Transition metal catalysts for the conversion of biomass inspired substrates
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Chapter 1
General Introduction
Chapter 1

1.1 Organometallic Chemistry and Homogeneous Catalysis

Contemporary society finds itself at a point where the fossil fuel reserves, supplying our fuels, chemicals and energy, are threatened to be depleted. In reaction to this, a general trend is emerging where renewable resources are being investigated to (partially) replace as well as alleviate the dependence on crude oil.\(^1\) One way to achieve this is to start using renewable resources, such as biomass feedstock. Catalysis plays a key role in the conversion of biomass, enabling or catalyzing reactions to form desired products. Both heterogeneous and homogeneous catalysts can be applied for this processing. The highly stable, cheap and solid heterogeneous catalysts are very suitable for the initial depolymerization step, needed to break down cellulose plant mass, and bulk processes for the production of simple molecules (fuels). For the subsequent specialistic processes, more selective homogeneous catalysts are more suitable. This is in particular true for fine-chemical and pharmaceutical industries that need very selective conversions and therefore very selective catalysts.

The fundamental feature of a homogeneous catalyst is that it resides in the same phase as the substrates it converts, usually the liquid phase (solution). Typically, it is an organometallic compound which is defined on a molecular level, consisting of at least one metal-center coordinated to one or more ligands. Choice and design of the ligand play a crucial role in the development of a catalyst, since the nature of ligands determines the properties and reactivity of the catalyst: ligands can steer, tune and amplify the performance of the catalyst.

As the knowledge of ligands and organometallic compounds keeps expanding, homogeneous catalysts are being designed in a more rational manner. The major part of this design concerns the ligands. Traditional ancillary ligands mostly have oxygen, nitrogen, phosphorus or sulfur at the binding site, binding through a lone-pair, or carbon binding via π-interactions, such as a benzene, diene or allyl-motif. More recently, carbenes were discovered as viable ligands for organometallic chemistry and catalysis.\(^2\)

\textit{N-Heterocyclic Carbene Ligands}

The use of carbenes as ligands is well developed in the field of transition metal complex chemistry.\(^3\) In particular, the \textit{N}-heterocyclic carbenes (NHC) class of imidazol-2-ylidines, first reported in the 1960’s,\(^4\) have received their share of attention since Arduengo isolated the bis-adamantyl NHC (see Figure 1) as the first example of a shelf-stable carbene species.\(^5\) However, a recent publication from the group of Siemeling\(^6\) shows that an example of a stable NHC has been right under our noses, being commercially available for over more than a century: Nitron (Figure 1).\(^7\) It was found that the reactivity of Nitron was less well
explained by its conventional Lewis structure, and better by its NHC type tautomer. Experiments using carbene trapping reagents revealed products that were comparable with typical nucleophilic carbene reactions. The fact that carbenes could be stable was in contrast to the common belief that every carbene is extremely reactive and therefore very unstable.

Imidazol-2-ylidenes, the NHCs that found wide applications in catalysis, are singlet carbenes. This means that the two non-bonding electrons are paired up as the sp²-hybridized lone-pair. The singlet carbene center is stabilized via a push-pull mechanism (see Figure 2): The two adjacent nitrogen atoms donate electron-density from the lone pairs into the empty p orbital of the carbene. This π-donating ability (the "push") into the pπ orbital of the carbene raises the relative energy of this orbital. Since the carbene σ-orbital remains similar in relative energy, the σ-pπ energy gap becomes larger and the singlet state of the carbene is stabilized. Secondly, there is also withdrawing electron density from the carbon, through σ-induction, to the more electronegative nitrogen atoms (the "pull"). It is also suggested that a certain aromaticity renders the NHC stability. This electronic structure of NHCs makes them stronger 2e- σ-donors than phosphines and at the same time also weak π-acceptors.

Additionally, by varying the substituents on nitrogen, there can be modulation of the steric properties on both the carbene and the coordinated metal, stabilizing or protecting it to a certain extent. This is well illustrated by Arduengo’s NHC which has bulky adamantyl moieties on both nitrogen atoms and is stable as a free carbene (Figure 1). Steric bulk is not a crucial factor however, since NHCs with small N-substituents like methyl are well known.

