 Novel Metal-Mediated Organic Transformations

Focusing on Microwave Acceleration and the Oxidative Heck Reaction

PER-ANDERS ENQUIST
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Abstract

Transition metals have played an important role in synthetic organic chemistry for more than a century, and offer catalytic transformations that would have been impossible with classical chemistry. One of the most useful and versatile of the transition metals is palladium, which over the years has catalyzed many important carbon-carbon forming reactions. Popular cross-coupling reactions such as the Suzuki, Stille and the Heck reaction are all catalyzed by palladium, or more correctly, by palladium in its ground state, Pd(0).

Recently, interest in palladium(II)-catalyzed transformations has started to grow, partly due to the development of the vinylic substitution reaction, commonly called the oxidative Heck reaction, presented in this thesis. This Pd(II)-catalyzed, ligand-modulated reaction occurs under air at room temperature, and for the first time a general protocol employing a wide range of olefins and arylboronic acids was obtained. Ligand screening showed that the bidentate nitrogen ligand, 2,9-dimethyl-1,10-phenanthroline (dmphen), was the most suitable ligand. Dmphen is believed to facilitate regeneration of active Pd(II), increase catalytic stability and improve the regioselectivity in the reaction. A mechanistic investigation was conducted using electrospray ionization mass spectrometry (ESI-MS), making it possible to observe cationic intermediates in a productive oxidative Heck arylation. The results obtained are in agreement with the previously proposed catalytic cycle.

The emerging discipline of high-speed synthesis is making contributions to society’s growing demand for new chemical entities. This inspired the development of two ultrafast, microwave-accelerated carbonylation reactions with dicobalt octacarbonyl acting both as an in situ carbon monoxide supplier and reaction mediator. A wide range of symmetrical benzophenones was produced in only 6 to 10 s, using aryl iodides as the substrate. The second carbonylation reaction provided symmetrical and unsymmetrical ureas in process times ranging from 10 s to 40 minutes using primary and secondary amines.

Keywords: palladium(II), oxidative Heck reaction, high-throughput-chemistry, microwave acceleration, dicobalt octacarbonyl, in situ carbonylation, urea, diaryl ketones, ESI-MS

Per-Anders Enquist, Department of Medicinal Chemistry, Organic Pharmaceutical Chemistry, Box 574, Uppsala University, SE-75123 Uppsala, Sweden
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List of Papers

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


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### Abbreviations

<table>
<thead>
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>API</td>
<td>atmospheric pressure ionization</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>CID</td>
<td>collision induced dissociation</td>
</tr>
<tr>
<td>CRM</td>
<td>charge residue model</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theory</td>
</tr>
<tr>
<td>DMAc</td>
<td>dimethylacetamide</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>dmphen</td>
<td>2,9-dimethyl-1,10-phenanthroline, neocuproine</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>equiv</td>
<td>equivalents</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>IDM</td>
<td>ion desorption model</td>
</tr>
<tr>
<td>IEM</td>
<td>ion evaporation mechanism</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
</tr>
<tr>
<td>LC</td>
<td>liquid chromatography</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>M</td>
<td>metal</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>MS-(+)</td>
<td>mass spectrometry measuring cations</td>
</tr>
<tr>
<td>MS/MS</td>
<td>tandem mass spectrometry</td>
</tr>
<tr>
<td>n-Bu</td>
<td>normal-butyl</td>
</tr>
<tr>
<td>NMM</td>
<td>N-methyl morpholine</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>Q</td>
<td>quadrupole</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tertiary-butyl</td>
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<td>TEA</td>
<td>triethylamine</td>
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<td>TEMPO</td>
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<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>Tol</td>
<td>tolyl</td>
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<td>turnover number</td>
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1 Introduction

1.1 Organometallic Chemistry: An Overview

1.1.1 General

During the second half of the 18th century, chemists started to acquire enough skill to isolate metal-containing compounds from e.g. ore, and with that the organometallic timeline began (Figure 1). To be precise, organometallic chemistry is the study of compounds containing a covalent bond between a metal and an element, most often a carbon, phosphine or hydrogen atom. There are many different classes of organometallic compounds, e.g. metal hydrides, carbonyls, metalloccenes, pincer and carbene complexes, and the term “metal” is rather broad as it also includes metalloids, like boron, arsenic and silicon.

Figure 1. The organometallic chemistry timeline

1760 L. de Gassicourt isolates one of the earliest organometallic complexes, (Me₂As)₂. This arsenic-containing compound was called kakodyl by J. J. Berzelius.

1827 Zeise’s salt is the first platinum-olefin complex.

1863 P. Sabatier starts to hydrogenate unsaturated organic compounds with metal catalysts.

1890 L. Mond discovers nickel carbonyl.

1899 Introduction of the Grignard reaction

1900 Nobel Prize to V. Grignard and P. Sabatier for their achievements in organometallic chemistry

1912 H. Gilman starts his work on lithium cuprates

1930 The Heck reaction

1968 Nobel Prize to G. Wilkinson and E. O. Fischer for organometallic sandwich complexes

1973 The Wacker process

2005 Nobel Prize to W. S. Knowles, R. Noyori and K. B. Sharpless for organometallic-catalyzed chiral transformations

2001 Nobel Prize to Y. Chauvin, R. Grubbs and R. Schrock for metal-catalyzed alkene metathesis

2005 Nobel Prize to K. Ziegler and G. Natta for their polymer-forming, aluminum-alkyl based, catalyst
1.1.2 Transition Metal Catalysis

Elements in the d-block of the periodic table are generally called transition metals or transition elements, and share some common characteristic properties (except Zn, Cd and Hg), which are listed below.

- They contain an incomplete \( d \) subshell.
- They are often silvery colored (except copper and gold).
- They are solids at room temperature.
- They are often paramagnetic.
- They have many different oxidation states.
- They form complexes.
- They are often good catalysts.

The last point concerning catalysis is very important (closely related to the two points above it) and the main reason why transition metals are so useful in synthetic organic chemistry.\(^{18}\) The metals at the end of the transition series are more disposed to exist in coordinatively unsaturated states, and thus, more prone to be active in catalytic transformations. Late transition metals have a higher “catalytic power”.\(^{17}\) As early as 1835 Jöns Jakob Berzelius defined his idea of “catalytic power” as the ability of substances…

“…to awaken affinities, which are asleep at a particular temperature, by their mere presence and not by their own affinity…”\(^{19}\)

Almost every functional group will coordinate to some transition metal thus altering the reactivity of the group to provide functionalization impossible with conventional methods. The reactions are site specific, leaving highly reactive functional groups untouched and, thus, avoid time-consuming protection and subsequent deprotection steps. This specificity can also be seen as a disadvantage, as a small modification of the reaction conditions might disturb the system so much that the catalytic turnover will cease. One can also regard it from another angle; it might be difficult to find optimal reaction conditions because the range is so narrow. To conclude, general conditions for transition metal-catalyzed reactions are rare.\(^{18}\)

Transition metal catalysis can roughly be divided into two groups, heterogeneous and homogeneous catalysis. In heterogeneous catalysis the catalyst is in a solid state or is attached to a solid-phase, which facilitates catalyst recovery, but elevated temperatures are often required, the specificity is low and it is more difficult to elucidate the mechanism behind the transformation. The metal-mediated organic transformations described in this thesis all take place in solution using soluble metal complexes and therefore belong to homogeneous catalysis.\(^{17,20}\)
1.2 Palladium-Catalyzed Organic Transformations

Palladium is a late transition metal in group 8 of the periodic table, which indicates that it has partially filled $d$-orbitals. This feature gives the metal both electron-donating and electron-accepting properties, which can be further fine-tuned by adding the appropriate donor or acceptor ligands for a desired transformation to take place. The change in electron density, caused by the ligand(s), depends on two different orbital interactions, $\sigma$-donation (increasing electron density at the metal) and $\pi$-back bonding (decreasing electron density at the metal), which are illustrated in Figures 2 and 3. In $\sigma$-donation, a filled $sp^3$-orbital on the ligand (or a filled $\pi$-bonding orbital if it is an alkene) can interact with a vacant $dsp$-hybrid orbital on the metal because of favorable symmetry and energy between them. Examples of $\sigma$-donating ligands are alkenes, $R_3P$, $R_3N$ and $R^\prime$. Back bonding, also called back donation, occurs when a filled $d$-orbital on the metal overlaps an empty $\pi^*$-antibonding unsaturated ligand. $^{18}$

![Figure 2](image1.png)

**Figure 2.** Examples of metal-ligand orbitals and their possible interactions, a) $\sigma$-donation and b) back bonding

Ligands may be both $\pi$-accepting and $\sigma$-donating in nature, but not necessarily to the same degree; e.g. carbon monoxide, which is strongly back donating but only a weak $\sigma$-donor (Figure 3). $^{18}$

![Figure 3](image2.png)

**Figure 3.** Bonding interactions between palladium and a) an olefin and b) carbon monoxide

13
The formation of carbon-carbon bonds is of great importance in synthetic organic chemistry and palladium is among the most versatile and commonly used transition metals in the periodic table. Below is a short list of reasons why palladium is such a useful tool:

- Easy to handle (relatively insensitive to moisture and acid)
- High functional group tolerance
- Attainable HOMO and LUMO energies facilitate faster reactions, due to favorable size and overlap of the orbitals
- Low susceptibility to undergo radical reactions
- Low energy barrier between its two preferred oxidation states (0 and +2) which facilitates catalytic activity
- A relatively high electronegativity (2.20 according to Pauling scale), which enables smooth transmetallation from most metal-carbon bonds
- Accurate polarizability for both coordination and easy dissociation of ligands, which is important for regeneration of the catalyst

1.2.1 Palladium(0) Catalysis

The properties mentioned in the section above make organopalladium coupling reactions a popular choice in synthetic organic chemistry, especially in medicinal chemistry, since they allow the preparation of many compounds (libraries) containing a variety of different functional groups from a common precursor. Palladium catalysis is a valuable tool in fine chemical synthesis, as well. A plethora of different transformations has been developed based on homogeneous palladium(0) catalysis, e.g. Suzuki, Still, Negishi, Kumada, Sonogashira and Heck couplings (Scheme 1). The first four (or five) reactions are called cross-coupling reactions, because they all undergo a transmetallation process and need reductive elimination to generate the product. In the following section, different mechanistic steps involved in palladium-catalyzed coupling reactions will be discussed briefly.

Palladium(0) complexes are quite unstable when stored, accordingly most chemists use palladium(II) salts. This causes no complications because of the simple in situ reduction of Pd(II) which takes place upon contact with various reducing agents such as phosphines or amines in the presence of water. The transformation is called the preactivation step and is applicable to every reaction in Scheme 1.
All six of the coupling reactions depicted in Scheme 1 have in common that they are Pd(0)-catalyzed. This means that they start each catalytic turn with the oxidative addition\(^{45}\) of a 14-electron Pd(0)L\(_2\) species, or sometimes a 12-electron species if a bulky and strongly electron-donating ligand is used,\(^{46}\) to an arylhalide (Ar-X),\(^{47}\) or pseudohalide (e.g. triflates,\(^{48,49}\) diazonium salts\(^{50}\) or sulfonyl chlorides\(^{51}\)), to generate the essential arylpalladium(II) \(\text{trans}\)-complex (Ar-PdL\(_2\)X)\(^{52}\). It is also possible to achieve palladium(0)-catalyzed couplings with vinylic, allylic or benzylic halides, but some problematic issues, such as rapid \(\beta\)-elimination from R-Pd(II)-X species, must be resolved before alkyl halides can successfully be coupled in a convenient way.\(^{53-55}\) However, since the beginning of the new millennium, progress in the development of alkyl cross-coupling methods has started to accelerate, largely thanks to the pioneering work by A. Suzuki in the early 1990s.\(^{56}\) G. Fu and coworkers are at the front line of present research in cross-coupling reactions of \(\beta\)-hydrogen-containing alkyl halides, and are utilizing both palladium\(^{57,58}\) and nickel.\(^{59,60}\) Nickel catalysts are less prone to undergo \(\beta\)-elimination than palladium, which often requires a hindered trialkylphosphane (\(P(t\text{-Bu})_2\text{Me}\) or \(\text{PCy}_3\)) as ligand to suppress the fast \(\beta\)-elimination.\(^{57}\)

