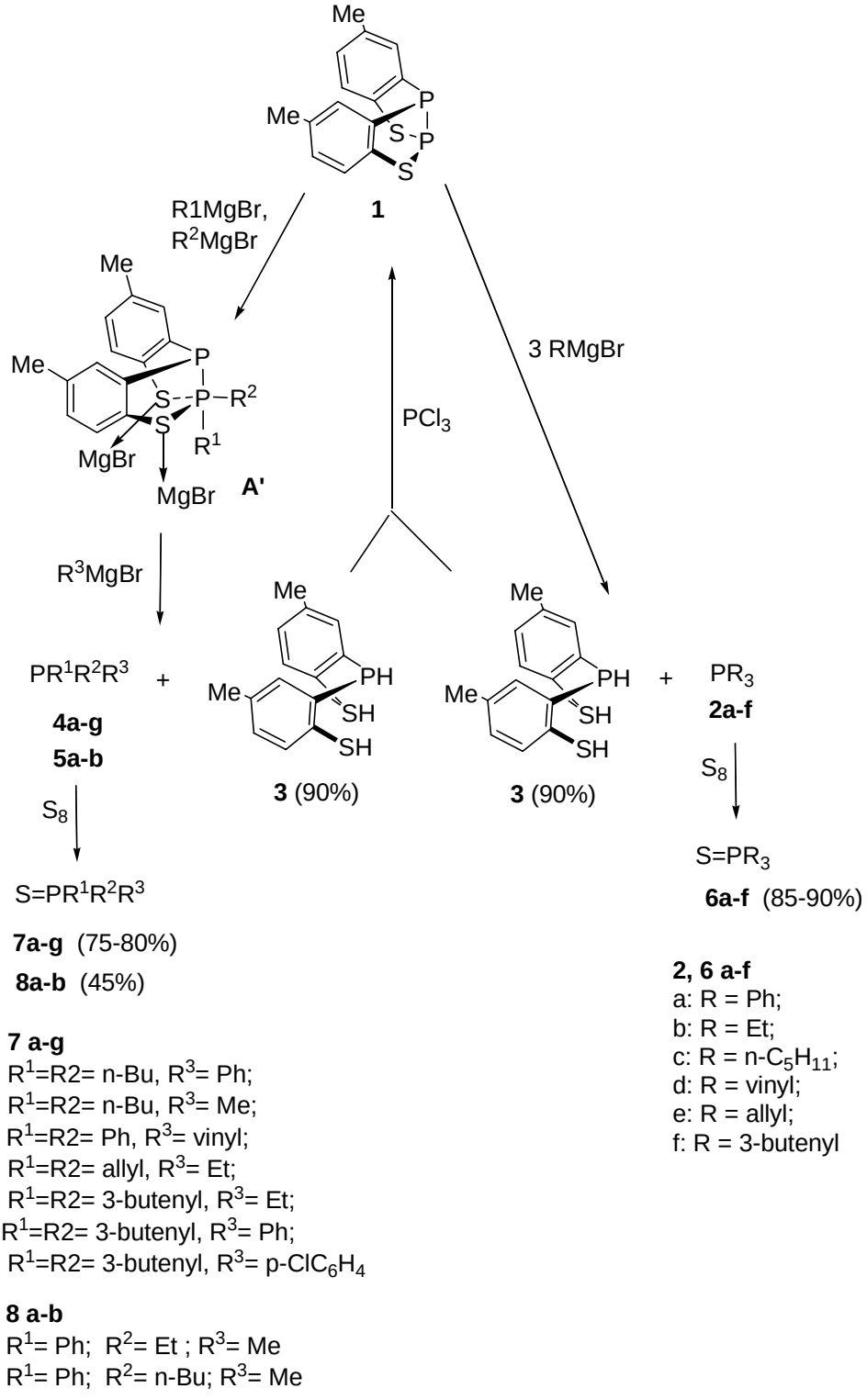
GENERAL SYNTHESIS OF ACYCLIC TERTIARY PHOSPHINE SULFIDES

6.1 Introduction

Tertiary phosphines (R_3P) are attracting considerable current interest due to their central role in coordination chemistry[1] and homogeneous catalysis.[2] However, the methods available for synthesizing acyclic tertiary phosphines containing different groups are long and tedious, sometimes difficult and dangerous, and in the case of tertiary asymmetric phosphines, give poor yields.[3-11] In addition, all of these procedures are made up of sequences of several reactions, some of which require forcing conditions. Although the publications on the synthesis of triaryl- or trialkylphosphines and their organic derivatives and their complexes are very numerous, the literature on the synthesis of trialkenylphosphines or alkenyl-containing phosphines is very limited. For example, trivinylphosphine was originally prepared via the Grignard method using vinylmagnesium bromide[12,13] and PCl_3 and subsequently has been synthesized via vinylsodium[14] and by a direct route from elemental phosphorus via potassium phosphide and acetylene.[15] All of these methods require controlled conditions (low temperature) but even under optimal conditions produce only low to moderate yields.[12b,13a] The tendency to produce only low to moderate yields has been attributed to the P-P coupling reactions of intermediates that form during the preparation of most tertiary phosphines with Grignard reagents.[16,17]

6.2 Results and discussion

From the beginning of our research, we found that the reaction between **1** and mono-Grignard reagents (Scheme 6.1) is more complex than the corresponding reaction in which a bis-Grignard reagent is used in the first step[18,19] (Chapter 4). In fact, if we added equimolar amounts of three different mono-Grignard reagents in three successive steps, we obtained a very complex reaction mixture without appreciable formation of the corresponding tertiary phosphines $PR^1R^2R^3$. The absence of the tertiary phosphines $PR^1R^2R^3$ suggested that the reaction proceeds via an intermediate such as **A'** (Scheme 6.1), which can be formed when mono-Grignard reagents are used. The intermediate **A'** is expected to have a shorter lifetime than **A** because the latter molecule is stabilized by the presence of the additional ring formed by the reaction of **1** with the bis(Grignard) reagent. With this in mind, we tried various procedures in which only a very short time elapsed between the addition of the three Grignard reagents. The simplest procedure tested was the simultaneous addition of 3 mol of RMgBr. When $R^1 = R^2 = R^3$, the yields are very high, as in the synthesis of phosphines **2** (85-90% yield), which are obtained by simple addition of three moles of RMgBr to a THF solution of one mole of **1**. It should be noted that using this procedure it is possible to obtain vinyl and allyl phosphines (**2d**,**e**) in better yields and in a more facile manner than using previously reported methods.[12-15] After quenching the reaction mixture with acid (HCl) water we obtained **2** and the end product **3** in 90% yield (Scheme 6.1). These two compounds can be easily separated by treating the organic solution with aqueous NaOH; in this way, the sodium salt of compound **3** dissolves in the aqueous solution, whereas the organic phase contains almost pure phosphine **2**, which can be further purified by bulb-to-bulb distillation. Compound **2** can be recovered, as reported previously,[20] from the basic aqueous layer by acidification and extraction, and then transformed to **1** for reuse.

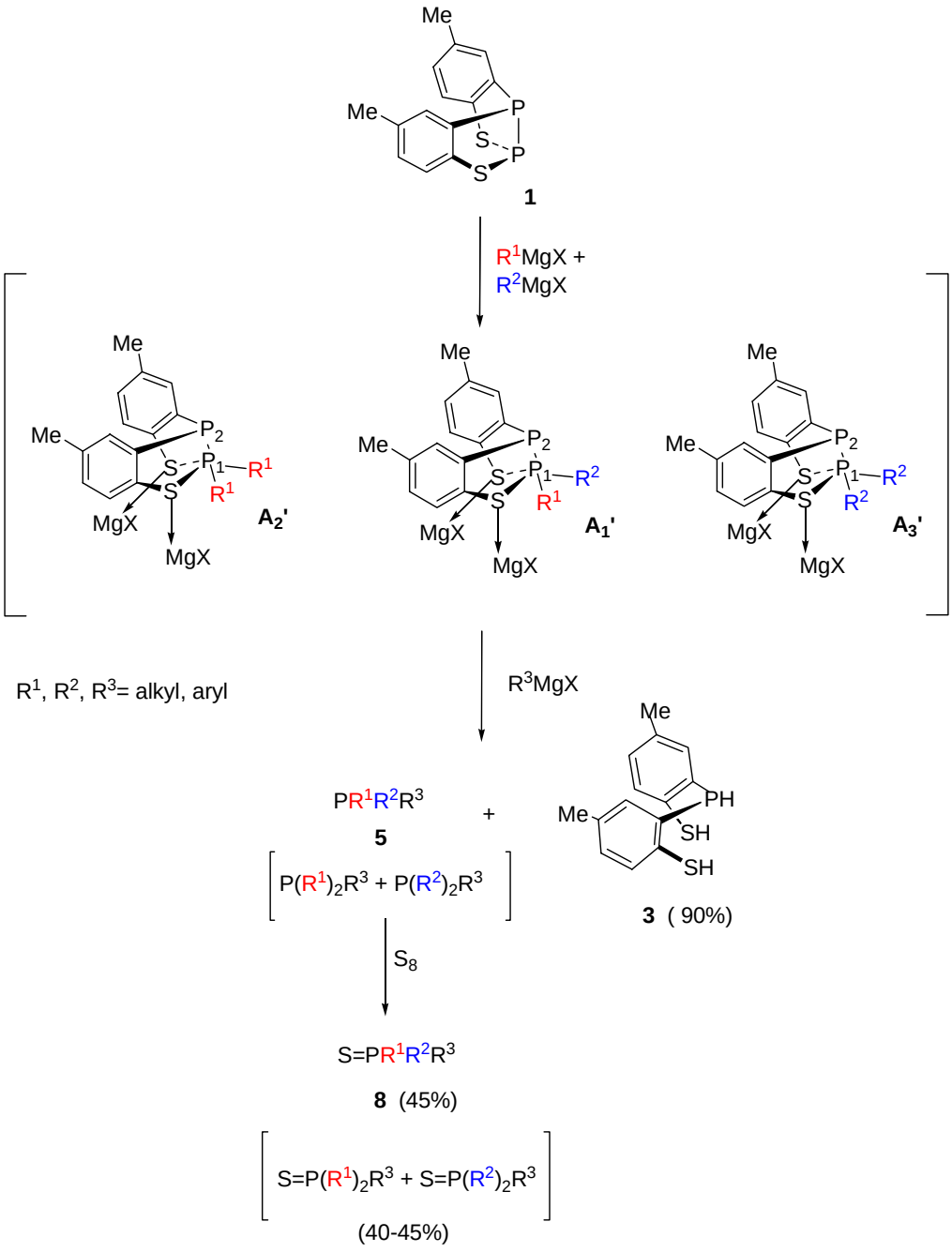


Scheme 6.1: the reaction between **1** and mono-Grignard reagents.

When $R^1=R^2\neq R^3$, a mixture of tertiary phosphines is obtained in which $P(R^1)_2R^3$ (**4**) is the most prevalent (about 45% of the mixture, from GC-MS analysis).

When $R^1 \neq R^2 \neq R^3$, $PR^1R^2R^3$ (**5**) is the most prevalent product, although it is only obtained in about 23% yield; the other nine possible symmetric tertiary phoshines such as $P(R^1)_3$ or $P(R^1)_2R^2$ are obtained in smaller yields (about 3% and 11%, respectively), indicating that the reaction is driven by statistical factors and implies a contemporaneous and equiprobable attack of the three different Grignard reagents on the phosphorus atom, independent of their steric hindrance. This can be explained by considering the structure of **1**, which possesses a folded geometry that is very suitable for this kind of attack. This behavior, which might be named the "butterfly effect", was recently observed in the facile formation of transition metal complexes containing a "dibenzo butterfly" moiety.[25]

To increase the yield of the desired product beyond the statistical limit, we tried a second procedure in which the different RMgBr reagents were added in two steps with very short reaction times (4-5 min) between the first and second steps. In this manner, it could be predicted, on a statistical basis, that the addition in the first step of equimolar amounts of two different Grignard reagents (R^1MgBr and R^2MgBr), followed by the addition in the second step of the third Grignard reagent (R^3MgBr) would give a final mixture containing $PR^1R^2R^3$ (50%), $P(R^1)_2R^3$ (25%), and $P(R^2)_2R^3$ (25%) (Scheme 6.2).



Scheme 6.2: The reaction of 1 and three different mono-Grignard reagent using the two-step procedure. In the scheme are reported the possible statistical intermediates.

In fact, when we used this two-step procedure we obtained asymmetric phosphines (**5a**,**b**) or their sulfides **8a**,**b** in 45% yield together with about 20-25% of the other symmetric phosphine sulfides, which were separated by column chromatography (Scheme 6.2). In this procedure, the end product **3** can be

recovered and recycled as described above. Using this one-pot two-step procedure, symmetric disubstituted phosphines **4a-g** (and their sulfides **7a-g**) were obtained in 75-80% yield. It should be noted that phosphines **2**, **4**, and **5** were analyzed only by GC-MS analysis, and were not isolated. Rather, they were immediately treated with sulfur to obtain the corresponding sulfides **6**, **7**, and **8** (Scheme 6.1), which are stable and thus were isolated and fully characterized.
It is worth noting that the synthesis reported herein makes it possible to obtain, in a simple one-pot procedure, sulfide derivatives of symmetric and asymmetric acyclic tertiary phosphines, also containing alkenyl groups (**6d-f** and **7c-g**); the synthesis of such compounds, which are of great interest in organic chemistry, has been previously studied only to a very limited extent.

6.3 Conclusion

In conclusion, the one-pot synthesis of symmetric and asymmetric tertiary acyclic phosphines reported can be achieved through a very simple, efficient, low-cost method and gives higher yields than previously reported methods. In these procedures, the byproduct **3** was recovered and transformed into the starting reagent **1**, making the process very atom-economic and environmentally friendly. It should be noted that this method can also be used to easily obtain trivinyl- or triallyl phosphines or alkenyl-containing phosphines, making this procedure a new general protocol and a very convenient, quite unique, method for the simultaneous construction of three different C-P bonds.

6.4 Experimental section

General: ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 300 (or 400) MHz, 75.46 (or 100.56, or 150.80) MHz, and at 121.47 (or 161.9) MHz, respectively. Chemical shifts are referenced to internal standard TMS (^{1}H NMR), to solvent (77.0 ppm for ^{13}C NMR), and to external standard 85% H_3PO_4 (^{31}P NMR). *J* values are given in Hz. MS spectra were recorded at an ionisation voltage of 70

eV. Flash chromatography (FC) was performed on silica gel (0.040-0.063 mm). Melting points are uncorrected. THF was distilled from sodium benzophenone ketyl. Air and moisture sensitive solutions and reagents were handled in a dried apparatus under an atmosphere of dry argon.

One-Step Procedure: Synthesis of Phosphine Sulfides with Simultaneous Addition of Grignard Reagents. The three Grignard reagents (R^1MgBr, R^2MgBr, R^3MgBr, 1.2 mmol of each) were simultaneously added to a solution of benzothiadiphosphole (**1**) (1.0 mmol) in anhydrous THF under a dry nitrogen atmosphere. After 30-40 min, the solvent was partially evaporated and the reaction mixture was treated with aqueous acid solution (HCl). Extraction with CH_2Cl_2 gave a mixture of phosphines and the residue **3**. The phosphines were easily separated from **3** by treating the organic solution with aqueous NaOH; after this treatment, the sodium salt of **3** was dissolved in the aqueous solution, whereas the phosphines were in the organic phase. Treatment of this layer with a slight excess of elemental sulfur gave the corresponding sulfides, which were purified by flash chromatography and fully characterized. Compound **3**[20] was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, and was then purified by distillation and stored under argon. Simple treatment of a dry solution of compound **3** with an equimolar amount of PCl_3 led to the regeneration of the starting reagent **1** in almost pure form, allowing it to be reused without further purification.

The yields of the phosphines obtained by the one-step procedure are as follows: When $R^1 = R^2 = R^3$, phosphine sulfides (**6a-f**) were obtained in 85-90% yields. Triphenylphosphine (**2a**) and triethylphosphine (**2b**) and their sulfides **6a** and **6b** were characterized by comparison with physicochemical data of commercially available authentic samples. When $R^1 = R^2 \neq R^3$, the reaction mixture contains a mixture of phosphines $P(R^1)_2R^3$, $P(R^1)_3$, $PR^1(R^3)_2$, and $P(R^3)_3$ in relative proportions (calculated by GC-MS analysis) of about 45%, 29%, 23%, and 3%, respectively. When $R^1 \neq R^2 \neq R^3$, the reaction mixture contains a mixture of phosphines, in which $PR^1R^2R^3$ is the most prevalent (23% yield; calculated by GC-MS analysis). The other nine possible symmetric tertiary phosphines such as

$P(R^1)_3$ or $P(R^1)_2R^2$ were present in smaller proportions (about 3% and 11%, respectively).

In these last two cases, phosphines **4** and **5** and the corresponding sulfides **7** and **8** were obtained in higher yields using the two-step procedure described below.

Two-Step procedure: Preparation of Phosphine Sulfides 7a-g and 8a,b. The first Grignard reagent (R^1MgBr, 2.4 mmol) was added to a solution of benzothiadiphosphole (**1**) (1.0 mmol) in anhydrous THF under a dry nitrogen atmosphere. After 4-5 min, the second Grignard reagent (R^2MgBr, 1.2 mmol) was added. After about 30-40 min, the reaction mixture was treated as described above for the one-step procedure. Phosphine sulfides **7a-g** were purified by FC and isolated in 75-80% yield. Phosphine sulfides **8a** and **8b** were obtained in 45% yield (they were easily separated from the other phosphine sulfides by FC) as described above for the preparation of compounds **7**; in this case, two different Grignard reagents, R^1MgBr (1.2 mmol) and R^2MgBr (1.2 mmol), instead of 2.4 mmol of the same organometallic, were added to **1** in the first step and the Grignard reagent R^3MgBr (1.2 mmol) was added in the second step.

Triphenylphosphine sulfide (6a): yield = 85 %; solid, m.p.: 161-163°C (from ethanol) Lit.[26]: 162-163 °C; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.25-7.50 (m., 9H), 7.50-7.80 (m, 6H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 128.5 (d, *J* = 13 Hz), 131.5 (d, *J* = 3 Hz), 132.2 (d, *J* = 11 Hz), 133.0 (d, *J* = 85 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 43.4 (m); MS (70 eV, EI): *m/z* : 294 [M^+, 90], 262 (15), 217 (15), 183 (100); HRMS calcd for $C_{18}H_{15}PS$, 294.0632; found: 294.0635. Anal Calcd for $C_{18}H_{15}PS$, C, 73.45; H, 5.14. found: C, 73.37; H, 5.15; IR (KBr)(ν, cm^{-1}): 640, 690, 710, 1105, 1440.

Triethylphosphine sulfide (6b): yield = 90 %; solid, m.p.: 96-98°C (from ethanol) Lit.[27]: 96-97 °C; R_F = 0.16 (petroleum ether : diethyl ether 4 : 1); ^1H NMR (300 MHz, $CDCl_3$) δ = 1.20 (dt, 9H, J_{P-H} = 18.2 Hz, J_{H-H} = 7.7 Hz), 1.84 (dq, 6H, J_{P-H} = 11.4 Hz, J_{H-H} = 7.7 Hz); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 6.5 (d, *J* = 5 Hz), 23.0 (d, *J* = 52 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 53.7 (m); MS

(70 eV, EI): *m/z* : 150 [M^+, 20], 122 (27), 117 (3), 94 (100), 65 (52); HRMS calcd for $C_6H_{15}PS$, 150.0632; found: 150.0634. Anal Calcd for $C_6H_{15}PS$, C, 47.97; H, 10.06. found: C, 47.90; H, 10.09; IR ($CHCl_3$)(ν, cm^{-1}): 667, 688, 759, 1043, 1453.

Tripentylphosphine sulfide[28] **(6c):** yield = 85 %; oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.91 (t, 9H, *J* = 6.6 Hz), 1.20-1.90 (m.s, 24H); ^{13}C NMR (150.80 MHz, $CDCl_3$) δ = 13.9, 22.1 (d, *J* = 4 Hz), 22.2, 30.8 (d, *J* = 50 Hz), 33.0 (d, *J* = 15 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ = 49.3 (m); MS (70 eV, EI): *m/z* : 276 [M^+, 31], 206 (41), 136 (100); HRMS calcd for $C_{15}H_{33}PS$, 276.2041; found: 276.2045. Anal Calcd for $C_{15}H_{33}PS$, C, 65.17; H, 12.03. found: C, 65.26; H, 12.06; IR ($CHCl_3$)(ν, cm^{-1}):726, 1067, 1457.

Trivinylphosphine sulfide[29] **(6d):** yield = 90 %; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.18 (ddd, 1H, *J* = 46.1 Hz, *J* = 10.6 Hz, *J* = 2.4 Hz,), 6.28-6.45 (m, 2H); ^{13}C NMR (100.56 MHz, $CDCl_3$) δ = 130.4 (d, *J* = 81 Hz), 133.5 (d, *J* = 2 Hz); ^{31}P NMR (161.9 MHz, $CDCl_3$) δ = 29.9; MS (70 eV, EI): *m/z* : 144 [M^+, 100], 118 (33), 111 (12), 85 (35), 63 (37); HRMS calcd for C_9H_9PS, 144.0163; found: 144.0160. Anal Calcd for C_9H_9PS, C, 49.98; H, 6.29. found: C, 49.93; H, 6.31; IR (neat)(ν, cm^{-1}):651, 705, 737, 909, 1265.

Triallylphosphine sulfide (6e): yield = 90 %; colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.58-2.75 (m, 6H), 5.10-5.30 (m, 6H), 5.70-5.92 (m, 3H, CH=); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 36.1 (d, *J* = 49 Hz), 121.0 (d, *J* = 12 Hz), 127.7 (d, *J* = 9 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 41.4 (m); MS (70 eV, EI): *m/z* : 186 [M^+, 4], 145 (19), 103 (46), 63 (100); HRMS calcd for $C_9H_{15}PS$, 186.0632; found: 186.0630. Anal Calcd for $C_9H_{15}PS$, C, 58.04; H, 8.12. found: C, 58.08; H, 8.14; IR(neat)(ν, cm^{-1}): 641, 729, 925, 991, 1417, 1634.

Tri(3-butenyl)phosphine sulfide (6f): yield = 85 %; colorless oil;^1H NMR (300 MHz, $CDCl_3$) δ = 2.43-2.62 (m, 6H), 2.85-3.08 (m, 6H), 5.55-5.80 (m, 6H), 6.35-6.55 (m, 3H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 26.5 (d, *J* = 3 Hz), 30.2 (d, *J* = 50 Hz), 115.7, 136.9 (d, *J* = 15 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 47.6 (m);

MS (70 eV, EI): *m/z* : 228 [M^+, 1], 174 (4), 120 (79), 63 (60), 55 (100); HRMS calcd for $C_{12}H_{21}PS$, 228.1102; found: 228.1100. Anal Calcd for $C_{12}H_{21}PS$, C, 63.12; H, 9.27. found: C, 63.03; H, 9.30; IR (neat)(ν, cm^{-1}): 791, 909, 989, 1440, 1637.

Dibutyl(phenyl)phosphine sulfide[28,30] (**7a**): yield = 77 %; solid; m.p.: 47-48°C (from ethanol) Lit.[3]: 47 °C; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.87 (t, 6H, *J* = 7.2 Hz), 1.20-2.50 (m.s, 12H), 7.40-7.56 (m, 3H), 7.78-7.95 (m, 2H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 13.6, 23.8 (d, *J* = 16 Hz), 24.3 (d, *J* = 3 Hz), 32.9 (d, *J* = 54 Hz), 128.5 (d, *J* = 12 Hz), 130.9 (d, *J* = 10 Hz), 131.3 (d, *J* = 3 Hz), 133.1 (d, *J* = 80 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 47.4 (m); MS (70 eV, EI): *m/z* (%): 254 [M^+, 33], 198 (55), 142 (100), 79 (25), 63 (15); HRMS calcd for $C_{14}H_{23}PS$, 254.1258, found: 254.1255; Anal Calcd for $C_{14}H_{23}PS$, C, 66.10; H, 9.11. found: C, 66.01; H, 9.14; IR ($CHCl_3$)(ν, cm^{-1}): 691, 739, 1104, 1435, 1458.

Dibutyl(methyl)phosphine sulfide[31] (**7b**): yield = 75 %; greasy solid, m.p.: 24-26°C (from ethanol) Lit.[30b]: 25-26 °C; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.89 (t, 6H, *J* = 7.2 Hz), 1.35-1.50 (m, 4H), 1.58 (d, 3H, *J* = 12.4 Hz), 1.50-1.75 (m, 4H), 1.75-1.95 (m, 4H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 13.6, 18.4 (d, *J* = 53 Hz), 23.9 (d, *J* = 16 Hz), 24.5 (d, *J* = 4 Hz), 32.7 (d, *J* = 52 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 41.9 (m); MS (70 eV, EI): *m/z* (%): 192 [M^+, 92], 136 (95), 94 (62), 80 (100), 63 (8), 55 (10); HRMS calcd for $C_9H_{21}PS$, 192.1102, found: 192.1100; Anal Calcd for $C_9H_{21}PS$, C, 56.21; H, 11.01. found: C, 56.30; H, 10.99; IR ($CHCl_3$) (ν, cm^{-1}): 728, 1094, 1450.

Diphenyl(vinyl)phosphine sulfide (7c): yield = 76%; colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.15-6.50 (m, 3H), 7.42-7.56 (m, 6H), 7.72-7.84 (m, 4H); ^{13}C NMR (150.80 MHz, $CDCl_3$) δ = 128.6 (d, *J* = 12 Hz), 131.4 (d, *J* = 80 Hz), 131.5 (d, *J* = 10 Hz), 131.6 (d, *J* = 3 Hz), 132.6 (d, *J* = 86 Hz), 134.3; ^{31}P NMR (161.9 MHz, $CDCl_3$) δ = 37.7 (m); MS (70 eV, EI): *m/z* (%): 244 [M^+, 100], 218 (19), 183 (55), 133 (26); HRMS calcd for $C_{14}H_{13}PS$, 244.0476, found: 244.0480; Anal Calcd for $C_{14}H_{13}PS$, C, 68.83; H, 5.36. found: C, 68.90; H, 5.38; IR (neat) (ν, cm^{-1}): 605, 636, 689, 712, 727, 1103, 1377, 1438.

Diallyl(ethyl)phosphine sulfide (**7d**): yield = 80 %; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.15-1.35 (m, 3H), 1.75-2.00 (m, 2H), 2.65-2.80 (m, 4H), 5.20-5.45 (m, 4H), 5.80-6.00 (m, 2H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 6.1 (d, *J* = 5 Hz), 22.8 (d, *J* = 52 Hz), 36.4 (d, *J* = 49 Hz), 120.6 (d, *J* = 12 Hz), 128.0 (d, *J* = 9 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 45.9 (m); MS (70 eV, EI): *m/z* (%): 174 [M^+, 5], 133 (19), 105 (13), 92 (7), 63 (100); HRMS calcd for $C_8H_{15}PS$, 174.0632, found: 174.0630; Anal Calcd for $C_8H_{15}PS$, C, 55.14; H, 8.68. found: C, 55.06; H, 8.71; IR (neat) (ν, cm^{-1}): 806, 922, 989, 1456, 1633.

Di(3-butenyl)ethylphosphine sulfide (**7e**): yield = 78 %; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.10-1.30 (m, 3H), 1.70-2.00 (m, 6H), 2.30-2.50 (m, 4H), 5.00-5.20 (m, 4H), 5.75-5.95 (m, 2H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 6.5 (d, *J* = 5 Hz), 24.4 (d, *J* = 51 Hz), 26.4 (d, *J* = 3 Hz), 29.5 (d, *J* = 50 Hz), 115.6, 137.0 (d, *J* = 15 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 49.7 (m); MS (70 eV, EI): *m/z* (%): 202 [M^+, 6], 174 (2), 147 (7), 120 (100), 92 (39), 63 (70); HRMS calcd for $C_{10}H_{19}PS$, 202.0945, found: 202.0948; Anal Calcd for $C_{10}H_{19}PS$, C, 59.37; H, 9.47. found: C, 59.33; H, 9.50; IR (neat) (ν, cm^{-1}): 792, 913, 997, 1441, 1639.

Di(3-butenyl)phenylphosphine sulfide (**7f**): yield = 80 %; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.98-2.20 (m, 4H), 2.30-2.50 (m, 4H), 4.85-5.02 (m, 4H), 5.62-5.80 (m, 2H), 7.37-7.50 (m, 3H), 7.74-7.85 (m, 2H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 26.2 (d, *J* = 2 Hz), 32.2 (d, *J* = 53 Hz), 115.4, 128.6 (d, *J* = 11 Hz), 130.9 (d, *J* = 10 Hz), 131.5 (d, *J* = 80 Hz), 131.6 (d, *J* = 3 Hz), 137.0 (d, *J* = 17 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 45.3 (m); MS (70 eV, EI): *m/z* (%): 250 [M^+, 2], 196 (6), 168 (6), 91 (29), 63 (100); HRMS calcd for $C_{14}H_{19}PS$, 250.0945, found: 250.0949; Anal Calcd for $C_{14}H_{19}PS$, C, 67.17; H, 7.65. found: C, 67.11; H, 7.67; IR (neat) (ν, cm^{-1}): 793, 910, 994, 1438, 1481, 1576, 1636.

Di(3-butenyl)4-chlorophenylphosphine sulfide (**7g**): yield = 78 % colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.95-2.25 (m, 4H), 2.30-2.60 (m, 4H), 4.90-5.17 (m, 4H), 5.70-5.90 (m, 2H), 7.49 (dd, 2H, *J* = 8.7 Hz, *J* = 2.1 Hz), 7.82 (dd, 2H, *J* = 11.8 Hz, *J* = 8.7 Hz); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 26.2, 32.3 (d, *J* = 54 Hz), 115.6, 128.9 (d, *J* = 12 Hz), 129.3 (d, *J* = 75 Hz), 132.4 (d, *J* = 10 Hz), 136.8

(d, *J* = 17 Hz), 138.4; ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 45.1 (m); MS (70 eV, EI): *m/z* (%): 284 [M^+, 1], 230 (3), 174 (5), 107 (29), 63 (100); HRMS calcd for $C_{14}H_{18}ClPS$, 284.0555, found: 284.0558; Anal Calcd for $C_{14}H_{18}ClPS$, C, 59.04; H, 6.37. found: C, 59.00; H, 6.39; IR ($CHCl_3$) (ν, cm^{-1}): 792, 908, 990, 1436, 1480, 1575, 1637.

Ethyl(methyl)phenylphosphine sulfide[32] **(8a)**: yield = 45 %; solid, m.p.: 32-34°C (from ethanol) Lit.[32a]: 33-34 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.98-1.20 (m, 3H), 1.87 (d, 3H, *J* = 12.9 Hz), 1.98-2.10 (m, 2H), 7.35-7.50 (m, 3H), 7.74-7.86 (m, 2H); ^{13}C NMR (75.46 MHz, $CDCl_3$) □ = 6.4 (d, *J* = 4 Hz), 20.1 (d, *J* = 56 Hz), 28.0 (d, *J* = 56 Hz), 128.5 (d, *J* = 12 Hz), 130.4 (d, *J* = 10 Hz), 131.4 (d, *J* = 3 Hz), 132.0 (d, *J* = 77 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$ δ = 42.0 (m); MS (70 eV, EI): *m/z* (%): 184 [M^+, 75], 156 (100), 141 (36), 109 (15), 78 (20), 63 (18); HRMS calcd for $C_9H_{13}PS$, 184.0476, found: 184.0474; Anal Calcd for $C_9H_{13}PS$, C, 58.67; H, 7.11. found: C, 58.61; H, 7.13; IR (neat) (ν, cm^{-1}): 694, 744, 1105, 1456.

Butyl(methyl)phenylphosphine sulfide[33] **(8b):** yield = 45 %; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.88 (t, 3H, *J* = 7.1 Hz), 1.30-1.54 (m, 2H), 1.54-1.76 (m, 2H), 1.95 (d, 3H, *J* = 12.8 Hz), 2.02-2.16 (m, 2H), 7.42-7.60 (m, 3H), 7.84-7.94 (m, 2H); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ = 13.6, 20.8 (d, *J* = 56 Hz), 23.7 (d, *J* = 17 Hz), 24.5 (d, *J* = 3 Hz), 34.7 (d, *J* = 55 Hz), 128.6 (d, *J* = 12 Hz), 130.4 (d, *J* = 10 Hz), 131.4 (d, *J* = 3 Hz), 132.6 (d, *J* = 77 Hz); ^{31}P NMR (121.47 MHz, $CDCl_3$) δ = 39.7 (m); MS (70 eV, EI): m/z (%): 212 [M^+, 38], 156 (100), 141 (24), 123 (11), 78 (14), 63 (10); HRMS calcd for $C_{11}H_{17}PS$, 212.0789, found: 212.0787; Anal Calcd for $C_{11}H_{17}PS$, C, 62.23; H, 8.07. found: C, 62.14; H, 8.10; IR (neat) (ν, cm^{-1}): 689, 739, 1106, 1433, 1456.

6.4 References

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Chapter 7

ONE-POT SYNTHESIS OF SECONDARY PHOSPHINES AND THEIR BORANE COMPLEXES

7.1 Introduction

Secondary phosphines are useful intermediates in organic synthesis and represent versatile synthons for the preparation of chiral mono- and bidentate phosphinic ligands.[1] However, the synthetic procedures for preparing such secondary phosphines are, as a rule, multistep and laborious with very low overall yields in the case of alkyl asymmetric secondary phosphines. Some indirect methods have been developed for the synthesis of secondary phosphines in which a monochlorophosphine is synthesised and subsequently converted into the desired phosphine by reduction with lithium alanate, sodium borohydride, or sodium.[2] Unfortunately, only a few monochlorophosphines are readily available by reaction of PCl_3 with Grignard reagents: in practice, this synthetic route is easy when the desired phosphines contains aryl groups, but becomes more complicated when they contain only alkyl groups, and further difficulties are encountered when the phosphines contain two different alkyl groups.

Another factor complicating the synthesis of secondary phosphines is their very high air-sensitivity, which makes them very difficult to handle and leads to the need for special equipment and experience that may not be available in every laboratory. To overcome this problem, secondary phosphines are often transformed into the corresponding phosphine–borane complexes, which are air-insensitive, present particular and very interesting reactivities, and are smoothly cleaved. In the last decade there has been considerable interest in the preparation and controlled reactivity of phosphine–borane complexes in particular those

involving secondary phosphines. Various applications for these complexes have been identified, including their use in carbonyl additions,[3] alkylation,[3,4] hydrophosphination,[5] and conjugate addition processes,[6] as well as in metal-mediated couplings.[7] Two recent reviews[8] highlight the importance of protecting secondary phosphines in the synthesis of chiral phosphine ligands as well as the expanded range of controlled synthetic possibilities available with phosphine-borane complexes in comparison to the parent phosphines. Secondary phosphine-boranes are generally obtained by one of the following procedures: reaction of the parent free phosphine with BH_3·THF or BH_3·SMe_2 complexes;[9] directly from parent phosphine oxides by in situ reduction with $LiAlH_4$ in the presence of $NaBH_4$ and $CeCl_3$;[10] or by reacting parent phosphine oxides with a large excess of BH_3·SMe_2 together with small amount of water.[11] Recently, a general synthesis of phosphine-borane complexes from parent free phosphines and $NaBH_4$/acetic acid has also been reported.[12]

7.2 Results and discussion

7.2.1 Developing of synthetic procedure

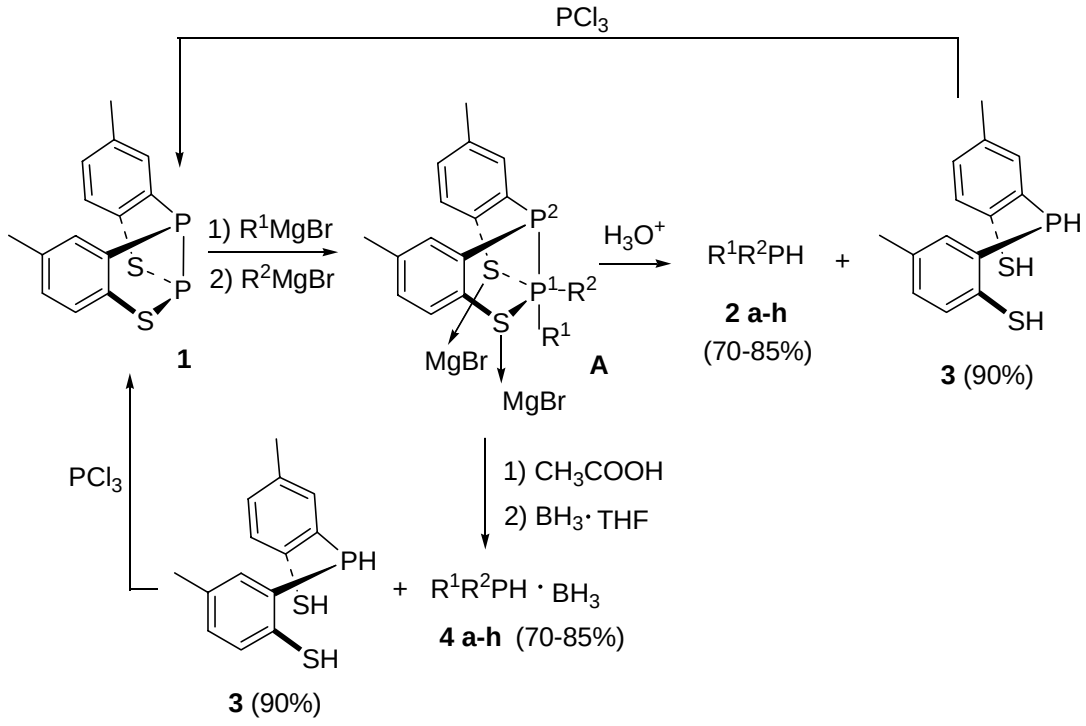
As reported in Chapter 6, we studied[13] the reaction between reagent **1** and mono-Grignard reagents. The symmetric tertiary phosphines, or their corresponding sulfides, were obtained in very high yield, and the asymmetric tertiary, or their sulfides, were obtained in 45% yield by addition of equimolar amounts of different Grignard reagents to a solution of **1** in two steps.

These findings prompted us to examine whether a similar one-pot procedure, employing the same phosphorus atom donor reagent **1**, could be used to synthesize acyclic symmetric and asymmetric diaryl-, arylalkyl-, and dialkylphosphines, and their borane complexes.

