Selectivity in Palladium- and Enzyme-Catalyzed Reactions

*Focusing on Enhancement of Reactivity*

BY

PETER NILSSON
Dissertation presented at Uppsala University to be publicly examined in B41, BMC, Uppsala, Friday, November 21, 2003 at 13:15 for the degree of Doctor of Philosophy (Faculty of Pharmacy). The examination will be conducted in English.

Abstract

Catalysis has a profound impact on all living species on the earth. Nature’s catalysts, the enzymes, have the ability to selectively promote a specific bio-chemical transformation, given the required substrate. As well as being highly selective, enzymes enhance the speed of these reactions, helping them to run at temperatures much lower than normally required, i.e. at body temperature. In comparison, reactions used in the production of new materials such as polymers, medicines, fragrances, petrochemicals, etc. are often catalyzed by transition metals. This thesis describes how the selectivity and activity of these catalysts can be influenced via two conceptually different methods: chelation control and microwave heating. The thesis primarily focuses on regio- and stereochemical aspects of the palladium-catalyzed arylation of olefins, i.e. the Heck reaction. Reaction rate enhancement of both palladium and enzyme (polymerase chain reaction [PCR]) catalysis by microwave heating is also discussed.

Novel chelation-controlled palladium-catalyzed multi- and asymmetric arylations of vinyl ethers were performed, resulting in tetra-substituted olefins as well as chiral quaternary carbon centers with excellent optical purity. In addition, a new synthetic route to diarylated ethanols, relying on a double chelation-controlled regioselective arylation followed by hydrolysis, has been discovered. High temperature conditions, using microwave heating, substantially reduce the reaction time for ligand-controlled asymmetric Heck arylation, while retaining levels of enantioselectivity in most cases. In addition, a potentially useful fast synthetic protocol for the employment of aryl boronic acids in oxidative Heck arylation was developed. Finally, microwave-assisted PCR was described for the first time; this method allows reductions in the run time of 50%.

Keywords: Palladium, Heck, PCR, Microwaves

Peter Nilsson, Department of Medicinal Chemistry, Box 574, Uppsala University, SE-75123 Uppsala, Sweden

© Peter Nilsson 2003

ISSN 0282-7484
ISBN 91-554-5765-7
urn:nbn:se:uu:diva-3625 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-3625)
Bra påbörjat är hälften gjort.

Grekiskt ordspråk
PAPERS INCLUDED IN THE THESIS

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

I Nilsson Peter, Larhed Mats, Hallberg Anders.
Highly Regioselective, Sequential and Multiple Palladium-Catalyzed Arylations of Vinyl Ethers Carrying a Coordinating Auxiliary: An Example of a Heck Triarylation Process

II Nilsson Peter, Larhed Mats, Hallberg Anders.
A New Highly Asymmetric Chelation-Controlled Heck Arylation

III Nilsson Peter, Gold Henrik, Larhed Mats, Hallberg Anders.
Microwave-Assisted Enantioselective Heck Reactions: Expediting High Reaction Speed and Preparative Convenience

IV Andappan M. S. Murugaiah, Nilsson Peter, Larhed Mats.
Arylboronic acids as versatile coupling partners in fast microwave promoted oxidative Heck chemistry
_In Print Mol. Div._

V Fermér Christian, Nilsson Peter, Larhed Mats.
Microwave-assisted high-speed PCR

Reprints were made with kind permission from the publishers, the American Chemical Society, Georg Thieme Verlag, Kluwer Academic Publishers, and Elsevier.
## Contents

1 Introduction .................................................................................................................. 9
  1.1 The Origin of Catalysis .......................................................................................... 9
    1.1.1 Catalyst Properties ...................................................................................... 10
    1.1.2 Thermodynamic and Kinetic Aspects of Catalysis ........................................ 10
  1.2 Transition Metals as Catalysts in Organic Synthesis ............................................ 11
    1.2.1 Historical Developments .............................................................................. 11
    1.2.2 Catalytic Properties of Late Transition Metals ............................................. 12
    1.2.3 Palladium-Catalyzed C-C Bond Formations .............................................. 14
  1.3 Enzymes as Catalysts in Organic Synthesis ......................................................... 15
    1.3.1 Enzyme Kinetics, Optimizing the Reaction Temperature .............................. 16
    1.3.2 Enzyme Stability ......................................................................................... 17

2 The Heck Reaction ...................................................................................................... 18
  2.1 Background ........................................................................................................... 18
  2.2 Generation of Aryl-Palladium ............................................................................. 19
    2.2.1 Transmetallation ......................................................................................... 19
    2.2.2 Electrophilic Palladation .......................................................................... 20
    2.2.3 Oxidative Addition ................................................................................. 20
  2.3 The Insertion Process ........................................................................................... 22
    2.3.1 Chelation-Controlled Insertion .................................................................. 24
    2.3.2 Asymmetric Insertion ............................................................................... 25

3 The Polymerase Chain Reaction (PCR) .................................................................. 28

4 Microwave-Assisted Organic Synthesis .................................................................. 30
  4.1 The Physical Background .................................................................................... 30
    4.1.1 Heating Mechanisms .................................................................................. 32
  4.2 Microwave Chemistry .......................................................................................... 32
    4.2.1 Microwave-Assisted High Speed Synthesis .............................................. 33

5 Aims of the Thesis ..................................................................................................... 34

6 Results and Discussion ............................................................................................... 35
  6.1 Chelation Control in Heck Chemistry (Papers I and II) ...................................... 35
    6.1.1 Chelation-Promoted Multiarylations ......................................................... 35
      6.1.1.1 Triarylation Experiments .................................................................... 36
      6.1.1.2 β,β-Diaryligration Experiments ..................................................... 39
      6.1.1.3 Liberation of Diarylated Acetaldehydes ......................................... 41
      6.1.1.4 α,β-Diaryligration Experiments ..................................................... 44
      6.1.1.5 Mechanistic Considerations of Chelation ......................................... 46
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1.2 Chelation-Promoted Formation of Quaternary Centers</td>
<td>48</td>
</tr>
<tr>
<td>6.1.3 Chelation-Controlled Asymmetric Insertion</td>
<td>48</td>
</tr>
<tr>
<td>6.2 Microwave-Assisted Enantioselective Heck Reactions (Paper III)</td>
<td>51</td>
</tr>
<tr>
<td>6.2.1 Selection of Reaction System</td>
<td>51</td>
</tr>
<tr>
<td>6.2.2 Benchmarking the High-Speed Protocol</td>
<td>53</td>
</tr>
<tr>
<td>6.3 Microwave-Enhanced Oxidative Heck Arylations (Paper IV)</td>
<td>55</td>
</tr>
<tr>
<td>6.3.1 Developing the Protocol</td>
<td>56</td>
</tr>
<tr>
<td>6.3.2 Scope and Limitation of the Oxidative Heck Reaction</td>
<td>58</td>
</tr>
<tr>
<td>6.4 Accelerated PCR using Microwave Irradiation (Paper V)</td>
<td>61</td>
</tr>
<tr>
<td>6.4.1 Optimization</td>
<td>61</td>
</tr>
<tr>
<td>6.4.2 Enzymatic Activity</td>
<td>63</td>
</tr>
<tr>
<td>7 Concluding Remarks</td>
<td>65</td>
</tr>
<tr>
<td>8 Acknowledgements</td>
<td>66</td>
</tr>
<tr>
<td>9 References</td>
<td>68</td>
</tr>
</tbody>
</table>
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>Bq</td>
<td>benzoquinone</td>
</tr>
<tr>
<td>CIP</td>
<td>Cahn, Ingold, Prelog</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino) propane</td>
</tr>
<tr>
<td>EDG</td>
<td>electron-donating group</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EWG</td>
<td>electron-withdrawing group</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>i-Pr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>n-Bu</td>
<td>normal-butyl</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>proton sponge</td>
<td>1,8-bis(dimethylamino)naphthalene</td>
</tr>
<tr>
<td>rac</td>
<td>racemic</td>
</tr>
<tr>
<td>RADAR</td>
<td>radio detection and ranging</td>
</tr>
<tr>
<td>SAMP</td>
<td>(S)-amino-2-methoxymethylpyrrolidine</td>
</tr>
<tr>
<td>TBME</td>
<td>tert-butyl methyl ether</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>temp</td>
<td>temperature</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMANO</td>
<td>trimethylamine N-oxide</td>
</tr>
<tr>
<td>TOF</td>
<td>turnover frequency</td>
</tr>
<tr>
<td>TON</td>
<td>turnover number</td>
</tr>
<tr>
<td>Tol</td>
<td>tolyl</td>
</tr>
<tr>
<td>Triflate</td>
<td>trifluoromethanesulfonyle</td>
</tr>
<tr>
<td>X</td>
<td>halide or pseudohalide</td>
</tr>
</tbody>
</table>
1 Introduction

1.1 The Origin of Catalysis

In 1836, the famous Swedish chemist J. J. Berzelius introduced the concept of catalysis. In the *Edinburgh New Philosophical Journal*, he proclaimed: “I hence will name it the catalytic force of the substances, and I will name decomposition by this force catalysis. The catalytic force is reflected in the capacity that some substances have, by their mere presence and not by their own reactivity, to awaken activities that are slumbering in molecules at a given temperature”. At the beginning of the 20th century, W. Ostwald presented the generally accepted definition of a catalyst as a species which increases the rate of a chemical reaction through the formation of intermediate compounds and which is restored at the end of the reaction. In 1909, Ostwald was awarded the Nobel Prize in Chemistry for his work on catalysis, chemical equilibrium and reaction velocities.

Catalysis is perhaps one of the most important technologies available, since it plays a critical role in the development of efficient production methods for a wide range of materials, from fuels to polymers, and in the development of more effective and safer pharmaceuticals. Catalysis is the occurrence by which certain chemicals (catalysts) can promote a chemical reaction without undergoing any permanent chemical transformation themselves. Thus, theoretically, recovery of the catalyst is possible after the reaction is completed, enabling it to be recycled. Without the proper catalyst, many reactions proceed infinitely slowly or not at all. Moreover, because of its effects on the kinetics of the reaction, which can lead to different chemical entities, the chemical nature of the catalyst can have a decisive impact on the selection of reaction manifolds. Over the last few decades, there has been rapid progress in the understanding, especially in homogeneous systems, of the molecular events (micro-steps) leading to the final products in some of these reactions. Subsequently, there has been a striking effect on the number of new catalyst systems currently under development. Combinatorial methods have recently been introduced in the catalyst discovery process for rapid screening of potential homogeneous and heterogeneous catalysts. Currently, around 90 per cent of the processes
Introduction

carried out in the chemical industry depend on efficiently working catalysts, and the number of these processes is increasing. In nature, all living processes rely on biological catalysts (e.g. enzymes). Exploration of the role of enzymes in molecular biology and the application of this biotechnology to the production of bulk and fine chemicals remains an ongoing and important goal.

1.1.1 Catalyst Properties

Irrespective of the constitution of the catalyst, it must be provided with certain properties to be useful. First, it must be highly active, meaning that the reaction must progress with a reasonably high speed. Most catalysts contain so-called 'active sites' in their structures. Interactions at the active site permit the reacting molecules to perform a certain chemical reaction at a much lower activation energy than would be possible in the absence of such sites. The total number of active sites and their accessibility control the turnover frequency of the process.

A second and very important property is selectivity; catalysts actually govern the product pattern of the reaction as well as increasing the reaction rate. Enzymes, for example, are generally very efficient and selective. Enzymes as well as transition metal based catalysts are capable of recognizing a reacting substrate by its three-dimensional shape and transforming it in a geometrically specific way (i.e. stereospecifically). Third, the catalyst’s lifetime (stability) is an important factor in the design of economical and environmentally considerate chemical processes.

1.1.2 Thermodynamic and Kinetic Aspects of Catalysis

The thermodynamics of a process are always the same, whether the process is catalyzed or uncatalyzed. It is only the lowering of the reaction barriers (activation energies for the relevant transformations) that allow the reaction to go faster, according to the Arrhenius equation. It should be emphasized that not all separate micro-steps in a catalytic cycle must be exo-energetic (ΔG < 0), as in Figure 1, for successful catalysis to occur.

Arrhenius equation: 

$$k_{\text{obs}} = A \cdot e^{-\Delta G^\ddagger / RT}$$

$k_{\text{obs}} = \text{macroscopic or observed rate constant}; \ A = \text{pre-exponential factor}; \ T = \text{temperature}; \ R = \text{gas constant}; \ \Delta G^\ddagger = \text{Gibbs free energy of activation}.$
Introduction

Catalysts can be roughly divided into three main categories: heterogeneous, in the form of solids (porous zeolites etc.), homogeneous catalysts, which are dissolved in the liquid reaction mixture, and elaborate biological catalysts in the form of enzymes. Presently, heterogeneous catalysis has by far the greater world economic impact, but homogeneous catalysts and enzymes have a great potential and are expected to be very important in the future. This thesis will deal with the latter two types, as exemplified by homogeneous palladium-catalyzed reactions and enzyme-catalyzed nucleic acid polymerizations.

