Synthesis of C($sp^2$)-P bonds by palladium-catalyzed reactions

Mechanistic investigations and synthetic studies

Marcin Kalek
To Paulina
Abstract

This thesis focuses on synthetic and mechanistic aspects of palladium-catalyzed C(sp²)-P bond-forming reactions, with the aim to develop mild and efficient methods for the synthesis of biologically active phosphorus compounds, e.g. DNA analogs.

The first part of the thesis is devoted to detailed mechanistic investigations of the palladium-catalyzed C-P cross-coupling reaction, in order to fully understand the underlying chemistry and by rational design of the reaction conditions, improve the overall efficiency of the process and broaden its applicability. In particular influence of palladium coordination by different anions on the rate of ligand substitution and reductive elimination steps of the reaction was studied. It was found that coordination of acetate ion results in unprecedented acceleration of both of the mechanistic steps, what leads to remarkable shortening of the overall reaction times. In-depth kinetic investigations enabled to ascribe the observed effects to ability of the acetate ion to act as a bidentate ligand for palladium. This causes considerable alternation of the reaction mechanism, comparing to the reaction involving halide-containing complexes, and results in significant rate increase.

Based on the above mechanistic studies an efficient method for the synthesis of arylphosphonates, using substoichiometric amounts of inorganic acetate additive and reduced amount of catalyst, was developed.

In the next part of the thesis, efforts to further enhance the palladium-catalyzed cross-coupling efficiency by using a microwave-assisted synthesis are described. These explorations resulted in a successful development of two protocols, one for a cross-coupling of H-phosphonates and the other for H,H-phosphinates, under the microwave heating conditions. Application of this energy source resulted in extremely short reaction times, measured in minutes.

The final chapter of this thesis deals with studies on palladium-catalyzed S_N2’ propargylic substitution reaction with phosphorus nucleophiles, which leads to allene products. Efficient procedure for the synthesis of allenylphosphonates and related compounds was developed. The method enables full control of stereochemistry in the allene moiety and at the asymmetric phosphorus center. Some conclusions on the mechanism of the reaction were also drawn.
This thesis is based on the following papers, referred to in the text by their Roman numerals:

I. **Pd(0)-catalyzed phosphorus-carbon bond formation. Mechanistic and synthetic studies on the role of the palladium sources and anionic additives.**
   Marcin Kalek and Jacek Stawinski

II. **Palladium-catalyzed C-P bond formation: mechanistic studies on the ligand substitution and the reductive elimination. An intramolecular catalysis by the acetate group in Pd^{II} complexes.**
   Marcin Kalek and Jacek Stawinski
   *Organometalics* **2008**, 27, 5876-5888.

III. **Preparation of arylphosphonates by palladium(0)-catalyzed cross-coupling in the presence of acetate additives: synthetic and mechanistic studies**
   Marcin Kalek, Martina Jezowska, and Jacek Stawinski

IV. **Microwave-assisted palladium-catalyzed cross-coupling of aryl and vinyl halides with H-phosphonate diesters**
   Marcin Kalek, Asraa Ziadi, and Jacek Stawinski

V. **Efficient synthesis of mono- and diarylphosphinic acids: a microwave-assisted palladium-catalyzed cross-coupling of aryl halides with phosphinate**
   Marcin Kalek and Jacek Stawinski

VI. **Palladium-catalyzed propargylic substitution with phosphorus nucleophiles: efficient, stereoselective synthesis of allenylphosphonates and related compounds**
   Marcin Kalek, Tommy Johansson, Martina Jezowska, and Jacek Stawinski
VII. Novel, stereoselective and stereospecific synthesis of allenylphosphonates and related compounds via palladium-catalyzed propargylic substitution
Marcin Kalek and Jacek Stawinski
*Advanced Synthesis & Catalysis* 2011, in press.

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Papers not included in this thesis:

**Effective modulation of DNA-duplex stability by reversible transition metal complex formation in the minor groove**
Marcin Kalek, Andreas S. Madsen, and Jesper Wengel

**Identification of efficient and sequence specific bimolecular artificial ribonucleases by a combinatorial approach**
Marcin Kalek, Peter Benedikson, Birte Vester, and Jesper Wengel
*Chemical Communications* 2008, 762-764.

**A new reagent system for efficient silylation of alcohols – silyl chloride-N-methylimidazole-iodine**
Agnieszka Bartoszewicz, Marcin Kalek, Johan Nilsson, Renata Hiresova, and Jacek Stawinski

**Iodine-promoted silylation of alcohols with silyl chlorides. Synthetic and mechanistic studies.**
Agnieszka Bartoszewicz, Marcin Kalek, and Jacek Stawinski
*Tetrahedron* 2008, 64, 8843-8850.

**The case for the intermediacy of monomeric metaphosphates during oxidation of H-phosphonothioate, H-phosphonodithioate, and H-phosphonoselenoate monoesters. Mechanistic and synthetic studies.**
Agnieszka Bartoszewicz, Marcin Kalek, and Jacek Stawinski

**On the sulfurization of H-phosphonate diesters and phosphite triesters using elemental sulfur**
Richard Wallin, Marcin Kalek, Agnieszka Bartoszewicz, Mats Thelin, and Jacek Stawinski
*Phosphorus, Sulfur and Silicon* 2009, 184, 908-916.
Preparation of benzylphosphonates via a palladium(0)-catalyzed cross-coupling of H-phosphonate diesters with benzyl halides. Synthetic and mechanistic studies.
Gaston Lavén, Marcin Kalek, Martina Jezowska, and Jacek Stawinski

$^{31}$P NMR and computational studies on stereochemistry of conversion of phosphoramidate diesters into the corresponding phosphotriesters
Linda Söderberg, Gaston Lavén, Marcin Kalek, and Jacek Stawinski
*Submitted to Nucleosides, Nucleotides and Nucleic Acids.*
Contents

Abstract ................................................................................................................. v
List of Publications .................................................................................................... vii
Contents .................................................................................................................. xi
Abbreviations ............................................................................................................ xiv

Chapter 1  Introduction ....................................................................................... 1
  1.1 Phosphates, phosphonates, and phosphinates ............................................. 2
  1.2 Aryl-, vinyl-, and allenylphosphonates and phosphinates ....................... 3
  1.3 Methods for the synthesis of \( C(sp^2) \)-P bonds ........................................ 5
  1.4 Objectives of the thesis .............................................................................. 7

Chapter 2  Overview of mechanistic aspects of the palladium-catalyzed cross-coupling reaction ................................................................. 9
  2.1 A general mechanism of cross-coupling reactions ................................... 9
  2.2 Palladium reduction process .....................................................................10
  2.3 Oxidative addition and catalyst resting states .........................................11
  2.4 Ligand substitution and isomerization in palladium(II) complexes ..........13
  2.5. Reductive elimination ..............................................................................15

Chapter 3  Mechanistic studies on a palladium-catalyzed C-P bond-forming cross-coupling (Papers I & II) ......................................................... 19
  3.1 Background ...............................................................................................19
  3.2 Comparison of different palladium sources – the role of palladium(0) complexation by H-phosphonate diesters ........................................20
  3.3 Effect of anionic additives on the rates of the cross-coupling between aryl halides and H-phosphonate diesters .......................................22
  3.4 Qualitative comparison of reactivity of different phenylpalladium(II) species in a ligand substitution step .......................................................23
  3.5 A mechanism of the ligand exchange process ..........................................26
    3.5.1 Ligand substitution in PhPdL_2X complexes (X = halide) ............26
    3.5.2 Ligand substitution in PhPdL_2(OAc) complexes..........................30
  3.6 Palladiumphosphonate complexes and the reductive elimination step ........................................................................................................34
    3.6.1 Complexes containing PPh_3 as a ligand .......................................34
    3.6.2 Palladium complexes containing a bidentate phosphine ligand ........39
3.7 Summary of the palladium-catalyzed C-P bond formation mechanisms ................................................................. 41

Chapter 4 Preparation of arylphosphonates by palladium-catalyzed cross-coupling in the presence of acetate additives (Paper III) ... 45
4.1 Effect of stoichiometric AcO− additive on the C-P bond forming reaction with different phosphine ligands ...................................................... 45
4.2 Effect of amount and source of the acetate additives ............ 48
4.3 Palladium-catalyzed synthesis of arylphosphonate diesters promoted by the acetate additive ........................................................................ 50
4.4 Conclusions .................................................................................................................. 54

Chapter 5 Application of microwave heating for the palladium-catalyzed cross-coupling with phosphorus nucleophiles (Papers IV & V) .............................................................................................................. 55
5.1 Introduction .................................................................................................................. 55
5.2 Microwave-assisted palladium-catalyzed cross-coupling of aryl and vinyl halides with H-phosphonate diesters ................................................................. 56
  5.2.1 Optimization of the reaction conditions ......................................................... 56
  5.2.2 Microwave-assisted synthesis of aryl- and vinylphosphonate diesters ................................................................. 58
  5.2.3 Conclusions .......................................................................................................... 61
5.3 Microwave-assisted palladium-catalyzed cross-coupling of phosphinate with aryl halides ............................................................. 61
  5.3.1 Optimization of the reaction conditions ......................................................... 61
  5.3.2 Microwave-assisted synthesis of monoarylphosphinic acids .... 64
  5.3.3 Microwave-assisted synthesis of diarylphosphinic acids .......... 66
  5.3.4 Conclusions .......................................................................................................... 68
5.4 Summary ..................................................................................................................... 68

Chapter 6 Palladium-catalyzed propargylic substitution with phosphorus nucleophiles: efficient, stereoselective synthesis of allenylphosphonates and related compounds (Papers VI & VII) .. 69
6.1 Introduction .................................................................................................................. 69
6.2 Optimization of the reaction conditions ................................................................. 71
6.3 Synthesis of allenylphosphonates and allenylphosphinates ........ 73
6.4 Stereochemistry of allenylphosphonates formation .............. 76
6.5 Reactions of diphenylphosphine oxide with propargylic derivatives 78
6.6 Synthesis of thio- and seleno- analogs of allenylphosphonates .... 79
6.7 Catalytic cycle for the Pd(0)-promoted allenylphosphonates formation ......................................................................................... 82
6.8 Conclusions .................................................................................................................. 84

Concluding remarks ........................................................................................................ 86
Acknowledgements ........................................................................ 87
References ...................................................................................... 89
# Abbreviations

The abbreviations and acronyms used are in agreement with the standards of the subject. Only nonstandard abbreviations that appear in this thesis are listed below.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>CytBz</td>
<td>4-N-benzoylcytosin-1-yl</td>
</tr>
<tr>
<td>dba</td>
<td>E,E-dibenzylideneacetone</td>
</tr>
<tr>
<td>DPEPhos</td>
<td>bis(2-diphenylphosphinophenyl)ether</td>
</tr>
<tr>
<td>dppb</td>
<td>1,4-bis(diphenylphosphonio)butane</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-bis(diphenylphosphonio)ethane</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1’-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>GuaBu</td>
<td>4-N-iso-butyrylguanin-9-yl</td>
</tr>
<tr>
<td>IMes·Cl</td>
<td>1,3-dimesitylimidazolium chloride</td>
</tr>
<tr>
<td>sq</td>
<td>square-planar (complex geometry)</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl</td>
</tr>
<tr>
<td>tbp</td>
<td>trigonal bipyramid (complex geometry)</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluromethylsulfonate (triflate)</td>
</tr>
<tr>
<td>Thy</td>
<td>thymin-1-yl</td>
</tr>
<tr>
<td>TS</td>
<td>transition state</td>
</tr>
<tr>
<td>Ts</td>
<td>4-methylphenylsulfonate (tosyl)</td>
</tr>
<tr>
<td>Xantphos</td>
<td>4,5-bis(diphenylphosphino)-9,9-dimethylxanthene</td>
</tr>
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</table>
Chapter 1

Introduction

Phosphorus-containing compounds are widespread in nature and are indispensible entities in the living world. The most prominent example are nucleic acids, in which phosphate diesters constitute the backbone of DNA and RNA strands. Phosphate groups are also ubiquitous intermediates in cell, as majority of species involved in metabolism of carbohydrates are phosphorylated sugars. The ultimate energy carrier in living organisms is ATP and it contains a triphosphate moiety. Last but no least, phosphate groups are important constituents of phospholipids, the building blocks of biological membranes.²

The abundance and importance of phosphorus compounds in nature caused a great demand for efficient chemical methods for their synthesis. Progress in many branches of biochemistry is tightly bound with the developments in phosphorus chemistry. The invention of PCR process (polymerase chain reaction) for instance, that was a breakthrough in molecular biology in 1980s (although its principles were founded more than 10 years earlier³), could not be possible without development of an efficient phosphoramidite method for oligonucleotide synthesis by Beaucage and Caruthers in 1981.⁴ The driving force for the advances in organic phosphorus chemistry is not only the synthesis of naturally occurring species, but also preparation of various analogs of biologically important compounds.

A traditional area of applications of organic phosphorus compounds is agriculture, where they are widely used as potent plant protection agents (herbicides, pesticides or fungicides).⁵ On the downside, phosphorus-containing compounds are also used as components of chemical warfare.⁶ Nowadays, various new fields emerge in which organophosphorus species find diverse applications, for example in medical diagnostics and the antisense/antigene approaches for modulation of gene expression.⁷
1.1 Phosphates, phosphonates, and phosphinates

The most abundant phosphorus compounds – phosphates, contain P(V) phosphorus atom in $\lambda^5 \sigma^4$ configuration (pentavalent, tetra-coordinated), as exemplified by the structure of a DNA unit (Figure 1a). This thesis, however, deals with the synthesis of phosphonates and phosphinates that are phosphate analogs, in which one or two of the P-O bonds has been replaced with a C-P bond. Phosphorus atom in phosphonates and phosphinates still has $\lambda^5 \sigma^4$ configuration, however, its oxidation state is P(III) and P(I), respectively.

Compounds containing C-P bonds occur also in nature, but both their number and distribution are quite limited. One of the first discovered member of this group of natural C-P compounds was 2-aminoethylphosphonate (AEP), depicted in Figure 1b. No evidence exists for the presence of phosphinates (compounds with two C-P bonds) in nature.

![Figure 1](image-url)

**Figure 1.** Examples of naturally occurring phosphate and phosphonate: (a) DNA contains phosphodiester linkages; (b) 2-aminoethylphosphonate has one C-P bond.

From the chemical point of view phosphates and phosphonates/phosphinates show many similarities. They share some common structural features, as indicated by identical valence/coordination number descriptor $\lambda^5 \sigma^4$. In both species the phosphorus atom is a hard electrophilic center and can form derivatives such as esters, amides, etc.

The main difference between phosphonates/phosphinates and phosphates is determined by stability of the C-P vs. P-O bonds. Although comparison of average bond dissociation energies speaks in favor of the P-O bond (90 kcal/mol vs. 70 kcal/mol for the P-O and C-P, respectively), a kinetic persistence of the C-P bond is orders of magnitude higher. This originates from the fact that leaving group ability of an alcoxide is much higher than that of a carboanion ($pK_a$ of the corresponding conjugated acids is 15-17 vs. >30, respectively), and this difference can be further increased by protonation of the oxygen atom. Importantly, a replacement of a P-O bond in phosphates by C-P bond in phosphonates usually results in a complete resistance of such an analog towards enzymatic cleavage or hydrolysis.
High stability conferred to phosphonates/phosphinates by the presence of the C-P bond and similarity of these compounds to naturally occurring phosphates, caused a growing interest in this class of compounds in biochemistry and medicinal chemistry.

1.2 Aryl-, vinyl-, and allenylphosphonates and phosphinates

A special group among phosphonates/phosphinates constitute compounds containing C(sp^2)-P bonds, which synthesis is addressed in this thesis. They are valuable intermediates in synthetic organic chemistry and also find numerous applications.

For instance, as far as the practical applications are concerned, arylphosphonates are used in designing new materials with special optical properties. These include so-called non-linear optical chromophores\(^\text{10}\) and photosensitizers employed in solar cells.\(^\text{11}\) Arylphosphonic acids-functionalized conducting polymers are used as fuel cell membrane materials, and exhibit superior properties to those bearing sulfonyl groups.\(^\text{12}\)

On the other hand, vinylphosphonates are established building blocks in polymer sciences.\(^\text{13}\) Also compounds containing mono- and diarylphosphinic structural motifs are finding applications in manufacturing of flame retardants,\(^\text{14}\) advanced polymers\(^\text{15}\) and artificial membranes.\(^\text{16}\)

Arylphosphonates having additional coordinating groups, for instance pyridine residues, have been recently employed as building blocks in construction of metal-organic frameworks (MOFs).\(^\text{17}\)

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Figure 2. (a) A mechanism of carboxylic esters hydrolysis involving a tetrahedral transition state/intermediate; (b) structure of cocaine and arylphosphonate analog used to prepare specific catalytic antibodies
In recent years there has been a growing interest in these classes of phosphorus compounds in bioorganic and medicinal chemistries. The resemblance to carboxylic group, and especially to tetrahedral intermediates formed during substitution at the carboxylic $sp^2$-carbon (Figure 2a), makes arylphosphonates/phosphinates potent enzyme inhibitors and efficient antagonists of biologically active carboxylic acids, for instance they were used as blockers of anion channels. Phosphonates/phosphinates proved to be also superior transition state analogs for the preparation of catalytic antibodies. As an example can serve preparation of antibodies degrading cocaine, via hydrolysis of its benzoate function. A structure of this drug along with arylphosphonates used in the process of antibodies production is depicted in Figure 2b.

Some compounds bearing C($sp^3$)-P bonds have been explored as potential therapeutics. These include arylphosphonates (anti-herpes agents), vinylphosphonates (antiviral), and even steroid derived allenylphosphonate, which was found to inhibit the sterol biosynthesis of a pathogen responsible for *Pneumocystis-carinii pneumonia* (PCP), the most abundant AIDS-related disease (Figure 3).

Finally, aryl- and vinylphosphonates find applications in nucleic acid chemistry and nucleic acid-based medicinal chemistry. In particular, they are used as analogs superior to natural phosphates in construction of modified oligonucleotides with potential application in the antisense/antigene techniques (gene therapy).

Among backbone modified oligonucleotides, which therapeutic potential was early recognized were phenylphosphonates (Figure 4a). The important feature of these compounds is lack of the negative charge. This property may be beneficial in the context of cell membrane penetration and a cellular uptake. Additionally, neutral oligonucleotides may form stronger duplexes with RNA due to elimination of electrostatic repulsion between the strands. Short oligonucleotides containing phenylphosphonate internucleotide linkages in selected position were synthesized first by Agarwal and co-workers. The authors have shown that at the site of modification such DNA is resistant to several nucleases.
The second arylphosphonate-type of modification evaluated at the oligonucleotidic level, were the isomeric 2-, 3- and 4-pyridylphosphonates (Figure 4b). The biophysical and biochemical studies have shown that replacement of the native negative phosphodiester bond by the neutral pyridylphosphonate moiety does not introduce significant geometric alternations of the double helical duplex structure. The modification has, however, conferred certain resistance of the modified oligonucleotides to nucleases.

Vinylphosphonates were used to prepare modified oligonucleotides as well, however, in this case a different structural motif was studied. Hayes and co-workers have prepared a vinylphosphonate dinucleotide unit, in which the 5’ oxygen has been replaced by methyldiene group (Figure 4c). The oligonucleotides with these modified residues incorporated have been used in studies on DNA-unwinding helicases.

1.3 Methods for the synthesis of C(sp^2)-P bonds

The most frequently used method for the formation of carbon-phosphorus bonds is the Michaelis-Arbuzov reaction. However, this approach is not applicable to the synthesis of aryl-, vinyl-, and allenylphosphonates, due to low reactivity of the corresponding sp^2-halides in nucleophilic substitution.

Access to arylphosphonates was for many years possible only via a few traditional methods, such as high temperature phosphorylation of aromatic compounds with P_2O_5 or Fridel-Crafts reaction with POCl_3. A more general, however still involving harsh reaction conditions, is addition of organometallic (for example organolithium) compounds to phosphorochloridates. This method has been also used for the synthesis of vinylphosphonates and phosphinates.

The major breakthrough in the area of aryl- and vinylphosphonates synthesis came with a series of reports from a group of Hirao on the palladium-catalyzed cross-coupling of aryl and vinyl halides with H-
phosphonate diesters.\textsuperscript{35,36} Cross-coupling reactions are of the trade tools of organic synthesis,\textsuperscript{37} and this has been ultimately recognized and acknowledged by the Nobel Prize in Chemistry for 2010 awarded to Ei-ichi Negishi, Akira Suzuki and Richard F. Heck. In addition to the traditional C-C bond forming reactions,\textsuperscript{38} cross-coupling involving heteroatom nucleophiles is also a rapidly expanding field.\textsuperscript{39} Although, the pioneering work by the Buchwald and Hartwig groups on nitrogen nucleophiles\textsuperscript{40,41} is usually recognized as the beginning of this kind of chemistry, it was the C-P forming cross-coupling that was the first discovered reaction in this class of transformations.

![Scheme 1](image_url)

**Scheme 1.** The Hirao’s cross-coupling of aryl and vinyl halides with H-phosphonate diesters.

The original Hirao’s procedure employed \( \text{Pd(PPh}_3\text{)_4} \) as a catalyst, and different aryl/vinyl halides and dialkyl H-phosphonates as substrates (Scheme 1). In the following years the scope of the reaction was broadened by including aryl and vinyl triflates as the coupling partners.\textsuperscript{42} Recently, it was demonstrated that also diaryl iodonium salts can be efficiently used as the aryl source.\textsuperscript{43} On the side of nucleophiles used, phosphinates,\textsuperscript{44} including \( \text{H,H-phosphinates} \),\textsuperscript{45} phosphine oxides,\textsuperscript{46} phosphines,\textsuperscript{47} and boranophosphines\textsuperscript{48} were successfully employed as substrates for this kind of coupling. There are several excellent reviews covering this topic.\textsuperscript{49,50}

The extensive progress in expanding scope of the reactants that can be coupled was not, however, paralleled by the development of new, more efficient catalytic systems. Although, since mid 1990s many new efficient ligands became available, it was \( \text{Pd(PPh}_3\text{)_4} \) that was most commonly used as a catalyst, as in the original procedures introduced by Hirao. Among a few exceptions there are reports on using other palladium sources (e.g. \( \text{Pd(OAc)}_2 \),\textsuperscript{51,52} \( \text{Pd(PPh}_3\text{)_2Cl}_2 \)) or different ligands (dppp,\textsuperscript{53} dppb,\textsuperscript{54} dpf\textsuperscript{55}), however, the changes introduced were the results of screening various reaction conditions, rather than due to better understanding of the underlying mechanism.