The simultaneous addition, at room temperature, of equivalent amounts of the Grignard reagents R^1MgBr and R^2MgBr to a solution of benzothiadiphosphole (**1**) gave, after quenching with acidic water, symmetrical or asymmetrical secondary phosphines **2** and compound **3** (Scheme 7.1). The intermediate of this reaction

was hypothesized to be a pentacoordinate phosphorus species such as **A** as reported previously reported.[13]

The proposed synthesis affords symmetrical secondary phosphines **2a-d** (R^1=R^2) in high yield (80-85%) and asymmetrical secondary phosphines ($R^1 \neq R^2$) in yields close to the maximum value of 50% imposed by statistical factors (Chapter 6).[13] In order to overcome this statistical limit and to obtain the highest yields of asymmetric secondary phosphines we carried out the reaction with sequential addition of the two different RMgBr reagents. We found that, with this procedure, asymmetric secondary phosphines **2e-h** were obtained in 70-75% yields.[14] As previously reported in Chapter 5 and 6, the byproduct **3** was recovered by basic-acid exstraction.



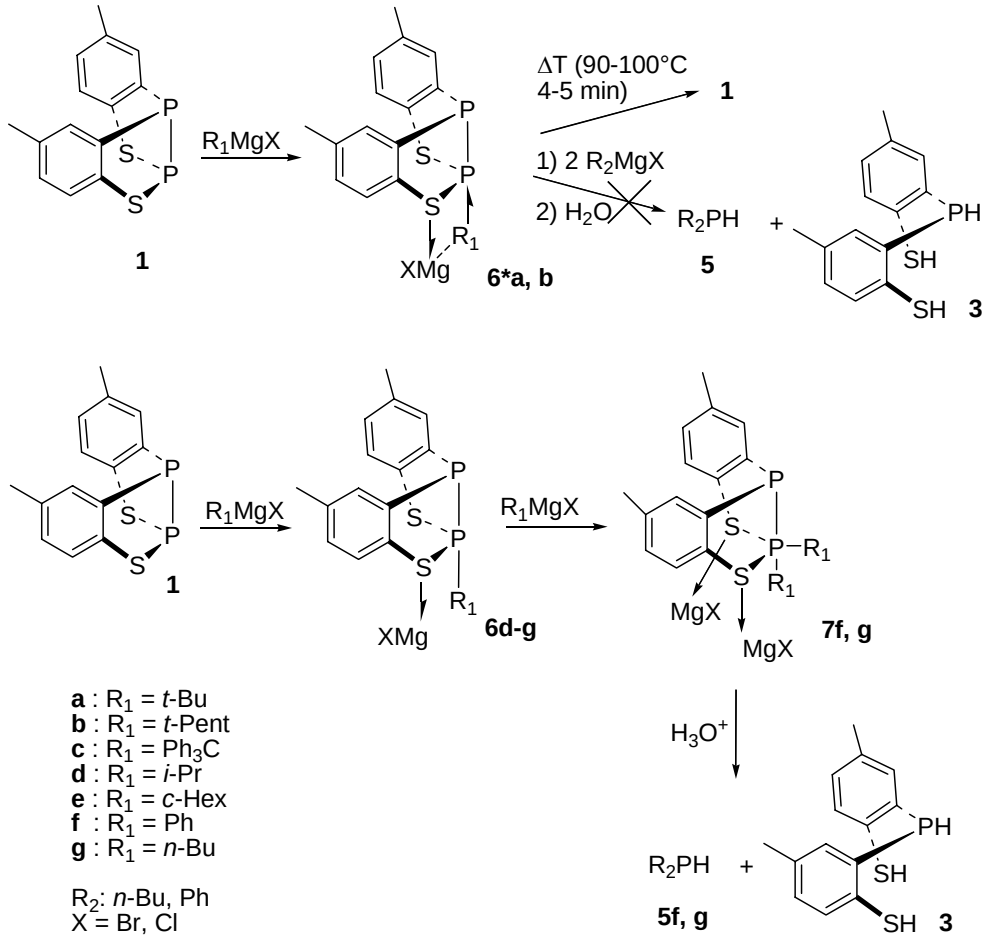
	a	b	c	d	e	f	g	h
R^1	Et	*n*-Bu	*n*-Pent	Ph	Me	Et	*n*-Bu	Et
R^2	Et	*n*-Bu	*n*-Pent	Ph	Ph	Ph	Ph	*n*-Hex

Scheme 7.1: Synthesis of secondary phosphines and their borane complexes.

The growing interest in the protection of secondary phosphines as phosphine-borane complexes prompted us to investigate whether the borane complexes of secondary phosphines could be obtained using our one-pot procedure without separation of free phosphine precursor. We found that treatment of the reaction mixture containing intermediates such as **A** with acetic acid followed by *in situ* addition of BH_3·THF complex (or BH_3·Me_2S or $NaBH_4$/acetic acid) did indeed afford phosphine–borane complexes **4** in high yields. Unexpectedly, we found that the secondary phosphine **3** was not complexed; this is of fundamental importance because it enabled easy recycling of **3** by treatment with PCl_3, which afforded the starting reagent **1**. It is noteworthy that reported syntheses[8b,11,12] of phosphine-borane complexes require, as starting material, the isolation of free phosphines or their derivatives. This method represent the first reported procedure for synthesizing secondary phosphine-boranes that does not require isolation of any phosphine derivatives as precursors. In this procedure, the three borane sources can be used without distinction.[14] However, it should be noted that secondary dialkylphosphines were easily and quantitatively tranformed into their BH_3 complexes by simple addition of one equivalent of BH_3·THF to the reaction mixture, whereas in the case of phosphines bearing phenyl groups, the complexation was slower and possibly incomplete because of the instability in the time of BH_3·THF solution. This latter limitation was easily overcome by adding further amounts of BH_3·THF solution in successive steps until the reaction was complete. This reaction is clean and does not use BH_3·Me_2S, which has a strong odour that is difficult to eradicate nor does it use the $NaBH_4$/AcOH system, which requires the removal of residue salts.

7.2.2 Study of intermediates

To evaluate whether secondary phosphanes are also formed using Grignard reagents bearing bulky groups, we attempted to react **1** with *t*-butylmagnesium chloride (Scheme 7.2).



Scheme 7.2: Intermediates of the reactions between above Grignard reagents and benzothiadiphosphole **1**.

GC-MS analysis of the reaction mixture showed only starting reagent **1**, indicating that the reaction between **1** and *t*-butylmagnesium chloride does not proceed, even in the presence of an excess of Grignard reagent. Surprisingly, however, when we subsequently added a less hindered Grignard reagent, R^2MgX (Scheme 7.2) to the reaction mixture containing **1** and *t*-butylmagnesium chloride, GC-MS analysis of the reaction mixture again showed only compound **1**, indicating that **1** also does not react with this new Grignard reagent. Given that, in the absence of *t*-butylmagnesium chloride, R^2MgX easily reacts[14,15] with **1** to afford the corresponding secondary symmetrical phosphane $R^2{}_2PH$ **5**, our finding of no apparent reaction between **1** and R^2MgX was unexpected. A plausible explanation for this would be that in the reaction mixture, **1** complexes with the *t*-butyl Grignard to form an instable intermediate, and that this intermediate decomposes

in the GC injector such that the GC-MS analysis indicates that only compound **1** is present. Thus, we conjectured that the *t*-butylmagnesium chloride may have complexed with the S-P bond of **1**, thus hindering the subsequent attack of the less hindered Grignard reagent. To gain more information about the hypothesized interaction between reagent **1** and *t*-butylmagnesium chloride, we recorded a ^{31}P NMR spectrum of the final crude reaction mixture. As expected, no signals characteristic of reagent **1** were observed in the spectrum, but two new sets of doublets (δ= 38.1 ppm (d, ^{1}J(P,P) = 275 Hz), 9.6 ppm (d, ^{1}J(P,P) = 275 Hz) strongly upfield with respect to those of **1 (**δ= 86.8 ppm (d, ^{1}J(P,P) = 208 Hz), 66.7 ppm (d, ^{1}J(P,P) = 208 Hz) were observed, suggesting the presence of a new species containing a P-P bond. In addition, these latter signals remained for several hours indicating the good stability of this intermediate. The ^{1}H NMR spectrum of the crude reaction mixture in [D_8]THF contains signals characteristic of the presence of two non-equivalent aromatic rings as well as a doublet with a coupling constant of 14 Hz in the region of *t*-butylic protons, which is ascribed to a $^{3}J_{P\text{-}H}$ coupling. This was confirmed by examination of the ^{13}C NMR spectrum, which contained two doublets of doublets, centered at 37.2 and 29.9 ppm, which can be assigned, respectively, to the tertiary and methylic carbon atoms of the *t*-butyl group each coupled with two phosphorus atoms linked in a P-P bond. Furthermore, to determine which phosphorus is adjacent to the *t*-butyl moiety, we carried out a ^{1}H, ^{31}P heteronuclear multiple bond correlation experiment (HMBC, Figure 7.1) optimized for coupling constants of 12.5 Hz (close to the observed three bond ^{3}J P-H coupling constant of the methyl signal of the *t*-butyl moiety). The HMBC spectrum showed a cross peak indicating a correlation between the proton resonance of the methyl doublet at 1.14 ppm with that of the ^{31}P doublet at 38.1 ppm.

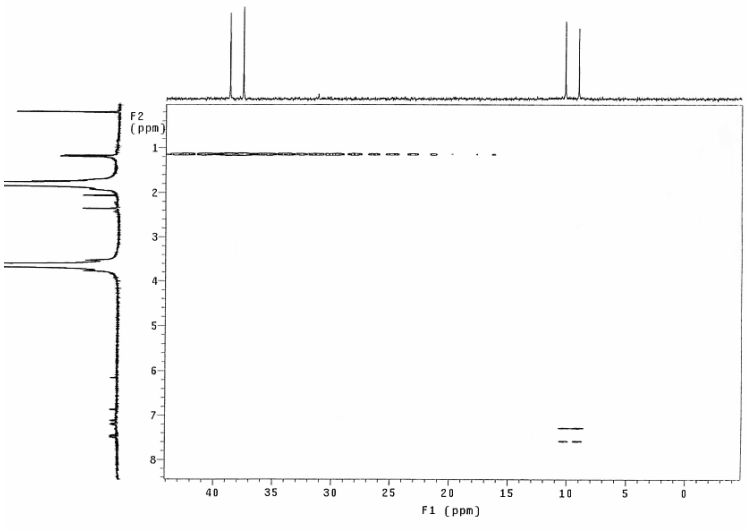


Figure 7.1: ^{1}H, ^{31}P HMBC spectrum of intermediate 6*a in [D_8]THF.

The spectrum additionally showed cross couplings in the aromatic region indicating connections with the phosphorus atom signal at 9.6 ppm (Figure 7.1). The NMR spectral data are consistent with a structure such as **6*a**, represented in Scheme 7.2, which contains a P-P-C$(CH)_3$ structure and is characterized by nonsymmetric aromatic rings. Such a configuration could form if one of the sulphur atoms in **1** coordinates with the magnesium atom of *t*-butylmagnesium chloride. To verify the thermal instability of this intermediate, as indicated by the GC-MS data, the crude reaction mixture containing only **6*a** was heated to 90-100°C and analyzed by ^{31}P NMR spectroscopy. After about 4-5 minutes at this temperature it was observed the disappearance of the signals corresponding to **6*a** and the concomitant appearance of signals related to starting compound **1** (Figure 7.2).

The fact that simple heating at 90-100 °C is sufficient to break the phosphorus-carbon bond, which is typically a very strong bond, supports the hypothesis that the intermediate has a structure like that of **6*a** (Scheme 7.2), in which the magnesium atom is coordinated both, with sulfur atom and, with a labile interaction, with the carbon atom of the *t*-butyl group.

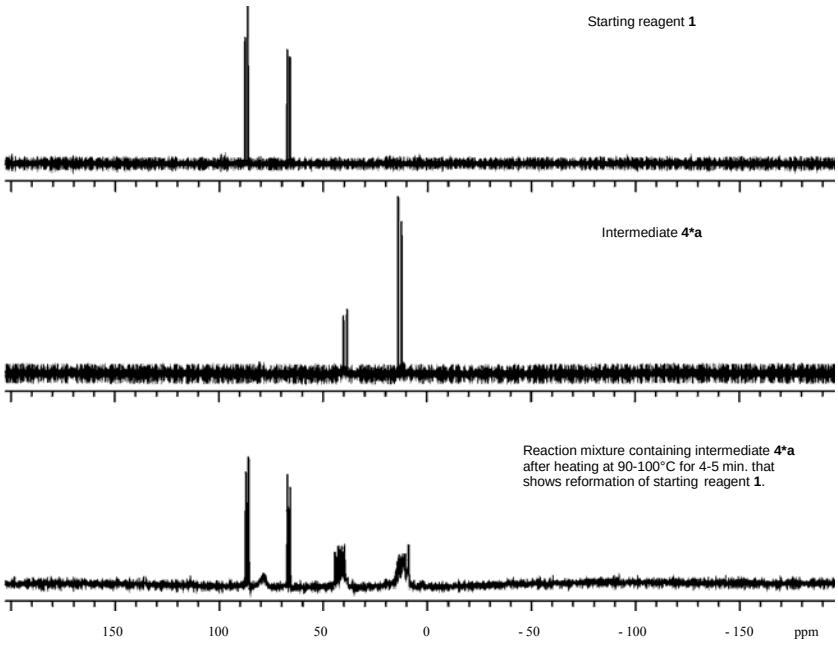


Figure 7.2: ^{31}P NMR spectra of the reaction between benzothiadiphosphole **1** and *t*-butylmagnesium chloride.

In order to check whether the behaviour showed by the reaction between compound **1** and *t*-butylmagnesium chloride could be observed also in other cases, we carried out the reaction with Grignard reagents characterized by different steric hindrance (Scheme 7.2). We found that the reaction between compound **1** and *t*-pentylmagnesium chloride produces intermediate **6*b** which, when heated, came back to starting reagents (see exsperimental section), as previously observed for **6*a**.

The reaction with tritylmagnesium chloride (case **c**) did not occur. When we carried out the reaction between **1** and one equivalent of phenylmagnesium bromide (case **f**), or *n*-butylmagnesium bromide (case **g**) we observed in the ^{31}P NMR spectrum a couple of doublets ascribed to intermediate **6f** (δ= 27.6 and 14.0 ppm (^{1}J(P,P) = 265 Hz) or **6g** (15.8 and 12.2 ppm (^{1}J(P,P) = 258 Hz). In these cases, after addition of further amounts of the same Grignard reagent, we observed the disappearance of the first doublets and the concomitant appearance of a second couple of doublets which were stable and are in accord with the new pentacoordinate phosphorus species such as **7f** (δ= -8.3 and -45.3 ppm (^{1}J(P,P) = 179 Hz) and **7g (**-31.6 and -43.3 ppm (^{1}J(P,P)=169 Hz). After addition of water to

these reaction mixtures we observed the immediate disappearance of signals of **7f**, (or **7g)** and the concomitant appearance of signals of **5f**, (or **5g**) and **3** (figure 7.3). It is interesting to note that a simple heating at 90-100 °C of a mixture of intermediates **6f,g** and **7f,g** is not able to break the phosphorus-carbon bonds derived from the reaction with the Grignard reagent, to give **1**. This might indicate a different strenght of the phosphorus-carbon bond both for **6f,g** and **7f,g** with respect to **6*a,b**, in agreement also with the observed trend, toward up-fields, of the chemical shifts of the corresponding signals. Then, in **6f,g** (Scheme 7.2) the C-Mg bond is completely broken and, consequently, a total coordination (only partial in case **6*a, b**) between sulphur and MgX group occurs. In agreement with this proposed mechanism and the two different structures **6*** and **6**, we have observed that the attack of the second equivalent of RMgX (R = phenyl, *n*-butyl) to **6** is favoured respect to that of the first equivalent of the same Grignard to **1**. Infact, the ^{31}P NMR spectrum obtained after addition of only one equivalent of phenylmagnesium- or *n*-butylmagnesium bromide to compound **1** showed presence of signals of both, **6f** and **7f** or **6g** and **7g,** respectively, together with those of unreacted **1.** This behaviour can be due to the complete coordination between sulphur and magnesium atoms in intermediates **6f,g** that make the adjacent phosphorus atom more prone to undergo the second attack of the Grignard reagent with respect to the first one.

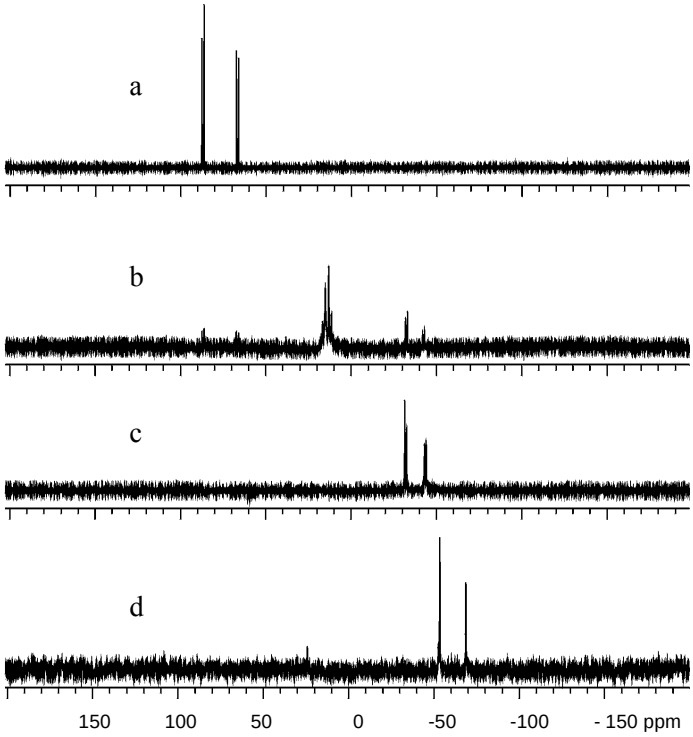


Figure 7.3: ^{31}P NMR spectra of the reaction between benzothiadiphosphole **1** and *n*-butylmagnesium bromide carried out in the NMR tube in THF. **a.:** spectrum of the starting reagent **1**. **b.:** after addition of one equivalent of the Grignard reagent respect to **1** (presence of intermediates **6g** and traces of **7g** and starting material **1**). **c.:** after addition of a further equivalent of Grignard reagent (only presence of **7g**). **d.:** spectrum of the reaction mixture containing only **7g** after addition of acidic water (formation of dibutylphosphine (**5g**) and compound **3**).

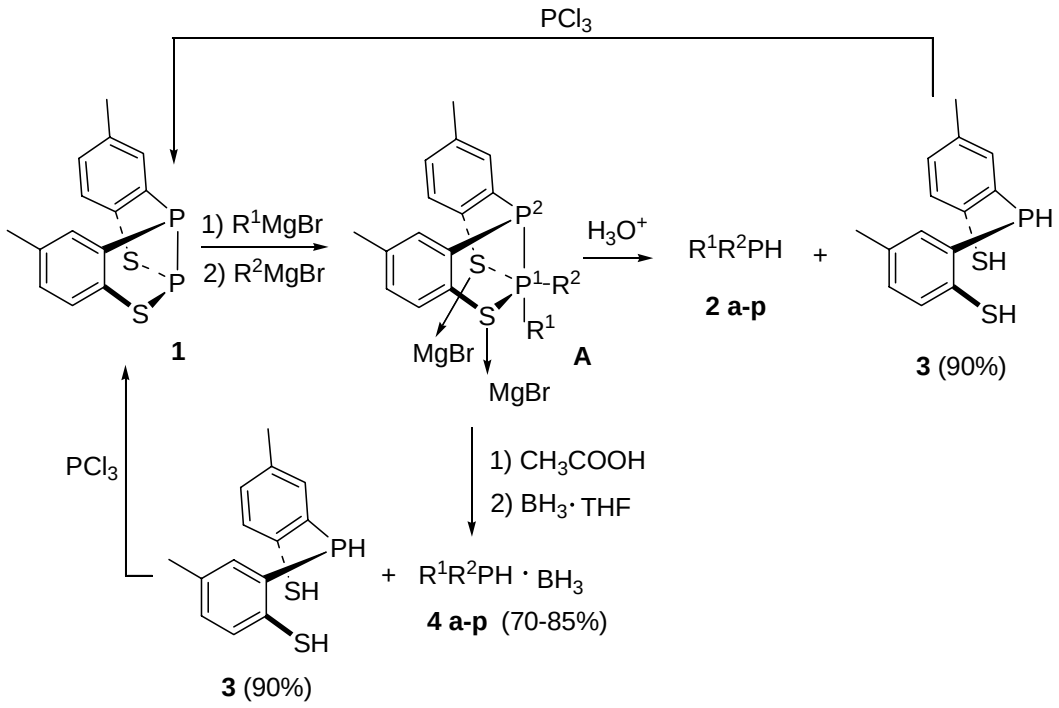
In the case of *i*-propylmagnesium chloride (case **d**) and *c*-hexylmagnesium chloride (case **e**) we observed only signals related to intermediates **6d** and **6e**, which resulted unchanged after heating at 90-100 °C even after 5-10 minutes. When the reaction was carried out with two or more equivalents of *i*-propylmagnesium chloride and *c*-hexylmagnesium chloride the spectrum again showed only presence of **6d** and **6e** without signals of **7d** and **7e**. Probably, the steric hindrance of this Grignard reagents are between that of cases **a, b** and **f, g** then the presence of the *i*-propylic and *c*-hexylic moiety on **6d** and **6e**, respectively, do not permit the attack of the second molecule of *i*-propylmagnesium chloride or *c*-hexylmagnesium chloride, so explaining the absence of formation of the corresponding intermediates **7d** and **7e**. Probably, we did not observed signals related to intermediates **6*d-g** because the limited steric

hindrance of the Grignard reagents makes these intermediates not detectable being they transformed, immediately after their formation, into **6d-g**.

7.2.3 Synthesis of secondary phosphines containing bulky group.

We found that using *i*-propylmagnesium chloride or *c*-hexylmagnesium chloride it was only possible to obtain the intermediates **6d,e**, this encouraging us to try to obtain secondary phosphine borane complexes using the previous reported procedure.

In this case, in order to obtain good yields, it is necessary to add as the first step the Grignard reagent containing the bulkiest group and the second in the successive step, leaving an opportune reaction time between the two steps. In fact for bulky groups (as *i*-propyl and *c*-hexyl) 3 or 4 minutes of reaction are necessary to completely form the intermediate **6d,e**-like. After the addition of the *i*-propylmagnesium chloride or *c*-hexylmagnesium chloride in this first step, the high steric hindrance of these moieties meant that only Grignard reagents with not high steric hindrance, such as phenylmagnesium bromide or methylmagnesium bromide, could be used in the following step. The use of *o*-metoxyphenylmagnesium bromide is possible only when *c*-hexylmagnesium chloride is used in the first step. The hindrance of *i*-propyl group is too high to permit the successive reaction with *o*-metoxyphenylmagnesium bromide. As previously reported, (*i*-propyl)$_2$PH and (*c*-hexyl)$_2$PH cannot be obtained by adding an excess of the corresponding Grignard reagent. This means that it is possible to add an excess of *i*-propylmagnesium bromide and *c*-hexylmagnesium chloride in the first step to increase the first step reaction rate without obtaining the corresponding symmetric secondary phosphines as a by-product. In general, this permits improvement of the yield in the asymmetric secondary phosphine (**2i-k**) bearing bulky groups to 80-85% instead of 70-75% when both Grignard reagents used have small steric hindrance.[14] With the exception of (*c*-hexyl)(2-metoxyphenyl)PH **2l** where the hindrance of 2-metoxyphenyl group permits the reaction with the intermediate **6e**, but at the same time makes this reaction very slow and difficult, giving secondary phosphine in a lower yield (70-75%).



	a	b	c	d	e	f	g	h	i	j	k	l
R^1	Et	*n*-Bu	*n*-Pent	Ph	Me	Et	*n*-Bu	Et	*i*-Pr	*c*-Hex	*c*-Hex	c-Hex
R^2	Et	*n*-Bu	*n*-Pent	Ph	Ph	Ph	Ph	*n*-Hex	Ph	Me	Ph	2-MeOPh

	m	n	o	p
R^1	2-MeOPh	2-MePh	4-MePh	$-(CH_2)_5-$
R^2	Me	2-MePh	4-MePh	-

Scheme 7.3 General synthesis of secondary phosphines.

When 2-metoxyphenylmagnesium bromide is added to **1** as a first Grignard reagent, its steric hindrance does not block the successive reaction of methylmagnesium bromide, giving the secondary phosphine **2m** in a 70-75% yield. Its reactivity can be compared with the reactivity of low steric hindrance groups.

We also obtained symmetric secondary phosphines containing the substituted phenyl group (o-tolyl)$_2$PH **2n** and (*p*-tolyl)$_2$PH **2o** in high yields (80-85%).

It should be noted that phosphines **2i-o**, were analyzed only by ^{31}P NMR spectroscopy and GC-MS analysis and were not isolated. They were isolated as borane complexes **4i-o**, which are stable derivatives and fully characterized.
To explore the generality of this procedure for synthesizing tertiary phosphine-borane complexes, we also used it to synthesize the borane complex of a cyclic secondary phosphine, namely the 1-phosphinane borane complex (**4p**), which was obtained in 80% yield.

7.3 Conclusion

In conclusion, this method represents a general protocol for the synthesis, in high yields, of acyclic-, cyclic-, symmetrical and asymmetrical secondary phosphines and their borane complexes using an almost identical, but independent, procedure. This generality arises because the method uses a phosphorus atom donor **1** and easily available Grignard reagents, and overcomes the limitations typical of the classical syntheses of secondary phosphines, which involve multistep syntheses and are limited by the availability of commercial sources of the organic phosphorus compounds that are used as starting reagents. In addition, using this one-pot procedure to obtain phosphine-borane complexes, free compound **3** was recovered and recycled to starting reagent **1**, making the whole process highly atom-economic and environmentally friendly.
Additionally, the reaction mechanism was studied identifying the intermediates involved. Different behaviour was observed depending on the steric hindrance of the used Grignard reagent. In fact, with bulky reagents, as *t*-butyl- and *t*-pentylmagnesium chloride, the reaction gave only formation of four-center intermediates **6*a, b** whereas with *i*-propylmagnesium chloride and *c*-hexylmagnesium chloride the only intermediates **6d,e** were observed and, in the other cases, the reaction can otherwise proceed toward intermediates **7e, f**.

7.4 Experimental section

General: ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 300 (or 400 or 600), at 75.46 (or 100.56 or 150.82) and 120.75 (or 161.89 or 242.77) MHz, respectively, in $CDCl_3$ or THF-d_8. Chemical shifts are referenced to internal standard TMS (^{1}H NMR), to solvent (77.0 ppm for ^{13}C NMR) or are referenced to solvent (THF-d_8, 1.8 ppm and 26.7 ppm for ^{1}H and ^{13}C NMR, respectively) and to external standard 85% H_3PO_4 (^{31}P NMR). *J* values are given in Hz. MS spectra were recorded at an ionisation voltage of 70 eV. Flash chromatography (FC) was performed on silica gel (0.040-0.063 mm). Melting points are uncorrected. IR spectra of compounds **11** and **12** showed characteristic bands (~2440 and 2400-2380, respectively, P-H), near 2370 and 2350 (BH_3 as. and symm str.), 1190-1120 and 1080-1040 (BH_3 as. and symm def.), 1000-900 (P-H def.), 790-720 (P-C). THF was distilled from sodium benzophenone ketyl and all solvents were purified appropriately before use and degassed immediately prior to use. All Grignard reagents used, both commercially available and prepared from the corresponding alkyl halide and magnesium turnings, were titrated immediately prior to use by standard methods.[16] Except tritylmagnesium chloride (Ph_3CMgCl), which was prepared according to Gilman.[17] Air and moisture sensitive solutions and reagents were handled in a dried apparatus under a dry argon atmosphere using standard Schlenk-type techniques. Reaction between benzothiadiphosphole **1** and tritylmagnesium chloride does not occur.

Preparation of phosphines 2a-p. **Typical procedure A**: Solutions of the two Grignard reagents (R^1MgBr: 1.0 mmol, R^2MgBr: 1.0 mmol)) were sequentially added (1-2 min. between the addition of the first and the second Grignard reagent) to a solution of benzothiadiphosphole (**1**) (1.0 mmol) in anhydrous THF and under an argon atmosphere (when $R^1=R^2$ the addition of two equivalents of the Grignard reagent is in one step). After about 20-30 min the solvent was partially evaporated and the reaction mixture was treated with degassed acidic (HCl) aqueous solution. Extraction with CH_2Cl_2 gave a mixture of phosphines and of the residue **3**. An

easy separation of these compounds was carried out by treating the organic solution with degassed aqueous NaOH; in this way the sodium salt of compound **3** is dissolved in the aqueous solution, whereas the organic one contains the phosphines **2** which were immediately purified by bulb to bulb distillation. Compound **3**[15] was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, purified by distillation and stored under argon. By simple treatment of a dry solution of compound **3** with an equimolar amount of PCl_3 the starting reagent **1** was regenerated in almost pure form so that it can be reused without further purification.

When Grinard reagents bearing bulky groups (as *i*-propylmagnesium chloride or *c*-hexylmagnesium chloride) are used, it is necessary adding this Grinard reagents in the first step. The quantity should be around 1.3-2 equivalent respect **1**, this is possible because of impossible to obtain the second attack on intermediate **4d,e**. Also the time between the two steps should be longer (3 or 4 minutes) to permit the completion formation of **4d,e**.
Phosphines **2i-o**, were analyzed in the reaction mixture only by ^{31}P NMR spectroscopy and GC-MS analysis, and were not isolated. They were isolated as borane complexes **4i-o**, which are stable and fully characterized.

Diethylphosphine 2a: colourless oil, b.p. 83-88 °C/760 mmHg (lit.[18]: 85 °C/760 mmHg), ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.90 (br. dm, $^1J_{P\text{-}H}$ = 190 Hz, 1H), 1.20-0.90 (m, 10 H) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = −55.5 (dm, $^1J_{P\text{-}H}$ = 190 Hz), GC-MS (m/z, %): 90 (M^+, 15), 89 (M – 1, 100), 61 (0.7); HRMS calcd. for $C_4H_{11}P$, 90.0598; found: 90.0595.

Dibutylphosphine 2b: colourless oil, b.p. 75-80 °C/18-20 mmHg (lit.[19]: 71-73 °C/17 mmHg), ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.98 (br. dm, $^1J_{P\text{-}H}$ = 189 Hz, 1 H), 2.40-1.05 (m, 12 H), 1.05-0.75 (m, 6 H) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = −69.0 (dm, $^1J_{P\text{-}H}$ = 189 Hz), GC-MS (m/z, %): 146 (M^+, 4), 117 (5), 104 (3), 90 (2), 89 (3), 75 (2), 62 (100), 57 (15); HRMS calcd. for $C_8H_{19}P$, 146.1224; found: 146.1229.

Dipentylphosphine 2c: colourless oil, b.p. 110-115 °C/18-20 mmHg (lit.[20a]: 100 °C/15 mmHg, lit.[20b]: 110 °C/15 mmHg), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.97 (br. dm, $^{1}J_{P\text{-}H}$ = 194 Hz, 1 H), 2.40-1.15 (m, 16 H), 1.00-0.80 (m, 6 H), ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = −69.1 (dm, $^{1}J_{P\text{-}H}$ = 194 Hz), GC-MS (m/z, %): 174 (M^+, 4), 159 (1), 145 (1), 131 (1), 118 (3), 103 (9), 76 (15), 62 (100), 55 (14); HRMS calcd for $C_{10}H_{23}P$, 174.1537; found: 174.1539.

Diphenylphosphine 2d: colourless oil, b.p. 159-164 °C/18-20 mmHg (lit.[21]: 160-162 °C/20 mmHg), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.40-6.50 (m, 10 H), 5.20-3.50 (br. s. 1H), ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = −41.0 (dm, $^{1}J_{P\text{-}H}$ = 219 Hz), GC-MS (m/z, %): 186 (M^+, 35), 152 (5), 115 (4), 108 (100), 92 (15); HRMS calcd for $C_{12}H_{11}P$, 186.0598; found: 186.0594.

Methyl(phenyl)phosphine 2e: colourless oil, b.p. 67-71 °C/18-20 mmHg (lit.[22]: 62.5-63 °C/13 mmHg), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.92-6.80 (m, 5 H), 4.32 (br. dm, $^{1}J_{P\text{-}H}$ = 203 Hz, 1H), 1.40-1.30 (m, 3 H) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = −71.5 (dm, $^{1}J_{P\text{-}H}$ = 203 Hz), GC-MS (m/z, %): 124 (M^+, 100), 109 (99), 78 (37), 63 (27); HRMS calcd for C_7H_9P, 124.0442; found: 124.0445.

Ethyl(phenyl)phosphine 2f: colourless oil, b.p. 90-93 °C/18-20 mmHg (lit.[23]: 92-92.5 °C/23 mmHg), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.58-7.00 (m, 5 H), 4.01 (dt, $^{1}J_{P\text{-}H}$ = 204 Hz, $^{2}J_{P\text{-}H}$ = 6.8 Hz, 1 H), 1.90-1.28 (m, 2 H) 0.90-0.80 (m, *J*= 1 H) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = −44.0 (dm, $^{1}J_{P\text{-}H}$ = 204 Hz); GC-MS (m/z, %): 138 (M^+, 92), 108 (100), 78 (46); HRMS calcd for $C_8H_{11}P$, 138.0598; found: 138.0601.

Butyl(phenyl)phosphine 2g: colourless oil, b.p. 110-114 °C/18-20 mmHg (lit.[24]: 110 °C/18 mmHg), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.0-6.0 (m, 5 H), 3.32 (dm, $^{1}J_{P\text{-}H}$ = 227 Hz, 1 H), 1.72-0.12 (m, 9 H) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = −53.4 (dm, $^{1}J_{P\text{-}H}$ = 227 Hz),

GC-MS (m/z, %): 166 (M^+, 40), 137 (6), 124 (100), 109 (56), 108 (50); HRMS calcd for $C_{10}H_{15}P$, 166.0911; found: 166.0907.

Ethyl(hexyl)phosphine 2h: colourless oil, b.p. 78-83 °C/18-20 mmHg (lit.[25]: 85 °C/23 mmHg), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.02 (dm, $^1J_{P-H}$ = 185 Hz, 1H), 1.62-1.18 (m, 12 H), 1.18-0.90 (m, 3 H) ppm; ^{31}P NMR (120.76 MHz, $CDCl_3$, 25 °C): δ = −61.3 (dm, $^1J_{P-H}$ = 185 Hz), GC-MS (m/z, %): 146 (M^+, 15), 131 (4), 117 (14), 89 (29), 76 (100), 62 (61); HRMS calcd for $C_8H_{19}P$, 146.1224; found: 146.1229.

Isopropyl(phenyl)phosphine 2i[26] : ^{31}P NMR {^{1}H} (161.9 MHz, THF-d_8) δ =-25.1 (dm, J_{P-H} = 201 Hz); GC-MS (m/z, %): 152 [M^+, 40], 108 (100) 83 (27) 57 (44).

Cyclohexyl(methyl)phosphine 2j : ^{31}P NMR {^{1}H} (161.9 MHz, THF-d_8) δ =-46.1 (dm, J_{P-H} = 177 Hz); GC-MS (m/z, %): 130 (M^+, 13), 83 (29), 55 (100).

Cyclohexyl(phenyl)phosphine 2k : ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C) δ = -29.8 (dm, J_{P-H}=196 Hz); GC-MS (m/z, %): 192 (M^+, 1), 110 (5), 83 (6), 55 (100).

Cyclohexyl(2-methoxyphenyl)phosphine 2l : ^{31}P{1H}NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= -42.6 (dm, J_{P-H} = 137 Hz); GC-MS (m/z, %): 222 (M^+, 22), 140 (100), 109 (40), 83 (75).

(2-Methoxyphenyl)(methyl)phosphine 2m : ^{31}P{^{1}H}NMR (161.89 MHz, $CDCl_3$, 25 °C): δ=-83.1 (dm, J_{P-H}= 205 Hz); GC-MS (m/z, %): 154 (M+, 77), 139 (37), 109 (65), 91 (100), 77 (73).

Bis(2-methylphenyl)phosphine 2n[26] : ^{31}P{^{1}H}NMR (161.89 MHz, THF-d_8, 25 °C): δ= -58.9 (dm, J = 220 Hz); GC-MS (m/z, %): 214 (M^+, 17), 122 (53), 91 (25), 78 (100).

Bis(4-methylphenyl)phosphine 2o[26] : $^{31}P\{^{1}H\}$NMR (161.89 MHz, THF, 25 °C): δ= -42.2 (dm, *J* = 215 Hz); GC-MS (m/z, %): 214 (M^+, 83), 183 (10), 122 (100), 78 (44).

Phosphinane 2p[27] : $^{31}P\{^{1}H\}$NMR (161.89 MHz, THF, 25 °C): δ= -65.0 (dm, *J* = 190 Hz); MS (70 eV, EI): *m/z* : 102 (M^+, 100), 87 (23), 74 (95), 72 (14), 69 (13), 60 (14), 57 (21).

Preparation of phosphine boranes 4a-h. **Typical procedure**: Solutions of the two Grignard reagents (R^1MgBr: 1.0 mmol, and R^2MgBr: 1.0 mmol) were sequentially added (1-2 min. between the addition of the first and the second Grignard reagent) to a solution of benzothiadiphosphole (**1**) (1.0 mmol) in anhydrous THF and under an argon atmosphere (when $R^1=R^2$ the addition of two equivalents of the Grignard reagent is in one step). After 20-30 min. the reaction mixture was treated with acid acetic glacial (2-3 mmol) and stirred for 5 min. The flask was immersed in an ice bath and BH_3-THF complex (1.5 mmol) was added during 2-3 h. The ice-bath was removed and the solvent was partially removed. The reaction mixture was treated with degassed acidic (HCl) aqueous solution. Extraction under argon atmosphere with CH_2Cl_2 gave a mixture of phosphine borane and of the residue **3**. An easy separation of these compounds was carried out by treating, under argon atmosphere, the organic solution with degassed aqueous NaOH; in this way the sodium salt of compound **3** is dissolved in the aqueous solution, whereas the organic one contains the phosphine borane complex **4** which was purified by chromatography on silica gel (*n*-hexane:EtOAc 95/5). Compound **3** can be recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, treatment with anhydrous Na_2SO_4, and concentration under *vacuum* (all these manipulations require argon atmosphere, in order to avoid oxidation of compound **3**). Compound **3** was purified by distillation and stored under argon. By simple treatment of the dry solution of compound **3** with an equimolar amount of PCl_3 the starting reagent **1** was regenerated in almost pure form so that it can be reused without further purification.

