Palladium(II)-Catalyzed Coupling Reactions

JONAS LINDH
Dissertation presented at Uppsala University to be publicly examined in B7:101, Biomedical Centre (BMC), Husargatan 3, Uppsala, Friday, October 15, 2010 at 13:15 for the degree of Doctor of Philosophy (Faculty of Pharmacy). The examination will be conducted in English.

Abstract

Sustainable chemical processes are becoming increasingly important in all fields of synthetic chemistry. Catalysis can play an important role in developing environmentally benign chemical processes, and transition metals have an important role to play in the area of green chemistry. In particular, palladium(II) catalysis includes many key features for successful green chemistry methods, as demonstrated by a number of eco-friendly oxidation reactions catalyzed by palladium(II).

The aim of the work presented in this thesis was to develop novel and greener palladium(II)-catalyzed coupling reactions. In striving to achieve this aim, the first open-vessel, room-temperature palladium(II)-catalyzed oxidative Heck reaction, using oxygen from the air as the reoxidant of palladium, was developed.

In a further investigation of the palladium(II)-catalyzed oxidative Heck reaction, base-free conditions for the transformation were identified and suitable conditions for microwave-assisted oxidative Heck reactions were established.

A convenient and low-cost palladium(II)-catalyzed method for the synthesis of styrene derivatives, by coupling aryloboranes with vinyl acetate, was developed. The reaction mechanism was studied using ESI-MS, which enabled the detection of cationic palladium intermediates in ongoing productive reactions, and a plausible catalytic cycle was proposed.

In an attempt to make the oxidative Heck and the styrene synthesis reactions more attractive from an industrial point of view, conditions for continuous flow synthesis were identified. The results were generally good and rapid synthesis of the desired products was obtained.

The first palladium(II)-catalyzed C–P bond-forming Hirao-type reaction, employing aryloboranes instead of the commonly used aryl halides, was developed. An ESI-MS study was performed, and a plausible catalytic pathway was suggested.

Finally, a novel method for synthesizing aryl ketones from benzoic acids and nitriles, via palladium(II)-catalyzed decarboxylation of the benzoic acids, was established. Further, the reaction mechanism was studied by ESI-MS and a plausible catalytic route presented.

Keywords: Palladium(II), oxidative Heck reactions, Microwaves, Styrenes, Aryl ketones, Continuous flow, ESI-MS

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ISSN 1651-6192
urn:nbn:se:uu:diva-130031 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-130031)
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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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1. Introduction

1.1 Sustainable Chemistry

The majority of organic chemistry processes have a negative impact on the environment. This fact has historically not been an issue of great concern, but since the extensive industrialization that took place in the 20th century, it has become impossible to ignore. The concept of sustainable development, in a broader sense, was introduced by Brundtland in 1987 and was defined as:

“Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs.”

Currently, the development of sustainable chemical synthetic methods, which have less negative environmental impact, is one of the key concerns in all fields of organic synthesis, and especially in large-scale production. The interest in environmentally benign chemical processes is a consequence of increasing general environmental concern. Furthermore, increasing costs and stricter legislation regarding waste handling have provided economic and judicial incentives for developing more efficient processes.

Ideally, a reaction should produce a single product from suitable substrates, without producing any byproducts or leaving any unreacted starting materials. Further, the reaction should not consume any energy or contaminate the surroundings. Regrettably, very few such synthetic reactions have been developed, if any. However, a great deal of effort is being devoted to developing ideal reactions, by following the concepts of sustainable chemistry. These efforts are manifested in the use of less toxic reagents, the use of renewable substrates, more efficient use of energy, restricted use of stoichiometric additives and increased use of catalysis.

Another concept that has evolved in parallel with, and in close relation to, sustainable chemistry, is the green chemistry concept. Green chemistry can be considered a somewhat broader concept than sustainable chemistry, as it also emphasizes the use of methods that are safe for the user. Anastas and Warner have formulated twelve principles of green chemistry to guide chemists in their work.
1. Prevention of waste production rather than clean up of waste produced
2. Design of synthetic methods to maximize the incorporation of all materials used in the process into the final product, *i.e.* atom economy
3. Use of less hazardous or toxic chemicals, regarding human health and the environment
4. Design of safer chemical products
5. Use of safer solvents and auxiliaries
6. Design for energy efficiency to minimize the amount of energy required
7. Use of renewable materials
8. Reduction in the use of derivatives and minimization of the number of synthetic steps
9. Use of catalytic rather than stoichiometric reactions
10. Design of products that are degradable
11. Use of real-time analysis to prevent pollution
12. Use of inherently safer chemistry to prevent accidents

The concept of green chemistry is of great importance in all fields of chemistry, and particularly in the pharmaceutical chemistry, as it produces a disproportionate amount of waste compared to other areas. Catalysis, which had a vital impact on the chemistry developed in the 20th century, has a very important role to play in the development of new, more sustainable/greener chemical processes, *e.g.* by enabling more efficient processes or by replacing stoichiometric reagents.

The principles formulated by Anastas and Warner have, when applicable, served as guidelines in the work described in this thesis.

### 1.2 Palladium Catalysis

Since Wollaston’s discovery of elemental palladium in 1803 it has been employed in, *e.g.* jewelry, pharmaceuticals, photography, electronic components and, most importantly, in catalysis. The late transition metal palladium is extensively used as a catalyst in a number of synthetic transformations and an array of different palladium-mediated methods for the preparation of carbon–carbon and carbon–heteroatom bonds has been developed in recent years, in both homogeneous and heterogeneous catalysis. This thesis is focused on homogeneous palladium(II)-catalyzed coupling reactions, but a brief introduction will be given to certain palladium(0)-catalyzed reactions of particular relevance to the work described.
1.3 Palladium(0) Catalysis

During recent decades an abundance of palladium(0)-catalyzed coupling reactions has been developed. These coupling reactions have found widespread use in many areas of organic chemistry, e.g. medicinal chemistry and the preparation of fine chemicals. Some of the most frequently used palladium(0)-catalyzed coupling reactions are shown in Scheme 1.

![Scheme 1. Palladium(0)-catalyzed coupling reactions](image)

All the coupling reactions presented above have in common that they start each catalytic turnover by oxidative addition of a palladium(0) species to an organohalide (I, Br, Cl) or halide surrogate, e.g. triflate, diazonium salt, tosylate, to generate an organo–palladium(II) species. Generally, organohalides lacking β-hydrogens on sp3 carbons, such as acrylic, vinlylic and benzylic halides, are suitable for organo–palladium formation, whereas β-hydrogen-containing alkyl halides are difficult to use, due to rapid β-hydrogen elimination from the R–Pd(II)–X species. In all the cross-coupling reactions above, but not in the Heck reaction, the second step of the reaction is a transmetallation process. In this process an organic moiety is transferred from a main group metal, e.g. Mg, Cu, Zn, Sn, B or Si, to a metal that is more electronegative, such as palladium. The driving force for this transformation is the formation of a less polar bond, resulting in higher stability of the complexes formed. To complete the catalytic cycle of cross-coupling reactions, reductive elimination takes place.
elimination, the organic moieties must be coordinated to the palladium(II) center in a *cisoid* fashion, which upon reductive elimination is reduced to palladium(0) and a new σ-bond is created between the two organic moieties as they are released from the palladium species.  

1.3.1 The Heck Reaction

In the early 1970s, palladium(0)-catalyzed arylation and vinylation of olefins, using aryl- or alkenyl halides as precursors, was independently reported by Heck and Mizoroki. This pioneering work has since received considerable attention, and the reaction has been vastly improved and developed into a versatile carbon–carbon bond-forming tool in both laboratory and industrial scale synthetic chemistry. Compared to the cross-coupling reactions in Scheme 1, the Heck reaction does not require an organometallic reactant, but employs simple olefins. This important difference has implications for the reaction mechanism, as demonstrated in Scheme 2. As in all palladium(0)-catalyzed coupling reactions, the reaction is initiated by oxidative addition (1) of an organohalide to the palladium(0) species to generate complex B. In the subsequent step (2), an olefin coordinates to the organo–palladium(II) species to form complex $C_\sigma$. Migratory insertion (3) follows to generate a σ-complex $C_\sigma$, which, after internal rotation, undergoes β-hydrogen elimination (4) to generate the substituted olefin, π-coordinated to a palladium–hydride species $D$. The substituted olefin product is released (5) and the starting palladium(0) species A is regenerated from the palladium–hydride complex with the assistance of a base (6).

![Scheme 2. General mechanism for the Heck reaction](image-url)
1.4 Palladium(II) Catalysis

Palladium(II) catalysis differs mechanistically from palladium(0) catalysis and in coupling reactions has often been overshadowed by the significant advances in palladium(0) catalysis. Whereas palladium(0)-catalyzed coupling reactions initially utilize organic oxidants, which are ultimately included in the product, palladium(II)-catalyzed coupling reactions use a terminal oxidant, which is not incorporated into the product. The requirement of a stoichiometric oxidant, in order to make the reaction catalytic with respect to palladium, has hampered the development of palladium(II)-catalyzed transformations. Although some of the industrially most important and longest known transition-metal-catalyzed reactions, such as the Wacker process and the synthesis of vinyl acetate from ethylene and HOAc, are palladium(II)-catalyzed (Scheme 3), the use of palladium(II)-catalyzed coupling reactions has been paid scant attention, until relatively recently. The current rise in interest in palladium(II)-catalyzed coupling reactions probably stems from the increasing demand for greener transformations, and has also extended the scope of available substrates and types of coupling reactions.

Scheme 3. Industrially important palladium(II)-catalyzed processes

The palladium(II)-catalyzed oxidation of alcohols, in which alcohols are oxidized to their corresponding ketones or aldehydes, has been thoroughly investigated and extensively developed during the past decade (Scheme 4). The advances achieved in the area of alcohol oxidation have led to a greater understanding of the mechanistic aspects of palladium(II) catalysis, and have also spurred on research in related palladium(II)-catalyzed reactions.

Scheme 4. Palladium-catalyzed oxidation of alcohols
1.4.1 Reoxidation of Palladium

The first palladium(II)-mediated coupling reactions employed stoichiometric amounts of palladium. As palladium(II)-catalyzed coupling reactions often generate palladium(0) at the end of each turnover, a reoxidant to regenerate palladium(II) is usually required. The greater part of the knowledge acquired on palladium reoxidation has been gained from palladium-catalyzed oxidation of alcohols (Scheme 4).

Commonly used reoxidants are metal salts, such as copper and silver salts, MnO₂, p-benzoquinone, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), desyl chloride and peroxides. The use of copper or silver salts is expensive and p-benzoquinone (p-BQ) is toxic and relatively expensive, as is TEMPO and desyl chloride. All of these reoxidants produce stoichiometric amounts of waste, which may complicate purification procedures and have a negative environmental impact. Hydrogen peroxide, on the other hand, is cheap and produces water as byproduct, but is too strong an oxidant for certain functionalities. The ultimate reoxidant, however, is oxygen, preferably from the air, as it is virtually cost-free and environmentally benign. The use of oxygen as the terminal stoichiometric reoxidant in reactions employing co-catalysts, such as copper in the Wacker process, has been long known. The use of oxygen as the sole reoxidant, on the other hand, is a relatively new strategy. In the early reactions using oxygen as the sole reoxidant, high pressures were often employed, severely hampering the utility of the reactions in laboratory small-scale synthesis.

During the past decade, the mechanistic understanding of oxygen-mediated reoxidation of palladium has increased as a result of important contributions by the groups of Stahl, Sigman, Bäckvall, Jutand and Goddard. This improved understanding of reoxidation has led to improved reactions. Two main reoxidation pathways have been proposed; the palladium(II)-hydride pathway and the palladium(0)-protonolysis pathway (Scheme 5).

In the palladium(II)-hydride pathway, a palladium–hydride intermediate undergoes direct reaction with O₂ to generate a palladium(II)–hydroperoxide intermediate. Protonation of the palladium(II)–hydroperoxide intermediate reforms the palladium(II) catalyst and hydrogen peroxide is released.

As the name implies, the palladium(0)-protonolysis pathway involves the formation of palladium(0). The palladium(0) intermediate is proposed to be generated by reductive elimination of an acid (HX) from the palladium(II)–hydride intermediate. The palladium(0) intermediate is oxidatively added to
O₂ to form a palladium(II)–peroxo intermediate, which then reacts with two equivalents of acid to first provide a palladium(II)–hydroperoxide intermediate and subsequently the initial palladium(II) catalyst and hydrogen peroxide.\textsuperscript{32,59}

Mechanistic investigations have, so far, not been able to provide conclusive evidence for one mechanistic pathway over the other, and it seems likely that either pathway may be possible, depending on the ligands, solvents, additives and substrates used.\textsuperscript{32,54,59}

Scheme 5. Oxygen mediated regeneration of active palladium(II) species

A potentially important palladium(II)-reforming mechanism is the β-elimination of heteroatom groups, such as OAc,\textsuperscript{71} OH, Br and Cl, which generates a palladium(II) salt (Scheme 6),\textsuperscript{72} in contrast to β-hydride elimination, which requires a reoxidant to generate the palladium(II) species. The elimination of heteroatom groups is generally faster than that of hydrogen and can provide an efficient route to catalytic reactions, without the addition of an external reoxidant.

Scheme 6. Palladium(II)-catalyzed phenylation, with reformation of active Pd(II) species by anti-β-acetate elimination\textsuperscript{72}
1.4.2 Formation of Aryl–Palladium Species

In palladium(0) catalysis, the arylating agent is an organic oxidant, such as an arylhalide or a halide surrogate, and the aryl–palladium species is formed through oxidative addition. In palladium(II) catalysis an array of different arylating agents can be employed. The aryl–palladium species can be generated by transmetallation of a number of different aryl-metal or metalloid compounds, e.g. mercury, 73,74 magnesium, 75 lithium, 76 zinc, 77 thallium, 78 tellurium, 79 copper, 74 tin, 21,74,80,81 silicon, 82 phosphorous, 83 antimony, 84 bismuth, 85 arsenic 85 or boron. 86 It is also possible to generate the aryl–palladium species from arenes by C–H activation, 87 or from benzoic acids by decarboxylation. 40 In the work included in this thesis, arylboranes and benzoic acids were employed as aryl–palladium precursors and a more detailed description of these precursors is given below.

Organoboranes

Organoboranes are attractive coupling partners, as they are widely commercially available. Moreover, they are generally relatively tolerant to air and moisture, tolerate a wide variety of functional groups, and are easy to handle. 88 The by-products formed in coupling reactions of organoboranes are usually non-toxic and water soluble, making organoboranes an attractive class of synthetic intermediates from an environmental point of view. 88

Several different organoboranes are used in transition-metal-catalyzed coupling reactions, e.g. organoboronic acids, organoboronic esters and organotrifluoroborates. The most frequently employed organoboranes are organoboronic acids. Organoboranes can be synthesized from a number of different substrates and some examples are presented in Scheme 7.