As mentioned previously, in all cross-coupling reactions a \textit{transmetallation process} follows oxidative addition.\(^{61-63}\) Simplified, this process can be considered as the transfer of an organic moiety from a main-group metal, such as Mg, Zn, B, Al, P, Sn, Si or Hg, to a metal complex with higher electronegativity (Scheme 2). The driving force in this process is the nature of the bond formed. With a smaller difference in electronegativity between the organic moiety and the metal, a bond with a more covalent character is
formed, which facilitates transmetallation as a result of the higher stability gained by the resulting complex.\textsuperscript{30}

\begin{equation}
M-L + R-M' \rightarrow M-R + L-M' \\
\text{Typically: } M = \text{Ni, Pd, Pt, Rh, Cu} \\
M' = \text{Li, Mg, Zn, Al, B, Si, Sn and Hg}
\end{equation}

Scheme 2. The transmetallation process

The concluding step in the catalytic cycle of cross-coupling reactions is reductive elimination,\textsuperscript{64} where the palladium(II) moiety, containing two cis-coordinating ligands,\textsuperscript{65} is reduced to Pd(0) and a σ-bond is created between the two ligated species as they are released from the metal’s coordinating sphere.\textsuperscript{66}

An excellent review regarding mechanistic aspects of palladium-catalyzed cross-coupling reactions has been authored by Amatore and Jutand.\textsuperscript{67}

The Heck Reaction

Independent research by R. F. Heck and T. Mizoroki in the early 1970s led to the discovery of transition metal catalyzed vinylic substitution, nowadays commonly called the Heck reaction (Scheme 1). This highly versatile and useful carbon-carbon bond forming methodology has gained much interest over the years, and is a frequently employed tool in research laboratories, e.g. in early stage drug development.\textsuperscript{21} Industrial applications of the Heck reaction in the synthesis of drugs\textsuperscript{1} and fine chemicals\textsuperscript{25} have also been reported, but are less common because of high demands on avoiding salt formation and the amounts of palladium residues in the products.\textsuperscript{22}

The Heck reaction is a palladium(0)-catalyzed reaction, and as previously mentioned, initiates by oxidative addition to an aryl halide followed by coordination and insertion of an olefin. In contrast to cross-coupling reactions, the arylated product of the Heck reaction is a result from a β-elimination process which, in addition generates a palladium hydride that, with the assistance of a base, will recreate active Pd(0).\textsuperscript{68-70} Since this step and the preceding insertion are identical to those taking place in the oxidative Heck reaction, they will be discussed in more detail in Section 1.2.3.

1.2.2 Palladium(II) Catalysis

This section will discuss some general mechanistic concepts in palladium(II)-catalyzed chemical reactions without any emphasis on the different synthetic methodologies that exist. The prime focus will be on distinctions
between Pd(II) and Pd(0) chemistry, e.g. the need for a reoxidation step in Pd(II) catalysis.

Scheme 3. Mechanistic comparison between a Pd(0)-catalyzed cross-coupling reaction and Pd(II)-catalyzed alcohol oxidation. 

The basic concept of palladium(II)-mediated reactions has been known for a long time. It was introduced as early as the 19th century, albeit with the use of stoichiometric amounts of palladium.72 With the discovery of the palladium(II)-catalyzed Wacker process,73-75 interest increased significantly. For many decades, the progress in palladium(0) catalysis overshadowed the slower developing area of Pd(II) catalysis.71 It is difficult to explain why, but it probably stems from the diverse level of understanding of the different mechanistic steps involved in the processes (Scheme 3). In Pd(II)-catalyzed chemistry, the reaction is often initiated by Lewis acid coordination to the substrate, followed by nucleophilic attack. The palladium atom may be released from the product as a Pd hydride, by β-elimination, which can soon after be converted into Pd(0). It is at this point that the key issue in Pd(II) catalysis arises: in order for the catalytic cycle to be completed and to ensure reasonable reaction times, Pd(0) must be efficiently reoxidized to Pd(II).76 Historically, the regeneration of active Pd(II) was often solved by the addition of stoichiometric amounts of an oxidizing agent such as Cu(II) salts77 or benzoquinones.78 This might in fact be the reason why there has been a lack of interest in Pd(II) chemistry – even though the reaction is catalytic in accordance to palladium, stoichiometric amounts of an oxidant are still needed. During the late 1980s several developments led to progress in the field. Bäckvall and coworkers (pioneers in the area of Pd(II)-catalyzed reactions)
developed reoxidation systems such as the one illustrated in Scheme 4, using redox-active cocatalysts and molecular oxygen as the terminal oxidant.\textsuperscript{79}

\begin{center}
\begin{tikzpicture}
    \node (A) at (0,0) {$\text{Pd(II)}$};
    \node (B) at (1,0) {$\text{Pd(0)}$};
    \node (C) at (2,0) {$\text{LM}^{n+2}$};
    \node (D) at (3,0) {$\text{H}_2\text{O}$};
    \node (E) at (0,-1) {$\text{AcO}_2\text{H}$};
    \node (F) at (1,-1) {$\text{Pd(0)}$};
    \node (G) at (2,-1) {$\text{LM}^{n+}$};
    \node (H) at (3,-1) {$\frac{1}{2} \text{O}_2$};
    \node (I) at (0,-2) {$\text{HOAc}$};
    \node (J) at (1,-2) {$\text{HOAc}$};
    \node (K) at (2,-2) {$\text{Pd(II)}$};
    \node (L) at (3,-2) {$\text{H}_2\text{O}$};
    \draw[->] (A) -- (B);
    \draw[->] (B) -- (C);
    \draw[->] (C) -- (D);
    \draw[->] (E) -- (F);
    \draw[->] (F) -- (G);
    \draw[->] (G) -- (H);
    \draw[->] (I) -- (J);
    \draw[->] (J) -- (K);
    \draw[->] (K) -- (L);
\end{tikzpicture}
\end{center}

\textbf{Scheme 4.} Coupled catalytic system for 1,4-oxidation of dienes with molecular oxygen as terminal oxidant\textsuperscript{79}

More recently, a more environmentally benign reoxidation alternative has been developed, utilizing direct molecular oxygen-coupled Pd(II) reoxidation, which has been successfully employed in a number of different palladium(II)-catalyzed transformations.\textsuperscript{80-84} Some systems have also been developed (mostly alcohol oxidation) in which ambient air has been exploited as a reoxidant.\textsuperscript{81,82,85} The improved oxidative technologies that have evolved during the past decade are mainly due to the development of new ligands that not only facilitate reoxidation, but also stabilize the catalytic system (higher TON), improve selectivity and are robust enough to withstand the oxidative conditions in the reaction mixture. The triphenylphosphine ligand, which has been successfully used in Pd(0) chemistry for many years, decomposes into phosphine oxide under oxidative conditions.\textsuperscript{86} In contrast, oxidatively stable nitrogen and carbene ligands are finding increased use in Pd(II)-catalyzed transformations.\textsuperscript{87-89}

1.2.3 The Oxidative Heck Reaction

\textbf{Background to the Oxidative Heck Reaction}

The palladium(II)-mediated vinylic substitution of organoboronic acids, known as the oxidative Heck reaction, was first developed by R. F. Heck in 1975, using stoichiometric amounts of palladium acetate.\textsuperscript{90} This non-catalytic coupling did not cause much attention until almost two decades later when the first catalytic protocol was reported by Uemura and coworkers, employing acetic acid as solvent.\textsuperscript{91} The first method using a specific reoxidant, Cu(OAc)_2, to regenerate Pd(II) from Pd(0) was introduced by Du et al. in 2001.\textsuperscript{92} Jung and Larhed independently and almost simultaneously discovered that molecular oxygen could be an efficient reoxidant of palla-
Larhed also introduced the first ligand-modulated oxidative Heck reaction employing 2,9-dimethyl-1,10-phenanthroline (dmphen) to facilitate reoxidation, to increase catalytic stability and to improve regioselectivity (Scheme 5). Furthermore, the palladium loadings could be reduced, presumably because of less palladium black formation when a bulky nitrogen bidentate ligand prevented clustering and aggregation of Pd(0) nanoparticles.

**Scheme 5.** The first ligand-modulated oxidative Heck reaction

Arylboronic acids or esters are commonly employed in the oxidative Heck reaction, but other arylating agents have also been reported, e.g. arylstananes, arylsilanes, arylphosphonic acids, and arylantimony compounds. Many of these alternative organometallic reagents are unstable and produce by-products that are highly toxic and difficult to remove. Arylboronic acids are comparatively moisture and air stable, less toxic and easily accessible.

**The Plausible Mechanism**

So far, there has been no detailed investigation which has positively identified the specific mechanism of the oxidative Heck reaction. Hence, one plausible mechanistic cycle (Scheme 6) is based on knowledge acquired from the study of other similar palladium-catalyzed reactions, such as the Suzuki and the Heck reaction, or alcohol oxidation.

**Scheme 6.** The plausible catalytic cycle of the palladium(II)-catalyzed oxidative Heck reaction
The formation of carbon-carbon bonds has always been a central theme in organic chemistry, and palladium has played a major part in the discovery of new catalytic pathways. The formation of organopalladium species is essential in palladium-mediated methodologies, for the reason that coupling cannot occur between two organic moieties unless at least one binds to the metal. In palladium(0)-catalyzed chemistry, it is very common to use oxidative addition to generate R-Pd-X species from R-X substrates. However, in palladium(II)-catalyzed chemistry, oxidative addition is more seldom proposed. If a Pd(II) species were to undergo oxidative addition it would lead to an unstable Pd(IV) intermediate. It has been debated whether Pd(IV) is an active intermediate in palladium-catalyzed reactions, as in the Heck reaction with palladacycles, and the general opinion is that it is unlikely under regular reaction conditions. An aryl-palladium(II) species is, however, generated in the oxidative Heck reaction through a transmetallation process between Pd(II) and an aryl precursor, such as an arylboronic acid.

Since the transmetallation process is present in many common cross-coupling reactions, it has been subjected to a number of mechanistic investigations. It has been shown that the choice of base is very important for the outcome of the Suzuki reaction, because the base can form an organoboronate complex by coordination to the boronic acid. This negatively charged organoboronate becomes even more prone to transfer of its organic component, via a transmetallation process, to a metal with higher electronegativity, e.g. palladium. After transmetallation the catalytic cycle of the oxidative Heck reaction is considered to be identical to the classical Heck reaction, apart from an additional reoxidation step at the end of the cycle.

Although the mechanism governing the regeneration of active Pd(II) has not been fully elucidated, a generally accepted proposal was presented by Stahl based on the results of a mechanistic investigation of the alcohol oxidation reaction (Scheme 7). The ligand, often a bidentate nitrogen ligand, plays a crucial part in the formation of the (η²-O₂)-Pdₐₐ species. A recent paper by Jutand indicates that the transmetallation process of the palladium-peroxy species is energetically more favorable than that of the free
Pd(II)L₁₀⁸ which could explain why the dmphen-supported oxidative Heck reaction works so well. There are also reports indicating that Pd(0) never exists in the catalytic cycle when bidentate nitrogen ligands are involved in oxygen-mediated reactions.¹⁰⁹ It has been proposed that O₂ is directly inserted into the L₂Pd(II) hydride to form an L₂Pd(II)-OOH species, which decomposes to active L₂Pd(II), oxygen and water.

