1 Introduction

1.1 Applied theoretical chemistry

The field of theoretical chemistry is evolving at an increasingly rapid rate. Significant in this development is the exponential increase of the available computing power. For example, the computing power available at the department of Theoretical Chemistry at the Vrije Universiteit, where the work for this thesis took place, has been expanded a number of times. At each increase, the newly installed capacity amounted to more computing power than had been cumulatively present up until that point in time. This increase in computing capacity has made it easier for many chemists to look at chemical reactions with the help of computational chemistry tools. However, as with many things, quantity is not the only important aspect. Above all, a chemist wants to understand why a chemical reaction happens, and be able to talk about this in a qualitative fashion. Many theoretical chemists have developed and employed various analytical tools in order to better understand chemical reactions from a theoretical perspective. This thesis is but one example in a rich history of theoretical investigations into chemical reactivity.

This thesis focuses on the subject of catalysis, in particular homogeneous catalysis (where the reacting species are dissolved in one medium) using palladium as a reducing agent. Although chemists throughout the world continuously progress to understand catalytic processes, it is still often difficult to rationalize the reactivity of catalytic agents. Even more difficult is actually predicting the reactivity of a proposed catalyst. A good number of catalytic compounds discovered are found by trial and error, which is of course not the desired way to practice chemistry. The above is true for many areas of chemistry, but is perhaps especially challenging in the field of homogeneous catalysis, in which the role of the various versatile ligand systems can become very complicated.

Through theoretical chemistry, however, we can hope to gain a better insight into the inner workings of reaction mechanisms. In this way, we can hope to expand and improve upon the ‘chemical intuition’ that chemists use to rationalize reactivity. The approach we adopt is one of a gradual increase of insight in the reaction mechanisms, starting from simple model systems. This strategy is previously outlined in earlier work.
as the ‘Fragment-oriented Design of Catalysts’,\textsuperscript{1,2} and focuses firstly on the intrinsic reactivity of model systems. On this we can expand by adding effects of ligands on the metal core, or the influence of changes in the substrates undergoing catalytic activation. This allows us to understand the changes in reactivity with relation to the core model system, and provide a more rational basis on which to design catalytic compounds to meet specific criteria for desired reactivity and selectivity.

1.2 Oxidative insertion of palladium

The 2010 Nobel Prize in Chemistry was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki “for palladium-catalyzed cross-couplings in organic synthesis”\textsuperscript{,3} The choice of the Nobel Prize committee could not have come at a better time regarding the subject of this thesis, and emphasizes the relevance of the work presented in this thesis! These cross-coupling reactions have become an important tool in modern chemistry, and still deserve all the attention they get from both experimental and theoretical perspectives. The theoretical work presented here tackles one of the fundamental reaction mechanism steps present in palladium-catalyzed cross-couplings: the oxidative insertion (in this thesis often abbreviated as ‘OxIn’, or alternatively: oxidative addition).

By now, it should not be surprising that the catalytic systems covered in this thesis are based on the transition metal palladium (Pd, see Figure 1.1). Palladium is considered a precious metal and is around twenty times more expensive than silver. The largest use of palladium nowadays is in catalytic converters, where, together with platinum and rhodium, it is the primary component that decreases vehicle exhausts emissions of hydrocarbons, carbon monoxides, oxides of nitrogen and other pollutants. Palladium is also widely used in jewelry, electronics, and as a component in alloys used for dentistry. Besides these applications palladium is, in many different forms, a widely used and versatile catalytic reagent in many different chemical processes.\textsuperscript{4} One other reason this thesis focuses on palladium is because it can serve excellently as the desired model system. The atomic ground state of Pd consists of a closed-shell $d^{10}$

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{Pd.png}
\caption{Palladium.}
\end{figure}
configuration, which facilitates comparison with more realistic transition metal complexes used in catalytic bond activation. Besides all that, the fact that palladium “won” the Nobel Prize also confirms that palladium oxidative insertion reactions are highly relevant in catalysis and a logical choice for investigation.

The main focus of this thesis is the oxidative insertion reaction, a key step, often rate-determining, in many catalytic cycles, in which a reactant (substrate) adds to a metal complex, forming the reactant complex (RC, see Figure 1.2).\textsuperscript{5-7} Since it is an important mechanism in catalytic reactions, numerous experimental\textsuperscript{8-15} and theoretical\textsuperscript{16-26} papers have appeared on this subject. This bond activation mechanism is also present in heterogeneous catalysis where, of course, interesting theoretical research can be found as well.\textsuperscript{27,28} In this step a relatively inert bond of the substrate is broken via a transition state (TS) and the electrons of this bond are formally transferred to the metal center, thereby oxidizing the substrate and forming the product (P). For example, if the C–Cl bond in chloromethane is activated by Pd this leads to the cleavage of the covalent bond between the methyl moiety and the chlorine atom. Simultaneously, two new bonds are formed in the resulting compound CH\textsubscript{3}−Pd−Cl. Because two previously non-bonding electrons of Pd have become involved in order to form these bonds, its formal oxidation state changes from Pd(0) to Pd(II). The formal character should be emphasized since the product should not be regarded as having a very strict internal charge separation of the type CH\textsubscript{3}−Pd\textsuperscript{2+}−Cl\textsuperscript{−}. The reverse reaction of oxidative addition is called reductive elimination; both processes are important in a large range of catalytic cycles.