When Grinard reagents bearing bulky groups (as *i*-propylmagnesium chloride or *c*-hexylmagnesium chloride) are used, it is necessary adding this Grinard reagents in the first step. The quantity should be around 1.3-2 equivalent respect **1**, this is possible because of impossible to obtain the second attack on intermediate **4d,e**. Also the time between the two steps should be longer (3 or 4 minutes) to permit the completion formation of **4d,e**.

Diethylphosphine borane 4a[28]**:** colourless oil, R_F = 0.35 (*n*-hexane : Ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.48 (d of sextets, $^1J_{P\text{-}H}$ = 355.3 Hz, *J* = 6.0 Hz, 1 H), 1.87-1.65 (m, 4 H), 1.22 (t, *J* = 16.8 Hz, *J* = 7.5 Hz, 3 H), 0.50 (br. q of doublets, $J_{B\text{-}H}$ = 95.8 Hz, *J* = 14.1 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 13.3 (d, *J* = 36.3 Hz), 8.6 (d, *J* = 3.7 Hz), ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 1.8 (q, $J_{B\text{-}P}$ = 52.4 Hz); ^{31}P{1H}NMR: δ = 1.8 (dm, $^1J_{P\text{-}H}$ = 355.3 Hz)**;** GC-MS (m/z, %): 90 (M^+-BH_3, 15), 89 (M – 1, 100), 61 (0.7).

Dibutylphosphine borane 4b[12]: colourless oil, R_F = 0.45 (*n*-hexane : Ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.54 (d of sextets, $^1J_{P\text{-}H}$ = 355.2 Hz, *J* = 5.9 Hz, 1 H), 1.85-1.35 (m, 12 H), 0,94 (t, *J* = 7.3 Hz, 6 H), 0.51 (br. q, $J_{B\text{-}H}$ ~ 98 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 26.5 (d, *J* = 3.2 Hz), 23.8 (d, *J* = 12.1 Hz), 20.2 (d, *J* = 36.4 Hz), 13.5; ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = -8.0 (br q, $J_{B\text{-}P}$ = 53 Hz); ^{31}P{1H}NMR: δ = -8.0 (dm, $^1J_{P\text{-}H}$ = 355.2 Hz); GC-MS (m/z, %): 146 (M^+-BH_3, 4), 117 (5), 104 (3), 90 (2), 89 (3), 75 (2), 62 (100), 57 (15).

Dipentylphosphine borane 4c: colourless oil, R_F = 0.48 (*n*-hexane : Ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.53 (d of sextets, $^1J_{P\text{-}H}$ = 354.6 Hz, *J* = 6.0 Hz, 1 H), 1.81-1.23 (m, 16 H), 0.91 (t, *J* = 7.0 Hz, 6 H), 0.50 (br. q, $J_{B\text{-}H}$ ~ 100 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 33.0 (d, *J* = 11.9 Hz), 24.1 (d, *J* = 3.1 Hz), 22.3, 20.6 (d, *J* = 35.2 Hz), 14.0, ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = -7.9 (br. q, $J_{B\text{-}P}$ ~ 48.0 Hz); ^{31}P{1H}NMR: δ = -7.9

(dm, $^{1}J_{P\text{-}H}$ = 354.6 Hz); GC-MS (m/z, %): 174 (M^{+}-BH_3, 4), 159 (1), 145 (1), 131 (1), 118 (3), 103 (9), 76 (15), 62 (100), 55 (14).

Diphenylphosphine borane 4d: greasy solid, m.p.: 42-44 °C, (Lit.[10b]: 43-44 °C); R_F = 0.40 (*n*-hexane : Ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.71-7.63 (m, 4 H), 7.54-7.42 (m, 6 H), 6.30 (dq, $^{1}J_{P\text{-}H}$ = 378.8 Hz, *J* = 6.9 Hz, 1 H), 1.07 (br. q, $J_{B\text{-}H}$ ~ 97 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 133.0 (d, *J* = 9.9 Hz), 131.6 (d, *J* = 1.6 Hz), 129.1 (d, *J* = 9.8 Hz), 126.2 (d, *J* = 57.4 Hz); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 1.9 (br. q, $J_{B\text{-}P}$ ~ 50 Hz); ^{31}P{1H}NMR: δ = 1.9 (dm, $^{1}J_{P\text{-}H}$ = 378.8 Hz); GC-MS (m/z, %): 186 (M^{+}-BH_3, 35), 152 (5), 115 (4), 108 (100), 92 (15).

Methyl(phenyl)phosphine borane 4e[29]: colourless oil, R_F = 0.35 (*n*-hexane : Ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.73-7.67 (m, 2 H), 7.55-7.44 (m, 3 H), 5.32 (d of septets, $^{1}J_{P\text{-}H}$ = 371.2 Hz, *J* = 5.9 Hz, 1 H), 1.62 (dd, *J* = 10.8 Hz, *J* = 5.9 Hz, 3 H), 0.83 (br. q, $J_{B\text{-}H}$ ~ 100 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 132.8 (d, *J* = 8.9 Hz), 132.2 (d, *J* = 2.9 Hz), 129.5 (d, *J* = 9.8 Hz), 126.9 (d, *J* = 56.8 Hz), 8.6 (d, *J* = 38.8 Hz), ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = -14.4 (br. q, $J_{B\text{-}P}$ ~ 48 Hz); ^{31}P{1H}NMR: δ = -2.3 (dm, $^{1}J_{P\text{-}H}$ = 371.2 Hz); GC-MS (m/z, %): 124 (M^{+}-BH_3, 100), 109 (99), 78 (37), 63 (27).

Ethyl(phenyl)phosphine borane 4f[29]: colourless oil, R_F = 0.37 (*n*-hexane : Ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.72-7.63 (m, 2 H), 7.58-7.32 (m, 3 H), 5.38 (d of sextets, $^{1}J_{P\text{-}H}$ = 367.8 Hz, *J* = 5.9 Hz, 1 H), 2.00-1.86 (m, 2 H), 1.13 (dt, *J* = 17.8 Hz, *J* = 7.9 Hz, 3 H), 0.81 (br. q, $J_{B\text{-}H}$ ~ 97 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 133.1 (d, *J* = 8.9 Hz), 132.0 (d, *J* = 1.9 Hz), 129.3 (d, *J* = 9.9 Hz), 125.6 (d, *J* = 54.9 Hz), 17.2 (d, *J* = 36.7.9 Hz), 8.9 (d, *J* = 3.1 Hz), ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 2.2 (br. q, $J_{B\text{-}P}$ ~ 45 Hz); ^{31}P{1H}NMR: δ = -2.3 (dm, $^{1}J_{P\text{-}H}$ = 367.8 Hz); GC-MS (m/z, %): 138 (M^{+}-BH_3, 92), 108 (100), 78 (46).

Butyl(phenyl)phosphine borane 4g: colourless oil, R_F = 0.34 (*n*-hexane : Ethyl acetate 85/15); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.75-7.62 (m, 2 H), 7.57-7.38 (m, 3 H), 5.41 (d of sextets, $^1J_{P\text{-}H}$ = 366.4 Hz, *J* = 6.4 Hz, 1 H), 2.10-1.80 (m, 2 H), 1.65-1.45 (m, 2 H), 1.45-1.33 (m, 2 H), 0.90 (t, *J* = 7.2 Hz, 3 H), 0.78 (br. q, $J_{B\text{-}H}$ ~ 94 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 132.8 (d, *J* = 8.9 Hz), 131.6 (d, *J* = 2.5 Hz), 129.0 (d, *J* = 9.8 Hz), 125.8 (d, *J* = 55.5 Hz), 26.4 (d, J = 3.4 Hz), 23.7 (d, J = 12.7 Hz), 23.3 (d, *J* = 35.8 Hz), 13.5, ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = -2.3 (br. q, $J_{B\text{-}P}$ ~ 45 Hz); ^{31}P{1H}NMR: δ = -2.3 (dm, $^1J_{P\text{-}H}$ = 366.4 Hz); GC-MS (m/z, %): 166 (M^+-BH_3, 40), 137 (6), 124 (100), 109 (56), 108 (50).

Ethyl(hexyl)phosphine borane 4h: colourless oil, R_F = 0.50 (*n*-hexane : Ethyl acetate 95/5); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.51 (d of sextets, $^1J_{P\text{-}H}$ = 355.0 Hz, *J* = 5.3 Hz, 1 H), 1.89-1.60 (m, 4 H), 1.47-1.24 (m, 8 H), 1.21 (dt, *J* = 16.7 Hz, *J* = 7.7 Hz, 3 H), 0.89 (t, *J* = 6.9 Hz, 3 H), 0.51 (br. q, $J_{B\text{-}H}$ ~ 103 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 31.2, 30.4 (d, *J* = 11.4 Hz), 24.4 (d, *J* = 2.7 Hz), 22.4, 20.0 (d, *J* = 35.5 Hz), 14.0, 13.7 (d, *J* = 36.3 Hz), 8.6 (d, *J* = 2.9 Hz), ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = -3.0 (br. q, $J_{B\text{-}P}$ ~ 51.5 Hz); ^{31}P{1H}NMR: δ = -3.0 (dm, $^1J_{P\text{-}H}$ = 355.0 Hz); GC-MS (m/z, %): 146 (M^+-BH_3, 15), 131 (4), 117 (14), 89 (29), 76 (100), 62 (61).

Isopropyl(phenyl)phosphine borane 4i[11] : colourless oil, (*n*-hexane : diethyl ether 90/10), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ= 7.78–7.63 (m, 2 H), 7.60–7.44 (m, 3 H), 5.30 (dq, 1 H, $J_{P\text{-}H}$ = 377 Hz), 2.35–2.16 (m, 1 H), 1.36–1.09 (m, 6 H), 0.63 (br q, *J* ~ 102 Hz, 3 H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 133.7 (d, *J* = 8 Hz), 132.1 (d, *J* = 2 Hz), 129.2 (d, *J* = 10 Hz), 125.1 (d, *J* = 53 Hz), 24.2 (d, *J* = 35 Hz), 18.2 (d, *J* = 50 Hz); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= 16.3 (br. q, $J_{B\text{-}P}$ ~ 44 Hz); ^{31}P{^{1}H}NMR: δ= 16.3(dm, $J_{P\text{-}H}$ = 377 Hz,); GC-MS (m/z, %): 152 [M^+ -BH_3, 40], 108 (100) 83 (27) 57 (44).

Cyclohexyl(methyl)phosphine borane 4j : colourless oil, (*n*-hexane : diethyl ether 90/10), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 4.47 (dsext, 1 H, *J* = 357 Hz,

J = 6 Hz), 1.98–1.88 (m, 2 H), 1.88–1.80 (m, 2 H), 1.77–1.69 (m, 2 H), 1.69–1.63 (m, 1 H), 1.40–1.20 (m, 4 H), 1.32 (dd, 3 H, *J* = 11 Hz, *J* = 6 Hz), 0.49 (br q, *J* ~ 98 Hz, 3 H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 31.4 (d, *J* = 36 Hz), 28.0 (d, *J* = 12 Hz), 26.3 (d, *J* = 12 Hz), 25.7, 2.9 (d, *J* = 36 Hz); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= -5.7 (br. q, $J_{B\text{-}P}$ ~ 50 Hz); ^{31}P{^{1}H}NMR: δ= -5.7 (dm, $J_{P\text{-}H}$ = 357 Hz). GC-MS (m/z, %): 130 (M^+ -BH_3, 13), 83 (29), 55 (100).

Cyclohexyl(phenyl)phosphine borane 4k[11] : colourless oil, (*n*-hexane : diethyl ether 90/10), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ= 7.77–7.42 (m, 5 H), 5.24 (dq, 1 H, $J_{P\text{-}H}$ = 364 Hz), 2.10–1.63 (m, 6 H), 1.46–1.12 (m, 5 H), 0.80 (br q, *J* ~99 Hz, 3 H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 133.7 (d, *J* = 8 Hz), 132.4 (d, *J* = 2 Hz), 129.1 (d, *J* = 10 Hz), 125.1 (d, *J* = 53 Hz), 33.7 (d, *J* = 37 Hz), 27.0 (d, *J* = 9 Hz), 26.8 (d, *J* = 10 Hz), 26.0; ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= 13.1 (dm, $J_{P\text{-}H}$ = 364 Hz); GC-MS (m/z, %): 192 (M^+ -BH_3, 1), 110 (5), 83 (6), 55 (100).

Cyclohexyl(2-methoxyphenyl)phosphine borane 4l[30] : colourless oil, (*n*-hexane : diethyl ether 90/10), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 7.75-7.67 (m, 1 H), 7.52-7.45 (m, 1 H), 7.10-7.00 (m, 1 H), 6.95-6.90 (m, 1 H), 5.51 (d, *J* = 381Hz, 1 H), 3.90 (s, 3 H), 2.20-1.65 (m, 6 H), 1.45-1.15 (m, 5 H), 0.67 (br. q, *J* ~100 Hz, 3 H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 160.6, 135.7 (d, *J* =13 Hz), 133.4, 121.1 (d, *J* =11 Hz), 113.1 (d, *J* =52 Hz), 110.5 (d, *J* = 4 Hz), 55.7, 31.7 (d, *J* =37 Hz), 26.7 (d, *J* = 10 Hz), 26.5 (d, *J* = 9 Hz), 25.7; ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= -8.2 (br. q, $J_{B\text{-}P}$ ~ 51 Hz); ^{31}P{^{1}H}NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= – 8.2 (dm, J_{PH}= 381 Hz); GC-MS (m/z, %): 222 (M^+ -BH_3, 22), 140 (100), 109 (40), 83 (75).

(2-Methoxyphenyl)(methyl)phosphine borane 4m[31] : colourless oil, (*n*-hexane : diethyl ether 90/10), ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ = 7.80-7.70 (m, H), 7.53-7.45 (m, 1 H), 7.10-7.00 (m, 1 H), 6.98-6.88 (m, 1 H), 5.67 (dsept, *J* = 385 Hz, *J* = 6 Hz, 1 H), 3.89 (s, 3 H), 1.54 (dd, *J* = 11 Hz, *J* = 6 Hz, 3 H), 0.76 (br q, *J* ~ 95 Hz, 3 H); ^{13}C NMR (75.46 MHz, $CDCl_3$, 25 °C): δ =160.8, 134.9 (d, *J* = 15

Hz), 133.9, 121.2 (d, J = 12 Hz), 114.3 (d, J = 55 Hz), 110.5 (d, J = 4 Hz), 55.8, 7.1 (d, J = 40 Hz); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= -29.3 (br. q, $J_{B\text{-}P}$ ~ 48 Hz); $^{31}P\{^1H\}$NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= -30.4 (dm, J = 385 Hz); GC-MS (m/z, %): 154 (M^+ -BH_3, 77), 139 (37), 109 (65), 91 (100), 77 (73).

Bis(2-methylphenyl)phosphine borane 4n : colourless oil, (*n*-hexane : diethyl ether 90/10), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 7.62 (dd, J = 14 Hz, J = 8 Hz, 2 H), 7.42 (app. t, J = 7 Hz, 2 H), 7.32-7.22 (m, 4 H), 6.49 (dq, J = 376 Hz, J = 7 Hz, 1 H), 2.34 (s, 6 H), 1.11 (br q, J ~ 92 Hz, 3 H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 141.5 (d, J = 4 Hz), 134.0 (d, J = 15 Hz), 131.7 (d, J = 2 Hz), 131.0 (d, J = 8 Hz), 126.5 (d, J = 12 Hz), 125.0 (d, J = 54 Hz), 20.9 (d, J = 5 Hz); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= -14.1 (br. q, $J_{B\text{-}P}$ ~ 48 Hz); $^{31}P\{^1H\}$NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= -14.1 (dm, J = 376 Hz); GC-MS (m/z, %): 214 (M^+ -BH_3, 17), 122 (53), 91 (25), 78 (100).

Bis(4-methylphenyl)phosphine borane 4o[26] : colourless oil, (*n*-hexane : diethyl ether 90/10), ^{1}H NMR (400 MHz, THF-d_8, 25 °C) δ = 7.65-7-60 (m, 4 H), 7.30 (d, J = 8 Hz, 4 H), 6.30 (dq, J = 379 Hz, J = 7 Hz, 1 H), 2.39 (s, 6 H), 1.10 (br q, J ~ 94 Hz, 3 H); ^{13}C NMR (100.56 MHz, THF-d_8, 25 °C): δ = 142.9 (d, J = 4 Hz), 133.9 (d, J = 16 Hz), 130.6 (d, J = 17 Hz), 125.2 (d, J = 92 Hz), 21.6; ^{31}P NMR (161.89 MHz, THF-d_8, 25 °C): δ= -1.1 (br. q, $J_{B\text{-}P}$ ~ 50 Hz); $^{31}P\{^1H\}$NMR (161.89 MHz, THF-d_8, 25 °C): δ= -1.1 (dm, J = 379 Hz); GC-MS (m/z, %): 214 (M^+ -BH_3, 83), 183 (10), 122 (100), 78 (44).

Phosphinane borane 4p : colourless oil, (*n*-hexane : diethyl ether 90/10), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ = 4.61 (d, J = 354 Hz, 1 H), 2.20-1.93 (m, 4 H), 1.69-1.50 (m, 6 H), 0.52 (br q, J ~ 97 Hz, 3 H); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 26.5 (d, J = 5 Hz), 24.9 (d, J = 8 Hz), 19.6 (d, J = 35 Hz); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ= -12.5 (br. q, $J_{B\text{-}P}$ ~ 52 Hz); $^{31}P\{^1H\}$NMR (161.89 MHz, THF-d_8, 25 °C): δ= -12.5 (dm, J = 358 Hz); GC-MS (m/z, %): 102 (M^+ -BH_3, 100), 87 (23), 74 (95), 72 (14), 69 (13), 60 (14), 57 (21).

Formation of intermediate 6*a and spectra of experiments showing its thermal instability.

To a solution of compound **1** (0.030g, 0.098 mmol), dissolved in 3 mL of THF-d_8, a solution of *t*-butylmagnesium chloride (1.5 eq., 1.0 M in THF) was added. After about 5-10 min. the reaction mixture, analyzed by GC-MS analysis (in the presence of an internal standard), showed only presence of all the starting reagent **1**. A sample of the same crude reaction mixture, analyzed by ^{31}P NMR spectroscopy, showed presence of signals of **6*a**, which was characterized also by ^{1}H NMR, ^{13}C NMR and ^{1}H-^{31}P HMBC (figure 7.1 of main text). The remaining reaction mixture, after heating at 90-100°C for 4-5 min. showed, at ^{31}P NMR analysis, complete disappearance of signals related to **6*a**, and concomitant appearance of those of starting reagent **1**. All attempts of crystallization of **6*a** do not permitted to obtain crystals suitable for X-Rays diffraction analysis.

Intermediate 6*a: ^{1}H NMR (600 MHz, THF-d8, 25°C): δ (ppm) = 7.58 (d, J =10.7 Hz, 1H), 7.53 (d, J =7.9 Hz, 1H), 7.29 (d, J =6.5 Hz, 1H), 7.20 (d, J =8.4 Hz, 1H), 6.94 (d, J =8.3 Hz, 1H), 6.21 (br. d, J ~3 Hz, 1H), 2.34 (s, 3H), 2.04 (s, 3H), 1.14 (d, ^{3}J(P,H)=14 Hz, 9H) ppm; ^{13}C NMR (150.82 MHz, THF-d_8, 25°C): δ (ppm) = 152.5 (dd, J=4 Hz, J=1 Hz), 149.7 (d, J=25 Hz), 143.6 (dd, J=26 Hz, J=2 Hz), 137.8, 136.4, 136.0 (d, J=9 Hz), 135.3 (d, J=33 Hz), 133.4 (d, J=4 Hz), 132.4, 131.7, 130.3, 126.7 (d, J=6 Hz), 37.2 (dd, ^{1}J(P,C)=31 Hz, ^{2}J(P,C)=18 Hz, $C(CH_3)_3$), 29.3 (dd, ^{2}J(P,C)=14 Hz, ^{3}J(P,C)=6 Hz, $C(CH_3)_3$), 22.5 (s, CH_3), 22.3 (s, CH_3); ^{31}P NMR (242.77 MHz, THF-d_8, 25°C, H_3PO_4 ext. std.): δ=38.1 (d, ^{1}J(P,P)=275 Hz), 9.6 (d, ^{1}J(P,P)=275 Hz).

Formation of intermediate 6*b and spectra of experiments showing its thermal instability.

Intermediate **6*b** was formed directly in the NMR tube by adding, under argon atmosphere, 0.15 mL of *t*-pentylmagnesium chloride (0.15 mmol, 1.0 M solution in diethyl ether) to compound **1** (0.035g, 0.11 mmol) dissolved in 1.0 mL of THF-d_8. After 5-10 minutes, the signals of starting reagent **1** (fig.7.4 spectrum **a)** disappeared and concomitantly appeared signals related to intermediate **6*b**

(fig.7.4 spectrum **b**) which was characterized by ^{1}H, ^{13}C NMR and ^{31}P NMR spectroscopy. Then the reaction mixture was transferred, under argon atmosphere, in a tree-necked round-bottom flask and heated for 1-2 min. at 90-100 °C then dissolved in THF and analyzed by ^{31}P NMR spectroscopy (fig.7.4 spectrum **c**) in which signals of compound **1** reappeared (in another experiment, when the solution was heated for more time, about 4-5 min., the spectrum showed complete disappearance of intermediate **6*b**). To the obtained mixture a further amount of *t*-pentylmagnesium chloride was added and the corresponding spectrum showed disappearance of signals of **1** (fig.7.4 spectrum **d**) which reappeared by further heating of the reaction mixture (fig.7.4 spectrum **d**). All attempts of crystallization of **6*b** do not permitted to obtain crystals suitable for X-Rays diffraction analysis.

Intermediate 6*b: ^{1}H NMR (400 MHz, [THF-d8, 25°C): δ (ppm) = 7.54 (d, J =8.5 Hz, 1H), 7.46 (d, J =8.0 Hz, 2H), 7.12 (d, J =8.0 Hz, 1H), 6.74 (d, J =7.8 Hz, 1H), 6.07 (br. d, J ~2 Hz, 1H), 2.38 (s, 3H), 2.02 (s, 3H), 1.60-1.45 (m, 2H), 1.10 (d, J(P,H)=11 Hz, 6H), 1.06-0.97 (m, 3 H); ^{13}C NMR (100.56 MHz, THF-d_8, 25°C): δ (ppm) = 151.3 (d, J=4 Hz), 148.2 (d, J=26 Hz), 142.4 (d, J=27 Hz), 136.5, 135.0, 134.5 (d, J=10 Hz), 133.8 (d, J=33 Hz), 132.1, 130.9, 130.2, 128.9, 125.2 (d, J=6 Hz), 39.0 (dd, ^{1}J(P,C)=37 Hz, ^{2}J(P,C)=11 Hz, $C(CH_3)_2$), 32.9 (d, J = 6 Hz), 23.6 (dd, ^{2}J(P,C)=12 Hz, ^{3}J(P,C)=6 Hz, C(CH_3)$_2$), 23.0 (dd, ^{2}J(P,C)=12 Hz, ^{3}J(P,C)=7 Hz, C(CH_3)$_2$), 20.3 (s, CH_3), 20.1 (s, CH_3), 8.3 (d, J = 12 Hz, CH_3); ^{31}P NMR (242.77 MHz, THF-d_8, 25°C, H_3PO_4 ext. std.): δ = 40.4 (d, ^{1}J(P,P)=281 Hz), 12.1 (d, ^{1}J(P,P)=281 Hz).

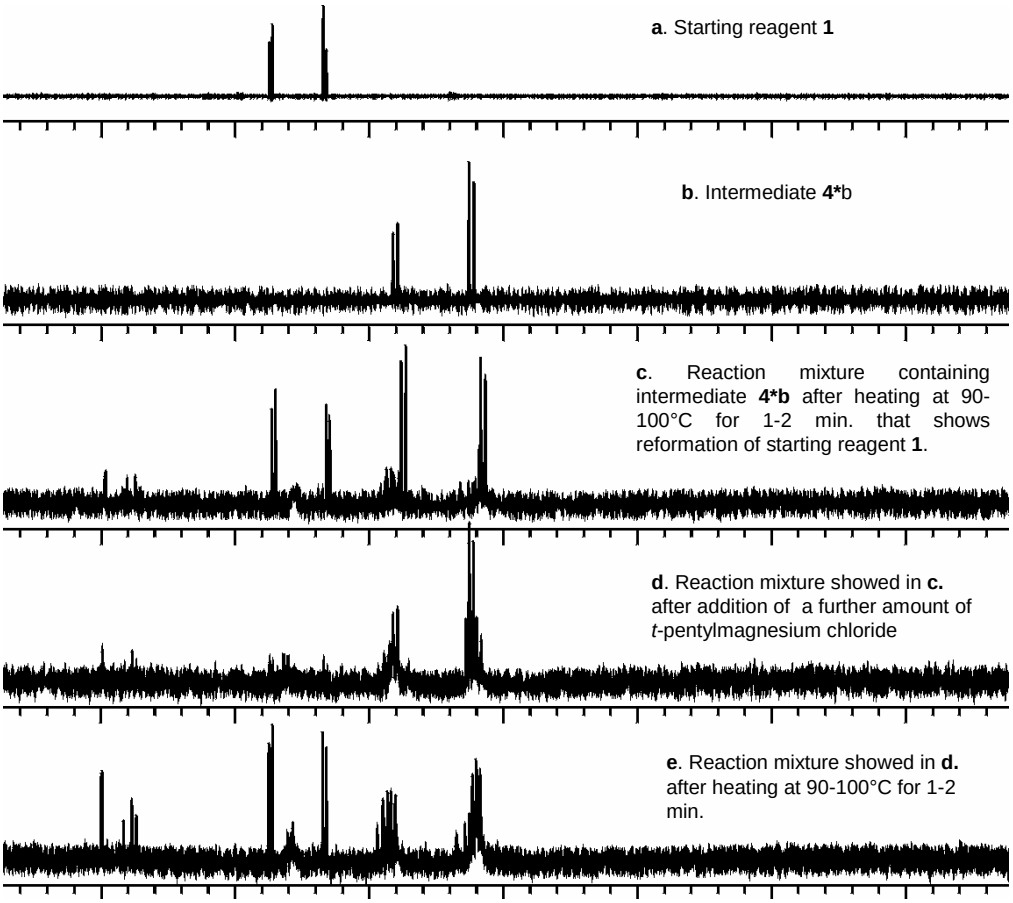


Figure 7.4: ^{31}P NMR spectra of the reaction between benzothiadiphosphole **1** and *t*-pentylmagnesium chloride.

Formation of intermediates 6d and 6e: The reaction between compound **1** and *i*-propylmagnesium chloride or *c*-hexylmagnesium chloride (1.5 equivalents), analyzed by ^{31}P NMR spectroscopy, showed presence of a couple of doublets (see below) which, after heating of the reaction mixture for 3-5 min at 90-100 °C, remained unchanged. In addition, when the reaction was carried out with an two or more equivalents of *i*-propylmagnesium chloride or *c*-hexylmagnesium chloride, respectively, the spectrum showed only presence of **6d** or**6e** without signals of **7d** or **7e**.

Intermediate 6d: ^{31}P NMR (161.89 MHz, THF, 25°C, H_3PO_4 ext. std.): δ= 28.5 (d, ^1J(P,P)=266 Hz), 15.1 (d, ^1J(P,P)=266 Hz).

Intermediate 6e: ^{31}P NMR (161.89 MHz, THF, 25°C, H_3PO_4 ext. std.): δ= 22.7 (d, ^1J(P,P)=265 Hz), 12.8 (d, ^1J(P,P)=265 Hz).

Formation of intermediates 6f, g and 7f, g:

To a solution of compound **1** (0.306g, 1.0 mmol), dissolved in 10 mL of THF, 1.5 equivalents of phenylmagnesium bromide (or *n*-butylmagnesium bromide) were added. After 1 min. the ^{31}P NMR spectrum of the crude reaction mixture showed presence of starting material **1** together with compound **6f** (or **6g**) and traces of **7f** (or **7g**)**.**

When the reaction was carried out using two equivalents of Grignard reagent the corresponding ^{31}P NMR spectrum showed only presence of intermediate **7f,g**.

Intermediate 6f: ^{31}P NMR (161.89 MHz, THF, 25°C, H_3PO_4 ext. std.): δ= 27.6 (d, ^1J(P,P)=265 Hz), 14.0 (d, ^1J(P,P)=265 Hz).

Intermediate 6g: ^{31}P NMR (161.89 MHz, THF, 25°C, H_3PO_4 ext. std.): δ= 15.8 (d, ^1J(P,P)=258 Hz), 12.2 (d, ^1J(P,P)=258 Hz).

Intermediate 7f: ^{31}P NMR (161.89 MHz, THF, 25°C, H_3PO_4 ext. std.): δ= -8.3 (d, ^1J(P,P)=179 Hz), -45.3 (d, ^1J(P,P)=179 Hz).

Intermediate 7g: ^{31}P NMR (161.89 MHz, THF, 25°C, H_3PO_4 ext. std.): δ= -31.6 (d, ^1J(P,P)=169 Hz), -43.3 (d, ^1J(P,P)=169 Hz).

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Chapter 8

SYNTHESIS OF TERTIARY PHOSPHINE-BORANE COMPLEXES

8.1 Introduction

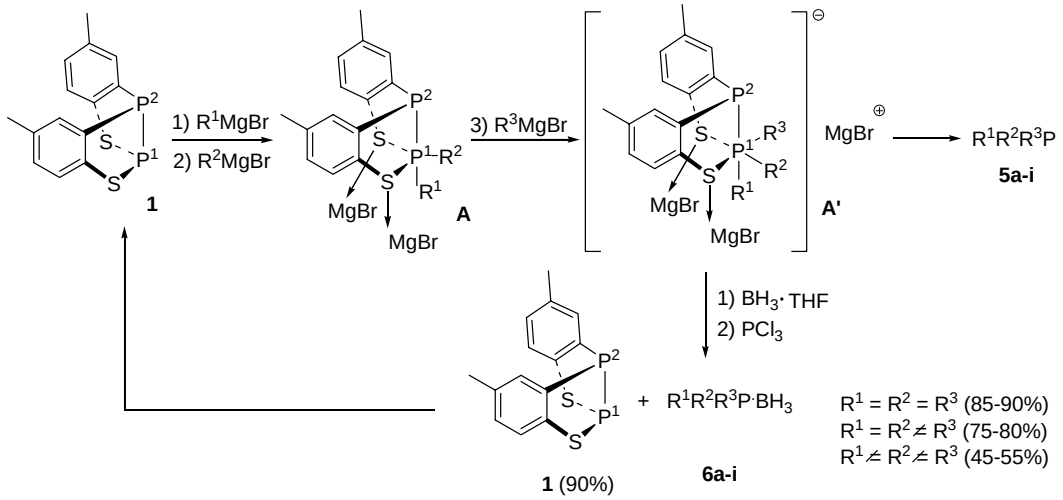
Phosphine-borane complexes are an important class of compounds that have attracted increasing interest since the first reported synthesis over 50 years ago.[1] In phosphine-boranes, the BH_3 is not only a valuable and protective group that can be easily removed, it also imparts useful reactivity features not found in typical tetracoordinated phosphorus derivatives.[2] Phosphine-borane complexes are now used in a variety of applications, including alkylations,[3,4] conjugate addition processes,[5] and deprotonation followed by metal-mediated coupling.[6] Moreover, numerous recent studies have demonstrated the importance of tertiary phosphine-borane complexes in the synthesis of chiral phosphorus ligands, and have expanded the range of synthetic procedures by using air-stable phosphine-boranes instead of the analogous phosphines.[6,7] Tertiary phosphine-boranes are generally obtained by reaction of the parent free phosphine with BH_3.THF, BH_3.SMe_2 complexes or $NaBH_4$/acetic acid,[8] or directly from parent phosphine oxides by *in situ* reduction with $LiAlH_4$ in the presence of $NaBH_4$ and $CeCl_3$.[9] However, currently available methods for the synthesis of acyclic and cyclic tertiary phosphines are usually long and tedious procedures involving multiple steps,[10-21] and are difficult and dangerous in some cases because they require pyrophoric and air-sensitive reagents such as primary and secondary phosphines and halophosphines. Moreover, in the case of acyclic tertiary asymmetrical phosphines, available synthetic procedures result in poor yields.[10]

8.2 Results and discussion

Using the previously reported[22] procedure (Chapter 6) for obtaining acyclic tertiary phosphines **5a-c**, we reacted **1** with three equivalents of mono-Grignard reagents. We then found that treatment of this reaction mixture with BH_3.THF directly afforded the tertiary phosphine-borane complexes **6a-c** in high yield (85-90%) without isolation of the free phosphines (Scheme 8.1). Simultaneous with the formation of the tertiary phosphines, we observed the formation of the magnesium salt of compound **3**, which is the residue of **1**. As a consequence, after completion of the complexation of the tertiary phosphines to give the corresponding borane complexes, the precursor magnesium salt of **3** can be transformed *in situ* into reagent **1** by addition of a small excess of PCl_3. Compared to the previous procedure[23] for recycling **1**, which involved treatment of the reaction mixture containing the magnesium salt of **3** with acidic water followed by the isolation of **3**, this new *in situ* recycling process is very easy and fast.

The procedure reported here is made possible by the chemical stability of tertiary phosphine borane complexes also in the presence of PCl_3, which can be added directly to the reaction mixture. It should be noted that this procedure cannot be applied to secondary phosphine borane complexes due to the high reactivity of the P-H bond with PCl_3, which causes a reduction in the yields.

The reformed reagent **1** is almost quantitatively separated from the reaction mixture by simple crystallization[24] whereas the phosphine-borane complex, present in the mother liquor, is purified by chromatography.



	a	b	c	d	e	f	g	h	i
R^1	*n*-Bu	*n*-Hex	Ph	*n*-Hex	Et	*c*-Hexyl	*i*-Pr	*n*-Hex	R^1-R^2 = -$(CH_2)_5$-
R^2	*n*-Bu	*n*-Hex	Ph	*n*-Hex	Et	Me	Me	*n*-Bu	-
R^3	*n*-Bu	*n*-Hex	Ph	*n*-Bu	*n*-Pent	Me	Me	Et	Et

Scheme 2 Synthesis of tertiary phosphine borane complexes with *in situ* recycling starting reagent **1.**

In the case of the synthesis of symmetrical ($R^1 = R^2 \neq R^3$) (**5d,e**) and asymmetrical ($R^1 \neq R^2 \neq R^3$) (**5h**) tertiary phosphines, two Grignard reagents (R^1MgBr and R^2MgBr) were added in the first step and, after 4-5 min, the third Grignard reagent (R^3MgBr) was added. In this manner it was possible to obtain the symmetrical tertiary phosphine-borane complexes **6d,e** ($R^1{}_2R^3PBH_3$) in high yield (75-80%) and the asymmetrical tertiary phosphine-borane complex **6h** ($R^1R^2R^3PBH_3$) in moderate yield (45%). To further increase the yield of the desired product beyond the statistical limit[22] (Chapter 6), we tried a procedure similar to that previously reported for the synthesis of secondary asymmetrical phosphines,[25] in which the three different mono-Grignard reagents were added in three successive steps with very short reaction times between the steps. We found that the best yields were obtained by a 1 min reaction time between the addition of the first and second Grignard reagents, followed by a 2 min reaction time between the addition of the second and third Grignard reagents. In this way, the

asymmetrical tertiary phosphine-borane complex **6h** was obtained in 55% yield, which is over the statistical limit.

It is important to note that Grignard reagents with a bulky moiety, such as *c*-hexyl and *i*-propyl, must be used in the first attack on reagent **1**. After the addition of the *c*-hexyl or *i*-propyl groups in this first step, the high steric hindrance of these moieties meant that only Grignard reagents with very small steric hindrance, such as methylmagnesium bromide, could be used in the following step. In this manner it was possible to obtain cyclohexyl(dimethyl)phosphine (**5f**) and isopropyl(dimethyl)phosphine (**5g**) and their complexes with BH_3.

To explore the generality of this procedure for synthesizing tertiary phosphine-borane complexes, we also used it to synthesize the borane complex of a cyclic tertiary phosphine, namely the 1-ethylphosphinane borane complex (**6i**), which was obtained in 70% yield.

It is noteworthy that the complexation of secondary phosphines[25] requires addition of acetic before BH_3.THF, in order to break the pentacoordinated intermediate **A**, which is more stable than the hexacoordinated intermediate **A'**, which spontaneously collapses. Acetic acid is also necessary as a proton source to form the P-H bond in secondary phosphines. Obviously, in our complexation procedure of tertiary phosphines, the addition of acetic acid is not necessary because in this case the hexacoordinate intermediate **A'** is the direct precursor of tertiary phosphine.

We chose BH_3.THF as the complexation agent because after complexation of the tertiary phosphines at –8 to –5°C, the excess BH_3 could be easily removed simply by allowing the reaction mixture to stand at room temperature. In fact, the decomposition at room temperature of the BH_3.THF complex produces gaseous BH_3 and THF (the reaction solvent). The use of other complexation agents, as $BH_3.Me_2S$ or $NaBH_4$/acetic acid, must be avoided because the PCl_3 added *in situ* in the recycling step from magnesium salt of compound **3** to starting reagent **1**, could react with these borane sources, that are not easy to remove at room temperature.

The easy obtainement of tertiary phosphines through our procedure can be explained by the intervention of hypervalent phosphorus intermediates (penta- and

hexacoordinated) such **A** and **A'** (see Schemes 8.1). The formation of such intermediates is favored by the "dibenzo-butterfly" structure of **1**, as we reported for the synthesis of cyclic tertiary phosphines.[26]

Previously[22,26] we thought that the hexacoordinated intermediate **A'** required a nucleophilic attack, for example by water or an acid, in order to decompose it. During the present study, however, we observed by ^{31}P NMR spectroscopy that **A'** is unstable and spontaneously collapses to give the corresponding tertiary phosphines, presumably due to its high steric hindrance. Consequently, about 30 minutes after the addition of the final Grignard reagent, BH_3.THF can be added to the reaction mixture to obtain the complexation of the tertiary phosphines formed by the spontaneous decomposition of **A'**. It is important to wait until the reaction between intermediate **A** and the final Grignard reagent, producing the tertiary phosphine, has gone to completion (at least 30 minutes) before adding BH_3.THF. If this reaction has not gone to completion, the BH_3 may complex with the hypercoordinated intermediates, thereby hindering the evolution of the process toward the desired products.