When it comes to the bonding of an NHC with a transition metal, both the steric and electronic effects must be taken into account. In the beginning NHCs were viewed as simple
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σ-donors, donating electron density into an acceptor orbital of the metal. This simplified picture has been adjusted throughout the years when it became obvious that filled and empty π and π* orbitals can also contribute to the metal-NHC bond. Delocalization of the filled π-orbitals on the NHC into metal d-orbitals are a very relevant interaction. The NHC can also function as an acceptor by receiving electron density from electron-rich late transition metals into the π* orbital of the NHC. The interactions of the d-orbitals are visualized in Figure 2. Basically this means that when the metal is more or less electron-rich, the NHC will be more, or less, an acceptor. This is contrary to common belief that NHC are “better donors than phosphines”, making the NHC a ligand with chameleon-like properties.

An advantage of NHCs over phosphines is that NHCs are less prone to oxidations, which enables processes under aerobic conditions to occur without catalyst degradation. The strong M-carbene bond is more stable under catalytic conditions, generally encompassing high temperatures and pressures. Despite the advantages of NHCs, their application in transition metal catalyzed direct hydrogenation has been limited. In addition to NHC’s being a monodentate coordinating ligand, bi- or polydentate ligands have been developed, creating additional stability. One of the easiest strategies to achieve this is through N-substitution of the NHC with a coordinating moiety.

Figure 2. The “push-pull” mechanism stabilizing the NHC (left), and a schematic representation of the important orbital interaction in the M-NHC bond, adapted from ref [15].
Cooperativity: Hemilabile and Bifunctional Ligands

When a bidentate ligand has one functionality that (potentially) participates in catalysis (an ‘actor’ instead of a ‘spectator’) one arrives in the realm of cooperative catalysis. Cooperative ligands participate directly in a reaction, along with the metal center, and undergo reversible chemical transformation: together they facilitate a chemical process. \(^{[21,22]}\) We aimed at creating a hemilabile and/or bifunctional ligand (Figure 3). The term hemilabile ligand was first introduced by Rauchfuss in 1979, and studies by the group of Fryzuk further formed the basics of the concept cooperativity.\(^{[23,24]}\) A hemilabile ligand consists of a strongly bound donor group, in our case the NHC, and one that binds weakly and reversible to the metal center;\(^{[22]}\) upon dissociation it creates a vacant site to facilitate substrate coordination. Metal-ligand bifunctional catalysis encompasses a mode of action where both the metal and the surrounding ligand participate in the bond-forming and breaking steps of the reaction, and no (partial) dissociation of the ligand is needed.\(^{[25]}\)

**Figure 3.** Schematic representation of the concept of a hemilabile and a bifunctional system, using a bidentate ligand L-X (X = N, O, P).

Amine ligands are recognized both as potential hemilabile and bifunctional cooperative ligands and are therefore renowned for their role in hydrogenation catalysis. This new type of mechanism was discovered in pioneering work from Noyori and coworkers. Already in 1995, Noyori reported on a very active ruthenium(II) catalyst that was able to quickly convert aromatic ketones into alcohols at room temperature in a highly selective manner.\(^{[26]}\) In 2000, Noyori coined the term ‘NH-effect’ for his hydrogenation catalysts,\(^{[25]}\) explaining a range of experimental observations including ligand acceleration effects, the effect of amine moieties in ligands and the structural characteristics of the ruthenium catalyst. This model was the introduction of the metal-ligand bifunctionality, contrary to many other metal-centered catalysis. (More details on the role of bifunctional ligands in hydrogenation will be described below under Hydrogenation of Polar Bonds).

Many examples of cooperative mechanisms are found in biological systems, where enzymes establish very fast and selective conversions facilitated by an active site with very specific
interacting surroundings. The utilization of cooperative systems in the field of homogeneous catalysis is developing fast and several recent advances are mentioned here (Figure 4). Species known to display cooperativity and hemilability are the pincer-type ligands such as PNP or PNN. In PNP and PNN ligands containing pyridine, cooperation via the aromatization/dearomatization mechanism, and hemilability via the dissociation of the phosphine arm, was shown by Milstein\(^{[27]}\) to play a crucial role in the formation of imines from alcohols and amines. The authors even found that if one of the phosphines was replaced by an amine, creating a PNN ligand, the preferred product was an amide, showing a remarkable influence of the coordination strength of the hemilabile arm.\(^{[28,29]}\) Alternatively, hemilabile backbone cooperativity is also possible in some pincer systems. In a recent publication by Parvez,\(^{[30]}\) it was shown that in a PC(carbene)P pincer containing nickel complex, the Ni-carbene donor is non-innocent, and can switch between coordination as a carbene to a non-coordinating moiety by addition of E-H bonds across the Ni=C bond. This allows for the activation of small molecules, such as H\(_2\) or NH\(_3\).