1.2 Transition Metals as Catalysts in Organic Synthesis

1.2.1 Historical Developments

An organometallic compound is defined as a metal connected to an organic entity by a π-bond or a σ-bond. The first organometallic π-complex was K\(^{+}\)Pt\(^{II}\)Cl\(_3\)(η\(^3\)-C\(_2\)H\(_4\)), discovered by W. C. Zeise in 1827, and subsequently named Zeise’s salt. The first transition metal σ-complex (Me\(_3\)PtI) was not discovered until 82 years later by Pope. Industrial large-scale applications employing organometallic chemistry started to emerge shortly thereafter. In 1938, O. Roelen discovered the important metal-catalyzed hydroformylation of olefins, the oxo process (Scheme 1).
Introduction

Scheme 1. The classical oxo process utilizing a cobalt catalyst

The oxo process was further developed by Union Carbide, using the transition metal complex (PPh₃)₃Rh(CO)H as the precatalyst. The oxo process is the world’s largest-scale homogeneously catalyzed industrial process.⁷

Since transition metals are normally expensive, and sometimes toxic, it is important that they can be used in sub-stoichiometric amounts. A nicely engineered solution is exemplified in the commercially important Wacker process, which was discovered in 1959 by German chemists (Scheme 2).

Scheme 2. Palladium-catalyzed oxidation of an olefin, the Wacker process⁸,⁹

Here, palladium dichloride is used as the catalyst and is regenerated after each cycle with the help of catalytic amounts of copper, which in turn is reoxidized by cheap and environmentally friendly oxygen gas.

The very versatile vinylic substitution reaction, the Heck coupling, employing aryl iodides, was developed around a decade later (Scheme 3).¹⁰

Scheme 3. Palladium-catalyzed arylation of an olefin

The Heck coupling is one of the most useful transition metal catalyzed reactions available since the substrate scope is very broad.

1.2.2 Catalytic Properties of Late Transition Metals

The extended possibility for coordination of ligands as a result of access to partially filled d-orbitals makes transition metals, especially the late, more versatile than the main group metals in a catalytic sense. This partial occupation of the d-orbitals also results in new features such as simultaneous electron-accepting and electron-donating characteristics. The interaction with ligands such as olefins,¹¹ carbon monoxide, arenes, isocyanide, alkynes,
Introduction

Nitric oxide etc, which have the same kind of acceptor/donor capabilities, gives rise to a situation where both “bonding” and “backbonding” are possible. In this thesis, the interaction between palladium and an olefin (Figure 2) in the Heck reaction (Scheme 3) will be examined.

**Figure 2.**
*Ethene coordinating palladium in η¹-mode, according to the Dewar-Chatt-Duncanson π-bond model*

A “bonding” interaction develops between the filled olefin π-orbital and the spd hybrid on the metal, whereas “backbonding” occurs between the empty olefin antibonding orbital and the filled dₓz orbital on the metal. The “bonding” interaction is classified as a σ-bond, since it is symmetric when rotated around the z-axis. Accordingly, the “backbonding” interaction is defined as a π-bond (anti-symmetric). In combination with the 18-electron rule, this bonding situation opens up very rich coordination chemistry where the electron density (changes in the HOMO and LUMO levels) on the metal can be easily varied by the judicious choice of ligands. The reactivity and selectivity of the transition metal complex, employed as a homogeneous catalyst, can therefore be fine-tuned. Since nearly every organic functional group is potentially capable of coordination to transition metals, there is a good probability of finding a suitable catalyst for the desired transformation. Transition metals can reverse the polarity (i.e. electron density) of coordinated functional groups and introduce complementary reactivity (Scheme 4).

**Scheme 4.** *Coordination to electrophilic palladium facilitates subsequent nucleophilic attack on the diene by acetate anion¹²*
1.2.3 Palladium-Catalyzed C-C Bond Formations

Protocols that allow for the convenient generation of new carbon-carbon bonds are of great importance in organic synthesis. Metallation procedures are commonly employed to transform carbon into a useful nucleophile for a subsequent reaction with an electron-deficient carbon. The character of the transition metal carbon σ-bond is largely covalent, in contrast to that of the electropositive alkaline and alkaline-earth metals, which have highly polarized metal carbon bonds. Consequently, apart from being merely a carbanion equivalent, new reactivity can be accessed via the proximity effect from the coordination of other ligands due to the higher valency of the transition metal. Furthermore, it is possible to use transition metals in catalytic amounts, in contrast to the group I, II and III metals, which are always depleted in stoichiometric amounts.

Palladium is perhaps the most versatile, and easy to handle, carbon-carbon forming metal catalyst in the periodic table. Of note, palladium:

- Has a pronounced preference for the 0 and +2 oxidation states, thus facilitating regeneration of the catalytic palladium species.
- Is reluctant to undergo one-electron transfers (radical processes), thus avoiding unwanted side reactions.
- Has impressive functional group tolerance, i.e. chemoselectivity, which makes Pd-catalysis applicable to a large number of different substrates.
- Has a suitable van der Waals radius, which allows tetrahedral coordination of four ligands to Pd(0) and thus fulfillment of the 18-electron rule. The same applies to Pd(II) which, with square planar alignment of four ligands, forms a relatively stable 16-electron complex.
- Is relatively insensitive to moisture, oxygen and acid.
- Has accessible HOMO and LUMO orbitals, which facilitates concerted reactions of relatively low activation barriers.
- Has comparatively high electronegativity (2.2 Pauling), which allows relatively nonpolar Pd-C bonds and accordingly low reactivity toward electrophiles.

Organopalladium coupling transformations mainly involve two types of complex: σ- and π-complexes. Among the reactions involving the σ-species are the well known Stille, Suzuki, Sonogashira, Kumada and Negishi cross-coupling reactions, which are all catalytic with palladium but also use tin, boron, copper, magnesium and zinc as the respective transmetallating partners. The catalytic cycle of all these reactions involves a reductive
elimination step, during which the new carbon-carbon bond is created (Scheme 5).

Scheme 5. Catalytic cross-coupling process involving a Pd σ-complex

The second type of palladium reaction involves the π-bonded ligands. The usual reaction path involves electrophilic Pd(II) coordination to an electron-rich double bond, causing reduced electron density at the C=C bond, which facilitates subsequent attack by various nucleophiles (Scheme 6).

Scheme 6. Chelation-controlled carbopalladation of an alkene as a key step in the synthesis of prostaglandin PGF$_{2\alpha}$

The Heck reaction employs both σ- and π-bonded ligands (Scheme 3). The presented palladium-catalyzed transformations constitute only a small fraction of the immense number of processes involving organopalladium intermediates.

1.3 Enzymes as Catalysts in Organic Synthesis

The catalytic action of enzymes was proved by W. Ostwald in 1893. Today, enzyme-catalyzed reactions are being increasingly utilized in the production of fine and bulk chemicals. This trend is based on:

- The existence of an enzyme for almost every organic transformation.
- The achievement of high rates of acceleration ($10^8$-$10^{11}$).6
- The generally chemoselective, regioselective and/or stereoselective nature of enzyme-catalyzed reactions.17
Introduction

- The possibility of employing mild reaction conditions.\(^6\)
- The production of less toxic waste from the catalyst, compared with metal catalysis.

Hence, it is obvious that enzymes are valuable catalysts for organic transformations.\(^18\) Nonetheless, it often remains to be clarified whether an enzymatic approach is more convenient than a purely artificial counterpart. If there is a suitable enzyme for the planned synthetic step, it is still necessary to find the best conditions in terms of pH, solvent, regulators and temperature. Furthermore, an investigation of the catalytic activity is necessary, to see if the selectivity and stability of the enzyme are satisfactory for the desired transformation. Enzymes can also be chemically or genetically engineered to catalyze reactions with changed substrate selectivity\(^19\) and stereoselectivity\(^20\).

Scheme 7. Synthesis of Solanapyrone using a bifunctional enzyme (SPS)

A nice example of the usefulness of enzymes in total synthesis is the final step in the synthesis of (-)Solanapyrone (Scheme 7). Here, the use of SPS, a Diels-Alderase with oxidizing capability, proved to be superior to both the Lewis acid catalyzed and the uncatalyzed method.\(^21\)

1.3.1 Enzyme Kinetics, Optimizing the Reaction Temperature

The reaction temperature is important for the enzyme kinetics and, therefore, for the catalytic turnover frequency (TOF = reaction rate divided by catalyst concentration). The turnover number (TON = number of catalytic cycles divided by the number of catalytically active units) is governed by the stability of the enzyme at the given temperature. The selectivity of the enzyme can also be influenced by the reaction temperature. Some enzymes have a very narrow temperature interval in which they work efficiently, whereas others can work in a broader temperature range. Temperature-dependent inactivation of an enzyme can be described as a first-order process. The rate expression for the disappearance of the active enzyme E is:
Introduction

\[
\frac{d[E]}{dt} = -k[E]
\]

Integration gives the expression for the half-life \((t_{1/2})\) of the enzyme:

\[
t_{1/2} = \frac{\ln 2}{k}
\]

which is an important measure of enzyme stability. Furthermore, the first-order rate constant for enzyme inactivation also appears in the Arrhenius equation and thus gives an estimation of the free activation energy of enzyme inactivation. The balance between the activation energy of the reaction and the enzyme inactivation process determines the optimal temperature at which the whole process should be carried out in order to be most efficient.

1.3.2 Enzyme Stability

It has been suggested that thermal stability is closely related to the flexibility of the enzyme.\(^{22}\) A rigidification of an enzyme is unfavorable entropically but this may be compensated for by improvement in the enthalpic stabilization of the transition state structure. For example, decreased flexibility can increase stability by lowering the probability of solvent penetration into the hydrophobic core, which would lead to unfolding. Enzyme engineering\(^{23,24}\) offers several possibilities for thermal stabilization, such as:

- Immobilization of the enzyme on a solid support; for example, cross-linking the enzyme to the surface of particles may offer improved thermal stability as its movement is restricted.\(^{25}\)
- Site-specific modifications; chemical modification of a specific amino acid yielding a semisynthetic enzyme.\(^{26,27}\)
- Site-directed mutagenesis; stability enhancement through genetic modification of selected amino acid moieties.\(^{28}\)
- Use of hydrophobic solvents; usually, enzymes exhibit better conformational rigidity in a dehydrated state.\(^{29}\)
- Enzyme stabilization by low molecular weight solutes; compounds like salts and sugars can alter the kinetics of unfolding by binding to the enzyme.\(^{30}\)

Often it is desirable to increase the thermal stability, and thus the lifetime, of the enzyme without losing too much of its low-temperature activity.\(^{31}\)
2 The Heck Reaction

2.1 Background

The palladium(0)-catalyzed arylation and vinylation of olefins, using an aryl or alkenyl halide as precursor, were disclosed in the early seventies at approximately the same time by the pioneering work of Mizoroki\textsuperscript{32,33} and his co-workers in Japan and Heck\textsuperscript{10} in the US. This olefinic coupling, sometimes denoted the Mizoroki-Heck reaction, is a highly versatile carbon-carbon coupling method that has gained substantial interest during the last three decades.\textsuperscript{34,35} The general features of the Pd(0)/Pd(II) catalytic mechanism are presented below; and is currently the most widely accepted, although there has been recent debate about possible involvement of Pd(IV) species.\textsuperscript{36,37}

\begin{itemize}
  \item[(A)] A catalyst precursor is added to start the catalytic cycle, normally a Pd(0) compound such as Pd\textsubscript{2}(dba)\textsubscript{3}, Pd(PPh\textsubscript{3})\textsubscript{4} or a Pd(II) salt such as Pd(OAc)\textsubscript{2} or PdCl\textsubscript{2} which is reduced \textit{in situ} to Pd(0). The reducing agent can be either added phosphine ligands\textsuperscript{38} or the base\textsuperscript{39,40} but even the olefin\textsuperscript{40} and solvent\textsuperscript{41} have been proposed.
  \item[(B)] The electron-rich, nucleophilic Pd(0) forms an oxidative addition complex with an aryl halide or pseudo-halide (e.g. triflate, diazonium salt).
  \item[(C)] Association of an alkene affords an aryl-Pd-alkene $\pi$-complex.
  \item[(D)] Migratory insertion produces a $\sigma$-alkyl Pd species, often the slowest step in the catalytic cycle.
  \item[(E)] After rotation of the C-C bond, a $\beta$-hydrogen elimination occurs, furnishing a hydrido-Pd-olefin $\pi$-complex.\textsuperscript{42}
  \item[(F)] The product dissociates from the metal.
  \item[(G)] The base abstracts a proton from the hydrido-palladium species and thus reduces Pd(II) back to Pd(0), closing the catalytic cycle.
\end{itemize}
The Heck Reaction

Intramolecular Heck reactions, using vinyl or aryl halide-tethered olefins as starting material, have frequently been used in the synthesis of natural products. Intramolecular Heck couplings enjoy higher inherent reactivity than their intermolecular counterparts, possibly because of easier formation of the transient π-complex. Accordingly, the reaction times are appreciably shorter (hours) in comparison with intermolecular reactions (days). The remainder of this thesis will deal with intermolecular Heck arylation reactions.

2.2 Generation of Aryl-Palladium

The first step in the Heck reaction concerns the generation of the starting aryl palladium(II) complex from a suitable precursor. There are three distinct ways to generate the required aryl palladium(II) intermediate: transmetallation, electrophilic palladation or oxidative addition procedures. Transmetallation and electrophilic palladation can only occur with Pd(II) species, while oxidative addition takes place with Pd(0).

