New aspects of palladium-catalysed carbon-carbon bond formation reactions
Boele, M.D.K.

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CHAPTER 1

General Introduction

1.1 Catalysis

One of the most challenging problems being faced by the chemical industry nowadays is to meet the worldwide growing need for chemical products in a responsible and sustainable manner. The growing environmental burden that this increase in demand poses, necessitates the development of alternative, 'green' production methods. In this context, 'green chemistry' can be described as chemical conversions that consume a minimal amount of energy and resources, and produce the least waste. One of the key solutions to this problem is catalysis.

So far, heterogeneous catalysis has played a major role in the oil processing industry, because of the general robustness of the catalysts and easy separation of the products from the catalyst. Homogeneous catalysis can in many views be regarded as being complementary to its heterogeneous counterpart, since the generally better mechanistic understanding of the catalytic cycle allows the catalysts to be tailored to the particular problem involved. In transition metal catalysis, change of the ligand environment of the metal centre by rational fine-tuning of the steric and electronic properties of the ligands can result in the desired catalytic reactivity and selectivity. For this reason, the field of homogeneous catalysis (together with that of organometallic chemistry) has been experiencing a rapid growth during the last decades.

1.2 Catalysis in Fine-Chemical Synthesis

Some huge break-throughs have been accomplished in the application of homogeneous catalysts in large-scale chemical processes, e.g. the polymerisation and hydroformylation of olefins. However, its potential also lies in the field of specialty- and fine-chemical synthesis, where the production of high-value intermediates and products in high purity easily justifies the need for flexible, tailor-made catalyst development. Conventional synthetic routes often consist of a large number of reaction steps, each one with its own atom economy, selectivity and waste production. The use of homogeneous catalysis can in many cases reduce the number of steps that is required for the synthesis, lower the energy consumption and amount of resources needed, and give higher yields to the desired product. An example is the development of the Heck reaction, which is a mild
catalytic method for functionalising aromatic compounds. This Heck type chemistry can replace the older Friedel-Crafts alkylation, which requires harsh conditions and the presence of a large excess of aluminum reagent that ultimately ends up in a large amount of salts. In the classic form of the Heck reaction, only an equimolar amount of halide side-product is formed, reducing the waste-stream considerably. Of course, a further reduction of this amount of waste is desirable and much research effort is being devoted to this problem.

*Enantioselective* homogeneous catalysis undoubtedly has evolved to one of the most important fields in modern chemistry. The demand for enantiomerically pure compounds in fine-chemical synthesis will continue to show rapid growth in the future. Because of the ability of a small amount of designed catalyst to pass chirality to a large amount of substrate into chiral product with high reactivity and (enantio)selectivity, chiral transition metal catalysts are among the most promising candidates. This importance has recently been illustrated by the 2001 Nobel-prize for chemistry, which has been awarded to Knowles, Sharpless and Noyori for their work on asymmetric catalysis.\[4\]

### 1.3 Palladium-catalysed C-C Bond Formation Reactions; Cross-coupling Chemistry

#### 1.3.1 General Aspects.** Catalytic transformations in which a new carbon-carbon bond is formed are of huge importance in many fields of chemistry, since they allow the building of more complex compounds from simple precursors. In the past 30 years, many transition metals have been found that catalyse this type of transformations. Among them, palladium is the most versatile. Examples of reactions that are palladium-catalysed include the carbonylation of alkenes, the allylic alkylation, the co-polymerisation of alkenes and CO, the hydroarylation, cross-coupling reactions, the Heck

![Scheme 1](image)

**Scheme 1.** Schematic representation of the generally accepted catalytic cycle in cross-coupling reactions.
reaction, the 1,4-addition to dienes, etc. The amount of literature that has been published within these areas is huge. A recent literature search (July 2002) in the SciFinder database for "palladium-catalysed C-C bond formation" resulted in close to 10,000 hits. The actual number of papers involved is likely to be much larger. The work described in this thesis will mainly focus on palladium-catalysed C-C bond formation reactions that occur through a cross-coupling- or closely related mechanism. Since excellent and extensive reviews and books on these topics appear regularly, this introduction will only cover the main aspects of the reactions of interest, together with several important recent highlights.

