Palladium-Catalysed Carbon–Carbon Coupling Reactions

Focusing on Microwave Heating, Low Catalyst Concentrations, Aqueous Conditions, Regioselectivity and Medicinal Chemistry Applications

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Abstract

It is widely accepted that palladium is one of the most useful catalysts in organic chemistry, and many palladium(0)-catalysed carbon–carbon bond-forming reactions have been developed over the years. In addition, the ever-growing need for more environmentally benign processes in the chemical industry has driven scientists to look for greener options while developing new methodologies for organic synthesis. This thesis describes a series of studies on Suzuki and Heck coupling reactions in water and the application of palladium(0) catalysis to the development of new HIV-1 integrase inhibitors.

The previously described 'transition-metal-free Suzuki-type coupling' reaction was shown to take place due to sub-ppm levels of palladium contaminants present in the commercially available sodium carbonate base. Based on this finding, a new, microwave-assisted Suzuki protocol utilizing ppb/ppm levels of palladium in water was developed. This methodology was adapted to terminal Heck coupling, although the scope of the protocol was found to be rather limited. Finally, both Suzuki and Heck reaction processes were successfully scaled up to 100 mmol using an automated batch stop-flow microwave apparatus.

As the methodologies utilizing ultralow palladium concentrations were not applicable to aryl chlorides, attention was shifted towards palladium on carbon. This simple catalyst, together with microwave heating employing simultaneous cooling, was found to be beneficial in the Suzuki coupling of aryl chlorides with phenylboronic acid in water.

Ligand-controlled internal arylation of ethylene glycol vinyl ether with aryl halides was shown to be possible in water alone without any additives. Reactions were run under air, using conventional heating and the products formed were isolated as aryl methyl ketones in good to excellent yields. The electron-rich (dippP),Pd complex was shown to be beneficial for the microwave-assisted internal arylation of some aryl chlorides. Furthermore, the active role of the hydroxyl group of ethylene glycol vinyl ether in the formation of a cationic intermediate leading to internal Heck coupling product was elucidated.

Finally, to demonstrate the usefulness of palladium(0) catalysis in the development of new pharmaceutical entities, a series of HIV-1 integrase inhibitors was synthesised and evaluated in strand transfer assays and in vitro. Based on the results and docking studies performed, valuable information related to the structure–activity relationship was obtained.

Keywords: Suzuki coupling, Heck reaction, palladium, microwave heating, water, vinyl ether, regioselective, HIV-1 integrase inhibitor

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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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<th>Definition</th>
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<tbody>
<tr>
<td>3’-P</td>
<td>3’-processing</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Asp</td>
<td>aspartic acid</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)1,1’-binaphthyl</td>
</tr>
<tr>
<td>bmim</td>
<td>1-&lt;i&gt;n&lt;/i&gt;-butyl-3-methylimidazolium</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>cDNA</td>
<td>double-stranded DNA copy of RNA</td>
</tr>
<tr>
<td>concd</td>
<td>concentrated</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>dipp</td>
<td>1,3-bis(diisopropylphosphino)propane</td>
</tr>
<tr>
<td>DKA</td>
<td>diketo acid</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>EC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>effective concentration required to reduce cytopathic effect by 50 %</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>GC/MS</td>
<td>gas chromatography mass spectrometry</td>
</tr>
<tr>
<td>Glu</td>
<td>glutamic acid</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>concentration required to inhibit enzymatic activity by 50 %</td>
</tr>
<tr>
<td>ICP-AA</td>
<td>inductively coupled plasma atomic absorption</td>
</tr>
<tr>
<td>ICP-AES</td>
<td>inductively coupled plasma atomic emission spectrometry</td>
</tr>
<tr>
<td>ICP-MS</td>
<td>inductively coupled plasma mass spectrometry</td>
</tr>
<tr>
<td>IL</td>
<td>ionic liquid</td>
</tr>
<tr>
<td>IN</td>
<td>integrase</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>MAOS</td>
<td>microwave-assisted organic synthesis</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mw</td>
<td>microwave heating</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppb</td>
<td>parts per billion</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PTC</td>
<td>phase transfer catalyst</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>S</td>
<td>solvent</td>
</tr>
<tr>
<td>ST</td>
<td>strand transfer</td>
</tr>
<tr>
<td>STI</td>
<td>strand transfer inhibitor</td>
</tr>
<tr>
<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TPPTS</td>
<td>tris(3-sulfophenyl)phosphine trisodium salt</td>
</tr>
</tbody>
</table>
1. Introduction

1.1 Palladium-Catalysed Carbon–Carbon Coupling Reactions

1.1.1 General Introduction

Today, palladium is widely accepted as being one of the most versatile and beneficial metals used in organic synthesis, together with metals such as lithium, magnesium and copper. This silvery-white precious metal, found mainly in Russia, South Africa, the USA and Canada, was first discovered by British chemist William Hyde Wollaston in 1803.\textsuperscript{1,2} He later named this new element ‘palladium’ after the asteroid Pallas, which had been discovered a few years earlier.\textsuperscript{1}

In addition to catalysis, palladium is used in a variety of applications such as electronics, jewellery, fuel cells, water treatment and oil refining.\textsuperscript{2} However, a major share of the palladium produced today is used in catalytic converters, which transform exhaust gases released by gasoline engines to less harmful substances.\textsuperscript{2,3}

In chemistry, palladium was not much utilized until the 20\textsuperscript{th} century. The invention of the Wacker process, i.e. the oxidation of ethylene to acetaldehyde catalysed by PdCl\textsubscript{2} and CuCl\textsubscript{2}, in 1959 and following mechanistic studies performed by Tsuji et al. started the modern era in organopalladium chemistry.\textsuperscript{1,4} Since then, several palladium-catalysed organic transformations and new protocols associated with them have been developed. The main focus of the work presented in this thesis is the two, possibly most important palladium-catalysed carbon–carbon bond-forming reactions, namely the Suzuki and Heck reactions.

1.1.2 Key Catalytic Properties of Palladium

Almost all organic functional groups can form complexes with transition metals. This coordination often results in a change in the reactivity of the functional group in question, making it possible to develop highly specific and efficient organometallic reaction pathways.\textsuperscript{5}

So, what makes palladium so special? Palladium belongs to a series of a few second-row transition metals possessing very favourable properties with
regard to catalysis. Most of the key properties making it such a diverse catalyst can be explained by its location in the periodic table. Below are listed some of the factors influencing the catalytic activity of palladium.\(^1,5,6\)

- Due to the moderate size of palladium, its complexes are often relatively stable ensuring a controlled and wide-ranging reactivity pattern.
- Oxidation states 0 and +2 prevail, enabling facile oxidation and reduction processes needed for catalytic activity.
- The low tendency of palladium towards one-electron or radical processes limits possible by-product formation.
- Easily accessible HOMO and LUMO orbitals enable participation in a range of concerted processes with low activation energies.
- The properties of Pd complexes can be easily fine-tuned by changing the electronic and steric nature of ligands bound to the metal centre.
- The relatively high electronegativity (2.2 on the Pauling scale) makes carbon–palladium bonds fairly non-polar, rendering them unreactive towards polar functional groups. This increases the chemoselectivity and complements organometallic chemistry performed by Grignard and organolithium reagents.
- Finally, the general lack of toxicity, high tolerance to different functional groups and ease of handling make palladium catalysis a useful tool for modern organic chemistry.

### 1.1.3 Palladium-Catalysed Cross-Coupling Reactions

Historically, carbon–carbon bond-forming reactions have played a significant role in the development of organic chemistry as we know it today. Palladium-catalysed and, to some extent, nickel-catalysed, cross-coupling reactions (defined as the transition-metal catalysed substitution of an organic halide or related electrophile by a nucleophile)\(^7\) have proven to be especially important.\(^8,9\) Due to many benefits of these reactions, such as high productivity, atom economy, potential recycling of the catalyst and mild reaction conditions, they have become increasingly valuable, for example, in the pharmaceutical and fine chemical industries and natural product synthesis.\(^10-14\)

The general reaction mechanism for Pd(0)-catalysed cross-coupling reactions is presented in Scheme 1. Based on the organometallic counterpart delivered in the transmetallation step, different coupling reactions have emerged, including the Suzuki, Stille, Negishi, Kumada and Hiyama reactions.\(^9,15\)
Scheme 1. General mechanism for Pd(0)-catalysed cross-coupling reactions. M = BY₂ (Suzuki), SnR₃ (Stille), ZnX (Negishi), MgX (Kumada) or SiR₃ (Hiyama), etc.

The fundamental reactions of the catalytic cycle can be described as follows.

**Oxidative addition:** Prior to oxidative addition, the formation of an active 14-electron palladium(0) species, Pd(0)L₂, with two vacant coordination sites is required.¹⁶,¹⁷ This can be achieved directly by the loss of one or more spectator ligands from Pd(0) complexes such as Pd(PPh₃)₄ and Pd₂(dba)₃. These complexes are, however, often unstable, and easily accessible and robust palladium salts, such as Pd(OAc)₂ and PdCl₂, are therefore frequently used.¹⁶-¹⁸ The *in situ* reduction of Pd(II) to Pd(0) can be accomplished by the addition of phosphine ligands.¹⁹-²² A few years ago, Amatore et al. reported that an anionic 16-electron complex [Pd(0)(PPh₃)₂OAc]⁻ was the active palladium species when Pd(OAc)₂ is used with an excess of PPh₃.²³ In phosphine-free reactions, it has been reported that reduction can be promoted by olefin²⁴,²⁵, amine base²⁶, solvent²⁷,²⁸ or even tetrabutylammonium salts²⁹.

In oxidative addition, palladium(0) is inserted into the R–X bond, while the formal charge on the metal changes from 0 to 2. The reactivity order of aryl halides and triflates (I > OTf > Br >> Cl) follows the bond strength of the C–X bonds to be broken.⁴,¹⁸,³⁰,³¹ The reaction rate can, however, also be influenced by electron-rich spectator ligands, which increase the nucleophilicity of the palladium centre, or by introduction of electron-poor substituents on the aryl substrate.¹⁶,¹⁸,³⁰,³²

**Transmetallation:** Transmetallation is defined as a ligand exchange process between two metals, e.g. Pd(II) and M. To ensure successful transmetallation, the main group organometallic M must generally be more electroposi-
tive than palladium. Some typical examples of transmetallating agents are presented in Scheme 1.

**Reductive elimination:** Reductive elimination can be considered to be the reverse process to oxidative addition. This step completes the catalytic cycle and releases Pd(0), while the two organic groups, R and R′, are combined and eliminated as free R–R′. Before the formation of a new C–C bond, rearrangement of ligands R and R′ from the trans to cis configuration takes place.

1.1.3.1 The Suzuki Reaction

The first examples of Suzuki coupling, also called Suzuki-Miyaura coupling, were reported in 1979. This reaction is defined as a cross-coupling reaction between organic electrophiles, such as aryl or alkenyl halides, and organoboron compounds in the presence of a stoichiometric amount of base (Scheme 2). Organoboranes, organoboronic acids and esters, and lately even organotrifluoroborates, have been successfully utilized as transmetallating agents. Recently, electron-rich N-heterocyclic carbene ligands were shown to be beneficial for the Suzuki reaction, allowing the coupling of two sp3-hybridized carbon centres. Furthermore, the usefulness of these ligands in the activation of aryl chlorides towards various cross-coupling reactions has been reported.

![Scheme 2](https://example.com/scheme2.png)

**Scheme 2.** Palladium-catalysed Suzuki coupling.

Suzuki coupling has become especially important for biaryl synthesis in the pharmaceutical industry, and this privileged structure can be found, for instance, in the Sartan group, which is the fastest growing group of prescription drugs for hypertension (Figure 1). The usefulness of the Suzuki reaction is derived from the many beneficial features of boronic reagents. They show, for example, remarkable tolerance to a variety of functional groups, they are relatively bench-stable allowing easy handling, and organoboron compounds are not toxic. However, protodeboronation of boronic acids in water, ethanol or, in some cases, even by moisture can occasionally cause problems.

The electronegativities of boron and carbon are about 2.0 and 2.5, respectively. This makes the boron–carbon bond relatively non-polar and renders
organoboron reagents relatively stable. However, this makes them also fairly unreactive and boronic derivatives therefore require activation to participate in transmetallation. This can be done, for example, by quaternisation of boron by aqueous anionic bases to give $R^\prime BY_2OH^{-}$.

![Figure 1](image1.png)

**Figure 1.** The Sartan group of pharmaceuticals used to treat hypertension.

### 1.1.4 The Heck Reaction

The first palladium-catalysed coupling reactions of aryl and vinyl halides with alkenes were independently reported by Heck and Nolley and Mizoroki et al. at the beginning of the 1970s. Soon after this, Richard Heck and co-workers demonstrated the adaptability and usefulness of this catalytic transformation, today known as the Heck reaction or Heck olefination (Scheme 3). After a rather slow induction period, Heck coupling has gained steadily in popularity, as evidenced by the numerous reviews and book chapters published since its discovery. Among its many benefits, the high flexibility to functional groups and leaving groups on aryl/vinyl counterparts and the generally mild reaction conditions have made this reaction one of the most versatile and important carbon–carbon bond-forming reactions. Both inter- and intramolecular Heck reactions are known, the latter being frequently used for construction of rings of variable size with a high degree of regio- and stereoselectivity. As a result, Heck reaction is used in a wide range of applications, from the preparation of hydrocarbons, novel polymers and dyes, to total synthesis of pharmaceuticals and natural products.

![Scheme 3](image2.png)

**Scheme 3.** The intermolecular Heck reaction.
A traditional, simplified mechanism describing the Heck reaction is presented in Scheme 4. Although the catalytic cycle starts with oxidative addition (discussed in Section 1.1.3), it deviates significantly from the mechanism presented for Pd(0)-catalysed cross-coupling reactions. The additional steps are described below.