![Figure 4. Overview of interesting hemi-lability and cooperativity in pincer containing complexes reported by Milstein (top), Parvez (middle) and van der Vlugt (bottom).](image)

In another example of backbone cooperativity, van der Vlugt showed that PNP ligands can also display hemilabile backbone cooperativity between the pyridine-N and a cationic Cu(I) metal center.\(^{[31,32]}\) This is a useful property in catalysis, functioning as a ‘coordination-switch’
creating a vacant site. Upon treatment with base, the complex showed dearomatization, creating the possibility of methylation of the linker which, in turn, can lead to a new set of analogous, chiral complexes. Besides the archetypal pincer structure, several varieties of the PNN structures have been reported, obtaining, amongst others, modular ligands with variable linker length and rigidity or donor strength.\textsuperscript{[33]}

Metal-ligand bifunctional catalysis is known somewhat longer, and although Noyori coined the term ‘NH-effect’, Shvo\textsuperscript{[34]} and Casey\textsuperscript{[35]} are also two pioneers in the field of bifunctional catalysis (see Figure 5). Shvo’s catalyst is a hydroxycyclopentadienyl-Ru complex, where the cyclopentadienyl ligand can switch between a neutral and an anionic form, transferring separate protons or hydrides to or from the metal center and ligand.\textsuperscript{[36]} Casey investigated the mechanistics of the Shvo catalyst in detail.\textsuperscript{[35]} Later he went on to examine the iron analogue of Shvo’s catalyst and found that it follows a very similar pathway in hydrogenations, and as such was the first to describe an efficient bifunctional Fe-catalyst for the reduction of ketones and aldehydes.\textsuperscript{[37]} In both catalysts, the ligand participates in the hydrogenation of the polar bond of the substrate.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Famous examples of bifunctionality: Shvo’s Ru-catalyst (top), where the dimeric precatalyst can form two monomeric oxidized and reduced complexes upon dissociation in solution. These are interconvertible in the presence of a hydrogen acceptor or donor. Casey’s Fe-analogue (bottom) is shown with the bifunctional mechanism for H\textsubscript{2}-hydrogenation.}
\end{figure}

Developments such as cooperativity and the creation of hemilabile or bifunctional ligands contribute greatly to the feasibility of the application of homogeneous systems on an in-
They form highly active catalysts that only need moderate temperatures and low pressures to generate the product. Not only does this improve on the efficiency and economy of current processes, it is also more environmentally friendly.

1.2 Biomass

With all the contemporary environmental issues and the depletion of fossil fuel reserves, society has started investing in the development of renewable sources of energy and materials; sources that are either inexhaustible or replaceable. Besides the straightforward options like wind, sun and water to function as renewable energy resource, biomass is the feedstock of choice when it comes to finding a renewable carbon source (see Figure 6). Besides replacing fossil fuels as transportation fuels (via fermentation to bio-ethanol) or burning it to generate energy, biomass is able to provide the chemical industry with sustainable resources. There are several forms of biomass: vegetable oils (soy bean or waste oils), starch (obtained primarily from sugarcanes) and lignocellulosic biomass, the most abundant form. Lignocellulosic biomass is a so-called second-generation feedstock, which is obtained from non-edible forms of biomass (woody biomass, grasses or crop waste). Using non-edible biomass prevents competition with land-use for food production, which is not a viable option both ethically and from the point of view of effective and sustainable re-use of crop waste. Lignocellulosic biomass consists of the biopolymers cellulose, hemi-cellulose and lignin,[38] which are naturally rich in oxygen and structurally complex. The C₆ sugars that are present in lignocellulosic biomass (in particular in hemi-cellulose) can be transformed into a considerable range of chemical building blocks with high application potential.[39,40] The high oxygen content makes it the most difficult form of biomass to convert, but also one of the most valuable ones. Retaining a high degree of functionality throughout

![Figure 6. Schematic supply chain from low-value biomass to high-value end products.](image-url)
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Chemical transformations provides an effective route to use and employ the natural complexity directly in a highly functionalized product. Current strategies encompass starting from the smallest building blocks (obtained by reforming to CO/H₂ using Fischer Tropsch) and adding the functionality in the end. Hence, using biomass instead, potentially a lot of energy can be saved. The high degree of functionalization is desired when it comes to agricultural, pharmaceutical or fine-chemical industries (Figure 6).