Regioselectivity

The regiosomeric outcome of the oxidative Heck reaction is believed to follow the same pattern as the classical Heck reaction, and is therefore dependent on the coordination-insertion of the olefin. How the olefin approaches and coordinates the arylpalladium species and, in the following *syn*-addition, which carbon the palladium and the aryl group will bind to after the insertion, are strongly related to the steric and electronic properties of both the olefin and palladium moiety. Olefins can be roughly divided into three groups, electron-poor, neutral and electron-rich olefins. Electron-poor olefins lead to almost exclusively terminal arylation, favored by both steric and electronic (mesomeric and inductive) properties. The product ratios arising from the use of neutral olefins, like styrenes and aliphatic alkenes, are mostly governed by steric factors and thus are dominated by linear products.¹¹⁰

Scheme 8.  Coordination and insertion steps for electron-rich olefins in the neutral and cationic pathway

As long as the two directing factors (steric and electronic) do not oppose each other good selectivity is obtained, but problems arise when electron-rich olefins are employed. Mesomerically, the β-carbon (the terminal carbon) is more electron-rich and more prone to bind to electron-poor palladium(II), than to the sp²-carbon in the aryl group connected to Pd, while on the other hand, formation of the branched α-product is more sterically demanding. These conflicting factors result in poor selectivity, and a mixture of α- and β-product is produced. The problem was solved by Cabri in the
mid 1990s when he introduced the cationic pathway for the Heck reaction, employing aryl triflates and bidentate ligands as an alternative to the neutral pathway presented above.\textsuperscript{110} In the cationic pathway, electronic factors are given more weight, which results in complete $\alpha$-selectivity for electron-rich olefins. However, bidentate ligands and weakly coordinating anions, such as triflates (Scheme 8), are needed. It is also possible to use aryl halides, if additives like silver(I) and thallium(I) salts are employed as halide-sequestering agents,\textsuperscript{48,111} or by using highly polar reaction mixtures.\textsuperscript{112,113} Cabri’s pioneering work on bidentate nitrogen ligands\textsuperscript{114,115} resulted 10 years later in the first regioselective oxidative Heck reaction for electron-rich olefins.\textsuperscript{94}

1.3 Cobalt Carbonyl-Mediated Organic Reactions

Modern organometallic chemistry would not be what it is today without transition metal carbonyl complexes. More than a century ago, chemists learned how to prepare such complexes\textsuperscript{116} and have over the years discovered their ever-increasing potential as stoichiometric and catalytic reagents in organic synthesis.

The first method of preparing dicobalt octacarbonyl (Co\textsubscript{2}(CO)\textsubscript{8}) originates from 1910, and involves heating elemental cobalt (made by reducing cobalt oxalate) in a chamber with carbon monoxide at high pressure (30–40 atm) at 150 °C.\textsuperscript{117} The synthetic versatility of Co\textsubscript{2}(CO)\textsubscript{8} was soon exploited and some of the most-utilized reactions involving Co\textsubscript{2}(CO)\textsubscript{8} are presented below.

1.3.1 Hydroformylation Reactions

Since the discovery of the dicobalt octacarbonyl-mediated hydroformylation of olefins (Scheme 9), also called the oxo process, by Roelen 1938,\textsuperscript{118} much has happened. The process has undergone a number of improvements compared to the original, employing stoichiometric amounts of metal carbonyls and harsh reaction conditions. The result is a robust, regioselective and catalytic industrial process of great economic interest. The reaction is a straightforward addition reaction, which means good atom economy. Furthermore, the cheap starting materials and the low amount of by-product formation makes it an attractive way to synthesize solvents, plasticizers and detergent alcohols.\textsuperscript{119}

\[
\text{R} = \text{CO} + \text{H}_2 \xrightarrow{\text{Co}_2(\text{CO})_8} \text{RCH(OH)} + \text{RCH}_2\text{CHO} \\
\text{Branched} \quad \text{Linear}
\]

\textbf{Scheme 9.} Hydroformylation of olefins with cobalt carbonyl as catalyst
The process starts with an alkene coordinating to HCo(CO)₃, the active species that is generated from dicobalt octacarbonyl (Scheme 10), forming a HCo(CO)₃(η²-olefin) complex. Next, the olefin undergoes a 1,2-insertion, disrupting the bond between the hydrogen and the metal and reducing the double bond. An additional carbon monoxide molecule fills the vacant coordination site on the metal, and a CO enters the R-Co bond, generating an acyl-cobalt complex. The next step is proposed to be the oxidative addition of H₂ to the complex, followed by irreversible reductive elimination, yielding the aldehyde. In the past there was a problem of poor regioselectivity between the branched and linear product, but since the emergence of rhodium catalysts and new ligands, the reactivity can be tuned. The coveted linear aldehyde, which is more advantageous if further transformation to detergent alcohols is desired, can thus be predominantly formed. Today, HRh(CO)₉L₉ complexes are dominating catalysts in hydroformylation reactions, where L is often a phosphine ligand. Rhodium hydrides act as active catalysts in industrial oxo processes, providing not only better regioselectivity, but also milder reaction conditions.

Scheme 10. Generation of the catalytically active species in hydroformylation reactions

1.3.2 Cycloaddition Reactions

The most well-known dicobalt octacarbonyl-mediated cycloaddition reaction is the Pauson-Khand reaction, which is the [2+2+1] cycloaddition of an alkyne, an alkene and carbon monoxide (Scheme 11) in a highly convergent manner. The reaction is a useful tool for the synthesis of cyclopentenones, and was first reported in 1973 as a stoichiometric cobalt carbonyl-mediated reaction, but since 1990 it is also performed in a catalytic manner. Furthermore, it has been reported that the Pauson-Khand reaction can be performed stereoselectively, and by using the intramolecular version, bicyclic ring systems can be formed.

Scheme 11. The Pauson-Khand reaction

The key to activity is the strong coordination of Co₂(CO)₈ to alkynes, which results in an (alkyne)Co₂(CO)₈ complex. Next, the alkene is proposed to insert into the least hindered alkyne-cobalt site, followed by carbon monox-
ide insertion on the alkyl side. Finally, a reductive elimination connects the terminal carbons to a 5-membered ring. Dicobalt octacarbonyl exists in equilibrium with tetracobalt dodeca-carbonyl, and at elevated temperatures it is shifted towards the latter. At 50 °C a significant amount of Co$_2$(CO)$_8$ has been converted to Co$_4$(CO)$_{12}$, which cannot form the crucial alkyne-cobalt complex. The pressure of CO can then be used to manipulate the equilibrium between the two cobalt carbonyl complexes. Higher CO pressure will result in higher amounts of Co$_2$(CO)$_8$, according to the equilibrium constant defined below (Eq. 1). This is the reason why elevated carbon monoxide pressure is sometimes used in the Pauson-Khand reaction.

\[
K_p = \frac{[\text{Co}_4(\text{CO})_{12}] \cdot P_{\text{CO}}^2}{[\text{Co}_2(\text{CO})_8]^2}
\]

(1)

1.3.3 Carbonylation Reactions

The need for carbonylation protocols is always high because of the versatile transformations possible from the carbonyl group. Knowledge of the delicate chemistry between transition metals and carbon monoxide has paved the way for many successful synthetic carbonylation reactions, both on laboratory and industrial scale. Dicobalt octacarbonyl is involved in many different organic carbonylation reactions; some selected examples will be discussed below.

In organic synthesis, the development of new tandem reactions is encouraged, because it is a convenient and efficient way to create multiple carbon-carbon bonds (and other bonds) in a consecutive manner, avoiding intermediate purification steps. The hydroalkoxycarbonylation of acrylonitrile, with alcohol over a catalytic amount of Co$_2$(CO)$_8$ and pyridine as base yielding 2,4-dicyano-2-methylbutanoic acid esters, is an example of an efficient dicobalt octacarbonyl-mediated carbonylation reaction (Scheme 12).

\[
\text{Scheme 12. Tandem hydroalkoxycarbonylation of acrylonitrile}
\]

Amidocarbonylation can be performed using dicobalt octacarbonyl as catalyst with aldehydes or olefins to form N-acyl amino acids. In spite of the fact that this amidocarbonylation reaction cannot compete with cheap natural sources or fermentation for the synthesis of amino acids, this salt-free process is a good alternative to the conventional Strecker reaction for the synthesis of non-natural amino acids. The synthesis of N-acyl phenylalanine
(Scheme 13), which is a key intermediate for aspartame (a sweetener) production, is an example of an application of \( \text{Co}_2(\text{CO})_8 \)-mediated amidocarbonylation.

\[
\text{CH}_3\text{CONH}_2 + \text{CH}_3\text{CHOH} \xrightarrow{\text{Co}_2(\text{CO})_8, \text{DIPHOS}} \text{H}_2\text{O} \xrightarrow{80 \degree C, 150 \text{ atm}} \text{N-acyl phenylalanine}
\]

Scheme 13. Amidocarbonylation of phenylacetaldehyde into \( N \)-acyl phenylalanine

Dicobalt octacarbonyl has also been reported to produce benzophenones in the presence of iron pentacarbonyl, under phase-transfer conditions using a strong base and aryl iodide (Scheme 14). This reaction is performed under 1 atm of carbon monoxide and is suggested to proceed via an SrN1 reaction mechanism.\(^{\text{129,130}}\)

\[
\text{Ar-I} \xrightarrow{\text{Fe(CO)}_5\text{Co}_2(\text{CO})_8, \text{NaOH/Benzene}, \text{NBu}_4\text{Br}, \text{CO (1 atm), 65 \degree C}} \text{Ar}_2\text{O}
\]

Scheme 14. Dicobalt octacarbonyl in a bimetallic-catalyzed reaction in the synthesis of benzophenones

The ability of dicobalt octacarbonyl to form ureas from primary amines is by no means a new disclosure. In 1952 G. Natta reported a reaction employing high temperature and CO pressure affording diphenylurea at high yields (Scheme 15).\(^{\text{131}}\) Generally harsh conditions are required for the transformation to occur, but by adding a hydrogen acceptor milder conditions can be applied.\(^{\text{132}}\) Several other metal carbonyls, involving e.g. W,\(^{\text{133}}\) Ni,\(^{\text{134}}\) and Ru,\(^{\text{132}}\) are also known to facilitate urea formation from primary amines.

\[
\text{NH}_2 \xrightarrow{\text{Co}_2(\text{CO})_8, 250 \text{ atm CO, styrene, 200 \degree C}} \text{N} \text{N} \text{O}
\]

Scheme 15. The first synthesis of urea facilitated by dicobalt octacarbonyl\(^{\text{131}}\)

1.4 Microwave-Assisted Organic Synthesis

High-throughput chemistry is a hot topic in organic synthesis today because of the drug discovery community’s large and ever-increasing demand for new chemical entities.\(^{\text{135-138}}\) This demand combined with the need to develop more sustainable (“green”) chemistry\(^{\text{139}}\) have stimulated research towards
controlled microwave-assisted organic synthesis,\textsuperscript{140} which can be illustrated by the more than 2000 articles published in the area since microwaves were first introduced as an efficient energy source for acceleration of organic transformations.\textsuperscript{141-143}

1.4.1 History

A common misunderstanding is that Robert Bunsen, in 1855, invented the famous burner. Actually, Michael Faraday described a similar laboratory gas burner already in 1827, but it was not until Robert Bunsen’s assistant improved the instrument that it become widely used, and was named “the Bunsen burner” after his boss.\textsuperscript{144} This heating device made it possible for contemporary scientists to apply heat in a new, more controlled manner, and it was a milestone in the development of modern chemistry. The Bunsen burner has largely been superseded by safer and more controllable heating techniques like the oil-bath and the heating mantle. All these methods will in the following sections be referred to as classical heating techniques.

During World War II a great deal of effort was devoted to developing advanced magnetrons to improve radar devices, which utilize microwave radiation to detect objects, such as enemy planes, at large distances. Rumor says that a man working with radar noticed how a chocolate bar in his pocket started to melt when he was standing in the magnetic field. Ten years after the war had ended the knowledge attained resulted in the first commercial domestic microwave oven (based on an appliance called a Radarange, from 1947 also used in food processing).\textsuperscript{145} However, it took more than 30 years for the microwave oven to take the step from the kitchen into the laboratory,\textsuperscript{146-148} mainly due to the lack of safety arrangements, reproducibility and control.\textsuperscript{142} In addition, the common misunderstanding that microwaves could heat only water delayed the development.

