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Sauli Vuoti

SYNTHESES AND CATALYTIC PROPERTIES OF PALLADIUM (II) COMPLEXES OF VARIOUS NEW ARYL AND ARYL ALKYL PHOSPHANE LIGANDS

FACULTY OF SCIENCE,
DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF OULU

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SAULI VUOTI

SYNTHESES AND CATALYTIC PROPERTIES OF PALLADIUM (II) COMPLEXES OF VARIOUS NEW ARYL AND ARYL ALKYL PHOSPHANE LIGANDS

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Abstract

Thirty three aryl and aryl alkyl phosphane ligands were prepared and characterized for catalytic purposes. The aryl groups in both types of ligands were modified with alkyl substituents (methyl, ethyl, isopropyl, cyclohexyl, phenyl) or hetero substituents (methoxy, N,N-dimethylaniline, thiomethyl). The alkyl groups directly attached to the phosphorous atom were ethyl, isopropyl or cyclohexyl. Mono- and in some cases also dinuclear palladium (II) complexes of the ligands were prepared and characterized. The syntheses of the palladium complexes are solvent-dependent and afford either mono- or dinuclear complexes depending on the choice of the solvent. Additionally, two 2-mercaptobenzothiazole palladium complexes were synthesized and characterized. A rare distorted lantern-type structure was presented for the first time.

The ligands were characterized by ^{1}H, ^{13}C, ^{31}P NMR spectroscopy and mass spectrometry. The palladium complexes were characterized by ^{31}P NMR spectroscopy, X-ray crystallography and elemental analysis. Links between the NMR data of the palladium complexes and ligands and their catalytic activity was screened and correlation found. The crystal structures of the palladium complexes were studied for possible attractive interactions between two ligands. Such interactions were found from two examples. There is an attractive interaction between the phenyl and quinolinyl moieties of 2-quinolinyldiphenyl phosphane. A similar interaction was found between the methyl substitute and phenyl ring of *o*-tolylphosphane.

The ligands and palladium complexes presented in this thesis were prepared in hope of finding suitable catalysts for Suzuki coupling reactions of various bulky aryl halides and phenyl boronic acids to prepare sterically hindered bi- and triaryls under microwave irradiation. A selection of aryl alkyl phosphane ligands catalyzed the couplings of bulky aryl bromides and even unactivated aryl chlorides efficiently and produced high yields. The reaction conditions of a new catalyst system were optimized, and it was noticed that the addition of a small amount of water enhanced the purity and yield of the coupling products further.

Keywords: alkyl phosphane, Aryl phosphane, palladium complex, Suzuki coupling, unactivated aryl chloride

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The present study was carried out in the Department of Chemistry at the University of Oulu during the years 2003-2007.

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Oulu, October 2007 Sauli Vuoti

Symbols and abbreviations

Bu	butyl
cod	cyclooctadiene
Cyc	cyclohexyl
DMF	dimethylformamide
Et	ethyl
i-Pr	isopropyl
K_2CO_3	potassium carbonate
L	ligand
Me	methyl
$MgSO_4$	magnesium sulphate
MW	microwave irradiation
NMe_2	dimethylamino
NMR	nuclear magnetic resonance
OMe	methoxy
Pd	palladium
Pd : P	ratio of palladium to phosphorous
Ph	phenyl
SMe	thiomethylphenyl
THF	tetrahydrofuran
Tolyl	methylphenyl

List of original papers

I Vuoti S, Haukka M, Pursiainen J (2007) Mono and dinuclear palladium complexes of o-alkyl substituted arylphosphane ligands: solvent-dependent syntheses, NMR-spectroscopic characterization and X-ray crystallographic studies. J. Org. Met. Chem. 22, 5044-5052.

II Vuoti S, Haukka M, Pursiainen J (2007) Two isomers of $Pd_2(S_2NC_7H_4)_4$. Acta Cryst. Article in press.

III Autio J, Vuoti S, Haukka M, Pursiainen J (2007) Palladium (II) complexes of 2-, 3-, and 4-quinolinyl(diphenyl)phosphane and di-(3-quinolinyl)phenyl-phosphane: Synthesis, characterization, and catalytic screening. Inorg. Chim. Acta. Article in press.

IV Vuoti S, Autio J, Laitila M, Haukka M, Pursiainen J (2007) Palladium-catalyzed Suzuki-Miyaura cross-coupling of various aryl halides using ortho-alkyl substituted arylphosphanes and (ortho-alkylphenyl)alkyl phosphanes under microwave heating. Eur. Jour. Inorg. Chem. Article in press.

V Vuoti S, Autio J, Haukka M, Lajunen M, Pursiainen J (2007) Effective new palladium catalysts for the Suzuki coupling of various halo xylenes to prepare sterically hindered bi- and triaryls. Journal of Molecular Catalysis A: Chemical. Submitted.

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1 Introduction

Coordination chemistry is understood, in classical terms, as the interaction between a metal center and ligands. The latter are complexing groups that can either donate electron density to or accept it from a metal atom. Ligands can be charged ions or neutral molecules possessing lone pairs of electrons, which can interact with a metal center in various ways. The easiest and most straightforward way to affect the chemical behavior of a metal ion and its properties as a metal complex is through changes in its ligands. One of the basic principles of coordination chemistry is that changes within the first coordination sphere of a metal ion can have a striking impact on the entire complex and its chemical properties [1].

In coordination chemistry, it is essential to understand how ligands are bonded to the metal atoms in order to understand their chemical properties as metal complexes. The metal atoms in organometallic complexes are usually in low-positive, zero or negative formal oxidation states. Forming bonds with ligands typically stabilize these low oxidation states by delocalizing the high electron density of the metal atom onto the ligand. The interactions between ligands and metal atoms depend on the orientation of the orbitals with respect to each other. Ligands are normally classified into three types according to their interactions: σ-donor ligands, π-acceptor ligands and π-donor ligands. The σ-donor ligands have an electron pair capable of being donated directly to an empty metal orbital. π-donor ligands can donate electrons from a filled p-orbital of a ligand. In π-acceptor ligands, σ-donation is complemented by the ability of the ligand to accept electron density from the metal onto suitable acceptor orbitals. In the past the most common ligand known to implement simultaneous σ-donation and π-acceptor properties was the carbonyl ligand CO. However, in recent decades CO has been replaced by various phosphane ligands, which allow strict control of the ligand's properties by introducing particular substituents onto the phosphorous atom [2-4].

Coordination compounds of metal-phosphane complexes play an important role in homogenous catalysis, where the organotransition metal catalyst and reagents are present in the same phase. Moreover, the coordination of substrates and loss of products in catalysis must occur with low activation energy, which requires that the metal complexes must be labile. These labile complexes are often coordinatively unsaturated in the sense that they contain a free coordination site or at most a site that is only weakly coordinated. Phosphanes serve as perfect ligands for these purposes [5].

Preparing new ligands and their metal complexes and screening them for catalytic purposes has been one of the major areas of development in organometallic chemistry for several years now [5].

1.1 Phosphane ligands

Phosphane ligands contain a lone electron pair on the phosphorous atom, which is used for the formation of a σ-bond with metals. π-back bonding from the d-orbitals of metals in low oxidation states is important in electron-rich metals. The P-R σ*-orbitals are utilized for π-back bonding, and the empty phosphorous 3d-orbitals also play a role in this. This role is greater for alkylphosphanes than for trifluorophosphanes and other phosphanes with electron withdrawing groups. The nature of the R-groups attached to the phosphorous determines the relative donor/acceptor ability of the ligand. Therefore altering the R-group can elicit changes in the properties of the ligands. The steric qualities of a phosphane can also be altered through various sizes and shapes of the R-groups. Steric and electronic properties provide the basis for the selection of a particular ligand for catalytic purposes. Understanding of the ligand system is regarded as the first essential step toward catalyst design, since steric and electronic properties of the ligand can radically influence the rate and selectivity of catalytic reactions [1, 3, 6].

Most commercial homogenous catalysts are based on phosphane-metal complexes. Typical catalytic reactions include hydrogenation, hydroformylation, hydrosilylation, hydrocyanation, oligomerization, polymerization and various inter- and intramolecular coupling reactions. Phosphanes have an ability to stabilize low oxidation states of transition metals. Arylphosphanes have a greater steric bulk and weaker bonding affinity for metals relative to the alkylphosphanes and therefore are ideal for the formation of empty or potentially reactive coordination sites in the metal reaction sphere [5].

Tertiary phosphanes of the form PR_3 or PR_2R' are of special importance in organometallic chemistry and are the most widely used type of phosphanes used in homogenous catalysis. Tertiary phosphanes are usually prepared from phosphorous halides and organolithium or Grignard reagents. Tertiary phosphanes are organic derivatives of PH_3, where all hydrogen atoms have been replaced by substituents, which include aryl, alkyl and heteroaryl groups [1, 5]. Triphenylphosphane is probably the most common tertiary phosphane used in homogenous catalysis mainly due to its ready availability and it being quite stable in air [7]. Typically, trialkylphosphanes and mixed arylalkylphosphanes are

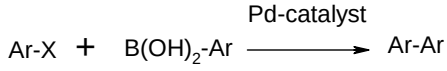
subject to oxidation in air, are expensive, and also are noxious making them awkward to handle. However, when attached to a metal centre, these phosphanes are easy to handle, stable and can be worked on in air. The major difference between the trialkyl and the triaryl phosphanes is the greater σ-donor ability of the former, which provides much higher electron density to the metal [8]. There are examples where either type of phosphanes, trialkyl or triaryl, have been catalytically more efficient than the other. Preparing mixed aryl alkyl phosphanes has given promising results in combining catalytically relevant elements of both types of ligands [9, 10].

Heterodonor phosphanes, which are phosphanes with a heteroatom as a functional group, are also one of the most interesting types of phosphanes from the point of view of catalysis. The different properties of the donor atoms in functionalized phosphane ligands make the environment of the metal centre asymmetrical, and this may considerably alter the reactivity of the complex. Furthermore, ligands that give rise to relatively weak chelate interactions have the possibility for coordinative unsaturation without permanent ligand loss [11].

1.2 Palladium catalyzed coupling reactions

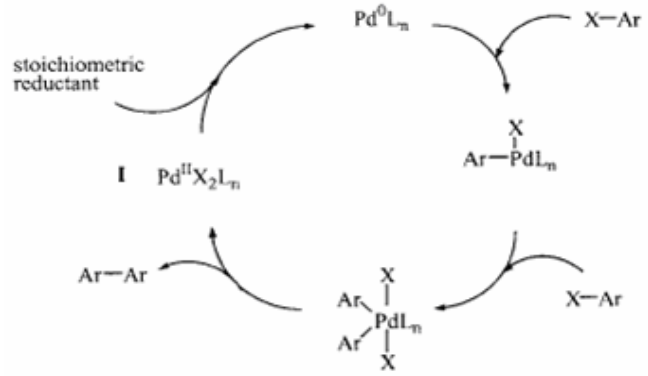
Transition-metal-catalyzed cross-coupling is currently recognized to be one of the most powerful carbon–carbon bond forming reactions. Palladium-catalyzed carbon-carbon and carbon-nitrogen bond forming reactions are widely used in modern organic chemistry. Such catalytic procedures have numerous applications in the preparation of many natural products, in addition to their uses in materials science and the agrochemical industry [12]. The palladium-catalyzed coupling of aryl halides or their synthetic equivalents are very often used in the synthesis of biaryl molecules, whose skeletons are found in a wide range of important compounds including natural products, organic functional materials and building blocks for medicinal products [13].

Among palladium-catalyzed cross-coupling processes, the Suzuki reaction of aryl and vinyl halides/triflates with boronic acids is emerging as a favorite and it has been applied industrially to the production of compounds such as Losartan, a Merck antihypertensive drug. The reaction’s popularity is attributable to a variety of factors, such as the commercial availability of a large number of boronic acids, in addition to their nontoxic nature and stability to heat, air and moisture. Furthermore, the boron-containing by-product of the Suzuki cross-coupling can readily be separated from the desired compound [12,14].



Scheme 1. The Suzuki reaction.

Great efforts have been directed toward the development of efficient catalytic systems for Suzuki cross-coupling reaction during the past few years [15]. Access to new ligand types is a critical factor in the design of novel homogeneous transition metal catalysts. Because radical changes in catalytic activity can result from apparently minor modifications of ligand structure, ligand designs that allow systematic variation of steric and electronic properties are particularly valuable [16, 17]. Bulky electron-rich phosphanes, such as trialkylphosphanes and dialkylbiphenylphosphanes, are reported to be highly effective for Suzuki couplings. This is mainly due to their good electronic properties and resistance to oxidation [9, 10, 13, 15]. One of the advantages of ligands that bear the biphenyl and phenyl moieties are that sterically and electronically flexible perturbations are possible by introducing appropriate substituents on the benzene rings. Recently, various bulky and electron rich phosphanes [9, 10, 12] and N-heterocyclic carbenes (NHCs) [13] have been developed as ligands to promote the cross-coupling reaction. The ligands may provide coordinatively unsaturated monophosphane- or monocarbene-ligated complexes and accelerate catalytic steps such as oxidative addition, transmetalation and reductive elimination. As a result, even relatively less-reactive aryl halides can be used effectively in the coupling [10, 13]. Furthermore, these concepts can be applied to other palladium-catalyzed coupling reactions, including those that occur through C-H or C-C cleavage [13].



Scheme 2. A general catalyst cycle for the Suzuki coupling reaction[18].

Collectively, palladium-catalyzed coupling reactions represent some of the most powerful and versatile tools available for synthetic organic chemists. Their widespread popularity partly stems from the fact that they are generally tolerant of a large number of functional groups, which allows them to be utilized in a wide range of applications. However, a major limitation of palladium-catalyzed coupling processes for many years has been the poor reactivity of aryl chlorides. Yet aryl chlorides are more attractive substrates than the corresponding bromides, iodides and triflates from the standpoints of cost and availability. Conventional palladium/triarylphosphane catalysts are only effective for the coupling of certain activated aryl chlorides such as heteroaryl chlorides and substrates that bear electron-withdrawing groups. However, such catalysts are not effective for aryl chlorides in general. Since 1998, major advances have been reported by a number of research groups addressing this challenge. These advances include: the use of catalysts based on bulky, electron-rich phosphanes and heterocyclic carbenes, which have been found to be particularly mild and versatile [12, 18, 19]. However, to date these catalysts have not been successfully used with modern synthetic methods such as microwave-assisted catalysis.