2.2.1 Transmetallation

Transmetallation of an organic moiety is a fundamental process in organometallic chemistry, yet little is known about the detailed mechanism. The physical driving force is the generation of less polar bonds. The transfer of the organic ligand to a more electronegative metal (e.g. from an alkaline earth metal to a transition metal) is always thermodynamically favorable (Scheme 8). The process proceeds smoothly, typically at room temperature.

\[
\text{Scheme 8. Transmetallation process involving Pd(II) and a main group metal}
\]

Unfortunately, the transmetallation procedure consumes stoichiometric amounts of palladium, since Pd(0) is produced at the end of the Heck cycle. Therefore, a Wacker type reoxidation of palladium with cupric halides and oxygen was successfully developed to yield a catalytic process. Nonetheless, the transmetallating agent is necessarily used in stoichiometric amounts in conjunction with catalytic amounts of palladium and, therefore, a large amount of metal-salt waste is produced. Organomercurials were most commonly used for this purpose in the sixties and early seventies (Scheme 9).
The Heck Reaction

\[
\text{PhHgCl} + \text{MeCN} \xrightarrow{\text{LiPdCl}_3} \text{HgCl}_2 + \text{HCl} + \text{LiCl} + \text{Pd(0)}
\]

**Scheme 9. Early Heck coupling utilizing the transmetallation approach and stoichiometric amounts of palladium(II)**

These days, several more suitable and less toxic aryl-metalloid precursors such as organo-boranes,\textsuperscript{50} silanes,\textsuperscript{51} stannanes,\textsuperscript{52} bismuth,\textsuperscript{53,54} antimony,\textsuperscript{55} and phosphonic acids\textsuperscript{56} are used, which has resulted in a revitalization of the procedure, especially because of the development of oxygen gas-based oxidation protocols. These procedures are now commonly named oxidative Heck couplings.

### 2.2.2 Electrophilic Palladation

In 1967, concurrently with Heck’s first organomercury protocol for vinylic substitutions, Fujiwara and Moritani discovered a Pd(II)-mediated method of generating the aryl metal intermediate, starting from unfunctionalized arenes.\textsuperscript{57,58}

\[
\text{ArH} + \text{PdX}_2 \rightarrow \text{'ArPd'}
\]

If the arene is functionalized, it is difficult to obtain selective ortho-, meta-, or para-palladation, and regioisomeric mixtures result.\textsuperscript{59}

\[
\begin{array}{c}
\text{Ph} - \text{OMe} \\
\text{Pd(OAc)}_2
\end{array}
\rightarrow
\begin{array}{c}
\text{Ph} - \text{OMe} \\
\alpha-\text{Methoxystilbene 30%} \\
\sigma-\text{Methoxystilbene 5%} \\
\rho-\text{Methoxystilbene 48%}
\end{array}
\]

This procedure seems attractive in terms of atom economy, since no stoichiometric metal or organic salt waste is produced, provided an effective palladium(0) reoxidation system is used.\textsuperscript{60-62}

### 2.2.3 Oxidative Addition

The most common method of obtaining palladation of the arene is by an oxidative addition process between an aryl-X (X = halide or pseudo-halide) and the palladium(0) moiety.\textsuperscript{63}

\[
\text{ArX} + \text{Pd(0)} \rightarrow \text{'ArPdX'}
\]
The order of reactivity for the commonly used X leaving groups is thought to be: diazonium salt > iodide > triflate > bromide > chloride. Aryl iodides, which have been studied the most, are usually reactive at relatively low temperatures (~40 °C). In practice, the required Pd(0) is often generated in situ from a Pd(II) precatalyst, because of the air and moisture sensitivity of common Pd(0) complexes. The ligands serve as effective reducing agents for Pd(II) as well as promoting the oxidative addition by coordination. A successful Heck reaction often depends on the selection of leaving group and ligand. For instance, in a process developed at Merck, the use of a triflate leaving group and PPh₃ furnished inferior yield (66 %) compared to bromide as leaving group and tri(o-tolyl)phosphine ((o-tol)₃P) as the ligand (91% yield; Scheme 10).

Scheme 10. Heck chemistry employed in the synthesis of a new class of LTD₄ antagonists

The cost and ready availability of the aryl chlorides makes them the most attractive coupling partners in Heck chemistry. Unfortunately, aryl chlorides are the most sluggish precursors (they have a high C-Cl bond dissociation energy). Thus, efficient catalysis requires high temperatures in combination with highly basic and air-sensitive phosphines as ligands to allow oxidative addition. Recently, the development of a procedure using air-stable tri-t-butyl phosphonium tetrafluoroborate by Fu and co-workers has simplified the implementation of sluggish aryl chlorides in the Heck process. With this phosphine precursor, the active ligand is liberated inside the reaction medium. The substitution pattern of the arene also plays an important role, since electron-withdrawing groups facilitate oxidative addition, while electron-donating groups restrain the process. Diazonium salts, iodides, triflates and electron-deficient bromides do not generally require ligands to undergo oxidative addition but are more disposed to undergo protonolysis and biaryl formation during the reaction. Ligandless
conditions therefore open up the possibility of a chemoselective substitution of the latter in the presence of e.g. chloride on the same arene.

2.3 The Insertion Process

The insertion process is, along with the oxidative addition step, generally rate-determining. Since the insertion process (syn addition, carbopalladation) is decisive for the regiochemical and stereochemical (in the case of prochiral olefins) outcome of the reaction, it may actually be the most important step in the catalytic cycle. Steric influences on the alkene moiety are also a deciding factor for the reactivity and selectivity of the reaction. As a rule of thumb, the more substituted the alkene, the more difficult the insertion. The regioselectivity for electron-rich olefins is governed by steric and electronic effects, acting in a synchronized manner. It has been suggested that two pathways can precede the insertion (the neutral and the cationic, named for the formal charge on the first formed Pd(II)-olefin species in each pathway); these involve different π-complexes and deliver different products (Scheme 11).

Scheme 11. Product manifold from a Heck reaction with an electron-rich monosubstituted olefin, proceeding via neutral or cationic π-complexes

If no precautions are taken, the two pathways are likely to operate simultaneously, resulting in mixtures of products employing electron-rich olefins. The cationic route was originally suggested by Cabri and Hayashi in the early nineties, and is promoted by the use of aryl triflates in combination with bidentate ligands. If no other strong bonding and negatively charged ligands are present, the weakly coordinating triflate anion will dissociate, particularly in polar solvents, which makes the palladium-olefin π-complex formally cationic. Alternatively, silver or thallium salts can be used to abstract the halide counterion from the palladium π-
The Heck Reaction

complex, which promotes the cationic route. Recently, procedures have been reported which avoid the use of scavenging metals and instead use highly polar solvents to promote dissociation of the halide. Employment of aryl diazonium tetrafluoroborate salts also encourages the cationic pathway.

A cationic palladium species will more strongly favor electronic requirements at the expense of steric requirements. The electronic effect relates to the polarization of the Ar-Pd σ-bond and the formally cationic palladium preferentially migrates to the more negatively charged vinylic carbon. In the insertion step, the aryl moiety behaves as the larger part and, accordingly, the neutral pathway promotes terminal (linear) products for steric reasons. Steric factors mostly favor terminal arylation, while electronic effects favor internal arylation on olefins substituted with mesomerically electron-donating (+M) groups. When the olefin has a mesomerically electron-withdrawing (-M) group, both steric and electronic factors favor terminal substitution. Mesomeric effects are more important than inductive effects. Some illustrative examples are given in Table 1.

Table 1. Regiochemistry From Arylation of Commonly Used Olefins

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mono-functionalized olefin</th>
<th>Inductive effect</th>
<th>Mesomeric effect</th>
<th>Regioisomeric products Neutral conditions</th>
<th>Cationic conditions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>= 0</td>
<td>-M</td>
<td>Terminal arylation predominates</td>
<td>Mixture</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>CN</td>
<td>-I</td>
<td>-M</td>
<td>Exclusive terminal arylation</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>SiR₃</td>
<td>+I</td>
<td>0</td>
<td>Arylation and elimination of silicon</td>
<td>Exclusive terminal arylation</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>NR'-COR</td>
<td>-I</td>
<td>+M</td>
<td>Mixture</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>OR</td>
<td>-I</td>
<td>+M</td>
<td>Mixture</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>COOR</td>
<td>-I</td>
<td>-M</td>
<td>Exclusive terminal arylation</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>CₓFₘ₋ₙ+2</td>
<td>-I</td>
<td>0</td>
<td>Exclusive terminal arylation</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>+I</td>
<td>0</td>
<td>Terminal arylation predominates</td>
<td>Internal arylation predominates</td>
<td>89</td>
</tr>
</tbody>
</table>
The Heck Reaction

Enol ethers are a class of electron-rich, heteroatom-substituted olefins that have been of less interest as substrates in Heck chemistry than their styrene or electron-poor, acrylate-type counterparts. This is mainly due to the aforementioned regioselectivity problem associated with electron-rich olefins, where the steric and electronic factors work in opposite directions, causing product mixtures. If this problem could be overcome, the enol ethers would be useful, since they are masked carbonyl functionalities. In 1990, Cabri and co-workers reported the use of cationic conditions facilitating selectively produced internally arylated products in the Heck arylation of enol ethers. Preparatively useful and fairly regioselective terminal β-arylations using aryl triflates or aryl chlorides as arylating agents were published by Andersson and Hallberg in the late eighties. The β-selectivity was later improved by the development of amino functionalized enol ethers.

2.3.1 Chelation-Controlled Insertion

The expression ‘chelate’ is derived from Greek chele meaning claw. In a chemical context, chelation means that a ligand binds at at least two sites to a metal. In the literature there are several examples of X-ray structures of olefin/heteroatom-containing compounds that simultaneously coordinate to a Pd(II)-atom in a bidentate manner (Scheme 12).

Scheme 12. Examples of substrate (π,σ) chelation to palladium

The insertion step in Heck reactions is controlled by the stability and the size of the chelated ring. The bonding between palladium and the heteroatom must be of intermediate strength, strong enough to present the Pd atom to the olefin but weak enough to release Pd after the insertion and subsequent β-elimination. The latter is a prerequisite for successful catalysis to occur. The equilibrium formation constants for amines to Pd(II), investigated by Trogler et al., indicate that both steric factors and hybridization are important. Amines have the advantage over phosphines in that they are not sensitive to oxidation under Heck conditions. Oxygen, being more electronegative and thus ‘harder’, in most cases, coordinates too weakly to the ‘soft’ Pd to be generally useful in chelation.
The Heck Reaction

Substrate chelation in Heck chemistry opens for a number of sophistications. Among these the following are included:

- Attaching the substrate at two coordinating sites, one π-bonding olefin and an additional σ-bonding auxiliary, facilitates the π-complex formation (entopically favorable) and thus enhances the reaction rate (provided that the insertion is the rate-determining step).97,107

- Using the neutral pathway in combination with chelation strongly moderates the electronic effects and therefore provides good control over the regiochemistry.96,98,110,111

- A prochiral double bond can be asymmetrically presented to the palladium if the σ-bonding auxiliary is chiral.112

- Sterically demanding insertions can be eased by the additional σ-coordination.113

- After β-elimination, double-bond migrations can be minimized by preventing readdition of palladium–hydride species.114

2.3.2 Asymmetric Insertion

If the employed olefin is prochiral it is possible to perform asymmetric insertion, i.e. to design the system so that one face of the olefin is preferentially inserted (Scheme 13).115

![Scheme 13. Model of an arylation at the β-position of an enol ether, insertions from both enantiotopic faces](image)

Provided that the β-elimination after insertion moves the double bond away from its original position, a new chiral center may be formed by the Heck process.85,116 Two general methods are available: ligand control and chiral auxiliary methods.

Ligand control: Asymmetric transfer is most successfully carried out using a chiral enantiopure bidentate ligand117-120 and cationic conditions.121,122 Notably, examples of intramolecular asymmetric Heck reactions, run under neutral conditions with monodentate and bidentate
The Heck Reaction

ligands, have been reported by Overman\textsuperscript{123} and Feringa\textsuperscript{124,125}. It is believed that cationic conditions ensure that both coordinating sites at the bidentate ligand are attached to palladium during the insertion, along with a better Pd-olefin interaction. Because of the tighter complexation, larger energy differences in the diastereomeric transition states of \( \text{Re-} \) and \( \text{Si-} \) face insertion are expected, with subsequently better stereo-differentiation. A great number of ligands have been employed in asymmetric Heck reactions; two of the most successful are the P,P–bidentate and axially chiral \( \text{A} \) ((\( R \))-BINAP), developed by Noyori\textsuperscript{126}, and the chiral N,P-bidentate phosphineoxazoline \( \text{B} \), discovered by Pfaltz\textsuperscript{127,128}.

These ligands are very useful in a number of transformations relying on chiral catalysis. Enantioselectivities employing BINAP in Heck arylations are mostly high, but intramolecular Heck applications are often more successful than intermolecular applications.\textsuperscript{129} Proven highly useful in \( \pi \)-allyl palladium substitution reactions, the phosphineoxazoline \( \text{B} \) also delivers high enantioselectivities in Heck arylations and vinylations (Scheme 14).\textsuperscript{130}

Scheme 14. Asymmetric Heck arylation under cationic conditions

Obviously, ligand controlled asymmetric Heck chemistry has the benefit of being economical in the use of chirally enriched material (a catalytic amount of chiral ligand is sufficient). However, the cationic conditions that are generally required essentially limit the scope of the reaction to electron-rich olefins.