![Scheme 4. General mechanism for the Heck reaction.](image)

**π-Complex formation and migratory insertion:** In the process following oxidative addition, the olefin is coordinated to the Pd(II) centre, while one of the ligands (neutral or anionic) dissociates and leaves the catalytic complex. The π-coordinated olefin further rotates to an in-plane position to allow a concerted syn insertion, leading to the formation of a new σ-bond. This insertion is governed by both steric and electronic factors, and is responsible for regio- and stereoselectivity, and the substrate selectivity of the Heck reaction. The regioselectivity of the Heck reaction is further discussed in the next section.

**β-Hydride elimination and regeneration of Pd(0):** These two final steps complement the catalytic cycle by releasing the olefinic product and the active palladium(0) species. β-H elimination can occur only in syn fashion and therefore rotation about the Cα–Cβ bond is required. Elimination is a reversible process favouring the formation of a thermodynamically stable trans isomer. Reversibility can, however, also lead to migration of the
double bond if the dissociation of the product from the catalytic complex is slow.\textsuperscript{16,18} Finally, the Pd(II) species is reduced to Pd(0) by a base-mediated process and can now be inserted into the next R–X bond via oxidative addition.\textsuperscript{16,17}

1.1.4.1 Regioselectivity of the Heck Reaction

The regiochemical outcome of the Heck reaction is defined in the migratory insertion step. From a variety of factors influencing the regioselectivity, two major parameters can be highlighted, namely steric and electronic effects.\textsuperscript{16,18,51-53} While the formation of terminal products from electron-deficient olefins is favoured by both of these factors, electron-rich olefins tend to give mixtures of internal α- and terminal β-products under standard intermolecular Heck reaction conditions.\textsuperscript{16}

Due to the substantial amount of work done by several groups, a great deal is known today about the regiocontrol of the Heck arylation of electron-rich olefins.\textsuperscript{54} The major breakthrough came at the beginning of the 1990s when Cabri et al. reported bidentate phosphine ligand controlled regioselectivity in the arylation of vinyl ethers with aryl triflates.\textsuperscript{55,56} Similar results were later obtained with aryl halides when thallium or silver salts were used to scavenge halide ions from the solution.\textsuperscript{57,58} Based on these findings, Cabri and Candiani suggested that the Heck reaction could proceed via two possible pathways, neutral or cationic, depending on the aryl substrate and the catalytic system chosen (Scheme 5).\textsuperscript{59}

\begin{center}
\textbf{Scheme 5.} The two possible pathways for Heck arylation.
\end{center}
Based on Cabri’s model, bidentate phosphine ligands, such as strongly coordinating dppp (1,3-bis(diphenylphosphino)propane) in conjunction with triflates as leaving groups lead to the selective formation of a cationic π-complex giving only internal arylation products.\textsuperscript{16,59} The application of strongly Pd(II)-coordinating groups, such as halide ions, or weakly binding monodentate ligands, on the other hand, causes dissociation of the neutral ligand resulting in a shift of the mechanism towards a neutral pathway, leading to mixtures of α- and β-products.\textsuperscript{16,59} However, as mentioned previously, the precipitation of halides as insoluble metal salts has a beneficial effect on the α-selectivity.\textsuperscript{57} Furthermore, methodologies utilizing highly polar reaction media, such as DMF-water mixtures and ionic liquids, in the arylation of electron-rich olefins with aryl bromides, were reported at the beginning of the 21\textsuperscript{st} century.\textsuperscript{60-62} The applicability of ionic liquids as the sole solvent or as an additive has been expanded to include the arylation of a wide range of electron-rich olefins regioselectively with aryl and heteroaryl halides.\textsuperscript{63-67} As further proof of this concept, Jutand et al. very recently reported [Pd(dppp)(S)Ph]\textsuperscript{+} (S = solvent) to be the most reactive complex formed in the oxidative addition of PhI to the Pd(0)/dppp-complex; its overall role in directing the regioselectivity increasing at high ionic strengths.\textsuperscript{68,69}

1.1.5 The Role of Nanoparticles in Ligand-Free Palladium-Catalysed Coupling Reactions

Although phosphine ligands are known to have a positive influence on the stability and catalytic activity of palladium, they are often toxic, unrecoverable, and can disturb the isolation and purification of the products formed.\textsuperscript{11,70,71} As they can also be rather expensive, the use of ligand-free palladium catalysis has become an increasingly interesting area of research. Since the original studies of the ligand-free Heck reaction,\textsuperscript{45,46} stabilisation of the labile palladium species with, for example, quaternary ammonium salts, such as nBu\textsubscript{4}NCl and water, has been reported by Jeffery\textsuperscript{72} and Beletskaya\textsuperscript{18}, respectively.

In the late 1990s, Reetz et al. described phosphine-free Heck and related C–C bond-forming reactions being catalysed by nanosized palladium colloids formed from simple palladium salts.\textsuperscript{73,74} These colloids, which can be stabilised by phase transfer salts, were shown to be effective in the activation of aryl iodides and bromides but failed, unfortunately, in the case of aryl chlorides. In a following study, de Vries et al. reported that homeopathic doses (0.01–0.10 mol %) of ligand-free palladium were able to catalyse Heck reactions of aryl bromides in organic solvents.\textsuperscript{75} Interestingly, catalyst loadings higher than 1 mol % resulted in the noticeable formation of palladium black and termination of the reaction, whereas with a catalyst loading
of 0.00125 mol %, the catalyst was still active after several hours, although the rate of the reaction became too slow to be practical (Figure 2).

![Chemical reaction diagram](image)

**Figure 2.** Effect of palladium/substrate ratio on the yield of the Heck reaction between bromobenzene and \(n\)-butyl acrylate.\(^{75}\)

Based on these results, a mechanism explaining the increasing turnover frequency with decreasing catalyst concentration was suggested.\(^{75-77}\) According to this suggestion (Scheme 6), soluble nanoparticles are in equilibrium with active monomeric or possibly dimeric anionic species. As described in terms of Le Chatelier’s principle, the equilibrium favours the formation of lower order monomeric and dimeric species when the catalyst concentration is low. On the other hand, palladium colloids are formed more rapidly at a higher palladium concentration. Finally, when these soluble colloids grow beyond a certain size, palladium black starts to form, negatively affecting the catalytic activity. Similar results have also been reported by Holder et al. and Schmidt and Smirnov.\(^{78,79}\) This phenomenon is especially important for aryl bromides for which oxidative addition is often rate-limiting and therefore most of the palladium will be in the form of Pd(0).\(^{77}\) When aryl iodides are used, the fast oxidative addition step prevents the formation of the colloids and, consequently, the palladium black during the reaction. When the reaction is completed, however, the rate of the colloid formation increases, and finally leads to the precipitation of palladium.\(^{71}\) Very recently, Köhler and co-workers reported the first ligand-free Heck reaction utilizing a soluble Pd catalyst (0.001–0.010 mol %) in the activation of aryl chlorides.\(^{80}\) However, only 4-chloroacetophenone worked well, while non-activated chlorobenzene and deactivated 4-chlorotoluene were found to be less reactive. The same authors also illustrated that 3 x 10\(^{-7}\) mol % of soluble ligand-free palladium is suffi-
cient to catalyse coupling between bromobenzene and styrene, this being the lowest ever reported amount of palladium needed for the coupling of non-activated aryl bromides.80

![Scheme 6. Equilibrium between the different forms of palladium under ligand-free conditions.](image)

In addition to concentration-controlled prevention of the formation of Pd black, a number of other approaches have been developed. 81,82 These include palladium nanoparticle stabilisation by, for example, immobilisation in ionic liquids, 83,84 polymers, 85 polymeric micelles 86,87 and other appropriate supports 88-91. The formation of highly active palladium species from palladacycles 92,93 and leaching of palladium from heterogeneous palladium catalysts 94-97 has also been reported.

1.2 Microwave-Assisted Organic Synthesis

1.2.1 Introduction

The first reliable device able to produce microwaves of fixed frequencies was introduced during World War II as part of the development of radar. It was later discovered that microwaves can be used to heat water and food very efficiently, and the first commercial domestic and industrial appliances became available in the USA in the 1950s. 98,99 An improvement and simplification of the microwave generator, the magnetron, in the 1970s decreased prices considerably and since then microwave ovens have been used for cooking and heating food worldwide. 100

Microwave ovens were introduced to chemistry in the late 1970s and the first reports suggesting that microwaves could be used to accelerate organic reactions appeared in 1986. 101,102 The uptake of this new technology was initially slow due to the lack of reproducibility and controllability, and safety aspects, together with a generally low degree of understanding of the basics of microwave dielectric heating. 100,103,104 However, it has gained in popularity, and sophisticated microwave systems can today be found in most well-equipped laboratories in industry and academia. The reason behind its popularity lies in its outstanding ability to reduce reaction times. 105-107 In addition,
it is often possible to obtain higher yields and enhanced product purities, and it also offers the possibility of using more environmentally friendly solvents, such as water or ionic liquids, as the reaction medium.

Almost all domestic microwave ovens, as well as the commercial ovens found in laboratories, operate at 2.45 GHz in order not to interfere with the wavelengths used for radar or telecommunication. This frequency corresponds to the wavelength of 12.2 cm and is located between the infrared and radiowave wavelengths in the electromagnetic spectrum (Figure 3).

Figure 3. The electromagnetic spectrum.

1.2.2 Microwave Dielectric Heating

In microwave dielectric heating, the electromagnetic radiation is transformed into heat and thus acts as a driving force for the reaction. As the name ‘electromagnetic’ implies, microwaves contain both electronic and magnetic field components, the former being responsible for the heating effect induced by dipolar polarization and/or ionic conduction mechanisms. This in situ energy conversion has many advantages over conventional heating methods, one being the direct homogeneous heating of the contents of a vessel (when appropriate, microwave-transparent vessels are used) instead of heating through the vessel walls which is the case in conventional heating. In addition, superheating can occur in sealed microwave vessels and therefore solvents with low boiling points can often be used at temperatures much higher than their conventional boiling points.

Dipolar polarization is the main mechanism accounting for microwave heating in polar systems lacking ionic components. In this heating mechanism, permanent or induced dipoles try to follow the oscillation of the applied electric field, but at the frequencies used in microwave dielectric heating, the dipoles do not have enough time to align themselves perfectly with the field, but instead they lose energy in the form of heat (Figure 4). The loss tangent, \( \tan \delta \), describes the ability of a material to convert electromagnetic energy into heat at a fixed frequency and temperature. The loss tangent can be defined as \( \tan \delta = \varepsilon''/\varepsilon' \), where the dielectric loss factor \( \varepsilon'' \) defines the
efficiency with which the heat is generated from absorbed electromagnetic radiation, and $\varepsilon'$ is the dielectric constant of the material and is a measure of the ability of a molecule to be polarized by an electric field. The ideal material (e.g. reactant, solvent) to be used in microwave-assisted reactions is one with a high loss tangent, which guarantees efficient energy absorption and, consequently, rapid heating.\textsuperscript{100,103,108,109}

![Image](image_url)

**Figure 4.** Microwave dielectric heating by (a) dipolar polarization and (b) ionic conduction.\textsuperscript{100}

In materials containing ions, ionic conduction starts to prevail. The ions will oscillate through the solution under the influence of the electric field, resulting in strong heating due to the conversion of kinetic energy to heat via collisions of the ions (Figure 4).\textsuperscript{99,100} As ionic conduction results in very effective and fast heating of otherwise non-polar reaction media, polar additives, such as ionic liquids, can be used to ensure adequate heating.

### 1.2.3 Microwave Effects

Since the early days of microwave-assisted organic synthesis (MAOS), the scientific community has been debating about the existence of ‘non-thermal microwave effects’.\textsuperscript{110-114} These effects are thought to arise from the direct interaction of the electric field with specific molecules in a reaction mixture, leading to an increase in a pre-exponential factor in the Arrhenius equation or to a decrease in the activation energy of the reaction.\textsuperscript{113,115} Today, it is largely accepted that the observed increase in reaction rates and the differences in the outcome of the reactions are the result of purely thermal/kinetic effects, and can be explained by favourable heat profiles and the inaccuracy in temperature measurements.\textsuperscript{109,114,116}

In conventional heating methods, such as oil baths and heat blocks, the heat is conducted through the reaction mixture via vessel walls. This results in an uneven heat distribution and, as it often takes a long time for a reaction mixture to reach reasonable thermal equilibrium, some by-product formation and/or decomposition of materials may occur.\textsuperscript{99,109} On the other hand, the direct and efficient heating of the reaction mixture by microwaves produces a uniform heating profile in a very short time providing the mixture is stirred while being heated.\textsuperscript{116} This fact, together with the superheating phenomenon mentioned above and the possibility of differential heating, often has a positive influence on reaction rates, yields and product distribution.\textsuperscript{109}
1.2.4 Microwave Reactors

Most of the pioneering experiments were carried out using domestic microwave ovens. These ovens produce a random distribution of microwaves within a cavity due to an on-off cycle of a power supply, leading to problems associated with reproducibility and the accuracy of temperature measurements.\textsuperscript{98,99,117} Furthermore, domestic microwave ovens lack sufficient shielding of the cavity in the case of an explosion, and are associated with other safety hazards. To solve the problems mentioned above, modern, scientific microwave ovens were developed in the mid 1990s and today there are several models and manufactures available on the market.

When microwaves enter the sample cavity, they are reflected by the oven walls creating a three-dimensional pattern of standing waves called modes.\textsuperscript{100} In single-mode ovens, the random intensity problem associated with domestic multi-mode ovens is overcome by using one, continuous standing wave with well-defined maximal and minimal field strengths.\textsuperscript{100,117} This new technology, combined with improved safety, an adjustable power throughput and reliable temperature and pressure monitoring, together with feedback control, provides optimal reproducibility and energy efficiency.\textsuperscript{118,119} Single-mode microwave ovens are, however, only applicable to small-scale reactions and, therefore, multi-mode units containing a larger microwave cavity have been developed. These instruments rely on continuous rotation of the samples in the cavity to ensure an even energy distribution, suitable for heating larger reaction vessels.\textsuperscript{99,120} Consequently, scientific multi-mode ovens provide a convenient option for direct scale-up of the reaction processes.