Despite the fact that recently some new methods for the synthesis of aryl- and vinylphosphonates, including those based on application of transition metal catalysts, have been developed,\textsuperscript{56} the palladium-catalyzed cross-coupling of H-phosphonates and related compounds containing H-P bonds remains current state of the art in the area.
A separate group of C(sp²)-P bond-containing compounds are allenylphosphonates. Their synthesis has been dominated by the [2,3]-sigmatropic rearrangement, discovered in the early sixties (Scheme 2). In this reaction propargylic phosphites, obtained from the corresponding propargylic alcohols, spontaneously rearrange to form allenylphosphonates. The method has a very broad scope with respect to the precursor propargylic substitution patterns in the allene moiety. Due to the concerted nature of the rearrangement, the reaction is stereospecific, enabling synthesis of chiral allenylphosphonates in enantiopure form, starting from enantiopure propargylic alcohols. Despite these advantages, the method suffers from a serious drawback, namely, a limited number of phosphonate derivatives that can be prepared. Phosphorus compounds that are used for the synthesis of propargylic phosphites are phosphoro-chloridites, highly reactive, prone to hydrolysis and oxidation compounds, and thus only simple alkyl derivatives can be used for the preparation of allenylphosphonates. This feature limits applicability of the procedure to the synthesis of only symmetrical allenylphosphonates bearing two identical, and usually simple alkyl substituents, at the phosphorus center.

1.4 Objectives of the thesis

This thesis aims at the development of new, more efficient methods for the synthesis of C(sp²)-P bonds, based on palladium catalysis.

We envisioned that in order to realize the above goal a better understanding of the palladium-catalyzed C-P bond-forming cross-coupling mechanism is required. Therefore, the thesis starts with a description of an in-depth mechanistic investigations of this reaction (Chapter 3). The obtained knowledge has been directly applied to the development of a superior method for the C-P bond formation, described in Chapter 4.

In Chapter 5 studies on the possibility of utilizing microwave heating to facilitate the synthesis of aryl- and vinylphosphonates and phosphinates are presented.

Finally, we set out to develop a completely novel methodology for the synthesis of allenylphosphonates and related compounds, employing palladium catalysis. Work on this subject is described in the final chapter of this thesis (Chapter 6).
Chapter 2

Overview of mechanistic aspects of the palladium-catalyzed cross-coupling reaction

In order to rationally design a set of conditions (a catalyst, solvent, temperature, additives, etc.) for an efficient transformation of the reactants into products a detailed knowledge of a reaction mechanism is indispensible. This thesis focuses on the palladium-catalyzed cross-coupling (and related $S_N2'$ substitution – Chapter 6) reactions involving phosphorus nucleophiles. There have been only a limited number of studies on the mechanism of the C-P forming cross-coupling, however, a large literature exists about the mechanism of the other carbon-heteroatom and the C-C forming cross-couplings. This chapter provides an overview of selected mechanistic findings relevant to the thesis subject. It also constitutes a background for Chapter 3, in which our own mechanistic investigations of the cross-coupling with phosphorus nucleophiles are presented.

2.1 A general mechanism of cross-coupling reactions

Despite some controversies, there is a consensus that palladium-catalyzed cross-coupling reactions with heteroatom nucleophiles follow a generic three step catalytic cycle, which is depicted in Scheme 3.

The catalytically active species is a palladium(0) complex that first undergoes an oxidative addition with aryl halide to produce palladium(II) complex, containing the $\sigma$-bonded aryl ligand. Next, one of the other ligands in this complex is exchanged by the nucleophile (Nu), with an aid of a base that intercepts the proton. Finally, the cycle is closed by reductive elimination process, in which the new C-Nu bond is formed and Pd(0) catalyst regenerated.

A catalytically active palladium(0) species must first be generated from a precatalyst, either by ligand exchange (for Pd(0) precursors, for instance from Pd(dba)$_2$) or by palladium reduction (for Pd(II) precursors, e.g. Pd(OAc)$_2$). Additionally, at the level of palladium(0) the catalyst may be reversibly converted into an inactive form, so-called resting state.
Scheme 3. A general mechanism of palladium catalyzed cross-coupling. L – supporting ligand (usually phosphine or carbene); L' – additional ligand(s) present on palladium in the resting state.

In the following sections the individual steps of a catalytic cycle are described in more detail.

2.2 Palladium reduction process

Precatalysts containing palladium(II) are often used in cross-coupling reactions due to their high stability and low cost. Two most frequently employed compounds are palladium acetate and palladium chloride. In the case of regular C-C bond-forming cross-couplings, reduction of palladium(II) to zero oxidation state takes place simply by double transmetallation and a subsequent reductive elimination, to produce minute amounts of a homocoupling product. However, for the Heck reaction, as well as for the C-heteroatom cross-couplings, such pathway is impossible and other mechanisms of the palladium reduction must operate.

It was shown in the studies by Jutand and Amatore,\textsuperscript{60,61} that when Pd(OAc)\textsubscript{2} is used as the palladium source, the reduction occurs with the aid of a phosphine ligand coordinated to palladium (complex 1), with ultimate expulsion of phosphine oxide (5, Scheme 4). Importantly, this process requires presence of water to hydrolyze the ‘reductive elimination’ product 2 to phosphine oxide and acetic acid.\textsuperscript{62} A low-ligated palladium(0) species formed (3) is instable and an additional phosphine ligand has to be provided
to keep the palladium in solution. Therefore, a mixture of Pd(OAc)$_2$ + 3 equiv. of monodentate phosphine must be used to obtain an active catalyst.

![Scheme 4](image)

**Scheme 4.** The mechanism of a phosphine-assisted palladium reduction of Pd(OAc)$_2$.

In case when a bidentate phosphine ligand is used (2 equiv.) a similar reaction occurs, resulting in a palladium(0) complex 6, bearing additionally one half-oxidized, now monodentate, phosphine ligand (Scheme 5).$^{63}$

![Scheme 5](image)

**Scheme 5.** Reduction of Pd(OAc)$_2$ with 2 equiv. of bidentate phosphine ligand.

The phosphine-assisted palladium reduction operates also for other palladium(II) salts of oxyacids, e.g. for Pd(NO$_3$)$_2$, however, it is not a valid mechanism in the case of halide salts, e.g. PdCl$_2$. It was suggested that when PdCl$_2$ is used as the Pd(0) precursor, it is a tertiary amine, present in the reaction mixture, that reduces the palladium.$^{37}$ The putative mechanism of such amine-assisted palladium reduction would involve $\beta$-elimination of hydride from amine as a key step.

### 2.3 Oxidative addition and catalyst resting states

During oxidative addition the C(sp$^2$)-X bond is broken and a palladium(II) complex bearing both aryl and halide components as ligands is formed. The rate of oxidative addition depends both on the structure of the aryl halide and the ligands present in the initial palladium(0) complex. In the course of the reaction palladium to some extent acts as a nucleophile attacking sp$^2$ carbon, however, bond breaking to the leaving group is also involved in the rate determining step.
Therefore, an order of reactivity of halobenzenes is in agreement with C-X bond strengths, namely, oxidative addition of PhI is faster than PhBr, and this is faster than the reaction of PhCl\textsuperscript{64} (bond dissociation energies for PhX: Cl - 96 kcal/mol; Br - 81 kcal/mol; I - 65 kcal/mol\textsuperscript{65}). Also other substituents present in the aromatic ring influence rates of the oxidative addition in a similar manner as for ‘normal’ aromatic nucleophilic substitution, i.e. electron-withdrawing groups accelerate the process and electron-donating ones slow it down.

On the other hand, the more electron-rich palladium(0) complex is, the faster oxidative addition occurs. Hence, to improve the oxidative addition rate, strongly donating supporting ligands such as alkylphosphines, phosphites, or N-heterocyclic carbenes are used. Application of these ligands enables the oxidative addition of even highly unreactive aryl chlorides.\textsuperscript{65} In another approach, anionic Pd(0) complexes, e.g. Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsuperscript{-} or Pd(PPh\textsubscript{3})\textsubscript{2}(OAc)\textsuperscript{-} (4), are used.\textsuperscript{66,67} Due to the presence of a negative charge they exhibit higher reactivity then the neutral complexes. Computational studies have shown that during the oxidative addition the anion leaves the inner coordination shell (Scheme 6a), but stays coordinated in the second ligand layer, what lowers the energy barrier by ~4 kcal/mol, comparing to reaction involving the neutral complex.\textsuperscript{68,69}

![Chemical structure](image)

**Scheme 6.** The course of oxidative addition to different palladium(0) species (for bidentate ligands, the final Pd(II) complexes will be *cis*).

Oxidative addition in general requires low ligated 14-electron palladium complexes. Therefore, a dissociation of ligands is necessary in case of 18-electron complexes, such as Pd(PPh\textsubscript{3})\textsubscript{4}. Thus some fraction of Pd(0) present in the reaction mixture may be trapped in an inactive form – so-called resting state (for instance PdL\textsubscript{4} and PdL\textsubscript{3} in Scheme 6b). In addition to phosphines, also other species are able to bind to palladium(0) and form ‘resting’ complexes, hence lowering the efficiency of catalyst. An important example
here is a dba molecule, brought into the solution when Pdₓ(dba)ᵧ are used as the palladium sources. It forms relatively strong complex (PdL₂(dba) in Scheme 6c) and its presence always slows down oxidative addition considerably.⁷⁰ Recently Buchwald et al. has reported a smartly designed catalyst precursor, that in the reaction mixture is transformed into a Pd(0) complex bearing only a single phosphine ligand. Such super low-ligated (12-electron) system displayed a superior reactivity in the oxidative addition.⁷¹

### 2.4 Ligand substitution and isomerization in palladium(II) complexes

Palladium(II) complexes, formed in the oxidative addition step, are tetra-coordinated, 16-electron, square-planar species, in which ligand substitution can occur via two distinct reaction pathways (Scheme 7): (a) an associative path, involving penta-coordinated, 18-electron square-pyramid and trigonal bipyramid intermediates (or transition states), or (b) a dissociative path, which proceeds via tri-coordinated, 14-electron, T-shaped species.⁷²

![Scheme 7. Associative and dissociative mechanisms of ligand exchange in palladium(II) complexes.](image)

The ligand exchange process is important for the cross-coupling reactions involving heteroatom including phosphorus, nucleophiles, on multiple accounts.

Firstly, the anionic ligand in a palladium(II) complex formed in the oxidative addition (usually the leaving group from the aryl electrophile reactant) can be replaced by another anion, if such is present in the reaction mixture (Scheme 8a).⁶⁶ These two complexes may have different stabilities and reactivities towards the nucleophile, thus a possibility exists to improve cross-coupling efficiency by using anionic additives.⁷₅ Such strategy is employed for instance when aryl and vinyl triflates are used as the starting materials, which upon oxidative addition form often unstable palladium(II) species. This problem can be overcame by carrying out the reaction in presence of chloride ion additives, which replace triflate ions, resulting in more stable complexes (Scheme 8b).⁷⁴
bipyramid complex can undergo a pseudorotation. More elaborate kinetic investigations revealed the detailed mechanism of this process, implying that the intermediate trigonal bipyramidal complex can undergo a pseudorotation. The possibility of cis-trans isomerization is important when monodentate supporting ligands are used in a cross-coupling reaction, enabling proper orientation of the ligands for the reductive elimination step (see section 2.5).

Finally, and probably most importantly, the process of a ligand substitution is crucial for the cross-coupling reactions involving heteroatom nucleophiles, as it is a step of the catalytic cycle responsible for the incorporation of the nucleophile into the palladium complex. Nevertheless, this mechanistic step has not been subject of extensive investigation.

The notable exception in this area is work by Jutand, who studied a mechanism of ligand displacement during C-S forming cross-coupling catalyzed by palladium-dppf complex. The kinetic investigation revealed that the complex is attacked by thiol and not thiolate, due to too low acidity of the former to undergo prior deprotonation. Importantly, it is not the anionic iodide that is exchanged initially, but one arm of the chelating supporting ligand departs first (Scheme 10a). Now, the deprotonation at sulfur can occur (acidity increases due to coordination to Pd(II) center), followed by restoration of the chelate structure and expulsion of iodide.

Recently, a computational study of the ligand exchange process in the C-N forming cross-coupling, in a presence of a bulky monodentate phosphine supporting ligand, has been published (Scheme 10b). Due to the size of the ligand, the complex undergoing the substitution is three-coordinate and the
amine can coordinate directly. However, also in this case the departure of the anionic leaving group (Cl⁻) occurs only after prior deprotonation of the nucleophile.

The only example of the ligand exchange during the cross-coupling reaction described in the literature, when the palladium(II) complex is attacked by an anionic nucleophile is the coupling with hydrogen sulfide. In this case, according to the DFT calculations, the nucleophile directly replaces anionic ligand (Cl⁻) in a single reaction step (Scheme 10c).

![Scheme 10.](https://example.com/scheme10.png)

**Scheme 10.** Incorporation of heteroatom nucleophiles into the Pd(II) complex: (a) experimentally established pathway for thiols; computed pathways for (b) amines and (c) hydrosulfide anion.

### 2.5. Reductive elimination

Reductive elimination step has been studied extensively both for C-C and C-heteroatom forming processes. As an reaction opposite to oxidative addition (section 2.3), reductive elimination is facilitated by low electron density at the metal center.

As far as the geometric aspects are concerned, the common sense suggests that the eliminating groups should occupy adjacent positions in a palladium(II) complex. It was indeed proven very early that that only cis-Pd(PPh₃)₂Me₂ complex is able to eliminate ethane, whereas the trans complex must first isomerize to a cis form to undergo reductive elimination.
Observation of reductive elimination from the *cis* square-planar complex led to development of bidentate supporting ligands that enforce such alignment of the two groups to be eliminated. It was shown on many occasions for C-N, C-O, C-S, and C-P forming eliminations that, if a bidentate supporting ligand was present, the reaction occurred directly from a square-planar complex (Scheme 11a). The important parameter of bidentate ligands is so-called bite-angle: the ligands with wider bite-angles ‘press’ the eliminating groups towards each other, resulting in a more facile reaction.

In case of complexes containing monodentate ligands the situation is less clear. The reductive elimination can occur directly from the 16-electron square-planar complex (*cis* isomer), however, other reaction pathways are also possible. Hartwig et al. has shown, for instance, that reductive elimination from *trans*-ArPd(PPh₃)₂(NPh₂) complexes was inhibited by the added PPh₃, which pointed out to 3-coordinate T-shape complex as a reaction intermediate (Scheme 11b). Similar species are probably involved in reductive eliminations during cross-coupling using newer generation monodentate ligands, like P(t-Bu)₃ or PC₃ and related species. Also the bidentate Xanthphos ligand is believed to be able to dissociate easily one of the chelating arms and in this way promote facile reductive elimination from the three-coordinate complex. The enhancement of reductive elimination caused by ligand removal is explained by reduction of the electron density at palladium occurring during this process.

![Scheme 11. Possible reductive elimination pathways](image)

Finally, a reductive elimination from 5-coordinate trigonal bipyramid is symmetry allowed, however, it is rather rare for Pd(II) complexes.

The C-P forming reductive elimination has been studied by Stockland et al. They showed that also in this type of reductive elimination efficiency of the reaction depends on the bite-angle of a bidentate ligand used, as it was apparent from increasing of the reaction rate in the order: dppe < dppp < dppb < dppf. Very high rate of the reductive elimination observed in the
same study for a complex containing Xantphos ligand may suggest involvement of the three-coordinate species in the process.  

Scheme 12. Dependence of the C-P forming reductive elimination rate on the electronic properties of the eliminating aryl group.

Interesting trends of the reactivity were observed in a series of complexes containing eliminating groups with controllable electronic properties. It was found that the C-P reductive elimination accelerated with an increasing electron density on the aryl group (Scheme 12). This is an opposite direction of reactivity than was found for the other C-heteroatom (N, O, and S) forming reductive eliminations.
Chapter 3

Mechanistic studies on a palladium-catalyzed C-P bond-forming cross-coupling (Papers I & II)

3.1 Background

A usual approach for development of a synthetically useful reaction involves screening of numerous reaction parameters, such as a catalyst composition (precatalyst, ligands), solvents, additives, temperature, etc. Such a strategy is far from being ideal when applied alone. A better design of a chemical transformation can be achieved only when in parallel a ground research on a mechanism of the investigated reaction is carried out. By knowing the mechanism, a chemist can make directed changes in the reaction conditions in order to achieve the desired effects. To introduce rational, not random modifications of a chemical process, a good understanding of the underlying reaction mechanism is necessary.

In the case of C-P bond-forming palladium-catalyzed cross-coupling, a lot of different reaction conditions have been tried over the years, since this reaction was discovered. Two general trends can be observed in the experimental data that have been collected. First, the reactions seem to proceed well when wide-bite-angle supporting ligands are used, and the best results were usually obtained with the dppf ligand. This can be explained in a satisfactory way by taking into account the effect of the ligand bite angle on the efficiency of reductive elimination, as shown by Stockland et al. (section 2.5). The second issue, which appeared more intriguing for us, was the origin of variable reactivity, when different precatalysts were used for the reaction. Studies from our and other laboratories have consistently shown, that application of Pd(OAc)$_2$ as a palladium source gave best results. The investigations by Jutand and Amatore provided some insight into a role of anions (including acetates) in oxidative addition step of the reaction (section 2.3), however, possible participation of these species in other steps of a catalytic cycle has not been studied before.

Kindled by the hope of better understanding of these processes and possibly enhancing efficiency of the reaction, we have undertaken
systematic mechanistic studies on a palladium-catalyzed coupling between aryl halides and H-phosphonate diesters.

3.2 Comparison of different palladium sources – the role of palladium(0) complexation by H-phosphonate diesters

The first problem we decided to investigate was how different palladium sources affect efficiency of the C-P forming cross-coupling reaction. For the purpose of this study a model coupling reaction of diethyl H-phosphonate (7) with bromo- and iodobenzene was studied (Table 1). Performing the reactions under exactly the same conditions enabled us to reveal relatively small changes in coupling efficiency.

**Table 1.** Comparison of different palladium sources.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Palladium source</th>
<th>Reaction time (h)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh(_3))(_4)</td>
<td>PhI: 8, PhBr: 18</td>
</tr>
<tr>
<td>2(^{[c]})</td>
<td>Pd(OAc)(_2) + 3PPh(_3)</td>
<td>PhI: 7, PhBr: 16</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)(_2) + 2PPh(_3)</td>
<td>PhI: 10, PhBr: 24</td>
</tr>
<tr>
<td>4</td>
<td>PdCl(_2) + 2PPh(_3)</td>
<td>No reaction, No reaction</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Reaction conditions: 0.03 mmol Pd source (10 mol\% Pd), PPh\(_3\) as in the table, 0.30 mmol 7, 0.33 mmol PhX, 0.36 mmol Et\(_3\)N, 3 mL THF (0.1 M). \(^{[b]}\) >95% conversion (\(^{31}\)P NMR spectroscopy). \(^{[c]}\) A 15 min palladium reduction performed prior to the addition of PhX and 7.

For bromo- and iodobenzene the shortest reaction times were found when the reactions were carried in a presence of a catalyst generated from Pd(OAc)\(_2\) (entry 2). Pd(PPh\(_3\))\(_4\), the most commonly used catalyst, gave slightly longer reaction times (entry 1), while using Pd(dba)\(_2\) as a palladium source, resulted in the slowest reactions (entry 3). Somewhat surprisingly, no product formation was observed with PdCl\(_2\) (entry 4).

The above differences in efficiency of the cross-coupling using Pd(PPh\(_3\))\(_4\), Pd(OAc)\(_2\) and Pd(dba)\(_2\) are in agreement with the expected reactivity of the corresponding palladium(0) species in the oxidative addition step. Namely, in case of Pd(dba)\(_2\) and Pd(PPh\(_3\))\(_4\) some fraction of Pd(0) is tied in the resting state (Scheme 6b,c), whereas for Pd(OAc)\(_2\) 100% of Pd(0) is in the form of reactive complex (Scheme 6a).
The reason why the catalytic system generated form PdCl$_2$ was inactive in the studied cross-coupling reactions, remained unclear. Additionally, we found puzzling the fact that in the instance of Pd(OAc)$_2$ it was necessary to perform the palladium reduction (section 2.2) prior to the addition of phenyl halide and H-phosphonate 7, otherwise product 8 was not formed. Because both PdCl$_2$ and Pd(OAc)$_2$ require the preceding palladium reduction, to address the above issues more detailed investigations of this process were performed, using $^{31}$P NMR spectroscopy.

![Diagram of Scheme 13. Formation of a catalytically active Pd(0) complex from Pd(OAc)$_2$ and PPh$_3$ (path A), and suppression of its formation in presence of (EtO)$_2$P(O)H excess (path B).](image-url)

For the reactions using palladium acetate, it is known that neither Et$_3$N nor aryl halides interfere with the reduction (Scheme 4), hence apparently presence of H-phosphonate 7 was the problem. $^{31}$P NMR studies showed that indeed, if the PPh$_3$ was added to a THF solution of Pd(OAc)$_2$ in presence of 7, instead of the expected palladium(0) complex 4, another species resonating at 95.5 ppm was formed. Importantly, in this reaction triphenylphosphine oxide was also produced, indicating that the reduction took place. Therefore, we concluded that the H-phosphonate 7 was apparently able to intercept the transient low-ligated complex 3, formed during the palladium reduction. Determination of the reaction stoichiometry (2 equiv. of 7 were required per 1 equiv. of Pd) and lack of the P-H bonds in the new complex, led us to ascribe it a structure depicted in Scheme 13 (9).
Importantly, complex 9 did not undergo oxidative addition with iodobenzene, hence its formation halts the cross-coupling reaction.