1.4.2 Microwave Theory

Electromagnetic radiation in the region between infrared radiation and radio waves is called microwaves (Figure 4), and these waves oscillate with frequencies ranging from 0.3 to 300 GHz. The microwave region is used for telecommunication (cellular phones) and radar. Consequently, to avoid interference between different sources, the frequency used in domestic microwave ovens, as well as in commercially available microwave synthesizers, is limited to 2.45 GHz, which corresponds to a wavelength of 12.24 cm.\textsuperscript{146} The energy from such a frequency is too low to break any chemical bonds,\textsuperscript{141,142} but well suited to inducing microwave dielectric heating.
Figure 4. The electromagnetic spectrum

There are two main heating mechanisms for liquids and solutions, which both are dependent on the electric component of the oscillating field. First, there is the dipolar polarization mechanism (Figure 5a), which causes dipoles in the irradiated sample to attempt to align according to the applied electromagnetic field. However, the field is oscillating and the dipoles have to realign to be in the correct phase, resulting in a rotation or flip of the molecule. In this process, the electromagnetic energy is transformed into heat through molecular friction (dielectric loss). The second heating mechanism is dependent on ionic conductance. When ions are under the influence of an applied electric field, they will oscillate up and down with the field (Figure 5b) and this extra kinetic energy will be dissipated, due to an increase in collision rate, in the form of heat.\(^{150,151}\)

Figure 5. Microwave dielectric heating mechanisms: a) dipolar polarization mechanism, b) conductive mechanism

The amount of heat generated by the dielectric heating mechanism described above is dependent on the ability of the dipole to align with the oscillating field. If the frequency of the field is too high for the dipole to realign, or if it realigns too quickly, no heat will be formed. Frequencies in the microwave radiation region are suitable for most organic compounds to rotate with the applied field and thus microwave irradiation is converted into heat. In order to quantify a substrate’s ability to convert electromagnetic energy into heat, the loss tangent (\(\tan \delta\)), also known as the energy dissipation factor, was introduced.\(^{151}\) It is expressed as the quotient between the dielectric loss \(\varepsilon''\) and the dielectric constant \(\varepsilon'\) (Eq. 2). The loss factor (\(\varepsilon''\)) describes the effi-
ciency with which the absorbed energy is converted into heat, and the dielectric constant \((\varepsilon')\) is a measure of the material’s ability to store electrical potential energy under the influence of an electric field.\(^{142}\)

\[\tan \delta = \varepsilon''/\varepsilon'\] (2)

However, Eq. 2 can sometimes be misleading by its mathematical simplicity. A low \(\varepsilon’\) does not necessarily produce a high \(\tan \delta\), for the reason that the loss factor and the dielectric constant are dependant on each other. It is more straightforward to relate a compound’s ability to induce heat from microwave irradiation by its polarity. A more polar molecule results in more efficient heating when exposed to microwave irradiation. Accordingly, non-polar solvents like \(n\)-hexane would seem to be useless in microwave-assisted organic synthesis, but this is not the case. Generally, a polar component can be added to the reaction mixture in order to accelerate the heating. Often, simply the reagents, or an added salt or ionic liquid, can constitute the microwave-absorbing mediator that transfers energy to the surrounding molecules.\(^{141}\)

1.4.3 Microwave Effects and Heating Phenomena

The main advantage of using microwave-assisted organic synthesis is the shorter reaction time compared to classical heating. However, there are also examples of microwave-accelerated synthesis that cannot be achieved using conventional heating.\(^{152,153}\) It has been debated whether these results are due to non-thermal microwave effects,\(^{143,154,155}\) but the generally accepted opinion today is that most of the, sometimes exceptional, results are the consequence of the rapidly obtained high temperature resulting from the irradiated polar medium (in the microwave field).\(^{141}\) In an early paper, Raner and co-workers reported identical reaction rates independent of the heating method used (classical or microwave heating).\(^{156}\) Overheating, “hot spots”\(^7\) and technical problems in measuring a correct bulk-temperature are examples of heating phenomena that can explain some unexpected outcomes. Overheating, in the form of boiling point elevation, is associated with pressure, and can be observed when a solvent (or reaction mixture) is heated in a closed vessel. In the gas state the molecules are too far from each other to produce any friction, consequently the heating mechanisms described above do not apply. The reason why the solvent can be heated to a higher temperature than its boiling point, is simply derived from elemental physics. When a liquid is heated in a closed system the (external) pressure becomes higher. As liquids cannot boil until the internal pressure is equal to or higher than the external pressure, this results in an elevated boiling point of the confined solvent. A similar phenomenon, called superheating, also causes polar solvents to boil at temperatures higher than their normal boiling points, but
applies to open vessels at atmospheric pressure. The elevated boiling points are generated by limited formation of “boiling nuclei” during dielectric heating, but are not as pronounced as in the closed systems; temperatures up to 26 °C above the normal boiling point have been reported. It is important to note that the reactions performed using sealed reaction vessels in dedicated microwave equipment described in Chapter 5 are examples of overheating and not superheating. Samples exposed to microwave irradiation sometimes experience inhomogeneous fields, which create areas of a much higher temperature than the macroscopic temperature. These unpredictable, so-called “hot spots”, can e.g. be conveyed by the influence of decomposed catalysts, yielding unexpected synthetic results that are difficult to reproduce.

1.5 Electrospray Ionization Mass Spectrometry

The research on the electrospray process, carried out by Dole in the late 1960s laid the foundation for the successful coupling of electrospray ionization (ESI) to mass spectrometry (MS) introduced by Fenn and Yamashita in the mid 1980s. In a mass spectrometer the sample must be gaseous, but many unstable or high-boiling-point molecules would decompose at such elevated temperatures and are, thus, unsuitable for MS analysis. With the emergence of the electrospray as an interface to the quadrupole mass spectrometer, the range of possible analytes was widely extended to include large polar organic macro-molecules (e.g. proteins) and short-lived reaction intermediates, which without electrospray ionization would be impossible to obtain in the gaseous phase. Today, ESI-MS is of great importance in the study of new biochemical reactions, as well as in the study of organometallic mechanisms.

1.5.1 Mechanism of Electrospray Ionization Mass Spectrometry

Electrospray Ionization

Although one says “electrospray ionization”, ESI is not an ionization process in the sense that it ionizes neutral molecules into ions, but should be seen as a technique that allows the transfer of ions from the solution to the gas phase.
A polar solvent containing soluble electrolytes is introduced into the system through a capillary. When the instrument is turned on a voltage is applied to the metal capillary tip, which will penetrate the solution and force positive and negative electrolytes away from each other. Figure 6 shows what happens when the capillary acts as a positive electrode and attracts anions, while the surplus positive ions are forced to the liquid surface. If the voltage is high enough, the dissolved ions will overcome the surface tension, form a so-called Taylor cone and finally disperse as a fine jet at the cone tip. This jet will soon break up into small solvent droplets that contain an excess of positively charged electrolyte ions. These charged droplets will shrink, due to solvent evaporation, causing the charge concentration (and thus the repulsion) inside the droplet to increase, as it drifts towards the end wall of the chamber. This will continue until the Rayleigh stability limit is reached, at which point the droplet will explode, since the magnitude of the Coulomb interaction is greater than the surface tension. This phenomenon produces a number of daughter droplets that will also evaporate, and the scenario will repeat itself until the droplets are so small that they only contain the analyte ion. There is another model describing how the analyte ion is separated from the droplet, which is called the ion desorption model (IDM) or the ion evaporation mechanism (IEM). IDM/IEM differs from the charge residue model (CRM) described above, in the sense that a single analyte ion is proposed to be emitted from a droplet with a critical radius larger than the Rayleigh limit. In the end, both models result in the transfer of analyte ions into the gas phase, and in the next step they are allowed to pass
through an orifice that leads to the vacuum chamber of the mass spectrometer.\textsuperscript{167,171,172}

The strength of ESI, compared to other mass-spectrometric ionization techniques, lies in three features. Firstly, its ability to produce multiply charged ions. This is particularly important when large macro-molecules are to be analyzed. Secondly, samples are generally introduced in solution, which makes it less complicated to couple separation techniques like LC\textsuperscript{173} or capillary electrophoresis\textsuperscript{174} to the MS-system. Lastly, as mentioned above, ESI is an exceptionally mild method of forming gaseous ions which even allows a weak non-covalent bond to remain intact when transferred from solution to the gas phase.\textsuperscript{166}

**Tandem Mass Spectrometry**

Organic mass spectrometry began to grow rapidly between 1958 and 1966, but almost entirely on an empirical basis. With a deeper understanding of the chemistry and physics behind the process, mass spectrometry became what it is today – one of the most powerful and important analytical tools available.

![A triple-quadrupole mass spectrometer system](image.png)

Figure 7. A triple-quadrupole mass spectrometer system\textsuperscript{175}

No attempt will be made in this thesis to cover the enormous area of MS, but only to mention one, very useful advancement, namely tandem mass spectrometry (MS/MS). MS/MS combined with an electrospray interface allows the user to identify and elucidate the structure of unstable ligated ionic species in very complex sample mixtures. To be able to run an MS/MS experiment a triple-quadrupole instrument is needed (Figure 7), which can be visualized as a tunnel containing different chambers (quadrupoles) in vacuum and where an applied voltage accelerates the ions as they enter each section. The first quadrupole (Q1) selects a particular ion based on its $m/z$ ratio, also called ion-fishing, and the ion is sent into the collision cell (Q2) where it collides with a neutral, inert gas. These collisions allow kinetic energy to be converted into internal energy in the ions, which causes fragmentation.
(CID). Fragments leaving Q2 are mass analyzed in the third and last quadrupole, Q3, before they enter the detector.\textsuperscript{165,175}

1.5.2 Electrospray Ionization of Organopalladium Complexes

Modern ESI-MS and ESI-MS/MS instruments are excellent tools in studies aimed at determining the mechanisms prevailing in organometallic catalysis,\textsuperscript{164,165,176} but also for screening of metal catalysts.\textsuperscript{177,178}

Organometallic catalysis has been subjected to a number of mechanistic investigations based on techniques such as NMR,\textsuperscript{43,108,179,180} cyclic voltametry,\textsuperscript{42,181} kinetic measurements,\textsuperscript{108,182,183} X-ray\textsuperscript{184} and computational studies.\textsuperscript{106,183,185,186} Many of these techniques, however, demand stoichiometric amounts of the catalyst, or require alterations to the system, such as investigations of isolated systems featuring isolated steps of a postulated catalytic cycle.\textsuperscript{67} The advantage of ESI-MS is that a “real” active catalytic system, with reactive intermediates, can be monitored on-line, directly from a productive reaction mixture.\textsuperscript{187} Palladium-containing complexes are convenient to analyze because their characteristic natural isotopic distribution pattern makes them easily recognizable in the MS spectrum.

There are a large number of palladium(0)-catalyzed reactions whose mechanisms have been elucidated by ESI-MS investigations, e.g. the Heck\textsuperscript{188-190} and the Suzuki reaction.\textsuperscript{191} In general, ESI-MS makes it possible to observe intact ionic organopalladium intermediates, transferred from catalytic reactions in solution to the gas phase. This is a great advantage, but relevant disadvantages should also be mentioned, such as the fact that neutral complexes cannot be detected, and that seeing and identifying the most abundant complex in reaction mixture from the MS spectrum does not necessarily mean that it is an active catalytic intermediate (it could be a resting state outside the catalytic cycle). However, there are ways to by-pass these problems, e.g. a potential ionic intermediate can be isolated (ion-trap) and allowed to react with a certain substrate (charge-labeled in the neutral case). If the expected product is formed and detected it verifies the role of the complex as an active intermediate.\textsuperscript{192}
2 Aims of the Present Study

Over the years, palladium has played an important role in homogeneous catalysis, mainly because of its capacity to mediate versatile and mild formation of carbon-carbon bonds. The development of new improved procedures is always important, and the oxidative Heck reaction is an example of such a relatively new, undeveloped method. It is a palladium(II)-catalyzed, halide-free methodology that shows potential of being a “greener” alternative than the more established Heck arylation. Development of sustainable chemistry is of fundamental importance for the future and new, more environmentally friendly methodologies are required, as well as an increased understanding of how the reactions actually work.

The goal of the emerging discipline of high-speed synthesis is to carry out organic transformations at an ever-increasing rate. Thus, it is not sufficient to synthesize the right product at high yields and purities; the process must also be rapid. Preferably, reaction times should be reduced from days and hours to minutes and seconds.