2 Aims of the work

The aim of the present study was to develop new palladium catalysts for the Suzuki coupling reaction of various bulky, and unactivated aryl halides and phenyl boronic acids to prepare sterically hindered biaryls, which are commonly used by the medical industry and other industries. The primary focus was on the development of the synthetic methods and the preparation of palladium complexes and their groundwork catalytic screening when used in conjunction with microwave heating. A second objective was to prepare new mixed aryl alkyl phosphane ligands that would enhance the catalytic activities in Suzuki coupling reactions.

Electronic and steric properties of the ligands were modified by combining different aryl and alkyl groups. This was done in the hope of finding a combination that would lead to high yields for most coupling reactions and especially those involving sterically hindered aryl bromides and unactivated aryl chlorides. As a starting point for the research, previously synthesized aryl and aryl alkyl phosphane ligands with known good catalytic qualities were used, but various new ligands were synthesized when the work progressed. The catalytic activities of these ligands and the factors affecting these activities were studied systematically. Some new building blocks for the syntheses of the new ligands were also used. Both mononuclear and the virtually untested dinuclear palladium complexes of the phosphane ligands were prepared, characterized and screened as potential catalysts in various simple and more demanding coupling reactions between aryl halides and phenyl boronic acids. The previously known ligands studied in this research had not been tested as ligands for the Suzuki coupling reactions before. Furthermore, their palladium complexes are new to science. In general, there are only a few reports in the literature about studies with similar ligands that had been incorporated in palladium chlorides and which also used modern catalytic systems involving microwave heating.

Publications **I-II** describe the development of synthetic methods for convenient and systematic preparation of mono- and dinuclear palladium complexes of various *ortho*-alkyl substituted arylphosphanes. A standard method for producing complexes with the desired nuclearity has not been previously reported, and the formation of complexes with the undesired nuclearity was described as a problem in various papers. Several mono- and dinuclear complexes were prepared, and the structural and chemical features were studied with the emphasis on a few irregularities and general solutions as to how to deal with them.

A study on whether it is possible to combine conventional *ortho*-alkyl substituted arylphosphanes with modern 2-mercaptobenzothiazole units is also included.

In publication **III** we prepared and characterized completely new types of quinolinyldiphenyl and diquinolinylphenyl phosphanes and their palladium complexes. The quinolinyl moieties were initially chosen due to excellent results received with similar pyridyl and N,N-dimethylaniline containing ligands and other chemically related functional groups, which have shown that π-stacking and chelating effects can sometimes remarkably enhance the catalytic activities. The quinolinyl phosphane ligands and their complexes have been screened as potential catalysts using the previously optimized catalyst system. The phosphanes catalyze the coupling reactions of simpler aryl halides and phenyl boronic acids efficiently, but fail to work with more complex building blocks. Similar catalytic activity enhancing effects as described for the aforementioned pyridyl and other related phosphane ligands were not observed.

In publication **IV** the same palladium complexes prepared in publication **I**, as well as a systematical selection of new mixed aryl alkyl ligands and their corresponding palladium complexes based on known efficient building blocks were tested as potential catalysts for the Suzuki coupling reaction. Some general as well as a few more demanding aryl halides and phenyl boronic acids were used in these coupling reactions. An optimized modern catalyst system for the syntheses of various bi- and triaryls under microwave irradiation is also presented. Excellent results can be achieved with some of the new phosphanes under the conditions that were used. Even unactivated aryl chlorides can be utilized as substrates.

In publication **V** we pursued the initial idea of the research even further, keeping in mind the acquired results of publications **III** and **IV**. We prepared sixteen new phosphanes and their palladium complexes in order to complete the series and to find the catalytically most efficient combination of groups. Some of the phosphanes also contained heterodonor groups. The catalysts have been screened and compared with each other in the very demanding coupling reactions involving bulky halo xylenes and a variety of phenyl boronic acids. The results showed that excellent results can be obtained even from the most demanding coupling reactions when particular phosphane ligands are used. The developed catalyst system was also improved to be more environmentally friendly by replacing a part of the organic solvent by water. Previously water was reported to have a yield enhancing effect in a few Suzuki coupling reactions, but in our experiments the method was systematized and successfully used for all types of aryl chloride substituents when microwave irradiation was used.

In this thesis, the results from the aforementioned publications in addition to supplementary structural, synthetic and catalytic data from the research are presented. Moreover, some crystal structures are presented here for the first time. Large-scale correlations between the catalytic data and structural elements are also given. These correlations are based on all the new and previously known phosphane ligands and their palladium complexes studied in the research.

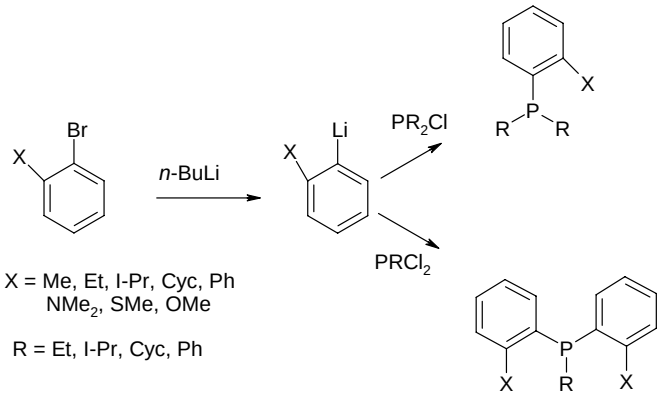
The X-ray crystallographic work was carried out at the University of Joensuu. All synthetic work as well as catalytic screening was performed at the University of Oulu.

3 Synthetic work

3.1 Reagents

Diethyl ether (Lab Scan) was distilled over sodium-benzophenone ketyl under a nitrogen atmosphere before use. Argon was bubbled through dichloromethane (Lab Scan), ethanol (Altia) and n-hexane (Lab Scan) before use. Other solvents were acquired from Lab Scan and nitrogen was bubbled through the solvents if necessary. Argon was bubbled through the silica gel (40 µm, Merck) before the purification of the prepared phosphane ligands. Dry $MgSO_4$ (Merck) was used as a drying agent in the coupling reactions. K_2CO_3 was used without further purification. Other commercial reagents were acquired from Lancaster, Merck or Aldrich and used as received.

3.2 A general procedure for preparing the phosphane ligands



Scheme 3. General reaction routes for preparing the phosphanes presented in this work.

The previously known phosphane ligands *ortho*-methyldicyclohexylphosphane, bis(*ortho*-methylphenyl)isopropylphosphane and *ortho*-cyclohexyldicyclohexylphosphane were used as reference compounds for the preparation of the new arylalkyl phosphane ligands. Modification was achieved by combining either ethyl, isopropyl or cyclohexyl groups directly attached to the phosphorous atom with a methyl, ethyl, isopropyl, cyclohexyl or phenyl group in the *ortho*-position of the

phenyl ring. Furthermore, the alkyl/aryl ratio of the ligand was varied if required by combining two aryl groups and one alkyl group or vice versa. A heterodonor atom (oxygen, nitrogen or sulphur) was also used in the *ortho*-position in some ligands. There are reports in the literature of chelating or stacking effects either enhancing catalytic activity through η^1-π interactions [20-22] and chelating effects [23] or blocking catalytic activity due to chelating effects [24-29]. Therefore a series of bulky, electron rich triphenylphosphane ligands to study potential η^1-π interactions between the *ortho*-substituent and the metal atom were prepared.

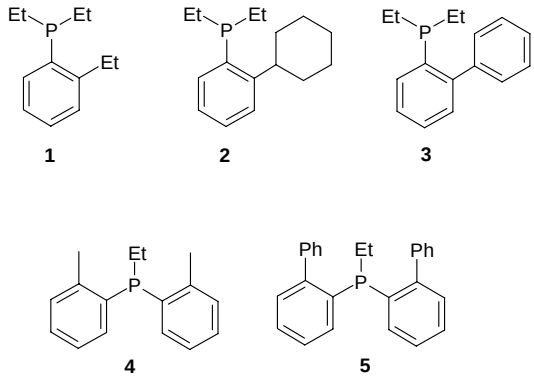
The phosphane ligands were prepared by lithiating a bromoalkylbenzene with *n*-butyl lithium at 0 °C or lower and then adding the appropriate chlorophosphane. The commercial *n*-butyl lithium solution was transferred dropwise *via* a canula into a freshly prepared solution of a bromoalkylbenzene in diethyl ether. After several hours of stirring at 0 °C or less, a solution of the appropriate chlorophosphane in diethyl ether was added dropwise into the mixture and stirring was continued overnight, letting the mixture slowly warm to ambient temperature. The formed solid and liquid layers were separated, and the solid material extracted with diethyl ether. The liquid layers were combined and the solvent removed *in vacuo*. The products were white solids or bright viscous oils after purification. The solid products were recrystallized from ethanol or ethanol/*n*-hexane 1:2 mixture and purified by column chromatography if necessary by using dichloromethane/*n*-hexane 1:2 mixture as the eluent. The oily products were treated with a similar recrystallization procedure and purified by column chromatography whenever possible. All reactions were performed in an inert atmosphere with standard Schlenk-techniques. The reaction route is presented in Scheme 3.

3.2.1 Mixed aryl alkyl phosphane ligands [IV, V]

The bulk of the alkyl groups and the *ortho*-substituents were altered systematically in the hope of finding correlations between the catalytic efficiencies and the steric and electronic properties of the ligands. In general, alkyl phosphane ligands form more stable complexes with metals than those of the aryl phosphanes. This phenomenon is mainly due to the greater σ-donor ability and better orbital overlap of the alkyl phosphanes, which makes the metal-ligand bond stronger [30]. The electronic properties of the mixed aryl alkyl phosphane ligands have not yet been studied extensively. The structures of the ligands prepared in this work are presented in Schemes 4-6.

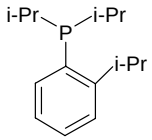
All the ligands were prepared according to the method described in the literature [31] and under the previous heading (section 3.2). Ligands **7**, **11** and **13** are known and their syntheses have been described in the literature [28]. However, it was necessary to prepare the ligands to complete the series and study the effect of increasing the bulk of the phosphanes on the catalytic activities. Furthermore, the obtained yields for ligands **7**, **11** and **13** were higher than that reported in literature. This is apparently due to the prolonged reaction time in the phosphination phase. The other phosphanes are new and their syntheses have not been described previously. There are a few examples of similar types of phosphane ligands in the literature, but these ligands have been synthesized by different methods and have not been tested as potential catalysts in the Suzuki coupling reactions. Additionally, these phosphane ligands have been made using different synthetic principles and for different purposes.

The *ortho*-alkylphenyldiethylphosphane ligands **1**-**3** were prepared by increasing the bulk of the *ortho*-substituent from ethyl to cyclohexyl and then to the electronically different phenyl group. All three phosphanes were yellow viscous oils before the recrystallization procedure from ethanol, which turned the oils brighter. The ligands were further purified by column chromatography using dichloromethane/*n*-hexane 1:2 mixture as the eluent. The phosphane ligands **1-3** are extremely air sensitive and when unprotected, show observable oxidation in less than one hour. Consequently, extreme precaution is demanded in their purification processes. The final products were bright, viscous oils. The bis(*ortho*-alkylphenyl)ethylphosphanes **4** and **5** were prepared in a similar manner with ethyl and phenyl groups in the *ortho*-position. The ligands were recrystallized using ethanol/*n*-hexane 1:2 mixture, but the ligands could not be purified using column chromatography. The final products were bright/slightly yellow viscous oils.



Scheme 4. Schematic structures of *o*-ethylphenyldiethylphosphane 1, *o*-cyclohexylphenyldiethylphosphane 2, *o*-phenylphenyldiethylphosphane 3, bis(*o*-methylphenyl)ethylphosphane and bis(*o*-phenylphenylethylphosphane) 5.

The lone *ortho*-isopropylphenyldiisopropylphenylphosphane **6** was similarly prepared and recrystallized from ethanol. The final product was a white solid. The bis(*ortho*-alkylphenyl)isopropylphosphane ligands **7**-**10** were prepared by increasing the bulk of the *ortho*-substituent from the small methyl group through the isopropyl group to the cyclohexyl group and finally to the phenyl group. The phosphane ligands **7**, **8** and **10** initially appeared as yellow solids, which turned white after recrystallization from ethanol and purification by column chromatography using dichloromethane/*n*-hexane 1:2 mixture. Ligand **9** was obtained as a light yellow viscous oil after the recrystallization procedure from ethanol/*n*-hexane 1:2 mixture. All attempts to purify further the ligand by column chromatography failed. Again it was noted that the ligand was very air-sensitive.



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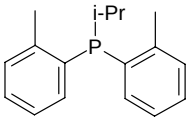

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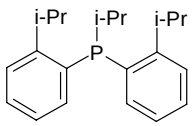

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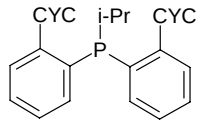

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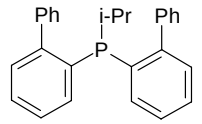

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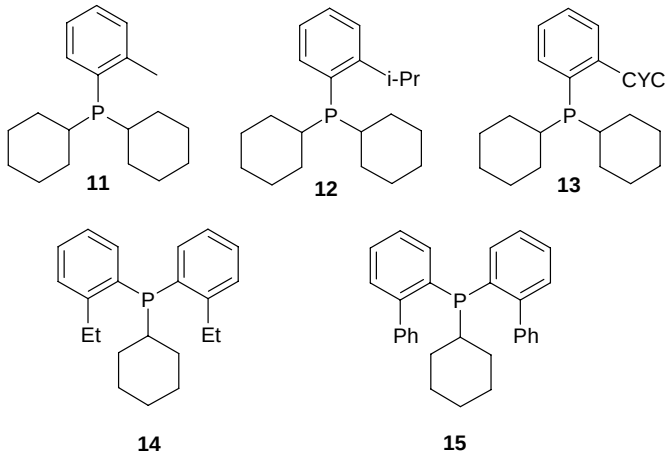
Scheme 5. Schematic structures of *o*-isopropylphenyldiisopropylphosphane 6, bis(*o*-methylphenyl)isopropylphosphane 7, bis(*o*-isopropylphenyl)isopropylphosphane 8, bis(*o*-cyclohexylphenyl)isopropylphosphane 9 and bis(*o*-phenylphenyl)isopropylphosphane 10.