Chelation control: The palladium \( \pi \)-complex can be effectively asymmetrically presented to the diastereotopic faces of the olefin by introducing a chelating chiral auxiliary. A nice example published by the group working with Carretero is the arylation of \( \sigma \)-(\( N,N \)-Dimethylamino)phenyl-substituted vinylsulfoxides (Scheme 15).\textsuperscript{131}
Scheme 15. *A chelation-controlled asymmetric arylation performed with an electron-poor olefin under cationic conditions*

A chiral pyrrolidine auxiliary (SAMP) has also been employed in intramolecular Heck chemistry by Grigg and co-workers. Unfortunately, the yield of the transformation was not disclosed in the letter.\textsuperscript{132} Furthermore it is not clear whether the diastereoselectivity in this case was induced by chelation or steric influences.

The chirality of the proline-derived pyrrolidine ring has been used extensively in asymmetric synthesis.\textsuperscript{115,133} The usefulness of the chelation methodology is often dictated by the availability of cheap and recyclable enantiopure chiral auxiliaries. Furthermore, the attachment and detachment procedures must be high yielding and easy to carry out. Importantly, chelation control can be utilized to induce asymmetric insertion of the oxidative addition complex to both electron-rich and electron-poor olefins under both neutral and cationic conditions.
3 The Polymerase Chain Reaction (PCR)

The polymerase chain reaction was discovered in 1983 by the American Kary B. Mullis. This very important methodology brought him a shared Nobel Prize in 1993 for “contributions to the development of methods within DNA-based chemistry”. The PCR method is used to amplify a specific region of a DNA sample. PCR mimics the natural method of DNA replication. A normal PCR run involves a number of cycles for amplification of a nucleic acid sequence. Each cycle is a three-step process that is repeated a specified number of times. This amplification process takes place in a thermocycler, a device that controls and changes the temperatures for programmed time intervals for the appropriate number of PCR cycles (around 20-40).

One PCR cycle consists of the following steps:

1. Denaturation of the DNA helix to obtain single-stranded DNA, i.e. all hydrogen bonds between the bases are broken. This is achieved by raising the temperature above 90 °C.

2. Annealing of primers. The beginning of the sequence of interest is recognized by the primers, which are present in excess and anneal (bind) to the complementary sequence. A temperature between 40 and 60 °C is normally employed to ensure high specificity when the primers bind via weak hydrogen bonds to the target sequence.

3. Synthesis of new DNA. Raising the temperature to approximately 72 °C activates the enzyme Taq DNA polymerase which facilitates the binding and incorporation of the complementary nucleotides that are free in solution (dNTPs) to synthesize new DNA strands.

Taq DNA polymerase, originally found in the hot springs of Yellowstone National Park, is a thermostable enzyme isolated from the thermophilic bacterium *Thermus aquaticus*. Unlike normal polymerase enzymes, Taq is stable and active at high temperatures. Taq DNA polymerase synthesizes only in the 5’ to 3’ direction. Therefore, free nucleotides in the solution are
The Polymerase Chain Reaction only added to the 3' end of the primers constructing the complementary strand of the targeted DNA sequence (Figure 3).

**Figure 3. Sketch of the Taq catalyzed incorporation of nucleotides to synthesize new DNA strands**

PCR technology is now extensively used in molecular biology and has become the mainstay of techniques involved with identification of organisms, criminal suspects, and disease-causing bacteria and viruses, etc. Furthermore, PCR has become a powerful tool in both screening and optimization processes in the search for catalytically active RNA sequences. Since PCR is such an important technique, it is under constant development. The focus is mainly on improving polymerase activity and the efficiency of the heating devices to allow faster and more reliable amplifications.
4 Microwave-Assisted Organic Synthesis

4.1 The Physical Background

Microwaves consist of electromagnetic radiation with frequencies in the region between infrared and radio waves. Microwaves are today commonly used in many technical applications, e.g. equipment for telecommunications, RADAR, and industrial applications (textile drying, drying of coffee beans, sterilization of medical waste, ceramics, vulcanization of various rubber products, etc). To most of us, however, the domestic microwave oven, used for heating food, is probably the first thing that comes to mind in association with microwaves. To avoid interference with radar and telecommunications, a specific frequency (2.45 GHz) in the microwave band (0.3-300 GHz) has been designated for commercial microwave ovens. Contrary to popular belief, this frequency was not chosen in order to maximize the absorbance for water, which is more likely to peak at around 10 GHz. Perhaps a more relevant fact is the penetration depth of the microwaves for normal loads (food), which is generally good (uniform) at a frequency of 2.45 GHz.

In basic chemistry courses, it is normally concluded that the energy content of microwave radiation is too low to affect the vibrational levels of a molecule and that it is the quantized energy levels of the rotational modes that absorb radiation in the microwave region (Figure 4). This is the theoretical basis for Raman spectroscopy. Importantly, this is only applicable in the gas phase and not in the more dense liquid and solid states, where the quantization of the energy levels has been transformed to a continuum. This thesis will only deal with dielectric heating of various liquid phases used in organic synthesis.

Heating a sample by microwave irradiation occurs by a phenomenon called dielectric loss. A material that contains either permanent or induced dipoles can be made to store electrical charge. Permittivity ($\varepsilon$) is a measure of this charge-storing ability, although the relative permittivity $\varepsilon_r$ (the permittivity compared to a vacuum space, which is a complex number), also called the dielectric constant, is more commonly used.
Figure 4. Electromagnetic radiation energy and the corresponding effect on molecules

The polarization (P) of a substance can be described as its electric dipole moment density. This varies with the applied field \( E = E_{\text{max}}e^{t} \) and the permittivity (Figure 5). Electromagnetic radiation consists of oscillating electric and magnetic vectors mutually orthogonal to each other. Normally, the magnetic field has no effect on solution phases. The oscillating electric fields couple with the dipoles in the irradiated sample and force them to rotate. If the applied radiation has a frequency that exceeds the response time for polar molecules to align to the electric field, microwave energy will be converted to thermal energy inside the sample.

Figure 5. The polarization lags behind the electric field by an angle \( \delta \)

The ability of a material to absorb microwave energy at a given temperature and frequency is expressed by the Dielectric Loss Tangent Equation:

\[
\tan \delta = \frac{\varepsilon''}{\varepsilon'}
\]

\( \varepsilon'' \) is the imaginary part of the dielectric constant known as the loss factor, which corresponds to the conductance of the material. \( \varepsilon' \) is the real part of the dielectric constant.
Microwave-Assisted Organic Synthesis

ε" is used to estimate the percentage of the applied power that is converted to heat, and can be thought of as the "heat yield". Tan δ can also be visualized by considering that the total current is the vector sum of the loss current and the charging current (Figure 6).

4.1.1 Heating Mechanisms

The shape and polarity of molecules dictates their inertia and hence the time they take to respond to the applied electric field. The subsequent efficiency of microwave absorbance will therefore vary markedly with microwave frequency for liquid molecules. This mechanism of heating samples using microwaves is called dipolar polarization. A second mechanism that gives rise to heat involves ionic conduction. If the irradiated sample is an electrical conductor, the charge is carried through the material via electrons, ions, protons, etc. under the influence of the applied electric field, resulting in polarization and thus heat. A third possible heating mechanism involves interfacial polarization. When the irradiated material is heterogeneous and the components differ significantly in their conductivity, there will be an interface where charges can be built up very quickly. This latter mechanism is difficult to derive mathematically and therefore is not as well understood as the first two effects.

4.2 Microwave Chemistry

The first commercial household microwave oven was introduced in 1955, shortly after the Second World War, during which RADAR devices had boosted the development of magnetrons. Industrial applications were developed immediately thereafter, but it was not until about 30 years later that the first scientific papers on microwave-assisted organic chemistry appeared. These first experiments utilized modified multi-mode household ovens. Since then, development in the area of microwave-assisted organic synthesis has been substantial. Specially designed mono-mode laboratory microwave ovens are now available. The term mono-mode means that the irradiation is focused at the sample position (with one standing wave) and not randomly distributed in the cavity, as is the case with multi-mode ovens. Furthermore, devices for monitoring both temperature and
Microwave-Assisted Organic Synthesis

pressure (in the case of sealed vessels) have been included ‘on line’, thus facilitating accurate control over the reaction conditions.\textsuperscript{150,151}

4.2.1 Microwave-Assisted High Speed Synthesis

The loss tangent value (\(\tan \delta\)) of the solvent is particularly important for optimal heating of the reaction sample (Table 2). The value of \(\varepsilon'\) corresponds to the polarity of the solvent. The boiling point provides information on the vapor pressure expected in pressurized systems at the planned reaction temperature.

\textbf{Table 2. Important Parameters for Some Common Solvents}\textsuperscript{143}

<table>
<thead>
<tr>
<th>Solvent</th>
<th>(\varepsilon')</th>
<th>(\tan \delta)</th>
<th>boiling point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>21</td>
<td>0.045</td>
<td>56</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>38</td>
<td>0.062</td>
<td>82</td>
</tr>
<tr>
<td>DCM</td>
<td>9</td>
<td>0.042</td>
<td>40</td>
</tr>
<tr>
<td>DMF</td>
<td>36</td>
<td>0.161</td>
<td>153</td>
</tr>
<tr>
<td>DMSO</td>
<td>49</td>
<td>0.825</td>
<td>189</td>
</tr>
<tr>
<td>Methanol</td>
<td>33</td>
<td>0.659</td>
<td>65</td>
</tr>
<tr>
<td>THF</td>
<td>8</td>
<td>0.047</td>
<td>66</td>
</tr>
<tr>
<td>Water</td>
<td>80</td>
<td>0.123</td>
<td>100</td>
</tr>
</tbody>
</table>

Using a solvent with a high \(\tan \delta\) value provides fast ramping of the reaction temperature and often better reproducibility. It should be borne in mind that the dielectric constant always decreases with increasing temperature, e.g. water at 170 °C has comparable polarity to acetonitrile at ambient temperature. Fast heating, in combination with pressurized systems, sets new boundaries for the kinetics in any heat-driven reaction. In practice, this technique provides an opportunity to develop new, as well as improving existing, chemical reactions. Moreover, microwave heating also opens the possibility for selective heating; when two mutually insoluble solvents with largely different \(\tan \delta\) values are exposed to microwave irradiation, differential heating occurs, resulting in a significant temperature difference between the layers.\textsuperscript{152} Microwave irradiation may also be involved in the kinetics and folding process of proteins.\textsuperscript{153-155}
5 Aims of the Thesis

The palladium-catalyzed vinylic substitution process, commonly named the Heck reaction, is regarded as an efficient method of forming carbon-carbon bonds. The usefulness of this reaction in synthetic processes is in principle very broad. However, low regioselectivity is sometimes encountered along with low reactivity and extended reaction times. Development of new methods using the Heck arylation process but providing higher reactivity and better selectivity with different types of olefins is therefore particularly important.

While the use of bio-catalysis techniques is expanding rapidly, understanding the relationship between the selectivity and thermal stability of enzyme-catalyzed transformations is crucial to the development of more efficient processes.

The objectives of this thesis were:

- To design new, highly regioselective, enantioselective and diastereoselective Heck arylation protocols using electron-rich olefins as substrates.
- To develop a protocol for efficient hydrolysis of arylated enol ethers to the corresponding aryl acetaldehydes.
- To utilize microwaves for fast and selective palladium- and enzyme-catalyzed transformations.
- To examine the possibility of using arylboronic acids as reactants in rapid microwave-promoted and selective Heck arylation reactions.
6 Results and Discussion

6.1 Chelation Control in Heck Chemistry (Papers I and II)

We are currently experiencing a renaissance in the area of the Heck coupling reaction as a result of the impact of new efficient Pd-catalysts such as palladacycles,\textsuperscript{156,157} pincers,\textsuperscript{158} and palladium carbenes,\textsuperscript{159,160} together with new reaction media such as ionic liquids\textsuperscript{161,162} or water\textsuperscript{163}. New kinds of leaving groups (e.g. aroyl halides,\textsuperscript{93-95} anhydrides\textsuperscript{164,165}) along with other carboxylic acid\textsuperscript{166} derivatives have also been introduced in Pd(0)-catalyzed classic Heck reactions. Furthermore, new ligands have allowed the use of cheap, freely available aryl chlorides as substrates.\textsuperscript{167} In the field of oxidative Heck chemistry, new organopalladium precursors are rapidly being discovered.\textsuperscript{50,51,55,56} Nonetheless, many problems associated with selectivity,\textsuperscript{77,168,169} double-bond migrations, and long reaction times, plague the methodologies. There is thus a need for the development of new innovative procedures. Accordingly, our group has studied the influence of a palladium-coordinating amino group on the problem of poor regioselectivity that is encountered in palladium(0)-catalyzed Heck arylations of vinyl ethers.\textsuperscript{96-98}

6.1.1 Chelation-Promoted Multiarylations

The arylation of unsubstituted enol ethers (e.g. butyl vinyl ether) is preferentially run under cationic conditions, giving both good reactivity and (internal) regioselectivity.\textsuperscript{170} Problems arise when terminal arylation is desired, since a switch to neutral conditions gives product mixtures.\textsuperscript{171,172} Multiarylations\textsuperscript{173} are even more troublesome mainly because of incomplete conversion. Multiple arylations of mono-substituted olefins have been exemplified in the literature using electron-poor, acrylate type, olefins, furnishing β,β-diarylated products.\textsuperscript{174-176} Because of the present lack of Heck protocols for α-arylation of acrylate type olefins, no further substitution is possible. However, for electron-rich olefins such as enol ethers, α-arylation
Results and Discussion

is a smooth process. Previous studies in our group have shown that by introducing a palladium-coordinating nitrogen functionality, very high external (β) selectivity can be achieved. In these studies, the length of the oxygen-nitrogen tether was found to be optimal (affording superior β-selectivity) at a distance of two carbons. Thus, the following enol ethers were considered for a multiarylation study:

\[
\begin{align*}
1 & \quad 2 & \quad 3 & \quad 4 & \quad 5 \\
\text{O} & \text{N} & \text{O} & \text{N} & \text{O} \\
\end{align*}
\]