The specific objectives of this study were:

- to develop a general, environmentally benign protocol for the ligand-modulated oxidative Heck reaction using air-promoted regeneration of active palladium(II) at room temperature,
- to investigate the mechanism of the oxidative Heck reaction by detection of reaction intermediates directly from the reaction mixture,
- to identify a highly convenient and fast in situ carbonylation reaction for the generation of benzophenones and urea compounds, and
- to investigate how much it is possible to minimize the reaction times of a carbonylation procedure with the aid of high-density microwave irradiation.
3 Open-Air Oxidative Heck Reactions with Arylboronic Acids (Paper I)

3.1 Results

“Green chemistry” is often mentioned in chemistry discussions and most chemists associate it with environmentally friendly chemical reactions, but it is more than that. The safety of the user (the chemist) and cost are also included in the concept, and that is what inspired the further development of the ligand-modulated oxidative Heck reaction in this work. The use of pure molecular oxygen as reoxidant is indeed much more environmentally benign than heavy-metal waste-producing copper(II) salts, but it involves a risk in the employment of O$_2$ gas tubes in the laboratory. Atmospheric air contains only 21% dioxygen, but both cost and risks are reduced, and simple open-vessel conditions can be employed. The ambition of our investigation was to establish that efficient arylation of both electron-poor and electron-rich olefins could be conducted in air, even at ambient temperature, with a diverse series of arylboronic acids.

3.1.1 Ligand Screening

By optimizing the reaction conditions for the oxidative Heck reaction with regard to the choice of ligand, yield, regioselectivity and reoxidation rate can be improved. No screening of ligands employed in the oxidative Heck reaction has previously been published, therefore one may be led to believe that the choice of dmphen as ligand in the first place was probably inspired by other areas. Cabri’s acclaimed investigation of phenanthroline-based ligands in the palladium(0)-catalyzed Heck reaction and in successful alcohol oxidation reactions, utilizing the same class of ligands due to their oxidative capacity, were probably the reasons why dmphen (3e) was selected. To explore the compatibility of the Pd(II)-catalyzed oxidative Heck reaction with other ligands (3) a previously developed test-reaction (Scheme 16) was used as a benchmark to measure the efficiency of seven alternative ligands. The results are presented in Table 1, and were performed in acetonitrile using 2 equiv $p$-tolylboronic acid (1c), 1 mmol $n$-butyl acrylate (2a), 2 equiv
N-methyl morpholine (NMM) as base, 2.4% ligand and 2% Pd(OAc)$_2$ as palladium source.

Scheme 16. Test-reaction for ligand screening

Each ligand in Table 1 including the 2-bipyridyl substructure gave rise to a productive catalytic reaction, with dmphen as the most efficient alternative (Table 1, entry 5), while pyridine yielded no product at all (Table 1, entry 1). Although the transformation was slower, the dmphen-related bisphenylated ligand 3f also gave a satisfactory 87% yield of product 4c. Surprisingly, and in contrast to previous experience of phosphine based ligands, the oxidatively sensitive bidentate phosphine ligand, dppp (1,3-bis(diphenylphosphino)propane), 3h, furnished an 81% yield after 24 h (Table 1, entry 8). Since the reaction was conducted under open-vessel conditions and acetonitrile is known to absorb moisture, a reaction employing a 95:5 water:acetonitrile solution was conducted, without further optimization of the applied standard conditions, to investigate the impact of water. This perturbed reaction was much slower but still produced a 35% yield (Table 1, entry 5). When the reaction was performed in pure water poor solubility hampered the reaction and difficulties were encountered in monitoring the reaction.
Table 1. Impact of different ligands 3 on oxidative arylation of n-butyl acrylate (2a) with p-tolylboronic acid (1c) under air at 80 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand, 3</th>
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<th>Yield of 4c (%)b</th>
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<tr>
<td>8</td>
<td><img src="image" alt="3h" /></td>
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</tr>
</tbody>
</table>

a Reaction conditions: open vessel charged with p-tolylboronic acid (2.0 mmol), n-butyl acrylate (1.0 mmol), N-methylmorpholine (2.0 mmol), Pd(OAc)2 (0.02 mmol), ligand (0.048 mmol 3a or 0.024 mmol 3b-h) and acetonitrile (3 mL). Rapid stirring. b Isolated yield. c Performed at rt. d Water:acetonitrile = 95:5. e Water as solvent.

3.1.2 Olefin Screening

After dmphen was established as the superior ligand in the open-vessel procedure, a broad range of olefins, utilizing p-tolylboronic acid (1c) as transmetallation agent, was evaluated at both ambient temperature and at 60–80 °C (Table 2). Good yields were obtained for both electron-poor and electron-rich olefins independent of reaction temperature, except for butyl vinyl ether (2g) which produced significantly reduced yields at rt. Sterically demanding olefins such as disubstituted 2b or prochiral 2h also reacted more sluggishly, but independently of reaction temperature. Although the yield seemed to be unaffected by the reaction temperature, the reaction time varied considerably.
Table 2. Oxidative arylation of different olefins 2 with \( p \)-tolylboronic acid (1c) at ambient and elevated temperatures

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Reaction time (h)</th>
<th>Temp (°C)</th>
<th>Product, 4</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>24 1</td>
<td>rt 80</td>
<td>4c</td>
<td>93 94</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>96 1</td>
<td>80</td>
<td>5a 5b</td>
<td>35(^c)</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>96 1</td>
<td>rt</td>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>24 96</td>
<td>80</td>
<td>7</td>
<td>85(^d) 75(^e)</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>48 6</td>
<td>80</td>
<td>8a</td>
<td>71 68</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>144 24</td>
<td>80</td>
<td>9</td>
<td>57 67</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>24 24</td>
<td>80</td>
<td>10</td>
<td>35(^c) 91(^e)</td>
</tr>
<tr>
<td>8</td>
<td>2h</td>
<td>18 6</td>
<td>80</td>
<td>11</td>
<td>35 45</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: open vessel charged with \( p \)-tolylboronic acid (2.0 mmol), olefin (1.0 mmol), \( N \)-methylmorpholine (2.0 mmol), \( \text{Pd(OAc)}_2 \) (0.02 mmol), dmphen (0.024 mmol) and acetonitrile (3 mL). Rapid stirring. \(^b\) Isolated yield >95% pure according to GC-MS. \(^c\) 5a:5b=40:60, determined by NMR. \(^d\) \( \alpha/\beta = 15/85 \), determined by GC-MS. \(^e\) Isolated as the corresponding \( p \)-tolylmethyl ketone, after acidic in situ hydrolysis (glacial \( \text{HOAc} \)).

As would be anticipated in a system exploiting a bidentate ligand under cationic reaction conditions, the insertions were governed mainly by electronic factors, furnishing either predominantly terminal (4c, 5–7) or branched (8a–10) products. Olefin 2a furnished excellent yields (93%) at room temperature after 24 h, and at elevated temperatures the yield was maintained, while the reaction time decreased to 1 h (entry 1).

The high reactivity of electron-poor compared to electron-rich olefins under cationic conditions was not expected. To investigate this matter more thoroughly a series of competitive experiments was performed. Equal amounts of electron-poor \( n \)-butyl acrylate (2a) and electron-rich \( N \)-vinyl-2-pyrroldinone (2e) were reacted in parallel at room temperature under open air. The results presented in Table 3 indeed illustrate the more rapid formation of arylated acrylate 4e than enamide product 8a. A completely different
result from that obtained in the Pd(0)-catalyzed cationic situation for aryl triflates, which react faster with electron-rich olefins. The product ratio (4c:8a) reached its maximum after 4 h and was maintained for 26 h, until it slowly started to decrease, probably because of too low a concentration of olefin 2a.

**Table 3.** Competitive experiment between n-butyl acrylate (2a) and N-vinyl pyrrolidinone (2e) using 1c as arylating agent at room temperature
d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Yield(^a) 4c (%)</th>
<th>Yield(^b) 8a (%)</th>
<th>Ratio(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>8</td>
<td>5</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>13</td>
<td>8</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>24</td>
<td>9</td>
<td>2.8</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>63</td>
<td>23</td>
<td>2.7</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>80</td>
<td>30</td>
<td>2.8</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>92</td>
<td>33</td>
<td>2.7</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>99</td>
<td>41</td>
<td>2.5</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: open vessel charged with p-tolylboronic acid (1.5 mmol), N-vinyl-2-pyrrolidinone (0.5 mmol), n-butyl acrylate (0.5 mmol), N-methylmorpholine (2.0 mmol), Pd(OAc)\(_2\) (0.02 mmol), dmphen (0.024 mmol) in acetonitrile (3 mL) and rapid stirring at room temperature. \(^b\) NMR yield. \(^c\) Product ratio of 4c:8a.

### 3.1.3 Arylboronic Acid Screening

Next, the scope of arylboronic acids, 1, was investigated using n-butyl acrylate (2a) as coupling substrate (Table 4). A clear trend could early be distinguished, namely, electron-rich arylboronic acids (Table 4, entries 1–4, 6 and 7) are more productive than electron-deficient transmetallation precursors, which could be expected on the basis of recent DFT calculations of the oxidative Heck reaction. The calculated energies of the species involved in the migratory insertion of the olefin, indicated that electron-withdrawing groups on the aryl will produce too stable a π-complex, more unwilling to undergo insertion than aryl groups containing electron-donating groups which, in addition, also showed lower insertion barriers. Nevertheless, under the conditions employed electron-poor arylboronic acids still furnished useful yields, and p-acetylphenylboronic acid, which has previously been reported to be inert to n-butyl acrylate (2a), was isolated at a satisfactory yield of 61% (Table 4, entry 12).
Table 4. Dmphen-modulated oxidative arylation of \( n \)-butyl acrylate (2a) with a set of arylboronic acids\(^d\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arylboronic acid</th>
<th>Reaction time (h)</th>
<th>Temp (°C)</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>72</td>
<td>80</td>
<td>4a</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>48</td>
<td>rt</td>
<td>4b</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>24</td>
<td>rt</td>
<td>4c</td>
<td>94(^c)</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>1</td>
<td>80</td>
<td>4e</td>
<td>95(^c)</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>24</td>
<td>80</td>
<td>4e</td>
<td>0(^d)</td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>24</td>
<td>80</td>
<td>4d</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>1e</td>
<td>24</td>
<td>rt</td>
<td>4e</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>1f</td>
<td>48</td>
<td>rt</td>
<td>4f</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>1g</td>
<td>24</td>
<td>80</td>
<td>4g</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>1h</td>
<td>96</td>
<td>80</td>
<td>4h</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>1i</td>
<td>18</td>
<td>80</td>
<td>4i</td>
<td>67</td>
</tr>
<tr>
<td>12</td>
<td>1j</td>
<td>120</td>
<td>rt</td>
<td>4j</td>
<td>61</td>
</tr>
<tr>
<td>13</td>
<td>1j</td>
<td>24</td>
<td>80</td>
<td>4j</td>
<td>64</td>
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<tr>
<td>14</td>
<td>1k</td>
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<td>80</td>
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<tr>
<td>15</td>
<td>1l</td>
<td>18</td>
<td>80</td>
<td>4l</td>
<td>64</td>
</tr>
<tr>
<td>16</td>
<td>1m</td>
<td>96</td>
<td>80</td>
<td>4m</td>
<td>50</td>
</tr>
</tbody>
</table>

\(^d\) Reaction conditions: open vessel charged with boronic acid (2.0 mmol), \( n \)-butyl acrylate (1.0 mmol), N-methylmorpholine (2.0 mmol), Pd(OAc)\(_2\) (0.02 mmol), dmphen (0.024 mmol) and acetonitrile (3 mL). Rapid stirring. \(^b\) Isolated yield \( >95\% \) pure according to GC-MS. \(^c\) 0.02 mmol Pd\(_2\)(dba)\(_3\) instead of Pd(OAc)\(_2\). \(^d\) Closed vessel with nitrogen atmosphere.