Scheme 7. Methods for the synthesis of boronic acids
Organoboranes are relatively stable due to the low polarity of the boron–carbon bond (electronegativity of boron 2.0 and carbon 2.5, according to the Pauling scale). Consequently, organoboranes are relatively unwilling to undergo transmetallation with palladium (electronegativity of 2.2). In order for arylboronic acids to become sufficiently reactive for efficient transmetallation with palladium, they require coordination of a Lewis base, to form a tetracoordinated boronate anion, which is more susceptible to transmetallation than the free boronic acid.89

Although organoboronic compounds are fairly stable, they often undergo side reactions during transition-metal-catalyzed coupling reactions. A common side reaction is protodeboronation. Protodeboronation rarely occurs in the absence of a transition metal under neutral conditions, even at elevated temperatures.47 In highly acidic or basic aqueous solutions, on the other hand, protodeboronation may be a fairly fast process.90 Several metal ions, (Cu(II), Ag(I), Zn(II), Ni(II), Pd(II)), can induce protodeboronation in water via the formation of an aryl–metal intermediate.91

Another possible side reaction is the oxidation of boronic acids, providing the corresponding alcohol. Formation of phenols by treating arylboronic acids with hydrogen peroxide was reported by Challenger92 in 1930, and other oxidants such as Oxone93 and sodium perborate94 can also be employed for oxidation. The proposed mechanism for the oxidation of boronic acids in aqueous solution is presented below (Scheme 8).95

![Scheme 8. Oxidation of boronic acids](image)

A side reaction often observed under palladium-catalyzed oxidative conditions is biaryl formation via the homocoupling of arylboronic acids. However, the homocoupling reaction is often relatively slow and constitute a greater problem for sluggish reactions. Moreno-Mañas et al.96 reported their pioneering work on palladium-catalyzed homocoupling of arylboronic acids in 1996 and in 2005 Amatore and Jutand67 published a thorough mechanistic investigation. Their investigation demonstrated that the reaction was palladium(II)-catalyzed and required dioxygen to form the active peroxo–palladium complex, ($\eta^2$-O$_2$)PdL$_2$, generated by the reaction of dioxygen and palladium(0) (Scheme 9).
Scheme 9. Palladium-catalyzed homocoupling of arylboronic acids

Organotrifluoroborate salts are a class of organoboranes, that have gained in popularity during the past five years, due to their low sensitivity to oxidation and nucleophilic substitution. The trifluoroborate salts are easily prepared from their corresponding boronic acids or esters and are easy to purify. Further, organotrifluoroborate salts are often good substrates for the same reaction processes that employ boronic acids, which can be explained by the observed hydrolysis of the trifluoroborate salt to generate the corresponding boronic acid.

Carboxylic Acids
Benzoic acids can function as aryl–palladium(II) precursors. Carboxylic acids are cheap, non-toxic, widely commercially available, stable and easily prepared. Benzoic acids can be synthesized by the oxidation of side chains of an aryl, preferably using oxygen as the oxidant. The possibility of using benzoic acids as aryl–palladium(II) precursors merits attention, as carboxylic acids are more widely commercially available and cheaper than their corresponding transmetallating agents, such as boronic acids. The use of carboxylic acids as substrates in transition-metal-mediated processes has been reported occasionally in the literature during the 20th century. In 1930 Shepard et al. performed copper-mediated protodecarboxylation of halogen-substituted furioic acids under relatively harsh reaction conditions. Nilsson reported copper-mediated decarboxylation in two papers regarding the Ullmann coupling in 1958 and 1966. In 1970, Cohen et al. reported a mechanistic proposal for copper-mediated decarboxylation, and in the same year Sheppard et al. isolated an organocopper intermediate.
formed after decarboxylation. These early reports of copper-mediated decarboxylation did not gain much attention at the time.

During the past decade, a number of efficient catalytic methods for the decarboxylation of benzoic acids have been reported. To form an aryl–metal species from an arylcarboxylic acid and a metal, the carboxylic acid must undergo decarboxylation. Initially, a metal–carboxylate intermediate is formed, which is subsequently converted into an aryl–metal species with the loss of CO₂ (Scheme 10).

Scheme 10. Metal-mediated decarboxylation of benzoic acids

Mono-metallic palladium(II)-catalyzed decarboxylation is usually highly endothermic and difficult to achieve, but can be efficient for certain ortho-substituted benzoic acids, as was demonstrated by Myers in an elegant decarboxylative Heck reaction (Scheme 11). The pioneering work by Myers required stoichiometric amounts of expensive silver salts and high palladium loadings, which limited the usefulness of the reaction. Recently, Su et al. reported a silver-free catalytic system employing p-benzoquinone as the stoichiometric palladium reoxidant, which lowered the cost of the reaction (Scheme 11).

Scheme 11. Palladium(II)-catalyzed decarboxylative Heck reactions

A number of bimetallic catalytic systems (Cu–Pd or Ag–Pd), have been developed, foremost by Goossen, which can expand the range of usable benzoic acids beyond the ortho-substituted. These recent breakthroughs regarding catalytic decarboxylation have been applied in a number of transition-metal-catalyzed coupling reactions, such as the synthesis of biaryls from arylcarboxylic acids and arylhalides in a decarboxylative version of the Suzuki reaction by e.g. Goossen and Becht (Scheme 12).
Scheme 12. Palladium(II)-catalyzed decarboxylative Suzuki reactions

1.5 Oxidative Heck Reactions

In 1968, Heck reported the first palladium(II)-catalyzed arylation of olefins, from arylmercuric chlorides, using catalytic amounts of CuCl₂ and oxygen as the palladium reoxidants. Further, in 1975 Heck reported the first palladium(II)-mediated vinylic substitution of organoboronic acids, sometimes referred to as the oxidative Heck reaction, using stoichiometric amounts of palladium acetate. This coupling reaction was overshadowed by the palladium(0)-catalyzed Heck reaction, and did not receive much attention until the mid 1990s, when Uemura et al. reported the first catalytic protocol using acetic acid as solvent. This pioneering work provided good yields of arylated olefins. Uemura also suggested a mechanistic proposal based on palladium(0)-catalyzed oxidative addition of the arylboronic acids to palladium. In 2001, Mori et al. reported the first method to use a dedicated reoxidant, Cu(OAc)₂, to regenerate Pd(II) from Pd(0), and also concluded that the reaction was palladium(II)-catalyzed and that it was initiated by transmetallation of the arylboronic acid. Cu(OAc)₂ was also successfully employed in the first microwave-assisted oxidative Heck method developed by Larhed et al. As the use of Cu(OAc)₂ as a stoichiometric reoxidant produces stoichiometric amounts of heavy metal salts, it spurred on the search to find more benign and cheaper reoxidants. Jung and Larhed independently discovered that molecular oxygen could be employed as an efficient reoxidant of palladium in oxidative Heck reactions. Larhed also developed the first ligand modulated oxidative Heck reaction, using the nitrogen bidentate phenanthroline ligand dmphen (2,9-dimethyl-1,10-phenanthroline). The use of the dmphen ligand facilitated reoxidation, improved the regioselectivity and reduced the amount of palladium required to catalyze the reaction, presumably by preventing palladium black formation.
Mechanism
Mechanistic insights regarding the oxidative Heck reaction have, to a large extent, been provided by the palladium(0)-catalyzed Heck reaction. A recent mechanistic investigation by our group illuminated some interesting aspects of the reaction, and confirmed many of the previously hypothesized mechanistic steps. A number of palladium-containing intermediates were identified using electrospray ionization mass spectrometry (ESI-MS) and MS/MS to detect cationic palladium complexes directly from the catalytic reaction mixture. Based on the intermediates detected, a plausible catalytic cycle, following the palladium(II)-hydride pathway for palladium(II) reformation, was proposed (Scheme 13). The reaction begins with transmetallation (1) of an arylboronic acid to the palladium(II) catalyst to form the aryl–palladium intermediate B. An olefin coordinates to the aryl–palladium intermediate (2) to form the π-complex, C_π. Migratory insertion (3) generates the σ-complex C_σ, and internal rotation followed by β-hydride elimination (4) generates species D. The arylated olefin is released (5) from intermediate D to form species E. Finally, the starting palladium(II) catalyst, A, is regenerated from the palladium–hydride intermediate, E, using oxygen (6), and hydrogen peroxide is formed. As hydrogen peroxide rapidly oxidizes arylboronic acids to their corresponding phenols, it might be beneficial to add a catalyst, such as MnO_2, which can assist in the decomposition of the hydrogen peroxide formed.

Scheme 13. Proposed catalytic cycle for the oxidative Heck reaction using a bidentate nitrogen ligand and an electron-rich olefin, based on detected cationic palladium species using ESI-MS and MS/MS. 

23
Regioselectivity

The regioselectivity is governed by the steric and electronic properties of the olefin, the aryl–palladium species and the ligand. Electron-poor monosubstituted olefins are arylated in the terminal (β) position, as favored by both steric and electronic factors, to yield the linear arylated product. Electron-rich olefins, with mesomerically donating groups, such as vinyl ethers and enamides, experience counteracting influences from steric and electronic effects. The electronic effects direct the aryl to the internal (α) position, as the electrophilic palladium is more prone to bind to the more electron-rich terminal (β) carbon, while the steric factors direct the aryl to the less sterically demanding terminal (β) carbon. The opposing steric and electronic effects lead to poor regioselectivity, giving mixtures of linear and branched products.

The problem of poor regioselectivity in Pd(0)-catalyzed Heck reactions, using electron-rich olefins, was solved by Cabri. He developed the cationic pathway for the Heck reaction, using bidentate ligands and aryltriflates, as a useful alternative to the commonly employed neutral pathway (Scheme 14). The electronic effects become more important in the cationic pathway, providing a higher selectivity for internally (α) arylated branched products. Recent density functional theory (DFT) calculations have provided further support for this rationale. The cationic pathway can also be accessed by arylhalides by using silver or thallium salts as halide scavengers. Additionally, regioselective methods employing highly polar solvents, such as water–DMF mixtures, ionic liquids or neat water, in the arylation of electron-rich olefins with arylhalides, have recently been reported. The arylation of less polar olefins, such as aliphatic alkenes and styrenes, is mostly directed by steric factors, providing the linear products, but small amounts of branched products are often also obtained as a result of electronic effects.

Scheme 14. The neutral and the cationic pathways
The selectivity of the oxidative Heck reaction follows the same pattern as the palladium(0)-catalyzed Heck reaction, i.e. the regioselectivity is determined by the insertion of the olefin, and the E/Z-selectivity is governed by sterical factors in the \textit{syn}-\beta-elimination step (Scheme 15).\cite{38,39} However, post isomerization of the product to the thermodynamically most stable product often occurs.\cite{14}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme15.png}
\caption{Mechanistic proposal explaining the regioselectivity outcome in the oxidative Heck reaction using electron-rich and electron-poor olefins}
\end{figure}

1.6 Styrene Synthesis

Styrene is one of the most important monomers in the petrochemical industry, with a worldwide production of approximately 20 million tons per year. The major part is produced by the dehydrogenation of ethyl benzene, catalyzed by potassium-promoted iron oxide, and the styrene formed is used mainly in the production of different polymeric materials, \textit{e.g.} polystyrene.\cite{140}

Styrene derivatives are also frequently used on a more moderate scale as substrates for \textit{e.g.} oxidation,\cite{141} metathesis\cite{142} and Diels-Alder reactions.\cite{143} To meet this demand several transition-metal-catalyzed coupling methods have been developed. The aromatic moiety in these coupling reactions is generally introduced by oxidative addition of an aryl halide to the metal used. A number of palladium(0)-catalyzed coupling reactions have been reported, where aryl halides are used as the aryl source, \textit{e.g.} in Hiyama,\cite{144} Stille,\cite{145} Suzuki,\cite{146} and Heck\cite{147} type reactions (Scheme 16).
Scheme 16. Palladium(0)-catalyzed styrene synthesis using aryl halides

All these reactions have drawbacks. The vinyl silicon substrates used in Hiyama coupling are expensive. The Stille reaction is unattractive due to the toxicity of organic stannanes and the often complicated purification. In Suzuki-type styrene synthesis, the cost of the trivinylcyclotriboroxane is high. The Heck reaction with aryl halides and ethylene suffers from problems associated with the handling of flammable pressurized gases.

Arylboronic acids can provide styrenes by Suzuki coupling with vinyl halides. Unfortunately, vinyl halides have low boiling points and vinyl iodide is the only vinyl halide that is liquid at atmospheric pressure. Unfortunately, vinyl iodide suffers from low stability. The problem of handling gaseous vinyl halides was elegantly circumvented by Monterio et al. by in situ generation of vinyl bromide, using 1,2-dibromoethane as the vinylic precursor (Scheme 17). Skrydstrup et al. recently reported a smooth Suzuki coupling reaction in which vinyl tosylates and arylboronic acids were coupled to generate styrenes using a preformed catalyst containing dimethylaminomethyl ferrocene palladacycle and bis(2-norbornyl)phosphine ligands (SK-CC02-A, Scheme 17). The lack of commercially available vinyl tosylates limits the use of this procedure.

Scheme 17. Palladium(0)-catalyzed styrene synthesis using arylboronic acids
1.7 C–P Bond Formation

Extensive advances have been achieved in the area of carbon–heteroatom bond formation in recent decades. Most of the advances have been made in palladium-catalyzed C–N and C–O-forming reactions. The formation of C–P bonds, on the other hand, has received relatively little attention. Given the importance of organophosphorus compounds in, e.g. medicinal chemistry, agriculture and transition metal catalysis, there is a need for efficient methods of synthesizing organophosphorus compounds. In addition, ways of forming C–P bonds are highly important in the destruction of chemical weapons, which although they are prohibited, are still present in vast amounts awaiting suitable methods of destruction.

The formation of carbon–phosphorus bonds has been known since the late 19th century; it was discovered by Michaelis, and soon after further developed by Arbuzov. The Michaelis-Arbuzov reaction, in which trialkyl phosphites react with alkyl halides, leads to the formation of phosphonates. In order to achieve reactions with aryl or vinyl halides, the addition of a transition metal is required. The palladium(0)-catalyzed reaction of aryl and vinyl bromides with dialkyl phosphites was developed by Hirao in the early 1980s, and has found extensive use in medicinal chemistry (Scheme 18). Stille developed the first direct phosphine synthesis by cross-coupling reactions between trimethylstannyl-diphenylphosphines or trimethylsilyldiphenylphosphines and aryl iodides, using a palladium catalyst (Scheme 18).