1.3.2 Cross-coupling reactions. The various cross-coupling reactions catalysed by palladium complexes (or the closely related nickel analogues) in most cases proceed via a similar general mechanistic pathway (see Scheme 1). This catalytic cycle can be divided into three main elementary processes, which are (i) oxidative addition of an electrophile, typically an organic halide or triflate to a 14 electron Pd(0) species to form the corresponding Pd(I)(organyl) complex, (ii) transmetalation of an (organometallic) nucleophilic coupling partner to this complex and (iii) reductive elimination to yield the cross-coupling product together with the starting Pd(0) complex that can re-enter the catalytic cycle. Cross-coupling reactions are usually classified according to the nature of the organometallic substrate applied and often named after their discoverers. The most important examples include the Grignard cross-coupling (or Kumada coupling, M = Mg), \[ \text{Suzuki-} (M = B) \]\[ \text{Stille-} (M = Sn) \]\[ \text{and the Negishi reaction} (M = Zn). \]

1.3.3 Substrates. An extremely wide variety of organic electrophiles can be applied in cross-coupling reactions. Usually, aryl and vinyl iodides and bromides are employed, but other leaving groups, e.g. triflates, can also be used. Often, the order of reactivity found for aryl substrates ArX is \( I > OTf \geq Br > Cl \) which roughly reflects the ease of cleavage of the C-X bond. Unfortunately, the more reactive aryl iodides and triflates are less widely available and more expensive than the corresponding bromides and especially chlorides. Moreover, on a weight basis, chlorides are most attractive in the perspective of 'green' industrial chemistry. Therefore, much effort has been devoted to the development of catalysts that enable the conversion of chloride substrates under mild conditions (vide infra). Aliphatic halide-substrates are less suitable for cross-coupling reactions, since extensive side-reactions from the unstabilised (σ-alkyl)Pd complexes, e.g. β-hydride elimination or homolytic cleavage of the metal-carbon bond, usually occurs. However, improved yields in the application of sp\(^3\)-hybridised halides have been reported recently by several research groups.

The scope on the side of the organometallic substrates is also very broad. The reactivity within the series of the most widely used reactants usually follows the order Mg > Zn > Sn > B. This trend can be explained in terms of decreasing polarity of the metal-carbon bond, diminishing the actual nucleophilicity of the organic fragment. In addition, the decreasing thermodynamic driving force of the salt formation plays a role. The less reactive nucleophiles have the advantage of a broader
functional group tolerance and higher chemoselectivity in the reaction and are easier to handle due to their higher stability towards both hydrolysis and oxidation. However, because of the diminished reactivity they often require relative long reaction times and high temperatures.

1.3.4 Influence of the Metal. Palladium catalysts are generally more chemo- and stereoselective and have a wider scope in the organic substrates that can be coupled than the corresponding nickel complexes. The main advantage of nickel is its higher reactivity towards the organic electrophile, enabling for example the facile activation of aryl chlorides. Combined with the much lower catalysts costs, this feature makes nickel an attractive alternative for larger-scale industrial applications of cross-coupling reactions. On the other hand, the much larger diversity of palladium generally more than counterbalances the advantageous properties of nickel. Hence, in most studies concerning cross-coupling reactions, palladium is applied as the metal catalyst.

1.3.5 Ligand Effects. An extremely important factor in determining the course of the reaction using a metal catalyst are the ligands employed. With the development of tailored ligands the reactivity, selectivity and stability of the catalysts have been greatly improved, although not in every case the origin of the observed effects is completely understood. Important characteristics of the ligand that influence the metal centre and therefore the outcome of the reaction are the electronic and steric properties. For bidentate diphosphines, the bite angle (the P-M-P angle) that is enforced by the ligand also can have a pronounced influence on the course of the catalytic reaction. A problem inherent to a catalytic cycle is that accelerating a specific step in the cycle by adjusting the ligand properties retards one of the other elementary steps. A fast catalyst therefore should preferentially show similar rates for each elementary step of the cycle. Some general, important ligand effects on individual steps in the catalytic cycle of palladium-catalysed cross-coupling reactions will be discussed shortly below.