A possibility of a similar palladium(0) complexation by (EtO)$_2$P(O)H (7) was studied when PdCl$_2$ was used as a palladium source. Indeed, also in this case a characteristic signal at 95.5 ppm appeared (accompanied by extra peaks, probably from complexes containing additional chloride ligands), indicating that the cross-coupling reaction with this palladium source was suppressed due to complexation of Pd(0) by the H-phosphonate reactant.

Finally, it is important to mention that the complexation of palladium by H-phosphonate diesters and secondary phosphine oxides is a known phenomenon. Although, some of the H-phosphonate-ligated Pd(0) species are able to undergo oxidative addition and thus catalyze cross-coupling reactions, apparently the one with (EtO)$_2$P(O)H as a ligand (9), is not.

3.3 Effect of anionic additives on the rates of the cross-coupling between aryl halides and H-phosphonate diesters.

During the cross-coupling reactions, which results are depicted in Table 1, halide ions are formed in stoichiometric amounts (in a form of triethylammonium salts). These ions can coordinate to both catalytically active palladium(0) and palladium(II) species, and thus a mechanism of the individual steps of the catalytic cycle may change as the reaction proceeds. Such effect is expected to be especially pronounced when Pd(OAc)$_2$ is used as the precatalyst, because the acetate ions are introduced only in small amounts and, due to higher affinity towards palladium, halides can effectively compete with them. In order to level down the influence of halide ions produced during the course of the reaction, and expose the real effects of given anions on the cross-coupling efficiency, we decided to carry out the reactions in the presence of stoichiometric amounts of the appropriate salts as additives.

The obtained results are shown in Table 2. Upon additions of Cl$^-$, Br$^-$, and AcO$^-$, the times for completion of all the reactions investigated became shorter, approximately to the same extent, irrespective of the palladium source used (Pd(PPh$_3$)$_4$ vs. Pd(OAc)$_2$). The most notable effect was that of the acetate ions, for which a remarkable acceleration (entry 7), much higher than those for chlorides or bromides (entries 2, 5 and 3, 6 respectively), was observed. Such pronounced differences in the reaction times suggested that the role of the anions was not limited to the oxidative addition, and other steps of the catalytic cycle were also affected.
Table 2. Effect of anionic additives on the reaction times of 7 with bromo- and iodobenzene.$^{[a]}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Palladium source (+ ligand and additive)</th>
<th>Reaction time$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PhBr</td>
</tr>
<tr>
<td>1</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>18 h</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh$_3$)$_4$ + 10Cl$^-$</td>
<td>11 h</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh$_3$)$_4$ + 10Br$^-$</td>
<td>10 h</td>
</tr>
<tr>
<td>4$^{[c]}$</td>
<td>Pd(OAc)$_2$ + 3PPh$_3$</td>
<td>16 h</td>
</tr>
<tr>
<td>5$^{[c]}$</td>
<td>Pd(OAc)$_2$ + 3PPh$_3$ + 10Cl$^-$</td>
<td>11 h</td>
</tr>
<tr>
<td>6$^{[c]}$</td>
<td>Pd(OAc)$_2$ + 3PPh$_3$ + 10Br$^-$</td>
<td>11 h</td>
</tr>
<tr>
<td>7$^{[c]}$</td>
<td>Pd(OAc)$_2$ + 3PPh$_3$ + 10AcO$^-$</td>
<td>2.5 h</td>
</tr>
</tbody>
</table>

$^{[a]}$ Reaction conditions: 0.03 mmol Pd source (10 mol% Pd), PPh$_3$ as above, 0.30 mmol 7, 0.33 mmol PhX, 0.36 mmol Et$_3$N, 3 mL THF (0.1 M), anions were added as the corresponding n-Bu$_4$N$^+$ salts (as in the table).$^{[b]}$ >95% conversion ($^{31}$P NMR spectroscopy).$^{[c]}$ A 15 min palladium reduction performed prior to the addition of PhX and 7.

3.4 Qualitative comparison of reactivity of different phenylpalladium(II) species in a ligand substitution step

Since the data from Table 2 cannot be explained on the ground of rates of the oxidative additions (or the reductive eliminations), we concluded that the observed differences must originate from distinct reactivities of the Pd(II) species during the ligand substitution (transmetallation) step.

\[
\begin{align*}
\text{Ph} & \text{--Pd--I} \\
\text{L} & \text{L} \\
\text{10} & \text{10} \\
\text{Ph} & \text{--Pd--Br} \\
\text{L} & \text{L} \\
\text{11} & \text{11} \\
\text{Ph} & \text{--Pd--Cl} \\
\text{L} & \text{L} \\
\text{12} & \text{12} \\
\text{Ph} & \text{--Pd--OAc} \\
\text{L} & \text{L} \\
\text{13} & \text{13}
\end{align*}
\]

L = PPh$_3$

Figure 5

To establish relative reactivities of Pd(II) complexes coordinated with different anions (10-13, Figure 5) in the reaction with (EtO)$_2$P(O)H (7), $^{31}$P NMR investigations were performed. We decided to generate simultaneously two Pd(II) complexes, each containing different anion, and observe their decay upon addition of H-phosphonate 7. Such competition experiments
would provide information about relative rates of the complexes equilibria and reactivity towards the H-phosphonate diester.

The ~1:1 mixtures of PhPd(PPh₃)₂X complexes, bearing two different anions, were prepared by taking advantage of the known affinity of anions to palladium(II) center, which decreases in an order: Cl > Br > I ~ AcO. The procedure used for each pair of complexes is depicted in Figure 6, that also shows progress of the reactions with H-phosphonate 7 (in presence of Et₃N). Interestingly, in all cases it was possible to observe faster decay of one of the NMR signals, what implied that the reaction with 7 was faster than the equilibration of the complexes (i.e. exchange of the anionic ligands).

As it is visible from Figure 6a and 6b, the palladium(II) complexes containing Br⁻ (11) and Cl⁻ (12) anions are noticeably more reactive than that with I⁻ (10), since the peaks due to 11 and 12 disappeared faster than that for 10. Unfortunately, because of almost identical ³¹P NMR chemical shifts of 11 and 12 we were not able to determine relative reactivities of these two species. However, the most striking difference was observed for the complex containing acetate anion (13). While PhPd(PPh₃)₂Cl (12) displayed comparable reactivity to PhPd(PPh₃)₂Br (11, Figure 6b vs. 6a, respectively) as judged from the rates of disappearance of their ³¹P NMR signals (ca 45 min), the signal originating from PhPd(PPh₃)₂(OAc) (13) could not be detected after 1 minute (the time required for placing NMR tube back into the spectrometer and to register the spectra), upon addition of 7 (Figure 6c-e). It demonstrated a remarkably high rate of the reaction between this species and the H-phosphonate diester.

To sum up, reactivity of the Pd(II) complexes in the ligand substitution reaction with diethyl H-phosphonate 7 decreased in the following order: PhPd(PPh₃)₂(OAc) >> PhPd(PPh₃)₂Cl, PhPd(PPh₃)₂Br > PhPd(PPh₃)₂I. In light of these, one can rationalize the results and the trends observed in Table 2. The anions present in the reaction mixture influence both oxidative addition and ligand exchange steps, however, it seems that the impact on the latter one is more important for the overall reaction rate.

Without added anions, the main role is played by halides released during the reaction from aryl halide substrates. It explains rather modest acceleration of the reactions carried out using Pd(OAc)₂ as a palladium source, comparing to that in which Pd(PPh₃)₄ was used (Table 2, entry 1 vs. 4).

Performing the reaction with Br⁻ or Cl⁻ as additives (Table 2, entries 2, 3, 5 and 6) lead to exclusive formation of Pd(0) species ligated by these anions, and this resulted in acceleration at the level of the oxidative addition. The ligand substitution step was probably affected, however, since reactivity of 11 and 12 are just slightly higher than that of 10, this had only mediocre contribution to the overall acceleration.
Finally, when the acetate additive was used (Table 2, entry 7), the reactive species 4 and 13 were apparently present throughout the reaction, accelerating both the oxidative addition and the ligand substitution steps, and lend themselves to a remarkable shortening of the cross-coupling reaction time.

**Figure 6.** $^{31}P$ NMR competition experiments between Pd(II) species ligated with different anions in the reaction with 7: (a) Br$^-$/I$^-$/ (b) Cl$^-$/I$^-$/ (c) I$^-$/AcO$^-$/ (d) Br$^-$/AcO$^-$/ (e) Cl$^-$/AcO$^-$(L = PPh$_3$). Small signal at 23.7 ppm originated from contamination with Ph$_3$PO, signal of 7 (6.9 ppm) is outside the spectra region shown.
3.5 A mechanism of the ligand exchange process

Having established qualitatively the reactivity order of different palladium(II) complexes (10-13), and inspired by the idea that a ligand substitution step may be responsible for the overall rate of cross-coupling reactions, we set out to perform in-depth investigations on this process. To obtain additional insight, complexes containing bidentate ligand have also been included in this study.

3.5.1 Ligand substitution in PhPdL₂X complexes (X = halide)

For the ligand substitution in trans-PhPd(PPh₃)₂X complexes with the H-phosphonate nucleophile, both dissociative (paths A and C, Scheme 14) and associative (path B, Scheme 14) pathways can be considered. The latter may occur on two ways via exchange of a halide or phosphine ligand. Additionally, the attacking nucleophile may be a neutral species or its deprotonation may precede the ligand exchange.

![Scheme 14](image_url)

**Scheme 14.** Possible reaction pathways for the ligand substitution in PhPdL₂X complexes with H-phosphonate diester as a nucleophile (L = PPh₃).

To evaluate a possible participation of these mechanisms during ligand substitution with H-phosphonate diesters as nucleophiles, we carried out kinetic investigations of the decay of PhPd(PPh₃)₂X complexes (10-12, Figure 5) under various experimental conditions, using $^{31}$P NMR spectroscopy to monitor progress of the reactions. The reactions were performed using large excess of H-phosphonate 7 and base to secure a pseudo-first-order decay of a palladium complex.

Figures 7-9 show the observed first-order rate constants for the decay of complex 10, as functions of concentrations of H-phosphonate (7), the base, and PPh₃, respectively. As it is apparent from the presented data, the reaction
showed a linear dependence on the H-phosphonate concentration (Figure 7), but was rather insensitive to the amounts of the base or PPh$_3$ used (Figures 8 and 9). One should note that although for the reactions investigated base is an indispensable reaction component, it did not enter into the kinetic equation. This, and the fact that using bases of various strengths resulted only in mediocre changes in the reaction rates (Figure 8), suggested that deprotonation of the H-phosphonate diester occurred at kinetically unimportant step of the reaction. To ascertain further that the P-H bond breaking did not influence the overall reaction rate, we measured a kinetic isotope effect, using the deuterated H-phosphonate 7 – (EtO)$_2$P(O)D. The obtained value of $k_H/k_D = 1.17 \pm 0.05$ was indeed very small and excluded possibility of a significant degree of the P-H bond breaking in the rate-determining step.

**Figure 7.** Dependence of the rate of decay of 10 on concentration of 7 in THF at 40 ºC.

**Figure 8.** Dependence of the rate of decay of 10 on concentration and the kind of a base in THF at 40 ºC.

**Figure 9.** Dependence of the rate of decay of 10 on concentration of PPh$_3$ in THF at 40 ºC.

The rate constants measured for the complexes bearing different halide ligands (Table 3) were in perfect agreement with the previously reported qualitative results (section 3.4). Comparable values of the rate constants for the reaction in toluene and THF (Table 3, entries 1 and 2) indicated no involvement of a solvent-assisted substitution mechanism, and the lack of inhibitory effect of the added PPh$_3$ (Figure 9), ruled out path C (Scheme 14) as a possible mechanism.

<table>
<thead>
<tr>
<th>Ent.</th>
<th>Palladium complex</th>
<th>Solv.</th>
<th>$k_{obs}$ (min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhPdL$_2$I (10)</td>
<td>THF</td>
<td>0.0101</td>
</tr>
<tr>
<td>2</td>
<td>PhPdL$_2$I (10)</td>
<td>toluene</td>
<td>0.0138</td>
</tr>
<tr>
<td>3</td>
<td>PhPdL$_2$Br (11)</td>
<td>THF</td>
<td>0.0192</td>
</tr>
<tr>
<td>4</td>
<td>PhPdL$_2$Cl (12)</td>
<td>THF</td>
<td>0.0336</td>
</tr>
</tbody>
</table>

$^{[a]}$ L = PPh$_3$
To evaluate a possible participation of the second dissociative pathway (Scheme 14, Path A) in the ligand substitution step, one should take into account the affinity order of halide anions towards a Pd(II) center. As it was mentioned previously, contrary to the hard-soft acid base principle prediction, the affinity of halides to the palladium in \textit{trans}-PhPd(PPh$_3$)$_2$X complexes decreases in order: Cl > Br > I.\textsuperscript{66,92,93} Thus, if the ligand substitution would indeed follow path A, the fastest reaction should be expected for the iodide-ligated complex 10, followed by the bromide (11) and chloride (12) derivatives, according to relative concentrations of free cationic 14-electron species PhPd(PPh$_3$)$_2^+$ produced from these complexes. However, the data in Table 3 display an opposite order of reactivity, and this, to high probability, excludes path A as a plausible reaction mechanism.

Apparently only path B was consistent with the observed kinetic data. Also the trend in reactivity of Pd(II) complexes bearing different halides (Table 3) can be satisfactorily explained on the basis of this mechanism. The first step of the reaction, the attack of the H-phosphonate diester on PhPd(PPh$_3$)$_2$X, should be facilitated by low electron density at the palladium center, hence the reaction rates were expected to follow the electronegativity order of the halogen atoms (Cl > Br > I) present in these complexes.

![Scheme 15](image)

**Scheme 15.** Possible associative pathways for ligand substitution in PhPdL$_2$X complexes with H-phosphonate diester as a nucleophile (L = PPh$_3$).

One can envisage two distinct scenarios for the associative process, regarding involvement of the base (Scheme 15): (i) a base-mediated, rapid pre-equilibrium between the H-phosphonate and its anion, followed by attack of the generated anionic phosphorus nucleophile on the palladium complex (path B1), and (ii) an attack of the neutral H-phosphonate diester on
the Pd(II) complex, followed by abstraction of the phosphorus-bounded proton by a base (path B2). Importantly, in the latter case, due to lack of a lone electron pair at phosphorus atom, it must be the phosphoryl oxygen that attacks palladium. Therefore, there is a necessity of an additional rearrangement step (change of coordination from O to P) following the deprotonation.

Analysis of kinetic equations derived for both pathways, led to a conclusion that the latter one (path B2) represents a true reaction mechanism. The main arguments against path B1 were that it predicts large dependence of the reaction rate on base strength and its concentration. On the other hand, assuming that the proton abstraction process in the second pathway, is much faster than reverse dissociation of H-phosphonate from palladium, the rate law that it predicts is identical to that experimentally found:

$$\frac{-d[\text{PhPdL}_2X]}{dt} = \frac{k_1k_2[(\text{RO})_2\text{P(O)H}][\text{base}][\text{PhPdL}_2X]}{k_{-1} + k_2[\text{base}]}$$

(1)

For $k_2[\text{base}] >> k_{-1}$ (1) it simplifies to:

$$\frac{-d[\text{PhPdL}_2X]}{dt} = k_1[(\text{RO})_2\text{P(O)H}][\text{PhPdL}_2X]$$

(2)

Figure 10. The Eyring plot for the attack of 7 on 10 ($k_1$ in eq. (2), measured over 20-60 °C temperature range).

Moreover, since the experimentally obtainable rate constant ($k_{\text{obs}}$) corresponded to elementary second-order rate constant $k_1$ for nucleophilic attack of the H-phosphonate diester on the palladium center ($k_1 = k_{\text{obs}}/([\text{EtO}]_2\text{P(O)H})$), it was possible to determine thermodynamic activation parameters for this step. A highly negative value of the entropy of activation ($\Delta S^\dagger = -17.2 \text{ cal/(mol-K)}$) determined from the Eyring plot (Figure 10),
supported the associative character of this initial event in the ligand substitution step.

![Figure 11](image_url)

Figure 11

After having established the mechanistic basis for the ligand exchange in halide-containing complexes with monodentate supporting ligands (trans-PhPd(PPh$_3$)$_2$X), we investigated the analogous reaction of the Pd(II) complexes containing a bidentate ligand dppp, that forces a cis geometry. In Table 4, the measured rate constants for the decay of (dppp)Pd(Ph)X complexes (14-16, Figure 11) bearing various halide substituents, determined under the same reaction conditions as those used for the PPh$_3$ complexes, are shown. As it is apparent from the presented data, the rate constants for ligand substitution in complexes bearing this bidentate ligand were noticeably higher, but followed the same order of reactivity as those for the PhPd(PPh$_3$)$_2$X complexes (Table 3). These suggested that also complexes with bidentate ligands follow a similar associative mechanistic pathway of ligand substitution as that described above for their monodentate phosphine-containing counterparts.

**Table 4.** The observed first order rate constants ($k_{obs}$) of the decay of (dppp)Pd(Ph)X complexes at 40 °C in THF.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Palladium(II) complex</th>
<th>$k_{obs}$ (min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(dppp)Pd(Ph)I (14)</td>
<td>0.0581</td>
</tr>
<tr>
<td>2</td>
<td>(dppp)Pd(Ph)Br (15)</td>
<td>0.1060</td>
</tr>
<tr>
<td>3</td>
<td>(dppp)Pd(Ph)Cl (16)</td>
<td>0.1697</td>
</tr>
</tbody>
</table>

3.5.2 Ligand substitution in PhPdL$_2$(OAc) complexes

As it was established in section 3.4, PhPd(PPh$_3$)$_2$(OAc) complex (13) exhibited a remarkably high reactivity in ligand substitution reactions with H-phosphonate nucleophile. This phenomenon could not be explained on the basis of the mechanism discussed in the previous section for the halide complexes using the electronegativity argument, and thus for the acetate complexes probably a distinct mechanism was operating. Path A in Scheme 14, which involved the initial dissociation of an anion, seemed to be unlikely due to similar affinity of AcO$^-$ and I$^-$ ions to the palladium(II) center. One
should, however, consider an other dissociative pathway (path C, Scheme 14), but in a slightly modified version, namely, with the carbonyl oxygen atom of the acetate group acting as an intramolecular nucleophilic catalyst in substitution of one of the phosphine ligands (Scheme 16). The intermediate 17, bearing a bidentate acetate ligand, formed in this reaction step would then react with H-phosphonate diester (Scheme 16, path B) or its anion (Scheme 16, path A), to give a ligand substitution product (after the additional deprotonation and rearrangement steps). An intramolecular nucleophilic catalysis by the acetate group would explain high rate acceleration observed in such reactions, due to favorable entropy changes, similarly as for neighboring group participation processes. Feasibility of this reaction pathway is supported by a number of reports describing metal complexes bearing bidentate (κ²) acetate or amidate ligands, that have been observed in solution, solid state, as well as reaction intermediates. 54,94

Scheme 16. Plausible reaction pathways for the ligand substitution in complex 13 with an H-phosphonate diester as a nucleophile (L = PPh₃).

To verify a possible intermediacy of bidentate acetate complexes in ligand substitution involving complex 13, we measured rates of the disappearance of 13 as a function of PPh₃, H-phosphonate 7, and Et₃N concentrations. It was found that with excess of PPh₃, 7, and Et₃N, the decay of 13 followed the first-order kinetics (³¹P NMR experiments). A plot in Figure 12, 1/k_obs vs. concentration of PPh₃, showed a linear relationship, with a positive slope, and nonzero y-intercept, that indicated inhibition of the reaction by the phosphine ligand. The plot of 1/k_obs vs. 1/[(EtO)₂P(O)H], was also linear,
with a nonzero y-intercept (Figure 13), and the reaction was found to be independent on the base (Et$_3$N) concentration (Figure 14).

**Figure 12.** Plot of $1/k_{obs}$ vs. $1/[\text{PPh}_3]$ for the decay of 13 in THF at 15 ºC.

**Figure 13.** Plot of $1/k_{obs}$ vs. $1/\text{[(EtO)$_2$P(O)H]}$ for the decay of 13 in THF at 15 ºC.

**Figure 14.** Dependence of the rate of 13 decay on the concentration of Et$_3$N in THF at 15 ºC.

To find out which of the reaction pathways in Scheme 16 was compatible with the experimental kinetic data, we derived rate laws for path A and path B. Similarly as in the halide complexes case, the mechanism involving H-phosphonate anion (path A) implicated presence of the base concentration in the rate equations, and therefore it was inconsistent with the kinetic data. Instead, the second mechanistic pathway, namely path B, turned out to be in a good agreement with the results shown in Figures 12-14:

$$- \frac{d[\text{PhPdL}_2(\text{OAc})]}{dt} = \frac{k_1 k_2 [(\text{RO})_2 \text{P(O)H}] [\text{PhPdL}_2(\text{OAc})]}{k_{-1}[\text{L}] + k_2 [(\text{RO})_2 \text{P(O)H}]}$$  \hspace{1cm} (3)

$$\frac{1}{k_{obs}} = \frac{k_{-1}[\text{L}]}{k_1 k_2 [(\text{RO})_2 \text{P(O)H}]} + \frac{1}{k_1}$$  \hspace{1cm} (4)

For this mechanism, base concentration was not present in the rate law (3), since the P-H bond breaking occurred after the rate-determining step and thus was kinetically insignificant. Equation (4) correctly predicts also the observed linear dependencies of $1/k_{obs}$ vs. [PPh$_3$] and vs. $1/[(\text{EtO})_2\text{P(O)H}]$.  