![Scheme 18. Carbon–phosphorus bond-forming reactions](image)

This section focuses on the Hirao-type coupling, as it is of the greatest relevance to my work in the area. The Hirao coupling has been extensively developed and thoroughly studied from a mechanistic point of view. These mechanistic studies support a catalytic cycle (Scheme 19) initiated by oxidative addition (1) of an arylhalide to the Pd(0) catalyst A, to form aryl–palladium complex B. In the following step (2), the phosphorus nucleophile coordinates to the aryl–palladium species to generate complex C. The H–phosphonate diester is deprotonated with a base (3) and complex D is formed, which subsequently undergoes reductive elimination (4) to produce the aryl phosphonate product.
1.8 Aryl Ketone Synthesis

Aryl ketones are a common functionality in many types of organic compounds. As a result of their widespread use, aryl ketones can be prepared from a number of different substrates, by a wealth of methods. This thesis focuses mainly on palladium-catalyzed synthesis of aryl ketones from carboxylic acids.

Classic aryl ketone synthesis from carboxylic acids or acid derivatives generally requires harsh reaction conditions, and consequently there is a need for milder preparative routes in the production of fine chemicals. Based on the recent advances in transition-metal-catalyzed decarboxylation, a number of palladium-catalyzed methods for preparing aryl ketones from carboxylic acid derivatives and arylboronic acids have been reported (Scheme 20). In 2001, Goossen reported a synthetic route in which carboxylic acids are converted, \textit{in situ}, to more active anhydrides with pivalic anhydride, and then coupled with arylboronic acids to generate the aryl ketone (a, Scheme 20). This reaction was subsequently further developed by Yamamoto and Goossen, independently, by replacing pivalic anhydride with dimethyl dicarbonate, as the activating reagent (b, Scheme 20). When using dimethyl dicarbonate, more volatile side products such as CO$_2$ and methanol are formed.

A bimetallic catalytic system was developed by Goossen, in which \(\alpha\)-oxocarboxylates were coupled with aryl bromides to generate aryl ketones (c, Scheme 20). In this process, the \(\alpha\)-oxocarboxylates are decarboxylated by the copper catalyst to form an acyl–copper intermediate, while oxidative addition of the aryl bromide to the palladium catalyst generates an aryl-palladium intermediate. Subsequent transmetallation of the acyl–copper to

Scheme 19. Proposed catalytic cycle for the palladium(0)-catalyzed cross-coupling of aryl halides with dialkyl phosphites
the aryl–palladium yields an aryl–palladium–acyl intermediate, and the aryl ketone is formed by reductive elimination. These reactions all require activation of the carboxylic acids to more reactive derivatives, such as anhydrides, which in turn requires stoichiometric additives. A limitation of these coupling reactions is their use of boronic acids or halides, as they essentially restrict the possible coupling moieties to aryls or vinyls, due to the fast β-elimination when employing alkylboronic acids or alkyl halides in palladium-catalyzed coupling reactions.

Scheme 20. Formation of aryl ketones by coupling of arylboronic acids or aryl bromides with carboxylic acids

Larock et al. reported the elegant synthesis of aryl ketones from the coupling of arenes or arylboronic acids with nitriles, followed by hydrolysis of the ketimine formed (Scheme 21). This constitutes a more benign and convenient alternative to commonly employed Grignard reagents in the synthesis of aryl ketones from nitriles. The Larock method has been further developed with less harsh conditions employing milder solvents and arylboronic acids as arylating agents. The use of unfunctionalized arenes is commendable in many respects, e.g. low cost, high atom economy and low environmental impact, but suffers from one major drawback; poor
regiocontrol. This does not pose a severe problem for certain substrates, but it may be insurmountable for others. The use of arylboronic acids offers regiocontrol and a broad scope, but their cost is higher and they are less commercially available than arenes.

**Scheme 21.** Formation of aryl ketones by palladium(II)-catalyzed coupling of arenes or arylboronic acids to nitriles

### 1.9 Microwave-Assisted Organic Synthesis

The chemical industry in general and the pharmaceutical industry in particular, is under increasing pressure to produce new compounds, rapidly and in a sustainable way. Microwave-assisted organic synthesis can be of help in satisfying these demands. The use of microwave irradiation as a means of heating reactions in organic synthesis has gained enormously in popularity over the past decade, and is no longer a peculiarity, but rather standard procedure.

Research in microwaves took off in the 1940s, with the development of aircraft radar. There are several anecdotes concerning how the effect of microwaves on food was discovered by the accidental exposure of food to microwaves from radar devices. The first commercial microwave ovens for food processing were introduced in 1947 and are today indispensible. Their use in organic synthesis came much later, possibly due to the misconception that microwaves were only suitable for heating water. 1986 saw the first reports on the use of microwaves in organic synthesis. These pioneering studies were performed in domestic microwave ovens,
without the possibility of controlling or monitoring the reaction temperature or pressure, making the reactions dangerous and difficult to reproduce. By the mid 1990s, dedicated organic synthesis microwave reactors started to appear, enabling the reactions to be carefully controlled, thereby improving reproducibility and safety. The availability of commercial microwave reactors in the past decade has led to a dramatic increase in microwave-assisted organic synthesis, and microwave reactors are today standard laboratory equipment in most pharmaceutical and in many academic laboratories.

1.9.1 Theoretical Background

Electromagnetic radiation with frequencies ranging from 0.3 to 300 GHz is called microwaves. As microwaves are also used for radar and telecommunication, certain restrictions are necessary to avoid interference between different applications. Consequently, microwave heating has been assigned the frequency of 2.45 GHz. The energy from radiation of this frequency is sufficient to efficiently heat most reaction mixtures, but too low to break any chemical bonds.185,186

Microwave heating differs from classical conductive heating, (e.g. oil baths and heating mantles), as heat is generated inside the sample, providing rapid and relatively uniform heating. The heat can be generated by two main mechanisms when irradiating liquids and solutions: ionic induction and dipolar polarization.186 Ionic induction can only take place in a solution that contains ions. When the solution is exposed to an electric field, the ions are forced to oscillate through the solution by the applied electric field. The kinetic energy gained by the ions is converted into heat, as a result of an increase in collision rate.186 Dipolar polarization affects radiated dipoles, which try to align themselves in accordance with the applied electric field. Dipoles experiencing low-frequency irradiation will rotate in phase with the oscillating electric field. This complete, in-phase alignment will lead to the molecules gaining some energy, but the heating effect will be small. If the dipoles are subjected to a high-frequency electric field, on the other hand, they will not have sufficient time to respond to the oscillating field and no heating will occur. If the electric field is at an intermediate frequency, efficient heating can occur. At a suitable frequency, the dipoles will have enough time to respond to the alternating electric field and rotate, but not long enough to precisely follow the field, which will cause a phase difference between the dipole and the electric field. The phase difference will cause the conversion of kinetic energy into heat by molecular friction and collisions. This is referred to as dielectric heating.186
1.10 Continuous Flow Chemistry

In continuous flow chemistry, the reaction is performed in a constantly flowing stream rather than in a batch. Continuous flow chemistry has been employed in the industrial large-scale production of pharmaceuticals, agrochemicals and polymers, but has remained relatively unexplored on the small scale, until recently.\textsuperscript{187,188} Through the introduction of microreactors and other small-scale flow reactors, the use of continuous flow chemistry in organic synthesis is developing into an area of intensive research.\textsuperscript{189-199} The interest in continuous flow chemistry is justified by several beneficial qualities. As the reaction mixture is constantly pumped through the reaction chamber only a small fraction of the total amount of reagents will react at a time, making it safer than a batch reaction, and also enabling an array of reaction parameters to be evaluated using only small amounts of reagents.\textsuperscript{187,188} Furthermore, the product formed can be rapidly extracted and stored under suitable conditions. The reaction can be monitored online, which facilitates optimization of the reaction, and multi-step reactions can be carried out in sequence, which may be beneficial for reactions in which unstable intermediates are formed. Scaling up the reaction is simple, either by allowing the reaction to flow for a longer time, or by scaling out \textit{i.e.} running several reactions in parallel.\textsuperscript{187,188}

Continuous flow chemistry has one major limitation: the reagents, catalysts and products must be soluble. This drawback may be avoided in certain types of reactions, particularly in catalysis. If the catalyst is insoluble or only partially soluble it can be immobilized in the reactor.\textsuperscript{187}

1.11 Electrospray Ionization Mass Spectrometry

ESI-MS has emerged as an increasingly important analytical technique over recent decades.\textsuperscript{200-202} It is probably the mildest ionization technique available for mass spectrometry, and it provides a robust but sensitive tool for studying non-volatile and thermally labile biomolecules\textsuperscript{203} and organometallic species.\textsuperscript{127,204-210} Development and research in the areas of ESI and MS are extensive, and no attempt will be made here to cover this enormous field. However, a brief overview of the techniques that I have benefitted from will be given below.

To be able to separate and detect analytes in a mass spectrometer, ions of the analytes have to be present in the gas phase. ESI utilizes electrical energy to transfer ions from a solution into the gas phase. Somewhat simplified, this can be divided into the following four steps: 1) nebulization of a sample solution into electrically charged droplets, 2) solvent evaporation, 3)
liberation of ions from droplets and 4) transportation of ions from the ionization source region into the analyzer. A somewhat more detailed description is given below.\textsuperscript{200,202,211}

In the ESI source, a continuous flow of the sample solution is passed through a capillary tube, which is usually maintained at a high voltage relative to the inlet of the mass spectrometer (Figure 1). Under the force of the electric field, the ions in solution will migrate, leading to charge separation. Ions of the same polarity as the capillary tube migrate towards the surface of the liquid front. Electrostatic forces between the ions and the counter-electrode, \textit{i.e.} of opposite charge (the mass spectrometer inlet), causes the liquid surface to bend into a cone shape (Figure 1).\textsuperscript{202,211} When the forces creating the cone shape exceed the surface tension of the liquid, charged droplets will be formed and a spray of highly charged droplets, with the same polarity as the capillary, will be emitted. In positive mode, the capillary acts as an anode and attracts anions, while the cations are forced to the liquid surface. In order to promote aerosol formation a nebulizing gas can be applied (Figure 1).\textsuperscript{202,211} The electrostatic attraction between the ions and the counter-electrode will draw the charged droplets towards the mass analyzer. The droplet size is continuously reduced by evaporation of the solvent using a drying gas or an elevated ESI source temperature, until the droplets reach a critical size, at which the repulsion due to an excess of either positive or negative ions will cause the droplets to explode and form smaller daughter droplets (Figure 1). This process will continue, either until ions are released directly into the gas phase, or until single molecules remains in very small droplets, which are allowed to enter the vacuum chamber of the mass spectrometer.\textsuperscript{200,202,211}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{esystem.png}
\caption{Schematic diagram of the electrospray system in positive mode}
\end{figure}
When the ionic species have been transferred from solution into the gas phase, they can be sampled and detected by a mass analyzer, where quadrupole mass analyzers are the most commonly used. A very useful advance is tandem mass spectrometry (MS/MS), which, in combination with an ESI interface, can provide structural information about the adduct ions from their fragmentation patterns. In order to perform an MS/MS experiment, three quadrupoles are arranged in a linear fashion (Figure 2). In the first quadrupole (Q1), the analyte ion of interest (precursor ion) is selected based on its \( m/z \) ratio. The selected ion is exposed to a collision gas in the second quadrupole (Q2), where kinetic energy is converted into internal energy, and fragmentation is initiated. This process is known as collision-induced dissociation (CID). The resulting fragment ions from CID, which are related to the molecular structure of the precursor ion, are separated by a third quadrupole (Q3).

![Figure 2. Schematic diagram of a triple-quadrupole mass spectrometric system](image)

Many mechanistic investigations have been carried out on transition-metal-catalyzed reactions based on techniques such as NMR, kinetic measurements, X-ray, cyclic voltammetry, isotopic labeling and computational studies. No single technique is ideal when it comes to mechanistic investigations. Several of the techniques mentioned above require stoichiometric amounts of the catalyst, changes in the reaction, simplified conditions or the isolation of postulated intermediates. In online ESI-MS, fully productive catalytic systems can be monitored directly from the reaction mixture. ESI-MS enables the detection of intact, short-lived, unstable and sensitive reaction intermediates, even at very low concentrations. These properties are valuable for investigations of transition-metal-catalyzed reactions and ESI-MS has been successfully employed in a number of mechanistic investigations. Charged palladium-containing complexes are particularly well suited for ESI-MS studies, as they have a characteristic and easily identified natural isotopic distribution (Figure 3). A number of palladium-catalyzed reactions have been studied by ESI-MS, e.g. the Heck and the Suzuki reactions.
As stated above, no technique, including ESI-MS, is perfect. Neutral complexes cannot be detected, and all the complexes detected might not be part of the catalytic cycle (i.e. resting state). These problems can sometimes be circumvented. In the case of neutral complexes, a permanently charged ligand can be added. To investigate whether a detected complex is catalytically active (or in a resting state), the complex can be isolated by “ion-trapping” and allowed to react with a suitable substrate. Detection of the expected product “confirms” the role of the complex as active in the catalytic cycle.\textsuperscript{212}
2. Aims of the Present Study

The main aim of the work presented in this thesis was to study palladium(II)-catalyzed coupling reactions, with the emphasis on developing new and greener methods. The specific aims were as follows.

- To develop a room-temperature oxidative Heck reaction, utilizing oxygen from the surrounding air as the palladium reoxidant.
- To identify suitable conditions for a base-free oxidative Heck reaction, that can be performed at room temperature or with microwave heating, and to scale up the reaction.
- To develop a method for the synthesis of styrene derivatives from arylboranes and vinyl acetate.
- To study the base-free oxidative Heck reaction and the styrene synthesis method under continuous-flow conditions.
- To develop a palladium(II)-catalyzed method for arylation of dialkyl phosphite using arylboranes.
- To employ benzoic acids and nitriles in the synthesis of aryl ketones.
3. Open-Air Oxidative Heck Reactions at Room Temperature

3.1 Overview

The concept of green chemistry has gained importance in recent years, following the general increase in environmental concern. Green chemistry covers more than environmental impact, it also includes the safety of the user.2-7 The hitherto developed oxidative Heck reaction protocols do not fulfill many of the requirements of green chemistry, which inspired us to develop a greener oxidative Heck method. The use of molecular oxygen as reoxidant, previously reported by our group38,39 and by Jung et al.124 constitutes an important advance compared to copper(II) salts, and certainly meets the demand of being environmentally benign, but is not as good from the point of view of safety or convenience, as it involves the handling of gas tubes. By using oxygen from the surrounding air both risk and costs can be reduced, and convenient open-vessel conditions can be employed. As the oxygen content in air is relatively low (~21%), sufficient mass transport of oxygen into the reaction mixture may pose problems. In order to overcome this, reaction vessels, which allowed for a large surface area (round bottom flasks) and vigorous stirring, were employed. The possibility of performing the reactions at room temperature was investigated, as this would be advantageous regarding the safety and convenience of the process. Further, performing reactions at ambient temperature would be beneficial for substrates with sensitive functionalities and would in addition save energy.