The oxidative addition probably forms the most extensively studied elementary step in cross-coupling chemistry. A lot of mechanistic insight has been gained by investigation of stoichiometric reactions of numerous organic halides and Pd(0)-precursors. From these studies, it can be concluded that the rate of oxidative addition generally increases upon the use of electron-donating ligands together with an electron poor organic halide fragment. Furthermore, the bite angle plays an important role, as shown by Milstein and co-workers. They found that the oxidative addition is faster with decreasing bite angle. Other factors can also have a large influence on the course of the oxidative addition by radically changing the preferred coordination modes of the ligand(s) in the complex. However, it should be noted that stoichiometric studies can deliver incomplete pictures of the true catalytic reactions in many cases, as they often do not take into account other substrates and counterions that are present during the catalysis. The latter, for instance, can coordinate to low-ligated palladium species, giving rise to alternative reactive anionic complexes.
The next step in the catalytic cycle, the transmetallation, is more difficult to study. For monodentate ligands evidence has been collected in favour of a dissociative pathway, in which a vacant site for the nucleophile is created by the decomplexation of one of the ligands from the Pd(II) complex. However, cases with associative or multiple pathways within one system have also been reported. To date, a systematic study of ligand effects on the transmetallation step has not been performed.

The reductive elimination can be regarded as the reverse of the oxidative addition step, which implies that the ligand effects should follow opposite trends. In fact, this is what is observed for the bite angle trend; the rate of reductive elimination increases with a larger P-M-P angle. When the bite angle becomes too large, the ligand coordinates in a trans fashion, and the complex resists reductive elimination. It has been shown that upon addition of excess alkyl halide these trans complexes may undergo facile reductive elimination, suggesting a mechanism which involves Pd(IV) species formed after oxidative addition to the starting Pd(II) complex. An alternative mechanism based on intermolecular exchange of the organic groups has also been proposed.

For different ligand systems both dissociative mechanisms and direct elimination from a four-coordinate species have been suggested. The course of the reductive elimination step is thought to proceed through a migratory mechanism, as opposed to a concerted pathway in which both Pd-C bonds are simultaneously broken.

From the above, it will be clear that the exact mechanism of cross-coupling reactions is not always straightforward and may differ from case to case, depending strongly on the substrates and ligands used.

1.3.6 Recent Advances. The number of reports on ligand variations in cross-coupling reactions is huge and still rapidly increasing. In the first studies, simple monodentate phosphine complexes, e.g. Pd(PPh₃)₄ or Pd(OAc)$_2$ + PPh$_3$, were employed and these compounds still are among the first potential catalysts to be tested in a desired conversion. Bidentate P-P and N-N ligands have been applied later. The chelating properties of bidentate ligands often have beneficial effects on the stability and selectivity of the catalysts. Yet, most of these catalytic procedures

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\begin{align*}
\text{R} &= \text{o-tolyl, mesityl, t-butyl, cyclohexyl} \\
\text{X} &= \text{halide, OAc}
\end{align*}
\]

Scheme 2. General structure of Herrmann’s palladacycles.
require relatively high palladium loadings to achieve good conversions and show no or poor reactivity in the application of electron-rich aryl bromides or chlorides.

A major breakthrough concerning the scope of the substrates was the recent introduction of palladacycles derived from tris(o-tolyl)phosphine as catalysts by Herrmann et al. (see Scheme 2). These complexes were shown to be able to couple deactivated aryl bromides at unprecedentedly low palladium loadings. The extraordinary reactivity of this type of catalysts is believed to stem from the fact that the active Pd-species only has one phosphine coordinated to the palladium centre, leaving the metal in a coordinatively unsaturated state. Because of this unsaturation the intermediate metal complexes in the catalytic cycle display increased reactivity towards the substrates, resulting in high reaction rates. The palladacycles probably represent the stable resting state of the catalyst. These complexes are extremely stable, both thermally and towards air, enabling very high turn-over numbers to be reached. This type of catalysts represents one of the first examples of cross-coupling catalysts that have reached industrial application.

Later, other groups have reported on other metalated ligand systems that show similar or even improved reactivity and stability. Other related successful examples include pincer-type metal complexes. Still, the high temperatures required by these catalysts is a drawback.