32
Nonzero y-intercepts for these plots, that correspond to $1/k_1$, indicated that the rate law (3) could not be simplified by dropping one of the terms in the denominator. In mechanistic terms it meant that the intermediate bidentate acetate complex 17 reacted with comparable rates, both “backwards” with PPh$_3$ and “forward” with the H-phosphonate. Actually, by substituting into equation (4) the measured values of $k_{obs}$, the known concentrations of the reactants, and $k_1$ (from the intercept), the $k_2/k_1$ ratio could be calculated. The obtained value of ~0.9, showed that the transient complex 17 was not selective towards different nucleophiles (PPh$_3$ vs. H-phosphonate), as one should expect for a highly reactive intermediate.

To support further the proposed mechanism for the ligand substitution in complex 13, we determined thermodynamic activation parameters for the initial step of the reaction, namely the dissociation of the phosphine ligand. To this end $k_1$ rate constants were determined at three temperatures (5, 10 °C, and 15 °C; from intercepts of the plots $1/k_{obs}$ vs. PPh$_3$) and used in the Eyring plot (Figure 15). A highly positive entropy of activation ($\Delta S^\ddagger = 12.7$ cal/(mol·K)) obtained, confirmed a dissociative character of this key step of the reaction.

![Figure 15](image)

**Figure 15.** The Eyring plot for the first step of the ligand substitution in complex 13 ($k_1$ in eq. (3), measured over 5-15 °C temperature range).

Finally, we attempted to measure the ligand substitution rate for a complex containing an acetate group and a bidentate ligand – (dppp)Pd(Ph)(OAc) (18). Unfortunately, the reaction was too fast to be followed by means of $^{31}$P NMR spectroscopy (completion in < 3 min). Anyway, very high rate for this reaction suggested that probably a mechanism analogous to that described above (Scheme 16, path B) operated also for this bidentate phosphine complex. Such a mechanism would imply, that at least at some stages of the reaction, only one phosphorus atom of the dppp ligand would be engaged in the complexation. The studies on reactivity of dppf palladium(II) complexes with sulfur nucleophiles mentioned in section 2.4, lend support for such a scenario.
3.6 Palladiumphosphonate complexes and the reductive elimination step

The investigations discussed so far focused on incorporation of the phosphorus nucleophile into the palladium(II) complex. However, an important issue that has not been addressed yet, is a structure of palladiumphosphonate complexes formed in the ligand substitution step and their further transformations, leading eventually to the reductive elimination of an arylphosphonate product (Scheme 17).

Scheme 17

3.6.1 Complexes containing PPh₃ as a ligand

To obtain a mechanistic insight into the steps following the ligand exchange, we decided to generate palladiumphosphonate intermediates in the reaction of PhPd(PPh₃)₂X complexes (10-13) with H-phosphonate 7 and Et₃N, and to follow the further reactions by ³¹P NMR spectroscopy. Such approach has the advantage of a close resemblance to the actual conditions, that are present during the normal catalytic reaction.

Interestingly, under such conditions we were able to observe (by ³¹P NMR) only the starting complexes (10-13) and the final reductive elimination product (8), whereas no signals from any putative intermediate complexes could be seen. Nevertheless, the quantitative analysis of the obtained data (Figures 16-19) has revealed that in some cases a “fraction of phosphorus” was missing from the spectra. Namely, as it is apparent from graphs for complexes 11 and 12 (Figures 17 and 18, respectively), the reductive elimination product formation lagged behind the disappearance of the starting palladium complexes, i.e. the amount of 8 formed after a given time, was less than expected from the substrate consumption. The “missing” amount, calculated as difference in the integrals of 8 and PhPd(PPh₃)₂X signals, which should correspond to the “intermediates” in Scheme 17, is shown in the graphs as open triangles. The fact that these intermediates, although present in a relatively large concentrations, were not detectable by the ³¹P NMR spectroscopy could be due to their involvement in a complex equilibria system, and probably extensive splitting pattern of the resonances, that could ultimately lead to broadening of the signals into the baseline. A similar phenomenon, ascribed to a dynamic solution behavior of
palladium(II)phosphonate complexes, was already reported for species containing triarylphosphines. Interestingly, this effect of accumulation of equilibrating palladiumphosphonate intermediates, was observed mainly for the reactions involving complexes 11 and 12 (Figures 17 and 18), and to a smaller extent for 10 (Figure 16).

Due to expected difficulties in dealing with series of sequential reactions, that could lead to complex kinetic expressions, we decided to study the reductive elimination from the equilibrating mixture of palladiumphosphonate complexes, rapidly generated from PhPd(Ph₃)₂X and a powerful phosphorus nucleophile, namely sodium diethyl phosphite (19, Scheme 18). Application of the sodium salt, instead of the most commonly used for this purpose silver derivative, was dictated by the observed differences in behavior of complexes containing different halides (Figures 16-18). Such results implied some involvement of the halide ions in the undergoing processes, thus their complete removal as insoluble silver salts was deemed to be undesired.

A typical outcome of these experiments is exemplified by the reaction, in which iodide-containing complex 10 (PhPdL₂I) was used as a starting material (Figure 20). Addition of 0.9 equiv. of sodium phosphite 19 to a solution of 10 in THF, containing PPh₃ (the presence of PPh₃ was necessary to avoid Pd black precipitation), resulted in a rapid consumption of an equimolar amount of the starting complex. The signal from 19 could not be
detected and the resonance due to free PPh$_3$ disappeared completely. Such an appearance of the $^{31}$P NMR spectrum suggested that the expected equilibrating mixture of palladiumphosphonate complexes was, indeed, rapidly formed, and that free PPh$_3$ (but not 10) was engaged into this equilibria system. After ca 10 min, a signal of the expected reductive elimination product, diethyl phenylphosphonate 8, started to emerge, together with a broad peak from PPh$_3$ coordinated to Pd(0) species. The formation of 8 displayed a first-order kinetics and the corresponding rate constant could be determined (Table 5, entry 1). A similar behavior was observed for the other PhPd(PPh$_3$)$_2$X complexes (11-13) and the corresponding rate constants for a reductive elimination are listed in Table 5. Also, the effect of added PPh$_3$ on rates of the reductive eliminations, was investigated.

**Scheme 18.** Reactions of complexes 10-13 with sodium diethyl phosphite (19) as the nucleophile.

![Scheme 18](image)

**Figure 20.** Generation of the equilibrating Pd(II) phosphonate complexes by addition of 19 to a solution of 10, and the following formation of reductive elimination product 8, in THF at 40 °C.

The trend of reactivity found for the complexes containing halides (Table 5, entries 1-3) explained the observed accumulation of the intermediate palladiumphosphonate complexes during reactions of PhPd(PPh$_3$)$_2$X with H-phosphonate 7 (Figures 16-19) and the observed lag in the product formation, when X = Cl and Br. This was consistent with the fact that rates of reaction of 7 with PhPd(PPh$_3$)$_2$X (Scheme 17, the first step) decreased in
order: $X = \text{Cl} > \text{Br} > \text{I}$ (Table 3), while those of the reductive elimination (Scheme 17, the second step), decreased in an opposite direction ($I > \text{Br} \sim \text{Cl}$). These caused that for $X = \text{Cl}$ or $\text{Br}$, the intermediate Pd(II) phosphonate complexes were quickly formed, but collapsed slowly to the product 8, whereas for $X = \text{I}$, formation of the intermediate complexes was slower than the subsequent reductive elimination step.

Table 5. The observed first-order rate constants ($k_{\text{obs}}$) of the formation of 8 from the mixtures of equilibrating Pd(II) phosphonate complexes, generated from different PhPd(PPh$_3$)$_2$X precursors and 19, in THF at 40°C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PhPd(PPh$_3$)$_2$X precursor and the amount of PPh$_3$ added</th>
<th>$k_{\text{obs}}$ (min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhPd(PPh$_3$)$_2$I (10) + PPh$_3$</td>
<td>0.0141</td>
</tr>
<tr>
<td>2</td>
<td>PhPd(PPh$_3$)$_2$Br (11) + PPh$_3$</td>
<td>0.0077</td>
</tr>
<tr>
<td>3</td>
<td>PhPd(PPh$_3$)$_2$Cl (12) + PPh$_3$</td>
<td>0.0074</td>
</tr>
<tr>
<td>4</td>
<td>PhPd(PPh$_3$)$_2$I (10) + 10PPh$_3$</td>
<td>0.0346</td>
</tr>
<tr>
<td>5</td>
<td>PhPd(PPh$_3$)$_2$Br (11) + 10PPh$_3$</td>
<td>0.0291</td>
</tr>
<tr>
<td>6</td>
<td>PhPd(PPh$_3$)$_2$Cl (12) + 10PPh$_3$</td>
<td>0.0121</td>
</tr>
<tr>
<td>7</td>
<td>PhPd(PPh$_3$)$_2$(OAc) (13) + PPh$_3$</td>
<td>0.7412</td>
</tr>
</tbody>
</table>

To explain the observed trends one must consider relative reactivities of the different possible complexes being in equilibrium, and changes in concentrations of these complexes under the reaction conditions. Since PPh$_3$ accelerates the process, it is reasonable to exclude a dissociative pathway (similar to that shown in Scheme 11b) as a plausible reaction mechanism. From electronic and structural point of view, more susceptible to reductive elimination are complexes with low electron density and bulky spectator ligands present. In light of this, palladium complexes containing halides (20 and 21 in Figure 21), should exhibit rather low reactivity in reductive elimination, both due to net negative charge present and small steric demands for spherical halide anions. However, if the halide anion would be expelled, the resulting complex, ligated only by phenyl, a phosphonate, and PPh$_3$ (23, Figure 21), should be more susceptible to the reductive elimination. We believe that the observed trend in reactivity of Pd(II) phosphonate complexes as a function the halide present in the solution, i.e. $\Gamma > \text{Br}^- \sim \text{Cl}^-$, originated from different affinity of these anions towards the Pd center. A weakly bounded $\Gamma$ is expected to be more easy replaced by PPh$_3$ than a strongly bounded Cl$^-$. In the presence of excess phosphine ligand, the equilibrium is shifted towards the neutral, more sterically hindered species, from which reductive elimination should be facilitated. The observed acceleration by PPh$_3$ can originate also from the increasing rates of equilibration between trans-complexes (22 and 24) and the cis-counterparts (20, 21, and 23), as in the example shown in section 2.4 (Scheme 9).
Finally, there was a case of a remarkably fast reductive elimination, when the acetate group was present in the precursor complex (13; Table 5, entry 7). Since this reaction was more than an order of magnitude faster than that for the halide derivatives, it seems that a distinct mechanism might operate for the acetate-containing palladium complexes. The high reactivity of 13 in ligand substitution was discussed above, and it was attributed to generation of a highly reactive $\kappa^2$-acetate species (Scheme 16). The enhanced reactivity observed in the reductive elimination step of the acetate-containing complexes can be tentatively ascribed to a similar feature of the generated palladiumphosphonate intermediates, namely a tendency of the acetate group to act as a bidentate ligand.

![Figure 21](image_url)

**Figure 21.** Possible palladiumphosphonate complexes involved in equilibrium (for the discussion on their relative reactivity in reductive elimination, see the text).

Since presence of the acetate ligand was responsible for the high reactivity, one can assume that it is not expelled from the complex during the phosphonate ligand incorporation. There are several different ways on which presence of the acetate can facilitate the reductive elimination in the studied system, all of them taking into account ability of the acetate to act as a $\kappa^2$ bidentate ligand (Figure 22).

First, the acetate may cause fast cis-trans isomerization of the complexes (via the associative mechanism), providing a constant supply of the cis complex. However, the rate of reductive elimination in entry 7 (Table 5) was more than an order of magnitude higher than that for the most reactive halide derivative 10 in presence of PPh$_3$ excess that secured fast equilibration and neutrality of the reacting complexes (Table 5, entry 4). It means that probably the reductive elimination, in case of complex 13, did not take place directly from 25 and/or 26 (Figure 22), which are anionic, hence less reactive species.

Therefore, we considered an associative reductive elimination, involving penta-coordinate intermediates (transition states?) 27 and/or 28, as a viable option for the acetate-containing complexes. Due to expected positional preference, the $\kappa^2$-acetate group should occupy an equatorial-apical position in tbp, and thus a number of tbp formed, should be limited to three shown in Figure 22 (27-29). Due to steric demands for a bulky PPh$_3$, this ligand should show preference for an equatorial position in tbp, and thus formation
of *thp* species with an apical-equatorial arrangement of the groups to be eliminated (27 and 28), should be energetically favored.

![Chemical structures](image)

**Figure 22.** Possible palladiumphosphonate complexes containing acetate ligand (for discussion on their relative reactivity in reductive elimination see the text).

Finally, there is one more possible interpretation of the high reductive elimination rate, also involving bidentate acetate ligand. Namely, one can imagine a complete expulsion of **PPh₃** from the complex and formation of *sq* structure 30 (Figure 22), from which reductive elimination could occur. Additionally, it is very probable that this complex might have high tendency for opening of four-member ring to produce T-shaped species 31, enabling a dissociative reductive elimination pathway.

Unfortunately, a distinction between the mechanisms proposed above is not possible on the basis of the available kinetic data. It seems that a computational approach would be most suitable for this purpose.

### 3.6.2 Palladium complexes containing a bidentate phosphine ligand

To obtain further insight into the process of reductive elimination, we conducted additional experiments with complexes bearing a bidentate ligand (dppp). In this instance, in contradistinction the monodentate complexes of type PhPd(PPH₃)₂X, treatment of (dppp)Pd(Ph)X (X = I, Br, Cl; 14-16) with (EtO)₂PONa (19) afforded a palladiumphosphonate species with a well defined ³¹P NMR characteristics (3 groups of resonances in the region of
chemical shifts of ca 1 ppm, 4 ppm, and 82 ppm, Scheme 19). This complex was formed irrespective of the kind of halide present in the parent compound (Scheme 19), and on the basis of the chemical shift values and the splitting pattern of the signals, its structure was assigned as (dppp)Pd(Ph)(PO(EtO)_2) (32). Apparently, the entropically driven chelating effect of the dppp ligand made this Pd(II) phosphonate complex by far less fluxional compared to the complexes with monodentate PPh₃ ligands. Formation of this complex was in agreement with the earlier reports on analogous Pd(II) phosphonate complexes bearing bidentate phosphine ligands.³⁸,⁹⁵

![Scheme 19. Reactions of complexes 14-16 with sodium diethyl phosphite (19) as the nucleophile.](image)

**Table 6.** The observed first-order rate constants ($k_{obs}$) for the formation of diethyl phenylphosphonate 8 from the palladiumphosphonate intermediate, generated from (dppp)Pd(Ph)X and 19, in THF at 40°C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(dppp)Pd(Ph)X precursor and the amount of PPh₃ added</th>
<th>$k_{obs}$ (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(dppp)Pd(Ph)I (14) + PPh₃</td>
<td>0.0568</td>
</tr>
<tr>
<td>2</td>
<td>(dppp)Pd(Ph)Br (15) + PPh₃</td>
<td>0.0499</td>
</tr>
<tr>
<td>3</td>
<td>(dppp)Pd(Ph)Cl (16) + PPh₃</td>
<td>0.0500</td>
</tr>
<tr>
<td>4</td>
<td>(dppp)Pd(Ph)I (14) + 10PPh₃</td>
<td>0.0497</td>
</tr>
<tr>
<td>5</td>
<td>(dppp)Pd(Ph)(OAc) (18) + PPh₃</td>
<td>0.4013</td>
</tr>
</tbody>
</table>

For complex 32, generated from different precursors, a kinetics of reductive elimination was investigated, and the first-order rate constants were determined. These are listed in Table 6, together with the rate constant for the reaction when 10 molar excess of PPh₃ was used (Table 6, entry 4). For all the precursor complexes bearing different halides, similar rate constants were obtained. Since the addition of extra PPh₃ did not influence significantly the rate of this reaction, it seemed that the reductive elimination occurred directly from the cis-configured complex 32.
As to the acetate-containing complex 18, also in this instance it behaved differently from the halide complexes of type (dppp)Pd(Ph)X. Firstly, it reacted an order of magnitude faster than the other bidentate complexes investigated (Table 6, entry 5), and secondly, the expected palladiumphosphonate 32, could not be detected by $^{31}$P NMR spectroscopy. Instead, upon addition of sodium phosphite (19) to the reaction mixture, the signal from complex 18 disappeared immediately, and a fast formation of the reductive elimination product 8 was observed. This phenomenon appeared to be similar to that observed for the reaction of PhPd(PPh$_3$)$_2$X complexes with 19, and pointed to the formation of an equilibrating mixture of palladiumphosphonate species. Although structures of such complexes remained cryptic, one can speculate they should be similar to those shown in Figure 22. Since it was postulated before that the acetate can break down a chelating system of a bidentate ligand during the ligand exchange process (section 3.5.2), the dppp can be then treated in this instance as a monodentate ligand.

Irrespective of the mechanistic details, which remain to be clarified, an important feature of the acetate group as a ligand in palladium complexes, is its ability to form bidentate ($\kappa^2$) acetate species that may have enhanced reactivity in ligand substitution and reductive elimination steps.

### 3.7 Summary of the palladium-catalyzed C-P bond formation mechanisms

The above mechanistic studies on ligand substitution and reductive elimination, appended with the existing knowledge about oxidative addition, lend themselves to a more detailed picture of two catalytic cycles for the palladium-mediated the C-P bond formation, that are summarized in Schemes 20 and 21.

Scheme 20 depicts a catalytic cycle for the reaction, in which halide anions are involved. This is by far the most common situation for cross-coupling reactions using aryl halides, since even in the absence of external halide additives, these anions are released during the course of the reaction and can interact with various palladium species at different stages of the cycle.

The first step, oxidative addition of an aryl halide to a Pd(0) complex, results in formation of arylpalladium(II) complexes. Reactivity of the complexes in this step depends on the halide anions ligating Pd(0), and decreases in order: Cl > Br > I. Additional complexation by phosphine excess or dba (L$^*$), brings the catalyst into the resting state. The next step is a reaction of a palladium(II) complex with a phosphorus nucleophile, usually referred to as a ligand substitution or transmetallation. Reactivity of Pd(II)
complexes, irrespective of denticity of the supporting ligand used (mono- or bidentate), follows the same trend as that for the oxidative addition, namely, the reaction is fastest when $X = \text{Cl}$, followed by $\text{Br}$ and $\text{I}$. These two steps of the cycle are responsible for the overall acceleration of a cross-coupling reaction, when chlorides or bromides are added to the reaction mixture (Table 2, entries 2, 3, 5 and 6). A nucleophilic attack is slow compared to the subsequent deprotonation, and thus strength of a base used for the reaction, and its concentration, practically do not affect the rates of the palladiumphosphonate complexes formation. Importantly, the whole incorporation process of a phosphonate ligand, is not influenced by PPh$_3$ ligand concentration.

Scheme 20. A proposed catalytic cycle for the palladium-catalyzed cross-coupling of H-phosphonates with aryl halides. Structures to the left and to the right refer to PPh$_3$ or a bidentate ligand, respectively. Complexes’ charges were omitted for clarity.

Depending on denticity of a supporting ligand used, there are two scenarios. For monodentate ligand PPh$_3$, the Pd(II) phosphonates are involved in a complex equilibria system, powered by the halide anions and PPh$_3$ present. Reductive elimination of the product Ar-P(O)(OR)$_2$ from such an equilibrating mixture is highest if $\text{I}^-$ are engaged in the equilibria, and somewhat slower for $\text{Br}^-$ and $\text{Cl}^-$. The added PPh$_3$, accelerates further this reductive elimination. For bidentate phosphines used as supporting ligands, less fluxional, tetra-coordinate palladiumphosphonate complexes, with
defined cis-configuration of an aryl and a phosphonate group, are formed. Rates of reductive elimination from such complexes are not affected by the kind and concentration of the halide anions present, nor by the added PPh₃.

The above catalytic cycle is modified to a large extent when the acetate ion is involved in complexation of palladium species at different stages of a cross-coupling reaction, and this is shown in Scheme 21.

**Scheme 21.** A proposed catalytic cycle for the palladium-catalyzed cross-coupling of H-phosphonates with aryl halides, involving acetate as a ligand. Structures to the left and to the right refer to PPh₃ or a bidentate ligand, respectively. Complexes’ charges were omitted for clarity.

The acetates can be brought to the reaction mixture together with the palladium source (e.g. Pd(OAc)₂) or may be introduced as an external additive. Due to rather weak affinity of the acetate ion to palladium(II) center (Cl⁻ > Br⁻ > AcO⁻ ~ I⁻),⁶⁶,⁹³ the halides released during the course of a cross-coupling reaction, may effectively compete with acetate ions, and ultimately, the reaction may switch to the “halide cycle” (Scheme 20). This is usually manifested in a gradual slowing down of a cross-coupling reaction with limited amount of acetates present. However, if the reaction is carried out in the presence of externally added acetate anions (e.g. n-Bu₄N(OAc)), a remarkable shortening in the reaction time is observed (Table 2, entry 7).

In this acetate-type of a catalytic cycle, the oxidative addition of aryl halides to Pd(0) complex bearing an acetate group, is slower than a reaction with a palladium catalyst with coordinated halides.⁶⁷ The observed overall
acceleration of cross-coupling reactions upon addition of acetate anions, is due to mechanistic changes in ligand substitution and reductive elimination steps.