One, particularly difficult, problem associated with modern microwave-assisted organic chemistry is the correct measurement of the reaction temperature. These measurements are typically made using infrared sensors located outside the reaction vessel. As IR sensors actually measure the temperature of the reaction vessel walls, they will not always reflect the temperature inside the vessel.\textsuperscript{99} Therefore fibre-optic sensors immersed in the reaction mixture should be used.\textsuperscript{116,121,122} Furthermore, Kappe et al. showed very recently that efficient stirring is important to obtain a uniform temperature distribution and, consequently, an accurate value of the temperature.\textsuperscript{116}

Another problem relating to microwave chemistry has been scalability of reaction processes. However, it seems that this problem may soon be overcome, and there are already several options available for scaling-up reactions. In addition, a substantial amount of work is being devoted to the development of new, large-scale microwave systems.\textsuperscript{120,123,124}
1.3 Aqueous Palladium Catalysis

1.3.1 Water as a Solvent

Today, there is an ever-growing need for more environmentally benign processes in the chemical industry. This trend, known as Green Chemistry, emphasizes the importance of aspects such as resource efficiency, energy efficiency, product selectivity, operational simplicity and the impact on health and environmental safety.\textsuperscript{108,125-127} Some of these have already been discussed in this thesis, namely energy efficiency, in the form of microwave heating, and resource efficiency, in terms of low catalyst loadings. The third important aspect, which has been receiving much attention recently, is the use of water as an alternative solvent or co-solvent. Water, as a solvent of nature, has unique solvation properties that can, at least partially, be explained by its perfectly structured character in the liquid state.\textsuperscript{128} As a solvent, water is cost efficient, safe and readily available, making it a desirable alternative to a variety of organic solvents. In addition, water has been proven to be beneficial in terms of reaction rate enhancement and selectivity in many types of organic transformations.\textsuperscript{70,108} Finally, the work-up procedures at the end of the reaction are often simplified by easy phase separation, which allows for simple recycling of water-soluble catalysts and reagents.\textsuperscript{70,129,130} On the negative side, most organic materials are almost insoluble in water, limiting the use of pure water as a solvent. This problem can often be overcome by using phase transfer catalysts (PTCs), organic co-solvents, ionic derivatisation, surfactants or hydrophilic auxiliaries.\textsuperscript{70,108}

Based on its loss tangent value of 0.123, water is classified as a moderate microwave-absorbing solvent.\textsuperscript{108} Nevertheless, even in the absence of any additives, it can be heated up rapidly by microwave irradiation, making it an excellent solvent for microwave-assisted organic synthesis. Furthermore, when using sealed vessels together with strongly microwave-absorbing reagents/catalysts/additives, water can be used at temperatures high above its boiling point.

1.3.2 Palladium-Catalysed Carbon–Carbon Coupling Reactions in Aqueous Media

The pioneering work in the field of aqueous palladium-catalysed carbon–carbon coupling reactions was carried out by Beletskaya et al. in the late 1980s. This group showed that it is possible to couple aryl halides with acrylic acid and acrylonitrile in water, in the presence of Pd(OAc)\textsubscript{2} and an inorganic base (Scheme 7).\textsuperscript{131} Furthermore, water-soluble aryl halides were coupled in water with phenylboronic acid using a simple palladium salt at room temperature.\textsuperscript{132} In both cases, high yields of the products were obtained.
Scheme 7. Synthesis of substituted cinnamic acids and cinnamionitriles in aqueous media.

In principle, the aqueous palladium-catalysed coupling reactions can be divided into two categories, so-called ligand-free and phosphine-assisted coupling reactions.\textsuperscript{70} In the case of the former, the presence of water has been shown to be beneficial as it prevents the formation of bridged polymeric catalyst-complexes by ligand exchange processes, thus making the catalyst more prone to participate in the catalytic cycle.\textsuperscript{128} Water is also likely to be involved in the displacement of ligands blocking the palladium coordination sphere, leaving the palladium centre available for ligands taking part in the reaction.\textsuperscript{133} Furthermore, there is evidence pointing towards the red-ox properties of palladium being enhanced, enabling smooth reduction of Pd(II) to Pd(0) by any electron-rich species in the solution.\textsuperscript{128}

Although water is considered especially suitable for ligand-free coupling reactions, it also facilitates phosphine-assisted reactions. In these reactions, the oxygen atom in phosphine oxide, formed by the reduction of Pd(II) by the respective phosphine ligand, originates from a water molecule.\textsuperscript{133} This has been shown to be particularly important when using water-soluble phosphines, such as TPPTS (tris(3-sulfophenyl)phosphine trisodium salt, Figure 5).

![Figure 5](image_url)
1.4 HIV-1 Integrase Inhibitors

1.4.1 A Short History of AIDS and Current Status

The first cases of patients suffering from AIDS (acquired immunodeficiency syndrome) were reported in 1981.\textsuperscript{134-136} This, at that time unknown, disease resulted in the emergence of a number of opportunistic infections, such as \textit{Pneumocystis carinii} and \textit{Candida albicans}, and a rare form of cancer, Kaposi’s sarcoma.\textsuperscript{137} After much research by several groups around the world, a retrovirus causing AIDS was isolated in 1983.\textsuperscript{138,139} A similar virus, differing in some of its antigenic components, was discovered a few years later.\textsuperscript{140} These viruses are today known as human immunodeficiency viruses HIV-1 and HIV-2, the former being mainly responsible for new cases of infections in the human population.\textsuperscript{141,142}

According to the United Nations (Joint Programme on HIV/AIDS), there were an estimated 33.2 million people living with HIV in 2007.\textsuperscript{143} Sub-Saharan Africa remains as the most seriously affected area, with AIDS being the primary cause of death.

1.4.2 HIV-1 Integrase and Its Inhibition

The lifecycle of the HIV-1 virus has several possible targets for drug development, and today compounds belonging to five different classes of antiviral drugs are available on the market.\textsuperscript{144} These include fusion inhibitors, reverse transcriptase inhibitors, protease inhibitors, one integrase inhibitor and one co-receptor antagonist. In spite of the large amount of medication available, new anti-HIV drugs are needed to fight the rapidly mutating HIV-1 virus.

The genome of the HIV-1 virus consists of single-stranded RNA. During infection, viral particles fuse to the cell membrane and RNA is then released into the host cell. In the subsequent processes, the viral genome and viral genes are transcribed, viral proteins are synthesised and new infectious particles are created and released. The incorporation of viral cDNA (a double-stranded DNA copy of RNA) into the host DNA is catalysed by an enzyme called integrase (IN). This enzyme consists of three structural and functional domains: the N-terminal, the catalytic domain and the C-terminal. Of these, the catalytic domain is responsible for the integration step. More specifically, the three essential amino acids, Asp64, Asp116 and Glu152, found in the catalytic domain coordinate to one or most likely to two divalent cations (Mg\textsuperscript{2+} or Mn\textsuperscript{2+}) forming a complex with the viral DNA substrate. In the next step, the viral DNA is hydrolysed from the 3’-end by a water molecule in a process called 3’-processing (Figure 6a). This is followed by strand transfer (ST) in which the nucleophilic 3’-OH ends of the donor DNA are inserted into the host DNA backbone in a transesterification process (Figure 6b and
c). This process can be inhibited by so-called strand transfer inhibitors (STIs) that are able to displace the host DNA from the catalytic site and thus prevent the integration process (Figure 6b').

![Figure 6. The steps of retroviral integration and proposed binding of strand transfer inhibitors.](image)

RALTEGRAVIR

Raltegravir is the first FDA approved integrase inhibitor for the treatment of AIDS (Figure 7). This compound, which was approved in October 2007, belongs to a class of diketo acids (DKAs) and it most likely inhibits strand transfer by chelating to cationic metals with its diketo acid moiety. In addition, elvitegravir, the core structure of which is derived from the quinolone antibiotics, is undergoing clinical phase III trials. Like raltegravir, its mechanism of action involves chelation to the metals present in the active site.

![Figure 7. HIV-1 integrase inhibitors raltegravir and elvitegravir.](image)
2. Aims of the Present Study

The main purpose of this research was to study Pd(0)-catalysed carbon–
carbon coupling reactions in water, with special focus on the Suzuki and
Heck reactions. The specific aims were as follows.

- To reassess the transition-metal-free Suzuki-type coupling
  methodology reported earlier by Leadbeater et al. with the
  intention of developing a new, reproducible protocol for
  microwave-assisted, aqueous Suzuki coupling utilizing ul-
  tralow catalyst loadings.

- To determine the lower threshold of catalyst loading in
  microwave-assisted terminal Heck coupling in water, and to
  develop an easy, reliable protocol for the Heck reaction em-
  ploying a commercially available palladium standard solu-
  tion.

- To scale up the microwave-assisted Suzuki and Heck reac-
  tions in water utilizing ultralow catalyst loadings.

- To investigate the concept of microwave heating with simul-
  taneous cooling, and to exploit this technique in the coupling
  of aryl chlorides with phenylboronic acid in water.

- To develop a protocol for aqueous regioselective internal
  Heck arylation of hydroxyalkyl vinyl ethers by aryl halides.

- To use palladium catalysis in the synthesis of a series of new
  HIV-1 integrase inhibitors and to study the effects of struc-
  tural changes on their anti-IN activity.
3. Palladium-Catalysed Suzuki and Heck Coupling Reactions in Water using Ultralow Catalyst Concentrations (Papers I, II and III)

3.1 Background

In 2003, Maria Marco and Nicholas Leadbeater reported that, when using aqueous conditions, it was possible to perform Suzuki-type coupling of aryl bromides with phenylboronic acid without the need for a transition-metal catalyst (Scheme 8). This reaction was termed a ‘transition-metal-free Suzuki-type coupling’ as the levels of palladium were found to be below 0.1 ppm, this being the detection limit of the inductively coupled plasma atomic absorption (ICP-AA) spectrometer used for the analysis of crude reaction mixtures. Reaction mixtures were also analysed regarding the presence of other transition metals, but none was found to be present above a concentration of 0.1 ppm. However, at roughly the same time, several groups suggested that carbon–carbon coupling reactions could be catalysed by colloidal palladium nanoparticles. These palladium clusters could be formed, for example, by the addition of homeopathic doses of soluble palladium catalyst, by leaching of Pd(0) from palladium complexes or by stabilising nanoparticles on a support (for further information, see Section 1.1.5). Based on these reports, the possibility of the presence of exceedingly low amounts of palladium in the transition-metal-free Suzuki-type coupling methodology could not be excluded. Therefore, it was deemed necessary to reassess this methodology.

![Scheme 8. Transition-metal-free Suzuki-type coupling of aryl bromides with phenylboronic acid.](image)

<table>
<thead>
<tr>
<th>R</th>
<th>yield</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-COMe, 1a</td>
<td>96 %</td>
<td>3a</td>
</tr>
<tr>
<td>H, 1b</td>
<td>90 %</td>
<td>3b</td>
</tr>
<tr>
<td>4-Me, 1c</td>
<td>82 %</td>
<td>3c</td>
</tr>
<tr>
<td>4-OMe, 1d</td>
<td>53 %</td>
<td>3d</td>
</tr>
</tbody>
</table>
3.2 Reassessment of Transition-Metal-Free Suzuki-Type Coupling Methodology (Paper I)

3.2.1 Analysis of Reaction Parameters

In the original studies on transition-metal-free Suzuki-type coupling, the coupling of aryl bromides was limited to phenylboronic acid (2a, Scheme 8), while other boronic acids showed no activity at all. As this lack of reactivity could not be explained satisfactorily, an investigation into the details behind this reaction was initiated. Expanding the scope of this methodology to include other boronic acids was the preliminary aim. First, the possible presence of contaminants in boronic acids was studied as it was hypothesized that possible impurities, even at microscopic amounts, could be enough to stop the reaction from taking place. A series of arylboronic acids was re-purified using column chromatographic methods and re-crystallisation. These boronic acids (2b–e) were tested in the transition-metal-free coupling methodology with some positive results (Table 1); a few previously un-reactive boronic acids showed now some activity in this aqueous Suzuki-type coupling reaction. Good to excellent yields were obtained from the coupling of 4-bromoacetophenone (1a) with arylboronic acids containing both electron-rich and electron-withdrawing functionalities (entries 1, 3, 6 and 7). Also, 4-bromotoluene (1c) showed high reactivity with 4-methoxybenzeneboronic acid (2c) (entry 4), while 4-bromoanisole (1d) generally gave poor results with an electronically variable group of boronic acids (entries 2, 5 and 8). Altogether, the scope of boronic acids was still rather limited.

To broaden the methodology towards non-aromatic boronic acids, trans-2-phenylvinylboronic acid (2f) was screened, using identical conditions to those for the reactions presented in Table 1. Of several aryl bromides tested, only 4-bromoacetophenone gave a synthetically significant yield of the trans-stilbene product (Table 2, entry 1). With other aryl bromide coupling partners, the yields were generally low, and protodeboronation of 2f and decomposition of the starting material and/or products became an increasingly serious problem (Table 2, entries 2–6). However, unsaturated β-bromostyrene (1i) gave a good 77 % yield of 4g (entry 7).
Table 1. Suzuki-Type Coupling of Aryl Bromides with Arylboronic Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Boronic acid</th>
<th>Product</th>
<th>Yield / %</th>
</tr>
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<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
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<tr>
<td>3</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
<td>3f</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
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<tr>
<td>5</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
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<tr>
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<td><img src="image24.png" alt="Image" /></td>
<td>3k</td>
</tr>
</tbody>
</table>

Reactions were run in sealed vessels using 1 mmol aryl bromide (1), 1.3 mmol arylboronic acid (2), 3.7 mmol Na₂CO₃, 1 mmol TBAB and 2 mL water. No palladium was added. Reaction mixtures were irradiated with microwaves at 150 °C for 5 min.