To gain more information about the mechanism of this reaction, we performed the reaction between **1** and *n*-butylmagnesium bromide in an NMR tube, and monitored the progress of the reaction using ^{31}P NMR spectroscopy. After the addition of two equivalents of *n*-butylmagnesium bromide to a THF solution containing one equivalent of **1**, we observed the formation of the pentacoordinated intermediate **A** [δ= -31.6 (d, ^1J(P,P)=169 Hz), -43.3 (d, ^1J(P,P)=169 Hz) ppm] (figure 8.1); this intermediate was stable and could remain in solution in the NMR tube for about 1 h.

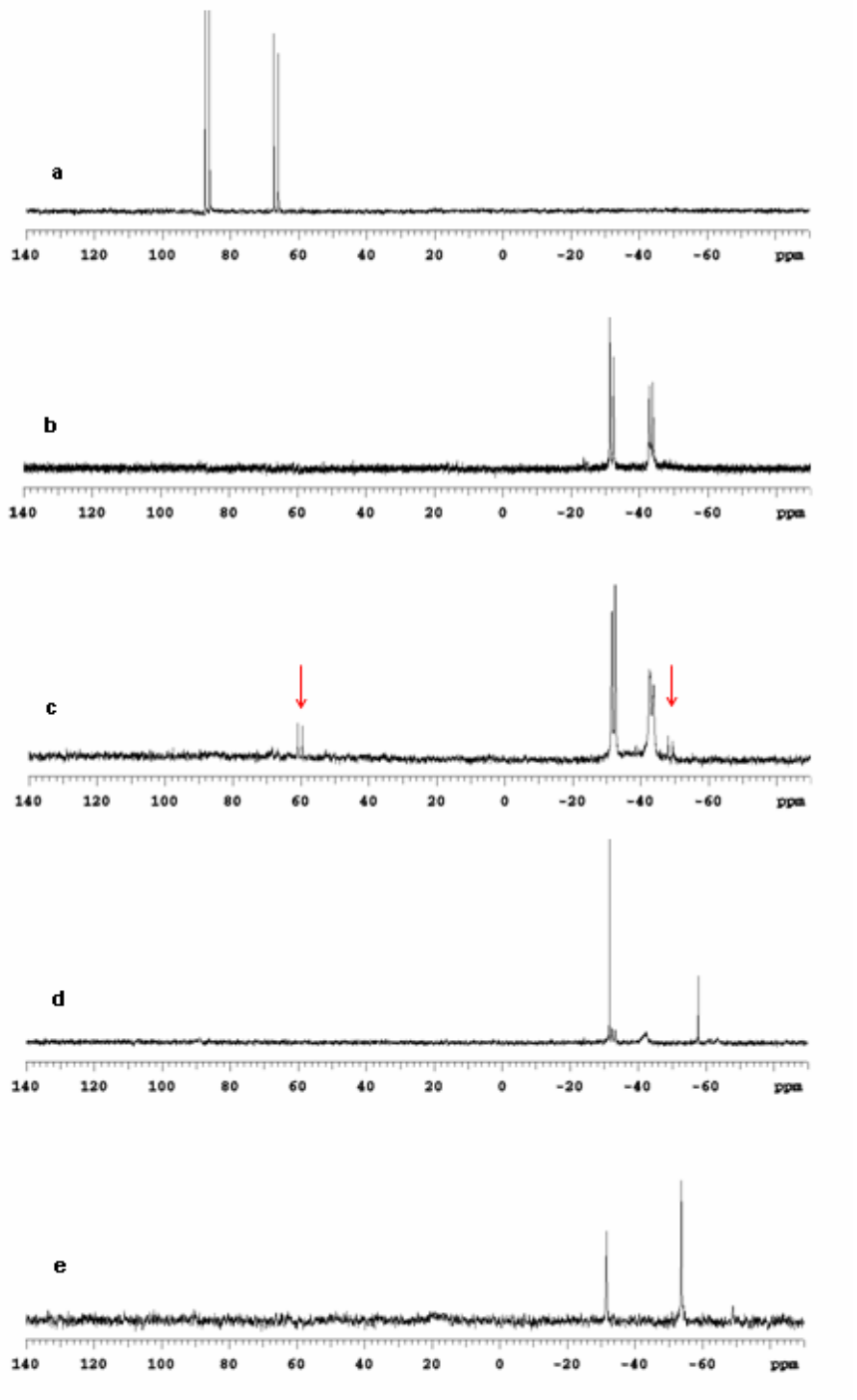


Figure 8.1: ^{31}P NMR spectra of the reaction between benzothiadiphosphole **1** and *n*-butylmagnesium bromide carried out in the NMR tube in THF. **a**.: spectrum of the starting reagent **1**. **b**.: after addition of two equivalent of the Grignard reagent respect to **1** (presence of intermediates **A**). **c**.: after addition of a further equivalent of Grignard reagent (presence of **A** and **A'** (red)). **d**.: spectrum of the reaction mixture after time (presence of **5a** δ= -31.6 ppm, magnesium salt of **3,** δ= -57.7 ppm and traces of **A**). **e**.: after addition of acidic water (formation of tributylphosphine (**5a**), compound **3** δ= -52.0 ppm and traces of dibutylphosphine).

Then, after addition of a small excess of *n*-butylmagnesium bromide, we observed the slow disappearance of the pentacoordinated intermediate signals and the concomitant appearance of two signals corresponding to the tributylphosphine **5a** (δ= -31.6 ppm) and the magnesium salt of **3** (δ= -57.7 ppm), respectively. Concomitant signals at δ= 60.1 (d, ^{1}J(P,P)=225 Hz) and -48.7 (d, ^{1}J(P,P)=225 Hz) ppm were ascribed to the hexacoordinated intermediate **A'**, and were observed only during the initial stage of the reaction because this intermediate readily decomposes to form the tertiary phosphine **5a** and the magnesium salt of **3**. These findings are of great importance because they represent the first observation of the hexacoordinated intermediate **A'**, which until now has only been hypothesized, and hence afford us a complete picture of the reaction mechanism.

8.3 Conclusion

In conclusion, a one-pot method for synthesizing tertiary phosphine borane complexes without previous isolation of free phosphines is reported. The method is general, in that it can be used to obtain acyclic-, cyclic-, symmetrical and asymmetrical phosphine-borane complexes. The most important aspect of this procedure is that the starting reagent **1** is re-formed directly in the reaction mixture and then recovered by simple crystallization, making the full process both highly atom-economic and environmentally friendly. It should be noted that this improved synthetic procedure avoids the long and tedious work-up associated with the use of air- and moisture-sensitive compounds. In addition, the observation of all hypervalent phosphorus intermediates (penta- and hexacoordinated) permitted a clear identification of the mechanism of this reaction.

8.4 Experimental section

***General*:** ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 400, at 100.56 and 161.89 MHz, respectively. Chemical shifts are referenced to internal standard TMS (^{1}H NMR), to solvent (77.0 ppm for ^{13}C NMR) and to external standard 85% H_3PO_4 (^{31}P NMR). *J* values are given in Hz. MS spectra were recorded at an ionisation voltage of 70 eV. Flash chromatography (FC) was performed on silica gel (0.040-0.063 mm). Melting points are uncorrected. IR spectra of compounds **6a-i** showed characteristic bands near 2370 and 2350 (BH_3 as. and symm str.), 1190-1120 and 1080-1040 (BH_3 as. and symm def.), 790-720 (P-C). THF was distilled from sodium benzophenone ketyl and all solvents were purified appropriately before use and degassed immediately prior to use. All Grignard reagents used were commercially available and were titrated immediately prior to use by standard methods.[27] Air and moisture sensitive solutions and reagents were handled in a dried apparatus under a dry argon atmosphere using standard Schlenk-type techniques.

Preparation of acyclic tertiary phosphine boranes 6a-h. **Typical two-step procedure:** To a solution of benzothiadiphosphole (**1**) (0.306 g, 1.0 mmol) in anhydrous THF (10 mL) under a dry argon atmosphere, the first Grignard reagent (R^1MgBr, 2.4 mmol) was added. After 4-5 min., the second Grignard reagent (R^2MgBr, 1.2 mmol) was added. After about 30-40 min, the flask was immersed in a salt-ice bath (-5 to -8°C) and BH_3-THF complex (1.5-2.0 mmol) was added portion-wise (first 1 mmol, then after about 1 h, 0.5 mmol was added each 30 min). The salt-ice bath was removed and the reaction mixture was allowed to stand at room temperature. The resulting solution was stirred under gentle pressure of argon (in order to remove the excess of BH_3), and then PCl_3 was added (1.5 mmol). After 5-10 min, the reaction mixture was treated with acidic (HCl) aqueous solution (0.5 mL) and the solvent was partially removed under vacuum. Extraction with CH_2Cl_2, treatment with anhydrous Na_2SO_4, and concentration under vacuum gave a mixture of phosphine-borane complex and reagent **1**. Compound **1** was recovered by crystallization from CH_2Cl_2/diethyl

ether in 70-80% yield. Flash chromatography (FC) of the concentrated mother liquor gave phosphine-borane complex **6d, e** in 75-80% yield, and a further amount of **1** in 10-20% yield.

The tertiary phosphine-borane complex **6h** was obtained in 45% yield (it was easily separated from the other possible phosphine-borane complexes by FC) following the method described above for preparing **6d,e**, except that in this case two different Grignard reagents, R^1MgBr (1.2 mmol) and R^2MgBr (1.2 mmol), were added to **1** in the first step (instead of 2.4 mmol of the same organometallic), and the third Grignard reagent R^3MgBr (1.2 mmol) was added in the second step.

When $R^1=R^2=R^3$, the three Grignard reagents (3.2 mmol) were simultaneously added to a solution of benzothiadiphosphole (**1**) and the phosphine-borane complexes **6a-c** were obtained in 85-90% yields.

For the synthesis of tertiary phosphines containing bulky moieties, such as dimethyl(*c*-hexyl)phosphine borane (**6f**) and dimethyl(*i*-propyl)phosphine borane (**6g**), the Grignard reagent with the bulky group was added first.

Preparation of unsymmetric tertiary phosphine borane 6h; **three-step procedure:** The first and the second Grignard reagents (R^1MgBr, 1.0 mmol + R^2MgBr, 1.0 mmol) were sequentially added (1 min between the two steps) to a solution of benzothiadiphosphole (**1**) (0.306 g, 1.0 mmol) in anhydrous THF (10 mL) and under a dry argon atmosphere. After 2 min., the third Grignard reagent (R^3MgBr, 1.2 mmol) was added. After about 30-40 min, the flask was immersed in an salt-ice bath (-5 to -8°C) and BH_3.THF complex (1.5-2.0 mmol) was added portion-wise (firstly 1 mmol, then after about 1h, 0.5 mmol each 30 min). The salt-ice bath was removed and the reaction mixture was allowed to stand at room temperature. The resulting solution was stirred under gentle pressure of argon (in order to remove the excess of BH_3), than PCl_3 was added (1.5 mmol). After 5-10 min, the reaction mixture was treated with acidic (HCl) aqueous solution (0.5 ml) and the solvent was partially removed under *vacuum*. Extraction with CH_2Cl_2, treatment with anhydrous Na_2SO_4, and concentration under *vacuum* gave a mixture of phosphine-borane complex and reagent **1**. Compound **1** was recovered by crystallization from CH_2Cl_2 /diethyl ether in 70-80% yield. FC of the mother

liquor gave unsymmetrical phosphine-borane complex **6h** in 55% yield, and futher amount of compound **1** in 10-20% yield.

Preparation of 1-ethylphosphinane borane 6i: The bis-Grignard reagent $BrMg(CH_2)_5MgBr$ (1 mmol) was added to a solution of **1** (0.306 g, 1 mmol) in THF (10 mL), at room temperature. The mixture was stirred for 15 min, then ethylmagnesium bromide (1 mmol) was added. The reaction mixture was stirred for 1 h after that the flask was immersed in an salt-ice bath (-5 to -8°C) and BH_3.THF complex (1.5-2.0 mmol) was added portion-wise (firstly 1 mmol, then after about 1h, 0.5 mmol each 30 min). The salt-ice bath was removed and the reaction mixture was allowed to stand at room temperature. The resulting solution was stirred under gentle pressure of argon (in order to remove the excess of BH_3), than PCl_3 was added (1.5 mmol). After 5-10 min, the reaction mixture was treated with acidic (HCl) aqueous solution (0.5 mL) and the solvent was partially removed under *vacuum*. Extraction with CH_2Cl_2, treatment with anhydrous Na_2SO_4, and concentration under *vacuum* gave a mixture of phosphine-borane complex and reagent **1**. Compound **1** was recovered by crystallization from CH_2Cl_2 /diethyl ether in 70-80% yield.
FC of the mother liquor gave 1-ethylphosphinane borane complex (**6i**) in 70% yield, and further amount of compound **1** in 10-20% yield.

Tributylphosphine borane (6a): colourless oil, R_F = 0.10 (*n*-hexane : ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.62-1.52 (m, 6 H), 1.53-1.35 (m, 12H), 0,93 (t, J = 7.0 Hz, 9 H), 0.38 (br. q, J_{B-H} ~ 82 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 24.9 (d, J = 2.2 Hz), 24.6 (d, J = 12.3 Hz), 24.0 (d, J = 34.9 Hz), 13.8; ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 15.0 (br q, J_{B-P} = 54 Hz); MS (70 eV, EI): *m/z* : 262 [M^+ -BH_3, 66], 183 (100), 152 (20), 108 (81), 77 (29), 51 (77).

Trihexylphosphine borane (**6b**)**:** colourless oil, R_F = 0.25 (*n*-hexane : ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.60-1.43 (m, 10 H), 1.42-1.24 (m, 20 H), 0.89 (t, J = 6.9 Hz, 9 H), 0.50 (br. q, J_{B-H} ~ 100 Hz, 3 H)

ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 31.6, 31.2 (d, *J* = 12.2 Hz), 23.4 (d, *J* = 35.0 Hz), 22.9 (d, *J* = 2.1 Hz), 22.8, 14.3, ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 15.0 (m). MS (70 eV, EI): *m/z* : 286 [M^+ -BH_3, 30], 271 (19), 257 (60), 229 (100), 202 (41), 187 (25), 159 (39), 146 (40), 132 (56), 117 (23), 90 (28), 76 (72), 62 (44).

Triphenylphosphine borane (**6c**): white solid, m.p.: 186-187 °C; R_F = 0.39 (*n*-hexane : ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.61-7.55 (m, 6 H), 7.53-7.48 (m, 3 H), 7.47-7.41 (m, 6H), 1.30 (br. q, J_{B-H} ~ 83 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 133.5 (d, *J* = 10.3 Hz), 131.6 (d, *J* = 2.4 Hz), 129.5 (d, *J* = 58.4 Hz), 129.1 (d, *J* = 10.4 Hz); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 21.2 (m). MS (70 eV, EI): *m/z* : 202 [M^+ -BH_3, 41], 173 (28), 160 (20), 146 (47), 118 (39), 76 (100), 55 (40).

Dihexyl(butyl)phosphine borane (**6d**)**:** colourless oil, R_F = 0.35 (*n*-hexane : ethyl acetate 85/15); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.52-1.45 (m, 6 H), 1.43-1.27 (m, 12 H), 1.26-1.19 (m, 8 H), 0.86 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 6.8 Hz, 6H), 0.31 (br. q, J_{B-H} ~ 82 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 31.6, 31.3 (d, *J* = 12.7 Hz), 25.0 (d, *J* = 1.6 Hz), 24.7 (d, *J* = 12.3 Hz), 23.4 (d, *J* = 34.6 Hz), 23.1 (d, *J* = 34.2 Hz), 22.9 (d, *J* = 1.5 Hz), 22.8, 14.3, 13.9, ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 15.2 (m). MS (70 eV, EI): *m/z* : 258 [M^+ -BH_3, 33], 229 (16), 201 (20), 174 (37), 132 (25), 118 (23), 104 (436), 76 (100), 62 (81), 55 (81).

Diethyl(pentyl)phosphine borane (**6e**)**:** colourless oil, R_F = 0.37 (*n*-hexane : ethyl acetate 90/10); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.66-1.54 (m, 4 H), 1.56-1.43 (m, 4 H), 1.40-1.30 (m, 4 H), 1.12 (dt, *J* = 15.3 Hz, *J* = 7.6 Hz, 6 H), 0.90 (t, *J* = 7.3 Hz, 3 H), 0.37 (br. q, J_{B-H} ~ 94 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 33.4 (d, *J* = 12.0 Hz), 22.1, 22.2, 22.3 (d, *J* = 2.2 Hz), 15.6 (d, *J* = 37.3 Hz), 13.8, 6.7 (d, *J* = 2.9 Hz), ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 19.2 (br. q, J_{B-P} ~ 59 Hz). MS (70 eV, EI): *m/z* : 160 [M^+ -BH_3, 34], 143 (12), 117 (20), 104 (49), 90 (47), 76 (100), 59 (33).

Dimethyl(*c*-hexyl)phosphine borane (6f)[28]**:** yellow grease oil, R_F = 0.29 (*n*-hexane : ethyl acetate 80/20); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.94-1.50 (m's, 7 H), 1.34-1.15 (m, 4 H), 1.23 (d, J = 10.3 Hz, 6 H), 0.42 (br. dq, J_{B-H} ~ 95 Hz, J_{P-H} ~ 15 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 34.8 (d, J = 37.2 Hz), 26.8 (d, J = 10.6 Hz), 26.42, 26.13, 8.93 (d, J = 37.5 Hz); ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 9.6 (br. q, J_{B-P} ~ 62 Hz). MS (70 eV, EI): *m/z* : 144 [M^+ -BH_3, 13], 129 (2), 103 (7), 83 (18), 64 (65), 55 (100).

Dimethyl(*i*-propyl) phosphine borane (6g)[28,29]**:** grease solid, R_F = 0.22 (*n*-hexane : ethyl acetate 80/20); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.88-1.76 (m, 1 H), 1.24 (d, J = 10.0 Hz, 6 H), 1.16 (dd, J = 15.1 Hz, J = 7.2 Hz, 6 H), 0.43 (br. dq, J_{B-H} ~ 95 Hz, J_{P-H} ~ 16 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 24.9 (d, J = 36.4 Hz), 16.7 (d, J = 26.6 Hz), 8.8 (d, J = 36.5 Hz), ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 13.4 (br. q, J_{B-P} ~ 61 Hz). MS (70 eV, EI): *m/z* : 104 [M^+ -BH_3, 80], 89 (15), 74 (32), 62 (100).

Hexyl(butyl)(ethyl) phosphine borane (**6h**)**:** colourless oil, R_F = 0.31 (*n*-hexane : ethyl acetate 90/10); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.68-1.25 (m, 18 H), 1.12 (dt, J = 8.0 Hz, J = 15.6Hz, 3 H), 0.93 (t, J = 7.2 Hz, 3 H), 0.89 (t, J = 7.0 Hz, 3 H), 0.62 (br. q, J_{B-H} ~ 97 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 31.6, 31.3 (d, J = 13.0 Hz), 25.0 (d, J = 2.7 Hz), 24.7 (d, J = 12.8 Hz), 22.9 (d, J = 34.5 Hz), 22.8 (d, J = 2.3 Hz), 22.8, 22.7 (d, J = 34.1 Hz), 16.4 (d, J = 34.6 Hz), 14.3, 13.9, 7.1 (d, J = 2.6 Hz), ^{31}P NMR (161.89 MHz, $CDCl_3$, 25 °C): δ = 17.2 (br. q, J_{B-P} ~ 56 Hz). MS (70 eV, EI): *m/z* : 202 [M^+ -BH_3, 34], 187 (12), 173 (57), 145 (55), 131 (13), 118 (29), 103 (18), 90 (100), 76 (84), 62 (59), 55 (16).

1-ethylphosphinane borane (**6i**)**:** colourless oil, R_F = 0.27 (*n*-hexane : ethyl acetate 80/20); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.97-1.42 (m, 12 H), 1.14 (dt, J = 7.8 Hz, J = 16.1 Hz, 3 H), 0.43 (br. q, J_{B-H} ~ 93 Hz, 3 H) ppm; ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 24.6 (d, J = 5.8 Hz), 21.3 (d, J = 11.0 Hz), 21.1 (d, J = 39.4 Hz), 16.3 (d, J = 35.7 Hz), 6.4 (d, J = 1.69 Hz); ^{31}P NMR (161.89

MHz, $CDCl_3$, 25 °C): δ = 5.6 (br. q, J_{B-P} ~ 63 Hz). MS (70 eV, EI): *m/z* : 160 [M^+ -BH_3, 37], 143 (12), 117 (20), 104 (52), 90 (47), 76 (100), 59 (33).

8.5 References

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Chapter 9

CATALYTIC TRANSPORT SYSTEM OF ELEMENTS: SYNTHESIS OF ARSINE AND STIBINE DERIVATIVES

9.1 Introduction

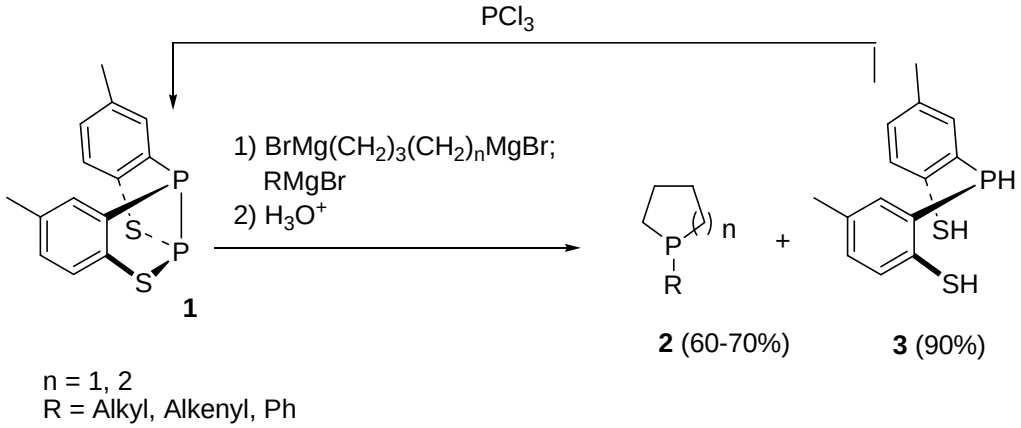
The heterocyclic chemistry of arsenic and antimony has its roots in medicinal chemistry of the early 1900s. With the discovery that an organoarsenic compound provided a cure for syphilis, many new arsenic compounds were prepared and tested for their potential medicinal properties. Interest in organoantimony compounds arose only after the chemotherapeutical properties of organoarsenic were discovered.[1]

Organoarsenic and organoantimony have received much less attention than the analogous organophosphorus compounds in past years. Only recently these compounds have been revaluated for their coordination properties and application as ligands in coordination chemistry.[2] Unfortunately the number of available syntheses is low and often required multi-step reactions.[3]

9.2 Results and discussion

In previous studies it was reported[4] that the formation of cyclic tertiary phosphines such as **2** is achieved in very high yields and in a one-pot reaction by simultaneous addition of a bis-Grignard and a mono-Grignard reagent to the reagent **1a** (Chapter 4). Treatment of the resulting reaction mixture with aqueous acid gave cyclic phosphines **2** and the end product **3**, which is the residue of **1a**.

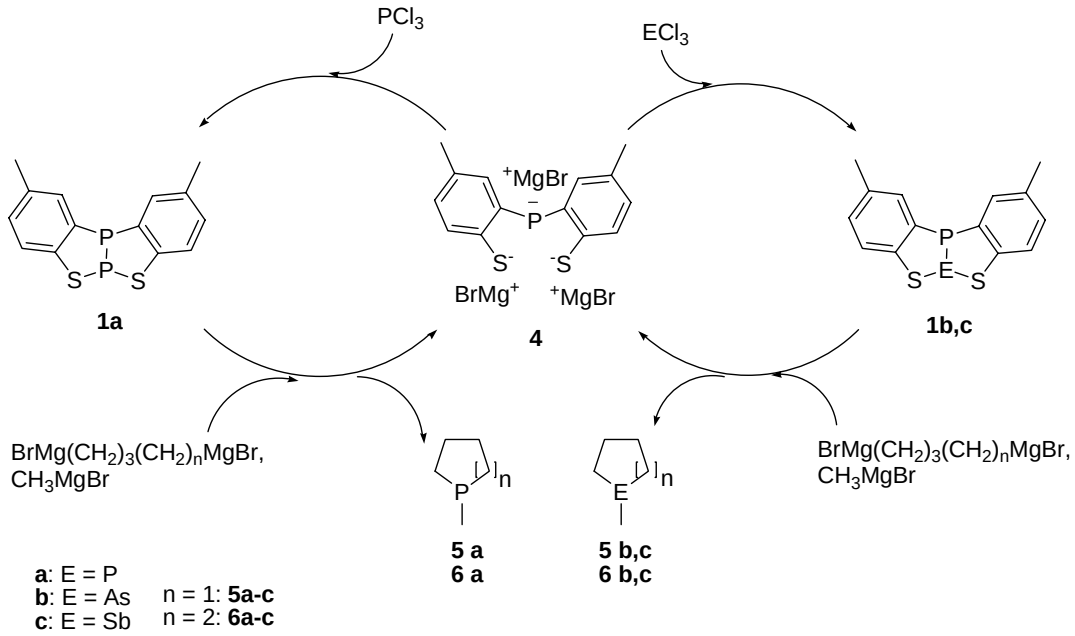
Treatment of **3** with PCl_3 quantitatively and immediately regenerates the starting reagent **1a** (Scheme 9.1).



Scheme 9.1 Synthesis of cyclic tertiary phosphines with recycling of reagent **1**.

Additional studies on the above reported reaction, showed that this reaction could be considered an unusual 'transport' system of elements (Scheme 9.2) formed by two molecules. The first is a benzothiadiphosphole derivative (**1a**), the phosphorus donor reagent that can react with different Grignard reagents. In the case of the simultaneous addition of an equimolar amount of bis- and a mono-Grignard reagent to **1a**, cyclic tertiary phosphines (**5,6a**) are easily obtained.

The second is the by-product **4** that is the residue of the reagent **1a** obtained after expulsion of the phosphorus atom, when tertiary phosphines (**5,6a**) are produced in a 70-80% yield.

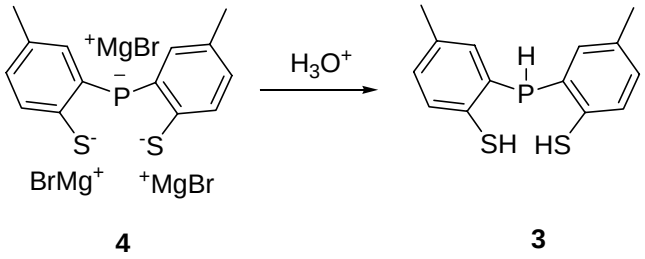


Scheme 9.2 Catalytic cycle using the catalyst **4.**

The compound **4** is the magnesium salt of **3**, that in previous reactions was recovered as the analogous acid derivatives **3** (Scheme 9.3). This compound **4** is easily retransformed into the starting reagent **1** by simple addition of PCl_3. When the addition of PCl_3 is done directly into the reaction mixture, after formation of phosphines, the starting reagent **1a** is directly regenerated without previous separation of the salt **4**. In this way the reagent **1a** can react again with the bis- and mono-Grignard reagents producing phosphines **5,6a** and the by-product **4**. Therefore it is possible to repeat this transport process of the P atom theoretically an infinite number of times.

The only limitation to the number of cycles is due to the quantity of starting material. In fact in every cycle 90% of initial **1a** is obtained, this means that after some cycles the quantity of **1a** is low (in respect to the other components of reaction mixture) and measuring out the amount of Grignard reagents to add is very difficult.

It is important to note that the molecule **4** is the true carrier of the P element and might be considered a “catalyst” both, for its ability to obtain products which are quite difficult to synthesize by other methods, and for the fact that it can be completely recovered at the end of the process.

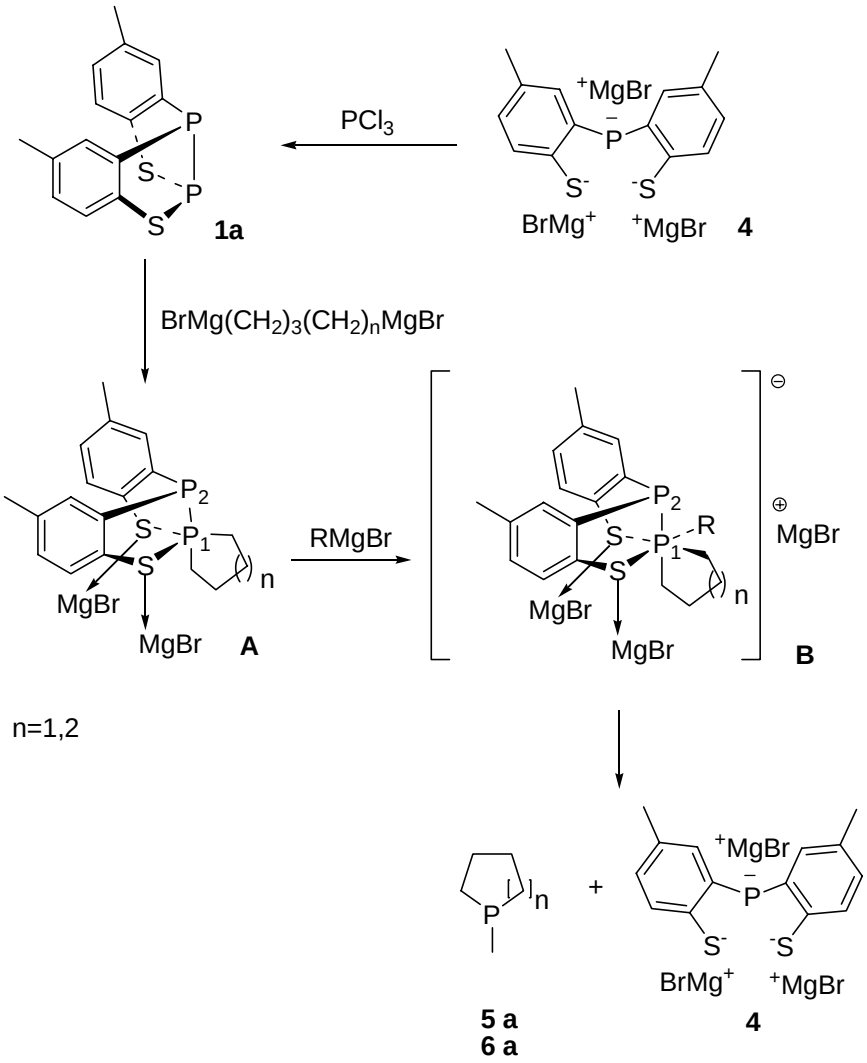


4 **3**

Scheme 9.3 Addition of H_3O^+ to compound **4** produces **3**

These results about phosphorus donation were explained[5] by the intervention of a pentacoordinate phosphorus intermediates such as **A,** which was also isolated and characterized by ^{31}P NMR, and a hexacoordinate species such as **B** very instable (Scheme 9.4) in which the folded "dibenzo-butterfly" moiety of reagent **1a**, greatly favours their formation.[6]

In fact, it is reported that in the hypervalent phosphorus species the presence of rings is a factor of enormous stability, reducing overcrowding.[6] For every cycle in a pentacoordinate species the stabilization is improved by a high factor (about 10^6- 10^8) in respect to the pentacoordinate species without the cycle. If an additional small ring is generated during the reaction, as in the case of bis-Grignard reagent, a further stabilization of these hypervalent intermediates is achieved. As a consequence, the reaction of bis-Grignard reagent that gives a new cycle around the phosphorus atom is highly preferred over the reaction of a mono-Grignard reagent in which there is not this cyclization. For this reason it is possible to carry out the reaction with the simultaneous addition of both bis- and mono-Grignard reagents always obtaining the same product **5,6a** in very high yields as occurs in the case of the subsequent addition of the two reagents.



Scheme 9.4 Mechanism of reaction.

The reaction between benzothiadiphosphole **1**, pentamethylenbis-(magnesium bromide) and methylmagnesium bromide was carried out in the NMR tube in THF and followed by ^{31}P NMR spectroscopy. After addition of one equivalent of bis-Grignard reagent respect to **1** only the presence of intermediates **A** [δ= -43.2 (d, *J*= 190 Hz), -46.7 (d, *J*= 190 Hz) ppm] was observed. Then after addition of a further equivalent of mono-Grignard reagent, the hexacoordinated intermediate **B** was observed in very low concentration (tentatively assigned [δ= 56.9 (d, *J*= 216 Hz), -56.8 (d, *J*= 216 Hz) ppm]). The spectrum of the reaction mixture after time showed presence of **6a** [*δ*= -41.7 ppm] and catalyst **4** [*δ*= -57.7 ppm].

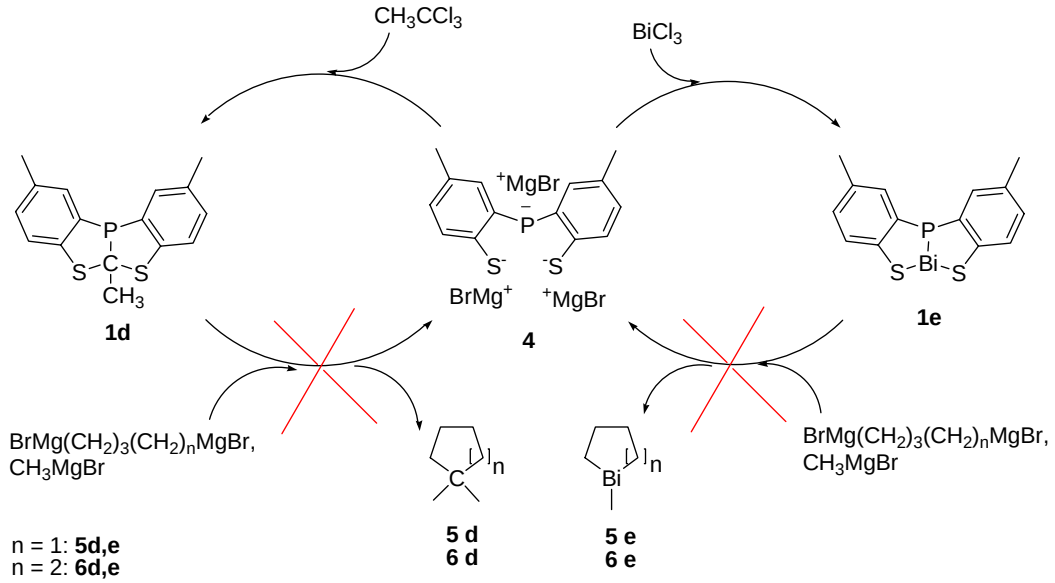
In addition, this process is highly favoured when organomagnesium derivatives are used, while it is highly disfavoured when zinc or lithium derivatives are used. The probable effect of Mg ions can be easily explained by imaging that the coordination of the magnesium atom to a sulfur atom would activate P^1 of

intermediate **A** toward a further nucleophilic attack to give the instable hexacoordinate **B**. A further indication of the importance of the magnesium in this process lies in the fact that when we carried out the reaction between **1a** and phenylzinc bromide, any phosphinic product such as **5,6a** was recovered and the use of analogous lithium reagent gave only ring opened products of **1a**.

These findings, together with the possibility of easily transforming the residue **4** in the starting reagent **1a** by the simple addition of PCl_3 prompted us to use **4** to obtain similar transport processes with other elements in which the formation of hypervalent species is easy as in the case P element. These elements are As and Sb which have analogous atom electron configuration. In fact, by simple treatment of compound **4** with $AsCl_3$ and $SbCl_3$, the arsenic-heterocycle **1b** and the antimonium-heterocycle **1c** were obtained. These heterocyclic compounds **1b,c**, as reported for **1a**, can be used as arsenic and antimonium donor reagents for the synthesis of tertiary cyclic arsine **5,6b** in 70-75% yield and tertiary cyclic stibine **5,6c** in 65-68% yield in a continuous cycle such as that depicted in Scheme 9.2. The reported mechanism in Scheme 9.4 can also be used to explain reaction in which As and Sb are involved and in general other elements which can have stable hypercoordinated species.

When the same process was carried out in order to obtain C or Bi derivative (treating catalyst 4 with CH_3CCl_3 for C and $BiCl_3$ for Bi) we obtained the corresponding intermediate **1d,e** (scheme 9.5) but the subsequent addition of bis- and mono-Grignard reagents did not generate the corresponding cyclic compounds **5d,e** and **6d,e**. This is in accord with the fact that in the case of C the hypervalent species, penta and hexacoordinated, are very unstable or impossible, while in the case of Bi these hypervalent species are predicted to be very stable and substituted by ionic species.

As follows the compound **4** can be compared with a catalyst, because it is used to catalyse different processes that cannot work without it and it is recovered at the end of the reaction. Instead the compounds **1a,b,c** could be seen as activated forms of the catalyst **4**.



Scheme 9.5 Carbon and bismuth heterocyclic derivatives **1d,e**.