Attempts to introduce a third aryl at the α-position using β,β-arylated products as starting materials proved to be unsuccessful, despite the use of several different Heck methodologies. Consequently, the α aryl substituent needed to be installed first. After initial α-phenylation, competitive studies showed that α-phenylated 6a easily underwent β,β-diphenylation with bromobenzene while 7 and non-chelating 8 gave moderate and poor yields of β-phenylated products, respectively (the yields were measured as the corresponding ketones 13 after hydrolysis) (Scheme 16).

\[
\begin{align*}
6a & \quad 1.0 \text{ equiv} & 7 & \quad 1.0 \text{ equiv} & 9a & \quad 0.57 \text{ equiv} & 10 & \quad 0.29 \text{ equiv} \\
\text{O} & \text{N} & \text{O} & \text{N} & \text{O} \\
\text{Ph} & \text{Ph} & \text{Ph} & \text{Ph} & \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
6a & \quad 1.0 \text{ equiv} & 8 & \quad 1.0 \text{ equiv} & 9a & \quad 0.67 \text{ equiv} & 12 & \quad 0.26 \text{ equiv} \\
\text{O} & \text{N} & \text{O} & \text{N} & \text{O} \\
\text{Ph} & \text{Ph} & \text{Ph} & \text{Ph} & \text{Ph} \\
\end{align*}
\]

Scheme 16. Competitive experiment between α-phenylated chelating and non-chelating enol ethers

6.1.1.1 Triarylation Experiments
Based on the outcome of the competitive experiments, and after extensive optimization of conditions, chelating 1 was chosen as a model substrate for the triarylation study, using a sterically and electronically diverse set of aryl halides (Scheme 17).
Results and Discussion

Scheme 17. Reaction sequence for the synthesis of triarylated ethanones 13

The cumulative isolated yields (Table 3) from the triarylation process are derived from the four-step transformation of the starting aryl bromide into the final ketone 13. Delicate electronic influences were found to be important for triarylation. Electron-poor aryls generally furnished lower yields (entries 4-6 and 9), while electron-rich aryls performed better. Entry 7 is a notable exception, but the poor yield may be explained by extensive scrambling from triphenylphosphine (a large amount of β-phenylated compound was found in the product mixture) and a difficult purification process. Consequently, switching to tri(p-tolyl)phosphine in entry 8 significantly improved the yield by removing the influence of scrambling. Steric factors also seem to be important, since 2-bromo-toluene only reluctantly performed the second β-arylation (7% yield, entry 10). In all reactions in Table 3, biaryl formation was a noticeable side-reaction. Disappointingly, under these conditions, when phenyl iodide (entry 11) or phenyl triflate were employed as the second arylating agent, neither resulted in any triarylation products. Because slow release of $N,N$-dimethylethanolamine, from hydrolyzed 9, inhibited the catalytic process, extra palladium acetate (6%) was routinely added after 18 h. The final hydrolyses of the tri-arylated products 9 to the corresponding ketones 13 were smoothly carried out using a two-phase TBME/HCl (aq) system.
### Results and Discussion

Table 3. Chelation-Accelerated Palladium-Catalyzed Triarylation of Vinyl Ether 1 and Subsequent Hydrolysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar(^1)X</th>
<th>Ar(^2)X</th>
<th>Ketone</th>
<th>Isolated Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>Br</td>
<td>[Ph(\text{Ph})]</td>
<td>13a 65%</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>Br</td>
<td>[Ph(\text{Ph})]</td>
<td>13b 66%</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>Br</td>
<td>[Ph(\text{Ph})]</td>
<td>13c 45%</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>Br</td>
<td>[Ph(\text{Ph})]</td>
<td>13d 50%</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>Br</td>
<td>[Ph(\text{Ph})]</td>
<td>13e 23%</td>
</tr>
<tr>
<td>6</td>
<td>CN</td>
<td>Br</td>
<td>[Ph(\text{Ph})]</td>
<td>13f 14%</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>Br</td>
<td>[Ph(\text{Ph})]</td>
<td>13g 21%</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>Br</td>
<td>[Ph(\text{Ph})]</td>
<td>13h 59% (76%)(^b)</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>Cl</td>
<td>[Cl(\text{Cl})]</td>
<td>13i 15%(^c)</td>
</tr>
<tr>
<td>10</td>
<td>Br</td>
<td>Br</td>
<td>[Cl(\text{Cl})]</td>
<td>13j 7%(^c)</td>
</tr>
<tr>
<td>11</td>
<td>no</td>
<td>13a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Based on the starting material Ar\(^1\)Br utilized in the \(\sigma\)-arylation reaction. >95\% purity by GC-MS.  
\(^b\) Isolated yield when tri(p-tolyl)phosphine was used as ligand.  
\(^c\) The corresponding D,E-diarylated compounds were instead obtained in useful yields, see Table 5.
Results and Discussion

6.1.1.2 β,β-Diarylation Experiments

Encouraged by the high reactivity derived from the coordinating dimethyl amino group, I proceeded to also perform the following diarylations:

A double arylation at the β-position provides a useful indication of the power of the chelation-controlled β-directing effect (Scheme 18). In addition, the corresponding β,β-products are members of a class of compounds found to be biologically active GABA inhibitors.  

Scheme 18. Reaction sequence for the synthesis of β,β-diarylated products

The mono-arylated product 14 was not isolated but was further arylated in a second step to avoid extensive purification. The first arylation furnished an E/Z product mixture in which the aryl group preferentially chose the Z-position (Table 4). A proposed reaction path for the chelation-controlled insertion followed by subsequent β-elimination, delivering the two diastereomeric products, is shown in Scheme 19. The scrambling experienced in the triarylation experiments motivated a switch to ligandless conditions, using reactive aryl palladium precursors and aqueous DMF. The β,β-diarylation procedure seemed to be less affected by electronic factors than the triarylation process. High β-selectivity for the second arylation step was experienced in all cases, and the last introduced aryl substituent preferred the Z-position. As expected, the iodine of 1-bromo-4-iodobenzene was chemoselectively substituted under ligandless conditions (entry 4). Introduction of electron-poor aryls in the second step provided slightly lower yields, although sometimes with high geometric selectivity (entry 6 and 7). Even sterically hindered 2-iodotoluene was equally smoothly introduced as the unhindered 4-iodotoluene (entry 2 and 3). The electron-poor 4-bromo-benzophenone was reactive, yielding 15g at slightly elevated temperatures (100 °C), with excellent β,β-selectivity in good yield (entry 8).
Results and Discussion

Table 4. Chelation-Controlled $\beta,\beta'$-Diarylation of Enol Ether 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>$\text{Ar}^1$</th>
<th>E/Z$^a$</th>
<th>$\text{Ar}^2X$</th>
<th>$\beta,\beta'$-Diarylated Vinyl Ether</th>
<th>$\alpha,\beta,\beta'$</th>
<th>E/Z$^b$</th>
<th>Isolated Yield of 15 (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>28/72</td>
<td></td>
<td>[Diagram]</td>
<td>3/97</td>
<td>3/7</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>30/70</td>
<td></td>
<td>[Diagram]</td>
<td>7/93</td>
<td>3/7</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>31/69</td>
<td></td>
<td>[Diagram]</td>
<td>1/99</td>
<td>4/6</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>26/74</td>
<td>Br</td>
<td>[Diagram]</td>
<td>3/97</td>
<td>3/7</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>48/52</td>
<td></td>
<td>[Diagram]</td>
<td>10/90</td>
<td>7/3</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>33/67</td>
<td></td>
<td>[Diagram]</td>
<td>1/99</td>
<td>2/8</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>27/73</td>
<td></td>
<td>[Diagram]</td>
<td>3/97</td>
<td>2/8</td>
<td>37</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>30/70</td>
<td>Br</td>
<td>[Diagram]</td>
<td>1/99</td>
<td>3/7</td>
<td>50</td>
</tr>
</tbody>
</table>

$^a$ Determined by GC-MS and $^b$H NMR. $^b$ Determined by GC-MS and NMR NOE experiments.

$^c$ Based on the starting material $\text{Ar}^1$ utilized in the first $\beta$-arylation reaction as a mixture of Z and E isomers. >95% purity by GC-MS.
Results and Discussion

During synthesis of the β,β-Diarylated products, no trace of triarylation was ever detected. An X-ray study of *N,N*-Dimethyl-2-[(2,2-diphenyl)ethenyl]oxy]ethanamine (15h) crystallized with PdCl₂ gave a possible explanation for the low reactivity of the β,β-product towards α-arylation, since the “propeller-like” conformation of the phenyl rings effectively blocked π-complex formation/insertion.

**Scheme 19. Mechanism for the geometric outcome of the first arylation**

6.1.1.3 Liberation of Diarylated Acetaldehydes

The synthesized β,β-arylated products 15 (Table 4) are in principle masked di-aryl acetaldehydes, and a smooth deprotection procedure opens a synthetically useful route to this class of compounds. Unfortunately, the use of conventional one-phase acidic hydrolysis produces a plethora of byproducts. Instead, using a two-phase approach in combination with microwave irradiation proved to be highly convenient. The β,β-diarylated...
Results and Discussion

Products were dissolved in toluene; when shaking this solution with acidic water, the yellow toluene layer turned colorless, accompanied by colorization of the water layer. Application of single-mode microwave irradiation allowed very fast heating (acidic water absorbs microwaves extremely well), liberating the free aryl acetaldehydes 16 in 1-2 minutes (Table 5). After cooling, easy separation of the two layers afforded diaryl acetaldehydes in the organic phase and the aminoalcohol in the water phase (Figure 7).

It is likely that the hydrophobic aldehyde rapidly partitions to the toluene layer after hydrolysis, and thereby avoids the acidic environment which promotes condensation, polymerization etc. The aryl acetaldehydes obtained after evaporation of the toluene are labile and easily oxidized, and should therefore be subjected to further transformations as soon as possible.

Figure 7. Differential heating of a two-phase system

Since protonation of the β-carbon is the rate-determining step, it is sensitive to substitution, requiring higher temperatures and harsher conditions when sterically hindered (Scheme 20).

Scheme 20. General mechanism for aqueous hydrolysis of an enol ether

Substitution at the α-position is, however, favorable since it stabilizes (especially from aryl conjugation) the formed carbocation intermediate. α-Arylated enol ethers are therefore always acid labile.
## Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enol ether</th>
<th>Aldehyde</th>
<th>Isolated Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Temp (°C)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15a</td>
<td>16a</td>
<td>93</td>
<td>180</td>
<td>2.0</td>
</tr>
<tr>
<td>2</td>
<td>15b</td>
<td>16b</td>
<td>98</td>
<td>180</td>
<td>2.0</td>
</tr>
<tr>
<td>3</td>
<td>15c</td>
<td>16c</td>
<td>91</td>
<td>180</td>
<td>2.0</td>
</tr>
<tr>
<td>4</td>
<td>15d</td>
<td>16d</td>
<td>83</td>
<td>180</td>
<td>2.0</td>
</tr>
<tr>
<td>5</td>
<td>15e</td>
<td>16e</td>
<td>80</td>
<td>150</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>15f</td>
<td>16f</td>
<td>80</td>
<td>180</td>
<td>2.0</td>
</tr>
<tr>
<td>7</td>
<td>15g</td>
<td>16g</td>
<td>82</td>
<td>180</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Conditions: Enol ether 15, 0.25 mL water, 0.25 mL concd HCl and 1 mL toluene were mixed and irradiated at the given time and temperature. <sup>a</sup> >95% purity by GC-MS.
Results and Discussion

6.1.1.4 α,β-Diarylation Experiments

The concept of chelation had so far not only enhanced the reactivity, allowing the assembly of sterically congested triarylated fully substituted olefins, but also improved regioselectivity. The next study included the selective formation of α,β-diarylated compounds to investigate how well the reaction could be controlled (Scheme 21).

Scheme 21. Reaction sequence for the synthesis of α,β-arylated products

Somewhat surprisingly, after α-arylation, the diarylated product 17 was less easily synthesized than the corresponding tri-arylated product 13 using aryl bromides (entry 3, Table 6). This was because full conversion of 6 produced both di- and triarylation products. Electron-rich bromides were therefore not used further. Under similar conditions to those used in the triarylation reactions, the use of electron-poor aryls without the propensity for triarylation led to successful α,β-arylations (entries 8-9, Table 6). Utilizing electron-poor triflates at high temperatures (100-105 °C) caused no triarylation problems but resulted in only moderate cumulative three-step yields of the corresponding ketones (entries 4-6). Unexpectedly, β-arylation reactions with aryl triflates furnished only one geometric isomer of 17 (entries 4-6). The final hydrolyses of crude α,β-diarylated products 17 were performed under microwave irradiation, employing a two-phase system.