After partial success with the preliminary aim, namely increasing the scope of the reaction, there were still some doubts about the nature and origin of the possible impurities. Therefore, both the water and sodium carbonate used in these reactions were analysed for trace amounts of palladium with ICP-MS (inductively coupled plasma mass spectrometry). ICP-MS was chosen as it allows palladium concentrations to be measured down to 0.01 ppb, thus providing a much more accurate method of detecting metal contaminations than ICP-AA spectrometer used in the original studies on transition-metal-free Suzuki reaction. The analysis of water indicated palladium levels of 0.24 ppb, which is believed to be too low to catalyse Suzuki coupling. Analysis of the sodium carbonate (3.7 mmol) dissolved in water (2 mL), on the other hand, showed palladium levels of 20–50 ppb. Albeit low, this amount could be responsible for Suzuki coupling. Further screening showed
that most of the sodium carbonate batches in the laboratory contained similar levels of palladium, while potassium carbonate, which showed no reactivity in transition-metal-free Suzuki-type coupling, contained essentially no palladium (0.09 ppb).

**Table 2. Suzuki-Type Coupling of Aryl Bromides and β-Bromostyrene with 2f**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl/Vinyl bromide</th>
<th>Product</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="" /></td>
<td><img src="image2" alt="" /></td>
<td>99</td>
</tr>
<tr>
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<td>3</td>
<td><img src="image5" alt="" /></td>
<td><img src="image6" alt="" /></td>
<td>26&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>4</td>
<td><img src="image7" alt="" /></td>
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<td>15&lt;sup&gt;b,c&lt;/sup&gt;</td>
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<td>7</td>
<td><img src="image13" alt="" /></td>
<td><img src="image14" alt="" /></td>
<td>77&lt;sup&gt;d&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Reactions were run in sealed vessels using 1 mmol aryl bromide (1) or 1i, 1.3 mmol trans-2-phenylvinylboronic acid (2f), 3.7 mmol Na₂CO₃, 1 mmol TBAB and 2 mL water. No palladium was added. Reaction mixtures were irradiated with microwaves at 150 °C for 5 min. <sup>b</sup> Significant quantities of styrene were observed. <sup>c</sup> Loss of material was observed. <sup>d</sup> Only the E,E isomer was formed.

To confirm the hypothesis that sub-ppm levels of palladium could be sufficient to catalyse this reaction, coupling of 4-bromoacetophenone (1a, 1 mmol) and phenylboronic acid (2a, 1.3 mmol) was run in water (2 mL) using tetrabutylammonium bromide (TBAB, 1 mmol) as the phase transfer catalyst and potassium carbonate (3.7 mmol) as the base. Instead of running this reaction without palladium, it was run in the presence of 100 ppb of aqueous Pd(OAc)₂, corresponding to approximately 50 ppb of palladium. The reaction mixture was irradiated at 150 °C for 5 minutes in a sealed vessel, giving a good yield (75 %) of 4-acetylbiphenyl (3a). Without the addition of any palladium, the same reaction resulted in yields of less than 5 %. Running the corresponding reaction in the presence of Na₂CO₃ instead of K₂CO₃ gave an
excellent 95 % of 3a. Finally, when running the reaction without the addition of any palladium and using a batch of Na₂CO₃ containing almost no palladium (0.21 ppb), no 3a was formed. However, when the same reaction was run with 100 ppb Pd(OAc)₂, this resulted in the formation of 90 % 3a. These experiments conclusively verify that this coupling is, indeed, catalysed by palladium, and does not represent a new, non-catalysed Suzuki pathway for the formation of biaryls.

The specific roles of water and tetrabutylammonium bromide used in the reaction were then investigated. Water is believed to be important here for two reasons. Firstly, it is needed simply to dissolve the inorganic carbonate base. Secondly, it is well known that water helps to stabilise palladium complexes and nanoparticles, and thus facilitates their catalytic action. In fact, when running this reaction neat, no product was formed at all. TBAB, on the other hand, is believed to act as a kind of ‘molecular mediator’ as it facilitates the migration of reactants in a heterogeneous system from one phase into another phase where reaction can take place. Furthermore, Badone et al. suggested that the rate enhancement of Suzuki coupling in aqueous media was caused by the formation of [ArB(OH)₃][Bu₄N]⁺. As it was already known from the initial study performed by Leadbeater and Marco that the presence of a phase transfer catalyst was absolutely necessary, it was now further investigated whether this PTC could be replaced by another one. To do this, a number of co-solvents (DMF, NMP, MeOH, BuOH and EtOH), able to dissolve organic reagents, were screened using 100 ppb aqueous Pd(OAc)₂, but without the addition of TBAB. Most of these solvents were found to be deleterious for product formation. However, ethanol worked well when used in 1:1 ratio with water, giving comparable yields to reactions in water/TBAB. This shows that in this case, TBAB acts mainly as a phase transfer catalyst, and most likely has only a minor effect or no other benefit on the overall reaction.

3.2.2 Development of an Improved Protocol for Aqueous Suzuki Reactions Utilizing Ultralow Palladium Concentrations

The final aim of this study was to develop a more general protocol for aqueous Suzuki coupling. To do this, phenylboronic acid (2a) was coupled with 4-bromoacetophenone (1a), 4-bromotoluene (1c) and 4-bromoanisole (1d) using palladium loadings of 100 ppb, 250 ppb and 2.5 ppm. Both carbonate bases, Na₂CO₃ and K₂CO₃, were screened and reactions were run using both microwave heating and conventional heating. In the first series of experiments, TBAB was used as a PTC (Table 3). All microwave-assisted reactions were run using readily water-soluble Pd(NO₃)₂, as it allows easier and more reliable preparation of an aqueous palladium stock solution than spar-
ingly soluble Pd(OAc)$_2$. Notably, when 1a was coupled with 2a using 100 ppb Pd(NO$_3$)$_2$ in the presence of sodium carbonate, a substantially lower yield of 3a (56 %) was obtained (Table 3, entry 1) than when using 100 ppb Pd(OAc)$_2$ (95 %), implying that the former had a poorer catalytic activity. However, when the palladium loading was increased to 2.5 ppm, excellent yields were obtained with 1a, 1c and 1d (entries 1–3). Potassium carbonate was found to be slightly less reactive, although at higher palladium concentrations the yields started to resemble those with sodium carbonate (entries 4–6). A similar trend was seen in the series of reactions run with conventional heating, although a direct comparison is not possible as the palladium source in this case was aqueous Pd(OAc)$_2$ (entries 7–10). Furthermore, the exact temperature of the reaction mixture in the oil bath was not recorded. A similar set of data to presented in Table 3 was acquired using 1:1 H$_2$O/EtOH mixtures with no TBAB (Table 4). It can be postulated that a water/ethanol system performs slightly better, especially at lower concentrations, but as this trend does not seem to be consistent throughout the data set, no clear conclusions can be drawn.

Table 3. Suzuki Coupling of Aryl Bromides with Phenylboronic Acid using TBAB$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd loading</th>
<th>Base</th>
<th>Heating</th>
<th>Product yield / %</th>
<th>1a</th>
<th>1c</th>
<th>1d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 ppb</td>
<td>Na$_2$CO$_3$</td>
<td>mw$^b$</td>
<td>56</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>250 ppb</td>
<td>Na$_2$CO$_3$</td>
<td>mw$^b$</td>
<td>94</td>
<td>41</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.5 ppm</td>
<td>Na$_2$CO$_3$</td>
<td>mw$^b$</td>
<td>99</td>
<td>92</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100 ppb</td>
<td>K$_2$CO$_3$</td>
<td>mw$^b$</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>250 ppb</td>
<td>K$_2$CO$_3$</td>
<td>mw$^b$</td>
<td>57</td>
<td>14</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.5 ppm</td>
<td>K$_2$CO$_3$</td>
<td>mw$^b$</td>
<td>89</td>
<td>81</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>100 ppb</td>
<td>Na$_2$CO$_3$</td>
<td>oil bath$^c$</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>250 ppb</td>
<td>Na$_2$CO$_3$</td>
<td>oil bath$^c$</td>
<td>70</td>
<td>60</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2.5 ppm</td>
<td>Na$_2$CO$_3$</td>
<td>oil bath$^c$</td>
<td>81</td>
<td>70</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2.5 ppm</td>
<td>K$_2$CO$_3$</td>
<td>oil bath$^c$</td>
<td>95</td>
<td>50</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Reactions were run in sealed vessels using 1 mmol aryl bromide (1), 1.3 mmol phenylboronic acid (2a), 3.7 mmol base, 1 mmol TBAB and a total water volume of 2 mL. $^b$ Pd(NO$_3$)$_2$ was used as a catalyst. The temperature was ramped from rt to 150 ºC where it was then held for 5 min. $^c$ Pd(OAc)$_2$ was used as a catalyst. The reaction mixture was placed in a preheated oil bath (150 ºC) and kept there for 7 min.

To test the general applicability of this newly optimised aqueous Suzuki protocol, a representative series of aryl bromides was coupled with *trans*-2-phenylvinylboronic acid (2f) using a palladium loading of 2.5 ppm (Table 5). The product yields follow a similar trend to that which can be seen in Table 2 but, quite expectedly, higher yields were obtained this time.
Table 4. Suzuki Coupling of Aryl Bromides with Phenylboronic Acid in a Water/Ethanol Mixture

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd loading</th>
<th>Base</th>
<th>Heating</th>
<th>Product yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 ppb</td>
<td>Na₂CO₃</td>
<td>mw</td>
<td>83, 6, 5</td>
</tr>
<tr>
<td>2</td>
<td>250 ppb</td>
<td>Na₂CO₃</td>
<td>mw</td>
<td>99, 60, 19</td>
</tr>
<tr>
<td>3</td>
<td>2.5 ppm</td>
<td>Na₂CO₃</td>
<td>mw</td>
<td>99, 99, 99</td>
</tr>
<tr>
<td>4</td>
<td>100 ppb</td>
<td>K₂CO₃</td>
<td>mw</td>
<td>13, 10, 3</td>
</tr>
<tr>
<td>5</td>
<td>250 ppb</td>
<td>K₂CO₃</td>
<td>mw</td>
<td>83, 21, 14</td>
</tr>
<tr>
<td>6</td>
<td>2.5 ppm</td>
<td>K₂CO₃</td>
<td>mw</td>
<td>80, 75, 71</td>
</tr>
<tr>
<td>7</td>
<td>100 ppb</td>
<td>Na₂CO₃</td>
<td>oil bath</td>
<td>5, 0, 0</td>
</tr>
<tr>
<td>8</td>
<td>250 ppb</td>
<td>Na₂CO₃</td>
<td>oil bath</td>
<td>78, 75, 0</td>
</tr>
<tr>
<td>9</td>
<td>2.5 ppm</td>
<td>Na₂CO₃</td>
<td>oil bath</td>
<td>95, 94, 85</td>
</tr>
<tr>
<td>10</td>
<td>2.5 ppm</td>
<td>K₂CO₃</td>
<td>oil bath</td>
<td>95, 71, 75</td>
</tr>
</tbody>
</table>

*a* Reactions were run in sealed vessels using 1 mmol aryl bromide (1), 1.3 mmol phenylboronic acid (2a), 3.7 mmol base, 1 mL EtOH and a total water volume of 1 mL. *b* Pd(NO₃)₂ was used as a catalyst. The temperature was ramped from rt to 150 °C where it was then held for 5 min. *c* Pd(OAc)₂ was used as a catalyst. The reaction mixture was placed in a preheated oil bath (150 °C) and kept there for 7 min.

Table 5. Coupling of Aryl Bromides with 2f using 2.5 ppm Pd(OAc)₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl bromide</th>
<th>Product</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1c</td>
<td>4h</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>MeO-1d</td>
<td>4b</td>
<td>81⁺</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>4i</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>Cl-1j</td>
<td>4j</td>
<td>56⁺</td>
</tr>
<tr>
<td>5</td>
<td>H₂N-1h</td>
<td>4f</td>
<td>56⁺</td>
</tr>
</tbody>
</table>

*a* Reactions were run in sealed vessels using 1 mmol aryl bromide (1), 1.3 mmol *trans*-2-phenylvinylboronic acid (2f), 3.7 mmol Na₂CO₃, 1 mmol TBAB and a total water volume of 2 mL. The reaction mixtures were irradiated with microwaves at 150 °C for 5 min. *b* Loss of material was observed.

In summary, it was shown that Suzuki coupling of aryl bromides with phenylboronic acid cannot be performed without transition-metal catalysis.
In fact, the earlier reported ‘transition-metal-free Suzuki-type coupling’ can now be concluded to take place due to sub-ppm levels of palladium contaminants found in the sodium carbonate. Based on this finding, a new, improved Suzuki protocol was developed using ppb/ppm levels of palladium, 2.5 ppm palladium being sufficient to produce good product yields.

3.3 Terminal Heck Coupling in Water (Paper II)

Having proved that the Suzuki coupling of aryl bromides is possible with only ppb/ppm levels of palladium, the next step was to investigate the lower boundary of the catalyst loading with other palladium-catalysed coupling reactions. To do this, the terminal Heck coupling of aryl halides with styrene was studied.

3.3.1 Selection of a Catalyst Source and Determination of the Lower Limit of Catalyst Loading

In order to achieve consistent and accurate results easily and reliably, a new catalyst source with known palladium concentration was needed. Therefore a 1000 ppm palladium standard solution stabilised with 20 % HCl was purchased. This solution is typically used for the calibration of ICP-AES and ICP-MS instruments. To meet the requirements of this study, the standard was diluted on a daily basis with water to the desired palladium concentrations. To further ensure that the palladium would not precipitate from the solution, a few drops of concentrated hydrochloric acid were added to freshly prepared reference solutions.

The coupling between 4-bromoanisole and styrene in water was chosen as a suitable model reaction (Scheme 9). The reactions were performed on a 1 mmol scale in water (2 mL) using 2 equivalents of styrene, an inorganic base and TBAB as a PTC. In this context, potassium carbonate was found to be superior to sodium carbonate and other inorganic bases, such as sodium hydroxide and potassium acetate.

![Scheme 9. Terminal Heck coupling of 4-bromoanisole with styrene in water.](image)

As the primary objective here was to investigate the lower limit of the catalyst loading, the reaction time and temperature were optimised rapidly, and found to be 10 minutes and 170 °C, respectively. A reaction using 0.38
mol % of the catalyst, corresponding to 200 ppm of palladium, together with a large excess (6 equiv) of base gave an excellent 90 % yield of 4-methoxy-trans-stilbene (Table 6, entry 1). The amount of base was further reduced to 3.7 equivalents, giving a yield of 4b of 92 % after 10 minutes’ irradiation at 170 °C (entry 2).