The *ortho*-alkylphenyldicyclohexyl phosphane ligands **11-13** were prepared with the respective methyl, isopropyl or cyclohexyl groups in the *ortho*-position. All the ligands were recrystallized from ethanol and the final products were white solids. The bis(*ortho*-alkylphenyl)cyclohexyl phosphane ligands **14** and **15** had ethyl or phenyl groups in the *ortho*-position. The ligands were recrystallized from ethanol and purified by column chromatography. The final products were bright, viscous oils. The yields of all the ligands are shown in Table 1.

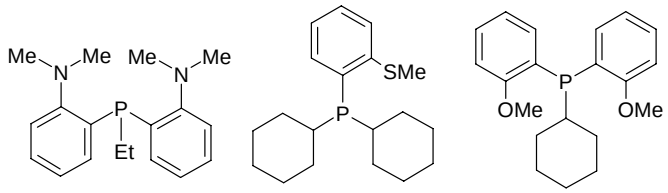


11 **12** **13**

14 **15**

Scheme 6. Schematic structures of *o*-methylphenyldicyclohexylphosphane 11, *o*-isopropylphenyldicyclohexylphosphane 12, *o*-cyclohexylphenyldicyclohexylphosphane 13, bis(*o*-ethylphenyl)cyclohexylphosphane 14 and bis(*o*-phenylphenyl)cyclohexylphosphane 15.

3.2.2 Aryl alkyl ligands containing hetero atoms[V]



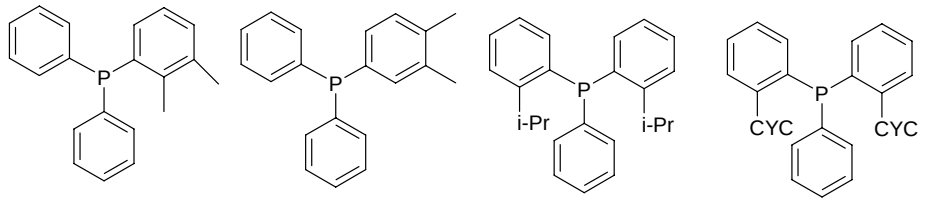
16 **17** **18**

Scheme 7. Schematic structures of bis(*o*-dimethylaminophenyl)ethylphosphane 16, *o*-thiomethylphenyldicyclohexylphosphane 17 and bis(*o*-methoxyphenyl)cyclohexylphosphane 18.

The ligands **16-18** were prepared by introducing a heterodonor group (dimethylamino, thiomethyl or methoxy) on the *ortho*-position of the phenyl ring in combination with alkyl groups directly attached to the phosphorous atom. The idea was to study potential stacking and chelating effects which have been reported to either enhance or to block catalytic activity of the ligands. The are no examples in the lit-

erature of mixed aryl alkyl phosphane ligands with similar hetero atoms in the *ortho*-position of the phenyl rings. The ligands were synthesized by the general procedure presented in section 3.2 by lithiating 2-bromo-N,N-dimethylaminobenzene, 2-bromothiomethylphenyl or 2-bromomethoxyphenyl followed by a reaction with the appropriate chlorophosphane. Ligand **16** is very air-sensitive and shows observable oxidation in fewer than 20 minutes. Therefore the ligand could not be purified by column chromatography and even recrystallization was very difficult to achieve. The ligand was isolated as a brown, viscous oil after a quick recrystallization procedure from ethanol. Ligand **17** was isolated as a white solid after recrystallization from ethanol and purification by column chromatography using a dichloromethane/*n*-hexane 1:2 mixture. Ligand **18** was isolated as a bright viscous oil after similar procedures to that of **16** and **17**. The yields of the ligands are shown in Table 1.

3.2.3 Aryl phosphane ligands [V]



19 **20** **21** **22**

Scheme 8. Schematic structures of 2,3-dimethylphenyldiphenylphosphane 19, 3,4-dimethylphenyldiphenylphosphane 20, bis(*o*-isopropylphenyl)diphenylphosphane 21 and bis(*o*-cyclohexylphenyl)diphenylphosphane 22.

There are some examples of dimethylphenyldiphenyl type phosphane ligands in the literature [28]. Of these the 2,5-dimethylphenyldiphenylphosphane is the most studied ligand. The catalytic activities of these ligands have been studied in hydroformylation experiments but not in Suzuki couplings. Ligands **19** and **20** were prepared in order to study possible catalytic correlations between the positions of the methyl groups and the catalytic activities of the respective ligand when the methyl groups are transferred to the 2,3- or 3,4-positions. Ligand **19** was isolated as a bright viscous oil and ligand **20** as a white solid after recrystallization from ethanol and purification by column chromatography. Ligand **19** was observed to slowly start crystallizing as a white solid.

Various bis(*ortho*-alkylphenyl)phenylphosphane ligands have been studied in the literature, but ligands with bulky substituents in the *ortho*-position are yet unknown. The previous studies in hydroformylation reactions demonstrated that increasing the steric bulk from methyl to ethyl and using two *ortho*-alkyl substituted phenyl rings instead of one notably increased the catalytic activity in hydroformylation reactions [32-33]. The idea was to increase further the bulk of the *ortho*-group to isopropyl and cyclohexyl in order to study possible correlations between the catalytic activity and steric properties of the ligands. This was necessary because, all triphenyl type phosphane ligands are electronically fairly similar to each other. Ligand **21** contained isopropyl groups in the *ortho*-position and was isolated as a white solid after recrystallization from ethanol and purification by column chromatography using a dichloromethane/*n*-hexane 1:2 mixture. Ligand **22** had cyclohexyl groups in the *ortho*-position and was isolated as a yellow viscous oil after a recrystallization procedure using a ethanol/*n*-hexane 1:2 mixture and purification by column chromatography. All aryl phosphane ligands **19-22** were prepared by the general reaction described in section 3.2. The yields of the ligands are given in Table 1.

Table 1. The reported yields for the new ligands prepared in this study.

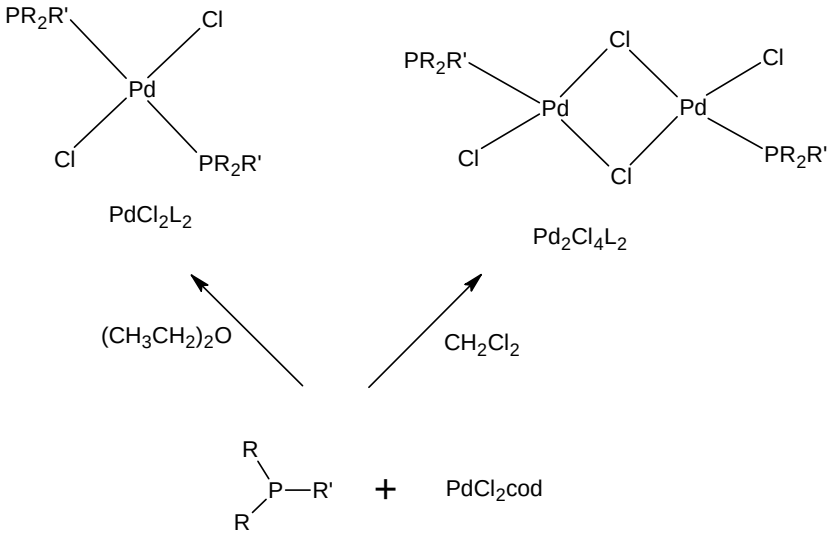
L	Name	Yield [%]
1	*o*-ethylphenyldiethylphosphane	97
2	*o*-cyclohexylphenyldiethylphosphane	54
3	*o*-phenylphenyldiethylphosphane	97
4	bis(*o*-methylphenyl)ethylphosphane	90
5	bis(*o*-phenylphenyl)ethylphosphane	73
6	*o*-isopropylphenyldiisopropylphosphane	95
7	bis(*o*-methylphenyl)isopropylphosphane	89
8	bis(*o*-isopropylphenyl)isopropylphosphane	61
9	bis(*o*-cyclohexylphenyl)isopropylphosphane	59
10	bis(*o*-phenylphenyl)isopropylphosphane	60
11	*o*-methylphenyldicyclohexylphosphane	90
12	*o*-isopropylphenyldicyclohexylphosphane	56
13	*o*-cyclohexylphenyldicyclohexylphosphane	88
14	bis(*o*-ethylphenyl)cyclohexylphosphane	57
15	bis(*o*-phenylphenyl)cyclohexylphosphane	56
16	bis(*o*-dimethylaminophenyl)ethylphosphane	53
17	*o*-thiomethylphenyldicyclohexylphosphane	61
18	bis(*o*-methoxyphenyl)cyclohexylphosphane	61
19	2,3-dimethylphenyldiphenylphosphane	50
20	3,4-dimethylphenyldiphenylphosphane	57
21	bis(*o*-isopropylphenyl)diphenylphosphane	64
22	bis(*o*-cyclohexylphenyl)diphenylphosphane	49

3.3 A general procedure for preparing mono- and dinuclear palladium complexes of the aryl and aryl alkyl phosphane ligands [I,III,V]

The mononuclear palladium complexes of all the new phosphane ligands described in the previous section were synthesized and characterized for catalytic purposes. The structures and bonding were also studied for possible correlations with their corresponding catalytic activities. Some dinuclear palladium complexes

were synthesized for comparison, but as the dinuclear complexes were not stable enough for catalytic studies, only a few examples were prepared.

As a starting point for the research, a series of mono- and dinuclear palladium complexes with known and well studied *ortho*-alkyl substituted aryl and heteroaryl phosphanes (see Table 2, entries **23-33**) were prepared and characterized. The complexes were also tested as potential catalysts for the Suzuki coupling reactions.



Scheme 9. A general pathway for preparing mono- or dinuclear palladium complexes.

The well known and widely used method of substituting cod (cyclooctadiene) from $PdCl_2$(cod) with an appropriate phosphane ligand was used to synthesize all the palladium complexes presented in this research. Interestingly, it was observed that nearly all the phosphanes preferentially formed mononuclear palladium complexes in diethyl ether and dinuclear, chlorine-bridged palladium complexes in dichloromethane. There were only a few exceptions to this trend. Myriads of mononuclear palladium complexes of various types of phosphane ligands have been reported in the literature, but in contrast, there are only a few reports of dinuclear palladium complexes available.

The mono and dinuclear complexes were prepared by dissolving $PdCl_2$(cod) and the phosphane ligand in the desired solvent and leaving the mixture to react at room temperature for 24 hours. In the preparation of the mononuclear complexes, the solid material was then filtered and washed with diethyl ether and *n*-hexane

and sometimes additionally with a small amount of dichloromethane. Further purification was achieved, if necessary, by using column chromatography with dichloromethane/*n*-hexane as the eluent. The dinuclear palladium complexes were isolated by removing the solvent *in vacuo*, and then purifying the solid material by using column chromatography and dichloromethane/*n*-hexane 1:2 as the eluent. In the few occasions when both mono and dinuclear complexes were formed, the complexes were separated by column chromatography using dichlorometha/*n*-hexane 1:3 as the eluent. Single crystals for X-ray crystallographic analysis were obtained by slow evaporation of the dichloromethane/*n*-hexane or chlorobenzene/*n*-hexane solvent mixture at room temperature or at 5-10 ° C.

The problem of the formation of palladium complexes with undesired nuclearity has been reported in various articles [29, 34-36] as a major nuisance. The explanations for these trends have varied in each case. In order to clarify the role of the solvent in this problem, THF, acetone, DMF and methanol were used as solvents for the reaction between $PdCl_2$(cod) and a selection of various phosphane ligands presented in this work. In all cases, the results were mononuclear complexes similarly as found in the reaction for diethyl ether. These studies were continued by observing the preparation of the mononuclear palladium complexes in chlorobenzene and chloroform. The reactions in both solvents produced dinuclear complexes. To rule out the possibility of the solvent itself reacting, the reaction was also done in bromoform and diiodomethane and then crystallized from the very same solvent. No introduction of bromine or iodine into the crystal structures of the complexes was observed, and there is no evidence that the solvent itself would react.

Early on it was observed that the palladium starting material, and to some extent even the phosphanes, were only slightly soluble in diethyl ether and other non-chlorinated solvents. However, the palladium starting material was readily soluble in the chlorinated solvents. To rule out stoichiometric factors, the reaction between $PdCl_2$cod and some of the phosphanes were carried out with phosphane/palladium ratios 4:1, 1:1, 1:2 and 1:4 both in diethyl ether and dichloromethane. The products were still mononuclear complexes in diethyl ether and dinuclear complexes in dichloromethane.

According to reports in the literature, dinuclear palladium complexes are formed from mononuclear palladium derivatives [37-40]. With particular *ortho*-alkyl substituted aryl phosphane ligands, the reaction produced both mono and dinuclear complexes in both diethyl ether and dichloromethane. However, the yields of the mononuclear complexes were higher in diethyl ether and dinuclear

complexes in dichloromethane. This suggests that dichloromethane promotes the formation of dinuclear complexes whereas diethyl ether enhances the formation of mononuclear complexes. When testing the various phosphane/palladium ratios with these ligands, it was noticed that the 4:1 ratio no longer produced dinuclear complex in diethyl ether. This was probably due to the high ligand to Pd ratio in solution. Even so, this does not explain why both mono and dinuclear complexes are formed in dichloromethane with these ligands. It was noticed that these ligands produced mononuclear complexes that were exceptionally poorly soluble even in chlorinated solvents. Such a phenomenon could prevent the proper solvation of the reaction intermediate and ultimately the formation of the respective dinuclear complex. Steric ligand effects have also been known to cause similar abnormalities in reactions [41-45].

To test the stability of the palladium complexes, the pure, isolated mononuclear complexes were reacted with $PdCl_2$(cod). As expected, the products were dinuclear complexes. It is also well known that the dinuclear complexes easily undergo bridge-splitting reactions with a variety of neutral ligands to yield mononuclear derivatives [5]. However, no splitting reactions were observed and the dinuclear complexes remained unreactive. Higher temperatures and prolonged reaction times resulted in the decomposition of the dinuclear complexes.

Based on these findings, it is believed that the nuclearity of the formed complexes is mainly dependent of the solubilities of the starting materials and solvent effects. These solvent effects include polarity of the solvent and the ability to stabilize the reaction intermediates. Therefore the syntheses can be controlled by the choice of the solvent in terms of solubility. Diethyl ether was found to be an optimal solvent for the production of mononuclear complexes and dichloromethane for dinuclear complexes. The problems caused by a few ligands can be surpassed either by providing the reaction mixture with an excess of the phosphane ligand or by isolating the complexes and further reacting the mononuclear complex with $PdCl_2$cod. The phosphane ligands producing both mono- and dinuclear complexes in the same reaction are specified in section 4.2.