More recently, the application of electron-rich alkylphosphines enabled the use of aryl chlorides as the electrophilic reactant. The strong electron-donating properties of these ligands result in a high electron-density on the metal centre, making the complex more reactive towards oxidative addition. When combined with steric bulk, thereby enforcing mono-coordination, these ligands can give rise to catalysts that give smooth conversion of chlorides at temperatures slightly above room temperature. A disadvantage of these ligand systems is their air-sensitivity, which makes their synthesis and handling quite difficult. It should be noted that, in contrast to what is commonly

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**Figure 1.** Examples of bulky, electron-rich phosphine ligands applied in cross-coupling reactions.

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**Figure 2.** Examples of N-heterocyclic carbene ligands.
assumed, palladium complexes with triaryl phosphine ligands do undergo oxidative addition of aryl chlorides. The high temperatures required for this process cause rapid ligand degradation through P-C bond cleavage and this makes this type of ligands unsuitable for the catalytic activation of aryl chlorides.  

Another milestone in cross-coupling chemistry is the introduction of N-heterocyclic carbene ligands, see Figure 2. These auxiliaries behave as strong $\sigma$-donors, in most cases even stronger than alkylphosphines. They show good stability towards air, are easy to prepare and can give rise to extremely high turn-over numbers ($>10^5$ in some cases) in the coupling of aryl bromides with various nucleophiles. Aryl chlorides can also be applied, albeit with less impressive TON’s, using both palladium and nickel. Recently, it was shown that selected carbenes even enable the oxidative addition of arylfluorides (which are the least reactive within the series of aryl halides) to Pd(0). These catalysts are claimed to have the potential to become a turning point in cross-coupling chemistry and organometallic catalysis in general.

1.4 The Heck Reaction

\[
\begin{align*}
\text{Scheme 3. General reaction scheme for the Heck reaction of aryl halides.}
\end{align*}
\]

1.4.1 General Aspects. The palladium-catalysed alkenylation of aryl- and vinyl halides, better known as the Heck (or Heck-Mizoroki) reaction (see Scheme 3), is closely related to the general cross-coupling chemistry, but it shows some important features that distinguish it from the other procedures. These characteristics will be discussed shortly here, together with the most important recent developments in this field.

![Figure 3](image-url)

**Figure 3.** Examples of industrially important products synthesised via Heck reactions.
The most important advantage of the Heck reaction, giving it enormous application potential, is the mildness of the reaction. Most functional groups remain intact under 'Heck conditions', whereas other methods often do not allow certain types of functionalities, e.g. in the Kumada coupling where Grignard reagents are employed. Heck reactions have found industrial application in the production of compounds such as a precursor to naproxen and of 2-ethylhexyl p-methoxy cinnamate, which is the most common UV-B sunscreen agent (Figure 3).

1.4.2 Scope. Since both the cross-coupling and Heck methodologies have the initial oxidative addition step in common in their mechanism (vide infra), they obey the same general rules for the halide substrates that are employed. The nucleophilic coupling partner in Heck chemistry is an alkene. In most cases, electron-poor alkenes react more readily and more selectively than electron-rich olefins. A wide variety of bases can be applied, ranging from inorganic salts to tertiary amines. Usually polar, non-protic solvents give rise to the highest conversions.

1.4.3 Mechanism of the Heck reaction. A generally accepted catalytic cycle of the Heck reaction is shown in Scheme 4. In this mechanism, the organic halide oxidatively adds to a Pd(0) species to give the corresponding Pd(II) complex. Next, the alkene coordinates to the palladium

Scheme 4. Schematic, simplified representation of the generally accepted 'classic' mechanism of the Heck reaction.
centre and subsequently inserts into the Pd-C bond to form a Pd(σ-alkyl) compound. In this step, the regioselectivity of the reaction is determined. After rotation of the C-C bond, syn β-H elimination takes place to yield the product alkene which dissociates from the metal centre. The resulting palladium hydride is then deprotonated by the base to give the starting Pd(0) species, which can re-enter the catalytic cycle.