Having found the roughly optimised reaction conditions, attention was turned to decreasing the catalyst concentration (Table 6, entries 2–7). As can be seen in Table 6, lowering the amount of palladium 20 times to 0.0188 mol % had little or no effect on the product yield. Below this, the yields of 4b slowly started to decrease; 0.0009 mol % still giving a somewhat respectable yield of 55 % after 10 minutes’ irradiation. Doubling of the reaction time to 20 minutes at 170 °C increased the yield of 4b to 80 %, demonstrating the possibility of using ultralow catalyst loadings, this time 500 ppb, in terminal Heck coupling reactions.

Table 6. Evaluation of the Lowest Possible Catalyst Concentration in the Heck Coupling of 4-Bromoanisole and Styrene in Water using Microwave Heating

<table>
<thead>
<tr>
<th>Entry</th>
<th>Palladium concentration / ppm</th>
<th>Catalyst loading / mol %</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>200</td>
<td>0.3773</td>
<td>90</td>
</tr>
<tr>
<td>2c</td>
<td>200</td>
<td>0.3773</td>
<td>92</td>
</tr>
<tr>
<td>3c</td>
<td>10</td>
<td>0.0188</td>
<td>90</td>
</tr>
<tr>
<td>4c</td>
<td>2.5</td>
<td>0.0047</td>
<td>83</td>
</tr>
<tr>
<td>5c</td>
<td>1.0</td>
<td>0.0019</td>
<td>59</td>
</tr>
<tr>
<td>6c</td>
<td>0.5</td>
<td>0.0009</td>
<td>55</td>
</tr>
<tr>
<td>7c,d</td>
<td>0.5</td>
<td>0.0009</td>
<td>80</td>
</tr>
</tbody>
</table>

*a* Reactions were run in sealed vessels using 1 mmol 1d, 2 mmol 5a, 1 mmol TBAB and a total water volume of 2 mL. The reaction mixtures were irradiated with microwaves at 170 °C for 10 min. *b* Using 6.0 equiv K₂CO₃. *c* Using 3.7 equiv K₂CO₃. *d* Run for a total reaction time of 20 min.

Interestingly, it was noted that stirring the reaction mixture during microwave irradiation was deleterious for the product yields. It is believed that without stirring, the reaction mixture forms two distinct layers, and the reaction takes place either at the aqueous/organic interface or palladium migrates from the water to the organic phase initiating the reaction. When the mixture is stirred, the organic material is more likely to be exposed to the basic aqueous medium and competing side-reactions may start taking place. In addition, a temperature gradient caused by differential heating is likely to exist and may further be beneficial for the product yields.
3.3.2 The Scope of the Methodology

Having investigated the role of the palladium loadings in the Heck coupling of 1d with 5a, the scope of this protocol was studied. A series of aryl bromides and aryl iodides containing both electron-rich and electron-withdrawing groups was tested using catalyst loadings of 0.0019 and 0.0009 mol % and reaction times of 10 and 20 minutes, respectively (Table 7, entries 1–16). Although good yields were obtained with certain substituents on aryl bromides, such as acetyl, methyl, methoxy and fluoride groups (entries 1, 3, 6, 8 and 10), the scope of this protocol seems to be limited to a few functionalities. Aryl iodides were found to give poorer yields than aryl bromides. The only aryl chloride tested, 4-chlorotoluene (1q), showed almost no reactivity in this protocol (entry 17). In an additional series of experiments, some aryl bromides were coupled with acrylic acid 5b (Table 7, entries 18–22). These couplings gave generally lower yields than the corresponding couplings with styrene.

**Table 7. Heck Coupling in Water using Ultralow Catalyst Concentrations**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Olefin</th>
<th>Product</th>
<th>Catalyst / mol %</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>5a</td>
<td>4a</td>
<td>0.0019</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>5a</td>
<td>4a</td>
<td>0.0009</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>5a</td>
<td>4h</td>
<td>0.0019</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>5a</td>
<td>4h</td>
<td>0.0009</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>1d</td>
<td>5a</td>
<td>4b</td>
<td>0.0019</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>5a</td>
<td>4b</td>
<td>0.0009</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>1b</td>
<td>5a</td>
<td>4i</td>
<td>0.0019</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>1e</td>
<td>5a</td>
<td>4c</td>
<td>0.0019</td>
<td>82</td>
</tr>
<tr>
<td>9</td>
<td>1j</td>
<td>5a</td>
<td>4j</td>
<td>0.0019</td>
<td>30</td>
</tr>
</tbody>
</table>
To summarise, terminal Heck coupling using homeopathic amounts of palladium (> 500 ppb) was shown to be possible utilizing a simple commercial palladium standard and microwave irradiation. Disappointingly, this methodology is today limited to simple functionalities on the aryl halide counterpart.
3.4 Scale-Up of Suzuki and Heck Coupling Reactions in Water (Paper III)

3.4.1 Scale-Up of Microwave-Assisted Reactions

Almost every synthetic chemist today would agree that microwave heating has beneficial effects, although the reasons for its effectiveness are still being debated. Most of the reported reactions have, however, been performed on the mmol scale, whereas industrial needs are often on a completely different level. Therefore, the challenge during the past decade has been, and surely several more to come will be, the scale-up of microwave-assisted reactions from the milligram to kilogram scale.

The two major scale-up options available at present are the use of batch reactors and a continuous-flow microwave cell technique. When using batch reactors, small-scale methodologies can often be scaled-up directly providing a fast and often effective way to increase the amount of the desired products. However, batch reactors suffer from the limited penetration depth of microwaves into absorbing materials. As the penetration depth is typically only of the order of a few centimetres, depending on the dielectric properties of the medium, this places an upper limit on batch reactors of approximately 1 L, when closed vessels are being used. Also, a higher amount of microwave energy must be used in larger reaction vessels reducing the overall energy efficiency of the technique. Furthermore, as the reaction handling (cooling, safety aspects relating to high pressures, etc.) is more complicated in larger batch reactors, the cost of these reactors is increased making them less desirable options for industrial use. Some of these problems can be solved, at least partially, by running reactions in open vessels or by using smaller reaction vessels in a parallel fashion but many experts in the field believe today that the solution to scaling-up issue lies in the continuous-flow approach.

The first continuous-flow reactor combining microwave heating and flow processing was introduced by Strauss et al. in the early 1990s. This technique allows microwave-assisted reactions to be carried out on a multigram scale in a very safe and simple manner using commercially available microwave reactors and flow cells. Problems arise from clogging of the tubing when heterogeneous reaction mixtures or highly viscous liquids are used. Due to this, direct scale-up is often not feasible, and the reaction conditions are instead optimised in order to find a suitable protocol for use with a continuous-flow microwave cell. As a consequence, the stop-flow technique, combining the advantages of both batch reactors and continuous-flow reactors, was developed. In this method, the reaction mixture is pumped into the reaction vessel, irradiated for the required time and then emptied in a fully computerised process, allowing a series of microwave-
heated reactions to be performed automatically during one run. As peristaltic pumps are used in stop-flow approach, which are capable of processing slurries or even solid reagents, this clearly represents an improvement to the continuous-flow technique.  

3.4.2 Results and Discussion

To study the prospects of the Suzuki and Heck couplings in water, a few representative reactions were scaled up using a CEM Voyager microwave stop-flow system. This instrument consists of a single-mode microwave apparatus with a cavity for an 80 mL microwave vessel connected to peristaltic pumps used to fill and empty the reaction vessel.

Before using the automated batch stop-flow microwave apparatus, the Suzuki and Heck protocols were scaled up from a 10 mL reaction vessel used in the preliminary studies (Papers I and II) to the larger 80 mL vessel. To ensure accurate temperature measurements, a fibre-optic temperature sensor was used. Starting with the Suzuki coupling of 4-bromoacetophenone (1a) with phenylboronic acid (2a), rapid optimisation of the reaction parameters was performed (Table 8). A water/ethanol mixture (1:1), which had previously been identified as a suitable reaction medium, was assumed to be superior in this context to water together with TBAB. First, the suitability of the commercial 1000 ppm palladium standard solution as the catalyst source was tested. Working on a 1 mmol scale using the optimised conditions reported in Paper I, an excellent yield of 99 % of 4-acetylbiphenyl 3a was obtained after 5 minutes’ irradiation at 150 °C (Table 8, entry 1). Scaling up this reaction 10-fold in the 80 mL reaction vessel gave a 96 % yield of 3a showing the direct scalability of this Suzuki coupling protocol (entry 2). As the chosen reaction medium, 1:1 H₂O/EtOH, allows the organic material to be pumped into the reaction vessel dissolved in ethanol, and the inorganic base dissolved in water, this protocol could have been used directly for the scale-up in the CEM Voyager module. However, a short scan of the reaction conditions showed that a decrease in the amount of the base to 1 equivalent and a catalyst loading of 50 ppb still gave a 99 % yield of 3a (entries 3–6). Lowering the amount of 2a to 1 equivalent gave only a marginally poorer yield of 96 % (entry 7). Furthermore, as cleaning of the narrow tubing in the batch stop-flow microwave apparatus is necessary in order to prevent blockages, the effect of a small amount of ethyl acetate was tested and found to be very small (entry 8). Finally, 4-bromotoluene (1c) and 4-bromoanisole (1d) were tested in this protocol using both 50 and 250 ppb catalyst loadings (entries 9–12). In both cases, the optimum catalyst concentration was found to be 250 ppb giving excellent yields of 3c and 3d of 99 % and 91 %, respectively.
Table 8. Optimisation of the Conditions for the Scale-Up of Microwave-Assisted Suzuki Coupling Reactions in Water

<table>
<thead>
<tr>
<th>Entry</th>
<th>1a / mmol</th>
<th>2a / mmol</th>
<th>Na₂CO₃/ mmol</th>
<th>H₂O/ mL</th>
<th>EtOH/ mL</th>
<th>Pd/ppb</th>
<th>Yield/%</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1.3</td>
<td>3.7</td>
<td>1</td>
<td>1</td>
<td>250</td>
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<td>2</td>
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<td>13</td>
<td>37</td>
<td>10</td>
<td>10</td>
<td>250</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
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<td>20</td>
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<td>10</td>
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<td>98</td>
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<td>91</td>
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<td>9ᶜ</td>
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<td>10</td>
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<td>10</td>
<td>10</td>
<td>50</td>
<td>75</td>
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<td>10</td>
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<td>10</td>
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<td>11ᵈ</td>
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<td>45</td>
</tr>
<tr>
<td>12ᵈ</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>250</td>
<td>91</td>
</tr>
</tbody>
</table>

ᵃ The temperature was ramped from rt to 150 °C where it was then held for 5 min. ᵇ Run using an additional 4 mL ethyl acetate as a co-solvent. ᶜ Using 4-bromotoluene (1c) as the aryl bromide substrate. ᵈ Using 4-bromoanisole (1d) as the aryl bromide substrate.

The ease of pumping the materials into and out of the microwave cavity of the CEM Voyager equipment was tested by running one cycle using the conditions reported in entry 8 (Table 8) but without the addition of ethyl acetate. The reagents dissolved in ethanol (1a, 2a and palladium) and water (sodium carbonate) were easily pumped into the reaction vessel. The removal of the product, 3a, from the vessel, however, was found to be problematic as the formed biphenyl solidified below 90 °C and blocked the exit tubing. This was easily overcome by pumping in 15 mL ethyl acetate before the solidification of 3a and then removing the biphenyl fully dissolved in the organic solvent. This allows easy removal of the product and also removes the need for an additional cleaning cycle between runs.

Consequently, ten cycles of 10 mmol Suzuki coupling reactions were run using 4-bromoacetophenone and 4-bromoanisole as aryl bromide counterparts (Scheme 10). Excellent yields of 95 % and 93 % of 3a and 3d, respectively, were obtained, showing proof of concept of the batch stop-flow microwave instruments.
Scheme 10. Scale-up of the aqueous Suzuki coupling reaction in the batch stop-flow microwave instrument.

In the second part of this project, the scale-up of the aqueous Heck protocol was investigated. A short optimisation study similar to that for Suzuki coupling was performed (Table 9). The coupling of 4-bromoanisole (1d) and styrene (5a) to give 4-methoxy-\textit{trans}-stilbene (4b) was selected as a good model. When working on the 1 mmol scale using the optimised conditions determined in the previous study (Paper II), a catalyst loading between 2.5 and 10 ppm seems optimal (Table 9, entries 1–3). In this case, a catalyst concentration of 5 ppm was chosen for direct 10-fold scale-up in the 80 mL vessel, giving a good yield (76 %) of 4b (entry 4). As was discussed in connection with Paper II, the best results were obtained without stirring. Unfortunately, the changes in the amounts of 5a, potassium carbonate and TBAB were not tolerated well, showing the fragile nature of this Heck coupling reaction (entries 5–7).