9.2.1 Penta and hexacoordinated phosphorus intermediate: a possible explanation of ribozyme and enzyme phosphoryl transfer reactions

The quite unique ability of enzymes to provide an enormous rate of enhancements (10^7-10^{19}–fold) of very important biological transformations is principally due to the high stabilization of high–energy transition states or intermediates along a new reaction coordinate. This very complex reaction is guided probably by multiple interactions at enzyme specific sites with the reactants. Numerous studies reveal that several enzymatic phosphoryl transfer processes are shown to take place via cyclic pentacoordinate phosphorus transition state species.[7] Also phosphoryl transfer reactions as hydrolyses of RNA [7], energy transfer and DNA formation via ATP [8] and many others processes go through the pentacoordinated phosphorus intermediates.[9]

It has also been recently reported that phospho-enzyme intermediates (E-P) in the action of protein tyrosinephosphatase (PTPs, signaling enzymes that control a diverse array of cellular processes) is assumed to be pentacoordinate forming

several cycles around the P atom by interaction with the enzyme site (Figure 9.1).[9,10]

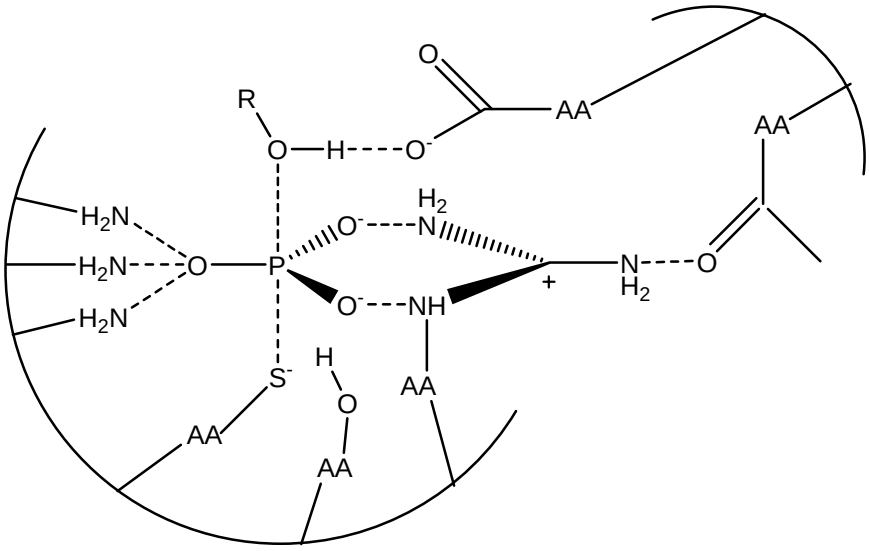


Figure 9.1 Transition state for the phospho-enzyme intermediate formation in PTPs.[9]

In addition, the most simple biological reactions involving ribozymes, RNA molecules, or the so called enzyme-like molecules, proceed through a cyclic phosphorus pentacoordinated intermediate or transition state.[11]

Additionally, as recently reported,[12] the easy formation of hexacoordinated phosphorus specie from a pentacoordinated species may also have an important role in formulating a possible mechanism in the active site of ribozymes or phosphoryl transfer enzymes. The energy associated with the conversion from five to six coordinate phosphorus species is found to be very small. In addition, the hexacoordinate state exhibits greater instability than pentacoordinate analogous species and this permit a easy collapse of the molecula. In fact, in hexacoordinate states the increase in coordination geometry will result in a loosening of all bonds to the phosphorus atom and allow the leaving group or groups to depart more readily than in pentacoordinate analogous species.

However, the full details of the mechanism of action of these enzymes or enzyme-like molecules and the factors which determine this very high rate of enhancement of this process remains to be elucidated.

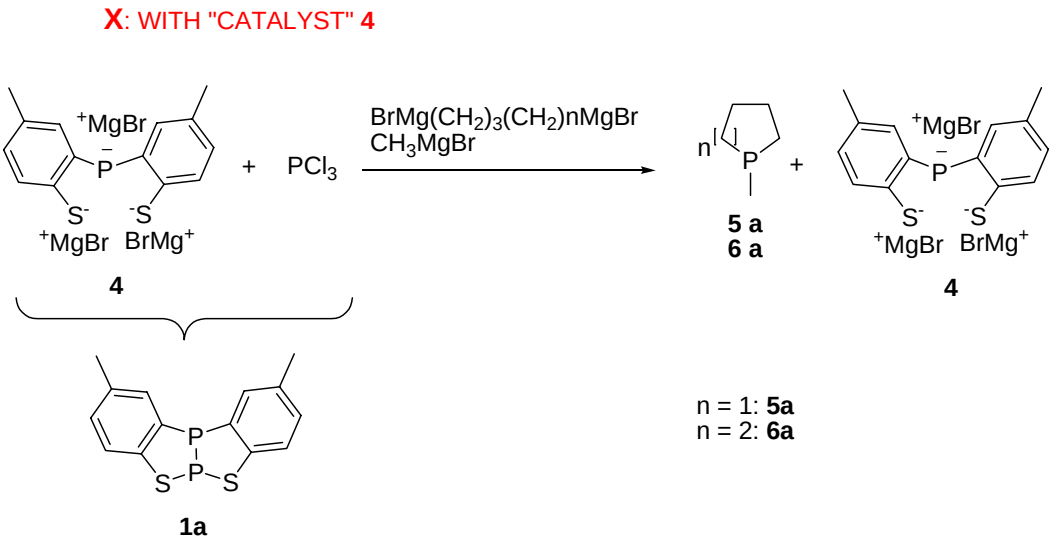
In the previous reaction presented (paragraph 9.2), the formation of cyclic pentacoordinated and hexacoordinated intermediates was demonstrated to be important in achieving a high velocity and selectivity of the processes.

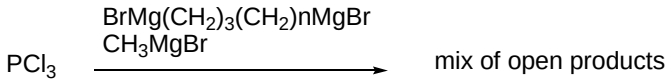
In effect, when an equimolar amount of bis- and mono-Grignard reagents were added simultaneously to the solution containing the "catalyst" **4** and PCl_3, cyclic tertiary phosphines **5,6a** were obtained as prevalent products, in few minutes (3-5 minutes) (case **X**, scheme 9.6). These results are in contrast with the same reaction carried out without "catalyst" **4**. In fact, when bis- and mono-Grignard reagents were simultaneously added to PCl_3 (case **Y**, scheme 9.6) no traces of cyclic tertiary phosphines **5,6a** were found. In the resulting reaction mixture analyzed after 2h of reaction, only a mix of several open products were identified.

These different results are due to the structural characteristics of "activated" form of **4** (**1a**) in respect to PCl_3. In case **X**, the rigid folded structure of **1a** with its bicyclic condensed system favours the formation of hypervalent intermediates (paragraph 9.2).[6] In the first stage, we have formation of a pentacoordinate phosphorus intermediates such as **A**, followed in the second stage, by the formation of a hexacoordinate specie such as **B** (scheme 9.4).

The selectivity of this process is driven by the formation of an additional cycle around the P atom, in the pentacoordinated intermediate **A**, providing an enormous enhancement of the additional reaction rate of a bis-Grignard reagent in respect to the mono-Grignard reagent.

Otherwise, when no cyclic pentacoordinated phosphorus intermediate is involved, in the reaction mechanism, the formation of cyclic phosphorus compounds, such as **5,6a** is not observed as in the reported case **Y**, scheme 9.6. This behaviour is in accord with the observation that only when rings are present in a tetracoordinated phosphorus, or when such rings are easily formed during the reaction, the formation of pentacoordinated intermediate is favoured, gaining both in thermodynamic and kinetic advantage.[13] Consequently, the intervention of cyclic pentacoordinated intermediate allows the easily formation of cyclic phosphorus compounds (case **X**), also when the acyclic corresponding derivatives are generally favoured (case **Y**).





Scheme 9.6 Reaction conducted with catalyst **4** (**X**) and without catalyst **4** (**Y**).

In addition, we found that pentacoordinated intermediate **A** is stable enough to stay in solution (1 hour) without decomposing. Therefore it is necessary to add a nucleophile to obtain the decomposition of intermediate **A**. This is explained with the formation of hexacoordinated intermediate **B** (for addition of a further nucleophile on intermediate **A**) that is unstable[12] and immediately collapses producing the cyclic tertiary phosphines **5,6a** and the starting "catalyst" **4** (scheme 9.4). As follows the resulting process (case **X**) is extremely fast, compared with the no-catalysed process (case **Y**). In fact when the reaction, with the catalyst **4**, was conducted adding simultaneously the bis- and mono-Grignard reagents, the reaction was completed only after few minutes (3-5 min), making it very difficult to individuate (by ^{31}P NMR spectroscopy) the pentacoordinated intermediate **A**.
Using this observation it could be possible to explain the high selectivity and reaction rate of the reaction catalyzed by enzyme or enzyme-like molecules in which cyclic phosphorus pentacoordinated intermediates are involved, but also to determinate the important role of hexacoordinated species.

In addition, the reactions catalyzed by enzyme-like molecules, as well as enzymatic processes often require divalent metal ions such as Mg^{2+} as cofactors.
For example recent structural determination of a crystal obtained in a phosphoryl tranfer process catalyzed by β-phosphoglucomutase (β-PGM) having Mg(II) as cofactor reveals as intermediate a pentacoordinated phosphorus stabilized also by coordination with magnesium ions.[9]
This behavior is in agreement with the role of magnesium ions assumed in our reaction. In fact in our "pattern", the coordination of the magnesium ions to the sulfur atom would activate the pentacoordinated phosphorus, in the intermediate **A**, to receive a nucleophilic attack giving the hexacoordinated intermediate **B**.
Moreover, as previously reported (paragraph 9.2), our "pattern" is applicable to other elements such as arsenic and antimony that have an analogous atom electron configuration of phosphorus. Therefore it could be possible to predict that the biological processes in which pentacoordinated intermediates are involved, can also work with these elements instead of phosphorus. Nevertheless the penta and hexacoordinated species of arsenic and antimony derivatives are more stable than the analogous phosphorus derivative, consequently the reaction is much slower.

9.3 Conclusion

The discovery and isolation of compound **4** permitted a study of a new cyclic catalytic process to obtain cyclic tertiary phosphines . The new catalyst **4** was applied also in the synthesis of tertiary arsine and stibine in good-high yields. Those reactions were explained with the intervention of penta and hexacoordinated intermediates, that were identified by ^{31}P NMR spectroscopy.
In addition the heterocyclic compounds containing carbon and bismuth **1d,e** ("activated" form of catalyst **4**) were synthesized. Nevertheless, due to the impossibility of the carbon atom to form stable hypervalent species and the high tendency of the bismuth atom to form extremely stable hypervalent species, their use in the synthesis of organo-compound derivatives was not possible.

In addition, studying the role of hypervalent intermediate species in the above reactions, it was possible to hypothesize a "pattern" that can be applied in the explanation of the mechanism of ribozyme and enzyme phosphoryl transfer reactions, in which cyclic pentacoordinated intermediates are involved.

9.4 Experimental Section

General. NMR spectra were recorded at 300 (400) and 121.45 (161.9) MHz for ^{1}H and ^{31}P, respectively. Chemical shifts are referenced to solvent THF (^{1}H NMR, 1.8 ppm and ^{13}C NMR, 26.7 ppm), and external standard 85% H_3PO_4 (^{31}P NMR). *J* values are given in Hz. THF was distilled from sodium benzophenone ketyl. All Grignard reagents used, both commercially available and prepared from the corresponding alkyl halide and magnesium turnings, were titrated immediately prior to use by standard methods.[14] Air and moisture sensitive solutions and reagents were performed under dry argon atmosphere using standard Schlenk-type techniques. All solvents were purified appropriately before use and degassed immediately prior to use. Benzothiadiphosphole **1a** was synthesized as decribed (Appendix 1).[15] From reagent **1a** and catalyst **4**, compound **5** is obtained easily, as reported in Appendix 2.[16]

Isolation and characterization of compound 4:

After reaction of reagent **1** with bis- and mono- Grignard reagent (see preparation of compounds **5,6**), and concentration of solution by vacuum pump (1/5 of the starting volume), the resulting suspension was filtered carefully under argon atmosphere. The white salt (**4**) was washed one time with 1-2 ml of anhydrous THF (the compound **4** is almost insoluble in THF, but reacts with traces of water to produce compound **3**). Compound **4** was conserved as suspension in anhydrous THF under argon (in this way it can be preserved for 2-3 days).

White solid; ^{1}H-NMR (400 MHz, THF d_8): δ = 7.42 (br s, 1H), 7.28 (br s, 1H), 7.05 (br s, *J* ~ 6.6 Hz, 1 H), 7.00 (br s, *J* ~ 6.6 Hz, 1 H), 6.54 (d, *J* = 6.8 Hz, 1 H), 6.48 (d, *J* ~ 6.8 Hz, 1 H), 2.20 (s, 3 H), 2.11 (s, 3 H); ^{13}C-NMR (100.56 MHz,

THF d_8): δ = 146.8, 146.1, 143.0 (d, *J* = 28 Hz,), 141.9 (d, *J* = 30 Hz), 135.9 (d, *J* ~ 91 Hz,), 134.1 (d, *J* ~ 91 Hz,), 135.2, 134.6, 133.4, 129.7, 127.1, 126.0, 22.7, 22.6; ^{31}P-NMR (161.9 MHz, THF d_8) δ = -79.4 (m).

Preparation of new heterocycles 1b and 1c:

To a suspension of compound **4** (0.588g, 1.0 mmol) in THF (10 mL) under argon atmosphere, one equivalent of arsenic trichloride or antimony trichloride, in the case of the formation of compound **1b** or **1c,** respectively, was added (particular care must be taken in the manipulation of these reagents because of their toxicity). The solution turned immediately pale yellow (or pale green in the case of the formation of compound **1c**). After 20 min. the solvent was removed giving quantitatively compound **1b** (or **1c**) which were immediately characterized and stored under argon atmosphere.

Compound **1c** has to conserve in diluted solution of THF, because it easily forms a solid precipitate that is insoluble.

When bismuth trichloride was added to **4**, immediately the formation of a red salt **1e** (almost insoluble) was observed.

In the case of addition of CH_3CCl_3 to **4**, the reaction was very slow and the resulting yield in **1d** was very poor. As a consequence, the heterocycle **1d** was not isolated but only identified in the reaction mixture by GC-MS and ^{31}P NMR spectroscopy, with reference to the same compound synthesized via the procedure reported in Appendix 3. Also in the reaction with bis- and mono-Grignard reagents, the compound **1d** was synthesized using the procedure reported in Appendix 3.

2,10-dimethyl[1,3,2]benzothiaphospharsolo[2,3-*b*][1,3,2] benzothiaphospharsole (1b)

^{1}H-NMR (400 MHz, THF d_8): δ = 7.54 (d, *J* = 9.5 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 6.96 (d, *J* = 8.0 Hz, 2 H), 2.28 (s, 6 H); ^{13}C-NMR (100.56 MHz, THF d_8): δ = 145.3, 143.8 (d, *J* = 33 Hz,), 137.0 (d, *J* = 8.9 Hz), 134.8 (d, *J* = 30 Hz,), 132.2, 127.6 (d, *J* = 2.5 Hz,), 22.2; ^{31}P-NMR (161.9 MHz, THF d_8) δ = 78.6 (t, J_{PH} = 8.7

Hz); GC-MS (m/z, %): 350 (M^+, 35), 243 (100), 107 (14); HRMS (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{12}AsPS_2$, 349.9334; found, 349.9332.

2,10-dimethyl[1,3,2]benzothiaphosphastibolo[2,3-*b*][1,3,2] benzothiaphosphastibole (1c)

^{1}H-NMR (400 MHz, THF d_8): δ = 7.54 (d, *J* = 10.3 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 6.84 (d, *J* = 8.0 Hz, 2 H), 2.26 (s, 6 H); ^{13}C-NMR (100.56 MHz, THF d_8): δ = 147.6, 137.6 (d, *J* = 30.6 Hz,), 135.5 (d, *J* = 9.5 Hz), 133.7 (d, *J* = 68.7 Hz,), 131.4, 130.7, 21.9; ^{31}P-NMR (161.9 MHz, THF d_8) δ = 52.7 (br s, line width 410 Hz); GC-MS (m/z, %): 396 (M^+, 23), 243 (100), 153 (6), 121 (12); HRMS (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{12}PS_2Sb$, 395.9156; found, 395.9152.

2,10-dimethyl[1,3,2]benzothiaphosphabismutholo[2,3-*b*][1,3,2] benzothiaphosphabismuthole (1e)

^{1}H-NMR (400 MHz, THF d_8): δ = 7.71 (d, *J* = 14.0 Hz, 2H), 7.25-7.08 (m, 4H), 2.29 (s, 6H). ^{31}P-NMR (161.9 MHz, THF d_8) δ = 35.0 (t, J_{PH} = 14.0 Hz).

Preparation of compounds 5 (or 6) with concomitant recycle of the reagent 1

A solution of bis-Grignard reagent $BrMg(CH_2)_3(CH_2)nMgBr$ (2.0 mmol, n =1, or 2) in THF was added, at room temperature, to a solution of benzothiadiphosphole (**1a**) (2.0 mmol) in anhydrous THF (20 mL) and under an argon atmosphere. The mixture was stirred for 15 min. to complete the phospholane ring formation, or for 90 min. in the case of phosphinane formation. A solution of methylmagnesium bromide (2.0 mmol) in THF was then slowly added dropwise. The reaction was monitored by GC-MS and ^{31}P NMR spectrometry: when the signals of reagent **1a** disappeared, with concomitant appearance of that of cyclic phosphine **5a** (or **6a**), an equivalent amount of PCl_3 was added to the crude reaction mixture and the concomitant formation of starting reagent **1a** was detected. The yield is nearly quantitative, and the cycle can be repeated more times, thus allowing to a continuous increase in the yield of cyclic phosphine. The isolation of the reaction products can be easily obtained by partial removal of the solvent and treatment of the reaction mixture with degassed acidic (HCl) aqueous solution. Extraction with

CH_2Cl_2 gave a mixture of phosphine and of the residue **3**. An easy separation of these compounds was carried out by treating the organic solution with degassed aqueous NaOH; in this way the sodium salt of compound **3** is dissolved in the aqueous solution, whereas the organic one contains the phosphine which was immediately purified by bulb-to-bulb distillation. Compound **3** was recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, purified by distillation and stored under argon.

After addition of equivalent amount of bis-Grignard and mono-Grignard reagent (Scheme 9.2) to a solution containing compound **1b** or **1c**, in a manner similar to that described above, the reaction was monitored by ^{31}P NMR and GC-MS spectrometry and when the formation of the corresponding cyclic arsine or stibine and concomitant disappearance of starting reagent **1** was detected, the reaction mixture containing the intermediate **4** was treated with an equivalent amount of $AsCl_3$ (or $SbCl_3$) and the concomitant formation of starting reagent **1b** (or **1c**) was detected. Also in this case the yield is nearly quantitative, and the cycle can be repeated more times, thus avoiding the step-by-step separation of reaction products which imply a decrease of yield since compounds **1b**, **1c**, and **5** are stable in solution but, once isolated, are air-sensitive and tend to transform into the corresponding oxides.

1-methylphosholane 5a : Colourless oil, bp 122-125°C (760 mmHg), Lit.[17] 122-124°C (760 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$): δ: 2.20-1.20 (m, 8 H), 1.28 (d, 3 H, J = 2.7 Hz); ^{31}P-NMR (121.45 MHz, $CDCl_3$) δ - 38.5. (m); GC-MS (m/z, %): 102 (M^+, 85), 87 (100), 59 (50), 56 (45), 46 (63); HRMS (*m*/*z*): $[M]^+$ calcd for $C_5H_{11}P$, 102.0598; found, 102.0601; analysis (% calcd, % found for $C_5H_{11}P$): C (58.81, 58.79), H (10.86, 10.88).

1-methylarsolane 5b : Colourless oil, bp 66-69°C (15-18 mmHg), Lit.[18] 65-66°C (15 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$): δ: 1.75-1.25 (m, 8 H), 0.83 (s, 3 H); GC-MS (m/z, %): 146 (M^+, 100), 131 (39), 132 (23), 103 (57), 90 (18), 55 (31); HRMS (*m*/*z*): $[M]^+$ calcd for $C_5H_{11}As$, 146.0624; found, 146.0626; analysis (% calcd, % found for $C_5H_{11}As$): C (41.11, 40.94), H (7.59, 7.56).

1-methylstibolane 5c : Colourless oil, bp 57-60°C (15-18 mmHg), Lit.[19] 67-68°C (30 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$): δ: 1.80-1.00 (m, 8 H), 0.52 (s, 3 H); GC-MS (m/z, %): 192 [194] (M^+, 75), 177 (44), 149 (58), 136 (100); HRMS (*m*/*z*): $[M]^+$ calcd for $C_5H_{11}Sb$, 191.9899; found, 191.9897; analysis (% calcd, % found for $C_5H_{11}Sb$): C (31.13, 31.24), H (5.75, 5.77).

1-methylphosphinane 6a : Colourless oil, bp 145-147°C (760 mmHg), Lit.[20] 146°C (760 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$): δ: 1.85-1.00 (m, 10 H), 1.32 (d, 3 H, *J* = 3.0 Hz); ^{31}P-NMR (121.45 MHz, $CDCl_3$) δ - 53.5. (m); GC-MS (m/z, %): 116 (M^+, 100), 101 (45), 73 (50), 70 (25), 46 (63); HRMS (m/z): $[M]^+$ calcd for $C_6H_{13}P$, 116.0755; found, 116.0752; analysis (% calcd, % found for $C_6H_{13}P$): C (62.05, 62.03), H (11.28, 11.31).

1-methylarsinane 6b : Colourless oil, bp 70-75°C (15-18 mmHg), Lit.[21] 153-155°C (760 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$): δ: 1.75-1.25 (m, 10 H), 0.90 (s, 3 H); GC-MS (m/z, %): 160 (M^+, 100), 145 (42), 69 (33); HRMS (m/z): $[M]^+$ calcd for $C_6H_{13}Sb$, 160.0233; found, 160.0230; analysis (% calcd, % found for $C_6H_{13}Sb$): C (45.02, 44.85), H (8.18, 8.15).

1-methylstibinane 6c : Colourless oil, bp 74-79°C (15-18 mmHg), Lit.[19] 77-79°C (19 mmHg); ^{1}H-NMR (300 MHz, $CDCl_3$): δ: 1.80-1.00 (m, 10 H), 0.66 (s, 3 H); GC-MS (m/z, %): 206 [208] (M^+, 56), 191 (39), 163 (36), 136 (100), 121 (42), 69 (82); HRMS (m/z): $[M]^+$ calcd for $C_6H_{13}Sb$, 206.0055; found, 206.0052; analysis (% calcd, % found for $C_6H_{13}Sb$): C (34.83, 34.95), H (6.33, 6.35).

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Chapter 10

GENERAL ONE-POT SYNTHESIS OF 1,2,5-DITHIAPHOSPHEPINES AND THEIR PRECURSOR PHOSPHINETHIOLS

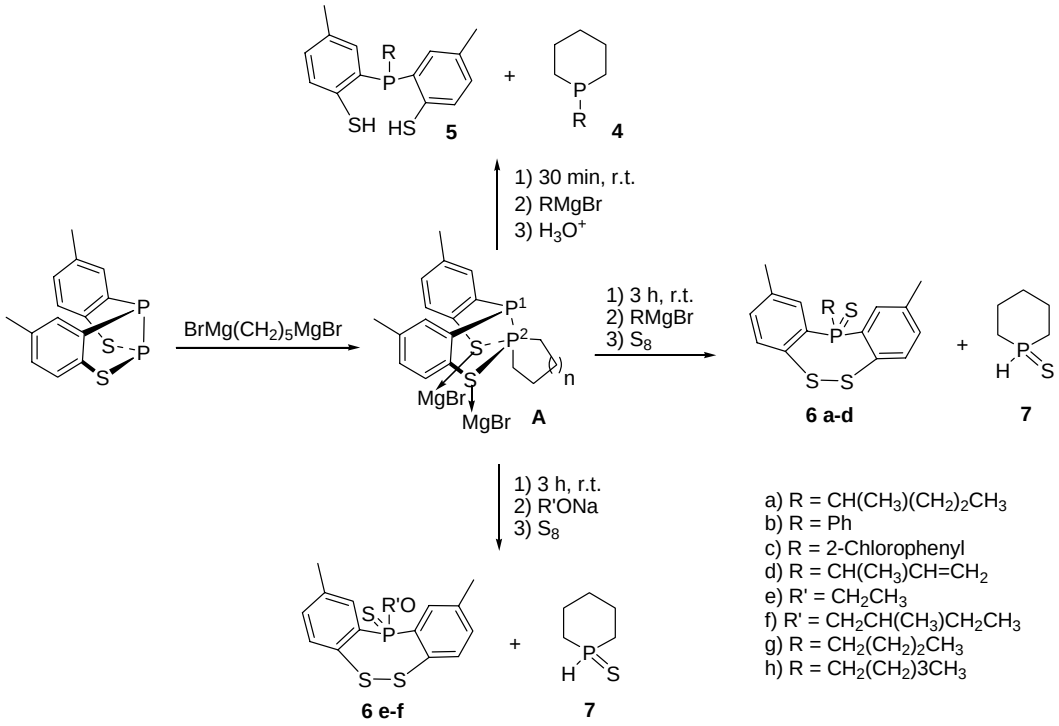
10.1 Introduction

The synthesis of heterocyclic systems containing phosphorus is of considerable current interest, principally because they play a central role in coordination chemistry and homogeneous catalysis.[1] In addition, cyclic systems containing both phosphorus and sulfur should be particularly interesting as bidentate or polydentate ligands but this type of compounds has received much less attention.
Also phoshinethiols are of considerable interest because recently attention has increasingly been paid to the coordination chemistry of polydentate ligands incorporating both thiolate and tertiary phosphine donor sites, as their combination is likely to confer unusual structures and reactivities on their metal complexes.[2]

10.2 Results and discussion

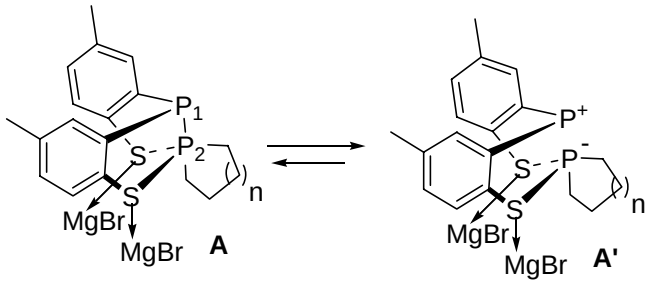
In the past years, in order to find further information about the reaction between compound **1** and bis-Grignard reagents a new type of transformation has been observed which occurs when the intermediate **A** reacts with RMgBr with high steric hindrance of the R group (Scheme 10.1). In these cases (cases **a**, **c**, **d**) there is the prevalent formation[3] of the new heterocyclic compounds **6** (75-80%) with the concomitant formation of cyclic phosphine sulfides **7**. When RMgX is sterically less demanding (case **b**) and the intermediate **A** was allowed to stand for

about 3 hours at room temperature before the reaction with RMgBr there is the formation of both **6** and **4** (tertiary phosphine) in a ratio depending on the reaction time of the first step of the reaction with the formation of intermediate **A**. In fact, when PhMgBr is immediately added to **A, 4** is the only product, while when PhMgBr is added to **A** after about 3 hours at ambient temperature also **6b** is found in 50% yield. This fact indicates that the pathway for formation of **6** is more complex than the one for explaining the formation of **4**.



Scheme 10.1 Synthesis of 1,2,5-Dithiaphosphepines

Presumably the new intermediate might be the isomeric ionic form **A'** (Scheme 10.2) which might explain the inversion of reactivity of the two P atoms. In this manner, the nucleophilic attack of the second reagent can occur on the P^2 atom which is now a very reactive phosphenium ion.[4] After this attack and addition of S_8 and water, the P^1 phosphoranide,[5] an unstable hypervalent species, collapses to form compounds **6** and **7**. The decomposition pathway is still unclear. A possibility is the formation of phosphinethiols such as **9** and **11** and their subsequent oxidation by S_8 , as reported in Scheme 10.3 and explained below.



Scheme 10.2 The isomeric ionic form **A'**

In a similar manner we obtained the 11-alkoxy derivatives **6e**,**f** using alcoholates as nucleophilic reagents.

Compounds **6** represent the first examples of derivatives with a new heterocyclic system, namely 11*H*-dibenzo[c,f][1,2,5] dithiaphosphepine 11-thione derivatives. The only related compound reported in the literature[6] is the 11-phenyl-11-oxo-derivative, obtained by a two-step procedure from lithium 2-lithiobenzenethiolate at -78°C with phenylphosphonic dichloride. Then the 2-mercaptophenyl phosphane oxide obtained is oxidized to the cyclic disulfide by DMSO at 90°C. It is clear that with this reported procedure it is necessary to use, for every cyclic disulfide, various $RPOCl_2$ reagents, which are very difficult to prepare when R is a simple alkyl group. On the other hand, in this case it is possible to obtain compounds **6** bearing several R or OR' groups only using different mono-Grignard reagents or sodium alcoholates in a one-pot two-step procedure carried out at room temperature.

With the purpose to check whether the new method to obtain dibenzo[c,f][1,2,5] dithiaphosphepine 11-thione derivatives can be generalized, the reaction was carried out using mono-Grignard reagents RMgBr having not relevant steric hindrance, namely *n*-butyl- and *n*-pentylmagnesium bromide (cases **g**, **h**). Also in these cases, the corresponding products **6g** and **6h** were obtained**,** thus confirming the possibility to prepare, through this new synthetic approach, a wide number of dithiaphosphepines.

In order to confirm unequivocally the structure of these new series of heterocyclic compounds by X-rays diffraction we repeated the reaction to prepare compound **6b** and were able to obtain suitable crystals for a single crystal X-ray diffraction study.

Compound **6b** (Figure 10.1) contains an unusual seven-membered heterocycle in which a phosphorus and two sulfur atoms forming an S-S bond are present. The molecule is asymmetric and the central heterocycle is rather distorted, presumably in order to optimize the bonding interactions. The S-S distance [2.033(2) Å] is comparable to that found in S_8 [2.059 Å] and the P-S distance [1.936(2) Å] indicates double bond order. In letterature only one other compound showing a similar seven-membered ring has been reported in the literature: $[OPS_3]_2$ where PS_3= $[P(C_6H_4\text{-}2\text{-}S)_3]$[7] (see Figure 10.2). In the latter case the molecule is dimeric and the phosphorus atoms are oxidized.

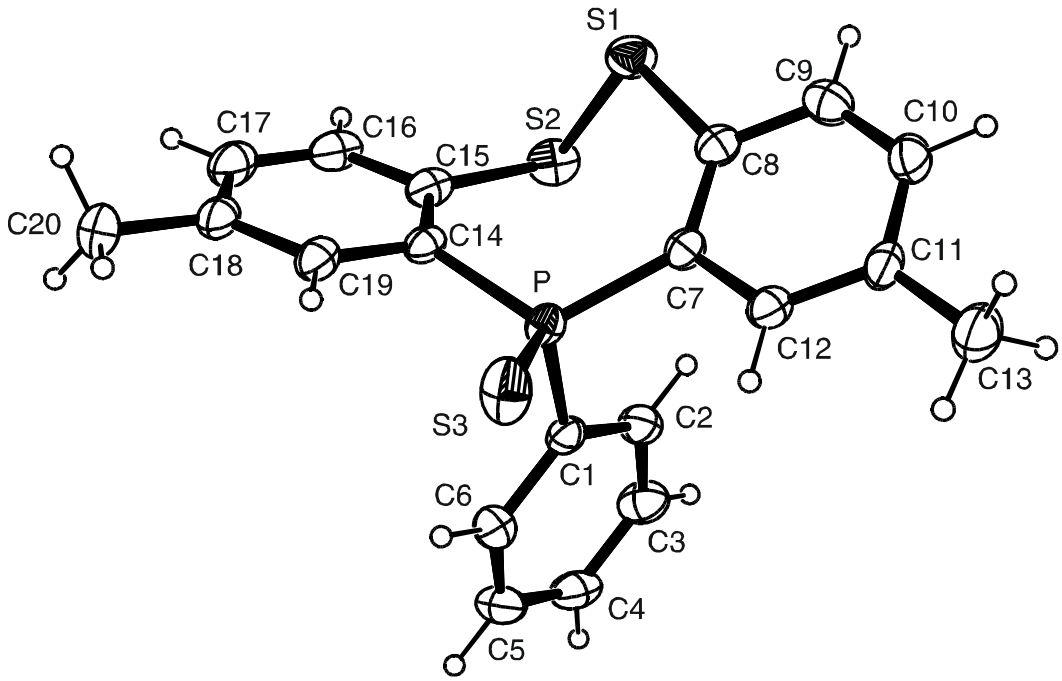


Figure 10.1. ORTEP drawing of **8b.**

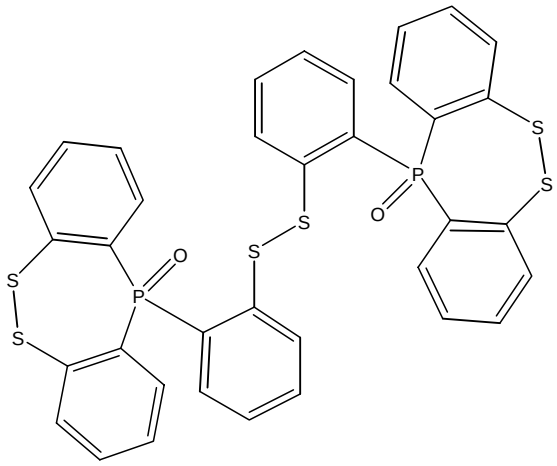
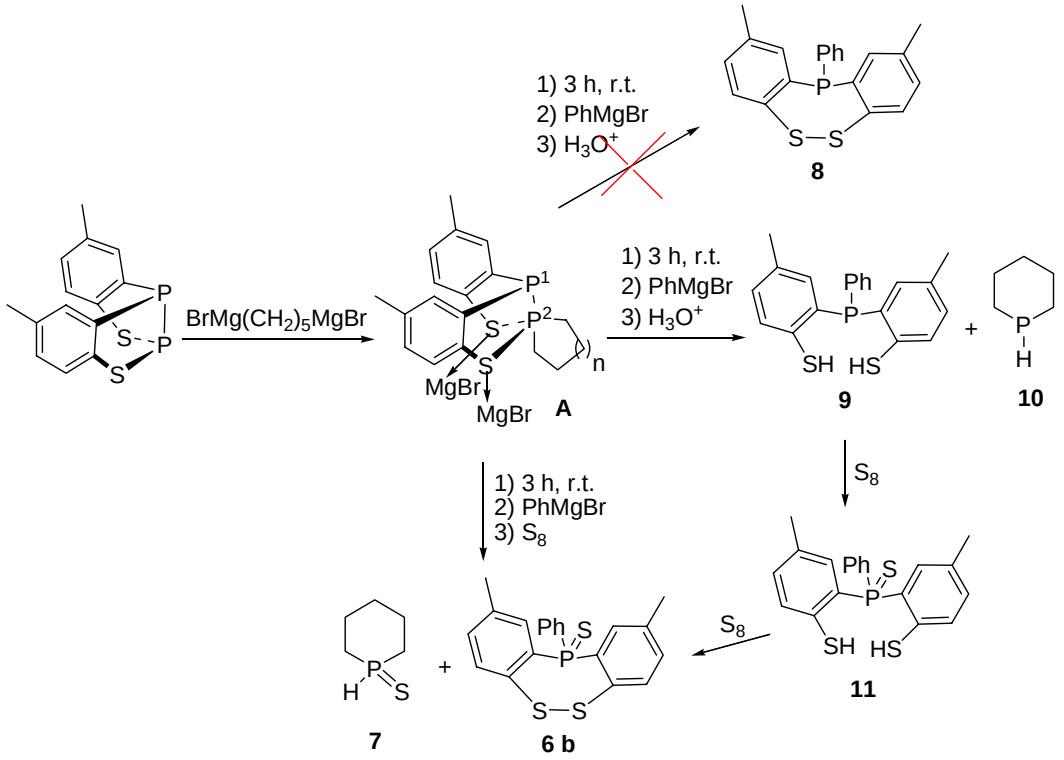


Figure 10.2

With the aim to obtain compound **8**,[8] which is the phosphinic form of **6b**, the reaction has been carried out in a similar manner but without the final treatment with sulfur. The final reaction mixture was treated with aqueous acid to recover also the secondary cyclic phosphane **10**, but surprisingly the phosphanethiol **9** was obtained together with phosphane **10**, which can be completely purified by bulb-to-bulb distillation. Compound **9** was separated from the residue by column chromatography and obtained in 50% yield. Compound **8** was not obtained. Small amounts of **4** (R=Ph) and **5** were also observed.

When compound **9** was treated with a stoichiometric amount of elemental sulfur the corresponding sulfide **11** was obtained quantitatively and completely characterized. Further treatment of **11** with sulphur gave the heterocyclic compound **6b**.[8]



Scheme 10.3 Synthesis of Phosphinethiols.

In addition, compounds **9** and **11** were found**,** when analyzed by GC-MS, showed mainly the presence of compounds **8** and **6b**, respectively, thus revealing a probable oxidation reaction from the thiolic to the disulfidic form in the mass injector.

The importance of this new simple route to phosphinethiols suggests us to try to synthesize also alkyl derivatives, that probably are less stable than the phenyl ones: work is still in progress to this objective.

10.3 Conclusion

In conclusion, with these new transformations of compound **1** it is possible to have a general method to produce the 1,2,5-dithiaphosphepinic system and to obtain also its precursor phosphanethiols **9** and **11**,[8] which are known as pincer ligands. Recently, the chemistry of this kind of S-P-S pincer ligands has attracted increasing interest, augmented by the observation of unusual structures containing

a 'dibenzo-butterfly' moiety, very similar to our intermediate **A**, in the resulting transition metal complexes.[2]

10.4 Exsperimental section

***General**:* ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Gemini 300 (or Inova 400) spectrometer at 300 (or 400) MHz, 75.46 (or 100.56) MHz and 120.75 (or 161.90) MHz, respectively, in $CDCl_3$. Chemical shifts are referenced to internal standard TMS (^{1}H NMR), to solvent (77.0 ppm for ^{13}C NMR), and to external standard 85% H_3PO_4 (^{31}P NMR). *J* values are given in Hz. Multiplicities were obtained from DEPT experiments (the symbols used are as follows: (+) for CH and CH_3, (-) for CH_2) I.R. spectra were recorded on a Perkin-Elmer spectrometer mod. 1600 FT-IR. MS spectra were recorded at an ionisation voltage of 70 eV on a VG 7070 E spectrometer. GC-MS analyses were performed on a HP-5890 gas chromatograph equipped with a methyl silicone capillary column and an HP-5970 mass detector. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254}. Melting points were measured with a Büchi apparatus and are uncorrected. THF was distilled from sodium benzophenone ketyl. All Grignard reagents used, both commercially available and prepared from the corresponding alkyl halide and magnesium turnings, were titrated immediately prior to use by standard methods.[9]

Typical procedure for the synthesis of compounds 6: A solution of $BrMg(CH_2)_5MgBr$ (1.0 mmol) in THF was added dropwise under dry nitrogen atmosphere to a solution of **1** (1.0 mmol) in THF (15-25 mL) at room temperature. The mixture was stirred for 30 min and allowed to stand for an additional 150 min, always at room temperature. A solution of mono-Grignard reagent (1.1 mmol) (or alcoholate, 2.0 mmol) was then added. The reaction mixture was allowed to stand for 25 h at room temperature then treated with elemental sulfur (2.0 mmol) for 60 min., quenched with water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous sodium sulfate and concentrated 'in vacuo'. Compounds **6** were isolated by FC on a silica gel column. According to

spectral data their purity is higher than 98%. Characterization data for compounds **6a,c,d,e,f** were reported previously.[3]

2,9-Dimethyl-11-(butyl)-11H-11λ^5-dibenzo[c,f][1,2,5]dithiaphosphepine-11-thione (**6g**):

greasy solid, 35 % yield, R_f = 0.44 (petroleum light : dichloromethane 2 : 1); δ_H (300 MHz, $CDCl_3$): 8.74 (dd, 2H, J_{P-H} = 17.0 Hz, J_{H-H}= 2.2 Hz), 7.36 (dd, 2H, *J* = 7.5 Hz, *J* = 4.4 Hz), 7.26-7.16 (m, 2H), 2.85-2.70 (m, 2H), 2.45 (s, 6H, CH_3), 2.40-1.40 (m, 4H), 0.90-0.70 (m, 3 H); δ_C (75.56 MHz, $CDCl_3$): 139.8 (d, *J* = 12.2 Hz), 139.3 (d, *J* = 12.4 Hz), 138.2 (d, *J* = 5.8 Hz), 133.7 (d, *J* = 75.6 Hz), 132.4 (d, *J* = 2.4 Hz), 131.3 (d, *J* = 8.9 Hz), 40.1 (d, *J* = 56.0 Hz), 24.2 (d, *J* = 3.4 Hz,), 23.4 (d, *J* = 18.1 Hz), 21.3, 13.6; δ_P (121.47 MHz, $CDCl_3$): 53.7; MS (m/z, %): 364 (M^+, 25), 331 (25), 308 (30), 275 (100), 243 (50), 211 (18), 185 (21); IR, ν (cm^{-1}): 617, 728, 1111, 1450, 1583; HRMS calcd. For $C_{18}H_{21}PS_3$: 364.0543, found: 364.0541.