3.1.1 Ligand Screening

The use of ligand-modulated oxidative Heck reactions has recently been introduced by our group, but no screening of suitable ligands has been previously published.38 By identifying a suitable ligand, the reaction can be optimized with regard to yield, reaction rate, reoxidation efficiency and regioselectivity. The stability of phenanthroline ligands under oxidative conditions and their ability to facilitate palladium reoxidation, as demonstrated in the oxidation of alcohols34 and in a recent ligand-modulated oxidative Heck method,38 render them promising ligand candidates.
A test reaction containing $p$-tolylboronic acid (1c) (2 mmol), $n$-butyl acrylate (2a) (1 mmol), N-methylmorpholine (NMM) (2 mmol) as base, Pd(OAc)$_2$ (0.02 mmol) and ligand (0.024 mmol) was used to evaluate a series of eight ligands (Table 1). The ligands were evaluated based on the isolated yield of the cinnamate product (4c) and the reaction rate (Table 1). All reactions were allowed to reach full conversion (defined as complete consumption of olefin 2a according to GC-MS). Each of the seven bidentate ligands yielded productive reactions, whereas monodentate pyridine (3a) gave no product at all (Table 1). The bipyridine ligands 3b and 3c both provided relatively efficient and high-yielding reactions (Table 1, entries 2 and 3), although the reaction with 3c had to be performed at room temperature to avoid the formation of palladium black. The use of phenanthroline (3d) resulted in a relatively sluggish and poor-yielding reaction (Table 1, entry 4). Previously employed dmphen (3e) proved efficient and resulted in a high isolated yield of 4c of 94% (Table 1, entry 5). The bisphenylated phenanthroline, bathocuproine (3f), also provided a high-yielding and relatively fast reaction, as did the related water-soluble 3g (Table 1, entries 6 and 7). Surprisingly, the oxidatively sensitive phosphine ligand, dppp (1,3-bis-(diphenylphosphino)propane) (3h), gave a good yield of 4c of 81% (Table 1, entry 8). As the reactions were conducted in open vessels, and acetonitrile is known to absorb moisture, the impact of water content on the outcome of the reaction was investigated by running the reaction in a 95:5 water:acetonitrile mixture. The reaction was considerably slower, but still provided a reasonable amount of product (Table 1, entry 5). Based on reaction rate and the isolated yield of product 4c, dmphen (3e) was selected as the ligand for further investigations.
Table 1. Ligand screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (h)</th>
<th>Yielda (%)</th>
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<tr>
<td>1</td>
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<td>35</td>
<td>8</td>
<td>3h</td>
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</table>

Reaction conditions: Open vessel charged with p-tolylboronic acid (2.0 mmol), n-butyl acrylate (1.0 mmol), N-methylmorpholine (2.0 mmol), Pd(OAc)2 (0.02 mmol), ligand (0.048 mmol 3a or 0.024 mmol 3b-h) and MeCN (3 mL) under vigorous stirring. a Isolated yield, >95% pure according to GC-MS.

3.1.2 Olefin Screening

After having identified dmphen as a suitable ligand, a range of different olefins was evaluated using p-tolylboronic acid (1c) as the aryl–palladium precursor, at both ambient temperature and at 60-80 °C (Table 2). Both electron-poor and electron-rich olefins provided good yields, although the reaction times for the different olefins varied considerably. The temperature had relatively little impact in the outcome of the reaction, except in the arylation of butyl vinyl ether (2g), where a considerably lower yield was obtained at room temperature (Table 2, entry 7). As expected, the reaction temperature had considerable impact on the reaction rate; elevated temperatures drastically increased the reaction rates. Sterically hindered olefins, such as disubstituted 2b and 2h, reacted sluggishly, indicating a possible limitation of the scope of olefins (Table 2, entries 2 and 8). The regioselectivity of the reactions was mainly controlled by electronic factors, as would be expected from the use of bidentate ligands under halide-free cationic conditions,131 where electron-poor olefins provided terminal products (4-6), and electron-rich olefins gave branched products (8-10).
Somewhat unexpectedly, the electron-poor olefins displayed a high reactivity relative to the electron-rich olefins. To further investigate this preference a series of competitive experiments was performed. A reaction containing equal amounts of electron-poor $n$-butyl acrylate ($2a$) and electron-rich $N$-vinyl-2-pyrrolidinone ($2f$) was performed in an open vessel at room temperature (Table 3). Product formation was monitored by NMR, confirming the more rapid formation of the cinnamic ester ($4c$), than the
enamide product (9), which is in complete contrast to the results obtained in palladium(0)-catalyzed Heck reactions with aryl triflates under cationic conditions.125,126

Table 3. Competitive experiments

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Yield 4c(^\text{a})</th>
<th>Yield 9(^\text{a})</th>
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<td>80%</td>
<td>30%</td>
<td>2.8</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>92%</td>
<td>33%</td>
<td>2.7</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>99%</td>
<td>41%</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Reactions conditions: open vessel charged with \(p\)-tolylboronic acid (1.5 mmol), N-vinyl-2-pyrrolidinone (0.5 mmol), \(n\)-butyl acrylate (0.5 mmol), N-methylmorpholine (2.0 mmol), Pd(OAc)\(_2\) (0.02 mmol), dmphen (0.024 mmol) in MeCN (3 mL) under vigorous stirring at room temperature. \(^\text{a}\) NMR yield.

3.1.3 Arylboronic Acid Screening

To investigate the scope and limitations of arylboronic acids, thirteen arylboronic acids were coupled with \(n\)-butyl acrylate (2a). As can be seen in Table 4, electron-rich arylboronic acids (1a-d) were more productive than electron-deficient boronic acids, in agreement with previous reports and recent DFT calculations on the oxidative Heck reaction.39 The electron-rich arylboronic acids provided good to excellent yields of arylated acrylate, while electron-deficient arylboronic acids resulted in good to usable yields. Even \(p\)-acetylphenylboronic acid (1j), which has previously been reported to be inert in oxidative Heck coupling with \(n\)-butyl acrylate (2a), provided a good yield of 4j of 61% (Table 4, entry 10).39 Bromo-substituted arylboronic acids 1f and 1g provided good yields of 4f and 4g, without any traces of palladium(0)-catalyzed formation of the Suzuki or Heck products (Table 4, entries 6 and 7). The excellent chemoselectivity, observed as the absence of palladium(0)-catalyzed product formation, indicates smooth reoxidation of palladium and efficient transmetallation. To further investigate the efficiency of the aerobic reoxidation system, a reaction starting from a palladium(0) source (Pd\(_2\)(dba)\(_3\)) was performed (Table 4, entry 3). The yield obtained was as high as when starting from a palladium(II) source, again demonstrating the efficiency of the reoxidation system. As expected, complete inhibition of the catalytic turnover was observed when performing the reaction under an atmosphere of nitrogen (Table 4, entry 3).
Table 4. Arylboronic acid screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acid</th>
<th>Product</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>60</td>
<td>72</td>
<td>82</td>
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<td>rt</td>
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<td>13</td>
<td></td>
<td></td>
<td>60</td>
<td>95</td>
<td>50</td>
</tr>
</tbody>
</table>

Reaction conditions: Open vessel charged with arylboronic acid (2.0 mmol), n-butyl acrylate (1.0 mmol), N-methylmorpholine (2.0 mmol), Pd(OAc)$_2$ (0.02 mmol), dmphen (0.024 mmol) and MeCN (3 mL) under vigorous stirring. a Isolated yield, >95% pure according to GC-MS. b 0.01 mmol Pd$_2$(dba)$_3$ instead of Pd(OAc)$_2$. c Sealed vessel purged with nitrogen. d Open vessel charged with arylboronic acid (100 mmol), n-butyl acrylate (50 mmol), N-methylmorpholine (100 mmol), Pd(OAc)$_2$ (1 mmol), dmphen (1.2 mmol) and MeCN (50 mL) under vigorous stirring.
4. Base-Free Oxidative Heck Reactions

4.1 Overview

All of the oxidative Heck reactions developed so far have been conducted in the presence of a base (e.g. NMM, K$_2$CO$_3$), which is added to make the boronic acids more susceptible to transmetallation. In a recent mechanistic study performed by our group an intermediate leading to a Suzuki-type homocoupled biaryl byproduct was detected.$^{127}$ There were indications that the choice of base had a decisive impact on both oxidative Heck and Suzuki-type product formation. To further investigate the influence of different bases, the model reaction described in Paper I was chosen, and a number of different bases were screened (Scheme 23).

![Scheme 23. Model reaction for base screening](image)

Bases known to promote Suzuki or oxidative Heck reactions, with a wide span in base strength and structure, were investigated. Strong bases such as sodium hydroxide resulted in very little oxidative Heck product formation, but extensive biaryl formation was observed. As the use of a weak base such as sodium acetate provided a high yield of the desired oxidative Heck product, a reaction was performed without the addition of a base. The result of this base-free reaction greatly surpassed our expectations, resulting in a reaction that was both higher yielding and faster than any of the base-promoted reactions. Additionally, and equally important, no trace of biaryl formation was detected. During the work described in this paper, Jung et al. reported the first base-free oxidative Heck reaction, employing the previously utilized dmphen ligand and molecular oxygen as reoxidant.$^{213}$ The use of molecular oxygen is, however, inconvenient, expensive and hazardous, compared to the use of oxygen from the surrounding air.
4.1.1 Arylboronic Acid Screening

Encouraged by the outcome of the base-free test reaction, an investigation of the scope of the coupling with respect to the aryl coupling partner was performed. An array of arylboronic acids, ranging from electron-rich to electron-poor, was successfully vinylated with n-butyl acrylate (Table 5). Interestingly, all reactions except entry 2 provided higher yielding and faster reactions than the NMM base-promoted method described in Paper I (Table 5). It is noticeable that electron-deficient arylboronic acids (1j, 1p and 1h) benefitted significantly from the base-free conditions, providing the cinnamic ester products at excellent yields. To verify the scalability of the method, a large-scale experiment, in which 50 mmol of 2a was arylated with 1c, produced a 97% yield of product 4c (Table 5, entry 3).

Table 5. Arylboronic acid screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acid</th>
<th>Product</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1n</td>
<td>4n</td>
<td>rt</td>
<td>24 h</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>15 min</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>1d</td>
<td>4d</td>
<td>rt</td>
<td>18 h</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>15 min</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>4c</td>
<td>rt</td>
<td>18 h</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>12 min</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>4e</td>
<td>rt</td>
<td>24 h</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>12 min</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>4b</td>
<td>rt</td>
<td>48 h</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>12 min</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>4f</td>
<td>rt</td>
<td>24 h</td>
<td>93</td>
</tr>
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<td></td>
<td></td>
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<td>100</td>
<td>12 min</td>
<td>69</td>
</tr>
<tr>
<td>7</td>
<td>1j</td>
<td>4j</td>
<td>rt</td>
<td>72 h</td>
<td>92</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>12 min</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>1h</td>
<td>4h</td>
<td>rt</td>
<td>48 h</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>12 min</td>
<td>65</td>
</tr>
</tbody>
</table>

Reactions at room temperature: Open vessel charged with arylboronic acid (2.0 mmol), n-butyl acrylate (1.0 mmol), Pd(OAc)₂ (0.02 mmol), dmphen (0.024 mmol) and MeCN (3 mL) under vigorous stirring.

Reactions at elevated temperatures: Pyrex glass vial charged with arylboronic acid (1.0 mmol), n-butyl acrylate (0.5 mmol), p-benzoquinone (0.5 mmol), Pd(OAc)₂ (0.01 mmol), dmphen (0.012 mmol), MeCN (2 mL), sealed under air and exposed to microwave irradiation. *Isolated yield with purity > 95% (GC-MS). +Open vessel charged with arylboronic acid (100 mmol), n-butyl acrylate (50 mmol), Pd(OAc)₂ (1 mmol), dmphen (1.2 mmol) and MeCN (100 mL) under vigorous stirring.

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As the conditions developed in this work bear a strong resemblance to the palladium(II)-catalyzed methods used for the oxidation of alcohols, it was deemed interesting to investigate the chemoselectivity using a boronic acid substituted with a benzylic hydroxyl group (1o). Using our Pd(II)-dmphen-air catalytic system, product 4o was isolated at a yield of 83%, without any traces of oxidation products in the form of aldehydes or the corresponding benzoic acid derivatives. When the same reaction was carried out under an atmosphere of pure oxygen, a 4:1 mixture of the vinylated aryl alcohol 4o and the aldehyde 4p was produced at a total yield of 75%, demonstrating a reduction in chemoselectivity using molecular oxygen as the reoxidant (Scheme 24).

![Scheme 24. Investigation of chemoselectivity using oxygen from the air and molecular oxygen](image)

As rapid and efficient transformations are highly desirable in modern organic chemistry, attempts were made to speed up the reactions using microwave irradiation. Small-scale microwave reactions (~5 mL) are commonly carried out in single-mode synthesizers using septa-sealed reaction vessels with a restricted head-space. The limited head-space severely complicates the use of large amounts of gases, such as the use of air as the reoxidant of palladium(0). This compelled us to search for an alternative reoxidant. Pure oxygen would require a substantially smaller gas volume and thus lower pressure. However, the use of oxygen gas with a flammable solvent in sealed vessels during microwave heating is a hazardous combination, therefore the use of neat water as solvent was investigated. The use of water as solvent initially seemed promising for the reaction between 1c and 2a, providing 4c at a yield of 74% (Table 6, entry 1), but it resulted in lower yields of 7a (60%) and 16a (10%) (Table 6, entries 9 and 12), and the water–oxygen combination was therefore abandoned. Previously employed Cu(OAc)₂ is not a viable option in the dmphen-modulated oxidative Heck reaction, as dmphen efficiently coordinates to copper,²¹⁴,²¹⁵ resulting in low catalytic activity, poor reoxidation of palladium and low regioselectivity with electron-rich olefins.
Hydrogen peroxide, which would be a tempting benign alternative, is known to oxidize boronic acids to their corresponding phenols, and is therefore not suitable as a reoxidant in these transformations.\textsuperscript{47,48} As none of the reoxidants above was appropriate, \textit{p}-benzoquinone was investigated.\textsuperscript{43} To assess the efficiency of \textit{p}-benzoquinone, the room-temperature reaction between \textit{1c} and \textit{2a}, with the addition of 1 equivalent of \textit{p}-benzoquinone, was carried out under an atmosphere of nitrogen, which resulted in an excellent isolated yield of product \textit{4c} of 94\% (Table 5, entry 3). The simple addition of 1 equivalent of \textit{p}-benzoquinone enabled direct transformation of the open-vessel method into a rapid microwave-promoted method. The open-vessel room-temperature reactions listed in Table 5 were successfully repeated under microwave conditions, using \textit{p}-benzoquinone as the reoxidant. At a temperature of 100 °C, the reaction times were reduced from days to 10-20 minutes. The yields remained essentially the same or higher, except for the reaction of acetalboronic acid \textit{1b}, which was partially hydrolyzed at the higher temperature (Table 5, entry 5).