The presence of an acetate group in Pd(II) complexes (Scheme 21) formed in oxidative addition, opens a new mechanistic pathway for the reaction with H-phosphonate diesters. Namely, the acetate may act as an internal nucleophile and expel the phosphine ligand, producing highly reactive intermediate, with \( \kappa^2 \)-acetate ligand. From this species, after nucleophilic attack of H-phosphonate diester and its subsequent deprotonation, an equilibrium mixture of the palladiumphosphonates is formed. Due to high reactivity of \( \kappa^2 \)-acetate complexes, the overall incorporation a phosphonate moiety is very fast compared to that in the halide-type catalytic cycle (Scheme 20). Irrespective of the denticity of the supporting ligands used, palladiumphosphonate complexes in this instance are formed as an equilibrating mixture. The reductive elimination from such palladiumphosphonate complexes is extremely fast, most likely due to ability of the acetate group to act as a \( \kappa^2 \) bidentate ligand.
Chapter 4

Preparation of arylphosphonates by palladium-catalyzed cross-coupling in the presence of acetate additives (Paper III)

On the basis of the mechanistic findings described in Chapter 3, we set out to develop a practical protocol for the synthesis of arylphosphonates by the palladium-catalyzed cross-coupling in the presence of acetate ion additives. Importantly, the acceleration of ligand exchange and reductive elimination in complexes containing acetate ligand was observed also when a bidentate phospine ligand (dppp) was used. Since many of the C-P forming cross-couplings worked better with bidentate phosphine ligands, we aimed at combining these two effects and thus providing a very efficient method for the synthesis of arylphosphonates.

4.1 Effect of stoichiometric $\text{AcO}^-$ additive on the C-P bond forming reaction with different phosphine ligands

We started our study with examination on how external acetate ions additives influence rates of the C-P bond formation, as a function of a leaving group in an electrophilic aromatic substrate and phosphine supporting ligands used. For this purpose, a series of model reactions, in which diethyl H-phosphonate (7) was coupled with iodobenzene, bromobenzene, and phenyl triflate (Table 7) were performed. In all cases 10 mol% of the palladium pre-catalyst, in the form of Pd(OAc)$_2$ (except for the benchmark reaction with Pd(PPh$_3$)$_4$ – Table 7, entry 1), was used, together with an appropriate phosphine that acted both as a reducing agent for palladium(II) and a supporting ligand for the catalytic complex formed.$^{60,61,63}$ Each reaction was carried out separately in the absence and in the presence of $n$-Bu$_4$N(OAc) (1 equiv.).
Table 7. Effect of AcO⁻ additives on the cross-coupling using different phosphine ligands.

<table>
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<tr>
<th>Entry</th>
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<th>Reaction time (h)[c]</th>
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<td></td>
<td></td>
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</tr>
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<td></td>
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<tr>
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<td>1.5</td>
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</table>

[a] Reaction conditions: 0.30 mmol 7, 0.33 mmol PhX, 0.36 mmol Et₃N, 3 mL THF, 60 °C; entry 1: 0.03 mmol Pd(PPh₃)₄; entries 2-11: 0.03 mmol Pd(OAc)₂, 0.09 mmol monodentate or 0.06 mmol bidentate ligand, 15 min palladium reduction was performed before addition of 7 and PhX. [b] 1 equiv. n-Bu₃N(OAc). [c] >95% conversion (³¹P NMR spectroscopy).

As it is apparent from data in Table 7, reactivity of PhI, PhBr and PhOTf in a cross-coupling reaction catalyzed by Pd(PPh₃)₄ (entry 1) paralleled their relative rates of oxidative addition.²⁴ By using Pd(OAc)₂ as the palladium source (entry 2; 0.2 equiv. of AcO⁻ is introduced to the reaction mixture with this precatalyst), a slight acceleration of the product formation was observed for PhI and PhBr, whereas for PhOTf, this effect was significantly stronger (shortening of the reaction time from 23 to only 5 hours). A completely different picture emerged upon external addition of acetate to the reaction mixture (entry 3). In this instance, a significant shortening of the reaction time was observed for the aryl halides, while for phenyl triflate, the effect was only moderate (from 5 to 3 hours). This pattern of reactivity was observed for all ligands investigated (Table 7, cf. even number vs. odd number entries).

On the whole, the data in Table 7 are consistent with a catalytic cycle in Scheme 21 and point to the importance of the acetate-mediated ligand exchange and reductive elimination processes that seem to operate for all the bidentate supporting phosphine ligands. Crucial to the final outcome of these
reactions is probably an equilibria system shown in Scheme 22 that controls the relative amounts of different Pd(II) complexes that undergo ligand exchange with phosphorus nucleophiles (H-phosphonate diesters).

Scheme 22. Equilibrium between palladium(II) complexes that undergo ligand exchange with H-phosphonate diesters. L* stands for a neutral ligand, e.g. solvent molecule or diphosphine monoxide (see Scheme 5). For monodentate ligands the presented Pd(II) complexes have trans configuration.

A dramatic accelerating effect of acetate observed in the reactions involving phenyl triflate can be ascribed to a weak bonding of triflate anion to a palladium(II) center. Due to this, even in presence of substoichiometric amount of acetate ions (introduced to the reaction mixture along with Pd(OAc)₂), the equilibrium is apparently shifted towards reactive acetate-ligated species (Scheme 22). For PhI and PhBr, however, relatively high affinity of halides vs. AcO⁻ towards Pd(II) caused that highly reactive acetate-containing Pd(II) complexes were formed in significant amounts only at the beginning of the reaction, when concentration of halide ions was low. As the reactions progressed, the dominant Pd(II) species became those with coordinated halides, and this slowed down the ligand exchange process, and in consequence, the whole cross-coupling. In contrast to this, when stoichiometric amount of acetate was present in the reaction mixture (external addition), then throughout of the reaction the dominant Pd(II) species contained coordinated acetate. This secured high rates of the individual steps and made differences between reactions involving various aryl substrates (aryl halides vs. triflate) small.

The above results show that the ligand exchange process has the largest impact on the overall reaction kinetics in the C-P bond forming cross-coupling with H-phosphonate diesters, although, the rate of oxidative addition also matters. Since for the cross-coupling reactions in the presence of acetate all phosphine ligands investigated showed similar efficiency, it
means that differences observed in the absence of this additive reflected ability of the supporting ligands to facilitate a ligand exchange process. In this respect, the most efficient seemed to be monodentate PPh$_3$ and a wide-bite-angle phosphine dppf (Table 7, entries 2 and 8), and the latter was used in our further studies.

4.2 Effect of amount and source of the acetate additives

To assess how amount of the externally added acetate affects efficiency of the cross-coupling reaction, we used a well soluble in organic solvent $n$-Bu$_4$N(OAc) as an acetate source. By carrying out experiments with different amounts of acetate ions we noticed that the reactions were fastest with 1 equiv. $n$-Bu$_4$N(OAc), but then slowed down, and with 5 equiv. of the added $n$-Bu$_4$N(OAc), no product formation could be observed (Table 8, entries 1-3). The same phenomenon we observed for another acetate salt soluble in organic solvents – Et$_3$NH(OAc) (Table 8, entries 4 and 5). A smaller accelerating effect exerted by this salt vs. $n$-Bu$_4$N(OAc) (Table 8 entry 4 vs. 2) originated probably from a partial hydrogen bonding of AcO$^-$ with Et$_3$NH$^+$, that lowered its effective activity. The $^{31}$P NMR experiments revealed that high concentration of the acetate ions apparently inhibited the oxidative addition step, as no reaction occurred between bromobenzene and Pd(PPh$_3$)$_4$ in the presence of 5 equiv. $n$-Bu$_4$N(OAc). Also some interference in the reduction step of Pd(OAc)$_2$ was observed at high concentration (5 equiv.) of the acetate ions.

Although using $n$-Bu$_4$N(OAc) secured homogenous reaction conditions, its high price, hydroscopic properties, and problems with its removal during work-up, prompted us to look for another sources of acetate anions. To this end we investigated various alkali metal acetates (Li, Na, Cs, and K) (Table 8, entries 6-9). Interestingly, although these salts were only sparingly soluble in THF under reflux (<1 mg/mL), they gave a reasonable shortening of the reaction times. Since the reactions occurred under heterogeneous conditions and concentration of the acetate ions was controlled by the solubility factor, using smaller amounts of these salts (e.g. entries 9-12 for KOAc), did not affect the reaction time (within the experimental error).

The interesting phenomenon of a significant shortening of the reaction time achieved with only small amounts of potassium acetate added requires some consideration. If the equilibrium between the Pd(II) complexes coordinated with different ions (AcO$^-$ vs. X$^-$) is described by expression (5), then the palladium complexes’ ratio is controlled by the ratio of [AcO$^-$]/[X$^-$] in the reaction media (6). Since [AcO$^-$] is relatively small, it means that under the heterogeneous conditions, the halides must be removed from the reaction mixture in form of a precipitate.
Table 8. Effect of different acetate additives on the cross-coupling of diethyl H-phosphonate 7 with PhBr, using Pd(OAc)$_2$ + dpff.$^{[a]}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd loading (mol%)</th>
<th>Acetate additive</th>
<th>Acetate equiv.</th>
<th>Reaction time (h)$^{[b]}$</th>
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<td>none</td>
<td>na</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
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<td>2</td>
</tr>
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<td>3</td>
<td>10</td>
<td>$n$-Bu$_4$N(OAc)</td>
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<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>Et$_3$NH(OAc)</td>
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<td>Et$_3$NH(OAc)</td>
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$^{[a]}$ Reaction conditions: 0.30 mmol 7, 0.33 mmol PhBr, 0.36 mmol Et$_3$N, 3 mL THF, 60 °C; 15 min palladium reduction was performed before addition of 7 and PhX. $^{[b]}$ >95% conversion ($^{31}$P NMR spectroscopy).

\[
K = \frac{[\text{PhL}_2\text{Pd(OAc)}][X^-]}{[\text{PhL}_2\text{PdX}][\text{AcO}^-]} \quad (5)
\]

\[
\frac{[\text{PhL}_2\text{Pd(OAc)}]}{[\text{PhL}_2\text{PdX}]} = K \frac{[\text{AcO}^-]}{[X^-]} \quad (6)
\]

A postulated model for such a scenario is depicted in Scheme 23. At the beginning of a cross-coupling reaction bromides are removed from the reaction media via precipitation of insoluble in organic solvents potassium bromide, so at some point (e.g. 10% conversion for entry 12, or 20% conversion for entry 11) the whole amount of AcO$^-$ ions is transferred into solution in a form of Et$_3$NH(OAc). As the reaction progresses, the bromides produced are still removed from the solution, this time in a form of Et$_3$NHBr precipitate. In consequence, the ratio [AcO$^-$/[Br$^-$]] remains steady for the most part of the reaction and secures a fast cross-coupling, even when only 10 mol% KOAc additive was used for the reaction.
4.3. Palladium-catalyzed synthesis of arylphosphonate diesters promoted by the acetate additive

Using the optimized reaction conditions we successfully synthesized various arylphosphonates with diverse structural features both in the aryl and in the ester moieties (Scheme 24, Tables 9-11). All the reactions in Tables 9-11 were run to >95% conversion ($^{31}$P NMR spectroscopy) and the products were isolated by silica gel chromatography.

First, aryl substrates containing different leaving groups, namely iodobenzene, bromobenzene and phenyl triflate, were coupled with diethyl H-phosphonate. As is apparent from entries 1-3 (Table 9), all of them showed comparable reactivity in the cross-coupling reactions in the presence of acetate ions. Dimethyl H-phosphonate 33 (Table 9, entry 4) reacted with bromobenzene similarly to diethyl H-phosphonate (3 h for the completion), but the presence of two isopropyl groups (entry 5) in the H-phosphonate moiety visibly slowed down the cross-coupling reactions (10 h), most likely due to the steric hindrance.
Table 9. Acetate-promoted cross-coupling of aryl halides with H-phosphonate diesters.\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>H-phosphonate</th>
<th>Rxn time (h)\textsuperscript{[b]}</th>
<th>Product</th>
<th>Product no.</th>
<th>Yield (%)\textsuperscript{[c]}</th>
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\textsuperscript{[a]} Reaction conditions: 0.03 mmol Pd(OAc)\textsubscript{2} (2.5 mol%), 0.06 mmol dpff, 1.5 mmol Et\textsubscript{3}N, and 0.13 mmol KOAc in 5 mL THF, 68 °C, 15 min; then 1.25 mmol H-phosphonate and 1.38 mmol ArX were added. \textsuperscript{[b]} >95% conversion (\textsuperscript{31}P NMR spectroscopy). \textsuperscript{[c]} Isolated yield.
Then, cross-couplings with aryl bromides bearing polycyclic aromatic moieties were investigated (Table 9, entries 6-9). 2-Bromonaphtalene (entry 6) reacted similarly to bromobenzene (ca 2 h), but its positional isomer, 1-bromonaphtalene (entry 7), 9-bromophenanthrene (entry 8), and 1-bromopyrene (entry 9) underwent cross-coupling with diethyl H-phosphonate significantly slower (23-32 h), probably due to highly unfavorable interactions with the peri-hydrogen atoms. This slow kinetics, however, did not affect efficiency of the reactions, and the isolated yields of the corresponding arylphosphonates were rather high. In line with the importance of steric factors in this type of reactions, a very slow cross-coupling was observed for 2-bromotoluene (Table 3, entry 13).

Concerning the influence of electronic factors, the cross-coupling was rather insensitive to the presence of electron-withdrawing substituents in the aromatic ring of the electrophilic substrates (e.g. 4-nitro- and 4-fluorobromobenzene, entries 10 and 11, respectively), but introduction of a strongly electron-donating methoxy group in the para position (entry 12) significantly slowed down the reaction (10 h).

Since pyridylphosphonates emerged recently as potential, biologically important nucleotide analogs\textsuperscript{29} as well as building blocks for the development of metal-organic frameworks (MOFs),\textsuperscript{17} we carried out two cross-coupling reactions involving 3-bromopyridine (entry 14) and 4-bromopyridine (entry 15). The reactions proceeded smoothly and the corresponding diethyl pyridylphosphonates were isolated in high yields.

Looking for a possible chemo- and regioselectivity in this type of cross-coupling reactions, aromatic dihalides were investigated as possible substrates (Table 10). To this end we reacted 4-bromoiodobenzene (Table 10, entry 1) and 2,5-dibromopyridine (Table 10, entry 2) with diethyl H-phosphonate 7 under the developed reaction conditions. In both instances the reactions were high yielding and completely chemo- or regioselective. For 4-bromoiodobenzene, it was the iodine atom that was replaced by the phosphorus nucleophile forming diethyl 4-bromophenylphosphonate, and for

**Table 10. Selectivity in the acetate-promoted cross-coupling of aryl dihalides.\textsuperscript{[a]}**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>H-phosphonate</th>
<th>Rxn time (h)\textsuperscript{[b]}</th>
<th>Product</th>
<th>Product no.</th>
<th>Yield (%)/\textsuperscript{[c]}</th>
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\textsuperscript{[a]} Reaction conditions: 0.03 mmol Pd(OAc)\textsubscript{2} (2.5 mol%), 0.06 mmol dppf, 1.5 mmol Et\textsubscript{3}N, and 0.13 mmol KOAc in 5 mL THF, 68 °C, 15 min; then 1.25 mmol H-phosphonate and 1.38 mmol ArX were added.\textsuperscript{[b]} >95% conversion (\textsuperscript{31}P NMR spectroscopy).\textsuperscript{[c]} Isolated yield.
2,5-dibromopyridine, the bromine at the C2 position of the pyridine ring reacted selectively to produce diethyl 5-bromopyridin-2-yl-phosphonate.

As a final part of these investigations we tested efficacy of the developed cross-coupling method in the synthesis of more complex arylphosphonates diesters (Table 11) that are of potential importance to medicinal chemistry\textsuperscript{19,21,96} and nucleic acids-based therapeutics.\textsuperscript{9,26,28,29}

<table>
<thead>
<tr>
<th>Ent.</th>
<th>Aryl derivative</th>
<th>H-phosphonate</th>
<th>Rxn</th>
<th>Product</th>
<th>Yield (%) \textsuperscript{[c]}</th>
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<tr>
<td>2\textsuperscript{[d]}</td>
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<td>![OEi][55]</td>
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<td>![Br][55]</td>
<td>71</td>
</tr>
<tr>
<td>3\textsuperscript{[d]}</td>
<td>![Br][51]</td>
<td>![OEi][56]</td>
<td>1.5</td>
<td>![Br][56]</td>
<td>54</td>
</tr>
<tr>
<td>4\textsuperscript{[d]}</td>
<td>![Br][52]</td>
<td>![OEi][57]</td>
<td>7</td>
<td>![Br][57]</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>![Br][58]</td>
<td>![OEi][59]</td>
<td>5.5</td>
<td>![Br][59]</td>
<td>63 \textsuperscript{(R_P)}</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: 0.01 mmol Pd(OAc)\textsubscript{2} (2.5 mol%), 0.02 mmol dppf, 0.48 mmol Et\textsubscript{3}N, and 0.04 mmol KOAc in 4 mL THF, 68 °C, 15 min; then 0.40 mmol H-phosphonate and 0.44 mmol ArX were added. \textsuperscript{[b]} >95% conversion (\textsuperscript{31}P NMR spectroscopy). \textsuperscript{[c]} Isolated yield. \textsuperscript{[d]} Mixture of the H-phosphonate diastereomers (ca 1:1) was used.
In entry 1 (Table 11), a protected tyrosine triflate derivative 49 in the reaction with diethyl H-phosphonate was successfully converted into the corresponding arylphosphonate 54 in high yield. Entry 2 (Table 11) shows a transformation of cholesteryl H-phosphonate diester 50 into a highly lipophilic 2-naphtylphosphonate derivative 55. Also various dinucleoside H-phosphonates 51-53 (Table 11, entries 3-5) reacted efficiently with bromobenzene to produce the corresponding dinucleoside phenylphosphonates. The reaction time varied depending on nucleosidic composition and the protecting groups present, but it did not exceed 7 h. Although in all instances the $^{31}$P NMR spectroscopy indicated a complete conversion into the corresponding phenylphosphonates 56-58, the isolated yields were lower than for other arylphosphonates, due to loses during purifications.

To find out if the involvement of acetates in a catalytic cycle (Scheme 21) does not erode stereochemistry at the phosphorus center, separate diastereomers of dithymidine H-phosphonate 53 (($R_P$)-53 and ($S_P$)-53) were subjected to a cross-coupling with bromobenzene (Table 11, entry 5). The $^{31}$P NMR spectra revealed that the reactions were completely stereospecific (($R_P$)-53 $\rightarrow$ ($R_P$)-58 and ($S_P$)-53 $\rightarrow$ ($S_P$)-58) and thus confirmed that the developed procedure did not compromise the usual stereospecificity of this type of cross-coupling reactions. 97

4.4 Conclusions

We have developed a novel, mild, and efficient procedure for the synthesis of aryl phosphonates that makes use of an acetate-promoted, palladium-catalyzed cross-coupling reaction of aryl halides (or triflates) with H-phosphonate diesters. The reaction conditions of the new protocol were optimized in terms of supporting ligands, kinds and amounts of the acetate additive, and the catalyst load. The method seems to be rather general, accepts wide range of electrophilic aryl (iodide, bromide and triflate derivatives), and H-phosphonate substrates (simple alkyl, cholesteryl, dinucleosides), and may provide a convenient entry to complex arylphosphonate diesters of biological importance.
Chapter 5

Application of microwave heating for the palladium-catalyzed cross-coupling with phosphorus nucleophiles (Papers IV & V)

5.1 Introduction

During the last 25 years the use of microwave heating became increasingly popular in chemical synthesis. A large number of reports have been published in the area of microwave-assisted organic synthesis, since the pioneering work of Gedye, Giguere, and Majetich on acceleration of chemical reactions by the microwave irradiation.\textsuperscript{98} With the advent of dedicated laboratory microwave ovens, enabling full control of the reaction conditions, the microwave energy became a standard tool of organic chemist. In the recent years large reactors and instruments have been introduced,\textsuperscript{99} permitting direct scale-up (> 1 kg) without reoptimization of the reaction conditions, making microwave heating a viable alternative also under industrial settings.

Among various chemical transformations investigated,\textsuperscript{100} the palladium-catalyzed cross-coupling reactions have been recognized as an exceptionally successful area of application of this controllable thermal source for conducting organic reactions. Both the C-C bond-forming cross-coupling reactions, as well as those for the C-N and C-O bond formation, using the Buchwald-Hartwig chemistry, were efficiently carried out under the microwave irradiation conditions.\textsuperscript{100,101} In contrast to these, the usage of microwaves to facilitate cross-coupling reactions involving phosphorus nucleophiles still remains largely unexplored. Only recently, a couple of reports on a Pd-catalyzed microwave-assisted coupling of H-phosphonate and H-phosphinate derivatives have appeared.\textsuperscript{96,102}

Due to synthetic and practical importance of aryl- and vinylphosphonate, and also phosphinate derivatives, we decided to undertake a systematic investigations on application of the microwave heating as an alternative means of facilitating the C-P forming cross-coupling reaction.
5.2 Microwave-assisted palladium-catalyzed cross-coupling of aryl and vinyl halides with H-phosphonate diesters

First we set out to develop a general-purpose protocol for the synthesis of aryl- and vinylphosphonates under microwave irradiation conditions. Although a plethora of ligands for the cross-coupling reactions involving palladium have been developed, and some of them were successfully applied in the reactions with H-phosphonate nucleophiles, the most used catalyst for this kind of chemistry remains Pd(PPh₃)₄.³⁹,⁵⁰ Since our aim was to examine the applicability and usefulness of the microwave heating for the C-P forming cross-coupling, we decided to use this simple, one-component palladium catalyst.

5.2.1 Optimization of the reaction conditions

For the purpose of optimization of the experimental conditions, we chose as a model reaction, coupling between bromobenzene and diethyl H-phosphonate 7. All experiments were performed in pressure sealed microwave vessels, under an inert gas atmosphere. First, screening of various common solvents was carried out by comparing a degree of conversion into diethyl phenylphosphonate (8) after 3 min heating at 120 °C (Table 12).