As the organic reagents for this Heck reaction cannot be pumped into the microwave vessel dissolved in water alone, the effects of adding small amounts of NMP, ethanol and DMF were studied (Table 9, entries 8–13). DMF was found to be the best, although it was necessary to extend the reaction time to compensate for the deleterious effect of the co-solvent (entry 11). In a protocol suitable for the batch stop-flow reactor, organic materials and palladium were dissolved in 2.5 mL of DMF followed by the addition of 1 mL of DMF to rinse the tubing. Potassium carbonate was dissolved in water (17.5 mL) after which the water-DMF mixture was irradiated at 170 °C for 20 minutes, giving a 74 % yield of stilbene product 4b (entry 13). Screening of 4-bromoacetophenone (1a) and 4-bromotoluene (1c) demonstrated the applicability of this methodology to other aryl bromide substrates, giving a 92 % yield of 4a (after 15 minutes’ heating) and a 74 % yield of 4h (after 20 minutes’ heating) (entries 14–17).
Table 9. Optimisation of the Conditions for the Scale-Up of Microwave-Assisted Heck Coupling Reactions in Water

![Chemical Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>1d / mmol</th>
<th>5a / mmol</th>
<th>K₂CO₃/ mmol</th>
<th>TBAB/ mmol</th>
<th>H₂O/ mL</th>
<th>Co-solvent</th>
<th>Pd/ ppm</th>
<th>Yield/ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3.7</td>
<td>1</td>
<td>2</td>
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<td>10</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3.7</td>
<td>1</td>
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<td>none</td>
<td>2.5</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3.7</td>
<td>1</td>
<td>2</td>
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<td>32</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>12</td>
<td>37</td>
<td>10</td>
<td>20</td>
<td>none</td>
<td>5</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>20</td>
<td>none</td>
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<td>53</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>20</td>
<td>37</td>
<td>10</td>
<td>17.5</td>
<td>NMP, 2.5 mL</td>
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<td>27</td>
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<td>10</td>
<td>10</td>
<td>20</td>
<td>37</td>
<td>10</td>
<td>17.5</td>
<td>DMF, 2.5 mL</td>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>20</td>
<td>37</td>
<td>10</td>
<td>17.5</td>
<td>DMF, 2.5 mL</td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>20</td>
<td>37</td>
<td>10</td>
<td>15</td>
<td>DMF, 5 mL</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>10</td>
<td>20</td>
<td>37</td>
<td>10</td>
<td>17.5</td>
<td>DMF, 3.5 mL</td>
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<td>74</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>20</td>
<td>37</td>
<td>10</td>
<td>17.5</td>
<td>DMF, 2.5 mL</td>
<td>5</td>
<td>74</td>
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<tr>
<td>15</td>
<td>10</td>
<td>20</td>
<td>37</td>
<td>10</td>
<td>17.5</td>
<td>DMF, 2.5 mL</td>
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<td>16</td>
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<td>20</td>
<td>37</td>
<td>10</td>
<td>17.5</td>
<td>DMF, 2.5 mL</td>
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<td>79</td>
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<tr>
<td>17</td>
<td>10</td>
<td>20</td>
<td>37</td>
<td>10</td>
<td>17.5</td>
<td>DMF, 2.5 mL</td>
<td>5</td>
<td>92</td>
</tr>
</tbody>
</table>

* The temperature was ramped from rt to 170 °C where it was then held for 10 min.

Run for a total reaction time of 20 min. Using 4-bromotoluene (1c) as the aryl bromide substrate. Run for a total reaction time of 15 min. Using 4-bromoacetophenone (1a) as the aryl bromide substrate.

Finally, 10 cycles of 10 mmol coupling reactions of 4-bromoanisole and styrene were run using the CEM Voyager equipment. As in the Suzuki reactions, 15 mL of an organic solvent, this time DMF, was pumped into the reaction vessel after each cycle in order to prevent the solidification of the stilbene products formed and allow for the easy removal of the material via the exit tube. An overall reaction yield of 71 % of 4b was obtained (Scheme 11). The process was then repeated with 4-bromoacetophenone 1a using a slightly shorter reaction time of 15 minutes per cycle, giving an overall yield of 85 % of 4a after 10 cycles.
Scheme 11. Scale-up of the aqueous Heck coupling reaction in the batch stop-flow microwave instrument.

In conclusion, the earlier developed Suzuki and Heck coupling protocols utilizing only ppb/ppm levels of palladium were easily scaled up using an automated stop-flow CEM Voyager microwave apparatus. Although this work can still be considered as done on a relatively small scale, it shows proof of concept and offers an easy, fast, safe and relatively cheap means of producing biphenyl or stilbene products.
4. Suzuki Coupling of Aryl Chlorides in Water using Microwave Heating with Simultaneous Cooling (Paper IV)

4.1 Introduction

Organochlorides represent a group of readily available and cheap starting materials for many palladium-catalysed transformations. As a result, a considerable amount of work has been devoted to finding new, efficient ways of activating sluggish C–Cl bonds towards the oxidative addition to palladium. Today, several palladium complexes and ligands, such as palladacycles, electron-rich and/or bulky phosphine ligands and N-heterocyclic carbenes, specifically designed to be used with aryl chlorides, are commercially available.

In an effort to find new microwave-assisted palladium-catalysed carbon–carbon coupling reactions in water, the Suzuki coupling of aryl chlorides was also studied. Unfortunately, the previously described methods utilizing ultralow palladium concentrations in water gave poor results, if any, when aryl chlorides were employed (Papers I and II). A quick survey of the literature showed this to be generally true when using unactivated aryl chlorides together with simple palladium sources such as Pd(OAc)$_2$, PdCl$_2$ and palladium on carbon (Pd/C) without any extra activation by, for example, electron-rich phosphine ligands.

4.2 Results and Discussion

As the earlier aqueous protocols failed in the activation of C–Cl bonds, focus was shifted towards another simple catalyst source, namely palladium on carbon. This heterogeneous catalyst has been used rather extensively to catalyse Suzuki couplings, particularly in aqueous media.

First, a coupling of 4-chlorotoluene and phenylboronic acid was studied (Scheme 12). Typically, 1 mmol of 1q together with 1.3 mmol of 2a in water (2 mL) was irradiated in the presence of 1 mol % Pd/C, Na$_2$CO$_3$ (3.7 mmol) and TBAB (1 mmol); the role of TBAB being as a phase transfer catalyst.
Scheme 12. Suzuki coupling of 4-chlorotoluene with phenylboronic acid.

An analysis of the reaction mixture after a preliminary heating period at 120 °C for 10 minutes showed a significant loss of material (Table 10, entry 2). This was assumed to be related to the thermal decomposition of 4-chlorotoluene as the formed biphenyl (3c) is thought to be relatively stable under the conditions used here. Several reaction temperatures were tested in order to prevent this unwanted side-reaction (entries 1, 3 and 4) but unfortunately, in all cases, major problems were encountered in the form of the decomposition of 1q.

Table 10. Coupling of 4-Chlorotoluene with Phenylboronic Acid in Water

<table>
<thead>
<tr>
<th>Entry</th>
<th>T / °C</th>
<th>Simultaneous cooling</th>
<th>Material recovered / mmol</th>
<th>Product / mmol</th>
<th>4-Chlorotoluene</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<td>0.19</td>
<td>0.38</td>
</tr>
<tr>
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<td>0.19</td>
<td>0.19</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>no</td>
<td>0.40</td>
<td>0.23</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>no</td>
<td>0.56</td>
<td>0.08</td>
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<td></td>
</tr>
<tr>
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<td>no</td>
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<td>0.10</td>
<td>0.71</td>
<td></td>
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<td>100</td>
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<td>0.12</td>
<td>0.52</td>
<td></td>
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<tr>
<td>6</td>
<td>120</td>
<td>yes</td>
<td>0.75</td>
<td>0.07</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>7</td>
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<td>yes</td>
<td>0.71</td>
<td>0.10</td>
<td>0.81</td>
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</tr>
<tr>
<td>8</td>
<td>150</td>
<td>yes</td>
<td>0.56</td>
<td>0.19</td>
<td>0.75</td>
<td></td>
</tr>
</tbody>
</table>

*Reactions were run in sealed vessels using 1 mmol 4-chlorotoluene (1q), 1.3 mmol phenylboronic acid (2a), 1 mol % Pd/C, 3.7 mmol Na₂CO₃, 1 mmol TBAB and 2 mL water. Reaction mixtures were irradiated with microwaves at the target temperature for 10 min. The temperature was measured using a fibre-optic device inserted into the reaction vessel. Yields were determined by comparison to internal standard in ¹H NMR analysis.

In an attempt to control the course of the reaction, the technique of ‘microwave heating with simultaneous cooling’ was explored. This relatively new technique allows, in principle, a higher level of microwave energy to be introduced into the sample while maintaining the desired temperature by cooling the reaction vessel with a stream of compressed air or with the aid of a cooling fluid. According to some early reports, this technique increases the product yields and may even open up new, previously unattainable, reaction pathways, once again raising the question of the existence of non-thermal microwave effects.¹⁷₀,¹⁷¹ Recent detailed studies by the groups of Leadbeater and Kappe show, however, that measurements using IR temperature sensors
located outside the reaction vessels are easily affected by the simultaneous cooling, thus limiting the credibility of these early reports.\textsuperscript{116,121,122}

All the preliminary reactions at different temperatures were repeated using the simultaneous cooling technique (Table 10, entries 5–8). To ensure the accuracy of temperature measurements, a fibre-optic temperature sensor, located inside the reaction vessel, was used. The total recovery of material was significantly higher when using simultaneous cooling, at all the temperatures tested, the best results being obtained at 120 °C. Moreover, the yields were often higher than without cooling. These improvements are probably due to a reduction in the rate of decomposition of 4-chlorotoluene due to cooling of the reaction vessel walls. It must be emphasized that both series of results (with and without cooling) were obtained using otherwise identical reaction conditions and temperature sensor. Furthermore, variations in reaction temperatures and times were carefully controlled and observed to be very small, as can be seen in Figure 8.

![Figure 8](Image)

**Figure 8.** Heating profiles for Suzuki coupling of 4-chlorotoluene with 2a at 120 °C with and without simultaneous cooling.

Encouraged by the good results obtained, a variety of aryl chlorides were screened at 120 °C with and without simultaneous cooling (Table 11). The effects of simultaneous cooling were insignificant on the product yields when using substrates bearing electron-withdrawing groups (entries 1–3). This is not highly surprising since these activated aryl chlorides are known to react relatively fast in this type of coupling reactions, thus competing efficiently with possible side-reactions. Electron-neutral and electron-rich aryl chlorides, on the other hand, benefited markedly from the simultaneous cooling technique (entries 4–9). Both the product yields and the total recovery of material were found to be higher in all cases, demonstrating the usefulness of simultaneous cooling in controlling undesirable side-reactions.
Table 11. Coupling of Aryl Chlorides with Phenylboronic Acid in Watera

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl chloride</th>
<th>Simultaneous cooling</th>
<th>Product / mmol</th>
<th>Aryl chloride recovered / mmol</th>
<th>Total material recovered / mmol</th>
</tr>
</thead>
<tbody>
<tr>
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<td>![Cl]</td>
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<td>0.05</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>![Cl]</td>
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<td>0.90</td>
<td>0.05</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>![Cl]</td>
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<td>0.01</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
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<td>0.79</td>
<td>0.17</td>
<td>0.96</td>
</tr>
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<td>3</td>
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<td>0.96</td>
<td>0.04</td>
<td>1.00</td>
</tr>
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<td>0.20</td>
<td>1.00</td>
</tr>
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<td>0.23</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
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<td>0.75</td>
<td>0.07</td>
<td>0.82</td>
</tr>
<tr>
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<td>0.06</td>
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</tr>
<tr>
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<td>0.64</td>
<td>0.01</td>
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<td>0.01</td>
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<td>0.01</td>
<td>0.65</td>
</tr>
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<td>0.64</td>
<td>0.85</td>
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<td>0.56</td>
<td>0.36</td>
<td>0.92</td>
</tr>
<tr>
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<td>no</td>
<td>0.36</td>
<td>0.24</td>
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<tr>
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<td>0.65</td>
<td>0.26</td>
<td>0.91</td>
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<tr>
<td>9</td>
<td>![Cl]</td>
<td>no</td>
<td>0.22</td>
<td>0.53</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>![Cl]</td>
<td>yes</td>
<td>0.48</td>
<td>0.42</td>
<td>0.90</td>
</tr>
</tbody>
</table>

a Reactions were run in sealed vessels using 1 mmol aryl chloride (1), 1.3 mmol phenylboronic acid (2a), 1 mol % Pd/C, 3.7 mmol Na₂CO₃, 1 mmol TBAB and 2 mL water. Reaction mixtures were irradiated with microwaves at 120 °C for 10 min. The temperature was measured using a fibre-optic sensor inserted into the reaction vessel. Yields were determined by comparison to internal standard in ¹H NMR analysis. b It was not possible to quantify the exact amount of the remaining aryl chloride due to possible evaporation during the work-up procedure. c Run for a total reaction time of 30 min.

To summarise, the concept of microwave heating with simultaneous cooling was studied as part of the development of a reliable, protocol for aqueous Suzuki coupling of aryl chlorides with phenylboronic acid using palladium on carbon (Pd/C) as a simple catalyst. Simultaneous cooling was found to have a significant positive effect on the product yields of unactivated and neutral aryl chlorides. This effect is believed to be related to the prolongation of the lifetime of the aryl chloride substrates and is assumed to be of thermal origin. Thus, the presence of non-thermal microwave effects is not postulated. Similar beneficial effects have been since reported by a few other scientific groups. 172-177
5. Highly Regioselective Internal Heck Arylation in Water (Paper V)

5.1 Introduction

As discussed in Section 1.1.4.1, electron-rich olefins tend to give mixtures of internal $\alpha$- and terminal $\beta$-products when run under standard Heck reaction conditions.\textsuperscript{16} Regioselectivity giving only internal products can, however, be controlled by using bidentate phosphine ligands in conjunction with triflates as leaving groups.\textsuperscript{55,56} Similarly, thallium and silver salts have been used to scavenge halide ions from the solution, resulting in excellent $\alpha$-regioselectivity.\textsuperscript{57}

Although the use of triflates and other sulfonate ester derivatives may seem appealing, they are rarely commercially available and often expensive. Aryl halides, on the other hand, are easily available and relatively cheap starting materials. The use of heavy metal salts for regiocontrol of the Heck reaction is not, however, an attractive option, bearing in mind the effects they may have on the environment. A few years ago, the groups of Hallberg and Xiao reported methodologies for highly regioselective $\alpha$-arylation of electron-rich butyl vinyl ether with aryl halides in DMF-water mixtures and in ionic liquids without the need for toxic thallium or expensive silver additives (Scheme 13).\textsuperscript{60-62} These methods utilized a highly polar DMF-water-K$_2$CO$_3$ cocktail or imidazolium-based ionic liquids, [bmim][BF$_4$] and [bmim][PF$_6$], to direct the reaction towards the formation of charged intermediates giving rise to full $\alpha$-selectivity. To further develop internal Heck arylation in a greener direction, the possibility of utilizing water alone in these reactions was investigated.
Scheme 13. Heck arylation of electron-rich olefins in DMF-water-K$_2$CO$_3$ mixtures or in ionic liquids.