3.3.1 Palladium complexes of quinolinyl diphenyl and diquinolinyl phenyl phosphane ligands [III]

A series of palladium complexes of quinolinyl diphenyl and diquinolinyl phenyl phosphane ligands (see Table 2, entries **34**-**37**) was also prepared for catalytic purposes. The solvent effect remained the same: mononuclear complexes were pro-

duced in diethyl ether and dinuclear in dichloromethane. Interestingly, the 2-quinolinyl diphenyl phosphane produced a *cis*-isomer instead of a *trans*-isomer. It is a consistent finding that *trans*-isomers are almost exclusively the isomers that square-planar palladium complexes form. Similar effects have been previously observed with various pyridyl phosphane ligands that caused tungsten carbonyl complexes to take up *cis*-conformations due to attractive interactions within the molecules [46, 47]. The crystal structure of the mononuclear palladium complex of 2-quinolinyldiphenyl phosphane (see Figure 7.) showed offset π-stacking interaction between the quinolinyl and phenyl moieties. Such an effect was not observed in the dinuclear complex of 2-quinolinyldiphenylphosphane due to the much longer distances between the ligands (see Figure 8.).

3.3.2 Palladium complexes of 2-mercaptobenzothiazole [II]

In the attempts to try to create a mixed ligand with a phosphane and a mercaptobenzothiazole unit by a reaction between $PdCl_2$cod, 2-mercaptobenzothiazole and an appropriate phosphane ligand, it was observed that instead of a mixed ligand being formed, the phosphane ligand seems to catalyze the formation of tetra(2-mercaptobenzothiazole)bispalladium. Using *ortho*-methylphenyldiphenylphosphane in the reaction produced isomer 1 (see Figure 1.) and using *ortho*-isopropylphenyldiphenylphosphane isomer 2 (see Figure 2.). The structures of the isomers have been thoroughly examined in section 4.2.3.3. Isomer 1 is described in the literature[II], but isomer 2 is completely new.

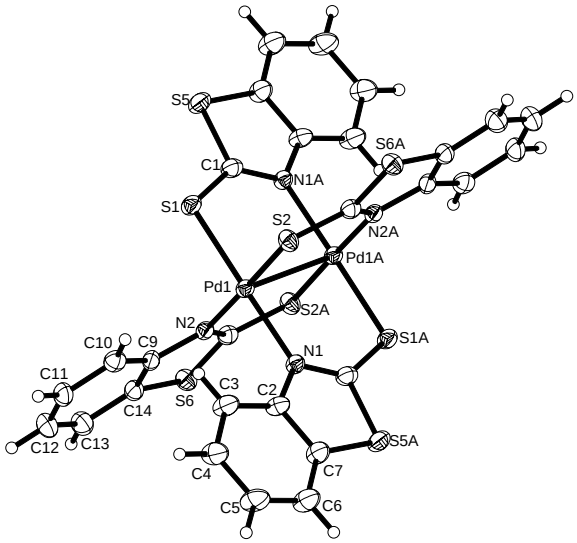


Fig. 1. Crystal structure of tetra(2-mercaptobenzothiazole)bispalladium.

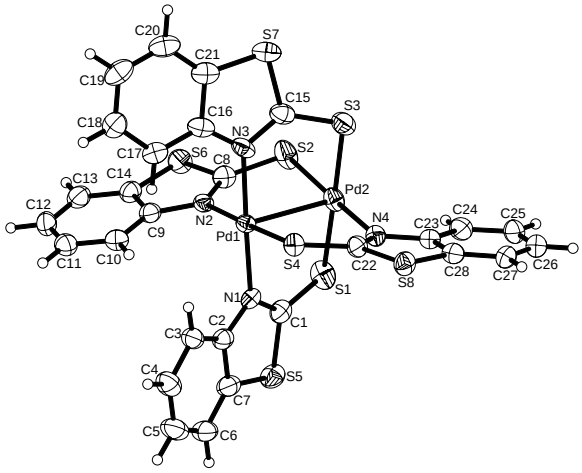


Fig. 2. Crystal structure of the isomer of tetra(2-mercaptobenzothiazole)bispalladium.

3.3.3 Suzuki coupling reactions [III-V]

The Suzuki coupling reactions were conducted by the general method of reacting a proper aryl halide with a slight excess of the desired phenyl boronic acid in the presence of two equivalents of the base (K_2CO_3) and the desired palladium com-

plex (0.5 mol%) with DMF (2.5 ml) as the solvent. In some reactions H_2O (0.5 ml) has been used to improve the purity of the coupling products further [48, 49]. Microwave heating was initially chosen for Suzuki coupling reactions instead of conventional heating methods due to the numerous reports of improved yields, enhanced reaction rates, associated green chemistry procedures, energy efficiency and new catalytic routes made achievable by the use of microwave heating [49-51] in Suzuki coupling reactions. Furthermore, lengthy metal catalyst extraction steps for product purification are not required because such small quantities of metal catalyst are used in contrast with traditional Suzuki coupling reactions [50, 51].

Microwave heating has been readily used in various chemical reactions since the mid 80's. Microwave-promoted chemistry is founded on the fact that materials, be they solvents or reagents, can absorb microwave energy and convert it to heat. This is done much more efficiently and without the differences that arise among different regions of the reactants found with conventional heating methods. This results in lower temperatures, faster reaction times, lower amounts of reactants and better reactivity overall. Polar solvents are often used for rapid, efficient heating by microwave irradiation. However, their use is often not essential, and sometimes even simple and nontoxic solvents can be used since either the substrates, or some of the reagents, or the catalysts are polar [50]. Unstable substances, which decompose quickly when traditional heating methods are used, can be successfully used in Suzuki coupling reactions when microwave heating is used. Shorter reactions times also minimize the formation of byproducts and homocoupling derivatives.

The microwave pressure vessel (2-5 ml) was charged with the reactants and the mixture warmed at 150 °C for 30-50 minutes under standard irradiation mode. The reaction mixture was then cooled to room temperature, and water was added to the mixture. The organic layer was separated, and the aqueous layer extracted three times using diethyl ether. The ether extracts were combined with the organic layer and dried with $MgSO_4$, and the solvent was then removed *in vacuo*. The remaining residue was purified by column chromatography using silica gel and dichloromethane/*n*-hexane 1:3 mixture as the eluent. It was noticed that the coupling reactions did not need to be run in an inert atmosphere as described in most reports in the literature. This was due to the air tolerant nature of the palladium complexes. The coupling reactions are described in detail in section 5.

4 Characterization

4.1 Instrumentation and measurements

NMR-spectroscopy: The phosphane ligands studied in this publication have been characterized by ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ spectra. The palladium complexes were characterized mainly only by $^{31}P\{^{1}H)$ spectra due to solubility problems. The spectra were mostly recorded on a Bruker DPX400 spectrometer or a Bruker DPX200 spectrometer using deuterated chloroform (99.8 % D, 0.03 % TMS). The ^{1}H and ^{13}C spectra were referenced to internal tetramethylsilane (TMS) and ^{31}P spectra to external 85 % H_3PO_4.

Mass spectrometry: Accurate masses were recorded by a Micromass LCT spectrometer using ESI+ method and a TOF mass analyzer. The mass peaks for the Suzuki reaction coupling products were determined using a Hewlett Packard HP 6890 Series GC-system coupled with a 5973-MSD (Mass Selective Detector; quadrupole).

Elemental analysis: C, H and N analyses for the palladium complexes from the purified, solid metal complex powders were performed on a Perkin-Elmer 2400 CHNS analyzer.

X-ray crystallography: The X-ray measurements were performed using a Nonius KappaCCD diffractometer at the University of Joensuu. Further details of the measurements can be found in the original papers.

4.2 Structures of the phosphane ligands and their palladium complexes

The structures of the phosphane ligands were mainly determined by ^{1}H, ^{13}C and ^{31}P NMR spectra and further verified by measurements of their accurate mass peaks. The crystal structures of the palladium complexes gave further support for the presumed structures of the phosphanes. The structures of the palladium complexes were verified by ^{31}P-NMR and elemental analyses. The complexes were crystallized and their crystal structures determined whenever possible. Chemical shifts of palladium complexes of the new phosphane ligands **1**-**22** and the new palladium complexes of the previously known phosphane ligands **23**-**37** are presented in Table 2.

4.2.1 $^{31}P\{^{1}H\}$ NMR spectra and the chemical coordination shifts

The ^{31}P-NMR signals of the free ligands were characteristic for each of the phosphane ligand types and the chemical shifts were generally found on the high field. It is well known, that even if the electronic properties of the substitutes influence the chemical shifts to some extent, the shifts of alkyl and aryl phosphanes are primarily affected by steric factors [28, 52]. As the substituents near the phosphorous atom become sterically more demanding, the ^{31}P-nucleus experiences an increasing shielding effect. This is best demonstrated by comparing the chemical shifts between the electronically fairly similar ligands **19** and **20**. For the polyaromatic ligands **3**, **5**, **10**, **15** and **33** the ring current effect also influences the shielding.

The chemical shifts of the mono- and dinuclear palladium complexes are also typical for complexes of these types of phosphane ligands. The dinuclear complexes generally appear in a 10-20 ppm lower field than those for the corresponding mononuclear complexes. In dinuclear complexes the Pd(II)-ions are bonded to three chlorine atoms in contrast to only two chlorine ions in the mononuclear complexes. This results in their signals shifting to a lower field than the corresponding signals of the mononuclear complexes. All signals of the mononuclear and dinuclear palladium complexes were singlets. The exception to this were the complexes of ligands **28**, **30** and **31**, in which both the mononuclear and dinuclear complexes initially appeared together. However, after separation by column chromatography the signals were singlets.

The chemical coordination shifts (Δ) are useful for comparing the strength of the bonding between the ligands and the metal atom. They also provide information about the electronic properties of the ligands. Generally speaking, the higher the chemical coordination shift is, the stronger is the metal-ligand bond. The chemical coordination shift values also reflect the distances between the *ortho*-substituents in the phenyl rings of the mixed aryl alkyl ligands and the metal atoms. Bulky, sterically more demanding substituents are known to reduce the values of the chemical coordination shifts, because steric repulsion maximizes the distances between the bulky groups and therefore weakens the metal-ligand bond. Electron rich ligands can therefore form very strong bonds with metal ions if steric repulsion does not prevent close contact. Furthermore, attractive interactions between ligands or metal/ligand can also influence the chemical coordination shifts by weakening or strengthening the metal-ligand bonds.

The chemical coordination shifts data presented in Table 2 are in good accordance with the structures of the palladium complexes and the free phosphanes. The

chemical coordination shifts are affected by both the electron richness and steric properties of the ligands. More electron-rich ligands, such as those with isopropyl or cyclohexyl groups attached to the phosphorous atom, formed stronger bonds with the metal ion and also experienced higher chemical coordination shifts unless steric repulsion interfered. The steric effect can be clearly seen for the ligands **8** and **9**. The latter experienced a somewhat lower chemical coordination shift than the former. The effect was just the opposite when ligands **12** and **13** were compared. In this case electronic effects influenced the chemical coordination shift to a larger extent than the steric effects.

The chemical coordination shifts can also be used to evaluate the bonding mode of the phosphane ligands with hetero atoms in the *ortho*-position. Chelated metal complexes generally experience much higher chemical coordination shifts as is demonstrated with the crystallized complexes (see section 4.2.3) of ligands **17**, **24** and **25**. Similarly, it can be presumed that the nitrogen atom in the complex of ligand **16** formed a bond with the Pd-atom. In contrast, in ligand **18** a bond between the oxygen and the Pd-atom did not appear to form. Based on this presumption, the quinoline phosphane ligands **34-37** have not either formed a bond with the metal atom. The acquired crystal structure for the complex **34** further supports this presumption.

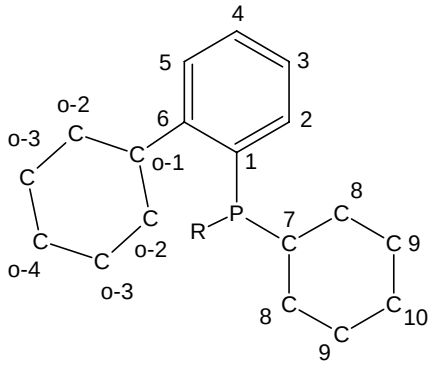
Table 2. ^{31}P-NMR shifts of the free ligands and their corresponding palladium complexes prepared in this thesis. Ligands 23-37 are previously known in the literature. The chemical coordination shifts ($\Delta = \delta_{complex} - \delta_L$) are given in parenthesis.