4.1.2 Olefin Screening

After the successful coupling of a number of arylboronic acids to \textit{n}-butyl acrylate (\textit{2a}), an investigation of the scope of olefins was performed. Nine different olefins, ranging from electron-rich to electron-poor, were subjected to arylation with one electron-rich (\textit{1c}), and one electron-deficient boronic acid (\textit{1j}). The reactions were performed both at room temperature under open-vessel conditions, and at 100 °C under microwave irradiation. All room-temperature reactions between the electron-rich boronic acid \textit{1c} and the different olefins resulted in good yields. When performing the same reaction under microwave conditions, the reaction time needed to reach full conversion was considerably shorter, while the yields were essentially unchanged or improved, except for the arylation of olefins \textit{2j}, \textit{2k} and \textit{2m}, which provided lower yields (Table 6, entries 6, 8 and 14). Arylation with electron-deficient boronic acid, \textit{1j}, also benefitted from microwave heating in terms of shorter reaction times and higher yields; most dramatically in the reactions with olefins \textit{2i} and \textit{2f} (Table 6, entries 5 and 13).
Table 6. Olefin screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Product</th>
<th>T. (°C)</th>
<th>Time</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>1c</td>
<td>rt</td>
<td>24 h</td>
<td>68%</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>2d</td>
<td>rt</td>
<td>24 h</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>5b</td>
<td>120 °C</td>
<td>1 h</td>
<td>79%</td>
</tr>
<tr>
<td>4</td>
<td>2i</td>
<td>12a</td>
<td>rt</td>
<td>24 h</td>
<td>71%</td>
</tr>
<tr>
<td>5</td>
<td>2i</td>
<td>12b</td>
<td>rt</td>
<td>120 °C</td>
<td>22 min</td>
</tr>
<tr>
<td>6</td>
<td>2j</td>
<td>13a</td>
<td>rt</td>
<td>24 h</td>
<td>62%</td>
</tr>
<tr>
<td>7</td>
<td>2j</td>
<td>13b</td>
<td>rt</td>
<td>48 h</td>
<td>63%</td>
</tr>
</tbody>
</table>

Reactions at room temperature: Open vessel charged with arylboronic acid (2.0 mmol), olefin (1.0 mmol), Pd(OAc)₂ (0.02 mmol), dmphen (0.024 mmol) and MeCN (3 mL) under vigorous stirring. Reactions at elevated temperatures: Pyrex glass vial charged with arylboronic acid (1.0 mmol), olefin (0.50 mmol), Pd(OAc)₂ (0.01 mmol), dmphen (0.012 mmol), p-benzoquinone (0.50 mmol), MeCN (2 mL), sealed under air and exposed to microwave irradiation.

a Isolated yield with purity > 95% (GC-MS).
b 1.0 equivalent of p-benzoquinone, under N₂.
c Water as solvent, molecular oxygen as reoxidant.
d 5 mmol scale, p-benzoquinone as reoxidant.
e 5a:5b 95:5 (GC-MS). Yield based on 5a:5b mixture.
f 5a:5b 90:10 (GC-MS). Yield based on 5a:5b mixture.
g 5c:5d 95:5 (GC-MS). Yield based on 5c:5d mixture.
h 5c:5d 85:15. Yield based on 5c:5d mixture. i α/β 20:80 (GC-MS). Yield based on α/β mixture.

4.1.3 Microwave Scale-Up

As a reaction under the room-temperature, open-vessel conditions had been successfully scaled up (Table 5, entry 3), it was considered interesting to investigate the possibility of scaling up the reactions under microwave
conditions. To scale up the reactions a multimode, one-vessel, batch-type reactor, with a maximum output of 1200 W, efficient overhead stirring, a 350 mL Teflon reaction vessel and the possibility of introducing pressurized gases during irradiation, was employed. A medium-scale (5 mmol) reaction was performed in a 20 mL sealed reaction vessel using a single-mode reactor, to verify the safety and productivity of the reaction under scaled-up microwave conditions (Table 6, entry 1). The 5 mmol reaction was safely executed and the product 4c was isolated at a yield of 91%, allowing further investigations of the large-scale reactions to proceed. Two 50 mmol-scale reactions were performed to verify the scalability of the p-benzoquinone-promoted reactions, which both resulted in good yields (Scheme 25). However, stoichiometric use of p-benzoquinone is not a viable option for large-scale synthesis, as it produces stoichiometric amounts of waste. Consequently, after having established the efficiency of the large-scale reaction using p-benzoquinone, the reaction using oxygen from the air as reoxidant was studied (Scheme 25). When introducing pressurized air (4 bar) into the sealed reaction chamber at a temperature of 100 °C, the yield of the reaction between 1c and 2a was isolated in 95% after 20 minutes of irradiation (Scheme 25). A second large-scale reaction between 1j and 2b was also successfully carried out, giving a yield of 88% (Scheme 25).

\[
\begin{align*}
\text{CO}_2\text{Bu} \quad \text{B(OH)}_2 & \quad \frac{50 \text{ mmol}}{100 \text{ mmol}} \\
\text{2b} & \quad \text{1c} & \quad \text{Pd(OAc)}_2 (2 \text{ mol%}) & \quad \text{dmphen} (2.4 \text{ mol%}) \\
\text{MeCN, 100 °C, 20 min} & \\
\text{5a} & \quad 90 : 10 & \quad 91\% \\
\text{CO}_2\text{Bu} \quad \text{B(OH)}_2 & \quad \frac{50 \text{ mmol}}{100 \text{ mmol}} \\
\text{2b} & \quad \text{Ac} \quad \text{1j} & \quad \text{Pd(OAc)}_2 (2 \text{ mol%}) & \quad \text{dmphen} (2.4 \text{ mol%}) \\
\text{MeCN, 100 °C, 20 min} & \\
\text{5c} & \quad 85 : 15 & \quad 87\% \\
\text{CO}_2\text{Bu} \quad \text{B(OH)}_2 & \quad \frac{50 \text{ mmol}}{100 \text{ mmol}} \\
\text{2a} & \quad \text{1c} & \quad \text{Air (4 bar)} & \\
\text{MeCN, 100 °C, 20 min} & \\
\text{4c} & \quad 95\% \\
\text{CO}_2\text{Bu} \quad \text{B(OH)}_2 & \quad \frac{50 \text{ mmol}}{100 \text{ mmol}} \\
\text{2b} & \quad \text{Ac} \quad \text{1j} & \quad \text{Air (4 bar)} & \\
\text{MeCN, 100 °C, 20 min} & \\
\text{5e} & \quad 85 : 15 & \quad 88\% \\
\end{align*}
\]

Scheme 25. Large-scale oxidative Heck reactions using microwave irradiation

4.1.4 Outlook

Since the publication of this work, a number of important contributions in the area of oxidative Heck reactions have been reported. Xiao et al. recently developed a method of performing base-free oxidative Heck reactions, using acetone as solvent, in which no dedicated reoxidant was added. They hypothesized that acetone would act as a hydrogen acceptor and obviate the
need for reoxidants, as in a previously published method by Darses et al., using a rhodium catalyst.\textsuperscript{217} However, acetone did not serve as a hydrogen acceptor, but electron-poor olefins appeared to act as hydrogen acceptors, resulting in stoichiometric production of reduced olefins.\textsuperscript{216} The method of Xiao et al. is beneficial for reactions using oxidatively sensitive substrates.

A number of attempts to perform asymmetric oxidative Heck reactions have been reported. Mikami et al. developed an asymmetric oxidative Heck reaction, using the phosphine ligand (S,S)-chiraphos, Pd(OAc)$_2$ and molecular oxygen, to arylate cyclopent-1-enecarboxylate derivatives.\textsuperscript{218} However, the scope of the method was very limited, and only the electron-poor arylboronic acid $p$-trifluoromethylphenylboronic acid could be coupled in reasonable yields and modest enantiomeric excess.\textsuperscript{218} In 2007, Gelman and co-workers reported a method for asymmetric arylation of 2,3-dihydrofuran, using (R)-BINAP or (R)-MeO(biphenylphosphine) as ligands, and Cu(OAc)$_2$ as stoichiometric reoxidant. The results were fairly good for phenylboronic acid, but the reaction was sensitive to steric effects.\textsuperscript{219} Jung et al. developed asymmetric oxidative Heck reactions using a pregenerated oxazoline–palladium complex, to arylate two different acyclic olefins, providing good product yields, but modest enantiomeric excess.\textsuperscript{220} Recently, Jung and co-workers employed chiral tridentate carbene NHC-amidate-alkoxide ligands in oxidative Heck coupling. The use of chiral tridentate ligands has, with some substrates, resulted in relatively high enantiomeric excess for reactions performed under an oxygen atmosphere.\textsuperscript{221,222}
5. Synthesis of Styrenes by Palladium(II)-Catalyzed Vinylation of Arylboranes Using Vinyl Acetate

5.1 Overview

Small-scale synthesis of styrenes often requires relatively expensive reagents, inconvenient and hazardous reaction setups or multistep reactions. Convenient, low-cost synthesis should, however, be possible using a palladium(II)-catalyzed Heck-type reaction between arylboronic acids and vinyl acetate. This reaction should proceed without the addition of a base or an external reoxidant, as β-acetate elimination will regenerate the active palladium(II) species, thus, providing a low-cost, simple and sustainable route to styrene derivatives, on a small scale.

5.1.1 Reaction Optimization

As a point of departure, a model reaction was used under microwave heating at 140 °C for 30 minutes in sealed vessels, employing 4-biphenylboronic acid (1q, 1 mmol) and vinyl acetate (10 mmol) as substrates, to investigate the influence of different ligands and solvents (Table 7).

Previously employed dmphen resulted in a poor yield of styrene 17q, extensive protodeboronation of 1q to generate 18q, and also led to the formation of styryl ester 19q (Table 7, entry 1). The bidentate phosphine ligand dppp soon emerged as the most promising ligand, and was investigated in combination with a variety of different solvents (Table 7, entries 6, 10-16). Although phosphine oxidation was expected as a potential problem, the use of an inert atmosphere was not necessary. Satisfactory results were obtained using dppp as ligand and DMF as solvent, providing 75% of styrene 17q and only 6% of the undesirable 18q (Table 7, entry 6). Somewhat surprisingly, only trace amounts of the styryl ester 19q were formed and no stilbene-type product, resulting from a second oxidative Heck arylation, was detected.
Table 7. Optimization of reaction parameters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Isolated yield&lt;sup&gt;a&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dmphen</td>
<td>DMF</td>
<td>5 2 17</td>
</tr>
<tr>
<td>2</td>
<td>dmphen</td>
<td>MeCN</td>
<td>14 8 14</td>
</tr>
<tr>
<td>3</td>
<td>PPh₃</td>
<td>DMF</td>
<td>3 4 n.d.</td>
</tr>
<tr>
<td>4</td>
<td>P(o-tol)₃</td>
<td>DMF</td>
<td>trace 5 n.d.</td>
</tr>
<tr>
<td>5</td>
<td>dppe</td>
<td>DMF</td>
<td>43 17 trace</td>
</tr>
<tr>
<td>6</td>
<td>dppp</td>
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<td>75 6 trace</td>
</tr>
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<td>dppb</td>
<td>DMF</td>
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</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>none</td>
<td>DMF</td>
<td>n.d. trace n.d.</td>
</tr>
<tr>
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<td>dppp</td>
<td>DMF</td>
<td>57 7 trace</td>
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<sup>a</sup> Isolated yield, >95% pure according to GC-MS.

<sup>b</sup> No catalyst added.

<sup>c</sup> 0.2 mmol Pd(OAc)₂ and 0.22 mmol dppp were used.

<sup>d</sup> 0.1 mmol Pd₂(dba)₃ was used as Pd-source. n.d. = not detected by GC-MS analysis of the crude mixture.

A time-temperature investigation was performed with the aim of reducing the reaction time and increasing the yield of styrene 17q (Table 8). A time of 30 min and a temperature of 140 °C were found to provide a consistently high yield of 17q in the model reaction. Extending the reaction time to 60 min resulted in a moderate improvement in the yield (80 vs. 79%) (Table 8, entries 4 and 5). Accordingly, 30 min of microwave heating at 140 °C were chosen as the standard conditions. To study the robustness of the reaction with respect to reaction temperature, a reaction was performed in a sealed vessel at room temperature. The reaction time required to reach full conversion was long (72 h), but the yield of the isolated product was good, 71% (Table 8, entry 8).

A number of reactions were performed with the aim of establishing the optimal amount of vinyl acetate with respect to the 17q:18q ratio (Table 8, entries 9-13). The use of 10 equivalents of vinyl acetate was identified as the optimal amount, as smaller amounts increased the formation of 18q and larger amounts had no positive impact on the 17q:18q ratio (Table 8, entry 13).
Table 8. Optimization of reaction parameters

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<thead>
<tr>
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<th>Temp. (°C)</th>
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<th>Yield 17qb(%)</th>
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<tr>
<td>13</td>
<td>140</td>
<td>30 min</td>
<td>15</td>
<td>90:10</td>
<td>71c</td>
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Reaction conditions: A 5 mL Pyrex glass vial was charged with 1q (1.0 mmol), vinyl acetate (2.0-15 mmol), Pd(OAc)₂ (0.02 mmol), dppp (0.022 mmol) and DMF (2 mL). The vial was thereafter sealed under air and exposed to microwave irradiation. a Determined by GC-MS and ¹H NMR. b Isolated yield, >95% pure according to GC-MS. c Stirred at room temperature. d Yield not determined.

5.1.2 Organoborane Screening

Having identified suitable reaction conditions, ten arylboronic acids were subjected to vinylation. All the arylboronic acids were vinylated and good yields were obtained (Table 9). The yield of chloro-functionalized 17s was 71%, without any side product formation from palladium(0) activation (Table 9, entry 2). No trend, based on substitution pattern, could be observed for the ortho-, meta- or para-biphenylboronic acids, the yields of which were 78-82% (Table 9, entries 4-6). To broaden the scope of coupling partners, four different aryltrifluoroborates were tested. With the addition of 2 mmol of sodium TFA (CF₃COONa), the aryltrifluoroborates provided useful reactions, although the styrene derivatives were generally obtained at slightly lower yields than in the reactions with their corresponding arylboronic acids. Finally, a vinylboronic acid was successfully vinylated to generate the corresponding diene (17x) at a yield of 64% (Table 9, entry 15).
Table 9. Organoborane screening

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Product</th>
<th>Yield(^a)</th>
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Reaction conditions: A 5 mL Pyrex glass vial was charged with 1 (1.0 mmol), vinyl acetate (10.0 mmol), Pd(OAc)\(_2\) (0.02 mmol), dppp (0.022 mmol) and DMF (2 mL). The vial was thereafter sealed under air and exposed to microwave heating for 30 min at 140 °C. \(^a\) Isolated yield, >95% pure according to GC-MS. \(^b\) 20 (1 mmol), NaTFA (2 mmol) was used as an additive.