2,9-Dimethyl-11-(pentyl)-11H-11λ^5-dibenzo[c,f][1,2,5]dithiaphosphepine-11-thione (**6h**):

greasy solid, 45 % yield, R_f = 0.44 (petroleum light : dichloromethane 2 : 1); δ_H (300 MHz, $CDCl_3$): 8.74 (dd, 2H, J_{P-H} = 16.3 Hz, J_{H-H}= 1.6 Hz), 7.37 (dd, 2H, *J* = 7.8 Hz, *J* = 4.7 Hz), 7.25-7.16 (m, 2H), 2.80-2.62 (m, 2H), 2.45 (s, 6H, CH_3), 1.70-1.00 (m, 4H), 0.98-0.88 (m, 2H), 0.83-0.74 (m, 3H); δ_C (75.56 MHz, $CDCl_3$): 139.8 (d, *J* = 12.2 Hz), 139.3 (d, *J* = 12.2 Hz), 138.2 (d, *J* = 5.4 Hz), 133.8 (d, *J* = 75.7 Hz), 132.4 (d, *J* = 3.2 Hz), 131.4 (d, *J* = 9.1 Hz), 40.2 (d, *J* = 55.6 Hz), 32.4 (d, *J* = 17.8 Hz), 22.1, 22.0 (d, *J* = 3.6 Hz), 21.4, 13.9; δ_P (121.47 MHz, $CDCl_3$): 53.6; MS (m/z, %): 378 (M^+, 24), 345 (30), 308 (32), 275 (100), 243 (31), 211 (16), 185 (25); IR, ν (cm^{-1}): 613, 717, 1117, 1456, 1583; HRMS calcd. For $C_{19}H_{23}PS_3$: 378.0700, found: 378.0698.

Physical and crystallographic data of 11-(phenyl)-2,9-dimethyl-11*H*-11λ^5-dibenzo[c,f][1,2,5]dithiaphosphepine-11-thione (**6b**):

The reaction was carried out following the typical procedure described above. Compound **6b** was obtained in 50% yield, m. p.: 162-164 °C (from dichloromethane) R_f = 0.45 (petroleum light : dichloromethane 2 : 1); δ_H (300 MHz, $CDCl_3$): 8.58 (dm, 2H, $^3J_{P\text{-}H}$ = 16.6 Hz), 7.42-7.20 (m, 9H), 2.43 (s, 6H, CH_3); δ_C (75.56 MHz, $CDCl_3$): 139.8 (d, *J* = 70.1 Hz), 139.5 (d, *J* = 12.8 Hz), 139.1 (d, *J* = 13.1 Hz), 139.0 (d, *J* = 7.4 Hz), 133.7 (d, *J* = 83.0 Hz), 132.8 (d, *J* = 2.9 Hz), 131.3 (d, *J* = 8.9 Hz), 130.7 (d, *J* = 3.3 Hz), 130.3 (d, *J* = 11.3 Hz), 128.3 (d, *J* = 13.3 Hz), 21.3; δ_P (121.47 MHz, $CDCl_3$): 49.0; MS (m/z, %): 384 (M^+, 59), 352 (14), 320 (74), 275 (70), 243 (100), 211 (51), 185 (62); IR, ν (cm^{-1}): 488 (S-S), 690 and 745 (P=S), 1100 (PC), 1583; HRMS calcd. for $C_{20}H_{17}PS_3$: 384.0230, found: 384.0221.

Crystal structure of **6b**: $C_{20}H_{17}PS_3$, F_w = 384.49, monoclinic, space group *C*c, *a* = 9.351(2), *b* = 16.050(3), *c* = 12.474(3) Å, β = 102.93(3)°, *V* = 1824.5(6) Å^3, *Z* = 4, *D* = 1.400 Mg/m^3, μ(Mo-K_α)= 0.493 mm^{-1}, R_1 = 0.0348, [$I > 2\sigma(I)$], absolute structure parameter = 0.05(11), R_w = 0.0911 (all data), GOF = 1.002.

Synthesis of compounds 9 and 11: A solution of $BrMg(CH_2)_5MgBr$ (1.0 mmol) in THF was added dropwise under a dry nitrogen atmosphere to a solution of **1** (1.0 mmol) in THF (15-25 mL) at room temperature. The mixture was stirred for 30 min and allowed to stand for an additional 150 min at room temperature. A solution of phenylmagnesium bromide (1.1 mmol) was then added. The reaction mixture was allowed to stand for 25 h at room temperature then treated with aqueous acid and extracted with CH_2Cl_2. The organic layer was dried over anhydrous sodium sulfate and concentrated ‘in vacuo’. Compound **9** was isolated by FC on a silica gel column (eluent: petroleum light: dichloromethane 2 : 1). It contains small amounts (about 3%) of its oxide **12**, probably formed during the work-up and/or the chromatographic purification process. The oxide **12** was characterized only by ^{1}H, ^{31}P NMR and MS spectroscopy as reported below.

Treatment of a solution of **9** in dichloromethane with an equimolar amount of elemental sulfur gave quantitatively the corresponding sulphide **11**, which was

isolated and fully characterized. Further addition of sulfur to this solution gave formation of compound **6b**. Also when the solution containing pure **9** was treated with a large excess of elemental sulfur, the reaction, monitored by ^{1}H NMR analysis, showed the presence of both **11** and **6b**, with gradual decreasing of **11** and the parallel increasing of **6b** until the presence of the latter alone.

4-Methyl-2-[(5-methyl-2-sulfanylphenyl)(phenyl)phosphino]benzenethiol (**9**): 50% yield, R_f = 0.10 (petroleum light : dichloromethane 1 : 2); δ_H (400 MHz, $CDCl_3$): 7.42-7.34 (m, 3H), 7.32-7.24 (m, 4H), 7.08-7.03 (m, 2H), 6.61-6.57 (m, 2H), 3.94 (d, 2H, *J* = 1.3 Hz, disappears after addition of D_2O), 2.17 (s, 6H); δ_C (100.56 MHz, $CDCl_3$) (selected data): 136.0, 134.7 (d, *J* = 6.5 Hz), 134.4, 134.2 (d, *J* = 20.2 Hz), 130.9 (d, *J* = 3.2 Hz), 130.5, 129.2, 128.8 (d, *J* = 7.3 Hz), 21.1; δ_P (161.90 MHz, $CDCl_3$): -18.3; MS (m/z, %): 353 (M^+-1, 2), 352 (9), 320 (6), 243 (100), 211 (17); IR, ν (cm^{-1}): 696, 746, 807, 1038, 1111, 1263, 1434, 1453, 2487, 2547; HRMS calcd. for $C_{20}H_{19}PS_2$: 354.0666, found: 354.0662.

4-Methyl-2-[(5-methyl-2-sulfanylphenyl)(phenyl)phosphorothioyl]benzene thiol (11): m. p.: 169-171 °C (from dichloromethane), quantitative yield from **11b**, R_f = 0.30 (petroleum light : dichloromethane 1 : 2); δ_H (400 MHz, $CDCl_3$): 7.80 (dd, 2H, *J* = 13.7 Hz, *J* = 7.1 Hz), 7.64-7.44 (m, 3H), 7.38-7.28 (m, 2H), 7.22-7.14 (m, 2H), 6.95 (dd, 2H, *J* = 15.2 Hz, *J* = 1.3 Hz), 6.13 (s, 2H, disappears after addition of D_2O), 2.18 (s, 6H); δ_C (100.56 MHz, $CDCl_3$): 135.3 (d, *J* = 7.3 Hz), 135.0 (d, *J* = 11.3 Hz), 134.6 (d, *J* = 11.3 Hz), 133.2 (d, *J* = 10.5 Hz), 133.0 (d, *J* = 9.7 Hz), 132.8 (d, *J* = 2.4 Hz), 132.1 (d, *J* = 3.2 Hz), 129.4 (d, *J* = 86.6 Hz), 128.6 (d, *J* = 13.0 Hz), 127.4 (d, *J* = 89.1 Hz), 21.0; δ_P (161.90 MHz, $CDCl_3$): 44.5; MS (m/z, %): 386 (M^+, 12), 385 (20), 384 (80), 352 (10), 320 (100), 275 (97), 243 (86), 185 (85); IR, ν (cm^{-1}): 692, 715, 730, 814, 905, 1118, 1267, 1380, 1434, 1464, 2373; HRMS calcd. for $C_{20}H_{19}PS_3$: 386.0387, found: 386.0384.

4-Methyl-2-[(5-methyl-2-sulfanylphenyl)(phenyl)phosphoryl]benzenethiol (12): δ_H (400 MHz, $CDCl_3$): 7.70-7.05 (m, 9H), 6.79 (d, 2H, *J* = 14.3 Hz), 5.95 (s,

2H, disappears after addition of D_2O), 2.19 (s, 6H); δ_P (161.90 MHz, $CDCl_3$): 39.0; MS (m/z, %): 370 (M^+, 11), 369 (25), 368 (100), 335 (13), 259 (63), 244 (18), 211 (22).

10.4 References

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Chapter 11

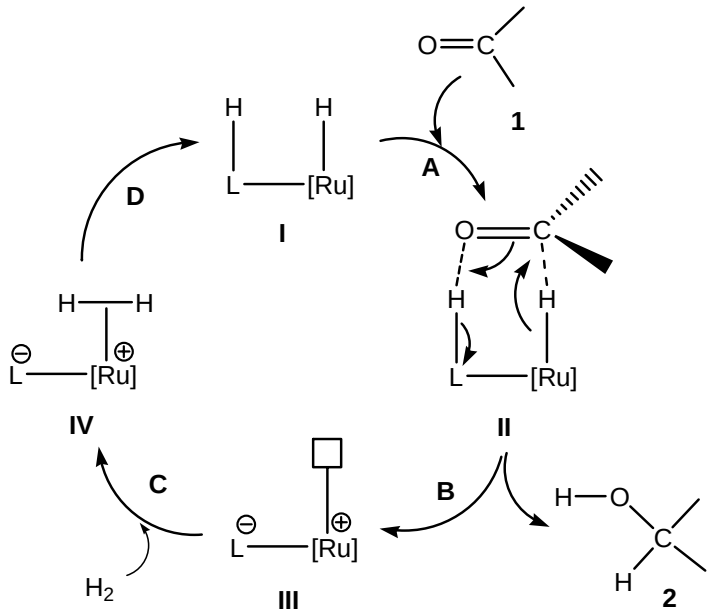
SYNTHESIS AND EVALUATION OF A NEW SERIES OF LIGANDS DERIVING FROM MeOXuPHOS IN THE ASYMMETRIC HYDROGENATION OF KETONES

11.1 Introduction

A large number of optically active compounds contain a hydrogen atom at the stereogenic centre. This hydrogen atom can be introduced into appropriate unsaturated prochiral precursors by asymmetric hydroboration,[1] hydrosilylation[2] and transfer hydrogenation using organic hydrogen donors[3] as well as hydrogenation using hydrogen gas.[4]

Catalytic asymmetric hydrogenation of polar bonds is a key reaction in the fine chemical industry. Ruthenium complexes exhibit good reactivity and selectivity, especially in the catalytic reduction of polar bonds and with amino ligands these are much more active than other metal complexes for the H_2-hydrogenation of ketones, particularly those devoid of heteroatom functionality, this high activity often comes with high enantioselectivity.[5]

The most recent mechanism of polar bond reduction by ruthenium complexes, was proposed by Noyori,[4, 6] the "metal-ligand bifunctional catalysis" operates by hydride transfer to the substrate in the outer coordination sphere of the Ru complex. In these cases the ancillary ligand provides a proton that can be transferred when the hydride is transferred.[7]



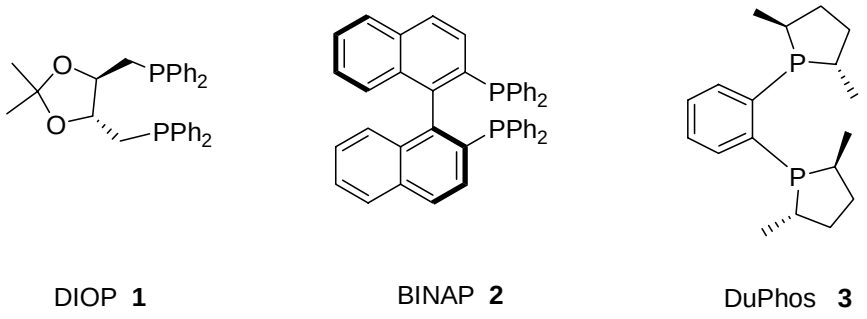
Scheme 11.1: General scheme for H_2-hydrogenation of polar bonds by the "metal-ligand bifunctional catalysis" mechanism.

This mechanism can be subdivided in four stages (Scheme 11.1). In step **A** the substrate **1** coordinates by forming an interaction between the oxygen and carbon atoms and the proton and the hydride of the complex **I**. This interaction produces a six membered-cyclic intermediate **II** from which the simultaneous transfer of the hydride and the proton (step **B**) produced the substrate **2** and the ruthenium complex with a vacant coordination site, **III**. Hydrogen gas can then coordinate at this open site (step **C**) producing intermediate **IV**. The coordinated H_2 molecule to the complex heterolytically breaks (step **D**) to generate the starting hydride complex **I**.[7]

The hydride affinities of the polar bonds are low, consequently the ruthenium complex must be sufficiently hydridic to promote the hydride transfer reaction. For this reason usually, they contain ancillary ligands that stabilize the positive charge that is left on the metal after the hydride transfer step (Scheme 11.1, **III**). These ligands could include strongly basic hydride, phosphine, and cyclopentadienide ligands with electropositive donor elements.[7]

11.1.1 Monodentate Phosphorus Ligands in Catalysis for Asymmetric Hydrogenation

Chiral monophosphines were the first ligands successfully applied in the pioneering studies on enantioselective hydrogenation.[8] This area has been dominated by chiral bidentate ligands for more than three decades.[9] As a common view, bidentate ligands were considered a condition necessary to achieve high stereoselectivity in catalytic asymmetric hydrogenation reactions. An enormous number of chiral bidentate ligands have been developed for enantioselective hydrogenation, but only a limited number including DIOP **1**, BINAP **2** and DuPhos **3** and its analogues (Figure 11.1) are commercially available, and even fewer are used in industrial processes.[10]



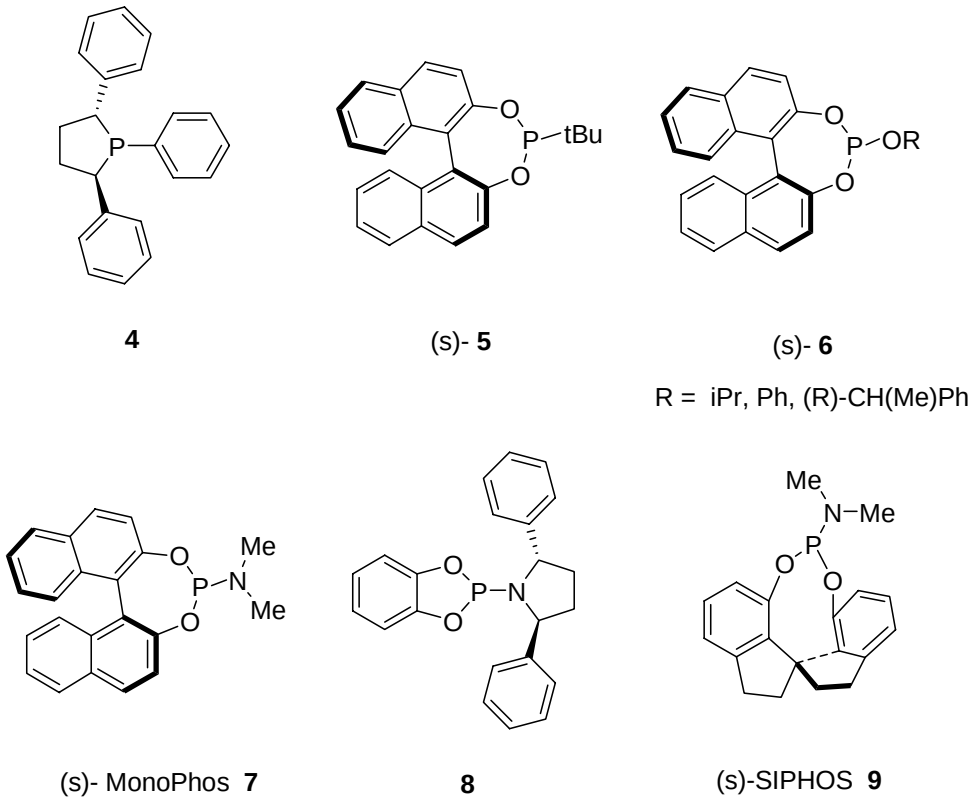
DIOP **1** BINAP **2** DuPhos **3**

Figure 11.1: Biphosphorus ligands

One of the major disadvantages of bidentate phosphorus ligands, especially phosphines, is their often inconvenient synthesis. This, in turn, makes them relatively expensive. In addition, it is very difficult to establish a library of bidentate ligands for fine-tuning to a specific target molecule.[11]

Recent progresses have shown that the use of a bidentate ligand is not essential to obtain good stereodiscrimination. Chiral monodentate phosphorus ligands have been proven to be able to induce excellent enantioselectivity in rhodium-catalyzed asymmetric hydrogenation reactions, comparable to or better than those reached by bidentate ligands.[12] Thus monodentate phosphines,[13] phosphonites,[14] phosphites,[15]

and phosphoramidites[16,17,18] have been successfully applied in rhodium-catalyzed asymmetric hydrogenation (Figure 11.2).



4 (s)- **5** (s)- **6**

R = iPr, Ph, (R)-CH(Me)Ph

(s)- MonoPhos **7** **8** (s)-SIPHOS **9**

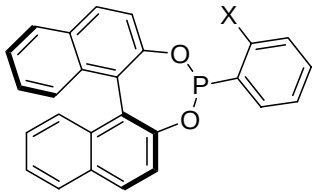
Figure 11.2: Monophosphorus ligands.

Fiaud reported monophosphine ligand **4** which was examined as a chiral ligand in the hydrogenation of N-acetyl dehydrophenylalanine methyl ester with complete conversion and 82% ee's.[13] Orpen and Pringle have developed a series of biarylphosphonite ligands such as **5** which achieve up to 92% ee's for the asymmetric hydrogenation of methyl (2-acetamide)acrylate.[12] Reetz reported a series of monophosphite ligands such as **6** which have provided up to 99% ee's for the asymmetric hydrogenation of dimethyl itaconate.[15] Feringa developed a phosphoramidite ligand known as MonoPhos **7**, which showed excellent reactivities and enantioselectivities for the hydrogenation of dehydroamino acid derivatives and

arylenamides.[14] Recently he has also reported a new class of achiral catechol- based phosphoramidites **8** that were applied to obtain up to 99% ee in the hydrogenation of the same classes of substrates reported above.[15] Finally, Zhou reported a monophosphoramidite ligand SIPHOS **9** on the basis of a chiral 1,1'-spirobiindane-7,7'-diol. Up to 99% ee's have been obtained in asymmetric hydrogenation of α-dehydroamino acids, aryllenamides, and itaconares.[18]

11.1.2 A New family of Monodentate Phosphorus Ligand: XuPHOS

The XuPHOS ligands represent a new series of monodentate phosphorus BINOL-derived ligands containing a substituted aromatic ring attached to the phosphorus atom (Figure 11.3).



X= H, Ph, OMe, Br, Me

XuPHOS

Figure 11.3: XuPHOS ligands.

During the preliminary studies on this new series of monodentate phosphorus ligands, the ortho-bromo and ortho-methoxy ligands gave good results in the asymmetric reduction of ketones by hydrogenation.[19]

Consequently, the BrXuPHOS ligand was chosen to extend the investigations to further substrates. The best results were obtained for the reduction of methyl ketone containing an ortho-substituted aromatic ring, where it was possible to obtain the alcohol derivative with 99% e.e.[20] Moreover It was found that the best e.e. results were obtained when both phosphorus and diamine ligands in the complex had the

same combination of configurations. In fact, the (*S*,*S*,*SS*) complex gave a 90% (R) e.e. in the reduction of acetophenone, while the corresponding complex of (S,S,RR) configuration gave only 33% (S) e.e. [19]

The structural analogy of this complex with the Noyori complex suggests that the reduction mechanism for the XuPHOS-Ru-DPEN complex involves "metal-ligand bifunctional catalysis". Therefore the oxygen atom of the C=O interacts with an axial hydrogen of the amino group belonging to DPEN, while the carbon atom of the C=O interacts with the hydride on the ruthenium atom. The high stereocontrol of the catalyst can be explained with the two BINOL groups attached on the phosphorus atoms causing a sterical hindrance, consequently the smallest group on the substrate, is favoured to occupy the region of space between the binaphtyl groups (Figure 11.4, B).[20]

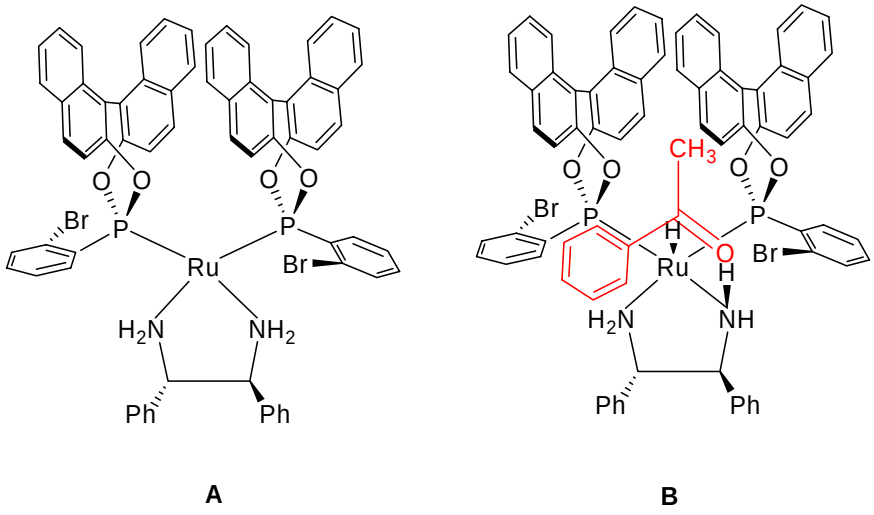


Figure 11.4: (A) Catalyst structure; (B) Favoured ketone approach.[20]

The first results using the Ru-MeOXuPHOS complex were comparable to the Ru-BrOXuPHOS complex. Acetophenone was reduced with full conversion and 88% e.e.,[19] but unfortunately it was not studied as much as the ortho-bromo derivative.

11.2 Results and discussion

The aim of this project was to synthesize and evaluate a new series of ortho-OR ligands derived from MeO XuPHOS in order to study the effect of the ortho-OR group on the activity and selectivity of the catalysts.

In order to determine which structural hindrance was necessary for a successful ligand, the synthesis of a series of ortho-OR ligands with R= Me, Et, ^{t}Bu, Ph, $SiPh_2{}^{t}Bu$ (Figure 11.5) was attempted.

The synthesized ligands were used to prepare ruthenium (II) diamine catalysts which were tested in ketone reduction by hydrogenation.

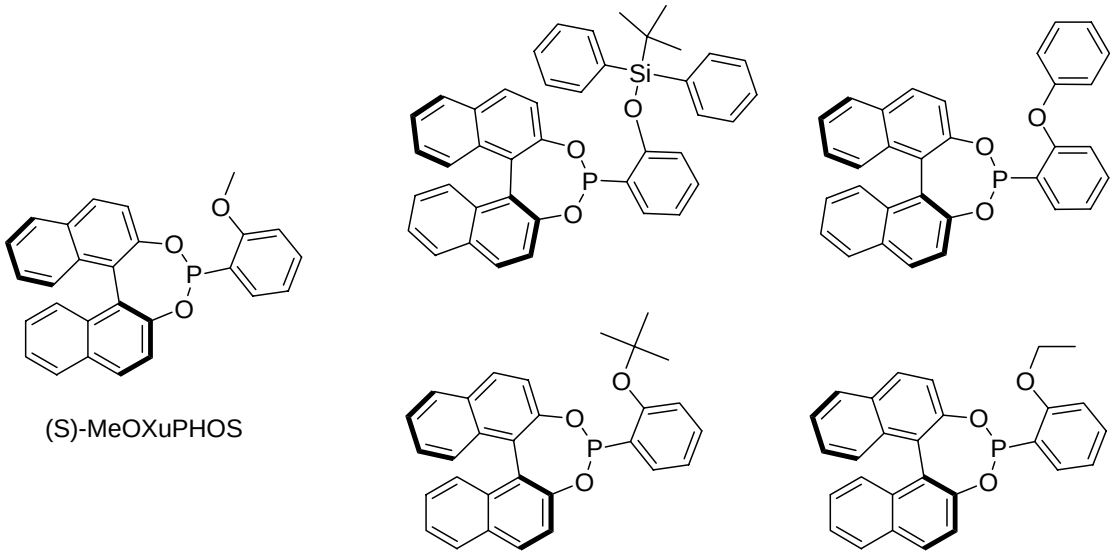
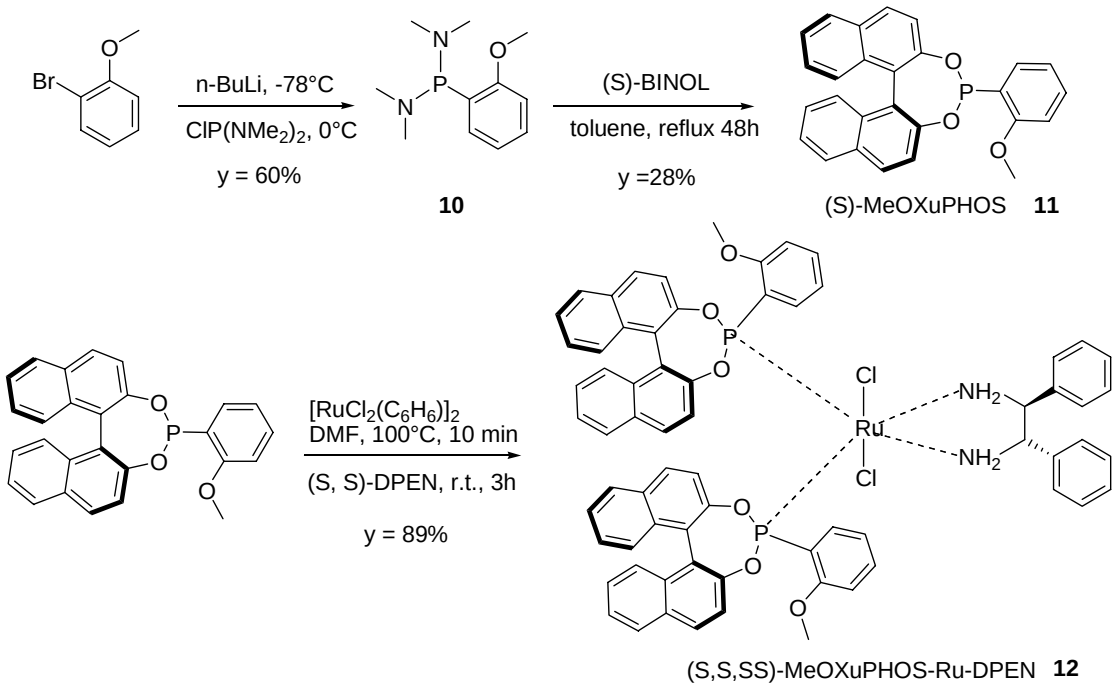


Figure 11.5: (*S*)-MeOXuPHOS and its derived ligands.

11.2.1 Synthesis of ligands and corresponding Ru-DPEN complexes

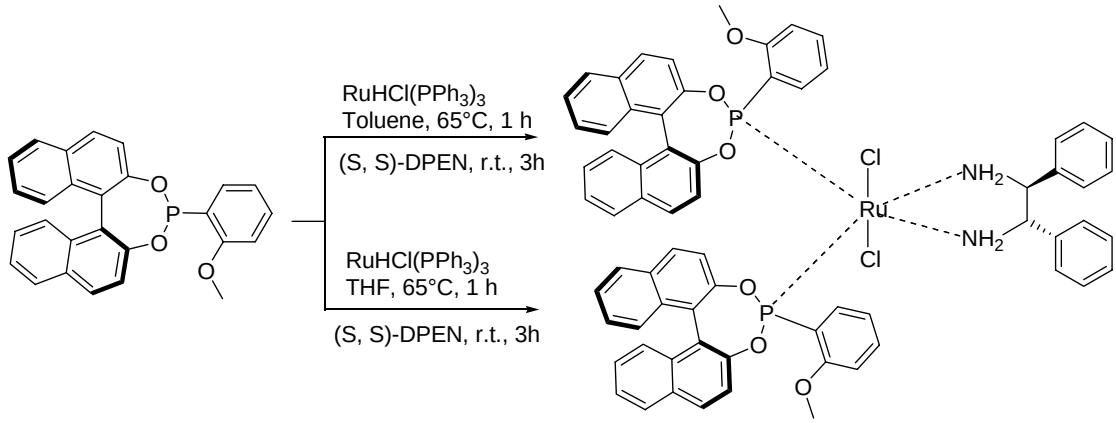
In order to became familiar with the synthesis procedure, the known synthesis of the (*S*)- and (*R*)- MeOXuPHOS ligand and the MeOXuPHOS-Ru-DPEN complex were reproduced,[19] after that the catalyst was used to carry out the hydrogenation of different ketones, in order to obtain more information about its reactivity.



Scheme 11.2: Synthetic route to the (S)- and (R)- MeOXuPHOS ligand and the (S,S,SS)- and (R,R,RR)- MeOXuPHOS-Ru-DPEN complex.

A new procedure of complex synthesis was attempted in order to simplify the purification step. The removal of the DMF solvent was problematic, causing a decrease of the purity of the complex catalyst.

A synthetic procedure recently published by R. H. Morris and co-workers was attempted to synthesize the RuHCl(diphosphonite)(diamine) complexes in a one-pot two step procedure, where they had used $RuHCl(PPh_3)_3$, BINOP as the phosphorus ligand, and DPEN.[21] Therefore, the reaction was repeated trying different solvents, toluene and THF as reported in Scheme 11.3.



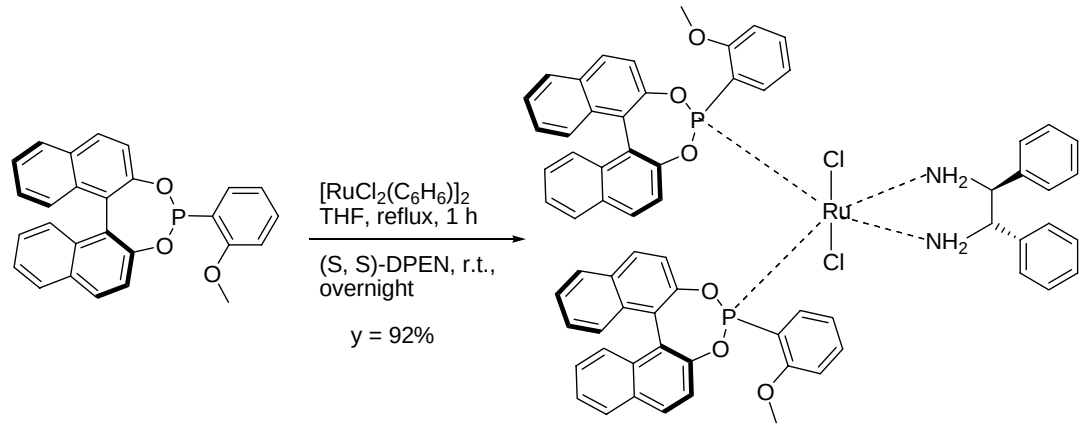
(S)-MeO XuPHOS **11**

(S,S,SS)-MeO XuPHOS-Ru-DPEN **12**

Scheme 11.3: Synthesis of (*S,S,SS*)-MeOXuPHOS-Ru-DPEN complex using the R. H. Morris and co-workers' procedure.[21]

Only the reaction carried out in THF led to traces of the complex **12**. Possibly, in the case reported by Morris, the reaction worked because the phosphorus ligand was bidentate; the structure of the ligand could be favoured by the substitution of PPh_3 with the ligand on the metallic centre.

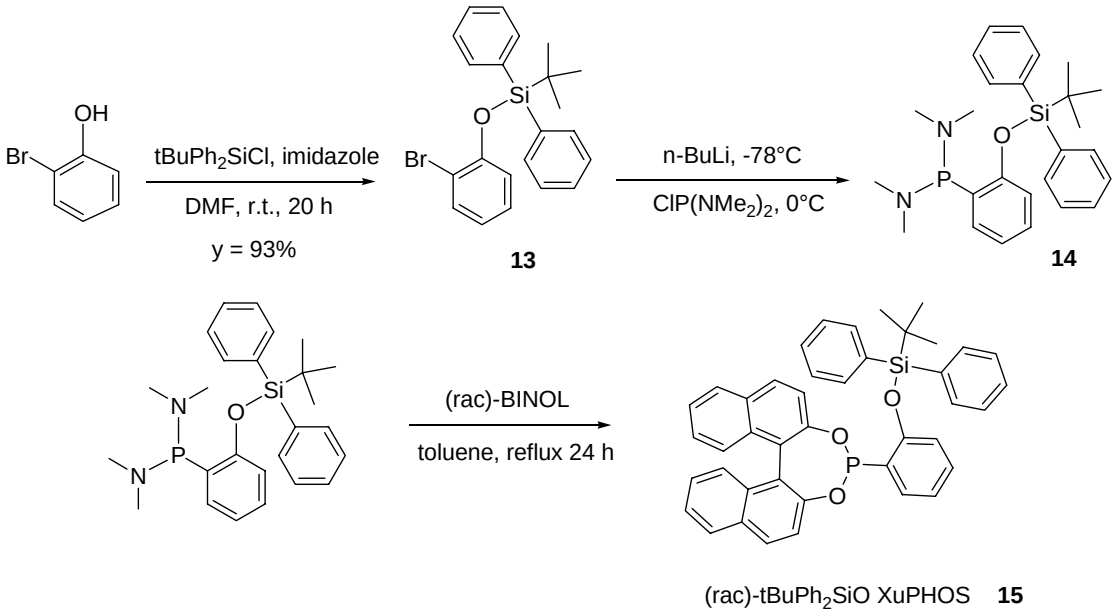
This result suggested that the complex could be formed in a different solvent than DMF. Consequently the complexation reaction was carried out in THF using the Morris procedure, but $[RuCl_2(C_6H_6)]_2$ was used instead of $RuHCl(PPh_3)_3$ as a starting material (Scheme 11.3). In this case the MeOXuPHOS-Ru-DPEN complex was obtained and problem of removing the solvent from the complex was avoided.



(S)-MeO XuPHOS **11** (S,S,SS)-MeO XuPHOS-Ru-DPEN **12**

Scheme 11.3: Synthesis of the (*S*,*S*,*SS*)-MeOXuPHOS-Ru-DPEN complex in THF.

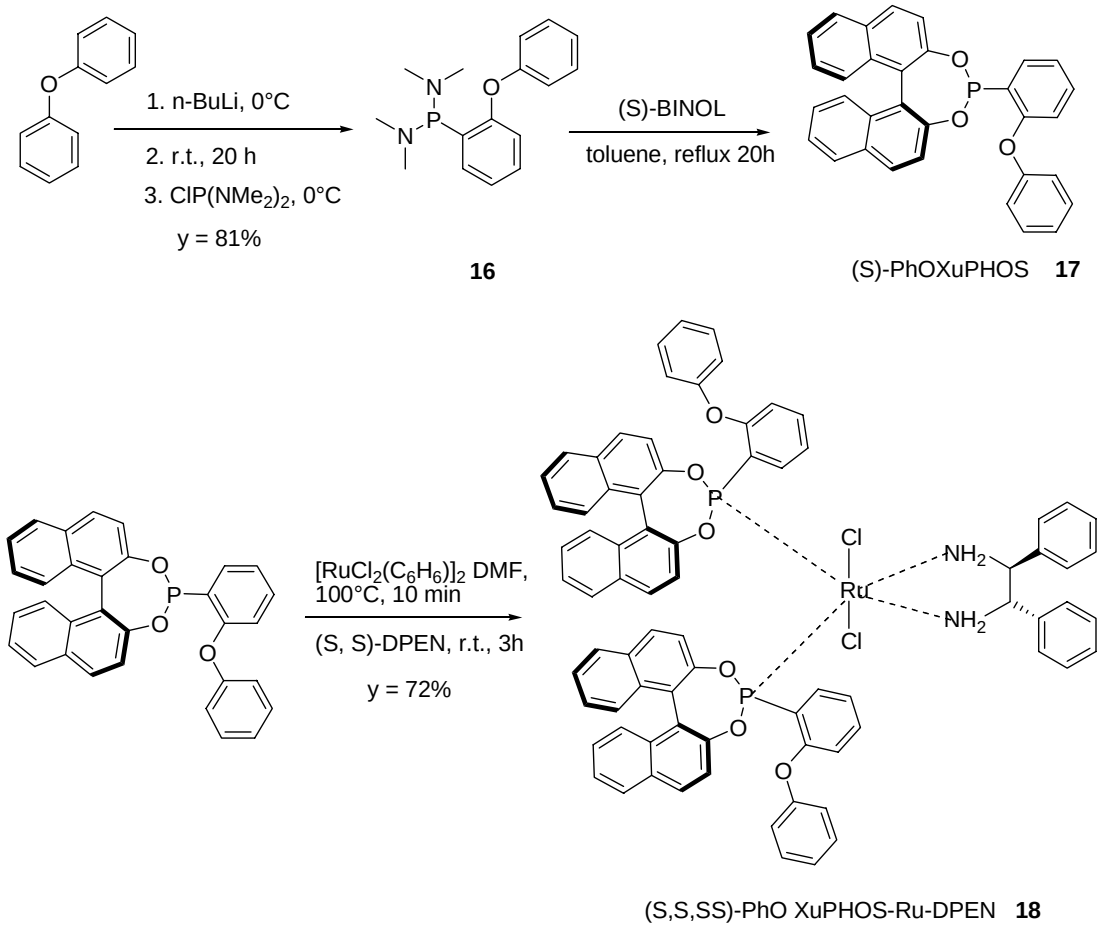
Following a procedure close to the synthesis of the MeOXuPHOS ligand, the synthetic route to the ^{t}BuPh$_2$SiOXuPHOS ligand reported in Scheme 11.4 was proposed. In this case the (2-bromophenoxy)(tert-butyl)diphenylsilane (**13**) was not commercially available, but was obtained by *o*-silylation of ortho-bromophenol (Scheme 11.4).[22] The products **14** and **15** were obtained using the same procedure to prepare MeOXuPHOS ligand (Scheme 11.4).