L	Name	δ_P	$PdCl_2L_2(\Delta)$	$Pd_2Cl_4L_2(\Delta)$
1	*o*-ethylphenyldiethylphosphane	-31.5	11.1 (42.6)	
2	*o*-cyclohexylphenyldiethylphosphane	-28.5	11.7 (40.2)	
3	*o*-phenylphenyldiethylphosphane	-25.5	27.6 (53.1)	
4	bis(*o*-methylphenyl)ethylphosphane	-31.9	20.3 (52.2)	
5	bis(*o*-phenylphenyl)ethylphosphane	-25.8	27.6 (53.4)	
6	*o*-isopropylphenyldiisopropylphosphane	-7.4	24.6 (32.0)	
7	bis(*o*-methylphenyl)isopropylphosphane	-22.3	27.9 (50.2)	40.2 (62.5)
8	bis(*o*-isopropylphenyl)isopropylphosphane	-26.1	33.2 (59.3)	
9	bis(*o*-cyclohexylphenyl)isopropylphosphane	-25.3	27.1 (52.4)	
10	bis(*o*-phenylphenyl)isopropylphosphane	-19.5	35.0 (54.5)	
11	*o*-methylphenyldicyclohexylphosphane	-11.6	20.5 (32.1)	44.3 (55.9)
12	*o*-isopropylphenyldicyclohexylphosphane	-15.2	16.9 (32.1)	
13	*o*-cyclohexylphenyldicyclohexylphosphane	-14.6	25.8 (40.4)	
14	bis(*o*-ethylphenyl)cyclohexylphosphane	-32.3	23.3 (55.6)	
15	bis(*o*-phenylphenyl)cyclohexylphosphane	-25.0	33.3 (58.3)	
16	bis(*o*-dimethylaminophenyl)ethylphosphane	-50.2	41.3 (91.5)	
17	*o*-thiomethylphenyldicyclohexylphosphane	-12.6	84.4 (97.0)	
18	bis(*o*-methoxyphenyl)cyclohexylphosphane	-28.2	30.7 (58.9)	
19	2,3-dimethylphenyldiphenylphosphane	-18.7	18.7 (37.4)	
20	3,4-dimethylphenyldiphenylphosphane	-10.0	35.9 (45.9)	
21	bis(*o*-isopropylphenyl)diphenylphosphane	-30.3	24.1 (54.4)	
22	bis(*o*-cyclohexylphenyl)diphenylphosphane	-23.2	36.6 (59.8)	
23	2,4,5-trimethylphenyldiphenylphosphane	-12.9	20.4 (33.3)	
24	*o*thiomethylphenylbis(*o*methoxyphenyl)phosphane	-34.1	54.3 (88.4)	
25	*o*methoxyphenylbis(*o*thiomethylphenyl)phosphane	-30.0	57.4 (87.4)	
26	bis(*o*-methylphenyl)phenylphosphane	-19.9	25.3 (45.2)	37.0 (56.9)
27	tri-*o*-tolylphosphane	-23.2	23.6 (46.8)	28.9 (52.2)
28	bis(*o*-ethylphenyl)phenylphosphane	-23.5	28.3 (51.8)	36.7 (60.2)
29	(*o*-methylphenyl)diphenylphosphane	-10.7	19.6 (30.3)	29.8 (40.5)
30	(*o*-ethylphenyl)diphenylphosphane	-14.2	20.1 (34.3)	30.0 (44.2)
31	(*o*-isopropylphenyl)diphenylphosphane	-13.8	20.3 (34.1)	31.2 (45.0)
32	(*o*-cyclohexylphenyl)diphenylphosphane	-13.6	21.0 (34.6)	29.4 (43.0)
33	(*o*-phenylphenyl)diphenylphosphane	-11.9	22.3 (34.2)	28.4 (40.3)
34	2-diphenylphosphanequinoline	-0.1	23.8 (23.9)	31.0 (31.1)
35	3-diphenylphosphanequinoline	-10.0	28.2 (38.2)	36.1 (46.1)
36	4-diphenylphosphanequinoline	-13.8	19.9 (33.7)	28.7 (42.5)
37	di-(3-quinolinyl)phenylphosphane	-13.9	17.2 (31.1)	23.8 (37.7)

4.2.2 ^{1}H and ^{13}C{^{1}H} NMR spectra

The spectroscopic differences between the ethyl, isopropyl and cyclohexyl and various other groups can be used to make correlations between their catalytic activities if drastic changes are observed. The acquired ^{1}H and ^{13}C{^{1}H} NMR spectra for the new phosphane ligands were generally characteristic for each substituent type. Steric and electronic effects are both known to influence chemical shift data [5].

The aryl phosphane ligands **19**-**22** followed the general trends reported in the literature for these types of phosphane ligands. These studies describe the extent of the bulkiness of the ligands decreasing the shielding of the carbon atom to which the *ortho*-substituent is directly attached [28]. A similar phenomenon was also observed for the mixed aryl alkyl phosphane ligands. The chemical shifts of the phenyl rings in the mixed aryl alkyl phosphane ligands also follow the general trends reported in the literature [28, 32-33, 52] for a variety of phosphane ligands that contain phenyl rings with *ortho*-substituents and alkyl groups directly attached to the phosphorous atom. Some differences in the ^{1}H and ^{13}C NMR shifts of the *ortho*-substituents and the alkyl atoms directly attached to the phosphorous atom are due to electronic and steric dissimilarities of the phosphane ligands described in this section.



Scheme 10. NMR-numbering in the various aryl alkyl phosphane ligands.

A general problem with the ^{1}H-spectra of the mixed aryl alkyl phosphane ligands with cyclohexyl groups either in the *ortho*-position or directly attached to the phosphorous atom was that some of the alkyl signals were completely masked by the broad resonance of the cyclohexyl peaks. Furthermore, peak broadening and unclear multiplicity are recognized problems with these types of ligands even if

the assignment of each signal is normally relatively straightforward. Therefore this phenomenon prevents the calculation of some coupling constants and complete assignment of some of the signals [52, 53].

The shielding/deshielding effects of the alkyl hydrogens in the ethyl and diethyl substituted phosphane ligands were just the opposite. In the diethyl substituted ligands the shielding effect increased when the *ortho*-ethyl substituent was replaced by the electronically different phenyl ring. In the mono ethyl substituted ligands the effect was exact the opposite; the shielding decreased. Similar effects can be seen for the C^7 carbon atoms of the alkyl groups and also to some extent for the C^8 atoms. This phenomenon underlines the electronic differences between aryl and alkyl moieties. The phenyl group is electronically quite different to that of the alkyl groups. In the phosphane ligands with directly bound isopropyl and cyclohexyl groups the shielding effect also increased when a phenyl group was in the *ortho*-position of the phenyl ring.

The differences between ligands with mono and dialkyl substituted phosphorous atoms with similar *ortho*-substituents is most clearly observed for the H^7 and H^8 when the analogues **6** and **8** were compared. This difference was still observed even when the shifts of the carbon atoms were almost completely the same. The effect of the increased steric bulk when an alkyl group is replaced with an additional *ortho*-substituted phenyl ring also affected the shielding.

Table 3. ^{13}C and ^{1}H -NMR shifts of the ethyl groups directly attached to the phosphorous atom and the ortho-alkyl substituents in ethyl and diethyl substituted phosphane ligands 1-5. The $^{3}J_{H-H}$ coupling constants for the hydrogens and the J_{C-P} coupling constants for the carbon atoms are given in parentheses.

L	H^7	H^8	C^7	C^8	H^{o-1}	H^{o-2}	C^{o-1}	C^{o-2}	C^{o-3}	C^{o-4}
1	2.02	1.36 (5.2)	22.3/23.0	5.8/5.9	2.95	1.14 (4.6)	27.6 (16)	16.3		
2			20.2	9.8/9.9	3.45		41.0	34.5/34.7	26.8	26.2
3	1.46	1.03 (9.0)	19.09	9.5			131.2	128.1	127.4	127.8
4	1.34	1.18	20.1	10.4	2.6		21.5			
5	1.83	1.44 (8.1)	21.2	10.4 (13.8)			142.14	128.9/129.2	127.4/127.7	128.5

Overall, the increase of the steric bulk of the *ortho*-substituent decreased the shielding of the carbon and hydrogen atoms bound directly to the phosphorous atom in the case of all ligands. In the isopropyl substituted phosphanes this was reflected both in the C^7, H^7 and H^8 shifts. In the cyclohexyl substituted phosphane

ligands' C^7 and C^8 atoms the shielding effect also decreased, even if the distal carbons C^9 and C^{10} were less affected. A similar effect was experienced for the carbons and hydrogens of the *ortho*-substituents. Namely, when the steric bulk of the alkyl groups directly bound to the phosphorous atom increased, the shielding decreased slightly. The chemical shifts of the phosphane ligands with a hetero atom in the *ortho*-position also followed similar patterns of lowered shielding.

In some cases two signals for some of the chemically equivalent carbon and hydrogen atoms of the alkyl groups directly attached to the phosphorous were observed. Similar magnetic nonequivalency has been reported for other parallel types of ligands and described in detail in the literature [28]. Steric crowding is known to cause chemical nonequivalency and to prevent normal rotation around the P-C bonds. Rotation then becomes restricted on the NMR-timescale.

Table 4. ^{13}C and ^{1}H -NMR shifts of the isopropyl groups directly attached to the phosphorous atom and the ortho-alkyl substituents in isopropyl and diisopropyl substituted phosphane ligands 6-10. The $^{3}J_{H-H}$ coupling constants for the hydrogens and the J_{C-P} coupling constants for the carbon atoms are given in parentheses.

L	H^7	H^8	C^7	C^8	H^{o-1}	H^{o-2}	H^{o-3}	H^{o-4}	C^{o-1}	C^{o-2}	C^{o-3}	C^{o-4}
6	2.08	0.89 (7.4)	24.2 (28.5)	20.4 (21.4)	4.09	1.05 (6.9)			30.7 (27)	25.9		
7	2.40	1.11 (6.8)	25.4 (8.0)	19.7 (20.6)					21.5 (22.0)			
8	2.65	1.23/1.40	24.2 (27.6)	20.4 (21.4)	4.32	1.54			31.0 (26.0)	26.0		
9			25.9 (22.2)	20.0 (20.7)	3.50 (7.0)	1.02	1.18	0.89	41.7 (6.2)	34.5	26.7	26.5
10	2.27	0.93	26.7	19.6 (19.2)					142.3	128.6		

The prepared mono and dinuclear palladium complexes were not sufficiently soluble to produce proper ^{13}C-NMR spectra. However, when exceptionally long measurement times were used, the ^{1}H-NMR spectra could be detected, even if the peaks of tiny impurities in the solvent and NMR-tube overlapped with the signals of the complexes. The ^{1}H-NMR spectra were determined in an overnight measurement run for the mono- and dinuclear palladium complexes of ligands **29-33**. Their respective chemical shifts barely changed at all. Similar experiments with the catalytically active complexes of ligands **6** and **8** also showed that the shifts of the aryl hydrogens did not change noticeably. However, the shifts of the alkyl group had changed a bit more, though not substantially enough to make correlations between their catalytic activities. Therefore these measurements were not carried out for the rest of the complexes.

Table 5. ^{13}C and ^{1}H –NMR shifts of the cyclohexyl groups directly attached to the phosphorous atom and the ortho-alkyl substituents in cyclohexyl and dicyclohexyl substituted phosphane ligands 11-15.

L	C^{7}	C^{8}	C^{9}	C^{10}	H^{o-1}	C^{o-1}	C^{o-2}	C^{o-3}	C^{o-4}
11	33.7	29.0/30.3 (7.3)	27.1/27.2 (9.2)/(12.9)	26.4	2.56	22.3 (22.2)			
12	34.3	30.7 (13.8)	26.4/27.2	24.1		30.4	25.0		
13	34.5	29.3/30.8 (8.4)/ (17.0)	27.2/27.3 (7.0)/(11.6)	26.5	3.66	41.1 (26.1)	34.6	26.7	26.4
14	36.5	27.5 (22.2)	26.6/27.0	25.9		27.1	15.6		
15	38.1	29.4/29.5	26.4/26.9	26.0		142.4	129.4/130.4	127.2/127.6	128.8

4.2.3 X-ray crystal structures

The crystals of the palladium complexes of the ligands presented in this publication were grown from the slow evaporation of the dichloromethane/*n*-hexane or chlorobenzene/*n*-hexane solvent mixture at room temperature or at 5-10 °C. The mononuclear palladium complexes of ligands **1-37** and the dinuclear palladium complexes of ligands **3**, **7**, **11** and **26-37** were crystallized to observe possible structural correlation with the catalytic activities. Approximately half of the complexes formed single crystals and their structures could be determined. The structure determinations were carried out at the University of Joensuu. The bond lengths and angles of the acquired structures were mainly in the predictable range with values previously reported for these types of ligands. A selection of the acquired X-ray crystal structures are presented in Figures 3-8.

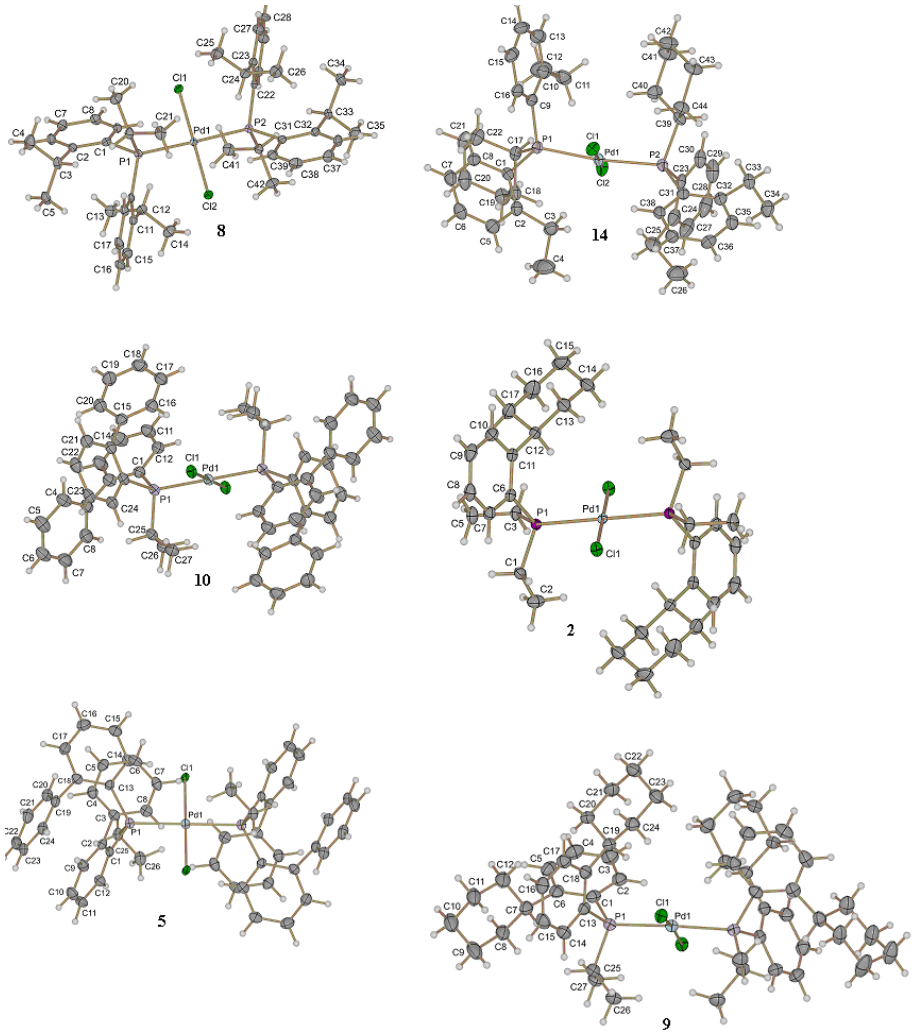
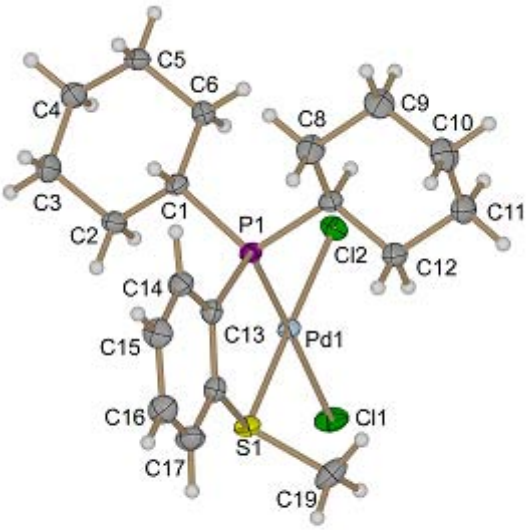


Fig. 3. Crystal structures of the mononuclear palladium complexes of ligands *o*-cyclohexylphenyldiethylphosphane 2, bis(*o*-phenylphenyl)ethylphosphane 5, bis(*o*-isopropylphenyl)isopropylphosphane 8, bis(*o*-cyclohexylphenyl)isopropylphosphane 9, bis(*o*-phenylphenyl)isopropylphosphane 10 and bis(*o*-ethylphenyl)cyclohexylphosphane 14 showing the regular geometry of *trans*-$PdCl_2L_2$ complexes.