It is worth mentioning that the non-chelating olefin 8 was not readily diarylated under any of the investigated conditions. In a separate experiment the diethylamino analog 7, having a more sterically hindered nitrogen, produced negligible amounts of triarylated product, but the reaction was slow and showed incomplete conversion at 100 °C. Disappointingly, raising the temperature to speed up the reaction caused the triarylation to start again.
### Results and Discussion

Table 6. Chelation-Accelerated Palladium-Catalyzed α,β-Diarylation of Vinyl Ether 1 and Subsequent Microwave-Assisted Hydrolysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar(^1)X</th>
<th>Ar(^2)X</th>
<th>Temp(^a) (°C)</th>
<th>Time(^a) (h)</th>
<th>Ketone</th>
<th>Isolated Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TfO</td>
<td></td>
<td>50</td>
<td>37</td>
<td></td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>TfO</td>
<td></td>
<td>50</td>
<td>72</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>TfO</td>
<td>O</td>
<td>105</td>
<td>13</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>TfO</td>
<td>O</td>
<td>105</td>
<td>4</td>
<td></td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>TfO</td>
<td>NC</td>
<td>100</td>
<td>5</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>TfO</td>
<td>NC</td>
<td>100</td>
<td>5</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>TfO</td>
<td>F(_3)C</td>
<td>130</td>
<td>72</td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td></td>
<td>100</td>
<td>48</td>
<td></td>
<td>70(^c)</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>Br</td>
<td>100</td>
<td>44</td>
<td></td>
<td>54(^c)</td>
</tr>
</tbody>
</table>

\(^a\) In the β-arylation, time and temperature were optimized to obtain maximum conversion of 6 without producing 13. \(^b\) Based on the starting material Ar\(^1\)X for the α-arylation reaction. >95% purity by GC-MS. \(^c\) Entry 8-9 were performed according to the conditions used in the triarylation reactions.
Crystallographic studies were performed in order to gain more insight into the mechanism of chelation. McCrindle has reported the co-crystallization of palladium(II) with an amino functionalized enol ether to form a π-complex. Attempts to make a similar complex with 1 were regrettably unsuccessful. The pyridine-substituted 4 is known to undergo highly regioselective β-arylation, comparable to that in 1. In early multiarylation experiments, α-phenylated 4 resisted any attempts to force further arylation. This indicated that the sp²-hybridized nitrogen in 4 might form a much stronger bond to palladium than the tertiary nitrogen in 1, thus creating a more stable π-complex and thereby disrupting the catalytic cycle. The assumption that 4 and 5 would be more suitable substrates for crystallization with palladium is also supported by the equilibrium binding constants of amines, as reported by Seligson. Smooth crystallization occurred in CH₂Cl₂ using Pd(MeCN)₂Cl₂ with 4 and 5 delivering the π-complexes 19 and 20. Evidently, both complexes show a chelate binding mode between the organic ligand and palladium. A plausible explanation for the origin of the excellent β-directing power of the amino-functionality is that, via chelate formation, the double bond is forced to adopt a conformation that attenuates the mesomeric conjugation from the oxygen atom, thus reducing the electron density and ultimately favoring the β-directing inductive electronic effect at the expense of the mesomeric effect. However, neither of the X-ray complexes support such an assumption, since the bond length between oxygen and the vinyl group is 1.34 Å, falling between those of carbonyl (1.22 Å) and ether (1.54 Å), indicating substantial conjugation. Furthermore, the O-C=C is indeed planar in both structures.

It is important to recognize that the chlorine situated trans to nitrogen should actually be an organic group to function as a real intermediate, and that the crystallized complexes are adopting a twisted conformation (the double bond is approximately perpendicular to the N-Pd-Cl₂ plane) rather than an eclipsed mode (favorable for syn insertion). However, crystallized structures are not expected to be ‘true’ intermediates in a catalytic cycle, since they are too stable. Nevertheless, some information about the mode of binding can still be extracted. After insertion, it seems reasonable to believe that palladium is still coordinated to the nitrogen, thus forming a six- or seven-membered palladacyclic ring with enol ether 4 or 5, respectively (indicated with blue bonds in Fig. 8 and 9). Weaker Pd-olefin coordination (2.27 Å) in complex 20 than in 19 (2.22 Å), and a more flexible seven-membered ring might account for the lower β-selectivity exhibited by enol ether 5 than that in 4 in monoarylation experiments.
Results and Discussion

Reactivity enhancement by the chelation effect could involve the following two factors: 1) entropically driven presentation of the oxidative addition complex and 2) enthalpic stabilization of the σ-alkyl Pd intermediate formed after insertion. The first factor would account for the increased reaction rate by lowering the activation energy ($G^\ddagger$) of the association and insertion, which should be rate determining for the reaction. The second factor would have an influence on the conversion and selectivity and thus the yield of the reaction.
Results and Discussion

6.1.2 Chelation-Promoted Formation of Quaternary Centers

It is well known that a high degree of substitution in an olefin makes it less reactive in most addition reactions. In organometallic catalysis, the reactivity towards olefins parallels the coordination ability. The Heck arylation reaction is no exception. Consequently, investigating whether use of the developed chelation concept could help to arylate a fully substituted enol ether seemed worthwhile. Compound 21 was prepared as a highly substituted analog to 1 and was used as a model substrate in Heck arylations (Scheme 22).

\[
\begin{align*}
\text{O} - \text{O} - \text{O} &+ \text{HO-} - \text{N} \rightarrow \text{H}^+ \\
\text{Distillation} &\rightarrow \text{N} - \text{O} - \text{N} \rightarrow \text{O} - \text{O} - \text{N} + \text{21} \\
\text{25\%} &+ \text{27\%}
\end{align*}
\]

Scheme 22. An acid-catalyzed transacetalization-elimination process furnishing readily separable isomeric products

Regioselective arylation of 21 would create a new, all carbon, quaternary center in the product and would therefore be a valuable alternative to other existing methods of synthesis. Rewardingly, initial arylation studies proved that 21 was reactive under the chosen Heck conditions, delivering the desired product after hydrolysis (Scheme 23).

\[
\begin{align*}
\text{N} - \text{O} &+ \text{ArI} \rightarrow \text{Pd(OAc)}_2 \rightarrow \text{H}_3\text{O}^+ \\
\text{Ar} &\rightarrow (\pm) 22 \\
22a, \text{Ar} &= 2-\text{Me-Ph}, 49\% \\
22b, \text{Ar} &= 2-\text{OMe-Ph}, 49\% \\
22c, \text{Ar} &= 3-\text{OMe-Ph}, 57\%
\end{align*}
\]

Scheme 23. Heck arylation reactions employing aqueous DMF, with subsequent hydrolysis to produce racemic 2-aryl-2-methyl cyclopentanones

6.1.3 Chelation-Controlled Asymmetric Insertion

A convenient method for enantioselective synthesis of chiral quaternary carbon utilizing palladium catalysis and an axially chiral ligand has been reported by Buchwald and co-workers (Scheme 24). This impressive application requires a protection/deprotection procedure at the cyclopentanone ring to avoid arylation at the non-methylated α-position.
The assumption that a chelation effect was responsible for the enhanced reactivity in our Heck system justified an investigation of the corresponding chiral aminofunctionality derived from the amino acid (S)-proline. If the model of the chelation in the catalytic Heck cycle was correct, then the prochiral olefin 23 would be preferentially inserted from the Si-face, under the influence of the (S)-chirality on the pyrrolidine ring. The use of similar synthetic methods to those used for 21 delivered 23 in 39% yield after purification. Rewardingly, following the procedure in Scheme 25, extremely high enantiomeric excesses (90-98%) were obtained with all employed aryl halides.

Electronic influences do not seem to affect the enantioselectivity (cf. entries 1 and 8, Table 7). However, steric interactions appear to influence the insertion step to a certain extent, since the large 1-iodo- and 1-bromonaphthyls delivered lower yields and enantioselectivities. In contrast, steric requirements from ortho-substitutions are of minor significance (entries 1 and 3), comparing favorably with the method by Buchwald (Scheme 23) who reports a significant drop in ee when employing ortho-substituted aryl halides.194 The electron-poor 4-bromobenzophenone reacted smoothly under the ligandless conditions, delivering high yields and highly satisfactory enantioselectivity at a rather high reaction temperature (entry 9). Notably, entry 1 represents the highest enantiomeric excess reported to date for an asymmetric Heck arylation where a kinetic resolution process was not
Results and Discussion

involved. All in all, the presented method for preparation of chiral quaternary carbons results in excellent enantiopurity and should be able to be extended to other ring sizes and perhaps to open chain analogs.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl Halide</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Isolated Yielda (%)</th>
<th>ee^b (%)</th>
<th>[α]^23_D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![ Aryl Halide ]</td>
<td>70</td>
<td>24</td>
<td>22b</td>
<td>67</td>
<td>98</td>
<td>+39°</td>
</tr>
<tr>
<td>2</td>
<td>![ Aryl Halide ]</td>
<td>70</td>
<td>18</td>
<td>22d</td>
<td>54</td>
<td>93</td>
<td>+88°</td>
</tr>
<tr>
<td>3</td>
<td>![ Aryl Halide ]</td>
<td>80</td>
<td>30</td>
<td>22a</td>
<td>50</td>
<td>94</td>
<td>+60°</td>
</tr>
<tr>
<td>4</td>
<td>![ Aryl Halide ]</td>
<td>70</td>
<td>68</td>
<td>22e</td>
<td>61</td>
<td>94</td>
<td>+54°</td>
</tr>
<tr>
<td>5</td>
<td>![ Aryl Halide ]</td>
<td>70</td>
<td>18</td>
<td>22c</td>
<td>68</td>
<td>93</td>
<td>+88°</td>
</tr>
<tr>
<td>6</td>
<td>![ Aryl Halide ]</td>
<td>80</td>
<td>48</td>
<td>22f</td>
<td>45</td>
<td>90</td>
<td>+77°</td>
</tr>
<tr>
<td>7</td>
<td>![ Aryl Halide ]</td>
<td>100</td>
<td>48</td>
<td>22f</td>
<td>49</td>
<td>91</td>
<td>+80°</td>
</tr>
<tr>
<td>8</td>
<td>![ Aryl Halide ]</td>
<td>80</td>
<td>24</td>
<td>22g</td>
<td>47^c</td>
<td>97</td>
<td>+48°</td>
</tr>
<tr>
<td>9</td>
<td>![ Aryl Halide ]</td>
<td>100</td>
<td>24</td>
<td>22g</td>
<td>78</td>
<td>94</td>
<td>+45°</td>
</tr>
</tbody>
</table>

---

^a Cumulative two-step yield after silica column chromatography (>95% purity by GC-MS).

^b Ee of (+) isomer of 22 as determined by chiral HPLC or chiral GC.

^c Yield calculated after intermediate isolation of arylated product (53%) and subsequent hydrolysis (88%).
Results and Discussion

6.2 Microwave-Assisted Enantioselective Heck Reactions (Paper III)

In asymmetric syntheses, the application of chiral catalysis is an economically viable methodology. In fact the concept of chiral catalysis was recognized to be so important that its investigators were awarded the Nobel Prize in 2001. One of the laureates, Ryoji Noyori, developed the very versatile ligand BINAP in the late seventies. This atropisomeric chiral bis(triaryl)phosphine was originally used in rhodium(I)-catalyzed asymmetric hydrogenations. Since then, BINAP has found utility in several transformations catalyzed by transition metals, e.g. allylic substitutions, isomerizations, hydrogenations, hydroborations and hydrolysilylations. In addition, several Heck chemistry processes have benefited from using BINAP as chiral messenger. A nice application was published by Hayashi et al. using (R)-BINAP in the total synthesis of an antagonist for human platelet activating factor (PAF). The first arylation proceeds with high enantioselectivity and facilitates the second step with high diastereoselectivity by steric control (Scheme 26).

![Scheme 26](image)

Scheme 26. A two step one-pot Heck procedure followed by hydrogenation affording a single enantiomer of the trans product

6.2.1 Selection of Reaction System

In intermolecular asymmetric Heck applications, the N,P-chelating phosphineoxazoline ligand induces high enantioselectivity and controls double-bond migrations, but the reaction times (several days) are often longer than with the P,P-chelating BINAP ligand (see page 26). Bidentate ligands are known to stabilize palladium-catalyzed reactions by preventing formation of precipitated palladium black, thus ensuring high conversions.
Results and Discussion

and minimization of side product formation. The absence of reported methods for intermolecular asymmetric Heck arylation of electron-poor olefins motivated the selection of the following model system for asymmetric Heck chemistry;

![Chemical reaction diagram]

since it allowed us to compare our microwave-enhanced methodology with the originally reported conventional methods.\(^{81,128,207}\) In these systems it is important to have control over the double-bond migrations.\(^{208,209}\) When using dihydrofuran as the olefin, BINAP mainly produces the conjugated product \(25\), while the phosphineoxazoline-based catalyst produces \(24\) as its main product. With cyclopentene, the dominant product is \(27\) using the latter ligand. Moreover, cyclic unsubstituted systems exhibit dynamic kinetic resolution processes due to different rates of double-bond isomerization (Scheme 27).\(^{210}\)

![Enantiodifferentiation diagram]

**Scheme 27. Possible pathways leading to the different products**

Ligand B has been highly successful in allylic alkylations,\(^{211}\) especially in microwave-heated high-speed applications.\(^{212-214}\) Under high temperature

52
6.2.2 Benchmarking the High-Speed Protocol

Initial experiments, utilizing microwave heating with dihydrofuran and phenyl triflate and ligand B, indicated that benzene in combination with the base, proton sponge, provided the best conditions to achieve full conversions, although THF promoted slightly higher enantioselectivities. Notably, it has also been reported that Heck couplings can benefit from high-pressure conditions (>500 bar) but, in practice, when using low boiling solvents in sealed vessels under microwave irradiation, pressures of up to only around 20 bar can be obtained. Thus, the experienced rate enhancement should be of thermal origin. The phenylation reaction of dihydrofuran showed that the reaction time could be considerably decreased from the 7 days reported by Pfaltz to 55 minutes at 145 °C (Figure 9). Disappointingly, as well as an acceptable lowering of the enantioselectivity, the yield was notably diminished (entry 3, Table 8) in comparison with the reported (yield=87%, ee=97%) conventional methods.