Scheme 11.4: Synthetic route to $^{t}BuPh_2SiOXuPHOS$ ligand

In the first attempt, the synthesis of **14** was carried out using a small amount of crude product **13** containing the starting material $^{t}BuPh_2SiCl$. Purification of the final product **15** was attempted by crystallization. However, due to the small quantity of compound **15** it was not possible to separate it from the $^{t}BuPh_2SiCl$.
During the development of the synthesis on a larger scale, obtaining compound **14** cleanly from its corresponding oxidized compound proved difficult.
Due to the difficulties encountered in the synthesis, and also because of the instability of the O-Si bond, the synthesis of $^{t}BuPh_2SiOXuPHOS$ ligand was abandoned.

In the case of MeOXuPHOS ligand, the available starting material was diphenyl ether, therefore the synthetic route reported in Scheme 11.5 was adopted.



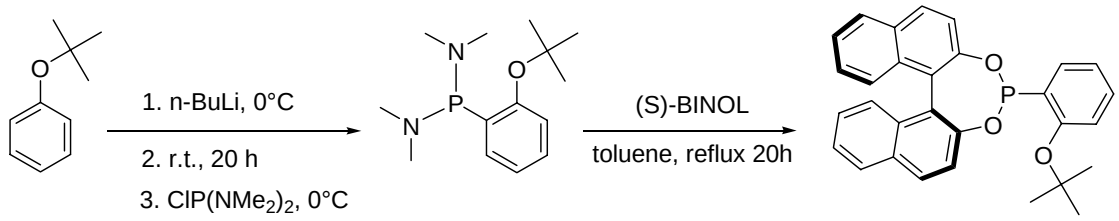
Scheme 11.5: Synthetic route to the (*S*)-PhOXuPHOS ligand and the (*S,S,SS*)-PhOXuPHOS-Ru-DPEN complex.

The first step was different from the synthetic approach used to prepare the MeOXuPHOS ligand as it consisted of an ortholithiation. Consequently, the reaction was tested using the electrophilic reagent CO_2. The test reaction to obtain 2-phenoxybenzoic acid gave an impure product. Nevertheless the equivalent reaction was carried out using $ClP(NMe_2)_2$. The reaction gave a product not as clean as in the case of the bromo-lithium exchange.

The condensation reaction between **16** and (*S*)-BINOL gave **17** impure of BINOL.

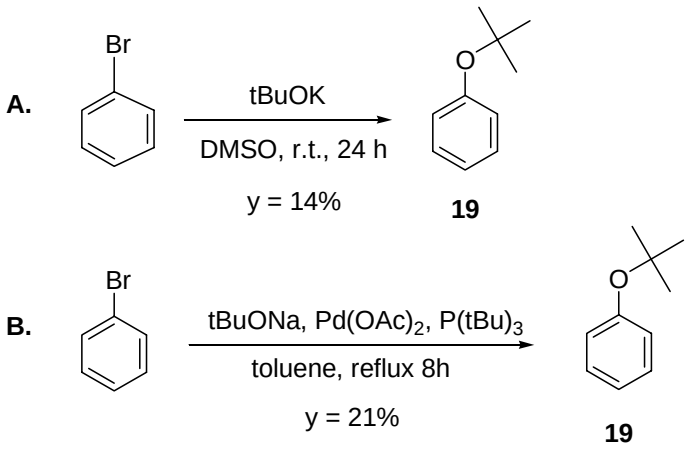
The compound **18** was purified by crystallisation from toluene, however only BINOL crystals were obtained. This indicates that the formation of compound **18** is difficult, probably because of the big sterical hindrance caused by the phenyl groups.
Nevertheless, the Ru complex was synthesised using the impure (*S*)-PhOXuPHOS ligand. The obtained complex **18** was also impure.
It was not possible to quantify by ^{1}H-NMR spectrum the percentage of impurity, because the proton chemical shift of **17** and **18** were very similar to the protons in BINOL and as a result some signals were overlapped. The impure (*S,S,SS*)-PhOXuPHOS-Ru-DPEN complex **18** was tested on the reduction of acetophenone by H_2-hydrogenation; the result is reported in section 11.2.2.

Based on the analogy of the PhOXuPHOS ligand's synthetic route, the synthetic route reported in Scheme 11.6 was proposed.
Compound **19** was not commercially available; therefore a synthetic route was necessary to synthesise it. Two different approaches were tried, a nucleophilic aromatic substitution *via* a benzyne mechanism[23] (Scheme 11.7 A) and a palladium-catalysed carbon-oxygen bond formation[24] (Scheme 11.7 B). In both cases, the yield in **19** was low.



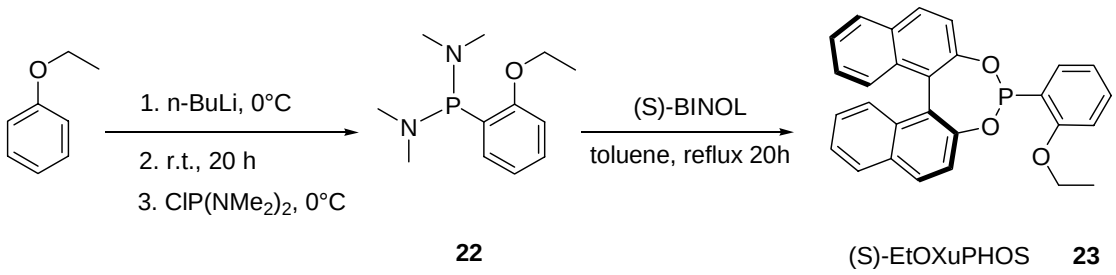
Scheme 11.6: Initially proposed synthetic route for the ^{t}BuOXuPHOS ligand.

The successive step gave compound **20** only in traces. Due to the difficulties that occurred in the synthesis reported above, the synthesis of ^{t}BuOXuPHOS ligand was abandoned.



Scheme 11.7: Synthetic route to 19.

Also in this case, based on the analogy of the PhOXuPHOS and ^{t}BuOXuPHOS ligands' synthetic route, the proposed synthetic route for (*S*)-EtOXuPHOS is reported in Scheme 11.8.



Scheme 11.8: Initially proposed synthetic route for EtOXuPHOS ligand.

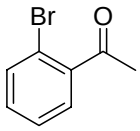
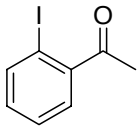
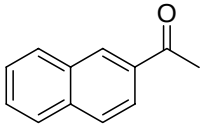
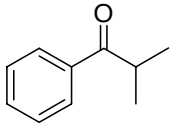
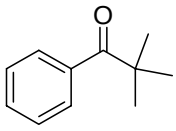
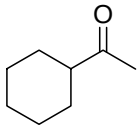
The available starting material was phenetole, and the ortholithiation was attempted, as in the two cases reported above. Unfortunately the reaction gave only a small amount of the product **22**.

11.2.2 Asymmetric hydrogenation of ketones

In order to check the activity of the synthesised catalyst (*S*,*S*,*SS*)-MeOXuPHOS-Ru-DPEN (with standard method), the asymmetric hydrogenation of acetophenone was carried out (reaction conditions: S/C:500; Time:20h; P:40bar; r.t.). The test gave moderate ee's of 75% (R) , but the conversion was low (21%). The catalyst was made impure by DMF, probably for this reason it was not possible to obtain good results. Nevertheless it was decided to proceed with testing of other ketone substrates using this catalyst.

In addition the (*S*,*S*,*SS*)-MeOXuPHOS-Ru-DPEN complex, obtained using THF as solvent (Scheme 11.2), was used to carry out the same reaction reported above (reaction condition: S/C:500; Time:20h; P:40bar; r.t.). The reaction gave the same ee's (76% (R)) as the previous case, but the conversion was improved (60%). Also in this case the catalyst was impure, perhaps for this reason it was not possible to improve the results.

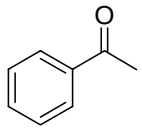
Further ketones were reduced using the same complex and the results are reported in table 11.1. In all cases, except one, the conversion was very low, probably for the reason previously reported. The ee's were generally low as well, except in the cases of hydrogenation of 2-iodoacetophenone and 2-acetonaphtone which gave 70% (R) and 79% (R) respectively.

Ketone	S / C	t / h	P / bar	T	Conv. (%)[a]	e.e. (%)[a]
	500	20	50	r.t.	4.6	47 (R)
	500	20	50	r.t.	10.3	70 (R)
	500	20	50	r.t.	93	79 (R)
	500	20	50	r.t.	21	52 (R)
	500	20	50	r.t	33	54 (R)
	500	20	50	r.t	32	0

Reaction was conducted in 2-propanol with a 0.15 M solution of ketone, 10 equiv of base (^{t}BuOK) wrt catalyst. (a) Determined by chiral GC

Table 11.1: Asymmetric hydrogenation of ketones using (*S*,*S*,*SS*)-MeOXuPHOS-Ru-DPEN.

The complex derived from the PhOXuPHOS ligand was not clean, nevertheless it was decided to examine its activity. The conversion and the ee's were very low (table 11.2). It was envisaged that these poor results could be explained by the high hindrance of the phenyl group.

Ketone	S / C	t / h	P / bar	T	Conv. (%)[a]	e.e. (%)[a]
	500	20	50	r.t.	2.5	44 (R)

Reaction was conducted in 2-propanol with a 0.15 M solution of ketone, 10 equiv of base (^{t}BuOK) wrt catalyst. (a) Determined by chiral GC

Table 11.2: Asymmetric hydrogenation of acetophenone using (*S*,*S*,*SS*)-PhOXuPHOS-Ru-DPEN.

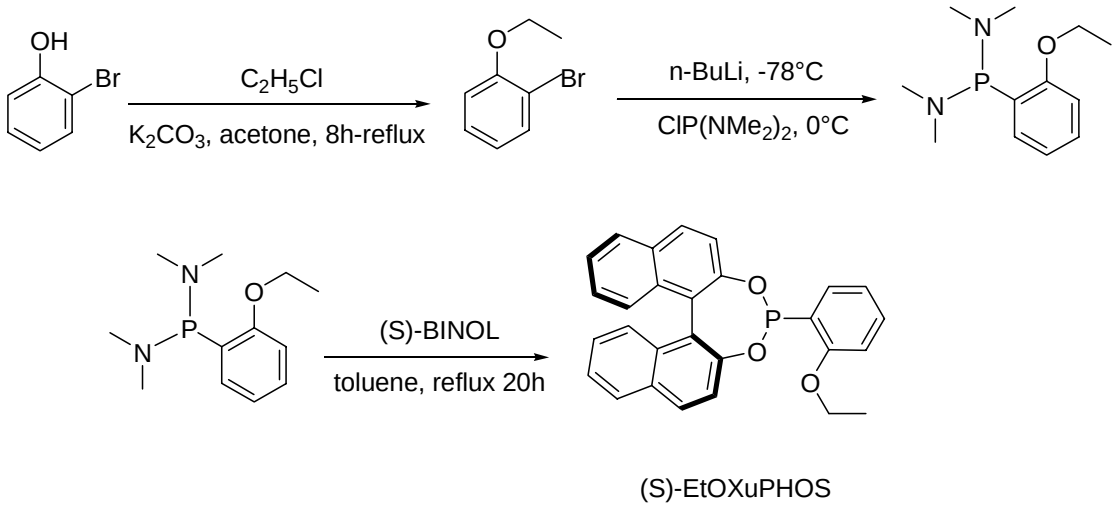
11.3 Conclusion

The results obtained from the PhOXuPHOS-Ru-DPEN complex, demonstrated that a bulky group as a substitute decreases the performance of the catalyst in the steroselectivity and, presumably, also in the activity.

Consequently, it could be interesting to try to decrease the sterical hindrance, using a smaller R group such as an ethyl group. For this reason it might be necessary to change the proposed initially synthetic route for EtOXuPHOS (Scheme 11.8). A proposal is reported below (Scheme 11.9).

Promising results obtained in the asymmetric hydrogenation of ketones (Table 11.2) suggest that using pure MeOXuPHOS-Ru-DPEN complex, it would be possible to improve both the conversion and ee's, in particular for the substrates, 2-iodoacetophenone and 2-acetonaphtone that have shown to give good ee's.

Moreover the new procedure to synthesise the complex in THF gave good results, consequently it could be useful to repeat it in order to find the best reaction and purification conditions.



(S)-EtOXuPHOS

Scheme 11.9: New proposed synthetic route for EtOXuPHOS ligand.

11.4 Experimental Section

General: All reactions, unless otherwise stated, were run under an atmosphere of argon inflame or oven dried glassware (round bottomed flasks or Schlenk tubes). Room temperature refers to ambient room temperature (20-22 °C), 0 °C refers to an ice slush bath and -78 °C refers to a dry ice-acetone bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by Thin Layer Chromatography (TLC) using aluminium backed silica gel 60 (F254) plates, visualized using UV254 nm and PMA, potassium permanganate or ninhydrin dips as appropriate. Flash column chromatography was carried out routinely using 60 Å silica gel (Merck). NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or DPX-400 (400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million downfield from $(CH_3)_4Si$. Coupling constants (J) are measured in hertz. Enantiomeric excesses were determined by GC analysis (Hewlett Packard 5890A gas chromatography, Cyclodextrin-β-236M-19 (CHROMPAC, 50m)) as stated. Elemental analyses were performed using the Exeter Analytical Model CE440.

Synthesis of ortho-bis(dimethylaminophosphino)anisole (10)[19]

In an oven-dried 100 mL round bottom flask twice purged with nitrogen, 2-bromoanisole (1.496 g, 8 mmol, 1.4 mL) was dissolved in freshly distilled diethyl ether (25 mL) and it was allowed to cool to –78 °C. To the resulting solution was added *n*-butyllithium (1.6 M, 8.8 mmol, 5.5 ml, 1.1 eq) and the mixture was allowed to stir for 30 min whilst being maintained at –78 °C. The reaction mixture was then allowed to warm to 0 °C and bis-(dimethylamino)chlorophosphane (8.8 mmol, 1.33 g, 1.3 mL, 1.1 eq) was added dropwise *via* a nitrogen purged syringe and the reaction mixture was allowed to stir 20-30 min at room temperature. The resulting white suspension was washed with saturated degassed sodium hydrogen carbonate solution (25 mL), diluted with diethyl ether (25 mL) and transferred into a separating funnel, the organic layer was collected and the aqueous layer back extracted with a further aliquot of ether (5 mL). The combined organic layers were dried over anhydrous magnesium sulphate for half an hour, filtered and concentrated under reduced pressure to give the crude product as a pale green oil (1.09, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.70-7.66 (m, 1H), 7.29-7.22 (m, 1H), 7.09-7.07 (m, 1H), 6.65 (dd, *J*= 4.3Hz, *J* 8.1Hz,1H), 3.77 (s, 3H), 2.58 (d, J_{PH}= 18.4Hz, 12H); ^{31}P NMR (162 MHz, $CDCl_3$) δ= 97.7

Synthesis of (S)-MeOXuPHOS (11) [19]

To a solution containing 2-bis-(dimethylaminophosphino)-anisole (1.01g, 4.42 mmol) dissolved in toluene (25 mL) was added the *(S)*-bi-2-naphthol (1.26 g, 4.42 mmol) dissolved in anhydrous toluene (25 mL). The reaction flask was placed in an oil bath and stirred at room temperature for 10 min. It was heated up to reflux for 24 h. The reaction was monitored by ^{31}P NMR, and also the releasing dimethylamine gas was monitored by pH paper. After the reaction finished, it was allowed to cool down to room temperature. Solvent was removed to get a off-white solid and dried under high vacuum. The white solid was purified by recrystallization from toluene (529 mg, 28%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.96-7.93 (1H, m), 7.83-7.79 (1H, m), 7.60 (t, *J* 8.1Hz, 2H), 7.49-7.35 (m, 4H), 7.33-7.18 (m, 3H), 7.13-7.09 (m, 1H), 6.96-6.85 (m, 1H), 6.80-6.77 (m,1H), 6.69-6.64 (m,1H), 3.96 (s, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ= 180.

Synthesis of (S,S,SS)- MeOXuPHOS-Ru-DPEN complex (12) [19]

$[RuCl_2(C_6H_6)]_2$ (100mg, 0.200mmol) and *(S)*-MeOXuPHOS (338mg, 0.800mmol, 4e.q.) were placed in a 25-mL Schlenk flask. After the air in the flask was replaced with argon, anhydrous DMF (10 ml) was added, the mixture was degassed and stirred under argon at 100 °C for 10 min to form a reddish brown solution. After the solution was cooled to 25 °C, *(S, S)*-DPEN (85mg, 0.400mmol) was added and the mixture was degassed again before it was stirred for 3h. After the reaction finished, the solvent was removed under reduced pressure., and CH_2Cl_2 was added in for several times into the reaction mixture, and at each time it was turned on the high vacuum and back to argon. The resulting dark green (yellow) solid was dried under the high vacuum to give the metal complex (S,S,SS)- MeOXuPHOS-Ru-DPEN (438 mg, 89%).

^{1}H NMR (400MHz, $CDCl_3$): δ= 7.72 (d, *J* 7.95Hz, 2H), 7.66 (d, *J* 7.91Hz, 2H), 7.61 (t, *J* 12.00Hz, 2H), 7.49 (d, *J* 8.83Hz, 2H), 7.44 (t, *J* 8.23Hz, 2H), 7.35 (t, *J* 7.99Hz, 2H), 7.28-7.24 (m, 8H), 7.16-7.13 (m, 8H), 7.10 7.06 (m, 6H), 7.02-7.00 (m, 6H), 6.87 (t, 2H), 4.58 (m, 2H), 4.47-4.45 (m, 2H), 4.14-4.10 (m, 2H), 3.97 (s, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ= 206.3.

Synthesis of (S,S,SS)-MeOXuPHOS-Ru-DPEN complex (12) using THF.

$[RuCl_2(C_6H_6)]_2$ (25 mg, 0.05 mmol) and *(S)*-MeOXuPHOS (85 mg, 0.20 mmol, 4e.q.) were placed in a 50-mL Schlenk flask. After the air in the flask was replaced with argon, anhydrous THF (15 ml) was added, the mixture was degassed and stirred under argon at reflux for 1 h to form a yellow brown solution. After the solution was cooled to 25 °C, *(S, S)*-DPEN (21 mg, 0.10 mmol) was added and the mixture was degassed again before it was stirred overnight. After the reaction finished, the solvent

was removed under reduced pressure. The resulting yellow brown solid was dried under the high vacuum to give (S,S,SS)-MeOXuPHOS-Ru-DPEN complex (107 mg, 92 %).

^{31}P NMR (162 MHz, $CDCl_3$) δ= 206.8.

Synthesis of (2-bromophenoxy)(tert-butyl)diphenylsilane (13)[22]

To an ice-cold bath of 2-bromophenol (1.81 g, 10.48 mmol, 1.2 ml) in DMF (75 mL) was added $tBuPh_2SiCl$ (3.17 g, 11.53 mmol, 1.1 eq, 3.0 ml) and imidazole (1.5 g, 22.01 mmol, 2.1 eq). The mixture was allowed to stir at ambient temperature overnight. After the reaction finished, the mixture was diluted with ethyl acetate (70 ml) and washed with water and brine, dried over magnesium sulphate for half an hour, than concentrated in vacuo. The crude product was purify by chromatography (SiO_2, hexane, r.f. (AcOEt/Hexane 5:95) = 0.42) to give a white solid (3.97 g, 93%).

IR: *v*max solid/cm-1 = 2928, 2855, 1476, 1296, 1028, 929; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.75-7.69 (m, 4H), 7.42 (dd, J 1.7 Hz, J 7.7 Hz, 1H), 7.44-7.35 (m, 6H), 6.83 (ddd app. dt, J 1.7 Hz, J 7.3 Hz, 1H), 6.71 (ddd app. dt, J 1.7 Hz, J 7.9 Hz, 1H), 6.45 (dd, J 1.5 Hz, J 8.1 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 152.0, 135.3, 133.0, 132.0, 129.8, 127.7 (*2* CH), 121.8, 119.6, 114.4, 26.2, 19.5; Anal. Calculated for $C_{22}H_{23}BrOSi$: C, 64.23; H, 5.63. Found: C. 64.20; H, 5.53.

Synthesis of 2-bis(dimethylaminophosphino)terbutyl diphenylsililoxybenzene (14)

In a dried 100 mL Schlenk flask twice purged with nitrogen, (2-bromophenoxy)(tert-butyl)diphenylsilane (1.5 g, 3.69 mmol) was dissolved in freshly distilled diethyl ether (35 mL) and it was allowed to cool to –78 °C. To the resulting solution was added *n*-butyllithium (1.6 M, 4.06 mmol, 2.5 mL, 1.1 eq) and the mixture was allowed to stir for 30 min whilst being maintained at –78 °C. The reaction mixture was then allowed to warm to 0 °C and bis-(dimethylamino)chlorophosphane (0.612 g, 4.06 mmol, 0.6 mL, 1.1 eq) was added dropwise *via* a nitrogen purged syringe and the reaction mixture was allowed to stir 20-30 min at ambient temperature. The resulting white suspension was washed with saturated degassed sodium hydrogen

carbonate solution (35 mL), diluted with diethyl ether (35 mL) and transferred to a separating funnel, the organic layer was collected and the aqueous layer back extracted with a further aliquot of ether (5 mL). The combined organic layers were dried over magnesium sulphate for half an hour, filtered and concentrated under reduced pressure to give the crude product as pale yellow oil. It was not possible to purified the product.

IR: *v*max neat/cm^{-1} = 3063, 2932, 2850, 1467, 1418, 1026; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.75-7.68 (m, 4H), 7.52 (dd, J 1.9 Hz, J 7.9 Hz, 1H), 7.40-7.35 (m, 6H), 6.84 (ddd app. dt, J 1.7Hz, J 7.5Hz, 1H), 6.71 (ddd app. dt, J 1.5Hz, J 7.7Hz,1H), 6.45 (dd, J 1.5 Hz, J 8.1 Hz, 1H), 2.47 (d, J_{P-H} 9.4Hz, 12H), 1.14 (s, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ= 126.

Oxidized derivative of 14: ^{31}P NMR (162 MHz, CDCl3) δ= 39.

Synthesis of (Rac)-tBuPh$_2$SiOXuPHOS (15)

To a solution containing 2-bis(dimethylaminophosphino)terbutyl diphenylsililoxybenzene (88 mg, 1.9 mmol) dissolved in toluene (15 mL) was charged the *(Rac)*-bi-2-naphthol (56 mg, 1.9 mmol) dissolved in anhydrous toluene (60 mL). The reaction flask was placed in an oil bath and stirred at room temperature for 10 min. It was heated up to reflux for 24 h. The reaction was monitored by ^{31}P NMR, and also the releasing dimethylamine gas was monitored by pH paper. After the reaction finished, it was allowed to cool down to room temperature. Solvent was removed to get a white solid and dried under high vacuum. It was not possible to purify the product.

^{31}P NMR (162 MHz, $CDCl_3$) δ= 138.

Synthesis of ortho-bis(dimethylaminophosphino)diphenyl ether (16)

In a dried 100 mL Schlenk flask twice purged with nitrogen, diphenyl ether (1.07 g, 6.3 mmol) was dissolved in freshly distilled diethyl ether (20 mL) and it was allowed to cool to 0 °C. To the resulting solution was added *n*-butyllithium (1.6 M, 6.3 mmol, 3.9 mL, 1 eq) and the mixture was allowed to stir at ambient temperature overnight.

The reaction mixture was then allowed to warm to 0 °C and bis-(dimethylamino)chlorophosphane (6.9 mmol, 1.04 g, 1 mL, 1.1 eq) was added dropwise *via* a nitrogen purged syringe and the reaction mixture was allowed to stir 20-30 min at ambient temperature. The resulting white suspension was washed with saturated degassed sodium hydrogen carbonate solution (25 mL), diluted with diethyl ether (25 mL) and transferred to a separating funnel, the organic layer was collected and the aqueous layer back extracted with a further aliquot of ether (5 mL). The combined organic layers were dried over magnesium sulphate for half an hour, filtered and concentrated under reduced pressure to give the crude product as pale yellow oil (1.723 g, 81%). It was not possible to purify the product.

IR: *v*max neat/cm-1 = 3052, 2861, 2774, 1581, 1478, 955; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.52-7.45 (m, 1H), 7.35-6.92 (m, 7H), 6.88-6.81 (m, 1H), 2.68 (d, *J*PH Hz, 12H); ^{31}P NMR (162 MHz, $CDCl_3$) δ= 95.9.

Synthesis of (S)-PhOXuPHOS (17)

To a solution containing ortho-bis(dimethylaminophosphino)diphenyl ether (406 mg, 1.48 mmol) dissolved in toluene (10 mL) was charged the *(S)*-bi-2-naphthol (423 mg, 1.48 mmol) dissolved in anhydrous toluene (30 mL). The reaction flask was placed in an oil bath and stirred at room temperature for 10 min. It was heated up to reflux for 20 h. The reaction was monitored by ^{31}P NMR, and also the releasing dimethylamine gas was monitored by pH paper. After the reaction finished, it was allowed to cool down to room temperature. Solvent was removed to get an oil that was washed with diethyl ether. After solvent was removed, a white solid was obtained that was dried under high vacuum. It was not possible to purify the product.

^{31}P NMR (162 MHz, CDCl3) δ= 178.

Synthesis of (S, S,SS)-PhOXuPHOS-Ru-DPEN complex (18)

$[RuCl_2(C_6H_6)]_2$ (28 mg, 0.057 mmol) and *(S)*-PhOXuPHOS (111 mg, 0.230 mmol, 4 e.q.) were placed in a 50-mL Schlenk flask. After the air in the flask was replaced with argon, anhydrous DMF (5 ml) was added, the mixture was degassed and stirred

under argon at 100 °C for 10 min to form a reddish brown solution. After the solution was cooled to 25 °C, *(S, S)*-DPEN (23 mg, 0.110 mmol) was added and the mixture was degassed again before it was stirred for 3h. After the reaction finished, the solvent was removed under argon flow, and CH_2Cl_2 was added in for several times into the reaction mixture, and at each time it was turned on the high vacuum and back to argon. The resulting brown solid was dried under the high vacuum to give the metal complex (105 mg, 72 %). It was not possible to purify the product.
^{31}P NMR (162 MHz, $CDCl_3$) δ= 210.

Synthesis of 1- tert butoxy benzene; procedure B (19) [23]

In a schlenk flask under argon, at a solution of 2-bromobenzene (2,98 g, 17.2 mmol, 2 mL) and sodium *tert*-butoxide (2 g, 20.64 mmol) in toluene (60 mL), was added $Pd(OAc)_2$ (0.047g, 0.21mmol) and $P(tBu)_3$ (0.127 g, 0.63 mmol, 0.15 mL). The mixture was stirred at reflux for 8 h. After the reaction finished, the mixture was diluted with ethyl acetate (50 mL) and washed with water (50 mL), dried over magnesium sulphate for half an hour, filtered and concentrated under reduced pressure to give the crude product that was purified by chromatography (SiO_2, Hexane). The product was as oil (0.55 g, 21%).
^1H NMR (300 MHz, $CDCl_3$) δ= 7.26 (t, J 7.5 Hz, 2H), 7.08 (t, J 7.5 Hz, 1H), 6.99 (d, J 7.5 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 155.1, 128.5, 124.0, 123.1, 78.1, 28.6.

Synthesis of ortho-bis(dimethylaminophosphino) tert butoxy benzene (20)

In a dried 100 mL Schlenk flask twice purged with nitrogen, 1- tert butoxy benzene (0.5 g, 3.3 mmol) was dissolved in freshly distilled diethyl ether (10 mL) and it was allowed to cool to 0 °C. To the resulting solution was added *n*-butyllithium (1.6 M, 3.3 mmol, 2.1 mL, 1 eq) and the mixture was allowed to stir at ambient temperature overnight. The reaction mixture was then allowed to warm to 0 °C and bis-(dimethylamino)chlorophosphane (3.7 mmol, 0.56 g, 0.55 mL, 1.1 eq) was added dropwise *via* a nitrogen purged syringe and the reaction mixture was allowed to stir

20-30 min at ambient temperature. The resulting white suspension was washed with saturated degassed sodium hydrogen carbonate solution (10 mL), diluted with diethyl ether (10 mL) and transferred to a separating funnel, the organic layer was collected and the aqueous layer back extracted with a further aliquot of ether (5 mL). The combined organic layers were dried over magnesium sulphate for half an hour, filtered and concentrated under reduced pressure to give the crude product as pale yellow oil. The product was obtained only in trace.

Synthesis of ortho-bis(dimethylaminophosphino) phenetole (22)

In a dried 100 mL Schlenk flask twice purged with nitrogen, phenetole (0.41 g, 3.3 mmol) was dissolved in freshly distilled diethyl ether (10 mL) and it was allowed to cool to 0 °C. To the resulting solution was added *n*-butyllithium (1.6 M, 3.3 mmol, 2.1 mL, 1 eq) and the mixture was allowed to stir at ambient temperature overnight. The reaction mixture was then allowed to warm to 0 °C and bis-(dimethylamino)chlorophosphane (3.7 mmol, 0.56 g, 0.55 mL, 1.1 eq) was added dropwise *via* a nitrogen purged syringe and the reaction mixture was allowed to stir 20-30 min at ambient temperature. The resulting white suspension was washed with saturated degassed sodium hydrogen carbonate solution (10mL), diluted with diethyl ether (10 mL) and transferred to a separating funnel, the organic layer was collected and the aqueous layer back extracted with a further aliquot of ether (5 mL). The combined organic layers were dried over magnesium sulphate for half an hour, filtered and concentrated under reduced pressure to give the crude product as read oil. The product was obtained only in trace.

General procedure for the asymmetric hydrogenation catalysed by (S,S,SS) and (R,R,RR)-MeOXuPHOS-Ru-DPEN and (S,S,SS)-PhOXuPHOS-Ru-DPEN [19]

In a dried round bottom flask (150 mL), acetophenone (0.48 mL, 0.5 g, 4.16 mmol) and $(CH_3)_3COK$ (9 mg, 0.083 mmol, 0.5 mol %) were dissolved in dry and degassed 2-propanol (28 mL). (S,S,SS)-MeOXuPHOS-Ru-DPEN (10 mg, 0.0083 mmol, 0.05 mol %) was dissolved in anhydrous and degassed CH_2Cl_2 (1 mL), which was used as

the catalyst stock solution and was transferred into the reaction solution above under argon. The mixture was degassed by three vacuum-filling with argon cycles and then it was quickly transferred into the autoclave. It was purged with hydrogen for 10 seconds and finally the hydrogen was introduced to 50 bar. The reaction mixture was stirred vigorously at 20-22 ^{o}C (or 0 ^{o}C refers to an ice slush bath) for 20h. The mixture was filtered through a pad of silica gel and the pad was washed with a 50% solution of ethyl acetate in hexane (120 mL). The filtrate was concentrated under reduced pressure to afford the reduction product.

11.5 References

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Chapter 12

RUTHENIUM-CATALYZED HYDROGENATION OF KETONES AND AROMATIC RINGS

12.1 Introduction

The arene hydrogenation by molecular catalysis is a current area of research in which many highly innovative catalysts have been evaluated. Arene hydrogenation has many applications ranging from small scale synthesis to industrial processes such as the synthesis of cyclohexane and the removal of aromatic compounds from fuels.[1]

The reduction of aromatic rings can be obtained by numerous methods: heterogeneous and homogeneous catalysis, dissolving metal reduction (Na/K in liquid NH_3).[2] Usually, heterogeneous catalytic hydrogenation is carried out under drastic conditions (high pressure and temperature) and the metals used are Raney-Ni, Pd, Ru and Rh. Recently, new research has made progress in the reaction conditions using moderate temperatures, low pressure and water as solvent, but the problem still is the quantity of catalyst used; around 10% w/w. In a recent paper, Tsukinoki et al.[3] found a new heterogeneous method to reduce aromatic rings in high yields under mild conditions. They performed a method using Raney-Ni-Al alloy as catalyst, and dilute aqueous alkaline solution (KOH) in water at 90°C. More recently, Sajiki et al. used Rh/C for a similar reaction that proceeds at 80°C, in water under 5 atm of H_2.[4]

To compare, the homogeneous catalysis is not studied as much as the heterogeneous, generally it is carried out under milder conditions than those for heterogeneous hydrogenation, and sometimes in atmospheric hydrogen pressure and at room temperature. One of the first catalysts, organocobalt molecule, η^3-

$C_3H_5Co[P(OCH_3)_3]_3$ discovered by Muetterties in 1973 has been used as catalyst for the hydrogenation of aromatic hydrocarbons.[5] Reaction conditions were mild (1 atm hydrogen, room temperature) and the cobalt-catalyst was demonstrated to be stereoselective and chemoselective. Unfortunately, there were limiting factors such as steric (arene-substitution), electronic (strongly electron-withdrawing groups such as F and NO_2) and protonic substituents (OH, COOH).

The generally accepted mechanism for the hydrogenation of arenes was proposed in 1974.[6] The mechanism took place in a number of metal-arene complexes and the so called "arene-exchange mechanism" is shown in figure 12.1.

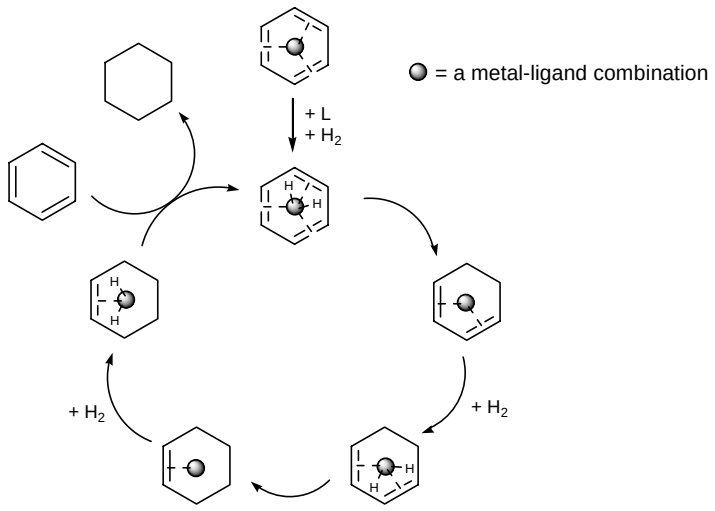


Figure 12.1: General scheme for arene hydrogenation catalysis by the "arene-exchange mechanism".[8]

Typically, heterogeneous catalysts use metals supported on fixed beds, or metal colloids and nanoparticles, which can be used under milder conditions.[7] A number of molecular compounds have been reported to homogeneously catalyse the hydrogenation of arene, although many have since been shown to be precursors to heterogeneous catalysis.[8] Actually, the active catalysis was later discovered to be colloidal and compared to many of the apparently homogeneous catalyses that have been reported, these colloidal catalysts operated under much milder conditions and are often more active, in discordance with the general assumption

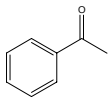
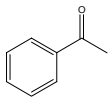
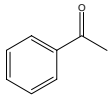
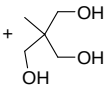
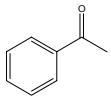
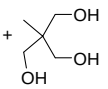
that homogeneous catalysis are more active than heterogeneous catalysis under ambient conditions.[8]

12.2 Results and discussion

During the study of hydrogenation reaction catalyzed by $RuCl_3$ and sodium alkoxide, a new catalyst was discovered. It was shown to be active in reducing ketones and aromatic rings at the same time.
The aim of this project was to find the best reaction conditions using this new catalyst. Moreover an initial study of improvement of the ligand was attempted.

12.2.1 Hydrogenation reaction catalyzed by $RuCl_3$, 1,1,1-Tris(hydroxymethyl)ethane and bases

Sodium alkoxide was used as a base in the hydrogenation reaction of acetophenone catalyzed by $RuCl_3$ (tab 12.1, entry 1). Unexpectedly, we got not only the reduction of the ketone group, but the aromatic rings as well. As a result the crude reaction was composed of three products: 1-phenyl-ethanol, 1-cyclohexyl-ethanol and cyclohexyl methyl ketone, in the ratio reported in tab. 12.1 entry 1.

Entry	*Substrate*	*Catalyst*	*Base*	*Conv (%)[a] 20h*		
						
1		$RuCl_3$	3.5 eq CH_3ONa	29	4	6.5
2		$RuCl_3$	No base	30	16	6
3		$RuCl_3$ + 	3.5 eq CH_3ONa	46	44	10
4		$RuCl_3$ + 	No base	13	6	2

Reactions were conducted in methanol with a 0.6 M solution of ketone, 1mol% of catalyst wrt substrate, eq. base wrt catalyst, pressure of H_2 10 bar, room temperature. (a) Determined by ^1H NMR.

Table 12.1: Hydrogenation of acetophenone using ruthenium-catalyst and sodium alkoxides.

In order to determinate the role of sodium methoxide, the reaction was repeated using any base (entry 2, table 12.1). The conversion was a slight better than the previous result (entry 1), indicating apparently, that the base did not play an important function in the catalysis.

Nevertheless, the reaction was repeated again using the same conditions used in entry 1, and adding the 1,1,1-tris(hydroxymethyl)ethane (entry 3, table 12.1). The result this time was much better than the previous two attempts and complete conversion was obtained. As for the reaction, entry 1, the reaction, entry 3, was repeated without base as well (entry 4, table 12.1). But this time the result was inferior in respect to all previous tests (entry 1,2, 3, table 12.1).