1.4.4 Insertion and Regioselectivity. The insertion step in the Heck reaction is an important step, since the regioselectivity of the product is determined at this stage. For alkene coordination and subsequent insertion to occur in tetracoordinated Pd(II) complexes, ligand dissociation has to take place. Depending on the nature of the dissociating group, the reaction pathway is neutral (if a non-charged group dissociates from palladium) or cationic (or polar as suggested by some authors, if the leaving group is anionic, often the halide from the oxidative addition substrate).

![Scheme 5. Origin of regioselectivity in the insertion step in the Heck reaction.](image)

This nomenclature should be regarded as being purely formal, and does hardly reflect the actual electrophilicity of the Pd fragment. The π-complexed alkene has to rotate to an in-plane position before the insertion step can take place. This process may be seen as a concerted reaction pathway and is highly dependent on the electronic and steric demands of the substrates and ligands. Attempts to find a correlation between the cationic nature of the palladium complex and the regioselectivity in intermolecular Heck reactions have not resulted in simple absolute rules. However, some generalisations may be made. Electron-deficient olefins preferentially give rise to (1,2)-arylation, whereas electron-rich alkenes result in increased formation of the 1,1-substituted product. This selectivity reflects to some extent the relative stability of the two possible carbocations formed after formal electrophilic addition of cationic palladium to the double bond.
The electronic influence can nevertheless be overruled easily by steric factors. This latter aspect is demonstrated by the large influence the bite angle of bidentate diphosphines has on the regioselectivity of the Heck arylation, as shown by Hallberg and Akermark. Dppp and dppf usually give the highest proportion of 1,1-substituted product, while ligands with smaller bite angles direct the outcome of the reaction towards substitution at the terminal carbon atom (see Scheme 5). In intramolecular Heck couplings, steric factors also prevail. In a special enantioselective case studied by Overman, both cationic and five-coordinated neutral palladium complexes are proposed to be involved. Recently, a ($\pi$-alkyl)Pd-intermediate capable of $\beta$-H elimination formed after olefin insertion was actually isolated and characterised.

![Scheme 6](image_url)

**Scheme 6.** Stereoselectivity in the $\beta$-H elimination in the Heck reaction.

1.4.5 $\beta$-Hydride Elimination and Stereoselectivity. In the $\beta$-hydride elimination step the product alkene is generated and, after decomplexation, the palladium is reduced to Pd(0) and able to react with halide substrate to start a new catalytic cycle. Most experimental and theoretical studies support a concerted *syn*-elimination of the palladium hydride species. This step determines the stereoselectivity of the alkene product formed, and is likely to proceed without any involvement of the base present (which would mean an E2-type mechanism). In many cases, the *E*-isomer is formed predominantly, as the Pd(alkyl) species in the transition state with the aryl group and alkene substituent in *anti* configuration has the lowest barrier (assuming Curtin-Hammett conditions) (see Scheme 6). However, several examples exist in which the strength of the base is shown to have an important role in the stereoselectivity observed, implying a possible base-assisted hydride elimination. A complicating factor in these discussions is the possibility of product isomerisation before or after deprotonation of the Pd(H)(alkene) complex formed. Such an elimination/reinsertion sequence is believed to play an important role in certain enantioselective Heck arylations.

1.4.6 Alternative Mechanisms. Both ligand-free and ligand-containing palladium complexes are known to be capable of catalysing Heck reactions under the appropriate conditions. Most ligands employed are phosphines, which can be monodentate or bidentate, although chelating diphosphines were long regarded as poor ligands. Also tridentate pincer-type...
complexes\textsuperscript{[84, 85, 101, 102, 131]} and more recently even tetradeionate ligands\textsuperscript{[132]} have been reported to yield effective Heck catalysts. This broad ligand applicability raises the question whether the same mechanism is operative for all these ligands used. Especially in the case of bidentate (or higher hapticity) ligands and palladacycles it is unclear what the exact composition of the active palladium-species is. Shaw has proposed a Pd(II)-Pd(IV) mechanism to account for the observed activity of some systems, see Scheme 7.\textsuperscript{[133, 134]} In this reaction sequence, the alkene undergoes nucleophilic attack after complexation to Pd(II). After oxidative addition of the aryl halide to give a Pd(IV) complex, elimination of the nucleophile followed by insertion and subsequent $\beta$-H elimination yields the product. An alternative Pd(II)-Pd(IV) sequence was suggested by Jensen to account for the reactivity found for certain pincer-type catalysts.\textsuperscript{[135]} Tetravalent palladium species containing phosphorus donors have been observed and isolated in some cases.\textsuperscript{[136-138]} Still, the evidence in favour of a ‘classic’ Pd(0)-Pd(II) mechanism seems to be mounting as the mechanistic research progresses.\textsuperscript{[102, 139-141]}