From processed biomass a set of key intermediates with a high application potential, called platform molecules, have been defined. These can be transformed into any valuable product of choice. To achieve this, new methods for the re- and defunctionalization of biogenic substrates have to be developed, creating a toolkit filled with selective, catalytic conversions that a chemist can use to create the desired product structure in a renewable fashion.

The CatchBio program (catalysis for sustainable chemicals from biomass) aims to develop clean and efficient processes for biomass conversion into low-cost and sustainable biofuels, chemicals and pharmaceuticals. As a part of this program, the work described in this Thesis focuses on the application of newly developed systems in processes that play a role in the conversion of biomass. Since the metal complexes that were designed here are to be applied as homogeneous catalysts, the applications and the catalytic conversions that were looked at find their use in the fine chemicals and pharmaceutical section. In this area of expertise it is important to very specifically convert one of more functionalities. The method is softer than heterogeneous methods, where harsh conditions generally break down each interesting functionality in a molecule.

Biomass or processed biomass contains many functionalities including polar bonds. Focus was put on the reduction and functionalization of these bonds, and in the next section the catalytic conversions investigated in this thesis will be discussed.

1.3 Catalytic Transformations

Hydrogenation of Polar Bonds

Catalytic hydrogenation of polar bonds (see Scheme 1) using molecular hydrogen is an environmentally benign and cost-efficient process. Together with hydrogenolysis (see below) it is among the most extensively studied reactions in chemistry, being of fundamental importance in both the laboratory and industry and playing a pivotal role in the synthesis of all kinds of chemicals. Traditionally, stoichiometric reducing agents such as sodium borohy-
dride or lithium aluminium hydride were employed, but these powerful reductants unfortunately produce large amounts of waste.

\[ \begin{align*}
X & \quad \text{H}_2 \\
R \quad \text{cat} \quad R' & \xrightarrow{} \quad XH \\
& \quad R \quad R'
\end{align*} \]

\( X = O, NR \)

**Scheme 1.** The \( \text{H}_2 \)-hydrogenation of polar bonds.

When used in a laboratory environment this doesn’t pose a direct problem, but in industry there is a demand for cleaner and more atom-economical methods that are at the same time cheap, straightforward and environmentally friendly. Molecular hydrogen is abundantly available, relatively cheap and clean and converts the substrate into the product without any waste. For these reasons it constitutes an attractive method to convert biomass into useful chemicals. However, molecular hydrogen is in most cases unreactive towards the substrate, and a catalyst is needed to activate dihydrogen and, in some cases, the substrate.

Most large-scale industrial processes run a heterogeneous catalyst system for their hydrogenations. However, when a system requires a large functional group tolerance and chemoselectivity, the harsh conditions of heterogeneous catalysis are less desirable. Homogeneous catalysts operate under milder conditions and are designed to have a certain chemoselectivity and a very high functional group tolerance (“sophisticated degree of selectivity”). Therefore, fine-chemical, pharmaceutical and life-science industries put a lot of effort into the development of homogeneous systems.

Although the first hydrogenation catalyst was officially reported in the 1930’s (a copper catalyst for the hydrogenation of alkenes), the field really started developing in the 1960’s when Wilkinson reported the first catalyst to perform this reduction, \( \text{RhCl}(\text{PPh}_3)_3 \). In the 1970’s the first rhodium and ruthenium complexes that were applicable in the hydrogenation of C=O polar bonds were reported. In 1989, Noyori and coworkers reported on the first asymmetric hydrogenation of \( \alpha,\beta \)-keto esters, which was awarded with the Nobel prize in 2001. In the pharmaceutical industry the asymmetric hydrogenation is increasingly used to introduce stereogenic centers into products, making it an important reaction for the fine-chemical industry, universities and research institutes.

Especially, Noyori’s discovery of a bifunctional mechanism he called the NH-effect provided a breakthrough in these hydrogenation reactions. Before this, these reactions were generally accepted to follow the classic route, where cleavage of molecular hydrogen was
performed on the metal centre, generating metal-hydrides. An ancillary ligand then had to dissociate in order to make room for the substrate. When the substrate, for example a ketone, binds to the metal center, it is transformed into the metal-alkoxide, followed by hydrogenation to give the product alcohol. This reaction proceeds through what is called a classical inner-sphere mechanism (see Figure 7).

The bifunctional mechanism, on the other hand, is proposed to proceed in the outer coordination sphere. First, the hydridoamido complex heterolytically cleaves the $H_2$ molecule over the Ru-N amido bond to produce a hydride species. The NH moiety then activates, for example, a carbonyl containing substrate via an NH•••O=C hydrogen bond, pre-organizing and facilitating the attack of the carbonyl group by the metal hydride in a pericyclic six-membered transition state, without binding to the metal (Figure 5). This is called the non-classical outer-sphere mechanism and is shown in Scheme 2 for the Noyori-type catalyst.