This might have been the result of the unexpected formation of 26, which would reduce the yield of the desired product. In addition, 26 could also have decomposed (since it is more hydrolytically sensitive than 24 and 25) under the harsh conditions employed. It was surprising that only phenyl triflate, and not the electron-rich p-methoxyphenyl triflate or the electron-poor 1-naphthyl triflate, promoted formation of 26 (entries 1-6, Table 8). A possible mechanistic pathway for the formation of 26 is depicted in Scheme 26. A more gratifying result was encountered in the novel reaction using the
Results and Discussion

electron-rich p-methoxyphenyl triflate, resulting in a single isomer in high yield in conjunction with satisfying ee (entries 4 and 5). In opposite, employing the electron-poor 4-cyanophenyl triflate produced only minor amounts of arylated product. The slowest reaction rate was experienced with the sterically demanding 1-naphthyl triflate, but this nevertheless provided a single isomer with the highest ee in the study (entry 6), comparable with the selectivity from conventional heating (95% ee).207 In contrast, very rapid reactions (10-30 min) were able to be performed using the P,P-ligand A, with essentially the same yield and regioselectivity as achieved with the conventionally heated methods reported by Hayashi81 (yield=63%, ee=93%), but with lower enantioselectivity (entries 7 and 8). Cyclopentene was included in the asymmetric arylation since it is a ubiquitous substrate and is also less electron-rich than dihydrofuran.220,221 The reaction, employing ligand B, was very slow but high yielding. Unfortunately, the good regioselectivity was accompanied by low ee (entries 9 and 10, Table 8). The weaker coordination of cyclopentene to the formally cationic palladium, which resulted in a looser π-complex formation, might account for the poorer chirality transfer under high temperature conditions compared to conventional conditions128 (70 °C, yield=80%, ee=86%, THF). In summary, the employment of microwave-induced high-temperature conditions allowed substantial shortening of the reaction times compared with conventional low temperature protocols. However, the enantioselectivity (ee) and the productivity (yield) could only in certain cases (cf. entries 4 and 6) be satisfactorily compared with the original procedures employing conventional heating.
Results and Discussion

6.3 Microwave-Enhanced Oxidative Heck Arylations (Paper IV)

One of the most often used and most versatile cross couplings is the palladium(0)-catalyzed Suzuki coupling between e.g. an aryl halide and an organoboronic acid (Scheme 28). The versatility of this reaction has stimulated several chemical suppliers to provide a wide range of boronic acids. The first report on the use of vinylboronic acid in Heck couplings was from Rickard Heck’s group in 1975. This group used stoichiometric

---

Table 8. Palladium Catalyzed Asymmetric Arylation of Prochiral Olefins Using Microwave Heating

<table>
<thead>
<tr>
<th>Entry</th>
<th>Main Product</th>
<th>[Pd] / Ligand</th>
<th>Temperature (°C)</th>
<th>Time (h)(a)</th>
<th>Isolated Yield (%)(b)</th>
<th>Isomeric Ratio(c)</th>
<th>ee(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Pd(_2)dba(_3) / B</td>
<td>120</td>
<td>3</td>
<td>64</td>
<td>24:26 / 90:10</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Pd(_2)dba(_3) / B</td>
<td>140</td>
<td>1</td>
<td>66</td>
<td>24:26 / 96:4</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Pd(_2)dba(_3) / B</td>
<td>145</td>
<td>55 min</td>
<td>58</td>
<td>24:26 / 90:10</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>MeO</td>
<td>Pd(_2)dba(_3) / B</td>
<td>120</td>
<td>4</td>
<td>85</td>
<td>24 / 100</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Pd(_2)dba(_3) / B</td>
<td>140</td>
<td>1</td>
<td>73</td>
<td>24 / 100</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Pd(_2)dba(_3) / B</td>
<td>120</td>
<td>8(e)</td>
<td>80</td>
<td>24 / 100</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Pd(_2)dba(_3) / A</td>
<td>160</td>
<td>30 min</td>
<td>66</td>
<td>25:23 / 83:17</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Pd((_{\text{OAc}}))(_2) / A</td>
<td>160</td>
<td>10 min</td>
<td>53</td>
<td>25:23 / 94:6</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>Pd(_2)dba(_3) / B</td>
<td>120</td>
<td>8</td>
<td>80</td>
<td>27:28 + 29 / 99:1</td>
<td>45(f)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>Pd(_2)dba(_3) / B</td>
<td>140</td>
<td>4</td>
<td>78</td>
<td>27:28 + 29 / 98:2</td>
<td>42(f)</td>
</tr>
</tbody>
</table>

All reactions were performed in benzene with proton sponge as base. \(a\) Reactions were irradiated until all of the starting aryl triflate was consumed as deduced by GC-MS. \(b\) Main product after silica column chromatography (> 95% pure according to GC-MS). \(c\) Measured by GC-MS, double bond isomers were assumed to have identical response factors. \(d\) Ee of major isomer as measured by chiral HPLC. \(e\) Small amounts of starting material remained. \(f\) Ee of major isomer as measured by optical rotation.
amounts of palladium, thus avoiding the need for a reoxidation system. Despite this early finding, it took about 20 years before the catalytic version was developed by Uemura,\textsuperscript{50} who reported a procedure for vinylation of arylboronic acids with acetic acid as solvent. Mori \textit{et al.} very recently published a modified protocol using DMF as solvent in the presence of a catalytic amount of palladium(II) and a reoxidant, preferably Cu(OAc)\textsubscript{2}.\textsuperscript{224} A convenient protocol using oxygen gas as the reoxidant has been reported by Jung and co-workers.\textsuperscript{225} This method allowed even arylboronic esters to be used as substrates, but quite high catalyst loading was used (10\% Pd).

![Scheme 28. Mutual relations among Heck, Suzuki and oxidative Heck reaction](image)

The reaction protocols reported by Mori and Jung are rather slow (3-6 h) but attractive, since they expand the number of available starting materials for the Heck methodology. It also opens up the use of chemoselective substitutions of halides in the presence of boronic functionalities, and vice versa. Accordingly, I aimed to develop a microwave-enhanced protocol that would increase the utility of the reaction for general purposes, but mainly for medicinal high-throughput chemistry.

### 6.3.1 Developing the Protocol

In the literature, there have been several reports of Pd(0)-catalyzed transformations conducted under microwave irradiation. Surprisingly, reports about the corresponding Pd(II)-catalyzed methods seem to be absent. With microwave heating, precautions must be taken when using metal-catalyzed reactions which are not homogeneous because of the risk of metal precipitation and subsequent arcing and/or uncontrolled superheating.\textsuperscript{226,227} We thus attempted to optimize the reaction system with respect to the catalyst, base, reoxidant, temperature and heating time, using phenylboronic acid (30) and \textit{n}-butyl acrylate (31) as model substrates (Table 9).
Table 9. Optimization of the Reaction System

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Base</th>
<th>Temp. (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂</td>
<td>Cu(OAc)₂</td>
<td>LiOAc</td>
<td>100</td>
<td>15</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>Cu(OAc)₂</td>
<td>LiOAc</td>
<td>125</td>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>Cu(OAc)₂</td>
<td>LiOAc</td>
<td>125</td>
<td>15</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>Cu(OAc)₂</td>
<td>LiOAc</td>
<td>125</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂</td>
<td>Ag₂CO₃</td>
<td>-</td>
<td>125</td>
<td>15</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂</td>
<td>TMANO</td>
<td>LiOAc</td>
<td>125</td>
<td>15</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂</td>
<td>Cu(OAc)₂</td>
<td>NaOAc</td>
<td>125</td>
<td>15</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)₂</td>
<td>Cu(OAc)₂</td>
<td>Pyridine</td>
<td>125</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>Pd(MeCN)₂Cl₂</td>
<td>Cu(OAc)₂</td>
<td>LiOAc</td>
<td>125</td>
<td>15</td>
<td>61</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OCOCF₃)₂</td>
<td>Cu(OAc)₂</td>
<td>LiOAc</td>
<td>125</td>
<td>15</td>
<td>64</td>
</tr>
</tbody>
</table>

Reaction conditions: Phenylboronic acid (1.0 mmol), n-butyl acrylate (2.5 mmol), palladium(II) salt (0.05 mmol), oxidant (2.0 mmol), base (3.0 mmol), and DMF (2.0 mL).

The most effective reaction parameters were identified in entry 3. No benefit was realized from employing the more electrophilic palladium trifluoroacetate instead of the standard palladium acetate. Pyridine was unsuitable as a base since low yield was encountered along with the appearance of a characteristic green color, possibly caused by unwanted complexation between Cu(II) and pyridine. Copper acetate was used in two equivalents, and the metal precipitates caused no problems during microwave heating. Performing the reaction at a higher temperature than 125 °C produced inferior yields. While the reaction performed very poorly in the absence of Cu(OAc)₂, removal of the Pd(II) source from the reaction furnished no product 32. Unexpectedly, while the phenylboronic acid smoothly coupled to the olefin, the corresponding cyclic boronic ester was inert under the reaction conditions.
6.3.2 Scope and Limitation of the Oxidative Heck Reaction

The conditions in entry 3, Table 9, were used as standard conditions, although the time and temperature was further adjusted for some of the individual reactions. A set of stERICALLY and electronically different arylboronic acids were coupled with the following electron-poor olefins:

From the preparative results in Table 10, it is evident that the protocol is quite general, producing arylated products in useful yields (45-85%). The strong preference for (E)-configuration in all products is notable, especially among the products from the inductively electron deficient olefin 36 (entries 14-16). In general, the electron-rich aryl boronic acids gave the cleanest reactions and the best yields. Deboronations were competing side reactions whenever more sluggish electron-poor arylboronic acids were used (entries 7-9). Careful exclusion of water had no effect in trying to avoid deboronation. In contrast to my experience, it was reported by Mori et al. that yields from related couplings were uncorrelated to the electronic character of arylboronic acids, using conventional heating and lower temperatures (100 °C).224

In an attempt to improve the relatively low-yielding reactions in entries 6 and 8, a switch to non-polar, microwave-transparent 1,4-dioxane was investigated. In the coupling with electron-rich 42, this solvent improved the yield, despite a less-powerful heating ramp (entry 6). However, the attempt to use 1,4-dioxane in the coupling of electron-poor 44 met with an inferior result (entry 8).

It is worth mentioning that the olefin was used in excess, in contrast with normal Suzuki conditions where a large excess of boronic acid is normally employed. Attempts to use electron-rich olefins (e.g. enol ethers) as substrates under the prevailing standard conditions proved unsuccessful, mainly giving poor conversions and hydrolyzed products. In short, the microwave-promoted and Pd(II)-catalyzed oxidative Heck reaction employing arylboronic acids provides an effective high-speed approach to arylated olefins with Cu(OAc)₂ as a robust reoxidant.
Table 10. Heck Vinylation of Arylboronic Acids with Microwave Heating

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arylboronic acid</th>
<th>Olefin</th>
<th>Product</th>
<th>Temp / Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Arylboronic acid 1" /></td>
<td><img src="image2" alt="Olefin 1" /></td>
<td><img src="image3" alt="Product 1" /></td>
<td>125 / 15</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Arylboronic acid 2" /></td>
<td><img src="image5" alt="Olefin 2" /></td>
<td><img src="image6" alt="Product 2" /></td>
<td>125 / 15</td>
<td>45&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Arylboronic acid 3" /></td>
<td><img src="image8" alt="Olefin 3" /></td>
<td><img src="image9" alt="Product 3" /></td>
<td>125 / 30</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10" alt="Arylboronic acid 4" /></td>
<td><img src="image11" alt="Olefin 4" /></td>
<td><img src="image12" alt="Product 4" /></td>
<td>140 / 15</td>
<td>51&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="image13" alt="Arylboronic acid 5" /></td>
<td><img src="image14" alt="Olefin 5" /></td>
<td><img src="image15" alt="Product 5" /></td>
<td>170 / 15</td>
<td>51&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td><img src="image16" alt="Arylboronic acid 6" /></td>
<td><img src="image17" alt="Olefin 6" /></td>
<td><img src="image18" alt="Product 6" /></td>
<td>125 / 15</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td><img src="image19" alt="Arylboronic acid 7" /></td>
<td><img src="image20" alt="Olefin 7" /></td>
<td><img src="image21" alt="Product 7" /></td>
<td>125 / 15</td>
<td>84&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td><img src="image22" alt="Arylboronic acid 8" /></td>
<td><img src="image23" alt="Olefin 8" /></td>
<td><img src="image24" alt="Product 8" /></td>
<td>100 / 15</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>a</sup> Table 10. Heck Vinylation of Arylboronic Acids with Microwave Heating

<sup>b</sup> Product structures are shown in the corresponding entries.