The most interesting aspect of arylboronic acid 1g is not the high yield (87\%, Table 4, entry 9), but the high chemoselectivity demonstrated by this bromo-substituted compound. The absence of a classical Heck product indicates that the reaction conditions are finely tuned to transmetallation in the
Pd(II)-catalyzed oxidative Heck reaction, and not the competing Pd(0)-requiring process of oxidative addition. To further investigate this supposedly Pd(II)-catalyzed oxidative Heck reaction, with its aerobic reoxidation system, a zero-valent palladium source (Pd$_2$(dba)$_3$) was chosen as catalyst. The results were encouraging; under open-vessel conditions the Pd(0) was oxidized to Pd(II) and reacted just as well as when Pd(OAc)$_2$ was used (Table 4, entries 3 and 4). In a second test Pd(OAc)$_2$ was utilized, but instead of open air a closed system filled with nitrogen was employed. The nitrogen atmosphere resulted in the complete inhibition of the catalytic system, probably due to the lack of a reoxidation system (Table 4, entry 5).
4 ESI-MS Detection of Reaction Intermediates in the Oxidative Heck Reaction (Paper II)

4.1 Background

In order to detect existing cationic palladium complexes during a productive ligand-controlled oxidative Heck reaction between an electron-rich olefin and an arylboronic acid, MS spectra were recorded using electrospray ionization. The dmphen-mediated oxidative Heck reaction is believed to proceed under cationic conditions,\textsuperscript{94} suggesting that key Pd(II) $\sigma$- and $\pi$-intermediates are positively charged and thus observable with MS. The reason why the electron-rich olefin 2e was employed is that in the event that selective internal arylation is obtained this would give indirect proof of cationic key intermediates in the reaction.

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme17}
\end{center}
\caption{The plausible catalytic cycle of the phenanthroline mediated, oxygen-promoted oxidative Heck reaction with an electron-rich olefin. The different types of cationic intermediates in the catalytic cycle are assigned letters from A to E and catalytic steps are labeled I–VI.}
\end{scheme}
The catalytic cycle in Scheme 17 displays intermediates (A–E) involved in different steps (I–VI) of the oxidative Heck reaction. 81,93 Step I in the catalytic cycle corresponds to the starting point, where different Pd(II) species of class A participate in a transmetallation process and produce arylpalladium(II) complexes of class B. In step II the metal center coordinates to an olefin, generating a π-complex of type C_π. Thereafter, the C_π species undergoes a migratory insertion process forming a σ-complex (C_σ, step III). After subsequent β-elimination (step IV), a palladium hydride is formed which is believed to first coordinate to the arylated olefin (D) before dissociating, forming free Heck product and palladium hydride (step V). The last, closing step (step VI) of the catalytic cycle is the regeneration of active Pd(II) species with molecular oxygen.

4.2 Results

The oxidative Heck protocol utilized in this ESI-MS investigation differs slightly from the one discussed in Chapter 3, in that the base, N-methylmorpholine (NMM), was replaced by an alternative inorganic base, sodium acetate, in order to improve the signal-to-noise ratio in the MS spectrum. The reaction proceeds under open-vessel conditions at room temperature with NaOAc (2.0 equiv) and dmphen (3e, 0.024 equiv) as the ligand, p-Tolyboronic acid (1c, 2.0 equiv) and the electron-rich enamide (0.5 mmol, 1.0 equiv) with Pd(OAc)_2 (0.02 equiv) as palladium(II) source, were chosen as the standard reaction system for the ESI-MS analysis (Scheme 18). Changing the base did not affect the outcome of the reaction to any significant degree, except that it became faster and furnished somewhat lower yield (63% after 24 h, Table 5, entry 1) than the corresponding reaction with NMM (71% after 48 h, Table 2, entry 5).

Scheme 18. Investigated oxidative Heck reactions and subsequent hydrolysis
The new reaction conditions, with the alternative base, were also applied to arylboronic acid 1d, enamide 2f, ligand 3f and propionitrile as solvent (Scheme 18 and Table 5). To investigate the impact of water on the reaction system, the solvent in the standard reaction was replaced by a 50:50 acetonitrile:water solution. The reaction furnished slightly reduced yield of product 12a when isolated (50%, Table 5, entry 7, instead of 63%, Table 5, entry 1), but indicated that the open-vessel oxidative Heck reaction is not much hampered by moisture.

**Table 5.** Productivity of the catalytic systems using selected reaction components at room temperature$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArB(OH)$_2$</th>
<th>Olefin</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield$^b$(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1c</td>
<td>2e</td>
<td>3e</td>
<td>MeCN</td>
<td>12a, 63</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>2e</td>
<td>3e</td>
<td>MeCN</td>
<td>12a, 72$^c$</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>2e</td>
<td>3e</td>
<td>MeCN</td>
<td>12b, 76</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>2e</td>
<td>3f</td>
<td>MeCN</td>
<td>12a, 55</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>2f</td>
<td>3e</td>
<td>MeCN</td>
<td>12a, 59$^d$</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>2e</td>
<td>3e</td>
<td>EtCN</td>
<td>12a, 69</td>
</tr>
<tr>
<td>7</td>
<td>1e</td>
<td>2e</td>
<td>3e</td>
<td>MeCN/H$_2$O</td>
<td>12a, 50$^e$</td>
</tr>
</tbody>
</table>

$^a$ Arylboronic acid (1, 2 equiv), olefin (2, 1 mmol, 1 equiv), ligand (3, 0.024 equiv), NaOAc (2 equiv), Pd(II) salt (0.02 equiv) in 3 mL solvent stirred in an open vessel for 24 h. In all reactions, except entry 4, 1–4% biaryl formation was observed. $^b$ Isolated yield of the corresponding aryl methyl ketone 12 after acidic hydrolysis. $^c$>95% pure according to GC-MS. $^d$ Palladium propionate instead of palladium acetate and increased reaction time to 30 h. $^e$ Increased reaction time to 7 days. $^f$ Acetonitrile:water = 50:50

**4.2.1 Observed Complexes**

Before ESI-MS-(+) analysis the withdrawn sample from the reaction mixture was diluted 10 times with acetonitrile after 3 hours of vigorous stirring in an open vessel at ambient temperature. The diluted reaction mixture was introduced into the equipment by continuous infusion with the aid of a syringe pump. The analysis was performed after 3 h reaction as investigations at different time intervals showed that although all the detected palladium intermediates were present already after 10 minutes it was necessary to wait 3 h to avoid the induction period producing irrelevant immature Pd species. Furthermore, after 3 h around 50% conversion of the yield determining olefins was achieved.

After sample injection, a full MS spectrum was obtained (Figure 8) by scanning the first quadrupole in the triple-quadrupole API+ instrument. The
largest peaks correspond to sodium adducts from arylated olefin (monomers, dimmers and trimers), but un-reacted olefin and solvent molecules were sometimes also involved in the complexes.

Figure 8.  ESI-MS-(+) spectrum for the standard reaction, using 1c, 2e, 3e, NaOAc and MeCN under air at room temperature after 3 h (entry 1, Table 5). Palladium complexes denoted according to Table 6.

The smaller and somewhat broader peaks originate from the isotopic distribution of palladium, which made it easy to recognized palladium-containing species. The enlargement of the aryl palladium species B2 in Figure 9 displays a typical isotopic pattern of natural Pd. The m/z ratio is assigned from the ion with the strongest intensity in each complex, which is derived from the palladium isotope with the highest natural abundance, namely 106Pd.

Figure 9.  ESI-MS-(+) spectrum of palladium complex B2 (m/z = 446) solid line, and theoretical isotopic pattern, dotted line
The m/z separation between adjacent peaks reveals whether the complex contains one or more positive charges. In this case there is only one unit between the peaks, thus a monocharged cationic species is observed. By utilizing all three quadrupoles in the mass spectrometer a tandem mass spectrum can be recorded by separation of a specific ion (in Q1) that will undergo secondary fragmentation when colliding with gas molecules in Q2. The fragments are analyzed (in Q3) and an MS/MS spectrum is obtained, which makes it possible to deduce a structural proposition (Figure 10). A proposed structure for palladium complex B2 was constructed by observing the loss of neutral fragments from the mother ion (m/z = 446). The somewhat surprising elimination of toluene, although only a tolyl group is attached to the palladium center, is not unheard of when benzylic hydrogens are located close by. The large signal at m/z = 224 is not believed to originate from the B2 mother ion, as it was not visible when the tandem mass spectrometry spectra were recorded for other palladium isotopes than 106Pd.

![Figure 10](image)

Proposed structures of all palladium-containing peaks were deduced using MS/MS and the results are presented in Table 6. The different complexes are labeled according to where in the catalytic cycle in Scheme 16 they could be fitted.

**Initial Pd(II) complexes (A):** Three different dmphen- and acetate-coordinating palladium species of class A were detected. The coordinatively unsaturated complex A1 is probably formed by in-source collision-induced dissociation of the 16-electron complex A3. Monoligated A2 was the complex with the lowest intensity of all observed palladium species.

**Aryl-Pd(II) complexes (B):** Potential transmetallation intermediates bidentately bound to dmphen could be distinguished by MS/MS. The major complex fully ligated B2, whose MS/MS spectrum is illustrated in Figure 10 as previously discussed, is almost identical to the MS/MS spectrum of B1 except that a solvent molecule must first dissociate from B2.
Table 6. Singly charged cationic palladium(II) complexes detected in the standard oxidative Heck reaction using ESI-MS-(+) analysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>m/z&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pd(II) Complex&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>373</td>
<td><img src="image1.png" alt="image" /> A1</td>
</tr>
<tr>
<td>2</td>
<td>455</td>
<td><img src="image2.png" alt="image" /> A2</td>
</tr>
<tr>
<td>3</td>
<td>581</td>
<td><img src="image3.png" alt="image" /> A3</td>
</tr>
<tr>
<td>4</td>
<td>405</td>
<td><img src="image4.png" alt="image" /> B1</td>
</tr>
<tr>
<td>5</td>
<td>446</td>
<td><img src="image5.png" alt="image" /> B2</td>
</tr>
<tr>
<td>6</td>
<td>613</td>
<td><img src="image6.png" alt="image" /> B3</td>
</tr>
<tr>
<td>7</td>
<td>516</td>
<td><img src="image7.png" alt="image" /> or  C1</td>
</tr>
<tr>
<td>8</td>
<td>538</td>
<td><img src="image8.png" alt="image" /> F1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reported m/z values are based on $^{106}$Pd. <sup>b</sup> Structures supported by MS/MS-(+) analysis.
An interesting feature, observed when the intensities of complexes from class A and B were compared over time, was that A1 and A3 increased throughout the reaction, while the B complexes displayed decreased intensity. This trend may be the result of the continuous consumption of arylboronic acid during the reaction, making the transmetallation step slower.

Pd(II) complexes (C): Despite considerable effort, it was not possible to propose an unambiguous structure for C1. There are two possibilities: either the olefin coordinates to the arylated Pd(II) species as in a π-complex (Cπ in Scheme 16) or it has been inserted and formed a σ-complex (Cσ in Scheme 16). Both complexes have identical m/z ratios and in the MS/MS spectrum the dissociation of both olefin and product can be observed. It is known that CID can bring about β-elimination, thus both options are possible. However, it was possible to exclude a third possibility, namely a π-complex of class D (Scheme 17), which also has the same m/z ratio as Cπ and Cσ. The reason why complex D can be ruled out lies in the observation of olefin dissociation in the MS/MS spectrum. The elimination step from Cσ to D (step IV in Scheme 16) is, however, considered irreversible since a carbon-carbon bond is formed. Palladium hydrides are rarely identified during the course of a catalytic Heck reaction. 

Pd(II) complex (F): Complexes of class F are not mentioned in Scheme 16, but complex F1 will be dealt with because it is related to the oxidative Heck reaction in the sense that it is a precursor to a frequent by-product. F1 will form bitolyl, a Suzuki-type by-product known to be formed in the oxidative Heck reaction in small amounts, upon reductive elimination. The proposed structure was supported by the similar dissociation chemistry to that of complex B2, even though it was not possible to distinguish between the cis- and the alternative trans-isomer.

4.2.2 Chemical Verification
To further support the proposed identity of the observed complexes in the standard reaction, a series of additional reactions was conducted. In each reaction one component of the standard reaction was replaced by a chemically equivalent one (Scheme 18 and Table 7), which would deliver analogous Pd(II) complexes, but a different m/z ratio, compared to the corresponding complex in Table 6. Each reaction was monitored by ESI-MS(+) and scanned for the expected homologous Pd(II) species (proposed structures presented in Table 7) to verify that the investigated complexes (A–C and F), with their proposed identity from the first round, were as expected and furthermore, exhibited the correct corresponding dissociation pattern in MS/MS spectra.