![Figure 7](image_url)  
**Figure 7.** Inner and outer sphere mechanism, including ligand assistance via an electrophilic ancillary ligand moiety, adapted from ref[48]. The inner-sphere coordination mode here displays a hemilabile ligand, where NH$_2$ dissociates from the metal center to facilitate substrate coordination.

![Scheme 2](image_url)  
**Scheme 2.** Bifunctional mechanism shown for Noyori-type complexes in the hydrogenation of ketones. The role of the cooperating amido-ligand is clearly shown here.
Since its discovery, bifunctional catalysis has played a key role in several pioneering reports on polar bond hydrogenation reactions, most notably by Noyori,\textsuperscript{[25]} Morris,\textsuperscript{[51]} Clarke\textsuperscript{[52]} and Milstein.\textsuperscript{[27]} The complexes that were applied by these authors are shown in Figure 8.

As can be seen in Figure 8, most of the complexes reported involve bidentate combinations of phosphines, amines, tridentate pincers and an NHC. The group of Morris is the only one that explored NHC-amine ligands in direct hydrogenation.\textsuperscript{[53-55]} He shows, based on DFT calculations, that not only the bidentate ligand with a possible bifunctional moiety influences the course of the reaction: depending on the ancillary ligand (p-cymene or Cp*), M-complexes (M = Ru, Ir) with this NHC-amine motif follow either an inner-sphere cooperative or an outer-sphere cooperative mechanism.

**Figure 8.** Some examples of complexes containing bifunctional ligands, with a reported NH-effect in hydrogenation reactions.

Hydrogenation of ketones is an important reaction, as mentioned before, and it is often used as a benchmark reaction. The order of relative reactivity\textsuperscript{[56]} in hydrogenation of the polar moieties is as follows:

\textit{Acid Chlorides > Aldehydes > Ketones > Anhydrides > Esters > Carboxylic Acids > Amides}

Ketones are intermediately easy to hydrogenate while reduction of an ester bond, for example, requires more powerful reducing agents or catalysts.
Hydrogenolysis of Esters

Hydrogenation concerns the addition to or incorporation of hydrogen in an (organic) molecule. Generally, addition to a double or a polar bond takes place. However, when the reacting bond is cleaved, the correct term is hydrogenolysis.

Esters, carboxylic acids and amides are considered difficult substrates for catalytic hydrogenolysis due to their thermodynamic stability. The hydrogenolysis of esters, for instance, is in many cases only thermodynamically feasible at elevated temperatures. The stability of esters stems mainly from the fact that the electrons of the carbonyl moiety are delocalized. The $\Delta H$ gained during the reaction is small and the $\Delta S$ under standard conditions is negative. The hydrogenolysis of esters (Scheme 3) encompasses the reduction of the ester to the corresponding alcohols by cleaving C-O bonds using molecular hydrogen. It is an industrially important but difficult reaction. As with the hydrogenation of polar bonds, stoichiometric amounts of LiAlH$_4$ were traditionally used for the reduction, generating equal amounts of waste and here also, molecular hydrogen is the cleaner and 'greener' solution. The scenario is similar to that of hydrogenation, where unselective, in this case even carcinogenic, heterogeneous copper-chromite catalysts are calling to be replaced by a more selective, environmentally friendly homogeneous counterpart. Ester hydrogenolysis catalysts can also be applied in the processing of biomass, where esters and cyclic esters (lactones) are present.

\[
\begin{align*}
\text{O} & \quad \text{R}_1 \quad \text{O} \quad \text{R}_2 \\
\text{2H}_2 & \quad \text{[cat]} \\
\text{R}_1 \text{OH} & + \quad \text{R}_2 \text{OH}
\end{align*}
\]

Scheme 3. The hydrogenolysis of esters to alcohols.