As in the general palladium-catalysed cross-coupling reactions, major improvements have been reported recently in the activation of relatively unreactive substrates (e.g. aryl chlorides) and the

\begin{center}
\textbf{Scheme 7.} Alternative Pd(II)-Pd(IV) mechanism as proposed by Shaw.\textsuperscript{[134]}
\end{center}
increase in turn-over numbers. Many ligands that perform well in cross-coupling reactions also show promising features in the Heck reaction. Thus, auxiliaries that result in much more efficient catalysts are for example P(rj-Tol)- and palladacycles thereof (see Scheme 2). Bulky alkylphosphines \(^{41}\) (see Figure 1) and \(V\)-heterocyclic carbene complexes (Figure 2).

### 1.4.7 Other Recent Developments.

Many studies have been performed that focus on other aspects of the Heck catalysis, such as catalyst immobilisation and recycling. As in other fields of homogeneous catalysis, the use of molten salts (ionic liquids) in Heck reactions has experienced a rapidly growing popularity.\(^{124-126}\) These systems offer the advantage of easy separation of the product mixture without the occurrence of metal leaching. Furthermore, the ionic nature of the solvent has been found to have a beneficial effect on the stability of the catalyst. This might be caused by the increased polarity of the solution or the formation of anionic palladium complexes. Moreover, tetraalkylammonium salts are known to stabilise colloidal species that might also be present and function as catalytically active species. Indeed, 'ligand-free' palladium catalysts have been shown to result in efficient Heck reactions at higher temperatures.\(^{127-129}\) The exact nature of the species has not yet been completely resolved, but solutions of colloidal palladium nanoparticles are likely to be involved.\(^{130-132}\) Other alternative media that have been applied in Heck reactions include supercritical carbon dioxide,\(^{133-135}\) water,\(^{136-138}\) and biphasic reaction systems.\(^{139}\) Heterogenised catalysts have also been employed extensively.\(^{140}\) Although the palladium-catalyst is immobilised onto a certain solid support in these cases, strong indications exist that small amounts of catalytically active metal are present in the solution, thus resulting in actual heterogeneous catalysis. If redeposition onto the support occurs after the reaction or during work-up, no leaching of palladium is observed.\(^{141-143}\) Finally, papers have appeared recently in which the extension of 'standard' Heck reactions towards less usual reactants and catalysts has been shown. For example, ruthenium and rhodium catalysts have been applied, and several Heck type couplings involving heteroatoms have been reported.\(^{144-146}\)

Future developments will most likely involve further improvements on some of the themes mentioned briefly here together with many others. For example, new procedures strongly related to this type of catalytic chemistry have been reported recently, such as the palladium-catalysed C-N and C-O bond formation reactions as introduced by Buchwald and Hartwig.\(^{147-150}\) The design of new, active, stable, and selective catalysts will lead to efficient catalysis that is generally applicable and eventually to more processes that are economically and ecologically feasible.
1.5 Allylic Substitution Reactions

\[ \text{Nu} = \text{soft nucleophile, e.g. } \text{'CH(COOR)}_2, \text{NR}_3, \text{'PR}_2 \text{etc.} \]

Scheme 8. General reaction scheme for palladium-catalysed allylic substitution reactions.