![Table 12. Solvents screening](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion [b] (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>65*[c]</td>
</tr>
<tr>
<td>3</td>
<td>acetone</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>dioxane</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>NMP</td>
<td>51*[c]</td>
</tr>
<tr>
<td>7</td>
<td>toluene</td>
<td>28</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.25 mmol 7, 0.28 mmol PhBr, 0.30 mmol Et₃N, 0.025 mmol Pd(PPh₃)₄ (10 mol%), 5 mL solvent (0.1 M); after initial heating reaction temperature was maintained for 3 minutes at 120 °C. [b] Determined by ³¹P NMR spectroscopy. [c] At concentrations higher than 0.1 M starting material decomposition was observed.
As it is apparent from Table 12, the reaction proceeded reasonably well in all solvents tested. Although the best results were obtained for DMSO and NMP (Table 12, entries 2 and 6), severe side reactions occurred, when the concentration of the reactants was increased to 0.25 M (a concentration range convenient for preparative syntheses). In DMSO, the starting H-phosphonate was oxidized to P(V) species, probably via a Swern-type of oxidation (formation of Me₂S), while in NMP, a partial cleavage of one of the ethyl groups from (EtO)₂P(O)H was observed. Therefore, for the further studies, THF (Table 12, entry 1) was selected as solvent, due to its good efficiency in the coupling reaction, and easy handling during the work-up procedure.

In the next step of the screening procedure, different bases were examined for their ability to promote the cross-coupling of the model substrates (Table 13). Best results were obtained for Et₃N and Cs₂CO₃ (Table 13, entries 1 and 4), which provided ca 40% conversion into phenylphosphonate 8 within 3 min at 120°C. The other carbonates investigated, as well as K₃PO₄ and propylene oxide, were by far less efficient.

Table 13. Bases screening.\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conversion\textsuperscript{[b]} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>Na₂CO₃</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Cs₂CO₃</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>K₃PO₄</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>propylene oxide</td>
<td>4</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: 0.25 mmol 7, 0.28 mmol PhBr, 0.30 mmol base, 0.025 mmol Pd(PPh₃)₄ (10 mol%), 5 mL THF (0.1M); after initial heating reaction temperature was maintained for 3 minutes at 120 °C. \textsuperscript{[b]} Determined by \textsuperscript{31}P NMR spectroscopy.

Attempted increasing the coupling rate, by applying temperatures higher than 120 °C, failed due to progressing decomposition of the starting material (diethyl H-phosphonate) and the reaction product. Further tuning of the reaction conditions led us to decreasing the catalyst load to 5 mol% of Pd(PPh₃)₄, and to extend the heating time to 10 min.
5.2.2 Microwave-assisted synthesis of aryl- and vinylphosphonate diesters

The conditions developed above, when applied to the preparative syntheses of aryl- and vinylphosphonate diesters (Table 14), secured a complete conversion (as determined by $^{31}$P NMR) to the corresponding products of all the tested combinations of different aryl and vinyl halides and H-phosphonate diesters.

**Table 14.** Microwave-assisted synthesis of aryl- and vinylphosphonate diesters.^[a]^  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>H-phosphonate</th>
<th>Product</th>
<th>Product no.</th>
<th>Yield (%)^[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{Ar}^-\text{I}$</td>
<td>$\text{H-P-OEi}$</td>
<td>$\text{Ar}^-\text{P-OEi}$</td>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>$\text{Ar}^-\text{Br}$</td>
<td>$\text{H-P-OEi}$</td>
<td>$\text{Ar}^-\text{P-OEi}$</td>
<td>8</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>$\text{Ar}^-\text{OTf}$</td>
<td>$\text{H-P-OEi}$</td>
<td>$\text{Ar}^-\text{P-OEi}$</td>
<td>8</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>$\text{Ar}^-\text{Br}$</td>
<td>$\text{H-P-OMe}$</td>
<td>$\text{Ar}^-\text{P-OMe}$</td>
<td>35</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>$\text{Ar}^-\text{Br}$</td>
<td>$\text{H-P-OPr}$</td>
<td>$\text{Ar}^-\text{P-OPr}$</td>
<td>36</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>$\text{Ar}^-\text{Br}$</td>
<td>$\text{H-P-OBn}$</td>
<td>$\text{Ar}^-\text{P-OBn}$</td>
<td>60</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>$\text{Ar}^-\text{Br}$</td>
<td>$\text{H-P-OEi}$</td>
<td>$\text{Ar}^-\text{P-OEi}$</td>
<td>41</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>$\text{Ar}^-\text{Br}$</td>
<td>$\text{MeO}$</td>
<td>$\text{Ar}^-\text{P-OEi}$</td>
<td>43</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>$\text{Ar}^-\text{Br}$</td>
<td>$\text{H-P-OEi}$</td>
<td>$\text{Ar}^-\text{P-OEi}$</td>
<td>37</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>$\text{Ar}^-\text{Br}$</td>
<td>$\text{H-P-OEi}$</td>
<td>$\text{Ar}^-\text{P-OEi}$</td>
<td>38</td>
<td>73</td>
</tr>
<tr>
<td>11</td>
<td>$\text{Ar}^-\text{Br}$</td>
<td>$\text{H-P-OEi}$</td>
<td>$\text{Ar}^-\text{P-OEi}$</td>
<td>39</td>
<td>72</td>
</tr>
</tbody>
</table>

continued on the next page
As it is apparent from data in Table 14, the substrates bearing different leaving groups (iodide, bromide and triflate; entries 1-3) were all efficiently coupled under the microwave irradiation conditions. It is worth mentioning that using conventional heating, the reactions from entries 1 and 2 went to completion within 2.5 to 18 h, depending on the specific method used.\textsuperscript{36,103} Aryl groups with electron-withdrawing and electron-donating substituents (entries 7 and 8) and H-phosphonate diesters bearing different alkyl groups (entries 4-6), also coupled efficiently under these reaction conditions.

As far as the size of the aryl group is concerned, four arylphosphonates with larger aryl moieties were also synthesized in good isolated yields (entries 9-12). Additionally, a heteroaromatic derivative, 3-bromopyridine, was successfully coupled with diethyl H-phosphonate, producing the corresponding pyridylphosphonate 45 (entry 13). Importantly, the NMR spectra of the isolated products from entries 7-13 have shown that the attachment point of the phosphorus atom was the same as that of the halide in the starting materials.

Finally, three vinyl bromides were used for a cross-coupling reaction with diethyl H-phosphonate 7 (entries 14-16). Also in these instances, the yields of the isolated products were high, and for vinylphosphonates 62 and 63, the substituent arrangements at the double bond were preserved.

To demonstrate compatibility of the developed microwave-assisted cross-coupling conditions with more complex, functionalized systems, we carried out a P-arylation of cholesteryl ethyl H-phosphonate with bromobenzene (Table 15, entry 1). The reaction was uneventful and afforded the expected

---

**Table 14 (continued)**

| Entry | Aryl halide | H-phosphonate | Product | Product no. | Yield (%)\textsuperscript{[c]}
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td><img src="image1" alt="Aryl halide" /></td>
<td>$\text{H-P-}^\text{OEt}_7$</td>
<td><img src="image2" alt="Product" /></td>
<td>40</td>
<td>77</td>
</tr>
<tr>
<td>13</td>
<td><img src="image3" alt="Aryl halide" /></td>
<td>$\text{H-P-}^\text{OEt}_7$</td>
<td><img src="image4" alt="Product" /></td>
<td>45</td>
<td>86</td>
</tr>
<tr>
<td>14</td>
<td><img src="image5" alt="Aryl halide" /></td>
<td>$\text{H-P-}^\text{OEt}_7$</td>
<td><img src="image6" alt="Product" /></td>
<td>61</td>
<td>84</td>
</tr>
<tr>
<td>15</td>
<td><img src="image7" alt="Aryl halide" /></td>
<td>$\text{H-P-}^\text{OEt}_7$</td>
<td><img src="image8" alt="Product" /></td>
<td>62</td>
<td>91</td>
</tr>
<tr>
<td>16</td>
<td><img src="image9" alt="Aryl halide" /></td>
<td>$\text{H-P-}^\text{OEt}_7$</td>
<td><img src="image10" alt="Product" /></td>
<td>63</td>
<td>88</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: 1.25 mmol H-phosphonate diester, 1.38 mmol ArX or vinyl-X, 1.50 mmol Cs$_2$CO$_3$, 0.06 mmol Pd(PPh$_3$)$_4$ (5 mol%), 5 mL THF (0.25 M); after initial heating reaction temperature was maintained for 10 minutes at 120 °C. \textsuperscript{[b]} Isolated yield.
cholesteryl ethyl phenylphosphonate 64 in isolated high of 86%. As a second example of more complex systems, we chose a cross-coupling of a dinucleoside H-phosphonate 53 with iodobenzene, to produce a compound with a phenylphosphonate internucleotide linkage (Table 15, entry 2). The important feature of dinucleoside-phosphonates is that, in contrast to the ethyl cholesteryl diester, their P-diastereomers, possessing opposite configurations at the phosphorus atom, are easily available. This opened a possibility to verify if the microwave heating did not deteriorate a complete stereospecificity of this reaction (retention of the configuration) observed under conventional heating.97

Table 15. Synthesis of some biologically relevant arylphosphonate derivatives.[a]  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl derivative</th>
<th>H-phosphonate</th>
<th>Product</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[c]</td>
<td><img src="image1" alt="Aryl derivative" /></td>
<td><img src="image2" alt="H-phosphonate" /></td>
<td><img src="image3" alt="Product" /></td>
<td>86</td>
</tr>
<tr>
<td>2[d]</td>
<td><img src="image4" alt="Aryl derivative" /></td>
<td><img src="image5" alt="H-phosphonate" /></td>
<td><img src="image6" alt="Product" /></td>
<td>81 (R_P)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>84 (S_P)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.50 mmol H-phosphonate diester, 0.55 mmol ArX, 0.60 mmol base, 0.024 mmol Pd(PPh₃)₄ (5 mol%), 5 mL THF (0.10 M); after initial heating reaction temperature was maintained for 10 minutes at 120 °C. [b] Isolated yield. [c] Cs₂CO₃ was used as a base. [d] Et₃N was used as a base.

Somewhat surprisingly, application of the previously developed reaction conditions to a dinucleoside H-phosphonate 53 caused that no phosphorus resonance signals could be detected in the ³¹P NMR spectra. We speculated that this could be due to absorption of the substrate on the solid Cs₂CO₃, and to alleviate this problem, we replaced Cs₂CO₃ with Et₃N. This later base, during our screening (Table 13, entry 1 vs. 4) showed similar efficiency to Cs₂CO₃, and it was also used before for the cross-coupling reactions under the conventional heating conditions.104,105 It was rewarding to see that with Et₃N used as a base, both diastereomers of dinucleoside H-phosphonate 53 could be successfully coupled with iodobenzene, without any noticeable decomposition. Additionally, a complete stereospecificity of the reaction was observed, since each of the diastereomers of the dinucleoside H-phosphonate 53 was exclusively transformed into a single diastereomer of the product 58.
5.2.3 Conclusions

In summary, we have developed a convenient and general method for the microwave-assisted preparation of aryl- and vinylphosphonates based on Pd-catalyzed cross-coupling. The procedure is highly efficient and provides a rapid access to a broad spectrum of phosphonate diesters, including more complex compounds, as it was illustrated in the synthesis of cholesteryl (64) and dinucleoside (58) derivatives. On the stereochemistry part, the reaction is completely stereospecific, and also a configuration in the vinyl moiety is preserved.

5.3 Microwave-assisted palladium-catalyzed cross-coupling of phosphinate with aryl halides

Encouraged by the successful application of microwave heating to cross-coupling of H-phosphonate diesters, we decided to extend this methodology to other phosphorus nucleophiles, namely, H,H-phosphinates.

![Scheme 25. Synthesis of mono- and diarylphosphinates via the cross-coupling reaction.](image)

Due to the presence of two protons on the phosphorus atom, phosphinates can serve as precursors to both mono- and diarylphosphinates (Scheme 25). Under the conventional heating conditions, monoaryl derivatives are most conveniently prepared from anilinium phosphinate according to a protocol developed by Montchamp et al. Since this is an ionic species it seemed to be perfectly suited for the application of the microwave heating, due to expected very efficient absorbance of the microwave energy via a conduction mechanism. For this reason we decided to adopt anilinium phosphinate as a starting material for the synthesis of both mono- and diarylphosphinates.

5.3.1 Optimization of the reaction conditions

We started our investigations by examining a number of common ligands for their efficiency to promote a cross-coupling between model substrates, namely, bromobenzene and anilinium phosphinate 65 (Scheme 26). All experiments were performed in sealed pressure-proof microwave vessels, in THF under an inert gas atmosphere, with 3 mol% palladium catalyst and triethylamine as a base. The composition of the reaction mixtures was determined by $^{31}$P NMR spectroscopy after 5 min heating at 120 °C (Table...
In addition to the starting material 65 and product 66, in several cases signals originating from H-phosphonate (67) and H-pyrophosphonate (68) could be observed in the NMR spectra (Scheme 26). These undesired P(III) side-products were formed, most likely, due to reduction of bromobenzene to benzene via transfer hydrogenation.

Scheme 26. A model reaction used for screening of the reaction conditions.

The catalyst most frequently used under thermal conditions, Pd(PPh₃)₄, did not produce the desired phosphinate 66, but only oxidation products 67 and 68 (Table 16, entry 3). Also Pd(0) with other monodentate ligands (entries 8, 9, 12) seemed to favor transfer hydrogenation rather than cross-coupling. Among the ligands investigated, only bidentate ligands promoted synthesis of the phosphinate 66, and the highest conversion (95%) was observed for the reaction with Xantphos (entry 11).

Table 16. Ligands screening.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst[b]</th>
<th>Substrate 65 (%)[c]</th>
<th>Product 66 (%)[c]</th>
<th>Side-products 67 and 68 (%)[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>100</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>Pd₂(db₃)CHCl₃</td>
<td>77</td>
<td>nd</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₄</td>
<td>76</td>
<td>nd</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>dppp</td>
<td>35</td>
<td>47</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>dppb</td>
<td>80</td>
<td>20</td>
<td>nd</td>
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<tr>
<td>6</td>
<td>dppf</td>
<td>14</td>
<td>86</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>BINAP</td>
<td>59</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>PC₂₃</td>
<td>83</td>
<td>nd</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>PrBu₃</td>
<td>85</td>
<td>nd</td>
<td>15</td>
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<tr>
<td>10</td>
<td>DPEPhos</td>
<td>23</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>Xantphos</td>
<td>3</td>
<td>95</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>IMes-HCl</td>
<td>77</td>
<td>nd</td>
<td>23</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.25 mmol 65, 0.25 mmol PhBr, 0.63 mmol Et₃N, 3 mol% Pd catalyst and 3 mol% of the appropriate ligand (entries 4-12), 1 mL THF; after initial heating the power was adjusted to maintain the reaction temperature at 120 °C for 5 min. [b] In entries 4-12 Pd₂(db₃)CHCl₃ was used as the palladium source. [c] Determined by ³¹P NMR spectroscopy.
The fact that other wide-bite-angle ligands, e.g. dppf (entry 6) and to smaller extent dppp and DPEPhos (entries 4 and 10, respectively), also provided good conversions to 66, might suggest that the reductive elimination was a turnover-limiting step of the catalytic cycle. Nevertheless, one cannot exclude the importance of an attack of the phosphorus nucleophile on palladium(II) complexes (the ligand exchange process), that was found to be crucial for the overall rate of cross-couplings involving H-phosphonate diesters (see Chapter 3). This step might be facilitated by ligands distorting the square planar geometry of the palladium(II) complex.

Table 17. Solvents and heating modes screening.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Substrate 65 (%)[b]</th>
<th>Product 66 (%)[b]</th>
<th>P(III) side-prod. (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>120</td>
<td>18</td>
<td>82</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>acetone</td>
<td>120</td>
<td>20</td>
<td>49</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>dioxane</td>
<td>120</td>
<td>46</td>
<td>37</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>120</td>
<td>97</td>
<td>3</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>120</td>
<td>23</td>
<td>77</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>i-PrOH</td>
<td>120</td>
<td>100</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
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<td>76</td>
<td>24</td>
<td>nd</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>120</td>
<td>65</td>
<td>35</td>
<td>nd</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>120</td>
<td>nd</td>
<td>100</td>
<td>nd</td>
</tr>
<tr>
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<td>THF</td>
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<td>25</td>
<td>75</td>
<td>nd</td>
</tr>
<tr>
<td>11[c]</td>
<td>THF</td>
<td>100</td>
<td>36</td>
<td>64</td>
<td>nd</td>
</tr>
<tr>
<td>12[d]</td>
<td>THF</td>
<td>100</td>
<td>nd</td>
<td>64</td>
<td>31</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.25 mmol 65, 0.25 mmol PhBr, 0.63 mmol Et3N, 0.0038 mmol Pd2(dba)3·CHCl3 (3 mol% Pd), 0.0075 mmol Xantphos, 1 mL THF; Except for entries 11 and 12, after initial heating, the power was adjusted to maintain the reaction mixture at indicated temperature for 2 min. [b] Determined by 31P NMR spectroscopy. [c] Bromobenzene was added to the reaction mixture preheated to 100 °C in an oil bath, and this temperature was maintained for 2 min. [d] After initial heating, the reaction vessel was simultaneously cooled with a stream of air and heated with the power adjusted to maintain the reaction temperature at 100 °C for 2 min.

Next, we evaluated various solvents as reaction media for the cross-coupling reaction in Scheme 26. In order to observe clear differences between the solvents, the reaction time was shortened to 2 min, while keeping the catalyst load unchanged (3 mol%). For most solvents investigated, except acetone and dioxane (Table 17, entries 2 and 3), the transfer hydrogenation was not the issue when standard microwave heating mode was applied (see Table 17, footnote a). However, significant differences in coupling rates in various solvents were observed, and only for THF (entry 9), did a quantitative conversion to 66 occurred within 2 min, at 120 °C. For the sake of comparison, we carried out also an analogous cross-
coupling reaction at 100 °C using an ordinary oil bath heating (entry 11). Since this led to the result comparable to that of using microwave irradiation at the same temperature (entry 10), probably, the acceleration of cross-coupling reactions by microwave heating has mostly thermal basis as predicted by the Arrhenius equation.

To find out if there was any microwave specific effect involved, we carried out an experiment in which the reaction vessel was cooled during irradiation. Under standard mode of irradiation, due to efficient absorption of microwaves by the reaction mixtures, only a minimal microwave power was required to maintain a high temperature of the sample. Heating with a simultaneous cooling increased exposure to microwave irradiation, since much higher power had to be administered to the sample to keep the temperature constant. Application of such a heating mode resulted in a full conversion of the starting material even at 100 °C within 2 minutes (entry 12), but unfortunately the transfer hydrogenation became a prominent reaction pathway under such conditions. This may indicate some microwave specific effect that promote the transfer hydrogenation.

5.3.2 Microwave-assisted synthesis of monoarylphosphinic acids

Having established the optimal reaction conditions, we assessed next the scope and limitation of the method, first in the synthesis of monoarylphosphinic acids (Table 18).

The reactivity of aryl halides strongly depended on steric factors and for more hindered starting materials (ortho substituted aryls), higher catalyst loading was required (entries 14-18). In contrast to bromides, only activated aryl chlorides (entry 5) underwent coupling with phosphinate 65, albeit a higher catalyst load was required. In this instance (entry 5) a noticeable lower yield was due to extensive transfer hydrogenation.

A broad spectrum of functional groups, both electron-withdrawing and electron-donating, was tolerated under this set of the reaction conditions. Notably, double bonds (entry 7) were found to be compatible with the reaction conditions, even though a similar catalytic system (Pd$_2$(dba)$_3$+Xantphos) was earlier reported to promote hydrophosphinylation of alkenes.

Also vinyl bromide (entry 12), 2-bromothiophene (entry 13), and benzyl chloride (entry 18) underwent smooth coupling with phosphinate 65 affording in good yields the corresponding phosphinates. In all instances, excellent selectivity was observed for the formation of monoaryl- over the diarylphosphinates. This feature enabled isolation of pure phosphinic acids 66-83 in good yields, via a simple extractive work-up.
Table 18. Microwave-assisted synthesis of monoarylphosphinic acids.\(^{[a]}\)

![Chemical structure](https://example.com/structure.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Product</th>
<th>Prod no.</th>
<th>Pd (mol%)</th>
<th>Yield (%)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Ph}^-)</td>
<td>(\text{PhPO}^-)</td>
<td>66</td>
<td>0.1</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>(\text{PhBr}^-)</td>
<td>(\text{PhPO}^-)</td>
<td>66</td>
<td>0.1</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>(\text{PhBr}^-)</td>
<td>(\text{PhPO}^-)</td>
<td>67</td>
<td>0.1</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>(\text{O}_2\text{NPhBr}^-)</td>
<td>(\text{O}_2\text{NPhPO}^-)</td>
<td>68</td>
<td>0.1</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>(\text{O}_2\text{NPhCl}^-)</td>
<td>(\text{O}_2\text{NPhPO}^-)</td>
<td>68</td>
<td>1.0</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>(\text{MePhBr}^-)</td>
<td>(\text{MeNO}_{2}\text{PhPO}^-)</td>
<td>69</td>
<td>0.1</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>(\text{MeCOPhBr}^-)</td>
<td>(\text{MeCOPhPO}^-)</td>
<td>70</td>
<td>0.1</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>(\text{PhCH}=	ext{CHPhBr}^-)</td>
<td>(\text{PhCH}=	ext{CHPhPO}^-)</td>
<td>71</td>
<td>0.1</td>
<td>91</td>
</tr>
<tr>
<td>9(^{[c]})</td>
<td>(\text{HOPhBr}^-)</td>
<td>(\text{HOPhPO}^-)</td>
<td>72</td>
<td>0.1</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>(\text{MeOPhBr}^-)</td>
<td>(\text{MeOPhPO}^-)</td>
<td>73</td>
<td>0.1</td>
<td>89</td>
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<tr>
<td>11</td>
<td>(\text{HOPhBr}^-)</td>
<td>(\text{HOPhPO}^-)</td>
<td>74</td>
<td>0.1</td>
<td>83</td>
</tr>
<tr>
<td>12(^{[d]})</td>
<td>(\text{PhCH}=	ext{CHPhBr}^-)</td>
<td>(\text{PhCH}=	ext{CHPhPO}^-)</td>
<td>75</td>
<td>0.1</td>
<td>89</td>
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<td>(\text{BrPh}^-)</td>
<td>(\text{BrPhPO}^-)</td>
<td>77</td>
<td>1.0</td>
<td>73</td>
</tr>
<tr>
<td>15</td>
<td>(\text{BzBr}^-)</td>
<td>(\text{BzBrPO}^-)</td>
<td>78</td>
<td>1.0</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^{[a]}\) See text for conditions.