About three decades ago, Grey and Pez were able to convert several activated carboxylic acid esters and a little later also the simple aliphatic ester methyl acetate. Matteoli was the first to report on the conversion of both ester functional groups in dimethyl oxalate (DMO), using neutral ruthenium acetate carbonyl tributylphosphine complexes (such as Ru(CO)$_2$(CH$_3$COO)$_2$(PBu$_3$)$_2$). The authors reported 26% formation of the doubly hydrogenolyzed product ethylene glycol, leaving the remaining 74% as mono hydrogenolyzed product methyl glycolate. However, the conditions used were rather harsh: 130 bar $\text{H}_2$ at 180 °C for 144 hr. Then, during the 1990's, the first of a series of publications from the Elsevier group appeared where an active system was reported based on Ru(acac)$_3$/ triphos (see Figure 9) which is able to almost quantitatively convert dimethyl oxalate to ethylene glycol under less forcing conditions (100 bar $\text{H}_2$, 70 °C, 16 hr) using hexafluoro-i-propanol as the solvent. Moreover, it was possible to quantitatively convert benzyl benzoate, dimethyl...
maleate and methyl palmitate into their product alcohols.\cite{65,66,58}

The next series of breakthroughs came about a decade later when, in cooperation with the pharmaceutical companies Takasago and Firmenich, Kuriyama and Saudan reported a series of complexes where the ligands contained both phosphine and amine moieties.\cite{67,68} \((R,R)\) or \((S,S)\)-[RuH(η\(^1\)-BH\(_4\))(dppp)(dpen)] was found by Takasago to hydrogenate optically active \(\alpha\)- and \(\beta\)-substituted esters without loss of optical purity to the chiral alcohols at 50 bar and 80 °C, but benzoic acid esters (e.g. benzyl benzoate) remained a challenge. The most recent report from Takasago is Ru-MACHO, a very simple and achiral, yet effective catalyst able to convert multiple types of esters with high activity at similar conditions.\cite{69,70} Beller reported the use of Ru-MACHO-BH\(_3\) complex in the conversion of DMO and derivatives thereof at room temperature without the need of a base (the chloride ion is replaced by hydride-BH\(_3\) so abstraction using a base was unnecessary).\cite{71} Clarke also reported on a novel chiral tridentate phosphine-amino containing complex\cite{72} and found later that these systems provide excellent activities for a range of aromatic esters at 50°C and 50 bar \(H_2\) using a cat/base/substrate ratio of 1/50/200.\cite{73} Milstein developed a different type of system working via the cooperative aromatization/dearomatization mechanism of the pincer arm of the complex\cite{28} (see Figure 9). This type of complexes is also active in the hydrogenation of amides to alcohols and amines and in the reverse reactions, dehydrogenation and direct coupling of alcohols.\cite{74-76}

![Figure 9. Overview of recently reported complexes that have been successfully applied in ester hydrogenolysis.](image-url)
Inspired by the design of Milstein’s PNN complex which was more active than its PNP analogue, Gusev improved on his previously reported catalyst (an iridium catalyst for hydrogenations) by replacing the MACHO-type PiPr$_2$-NH-PiPr$_2$ ligand\[^{77}\] with the hemilabile Npyr-NH-PiPr$_2$ ligand\[^{78}\] containing a pyridyl moiety instead of one of the phosphines. Reacting the obtained Ru and Os monomeric complexes with KOTBu resulted in dimeric structures. These were reported to fully convert a range of esters without further addition of a base, at 100 °C and 50 bar H$_2$, but curiously enough completely failed to convert DMO.\[^{78}\]

In a second variation of the Ru-MACHO structure, Gusev replaced the phosphines for sulphur, creating an SNS pincer which showed excellent activity at 40°C and 50 bar H$_2$ in the hydrogenation of esters, ketones and imines; as well as in the reverse reaction: dehydrogenative coupling of ethanol to ethyl acetate.\[^{79}\]

There are, to the best of our knowledge, three examples of functionalized NHC containing complexes that are applied in ester hydrogenolysis. The first two were reported simultaneously in the groups of Annibale\[^{80}\] and Milstein\[^{81}\] in 2011, both reporting on an NHC and pyridine or bipyridine containing ligand active at low pressures and moderate temperatures (5,3 bar H$_2$, 105 °C/135 °C). The third is the RuCp*Cl(NHC-amine) complex from Morris which was previously applied in hydrogenation of ketones under very mild conditions (8 bar H$_2$, 25 °C) and was later successfully extended to certain esters and lactones (25 bar H$_2$, 50 °C). They were also the first to report a computational study on an outer-sphere bifunctional mechanism operating for this catalyst in ester hydrogenolysis.\[^{55,82}\]

A schematic representation of a catalytic cycle of ester hydrogenolysis is shown in Scheme 4. It displays a classical mechanism, where the strength and formation of the metal-hydride are of great importance. Chapter 2 specifically deals with the hydrogenolysis of esters. The
ligands for this project were designed to increase the hydricity of the metal-hydride. The structure of the ligands leaves no room for a bifunctional mechanism, which is why the classical mechanism is discussed here. There have been several reports on ester hydrogenolysis mechanisms encompassing solvent-assistance, but this is omitted in this simplified scheme. In the cycle, the initial hydrogen transfer to the ester carbonyl complex is the slowest and thus rate determining step due to the relative inertness of the ester bond. Once this has taken place, the hemi-acetal is formed which, unstable under the reaction conditions, splits to form the first product-alcohol and an aldehyde. The aldehyde coordinates again to the complex and in a second, fast, hydrogenation step the second product-alcohol is formed.