5.1.3 Mechanistic Study

As this reaction has not been reported in the literature previously, it was interesting to study the reaction mechanism. It was hypothesized that two different arylation pathways were possible (Scheme 26): either a) ethylene is first generated from Pd-β-acetate elimination of vinyl acetate and subsequently undergoes an oxidative Heck reaction, or b) styrene formation occurs by carbopalladation of vinyl acetate, followed by styrene formation through Pd-β-acetate elimination.
To investigate which pathway was in operation, a mechanistic study was performed using ESI-MS analysis to detect cationic palladium-containing intermediates in ongoing reactions. The mechanistic investigation was initiated by studying the room-temperature reaction depicted in Table 8, entry 8. An aliquot was withdrawn from the reaction mixture after 6 h and quickly diluted with DMF. The ESI-MS(+) spectrum was immediately recorded by scanning the first quadrupole (Q1) of a triple-quadrupole instrument. Several groups of signals corresponding to the characteristic isotopic pattern of cationic monopalladium complexes were identified (Figure 4).

![Scheme 26. Plausible vinylation pathways](image)

All the detected palladium-containing complexes were subjected to MS/MS(+) by selecting the isotopic ions with the strongest and the second strongest intensity from each complex (corresponding to $^{106}\text{Pd}$ and $^{108}\text{Pd}$, respectively). By analyzing the information from the MS and MS/MS experiments, proposals for the structures of the complexes could be made (Table 10). Based on the fragmentation pattern, certain assumptions were made regarding the structure of possible complexes with the same $m/z$. The
complex with $m/z=605$ for $^{106}$Pd, which was separated (Q1) and fragmented (Q2), resulting in a detected signal at $m/z=577$, corresponding to the mother ion minus 28 mass units, which indicates the loss of ethylene. The loss of ethylene is followed by the loss of HOAc ($m/z=60$). This MS/MS CID pattern supports the assignment of structure $B_{n2}$ to the complex with $m/z=605$ (Table 10). The CID pattern of the ion with $m/z=699$ supports the structural assignment of palladium–hydride $H_{n2}$, due to the loss of the $\pi$-coordinated styrene product. The ion with $m/z=757$ was assigned the $I_{n1}$ structure due to the loss of the styrene product ($m/z=180$) followed by the loss of HOAc ($m/z=60$).

To further validate the proposed structures, a series of additional reactions was analyzed by ESI-MS and MS/MS. Each component in the reaction was replaced, one at a time, by a chemical equivalent, thus providing the analogous palladium(II) complexes, but with different $m/z$ ratios. Boronic acid $1q$ was replaced by $1l$, DMF by DMSO, vinyl acetate by vinyl propionate, and dppp for the related $(2S,4S)$-(-)-2,4-bis(diphenylphosphino)-pentane. All the replacement reactions were catalytically active and provided the corresponding styrene derivatives at yields of 36-68%. All previously assigned intermediates were supported by identification of the analogous intermediates with the chemical equivalents.

As a final verification experiment, vinyl acetate was replaced by fully deuterated vinyl acetate ([D$_6$]vinyl acetate), affording [D$_3$]17$q$, with no detection of deuterium-hydrogen scrambling, at a yield of 59%. Structures of the detected palladium-containing signals were proposed (Table 10), and the previous structural assignments of all the ethylene-, vinyl acetate- and styrene-containing ionic complexes were supported.
Table 10. Mono-charged cationic palladium(II) complexes detected by ESI-MS

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<th>m/z</th>
<th>Pd(II)-complex</th>
<th>m/z</th>
<th>Pd(II)-complex</th>
<th>m/z</th>
<th>Pd(II)-complex</th>
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<th>Pd(II)-complex</th>
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<td>1383</td>
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<sup>a</sup> Reported m/z values based on \(^{106}\text{Pd}\), dppp as ligand and 1q as the aryl substrate (Ar). <sup>b</sup> Structures supported by MS/MS(+) analysis. <sup>c</sup> Reported m/z values based on \(^{106}\text{Pd}\), dppp as ligand, 1q as the aryl substrate (Ar) and [D6]vinyl acetate.

The \(m/z=605\) signal in Table 10 indicates arylation of ethylene and not vinyl acetate (pathway a, Scheme 26), as MS/MS showed the structural composition of the \(\pi\)-intermediate \(B_{n2}\). This is further supported by the [D6]vinyl acetate study, in which the CID pattern of the analogous ionic complex with \(m/z=612\) \(^{106}\text{Pd}\) \([D_7]B_{n2}\), indicates the dissociation of [D4]ethylene (loss of \(m/z=32\)), followed by the loss of [D3]HOAc (\(m/z=63\)) (Table 10). The CID pattern of the ionic complex with \(m/z=699\), with the loss of styrene product to give a signal with \(m/z=519\), assigned as \(H_{n2}\), was also supported by the [D6]vinyl acetate study, as it generated a signal with \(m/z=520\), corresponding to the [D1]palladium–hydride complex.

Although all the detected cationic palladium complexes might not be catalytically active, the results from the ESI-MS study support pathway a in Scheme 26, in which ethylene is first produced from vinyl acetate and thereafter arylated. Based on the proposed structures of the detected palladium complexes, a plausible reaction mechanism is suggested, as depicted in Scheme 27. Association (1) of vinyl acetate with a palladium–hydride complex affords the charged \(\pi\)-intermediate \(B_{n1}\), followed by migratory insertion (2) and \(\beta\)-elimination (3) of the acetate to produce species \(B_{n2}\). Associative transmetallation (4) with an arylboronic acid and intermediate \(B_{n2}\) would generate the \(H_{n1}\) species. Alternatively, and perhaps less likely, olefin dissociation may generate free ethylene and intermediate C, or possibly the acetate may dissociate leaving the ethylene coordinated to the palladium (resulting in an undetected intermediate). It is reasonable to assume that transmetallation (5) then occurs, leading to the formation of the
intermediates D-G, followed by coordination (6) of the olefin to generate the cationic π-intermediate H_{π1}. Migratory insertion (7) is followed by β-hydride elimination (8) to form complex H_{π2}, which dissociates (9) to give the free styrene product and a palladium–hydride species. Alternatively, complex B_{π1} might be generated directly from complex H_{π2} in an associative ligand exchange process. The required initial formation of a palladium–hydride might result from oxidative Heck arylation of vinyl acetate, with Pd-β-hydrogen elimination instead of Pd-β-acetate elimination providing trace amounts of product 19q (Table 7). This source of palladium–hydride is supported by the [D₆]vinyl acetate study and the detection of [D₇]B_{π2} using ESI-MS. The excess vinyl acetate and the high reactivity of the unsubstituted ethylene probably explain the selectivity for monoarylation.

Scheme 27. Proposed mechanism based on the detection of cationic palladium complexes using ESI-MS
6. Continuous Flow Oxidative Heck Reactions

6.1 Overview

Continuous-flow processing is an emerging technique in organic synthesis, which can be employed to quickly deliver target products on different scales. As we are working on improving oxidative Heck reactions and making them more accessible on larger scales, we turned to continuous-flow processing. A number of palladium(0)-catalyzed coupling reactions with arylhalides have been investigated under continuous-flow conditions, whereas palladium(II)-catalyzed coupling reactions with arylboranes remain unexplored. Fortunately, we were given the opportunity to investigate our previously developed oxidative palladium(II)-catalyzed reactions under continuous-flow conditions using a commercially available flow reactor.

6.1.1 Styrene Synthesis

The styrene synthesis method described in Paper III was investigated under the catalytic conditions employed previously (2 mol% Pd(OAc)$_2$, 2.2 mol% dpdp) with $p$-acetylphenylboronic acid and vinyl acetate, as the model reaction. By using two sample loops, one loaded with a reactant solution containing $p$-acetylphenylboronic acid (0.5 M) and vinyl acetate (5 M) in DMF, and the other with a catalyst solution consisting of Pd(OAc)$_2$ (0.01 M) and dpdp (0.011 M) in DMF, which were simultaneously pumped through a T-inlet and into the preheated reaction chamber (2 mL, 1 mm inner diameter), optimization of residence time and reaction temperature could be easily carried out. The optimization experiments showed that full conversion of $p$-acetylphenylboronic acid was obtained with a residence time of 2 min at 150 °C, providing the desired styrene derivative at an isolated yield of 86% (Table 11, entry 10). No traces of acetophenone, resulting from protodeboronation of $p$-acetylphenylboronic acid, or the corresponding stilbene, resulting from an oxidative Heck reaction between the styrene formed and the boronic acid, were detected, possibly as a result of the short interaction time between the boronic acid and the palladium catalyst. The absence of side product formation under continuous-flow conditions constitutes a considerable advantage over previously performed batch reactions. To investigate the scope of the method, twelve additional boronic acids were vinylated (Table 11). All the reactions were catalytically
productive, providing moderate to good yields of the desired styrene derivatives. Both electron-rich and electron-deficient boronic acids were tolerated, and no clear trend was observed based on electronic factors. Although the reaction temperature was relatively high, the potentially palladium(0) labile carboxybenzyl amino protecting group was unaffected (Table 11, entry 5). The reaction between p-methoxyphenylboronic acid (1n) and vinyl acetate was successfully scaled up, giving a 77% yield of the corresponding styrene (Table 11, entry 4).

Table 11. Arylboronic acid screening

<table>
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<th>Product</th>
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Reaction conditions: Arylboronic acid (1 mmol, 0.5 M), vinyl acetate (10 mmol, 5 M), Pd(OAc)₂ (0.02 mmol, 0.01 M), dppp (0.022 mmol, 0.011 M) in DMF, 150 °C, residence time 2 min. a Isolated yield, >95% pure according to LC–MS and ¹H NMR spectroscopy. b Reaction carried out on a 10 mmol scale.

6.1.2 Oxidative Heck Arylation of Olefins

Having established the conditions for efficient styrene synthesis under continuous flow with vinyl acetate, efforts were directed towards identifying
suitable conditions for the oxidative Heck arylation of other olefins. Using the previously developed microwave conditions (Paper II), 2 mol% Pd(OAc)$_2$, 2.2 mol% dmphen and 1 equivalent of $p$-benzoquinone were employed in the coupling of $p$-acetylphenylboronic acid (1j) and $n$-butyl acrylate (2a) as a test reaction. As the amount of protodeboronation in the styrene synthesis reactions was low, arylboronic acid was used as the limiting reactant, resulting in a more cost- and atom-efficient reaction. The previously employed reaction conditions with dmphen as ligand proved unstable, as the catalyst stock solution precipitated with time and could only be stored for a few hours at room temperature. Replacing dmphen by dppp provided a stable catalyst solution, capable of promoting the desired reaction. One of the two sample loops was loaded with a catalyst solution consisting of Pd(OAc)$_2$ (0.005 M), dppp (0.0055 M) and $p$-benzoquinone (0.25 M) in DMF, and the other loop with a reactant solution containing $p$-acetylphenylboronic acid (0.25 M) and $n$-butyl acrylate (0.5 M) in DMF. Optimization of reaction temperature and residence time showed that full conversion was afforded after 5 min residence time at 130 °C, providing an 85% isolated yield of the desired cinnamic ester (Table 12, entry 8). To investigate the scope of the method, a number of arylboronic acids were coupled with $n$-butyl acrylate (Table 12). Both electron-rich and electron-deficient boronic acids were well tolerated, and afforded the cinnamic esters at moderate to good yields. Once again, the sensitive carboxybenzyl-protected aniline served as a useful arylating agent, providing the desired product at a yield of 81% (Table 12, entry 3). Also bromo-substituted 1af proved a useful substrate, without any detectable palladium(0)-catalyzed bromine activation (Table 12, entry 7).

To expand the scope of the reaction, a number of arylboronic acids were coupled with electron-rich $n$-butyl vinyl ether (Table 13). As expected with the use of a bidentate ligand under cationic conditions, the reactions were highly regioselective in providing the internally arylated products. The products were hydrolyzed and isolated as the corresponding methyl ketones giving moderate to good yields (Table 13).
### Table 12. Arylboronic acid screening

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<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
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Reaction conditions: Arylboronic acid (0.5 mmol, 0.25 M), 2a (1 mmol, 0.5 M), p-benzoquinone (0.5 mmol, 0.25 M), Pd(OAc)<sub>2</sub> (0.01 mmol, 0.005 M), dppp (0.011 mmol, 0.055 M) in DMF, 130 °C, residence time 5 min. <sup>a</sup> Isolated yield, >95% pure according to LC-MS and 1H NMR spectroscopy.

### Table 13. Arylboronic acid screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arylboronic acid</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Entry</th>
<th>Arylboronic acid</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
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Reaction conditions: Arylboronic acid (0.5 mmol, 0.25 M), 2g (1 mmol, 0.5 M), p-benzoquinone (0.5 mmol, 0.25 M), Pd(OAc)<sub>2</sub> (0.01 mmol, 0.005 M), dppp (0.011 mmol, 0.055 M) in DMF, 130 °C, residence time 5 min. Subsequent hydrolysis with 1 M HCl (aq). <sup>a</sup> Isolated yields >95% pure according to LC–MS and 1H NMR spectroscopy. <sup>b</sup> Residence time 10 min.
Finally, the possibility of synthesizing stilbene derivatives, by a sequential, two-step continuous-flow process, was explored. By employing the electron-rich arylboronic acid 1n and the electron-deficient 1ac, and altering the reaction step in which they take part, two different stilbene products were obtained as an effect of the electron-density of the intermediately formed styrene (Scheme 28). The results were in agreement with the expected regioselectivity for arylation of styrenes under cationic conditions.\textsuperscript{125,224}

\textbf{Scheme 28.} Two-step continuous-flow processes
7. Palladium(II)-Catalyzed C–P Bond Formation

7.1 Overview
Following the pioneering work of Hirao\textsuperscript{157,158} on palladium(0)-catalyzed arylation of dialkyl phosphites, several efficient methods for palladium(0)-catalyzed C–P bond formation have been developed.\textsuperscript{163,165} Aryl and vinyl phosphonates have found extensive use in \textit{e.g.} polymer and medicinal chemistry, and are also important in the development of phosphine ligands.\textsuperscript{152-154} Although considerable advances have been made in the palladium(0)-catalyzed P–arylation of arylhalides, the corresponding palladium(II)-catalyzed coupling with arylboranes has not been explored. Based on our findings from the oxidative Heck reactions, we decided to investigate the possibility of using arylboronic acids and aryltrifluoroborates, as less environmentally harmful aryl–palladium precursors, in a palladium(II)-catalyzed C–P bond-forming reaction with dialkyl phosphites.

7.1.1 Reaction Optimization
Based on a previously developed protocol (Paper II), a test reaction was performed using Pd(OAc)\textsubscript{2} (4 mol%) and dmphen (6 mol%) as the catalytic system, and \textit{p}-tolylboronic acid (1 mmol) and diethyl phosphite (0.5 mmol) as substrates. A number of reoxidants (0.5 mmol), solvents (2 mL) and reaction temperatures were investigated using sealed vessels and 30 min of microwave irradiation (Table 14). \textit{p}-Benzoquinone was identified as the most efficient reoxidant and DMF as a suitable solvent. Running the reaction at 100 °C resulted in a good yield of 89% of P–arylated product 21c (Table 14, entry 5), while lower temperatures provided inferior yields (Table 14, entries 10 and 11). Performing the reaction with conventional heating (100 °C), required a substantially longer reaction time to reach full conversion, and the reaction was performed over night providing an 70% isolated yield (Table 14, entry 12).