All the obtained crystal structures the palladium atoms had a slightly distorted square planar environment. In the triaryl-type phosphane ligands **29**-**33**, the *ortho*-alkyl groups were pointed outside the cone of the ligand in all the structures. Simi-

lar effects were observed for the mixed aryl alkyl phosphane ligands that had only one *ortho*-substituted phenyl ring. When the number of the *ortho*-substituted phenyl rings increased to two or more, the *ortho*-substituents also took up other orientations. In general, the phosphanes formed conformations in which the bulky substituents, either in the phenyl rings or directly connected to the phosphorous atom, were located on the opposite sides of the Pd-P axis. A similar phenomenon was observed between both phosphane ligands in the mononuclear complexes; the phosphanes took up conformations where their steric repulsion was minimized along the P-Pd-P axis. The majority of bulky biaryl alkyl complexes the structures became very congested and the alkyl or aryl groups in the *ortho*-position were consequently forced closer to the alkyl group almost as if attractive forces were involved (see Figure 3, complexes **9**, **14** and **10**). Similar interactions were sometimes observed between the alkyl or aryl substituents and the aryl rings bonded to the phosphorous atom. For similar reasons, some of the hydrogens in the *ortho*-substituents were located very close to the metal centre, even if actual bonding was not observed. This phenomenon was especially true for the complexes of the biaryl alkyl ligands where isopropyl, cyclohexyl or phenyl substituents were in the *ortho*-position.

The conformations of the chelated complexes (see Figure 4.) behaved in a similar way as for the standard aryl and mixed aryl alkyl phosphanes; the conformations tend to minimize steric repulsion despite the bidentate bonding mode. Furthermore, the chelating effects of ligands **16-17** and **24-25** prevented the preparation of dinuclear complexes.



17

Fig. 4. Chelated palladium complex of *o*-thiomethylphenyldicyclohexylphosphane 17.

There are no completely characterized examples of dinuclear palladium complexes of mixed aryl alkyl phosphane ligands in the literature, which makes comparisons difficult. However, there are a few examples of complexes of triaryl type phosphane ligands (see publication I for a complete list of references). The bridging chlorides, terminal chlorides and the phosphorous atoms in the dinuclear palladium complexes of the ligands in this study are generally planar. Again, steric forces slightly distorted the structures; especially those of the mixed aryl alkyl phosphanes (see Figure 5.). The bridging chlorides, terminal chloride and a phosphorous atom formed two square planes around the palladium atoms in the dinuclear complex of ligand **30**. Such bending shortened the Pd-Pd distance in comparison with the other dinuclear complexes.

An interesting observation was that both in the mononuclear and the dinuclear palladium complexes of *ortho*-phenylphenyldiethylphosphane **3**, the other terminal chlorine atom had been replaced with a bromine atom. The purification of the free ligand is extremely difficult due to its sensitivity towards oxidation. Therefore the palladium complexes were synthesized from the unpurified solution of the

phosphane. It was observed that such a procedure is possible due to the palladium starting material only reacting with the unoxidized free ligand. The preparation procedure of the phosphane ligands enabled free Br^- ions to exist in solution, and no other possible source for the bromine existed. A regular palladium (II) chloride complex was prepared by using a completely purified ligand, but the yield remained very low and most of the ligand was oxidized.

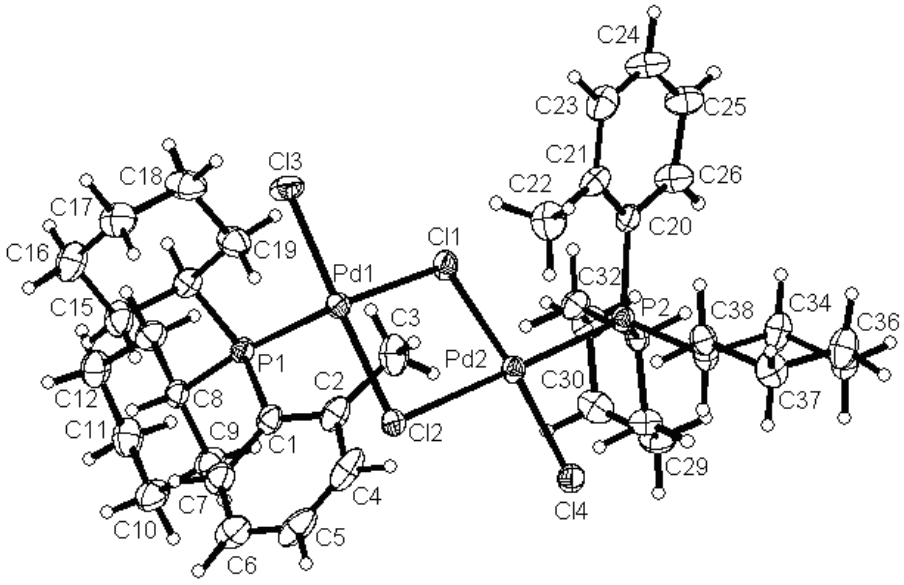


Fig. 5. Dinuclear palladium complex of *o*-methylphenyldicyclohexylphosphane 11.

Both mononuclear and dinuclear palladium complexes tend to form *trans*-isomers due to steric reasons. Interestingly, a *cis*-isomer of the dinuclear complex of tri-*ortho*-tolylphosphane **27** (see Figure 6) was detected. The isomer showed an attractive interaction between the two ligands. The mononuclear analogue forms a regular *trans*-isomer. The dinuclear complex can take up a conformation on which the ligands could interact with each other. This phenomenon further underlines, how comparatively small perturbations in the structures of the ligands can cause large-scale changes in the conformations of palladium complexes.

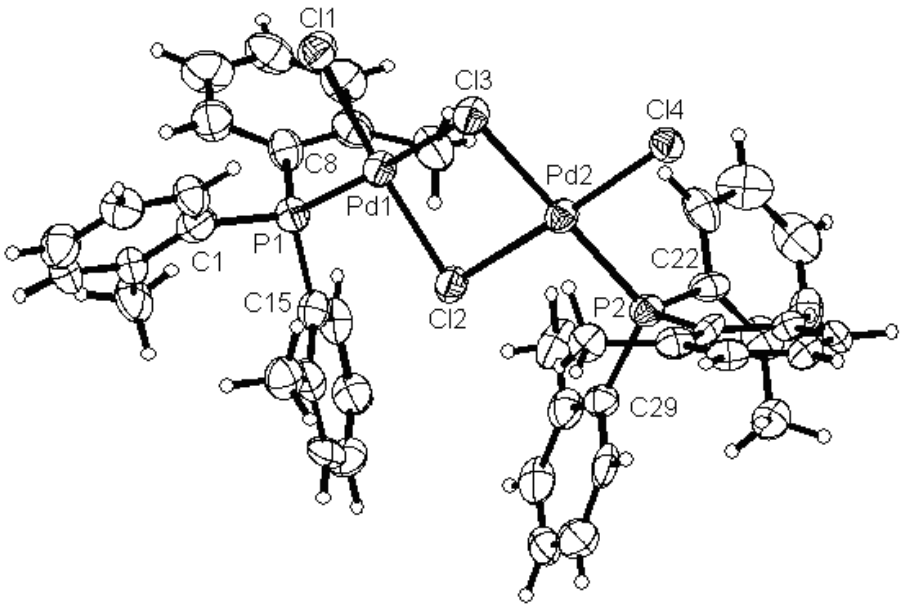


Fig. 6. *Cis-sym*-isomer of the dinuclear palladium complex of tri-*o*-tolylphosphane 27.

Crystal structures of the quinolinyl phosphane ligands

The crystal structure of the mononuclear (see Figure 7.) palladium complex of 2-diphenylphosphanequinoline **34** shows an attractive interaction between the quinolinyl and phenyl moieties and thus formed a *cis*-isomer. Such an effect was not observed in the dinuclear complex probably due to long distances between the ligands. The dinuclear complex was a standard *trans*-isomer (see Figure 8). Similar π-stacking interactions between pyridyl and phenyl moieties have been observed previously [47, 55]. The slipped conformation observed in our findings is a regular type of conformation for similar complexes. Moreover, π-stacking interactions are typical for polyaromatic and aromatic rings in which carbon atoms are replaced by a hetero atom [47].

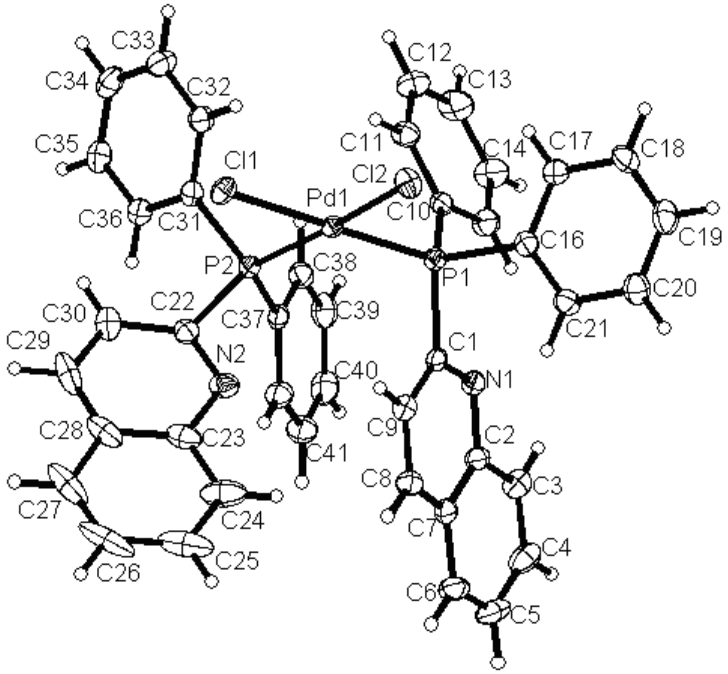


Fig. 7. Mononuclear *cis*-palladium complex of 2-diphenylphosphanequinoline (34).

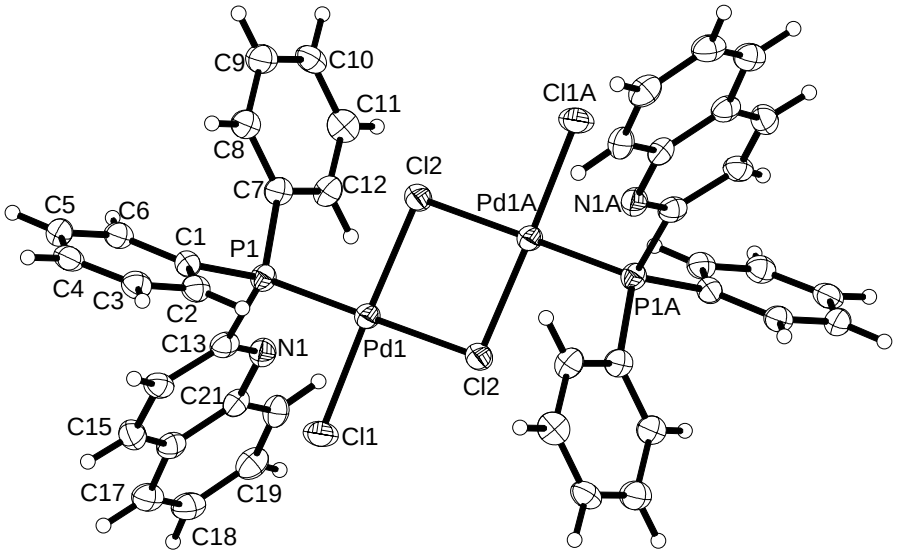


Fig. 8. Dinuclear *trans*-palladium complex of 2-diphenylphosphanequinoline 34.

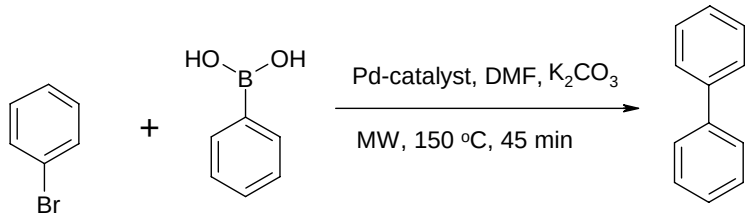
Crystal structures of the two isomers of tetra(2-mercaptobenzo-thiazole)bispalladium

The two isomers of tetra(2-mercaptobenzothiazole)bispalladium are presented in Figures 1 and 2. The first isomer (see Figure 1.) has previously been described in the literature [55]. In this isomer, two 2-mercaptobenzothiazole units are bonded with a Pd-N bond to Pd-atom 1 and with a Pd-S bond to Pd-atom 2, and the two other 2-mercaptobenzothiazole units with a Pd-N bond to Pd-atom 2 and with a Pd-S bond to Pd-atom 1. The 2-mercaptobenzothiazole units with the same type of bonds were on the same side of the Pd-Pd axis. These types of conformations are generally known as lantern-type structures[II]. The other isomer (see Figure 2.) presented a distorted lantern-type structure with three 2-mercaptobenzothiazole units forming a Pd-N bond with Pd-atom 1 and a Pd-S bond with Pd-atom 2, and one 2-mercaptobenzothiazole unit forming a Pd-S bond with Pd-atom 1 and a Pd-N bond with Pd-atom 2. The three similarly bonded 2-mercaptobenzothiazole units were located on the same side of the Pd-Pd axis and the lone unit remained on the opposite side. This type of distorted lantern structure was previously unknown in the literature.