Validation of initial Pd(II) complexes (A): The structures of complexes A1–3 were validated by employing bathocuproine (3f), instead of dmphen
(3e) as ligand. The 152 g/mol heavier dmphen derivative 3f furnished product 12a in comparable yields (Table 5, 63% entry 1 and 55% entry 4) with full internal selectivity. When the peaks of the new complexes of class A (with a higher m/z ratio of 152 units) were analyzed by tandem MS they showed almost identical dissociation patterns to the original ones (A1 and A3), except complex A2, which was not observed. The disappearance of complex A2 was not surprising, since the intensity of the peak was low even with dmphen (3e), and certainly did not gain in intensity when the more bulky ligand 3f was employed.

Table 7. ESI-MS(+) detected singly charged cationic complexes in oxidative Heck reactions using homologous reaction components

<table>
<thead>
<tr>
<th>Entry</th>
<th>Standard Pd(II) complex</th>
<th>Homolog</th>
<th>Pd(II) complex</th>
<th>m/z</th>
<th>Entry</th>
<th>Standard Pd(II) complex</th>
<th>Homolog</th>
<th>Pd(II) complex</th>
<th>m/z</th>
</tr>
</thead>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>A1</td>
<td>3f</td>
<td>A1'</td>
<td>525</td>
<td>10</td>
<td>C1</td>
<td>3f</td>
<td>or</td>
<td>668</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>C1'</td>
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<tr>
<td>2</td>
<td>A3</td>
<td>3f</td>
<td>A3'</td>
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<td>11</td>
<td>C1</td>
<td>2f</td>
<td>or</td>
<td>544</td>
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<td>C1''</td>
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<td>B1</td>
<td>3f</td>
<td>B1'</td>
<td>557</td>
<td>12</td>
<td>C1</td>
<td>1d</td>
<td>or</td>
<td>558</td>
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<td>C1''</td>
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<tr>
<td>4</td>
<td>B1</td>
<td>1d</td>
<td>B1''</td>
<td>447</td>
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<tr>
<td>5</td>
<td>B2</td>
<td>3f</td>
<td>B2'</td>
<td>598</td>
<td>7</td>
<td>B2</td>
<td>EtCN</td>
<td>B2''</td>
<td>460</td>
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<td></td>
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<tr>
<td>6</td>
<td>B2</td>
<td>1d</td>
<td>B2''</td>
<td>488</td>
<td>13</td>
<td>F1</td>
<td>1d</td>
<td>F1'</td>
<td>622</td>
</tr>
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<td></td>
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<tr>
<td>7</td>
<td>B2</td>
<td>EtCN</td>
<td>B2'''</td>
<td>917</td>
<td>14</td>
<td>F1</td>
<td>EtCN</td>
<td>F1''</td>
<td>552</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>8</td>
<td>B3</td>
<td>3f</td>
<td>B3'</td>
<td>655</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>B3</td>
<td>1d</td>
<td>B3''</td>
<td>655</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

48
Validation of aryl-Pd(II) complexes (B): All of the complexes of class B (B1–3) contain dmphen (3e) and a tolyl group coordinating to Pd(II). The ligand 3f was used as a replacement and subsequent MS/MS analysis again supported the proposed structure by demonstrating homologous complexes B1′–B3′ (Table 7). To further establish the identities a second investigation was conducted in which arylboronic acid, p-tolylboronic acid (1d), used in the standard reaction, was replaced by the chemically equivalent p-(n-butyl)phenylboronic acid (1d). After MS/MS analysis, the observed peaks followed the expected dissociation pattern when subjected to CID. Finally, the structure of complex B2 was also evaluated by changing the solvent. When propionitrile was used instead of acetonitrile and the reaction mixture analyzed with MS, the mother ion B2′′′ had, as expected, a 14-unit higher m/z ratio, and subsequent daughter ion dissociation resulted in the expected pattern.

Validation of Pd(II) complexes (C): Complex C1 was investigated using the same replacement strategy as described above. Chemically equivalent arylboronic acid 1d and the ligand 3f were successfully employed, supporting the suggested C1 structure by forming complex C1′ and C1′′′ (Table 7), but an olefin analog was also required. The analog chosen was the slightly larger enamide N-vinylcaprolactame (2f), which produced almost identical yield and selectivity, but required increased reaction time (1 week, Table 5, entry 5, instead of 24 h). Although produced at a slower reaction rate, the potential reaction intermediate C1′′′ was easily recognized in the mass spectrum and the MS/MS analysis provided the expected results.

Validation of Pd(II) complexes (F): The last structure to be verified was that of the biaryl precursor, F1. The three variable components in the complex was replaced, one at a time, by a suitable homolog, such as ligand 3f, aryl group 1d and propionitrile as solvent. When the bathocuproine ligand (3f) was employed, no biaryl intermediate was observed, probably because of the increased steric bulk with two additional phenyl groups. Unfortunately, this feature did not lead to increased main product formation (Table 5, entry 4), since the olefin and not the boronic acid was yield determining. The MS/MS-(+) dissociation patterns of the two remaining complexes (F1′ and F1′′′) were easily interpreted due to the rapid loss of coordinating aryl and solvent molecule, resulting in the characteristic daughter ion of Pd(II)-dmphen complex (m/z = 313).
5 Ultrafast Cobalt Carbonyl-Mediated Carboxylations (Papers III and IV)

The development of high-speed synthesis has for some years been a key issue in the pharmaceutical industry.\textsuperscript{135} New, fast functional group interconversions are always important in speeding up the optimization process.\textsuperscript{140} By utilizing controlled microwave irradiation together with cobalt carbonyl (CO\textsubscript{2}(CO)\textsubscript{8}) two different ultrafast carboxylation reactions were developed in the present work. The metal carbonyl had a dual role as it acted both as a mediator of the reaction, as well as providing the required carbon monoxide in situ in the sealed system.

5.1 Synthesis of Diaryl Ketones

5.1.1 Background

Inspired by the pioneering work of Brunet\textsuperscript{129,130} who produced diaryl ketones from aryl iodides (Scheme 10), the aim of the present work was to find a convenient and robust in situ carboxylation procedure for the synthesis of benzophenones, and also to optimize the reaction regarding reaction rate, aiming to accelerate the transformation as much as possible. Like in Brunet’s reactions, aryl halides were utilized, but phase-transfer conditions, a strong base, a carbon monoxide atmosphere or 24 h reaction time were not required.

The benzophenone moiety contains a common framework, considered in medicinal chemistry to be a “privileged structure”, which is able to provide ligands for various receptors.\textsuperscript{196} This feature of diaryl ketones makes them an important moiety for high-throughput library synthesis in medicinal chemistry.

\[
\begin{align*}
\text{ArI} & \xrightarrow{\text{Co}_2(\text{CO})_8, \text{CH}_3\text{CN}} \text{Microwaves, 10 s, air} \nonumber \\
13a-j & \text{Ar} \text{ Ar} \nonumber \\
& 14a-j 
\end{align*}
\]

\textit{Scheme 18.} Synthesis of Diaryl Ketones employing aryI iodides.
5.1.2 Results

The synthetic procedure for this coupling was very convenient. Aryl iodide (0.6 mmol, 1 equiv), cobalt carbonyl (0.66 equiv) and dry acetonitrile (3 mL) were added to a microwave transparent glass vessel under air before it was sealed and exposed to microwave irradiation (300 W) for 6–10 s using a commercially available batch reactor (Scheme 18). The powerful irradiation of the sealed vessel produced a high pressure and thus, overheating of the reaction mixture was possible.

Table 8. Ultrafast generation of benzophenones under air in sealed vessels

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl iodide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13a</td>
<td>14a</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>13b</td>
<td>14b</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>13c</td>
<td>14c</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>13d</td>
<td>14d</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>13e</td>
<td>14e</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>76&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>75&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>13f</td>
<td>14f</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>13g</td>
<td>14g</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>13h</td>
<td>14h</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>13i</td>
<td>14i</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>13j</td>
<td>14j</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>13k</td>
<td>14k</td>
<td>&lt;5&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Aryl iodide (13, 0.6 mmol, 1 equiv), Co<sub>2</sub>(CO)<sub>8</sub> (0.66 equiv) in acetonitrile (3 mL) and exposed to microwave irradiation for 10 s. <sup>b</sup> Isolated yield based on 13 (>95% purity of 14 established by GC-MS). <sup>c</sup> 6 s of microwave irradiation. <sup>d</sup> Performed with a pre-heated oil-bath (oil temperature 140 °C) for 2 min using an open reaction vessel. <sup>e</sup> Not isolated, less than 5% according to GC-MS.
The starting aryl iodides were chosen so as to cover aspects such as being electron-poor and electron-rich, sterically demanding, and containing potentially reactive functional groups and heteroaromatics. All reactions underwent full conversion and furnished good to excellent isolated yields (78–97%), except for the sterically hindered 13b (60%, Table 8, entry 2) and electron-rich 13a (57%, Table 8, entry 1), mainly due to competing dehalogenation. The parent compound 13e was further optimized regarding irradiation time, down to 6 s, with maintained yield (Table 8, entry 5). Dihalo-genated 13g showed proof of good chemoselectivity while only the iodine, and not the chlorine, reacted with Co2(CO)8 to form a benzophenone with two intact reactive tags. The heteroaromatic compound 13d underwent very efficient coupling (96%), while the pyridine-based 13k did not produce more than trace amounts of product.

In general, no large amounts of by-product were formed, but the trend was for benzil to be the most common one, except with electron-poor aryl iodides, which tended to form trace amounts of homocoupled biaryls.

Aryl bromides were also tested as substrates, but provided a much more sluggish reaction with no consistency regarding irradiation time, amount of Co2(CO)8 or temperature. No general protocol could be obtained and the two substrates that actually produced benzophenones furnished unsatisfactory yields (43% and 64%, Scheme 20).

Mottram et al. recently applied this cobalt carbonyl-mediated benzophenone synthesis in the construction of fluorophores, working as molecular probes in studies of cellular biology, obtaining excellent yields (96%) with tetra-substituted aryl iodide.198

**5.1.3 Mechanistic Discussion**

Brunet et al. suggested that benzophenone formation proceeds through a radical S_{RN}1-like reaction.130 Cobalt carbonyl might act as an initiator by homolytic cleavage of Co2(CO)8 into two Co(CO)₅ radicals that are detected at higher temperatures.199,200 I am tempted to agree with Brunet that the reaction might occur via a radical pathway, especially since the addition of radical scavengers, such as nitrobenzene, completely inhibited the reac-
tion. Furthermore, when 1.3 equiv of TEMPO, another scavenger, was added the yield was reduced to less than 10%.

The cobalt carbonyl reagent has a dual action; it is able to both mediate the coupling of the building blocks, and also deliver the carbon monoxide that will form the carbonyl. Homolytic cleavage would generate two equivalent cobalt carbonyl radicals; thus a stoichiometric reaction would require at least 0.5 equiv of Co$_2$(CO)$_8$. Interestingly, when 0.35 equiv Co$_2$(CO)$_8$ was employed in the synthesis of 14f the reaction went to full conversion of 13f and a high yield was observed (91%). When 0.3 equiv Co$_2$(CO)$_8$ was used it resulted in an incomplete reaction, maybe because of insufficient availability of carbon monoxide. Possibly, the catalytic coupling is hampered by the continuous release of carbon monoxide, which might explain why the number of turnovers is so low. To investigate the importance of the accumulated carbon monoxide atmosphere in the closed vessel and the need for microwave irradiation, the reaction was also conducted under open-vessel conditions using an oil-bath as heating source (140 °C). The reaction required a longer heating time (2 min) for full conversion, but the yield remained fairly high (75% compared to 78%, Table 8, entry 5). This indicates that the carbon monoxide released does not participate directly in the reaction.

After a screening of different solvents it was found that acetonitrile and propionitrile were superior to the other tested solvents (benzene, THF, DMF and DMAc). These results imply that the nitrile group is very important for the outcome of the reaction, perhaps because it coordinates to cobalt with the right strength to substitute carbon monoxide, but also easily dissociates. This is in line with a report from the mid 1980s by Pályi et al., describing the importance of nitrile solvents in Co$_2$(CO)$_8$ radical processes.

### 5.1.4 Microwave Acceleration

The obvious method to try when attempting to accelerate a chemical reaction is to employ high-density microwave irradiation produced by a dedicated microwave reactor. It is not uncommon for the reaction time to be reduced to 5 min, or even less. However, when transformation is completed in less than 10 s, it is important to be aware of how the microwave power is controlled by the microwave reactor.