\(^{[b]}\) Isolated yield.

\(^{[c]}\) Reaction time: 1 h.

\(^{[d]}\) Reaction time: 2 h.
Table 18 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Product</th>
<th>Prod no.</th>
<th>Pd (mol%)</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>79</td>
<td>1.0</td>
<td>84</td>
</tr>
<tr>
<td>17[c]</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>80</td>
<td>1.0</td>
<td>80</td>
</tr>
<tr>
<td>18</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>81</td>
<td>1.0</td>
<td>69</td>
</tr>
<tr>
<td>17</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>82</td>
<td>5.0</td>
<td>82</td>
</tr>
<tr>
<td>18</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td>83</td>
<td>5.0</td>
<td>87</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1.25 mmol 65, 1.25 mmol ArX, 3.13 mmol Et₂N, Pd/Xantphos ratio = 1, 5 mL THF; after initial heating, the power was adjusted to maintain the reaction temperature at 120 °C for 10 min. [b] Isolated yield. [c] 4.38 mmol (3.5 equiv.) Et₂N was used. [d] Commercial β-bromostyrene (Z/E 1:9) was used, producing mixture of phosphinic acids (in analogous Z/E ratio).

5.3.3 Microwave-assisted synthesis of diarylphosphinic acids

Next, we investigated a possibility of diarylphosphinate synthesis (Table 19). The initial experiments showed that the second coupling step was much more difficult to accomplish than the attachment of the first aryl moiety. The most likely reason for this seemed to be reduced nucleophilicity of arylphosphinates (steric hindrance), and pointed to the importance of the ligand substitution step. To remedy this problem, higher catalyst loading and prolonged reaction times were used in the second coupling step to obtain diarylphosphinic acids in good yields (Table 19).

Under these conditions various diarylphosphinic acids without ortho substituents in the aromatic ring (Table 19, entries 1-5) or bearing one ortho-substituted aryl group (Table 19, entries 6 and 7), were synthesized.

The symmetrical diaryl derivatives (Table 19, entries 1 and 2) could always be obtained in high purity, just by using 2.5 equiv. of the appropriate aryl halide for the reaction, followed by the extractive work-up. However, attempted one-pot synthesis of unsymmetrical phosphinic acids (e.g. entries 3-7), by sequential addition of different aryl halides, resulted in products contaminated with symmetrical derivatives (up to 15%). Since purification of these compounds posed some problems due to their ionic nature, we decided to carry out the reactions in a stepwise manner, with extractive
isolation of the intermediate monoarylphosphonic acid. Such a strategy appeared to be successful and unsymmetrical diaryl derivatives 86-90 could be obtained in high yields and purities.

Table 19. Microwave-assisted synthesis of diarylphosphinic acids.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide(s)</th>
<th>Product</th>
<th>Prod. no.</th>
<th>Pd (mol%)</th>
<th>Time (min)</th>
<th>Yield (%)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td><img src="image1.png" alt="Product 1" /></td>
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<td>2.0</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td><img src="image2.png" alt="Product 2" /></td>
<td>85</td>
<td>2.0</td>
<td>15</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td><img src="image3.png" alt="Product 3" /></td>
<td>86</td>
<td>0.1</td>
<td>10</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td><img src="image4.png" alt="Product 4" /></td>
<td>87</td>
<td>2.0</td>
<td>15</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td><img src="image5.png" alt="Product 5" /></td>
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<td>0.1</td>
<td>10</td>
<td>76</td>
</tr>
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<td>6</td>
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<td>89</td>
<td>1.0</td>
<td>10</td>
<td>81</td>
</tr>
</tbody>
</table>

continued on the next page
Table 19 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide(s)</th>
<th>Product</th>
<th>Prod. no.</th>
<th>Pd (mol%)</th>
<th>Time (min)</th>
<th>Yield (%)^[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>MeO-Br</td>
<td><img src="image" alt="Product Image" /></td>
<td>90</td>
<td>1.0</td>
<td>10</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>OMe</td>
<td><img src="image" alt="Product Image" /></td>
<td></td>
<td>3.0</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

^[a] Reaction conditions: entries 1 and 2: 1.25 mmol 65, 3.31 mmol ArX, 4.38 mmol Et$_3$N, Pd/Xantphos ratio = 1, 5 mL THF; entries 3-7: first coupling: 1.25 mmol 65, 1.25 mmol Ar'$^1$X, 3.13 mmol Et$_3$N, Pd/Xantphos ratio = 1, 5 mL THF, followed by extractive work-up, second coupling: 1.88 mmol Ar'$^2$X, 3.13 mmol Et$_3$N, Pd/Xantphos ratio = 1, 5 mL THF. After initial heating, the power was adjusted to maintain the reaction temperature at 120 °C for the time indicated for each step of the reaction. [^b] Isolated yield.

5.3.4 Conclusions

We have developed a convenient and general method for the microwave-assisted synthesis of mono- and diarylphosphinic acids catalyzed by Pd(0) and Xantphos as a supporting ligand. The procedure is highly efficient and provides a rapid access to a broad spectrum of arylphosphinate derivatives. A large range of aryl halides could be phosphinylated using 0.1 mol% of palladium, and only for sterically hindered aryl halides, the loading of the catalyst had to be higher (up to 5%). Also, unsymmetrical diarylphosphinic acids could be for the first time efficiently synthesized using the developed reaction conditions.

5.4 Summary

The results presented in this chapter clearly show usefulness of the microwave heating in the cross-coupling reactions involving phosphorus nucleophiles. In case of H-phosphonate diesters application of the microwave heating, enabled very efficient synthesis of a variety of products in a remarkably short reaction time, even while using one of the simplest available palladium catalysts – Pd(PPh$_3$)$_4$. For H,H-phosphinate, more complex, but not sophisticated, supporting ligand was required, however for most of the reactions, very low catalyst loading (0.1 mol%) was sufficient to obtain full conversions in a short time. On the other hand, synthesis of 2,6-disubstituted arylphosphinic acids was achieved for the first time, although with higher amount of catalyst. Also for the first time, an easy access to a diarylphosphinic acids has been established.
Chapter 6

Palladium-catalyzed propargylic substitution with phosphorus nucleophiles: efficient, stereoselective synthesis of allenyl-phosphonates and related compounds (Papers VI & VII)

6.1 Introduction

In the recent years, allenes have rapidly evolved from intriguing chemical entities into one of the most flourishing research subject in the organic chemistry. An allene structural motif has been discovered in many natural products and started to attract an increasing attention of the pharmaceutical research. Due to the development of novel synthetic methods, allenes became also useful intermediates in chemical synthesis, often enabling a rapid molecular complexity increase in a single reaction step, inter alia, due to an efficient transfer of chirality to the newly formed stereocenters.

A special class of allenes constitute allenylphosphonates and related compounds. Their important feature is diverse reactivity, that with substituent-loading capability and axial chirality of the allene unit, make them potentially useful synthetic intermediates. As phosphorus-containing compounds allenylphosphonates are attractive targets in biological and medicinal chemistry, as they may serve as analogs of biologically important compounds, e.g. nucleic acids, phospholipids, phosphorylated sugars, or to be used as enzyme inhibitors. Although an allene moiety has been extensively used in pharmacologically active compounds, allenylphosphonates have not been explored yet in this context (section 1.2). We believe that this can be attributed to the lack of universal synthetic methods meeting the requirements of the preparation of complex natural products analogs.

As described in section 1.3, synthesis of allenylphosphonates has been dominated by [2,3]-sigmatropic rearrangement of propargyl phosphites (Scheme 2), that has a broad scope with respect to the precursor
propargylic alcohols used and it enables synthesis of allenylphosphonates with various substitution patterns in the allene moiety. Despite these, the approach suffers from a serious drawback, namely, a limited kind of substituents that can be attached to the phosphonate center.

In order to overcome these limitations of the methods based on the sigmatropic rearrangement, we turned our attention to a completely unexplored in this context transition metal-catalyzed propargylic substitution (S_N2') reaction as a means of synthesis of allenylphosphonates. Although, this is a well established synthetic approach to a variety of allenes, the reaction has never been used for the formation of carbon-phosphorus bond. An appealing feature of this type of palladium or copper-catalyzed reactions is that often stereoselectivity and chirality transfer from the propargylic substrate to the allene moiety is observed. Since Pd-catalyzed C-P bond formation has been shown to work well in the synthesis of biologically important phosphorus compounds, and mechanistic aspects of the reaction has been studied in-depth, we expected that these may lend themselves to a new methodology for the construction of complex allenylphosphonate derivatives.

Scheme 27. Possible reaction pathways for Pd-catalyzed propargylic substitution with phosphonate nucleophile (additional ligands at the Pd center were omitted for clarity).

There is also an interesting mechanistic aspect of a Pd-catalyzed synthesis of C-allenes vs. heteroatom-substituted allenes (e.g. allenylphosphonates). Apart from a transmetallation (ligand exchange) of the equilibrating allenyl-
and propargylpalladium species\textsuperscript{117} (Scheme 27, paths a and c; formation of an allenyl- and propargylpalladiumphosphonate intermediates, respectively), a ‘soft’ heteroatom nucleophile may attack a central carbon atom of the ligand (Scheme 27, path b).\textsuperscript{114,115,118} In the first instance, for phosphorus nucleophiles, an allenylphosphonate (or propargylphosphonate) should be formed after reductive elimination, while in the second scenario, formation of either diene (via $\beta$-hydride elimination, path b1) or bisphosphonate (path b2) might be favored. As shown by the work of Kozawa \textit{et al.} on amide nucleophiles, the outcome of the reaction can be controlled by the supporting ligands used.\textsuperscript{119}

### 6.2 Optimization of the reaction conditions

The initial screening revealed that only bidentate ligands with wide bite angles were able to promote a coupling of propargylic derivatives with H-phosphonate diesters, and the highest reaction rate was observed for DPEPhos. To our delight, the desired allenylphosphonate was always the sole product of the reaction, irrespective of the bidentate ligand used.

**Table 20. Effect of the leaving group and additives.\textsuperscript{[a]}**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Leaving group (X)</th>
<th>Additive\textsuperscript{[b]}</th>
<th>Reaction time\textsuperscript{[c]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>Et$_3$N</td>
<td>R = H 1.5 h</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>--</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>OCO$_2$Me</td>
<td>--</td>
<td>R = H 7 h 30 min</td>
</tr>
<tr>
<td>4</td>
<td>OTs</td>
<td>Et$_3$N</td>
<td>R = n-C$<em>3$H$</em>{11}$ 10 h\textsuperscript{[d]}</td>
</tr>
<tr>
<td>5</td>
<td>OTs</td>
<td>--</td>
<td>V. slow react.</td>
</tr>
<tr>
<td>6</td>
<td>OAc</td>
<td>Et$_3$N</td>
<td>V. slow react.</td>
</tr>
<tr>
<td>7</td>
<td>OAc</td>
<td>--</td>
<td>R = H 24 h\textsuperscript{[d]}</td>
</tr>
<tr>
<td>8</td>
<td>OTs</td>
<td>Et$_3$N, Cl$^-$</td>
<td>8 h\textsuperscript{[e]}</td>
</tr>
<tr>
<td>9</td>
<td>OTs</td>
<td>Et$_3$N, AcO$^-$</td>
<td>1.5 h 1.5 h</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: 0.28 mmol propargyl derivative, 0.25 mmol 7, 0.0038 mmol Pd$_2$(dba)$_3$·CHCl$_3$ (3 mol% Pd), 0.0075 mmol DPEPhos, 1 mL THF (0.25 M), 68 °C. \textsuperscript{[b]} 0.30 mmol Et$_3$N or 0.075 mmol (30 mol%) $n$-Bu$_3$N$^+$X$^-$. \textsuperscript{[c]} >95% conversion ($^3$P NMR spectroscopy). \textsuperscript{[d]} Partial isomerization of the product to 1-alkynylphosphonate (ca 50%). \textsuperscript{[e]} Formation of 1,3-dienylphosphonate and other by-products (total ca 40%).
To investigate and optimize further the experimental conditions, the reactions with primary and secondary propargylic derivatives bearing different leaving groups (Cl, MeOCO₂, TsO, AcO) were carried out. In all cases 3 mol% palladium loading was used together with DPEPhos ligand. For some entries also an effect of a base (Et₃N) and anionic additives was studied (Table 20).

The data from Table 20 provide practical guidelines for designing a synthetic method based on this reaction and also bear some mechanistic hints. As it is apparent from entry 1, the propargyl chlorides showed relatively high reactivity, that did not depend on the presence or absence of an alkyl substituent on C1 (primary vs. secondary propargylic derivatives). As expected, this reaction required presence of stoichiometric amount of a base (Table 20, entry 2). Propargyl carbonates, on the other hand, did not require an external base, and exhibited significant differences in rates between primary vs. secondary substrates (entry 3), with the later ones reacting much faster (30 min vs. 7 h). The tosyl derivatives (Table 2, entry 4) were less reactive than the corresponding chlorides and in case of a primary propargyl derivative, a partial isomerization of the product to 1-alkynylphosphonate derivative was observed, apparently due to prolonged exposure to the base, necessary for reaching the full conversion. Finally, propargyl acetates were investigated (entries 6 and 7). These were found to be rather poor substrates for the reaction, and in the presence of Et₃N a large fraction of the products isomerized to the corresponding 1-alkynylphosphonates, due to very long reaction times (Table 2, entry 6). In the absence of a base, the reactivity improved for these compounds, but acidification of the reaction mixtures by AcOH formed during the course of the reaction, lead to formation of multiple side-products (Table 2, entry 7).

We also studied possible effects of anionic additives on the outcome of the reaction with propargyl tosylates. Since tosylate anions are weakly bonding to the palladium(II) center, their replacement with the added anions (chloride or acetate) could potentially affect the ligand exchange step. Indeed, addition to the reaction mixture of tetra-n-butylammonium chloride shorten down the reaction times to 1.5 h for both primary and secondary propargylic derivatives (Table 2, entry 8), a value identical to that observed when propargylic chlorides were used as substrates (Table 2, entry 1). Addition of external acetate anions (n-Bu₄N(OAc)) resulted also in a remarkable shortening of the reaction times to 45 min (Table 2, entry 9), and this indicated that the observed poor reactivity of propargylic acetates in this reaction (Table 2, entries 6 and 7) was apparently due to an inefficient oxidative addition step.
6.3 Synthesis of allenylphosphonates and allenylphosphinates

Having established reactivity of different propargylic substrates under various experimental conditions, we decided to examine the scope of the reaction. Since propargylic chlorides and carbonates gave the best results without necessity of using any additives, these two groups of substrates were used in the further investigations (Table 21).

Table 21. Synthesis of allenylphosphonates and related compounds.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Propargylic substrate</th>
<th>P-nucleophile</th>
<th>Product</th>
<th>Reaction time[b]</th>
<th>Yield (%)[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl≡C</td>
<td>MeO-P-OEt</td>
<td>91</td>
<td>1.5 h</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
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<td>MeO-P-OEt</td>
<td>91</td>
<td>7 h</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>Cl≡nC₆H₄</td>
<td>MeO-P-OEt</td>
<td>92</td>
<td>1.5 h</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>MeO₂CO≡C₆H₄</td>
<td>MeO-P-OEt</td>
<td>92</td>
<td>30 min</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>Cl≡CMe</td>
<td>MeO-P-OEt</td>
<td>93</td>
<td>1.5 h</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
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<td>MeO-P-OEt</td>
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<td>20 min</td>
<td>91</td>
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<tr>
<td>7</td>
<td>Ph≡C≡Cl</td>
<td>MeO-P-OEt</td>
<td>94</td>
<td>15 min</td>
<td>87</td>
</tr>
<tr>
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<tr>
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<td>69</td>
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<tr>
<td>10</td>
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</tbody>
</table>

continued on the next page
<table>
<thead>
<tr>
<th>Entry</th>
<th>Propargylic substrate</th>
<th>P-nucleophile</th>
<th>Product</th>
<th>Reaction time (^{[b]})</th>
<th>Yield (^{(%)}^{[c]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>11(^{[d]})</td>
<td>(\text{MeO}_2\text{CO} \equiv \text{Ph})</td>
<td>7</td>
<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
<td>10 min</td>
<td>77</td>
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<tr>
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<td>7</td>
<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
<td>1 h</td>
<td>90</td>
</tr>
<tr>
<td>13</td>
<td>(\text{CO}_2\text{Me} \equiv \text{Me})</td>
<td>7</td>
<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
<td>30 min</td>
<td>92</td>
</tr>
<tr>
<td>14</td>
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<td>80</td>
</tr>
<tr>
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<td>(\text{Cl} \equiv \text{Me})</td>
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<td>47% conv. after 24 h</td>
<td>na</td>
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<tr>
<td>16</td>
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<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
<td>45 min</td>
<td>89</td>
</tr>
<tr>
<td>17</td>
<td>(\text{MeO}_2\text{CO} \equiv \text{Ph})</td>
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<td>5 h</td>
<td>83</td>
</tr>
<tr>
<td>18</td>
<td>(\text{Cl} \equiv \text{Me})</td>
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<td>Not isolated</td>
<td>80% conv. after 24 h</td>
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<tr>
<td>19</td>
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<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
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<td>78</td>
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<tr>
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<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
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<td>66</td>
</tr>
<tr>
<td>21</td>
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<td>7</td>
<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
<td>16 h</td>
<td>78</td>
</tr>
<tr>
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<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
<td>16 h</td>
<td>84</td>
</tr>
<tr>
<td>23</td>
<td>(\text{Cl} \equiv \text{Me})</td>
<td>7</td>
<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
<td>2 h</td>
<td>89</td>
</tr>
<tr>
<td>24</td>
<td>(\text{MeO}_2\text{CO} \equiv \text{Ph})</td>
<td>7</td>
<td>(\text{EtO}_2\text{P} \equiv \text{Et} \equiv \text{Ph})</td>
<td>36 h</td>
<td>67</td>
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</table>

\(^{[a]}\) Reaction conditions: 1.38 mmol propargylic substrate, 1.25 mmol P-nucleophile, 0.019 mmol \(\text{Pd}_2(\text{dba})_3\text{CHCl}_3\) (3 mol% Pd), 0.038 mmol DPEPhos, 5 mL THF (0.25 M), 68 °C; For propargylic chlorides, additionally 1.5 mmol \(\text{Et}_3\text{N}\). \(^{[b]}\) \(>95\%\) conversion (\(^{31}\)P NMR spectroscopy). \(^{[c]}\) Isolated yield. \(^{[d]}\) 10 min microwave irradiation at 120 °C.
The scope of the reaction with regard to a substitution pattern in propargylic substrates was investigated using diethyl H-phosphonate (7) as a P-nucleophile. As it is apparent from entries 1-19 (Table 21), the following trends in reactivity can be observed. Presence of one or two substituents (R₁ and R₂) at C1 carbon greatly increased the reaction rate of the propargylic carbonates, while it had only a minor effect on the reaction times of the corresponding propargylic chlorides. On the other hand, any substituent in the terminal position of the alkyne (R₃) dramatically slowed down the reaction for both the leaving groups. These two opposite effects appeared to be approximately additive. Importantly, good conversions in case of the starting materials containing the R₃ substituent could only be achieved when carbonate was the leaving group (Table 21, entries 9, 11, 16, 17, and 19). However, in line with what was stated above, primary propargylic carbonates with terminal substituents reacted very slowly (Table 21, entries 9 and 11, respectively), and in the latter case a microwave irradiation was required to drive the reaction to completion. Hence, except for the simple unsubstituted propargyl system (Table 21, entries 1 and 2), the propargylic carbonates displayed higher reactivity than the corresponding chlorides. Overall, the Pd-catalyzed reaction fully matched the scope of the method based on a sigmatropic rearrangement (Scheme 2), enabling synthesis of unsubstituted (entries 1 and 2), mono- (Table 21, entries 3-11), di- (entries 12-17), and trisubstituted (entries 18 and 19) allenylphosphonates. Interestingly, in a separate experiment we found that also chloroallene (Table 21, entry 7) could be efficiently used as a substrate in an analogous cross-coupling reaction.

Next, various phosphorus nucleophiles were tested, including different H-phosphonate diesters (Table 21, entries 20 and 21), and three H-phosphinates (entries 22-24). All these could be efficiently transformed into the corresponding allenylphosphonates and allenylphosphinates, although it became apparent that the reaction was sensitive to steric hindrance (Table 21, entries 21 and 24). One should note, however, that due to essentially neutral pH of the reactions mixtures involving propargylic carbonates as substrates, long reaction times did not result in any deterioration (isomerization) of the products. Although, the last two products could technically be also obtained using the sigmatropic rearrangement reaction, preparation of suitable tervalent phosphorus precursors, however, would pose considerable difficulty. In contrast to those, aryl- and vinylphosphinates used in our palladium-catalyzed propargylic substitution reaction can be easily synthesized.⁴⁵,¹²¹
6.4. Stereochemistry of allenylphosphonates formation

As it was mentioned in the introduction, synthesis of allenylphosphonates via a sigmatropic rearrangement occurs with stereospecificity of the allenyl moiety formation. Therefore, we set out to investigate if the palladium-catalyzed reaction also can compete with the sigmatropic rearrangement method in this respect. In order to evaluate this possibility, enantioenriched propargylic chloride and propargylic carbonate (obtained from the corresponding alcohols), were allowed to react with diethyl H-phosphonate 7 under the developed conditions (Scheme 28).

\[
\text{Scheme 28. Reaction of the enantioenriched propargylic chlorides and carbonates with H-phosphonate 7.}
\]

As it is apparent from the results presented in Scheme 28, the stereochemical outcome of the reaction depended on the leaving group present in the starting material. Using enantiomeric propargylic chlorides as substrates resulted in opposite enantiomers of allenylphosphonate 92, however, the products ee was reduced to ~93% of that of the reactants. In contradistinction to this, propargylic carbonates were transformed into the corresponding enantiomers of 92 with complete (within the experimental error) stereospecificity.