<sup>c</sup> Yields were determined by NMR analysis.

<sup>d</sup> Reaction carried out at 100 °C for 25 h.

<sup>e</sup> Additional microwave heating at 125 °C for 15 h.

<sup>f</sup> Reaction carried out at 125 °C for 15 h.

<sup>g</sup> Reaction carried out at 125 °C for 15 h.

<sup>h</sup> Reaction carried out at 125 °C for 15 h.
## Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arylboronic acid</th>
<th>Olefin</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Temp / Time (°C / h)</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td><img src="arylboronic_acid.png" alt="" /></td>
<td><img src="olefin.png" alt="" /></td>
<td><img src="product.png" alt="" /></td>
<td>125 / 15</td>
<td>58&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td><img src="arylboronic_acid.png" alt="" /></td>
<td><img src="olefin.png" alt="" /></td>
<td><img src="product.png" alt="" /></td>
<td>125 / 15</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td><img src="arylboronic_acid.png" alt="" /></td>
<td><img src="olefin.png" alt="" /></td>
<td><img src="product.png" alt="" /></td>
<td>125 / 15</td>
<td>60</td>
</tr>
<tr>
<td>12</td>
<td><img src="arylboronic_acid.png" alt="" /></td>
<td><img src="olefin.png" alt="" /></td>
<td><img src="product.png" alt="" /></td>
<td>125 / 15</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>125 / 30</td>
<td>72</td>
</tr>
<tr>
<td>13</td>
<td><img src="arylboronic_acid.png" alt="" /></td>
<td><img src="olefin.png" alt="" /></td>
<td><img src="product.png" alt="" /></td>
<td>125 / 15</td>
<td>73&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td><img src="arylboronic_acid.png" alt="" /></td>
<td><img src="olefin.png" alt="" /></td>
<td><img src="product.png" alt="" /></td>
<td>125 / 15</td>
<td>74&lt;sup&gt;i,k&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td><img src="arylboronic_acid.png" alt="" /></td>
<td><img src="olefin.png" alt="" /></td>
<td><img src="product.png" alt="" /></td>
<td>125 / 15</td>
<td>58&lt;sup&gt;i,j&lt;/sup&gt;</td>
</tr>
<tr>
<td>16</td>
<td><img src="arylboronic_acid.png" alt="" /></td>
<td><img src="olefin.png" alt="" /></td>
<td><img src="product.png" alt="" /></td>
<td>110 / 30</td>
<td>85&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: Arylboronic acid (1.0 mmol), alkene (2.5 mmol), Pd(OAc)<sub>2</sub> (11.2 mg, 0.05 mmol), Cu(OAc)<sub>2</sub> (0.36 g, 2.0 mmol), LiOAc (0.20 g, 3.0 mmol), and DMF (2.0 mL), except as noted.  
<sup>b</sup> All new compounds gave satisfactory <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and combustion analysis data.  
<sup>c</sup> Isolated yields with purity >95% as estimated by GC-MS and <sup>1</sup>H NMR analysis.  
<sup>d</sup> E/Z = 21:1 (<sup>1</sup>H NMR).  
<sup>e</sup> E/Z = 18:1 (GC-MS).  
<sup>f</sup> 1,4-Dioxane as solvent.  
<sup>g</sup> E/Z = 15:1 (<sup>1</sup>H NMR).  
<sup>h</sup> Molecular sieves (4 Å) as additive.  
<sup>i</sup> E/Z = 25:1 (<sup>1</sup>H NMR).  
<sup>j</sup> The molar ratio of arylboronic acid and olefin was 2:1 (mmol).  
<sup>k</sup> E/Z = 94:1 (GC-MS).  
<sup>l</sup> E/Z = 32:1 (GC-MS).
Results and Discussion

6.4 Accelerated PCR using Microwave Irradiation
(Paper V)

Historically, microwave irradiation has been utilized in biological research mainly for denaturation purposes.\textsuperscript{230,232} Recently, reports on enzyme catalysis under microwave irradiation have indicated its usefulness also in biosyntheses.\textsuperscript{233-237} DNA polymerase replicates DNA with surprisingly high fidelity despite the small energy differences in hydrogen bonding between correct and incorrect base pairs. This property makes it attractive to study the influence of microwave irradiation on nucleic acid stability as well as enzyme stability under microwave-promoted high temperature conditions. Since the optimal working temperature for the Taq enzyme, utilized in polymerase chain reactions, is around 72 °C, its half-life will decrease as the temperature increases. Nonetheless, temperatures of at least around 90 °C are required to denature DNA (longer DNA templates will require even higher temperatures) in order to perform a successful PCR cycle. Accordingly, it is highly desirable to shorten the time needed to ramp the temperatures between the separate stages of the cycle. The total time for the PCR run would then also be shortened. Much attention has therefore been focused on the development of faster heating devices.\textsuperscript{238} An attractive feature of microwave dielectric heating, compared with conventional heating, is its ability to rapidly heat substances \textit{in situ}. Notably, it has been suggested in the literature that microwaves can affect protein configurations independently of the bulk temperature.\textsuperscript{153,154,239,240} Therefore, an investigation on focused microwave irradiation as a novel approach to performing faster PCR seemed worthwhile.

6.4.1 Optimization

A study was undertaken to see if a microwave energy input could replace the conventional heating from the thermocycler in a commercial PCR machine. A 220 base pair segment of the chromosomal 23S rRNA gene of the thermophilic campylobacters was selected as target for the PCR, using the primer pair Therm1 / Therm2. A mono-mode microwave cavity was used and the reaction vial, a polypropylene tube, was manually transferred for each new cycle to the water bath for annealing. The workflow is presented in the chart below.
Results and Discussion

**Workflow**

The microwave energy input was determined empirically and the outcome of the most successful run (Lane 3 Figure 10) showed that nearly 70% of the efficiency, compared with conventional PCR, can be reached using microwave irradiation.

<table>
<thead>
<tr>
<th>Lane</th>
<th>First MW pulse</th>
<th>Second MW pulse</th>
<th>No. of cycles</th>
<th>Template DNA</th>
<th>Relative band intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75W</td>
<td>120W</td>
<td>25</td>
<td>Plasmid</td>
<td>0.11</td>
</tr>
<tr>
<td>2</td>
<td>90W</td>
<td>120W</td>
<td>25</td>
<td>Plasmid</td>
<td>0.42</td>
</tr>
<tr>
<td>3</td>
<td>100W</td>
<td>130W</td>
<td>25</td>
<td>Plasmid</td>
<td>0.67</td>
</tr>
<tr>
<td>4</td>
<td>100W</td>
<td>130W</td>
<td>35</td>
<td>Chromosomal</td>
<td>0.20</td>
</tr>
<tr>
<td>5</td>
<td>Conventional PCR</td>
<td>25</td>
<td>Plasmid</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 10.**

*Optimization of the microwave pulses*
Results and Discussion

This is the first report of successful microwave-assisted PCR. Comparing the total run time between lanes three (~1 h) and five (~2 h) reveals that using microwaves as the heating source can allow for nearly twice as fast run time compared with conventional heating with a standard PCR instrument. It is notable that the more complex chromosomal DNA templates (lane 4) also amplify under these conditions.

6.4.2 Enzymatic Activity

To check the thermostability of the Taq polymerase, small aliquots of the reaction mixture were collected after 25 and 35 cycles. Comparison of the relative intensities after 25 and 35 cycles of the same reaction mixture shows that the polymerase continues to exhibit catalytic activity even after the first 25 cycles (Figure 11).

<table>
<thead>
<tr>
<th>Lane</th>
<th>First MW pulse</th>
<th>Second MW pulse</th>
<th>No. of cycles</th>
<th>Template DNA</th>
<th>Relative band intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100W</td>
<td>130W</td>
<td>25</td>
<td>Plasmid</td>
<td>0.13</td>
</tr>
<tr>
<td>4</td>
<td>100W</td>
<td>130W</td>
<td>35</td>
<td>Plasmid</td>
<td>0.38</td>
</tr>
<tr>
<td>5</td>
<td>Conventional PCR</td>
<td>25</td>
<td>Plasmid</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 11.** Taq polymerase activity under microwave irradiation
Results and Discussion

In contrast to our findings on enzyme activity and stability under microwave irradiation, Franceschetti et al report significant time-dependent loss of activity when comparing conventional and microwave heating at 70 °C, employing thermophilic β-galactosidase.\textsuperscript{241} Inaccurate temperature measurements are often a plausible explanation for deviations between conventional and microwave heating processes. Homogeneous heating (i.e. no ‘hot spots’) by microwaves are technically difficult to obtain, therefore a temperature measurement at a ‘cold spot’ can give quite misleading interpretation of the results.\textsuperscript{145}

In summary, this largely empirical investigation indicates that microwave heating is a promising technique for enhancing the efficiency of the polymerase chain reaction. Furthermore, since microwaves can facilitate fast heating of larger volumes, an attractive extension of this study could be the development of large (mL scale), one-pot PCR reaction equipment. Currently, the yields from several small-scale runs are pooled together to obtain larger quantities of DNA.
7 Concluding Remarks

This thesis has described how two different classes of catalytic processes, the palladium-catalyzed Heck reaction and the enzyme-catalyzed polymerase chain reaction, can be enhanced with respect to both reaction rate and selectivity.

In summary, the specific conclusions are:

- Highly regio- and diastereoselective catalytic processes for Heck arylations of electron-rich olefins can be achieved through the use of chelation control.

- Chelation-accelerated Heck arylations exhibit increased reactivity and therefore allow the assembly of highly substituted olefins.

- Chelation sufficiently enhances reactivity to facilitate Heck arylation of sluggish tetra-substituted olefins.

- Acid-catalyzed liberation of sensitive aryl acetaldehydes from the corresponding enol ethers can conveniently be carried out with high yields and purity, using a differential microwave-heated biphasic system.

- High reaction rates in ligand-controlled enantioselective Heck arylations can be obtained, while maintaining the level of enantioselectivity, by employing microwave heating.

- Fast, selective Heck arylations can be performed using arylboronic acids under microwave irradiation with copper acetate as a convenient reoxidant.

- The first ever microwave-promoted PCR process has been reported.

- Enzyme catalysis shows similar behavior to transition metal catalysis with regard to both stability and reaction rates under focused microwave irradiation.
First of all I would like to thank my supervisor Professor Anders Hallberg for accepting me as a PhD student. Your great leadership skills in combination with your broad scientific knowledge have provided an enjoyable and stimulating working atmosphere at the department.

I would also like to gratefully acknowledge:
My assistant supervisor, Dr Mats Larhed, for your great support of all my ideas, the good ones as well as the not so good ones! I really appreciate your friendship and enthusiasm. Your guidance in areas other than chemistry is also gratefully acknowledged.

My co-authors: Dr Murugaiah Andappan for your skillful work!
Henrik Gold for your contributions to the project during your diploma work.
Dr Christian Fermér for your easy cooperation.

Gunilla Eriksson, for always being so friendly and helpful in all administrative matters. Sorin Srbu, for solving all my computer-related issues. Arne Andersson and Marianne Åström for all the help during the years with so many practical matters. Doc. Adolf Gogoll for your expertise in NMR, both when I was an undergraduate at kemikum and as a PhD student. Ph. Lic Máté Erdélyi for helping me out with NMR-related problems. Dr. Nils-Fredrik Käiser for creative discussions! Doc. Gunnar Lindeberg for keeping the LC-MS equipment in excellent shape!

Dr. Johan Hultén, Doc. Uno Svensson and Doc. Anders Karlén, for excellent collaboration in educative matters.

My diploma workers Meral Sari, Peter Fritzøn and Jonas Sävmarker for the good times in the lab.
All members of the SELCHEM program for the pleasant meetings.

Dr Wilfried A. König for help with the chiral GC.
Dr Wesley Schaal and Dr Kristofer Olofsson and Dr Karl Vallin for constructive criticism and linguistic revision of the thesis.

The Swedish Foundation for Strategic Research (SSF), CD Carlsson stiftelse and PersonalChemistry for making it possible for me to participate at several conferences. Financial support was received from SSF (the SELCHEM program), the Swedish Research Council and the Knut and Alice Wallenberg Foundation.

Finally, to all the colleagues I have come to know at the department during these years: thank you for making it such an enjoyable time.

Kristin, för att du hjälper mig att prioritera i livet (the best things..).
Joakim och Erik som håller pappa i form.
Och slutligen tack till alla övriga i släkten för ert stöd.
9 References

(14) Copper-free applications have also been developed see: Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* 1993, 34, 6403.
(40) Trost, B. M.; Murphy, D. J. Organometallics 1985, 4, 1143.
(56) Inoue, A.; Shinokubo, H.; Oshima, K. J. Am. Chem. Soc. 2003, 125,
(76) The phrase ligandless is used when no additional ligand, e.g. a phosphine is added to the reaction mixture.
(154) Bohr, H.; Bohr, J. Bioelectromagnetics 2000, 21, 68.


(187) Initial experiments revealed that the reaction with 1-methoxy-cyclopentene was very sluggish.


1988, 110, 629.
9, 1521.
A doctoral dissertation from the Faculty of Pharmacy, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series *Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy*. (Prior to July, 1985, the series was published under the title “Abstracts of Uppsala Dissertations from the Faculty of Pharmacy”.)