This improved result could be explained with the formation of a complex between $RuCl_3$ and the 1,1,1-tris(hydroxymethyl)ethane promoted by the base with the elimination of NaCl, as reported in figure 12.2.

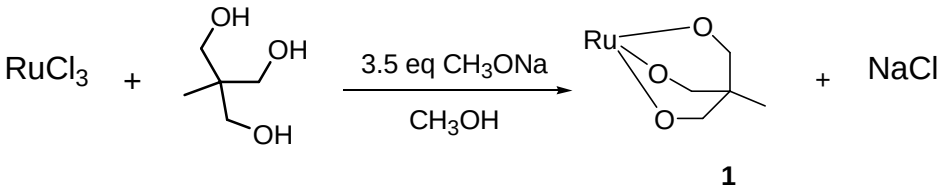
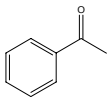
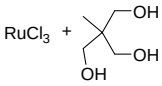
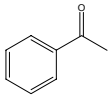
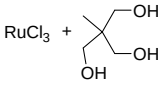
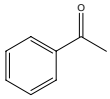
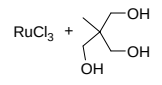
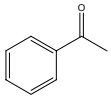
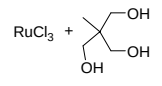
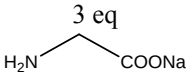


Figure 12.2: Formation of new ruthenium-1,1,1-tris(hydroxymethyl)ethane complex.

To demonstrate the importance of this base, the reaction was repeated using 3.5 eq (entry 1, table 12.2) and 2 eq. of base (entry 2, table 12.2). As the results show, reported in table 12.2, the reaction conducted using 2 eq of base (entry 2) was much slower than the reaction where 3.5 eq of base was added (entry 1). This indicates that almost 3 times the stoichiometric amount of base is necessary for the complex formation.

Entry	*Substrate*	*Catalyst*	*Base*	*Conv (%)[a] 21h*		
						
1			3.5 eq CH_3ONa	7	92.6	0.4
2			2 eq CH_3ONa	26	59	14
3			3 eq Et_3N	CH_2Cl_2 0.6M	8	7
4			3 eq 	CH_3OH 0.6M	8	4

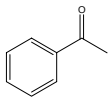
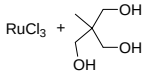
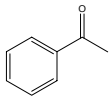
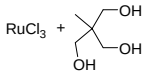
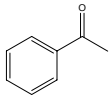
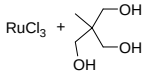
Reactions were conducted in methanol with a 0.6 M solution of ketone, 1 mol% of catalyst wrt substrate, the quantity of base wrt catalyst, pressure of H_2: 10 bar, room temperature. (a) Determined by ^1H NMR.

Table 12.2: Hydrogenation of acetophenone using ruthenium-catalyst and sodium alkoxides.

The use of different bases was analysed, in particular using Et_3N and sodium glycinate (entry 3 and 4 respectively, table 12.2), but the results reported in table

12.2 show a conversion decrement, indicating that the best base for the catalyst formation was sodium alkoxide.

To evaluate the catalyst activity, the reaction was carried out using 0.1mol% instead of 1mol% of catalyst (entry 2, table 12.3). Also in this case the conversion was complete, but the reaction trend showed slower reaction rate in the reduction of substrate.

Entry	*Substrate*	*Catalyst*	*Catalyst %*	*Pressure (bar)*	*Conv (%)[a] 21h*		
							
1			1	10	7	92.6	0.4
2			0.1	10	65	33	2
3			0.1	20	36	58	6

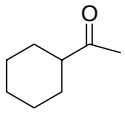
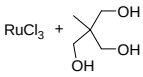
Reactions were conducted in methanol with a 0.6 M solution of ketone, mol% catalyst wrt substrate, 3.5 eq CH_3ONa wrt catalyst, room temperature. (a) Determined by ^1H NMR.

Table 12.3: Hydrogenation of acetophenone using ruthenium-catalyst and sodium alkoxides.

In addition, the influence of the pressure was studied: the reaction was carried out under a pressure of 20 bar instead of 10 bar (entry 2 and 3 respectively, table 12.3), and as expected, the reaction rate increased with the increment of pressure.

.

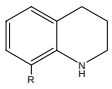
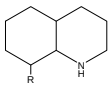
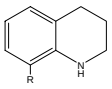
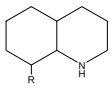
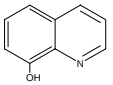
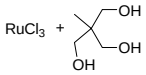
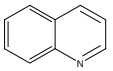
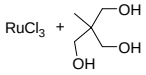
In order to study the catalyst activity on ketone reduction different substrates were considered. Cyclohexyl methyl ketone was chosen as it lacks carbon-carbon double bonds that could be reduced by the catalyst. The reduction of cyclohexyl methyl ketone (entry 1, table 12.4), was followed by ^1H NMR spectroscopy, and the reaction trend shows that in the first 6 hours the reaction velocity was quite high with a 61% conversion, but subsequent to this time and even after 20 hours, the conversion was not completed.

Entry	*Substrate*	*Catalyst*	*Conv (%)[a] 2h*	*Conv (%)[a] 4h*	*Conv (%)[a] 6h*	*Conv (%)[a] 20h*
1			22	39	61	95

Reactions were conducted in methanol with a 0.6 M solution of ketone, 1 mol% catalyst wrt substrate, 3.5 eq CH_3ONa wrt catalyst, pressure of H_2: 10 bar, room temperature. (a) Determined by ^1H NMR.

Table 12.4: Hydrogenation of cyclohexyl methyl ketone using ruthenium-catalyst and sodium alkoxides.

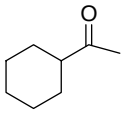
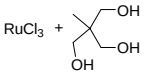
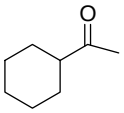
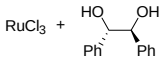
The catalytic activity was tested on aromatic substrate as well, in particular quinoline was used. The optimized reaction conditions were applied for both entry 1 and 2, table 12.5 and in both cases the conversion after 20 hours was low and selective for only reduction of pyridine ring. It should be noted that when a high pressure was applied (30 bar, entry 2), traces of completed reduction product were observed.

Entry	*Substrate*	*Catalyst*	*Pressure (bar)*	*Conv. (%)[a] 6h*		*Conv. (%)[a] 20h*	
							
1			10	-	-	32	-
2			30	7	-	25	traces

Reactions were conducted in methanol with a 0.6 M solution of ketone, 1mol% catalyst wrt substrate, 3.5 eq CH_3ONa wrt catalyst, room temperature. (a) Determined by ^1H NMR.

Table 12.5: Hydrogenation of aromatic substrates using ruthenium-catalyst and sodium alkoxide.

Subsequently, an optical pure diol ((S, S)-1,2-diphenyl-1,2-ethanediol) was tested as a ligand instead of the triol (1,1,1-Tris(hydroxymethyl)ethane). The conversion was lower (entry 2, table 12.6) in respect to the reaction carried out with the triol (entry 1, table 12.6). In order to verify the possibility of enantioselectivity induced by the chiral ligand used, the crude reaction was analysed by chiral GC, but the result showed no enantioselectivity.

Entry	*Substrate*	*Catalyst*	*Conv (%)[a] 20h*
1			95
2			71 (0% ee')

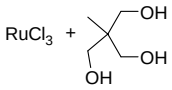
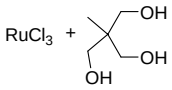
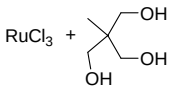
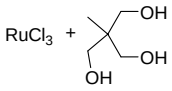
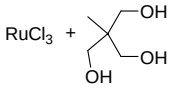
Reactions were conducted in methanol with a 0.6 M solution of ketone, 1mol% catalyst wrt substrate, 3.5 eq CH_3ONa wrt catalyst, pressure of H_2 10 bar, room temperature. (a) Determined by ^1H NMR.

Table 12.6: Hydrogenation of cyclohexyl methyl ketone using ruthenium-catalyst and sodium alkoxides

The temperature was identified as an important parameter in the reaction, and some tests were carried out at different temperatures from 14-18°C to 35°C (entry 1-3, table 12.7). Simultaneously, a new procedure for "activating catalyst" was attempted; the catalyst was heated at 35°C, 50 bar for 5h, than after cooling down the solution, the substrate was added. The best compromise temperature for the reaction was found to be 25°C. Also the "activating catalyst" procedure seems to improve the catalyst activity.

Other tests, using different bases, were carried out. In particular sodium hydroxide was used as a base instead of sodium methoxide (entry 4, table 12.7). In this case, the conversion was completed and comparable to the result obtained in entry 1, table 12.2. Sodium hydroxide demonstrates that other strong bases can be used instead of sodium alkoxide. The excess of base (in respect to the previous reactions, 4.2 eq NaOH instead 3.5 eq CH_3ONa) could also improve the catalyst activity because, as reported by Dyson,[8a] in some cases of arene hydrogenation catalysis, efficiency increases with increasing pH.

The best result was found by adding water after catalyst formation (entry 5), (same reaction condition of entry 4, table 12.7), in this case the conversion was complete and only 1-cyclohexyl-ethanol was obtained.

Entry	*Catalyst*	*Base*	*Temperature*	*Conv (%)[a] 16h*		
						
1		3.5 eq CH_3ONa	Room temperature (14-18°C)	49	20	16
2		3.5 eq CH_3ONa	25°C	50.7	23.8	24.8
3		3.5 eq CH_3ONa	35°C	42.5	26	16.6
4		4.2 eq NaOH	25°C	15.6	80.8	3.6
5		4.2 eq NaOH	25°C	-	100[d]	-

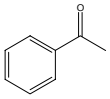
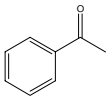
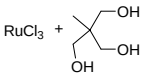
Reactions were conducted in methanol with a 0.1 M solution of ketone, 1 mol% catalyst wrt substrate and the catalyst was heated at 35°C, 50 bar for 5h before to add the substrate ("catalyst activation"), eq base wrt catalyst, substrate: acetophenone, pressure 10 bar; Mechanical stirrer (rpm 685 MAX). (a) Determined by ^1H NMR; (b) reactions were conducted without previous "catalyst activation"; (c) Reactions were conducted in methanol with a 0.6 M solution of ketone, for 21h; (d) solvent:: methanol 95ml and water 30ml.

Table 2.7: Hydrogenation of aromatic substrates using ruthenium-catalyst

12.2.2 Synthesis of phosphorus ligands

The possibility of introducing phosphorus groups in the ligand was analyzed. In fact phosphorus and amine compounds are good ligands often used with transition metal for the catalytic reduction of aromatic rings.[9]

Initially PPh_3 was used; two tests were carried out, the first using $RuCl_3$ and three equivalents of PPh_3 (entry 1, table 12.8), but the conversion was much lower than the same reaction carried out without phophorus ligands (entry 2, table 12.1).

Entry	*Substrate*	*Catalyst*	*Base*	*Conv. (%)[a] 20h*		
						
1		$RuCl_3$ + 3eq PPh_3	-	2.6	2.4	1
2		 + 1eq PPh_3	3.5 eq CH_3ONa	18	6	4.5

Reactions were conducted in methanol with a 0.6 M solution of ketone, 1mol% catalyst wrt substrate, eq CH_3ONa wrt catalyst, pressure of H_2 10 bar, room temperature. (a) Determined by ^1H NMR.

Table 12.8: Hydrogenation of acetophenone using ruthenium-catalyst and sodium alkoxides.

The second experiment was done adding 1 equivalent of PPh_3 to $RuCl_3$, 1,1,1-tris(hydroxymethyl)ethane, and sodium methoxide (entry 2, table 12.8), however as in the previous reaction (entry 1), the conversion was lower than the corresponding reaction conducted without PPh_3 (entry 3, table 12.1).

Nevertheless, the phosphorus group was introduced in the ligand structure. The ligand **2** (figure 12.3) was obtained from 3-methyl-3-oxetanemethanol using $LiPPh_2$ as nucleophilic reagent, after previous alcohol deprotonation by *n*-BuLi. The product **2** was purified by crystallization from toluene and pentene.

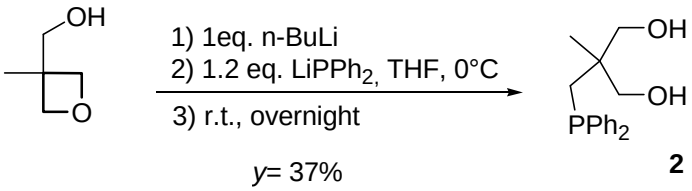
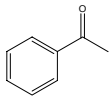
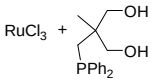


Figure 12.3: Synthesis of 2-((diphenylphosphino)methyl)-2-methylpropane-1,3-diol.

It was tested in the reduction of acetophenone and the conversion was very poor (entry 1, table 12.9),. The amount of base was reduced because in the ligand there were only two OH to deprotonate.

Entry	*Substrate*	*Catalyst*	*Base*	*Conv. (%)[a] 20h*		
						
1			2 eq CH_3ONa	4.5	1.5	1

Reactions were conducted in methanol with a 0.6 M solution of ketone, 1mol% catalyst wrt substrate, eq CH_3ONa wrt catalyst, pressure of H_2 10 bar, room temperature. (a) Determined by ^1H NMR.

Table 12.9: Hydrogenation of acetophenone using ruthenium-ligand **2** complex.

Therefore also an amino group was also introduced in the ligand, and compound **7** was synthesized using the following procedure (figure 12.4). After synthesis of compound **3**, from 3-methyl-3-oxetanemethanol by easily nucleophilic substitution with MsCl, NaN_3 was used as nitrogen nucleophile to obtain **4**. The crude reaction of **4** was immediately converted into the amine **5** because of the instability of **4**. The azide **4** was converted into amine **5** using Staudinger Reaction (mild azide reduction) as reported in literature[10] and the reaction product **5** was purified by chromatography.

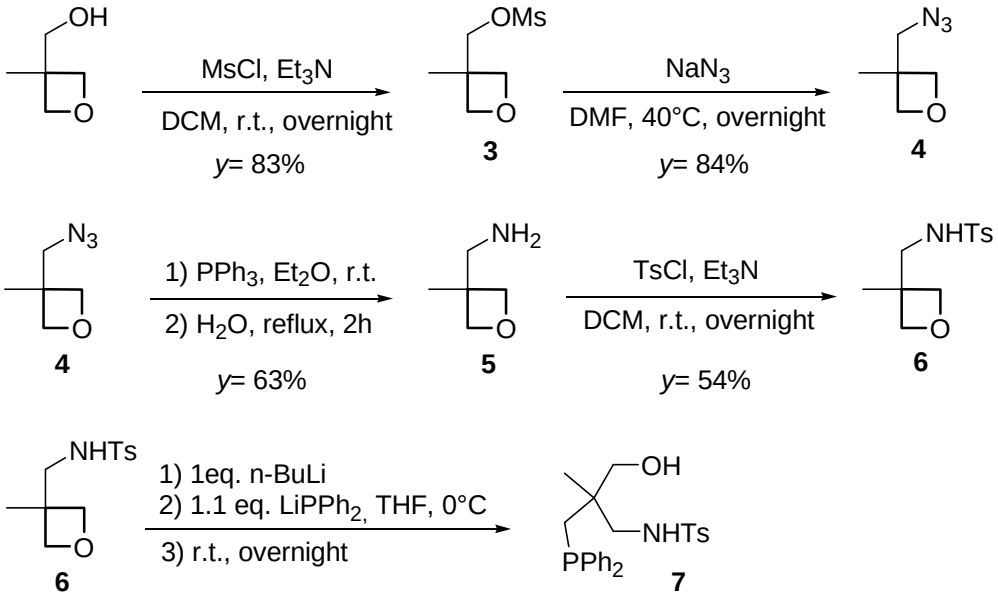
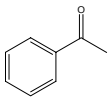
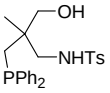


Figure 12.4: Synthesis route for ligand **7**.

The ligand **7** (figure 12.5) was obtained from compound **6** using the same procedure utilized for obtaining ligand **2**. Unfortunately, compound **7** was obtained as white oil impure with starting material **6** and $HPPh_2$. Despite that the ligand (**7**) was not pure, the hydrogenation reaction carried out using **7** as ligand was attempted. The conversion was very low (entry 1, table 12.10).

Entry	*Substrate*	*Catalyst*	*Temperature*	*Pressure*	*Conv (%)[a] 21h*		
							
1		$RuCl_3$ + 	25°C	10 bar	3	1.3	1

Reactions were conducted in methanol with a 0.1 M solution of ketone, 1mol% catalyst wrt substrate , 3.5 eq CH_3ONa wrt catalyst, Mechanical (rpm 685 MAX). (a) Determined by ^1H NMR.

Table 12.10: Hydrogenation of acetophenone using ruthenium-ligand **7** complex.

12.3 Conclusion

During the optimization of reaction conditions, temperature was found to be very important for the catalyst activity (25°C). Pressure does not seem to have a strong influence on the conversion, but the stirrer has a big effect. For this reason, the stirrer and the concentration of substrate should be studied more, because we hypothesise that the catalyst does not operate effectively in homogeneous phase, but in colloidal phase (heterogeneous). In a recent review of Dyson[8], it has been reported that a large number of catalysts for arene hydrogenation work in colloidal phase.

Sodium hydroxide showed to be a good base, and more easy to handle than sodium methoxide. The ratio base wrt catalyst seems to be a influence parameter on the reaction, probably because a higher pH of reaction could improve the catalyst activity.[8] Nevertheless, the best reaction conditions were obtained using NaOH as base and adding water and methanol together as solvent, in this case a complete conversion in 1-cyclohexyl-ethanol was obtained. Actually, water seems

to be a good solvent for the catalyst, this was also demonstrated as no catalyst was found on the bottom of the autoclave like in the previous cases (see figure 2.11, experimental section).

Phosphorus ligands (**2** and **7**) were used instead of triol, in order to improve the catalytic performance but, as the results show, phosphines and amine compounds are not good ligands for this type of catalyst.

Also diol was tested as a ligand and the result obtained in the hydrogenation reaction of cyclohexyl methyl ketone (entry 1, table 12.4) was good (71% conv. vs 95% conv. of triol). This data suggests further study of alcohol ligands as they seem to be more active.

12.4 Experimental Section

General: All reactions, unless otherwise stated, were run under an atmosphere of argon in flame or oven dried glassware (round bottomed flasks or Schlenk tubes). Room temperature refers to ambient room temperature (20-22 °C); 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by Thin Layer Chromatography (TLC) using aluminium backed silica gel 60 (F254) plates, visualized using UV254 nm and PMA, potassium permanganate or ninhydrin dips as appropriate. Flash column chromatography was carried out routinely using 60 Å silica gel (Merck). NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or DPX-400 (400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million downfield from $(CH_3)_4Si$. Coupling constants (J) are measured in hertz. Enantiomeric excesses were determined by GC analysis (Hewlett Packard 5890A gas chromatography, Cyclodextrin-β-236M-19 (CHROMPAC, 50m)) as stated. Elemental analyses were performed using the Exeter Analytical Model CE440. The hydrogenation reactions were conducted in a high pressure autoclave (300 ml) which is commercially available from the Parr Ltd. Company.

NaH 60% in mineral oil was used after washed 3 times with anhydrous pentane, immediately before use (the quantity of NaH reported refers to NaH 60% in mineral oil).

General procedure for the hydrogenation catalysed by $RuCl_3$, 1,1,1-Tris(hydroxymethyl)ethane and sodium methoxide.

In a dried round bottom flask, anhydrous methanol (10 mL) was added to NaH (17 mg, 0.437 mmol, 3.5 eq). In another dried round bottom flask, $RuCl_3.3H_2O$ (26 mg, 0.125 mmol, 1 mol%) and 1,1,1-tris(hydroxymethyl)ethane (15 mg, 0.125 mmol) were dissolved in anhydrous methanol (10 mL), then stirred for 5 min. The solution of sodium methoxide was added and the mixture was allowed to stir for 30 min, the colour change from black to dark brown. Then acetophenone (1.15 mL, 12.48 mmol) was added to solution of catalyst. The mixture was transferred into the autoclave. It was purged with hydrogen for 10 seconds and finally the hydrogen was introduced to 10 bar. The reaction mixture was stirred vigorously at the temperature and for the time each time indicated. The mixture was filtered through a pad of silica gel and the pad was washed with a 50% solution of ethyl acetate in hexane (50 mL). The filtrate was concentrated under reduced pressure to afford the reduction reaction crude.

2-((diphenylphosphino)methyl)-2-methylpropane-1,3-diol (2) [10]

To a solution of 3-methyl-3-oxetanemethanol (0.25g, 0.25mL, 2.5mmol) in THF (5mL) was added dropwise at 0ºC, *n*-BuLi (1mL, 2.5mmol, 1.0eq). The solution was allowed to stir at room temperature for 1h. To a solution of Ph_2PH (0.56g, 0.52mL, 3mmol, 1.2eq) in THF (6 ml) at 0ºC was added drop wise n-BuLi (1.2mL, 3mmol, 1.2eq), and the solution was allowed to stir at room temperature for 1h.

Than to the first solution was cooled again at 0ºC, and the solution of Ph_2PLi was added drop wise. The resulting red-orange mixture was stirred at room temperature overnight. Than the solvent was removed under reduce pressure. To the residue oil was added water (5ml, degassed) and extract with ether (10ml, degassed). The aqueous layer was washed two times with ether (2 x 10ml, degassed). The organic layers were dried over $MgSO_4$.

The product was obtained as a white crystalline solid (0.26g, 37%), for crystallization from toluene and pentane.

mp= 95-97°C, ν (solid)/cm^{-1}: 3298, 1437, 1178, 1026; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.51-7.50 (2H, m, Ar-H), 7.34-7.32 (3H, m, Ar-H), 3.63 (2H, d, J=11.93 Hz, CH_2O), 3.56 (2H, d, J=11.49 Hz, CH_2O), 4.62 (2H, d, $^{2}J_{P-H}$ =3.39 Hz, CH_2OH), 0.89 (3H, t, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 164.23 (d, $^{1}J_{P-C}$= 48 Hz, C-Ar), 132.87 (d, $^{2}J_{P-C}$ =19 Hz, 2CH-Ar), 128.81 (s, CH-Ar), 128.57 (d, $^{3}J_{P-C}$ =7.5 Hz, 2CH-Ar), 70.79 (d, $^{3}J_{P-C}$ =8.6 Hz, $2CH_2$), 39.99 (d, $^{2}J_{P-C}$ =11.1 Hz, C), 34.15 (d, $^{1}J_{P-C}$ =14.9 Hz, CH_2), 20.45 (d, $^{3}J_{P-C}$ =9.8 Hz, CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ= -26.02. HRMS: calc. for C17H21O2P: 288.1279. Found: 288.1288. MS: m/z (EI)= 288(M+,13), 199(100), 183(63), 108(33), 91(27). Anal. Calculated for $C_{17}H_{21}O_2P$: C 70.82; H 7.34; P 10.74. Found: C 70.52; H 7.29; P 11.02.

(3-methyloxetan-3-yl)methylmethanesulfonate (3)

To a solution of 3-methyl-3-oxetanemethanol (0.25g, 0.25mL, 2.5mmol) in DCM at 0ºC were added Et_3N (0.76g, 1mL, 7.5mmol, 3eq) and dropwise methanesulfonate chloride (0.37g, 0.25mL, 3.25mmol, 1.3eq). The mixture was stirred for 30 minute at 0ºC then overnight at room temperature.

The mixture solution was quenched with saturated solution of $NaHCO_3$ (40mL). The organic layer was collected and the aqueous layer was further extracted with ether (2 X 20mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give the crude, that was purify by chromatography (R_f.(Et_2O)=0.15) to give a pale yellow solid (3.37g, 83%);

mp= 42-43°C, ν (solid)/cm^{-1}: 2966, 2883, 1339, 1165; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 4.52 (2H, d, J 6.2Hz, CH_2O), 4.43 (2H, d, J 6.2Hz, CH_2O), 4.32 (2H, s, CH_2OS), 3.07 (3H, s, CH_3S), 1.39 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 78.82 (s, $2CH_2O$), 73.28 (s, CH_2OS), 39.28 (s, C), 37.34 (s, CH_3S), 20.63 (s, CH_3); Anal. Calculated for $C_6H_{12}O_4S$: C, 39.99; H, 6.71. Found: C.39.86; H, 6.63.

3-(azidomethyl)-3-methyloxetane (4) [10]

To a solution of (3-methyloxetan-3-yl)methylmethanesulfonate (1.50g, 8.32mmol) in DMF (45mL) at 40ºC was added NaN_3 (2.71g, 41.62mmol, 5eq), and then the reaction mixture was allowed to stir at 40ºC overnight.

Diethyl ether (45mL) and water (45mL) were then added. The organic phase was extracted with diethyl ether (2 x 45mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure to give the crude product as a pale yellow oil (0.88g, 84%);

V (neat)/cm^{-1}: 2932, 2869, 2094; ^1H NMR (300 MHz, $CDCl_3$): δ=4.46 (2H, d, J=6.0Hz, CH_2O), 4.39 (2H, d, J=6.2Hz, CH_2O), 3.55 (2H, s, CH2N3),1.34 (3H, s, CH_3); ^{13}C NMR (100Hz, $CDCl_3$): δ= 80.0, 58.5, 40.2, 21.6.

(3-methyloxetan-3-yl)methanamine (5) [10]

PPh_3 (10.94g, 41.74mmol, 6eq) was added to a stirred solution of crude product 3-(azidomethyl)-3-methyloxetane (0.88g, 6.95mmol) in diethyl ether (250mL). The reaction mixture was then stirred under nitrogen at room temperature overnight. To the mixture was then additioned of water (1mL) and it was refluxed for 2h. The solvent was removed under reduced pressure. The residue was purified by filtration on silica pad with diethyl ether to remove the phosphorus compounds, then with methanol to obtain the product as a brown oil (0.44g, 63%)

V (neat)/cm^{-1}: 3357, 2959, 2872, 1570, 1316; ^1H NMR (400MHz, $CDCl_3$): δ= 4.44 (2H, d, J=5.8Hz, CH_2O), 4.37 (2H, d, J=5.8HZ, CH_2O), 2.88 (2H, s, CH_2NH_2), 1.40 (2H, br s, NH_2), 1.28 (3H, s, CH_3); ^{13}C NMR (100MHz, $CDCl_3$): δ= 80.39 (2C), 49.3, 40.5, 21.3.

4-methyl-n-((3-methyloxetan-3-yl)methyl)benzenesulfonamide (6)

To a solution of (3-methyloxetan-3-yl)methanamine (0.44g, 4.39mmol) in CH_2Cl_2 at 0ºC were added Et_3N (0.76g, 1mL, 7.5mmol, 1.7eq) and drop wise *p*-toluenesulfonyl chloride (0.84g, 4.39mmol, 1eq). The mixture was stirred for 30 minute at 0ºC than overnight at room temperature.

The mixture solution was quenched with water (10mL) and extracted with CH_2Cl_2 (2 x 10mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give the crude, that was purify by chromatography (R_f.(Et_2O)=0.35) to give a white solid (0.60g, 54%);

mp= 90-91°C; V (solid)/cm^{-1}: 3172, 2953, 2885 , 2360, 1327,1157; ^1H NMR (400MHz, $CDCl_3$): δ= 7.76 (2H, d, J=8.3Hz, Ar-H), 7.33 (2H, d, J=8.0Hz, Ar-H),

4.71 (1H, br s, NH), 4.35 (2H, d, J=6.0Hz, CH_2O), 4.33 (2H, d, J=6.3Hz, CH_2O), 3.12 (2H, d, J=6.8Hz, CH_2NH), 2.44 (3H, s, CH_3-Ar), 1.26 (3H, s, CH_3-C); ^{13}C NMR (100MHz, $CDCl_3$): δ= 143.73 (1C, s, C-Ar), 136.75 (1C, s, C-Ar), 129.87 (2C, s, CH-Ar), 127.12 (2C, s, CH-Ar), 79.93 (2C, S, CH_2O), 49.87 (1C, s, CH_2NH), 39.44 (1C, s, C-CH_3), 21.55 (2C, s, CH_3-C+CH_3-Ar).

HRMS: calc. for $C_{12}H_{17}NO_3S$: 256.1005. Found: 256.1007 MS: m/z (EI)= 256(M+,6), 183(6), 154(29), 90(100), 70(54). Anal. Calculated for $C_{12}H_{17}NO_3S$: C 56.45; H 6.71; N 5.49. Found: C 56.40; H 6.68; N 5.35.

n-{2-[(Diphenylphosphanyl)-methyl]-3-hydroxy-2-methyl-propyl}-4-methyl-benzenesulfonamide (7) [10]

To a solution of 4-methyl-n-((3-methyloxetan-3-yl)methyl)benzenesulfonamide (0.30g, 1.2 mmol) in THF (10 ml), n-BuLi (0.75 mL, 1.2 mmol) was added drop wise at 0ºC. The solution was allowed to stir at room temperature for 1h. To a solution of Ph_2PH (0.26g, 0.24mL, 1.4mmol, 1.1 eq) in THF (5 mL) at 0ºC n-BuLi (0.87 mL, 1.4 mmol) was added dropwise, and the solution was allowed to stir at room temperature for 1h.

Then the first solution was cooled again at 0ºC, and the solution of Ph_2PLi was added drop wise. The resulting red-orange mixture was stirred at room temperature overnight. Then the solvent was removed under reduced pressure. The residue oil was treated with water (5ml, degassed) and extract with ether (10mL, degassed). The aqueous layer was washed two times with diethyl ether (2 x 10mL, degassed). The organic layers were dried over $MgSO_4$.

The product was difficult to purify and was obtained as a white oil impure of starting material and of diphenylphosphine (crude: 0.54g).

^1H NMR (400 MHz, $CDCl_3$): δ= 7.58 (2H, d, J=8.28 Hz, Ar-H Ts), 7.49-7.41 (4H, m, Ar-H), 7.35-7.30 (6H, m, Ar-H), 7.27 (2H, d, J=8.40 Hz, Ar-H Ts), 4.49 (1H, t, J=6.78 Hz, NH), 3.61 (1H, d, J=11.54 Hz, CH_2OH), 3.35 (1H, d, J=11.54 Hz, CH_2OH), 2.83 (1H, q, J=13.55 Hz, J=7.28 Hz, CH_2NH), 2.77 (1H, q, J=13.55 Hz, J=7.28 Hz, CH_2NH), 2.42 (3H, s, CH_3-Ts), 2.13 (2H, d, J=3.01 Hz, CH_2-P), 0.91 (3H, s, CH_3-C); ^{31}P NMR (121 MHz, $CDCl_3$) δ= -28.0.

12.4 References

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Appendix

Appendix 1

1.1 One pot three-steps procedure for reagent fused benzo-1,2,3-thiadiphosphole

The reaction was conducted in a 150 mL three-necked flask equipped with a condenser, a dropping funnel, and with inlet for dry N_2. A mixture of *p*-methylthioanisole (0.04 mol) and $AlCl_3$ (0.03 mol) was stirred under N_2 for about 10 minutes (until the $AlCl_3$ was completed soluble) during which the colour changed to yellow-pink. Then PCl_3 (0.04 mol) was added, and the resulting red-brown solution stirred for 10 minutes. After that other PCl_3 (0.012 mol) was added, the N_2 flow stopped and the mixture heated to reflux (90-100°C) for 6-8 hours.

The reaction was monitored using GC-MS. When the reaction was finished the solution was cooled down to 0°C and CH_2Cl_2 (30 mL) was added. The resulting solution was treated under stirring with water. Extraction with CH_2Cl_2 (30 mL) and subsequent crystallization of the crude product from CH_2Cl_2-Et_2O gave pure reagent **1**.

40-60%; White crystals; m.p. = 157-159°C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.41 (d, 2H, J_{PH} = 8.0 Hz), 7.25 (d, 2H, $^1J_{HH}$ = 7.5 Hz), 6.98 (d, 2H, $^1J_{HH}$ = 7.5 Hz), 2.28 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$ 75.46): 141.6, 139.96 (d, J_{PC} = 29.6 Hz), 135.5 (d, J_{PC} = 7.4 Hz), 131.7 (d, J_{PC} = 27.7 Hz), 130.5, 124.9, 20.8; ^{31}P NMR (121.47 MHz, $CDCl_3$, ext. 85% H_3PO_4): 65.4 (d, J_{PP} 211.5 Hz), 88.3 (d, J_{PP} 211.5 Hz); GC-MS (m/z, %): 243 (M^+), 211, 153, 121, 77, 63; HRMS (EI) calcd for $C_{14}H_{12}P_2S_2$: 305.9855, found: 305.9859.[1]

2,10-dimethyl[1,2,3]benzothiadiphospholo[2,3-b][1,2,3]benzothiadiphosphole 12-oxide (1') : ^{31}P NMR (161.90 MHz, $CDCl_3$, ext. 85% H_3PO_4): 20.0 (d, J_{PP} 256.6 Hz), 100.9 (d, J_{PP} 256.6 Hz).

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Appendix 2

2.1 Characterization of 4-methyl-2-[(5-methyl-2-sulfanylphenyl) phosphanyl]benzenethiol (A)

After the reaction between reagent **1** and Grignard reagents, the solvent is partially evaporated and the reaction mixture is treated with aqueous acid solution (HCl). Extraction with CH_2Cl_2 give a mixture of phosphines and the residue **A**. The phosphines are easily separated from **A** by treating the organic solution with aqueous NaOH; after this treatment, the sodium salt of **A** is dissolved in the aqueous solution, whereas the phosphines are in the organic phase. Compound **A** is recovered (90%) from the basic aqueous layer by acidification and extraction with dichloromethane, and is then purified by distillation and stored under argon. Simple treatment of a dry solution of compound **A** with an equimolar amount of PCl_3 led to the regeneration of the starting reagent **1** in almost pure form, allowing it to be reused without further purification.[1]

4-Methyl-2-[(5-methyl-2-sulfanylphenyl)phosphanyl]benzenethiol[1] (**A**): 90%, colorless liquid, b.p. 110–1158C (0.5 mmHg);[1]H NMR (400 MHz, $CDCl_3$, TMS): 2.23 (s, 6H, CH_3), 4.30 (br s, 2H, exch. with D_2O, SH), 5.29 (d, 1H, J_{PH}=228 Hz, PH), 6.99–7.07 (m, 2H), 7.07–7.12 (m, 2H), 7.63–7.72 (m, 2H); ^{31}P NMR (161.89 MHz, $CDCl_3$, ext. 85% H_3PO_4): -52.0 ppm (br d, J_{PH}=228 Hz). HRMS (EI) calcd for $C_{14}H_{15}PS_2$: 278.0353, found: 278.0355.

2.2 Reduction of 2,2'-(oxidophosphoranediyl)bis(4-methylbenzenethiol) (A')

After a long storage (also under argon) or after extraction, it is possible to find compound **A** impure of corresponding oxidized derivate **A'**. In these cases it is not necessary purified again compound **A** by distillation, because also the oxide derivative **A'** can react with PCl_3 to produce the corresponding oxidized compound of reagent **1** (**1'**).

Reduction procedure of a mixture of 1 and 1': To a mixture containing both compounds **1** and **1'** was added toluene as solvent and an excess of $HSiCl_3$ (respect to the quantity of **1'**). The solution was heated to reflux for 2-3 hours, until the reduction was completed (reaction followed by ^{31}P NMR spectroscopy). Then the solution was cooled down and added 1-2 ml of water (to remove the excess of $HSiCl_3$). The mixture was extracted with CH_2Cl_2, and reagent was re-crystallized from a solution of CH_2Cl_2 and Et_2O.

2,2'-(oxidophosphoranediyl)bis(4-methylbenzenethiol) (**A'**): white grease solid; ^1H NMR (300 MHz, $CDCl_3$, TMS): 2.30 (s, 6H) 7.26-7.18 (m, 2H), 7.34-7.27 (m, 2H), 7.43-7.52 (m, 2H) 8.29 (d, 1H, J_{PH}= 509 Hz, PH); ^{13}C NMR (75.46 MHz, $CDCl_3$): 136.3 (d, *J*=12 Hz), 134.3 (d, *J*=12 Hz), 133.8 (d, *J*=11 Hz), 133.5 (d, *J*=2.4 Hz), 132.9 (d, *J*=9 Hz), 129.1 (d, *J*=106 Hz), 20.6; ^{31}P NMR (121.45 MHz, $CDCl_3$, ext. 85% H_3PO_4): 19.0 ppm (br d, J_{PH}= 509Hz).

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Appendix 3

3.1 Synthesis of cis-2,6,10-trimethyl[1,3] benzathiophospholo-[2,3b]benzathiophosphole

To a stirred slurry of anhydrous $AlCl_3$ (16.8 mmol) in 1,2-dichloroethane (15 mI) was added dropwise CH_3COCl (10 mmol) the temperature being kept at 5-10 °C. fused benzo-1,2,3-thiadiphospholes (7.2 mmol) was then added similarly over ca. 10 min. The mixture was brought to, and held at 25°C with stirring for 20 min. The reaction was monitored by t.l.c. (light petroleum as eluant) and GC-MS spectrometry. The cis-product was purified by filtration of the mixture on a Florisil column with cyclohexane-CH_2Cl_2 (90:10) as eluant and obtained in 79% yield.

cis-2,6,10-trimethyl[1,3] benzathiophopholo-[2,3b]benzathiophosphole [1]:
white solid, p.f. 160-163°C; ^{1}H NMR(200Hz, $CDCl_3$) δ= 2.21 (d, J_{HP} 16.4 Hz, 3H), 2.29 (s, 6H), 7.01-7.08(m,4H),7.27 (bd, J_{HP} 7.0 Hz, 2H); ^{13}C NMR(50.30Hz, $CDCl_3$) δ= 20.7, 27.8 (d, J_{CP} 28.5 Hz), 71.3 (d, J_{CP} 23.6 Hz), 121.7, 130.7, 130.7 (d, J_{CP} 23.5 Hz), 135.4 (d, J_{CP} 7.2 Hz), 136.6 (d, J_{CP} 14.8 Hz), 142.9(d, J_{CP} 2.8 Hz), ^{31}P NMR{1H}(32.20Hz, $CDCl_3$, ext. 85% H_3PO_4) δ= 63.4; HRMS (EI) calcd for $C_{14}H_{15}PS_2$: 302.0353, found: 302.0353; Elem. Anal.: found H, 5.03; C, 63.54; P, 10.25; S, 21.18. $C_{16}H_{15}PS_2$ calcd H, 5.00; C, 63.55; P, 10.24; S,21.19%.

(1) Baccolini, G., Mezzina, E., *J. Chem. Soc., Perkin trans 1* **1990**, 19.