Additional experiments have revealed that allenylphosphonate 92 was prone to racemization by prolonged heating (in THF, at 68 °C), and this process was substantially accelerated by nucleophilic species, such as Cl⁻, AcO⁻, and palladium(0) (but not palladium(II)) complexes. It is likely that observed racemization occurred via a reversible addition of the nucleophile to the central carbon of the allenic system. Since the reactions with propargylic chlorides took longer time than those with propargylic carbonates (1.5 h vs. 30 min, respectively, see Table 21, entry 3 vs. 4), and in the former case also Cl⁻ ions were present in the reaction mixture, these can account for the observed reduced stereoselectivity when propargylic chlorides were used as substrates. However, one can not exclude a possibility that other factors may also contribute to a partial racemization during the course of the reaction.

76
Scheme 29. Stereochemical correlation of the allenylphosphonates 92 synthesized by the sigmatropic rearrangement and Pd-catalyzed propargylic substitution.

The absolute stereochemistry of the enantiomeric allenylphosphonates 92 was established by comparing their optical rotations with those of 92 enantiomers synthesized via a sigmatropic rearrangement, that is known to be a stereospecific reaction (Scheme 29). The anti-stereochemistry of palladium-catalyzed reaction found was in accordance with the earlier results on this reaction involving carbon nucleophiles.122,123

Scheme 30. Reactions of separate diastereomers of dinucleoside H-phosphonate 53 with propargyl chloride.

Center to axis chirality transfer described above does not exhaust stereochemical features of the allenylphosphonate synthesis. The other equally important aspect is chirality at the phosphorus center. Therefore we
studied a stereochemical course of the investigated reaction, when the starting material contained a stereogenic phosphorus center. To this end, two diastereomeric dinucleoside H-phosphonates, with opposite configurations at the phosphorus, (**R**)-53 and (**S**)-53, were subjected separately to coupling with propargyl chloride under the developed reaction conditions (Scheme 30). It was found that each of dinucleoside 53 diastereomers was transformed quantitatively into the corresponding diastereomer of the product (Scheme 30, (**R**)-111 and (**S**)-111, respectively) and this proved that the palladium-catalyzed process was completely stereospecific, and the configuration at the phosphorus center in the product was determined by the configuration in the starting material. Such outcome was not unexpected, since Pd-catalyzed cross-coupling reactions of H-phosphonates with electrophiles, such as aryl-, vinyl- and benzyl halides, are known to be stereospecific and occur with retention of the configuration at the phosphorus center. It is important to mention that this aspect of the allenylphosphonates synthesis, i.e. control of stereochemistry at the phosphorus atom, is unattainable by the original sigmatropic rearrangement method.

6.5 Reactions of diphenylphosphine oxide with propargylic derivatives

Exclusive formation of allenylphosphonates or allenylphosphinates in the reactions discussed above might indicate that in the ligand exchange step (Scheme 27) H-phosphonates and H-phosphinates acted as hard nucleophiles. To explore a mechanistic part of this Pd-catalyzed reaction, we searched for a softer phosphorus nucleophile that could attack a central carbon atom in the a palladium complex rather than palladium itself (path b in Scheme 27). Indeed, when diphenylphosphine oxide 112 was subjected to the reaction with either propargyl chloride or carbonate in the presence of a palladium(0) catalyst (Table 22) an approximately equimolar amounts of allenylphosphine oxide (113) and bis(phosphine oxide) (114) were obtained (Table 22, entries 1 and 2). Formation of the latter product could be explained assuming mechanism 2b in Scheme 27, a reaction pathway that is favored by soft nucleophiles (e.g. malonate anion). Since steric hindrance at C1 of propargylic substrate should disfavor this mechanistic pathway but not those involving a transmetallation, we expected that reaction of C1-disubstituted derivatives would afford mainly the corresponding allenylphosphine oxides. As it is apparent from entries 3 and 4 in Table 22, the reactions of dimethyl-substituted propargylic substrates
with diphenylphosphine oxide \textsuperscript{112} indeed afforded exclusively the allenylphosphine oxide \textsuperscript{115}.

Table \textsuperscript{22}. Reactions of diphenylphosphine oxide with propargyl derivatives.\textsuperscript{[a]}

\[
\begin{array}{cccccc}
\text{Entry} & \text{Propargylic deriv} & \text{P-nucleophile} & \text{Products} & \text{Reaction time}\textsuperscript{[b]} & \text{Isolated yield} \\
1 & \text{Cl} & \text{Ph-P-Ph} & \text{112} & \text{113 - 42\%} & \text{114 - 31\%} \\
2 & \text{MeO\textsubscript{2}CO} & \text{Ph-P-Ph} & \text{112} & \text{113 - 53\%} & \text{114 - 27\%} \\
3 & \text{Me} & \text{Me} & \text{Ph-P-Ph} & \text{112} & \text{115} & \text{77\%} \\
4 & \text{MeCO\textsubscript{2}Me} & \text{Me} & \text{Ph-P-Ph} & \text{112} & \text{115} & \text{84\%} \\
\end{array}
\]

\textsuperscript{[a]} Reaction conditions: 1.38 mmol propargylic substrate, 1.25 mmol P-nucleophile, 0.019 mmol \text{Pd\textsubscript{2}(dba\textsubscript{3})\textsubscript{3}Cl\textsubscript{3}} (3 mol\% Pd), 0.038 mmol DPEPhos, 5 mL THF (0.25 M), 68 °C; For propargylic chlorides, additionally 1.5 mmol \text{Et\textsubscript{3}N}. \textsuperscript{[b]} >95\% conversion (\textsuperscript{31}P NMR spectroscopy).

\section*{6.6 Synthesis of thio- and seleno- analogs of allenylphosphonates}

To expand scope of this reaction further, we turned our attention to H-phosphonothio- and H-phosphonoseleno diesters, as possible phosphorus nucleophiles, since compounds containing sulfur or selenium bound to the phosphorus are attractive synthetic targets due to their often favorable biochemical properties.\textsuperscript{7,125}

First, the reactions of different propargylic derivatives with a model diethyl H-phosphonothioate (116) were carried out using the developed synthetic protocol (Table \textsuperscript{23}, entries 1-3). Somewhat surprisingly, in contradistinction to diethyl H-phosphonate, that in the reaction with simple
propargylic derivatives produced exclusively allenylphosphonates, the thio congener 116 strayed the reaction towards propargylphosphonothioate derivatives. For primary propargylic compounds containing chloride or carbonate as a leaving group, the reaction afforded a mixture of the desired allenylphosphonothioate (e.g. 117) and the isomeric propargylphosphonothioate (e.g. 118; Table 23, entries 1 and 2). A similar outcome of the reaction was observed with terminally substituted propargyl carbonate (Table 23, entry 3), and also when simple H-phosphonothioate 116 was replaced with more complex dinucleosidic compound 121 (Table 23, entry 4). In the absence of the palladium catalyst, no reaction could be observed between propargylic substrates and H-phosphonothioate 116. These results suggested that for H-phosphonothioate nucleophiles transmetallation of the propargylpalladium(II) complexes became a feasible reaction pathway (Scheme 27, path c).

Since isomeric allenyl- and propargylphosphonothioates turned out to be inseparable using standard experimental techniques, we attempted to suppress formation of undesirable in this study propargylphosphonothioates. On a mechanistic ground, it seemed likely that transmetallation of propargylpalladium(II) complexes should be sensitive to steric hindrance from substituents on C1, and thus mono- and disubstituted propargylic derivatives might favor transmetallation of allenylpalladium(II) species, and in consequence, formation of allenylphosphonothioates. Indeed, the reaction of propargylic derivatives bearing one or two C1-substituents (R1 and R2) with H-phosphonothioate 116 resulted in exclusive formation of allenylphosphonothioates 124 and 125, which were isolated in ca 60% yield (Table 23, entries 5 and 6).

With this knowledge, we decided to examine if more complex H-phosphonothioates also follow this pattern. Therefore, two separate diastereomers of dinucleoside H-phosphonothioate 121, with opposite configurations at the phosphorus center, were subjected to the reaction with a single enantiomer of propargyl carbonate (Table 23, entry 7). To our delight, the synthesis of allenylphosphonothioates (R,Rp)-126 and (R,Sp)-126 was uneventful and completely stereospecific at the phosphorus center, although due to a longer reaction time (2 h), a slight epimerization at the allene moiety occurred.

Finally, a dinucleoside H-phosphonoselenoate 127, also as separate diastereomers, was used as a phosphorus nucleophile in the coupling reaction with propargyl chloride (Table 23, entry 8). In this instance, a rapid, stereospecific reaction (10 min) took place, but in contrast to H-phosphonothioate diesters, only diastereomeric allenylphosphonoselenoates 128 were formed formation.126
### Table 23. Synthesis of allenylphosphonothio- and allenylphosphonoselenoates.\(^{[a]}\)

![Chemical structure](image)

\(Y = \text{S, Se}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Propargylic substrate</th>
<th>P-nucleophile</th>
<th>Product</th>
<th>Reaction time(^{[b]}) (yield)(^{[c]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl-Ch</td>
<td>S</td>
<td>116</td>
<td>5 h(^{[d]})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S-P-O-PEt</td>
<td>117 118</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>MeO₂CO-Ch</td>
<td>S</td>
<td>116</td>
<td>7 h(^{[d]})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S-P-O-PEt</td>
<td>117 118</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MeO₂CO-ChMe</td>
<td>S</td>
<td>116</td>
<td>24 h(^{[d]})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S-P-O-PEt</td>
<td>117 118</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cl-Ch</td>
<td>S-P-O-ODMT-Thy</td>
<td>119 120</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>S-P-O-ODMT-Thy</td>
<td>121 122</td>
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</tr>
<tr>
<td></td>
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<td>S-P-O-ODMT-Thy</td>
<td>123</td>
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</tr>
<tr>
<td>5</td>
<td>MeO₂CO-(\alpha)-C₅H₅</td>
<td>S</td>
<td>116</td>
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<tr>
<td></td>
<td></td>
<td>S-P-O-PEt</td>
<td>117 124</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Cl-ChMe</td>
<td>S</td>
<td>116</td>
<td>1.5 h (64%)</td>
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<tr>
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<td></td>
<td>S-P-O-PEt</td>
<td>117 125</td>
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</tr>
<tr>
<td>7</td>
<td>MeO₂CO-(\alpha)-C₅H₅</td>
<td>S-P-O-ODMT-Thy</td>
<td>121 122</td>
<td>2 h ((R_F) 74% ; (S_F) 71%)</td>
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<tr>
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<td>S-P-O-ODMT-Thy</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Cl-Ch</td>
<td>Se</td>
<td>116</td>
<td>10 min ((R_F) 57% ; (S_F) 67%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Se-P-O-ODMT-Thy</td>
<td>127 128</td>
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<tr>
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<td></td>
<td>S-P-O-ODMT-Thy</td>
<td>123</td>
<td></td>
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</table>

\(^{[a]}\) Reaction conditions: 1.38 mmol propargylic substrate, 1.25 mmol P-nucleophile, 0.019 mmol \(\text{Pd}_3(\text{dba})_3 \cdot \text{CHCl}_3\) (3 mol% Pd), 0.038 mmol DPEPhos, 5 mL THF (0.25 M), 68 °C; for propargylic chlorides additionally 1.5 mmol Et₃N. \(^{[b]}\) >95% conversion \(^{[1]}\)P NMR spectroscopy. \(^{[c]}\) Isolated yield. \(^{[d]}\) Inseparable mixture.
6.7 Catalytic cycle for the Pd(0)-promoted allenylphosphonates formation

The results presented above suggest that the palladium-catalyzed propargylic substitution involving H-phosphonate diesters and related compounds follows a mechanistic pathway similar to that of other nucleophiles. Details of this mechanism are depicted in Scheme 31.

Scheme 31. Proposed mechanism for the palladium-catalyzed propargylic substitution with phosphorus nucleophiles.

The catalytic cycle starts with an oxidative addition of a propargylic substrate to Pd(0) complex in an anti fashion, and this step is responsible for the overall reaction stereochemistry. The rate of the oxidative addition depended on the leaving group X, as well as on the presence of substituents (R^2, R^3) at C1. When the oxidative addition was slow, it became apparently a turnover-limiting step of the reaction, as for example, for propargylic acetates (Table 20, entries 6 and 7) and primary propargylic carbonates (Table 20, entry 3; Table 21, entries 2, 9, 11). In all other cases, the overall reaction rate seemed to be determined by the efficiency of the next, and mechanismly most interesting step, i.e. the ligand exchange (transmetallation).

It has been shown before by means of kinetic (section 3.5.1) and mass spectrometry studies, that formation of Pd(II)-phosphonate complexes from H-phosphonates (ligand exchange) is a multi-step process. First, an H-phosphonate, most likely, attacks the palladium with the phosphonyl oxygen, what increases the acidity of the phosphorus-bound proton and facilitates its abstraction by a base (Scheme 15). The resulting complex, containing
phosphate ligand (O-bonded), then undergoes a rearrangement to a palladiumphosphonate complex (P-bonded).

We believe, that such a course of the ligand substitution is a key to the observed selective formation of allenylphosphonates, in favor of other possible products (i.e. paths a and c vs. path b in Scheme 27, respectively). Somewhat unexpected behavior of H-phosphonates as hard nucleophiles can be explained by the fact that only negligible amounts of a free phosphonate anion are present in the reaction mixture, therefore no products due to its external attack on the allenylpalladium species are formed. The only exception from this trend was the case of diphenylphosphine oxide, that apparently, due to lack of or attenuated back-donation from the C-P bonds, exhibited a higher acidity, enabling formation of larger amounts of the corresponding anion, that can attack the central carbon atom in a Pd-complex (Scheme 27, path b) and lead eventually to the bis(phosphine oxide) formation (Table 22, entries 1 and 2).

Our previous studies on the palladium-catalyzed cross-coupling reactions involving H-phosphonate nucleophiles revealed that ligand exchange often determines the overall rate of the reaction. We have found that the rate of this mechanistic step strongly depends on the kind of the anion present in the Pd(II) complex (sections 3.4 and 3.5). Direct transposition of these findings to the propargylic substitution reaction studied herein seems to be a viable action, as it leads to a plausible explanation of the collected experimental data. Thus, the expected reactivity order of the allenylphosphonate complexes coordinated by different anions, shown in Scheme 31, is consistent with the results in Table 20 (especially, the experiments involving anionic additives were very helpful in that respect – Table 20, entries 8 and 9). In particular, the accelerating effect of the acetate additives (Table 20, entry 9) is in agreement with our previous findings that the palladium(II) complexes bearing an acetate ligand undergo the ligand exchange much faster than those bearing chloride (sections 3.4 and 3.5). Notably, palladium(II) complexes with MeO ligand displayed the highest reactivity, and this made the propargylic carbonates the substrates of choice for this reaction. The increase of the reaction time, when terminally substituted propargylic derivatives (R^1 in Scheme 31) and/or P-nucleophiles bearing bulky groups (R^4, R^5) were used as the substrates, is also fully understandable in this context.

The other aspect possibly connected to ligand substitution step is formation of propargylphosphonothioates as side-products during the coupling of propargyl derivatives with H-phosphonothioates (Table 23, entries 1-4). It has been shown on many occasions that the η^1-allenic and η^1-propargylic palladium complexes in solution may exist in an equilibrium.\textsuperscript{114,123,128} Ma \textit{et al.} reported detailed studies demonstrating that these species can display different preferences towards transmetallation with various nucleophiles and that steric hindrance is a dominating factor.
governing the regioselectivity. In line with these, it is probable that for H-phosphonothioates the ligand exchange is feasible for both of these isomeric complexes, however, introduction of substituents (R$_2$, R$_3$) at C1, efficiently prevents the reaction of the propargylic complex, and ultimately formation of the propargylphosphonothioate derivative. Reason, why H-phosphonoselenoates in the reaction with propargylic compounds afforded exclusively the corresponding allenylphosphonoselenoates remains unclear. However, significantly higher reactivity of these compounds in the investigated reaction than that of H-phosphonate and H-phosphonothioate diesters, indicates on kinetic importance of other factors during the ligand substitution step.

As to reductive elimination, we cannot exclude it as a possible turnover-limiting step of the catalytic cycle, since this Pd-catalyzed propargylic substitution proceeded well only with bidentate, large bite angle phosphine ligands that are known to accelerate reductive elimination from metalphosphonate complexes. In such a scenario, it could be the activation energy for the reductive elimination of the product that determine predominant (or exclusive) formation of allenylphosphonates vs. propargylphosphonates or allenylphosphonothioates vs. propargylphosphonothioates.

Irrespective of these mechanistic aspects, it seems that throughout of the reaction a stereochemical integrity at the phosphorus center is preserved and this results in a stereospecific outcome of the reaction (most likely, retention of configuration).

6.8 Conclusions

We have developed a novel, general method for efficient preparation of allenylphosphonates and related compounds via a Pd(0)-catalyzed S$_N$2’ reaction of propargylic derivatives with H-phosphonate, H-phosphonothioate, and H-phosphonoselenoate diesters or their analogs. Several ligands have been evaluated for their ability to catalyze this C–P bond-forming reaction, and the most efficient catalytic system was found to consist of Pd$_2$(dba)$_3$·CHCl$_3$ as a palladium source and bis(2-diphenylphosphinophenyl)ether (DPEPhos) as a supporting ligand. Some mechanistic aspects of the reaction were investigated and this permitted us to optimize the reaction conditions and suppress side-products formation. The transformation into allenylphosphonates is stereospecific at the phosphorus center (most likely retention of configuration) and occurs with a complete center to axial chirality transfer from the propargyl to the allene moiety. Since both type of substrates used for the reaction, i.e. propargylic compounds and H-phosphonate derivatives and their analogs are easily available, complex organic structures can be generated. This new protocol
may expand the range of biologically important C-P bond-containing analogs with predefined stereochemistry at the phosphorus center and diverse substitution pattern in the allene moiety, that can be prepared under mild conditions and in high efficiency.
The work described in this thesis was aiming at increasing efficiency and scope of the palladium-catalyzed C-P bond-forming reactions. The driving force for the conducted research were growing applications of phosphorus-containing compounds, especially those in biological sciences and medicine. Although primary objectives of the undertaken projects were basic academic research, we always had in mind practical aspects of the studies. Therefore, whenever possible, the applicability of the developed methodologies to the synthesis of biologically relevant structures was demonstrated.

From a point of view of fundamental research, the mechanistic studies performed contributed to filling a gap in the knowledge about the details of the ligand exchange and reductive elimination steps during the C-P bond-forming cross-coupling. The synthetic and kinetic investigations permitted us to elucidate a crucial catalytic role of an acetate ligand in Pd(II) complexes, and to propose two distinctive catalytic cycles, that complemented traditional Pd(0)/Pd(II) mechanistic schemes. This may have important bearing on general organometallic chemistry of the C-P bond formation, both from synthetic and mechanist point of view.

The remarkable rate enhancement of the C-P bond formation in presence of acetate ions, now well understood on the mechanistic ground, laid foundations to the development of a superior procedure for the arylphosphonates synthesis.

In order to further facilitate synthesis of phosphorus-containing compounds via palladium-catalyzed cross-coupling, we investigated also application of microwaves as an energy source. This proved to be exceptionally successful and lead to the development of two new protocols, that enable a rapid access to libraries of diverse compounds, useful for instance, when searching for a lead structure during rational drug design.

The final project – palladium-catalyzed synthesis of allenylphosphonates and related compounds, furnishes an entry to largely unexplored group of C-P bond-containing compounds. Capability of attaching various groups at the phosphorus center, combined with a full control of stereochemistry both at phosphorus and the allene moiety, opens new opportunities for fine tuning of chemical and biological properties of organophosphorus compounds.
Acknowledgements

I would like to express my gratitude to the following people:

My supervisor Prof. Jacek Stawiński for sharing his knowledge, excellent guidance, and great support.

Prof. Jan-Erling Bäckvall for showing interest in this thesis.

Members of the JS group, especially Gaston Lavén, Renáta Hírešová, Agnieszka Bartoszewicz, Asraa Ziadi, Martina Jeżowska, and Linda Söderberg.

Prof. Jesper Wengel for accepting me as an exchange PhD student in his group and being a patient and understanding supervisor during my initial period of the graduate studies.

My collaborators at University of Southern Denmark in Odense: Andreas S. Madsen, Birte Vester, Peter Benediktson, and Lykke Hansen.

Morten B. Hansen, Andreas S. Madsen, Nicolai K. Andersen, Niels Langkjær, Liv Thomsen, Patrick J. Hrdlicka, Santhos Kumar, Tadashi Umemoto, Torben Højland, and Daniel Globisch for making my stay in Denmark unforgettable!

Gaston Lavén for introducing me to the Swedish culture (including my favorite surströmming) and all the fruitful discussions we had.

The TA staff, especially Britt Erikson, Kristina Romare, and Ola Andersson.

All the people at the Department of Organic Chemistry.

All the people who taught me chemistry and more importantly showed how interesting it can be, especially Jan Antoniak, Dr. Jacek Jemieliś, and Prof. Jacek Stawiński.

My countless Green Villa companions, in the order of appearance: Pawel, Luca, Gaston, Martina, …

My friends back in Poland, and ones in Sweden.
My family

Agnieszka for patience and constant support – dzięki.

My daughter Paulina for sleeping just long enough during my paternity leave, so that I could have finished writing this thesis on time.
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126. A very fast reaction involving H-phosphonoselenoate 127 might have suggested an uncatalyzed propargylic $\text{S}_\text{N}_2'$ substitution. This possibility, however, was ruled out since a control reaction without the catalyst resulted in no product formation even after 2 h heating at 60 °C.