**Direct Alkylation**

Another important transformation where organometallic chemistry and catalysis have significantly contributed in its progress and development is the area of C-C coupling reactions, shown in a generalized manner in Scheme 5. Similar to the previous examples, choosing homogeneous catalysts over heterogeneous catalysts in these reactions improves the selectivity and functional group tolerance. Famous examples of C-C bond coupling reactions are, the Kumada coupling (coupling of Grignard reagents with organohalides), the Negishi coupling (where an organozinc compound is coupled with an organohalide), the Suzuki reaction (reacting a boronic acid with an organohalide) and the Stille reaction (coupling organotin compounds with alkylhalides or pseudohalides).

\[
\begin{align*}
R^1\cdot X & \quad + \quad M\cdot R^2 & \quad \xrightarrow{[\text{cat}]} & \quad R^1\cdot R^2 & \quad + \quad MX \\
X &= \text{halide} & \quad [\text{cat}] &= \text{usually Pd} \\
M &= \begin{cases} 
Mg & \text{Kumada coupling} \\
Zn & \text{Negishi coupling} \\
Sn & \text{Stille reaction} \\
B & \text{Suzuki reaction}
\end{cases}
\]

**Scheme 5.** Schematic representation of C-C coupling reactions.

In organic chemistry, C-C bond formation is often achieved via α-alkylation next to a polar functional group. Where ketones are concerned, α-alkylation is performed between nucleophilic enolates or enolate equivalents and electrophilic alkylating agents. The main disadvantage of this reaction, together with all the classical C-C bond formation reactions mentioned above, is the generation of stoichiometric amounts of halide salts. There are also some selectivity issues, since treatment of unsymmetrical ketones with a base leads to a mixture of the formed enolates, giving rise to both α- and α’-alkylated products. A more
atom efficient and environmentally benign route towards α-alkylated ketones could be established using an alcohol as alkylating agent with the aid of a transition metal catalyst.\textsuperscript{[87]} This would result in a less polluting, cleaner route where fewer side products are formed, with the additional possibility that a homogeneously catalyzed process could also benefit the regioselectivity of the process.

Pioneers in the work of α-alkylation next to a polar functionality, using an hydroxyl group as nucleophile, were Tsuji and Trost. In 1965, the group of Tsuji reacted diethyl malonate with ethanol, obtaining the mono and dialkylated product.\textsuperscript{[89]} The catalyst (usually a Pd-species) activates the malonate, to form an allylic enolate which can subsequently be alkylated (see Scheme 6). In 1973, Trost improved the reaction via the introduction of phosphine ligands, enabling asymmetric allylic alkylation of carboxylates.\textsuperscript{[90,91]}

Catalytic C-C bond formation, most notably palladium catalyzed, has shown to be an immensely valuable type of reaction for applications in the pharmaceutical, fine-chemical and agrochemical industry.\textsuperscript{[92]} In the context of this project it is therefore worthwhile to investigate this 'greener' version of C-C bond formation. The direct α-alkylation of ketones with non-allylic alcohols was first reported by Cho in 2001.\textsuperscript{[93]}

While investigating ruthenium catalyzed reactions and focusing on the transfer hydrogenation of ketones and alcohols (see Scheme 7, route a), he found that unconventional, alkylated products were formed in each run (route b). The product of route b is a mixture of both the alcohol and the ketone in the alkylated form. The reaction was performed using the alcohol in threefold excess, generating the product alcohol as the preferred product with only trace amounts of the product ketone.\textsuperscript{[93]}