5.2 Reactions with Aryl Bromides and Iodides

As a starting point, the reaction between 4-bromoanisole (1d) and ethylene glycol vinyl ether (5c), carrying a hydrophilic hydroxyl group, was studied (Scheme 14). Reactions were run in water, under air, using conventional oil bath heating, and the α-products formed were isolated as ketone 7a after hydrolysis by aqueous hydrochloric acid. Potassium carbonate, K$_2$CO$_3$, was chosen as a suitable base for the reaction, and a simple catalytic system consisting of Pd(OAc)$_2$ and dppp was found to work well in the arylation of ethylene glycol vinyl ether.

Initial arylation of olefin 5c (5 equiv) with 1d at 100 °C using 2.5 mol % Pd(OAc)$_2$, 5 mol % dppp and 3.7 equivalents of K$_2$CO$_3$ in 1 mL deionised water resulted in an encouraging α/β ratio of 88:12. Despite full conversion, only a 44 % yield of 7a was recorded, revealing a major loss of material (Table 12, entry 1). Decreasing the temperature to 90 °C was beneficial to both yield and regioselectivity, resulting in full regiocontrol and a 74 % isolated yield of 7a (entry 2). Decreasing the reaction temperature further to 80 °C led to only traces of the product after 24 hours, highlighting the sensitivity of this protocol to the chosen temperature.
Table 12. Optimisation of Internal Arylation of Ethylene Glycol Vinyl Ether in Water\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>5c / equiv</th>
<th>K(_2)CO(_3) / equiv</th>
<th>T / °C</th>
<th>t / min</th>
<th>6a / 4a(^b)</th>
<th>7a / %(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0</td>
<td>3.7</td>
<td>100</td>
<td>120</td>
<td>88:12</td>
<td>44(^{d,e})</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>3.7</td>
<td>90</td>
<td>120</td>
<td>99:1</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>3.0</td>
<td>90</td>
<td>120</td>
<td>99:1</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>2.0</td>
<td>90</td>
<td>120</td>
<td>99:1</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>1.2</td>
<td>90</td>
<td>120</td>
<td>99:1</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>5.0</td>
<td>1.2</td>
<td>90</td>
<td>100</td>
<td>99:1</td>
<td>69</td>
</tr>
<tr>
<td>7</td>
<td>5.0</td>
<td>1.2</td>
<td>90</td>
<td>80</td>
<td>99:1</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
<td>1.2</td>
<td>90</td>
<td>60</td>
<td>99:1</td>
<td>71(^f)</td>
</tr>
<tr>
<td>9</td>
<td>3.0</td>
<td>1.2</td>
<td>90</td>
<td>120</td>
<td>99:1</td>
<td>41(^f)</td>
</tr>
<tr>
<td>10</td>
<td>5.0</td>
<td>1.2</td>
<td>90</td>
<td>80</td>
<td>99:1</td>
<td>41(^f,g)</td>
</tr>
</tbody>
</table>

\(^a\) Constant in all experiments: 1d (0.50 mmol), Pd(OAc)\(_2\) (2.5 mol %), dppp (5.0 mol %), H\(_2\)O (1.0 mL). Hydrolysis of 6a was performed by addition of concd HCl (aq.). \(^b\) \(1H\) NMR and/or GC/MS. \(^c\) Isolated yield. Purity >95 % according to GC/MS. \(^d\) Yield determined by comparison to internal standard in \(1H\) NMR analysis. \(^e\) Major loss of material. \(^f\) Conversion of 1d to product(s) not complete. \(^g\) Pd(OAc)\(_2\) (1.0 mol %), dppp (2.0 mol %).

Based on the optimal reaction temperature determined, further optimisation of other relevant reaction parameters was performed (Table 12, entries 2–10). At best, a 73 % isolated yield of 7a was obtained after only 80 minutes’ heating at 90 °C using 1.2 equivalents of base (entry 7). It is notable that the reaction time is considerably shorter than in most of the protocols known today, making this route an attractive possibility for the synthesis of aryl methyl ketones.\(^{60,61,63-67}\) In addition, the reaction proceeds in water, generates no heavy metal waste and can be performed under ambient atmosphere. Unfortunately, it was not possible to reduce the catalyst loading nor the amount of olefin (entries 9 and 10).

Having found the optimal reaction conditions for the selective formation of the \(1\)-product 7a at good yields, several aryl bromides and some iodides were screened using this protocol (Table 13). It was soon observed that with substrates containing electron-withdrawing groups, the amount of base was crucial for the reactivity. In fact, 4-bromobenzophenone 1ad showed almost no activity towards the reaction when only a slight excess of base was used (entry 8, Method A). When the amount of K\(_2\)CO\(_3\) was increased to 3 equivalents, the yield improved dramatically; 1ad now giving an excellent yield of 7h of 99 % after 80 minutes’ heating at 90 °C (entry 8, Method B). Based on a report by Hallberg et al., it is likely that the increase in basicity and ionic strength of the reaction mixture with excess base promotes ionisation and facilitates the olefin insertion step of this electron-poor Pd-aryl intermediate.\(^{60}\)
Similar behaviour was observed with other aryl bromide substrates (Table 13, entries 1–9) and Method B, utilizing a large excess of carbonate base, was found to be more general and absolutely necessary when using aryl bromides with electron-withdrawing functionalities. Good to excellent yields of ketones 7a–i were obtained from reactions proceeding with full α-selectivity. Excellent regioselectivities were also achieved with a few aryl iodides although the yields decreased with increasing amount of dehalogenation of the starting aryl iodide (entries 12–14). The only substrate that failed this aqueous methodology was 4-bromonitrobenzene, which gave some nitrobenzene and a mixture of α- and β-products, together with a substantial loss of material. This unfortunate outcome was not totally unexpected as difficulties with 4-nitrophenyl substrates have long been known to exist.178 To test the limits of this protocol further, a few heteroaryl bromides, namely 3-bromothiophene (1af) and 3-bromopyridine (1ag) were screened, giving a good yield of 7j (73 %) and a rather poor yield of 7k (28 %) (entries 10 and 11). Finally, the scalability of the protocol was tested by arylating ethylene glycol vinyl ether with 4-bromoanisole on the 50 mmol scale, giving an excellent isolated yield of 7a of 88 % (entry 1).

Table 13. Regioselective Internal Heck Arylation of Ethylene Glycol Vinyl Ether with Aryl Bromides and Iodides in Water

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>α / β</th>
<th>Product</th>
<th>Method</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1d</td>
<td>99:1</td>
<td>7a</td>
<td>A</td>
<td>73 ± 88</td>
</tr>
<tr>
<td>2</td>
<td>1aa</td>
<td>99:1</td>
<td>7b</td>
<td>A, B</td>
<td>79 ± 84</td>
</tr>
<tr>
<td>3</td>
<td>1ab</td>
<td>99:1</td>
<td>7c</td>
<td>A, B</td>
<td>84 ± 92</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>99:1</td>
<td>7d</td>
<td>A, B</td>
<td>60 ± 63</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>99:1</td>
<td>7e</td>
<td>A, B</td>
<td>37 ± 52</td>
</tr>
<tr>
<td>6</td>
<td>1ac</td>
<td>99:1</td>
<td>7f</td>
<td>A, B</td>
<td>16 ± 60</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>99:1</td>
<td>7g</td>
<td>A, B</td>
<td>89 ± 91</td>
</tr>
<tr>
<td>8</td>
<td>1ad</td>
<td>99:1</td>
<td>7h</td>
<td>A, B</td>
<td>8 ± 99</td>
</tr>
</tbody>
</table>
The reactions were performed on the 0.50 mmol scale (1) with 5.0 equiv of 5c, 2.5 mol % Pd(OAc)$_2$, 5.0 mol % dpdp and 1.2–3.0 equiv K$_2$CO$_3$ in 1.0 mL water by heating at 90 °C for 80 min. Hydrolysis of 6 was performed by the addition of concd HCl (aq.). $^b$ Determined by GC/MS. $^c$ Method A: 1.2 equiv of K$_2$CO$_3$. Method B: 3.0 equiv of K$_2$CO$_3$. $^d$ Isolated yield. Purity >95 % according to GC/MS. $^e$ Reaction was performed on the 50 mmol scale. $^f$ Conversion of 1 to product(s) not complete. $^g$ Substantial loss of material. $^h$ Yield determined by comparison with internal standard in $^1$H NMR analysis. $^i$ Reaction time of 120 min. $^j$ Formation of some dehalogenation product.

5.3 Reactions with Aryl Chlorides

Disappointingly but not unexpectedly, aryl chlorides showed no reactivity in the aqueous internal Heck reaction. This can be attributed to the inefficiency of Pd(OAc)$_2$/dpdp to activate strong Ar–Cl bonds towards oxidative addition. $^{18,32}$ There were, in fact, only two reports on internal Heck arylation utilizing aryl chlorides found in the literature. In these, Xiao et al. describe successful arylation of butyl vinyl ether and N-vinylacetamide by a few activated aryl chlorides using ionic [HNEt$_3$][BF$_4$] or [H$_2$NiPr$_2$][BF$_4$] as an extra activator for the reaction. $^{179,180}$ It is well-documented in the literature that electron-rich phosphine ligands can facilitate the oxidative addition of aryl chlorides. $^{162}$ Therefore, the focus of this study was turned towards electron-rich, chelate-stabilised (dippp)$_2$Pd(0) (dippp = 1,3-bis(diisopropylphosphino)propane). This catalyst, which can also be formed in situ from Pd(OAc)$_2$ and dippp, has been extensively used in, for example, the carbonylation and dechlorination of...
aryl chlorides.\textsuperscript{181-184} To study whether it would work in the internal Heck arylation, a test reaction was performed using 5 mol % (dippp)\textsubscript{2}Pd(0) in the arylation of ethylene glycol vinyl ether (5c) by 4-chloroacetophenone (1r). The conditions used in this reaction were otherwise the same as those in the previously optimised arylation protocol (Table 13, Method B). Indeed, the reaction proceeded with full regioselectivity (99:1), giving a 38 % isolated yield of 7g in addition to some dehalogenated by-product (Table 14, entry 1). It was possible to increase the yield to a respectable 89 % by pre-activation of the catalyst at 50 °C followed by microwave irradiation at 130 °C for 90 minutes, although a slight decrease in regioselectivity was observed (entry 1).

Table 14. Regioselective Internal Arylation of Ethylene Glycol Vinyl Ether with Aryl Chlorides in Water\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl chloride</th>
<th>$\alpha / \beta$ \textsuperscript{b}</th>
<th>Product</th>
<th>Yield / %\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1r</td>
<td>99:1 94:6</td>
<td>7g</td>
<td>38\textsuperscript{d,e,f} 89\textsuperscript{f}</td>
</tr>
<tr>
<td>2</td>
<td>1ai</td>
<td>99:1</td>
<td>7c</td>
<td>71\textsuperscript{e,f}</td>
</tr>
<tr>
<td>3</td>
<td>1q</td>
<td>96:4</td>
<td>7d</td>
<td>15\textsuperscript{e,f}</td>
</tr>
<tr>
<td>4</td>
<td>1y</td>
<td>95:5</td>
<td>7a</td>
<td>33\textsuperscript{e,f}</td>
</tr>
<tr>
<td>5</td>
<td>1aj</td>
<td>76:24</td>
<td>7h</td>
<td>46\textsuperscript{g}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The reactions were performed on the 0.25 mmol scale (1) with 5.0 equiv of 5c, 5.0 mol % (dippp)\textsubscript{2}Pd and 3.0 equiv K\textsubscript{2}CO\textsubscript{3} in 1.0 mL water by irradiation with microwaves at 130 °C for 90 min. Hydrolysis of 6 was performed by addition of concd HCl (aq.). \textsuperscript{b}Determined by GC/MS. \textsuperscript{c}Isolated yield. Purity >95 % according to GC/MS. \textsuperscript{d}Conventional heating at 90 °C for 80 min. \textsuperscript{e}Conversion of 1 to product(s) not complete. \textsuperscript{f}Formation of some dehalogenation product observed. \textsuperscript{g}33 % benzophenone formed as a by-product.

A short scan of aryl chlorides with different functionalities quickly revealed that although good yields and regioselectivities were obtained with 4-chloroacetophenone and 2-chloronaphthalene (Table 14, entries 1 and 2), oxidative addition still represents a serious problem when unactivated aryl chlorides are employed (entries 3 and 4). With electron-deficient 1aj, on the other hand, it is likely that the insertion of olefin will be the rate-limiting step, enabling the competitive dehalogenation process (entry 5). In addition, a partial loss of regiocontrol was noted with 1aj, which could partly be ex-
plained by a high reaction temperature. However, the inability of the electron-deficient ArPd(dippp)Cl-intermediate to release the chloride ion might also give rise to partial displacement of the dippp-ligand by an incoming olefin, allowing the formation of a neutral intermediate leading to a mixture of α- and β-products.

5.4 Mechanistic Discussion and Conclusions

In an attempt to widen the scope of the aqueous α-arylation, a small number of electron-rich olefins were arylated with 4-bromoanisole (1d) using Method B reported in Table 13. Notably, all the reactions with hydroxyalkyl vinyl ethers proceeded with full regiocontrol without any by-product formation (Table 15, entries 1–4). The yields of extended vinyl ethers 5d–f were, however, quite modest and prolongation of the reaction time to 6 hours had only a minor effect on the yields (entries 2 and 3). When using vinyl ethers without hydroxyl functionality, the regioselectivity gradually deteriorated due to elongation of the alkyl chain (entries 5 and 6). Ethylene glycol butyl vinyl ether (5i) also showed a similar loss in selectivity (entry 7). This can be explained by the decreasing polarity of vinyl ethers 5g–i, making them increasingly insoluble in water. The reaction mixture therefore divides into two separate layers, aqueous and organic, and the reaction takes place in the non-polar organic phase, favouring the formation of a mixture of α- and β-products. Furthermore, [2-(dimethylamino)ethoxy]ethane (5j) and allyl alcohol (5k) showed no reactivity in this aqueous protocol (entries 8 and 9).