1.5.1 General Aspects. Besides the above-mentioned cross-coupling and Heck chemistry, transition metal-catalysed allylic alkylation reactions also comprise an important and mild method for constructing new carbon-carbon bonds. Because of its enormous potential in synthetic organic chemistry, the reaction between allylic substrates and 'soft' nucleophiles (defined as bases derived from conjugate acids with $pK_a < 25$) has been the subject of intensive and detailed mechanistic studies. Since its first discovery by Tsuji[175] and Trost,[176] huge research efforts by many groups have resulted in generally applicable procedures for forming carbon-carbon or carbon-heteroatom bonds at allylic positions. From this research, palladium has emerged as the most versatile metal, although the number of alternative metals that can be employed is large. In general the rates and yields obtained using palladium catalysts exceed those obtained with other metals, although in some cases beneficial regio- and stereoselectivities are found for metal catalysts other than palladium.[177-181]

Scheme 9. General representation of the catalytic cycle in the palladium-catalysed allylic substitution using a soft nucleophile (Nu).
1.5.2 Ligand Effects. The type of ligands that can be employed in palladium-catalysed allylic alkylation reactions is virtually unlimited, with phosphorus and/or nitrogen donor atoms being most successful. The ligand properties have been shown to have an enormous effect on the rate and selectivity of the reaction by altering the steric and electronic environment of the Pd-allyl fragment on which the nucleophile attacks. This becomes an even more important factor when asymmetric allylic alkylation reactions are performed. Using soft nucleophiles, the nucleophilic attack takes place directly on the coordinated allyl species, and therefore outside the inner coordination sphere of the metal. This feature puts high demands on the chiral ligand, which has to "transfer" its chirality from the other face of the allyl moiety to the incoming nucleophile. In this respect, it is quite surprising that so many different ligands have been reported that give high enantoiselectivities in the alkylation of similar allylic substrates. Apparently, the substitution pattern of the allylic moiety plays an important role in determining the stereoselectivity of the reaction. Steric interactions between the chiral ligands and the allyl fragment during the course of the reaction cause enantiodiscrimination. This seems especially to be the case with large substrates, e.g. 1,3-diphenylallyl acetate, as most ligands that are successful with this substrate, fail when the large phenyl groups are replaced by smaller substituents. Excellent enantoiselectivities have been obtained using C₂ symmetrical bidentate diphosphines as illustrated by Trost et al. The observed stereoselectivities for these and other systems can often be explained by the concept of a 'chiral pocket'. Within this model, the chiral induction stems from the selective clockwise or anticlockwise rotation of the allyl moiety in this pocket upon nucleophilic attack to form the product η⁵-alkene complex. Alternatively, a mechanism involving an early transition state has been proposed in several studies. In this pathway, the outcome of the reaction is mainly determined by the electronic structure of the η⁵-allyl complex. The distinction between an early- or late transition state mechanism remains a matter of continuing debate and probably cannot be generalised.
More recently, other classes of ligands have been explored, with chiral phosphinooxazoline P-N ligands being most successful. The different trans influences of mixed donor atom-containing ligands offer the possibility of directing the site of nucleophilic attack in non-symmetrically substituted allyl substrates, and inducing enantioselectivity in the case of chiral ligands.

A similar influence on the selectivity can, at least in principle, be achieved by the use of monodentate ligands. The dissymmetry of the ligand environment in the Pd allyl complexes is then formed by coordination of the anion and the (chiral) ligand. This approach has not been explored often so far. This probably stems from the assumption that bidentate ligands can exercise a larger sterically influence by embracing the metal atom than monodentates and therefore better induce enantioselectivity at the face of the allyl moiety. More importantly, monocoordinated ligands lack the chelate effect, and as a result the rigidity of the chiral environment that the substrate encounters during the catalytic conversion is lower. When using monosubstituted allyl compounds in Pd catalysis, most systems predominantly give rise to nucleophilic attack on the less-substituted allyl terminus, resulting in linear, achiral product isomer formation. Therefore, ligands are required that show both good regioselectivity and a high level of enantiocontrol. One class of ligands that show promising properties are the so-called MOP-type ligands. These have been shown to induce excellent regio- and enantioselectivity in the allylic alkylation and allylic reduction reaction of allylic esters with formic acid (Scheme 10).

**Scheme 10.** Regioselectivity in allylic alkylation using monodentate MOP-type ligands.
1.5.3 Memory Effects. Another important aspect of Pd-allyl chemistry often observed when monodentate ligands are employed, is the existence of so-called memory effects. This can be described as the effect in which the regio- and stereochemical outcome of the reaction is dependent on the original structure of the allyl reactant; the product ratio formed is dependent on the substrate used, in spite of the fact that in the classical mechanism both starting compounds react through seemingly identical intermediates (see Scheme 11).