5 Catalysis

5.1 General reaction conditions

Suzuki coupling reactions have been one of the most studied catalytic reactions involving palladium complexes already for decades. Today the Suzuki coupling reaction is the most widely used method for the preparation of C-C bonds and the backbone in the synthesis of bi- and triaryl compounds. These compounds are vital for medicine and agricultural industry, the preparation of natural products and materials sciences. The Suzuki reaction can be utilized on both the industrial and laboratory scale. The wide ranges of use and endless development possibilities have made Suzuki coupling reactions a resourceful prospect of the future. A general reaction set-up is presented in Scheme 11.



Scheme 11. The Suzuki coupling reaction and typical reaction conditions illustrated by the coupling between bromobenzene and phenyl boronic acid to prepare the simplest biaryl: biphenyl.

Even the tiniest modifications in ligand structure are known to have a large influence in the catalytic activities in the Suzuki coupling reactions. In an ideal case, varying the catalyst's properties through fine tuning of the ligand structure allows a strict control for the selectivity and activity of the catalyst. Reaction mechanisms are always similar in Suzuki coupling reactions, and various ligands do not influence the mechanism directly. Instead they exert their influence through the structure and stability of the Pd-catalyst [18]. Phosphane ligands are electron-rich and stable enough when bonded to a metal to allow various interactions, and their structures can be easily modified. Therefore phosphane ligands serve as perfect ligands for Suzuki coupling reactions [15].

In these studies the reaction conditions were first optimized to create the most favorable circumstances for the Suzuki couplings. The activities and efficiencies of the various palladium catalysts could then be compared based on donor/accep-

tor and steric properties of the respective ligands. The catalytic testing was started with basic coupling reactions between simple aryl halides and phenyl boronic acids and later expanded to a selection of more sterically demanding and difficult reactions.

Apart from the ligand and catalyst structures, the general parameters that were optimized for the Suzuki coupling reactions are: temperature, time, solvent, loading of the catalyst and base. The base forms a more electron-rich intermediate with the boronic acid. This intermediate is more reactive towards the attack of Pd(II) complexes than the original boronic acid [49]. There are numerous examples of bases used in Suzuki couplings in the literature. In these studies, the bases were chosen according to price and their ready availability. The choice of the base varies greatly in the literature. This depends on the reaction conditions with several effective bases in some particular types of reactions failing completely in other types. K_3PO_4, K_2CO_3, KF and Cs_2CO_3 are known as effective bases, and more recently, new bases such as NaO^tBu and KO^tBu have been used. In these experiments K_3PO_4, K_2CO_3, KOH, KF and Na_2CO_3 were screened as potential bases in the simple coupling reaction between 4-bromotoluene and phenyl boronic acid. All bases provided us with at least moderate yields, but the most effective bases were clearly K_3PO_4 and K_2CO_3, of which the latter was chosen due to its ready availability. The quantity of the base is normally three times that of the stated amount of aryl halide. However, the preliminary screening showed that even two equivalents were enough and the yield was not further improved by additional quantities of the base. The separation process of the coupling products was easier when a minimum amount of base is used in the reaction.

The most regular solvents in the Suzuki couplings are DMF (dimethylformamide) and dioxane, of which the use of the latter has recently been restricted to a minimum due to its high toxicity. Other solvents commonly used include toluene, THF (tetrahydrofuran) and various alcohols. The solvent is generally chosen on the basis of the ready solubility of the reaction starting materials, which of the catalyst is normally the most demanding component. In these studies water, toluene, ethanol, THF and DMF were screened as potential solvents. DMF proved to be the best solvent in this screening.

The reaction time and temperature are the parameters that are most often optimized in Suzuki coupling reactions involving conventional methods. When using conventional heating methods, time and the required temperature are important factors that affect the outcome of the reaction and also often determine the reaction's potential for industrial use. Normal reaction temperatures range from room

temperature to as high as 200 °C, and the reaction times from four to 48 hours. A common problem using traditional heating methods is that the Pd-catalysts are not stable enough to withstand high temperatures for the required long time periods, which limits the choices of potential catalysts and ligands.

When using microwave heating instead of conventional heating methods, the reaction times generally vary from five minutes to two hours. In these experiments the reaction time was between 30 to 45 minutes depending on the reaction, which suggests that the reaction conditions do not lead to short reaction times on the microwave scale. But by using microwave heating, the reaction times are relatively fast even in the most demanding coupling reactions, and the reaction times are always shorter compared with conventional heating methods. Additionally, other reaction conditions often become a secondary issue whereas the success of the coupling is the primary issue. The temperature in coupling reactions using microwave heating is normally between 100 to 150 °C. As the early experiments suggested that the Pd-catalysts and coupling products were stable even at 150 °C, this temperature was used throughout our experiments to ensure a proper reaction.

The loading of the catalyst is primarily dependent upon the activity of the catalyst. In addition the catalyst's solubility, the starting materials and the general reaction conditions also influence the required loading. The catalyst loading has in some cases been reported to be as low as 0.001 % [56] when phosphane ligands were used. Even so, in recent microwave studies the amount generally ranges from 0.1 % to 1.0 %. This is much lower than the 5-10.0 % used in coupling experiments that used conventional heating methods. In these studies the loading of the catalyst was optimized to between 0.1-0.5 %.

The main reason for the urge to minimize the use of the catalyst has been due to the problems in the separation of the catalyst and the coupling products from the reaction mixture. In conventional Suzuki coupling procedures the scale of the reaction was much larger and therefore the required amounts of the catalyst have often made the experiments very expensive. In contrast, the scale of the reaction using microwave heating is much smaller and the costs can be kept at minimum even at higher loadings compared with the conventional methods. Furthermore, even in the majority of the most recent reports the attributes of the ligands have often necessitated the complex be formed *in situ* instead of providing the reaction mixture with strictly controlled amounts of isolated and purified Pd-catalysts. This has often resulted in the need for continuous addition of the expensive ligands to the reaction mixture. This has created a strict demand to minimize the loading of

the catalyst. Such high amounts of the catalyst are not needed when Pd(II) complexes and aryl alkyl phosphane ligands are used.

The Pd-complexes used in combination with phosphorous containing ligands in Suzuki couplings have usually been of the Pd(0)-type. Because of the lack of well-defined Pd/phosphane ligand catalyst systems, Pd(0) often demands the use of the phosphane as a free ligand and this frequently results in the requirement for an excess of the ligand. Other ligands, such as heterocyclic carbenes and a variety of bidentate species, have been generally used as Pd(II) complexes and do not require the constant addition of the free ligand [56]. However, these types of ligands are more difficult to prepare and do not remain stable over many catalyst cycles [57]. Pd(II) complexes of various phosphanes have been successfully used as catalysts in Suzuki coupling reactions [9, 10, 17, 20, 22, 56], but the stability of the complexes has been a major problem. The recent innovation of the microwave heating technique has shortened the reaction times and made it possible for Pd(II)/phosphane ligand complexes to be used without major problems with stability. The small reaction scale also makes the separation process of the products relatively easy.

The reaction conditions described were therefore regarded as very convenient. In addition, Pd(II) complexes of the phosphane ligands are not air or moisture sensitive and remain stable in air for the length of the reactions. Therefore Schlenk-techniques for the catalytic experiments were not needed. This contrasts with most reports in which heterocyclic carbenes and other related species have been used [56-59]. The resistance to oxidation is an important property of bulky phosphane ligands and allows the reaction to be carried out in air [15]. The acquired results show that a new, efficient and well-defined Pd(II)/phosphane ligand catalyst system with a strict control for the amount of the catalyst under microwave irradiation can be optimized.

5.2 Aryl phosphane ligands

At the end of last century studies had mainly focused on the development of new ligands, especially phosphorus-containing ligands to attain a high degree of efficiency in cross-coupling reactions. Among the most studied phosphane ligands for Pd-catalyzed cross-coupling reactions, bulky electron-rich phosphanes such as trialkylphosphanes or biarylalkylphosphanes have met with great success [60, 61]. In these studies the catalytic screening was started with triaryl phosphanes due to the fact that their electronic and steric properties are well known.

The mononuclear complexes of the *ortho*-alkyl substituted aryl phosphanes produced excellent yields from the simple coupling reaction of 4-bromotoluene and phenyl boronic acid. They also produced very good yields from the coupling reactions of 2-isopropylbromobenzene and 2,4,5-trimethylbromobenzene with phenyl boronic acid under the optimized catalytic system. Even if the other *ortho*-alkyl substituted aryl phosphane ligands failed to produce more than mediocre yields in the more demanding coupling reactions, the palladium complex of *o*-ethylphenyldiphenylphosphane **30** still produced a very good yield in the coupling reaction of 3-bromopyridine and phenyl boronic acid. In the more demanding coupling reactions of 2-chloroquinoline and 3-bromoxylene with phenyl boronic acid, and 4-bromotoluene with biphenyl boronic acid, the yields were good or mediocre, but clearly lower than with the other types of phosphane ligands. Therefore the aryl phosphanes were not tested further. The steric hindrance between the phosphane ligand and the bulky reactants most likely prevented a fast and complete reaction.[IV]

The differences between the ligands with different substituents in the *ortho*-position were minimal. Some substituents seemed to produce slightly better yields than others in one particular reaction, but their rankings could completely switch for another reaction. However, it appears that the aryl phosphanes with an increased amount of the alkylphenyl moities (bis- or tris-alkylphenyl) worked slightly better in the more demanding coupling reactions than those of the mono-alkylphenyl moieties. The main difference between the mono and bi/tri alkylphenyl ligands was the slightly larger electron density of the latter.[IV] Even so the yields remained lower than for the other types of phosphane ligands. The bis(*ortho*-isopropyl- and *ortho*-cyclohexylphenyl)phenylphosphanes **21** and **22** produced only mediocre yields in the demanding coupling reactions between the various bromoxylenes and phenyl boronic acids. However, the isopropyl substituted phosphane produced a higher yield than the cyclohexyl substituted phosphane in all reactions, which suggests that the large steric bulk of the *ortho*-cyclohexyl prevents the more difficult couplings even if it is electronically richer.[V]

The 2,3- and 3,4-dimethylphenyldiphenyl phosphanes **19** and **20** produced low or mediocre yields in the demanding coupling reactions between various bromoxylenes and phenyl boronic acids. Moreover, the earlier suggestions about the steric hindrance were again thought to be the cause of the low yields.[V] The 2,4,5-trimethylphenyldiphenylphosphane **23** produced good yields in the easier coupling reactions but failed to work in the more demanding reactions. A similar finding was observed for the *ortho*-alkyl substituted aryl phosphanes. Interestingly, the

yield was very good in the coupling of 2-chloroquinoline and phenyl boronic acid.[IV]

The chelated palladium complexes of the aryl phosphane ligands with hetero atoms in the ortho-position (ligands **24** and **25**) produced mainly low or mediocre yields. It seems that the chelating effect of the ligands blocks a proper reaction, even though there are examples in the literature that report the effect to sometimes be exactly the opposite.[III]

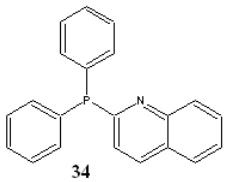
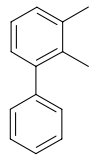
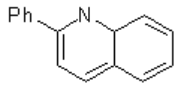
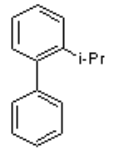
The dinuclear analogues of the *ortho*-alkylphenyldiphenyl phosphanes worked well in the easiest couplings, but failed in the more demanding coupling reactions. Furthermore, it was observed that the dinuclear complexes were destroyed quite early on in the reaction, which prevents a proper catalytic reaction from proceeding.[IV]

In most cases the selectivities of the aryl phosphane ligands were similar and only tiny amounts of homocoupling products of the phenyl boronic acid were observed.

5.3 Quinolinyl phosphane ligands

The quinolinyl phenyl and diquinolinyl phenyl phosphanes **34-38** were tested in various simple and more demanding coupling reactions. Some of the results for ligands **34-36** are compared in Tables 6-8.

Table 6. Yields in various coupling reactions produced by the mononuclear palladium complex of 2-diphenylphosphanequinoline 34.

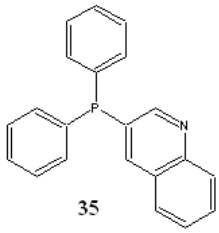
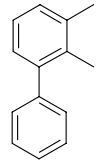
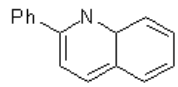
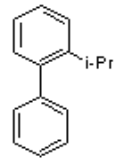
	Product	Yield (%)
 34		64
		55
		59

The palladium complex of diquinolinylphenylphosphane **37** produced only low yields even in the simplest coupling reactions. This was probably due to its bulky structure. Therefore the ligand was not extensively tested. The differences between the catalytic efficiencies of the 2-diphenylphosphanequinoline **34** and 3-diphenylphosphanequinoline **35** were only small. Interestingly, the 4-diphenylphosphanequinoline **36** produced higher yields than the phosphane ligands **34** and **35**. However, even ligand **36** produced only low yields in the more demanding reactions. It is possible that the nitrogen electron pair interferes with the addition reaction of the aryl halide and the phenyl boronic acid and therefore slows down the reaction with ligands **34** and **35**. Another possible explanation simply is the large size of the ligand. When the nitrogen atom was transferred to the *para*-position in ligand **36**, the effect became smaller and the yields were higher. Electronically the ligands are fairly similar. It is also possible that ligand **35** forms a *cis*-isomer similar to that of ligand **34**, and ligand **36** a *trans*-isomer, which results in higher yields for **36**. Only a few examples of comparison of *cis*- and *trans*-isomers' catalytic efficiencies were found in the literature[III]. Nevertheless, it is known that steric

repulsion is regularly larger with *cis*-isomers. Steric repulsion is known to affect the catalytic efficiencies when bulky starting materials are used [1].

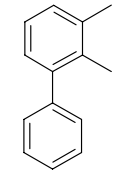
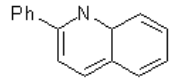
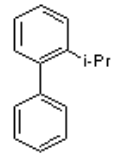
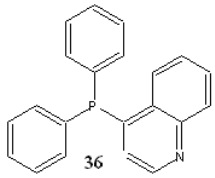
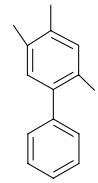
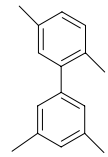
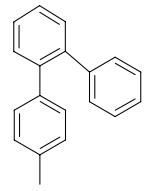
The selectivity of the catalysts started to decrease in the most demanding reactions, and the homo-coupling products started to predominate over the desired products. Therefore the quinolinyl diphenyl phosphanes are not active enough to be used as catalysts in the more demanding coupling reactions.