The experiments performed were conducted in a Smith Microwave Synthesizer from Biotage. The initial heating is produce by a 2.5 s microwave pulse of maximum effect (300 W) before the IR temperature feedback system temporarily cuts off the irradiation. After about 2 s of computer-controlled calibration, the next heating period brings the reaction mixture up to the final temperature of around 130 °C. The microwave-producing magnetron is thereafter turned off and the reaction vial is cooled with a jet of air. The process is illustrated in Figure 11 in the form of a graph showing how temperature and pressure are related to reaction time using the standard 0.66
equiv of Co$_2$(CO)$_8$. A reaction loaded with 0.4 equiv of Co$_2$(CO)$_8$ was also conducted resulting in a slightly different profile. The temperature is measured using an IR sensor, based on the technique called IR pyrometry. This means that the temperature at the surface of the reaction vial is measured and not the internal temperature. Another aspect of this technique is that the response of the IR thermometer lags behind the actual reaction temperature, which is probably one reason why the temperature maximum in Figure 11 is shown a couple of seconds after the microwave irradiation has been turned off and cooling has started.

![Figure 11. Temperature, pressure and power profiles for the synthesis of 14e with 0.66 equiv Co$_2$(CO)$_8$ (A) (Table 8, entry 5) and 0.4 equiv Co$_2$(CO)$_8$ (B)](image)

Another explanation of the shifted temperature maximum could also be that an exothermic process is taking place after the external energy input has ceased. The amount of cobalt carbonyl seems to affect the shift in temperature maximum, as well as the amplitude of the maximum. When the reaction is run with only 0.15 equiv, or completely without Co$_2$(CO)$_8$, the maximum temperature is closer to the time at which irradiation was stopped (Figure 12). Significantly lower maximum temperatures are also obtained. This might be an indication of an exothermic reaction, but could just as well mirror the differences in the dielectric properties or the amount of ions in the reaction mixtures when they are charged with different amounts of cobalt carbonyl.

To conclude, I would like to point out that there were no indications that the microwave irradiation acted as anything other than a highly efficient heat
inducer. No non-thermal microwave-promoted processes, e.g. in the radical initiation step, are thus likely to have taken place.

Figure 12. Temperature, pressure and power profiles for the synthesis of 14e with 0.15 equiv (A) and 0.00 equiv (B) Co2(CO)8

5.2 Synthesis of Urea Compounds

5.2.1 Background

Urea compounds play an important role in the pharmaceutical industry as motifs in many active compounds, e.g. HIV-1 protease inhibitors. As a consequence, the development of efficient preparative protocols for such compounds is of fundamental value for synthetic research. Classical synthetic methods employ hazardous reagents such as phosgene and isocyanates, but there are also newer, safer methods using, e.g., carbonyldiimidazole or metal-catalyzed oxidative carbonylation under high-pressure carbon monoxide. With the aid of controlled microwave irradiation the hitherto little-developed, cobalt carbonyl-mediated, carbon monoxide-free, high-speed synthesis of both symmetrical and unsymmetrical urea compounds from primary and secondary amines has been improved.

5.2.2 Symmetrical Urea Formation

The protocol for the synthesis of different symmetrical urea compounds has many similarities to the benzophenone-forming methodology discussed in the previous section. Some examples of parallelism are that they both utilize Co2(CO)8 and microwave processing, and are carried out in sealed
microwave-transparent vessels under air with acetonitrile as solvent. As a consequence both transformations are very fast and the only difference is that primary amines 15 instead of aryl halides were used as substrates, and a base were needed in the synthesis of 16 (Scheme 21).

Scheme 21. Synthesis of symmetrical urea compounds employing primary amines

Each reaction in Table 9 was optimized with regard to reaction rate and yield, as that it was not possible to apply a general protocol. Most reactions resulted in full conversion of the amine 15 in 10–13 s at maximum microwave power (300 W), but when full conversion could not be achieved in such short reaction times, constant temperatures combined with longer irradiation times were used (to avoid over-pressurization of the sealed vessel). Constant temperatures were most often required when sterically hindered (Table 9, entries 8 and 9) or weakly nucleophilic amines (Table 9, entry 10) were employed. Unsubstituted aniline did not produce any urea at all, but needed an electron-donating group to increase the nucleophilicity and hence, be able to undergo the transformation. The best yields were, obviously, obtained when unhindered primary aliphatic amines, without competing functional groups, were used. The limited number of different functional groups present among the productive amines in Table 9 is probably a consequence of interfering interactions between cobalt and coordinating heteroatoms. Non-coordinating or weakly coordinating groups, such as ethers (Table 9, entries 4, 6 and 10) or alkyl fluorides (Table 9, entry 5) can exist on the amine. Other functional groups such as alkenes (Table 9, entry 7) or esters seem to disturb the process and thus, suffer from poor yields. Different solvents were tested with cyclohexylamine (15a) as substrate (Table 9, entry 1) and it was found that toluene and acetonitrile furnished identical yields, but when the two solvents were compared using ether-containing amine 15f, an apparent difference in isolated yields was observed, favoring acetonitrile. When comparing the heating profile for toluene and acetonitrile a clear distinction can be seen regarding their ability to absorb microwave energy. Acetonitrile has a relatively high capacity, whereas toluene, with its lower $\tan\delta$ value, has a considerably slower heating rate (Figure 13). Please note that the maximum temperatures also in these cases were reached after turning off the microwave power. This faster heating when the more polar solvent is used may be the reason why acetonitrile supports transformations
of a broader scope of amines. These results led to the choice of acetonitrile as the standard solvent.

Table 9. Microwave-assisted generation of symmetrical ureas from primary amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Time (s)</th>
<th>Temp (ºC)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15a</td>
<td>10</td>
<td>Variable</td>
<td>16a</td>
<td>84</td>
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<td></td>
<td></td>
<td>10</td>
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<td>Variable</td>
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<td>16d</td>
<td>66</td>
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<td></td>
<td></td>
<td>10</td>
<td>Variable</td>
<td>16j</td>
<td>46</td>
</tr>
</tbody>
</table>

* Employing 1.0 equiv amine, 0.66 equiv Co₂(CO)₈ and 2.0 equiv triethylamine in 2.5 mL acetonitrile. ¹ Variable temperature means: 300 W power for 2.5 s, 2 s pause, thereafter 300 W power. ² Isolated yield based on 15 (>95% purity of 16 confirmed by GC-MS). ³ DMSO as solvent. ⁴ THF as solvent. ⁵ Toluene as solvent. ⁶ Room temperature for 5 h. ⁷ 1.0 equiv of propylene carbonate added.

Sometimes when longer reaction times were applied (Table 9, entries 3 and 10) Co₂(CO)₈ was decomposed to inactive metallic cobalt. This problem was avoided by adding propylene carbonate to stabilize the system allowing the reactions to proceed to full conversion of the starting materials.
5.2.3 Mechanistic Discussion

During the optimization phase, the preparative outcome of selected long-time reactions was monitored over time by GC-MS. In entries 1, 3 and 10 (Table 9) small amounts of isocyanate were observed throughout almost the whole duration of the reaction. This information provided insight into the possible mechanism behind urea formation. The highly reactive isocyanate were interpreted as an intermediate, which when it has formed reacts with an amine or, alternatively, undergoes self-condensation producing the urea compound (Scheme 22). Attempts to synthesize symmetrical ureas from secondary amines did not yield any product, which was expected, based on secondary amines inability to form isocyanates. To further substantiate the isocyanate route, the synthetic credibility was investigated by allowing amine 15a to react directly with free isocyanate 17a. The reaction was swift and clean when the isocyanate was added slowly to a stirred solution of cyclohexylamine (15a) in acetonitrile to produce the corresponding urea 16a with 93% isolated yield.

\[
\begin{align*}
\text{R-} & \text{NH}_2 + \text{Co}_2(\text{CO})_8 & \rightarrow & \text{R-N(CO)}_2 & \rightarrow & \text{R-NH} - \text{NH} \\
15 & & & 17 & & 16
\end{align*}
\]

Scheme 22. Proposed mechanism for urea formation with isocyanate 17 as key intermediate.
In contrast to the above proposed mechanistic path, Hong et al. have suggested an alternative mechanism, based on Co$_2$(CO)$_8$-mediated urea formation from methylamines, utilizing DFT calculations. The results, displayed in Scheme 23, are in line with previously presented mechanistic proposals.

Scheme 23. DFT-based proposed mechanism for urea formation using primary amine and Co$_2$(CO)$_8$ by Hong et al.

5.2.4 Unsymmetrical Urea Formation

Conventional methods of synthesizing unsymmetrical urea compounds often involve isolated isocyanates or solid-supported reactants (pseudodilution). As expected, when two different primary amines were used in the standard protocol it resulted in a mixture of symmetrical and unsymmetrical products. The suggested mechanism of primary amines forming isocyanates as intermediates, motivated the development of a new protocol for the generation of unsymmetrical urea compounds, utilizing the inability of secondary amines to be transformed into isocyanates. A primary amine was therefore mixed with an excess of secondary amine to allow the isocyanate to be trapped by a secondary amine as soon as it was formed. However, in the attempt to transform theory into practice the ultrafast microwave-accelerated protocol furnished unsymmetrical ureas at disappointingly low isolated yields 35–55% (Table 10). This might be an indication that urea formation is not proceeding through the previously suggested isocyanate route.
**Table 10.** Microwave-heated generation of unsymmetrical ureas from primary and secondary amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amines</th>
<th>Time (s)</th>
<th>Product</th>
<th>Yield(^d) (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>15a + HN((\beta)-Pr)(_2) + 18a</td>
<td>10</td>
<td><img src="image" alt="19a" /></td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25(^c)</td>
</tr>
<tr>
<td>2</td>
<td>15a + HN((\beta)-Pr)(_2) + 18b</td>
<td>10</td>
<td><img src="image" alt="19b" /></td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>15b + 18a</td>
<td>10</td>
<td><img src="image" alt="19c" /></td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>15f + 18a</td>
<td>10</td>
<td><img src="image" alt="19d" /></td>
<td>41</td>
</tr>
</tbody>
</table>

\(^a\) Employing 1.0 equiv primary amine, 5.0 equiv secondary amine, 0.66 equiv Co\(_2\)(CO)\(_8\) and 2.0 equiv triethylamine in acetonitrile. \(^b\) Isolated yield based on 15 (>95% purity of 19 confirmed by GC-MS). \(^c\) Performed under 20 min of microwave irradiation at 130 °C.
6 Concluding Remarks

The present work has contributed to the field of palladium(II)-catalyzed carbon-carbon bond-forming reactions. It was demonstrated that air could be employed as a reoxidant and that the reaction could be conducted at ambient temperature. Furthermore, in the field of high-throughput chemistry, two different ultrafast protocols utilizing dicobalt octacarbonyl were developed for the generation of benzophenones and urea compounds.

The specific conclusions are summarized below.

- Palladium(II)-catalyzed oxidative Heck reactions can be performed at room temperature with air as sole reoxidant, which makes the reaction greener, in the sense that it is more energy efficient and user-friendly.

- A general and robust protocol was developed which successfully couples a wide range of olefins and arylboronic acids.

- A ligand screening revealed that inexpensive 2,9-dimethyl-1,10-phenanthroline (dmphen) is a highly efficient ligand in oxidative Heck reactions. This bidentate nitrogen ligand improves regioselectivity for electron-rich olefins and is also believed to facilitate the reoxidation process.

- Potential oxidative Heck reaction intermediates were observed in an active catalytic system using ESI-MS and were identified by tandem MS. The results increase the plausibility of the proposed cationic catalytic cycle.

- Dicobalt octacarbonyl can act both as an in situ carbon monoxide supplier and a reaction mediator when utilizing a user-benign, microwave-heated protocol in the synthesis of benzophenones and urea compounds.

- With the aid of Co$_2$(CO)$_8$ a wide range of aryl iodides can be transformed into symmetrical diaryl ketones by 6–10 s of microwave irradiation.
With microwave irradiation lasting 10 s–40 min dicobalt octacarbonyl can transform primary amines into symmetrical urea compounds. In addition, when secondary amines are used in excess, together with a primary amine, it is possible to obtain unsymmetrical ureas in 10 s.
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