To enable the use of aryltrifluoroborates as aryl–palladium precursors, some alterations had to be made to the conditions; replacing Pd(OAc)\textsubscript{2} by
Pd(O$_2$CCF$_3$)$_2$ and DMF by MeOH provided good yields of arylphosphonates after 20 min of irradiation at 120 °C.

Table 14. Investigation of reaction parameters

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<th>Entry</th>
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<th>Reoxidant</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
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</tr>
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<td>DMF</td>
<td>Cu(OAc)$_2$</td>
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</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>PhCO$_2$t-Bu</td>
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<tr>
<td>8</td>
<td>DMF</td>
<td>H$_2$O$_2$</td>
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Reaction conditions: A 5 mL Pyrex glass vial was charged with $p$-tolylboronic acid (1.0 mmol), diethyl phosphite (0.5 mmol), reoxidant (0.5 mmol), Pd(OAc)$_2$ (0.02 mmol), dmphen (0.03 mmol), and solvent (2 mL). The vial was sealed under air and thereafter exposed to microwave heating for 30 min at the temperature given in the table. $^a$ Conventional heating instead of microwave heating and run overnight to reach full conversion.

7.1.2 Organoborane Screening

To investigate the scope of the transformation, with respect to the aryl moiety, a number of arylboronic acids and aryltrifluoroborates were employed (Table 15). The 3,4-dimethoxyphenylboronic acid 1ag provided a useful yield of 67% (Table 15, entry 1). A decrease in yield was observed using the sterically demanding $o$-tolylboronic acid 1ah, compared to its $para$-substituted counterpart 1c (70 vs. 89%, Table 15 entry 2 and Table 14 entry 5). When comparing the $ortho$- and $para$-substituted trifluoroborates 20e and 20f, no clear trend was seen (77 vs. 81%, Table 15, entries 3 and 5). The coupling product of phenylboronic acid 1e was isolated at a yield of 65%, while the yield of the corresponding product from the phenyltrifluoroborate (20g) was 85% (Table 15, entries 7 and 8). The naphthyl- and biphenylboronic acids 1l and 1v provided efficient reactions, and good yields were obtained of the corresponding arylated phosphonates 21f and 21g (90 and 83%, Table 15, entries 9 and 10). The $p$-bromophenylboronic acid 1af was an efficient arylating agent, providing 75% of product 21h (Table 15, entry 11), without any trace of Suzuki product; a result which can be difficult to obtain under palladium(0)-catalyzed conditions.225 The $m$-bromophenyltrifluoroborate 20h provided product 21i at a moderate yield of 44% (Table 15, entry 12), due to extensive dehalogenation, but once again no biaryl Suzuki product was detected.
Electron-poor arylboranes provided useful yields of 21j-k (67-51%, Table 15, entries 13-15). Finally, the coupling of vinylboronic acid 1x gave a less satisfactory yield of 37% of product 21l (Table 15, entry 16).

Table 15. Organoborane screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Organoborane</th>
<th>Product</th>
<th>Yielda</th>
<th>Entry</th>
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<th>Product</th>
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<td>BF3K</td>
<td>21h</td>
<td></td>
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</table>

Table 15. Organoborane screening

Reaction conditions: A 5 mL Pyrex glass vial was charged with ArB(OH)2 or vinylB(OH)2 (1.0 mmol), diethyl phosphite (0.5 mmol), p-benzoquinone (0.5 mmol), Pd(OAc)2 (0.02 mmol), dmphen (0.03 mmol), and DMF (2 mL). The vial was sealed under air and thereafter exposed to microwave heating for 30 min at 100 °C. a Isolated yield, >95% pure according to GC-MS. b A 5 mL Pyrex glass vial was charged with ArBF3K (1.0 mmol), diethyl phosphite (2.0 mmol), p-benzoquinone (1.0 mmol), Pd(O2CCF3)2 (0.02 mmol), dmphen (0.03 mmol), and MeOH (3 mL). The vial was sealed under air and thereafter exposed to microwave heating for 20 min at 120 °C. c Performed at room temperature with a reaction time of 24 h and performed in an open vial with air as the reoxidant (no p-benzoquinone). d The same reaction conditions as c but with a reaction time of 48 h.

The excellent chemoselectivity of the reaction of bromo-substituted arylboranes with diethyl phosphite, was utilized to synthesize a known inhibitor of Mycobacterium tuberculosis glutamine synthetase. Using 3-bromophenylboronic acid (1f) and diethyl phosphite, aryl phosphonate 21i was isolated at a yield of 61%. Subsequent CuI-catalyzed aromatic substitution using unprotected glycine produced the inhibitor at a yield of 42%.
Scheme 29. Synthesis of an inhibitor of Mycobacterium tuberculosis glutamine synthetase

7.1.3 Mechanistic Investigation

Mechanistic investigations and proposals for the palladium(0)-catalyzed P–arylation of H–phosphonate diesters have recently been reported by Stawinski and Stockland. They suggested that the arylhalide undergoes oxidative addition to Pd(0), followed by coordination of the H–phosphonate diester nucleophile. Importantly, a base is needed to deprotonate the H–phosphonate diester before the arylated phosphonate diester is quickly generated by reductive elimination. In our protocol no base was added, which raises questions regarding the reaction mechanism. ESI-MS analysis was therefore used to study the reaction mechanism of this palladium(II)-catalyzed reaction.

ESI-MS analysis was performed to detect cationic palladium-containing intermediates in ongoing C–P bond-forming reactions. To initiate the investigation, the room temperature reaction with 1l and diethyl phosphite depicted in Table 15, entry 9, was selected as the model reaction. To find a suitable reaction time at which to study the reaction, aliquots were withdrawn from the reaction mixture every other hour during the first 8 h, and quickly diluted tenfold with DMF. The initial ESI-MS(+) studies indicated that most relevant monocharged organopalladium complexes could be observed after 4 h. Accordingly, ESI-MS analysis of all the reactions studied was performed after 4 h reaction time. To acquire more information on the palladium complexes detected, MS/MS was employed, which enabled more accurate structural propositions to be determined for each of the detected ions. The isotopic ions with the strongest and the second strongest intensity for each organopalladium complex (containing $^{106}$Pd and $^{108}$Pd, respectively) were selected for further MS/MS(+) analysis. The different complexes were classified and labeled according to where in the proposed catalytic cycle they might occur (Figure 5).

To further validate the observed complexes, a series of additional reactions was analyzed by ESI-MS(+) and MS/MS(+) Each component in the standard reaction with diethyl phosphate and 1l was replaced by a chemical equivalent, providing the analogous Pd complexes in situ but with different
m/z ratios. Hence, 1-naphthylboronic acid 1l was replaced by p-tolylboronic acid (1c), diethyl phosphite by dimethyl phosphite, and dmphen by the related bathocuproine (2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline). These substitutions were evaluated one at a time, all providing productive coupling reactions, yielding 57-78% of the arylated phosphonates 21c, 21d and 21f. The reactions provided the analogous and chemically equivalent Pd(II) intermediates according to ESI-MS and MS/MS analysis, further supporting the assignment of Pd complexes A and B (Figure 5).

The outcome of the ESI-MS study support a catalytic cycle that includes transmetallation of the boronic acid and nucleophilic coordination of the diethyl phosphite (Scheme 30). Complexes A1-A3 (Figure 5) are proposed to exist in equilibrium with each other and to serve as starting Pd(II) complexes. The reaction differs from the Pd(0)-catalyzed version in the formation of the aryl–palladium species (complexes B1-B3, Figure 5), which are formed through transmetallation instead of oxidative addition. The catalytic cycle is initiated by dissociation of the phosphite anion, followed by transmetallation of the arylboronic acid, to generate intermediate B. The neutral reductive elimination precursor C may be formed by coordination of the neutral phosphite nucleophile, as in the Pd(0)-catalyzed reaction, and subsequent deprotonation (Scheme 30). However, it is more likely that complex C is formed directly in an associative manner, A to C, without dissociation of the phosphite anion. The arylated phosphonate and Pd(0) complex D is generated by reductive elimination. Finally, Pd(0) species D is oxidized by p-benzoquinone to regenerate the Pd(II) complex A.
Contrary to all published Pd(0)-catalyzed Hirao-type reactions, no external base was added to the reaction mixture in our protocol, although it has been suggested that it is a requirement for a base to deprotonate the H-phosphonate diester in order for it to act as a nucleophile. To further investigate this, the pH of the reaction mixture was measured. At the start of the reaction it was about 6, and decreased to ~3, when full conversion was reached (after 30 min of microwave irradiation at 100 °C). To examine the effects of an added base, the reaction between 1v and diethyl phosphite was performed with the addition of 2 equivalents of Et$_3$N (pH of reaction mixture ~9-10), which did not provide any product 21g. To investigate the pH range in which the reaction was productive, 2 equivalents of HOAc were added (pH of reaction mixture ~4-5), yielding product 21g at a yield of 80%. Interestingly, this outcome was almost identical to that without the addition of HOAc (83% 21g, Table 2, entry 10). To further lower the pH of the reaction mixture, 2 equivalents of TFA (pH of reaction mixture ~1) were added, which gave a yield of product 21g of 68%. At the lower pH, extensive protodeboronation of 1v was observed, which could explain the lower yield of 21g. The tolerance to acidic conditions with our palladium(II)-catalyzed protocol provides a valuable alternative to the alkaline conditions employed in palladium(0)-catalyzed methods, when using base-sensitive functionalities. Based on these experiments, we suggest that deprotonation of the phosphite prior to Pd(II) coordination is not required under our conditions. Furthermore, it is not necessary to add a base to deprotonate the metal-coordinated nucleophile. However, the phosphite requires deprotonation, and intramolecular deprotonation by dmphen is one way in which the Pd(II)-coordinated phosphite could be deprotonated. Another possibility is that p-benzoquinone might act as base, although the room-temperature reactions were carried out in the absence of p-
benzoquinone and still provided highly productive reactions (Table 15, entries 4, 6 and 9).

Finally, a few other Pd sources, (PdCl₂, Pd₂(dba)₃, Pd(O₂CCF₃)₂), were evaluated. All the Pd sources provided efficient reactions (full conversion according to GC-MS), which rules out the possibility of acetate acting as an essential catalytic base. Interestingly, the P–arylation starting from zero-valent Pd₂(dba)₃ was as smooth as with the Pd(II) sources, demonstrating the efficient \( p \)-benzoquinone mediated oxidation of Pd(0) species. An explanation of the high reactivity at low pH and the non-existent reactivity under alkaline conditions could be Pd trapping by the base-promoted formation of unreactive Pd complexes.
8. Synthesis of Aryl Ketones by Palladium(II)-Catalyzed Decarboxylative Addition of Benzoic Acids to Nitriles

8.1 Overview

Aryl ketones are important functionalities in many types of organic compounds. Recently developed methods for the synthesis of aryl ketones have broadened the scope with respect to usable substrates.\textsuperscript{99,109,111,167-172} By combining Larock’s method, where arenes or arylboronic acids are coupled to nitriles and generate aryl ketones via the hydrolysis of the intermediate ketimine,\textsuperscript{172,173} with the advances made in decarboxylation of benzoic acids,\textsuperscript{99} the scope can be even further expanded. The use of arenes as aryl–palladium precursors, by C–H activation is in many respects the optimal arylation method. However, this type of C–H activation is associated with a major drawback: the lack of regiocontrol in the absence of directing groups. Arylboronic acids are also good aryl–palladium precursors and offer regioselectivity, but their cost is relatively high and they are not as widely commercially available as arenes. Using benzoic acids as aryl–palladium precursors will lower the cost of the aryl moiety, while still offering regiocontrol and wide availability. Based on these factors, the possibility of developing a palladium(II)-catalyzed method for the synthesis of aryl ketones from benzoic acids and nitriles was explored.

8.1.1 Ligand Screening

A test reaction using Pd(O\textsubscript{2}CCF\textsubscript{3})\textsubscript{2} as the catalyst, 2,6-dimethoxybenzoic acid as the substrate and MeCN as the reactant/solvent, was used to evaluate a series of ligands. The reaction was heated by microwave irradiation at 130 °C for 30 min. Several different bipyridine derivatives and phenanthroline derivatives were tested (Table 16). One bidentate phosphine ligand (dppp) was also evaluated with disappointing outcome (Table 16). The use of DMSO as ligand proved inefficient, as did the ligand-free experiment. Among the bidentate nitrogen ligands, three provided considerably higher yields than the others; 6-methyl-2,2'-bipyridine (3j), dmphen (3e) and 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline (3f). Based on the yield of the aryl methyl ketone 24a, 6-methyl-2,2'-bipyridine (3j) was selected as the ligand for further studies. To improve the reaction productivity, temperatures, catalyst loadings and reaction times were evaluated. Heating
the reaction in a heating block at 100 °C required prolonged reaction time
and resulted in lower yields. Extending the exposure to microwave
irradiation from 30 to 60 min and increasing the catalyst loading from 4 to 8
mol% improved the yield of $24a$ from 73 to 80%. Increasing the reaction
temperature above 130 °C resulted in palladium black formation and lower
yields, whereas lowering the temperature, as expected, led to prolonged
reaction times. Although no visible formation of palladium black could be
observed at 130 °C, a reaction with the addition of 1.2 equivalents of $p$-
benzoquinone was performed to assure efficient generation of palladium(II)
from any palladium(0) possibly formed. The addition of $p$-benzoquinone had
no beneficial impact on the isolated yield of $24a$, indicating that the
formation of palladium(0) is not a problem under the reaction conditions
employed. An investigation on the impact of acidic and basic additives was
carried out by adding 1 equivalent of acid (TFA or HOAc) or 1 equivalent of
base (Et$_3$N or K$_2$CO$_3$), which in all cases led to the formation of palladium
black. A brief investigation was carried out on the possibility of using a
bimetallic catalytic system to expand the scope of accessible benzoic acids.
The reactions were evaluated using $o$-anisic acid and MeCN as substrates,
and Pd(O$_2$CCF$_3$)$_2$ in combination with Cu$_2$O or AgOAc and ligand 3j, but
did not provide higher yields of the desired aryl ketone than the use of
Pd(O$_2$CCF$_3$)$_2$ on its own.