In their publication from 2006, Mo and Xiao discussed the existence of hydrogen-bond-induced regiocontrol and acceleration of the overall reaction rate of internal α-arylation in ionic liquids or DMF. Specifically, they suggested that the HNEt₃⁺ ion from [HNEt₃⁺][BF₄⁻] could form a hydrogen bond with a halide ion bound to the palladium centre in the oxidative addition step. This newly formed hydrogen bond would then gradually weaken and finally break the Pd–halide bond thus promoting the formation of the cationic π-complex leading to internal arylation products (Scheme 15).

Scheme 15. Hydrogen-bond-induced regiocontrol reported by Xiao et al.¹⁷⁹

As hydrogen-bond-induced regioselectivity could also explain the good results obtained with the vinyl ethers 5c–f, the possibility of this phenomenon existing was carefully studied by running a few representative reactions in
non-polar toluene (Table 16). Quite surprisingly, the reaction of 4-bromoanisole (1d) with olefin 5c proceeded with full regiocontrol, giving a similar yield to that in water-mediated internal Heck arylation (Table 13, entry 1 and Table 16, entry 1). Similar results were obtained without any co-solvent and also with 2-bromonaphthalene (1ab) in toluene (Table 16, entries 1 and 2). These results together indicate the participation of the hydroxyl group in halide removal. Somewhat lower yield and regioselectivity were observed using electron-deficient 4-bromobenzophenone (1ad, entry 3). This aryl bromide substrate also gave 20 % dehalogenated benzophenone, indicating problems in the insertion of the olefin. Finally, upon the removal of the hydroxyl group, the regioselectivity was almost completely lost and the reaction rate decreased significantly (entry 4).

**Table 15. Comparative Arylation of Some Vinyl Ethers and Allyl Alcohol with 4-Bromoanisole in Water**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>α/β</th>
<th>7a/%</th>
<th>4/%</th>
<th>1d/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5c</td>
<td>99:1</td>
<td>73c</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5d</td>
<td>99:1</td>
<td>23</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5e</td>
<td>99:1</td>
<td>24</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5f</td>
<td>99:1</td>
<td>17</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>5g</td>
<td>80:20</td>
<td>16</td>
<td>4</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>5h</td>
<td>61:39</td>
<td>21</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>5i</td>
<td>78:22</td>
<td>25</td>
<td>nd</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>5j</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>5k</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*a* The reactions were performed on the 0.50 mmol scale (1d) with 5.0 equiv of olefin 5, 2.5 mol % Pd(OAc)₂, 5.0 mol % dppp and 3.0 equiv K₂CO₃ in 1.0 mL water by heating at 90 °C for 80 min. Hydrolysis of 6 was performed by the addition of concd HCl (aq.). *b* Determined by GC/MS and/or isolation. *c* Isolated yield. Purity >95 % according to GC/MS. *d* Amount of 1d recovered at the end of the reaction. *e* With 1.2 equiv of K₂CO₃. *f* Reaction time 6 h. *g* nd = not determined. Reaction not complete, although the amount of remaining starting material was not determined. *h* The formed β-products were not isolated after the reaction. *i* No product formation observed.

Taking into account the observations described above, a reaction pathway proceeding via a pentacoordinated π-complex can be suggested (Scheme 16).
This assumption is partly supported by Overman’s suggestion of asymmetric intramolecular Heck reactions with aryl halides, where axial olefin coordination is essential for chiral discrimination. Here, the removal of the halide ion is likely to take place via one of two possible pathways, hydrogen-bond-assisted removal or ligand exchange, both of which may be assisted by the hydroxyl group of the olefin. The existence of the former is strongly supported by two observations. First, the olefins 5i and 5j fail to induce any regioselectivity, although they are able to coordinate to palladium via lone pairs on oxygen or nitrogen (Table 15, entries 7 and 8). Secondly, olefins 5c and 5f showed rather different reactivities in aqueous internal Heck arylation, 5c demonstrating a significantly higher reaction rate (Table 15, entries 1 and 4). As these two olefins are structurally quite similar, i.e. both contain an oxygen atom linked to vinyl ether by a two-carbon linker, they should exhibit similar reactivity if the reaction proceeded via the ligand exchange process. If, on the other hand, the reaction proceeds via hydrogen-bond-assisted halide removal, one would expect the reaction rate to decrease with elongation of the linker connecting the hydroxyl and double bond moieties. This was, in fact, observed in this study, and it is therefore my belief that this reaction proceeds via hydroxyl-group-assisted halide removal (Scheme 16).

Interestingly, Xiao et al. and Pike and co-workers recently reported that the internal arylation of aryl and heteroaryl bromides proceeds smoothly in alcohols such as ethylene glycol and 2-propanol, without any additives, strengthening the preliminary assumptions made during the study summarised here.

Table 16. Comparative Arylation of Ethylene Glycol Vinyl Ether in Toluene or in Solventless Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArBr</th>
<th>Method&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product</th>
<th>Toluene α / β&lt;sup&gt;c&lt;/sup&gt;</th>
<th>7 / %&lt;sup&gt;d&lt;/sup&gt;</th>
<th>No solvent α / β&lt;sup&gt;c&lt;/sup&gt;</th>
<th>7 / %&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1d</td>
<td>A</td>
<td>7a</td>
<td>99:1</td>
<td>81</td>
<td>99:1</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>1ab</td>
<td>A</td>
<td>7c</td>
<td>99:1</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1ad</td>
<td>B</td>
<td>7h</td>
<td>96:4</td>
<td>62&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>B</td>
<td>7a</td>
<td>73:27</td>
<td>24&lt;sup&gt;f,g&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The reactions were performed on the 0.50 mmol scale (1) with 5.0 equiv of 5c. Hydrolysis of 6 was performed by the addition of concd HCl (aq.).<sup>b</sup> Method A: 1.2 equiv of K<sub>2</sub>CO<sub>3</sub>. Method B: 3.0 equiv of K<sub>2</sub>CO<sub>3</sub>.<sup>c</sup> Determined by GC/MS. Isolated yield. Purity >95 % according to GC/MS. 20 % benzophenone formed as a by-product.<sup>f</sup> 5h used instead of 5c. Conversion of 1d to product(s) not complete.
Scheme 16. Internal arylation of ethylene glycol vinyl ether by aryl halides in water proceeding by halide removal either via hydrogen bond formation or via a ligand exchange process.

In conclusion, a protocol for the aqueous internal arylation of ethylene glycol vinyl ether with aryl and heteroaryl bromides and iodides was developed. The α-products formed were hydrolysed and isolated as acetophenones at good to excellent yields. Additionally, a small number of aryl chlorides were transformed to aryl methyl ketones using the (dippp)2Pd complex in conjunction with microwave irradiation. Finally, the hydroxyl group of ethylene glycol vinyl ether was shown to play a major role in directing the regiocontrol towards the formation of exclusively internal arylation products.
6. Synthesis and Structure–Activity Relationship of New HIV-1 Integrase Inhibitors Containing a Quinolone Moiety (Paper VI)

6.1 Introduction

As discussed in Section 1.4.2, HIV-1 integrase is essential for viral replication and as such represents an interesting and important target for the development of new anti-HIV drugs. Quite recently, Sato et al. reported that the core structure of quinolone antibiotics can be used as an alternative diketo acid motif in HIV-1 integrase inhibitors. The best example of this series (Figure 9, 8c, elvitegravir) shows strong inhibition of IN-catalysed DNA strand transfer (ST) and in vitro antiviral activity, and is being tested in ongoing clinical phase III studies.

![Figure 9. Design of elvitegravir.](image)

6.2 Study Design and Synthesis of Series of New HIV-1 Integrase Inhibitors Containing a Quinolone Moiety

HIV-1 integrase inhibitors having quinolone substructure are fairly unknown and only limited data related to structure–activity relationships of this class
of compounds can be found in the literature. Therefore, a series of compounds containing the 4-quinolone-3-carboxylic acid motif found in elvitegravir was synthesised. According to Sato et al., the inhibition of the ST process is improved substantially by the introduction of a methoxy group at the 7-position of 8a (Figure 9, 8a and 8b). Furthermore, a slight improvement in IC50 values is observed when an additional isopropyl group is introduced into the 1S position of the hydroxyethyl moiety (Figure 9, 8c). These changes together have a remarkable synergistic effect on antiviral EC50 values. In the study presented here, a simplified model corresponding to 8a was investigated based on the synthetic ease of access to this class of compounds. The specific aims of the study were to investigate: (i) the impact of the length of the hydroxyalkyl chain on the anti-IN activity, (ii) the importance of a free hydroxyl group in the inhibition of IN function, and (iii) the effect of replacing the benzyl group with potential isosteres on the strand transfer ability of the IN enzyme.

First, compounds 9a–j containing a quinolone core structure and compounds 10a–d containing a similar quinone structure were synthesised (Scheme 17). In addition, a compound 11 containing bromide in the 6-position of the quinolone scaffold was prepared and utilized in a series of microwave-assisted palladium-catalysed coupling reactions (Scheme 18). The products obtained via Suzuki coupling, N-amidation, aminocarbonylation and Buchwald-Hartwig amination were further hydrolysed to give compounds 9k–p.

Scheme 17. New HIV-1 IN inhibitors containing quinolone or quinone moieties.

6.3 Inhibition of HIV-1 Integrase Activity

Compounds 9c–e, differing from 8a only in the length of the hydroxyalkyl chain at the N-1 position and the substitution of the benzyl moiety, were found to be several magnitudes poorer in the inhibition of IN in the strand transfer assay (Table 17, entries 3–5 and 21). A further decrease in the activity was observed when these hydroxyalkyl chains were replaced by methoxyethyl and dimethylaminoethyl groups (9f–g, entries 6–7). These observations together highlight the importance of the free alcohol group at the N-1 position.
When the benzyl group in $9c$–$e$ was replaced by a benzoyl moiety, all the anti-IN activity in the ST assay was lost (Table 17, entries 8–10). Replacing the 2,4-dichlorobenzyl group of $9c$ with 3-chloro-4-fluorophenoxy in $9a$ also resulted in a total loss of activity (entry 1). However, the unsubstituted thio-phenyl group of $9b$ seems to be partially tolerated, although the anti-IN activity of $9b$ lies in a higher micromolar range (entry 2). Furthermore, when the linker between the two aromatic moieties of $9c$–$e$ is shortened ($9l$–$m$) or lengthened by rigid systems such as a double bond ($9k$), an amide ($9o$) or an inverse amide ($9n$), the ST activity is lost altogether (entries 11–16).

Finally, the anti-IN activity of the unsubstituted quinone $10a$ in an ST assay was increased substantially by the introduction of 3-chloro-4-fluorophenylamino or phenylthio moieties, and IC$_{50}$ values close to those of $9c$–$e$ were obtained (entries 17, 19–20). This could be attributed to the positive effect of an additional chelating carbonyl group. Quite interestingly, all the ST activity was lost upon changing the phenylamino group of $10c$ to 2-fluoro-3-chlorophenylamino group ($10b$, entry 18).
6.4 Docking Studies

To gain more knowledge about the activity/inactivity of the newly synthesised HIV-1 IN inhibitors, the binding mode of these compounds was compared to the binding of 8c in docking studies. From these studies, it could be concluded that the active compounds 9b–g are likely to bind in a similar fashion to 8c. The lower activity of 9f and 9g can be explained by the lack of hydrogen bond between the side chain OH and serine residue present in the active site. Furthermore, 9a and 9k–p cannot adopt the conformation required for the inhibition of IN enzyme due to the increased rigidity of these structures.

Quite interestingly, the inactivity of the compounds 9h–j cannot be explained by their binding modes, as these resemble the binding of 8c. Therefore, theoretical quantum mechanics calculations were performed. Based on these calculations, it was suggested that the electron-withdrawing effect of the carbonyl group in the C-6 position of quinolone ring weakens the metal chelating ability of the diketo acid motif, resulting in a loss of inhibition of the IN strand transfer process.
7. Concluding Remarks

This thesis describes the development of new palladium-catalysed carbon–carbon coupling methodologies in water and the application of palladium catalysis to the development of new HIV-1 integrase inhibitors. The specific results and conclusions are as follows.

- Reassessment of transition-metal-free Suzuki-type coupling methodology revealed that Suzuki coupling of aryl halides cannot be performed without transition-metal catalysis. Based on this finding, a new, aqueous, microwave-assisted Suzuki coupling protocol utilizing ppb/ppm levels of palladium was developed.

- The above described methodology for aqueous Suzuki coupling was adapted to terminal Heck coupling in water. A commercially available palladium standard was found to be a practical and reliable source of low catalyst loading. Although it was found that exceedingly low palladium concentrations (500 ppb) were adequate in providing reasonable yields, the methodology is unfortunately limited to a few aryl bromides and iodides.

- The Suzuki and Heck coupling reactions utilizing ppb/ppm levels of palladium were successfully scaled up to 100 mmol using an automated batch stop-flow microwave apparatus.

- The technique of microwave heating with simultaneous cooling was studied and found to be beneficial in prolonging the lifetime of the aryl chloride substrates, allowing a reliable and fast protocol for aqueous Suzuki coupling of aryl chlorides with phenylboronic acid to be developed.

- Internal arylation of ethylene glycol vinyl ether with aryl and heteroaryl bromides and iodides was shown to be possible in water without ionic liquids or heavy-metal additives. Additionally, the electron-rich (dippp)$_2$Pd complex was shown to be beneficial for the internal arylation of some aryl chlorides. Finally, the active role of the hydroxyl group of ethylene glycol vinyl ether in the formation of the cationic intermediate leading to full $\alpha$-selectivity was revealed.
A series of HIV-1 integrase inhibitors were synthesised and evaluated with regard to the inhibition of HIV-1 IN enzyme function. The pattern of activity of these IN inhibitors was further explained by plausible binding modes derived from docking experiments.
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