Table 7. Yields in various coupling reactions produced by the mononuclear palladium complex of 3-diphenylphosphanequinoline 35.

	Product	Yield (%)
 35		70
		72
		54

The dinuclear analogues of the palladium complexes of quinolinyl phosphane ligands had similar catalytic properties to those of the aryl phosphanes. The yields were generally smaller than those produced with the mononuclear complexes, apparently because of the quick destruction of the complexes.

Table 8. Yields in various coupling reactions produced by the mononuclear palladium complex of 4-diphenylphosphanequinoline 36.

	Product	Yield (%)
		75
		80
		81
 36		70
		27
		35

The replacement of a small amount of the organic solvent by water has been reported to improve reaction yields by improving the solvation of the materials

such as alkalimetal bases, which normally are insoluble in organic solvents. A more effective heat transfer compared to organic solvents has also been suggested as one of the factors improving the yields [49]. In these experiments the effect of the addition of water with the only moderately active quinolinyl phenyl phosphanes was tested. The results are presented in Table 9. The acquired results show, that the addition of water improved the yields in each case notably.

Table 9. Effect of the addition of H_2O on the yields of various coupling reactions.

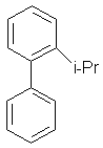
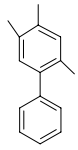
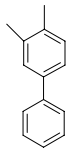
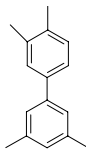
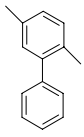
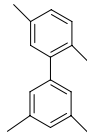
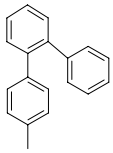
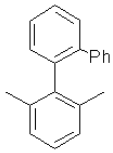
Product	Catalyst	Yield (%)	Yield (%) (H_2O added)
	34	59	80
	35	54	71
	35	64	82
	34	62	79
	35	69	80
	36	56	66
	34	53	62
	35	72	86
	34	69	80
	36	70	79
	34	71	84
	36	64	78
	35	65	77
	35	76	85
	34	65	84
	36	62	68

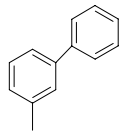
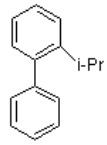
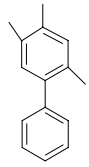
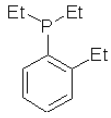
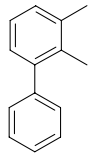
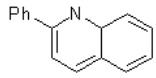
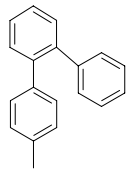
Table 9. Continued

Product	Catalyst	Yield (%)	Yield (%) (H_2O added)
	34	61	68
	35	38	51
	36	32	49
	34	40	49
	35	29	39
	36	31	38

5.4 Mixed aryl alkyl phosphane ligands

The main emphasis on these catalytic studies was to examine and compare the catalytic efficiencies of various mixed aryl alkyl phosphane ligands, which initially were found to be the best catalysts. Both the size of the alkyl groups directly attached to the phosphorous atom and the alkyl groups in the *ortho*-position of the phenyl ring were systematically increased from smaller (methyl, ethyl) to larger groups (isopropyl, cyclohexyl, phenyl) in order to find the optimum combination of steric and electronic properties. The results for some of the most effective ligands are presented in Tables 10-14.

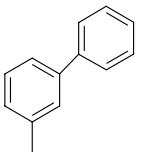
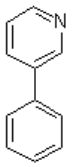
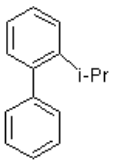
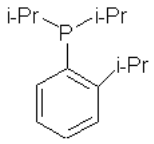
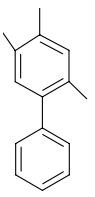
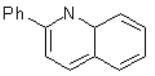
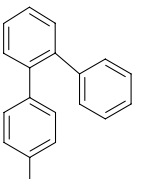
Table 10. Yields in various coupling reactions produced by the mononuclear palladium complex of *o*-ethylphenyldiethylphosphane 1.

	Product	Yield (%)
		70
		91
		94
 1		96
		86
		86

The structures and electronic properties of the aryl alkyl ligands are fairly similar. Accordingly it was observed that most mixed aryl alkyl phosphane ligands worked well as catalysts in the majority of the coupling reactions and produced at least average yields with only a few exceptions. Consequently, all of the synthesized aryl alkyl phosphane ligands could be used as catalysts to some extent. Apparently both the electron richness and the sterically smaller size, compared to triphenyl

phosphane moieties, make the aryl alkyl ligands more suitable as catalysts. The chelated phosphane ligands **16-18** were the only exceptions. The yields those produced were only low or mediocre, as was in the findings for the chelated aryl phosphane ligands.

Table 11. Yields in various coupling reactions produced by the mononuclear palladium complex of *o*-isopropylphenyldiisopropylphosphane 6.

	Product	Yield (%)
		82
		92
		96
 6		96
		96
		96

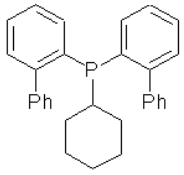
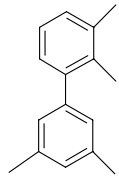
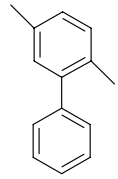
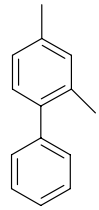
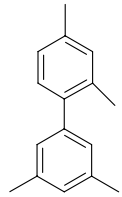
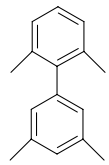
Differences between the various alkyl groups directly attached to the phosphorous were found to have the largest effect on the catalytic efficiencies of the ligands. The electronic properties of the ethyl and isopropyl substitutes were almost identical, though the cyclohexyl group is more electron-rich. Ethyl and especially isopropyl groups produced somewhat higher yields than the electronically richer cyclohexyl groups even if the differences were only small in some cases. The electron-rich alkyl ligands formed a strong bond with the metal ion and therefore remained stable throughout the reaction and ultimately produced high yields. However, when cyclohexyl groups are involved, steric repulsion can prevent a proper interaction and the metal-ligand bond can become weaker. The best catalysts are therefore electron-rich but not sterically too complex so that the metal-ligand bond is not weakened and does not block the interaction between the substrate and the Pd-complex either. This is clearly reflected in the case of ligands **8** and **9**, of which the former had a larger chemical coordination shift even though the latter was more electron-rich. The steric bulk of ligand **9** prevented the formation of a strong bond as that for ligand **8**, therefore the palladium complex of ligand **8** was more stable as a catalyst.

Comparing the diaryl alkyl and dialkyl aryl moieties revealed that the differences were the smallest between the isopropyl substituted ligands and largest between the cyclohexyl substituted ligands. The bis(*ortho*-alkylphenyl)cyclohexyl phosphane ligands produced higher yields than the corresponding dicyclohexyl species. However, the steric repulsion was not observed to have effected the catalytic efficiencies in a completely straightforward manner, since only small differences between the dialkyl aryl and diaryl alkyl species were sometimes shown. This further implicates that the different electronic properties of the ligands have a substantial influence on the catalytic activities.

Trialkyl phosphane ligands do not work as well as catalysts as mixed aryl alkyl ligands, Buchwald *et al.* reported that a phenyl ring with a substitute is one of the key factors which makes the Pd-catalysts of these types of ligands resistant towards oxidation and therefore catalytically highly active [15].

An earlier study showed the δ-donation of the alkyl group directly attached to the phosphorous as one of the factors affecting catalytic activity. This was especially the case for the alkyl phosphane ligands [62]. The strength of donation therefore influences the strength of the bonding between the metal and the ligand and ultimately the interaction between the substrate and the catalyst.

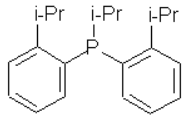
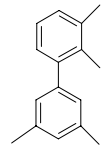
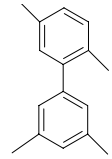
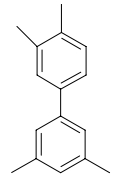
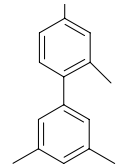
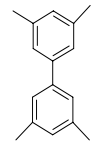
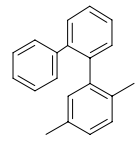
Table 12. Yields in various coupling reactions produced by the mononuclear palladium complex of bis(*o*-phenylphenyl)cyclohexylphosphane 15.

	Product	Yield (%)
 15		87
		91
		84
		81
		92

When the steric bulk of the *ortho*-substituents on the phenyl rings were altered, the differences were only small in most cases. However, comparing the catalytic effi-

ciencies between the phosphanes with the smallest groups and largest groups always showed notable differences. Therefore the variation between a small and a large substituent always affected the outcome. *Ortho*-substituents are known to affect catalysis mainly through steric and attractive forces such as those described in this publication and in other publications [5].

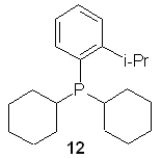
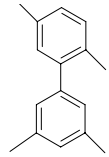
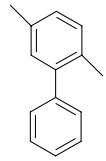
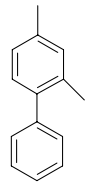
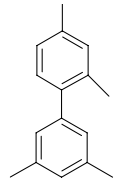
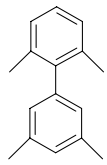
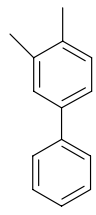
Table 13. Yields in various coupling reactions produced by the mononuclear palladium complex of bis(*o*-isopropylphenyl)isopropylphosphane 8.

	Product	Yield (%)
 8		90
		95
		90
		85
		80
		95

In these studies an overall supreme catalyst was not found. Nevertheless, diisopropyl aryl phosphane ligands and diethyl aryl phosphane ligands generally produced high yields in all coupling reactions. The corresponding diaryl alkyl phosphanes and the diaryl cyclohexyl phosphanes ranked slightly lower. The main reasons for the activity of these catalysts include a sterically optimal structure and electron-richness. An isopropyl or cyclohexyl group in the *ortho*-position was found to be the best component sterically. In most cases the electronically different phenyl group in the *ortho*-position produced higher yields than the small alkyl groups ethyl and methyl.

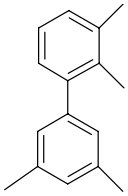
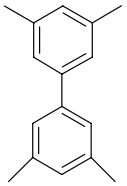
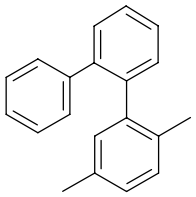
It was noted, that there was a specific catalyst that produced the highest yield for each reaction. Even if some of the catalysts produce high yields in many reactions, a precise catalyst for each coupling reaction can be assigned if the yields are fine tuned to a maximum. Small differences in the structures of the phosphanes sometimes affect the catalytic efficiencies to a large extent.

Table 14. Yields in various coupling reactions produced by the mononuclear palladium complex of (o-isopropylphenyldicyclohexylphosphane 12.

	Product	Yield (%)
 12		83
		85
		85
		85
		81
		73

The effects of adding a small amount of water to the reaction mixture are presented in Table 15. It is once again shown that adding water into the reaction mixture improved the yields in all cases. Using water also further reduced the differences between the yields produced by different ligands, and enhanced the potential for extensive use of most aryl alkyl catalysts.

Table 15. Effect of H_2O on the catalytic efficiencies of various Suzuki coupling reactions

Product	Catalyst	Yield (%)	Yield (%) (H_2O added)
	5	70	90
	15	69	92
	22	58	74
	2	82	97
	21	74	95
	15	73	90
	22	71	80

Unactivated aryl chlorides are the cheapest catalytic reagents available for the Suzuki couplings of various aryl components, and their use has been standardized for conventional heating methods. Up until now their use together with microwave heating had only achieved limited success. Due to the promising results with the coupling reactions presented in our earlier studies, the experiments were continued with a series of more demanding unactivated aryl chlorides and bulky phenyl boronic acids. High yields and an almost perfect purity of the coupling products were earlier obtained when water was added to the reaction mixture. Therefore water was added systematically in the later experiments of this study. [IV, V]

Palladium complexes of ligands **6** and **8** were used for the experiments due to the low price of the starting materials and the relatively good air tolerant nature of the free ligands. In publication IV it was shown that aryl chlorides with various functional groups (NMe_2, OCH_3, $COCH_3$, SMe, OH, CN) in addition to bulky components (biphenyl, *o*-xylene) could be coupled with high yields of the product. In publication V, the measurements were continued with a series of various chloroxylenes and also more demanding and complex bulky phenyl boronic acids such as 2,6-dimethyl phenyl boronic acid. Once again the yields were high for almost all coupling products. This result suggests that this catalyst system can be successfully used to couple various types of unactivated aryl chlorides that had previously been coupled but which gave only low yields using microwave irradiation. Therefore the catalyst system has high potential to be developed even further.

6 Conclusions

The aim of this research was to prepare and to characterize a series of new aryl and mixed aryl alkyl phosphane ligands and their corresponding palladium complexes. These were catalytically screened in the search for potential new catalysts for the Suzuki coupling reactions of various aryl halides and phenyl boronic acids.

A method for the preparation of Pd-complexes with a desired nuclearity was developed, which allows for the production of Pd complexes simply by the choice of the solvent. A selection of Pd-catalysts prepared from the mixed aryl alkyl phosphanes produced excellent yields in various standard and more demanding coupling reactions. The phosphane ligands with ethyl, isopropyl and cyclohexyl groups directly attached to the phosphorous atom produced the best yields in a variety of coupling reactions. This was due to their electron richness, resistance towards oxidation as Pd-complexes and stability of the metal-ligand bond. However, steric forces can adversely affect the catalytic properties to a large extent when bulky substituents are used. The Pd-complexes of ligands **1**, **6**, **8** and **15** were clearly shown to be the most effective catalysts in these studies. Furthermore, steric and electronic properties of the phosphane ligands can be used to predict the catalytic characteristics of the formed Pd-complexes.

A new, convenient catalyst system for the Suzuki coupling of various substrates was developed. The catalyst system is a very versatile tool and makes it possible to conduct Suzuki coupling reactions in air using low catalyst loadings with fast reaction times and high yields. The procedure is straightforward and cost-effective and known problems in conventional Suzuki reaction set-ups can be avoided using this method. Using microwave heating and replacing a portion of the organic solvent by water enhances the potential applications for this system even further and makes the process more environmentally friendly and energy efficient. The addition of a small amount of water into the reaction mixture improved the yields by as much as 15 %.

A wide variety of previously only mildly reactive unactivated aryl chlorides with various functional groups and bulky substituents could be coupled, giving high yields using the catalyst system described in this thesis. Large-scale extensions and a growing range of use for the system are highly probable in the future.

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