Table 16. Ligand screening

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<th>Ligand</th>
<th>Yield a (%)</th>
<th>Ligand</th>
<th>Yield a (%)</th>
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Reaction conditions: A 5 mL Pyrex glass vial was charged with 2,6-dimethoxybenzoic acid (0.5 mmol), Pd(O$_2$CCF$_3$)$_2$ (0.02 mmol), ligand (0.024 mmol), H$_2$O (200 μL) and MeCN (2 mL). The vial was thereafter sealed under air and exposed to microwave heating for 30 min at 130 °C. a Isolated yield, >95% pure according to GC-MS. b Pd(O$_2$CCF$_3$)$_2$ (0.04 mmol), 6-methyl-2,2'-bipyridine (0.048 mmol), exposed to microwave heating for 60 min at 130 °C. c Heated in a heating block at 100 °C for 48 h. d Same as c but with Pd(O$_2$CCF$_3$)$_2$ (0.04 mmol), 6-methyl-2,2'-bipyridine (0.048 mmol). e Pd(OAc)$_2$ (0.04 mmol) used instead of Pd(O$_2$CCF$_3$)$_2$. f 100 μL DMSO was added.
8.1.2 Substrate Scope

After having identified a suitable ligand in 6-methyl-2,2'-bipyridine (3j), a number of different nitriles and benzoic acids were evaluated. To study the scope of the reaction with respect to the nitrile part, a total of five different liquid nitriles were coupled with 2,6-dimethoxybenzoic acid (22a) (Table 17, entries 1-5). In order to optimize the yield of the reaction, several different reaction conditions were applied for each nitrile. In the coupling of 22a with MeCN an excellent yield of 24a of 94% was obtained with a relatively high catalyst loading and using a heating block at 100 °C for 48 h (Table 17, entry 1, 20 mol% Pd). A somewhat lower yield of 78% was obtained when the reaction was exposed to microwave irradiation at 130 °C for 60 min, although full conversion was reached (monitored as complete consumption of the benzoic acid according to LC-MS). As sterically hindered ketimines might be very stable to hydrolysis, the microwave heating reaction was repeated and subsequently subjected to hydrolysis with the addition of 1 mL 2 M HCl(aq), at 100 °C for 16 h, resulting in an improved isolated yield of 90% of product 24a. However, hydrolysis with 2 M HCl may be too harsh for certain substrates, which motivated the evaluation of a milder method using 1 mL of formic acid at 100 °C for 1 h, providing a rewarding yield of 24a of 88%. Lowering the catalyst loading from 20 to 8 mol% resulted in a moderately reduced yield of 24a to 86%. The use of propionitrile (23b) provided the product at a good yield, under both microwave and conventional heating (Table 17, entry 2). Butyronitrile (23c) gave a good yield of product 24c, while benzonitrile (23d) resulted in a low yield of 24d of 20% (Table 17, entries 3 and 4). The reaction of phenyl cyanide (23e) with benzoic acid 22a benefitted substantially from hydrolysis with formic acid (50 vs. 73% isolated yield of 24e, Table 17, entry 5).

After having investigated the scope of the nitrile moieties, a number of ortho-substituted benzoic acids 22b-o were reacted with MeCN (Table 17, entries 6-19). Trimethoxy substituted 22b provided product 24f at a yield of 57-71%, depending on the conditions employed (Table 17, entry 6). Diethoxybenzoic acid (22c) gave product 24g at a yield of 50-74% (Table 17, entry 7), and displayed similar reactivity to the dimethoxy counterpart 22d (59-70%, Table 17, entry 8). The bromo-substituted benzoic acid 22e provided product 24i in 45-61% (Table 17, entry 9), without any traces of Pd(0) activation in the form of dehalogenation or decarboxylative Suzuki product, indicating the absence of Pd(0) formation in the reaction. Trimethoxy-substituted 22f was a good substrate for this coupling, and gave a yield of 91% of product 24j under the best conditions employed. An attempt to scale up the reaction from the 0.5 mmol to 10 mmol scale resulted in a lower yield of 67% (Table 17, entry 10). 2,5-Dimethoxy benzoic acid (22g) gave the corresponding aryl methyl ketone 24k at a yield of 20-26%
Fluoro-substituted $22h$ provided product $24l$ at a yield of 63%, demonstrating the possibility of using ortho-fluoro substituents. A dramatic increase in isolated yield was obtained in the reaction with mesitylene carboxylic acid ($22i$) and MeCN upon hydrolysis, where the yield of $24m$ increased from 11 to 85% (Table 17, entry 13), in agreement with earlier reports on the stability of ketimines involving mesitylene functionalities. Naphthyl carboxylic acid ($22j$) was a poor substrate for this reaction and provided product $24n$ at a mere 25-27% (Table 17, entry 14). Furan derivative $22k$ gave good yields of product $24o$, 61-90% (Table 17, entry 15), as did thiophene derivatives $22l$, $22m$ and $22n$, providing products $24p$, $24q$ and $24r$ at yields of 57-84%, 62% and 51%, respectively (Table 17, entries 16-18). Finally, pyridine derivative $22o$ gave product $24s$ at a yield of 53% (Table 17, entry 19). As can be seen in Table 17, many of the reactions required an extra hydrolysis step to increase the yield of isolated aryl ketone.
Table 17. Palladium(II)-catalyzed reactions of benzoic acids and nitriles

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCO₂H</th>
<th>K</th>
<th>Product</th>
<th>Yield(%)</th>
<th>Entry</th>
<th>ArCO₂H</th>
<th>K</th>
<th>Product</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24a]</td>
<td>78%(^f)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24b]</td>
<td>50%(^f)</td>
</tr>
<tr>
<td>2</td>
<td>[22b]</td>
<td>Et</td>
<td>[23b]</td>
<td>60%(^f)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24c]</td>
<td>68%(^f)</td>
</tr>
<tr>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24c]</td>
<td>86%(^f)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24d]</td>
<td>66%(^f)</td>
</tr>
<tr>
<td>3</td>
<td>[22c]</td>
<td>Ph</td>
<td>[23c]</td>
<td>69%(^g)</td>
<td></td>
<td>[24d]</td>
<td>Ph</td>
<td>[24e]</td>
<td>77%(^g)</td>
</tr>
<tr>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24e]</td>
<td>72%(^g)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24f]</td>
<td>59%(^f)</td>
</tr>
<tr>
<td>4</td>
<td>[22d]</td>
<td>Pr</td>
<td>[23d]</td>
<td>20%(^h)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24g]</td>
<td>25%(^f)</td>
</tr>
<tr>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24g]</td>
<td>27%(^f)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24h]</td>
<td>25%(^f)</td>
</tr>
<tr>
<td>5</td>
<td>[22e]</td>
<td>C₆H₅</td>
<td>[23a]</td>
<td>50%(^i)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24i]</td>
<td>67%(^h)</td>
</tr>
<tr>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24i]</td>
<td>73%(^i)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24j]</td>
<td>61%(^h)</td>
</tr>
<tr>
<td>6</td>
<td>[22f]</td>
<td>VeO</td>
<td>[23a]</td>
<td>57%(^j)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24k]</td>
<td>52%(^j)</td>
</tr>
<tr>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24k]</td>
<td>71%(^j)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24l]</td>
<td>56%(^j)</td>
</tr>
<tr>
<td>7</td>
<td>[22g]</td>
<td>VeO</td>
<td>[23a]</td>
<td>50%(^k)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24m]</td>
<td>59%(^j)</td>
</tr>
<tr>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24m]</td>
<td>56%(^k)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24n]</td>
<td>51%(^j)</td>
</tr>
<tr>
<td>8</td>
<td>[22h]</td>
<td>VeO</td>
<td>[23a]</td>
<td>50%(^k)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24o]</td>
<td>51%(^j)</td>
</tr>
<tr>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24o]</td>
<td>54%(^k)</td>
<td></td>
<td>[OWe]</td>
<td></td>
<td>[24p]</td>
<td>54%(^k)</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield, >95% pure according to GC-MS. \(^b\) A 5 mL Pyrex glass vial was charged with ArCOOH (0.5 mmol), Pd(O₂CCF₃)₂ (0.10 mmol), 6-methyl-2,2'-bipyridine (0.12 mmol), H₂O (200 μL), and nitrile (2 mL). The vial was thereafter sealed under air and heated in a heating block at 100 °C for 60 min. \(^c\) Same as b but exposed to microwave heating for 60 min at 130 °C. \(^d\) Same as c with subsequent addition of 1 mL 2 M HCl(aq) and heating at 100 °C for 16 h. \(^e\) Same as c but with subsequent addition of 1 mL formic acid and heating at 100 °C for 1 h. \(^f\) Same as e but with Pd(O₂CCF₃)₂ (0.04 mmol), 6-methyl-2,2'-bipyridine (0.048 mmol). \(^g\) Same as e but with Pd(O₂CCF₃)₂ (0.04 mmol), 6-methyl-2,2'-bipyridine (0.048 mmol). \(^h\) A 20 mL Pyrex glass vial was charged with ArCOOH (10.0 mmol), Pd(O₂CCF₃)₂ (0.8 mmol), 6-methyl-2,2'-bipyridine (0.96 mmol), H₂O (2.0 mL) and MeCN (10.0 mL). The vial was thereafter sealed under air and exposed to microwave heating for 60 min at 130 °C, with subsequent addition of 5 mL formic acid and heating at 100 °C for 60 min.
8.1.3 Mechanistic Investigation

To study the reaction mechanism, an online ESI-MS study was performed. ESI-MS(+) analysis was performed on aliquots directly withdrawn from an ongoing reaction, to detect cationic palladium intermediates. The reaction performed at 100 °C in a heating block with 3j, depicted in Table 16, was chosen as the model reaction. An aliquot was withdrawn from the reaction after 6 h, diluted tenfold with MeCN and immediately subjected to ESI-MS(+) analysis. The spectrum was recorded by scanning the first quadrupole (Q1) of a triple quadrupole instrument (Figure 6). As expected, several groups of signals, with the characteristic natural isotopic pattern of monopalladium complexes, were detected, together with a few non-palladium-containing ions. All the detected palladium-containing complexes were subjected to MS/MS(+) by selecting the isotopic ions with the strongest and the second strongest intensity from each complex (corresponding to $^{106}$Pd and $^{108}$Pd, respectively). Proposals of the structures of the complexes were made by analyzing the information from the MS and MS/MS experiments (Figure 6). The corresponding ESI-MS(-) study was also performed, but no anionic Pd-complexes were observed.

Based on the detected intermediates a plausible reaction mechanism was suggested, in agreement with mechanistic proposals for related reactions (Scheme 31). The catalytic cycle involves the following key steps. 1) coordination of the carboxylic acid to the Pd(II)-center to generate complex A, 2) decarboxylation of the benzoic acid to give the Ar–Pd complex B, 3) coordination of the nitrile to form complex C, 4) 1,2-carbopalladation of the
nitrile to form ketimine complex D and 5) protonation of the ketimine by the benzoic acid to afford the free ketimine and a palladium(II) species.

Scheme 31. Proposed catalytic cycle based on cationic palladium(II) complexes detected with ESI-MS
9. Concluding remarks

The work included in this thesis describes the development of novel palladium(II)-catalyzed coupling methods. The specific results and conclusions are as follows:

- An open-vessel, room-temperature oxidative Heck reaction, utilizing arylboronic acids as aryl–palladium precursors and oxygen from the air as the palladium reoxidant was developed. This constitutes a cheaper and greener methodology than previously developed oxidative Heck reactions.
- A base-free oxidative Heck reaction was developed. Efficient reactions were achieved at room temperature, using oxygen from the air as reoxidant, or with microwave heating, employing $p$-benzoquinone as reoxidant. The reactions were successfully performed on 50 mmol scale, both at room temperature and with microwave heating. The base-free conditions enable the use of base-sensitive substrates.
- An efficient and simple method for the synthesis of styrene derivatives from arylboranes and vinyl acetate was developed. The reaction mechanism was studied using ESI-MS and a plausible catalytic cycle was presented. The method developed could be considered as one of the simplest and cheapest for small-scale synthesis of styrene derivatives.
- Conditions were identified for the base-free oxidative Heck reaction and styrene synthesis under continuous flow. This advance demonstrates the possibility of using these transformations in large-scale production in a safe and convenient way.
- A palladium(II)-catalyzed method was developed for arylation of dialkyl phosphite using arylboranes. The reaction mechanism was investigated using ESI-MS and a plausible catalytic cycle was presented. This method expands the scope of C–P bond-forming reactions, and provides an alternative to commonly employed palladium(0)-catalyzed methods.
- A novel method for synthesizing aryl ketones from benzoic acids and nitriles was developed. The reaction mechanism was studied using ESI-MS and a catalytic cycle was proposed. This efficient method constitutes a green route for the production of aryl ketones.
I would like to express my sincere gratitude to the following people.

My supervisor Professor Mats Larhed, for being a superb and extremely efficient supervisor. For your support and input, and for letting me explore new ideas.

Dr. Peter Nilsson, my co-supervisor, for your enthusiasm, support, and friendship.

Professor Anders Hallberg, my co-supervisor, for giving me the opportunity to initiate my PhD studies and for creating a great atmosphere at the department.

My MSc student, Marc Stevens, and my summer workers, Ashkan Fardost and Ali-Reza Nadjimi, for doing a great job and for keeping me company in the lab.

Dr. Per Sjöberg, the ESI-MS guru, for fruitful collaboration and for skillful handling of the ESI-MS instrument.

Professor Pino Pilotti, for valuable assistance during large-scale microwave reactions.

Dr. Tomas Gustafsson, for introducing me to continuous flow chemistry and for nice company in Mölndal.

Dr. Ola Åberg, for good collaboration in the PET-project.

My co-authors at the department, Dr. Per-Anders Enquist, Jonas Sävmarker, Dr. Luke Odell and Dr. Mounir Andaloussi, for all your efforts.

My roommate Jonas Sävmarker for five enjoyable years and for constructive criticism of this thesis. It has truly been a pleasure working with you and an even greater pleasure beating you on the court.
The NMR group, Jonas and Johan, for all those long hours spent in the basement.

Former and present lab mates, Jonas, Jenny, Olle and Krz, for all the good times in the lab.

All former and present colleagues at the department. It has been a pleasure working with you. A special thanks to my sporting friends, Särmarker, Robert, Johan, P-A and Peter, for the running, biking, badminton, squash, tennis, table tennis and good times. To my conference co-travelers, Jonas, Johan, Anna and Rebecca, for making the conferences even more enjoyable.

To Biotage for letting me use the Advancer microwave reactor and to AstraZeneca Mölndal for giving me opportunity to use the Vapourtec flow reactor.

Till Macke, Bobo, Ante, Thomas och Annelie för allt kul vi har haft och kommer att ha.

Till Jon, Daniel, Gustav, Erik, Martin och Axel, för att ni gjorde studietiden betydligt roligare.

Till min svärfamilj för alla trevliga sammankomster med en aldrig sinande stöm av nya släktingar. Hur många är ni?

Till mina kära föräldrar för allt stöd, uppmuntran och apanage.

Till min syster med familj för allt roligt vi har haft, men mest för att ni har skaffat Vix.

Till min älskade fru, Dr Emma, för att du alltid är glad och positiv. För all uppmuntran och allt stöd.
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