\begin{center}
\textbf{Scheme 6.} Mechanism of allylic alkylation, discovered by Tsuji and Trost. The catalytic cycle is shown for the attack of a soft nucleophile. In the case of a hard nucleophile, the nucleophile first attaches to the metal followed by reductive elimination.
\end{center}
Based on these observations, Cho proposed a catalytic cycle which is displayed in Scheme 8. A “hydrogen borrowing system” plays a crucial role in this cycle. Hydrogen-borrowing activation of alcohols omits the need for alkylating agents in an alkylation. Alcohols are frequently used as starting materials but are unreactive due to the poor leaving group ability of the OH group. Traditionally, alcohols were activated by replacing them with a halide or a sulfonate but this brings along the problems of toxicity (of alkyl-bromides for example), addition of an extra reaction step and the waste generated in the end. Instead, in this catalytic cycle, an organometallic catalyst can be applied to dehydrogenate the alcohol, thereby creating an aldehyde or a ketone. A base-catalyzed cross aldol condensation between the resulting aldehyde and the substrate ketone forms an α,β-unsaturated ketone which is hydrogenated to the product ketone via the metal hydride formed in the initial oxidation step, and can be further hydrogenated to the product alcohol. The hydrogens are essentially ‘borrowed’ from the starting material and returned in the final step to form the product, creating an overall redox-neutral reaction pathway. The mechanism of this reaction is supported by deuteration studies of Ishii using butanol-d9, where an M-HD species is generated from dehydrogenation of the deuterated butanol.

Scheme 8. Catalytic cycle of direct α-alkylation of ketones with alcohols, showing the hydrogen borrowing mechanism (step 1 and 3) and the base-catalyzed aldol condensation (step 2), shown in more detail in the frame.

Work-up in between steps is not necessary: three reaction steps are combined in one reaction. In essence, the α-alkylation of ketones with alcohols is a variation of the Guerbet reac-
Chapter 1

tion, where the dehydrogenated alcohol homocouples to its second dehydrogenated form and also reduces the ketone in the product to the alcohol since there is a second equivalent of oxidized catalyst available.\footnote{Cho and Ishii were one of the firsts to develop this reaction as an α-alkylation reaction between ketones and alcohols.}

1.4 Outline of This Thesis

The work described in this thesis aims to develop a new set of homogeneous catalysts that will be applied in catalytic conversions focused on the reduction and functionalization of substrates containing polar bonds. Primarily, fundamental insight is gained into the structural features of newly developed catalysts. The performance of the catalysts in several types of catalytic conversions is investigated, supplying us with an improved understanding of the functioning of the catalyst. The catalytic reactions that are chosen to test these complexes and their abilities all relate to the conversion of highly functionalized substrates obtained from biomass or substrates inspired thereon.

The topic of Chapter 2 concerns a re-evaluation and extension of a system for the hydrogenolysis of esters, based on Ru(acac)$_3$ and a triphosphine ligand, that was developed in our group. The goal was to evaluate results that were obtained previously and to search for improved hydrogenolysis catalysts that operate in an environmentally more benign solvent, aiming to prevent the use of fluorinated solvents and additives. The improvement was sought primarily in the design and synthesis of ancillary ligands, which was addressed by substituting one or more P-donor atoms for C$_2$NHC donors, and creating novel ruthenium complexes (pre-catalysts) containing this motif.

Furthermore, we wanted to explore the design and applications of a novel type of bidentate NHC-amine ligand. In Chapter 3, we describe the synthesis of this ligand and late transition metal half-sandwich complexes thereof. Structural comparisons with analogous complexes reported in literature were made. The electronic nature of the ligand was investigated, as well as its influence on the structure of the complexes.

In Chapter 4 we describe the synthesis of a set of late transition metal complexes containing several different coordination modes of the NHC-amine ligand. Using these complexes, we investigated in more detail the influence of a monoanionic charge on the ligand structure by comparing structural parameters of monoanionic and neutral bonding modes of the ligand.

Chapter 5 and 6 concern the catalytic applications of the complexes described in Chapter 3 and 4. In Chapter 5, the half-sandwich complexes were applied in the hydrogenation of po-
lar bonds. The influence of structural variations on catalytic activity was investigated, elucidating which catalytic features influence the catalysis most and what would be a plausible mechanism. We also describe our investigations to broaden the substrate scope, including biomass inspired substrates.

In Chapter 6 we describe the application of our newly developed NHC-aniline complexes (described in Chapter 3 and 4) in the direct α-alkylation of ketones with alcohols. We explored the feasibility of the NHC-aniline containing catalysts to function as internal base in this reaction. The applicability of these complexes as well as the possibilities of the substrate scope was investigated, also including natural alcohols to probe the extent to which this reaction can be developed and applied in conversion of biomass to produce sustainable chemicals.

1.5 References

Chapter 1

Chapter 1


Chapter 1


Chapter 1