Figure 1.3 shows a schematic example of a catalytic cycle: the aforementioned, Nobel Prize winning, cross-coupling reaction. Here, Pd(0) activates the aryl–X bond in the oxidative addition step, forming the Ar−Pd−X compound. After this, a substitution can occur by a nucleophile, followed by the reverse reaction of reductive elimination. In this step, the product of the catalytic cycle is formed, and simultaneously the catalytic compound Pd(0) is recovered. The first step in the cycle is primarily the breaking of the aryl–X bond, and is thus also often called the bond activating or
bond-breaking step. This bond-breaking step is the part of the catalytic cycle which this thesis focuses on, since it is often not only the rate-determining step, but also important in defining the selectivity of the catalytic process.

Important in the catalytic behavior of the central metal atom is the influence of the ligands. Different ligands can enhance or decrease catalytic activity, but can also steer its selectivity, both by influencing orbital energies and the steric properties of the catalytic compound. In many theoretical investigations the simple analogues of phosphine-based ligands are employed in the form of \( \text{PH}_3 \) ligands forming \( \text{Pd}(\text{PH}_3)_2 \). Another ligand that is routinely used in our investigations is anionic \( \text{Cl}^- \), which has the overall effect of lowering barriers. A recurring theme throughout this thesis will be the steric nature of the geometrical (bite and twist angle) features of phosphine ligand systems.

1.3 This thesis

As must be clear by now, this thesis concentrates on a theoretical investigation of palladium-mediated bond-activation reactions. This is done by investigating the intrinsic reactivity of palladium toward series of archetypal bonds, and similarly series of archetypal ligands. Before going into the detailed analyses of the reactions, chapter 2 will give a thorough overview of the model analysis that is employed in this thesis: the activation strain model. Correctly understanding this type of analysis is a fundamental aspect, and this thesis will hopefully aid those interested in learning more about the activation strain model. This chapter also introduces the fundamentals of Density Functional Theory (DFT), as well as the computational details of the ADF program that performs the DFT calculations.

Chapter 3 will introduce and investigate the concept of the ‘bite angle’; the ligand–metal–ligand angle in bidentate (and \( \text{PH}_3 \)-bisligated) systems. In the case of the analysis with palladium, phosphines are useful model ligands, and the bite angle becomes

![Figure 1.3 A schematic catalytic cycle including an oxidative insertion (OxIn) step of Pd into Ar–X.](image-url)
the P–Pd–P angle. Through a series of analyses we elucidate the steric nature of this bite angle, and also that of the related twist angle in the transition state geometry.

Chapter 4 and 5 will introduce a range of CR\textsubscript{3}–H and CR\textsubscript{3}–CR\textsubscript{3} bonds, with the CR\textsubscript{3} groups becoming increasingly sterically congested. The chapters analyze the effect of an increasing number of sterically hindering substituents that become especially interesting when the bond is fully saturated with these groups.

Chapter 6 and 7 focus on the series of simple second period bonds: H–AH\textsubscript{n} and CH\textsubscript{3}–AH\textsubscript{n} with AH\textsubscript{n} = CH\textsubscript{3}, NH\textsubscript{2}, OH, and F. The first of these two chapters has a slightly different focus, as it shows an analysis of the bonds to explain apparent anomalies in the trends of bond strengths found in these series of increasingly polar bonds across the second period. The second chapter proceeds with the by then familiar treatment of the activation of these bonds by model palladium compounds.

Chapter 8 treats another interesting series of bond activations, comprised of a series of differently hybridized bonds C\textsubscript{2}H\textsubscript{5}–X, C\textsubscript{2}H\textsubscript{3}–X, C\textsubscript{2}H–X (with X = H, CH\textsubscript{3}, Cl). Similar as in the previous chapter, an important aspect of understanding the activation of these bonds lies in the balance between bond strengths (i.e. how difficult is it to break the bond) and the interaction strength between palladium and the substrate. It turns out that there are quite some similarities to be found in this analysis compared to chapter 7.

1.4 This thesis (practicalities)

Supporting information in the form of various videos depicting the reaction paths calculated for the reactions under consideration for each chapter can be found via http://www.few.vu.nl/~bickel. It can be very instructive to really ‘see’ the reaction happening, especially since it can often nicely visualize the deformation of catalyst complexes and substrates.

As this thesis will only have a limited hard copy circulation, the emphasis of the distribution will be on the PDF-version. Because of this, the ‘dead-tree edition’ will be a black and white print, and may not display all the nice color graphs as beautifully as compared to the electronic version, which should be preferably viewed on a full color computer screen, eReader, or iPad. The reasons for the limited amount of printed copies are: 1) a desire for a paperless future where hard copies are considered nostalgic; 2) environmental considerations.