Hayashi described strong regiochemical memory effects when using Pd/MeO-MOP in the alkylation of 1-substituted 2-propenyl acetates and 1-deuterio-2-cyclohexenyl acetate. More recently, Kocovsky and coworkers reported stereochemical memory effects using both MOP and MAP ligands. MAP was shown to behave quite differently to MOP with respect to regioselectivity, but, surprisingly, both ligands displayed an unusual bidentate (P,C)-coordination mode (through the ipso carbon atom, see Scheme 10). These complexes exist as two diastereomeric rotamers which can interconvert. The relative rate of this equilibration is thought to play an important role in the memory effects observed.

Scheme 11. Schematic representation of the memory effect in monosubstituted substrates.

1.6 Aim and Outline of this Thesis

The research described in this thesis was sponsored by DSM Research and the Netherlands Ministry of Economic Affairs through an EET grant. The EET project aims at developing new technologies that are ecologically benign on an economically competitive basis. More in particular, the goal of this research project was the development of new, sustainable catalysts for the ‘green’ production of fine-chemicals. To this purpose, new transition metal complexes have been
developed in collaboration with DSM that serve as efficient catalysts in several selected carbon-carbon bond formation reactions. Mechanistic understanding of the reaction forms an important tool in this research, since a better insight into the details of the reaction mechanism can help the design of better catalysts through variation of the ligand and other reaction parameters now and in the future. The combination of fundamental and applied catalysis through collaboration of academia and industry can be of utmost importance for future developments.

In Chapter 2, the influence of the ligand bite angle in several Pd(diphosphine)-catalysed cross-coupling reactions is studied systematically. To this purpose, the geometry of the corresponding (P-P)Pd(H)-complexes has been investigated. These structures show some unexpected features, which can help to explain the observed trends and differences in their catalytic behaviour.

Focus is shifted from bidentate diphosphine ligands to a different class of ligands in Chapter 3: the bulky monodentate phosphoramidites. These show very high activity in the Heck reaction of aryl iodides. Kinetic studies indicate that this originates from the fast oxidative addition of the aryl halide, caused by the mono-coordination and electronic properties of these ligands. The active state of the catalyst is shown to be a monomeric species, whereas the corresponding dimeric form functions as the resting state of the catalyst.

Chapter 4 deals with the extension of the promising bulky phosphoramidites to chiral auxiliaries in asymmetric Heck reactions. The synthesis of several ligands based on chiral BINOL and TADDOL backbones is described. After ligand optimisation, good enantioselectivities can be obtained at high reaction rates in asymmetric intramolecular Heck reactions. The origin of the enantioselectivity is discussed in terms of a kinetic resolution mechanism.

A related reaction is described in Chapter 5: the asymmetric Suzuki reaction. The application of bulky chiral phosphoramidites is shown to give rise to very smooth coupling of naphthyl-substrates to yield axially chiral binaphthyls.

In Chapter 6 the applicability of the phosphoramidite ligands will be extended to another important C-C bond formation reaction: the allylic alkylation. The influence of the ligand structure on regio- and stereoselectivity will be presented, together with mechanistic considerations that can explain the observed memory effect and selectivities.

In Chapter 7 a novel catalytic reaction is described, that comprises the mild and selective oxidative functionalisation of substituted aromatic amide compounds with alkenes through a C-H bond activation mechanism. The reaction can be carried out in acidic media using Pd(OAc)$_2$ as the catalyst, while the amide group directs the reaction through selective ortho-activation by coordination to the palladium centre. This conversion brings a real waste-free Heck type coupling reaction a step closer. The scope of the procedure will be discussed, and it will be shown that the mechanism occurs through electrophilic aromatic substitution.
References


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[128] chapter 4 in this thesis.


[155] Phosphonium salts have been used; see for an early example: M. Sakamoto, I. Shimitzu, A. Yamamoto, Chem. Lett. 1995, 1101.


General Introduction